Universitat Autònoma de Barcelona

Departament de Química

Photochemical preparation of highly substituted cyclobutane and cyclobutene compounds. Stereoselective synthesis of cyclobutane nucleoside analogues.

Ramon Flores Pons

July 2008

Memòria presentada per aspirar al grau
de Doctor en Química per Ramon Flores Pons

Ramon Flores Pons

Vist i plau

Dr. Josep Font i Cierco

Dr. Ramon Alibés i Arqués

Bellaterra, Juliol de 2008

Aquest treball ha estat realitzat a la Unitat de Química Orgànica del Departament de Química de la Universitat Autònoma de Barcelona sota la direcció del Dr. Josep Font i el Dr. Ramon Alibés.

En primer lloc, m'agradaria agrair al Dr. Font l'haver-me donat la oportunitat de formar part del seu grup de recerca, fer-me sentir part activa del mateix i l'haver-me ofert la seva confiança, experiència i els seus assenyats consells.

Al Dr. Ramon Alibés li he d'agrair moltes coses, la primera d'elles que aquest treball hagi arribat a bon port. Sembla que va ser ahir que vaig trucar a la seva porta buscant una oportunitat i gràcies a que vaig escollir la porta adequada avui sóc on sóc. Aquesta mateixa porta ha estat oberta per a mi cada vegada que m'han sorgit obstacles i això és quelcom que no puc més que agrair-li sincerament. És difícil d'expressar en poques paraules tot lo après treballant sota la seva direcció gràcies a la seva ajuda, coneixements, entusiasme i dedicació però també gràcies a la confiança que ha dipositat en la meva feina i l'haver-me permès treballar amb total llibertat en el dia a dia.

Vull donar les gràcies també a la Dra. Marta Figueredo pel tracte i l'ajuda que sempre m'ha dispensat i el seu valuós punt de vista químic. També vull agrair al Dr. Pere de March la confiança dipositada en mi en temes de docència i d'indústria que m'han permès completar el paquet d'experiències viscudes. No vull deixar d'agrair als Drs. Pau Bayón, Fèlix Busqué i Jordi Hernando el seu recolzament constant com a veterans i les incomptables converses sobre química, música i tot el que ha calgut.

Un cop arribat aquest punt m'adono que no és possible fer agraïments personalitzats als companys de laboratori doncs he pogut conèixer a un munt de gent extraordinària i no voldria destacar ni obviar a ningú per sobre de la resta. El que tinc clar és que la tesi és només un resum de cinc anys increïbles de la meva vida; la gent que he tingut la sort de conèixer aquí, són un record encara més valuós que m'enduc i entre ells un grapat de bons amics que espero poder mantenir d'ara en endavant.

Vull tenir també un moment per a donar les gràcies als meus amics de sempre que segueixin estan tan propers. En molts sentits, seguim sent els mateixos de sempre...

Als meus pares, la Gemma, la iaia i la resta de la meva família vull agrair-los tot el que m'han ofert incondicionalment sempre i que m'ha permès arribar fins aquí.

Last but not least, vull agrair a la Demelsa per fer aquest viatge al meu costat i per haver escollit experimentar amb mi les petites coses de cada dia que donen sentit a la vida.

“Oh it's a mystery to me.
We have a greed, with which we have agreed
and you think you have to want more than you need
until you have it all, you won't be free

When you want more than you have, you think you need
and when you think more than you want, your thoughts begin to bleed.
I think I need to find a bigger place
cause when you have more than you think, you need more space.

Society, you're a crazy breed.
I hope you're not lonely without me.”

Society, Jerry Hannan

A la Demelsa

Als meus pares i la meva germana

Table of contents

TABLE OF CONTENTS

I. Introduction and objectives

1. Introduction: nucleoside analogues as antiviral agents

Although vaccines have helped to control several of the most important viral pathogens, there is currently little prospect of an effective vaccine for human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency sindrome (AIDS). According to the last annual epidemic update published by the World Health Organization, in December 2007 the number of people infected by HIV was 33.2 million.[1] Furthermore, around 2.5 million deaths were caused worldwide by this pathogen during 2007.

The fundamental characteristic of viruses is their absolute dependence on a living host organism for reproduction; they are obligate parasites. Among them, retroviruses are a family of RNA-based viruses which possess an enzyme called reverse transcriptase (RT) that provides them the unique property of transcribing their RNA genome into DNA, which can then be integrated into the host's genome. Considering its importance in the replication of HIV and the lack of a biological counterpart in the eukaryotic systems, reverse transcriptase has been an attractive target for the development of selective inhibitors since its discovery.

The life cycle of a retrovirus such as HIV starts with the interaction between the envelope proteins of the virus and the host cell, leading to the fusion of the viral envelope and the host cytoplasmatic membrane (Figure 1). Fusion creates a pore through which the viral capsid enters the cell, releasing its viral RNA genome. Then, the viral reverse transcriptase enzyme catalyzes the conversion of viral RNA into DNA. This viral DNA enters the nucleus and becomes inserted into the chromosomal DNA of the host-cell by the viral enzyme integrase. Once integrated, expression of the viral genes leads to production of precursor viral proteins. These proteins, along with viral RNA, are assembled at the cell surface into new viral particles which are able to infect new healthy cells and leave the host cell by a process called budding. Each infected cell may produce thousands of infectious viral particles what rapidly spreads the infection all over the host-organism.

[1] UNAIDS. AIDS epidemic update: December 2007. (http://www.unaids.org).

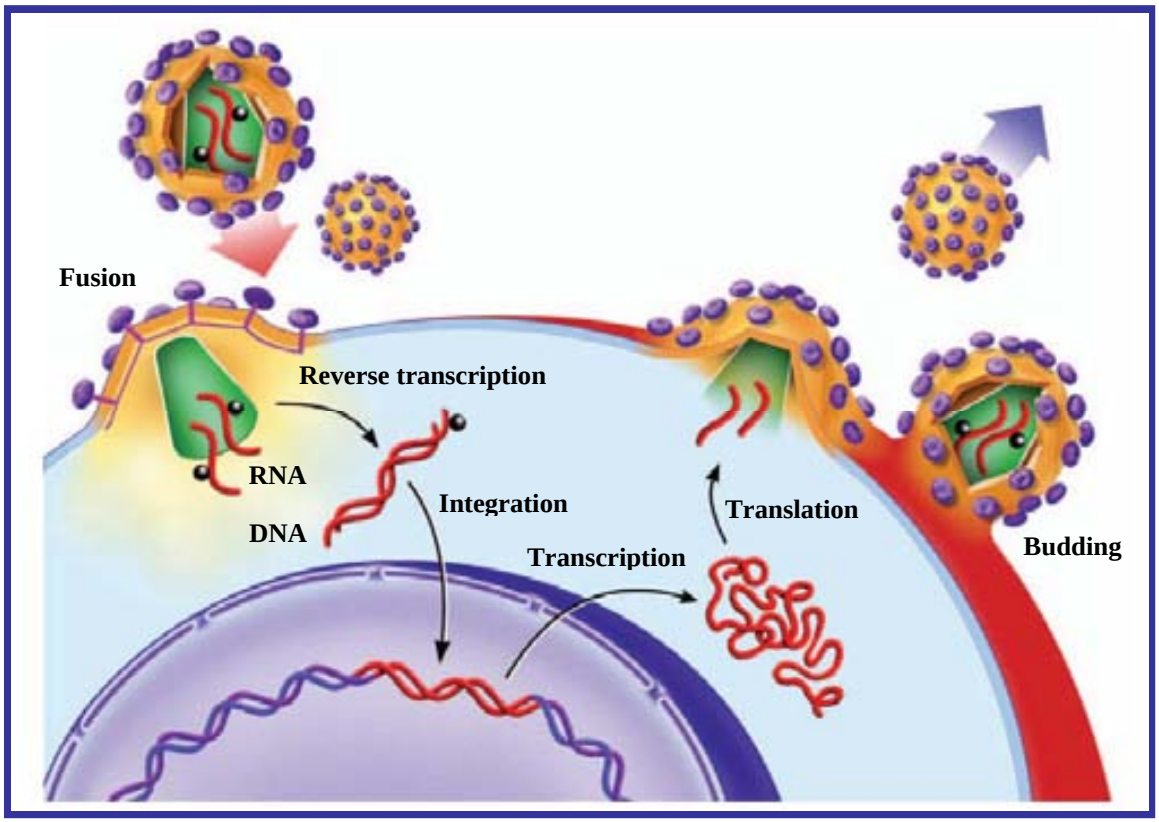


Figure 1. Simplified scheme of HIV life cycle.

Drug discovery and development efforts for HIV treatment have transformed what used to be a rapid and lethal infection into a chronic condition that can be controlled for many years through combination therapies with different classes of antiviral drugs, known as highly active antiretroviral therapy (HAART). These antiviral drugs are classified on the basis of the stage of the viral life cycle they target: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors.

Nucleoside reverse transcriptase inhibitors have been the cornerstone of antiviral therapy over the past thirty years. So far, seven nucleoside analogues, as well as one nucleotide analogue, have been approved by the US Food and Drug Administration (FDA) for the treatment of HIV (Table 1 and Figure 2).[2] Moreover, several other nucleosides are currently being investigated in human trials.[3] On the other hand, nucleoside analogues are also used for the treatment of many other viruses, such as

[2] a) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115-133. b) Warnke, D.; Barreto, J.; Temesgen, Z. *J. Clin. Pharmacol.* **2007**, *47*, 1570-1579.
[3] Stellbrink, H.-J. *Eur. J. Med. Res.* **2007**, *12*, 483-495.

varicella–zoster virus (VZV), human cytomegalovirus (HCMV), herpes simplex virus (HSV), hepatitis B virus (HBV) or hepatitis C virus (HCV).[2,4]

trademark	Active Principal Ingredient (API)	synonyms
Retrovir®	3'-azido-2',3'-dideoxythymidine	AZT, zidovudine
Hivid®	2',3'-dideoxycytidine	ddC, zalcitabine
Videx®	2',3'-dideoxyinosine	ddI, didanosine
Zerit®	2',3'-didehydro-2',3'-dideoxythymidine	d4T, stavudine
Viread®	9-(2-phosphonylmethoxypropyl)adenine	TDF, tenofovir disoproxil
Epivir®	2',3'-dideoxy-3'-thiacytidine	(-)-3TC, lamivudine
Emtriva®	2',3'-dideoxy-3'-thia-5-fluorocytidine	(-)-FTC, emtricitabine
Ziagen®	[4-(2-amino-6-cyclopropylamino-9*H*- purin-9-yl)-1-cyclopent-2-enyl]-methanol	ABC, abacavir

Table 1. Nucleoside reverse transcriptase inhibitors FDA approved for AIDS treatment.

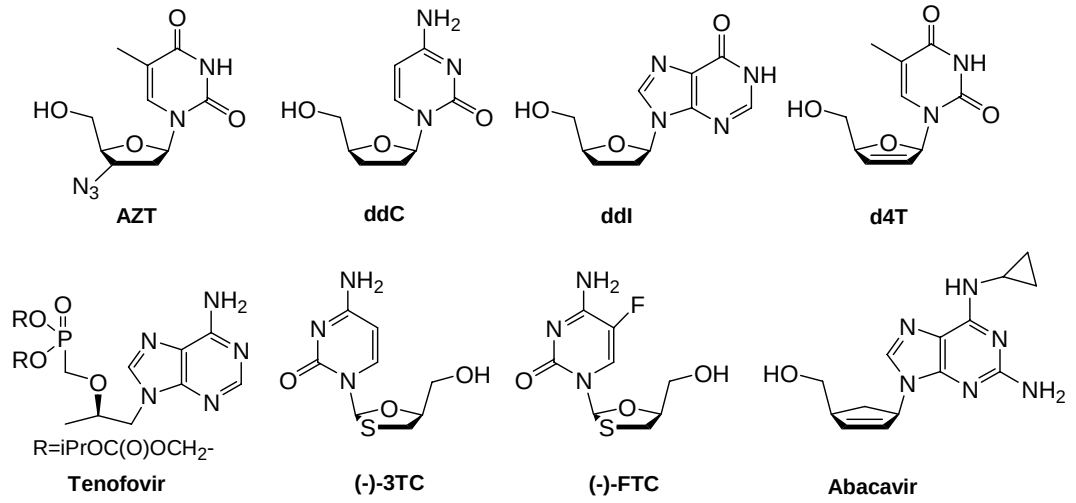


Figure 2. Structures of the nucleoside analogues present in anti-HIV drugs.

With the exception of the acyclic nucleotide tenofovir, the remaining approved NRTIs are 2',3'-dideoxynucleoside analogues. The discovery that the replication of HIV was inhibited by the nucleoside 3'-azido-2',3'-dideoxythymidine (**AZT**) stimulated the search for other dideoxynucleosides, such as 2',3'-dideoxycytidine (**ddC**), 2',3'-dideoxyinosine (**ddI**) and 2',3'-didehydro-2',3'-dideoxythymidine (**d4T**).[5] Moreover, the development of (-)-2',3'-dideoxy-3'-thiacytidine [**(-)-3TC**] as a clinically

[4] a) Hexlett, G.; Hellenberger, S.; Rübsamen-Waigmann, H. *Curr. Opin. Pharmacol.* **2004**, *4*, 453-464. b) De Clercq, E. *Nature Rev. Drug Discov.* **2007**, *6*, 1001-1018.
[5] Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768.

useful anti-HIV agent[6] suggested that even major modifications in the carbohydrate moiety, including changes in absolute stereochemistry from D to L, could lead to active compounds. Finally, the substitution of the furanose ring for a cyclopentenyl moiety has also succeeded in the preparation of active carbocyclic nucleosides such as abacavir.[7]

These active compounds are analogues of the naturally occurring 2'-deoxy nucleosides, the building blocks of DNA. Their mechanism of action involves intracellular phosphorylation (bioactivation) to their 5'-triphosphates, through three different enzymatic steps catalyzed by their corresponding cellular kinases (Figure 3).[8] Then, the resulting 5'-triphosphates derivatives (nucleotides) must interact with the viral reverse transcriptase. However, when 2',3'-dideoxynucleosides are accepted as substrates by this DNA polymerase and incorporated into a growing strand of DNA, the absence of a 3'-hydroxyl group prohibits further strand elongation. Thus, it is primarily through the inhibition of DNA synthesis, either by chain termination and/or by competitive inhibition of the reverse trascriptase, that 2',3'-dideoxynucleosides exhibit their antiviral activity.

Unfortunately, the dideoxynucleoside triphosphates, as well as the intermediate mono and diphosphates, often have affinity for other cellular enzymes. This affinity is thought to cause some of the undesired side effects observed in patients treated with these drugs. The selectivity filter between activity and DNA toxicity is hence only dependent on the substrate specificity of the triphosphates for two related enzymes. Additionally, the efficacy of the NRTIs has been compromised by the development of resistant variants of the virus.[9] Approaches to address these problems include using drugs with different resistance profiles and mechanisms.

[6] Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217-2219.

[7] Daluge, S. M. U.S. Patent 5034394, 1991.

[8] a) Furman, P. A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Lehrman, S. N.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. *Proc. Natl. Acad. Sci. USA*, **1986**, *83*, 8333-8337. b) Hertzberg, R. P. 'Agents Interfering with DNA Enzymes'. In: '*Comprehensive Medicinal Chemistry: The Rational Design, Mechanistic Study & Therapeutic Application of Chemical Compounds*', Hansch, C.; Sammes, P. G.; Taylor, J. B. Ed.; Pergamon Press. 1990, Vol. 2, p. 753-789. c) Arts, E. J.; Wainberg, M. A. *Antimicrob. Agents Chemother.* **1996**, *40*, 527-540.

[9] Larder, B. A.; Darby, G.; Richman, D. *Science* **1989**, *243*, 1731-1734.

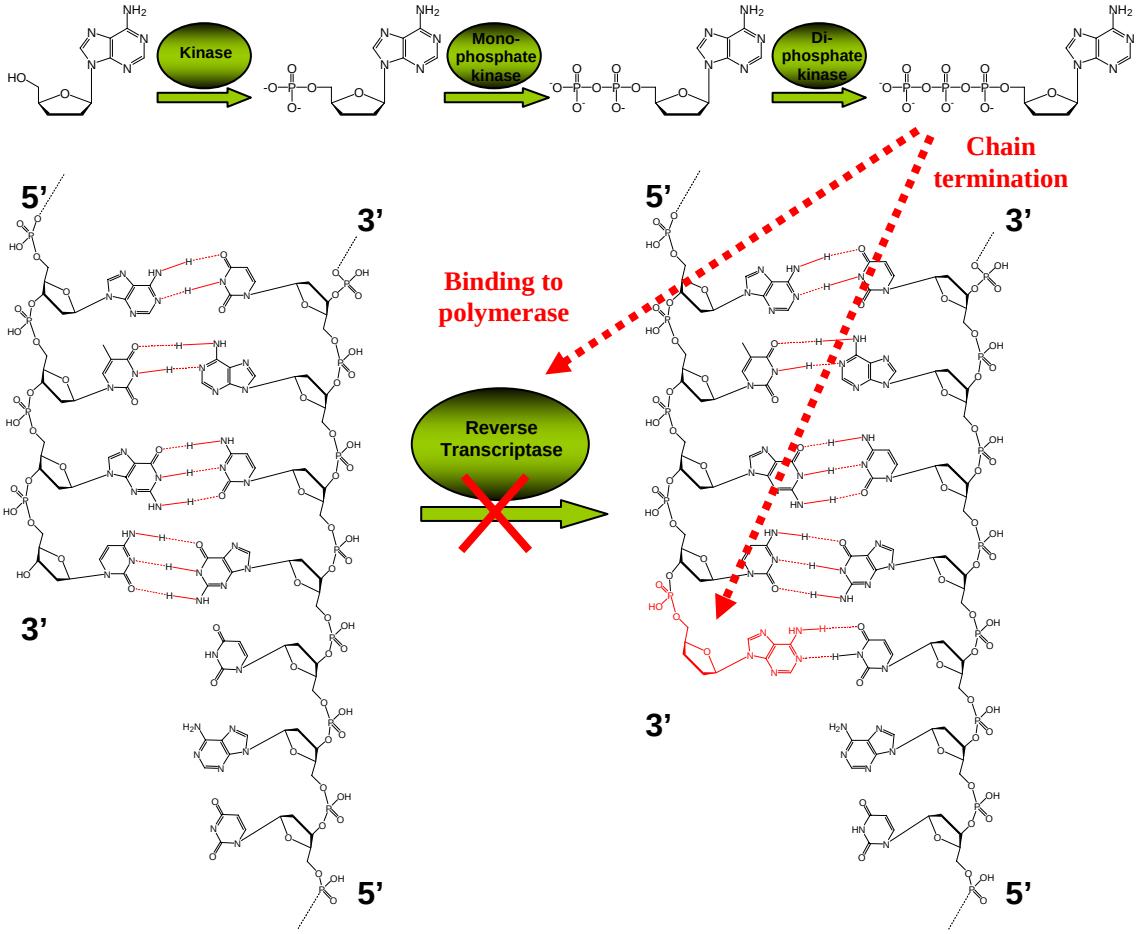


Figure 3. Mechanism of inhibition of the viral replication by 2',3'-dideoxynucleosides.

In the search for new active nucleoside analogues, efforts have been primarily focused on modification of the carbohydrate portion of these molecules, since the cellular kinases are more tolerant of these changes than those related with the base moiety.

Fluorine substitution has been extensively investigated in drug research as a means of enhancing both the biological activity and the metabolic stability. Important factors in the substitution of fluorine for hydrogen are the comparable size of the two atoms, the powerful electron-withdrawing properties of fluorine relative to hydrogen, and the increased stability of the carbon-fluoride bond relative to the carbon-hydrogen bond. Furthermore, it is well established that purine 2',3'-dideoxynucleosides are quite unstable in acidic media, resulting in glycosyl bond cleavage, thus limiting their use as bioavailable drugs. Since the introduction of a fluorine atom at the 2'-position in these 2',3'-dideoxynucleosides was found to stabilize the glycosyl bond, different 2'-

fluoronucleoside analogues have been synthesized (Figure 4).[10] These compounds have been shown to exhibit from moderate to potent anti-HIV activity.

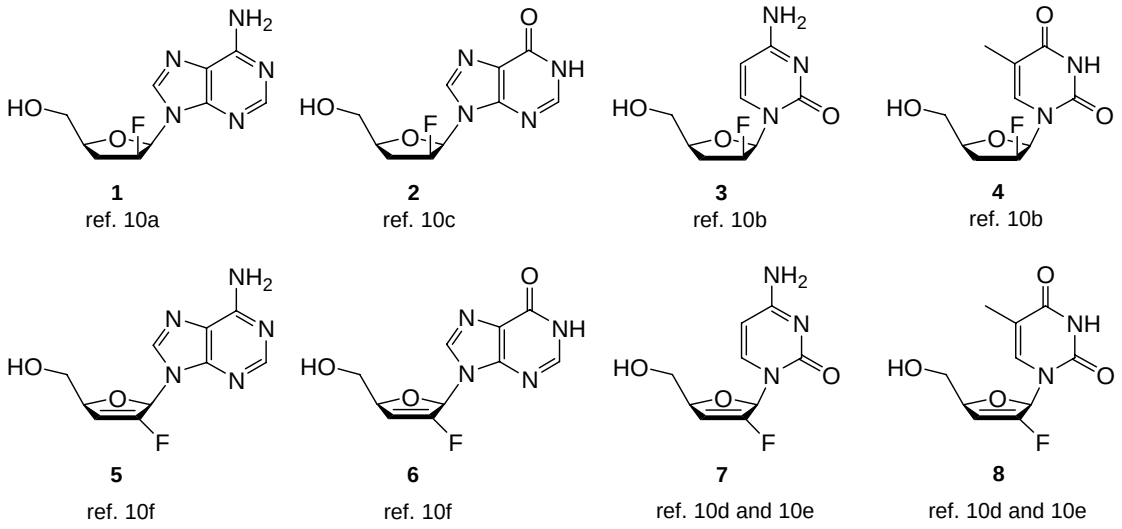


Figure 4. Some examples of anti-HIV active 2'-fluoro-2',3'-dideoxynucleosides.

However, contrary to the large number of publications dealing with fluorinated nucleosides, relatively little efforts have been devoted to the synthesis of their parent chloro-analogues. At present, only few examples of 2'-chloro-2',3'-dideoxynucleosides have been described,[11] without appreciable anti-HIV activity though (Figure 5).

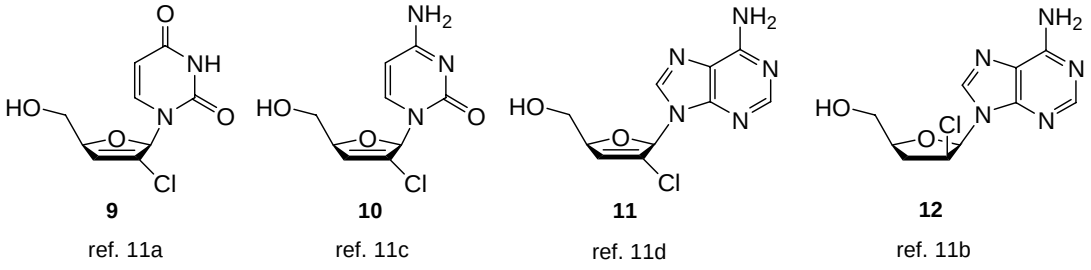
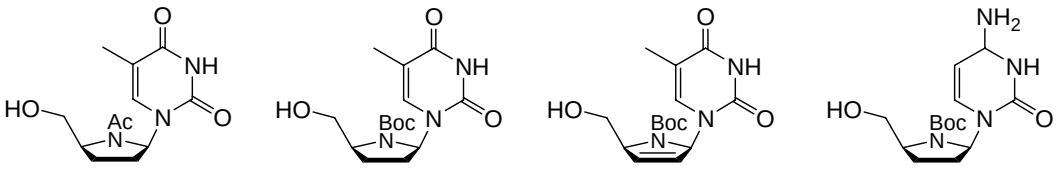


Figure 5. Some examples of 2'-chloro-2',3'-dideoxynucleosides described in the literature.

[10] a) Marquez, V. E.; Tseng, C. K.-H.; Kelly, J. A.; Mitsuya, H.; Broder, S.; Roth, J. S.; Driscoll, J. S. *Biochem. Pharmacol.* **1987**, *36*, 2719-2726. b) Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; de Clercq, E. *J. Med. Chem.* **1989**, *32*, 1743-1749. c) Marquez, V. E.; Tseng, C. K.-H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford Jr., H.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S. *J. Med. Chem.* **1990**, *33*, 978-985. d) Martin, J. A.; Bushell, D. J.; Duncan, I. B.; Dundson, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. *J. Med. Chem.* **1990**, *33*, 2137-2145. e) Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150-2157. f) Lee, K.; Choi, Y.; Gumina, G.; Zhou, W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2002**, *45*, 1313-1320.

[11] a) Pankiewicz, K. W.; Watanabe, K. A. *Chem. & Pharm. Bull.* **1987**, *35*, 4498-4502. b) Herdewijn, P.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; de Clercq, E. *J. Med. Chem.* **1988**, *31*, 2040-2048. c) Van Aerschot, A.; Herdewijn, P. *Bull. Soc. Chim. Belg.* **1989**, *98*, 931-936. d) Mikhailopulo, I. A.; Pricota, T. I.; Sivets, G. G.; Altona, C. *J. Org. Chem.* **2003**, *68*, 5897-5908.

The recent upsurge of interest in novel nucleoside analogues having a modified hetereocyclic sugar unit, has led to the development of novel nucleoside analogues, the azanucleosides, in which the glycone oxygen atom is replaced with a nitrogen atom.[12] The presence of this nitrogen atom represents a structural change which is believed to cause effects of biological significance. However, the first attempts to prepare nucleosides containing a free-pyrrolidine moiety were unsuccessful due to the decomposition of the products, presumably as a consequence of rapid elimination of the heterocyclic base.[13] This is the reason why azanucleosides have been most commonly synthesized with a protected amine function. Thus, several examples of pyrimidine *N*-acyl-2',3'-dideoxyazanucleosides have been reported in the literature (Figure 6).[14]



13 ref. 14a and 14g

14 ref. 14b,14d and 14f

15 ref. 14f

16 ref. 14d

Figure 6. Some examples of pyrimidine 2',3'-dideoxyazanucleosides described in the literature.

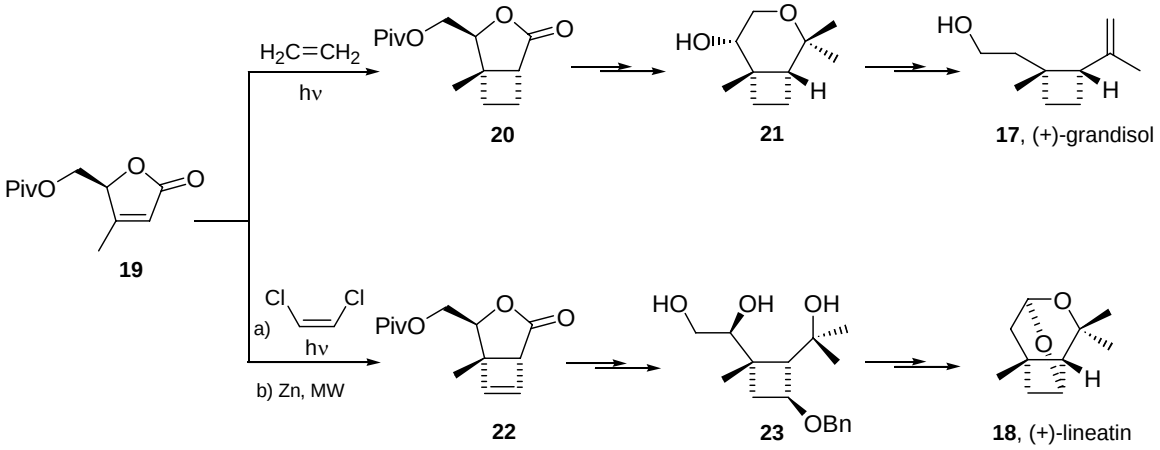
Unfortunately, none these azanucleosides have shown significant antiviral activity. On the other hand, to the best of our knowledge no examples of purine 2',3'-dideoxyazanucleosides have been reported.

Despite the remarkable number of active nucleoside analogues described in the last years, there is still an urgent need for new and potent RT inhibitors, possessing different resistance profiles, to provide a greater choice of drug combinations.[15]

[12] Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541-1554.
[13] Reist, E. J.; Fisher, L. V.; Goodman, L. *J. Org. Chem.* **1967**, *32*, 2541-2545.
[14] a) Altmann, K.-A. *Tetrahedron Lett.* **1993**, *34*, 7721-7724. b) Pickering, L.; Malhi, B. S.; Coe, P. L.; Walker, R. T. *Nucleosides Nucleotides* **1994**, *13*, 1493-1506. c) Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G. *Tetrahedron Lett.* **1994**, *35*, 4019-4022. d) Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168-180. e) Varaprasad, C. V.; Averett, D.; Ramasamy, K. S.; Wu, J. *Tetrahedron* **1999**, *55*, 13345-13368. f) Costenaro, E. R.; Fontoura, L. A. M.; Oliveira, D. F.; Correia, C. R. D. *Tetrahedron Lett.* **2001**, *42*, 1599-1602. g) Varaprasad, C. V. N. S.; Ramasamy, K. S.; Hong, Z. *J. Heterocyclic Chem.* **2006**, *43*, 325-336.
[15] a) Herdewijn, P. *Drug Discov. Today* **1997**, *2*, 235-242. b) Rando, R. F.; Nguyen-Ba, N. *Drug Discov. Today* **2000**, *5*, 465-476.

2. Objectives

In the last decade, our research group has been interested in the synthesis of naturally occurring cyclobutane pheromones, such as (+)-grandisol,[16] **17**, and (+)-lineatin,[17] **18**, using a [2+2] photochemical reaction of chiral 2(5*H*)-furanones with alkenes as a key step (Scheme 1).[18] In the first case, the [2+2] photocycloaddition of 2(5*H*)-furanone **19** to ethylene led mainly to the bicyclic lactone **20** which by subsequent synthetic modifications was converted into the target molecule (+)-**17** in 6 steps and 24% global yield.



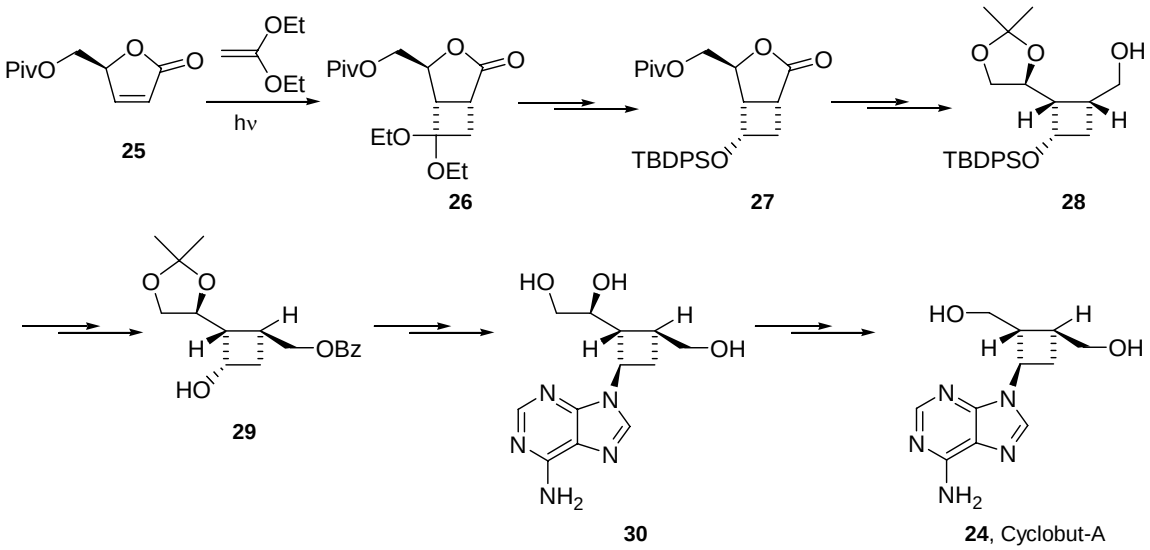
Scheme 1. Synthesis of (+)-grandisol, **17**, and (+)-lineatin, **18**, Font and co-workers.

On the other hand, the synthesis of (+)-lineatin, **18**, started with the [2+2] photocycloaddition of **19** to *cis*-1,2-dichloroethylene followed by Zn promoted didehalogenation to give the cyclobutene derivative **22** which was transformed via the the intermediate triol **23** into the pheromone (+)-**18** in 14 steps and 14% overall yield.

The experience acquired in the preparation of enantiomerically pure cyclobutane and cyclobutene compounds, as well as the biological activity shown by some

[16] Alibés, R.; Bourdelande, J. L.; Font, J.; Parella, T. *Tetrahedron* **1996**, *52*, 1279-1292.
[17] Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Parella, T. *Org. Lett.* **2004**, *6*, 1449-1452.
[18] a) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267-1278. b) Gregori, A.; Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1998**, *39*, 6961-6962. c) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M. *Tetrahedron Lett.* **2001**, *42*, 6695-6697. d) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Fu, X.; Racamonde, M.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 1283-1289.

cyclobutane nucleoside analogues,[19] prompted our group to start a research program focused on this field. As a result, the total synthesis of Cyclobut-A, **24**, a cyclobutane nucleoside analogue of the naturally occurring oxetanocin-A,[20] reported to be active against a broad spectrum of herpes virus and HIV,[21] was accomplished by means of a regio and stereoselective [2+2] photocycloaddition of lactone **25** to ketene diethyl ketal which furnished mainly the bicyclo derivative **26** (Scheme 2). The synthesis of the desired nucleoside was completed in 17 steps and 4% overall yield.[22]



Scheme 2. Synthesis of Cyclobut-A, **24**, Alibés and co-workers (2007).

The preparation of a novel family of cyclobutane- and cyclobutene-fused nucleoside analogues **31** and **32**, designed as conformational mimics of the active 2',3'-didehydro-2',3'-dideoxynucleosides **d4T** and **d4A**, has also been achieved from 2(5*H*)-furanone **33** (Scheme 3).[23]

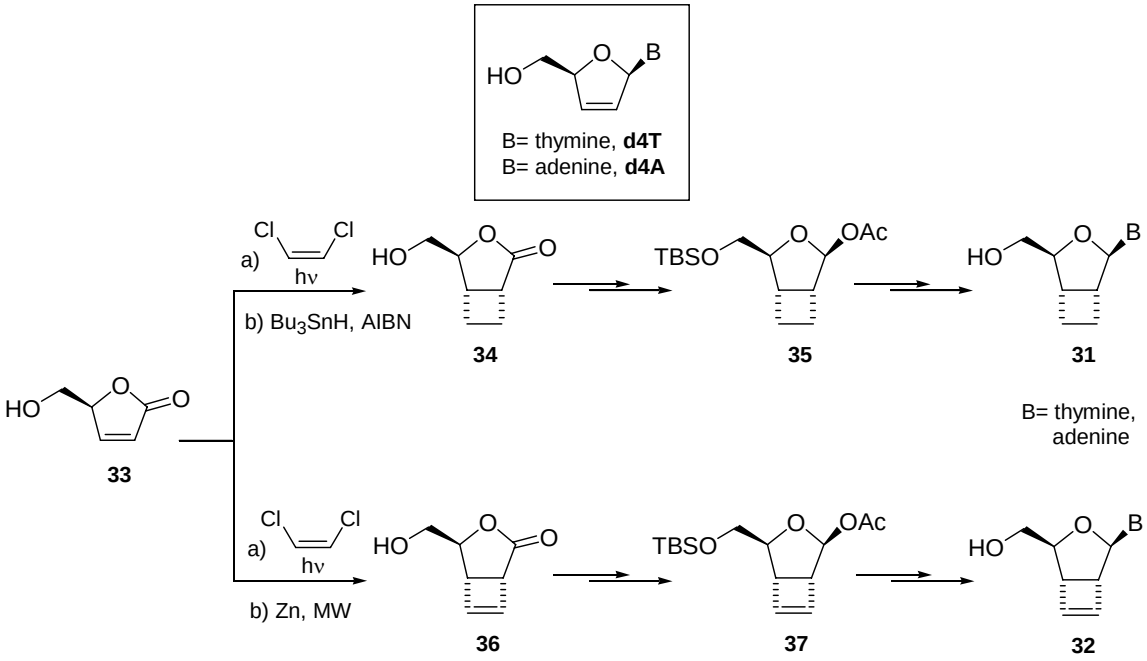
[19] a) Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1-28. b) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y.; *Curr. Org. Chem.* **2005**, *9*, 237-259 and references cited therein.

[20] a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623-1625. b) Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *J. Antibiot.* **1986**, *39*, 1626-1629.

[21] a) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hady, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281-1285. (b) Field, A. K.; Tuomari, A. V.; McGeever-Rubin, B.; Terry, B. J.; Mazina, K. E.; Haffey, M. L.; Hagen, M. E.; Clark, J. M.; Braitman, A.; Slusarchyk, W. A.; Young, M.G.; Zahler, R. *Antiviral Res.* **1990**, *13*, 41-52.

[22] Rustullet, A.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *Org. Lett.* **2007**, *9*, 2827-2830.

[23] a) Alibés, R.; Alvarez-Larena, A.; de March, P.; Figuredo, M.; Font, J.; Parella, T.; Rustullet, A. *Org. Lett.* **2006**, *8*, 491-494. b) Rustullet, A. Doctoral Thesis, UAB, 2006.



Scheme 3. Synthesis of cyclobutane and cyclobutene nucleoside analogues, Alibés and co-workers.

Thus, photochemical reaction of **33** with *cis*-1,2-dichloroethylene followed by a dihydrodehalogenation reaction afforded the cyclobutane lactone **34** which was transformed into the pivotal bicyclic acetate **35**. Condensation of **35** with the corresponding nucleobase yielded the target cyclobutane nucleosides **31**. On the other hand, the cyclobutene lactone **36** was prepared by the [2+2] photocycloaddition of **33** to *cis*-1,2-dichloroethylene and subsequent Zn-promoted didehalogenation reaction. The intermediate **37** was then converted into the desired cyclobutene nucleosides **32**.

In this context, the present work pursues the preparation of a family of highly substituted cyclobutene derivatives, as well as the synthesis of novel enantiomerically pure cyclobutane nucleoside analogues, with the aim of evaluating their antiviral activity. Therefore, at the outset of our work three main objectives were targeted, all of them involving a photochemical reactivity study.

The *anti*/*syn* nomenclature that has been used in the present work describes the cycloadducts derived from the two different approaches of the unsaturated substrates to the diastereotopic faces of the 5-substituted 2(5*H*)-furanones (Figure 7). Thus, an *anti* attack takes place when the unsaturated substrate approaches the furanone through its less hindered β face whereas a *syn* attack is produced when approaches the contrary face (α face).

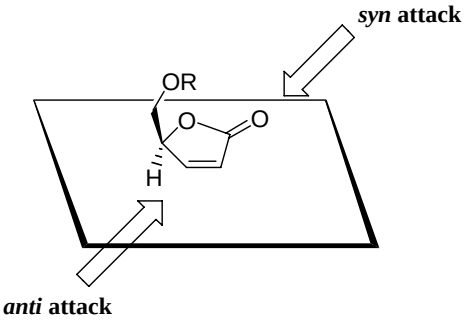
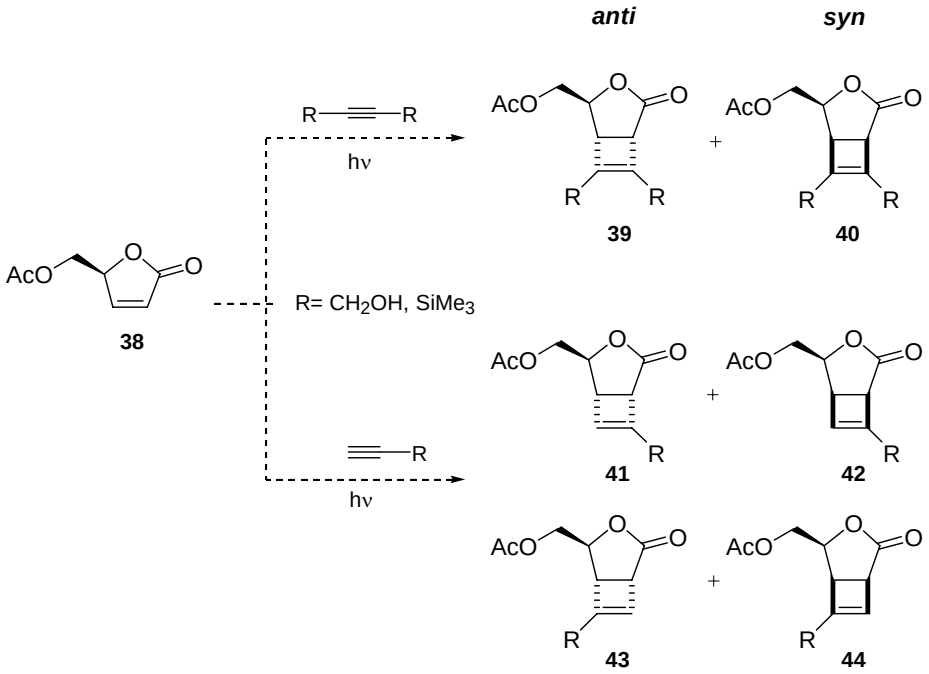


Figure 7. *Anti/syn* approaches of an unsaturated substrate to homochiral 2(5*H*)-furanones.

Objective 1: Study of the [2+2] photocycloaddition of 2(5*H*)-furanones to symmetric and asymmetric alkynes. Development of a new synthetic strategy to substituted cyclobutene derivatives.

Initially, we plan to develop a new synthetic methodology to prepare substituted cyclobutene derivatives, which are useful intermediates in organic chemistry.[24] The scope of the photochemical reaction of the chiral lactone **38** with symmetric and asymmetric hydroxymethyl- and trimethylsilyl-substituted alkynes as a practical synthetic strategy will be investigated (Scheme 4).



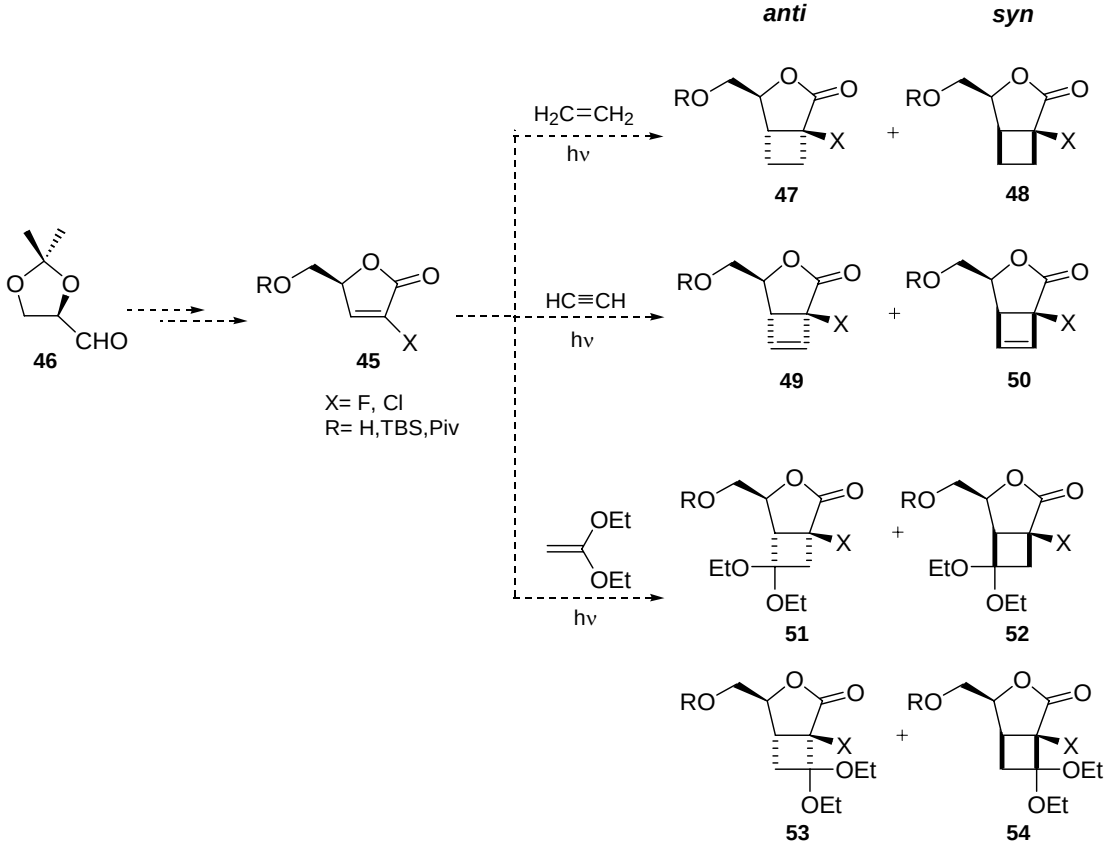
Scheme 4. Photochemical reactivity of 2(5*H*)-furanone **38** to symmetric and asymmetric alkynes.

[24] Gauvry, N.; Lescop, C.; Huet, F. *Eur. J. Org. Chem.* **2007**, 5207-5218.

The symmetric alkynes can give rise to a polyvalent family of diastereomeric tetrasubstituted cyclobutene derivatives **39** and **40**, whereas the monosubstituted alkynes can afford up to four isomeric cyclobutene compounds **41-44**. The diastereo- and regioselectivity of these reactions will be evaluated.

Objective 2: Study of the [2+2] photocycloaddition of homochiral 3-fluoro- and 3-chloro-2(5*H*)-furanones to ethylene, acetylene and ketene diethyl ketal. Synthesis of 2'-chloro and 2'-fluoronucleosides conformationally restricted by a cyclobutane ring.

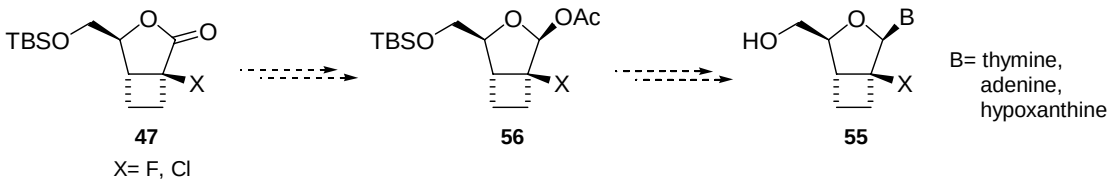
Up to date, few efforts have been devoted to study the photochemical behaviour of 3-halolactones. Herein, the preparation of homochiral 3-fluoro and 3-chloro-2(5*H*)-furanones **45** and their [2+2] photocycloaddition to ethylene, acetylene and ketene diethyl ketal will be investigated (Scheme 5).



Scheme 5. Photochemical reactivity of 3-halo-2(5*H*)-furanones **45** with ethylene, acetylene and ketene diethyl ketal.

Whereas the preparation of some of the required 3-fluoro-2(5*H*)-furanones **45** has already been described, their chloro-analogues will be synthesized for the first time. In both cases the starting material will be the D-glyceraldeyde derivative **46**.

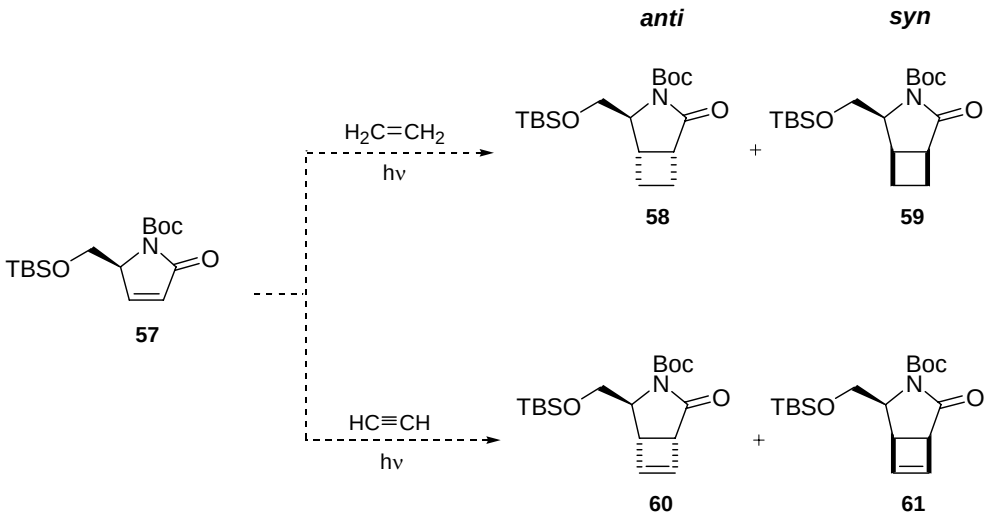
The photochemical reactions of these lactones with the unsaturated substrates shown in Scheme 5 will be investigated to obtain preferentially the *anti* cycloadducts **47**, **49**, **51** and **53** which are potential precursors for the synthesis of new halonucleoside analogues. Thus, the methodology used in our laboratories for the preparation of conformationally restricted analogues of the active **d4T** and **d4A**, will be applied to the synthesis of cyclobutane-fused analogues of 2'-chloro and 2'-fluoronucleosides, **55** (Scheme 6). The cycloadducts **47** will be converted into the bicyclic acetates **56** which by condensation with the corresponding nucleobase will lead to the target nucleoside analogues **55**.



Scheme 6. Synthetic pathway foreseen for the preparation of enantiomerically pure cyclobutane-fused 2'-chloro and 2'-fluoronucleoside analogues **55**.

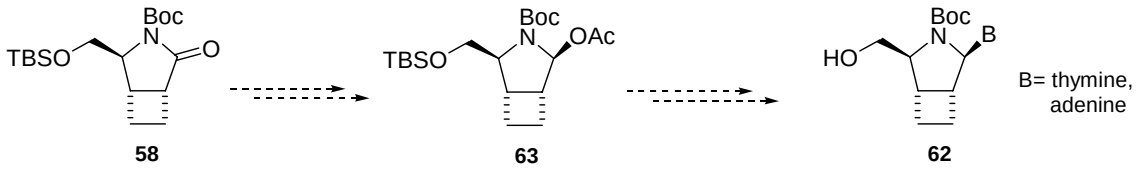
Objective 3: Study of the [2+2] photocycloaddition of the homochiral γ-lactam 57 **to ethylene and acetylene. Synthesis of azanucleoside analogues conformationally restricted by a cyclobutane ring.**

Finally, the [2+2] photocycloaddition of the α,β-unsaturated homochiral γ-lactam **57** to ethylene and acetylene will be evaluated (Scheme 7).



Scheme 7. Photochemical reactivity of γ-lactam **57** with ethylene and acetylene.

The *anti* bicyclic lactam **58** is foreseen as the starting building block for the preparation of cyclobutane azanucleoside analogues **62** (Scheme 8). Following a strategy similar to that showed above, the cycloadduct **58** will be transformed into the key intermediate **63** which after condensation with different nucleobases will furnish the expected azanucleosides **62**.



Scheme 8. Synthetic pathway designed for the preparation of enantiomerically pure cyclobutane azanucleoside analogues **62**.

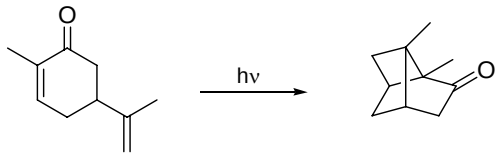
II. [2+2] Photocycloaddition of cyclic enones to unsaturated substrates: Precedents

1. Introduction

As it has been previously mentioned, the key step in our synthetic pathways towards the preparation of enantiomerically pure cyclobutane and cyclobutene derivatives is the [2+2] photocycloaddition of chiral α,β-unsaturated lactones and lactams to alkenes and alkynes. Photochemical reactions of cyclic enones with olefins have been successfully used in the preparation of versatile cyclobutane building blocks which have allowed to synthesize natural products and compounds with quite unusual structures.[25]

The first [2+2] photochemical reaction was reported one hundred years ago in a classical work by Ciamician and Silber[26] which, using the sun as energy source, induced the transformation of several organic compounds, carvone among them, although at that time the structure of the photoproducts could not be univequivocally established.

About fifty years later, Büchi and co-workers exposed carvone to California's sunlight and described the formation and characterization of a [2+2] cycloadduct, which was called photocarvone (Scheme 9).[27]



Scheme 9. Intramolecular [2+2] photocycloaddition of carvone.

The latter publication brought the photochemical reactions to the spotlight and its synthetic potential was suggested in successive studies published by Corey,[28] Eaton[29] and de Mayo.[30] Ever since, the interest for this reaction emerged from a mechanistic, theoretic and synthetic application points of view.

[25] a) Baldwin, S. W. *Organic Photochemistry*; Padwa, A. Ed.; Marcel Dekker: New York, **1981**; chapter 2, p 123. b) Coyle, J. D. *Photochemistry in Organic Synthesis*; The Royal Society of Chemistry; London; **1986**, chapter 9, p 163. c) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145-162. d) Crimmins, M. T. *Comprehensive Organic Synthesis* **1991**, *5*, 123-150. e) Bach, T. *Synthesis* **1998**, 683-703. f) Lee-Ruff, E.; Madenova, G. *Chem. Rev.* **2003**, *103*, 1449-1484. g) Namyslo, J. C.; Kaufmann, D. *Chem. Rev.* **2003**, *103*, 1485-1537. h) Iriondo-Alberdi, J.; Greaney, M. F. *Eur. J. Org. Chem.* **2007**, 4801-4815. i) Hoffmann, N.; *Chem. Rev.* **2008**, *108*, 1052-1103.

[26] Ciamician, G.; Silber, P. *Ber.Dtsch. Chem. Ges.* **1908**, *41*, 1928-1935.

[27] Büchi, G.; Goldman, I. M. *J. Am. Chem. Soc.* **1957**, *79*, 4741-4748.

[28] Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570-5583.

[29] Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50-57.

[30] a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41-47. b) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559-3565.

For more than forty years, the [2+2] photocycloaddition of cyclic enones to unsaturated substrates has been widely used in the total synthesis of natural products such as annotinine, **64**,[31] caryophyllene, **65**,[32] (+)-fomannosin, **66**,[33] (-)-italicene, **67**,[34] (-)-sulcatine G, **68**,[35] and (+)-pentacycloanammoxic acid, **69**[36] (Figure 8).

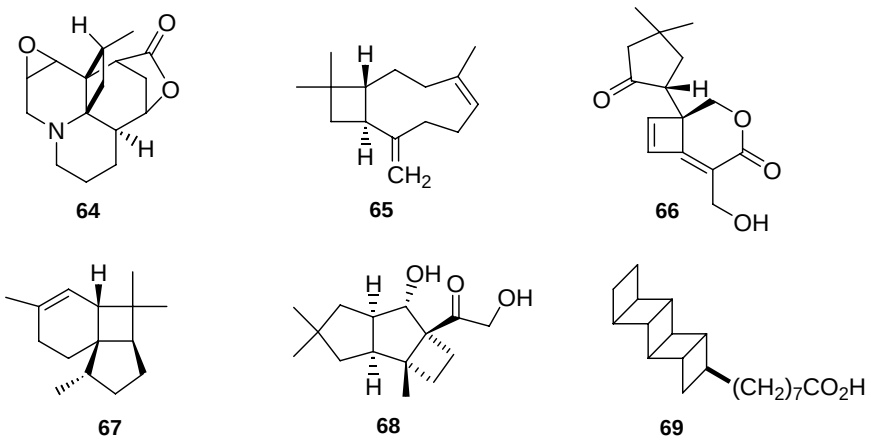
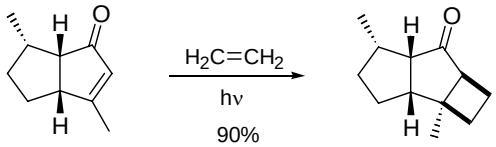


Figure 8. Natural products prepared by means of [2+2] photocycloaddition of enones to unsaturated substrates.

Furthermore, many studies about induction of stereoselectivity in this photochemical reaction have been performed and applied to stereoselective synthesis.[37] A stereogenic center within the cyclic enone has been described to act as an effective control device giving good facial diastereoselectivities in many cases.

As an example, Piers and Orellana described the preparation of the tricyclic ketone **71** with a total stereoselectivity resulting from an exclusive approach of the ethylene from the less sterically hindered face of the enone **70** (Scheme 10).[38]

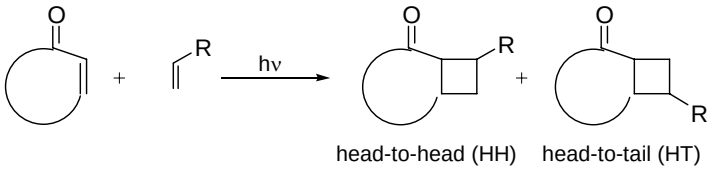
[31] Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433-444.
[32] Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485-492.
[33] Matsumoto, T.; Miyano, K.; Ohfune, Y.; Azuma, S. *Tetrahedron Lett.* **1974**, 1545-1549.
[34] Faure, S.; Piva, O. *Tetrahedron Lett.* **2001**, *42*, 255-259.
[35] Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2002**, *43*, 3319-3321.
[36] Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118-3119.
[37] a) Ogino, T.; Yamada, K.; Isogai, K. *Tetrahedron Lett.* **1977**, 2445-2448. b) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1982**, *104*, 1742-1744. c) Lange, G. L.; Decicco, C.; Tan, S. L.; Chamberlain, G. *Tetrahedron Lett.* **1985**, *26*, 4707-4710. d) Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A. K.; Kruger, C.; Tsay, Y.-H. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1117-1119. e) Lange, G. L.; Decicco, C.; Lee, M. *Tetrahedron Lett.* **1987**, *28*, 2833-2836. f) Lange, G. L.; Organ, M. G. *Tetrahedron Lett.* **1993**, *34*, 1425-1428. g) García-Expóxito, E.; Álvarez-Larena, A.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 1120-1125.
[38] Piers, E.; Orellana, A. *Synthesis* **2001**, 2138-2142.



70 **71**

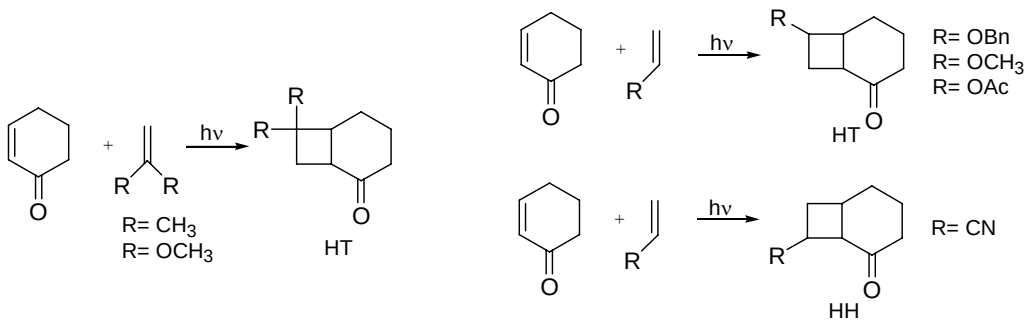
Scheme 10. [2+2] Photocycloaddition of the enone **70** to ethylene, Piers and Orellana (2001).

When working with asymmetric alkenes, the regioselectivity of the [2+2] photocycloaddition may be a drawback which limits the synthetic utility of the reaction since mixtures of head-to-head (HH) and head-to-tail (HT) compounds may be obtained (Scheme 11). This nomenclature takes the carbonyl group of the enone (head) as a reference; if the substituted end of the cyclobutane lies at the same side than the carbonyl group, the isomer is called head-to-head (HH) whereas if it lies at the opposite side it is called head-to-tail isomer (HT).



Scheme 11. Possible regioisomers obtained in the [2+2] photocycloaddition of cyclic enones to asymmetric alkenes.

The first example of a [2+2] photocycloaddition of a cyclic enone to an asymmetric olefin was published in 1964 by Corey and co-workers wherein the photochemical reaction between 2-cyclohexenone and isobutene was investigated.[32] Moreover, the same group studied extensively the [2+2] photocycloaddition of 2-cyclohexenone to different mono and disubstituted alkenes, establishing the main features of the reaction and also proposing a mechanism.[28] The cycloadducts obtained are shown in Scheme 12.



Scheme 12. [2+2] Photocycloaddition of 2-cyclohexenone to different mono and disubstituted alkenes, Corey and co-workers (1964).

The observation that electronically rich olefins delivered mainly head-to-tail regioisomers while electronically deficient olefins gave preferentially head-to-head regioisomers led Corey to propose a mechanism for the photochemical reaction of enones with asymmetric alkenes. Initially, Corey suggested that the reaction takes place exclusively through the $n\pi^*$ triplet state of the enone. Then, the formation of a π-oriented complex between this excited specie and the ground state olefin, named exciplex, was postulated. According to this mechanism, the exciplex would proceed via a 1,4-biradical intermediate to a cyclobutane adduct possessing the same regiochemistry as the initial exciplex. The formation of the exciplex would be governed by electrostatic attractions between partial charges of the polarized excited enone (with a polarization opposite to that of its ground state) and the alkene in its ground state polarization (Figure 9) thus favouring the formation of some 1,4-biradicals intermediates over others.

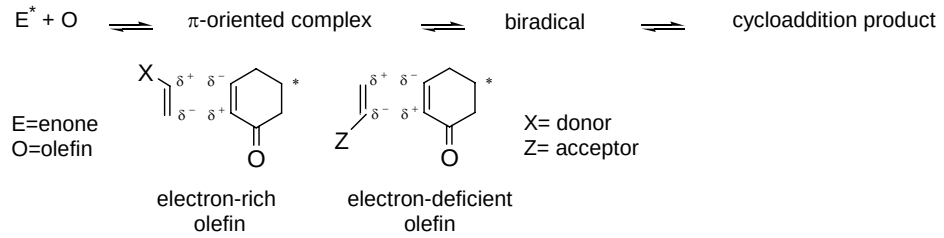


Figure 9. Mechanistic scheme proposed by Corey.

Since the orientation of the exciplex is determined by the polarization of the unsaturated substrate, the so-called Corey's orientation rule, lately widely supported by de Mayo,[30] allows to predict the regioselectivity of the reaction. Although this model nicely rationalizes most of the experimental results, it is not completely concordant with some experimental evidences such as the reaction with olefins bearing an electron-withdrawing group or the [2+2] photocycloaddition of enones to 1-alkynes. Furthermore, no experimental support for the formation of an initial exciplex has been found. Soon, an alternative mechanism was proposed by Bauslaugh[39] which invoked the direct formation of all the possible isomeric 1,4-biradical intermediates without the requirement of an exciplex precursor (Figure 10). Thus, the regioselectivity of the reaction would be governed by the partitioning of biradical intermediates between cyclization to afford the cycloadduct and fragmentation to revert to starting materials.

[39] Bauslaugh, P. G. *Synthesis* **1970**, 287-300.

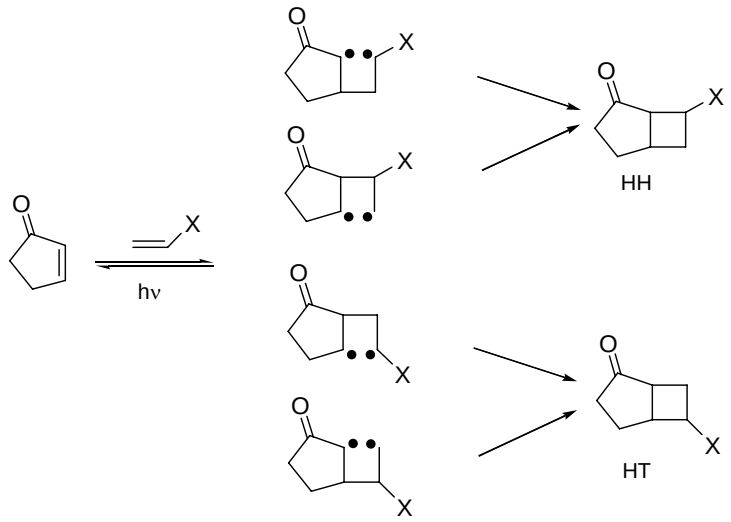


Figure 10. Biradical intermediate species postulated for [2+2] photocycloaddition reactions to asymmetric alkenes.

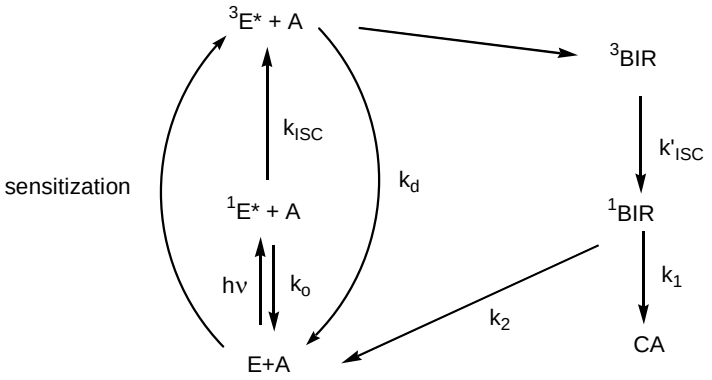
Schuster and co-workers[40] experimentally proved that, in most of the studied examples, the reaction takes place through the $\pi\pi^*$ state of the enone which has a different polarization from that proposed by Corey. Theoretic studies have also located the $\pi\pi^*$ state lower in energy than the $n\pi^*$ state.[41] On the other hand, Weedon and co-workers by radical trapping experiments showed that 1,4-biradical intermediates are formed in similar ratio for both regiochemistries, head-to-head and head-to-tail, demonstrating that Bauslaugh's hypothesis was correct.[42] It was then concluded that the regiochemistry of the photochemical reaction is dominated by the manner in which the biradical intermediates partition between products and ground state precursors and not by the relative rates at which they are formed. Nowadays is widely accepted that there is no exciplex preceding the formation of the 1,4-biradicals. Figure 11 shows the representation of the mechanism known as Bauslaugh-Schuster-Weedon.[43]

[40] a) Schuster, D. I.; Heibel, G. E.; Caldwell, R. A.; Tang, W. *Photochem. Photobiol.* **1990**, *52*, 645-648. b) Schuster, D. I.; Dunn, D. A.; Heibel, G. E.; Brown, P. B.; Rao, J. M.; Woning, J.; Bonneau, R. *J. Am. Chem. Soc.* **1991**, *113*, 6245-6255. c) Kaprinidis, N. A.; Lem, G.; Courtney, S. H.; Schuster, D. I. *J. Am. Chem. Soc.* **1993**, *115*, 3324-3325.

[41] Wilsey, S.; González, L.; Robb, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 5866-5876.

[42] a) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8525-8527. b) Andrew, D.; Hastings, D. J.; Oldroyd, D. L.; Rudolph, A.; Weedon, A. C.; Wong, D. F.; Zhang, B. *Pure & Appl. Chem.* **1992**, *64*, 1327-1334. c) Andrew, D.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117,* 5647-5663.

[43] Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3-22.

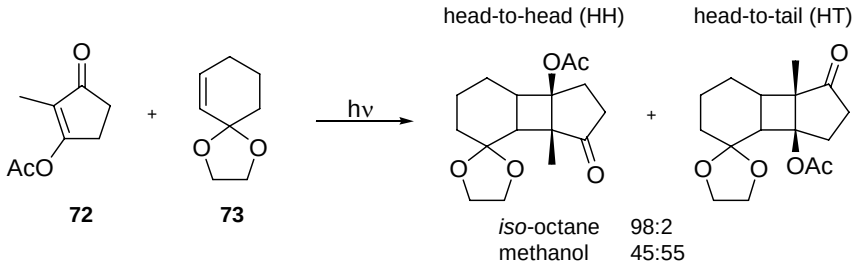


E: enone; A: alkene; BIR: 1,4-biradical; CA: cycloadducts.

Figure 11. The Bauslaugh-Schuster-Weedon biradical mechanism for enone-alkene [2+2] photocycloaddition reactions.

According to this model, excitation of an α,β-unsaturated carbonyl compound leads to the lowest excited singlet state (^{1}E) through an $n\pi^*$ or $\pi\pi^*$ excitation which, by an intersystem crossing process, evolves to the excited triplet state (^{3}E). It is also possible to promote an enone directly to its triplet state by a sensitizing reaction. If its triplet energy is lower than the triplet energy of the sensitizer a rapid energy transfer occurs. Once the triplet 1,4-biradical intermediate (BIR) is formed, spin inversion gives the singlet biradical which can either revert to ground state starting materials or cyclize to afford the cycloadducts (CA).

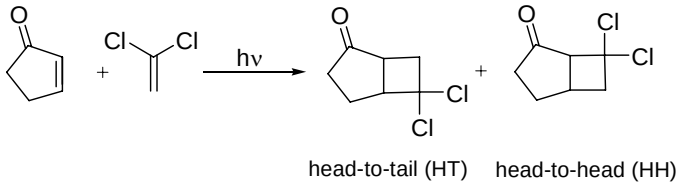
Several examples can be found in the literature showing a significant influence of the solvent polarity on the regioselectivity of the reaction. A study of the [2+2] photocycloaddition of the cyclopentenone **72** to the alkene **73** was published by Challand and de Mayo in 1968 (Scheme 13).[44] A remarkable variation of the regioisomers distribution was observed when the solvent polarity was changed.



Scheme 13. Solvent polarity effect on regioselectivity, Challand and de Mayo (1968).

[44] Challand, B. D.; de Mayo, P. *Chem. Comm.* **1968**, 982-983.

Soon after, Loufty and de Mayo studied the [2+2] photocycloaddition of cyclopentenone to 1,1-dichloroethylene which delivered mainly the expected head-to-tail regioisomers.[45] The regioselectivity of the reaction diminished when the polarity of the solvent was increased (Scheme 14). In this work de Mayo also establishes a parallelism between the photochemical behaviour of 1,1-dichloroethylene and ketene dimethyl ketal, previously used by Corey.[28]

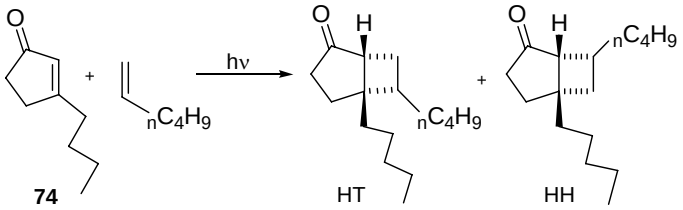


head-to-tail (HT) head-to-head (HH)

solvent	HT:HH (%)
cyclohexane	85:15
diethyl ether	84:16
acetonitrile	71:29

Scheme 14. Solvent polarity effect on the regioselectivity of the [2+2] photocycloaddition of cyclopentenone to 1,1-dichloroethylene, Loufty and de Mayo (1972).

Generally speaking, it has been found that predictions made following Corey's rule are more accurate in apolar solvents than in polar solvents. However, deviations from this rule have been described. For instance, de Mayo and co-workers found that in the photochemical reaction of **74** with 1-hexene, the head-to-head isomer (HH) decreased when the polarity of the solvent was increased, although Corey's rule predicts the contrary effect (Scheme 15).[46]



74 HT HH

solvent	ε[a]	HT:HH (%)
cyclohexane	2.02	53:47
diethyl ether	4.34	57:43
ethyl acetate	6.02	59:41
methanol	32.63	62:38
acetonitrile	37.50	63:37

[a] data taken from the cited article.

Scheme 15. Unusual evolution of the HT:HH ratio with solvent polarity, de Mayo and co-workers (1982).

[45] Loufty, R. O.; de Mayo, P. *Can. J. Chem.* **1972**, *50*, 3465-3471.
[46] Berenjian, N.; de Mayo, P.; Sturgeon, M.-E.; Sydnes, L. K.; Weedon, A. C. *Can. J. Chem.* **1982**, *60*, 425-436.

Unfortunately, the Bauslaugh-Schuster-Weedon mechanism does not allow an intuitive prediction of the effect of the solvent polarity on the regioselectivity. Therefore, in any study of a [2+2] photocycloaddition of a cyclic enone to an asymmetric unsaturated substrate, the influence of solvent polarity on the reaction must be evaluated.

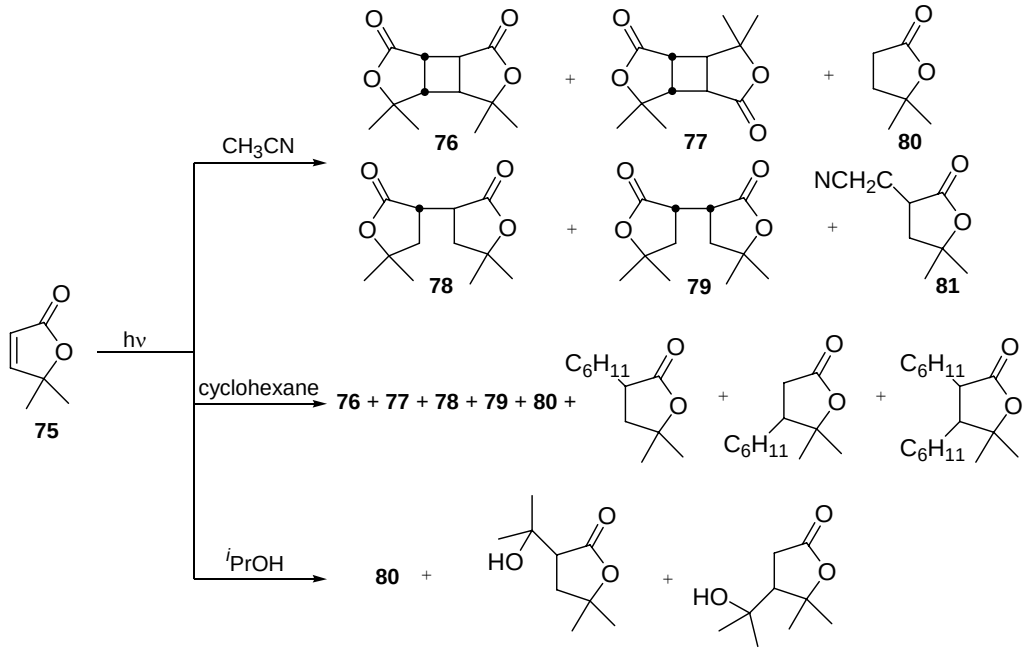
2. [2+2] Photocycloaddition of 2(5*H*)-furanones to alkenes

Although the [2+2] photocycloaddition of cyclic enones to alkenes has been extensively studied, less efforts have been focused on the use of α,β–unsaturated lactones in such reactions.[25e,47] Few studies of the photochemical behaviour, facial diastereoselectivity and induction of stereoselectivity in the [2+2] photocycloaddition of these lactones have been carried out.

Interest for knowing the photochemical reactivity of 2(5*H*)-furanones led different authors to irradiate them in the absence of alkene. These studies have shown their high capability to undergo dimerization and to react with the solvent to give solvent adducts and photoreduction products.

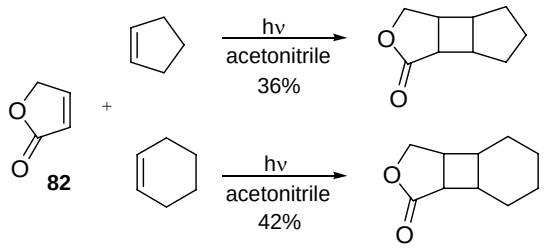
For instance, in 1983 Anklam and Margaretha[48] studied the photochemical behaviour of the 5,5-dimethyl-2(5*H*)-furanone, **75**. Thus, when **75** was irradiated in acetonitrile through a quartz filter, a mixture of six products was obtained: the dimeric compounds **76** and **77**, the diastereomeric hydrodimers **78** and **79**, the saturated lactone **80** and the solvent adduct **81** (Scheme 16). Product distribution was found to be dependent on lactone concentration. When the reaction was performed in cyclohexane and isopropanol, besides some of the previously described products, different isomers coming from the addition of solvent to the furanone **75** were also produced.

[47] Fillol, L.; Miranda, M. A.; Morera, I. M.; Sheikh, H. *Heterocycles*, **1990**, *31*, 751-782.
[48] Anklam, E.; Margaretha, P. *Helv. Chim. Acta* **1983**, *66*, 1466-1474.



Scheme 16. Irradiation of lactone **75** in different solvents, Anklam and Margaretha (1983).

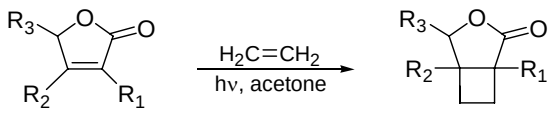
The first work reporting a photochemical reaction of 2(5*H*)-furanones with alkenes was published by Tada and co-workers in 1972,[49] wherein the [2+2] photocycloaddition of crotonolactone, **82**, to cyclopentene and cyclohexene proceeded in 36% and 42% yield, respectively (Scheme17). It was also suggested that the reaction takes place through the excited triplet state of the lactone.



Scheme 17. [2+2] Photocycloaddition of **82** to cyclopentene and cyclohexene, Tada and co-workers (1972).

Kosugi *et al.*[50] published in 1976 an article that has become a point of reference in the study of the photochemical reactions of 2(5*H*)-furanones with unsaturated substrates. The reaction conditions and substituent effects on the [2+2] photocycloaddition of crotonolactone, **82**, and its derivatives **83-86**, to ethylene were extensively studied and it was found that acetone, which plays a sensitizer role, was the best solvent (Scheme 18).

[49] Tada, M.; Kokubo, T.; Sato, T. *Tetrahedron* **1972**, *28*, 2121-2125.
[50] Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520-528.



87

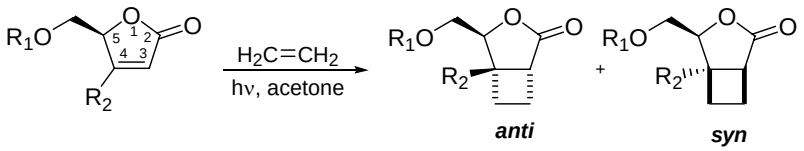
82	R_1=R_2=R_3=H	70%
83	R_1=R_3=H, R_2=Me	44%
84	R_1=R_3=H, R_2=Ph	49%
85	R_1=Ph, R_2=R_3=H	52%
86	R_1=R_2=H, R_3=Me	35%

Scheme 18. [2+2] Photocycloaddition of 2(*5H*)-furanones to ethylene, Kosugi *et al*. (1976).

The photoreactions afforded the expected cycloadducts **87** albeit in moderate yields. The cycloadducts derived from the 5-methyl-2(5*H*)-furanone (β-angelica lactone) **86** were obtained as a 60:40 *anti*:*syn* diastereomeric mixture.

A work published in 1991[51] was the first of a number of studies performed in our research group in the field of the [2+2] photocycloaddition reactions of chiral 2(5*H*)-furanones to ethylene.[18a,52] The main aim of these studies was to get a deeper insight into the factors controlling the facial diastereoselectivity of these reactions. Thus, variables such as the 2(5*H*)-furanone substitution, the temperature, the solvent and the filter were evaluated.

The most representative results achieved in the photochemical reaction of different 2(5*H*)-furanones with ethylene are shown in Scheme 19.



R_1	R_2	yield (%)	*anti:syn* (%)
Ac	H	82	74:26
Piv	H	59	78:22
Ac	CH_3	65	54:46
Piv	CH_3	70	62:38

Scheme 19. [2+2] Photocycloaddition of homochiral 2(*5H*)-furanones to ethylene, Font and co-workers.

The best yields were achieved by irradiation trough a pyrex filter in acetone although in most cases yields were only moderate. Diastereofacial differentiation is

[51] Alibés, R; Bourdelande, J. L.; Font, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1391-1402.

[52] a) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1993**, *34*, 7455-7458. b) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1994**, *35*, 2587-2588. c) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A. *J. Braz. Chem. Soc.* **1995**, *6*, 119-121.

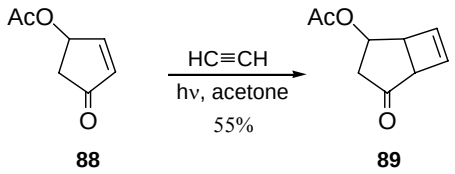
consistent with the alkene approaching to the less hindered face of the lactone affording mainly the *anti* adducts. The highest facial diastereoselectivity was achieved when the hydroxyl was protected as a pivalate (R_1=Piv). Moreover, facial diastereoselectivity was decreased by the presence of a methyl group at C-4 (R_2=CH_3). It was also found that the cycloadducts ratio was not influenced by temperature, although yields were increased when the reaction was performed at low temperatures.

3. [2+2] Photocycloaddition of cyclic enones to alkynes

Despite the fact that alkynes have an electronic structure very similar to that of alkenes, when irradiated they tend to produce polymeric material limiting the synthetic applicability of their photoreactions and making the mechanistic studies even more complicated.[53] For this reason the use of [2+2] photocycloaddition of cyclic enones to alkynes in natural products synthesis has been very limited.

In general, these reactions take place with a variable efficiency since the strained cyclobutene derivatives formed can also be excited to undergo many competitive reactions such as photoreductions or further cycloadditions.[54] Nevertheless, several examples of irradiation of cyclic enones with alkynes have been reported in the literature and will be discussed.

For instance, Murata and co-workers reported in 1977 the [2+2] photocycloaddition of 4-acetoxy-2-cyclopentenone, **88**, to acetylene which gave the cyclobutene derivative **89** in 55% yield (Scheme 20).[55]



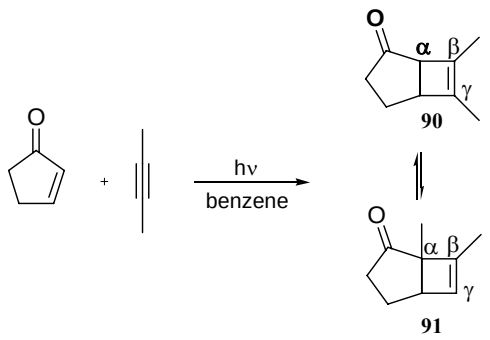
88 **89**

Scheme 20. [2+2] Photocycloaddition of 4-acetoxy-2-cyclopentenone, **88**, to acetylene, Murata and co-workers (1977).

One of the first photochemical reactions involving a substituted alkyne was published in 1964.[56] Eaton studied the reaction of 2-cyclopentenone with 2-butyne which

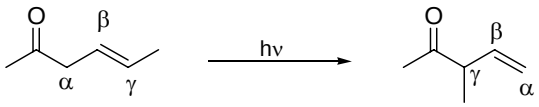
[53] Coyle, J. D. *Introduction to Organic Photochemistry*, John Wiley & Sons, **1989**, p. 72.
[54] a) Houk, K. N. *Chem. Rev.* **1976**, *76*, 1-74. b) Ninomiya, I.; Naito, T. *Photochemical Synthesis;* Academic Press; London; **1989**, chapter 6, p.79.
[55] Sugihara, Y.; Morokoshi, N.; Murata, I. *Tetrahedron Lett.* **1977**, *18*, 3887-3888.
[56] Eaton, P. E. *Tetrahedron Lett.* **1964**, 3695-3698.

afforded the expected primary cycloadduct **90** and the rearranged derivative **91** (Scheme 21). Eaton also described that a photostationary state was reached when these products were irradiated separately leading always to a 60:40 mixture of **90** and **91**.



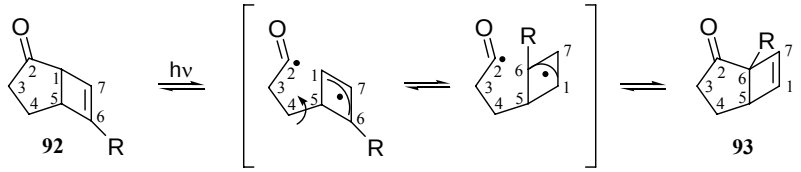
Scheme 21. [2+2] Photochemical reaction of 2-cyclopentenone with 2-butyne, Eaton (1964).

This work is the first example of a 1,3-acyl shift rearrangement of β,γ-unsaturated ketones as active chromophore which is one of the competitive reactions that has been more often reported for the cyclobutene derivatives (Scheme 22).



Scheme 22. 1,3-Acyl shift rearrangement of β,γ-unsaturated ketones.

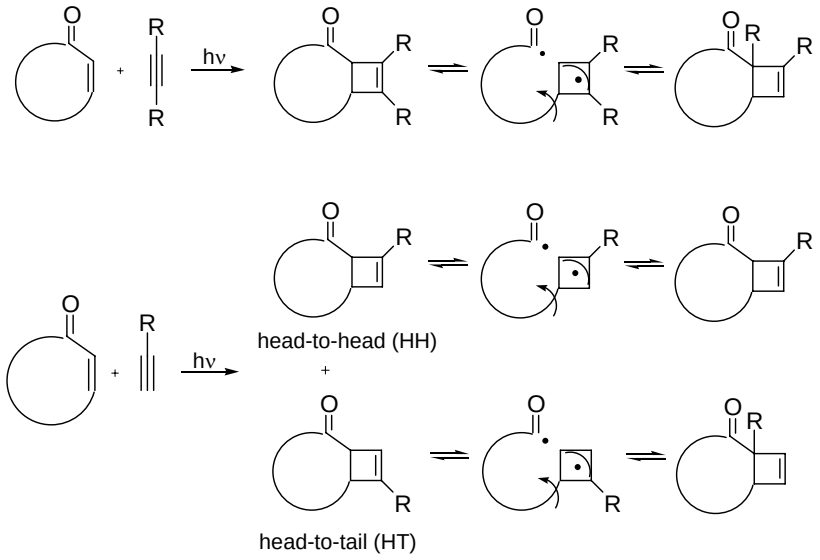
The accepted mechanism for the rearrangement undergone by a β,γ-unsaturated enone like **92** starts with a Norrish I type cleavage which leads to an acyl-allyl biradical intermediate (Scheme 23). Rotation around the C_4-C_5 bond allows the biradical to collapse through the C_2-C_6 positions affording the new product **93** which in turn is able to revert to the starting material.



Scheme 23. Mechanistic proposal for the 1,3-acyl shift rearrangement.

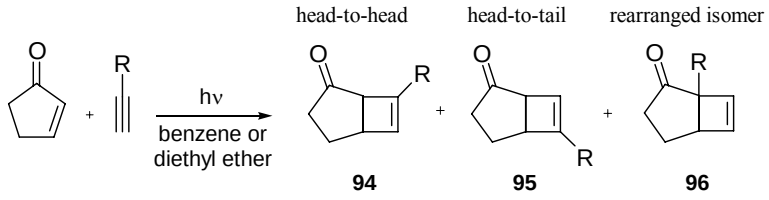
Examples of 1,3-acyl shift have been described in the [2+2] photocycloaddition reactions of enones to both mono- and disubstituted alkynes (Scheme 24). In reactions

carried out with 1-alkynes it should be noted that the 1,3-acyl shift can only be observed in the head-to-tail (HT) regioisomers.[57] For the head-to-head (HH) cycloadducts, as well as for acetylene adducts (R=H), the rearrangement is undetectable.



Scheme 24. Photochemical addition of enones to symmetric and asymmetric alkynes and 1,3-acyl shift rearrangement.

In the late 1970's, Serebryakov and co-workers studied extensively the [2+2] photocycloaddition of 2-cyclopentenone to different monosubstituted alkynes (Table 2).[58]



entry	R	time (h)	yield (%)	94:95:96
1	*n*-C_4H_9	70	35	69:19:12
2	*t*-C_4H_9	40	25	87:13:-
3	CH_2Cl	42	28	72:19:9
4	CH_2OH	48	8	69:20:11
5	CO_2Me	52	7	49:48.5:2.5

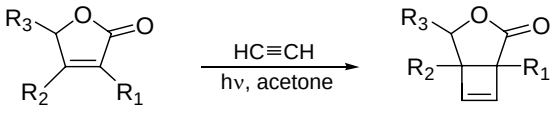
Table 2. Reactivity of 2-cyclopentenone with asymmetric alkynes, Serebryakov and co-workers (1979).

[57] Ninomiya, I.; Naito, T. *Photochemical Synthesis;* Academic Press; London; **1989**, chapter 6, p.79.
[58] a) Serebryakov, P.; Burstein, K. Ya. *Tetrahedron,* **1978**, *34*, 3233-3238. b) Serebryakov, E. P.; Kulomzina-Pletneva, S. D.; Margaryan, A. Kh. *Tetrahedron* **1979**, *35*, 77-86.

As a general trend the photochemical reactions proceeded in very low yields and required long reaction times. In most of the cases the head-to-head isomers **94** were preferentially formed (entries 1-4) albeit when the alkyne bears an electron withdrawing group (entry 5) the reaction took place without any regioselectivity. Moreover, with the exception of the *tert*-butyl substitution, the 1,3-rearranged cyclobutene derivatives **96** were also produced.

4. [2+2] Photocycloaddition of 2(5*H*)-furanones to alkynes

Even less efforts have been focused on the photochemical reaction of α,β-unsaturated lactones with alkynes. The first published work, previously discussed, appeared in 1976 by Kosugi *et al.* which studied the [2+2] photocycloaddition of several 2(*5H*)-furanones **82-86** to acetylene (Scheme 25).[50]



97

82	R_1=R_2=R_3=H	54%
83	R_1=R_3=H, R_2=Me	29%
84	R_1=R_3=H, R_2=Ph	8%
85	R_1=Ph, R_2=R_3=H	23%
86	R_1=R_2=H, R_3=Me	14%

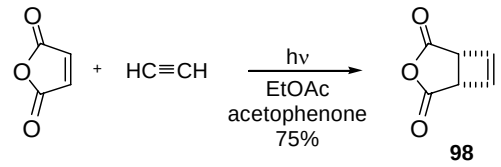
Scheme 25. [2+2] Photocycloaddition of 2(*5H*)-furanones to acetylene, Kosugi *et al*. (1976).

The photoreactions afforded the expected cycloadducts **97** although in moderate to poor yields. The most significant features of the reactions were the slower reaction rates and yields compared to the reactions with ethylene and the formation of a large amount of by-products at the end of the reaction periods. Consequently, the progress of the reaction needed to be carefully monitored and stopped at appropriate reaction times. The cycloadducts derived from β-angelica lactone **86** were obtained as a 54:46 *anti*:*syn* diastereomeric mixture, slightly lower than that reported for ethylene (60:40).

The same year, Bloomfield and Owsley[59] described the [2+2] photocycloaddition of maleic anhydride to acetylene in ethyl acetate and acetophenone as sensitizer to furnish the bicyclic anhydride **98** in 75% yield (Scheme 26) which has been used as a precursor for the

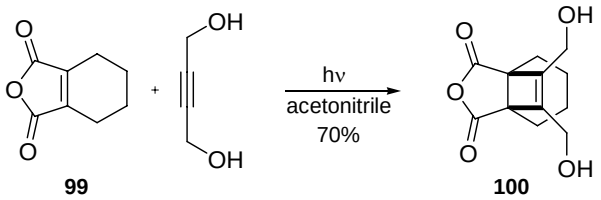
[59] Bloomfield, J. J.; Owsley, D. C. *Org. Photochem. Synth*. **1976**, *2,* 32-35.

preparation of several products such as conjugated dienes via electrocyclic ring opening,[60] and carbocyclic nucleoside analogues.[61]



Scheme 26. [2+2] Photocycloaddition of maleic anhydride to acetylene, Bloomfield and Owsley (1976).

One of the few described examples of reactions involving a disubstituted alkyne was published in 1999, wherein the [2+2] photocycloaddition of the unsaturated bicyclic anhydride **99** to 2-butyne-1,4-diol was performed in acetonitrile affording the expected cyclobutene derivative **100** in 70% yield (Scheme 27).[62]



Scheme 27. [2+2] Photocycloaddition of **99** to 2-butyne-1,4-diol, Booker-Milburn and co-workers (1999).

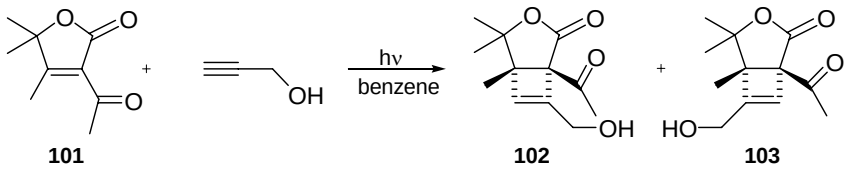
A work describing the photochemical reactivity of 2(*5H*)-furanones and 1-alkynes was published in 1989 by Avetisyan and co-workers.[63] Therein the [2+2] photocycloaddition of the 3,4,5,5-tetrasubstituted 2(5*H*)-furanone **101** to propargyl alcohol gave rise to a 55:45 mixture of the cycloadducts HH **102** and HT **103** in 40% yield (Scheme 28).

[60] Binns, F.; Hayes, R.; Ingham, S.; Saengchantara, S.; Turner, R.W.; Wallace T. *Tetrahedron* **1992**, *48*, 515-530.

[61] a) Jung, M. E.; Sledeski, A. W. *J. Chem. Soc., Chem. Commun.* **1993**, 589-594. b) Gourdel-Martin, M. E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166-2172. c) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem*. **2000**, *65*, 7139-7144.

[62] Booker-Milburn, K. I.; Cowell, J. K.; Jiménez, D.; Sharpe, A.; White, A. J. *Tetrahedron* **1999**, *55*, 5875-5888.

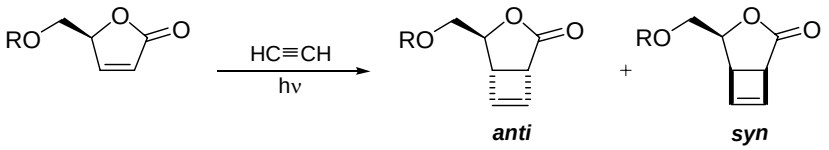
[63] Avetisyan, A. A.; Margaryan, A. Kh.; Nalbandyan, G. K.; Avetisyan, T. V. *Zhum. Org. Khim.* **1989**, *25*, 530-536.



101 **102** **103**

Scheme 28. [2+2] Photocycloaddition of furanone **101** to propargyl alcohol, Avetisyan and co-workers (1989).

Our research group reported in 2001 the first example of [2+2] photocycloaddition of chiral 2(5*H*)-furanones to acetylene.[18c,d] The effect of the furanone substitution (R), the solvent and the reaction conditions on the facial diastereoselectivity of the reaction were studied (Scheme 29).



anti ***syn***

R_1	solvent	filter	yield	*anti*:*syn* ratio
Piv	acetonitrile	quartz	74	66:34
Piv	acetone	pyrex	53	70:30
CO_2Mnt	acetonitrile	quartz	57	59:41
CO_2Mnt	acetone	pyrex	51	66:34
Bz	acetonitrile	quartz	25	66:34
Bz	acetone	pyrex	26	68:32

Scheme 29. [2+2] Photocycloaddition of chiral 2(*5H*)-furanones to acetylene, Font and co-workers (2003).

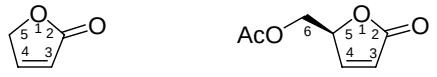
Data collected in Scheme 29 shows that acetylene reacts mainly by the less hindered face of the lactone affording the *anti* isomer as the major product. In general, irradiations performed through a quartz filter in acetonitrile gave better yields albeit with lower selectivity. On the other hand, facial selectivity values, as well as yields, were lower than those obtained in the [2+2] photocycloaddition of 2(5*H*)-furanones to ethylene.[51,52]

To the best of our knowledge, studies of the photochemical reaction of homochiral 2(*5H*)-furanones with substituted alkynes have not been described in the literature.

III. Study of the [2+2] photocycloaddition of 2(5*H*)-furanones to symmetric and asymmetric alkynes.

Development of a new synthetic strategy to substituted cyclobutene derivatives

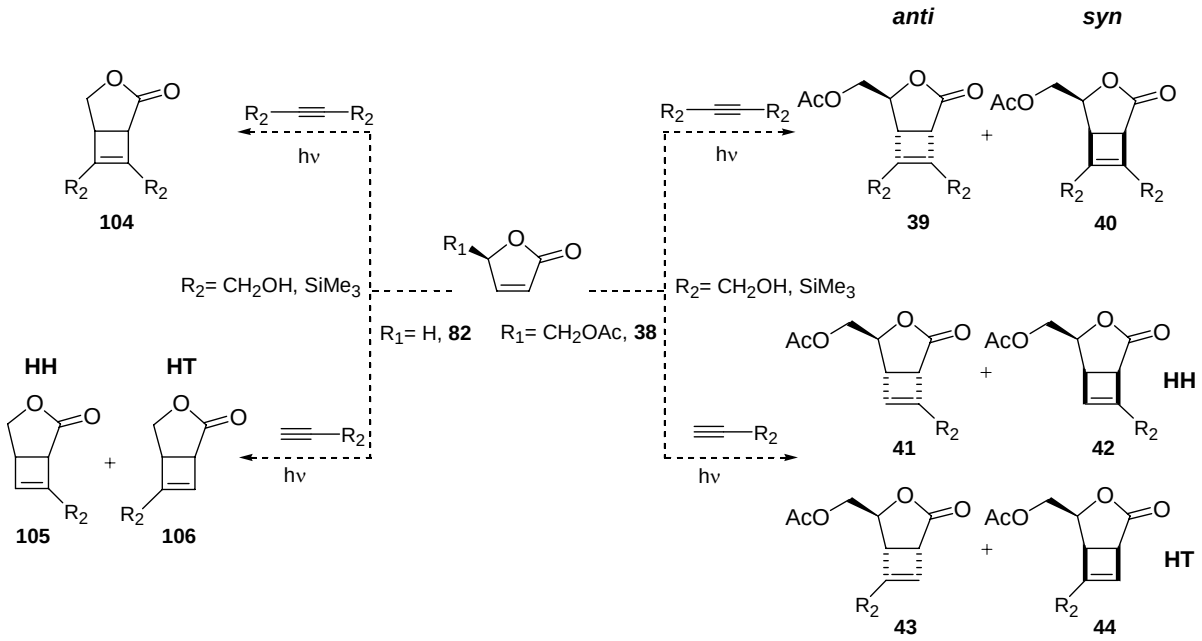
The first task of the present work is to study the photoreactivity of 2(5*H*)-furanones with mono and disubstituted alkynes to develop a synthetic methodology to prepare highly functionalized cyclobutene compounds. In order to carry out this photochemical study, crotonolactone, **82**, which is commercially available, and the homochiral (-)-(*S*)-5-acetyloxymethyl-2(5*H*)-furanone, **38**, have been selected as α,β-unsaturated lactones.



82 **38**

Figure 12. Structures of 2(5*H*)-furanones **82** and **38** selected to study their photochemical reactivity.

All the photochemical reactions with symmetric and asymmetric hydroxymethyl- and trimethylsilyl-substituted alkynes will be investigated first with lactone **82** (Scheme 30). On the other hand, the 2(5*H*)-furanone **38** has been chosen because it would allow to monitor the reactions by gas chromatography (GC) and the acetyl protecting group would not involve a great steric effect on facial diastereoselectivity.[64] The number of expected cycloadducts from lactone **38** is the double to that expected for **82** due to the presence of a stereogenic center at C-5. Furthermore, the effect of the acetyloxymethyl substituent on the regioselectivity of the reaction will also be evaluated.



Scheme 30. Photochemical reactivity of 2(5*H*)-furanones **82** and **38** to symmetric and asymmetric alkynes.

[64] Rustullet, A. *Doctoral thesis*. Universitat Autònoma de Barcelona, **2006**.

All the photochemical reactions reported in this chapter were conducted with a 125 W high pressure mercury lamp (Cathodeon HPK125), cooling externally the reactor to -40 ºC and with a -15 ºC cooled MeOH flow through the reactor refrigeration jacket. Evolution of the reaction was controlled by GC except for reactions carried out with alkynes bearing hydroxymethyl groups which were controlled by TLC. Irradiation was stopped in function of by-products formation. Product characterization was accomplished by NMR techniques. Structural determination of the isolated compounds is discussed at the end of the present chapter.

1. Synthesis of 2(5*H*)-furanone 38

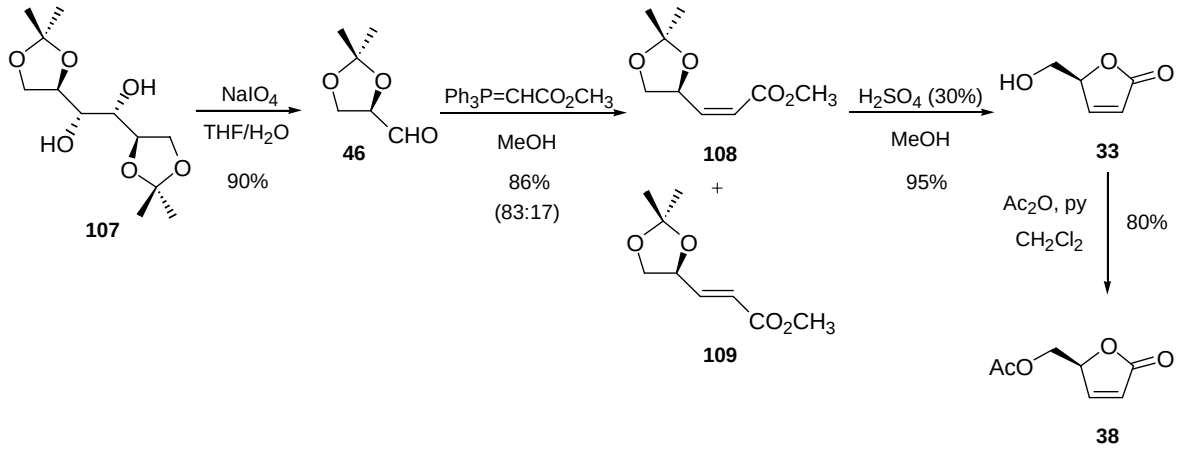
A research program with the main objective of synthesizing and studying the reactivity of chiral 2(5*H*)-furanones as well as their use in the preparation of natural products has been developed in our research group since 1981.[65] The (*S*)-5-hydroxymethyl-2(5*H*)-furanone, **33**, and its *O*-substituted derivatives have been extensively used by us and other groups as intermediates in the diastereoselective total synthesis of molecules of biological interest.[65b,66]

The preparation of lactone **33** was achieved following the synthetic procedure described by Mann and co-workers (Scheme 31).[67] This methodology allows its synthesis on a multi-gram scale and in satisfactory yield starting from the commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol, **107**.

[65] a) Camps, P.; Font, J.; Ponsatí, O. *Tetrahedron Lett.* **1981**, *22*, 1471-1472. b) Ortuño, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1987**, *43*, 2199-2202. c) Ortuño, R. M.; Mercé, R.; Font, J. *Tetrahedron* **1987**, *43*, 4497-4506. d) Ortuño, R. M.; Ballesteros, M.; Corbera, J.; Sanchez-Ferrando, F.; Font, J. *Tetrahedron* **1988**, *44*, 1711-1719. e) Ariza, J.; Font, J.; Ortuño, R. M. *Tetrahedron* **1990**, *46*, 1931-1942. f) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S.; Soria, A. *Tetrahedron* **1993**, *49*, 3857-3870.

[66] a) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652-653. b) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311-316. c) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303-1312. d) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737-738. e) Hannesian, S.; Murray, P. *Can. J. Chem.* **1986**, *64*, 2231-2234. f) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641-648.

[67] Mann, J.; Parlett, N. K.; Thomas, A. *J. Chem. Res. Synop.* **1987**, 369.

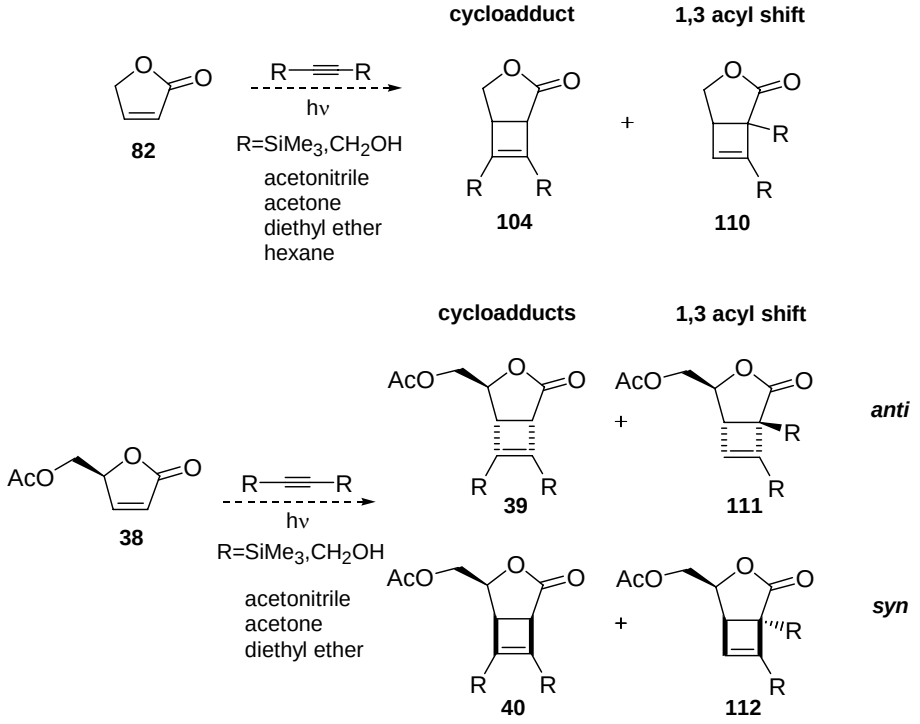


Scheme 31. Synthesis of 2(5*H*)-furanone **38**.

The synthetic pathway started with the oxidative cleavage of the D-mannitol diacetonide derivative **107** with sodium periodate in a 10:1 THF/H_2O mixture at room temperature to afford the 2,3-*O*-isopropylidene-D-glyceraldehyde, **46**. Reaction of aldehyde **46** with methoxycarbonylmethylene(triphenyl)phosphorane in methanol at 0 ºC gave a 83:17 mixture of (*Z*)- and (*E*)-alkenes **108** and **109**, respectively. The major isomer **108** was treated with acidic methanol to afford the 2(5*H*)-furanone **33** in 95% yield, which was eventually converted into lactone **38** by reaction with acetic anhydride and pyridine in CH_2Cl_2 in 80% yield, (45% global yield from **107**), $[\alpha]_D$: -123.6 (*c* 3.68, $CHCl_3$), bp: 125 ºC / 0.2 mm Hg.

2. Photocycloaddition of 2(5*H*)-furanones to symmetric alkynes

The first part of the study was performed evaluating the photochemical reactivity of **82** and **38** with the disubstituted alkynes bis(trimethylsilyl)acetylene and 2-butyne-1,4-diol since their symmetry reduces the number of expected products (Scheme 32).



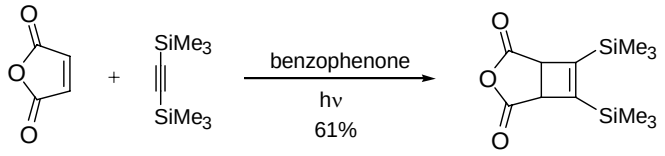
Scheme 32. Study of the [2+2] photocycloaddition of 2(5*H*)-furanones **82** and **38** to symmetric alkynes.

The effect of the experimental conditions (solvents, filters and reaction times) of the photoreactions on the yield, the facial diastereoselectivity and the formation of 1,3-acyl shift rearrangement products has been evaluated.

2.1. [2+2] Photocycloaddition of 2(5*H*)-furanones 82 and 38 to bis(trimethylsilyl)acetylene

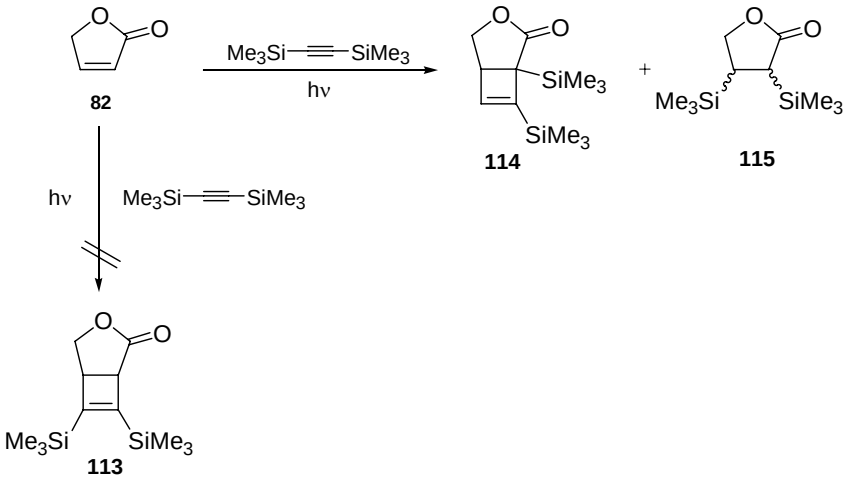
Very few studies dealing with photochemical reactions of α,β-unsaturated carbonyl compounds with bis(trimethylsilyl)acetylene have been reported in the literature.[68] Among them, the best synthetic results were described by Birkofer and Eichstädt[68a] in 1978 wherein the irradiation through a quartz filter of maleic anhydride to bis(trimethylsilyl)acetylene in acetone and benzophenone as a photosensitizer, afforded the expected cycloadduct in 61% yield (Scheme 33).

[68]a) Birkofer, L.; Eichstädt, D. *J. Organomet. Chem.* **1978**, *145,* C29-C30. b) Sugihara, Y.; Morokoshi, N.; Murata, I. *Chem. Lett.* **1979**, 745-748. c) Maier, V.G.; Lage, H. W.; Reisenauer, H. P. *Angew. Chem.* **1981**, *93*, 1010-1011. d) Rainer, A.; Hoffmann, J. *Chem. Ber.* **1991**, *124*, 2307-2313.



Scheme 33. [2+2] Photocycloaddition of maleic anhydride to bis(trimethylsilyl)acetylene, Birkofer and Eichstädt. (1978).

In first place, the photochemical reaction of lactone **82** with bis(trimethylsily)acetylene under several different reaction conditions was investigated (Table 3).



entry	filter	solvent	time	yield (%)	
				114	**115**
1	quartz	acetone	5 h	-	-
2	quartz	acetonitrile	6 h	16 (21)[a]	47 (62)[a]
3	quartz	hexane	6.5 h	6 (9)[a]	25 (33)[a]
4	quartz	diethyl ether	3.75 h	6	19
5	pyrex	acetone	2 h	-	-

[a] Corrected yield after considering the % of consumed starting material.

Table 3. [2+2] Photocycloaddition of 2(5*H*)-furanone **82** to bis(trimethylsilyl)acetylene.

Initially, the experimental conditions described by Birkofer and Eichstädt[68a] were evaluated (Table 3, entry 1). Unfortunately, when lactone **82** and one equivalent of bis(trimethylsilyl)acetylene were irradiated through a quartz filter for 5 h in acetone in the presence of benzophenone (0.05 equivalents) only decomposition products were obtained.

At this point it was decided to apply the usual conditions used in our laboratory for the photoreactions of 2(5*H*)-furanones with alkenes.[69] Thus, irradiation of **82** and a 5 molar excess of bis(trimethylsilyl)acetylene through a quartz filter in acetonitrile afforded, after column chromatography, the rearranged bicyclic compound **114** (16% yield) and the bis(trimethylsilyl)lactone **115** (47% yield) (entry 2). Despite the presence of remaining starting material **82** (25%), the irradiation was stopped due to the formation of multiple by-products.

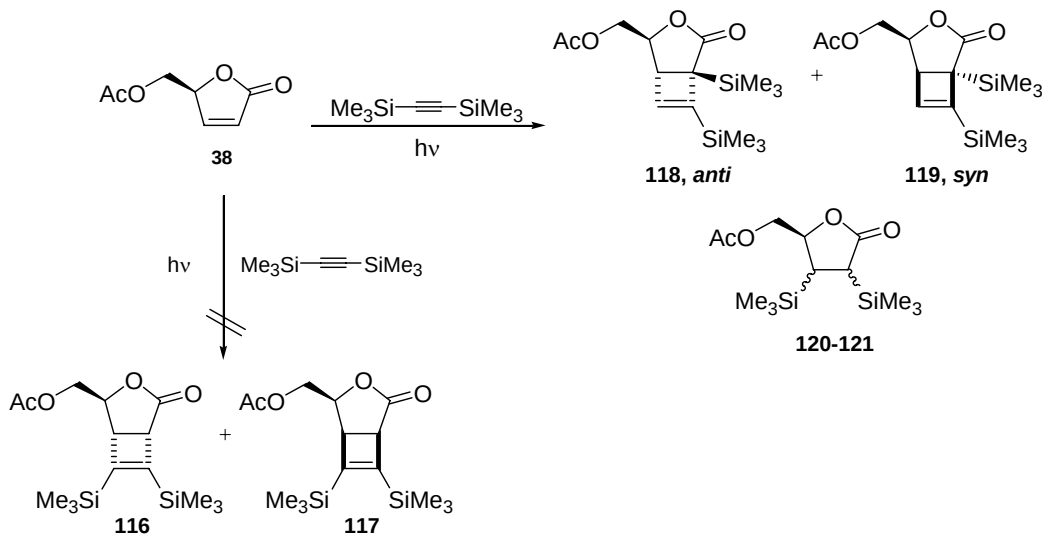
Similar ratios of compounds **114** and **115** were obtained when the reaction was carried out in hexane and diethyl ether albeit in lower yields (entries 3 and 4). The reaction in diethyl ether occurred in a faster way leading to the formation of **114** (6% yield) and **115** (19% yield) along with unidentified decomposition compounds without recovering starting material.

Finally, all attempts to carry out the photochemical reaction in acetone by using a pyrex filter met with failure. The starting furanone **82** underwent decomposition to unidentified products.

It is noteworthy that the desired primary cycloadduct **113** was not detected in any of the photoreactions investigated and that the 3,4-bis(trimethylsilyl)-lactone **115** was the major isolated compound irrespective the experimental conditions used.

Next, the photochemical reaction of the 5-substituted lactone **38** with bis(trimethylsilyl)acetylene in acetonitrile and acetone was evaluated (Table 4).

[69] Alibés, R.; de March, P.; Figueredo, M.; Font. J.; Racamonde, M.; Rustullet, A.; Alvarez-Larena, A.; Piniella, J. F.; Parella, T. *Tetrahedron Lett.* **2003**, *44*, 69-71.



entry	filter	solvent	time	yield (%) 118+119	product ratio[b] 118:119	yield (%) 120+121	product ratio[b] 120:121
1	quartz	acetonitrile	4 h	12 (18)[a]	41:59	35 (50)[a]	79:21
2	pyrex	acetone	2 h	-	-	-	

[a] Corrected yield after considering the % of consumed starting material. [b] Ratio determined by GC and ^{1}H-NMR.

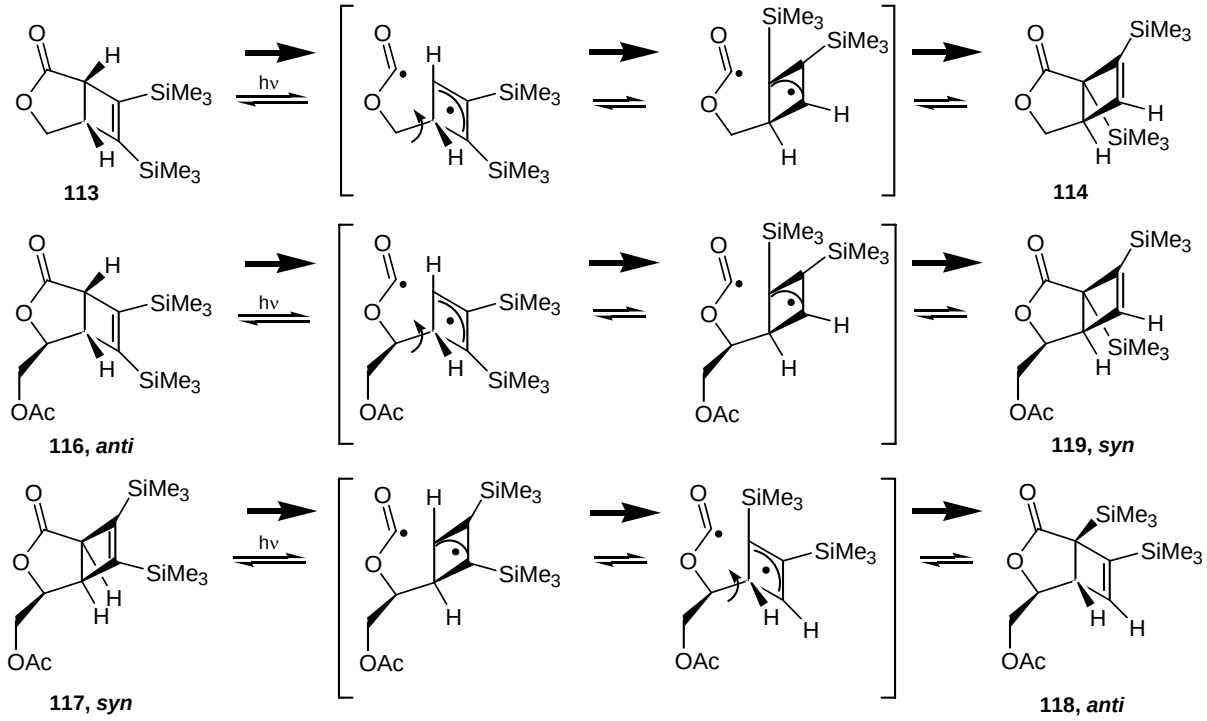
Table 4. [2+2] Photocycloaddition of 2(5*H*)-furanone **38** to bis(trimethylsilyl)acetylene.

Irradiation trough a quartz filter of an acetonitrile solution of the chiral 2(5*H*)-furanone **38** and a five molar excess of bis(trimethylsilyl)acetylene afforded a 57:16:16:11 mixture of four products. Despite the presence of 31% of the starting material, after 4 h of irradiation the reaction was stopped due to the formation of many peaks in the reaction crude analysis by GC. Purification of the crude mixture by column chromatography afforded the following fractions: i) a 41:59 mixture of the *anti* and *syn* rearranged cyclobutene derivatives **118** and **119** (12% yield); ii) a 79:21 mixture of the diastereomeric bis(trimethylsilyl)lactones **120** and **121** (35% yield); and iii) unreacted lactone **38** (Table 4, entry 1). Isolation of the major compound **120** and enriched fractions of **118**, **119** and **121**, was achieved after several purifications by column chromatography of each mixture. As it happened with 2(5*H*)-furanone **82**, the presence of the primary cycloadducts **116** and **117** could not be detected. It is also noteworthy to mention the inversion of the expected facial diastereoselectivity of the reaction, since the *syn* rearranged isomer **119** was preferably formed.

When the reaction was attempted irradiating through a pyrex filter in acetone, disappearance of the starting material was observed even though neither the desired products nor the previously described derivatives **118-121** were present in the reaction mixture.

The results found in the [2+2] photocycloaddition of 2(5*H*)-furanones **82** and **38** to bis(trimethylsilyl)acetylene largely differed from those expected. The most remarkable fact is that the desired cycloadducts **113** and **116-117** were not obtained, irrespective the reaction conditions chosen. Moreover, no signal of significant intensity other than those of the described compounds was detected at short reaction times neither by NMR nor by GC analysis of the reaction crude.

Products **114** and **118-119** come from the 1,3-acyl shift rearrangement undergone by the undetected primary cycloadducts **113** and **116-117**, respectively (Scheme 34). The 1,3-acyl shift processes observed herein are completely displaced to the final products even though this rearrangement has been usually described in the literature as an equilibrium. The driving force for this complete displacement of the equilibrium would be the high strain suffered by the cyclobutene ring fused to a five membered lactone and substituted with two bulky trimethylsilyl groups on the vinylic positions.



Scheme 34. Possible relationship between the expected cycloadducts **113**, **116** and **117**, and the isolated compounds **114**, **118** and **119**.

The facial diastereoselectivity achieved in the photocycloaddition of the chiral furanone **38** to bis(trimethylsilyl)acetylene is also influenced by the 1,3-acyl shift as shown in Scheme 34. The *anti*:*syn* final products ratio is (41:59) which would represent a major approximation of the alkyne through the most sterically hindered face of **38**. However, it

must be considered that during the rearrangement the *anti* cycloadduct **116** becomes the *syn* compound **119**. Similarly, the *syn* cycloadduct **117** becomes the *anti* rearranged compound **118**. Therefore, taking into account these processes, a 59:41 *anti*:*syn* ratio can be deduced for the photocycloaddition.

The fact that 1,3-acyl shift usually occurs from the β,γ-unsaturated carbonyl system excited singlet state S_1 (although evidences have been found which demonstrate that in certain cases a higher triplet state T_2 may be involved), and not from its T_1, is accepted in the bibliography.[70] Thus, 1,3-acyl shift reactions have been mainly described when the photochemical reaction is carried out through a quartz filter whereas fewer examples using acetone or any other triplet sensitizer have been published. Herein, this photochemical rearrangement has been observed irradiating through a quartz filter in acetonitrile, hexane and diethyl ether.

Not only the presence of rearranged compounds instead of the desired cycloadducts was unexpected but also the fact that these products were always obtained as the minor components of the reaction mixture in front of the 3,4-bis(trimethylsilyl)lactone derivatives **115** and **120**-**121**. The structure of these compounds was determined with the help of COSY (Correlation Spectroscopy), HMQC (Heteronuclear Multiple Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Connectivity) experiments. Figure 13 shows the COSY experiment registered for **115** which provides information about the ^{1}H-^{1}H coupling and permits the assignment of H-3 and H-4.

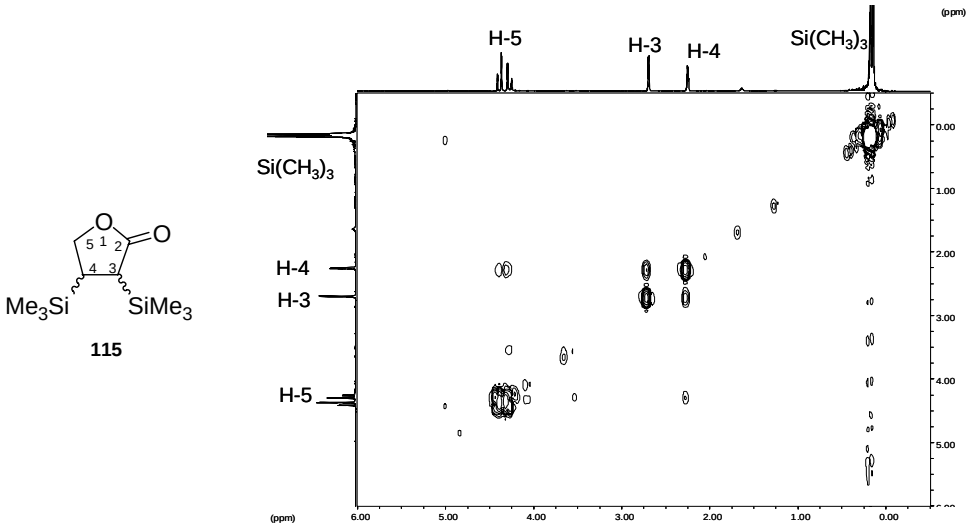


Figure 13. COSY experiment of lactone **115** ($CDCl_3$, 250 MHz).

[70] Padwa, A.; Zhi, L.; Fryxell, G. E. *J. Org. Chem.* **1991**, *56*, 1077-1083.

The HMQC and HMBC experiments of **120** provide information about the ^{1}H-^{13}C correlation and the ^{1}H-^{13}C connectivity at 2-3 bonds of the molecule, respectively (Figure 14).

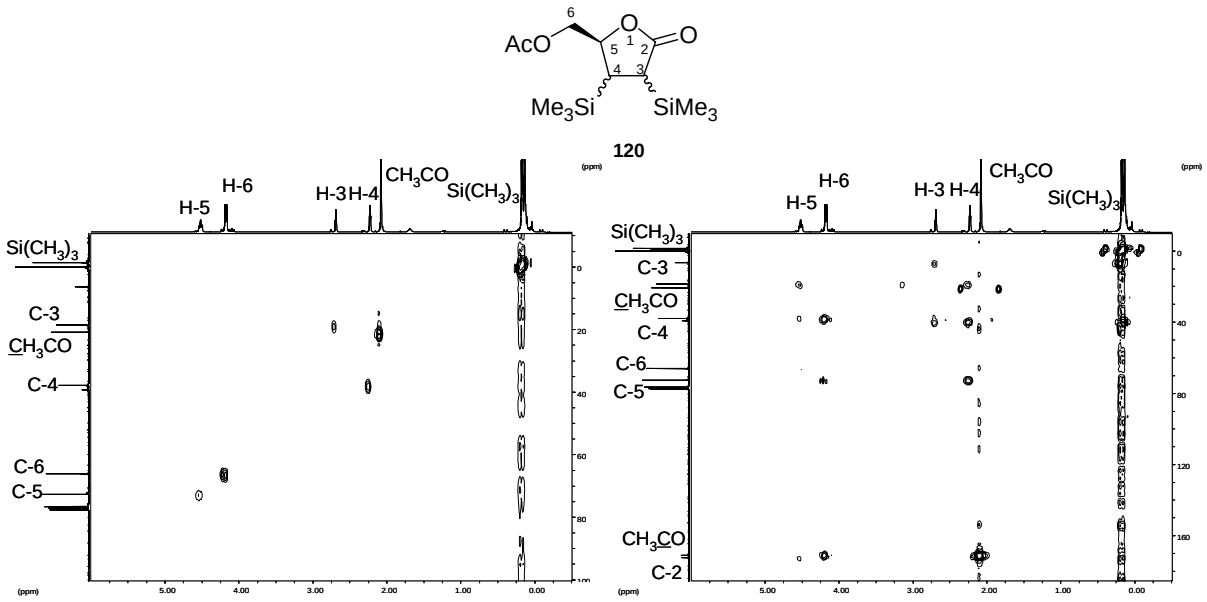
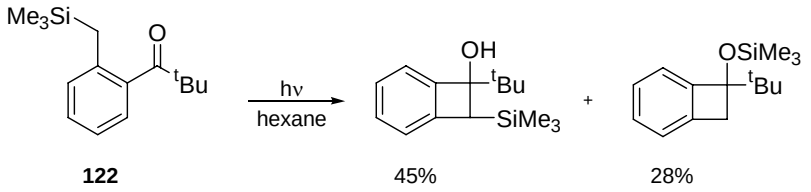


Figure 14. HMQC and HMBC experiments of lactone **120** ($CDCl_3$, 250 MHz).

The establishment of the relative stereochemistry of the trimethylsilyl substituents present in lactones **115** and **120** and **121** was attempted studying the values of the proton-proton vicinal constant coupling as well with n.O.e. differential experiments. Nevertheless, no conclusive data was obtained.

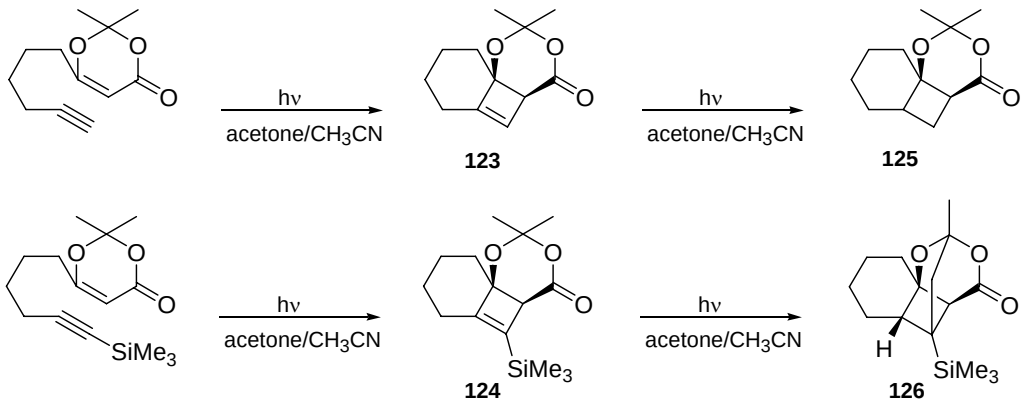
Several examples of photoreduction of a double bond by hydrogen radicals coming from solvent molecules have been described in the literature.[54a] In our case, a similar behaviour from trimethylsilyl radical groups derived from the photolysis of the carbon-silicon bond of the alkyne would be the explanation for the formation of these lactones. As an example of the well-known high migratory aptitude described for silyl groups, Yoshioka and co-workers[71] have recently reported the silyl migration undergone by the 2-trimethylsilylmethylphenyl ketone **122** when irradiated through a pyrex filter in hexane (Scheme 35).

[71] Saito, M.; Saito, A.; Ishikawa, Y.; Yoshioka, M. *Org. Lett.* **2005**, *7*, 3139-3141.



Scheme 35. Silyl migration observed in the photochemical reaction of ketone **122**, Yoshioka and co-workers (2005).

Furthermore, the formation of secondary photoproducts from cyclobutene photoadducts containing vinylic trimethylsilyl groups has also been reported. Winkler and McLaughlin[72] described in 2005 the photoinduced intramolecular formation of the cyclobutene derivatives **123** and **124**, which were unstable under the reaction conditions and afforded secondary photoproducts whose structures differed markedly as a function of the substituent on the alkyne photosubstrate (Scheme 36). Therefore, whereas **123** afforded the photoreduced product **125**, trimethylsilyl-substituted **124** gave the bridged product **126**.

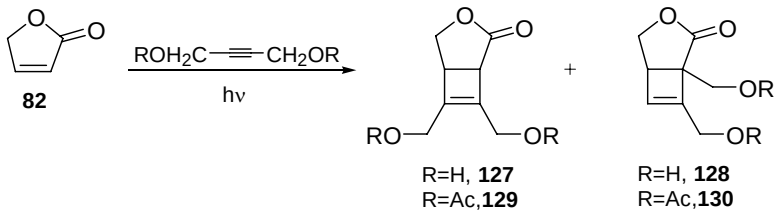


Scheme 36. Formation of secondary photoproducts form cyclobutene photoadducts, Winkler and McLaughlin (2005).

2.2. [2+2] Photocycloaddition of 2(5*H*)-furanones 82 and 38 to 2-butyne-1,4-diol and 1,4-bis(acetyloxy)-2-butyne

The photochemical reaction of lactones **82** and **38** with 2-butyne-1,4-diol and its derivative 1,4-bis(acetyloxy)-2-butyne was also investigated. As before, the results accomplished with **82** are first presented (Table 5).

[72] Winkler, J. D.; McLaughlin, E. C. *Org. Lett.* **2005**, *7*, 227-229.



entry	R	filter	solvent	time	yield (%)
1	H	quartz	acetonitrile	3 h	**127** (42), **128** (15)
2	Ac	quartz	acetonitrile	6.5 h	**129** (22), **130** (15)
3	H	pyrex	acetone	2 h	-
4	Ac	pyrex	acetone	2 h	-

Table 5. [2+2] Photocycloaddition of 2(5*H*)-furanone **82** to 2-butyne-1,4-diol and 1,4-bis(acetyloxy)-2-butyne.

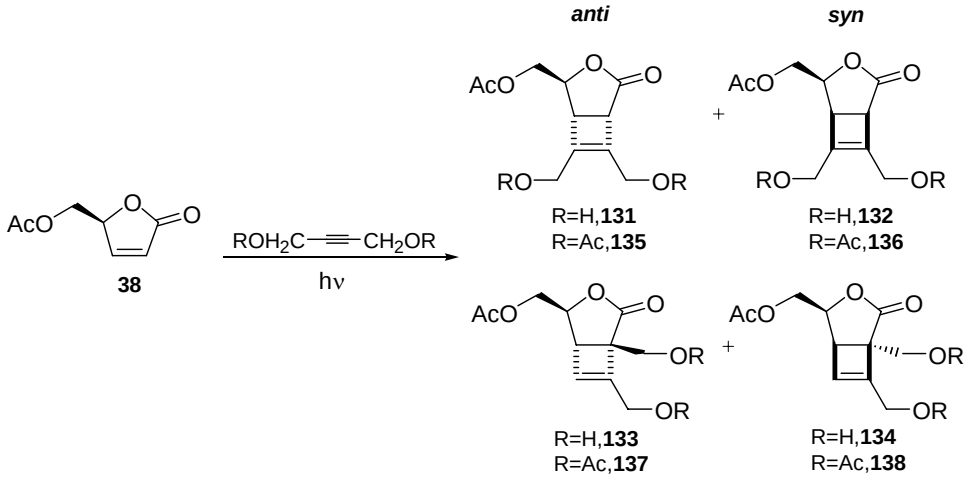
The reaction between lactone **82** and a five molar excess of 2-butyne-1,4-diol in acetonitrile afforded, after purification by column chromatography, the cycloadduct **127** in 42% yield and the rearranged cyclobutene compound **128** in 15% yield (Table 5, entry 1). It is noteworthy to mention that by irradiation under the above conditions, the primary cycloadduct **127** led to the formation of the rearranged cyclobutene **128** along with unidentified decomposition products.

Because of the low solubility shown by **127** and **128** in most of the solvents evaluated, their purification was rather difficult and it was decided to assay the [2+2] photochemical reaction of **82** with the bisacetylated alkyne.

Thus, the photochemical reaction of **82** with a five molar excess of 1,4-bis(acetyloxy)-2-butyne in acetonitrile afforded, after purification by column chromatography, the cycloadduct **129** in 22% yield and its rearranged isomer **130** in 15% yield (entry 2). Both the yield and the reaction rate were lower than those observed in the [2+2] photocycloaddition reaction with 2-butyne-1,4-diol. On the other hand, the amount of the rearranged cyclobutene was significantly increased in the reaction with 1,4-bis(acetyloxy)-2-butyne which it may be attributed to an steric effect. The low yields obtained in these photoreactions were due to the presence of many undefined by-products at the end of the reaction.

Finally, the photochemical reactions performed in acetone, by irradiation through a pyrex filter met with failure (entries 3 and 4). Although the starting material disappeared, no defined products could be identified by the analysis of the NMR spectra.

Next, the photochemical behaviour of lactone **38** in the presence of 2-butyne-1,4-diol and 1,4-bis(acetyloxy)-2-butyne was investigated (Table 6).



entry	R	filter	solvent	time	global yield (%)	product ratio [b] 131:132:133:134	*anti*:*syn* [c]
1	H	quartz	acetonitrile	3 h	49 (62)[a]	52:15:7:26	59:41 (78:22)[d]
2	Ac	quartz	acetonitrile	2.5 h	-	-	-

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration. [d] In brackets, estimated results (*anti*:*syn*) once considered the 1,3-acyl shift mechanism.

Table 6. [2+2] Photocycloaddition of 2(5*H*)-furanone **38** to 2-butyne-1,4-diol and 1,4-bis(acetyloxy)-2-butyne.

Irradiation of 2(5*H*)-furanone **38** with a 5 molar excess of 2-butyne-1,4-diol resulted in the formation of a 52:15:7:26 mixture of the *anti* and *syn* cycloadducts **131** and **132**, and the *anti* and *syn* rearranged isomers **133** and **134** in 49% global yield whereas 20% of the starting material was recovered (Table 6, entry 1). Repeated column chromatography afforded pure **131** and **134** whereas only enriched mixtures of the minor products were obtained.

According to the mechanistic stereochemical issues previously discussed each rearranged product comes from the primary cycloadduct of the contrary relative stereochemistry. Thus, *anti* **133** is formed from the *syn* cycloadduct **132** whereas *syn* **134** comes from the *anti* primary cycloadduct **131**. Considering the rearranged products, the *anti:syn* estimated ratio assigned for the primary cycloadducts is 78:22 which is consistent with a major approach of the alkyne through the less hindered face of the lactone.

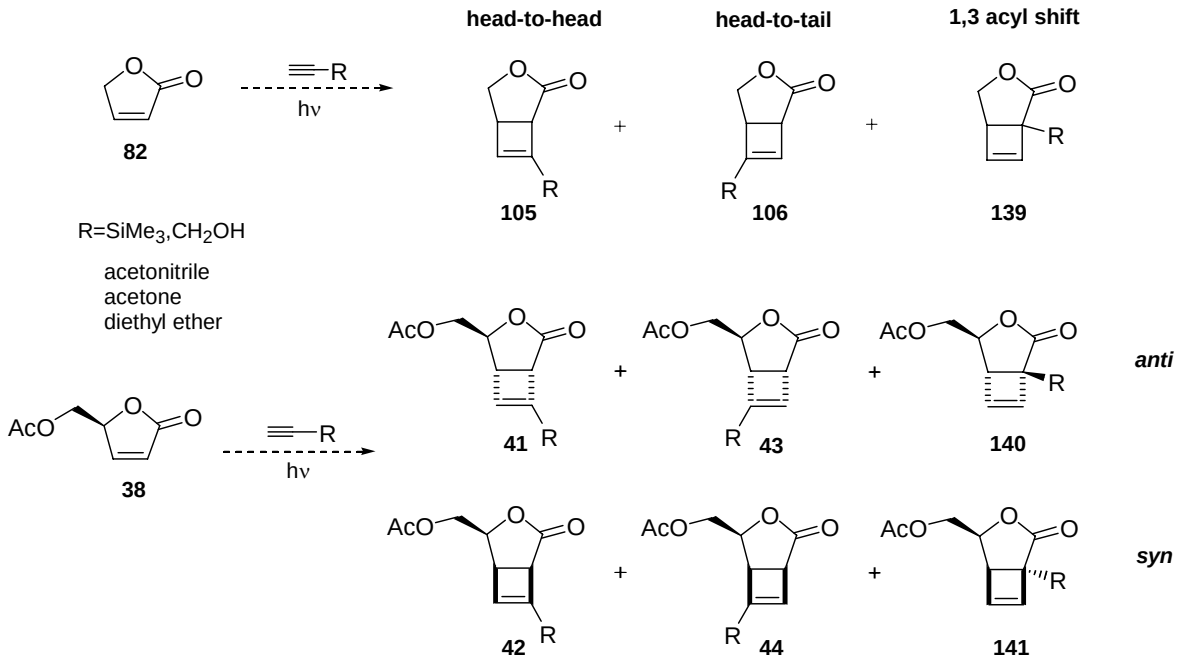
Surprisingly, the irradiation of lactone **38** in the presence of 1,4-bis(acetyloxy)-2-butyne in acetonitrile gave a complex reaction crude which ^{1}H- and ^{13}C-NMR analysis did

not allow the identification of any compound containing the expected cyclobutene moiety although consumption of the starting material took place during the reaction.

Finally, contrary to the photochemical reaction with bis(trimethylsilyl)acetylene, the reaction of lactones with 2-butyne-1,4-diol afforded the primary cycloadducts as the major products, being the 1,3-acyl shift only a minor process.

3. Photocycloaddition of 2(5*H*)-furanones to asymmetric alkynes

Once completed the photochemical study with symmetric alkynes, we turned out our attention to the photochemical reactivity of lactones **38** and **82** with the monosubstituted alkynes, trimethylsilylacetylene and propargyl alcohol. As before, these reactions have been first investigated with **82** which could give up to 3 products: the head-to-head regioisomers **105**, the head-to-tail regioisomers **106** and the rearranged cyclobutene derivatives **139** (Scheme 37). The photochemical reactivity of the chiral lactone **38**, which could afford up to 6 isomeric cyclobutene derivatives: the *anti* head-to-head **41**, the *syn* head-to-head **42**, the *anti* head-to-tail **43**, the *syn* head-to-tail **44**, the *anti* rearranged derivative **140** and the *syn* rearranged cyclobutene **141**, has been also evaluated.



Scheme 37. Study of the [2+2] photocycloaddition of 2(*5H*)-furanones **82** and **38** to asymmetric alkynes.

As previously discussed, the solvent is one of the most influent factors in terms of yield, facial diastereoselectivity and, specially, regioselectivity on the [2+2] photochemical reactions. Thus, the election of the solvent is essential when designing a photochemical experiment. In the present work solvents of different polarity have been tested (Table 7).

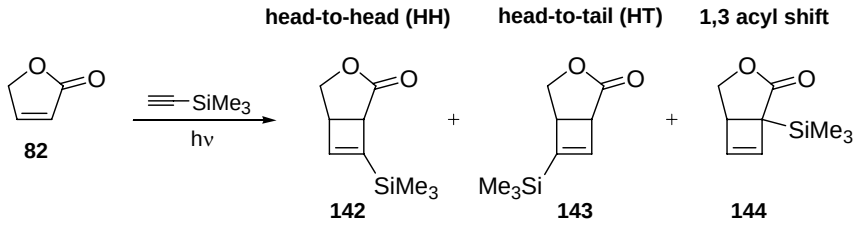
solvent	ε[73]
diethyl ether	4.2
acetone	20.7
acetonitrile	35.9

Table 7. Dielectric constant values of the solvents used in this photochemical study.

Herein, the effect of the solvent polarity on the regio and the diastereoselectivity of the reactions and the scope of the 1,3-acyl shift, has been investigated.

3.1. [2+2] Photocycloaddition of 2(5*H*)-furanones 82 and 38 to trimethylsilylacetylene

The first reaction studied was the [2+2] photocycloaddition of 2(5*H*)-furanone **82** to trimethylsilylacetylene (Table 8).



entry	filter	solvent	time	global yield (%)	product ratio[b] 142:143:144
1	quartz	acetonitrile	8.5 h	56 (74)[a]	58:15:27
2	quartz	diethyl ether	3.5 h	24	100:-:-
3	pyrex	acetone	5.5 h	20	61:39:-

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR.

Table 8. [2+2] Photocycloaddition of 2(5*H*)-furanone **82** to trimethylsilylacetylene.

Irradiation of lactone **82** with a 5 molar excess of trimethylsilylacetylene in acetonitrile through a quartz filter afforded a 58:15:27 mixture of the head-to-head (HH) isomer **142**, the head-to-tail (HT) isomer **143** and the rearranged product **144** in 56%

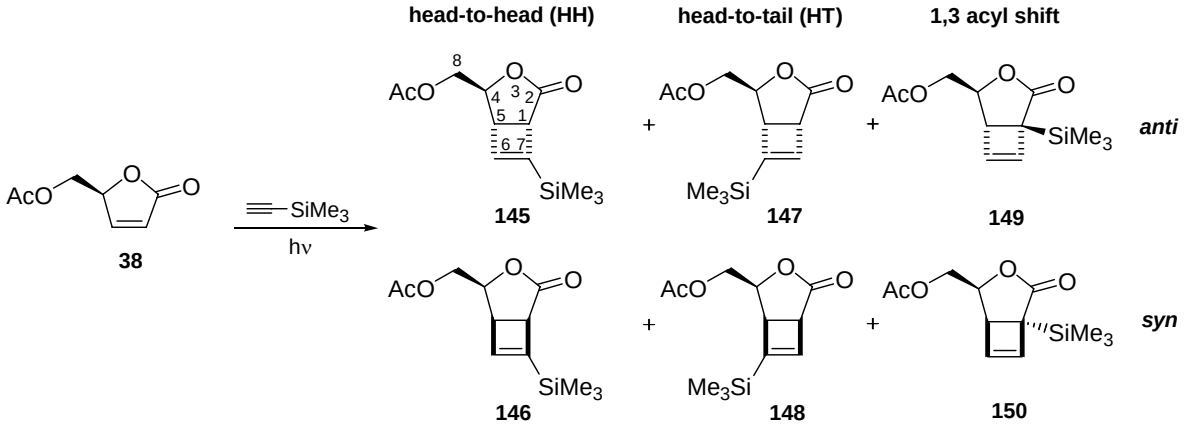
[73] Solvent dielectric constants values: Reichardt, C. *Solvents and solvent effects in organic chemistry*. Wiley-VCH, Weinheim, 2003.

overall yield, as well as 25% of the starting material (Table 8, entry 1). The irradiation was stopped after 8.5 h due to the increasing presence of by-products. Separation of all three isomers was achieved by successive column chromatography.

The photoreaction performed in diethyl ether resulted in the formation of a complex crude mixture due to the presence of many degradation by-products from where only the HH isomer **142** could be isolated in low yield (24%) (entry 2).

Finally, when the reaction was carried out in acetone a 61:39 mixture of the HH cycloadduct **142** and its HT isomer **143** was isolated in 20% global yield (entry 3). No presence of the rearranged isomer **144** was detected.

Then, the photochemical reaction of the chiral lactone **38** with trimethylsilylacetylene was investigated (Table 9).



entry	filter	solvent	time	global yield (%)	product ratio[b] 145:146:147:148;149:150	*anti:syn*[c]
1	quartz	acetonitrile	4 h	40 (61)[a]	30:36:-:-:6:28	36:64 (58:42)[d]
2	quartz	diethyl ether	2.75 h	12	55:45:-:-:-:-	55:45
3	pyrex	acetone	2 h	53 (83)[a]	31:34:18:17:-:-	49:51

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration. [d] In brackets, estimated results (*anti*:*syn*) once considered the 1,3-acyl shift mechanism.

Table 9. [2+2] Photocycloaddition of 2(5*H*)-furanone **38** to trimethylsilylacetylene.

Irradiation of furanone **38** and a 5 molar excess of trimethylsilylacetylene in acetonitrile for 4 h furnished a 30:36:6:28 mixture of the HH *anti* and *syn* isomers **145** and **146** and the *anti* and *syn* rearranged cyclobutene derivatives **149** and **150** (40% global yield) along with unreacted starting material (35%) (Table 9, entry 1). Repeated column chromatography allowed the isolation of pure **145, 146** and **150** and an enriched fraction of

149 that made its characterization possible. Irradiation was stopped before total consumption of **38** due to the presence of by-products at prolonged reaction times. The reaction was monitored by GC and signals from the head-to-tail cycloadducts **147** and **148** were not detected.

It is noteworthy to mention that this result differs from that found with crotolactone, **82**, wherein the HT cycloadduct **143** was isolated in 15% yield. The steric interaction between the C-4 substitution and the trimethylsilyl group in the HT isomers **147** and **148** may account for their fast conversion to the rearranged compounds **149** and **150**.

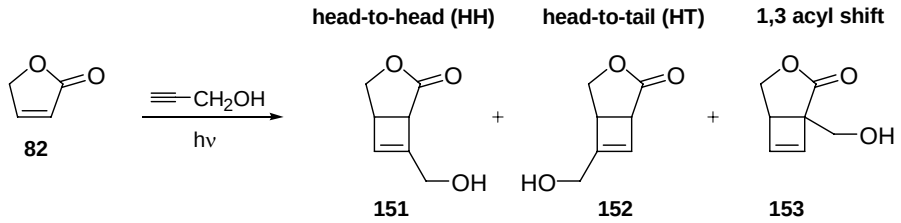
When the photoreaction was performed in diethyl ether the irradiation resulted in the formation of a complex crude mixture from where only the HH isomers **145** and **146** could be isolated in poor yield (12%) (entry 2). At short reaction times the HT isomers **147** and **148** were detected by GC analysis, although they evolved to unidentified products. The 1,3-acyl shift rearranged cyclobutenes **149** and **150** were not observed among these side products.

Finally, when the reaction was performed in acetone a 31:34:18:17 mixture of cycloadducts **145-148** was obtained in 53% global yield along with 37% of the starting furanone **38** (entry 3). The 1,3-acyl shift derivatives were not detected during the reaction. Isolation of enriched fractions of **147** and **148** was accomplished after several purifications by column chromatography.

In terms of facial diastereoselectivity, it is worth to point out the inversion of the expected facial diastereoselectivity observed in the reaction carried out in acetonitrile, since the *syn* isomers **146** and **150** were preferably formed. Nevertheless, according to the previously discussed mechanistic hypothesis, which imply an inversion of the relative configuration of the cyclobutene derivatives through the 1,3-acyl shift rearrangement, the results observed in acetonitrile ratio must be corrected. Thus, an orientative initial *anti*:*syn* ratio of the [2+2] photocycloaddition reaction would be 58:42, being this result quite similar to those observed for acetone and diethyl ether.

3.2. [2+2] Photocycloaddition of 2(5*H*)-furanones 82 and 38 to propargyl alcohol

The photochemical reactivity of lactone **82** with the last selected alkyne, propargyl alcohol, was investigated (Table 10).



entry	filter	solvent	time	global yield (%)	product ratio[b] 151:152:153
1	quartz	acetonitrile	2.5 h	66 (93)[a]	57:29:14
2	quartz	diethyl ether	2.5 h	64 (76)[a]	58:42:-
3	pyrex	acetone	3 h	76	67:33:-

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by ^{1}H-NMR.

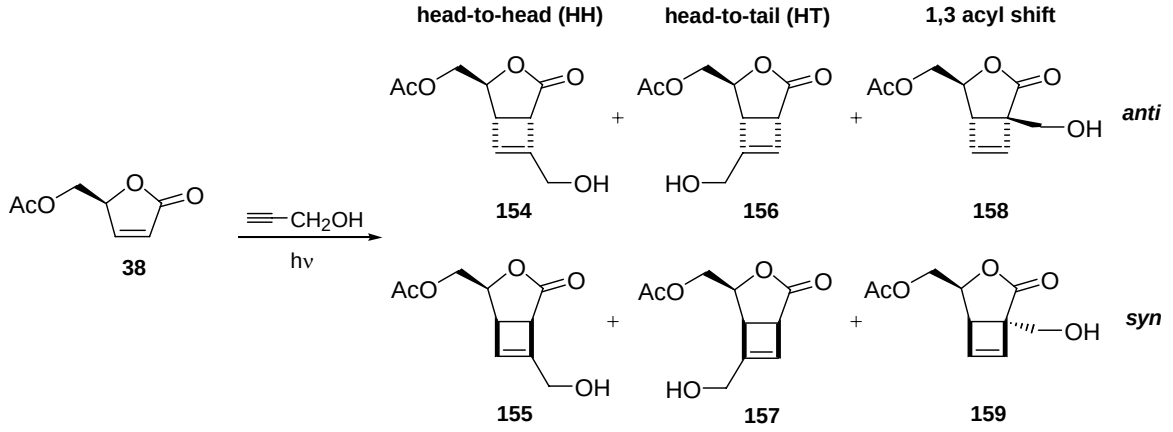
Table 10. [2+2] Photocycloaddition of 2(5*H*)-furanone **82** to propargyl alcohol.

Irradiation of a mixture of lactone **82** and a 5 molar excess of propargyl alcohol in acetonitrile gave rise to a 57:29:14 mixture of the HH isomer **151**, the HT isomer **152** and the rearranged cyclobutene **153** in 66% global yield, along with recovered starting material (29%) (Table 10, entry 1). Irradiation was stopped after 2.5 h due to the formation of a large amount of by-products. Repeated column chromatography allowed the complete separation of the three isomers.

Reaction in diethyl ether afforded a 58:42 mixture of cycloadducts **151** and **152** in 64% overall yield without the presence of the 1,3-acyl shift product **153** while 17% of the starting material was recovered (entry 2).

When the reaction was performed in acetone, a 67:33 mixture of cycloadducts **151** and **152** was obtained in 76% global yield (entry 3).

Finally, the photochemical reactivity of the chiral 2(5*H*)-furanone **38** with propargyl alcohol was studied (Table 11).



entry	filter	solvent	time	global yield (%)	product ratio[b] 154:155:156:157:158:159	*anti:syn*[c]
1	quartz	acetonitrile	1.5 h	60 (81)[a]	35:30:20:8:2:5	57:43 (60:40)[d]
2	quartz	diethyl ether	2 h	38	36:23:32:9:-:-	68:32
3	pyrex	acetone	2 h	49 (68)[a]	45:24:24:7:-:-	69:31

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration. [d] In brackets, estimated results (*anti*:*syn*) once considered the 1,3-acyl shift mechanism.

Table 11. [2+2] Photocycloaddition of 2(5*H*)-furanone **38** to propargyl alcohol.

The photochemical reaction between the chiral furanone **38** and a 5 molar excess of propargyl alcohol in acetonitrile afforded a 35:30:20:8:2:5 mixture of the HH *anti* and *syn* cycloadducts **154** and **155**, the HT *anti* and *syn* derivatives **156** and **157**, and the *anti* and *syn* rearranged isomers **158** and **159** in 60% overall yield along with unreacted starting material (26%) (Table 11, entry 1). After several purifications by column chromatography pure samples of the isomers **154** and **159** were isolated whereas only enriched mixtures of the remaining isomers were obtained. Nevertheless characterization of all isomers was achieved by ^{1}H and ^{13}C-NMR.

Irradiation of a mixture of **38** and propargyl alcohol in diethyl ether afforded a 36:23:32:9 mixture of the cycloadducts **154-157** in 38% global yield (entry 2). The 1,3-acyl shift derivatives **158** and **159** were detected by ^{1}H-NMR of the reaction crude albeit in very small scale what made quantification impossible.

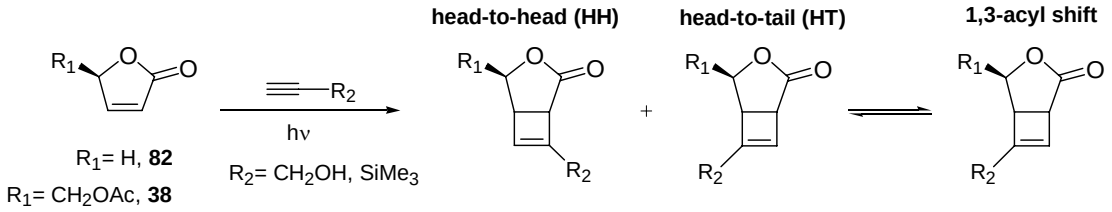
Finally, the same reaction was performed in acetone with a pyrex filter affording a 45:24:24:7 mixture of the isomers **154-157** in 49% yield along with 28% of the starting material (entry 3).

In all the cases the reactions were stopped at appropriated reaction times due to the formation of a large amount of by-products.

The observed facial diastereoselectivity in the reactions performed with propargyl alcohol was slightly higher than that observed in reactions with trimethylsilylacetylene for all the evaluated solvents.

3.3. Solvent effect on the regioselectivity and the 1,3-acyl shift rearrangement

The regiochemistry results of the [2+2] photocycloaddition reactions carried out with lactones **82** and **38** to asymmetric alkynes in acetonitrile, diethyl ether and acetone are collected on Table 12.



lactone	R_1	R_2	head-to-head (HH) : head-to-tail (HT) : 1,3-acyl shift		
			acetonitrile [a]	diethyl ether	acetone
82	H	$SiMe_3$	58:15:27 (58:42)	100:-:-	61:39:-
82	H	CH_2OH	57:29:14 (57:43)	58:42:-	67:33:-
38	CH_2OAc	$SiMe_3$	66:-:34 (66:34)	100:-:-	65:35:-
38	CH_2OAc	CH_2OH	65:28:7 (65:35)	59:41:-	69:31:-

[a] In brackets, estimated results (HH:HT) once added the HT and the 1,3-shift products ratio.

Table 12. Regioselectivity in the [2+2] photocycloaddition of 2(5*H*)-furanones **82** and **38** to trimethylsilylacetylene and propargyl alcohol.

First of all, it is remarkable that the HH isomers were formed preferentially in all the reactions evaluated. The HH:HT ratios accomplished in different solvents are quite similar with the exception of the photoreactions performed with trimethylsilylacetylene in diethyl ether where only the HH isomers could be detected. However, the low yields achieved in these reactions give little significance to the results. Thus, the highest regioselectivity was generally obtained in polar solvents (acetone and acetonitrile).

Finally, 1,3-acyl shift rearranged derivatives were only obtained in reactions performed in acetonitrile and through a quartz filter.

At sight of these results, it can be concluded that the solvent plays a key role on the outcome of the photochemical reaction.

The preferred regiochemistry observed in the present work, head-to-head, is the same described in the literature for propargyl alcohol[58,63] and trimethylsilylacetylene.[74]

Considering the low yields obtained for most of the reactions investigated along with the formation of by-products and the laborious separation of the target cycloadducts, the application of any of these photochemical reactions in a synthetic methodology devised to the preparation of more elaborated cyclobutene derivatives becomes unlikely. However, the photochemical study has provided us with highly interesting results from a mechanistic point of view.

4. Structural determination of the cycloadducts

The structural assignment of the synthesized cycloadducts was carried out by ^{1}H and ^{13}C-NMR. Signals were assigned with the help of DEPT, COSY, HMQC, HMBC and n.O.e. differential experiments.

Some of the most significant ^{1}H and ^{13}C-NMR signals to determine the stereochemistry of the compounds obtained in the [2+2] photocycloaddition of 2(5*H*)-furanone **38** to bis(trimethylsilyl)acetylene, 2-butyne-1,4-diol, trimethylsilylacetylene and propargyl alcohol are shown in Table 13.

Since the cycloadducts are rigid, the coupling constants between H-4 and H-5, $J_{4,5}$, have been used to elucidate the structure. Low values of $J_{4,5}$ are expected for *anti* cycloadducts, coming from the approach of the alkyne through the less hindered face of the furanone (larger dihedral angle) and higher values for *syn* cycloadducts, coming from the attack through the other face (smaller dihedral angle) (Figure 15).

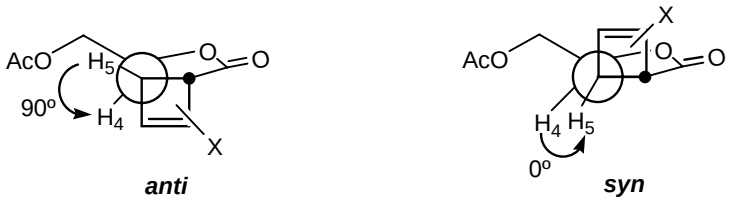


Figure 15. Expected dihedral angles for the *anti* and *syn* cycloadducts prepared.

[74] Soulie, J.; Pouet, M. J. *Tetrahedron* **1978**, *33*, 2521-2525.

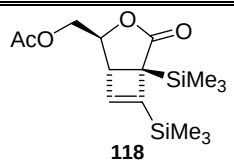
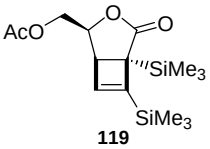
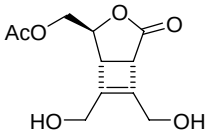
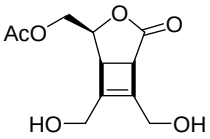
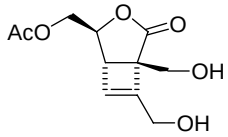
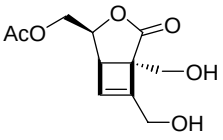
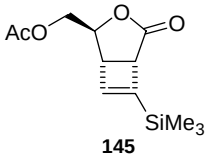
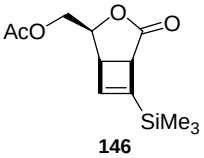
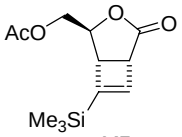
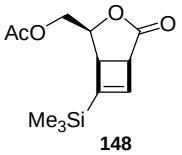
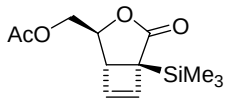
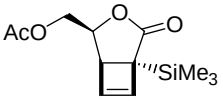
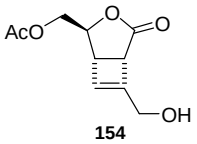
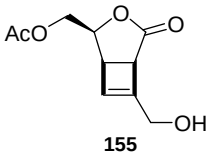
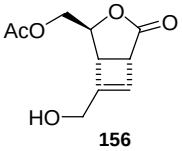
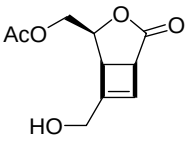
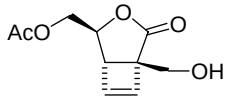
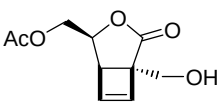
product	$J_{4,5}$	C-1	product	$J_{4,5}$	C-1
 **118**	2.2	52.4	 **119**	7.3	53.6
 **131**	1.6	44.4	 **132**	6.4	44.6
 **133**	1.6	58.8	 **134**	7.1	59.2
 **145**	2.0	47.8	 **146**	7.4	48.8
 **147**	1.5	47.6	 **148**	6.7	48.2
 **149**	1.4	51.4	 **150**	6.8	52.0
 **154**	1.4	46.7	 **155**	7.5	47.0
 **156**	1.5	44.0	 **157**	7.5	43.9
 **158**	1.0	58.7	 **159**	7.0	59.6

Table 13. Significant ^{1}H and ^{13}C-NMR data of the products of the [2+2] photocycloaddition of 2(5*H*)-furanone **38** to bis(trimethylsilyl)acetylene and 2-butyne-1,4-diol. Chemical shifts are expressed in ppm and coupling constants in Hz. Solvent was always $CDCl_3$ except for **131** (acetone-d6) and **132** (pyridine-d5).

As seen in Table 13, experimental results agree with the stereochemistry prediction in terms of H-4/H-5 vicinal coupling constant. In all cases, the *anti* cycloadducts showed $J_{4,5}$ values ranging between 1.0 and 2.2 Hz while the *syn* isomers showed values between 6.4 and 7.5 Hz. On the other hand, the C-1 chemical shift observed in the rearranged derivatives is displaced to lower fields than that of primary cycloadducts since the 1,3-acyl shift transforms this position into a quaternary center. Indeed, this effect is more remarkable in the hydroxymethyl derivatives (12-16 ppm) than in the trimethysilyl compounds (3-4 ppm).

Connectivity of the cyclobutene derivatives was determined with the help of HMQC and HMBC experiments. The latter is a useful experiment to determine the regiochemistry of the cycloadducts since correlation between H-4 and the vinylic carbon atom C-6 is observed (Figure 16). As an example, the assignments of the head-to-head cycloadduct **151** (Figure 17), the head-to-tail cycloadduct **143** (Figure 18) and the rearranged derivative **150** (Figure 19) are shown.

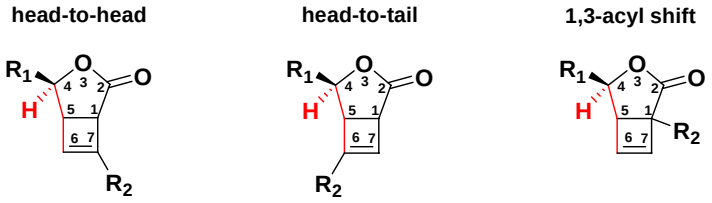


Figure 16. Determination of the regiochemistry of the cycloadducts on the basis of HMBC experiments.

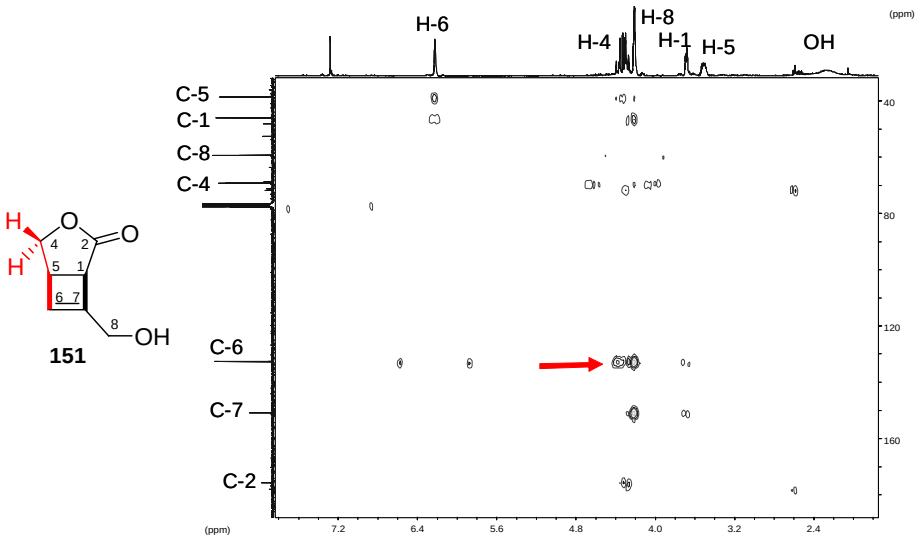


Figure 17. HMBC experiment of product **151** ($CDCl_3$, 250 MHz). Determination of the head-to-head regiochemistry.

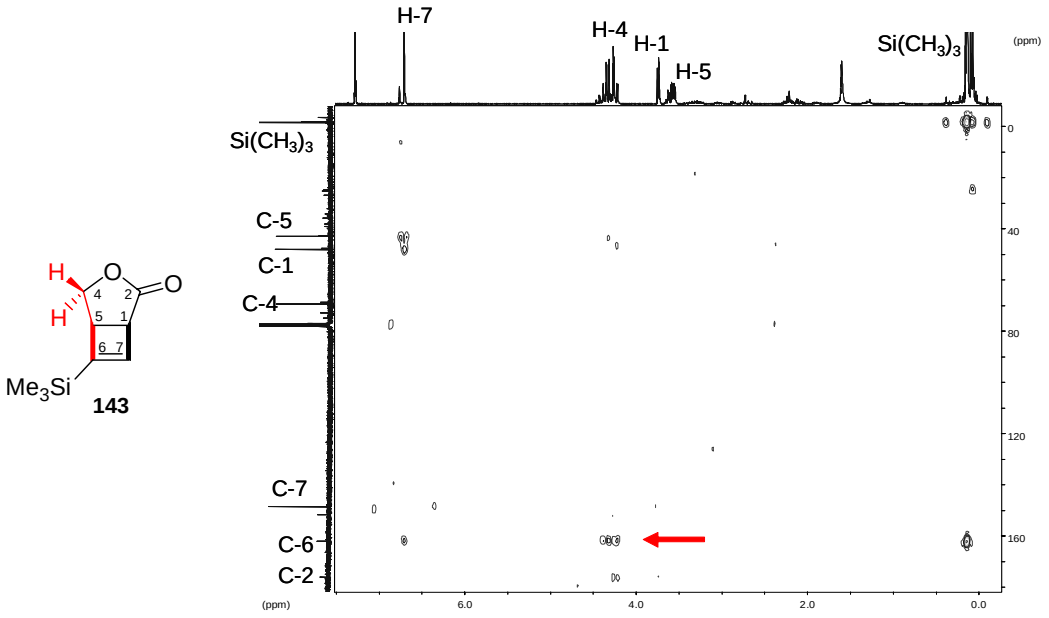


Figure 18. HMBC experiment of product **143** ($CDCl_3$, 250 MHz). Determination of the head-to-tail regiochemistry.

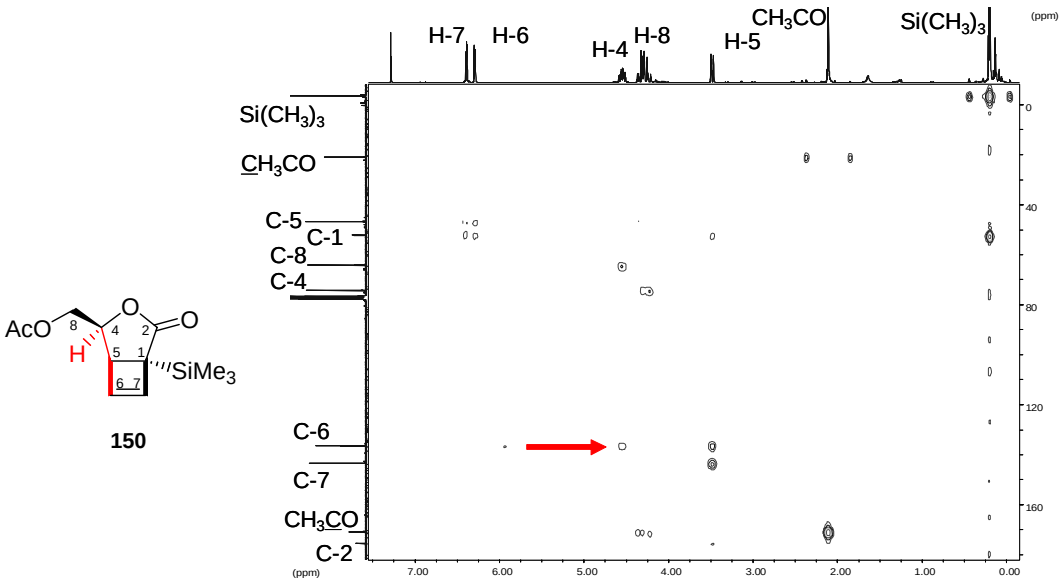
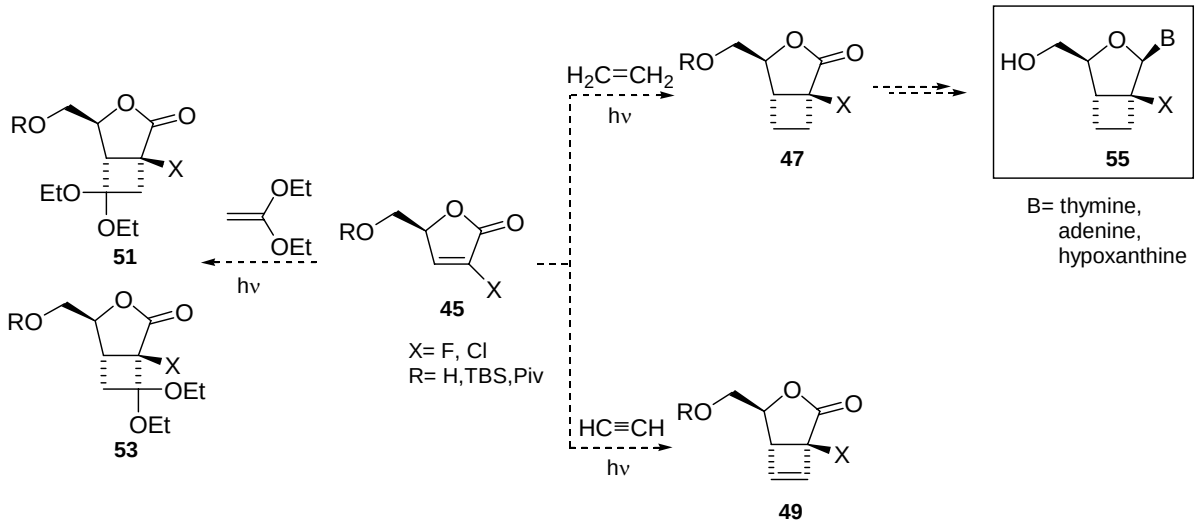


Figure 19. HMBC experiment of product **150** ($CDCl_3$, 250 MHz).

IV. Study of the [2+2] photocycloaddition of homochiral 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene, acetylene and ketene diethyl ketal.

Synthesis of 2'-chloro and 2'-fluoronucleosides conformationally restricted by a cyclobutane ring

The second goal of the present work is focused on developing a photochemical methodology to prepare diastereoselectively chloro and fluoro cyclobutane and cyclobutene derivatives. Therefore, the [2+2] photocycloaddition of the homochiral 3-fluoro and 3-chloro-2(5*H*)-furanones **45** to ethylene, acetylene and ketene diethyl ketal will be investigated with the aim of preparing the *anti* cycloadducts **47**, **49**, **51** and **53** (Scheme 38).



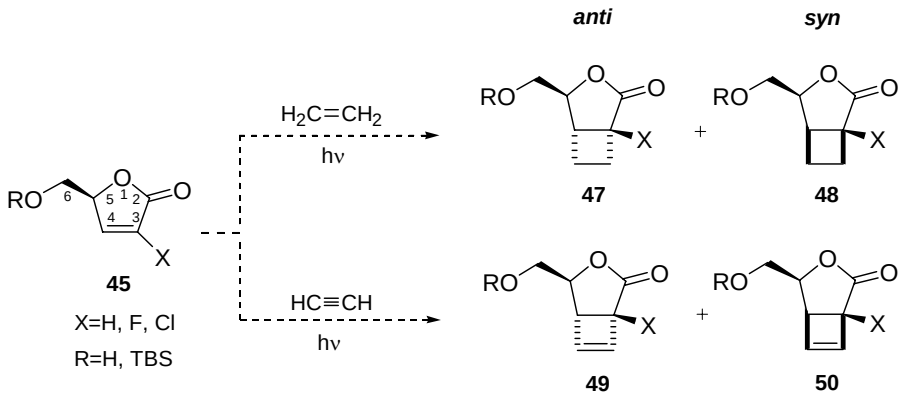
Scheme 38. Photochemical reactivity of 3-halo-2(5*H*)-furanones **45** with ethylene, acetylene and ketene diethyl ketal. Preparation of the cyclobutane-fused halonucleoside analogues **55**.

These novel *anti* bicyclic lactones are envisioned as potential precursors for the synthesis of new target halo-compounds such as the cyclobutane-fused chloro and fluoronucleoside analogues **55**.

To the best of our knowledge, photochemical reactions of 3-halo-2(5*H*)-furanones with unsaturated substrates have not been described.

1. [2+2] Photocycloaddition of 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene and acetylene

The first task was directed to study the [2+2] photocycloaddition reaction of 3-chloro and 3-fluoro-2(5*H*)-furanones **45** to ethylene and acetylene (Scheme 39). The effect of the halide substituent on the stereochemical outcome of the reaction has been established by comparison with the corresponding reactions with 3-dehalo-2(5*H*)-furanones.

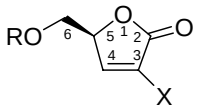


Scheme 39. [2+2] Photocycloaddition of 3-dehalo, 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene and acetylene.

All the photochemical reactions reported herein were conducted with a 125W high pressure mercury lamp (Cathodeon HPK125), cooling externally the reactor to -20 ºC and with a -15 ºC cooled MeOH flow through the reactor refrigeration jacket and with external introduction of ethylene or acetylene. Evolution of the reaction was controlled by gas chromatography (GC) and by TLC. Irradiation was stopped in function of by-products formation. Product characterization was accomplished by NMR techniques. Structural determination of the isolated compounds is discussed at the end of the present chapter.

1.1. Synthesis of 2(5*H*)-furanones

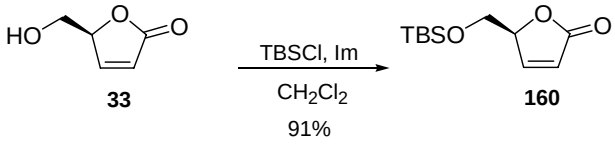
To accomplish the photochemical study with ethylene and acetylene, the 2(5*H*)-furanones **33** and **160-164** were synthesized (Figure 20). The *tert*-butyldimethylsilyl group (TBS) was selected as a bulky protecting group suitable for the subsequent synthetic strategy towards the preparation of cyclobutane chloro and fluoronucleoside analogues.



X=H	R=H	**33**
X=H	R=TBS	**160**
X=F	R=H	**161**
X=F	R=TBS	**162**
X=Cl	R=H	**163**
X=Cl	R=TBS	**164**

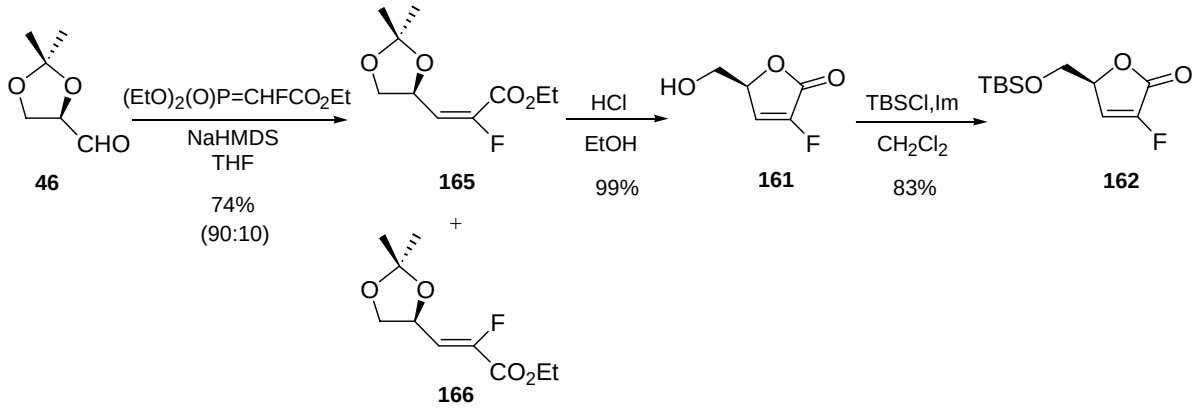
Figure 20. Different 3-dehalo-, 3-fluoro- and 3-chloro-2(5*H*)-furanones synthesized in the present chapter.

The synthesis of the silyl protected lactone **160** was easily achieved by treatment of **33** with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 in 91% yield, $[\alpha]_D$: -127.0 (*c* 4.8, $CHCl_3$) (Scheme 40).



Scheme 40. Synthesis of (-)-(5*S*)-5-*tert*-butyldimethylsilyloxymethyl-2(5*H*)-furanone, **160**.

The 3-fluoro-2(5*H*)-furanones **161** and **162** were synthesized following a previously described methodology (Scheme 41).[75,10f] These lactones are interesting building blocks due to the considerable attention received by fluorinated chiral molecules in biomedical, analytical and polymer sciences.[76]

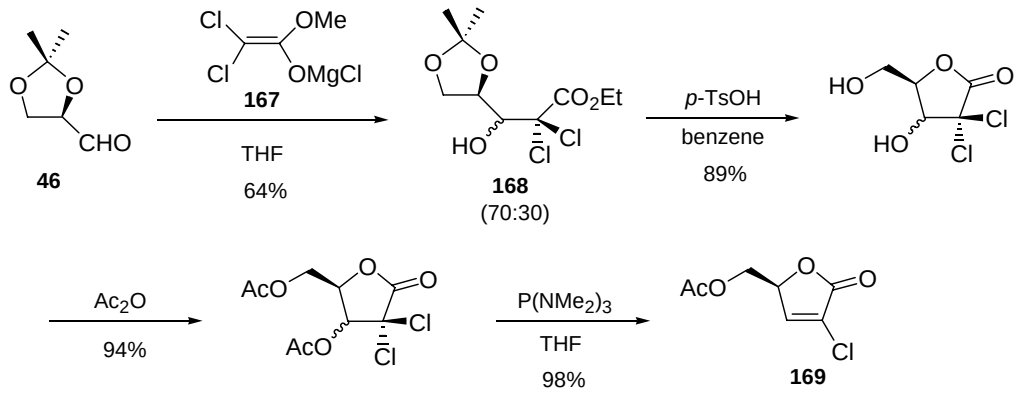


Scheme 41. Synthesis of 3-fluoro-2(5*H*)-furanones **161** and **162**.

[75] Patrick, T. B.; Lanahan, M. V.; Yang, C.; Walker, J. K.; Hutchinson, C. L.; Neal, B. E. *J. Org. Chem.* **1994**, *59*, 1210-1212.
[76] Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 241-231, and references cited therein.

The synthesis began with the reaction of the known D-glyceraldehyde acetonide **46** with triethyl 2-fluoro-2-phosphonoacetate and sodium hexamethyldisilylamide (NaHMDS) in dry THF at -78 ºC leading to a 90:10 mixture of (*E*)- and (*Z*)-alkenes **165** and **166** in 74% yield. Acid treatment of the major isomer **165** in EtOH afforded almost quantitatively the 3-fluoro-2(5*H*)-furanone **161** $[\alpha]_D$ -54.0 (*c* 1.0, $CHCl_3$). Finally, reaction of **161** with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2, gave the silyl protected lactone **162** in 83% yield $[\alpha]_D$ -104.3 (*c* 0.60, $CHCl_3$) (literature $[\alpha]_D$ -105.9 (*c* 0.5, $CHCl_3$))[10f], mp: 48-50 ºC.

The unique synthesis reported so far of a compound possessing the desired 3-chloro-2(5*H*)-furanone skeleton was described by Chapleur and co-workers in 1982 (Scheme 42).[77]



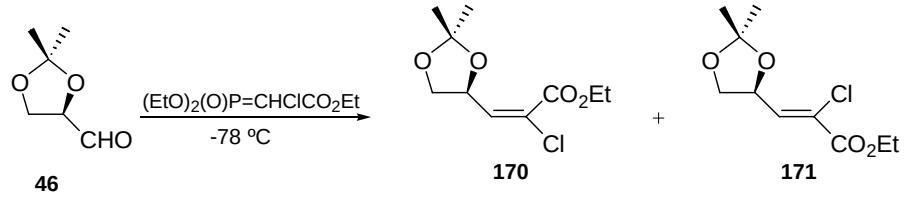
Scheme 42. Synthesis of the 5-acetyloxymethyl-3-chloro-2(5*H*)-furanone, **169**, Chapleur and co-workers (1982).

The key step of this synthesis was the condensation of aldehyde **46** with the magnesium dichloroenolate **167** which afforded the alcohol **168** as a 70:30 diastereomeric mixture in 64% yield. Subsequent lactonization, standard acetylation and elimination with tris(dimethylamino)phosphine furnished the 3-chloro-2(5*H*)-furanone **169**, (54% global yield from **46**).

Our approach to the previously unknown 3-chloro-2(5*H*)-furanones **163** and **164** followed a similar approximation to that used to prepare the fluoro-lactones **161** and **162**. Nevertheless, the Horner-Emmons reaction of aldehyde **46** with triethyl-2-chloro-2-phosponoacetate and NaHMDS in dry THF afforded the olefins **170** and **171** in 59% yield and with a poor *E*/*Z* selectivity (60:40) (Table 14, entry 1). The yield was increased when the reaction was carried out in the presence of LiCl albeit with the same selectivity (entry

[77] Rague, B.; Chapleur, Y.; Castro, B. *J. Chem. Soc. Perkin Trans 1* **1982**, 2063-2066.

2). A significant improvement of the selectivity, 86:14, was found when buthyl lithium was used as a base (entry 3). In order to optimize the reaction conditions, several experimental modifications, including variation of the solvent and the number of equivalents of each reagent, were investigated without improving the latter results in terms of combination of yield and *E*/*Z* selectivity (entries 4-6).



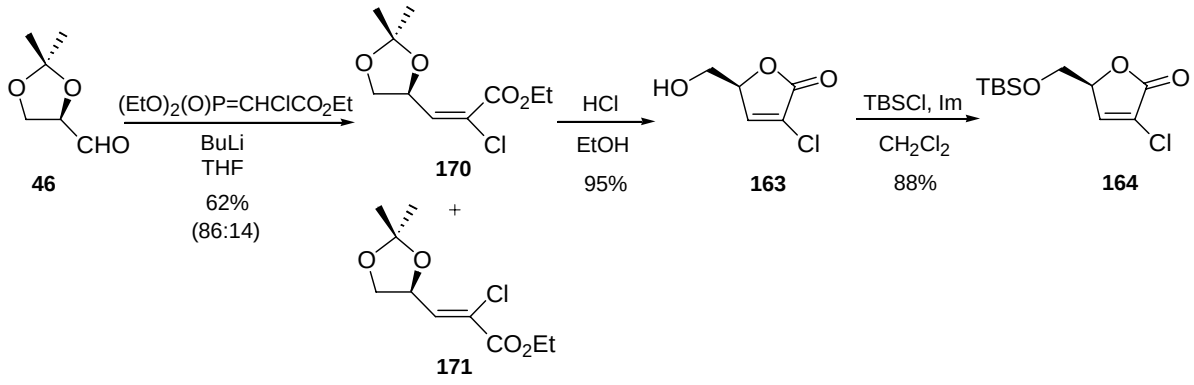
46 **170** **171**

entry	solvent	base (equiv)	phosphonate (equiv)	yield (%)	170:171 [a]
1	THF	NaHMDS (1.0 equiv)	1.0 equiv	59	60:40
2	THF	NaHMDS (1.3 equiv) [b]	1.3 equiv	71	60:40
3	THF	BuLi (1.3 equiv)	1.3 equiv	62	86:14
4	THF	BuLi (1.3 equiv)	1.0 equiv	50	88:12
5	THF	BuLi (1.0 equiv)	1.3 equiv	51	85:15
6	toluene	BuLi (1.3 equiv)	1.3 equiv	40	64:36

[a] Product ratio determined by GC and ^{1}H-NMR. [b] 1.3 equiv of LiCl were added.

Table 14. Horner-Emmons reaction of aldehyde **46** and triethyl-2-chloro-2-phosponoacetate.

The major isomer **170** was treated with HCl in EtOH to deliver the 3-chloro-2(5*H*)-furanone **163** in 95% yield (Scheme 43). The silyl protected 2(5*H*)-furanone **164** was prepared in 88% yield by reaction of **163** with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2, $[\alpha]_D$ -96.4 (*c* 0.56, $CHCl_3$), mp: 48-50 ºC.

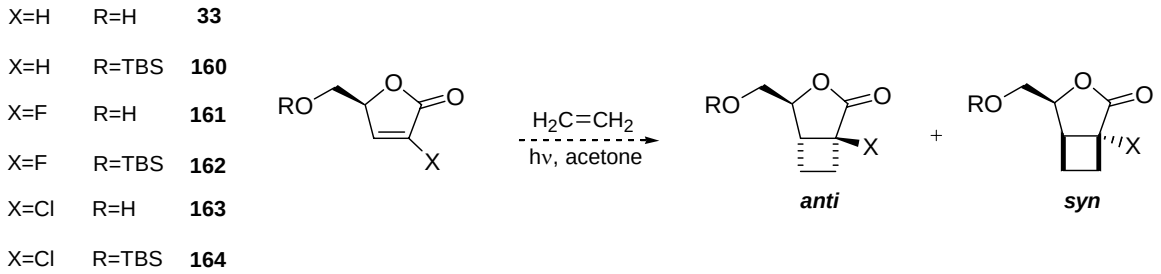


46 **170** **163** **164** **171**

Scheme 43. Synthesis of 3-chloro-2(5*H*)-furanones **163** and **164**.

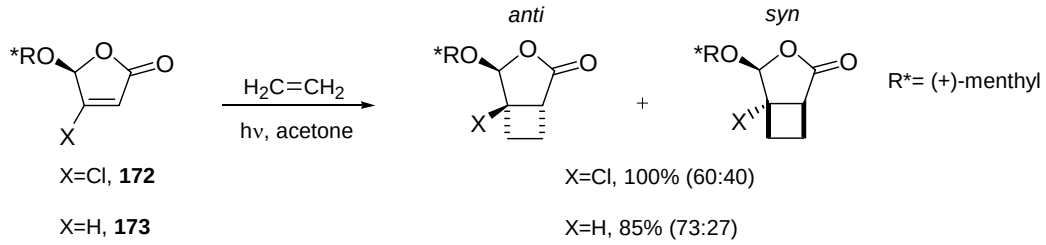
1.2. Photocycloaddition of 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene

With 3-dehalo, 3-fluoro and 3-chloro-2(5*H*)-furanones **33** and **160-164** in our hands, their [2+2] photocycloaddition reaction to ethylene was studied (Scheme 44).



Scheme 44. Study of the [2+2] photocycloaddition of 3-dehalo, 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene.

In 1996, the [2+2] photocycloaddition of the chiral 4-chloro-2(5*H*)-furanone **172** to ethylene was described by Scharf and Curtius (Scheme 45).[78]



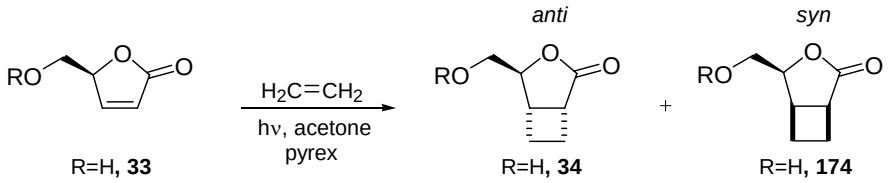
Scheme 45. [2+2] Photocycloaddition of chiral 2(5*H*)-furanones to ethylene, Scharf and Curtius, (1996).

At -70 ºC this reaction proceeded in quantitative yield although with a low *anti*:*syn* ratio (60:40). Few years before, the same authors had described that the photochemical reaction of the 4-dehalo-lactone **173** with ethylene at -75 ºC took place in 85% yield and a 73:27 diastereomeric ratio.[79] According to the authors, the reaction with **172** was faster due to the intersystem crossing acceleration caused by the chlorine atom.

[78] Curtius, F. W.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 2957-2961.
[79] Hoffmann, N.; Scharf, H.-D.; Runsink, J. *Tetrahedron Lett.* **1989**, *30*, 2637-2638.

1.2.1. [2+2] Photocycloaddition of 2(5*H*)-furanones 33 and 160 to ethylene

Initially, the photoreaction of 3-dehalo-2(5*H*)-furanones **33** and **160** to ethylene was investigated (Table 15).



R=H, **33** R=TBS, **160** | R=H, **34** R=TBS, **175** | R=H, **174** R=TBS, **176**

entry	R	lactone	time	global yield (%)	*anti*:*syn* (%)[a]
1	H	**33**	5.5 h	66	66:34
2	TBS	**160**	3.5 h	31	73:27

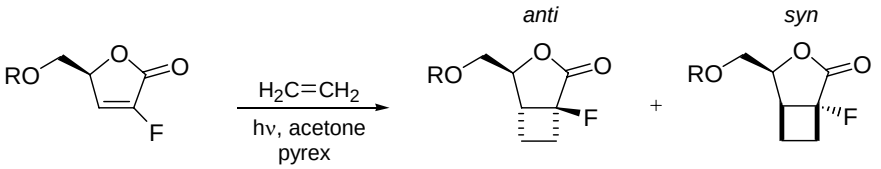
[a] Product ratio determined by GC and ^{1}H-NMR.

Table 15. [2+2] Photocycloaddition of 2(5*H*)-furanones to ethylene.

Irradiation through a pyrex filter of an ethylene saturated acetone solution of 2(5*H*)-furanone **33** afforded a 66:34 mixture of the *anti*:*syn* isomers **34** and **174** in 66% yield (Table 15, entry 1). The separation of the major component of the mixture was achieved by column chromatography.

The reaction of the silyl protected furanone **160** (entry 2) afforded a mixture of the expected cycloadducts **175** and **176** in low yield (31%) although in better selectivity (73:27). Partial decomposition of the starting material was observed. Repetitive column chromatography allowed to obtain pure **175** and an enriched fraction of **176**.

1.2.2. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanones 161 and 162 to ethylene



R=H, **161** R=H, **177** R=H, **178**

R=TBS, **162** R=TBS, **179** R=TBS, **180**

entry	R	lactone	time	global yield (%)	*anti*:*syn* (%)[a]
1	H	**161**	3.5 h	75	81:19
2	TBS	**162**	2.2 h	84	91:9

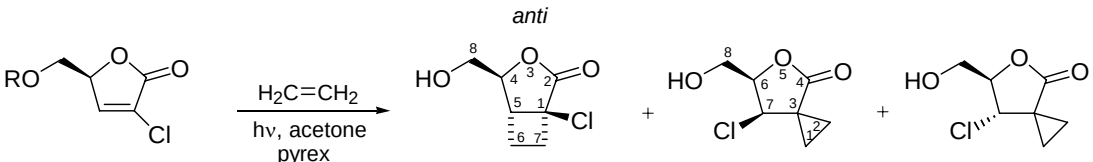
[a] Product ratio determined by GC and ^{1}H-NMR.

Table 16. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanones to ethylene.

Irradiation through a pyrex filter of an ethylene saturated acetone solution of 2(5*H*)-furanone **161** afforded a chromatographically separable 81:19 mixture of the *anti*:*syn* isomers **177** and **178** in 75% yield (Table 16, entry 1).

The reaction of the silyl protected furanone **162** (entry 2) took place faster and in better yield (84%) and facial diastereoselectivity (91:9). The separation of the isomers **179** and **180** was easily accomplished by column chromatography.

1.2.3. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanones 163 and 164 to ethylene



R=H, **163** **181** **182** **183**

R=TBS, **164**

entry	R	lactone	time	global yield (%)	181:182:183 (%)[a]
1	H	**163**	4.5 h	83	61:19:20
2	TBS	**164**	2 h	85	78:7:15

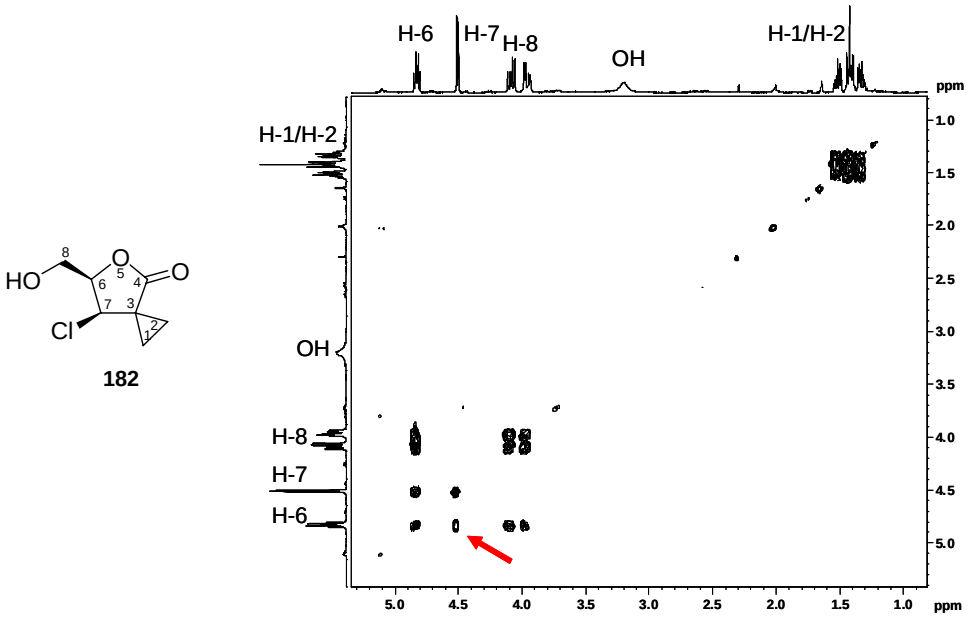
[a] Product ratio determined by ^{1}H-NMR.

Table 17. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanones to ethylene.

Irradiation through a pyrex filter of an ethylene saturated acetone solution of chloro-lactone **163** afforded, after purification by column chromatography, a 61:19:20 mixture of three isomeric compounds in 83% global yield (Table 17, entry 1). Further purification by column chromatography allowed the separation of all three products which were identified as the desired *anti* cycloadduct **181** and the two spiro-cyclopropane lactones **182** and **183**, being **181** the major component of the mixture. No presence of the expected *syn* cycloadduct was observed.

When the reaction was performed with the silyl-protected furanone **164** (entry 2) a 78:7:15 mixture of the above products **181-183** was obtained in 85% overall yield after purification by column chromatography indicating that the silyl moiety is cleaved in the purification process. Again, no presence of the *syn* cycloadduct could be observed.

The determination of the structure of the by-products **182** and **183** was accomplished on the basis of their ^{1}H and ^{13}C-NMR spectra and with the help of bidimensional experiments. Thus, the COSY experiment of **182** reveals two independent sets of signals: the first, containing 4 cyclopropane protons (H-1 and H-2), between 1.3 and 1.6 ppm, and the second, containing 4 protons (H-6, H-7 and H-8) including one doublet, identified as H-7, at 4.5 ppm which is coupled with H-6 (Figure 21).



182

Figure 21. COSY experiment of derivative **182** ($CDCl_3$, 360 MHz).

The HMQC experiment shows the presence of a quaternary carbon atom at 28.6 ppm which is assigned as C-3 (Figure 22). On the other hand, the HMBC shows correlation

between H-7 and C-1, C-2, C-3 and C-6. The high chemical shift of C-7 (62.8 ppm) makes it suitable to be directly bonded to the chlorine atom.

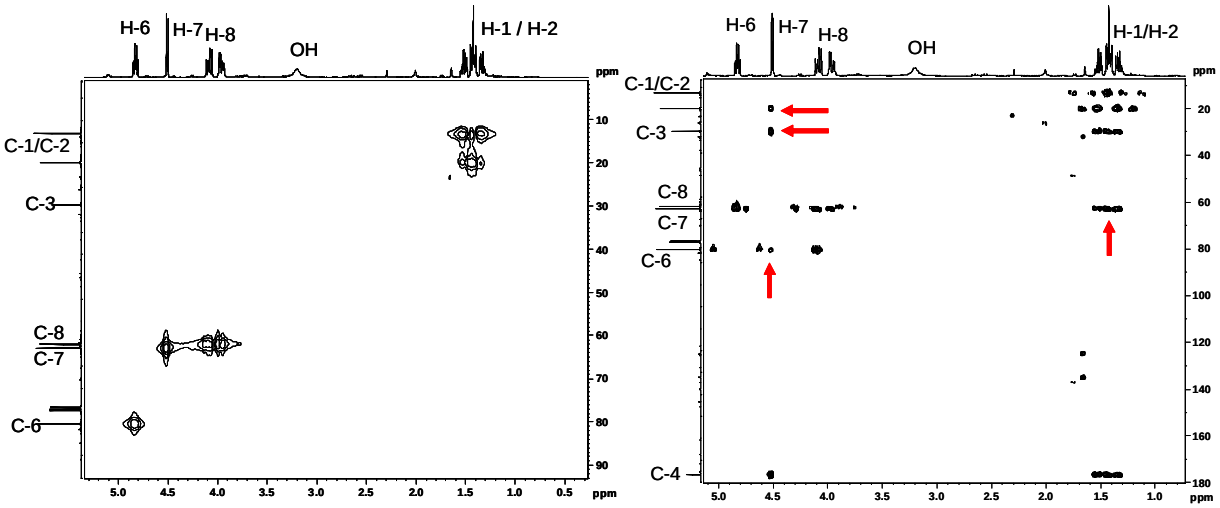


Figure 22. HMQC and HMBC experiments of derivative **182** ($CDCl_3$, 360 MHz).

Once the structure of the epimeric spirocyclopropane derivative **183** was determined following the same procedure described for **182**, the stereochemistry of the newly formed chiral center C-7 was investigated. A value of $J_{6,7}$=5.0 Hz is observed for **182** indicating a *cis* disposition between H-6 and H-7 whereas a lower value ($J_{6,7}$=3.3 Hz) is observed for **183**, indicating a *trans* relationship. These assignments were further confirmed with NOESY experiments which showed cross-peak between H-6 and H-7 for **182** (Figure 23) and between H-7 and both H-8 for its epimer **183** (Figure 24).

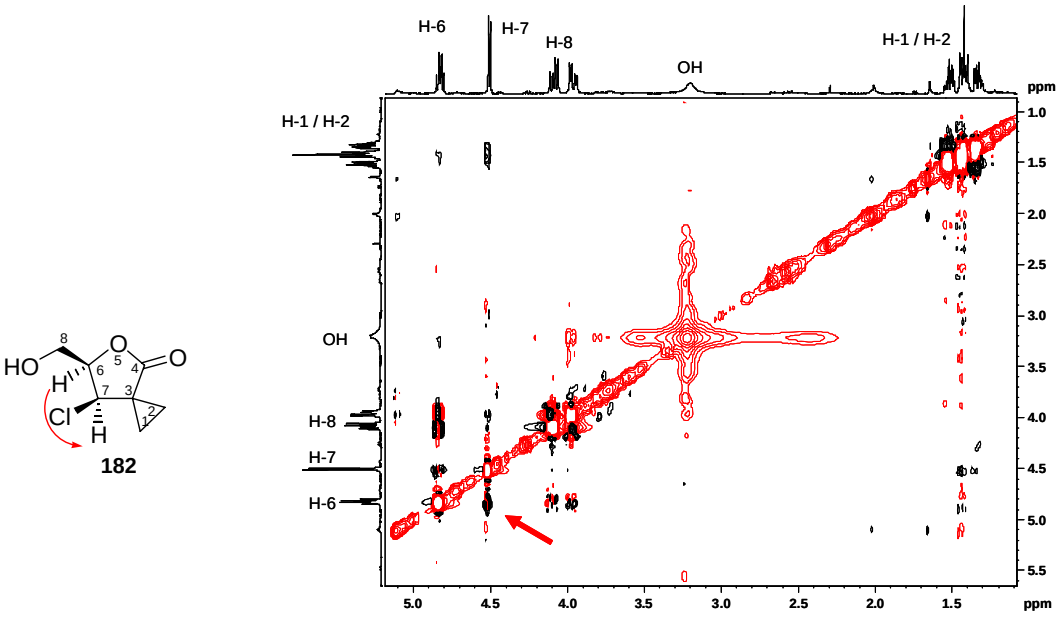


Figure 23. NOESY experiment of derivative **182** ($CDCl_3$, 360 MHz).

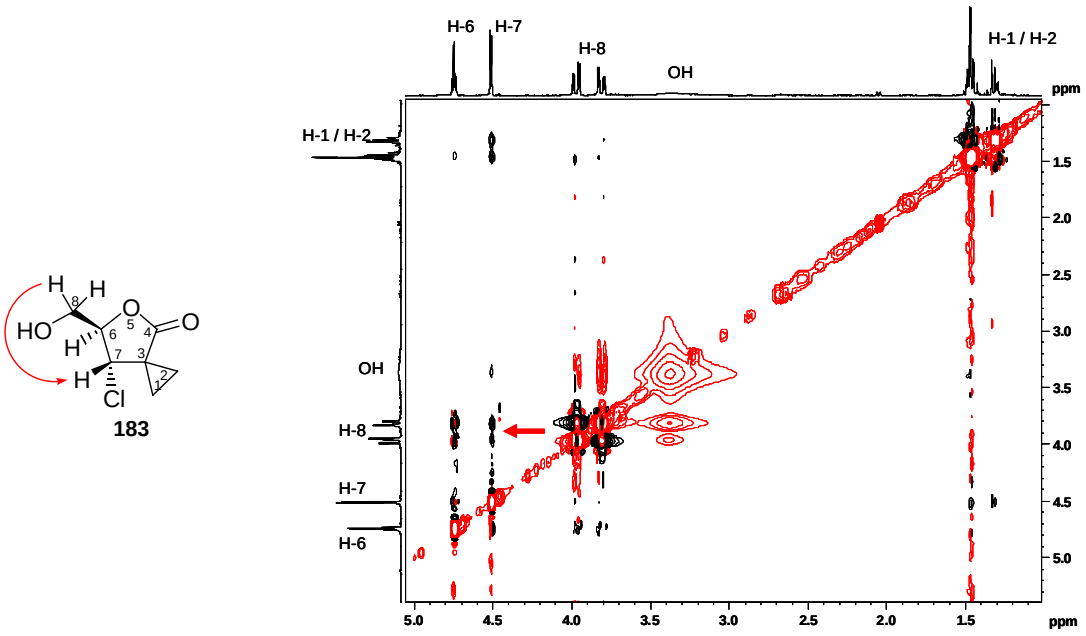
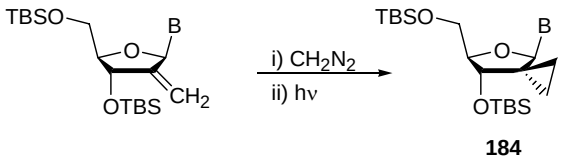


Figure 24. NOESY experiment of derivative **183** ($CDCl_3$, 360 MHz).

Furanose building blocks containing an exocyclic olefin were used by Samano and Robins in the preparation of a family of 2'-spirocyclopropyl nucleoside analogues **184** (Scheme 46).[80] Therefore, the synthesis of **182** and **183** in the present work opens the door for a future preparation of different novel compounds bearing this complex structure.



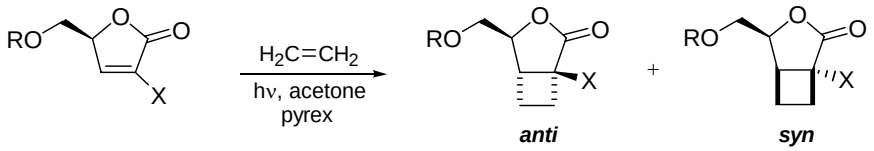
Scheme 46. Synthesis of 2'-spirocyclopropyl nucleoside analogues **184**, Samano and Robins (1992).

1.2.4. Effect of the vinylic halide on the [2+2] photocycloaddition of 2(5*H*)-furanones to ethylene

The formation of spirocyclopropane by-products and the absence of the expected *syn* cycloadduct in the photochemical reactions of 3-chlorolactones **163** and **164** with ethylene, make the comparison of these results with the other 3-dehalo and 3-fluorolactones difficult. Taking into account these latter lactones, it can be seen that the presence of a fluorine atom in the α-position of 2(5*H*)-furanones **161** and **162** increases the yield and also

[80] Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007-4008.

gives better facial diastereoselectivity compared to the results obtained for lactones **33** and **160** (Table 18).

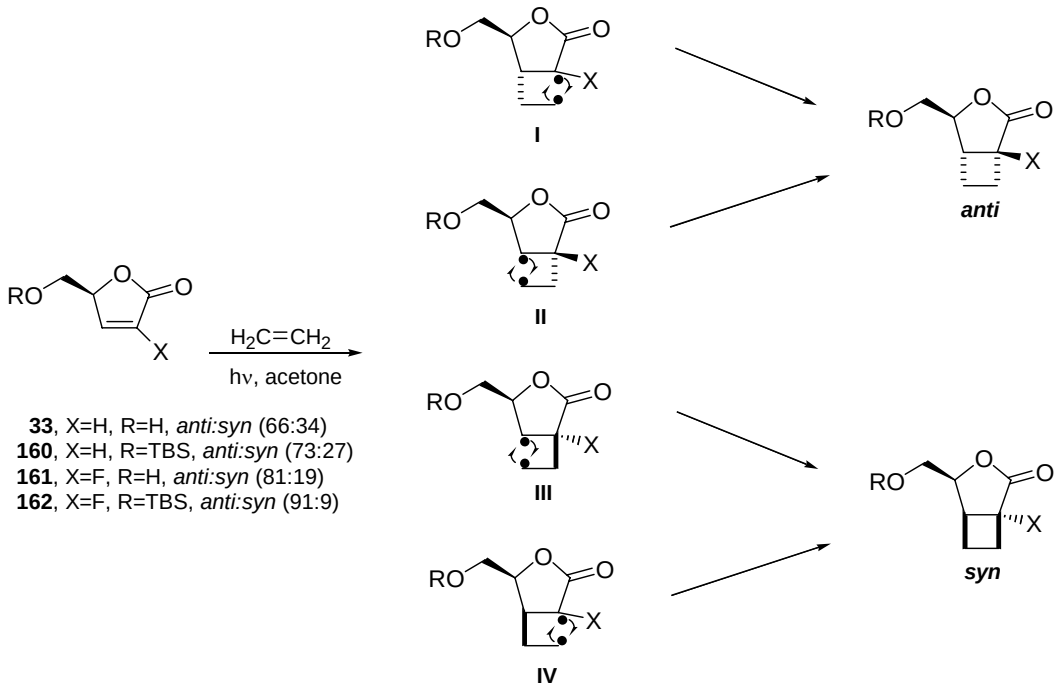


entry	X	R	lactone	yield (%)	*anti*:*syn* (%)
1	H	H	**33**	66	66:34
2	H	TBS	**160**	31	73:27
3	F	H	**161**	75	81:19
4	F	TBS	**162**	84	91:9

Table 18. [2+2] Photocycloaddition of differently substituted 2(5*H*)-furanones to ethylene.

Considering the proposed mechanism of the [2+2] photocycloaddition of enones to alkenes, the photoreactions studied in the present work may lead to four possible isomeric 1,4-biradical intermediates: **I** and **II** which give rise to the *anti* isomer, and **III** and **IV** which lead to the *syn* isomer (Scheme 47). The enhancement of the formation of the *anti* isomers for fluorolactones **161** and **162**, may be inferred to the presence of the fluorine atom which stabilizes the biradicals **I** and **IV** and at the same time difficults the formation of the biradicals **II** and **III**.[81] Moreover, the steric effect of the substituent directs the approach of ethylene through the less hindered face of the lactone delivering preferentially the biradical intermediate **I** over the biradical **IV**. Theoretic calculations are planned to be performed to get a deeper insight of the mechanistic pathway of this reaction.

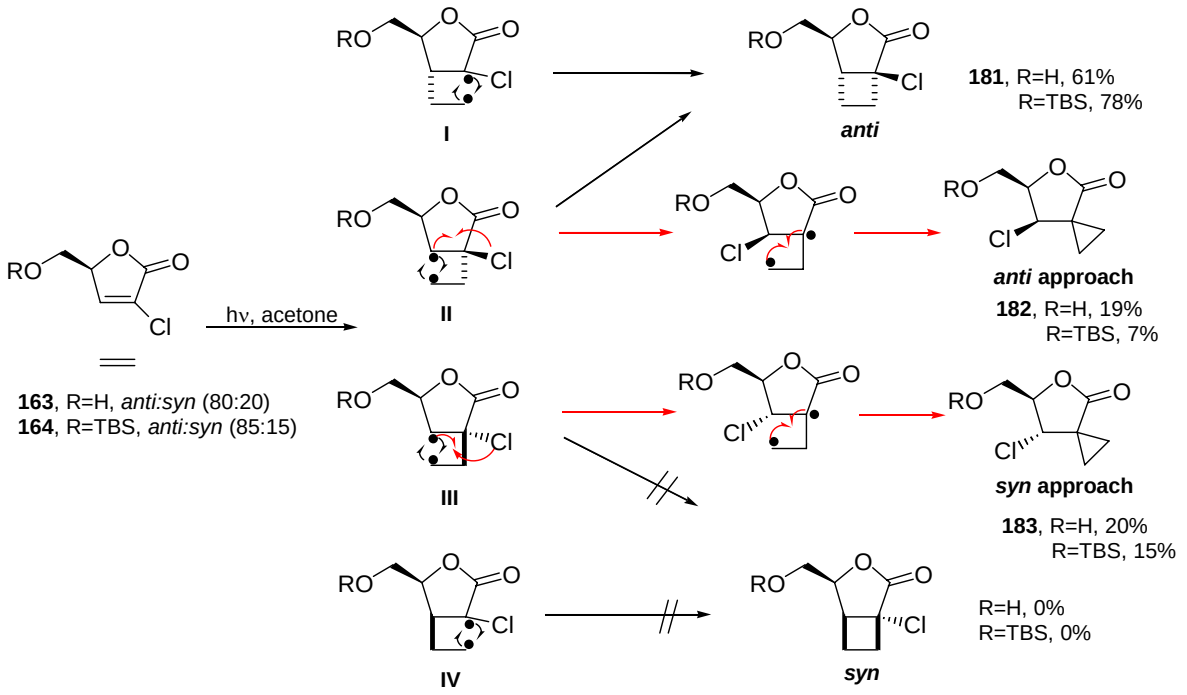
[81] Greenlee, M. L.; Fritzen Jr., E. L.; Swenton, J. S. *J. Org. Chem.* **1978**, *43*, 4512-4515.



33, X=H, R=H, *anti:syn* (66:34)
160, X=H, R=TBS, *anti:syn* (73:27)
161, X=F, R=H, *anti:syn* (81:19)
162, X=F, R=TBS, *anti:syn* (91:9)

Scheme 47. Proposed 1,4-biradical intermediates for the [2+2] photocycloaddition of 2(5*H*)-furanones to ethylene.

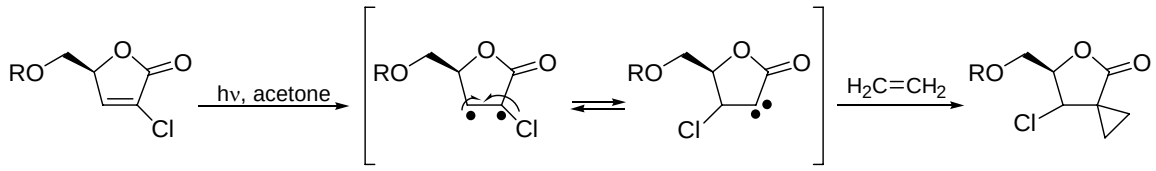
A similar mechanistic approach is useful to rationalize the results obtained in the photoreaction of 3-chloro-2(5*H*)-furanones **163** and **164** where the unprecedented formation of the spirocyclopropyl derivatives **182** and **183** was observed (Scheme 48). Again, four possible 1,4-biradical intermediates **I**-**IV** can be formed, leading **I** and **II** to the *anti* cycloadduct and **III** and **IV** to the *syn* isomer. However, the biradicalary species **II** and **III** may evolve through a competitive mechanism involving the rearrangement of the chlorine atom to furnish a spirocyclopropyl lactone structure. As previously discussed, the final products ratio would be governed by the tendency of each biradical to undergo coupling, rearrangement or reversion to the starting materials. In this occasion, it is noteworthy to mention that the formation of the *syn* cycloadduct is completely disfavoured in front of the other processes.



Scheme 48. Proposed mechanism for the photoreaction of 3-chloro-2(5*H*)-furanones with ethylene.

Moreover, if it is assumed that the chlorine atom of the biradicals **II** and **III** undergoes the rearrangement keeping the stereochemistry adopted in the approach of the alkene to the lactone, it is possible to estimate the facial diastereoselectivity of the reaction of 3-chloro-2(5*H*)-furanones to ethylene. Thus, the rearranged product **182**, derived from the intermediate **II**, would come from an *anti* approach whereas the cyclopropane **183,** derived from the intermediate **III**, would come from a *syn* approach. Accordingly, the facial diastereoselectivity of the reaction becomes 80:20 for **163** (R=H) and 85:15 for **164** (R=TBS). These results are similar to those obtained with fluorolactones.

A second mechanistic hypothesis can be postulated for the formation of the by-products **182** and **183** (Scheme 49). According to this proposal, chlorine rearrangement would take place in the excited triplet state of the lactone leading to the formation of a carbene at the α-position of the carbonyl. In a second step, this carbene would react with ethylene to yield the cyclopropane derivatives. Nevertheless, there are several drawbacks for this alternative mechanism; the low yield of the by-products **182** and **183** compared to the *anti* cycloadduct **181** and also the presence of the starting α,β-unsaturated lactone in the reaction mixture after more than 3 h of irradiation.

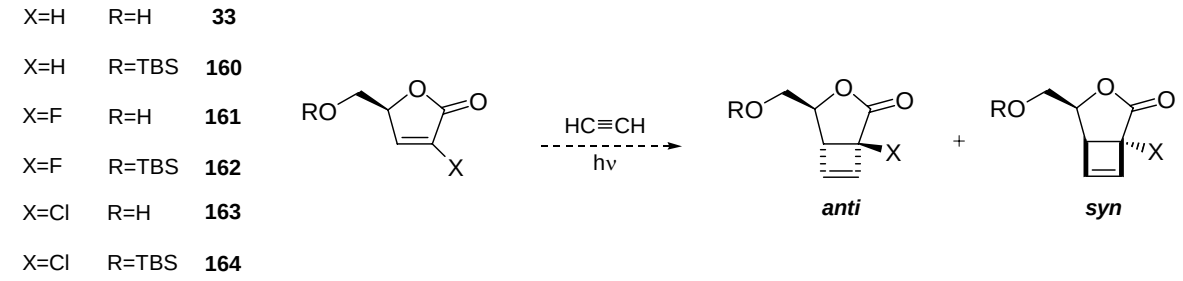


Scheme 49. Alternative mechanism postulated for the formation of spirocyclopropyl derivatives in the photoreaction of chloro-lactones to ethylene.

As a summary, despite the presence of by-products in the photoreaction of chlorolactones, high yields and facial diastereoselectivity values are obtained in the [2+2] photocycloaddition of both silyl-protected 3-chloro and 3-fluoro-2(5*H*)-furanones to ethylene. The preparation of the desired *anti* cycloadducts **179** and **181** was achieved in 76% and 66% yield, respectively. The facile separation of the diastereomers and the possibility of increasing the scale of the processes up to 500 mg without significant decrease of the yield, allows the application of these reactions into the designed synthetic strategy towards the preparation of cyclobutane analogues of chloro and fluoronucleosides.

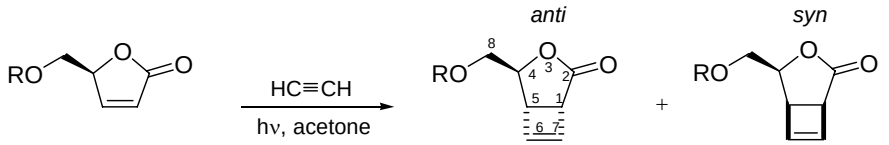
1.3. Photocycloaddition of 3-chloro and 3-fluoro-2(5*H*)-furanones to acetylene

Next, the [2+2] photocycloaddition of 3-dehalo, 3-chloro and 3-fluoro-2(5*H*)-furanones to acetylene was investigated (Scheme 50). No precedents of photochemical reaction of 2 or 3-halo-2(5*H*)-furanones with acetylene were found in the literature.



Scheme 50. Study of the [2+2] photocycloaddition of 3-dehalo, 3-chloro and 3-fluoro-2(5*H*)-furanones to acetylene.

1.3.1. [2+2] Photocycloaddition of 2(5*H*)-furanones 33 and 160 to acetylene



R=H, **33** R=H, **36** R=H, **185**

R=TBS, **160** R=TBS, **186** R=TBS, **187**

entry	R	lactone	filter	solvent	time	yield (%)	*anti*:*syn* (%) [b]
1	H	**33**	pyrex	acetone	5.25 h	44 (53)[a]	65:35
2	TBS	**160**	pyrex	acetone	5.5 h	21 (27)[a]	76:24

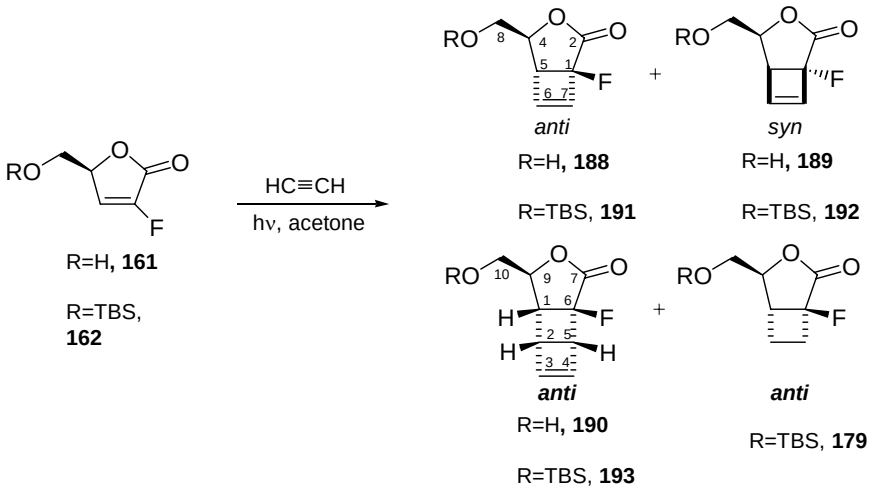
[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR.

Table 19. [2+2] Photocycloaddition of 2(5*H*)-furanones to acetylene.

Irradiation through a pyrex filter of a solution of 2(5*H*)-furanone **33** in acetone saturated with acetylene afforded a 65:35 mixture of the *anti* and *syn* isomers **36** and **185** in 44% yield along with starting material (18%) (Table 19, entry 1). The separation of the major component of the mixture was achieved by column chromatography.

The photoreaction of the silyl protected furanone **160** afforded the expected cycloadducts **186** and **187** in lower yield (21%) albeit in higher facial diastereoselectivity (76:24) (entry 2). Although 22% of the starting material was recovered, partial decomposition of **160** was observed. Repetitive column chromatography allowed the isolation of the *anti* cyclobutene **186**. In both cases, the irradiation was stopped due to the presence of by-products.

1.3.2. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanones 161 and 162 to acetylene



entry	R	lactone	filter	solvent	time	yield (%)	product ratio (%) [b]	*anti*:*syn* (%) [c]
1	H	**161**	pyrex	acetone	5.5 h	**188+189** (28) (42)[a] **190** (15) (23)[a]	**188:189:190** 59:3:38	97 : 3
2	TBS	**162**	pyrex	acetone	5 h	**191**+**192** (27) **193** (12) **179** (11)	**191:192:193:179** 40:11:24:21	89 : 11
3	TBS	**162**	quartz	acetonitrile	2 h	**191**+**192** (9)	**191:192** 95:5	95 : 5

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration.

Table 20. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanones to acetylene.

Irradiation through a pyrex filter of a solution of 3-fluoro-2(5*H*)-furanone **161** in acetone saturated with acetylene furnished a 59:3:38 mixture of 3 compounds (Table 20, entry 1). The reaction was stopped before the complete consumption of the starting material due to the appearance of multiple peaks in the reaction controls by GC. Purification by column chromatography of the reaction crude allowed the isolation of the following fractions; i) a 95:5 mixture of the *anti* and *syn* cycloadducts **188** and **189** in 28% yield; ii) another cyclobutene derivative, identified as the tricyclic lactone compound **190** (15% yield), and iii) recovered starting material (33%). Further column chromatography of the first fraction afforded a pure sample of the *anti* cycloadduct **188** but the isolation of the minor isomer **189** could not be achieved and enriched fractions had to be analyzed.

According to the assignment of the stereochemistry of the derivative **190** as *anti-endo*, it could be assumed that it was formed from a further photocycloaddition of the primary *anti* cycloadduct **188** to acetylene. Thus, the percentages of both compounds can be added to obtain an estimative 97:3 *anti*:*syn* ratio. However, this result is an approximation since yields are low and degradation of both *anti* and *syn* cycloadducts may occur during the reaction.

Next, an acetylene saturated solution of acetone containing the silylated lactone **162** was irradiated during 5 h to afford a 40:11:24:21 mixture of the *anti* and *syn* cyclobutenes **191** and **192**, the tricyclic derivative **193** and the previously described cyclobutane derivative **179** (entry 2). Again, the reaction was stopped due to the presence of a large amount of by-products. Purification of the reaction crude afforded the following fractions: i) a 80:20 mixture of the cycloadducts **191** and **192** in 27% yield; ii) the cyclobutene **193** in 12% yield; iii) the *anti* cyclobutane derivative **179** in 11% yield, and iv) recovered starting material (6%). Repetitive column chromatography of the first fraction afforded pure **191** whereas **192** could not be isolated and enriched fractions had to be analyzed.

Considering the cyclobutene **193** and the cyclobutane **179**, the estimated *anti*:*syn* ratio of the reaction is 89:11. However, the real facial discrimination of the reaction may be masked again by the presence of side reactions.

Finally, the irradiation of **162** was also performed through a quartz filter in an acetonitrile solution saturated with acetylene (entry 3). Although a much faster consumption of the starting material was observed, GC controls of the reaction showed an even more complex reaction crude than in the previous experiments and only a 95:5 mixture of the cycloadducts **191** and **192** could be isolated from the crude in 9% yield. Furthermore, lactone **162** showed partial degradation under these irradiation conditions.

The structure of the tricycle derivatives **190** and **193** was elucidated by NMR spectroscopy. In the HMQC experiment of **190** (Figure 25) it can be observed two additional allylic CH units, C-2 and C-5.

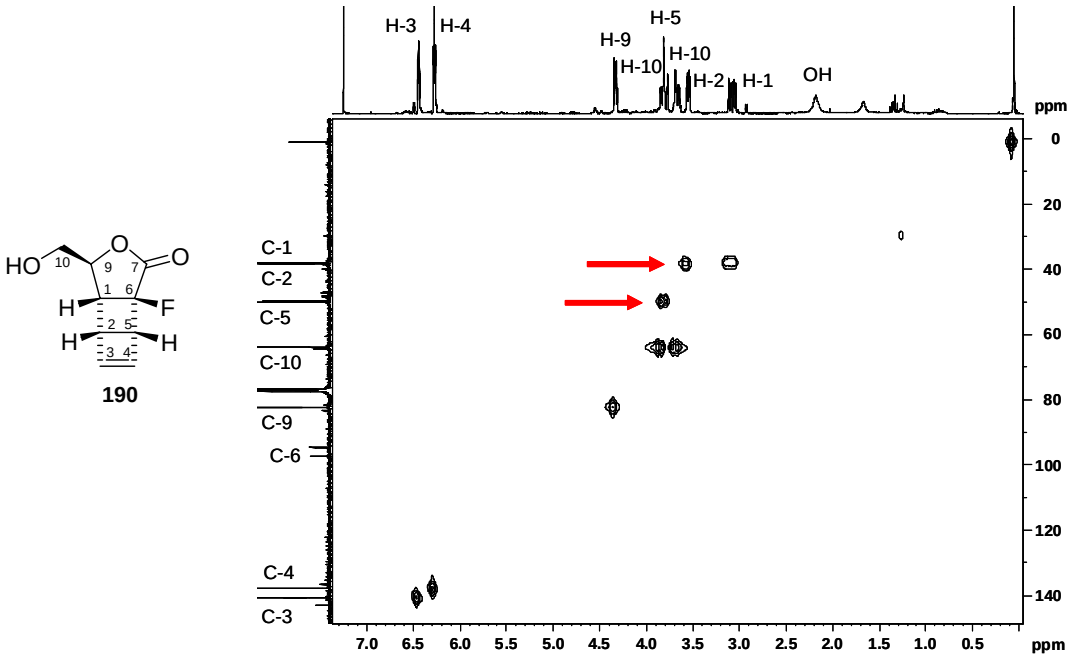


Figure 25. HMQC experiment of derivative **190** ($CDCl_3$, 360 MHz).

The HMBC spectrum of **190** helped to determine the connectivity of the C2-C4 fragment of the molecule (Figure 26). Moreover, the cross-peak between C-3 and H-1 allowed the discrimination of the olefinic signals.

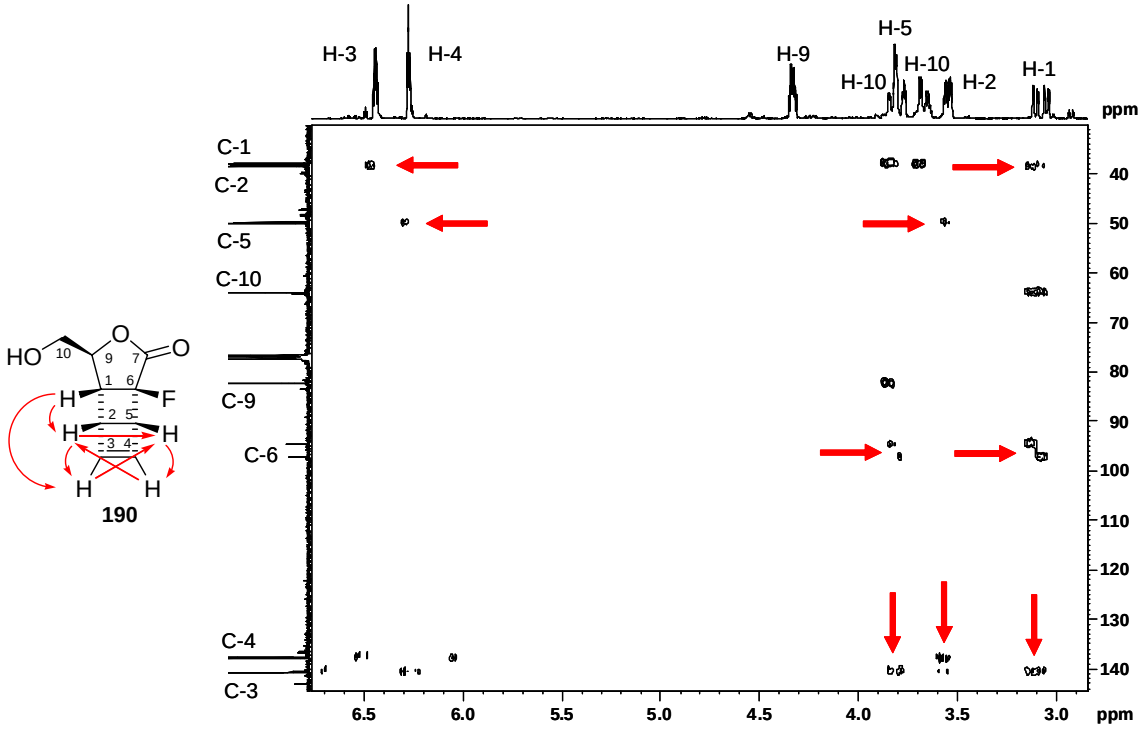


Figure 26. HMBC experiment of derivative **190** ($CDCl_3$, 360 MHz).

Finally, the stereochemistry of **190** was determined on the basis of the NOESY experiment (Figure 27). The cross-peak observed between H-3 and H-9 indicates an *anti-endo* configuration. This assignment is further confirmed by the correlation between H-1 and H-2 and H-1 and H-10. Furthermore, the observed $J_{1,9}$=1.5 Hz and $J_{1,2}$=8.0 Hz also corroborate these assignments. Similarly, a $J_{1,9}$~0 Hz and a $J_{1,2}$=7.9 Hz are observed for the silyl protected compound **193**.

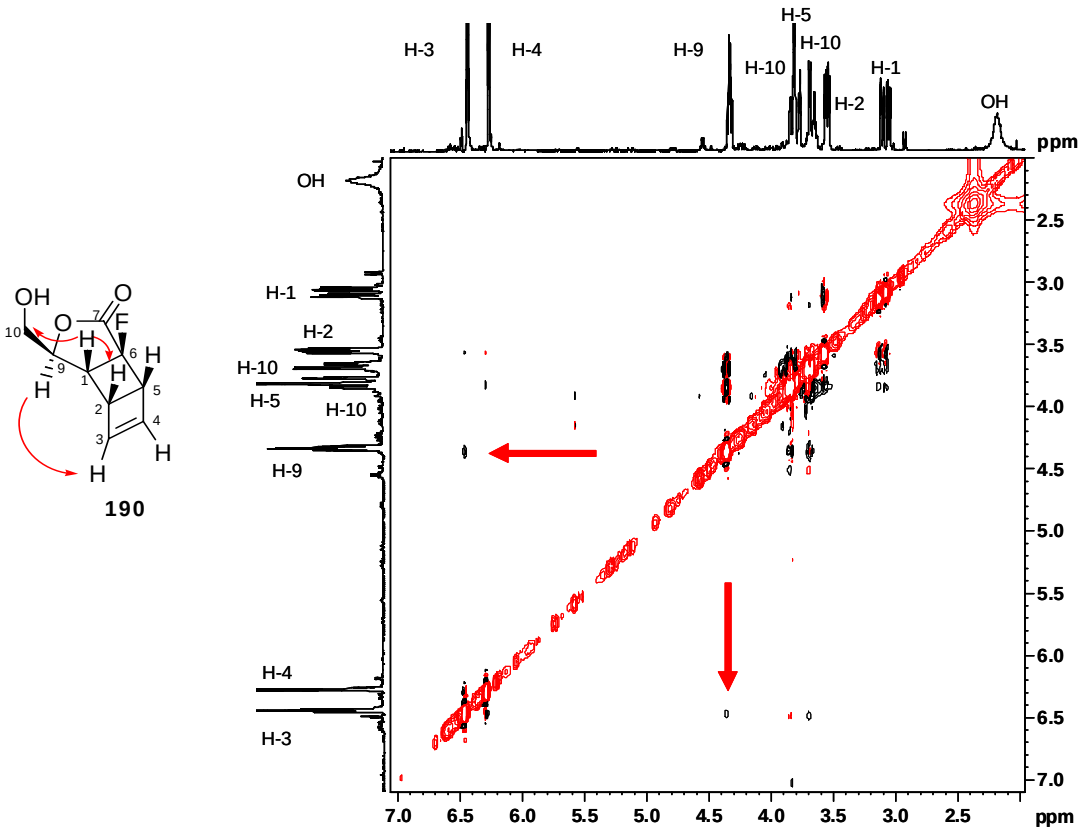
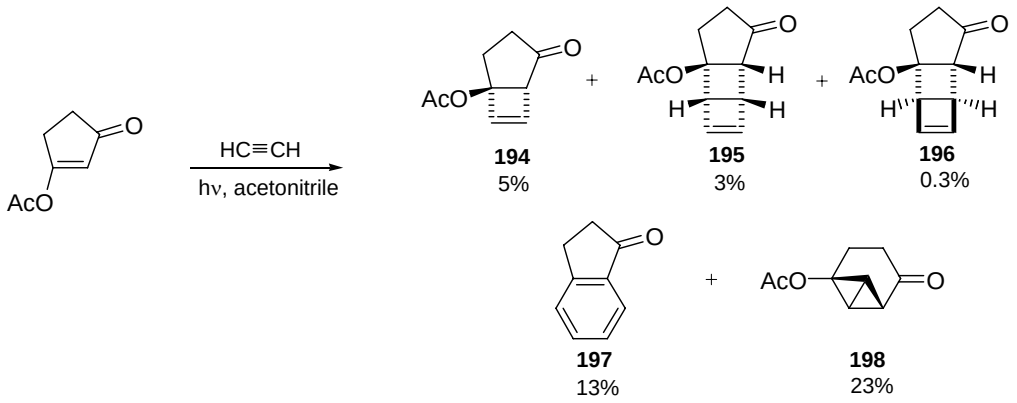


Figure 27. NOESY spectrum of derivative **190** ($CDCl_3$, 360 MHz).

The formation of the tricicycle derivatives **190** and **193** was surprising. However, by a literature survey it was found that the preparation of related products had been previously reported. Pietra and co-workers[82] described, in 1988, the formation of similar tricyclic compounds in the photocycloaddition of 3-acetyloxy-2-cyclopentenone to acetylene in acetonitrile (Scheme 51). The photochemical reaction furnished a mixture of 5 compounds, the expected primary cycloadduct **194** in 5% yield, two diastereomeric products of double addition of acetylene **195** and **196** in a 10:1 ratio (3% yield), indanone, **197**, (13%) and the oxa-di-π-methane rearrangement product **198** (23% yield). The assignment of the relative

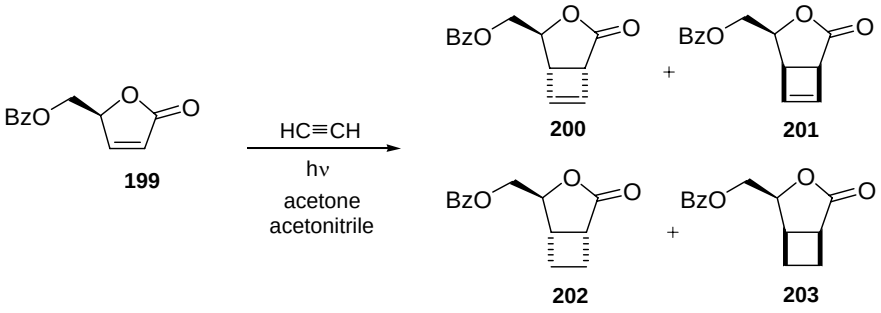
[82] Cavazza, M.; Guella, G.; Pietra, F. *Helv. Chim. Acta.* **1988**, *71*, 1608-1615.

stereochemistry of the tricycle derivatives **190** and **193** is on good terms with that described for the major isomer described by Pietra and co-workers **195**.



Scheme 51. [2+2] Photocycloaddition of 3-acetyloxy-2-cyclopentenone to acetylene, Pietra and co-workers (1988).

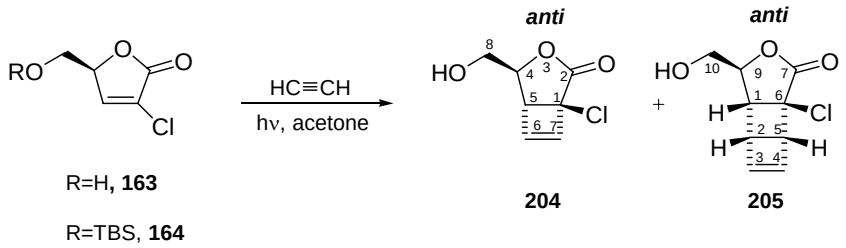
Finally, it is noteworthy to mention that the desired silylated *anti* cycloadduct **191** also underwent photoreduction. This phenomenon had already been described by Bartlett *et al.*[83] and also was observed in our laboratory in the photoreaction of lactone **199** with acetylene which furnished the expected cyclobutenes **200** and **201** along with variable amounts of the cyclobutane derivatives **202** and **203** (Scheme 52).[18d] This side reaction took place irradiating either through a pyrex or quartz filter.



Scheme 52. [2+2] Photocycloaddition of 2(5*H*)-furanone **199** to acetylene, Font and co-workers (2003).

[83] Bartlett, P. D.; Roof, A. A. M.; Winter, W. J. *J. Am. Chem. Soc.* **1981**, *103*, 6520-6522.

1.3.3. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanones 163 and 164 to acetylene



R=H, **163**

R=TBS, **164**

204 **205**

entry	R	lactone	filter	solvent	time	yield (%)	*anti*:*syn* (%)[b,c]
1	H	**163**	pyrex	acetone	4.5 h	**204** (17) (22)[a] **205** (6) (8)[a]	100 : 0
2	TBS	**164**	pyrex	acetone	4.5 h	**204** (26) **205** (9)	100 : 0

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration.

Table 21. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanones to acetylene.

Irradiation through a pyrex filter of a solution of 3-chloro-2(5*H*)-furanone **163** in acetone saturated with acetylene furnished a complex reaction crude from which two cyclobutene compounds, in a 75:25 ratio, could be identified in the reaction crude by ^{1}H and ^{13}C-NMR (Table 21, entry 1). The process was stopped after 4.5 h before the total consumption of the starting material due to the large number of degradation products observed in the reaction controls performed by GC. Purification of the reaction crude by column chromatography allowed the isolation of the *anti* cycloadduct **204** in 17% yield, the tricyclic cyclobutene compound **205** in 6% yield and starting material (26%). The presence of any cycloadduct or derivative possessing a *syn* stereochemistry could not be detected.

When the silyl protected lactone **164** was irradiated under the above conditions a complex reaction crude was also obtained (entry 2). Purification of the reaction mixture by column chromatography allowed the isolation of the previously described cyclobutene derivatives **204** and **205** in 26% and 9% yield, respectively, indicating that the silyl moiety is cleaved in the purification process. Again, no presence of the *syn* cycloadduct could be observed.

1.3.4. Effect of the vinylic halide on the [2+2] photocycloaddition of 2(5*H*)-furanones to acetylene

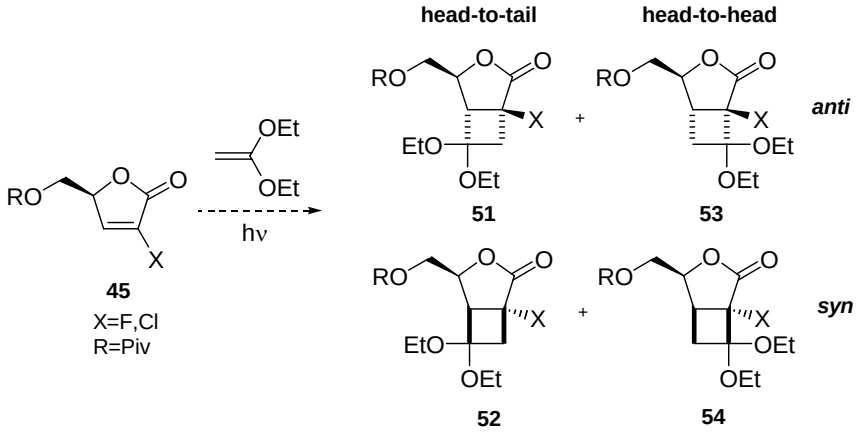
The presence of an halide at the α-position of the lactone has a wide effect on the [2+2] photocycloaddition of 2(5*H*)-furanones to acetylene. First, similarly to the case of the photoreaction to ethylene, the estimated diastereoselectivity is enhanced compared to the results achieved with non-halogenated furanones.

However, low yields have been achieved for all the reactions investigated. Moreover, different side reactions have been observed in the reactions performed with 3-chloro and 3-fluoro-2(5*H*)-furanones such as further [2+2] photocycloadditions and photoreductions. These reactions have not been observed with their parent 3-dehalo-(5*H*)-furanones.

Finally, as a result of the low yields and the complexity of the reaction mixtures obtained, the use of these reactions as a method for preparing cyclobutene chloro and fluoronucleoside analogues was discarded. Nevertheless, this photochemical study has provided us with highly interesting results from a reactivity point of view.

2. Photocycloaddition of 3-chloro and 3-fluoro-2(5*H*)-furanones to ketene diethyl ketal

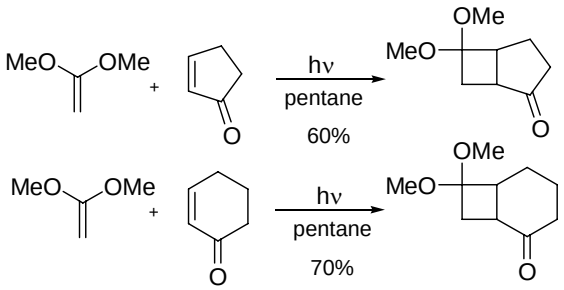
The study of the photochemical behaviour of 3-chloro and 3-fluoro-2(5*H*)-furanones was completed with their reaction with ketene diethyl ketal (Scheme 53). In this occasion up to four isomers **51-54** are expected.



Scheme 53. [2+2] Photocycloaddition of 3-chloro and 3-fluoro-2(*5H*)-furanones to ketene diethyl ketal.

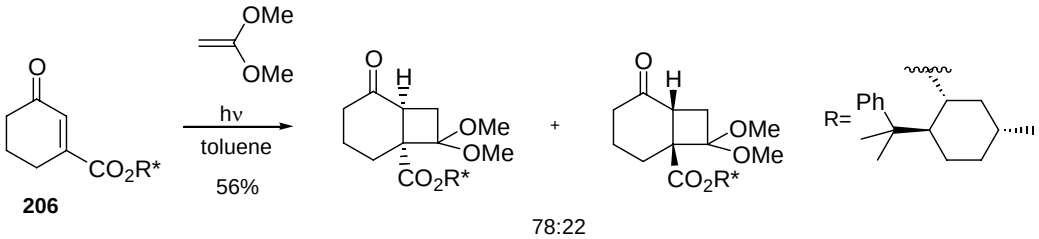
2.1. Introduction

Ketene ketals have been widely used as reagents in cyclobutane synthesis due to the presence of a ketone functionality masked in their structure. The first example of a [2+2] photocycloaddition reaction of cyclic enones to a ketene ketal was reported by Corey and co-workers in 1964.[28] Therein, the photochemical reactions of 2-cyclopentenone and 2-cyclohexenone with ketene dimethyl ketal proceeded in a high regioselective way affording exclusively the head-to-tail (HT) isomers (Scheme 54).



Scheme 54. First examples of [2+2] photocycloaddition of cyclic enones to ketene dimethyl ketal, Corey and co-workers (1964).

The induction of stereoselectivity in the photocycloaddition to ketene ketals has been studied by anchoring chiral auxiliaries to the enone.[84] Scharf and co-workers published in 1986 a study where a moderated 78:22 ratio was achieved when a mixture of the chiral enone **206** and ketene dimethyl ketal was irradiated through pyrex in toluene (Scheme 55).

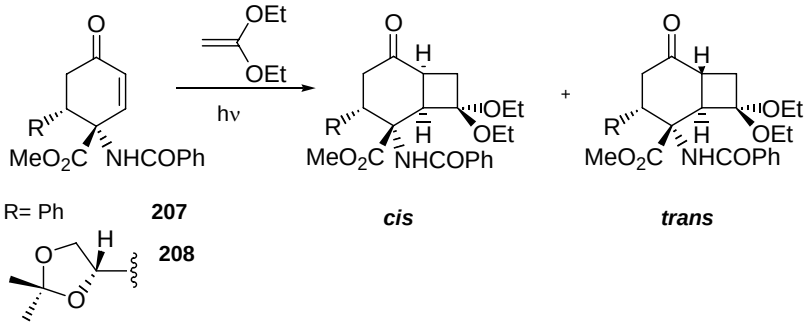


Scheme 55. [2+2] Photocycloaddition of **206** to ketene dimethyl ketal, Scharf and co-workers (1986).

More recently, Ortuño and co-workers reported that the [2+2] photocycloaddition of two enantiomericaly pure 2-cyclohexenones, **207** and **208**, to ketene diethyl ketal takes

[84] a) Herzog, H.; Koch, H.; Scharf, H.-D.; Runsink, J. *Tetrahedron* **1986**, *42*, 3547-3558. b) Herzog, H.; Koch, H.; Scharf, H.-D.; Runsink, J. *Chem. Ber.* **1987**, *120*, 1737-1740.

place with complete HT regioselectivity (Table 22).[37g] Moreover, theoretic calculations were performed with the aim of rationalizing the observed results. It was concluded that the regiochemistry of the reaction is determined by the rate of formation of the 1,4-biradical intermediates and not by their relative stability.

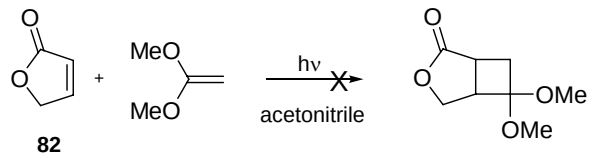


enone	filter	solvent	time (h)	yield (%)	*cis*:*trans* (%)
207	pyrex	acetone	2.7	49	82:18
207	pyrex	acetonitrile	3.7	77	69:31
208	pyrex	acetone	3.5	42	55:45
208	pyrex	acetonitrile	1.2	27	44:56

Table 22. Photochemical study of the [2+2] photocycloaddition of chiral cyclohexenones to ketene diethyl ketal, Ortuño and co-workers (2004).

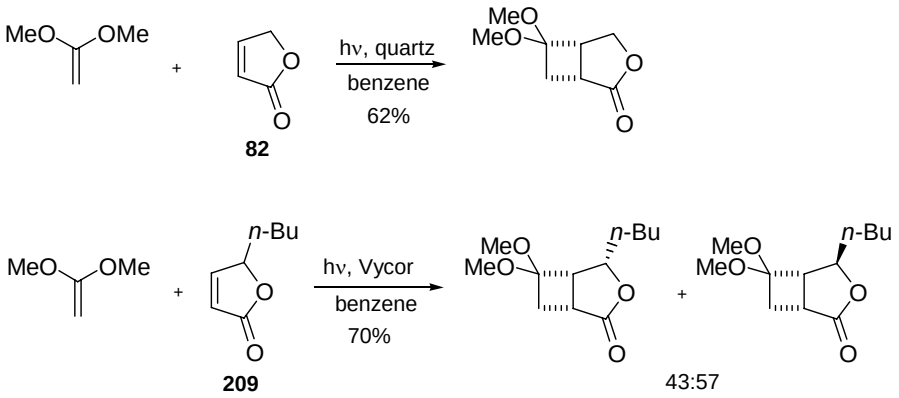
2.1.1. [2+2] Photocycloaddition of 2(5*H*)-furanones to ketene ketals

Tada *et al.*[49] assayed the reaction between crotonolactone, **82**, and ketene dimethyl ketal in acetonitrile, irradiating through a quartz filter with a 10W low pressure mercury lamp without observing evolution of the reaction in acetonitrile (Scheme 56). The authors inferred that an exciplex was formed between **82** and ketene dimethyl ketal which reverted to the starting materials through an ionic dissociation and subsequent electron transfer process.



Scheme 56. Attempt of [2+2] photocycloaddition of crotonolactone, **82**, to ketene dimethyl ketal, Tada *et al.* (1972).

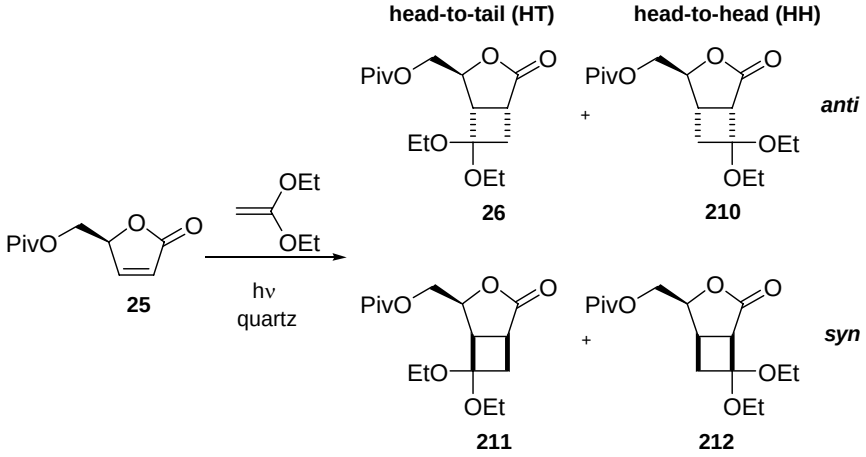
However, later Kosugi *et al.*[50] described that the photochemical reaction of **82** with ketene dimethyl ketal proceeded in 62% yield by irradiation through a quartz filter in benzene (Scheme 57). The unique regioisomer obtained was the HT. On the other hand, the *anti*:*syn* facial diastereoselectivity observed for the 4-butyl-2(5*H*)-furanone, **209**, was low (57:43). It was also described that this reaction could not be carried out in acetone due to the formation of oxetane derivatives between the solvent and the ketene ketal.



Scheme 57. Photochemical study with ketene dimethyl ketal, Kosugi *et al.* (1976).

The first example of [2+2] photocycloaddition of enantiomericaly pure 2(5*H*)-furanones to ketene ketals has been recently described by our research group.[85] Considering the regiochemistry (HT:HH) and the *anti*:*syn* approach, this reaction could yield up to four isomers (Table 23). Several protecting groups were investigated, being the best results in terms of yield and facial diastereoselectivity (*anti*:*syn*) obtained with the pivalate **25**.

[85] Rustullet, A. Doctoral Thesis, UAB, 2006.



solvent	yield (%)	time	26:210:211:212 (%)	HT:HH (%)	*anti*:*syn* (%)
acetonitrile	61	2 h	50:21:22:7	72:28	71:29
hexane	79	2.8 h	52:5:39:3	91:9	58:42
diethyl ether	72	2.3 h	58:5:34:3	92:8	63:37

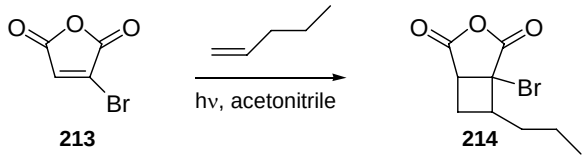
Table 23. [2+2] Photocycloaddition of 2(5*H*)-furanone **25** to ketene diethyl ketal.

An extensive study of the effect of the solvent, among other reaction conditions, on the facial diastereoselectivity and the regioselectivity of the process was performed to optimize the preparation of the *anti* HT isomer **26** which was the key intermediate in the synthesis of cyclobut-A.[22] Thus, it was found that the best results in terms of regioselectivity were obtained in apolar solvents (hexane or diethyl ether) and the highest facial diastereoselectivity was observed in acetonitrile.

2.2. [2+2] Photocycloaddition of 3-chloro- and 3-fluoro-2(5*H*)-furanones to ketene diethyl ketal

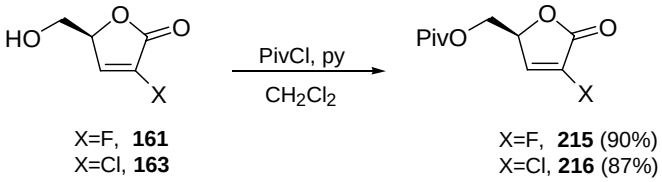
Even though no examples of photocycloaddition of halo-enones to ketene ketals have been found in the literature, a few examples of photoreactions of halo-enones to asymmetric alkenes have been previously reported. For instance, White and co-workers[86] described the photoreaction of bromomaleic anhydride **213** to 1-pentene in acetonitrile which proceed with complete regioselectivity to yield the head-to-head cyclobutane **214** as a mixture of stereoisomers (Scheme 58). No information about the yield is given.

[86] White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665-8671.



Scheme 58. [2+2] Photocycloaddition of **213** to 1-pentene, White and co-workers (2000).

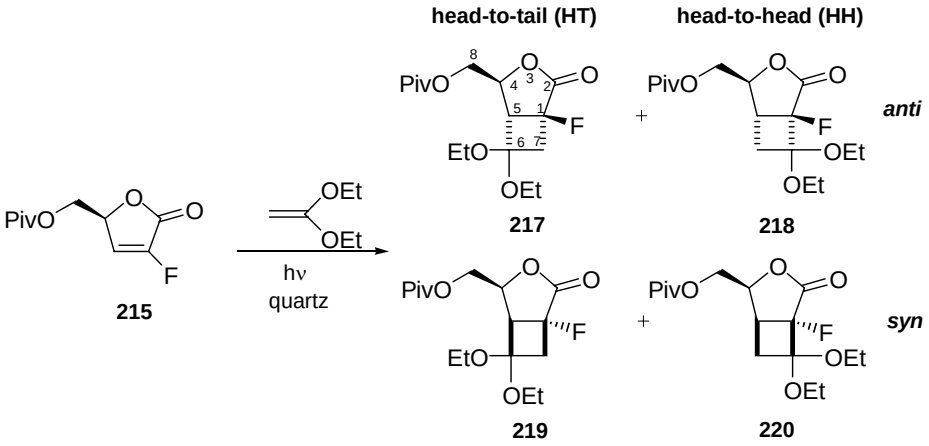
In order to compare the results obtained in the present work with the previous studies performed in our research group, it was decided to protect the hydroxyl group of the halolactones as a pivalate. Therefore, the 3-fluoro-2(5*H*)-furanone **161** was treated with pivaloyl chloride and pyridine to afford the protected lactone **215** in 90% yield, with, $[\alpha]_D$ -97.7 (*c* 2.15, $CHCl_3$) (Scheme 59). Similarly, the lactone **163** was treated with pivaloyl chloride and pyridine to afford the 3-chloro-2(5*H*)-furanone **216** in 87% yield, with, $[\alpha]_D$ -88.0 (*c* 1.5 $CHCl_3$).



Scheme 59. Synthesis of 3-fluoro and 3-chloro-5-pivaloyloxymethyl-2(5*H*)-furanones, **215** and **216**.

The following photochemical study has been carried out using acetonitrile or diethyl ether as solvents. The reactions were conducted with a 125W high pressure mercury lamp (Cathodeon HPK125), irradiating through a quartz filter, cooling externally the reactor to -40 ºC and with a -15 ºC cooled MeOH flow through the reactor refrigeration jacket. Evolution of the reaction was controlled by gas chromatography (GC) and by TLC. Product characterization was accomplished by NMR techniques.

2.2.1. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanone 215 to ketene diethyl ketal



entry	solvent	time	global yield (%)	product ratio 217:218:219:220 (%)[b]	HT:HH (%)	*anti*:*syn* (%) [c]
1	acetonitrile	3 h	43 (51)[a]	48:42:0:10	48:52	90:10
2	diethyl ether	3 h	21	83:17:0:0	83:17	100:0

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration.

Table 24. [2+2] Photocycloaddition of 3-fluoro-2(5*H*)-furanone **215** to ketene diethyl ketal.

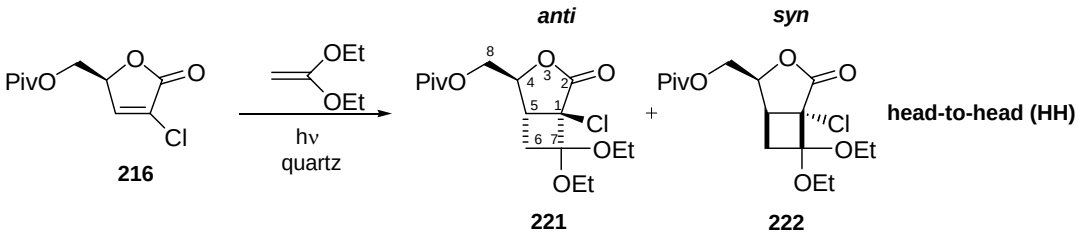
The photochemical reaction of fluorolactone **215** and ketene diethyl ketal in acetonitrile for 3 h resulted in the formation of a complex crude which was purified by column chromatography to afford a 48:42:10 mixture of the *anti* HT isomer **217**, the *anti* HH isomer **218** and the *syn* HH isomer **220** in 43% overall yield along with unreacted lactone **215** (16%) (Table 24, entry 1). Repetitive column chromatography afforded analytical samples of each cycloadduct. The reaction was stopped before the complete consumption of **215** due to the large amount of by-products observed by GC.

When the photochemical reaction was performed in diethyl ether (entry 2) after 3 h of irradiation, the reaction crude was even more complex than in the previous experiment. Analysis by ^{1}H and ^{13}C-NMR and GC of the reaction mixture showed the presence of the *anti* cycloadducts **217** and **218** in a 83:17 ratio. No presence of the *syn* isomers **219** and **220** could be observed. Purification by column chromatography furnished the *anti* regioisomers **217** and **218** in poor yield (21%).

In an attempt to gain an insight for the low yields obtained, lactone **215** was submitted to irradiation under the above conditions but in the absence of ketene diethyl

ketal. Complete consumption was observed by GC and TLC after 60 min and was later confirmed by ^{1}H-NMR analysis of the reaction crude which showed the presence of many unidentified products. It is worth to point out that a certain degree of instability of the silyl protected 3-fluorolactone **162** had also been observed in the study of photoreactivity to acetylene when it was irradiated through a quartz filter.

2.2.2. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanone 216 to ketene diethyl ketal



entry	solvent	time	global yield (%)	product ratio 221:222 (%) [b]	HT:HH (%)	*anti*:*syn* (%) [c]
1	acetonitrile	2.25 h	36 (48)[a]	75:25	0:100	75:25
2	diethyl ether	3 h	10	100:0	0:100	100:0

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by GC and ^{1}H-NMR. [c] Considering the % of products bearing the same relative configuration.

Table 25. [2+2] Photocycloaddition of 3-chloro-2(5*H*)-furanone **216** to ketene diethyl ketal.

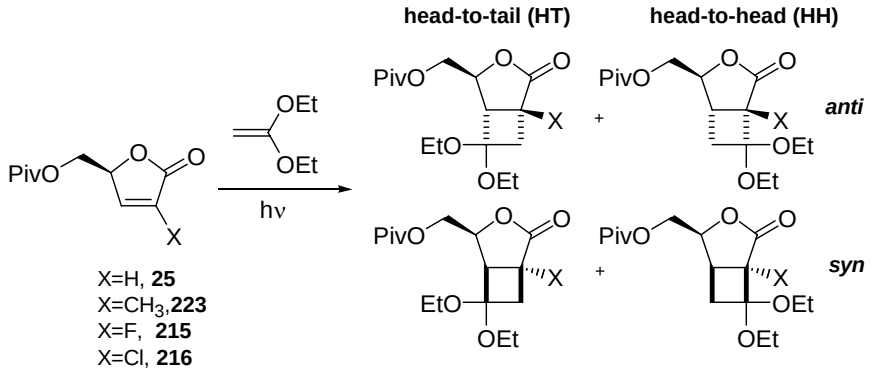
The photochemical reaction of chlorolactone **216** and ketene diethyl ketal in acetonitrile for 2.25 h resulted in the formation of a complex crude which was purified by column chromatography to afford a 75:25 mixture of the *anti* HH isomer **221** and the *syn* HH isomer **222** in 36% overall yield along with unreacted lactone **216** (20%) (Table 25, entry 1). Repetitive column chromatography afforded analytical samples of both cycloadducts. The reaction was stopped before the complete consumption of **216** due to the large amount of by-products observed by GC.

When the photochemical reaction was performed in diethyl ether (entry 2), after 3 h of irradiation the reaction crude was even more complex than in the previous experiment. Only the presence of the head-to-head cycloadduct **221** in the reaction mixture could be confirmed by GC and NMR analysis. Purification of the reaction crude by column chromatography furnished **221** in very poor yield (10%).

Analysis of both photoreactions were performed at short reaction times showing the decreasing presence of starting material and the formation of the cycloadducts described above along with multiple unidentified by-products. The formation of the expected head-to-tail isomers could not be detected. Moreover, the lactone **216** was submitted to irradiation under the above conditions in the absence of ketene diethyl ketal, experiencing complete consumption after 45 min to furnish unidentified by-products.

2.2.3. Effect of the vinylic halide and the solvent on the regioselectivity and the facial diastereoselectivity of the reaction

Table 26 shows the results of regioselectivity obtained in the [2+2] photocycloaddition reactions of different 2(5*H*)-furanones in acetonitrile and diethyl ether.



X	lactone	yield (%)		head-to-tail (HT) : head-to-head (HH)	
		acetonitrile	diethyl ether	acetonitrile	diethyl ether
H	**25**[a]	61	72	72:28	92:8
CH_3	**223**[a]	87	64	80:20	93:7
F	**215**	43	21	48:52	83:17
Cl	**216**	36	10	0:100	0:100

[a] Results obtained by Dr. Albert Rustullet.[85]

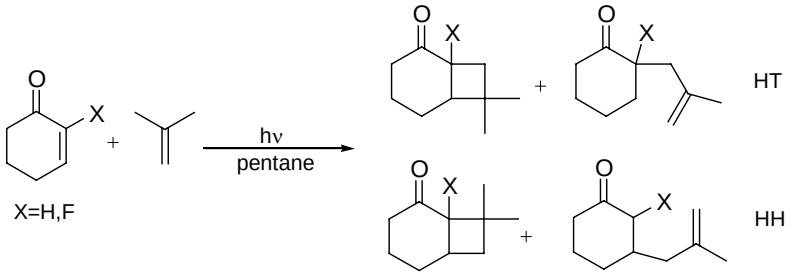
Table 26. Regioselectivity in the [2+2] photocycloaddition of 2(5*H*)-furanones to ketene diethyl ketal.

The results achieved in the present study should be cautiously analysed due to the low yields of the photoreactions, specially in diethyl ether. It must be considered the possibility that those regioisomers which could not be detected were formed and immediately degraded in the reaction conditions.

The results previously reported in our research group showed an increment of the regioselectivity towards the HT isomers when the polarity of the solvent decreased. For the fluorolactone **215**, the effect of the polarity of the solvent on the regioselectivity followed the same tendency above discussed: the regioselectivity was significantly increased in diethyl ether, despite the low yield observed. Nevertheless, higher amounts of HH isomers was observed, specially in acetonitrile, compared to dehalolactone **25**. Contrarily, a slight increment of the HT regiochemistry in both solvents had been observed in our laboratory with 3-methyl-2(5*H*)-furanone **223** which was inferred to steric effects that would difficult the formation of the HH isomers.

However, the most striking results were obtained in the reactions performed with chlorolactone **216** when only the HH isomers were isolated in both solvents albeit in low yields.

Swenton and co-workers[81] reported in 1978 that the photochemical reaction of 2-fluoro-2-cyclohexenone with isobutene furnished a mixture of the expected HH and HT regioisomers as well as their related disproportionation products (Table 27). If the ratio of products coming from the same regioisomeric approach of the alkene to the enone are added, the HT:HH ratio becomes 23:77. These results indicate an inversion of the preferred regioselectivity due to the presence of the vinylic fluorine when they are compared to the results of the study carried out by Corey and co-workers[28] with 2-cyclohexenone, where head-to-tail products were mainly obtained (85:15).



X	yield (%)	head-to-tail (HT) : head-to-head (HH)
H	39	85:15
F	65	23:77

Table 27. [2+2] Photocycloaddition of 2-substituted-2-cyclohexenones to isobutene, Corey and co-workers (1964), and Swenton and co-workers (1978).

In the present work an inversion of the preferred regiochemistry in the photoreactions with chlorolactone **216** as well as a lack of regioselectivity in the reaction of

3-fluoro-2(5*H*)-furanone **215** in acetonitrile were observed compared to dehalolactone **25**. Nevertheless, the presence of multiple by-products in all the reactions described herein, specially in diethyl ether, makes the comparison of the different regiochemical behaviour of **215** and **216** difficult.

Table 28 shows the results of facial diastereoselectivity obtained in the [2+2] photocycloaddition reactions of furanones to ketene diethyl ketal.

X	lactone	yield (%)		*anti* : *syn*	
		acetonitrile	diethyl ether	acetonitrile	diethyl ether
H	**25**[a]	61	72	71:29	63:37
CH_3	**223**[a]	87	64	77:23	69:31
F	**215**	43	21	90:10	100:0
Cl	**216**	36	10	75:25	100:0

[a] Results obtained by Dr. Albert Rustullet.[85]

Table 28. Facial diastereoselectivity in the [2+2] photocycloaddition of 2(5*H*)-furanones to ketene diethyl ketal.

Once again, the results achieved in the present study demand a careful analysis due to the low yields of the photoreactions since the real facial diastereoselectivity observed may be masked by side reactions involving the consumption of the minor isomers.

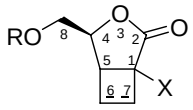
However, as reported for the photoreactions of 3-halofuranones to ethylene and acetylene, an enhancement of the diastereoselectivity was also observed in the [2+2] photocycloaddition of **215** and **216** to ketene diethyl ketal referred to the results obtained with 3-dehalolactone **25**. It is remarkable that an increment of the facial diastereoselectivity had already been observed in our laboratory as a consequence of the presence of a methyl group in lactone **223**, though less pronounced.

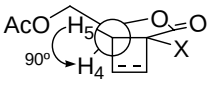
Finally, as a result of the poor yields obtained in all the photochemical reactions performed with ketene diethyl ketal, their application to the preparation of highly substituted halo cyclobutane derivatives was discarded. However, this photochemical study has provided us with interesting results from a mechanistic point of view.

3. Structural determination of the cycloadducts

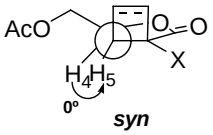
The structural elucidation of the cycloadducts obtained in the above photochemical reactions was carried out by ^{1}H and ^{13}C-NMR. Signals were assigned with the help of DEPT, COSY, HMQC, HMBC and NOESY experiments.

The stereochemistry *anti* or s*yn* of the cycloadducts was determined using the vicinal constant coupling values between proton H-4 and H-5 in the ^{1}H-NMR spectrum. $J_{4,5}$ values as well as significant chemical shifts of the cycloadducts obtained in the photoreactions of 2(5*H*)-furanones with ethylene, acetylene and ketene diethyl ketal are shown in Tables 29, 30 and 31, respectively.





anti



syn

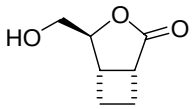
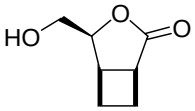
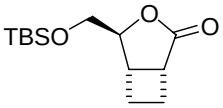
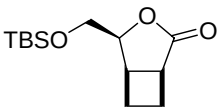
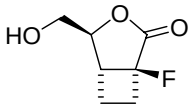
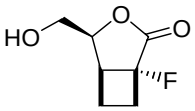
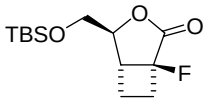
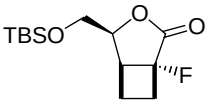
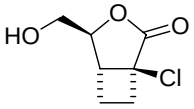
product	$J_{4,5}$	C-4	product	$J_{4,5}$	C-4
 **34**	1.2	86.3	 **174**	5.6	82.5
 **175**	~0	85.3	 **176**	-	81.2
 **177**	~0	84.1	 **178**	4.9	80.7
 **179**	0.5	83.9	 **180**	5.8	79.8
 **181**	0.5	84.4			

Table 29. Significant ^{1}H- and ^{13}C-NMR data of the products obtained in the photochemical reactions with ethylene. Chemical shifts are expressed in ppm and constant couplings in Hz. Solvent is always $CDCl_3$.

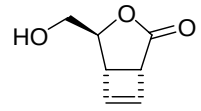
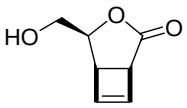
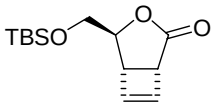
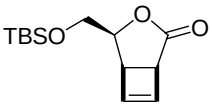
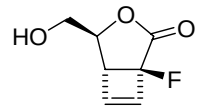
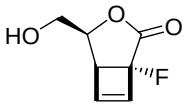
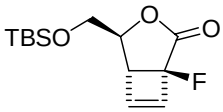
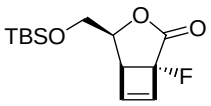
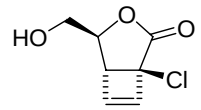
product	$J_{4,5}$	C-1	product	$J_{4,5}$	C-1
 **36**	1.7	47.9	 **185**	4.3	43.5
 **186**	1.3	48.2	 **187**	-	43.5
 **188**	1.5	91.5	 **189**	-	-
 **191**	1.9	91.4	 **192**	5.4-6.6	-
 **204**	1.5	64.0			

Table 30. Significant ^{1}H- and ^{13}C-NMR data of the products obtained in the photochemical reactions with acetylene. Chemical shifts are expressed in ppm and constant couplings in Hz. Solvent is always $CDCl_3$.

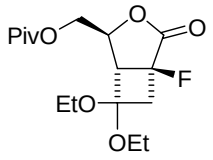
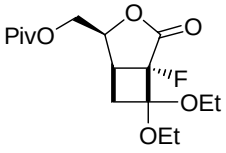
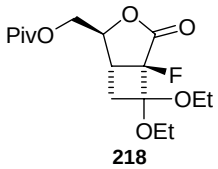
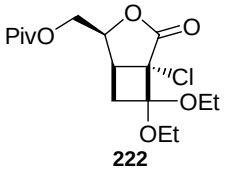
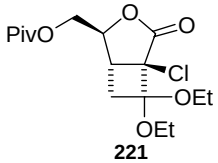
product	$J_{4,5}$	C-5	product	$J_{4,5}$	C-5
 **217**	-	51.7	 **220**	5.9	35.6
 **218**	1.0	35.2	 **222**	5.1	39.6
 **221**	1.6	38.8			

Table 31. Significant ^{1}H- and ^{13}C-NMR data of the products obtained in the photochemical reactions with ketene diethyl ketal. Chemical shifts are expressed in ppm and constant couplings in Hz. Solvent is always $CDCl_3$.

As seen in Tables 29-31, experimental results agree with the stereochemistry prediction in terms of H-4/H-5 vicinal constant coupling albeit the value of $J_{4,5}$ could not be obtained in some cases. Moreover, the C-4 chemical shifts observed in the *anti* cycloadducts obtained in the photochemical reactions with ethylene are between 3.4 and 4.1 ppm low field shifted compared to its *syn* counterparts. On the other hand, the C-1 chemical shifts observed in the *anti* cycloadducts obtained in the photochemical reactions with acetylene are also low field shifted with respect to those *syn* counterparts which ^{13}C-NMR sprectrum was recorded (4.4-4.7 Hz). In both cases, the larger steric congestion of the *syn* cycloadducts is the reason for the displacement of their signals to lower chemical shifts.

Finally, the C-5 chemical shift is a useful tool to elucidate the regiochemistry of the cycloadducts obtained in the photoreactions with ketene diethyl ketal since it is drastically low field shifted in the head-to-tail isomers due to the proximity of the ketal group. The regiochemistry of the cycloadducts **217-222** was further confirmed on the basis of HMBC experiments (Figure 28). Thus, the head-to-tail isomer **217** shows cross-peak between the acetalic carbon C-6 and H-4, and between the carbonyl C-2 and H-7 (Figure 29). On the other hand, the cycloadducts **218**, **220**, **221** and **222** show cross-peak between C-4 and H-6 and between C-6 and H-4 indicating a head-to-head regiochemistry (Figure 30).

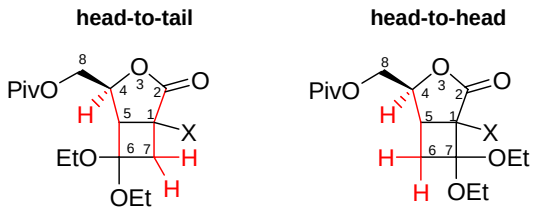


Figure 28. Determination of the regiochemistry of the cycloadducts on the basis of HMBC experiments.

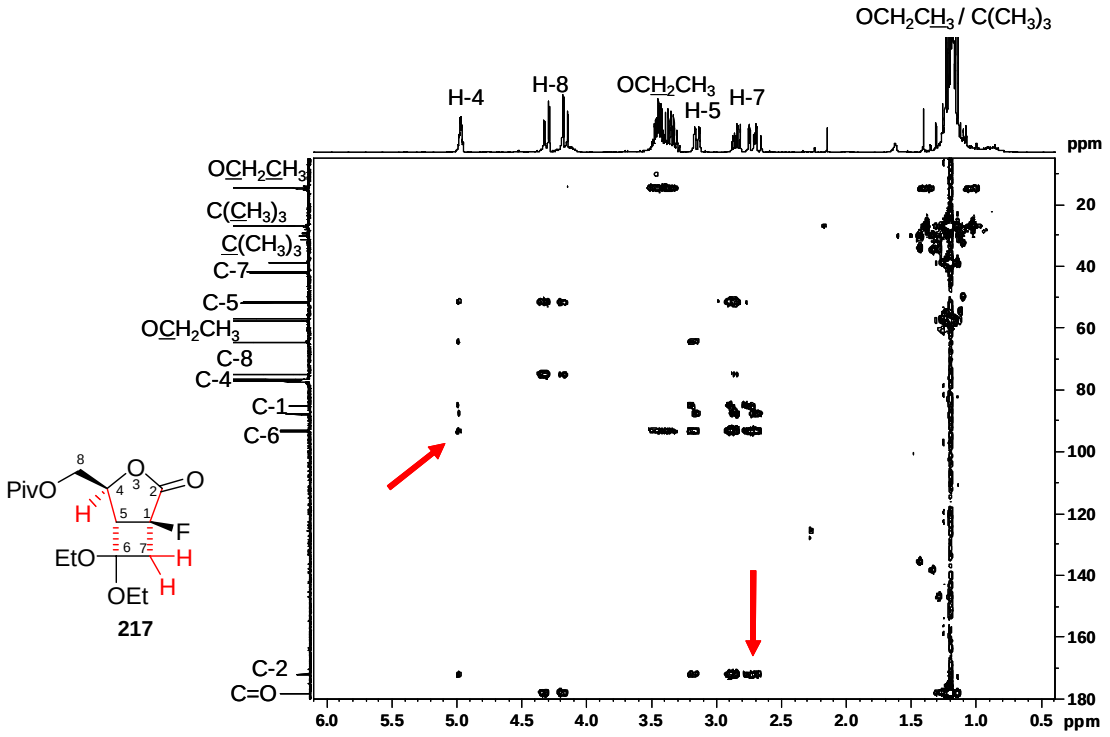


Figure 29. HMBC experiment of product **217** ($CDCl_3$, 360 MHz). Determination of the head-to-tail regiochemistry.

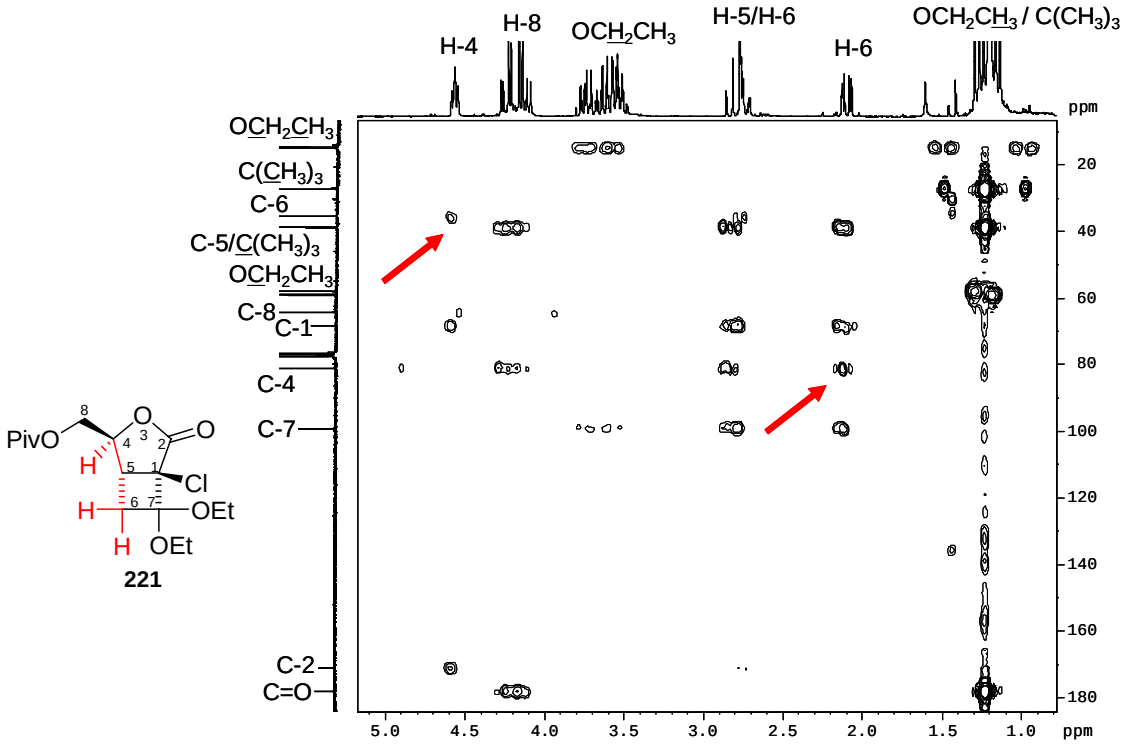


Figure 30. HMBC experiment of product **221** ($CDCl_3$, 250 MHz). Determination of the head-to-head regiochemistry.

4. Introduction to conformationally restricted nucleosides

The anti-HIV activity of 2'-3'-dideoxynucleosides is often modulated by the nature and stereochemical disposition of specific functional groups on the sugar moiety. Such functional groups have a profound effect on the conformation and puckering of the furanose ring. In general, the nucleoside requires a determined number of conformational features in order to bind to the target enzyme.[87] Hence, in the last decade the conformational behaviour of natural and modified nucleosides has come to be seen as of great importance in terms both of their metabolic pathways and of their final interactions with the target enzymes.[88] The complete definition of the conformation of a nucleoside involves the determination of three groups of structural parameters which are discussed next.[89]

4.1. Furanose ring conformation. The pseudorotational cycle

The furanose ring plays a central role in the determination of the conformations adopted by nucleosides. The conformation of this ring is considered in terms of the puckering relative to the best four-atom or three-atom planes, and the torsion angle about the ring bonds. Thus, if only one atom is significantly displaced out of plane, then the conformation is referred to as envelope (E), whereas if two atoms are significantly displaced the conformation is referred to as twist (T) (Figure 31).

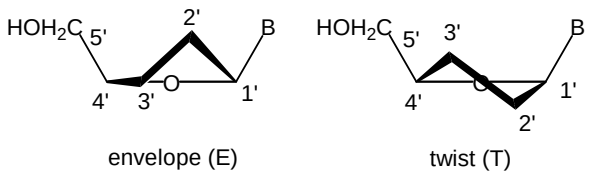


Figure 31. Envelope (E) and twist (T) conformations of the furanose ring.

However it must be taken into account that some conformational or puckering forms differ from a perfect twist or envelope conformation and intermediate forms must

[87] Marquez, V. E..; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford Jr., H.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi Jr.; J. J. *J. Am. Chem. Soc.* **1998**, *120*, 2780-2789, and references cited therein.
[88] Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489-1505, and references cited therein.
[89] Saenger, W. 'Defining terms for the nucleic acids'. At: '*Principles in Nucleic Acid Structure'*; Springer-Verlag: New York, NY, 1988, Chapter 2, p. 9-28.

be considered. Therefore the four atoms forming a plane in an envelope may not be completely coplanar or the deviation from the plane of two atoms in a twist may not be exactly the same. Hence, the maximum of these displacements is called major puckering whereas the minimum is called minor puckering.

In the abbreviated conformational nomenclature,[90] the subscript and superscript numbers denote the numbering of the out-of-plane atoms. The superscript denotes that the deviation is on the same side (endo) of the plane as C-5', while the subscript denotes that the deviation is on the opposite side (exo) of C-5'. Priority is given to the atom that exhibits the major puckering and it appears before the letter (E or T), while the atom showing the minor puckering follows the letter. Therefore, a C-3'-endo-C-2'-exo twist asymmetric conformation, where C-3' is more deviated from the plane (major puckering) than C-2' (minor puckering) is shown as ${}^{3}T_{2}$. On the other hand, if both atoms show the same deviation, the resulting symmetric twist form is shown as ${}^{3}_{2}T$. Finally, a C-3'-exo envelope is shown as ${}_{3}E$, whereas a C-2'-endo envelope as ${}^{2}E$ (Figure 32).

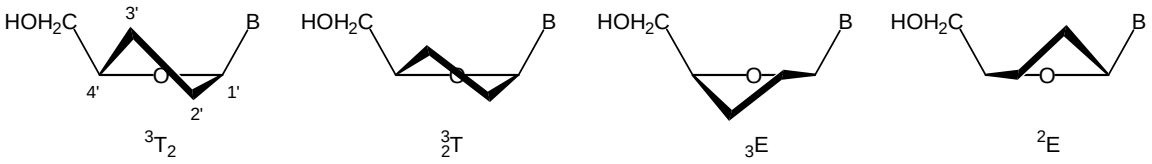
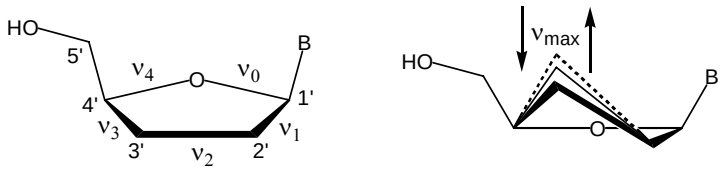


Figure 32. Examples of abbreviated representations of a nucleoside furanose ring.

The pseudorotation concept was introduced to describe the continuous interconversions of puckered forms of cyclopentane ring[91] and was latter applied to substituted furanoside rings.[92] Therefore, the puckering of the furanose ring and its deviation from planarity are described by the phase angle of pseudorotation *P* and the maximum out-of-plane pucker υ_{max} (Figure 33). The value of *P* depends on the five endocyclic sugar torsion angles υ_0-υ_4. On the other hand, the maximum out-of-plane pucker υ_{max} is a representation of the maximal deviation of the ring and can be calculated from *P* and the torsion angle υ_2.

[90] Sundaralingam, M. *J. Am. Chem. Soc.* **1971**, *93*, 6644-6647, and references cited therein.
[91] Kilpatrick, J. E.; Pitzer, K. S.; Spitzer, R. *J. Am. Chem. Soc.* **1947**, *69*, 2483-2488.
[92] Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205-8212.



$$\tan P = \frac{(\upsilon_4 + \upsilon_1) - (\upsilon_3 + \upsilon_0)}{2 \cdot \upsilon_2 \cdot (\sin 36^\circ + \sin 72^\circ)} \qquad \upsilon_{\max} = \frac{\upsilon_2}{\cos P}$$

Figure 33. Pseudorotational phase angle *P* and maximum out-of-plane pucker υ_{max}.

The conformation of the furanose ring can be easily described when values of *P* in combination with υ_{max} are plotted in the pseudorotational cycle (Figure 34). By convention, a phase angle *P*= 0º corresponds to an absolute north configuration possessing a symmetrical twist form ${}^{3}_{2}\mathrm{T}$, whereas its south antipode, ${}^{2}_{3}\mathrm{T}$ is represented by *P*=180º. Values of phase angles are given in multiples of 36º and vary from 0º to 360º. Twenty distinct twist (T) and envelope (E) conformations alternate every 18º. The T conformation is observed at even multiples of 18º, whereas E is found at odd multiples. For the great majority of natural nucleosides, the values of *P* are centred in the vicinity either of a North-type conformation (0º≤ *P* ≤36º, ${}^{3}\mathrm{E}$, C-3' endo) or a South-type conformation (144º≤ *P* ≤180º, ${}^{2}\mathrm{E}$, C-2' endo).[93] While in the solid state prevails one conformation, in solution, both conformations exist in a dynamic equilibrium. The energy barrier between them is low (4.7 kcal mol^{-1} is observed experimentally)[92] and a rapid transition from one to the other proceeds through the East (${}^{O}\mathrm{E}$, O-4'-endo) rather than the West (${}_{O}\mathrm{E}$, O-4'-exo) conformation.[94] Besides, the most common υ_{max} values are located approximately between 30º and 40º. For υ_{max} values lower than 20º the furanose ring is considered to be almost planar.

[93] De Leeuw, H. P. M.; Haasnoot, C. A. G.; Altona, C. *Isr. J. Chem.* **1980**, *20*, 108-126.
[94] Plavec, J.; Tong, W.; Chattopadhyaya, J. *J. Am. Chem.Soc.* **1993**, *115*, 9734-9746.

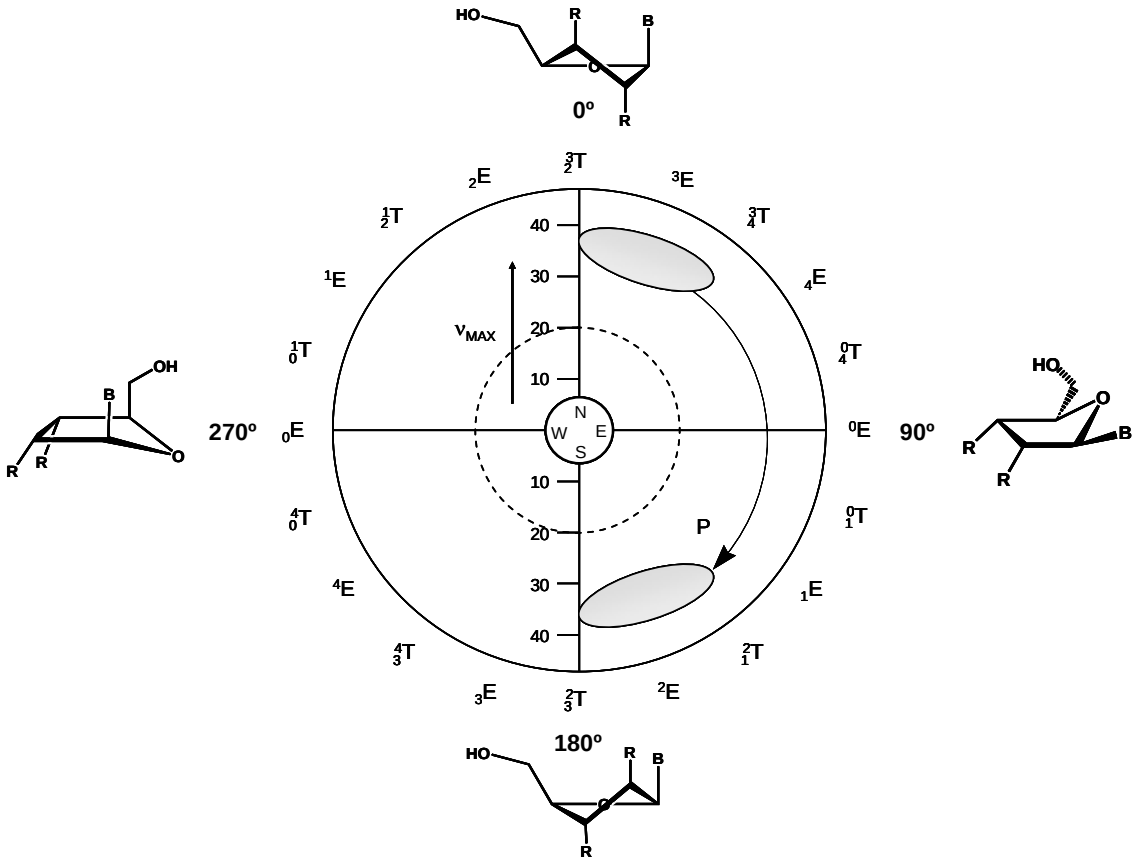


Figure 34. Pseudorotational cycle and the most common conformations in nucleosides.

4.2. Torsion angle χ

The glycosyl torsion angle χ determines the disposition of the base relative to the sugar moiety. For purine bases the torsion angle is defined by O4'-C1'-N9-C4, whereas for pyrimidine bases is defined by O4'-C1'-N1-C2. Thus, when χ=0º the O4'-C1' bond is eclipsed with the N9-C4 bond of purines and the N1-C2 bond of pyrimidines. Figure 35 shows an example of a *syn* purine nucleoside, with the C-4 atom of purine lying over the sugar ring, and an *anti* pyrimidine nucleoside, with the C-2 carbonyl of pyrimidine oriented in the opposite direction.

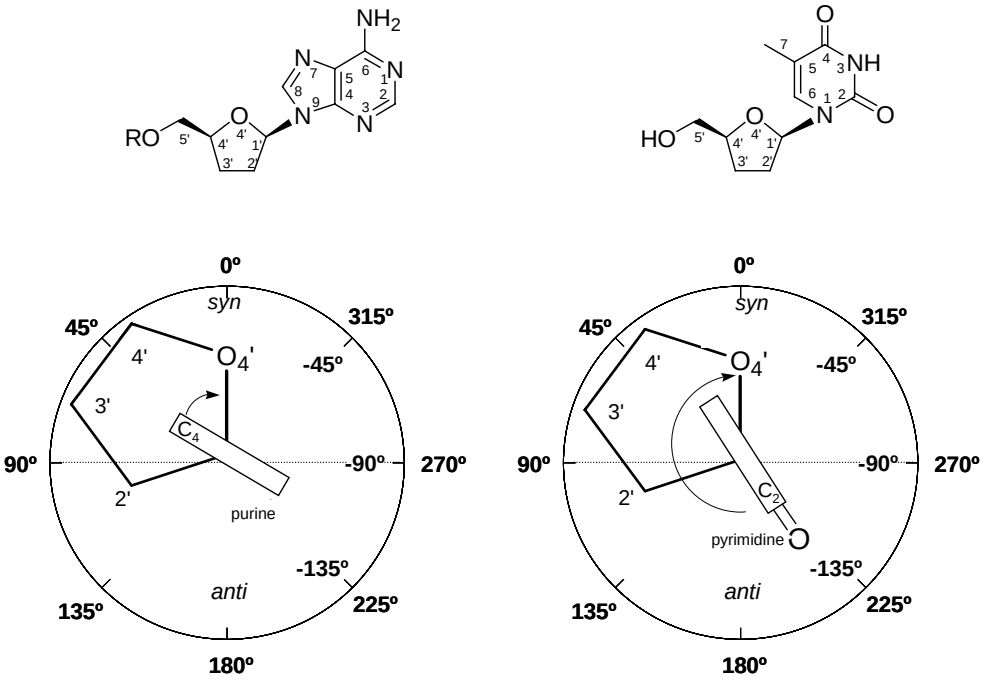


Figure 35. Definition of the torsion angle χ.

4.3. Torsion angle γ

The torsion angle γ determines the orientation of the 5'-hydroxyl with respect to C-3' as represented by three main rotamers, namely +gauche (γ^+) and -gauche (γ^-), when O-5' is located around 60º from C-3', and trans (γ^t), when O-5' is located antiperiplanar to C-3' (Figure 36).

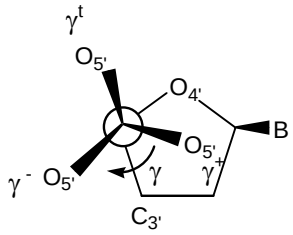


Figure 36. Definition of the torsion angle γ.

5. Precedents

During the past few years, the search for structurally modified nucleosides with enhanced chemotherapeutical potential has been devoted to the preparation of bicyclic dideoxy nucleoside analogues. This work has led to a variety of novel [3.1.0]-2',3'-fused bicyclic nucleosides, some of which have shown weak antiviral activity (Figure 37).[95,96] Conformational studies of these bicyclic nucleosides have shown that the sugar moiety is rigidly fixed outside the pseudorotational range characteristic of active nucleosides,[93] and it has also been suggested that a certain degree of conformational flexibility on the furanose ring is required for potent antiviral activity.[15a,97]

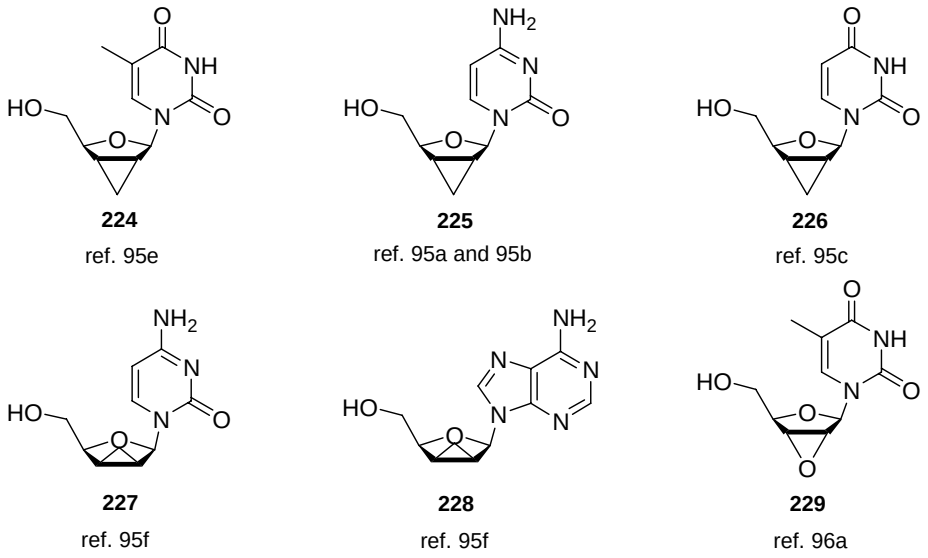


Figure 37. Examples of described bicyclic [3.1.0]-2',3'-fused nucleosides.

[95] 2'-3'-Cyclopropane nucleosides: a) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203-2206. b) Beard, A. R.; Butler, P. I.; Mann, J.; Parlett, N. K. *Carbohydr. Res.* **1990**, *205*, 87-91. c) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2587-2592. d) Koole, L. H.; Neidle, S.; Crawford, M. D.; Krayevsji, A. A.; Bursakaya, G. V.; Sandström, A.; Wu, J. C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem.* **1991**, *56*, 6884-6892. e) Sard, H. *Nucleosides Nucleotides* **1994**, *13*, 2321-2328. f) Hong, J. H.; Chun, B. K.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 225-228. g) Lescop, C.; Huet, F. *Tetrahedron* **2000**, *56*, 2995-3003. h) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685-693.

[96] For bicyclic nucleosides with a moiety other than a cyclopropane, see for instance: a) Miah, A.; Reese, C. B.; Song, Q. *Chem. Commun.* **1997**, 407-408. b) Porcari, A. R.; Ptack, R. G.; Borysko, K. Z.; Breitenbach, J. M.; Vittori, S.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2438-2448. c) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *Synlett* **2003**, 1271-1274.

[97] Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; de Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736-745.

On the other hand, [3.2.0]-2',3'-fused bicyclic nucleosides have received little attention. In 1996, Mikhailopulo and co-workers synthesized **230**,[98] a first member of this family of conformationally restricted nucleosides (Figure 38). Its anti-herpetic activity (HSV-1 and 2) was found to be low and no studies were performed to establish the effect of the oxetane on the conformation and puckering of the furanose ring.

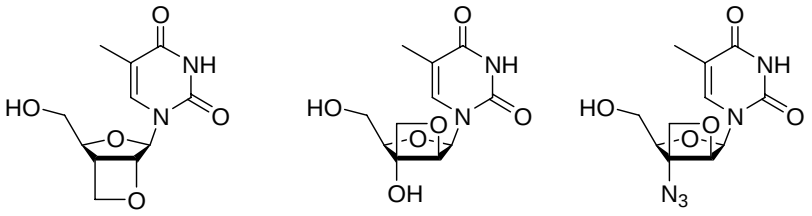


Figure 38. Bicyclic [3.2.0]-2',3'-fused nucleosides **230**, **231** and **232**.

In 1998, Wengel and co-workers described the preparation of **231** with the aim of incorporating this nucleoside into oligonucleotide chains.[99] With the help of NMR and molecular modelling studies, the conformation of **231** was established as O-4'-endo (^{O}E). Later, Nielsen and co-workers reported very similar results for the AZT analogue **232**.[100]

No examples of nucleosides possessing the glycon moiety conformationally restricted by a two-carbon chain between positions 2' and 3' had been published in the literature until the synthesis of the 2',3'-fused bicyclic nucleosides **233-236** in our laboratory (Figure 39).[23]

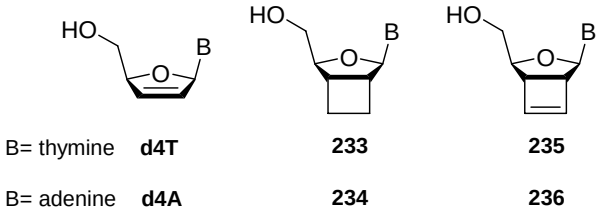


Figure 39. 2',3'-didehydro-2',3'-dideoxynucleosides **d4T** and **d4A** and their cyclobutane and cyclobutene analogues **233-226**.

[98] Mikhailopulo, I. A.; Poopeiko, N. E.; Tsvetkova, T. M.; Marochkin, A. P.; Balzarini, J.; de Clerq, E. *Carbohydr. Res.* **1996**, *285*, 17-28.
[99] Christensen, N. K.; Petersen, M.; Nielsen, P.; Jacobsen, J. P.; Olsen, C. E.; Wengel, J. *J. Am. Chem. Soc.* **1998**, *120*, 5458-5463.
[100] Sørensen, M. H.; Nielsen, C.; Nielsen, P. *J. Org. Chem.* **2001**, *66*, 4878-4886.

These compounds can be seen as analogues of the well-known antiviral 2',3'-didehydro-2',3'-dideoxynucleosides (d4N), such as **d4A** and **d4T**.[101] Analysis of the X-ray crystals obtained for the adenine derivatives **234** and **236** allowed the determination of the conformation features of the new nucleosides which have been compared to those of **d4A** and **ddA**. The crystallographic data for **d4A**[102] and **ddA**[103] was obtained from the *Cambridge Crystallographic Database*.[104] Table 32 shows the conformational parameters in solid state of **d4A**, **ddA**, **234** and **236**.[105]

compound	*P* [a] (º)	υ_{max} [b] (º)	χ [c] (º)	γ [d] (º)	*d* [e] (Å)
234	228.1	22.9	-157.1	173.8	3.7 (4.0)
236	259.8	25.7	-175.5	-75.6	3.4 (4.8)
ddA	190.4	35.7	-95.9	-178.7	3.9 (4.5)
d4A	243.5	7.5	-100.2	179.8	3.9 (4.6)

[a] *P*: phase angle of pseudorotation. [b] υ_{max}: maximum puckering amplitude. [c] χ: torsion angle O4'-C1'-N9-C4. [d] γ: torsion angle O5'-C5'-C4'-C3'. [e] *d*: distance between C-5' and N9 (distance between O5' and N9).

Table 32. Some conformational parameters of **234**, **236**, **ddA** and **d4A**.

Both 2',3'-fused bicyclic nucleosides **234** and **236** showed similar pseudorotational parameters to those described for **d4A**. All four derivatives are settled in the south-west region of the pseudorotational cycle. Despite the fact that the furanose ring of **234** (υ_{max}=22.9º) and **236** (υ_{max}=25.7º) is not as planar as that of **d4A** (υ_{max}=7.5º), they are flattened compared to **ddA** (υ_{max}=35.7º) which is a nucleoside with a non-restricted conformation. A graphical comparison is shown in Figure 40.

[101] Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; de Clercq, E.; Broder, S.; Johns, D.G.; *Mol. Pharmacol.* **1987**, *32*, 162-167.
[102] d4A (DHOADS01): Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217-2225.
[103] ddA (GAHHIG): Silverton, J. V.; Quinn, F. R.; Haugwitz, R. D.; Todazo, L. J. *Acta Crystallogr., Sect. C* **1988**, *44*, 321-324.
[104] Allen, F. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 380-388.
[105] The Altona pseudorotational parameters were calculated by the Pseudo-Rotational Online Service and Interactive Tool (PROSIT) available at http://cactus.nci.nih.gov/prosit. See: Sun, G. S.; Voight, J. H.; Filipov, I. V.; Marquez, V. E.; Nicklaus, M. C. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1752-1762.

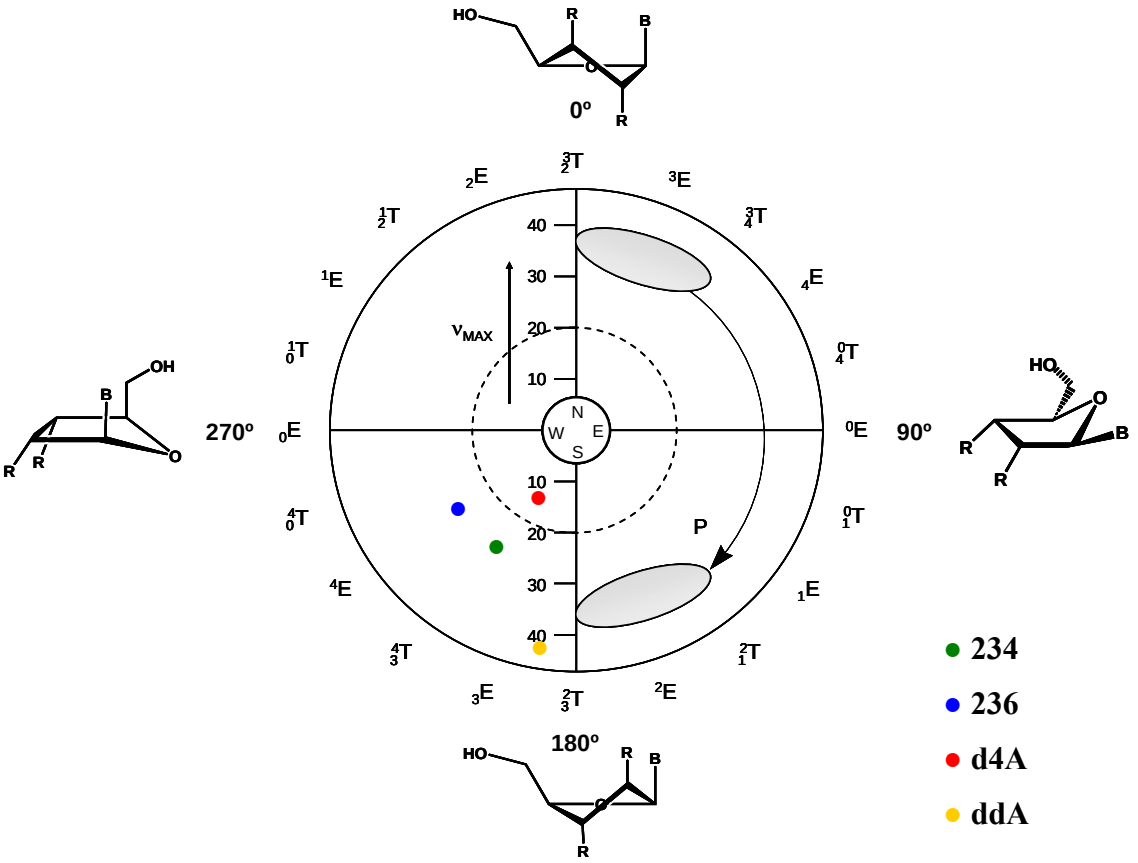


Figure 40. Graphic localisation of the nucleosides **234**, **236**, **d4A** and **ddA** in the pseudorotational cycle.

The conformations of all four nucleosides in solution were also investigated by means of 1D and 2D NOESY NMR studies showing that the preferred relative position of the base toward the sugar ring in **234** and **236** differed from that determined in the solid state. Hence, the [3.2.0]-2',3'-fused bicyclic nucleosides have some flexibility. Besides, their anti-HIV activity was evaluated, showing **234** a moderated activity (EC50= 17.8 μg/mL).

As one of the goals of the present work we planned to synthesize a new family of [3.2.0]-2',3'-fused bicyclic nucleosides bearing a chlorine or fluorine atom in their structure. The target cyclobutane-fused nucleosides **55** were envisioned as conformationally restricted analogues of the previously described 2'-chloro and 2'-fluoronucleosides (Figure 41).

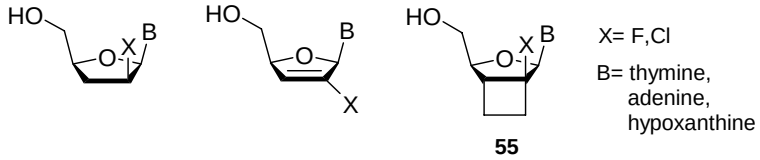


Figure 41. 2'-halo-2',3'-dideoxynucleosides and their cyclobutane analogues **55**.

The only reported example of conformationally restricted nucleoside bearing a fluorine atom in its structure was published by Robins and co-workers in 2007.[106] A family of 2',3'-dideoxynucleoside analogues with 2,2-difluorocyclopropane rings fused at C-3'-C-4' **237** were diastereoselectively synthesized and their solid state conformation was analysed showing a nearly planar furanose ring (Figure 42). Nevertheless, no biological evaluation of the whole series have been reported so far.

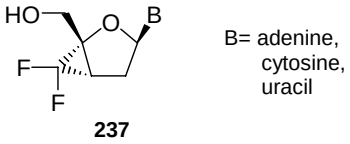
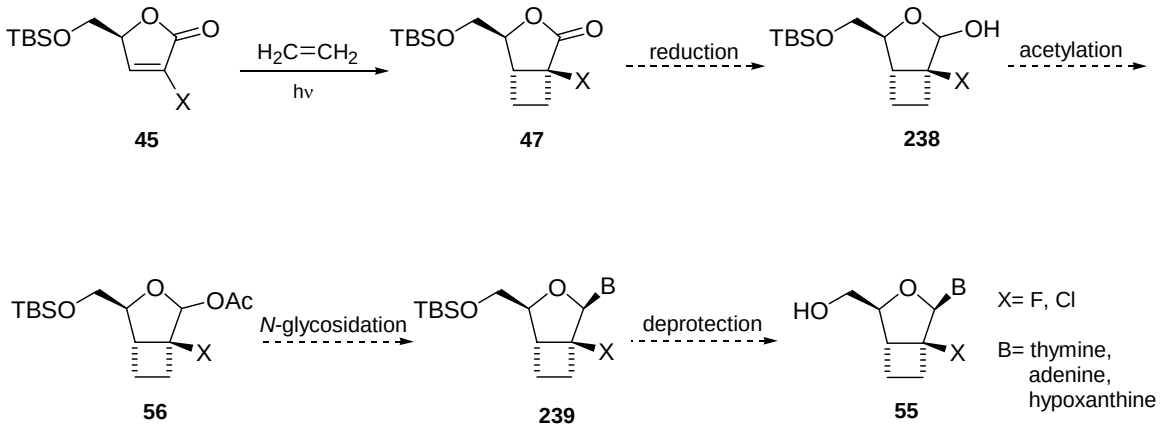


Figure 42. 3',4'-Conformationally constricted nucleosides **237**, Robins and co-workers (2007).

[106] Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2007**, *72*, 532-537.

6. Synthesis of 2'-chloro and 2'-fluoronucleoside analogues conformationally locked by a cyclobutane ring

The synthetic pathway foreseen for the preparation of cyclobutane 2'-chloro and 2'-fluoronucleoside analogues starts with the preparation of the corresponding cyclobutane lactones **47** following the methodology previously discussed (Scheme 60). Reduction of the lactone moiety of **47** to the lactol **238** followed by acetylation would lead to the formation of the key intermediate **56** which is a good substrate to introduce different nucleobases (thymine, adenine, hypoxanthine) by a *N*-glycosylation reaction. Finally, cleavage of the hydroxyl protecting group would afford the target bicyclic [3.2.0] nucleoside analogues **55**.

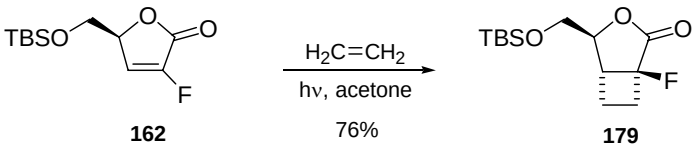


Scheme 60. Synthetic pathway foreseen for the preparation of cyclobutane-fused 2'-halo-2',3'-dideoxynucleosides.

Similar synthetic strategies have been designed for both 2'-chloro and 2'-fluoronucleoside analogues.

6.1. Synthesis of 2'-fluoronucleoside analogues conformationally locked by a cyclobutane ring

The synthesis of the required cyclobutane derivative **161** was performed following the methodology described in the chapter IV-1.2.2. (Scheme 61). Therefore, the [2+2] photocycloaddition of 3-fluoro-2(5*H*)-furanone **162** to ethylene afforded the cycloadduct **179** in 76% yield.

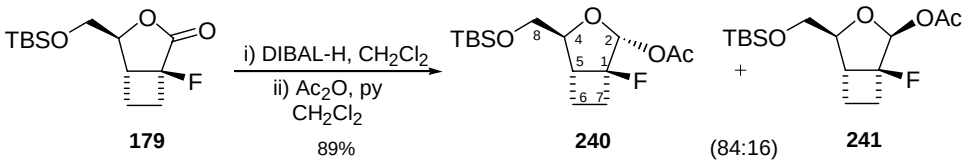


162 **179**

Scheme 61. Preparation of the cyclobutane derivative **179**.

6.1.1. Preparation of the bicyclic acetates 240 and 241

The reduction of the bicyclic lactone was performed by treating **179** with diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 at -78 ºC. The crude mixture of diastereomeric lactols was then treated with acetic anhydride and pyridine to afford a 84:16 mixture of α and β anomeric acetates in 89% yield for the two steps (Scheme 62).

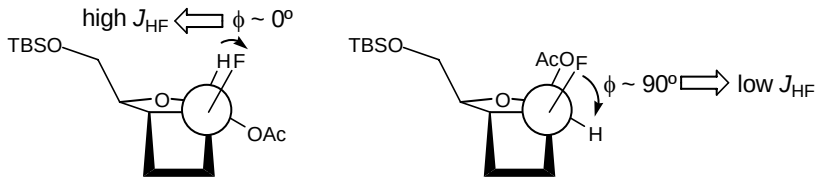


179 **240** (84:16) **241**

Scheme 62. Reduction of the bicyclic lactone **179** and subsequent acetylation.

The determination of the configuration of the anomeric center of **240** and **241** was established by the value of the vicinal proton-fluorine coupling constant between H-2 and the fluorine atom at C-1 which is anticipated to show a maximum value when the dihedral angle between them is close to 0º or 180º and a minimum value when the dihedral angle is close to 90º.[107] Thus, higher values of J_{HF} are expected for the α-anomer than for the β-anomer (Figure 43). Experimentally, a $J_{2,F}$ value of 14.5 Hz was observed for the major isomer **240** which led to the assignation of an α configuration of the anomeric center. On the other hand, a singlet was observed for the minor acetate, identified as the β-anomer **241**. These assignments were further confirmed by means of NOESY experiments which showed cross-peak between H-2 and H-8 for **240** and between H-2 and H-7endo for **241**.

[107] Williamson, K. L.; Li Hsu, Y.-F.; Hall, F. H.; Swager, S.; Coulter, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 6717-6722, and references cited therein.



α-anomer
240

β-anomer
241

Figure 43. Determination of the anomeric configuration by the proton-fluorine coupling constant.

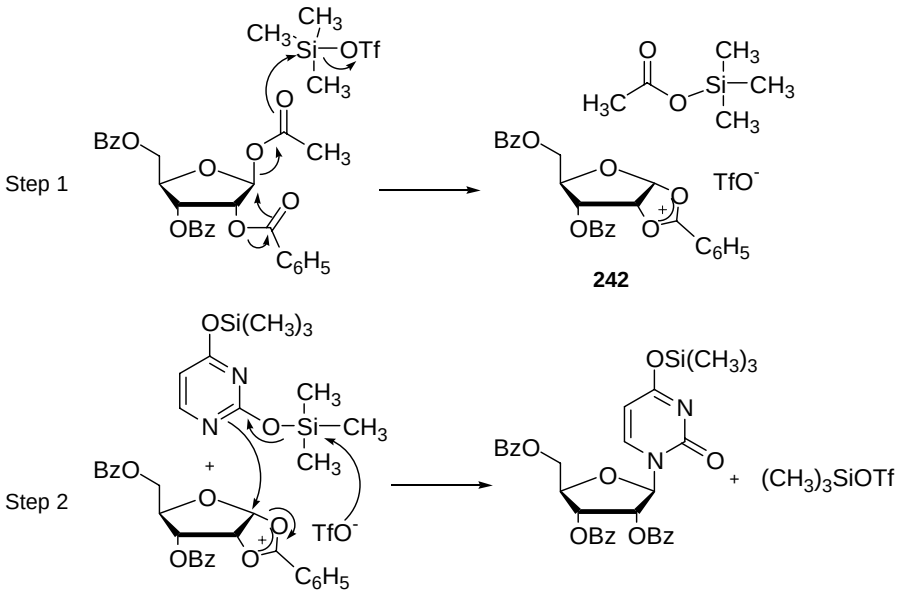
Even though the anomeric mixture can be easily separated by column chromatography separation is not necessary for synthetic purposes.

6.1.2. Vorbrüggen *N*-glycosylation reaction

Nowadays, the silyl variant of the Hilbert-Johnson procedure, catalyzed by Lewis acids, is the most common methodology for coupling a nucleobase to furanose type carbohydrates. This procedure was developed by Vorbrüggen and co-workers in the 1980's making this process applicable and practical.[108] This reaction is often known as the Vorbrüggen *N*-glycosylation or nucleosidation reaction and involves the use of trimethylsilylated pyrimidine or purine bases and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid.

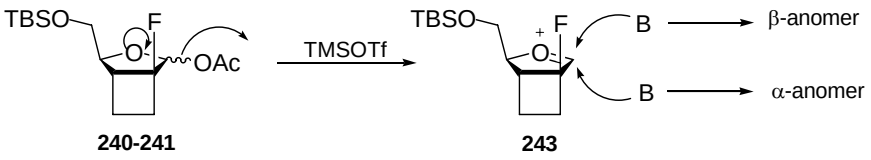
According to Vorbrüggen, the mechanism of the reaction starts with the formation of the oxonium ion **242** as a result of the loss of the acetate group. This process would take place with the participation of the vicinal ester group (Scheme 63).[109] In a second step this sugar cation is attacked by the *per*-silylated nucleobase which acts as the nucleophile. Although the catalyst is theoretically recovered, one equivalent of TMSOTf is inactivated during the process due to σ-complex formation with the base. Thus, application of 1.1-1.3 equivalents of TMSOTf dramatically shortens the reaction time.

[108] a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255. b) Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*, John Wiley & Sons: New York, 2001.
[109] Vorbrüggen, H.; Hoefle, G. *Chem. Ber.* **1981**, *114*, 1256-1268.



Scheme 63. Mechanistic proposal for the *N*-glycosylation catalyzed by trimethylsilyl triflate, Vorbrüggen (1981).

In the event of lacking a participating group, which is the case of acetates **240** and **241**, an oxonium ion like **243** is formed (Scheme 64). In general, the coupling reaction of 2-deoxysugars with silylated bases proceeds without selectivity. This is due to the planarity of the cation which is not expected to have any significant facial influence in the approach of the base. In the present case, despite the presence of the cyclobutane ring that might partially block the α-face of the sugar, the large electronegativity of the fluorine atom lying in the opposite face could play a significant role (i.e., dipole-dipole repulsion).[110] However, since the α-anomer is also interesting in order to evaluate its antiviral activity,[111] no efforts were made to achieve a diastereoselective reaction. In fact, the α-isomer of some of the 2'-fluoro-2',3'-dideoxy-2',3'-didehydronucleosides described by Chu's group displayed potent anti-HIV activity whereas their β-isomers were inactive.[10f]



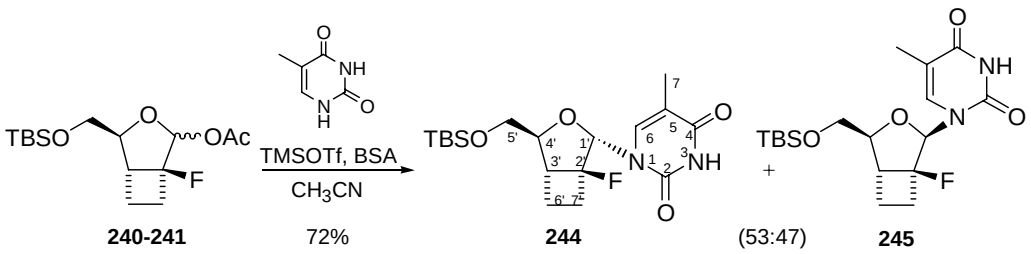
Scheme 64. Proposed intermediate in the Vorbrüggen nucleosidation.

[110] Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis*, **1995**, 1465-1479.
[111] Gosselin, G.; Bergogne, M.-C.; de Rudder, J.; de Clercq, E.; Imbach, J.-L. *J. Med. Chem.* **1986**, *29*, 203-213, and references cited therein.

The preparation of persilylated nucleoside bases can be achieved either in a previous step using HMDS (1,1,1,3,3,3-hexamethyldisilazane)[108a] or following a one-pot procedure described by Dudycz and Wright.[112] This modification uses BSA (*N*,*O*-bis(trimethylsilyl)acetamide) as a silylating reagent.

6.1.2.1. *N*-glycosylation: introduction of thymine

The latter methodology was applied to a mixture of acetates **240** and **241**. Thus, BSA was added to a suspension of thymine in acetonitrile and, once the mixture became a clear solution, an acetonitrile solution of **240**-**241** and TMSOTf were successively added, leading to a 53:47 mixture of two compounds identified by their NMR data as the thymine α- and β-nucleosides **244** and **245**, respectively, in 72% global yield (Scheme 65).[113] It must be pointed that it took 24 h for the reaction to be completed. This low reaction rate may be caused by the presence of the electronegative fluorine atom vicinal to the intermediate oxonium cation which would difficult its formation and the posterior approach of the nucleophile.



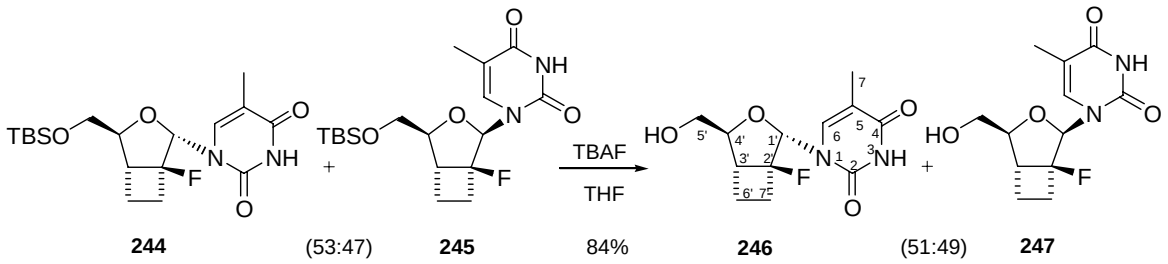
240-241 72% **244** (53:47) **245**

Scheme 65. Preparation of the nucleoside analogues **244** and **245** by Vorbrüggen nucleosidation.

Due to the impossibility to separate **244** from **245**, the silyl cleavage step was carried out with the mixture of nucleosides. Thus, treatment of a THF solution of **244** and **245** with TBAF at room temperature furnished, after purification by column chromatography, a white solid in 43% yield (28% overall yield from **179**) identified by its spectroscopical data as the α-nucleoside **246**, with $[\alpha]_D$: -103.3 (*c* 0.30, $CHCl_3$) and mp: 73-76 ºC; and another white solid, in 41% yield (26% overall yield from **179**),

[112] Dudycz, L. W.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33-44.
[113] Beyond this point the usual non-systematic numbering of nucleosides will be used for the synthesized nucleosides. The systematic numbering for these compounds will be used in the experimental section.

identified as the β-anomer **247**, with $[\alpha]_D$: +25.5 (*c* 0.55, $CHCl_3$) and mp: 147-149 ºC (Scheme 66).



Scheme 66. Cleavage of the protecting group of **244** and **245**.

The determination of the anomeric configuration was established through the analysis of their ^{1}H and ^{13}C-NMR spectra. In this case it is noteworthy that the $J_{1',F}$ on the β-nucleoside **247** is much higher (13.4 Hz) than it would be predicted according to the expected dihedral angle between H-1' and F. On the other hand, a $J_{1',F}$=15.2 Hz was assigned to the α-nucleoside **246**. This tendency will be a constant for all the fluoronucleosides prepared in the present work: both epimers show similar values of $J_{1',F}$ though always higher values are assigned to the α-nucleosides. A possible explanation for this behaviour may be an alteration of the expected dihedral angle in β-nucleosides caused by dipole-dipole repulsion between the fluorine atom and the aromatic nucleobase located in *cis*.

Analysis of the values of the $J_{C1'-F}$ carbon-fluorine coupling constant showed a great difference between the α-nucleoside, $J_{C1'-F}$=41.0 Hz, and the β-nucleoside, $J_{C1'-F}$=17.0 Hz. This tendency will also be observed for all the others fluoronucleoside analogues described in the present work, showing the α-nucleosides values of $J_{C1'-F}$ always close to 40 Hz whereas lower values, close to 18 Hz, will be observed for β-nucleosides. Therefore, the value of $J_{C1'-F}$ became a useful tool to determine the configuration of the anomeric position of the fluoronucleosides synthesized in the present chapter.

In order to confirm the assignment of **246** and **247**, NOESY experiments were recorded for both nucleosides. Thus, the analysis of the experiment performed with **246** shows correlation between the olefinic proton H-6 of the thymine moiety and H-4' and the cyclobutane H-6'endo indicating that the nucleobase and H-4' lie in the same face of the furanose (Figure 44). On the other hand, cross-peak exists between the anomeric

proton H-1’ and both hydroxymethylene protons H-5’ corroborating the assignment of the anomeric center as α. On the contrary, the NOESY experiment of the β-isomer **247** shows cross-peaks between H-6 and both H-5’ and between H-1’ and H-4’, indicating that the nucleobase and the hydroxymethyl group are on the same side of the sugar moiety (Figure 45).

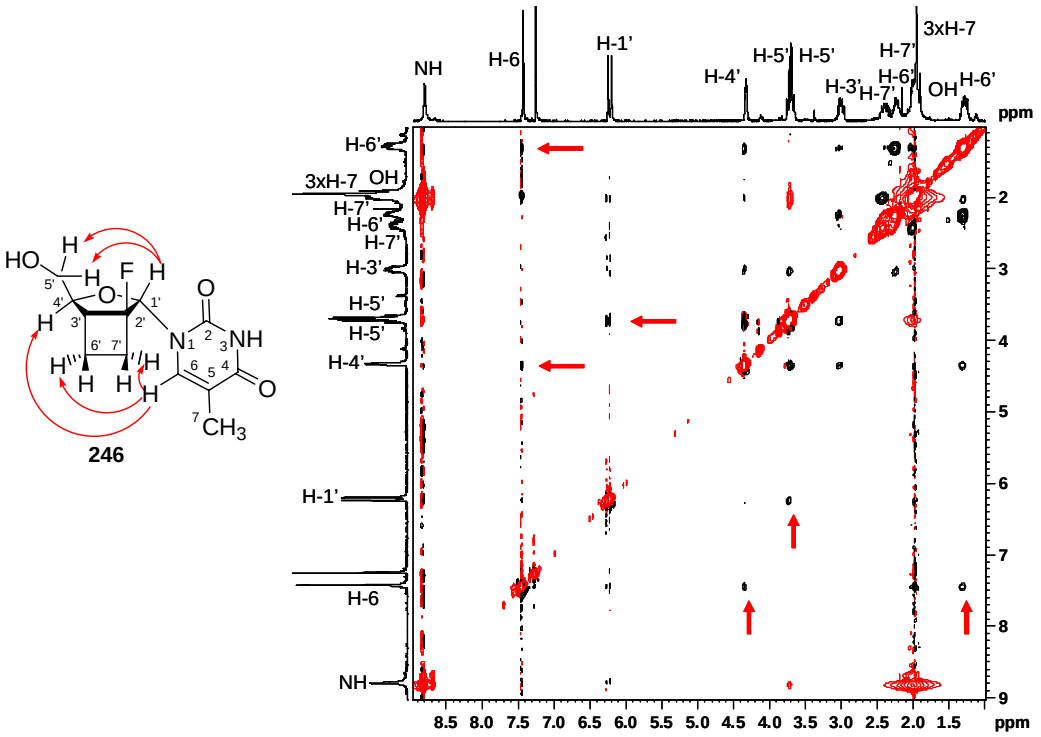


Figure 44. NOESY experiment of the α-isomer **246** ($CDCl_3$, 360 MHz).

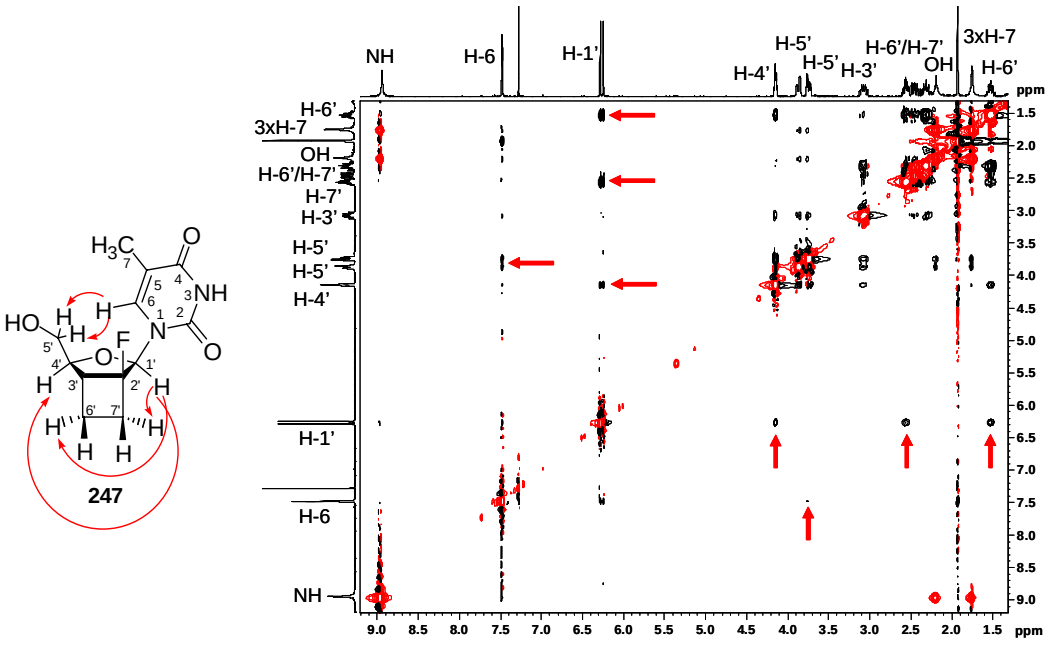
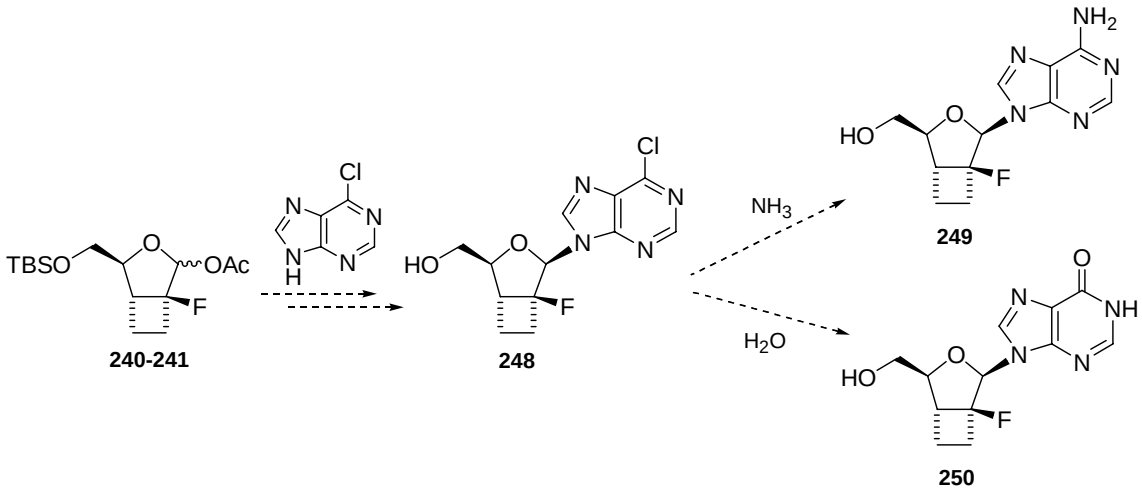


Figure 45. NOESY experiment of the β-isomer **247** ($CDCl_3$, 360 MHz).

Finally, the assignment of the attachment site of the pyrimidine base was determined on the basis of HMBC experiments which showed cross-peaks between H-6 and C-1' and between C-6 and H-1' for both isomers, indicating *N*-1 regioisomery.

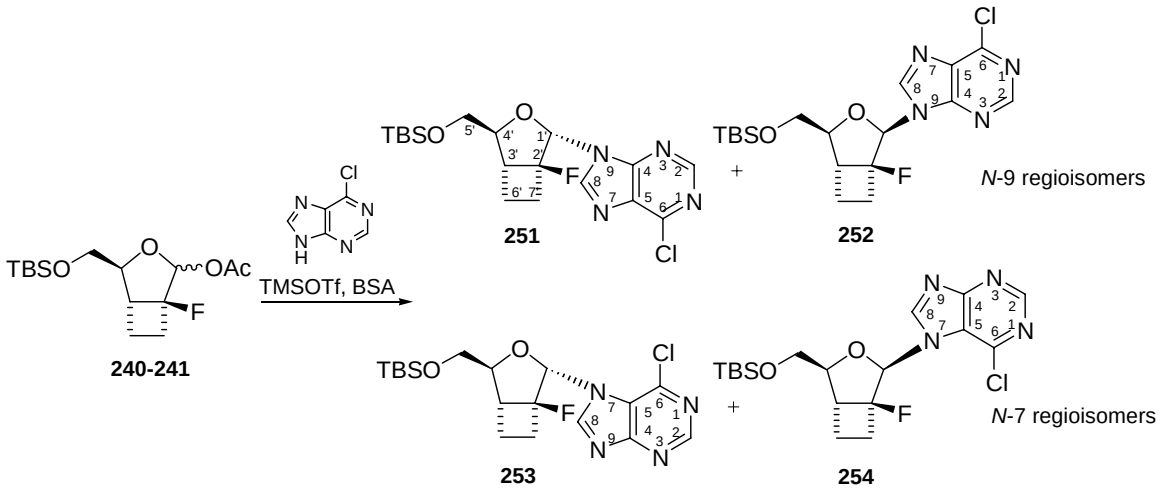
6.1.2.2. *N*-glycosylation: introduction of purine nucleobases

The preparation of the purine nucleoside cyclobutane analogues bearing an adenine or hypoxanthine nucleobase was achieved following a divergent methodology involving the introduction of 6-chloropurine (Scheme 67). The presence of an aromatic chlorine atom converts the 6-chloropurine derivative **248** into a polyvalent intermediate as it can be substituted by NH_2 and OH groups leading to the desired purine nucleosides **249** and **250**, respectively. Furthermore, the 6-chloropurine nucleoside **248** itself is interesting in order to evaluate its antiviral activity.



Scheme 67. Foreseen preparation of purine nucleosides **248**, **249** and **250**.

The reaction of the acetate mixture **240-241** under Vorbrüggen modified conditions carried out in acetonitrile at room temperature afforded a 35:28:22:15 mixture, determined by ^{1}H-NMR, of four nucleosides in 88% global yield (Table 33, entry 1). Purification of the reaction crude by column chromatography allowed the isolation of all four compounds: a white solid identified as the *N*-9 α-anomer **251** with $[\alpha]_D$: -13.8 (*c* 1.60, $CHCl_3$); a colourless oil identified as the *N*-9 β-anomer **252** with $[\alpha]_D$: -16.0 (*c* 0.50, $CHCl_3$); a yellow oil identified as the *N*-7 α-anomer **253** with $[\alpha]_D$: -63.1 (*c* 1.60, $CHCl_3$); and finally, a colourless oil identified as the *N*-7 β-anomer **254** with $[\alpha]_D$: +41.8 (*c* 1.10, $CHCl_3$).



entry	solvent	temperature	time	yield (%)	251:252:253:254 [a]	*N*-9:*N*-7	α:β
1	acetonitrile	25 ºC	7.5 h	88	28:15:35:22	43:57	63:37
2	DCE	83 ºC	2.5 h	77	34:20:23:23	54:46	57:43
3	toluene	100 ºC	1 h	90	59:35:3:3	94:6	62:38

[a] Product ratio was determined by ^{1}H-NMR.

Table 33. Different reaction conditions for the preparation of nucleosides **251-254**.

The lack of regioselectivity observed prompted us to search for different reaction conditions to try to enhance the amount of the *N*-9 isomers. It is known that *N*-9 purine nucleosides are thermodynamically favoured over their *N*-7 isomers,[114] and also that the polarity of the solvent plays a key role on the rate of formation of each regioisomer.[108b] Therefore, we decided to assay the reaction in more apolar solvents (Table 34) and also at higher temperatures.

solvent	ε [73]
acetonitrile	35.9
1,2-dichloroethane	8.0
toluene	2.4

Table 34. Dielectric constant values of the solvents used in the present study.

However, the reaction of the acetate mixture **240-241** in 1,2-dichloroethane (DCE) at 83 ºC with 6-chloropurine only furnished a slightly enriched mixture of the *N*-9 isomers (54:46) in 77% overall yield (entry 2).

[114] Miyaki, M.; Shimizu, B. *Chem. Pharm. Bull.* **1970**, *18*, 1446-1556.

Finally, when the reaction was carried out in toluene at 100 ºC the *N*-9:*N*-7 ratio was outstandingly increased to (94:6) as well as the global yield (90%) (entry 3). Hence, despite that the α:β ratio remained almost unaltered with the variation of polarity of the solvent, the experimental conditions set for the preparation of **251** and **252**, precursors of the target purine nucleosides, were satisfying enough. Nevertheless, it was decided to test the antiviral activity of their *N*-7 isomers as well.

Extensive NMR spectral data, including HMBC and NOESY experiments, provided strong support for the structures of compounds **251-254**. The assignment of the attachment site of the purine base on the *N*-9 isomers **251** and **252** was established by HMBC experiments, which showed correlation between H-1' and the aromatic carbon atoms C-4 and C-8 (Figure 46). On the other hand, cross-peaks were observed between H-1' and C-5 and C-8 for **254**, indicating *N*-7 regiochemistry (Figure 47).

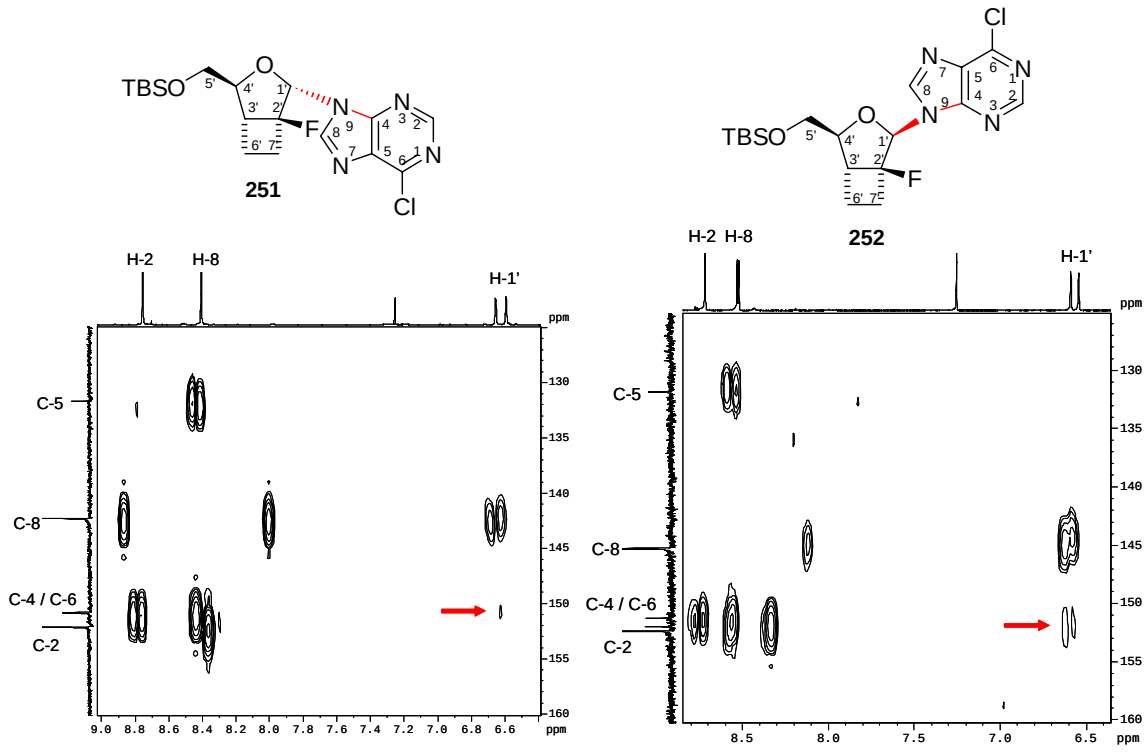


Figure 46. Detail of the HMBC experiment of **251** ($CDCl_3$, 250 MHz) and **252** ($CDCl_3$, 250 MHz), respectively. Elucidation of *N*-9 regiochemistry.

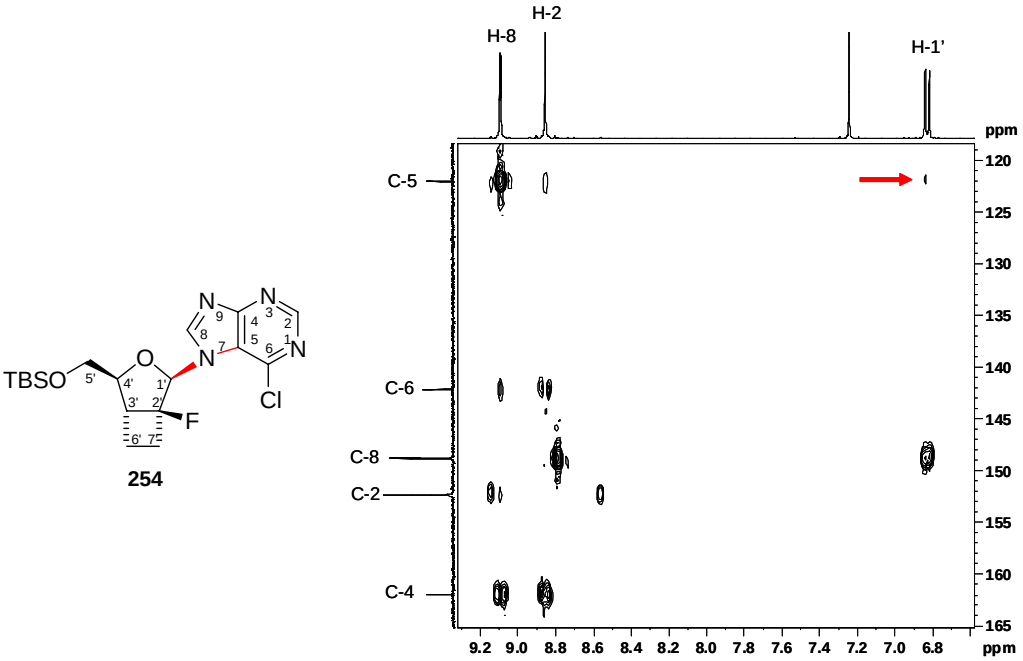


Figure 47. Detail of the HMBC experiment of **254** ($CDCl_3$, 360 MHz). Elucidation of *N*-7 regiochemistry.

However, no cross-peak was observed between H-1' and C-5 for **253**. In this case, the regiochemistry was supported by the higher chemical shift value of the purine C-4 carbon of the *N*-7 isomer **253** (δ 162.2 ppm) compared to that of the *N*-9 isomers **251** and **252** (δ 151.1 and 150.9 ppm, respectively), due to the larger steric congestion existing in the latter.[115] The contrary effect is also seen for C-5 and C-6 (Table 35).

isomer	regiochemistry	C-4 (ppm)	C-5 (ppm)	C-6 (ppm)
251	*N*-9	151.1	132.0	151.1
252	*N*-9	150.9/151.6	131.4	150.9/151.6
253	*N*-7	162.2	121.8	143.2
254	*N*-7	162.4	121.9	141.7

Table 35. Variations of the chemical shifts of aromatic C-4, C-5 and C-6 carbon atoms.

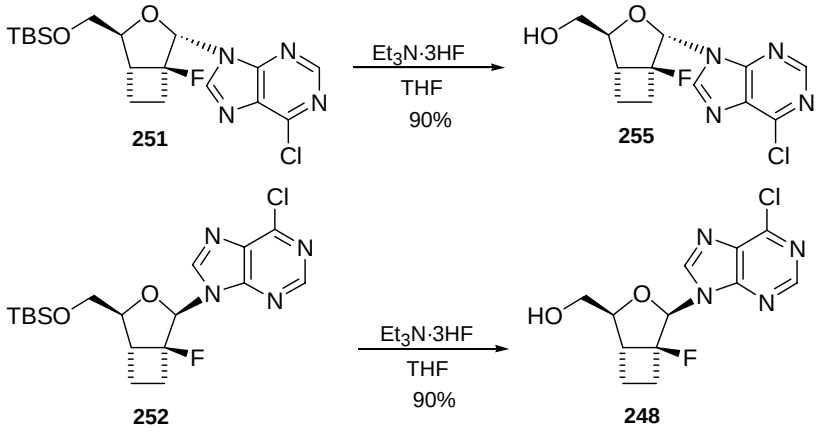
The relative stereochemistry of the new nucleoside analogues was established analyzing the values of proton- and carbon-fluorine coupling constants. The highest values of vicinal proton-fluorine coupling constant between H-1' and F were assigned

[115] Mévellec, L.; Huet, F. *Tetrahedron* **1997**, *53*, 5797-5812.

to the α-anomeric configuration ($J_{1',F}$=15.6 Hz for **251** and $J_{1',F}$=14.0 Hz for **253**) whereas the lowest values were assigned to the β-anomeric configuration ($J_{1',F}$=11.5 Hz for **252** and $J_{1',F}$=8.2 Hz for **254**). Moreover, the highest values of carbon-fluorine coupling constant between C-1' and F were assigned to the α-anomeric configuration ($J_{C\text{-}1',F}$=40.7 Hz for **251** and $J_{C\text{-}1',F}$=38.7 Hz for **253**) meanwhile the lowest values were assigned to the β-anomeric configuration ($J_{C\text{-}1',F}$=17.8 Hz for **252** and $J_{C\text{-}1',F}$=18.1 Hz for **254**). These assignments were further confirmed by n.O.e. differential and NOESY experiments with showed correlation between H-1' and H-5' for the α-anomers **251** and **253**, and between H-1' and H-4' for the β-anomers **252** and **254**. Finally, both *N*-9 and *N*-7 β-nucleosides **252** and **254** possess a characteristic long-range coupling between the fluorine atom and the H-8 proton of the purine that is not observed in their corresponding α-epimers.[116] A long-rage carbon-fluorine coupling constant is also exclusively observed in their ^{13}C-NMR spectra between the fluorine atom and C-8 for **252** and **254**.

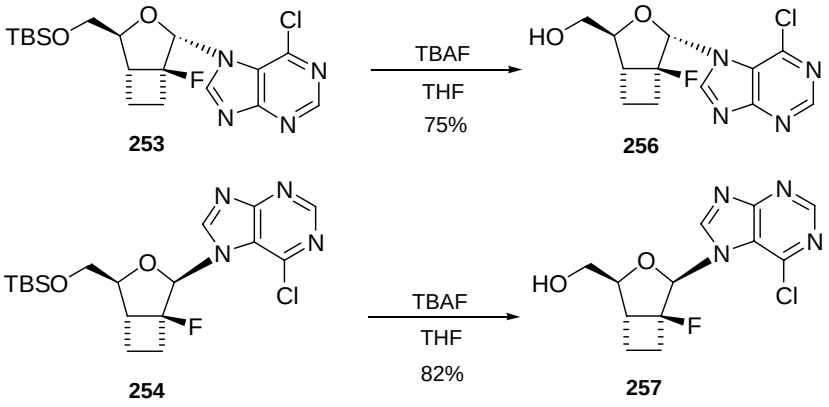
Next, we proceeded to the deprotection of the hydroxyl group of all four isomers in parallel to provide the required nucleosides for evaluation of the anti-HIV activity. Thus, reaction of the α-isomer **251** with $Et_3N{\cdot}3HF$ in THF afforded a white solid in 90% yield identified by its spectroscopical data as the nucleoside **255** with $[\alpha]_D$: -13.3 (*c* 1.05, $CHCl_3$) and mp: 123-126 ºC (Scheme 68). Deprotection of the silyl ether **252** under the same conditions, furnished in 90% yield a white solid identified by its spectroscopical data as the β-anomer **248** with $[\alpha]_D$: -16.7 (*c* 0.90, MeOH) and 283-287 ºC. In both cases, reactions performed with TBAF in THF afforded slightly lower yields.

[116] Herdewijn, P.; Pauwels, R.; Baba, M.; de Clercq, E. *J. Med. Chem,* **1987**, *30*, 2131-2137, and references cited therein.



Scheme 68. Cleavage of the silyl protecting group of **251** and **252**.

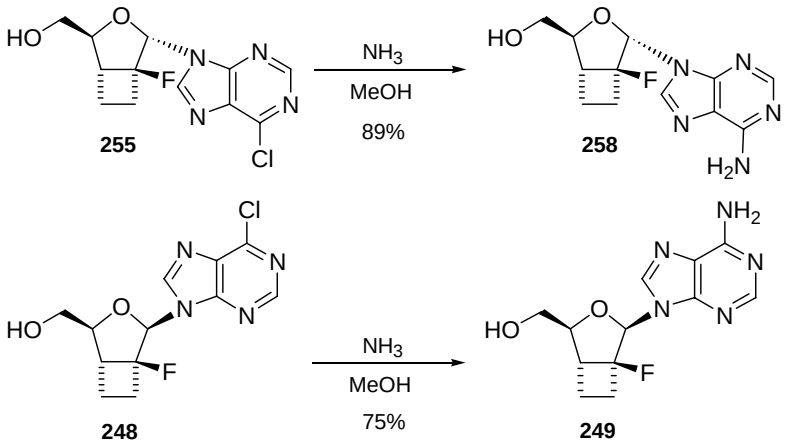
Contrary to the results discussed above for the *N*-9 isomers, the *N*-7 nucleosides underwent silyl cleavage in better yields using TBAF in THF. Thus, upon these conditions **253** afforded in 75% yield a white solid identified by its spectroscopical data as the α-anomer **256** with $[\alpha]_D$: -85.0 (*c* 0.80, MeOH) and mp: 122-124 ºC (Scheme 69). Finally, when the same procedure was applied to **254** a white solid was obtained in 82% yield being identified by its spectroscopical data as the β-anomer **257** with $[\alpha]_D$: +83.8 (*c* 0.65, MeOH) and mp: 148-151 ºC.



Scheme 69. Cleavage of the silyl protecting group of **253** and **254**.

The divergent synthetic pathway towards the preparation of adenine and hypoxanthine nucleosides was carried out exclusively with the *N*-9 anomers **255** and **248**. First, in order to substitute the aromatic chlorine atom by an amino group, the 6-chloropurine derivatives were reacted with ammonia in methanol at 90 ºC under pressure for 40 h. The reaction with the α-derivative **255** furnished, after purification by

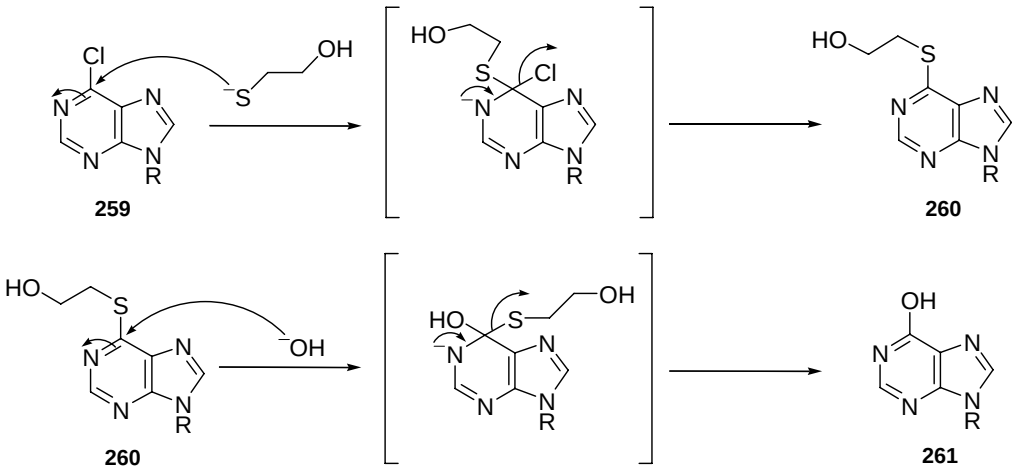
column chromatography and recrystallization in methanol, a white solid in 89% yield (38% overall yield from **179**) identified by its spectroscopical data as the adenine nucleoside **258** with $[\alpha]_D$: -45.7 (*c* 0.35, MeOH) and mp: 210-213 ºC (Scheme 70). The same reaction carried out with **248** furnished a white solid in 75% yield (19% overall yield from **179**) after purification by column chromatography, being identified by its spectroscopical data as the adenine nucleoside **249** with $[\alpha]_D$: -5.7 (*c* 0.35, MeOH) and mp: 248-251 ºC.



Scheme 70. Preparation of the adenine nucleosides **258** and **249**.

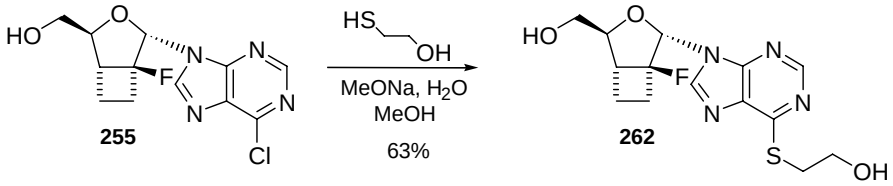
Finally, the substitution of the aromatic chlorine atom by an hydroxyl group was attempted. One of the most common methodologies to achieve this transformation lies in the treatment of a 6-chloropurine derivative **259** with 2-mercaptoethanol and sodium methoxide in refluxing aqueous methanol.[117] As depicted in Scheme 71, once the aromatic chlorine has been displaced by the sulphide, the high lability[118] of an intermediate **260** allows its facile hydrolysis under basic conditions to yield the hypoxanthine compounds type **261**.

[117] a) Lee, W. W.; Martinez, A. P.; Goodman, L.; Henry, D. W. *J. Org. Chem.* **1972**, *37*, 2923-2927. b) Pathak, T.; Bazin, H.; Chattopadhyaya, J. *Tetrahedron* **1986**, *42*, 5427-5441.
[118] Johnston, T. P.; Holum, L. B.; Montgomery, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 6265-6271.



Scheme 71. Mechanism of the reaction of preparation of hypoxanthine derivatives **261**.

Nevertheless, the above conditions did not result in direct hypoxanthine formation when they were applied to nucleoside **255**. Instead, the sulphide **262** was isolated in 63% yield as a colourless oil (Scheme 72).



Scheme 72. First attempt of preparation of an hypoxanthine nucleoside.

The presence of the mercaptoethanol moiety in **262** was confirmed by HRMS (High Resolution Mass Spectroscopy) and its site of attachment was elucidated with the help of the HMBC experiment which shows a strong correlation between the aromatic carbon C-6 and the α-sulphur protons H-1'' indicating the formation of a bond between C-6 and the sulphur atom (Figure 48).

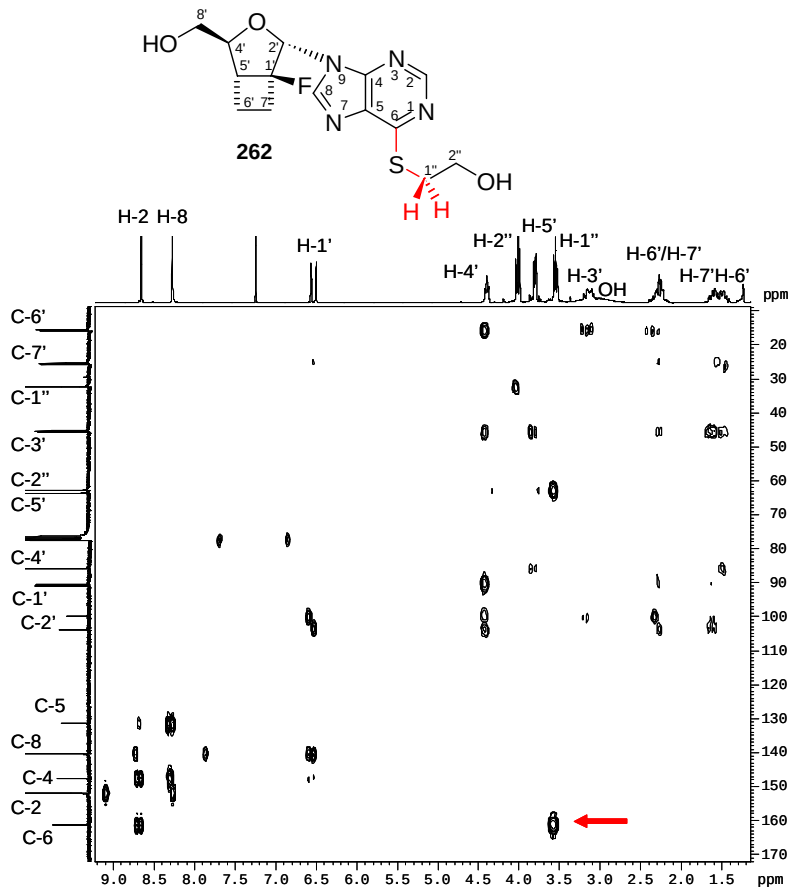
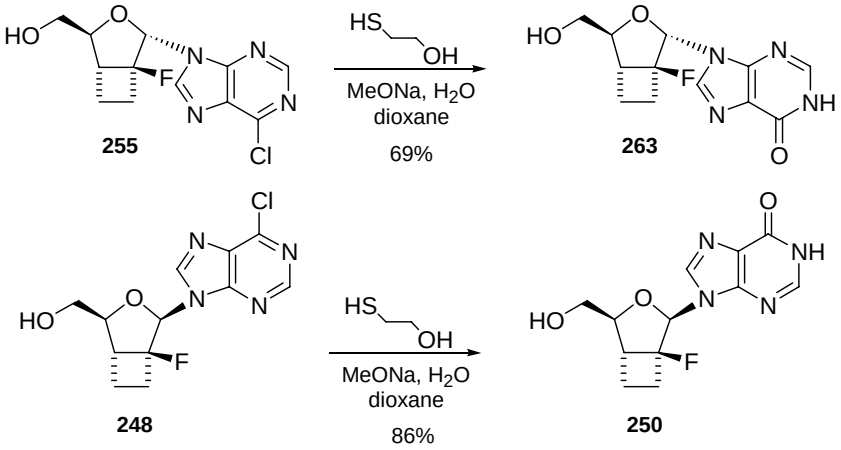


Figure 48. HMBC experiment of **262** ($CDCl_3$, 250 MHz).

Since prolonged reaction times and further addition of water and sodium methoxide were found to be ineffective in transforming **262** into the desired nucleoside, we decided to perform the reaction in refluxing dioxane.[119] Satisfyingly, this modification caused the targeted conversion to be complete after 4 days. Subsequent acidification with acetic acid, purification by column chromatography and recrystallization in methanol afforded a white solid in 69% yield (29% overall yield from **179**) identified by its spectroscopical data as the hypoxanthine derivative **263** with $[\alpha]_D$: -20.0 (*c* 0.30, DMSO) and mp: 244-246 ºC (Scheme 73). These optimized reaction conditions were applied to the β-nucleoside **248** leading to the formation of a white solid in 86% yield (22% overall yield from **179**) after column chromatography. Analysis of its spectroscopical data led to its identification as the hypoxanthine derivative **250** with $[\alpha]_D$: +8.0 (*c* 0.50, MeOH) and mp: 127-129 ºC.

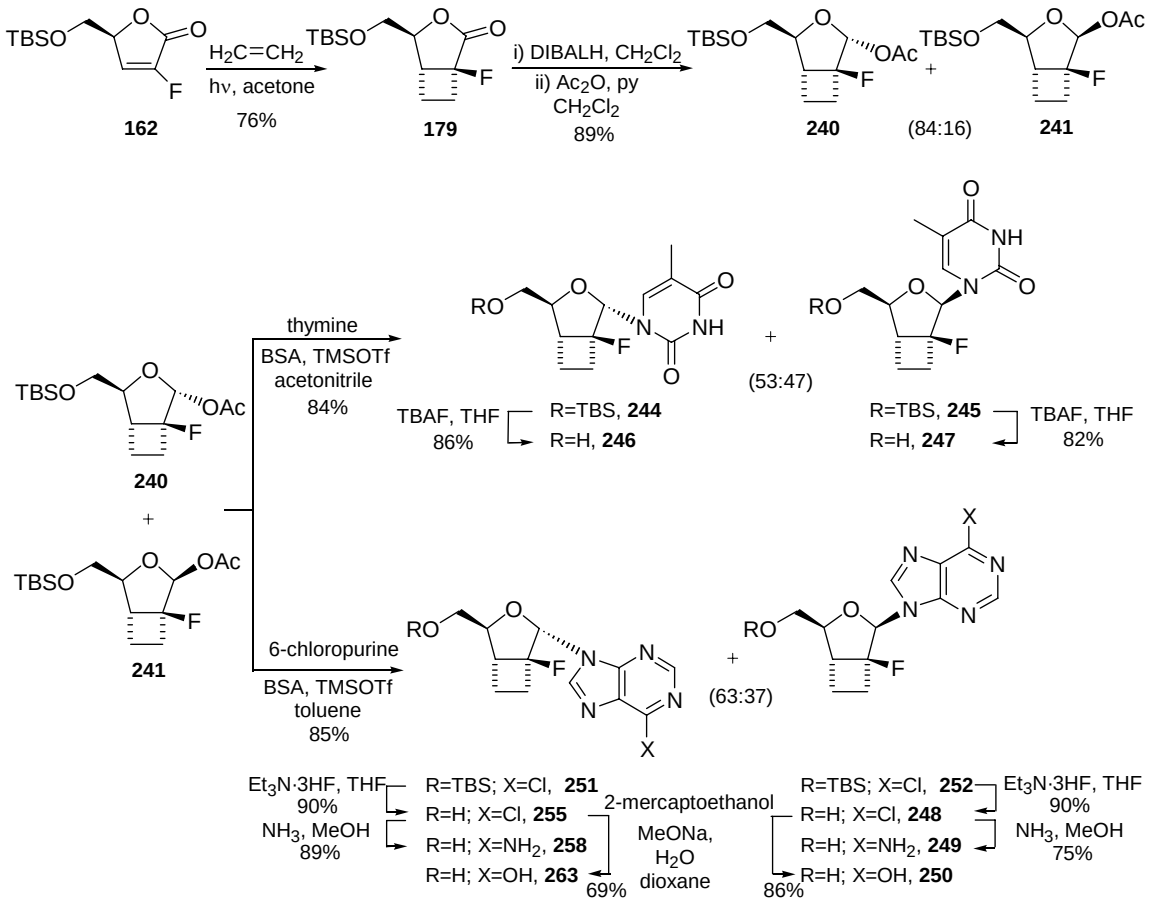
[119] Paquette, L. A.; Kahane, A. L. ; Seekamp, C. K. *J. Org. Chem.* **2004**, *69*, 5555-5562.



Scheme 73. Preparation of the hypoxanthine nucleosides **263** and **250**.

The structure of the hypoxanthine nucleosides **263** and **250** was confirmed by their characteristic NH broad signal in the ^{1}H-NMR at 12.40 and 12.30 ppm as well as the intense IR absorption of their carbonyl groups at 1691 and 1698 cm^{-1}, respectively.

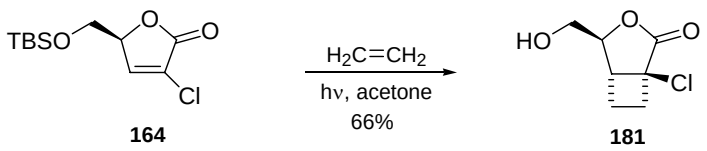
In summary, six new 2'-fluoronucleoside analogues bearing a cyclobutane ring fused to the furanose moiety have been synthesized in good yields following a short and divergent synthetic pathway (Scheme 74).



Scheme 74. Synthesis of 2'-fluoronucleoside analogues conformationally restricted by a cyclobutane ring.

6.2. Synthesis of 2'-chloronucleoside analogues conformationally locked by a cyclobutane ring

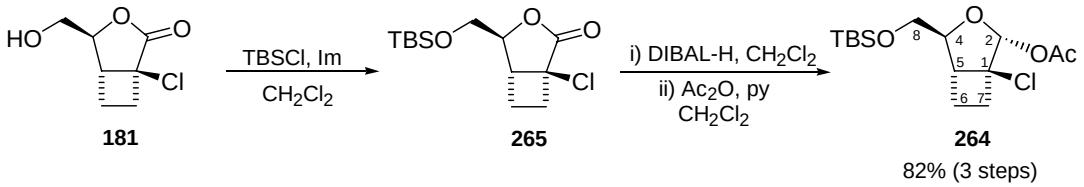
The synthesis of the required cyclobutane derivative **181** was performed following the methodology described in the chapter IV-1.2.3. (Scheme 75). Therefore, the [2+2] photocycloaddition of 3-chloro-2(5*H*)-furanone **164** to ethylene afforded the cycloadduct **181** in 66% yield.



Scheme 75. Preparation of the cyclobutane derivative **181**.

6.2.1. Preparation of the bicyclic acetate 264

Firstly, the hydroxyl group of **181** was protected using *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 to afford a clear crude containing the silyl ether **265** which was treated without further purification with DIBAL-H in CH_2Cl_2 at -78 ºC (Scheme 76). The resulting crude lactol reacted with acetic anhydride and pyridine in CH_2Cl_2 at room temperature to afford, after purification by column chromatography a unique compound, identified as the α-acetate **264** in 82% yield for the 3 steps.



Scheme 76. Synthesis of the α-acetate **264**.

The determination of the α configuration of the anomeric center of **264** was accomplished by a NOESY experiment which shows cross-peaks between H-2 and the hydroxymethylene protons H-8 indicating that they are located in the same face of the furanose ring (Figure 49).

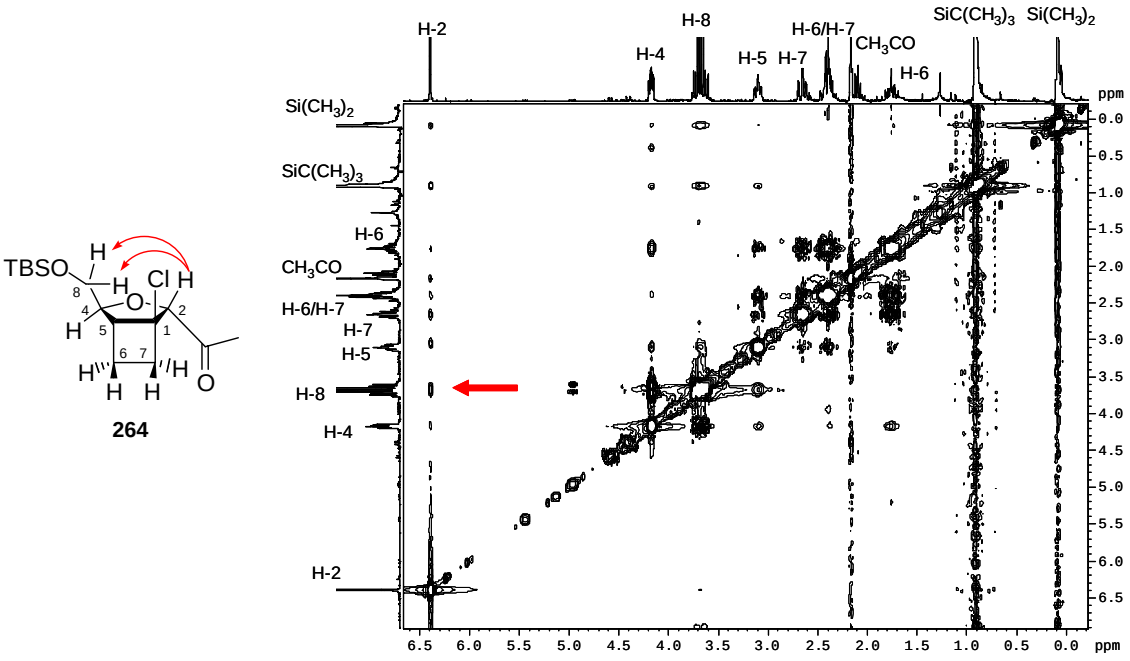
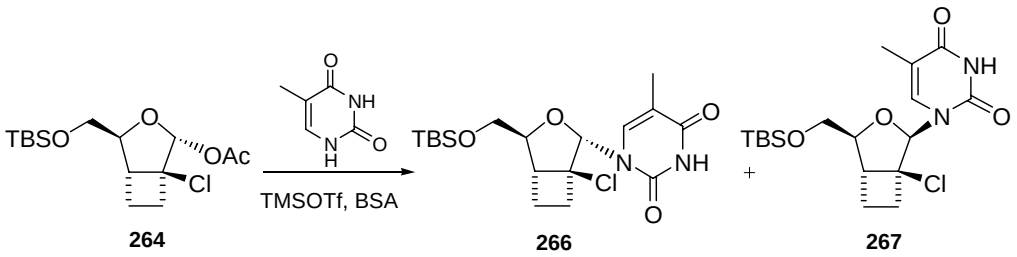


Figure 49. NOESY experiment of the acetate **264** ($CDCl_3$, 250 MHz).

6.2.2. *N*-glycosylation: introduction of thymine

Reaction of acetate **264** with thymine in acetonitrile using BSA as a silylating agent and TMSOTf as a Lewis acid, furnished, after purification by column chromatography, a 64:36 mixture of nucleosides **266** and **267** in 92% yield (Table 36, entry 1). All attempts to separate both isomers were unsuccessful and the assignment of the anomeric center of the nucleosides was determined in a later synthetic step. Accordingly, the major isomer was identified as the α-nucleoside **266** and the minor as the β-nucleoside **267**.



264 **266** **267**

entry	solvent	temperature	time	yield (%)	266:267 [a]
1	acetonitrile	25 º C	3 h	92	64:36
2	DCE	25 º C	27 h	97	56:44
3	toluene	25 º C	43 h	94	53:47

[a] Product ratio was determined by ^{1}H-NMR.

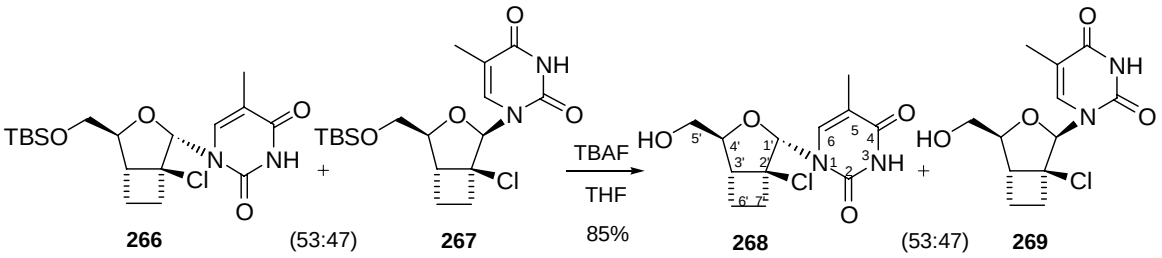
Table 36. Different reaction conditions for the preparation of the thymine nucleosides **266** and **267**.

The effect of the polarity on the outcome of the nucleobase coupling reaction was also investigated. The reaction was carried out in DCE leading to a 56:44 mixture of the nucleosides **266** and **267** with an even better yield (97%) (entry 2). Finally, the nucleosidation reaction was performed in toluene affording a 53:47 mixture of the same compounds in 94% yield (entry 3). These last experimental conditions turned to be the optimal as the ratio of products was very close to 50:50 whereas the excellent yield obtained was almost as good as in DCE.

It is noteworthy that similar diastereoselectivity values have been obtained for both fluoro and chloro building blocks in the *N*-glycosylation reaction with thymine.

Next, treatment of a 53:47 mixture of **266** and **267** in THF with TBAF at room temperature furnished, after column chromatography, the nucleosides **268** and **269** in 85% yield and in the same proportion than the starting mixture (Scheme 77). Pure

samples of both compounds were obtained by preparative HPLC, allowing the identification of the major isomer by its spectroscopical data as the α-nucleoside **268** with $[\alpha]_D$: -17.4 (*c* 0.46, $CHCl_3$) and mp: 127-130 ºC (35% overall yield from **181**); and the β-anomer **269** with $[\alpha]_D$: +55.7 (*c* 0.70, $CHCl_3$) and mp: 48-50 ºC (31% overall yield from **181**).



Scheme 77. Cleavage of the protecting group of 2'-chloronucleosides **266** and **267**.

The assignment of the configuration of the anomeric centers was determined on the basis of NOESY experiments. Thus, **268** shows cross-peak between the olefinic proton H-6 of the thymine moiety and H-4' indicating that both are on the same face of the furanose (Figure 50). Moreover, H-6 is also close in the space with the cyclobutane protons H-6'endo and H-7'endo. On the other hand, the anomeric proton H-1' has correlation with both hydroxymethylene protons H-5' corroborating the assignment of the anomeric center configuration.

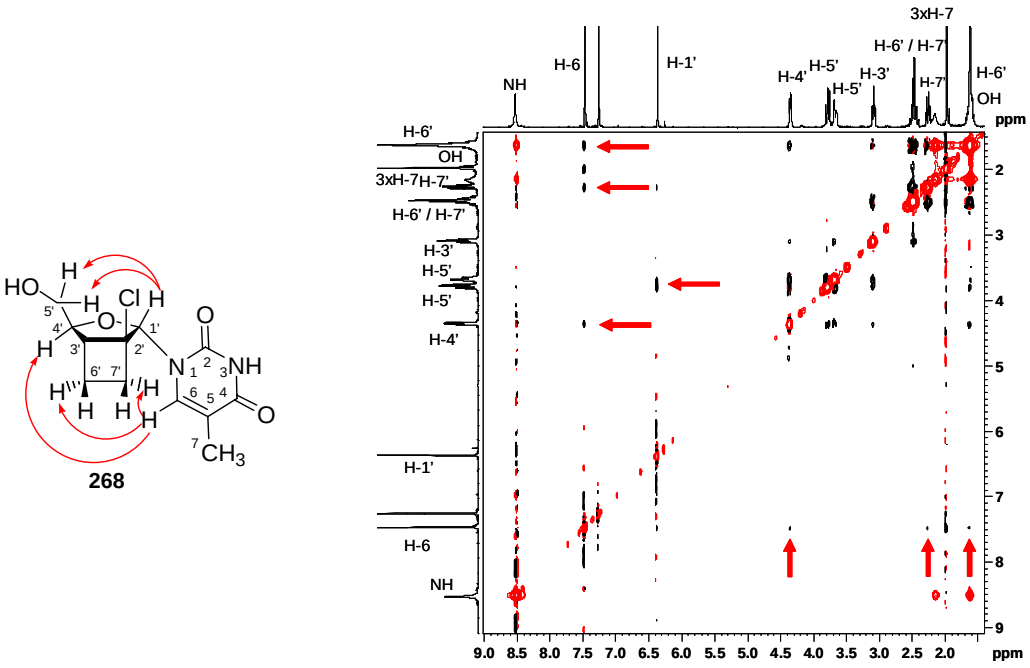


Figure 50. NOESY experiment of **268** ($CDCl_3$, 360 MHz).

On the contrary, the NOESY experiment of **269** shows cross-peak between H-6 and both H-5' protons indicating that the nucleoside base lies in the β face of the furanose ring (Figure 51). The same conclusion can be extracted by observation of the correlation between H-1' and H-4', H-6'endo and H-7'endo.

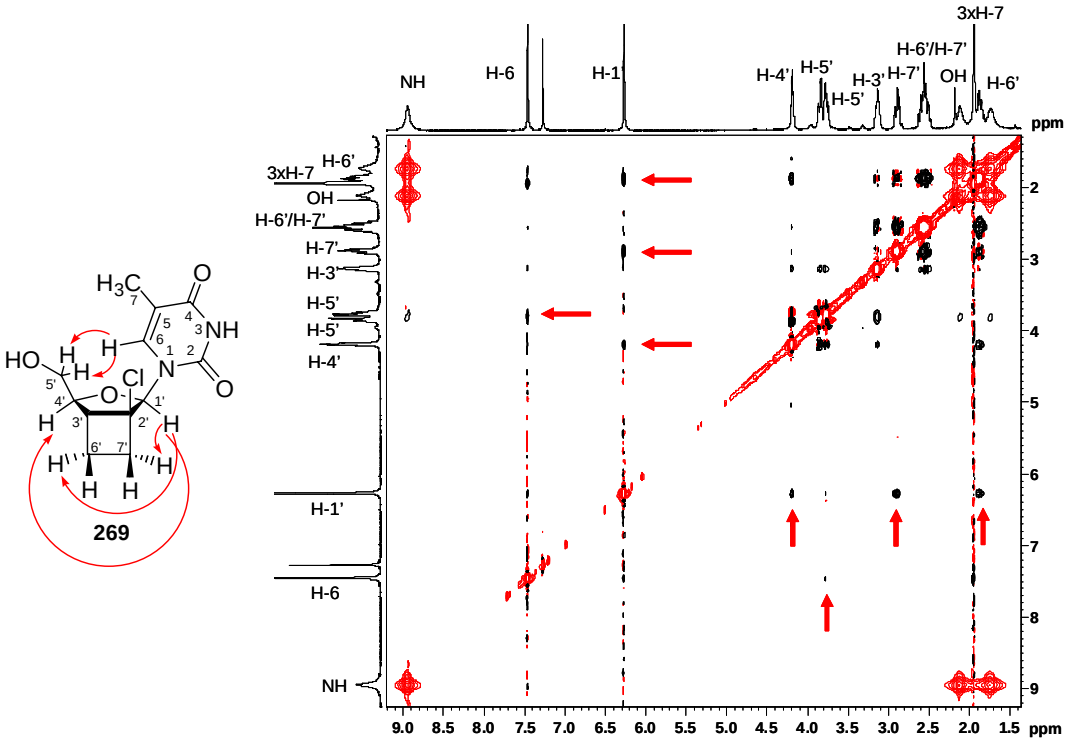
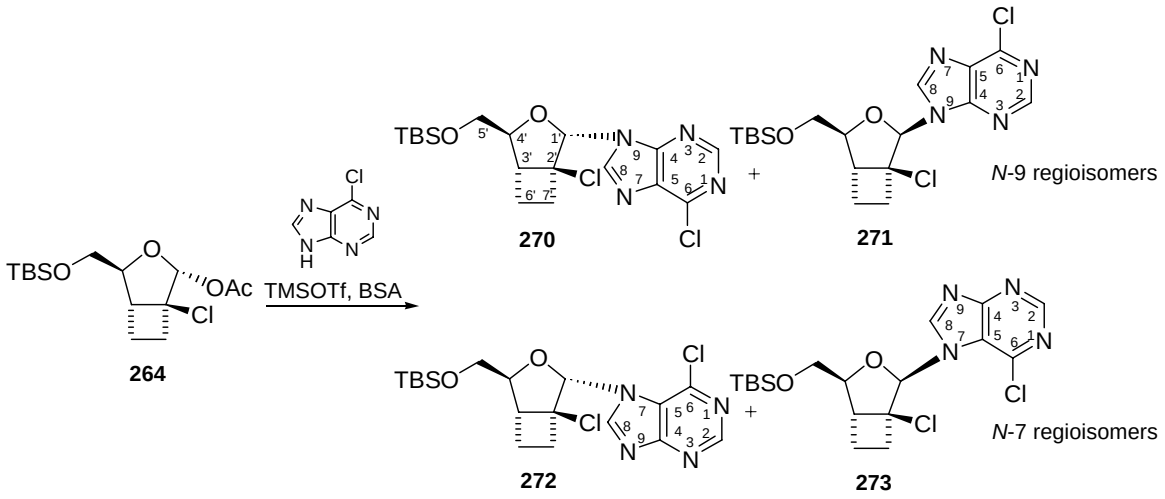


Figure 51. NOESY experiment of **269** ($CDCl_3$, 360 MHz).

6.2.3. *N*-glycosylation: introduction of purine nucleobases

Following the same strategy as in the synthesis of fluoronucleosides, the construction of adenine and hypoxanthine moieties was achieved following a divergent methodology involving the use of 6-chloropurine. Reaction of acetate **264** with silylated 6-chloropurine and TMSOTf in acetonitrile at room temperature afforded a 47:42:7:4 mixture of four nucleosides **270-273** in 87% global yield (Table 37, entry 1). The ratio of compounds was established by analysis of the crude ^{1}H-NMR spectrum. Purification by column chromatography of the reaction crude allowed the isolation of all four compounds. Analysis of their spectroscopical data permits the identification of a white solid as the *N*-9 α-anomer **270** with $[\alpha]_D$: +17.2 (*c* 2.5, $CHCl_3$); a colourless oil as the *N*-9 β-anomer **271** with $[\alpha]_D$: -30.0 (*c* 0.90, $CHCl_3$); a colourless oil as the *N*-7 α-

anomer **272** with $[\alpha]_D$: -36.8 (*c* 1.25, $CHCl_3$); and a colourless oil as the *N*-7 β-anomer **273** with $[\alpha]_D$: +52.5 (*c* 0.40, $CHCl_3$).



entry	solvent	temperature	time	yield (%)	270:271:272:273	*N*-9:*N*-7	*α*:*β*
1	acetonitrile	25 ºC	3.5 h	87	42:4:47:7	46:54	89:11
2	acetonitrile	82 ºC	1 h	95	74:13:8:5	87:13	82:18
3	DCE	25 ºC	27 h	65	31:1:58:10	32:68	89:11
4	DCE	83 ºC	0.5 h	78	70:11:13:6	81:19	83:17
5	toluene	25 ºC	16 h	38	39:5:50:6	44:56	89:11
6	toluene	100 ºC	1 h	77	85:15:0:0	100:0	85:15

[a] Product ratio was determined by ^{1}H-NMR.

Table 37. Different reaction conditions for the preparation of nucleosides **270-273**.

Once again, the lack of regioselectivity observed and the fact that the target *N*-9 β-anomer **271** was obtained in low yield (<4%) led us to search better reaction conditions. Thus, the reaction in acetonitrile was repeated heating the mixture at 82 ºC increasing the amount of *N*-9 isomers (87:13) (entry 2). Acetate **264** was also treated with silylated thymine in the less polar DCE at room temperature yielding a mixture of the four nucleosides being the undesired *N*-7 isomers the major compounds (32:68) (entry 3). The tendency was inverted (81:19) when the reaction was performed at 83 ºC (entry 4). Finally, **264** was also submitted to the same conditions in toluene at room temperature leading to a mixture of regioisomers close to (50:50) (entry 5). Higher temperature entailed the formation of the *N*-9 nucleosides with an outstanding complete regioselectivity and good yield, 77% (entry 6).

Despite the low yield in which **271** was prepared, and taking into account that the primary objective of the study was the evaluation of the antiviral activity of a new family of chloronucleosides, the latter experimental conditions for the preparation of **270** and **271**, were satisfactory enough. The antiviral activity of the hydroxyl-free derivatives of the *N*-7 isomers obtained in the preliminary assays was also tested.

From these results it can be concluded that the presence of a chlorine atom in the sugar moiety gave a higher α-stereoselectivity in the synthesis of 6-chloropurine nucleoside analogues compared to a fluorine atom. It is inferred that the bulkier halogen atom may difficult the approach of the 6-chloropurine not only by dipole-dipole repulsion but also by steric effects.

The structural elucidation of all four nucleosides was established with the help of HMBC experiments. Hence, cross-peak can be observed between H-1' and C-4 in the *N*-9 isomers **270** and **271** (Figure 52).

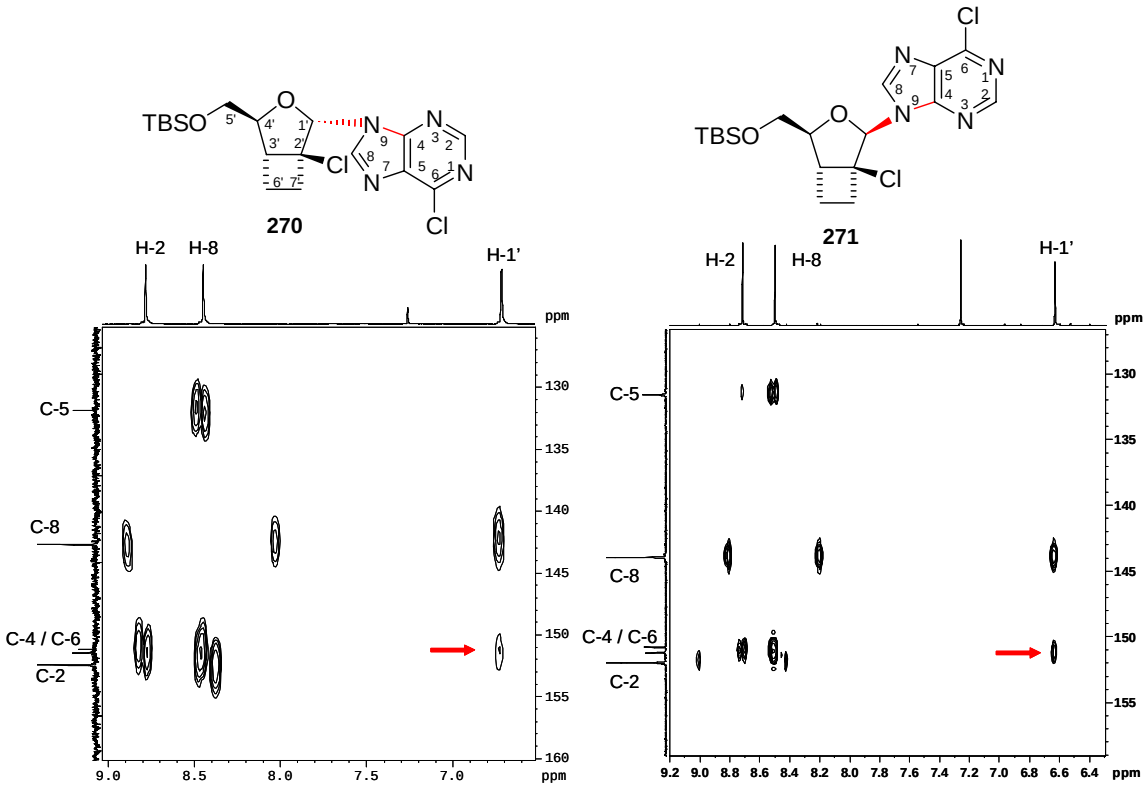


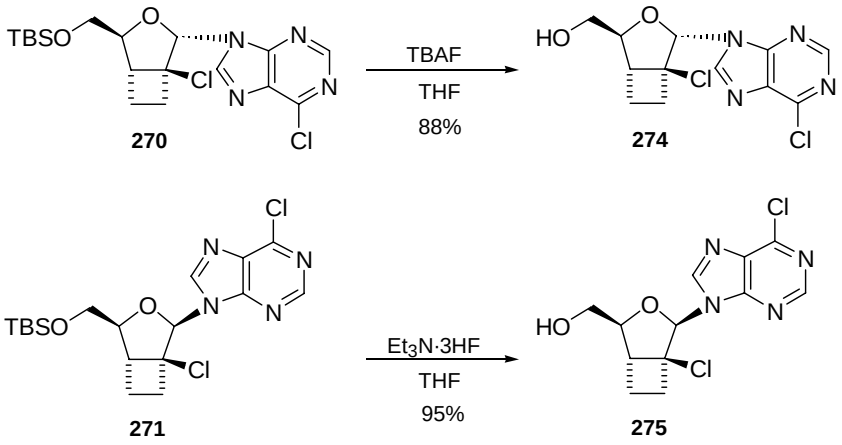
Figure 52. Detail of the HMBC experiment of **270** ($CDCl_3$, 250 MHz) and **271** ($CDCl_3$, 360 MHz). Elucidation of *N*-9 regiochemistry.

However, no cross-peak is observed between H-1' and C-5 for **272** and **273**. In this case, the *N*-7 regiochemistry is consistent with the displacement of the chemical shifts of the carbon atoms C-4, C-5 and C-6 referring to their *N*-9 isomers **270** and **271** (Table 38)

isomer	regiochemistry	C-4 (ppm)	C-5 (ppm)	C-6 (ppm)
270	*N*-9	151.4/151.1	131.6	151.4/151.1
271	*N*-9	151.2/150.8	131.6	151.2/150.8
272	*N*-7	162.1	122.1	143.1
273	*N*-7	162.4	122.0	142.0

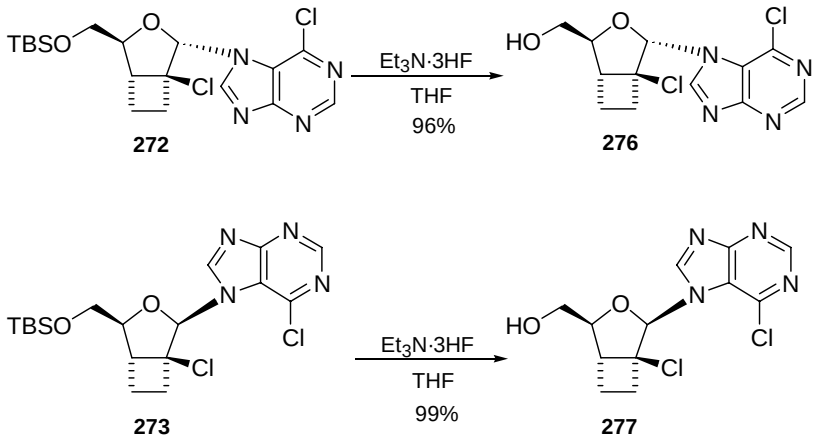
Table 38. Variations of the chemical shifts of aromatic C-4, C-5 and C-6 carbon atoms.

Next, it was proceeded to the deprotection of the hydroxyl group of all four nucleosides in parallel. The cleavage of the silyl ether **270** was performed with TBAF affording a white solid in 88% yield identified by its spectroscopical data as the α-anomer **274** with $[\alpha]_D$: +29.7 (*c* 0.74, $CHCl_3$) and mp: 127-129 ºC (Scheme 78). On the other hand, for **271** deprotection of the silyl moiety gave better results using $Et_3N{\cdot}3HF$ what furnished a colourless oil in 95% yield identified by its spectroscopical data as the β-anomer **275** with $[\alpha]_D$: -23.6 (*c* 0.55, $CHCl_3$).



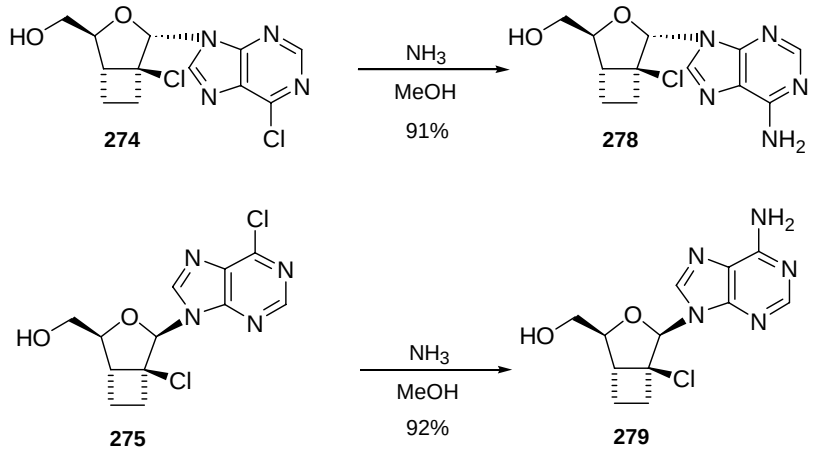
Scheme 78. Cleavage of the silyl protecting group of **274** and **275**.

N-7 α-nucleoside **272** underwent silyl cleavage with $Et_3N{\cdot}3HF$ to afford in 96% yield a white solid identified by its spectroscopical data as the 6-chloropurine derivative **276** with $[\alpha]_D$: -43.3 (*c* 0.60, MeOH) and mp: 125-126 ºC (Scheme 79). Finally, when the same procedure was applied to **273** a white solid was obtained in 99% yield which was identified by its spectroscopical data as the β-nucleoside **277** with $[\alpha]_D$: +72.0 (*c* 0.50, $CHCl_3$). The latter compound showed a certain degree of instability at room temperature.



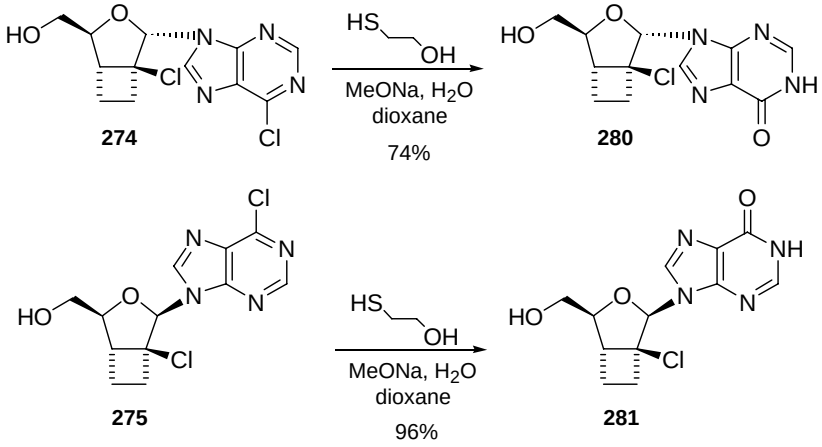
Scheme 79. Cleavage of the silyl protecting group of **276** and **277**.

The substitution of the aromatic chlorine by an amino group to prepare the target adenine nucleosides was achieved by heating **274** and **275** with ammonia in methanol at 90 ºC in a sealed tube for 68 h and 70 h, respectively. Thus, reaction of the α-nucleoside **274** afforded, after column chromatography, a white solid in 89% yield (43% overall yield from **181**) which was identified by its spectroscopical data as the adenine derivative **278** with $[\alpha]_D$: +26.7 (*c* 0.60, MeOH) and mp: 90-93 ºC (Scheme 80). The same reaction carried out with **275** furnished, after purification by column chromatography, a white solid in 92% yield (8% overall yield from **181**) identified by its spectroscopical data as the adenine derivative **279** with $[\alpha]_D$: -36.0 (*c* 0.25, MeOH) and mp: 233-235 ºC.



Scheme 80. Preparation of the adenine nucleosides **278** and **279**.

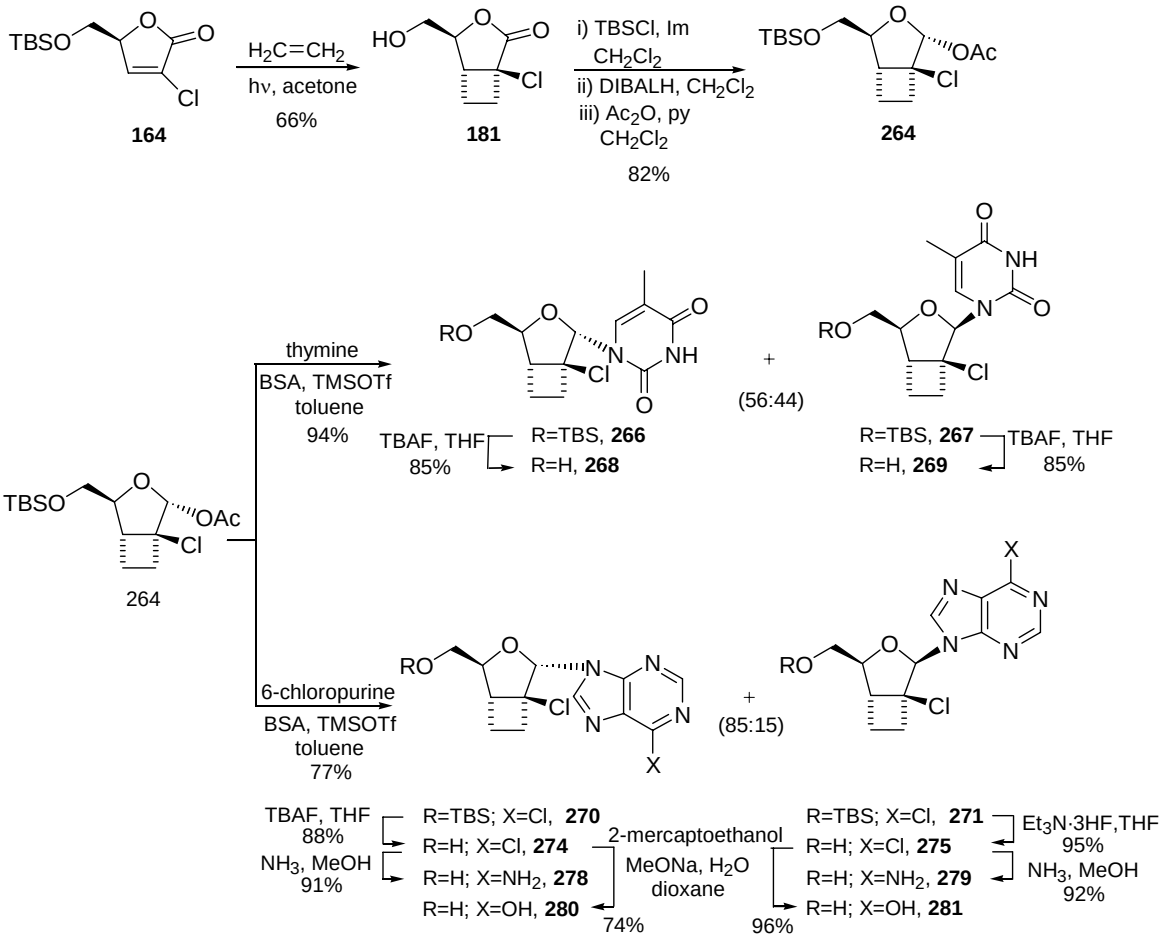
Finally, substitution of the aromatic chlorine atom by a hydroxyl group was performed using the optimized conditions established in the synthesis of fluoronucleoside analogues. Thus, **274** was treated with 2-mercaptoethanol and sodium methoxide in refluxing dioxane containing a few drops of water to furnish, after purification by column chromatography, a white solid in 74% yield (35% overall yield from **181**). This solid was identified by its spectroscopical data as the hypoxanthine derivative **280** with $[\alpha]_D$: +35.0 (*c* 0.80, MeOH) and mp: 206-208 ºC (Scheme 81). The same experimental conditions were applied to the β-nucleoside **275** leading to the isolation, after column chromatography, of the hypoxanthine derivative **281** as a white solid in 96% yield (9% overall yield from **181**) with $[\alpha]_D$: -18.0 (*c* 0.50, MeOH) and mp: 130-133 ºC.



Scheme 81. Preparation of the hypoxanthine nucleosides **280** and **281**.

The structure of the hypoxanthine nucleosides **280** and **281** was confirmed by their characteristic NH broad signal in the ^{1}H-NMR at 12.43 and 12.40 ppm, respectively, as well as the intense IR absorption of their carbonyl groups at 1684 cm^{-1}.

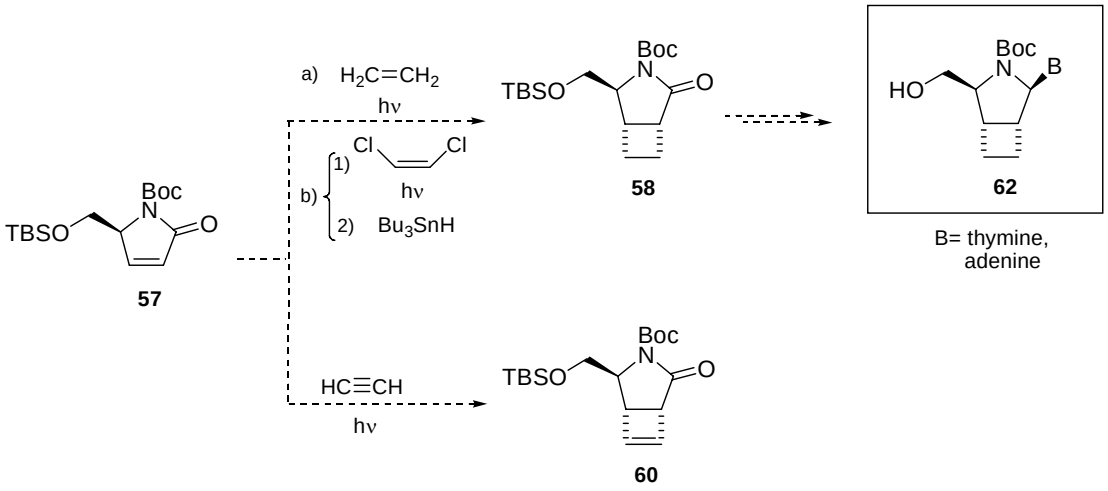
In summary, six new 2'-chloronucleosides bearing a cyclobutane ring fused to the furanose moiety have been prepared in good yields following a short and divergent synthetic pathway (Scheme 82).



Scheme 82. Synthesis of 2'-chloronucleoside analogues conformationally restricted by a cyclobutane ring.

V. Study of the [2+2] photocycloaddition of the homochiral γ-lactam 57 to ethylene and acetylene. Synthesis of azanucleoside analogues conformationally restricted by a cyclobutane ring

The last goal of the present work is focused on the diastereoselective photochemical preparation of the cyclobutane and cyclobutene derivatives **58** and **60** (Scheme 83). Therefore, the [2+2] photocycloaddition of the homochiral α,β-unsaturated γ-lactam **57** to ethylene, *cis*-1,2-dichloroethylene and acetylene will be investigated.



Scheme 83. Photochemical reactivity of lactam **57** with ethylene, *cis*-1,2-dichloroethylene and acetylene. Preparation of the cyclobutane-fused azanucleoside analogues **62**.

These bicyclic lactams are envisioned as potential precursors for the synthesis of new target compounds such as the cyclobutane-fused azanucleoside analogues **62**.

1. Synthesis of γ-lactam 57

The α,β-unsaturated γ-lactam **57** (Figure 53) was chosen to carry out the aforementioned photochemical study. In order to proceed further in the synthesis of cyclobutane azanucleoside analogues, the hydroxyl group was protected as the *tert*-butyldimethylsilyl ether (TBS) and a *tert*-butoxycarbonyl carbamate group (Boc) was introduced.

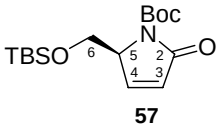
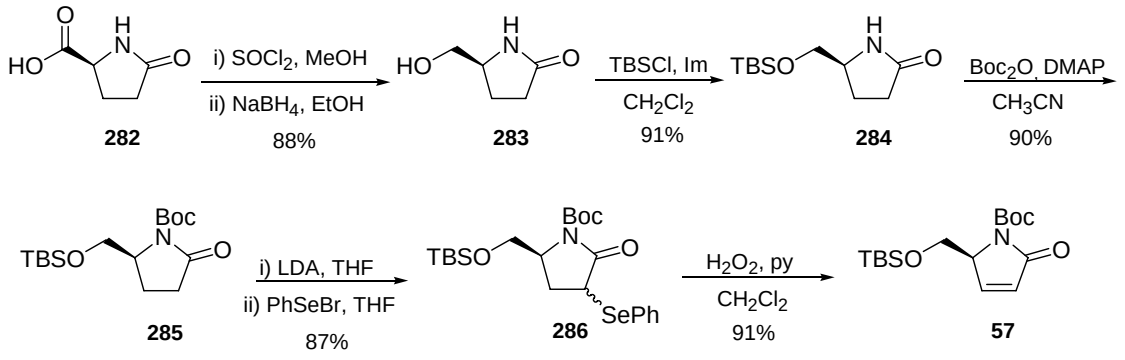


Figure 53. (-)-(5*S*)-*N*-(*tert*-butoxycarbonyl)-5-*tert*-butyldimethylsilyoxymethyl-3-pyrrolin-2-one, **57**.

The α,β-unsaturated lactam **57** has been widely used as a chiral template in the synthesis of natural products[120] and amino acid analogues.[121] Most of the previously described preparations of **57** follow similar strategies using the L-pyroglutamic acid, **282**, as the starting material although in some other cases it has been replaced by L-glutamic acid. In the present work, **57** has been prepared following the methodology described by Lipton and co-workers (Scheme 84).[121e]



Scheme 84. Synthesis of the unsaturated lactam **57**.

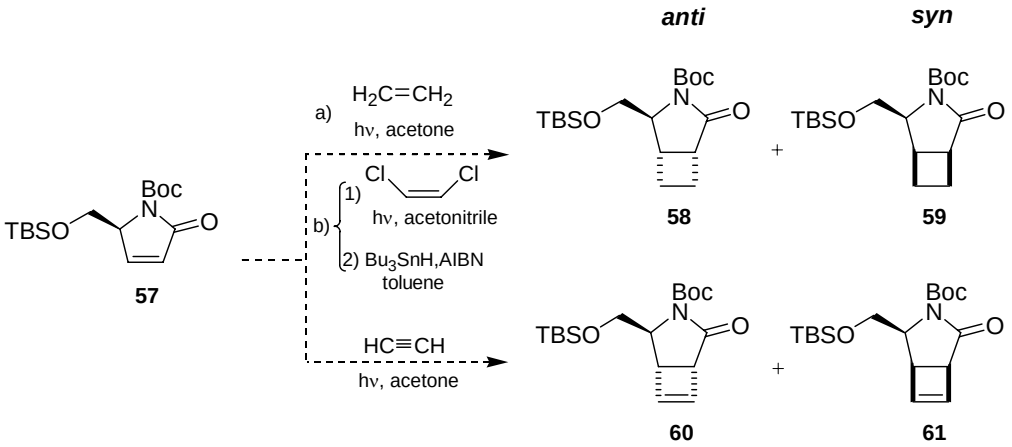
The synthetic pathway started with the reaction of L-pyroglutamic acid, **282**, with thionyl chloride in methanol to give the methyl ester derivative which was reduced with sodium borohydride in ethanol affording the hydroxy derivative **283** in 88% yield for the two steps. Treatment of **283** with *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 gave **284** in 91% yield. Subsequent reaction with di-*tert*-butyl dicarbonate in acetonitrile under basic catalysis delivered the carbamate **285** in 90% yield. α-Selenation of **285** was accomplished using lithium diisopropylamide and phenylselenenyl bromide, affording **286** as a mixture of diastereomers which was then subjected to oxidative elimination with H_2O_2 in the presence of pyridine to introduce the desired α,β-unsaturation. Thus, the target lactam **57** was obtained in 57% overall yield, $[\alpha]_D$ -173.2 (*c* 0.80, $CHCl_3$) (literature $[\alpha]_D$ -175.6 (*c* 1.0, $CHCl_3$),[120a, 121a, 121c]).

[120] a) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513. b) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999,** *64,* 6005-6018. c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473-1480. d) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173-2176.

[121] a) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167-4176. b) Woo, K.-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949-6952. c) Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 1193-1196. d) Drew, M. G. B.; Harrison, R. J.; Mann, J.; Tench, A. J.; Young, R. J. *Tetrahedron* **1999**, *55*, 1163-1172. e) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353-6359.

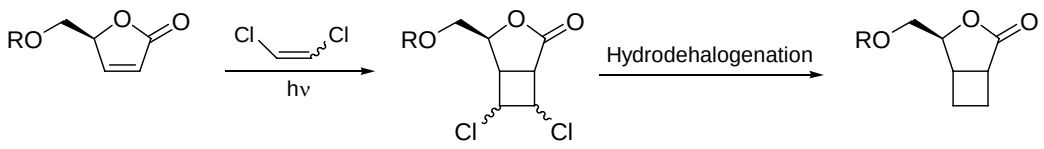
2. Photocycloaddition of γ-lactam 57 to ethylene, *cis*-1,2-dichloroethylene and acetylene

The photoreactivity of γ-lactam **57** with ethylene, *cis*-1,2-dichloroethylene and acetylene was investigated (Scheme 85).



Scheme 85. Study of the [2+2] photocycloaddition of γ-lactam **57** to ethylene, *cis*-1,2-dichloroethylene and acetylene.

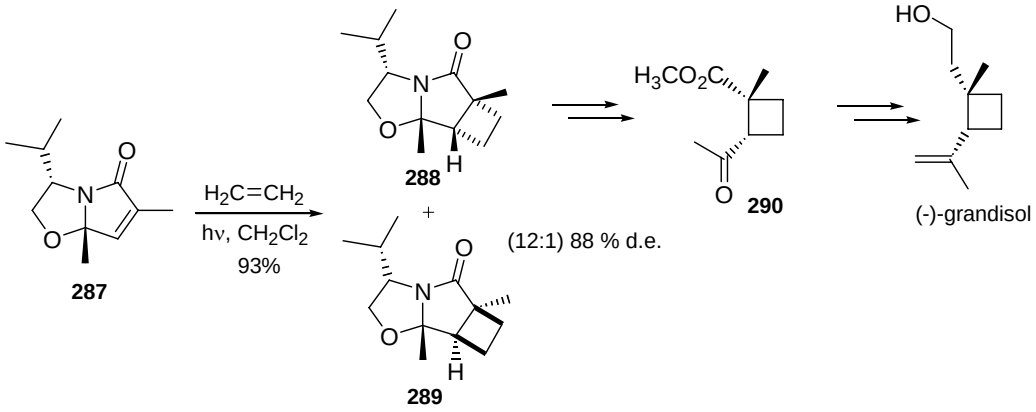
Whereas the preparation of the *anti* cyclobutene derivative **60** was attempted via [2+2] photocycloaddition of **57** to acetylene, the preparation of the cyclobutane **58** was approached following two different strategies: [2+2] photocycloaddition of **57** to ethylene and a new two-step protocol recently developed in our research group which involves the photoreaction of **57** with 1,2-dichloroethylene followed by a reductive treatment of the cycloadducts (Scheme 86).[69]



Scheme 86. New strategy for the preparation of cyclobutane derivatives, Font and co-workers (2003).

From a photochemical point of view, α,β-unsaturated lactams have been less studied than α,β-unsaturated lactones. Particularly, the photocycloaddition of α,β-unsaturated-γ-lactams to olefins had not been well documented until the work published

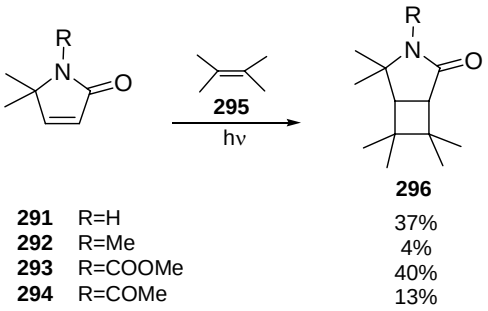
by Meyers and Fleming in 1986.[122] Therein, the chiral lactam **287** was subjected to photochemical reaction with ethylene furnishing a chromatographically separable 12:1 mixture of diastereomers **288** and **289** in 93% yield (Scheme 87). The major isomer **288** was converted into (-)-grandisol via the cyclobutane keto ester **290**.



Scheme 87. [2+2] Photocycloaddition of lactam **287** to ethylene, Meyers and Fleming. (1986).

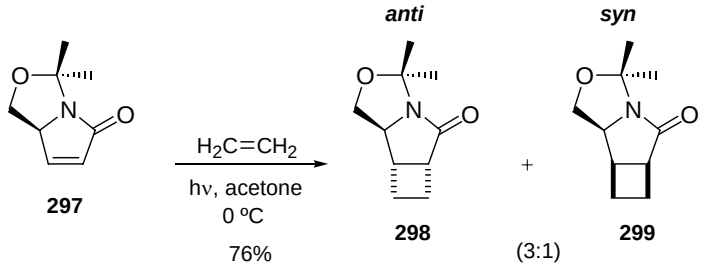
In 1992 Ihlefeld and Margaretha published a study of the photochemical behaviour of several α,β-unsaturated-γ-lactams **291-294** in front of 2,3-dimethyl-2-butene, **295** (Scheme 88).[123] Therein, the strong influence exerted by the substituents on the *N*-atom on the photochemical reactivity of these compounds was reported. As a general tendency, *N*-alkyl derivatives were found to react much slower and with less efficiency than the *N*-unsubstituted, *N*-acetyl or *N*-methoxycarbonyl lactams. Thus, irradiation of **291-294** in the presence of an excess of **295** afforded the cycloadducts **296** in low to moderate yields. All the photochemical reactions were performed under direct irradiation (254 nm) in acetonitrile with the exception of **294** which was reacted under acetone-sensitized conditions (300 nm).

[122] Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306-307.
[123] Ihlefeld, A.; Margaretha, P. *Helv. Chim. Acta* **1992**, *75*, 1333-1340.



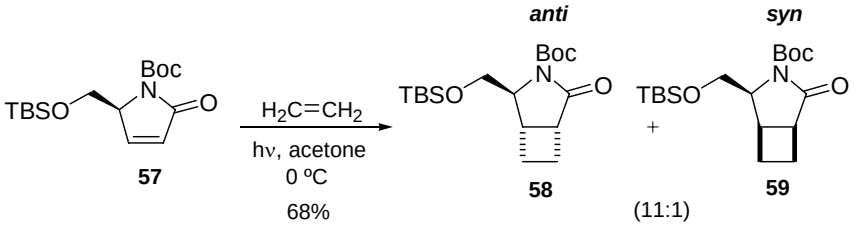
Scheme 88. [2+2] Photocycloaddition of α,β-unsaturated-γ-lactams to 2,3-dimethyl-2-butene, Ihlefeld and Margaretha (1992).

As part of a study to prepare conformationally restricted glutamate analogues, Ohfune and co-workers[121c] described the [2+2] photocycloaddition of γ-lactam **297**, bearing a fused bicyclo[3.3.0]octane system, to ethylene (Scheme 89). The reaction proceeded smoothly by irradiation with a 450 W high-pressure lamp mercury lamp through a pyrex filter in acetone at 0 ºC to give a mixture of cycloadducts **298** and **299** albeit with low stereoselectivity (3:1).



Scheme 89. [2+2] Photocycloaddition of γ-lactam **297** to ethylene, Ohfune and co-workers (1998).

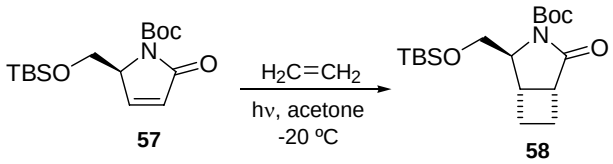
In the same article the authors also reported the photocycloaddition of the α,β-unsaturated lactam **57** to ethylene under the above conditions to afford a 11:1 mixture of the cycloadducts **58** and **59** (Scheme 90).



Scheme 90. [2+2] Photocycloaddition of γ-lactam **57** to ethylene, Ohfune and co-workers (1998).

The authors suggested that the poorer *anti*:*syn* stereoselectivity observed in **297** when compared to **57** could be attributed to the presence of a planar amide bond in **297** which increased the degree of the attack of ethylene occurred from the sterically more hindered face.

2.1. [2+2] Photocycloaddition of γ-lactam 57 to ethylene



filter	solvent	time	yield (%)	*anti*:*syn* (%) [a]
pyrex	acetone	2.5 h	62	100:0

[a] Product ratio determined by ^{1}H-NMR.

Table 39. [2+2] Photocycloaddition of γ-lactam **57** to ethylene.

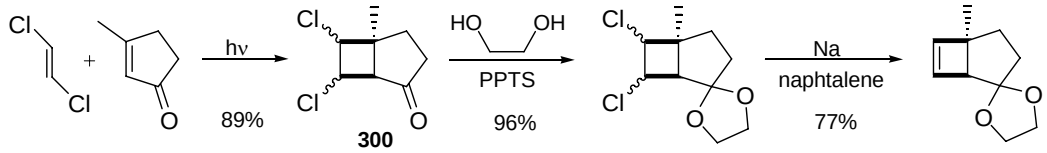
The photocycloaddition of **57** to ethylene described by Ohfune and co-workers was reproduced in our laboratory using a 125W high pressure mercury lamp and cooling externally the reactor to -20 ºC affording a unique product in 62% yield (Table 39). This cycloadduct was identified as the known *anti* isomer **58**.[121c] The relative configuration of the cycloadduct could be confirmed by the low value of the coupling constant between H-4 and H-5 (~0 Hz) and was further corroborated by a NOESY experiment which showed cross-peak between H-4 and the cyclobutane protons H-6. On the other hand, the presence of the *syn* cycloadduct **59** could not be detected by ^{1}H-NMR. Therefore, the facial diastereoselectivity was increased from (92:8) to a total diastereoselectivity by reducing the reaction temperature from 0 ºC to -20 ºC.

2.2. [2+2] Photocycloaddition of γ-lactam 57 to *cis*-1,2-dichloroethylene

As it has been previously discussed, the [2+2] photocycloaddition of enones and lactones to 1,2-dichloroethylene, followed by a reductive treatment of the cycloadducts, is an alternative approach for preparing cyclobutane and cyclobutene derivatives.

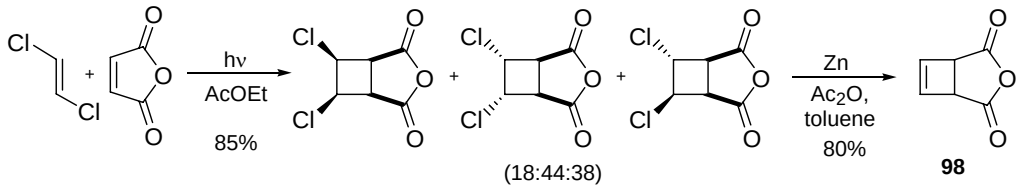
Several examples of preparation of cyclobutene derivatives from a dichlorinated cyclobutane intermediate under chlorine reductive elimination have been described in

the literature. Kowalczyk and co-workers[124] published in 1998 the preparation of different cyclobutene intermediates following this methodology which were used in the synthesis of *spatanes* (Scheme 91). The first step of the procedure was the [2+2] photoreaction of 3-methyl-2-cyclopentenone with *trans*-1,2-dichloroethylene to afford the cyclobutane **300** as a mixture of isomers in 89% yield. The cyclobutene product was reached reducing the vicinal dichloride with sodium and naphthalene, after previous protection of the carbonyl group as an acetal.



Scheme 91. Cyclobutene synthesis, Kowalczyk and co-workers (1998).

In another example, Huet and co-workers[125] published the synthesis of the cyclobutene derivative **98** in 68% overall yield via the photochemical reaction of maleic anhydride with *trans*-1,2-dichloroethylene and subsequent Zn-promoted dehalogenation (Scheme 92).

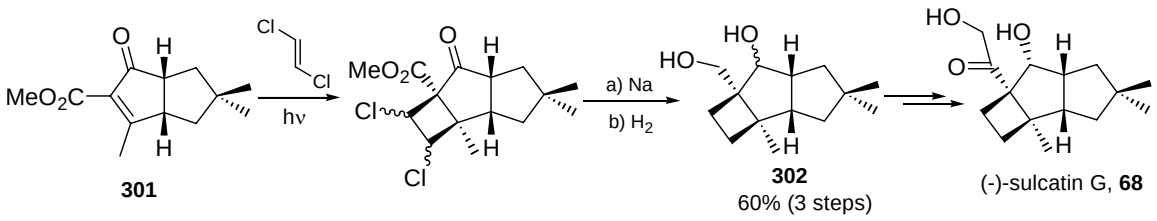


Scheme 92. Preparation of the cyclobutene derivative **98**, Huet and co-workers (1999).

Until the publication of the strategy developed in our laboratory, the preparation of cyclobutane derivatives coming from the dichlorinated intermediates was achieved by catalytic hydrogenation of the cyclobutene derivatives. This is the case of the synthesis of (-)-sulcatin G, **68**, published by Mehta and Sreenivas[35] in 2002 wherein the cyclobutane moiety present in the structure of this sesquiterpene was constructed using the following protocol: (i) [2+2] photocycloaddition of **301** to *trans*-1,2-dichloroethylene in benzene using a pyrex filter, (ii) dehalogenation reaction with sodium and naphthalene, and (iii) catalytic hydrogenation. The target cyclobutane

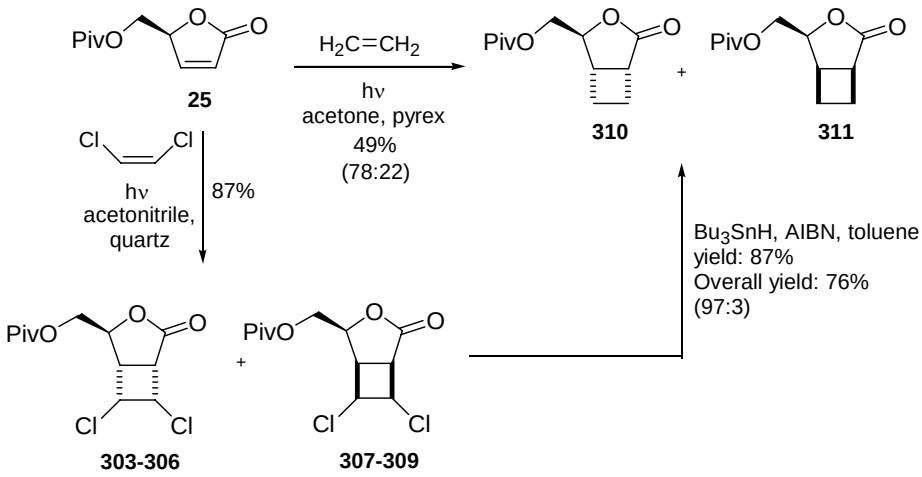
[124] Kowalczyk, B. A.; Smith T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379-1389.
[125] Gauvry, N.; Comoy, C.; Lescop, C.; Huet, F. *Synthesis* **1999**, *4*, 574-576.

intermediate **302** was prepared with a total diastereoselectivity and 60% overall yield for the three steps (Scheme 93).



Scheme 93. Cyclobutane synthesis by reduction of a cyclobutene, Mehta and Sreenivas (2002).

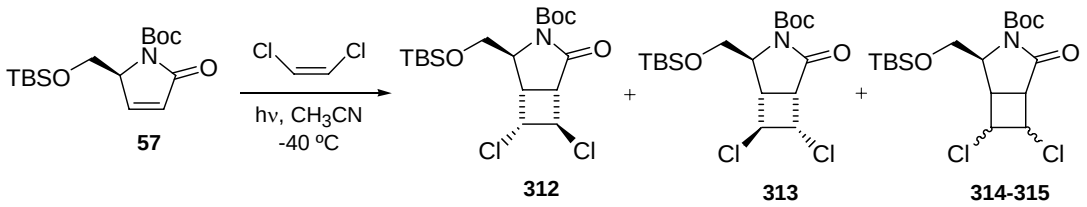
Bearing in mind these precedents, the alternative methodology developed in our laboratory to prepare cyclobutane derivatives is depicted in Scheme 94. The [2+2] photocycloaddition of 2(5*H*)-furanone **25** to *cis*-dichloroethylene proceeded smoothly in acetonitrile to afford a 34:19:14:23:5:4:1 mixture of seven isomeric cycloadducts **303-309** in 89% combined yield.[69] Even though separation was unnecessary for synthetic purposes, the major cycloadducts were isolated and completely characterized, being determined the *anti*:*syn* ratio as (90:10).



Scheme 94. Methodology developed for the synthesis of cyclobutane derivatives from 2(5*H*)-furanone **25** and comparison with photocycloadditions to ethylene, Font and co-workers (2003).

Posterior treatment of this mixture with an excess of Bu_3SnH and a catalytic amount of AIBN in refluxing toluene afforded the cyclobutane derivatives **310** and **311** in 76% overall yield and a 97:3 *anti*:*syn* ratio. These results implied a large improvement of the results obtained with the photoreaction of **25** with ethylene (49% yield, 78:22 ratio).

This two-step protocol for the synthesis of cyclobutane derivatives was applied to the unsaturated lactam **57** (Table 40).



filter	solvent	time	yield (%)	312:313:314:315 (%) [a]
quartz	acetonitrile	50’	87	36:25:21:18

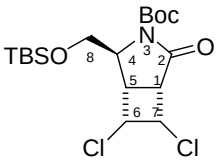
[a] Product ratio determined by ^{1}H-NMR.

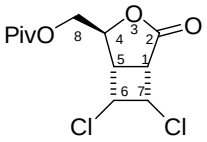
Table 40. [2+2] Photocycloaddition of lactam **57** to *cis*-dichloroethylene.

A solution of **57** and *cis*-1,2-dichloroethylene in acetonitrile was irradiated through a quartz filter for 50 min, affording a clean reaction crude whose analysis by NMR allowed the identification of 4 products in a 36:25:21:18 ratio which were obtained in 87% global yield after purification by column chromatography. Even though it was unnecessary for synthetic purposes, the major isomer was isolated and identified by its NMR data as the *anti* cycloadduct **312**. An enriched mixture of **313** and **314** allowed the identification of its major component **313** meanwhile the stereochemistry of **314** could not be established. Finally, the minor cycloadduct **315** was lost during the purification process.

The stereochemistry of the isomers **312** and **313** was elucidated by its ^{1}H-NMR data. Thus, whereas a $J_{4,5}$~0 Hz indicates an *anti* configuration for both cycloadducts, the relative stereochemistry of the chlorine substituents was inferred to the values of $J_{1,7}$ and $J_{5,6}$. High values of the coupling constant are expected for protons in a *cis* relative disposition and lower values for protons in a *trans* disposition. A *cis* relationship between H-1 and H-5 is assumed. Therefore, $J_{1,7}$=3.4 Hz (*trans*) and $J_{5,6}$=8.7 Hz (*cis*) are observed for **312**, while $J_{1,7}$=9.5 Hz (*cis*) and $J_{5,6}$=6.2 Hz (*trans*) are observed for **313**.

For **312**, these assignments were further confirmed by a NOESY experiment which shows strong correlation between H-5 and H-6 indicating their *cis* relationship. Finally, comparison with the known related derivatives **303-309**[69] also confirmed the stereochemistry of **312** and **313** (Table 41).





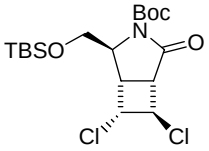
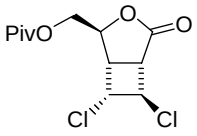
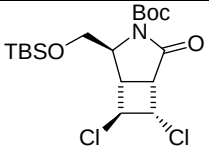
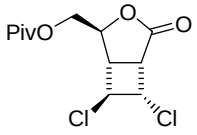
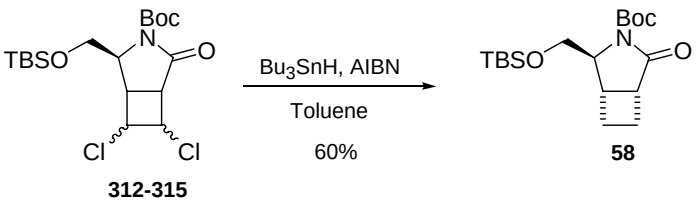
CYCLOADDUCT	H-1	H-4	H-5	H-6	H-7
 **312**	3.31 ddd J(1,5): 7.9 J(1,7): 3.4	4.44 m J(4,5):~ 0	3.41 dd J(5,6): 8.7 J(5,1): 7.9 J(5,4):~ 0	4.66 ddd J(6,5): 8.7 J(6,7): 4.3	4.34 ddd J(7,1): 3.4 J(7,6): 4.3
 **303**	3.30 ddd J(1,5): 8.0 J(1,7): 5.7	5.24 q J(4,5): 3.0	3.43 dddd J(5,6): 8.0 J(5,1): 8.0 J(5,4): 3.0	4.69 ddd J(6,5): 8.0 J(6,7): 4.7	4.39 ddd J(7,1): 5.7 J(7,6): 4.7
 **313**	3.48 ddd J(1,5): 7.6 J(1,7): 9.5	4.16 dd J(4,5):~ 0	2.85 dd J(5,6): 6.2 J(5,1): 7.6 J(5,4):~ 0	4.19 ddd J(6,5): 6.2 J(6,7): 7.4	4.55 ddd J(7,1): 9.5 J(7,6): 7.4
 **304**	3.61 ddd J(1,5): 7.5 J(1,7): 9.5	4.74 t J(4,5): 2.9	3.06 dddd J(5,6): 5.7 J(5,1): 7.5 J(5,4): 2.9	4.25 ddd J(6,5): 5.7 J(6,7): 7.0	4.59 ddd J(7,1): 9.5 J(7,6): 7.0

Table 41. Comparison of the most significant spectroscopical ^{1}H-RMN data of **312-303** and **313-304**. Chemical shifts are expressed in ppm and coupling constants in Hz. $CDCl_3$ was used in all cases.

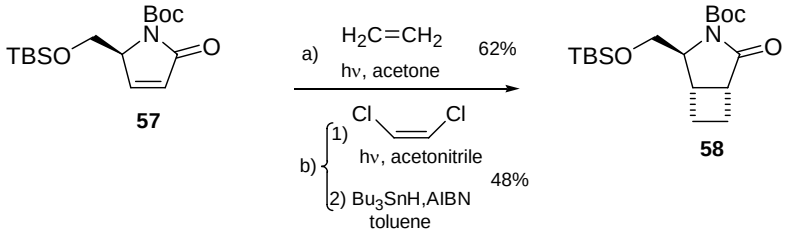
The mixture of diastereomers **312-315** was used in the following reaction without further purification (Scheme 95). The dihydrodehalogenation reaction of the mixture of the 4 diastereomers **312-315** was achieved by treating it with an excess of Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing toluene (Scheme 95). Thus, the *anti* cycloadduct **58** was obtained as the unique product of the reaction in 60% yield.



312-315 **58**

Scheme 95. Dihydrodehalogenation reaction of **312-315**.

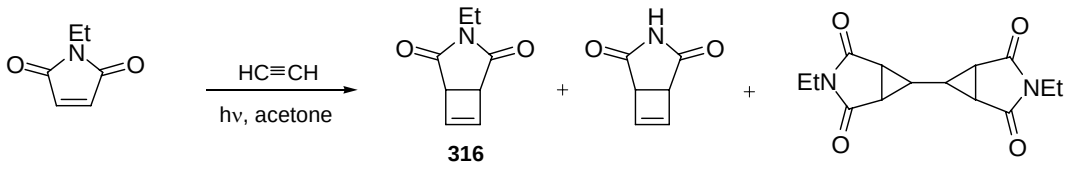
The overall yield of the cycloadduct **58** from lactam **57** was 48% using this two-step methodology meanwhile that from the photocycloaddition to ethylene was 62% (Scheme 96). Since the diastereoselectivity values were the same for both methodologies and the yield was better for the reaction with ethylene, the applicability of the two-step protocol in the foreseen synthetic pathway was unworthy.



Scheme 96. Comparison of the two synthetic strategies to prepare **58**.

2.3. [2+2] Photocycloaddition of γ-lactam 57 to acetylene

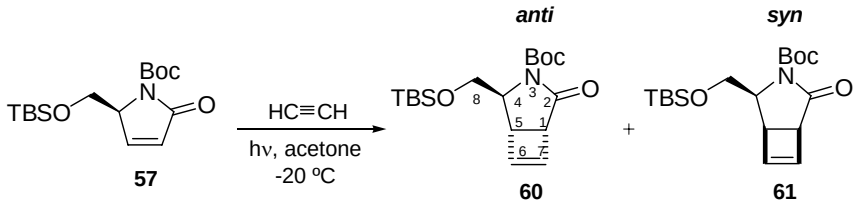
Few precedents of photochemical reactions between unsaturated lactams and acetylene were found in the literature. Among them, in 1966 Koltzenburg *et al.*[126] described the photochemical reaction of *N*-ethyl-maleimide with acetylene in acetone which afforded the expected cyclobutene **316** as well as some by-products (Scheme 97). No information about the yield is given.



Scheme 97. Photochemical reaction of maleimide and acetylene, Koltzenburg *et al.* (1966).

Therefore, we decided to investigate the [2+2] photocycloaddition of lactam **57** to acetylene (Table 42).

[126] Koltzenburg, G.; Fuss, P. G.; Leitich, J. *Tetrahedron Lett.* **1966**, *29*, 3409-3414.



filter	solvent	time	yield (%)	*anti*:*syn* (%) [b]
pyrex	acetone	5 h	50 (61) [a]	86:14

[a] Corrected yield after considering the % of consumed starting material. [b] Product ratio determined by ^{1}H-NMR.

Table 42. [2+2] Photocycloaddition of γ-lactam **57** to acetylene.

The homochiral γ-lactam **57** was irradiated through a pyrex filter in an acetone solution saturated with acetylene for 5 h to furnish a 86:14 mixture of two cycloadducts in 50% yield. Purification by column chromatography of the mixture allowed the isolation of the major cycloadduct **60**, an enriched fraction of its *syn* isomer **61** and some unreacted starting material (20%). The *anti* stereochemistry of **60** was assigned on the basis of the low value of the H-4/H-5 coupling constant, $J_{4,5}$=1.0 Hz.

Similar to the tendency reported previously for lactones, lactam **57** reacted slower with acetylene and gave lower yield and diastereoselectivity compared to ethylene. Nevertheless, the high *anti*:*syn* ratio obtained in the present work, the acceptable yield of the reaction and the absence of by-products makes the [2+2] photocycloaddition of **57** to acetylene suitable to be applied shortly in a synthetic strategy towards the preparation of cyclobutene analogues of azanucleosides.

3. Synthesis of azanucleoside analogues conformationally locked by a cyclobutane ring

The family of target cyclobutane-fused 2',3'-dideoxyazanucleosides **62** was envisioned as conformationally restricted analogues of the previously described 2',3'-azanucleosides (Figure 54).

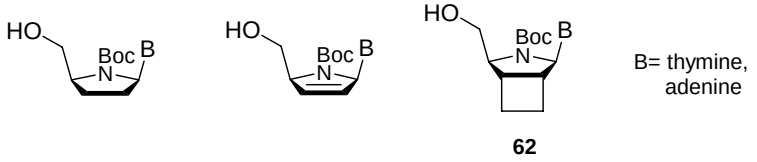
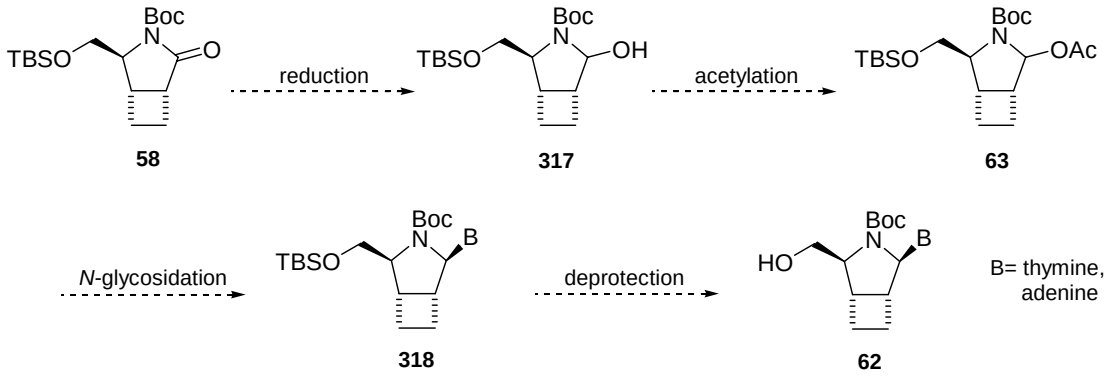


Figure 54. Aza-2',3'-dideoxynucleosides and their cyclobutane analogues **62**.

The synthetic pathway designed for the preparation of cyclobutane azanucleoside analogues **62** starts from the previously described bicyclic lactam **58** (Scheme 98).



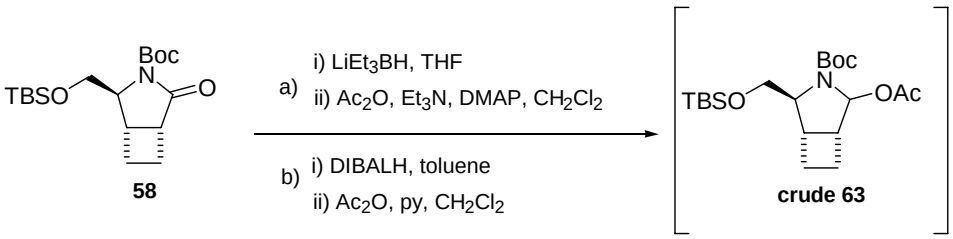
Scheme 98. Synthetic pathway designed for the preparation of cyclobutane-fused 2',3'-dideoxyazanucleosides.

Reduction of the lactam moiety to the hemiaminal **317** followed by acetylation would lead to the formation of the key intermediate **63** which is a good substrate to introduce the nucleobases by a *N*-glycosylation reaction. This methodology will give rise to pyrimidine (thymine) and purine (adenine) derivatives. Several examples of pyrimidine azanucleosides have been described in the bibliography following the Hilbert-Johnson or Vorbrüggen procedures, however the synthesis of a purine azanucleoside following any of these strategies has not been reported yet. Finally, cleavage of the silyl protecting group should afford the target bicyclic [3.2.0] azanucleoside analogues **62**.

3.1. Attempt to prepare the bicyclic acetate 63

The first step of the syntesis was the selective reduction of the bicyclic lactam **58** to the corresponding hemiaminal using superhydride ($LiEt_3BH$). Thus, treatment of **58** with $LiEt_3BH$ in dry THF at -78 ºC afforded a crude mixture of hemiaminals which was subsequently subjected to react with acetic anhydride, triethylamine and a catalytic amount of DMAP in CH_2Cl_2 (Scheme 99). Reaction evolved smoothly according to TLC controls. However, all attempts to isolate the resulting acetate **63** or the intermediate hemiaminals were unsuccessful and only decomposition products were

obtained. Analysis of a sample of the reaction crude dissolved in CD_2Cl_2 allowed the observation of a complex spectrum due to the presence of rotamers.

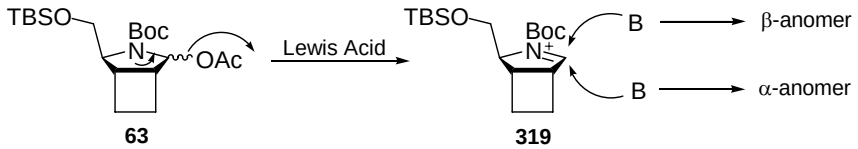


Scheme 99. Attempts of preparation of acetate **63**.

A second methodology was investigated to achieve the preparation of the acetate **63**. Thus, lactam **58** was treated with DIBAL-H in dry toluene at -78 ºC affording a crude mixture of hemiaminals which was subjected to react with acetic anhydride and pyridine in CH_2Cl_2. Again, complete consumption of the intermediate derivatives was observed by TLC but the isolation of **63** could not be achieved. It was then decided to use the crude mixture in the *N*-glycosylation reaction.

3.2. *N*-glycosylation reaction: introduction of thymine

The strategy for the synthesis of azanucleosides relies on the Lewis acid catalyzed generation of a suitable protected *N*-acyliminium ion **319** as a key intermediate (Scheme 100). In situ trapping of the highly reactive **319** with silylated nucleobases as nucleophiles should lead to the target nucleosides.

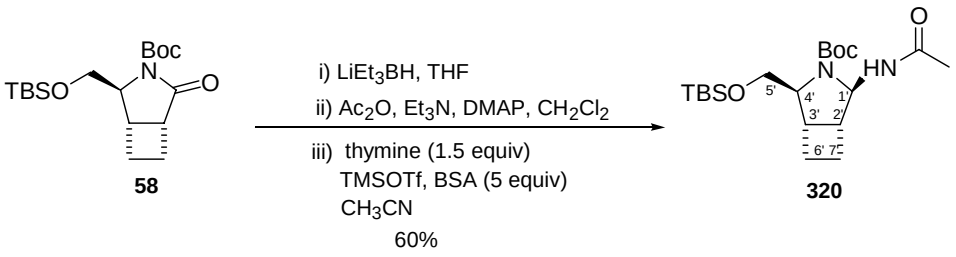


Scheme 100. Expected intermediate **319** in the *N*-glycosylation reaction.

As previously discussed, the Hilbert-Johnson *N*-glycosylation reaction is the most common methodology for the preparation of thymine azanucleosides.[12] Several

different experimental modifications, such as the Vorbrüggen nucleosidation, have been successfully described involving the Lewis acid, the silylating agent or the solvent.[14,127]

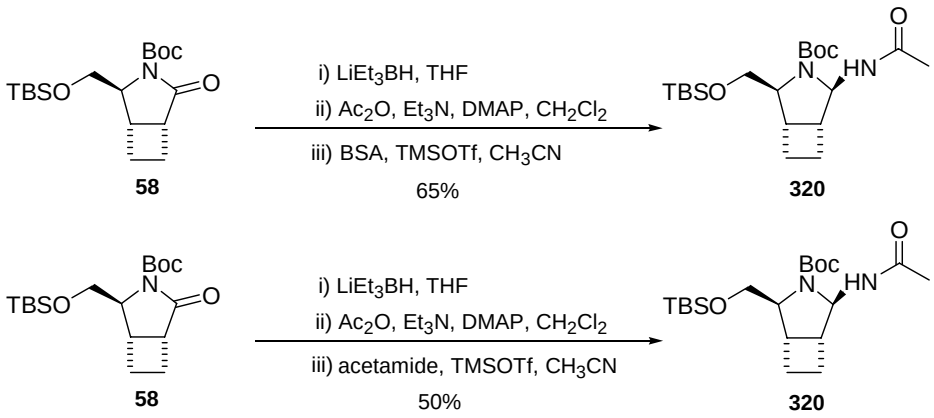
Due to the satisfying results obtained in the synthesis of chloro and fluoronucleoside analogues, the same conditions for the introduction of thymine were applied to the preparation of azanucleosides. Hence, crude **63** and TMSOTf were added to an acetonitrile solution of BSA (*N*,*O*-bis(trimethylsilyl)acetamide) and thymine in a previously used 5:1.5 ratio, furnishing a new product as a sole isomer and lacking the expected aromatic ring which was identified by NMR studies as the acetamide derivative **320** with $[\alpha]_D$: -51.9 (*c* 0.54, $CHCl_3$) in 60% yield from **58** (3 steps) (Scheme 101). It is noteworthy to mention that no significant differences were observed in the outcome of this reaction in function of the procedure followed to prepare the crude intermediate **63**. Only one of these conditions is depicted in the Scheme 101.



Scheme 101. First attempt of *N*-glycosylation of **58**.

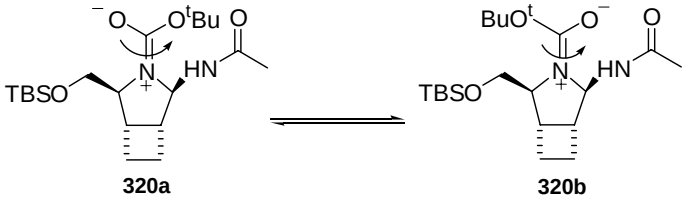
The formation of **320** was inferred to the nucleophile attack of either BSA and/or the resulting trimethylsilylacetamide and acetamide to the highly reactive *N*-acyliminium ion derived from the acetate **63**.[128] Two blank experiments were performed with the aim of confirming this hypothesis. In the first one, the aforementioned reaction conditions were repeated in the absence of thymine yielding **320** in 65% yield (3 steps) (Scheme 102). In the second reaction, the crude acetate **63** was reacted with acetamide and TMSOTf giving rise to **320** in 50% yield (3 steps).

[127] Qing, F.-L.; Yu, J.; Fu, X.-K.; *Collect. Czech. Chem. Commun.* **2002**, *67*, 1267-1276.
[128] Ochoa, C.; Provencio, R.; Jimeno, M. L.; Balzarini, J.; de Clercq, E. *Nucleosides Nucleotides* **1998**, *17*, 901-910.



Scheme 102. Blank experiments to confirm the formation of **320**.

The unfolding of a number of signals, specially those of H-1', H-4' and NH, was observed in the ^{1}H-NMR of **320**. When the sample was heated up to 330 K coalescence of the unfolded signals was observed showing a simple spectrum (Figure 55). A similar phenomenon had already been reported in 1966 by Reist *et al.*[129] when they described the ^{1}H-NMR spectra of various *N*-acetyl-pyrrolidine sugar derivatives. This behaviour is attributed to the hindered internal rotation about the *N*-carbamate bond so that the rate of interconversion between two rotational conformers is sufficiently slow to allow chemical shift difference from signals arising from the two conformers or rotamers (Scheme 103). At temperatures above room temperature this hindrance gradually vanishes and the spectrum shows a unique set of signals.



Scheme 103. Chemical interconversion between the two rotamers of **320**.

[129] Reist, E. J.; Gueffroy, D. E.; Blackford, R. W.; Goodman, L. *J. Org. Chem.* **1966**, *31*, 4025-4030.

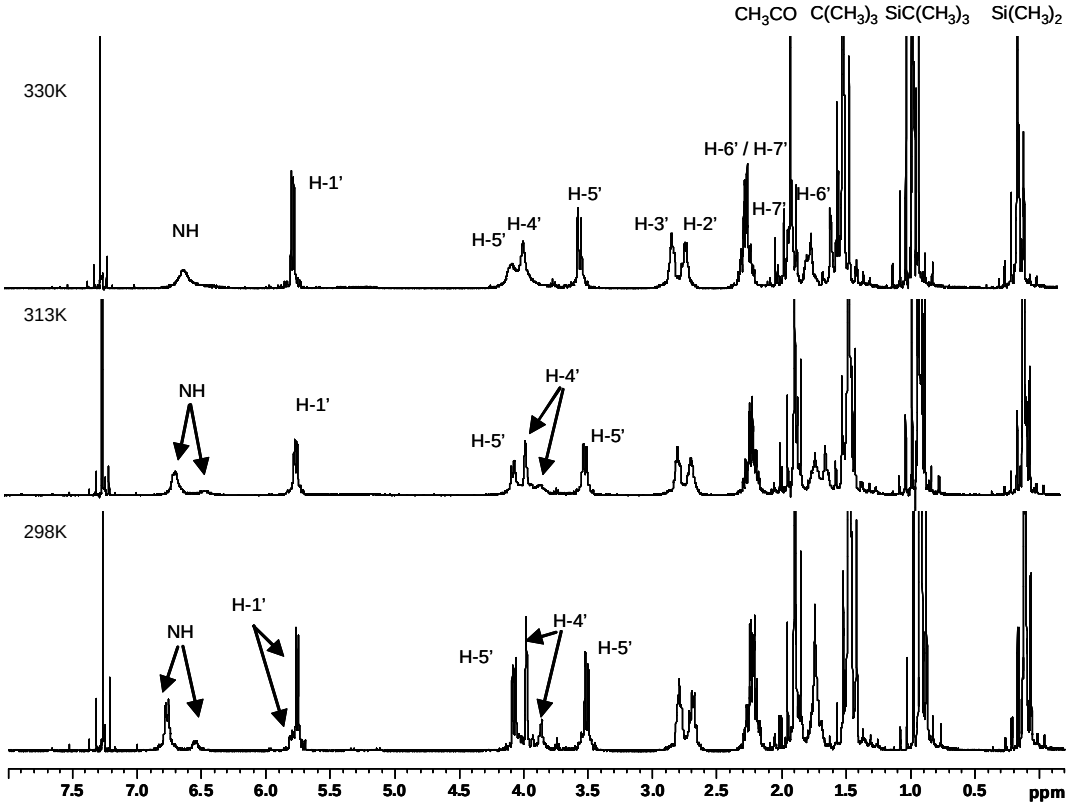


Figure 55. ^{1}H-NMR of compound **320** registered at different temperatures ($CDCl_3$, 400 MHz).

The stereochemistry of the anomeric center of the acetamide derivative **320** was established by the value of the vicinal proton-proton coupling constant between H-1' and H-2' (Figure 56). The signal corresponding to H-1' appears as a doublet, due to the coupling constant with the vicinal NH group, $J_{1',NH}$=8.8 Hz, indicating that $J_{1',2'}$ ~0 Hz. Thus, the stereochemistry of the anomeric center was established as β.

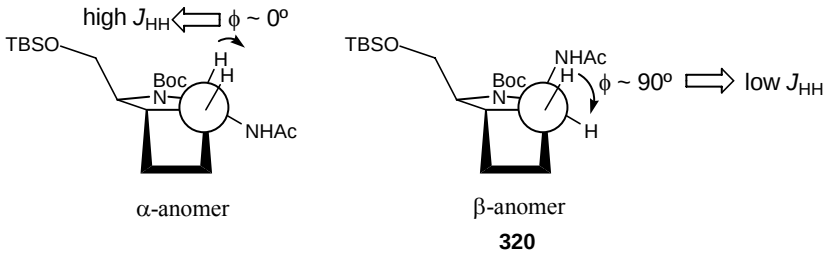


Figure 56. Determination of the anomeric configuration by the value of the vicinal proton-proton coupling constant H-1'/H-2'.

The assignment of the anomeric configuration was latter confirmed by a NOESY experiment which shows a cross-peak between H-1' and H-4' indicating that both protons lie in the α face of the pyrrolidine (Figure 57). Moreover, H-1' also shows

cross-peaks with the cyclobutane protons H-6'endo and H-7'endo. On the other hand, the NH proton shows correlation with the hydroxymethylene protons H-5' corroborating the assignment of the anomeric center as β.

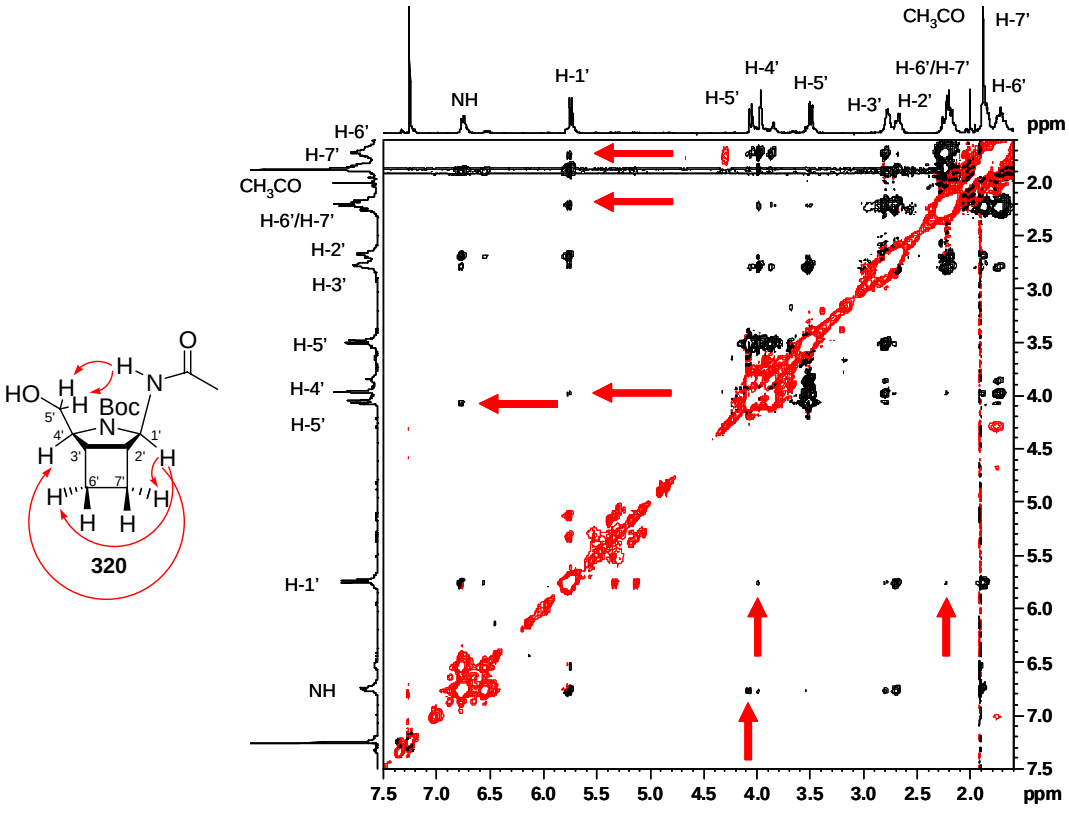
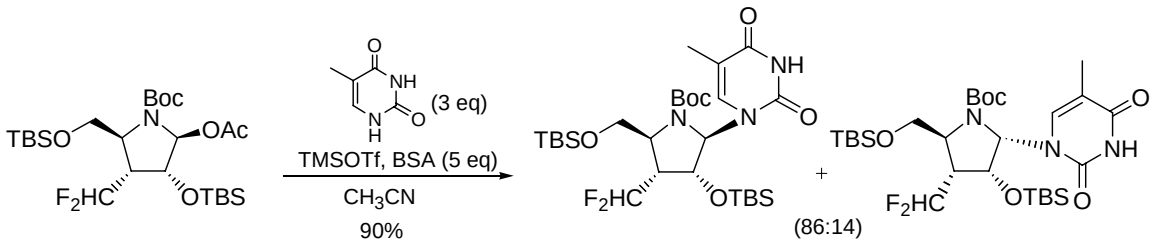


Figure 57. NOESY of compound **320** ($CDCl_3$, 400 MHz, 298 K).

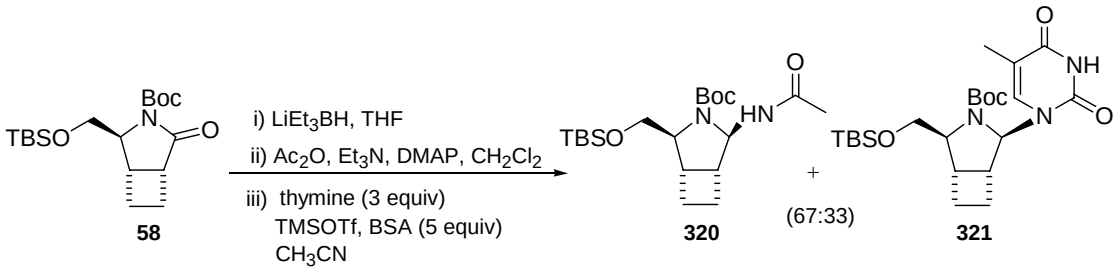
To the best of our knowledge no examples of any product containing the 2-pyrrodinyl-*N*-acetamide moiety present at **320** have been reported as a by-product of a Vorbrüggen *N*-glycosylation to prepare azanucleosides. Therefore, it was then decided to investigate the reason why the acetate intermediate unexpectedly reacted only with the acetamide derivatives instead of thymine under these reaction conditions. Qiu and Qing[130] have recently reported the synthesis of a family of 3'-deoxy-3'-difluoromethyl azanucleosides whose key step was a Vorbrüggen nucleosidation performed with the same reagents and solvent than in the present work albeit in a lower BSA/thymine ratio (5:3) (Scheme 104).

[130] Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2005**, *70*, 3826-3837.



Scheme 104. Synthesis of 3'-deoxy-3'-difluoromethyl azanucleosides, Qiu and Qing (2005).

When these conditions were applied to crude acetate **63** a 67:33 mixture of **320** and the desired nucleoside **321** was obtained (Scheme 105). Since BSA and thymine seemed to compete to react with the intermediate acetate species, it was decided to increase the ratio of thymine in the reaction media. Taking into account that the pyrimidine nucleobase is insoluble in acetonitrile unless silylated by BSA, a 1:1.1 BSA/thymine mixture of reagents was evaluated. Unfortunately, these results also afforded a 67:33 mixture of **320** and **321**. Finally, no presence of the desired thymine derivative was detected when the reaction was performed in dry toluene and with a 5:3 BSA/thymine ratio, being **320** the only product isolated in 70% yield (3 steps).

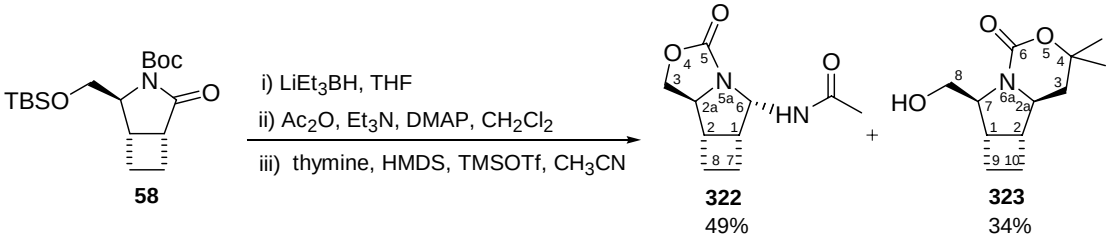


Scheme 105. *N*-glycosylation reaction of **58** using TMSOTf and BSA.

Due to the impossibility of separating these compounds by column chromatography, the establishment of the stereochemistry of **321**, which in its NMR sprectrum also showed the presence of rotamers at room temperature, was carried out in a later synthetic step.

In order to avoid the presence of BSA in the reaction media, an alternative formation of silylated nucleobases was investigated. Thus, thymine was heated overnight in HMDS (1,1,1,3,3,3-hexamethyldisilazane) in the presence of a catalytic amount of $(NH_4)_2SO_4$ and then reacted with the crude acetate **63** and TMSOTf at 0 ºC (Scheme 106). Surprisingly, not only the new conditions failed to afford the desired nucleoside in any extension but two unprecedented new compounds **322** and **323**, both

lacking the thymine moiety, were isolated after purification by column chromatography in 49% and 34% yield (3 steps), respectively, from **58**. This reaction was repeated several times and **322** and **323** were the unique compounds isolated each time.



Scheme 106. Attempt of *N*-glycosylation reaction using TMSOTf and previously silylated thymine.

The structures of the tricyclic derivatives **322** and **323** were established by detailed NMR analysis. It is noteworthy to mention that their ^{1}H-NMR do not show the presence of rotamers, indicating a higher degree of rigidity for these compounds compared to **320** and **321**.

The presence of the cyclic carbamate in **322** was established with the help of the HMBC experiment which shows cross-peaks between the carbamate carbonyl group, C-5, and H-2a and both H-3 (Figure 58). On the other hand, cross-peaks between H-6 and the acetamide and carbamate carbonyl groups as well as with C-2a and C-7 gave valuable information about the connectivity of the East-side of the molecule.

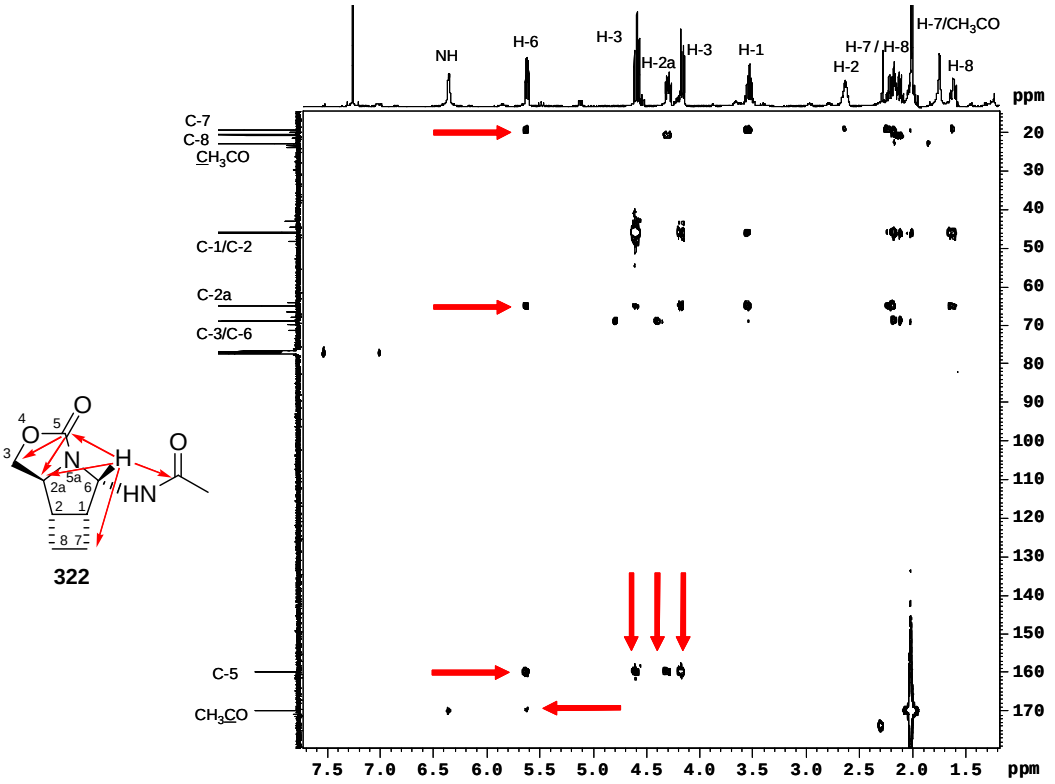


Figure 58. HMBC experiment of **322** ($CDCl_3$, 400 MHz, 298 K).

The configuration of the anomeric center of **322** was established as α on the basis of the high value of the vicinal proton-proton coupling constant, $J_{1,6}$=7.3 Hz and was further confirmed by a NOESY experiment which shows cross-peaks between NH and H-2a and H-8 indicating the presence of the acetamide moiety in the α-face of the compound. Moreover, correlation is also observed between H-6 and H-1 and H-2.

On the other hand, the most characteristic spectroscopical feature of **323** is the loss of symmetry experienced by the carbamate *tert*-butyl moiety resulting in two CH_3 groups and a CH_2 group as seen in the DEPT experiment (Figure 59). According to the COSY experiment, this new CH_2 group, C-3, is directly attached to the anomeric center, C-2a, since cross-peaks between H-2a and both H-3 protons are observed (Figure 60).

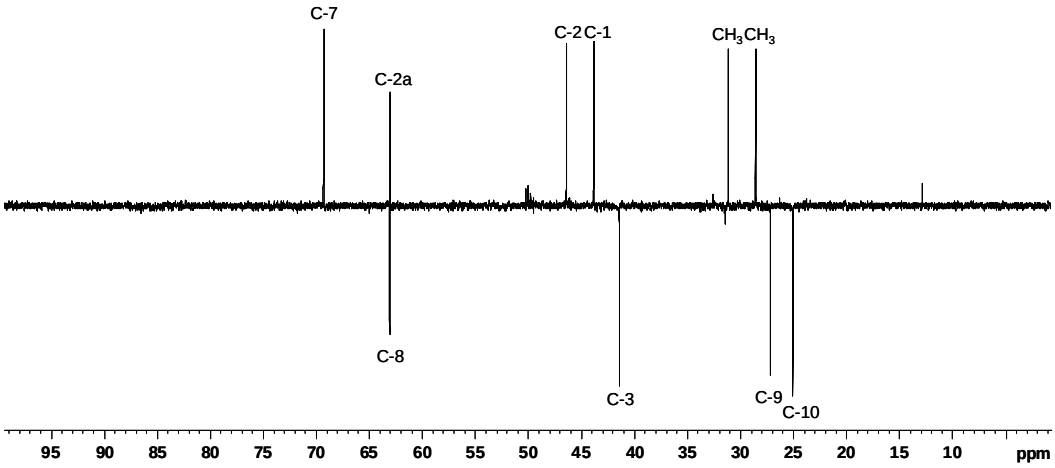


Figure 59. DEPT experiment of **323** (CD_3OD, 90 MHz, 298 K).

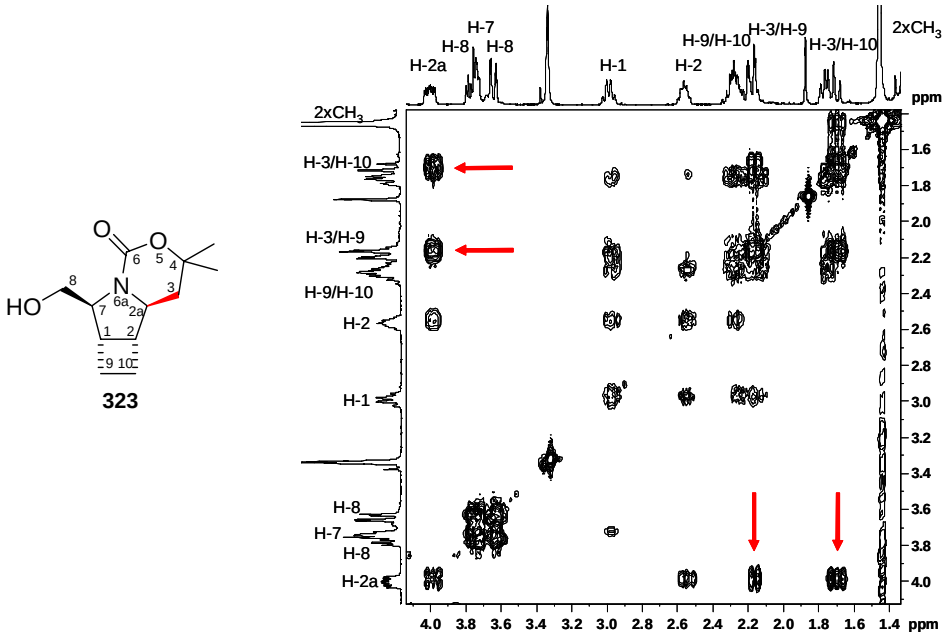


Figure 60. Detail of the COSY experiment of **323** (CD_3OD, 360 MHz, 298 K).

Furthermore, cross-peaks in the HMBC experiment between the quaternary C-4 and H-2a, H-3 and both methyl groups confirm the aforementioned loss of symmetry (Figure 61).

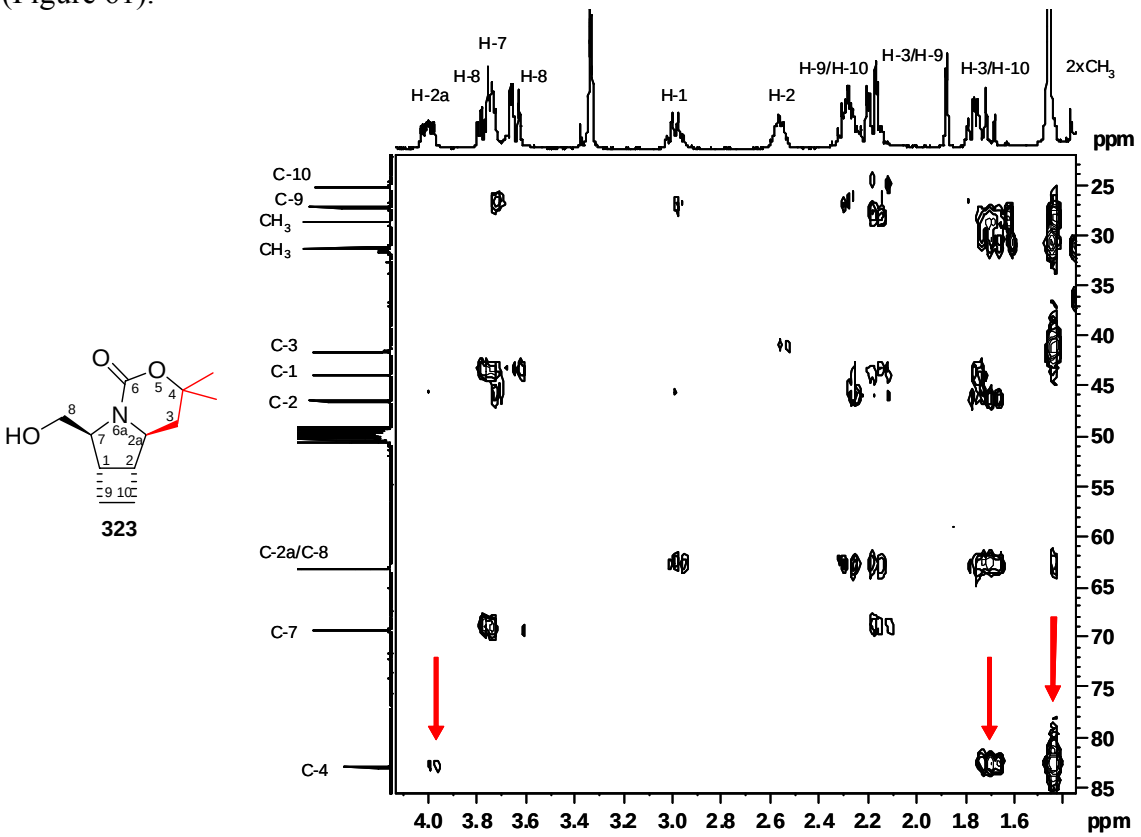
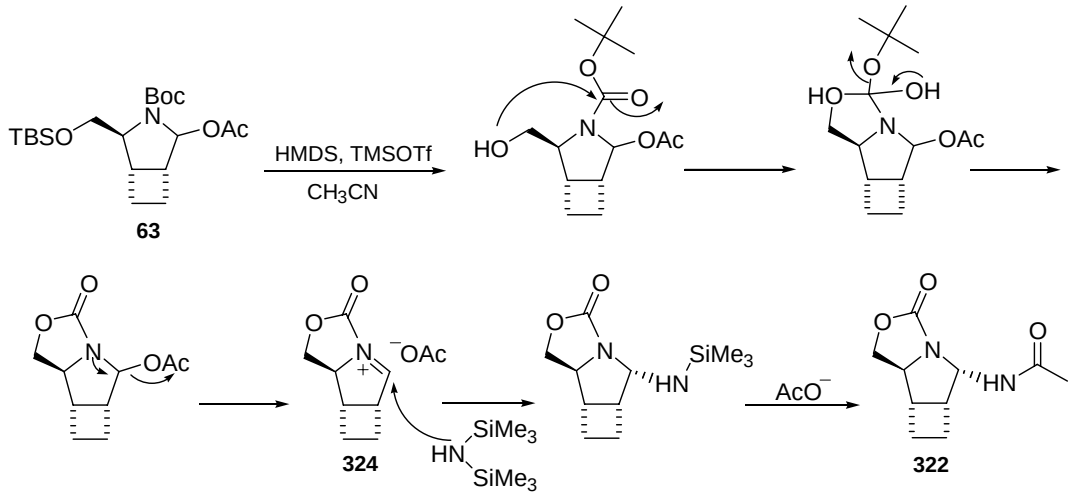


Figure 61. Detail of the HMBC experiment of **323** (CD_3OD, 360 MHz, 298 K).

The stereochemistry of **323** was established on the basis of a NOESY experiment which shows correlation between H-2a and H-7 indicating the presence of both protons in the same side of the molecule.

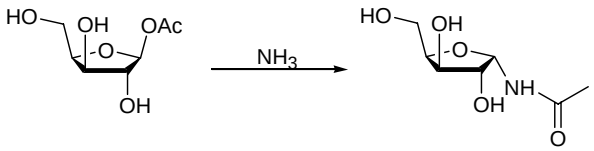
A mechanism for the formation of the cyclic carbamates **322** and **323** has been postulated. For **322** the cleavage of the silyl moiety would lead to the attack of the resulting free hydroxy group to the carbonyl present at the Boc moiety, building an intramolecular carbamate (Scheme 107). Either simultaneously or in a different step of the process, an acetamide moiety would be incorporated to the anomeric position. The presence of an acetamide unit in the absence of BSA would be inferred to the nuclepophile attack of HMDS, and/or the resulting ammonia,[108b] to a highly reactive intermediate *N*-acyl ion **324** and subsequent acetalyzation of the resulting amine with acetate ion. The presence of a Lewis acid (TMSOTf) in the reaction mixture would act as the promoter of the depicted transformations.



Scheme 107. Postulated formation of carbamate **322**.

This variation of the preferred configuration at the anomeric center may be attributed to a more sterically hindered β face due to the presence of the cyclic carbamate. Thus, the approximation of the nucleophile through this face to yield **322** would become more difficult than in the formation of the acetamide derivative **320**. This fact led us to postulate the formation of the intramolecular carbamate in an earlier step and subsequently blocking the β face of the pyrrolidine ring in the posterior attack of the amine.

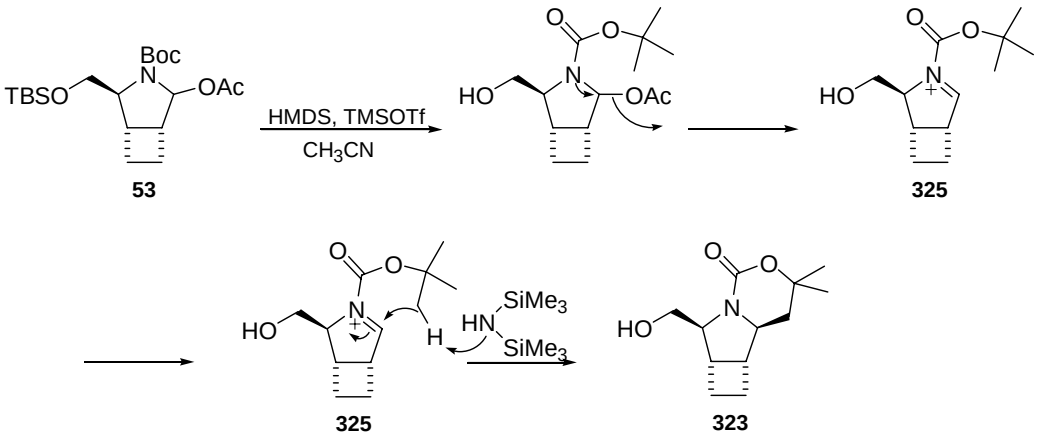
Similarly, the formation of *N*-acetyl sugar derivatives by reaction of ammonia with acetylated monosaccharides was reported by Cerezo and Deulofeu[131] in 1966 (Scheme 108), giving support to the mechanism inferred herein.



Scheme 108. Reaction of acetylated monosaccharides with ammonia, Cerezo and Deulofeu (1966).

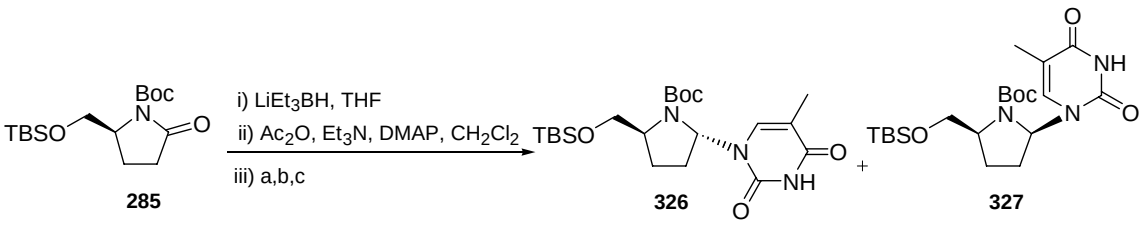
On the other hand, the tricyclic derivative **323** is thought to come from the abstraction of one proton of the methyl groups present in the Boc moiety of the iminium ion **325** by HMDS and simultaneous attack of the resulting electron pair to the anomeric position to form a new carbon-carbon bond affording a 6 member cyclic carbamate (Scheme 109). No precedents of a similar reaction have been found in the literature.

[131] Cerezo, A. S.; Deulofeu, V. *Carbohydr. Res.* **1966**, *2*, 35-41.



Scheme 109. Postulated formation of carbamate **323**.

Due to the synthetic difficulties found in the different attempts of preparing the expected cyclobutane azanucleoside analogues, it was decided to optimize the conditions working with the less valuable lactam **285**. Thus, **285** was reduced with $LiEt_3BH$ and subsequently treated with acetic anhydride, triethylamine and DMAP (Scheme 110). The resulting crude was subjected to different *N*-glycosylation reaction conditions, among them those unsuccessfully assayed for bicyclic lactam **58**. In all the cases, the previously described diastereomeric nucleosides **326** and **327**[14b,c,d,f] were obtained in good yields (51-61% from **285**) as a mixture of rotamers. No presence of an acetamide derivative structurally related to **320** could be detected indicating that its formation would be due to the steric hindrance caused by the cyclobutane moiety of **58** which would difficult the approach of the bulky silylated thymine.

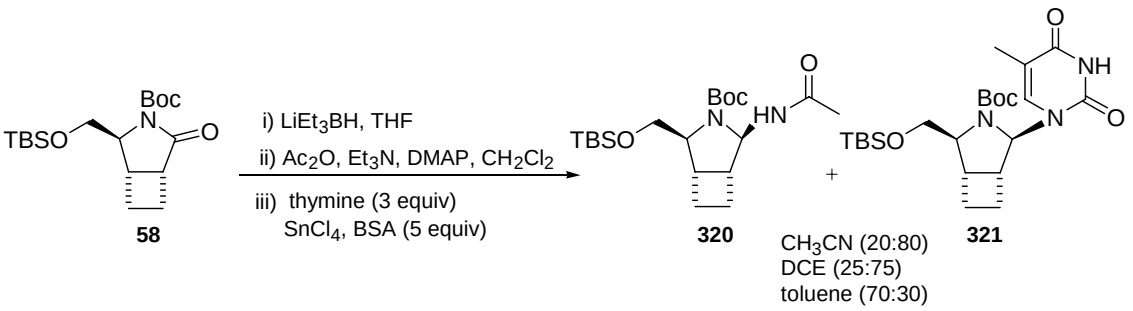


Reagents and conditions: iii) a. Thymine, BSA, TMSOTf, CH_3CN, 56% yield; b. Thymine, BSA, $SnCl_4$, CH_3CN, 61% yield; c. Thymine, HMDS, $SnCl_4$, CH_3CN, 51% yield.

Scheme 110. Synthesis of the thymine azanucleosides **326** and **327**.

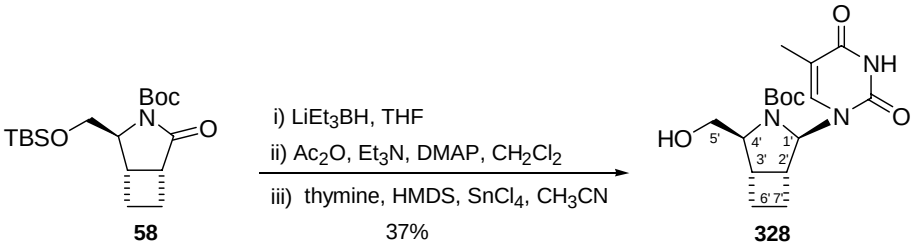
A new attempt to achieve the synthesis of the target thymine nucleoside was made using $SnCl_4$ as Lewis acid. Hence, crude acetate **63** and $SnCl_4$ were successively added to a solution of thymine and BSA in dry acetonitrile at 0 ºC affording a 20:80 mixture of the acetamide derivative **320** and the desired nucleoside **321** (Scheme 111).

The effect of the polarity of the solvent on the ratio of products obtained was analyzed as well, performing the reaction in dry DCE and toluene at 0 ºC. In DCE a 25:75 mixture of **320** and **321** was obtained whereas in toluene the presence of the undesired **320** was higher (70:30).



Scheme 111. *N*-glycosylation reaction using $SnCl_4$ and BSA.

Finally, the reaction catalyzed with $SnCl_4$ was also tested using the alternative methodology to prepare the silylated thymine. In this occasion, reaction of the crude acetate **63** and $SnCl_4$ with a previously prepared silylated thymine using HMDS, afforded a unique nucleoside (Scheme 112). As in the previous use of HMDS, cleavage of the TBS moiety was observed. The new product was obtained, after purification by column chromatography, as a white solid in 37% yield from **58** (4 steps including deprotection) and was identified by its spectroscopical data as the thymine derivative **328** with $[\alpha]_D$: -41.3 (*c* 0.80, $CHCl_3$) and mp: 56-59 ºC.



Scheme 112. Synthesis of the azanucleoside **328**.

The ^{1}H-NMR spectrum of the thymine nucleoside **328** again showed the presence of rotamers (Figure 62). Thus, a number of signals, specially H-1', H-2', H-3' and NH appeared partially unfolded at room temperature. Whereas a complete separation of the signals of each rotamer was observed by cooling the sample to 265 K, a gradual coalescence of the peaks was observed when the spectrum was repeated at each time higher temperatures until the obtaining of a unique group of signals at 333 K.

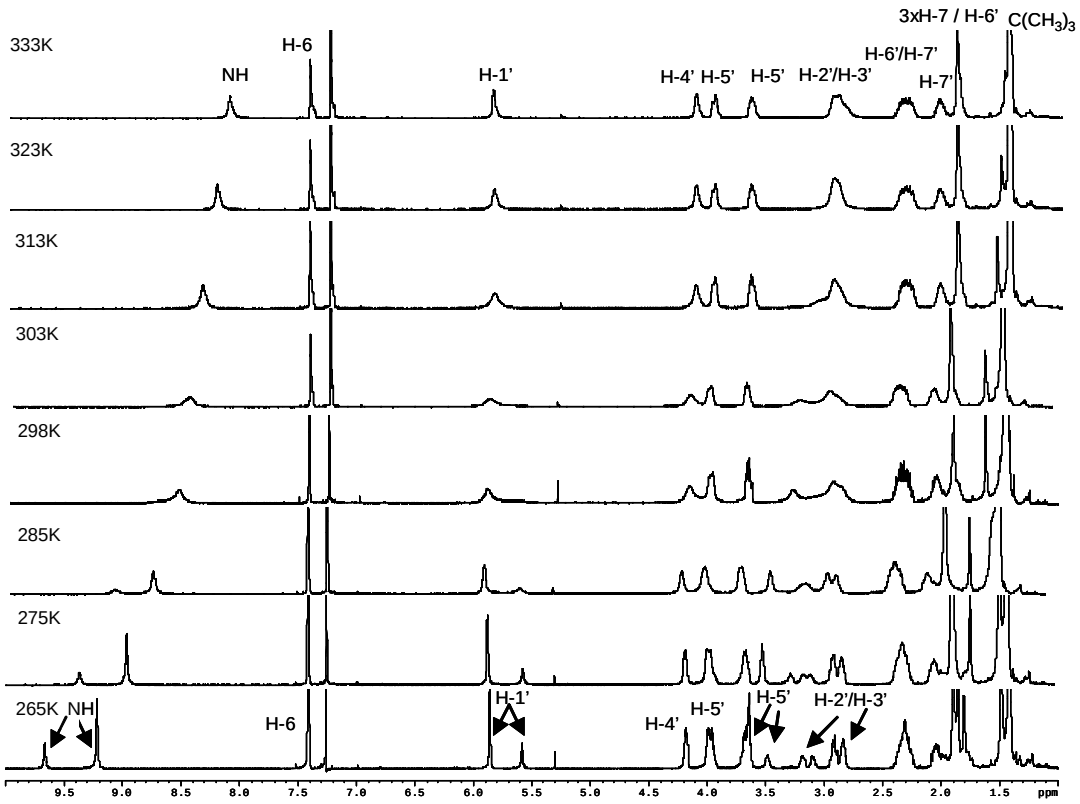


Figure 62. ^{1}H-NMR of compound **328** registered at different temperatures ($CDCl_3$, 400 MHz).

The establishment of the α/β anomeric configuration of this new azanucleoside was carried out analyzing the value of the vicinal proton-proton coupling constant. The proton H-1' appears as a singlet ($J_{1',2'} \sim 0$ Hz) indicating a β-configuration at the anomeric center.

The assignment of the anomeric configuration was further confirmed by a NOESY experiment (Figure 63) which shows cross peaks between H-1' and H-4' and the cyclobutane protons H-6'endo and H-7'endo. On the other hand, correlation between the base H-6 proton and the hydroxymethylene protons H-5' corroborates the above assignment.

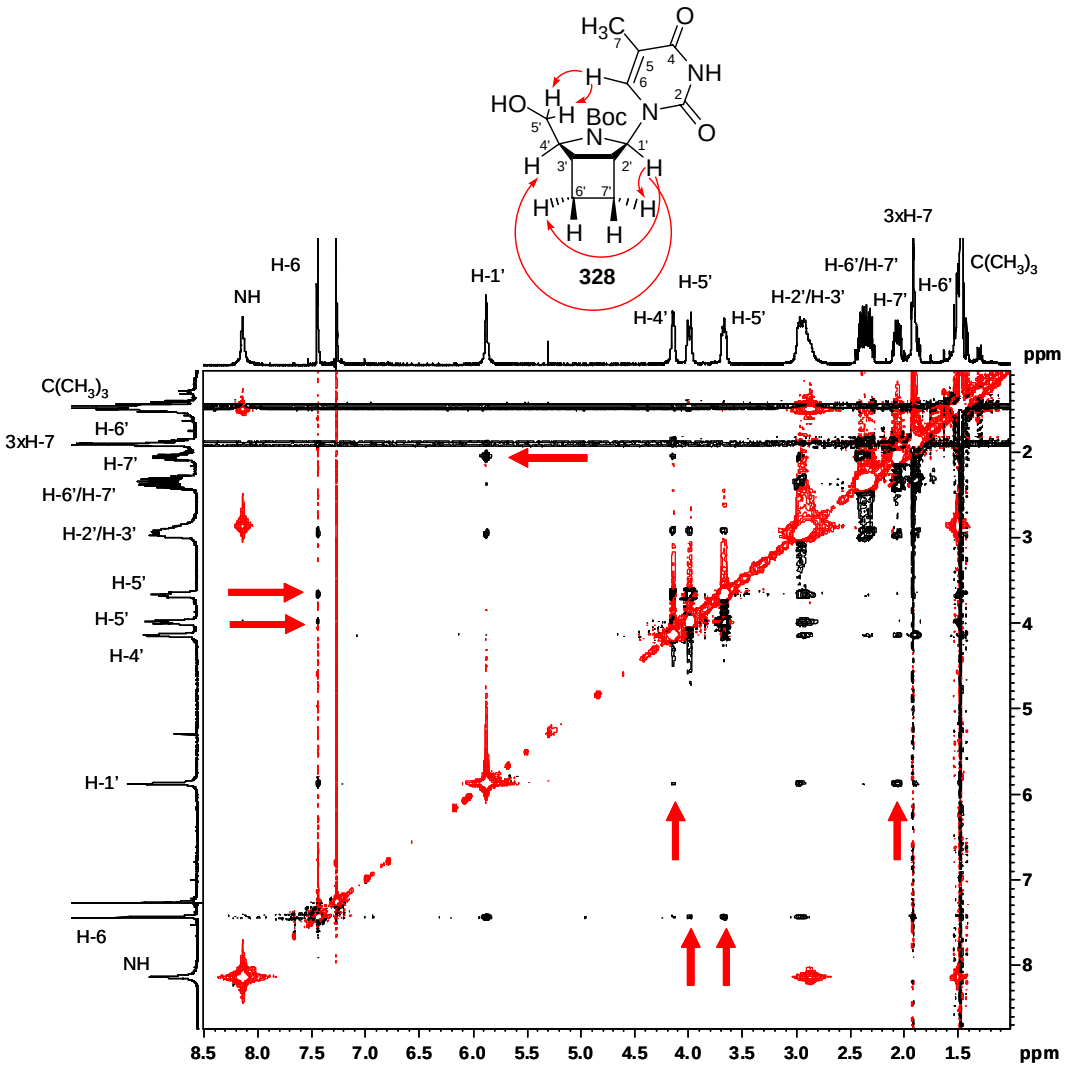
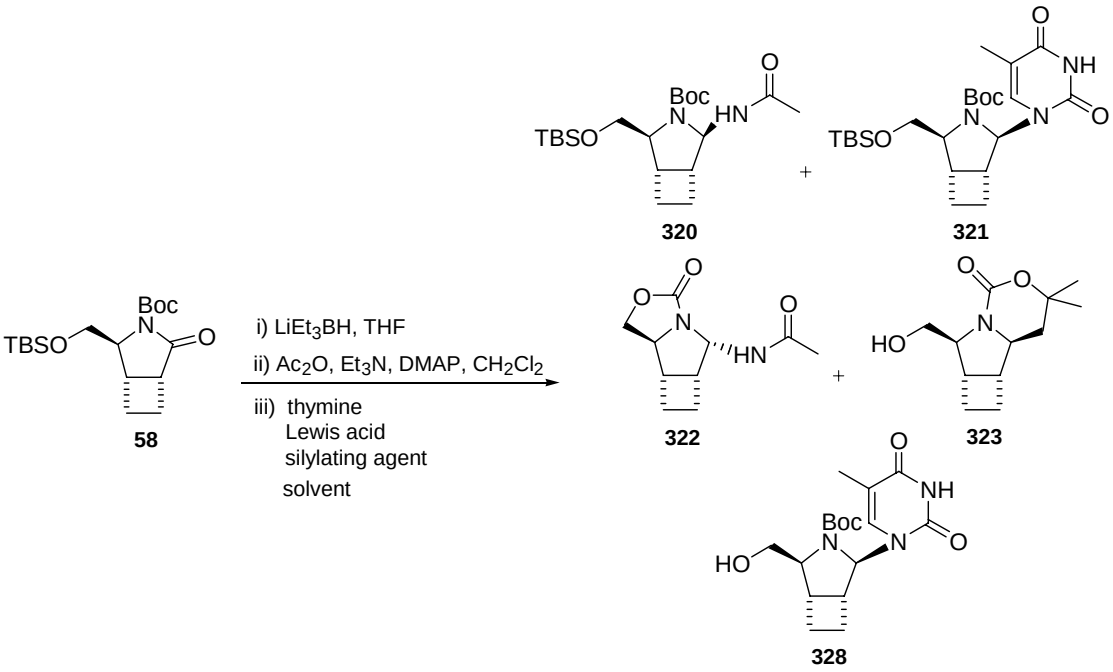


Figure 63. NOESY of compound **328** ($CDCl_3$, 400 MHz, 333 K).

A summary of all the reaction conditions investigated to achieve the preparation of cyclobutane-fused thymine azanucleoside analogues is shown in Table 43.



entry	solvent	Lewis acid	silylating agent	thymine	yield (%)	product ratio
1	acetonitrile	TMSOTf	BSA (5 equiv)	1.5 equiv	**320** (65)	-
2	acetonitrile	TMSOTf	BSA (5 equiv)	3 equiv	**320**+**321** (63)[a]	67:33
3	toluene	TMSOTf	BSA (5 equiv)	3 equiv	**320** (70)	-
4	acetonitrile	TMSOTf	HMDS	4 equiv	**322** (49) **323** (34)	58:42
5	acetonitrile	$SnCl_4$	BSA (5 equiv)	3 equiv	**320**+**321** (70)[a]	20:80
6	DCE	$SnCl_4$	BSA (5 equiv)	3 equiv	**320**+**321** (50)[a]	25:75
7	toluene	$SnCl_4$	BSA (5 equiv)	3 equiv	**320**+**321** (82)[a]	70:30
8	acetonitrile	$SnCl_4$	HMDS	4 equiv	**328** (37)	-

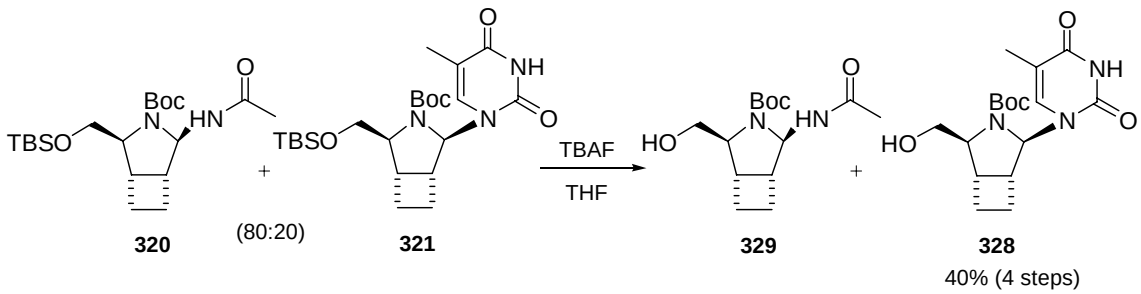
[a] Estimated global yield is given since the products **320** and **321** could not be separated.

Table 43. Different reaction conditions tested for the preparation of cyclobutane thymine azanucleosides.

It is noteworthy to point out the influence of the Lewis Acid in the outcome of these reactions. In first place, the competitive nucleophile attack of silylated thymine and BSA exists with both Lewis acids investigated although it can be governed under $SnCl_4$ catalysis to mainly afford the desired nucleoside **321** (entry 5). On the other hand, when using HMDS as the silylating agent instead of BSA, whereas TMSOTf catalyses the intramolecular formation of **322** and **323** (entry 4), $SnCl_4$ furnishes the deprotected nucleoside **328** (entry 5).

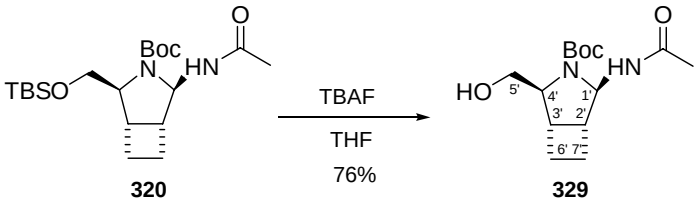
Since the minor presence of the by-product **320**, obtained along with **321** using BSA and $SnCl_4$ in acetonitrile (entry 5), could not be removed by column chromatography, it was decided to attempt the separation of these products once the

silyl moiety was cleaved. Therefore, the mixture of the silylated compounds **320** and **321** was treated with TBAF in THF (Scheme 113). After purification by column chromatography, the acetamide derivative **329** could be easily removed to furnish pure cyclobutane azanucleoside **328** in 40% yield from **58** (4 steps). Therefore, the preparation of the target azanucleoside **328** was achieved with comparable overall yields following two different synthetic methodologies.



Scheme 113. Cleavage of the silyl group of **320** and **321**.

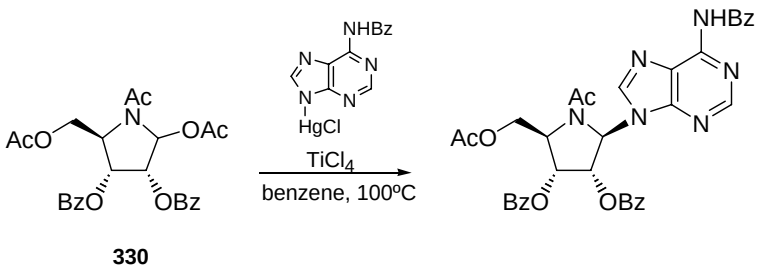
It was decided to evaluate the antiviral activity of **329** since the by-product **320** can be obtained in remarkable yield (70%, Table 73, entry 3). Thus, a THF solution of **320** was treated with TBAF to furnish, after purification by column chromatography, a colourless oil in 76% yield identified by its spectroscopical data as the acetamide derivative **329** with $[\alpha]_D$: -90.0 (*c* 0.30, $CHCl_3$) (Scheme 114). Again, the ^{1}H-NMR at room temperature of **329** showed a mixture of rotamers.



Scheme 114. Cleavage of the silyl group of **320**.

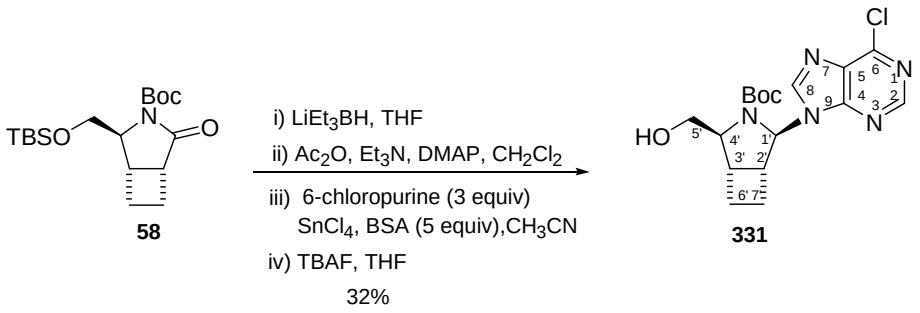
3.3. *N*-glycosylation reaction: introduction of adenine

Reist and co-workers accomplished the *N*-glycosylation of different aminosugars such as **330** by treating them with chloromercury-6-benzamidopurine in the presence of $TiCl_4$ (Scheme 115).[13,129] To the best of our knowledge, these publications are the unique examples of purine azanucleosides reported in the literature.



Scheme 115. *N*-glycosylation of **330**, Reist and co-workers (1967).

In our approach, the synthesis of the target adenine azanucleoside was designed via the 6-chloropurine precursor and the optimized conditions for the preparation of the thymine derivative **321** were chosen as the starting point of the study. Thus, the crude acetate **63** was reacted with 6-chloropurine, BSA and $SnCl_4$ in acetonitrile at 0 ºC affording a unique nucleoside which ^{1}H-NMR analysis showed the presence of rotamers (Scheme 116). No presence of the acetamide derivative **299** was observed in this occasion. Unfortunately, all attempts of purification resulted in partial cleavage of the silyl moiety. Thus, it was decided to attempt the deprotection reaction of the crude nucleoside. Treatment of the crude with TBAF in THF at room temperature afforded, after column chromatography, a colourless oil in 32% yield from **58** (4 steps). This oil was identified by its spectroscopical data as the azanucleoside **331** with $[\alpha]_D$: -18.6 (*c* 0.70, $CHCl_3$).



Scheme 116. Preparation of the 6-chloropurine azanucleoside **331**.

The ^{1}H-NMR spectrum of the 6-chloropurine azanucleoside **331** also showed the phenomenon of hindered internal rotation about the N-C=O carbamate bond (Figure 64). Thus, a number of signals, specially H-8, H-1', H-4' and H-5' appeared unfolded at room temperature. A gradual coalescence of the peaks was observed when the spectrum was repeated at higher temperatures.

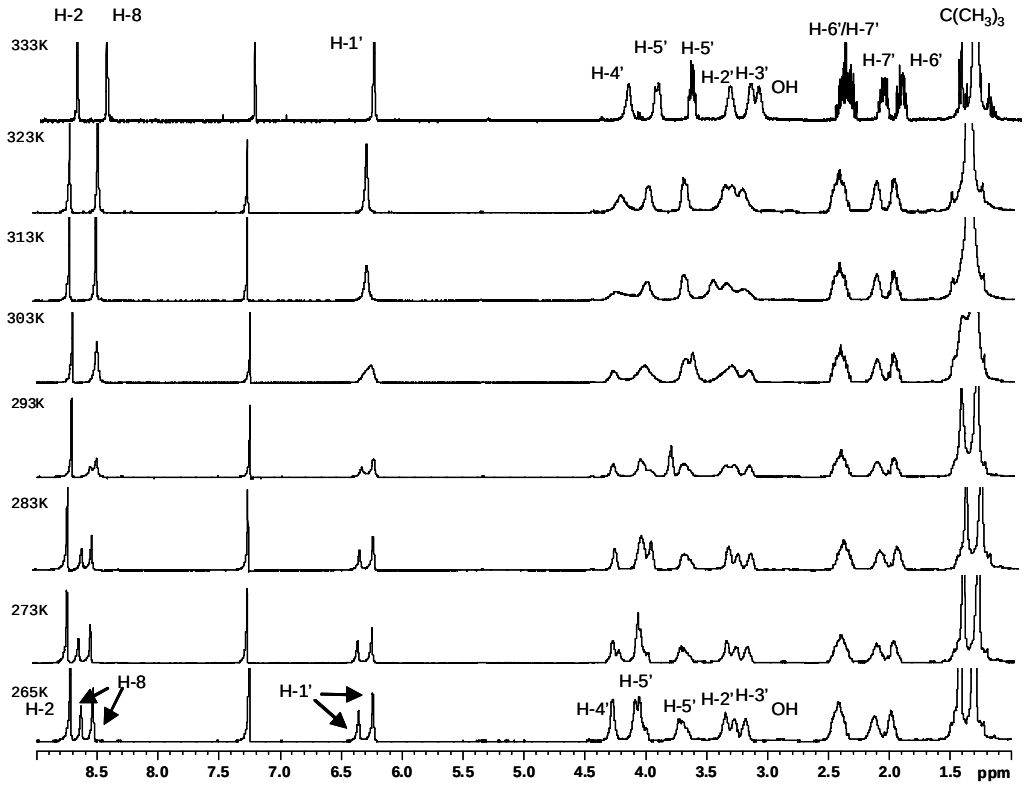


Figure 64. ^{1}H-NMR of compound **331** registered at different temperatures ($CDCl_3$, 400 MHz).

The structural elucidation of nucleoside **331** was established by an HMBC experiment wherein cross-peaks between H-1' and the aromatic carbons C-8 and C-4 is observed indicating *N*-9 regiochemistry (Figure 65).

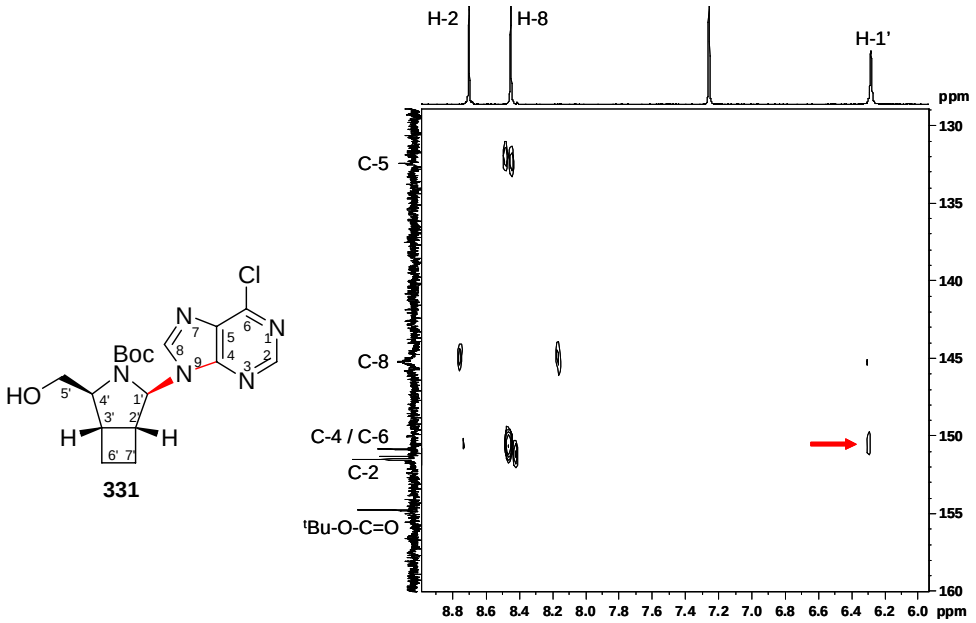
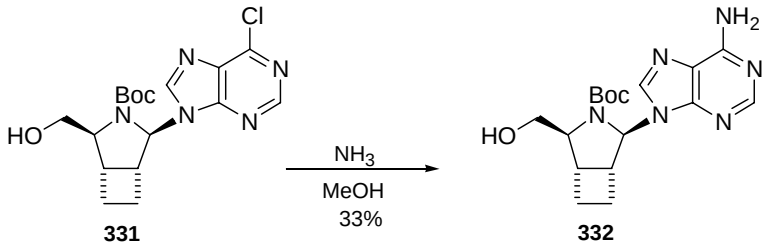


Figure 65. Detail of the HMBC experiment of **331** ($CDCl_3$, 400 MHz, 333 K). Elucidation of *N*-9 regiochemistry.

The establishment of the α/β anomeric configuration of **331** was carried out by a NOESY experiment which shows cross-peaks between H-1' and the cyclobutane protons H-6' and H-7' denoting a β-configuration at the anomeric center. Moreover, this assignment is further confirmed by a cross-peak between the aromatic proton H-8 and the hydroxymethylene protons H-5'.

Finally, the introduction of an amino moiety at C-6 was approached. The 6-chloropurine nucleoside **331** was treated with ammonia in methanol at 90 ºC in a sealed tube for 65 h (Scheme 117). Unfortunately, the desired adenine derivative could only be obtained in 33% yield, after purification by column chromatography, since partial decomposition was observed in the crude. The new nucleoside was isolated as a white solid and identified by its spectroscopical data as the adenine derivative **332**.



Scheme 117. Preparation of the adenine azanucleoside **332**.

Most of the signals in the ^{1}H-NMR of **332** appeared unfolded at room temperature due to the presence of rotamers (Figure 66). However, almost complete collapse of the signals was observed when the spectrum was repeated at 333 K although decomposition of the nucleoside was observed what avoided the performance of further experiments.

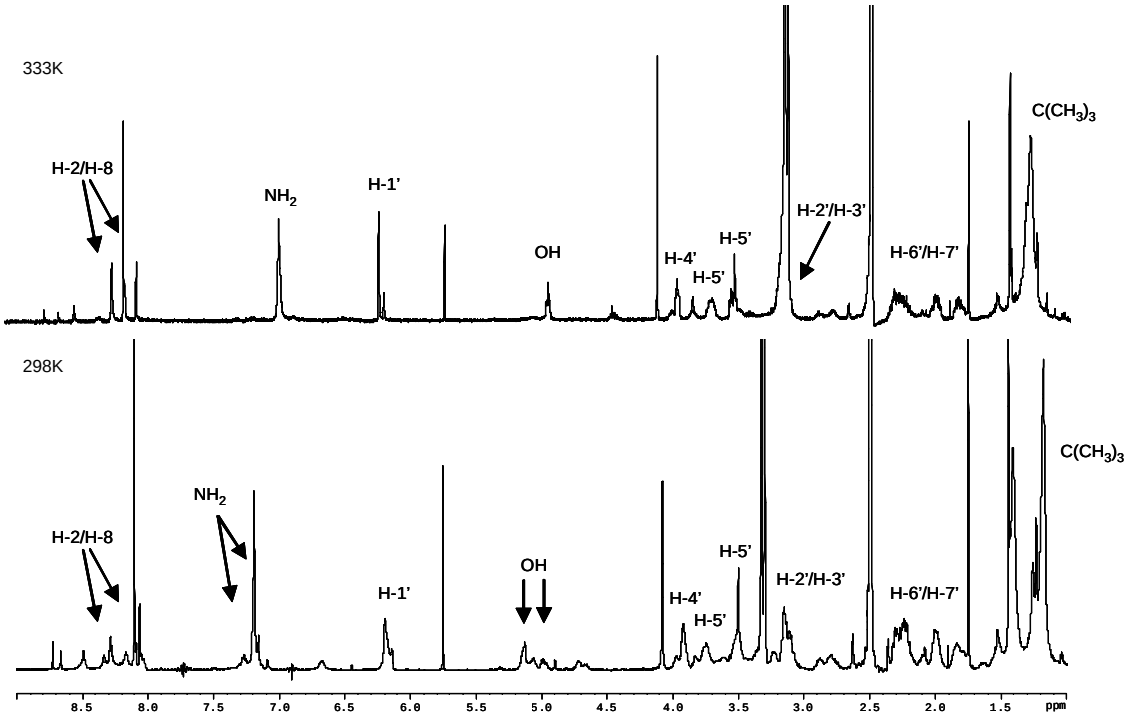
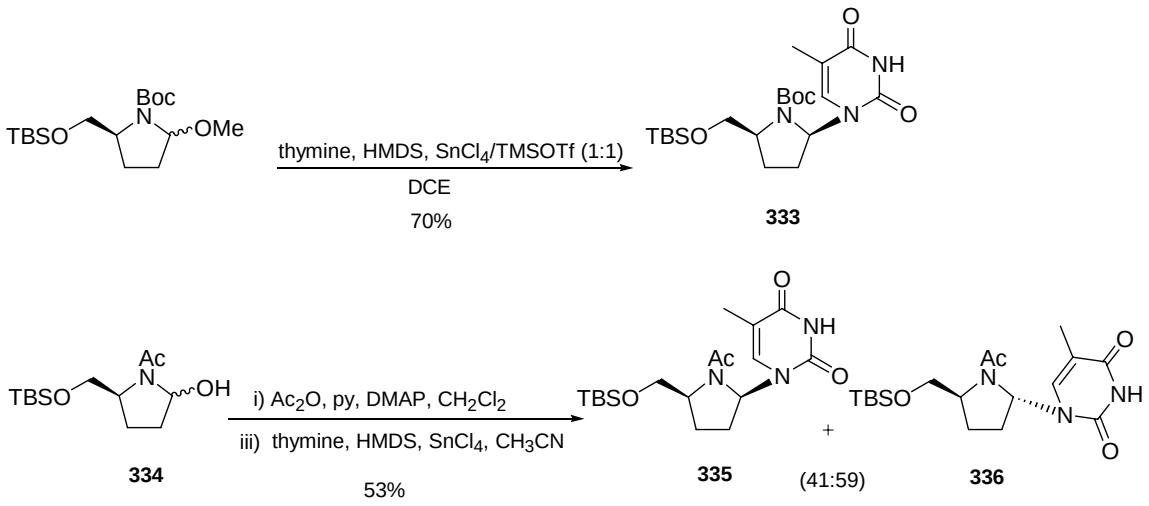


Figure 66. ^{1}H-NMR of compound **332** registered at different temperatures ($CDCl_3$, 400 MHz).

Quite unexpectedly, the nucleobase coupling behaviour of both 6-chloropurine and thymine proved highly stereoselective, providing exclusively the β-anomers of the desired azanucleosides. This selective formation of the β-anomeric compounds **320**, **321** and **331** during the Lewis acid catalyzed coupling of silylated bases with the *N*-Boc protected building block **63** is consistent with the results published by Rassu *et al.*[14d] whereas other studies dealing with similar syntheses of different *N*-Acyl pyrimidine nucleoside analogues have exhibited unselective nucleobase coupling behaviours.[14a,b,c,132] As an example, Scheme 118 shows the stereoselective preparation of the β-thymine nucleoside **333** by Rassu *et al.* and the *N*-glycosylation of the *N*-acetyl derivative **334** described by Altmann[14a] which afforded a 41:59 mixture of the β- and α-nucleosides **335** and **336**, respectively.

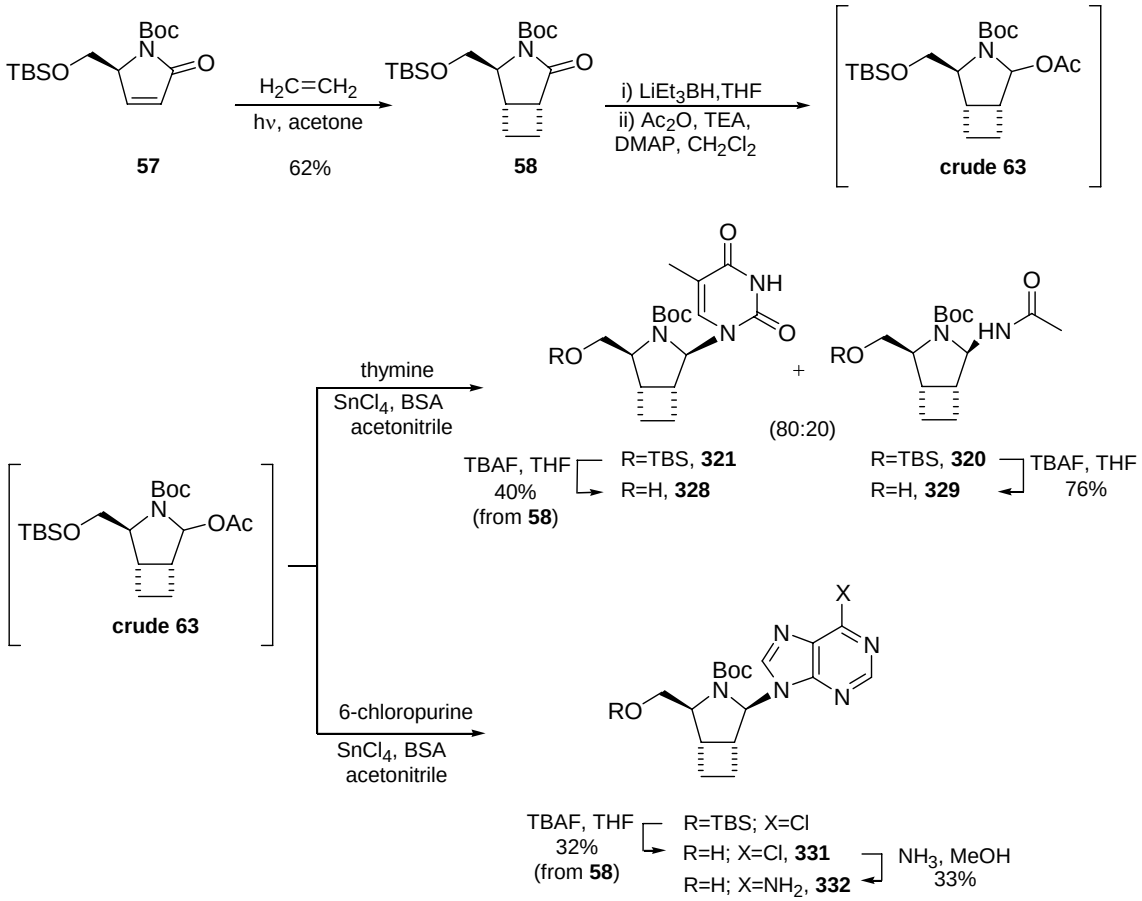
[132] a) Huang, B.; Chen, B.; Hui, Y. *Synthesis* **1993**, 769-771. b) Altmann, K.-H.; Freier, S. M.; Pieles, U.; Winkler, T. *Angew. Chem. Int. Ed.* **1993**, *33*, 1654-1657. c) Pickering, L.; Malhi, B. S.; Coe, P. L.; Walker, R. T. *Tetrahedron* **1994**, *51*, 2719-2728.



Scheme 118. Synthesis of the azanucleoside **333**, Rassu *et al.* (1997). Synthesis of the azanucleosides **335** and **336**, Altmann (1993).

The stereoselective formation of the β-azanucleosides in this work remains unclear and further studies will be necessary in order to elucidate and rationalize these results.

Summarizing, two new azanucleosides bearing a cyclobutane ring fused to the furanose moiety, **321** and **332**, have been stereoselectively synthesized following a short and divergent synthetic pathway, as well as a new acetamide derivative **329** (Scheme 119). It is noteworthy to mention that the adenine derivative **331** is the first example of purine azanucleoside ever synthesized following the Hilbert-Johnson *N*-glycosylation conditions. Moreover, the entry to new pyrimidine and purine azaderivatives reported herein will be applied to the preparation of further cyclobutane and cyclobutene azanucleoside analogues in the near future.



Scheme 119. Synthesis of azanucleoside analogues conformationally restricted by a cyclobutane ring.

VI. Conformational analysis in solid state and anti-HIV activity evaluation

1. Conformational analysis in solid state

Unfortunately, none of the newly synthesized β-nucleoside analogues provided adequate crystals for X-ray analysis avoiding then the comparison of their conformational data with that of known active 2',3'-dideoxynucleosides. Nevertheless, it was possible to crystallize the 2'-fluoro α-hypoxanthine derivative **263** in methanol which afforded a monocrystal suitable to obtain its structure through X-ray difraction (Figure 67).

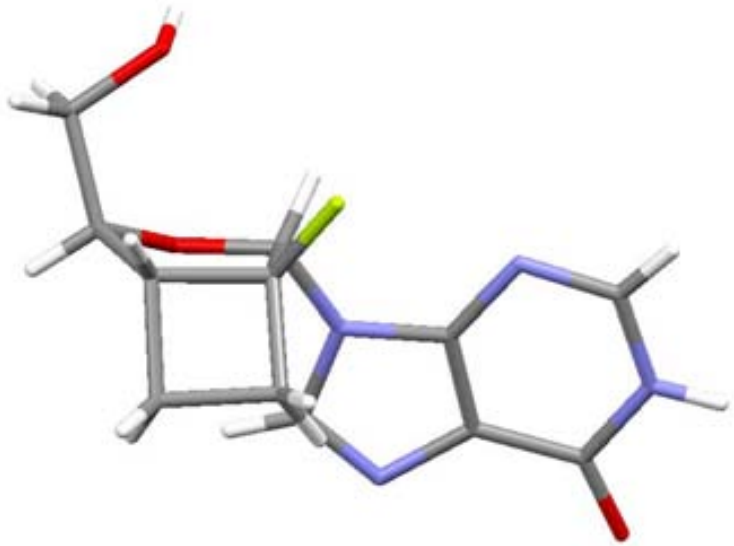
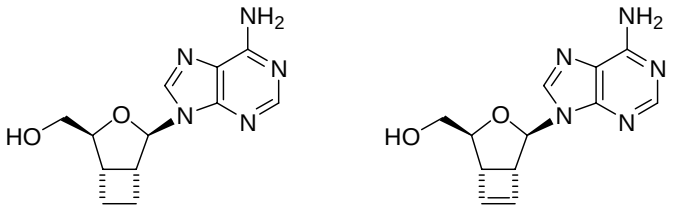


Figure 67. X-ray structure of cyclobutane nucleoside **263**.

Conformational analysis of the cyclobutane derivative **263**[105] in solid state revealed that the furanose ring adopts a C-4' endo (^4E) pucker with a pseudorotation phase angle P=247.1º and a maximum amplitude of puckering ν_{max}=27.5º. The conformation around the glycosylic bond is *anti* with a χ value of 163.6º, while the torsion angle γ is 56.6º, indicating that the preferred conformation around the C4'-C5' bond is +gauche (γ^+).

There is no suitable data to compare these results, since no X-ray from α-2'-fluoro-2',3'-dideoxynucleosides have been published to date. However, the degree of puckering of **263** can be compared with that of the conformationally locked adenine derivatives **234** and **236** previously described in our research group (Figure 68). Thus,

the observed ^{4}E pucker is the same as for cyclobutane **234**, whereas a O-exo ($_O$E) pucker was obtained for the cyclobutene derivative **236** (Table 44). On the other hand, **263** shows a similar flaterness, υ_{max} =27.5ºC, to **234** and **236**, υ_{max} =22.9º and 25.7º, respectively, though a little bit higher. Finally, the conformation around the glycosylic bond, χ, as well as the torsion angle, γ, can not be compared due to the different configuration of the anomeric centre.



234 **236**

Figure 68. Structure of the conformationally locked nucleoside analogues **234** and **236**.

Compound	P [a] (º)	υ_{max} [b] (º)	χ [c] (º)	γ [d] (º)
263	247.1	27.5	163.6	56.6
234	228.1	22.9	-157.1	173.8
236	259.8	25.7	-175.5	-75.6

[a] *P*: phase angle of pseudorotation. [b] υ_{max}: maximum puckering amplitude. [c] χ: torsion angle O4'-C1'-N9-C4. [d] γ: torsion angle O5'-C5'-C4'-C3'.

Table 44. Some conformational parameters of **263**, **234** and **236**.

Finally, a graphical comparison further confirms a remarkable similarity between the conformations of the furanose ring of the new nucleoside **263** and that of the conformationally locked adenine nucleosides **234** and **236** (Figure 69).

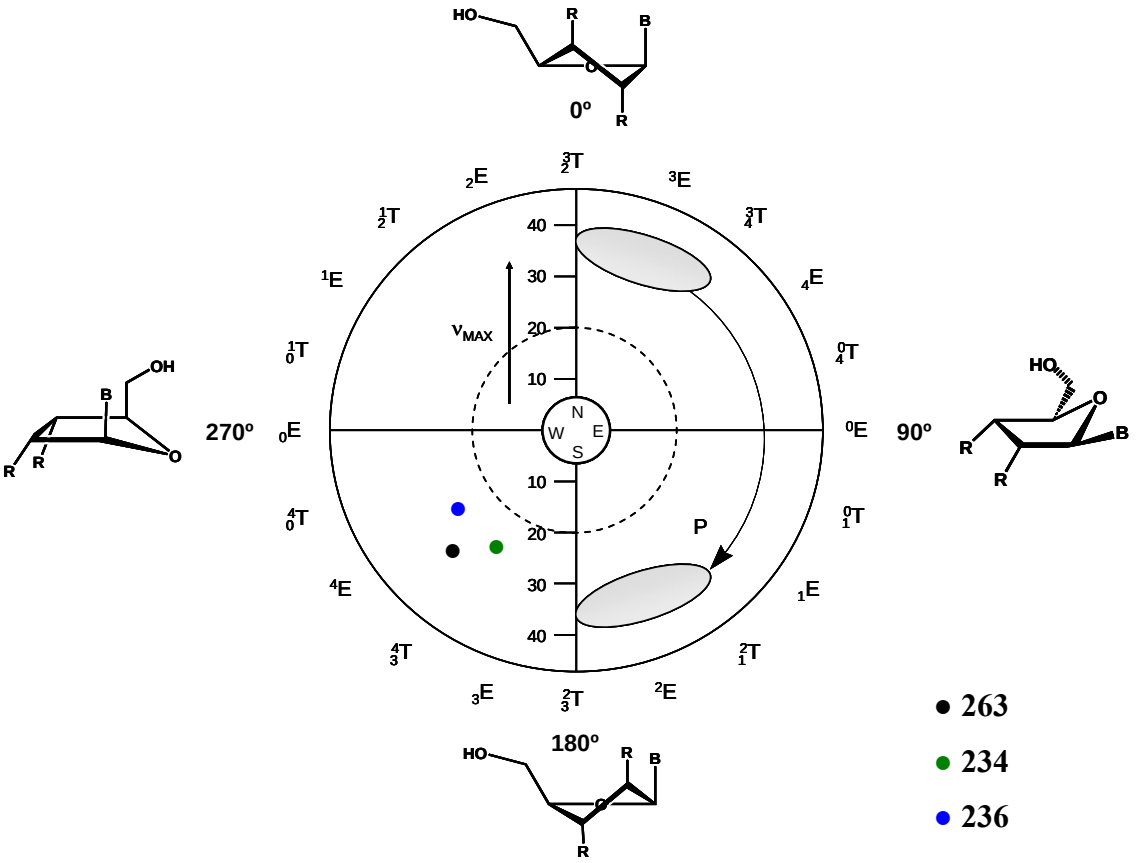


Figure 69. Graphic localisation of the nucleosides **263**, **234** and **236** in the pseudorotational cycle.

2. Evaluation of the anti-HIV activity

The anti-HIV activity of all the nucleoside analogues conformationally locked synthesized in the present work has been evaluated by the research group leaded by Dr. José A. Esté at the *Laboratori de Retrovirologia de la Fundació IrsiCaixa de l' Hospital Universitari Germans Trias i Pujol*. The experiments have been carried out against a HIV-1 NL4-3 wild type strain, using a MT-4 limfoid cellular line (received from the NIH AIDS Reagent Program).[133] Measures were performed taking the known antivirals **AZT** and **d4T** as reference, as well as the compound **AMD3100**,[134] a bicyclam which acts as an inhibitor of the VIH replication (Figure 70).

[133] Manetti, F.; Esté, J. A.; Clotet-Codina, I.; Armand-Ugón, M.; Maga, G.; Crespan, E.; Cancio, R.; Mugnani, C.; Bernardini, C.; Togninelli, A.; Carmi, C.; Alongi, M.; Petricci, E.; Massa, S.; Corelli, F.; Botta, M. *J. Med. Chem.* **2005**, *48*, 8000-8008.

[134] Esté, J. A.; Cabrera, C.; de Clercq, E.; Struyf, S.; Van Damme, J.; Bridger, G.; Skerlj, R. T.; Abrams, M. J.; Henson, G.; Gutierrez, A.; Clotet, B.; Schols, D. *Mol. Pharmacol.* **1999**, *55*, 67-73.

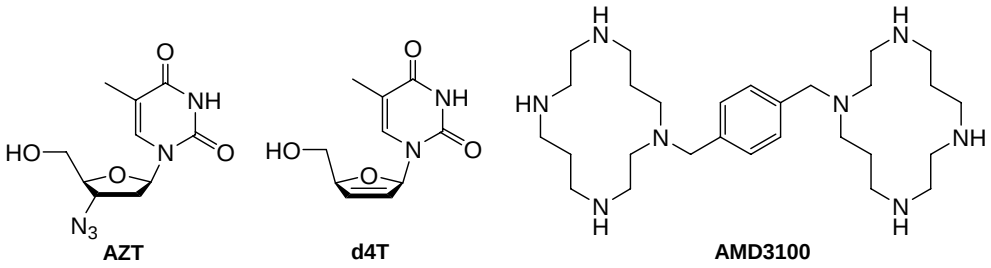
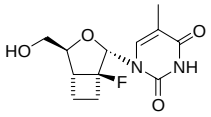
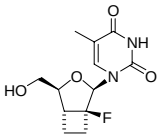
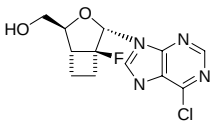
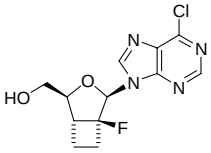
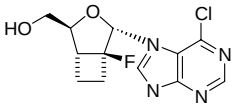
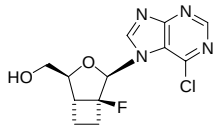
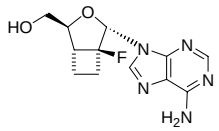
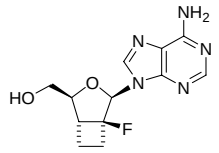
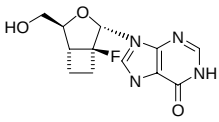
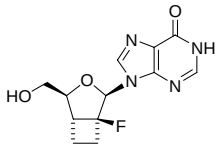
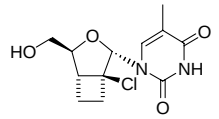
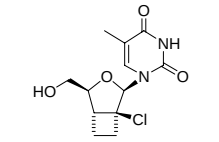
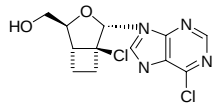
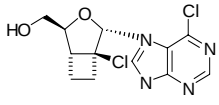
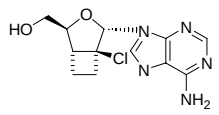
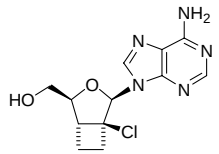
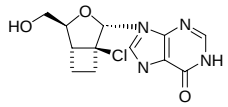
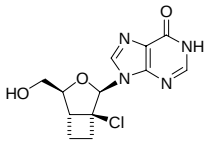
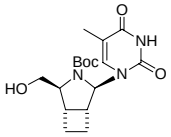
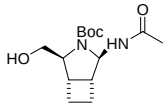


Figure 70. AZT, **d4T** and **AMD3100** structures.

Significant anti-HIV-1 activity was only observed for the adenine derivative **279** with an EC50 value of 22.92 μg/ml whereas the remaining nucleoside analogues synthesized showed no activity at concentration values below 25 μg/ml. (Table 45). In some cases, such as **272**, a moderated citotoxicity was observed as well, with a CC50 value of 6.85 μg/ml.

	maximum concentration used	HIV-1 NL4-3	non-infected cells
		EC50	CC50
AZT	1	0.0009	>1
AMD3100	1	0.0017	>1
d4T	2	0.024	>2
 **246**	25	>25	>25
 **247**	25	>25	>25
 **255**	25	>25	>25
 **248**	25	>25	>25
 **256**	25	>25	>25

 **257**	25	>25	>25
 **258**	25	>25	>25
 **249**	25	>25	>25
 **262**	25	>25	>25
 **250**	25	>25	>25
 **268**	25	>25	>25
 **269**	25	>25	>25
 **270**	25	>25	>25
 **272**	25	>6.85	6.85
 **278**	25	>25	>25
 **279**	25	22.92	>25

 **280**	25	>25	>25
 **281**	25	>25	>25
 **328**	25	>25	>25
 **329**	25	>25	>25

All values are given in μg/ml. EC50: Needed concentration to inhibit 50% HIV-induced cell death. CC50: Needed concentration to induce 50% death of non-infected cells.

Table 45. Measure of the activity of the nucleoside analogues prepared in the present work against VIH-1 wt and compared to **AZT**, **d4T** and **AMD3100**.

As previously discussed, in order to show antiviral activity, a nucleoside must be delivered to the blood cell surface, penetrate the cell membrane, anabolize in a cascade reaction of phosphorylation into its 5'-triphosphate form, and finally be utilized as alternative substrates by HIV Reverse Transcriptase. Since the virus does not encode its own nucleoside and nucleotide kinases, all phosphorylation steps must be catalyzed by the host cell enzymes. Therefore, nucleoside analogues, as these described herein, suffer from an absolute dependence on host cell kinase-mediated activation, a dependence which may lead to poor activity. Thus, any structure-activity relationship study is under the influence of the complexity of the anabolic processes of activation and the preferred conformation of a nucleoside should be evaluated at each enzyme driven step. Both antiviral activity and citotoxicity values are the final results of multienzymatic processes and no information is known about the point where the locked conformation plays a critic role.

Since the lack of activity observed for most of the newly synthesized compounds might be due to their incapability of being transformed to their 5'-triphosphorylated form, a new research line has been started in our group towards the synthesis of 5'-monophosphorylated cyclobutane nucleosides as well as other

nucleotide prodrugs (pronucleotides) that can avoid the first step of phosphorylation.[135] This fact prompted me to undertake a short stay at the Laboratory of Medicinal Chemistry (Leuven, Belgium) directed by Prof. Piet Herdewijn during the last year of my phD. The aim of the stay was to learn the chemistry related to phosphate and phosphonate synthesis and their application to the preparation of monophosphate derivatives of some of the novel nucleosides described herein.

Finally, an additional issue must be taken into account, the cyclobutane ring might cause steric repulsive interactions due to the presence of two methylene groups below the sugar ring. These interactions might also play a significant role related with the lack of activity observed for most of the cyclobutane nucleosides prepared here.

[135] Kukhanova, M.; Krayevsky, A.; Prussof, W.; Cheng, Y.-C. *Current Pharmaceutical Design*, **2000**, *6*, 585-598.

VII. Synthesis of phosphorylated nucleosides

1. Preparation of 5',3'-bisphosphorylated nucleosides

The goal of my 3 month stay in the Laboratory of Medicinal Chemistry of the K.U. Leuven (Belgium) directed by Prof. Herdewijn was the preparation of the 5',3'-bisphosphorylated nucleosides **337** and **338** (Figure 71). Both compounds, possessing a guanosine and a guanine *altro*-hexitol (altritol) skeleton respectively, are currently under study in a number of biological assays which are still to be published.

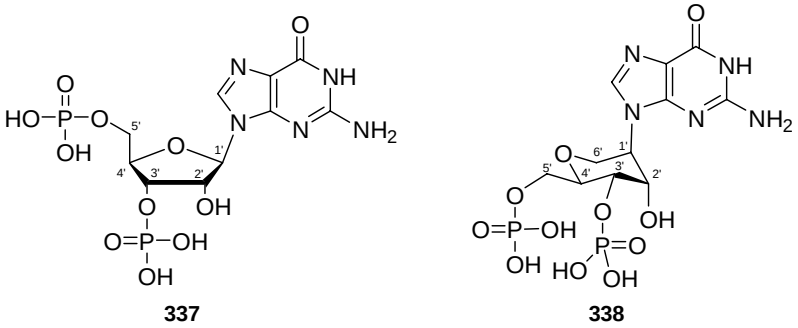


Figure 71. Target 5',3'-biphosphate nucleosides **337** and **338**.

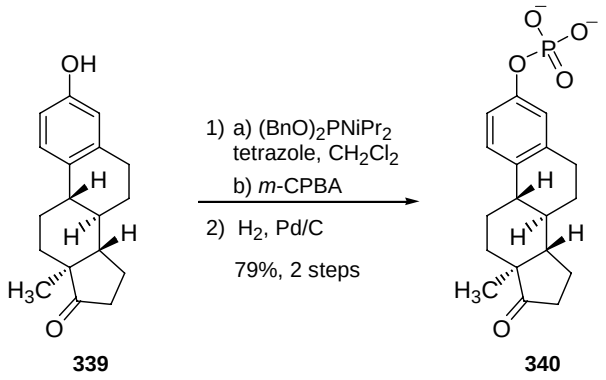
Whereas guanosine, one of the building blocks of RNA, is commercially available, altritol nucleosides were synthesized for the first time by Herdewijn and co-workers in 1999.[136] Their structure is based on a D-altritol backbone and a nucleobase at the 2-(*S*)-position of the carbohydrate residue. They are being successfully used as building blocks of a novel RNA analogue, the Altritol Nucleic Acid (ANA).[137] ANA-RNA and ANA-DNA duplexes have been found to exhibit high stability which is a promising issue for future results in the field of antisense oligonucleotides.[138]

The preparation of the building blocks precursors of the desired bisphosphates **337** and **338** was accomplished on a multi-gram scale following slight modifications of previously reported procedures.[136, 139]

Phosphoramidite chemistry was chosen to install the phosphate functions following a two-step procedure consisting on the introduction of two dibenzyl

[136] Allart, B.; Busson, R.; Rozenski, J.; Van Aerschot, A.; Herdewijn, P. *Tetrahedron* **1999**, *55*, 6527-6546.
[137] a) Kozlov, I. A.; Zielinski, M.; Allart, B.; Kerremans, L.; Van Aerschot, A.; Busson, R.; Herdewijn, P.; Orgel, L. E. *Chem. Eur. J.* **2000**, *6*, 151-155. b) Abramov, M.; Shepers, G.; Van Aerschot, A.; Herdewijn, P. *Eur. J. Org. Chem.* **2007**, 1446-1456.
[138] For a review on Antisense Oligonucleotides see: Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543-584.
[139] Serebryany, V.; Beigelman, L. *Tetrahedron Lett.* **2002**, *43*, 1983-1985.

phosphate moieties and posterior hydrogenolysis to provide the target phosphorylated derivative **340** described by Bertozzi and co-workers (Scheme 120).[140] Therein, a dibenzyl phosphate group was introduced by reaction of the tetracyclic alcohol **339** with dibenzyl diisopropylphosphoramidite in the presence of tetrazole in dry CH_2Cl_2 at 0 ºC, followed by oxidation with *meta*-chloroperbenzoic acid (*m*-CPBA). Subsequent Pd-mediated hydrogenolysis provided the desired phosphate **340** in 79% overall yield.



339 **340**

Scheme 120. Preparation of the phosphate **340**, Bertozzi and co-workers (2003).

This synthetic methodology was successfully applied to the synthesis of **338**. However, the first attempts failed to yield the desired derivative **337**.

2. Synthesis of monophosphorilated azanucleosides

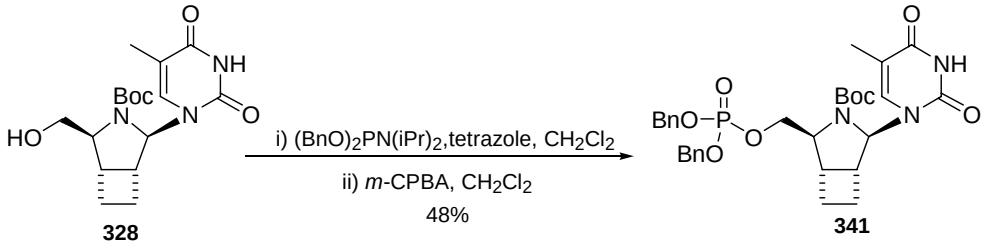
Without exception, nucleoside analogues possessing antiviral activity seem to require phosphorylation *in vivo* to reach their active nucleotide forms. Poor phosphorylation can be a major cause of poor activity, with several examples known where nucleoside analogues are inactive, whereas their corresponding triphosphates are inhibitors of their target enzyme.[141] The triphosphates themselves cannot be considered to be useful drugs due to their inherent hydrolytic instability and poor membrane permeation. However, it appears that in most cases the first phosphorylation to the 5'-monophosphate is the rate-limiting step,[142] leading to the consideration of the monophosphates as chemotherapeutic agents. In fact, nucleoside monophosphates suffer

[140] Armstrong, J. I.; Verdugo, D. E.; Bertozzi, C. R. *J. Org. Chem.* **2003**, *68*, 170-173.
[141] Tomassini, J. E.; Getty, K.; Stahlhut, M. W.; Shim, S.; Bhat, B.; Eldrup, A. B.; Prakash, T. P.; Carroll, S. S.; Flores, O.; MacCoss, M.; McMasters, D. R.; Migliaccio, G.; Olsen, D. B. *Antimicrob. Agents Chemoter*. **2005**, *49*, 2050-2058.
[142] Balzarini, J.; Herdewijn, P.; De Clercq, E. *J. Biol. Chem.* **1989**, *264*, 6127-6133.

from similar qualitative problems as triphosphates; instability (in this case to phosphatases and nucleotidases) and poor membrane permeation. Given these problems, and the perceived advantage of bypassing the nucleoside kinase dependence of nucleoside analogues, many groups have worked on phosphonate prodrug strategies.[143]

Nevertheless, despite the aforementioned drawbacks implicit in monophosphates, it was decided to take advantage of the experience acquired in the laboratory of Prof. Herdewijn to prepare the 5'-monophosphorylated derivative of the thymine azanucleoside **328**. The aim of the synthesis was comparing the anti-HIV activity of the nucleoside and its monophosphate. Besides, it should be the first approach to a family of phosphate and phosphonate nucleosides that are planned to be prepared in a near future in our research group.

Therefore, the thymine derivative **328** was submitted to the same reaction conditions described above. Treatment with dibenzyl diisopropylphosphoramidite and tetrazole and subsequent addition of *m*-CPBA furnished a colourless oil in 48% yield after column chromatography, identified by its spectroscopical data as the dibenzyl phosphate **341** with $[\alpha]_D$: -35.6 (*c* 0.90, $CHCl_3$) (Scheme 121). As expected, the ^{1}H-NMR spectrum of **341** also showed the phenomenon of hindered internal rotation about the N-C=O carbamate bond.

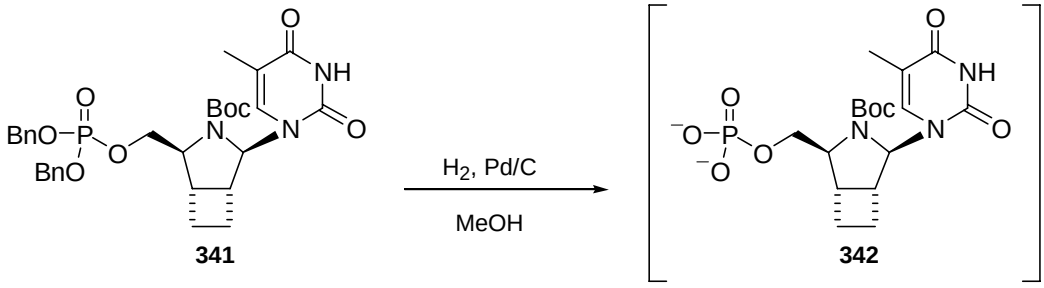


Scheme 121. Preparation of the phosphate derivative **341**.

Next, **341** was dissolved in MeOH and stirred overnight under a H_2 atmosphere (1 atm) in the presence of Pd/C. Apparently, reaction took place smoothly according to TLC controls (Scheme 122). However, all attempts to purify the final product by ion-exchange chromatography were in vain and only decomposition products were observed. Unfortunately, the lack of remaining **328** avoided further experimentation and

[143] Copperwood, J. S.; Gumina, G.; Boudinot, F. D.; Chu, C. K. 'Nucleoside and Nucleotide prodrugs'. In: 'Recent Advances in Nucleosides: Chemistry and Chemotherapy', Chu, C. K. Ed.; Elsevier Science B. V. 2002, p. 91-147.

the preparation of the target phosphorylated azanucleoside **342** had to be temporally abandoned.



Scheme 122. Failed attempt of preparing of the monophosphate **342**.

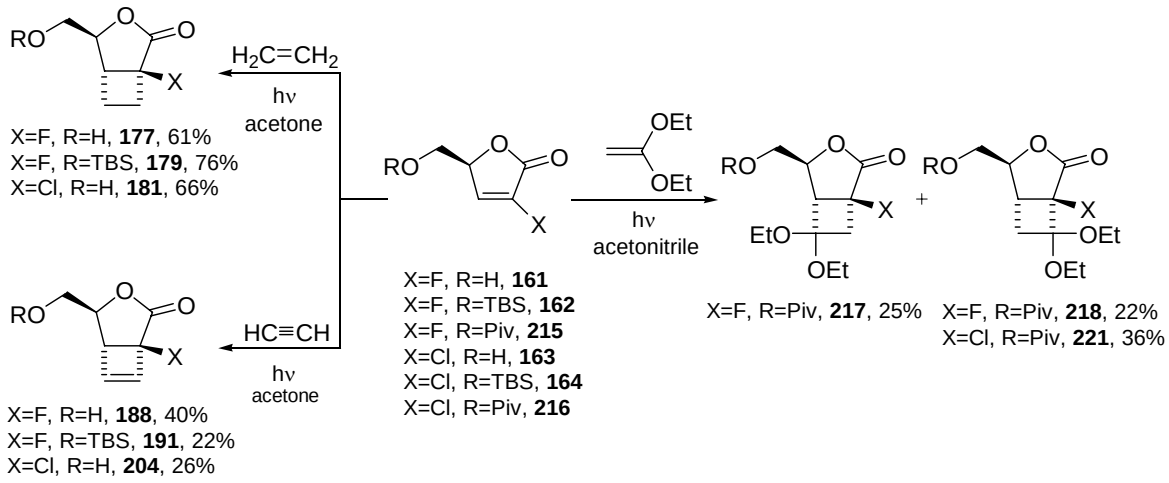
Despite the impossibility of isolating the expected monophosphate **342** this study has become the starting point of a promising new research line devised to prepare phosphate and phosphonate derivatives of nucleosides and evaluate their activity as prodrugs against HIV.

VIII. Summary and conclusions

1. Summary and conclusions

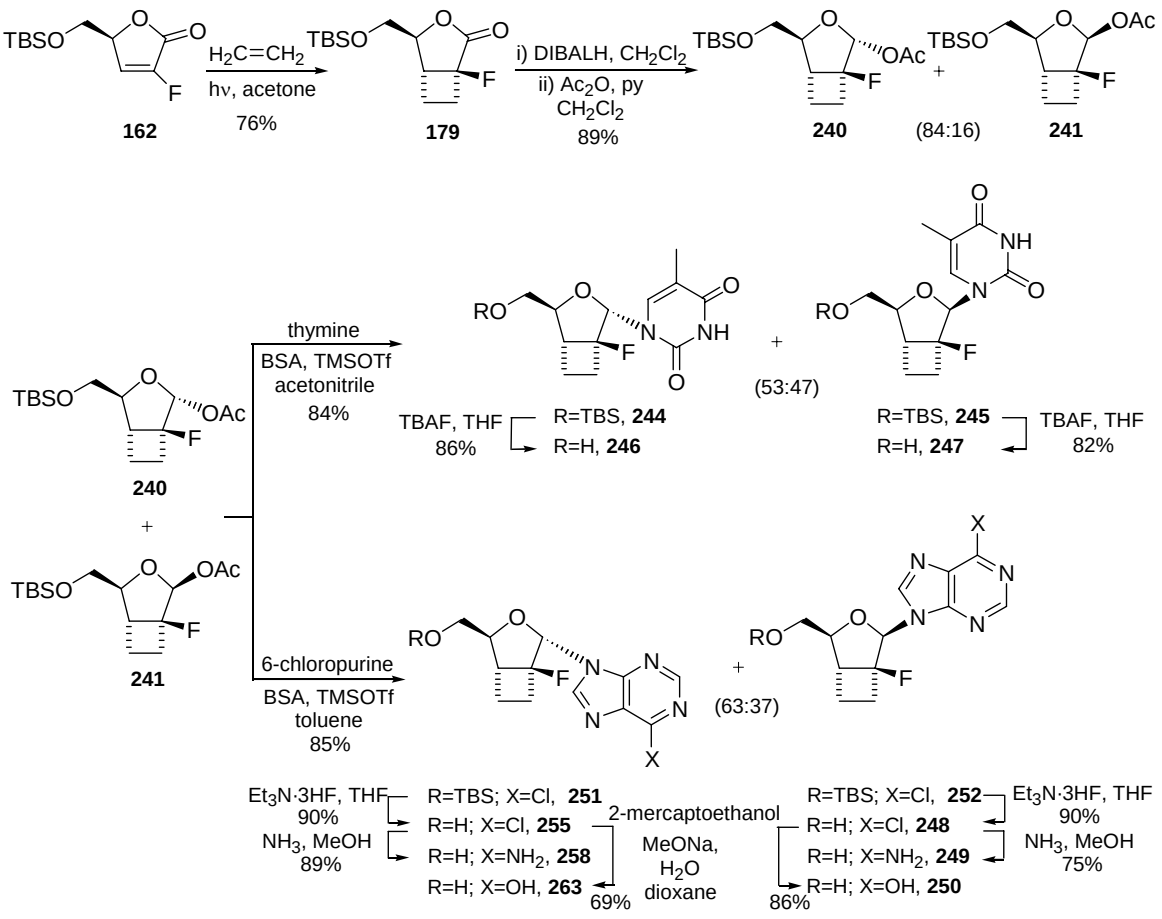
i) The photochemical reactivity of 2(5*H*)-furanones with mono and disubstituted alkynes has been investigated. The effect of the filter, the solvent and the alkyne substitution on the outcome of the reaction has been evaluated. As a consequence of the low yields and the presence of multiple by-products such as 1,3-acyl rearranged derivatives, the application of these photoreactions in a synthetic methodology devised to the preparation of more elaborated cyclobutene becomes unlikely. Nevertheless, the photochemical study has provided us with highly interesting results from a mechanistic point of view.

ii) The photochemical reactivity of 3-chloro- and 3-fluoro-2(5*H*)-furanones with ethylene, acetylene and ketene diethyl ketal has been investigated (Scheme 123). The high yields and facial diastereoselectivity values obtained in the [2+2] photocycloaddition of lactones **161** and **164** to ethylene have allowed the preparation of the *anti* cycloadducts **179** and **181** in 76% and 66% yield, respectively, which have been taken as the starting material for the synthesis of cyclobutane chloro and fluoronucleosides analogues. On the other hand, the low yields and the complexity of the reaction mixtures obtained in the reactions with acetylene and ketene diethyl ketal have prompted us to discard their use as a method for preparing more elaborated chloro and fluoro cyclobutene and cyclobutane derivatives.

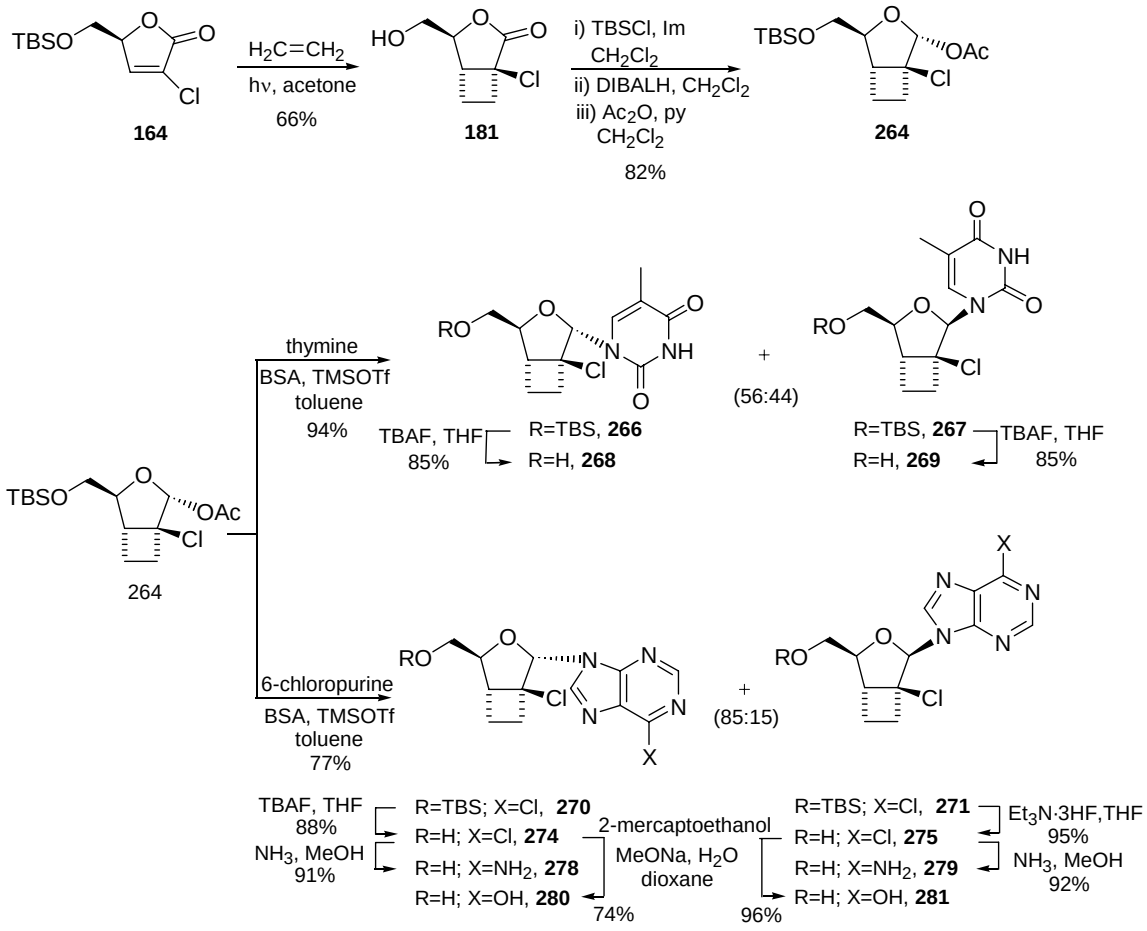


Scheme 123. [2+2] Photocycloaddition of 3-halo-2(5*H*)-furanones to ethylene, acetylene and ketene diethyl ketal.

iii) A new family of 2'-fluoro and 2'-chloronucleoside analogues conformationally restricted by a cyclobutane ring has been synthesized (Scheme 124 and 125). The anti-HIV activity of the new thymine, 6-chloropurine, adenine and hypoxanthine derivatives prepared has been evaluated showing the compound **279** a moderate activity.

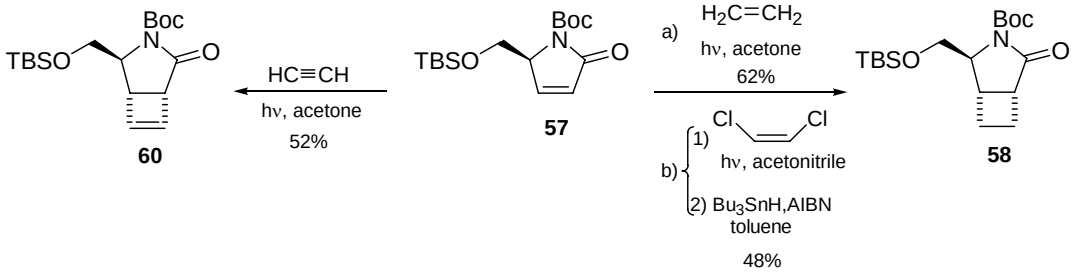


Scheme 124. Synthesis of cyclobutane 2'-fluoronucleoside analogues.



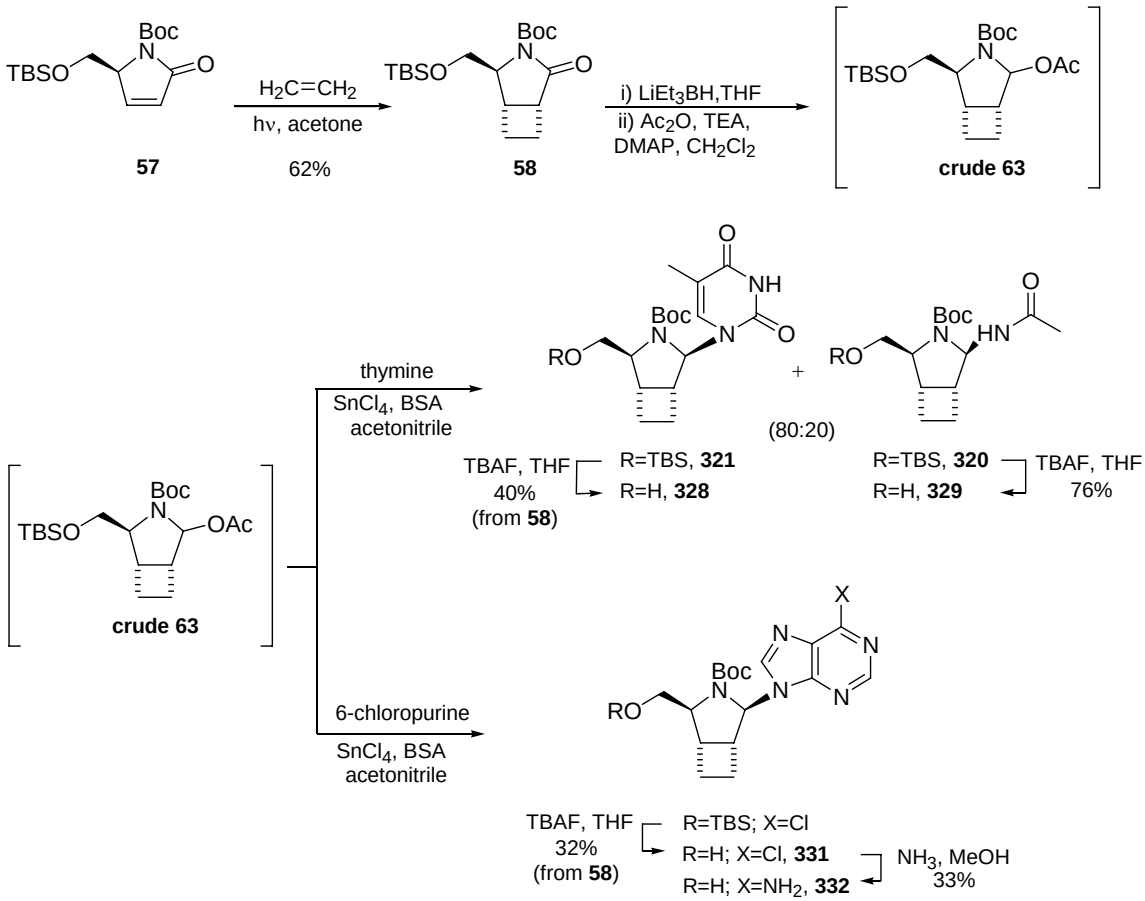
Scheme 125. Synthesis of cyclobutane 2'-chloronucleoside analogues.

iv) The photochemical reactivity of the homochiral γ-lactam **57** with ethylene, *cis*-1,2-dichloroethylene and acetylene has been evaluated allowing the diastereoselective preparation of the *anti* cyclobutane and cyclobutene lactams **58** and **60**, in 62% and 52% yield, respectively (Scheme 126). The bicyclic lactam **58** has been used as the starting material for the preparation of cyclobutane azanucleoside analogues whereas the cyclobutene **60** will be applied shortly in a synthetic strategy devised to prepare cyclobutene analogues of azanucleosides.



Scheme 126. Photochemical preparation of the cycloadducts **58** and **60**.

v) A new family of thymine and adenine azanucleoside analogues conformationally restricted by a cyclobutane ring has been synthesized (Scheme 127). The adenine derivative **331** is the first example of purine azanucleoside ever synthesized following the Hilbert-Johnson *N*-glycosylation conditions. Moreover, the synthesis of the acetamide derivative **329** has been also described. The anti-HIV activity of the thymine and acetamide derivatives **328** and **329** has been evaluated without showing significant activity.



Scheme 127. Synthesis of cyclobutane azanucleoside analogues.

IX. Experimental section

General Methods

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere and monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminum plates (0.25 mm thickness). Column column chromatography was performed using silica gel 60 Å, particle size 35-70 μm. Solutions were concentrated using an evaporator at 15-20 Torr. Melting points were determined on hot stage and are uncorrected. ^{1}H-NMR at 250 or 360 or 500 MHz, ^{13}C-NMR at 62.5 or 90 or 125 MHz, ^{19}F-NMR at 235 MHz and ^{31}P NMR at 146 MHz were recorded at the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona*. NMR signals were assigned with the help of DEPT, COSY, HMBC, HMQC and NOESY experiments. Infrared spectra were recorded on a Sapphire-ATR Spectrophotometer; peaks are reported in cm^{-1}. High resolution mass spectra (HRMS) were recorded at the *Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona* in a Bruker micrOTOFQ spectrometer using ESI–MS (QTOF). Microanalyses were performed at the *Servei d'Anàlisi Elemental de la Universitat Autònoma de Barcelona*. Optical rotations were measured at 22 ± 2 ºC.

The photochemical reactions were conducted with a 125 W high pressure mercury lamp (Cathodeon HPK125) (Figures 72 and 73). The photochemical reactor used is equipped with a quartz or pyrex refrigeration jacket (Figure 73).

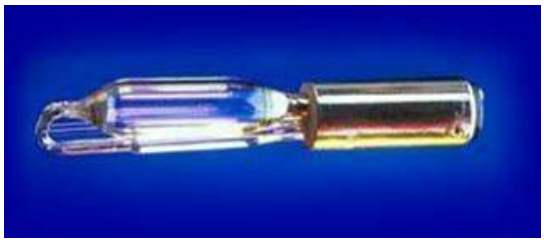


Figure 72. 125 W High pressure mercury lamp.

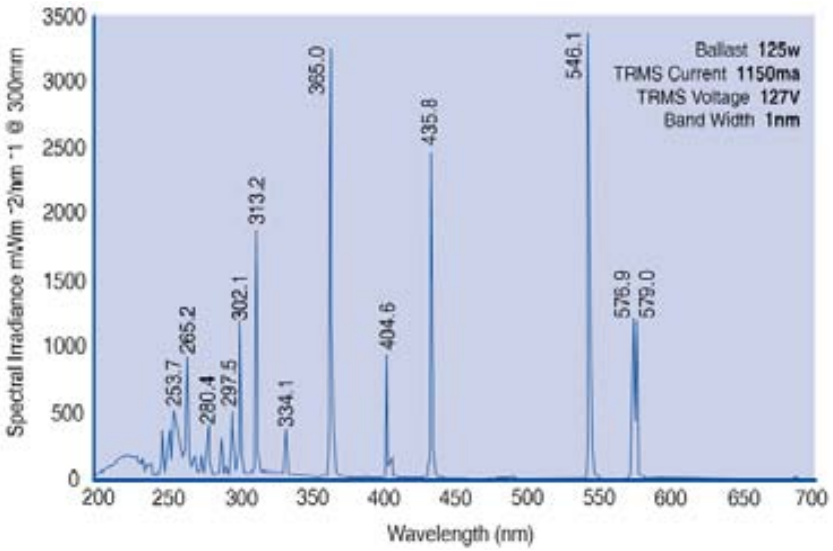


Figure 73. Spectral irradiance of the high pressure mercury lamp used in the present work.

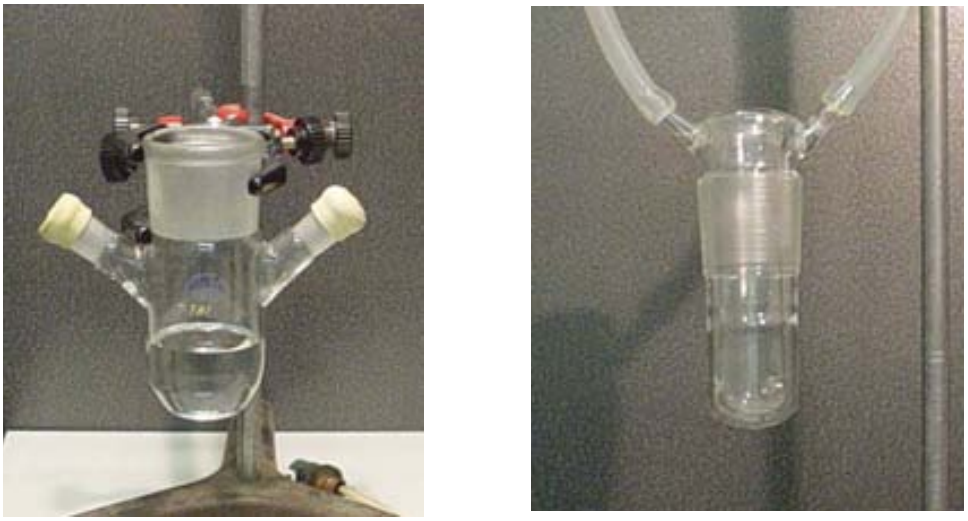
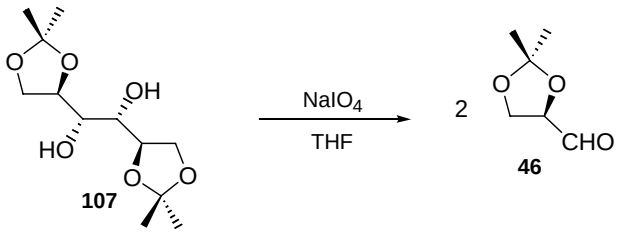


Figure 74. Photochemical reactor and refrigeration jacket.

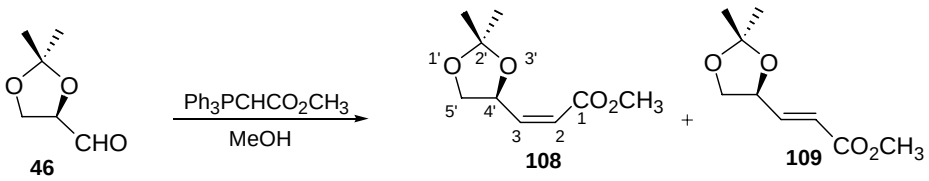
1. Synthesis of 2(5*H*)-furanones

1.1. 2,3-*O*-isopropylidene-D-gliceraldehyde (46)



To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, **107**, (12.00 g, 45.7 mmol) in THF (100 mL), a suspension of sodium periodate (10.80 g, 50.5 mmol) in a mixture of THF (37 mL) and H_2O (17 mL) was slowly added. The resulting white suspension was stirred at room temperature for 2 h. Then, diethyl ether (170 mL) was added and the mixture was stirred for 15 min prior to filtration of a white solid. The solvent was removed under reduced pressure and extracted with CH_2Cl_2 (3x25 mL). The organic layer was dried over anhidrous Na_2SO_4 and the solvent was carefully removed under reduced pressure to avoid the loss of aldehyde. Thus, a colourless oil (10.80 g, 83.0 mmol, 90% yield) was obtained and used in the next reaction without further purification. Variable amount of hydrated aldehyde was observed by NMR and IR.

1.2. Ethyl (2*Z*)-3-[(4*S*)-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)]-2-propenoate (108) and ethyl (2*E*)-3-[(4*S*)-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)]-2-propenoate (109)



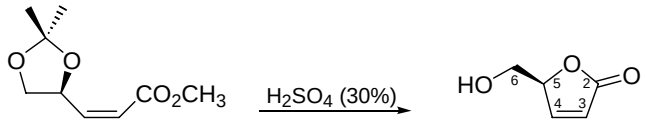
To an ice-cooled solution of aldehyde **46** (10.60 g, 81.4 mmol) in MeOH (75 mL), methoxycarbonylmethylene(triphenyl)phosphorane (27.21 g, 81.4 mmol) was carefully added in small portions. The mixture was allowed to warm to room temperature and stirred for 2 h. Then, the solvent was removed under reduced pressure and the resulting white solid was extracted with hot hexane. The solution was cooled at 0 ºC and the excess of triphenyl phosphine oxide was filtered. Evaporation of the solvent to dryness

and purification by column chromatography (hexane-diethyl ether 3:1) afforded the (*Z*)-isomer **108** (10.72 g, 57.6 mmol, 71% yield) as an oil and the (*E*)-isomer **109** (2.23 g, 12.0 mmol, 15% yield) as an oil.

108: **IR** (ATR) 2989, 2952, 2875, 1723, 1646, 1440, 1208, 1155; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.35 (dd, $J_{3,2}$=11.7 Hz, $J_{3,4'}$=6.9 Hz, 1H, H-3), 5.84 (dd, $J_{2,3}$=11.7 Hz, $J_{2,4'}$=1.5 Hz, 1H, H-2), 5.48 (dddd, $J_{4',5'}$=6.9 Hz, $J_{4',5'}$=6.9 Hz, $J_{4',3}$=6.9 Hz, $J_{4',2}$=1.5 Hz, 1H, H-4'), 4.36 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.9 Hz, 1H, H-5'), 3.70 (s, 3H, OC$\underline{H}_3$), 3.60 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.9 Hz, 1H, H-5'), 1.44 (s, 3H, C$\underline{H}_3$), 1.39 (s, 3H, C$\underline{H}_3$).

109: **IR** (ATR) 2989, 2950, 2880, 1727, 1663, 1438, 1264, 1217, 1125; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.87 (dd, $J_{3,2}$=15.9 Hz, $J_{3,4'}$=5.3 Hz, 1H, H-3), 6.09 (dd, $J_{2,3}$=15.9 Hz, $J_{2,4'}$=1.5 Hz, 1H, H-2), 4.65 (dddd, $J_{4',5'}$=7.0 Hz, $J_{4',5'}$=6.6 Hz, $J_{4',3}$=5.3 Hz, $J_{4',2}$=1.5 Hz, 1H, H-4'), 4.16 (dd, J_{gem}=8.5 Hz, $J_{5',4'}$=6.6 Hz, 1H, H-5'), 3.73 (s, 3H, OCH_3), 3.66 (dd, J_{gem}=8.5 Hz, $J_{5',4}$=7.0 Hz, 1H, H-5'), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

1.3. (*S*)-5-Hydroxymethyl-2(5*H*)-furanone (33)

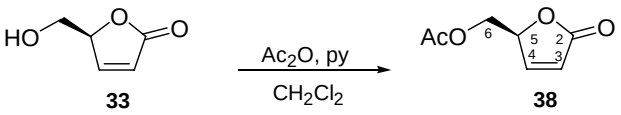


108 **33**

To a solution of **108** (10.72 g, 57.6 mmol) in MeOH (30 mL) was added a 30% aqueous solution of H_2SO_4 (260 μl). The reaction mixture was stirred for 3 h at room temperature and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (EtOAc) gave the lactone **33** (6.23 g, 54.6 mmol, 95% yield) as a white solid.

33: mp: 40-41 ºC (pentane-EtOAc); $[\alpha]_D$: -151.9 (*c* 2.4, H_2O); **IR** (KBr) 3680-3200, 3107, 2930, 2880, 1743, 1602, 1170; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.46 (dd, $J_{4,3}$=5.8 Hz, $J_{4,5}$=1.5 Hz, 1H, H-4), 6.19 (dd, $J_{3,4}$=5.8 Hz, $J_{3,5}$=2.2 Hz, 1H, H-3), 5.13 (dddd, $J_{5,6}$=5.1 Hz, $J_{5,6}$=3.6 Hz, $J_{5,3}$=2.2 Hz, $J_{5,4}$=1.5 Hz, 1H, H-5), 3.98 (ddd, J_{gem}=12.4 Hz, $J_{6,OH}$=6.9 Hz, $J_{6,5}$=3.6 Hz, 1H, H-6), 3.77 (ddd, J_{gem}=12.4 Hz, $J_{6,OH}$=6.9 Hz, $J_{6,5}$=5.1 Hz, 1H, H-6), 2.13 (dd, $J_{OH,6}$=6.9 Hz, $J_{OH,6}$=6.9 Hz, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 173.0 (C=O, C-2), 153.5 (CH, C-4), 123.0 (CH, C-3), 84.0 (CH, C-5), 62.4 (CH_2, C-6).

1.4. (*S*)-5-Acetyloxymethyl-2(5*H*)-furanone (38)



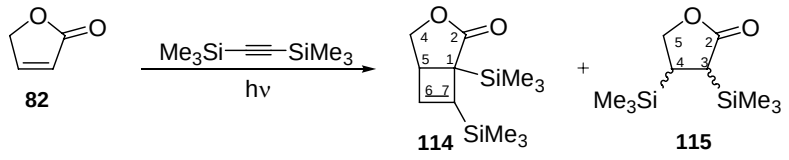
To a solution of lactone **33** (1.48 g, 12.98 mmol) in CH_2Cl_2 (90 mL) at 0 ºC, pyridine (2.80 mL, 34.7 mmol) and acetic anhydride (2.8 mL, 29.6 mmol) were added dropwise. The mixture was allowed to warm to room temperature and stirred for 21 h. Then, H_2O (30 mL) was added and the mixture was separated. The organic layer was successively washed with a 1% solution of HCl (3x30 mL), saturated $NaHCO_3$ solution (3x30 mL) and brine (3x30 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 2:1) to afford the furanone **38 (**1.63 g, 10.44 mmol, 80% yield) as a colourless oil.

38: bp: 125 ºC / 0.2 mm Hg; $[\alpha]_D$: -123.6 (*c* 3.68, $CHCl_3$); **IR** (ATR) 3100, 2959, 1745, 1616, 1183; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.40 (dd, $J_{4,3}$=5.8 Hz, $J_{4,5}$=1.5 Hz, 1H, H-4), 6.15 (dd, $J_{3,4}$=5.8 Hz, $J_{3,5}$=2.1 Hz, 1H, H-3), 5.19 (m, 1H, H-5), 4.30 (dd, J_{gem}=12.2 Hz, $J_{6,5}$=4.3 Hz, 1H, H-6), 4.23 (dd, J_{gem}=12.2 Hz, $J_{6,5}$=4.9 Hz, 1H, H-6), 1.98 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 171.9 (C=O, C-2), 170.1 (C=O, CH_3*C*O), 152.0 (CH, C-4), 122.9 (CH, C-3), 80.6 (CH, C-5), 62.4 (CH_2, C-6), 20.2 (CH_3, *C*H_3CO).

2. [2+2] Photocycloaddition of 2(5*H*)-furanones to symmetric alkynes

2.1. [2+2] Photocycloaddition of 2(5*H*)-furanones to bis(trimethylsilyl)acetylene

2.1.1. (1*RS*,5*RS*)-1,7-Bis(trimethylsilyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (114) and 3,4-bis(trimethylsilyl)dihydro-2(3*H*)-furanone (115)



A solution of crotonolactone, **82**, (119 mg, 1.40 mmol) and bis(trimethylsilyl)acetylene (1.20 g, 7.04 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 6 h at -40 ºC. Evaporation of the solvent and chromatography of the residue (hexane-EtOAc 20:1) afforded some unreacted **82** (30 mg, 0.35 mmol, 25%), the cyclobutene **114** (56 mg, 0.22 mmol, 16% yield) as a white solid and lactone **115** (150 mg, 0.65 mmol, 47% corrected yield) as a white solid.

When the irradiation was performed through a quartz filter in hexane (90 mL) for 6.5 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and bis(trimethylsilyl)acetylene (1.16 g, 6.81 mmol) after the purification of the crude material by column chromatography, the following fractions were obtained: lactone **82** (81 mg, 0.35 mmol, 25%), the cyclobutene **114** (23 mg, 0.09 mmol, 6% yield) as a white solid and lactone **115** (81 mg, 0.35 mmol, 25% yield) as a white solid.

When the irradiation was performed through a quartz filter in diethyl ether (90 mL) for 3.5 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and bis(trimethylsilyl)acetylene (1.02 g, 5.98 mmol) after the purification of the crude material by column chromatography, cyclobutene **114** (20 mg, 0.08 mmol, 6%) as a white solid and lactone **115** (60 mg, 0.26 mmol, 19%) as a white solid, were obtained.

114: mp: 62-65 ºC (from EtOAc-hexane); **IR** (ATR) 3019, 2958, 2899, 2856, 1730, 1247, 1147, 833, 745; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.78 (d, $J_{6,5}$=0.6 Hz, 1H, H-6), 4.23 (dd, J_{gem}=9.7 Hz, $J_{4,5}$=2.0 Hz, 1H, H-4), 4.12 (dd, J_{gem}= 9.7 Hz, $J_{4,5}$=7.6 Hz, 1H, H-4), 3.42 (ddd, $J_{5,4}$=7.6 Hz, $J_{5,4}$= 2.0 Hz, $J_{5,6}$=0.6 Hz, 1H, H-5), 0.18 (s, 9H, Si(CH_3)$_3$), 0.13 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 177.2 (C=O, C-2), 163.3 (C, C-7), 150.4 (CH, C-6), 66.8 (CH_2, C-4), 52.1 (C, C-1), 46.1 (CH, C-5), -2.0 (CH_3, Si(CH_3)$_3$), -3.2 (CH_3, Si(CH_3)$_3$). Anal. Calcd for $C_{12}H_{22}O_2Si_2$: C, 56.64; H, 8.71. Found: C, 57.02; H, 9.08.

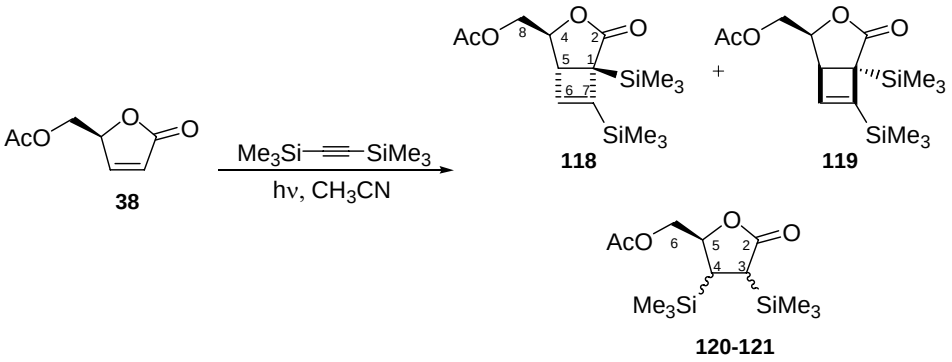
DEPT experiment was recorded for **114**.

115: mp: 31-35 ºC (from EtOAc-hexane); **IR** (ATR) 2955, 2894, 2787, 1706, 1248, 1201, 1055, 833, 745; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.39 (dd, J_{gem}=11.3 Hz, $J_{5,4}$=1.3 Hz, 1H, H-5), 4.27 (ddd, J_{gem}=11.3 Hz, $J_{5,4}$ =1.7 Hz, $J_{5,3}$ =0.7 Hz, 1H, H-5), 2.70 (dd, $J_{3,4}$=2.3 Hz, $J_{3,5}$=0.7 Hz, 1H, H-3), 2.25 (ddd, $J_{4,3}$=2.3 Hz, $J_{4,5}$=1.7 Hz, $J_{4,5}$=1.3 Hz, 1H, H-4), 0.18 (s, 9H, Si(CH_3)$_3$), 0.14 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 172.8 (C=O, C-2), 65.6 (CH_2, C-5), 36.2 (CH, C-4), 18.7 (CH, C-3), 0.0 (CH_3,

Si(CH_3)$_3$), -1.3 (CH_3, Si(CH_3)$_3$). All attempts to analyse the elementary structure of **115** failed due to its instability.

HMQC, HMBC and COSY experiments were recorded for **115**.

2.1.2. (1*R*,4*S*,5*R*)-4-Acetyloxymethyl-1,7-bis(trimethylsilyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (118), (1*S*,4*S*,5*S*)-4-acetyloxymethyl-1,7-bis(trimethylsilyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (119), (-)-5-acetyloxymethyl-3,4-bis(trimethylsilyl)dihydro-2(3*H*)-furanone (120) and 5-acetyloxymethyl-3,4-bis(trimethylsilyl)dihydro-2(3*H*)-furanone (121)



A solution of lactone **38** (240 mg, 1.54 mmol) and bis(trimethylsilyl)acetylene (1060 mg, 6.22 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 4 h at -40 ºC. A 56:16:16:11 mixture of 4 new compounds was determined by analysis of GC and ^{1}H-NMR of the reaction crude. Evaporation of the solvent and column chromatography of the resulting residue (hexane-EtOAc 20:1) afforded unreacted **38** (70 mg, 0.45 mmol, 31%), the cyclobutene derivatives **118** and **119** (66 mg, 0.20 mmol, 12% yield) as an oil and the bis(trimethylsilyl)lactones **120** and **121** (164 mg, 0.54 mmol, 35% yield) as a white solid. Whereas repeated column chromatography (from hexane to hexane-EtOAc 95:5) of the mixture of **120** and **121** provided pure **120** as a white solid and an enriched mixture of **121** and **120**, all attempts to separate **118** from **119** were unsuccessful and enriched fractions were analyzed.

118: **IR** (ATR) 3023, 2956, 2898, 1743, 1250, 1045, 833, 748; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.81 (d, $J_{6,5}$=0.5 Hz, 1H, H-6), 4.56 (ddd, $J_{4,8}$=7.3 Hz, $J_{4,8}$=5.1 Hz, $J_{4,5}$=2.2 Hz, 1H, H-4), 4.11 (dd, J_{gem}=11.7 Hz, $J_{8,4}$=5.1 Hz, 1H, H-8), 4.00 (dd, J_{gem}=11.7 Hz, $J_{8,4}$ =7.3 Hz, 1H, H-8), 3.11 (dd, $J_{5,4}$=2.2 Hz, $J_{5,6}$=0.5 Hz, 1H, H-5), 2.08 (s, 3H, CH_3CO), 0.20 (s, 9H, Si(CH_3)$_3$), 0.13 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$)

δ 175.9 (C=O, C-2), 170.7 (C=O, CH_3CO), 163.4 (C, C-7), 150.2 (CH, C-6), 75.4 (CH, C-4), 65.4 (CH_2, C-8), 52.4 (C, C-1), 47.1 (CH, C-5), 20.8 (CH_3, CH_3CO), -1.9 (CH_3, $Si(CH_3)_3$), -3.0 (CH_3, $Si(CH_3)_3$). Anal. Calcd for $C_{15}H_{26}O_4Si_2$: C, 55.17; H, 8.03. Found: C, 55.38; H, 8.43 (mixture of **118** and **119**).

DEPT and n.O.e. differential experiments were recorded for **118**.

119: **IR** (ATR) 2956, 2898, 1743, 1215, 1150, 832, 748; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.68 (d, $J_{6,5}$=0.7 Hz, 1H, H-6), 4.47 (ddd, $J_{4,8}$=7.9 Hz, $J_{4,5}$=7.3 Hz, $J_{4,8}$=4.1 Hz, 1H, H-4), 4.30 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=4.1 Hz, 1H, H-8), 4.21 (dd, J_{gem}=11.9 Hz, $J_{8,4}$ =7.9 Hz, 1H, H-8), 3.48 (dd, $J_{5,4}$=7.3 Hz, $J_{5,6}$=0.7 Hz, 1H, H-5), 2.09 (s, 3H, CH_3CO), 0.19 (s, 9H, $Si(CH_3)_3$), 0.13 (s, 9H, $Si(CH_3)_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.7 (C=O, C-2), 170.7 (C=O, CH_3CO), 164.6 (C, C-7), 146.9 (CH, C-6), 74.3 (CH, C-4), 64.2 (CH_2, C-8), 53.6 (C, C-1), 47.4 (CH, C-5), 20.8 (CH_3, CH_3CO), -1.9 (CH_3, $Si(CH_3)_3$), -3.2 (CH_3, $Si(CH_3)_3$).

DEPT, HMQC, HMBC and COSY experiments were recorded for **119**.

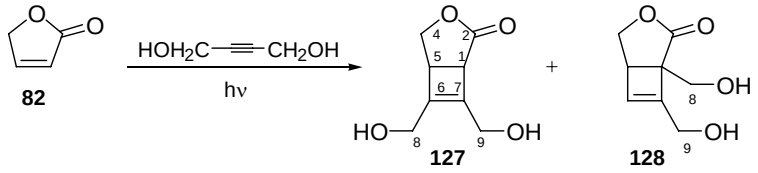
120: mp: 48-51 ºC (EtOAc-hexane); $[\alpha]_D$ -57.8 (*c* 0.9, $CHCl_3$); **IR** (ATR) 3083, 2953, 2902, 1740, 1702, 1237, 1198, 835, 754; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.53 (dddd, $J_{5,6}$=5.2 Hz, $J_{5,6}$=4.7 Hz, $J_{5,4}$=1.9 Hz, $J_{5,3}$=0.8 Hz, 1H, H-5), 4.21 (dd, J_{gem}=11.9 Hz, $J_{6,5}$=5.2 Hz, 1H, H-6), 4.15 (dd, J_{gem}=11.9 Hz, $J_{6,5}$=4.7 Hz, 1H, H-6), 2.69 (dd, $J_{3,4}$=2.1 Hz, $J_{3,5}$=0.8 Hz, 1H, H-3), 2.23 (dd, $J_{4,3}$=2.1 Hz, $J_{4,5}$=1.9 Hz 1H, H-4), 2.08 (s, 3H, CH_3CO), 0.18 (s, 9H, $Si(CH_3)_3$), 0.14 (s, 9H, $Si(CH_3)_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 172.2 (C=O, C-2), 170.7 (C=O, CH_3CO), 72.6 (CH, C-5), 66.0 (CH_2, C-6), 37.8 (CH, C-4), 20.8 (CH_3, CH_3CO), 18.5 (CH, C-3), 0.0 (CH_3, $Si(CH_3)_3$), -1.4 (CH_3, $Si(CH_3)_3$). Anal. Calcd for $C_{13}H_{26}O_4Si_2$: C, 51.61; H, 8.66. Found: C, 51.67; H, 8.31 (mixture of **120** and **121**).

DEPT, HMQC, HMBC and n.O.e. differential experiments were recorded for **120**.

121: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.60 (ddd, $J_{5,6}$=6.2 Hz, $J_{5,6}$=5.9 Hz, $J_{5,4}$=1.2 Hz, 1H, H-5), 4.30 (m, 2H, H-6), 2.76 (d, $J_{3,4}$=2.5 Hz, 1H, H-3), 2.32 (dd, $J_{4,3}$=2.5 Hz, $J_{4,5}$=1.2 Hz, 1H, H-4), 2.09 (s, 3H, CH_3CO), 0.18 (s, 9H, $Si(CH_3)_3$), 0.16 (s, 9H, $Si(CH_3)_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 172.0 (C=O, C-2), 170.6 (C=O, CH_3CO), 72.1 (CH, C-5), 66.1 (CH_2, C-6), 38.3 (CH, C-4), 20.8 (CH_3, $\underline{C}H_3CO$), 18.8 (CH, C-3), 0.2 (CH_3, $Si(CH_3)_3$), -1.3 (CH_3, $Si(CH_3)_3$).

2.2. [2+2] Photocycloaddition of 2(5*H*)-furanones to 2-butyne-1,4-diol and derivatives

2.2.1. (1*RS*,5*SR*)-6,7-Bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (127) and (1*RS*,5*SR*)-1,7-bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (128)



A solution of lactone **82** (119 mg, 1.40 mmol) and 2-butyne-1,4-diol (650 mg, 7.55 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 3 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (EtOAc – hexane 2:1) afforded **127** (100 mg, 0.59 mmol, 42%) as a colourless oil and **128** (35 mg, 0.21 mmol, 15%) as a colourless oil.

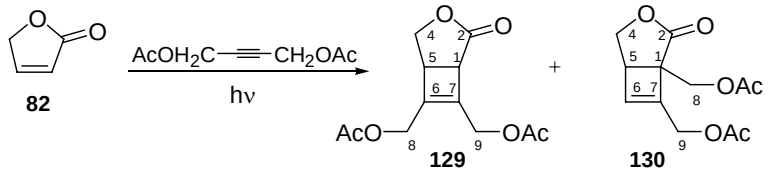
127: **IR** (ATR) 3600-3000, 2974, 2916, 2860, 1733; **^{1}H-NMR** (250 MHz, acetone-d_6) δ 4.49 (br s, 2H, OH), 4.34 (dd, J_{gem}=9.6 Hz, $J_{4,5}$=2.1 Hz, 1H, H-4), 4.26 (m, 3H, H-4, H-9), 4.17 (d, J_{gem}=15.7 Hz, 1H, H-8), 4.09 (d, J_{gem}=15.7 Hz, 1H, H-8), 3.49 (m, 1H, H-5), 3.43 (m, 1H, H-1); **^{13}C-NMR** (62.5 MHz, acetone-d_6) δ 174.9 (C=O, C-2), 145.6 (C, C-6), 142.2 (C, C-7), 67.7 (CH_2, C-4), 57.7 (CH_2, C-8), 57.4 (CH_2, C-9), 43.3 (CH, C-1), 39.1 (CH, C-5). **HRMS (ESI-TOF)** Calcd for $[C_8H_{10}O_4+Na]^+$: 193.0471. Found: 193.0477 (mixture of **127** and **128**).

COSY, HMQC and HMBC experiments were recorded for **127**.

128: **IR** (ATR) 3700-3000, 2923, 2852, 1741, 1634; **^{1}H-NMR** (250 MHz, acetone-d_6) δ 6.22 (t, $J_{6,9}$=1.7 Hz, $J_{6,9}$=1.7 Hz, 1H, H-6), 4.27 (dd, J_{gem}=9.6 Hz, $J_{4,5}$=6.9 Hz, 1H, H-4), 4.15 (dd, J_{gem}=9.6 Hz, $J_{4,5}$ =1.8 Hz, 1H, H-4), 4.05 (d, J_{gem}=11.3 Hz, 1H, H-8), 4.02 (m, 2H, H-9), 3.83 (d, J_{gem}=11.3 Hz, 1H, H-8), 3.41 (dd, $J_{5,4}$=6.9 Hz, $J_{5,4}$=1.8 Hz, 1H, H-5), 2.89 (br s, 2H, OH); **^{13}C-NMR** (62.5 MHz, acetone-d_6) δ 175.9 (C=O, C-2), 153.4 (C, C-7), 131.9 (CH, C-6), 67.9 (CH_2, C-4), 60.8 (CH_2, C-8), 59.0 (C, C-1), 57.8 (CH_2, C-9), 42.3 (CH, C-5).

COSY, HMQC and HMBC experiments were recorded for **128**.

2.2.2. (1*RS*,5*SR*)-6,7-Bis(acetyloxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (129) and (1*RS*,5*SR*)-1,7-bis(acetyloxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (130)



A solution of lactone **82** (83 mg, 0.99 mmol) and 1,4-bis(acetyloxy)-2-butyne (800 mg, 4.70 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 6.5 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtOAc 3:1) afforded **129** (50 mg, 0.21 mmol, 22%) as a colourless oil and **130** (37 mg, 0.15 mmol, 15%) as a colourless oil.

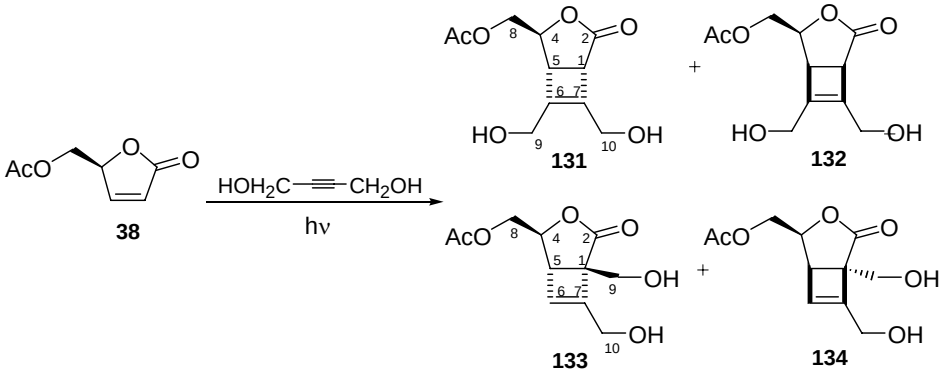
129: **IR** (ATR) 2970, 2922, 2852, 1769, 1733, 1171; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.80-4.60 (m, 4H, H-8, H-9), 4.37 (dd, J_{gem}=10.0 Hz, $J_{4,5}$=2.2 Hz, 1H, H-4), 4.29 (dd, J_{gem}=10.0 Hz, $J_{4,5}$=6.8 Hz, 1H, H-4), 3.56 (m, 1H, H-1), 3.51 (m, 1H, H-5), 2.09 (s, 6H, 2C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 170.7 (C=O, CH_3*C*O), 170.5 (C=O, CH_3*C*O), 142.9 (C, C-6), 141.0 (C, C-7), 67.4 (CH_2, C-4), 58.4/58.3 ($2CH_2$, C-8/C-9), 44.2 (CH, C-1), 39.9 (CH, C-5), 20.6 (CH_3, 2*C*H_3CO).

HMQC and HMBC experiments were recorded for **129**.

130: **IR** (ATR) 3068, 2966, 2908, 1762, 1734; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.30 (br s, 1H, H-6), 4.65 (dt, J_{gem}=14.4 Hz, $J_{9,6}$=1.5 Hz, $J_{9,5}$=1.5 Hz, 1H, H-9), 4.54 (d, J_{gem}=11.7 Hz, 1H, H-8), 4.50 (dt, J_{gem}=14.4 Hz, $J_{9,6}$ =1.6 Hz, $J_{9,5}$ =1.6 Hz, 1H, H-9), 4.43 (d, J_{gem}=11.7 Hz, 1H, H-8), 4.30 (dd, J_{gem}=9.9 Hz, $J_{4,5}$=6.9 Hz, 1H, H-4), 4.22 (dd, J_{gem}=9.9 Hz, $J_{4,5}$ =1.8 Hz, 1H, H-4), 3.42 (m, 1H, H-5), 2.08 (s, 3H, C*H*$_3$CO), 2.07 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 174.0 (C=O, C-2), 170.4 (C=O, CH_3*C*O), 170.3 (C=O, CH_3*C*O), 146.4 (C, C-7), 135.5 (CH, C-6), 67.3 (CH_2, C-4), 61.9 (CH_2, C-8), 58.9 (CH_2, C-9), 55.9 (C, C-1), 42.5 (CH, C-5), 20.7 (CH_3, *C*H_3CO), 20.6 (CH_3, *C*H_3CO).

COSY, HMQC and HMBC experiments were recorded for **130**.

2.2.3. (-)-(1*S*,4*S*,5*R*)-4-Acetyloxymethyl-6,7-bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (131), (1*R*,4*S*,5*S*)-4-acetyloxymethyl-6,7-bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (132), (1*S*,4*S*,5*S*)-4-acetyloxymethyl-1,7-bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (133) and (+)-(1*R*,4*S*,5*R*)-4-acetyloxymethyl-1,7-bis(hydroxymethyl)-3-oxabicyclo[3.2.0]hept-6-en-2-one (134)



A solution of lactone **38** (173 mg, 1.11 mmol) and 2-butyne-1,4-diol (453 mg, 5.26 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 3 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (EtOAc-hexane 3:1) afforded a 52:15:24:7 mixture of **131, 132**, **133** and **134** (132 mg, 0.55 mmol, 49% global yield) and some unreacted **38** (35 mg, 0.22 mmol, 20%). Repeated column chromatography (from EtOAc-hexane 1:1 to EtOAc-hexane 4:1) provided the following fractions: (i) an analytical sample of pure **131** as an oil, (ii) an analytical sample of pure **134** as an oil, (iii) a mixture of **131** and **132**, and (iv) a mixture of **133** and **134**. All attempts to separate **132** and **133** from **131** and **134**, respectively, were unsuccessful and enriched fractions were analyzed.

131: $[\alpha]_D$ +56.0 (*c* 0.25, MeOH); **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.72 (m, 1H, H-4), 4.32 (m, 4H, H-9, H-10), 4.29 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.2 Hz, 1H, H-8), 4.20 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.9 Hz, 1H, H-8), 3.57 (m, 1H, H-1), 3.31 (m, 1H, H-5), 2.11 (s, 3H, C*H*$_3$CO); **^{1}H-NMR** (250 MHz, acetone-d_6) δ 4.77 (dddd, $J_{4,8}$=4.4 Hz, $J_{4,8}$=3.8 Hz, $J_{4,5}$=1.5 Hz, $J_{4,1}$=0.5 Hz, 1H, H-4), 4.45 (m, 2H, OH), 4.28 (m, 2H, H-10), 4.24 (m, 1H, H-8), 4.20 (m, 1H, H-8), 4.14 (m, 2H, H-9), 3.51 (m, 1H, H-1), 3.36 (m, 1H, H-5), 2.03 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, acetone-d_6) δ 174.5 (C=O, C-2), 170.3 (C=O, CH$_3$*C*O), 145.4 (C, C-6), 142.7 (C, C-7), 76.6 (CH, C-4), 66.2 (CH_2, C-8), 58.1 (CH_2,

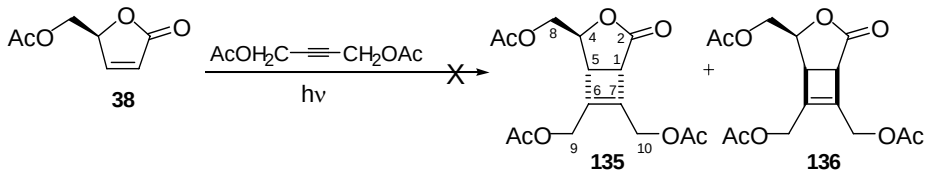
C-9), 57.8 (CH_2, C-10), 44.4 (CH, C-1), 41.7 (CH, C-5), 20.1 (CH_3, *C*H_3CO). **HRMS** (ESI-TOF) Calcd for $[C_{11}H_{15}O_6+H]^+$: 243.0863. Found: 243.0857 (mixture of **131-134**). COSY, HMQC and HMBC experiments were recorded for **131**.

132: **^{1}H-NMR** (250 MHz, pyridine-d_5) δ 6.34 (ddd, $J_{4,8}$=8.9 Hz, $J_{4,5}$=6.7 Hz, $J_{4,8'}$=3.2 Hz, 1H, H-4), 6.05 (m, 4H, 2H-9, 2H-10), 5.91 (m, 2H, H-8), 5.17 (m, 1H, H-1), 5.12 (m, 1H, H-5), 3.46 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, pyridine-d_5) δ 174.3 (C=O, C-2), 170.2 (C=O, CH$_3$*C*O), 144.5/143.8 (2C, C-6/C-7), 75.3 (CH, C-4), 64.9 (CH_2, C-8), 58.7/57.8 (2CH_2, C-9/C-10), 44.6 (CH, C-1), 40.8 (CH, C-5), 20.4 (CH_3, *C*H_3CO).

133: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.28 (br s, 1H, H-6), 4.60 (ddd, $J_{4,8}$= 3.6 Hz, $J_{4,8}$=3.3 Hz, $J_{4,5}$=1.4 Hz, 1H, H-4), 4.31 (m, 2H, H-8), 4.19-4.10 (m, 4H, H-9, H-10), 3.13 (d, $J_{5,4}$=1.4 Hz, 1H, H-5), 2.11 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.9 (C=O, C-2), 170.3 (C=O, CH$_3$*C*O), 152.2 (C, C-7), 132.6 (CH, C-6), 76.5 (CH, C-4), 65.4 (CH_2, C-8), 61.0 (CH_2, C-9), 58.8 (C, C-1), 58.2 (CH_2, C-10), 43.7 (CH, C-5), 20.7 (CH_3, *C*H_3CO).

134: $[\alpha]_D$ +42.2 (*c* 0.45, MeOH); **IR** (ATR) 3650-3100, 2962, 2924, 2853, 1763, 1735; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.18 (br s, 1H, H-6), 4.63 (ddd, $J_{4,8}$=7.5 Hz, $J_{4,5}$=6.8 Hz, $J_{4,8}$=4.5 Hz, 1H, H-4), 4.23 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=4.5 Hz, 1H, H-8), 4.18 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=7.5 Hz, 1H, H-8), 4.11 (m, 2H, H-10), 4.06 (d, J_{gem}=11.8 Hz, 1H, H-9), 3.93 (d, J_{gem}=11.8 Hz, 1H, H-9), 3.35 (br d, $J_{5,4}$=6.8 Hz, 1H, H-5), 2.30 (br s, 2H, OH), 2.03 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.2 (C=O, C-2), 170.6 (C=O, CH$_3$*C*O), 152.8 (C, C-7), 130.1 (CH, C-6), 75.6 (CH, C-4), 63.2 (CH_2, C-8), 61.1 (CH_2, C-9), 59.2 (C, C-1), 58.3 (CH_2, C-10), 43.0 (CH, C-5), 20.7 (CH_3, *C*H_3CO).
COSY, HMQC, HMBC and n.O.e. differential experiments were recorded for **134**.

2.2.4. Attempt of [2+2] photocycloaddition of (*S*)-5-acetyloxymethyl-2(5*H*)-furanone (38) to 1,4-bis(acetyloxy)-2-butyne

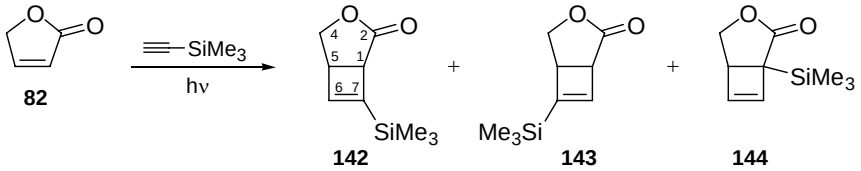


A solution of **38** (99 mg, 0.64 mmol) and 1,4-bis(acetyloxy)-2butyne (555 mg, 3.27 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 2.5 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (EtOAc-hexane 3:1) afforded a reaction crude which H-NMR data showed a complex system with no presence of either cyclobutene derivatives or starting material signals.

3. [2+2] Photocycloaddition of 2(5*H*)-furanones to asymmetric alkynes

3.1. [2+2] Photocycloaddition of 2(5*H*)-furanones to trimethylsilylacetylene

3.1.1. (1*RS*, 5*SR*)-7-Trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (142), (1*RS*, 5*SR*)-6-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (143) and (1*RS*,5*SR*)-1-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (144)



A solution of lactone **82** (119 mg, 1.40 mmol) and trimethylsilylacetylene (695 mg, 7.08 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 8.5 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtOAc 6:1) afforded a 58:15:27 mixture of products **142**, **143** and **144** (128 mg, 0.70 mmol, 56% global yield) and some unreacted **82** (32 mg, 0.37 mmol, 25%). Repeated column chromatography (from hexane-EtOAc 10:1 to hexane-EtOAc 6:1) allowed the separation of pure **142** as a colourless oil, **143** as a colourless oil and **144** as a colourless oil.

When the irradiation was performed through a quartz filter in diethyl ether (90 mL) for 3.5 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and trimethylsilylacetylene (619 mg, 6.20 mmol), after the purification of the crude material by column chromatography, only **142** (60 mg, 0.33 mmol, 24%) was obtained.

When the irradiation was performed through a Pyrex filter in acetone (90 mL) for 5.5 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and trimethylsilylacetylene (691 mg, 7.03 mmol), after the purification of the crude material by column chromatography, a 61:39 mixture of **142** and **143** (51 mg, 0.28 mmol, 20%) was obtained.

142: **IR** (ATR) 3027, 2958, 2900, 1756, 1161, 835, 757; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.73 (br s, 1H, H-6), 4.24 (m, 2H, H-4), 3.61 (m, 2H, H-1, H-5), 0.12 (s, 9H, Si(CH_3)$_3$); **^{1}H-NMR** (250 MHz, benzene-d_6) δ 6.21 (br s, 1H, H-6), 3.56 (dd, J_{gem}= 9.6 Hz, $J_{4,5}$=2.0 Hz, 1H, H-4), 3.43 (dd, J_{gem}= 9.6 Hz, $J_{4,5}$ =7.5 Hz, 1H, H-4), 3.16 (d, $J_{1,5}$=3.6 Hz, 1H, H-1), 2.67 (ddd, $J_{5,4}$=7.5 Hz, $J_{5,1}$=3.6 Hz, $J_{5,4}$=2.0 Hz, 1H, H-5), 0.09 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, benzene-d_6) δ 175.4 (C=O, C-2), 160.3 (C, C-7), 152.1 (CH, C-6), 67.9 (CH_2, C-4), 47.8 (CH, C-1), 43.0 (CH, C-5), -1.8 (CH_3, Si(*C*H_3)$_3$).

HMQC and HMBC experiments were recorded for **142**.

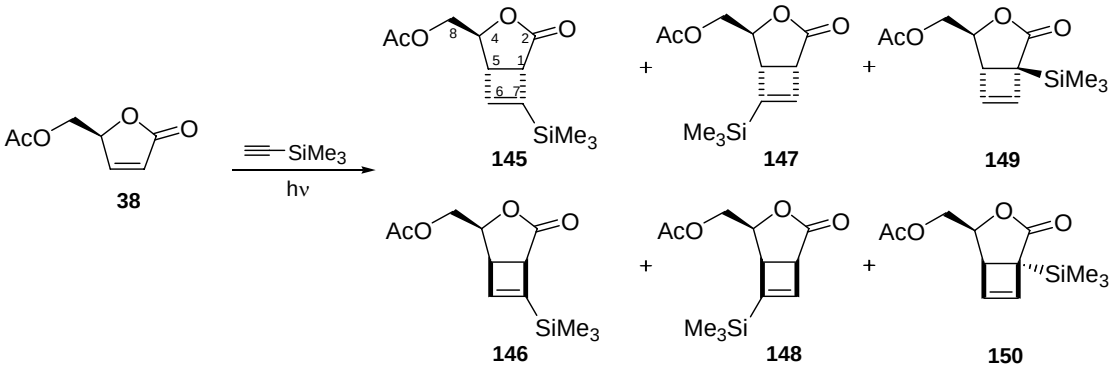
143: **IR** (ATR) 3032, 2958, 2901, 1760, 1163, 837, 756; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.70 (d, $J_{7,1}$=0.3 Hz, 1H, H-7), 4.34 (dd, J_{gem}= 9.8 Hz, $J_{4,5}$=7.3 Hz, 1H, H-4), 4.23 (dd, J_{gem}= 9.8 Hz, $J_{4,5}$ =2.1 Hz, 1H, H-4), 3.73 (br d, $J_{1,5}$=3.7 Hz, 1H, H-1), 3.56 (ddd, $J_{5,4}$=7.3 Hz, $J_{5,1}$=3.7 Hz, $J_{5,4}$=2.1 Hz, 1H, H-5), 0.14 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.6 (C=O, C-2), 161.5 (C, C-6), 148.0 (CH, C-7), 68.7 (CH_2, C-4), 47.4 (CH, C-1), 42.3 (CH, C-5), -2.1 (CH_3, Si(*C*H_3)$_3$).

COSY, HMQC and HMBC experiments were recorded for **143**.

144: **IR** (ATR) 3048, 2956, 2900, 1743, 1251, 1162, 835, 777; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.36 (d, $J_{6,7}$=2.5 Hz, 1H, H-6), 6.34 (d, $J_{7,6}$=2.5 Hz, 1H, H-7), 4.27 (dd, J_{gem}=9.8 Hz, $J_{4,5}$=2.1 Hz, 1H, H-4), 4.17 (dd, J_{gem}=9.8 Hz, $J_{4,5}$=7.4 Hz, 1H, H-4), 3.39 (dd, $J_{5,4}$=7.4 Hz, $J_{5,4}$=2.1 Hz, 1H, H-5), 0.18 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 176.9 (C=O, C-2), 142.5 (CH, C-7), 139.6 (CH, C-6), 66.9 (CH_2, C-4), 50.7 (C, C-1), 45.2 (CH, C-5), -3.6 (CH_3, Si(*C*H_3)$_3$).

DEPT and HMBC experiments were recorded for **144**.

3.1.2. (1*R*,4*S*,5*S*)-4-Acetyloxymethyl-7-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (145), (1*S*,4*S*,5*R*)-4-acetyloxymethyl-7-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (146), (1*R*,4*S*,5*S*)-4-acetyloxymethyl-6-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (147), (1*S*,4*S*,5*R*)-4-acetyloxymethyl-6-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (148), (1*S*,4*S*,5*R*)-4-acetyloxymethyl-1-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (149) and (+)-(1*R*,4*S*,5*S*)-4-acetyloxymethyl-1-trimethylsilyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (150)



A solution of lactone **38** (214 mg, 1.37 mmol) and trimethylsilylacetylene (639 mg, 6.50 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 4 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtOAc 5:1) afforded a 30:36:6:28 mixture of **145, 146**, **149** and **150** (139 mg, 0.55 mmol, 40% global yield) and some unreacted **38** (75 mg, 0.48 mmol, 35%). Repeated chromatography (from hexane-EtOAc 16:1 to hexane-EtOAc 10:1) furnished analytical samples of pure **145** as a colourless oil, **146** as a colourless oil, and **150** as a colourless oil, as well as a mixture of **149** and **150**. All attempts to separate **149** from **150** were unsuccessful and enriched fractions were analyzed.

When the irradiation was performed through a quartz filter in diethyl ether (90 mL) for 2.75 h at -40 ºC, from lactone **38** (207 mg, 1.33 mmol) and trimethylsilylacetylene (638 mg, 6.50 mmol) after the purification of the crude material by column chromatography, a 55:45 mixture of **145** and **146** (40 mg, 0.16 mmol, 12%) was obtained.

When the irradiation was performed through a Pyrex filter in acetone (90 mL) for 2 h at -40 ºC, from lactone **38** (162 mg, 1.04 mmol) and trimethylsilylacetylene (334 mg, 3.40 mmol) after the purification of the crude material by column chromatography,

a 31:34:18:17 mixture of **145-148** (79 mg, 0.55 mmol, 53% global yield) and some unreacted lactone **38** (60 mg, 0.38 mmol, 37%) were obtained. All attempts to separate **147** and **148** from **145** and **146**, respectively, were unsuccessful, and enriched fractions were analyzed.

145: **IR** (ATR) 3030, 2956, 2896, 1776, 1742, 1161, 839, 757; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.72 (t, $J_{6,1}$=0.7 Hz, $J_{6,5}$=0.7 Hz, 1H, H-6), 4.56 (dddd, $J_{4,8}$=4.1 Hz, $J_{4,8}$=3.4 Hz, $J_{4,5}$=1.6 Hz, $J_{4,1}$=0.7 Hz, 1H, H-4), 4.23 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=3.4 Hz, 1H, H-8), 4.12 (dd, J_{gem}=11.9 Hz, $J_{8,4}$ =4.1 Hz, 1H, H-8), 3.64 (dt, $J_{1,5}$=3.5 Hz, $J_{1,4}$=0.7 Hz, $J_{1,6}$=0.7 Hz, 1H, H-1), 3.41 (ddd, $J_{5,1}$=3.5 Hz, $J_{5,4}$=1.6 Hz, $J_{5,6}$=0.7 Hz, 1H, H-5), 2.07 (s, 3H, CH_3CO), 0.13 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.2 (C=O, C-2), 170.5 (C=O, CH_3*C*O), 160.2 (C, C-7), 150.1 (CH, C-6), 76.2 (CH, C-4), 65.7 (CH_2, C-8), 47.8 (CH, C-1), 44.4 (CH, C-5), 20.7 (CH_3, *C*H_3CO), -2.5 (CH_3, Si(*C*H_3)$_3$). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{18}O_4Si+Na]^+$: 277.0867. Found: 277.0862 (mixture of **145** and **146**).

HMQC, HMBC and n.O.e. differential experiments were recorded for **145**.

146: **IR** (ATR) 3028, 2956, 2897, 1772, 1741, 1229, 1163, 837, 759; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.64 (t, $J_{6,5}$=0.7 Hz, $J_{6,1}$=0.7 Hz, 1H, H-6), 4.57 (dddd, $J_{4,8}$=7.6 Hz, $J_{4,5}$=6.4 Hz, $J_{4,8}$=4.3 Hz, $J_{4,1}$=1.0 Hz, 1H, H-4), 4.29 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=4.3 Hz, 1H, H-8), 4.21 (dd, J_{gem}=11.9 Hz, $J_{8,4}$ =7.6 Hz, 1H, H-8), 3.65 (m, 2H, H-1, H-5), 2.08 (s, 3H, CH_3CO), 0.11 (s, 9H, Si(CH_3)$_3$); **^{1}H-NMR** (250 MHz, benzene-d_6) δ 6.11 (dd, $J_{6,5}$=0.6 Hz, $J_{6,1}$=0.5 Hz, 1H, H-6), 3.98 (m, 3H, H-4, H-8), 3.15 (ddd, $J_{1,5}$=3.5 Hz, $J_{1,4}$=0.8 Hz, $J_{1,6}$=0.5 Hz, 1H, H-1), 2.78 (ddd, $J_{5,4}$=6.1 Hz, $J_{5,1}$=3.5 Hz, $J_{5,6}$=0.6 Hz, 1H, H-5), 1.64 (s, 3H, CH_3CO), 0.06 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, benzene-d_6) δ 174.0 (C=O, C-2), 170.4 (C=O, CH_3*C*O), 161.4 (C, C-7), 148.7 (CH, C-6), 75.7 (CH, C-4), 64.5 (CH_2, C-8), 48.8 (CH, C-1), 44.3 (CH, C-5), 20.7 (CH_3, *C*H_3CO), -1.9 (CH_3, Si(*C*H_3)$_3$).

HMQC and HMBC experiments were recorded for **146**.

147: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.60 (d, $J_{7,1}$=0.7 Hz, 1H, H-7), 4.52 (m, 1H, H-4), 4.25 (m, 2H, H-8), 3.75 (ddd, $J_{1,5}$=3.5 Hz, $J_{1,4}$=0.7 Hz, $J_{1,7}$=0.7 Hz, 1H, H-1), 3.33 (dd, $J_{5,1}$=3.5 Hz, $J_{5,4}$=1.6 Hz, 1H, H-5), 2.08 (s, 3H, CH_3CO), 0.12 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 174.5 (C=O, C-2), 170.2 (C=O, CH_3*C*O), 160.6 (C, C-6), 147.7 (CH, C-7), 76.7 (CH, C-4), 65.4 (CH_2, C-8), 47.6 (CH, C-1), 44.2 (CH, C-5), 20.4 (CH_3, *C*H_3CO), -2.8 (CH_3, Si(*C*H_3)$_3$).

148: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.79 (d, $J_{7,1}$=0.9 Hz, 1H, H-7), 4.77 (ddd, $J_{4,5}$=7.1 Hz, $J_{4,8}$=4.7 Hz, $J_{4,8}$=3.5 Hz, 1H, H-4), 4.17 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=3.5 Hz, 1H, H-8), 4.09 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=4.7 Hz, 1H, H-8), 3.81 (dd, $J_{1,5}$=3.7 Hz, $J_{1,7}$=0.9 Hz, 1H, H-1), 3.65 (dd, $J_{5,4}$=7.1 Hz, $J_{5,1}$=3.7 Hz, 1H, H-5), 2.09 (s, 3H, CH_3CO), 0.08 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 179.7 (C=O, C-2), 170.7 (C=O, CH_3CO), 158.9 (C, C-6), 150.4 (CH, C-7), 76.1 (CH, C-4), 64.5 (CH_2, C-8), 48.2 (CH, C-1), 44.0 (CH, C-5), 20.7 (CH_3, CH_3CO), -1.9 (CH_3, Si(CH_3)$_3$).

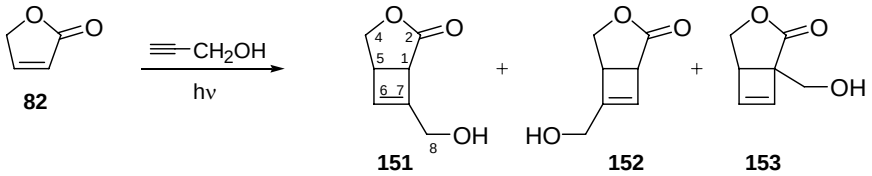
149: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.40 (dd, $J_{6,7}$=2.6 Hz, $J_{6,5}$=0.5 Hz, 1H, H-6), 6.35 (dd, $J_{7,6}$=2.6 Hz, $J_{7,5}$=0.5 Hz, 1H, H-7), 4.62 (ddd, $J_{4,8}$=6.5 Hz, $J_{4,8}$=4.8 Hz, $J_{4,5}$=2.0 Hz, 1H, H-4), 4.16 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=4.8 Hz, 1H, H-8), 4.04 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=6.5 Hz, 1H, H-8), 3.13 (ddd, $J_{5,4}$=2.0 Hz, $J_{5,6}$=0.5 Hz, $J_{5,7}$=0.5 Hz, 1H, H-5), 2.12 (s, 3H, CH_3CO), 0.21 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.7 (C=O, C-2), 170.7 (C=O, CH_3*C*O), 142.5 (CH, C-7), 139.1 (CH, C-6), 75.2 (CH, C-4), 65.4 (CH_2, C-8), 51.4 (C, C-1), 46.6 (CH, C-5), 20.8 (CH_3, *C*H_3CO), -3.5 (CH_3, Si(*C*H_3)$_3$).

150: $[\alpha]_D$ +40.0 (*c* 0.9, $CHCl_3$); **IR** (ATR) 3050, 2955, 2898, 1742, 1244, 1230, 1165, 1114, 839, 757; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.37 (d, $J_{7,6}$=2.6 Hz, 1H, H-7), 6.27 (dd, $J_{6,7}$=2.6 Hz, $J_{6,5}$=0.7 Hz, 1H, H-6), 4.53 (ddd, $J_{4,8}$=7.7 Hz, $J_{4,5}$=7.4 Hz, $J_{4,8}$=4.2 Hz, 1H, H-4), 4.32 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=4.2 Hz, 1H, H-8), 4.23 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=7.7 Hz, 1H, H-8), 3.46 (dd, $J_{5,4}$=7.4 Hz, $J_{5,6}$=0.7 Hz, 1H, H-5), 2.09 (s, 3H, CH_3CO), 0.18 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ: 175.4 (C=O, C-2), 170.7 (C=O, CH_3*C*O), 143.2 (CH, C-7), 136.3 (CH, C-6), 74.2 (CH, C-4), 64.0 (CH_2, C-8), 52.0 (C, C-1), 46.6 (CH, C-5), 20.7 (CH_3, *C*H_3CO), -3.7 (CH_3, Si(*C*H_3)$_3$).

COSY, HMQC, HMBC and n.O.e. experiments were recorded for **150**.

3.2. [2+2] Photocycloaddition of 2(5*H*)-furanones to propargyl alcohol

3.2.1.(1*RS*,5*RS*)-7-Hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (151), (1*RS*,5*RS*)-6-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (152) and (1*RS*,5*SR*)-1-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (153)



A solution of **82** (119 mg, 1.40 mmol) and propargyl alcohol (385 mg, 6.89 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 2.5 h at -40 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtOAc 2:1) afforded a 57:29:14 mixture of **151**, **152** and **153** (130 mg, 0.93 mmol, 66% global yield) and some unreacted lactone **82** (35 mg, 0.42 mmol, 29%). Repeated column chromatography (from hexane-EtOAc 3:1 to hexane-EtOAc 1:1) allowed the separation of pure **151** as a colourless oil, **152** as a colourless oil and **153** as a colourless oil.

When the irradiation was performed through a quartz filter in diethyl ether (90 mL) for 2.5 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and propargyl alcohol (392 mg, 7.00 mmol), after the purification of the crude material by column chromatography, a 58:42 mixture of cycloadducts **151** and **152** (127 mg, 0.90 mmol, 64% global yield) and some unreacted lactone **82** (20 mg, 0.24 mmol, 17%) were obtained.

When the irradiation was performed through a Pyrex filter in acetone (90 mL) for 3 h at -40 ºC, from lactone **82** (119 mg, 1.40 mmol) and propargyl alcohol (392 mg, 7.00 mmol) after the purification of the crude material by column chromatography, a 67:33 mixture of cycloadducts **151** and **152** (149 mg, 1.06 mmol, 76%) was obtained.

151: **IR** (ATR) 3700-3000, 2973, 2920, 2855, 1718, 1376, 1170; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.19 (br s, 1H, H-6), 4.32 (dd, J_{gem}=9.8 Hz, $J_{4,5}$=7.0 Hz, 1H, H-4), 4.25 (dd, J_{gem}=9.8 Hz, $J_{4,5}$ =2.2 Hz, 1H, H-4), 4.18 (m, 2H, H-8), 3.65 (br d, $J_{1,5}$=3.7 Hz, 1H, H-1), 3.47 (dddd, $J_{5,4}$=7.0 Hz, $J_{5,1}$=3.7 Hz, $J_{5,4}$=2.2 Hz, $J_{5,6}$=0.5 Hz, 1H, H-5), 2.22 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.6 (C=O, C-2), 150.7 (C, C-7), 132.5 (CH, C-6), 69.2 (CH_2, C-4), 59.3 (CH_2, C-8), 46.0 (CH, C-1), 38.5 (CH, C-5). **HRMS** (ESI-TOF) Calcd for $[C_7H_8O_3+Na]^+$: 163.0366. Found: 163.0364 (mixture of **151-153**). COSY, HMQC and HMBC experiments were recorded for **151**.

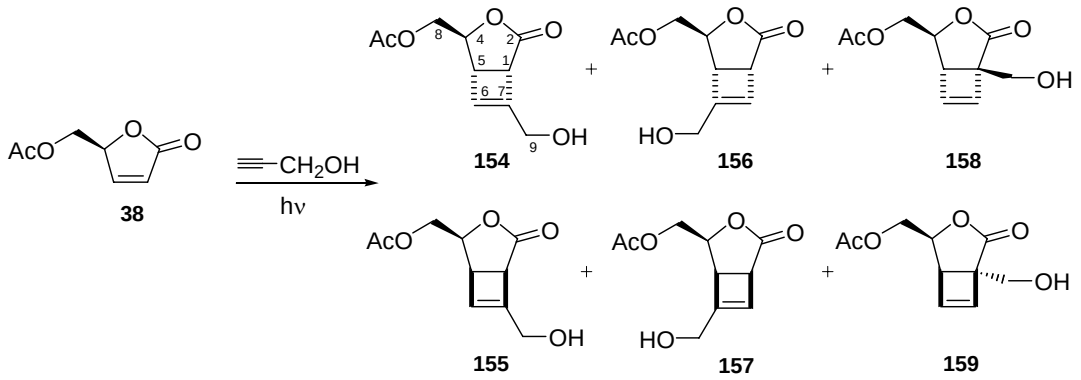
152: **IR** (ATR) 3600-3000, 2976, 2918, 2856, 1716, 1165; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.18 (br s, 1H, H-7), 4.41 (dd, J_{gem}=9.8 Hz, $J_{4,5}$=2.1 Hz, 1H, H-4), 4.31 (dd, J_{gem}=9.8 Hz, $J_{4,5}$=7.2 Hz, 1H, H-4), 4.24 (m, 2H, H-8), 3.65 (m, 1H, H-5), 3.53 (m, 1H, H-1), 2.0 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.7 (C=O, C-2), 153.3 (C, C-6), 130.4 (CH, C-7), 67.2 (CH_2, C-4), 59.2 (CH_2, C-8), 43.2 (CH, C-1), 41.3 (CH, C-5). HMQC and HMBC experiments were recorded for **152**.

153: **IR** (ATR) 3600-3100, 3056, 2974, 2913, 2875, 1753, 1176; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.46 (d, $J_{6,7}$=2.7 Hz, 1H, H-6), 6.29 (d, $J_{7,6}$=2.7 Hz, 1H, H-7), 4.33 (dd,

J_{gem}=9.8 Hz, $J_{4,5}$=7.2 Hz, 1H, H-4), 4.24 (dd, J_{gem}=9.8 Hz, $J_{4,5}$ =2.1 Hz, 1H, H-4), 4.10 (d, J_{gem}=11.4 Hz, H-8), 3.92 (d, J_{gem}=11.4 Hz, 1H, H-8), 3.49 (dd, $J_{5,4}$=7.2 Hz, $J_{5,4}$=2.1 Hz, 1H, H-5), 2.22 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 176.9 (C=O, C-2), 141.5 (CH, C-6), 139.9 (CH, C-7), 67.3 (CH_2, C-4), 62.0 (CH_2, C-8), 58.3 (C, C-1), 44.5 (CH, C-5).

DEPT and HMQC experiments were recorded for **153**.

3.2.2. (-)-(1*S*,4*S*,5*S*)-4-Acetyloxymethyl-7-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (154), (1*R*,4*S*,5*R*)-4-acetyloxymethyl-7-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (155), (1*R*,4*S*,5*R*)-4-acetyloxymethyl-6-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (156), (1*S*,4*S*,5*S*)-4-acetyloxymethyl-6-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (157), (1*R*,4*S*,5*S*)-4-acetyloxymethyl-1-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (158) and (1*S*,4*S*,5*R*)-4-acetyloxymethyl-1-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (159)



A solution of **38** (170 mg, 1.09 mmol) and propargyl alcohol (337 mg, 6.01 mmol) in acetonitrile (90 mL) was irradiated through a quartz filter for 1.5 h at -40 ºC. Evaporation of the solvent gave a residue which was purified by column chromatography (hexane-EtOAc 1:1) to afford a 35:30:20:8:2:5 mixture of **154**, **155**, **156**, **157**, **158** and **159** (135 mg, 0.64 mmol, 60% global yield) and some unreacted **38** (45 mg, 0.29 mmol, 26%). Repeated column chromatography (from hexane-EtOAc 2:1 to hexane-EtOAc 1:2) provided the following fractions: (i) an analytical sample of pure **154** as an oil, (ii) an analytical sample of pure **158** as an oil, (iii) an analytical sample of pure **159** as an oil (iv) a mixture of **154** and **155** and (v) a mixture of **156** and **157**. All

attempts to separate **155** and **156** from **154** and **157**, respectively, were unsuccessful and enriched fractions were analyzed.

When the irradiation was performed through a quartz filter in diethyl ether (90 mL) for 2 h at -40 ºC, from lactone **38** (150 mg, 0.97 mmol) and propargyl alcohol (337 mg, 6.01 mmol) after the purification of the crude material by column chromatography, a 36:23:32:9 mixture of **154-157** (78 mg, 0.37 mmol, 38% global yield) was obtained.

When the irradiation was performed through a Pyrex filter in acetone (90 mL) for 2 h at -40 ºC, from lactone **38** (170 mg, 1.09 mmol) and propargyl alcohol (337 mg, 6.01 mmol) after the purification of the crude material by column chromatography, a 45:24:24:7 mixture of **154-157** (110 mg, 0.52 mmol, 49% global yield) and some unreacted lactone **38** (50 mg, 0.32 mmol, 29%) were obtained.

154: $[\alpha]_D$ -56.2 (*c* 1.05, MeOH); **IR** (ATR) 3550-3100, 3020, 2964, 2924, 2854, 1769, 1737; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.21 (m, 1H, H-6), 4.60 (ddd, $J_{4,8}$=4.2 Hz, $J_{4,8}$=3.3 Hz, $J_{4,5}$=1.4 Hz, 1H, H-4), 4.26 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=3.3 Hz, 1H, H-8), 4.19 (m, 2H, H-9), 4.16 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=4.2 Hz, 1H, H-8), 3.70 (dd, $J_{1,5}$=3.5 Hz, $J_{1,6}$=0.4 Hz, 1H, H-1), 3.30 (m, 1H, H-5), 2.08 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 174.7 (C=O, C-2), 170.5 (C=O, CH_3*C*O), 150.8 (C, C-7), 131.7 (CH, C-6), 77.1 (CH, C-4), 65.6 (CH_2, C-8), 59.3 (CH_2, C-9), 46.7 (CH, C-1), 40.8 (CH, C-5), 20.6 (CH_3, *C*H_3CO). **HRMS** (ESI-TOF) Calcd for$[C_{10}H_{13}O_5+H]^+$: 213.0760. Found: 213.0757.
COSY, HMQC, HMBC and n.O.e. differential experiments were recorded for **154**.

155: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.13 (m, 1H, H-6), 4.67 (ddd, $J_{4,5}$=7.5 Hz, $J_{4,8}$=4.5 Hz, $J_{4,8}$=2.3 Hz, 1H, H-4), 4.20 (m, 4H, H-8, H-9), 3.74 (dd, $J_{1,5}$=3.6 Hz, $J_{1,9}$=1.0 Hz, 1H, H-1), 3.57 (m, 1H, H-5), 2.10 (s, 3H, C*H*$_3$CO), 1.95 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 170.6 (C=O, CH_3*C*O), 151.5 (C, C-7), 129.2 (CH, C-6), 76.3 (CH, C-4), 65.7 (CH_2, C-8), 63.3 (CH_2, C-9), 47.0 (CH, C-1), 40.1 (CH, C-5), 20.7 (CH_3, *C*H_3CO).

156: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.17 (br s, 1H, H-7), 4.74 (ddd, $J_{4,8}$=4.0 Hz, $J_{4,8}$=3.6 Hz, $J_{4,5}$=1.5 Hz, 1H, H-4), 4.29 (dd, J_{gem}=7.6 Hz, $J_{8,4}$=4.0 Hz, 1H, H-8), 4.23 (m, 2H, H-9), 4.20 (m, 1H, H-8), 3.56 (m, 1H, H-1), 3.43 (m, 1H, H-5), 2.08 (s, 3H, C*H*$_3$CO), 1.70 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 174.8 (C=O, C-2), 170.5 (C=O, CH_3*C*O), 152.5 (C, C-6), 130.7 (CH, C-7), 75.4 (CH, C-4), 65.7 (CH_2, C-8), 59.3 (CH_2, C-9), 44.0 (CH, C-1), 43.7 (CH, C-5), 20.7 (CH_3, *C*H_3CO).

157: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.25 (br s, 1H, H-7), 4.66 (ddd, $J_{4,5}$=7.5 Hz, $J_{4,8}$=4.4 Hz, $J_{4,8}$=3.8 Hz, 1H, H-4), 4.22 (m, 4H, H-8, H-9), 3.68 (m, 1H, H-1), 3.59 (m, 1H, H-5), 2.09 (s, 3H, C*H*$_3$CO), 1.75 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 173.4 (C=O, C-2), 170.6 (C=O, CH_3*C*O), 151.0 (C, C-6), 131.7 (CH, C-7), 75.7 (CH, C-4), 63.9 (CH_2, C-8), 63.3 (CH_2, C-9), 43.9 (CH, C-1), 42.3 (CH, C-5), 20.7 (CH_3, *C*H_3CO).

158: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.47 (d, $J_{6,7}$=2.7 Hz, 1H, H-6), 6.34 (d, $J_{7,6}$=2.7 Hz, 1H, H-7), 4.59 (ddd, $J_{4,8}$=5.1 Hz, $J_{4,8}$=3.9 Hz, $J_{4,5}$=1.0 Hz, 1H, H-4), 4.24 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=3.9 Hz, 1H, H-8), 4.16 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=5.1 Hz, 1H, H-8), 4.07 (d, J_{gem}=11.4 Hz, H-9), 3.95 (d, J_{gem}=11.4 Hz, 1H, H-9), 3.24 (d, $J_{5,4}$=1.0 Hz, 1H, H-5), 2.10 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.8 (C=O, C-2), 170.5 (C=O, CH_3*C*O), 140.7 (CH, C-6), 140.4 (CH, C-7), 75.4 (CH, C-4), 65.3 (CH_2, C-8), 61.7 (CH_2, C-9), 58.7 (C, C-1), 46.3 (CH, C-5), 20.7 (CH_3, *C*H_3CO). **HRMS** (ESI-TOF) Calcd for $[C_{10}H_{13}O_5+Na]^+$: 235.0577. Found: 235.0572 (mixture of **158-159**).

DEPT experiment was recorded for **158**.

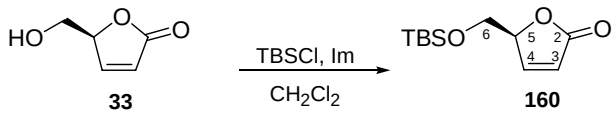
159: **IR** (ATR) 3700-3100, 3059, 2960, 2923, 2852, 1768, 1735, 1178; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.40 (dd, $J_{6,7}$=2.8 Hz, $J_{6,5}$=0.5 Hz, 1H, H-6), 6.33 (d, $J_{7,6}$=2.8 Hz, 1H, H-7), 4.67 (ddd, $J_{4,8}$=7.5 Hz, $J_{4,5}$=7.0 Hz, $J_{4,8}$=4.5 Hz, 1H, H-4), 4.32 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=4.5 Hz, 1H, H-8), 4.23 (dd, J_{gem}= 12.0 Hz, $J_{8,4}$=7.5 Hz, 1H, H-8), 4.13 (d, J_{gem}=11.4 Hz, H-9), 3.91 (d, J_{gem}=11.4 Hz, 1H, H-9), 3.55 (dd, $J_{5,4}$=7.0 Hz, $J_{5,6}$=0.5 Hz, 1H, H-5), 2.10 (s, 3H, C*H*$_3$CO); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.3 (C=O, C-2), 170.6 (C=O, CH_3*C*O), 140.7 (CH, C-7), 138.5 (CH, C-6), 74.6 (CH, C-4), 63.3 (CH_2, C-8), 61.9 (CH_2, C-9), 59.6 (C, C-1), 46.0 (CH, C-5), 20.7 (CH_3, *C*H_3CO).

HMQC, HMBC and n.O.e. differential experiments were recorded for **159**.

4. [2+2] Photocycloaddition of 2(5*H*)-furanones to ethylene, acetylene and ketene diethyl ketal

4.1. Synthesis of 2(5*H*)-furanones

4.1.1. (-)-(5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-2(5*H*)-furanone (160)

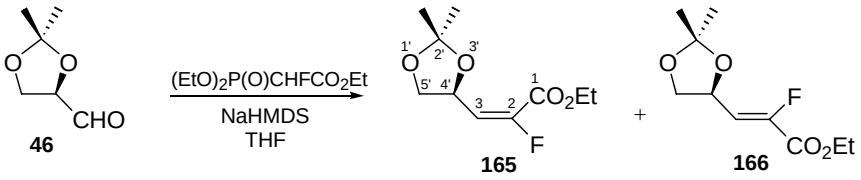


33 **160**

To a solution of **33** (1.00 g, mmol) in CH_2Cl_2 (10 mL) at 0 ºC, imidazole (834 mg, 13.7 mmol) and *tert*-butyldimethylsilyl chloride (1.72 g, 12.6 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. Then it was diluted with CH_2Cl_2 (20 mL) and water (20 mL) was added. The mixture was separated and the organic layer was washed with two more portions of water (15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent to dryness gave a reaction crude which was purified by column chromatography (hexane- EtOAc 6:1) to afford **160** (1.83 g, 8.01 mmol, 91% yield) as a white solid.

160: $[\alpha]_D$: -127 (*c* 4.8, $CHCl_3$); **IR** (ATR) 1747, 1605, 1331; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.49 (dd, $J_{4,3}$=5.8 Hz, $J_{4,5}$=1.6 Hz, 1H, H-4), 6.15 (dd, $J_{3,4}$=5.8 Hz, $J_{3,5}$=2.0 Hz, 1H, H-3), 5.05 (dddd, $J_{5,6}$=5.4 Hz, $J_{5,6}$=4.5 Hz, $J_{5,3}$=2.0 Hz, $J_{5,4}$=1.6 Hz, 1H, H-5), 3.93 (dd, J_{gem}=10.8 Hz, $J_{6,5}$=4.5 Hz, 1H, H-6), 3.79 (dd, J_{gem}=10.8 Hz, $J_{6,5}$=5.4 Hz, 1H, H-6), 0.86 (s, 9H, (C*H*$_3$)$_3$C), 0.07 (s, 3H, (C*H*$_3$)Si), 0.06 (s, 3H, (C*H*$_3$)Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 172.9 (C=O, C-2), 154.3 (CH, C-4), 122.5 (CH, C-3), 83.3 (CH, C-5), 62.9 (CH_2, C-6), 25.7 (CH_3, C(*C*H$_3$)$_3$), 18.2 (C, *C* (CH$_3$)$_3$), -5.5 (CH_3, (*C*H$_3$)Si), -5.6 (CH_3, (*C*H$_3$)Si).

4.1.2. Ethyl (2*E*)-3-[(4*S*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-2-fluoro-2-propenoate (165) and ethyl (2*Z*)-3-[(4*S*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-2-fluoro-2-propenoate (166)

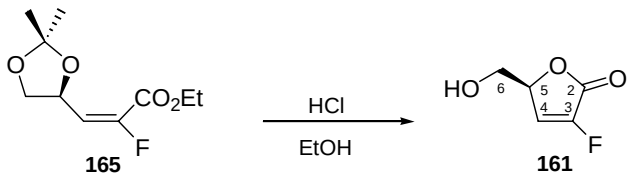


46 **165** **166**

To a -78 ºC cooled solution of triethyl-2-fluoro-2-phosphonacetate (4.0 mL, 18.93 mmol) in dry THF (9 mL), sodium hexamethyldisilylamide (NaHMDS) 1.0 M in THF was added dropwise (19 mL, 19,00 mmol) and the solution was stirred for 1 h at -78 ºC. Then a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde, **46**, (3.0 g, 23.1 mmol) in dry THF (10 mL) was added dropwise and the dark solution was kept at -78 ºC for 90 min. The reaction was quenched by adding a NH_4Cl saturated aqueous solution (5 mL) and it was allowed to slowly warm to room temperature. The mixture was diluted with CH_2Cl_2 (20 mL) and separated. The aqueous layer was extracted three times with CH_2Cl_2 (15 mL). The collected organic layer was washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 and evaporated. The resulting dark oil was purified by column chromatography (hexane-diethyl ether 10:1) affording a 90:10 mixture of olefins **165** and **166** (3.08 g, 14.1 mmol, 74% yield). Repetitive column chromatography (from hexane to hexane-diethyl ether 30:1) allowed the isolation of the major isomer **165** as a colourless oil.

165: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 5.99 (dd, $J_{3,F}$=19.1 Hz, $J_{3,4}$=7.7 Hz, 1H, H-3), 5.38 (dddd, $J_{4',F}$=13.0 Hz, $J_{4',3}$=7.7 Hz, $J_{4',5'}$=6.5 Hz, $J_{4',5'}$=2.8 Hz, 1H, H-4'), 4.29 (m, 3H, H-5', OCH_2CH$_3$), 3.65 (ddd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.5 Hz, $J_{5',F}$=0.5 Hz, 1H, H-5), 1.43 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34 (t, J=7.1 Hz, 3H, OCH$_2$CH_3).

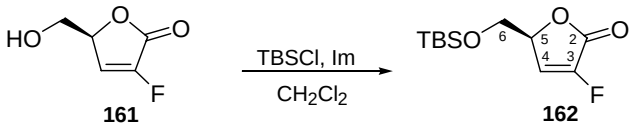
4.1.3. (-)-(5*S*)-3-fluoro-5-hydroxymethyl-2(5*H*)-furanone (161)



To a solution of **165** (2.66 g, 12.19 mmol) in EtOH (12 mL) at 0 ºC, concentrated HCl (2.5 mL, 32.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed in vacuo and the residue coevaporated with toluene (2x5 mL) to afford a reaction crude which was purified by column chromatography (EtOAc) to furnish **161** (1.61 g, 12.18 mmol, 99% yield) as a pale yellow oil.

161: $[\alpha]_D$ -54.0 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.72 (t, $J_{4,5}$=2.0 Hz, $J_{4,F}$=2.0 Hz, 1H, H-4), 5.09 (dddd, *J*=5.7 Hz, *J*=4.9 Hz, *J*=3.8 Hz, $J_{5,4}$=2.0 Hz, 1H, H-5), 4.30 (m, 2H, H-6), 2.12 (br s, 1H, OH).

4.1.4. (-)-(5*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-fluoro-2(5*H*)-furanone (162)

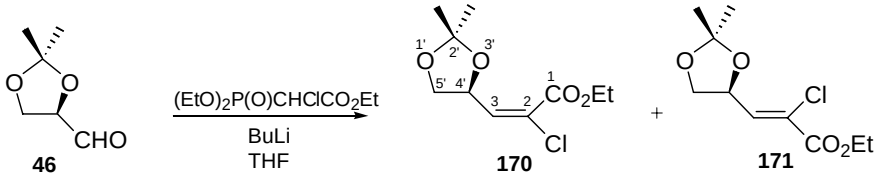


161 **162**

To a solution of lactone **161** (1.61 g, 12.18 mmol) in CH_2Cl_2 (30 mL) at 0 ºC, imidazole (1.85 g, 27.17 mmol) and *tert*-butyldimethylsilyl chloride (3.26 g, 21.73 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. Then, it was diluted with EtOAc (25 mL) and water (20 mL) was added. The mixture was separated and the organic layer was washed with two more portions of water (15 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The resulting reaction crude was purified by column chromatography (hexane-diethyl ether 10:1) to give **162** (2.47 g, 10.06 mmol, 83% yield) as a white solid.

162: mp: 48-50 ºC (from diethyl ether); $[\alpha]_D$: -104.3 (*c* 0.60, $CHCl_3$) (literature $[\alpha]_D$ -105.9 (*c* 0.5, $CHCl_3$))[10f]; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.71 (t, $J_{4,5}$=2.0 Hz, $J_{4,F}$=2.0 Hz, 1H, H-4), 4.98 (dddd, $J_{5,F}$=7.5 Hz, $J_{5,6}$=4.8 Hz, $J_{5,6}$=4.3 Hz, $J_{5,4}$=2.0 Hz, 1H, H-5), 3.89 (ddd, J_{gem}=11.9 Hz, $J_{6,5}$=4.3 Hz, $J_{6,F}$=0.8 Hz, 1H, H-6), 3.82 (ddd, J_{gem}=11.9 Hz, $J_{6,5}$=4.8 Hz, $J_{6,F}$=1.3 Hz, 1H, H-6), 0.85 (s, 9H, $(CH_3)_3C$), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si).

4.1.5. Ethyl (2*E*)-3-[(4*S*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-2-chloro-2-propenoate (170) and Ethyl (2*Z*)-3-[(4*S*)-2',2'-dimethyl-1',3'-dioxolan-4'-yl]-2-chloro-2-propenoate (171)



46 **170** **171**

To a -78 ºC cooled solution of triethyl-2-chloro-2-phosphonacetate (1.02 g, 3,93 mmol) in dry THF (2 mL), BuLi (2.44 mL, 3.91 mmol) 1.6 M in hexane was added dropwise and the solution was stirred for 1 h at -78 ºC. Then, a solution of aldehyde **46** (510 mg, 3.91 mmol) in dry THF (2 mL) was added dropwise and the dark solution was kept at -78 ºC for 2 h. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl (2 mL) and was allowed to slowly warm to room temperature. The mixture was diluted with CH_2Cl_2 (5 mL) and separated. The aqueous layer was extracted three times with CH_2Cl_2 (2 mL). The organic layer was washed with brine (3x4 mL), dried over anhydrous Na_2SO_4 and evaporated. The resulting dark oil was purified by column chromatography (hexane-diethyl ether 10:1) to afford a 86:14 mixture of olefins **170** and **171** (569 mg, 2.42 mmol, 62% yield). Repeated column chromatography (from hexane to hexane-diethyl ether 30:1) allowed to separate both isomers as colourless oils.

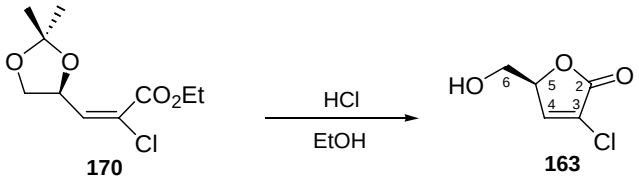
170: **IR** (ATR) 2985, 2937, 1714, 1208, 1058, 1024; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.57 (d, $J_{3,4'}$=6.9 Hz, 1H, H-3), 5.29 (ddd, $J_{4',3}$=6.9 Hz, $J_{4',5'}$=6.8 Hz, $J_{4',5'}$=6.3 Hz, 1H, H-4'), 4.32 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.8 Hz, 1H, H-5'), 4.28 (m, 2H, OCH_2CH$_3$), 3.70 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.3 Hz, 1H, H-5'), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, OCH$_2$CH_3); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 162.0 (C=O, C-1), 144.6 (CH, C-3), 123.7 (C, C-2), 110.0 (C, C-2'), 73.6 (CH, C-4'), 69.3 (CH_2, C-5'), 62.5 (CH_2, OCH_2CH$_3$), 26.5 (CH_3, C(CH_3)$_2$), 25.4 (CH_3, C(CH_3)$_2$), 14.0 (CH_3, OCH$_2$$CH_3$). **HRMS** (ESI-TOF) Calcd for $[C_{10}H_{15}ClO_4+Na]^+$: 257.0551. Found: 257.0547 (mixture of **170** and **171**).

COSY, HMQC and HMBC experiments were recorded for **170**.

171: **IR** (ATR) 2985, 2929, 1726, 1240, 1060, 1030; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.05 (d, $J_{3,4'}$=6.9 Hz, 1H, H-3), 4.97 (ddd, $J_{4',3}$=6.9 Hz, $J_{4',5'}$=6.8 Hz, $J_{4',5'}$=6.8 Hz, 1H, H-4), 4.24 (m, 3H, H-5', OCH_2CH$_3$), 3.66 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.8 Hz, 1H, H-5'), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.29 (t, J=7.1 Hz, 3H, OCH$_2$CH_3); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 161.5 (C=O, C-1), 140.0 (CH, C-3), 125.7 (C, C-2), 110.1 (C, C-2'), 73.3 (CH, C-4'), 68.1 (CH_2, C-5'), 62.5 (CH_2, OCH_2CH$_3$), 26.3 (CH_3, C(CH_3)$_2$), 25.4 (CH_3, C(CH_3)$_2$), 14.0 (CH_3, OCH$_2$$CH_3$).

DEPT, COSY and HMBC experiments were recorded for **171**.

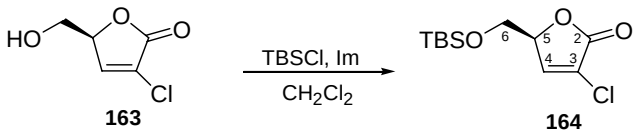
4.1.6. (-)-(5*S*)-3-chloro-5-hydroxymethyl-2(5*H*)-furanone (163)



To a solution of **170** (300 mg, 1.28 mmol) in EtOH (10 mL) at 0 ºC, concentrated HCl (0.4 mL, 5.12 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 4 h. Then, the solvent was removed in vacuo and the residue coevaporated with toluene (2x2 mL). The resulting crude was purified by column chromatography (EtOAc) yielding **163** (180 mg, 1.21 mmol, 95% yield) as a colourless oil.

163: $[\alpha]_D$: -54.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) 3409, 3097, 1752, 1029; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.35 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 5.12 (ddd, $J_{5,6}$=4.8 Hz, $J_{5,6}$=3.8 Hz, $J_{5,4}$=1.9 Hz, 1H, H-5), 4.00 (dd, J_{gem}=12.3 Hz, $J_{6,5}$=3.8 Hz, 1H, H-6), 3.83 (dd, J_{gem}=12.3 Hz, $J_{6,5}$=4.8 Hz, 1H, H-6), 2.37 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 167.7 (C=O, C-2), 145.0 (CH, C-4), 126.1 (C, C-3), 81.5 (CH, C-4), 62.3 (CH_2, C-6). **HRMS** (ESI-TOF) Calcd for $[C_5H_5ClO_3+Na]^+$: 170.9819. Found: 170.9825.

4.1.7. (-)-(5*S*)-5-*tert*-butyldimethylsilyloxymethyl-3-chloro-2(5*H*)-furanone (164)

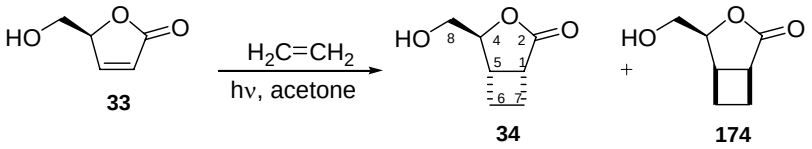


To a solution of **163** (170 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) at 0 ºC, imidazole (176 mg, 2.9 mmol) and *tert*-butyldimethylsilyl chloride (310 mg, 2.28 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. Then, it was diluted with EtOAc (10 mL) and water (20 mL) was added. The mixture was separated and the organic layer was washed with water (2x20 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude mixture which was purified by column chromatography (hexane-diethyl ether 20:1) to afford **164** (265 mg, 1.01 mmol, 88% yield) as a white solid.

164: mp: 48-50 ºC (diethyl ether); $[\alpha]_D$: -96.4 (*c* 0.56, $CHCl_3$); **IR** (ATR) 2929, 2857, 1764, 1041, 833, 777; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.33 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 5.03 (ddd, $J_{5,6}$=5.0 Hz, $J_{5,6}$=4.2 Hz, $J_{5,4}$=1.9 Hz, 1H, H-5), 3.93 (dd, J_{gem}=10.9 Hz, $J_{6,5}$=4.2 Hz, 1H, H-6), 3.83 (dd, J_{gem}=10.9 Hz, $J_{6,5}$=5.0 Hz, 1H, H-6), 0.87 (s, 9H, $(CH_3)_3C$), 0.07 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 168.0 (C=O, C-2), 146.1 (CH, C-4), 126.1 (C, C-3), 81.3 (CH, C-4), 63.1 (CH_2, C-6), 26.1 (CH_3, $(CH_3)_3C$), 18.5 (C, $(CH_3)_3C$), -5.1 (CH_3, CH_3Si), -5.2 (CH_3, CH_3Si). **HRMS** (ESI-TOF) Calcd for $[C_{11}H_{19}ClO_3Si+Na]^+$: 285.0684. Found: 285.0684.

4.2. [2+2] Photocycloaddition of 2(5*H*)-furanones to ethylene

4.2.1. (1*R*,4*S*,5*S*)-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (34) and (1*S*,4*S*,5*R*)-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (174)

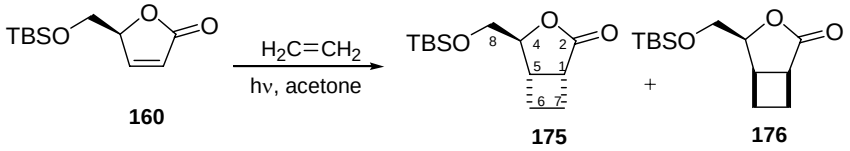


A solution of lactone **33** (155 mg, 1.36 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 5.5 h at -20 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtAcO 1:1) afforded a 66:34 mixture of **34** and **174** (127 mg, 0.90 mmol, 66% yield). Repetitive column chromatography (from hexane-EtAcO 3:1 to hexane-EtAcO 1:1) allowed to isolate pure **34** as a colourless oil and an enriched fraction of the *syn* isomer **174**.

34: bp: 115 ºC (oven)/0.1 torr; $[\alpha]_D$: -68.3 (*c* 1.2, $CHCl_3$); **IR** (ATR) 3444, 2944, 2869, 1740; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.44 (ddd, $J_{4,8}$=4.3 Hz, $J_{4,8}$=3.2 Hz, $J_{4,5}$=1.2 Hz, 1H, H-4), 3.80 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=3.2 Hz, 1H, H-8), 3.56 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=4.2 Hz, 1H, H-8), 3.15 (m, 1H, H-1), 3.03 (m, 1H, H-5), 2.66 (br s, 1H, OH), 2.55 (m, 1H, H-7exo), 2.39 (m, 1H, H-6exo), 2.13 (m, 2H, H-6endo, H-7endo); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 181.1 (C=O, C-2), 86.3 (CH, C-4), 64.2 (CH_2, C-8), 39.3 (CH, C-1), 36.2 (CH, C-5), 24.8 (CH_2, C-6), 23.8 (CH_2, C-7). **HRMS** (ESI-TOF) Calcd for $[C_7H_{10}O_3+H]^+$: 143.0708. Found: 143.0710.

174: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.53 (ddd, $J_{4,8}$=7.6 Hz, J=5.6 Hz, J=4.2 Hz, 1H, H-4), 3.90 (dd, J_{gem}=11.9 Hz, $J_{8,4}$=7.6 Hz, 1H, H-8), 3.53 (m, 1H, H-8), 3.25-3.00 (m, 2H, H-1, H-5), 2.73 (br s, 1H, OH), 2.58-2.00 (m, 4H, H-6, H-7); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 180.7 (C=O, C-2), 82.5 (CH, C-4), 61.5 (CH_2, C-8), 40.0 (CH, C-1), 36.1 (CH, C-5), 23.2 (CH_2, C-6), 19.1 (CH_2, C-7).

4.2.2. (1*R*,4*S*,5*S*)-4-*tert*-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (175) and (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (176)



160 **175** **176**

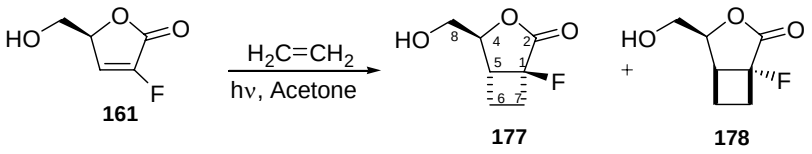
A solution of lactone **160** (110 mg, 0.45 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 3.5 h at -20 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-diethyl ether 10:1) afforded a 73:27 mixture of **175** and **176** (38 mg, 0.14 mmol, 31% yield). Repetitive column chromatography (from hexane-diethyl ether 30:1 to hexane-diethyl ether 10:1) allowed to isolate pure **175** as a white solid and an enriched fraction of the *syn* isomer **176**.

175: mp: 55-56 ºC (EtOAc-hexane); $[\alpha]_D$: -22.0 (*c* 0.70, $CHCl_3$); **IR** (ATR) 1755, 1250, 1163,1106; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.36 (dd, $J_{4,8}$=3.1 Hz, $J_{4,8}$=2.3 Hz, 1H, H-4), 3.77 (dd, J_{gem}=11.1 Hz, $J_{8,4}$=3.1 Hz, 1H, H-8), 3.58 (dd, J_{gem}=11.1 Hz, $J_{8,4}$=2.3 Hz, 1H, H-8), 3.07 (m, 2*H*, H-1, H-5), 2.54 (m, 1H, H-7), 2.39 (m, 1H, H-6), 2.14 (m, 2H, H-6, H-7), 0.85 (s, 9H, (C*H*$_3$)$_3$C), 0.04 (s, 3H, C*H*$_3$Si), 0.03 (s, 3H, C*H*$_3$Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 180.7 (C=O, C-2), 85.3 (CH, C-4), 64.8 (CH_2, C-8), 39.7 (CH, C-1), 36.8 (CH, C-5), 25.7 (CH_3, C(*C*H$_3$)$_3$), 24.5 (CH_2, C-6), 23.9 (CH_2, C-7), 18.1 (C, *C*(CH$_3$)$_3$), -5.6 (CH_3, *C*H$_3$Si), -5.7 (CH_3, *C*H$_3$Si). Anal. Calcd for ($C_{13}H_{24}O_3Si$): C, 60.89; H, 9.53. Found: C, 60.87; H, 9.45.

176: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.47 (m, 1H, H-4), 3.94 (dd, J_{gem}=10.7 Hz, $J_{8,4}$=5.9 Hz, 1H, H-8), 3.75 (m, 1H, H-8), 3.15-3-02 (m, 2H, H-1, H-5), 2.60-2.0 (m, 4H, H-6, H-7), 0.85 (s, 9H, (C*H*$_3$)$_3$C), 0.04 (s, 3H, C*H*$_3$Si), 0.03 (s, 3H, C*H*$_3$Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 180.7 (C=O, C-2), 81.2 (CH, C-4), 61.5 (CH_2, C-8), 39.7 (CH, C-1),

36.7 (CH, C-5), 25.7 (CH_3, C(CH_3)$_3$), 23.2 (CH_2, C-6), 19.1 (CH_2, C-7), 18.1 (C, $C(CH_3)_3$), -5.4 (CH_3, CH_3Si), -5.6 (CH_3, CH_3Si).

4.2.3. (-)-(1*S*,4*S*,5*R*)-1-fluoro-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (177) and (1*R*,4*S*,5*S*)-1-fluoro-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (178)



A solution of 3-fluoro-2(5*H*)-furanone **161** (135 mg, 1.02 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 3.5 h at -20 ºC. Evaporation of the solvent and column chromatography of the residue (hexane-EtOAc 3:1) afforded a 81:19 mixture of the cycloadducts **177** and **178** (120 mg, 0.75 mmol, 75% yield). Repetitive column chromatography (from hexane-EtOAc 5:1 to hexane-EtOAc 3:1) allowed to isolate pure **177** as a white solid and **178** as a colourless oil.

177: mp: 99-102 ºC (from EtOAc); $[\alpha]_D$: -36.0 (*c* 1.3, $CHCl_3$); **IR** (ATR) 3331, 2959, 1780, 1766, 1037; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.45 (ddd, $J_{4,8}$=4.4 Hz, $J_{4,F}$=3.9 Hz, $J_{4,8}$=3.4 Hz, 1H, H-4), 3.83 (dd, J_{gem}=12.3 Hz, $J_{8,4}$=3.4 Hz, 1H, H-8), 3.68 (dd, J_{gem}=12.3 Hz, $J_{8,4}$=4.4 Hz, 1H, H-8), 3.20 (ddd, *J*=17.2 Hz, *J*=10.6 Hz, *J*=6.9 Hz, 1H, H-5), 2.61 (m, 1H, H-7exo), 2.50 (m, 1H, H-7endo), 2.36 (m, 1H, H-6exo), 2.22 (br s, 1H, OH), 1.54 (m, 1H, H-6); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 174.0, 173.7 (d, $^2J_{C-F}$=25.9 Hz, C=O), 91.4, 88.7 (d, $^1J_{C-F}$=243.4 Hz, C, C-1), 84.1 (s, CH, C-4), 63.6 (s, CH_2, C-8), 42.0, 41.8 (d, $^2J_{C-F}$=17.7 Hz, CH, C-5), 29.0, 28.7 (d, $^2J_{C-F}$=23.8 Hz, CH, C-7), 15.5, 15.3 (d, $^3J_{C-F}$=16.1 Hz, CH, C-6); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -150.6 to -150.8 (m). Anal. Calcd for ($C_7H_9FO_3$): C, 52.50; H, 5.66. Found: C, 52.62; H, 5.72.

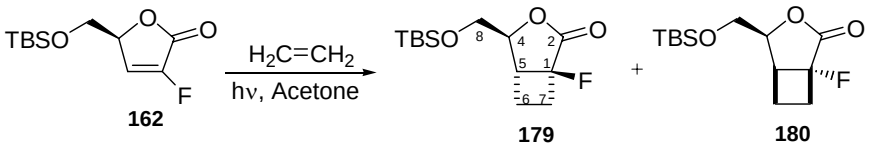
DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **177**.

178: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.37 (ddd, $J_{4,8}$=7.3 Hz, $J_{4,5}$=4.9 Hz, $J_{4,8}$=4.6 Hz, 1H, H-4), 3.91 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=7.3 Hz, 1H, H-8), 3.75 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=4.6 Hz, 1H, H-8), 3.35 (m, 1H, H-5), 2.57 (m, 1H, H-7), 2.51 (m, 1H, H-7), 2.10 (m, 1H, H-6), 1.75 (br s, 1H, OH), 1.65 (m, 1H, H-6); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 173.2, 172.8 (d, $^2J_{C-F}$=26.1 Hz, C=O), 92.4, 88.5 (d, $^1J_{C-F}$=243.8 Hz, C, C-1), 80.7 (s,

CH, C-4), 61.6 (s, CH_2, C-8), 42.7, 42.4 (d, $^2J_{C\text{-}F}$=18.8 Hz, CH, C-5), 28.5, 28.17 (d, $^2J_{C\text{-}F}$=21.8 Hz, CH, C-7), 9.9, 9,7 (d, $^3J_{C\text{-}F}$=16.3 Hz, CH, C-6); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -150.8 to -151.0 (m).

DEPT, HMQC, HMBC and NOESY experiments were recorded for **178**.

4.2.4. (-)-(1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptan-2-one (179) and (+)-(1*R*,4*S*,5*S*)-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptan-2-one (180)



162 **179** **180**

A solution of 3-fluoro-2(5*H*)-furanone **162** (270 mg, 1.10 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 2 h at -20 ºC. Evaporation of the solvent and chromatography of the residue (hexane-diethyl ether 10:1) afforded a 91:9 mixture of the cycloadducts **179** and **180** (251 mg, 0.92 mmol, 84% yield). A further column chromatography (from hexane-diethyl ether 20:1 to hexane-diethyl ether 12:1) allowed to isolate pure **179** as a white solid and **180** as a colourless oil.

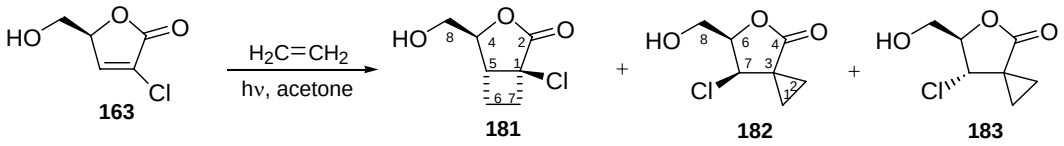
179: mp: 48-49 ºC (from diethyl ether); $[\alpha]_D$: -53.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) 2929, 1780, 1098, 1081, 827; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.37 (ddd, $J_{4,8}$=3.6 Hz, $J_{4,F}$=3.3 Hz, $J_{4,8}$=2.7 Hz, 1H, H-4), 3.81 (dd, J_{gem}=11.2 Hz, $J_{8,4}$=3.6 Hz, 1H, H-8), 3.67 (dd, J_{gem}=11.2 Hz, $J_{8,4}$=2.7 Hz, 1H, H-8), 3.21 (dddd, *J*=10.6 Hz, *J*=10.4 Hz, *J*=6.6 Hz, $J_{5,4}$=0.5 Hz, 1H, H-5), 2.59 (m, 1H, H-7exo), 2.50 (m, 1H, H-7endo), 2.32 (m, 1H, H-6exo), 1.52 (m, 1H, H-6endo), 0.87 (s, 9H, $(CH_3)_3C$), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 174.0, 173.6 (d, $^2J_{C\text{-}F}$=25.4 Hz, C=O), 92.0, 88.1 (d, $^1J_{C\text{-}F}$=243.2 Hz, C, C-1), 83.9, 83.9 (d, $^3J_{C\text{-}F}$=2.3 Hz, CH, C-4), 63.8 (s, CH_2, C-8), 42.8, 42.0 (d, $^2J_{C\text{-}F}$=17.8 Hz, CH, C-5), 29.3, 28.9 (d, $^2J_{C\text{-}F}$ =24.4 Hz, CH_2, C-7), 25.7 (s, CH_3, $(CH_3)_3C$), 18.2 (s, C, $(CH_3)_3C$), 15.7, 15.5 (d, $^3J_{C\text{-}F}$=15.8 Hz, CH_2, C-6), -5.7 (s, CH_3, CH_3Si), -5.8 (s, CH_3, CH_3Si); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -150.8 to -151.0 (m). **HRMS** (ESI-TOF) Calcd for $[C_{13}H_{23}FO_3SiH]^+$: 275.1473. Found: 275.1474.

COSY, HMQC and HMBC experiments were recorded for **179**.

180: $[\alpha]_D$: +4.4 (*c* 0.9, $CHCl_3$); **IR** (ATR) 2930, 1789, 1082, 836; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.67 (ddd, $J_{4,8}$=6.7 Hz, $J_{4,8}$=5.9 Hz, $J_{4,5}$=5.8 Hz, 1H, H-4), 3.90 (dd, J_{gem}=10.8 Hz, $J_{8,4}$=5.9 Hz, 1H, H-8), 3.69 (dd, J_{gem}=10.8 Hz, $J_{8,4}$=6.7 Hz, 1H, H-8), 3.34 (m, 1H, H-5), 2.51 (m, 1H, H-7exo), 2.40 (m, 1H, H-7endo), 2.06 (m, 1H, H-6exo), 1.63 (m, 1H, H-6endo), 0.88 (s, 9H, $(CH_3)_3C$), 0.07 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 173.4, 173.1 (d, $^2J_{C-F}$=25.9 Hz, C=O, C-2), 91.8, 89.1 (d, $^1J_{C-F}$=243.4 Hz, C, C-1), 79.8 (s, CH, C-4), 61.2 (s, CH_2, C-8), 43.1, 42.9 (d, $^2J_{C-F}$=17.9 Hz, CH, C-5), 28.2, 27.9 (d, $^2J_{C-F}$=23.0 Hz, CH_2, C-7), 25.7 (s, CH_3, $(CH_3)_3C$), 18.1 (s, C, $(CH_3)_3C$), 9.8, 9.6 (d, $^3J_{C-F}$=17.9 Hz, CH_2, C-6), -5.5 (s, CH_3, CH_3Si), -5.6 (s, CH_3, CH_3Si); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -151.3 to -151.6 (m). **HRMS** (ESI-TOF) Calcd for $[C_{13}H_{23}FO_3Si+Na]^+$: 297.1293. Found: 297.1284.

COSY, HMQC, HMBC and NOESY experiments were recorded for **180**.

4.2.5. (+)-(1*S*,4*S*,5*R*)-1-chloro-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (181), (+)-(6*R*,7*R*)-7-chloro-6-hydroxymethyl-5-oxaspiro[2.4]heptan-4-one (182) and (-)-(6*R*,7*S*)-7-chloro-6-hydroxymethyl-5-oxaspiro[2.4]heptan-4-one (183)



A solution of 3-chloro-2(5*H*)-furanone **163** (125 mg, 0.84 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 4.5 h at -20 ºC. Evaporation of the solvent gave a crude which was purified by column chromatography (hexane-EtAcO 3:1) to afford a 61:19:20 mixture of **181, 182** and **183** (124 mg, 0.70 mmol, 83% yield). Repetitive column chromatography (from hexane-EtAcO 5:1 to hexane-EtAcO 3:1) allowed to isolate **181** as a colourless oil, **182** as a colourless oil and **183** as a colourless oil.

181: $[\alpha]_D$: +12.7 (*c* 1.1, $CHCl_3$); **IR** (ATR) 3400, 2950, 2872, 1766, 1223; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 4.46 (dd, $J_{4,8}$=4.9 Hz, $J_{4,8}$=4.7 Hz, 1H, H-4), 3.76 (m, 2H, H-8), 3.22 (ddd, $J_{5,6}$=7.0 Hz, $J_{5,6}$=1.7 Hz, $J_{5,4}$=0.5 Hz, 1H, H-5), 2.67 (m, 1H, H-7), 2.60 (m, 1H, H-7), 2.51 (m, 1H, H-6exo), 2.49 (br s, 1H, OH), 1.88 (m, 1H, H-6endo); **^{13}C-NMR**

(62.5 MHz, $CDCl_3$) δ 175.5 (C=O, C-2), 84.4 (CH, C-4), 63.1 (CH_2, C-8), 59.5 (C, C-1), 45.7 (CH, C-5), 33.4 (CH_2, C-7), 20.2 (CH_2, C-6). **HRMS** (ESI-TOF) Calcd for $[C_7H_9ClO_3+Na]^+$: 199.0132. Found: 199.0129.

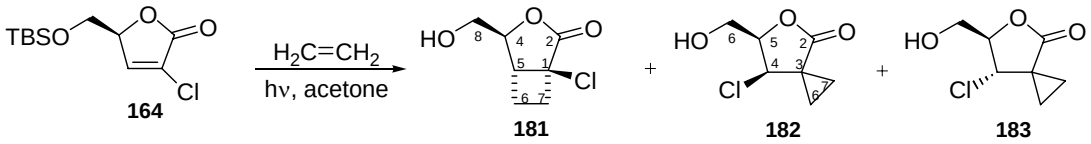
COSY, HMQC, HMBC and NOESY experiments were recorded for **181**.

182: mp: 39-41 ºC (EtOAc); $[\alpha]_D$: +172.2 (*c* 1.8, $CHCl_3$); **IR** (ATR) 3432, 2970, 1742, 1149, 1044; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.82 (ddd, $J_{6,8}$=6,7 Hz, $J_{6,8}$=5.0 Hz, $J_{6,7}$=5.0 Hz, 1H, H-6), 4.50 (d, $J_{7,6}$=5.0 Hz, 1H, H-7), 4.14 (dd, J_{gem}=12.3 Hz, $J_{8,6}$=6.7 Hz, 1H, H-8), 4.00 (dd, J_{gem}=12.3 Hz, $J_{8,6}$=5.0 Hz, 1H, H-8), 3.18 (br s, 1H, OH), 1.59-1.30 (m, 4H, H-1, H-2); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 176.2 (C=O, C-4), 80.0 (CH, C-6), 62.8 (CH, C-7), 62.2 (CH_2, C-8), 28.6 (C, C-3), 19.0/13.5 ($2CH_2$, C-1, C-2). **HRMS** (ESI-TOF) Calcd for $[C_7H_9ClO_3+Na]^+$: 199.0132. Found: 199.0132.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **182**.

183: $[\alpha]_D$: -69.7 (*c* 2.54, $CHCl_3$); **IR** (ATR) 3423, 2934, 1755, 1112, 1055; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.73 (ddd, $J_{6,8}$=3.5 Hz, $J_{6,8}$=3.3 Hz, $J_{6,7}$=3.3 Hz, 1H, H-6), 4.49 (d, $J_{7,6}$=3.3 Hz, 1H, H-7), 3.95 (dd, J_{gem}=12.7 Hz, $J_{8,6}$=3.3 Hz, 1H, H-8), 3.79 (dd, J_{gem}=12.7 Hz, $J_{8,6}$=3.5 Hz, 1H, H-8), 3.32 (br s, 1H, OH), 1.48-1.27 (m, 4H, H-1, H-2); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 177.6 (C=O, C-4), 86.4 (CH, C-6), 61.6 (CH_2, C-8), 59.8 (CH, C-7), 28.1 (C, C-3), 19.2/15.6 ($2CH_2$, C-1, C-2). **HRMS** (ESI-TOF) Calcd for $[C_7H_9ClO_3+Na]^+$: 199.0132. Found: 199.0134.

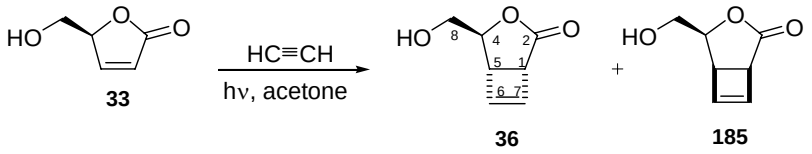
DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **183**.



When the reaction was performed irradiating through a Pyrex filter a solution of the 3-chloro-2(5*H*)-furanone **164** (110 mg, 0.42 mmol) in freshly distilled acetone (65 mL) with introduction of ethylene for 2 h at -20 ºC, evaporation of the solvent followed by column chromatography of the the resulting residue (diethyl ether-hexane 2:1) afforded a 78:7:15 mixture of **181**, **182** and **183** (63 mg, 0.36 mmol, 85% yield).

4.3. [2+2] Photocycloaddition of 2(5*H*)-furanones to acetylene

4.3.1. (1*R*,4*S*,5*S*)-4-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (136) and (1*S*,4*S*,5*R*)-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (185)

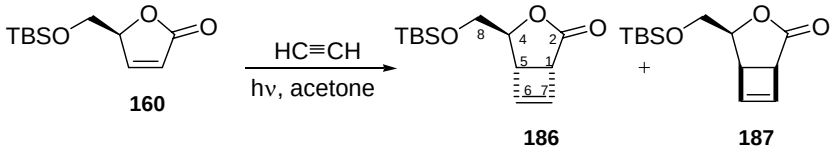


A solution of 2(5*H*)-furanone **33** (168 mg, 1.47 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 5.5 h at -20 ºC. Evaporation of the solvent and column chromatography of the resulting residue (hexane-EtAcO 1:1) afforded the following fractions: i) a 65:35 mixture of the cycloadducts **36** and **185** (90 mg, 0.64 mmol, 44% yield); and ii) unreacted lactone **33** (30 mg, 0.26 mmol, 17%). Repetitive column chromatography (from hexane-EtAcO 3:1 to hexane-EtAcO 1:1) allowed to isolate pure **36** as a colourless oil and an enriched fraction of the *syn* isomer **185**.

36: **IR** (ATR) 3422, 3056, 2939, 2874, 1737, 1171; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.34 (d, $J_{6,7}$=2.6 Hz, 1H, H-6), 6.26 (d, $J_{7,6}$=2.6 Hz, 1H, H-7), 4.45 (ddd, $J_{4,8}$=3.6 Hz, $J_{4,8}$=3.6 Hz, $J_{4,5}$=1.7 Hz, 1H, H-4), 3.86 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=3.6 Hz, 1H, H-8), 3.67 (d, $J_{1,5}$=3.5 Hz, 1H, H-1), 3.62 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=3.6 Hz, 1H, H-8), 3.48 (dd, $J_{5,1}$=3.5 Hz, $J_{5,4}$=1.7 Hz, 1H, H-5), 2.99 (br s, 1H, OH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 176.1 (C=O, C=2), 141.2 (CH, C-6), 138.6 (CH, C-7), 79.5 (CH, C-4), 64.4 (CH_2, C-8), 47.9 (CH, C-1), 44.1 (CH, C-5). **HRMS** (ESI-TOF) Calcd for $[C_7H_8O_3+H]^+$: 141.0552. Found: 141.0554.

185: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.44 (t, *J*=2.6 Hz, 1H, H-6), 6.39 (t, *J*=2.2 Hz, 1H, H-7), 4.54 (ddd, $J_{4,8}$=4.3 Hz, $J_{4,8}$=4.3 Hz, $J_{4,5}$=4.3 Hz, 1H, H-4), 3.95-3.45 (m, 4H, H-1, H-5, H-8), 1.94 (br s, 1H, OH); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 176.1 (C=O, C=2), 139.3 (CH, C-6), 138.7 (CH, C-7), 78.6 (CH, C-4), 62.6 (CH_2, C-8), 43.5 (CH, C-1), 40.1 (CH, C-5).

4.3.2. (1*R*,4*S*,5*S*)-4-*tert*-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (186) and (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (187)

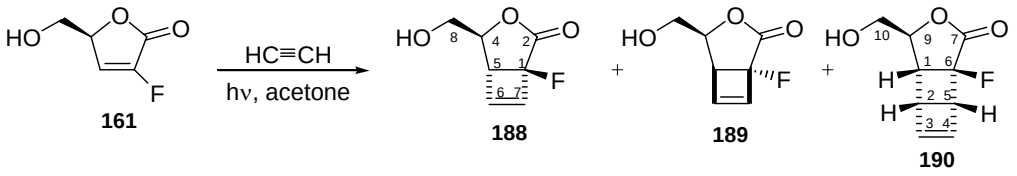


A solution of 2(5*H*)-furanone **160** (198 mg, 0.82 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 5.5 h at -20 ºC. Evaporation of the solvent and column chromatography of the resulting residue (hexane-diethyl ether 20:1) afforded the following fractions: i) a 76:24 mixture of the cycloadducts **186** and **187** (45 mg, 0.17 mmol, 21% yield); and ii) unreacted lactone **160** (45 mg, 0.19 mmol, 22%). Repetitive column chromatography (from hexane-diethyl ether 30:1 to hexane-diethyl ether 20:1) allowed to isolate pure **186** as a white solid and an enriched fraction of the *syn* isomer **187**.

186: mp: 49-50 ºC (pentane-EtOAc); $[\alpha]_D$: -221.9 (*c* 0.55, $CHCl_3$); **IR** (ATR) 2957, 2926, 2856, 1750, 1250, 1171, 1111; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.32 (ddd, $J_{6,7}$=2.7 Hz, $J_{6,5}$=0.7 Hz, $J_{6,1}$=0.7 Hz, 1H, H-6), 6.26 (dd, $J_{7,6}$=2.7 Hz, $J_{7,1}$=0.8 Hz, 1H, H-7), 4.39 (dddd, $J_{4,8}$=2.9 Hz, $J_{4,8}$=2.2 Hz, $J_{4,5}$=1.3 Hz, $J_{4,1}$=0.6 Hz, 1H, H-4), 3.83 (dd, J_{gem}=10.9 Hz, $J_{8,4}$=2.9 Hz, 1H, H-8), 3.63 (dd, J_{gem}=10.9 Hz, $J_{8,4}$=2.2 Hz, 1H, H-8), 3.59 (dddd, $J_{1,5}$=3.5 Hz, $J_{1,6}$=0.7 Hz, $J_{1,4}$=0.7 Hz, $J_{1,7}$=0.7 Hz, 1H, H-1), 3.48 (ddd, $J_{5,1}$=3.5 Hz, $J_{5,4}$=1.3 Hz, $J_{5,6}$=0.6 Hz, 1H, H-5), 0.86 (s, 9H, C(CH_3)$_3$), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.5 (C=O), 140.9 (CH, C-6), 138.9 (CH, C-7), 78.6 (CH, C-4), 65.0 (CH_2, C-8), 48.2 (CH, C-1), 44.6 (CH, C-5), 25.7 (CH_3, C(*C*H_3)$_3$), 18.0 (C, *C*(CH$_3$)$_3$), -5.7 (*C*H_3Si), -5.7 (*C*H_3Si). Anal. Calcd for ($C_{13}H_{22}O_3Si$): C, 61.38; H, 8.72. Found: C, 61.47; H, 8.47.

187: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.42 (ddd, *J*=3.0 Hz, $J_{6,7}$=2.5 Hz, *J*=0.5 Hz, 1H, H-6), 6.34 (ddd, $J_{7,6}$=2.5 Hz, *J*=2.0 Hz, *J*=0.4 Hz, 1H, H-7), 4.33 (m, 1H, H-4), 3.72 (dd, J_{gem}=11.0 Hz, $J_{8,4}$=3.2 Hz, 1H, H-8), 3.58 (dd, J_{gem}=11.0 Hz, $J_{8,4}$=2.7 Hz, 1H, H-8), 3.40 (m, 1H, H-1), 3.06 (m, 1H, H-5), 0.86 (s, 9H, C(CH_3)$_3$), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 175.5 (C=O), 140.9 (CH, C-6), 138.8 (CH, C-7), 82.8 (CH, C-4), 64.8 (CH_2, C-8), 43.5 (CH, C-1), 41.2 (CH, C-5), 25.7 (CH_3, C(*C*H_3)$_3$), 18.0 (C, *C*(CH$_3$)$_3$), -5.5 (*C*H_3Si), -5.6 (*C*H_3Si).

4.3.3. (1*S*,4*S*,5*R*)-1-floro-4-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (188), (1*R*,4*S*,5*S*)-1-fluoro-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (189) and (+)- (1*R*,2*S*,5*R*,6*S*,9*S*)-6-fluoro-9-hydroxymethyl-8-oxatricyclo[4.3.0.0^{2,5}]non-3-en-7-one (190)



A solution of 3-fluoro-2(5*H*)-furanone **161** (130 mg, 0.98 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 5.5 h at -20 ºC. The formation of three compounds in a 59:3:38 ratio was observed by GC and NMR. Evaporation of the solvent and column chromatography of the residue (from hexane- EtOAc 6:1 to hexane-EtOAc 4:1) afforded the following fractions: i) a 95:5 mixture of the cyclobutene derivatives **188** and **189** (44 mg, 0.27 mmol, 28% yield) as a colourless oil; ii) the tricyclic derivative **190** (26 mg, 0.15 mmol, 15%) as a colourless oil; and iii) unreacted lactone **161** (45 mg, 0.34 mmol).

188: **IR** (ATR) 3404, 2937, 2878, 1761, 1075; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.57 (ddd, $J_{6,F}$=11.4 Hz, $J_{6,7}$=2.8 Hz, $J_{6,5}$=0.6 Hz, 1H, H-6), 6.43 (ddd, $J_{7,6}$=2.7 Hz, $J_{7,F}$=1.3 Hz, $J_{7,5}$=0.6 Hz, 1H, H-7), 4.38 (dddd, $J_{4,F}$=4.5 Hz, $J_{4,8}$=3.2 Hz, $J_{4,8}$=2.9 Hz, $J_{4,5}$=1.5 Hz, 1H, H-4), 3.94 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=2.9 Hz, 1H, H-8), 3.71 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=3.2 Hz, 1H, H-8), 3.59 (dddd, $J_{5,F}$=2.6 Hz, $J_{5,4}$=1.5 Hz, $J_{5,6}$=0.6 Hz, $J_{5,7}$=0.6 Hz, 1H, H-5); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 171.2, 170.9 (d, $^{2}J_{C\text{-}F}$=28.9 Hz, C=O, C-2), 141.4, 141.2 (d, $^{3}J_{C\text{-}F}$=15.6 Hz, CH, C-6), 138.7, 138.5 (d, $^{2}J_{C\text{-}F}$=26.2 Hz, CH, C-7), 92.9, 90.2 (d, $^{1}J_{C\text{-}F}$=248.2 Hz, C, C-1), 78.3 (s, CH, C-4), 63.5 (s, CH_2, C-8), 49.7, 49.5 (d, $^{2}J_{C\text{-}F}$=16.4 Hz, CH, C-5); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -165.6 to -165.9 (m). **HRMS** (ESI-TOF) Calcd for $[C_7H_7FO_3+Na]^+$: 181.0199. Found: 181.0193.

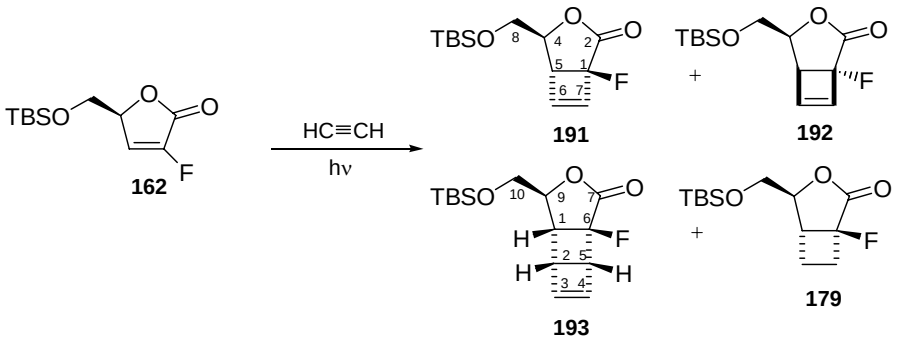
HMQC, HMBC and NOESY experiments were recorded for **188**.

189: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.71 (ddd, $J_{6,F}$=7.9 Hz, $J_{6,7}$=2.9 Hz, $J_{6,5}$=0.7 Hz, 1H, H-6), 6.23 (br d, $J_{7,6}$=2.9 Hz, 1H, H-7), 4.95 (m, 1H, H-4), 3.98 (dd, J_{gem}=12.3 Hz, $J_{8,4}$=2.8 Hz, 1H, H-8), 3.79 (dd, J_{gem}=12.3 Hz, $J_{8,4}$=4.9 Hz, 1H, H-8), 3.60 (m, 1H, H-5).

190: $[\alpha]_D$: +28.9 (*c* 0.44, $CHCl_3$); **IR** (ATR) 3399, 2940, 1762, 1225, 1063; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.45 (m, 1H, H-3), 6.19 (ddd, *J*=2.6 Hz, $J_{4,2}$=2.1 Hz, *J*=0.7 Hz,

1H, H-4), 4.34 (dddd, $J_{9,F}$=6.4 Hz, $J_{9,10}$=4.3 Hz, $J_{9,10}$=3.2 Hz, $J_{9,1}$=1.9 Hz, 1H, H-9), 3.84 (dd, J_{gem}=12.3 Hz, $J_{10,9}$=3.2 Hz, 1H, H-10), 3.78 (m, 1H, H-5), 3.68 (dd, J_{gem}=12.3 Hz, $J_{10,9}$=4.3 Hz, 1H, H-10), 3.56 (dddd, $J_{2,1}$=8.0 Hz, J=5.9 Hz, J=3.4 Hz, $J_{2,4}$=2.1 Hz, 1H, H-2), 3.09 (dddd, $J_{1,F}$=16.9 Hz, $J_{1,2}$=8.0 Hz, $J_{1,9}$=1.9 Hz, $J_{1,3}$=1.0 Hz, 1H, H-5), 2.19 (br s, 1H, OH); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 171.9, 171.6 (d, $^2J_{C-F}$=25.2 Hz, C=O, C-7), 140.7, 140.7 (d, $^4J_{C-F}$=3.3 Hz, CH, C-3), 137.8, 137.8 (d, $^3J_{C-F}$=4.2 Hz, CH, C-4), 97.3, 94.6 (d, $^1J_{C-F}$=238.9 Hz, C, C-6), 82.3, 82.3 (d, $^3J_{C-F}$=3.9 Hz, CH, C-9), 64.0 (s, CH_2, C-10), 50.0, 49.7 (d, $^2J_{C-F}$=49.9 Hz, CH, C-5), 38.4, 38.4 (d, $^3J_{C-F}$=4.6 Hz, CH, C-2), 38.0, 37.9 (d, $^2J_{C-F}$ =16.9 Hz, CH_2, C-1); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -168.0 to -168.2 (m). **HRMS** (ESI-TOF) Calcd for $[C_9H_9FO_3+Na]^+$: 207.0428. Found: 207.0430. COSY, HMQC, HMBC and NOESY experiments were recorded for **190**.

4.3.4. (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]hept-6-en-2-one (191), (1*R*,4*S*,5*S*)-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]hept-6-en-2-one (192), (-)-(1*R*,2*S*,5*R*,6*S*,9*S*)-9-*tert*-butyldimethylsilyloxymethyl-6-fluoro-8-oxatricyclo[4.3.0.0^{2,5}]non-3-en-7-one (193) and (-)-(1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptan-2-one (179)



A solution of 3-fluoro-2(5*H*)-furanone **162** (250 mg, 1.02 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 5 h at -20 ºC. Evaporation of the solvent and purification by chromatography (hexane-diethyl ether 15:1) afforded the following fractions: i) a 80:20 mixture of the cycloadducts **191** and **192** (76 mg, 0.28 mmol, 27% yield) as a colourless oil; ii) the tricyclic derivative **193** (35 mg, 0.12 mmol, 12% yield) as a colourless oil; iii) the cyclobutane **179** (30 mg, 0.11 mmol, 11% yield) as a white solid; and iv) unreacted

lactone **162** (15 mg, 0.06 mmol, 6%). Repetitive column chromatography (from hexane-diethyl ether 30:1 to hexane-diethyl ether 10:1) allowed to isolate **191** as a colourless oil and an enriched fraction of the *syn* isomer **192**.

When the reaction was performed in acetonitrile saturated in acetylene and through a quartz filter, **162** (199 mg, 0.81 mmol) was completely consumed after 2 h. Evaporation of the solvent gave a crude which was purified by column chromatography (hexane:diethyl ether 20:1) to furnish a 95:5 mixture of **191** and **192** (20 mg, 0.07 mmol, 9% yield).

191: **IR** (ATR) 2939, 2858, 1778, 1081, 779; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.54 (ddd, $J_{6,F}$=11.2 Hz, $J_{6,7}$=2.7 Hz, $J_{6,5}$=0.5 Hz, 1H, H-6), 6.41 (ddd, $J_{7,6}$=2.7 Hz, $J_{6,F}$=1.4 Hz, $J_{7,5}$=0.5 Hz, 1H, H-7), 4.32 (dddd, $J_{4,F}$=5.9 Hz, $J_{4,8}$=2.7 Hz, $J_{4,8}$=2.0 Hz, $J_{4,5}$=1.9 Hz, 1H, H-4), 3.92 (dd, J_{gem}=11.1 Hz, $J_{8,4}$=2.7 Hz, 1H, H-8), 3.67 (dd, J_{gem}=11.1 Hz, $J_{8,4}$=2.0 Hz, 1H, H-8), 3.56 (m, 1H, H-5), 0.89 (s, 9H, $(CH_3)_3C$), 0.08 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 170.9, 170.4 (d, $^{2}J_{C\text{-}F}$=28.6 Hz, C=O, C-2), 141.2, 141.0 (d, $^{3}J_{C\text{-}F}$=15.4 Hz, CH, C-6), 139.0, 138.6 (d, $^{2}J_{C\text{-}F}$=26.4 Hz, CH, C-7), 93.3, 89.4 (d, $^{1}J_{C\text{-}F}$=248.6 Hz, C, C-1), 77.8 (s, CH, C-4), 63.8 (s, CH_2, C-8), 50.0, 49.8 (d, $^{2}J_{C\text{-}F}$=16.4 Hz, CH, C-5), 25.5 (s, CH_3, $(CH_3)_3C$), 18.1 (s, C, $(CH_3)_3C$), -5.8 (s, CH_3, CH_3Si), -5.9 (s, CH_3, CH_3Si); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -165.8 to -166.1 (m). **HRMS** (ESI-TOF) Calcd for $[C_{13}H_{21}FO_3Si+Na]^+$: 295.1136. Found: 295.1134.

COSY, HMQC, HMBC and NOESY experiments were recorded for **191**.

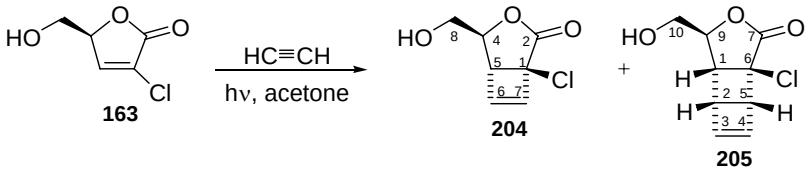
192: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 6.57 (ddd, $J_{6,F}$=11.6 Hz, $J_{6,7}$=2.6 Hz, $J_{6,5}$=0.6 Hz, 1H, H-6), 6.18 (ddd, $J_{7,6}$=2.4 Hz, $J_{7,6}$=2.6 Hz, $J_{7,5}$=0.6 Hz, 1H, H-7), 4.60 (ddd, J =6.6 Hz, J=5.6 Hz, J=5.4 Hz, 1H, H-4), 3.70 (m, 2H, H-8), 3.53 (m, 1H, H-5), 0.89 (s, 9H, $(CH_3)_3C$), 0.08 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si).

193: $[\alpha]_D$: -72.5 (*c* 0.4, $CHCl_3$); **IR** (ATR) 2930, 2858, 1779, 779; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.44 (dd, $J_{4,2}$=2.5 Hz, $J_{4,3}$=2.4 Hz, 1H, H-4), 6.28 (dd, $J_{3,4}$=2.4 Hz, $J_{3,5}$=2.1 Hz, 1H, H-3), 4.27 (ddd, $J_{9,F}$=5.7 Hz, $J_{9,10}$=3.1 Hz, $J_{9,10}$=2.7 Hz, 1H, H-9), 3.81 (dd, J_{gem}=11.2 Hz, $J_{10,9}$=3.1 Hz, 1H, H-10), 3.75 (m, 1H, H-5), 3.67 (dd, J_{gem}=11.2 Hz, $J_{10,9}$=2.6 Hz, 1H, H-10), 3.52 (ddd, $J_{2,1}$=7.9 Hz, $J_{2,5}$=3.1 Hz, $J_{2,4}$=2.1 Hz, 1H, H-2), 3.15 (dd, $J_{1,F}$=19.4 Hz, $J_{1,2}$=7.9 Hz, 1H, H-1), 0.88 (s, 9H, $(CH_3)_3C$), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 171.8, 171.6 (d, $^{2}J_{C\text{-}F}$=27.0 Hz, C=O, C-7), 140.5, 140.5 (d, $^{4}J_{C\text{-}F}$=3.4 Hz, CH, C-4), 137.9, 137.8 (d, $^{3}J_{C\text{-}F}$=4.4 Hz, CH,

C-3), 97.2, 94.5 (d, $^{1}J_{C\text{-}F}$=293.4 Hz, C, C-6), 82.0, 82.0 (d, $^{3}J_{C\text{-}F}$=3.8 Hz, CH, C-9), 64.2 (s, CH_2, C-10), 50.3, 50.0 (d, $^{2}J_{C\text{-}F}$=27.2 Hz, CH, C-5), 38.5, 38.4 (d, $^{3}J_{C\text{-}F}$=4.6 Hz, CH, C-2), 38.2, 38.0 (d, $^{2}J_{C\text{-}F}$ =16.8 Hz, CH_2, C-1), 25.7 (s, CH_3, $(CH_3)_3C$), 18.2 (s, C, $(CH_3)_3C$), -5.5 (s, CH_3, CH_3Si), -5.6 (s, CH_3, CH_3Si); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -168.6 to -168.8 (m). **HRMS** (ESI-TOF) Calcd for $[C_{15}H_{23}FO_3SiM+Na]^+$: 321.1293. Found: 321.1282.

COSY, HMQC, HMBC and NOESY experiments were recorded for **193**.

4.3.5. (-)-(1*S*,4*S*,5*R*)-1-chloro-4-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (204) and (1*R*,2*S*,5*R*,6*S*,9*S*)-6-chloro-9-*tert*-butyldimethylsilyloxymethyl-8-oxatricyclo[4.3.0.0^{2,5}]non-3-en-7-one (205)

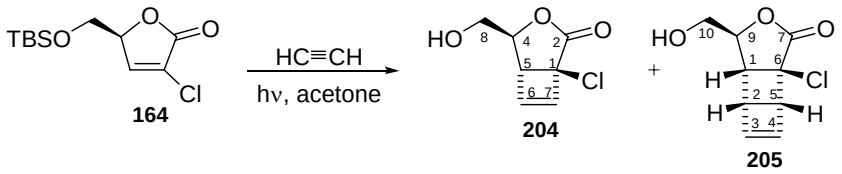


A solution of 3-chloro-2(5*H*)-furanone **163** (149 mg, 1.00 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 4.5 h at -20 ºC. Evaporation of the solvent and purification of the resulting residue by column chromatography (hexane-EtAcO 3:1) afforded the following fractions: i) the cycloadduct **204** (29 mg, 0.17mmol, 17% yield) as a colourless oil**;** the tricyclic derivative **205** (12 mg, 0.06 mmol, 6% yield) as a colourless oil; and iii) unreacted lactone **163** (36 mg, 0.24 mmol, 24%).

204: $[\alpha]_D$: -71.1 (*c* 2.54, $CHCl_3$); **IR** (ATR) 3405, 2933, 1755, 957; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.50 (dd, $J_{6,7}$=2.6 Hz, $J_{6,5}$=0.6 Hz, 1H, H-6), 6.37 (d, $J_{7,6}$=2.6 Hz, 1H, H-7), 4.44 (ddd, $J_{4,8}$=3.5 Hz, $J_{4,8}$=3.0 Hz, $J_{4,5}$=1.5 Hz, 1H, H-4), 3.93 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.0 Hz, 1H, H-8), 3.72 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.5 Hz, 1H, H-8), 3.60 (dd, $J_{5,4}$=1.0 Hz, $J_{5,6}$=0.6 Hz, 1H, H-5), 2.08 (br s, 1H, OH); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 171.5 (C=O, C-2), 140.5 (CH, C-7), 139.7 (CH, C-6), 78.1 (CH, C-4), 64.0 (C, C-1), 63.7 (CH_2, C-8), 53.5 (CH, C-5). **HRMS** (ESI-TOF) Calcd for $[C_7H_7ClO_3+Na]^+$: 196.9976. Found: 196.9972.

HMQC, HMBC and NOESY experiments were recorded for **204**.

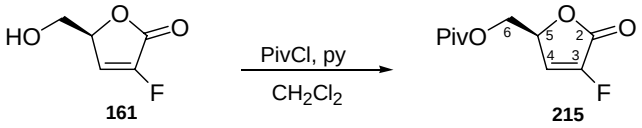
205: **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 6.49 (dd, $J_{3,5}$=2.6 Hz, $J_{3,4}$=2.4 Hz, 1H, H-3), 6.35 (dd, $J_{4,3}$=2.4 Hz, $J_{4,2}$=2.1 Hz, 1H, H-4), 4.39 (ddd, $J_{9,10}$=4.6 Hz, $J_{9,10}$=3.4 Hz, $J_{9,1}$=1.8 Hz, 1H, H-9), 3.81 (dd, J_{gem}=12.3 Hz, $J_{10,9}$=3.4 Hz, 1H, H-10), 3.75 (dd, $J_{5,2}$=2.8 Hz, $J_{5,3}$=2.6 Hz, 1H, H-5), 3.68 (dd, J_{gem}=12.3 Hz, $J_{10,9}$=4.6 Hz, 1H, H-10), 3.65 (ddd, $J_{2,1}$=7.9 Hz, $J_{2,5}$=2.7 Hz, $J_{2,4}$=2.1 Hz, 1H, H-2), 3.15 (dd, $J_{1,2}$=7.9 Hz, $J_{1,9}$=1.8 Hz, 1H, H-5), 1.90 (br s, 1H, OH); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 173.3 (C=O, C-7), 140.2/ 139.7 (2CH, C-3, C-4), 77.2 (CH, C-9), 64.0 (CH_2, C-10), 63.1 (C, C-6), 53.4 (CH, C-1), 43.6 (CH, C-5), 40.1 (CH, C-2). **HRMS** (ESI-TOF) Calcd for $[C_9H_9ClO_3+Na]^+$: 223.0132. Found: 223.0135.



When the reaction was performed irradiating through a pyrex filter a solution of the 3-chloro-2(5*H*)-furanone **164** (90 mg, 0.34 mmol) in freshly distilled acetone (65 mL) with introduction of acetylene for 4.5 h at -20 ºC, evaporation of the solvent followed by column chromatography of the resulting residue (diethyl ether-hexane 12 mg) afforded the bicyclic derivative **204** (15 mg, 0.08 mmol, 26% yield) and the tricyclic compound **205** (6 mg, 0.03 mmol, 9% yield).

4.4. [2+2] Photocycloaddition of 2(5*H*)-furanones to ketene diethyl ketal

4.4.1. (-)-(5*S*)-3-fluoro-5-pivaloyloxymethyl-2(5*H*)-furanone (215)



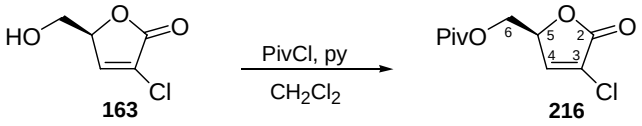
To a solution of **161** (1.00 g, 7.57 mmol) in CH_2Cl_2 (30 mL) at 0 ºC, pyridine (1.09 mL, 15.1 mmol) and pivaloyl chloride (1.50 mL, 13.63 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 19 h. Then, it was diluted with diethyl ether (25 mL) and washed with 1M HCl (3x15 mL), saturated aqueous $NaHCO_3$ solution (3x15 mL) and brine (3x15 mL). The organic layer

was dried (anhydrous Na_2SO_4), filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 5:1) to afford **215** (1.48 g, 6.81 mmol, 90% yield) as a colourless oil**.**

215: $[\alpha]_D$: -97.7 (*c* 2.15, $CHCl_3$); **IR** (ATR) 2974, 1783, 1730, 1681, 1147, 1108; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 6.67 (t, $J_{4,5}$=2.2 Hz, $J_{4,F}$=2.2 Hz, 1H, H-4), 5.18 (dddd, $J_{5,F}$=5.9 Hz, $J_{5,6}$=4.1 Hz, $J_{5,6}$=3.7, $J_{5,4}$=2.0 Hz, 1H, H-5), 4.41 (dd, J_{gem}=12.2 Hz, $J_{6,5}$=4.1 Hz, 1H, H-6), 4.35 (ddd, J_{gem}=12.2 Hz, $J_{6,5}$=3.7 Hz, $J_{6,F}$=1.4 Hz, 1H, H-6), 1.17 (s, 9H, (C*H*$_3$)$_3$C); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 177.9 (C=O), 164.0, 163.6 (d, $^2J_{C-F}$=32.2 Hz, C=O, C-2), 150.6, 147.5 (d, $^1J_{C-F}$=281.0 Hz, C, C-3), 122.3, 122.2 (d, $^2J_{C-F}$=7.2 Hz, CH, C-4), 75.4, 75.3 (d, $^3J_{C-F}$=7.4 Hz, CH, C-5), 61.9, 61.8 (d, $^4J_{C-F}$=2.7 Hz, CH_2, C-6), 38.9 (C, (CH$_3$)$_3$*C*), 27.0 (CH$_3$, (*C*H$_3$)$_3$C); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -139.6 to -139.9 (m). **HRMS** (ESI-TOF) Calcd for $[C_{10}H_{13}FO_4+H]^+$: 217.0871. Found: 217.0868.

DEPT experiment was recorded for **215**.

4.4.2. (-)-(5*S*)-3-chloro-5-pivaloyloxymethyl-2(5*H*)-furanone (216)



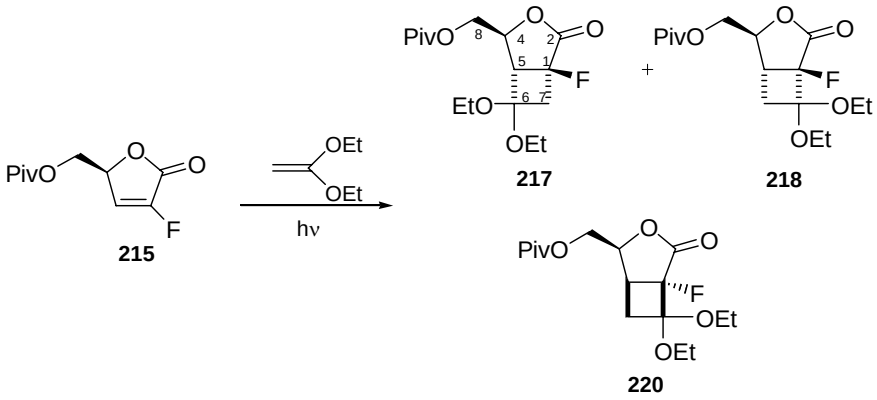
To a solution of **163** (190 mg, 1.28 mmol) in CH_2Cl_2 (5 mL) at 0 ºC, pyridine (190 μL, 2.56 mmol) and pivaloyl chloride (260 μL, 2.30 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 15 h. Then, it was diluted with diethyl ether (8 mL) and was washed with 1M HCl (3x5 mL), saturated aqueous $NaHCO_3$ solution (3x5 mL) and brine (3x5 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAC 10:1) to afford **216** (260 mg, 1.12 mmol, 87% yield) as a colourless oil.

216: $[\alpha]_D$: -88.0 (*c* 1.5, $CHCl_3$); **IR** (ATR) 3099, 2973, 1773, 1729, 1142, 1089; **^{1}H-NMR** (250 MHz, $CDCl_3$) δ 7.26 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 5.20 (ddd, $J_{5,6}$=4.0 Hz, $J_{5,6}$=3.6, $J_{5,4}$=1.9 Hz, 1H, H-5), 4.45 (dd, J_{gem}=12.2 Hz, $J_{6,5}$=4.0 Hz, 1H, H-6), 4.34 (dd, J_{gem}=12.2 Hz, $J_{6,5}$=3.6 Hz, 1H, H-6), 1.16 (s, 9H, (C*H*$_3$)$_3$C); **^{13}C-NMR** (62.5 MHz, $CDCl_3$) δ 178.0 (C=O), 167.1 (C=O, C-2), 143.8 (CH, C-4), 126.5 (C, C-3), 78.7 (CH,

C-5), 61.6 (CH_2, C-6), 39.0 (C, $(CH_3)_3C$), 27.0 (CH_3, $(CH_3)_3C$). **HRMS** (ESI-TOF) Calcd for $[C_{10}H_{13}ClO_4 + H]^+$: 255.0395. Found: 255.0389.

DEPT experiment was recorded for **216**.

4.4.3. (-)-(1*S*,4*S*,5*S*)-6,6-diethoxy-1-fluoro-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (217), (-)-(1*S*,4*S*,5*R*)-7,7-diethoxy-1-fluoro-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (218) and (1*R*,4*S*,5*S*)-7,7-diethoxy-1-fluoro-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (220)



A solution of 3-fluoro-2(5*H*)-furanone **215** (125 mg, 0.58 mmol) and ketene diethyl ketal (0.75 mL, 5.8 mmol) in acetonitrile (65 mL) was irradiated through a quartz filter for 3 h at -40 ºC. Evaporation of the solvent and chromatography of the residue (hexane-diethyl ether 2:1) afforded a 48:42:10 mixture of the cycloadducts **217, 218** and **220** (82 mg, 0.25 mmol, 43% yield) and unreacted lactone **215** (20 mg, 0.11 mmol, 16%). Repetitive column chromatography (from hexane-diethyl ether 10:1 to hexane-diethyl ether 1:1) gave analytical samples of **217** as a colourless oil, **218** as a colourless oil and an enriched mixture of **220** as a colourless oil**.**

When the irradiation was performed through a quartz filter in diethyl ether (65 mL) for 3 h, from lactone **215** (124 mg, 0.57 mmol) and ketene diethyl ketal (0.75 mL, 5.8 mmol) after purification of the crude material by column chromatography, a 83:17 mixture of **217** and **218** (40 mg, 0.12 mmol, 21% yield) was obtained.

217: $[\alpha]_D$: -48.6 (*c* 1.4, $CHCl_3$); **IR** (ATR) 2976, 1791, 1733, 1252; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.98 (m, 1H, H-4), 4.32 (dd, J_{gem}=12.4 Hz, $J_{8,4}$=3.1 Hz, 1H, H-8), 4.17 (dd, J_{gem}=12.4 Hz, $J_{8,4}$=3.0 Hz, 1H, H-8), 3.45 (m, 2H, OCH_2CH_3), 3.36 (m, 2H,

OC*H*$_2$CH$_3$), 3.16 (m, 1H, H-5), 3.16 (ddd, J_{gem}=14.2 Hz, $J_{7,F}$=7.6 Hz, $J_{7,5}$=1.1 Hz, 1H, H-7), 3.16 (ddd, $J_{7,F}$=19.0 Hz, J_{gem}=14.2 Hz, $J_{7,5}$=2.5 Hz, 1H, H-7), 1.32-1.09 (m, 15H, (C*H*$_3$)$_3$C, 2OCH$_2$C*H*$_3$); **^{13}C-NMR** (90 MHz, CDCl$_3$) δ 178.2 (s, C=O) 172.3, 172.0 (d, $^2J_{C-F}$=25.8 Hz, C=O, C-2), 93.5, 93.3 (d, $^3J_{C-F}$=21.8 Hz, C, C-6), 87.9, 85.2 (d, $^1J_{C-F}$=235.0 Hz, C, C-1), 75.0 (s, CH, C-4), 64.5 (s, CH$_2$, C-8), 57,7 (s, CH$_2$, O*C*H$_2$CH$_3$), 57,0 (s, CH$_2$, O*C*H$_2$CH$_3$), 51.8, 51.6 (d, $^2J_{C-F}$=17.8 Hz, CH, C-5), 42.1, 41.8 (d, $^2J_{C-F}$=25.1 Hz, CH, C-7), 38.9 (s, C, (CH$_3$)$_3$*C*), 27.0 (s, CH$_3$, (*C*H$_3$)$_3$C), 14.8 (s, CH$_3$, OCH$_2$*C*H$_3$), 14.8 (s, CH$_3$, OCH$_2$*C*H$_3$); **^{19}F-NMR** (235 MHz, CDCl$_3$) δ -163.9 to -164.2 (m). **HRMS** (ESI-TOF) Calcd for [C$_{16}$H$_{25}$FO$_6$+Na]$^+$: 355.1527. Found: 355.1515 (mixture of **217** and **218**).

COSY, HMQC, HMBC and NOESY experiments were recorded for **217**.

218: [α]$_D$: -10.0 (*c* 1.6, CHCl$_3$); **IR** (ATR) 2976, 1790, 1733, 1149; **^{1}H-NMR** (360 MHz, CDCl$_3$) δ 4.58 (m, 1H, H-4), 4.30 (dd, J_{gem}=12.4 Hz, $J_{8,4}$=2.9 Hz, 1H, H-8), 4.13 (dd, J_{gem}=12.4 Hz, $J_{8,4}$=2.9 Hz, 1H, H-8), 3.67 (m, 2H, OC*H*$_2$CH$_3$), 3.52 (m, 2H, OC*H*$_2$CH$_3$), 2.89 (dddd, $J_{5,F}$=16.7 Hz, $J_{5,6}$=10.5 Hz, $J_{5,6}$=6.1 Hz, $J_{5,4}$=1.0 Hz, 1H, H-5), 2.71 (ddd, J_{gem}=13.1 Hz, $J_{6,5}$=10.5 Hz, $J_{6,F}$=7.0 Hz, 1H, H-6exo), 1.87 (dd, J_{gem}=13.1 Hz, $J_{6,5}$=6.1 Hz, 1H, H-6endo), 1.27-1.16 (m, 15H, (C*H*$_3$)$_3$C, 2OCH$_2$C*H*$_3$); **^{13}C-NMR** (90 MHz, CDCl$_3$) δ 178.2 (s, C=O) 169.8, 169.5 (d, $^2J_{C-F}$=24.1 Hz, C=O, C-2), 99.5, 99.2 (d, $^2J_{C-F}$=21.6 Hz, C, C-7), 98.0, 95.1 (d, $^1J_{C-F}$=253.6 Hz, C, C-1), 81.2 (s, CH, C-4), 64.6 (s, CH$_2$, C-8), 58.9 (s, CH$_2$, O*C*H$_2$CH$_3$), 58.4, 58.3 (d, $^4J_{C-F}$=2.2 Hz, CH$_2$, O*C*H$_2$CH$_3$), 38.9 (s, C, (CH$_3$)$_3$*C*), 35.3, 35.1 (d, $^2J_{C-F}$=18.7 Hz, CH, C-5), 33.2, 33.0 (d, $^3J_{C-F}$=11.0 Hz, CH, C-6), 26.9 (s, CH$_3$, (*C*H$_3$)$_3$C), 15.1 (s, CH$_3$, OCH$_2$*C*H$_3$), 14.8 (s, CH$_3$, OCH$_2$*C*H$_3$); **^{19}F-NMR** (235 MHz, CDCl$_3$) δ -169.4 to -169.8 (m).

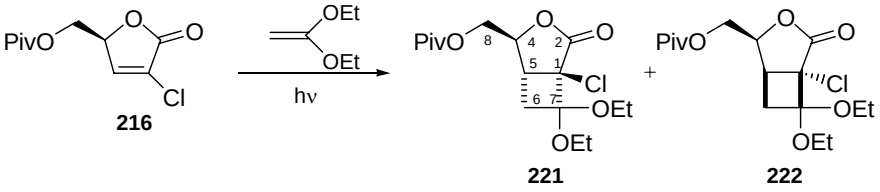
COSY, HMQC, HMBC and NOESY experiments were recorded for **218**.

220: **IR** (ATR) 2974, 1794, 1731, 1147; **^{1}H-NMR** (360 MHz, CDCl$_3$) δ 4.85 (ddd, $J_{4,5}$=5.9 Hz, $J_{4,8}$=5.9 Hz, $J_{4,8}$=5.9 Hz, 1H, H-4), 4.25 (m, 2H, H-8), 3.77-3.48 (m, 4H, 2OC*H*$_2$CH$_3$), 3.09 (m, 1H, H-5), 2.44 (m, 1H, H-6exo), 1.86 (dd, J_{gem}=13.2 Hz, $J_{6,5}$=7.3 Hz, 1H, H-6endo), 1.28-1.17 (m, 15H, (C*H*$_3$)$_3$C, 2OCH$_2$C*H*$_3$); **^{13}C-NMR** (90 MHz, CDCl$_3$) δ 177.9 (s, C=O) 169.4 (C=O, C-2), 99.0, 98.8 (d, $^2J_{C-F}$=21.7 Hz, C, C-7), 97.6, 95.0 (d, $^1J_{C-F}$=230.6 Hz, C, C-1), 77.1 (s, CH, C-4), 62.1 (s, CH$_2$, C-8), 59.2 (s, CH$_2$, O*C*H$_2$CH$_3$), 58.1 (s ,CH$_2$, O*C*H$_2$CH$_3$), 38.7 (s, C, (CH$_3$)$_3$*C*), 35.7, 35.5 (d, $^2J_{C-F}$=18.7 Hz, CH, C-5), 30.2, 30.1 (d, $^3J_{C-F}$=11.6 Hz, CH, C-6), 27.0 (s, CH$_3$, (*C*H$_3$)$_3$C), 15.0 (s,

CH_3, OCH_2CH_3), 14.8 (s, CH_3, OCH_2CH_3); **^{19}F-NMR** (235 MHz, $CDCl_3$) δ -169.9 to -170.3 (m).

COSY, HMQC and HMBC experiments were recorded for **220**.

4.4.4. (+)-(1*S*,4*S*,5*R*)-1-chloro-7,7-diethoxy-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (221) and (1*R*,4*S*,5*S*)-1-chloro-7,7-diethoxy-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (222)



A solution of 3-chloro-2(5*H*)-furanone **216** (150 mg, 0.64 mmol) and ketene diethyl ketal (0.80 mL, 6.4 mmol) acetonitrile (65 mL) was irradiated through a quartz filter for 2.25 h at -40 ºC. Evaporation of the solvent followed by purification by column chromatography of the resulting residue (hexane-diethyl ether 2:1) afforded a 75:25 mixture of **221** and **222** (80 mg, 0.23 mmol, 36% yield) and unreacted lactone **216** (30 mg, 0.13 mmol, 20%). Repetitive column chromatography (from hexane-diethyl ether 10:1 to hexane-diethyl ether 1:1) allowed to isolate analytical samples of **221** as a colourless oil and **222** as a colourless oil.

When the reaction was performed in acetonitrile for 1 h, only the presence of starting material and the major cycloadduct **221** could be confirmed by NMR and GC, along with many undefined signals.

When the reaction was performed irradiating through a quartz filter a solution of **216** (135 mg, 0.58 mmol) and ketene diethyl ketal (0.75 mL, 5.8 mmol) in diethyl ether (65 mL) for 3 h at -40 ºC, evaporation of the solvent and purification by chromatography of the resulting residue (hexane-diethyl ether 2:1) afforded **221** (21 mg, 0.06 mmol, 10% yield).

The reaction was also carried in diethyl ether during 1.25 h at -40 ºC and aliquots were taken every 15 minutes. In all cases only the presence of starting material and the cycloadduct **221** could be confirmed by NMR and GC, along with many undefined signals.

221: $[\alpha]_D$: +9.4 (*c* 1.6, $CHCl_3$); **IR** (ATR) 2976, 1783, 1731, 1142; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.57 (ddd, $J_{4,8}$=5.4 Hz, $J_{4,8}$=4.1 Hz, $J_{4,5}$=1.6 Hz, 1H, H-4), 4.24 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=4.1 Hz, 1H, H-8), 4.13 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=5.4 Hz, 1H, H-8), 3.74 (m, 1H, OC*H*$_2$CH$_3$), 3.57 (m, 3H, OC*H*$_2$CH$_3$), 2.81 (dd, J_{gem}=12.0 Hz, $J_{6,5}$=9.9 Hz, 1H, H-6exo), 2.75 (ddd, $J_{5,6}$=9.9 Hz, $J_{5,6}$=4.6 Hz, $J_{5,4}$=1.6 Hz, 1H, H-5), 2.11 (dd, J_{gem}=12.0 Hz, $J_{6,5}$=4.6 Hz, 1H, H-6endo), 1.29-1.15 (m, 15H, (C*H*$_3$)$_3$C, 2OCH$_2$C*H*$_3$); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 178.2 (s, C=O) 171.1 (C=O, C-2), 99.3 (C, C-7), 81.1 (CH, C-4), 68.3 (C, C-1), 64.3 (CH_2, C-8), 59.0 (CH_2, O*C*H$_2$CH$_3$), 57.9 (CH_2, O*C*H$_2$CH$_3$), 38.9 (C, (CH$_3$)$_3$*C*), 38.8 (CH, C-5), 35.3 (CH, C-6), 27.0 (CH_3, (*C*H$_3$)$_3$C), 14.9 (CH_3, OCH$_2$*C*H$_3$), 14.8 (CH_3, OCH$_2$*C*H$_3$). **HRMS** (ESI-TOF) Calcd for $[C_{16}H_{25}ClO_6+Na]^+$: 371.1232. Found: 371.1225.

COSY, HMQC, HMBC and NOESY experiments were recorded for **221**.

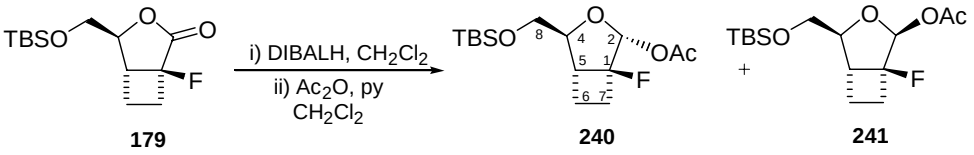
222: **IR** (ATR) 2975, 1789, 1732, 1142; **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 4.80 (m, 1H, H-4), 4.23 (m, 2H, H-8), 3.85 (m, 1H, OC*H*$_2$CH$_3$), 3.59 (m, 3H, OC*H*$_2$CH$_3$), 2.93 (ddd, $J_{5,6}$=9.6 Hz, $J_{5,6}$=7.8 Hz, $J_{5,4}$=5.1 Hz, 1H, H-5), 2.56 (dd, J_{gem}=13.1 Hz, $J_{6,5}$=9.6 Hz, 1H, H-6exo), 2.08 (dd, J_{gem}=13.1 Hz, $J_{6,5}$=7.8 Hz, 1H, H-6endo), 1.31-1.13 (m, 15H, (C*H*$_3$)$_3$C, 2 OCH$_2$C*H*$_3$); **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 178.2 (s, C=O) 171.1 (C=O, C-2), 98.1 (C, C-7), 76.5 (CH, C-4), 67.3 (C, C-1), 62.0 (CH_2, C-8), 59.3 (CH_2, O*C*H$_2$CH$_3$), 57.6 (CH_2, O*C*H$_2$CH$_3$), 39.6 (CH, C-5), 38.8 (C, (CH$_3$)$_3$*C*), 29.3 (CH, C-6), 27.1 (CH_3, (*C*H$_3$)$_3$C), 15.0 (CH_3, OCH$_2$*C*H$_3$), 14.7 (CH_3, OCH$_2$*C*H$_3$). **HRMS** (ESI-TOF) Calcd for $[C_{16}H_{25}ClO_6+Na]^+$: 371.1232. Found: 371.1225.

DEPT, HMQC and HMBC experiments were recorded for **222**.

5. Synthesis of cyclobutane-fused chloro and fluoronucleoside analogues

5.1. Synthesis of cyclobutane-fused fluoronucleoside analogues

5.1.1. (+)-(1*S*,2*R*,4*S*,5*R*)-2-acetyloxy-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptane (240) and (-)-(1*S*,2*S*,4*S*,5*R*)-2-acetyloxy-4-*tert*-butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptane (241)



179 **240** **241**

To a solution of **179** (1.79 g, 6.52 mmol) in dry CH_2Cl_2 (30 mL) at -78 ºC, a 1.0 M solution of DIBAL-H in CH_2Cl_2 (9.3 mL, 9.3 mmol) was added dropwise. After 2.5 h of stirring at -78 ºC, the reaction mixture was quenched by the slow addition of an aqueous HNO_3 3% solution (25 mL) and allowed to warm to room temperature. The two layers were separated and the aqueous was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude and pyridine (7.4 mL, 92.7 mmol) in CH_2Cl_2 (50 mL), acetic anhydride (5.9 mL, 61.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with HCl 3% (3x20 mL), saturated $NaHCO_3$ solution (3x20 mL) and brine (3x20 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The resulting crude residue was purified by column chromatography (hexane-diethyl ether 10:1) to afford a 84:16 mixture of acetates **240** and **241** (1.84 g, 5.78 mmol, 89% yield for the 2 steps). A further column chromatography (from hexane-diethyl ether 20:1 to hexane-diethyl ether 5:1) allowed to isolate pure α-acetate **240** and β-acetate **241** both as colourless oils.

240: $[\alpha]_D$: +22.4 (*c* 1.25, $CHCl_3$); **IR** (ATR) 2929, 1752, 1222, 1105; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 6.31 (d, $J_{2,F}$=14.5 Hz, 1H, H-2), 4.14 (dddd, $J_{4,8}$=5.6 Hz, $J_{4,8}$=4.2 Hz, $J_{4,5}$=2.1 Hz, $J_{4,F}$=2.1 Hz, 1H, H-4), 3.67 (dd, J_{gem}=10.7 Hz, $J_{8,4}$=4.2 Hz, 1H, H-8), 3.61 (dd, J_{gem}=10.7 Hz, $J_{8,4}$=5.6 Hz, 1H, H-8), 3.01 (m, 1H, H-5), 2.40 (m, 1H, H-7endo), 2.30 (m, 1H, H-7exo), 2.15 (m, 4H, H-6exo, C*H*$_3$CO), 1.50 (m, 1H, H-6endo), 0.89 (s,

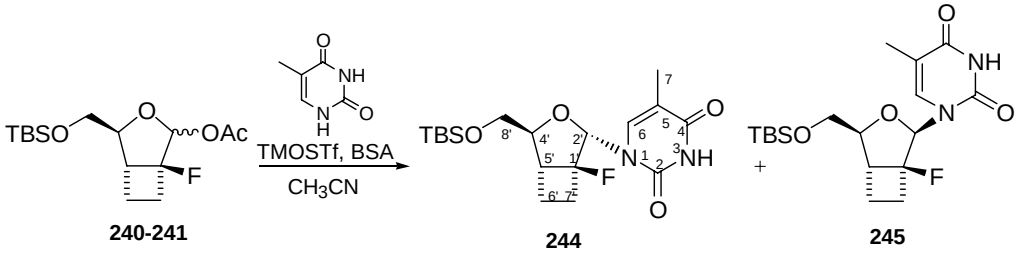
9H, (C*H*$_3$)$_3$C), 0.06 (s, 3H, C*H*$_3$Si), 0.05 (s, 3H, C*H*$_3$Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 169.5 (s, C=O), 104.1, 101.4 (d, $^1J_{C\text{-}F}$=234.2 Hz, C, C-1), 101.3, 100.8 (d, $^2J_{C\text{-}F}$=42.0 Hz, CH, C-2), 87.1 (s, CH, C-4), 64.6 (s, CH_2, C-8), 46.0, 45.7 (d, $^2J_{C\text{-}F}$=18.9 Hz, CH, C-5), 26.0, 25.8 (d, $^2J_{C\text{-}F}$=20.2 Hz, CH_2, C-7), 25.8 (s, CH_3, (*C*H$_3$)$_3$C), 21.0 (s, CH_3, *C*H$_3$CO), 18.3 (s, C, (CH$_3$)$_3$*C*), 16.4, 16.2 (d, $^3J_{C\text{-}F}$=17.4 Hz, CH_2, C-6), -5.4 (s, CH_3, *C*H$_3$Si), -5.5 (s, CH_3, *C*H$_3$Si); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -144.1 to -144.4 (m). **HRMS** (ESI-TOF) Calcd for $[C_{15}H_{27}FO_4Si+Na]^+$: 341.1555 . Found: 341.1550.

COSY, HMQC, HMBC and NOESY experiments were recorded for **240**.

241: $[\alpha]_D$: -78.3 (*c* 0.60, $CHCl_3$); **IR** (ATR) 2929, 1748, 1229, 1100, 1010; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 6.18 (s, 1H, H-2), 4.05 (ddd, $J_{4,8}$=8.4 Hz, $J_{4,8}$=5.7 Hz, $J_{4,F}$=3.0 Hz, 1H, H-4), 3.71 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=5.7 Hz, 1H, H-8), 3.56 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=8.4 Hz, 1H, H-8), 3.01 (m, 1H, H-5), 2.49 (m, 1H, H-7exo), 2.36 (m, 1H, H-7endo), 2.24 (m, 1H, H-6exo), 2.08 (s, 3H, C*H*$_3$CO), 1.50 (m, 1H, H-6endo), 0.88 (s, 9H, (C*H*$_3$)$_3$C), 0.07 (s, 3H, C*H*$_3$Si), 0.06 (s, 3H, C*H*$_3$Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 169.7 (s, C=O), 100.5, 97.8 (d, $^1J_{C\text{-}F}$=243.7 Hz, C, C-1), 99.4, 99.2 (d, $^2J_{C\text{-}F}$=18.2 Hz, CH, C-2), 87.5, 87.4 (d, $^3J_{C\text{-}F}$=2.8 Hz, CH, C-4), 64.5 (s, CH_2, C-8), 44.3, 44.1 (d, $^2J_{C\text{-}F}$=19.4 Hz, CH, C-5), 28.8, 28.6 (d, $^2J_{C\text{-}F}$=23.9 Hz, CH_2, C-7), 25.9 (s, CH_3, (*C*H$_3$)$_3$C), 21.2 (s, CH_3, *C*H$_3$CO), 18.3 (s, C, (CH$_3$)$_3$*C*), 17.0, 16.8 (d, $^3J_{C\text{-}F}$=12.7 Hz, CH_2, C-6), -5.3 (s, CH_3, *C*H$_3$Si), -5.4 (s, CH_3, *C*H$_3$Si); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -155.7 to -155.9 (m). **HRMS** (ESI-TOF) Calcd for $[C_{15}H_{27}FO_4Si+Na]^+$: 341.1555. Found: 341.1542.

COSY, HMQC, HMBC and NOESY experiments were recorded for **241**.

5.1.2. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-1-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (244) and (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-1-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (245)



240-241 244 245

N,O-Bis(trimethylsilyl)acetamide (BSA) (243 µl, 0.96 mmol) was added to a suspension of thymine (48 mg, 0.38 mmol) in dry acetonitrile (1.5 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 ºC. Then, a solution of a mixture of **240** and **241** (100 mg, 0.31 mmol) in dry acetonitrile (1 mL) and TMSOTf (86 µl, 0.45 mmol) were successively added and the reaction mixture was stirred at room temperature for 24 h. CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (2 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 3:1) to afford a 53:47 mixture of **244** and **245** (85 mg, 0.22 mmol, 72% yield). Successive column chromatography (from hexane-EtOAc 10:1 to hexane-EtOAc 4:1) allowed to isolate pure samples of the α-anomer **244** as a white solid and the β-anomer **245** also as a white solid.

244: $[\alpha]_D$: -38.3 (*c* 1.8, $CHCl_3$); **IR** (ATR) 3188, 2592, 1690, 1099; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.73 (br s, 1H, NH), 7.45 (m, *J*=1.2 Hz, 1H, H-6), 6.24 (dd, $J_{2',F}$=14.9 Hz, *J*=1.0 Hz, 1H, H-2'), 4.24 (ddd, $J_{4',8'}$=4.8 Hz, $J_{4',8'}$=4.4 Hz, $J_{4',F}$=4.4 Hz, 1H, H-4'), 3.73 (dd, J_{gem}=10.8 Hz, $J_{8',4'}$=4.8 Hz, 1H, H-8'), 3.69 (dd, J_{gem}=10.8 Hz, $J_{8',4'}$=4.4 Hz, 1H, H-8'), 3.1 (m, 1H, H-5'), 2.38 (m, 1H, H-7'exo), 2.22 (m, 1H, H-6'exo), 1.98 (m, 4H, H-7'endo, C*H*$_3$-C5), 1.27 (m, 1H, H-6'endo), 0.91 (s, 9H, (C*H*$_3$)$_3$C), 0.09 (s, 3H, C*H*$_3$Si), 0.08 (s, 3H, C*H*$_3$Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.5 (s, C=O, C-4), 150.0 (s, C=O, C-2), 134.7 (s, CH, C-6), 110.0 (s, C, C-5), 103.4, 100.7 (d, $^1J_{C-F}$=238.6 Hz, C, C-1'), 91.6, 91.1 (d, $^2J_{C-F}$=40.5 Hz, CH, C-2'), 86.1, 86.1 (d, $^3J_{C-F}$=1.1 Hz, CH, C-4'), 64.7 (s, CH_2, C-8'), 45.7, 45.4 (d, $^2J_{C-F}$=19.1 Hz, CH, C-5'), 25.8 (s, CH_3, (*C*H$_3$)$_3$C), 25.8, 25.6 (d, $^2J_{C-F}$=25.7 Hz, CH_2, C-7'), 18.3 (s, C, (CH$_3$)$_3$*C*), 15.8, 15.6 (d, $^3J_{C-F}$=16.3 Hz, CH_2, C-6'), 12.7 (s, CH_3, *C*H$_3$-C5), -5.5 (s, CH_3, 2*C*H$_3$Si); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -140.5 to -140.8 (m). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{29}FN_2O_4Si+H]^+$: 385.1953. Found: 385.1956 (mixture of **244** and **245**).

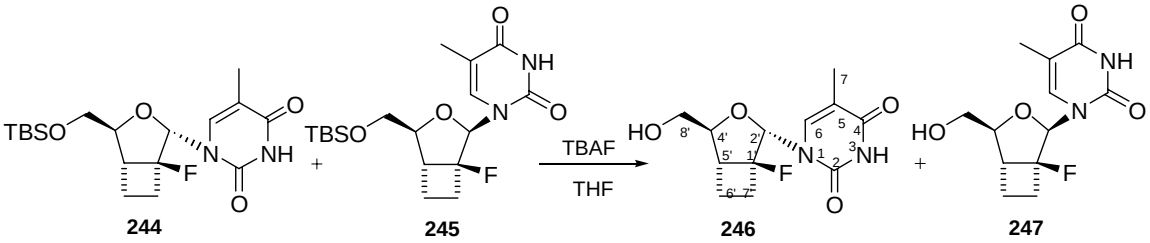
COSY, HMQC, HMBC and NOESY experiments were recorded for **244**.

245: mp 108-110 ºC (from EtOAc-hexane); $[\alpha]_D$: +11.3 (*c* 1.6, $CHCl_3$); **IR** (ATR) 3174, 2928, 1685, 1661, 1096; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.87 (br s, 1H, NH), 7.52 (dd, *J*=1.9 Hz, *J*=1.1 Hz, 1H, H-6), 6.23 (d, $J_{2',F}$=13.0 Hz, 1H, H-2'), 4.08 (ddd, $J_{4',5'}$=5.5 Hz, $J_{4',8'}$=3.6 Hz, $J_{4',8'}$=3.3 Hz, 1H, H-4'), 3.84 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.3 Hz, 1H, H-8'), 3.67 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.6 Hz, 1H, H-8'), 3.09 (m, 1H, H-5'),

2.53 (m, 1H, H-7'endo), 2.42 (m, 1H, H-7'exo), 2.25 (m, 1H, H-6'exo), 1.91 (d, *J*=1.1 Hz, 3H, C*H*$_3$-C5), 1.47 (m, 1H, H-6'endo), 0.92 (s, 9H, (C*H*$_3$)$_3$C), 0.10 (s, 3H, C*H*$_3$Si), 0.09 (s, 3H, C*H*$_3$Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.9 (s, C=O, C-4), 150.6 (s, C=O, C-2), 136.9 (s, CH, C-6), 109.5 (s, C, C-5), 99.3, 96.5 (d, $^1J_{C\text{-}F}$=250.1 Hz, C, C-1'), 89.8, 89.6 (d, $^2J_{C\text{-}F}$=18.1 Hz, CH, C-2'), 85.0 (s, CH, C-4'), 64.2 (s, CH_2, C-8'), 47.0, 46.8 (d, $^2J_{C\text{-}F}$=17.1 Hz, CH, C-5'), 28.6, 28.3 (d, $^2J_{C\text{-}F}$=21.7 Hz, CH_2, C-7'), 25.8 (s, CH_3, (*C*H$_3$)$_3$C), 18.3 (s, C, (CH$_3$)$_3$*C*), 16.7, 16.5 (d, $^3J_{C\text{-}F}$=19.9 Hz, CH_2, C-6'), 12.4 (s, CH_3, *C*H$_3$-C5), -5.5 (s, CH_3, 2*C*H$_3$Si); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -149.5 to -149.7 (m).

COSY, HMQC, HMBC and NOESY experiments were recorded for **245**.

5.1.3. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-1-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (246) and (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-1-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (247)



To a 53:47 solution of **244** and **245** (98 mg, 0.26 mmol) in THF (3 mL), a 1.0 M solution of TBAF in THF (0.55 mL, 0.55 mmol) was added and the resulting solution was stirred for 2.5 h. After removal of the solvent, the residue was purified by column chromatography (from EtOAc-hexane 1:1 to EtOAc-hexane 2:1) to give **246** (30 mg, 0.11 mmol, 43% yield) as a white solid and **247** (29 mg, 0.11 mmol, 41%) as a white solid.

246: mp: 73-76 ºC (from diethyl ether); $[\alpha]_D$: -103.3 (*c* 0.30, $CHCl_3$); **IR** (ATR) 3399, 3179, 2951, 1665, 1266, 1120; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.80 (br s, 1H, NH), 7.44 (m, *J*=1.1 Hz, 1H, H-6), 6.23 (dd, $J_{2',F}$=15.2 Hz, *J* =0.7 Hz, 1H, H-2'), 4.3 (ddd, $J_{4',8'}$=6.8 Hz, $J_{4',F}$=5.2 Hz, $J_{4',8'}$=4.2 Hz, 1H, H-4'), 3.74 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=6.8 Hz, 1H, H-8'), 3.68 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=4.2 Hz, 1H, H-8'), 3.02 (m, 1H, H-5'), 2.41 (m, 1H, H-7'exo), 2.24 (m, 1H, H-6'exo), 1.98 (m, 5H, H-7'endo, C*H*$_3$-C5, OH),

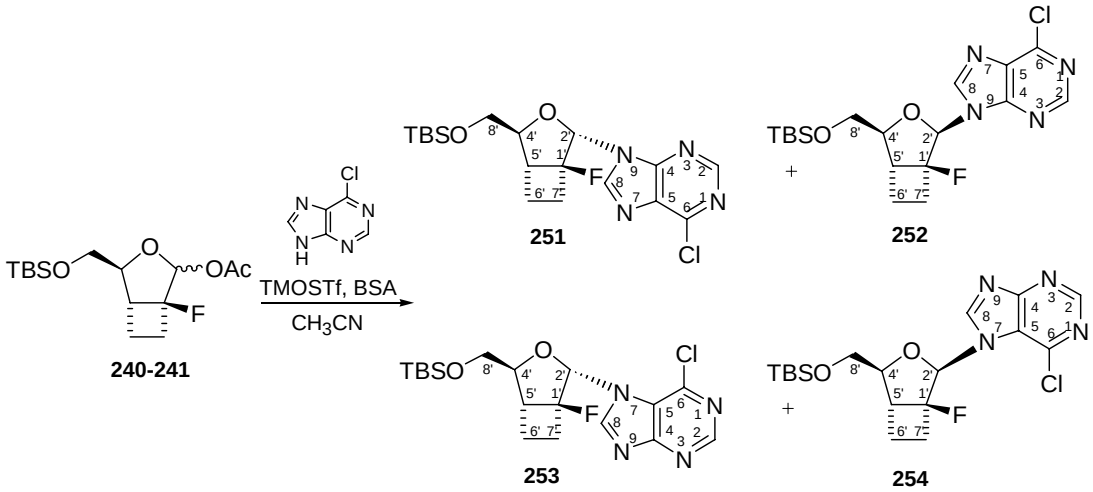
1.29 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.5 (s, C=O, C-4), 150.1 (s, C=O, C-2), 134.6 (s, CH, C-6), 110.3 (s, C, C-5), 103.4, 100.7 (d, $^1J_{C-F}$=238.4 Hz, C, C-1'), 91.2, 90.7 (d, $^2J_{C-F}$ =41.0 Hz, CH, C-2'), 86.2 (s, CH, C-4'), 63.7 (s, CH_2, C-8'), 45.3, 45.1 (d, $^2J_{C-F}$=19.1 Hz, CH, C-5'), 25.8, 25.6 (d, $^2J_{C-F}$=23.1 Hz, CH_2, C-7'), 15.6, 15.5 (d, $^3J_{C-F}$=16.3 Hz, CH_2, C-6'), 12.7 (s, CH_3, *C*H_3-C5); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -140.4 to -140.6 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{15}FN_2O_4+Na]^+$: 293.0908. Found: 293.0909.

COSY, HMQC, HMBC and NOESY experiments were recorded for **246**.

247: mp: 147-149 ºC (from diethyl ether); $[\alpha]_D$: +25.5 (*c* 0.55, $CHCl_3$); **IR** (ATR) 3353, 2926, 1699, 1648, 1280, 1102; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.84 (br s, 1H, NH), 7.46 (m, *J*=1.2 Hz, 1H, H-6), 6.25 (d, $J_{2',F}$=13.4 Hz, 1H, H-2'), 4.13 (ddd, $J_{4',F}$=8.0 Hz, $J_{4',8'}$=5.4 Hz, $J_{4',8'}$=3.3 Hz, 1H, H-4'), 3.85 (dd, J_{gem}=11.8 Hz, $J_{8',4'}$=3.3 Hz, 1H, H-8'), 3.72 (dd, J_{gem}=11.8 Hz, $J_{8',4'}$=5.4 Hz, 1H, H-8'), 3.06 (m, 1H, H-5'), 2.55 (m, 1H, H-7'endo), 2.42 (m, 1H, H-7'exo), 2.23 (m, 1H, 6'exo), 1.91 (m, 4H, CH_3-C5, OH), 1.51 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.8 (s, C=O, C-4), 150.6 (s, C=O, C-2), 136.9, 136.8 (d, $^4J_{C-F}$=3.4 Hz, CH, C-6), 109.9 (s, C, C-5), 99.5, 96.7 (d, $^1J_{C-F}$=248.6 Hz, C, C-1'), 89.2, 89.1 (d, $^2J_{C-F}$=17.2 Hz, CH, C-2'), 84.6 (s, CH, C-4'), 64.0 (s, CH_2, C-8'), 46.8, 46.6 (d, $^2J_{C-F}$=18.6 Hz, CH, C-5'), 28.4, 28.2 (d, $^2J_{C-F}$=22.5 Hz, CH_2, C-7'), 16.9, 16.7 (d, $^3J_{C-F}$=18.0 Hz, CH_2, C-6'), 12.6 (s, CH_3, *C*H_3-C5); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -149.4 to -149.7 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{15}FN_2O_4+Na]^+$: 293.0908. Found: 293.0906.

COSY, HMQC, HMBC and NOESY experiments were recorded for **247**.

5.1.4. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-9-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (251), (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-9-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (252), (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-7-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (253), and (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-7-(4'-*tert*-butyldimethylsilyloxymethyl-1'-fluoro-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (254)



N,O-Bis(trimethylsilyl)acetamide (BSA) (567 µl, 2.10 mmol) was added to a suspension of 6-chloropurine (172 mg, 1.10 mmol) in dry toluene (4 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 ºC. Then, a solution of a mixture of **240** and **241** (245 mg, 0.77 mmol) in dry toluene (2 mL) and TMSOTf (175 µl, 0.95 mmol) were successively added and the reaction mixture was stirred at 100 ºC for 1 h. Then, after allowing the solution to cool to room temperature, CH_2Cl_2 (10 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (4 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (from hexane-EtOAc 10:1 to hexane-EtOAc 2:1) to afford, the following fractions: i) **251** (94 mg, 0.23 mmol, 30% yield) as a colourless oil; ii) **252** (161 mg, 0.39 mmol, 53% yield) as a white solid; iii) **253** (9 mg, 0.02 mmol, 3% yield) as a colourless oil; and iv) **254** (9 mg, 0.02 mmol, 3% yield) as a yellow solid.

251: mp: decomposes over 60 ºC; $[\alpha]_D$: -13.8 (*c* 1.60, $CHCl_3$); **IR** (ATR) 3108, 2928, 1588, 1561, 1090; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.77 (s, 1H, H-2), 8.42 (s, 1H, H-8), 6.63 (d, $J_{2',F}$=15.6 Hz, 1H, H-2'), 4.33 (ddd, $J_{4',F}$=4.3 Hz, $J_{4',8'}$=4.1 Hz, $J_{4',8'}$=3.5 Hz, 1H, H-4'), 3.86 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=4.1 Hz, 1H, H-8'), 3.74 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=3.5 Hz, 1H, H-8'), 3.33 (m, 1H, H-5'), 2.29 (m, 2H, H-6'exo, H-7'exo), 1.59 (m, 1H, H-7'endo), 1.48 (m, 1H, H-6'endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.11 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 152.4 (s, CH, C-2), 151.1/151.1 (2s, 2C, C-4/C-6), 142.6 (s, CH, C-8), 132.0 (s, C, C-5), 103.9, 100.0 (d, $^1J_{C-F}$=238.5 Hz, C, C-1'), 91.9, 91.3 (d, $^2J_{C-F}$=40.7 Hz, CH, C-2'), 86.1, 86.0 (d, $^3J_{C-F}$=2.0 Hz, CH, C-4'), 65.1 (s, CH_2, C-8'), 46.0, 45.7 (d, $^2J_{C-F}$=18.8 Hz, CH, C-5'), 25.8 (s, CH_3, $(CH_3)_3C$), 25.8, 25.5 (d, $^2J_{C-F}$=24.6 Hz, CH_2, C-7'), 18.3 (s, C, $(CH_3)_3C$), 16.2, 15.9 (d, $^3J_{C-F}$=15.5 Hz, CH_2, C-6'), -5.5 (s, CH_3, $2CH_3Si$); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -142.7 to -143.1 (m). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}ClFN_4O_2Si+Na]^+$: 435.1390. Found: 435.1379.

COSY, HMQC, HMBC, NOESY and n.O.e. differential experiments were recorded for **251**.

252: $[\alpha]_D$: -16.0 (*c* 0.50, $CHCl_3$); **IR** (ATR) 3128, 2929, 1702, 1590, 1097; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (s, 1H, H-2), 8.54 (d, $J_{8,F}$=2.7 Hz, 1H, H-8), 6.58 (d, $J_{2',F}$=11.5 Hz, 1H, H-2'), 4.21 (ddd, $J_{4',F}$=5.6 Hz, $J_{4',8'}$=3.6 Hz, $J_{4',8'}$=3.5 Hz, 1H, H-4'), 3.87 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.5 Hz, 1H, H-8'), 3.74 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.6 Hz, 1H, H-8'), 3.28 (m, 1H, H-5'), 2.58 (m, 1H, H-7'endo), 2.50 (m, 1H, H-7'exo), 2.36 (m, 1H, H-6'exo), 1.62 (m, 1H, H-6'endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 152.0 (s, CH, C-2), 151.6/150.9 (2s, 2C, C-4/C-6), 144.9, 144.9 (d, $^4J_{C-F}$=4.6 Hz, CH, C-8), 131.4 (s, C, C-5), 100.0, 96.0 (d, $^1J_{C-F}$=250.6 Hz, C, C-1'), 89.5, 89.2 (d, $^2J_{C-F}$=17.8 Hz, CH, C-2'), 85.8 (s, CH, C-4'), 64.5 (s, CH_2, C-8'), 47.4, 47.1 (d, $^2J_{C-F}$=18.7 Hz, CH, C-5'), 28.8, 28.5 (d, $^2J_{C-F}$=22.8 Hz, CH_2, C-7'), 25.9 (s, CH_3, $(CH_3)_3C$), 18.4 (s, C, $(CH_3)_3C$), 16.7, 16.4 (d, $^3J_{C-F}$=18.2 Hz, CH_2, C-6'), -5.4 (s, CH_3, $2CH_3Si$); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -145.7 to -146.0 (m). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}ClFN_4O_2Si+Na]^+$: 435.1390. Found: 435.1377.

COSY, HMQC, HMBC, NOESY and n.O.e. differential experiments were recorded for **252**.

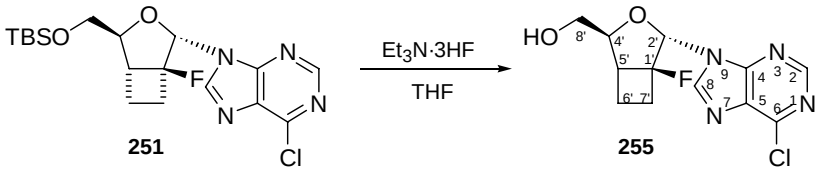
253: mp: 61-63 ºC; $[\alpha]_D$: -63.1 (*c* 1.60, $CHCl_3$); **IR** (ATR) 2927, 1377, 1254, 1099; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (s, 1H, H-2), 8.69 (s, 1H, H-8), 6.98 (d, $J_{2',F}$=14.0 Hz, 1H, H-2'), 4.39 (ddd, $J_{4',8'}$=3.5 Hz, $J_{4',F}$=3.3 Hz, $J_{4',8'}$=3.0 Hz, 1H, H-4'), 3.90 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=3.5 Hz, 1H, H-8'), 3.73 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=3.0 Hz, 1H, H-8'), 3.23 (m, 1H, H-5'), 2.28 (m, 2H, H-6'exo, H-7'exo), 1.47 (m, 1H, H-7'endo), 1.39 (m, 1H, H-6'endo), 0.92 (s, 9H, $(CH_3)_3C$), 0.11 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.2 (s, C, C-4), 152.6 (s, CH, C-2), 146.1 (s, CH, C-8), 143.2 (s, C, C-6), 121.8 (s, C, C-5), 103.2, 100.6 (d, $^1J_{C-F}$=240.0 Hz, C, C-1'), 93.3, 92.9 (d, $^2J_{C-F}$=38.7 Hz, CH, C-2'), 86.4, 86.4 (d, $^3J_{C-F}$=1.7 Hz, CH, C-4'), 65.5 (s, CH_2, C-8'), 46.1, 45.9 (d, $^2J_{C-F}$=19.0 Hz, CH, C-5'), 25.8 (s, CH_3, $(CH_3)_3C$), 25.7, 25.4 (d, $^2J_{C-F}$=23.3 Hz, CH_2, C-7'), 18.3 (s, C, $(CH_3)_3C$), 16.4, 16.3 (d, $^3J_{C-F}$=15.6 Hz, CH_2, C-6'), -5.5 (s, CH_3, $2CH_3Si$); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -142.5 to -142.6 (m). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}ClFN_4O_2Si+Na]^+$: 435.1390. Found: 435.1374.

COSY, HMQC, HMBC, NOESY and n.O.e. differential experiments were recorded for **253**.

254: $[\alpha]_D$: +41.8 (*c* 1.10, $CHCl_3$); **IR** (ATR) 2928, 1599, 1536, 1257, 838; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (d, $J_{8,F}$=1.6 Hz, 1H, H-8), 8.87 (d, $J_{2,F}$=1.2 Hz, 1H, H-2), 6.80 (d, $J_{2',F}$=8.2 Hz, 1H, H-2'), 4.27 (ddd, $J_{4',F}$=5.5 Hz, $J_{4',8'}$=4.2 Hz, $J_{4',8'}$=3.2 Hz, 1H, H-4'), 3.92 (dd, J_{gem}=11.5 Hz, $J_{8',4'}$=3.2 Hz, 1H, H-8'), 3.72 (dd, J_{gem}=11.5 Hz, $J_{8',4'}$=4.2 Hz, 1H, H-8'), 3.22 (m, 1H, H-5'), 2.68 (m, 1H, H-7'endo), 2.59 (m, 1H, H-7'exo), 2.36 (m, 1H, H-6'exo), 1.62 (m, 1H, H-6'endo), 0.91 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.4 (s, C, C-4), 152.2 (s, CH, C-2), 148.4, 148.4 (d, $^4J_{C-F}$=2.4 Hz, CH, C-8), 141.7 (s, C, C-6), 121.9 (s, C, C-5), 100.5, 97.7 (d, $^1J_{C-F}$=249.7 Hz, C, C-1'), 91.7, 91.6 (d, $^2J_{C-F}$=18.1 Hz, CH, C-2'), 86.5 (s, CH, C-4'), 64.3 (s, CH_2, C-8'), 46.8, 46.6 (d, $^2J_{C-F}$=19.1 Hz, CH, C-5'), 29.3, 29.0 (d, $^2J_{C-F}$=23.0 Hz, CH_2, C-7'), 25.8 (s, CH_3, $(CH_3)_3C$), 18.3 (s, C, $(CH_3)_3C$), 16.4, 16.2 (d, $^3J_{C-F}$=16.7 Hz, CH_2, C-6'), -5.5 (s, CH_3, $2CH_3Si$); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -146.1 to -146.3 (m). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}ClFN_4O_2Si+Na]^+$: 435.1390. Found: 435.1383.

COSY, HMQC, HMBC, NOESY and n.O.e. differential experiments were recorded for **254**.

5.1.5. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (255)

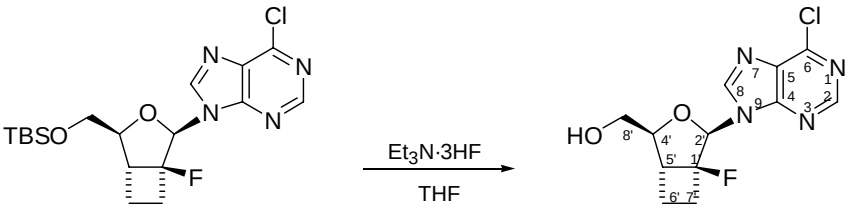


To an ice-cooled solution of **251** (80 mg, 0.19 mmol) in THF (5 mL), $Et_3N{\cdot}3HF$ (47 µl, 0.29 mmol) was added and the resulting solution was stirred for 5 h at room temperature. Then, more $Et_3N{\cdot}3HF$ (47 µl, 0.29 mmol) was added and after 24 h of stirring at room temperature, the solvent was removed. The residue was purified by column chromatography (EtOAc-hexane 2:1) to afford **255** (52 mg, 0.17 mmol, 90% yield) as a white solid.

255: mp: 123-126 ºC (from $CHCl_3$); $[\alpha]_D$: -13.3 (*c* 1.05, $CHCl_3$); **IR** (ATR) 3373, 2938, 1590, 1562, 1206, 1034; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.78 (s, 1H, H-2), 8.44 (s, 1H, H-8), 6.64 (dd, $J_{2',F}$=15.9 Hz, *J*=0.9 Hz, 1H, H-2'), 4.45 (ddd, *J*=5.1 Hz, *J*=5.0 Hz, *J*=4.8 Hz, 1H, H-4'), 3.83 (m, 2H, H-8'), 3.19 (m, 1H, H-5'), 2.32 (m, 2H, H-6'exo, H-7'exo), 2.16 (t, $J_{OH,8'}$=5.3 Hz, 1H, OH), 1.61 (m, 1H, H-7'endo), 1.53 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 152.5 (s, CH, C-2), 151.3/150.9 (2s, 2C, C-4/C-6), 142.5 (s, CH, C-8), 131.9 (s, C, C-5), 103.2, 100.6 (d, $^1J_{C\text{-}F}$=283.2 Hz, C, C-1'), 91.4, 91.0 (d, $^2J_{C\text{-}F}$=41.2 Hz, CH, C-2'), 86.1, 86.1 (d, $^3J_{C\text{-}F}$=1.3 Hz, CH, C-4'), 63.8 (s, CH_2, C-8'), 45.7, 45.5 (d, $^2J_{C\text{-}F}$=18.7 Hz, CH, C-5'), 25.8, 25.5 (d, $^2J_{C\text{-}F}$=23.2 Hz, CH_2, C-7'), 15.9, 15.8 (d, $^3J_{C\text{-}F}$=15.7 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -142.1 to -142.4 (m). **HRMS (ESI-TOF)** Calcd for $[C_{12}H_{12}ClFN_4O_2+Na)^+$: 321.0525. Found: 321.0530.

DEPT, COSY, HMQC and HMBC experiments were recorded for **255**.

5.1.6. (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (248)



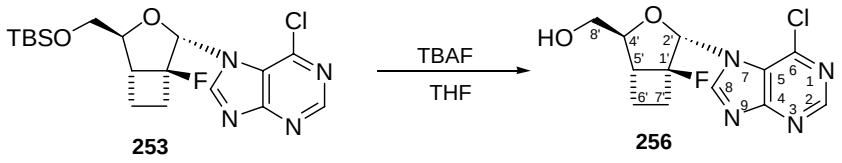
252 **248**

To an ice-cooled solution of **252** (54 mg, 0.13 mmol) in THF (3 mL), $Et_3N{\cdot}3HF$ (65 µl, 0.39 mmol) was added and the resulting solution was stirred for 7 h at room temperature. Then, more $Et_3N{\cdot}3HF$ (65 µl, 0.39 mmol) was added and after 24h of stirring at room temperature, the solvent was removed. The residue was purified by column chromatography (EtOAc-hexane 2:1) and recrystallizated with $CHCl_3$ to give **248** (35 mg, 0.12 mmol, 90% yield) as a white solid.

248: mp: 283-287 ºC (from $CHCl_3$); $[\alpha]_D$: -16.7 (*c* 0.90, MeOH); **IR** (ATR) 3313, 2924, 1592, 1562, 1204, 1141; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.75 (s, 1H, H-2), 8.41 (d, $J_{8,F}$=2.0 Hz, 1H, H-8), 6.47 (d, $J_{2',F}$=12.2 Hz, 1H, H-2'), 4.30 (ddd, $J_{4',F}$=5.7 Hz, $J_{4',8'}$=4.4 Hz, $J_{4',5'}$=2.4 Hz, 1H, H-4'), 3.96 (dd, J_{gem}=12.2 Hz, $J_{8',4'}$=2.4 Hz, 1H, H-8'), 3.74 (dd, J_{gem}=12.2 Hz, $J_{8',4'}$=4.4 Hz, 1H, H-8'), 3.41 (m, 1H, H-5'), 2.56 (m, 2H, H-7'exo, H-7'endo), 2.41 (m, 1H, H-6'exo), 1.63 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 151.9 (s, CH, C-2), 151.6/151.5 (2s, 2C, C-4/C-6), 144.6, 144.6 (d, $^4J_{C-F}$=3.3 Hz, CH, C-8), 132.0 (s, C, C-5), 99.8, 97.0 (d, $^1J_{C-F}$=250.6 Hz, C, C-1'), 91.0, 90.8 (d, $^2J_{C-F}$=18.1 Hz, CH, C-2'), 86.3 (s, CH, C-4'), 63.9 (s, CH_2, C-8'), 46.9, 46.7 (d, $^2J_{C-F}$=18.6 Hz, CH, C-5'), 28.8, 28.5 (d, $^2J_{C-F}$=22.9 Hz, CH_2, C-7'), 16.6, 16.4 (d, $^3J_{C-F}$=17.8 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -146.0 to -146.2 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}ClFN_4O_2+Na]^+$: 321.0525. Found: 321.0522. Anal. Calcd for ($C_{12}H_{12}ClFN_4O_2$): C, 48.25; H, 4.05; N, 18.76. Found: C, 48.12; H, 4.18; N, 18.62.

COSY, HMQC, HMBC, and NOESY experiments were recorded for **248**.

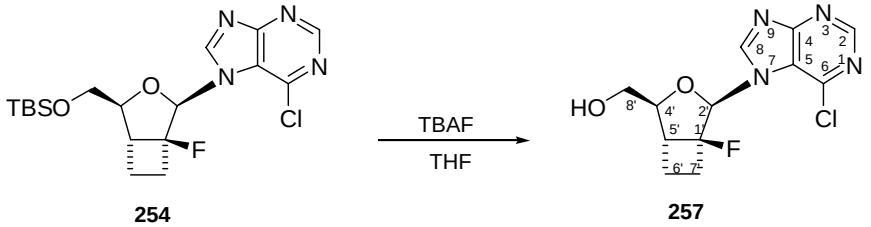
5.1.7. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-7-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (256)



To a solution of **253** (60 mg, 0.15 mmol) in THF (2 mL), a 1.0 M solution of TBAF in THF (0.22 mL, 0.22 mmol) was added and the resulting solution was stirred for 1 h. After removal of the solvent, the residue was purified by column chromatography (EtOAc-hexane 5:1) to give **256** (33 mg, 0.11 mmol, 75% yield) as a white solid.

256: mp: 122-124 ºC (from diethyl ether); $[\alpha]_D$: -85.0 (*c* 0.80, MeOH); **IR** (ATR) 3323, 2928, 2360, 1592, 1543, 1380, 1219; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.90 (s, 1H, H-2), 8.68 (s, 1H, H-8), 6.94 (d, $J_{2',F}$=14.3 Hz, 1H, H-2'), 4.51 (ddd, *J*=5.5 Hz, *J*=2.5 Hz, *J*=1.2 Hz, 1H, H-4'), 3.89 (m, 2H, H-8'), 3.22 (m, 1H, H-5'), 2.67 (br s, 1H, OH), 2.32 (m, 2H, H-6'exo, H-7'exo), 1.51 (m, 1H, H-7'endo), 1.36 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.2 (s, C, C-4), 152.8 (s, CH, C-2), 146.0 (s, CH, C-8), 143.3 (s, C, C-6), 121.8 (s, C, C-5), 103.5, 100.8 (d, $^1J_{C-F}$=239.7 Hz, C, C-1'), 93.3, 92.9 (d, $^2J_{C-F}$=39.4 Hz, CH, C-2'), 86.8, 86.8 (d, $^3J_{C-F}$=0.9 Hz, CH, C-4'), 64.0 (s, CH_2, C-8'), 46.1, 46.9 (d, $^2J_{C-F}$=19.0 Hz, CH, C-5'), 25.8, 25.6 (d, $^2J_{C-F}$=22.8 Hz, CH_2, C-7'), 16.3, 16.2 (d, $^3J_{C-F}$=16.2 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -140.8 to -141.1 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}ClFN_4O_2+Na]^+$: 321.0525. Found: 321.0517.
COSY, HMQC, HMBC and NOESY experiments were recorded for **256**.

5.1.8. (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-7-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (257)

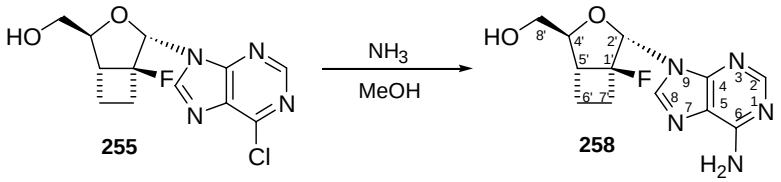


To a solution of **254** (37 mg, 0.09 mmol) in THF (1.5 mL), a 1.0 M solution of TBAF in THF (0.14 mL, 0.14 mmol) was added and the resulting solution was stirred for 1 h. After removal of the solvent, the residue was purified by column chromatography (EtOAc-hexane 4:1) to give **257** (22 mg, 0.07 mmol, 82% yield) as a white solid.

257: mp: 148-151 ºC (from MeOH); $[\alpha]_D$: +83.8 (*c* 0.65, MeOH); **IR** (ATR) 3322, 2973, 1596, 1539, 1449, 1150; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 9.11 (d, $J_{8,F}$=2.0 Hz, 1H, H-8), 8.89 (s, 1H, H-2), 6.85 (d, $J_{2',F}$=8.1 Hz, 1H, H-2'), 4.37 (ddd, $J_{4',F}$=7.4 Hz, $J_{4',8'}$=5.1 Hz, $J_{4',8'}$=2.4 Hz, 1H, H-4'), 4.03 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=2.4 Hz, 1H, H-8'), 3.83 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=5.1 Hz, 1H, H-8'), 3.78 (br s, 1H, OH), 3.30 (m, 1H, H-5'), 2.64 (m, 2H, H-7'exo, H-7'endo), 2.39 (m, 1H, H-6'exo), 1.66 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.0 (s, C, C-4), 152.3 (s, CH, C-2), 148.8, 148.8 (d, $^4J_{C\text{-}F}$=3.2 Hz, CH, C-8), 142.1 (s, C, C-6), 122.0 (s, C, C-5), 100.7, 98.0 (d, $^1J_{C\text{-}F}$=249.1 Hz, C, C-1'), 91.5, 91.3 (d, $^2J_{C\text{-}F}$=18.0 Hz, CH, C-2'), 86.6 (s, CH, C-4'), 63.4 (s, CH_2, C-8'), 46.6, 46.4 (d, $^2J_{C\text{-}F}$=19.1 Hz, CH, C-5'), 29.3, 29.1 (d, $^2J_{C\text{-}F}$=23.1 Hz, CH_2, C-7'), 16.6, 16.4 (d, $^3J_{C\text{-}F}$=16.1 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -146.8 to -147.0 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}ClFN_4O_2+Na]^+$: 321.0525. Found: 321.0516.

COSY, HMQC, HMBC and NOESY experiments were recorded for **257**.

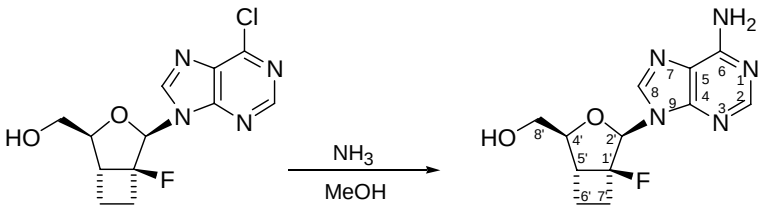
5.1.9. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-adenine (258)



A solution of **255** (20 mg, 0.07 mmol) and saturated NH_3/MeOH (4 mL) was heated at 90 ºC in a sealed tube for 40 h. After cooling at room temperature the solvent was removed under vacuum and the residue was purified by column chromatography (CH_2Cl_2-MeOH 10:1) and recrystallizated with MeOH to furnish **258** (17 mg, 0.06 mmol, 89% yield) as a white solid.

258: mp: 210-213 ºC (from MeOH); $[\alpha]_D$: -45.7 (*c* 0.35, MeOH); **IR** (ATR) 3326, 3214, 2920, 2852, 1651, 1600, 1080, 1015; **^{1}H NMR** (360 MHz, DMSO) δ 8.41 (s, 1H, H-8), 8.14 (s, 1H, H-2), 7.34 (br s, 2H, NH_2), 6.48 (d, $J_{2',F}$=16.7 Hz, 1H, H-2'), 5.05 (t, $J_{OH,8'}$=5.6 Hz, $J_{OH,8'}$=5.0 Hz, 1H, OH), 4.27 (t, *J*=5.0 Hz, 1H, H-4'), 3.54 (m, 2H, H-8'), 3.57 (m, 1H, H-5'), 2.18 (m, 2H, H-6'exo, H-7'exo), 1.59 (m, 2H, H-6'endo, H-7'endo); **^{13}C NMR** (90 MHz, DMSO) δ 155.9 (s, C, C-6), 152.8 (s, CH, C-2), 148.9 (s, C, C-4), 138.1 (s, CH, C-8), 118.7 (s, C, C-5), 103.3, 100.7 (d, $^1J_{C-F}$=235.4 Hz, C, C-1'), 90.0, 89.5 (d, $^2J_{C-F}$=40.8 Hz, CH, C-2'), 85.1 (s, CH, C-4'), 62.6 (s, CH_2, C-8'), 45.3, 45.1 (d, $^2J_{C-F}$=18.1 Hz, CH, C-5'), 25.3, 25.1 (d, $^2J_{C-F}$=23.0 Hz, CH_2, C-7'), 15.0, 14.8 (d, $^3J_{C-F}$=16.5 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, DMSO) δ -140.3 to -140.6 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{14}FN_5O_2+H]^+$: 280.1204. Found: 280.1202.
COSY, HMQC, HMBC and NOESY experiments were recorded for **258**.

5.1.10. (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-adenine (249)



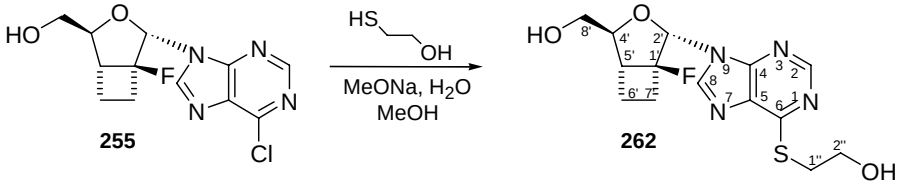
248 **249**

A solution of **248** (26 mg, 0.06 mmol) and saturated NH_3/MeOH (4 mL) was heated at 90 ºC in a sealed tube for 40 h. After cooling at room temperature the solvent was removed under vacuum and the residue was purified by column chromatography (CH_2Cl_2-MeOH, 13:1) to afford **249** (18 mg, 0.06 mmol, 75% yield) as a white solid.
249: mp: 248-251 ºC (from MeOH); $[\alpha]_D$: -5.7 (*c* 0.35, MeOH); **IR** (ATR) 3328, 3104, 2926, 1726, 1606, 1300, 1081, 1014; **^{1}H NMR** (360 MHz, DMSO) δ 8.28 (d, $J_{8,F}$=2.4 Hz, 1H, H-8), 8.15 (s, 1H, H-2), 7.32 (br s, 2H, NH_2), 6.50 (d, $J_{2',F}$=12.2 Hz, 1H, H-2'), 5.26 (t, $J_{OH,8'}$=5.1 Hz, $J_{OH,8'}$=4.8 Hz, 1H, OH), 4.16 (ddd, $J_{4',8'}$=5.4 Hz, $J_{4',8'}$=4.2 Hz, $J_{4',F}$=2.2 Hz, 1H, H-4'), 3.61 (ddd, J_{gem}=11.7 Hz, $J_{8',OH}$=4.8 Hz, $J_{8',4'}$=4.2 Hz, 1H, H-8'), 3.52 (ddd, J_{gem}=11.7 Hz, $J_{8',4'}$=5.4 Hz, $J_{8',OH}$=5.1 Hz, 1H, H-8'), 3.24 (m, 1H, H-5'), 2.45 (m, 1H, H-7'exo), 2.34 (m, 1H, H-7'endo), 2.23 (m, 1H, H-6'exo), 1.62 (m, 1H, H-

6'endo); **^{13}C NMR** (90 MHz, DMSO) δ 155.9 (s, C, C-6), 152.6 (s, CH, C-2), 149.1 (s, C, C-4), 139.4, 139.4 (d, $^{4}J_{C\text{-}F}$=3.4 Hz, CH, C-8), 118.2 (s, C, C-5), 99.4, 96.7 (d, $^{1}J_{C\text{-}F}$=247.6 Hz, C, C-1'), 88.5, 88.3 (d, $^{2}J_{C\text{-}F}$=17.7 Hz, CH, C-2'), 85.1 (s, CH, C-4'), 62.6 (s, CH_2, C-8'), 46.6, 46.4 (d, $^{2}J_{C\text{-}F}$=18.3 Hz, CH, C-5'), 28.1, 27.9 (d, $^{2}J_{C\text{-}F}$=22.5 Hz, CH_2, C-7'), 15.9, 15.7 (d, $^{3}J_{C\text{-}F}$=17.9 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, DMSO) δ -146.2 to -146.5 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{14}FN_5O_2+H]^+$: 280.1204. Found: 280.1203.

COSY, HMQC, HMBC and NOESY experiments were recorded for **249**.

5.1.11. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-(2-hydroxyethyl-thio)-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (262)



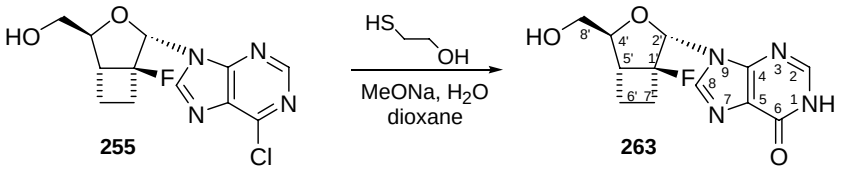
To a solution of **255** (25 mg, 0.06 mmol) and MeONa (14 mg, 0.24 mmol) in MeOH (4.5 mL), 2-mercaptoethanol (17 μL, 0.24 mmol) was added at room temperature. The solution was heated at 80 ºC for 22 h and then, after being cooled to room temperature, was neutralized with glacial HOAc. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc) to give **262** (18 mg, 0.04 mmol, 63% yield) as a colourless oil.

262: $[\alpha]_D$: -16.0 (*c* 0.75, $CHCl_3$); **IR** (ATR) 3323, 2925, 1564, 1330, 1202, 1141, 1046; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.67 (s, 1H, H-2), 8.28 (s, 1H, H-8), 6.54 (d, $J_{2',F}$=15.8 Hz, 1H, H-2'), 4.41 (dd, *J*=5.1 Hz, *J*=4.9 Hz, 1H, H-4'), 4.02 (t, J_{gem}=5.6 Hz, $J_{2'',1''}$=5.3 Hz, 2H, H-2''), 3.84 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=5.9 Hz, 1H, H-8'), 3.78 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=4.4 Hz 1H, H-8'), 3.56 (t, J_{gem}=5.8 Hz, $J_{1'',2''}$=5.3 Hz, 2H, H-1''), 3.15 (m, 1H, H-5'), 3.05 (br s, 1H, OH), 2.29 (m, 2H, H-7'exo/H-6'exo), 1.61 (m, 1H, H-7'endo), 1.47 (m, 1H, H-6'endo); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 161.3 (s, C, C-6), 152.1 (s, CH, C-2), 147.7 (s, C, C-4), 140.4 (s, CH, C-8), 131.5 (s, C, C-5), 103.9, 100.0 (d, $^{1}J_{C\text{-}F}$=243.8 Hz, C, C-1'), 91.1, 90.2 (d, $^{2}J_{C\text{-}F}$=41.0 Hz, CH, C-2'), 86.0, 85.9 (d, $^{3}J_{C\text{-}F}$=1.4 Hz, CH, C-4'), 63.7 (s, CH_2, C-8'), 62.8 (s, CH_2, C-2''), 45.9, 45.7 (d, $^{2}J_{C\text{-}F}$=18.7 Hz, CH, C-5'), 32.5 (s, CH_2, C-1''), 25.9, 25.7 (d, $^{2}J_{C\text{-}F}$=23.1 Hz, CH_2, C-7'), 16.0, 15.8 (d, $^{3}J_{C\text{-}F}$=15.8

Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, $CDCl_3$) δ -142.2 to -142.5 (m). **HRMS** (ESI-TOF) Calcd for $[C_{14}H_{17}FN_4O_3S+Na]^+$: 363.0898. Found: 363.0892.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **262**.

5.1.12. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-hypoxanthine (263)

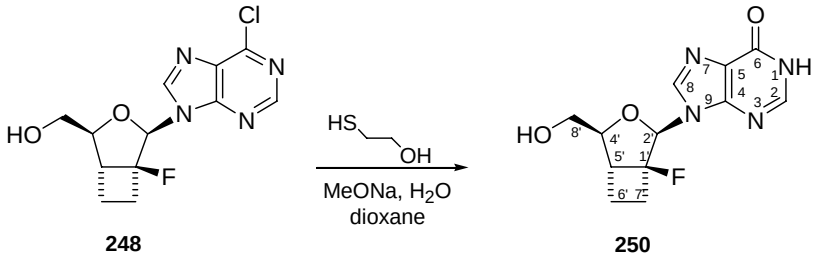


To a solution of **255** (34 mg, 0.11 mmol) and MeONa (26 mg, 0.45 mmol) in dioxane (2 mL) 2-mercaptoethanol (32 μL, 0.45 mmol) and 2 drops of H_2O were successively added at room temperature. The solution was heated at 110 ºC for 15 h when the same initial amount of MeONa, 2-mercaptoethanol and H_2O were added and heating was continued for 4 days. Then, the solution was neutralized with glacial AcOH. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc-MeOH 9:1) and recrystallizated with MeOH to give **263** (22 mg, 0.08 mmol, 69% yield) as a white solid.

263: mp: 244-246 ºC (MeOH); $[\alpha]_D$: -20.0 (*c* 0.30, DMSO); **IR** (ATR) 3319, 3061, 2853, 1691, 1169, 1033; **^{1}H NMR** (360 MHz, DMSO) δ 12.40 (br s, 1H, N-H), 8.37 (s, 1H, H-8), 8.10 (s, 1H, H-2), 6.46 (d, $J_{2',F}$=16.1 Hz, 1H, H-2'), 5.05 (br s, 1H, OH), 4.28 (dd, *J*=4.6 Hz, *J*=4.4 Hz, 1H, H-4'), 3.52 (m, 2H, H-8'), 3.17 (m, 1H, H-5'), 2.16 (m, 2H, H-6'exo/7'exo), 1.56 (m, 1H, H-6'endo/7'endo); **^{13}C NMR** (90 MHz, DMSO) δ 156.5 (s, C, C-6), 147.7 (s, C, C-4), 146.2 (s, CH, C-2), 137.5 (s, CH, C-8), 124.2 (s, C, C-5), 103.4, 100.8 (d, $^1J_{C-F}$=235.9 Hz, C, C-1'), 90.4, 89.9 (d, $^2J_{C-F}$=40.8 Hz, CH, C-2'), 85.4, 85.4 (d, $^3J_{C-F}$=1.4 Hz, CH, C-4'), 62.6 (s, CH_2, C-8'), 45.3, 45.1 (d, $^2J_{C-F}$=18.2 Hz, CH, C-5'), 25.3, 25.0 (d, $^2J_{C-F}$=22.8 Hz, CH_2, C-7'), 15.0, 14.8 (d, $^3J_{C-F}$=16.1 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, DMSO) δ -142.2 to -142.5 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{13}FN_4O_3+Na]^+$: 303.0864. Found: 303.0860.

COSY, HMQC, HMBC and NOESY experiments were recorded for **263**.

5.1.13. (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-9-(1'-fluoro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-hypoxanthine (250)



248 **250**

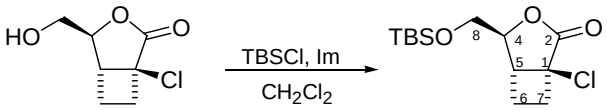
To a solution of **248** (15 mg, 0.05 mmol) and MeONa (10 mg, 0.20 mmol) in dioxane (3 mL), 2-mercaptoethanol (11 μL, 0.20 mmol) and 3 drops of H_2O were successively added at room temperature. The solution was heated at 110 ºC for 22 h and then, after being cooled to room temperature, was neutralized with glacial AcOH. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc-MeOH 10:1) to give **250** (12 mg, 0.04 mmol, 86% yield) as a white solid.

250: mp: 127-129 ºC (MeOH); $[\alpha]_D$: +8.0 (*c* 0.50, MeOH); **IR** (ATR) 3338, 3048, 2868, 1698, 1207, 1027; **^{1}H NMR** (360 MHz, DMSO) δ 12.30 (br s, 1H, N-H), 8.23 (d, $J_{8,F}$=2.4 Hz, 1H, H-8), 8.08 (s, 1H, H-2), 6.43 (d, $J_{2',F}$=11.4 Hz, 1H, H-2'), 5.10 (br s, 1H, OH), 4.14 (ddd, $J_{4',5'}$=6.6 Hz, $J_{4',8'}$=4.6 Hz, $J_{4',8'}$=4.2 Hz, 1H, H-4'), 3.59 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=4.2 Hz, 1H, H-8'), 3.52 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=4.6 Hz, 1H, H-8'), 3.23 (m, 1H, H-5'), 2.41 (m, 2H, H-7'exo/7'endo), 2.23 (m, 1H, H-6'exo), 1.63 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, DMSO) δ 156.6 (s, C, C-6), 147.8 (s, C, C-4), 146.2 (s, CH, C-2), 138.6, 138.6 (d, $^4J_{C-F}$=3.2 Hz, CH, C-8), 123.6 (s, C, C-5), 99.5, 96.8 (d, $^1J_{C-F}$=247.7 Hz, C, C-1'), 88.7, 88.5 (d, $^2J_{C-F}$=17.7 Hz, CH, C-2'), 85.3 (s, CH, C-4'), 62.5 (s, CH_2, C-8'), 46.5, 46.3 (d, $^2J_{C-F}$=18.3 Hz, CH, C-5'), 28.2, 27.9 (d, $^2J_{C-F}$=22.4 Hz, CH_2, C-7'), 15.8, 15.6 (d, $^3J_{C-F}$=17.7 Hz, CH_2, C-6'); **^{19}F NMR** (235 MHz, DMSO) δ -140.4 to -140.6 (m). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{13}FN_4O_3+Na]^+$: 303.0864. Found: 303.0856.

COSY, HMQC, HMBC and NOESY experiments were recorded for **250**.

5.2. Synthesis of cyclobutane-fused chloronucleoside analogues

5.2.1. (-)-(1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-1-chloro-3-oxabicyclo[3.2.0]heptan-2-one (265)



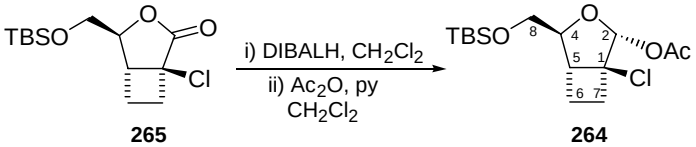
181 **265**

To a solution of **181** (490 mg, 2.77 mmol) in CH_2Cl_2 (20 mL) at 0 ºC, imidazole (390 mg, 5.7 mmol) and *tert*-butyldimethylsilyl chloride (580 mg, 3.87 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was successively washed with 5% aqueous citric acid solution (3x10 mL), saturated aqueous $NaHCO_3$ solution (3x10 mL) and brine (3x10 mL). Then, the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording 750 mg of a reaction crude which was used in the next reaction without further purification due to its instability. However, a small sample was purified allowing its complete characterization.

265: $[\alpha]_D$: -6.7 (*c* 1.1, $CHCl_3$); **IR** (ATR) 2927, 2855, 1766, 834, 778; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 4.37 (t, $J_{4,8}$=4.6 Hz, 1H, H-4), 3.73 (d, $J_{8,4}$=4.6 Hz, 2H, H-8), 3.28 (dd, *J*=8.9 Hz, *J*=6.6 Hz, 1H, H-5), 2.71-2.45 (m, 3H, H-6, 2H-7), 1.83 (m, 1H, H-6), 0.89 (s, 9H, $(CH_3)_3C$), 0.07 (s, 6H, $2CH_3Si$); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 175.3 (C=O, C-2), 84.1 (CH, C-4), 63.6 (CH_2, C-8), 59.6 (C, C-1), 45.7 (CH, C-5), 33.8 (CH_2, C-7), 25.8 (CH_3, CH_3CO), 20.3 (CH_2, C-6), 18.4 (C, $(CH_3)_3C$), -3.7 (CH_3, CH_3Si), -3.7 (s, CH_3, CH_3Si). **HRMS** (ESI-TOF) Calcd for $[C_{13}H_{23}ClO_3+Na]^+$: 313.0997. Found: 313.0991.

HMQC and HMBC experiments were recorded for **265**.

5.2.2. (+)-(1*S*,2*R*,4*S*,5*R*)-2-acetyloxy-4-*tert*-butyldimethylsilyloxymethyl-1-chloro-3-oxabicyclo[3.2.0]heptane (264)



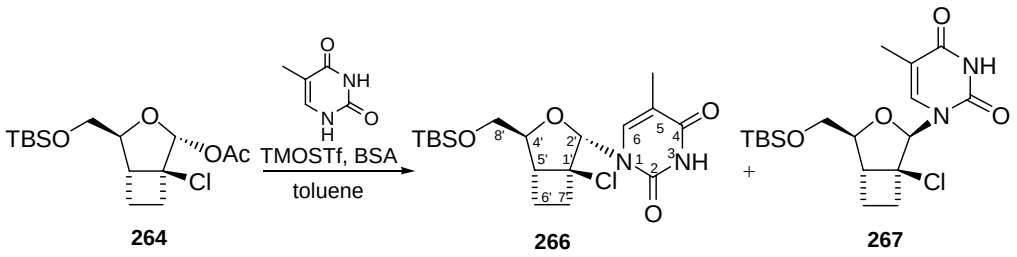
265 **264**

To a solution of crude **265** (750 mg, 2.57 mmol) in dry CH_2Cl_2 (10 mL) at -78 ºC, a 1.0 M solution of DIBAL-H in CH_2Cl_2 (4.9 mL, 4.9 mmol) was added dropwise. After 3.5 h of stirring at -78 ºC, the reaction mixture was quenched by the slow addition of a HNO_3 3% solution (9 mL) and allowed to warm to room temperature. The two layers were separated and the aqueous was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude and pyridine (2.8 mL, 36.1 mmol) in CH_2Cl_2 (25 mL), acetic anhydride (2.1 mL, 19.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with HCl 3% (3x15 mL), saturated aqueous $NaHCO_3$ solution (3x15 mL) and brine (3x15 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-diethyl ether 10:1) to afford the α-acetate **264** (758 mg, 2.26 mmol, 82% yield over 3 steps) as a colourless oil.

264: $[\alpha]_D$: +45.7 (*c* 1.40, $CHCl_3$); **IR** (ATR) 2929, 1751, 1221; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.37 (s, 1H, H-2), 4.15 (ddd, $J_{4,8}$=6.0 Hz, $J_{4,8}$=4.6 Hz, $J_{4,5}$=2.4 Hz, 1H, H-4), 3.69 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=4.6 Hz, 1H, H-8), 3.62 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=6.0 Hz, 1H, H-8), 3.08 (m, 1H, H-5), 2.62 (m, 1H, H-7endo), 2.37 (m, 2H, H-7exo, H-6exo), 2.15 (s, 3H, C*H*$_3$CO), 1.74 (m, 1H, H-6endo), 0.89 (s, 9H, (C*H*$_3$)$_3$C), 0.08 (s, 3H, C*H*$_3$Si), 0.07 (s, 3H, C*H*$_3$Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 169.5 (C=O), 103.8 (CH, C-2), 87.2 (CH, C-4), 71.1 (C, C-1), 64.4 (CH_2, C-8), 49.7 (CH, C-5), 30.2 (CH_2, C-7), 25.9 (CH_3, (*C*H$_3$)$_3$C), 21.1 (CH_3, *C*H$_3$CO), 20.9 (CH_2, C-6), 18.3 (C, (CH$_3$)$_3$*C*), -5.4 (CH_3, *C*H$_3$Si), -5.4 (CH_3, *C*H$_3$Si). **HRMS** (ESI-TOF) Calcd for $[C_{15}H_{27}ClO_4Si+Na]^+$ 357.1259. Found: 357.1245.

COSY, HMQC, HMBC and NOESY experiments were recorded for **264**.

5.2.3. (1'*S*,2'*S*,4'*S*,5'*R*)-1-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (266) and (1'*S*,2'*R*,4'*S*,5'*R*)-1-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (267)



264 266 267

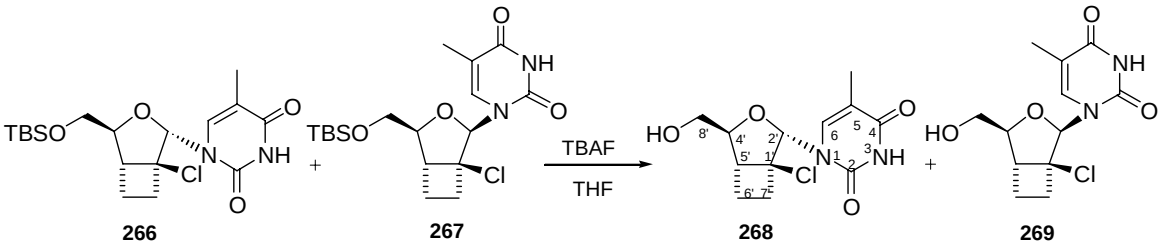
N,O-Bis(trimethylsilyl)acetamide (BSA) (138 µl, 0.54 mmol) was added to a suspension of thymine (34 mg, 0.27 mmol) in dry toluene (1 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 ºC. Then, a solution of **264** (60 mg, 0.18 mmol) in dry DCE (1 mL) and TMSOTf (43 µl, 0.23 mmol) were successively added and the reaction mixture was stirred at room temperature for 27 h. CH_2Cl_2 (4 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (2 mL). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtAcO 3:1) to afford a 53:47 mixture of **266** and **267** (70 mg, 0.17 mmol, 94% yield). The mixture of nucleosides could not be completely separated and only enriched mixtures could be analyzed.

266: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.43 (br s, 1H, NH), 7.45 (m, 1H, H-6), 6.35 (s, 1H, H-2'), 4.22 (ddd, $J_{4',8'}$=6.0 Hz, $J_{4',8'}$=5.7 Hz, $J_{4',5'}$=0.8 Hz, 1H, H-4'), 3.69 (m, 2H, H-8'), 3.17 (m, 1H, H-5'), 2.61-2.15 (m, 3H, H-6', 2H-7'), 1.95 (d, J=1.2 Hz, 3H, CH_3-C5), 1.56 (m, 1H, H-6'), 0.90 (s, 9H, (CH_3)$_3$C), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 163.9 (C=O, C-4), 150.2 (C=O, C-2), 134.9 (CH, C-6), 110.0 (C, C-5), 93.9 (CH, C-2'), 86.2 (CH, C-4'), 70.6 (C, C-1'), 64.1 (CH_2, C-8'), 49.9 (CH, C-5'), 29.8 (CH_2, C-7'), 25.9 (CH_3, (CH_3)$_3$C), 20.0 (CH_2, C-6'), 18.4 (C, (CH$_3$)$_3$*C*), 12.7 (CH_3, *C*H$_3$-C5), -5.4 (CH_3, 2*C*H$_3$Si). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{29}ClN_2O_4Si+H]^+$: 423.1477. Found: 423.1470 (mixture of **266** and **267**).

267: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.54 (br s, 1H, NH), 7.47 (m, 1H, H-6), 6.26 (s, 1H, H-2'), 4.09 (ddd, $J_{4',8'}$=6.8 Hz, $J_{4',8'}$=4.1 Hz, $J_{4',5'}$=2.7 Hz, 1H, H-4'), 3.78 (dd,

J_{gem}=11.0 Hz, $J_{8',4'}$=4.1 Hz, 1H, H-8'), 3.70 (m, 1H, H-8'), 3.17 (m, 1H, H-5'), 2.84 (m, 1H, H-7'), 2.45 (m, 2H, H-6', H-7'), 1.91 (d, *J*=1.2 Hz, 3H, CH_3-C5), 1.83 (m, 1H, H-6'), 0.91 (s, 9H, (CH_3)$_3$C), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 164.1 (C=O, C-4), 150.6 (C=O, C-2), 136.2 (CH, C-6), 109.1 (C, C-5), 91.9 (CH, C-2'), 85.3 (CH, C-4'), 71.9 (C, C-1'), 63.8 (CH_2, C-8'), 50.8 (CH, C-5'), 33.9 (CH_2, C-7'), 25.9 (CH_3, (*C*H_3)$_3$C), 21.6 (CH_2, C-6'), 18.4 (C, (CH_3)$_3$*C*), 12.5 (CH_3, *C*H_3-C5), -5.4 (CH_3, 2*C*H_3Si).

5.2.4. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-1-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (268) and (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-1-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)thymine (269)



To a 53:47 solution of **266** and **267** (85 mg, 0.21 mmol) in THF (3 mL), a 1.0 M solution of TBAF in THF (0.35 mL, 0.35 mmol) was added and the resulting solution was allowed to stir for 1 h. After removal of the solvent, the residue was purified by column chromatography (from EtOAc-hexane 1:1 to EtOAc-hexane 2:1) to afford a 53:47 mixture of **268** and **269** (52 mg, 0.18 mmol, 85%) as a white solid. Analytical samples of both isomers were obtained by preparative HPLC (hexane-iPrOH 70:30; flow: 7 mL/min; retention time **268**: 80 min; retention time **269**: 60 min).

268: mp: 127-130 ºC (from isopropyl alcohol); $[\alpha]_D$: -17.4 (*c* 0.46, $CHCl_3$); **IR** (ATR) 3436, 3217, 2950, 1686, 1665, 1273; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.53 (br s, 1H, NH), 7.47 (m, 1H, H-6), 6.37 (s, 1H, H-2'), 4.35 (dd, $J_{4',8'}$=7.5 Hz, $J_{4',8'}$=4.1 Hz, 1H, H-4'), 3.79 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=7.5 Hz, 1H, H-8'), 3.67 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=4.1 Hz, 1H, H-8'), 3.09 (dd, $J_{5',6'}$=8.6 Hz, $J_{5',6'}$=7.6 Hz, 1H, H-5'), 2.47 (m, 2H, H-6'exo, H-7'exo), 2.26 (m, 1H, H-7'endo), 2.16 (br s, 1H, OH), 1.98 (s, 3H, CH_3-C5), 1.62 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.2 (C=O, C-4), 150.1 (C=O, C-2), 134.7 (CH, C-6), 110.3 (C, C-5), 93.7 (CH, C-2'), 86.5 (CH, C-4'), 70.6 (C, C-1'), 63.2

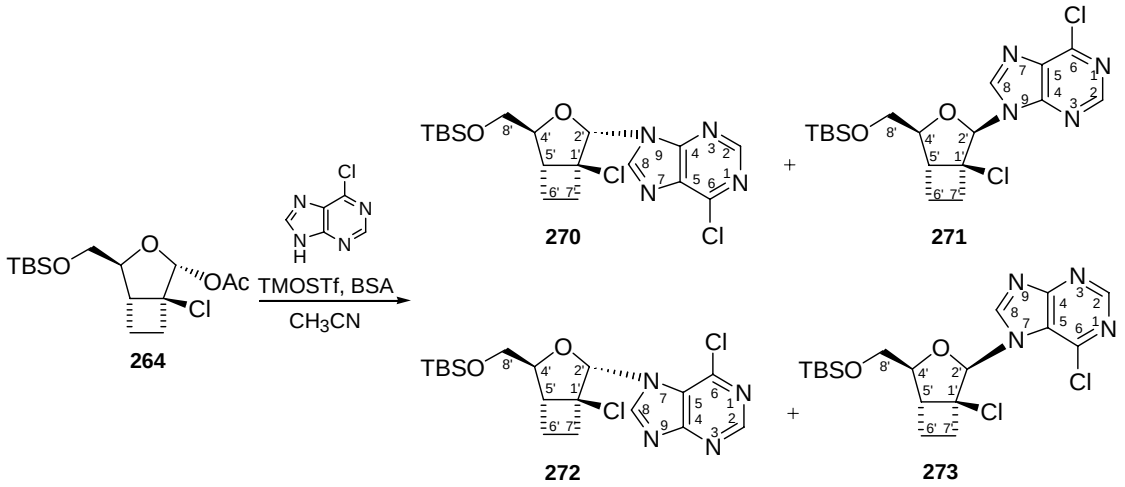
(CH_2, C-8'), 49.7 (CH, C-5'), 29.9 (CH_2, C-7'), 20.0 (CH_2, C-6'), 12.8 (CH_3, *C*H_3-C5). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{15}ClN_2O_4+Na]^+$: 309.0613. Found: 309.0612 (mixture of **268** and **269**).

COSY, HMQC, HMBC and NOESY experiments were recorded for **268**.

269: mp: 48-50 ºC (from isopropyl alcohol); $[\alpha]_D$: +55.7 (*c* 0.70, $CHCl_3$); **IR** (ATR) 3396, 3183, 2930, 1675, 1659, 1277; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.93 (br s, 1H, NH), 7.47 (m, *J*=1.1 Hz, 1H, H-6), 6.26 (s, 1H, H-2'), 4.18 (ddd, $J_{4',8'}$=5.5 Hz, $J_{4',5'}$=3.4 Hz, $J_{4',8'}$=3.2 Hz, 1H, H-4'), 3.84 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=3.2 Hz, 1H, H-8'), 3.75 (dd, J_{gem}=11.7 Hz, $J_{8',4'}$=5.5 Hz, 1H, H-8'), 3.13 (m, 1H, H-5'), 2.88 (m, 1H, H-7'endo), 2.54 (m, 2H, H-6'exo, H-7'exo), 2.11 (br s, 1H, OH), 1.93 (m, *J*=1.1 Hz, 3H, C*H*$_3$-C5), 1.86 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 163.8 (C=O, C-4), 150.4 (C=O, C-2), 136.1 (CH, C-6), 109.4 (C, C-5), 91.6 (CH, C-2'), 85.2 (CH, C-4'), 71.9 (C, C-1'), 63.6 (CH_2, C-8'), 50.5 (CH, C-5'), 33.7 (CH_2, C-7'), 21.5 (CH_2, C-6'), 12.6 (CH_3, *C*H_3-C5).

COSY, HMQC, HMBC and NOESY experiments were recorded for **269**.

5.2.5. (+)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-9-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (270), (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-9-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (271), (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-7-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (272) and (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-7-(4'-*tert*-butyldimethylsilyloxymethyl-1'-chloro-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (273)



N,O-Bis(trimethylsilyl)acetamide (BSA) (147 µl, 0.57 mmol) was added to a suspension of 6-chloropurine (44 mg, 0.29 mmol) in dry toluene (2 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 ºC. Then, a solution of **264** (63 mg, 0.19 mmol) in dry acetonitrile (1'5 mL) and TMSOTf (45 µl, 0.25 mmol) were successively added and the reaction mixture was stirred at 100 ºC for 1 h. Then CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (3 mL), after allowing the solution to cool to room temperature. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (from hexane-EtAcO 14:1 to hexane-EtAcO 1:1) to afford, the following fractions: i) **270** (10 mg, 0.02 mmol, 12% yield) as a colourless oil; ii) **271** (57 mg, 0.13 mmol, 70% yield) as a white solid; iii) **272** (4 mg, 0.01 mmol, 5% yield) as a colourless oil; and iv) **273** (6 mg, 0.02 mmol, 8% yield) as a colourless oil.

270: mp: decomposes over 70 ºC; $[\alpha]_D$: +17.2 (*c* 2.5, $CHCl_3$); **IR** (ATR) 3112, 2949, 2854, 1590, 1561, 1099; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.79 (s, 1H, H-2), 8.45 (s, 1H, H-8), 6.72 (s, 1H, H-2'), 4.34 (ddd, $J_{4',8'}$=4.7 Hz, $J_{4',8'}$=4.1 Hz, $J_{4',5'}$=1.0 Hz, 1H, H-4'), 3.85 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=4.7 Hz, 1H, H-8'), 3.77 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=4.1 Hz, 1H, H-8'), 3.29 (ddd, $J_{5',6'}$=8.2 Hz, $J_{5',6'}$=5.8 Hz, $J_{5',4'}$=1.0 Hz, 1H, H-5'), 2.55 (m, 1H, H-6'exo), 2.33 (m, 1H, H-7'exo), 2.12 (m, 1H, H-7'endo), 1.82 (m, 1H, H-6'endo), 0.94 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 152.4 (CH, C-2), 151.4/151.1 (2C, C-4/C-6), 142.7 (CH, C-8), 131.8 (C, C-5), 93.8 (CH, C-2'), 86.3 (CH, C-4'), 70.5 (C, C-1'), 64.7 (CH_2, C-8'), 49.7 (CH, C-5'), 29.7 (CH_2, C-7'), 25.9 (CH_3, $(CH_3)_3C$), 20.2 (CH_2, C-6'), 18.4 (C, $(CH_3)_3C$), -5.4 (s, CH_3, $2CH_3Si$). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}Cl_2N_4O_2Si+Na]^+$: 451.1094. Found: 451.1094.

COSY, HMQC, HMBC and NOESY experiments were recorded for **270**.

271: $[\alpha]_D$: -30.0 (*c* 0.90, $CHCl_3$); **IR** (ATR) 2928, 2856, 1589, 1561, 1215; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.71 (s, 1H, H-2), 8.50 (s, 1H, H-8), 6.63 (s, 1H, H-2'), 4.25 (ddd, $J_{4',8'}$=4.5 Hz, $J_{4',8'}$=4.5 Hz, $J_{4',5'}$=2.9 Hz, 1H, H-4'), 3.86 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=4.5 Hz, 1H, H-8'), 3.80 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=4.5 Hz, 1H, H-8'), 3.31 (m, 1H, H-5'), 2.91 (m, 1H, H-7'endo), 2.61 (m, 2H, H-6'exo, H-7'exo), 1.97 (m, 1H, H-6'endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 152.1 (CH, C-2), 151.2/150.8 (2C, C-4/C-6), 144.0 (CH, C-8), 131.6 (C, C-5), 91.9 (CH, C-2'), 86.4 (CH, C-4'), 71.7 (C, C-1'), 61.6 (CH_2, C-8'), 50.8 (CH, C-5'), 33.8 (CH_2, C-7'), 25.9 (CH_3, $(CH_3)_3C$), 21.5 (CH_2, C-6'), 18.4 (C, $(CH_3)_3C$), -5.3 (s, CH_3, CH_3Si), -5.4 (s, CH_3, CH_3Si). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}Cl_2N_4O_2Si+Na]^+$: 451.1094. Found: 451.1083.

COSY, HMQC, HMBC and NOESY experiments were recorded for **271**.

272: $[\alpha]_D$: -36.8 (*c* 1.25, $CHCl_3$); **IR** (ATR) 2928, 2856, 1680, 1094; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.91 (s, 1H, H-2), 8.68 (s, 1H, H-8), 7.00 (s, 1H, H-2'), 4.37 (ddd, $J_{4',8'}$=3.9 Hz, $J_{4',8'}$=3.6 Hz, $J_{4',5'}$=1.1 Hz, 1H, H-4'), 3.90 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=3.9 Hz, 1H, H-8'), 3.76 (dd, J_{gem}=11.0 Hz, $J_{8',4'}$=3.6 Hz, 1H, H-8'), 3.30 (ddd, $J_{5',6'}$=8.2 Hz, $J_{5',6'}$=5.8 Hz, $J_{5',4'}$=1.1 Hz, 1H, H-5'), 2.58 (m, 1H, H-6'exo) 2.36 (m, 1H, H-7'exo), 2.12 (m, 1H, H-7'endo), 1.78 (m, 1H, H-6'endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.12 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.1 (C, C-4), 152.7 (CH, C-2), 146.4 (CH, C-8), 143.1 (C, C-6), 122.1 (C, C-5), 94.3 (CH, C-2'), 86.6 (CH, C-

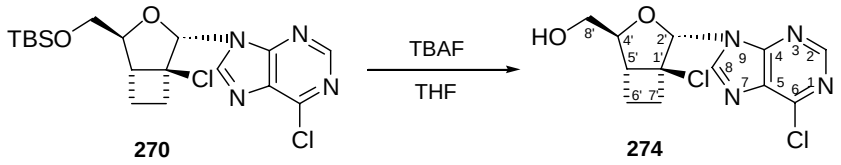
4'), 70.8 (C, C-1'), 65.3 (CH_2, C-8'), 49.8 (CH, C-5'), 30.1 (CH_2, C-7'), 26.0 (CH_3, $(CH_3)_3C$), 20.7 (CH_2, C-6'), 18.4 (C, $(CH_3)_3C$), -5.4 (CH_3, $2CH_3Si$). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}Cl_2N_4O_2Si+Na]^+$: 451.1094. Found: 451.1091.

COSY, HMQC, HMBC and NOESY experiments were recorded for **272**.

273: $[\alpha]_D$: +52.5 (*c* 0.40, $CHCl_3$); **IR** (ATR) 2928, 2856, 1252, 1052; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.91 (s, 1H, H-8), 8.89 (s, 1H, H-2), 6.90 (s, 1H, H-2'), 4.31 (ddd, $J_{4',8'}$=4.6 Hz, $J_{4',8'}$=3.7 Hz, $J_{4',5'}$=3.1 Hz, 1H, H-4'), 3.94 (dd, J_{gem}=11.3 Hz, $J_{8',4'}$=3.7 Hz, 1H, H-8'), 3.80 (dd, J_{gem}=11.3 Hz, $J_{8',4'}$=4.6 Hz, 1H, H-8'), 3.28 (m, 1H, H-5'), 2.98 (m, 1H, H-7'endo) 2.73 (m, 1H, H-7'exo), 2.59 (m, 1H, H-6'exo), 1.92 (m, 1H, H-6'endo), 0.90 (s, 9H, $(CH_3)_3C$), 0.15 (s, 3H, CH_3Si), 0.14 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.4 (C, C-4), 152.4 (CH, C-2), 147.7 (CH, C-8), 142.0 (C, C-6), 122.0 (C, C-5), 93.9 (CH, C-2'), 87.1 (CH, C-4'), 72.9 (C, C-1'), 63.8 (CH_2, C-8'), 50.7 (CH, C-5'), 34.5 (CH_2, C-7'), 26.0 (CH_3, $(CH_3)_3C$), 20.6 (CH_2, C-6'), 18.4 (C, $(CH_3)_3C$), -5.3 (CH_3, $2CH_3Si$). **HRMS** (ESI-TOF) Calcd for $[C_{18}H_{26}Cl_2N_4O_2Si+Na]^+$: 451.1094. Found: 451.1089.

COSY, HMQC, HMBC and NOESY experiments were recorded for **273**.

5.2.6. (+)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (274)



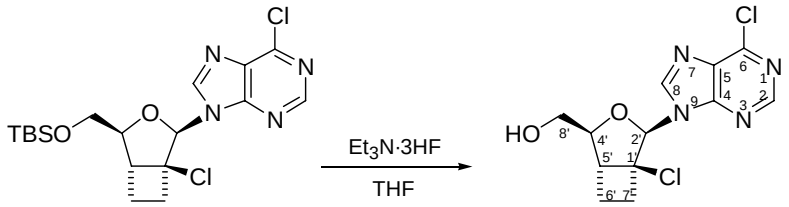
To an ice-cooled solution of **270** (132 mg, 0.31 mmol) in THF (4 mL), a 1.0 M solution of TBAF in THF (460 µl, 0.46 mmol) was added and the resulting solution was stirred for 1 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc-hexane 3:1) to afford **274** (85 mg, 0.27 mmol, 88% yield) as a white solid.

274: mp: 127-129 ºC (from $CHCl_3$); $[\alpha]_D$: +29.7 (*c* 0.74, $CHCl_3$); **IR** (ATR) 3380, 3124, 2946, 1593, 1562, 1199; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.75 (s, 1H, H-2), 8.45 (s, 1H, H-8), 6.66 (d, *J*=0.6 Hz, 1H, H-2'), 4.43 (ddd, $J_{4',8'}$=6.5 Hz, $J_{4',8'}$=4.0 Hz, $J_{4',5'}$=1.0 Hz, 1H, H-4'), 3.86 (ddd, J_{gem}=11.9 Hz, $J_{8',OH}$=6.3 Hz, $J_{8',4'}$=4.0 Hz, 1H, H-8'), 3.79 (ddd,

J_{gem}=11.9 Hz, $J_{8',4'}$=6.5 Hz, $J_{8',OH}$=4.5 Hz, 1H, H-8'), 3.21 (ddd, $J_{5',6'}$=8.2 Hz, $J_{5',6'}$=6.0 Hz, $J_{5',4'}$=1.0 Hz, 1H, H-5'), 2.91 (dd, $J_{OH,8'}$=6.3 Hz, $J_{OH,8'}$=4.5 Hz, 1H, OH), 2.53 (m, 1H, H-6'exo), 2.35 (m, 1H, H-7'exo), 2.04 (m, 1H, H-7'endo), 1.82 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 152.4 (CH, C-2), 151.3/151.2 (2C, C-4/C-6), 142.7 (CH, C-8), 131.7 (C, C-5), 93.4 (CH, C-2'), 86.4 (CH, C-4'), 70.2 (C, C-1'), 63.2 (CH_2, C-8'), 49.7 (CH, C-5'), 29.7 (CH_2, C-7'), 20.0 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}Cl_2N_4O_2+Na]^+$: 337.0230. Found: 337.0222.

HMQC, HMBC and NOESY experiments were recorded for **274**.

5.2.7. (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-purine (275)



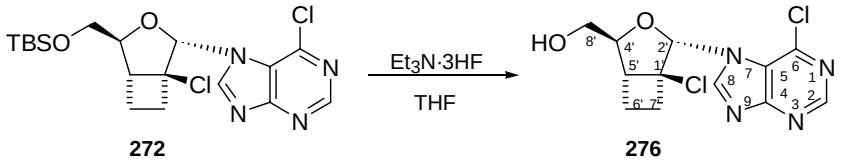
271 **275**

To an ice-cooled solution of **271** (40 mg, 0.09 mmol) in THF (3 mL), $Et_3N{\cdot}3HF$ (44 µl, 0.27 mmol) was added and the resulting solution was stirred 20h at room temperature. Evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc-hexane 2:1) to afford **275** (28 mg, 0.09 mmol, 95% yield) as a colourless oil.

275: $[\alpha]_D$: -23.6 (*c* 0.55, $CHCl_3$); **IR** (ATR) 3345, 3110, 2945, 1590, 1561, 1336, 1206; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.74 (s, 1H, H-2), 8.43 (s, 1H, H-8), 6.58 (s, 1H, H-2'), 4.36 (ddd, $J_{4',8'}$=4.5 Hz, $J_{4',8'}$=3.2 Hz, $J_{4',5'}$=3.2 Hz, 1H, H-4'), 3.97 (dd, J_{gem}=12.1 Hz, $J_{8',4'}$=3.1 Hz, 1H, H-8'), 3.81 (dd, J_{gem}=12.1 Hz, $J_{8',4'}$=4.5 Hz, 1H, H-8'), 3.39 (m, 1H, H-5'), 3.15 (br s, 1H, OH), 2.90 (m, 1H, H-7'endo), 2.65 (m, 2H, H-6'exo, H-7'exo), 1.99 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 151.9 (CH, C-2), 151.3/151.2 (2C, C-4/C-6), 144.0 (CH, C-8), 131.8 (C, C-5), 92.8 (CH, C-2'), 86.9 (CH, C-4'), 72.0 (C, C-1'), 63.4 (CH_2, C-8'), 50.2 (CH, C-5'), 34.1 (CH_2, C-7'), 21.4 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}Cl_2N_4O_2+H]^+$: 315.0410. Found: 314.0405.

COSY, HMQC, HMBC and NOESY experiments were recorded for **275**.

5.2.8. (-)-(1'*S*,2'*S*,4'*S*,5'*R*)-6-chloro-7-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (276)

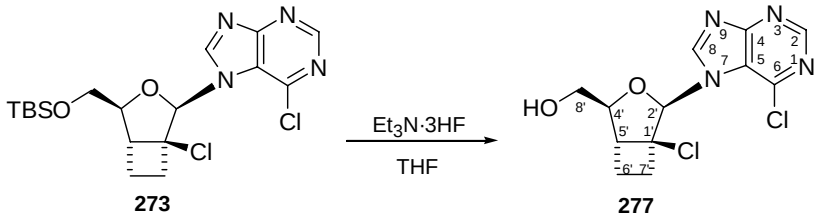


272 **276**

To an ice-cooled solution of **272** (35 mg, 0.08 mmol) in THF (2 mL), $Et_3N{\cdot}3HF$ (40 µl, 0.25 mmol) was added and the resulting solution was stirred for 22 h at room temperature. Evaporation of the solvent afforded a residue which was purified by column chromatography (EtOAc-hexane 4:1) to afford **276** (25 mg, 0.08 mmol, 96% yield) as a white solid.

276: mp: 125-126 ºC (from MeOH); $[\alpha]_D$: -43.3 (*c* 0.60, MeOH); **IR** (ATR) 3343, 2951, 1664, 1376, 1214, 974; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.92 (s, 1H, H-2), 8.67 (s, 1H, H-8), 7.00 (s, 1H, H-2'), 4.51 (ddd, $J_{4',8'}$=5.7 Hz, $J_{4',8'}$=5.7 Hz, $J_{4',5'}$=1.2 Hz, 1H, H-4'), 3.86 (m, 2H, H-8'), 3.27 (ddd, $J_{5',6'}$=7.8 Hz, $J_{5',6'}$=6.5 Hz, $J_{5',4'}$=1.2 Hz, 1H, H-5'), 2.56 (m, 1H, H-6'exo) 2.42 (m, 1H, H-7'exo), 2.00 (m, 1H, H-7'endo), 1.72 (m, 1H, H-6'endo), 1.68 (br s, 1H, OH); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.0 (C, C-4), 152.8 (CH, C-2), 146.3 (CH, C-8), 143.1 (C, C-6), 122.1 (C, C-5), 94.7 (CH, C-2'), 86.9 (CH, C-4'), 71.0 (C, C-1'), 63.7 (CH_2, C-8'), 50.0 (CH, C-5'), 30.2 (CH_2, C-7'), 20.8 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}Cl_2N_4O_2+Na]^+$: 337.0230. Found: 337.0223. COSY, HMQC, HMBC and NOESY experiments were recorded for **276**.

5.2.9. (+)-(1'*S*,2'*R*,4'*S*,5'*R*)-6-chloro-7-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-7*H*-purine (277)



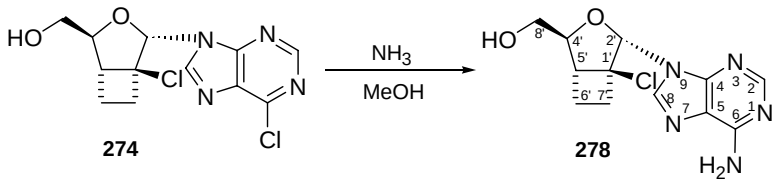
273 **277**

To a solution of **273** (8 mg, 0.02 mmol) in THF (1 mL), $Et_3N{\cdot}3HF$ (30 µL, 0.19 mmol) was added and the resulting solution was stirred for 16 h. Evaporation of the

solvent afforded a residue which was purified by column chromatography (EtOAc-hexane 6:1) to afford **277** (6 mg, 0.02 mmol, 99% yield) as a white solid which showed a certain degree of instability at room temperature.

277: $[\alpha]_D$: +72.0 (*c* 0.50, $CHCl_3$); **IR** (ATR) 3322, 2973, 1596, 1539, 1449, 1150, 955; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.92 (s, 1H, H-2), 8.67 (s, 1H, H-8), 7.00 (s, 1H, H-2'), 4.51 (ddd, $J_{4',8'}$=5.7 Hz, $J_{4',8'}$=5.6 Hz, $J_{4',5'}$=1.2 Hz, 1H, H-4'), 3.86 (m, 2H, H-8'), 3.27 (ddd, $J_{5',6'}$=7.8 Hz, $J_{5',6'}$=6.5 Hz, $J_{5',4'}$=1.2 Hz, 1H, H-5'), 2.56 (m, 1H, H-6'exo) 2.42 (m, 1H, H-7'exo), 2.00 (m, 1H, H-7'endo), 1.72 (m, 1H, H-6'endo), 1.68 (br s, 1H, OH); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.0 (C, C-4), 152.8 (CH, C-2), 146.3 (CH, C-8), 143.1 (C, C-6), 122.1 (C, C-5), 94.7 (CH, C-2'), 86.9 (CH, C-4'), 71.0 (C, C-1'), 63.7 (CH_2, C-8'), 50.0 (CH, C-5'), 30.2 (CH_2, C-7'), 20.8 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{12}Cl_2N_4O_2+Na]^+$: 337.0230. Found: 337.0223.

5.2.10. (+)-(1'*S*,2'*S*,4'*S*,5'*R*)-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-adenine (278)

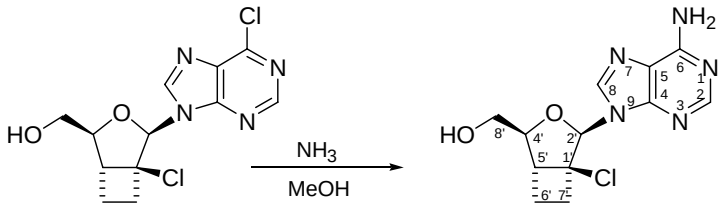


A solution of **274** (25 mg, 0.08 mmol) in saturated NH_3/MeOH (4 mL) was heated at 90 ºC in a sealed tube for 68 h. After cooling at room temperature, the solvent was removed under vacuum and the resulting residue was purified by column chromatography (CH_2Cl_2-MeOH, 10:1) to afford **278** (21 mg, 0.07 mmol, 91% yield) as a white solid.

278: mp: 90-93 ºC (from MeOH); $[\alpha]_D$: +26.7 (*c* 0.60, MeOH); **IR** (ATR) 3327, 3168, 2947, 2852, 1640, 1598, 1090, 1070; **^{1}H NMR** (360 MHz, DMSO) δ 8.48 (s, 1H, H-8), 8.16 (s, 1H, H-2), 7.34 (br s, 2H, NH_2), 6.57 (s, 1H, H-2'), 5.09 (t, $J_{OH,8'}$=5.5 Hz, 1H, OH), 4.28 (t, *J*=5.1 Hz, 1H, H-4'), 3.55 (m, 2H, H-8'), 3.22 (dd, $J_{5',6'}$=9.2 Hz, $J_{5',6'}$=6.1 Hz, 1H, H-5'), 2.41 (m, 1H, H-6'exo), 2.25 (m, 1H, H-7'exo), 2.11 (m, 1H, H-7'endo), 1.90 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, DMSO) δ 157.0 (C, C-6), 153.9 (CH, C-2), 150.2 (C, C-4), 139.3 (CH, C-8), 120.0 (C, C-5), 93.0 (CH, C-2'), 86.4 (CH, C-4'),

72.3 (C, C-1'), 63.0 (CH_2, C-8'), 50.2 (CH, C-5'), 30.5 (CH_2, C-7'), 20.3 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{14}ClN_5O_2+Na]^+$: 318.0728. Found: 318.0726.
COSY, HMQC, HMBC and NOESY experiments were recorded for **278**.

5.2.11. (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-adenine (279)

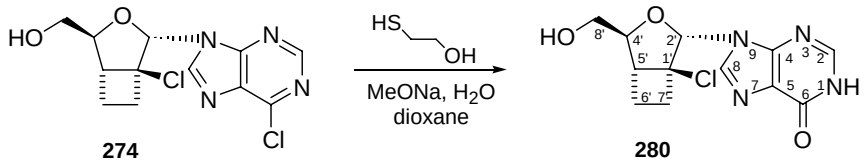


275 **279**

A solution of **275** (15 mg, 0.05 mmol) and saturated NH_3/MeOH (4 mL) was heated at 90 ºC in a sealed tube for 70 h. After cooling at room temperature, the solvent was removed under vacuum and the resulting residue was purified by column chromatography (CH_2Cl_2-MeOH, 10:1) to afford **279** (12 mg, 0.04 mmol, 92% yield) as a white solid.

279: mp: 233-235 ºC (from MeOH); $[\alpha]_D$: -36.0 (*c* 0.25, MeOH); **IR** (ATR) 3328, 3104, 2926, 1726, 1606, 1300, 1081, 1014; **^{1}H NMR** (360 MHz, DMSO) δ 8.29 (s, 1H, H-8), 8.14 (s, 1H, H-2), 7.30 (br s, 2H, NH_2), 6.56 (s, 1H, H-2'), 5.13 (t, $J_{OH,8'}$=6.0 Hz, $J_{OH,8'}$=5.7 Hz, 1H, OH), 4.29 (ddd, *J*=4.4 Hz, *J*=3.6 Hz, *J*=3.3 Hz, 1H, H-4'), 3.60 (m, 2H, H-8'), 3.24 (m, 1H, H-5'), 2.86 (m, 1H, H-7'), 2.45 (m, 2H, H-6'exo, H-7'), 1.99 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, DMSO) δ 156.9 (C, C-6), 153.7 (CH, C-2), 149.9 (C, C-4), 139.5 (CH, C-8), 119.4 (C, C-5), 91.6 (CH, C-2'), 86.6 (CH, C-4'), 73.5 (C, C-1'), 63.2 (CH_2, C-8'), 51.2 (CH, C-5'), 34.4 (CH_2, C-7'), 21.7 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{14}ClN_5O_2+H]^+$: 296.0909. Found: 296.0913.
HMQC and HMBC experiments were recorded for **279**.

5.2.12. (+)-(1'*S*,2'*S*,4'*S*,5'*R*)-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-hypoxanthine (280)

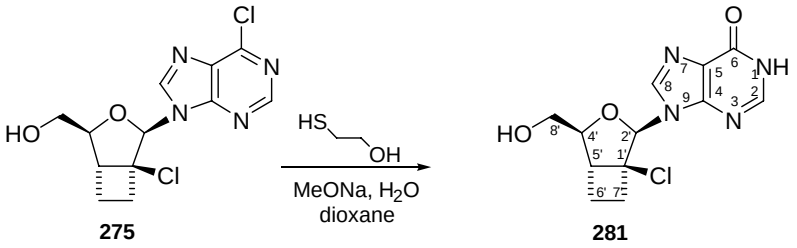


To a solution of **274** (37 mg, 0.12 mmol) and MeONa (27 mg, 0.47 mmol) in dioxane (2 mL), 2-mercaptoethanol (33 μL, 0.47 mmol) and 2 drops of H_2O were successively added at room temperature. The solution was heated at 110 ºC for 17 h when the same amount of MeONa, 2-mercaptoethanol and H_2O were added and heating was continued for 2 days. Then, the solution was neutralized with glacial AcOH. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc-MeOH 9:1) to afford **280** (26 mg, 0.09 mmol, 74% yield) as a white solid.

280: mp: 206-208 ºC (MeOH); $[\alpha]_D$: +35.0 (*c* 0.80, MeOH); **IR** (ATR) 3276, 3102, 3063, 2921, 2859, 1684, 1094; **^{1}H NMR** (360 MHz, DMSO) δ 12.43 (br s, 1H, N-H), 8.44 (s, 1H, H-8), 8.08 (s, 1H, H-2), 6.54 (s, 1H, H-2'), 5.08 (br s, 1H, OH), 4.29 (t, *J*=4.8 Hz, 1H, H-4'), 3.54 (m, 2H, H-8'), 3.23 (dd, $J_{5',6'}$=8.9 Hz, $J_{5',6'}$=6.4 Hz, 1H, H-5'), 2.40 (m, 1H, H-6'exo), 2.25 (m, 1H, H-7'exo), 2.06 (m, 1H, H-7'endo), 1.88 (m, 1H, H-6'endo); **^{13}C NMR** (90 MHz, DMSO) δ 157.5 (C, C-6), 148.9 (C, C-4), 147.2 (CH, C-2), 138.8 (CH, C-8), 125.1 (C, C-5), 93.4 (CH, C-2'), 86.7 (CH, C-4'), 72.4 (C, C-1'), 63.1 (CH_2, C-8'), 50.3 (CH, C-5'), 30.5 (CH_2, C-7'), 20.3 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{13}ClN_4O_3+Na]^+$: 319.0568. Found: 315.0558.

COSY, HMQC, HMBC and NOESY experiments were recorded for **280**.

5.2.13. (-)-(1'*S*,2'*R*,4'*S*,5'*R*)-9-(1'-chloro-4'-hydroxymethyl-3'-oxabicyclo[3.2.0]hept-2-yl)-9*H*-hypoxanthine (281)



275 **281**

To a solution of **275** (10 mg, 0.03 mmol) and MeONa (7 mg, 0.12 mmol) in dioxane (2 mL), 2-mercaptoethanol (9 μL, 0.12 mmol) and 2 drops of H_2O were successively added at room temperature. The solution was heated at 110 ºC for 16 h and then, after being cooled to room temperature, was neutralized with glacial AcOH. The solvent was removed under vacuum and the residue was purified by column chromatography (EtOAc-MeOH, 10:1) to give **281** (9 mg, 0.03 mmol, 96% yield) as a white solid.

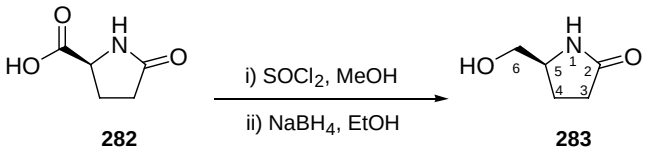
281: mp: 130-133 ºC (MeOH); $[\alpha]_D$: -18.0 (*c* 0.50, MeOH); **IR** (ATR) 3345, 3050, 2869, 1684, 1210; **^{1}H NMR** (360 MHz, DMSO) δ 12.40 (br s, 1H, N-H), 8.25 (s, 1H, H-8), 8.07 (s, 1H, H-2), 6.53 (s, 1H, H-2'), 5.08 (br s, 1H, OH), 4.21 (ddd, $J_{4',8'}$=5.2 Hz, $J_{4',8'}$=4.7 Hz, $J_{4',5'}$=3.6 Hz, 1H, H-4'), 3.61 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=4.7 Hz, 1H, H-8'), 3.56 (dd, J_{gem}=11.9 Hz, $J_{8',4'}$=5.2 Hz, 1H, H-8'), 3.23 (m, 1H, H-5'), 2.82 (m, 1H, H-7'exo), 2.45 (m, 2H, H-6'exo, H-7'exo), 1.98 (m, 1H, H-6'endo); **^{13}C NMR** (62.5 MHz, DMSO) δ 156.5 (C, C-6), 147.6 (C, C-4), 146.1 (CH, C-2), 137.9 (CH, C-8), 123.8 (C, C-5), 90.8 (CH, C-2'), 85.9 (CH, C-4'), 72.5 (C, C-1'), 62.1 (CH_2, C-8'), 50.1 (CH, C-5'), 33.4 (CH_2, C-7'), 20.5 (CH_2, C-6'). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{13}ClN_4O_3+Na]^+$: 319.0568. Found: 315.0551.

COSY, HMQC, HMBC and NOESY experiments were recorded for **281**.

6. [2+2] Photocycloaddition reactions of γ-lactam (57)

6.1. Synthesis of γ-lactam (57)

6.1.1. (5*S*)-5-hydroxymethyl-pyrrolidin-2-one (283)

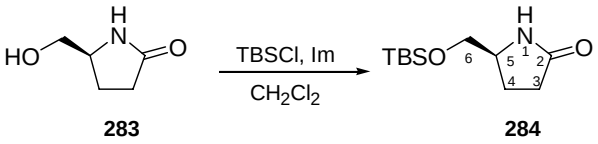


282 **283**

To a solution of L-piroglutamic acid, **282**, (3.89g, 30.13 mmol) in dry MeOH (25 mL), $SOCl_2$ (2.50 mL, 33.14 mmol) was added dropwise at -30 ºC under Nitrogen. Then, the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The solvent was removed under reduced pressure to afford a clear oil which was disolved in EtOH (120 mL) and cooled to 0 ºC. Then, $NaBH_4$ (2.30 g, 60.26 mmol) was slowly added. The resulting white suspension was stirred for 16 h at room temperature and filtered though celite. The solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (EtOAc) furnishing **283** (3.05 g, 26.50 mmol, 88% yield) as a colourless oil.

283: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (br s, 1H, NH), 4.89 (br s, OH), 3.78 (m, 1H, H-5), 3.66 (ddd, J_{gem}=11.4 Hz, $J_{6,5}$=3.0 Hz, J=1.7 Hz, 1H, H-6), 3.44 (ddd, J_{gem}=11.4 Hz, $J_{6,5}$=7.0 Hz, J=1.1 Hz, 1H, H-6), 2.32 (m, 2H, H-3), 2.14 (m, 1H, H-4), 1.79 (m, 1H, H-4).

6.1.2. (5*S*)-5-*tert*-butyldimethylsilyoxymethyl-pyrrolidin-2-one (284)



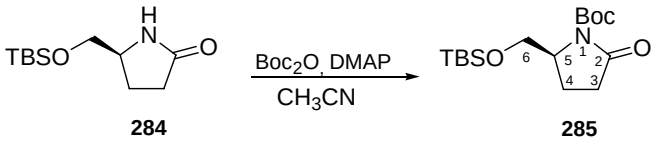
283 **284**

To a solution of **283** (3.05 g, 26.50 mmol) in CH_2Cl_2 (200 mL) at 0 ºC, imidazole (3.97 g, 58.3 mmol) and *tert*-butyldimethylsilyl chloride (8.00 g, 53.0 mmol) were successively added. The mixture was allowed to warm to room temperature and the resulting white suspension was stirred for 16 h. The white solid was filtered and the remaining clear solution was washed with brine (3x75 mL). The organic layer was dried

over anhydrous Na_2SO_4, filtered and evaporated to afford a yellowish oil. Column chromatography (EtOAc-hexane 2:1) allowed the isolation of **284** (5.55 g, 24.12 mmol, 91% yield) as a colourless oil.

284: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.13 (br s, 1H, NH), 3.73 (m, 1H, H-5), 3.60 (dd, J_{gem}=10.1 Hz, $J_{6,5}$=4.0 Hz, 1H, H-6), 3.44 (dd, J_{gem}=10.1 Hz, $J_{6,5}$=7.4 Hz, 1H, H-6), 2.32 (m, 2H, H-3), 2.16 (m, 1H, H-4), 1.73 (m, 1H, H-4), 0.87 (s, 9H, (C*H*$_3$)$_3$CSi), 0.04 (s, 3H, C*H*$_3$Si), 0.04 (s, 3H, C*H*$_3$Si).

6.1.3. (5*S*)-*N*-(*tert*-butoxycarbonyl)-5-*tert*-butyldimethylsilyoxymethyl-pyrrolidin-2-one (285)

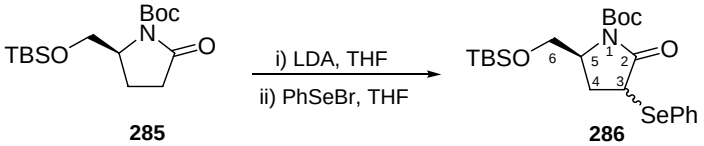


284 **285**

To a solution of **284** (2.10 g, 9.17 mmol) in CH_3CN (60 mL) at 0 ºC, DMAP (112 mg, 0.92 mmol) and di-*tert*-butyl dicarbonate (4.2 mL, 18.3 mmol) were added. The mixture was allowed to warm to room temperature and was stirred for 16 h. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (diethyl ether-hexane 3:1) to afford **285** (4.45 g, 8.25 mmol, 90% yield) as a colourless oil.

285: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.15 (dddd, $J_{5,4}$=8.3 Hz, $J_{5,6}$=4.0 Hz, $J_{5,6}$=2.3 Hz, $J_{5,4}$=0.8 Hz, 1H, H-5), 3.91 (dd, J_{gem}=10.4 Hz, $J_{6,5}$=4.0 Hz, 1H, H-6), 3.68 (ddd, J_{gem}=10.4 Hz, $J_{6,5}$=2.3 Hz, $J_{6,4}$=0.9 Hz, 1H, H-6), 2.69 (ddd, J_{gem}=17.5 Hz, $J_{3,4}$=10.2 Hz, $J_{3,4}$=0.8 Hz, 1H, H-3), 2.36 (ddd, J_{gem}=17.5 Hz, $J_{3,4}$=9.2 Hz, $J_{3,4}$=2.7 Hz, 1H, H-3), 2.06 (m, 2H, H-4), 1.53 (s, 9H, (C*H*$_3$)$_3$CO), 0.87 (s, 9H, (C*H*$_3$)$_3$CSi), 0.04 (s, 3H, C*H*$_3$Si), 0.04 (s, 3H, C*H*$_3$Si).

6.1.4. (5*S*)-*N*-(*tert*-butoxycarbonyl)-5-*tert*-butyldimethylsilyoxymethyl-3-phenylselenenyl-pyrrolidin-2-one (286)

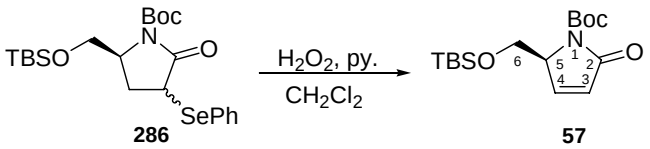


285 **286**

To a solution of **285** (2.70 g, 8.21 mmol) in dry THF (10 mL) at -78 ºC, lithium diisopropylamide (LDA) (1.8 M in THF, 6.70 mL, 12.31 mmol) was added dropwise under Nitrogen. After 2 h of stirring at -78 ºC, a solution of phenylselenenyl bromide (PhSeBr) (2.40 g, 13.14 mmol) in dry THF (15 mL) was added dropwise and the reaction mixture was further stirred for 2 h. Then, the reaction mixture was quenched by the slow addition of a saturated NH_4Cl aqueous solution (5 mL) and allowed to warm to room temperature. The mixture was separated and the aqueous layer was extracted with diethyl ether (3x30 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Purification of the crude by column chromatography (hexane-diethyl ether 15:1) afforded the mixture of diastereomers **286** (3.46 g, 7.14 mmol, 87% yield) as a yellow oil.

286 (major isomer): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (m, 2H, Ph), 7.29 (m, 3H, Ph), 4.20 (t, J=9.2 Hz, 1H, H-3), 3.98 (m, 1H, H-5), 3.94 (dd, J_{gem}=10.5 Hz, $J_{6,4}$=3.9 Hz, 1H, H-6), 3.60 (dd, J_{gem}=10.5 Hz, $J_{6,4}$=1.9 Hz, 1H, H-6), 2.44 (m, 1H, H-4), 2.16 (m, H-4), 1.56 (s, 9H, $(CH_3)_3CO$), 0.83 (s, 9H, $(CH_3)_3CSi$), 0.00 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si).

6.1.5. (-)-(5*S*)-*N*-(*tert*-butoxycarbonyl)-5-*tert*-butyldimethylsilyoxymethyl-3-pyrrolin-2-one (57)



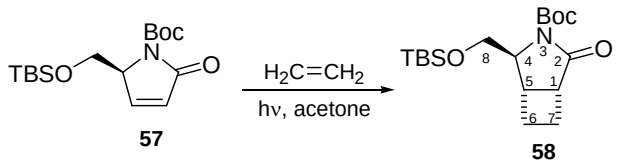
To a solution of the mixture **286** (2.60 g, 5.37 mmol) in CH_2Cl_2 (50 mL) at -78 ºC, pyridine (1.70 mL, 21.50 mmol) and 30% H_2O_2 (2.40 mL, 21.50 mmol) were successively added dropwise. The mixture was allowed to slowly warm to 0 ºC and was continuously controlled by TLC (hexane-EtOAc 3:1) until the complete consumption of the starting material. Then, the solution was diluted with diethyl ether (50 mL) and 5% citric acid aqueous solution (20 mL) was added and the mixture was allowed to warm to room temperature. The two layers were separated and the organic one was successively washed with 5% citric acid solution (3x20 mL), saturated $NaHCO_3$ aqueous solution (3x20 mL) and brine (3x20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated

to dryness. Purification of the crude by column chromatography (hexane-diethyl ether 6:1) afforded **57** (1.44 g, 4.40 mmol, 91% yield) as a white solid.

57: $[\alpha]_D$: -173.2 (*c* 0.80, $CHCl_3$) (literature $[\alpha]_D$ -175.6 (*c* 1.0, $CHCl_3$),[120a, 121a, 121c]); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.25 (dd, $J_{4,3}$=6.1 Hz, $J_{4,5}$=2.0 Hz, 1H, H-4), 6.12 (dd, $J_{3,4}$=6.1 Hz, $J_{3,5}$=1.7 Hz, 1H, H-3), 4.59 (dddd, $J_{5,6}$=6.7 Hz, $J_{5,6}$=3.7 Hz, $J_{5,4}$=2.0 Hz, $J_{5,3}$=1.7 Hz, 1H, H-5), 4.14 (dd, J_{gem}=9.7 Hz, $J_{6,5}$=3.7 Hz, 1H, H-6), 3.71 (dd, J_{gem}=9.7 Hz, $J_{6,5}$=6.7 Hz, 1H, H-6), 1.55 (s, 9H, $(CH_3)_3CO$), 0.85 (s, 9H, $(CH_3)_3CSi$), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 169.4 (C=O, C-2), 149.7 (CH, C-4), 149.5 (C=O), 127.1 (CH, C-3), 83.0 (C, $(CH_3)_3CO$), 63.6 (CH, C-5), 62.5 (CH_2, C-6), 28.1 (CH_3, $(CH_3)_3CO$), 25.7 (CH_3, $(CH_3)_3CSi$), 18.1 (C, $(CH_3)_3CSi$), -5.5 (CH_3, CH_3Si), -5.6 (CH_3, CH_3Si).

6.2. [2+2] Photocycloaddition of γ-lactam (57) to ethylene

6.2.1. (-)-(1*R*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptan-2-one (58)



57 **58**

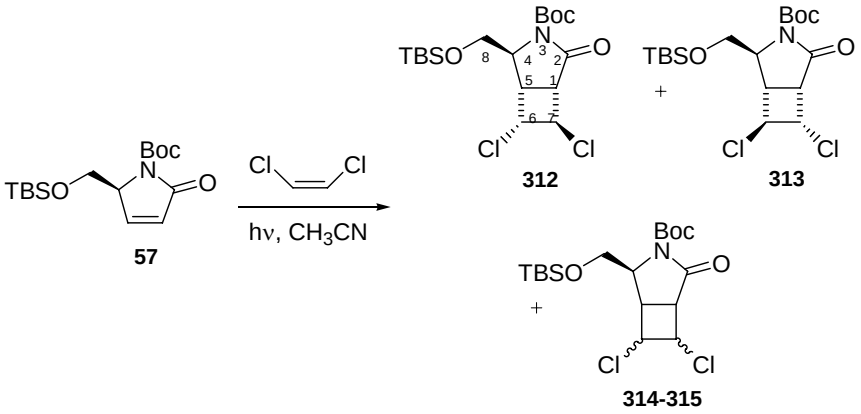
A solution of lactam **57** (215 mg, 0.66 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of ethylene for 2.5 h at -20 ºC. Evaporation of the solvent and chromatography of the residue (from hexane-diethyl ether 20:1 to hexane-diethyl ether 5:1) afforded **58** (146 mg, 0.41 mmol, 62% yield) as a white solid.

58: mp: 55-57 ºC (from diethyl ether); $[\alpha]_D$: -119.2 (*c* 1.3, $CHCl_3$) (literature $[\alpha]_D$ -118.8 (*c* 1.0 $CHCl_3$),[121c]); **IR** (ATR) 2951, 2930, 1736, 1708, 1249, 1098; **^{1}H NMR** (360 MHz, $CDCl_3$) δ 3.89 (br dd, $J_{4,8}$=3.5 Hz, $J_{4,8}$=2.1 Hz, 1H, H-4), 3.81 (dd, J_{gem}=10.3 Hz, $J_{8,4}$=3.5 Hz, 1H, H-8), 3.56 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=2.1 Hz, 1H, H-8), 3.00 (m, 1H, H-1), 2.89 (m, 1H, H-5), 2.46 (m, 1H, H-7exo), 2.26 (m, 1H, H-6exo), 2.08 (m, 1H, H-7endo), 2.00 (m, 1H, H-6endo), 1.54 (s, 9H, $(CH_3)_3CO$), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.01 (s, 3H, CH_3Si), -0.01 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 178.2 (C=O, C-2), 150.7 (C=O), 82.9 (C, $(CH_3)_3CO$), 65.2 (CH, C-4), 64.1 (CH_2, C-8), 43.4 (CH, C-1),

33.6 (CH, C-5), 28.1 (CH_3, (CH_3)$_3$CO), 25.9 (CH_3, (CH_3)$_3$CSi), 24.8 (CH_2, C-6), 24.3 (CH_2, C-7), 18.1 (C, (CH$_3$)$_3$CSi), -5.6 (CH_3, CH_3Si), -5.6 (CH_3, CH_3Si). Anal. Calcd for ($C_{18}H_{33}NO_4Si$): C, 60.81; H, 9.36; N, 3.94. Found: C, 60.81; H, 9.55; N, 3.82.
COSY, HMQC, HMBC and NOESY experiments were recorded for **58**.

6.3. [2+2] Photocycloaddition of γ-lactam (57) to *cis*-dichloroethylene

6.3.1. (1*R*,4*S*,5*S*,6*R*,7*S*)-*N*-(*tert*-butoxycarbonyl)-6,7-dichloro-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptan-2-one (312). (1*R*,4*S*,5*S*,6*S*,7*R*)-*N*-(*tert*-butoxycarbonyl)-6,7-dichloro-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptan-2-one (313) and *N*-(*tert*-butoxycarbonyl)-6,7-dichloro-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptan-2-one (314-315)



A solution of lactam **57** (200 mg, 0.61 mmol) and *cis*-1,2-dichloroethylene (250 μL, 3.31 mmol) in freshly distilled acetonitrile (65 mL) was irradiated through a quartz filter for 50 min at -40 ºC. Evaporation of the solvent and purification of the residue by column chromatography (hexane-EtOAc 2:1) afforded a 36:25:21:18 mixture of **312-315** (225 mg, 0.53 mmol, 87% yield). Repetitive column chromatography (from hexane-diethyl ether 20:1 to hexane-diethyl ether 5:1) allowed the isolation of pure **312** as a white solid which easily decomposed and enriched mixtures of **313** and **314**. **315** was lost during the purification process and could not be isolated.

312: **^{1}H NMR** (360 MHz, $CDCl_3$) δ 4.66 (ddd, $J_{6,5}$=8.7 Hz, $J_{6,7}$=4.3 Hz, $J_{6,1}$=2.0 Hz, 1H, H-6), 4.44 (m, 1H, H-4), 4.34 (ddd, $J_{7,6}$=4.3 Hz, $J_{7,1}$=3.4 Hz, $J_{7,5}$=1.1 Hz, 1H, H-7), 4.00 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=2.8 Hz, 1H, H-8), 3.61 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=1.9 Hz, 1H,

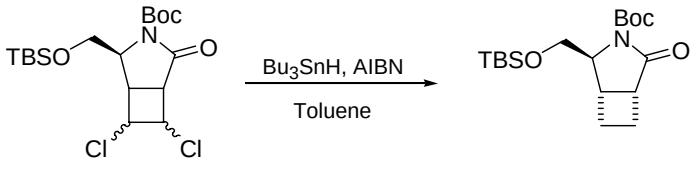
H-8), 3.41 (dd, $J_{5,6}$=8.7 Hz, $J_{5,1}$=7.9 Hz, 1H, H-5), 3.21 (ddd, $J_{1,5}$=7.9 Hz, $J_{1,7}$=3.4 Hz, $J_{1,6}$=2.0 Hz, 1H, H-1), 1.55 (s, 9H, $(CH_3)_3CO$), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 171.4 (C=O, C-2), 149.7 (C=O), 83.6 (C, $(CH_3)_3CO$), 64.0 (CH_2, C-8), 61.3 (2CH, C-6, C-7), 59.3 (CH, C-4), 50.8 (CH, C-1), 35.7 (CH, C-5), 28.0 (CH_3, $(CH_3)_3CO$), 25.7 (CH_3, $(CH_3)_3CSi$), 18.0 (C, $(CH_3)_3CSi$), -5.6 (CH_3, CH_3Si), -5.7 (CH_3, CH_3Si). All attempts to analyse the elementary structure of **312** failed due to its instability.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **312**.

313: **^{1}H NMR** (250 MHz, $CDCl_3$) δ 4.55 (dd, $J_{7,1}$=9.5 Hz, $J_{7,6}$=7.4 Hz, 1H, H-7), 4.19 (ddd, $J_{6,7}$=7.4 Hz, $J_{6,5}$=6.2 Hz, $J_{6,1}$=1.1 Hz, 1H, H-6), 4.16 (dd, $J_{4,8}$=2.8 Hz, $J_{4,8}$=1.9 Hz, 1H, H-4), 3.93 (dd, J_{gem}=10.7 Hz, $J_{8,4}$=2.8 Hz, 1H, H-8), 3.66 (dd, J_{gem}=10.7 Hz, $J_{8,4}$=1.9 Hz, 1H, H-8), 3.48 (ddd, $J_{1,7}$=9.5 Hz, $J_{1,5}$=7.6 Hz, $J_{1,6}$=1.1 Hz, 1H, H-1), 2.85 (dd, $J_{5,1}$=7.6 Hz, $J_{5,6}$=6.2 Hz, 1H, H-5), 1.55 (s, 9H, $(CH_3)_3CO$), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si).

314: **^{1}H NMR** (250 MHz, $CDCl_3$) δ 4.65 (d, J=6.0 Hz, 1H, H-6 or H-7), 4.55 (m, 1H, H-7 or H-6), 4.16 (m, 1H, H-4), 3.94 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=2.8 Hz, 1H, H-8), 3.68 (dd, J_{gem}=10.6 Hz, $J_{8,4}$=1.8 Hz, 1H, H-8), 3.28 (m, 2H, H-1, H-5), 1.55 (s, 9H, $(CH_3)_3CO$), 0.85 (s, 9H, $(CH_3)_3CSi$), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si).

6.3.2. (-)-(1*R*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptan-2-one (58)



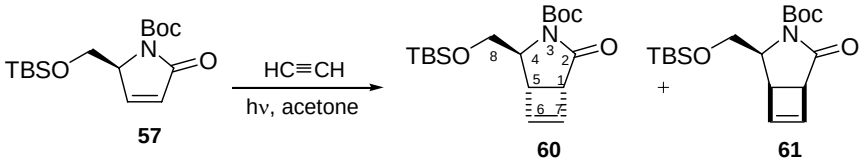
312-315 **58**

A solution of AIBN (54 mg, 0.30 mmol) in dry toluene (14 mL) under Nitrogen was heated at 90 ºC. Bu_3SnH (5.38 mL, 20.0 mmol) was added dropwise and the solution was heated at 110 ºC. Then a solution of the mixture **312-315** (850 mg, 2.00 mmol) in dry toluene (9 mL) was added dropwise and the resulting solution was refluxed for 3 h. After allowing the reaction mixture to cool to room temperature the solvent was removed under reduced pressure. The crude was purified by column

chromatography (from hexane-diethyl ether 30:1 to hexane-diethyl ether 5:1) to afford **58** (429 mg, 1.21 mmol, 60% yield) (48% for the last 2 steps) as a white solid.

6.4. [2+2] Photocycloaddition of γ-lactam (57) to acetylene

6.4.1. (-)-(1*R*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]hept-6-en-2-one (60) and (1*S*, 4*S*, 5*R*)-*N*-(*tert*-butoxycarbonyl)-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]hept-6-en-2-one (61)



A solution of γ-lactam **57** (200 mg, 0.61 mmol) in freshly distilled acetone (65 mL) was irradiated through a pyrex filter with introduction of acetylene for 5 h at -20 ºC. Evaporation of the solvent and purification of the residue by column chromatography (hexane-diethyl ether 3:1) afforded the following fractions: i) a 86:14 mixture of **60** and **61** (107 mg, 0.30 mmol, 61% yield); and ii) unreacted starting material **57** (40 mg, 0.12 mmol, 20%). Repetitive column chromatography (from hexane-diethyl ether 20:1 to hexane-diethyl ether 5:1) allowed the isolation of pure **60** as a white solid and an enriched fraction of **61**.

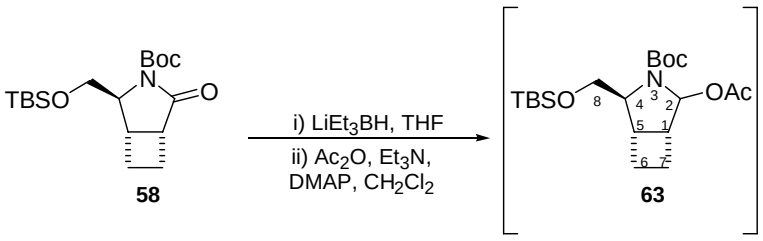
60: mp: 72-75 ºC (from EtOAc); $[\alpha]_D$: -91.5 (*c* 2.0, $CHCl_3$); **IR** (ATR) 2928, 2856, 1736, 1710, 1311, 1150; **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.27 (br s, 2H, H-6, H-7), 4.00 (ddd, $J_{4,8}$=3.4 Hz, $J_{4,8}$=2.1 Hz, $J_{4,5}$=1.0 Hz, 1H, H-4), 3.88 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=3.4 Hz, 1H, H-8), 3.64 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=2.1 Hz, 1H, H-8), 3.52 (br dd, $J_{1,5}$=3.3 Hz, *J*=0.8 Hz, 1H, H-1), 3.24 (br d, $J_{5,1}$=3.3 Hz, 1H, H-5), 1.51 (s, 9H, $(CH_3)_3CO$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.03 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 151.1 (C=O), 141.0 (CH, C-6), 139.6 (CH, C-7), 82.6 (C, $(CH_3)_3CO$), 64.3 (CH_2, C-8), 58.3 (CH, C-4), 51.5 (CH, C-1), 40.6 (CH, C-5), 28.0 (CH_3, $(CH_3)_3CO$), 25.7 (CH_3, $(CH_3)_3CSi$), 18.0 (C, $(CH_3)_3CSi$), -5.7 (CH_3, CH_3Si), -5.7 (CH_3, CH_3Si). Anal. Calcd for ($C_{18}H_{31}NO_4Si$): C, 61.15; H, 8.84; N, 3.96. Found: C, 60.89; H, 8.85; N, 3.72.

COSY, HMQC, HMBC and NOESY experiments were recorded for **60**.

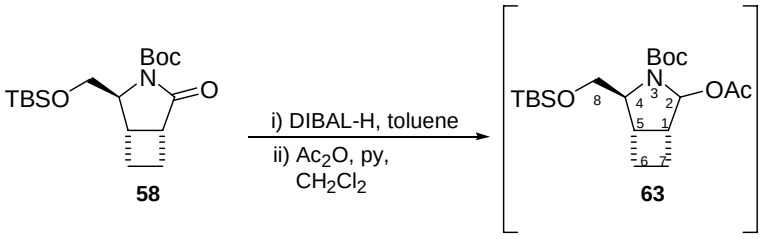
61: **^{1}H NMR** (250 MHz, $CDCl_3$) δ 6.35 (m, 1H, H-6 or H-7), 6.32 (m, 1H, H-7 or H-6), 4.10 (m, 1H, H-4), 3.73 (dd, J_{gem}=10.2 Hz, $J_{8,4}$=3.8 Hz, 1H, H-8), 3.57 (m, 2H, H-8 and H-1 or H-5), 3.43 (m, 1H, H-5 or H-1), 1.51 (s, 9H, $(CH_3)_3CO$), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.00 (s, 3H, CH_3Si), -0.01 (s, 3H, CH_3Si); **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 173.9 (C=O, C-2), 151.1 (C=O), 139.1, 138.0 (2CH, C-6, C-7), 82.9 (C, $(CH_3)_3CO$), 62.6 (CH_2, C-8), 56.7 (CH, C-4), 43.9, 43.7 (2CH, C-1, C-5), 29.6 (CH_3, $(CH_3)_3CO$), 28.0 (CH_3, $(CH_3)_3CSi$), 18.0 (C, $(CH_3)_3CSi$), -5.6 ($2CH_3$, CH_3Si).

7. Synthesis of cyclobutane-fused azanucleoside analogues

7.1. (1*R*,2*RS*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-acetyloxy-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptane (63)

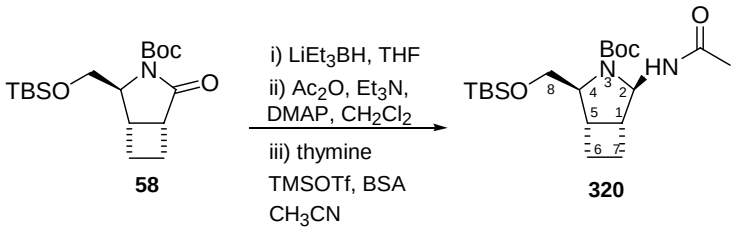


To a solution of **58** (150 mg, 0.42 mmol) in dry THF (8 mL) at -78 ºC, a 1.0 M solution of $LiEt_3BH$ in THF (1.05 mL, 1.05 mmol) was added dropwise. After 2 h of stirring at -78 ºC, the reaction mixture was quenched by the slow addition of H_2O (4 mL) and was allowed to warm to room temperature during 90 min. Then, H_2O (4 mL) was added, the mixture was diluted with diethyl ether (10 mL) and it was separated. The aqueous layer was extracted with diethyl ether (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude in CH_2Cl_2 (15 mL), DMAP (44 mg, 0.36 mmol), Et_3N (2.4 mL, 16.0 mmol) and acetic anhydride (850 µL, 9.0 mmol) were successively added dropwise. The mixture was stirred for 16 h at room temperature and then H_2O (5 mL) was added. The two layers were separated and the aqueous one was extracted with CH_2Cl_2 (3x10 mL). The collection of organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness using toluene as coevaporant. The crude residue was used in the next reaction without further purification.



To a solution of **58** (650 mg, 0.75 mmol) in dry toluene (25 mL) at -78 ºC, DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added dropwise. After 0.5 h of stirring at -78 ºC, DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) was added again and the mixture was stirred at -78 ºC for 2.5h. Then, MeOH (1.5 mL) was added and the mixture was allowed to warm to room temperature. EtOAc (1.5 mL) and saturated aqueous $NaHCO_3$ (0.6 mL) were successively added. After 20 min anhydrous Na_2SO_4 (2.3 g) was added and the resulting suspension was vigorously stirred overnight and filtered through celite. The solvent was removed and the resulting residue was dissolved in CH_2Cl_2 (10 mL). Pyridine (725 µL, 9.0 mmol) and acetic anhydride (709 µL, 7.5 mmol) were successively added dropwise. The mixture was stirred for 16 h at room temperature and then H_2O (5 mL) was added. The two layers were separated and the aqueous one was extracted with CH_2Cl_2 (3x10 mL). The collection of organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness using toluene as coevaporant. The crude residue was used in the next reaction without further purification.

7.2. (1*R*,2*S*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-acetamido-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptane (320)



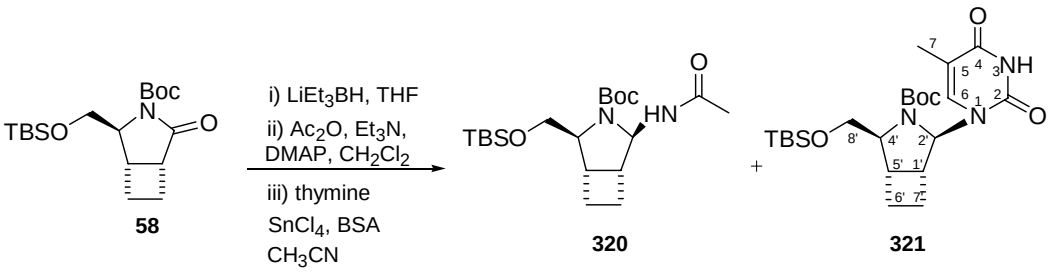
N,O-Bis(trimethylsilyl)acetamide (BSA) (220 µl, 0.90 mmol) was added to a suspension of thymine (45 mg, 0.36 mmol) in dry acetonitrile (2 mL) under argon atmosphere. Then, a solution of crude acetate **63** (0.30 mmol) in dry acetonitrile (1.5

mL) and TMSOTf (46 µl, 0.45 mmol) were successively added dropwise under argon atmosphere at 0 ºC. The reaction mixture was stirred at 0 ºC for 3.5 h. CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (2 mL). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 5:1) to afford **320** (70 mg, 0.17 mmol, 60% yield from **58**) as a colourless oil.

320: $[\alpha]_D$: -51.9 (*c* 0.54, $CHCl_3$); **IR** (ATR) 3335, 2927, 2855, 1698, 1695, 1376, 1104; **^{1}H NMR** (400 MHz, $CDCl_3$, 298K) δ 6.76 (d, $J_{NH,2}$=8.8 Hz) + 6.54 (d, $J_{NH,2}$=8.7 Hz) (1H, NH), 5.79 (d, $J_{2,NH}$=8.7 Hz) + 5.75 (d, $J_{2.NH}$=8.8 Hz) (1H, H-2), 4.07 (dd, J_{gem}=10.4 Hz, $J_{8,4}$=1.4 Hz, 1H, H-8), 3.97 (br s) + 3.85 (br s) (1H, H-4), 3.51 (dd, J_{gem}=10.4 Hz, $J_{8,4}$=1.6 Hz, 1H, H-8), 2.79 (m, 1H, H-5), 2.68 (m, 1H, H-1), 2.22 (m, 2H, H-6exo, H-7exo), 1.91-1.83 (m, 4H, H-7endo, CH_3CO), 1.73 (m, 1H, H-6endo), 1.46 (s, 9H, $(CH_3)_3CO$), 0.92 (s, 9H, $(CH_3)_3CSi$), 0.11 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); **^{1}H NMR** (400 MHz, $CDCl_3$, 330K) δ 6.62 (br s, 1H, NH), 5.77 (d, $J_{2,NH}$=8.5 Hz, 1H, H-2), 4.06 (m, 1H, H-8), 3.98 (br s, 1H, H-4), 3.53 (dd, J_{gem}=10.3 Hz, $J_{8,4}$=1.7 Hz, 1H, H-8), 2.80 (m, 1H, H-5), 2.69 (m, 1H, H-1), 2.24 (m, 2H, H-6exo, H-7exo), 1.89 (m, 4H, H-7endo, CH_3CO), 1.74 (m, 1H, H-6endo), 1.48 (s, 9H, $(CH_3)_3CO$), 0.94 (s, 9H, $(CH_3)_3CSi$), 0.12 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si); **^{13}C NMR** (100 MHz, $CDCl_3$, 298K) δ 167.7 (C=O, CH_3CO), 153.9 (C=O, $(CH_3)_3OCO$), 80.3 + 80.1 (C, $(CH_3)_3CO$), 69.9 + 69.4 (CH, C-2), 67.3 + 66.7 (CH, C-4), 65.3 + 64.4 (CH_2, C-8), 46.2 + 45.7 (CH, C-1), 40.0 + 39.1 (CH, C-5), 28.4 (CH_3, $(CH_3)_3CO$), 26.0 (CH_3, $(CH_3)_3CSi$), 24.6 (CH_2, C-6), 23.6 (CH_2, C-7), 23.4 (CH_3, CH_3CO), 18.6 (C, $(CH_3)_3CSi$), -5.1 (CH_3, CH_3Si), -5.4 (CH_3, CH_3Si). **HRMS** (ESI-TOF) Calcd for $[C_{20}H_{38}N_2O_4S+Na]^+$: 421.2493. Found: 421.2489.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **320**.

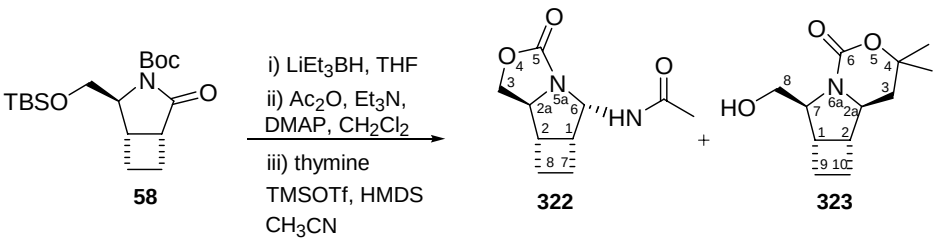
7.3. (1'*R*,2'*R*,4'*S*,5'*S*)-1-[*N*-(*tert*-butoxycarbonyl)-4'-*tert*-butyldimethylsilyoxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl]thymine (321) and (1*R*,2*S*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-acetamido-4-*tert*-butyldimethylsilyoxymethyl-3-azabicyclo[3.2.0]heptane (320)



N,O-Bis(trimethylsilyl)acetamide (BSA) (160 µl, 0.65 mmol) was added to a suspension of thymine (57 mg, 0.46 mmol) in dry acetonitrile (2 mL) under argon atmosphere. The reaction was allowed to stir for 20 min and cooled to 0 ºC. Then, a solution of crude **63** (0.13 mmol) in dry acetonitrile (1 mL) and $SnCl_4$ (23 µl, 0.20 mmol) were successively added dropwise and the reaction mixture was stirred at 0 ºC for 3 h. CH_2Cl_2 (3 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (1.5 mL). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtAcO 3:1) to afford 41 mg of a 80:20 mixture of **321** and **320** which could not be separated.

321: **^{1}H NMR** (400 MHz, $CDCl_3$, 333K) δ 8.37 (br s, 1H, NH), 7.51 (m, 1H, H-6), 6.03 (br s, 1H, H-2'), 3.98 (m, 2H, H-4', H-8'), 3.68 (dd, J_{gem}=10.7 Hz, $J_{8',4'}$=3.6 Hz, 1H, H-8'), 2.94 (m, 1H, H-1'), 2.80 (m, 1H, H-5'), 2.37 (m, 1H, H-7'exo), 2.23 (m, 1H, H-6'exo), 2.05 (m, 1H, H-7'endo), 1.94-1.85 (m, 4H, H-6'endo, CH_3-C5), 1.41 (br s, 9H, $(CH_3)_3CO$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.09 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$, 333K) δ 163.5 (C=O, C-4), 155.2 (C=O, $(CH_3)_3COCO$), 150.3 (C=O, C-2), 136.8 (CH, C-6), 109.2 (C, C-5), 81.5 (C, $(CH_3)_3CO$), 77.2 (CH, C-2'), 68.2 (CH, C-4'), 64.6 (CH_2, C-8'), 46.4 (CH, C-5'), 40.4 (CH, C-1'), 28.3 (CH_3, $(CH_3)_3CO$), 26.0, 25.8 (CH_3, $(CH_3)_3CSi$), 24.7 ($2CH_2$, C-6', C-7'), 18.4 (C, $(CH_3)_3CSi$), 12.5 (CH_3, CH_3-C5), -5.2 (CH_3, CH_3Si), -5.3 (CH_3, CH_3Si). **HRMS** (ESI-TOF) Calcd for $[C_{23}H_{39}N_3O_5Si+Na]^+$: 488.2551. Found: 488.2562.

7.4. *N*-(5-Oxo-hexahydro-4-oxa-5a-aza-cyclobuta[*a*]pentalen-6-yl)-acetamide (322) and 7-hydroxymethyl-4,4-dimethyl-octahydro-5-oxa-6a-aza-cyclobuta[*a*]inden-6-one (323)



A suspension of thymine (100 mg, 0.79 mmol) and $(NH_4)_2SO_4$ (40 mg, 0.30 mmol) in Hexamethyldisilazane (HMDS) (5 mL) was heated at 140 ºC becoming a clear solution which was stirred at this temperature overnight. Then, the solvent was removed under reduced pressure and the residue coevaporated with toluene (2x2 mL). The resulting clear oil was dissolved in dry CH_3CN (4 mL) and it was added to a solution of crude acetate **63** (0.14 mmol) in dry CH_3CN (1 mL). The solution was cooled to 0 ºC and TMSOTf (38 µl, 0.20 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 90 min. Then it was diluted with CH_2Cl_2 (6 mL) and saturated aqueous $NaHCO_3$ (3 mL) was added. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc-EtOH 10:1) to afford **322** (14 mg, 0.07 mmol, 49% yield from **58**) as a white solid and **323** (11 mg, 0.05 mmol, 34% yield from **58**) as a colourless oil and.

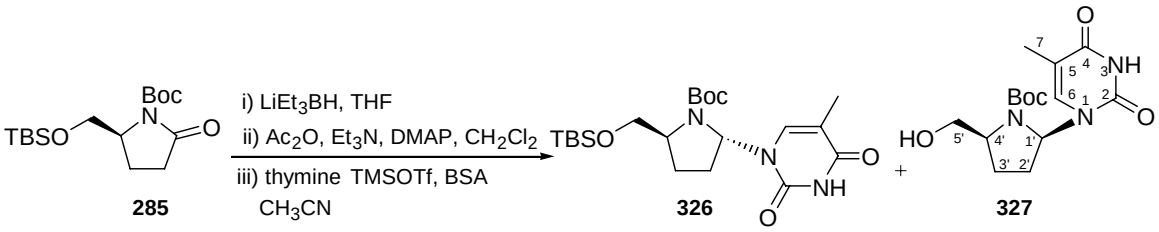
322: mp: unstable over 140 ºC; **IR** (ATR) 3360, 2954, 2921, 1729, 1675, 1535, 1204; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.36 (d, $J_{NH,6}$=4.7 Hz, 1H, NH), 5.62 (dd, $J_{6,1}$=7.3 Hz, $J_{6,NH}$=4.7 Hz, 1H, H-6), 4.59 (dd, J_{gem}=8.9 Hz, $J_{3,2a}$=8.2 Hz, 1H, H-3), 4.30 (ddd, $J_{2a,3}$=8.2 Hz, $J_{2a,2}$=7.0 Hz, $J_{2a,3}$=4.3 Hz, 1H, H-2a), 4.17 (dd, J_{gem}=8.9 Hz, $J_{3,2a}$=4.3 Hz, 1H, H-3), 3.54 (ddd, *J*=8.3 Hz, *J*=8.1 Hz, $J_{1,6}$=7.3 Hz,1H, H-1), 2.63 (m, 1H, H-2), 2.18 (m, 2H, H-7, H-8), 2.10 (m, 4H, C*H*$_3$CO, H-7), 1.62 (m, 1H, H-8); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0 (C=O, CH_3*C*O), 159.8 (C=O, O*C*ONH), 69.0/68.8 ($CH+CH_2$, C-3, C-6), 65.0 (CH, C-2a), 46.0/45.9 (2CH, C-1, C-2), 22.8 (CH_3, *C*H_3CO), 20.6 (CH_2, C-8), 19.3 (CH_2, C-7). **HRMS** (ESI-TOF) Calcd for $[C_{10}H_{14}N_2O_3+Na]^+$: 233.0897. Found: 233.0890.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **322**.

323: **IR** (ATR) 3431, 2976, 2931, 1657, 1253, 1197, 1032; **^{1}H NMR** (400 MHz, CD_3OD) δ 3.99 (ddd, *J*=11.9 Hz, *J*=6.6 Hz, *J*=3.0 Hz, 1H, H-2a), 3.77 (dd, J_{gem}=11.0 Hz, $J_{8,7}$=4.4 Hz, 1H, H-8), 3.70 (m, 1H, H-7), 3.60 (dd, J_{gem}=11.0 Hz, $J_{8,7}$=2.8 Hz, 1H, H-8), 2.97 (m, 1H, H-1), 2.54 (m, 1H, H-2), 2.26 (m, 2H, H-9exo, H-10), 2.16 (m, 2H, H-3, H-10endo), 1.71 (m, 2H, H-3, H-10), 1.44 (s, 3H, $(CH_3)_2CO$), 1.43 (s, 3H, $(CH_3)_2CO$); **^{13}C NMR** (100 MHz, CD_3OD) δ 156.2 (C=O, $(CH_3)_3COCO$), 83.1 (C, C-4), 69.3 (CH, C-7), 63.1/63.0 (CH+CH_2, C-2a, C-8), 46.6 (CH, C-2), 44.0 (CH, C-1), 41.4 (CH_2, C-3), 31.2 (CH_3, $(CH_3)_2CO$), 28.7 (CH_3, $(CH_3)_2CO$), 27.3 (CH_2, C-9), 25.2 (CH_2, C-10). **HRMS** (ESI-TOF) Calcd for $[C_{12}H_{19}NO_3+Na]^+$: 248.1257. Found: 248.1254.

COSY, HMQC, HMBC and NOESY experiments were recorded for **323**.

7.5. (1'*S*,4'*S*,)-1-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azacyclopent-2'-yl]thymine (326) and (1'*R*,4'*S*,)-1-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azacyclopent-2'-yl]thymine (327)



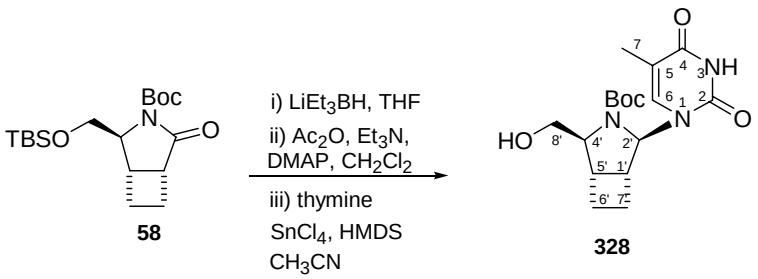
To a solution of **285** (120 mg, 0.37 mmol) in dry THF (7 mL) at -78 ºC, a 1.0 M solution of $LiEt_3BH$ in THF (0.90 mL, 0.90 mmol) was added dropwise. After 2 h of stirring at -78 ºC, the reaction mixture was quenched by the slow addition of H_2O (4 mL) and was allowed to warm to room temperature during 90 min. Then, H_2O (4 mL) was added, the mixture was diluted with diethyl ether (10 mL) and it was separated. The aqueous layer was extracted with diethyl ether (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude in CH_2Cl_2 (10 mL), DMAP (36 mg, 0.31 mmol), Et_3N (1.0 mL, 7.2 mmol) and acetic anhydride (340 μL, 3.6 mmol) were successively added dropwise. The mixture was stirred for 16 h at room temperature and then H_2O (5 mL)

was added. The two layers were separated and the aqueous one was extracted with CH_2Cl_2 (3x10 mL). The collection of organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness using toluene as coevaporant. The crude residue was used in the next reaction without further purification.

N,O-Bis(trimethylsilyl)acetamide (BSA) (440 µl, 1.80 mmol) was added to a suspension of thymine (159 mg, 1.11 mmol) in dry acetonitrile (7 mL) under argon atmosphere. Then, a solution of crude acetate (0.37 mmol) in dry acetonitrile (3 mL) and TMSOTf (98 µl, 0.88 mmol) were successively added dropwise under argon atmosphere at 0 ºC. The reaction mixture was stirred at 0 ºC for 70 min. Then, CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (2 mL). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 2:1) to afford a mixture of **326** and **327** (90 mg, 0.21 mmol, 56% yield from **285**) as a colourless oil which NMR showed the presence of rotamers. Repetitive column chromatography afforded a sample of the major isomer **327**.

327: **^{1}H NMR** (360 MHz, $CDCl_3$, 333K) δ 8.79 (br s, 1H, NH), 7.52 (s) + 7.26 (s) (1H, H-6), 6.09 (dd, $J_{1',2'}$=6.6 Hz, $J_{1',2'}$=5.5 Hz) + 6.04(m) (1H, H-1'), 4.10 (dd, J_{gem}=10.6 Hz, $J_{5',4'}$=3.6 Hz, 1H, H-5'), 3.98 (m, 1H, H-4'), 3.78 (dd, J_{gem}=10.6 Hz, $J_{5',4'}$=3.8 Hz) + 3.67 (dd, J_{gem}=10.6 Hz, $J_{5',4'}$=3.8 Hz) (1H, H-5'), 2.52 (m) + 2.31 (m) (1H, H-2'), 2.01 (m, 3H, H-2', 2H-3'), 1.89 (s, 3H, CH_3-C5), 1.37 (br s, 9H, (CH_3)$_3$CO), 0.92 (s, 9H, (CH_3)$_3$CSi), 0.12 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si); **^{13}C NMR** (90 MHz, $CDCl_3$, 333K) δ 163.8 (C=O, C-4), 154.2 (C=O, (CH_3)$_3$CO*C*O), 150.7, 150.2 (C=O, C-2), 135.7, 135.4 (CH, C-6), 110.1 (C, C-5), 81.3 (C, (CH_3)$_3$*C*O), 70.7 (CH, C-1'), 65.0 (CH, C-4'), 60.3, 60.1 (CH_2, C-5'), 31.7 (CH, C-2'), 28.3 (CH_3, (*C*H$_3$)$_3$CO), 26.0, 25.8 (CH_3, (*C*H$_3$)$_3$CSi), 25.5 (CH, C-3'), 18.5, 18.2 (C, (CH_3)$_3$*C*Si), 12.5, 12.4 (CH_3, *C*H$_3$-C5), -5.2 (CH_3, *C*H$_3$Si), -5.3 (CH_3, *C*H$_3$Si).

7.6. (-)-(1'*R*,2'*R*,4'*S*,5'*S*)-1-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl]thymine (328)

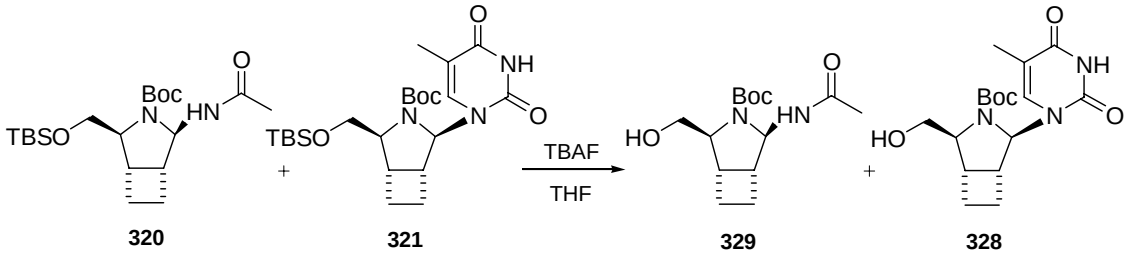


A suspension of thymine (57 mg, 0.46 mmol) and $(NH_4)_2SO_4$ (19 mg, 0.16 mmol) in Hexamethyldisilazane (HMDS) (3 mL) was heated at 140 ºC becoming a clear solution and the mixture was stirred at this temperature overnight. Then the solvent was removed under reduced pressure and the residue coevaporated with toluene (2x2 mL). The resulting clear oil was dissolved in dry CH_3CN (3 mL) and it was added to a solution of crude **63** (0.13 mmol) in dry CH_3CN (1.5 mL). The solution was cooled to 0 ºC and $SnCl_4$ (23 µl, 0.19 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 3.5 h. Then it was diluted with CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (3 mL) was added. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc- hexane 3:1) to afford **328** (17 mg, 0.05 mmol, 37% yield from **58**) as a white solid.

328: mp: 56-59 ºC (from EtOAc); $[\alpha]_D$: -41.3 (*c* 0.80, $CHCl_3$); **IR** (ATR) 3418, 3054, 2962, 2924, 1675, 1364, 1259, 1165; **^{1}H NMR** (400 MHz, $CDCl_3$, 333K) δ 8.13 (br s, 1H, NH), 7.44 (m, *J*=2.4 Hz, *J*=1.2 Hz, 1H, H-6), 5.87 (br s, 1H, H-2'), 4.14 (m, 1H, H-4'), 3.98 (dt, J_{gem}=11.0 Hz, *J*=3.3 Hz, *J*=3.1 Hz, 1H, H-8'), 3.66 (ddd, J_{gem}=11.0 Hz, *J*=5.8 Hz, *J*=3.6 Hz, 1H, H-8'), 2.92 (m, 3H, H-1', H-5', OH), 2.35 (m, 2H, H-6'exo, H-7'exo), 2.06 (m, 1H, H-7'endo), 1.92-1.83 (m, 4H, H-6'endo, CH_3-C5), 1.47 (s, 9H, $(CH_3)_3CO$); **^{13}C NMR** (100 MHz, $CDCl_3$, 333K) δ 163.5 (C=O, C-4), 155.3 (C=O, $(CH_3)_3COCO$), 150.3 (C=O, C-2), 137.6 (CH, C-6), 109.9 (C, C-5), 82.3 (C, $(CH_3)_3CO$), 77.2 (CH, C-2'), 69.0 (CH, C-4'), 65.2 (CH_2, C-8'), 45.5 (CH, C-1'), 40.6 (CH, C-5'), 28.4 (CH_3, $(CH_3)_3CO$), 25.0, 24.7 ($2CH_2$, C-6', C-7'), 12.1 (CH_3, CH_3-C5). **HRMS** (ESI-TOF) Calcd for $[C_{17}H_{25}N_3O_5+Na]^+$: 374.1686. Found: 374.1680.

COSY, HMQC, HMBC and NOESY experiments were recorded for **328**.

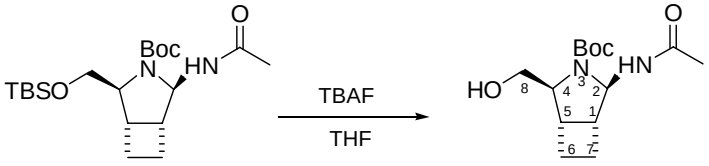
7.7. (-)-(1'*R*,2'*R*,4'*S*,5'*S*)-1-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl]thymine (328) and (-)-(1*R*,2*R*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-acetamido-4-hydroxymethyl-3-azabicyclo[3.2.0]heptane (329)



320 **321** **329** **328**

To an ice-cooled solution of **320** and **321** (20:80) (35 mg) in THF (2 mL), a 1.0 M solution of TBAF in THF (120 µl, 0.12 mmol) was added and the resulting solution was stirred for 2.5 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc-hexane 2:1) to afford **328** (15 mg, 0.04 mmol, 40% yield from **58**) as a white solid and traces of **329**.

7.8. (-)-(1*R*,2*R*,4*S*,5*S*)-*N*-(*tert*-butoxycarbonyl)-2-acetamido-4-hydroxymethyl-3-azabicyclo[3.2.0]heptane (329)



320 **329**

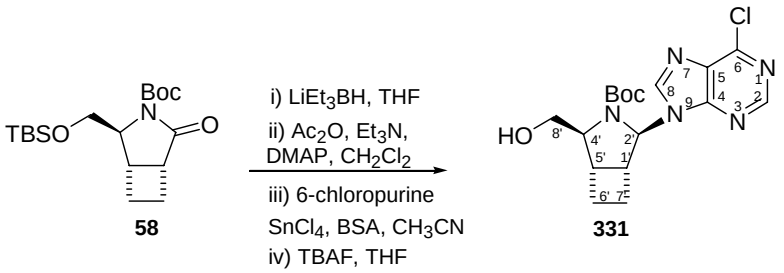
To an ice-cooled solution of **320** (35 mg, 0.09 mmol) in THF (2 mL), a 1.0 M solution of TBAF in THF (130 µl, 0.13 mmol) was added and the resulting solution was stirred for 4 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc-hexane 3:1) to afford **329** (19 mg, 0.07 mmol, 76% yield) as a colourless oil.

329: $[\alpha]_D$: -90.0 (*c* 0.30, $CHCl_3$); **IR** (ATR) 3306, 2976, 1699, 1655, 1384, 1162; **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.07 (d, $J_{NH,2}$=8.1 Hz) + 6.98 (d, $J_{NH,2}$=8.5 Hz) (1H, NH), 5.66 (d, $J_{2,NH}$=8.3 Hz, 1H, H-2), 4.02 (br s) + 3.96 (br s) (1H, H-4), 3.93 (m) + 3.85 (m)

(1H, H-8), 3.57 (m, 1H, H-8), 2.89 (m) + 2.82 (m) (1H, H-5), 2.75 (m, 1H, H-1), 2.58 (br s) + 2.44 (br s) (1H, OH), 2.25 (m, 2H, H-6exo, H-7exo), 1.87-1.85 (m, 4H, H-7endo, CH_3CO), 1.75 (m, 1H, H-6endo), 1.49 (s) + 1.46 (s) (9H, $(CH_3)_3CO$); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 168.3 + 167.7 (C=O, CH_3CO), 154.1 + 153.4 (C=O, $(CH_3)_3COCO$), 79.9 (C, $(CH_3)_3CO$), 69.5 (CH, C-2), 66.9 + 66.4 (CH, C-4), 64.0 + 63.7 (CH_2, C-8), 45.8 + 45.3 (CH, C-1), 40.0 + 39.2 (CH, C-5), 28.0 (CH_3, $(CH_3)_3CO$), 24.7 + 24.5 (CH_2, C-6), 23.3 (CH_3, CH_3CO), 23.3 + 23.1 (CH_2, C-7). **HRMS** (ESI-TOF) Calcd for $[C_{14}H_{24}N_2O_4+Na]^+$: 307.1628. Found: 307.1623.

DEPT, COSY, HMQC and HMBC experiments were recorded for **329**.

7.9. (-)-(1'*R*,2'*R*,4'*S*,5'*S*)-6-chloro-9-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl]-9*H*-purine (331)



N,O-Bis(trimethylsilyl)acetamide (BSA) (300 µl, 1.23 mmol) was added to a suspension of 6-chloropurine (137 mg, 0.88 mmol) in dry acetonitrile (6 mL) under argon atmosphere. The reaction was allowed to stir for 20 min and cooled to 0 ºC. Then, a solution of crude **63** (0.25 mmol) in dry acetonitrile (2 mL) and $SnCl_4$ (44 µl, 0.37 mmol) were successively added dropwise, and the reaction mixture was stirred at 0 ºC for 90 min. CH_2Cl_2 (5 mL) was added and the reaction was quenched with aqueous saturated $NaHCO_3$ (3 mL). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (3x7 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was used in the next reaction without further purification.

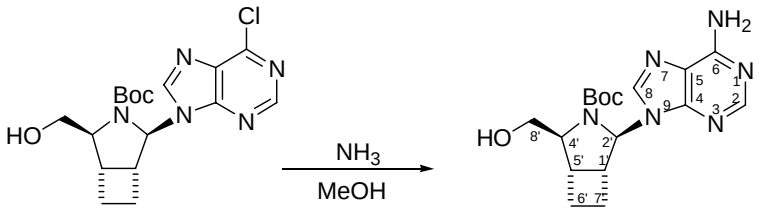
To an ice-cooled solution of the previous reaction crude in THF (6 mL), a 1.0 M solution of TBAF in THF (380 µl, 0.38 mmol) was added and the resulting solution was stirred for 2.5 h at room temperature. The solvent was removed and the resulting residue

was purified by column chromatography (EtOAc-hexane 1:1) to afford **331** (30 mg, 0.08 mmol, 32% yield from **58**) as a colourless oil.

331: $[\alpha]_D$: -18.6 (*c* 0.70, $CHCl_3$); **IR** (ATR) 3326, 3103, 2972, 2931, 1701, 1360, 1333, 1163, 1133; **^{1}H NMR** (400 MHz, $CDCl_3$, 333K) δ 8.70 (s, 1H, H-2), 8.46 (s, 1H, H-8), 6.29 (d, $J_{2',1'}$=1.3 Hz, 1H, H-2'), 4.22 (br s, 1H, H-4'), 3.98 (m, 1H, H-8'), 3.69 (dd, J_{gem}=10.9 Hz, $J_{8',4'}$=5.3 Hz, 1H, H-8'), 3.38 (br s, 1H, H-1'), 3.22 (br s, 1H, H-5'), 3.15 (br s, 1H, OH), 2.44 (m, 2H, H-6'exo, H-7'exo), 2.14 (m, 1H, H-7'endo), 1.98 (m, 1H, H-6'endo), 1.39 (s, 9H, $(CH_3)_3CO$); **^{13}C NMR** (100 MHz, $CDCl_3$, 333K) δ 154.8 (C=O, $(CH_3)_3COCO$), 151.5 (CH, C-2), 151.3, 150.9 (2C, C-4/C-6), 145.1 (CH, C-8), 132.4 (CH, C-5), 82.4 (C, $(CH_3)_3CO$), 77.2 (CH, C-2'), 69.2 (CH, C-4'), 64.9 (CH_2, C-8'), 45.5 + 45.3 (CH, C-1'), 40.9 (CH, C-5'), 28.3 (CH_3, $(CH_3)_3CO$), 24.9, 24.6 ($2CH_2$, C-6'/C-7'). **HRMS** (ESI-TOF) Calcd for $[C_{17}H_{22}ClN_5O_3+Na]^+$: 402.1303. Found: 402.1308.

DEPT, COSY, HMQC, HMBC and NOESY experiments were recorded for **331**.

7.10. (1'*R*,2'*R*,4'*S*,5'*S*)-9-[*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl]adenine (332)



331 **332**

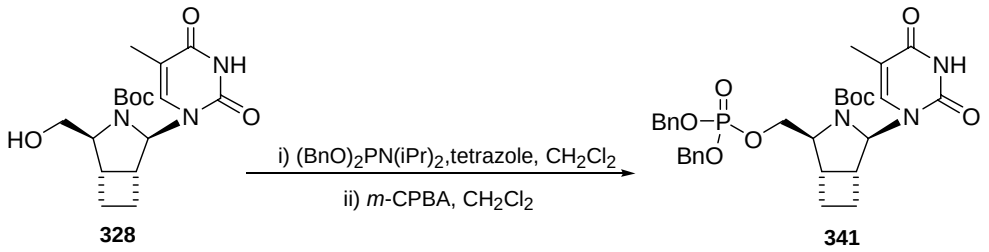
A solution of **331** (13 mg, 0.03 mmol) in saturated NH_3/MeOH (4 mL) was heated at 90 ºC in a sealed tube for 65 h. After cooling at room temperature the solvent was removed under vacuum and the residue was purified by column chromatography (CH_2Cl_2-MeOH 15:1) to afford **332** (4 mg, 0.01 mmol, 33% yield) as a white solid.

332: ^{1}H NMR (400 MHz, DMSO, 333K) δ 8.20 (s) + 8.12 (s) + 8.11 (s) + 8.0 (s) (2H, H-2 + H-8), 6.95 (br s, 2H, NH_2), 6.20 (s) + 6.17 (s) (1H, H-2'), 5.05 (br s) + 4.93 (t) (1H, OH), 4.00 (m) + 3.96 (m) (1H, H-4'), 3.70 (m, 1H, H-8'), 3.54 (m, 1H, H-8'), 3.20-3.10 (m, 2H, H-1', H-5'), 2.29 (m, 2H, H-6'exo, H-7'exo), 2.02 (m, 1H, H-7'endo), 1.85 (m, 1H, H-6'endo), 1.31 (br s, 9H, $(CH_3)_3CO$); **^{13}C NMR** (100 MHz,

DMSO, 333K) δ 156.6 (C, C-6), 152.9 (CH, C-2), 152.7 (C=O, $(CH_3)_3COCO$), 149.4 (C, C-4), 140.0 (CH, C-8), 119.7 (C, C-5), 80.8 (C, $(CH_3)_3CO$), 76.0 (CH, C-2'), 71.2 (CH, C-4'), 69.0 (CH_2, C-8'), 45.5 (CH, C-1'), 40.0 (CH, C-5'), 28.5 (CH_3, $(CH_3)_3CO$), 25.0/24.5 ($2CH_2$, C-6',C-7'). **HRMS** (ESI-TOF) Calcd for $[C_{17}H_{24}N_6O_3+Na]^+$: 383.1802. Found: 383.1806.

8. Synthesis of monophosphorilated azanucleosides

8.1. (-)-(1'*R*,2'*R*,4'*S*,5'*S*)-1-(*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2-yl)thymine-8'-di-O-benzyl-phosphate (341)



328 **341**

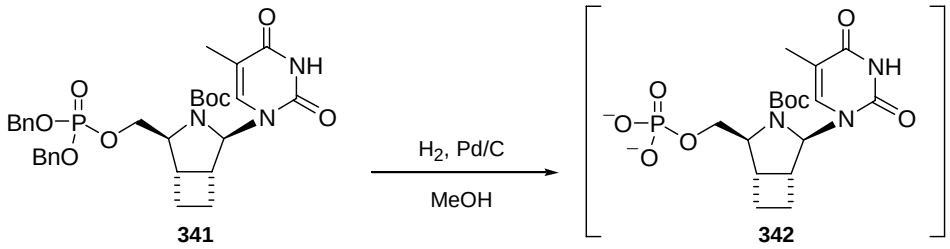
A mixture of **328** (25 mg, 0.07 mmol) and tetrazole (0.45M in CH_3CN, 635 μL, 0.28 mmol) was evaporated to dryness and suspended in dry CH_2Cl_2 (0.4 mL) under Argon atmosphere. The suspension was cooled to 0 ºC and dibenzyl diisopropylphosphoramidite (75 μL, 0.28 mmol) was added dropwise. The resulting suspension was stirred 1 h at 0 ºC and 1.5 h at room temperature. Then, the mixture was cooled again to 0 ºC and *m*-CPBA (88 mg, 0.28 mmol) was added in small amounts. The resulting clear solution was stirred at 0 ºC for 1.5 h and aqueous saturated $NaHCO_3$ (1 mL) was added. The mixture was diluted with EtOAc (3 mL), the layers separated and the organic layer was washed with saturated $NaHCO_3$ (3x1 mL), brine (3x1 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The resulting crude residue was purified by flash chromatography (EtOAc-hexane 2:1) to afford **341** (21 mg, 0.03 mmol, 48% yield) as a colourless oil.

341: $[\alpha]_D$: -35.6 (*c* 0.90, $CHCl_3$); **IR** (ATR) 3171, 3034, 2975, 1682, 1366, 1353; **^{1}H NMR** (360 MHz, $CDCl_3$, 333K) δ 7.97 (br s, 1H, NH), 7.34-7.30 (m, 11H, H-6, 2xPh), 5.91 (br s, 1H, H-2'), 5.0 (m, 4H, OCH_2Ph), 4.36 (m, 1H, H-8'), 4.13 (ddd, J_{gem}=10.1 Hz, $J_{8',4'}$=5.3 Hz, *J*=3.1 Hz, 1H, H-8'), 4.04 (ddd, $J_{4',8'}$=5.3 Hz, *J*=4.4 Hz, *J*=2.7 Hz, 1H, H-4'), 2.94 (m, 1H, H-5'), 2.78 (br s, 1H, H-1'), 2.28 (m, 2H, H-6', H-7'), 2.00 (m, 1H,

H-7'), 1.83 (m, 4H, H-6', CH_3CO), 1.41 (s, 9H, $(CH_3)_3CO$); **^{13}C NMR** (90 MHz, $CDCl_3$, 333K) δ 163.5 (C=O, C-4), 154.1 (C=O, $(CH_3)_3COCO$), 150.2 (C=O, C-2), 136.9 (CH, C-6), 135.9/135.8 (2xC, Ph), 128.7-128.0 (10xCH, Ph), 110.0 (C, C-5), 82.0 (C, $(CH_3)_3CO$), 77.2 (CH, C-2'), 69.7, 69.6, 69.6 (2xCH_2, OCH_2Ph), 68.1, 68.1 (d, $^2J_{C\text{-}P}$=5.5 Hz, CH_2, C-8'), 66.5, 66.4 ($^3J_{C\text{-}P}$=8.8 Hz, CH, C-4'), 45.8 (CH, C-1'), 40.2 (CH, C-5'), 28.3 (CH_3, $(CH_3)_3CO$), 25.0/24.7 (2xCH_2, C-6', C-7'), 12.1 (CH_3, CH_3-C5); **^{31}P NMR** (145.8 MHz, $CDCl_3$, 333K) δ 0.82 to 0.45 (m). **HRMS** (ESI-TOF) Calcd for $[C_{31}H_{38}N_3O_8P+Na]^+$: 634.2289. Found: 634.2302.

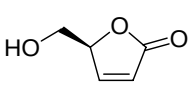
COSY, HMQC, HMBC and NOESY experiments were recorded for **341**.

8.2. Attempt of preparing (1'*R*,2'*R*,4'*S*,5'*S*)-1-(*N*-(*tert*-butoxycarbonyl)-4'-hydroxymethyl-3'-azabicyclo[3.2.0]hept-2'-yl)thymine-8'-phosphate (342)

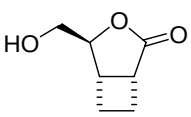


To a solution of **341** (8 mg, 0.0013 mmol) in MeOH (2 mL), Pd/C (14 mg) was added. The reaction was stirred under an atmosphere of H_2 (1 atm) for 17 h. Then, it was filtered through Celite and the filtrate was evaporated to dryness. The resulting residue was purified by diethylaminoethyl (DEAE) sepharose anion exchange chromatography (0 to 1M NH_4HCO_3 over 400 mL). Only undefined degradation compounds could be isolated.

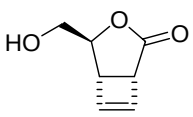
X. Formula index



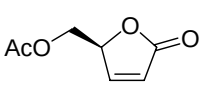
33



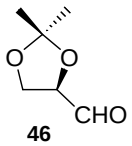
34



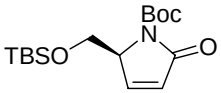
36



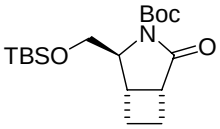
38



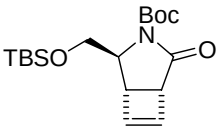
46



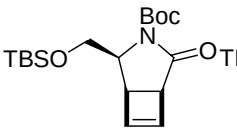
57



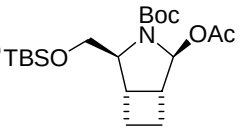
58



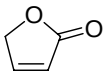
60



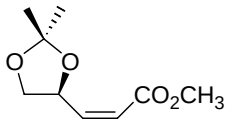
61



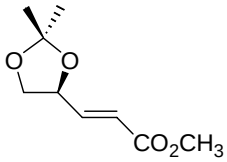
63



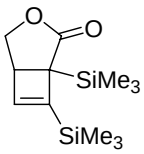
82



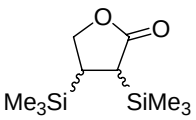
108



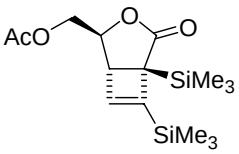
109



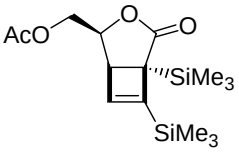
114



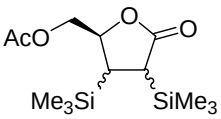
115



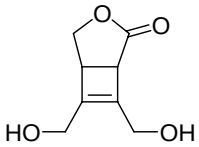
118



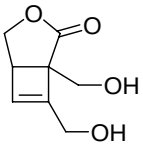
119



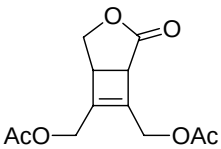
120-121



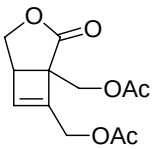
127



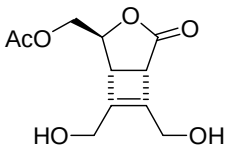
128



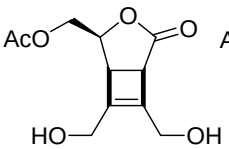
129



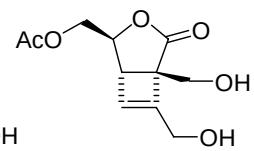
130



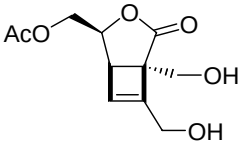
131



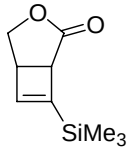
132



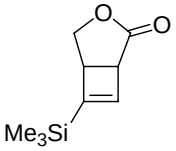
133



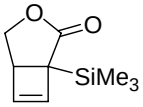
134



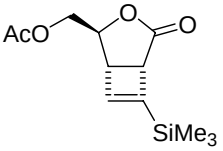
142



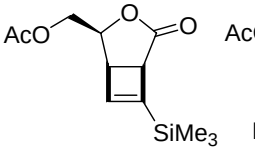
143



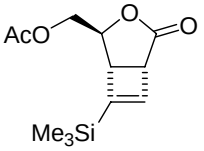
144



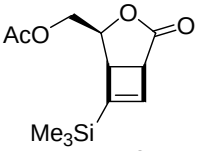
145



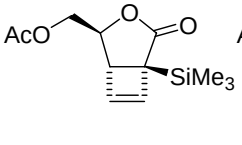
146



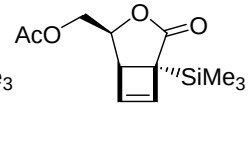
147



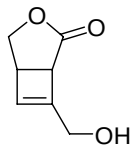
148



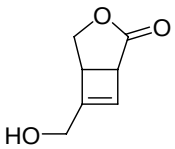
149



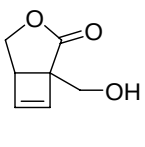
150



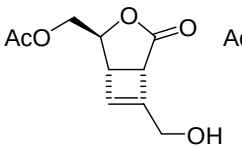
151



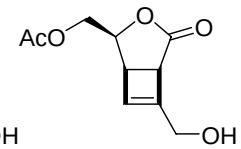
152



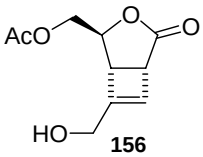
153



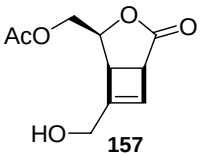
154



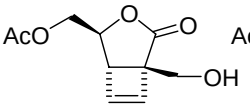
155



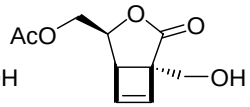
156



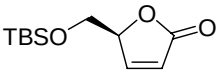
157



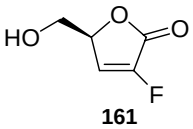
158



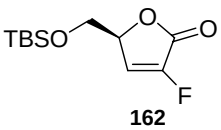
159



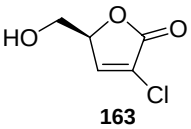
160



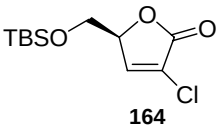
161



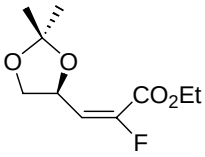
162



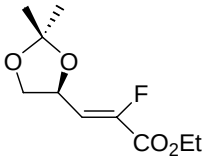
163



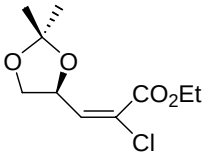
164



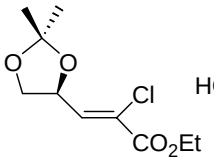
165



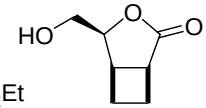
166



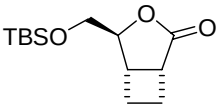
170



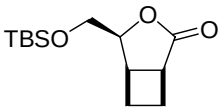
171



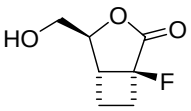
174



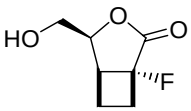
175



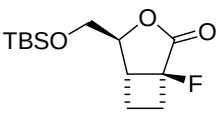
176



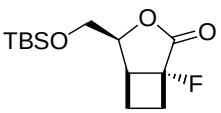
177



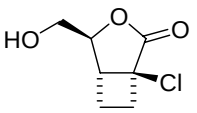
178



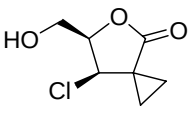
179



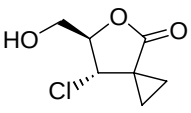
180



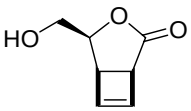
181



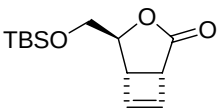
182



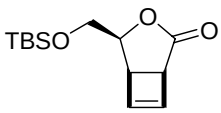
183



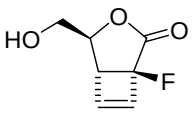
185



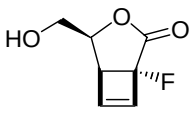
186



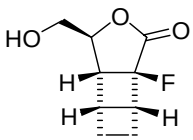
187



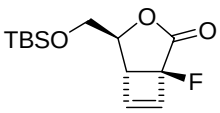
188



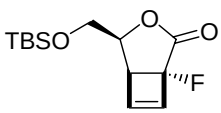
189



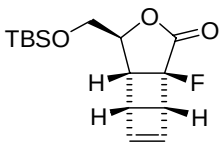
190



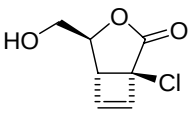
191



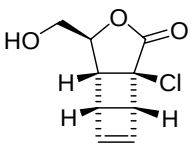
192



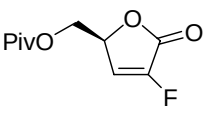
193



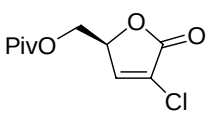
204



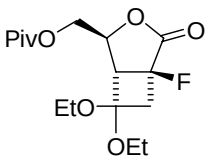
205



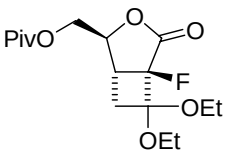
215



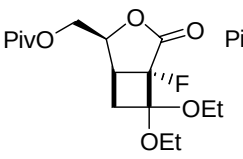
216



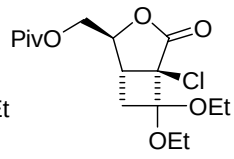
217



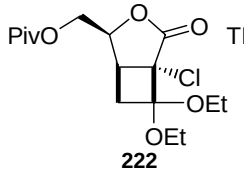
218



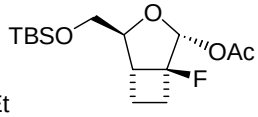
220



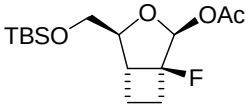
221



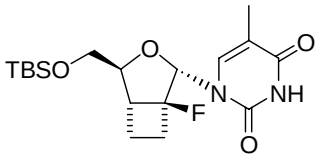
222



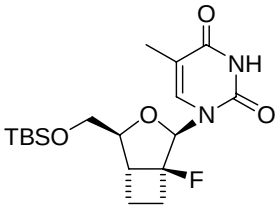
240



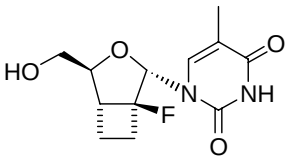
241



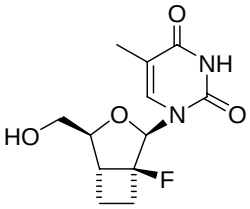
244



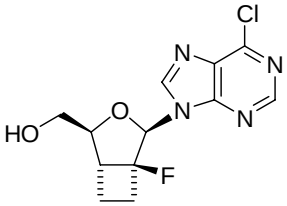
245



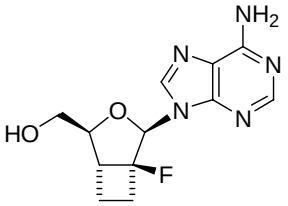
246



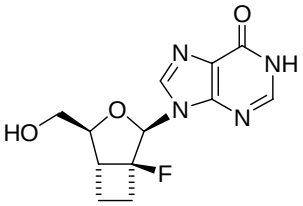
247



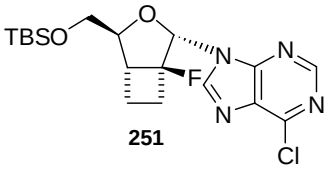
248



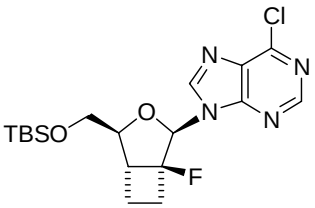
249



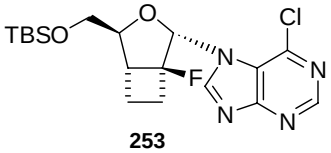
250



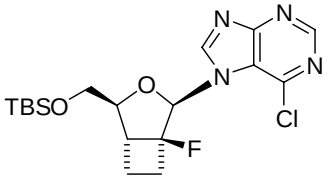
251



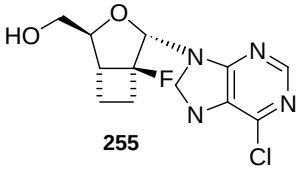
252



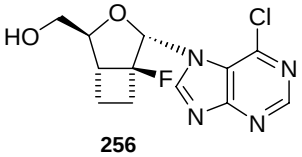
253



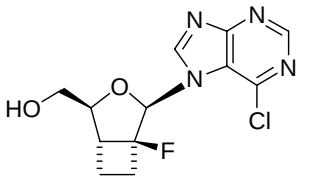
254



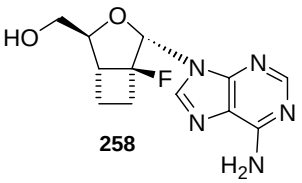
255



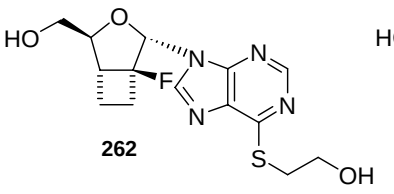
256



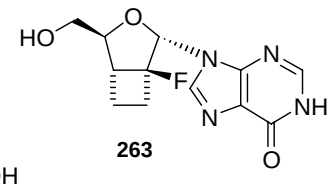
257



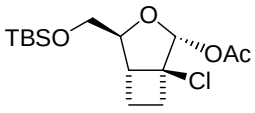
258



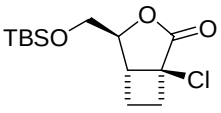
262



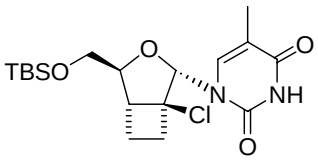
263



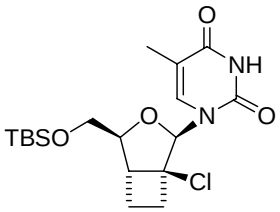
264



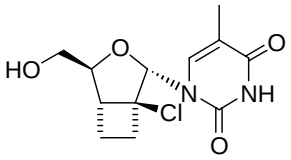
265



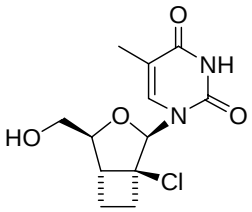
266



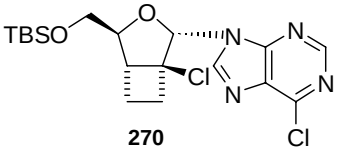
267



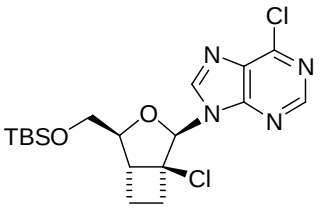
268



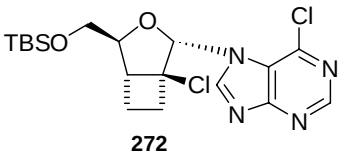
269



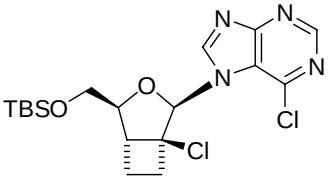
270



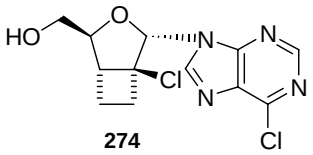
271



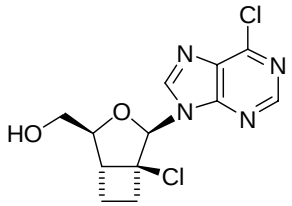
272



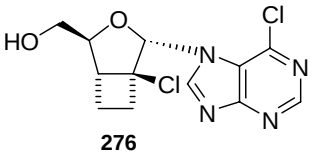
273



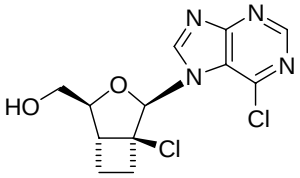
274



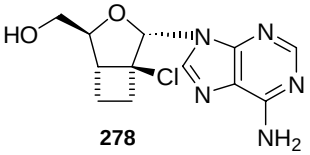
275



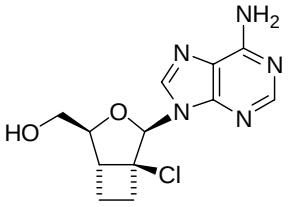
276



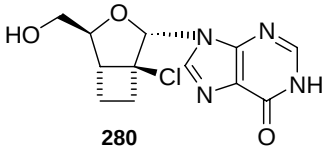
277



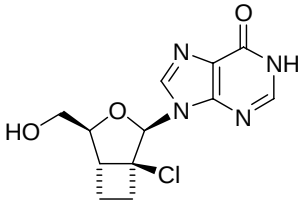
278



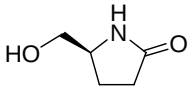
279



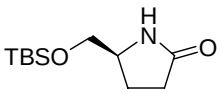
280



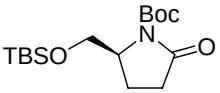
281



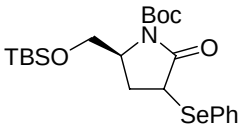
283



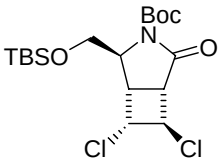
284



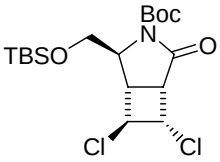
285



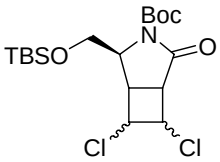
286



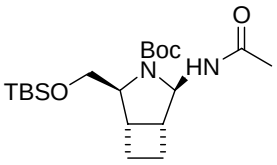
312



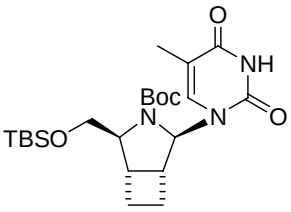
313



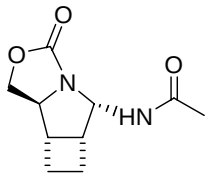
314-315



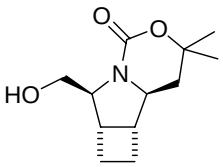
320



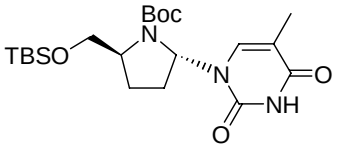
321



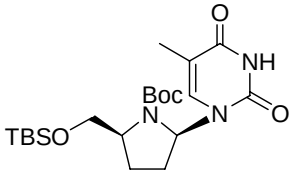
322



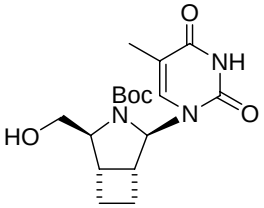
323



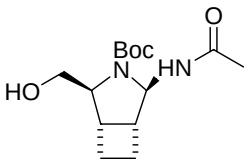
326



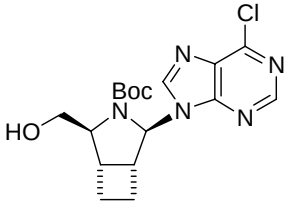
327



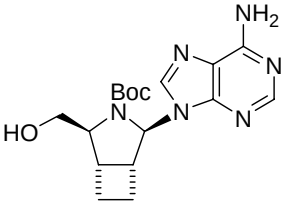
328



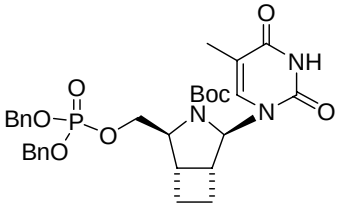
329



331



332



341

“Once divided, nothing left to subtract.
Some words when spoken, can’t be taken back.
Walks on his own with thoughts he can’t help thinking.
Future is above but in the past he’s slow and sinking.
Caught a bout of lighting, cursed the day he let it go.

Nothingman, isn’t it something?
Nothingman

(…) And he who forgets will be destined to remember ”

Nothingman, Pearl Jam