Universitat Autònoma de Barcelona

Rational Design and Synthesis of New Nucleoside Analogues Bearing a Cyclohexane Core

Beatriz Domínguez Pérez

Ph.D. Thesis

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Supervisors:

Dr. Ramon Alibés Arqués

Dr. Félix Busqué Sánchez

Dr. Jean-Didier Márechal

Departament de Química

Facultat de Ciències

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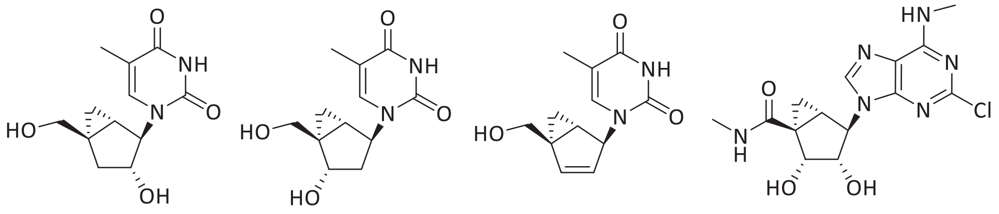
Chapter IV: Synthesis of bicyclo[4.1.0]heptane nucleoside analogues

1. Introduction

As aforementioned, during the last decades many efforts have been made trying to mimic the conformational behaviour of the sugar moiety of natural nucleosides.[1,2] In particular, conformationally locked carbocyclic analogues have been reported to present similar conformations, some of them showing high antiviral activity.[1–6]

Marquez and co-workers, reported a new family of conformationally rigid nucleoside analogues built on a bicyclo[3.1.0]hexane template that can lock the cyclopentane ring mimicking the *North* and *South* conformations of the natural furanose ring (Figure IV-1).[1–5,7,8] Namely, the introduction of the cyclopropane ring fused to the cyclopentene unit confers a certain degree of rigidity.



D-*iso*-**MCT** *N*-**MCT** *N*-**MCD4T** **MRS 2346**

Figure IV-1. Structures of conformationally locked nucleoside analogues built on a bicyclo[3.1.0]hexane scaffold with antiviral activity.

It was postulated that the conformation of the sugar ring plays an important role in determining the affinity of kinases and polymerases for nucleosides.[1] Since kinases and polymerases prefer different nucleoside conformations, the sugar moiety should not be completely rigid.

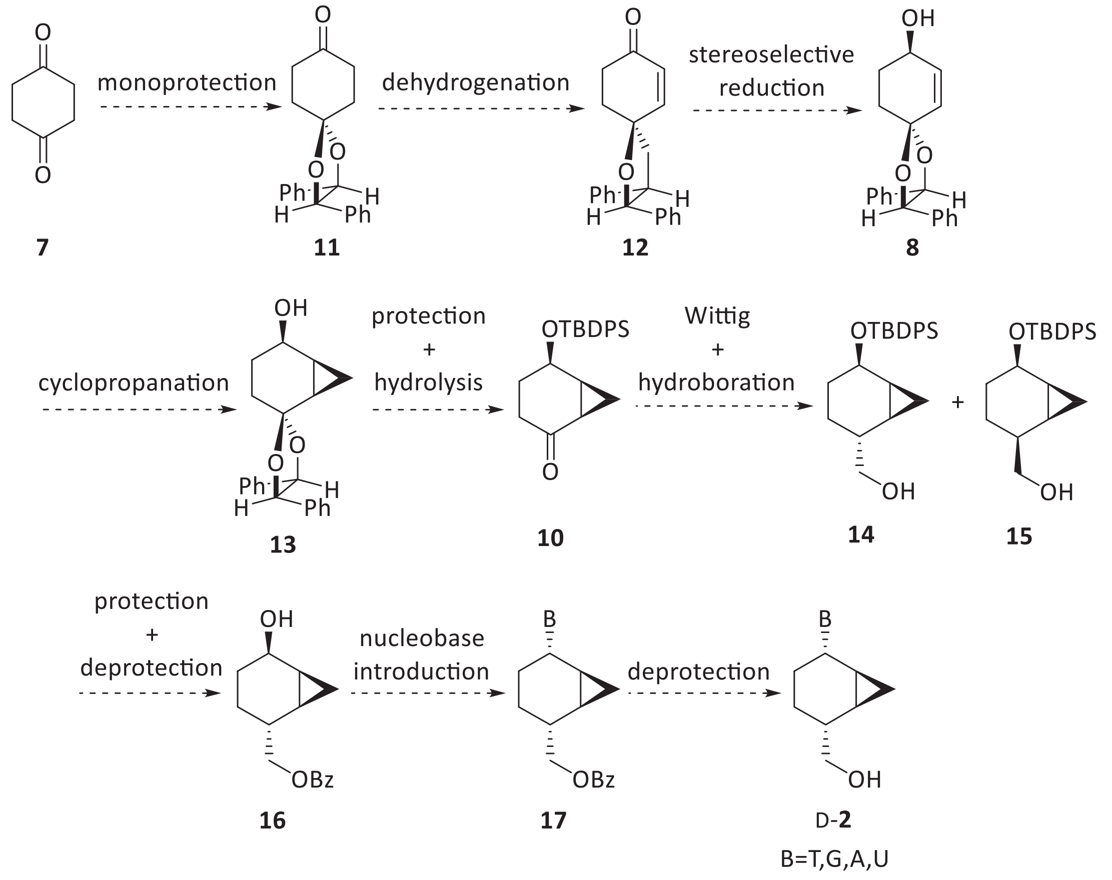
On the other hand, we have seen in the previous chapter of this thesis that compounds D- and L-**2** are good candidates to present anti-HSV activity according to our computational studies.

Taking all this information into account, we decided to synthesise a new class of cyclohexanyl nucleoside analogues with a cyclopropane ring fused to it, which would confer certain rigidity similar to that of a cyclohexene moiety. It is worth highlighting that this would be the first synthesis of nucleoside analogues built on a bicyclo[4.1.0]heptane scaffold.

2. Synthesis of bicyclo[4.1.0]heptane nucleoside analogues

2.1. Synthetic strategy

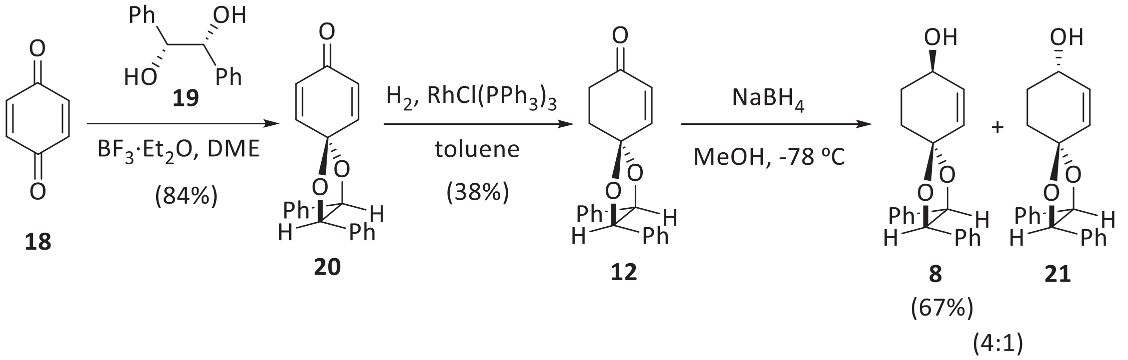
First, we undertook the synthetic pathway towards nucleoside analogue D-**2** (Scheme IV-1) taking advantage of the experience of the research group in the synthesis of similar compounds.[9] Thus, the synthetic route would start with the monoketalization of the commercially available 1,4-cyclohexanedione **7** using (*R*,*R*)-hydrobenzoin as a chiral auxiliary. Successive oxidation to the corresponding enone and stereoselective reduction of the carbonyl moiety would afford allylic alcohol **8**. Then, formation of the cyclopropane would lead to alcohol **13**, which would be converted into ketone **10** after protection of the alcohol and subsequent hydrolysis of the ketal. Wittig olefination followed by hydroboration would provide primary alcohols **14** and **15**. Alcohol **14** would be converted into the key intermediate **16** from which the nucleobase would be either introduced by direct coupling or constructed stepwise. Finally, removal of the protecting group would deliver the target nucleoside analogue D-**2**.



Scheme IV-1. Synthetic pathway foreseen to prepare bicyclo[4.1.0]heptane nucleoside analogues.

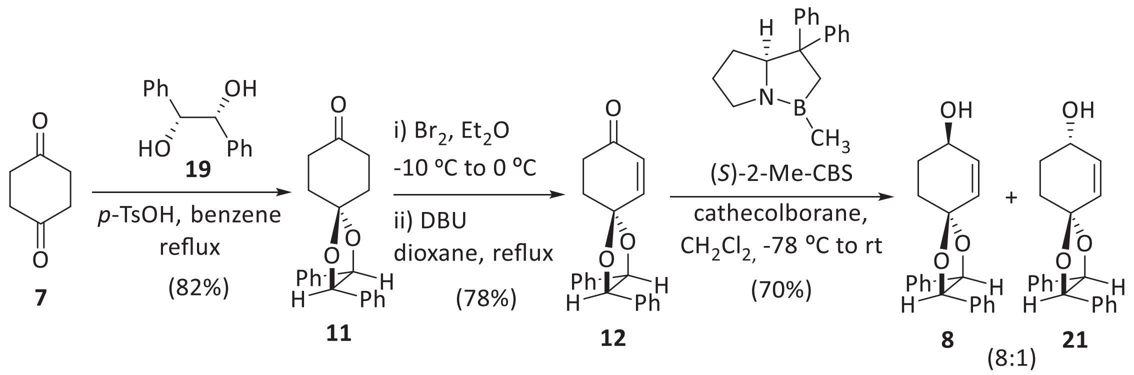
2.2. Diastereoselective synthesis of allylic alcohol 8

The enantiopure allylic alcohol **8** had been already synthesised in our research group from *p*-benzoquinone **18** in 3 steps and 21% overall yield (Scheme IV-2).[10] The synthetic approach started with a selective ketalization with (*R*,*R*)-hydrobenzoin **19** to afford monoketal **20** in 84% yield. Then, a partial hydrogenation using Wilkinson's catalyst led to enone **12** in low yield (38%), and finally, reduction using $NaBH_4$ delivered a 4:1 mixture of allylic alcohols **8** and **21**, which was enriched with the desired alcohol **8** (67% yield) after several recrystallizations. This methodology presented some disadvantatges: the low yield in the hydrogenation step and the poor diasteroselectivity achieved in the carbonyl reduction, requiring some recrystallizations to purify allylic alcohol **8**.



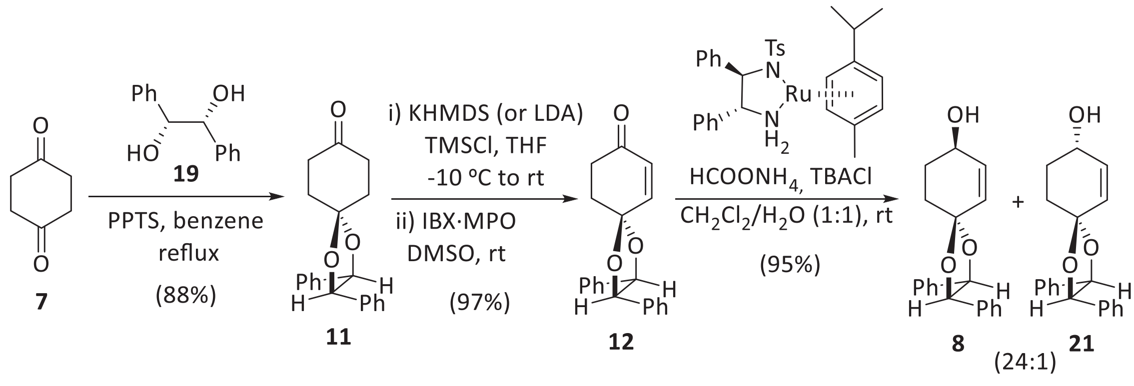
Scheme IV-2. Synthesis of allylic alcohol **8** previously developed in our research group.

With the aim of overcoming these problems, a more practical and multigram preparation of **8** was set up starting from 1,4-cyclohexanedione **7**, which afforded allylic alcohol **8** in 3 steps and 45% overall yield (Scheme IV-3).[11] This synthetic strategy started with the monoprotection of commercially available 1,4-cyclohexanedione **7** using (*R*,*R*)-hydrobenzoin **19** as a chiral auxiliary, providing ketone **11** in 82% yield. Then, sequential bromination of ketone **11** with Br_2 and dehydrobomination using DBU in 1,4-dioxane at the reflux temperature furnished enone **12** in 78% yield. Finally, reduction of the carbonyl group of enone **12** was carried out following the Corey-Bakshi-Shibata procedure,[12,13] delivering a 8:1 mixture of allylic alcohols **8** and **21**.



Scheme IV-3. Multigram methodology for the synthesis allylic alcohol **8** developed in our research group.

This synthetic strategy was later improved, affording allylic alcohol **8** in 3 steps and 81% overall yield (Scheme IV-4).[9] The yield of the selective ketalization was slightly enhanced by using pyridinium *p*-toluenesulfonate (PPTS) instead of *p*-TsOH, leading to monoketal **11** in 88% yield. Then, monodehydrogenation of ketone **11** was achieved following Nicolaou's methodology,[14,15] by treatment with KHMDS and TMSCl in anhydrous THF at -10 ºC and subsequent oxidation using a IBX·MPO complex in DMSO at room temperature, delivering enone **12** in 97% yield. Finally, reduction of the carbonyl group of enone **12** was carried out following an asymmetric transfer hydrogenation (ATH)[16,17] under mild conditions, delivering a 24:1 mixture of allylic alcohols **8** and **21**. However, when allylic alcohol **8** was prepared in multigram scale the obtained yields were barely reproducible and in consequence further development of the synthetic methodology was needed.

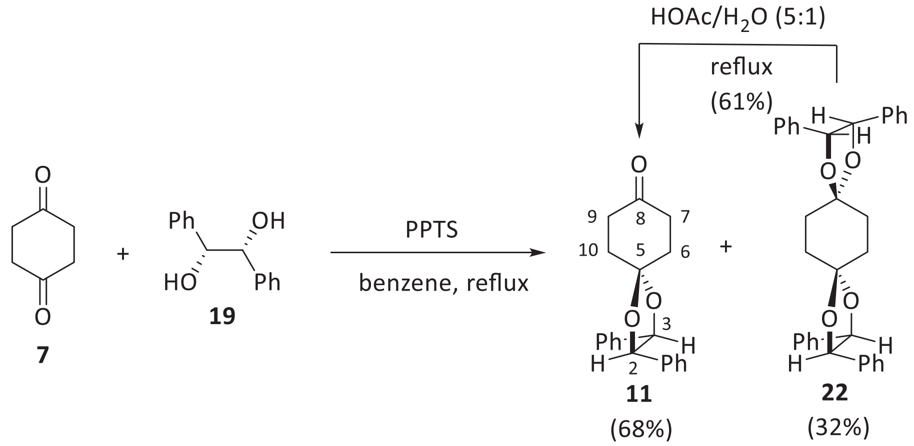


Scheme IV-4. New synthetic approach to allylic alcohol **8** developed in our research group.

According to these results, we adopted this last synthetic strategy to prepare allylic alcohol **8**, but performing some modifications.

2.2.1. Preparation of monoketal 11

The preparation of monoketal **11** was carried out by treatment of commercially available 1,4-cyclohexanedione **7** with (*R*,*R*)-hydrobenzoin in benzene at reflux temperature in the presence of pyridinium *p*-toluenesulfonate (PPTS), affording the monoketal **11** along with the corresponding bisketal **22** in 68% and 32% yield, respectively (Scheme IV-5). Monohydrolysis of **22** by treatment with a mixture of AcOH/H_2O (5:1) at the reflux temperature furnished an additional amount of **11**, being then the overall yield 88%.



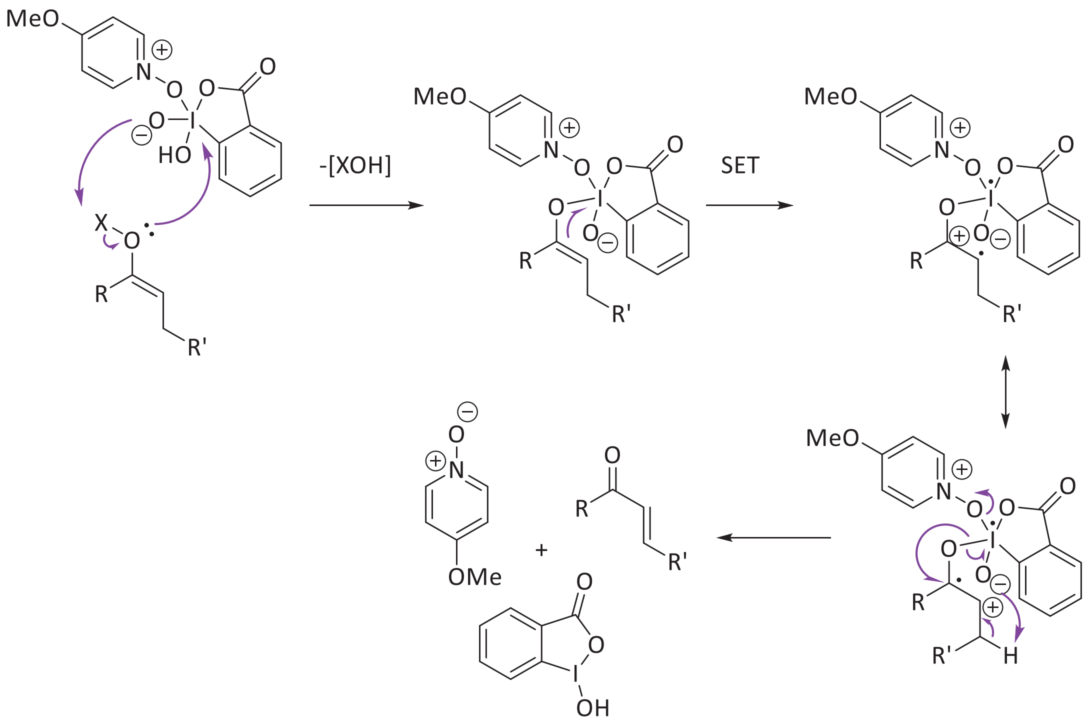
Scheme IV-5. Preparation of monoketal **11**.

The formation of monoketal **11** was confirmed by the ^{1}H-NMR spectrum, which shows a singlet signal at 4.84 ppm corresponding to both protons H-2 and H-3 due to the C_2 symmetry present in the compound. Moreover, a signal at 107.8 ppm in the ^{13}C-NMR spectrum corresponding to C-5 also confirms the formation of the ketal.

2.2.2. Preparation of enone 12

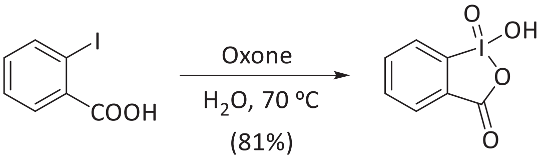
Then, we turned our attention to the dehydrogenation of monoketal **11** to get the corresponding enone **12**. The formation of enone **12** was proposed as a monodehydrogenation of monoketal **11** following Nicolaou's methodology,[14,15] which was devised to prepare α,β-unsaturated ketones and aldehydes in mild conditions from silyl enol ethers by using hypervalent iodine(V) species. In particular, the use of *o*-iodoxybenzoic acid (IBX) in complex with 4-methoxypyridine-*N*-oxide (MPO) in DMSO allows to oxidise silyl enol ethers to the corresponding α,β-unsaturated carbonyl compounds at room temperature.

The postulated mechanism for the IBX-mediated dehydrogenation consists of an enolization and consecutive capture of the enolate moiety, followed by single electron transfer (SET) to IBX and a rearrangement of the resulting radical cation to give the α,β-unsaturated carbonyl compound and *o*-iodosobenzoic acid (IBA) (Scheme IV-6).



Scheme IV-6. Postulated mechanism for the IBX-mediated dehydrogenation of ketones and aldehydes to α,β-unsaturated carbonyl compounds.

IBX is commercially available but it can be easily prepared in large scale following a protocol developed by Santagostino *et al.*,[18] which involves oxidation of *o*-iodobenzoic acid with Oxone® in water at 70 °C (Scheme IV-7).



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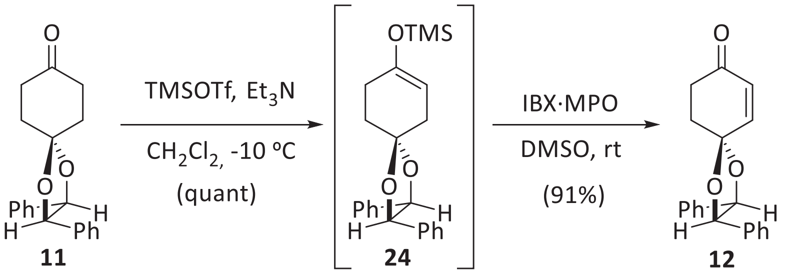
Scheme IV-7. Synthesis of IBX.

On that account, the reaction of monoketal **11** with potassium bis(trimethylsilyl)amide (KHMDS) or lithium diisopropylamide (LDA) in anhydrous THF at -78 °C and successive addition of TMSCl provided silyl enol ether **24**, which was oxidised with IBX·MPO complex following Nicolaou's protocol to achieve enone **12** in 97% overall yield. However, when the reaction was repeated at multigram scale, enone **12** was furnished in low yields, which prompted us to use an alternative base to generate the enolate. Thus, the reaction of monoketal **11** with Et_3N in dry dichloromethane at -10 °C and subsequent addition of TMSOTf led to silyl enol ether **24**, which was then oxidised with the IBX·MPO complex to provide enone **12** in 91% overall yield (Scheme IV-8). It is worth highlighting that for optimal results IBX must be pure, otherwise the presence of *o*-iodobenzoic acid or IBA under these conditions would cause a detrimental effect in the reaction rate and precipitation of IBX during the reaction.[15]



Scheme IV-8. Preparation of enone **12**.

The formation of enone **12** could be confirmed in the ^{1}H-NMR spectrum by the appearance of two new peaks at 6.13 ppm and 6.93 ppm, corresponding to the olefinic protons.

2.2.3. Preparation of allylic alcohol 8

The reduction of the carbonyl group of enone **12** was attempted by means of an asymmetric transfer hydrogenation (ATH). This reduction consists of the transference of an equivalent of hydrogen from a donor, using a chiral catalyst (Scheme IV-9).[16,17]

X = O, NR
DH_2 = hydrogen donor

Scheme IV-9. Asymmetric Transfer Hydrogenation (ATH).

In 1995, Noyori and co-workers reported a new methodology for ATH reactions using chiral ruthenium catalysts and isopropanol as solvent and H-donor.[19] The ruthenium catalyst features a chiral diamine and a *p*-cymene ring as ligands (Figure IV-2). This methodology was extensively studied on different functionalised ketones, aldehydes and imines, such as aromatic or α,β-unsaturated ketones,[17,20] because of its operational simplicity and high selectivity.

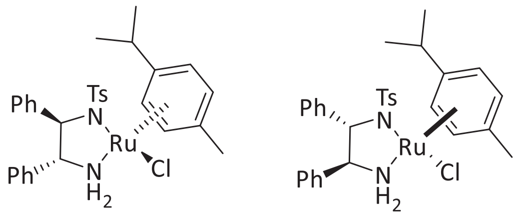
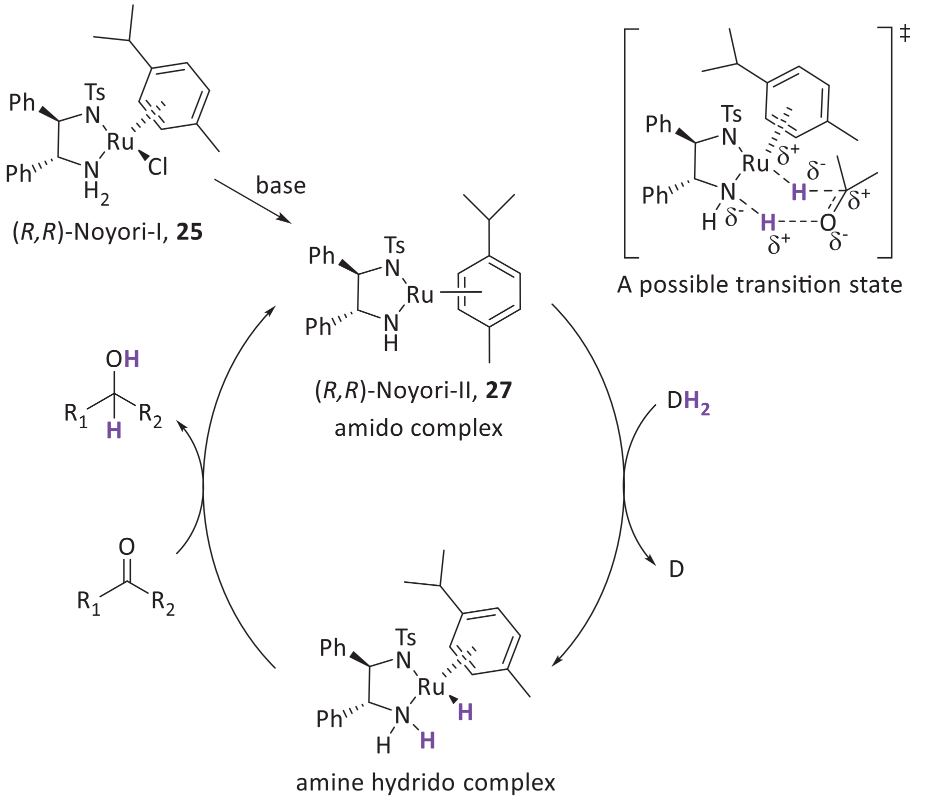

(*R*,*R*)-Noyori-I, **25**
(*S*,*S*)-Noyori-I, **26**

Figure IV-2. Structure of Noyori's catalysts.

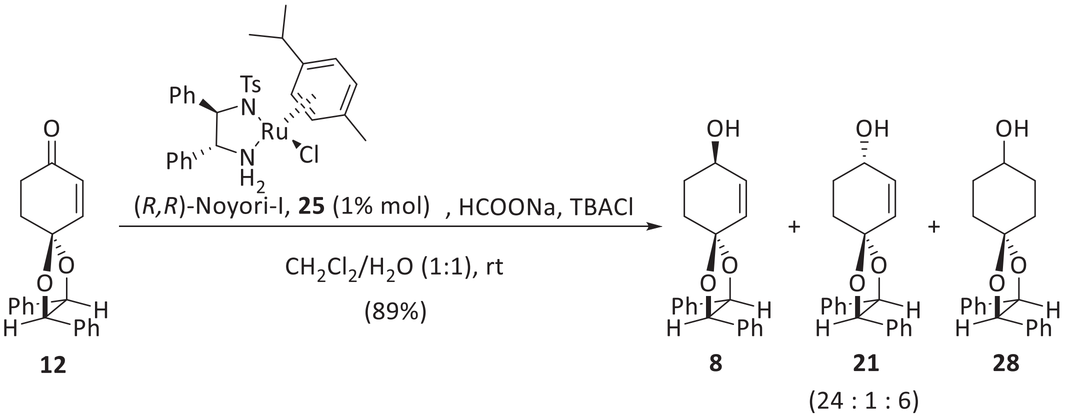
The postulated mechanism for this asymmetric reduction involves a previous reaction of the (*R*,*R*)-Noyori-I, **25**, with a base to generate the active catalyst (*R*,*R*)-Noyori-II, **27**, which is an amido Ru complex with a 16-electron square-planar geometry (Scheme IV-10).[21,22] Then, the amido Ru complex dehydrogenates 2-propanol to produce an amine hydrido Ru complex as a single diastereomer. The resulting amine hydrido Ru complex reduces the ketone or aldehyde to afford the corresponding alcohol.



Scheme IV-10. Postulated mechanism of the Asymmetric Tranfer Hydrogenation (ATH).

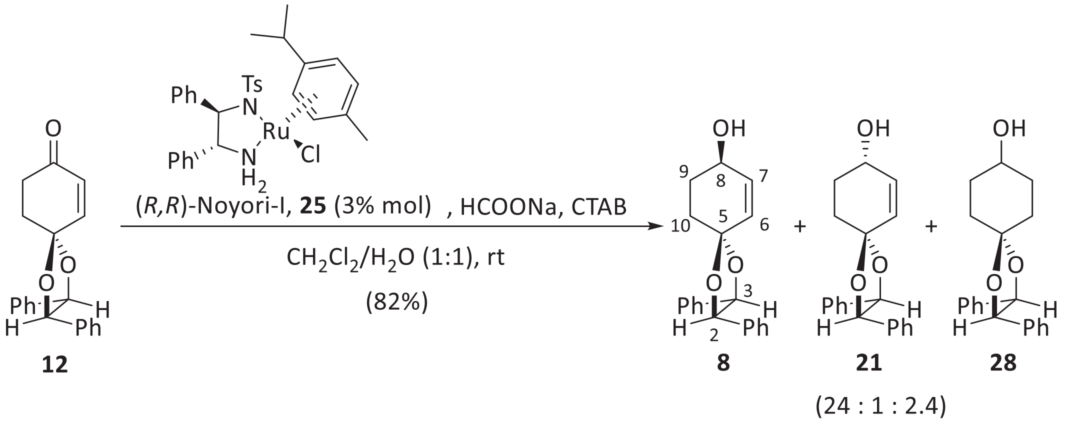
An inherent problem of ATH is the reversibility of the reaction, which prevents complete conversion to the products.[23] To overcome this problem, Noyori and co-workers suggested the use of formic acid and its salts instead of 2-propanol, since it decomposes into H_2 and CO_2 under the catalytic conditions leading to an irreversible reaction and, in theory, total conversion. In particular, an azeotropic mixture of HCOOH and Et_3N is frequently used as reducing agent. However, there are some restrictions to the use of HCOOH/Et_3N, since the azeotropic mixture is employed as a hydrogen source and as a solvent, the reaction is not stechiometric, and therefore the reduction is not selective to carbonyl groups but double or triple bonds can also be reduced.

To solve this problem, Cossy *et al*. reported a new methodology in a biphasic media CH_2Cl_2/H_2O (1:1) at room temperature, using tetrabutylammonium chloride (TBACl) as a phase-transfer agent and HCOONa as hydrogen donor in order to control the equivalents for the reaction.[24] Hence, the asymmetric transfer hydrogenation of enone **12** was performed following this procedure, affording allylic alcohol **8** and its diastereomer **21** in a 24:1 ratio, determined by ^{1}H-NMR (Scheme IV-11). However, these experimental conditions also hydrogenated the double bond leading to full-reduced alcohol **28** as a chromatographically inseparable impurity. Therefore, the ATH led to an inseparable mixture of allylic alcohols **8** and **21** and alcohol **28** in a 24:1:6 ratio. To avoid the hydrogenation of the double bond, the equivalents of HCOONa were reduced but without any success.



Scheme IV-11. Asymmetric transfer hydrogenation (ATH) of enone **12**.

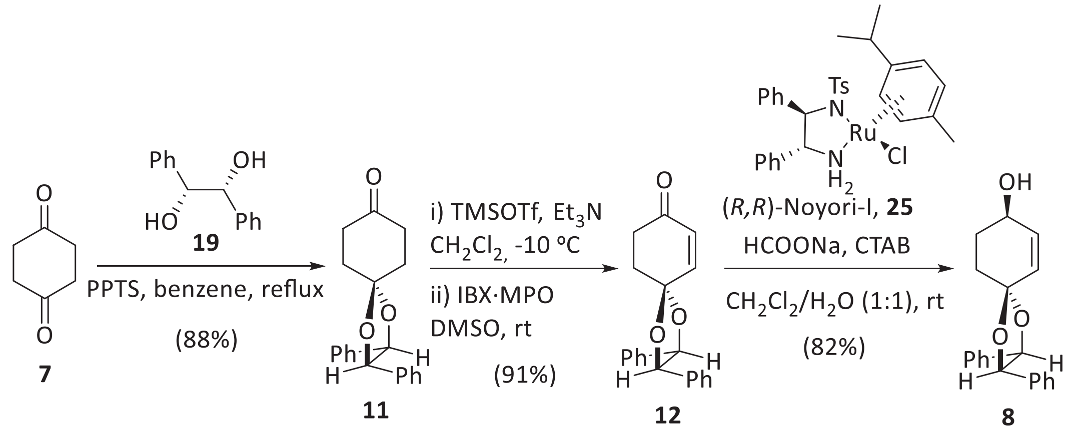
Deng and co-workers reported that the catalytic activity and enantioselectivity can be enhanced depending on the phase-transfer agent.[25] Considering this, we decided to use cetyltrimethylammonium bromide (CTAB) instead of TBACl as the phase-transfer catalyst. Thus, the asymmetric reduction of enone **12** in the same conditions as above but using CTAB as phase-transfer agent provided a mixture of allylic alcohols **8** and **21** with the same diastereomeric excess along with alcohol **28** in a 24:1:2.4 ratio and 82% yield (Scheme IV-12).



Scheme IV-12. Asymmetric transfer hydrogenation (ATH) of enone **12** using CTAB as the phase-transfer agent.

The formation of allylic alcohol **8** was observed in the ^{1}H-NMR spectrum by the appearance of a new peak at 4.29 ppm corresponding to the proton H-8, as well as by the displacement of the protons H-6 and H-7 to higher chemical fields (δ 5.92 and 6.05 for H-6 and H-7, respectively) due to the loss of conjugation.

In summary, we have developed a new stereoselective strategy to prepare allylic alcohol **8** in multigram quantities starting from the commercially available 1,4-cyclohexanedione, **7**, in 3 steps and 66% overall yield (Scheme IV-13). This new procedure has improved not only the diastereoselectivity of the reduction but also the overall yield.



Scheme IV-13. Synthesis of allylic alcohol **8**.

Interestingly, allylic alcohol **8** is also a precursor of 4-hydroxy-2-cyclohexenone, **29**, which has been used as a building block in the synthesis of several bioactive compounds, such as the anti-cholesterol agents compactin and ML-236A[26], the immunosuppressant FK-506[27] and the bacterial DNA primase inhibitor Sch 642305 (Figure IV-3).[28,29] Thus, we planned to check the suitability of our synthetic strategy to synthesise 4-hydroxy-2-cyclohexenone **29** in competitive yield with respect the precedents reported.

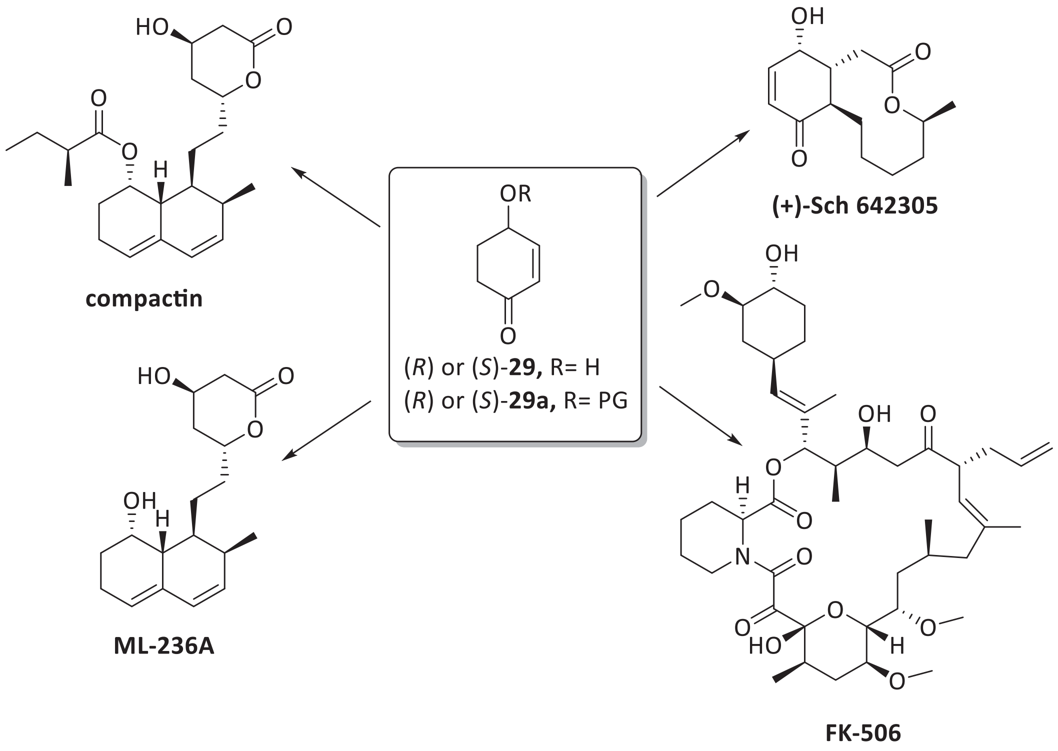


Figure IV-3. Some examples of 4-hydroxy-2-cyclohexenone **29** as a building block.

2.3. Preparation of 4-hydroxy-2-cyclohexenone 29

To date, several syntheses of both enantiomers of **29** as well as their *O*-protected derivatives have been published, based on different strategies such as enzymatic transformations,[30,31] kinetic resolutions,[32–37] the use of chiral auxiliaries[10,38–41] or from the chiral pool (Figure IV-4).[42–44] Many of these syntheses involve multi-step sequences with low overall yield. Furthermore, there are some practical problems related to the isolation of compound **29**, as it is highly soluble in water and volatile.

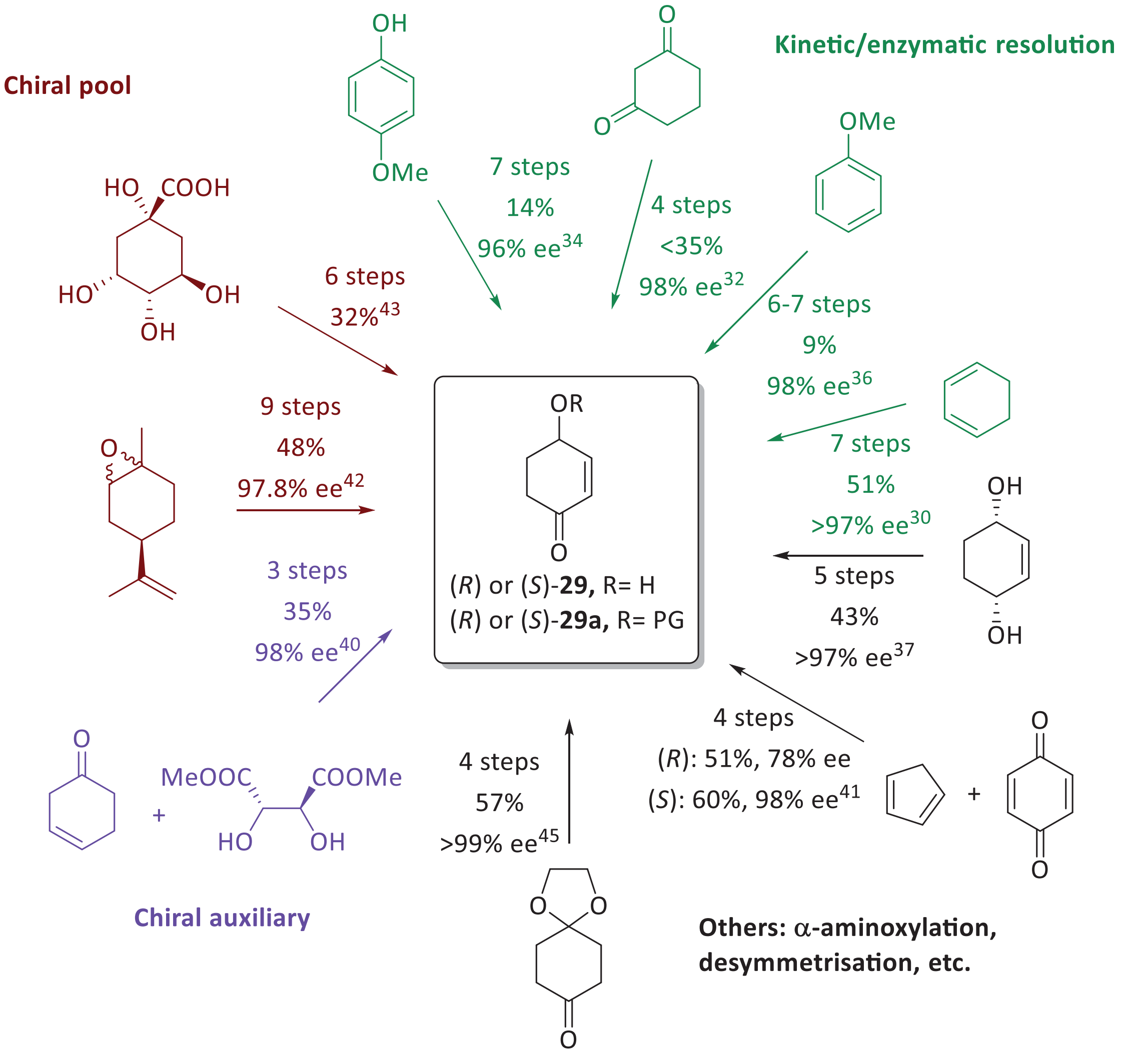
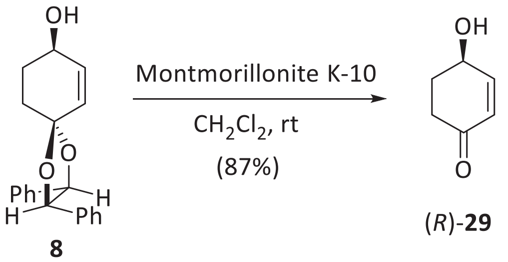


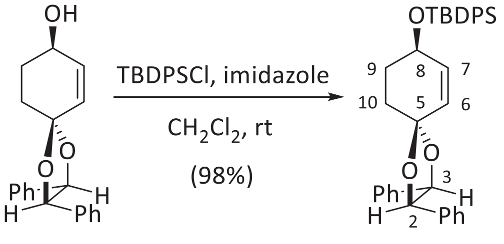
Figure IV-4. Some examples of reported synthesis of both enantiomers of 4-hydroxy-2-cyclohexenone **29**.

(4*R*)-4-hydroxy-2-cyclohexenone, (*R*)-**29**, has been previously synthesised in our research group in 87% yield by treatment of allylic alcohol **8** with montmorillonite K-10 in dichloromethane (Scheme IV-14),[10] according to the method described by Taylor and co-workers.[46] However, the yields were barely reproducible due to the volatility of 4-hydroxy-2-cyclohexenone. To overcome this problem, we decided to protect the hydroxyl group as a silyl ether before removal of the ketal.



Scheme IV-14. Hydrolysis of the ketal **8**.

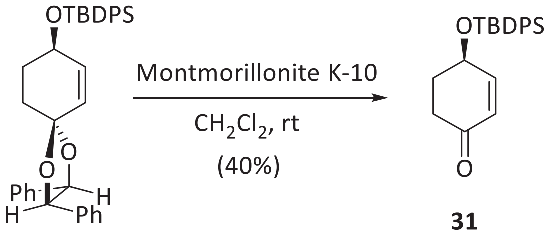
Thus, protection of allylic alcohol **8** was accomplished by reaction with TBDPSCl and imidazole in dichloromethane at room temperature, providing the corresponding silyl derivative **30** in 98% yield (Scheme IV-15). The formation of **30** was confirmed by ^{1}H-NMR, which showed three new signals (δ 1.09 ppm, 7.23 – 7.14 ppm and 7.72 ppm) corresponding to the *tert*-butyldiphenylsilyl group.



8 **30**

Scheme IV-15. Protection of allylic alcohol **8** using TBDPSCl.

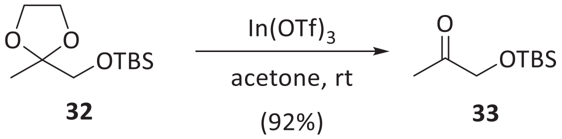
When the hydrolysis of the ketal **30** was carried out by treatment with Montmorillonite K-10 in dichloromethane at room temperature, enone **31** was afforded in 40% yield (Scheme IV-16). This low yield prompted us to use an alternative methodology to carry out the ketal hydrolysis.



30 **31**

Scheme IV-16. Removal of the ketal of **30**.

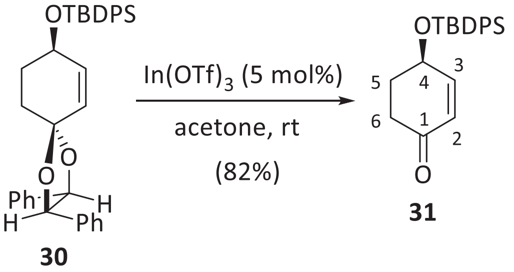
There are different methodologies in the literature to hydrolyse acetals under neutral conditions, such as the use of CAN, catalytic I_2 or $Bi(NO_3)_3·5H_2O$.[47–49] In this context, in 2007 Gregg and co-workers described a new procedure to remove acetals and ketals under mild neutral conditions via a transacetalization with acetone and indium(III) trifluoromethanesulfonate, In(OTf$_3$), as a catalyst, without removing silyl ethers (Scheme IV-17).[50]



32 **33**

Scheme IV-17. Example of hydrolysis of ketals catalysed by In(OTf)$_3$.

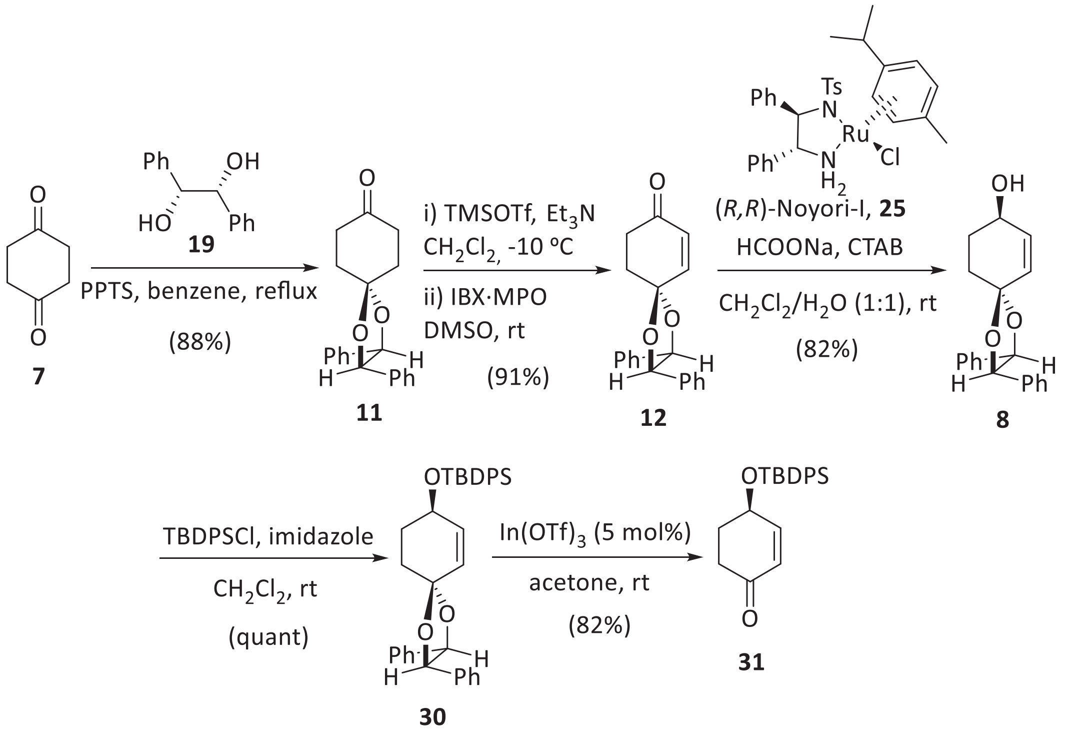
Accordingly, hydrolysis of the ketal was attempted following Gregg's procedure by treatment with $In(OTf)_3$ in acetone at room temperature to provide the desired ketone **31** in 82% yield (Scheme IV-18).



Scheme IV-18. Hydrolysis of the ketal **30**.

The formation of enone **31** could be confirmed by NMR spectroscopy. Thus, in the ^{1}H-NMR spectrum, proton H-3 appears downfield shifted (δ 6.80) and protons corresponding to the ketal have disappeared. Additionally, a new signal at 199.0 ppm corresponding to C-1 is observed in the ^{13}C-NMR spectrum.

Hence, we have developed a new procedure to prepare the enantiomerically pure *O*-protected derivative **31** starting from 1,4-cyclohexanedione **7** in 5 steps and 54% overall yield, which competes positively with the published methodologies (Scheme IV-19). The corresponding enantiomer could be synthesised following the same strategy but using (*S*,*S*)-Noyori-I as catalyst in the Asymmetric Transfer Hydrogenation (ATH) step.

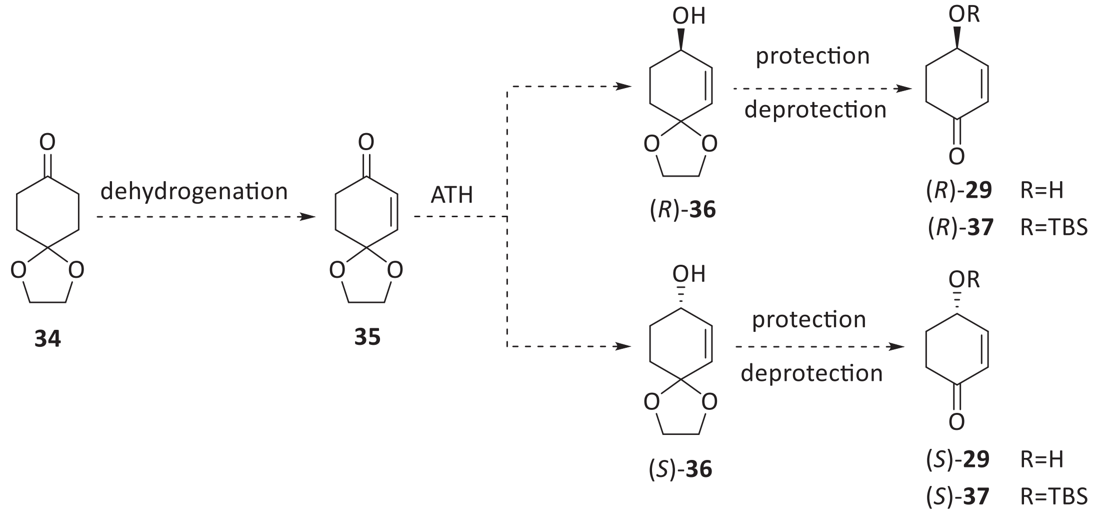


Scheme IV-19. Synthesis of enone **31**.

At this point, we wondered whether the high stereoselectivity achieved in the asymmetric reduction was due to a cooperative effect between the chiral auxiliary of **19** and the Noyori's catalyst **25** or the same results could be obtained without any chiral auxiliary. With this in mind, we planned to synthesise both enantiomers of 4-hydroxy-2-cyclohexenone, **29**, following the previous strategy but without using a chiral auxiliary.

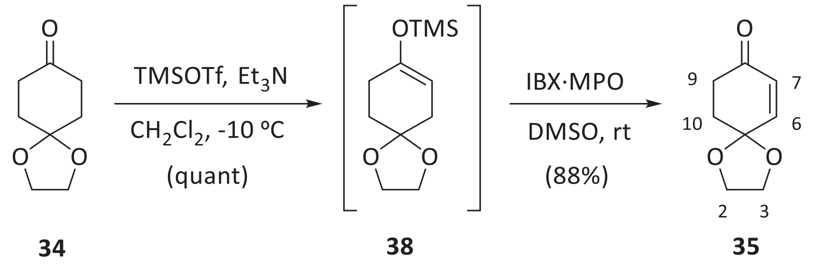
2.4. Enantioselective synthesis of both enantiomers of cyclohexenone 29 and their derivatives

The synthetic strategy would start with the monodehydrogenation of the commercially available monoketal **34** and successive asymmetric reduction, affording allylic alcohol **36**, which would lead either to enone **29** by ketal hydrolysis or its *O*-protected derivative **37** by protection and ketal hydrolysis (Scheme IV-20).



Scheme IV-20. Synthetic pathway foreseen to prepare both enantiomers of 4-hydroxy-2-cyclohexenone, **29**, and *O*-silyl derivatives **37**.

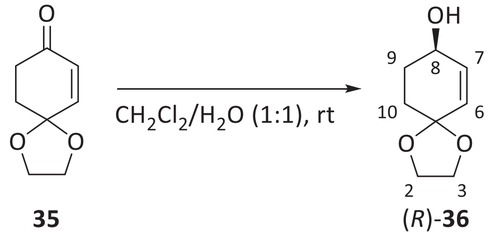
The synthesis began with the treatment of commercially available monoketal **34** with Et_3N and TMSOTf in anhydrous dichloromethane at -10 °C leading to the corresponding silyl enol ether, which was then oxidised with IBX·MPO complex to furnish enone **35** in 88% yield (Scheme IV-21). It is worth noting that IBX must be pure in order to avoid a possible hydrolysis of the ketal that would eventually lead to hydroquinone.



Scheme IV-21. Formation of enone **35**.

The asymmetric reduction of enone **35** was first carried out under similar conditions that the previously optimized for the reduction of enone **12**, in a biphasic media (CH_2Cl_2/H_2O 1:1), using (*R*,*R*)-Noyori-I, **25**, as catalyst, TBACl as a phase-transfer agent and $HCOONH_4$ as hydrogen source. Under these experimental conditions, allylic alcohol (*R*)-**36** was obtained along with its totally hydrogenated derivative H-**36** in a 6:1 ratio and 67% yield considering the starting material recovered (Table IV-1, entry 1). The poor conversion achieved was attributed to the degradation of the catalyst.

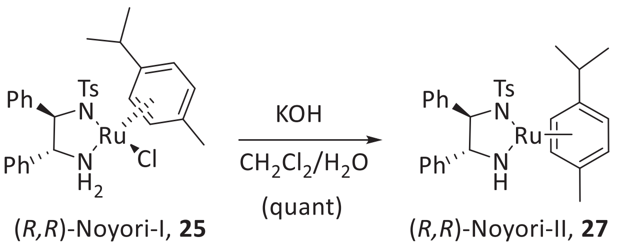
Table IV-1. Reaction conditions assayed in the asymmetric transfer hydrogenation.



Entry	Catalyst	Hydrogen donor	Phase-transfer agent	Conversion (%)	Yield (%)[a]
1	(*R*,*R*)-Noyori-I, **25**	$HCOONH_4$	TBACl	78	67
2	(*R*,*R*)-Noyori-II, **27**	$HCOONH_4$	TBACl	55	72
3	(*R*,*R*)-Noyori-II, **27**	HCOONa	TBACl	75	79

a) Yield considering starting material recovered.

To solve this problem, we proposed the activation of the Ru catalyst **25** before the ATH reaction. Baldwin *et al*. reported a procedure to prepare the active catalyst **27** by treatment of $[RuCl_2(p\text{-cymene})]_2$ with (*R*,*R*)-TsDPEN in the presence of KOH.[51] Taking this into account, we attempted the activation of the commercially Ru catalyst **25** by treatment with KOH in dichloromethane and subsequent addition of water, delivering the active complex **27** in quantitative yield (Scheme IV-22).

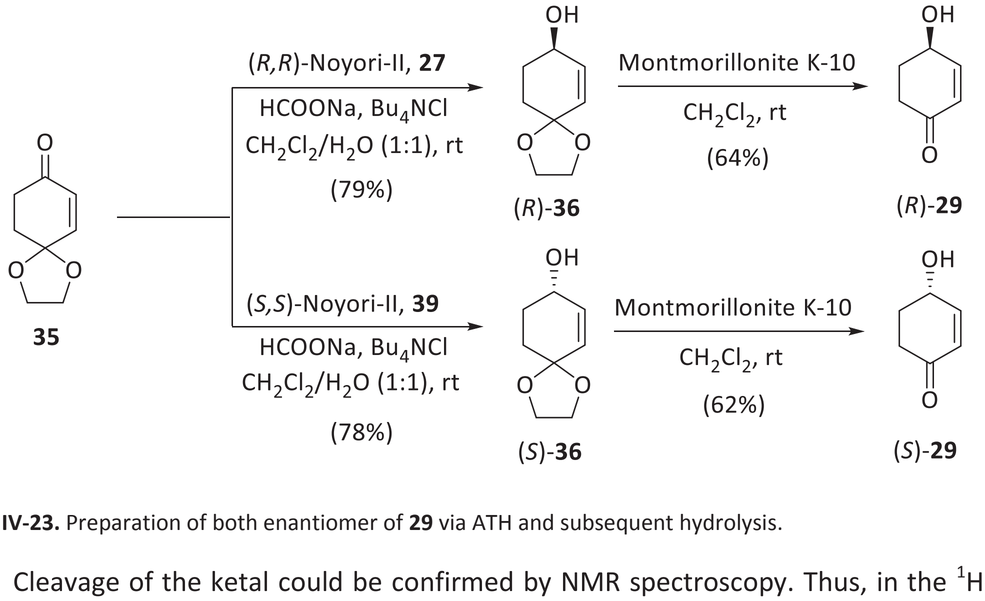


Scheme IV-22. Synthesis of catalyst (*R*,*R*)-Noyori-II, **27**.

When the ATH reaction was repeated using the active catalyst (*R*,*R*)-Noyori-II **27**, the yield was improved but some starting material was still recovered (entry 2). The low yields may be due to the hydrolysis of the acetal during the reaction, providing volatile enone **29**. To overcome this problem, the hydrogen source was changed to HCOONa in order to avoid acidic media, affording allylic alcohol (*R*)-**36** in higher yield (entry 3). Nevertheless, in all the cases the conversion was not completed.

With these results in hands, the asymmetric reduction was also performed with the (*S*,*S*)-Noyori-II catalyst, **39**, providing allylic alcohol (*S*)-**36** in 78% yield considering the starting material recovered (74% conversion)(Scheme IV-23).

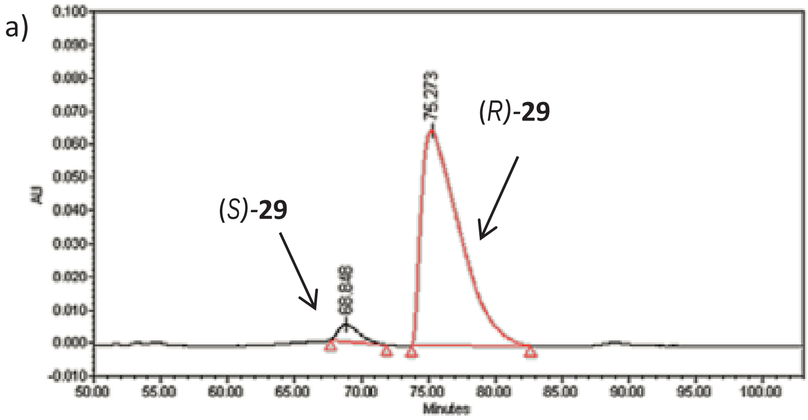
Next step involved the hydrolysis of the ketal **36**. Deprotection of the carbonyl group was attempted by treatment with montmorillonite K-10 in dichloromethane at room temperature, affording 4-hydroxy-2-cyclohexenone (*R*)-**29** and (*S*)-**29** in 64% and 62% yield, respectively (Scheme IV-23). It is worth mentioning that these yields may not be reproducible due to the volatility of 4-hydroxy-2-cyclohexenone, **29**.



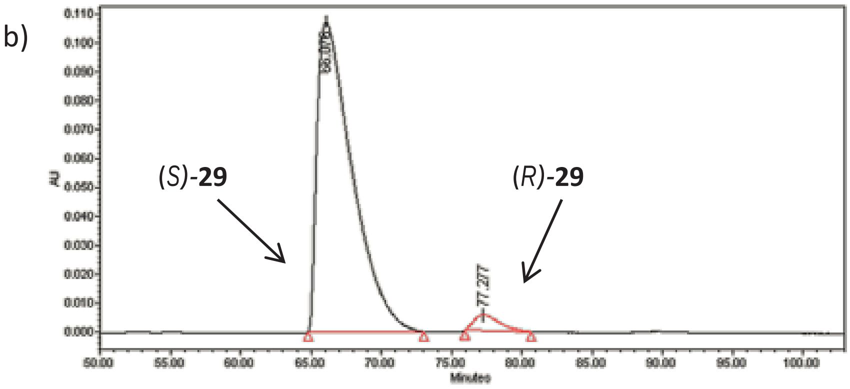
Scheme IV-23. Preparation of both enantiomer of **29** via ATH and subsequent hydrolysis.

Cleavage of the ketal could be confirmed by NMR spectroscopy. Thus, in the ^{1}H-NMR spectrum, proton H-3 appears downfield shifted (δ 6.95) and protons corresponding to the ketal disappeared. Additionally, a new signal at 199.1 ppm corresponding to C-1 is observed in the ^{13}C-NMR spectrum.

The enantiomeric excess (ee) was determined by chiral high-pressure liquid chromatography (CHPLC), using a chiral column Daicel IC[1] (0.46 cm x 0.25 cm) and a mixture of hexane:isopropanol 97:3 as eluent in 1ml/min flux (Figure IV-5).



Compound	Retention time (min)	Area (µV/sec)	Area (%)
***(S)*-29**	68.848	565378	4.14
***(R)*-29**	75.273	13074831	95.86



Compound	Retention time (min)	Area (µV/sec)	Area (%)
***(S)*-29**	66.076	18846502	96.22
***(R)*-29**	77.277	739663	3.78

Figure IV-5. Chiral high-pressure liquid chromatography (CHPLC) of a) (*R*)-**29** and b) (*S*)-**29**.

From the relative area of the peaks, it can be inferred that the ee was 92% in both cases. These results are similar to that of the asymmetric reduction using a chiral auxiliary. Therefore, it has been proved that the asymmetric induction in the reduction is not because of a cooperative effect between the chiral Noyori's catalyst **25** and the chiral auxiliary (*R*,*R*)-hydrobenzoin, but only due to the influence of Noyori's catalyst.

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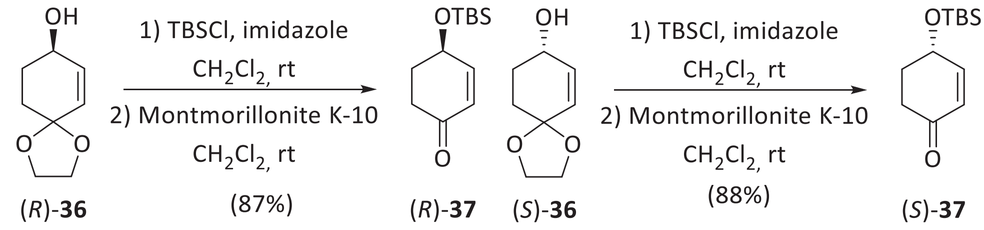
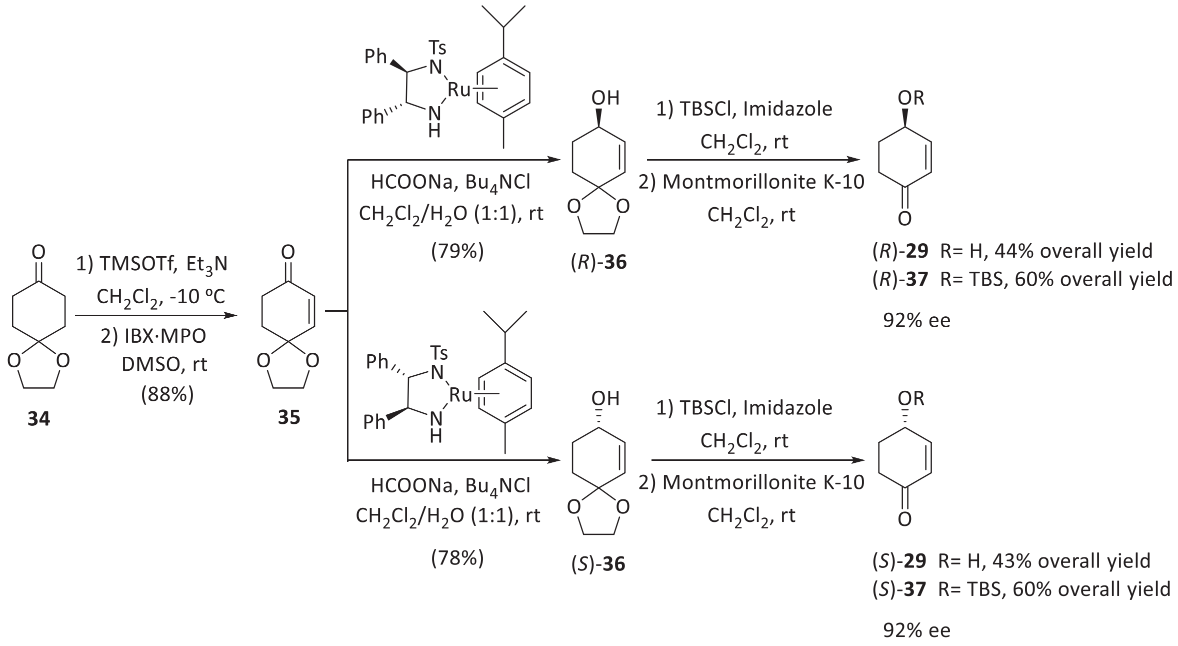
[1] Chiral column Daicel IC is based on cellulose tris(3,5-dichlorophenyl)carbamate, which is immobilized on to a wide pore silica matrix.

As aforementioned, the low yield of the asymmetric reduction could be attributed to the volatility of 4-hydroxy-2-cyclohexenone **29**. To overcome this problem, we decided to turn again to the protection of the hydroxyl group as a silyl ether before removal of the ketal. Thus, the protection of the alcohol **36** with imidazole and TBSCl in dichloromethane and subsequent hydrolysis of the ketal using Montmorillonite K-10, led to both enantiomers of **37** in 87% and 88% yield, respectively (Scheme IV-24).



Scheme IV-24. Synthesis of both enantiomers of **37**.

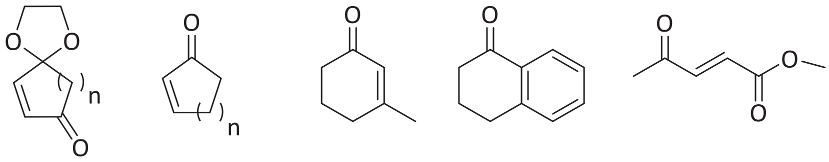
In summary, we have established a new practical, enantioselective procedure to prepare both enantiomers of 4-hydroxy-2-cyclohexenone and their *O*-silyl derivatives, which competes with the published methodologies. (*R*)- and (*S*)-**29** were synthesised in 4 steps and 44% and 43% overall yield, respectively, as well as their O-silyl derivatives (*R*)- and (*S*)-**37** in 5 steps and 60% overall yield (Scheme IV-25).



Scheme IV-25. Synthetic pathway to prepare both enantiomers of **29** and their *O*-silyl derivatives **37**.

2.5. Asymmetric Transfer Hydrogenation (ATH) Study

The good results achieved in the asymmetric transfer hydrogenation (ATH) step prompted us to investigate the ATH reaction with different enones, evaluating the stereoselectivity of the reaction. In particular, we planned to study several substrates, varying the ring size or the functionality of the molecule (Figure IV-6).

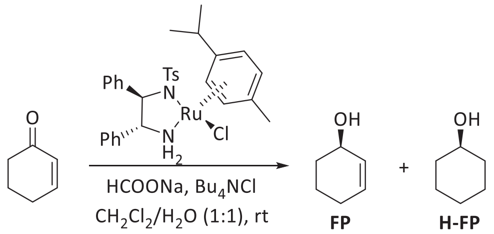


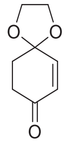
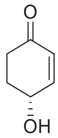
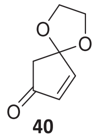
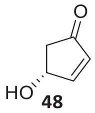
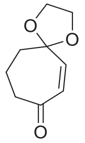
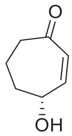
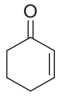
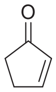
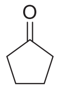
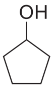
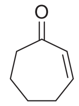
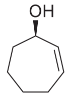
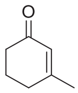
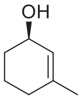
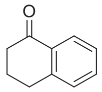
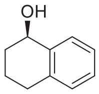
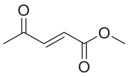
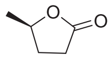
40, n=1 **42**, n=1 **45** **46** **47**
35, n=2 **43**, n=2
41, n=3 **44**, n=3

Figure IV-6. Different substatres for the ATH study.

In 2008, Xiao and co-workers reported a mechanistic study on the ATH.[52] They reported that CO_2 generated from the formate during the reaction, in some cases could inhibit the asymmetric reduction. According to this study, the asymmetric reduction of all these compounds was performed following the reported procedure by Cossy *et al.*, in a biphasic media CH_2Cl_2/H_2O (1:1) at room temperature using HCOONa as hydrogen source, (*R*,*R*)-Noyori-I **25** (3% mol) as catalyst and tetrabutylammonium chloride (TBACl) as phase-transfer agent but under a nitrogen flux.

Table IV-2. Asymmetric Transfer Hydrogenation (ATH) study.



Entry	Substrate	Product	Time (h)	Conversion (%)	FP:H-FP[a]	%ee[b]	(R) : (S)
1	 **35**	 **29**	3	100	6:1	92	96:4
2	 **40**	 **48**	5	100	2:1	20	60:40
3	 **41**	 **49**	5	100	3:1	70	85:15
4	 **43**	 **50**	24	90	2:1	92	96:4
5	 **42**	 +  **51** **52**	72	75	-	-	-
6	 **44**	 **53**	24	45	7:1	83	91.5:8.5
7	 **45**	 **54**	72	44	10:1	88	94:6
8	 **46**	 **55**	24	87	-	94	97:3
9	 **47**	 **56**	24	100	-	58[c]	79:21

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[a] Determined by ^{1}H-NMR (FP: final product, H-FP: hydrogenated final product).

[b] Determined by chiral high-pressure liquid chromatography (CHPLC).

[c] Determined by the specific optical rotation.

When the ATH reaction was carried out with 1,4-cyclohexenedione monoethylene ketal **35**, the conversion was completed in three hours, leading to alcohol **29** with high enantiomeric excess (92% ee) along with its totally hydrogenated derivative **H-29** in a 6:1 ratio (Table IV-2, entry 1). By contrast, asymmetric reduction of 1,4-cyclopentenedione monoethylene ketal **40** furnished alcohol **48** with low enantiomeric excess (20% ee) and its completely hydrogenated derivative **H-48** in a 2:1 ratio (entry 2), indicating that a five-membered ring is detrimental to the enantioselectivity as well as the chemoselectivity of the reaction. In the case of 1,4-cycloheptendione monoethylene ketal **41**, the asymmetric reduction provided the corresponding alcohol **49** with moderate enantiomeric excess (70% ee) along with the totally hydrogenated **H-49** in a 3:1 ratio (entry 3).

Then, the ATH reaction was carried out with 2-cyclohexenone **43**, delivering the corresponding alcohol **50** with the same enantiomeric excess (92% ee) than for **35** (entry 4), but with poor C=O/C=C selectivity, since a 2:1 mixture of the allylic alcohol **50** and its completely hydrogenated derivative **H-50** was obtained. It is worth mentioning that this reduction required more time (24 h) to achieve a 90% of conversion. Interestingly, when the asymmetric reduction was assayed with 2-cyclopentenone **42**, the expected allylic alcohol was not furnished but the corresponding cyclopentanone **51** and cyclopentanol **52** along with some starting material recovered **42** (entry 5), which suggests a high C=C selectivity. In this case, the reaction was performed for 72 h to achieve a 75% of conversion, indicating that the ATH reaction is less efficient with five-membered ring enones. Finally, the asymmetric reduction of 2-cycloheptenone **44** led to allylic alcohol **53** with better enantioselectivity (83% ee) than for **41**, along with its totally hydrogenated derivative **H-53** in a 7:1 ratio (entry 6), which indicates also a better chemoselectivity. Nevertheless, only a 45% of conversion was achieved after 24 h of reaction. Thus, these results also suggest that the enantio- and chemoselectivity of the reaction are dependent on the size of the ring.

The poor C=O selectivity obtained in the ATH reaction of 2-cyclohexenone **43** was improved by introducing a methyl group at the β position (entry 7), providing a mixture the corresponding allylic alcohol **54** and its totally hydrogenated derivative **H-54** in a 10:1 ratio. However, the enantioselectivity of the reaction was slightly lower (88% ee) and more time was required (72 h) to obtain only a 44% of conversion.

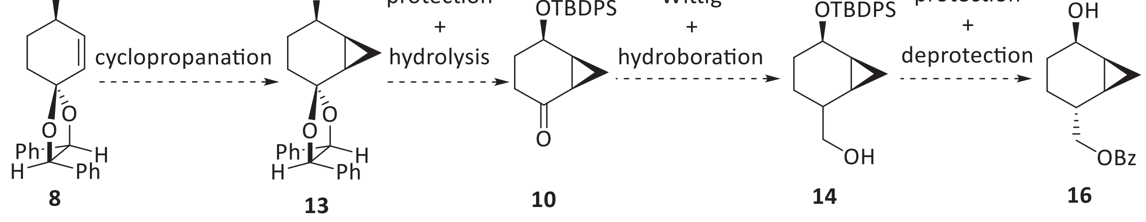
The effect of different functionalities was also evaluated. To that end, we attempted the ATH reaction with 1-tetralone **46**, where the double bond was replaced with an aromatic ring (entry 8). In this case, a 87% of conversion was achieved after 24 h, delivering allylic alcohol **55** with the highest enantioselectivity (94% ee). By contrast, the asymmetric reduction of acyclic enone **47** (entry 9), which features an ester group, provided (*R*)-valerolactone **56** with low enantioselectivity (58% ee), as a result of the reduction of both the ketone and the double bond and subsequent lactonization. These results suggest that the asymmetric reduction of acyclic compounds is less enantioselective than that of cyclic compounds. Moreover, although the ester group was not reduced during the reaction, either this functional group or the change of stereochemistry of the chain *cis* to *trans* seems to be detrimental to the chemoselectivity of the reaction, since both the carbonyl and the double bond were hydrogenated.

In summary, the enantio- and chemoselectivity of the ATH reaction are sensitive to the size of the ring as well as the different functionalities of the molecule. This study showed that among the cyclic compounds investigated, the best results were afforded with six-membered rings in both enantio- and C=O/C=C selectivity. On the other hand, the five-membered ring seems to be too small that diminishes the selectivity of the reaction, leading to a mixture of products. Regarding the functionalities of the molecule, the presence of an aromatic ring attached to the cyclohexane slightly enhances the enantioselectivity of the reaction.

2.6. Synthesis of the alcohol 16

With allylic alcohol **8** in hands, we moved back to the synthesis of the bicyclo[4.1.0]heptane nucleoside analogues. First, we turned our attention to prepare alcohol **16**, which is the pivotal intermediate foreseen in the synthesis of the different nucleoside analogues.

The synthesis would start from allylic alcohol **8**, which after a cyclopropanation reaction and subsequent protection of the hydroxyl group as a silyl ether followed by hydrolysis of the ketal would lead to ketone **10**. Then, a Wittig reaction and hydroboration would provide alcohol **14**, which would be converted into the key intermediate **16** after several transformations (Scheme IV-26).

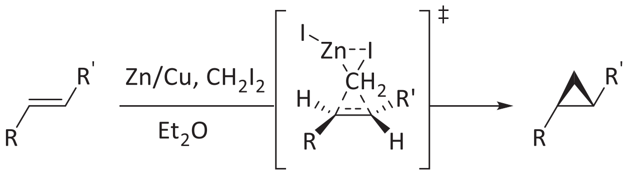


Scheme IV-26. Synthetic pathway foreseen to prepare key alcohol **16**.

2.6.1. Cyclopropanation reaction

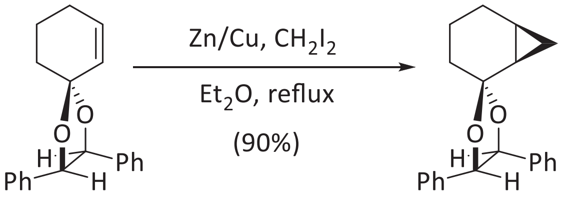
There are two classical methodologies to carry out a cyclopropanation of unsaturated compounds:[53] using a sulphur ylide (Corey-Chaykovsky reaction)[54] or using a iodomethylzinc carbenoid (Simmons-Smith reaction).[55] The Corey-Chaykovsky cyclopropanation is largely limited to use on electron-poor olefins, particularly α,β-unsaturated carbonyl compounds.

The Simmons-Smith reaction consists of a cyclopropanation using iodomethylzinc species ($IZnCH_2I$) to add a carbene into a double bond. These iodomethylzinc species are highly stereospecific, proceeding through a "butterfly-type" transition state (Scheme IV-27).



Scheme IV-27. Mechanism of Simmons-Smith cyclopropanation.

In 1990, Mash and co-workers reported a mechanistic study of the Simmons-Smith cyclopropanation in six-membered ring systems with different chiral acetals,[56] being (*S*,*S*)-hydrobenzoin one of the chiral auxiliaries studied. The cyclopropanation reaction of cyclohexene **57** afforded the corresponding cyclopropane-fused derivative **58** in 90% yield and 19:1 diastereomeric ratio (Scheme IV-28).



57

58

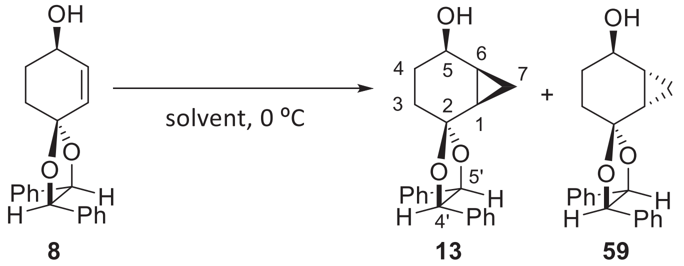
(19:1)

Scheme IV-28. Simmons-Smith cyclopropanation reported by Mash and co-workers.

Additionally, the presence of a proximal hydroxyl group can direct the attack of the reagent via zinc chelation. Hence, the presence of a chiral allylic alcohol in a cyclic system, can guide the reaction to obtain the cyclopropane *syn* to the alcohol.

To carry out the cyclopropanation of allylic alcohol **8**, different methodologies were assayed using different carbenoids, such as Furukawa's carbenoids (Et_2Zn, CH_2I_2 or ICH_2Cl)[57] or Shi's carbenoid,[58] which is based on trifluoroacetic acid (CF_3COOH, Et_2Zn, CH_2I_2). The results are summarised in Table IV-3.

Table IV-3. Reaction conditions assayed for the cyclopropanation of allylic alcohol **8**.



Entry	Reagents (eq.)	Solvent	Conversion (%)[a]	13:59[a]
1	Et_2Zn (5), CH_2I_2 (10)	Et_2O	15	3:1
2	Et_2Zn (5), CH_2I_2 (10)	CH_2Cl_2	95	3:1
3	Et_2Zn (5), ICH_2Cl (10)	CH_2Cl_2	99	16:1
4	Et_2Zn (2), CH_2I_2 (2), CF_3COOH (2)	CH_2Cl_2	99	32:1

[a] Determined by ^{1}H-NMR.

The reaction was first attempted with Et_2Zn and CH_2I_2 in diethyl ether or dichloromethane, following Furukawa's procedure leading to a mixture of alcohols **13** and **59** in a 3:1 diastereomeric ratio (entries 1 and 2). When allylic alcohol **8** was treated with ICH_2Cl and Et_2Zn in dichloromethane, the ratio was increased up to 16:1 (entry 3). However, the best results were achieved by using the Shi's carbenoid ($CF_3COOZnCH_2I$), generated *in situ* from Et_2Zn, CH_2I_2 and CF_3COOH, which provided cyclopropane-fused derivative **13** in 98% yield and 32:1 diastereomeric ratio (entry 4).

The formation of the cyclopropane was observed in the ^{1}H-NMR spectrum by the disappearance of the olefinic proton signals along with the presence of two new peaks at 0.96 and 0.83 ppm, corresponding to the H-7 protons of the cyclopropane ring. Additionally, a signal at 4.2 ppm in the ^{13}C-NMR, corresponding to the C-7, also confirms the formation of the cyclopropane ring (Figure IV-7).

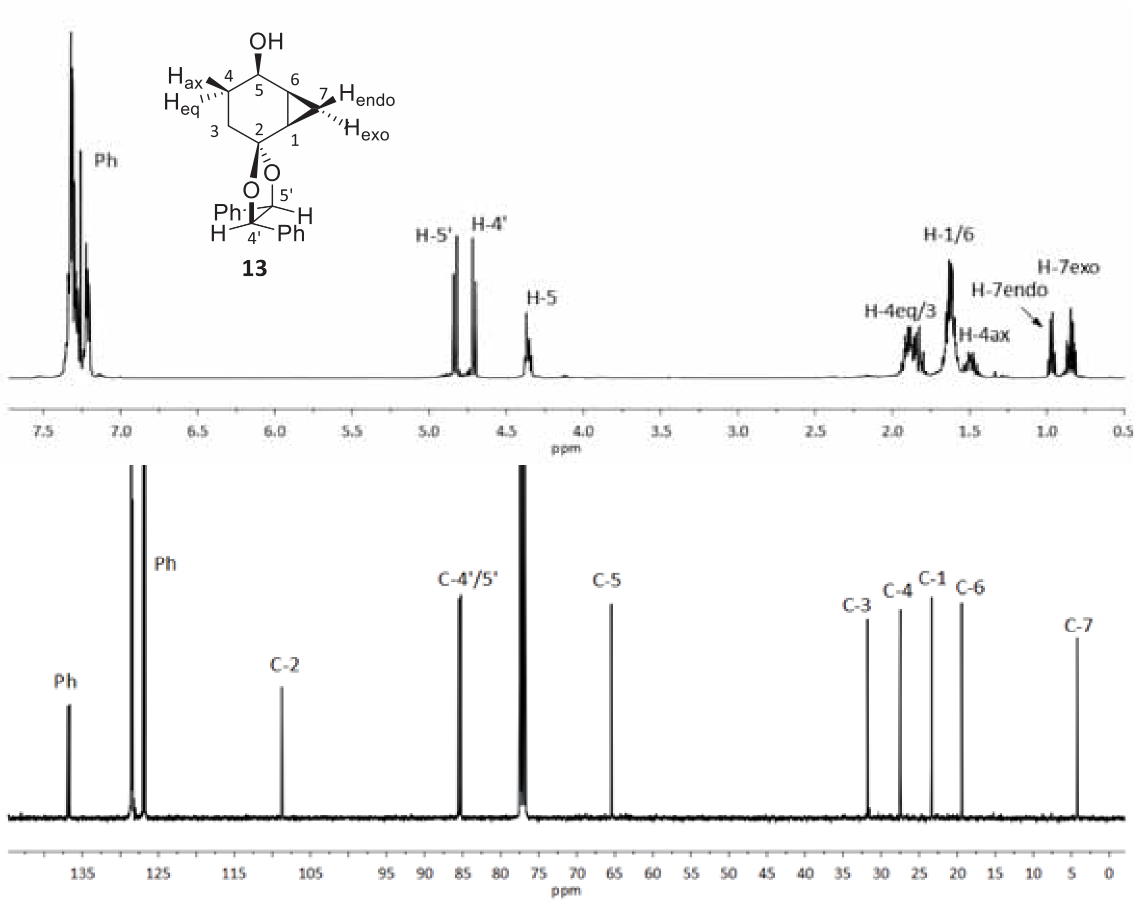


Figure IV-7. ^{1}H-NMR (250 MHz, $CDCl_3$) and ^{13}C-NMR (90MHz, $CDCl_3$) spectra of **X11**.

The *cis/trans* stereochemistry between the alcohol and cyclopropane moieties was determined by means of NOESY experiments. The spectrum of the *cis* adduct **13** shows a cross peak between H-4ax and H-7endo and the spectrum of the *trans* adduct **59** shows a cross peak between H-5 and H-7endo (Figure IV-8), indicating that the major diastereomer **13** is the *cis* adduct.

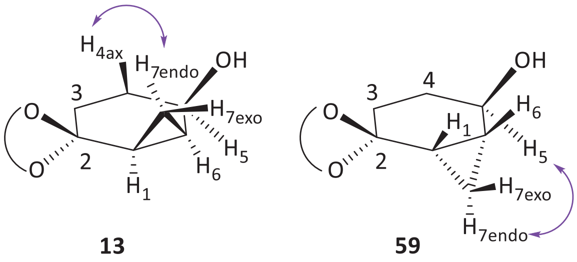
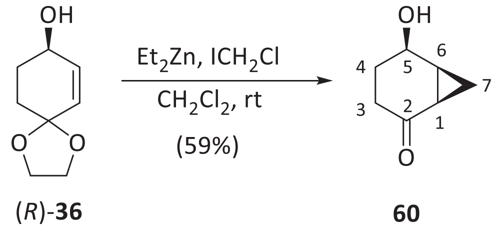


Figure IV-8. Cross peaks between H-4ax and H-7endo in the NOESY experiment of **13** and between H-5 and H-7endo in the NOESY experiment of **59**.

Considering the good results achieved in the cyclopropanation reaction with the Shi's carbenoid ($CF_3COOZnCH_2I$), we decided to perform the same reaction with the allylic alcohol (*R*)-**36**. However, during the reaction process the acetal was removed affording in 16% yield the keto alcohol **60**, which is a highly volatile compound, as a single diastereomer. The cyclopropanation was also attempted using Et_2Zn and ICH_2Cl in dichloromethane, providing the same compound **60** in 59% yield (Scheme IV-29).



Scheme IV-29. Cyclopropanation of (*R*)-**36** following Furukawa's procedure.

The formation of the cyclopropane was easily identified in the ^1H-NMR spectrum by the disappearance of the olefinic proton signals along with the presence of two new peaks at 1.44 and 1.14 ppm, corresponding to the H-7 protons of the cyclopropane ring. In addition, a signal at 207.5 ppm in the ^{13}C-NMR, corresponding to the carbonyl group confirms the cleavage of the acetal.

The *cis/trans* stereochemistry was determined by means of NOESY experiment. In a similar manner to the case of compound **13**, the spectrum of keto alcohol **60** shows a cross peak between H-7endo and H-4ax (Figure IV-9), indicating that this is the *cis* adduct.

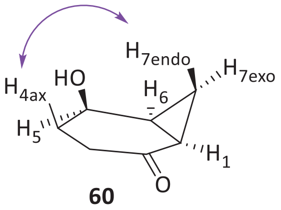
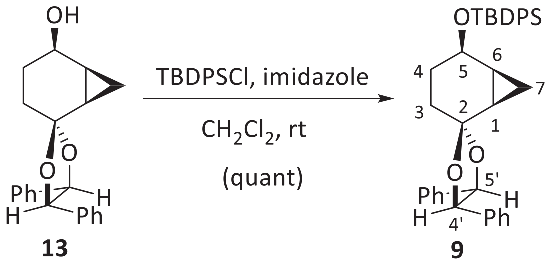


Figure IV-9. Cross peaks between H-7endo and H-4ax in the NOESY experiment of **60**.

2.6.2. Protection of the hydroxyl group of 13

The synthetic sequence was followed with the tricyclic compound **13** and the next step was the orthogonal protection of the alcohol. Initially, formation of *p*-methoxybenzyl ether (-OPMB) was assayed. However, treatment of **13** with sodium hydride (NaH) and *p*-methoxybenzyl chloride (PMBCl) did not allow to achieve the desired product, but only the starting material was recovered. Then, we decided to protect alcohol **13** as a *tert*-butyldiphenylsilyl ether (-OTBDPS). Hence, treatment of allylic alcohol **13** with TBDPSCl and imidazole in dichloromethane led to the protected derivative **9** in quantitative yield (Scheme IV-30).

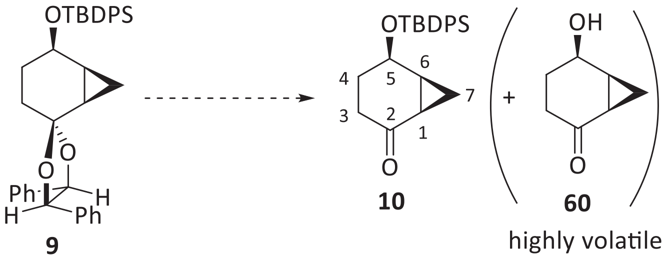


Scheme IV-30. Protection of alcohol **13** as a silyl ether.

The protection of the hydroxyl group was confirmed in the ^{1}H-NMR spectrum by the presence of a new peak at 1.13 ppm, corresponding to protons of the *tert*-butyl of the protecting group along with the presence of new aromatic signals at 7.77 and 7.21 ppm.

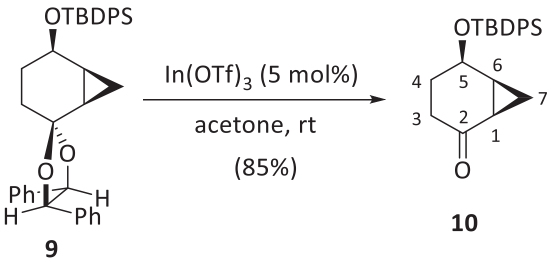
2.6.3. Hydrolysis of the ketal

Removal of the ketal group present in intermediate **9** to get the ketone **10** must be carried out in mild conditions in order to avoid concomitant deprotection of the alcohol and thus the formation of volatile alcohol **60** (Scheme IV-31).



Scheme IV-31. Hydrolysis of the ketal and possible elimination of the silyl ether.

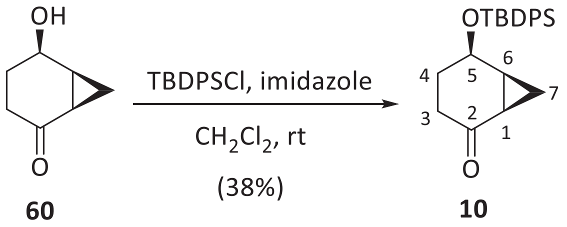
Hydrolysis of the ketal was assayed following the above mentioned Gregg's procedure. Thus, protected derivative **9** was treated with catalytic $In(OTf)_3$ (5% mol) in acetone at room temperature to furnish the desired enone **10** in 85% yield (Scheme IV-32).



Scheme IV-32. Hydrolysis of the ketal of **9** following Gregg's procedure.

Cleavage of the ketal can be observed in the ^{1}H-NMR spectrum by the disappearance of the aromatic signals as well as the benzilic signals, corresponding to the (*R*,*R*)-hydrobenzoin moiety. Moreover, the presence of a new peak at 208.0 ppm in the ^{13}C-NMR, corresponding to the carbonyl group also confirms the formation of ketone **10**.

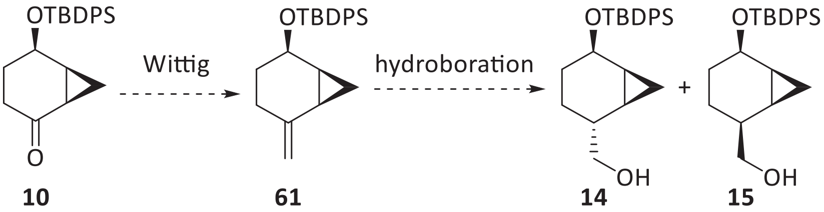
Ketone **10** can be also achieved by protection of alcohol **60** by treatment with TBDPSCl and imidazole in dichloromethane in 38% yield (Scheme IV-33). This low yield can be attributed to the volatility of the starting material **60**.



Scheme IV-33. Protection of alcohol **60** with TBDPSCl.

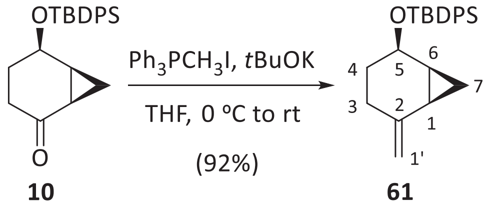
2.6.4. Preparation of alcohol 14

The continuation of the synthetic strategy to prepare alcohol **14** was envisaged as an olefination of ketone **10** via a Wittig reaction followed by a hydroboration (Scheme IV-34).



Scheme IV-34. Synthetic pathway foreseen to prepare alcohol **14**.

Thus, the treatment of ketone **10** with methyltriphenylphosphonium iodide (Ph_3PCH_3I) and *t*BuOK in the presence of anhydrous THF furnished alkene **61** in 92% yield (Scheme IV-35).



Scheme IV-35. Wittig reaction on ketone **10** to provide alkene **61**.

The formation of alkene **61** can be confirmed in the ^{1}H-NMR spectrum by the presence of two singlet signals at 4.84 and 4.75 ppm, corresponding to protons H-1’ (Figure IV-10) as well as the disappearance of the carbonyl group C-2 signal at 208.0 ppm in the ^{13}C-NMR spectrum. Nevertheless, exocyclic alkene **61** is unstable and rapidly isomerises to the endocyclic regioisomer **62**. The isomerization can be observed in the ^{1}H-NMR spectrum by the formation of a new singlet at 1.74 ppm and a doublet at 4.90 ppm, corresponding to the methyl group generated and the olefinic proton H-3, respectively (Figure IV-10).

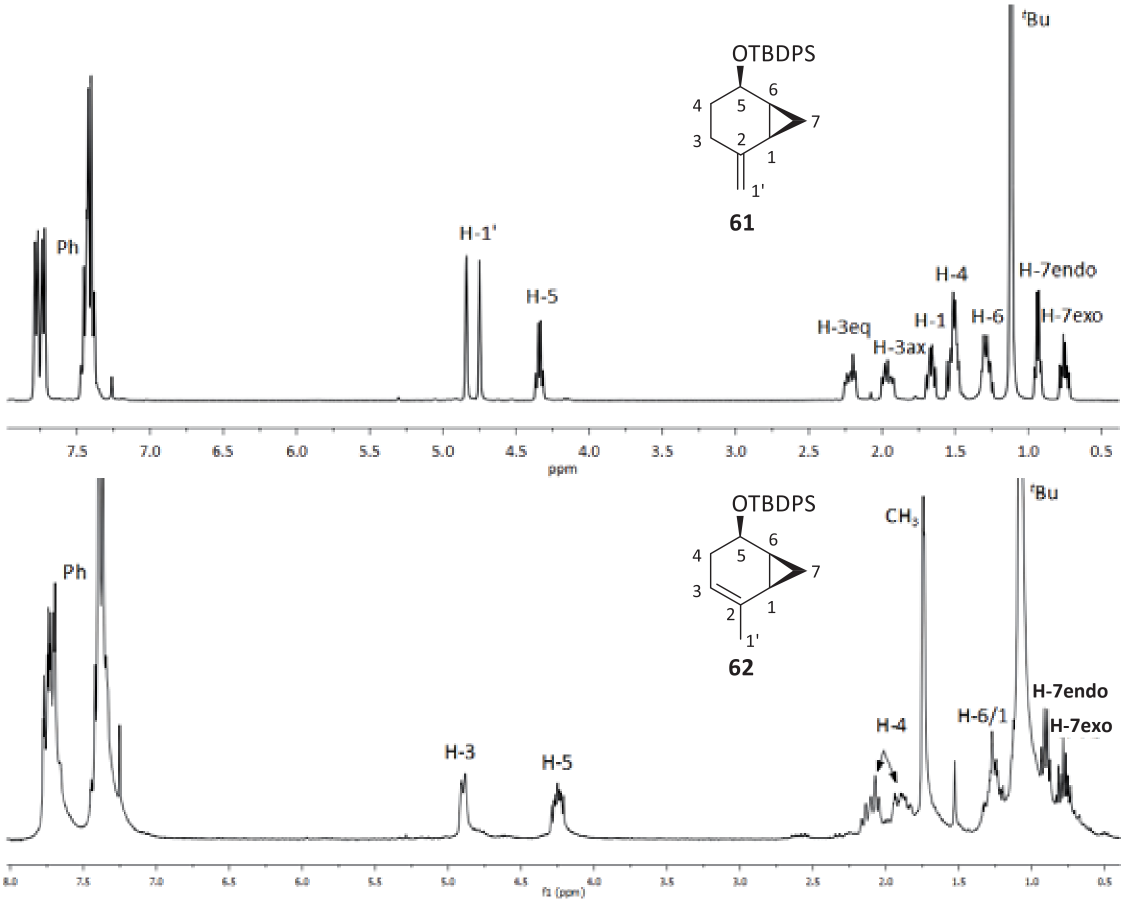
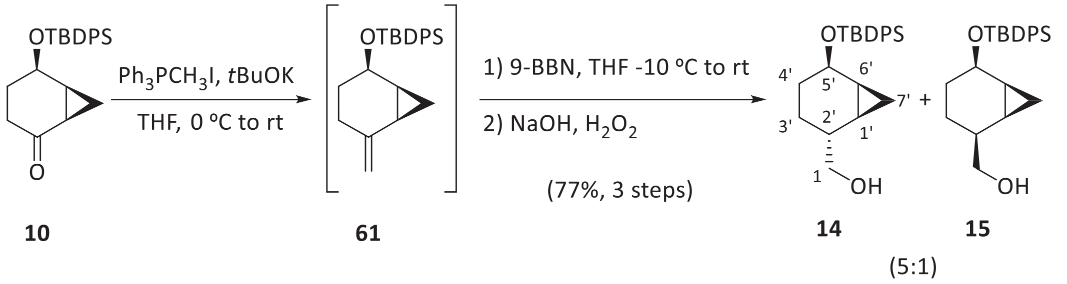


Figure IV-10. ^{1}H-NMR spectra of **61** (360 MHz, $CDCl_3$) and **62** (250 MHz, $CDCl_3$).

In order to avoid the isomerization process, the hydroboration was carried out immediately after the Wittig reaction without further purification of the olefin intermediate. Thus, treatment of alkene **61** with 9-borabicyclo[3.3.1]nonane (9-BBN) in anhydrous THF at -10 ºC led to the anti-Markovnikov addition of the borane, and was followed by addition of NaOH and H_2O_2 in water, furnishing an inseparable mixture of alcohols **14** and **15** in a 5:1 diastereomeric ratio (Scheme IV-36).



Scheme IV-36. Preparation of alcohols **14** and **15**.

The presence of a new peak at 3.51 ppm in the ^{1}H-NMR spectrum, corresponding to the H-1 of the hydroxymethyl group as well as at 68.2 ppm in the ^{13}C-NMR confirms the formation of the alcohol **14**.

In the hydroboration reaction, there are two possible approximations of the borane to the diastereotopic faces of the alkene **61**: an *anti* addition, in which 9-BBN approaches the alkene through its less hindered face, and a *syn* addition, in which the approach is through the face bearing the cyclopropane (Figure IV-11).

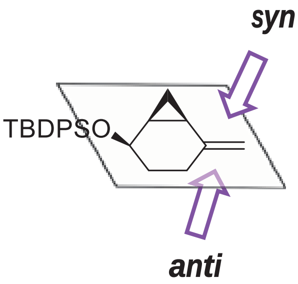


Figure IV-11. Anti/syn approaches of 9-BBN to alkene **61**.

The *syn/anti* stereochemistry of the product has been determined with the aid of a NOESY experiment. The spectrum of **14** shows cross peaks between H-7endo and H-2, indicating a *syn* addition of the borane (Figure IV-12).

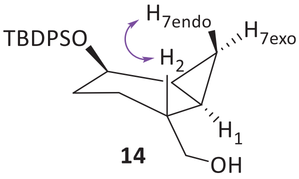


Figure IV-12. Cross peak between H-2 and H-7endo in the NOESY spectrum (400 MHz, $CDCl_3$) of **14**.

The diastereoselectivity of the borane attack achieved could be due to a possible steric hindrance generated by the H-3 axial which would make the *anti* approximation in alkene **61** more sterically hindered than the *syn* approximation (Figure IV-13).

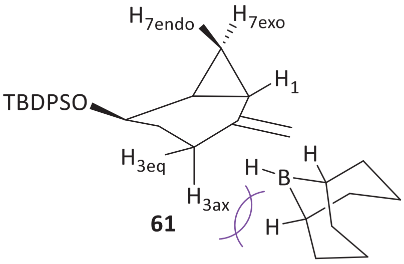
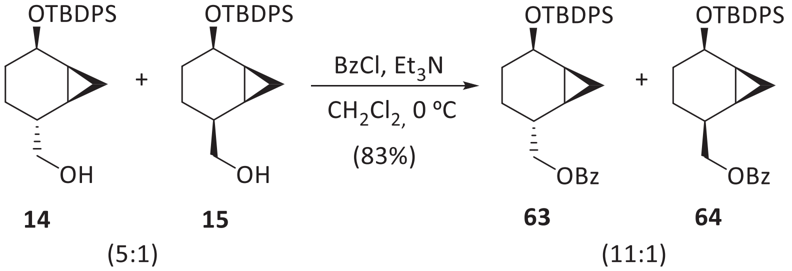


Figure IV-13. Possible steric hindrance in the *anti* approximation of the borane to **61**.

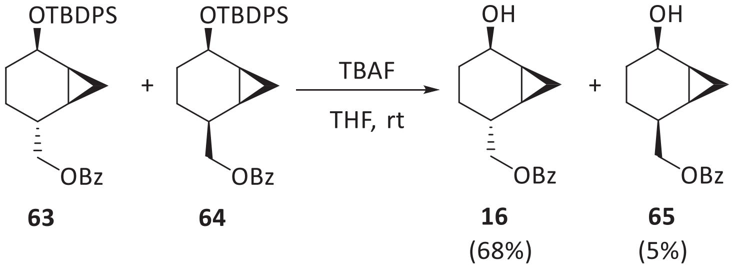
2.6.5. Preparation of alcohol 16

To achieve the synthesis of pivotal alcohol **16** the next transformation planned was the orthogonal protection of the hydroxyl group as a benzoate. Thus, treatment of the mixture of alcohols **14** and **15** with trimethylamine and benzoyl chloride in dichloromethane at 0 °C provided a mixture of alcohols **63** and **64** in 83% yield, which was enriched with the major compound **63** after successive purification by column chromatography (11:1 diastereomeric ratio) (Scheme IV-37).



Scheme IV-37. Protection of alcohols **14** and **15** with benzoyl chloride.

Subsequent cleavage of the silyl group was accomplished by using tetrabutylammonium fluoride (TBAF) in THF at room temperature, affording the desired alcohol **16** in 68% yield and its diastereomer **65** in 5% yield (Scheme IV-38).



Scheme IV-38. Removal of the silyl group using TBAF.

Removal of the silyl group was easily observed in the ^{1}H-NMR spectrum by the disappearance of the signals related to the *tert*-butyldiphenylsilyl group (Figure IV-14).

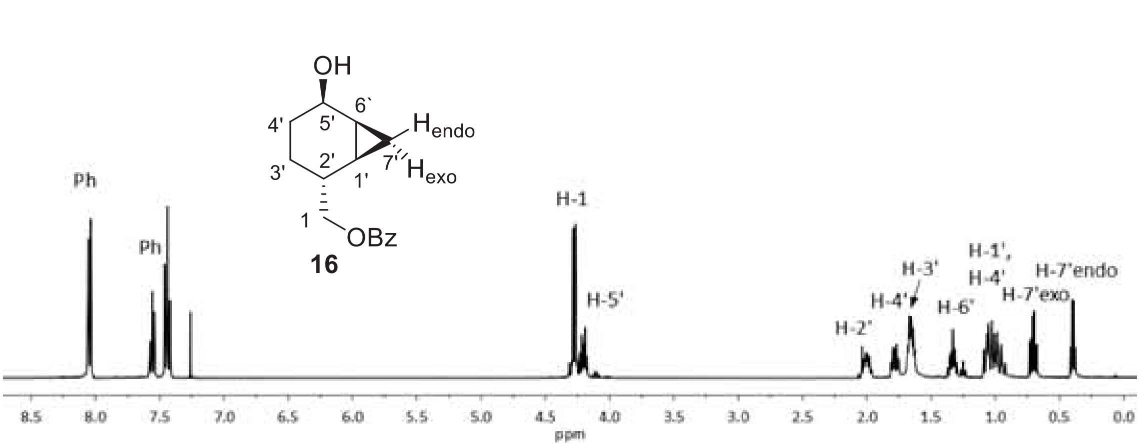


Figure IV-14. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of alcohol **16**.

Hence, alcohol **16**, which is the key intermediate to introduce the different nucleobases, has been synthesised in 7 steps and 36% overall yield starting from allylic alcohol **8**.

With this in hands, we turned our attention to the introduction of the base moiety.

2.7. Introduction of the base moiety

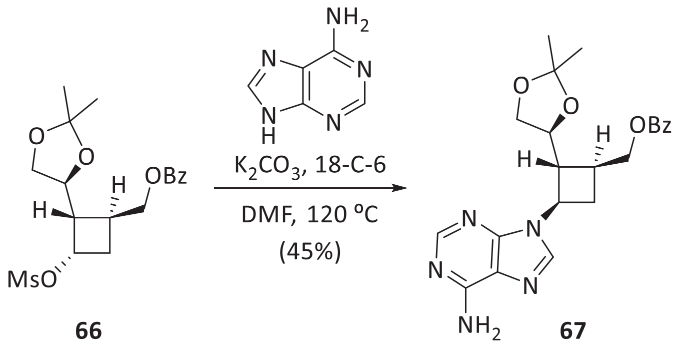
In the field of carbocyclic nucleosides, there are two fundamental approaches to introduce the nucleobase: coupling of the nucleobase with an appropriately functionalised carbocyclic ring or stepwise construction of the nucleobase from an amine substituent present on the carbocycle.[59]

Direct coupling of the nucleobase is the most widely used procedure and can be accomplished by several methods, such as the Mitsunobu reaction or converting the alcohol into a good leaving group (mesylate or tosylate) followed by a nucleophilic substitution.

Hence, our initial planned synthetic strategy was based on the direct coupling of the nucleobase via nucleophilic displacement of an activated hydroxyl as well as via a Mitsunobu reaction.

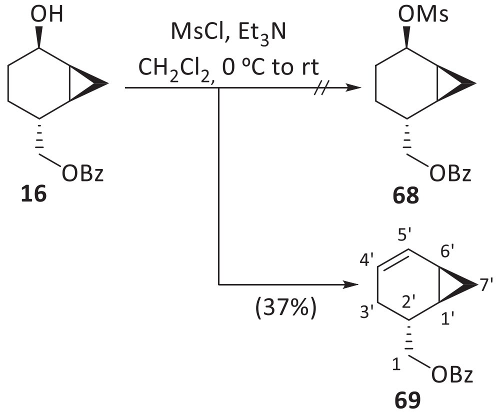
2.7.1. Nucleophilic substitution S_N2

Considering the difficult isolation of the desired product from the reaction mixture on Mitsunobu reactions,[60] the introduction of the base was initially pursued by the nucleophilic substitution of the corresponding mesylate. As an example, this methodology was used in our research group to introduce the nucleobase in the synthesis of Cyclobut-A, affording the corresponding product in moderate yield (Scheme IV-39).[61]



Scheme IV-39. Nucleophilic substitution of mesylate **66**.

Thus, to prepare the mesylate derivative **68**, alcohol **16** was treated with mesyl chloride and Et_3N in dichloromethane at 0 ºC (Scheme IV-40), affording in 37% yield, a colourless oil identified by its spectroscopic data as the cyclohexenyl derivative **69**, instead of the expected mesylate derivative **68**. The formation of cyclohexenyl derivative **69** was due a competitive elimination reaction. We assayed the reaction at lower temperatures, but all the attempts to avoid the formation of **69** met with failure.



Scheme IV-40. Attempted formation of mesylate derivative **68**.

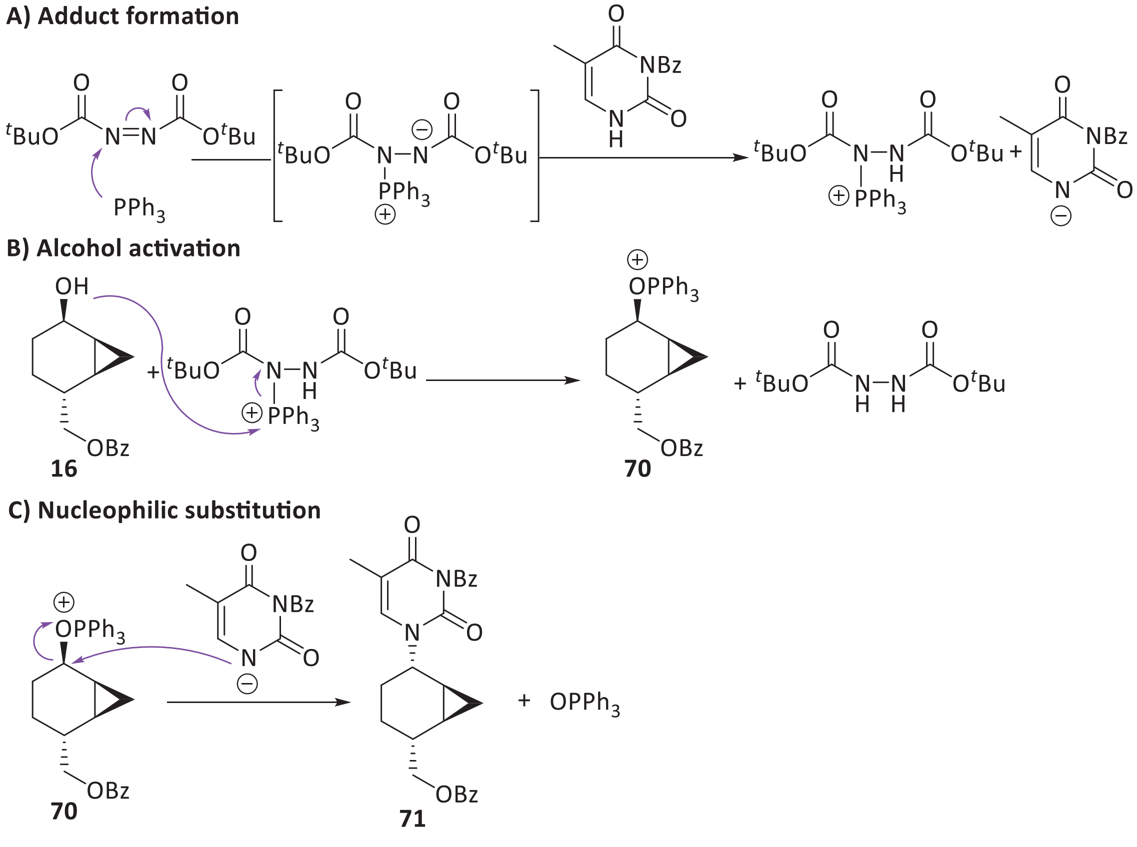
The formation of the cyclohexenyl derivative **69** was confirmed by the appearance of the double bond signals H-5' and H-4' in the ^{1}H-NMR spectrum at 6.08 and 5.33 ppm, respectively, as well as in the ^{13}C-NMR spectrum at 129.4 and 118.9 ppm, respectively.

At this point, we decided to investigate the introduction of the base moiety via a Mitsunobu reaction.

2.7.2. Mitsunobu reaction

As it has been pointed out, the Mitsunobu reaction is a commonly used methodology for the nucleobase introduction in the synthesis of carbocyclic nucleosides.[62,63] Nonetheless, one major drawback of this methodology is often the difficult isolation of the desired product form the reaction mixture, since two by-products (triphenylphosphine oxide and hydrazine) are formed during the reaction in stoichiometric amounts.[60]

The mechanism for the Mitsunobu reaction is depicted in Scheme IV-41 with alcohol **16**, *N*3-benzoylthymine, di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine (PPh_3) as representative reagents. The reaction starts with a nucleophilic addition of thiphenylphosphine to DBAD, providing the corresponding betaine that deprotonates the nucleobase. Then, the DBAD-triphenylphosphine adduct activates the alcohol, delivering intermediate **70** and DBAD-hydrazine, as a by-product. Nucleophilic displacement of triphenylphosphine oxide from **70** by the deprotonated base completes the reaction to furnish the desired compound **71** and triphenylphosphine oxide, as another by-product.



Scheme IV-41. Mitsunobu mechanism illustrated for the coupling of *N*3-benzoylthymine to alcohol **16**.

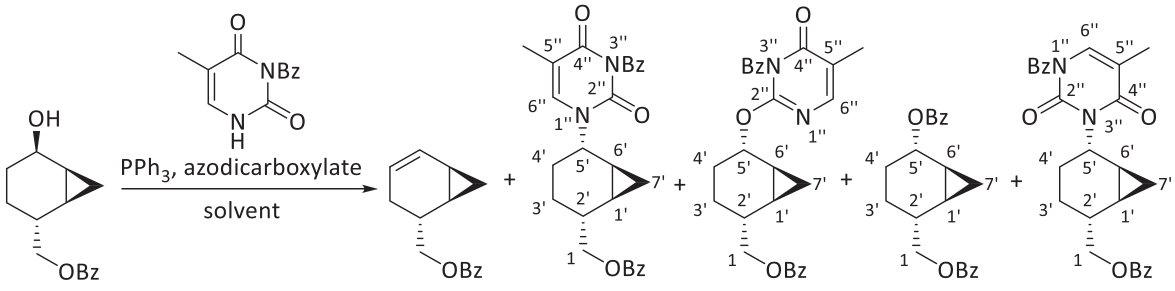
Initially, we selected thymine as the base to optimise the reaction. Since both *N*1 and *N*3 nitrogen atoms of thymine can act as nucleophiles, protection of the *N*3 position was required. The preparation of the *N*3 protected was performed following the procedure reported by Reese and co-workers, consisting of a dibenzoylation of thymine and subsequent pH-controlled cleavage of the benzoyl group at the *N*1 position.[64,65]

Then, the Mitsunobu reaction of alcohol **16** with *N*3-benzoylthymine was explored. Our first attempt involved the use of triphenylphosphine and DBAD as the azodicarboxylate in THF at 0 ºC. Unfortunately, under these conditions only starting material was recovered (Table IV-4, entry 1). When the reaction was repeated in toluene, the desired adduct **71** was not produced but a mixture of the *O*2''-adduct **72** and the dibenzoylated compound **73**, which indicated that the deprotection of the base takes place during the reaction process (entry 2).

In 2006, Ludek and Meier published a complete study on the introduction of nucleobases under Mitsunobu conditions,[66–68] evaluating, in particular, the influence of the solvent on the *N*1- vs *O*2-alkylation for pyrimidine compounds. It was concluded that the best solvents to favour the *N*1-alkylation were polar aprotic solvents such as DMF or acetronitrile (ACN).

Accordingly, the reaction was performed in ACN at -10 ºC (entry 3). Despite the formation of the *O*2-adduct **72** was avoided, the cyclohexenyl derivative **69** and the *N*3-adduct **74** were furnished instead of the desired *N*1-adduct **71**. The *N*3''-adduct **74** was formed due to a deprotection of the *N*3 nitrogen of the thymine ring during the reaction and concomitant protection of the *N*1. To circumvent the elimination reaction, the reaction was repeated at -40 ºC (entry 4), providing the desired compound **71** and the *N*3''-adduct **74** in 6% and 7% yield, respectively. No relevant amounts of starting material were recovered and thus the low yields obtained were due to the difficult isolation of these compounds from the reaction mixture, requiring several purification steps by column chromatography.

Table IV-4. Reactions conditions assayed for the Mistunobu reaction.



16 **69** **71** **72** **73** **74**

Entry	Azodicarboxylate	Solvent	Temperature (°C)	Yield (%)				
				69	71	72	73	74
1	DBAD	THF	0	-	-	-	-	-
2	DBAD	toluene	0	-	-	11[a]	18	-
3	DIAD	ACN	-10	17	-	-	16	23
4	DIAD	ACN	-40	-	6	-	-	7

[a] Determined by ^{1}H-NMR, since it is an inseparable mixture of **72** and DBAD.

The introduction of thymine on compound **71** was established in the ^{1}H-NMR spectrum by the presence of two new signals at 7.56 ppm and 1.89 ppm, corresponding to H-6'' and CH_3-C-5'', respectively (Figure IV-15).

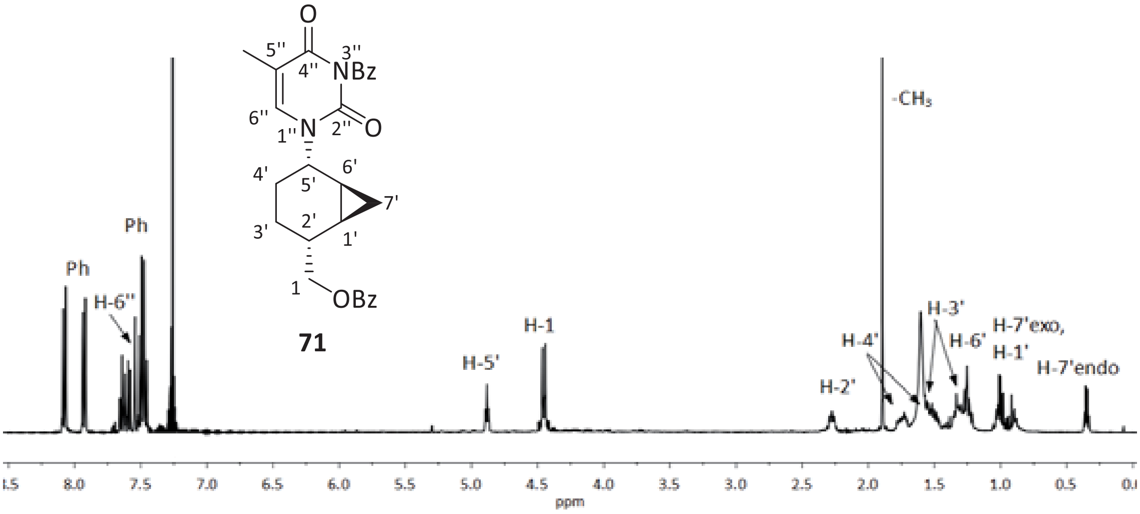
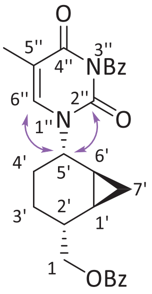


Figure IV-15. ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of product **71**.

In addition, the assignment of the attachment site of the pyrimidine base on compound **71** could be further confirmed by the ^{1}H-^{13}C HMBC spectrum, wherein correlation between proton H-5' and carbons C-6'' and C-2'' was observed (Figure IV-16).



71

Figure IV-16. Correlation between H-5' and C-6'' and C-2'' in HMBC experiment of **71** (400 MHz, $CDCl_3$).

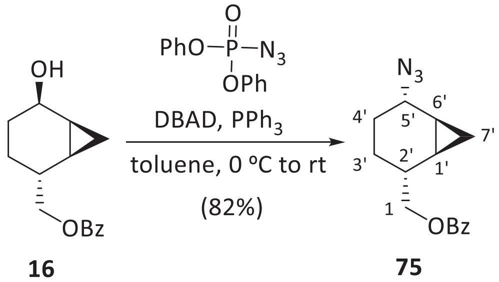
Therefore, the low yields achieved on these reactions prompted us to investigate the stepwise construction of the nucleobase as an alternative methodology.

2.7.3. Construction of the base moiety

One of the main advantage of constructing the base moiety stepwise is that the formation of the *N*7''-adduct and *N*3''-adduct for purine and pyrimidine compounds, respectively, can be avoided.

It is important to recall that for the construction of the nucleobase from an amine, an inversion of the configuration of the secondary alcohol on **16** is required. In the literature, there are several methodologies to convert an alcohol into an amine with inversion of the configuration, most of them based on a two-step sequence: formation of an azide and subsequent reduction to amine.[69–77]

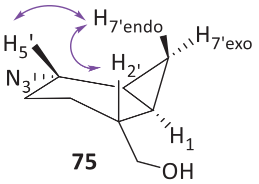
In 1977, Bose and co-workers reported a new procedure to prepare azides from alcohols, which consists of a Mitsunobu reaction using diphenylphosphoryl azide (DPPA).[72] Taking this into account, we carried out the formation of the azide **75** following the reported procedure. Thus, treatment of alcohol **16** with DPPA in the presence of DBAD and PPh_3 in toluene at 0 °C led to azide **75** in 82% yield with an inversion of the C-5’ configuration (Scheme IV-42).



16 **75**

Scheme IV-42. *C*5’ stereochemistry inversion via Mitsunobu reaction.

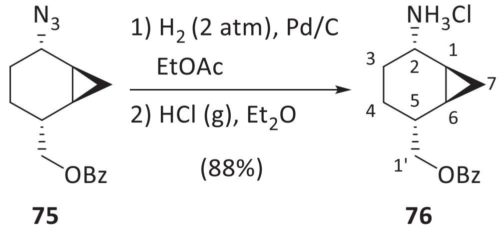
The formation of azide **75** was confirmed by the ^{13}C-NMR spectrum, in which the signal of C-5’ appeared upfield shifted (57.0 ppm) compared to the alcohol **16** (68.0 ppm). The assignment of C-5’ configuration could be established by the presence of cross peaks between H-7’endo and H-2’ and H-5’ in the NOESY spectrum (Figure IV-17).



75

Figure IV-17. Cross peaks between H-7’endo and H-2’ and H-5’ in the NOESY spectrum of azide **75**.

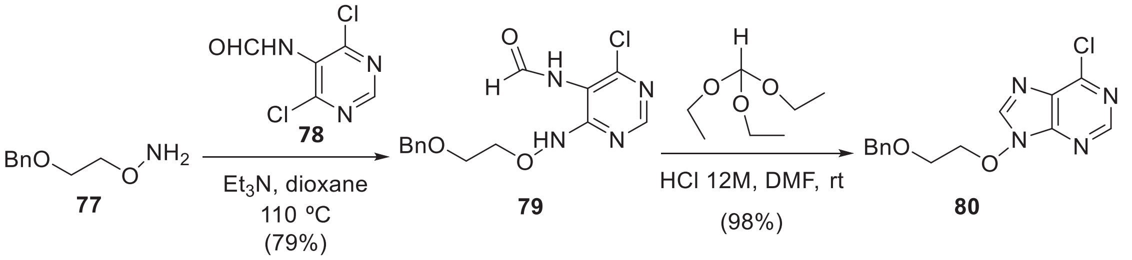
Finally, the generation of the required amine was achieved by a catalytic hydrogenation under hydrogen at 2 atm of pressure in the presence of Pd/C (10%), which was transformed to the ammonium chloride salt **76** by treatment with HCl (g) in diethyl ether (Scheme IV-43).



Scheme IV-43. Catalytic hydrogenation of azide **75**.

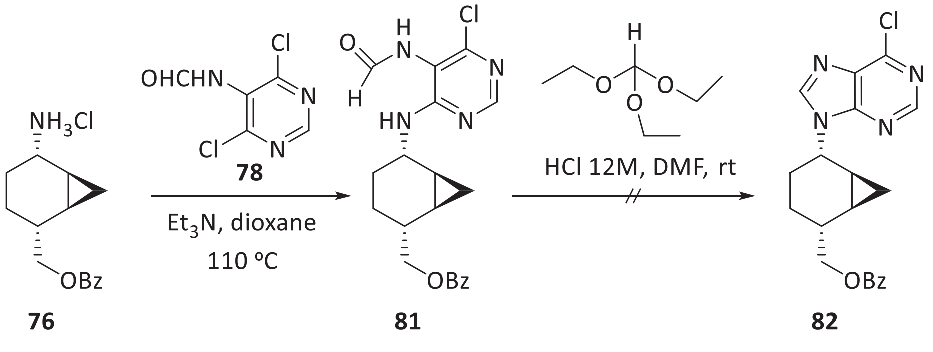
2.7.3.1. Synthesis of purine nucleosides

In 1990, Harnden and co-workers described a new methodology to construct purine bases.[78] This methodology consists of a nucleophilic aromatic substitution on the *N*-(4,6-dichloropyrimidin-5-yl)formamide **78** by the amino group of the alkoxyamine **77**, followed by a reaction with triethyl orthoformate and concentrated HCl to allow the closure of the ring, giving the corresponding chloropurine derivative **80** (Scheme IV-44). This procedure has been used for the synthesis of several nucleoside analogues.[79–81]



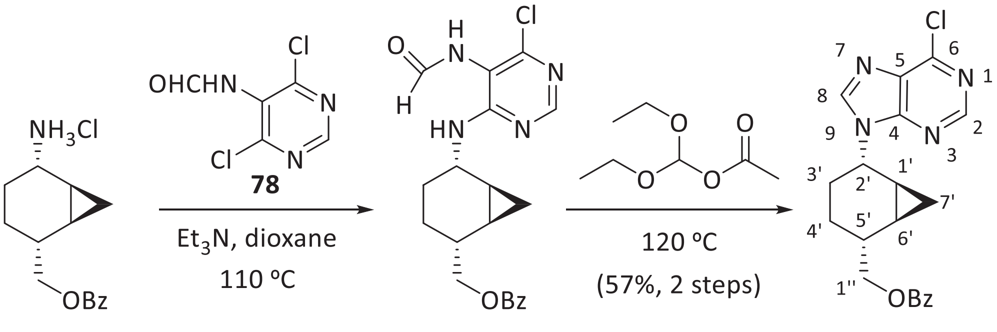
Scheme IV-44. Construction of purine ring reported by Harnden and co-workers.

With this in mind, we assayed the formation of the chloropurine derivative **82** by extrapolation of the previous methodology using our amine derivative **76**. Thus, treatment of the ammonium chloride **76** with formamidopyrimidine **78** and Et_3N in 1,4-dioxane at 110 ºC led to intermediate **81**, which was then treated with triethyl orthoformate and concentrated HCl in DMF leading to decomposition products due to the acidic conditions used for the closure of the ring (Scheme IV-45).



Scheme IV-45. Attempt of construction of purine ring following Harnden's procedure.

In the same work, Harnden *et al*. described the use of diethoxymethyl acetate as an alternative way to achieve the closure of the ring. Taking this into account, we attempted the construction of the purine ring following this procedure. Thus, treatment of the ammonium chloride **76** with formamidopyrimidine **78** and Et_3N in 1,4-dioxane at 110 ºC led to intermediate **81**, which was then treated with diethoxymethyl acetate at 120 ºC, to furnish chloropurine derivative **82** in 2 steps and 57% yield (Scheme IV-46).

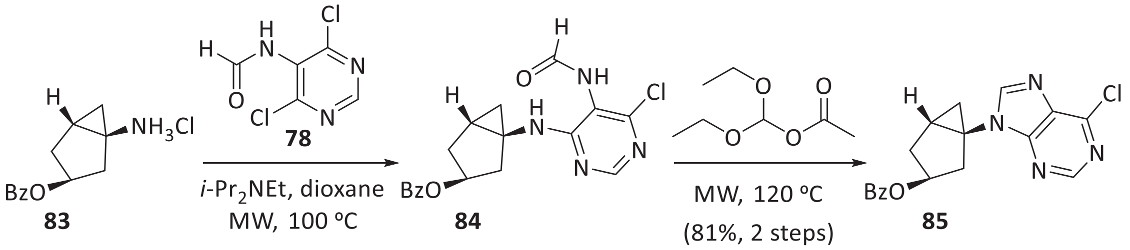


76 **81** **82**

Scheme IV-46. Preparation of chloropurine derivative **82**.

The formation of the purine ring was confirmed by the presence of two new peaks in the ^{1}H-NMR spectrum at 8.76 and 8.50 ppm, corresponding to H-2 and H-8, respectively as well as by the displacement of the signal of proton H-2' to higher chemical shifts (from 3.8 ppm in **76** to 5.2 ppm in **82**).

In 2010, Marquez and co-workers reported an alternative methodology to construct the purine ring, avoiding the acidic conditions of the cyclization and under microwave irradiation (Scheme IV-47).[69] Following this procedure the chloropurine derivative **85** was furnished in 81% yield by treatment of ammonium chloride **83** with formamidopyrimidine **78** and *i*-Pr_2NEt and successive cyclization using diethoxymethyl acetate, both under microwave irradiation.



83 **84** **85**

Scheme IV-47. Construction of the purine ring using microwave irradiation reported by Marquez and co-workers.

Taking this into account, the two-step construction of the purine ring in our compounds was attempted under microwave irradiation.

2.7.3.1.1. Microwave radiation in organic chemistry

Microwaves are a type of electromagnetic radiation with wavelengths comprised between 1 mm and 1 m, located between infrared radiation (IR) and radio waves. The energy of the microwave photon in this frequency region is too low to break chemical bonds, preventing microwaves to induce chemical reactions, in contrast to ultraviolet and visible radiations.

The usefulness of microwaves in organic synthesis is related to the efficient heating of materials by microwave irradiation. Microwave dielectric heating depends on the ability of a specific material (e.g. solvent or reagent) to absorb microwave energy and convert it into heat. This ability is, in its turn, strongly related to the dielectric properties of each particular material, and it is determined by the so-called loss factor (tan δ). This loss factor is expressed as the quotient $\tan \delta = \varepsilon''/\varepsilon'$, where ε'' is the dielectric loss, which quantifies the efficiency with which the absorbed energy is converted into heat, and ε' is the dielectric constant, representing the ability of molecules to store electrical potential energy under the influence of an electric field. The loss factors, as well as boiling points, dielectric losses and dielectric constants of some common organic solvents are summarized in Table IV-5.[82,83]

Table IV-5. Boiling point, loss factor, dielectric constant and dielectric loss data for some common organic solvents (2.45 GHz, 20 °C).

Solvent	b.p. (°C)	tan δ	ε’	ε’’
ethyleneglycol	197	1.35	37.0	49.950
ethanol	78	0.941	24.3	22.866
DMF	153	0.161	37.7	6.070
water	100	0.123	80.4	9.889
chlorobenzene	132	0.101	2.6	0.263
toluene	111	0.040	2.4	0.096
hexane	69	0.020	1.9	0.038

One of the main advantages of microwave irradiation over conventional heating systems is the achievement of dramatically reduced reaction times. While the external heat sources usually used in organic synthesis depend on thermal conductivity of the various materials that must be penetrated, microwave radiation passes through the walls of the reaction vessels and heats only the molecules (solvents, reagents, catalysts), producing an efficient internal heating. Thus, microwave irradiation raises the temperature of the whole volume simultaneously, producing a fast and homogeneous heating, whereas when using an oil bath the reaction mixture in contact with the vessel wall is heated first (Figure IV-18). Consequently, the heating profiles attained by microwave irradiation are very difficult to reproduce by standard thermal heating. Moreover, the monitoring mechanisms for temperature and pressure in modern microwave reactors allow for an excellent control of reaction parameters.

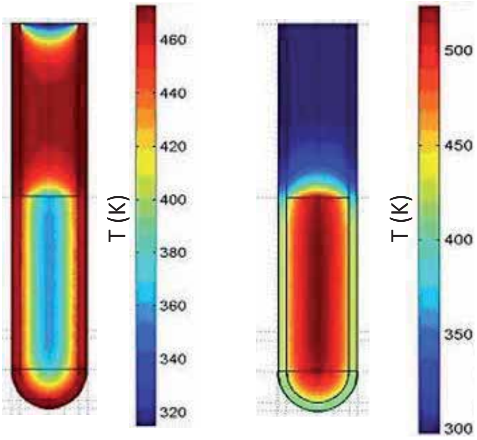


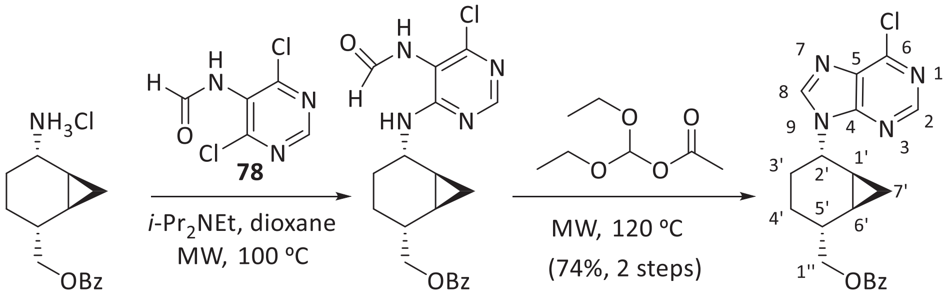
Figure IV-18. Difference in the temperature profiles after 1 minute of treatment in an oil bath (left) and microwave irradiation (right).

The stepwise construction of the base under microwave irradiation was carried out with a CEM Discover® microwave instrument, which allowed us to set several parameters, such as temperature, reaction time, power, maximum pressure and *PowerMAX*^{TM}.

Temperature corresponds to the set temperature that will be maintained during the *reaction time*. *Power* stands for the maximum power at which the sample will be irradiated, although the power may change in the course of the reaction. *PowerMAX*^{TM} is a technology that consists of a simultaneous cooling of the reaction with compressed gas on the outside of the reaction vessel, which enables more energy in the reaction (by increasing the power) while maintaining the temperature.[84] In all the reactions performed in this dissertation under microwave irradiation, *power* was set at 250 W, *maximum pressure* at 250 psi and the *PowerMAX*^{TM} option was always enabled. All the reactions were performed in a sealed vessel.

2.7.3.1.2. Synthesis of adenine nucleoside analogue D-2-A

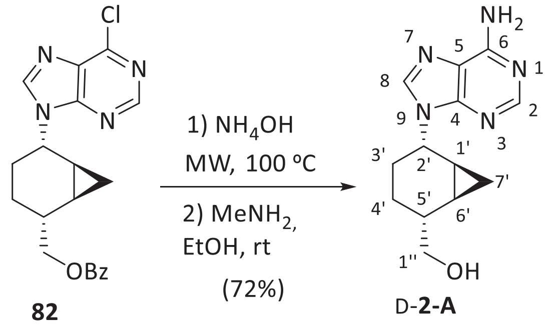
Treatment of ammonium chloride **76** with formamidopyrimidine **78** and *i*-Pr_2NEt in 1,4-dioxane at 100 °C under microwave irradiation for 20 min, followed by cyclization using diethoxymethyl acetate at 120 °C for 2 h also under microwave irradiation delivered the chloropurine derivative **82** in 74% yield (Scheme IV-48).



76 **81** **82**

Scheme IV-48. Purine ring formation using microwave irradiation.

To achieve the synthesis of the adenine nucleoside D-**2-A**, an ammonolysis step reaction followed by a simultaneous hydroxyl deprotection was required. The ammonolysis was carried out using microwave irradiaton, following the procedure above mentioned reported by Marquez and co-workers.[69] Thus, treatment of the chloropurine derivative **82** with NH_4OH in 1,4-dioxane at 100 °C for 40 min under microwave irradiation and successive exposure to a 33% solution of $MeNH_2$ in EtOH[64] furnished the desired adenine nucleoside analogue D-**2-A** in two steps and 72% overall yield (Scheme IV-49).



82 D-**2-A**

Scheme IV-49. Preparation of adenine nucleoside D-**2-A**.

The formation of adenine nucleoside D-**2-A** was confirmed by the disappearance of the peaks corresponding to the benzoyl group in ^{1}H-NMR and ^{13}C-NMR spectra of nucleoside analogue D-**2-A** as well as by the displacement of C-6 signal to lower chemical shifts (from 151.2 ppm in **82** to 120.5 ppm in D-**2-A**) (Figure IV-19).

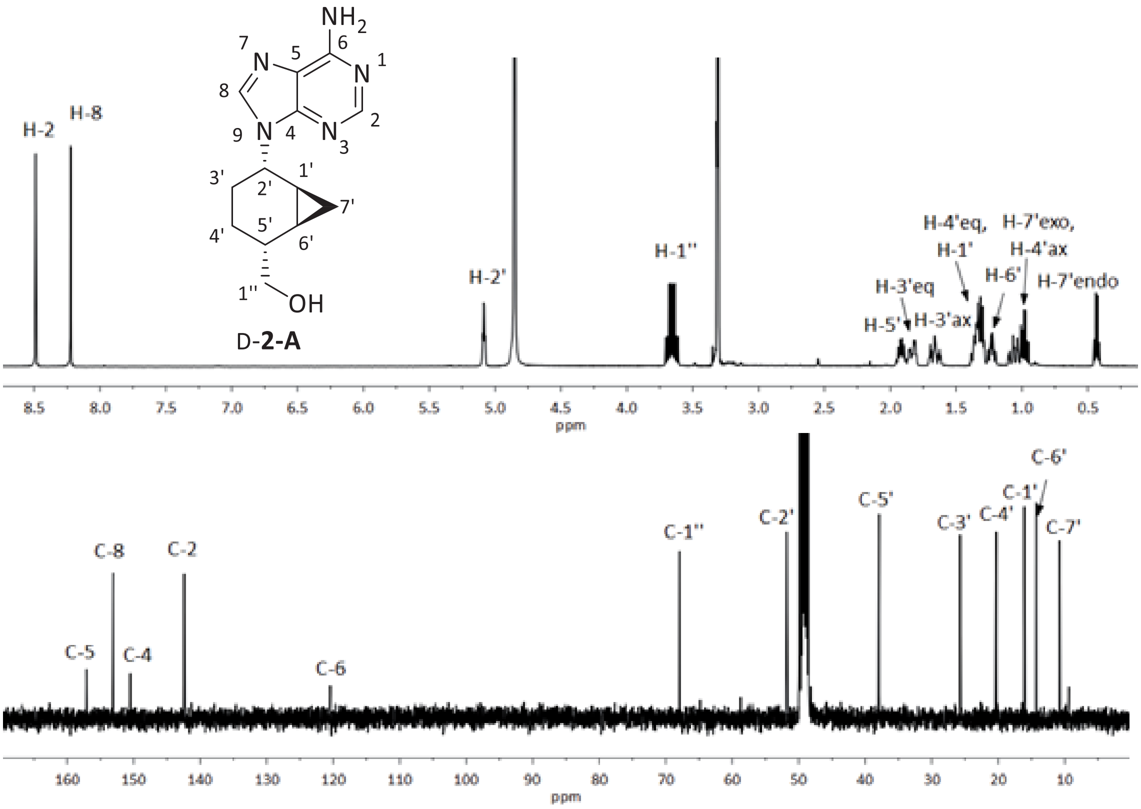
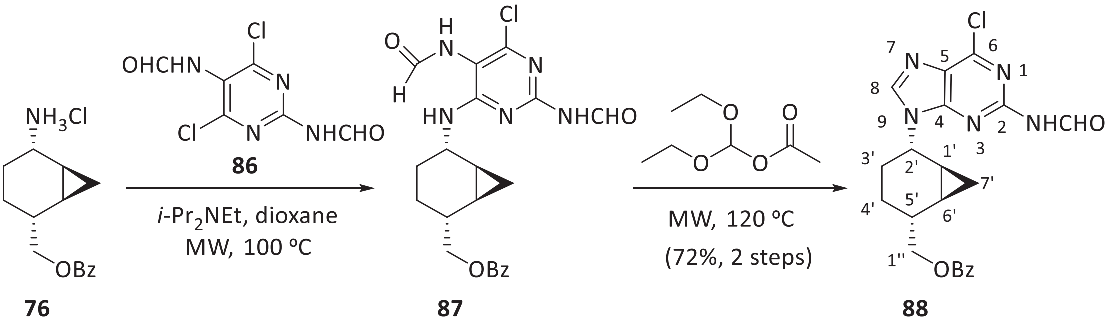


Figure IV-19. ^{1}H-NMR (400 MHz, MeOD) and ^{13}C-NMR (100 MHz, MeOD) of D-**2-A**.

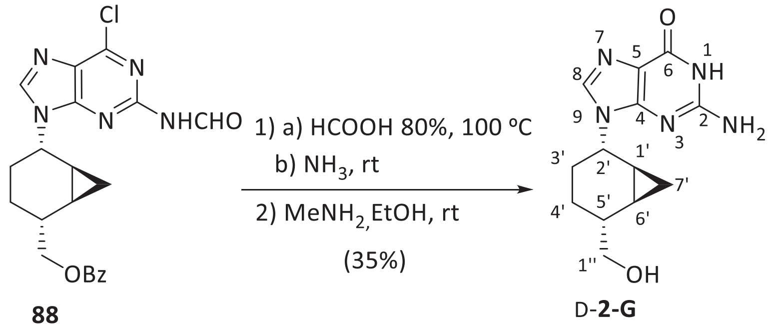
2.7.3.1.3. Synthesis of guanine nucleoside analogue D-2-G

Guanine nucleoside D**-2-G** was synthesised following the same procedure. Accordingly, ammonium chloride **76** was treated with the formyl derivative of 2,5-diamino-4,6-dichloropyrimidine **86** in the presence of *i*-Pr$_2$NEt in 1,4-dioxane at 100 °C under microwave irradiation to provide intermediate **87**. Then, ring closure in the presence of diethoxymethyl acetate at 120 °C afforded the chloropurine derivative **88** in 72% yield (Scheme IV-50). The purine ring could be easily identified in the ^{1}H-NMR spectrum, since two new signals corresponding to –CHO and H-8 appeared at 9.54 and 8.29 ppm, respectively.



Scheme IV-50. Preparation of chloropurine derivative **88**.

The transformation of the chloropurine derivative into guanine was attempted following a methodology reported by Harnden and co-workers.[78] Thus, treatment of the chloropurine derivative **88** with 80% formic acid at 100 °C followed by exposure to concentrated aqueous NH_3 at room temperature and subsequent reaction with a 33% solution of $MeNH_2$ in EtOH provided the desired nucleoside analogues D-**2-G** in 2 steps and 35% global yield (Scheme IV-51). The low yield may be due to the difficult isolation of the desired product from the reaction mixture.

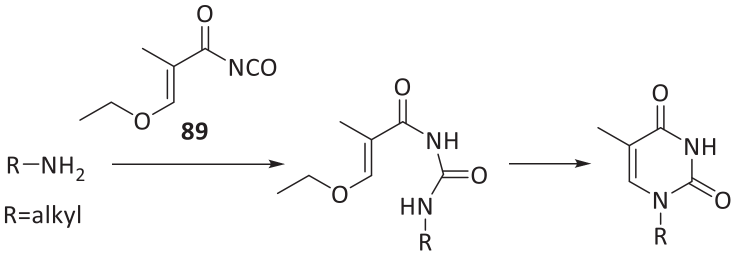


Scheme IV-51. Preparation of guanine nucleoside D-**2-G**.

As before, the formation of guanine nucleoside D-**2-G** was confirmed by the disappearance of the peaks corresponding to the benzoyl group and -CHO in ^{1}H-NMR and ^{13}C-NMR spectra of nucleoside analogue D-**2-G** as well as by the displacement of C-6 signal in the ^{13}C-NMR spectrum to higher chemical shifts (from 152.5 ppm in **88** to 159.5 ppm in D-**2-G**).

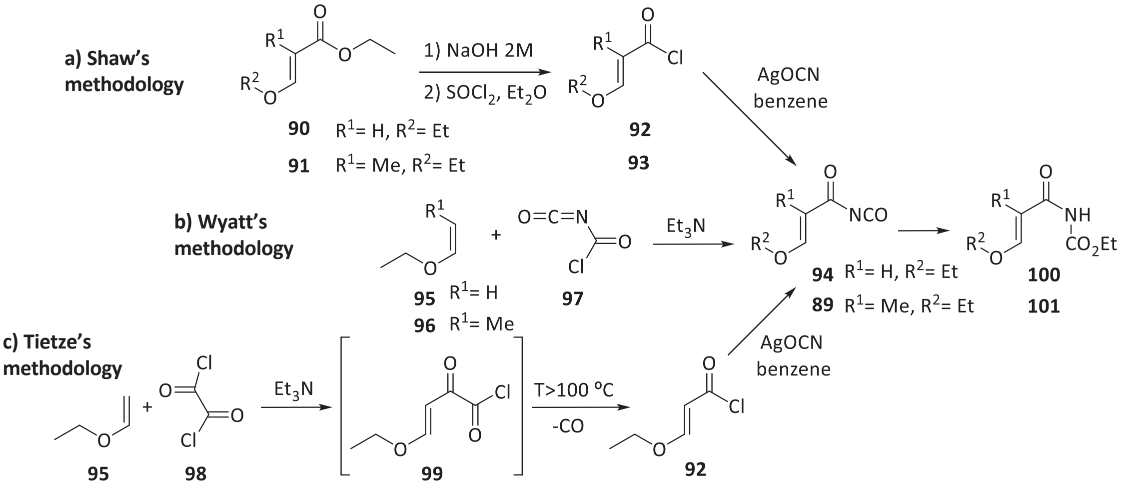
2.7.3.2. Synthesis of pyrimidine nucleosides

The first methodology to construct pyrimidine bases stepwise was reported by Shaw and Warrener in 1958.[85,86] This procedure was based on a two-step reaction consisting of the addition of an amine to an isocyanate **89** followed by a cyclization of the formed acryloyl urea (Scheme IV-52).



Scheme IV-52. Formation of thymine ring.

Isocyanate **89** can be prepared by different routes (Scheme IV-53).[85–88] Shaw and Warrener described the synthesis of isocyanate **89** starting from ethyl β-ethoxy-α-methylacrylate **91**.[85,86] Saponification and subsequent treatment with thionyl chloride provided chloride derivatives **93**, which was converted into the corresponding isocyanate **89** after reaction with AgOCN in dry benzene. In 1993, Tietze and co-workers published a new procedure by a nucleophilic addition of vinyl ethers **95** to oxalyl chloride **98** in the presence of Et_3N and subsequent decarbonylation to afford the chloride derivative **92**, which was then converted into isocyanate **94**.[87] Two years later, Wyatt and co-workers reported another procedure to generate isocyanate **94** consisting of the treatment of the vinyl ether **95** with chlorocarbonyl isocyanate **97**.[88]

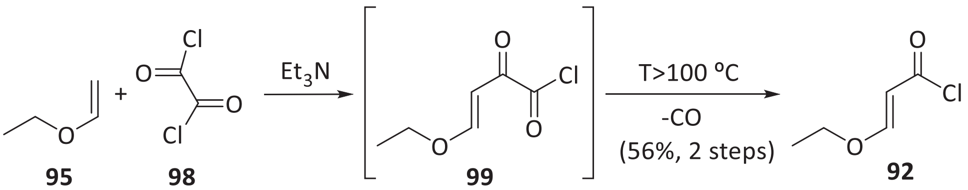


Scheme IV-53. Different methodologies to synthesise isocyanates **89** and **94**.

Isocyanates are very moisture-sensitive and reactive compounds and thus they are generally generated *in situ* for the construction of the base moiety.

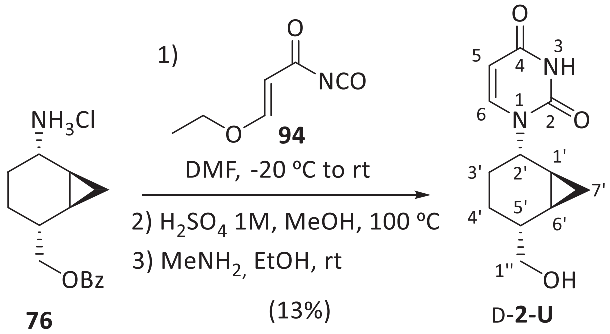
2.7.3.2.1. Synthesis of uracil nucleoside analogue D-2-U

We decided to prepare isocyanate **94** following Tietze's procedure,[87] since it was a more practical and economical procedure. Hence, treatment of ethyl vinyl ether **95** with oxalyl chloride **98**, followed by a thermal decarbonylation and purification by vacuum distillation provided acryloyl chloride **92** in 56% yield (Scheme IV-54).



Scheme IV-54. Preparation of acryloyl chloride **92**.

Afterwards, the formation of the uracil ring was performed following a methodology described by Garcia-Mera and co-workers.[89] Then, treatment of acryloyl chloride **92** with AgOCN in dry benzene at the reflux temperature led to the corresponding isocyanate **94**, which was directly added to a solution of amine **76** and Et_3N in dry DMF at -20 °C. Cyclization under acidic conditions (H_2SO_4 1M in MeOH) followed by the deprotection of the alcohol using a 33% solution of $MeNH_2$ in EtOH, gave the desired nucleoside analogues D-**2-U** in 13% overall yield (Scheme IV-55).

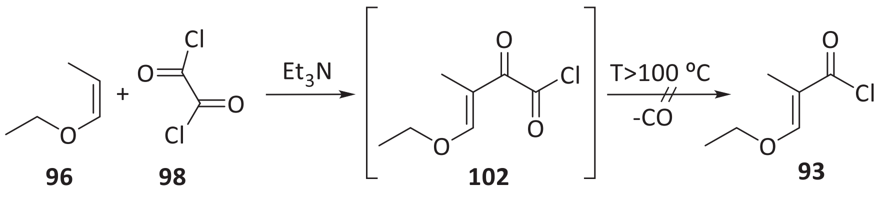


Scheme IV-55. Synthesis of uracil nucleoside D-**2-U**.

The presence of uracil base in D-**2-U** was confirmed by the ^{1}H-NMR spectrum, which showed two new peaks at 5.69 ppm and 8.05 ppm, corresponding to H-5 and H-6, respectively. Moreover, the deprotection of the alcohol was observed by the disappearance of the signals of the benzoyl group in ^{1}H-NMR and ^{13}C-NMR spectra.

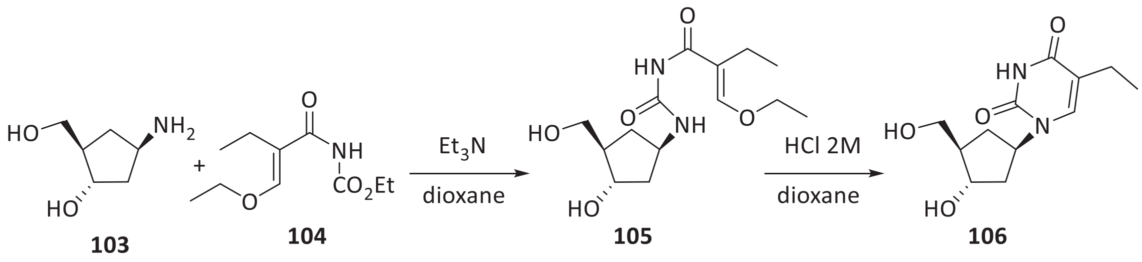
2.7.3.2.2. Synthesis of thymine nucleoside analogue D-2-T

Then, following the same methodology we attempted to prepare the 2-methyl acryloyl chloride derivative **93** to construct the corresponding thymine ring. However, treatment of ethyl-1-propenyl ether **96** with oxalyl chloride **97** in the presence of Et_3N, followed by a thermal decarbonylation and purification by vacuum distillation did not achieve the expected acryloyl chloride **93** but decomposition products (Scheme IV-56). Therefore, another synthetic methodology was needed to achieve the construction of the thymine ring.



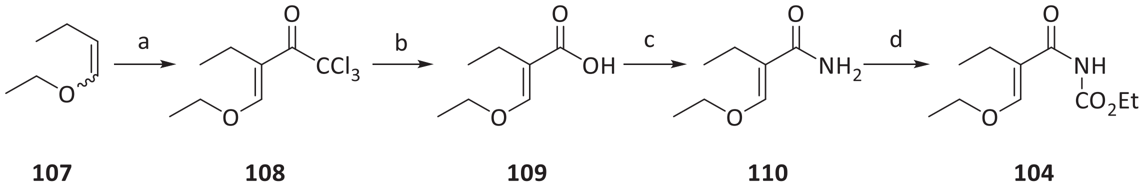
Scheme IV-56. Attempt of preparation of oxalyl chloride **93**.

It is well known that acyl carbamates react with amines to provide uracil derivatives under a range of conditions.[90] In 1995, Wyatt and co-workers investigated the reaction of acyl carbamate **104** with aminodiol **103** to prepare the 5-ethyluracil derivative **106** (Scheme IV-57).[88]



Scheme IV-57. Synthesis of 5-ethyluracil derivative **106** reported by Wyatt and co-workers.

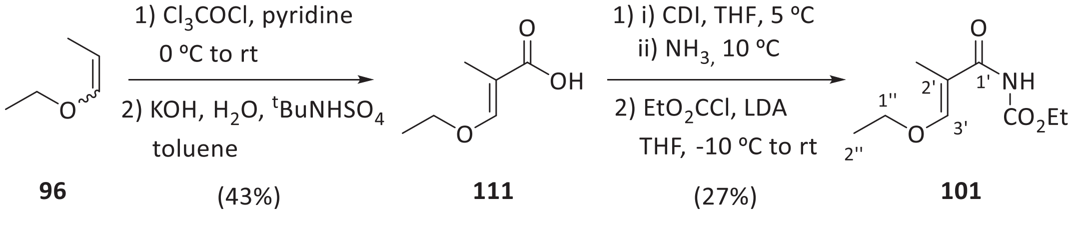
In this work, it was described a route to prepare the acyl carbamate **104** starting from buthenyl ethyl ether **107** (Scheme IV-58) in 4 steps and 35% overall yield.[88] Thus, the reaction of a *cis*/*trans* mixture of buthenyl ethyl ether **107** with trichloroacetyl chloride (Cl_3COCl) in pyridine afforded **108**, since only the *cis* isomer of **107** reacted. Hydrolysis of **108** under controlled conditions delivered the acid **109**, which was converted to the amide derivative **110** by reaction with 1,1'-carbonyldiimidazole (CDI) in THF and subsequent addition of NH_3. Finally, treatment of amide **110** with LDA in THF followed by reaction with ethyl chloroformate furnished the acyl carbamate **104**.



Reagents and conditions: a) Cl_3COCl, py; b) KOH, H_2O, toluene; c) i) CDI, THF, ii) NH_3; d) EtO_2CCl, LDA, THF.

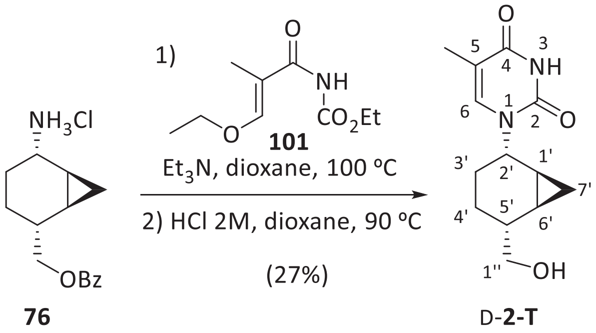
Scheme IV-58. Wyatt's procedure to prepare acyl carbamate **104**.

Taking this into account, we decided to apply this methodology to prepare the acyl carbamate **101**, necessary to construct the thymine ring. Hence, reaction of the ethyl propenyl ether **96** with Cl_3COCl and pyridine in chloroform and successive treatment with KOH, water and tetrabutylammonium hydrogen sulphate in toluene led to acid **111**. This acid was activated with CDI in THF and treated with concentrated aqueous NH_3 to provide the corresponding amide. Then, the treatment of the crude with ethyl chloroformate and LDA in THF afforded acyl carbamate **101** in 4 steps and 12% overall yield (Scheme IV-59).



Scheme IV-59. Preparation of the acyl carbamate **101**.

Then, acyl carbamate **101** was used for the synthesis of thymine nucleoside D-**2-T**, following Wyatt's methodology.[88] Accordingly, reaction of amine **76** with acyl carbamate **101** and Et_3N in 1,4-dioxane at 100 °C followed by acid promoting cyclization furnished the desired unprotected nucleoside analogue D-**2-T** in 2 steps and 27% yield (Scheme IV-60).



Scheme IV-60. Synthesis of thymine nucleoside D-**2-T**.

As before, the presence of the thymine base in D-**2-T** was confirmed by the ^1H-NMR spectrum, which showed two new peaks at 1.91 ppm and 7.92 ppm, corresponding to $-CH_3$ and H-6, respectively. Moreover, the deprotection of the alcohol was observed by the disappearance of the peaks corresponding to the benzoyl group in ^1H-NMR and ^{13}C-NMR spectra (Figure IV-20).

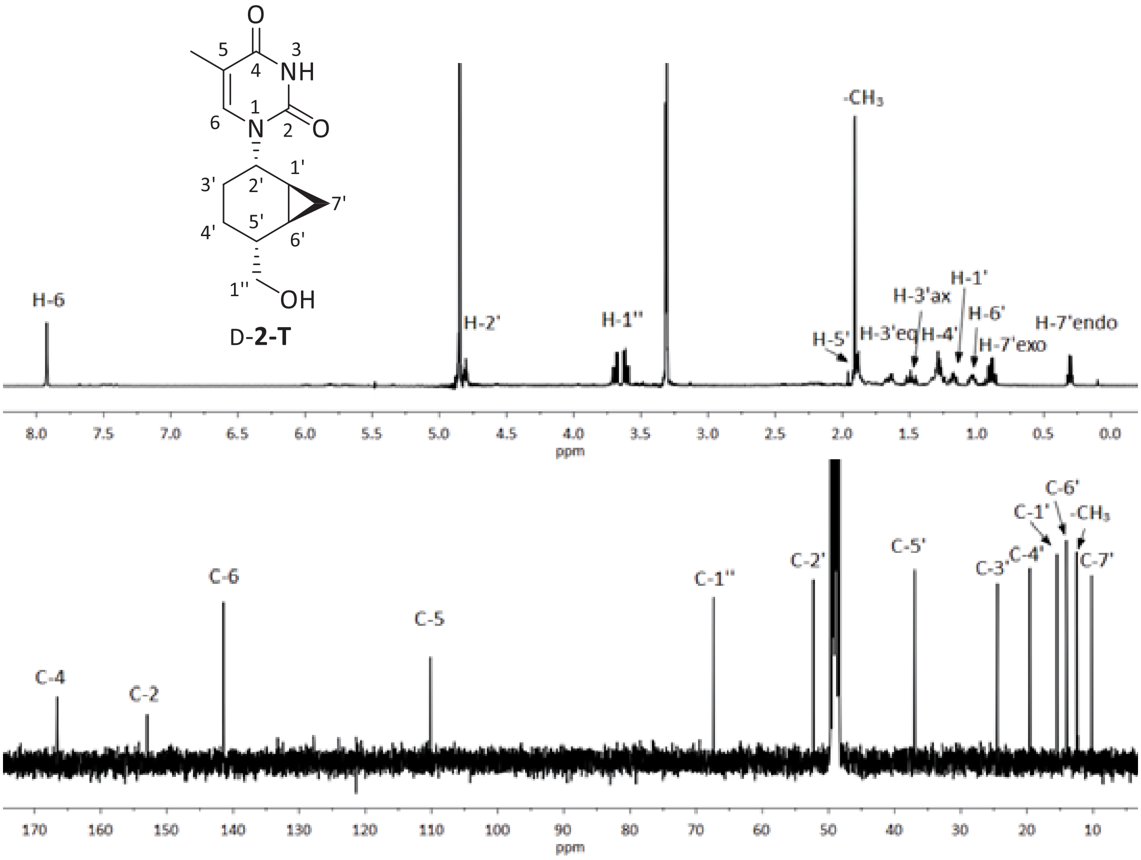
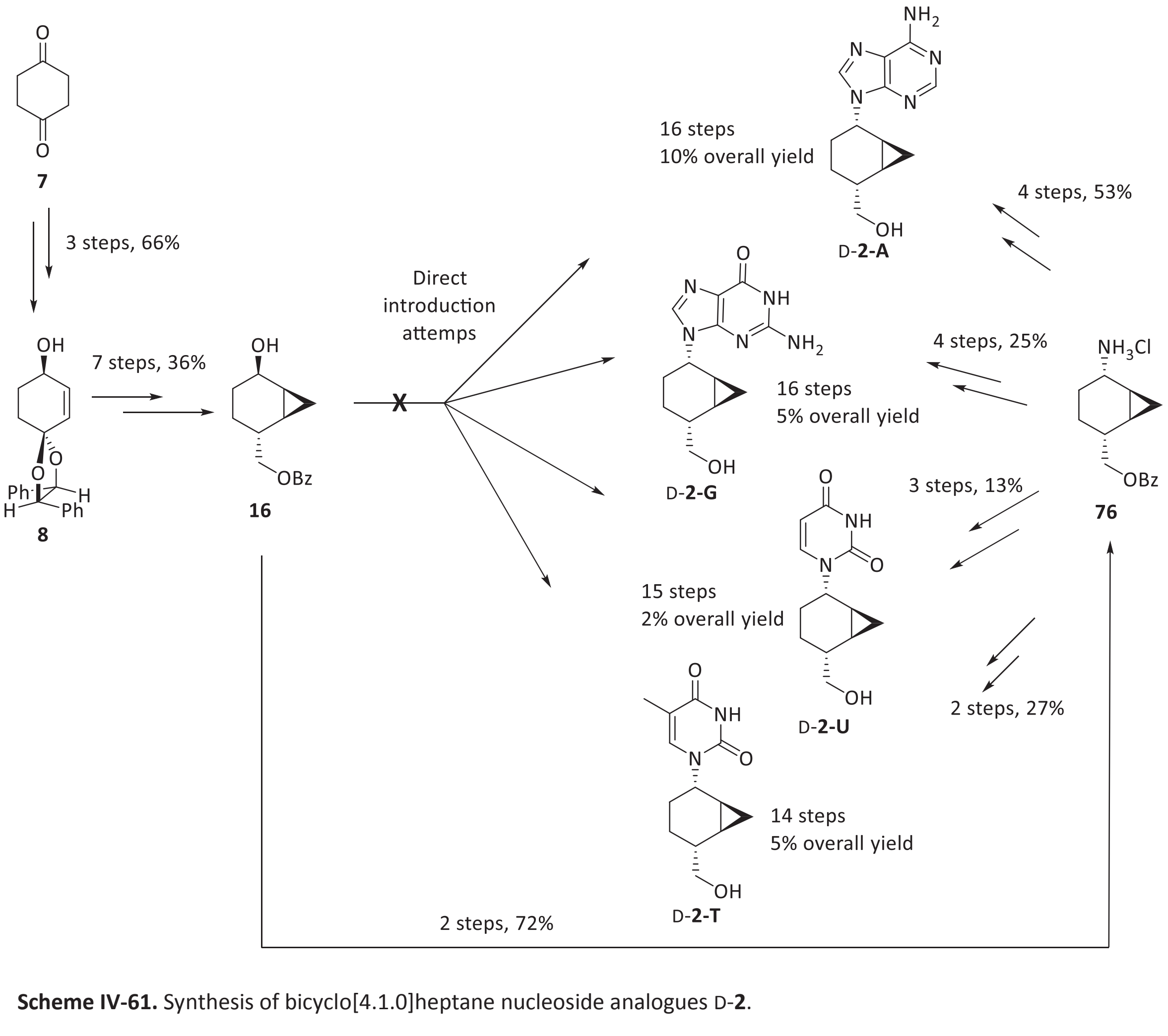


Figure IV-20. ^1H-NMR (400 MHz, MeOD) and ^{13}C-NMR (100 MHz, MeOD) of D-**2-T**.

2.8. Summary

In summary, the synthesis of four novel carbocyclic nucleoside built on a bicyclo[4.1.0]heptane scaffold have been described (Scheme IV-61) starting from commercially available 1,4-cyclohexanedione. Allylic alcohol **8** was obtained in 3 steps and 66% overall yield. This alcohol **8** was then converted into key intermediate **16** in 7 steps and 36% yield. All attempts to directly introduce the nucleobase from this intermediate failed, either activating the hydroxyl as a leaving group or using Mitsunobu methodology. Finally, the introduction of the base moiety was accomplished, in all cases, via stepwise construction of the nucleobase from ammonium chloride derivative **76**, which was afforded from alcohol **16** in 2 steps and 72% yield, leading to four new carbocyclic nucleosides D-**2**.



Scheme IV-61. Synthesis of bicyclo[4.1.0]heptane nucleoside analogues D-**2**.

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