Metodologies d'anulació en substrats heterocíclics: Reaccions de RCM i ciclacions de Heck

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METODOLOGIES D'ANULACIÓ EN SUBSTRATS HETEROCÍCLICS: REACCIONS DE RCM I CICLACIONS DE HECK

Memòria presentada per Sandra Alonso Serrano per optar al títol de doctor per la Universitat de Barcelona

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La present Tesi Doctoral es presenta com a *Compendi de publicacions*, en estar publicats els resultats que es descriuen. D'acord amb la normativa vigent, després de l'apartat d'*Introducció i objectius* (capítol 1), en el qual es presenten els treballs publicats i se'n justifica la temàtica, s'inclou un resum global dels resultats obtinguts amb la seva discussió (capítols 2 i 3), desglossats en subapartats que corresponen temàticament a les diferents publicacions. Després d'un apartat de *Conclusions* (capítol 4), es presenten com a Annex (capítol 5) les còpies completes dels treballs.

1. INTRODUCCIÓ: CONTEXTUALITZACIÓ I OBJECTIUS DE LA TESI DOCTORAL

Els sistemes heterocíclics es defineixen freqüentment en Química Mèdica com a subestructures *privilegiades*,[1] donada la seva capacitat d'unió a una gran varietat de receptors amb elevada afinitat. Com a conseqüència, el desenvolupament de nous procediments sintètics dirigits tant a la construcció dels propis sistemes heterocíclics com a la modificació del seu patró de substitució o funcionalització continua ocupant una posició rellevant en Síntesi Orgànica. En aquest context, el nostre grup de recerca centra des de fa uns anys el seu interès en l'estudi de noves estratègies sintètiques per a la formació d'anells en l'àrea heterocíclica amb l'objectiu final de construir molècules específiques amb esquelet policíclic, escollides tant per les seves característiques estructurals com per les seves interessants activitats biològiques.

D'entre els diferents heterocicles, l'indole té un paper preponderant ja que forma part de nombrosos compostos tant naturals com sintètics.[2] La ubiqüitat de l'indole a la natura és conseqüència de la seva presència a l'aminoàcid triptòfan, del qual en deriven els anomenats "alcaloides indòlics", un grup de productes naturals de complexitat estructural molt variada sovint proveïts de notables propietats biològiques.[3] Amb la intenció final d'obrir noves rutes sintètiques cap a estructures indòliques, en aquest treball s'ha prestat atenció a determinats aspectes de la versió intramolecular

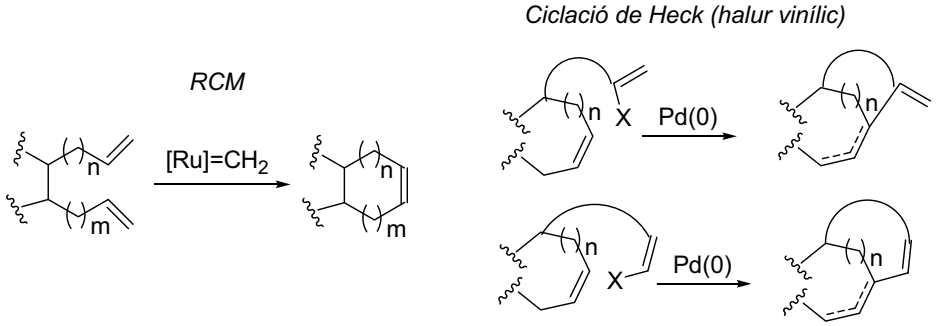
[1] (a) Horton, D. A.; Bourne, G. T.; Smythe, M.-L. *Chem. Rev*. **2003**, *103*, 893-930. (b) Costantino, L.; Barlocco, D. *Curr. Med. Chem*. **2006**, *13*, 65-85. (c) Schnur, D. M.; Hermsmeier, M. A.; Tebben, A. J. *J. Med. Chem*. **2006**, *49*, 2000-2009.

[2] (a) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996. (b) Joule, J. A. *Science of Synthesis* (*Houben-Weyl, Methods of Molecular Transformations*); Georg Thieme Verlag: Stuttgart, **2000**, Vol. 10, pp. 361-652.

[3] Ishikura, M.; Yamada, K. *Nat. Prod. Rep*. **2009**, *26*, 803-852, i revisions prèvies de la mateixa sèrie.

de dues reaccions d'eficàcia prou reconeguda en la formació d'enllaços C-C: la reacció de metàtesi d'alquens (ring-closing metathesis, RCM) i la reacció de Heck d'halurs vinílics.

Durant els darrers anys, les reaccions de RCM catalitzades per ruteni[4] han mostrat ser processos de gran utilitat per a la construcció d'una gran varietat d'estructures carbo- i heterocícliques[5] a partir de precursors dièn ics acíclics. En particular, la reacció de RCM resulta molt útil per a la síntesi d'anells mitjans,[6] el tancament dels quals pot ser problemàtic degut a factors entròpics desfavorables o bé a interaccions transanulars.



D'altra banda, d'entre les diferents reaccions d'acoblament creuat catalitzades per Pd(0)[7] destaca l'acoblament d'halurs insaturats amb olefines conegut com reacció de Heck,[8] la versió intramolecular de la qual també s'ha mostrat eficaç per a la síntesi d'heterocicles.[9] És important destacar que si bé la reacció de Heck es pot considerar un procés clàssic avui en dia, la majoria d'exemples descrits fan referència a

[4] Per a revisions generals, vegeu: (a) Grubbs, R. H., Ed.; *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003; Vol. 2. (b) Nicolaou, K. C.; Bulger. P. G.; Sarlah, D. *Angew. Chem*., *Int. Ed*. **2005**, *44*, 4490-4527. (c) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev*. **2009**, *109*, 3708-3742.

[5] Per a revisions específiques sobre la síntesi d'heterocicles mitjançant RCM, vegeu: (a) Walters, M. A. *Progress in Heterocyclic Chemistry*; Gribble, G.W., Joule, J. A., Eds.; Pergamon: Amsterdam, 2003; Vol. 15, pp 1–36. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, *104*, 2127-2198. (c) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199-2238. (d) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev*. **2007**, *36*, 55-66. (e) Compain, P. *Adv. Synth. Catal*. **2007**, *349*, 1829-1846. (f) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chemistry* **2008**, *14*, 5716-5726.

[6] Per a revisions sobre la formació d'anells mitjans per RCM, vegeu: (a) Maier, M. E. *Angew. Chem., Int. Ed*. **2000**, *39*, 2073–2077. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (c) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed*. **2006**, *45*, 5740–5750. (d) Shiina, I. *Chem. Rev*. **2007**, *107*, 239-273.

[7] Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-VCH: New York, 2002, Vol. I i II.

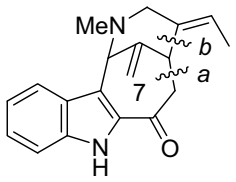
[8] Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions;* de Meijere, A.; Diederich, F., Eds; Wiley-WCH: New York, 2004; pp. 217-316.

[9] Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644-4680.

acoblaments d'alquens amb *halurs arílics*, sent minoritaris els que impliquen *halurs vinílics*.

Tenint en compte els antecedents esmentats, en la present Tesi Doctoral ens proposàrem avaluar les possibilitats sintètiques de la combinació d'aquestes dues metodologies d'anulació (RCM i Heck intramolecular d'halurs vinílics) per a la construcció de manera ràpida i eficient de les estructures policícliques complexes d'alguns alcaloides indòlics i compostos sintètics relacionats.[10] Concretament, les estructures representades a continuació es caracteritzen per presentar un anell de piperidina i un carbocicle de 7 baules o bé un azacicle de 8 baules formant diferents sistemes bicíclics amb pont fusionats per la cara *b* de l'indole: 2-azabiciclo[4.3.1]decà (alcaloide ervitsina), 1-azabiciclo[4.2.2]decà (alcaloide aparicina) i 1-azabiciclo[5.3.1]undecà (compost **I**, unitat superior de la vinorelbina). En tots els casos, una reacció de RCM a partir d'un diè indòlic (2,3-dialquenilindole) adequat generaria el carbocicle o azacicle fusionat amb l'indole, amb un doble enllaç que s'empraria per al posterior tancament de l'anell de piperidina mitjançant un acoblament intramolecular de Heck amb un halur vinílic.

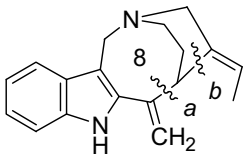
2-azabiciclo[4.3.1]decà



Ervitsina

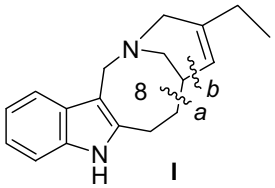
a RCM
b Ciclació de Heck

1-azabiciclo[4.2.2]decà



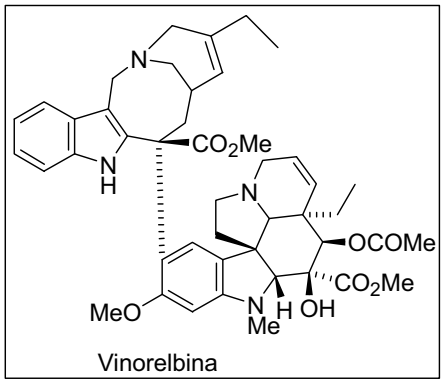
Aparicina

1-azabiciclo[5.3.1]undecà



I

Unitat superior
de la vinorelbina



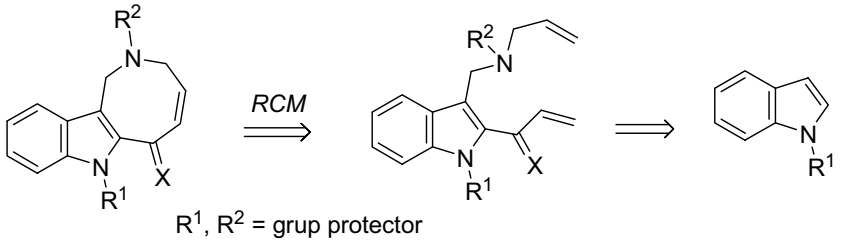
Vinorelbina

[10] Per a la construcció de sistemes bicíclics mitjançant seqüències de RCM i reaccions de Heck intramolecular d'halurs d'aril, vegeu: (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett*. **1998**, *39*, 4139-4142. (b) Grigg, R.; York, M. *Tetrahedron Lett*. **2000**, *41*, 7255-7278. (c) Lautens, M.; Zunic, V. *Can J. Chem*. **2004**, *82*, 399-407. (d) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem*. **2005**, *70*, 10538-10551. (e) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett*. **2007**, *9*, 4223- 4226. (f) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett*. **2007**, *9*, 5119-5122.

S'ha de destacar que acoblaments de Heck similars, implicant halurs vinílics i cicloalquens elaborats, han mostrat ser útils per a la formació dels sistemes bicíclics amb pont d'alguns alcaloides indòlics, com ara els alcaloides pentacíclics *Strychnos*,[11] l'estricnina,[11c,12] la minfiensina[13] i l'apogeissoschizina.[14] No obstant això, a excepció de l'últim cas on la ciclació té lloc sobre un anell de cicloheptè, tots els exemples descrits impliquen anells de ciclohexè. Per tant, les reaccions proposades entre halurs vinílics i anells d'azaciclooctè no tenen precedents a la literatura.

Els resultats obtinguts al llarg de la Tesi Doctoral s'han agrupat en dues parts diferenciades que corresponen als Capítols 2 i 3 de la present Memòria:

(a) Al Capítol 2 de la Memòria s'expliciten els estudis preliminars de la reacció de RCM en substrats indòlics dirigits a la preparació d'azacicles fusionats per la cara *b* de l'heterocicle, fonamentalment azocino[4,3-*b*]indoles, els quals constitueixen la subestructura tricíclica tant de l'alcaloide aparicina com de la unitat superior de la vinorelbina. Això ha requerit posar a punt procediments eficients per a la preparació dels corresponents diens indòlics, és a dir, 2,3-dialquenilindoles que incorporen un àtom de nitrogen en la cadena que connecta els dos dobles enllaços.



R^1, R^2 = grup protector
X = H, H; H, OTBDMS; O

(Resultats publicats a *Tetrahedron* **2007**, *63*, 861-866)

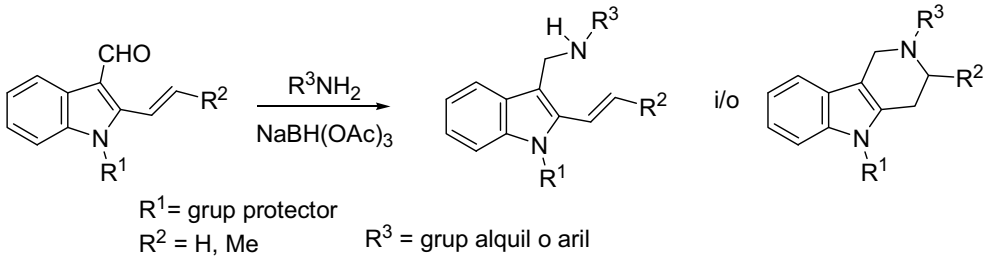
[11] (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett*. **1991**, *32*, 1695-1698. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc*. **1993**, *115*, 3030-3031. (c) Mori, M.; Nakanishi, M.; Kahishima, D.; Sato, Y. *J. Am. Chem. Soc*. **2003**, *125*, 9801-9807. (d) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472-3473.

[12] (a) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686. (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655-665. (c) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc*. **2001**, *123*, 9324-9337.

[13] (a) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. **2008**, *130*, 5368-5377. (b) Per a una aproximació relacionada, vegeu: Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed*. **2008**, *47*, 3618-3621.

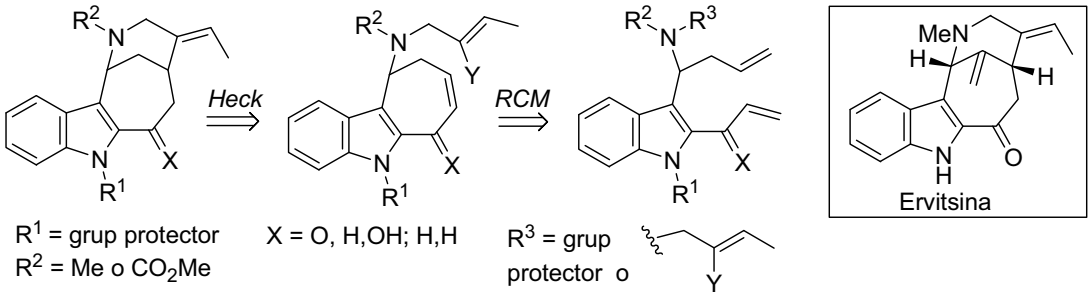
[14] Birman, V. B.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 9146-9147.

En aquest mateix context, es descriu la formació competitiva de tetrahidro-γ-carbolines a partir de 2-vinil-3-indolecarbaldehids en condicions d'aminació reductora.



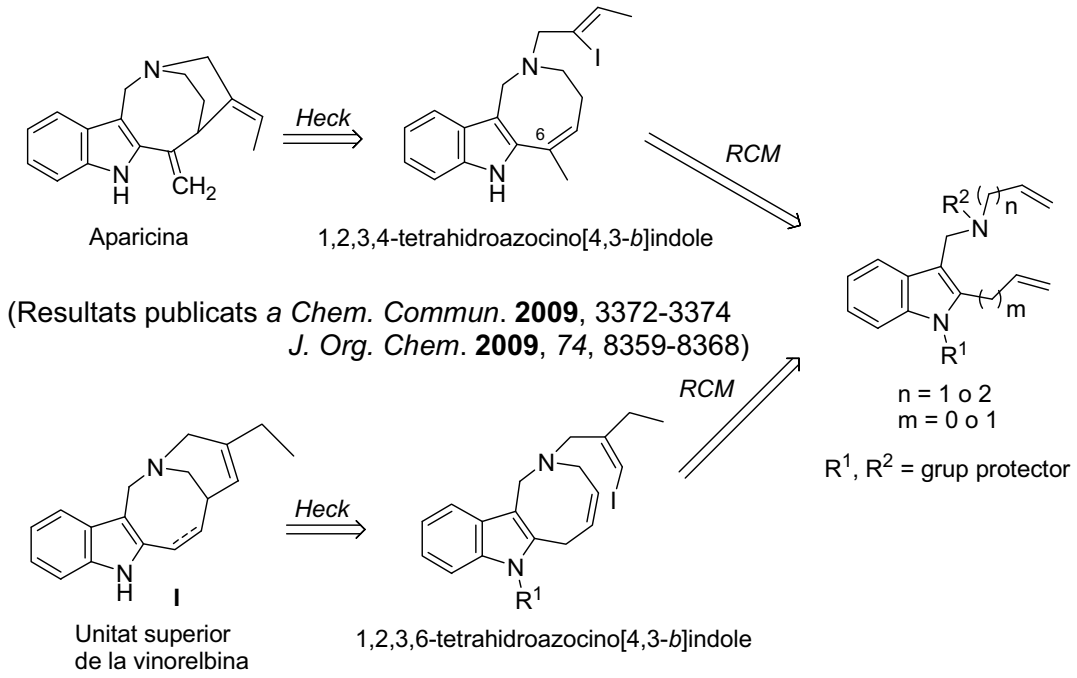
(Resultats publicats a *Tetrahedron Lett.* **2005**, *46*, 7881-7884)

(b) Al Capítol 3, més extens, s'exposen els resultats obtinguts en l'aplicació de l'estratègia de doble anulació RCM-ciclació de Heck per a la construcció d'estructures indòliques amb pont. En primer lloc, en el context de la síntesi de l'alcaloide ervitsina, es descriu la preparació de diens indòlics substituïts per un grup amino, la reacció de RCM per donar el sistema de ciclohepta[*b*]indole i la generació de l'esquelet tetracíclic de l'alcaloide per reacció de Heck d'un halur vinílic sobre l'anell de cicloheptè.



(Resultats publicats a *Synlett* **2008**, 667-670)

A continuació, es descriu l'estudi realitzat en el context de la síntesi de l'alcaloide aparicina que ha culminat en la primera síntesi total d'aquest producte natural. Amb l'experiència adquirida prèviament en la preparació d'azocino[4,3-*b*]indoles mitjançant la reacció de RCM s'ha accedit a un 1,2,3,4-tetrahidro derivat que incorpora un grup metil a la posició 6, a partir del qual ha estat possible dur a terme el tancament de l'anell de piperidina per acoblament intramolecular de Heck, amb la inclusió simultània dels dos dobles enllaços exocíclics de l'alcaloide.



(Resultats publicats *a Chem. Commun*. **2009**, 3372-3374
J. Org. Chem. **2009**, *74*, 8359-8368)

(Resultats no publicats)

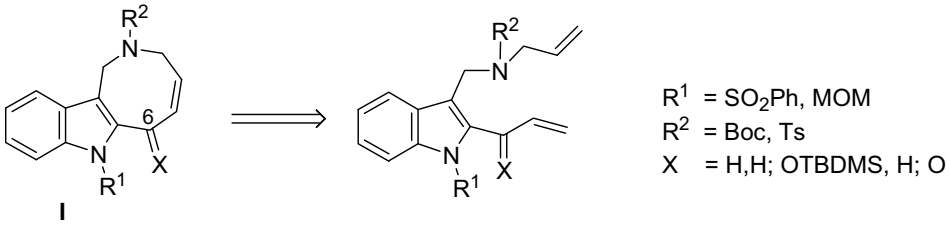
Finalment, es recull l'accés a la unitat superior de la vinorelbina a partir d'un 1,2,3,6-tetrahidroazocino[4,3-*b*]indole, per ciclació de Heck d'un halur vinílic que incorpora en aquest cas tres àtoms de carboni de l'anell de piperidina.

2. RCM EN SUBSTRATS INDÒLICS: ESTUDIS PRELIMINARS DIRIGITS A LA SÍNTESI D'AZACICLES 2,3-FUSIONATS AMB L'INDOLE

2.1 SÍNTESI D'AZOCINO[4,3-*b*]INDOLES

(*Tetrahedron* **2007**, *63*, 861-866)

D'acord amb els nostres objectius, a l'inici de la Tesi Doctoral decidírem estudiar la preparació d'azacicles fusionats per la cara *b* de l'indole mitjançant RCM de diens indòlics.[1,2] En concret centràrem la nostra atenció en els sistemes d'azocino[4,3-*b*]indole de tipus **I**, els quals constitueixen la subestructura tricíclica de l'alcaloide aparicina i de la unitat superior de la vinorelbina. Aquests sistemes es prepararien per ciclació de 2,3 dialquenilindoles que incorporen un àtom de nitrogen en la cadena que connecta els dos dobles enllaços.

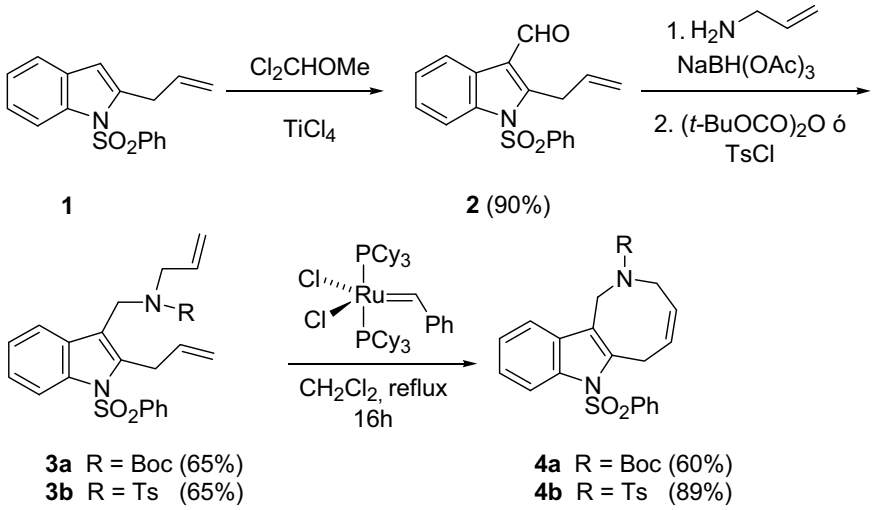


I

[1] Per a exemples previs de RCM de diens indòlics, vegeu: (a) Birman, V. B.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 9146-9147. (b) González-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett*. **2002**, *43*, 4765-4767. (c) Chacun-Lefèvre, L.; Bénéteau, V.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2002**, *58*, 10181-10188. (d) Kalinin, A.; Chauder, B. A.; Rahkit, S.; Snieckus, V. *Org. Lett*. **2003**, *5*, 3519-3521. (e) Bremmer, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G.; Witchard, H. M. *Tetrahedron* **2003**, *59*, 8741-8755. (f) Yang, X.; Althammer, A.; Knochel, P. *Org. Lett*. **2004**, *6*, 1665-1667. (g) Pelly, S. C.; Parkinson, C. J.; van Otterlo, W. A. L.; de Koning, C. B. *J. Org. Chem*. **2005**, *70*, 10474-10481. (h) Gagnon, D.; Spino, C. *J. Org. Chem*. **2009**, *74*, 6035-6041.

[2] Per a exemples específics de RCM d'enins indòlics, vegeu: (a) Schramm, M.-P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed*. **2001**, 49, 4274-4277. (b) Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Freire, G.; Pérez-Castells, J. *Tetrahedron* **2002**, *58*, 5407-5415. (c) González-Gómez, A.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett*. **2005**, *46*, 7267-7270. (d) González-Gómez, A.; Domínguez, G.; Amador, U.; Pérez-Castells, J. *Tetrahedron Lett*. **2008**, *49*, 5467-5470.

La viabilitat de la proposta s'explorà inicialment emprant com a precursors diènics els 2-al·lil-3-(al·lilaminometil)indoles **3**, que no es troben funcionalitzats a la posició α-benzílica de l'indole (C-6). Per a la preparació d'aquests compostos visualitzàrem una seqüència de formilació–aminació reductora a partir del 2-al·lilindole **1**,[3] protegit a l'àtom de nitrogen amb un grup fenilsulfonil, fortament atraient d'electrons, per tal de garantir l'estabilitat dels intermedis proposats de tipus gramina.[4]

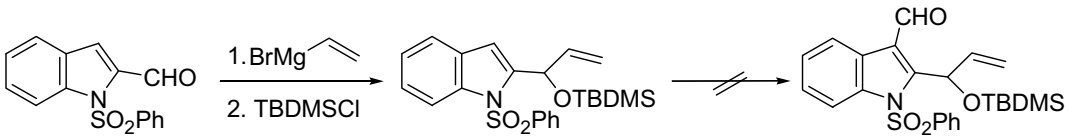


La reacció de Friedel-Crafts del compost **1** amb Cl_2CHOMe en presència de $TiCl_4$ proporcionà l'aldehid **2** amb un rendiment del 90%. Aquest compost es sotmeté a aminació reductora amb al·lilamina i, a continuació, l'amina secundària resultant es féu reaccionar amb dicarbonat de di-*tert*-butil o clorur de tosil. D'aquesta manera s'obtingueren els compostos **3a** i **3b**, protegits amb grups diferents al nitrogen alifàtic, amb un rendiment del 65% (a partir de **2**).

La reacció de RCM del diè **3a**, protegit amb un grup Boc, tingué lloc en presència del catalitzador de Grubbs de primera generació en diclorometà a reflux per donar l'azocinoindole **4a** amb un 60% de rendiment.[5] D'altra banda, la sulfonamida **3b** demostrà ser un millor substrat en la reacció de ciclació, ja que proporcionà el compost **4b** amb un rendiment superior (89%) en les mateixes condicions de reacció.

[3] Kondo, Y.; Takazawa, N.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1207-1208.
[4] Gramina: 3-(aminometil)indole.
[5] Posteriorment, **4a** s'ha pogut obtenir amb un rendiment superior (85%), emprant el catalitzador de Grubbs de segona generació en diclorometà a reflux durant 2 hores.

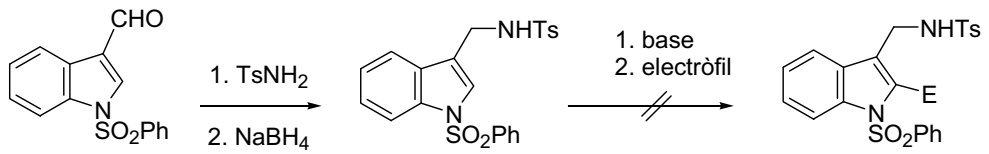
Un cop disposàvem d'un procediment adient per accedir al sistema d'azocino[4,3-*b*]indole model, abordàrem la preparació de derivats funcionalitzats al C-6. En primer lloc, decidírem estendre la seqüència sintètica de formilació-aminació reductora a un 2-(1-hidroxial·lil)indole protegit a l'àtom d'oxigen, com ara el silil èter **6**. Si bé aquest compost es pogué preparar fàcilment a partir de l'aldehid **5**[6] per reacció amb bromur de vinilmagnesi seguida de protecció de l'alcohol resultant amb clorur de *tert*-butildimetilsilil, quan s'intentà la introducció del grup formil mitjançant el protocol de Friedel-Crafts emprat a la sèrie anterior només s'obtingueren mescles complexes de reacció.



5 **6** (63%)

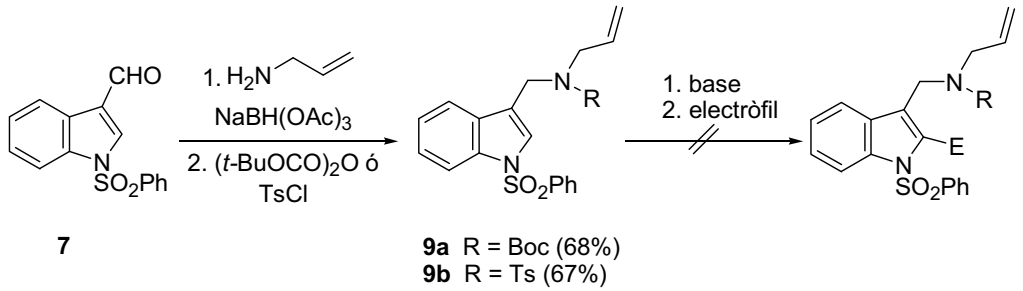
Aquest resultat ens impulsà a invertir l'ordre de les etapes sintètiques per accedir als precursors dièmics funcionalitzats, és a dir, a partir d'indoles ja substituïts a la posició 3 es funcionalitzaria la posició 2 per metal·lació i reacció amb un electròfil adequat.

Amb aquesta finalitat, es prepararen els 3-(aminometil)indoles **8** i **9** a partir de l'indole-3-carbaldehid **7**,[7] per aminació reductora amb tosilamina o bé amb al·lilamina seguida d'acilació o sulfonació. No obstant això, el tractament d'aquests substrats amb bases com ara LDA, *sec*-butil-liti o *tert*-butil-liti en THF en diferents condicions experimentals, seguit de l'addició de dimetilformamida, format de metil o acroleïna només conduïren a la recuperació dels productes de partida.



7 **8** (70%)

[6] Saulnier, M. G.; Gribble, G. W. *J. Org. Chem*. **1982**, *47*, 757-761.
[7] Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem*. **1992**, *57*, 5878-5891.

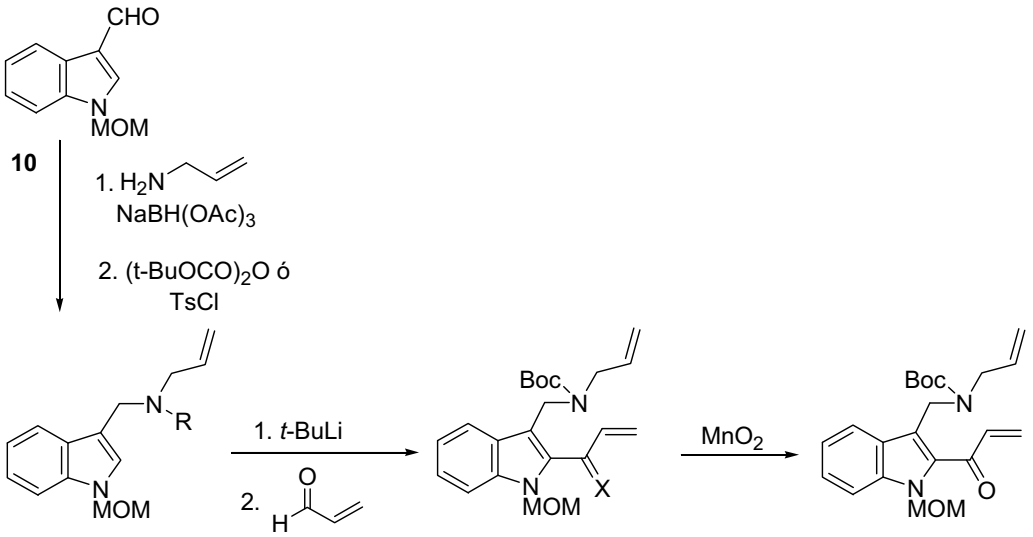


7

9a R = Boc (68%)
9b R = Ts (67%)

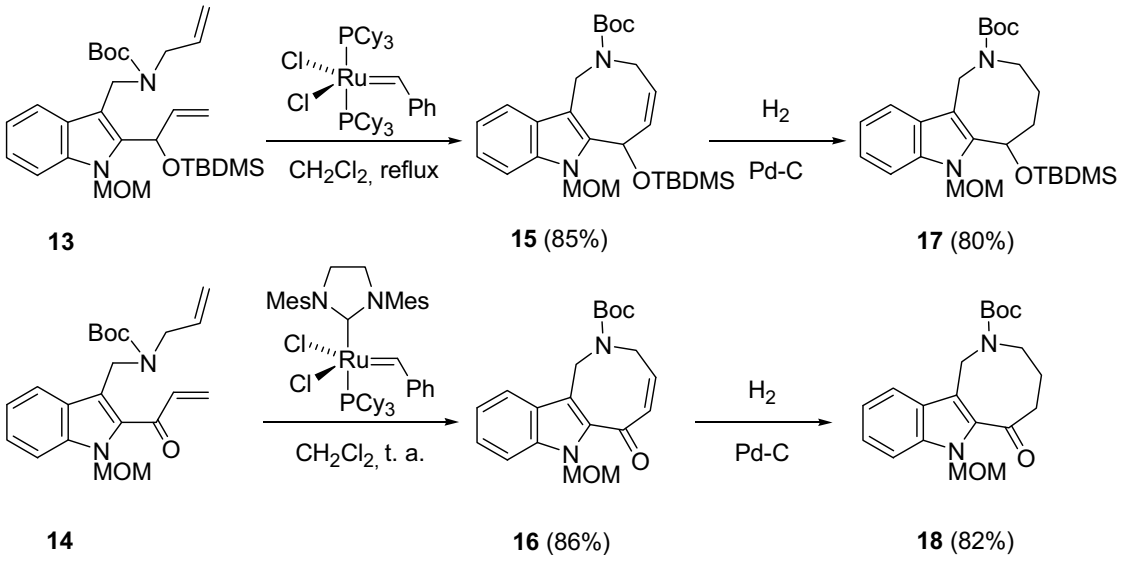
En aquest punt considerarem que la substitució del grup protector indòlic per un grup metoximetil (MOM), podria facilitar la litiació de la posició 2, tot i que també es podria veure afectada l'estabilitat dels intermedis sintètics degut al menor caràcter atraient d'electrons d'aquest grup.

L'aldehid **10**[8] es convertí en els al·lilaminometil derivats **11a** i **11b** en les condicions usuals d'aminació reductora i protecció. Donat que en aquest cas la sulfonamida **11b** resultà ser un compost inestable que descomposava durant el procés de purificació per cromatografia en columna, la síntesi es continuà amb el carbamat **11a**, que s'obtenia amb un rendiment reproduïble del 72%. D'acord amb els nostres interessos, la litiació del compost **11a** fou possible per tractament amb *tert*-butil-liti en el si de THF a la temperatura de -78ºC. Després de la reacció de l'intermedi 2-litioindole amb acroleïna s'obtingué l'alcohol **12** com a un compost inestable, el qual es protegí immediatament amb clorur de *tert*-butildimetilsilil per donar el derivat sililat **13** (64%) o, alternativament, s'oxidà amb MnO_2 per donar la cetona **14** (64%).



[8] Comins, D. L.; Killpack, M. O. *J. Org. Chem*. **1987**, *52*, 104-109.

De manera satisfactòria, quan **13** es sotmeté a la reacció de metàtesi amb el catalitzador de Grubbs de primera generació s'obtingué el compost tricíclic **15** amb un rendiment del 85%. En canvi, la ciclació de la cetona **14** no tingué lloc en aquestes condicions, probablement per la presència d'un doble enllaç pobre en electrons. Aquest problema es solucionà amb l'ús del catalitzador de Grubbs de segona generació a temperatura ambient, la qual cosa permeté aïllar la cetona **16** amb un rendiment del 86%. Finalment, la hidrogenació catalítica dels azabicicles **15** i **16** proporcionà els derivats heterocíclics saturats de 8 baules **17** i **18**, respectivament.



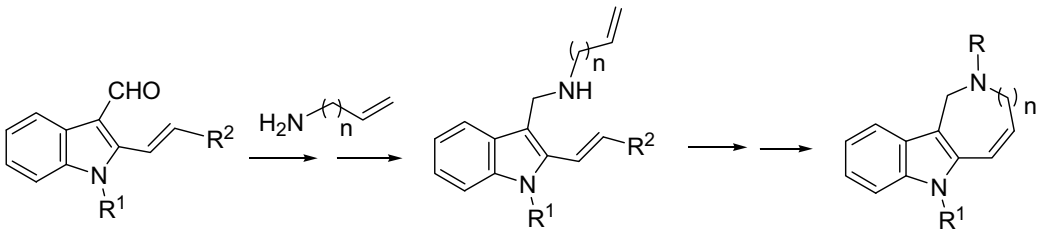
Com a resum, podem afirmar que la reacció de RCM de diens indòlics constituex una nova via d'accés a sistemes d'azocino[4,3-*b*]indole.[9] L'eficiència de la ciclació, combinada amb la facilitat de preparació dels substrats diènics a partir de compostos indòlics senzills, determina que l'estratègia pugui ser aplicada a la síntesi de les subestructures tricícliques precursores tant de l'alcaloide aparicina com de la unitat superior de la vinorelbina (vegeu Capítols 3.2 i 3.3).

[9] Per a una aproximació diferent a azocino[4,3-*b*]indoles, vegeu: Street, J. D.; Harris, M.; Bishop, D. I.; Heatley, F.; Beddoes, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1599-1606.

2.2. FORMACIÓ COMPETITIVA DE TETRAHIDRO-γ-CARBOLINES EN L'AMINACIÓ REDUCTORA DE 2-VINIL-3-INDOLECARBALDEHIDS

(*Tetrahedron Lett.* **2005**, *46*, 7881-7884)

En el context de la preparació de diens indòlics, al capítol anterior s'ha descrit l'ús de la reacció d'aminació reductora de diversos indole-3-carbaldehids per instal·lar cadenes d'al·lilaminometil sobre la posició 3 de l'heterocicle. A continuació, considerarem d'interès estendre aquestes reaccions a derivats 2-vinílics (per exemple, **1**-**3**), a partir dels quals es podrien preparar diens de tipus **A**, precursors per RCM d'altres azacicles, tant azocinoindoles (quan n = 2) com azepinoindoles (quan n = 1), amb un doble enllaç conjugat amb l'indole.



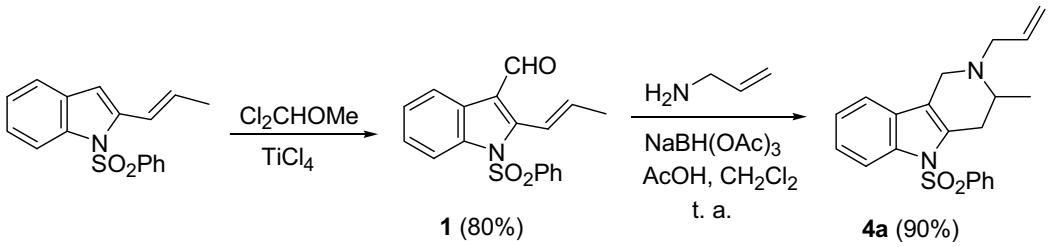
1 $R^1 = SO_2Ph$; $R^2 = Me$
2 $R^1 = SO_2Ph$; $R^2 = H$
3 $R^1 = MOM$; $R^2 = H$

A

n = 1 o 2

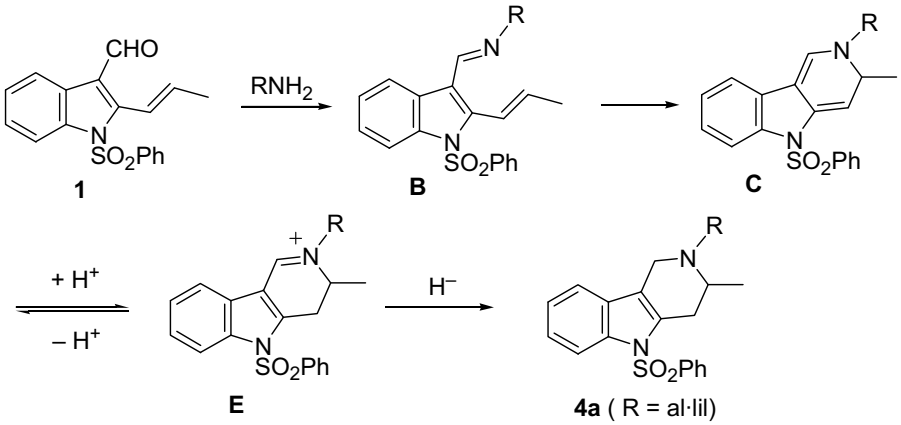
Durant l'estudi dirigit a la preparació d'azepinoindoles es preparà l'aldehid **1** per formilació de Friedel-Crafts de l'1-(fenilsulfonil)-2-(1-propenil)indole[1] i, a continuació, es féu reaccionar amb al·lilamina en les condicions usuals d'aminació reductora. De manera sorprenent, l'amina secundària esperada no es detectà en el medi de reacció sinó que s'obtingué la tetrahidro-γ-carbolina **4a** amb un rendiment del 90%.

[1] Preparat per isomerització del 2-al·lil-1-(fenilsulfonil)indole: Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481-5484.

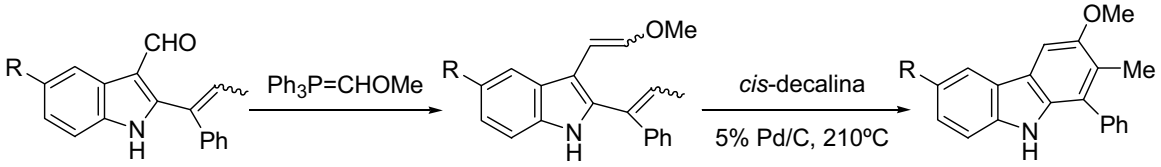


1 (80%) **4a** (90%)

Inicialment, aquest resultat inesperat es racionalitzà considerant que l'imina **B**, que es formaria per reacció de l'amina primària amb el grup carbonil de l'aldehid, enlloc de ser reduïda per l'hidrur, experimentaria una reacció de ciclació sobre el doble enllaç C-C, probablement a través d'un procés electrocíclic on participaria l'enllaç 2,3 de l'indole. La reducció posterior del tetracicle **C** resultant, per exemple, a través del catió imini **E**, explicaria la formació del nucli de tetrahidro-γ-carbolina.

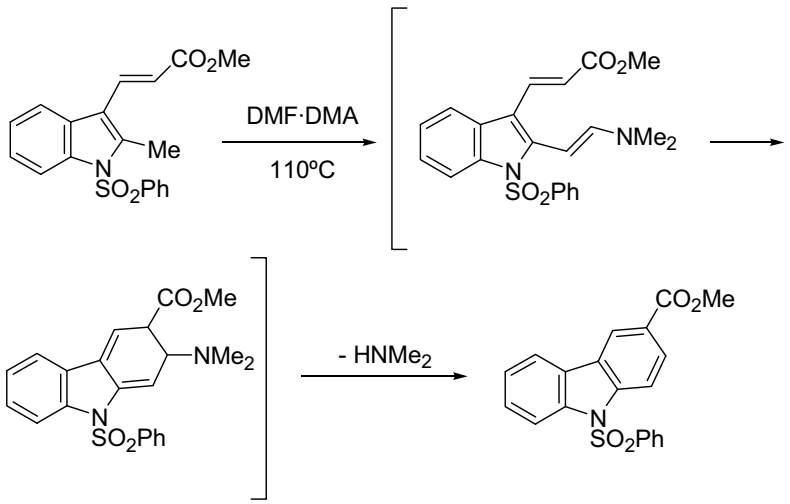


A la literatura es poden trobar nombrosos exemples de ciclacions electrocícliques tèrmiques a partir de sistemes indòlics relacionats que contenen l'agrupació d'1,3,5-hexatriè o 1-aza-1,3,5-hexatriè.[2] Així, per exemple, s'ha descrit la síntesi de carbazoles a partir de 2,3-divinilindoles, generats per reacció de Wittig del corresponent indole-3-carbaldehid. La ciclació té lloc per calefacció en el si de *cis*-decalina com a dissolvent en presència de Pd-C com a agent de deshidrogenació.[3]

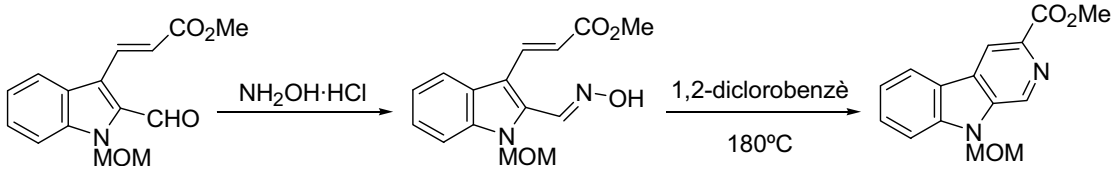


[2] Per a l'aplicació d'aquestes reaccions a la síntesi de productes naturals amb el sistema de carbazole, vegeu: Knölker, H.-J.; Reddy, K. R. *Chem. Rev*. **2002**, *102*, 4303-4427.
[3] Kano, S.; Sugimo, E.; Shibuya, S.; Hibino, S. *J. Org. Chem*. **1981**, *46*, 3856-3859.

També s'han descrit ciclacions electrocícliques d'enamines, generades in situ per reacció d'alquilvinilindoles amb el dimetilacetal de la dimetilformamida (DMF·DMA). L'aromatització al sistema de carbazole s'aconsegueix per eliminació final del grup dimetilamino.[4]



En treballs més relacionats amb el nostre, Hibino ha estudiat exhaustivament ciclacions electrocícliques tèrmiques de viniloximes per donar β-[5,6] i γ-carbolines.[7] L'aromatització s'aconsegueix en aquest cas per deshidratació.[8,9]



[4] (a) Mohanakrishnan, A. K.; Balamurugan, R. *Tetrahedron Lett.* **2005**, *46*, 4045-4048. (b) Sureshbabu, R.; Balamurugan, R.; Mohanakrishnan, A. K. *Tetrahedron* **2009**, 65, 3582-3591.

[5] (a) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, 48, 108-113, i referències citades. Vegeu també: (b) Kusurkar, R. S.; Goswami, S. K.; Vyas, S. M. *Tetrahedron Lett*. **2003**, *44*, 4761-4763.

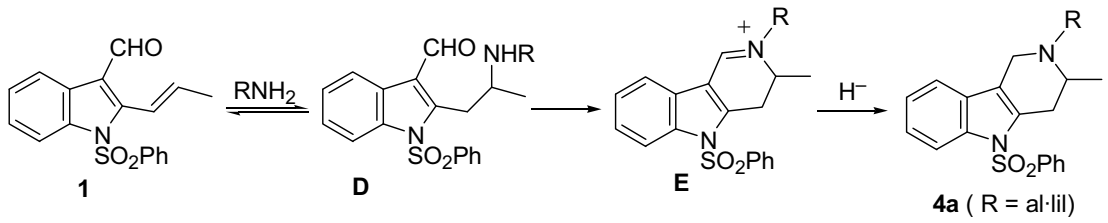
[6] Per a un exemple més recent, vegeu: Omura, K.; Choshi, T.; Watanabe, S.; Satoh, Y.; Nobuhiro, J.; Hibino, S. *Chem. Pharm. Bull* **2008**, 56, 237-238.

[7] (a) Hibino, S.; Kano, S.; Mochizuki, N.; Sugino, E. *J. Org. Chem*. **1984**, *49*, 5006-5008. (b) Hibino, S.; Sugino, E.; Kuwada, T.; Ogura, N.; Sato, K.; Choshi, T. *J. Org. Chem*. **1992**, 57, 5917-5921. Vegeu també: (c) Gilchrist, T. L.; Kemmit, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447-4456.

[8] Les ciclacions tèrmiques de vinilimines són menys freqüents. Per exemple, vegeu: Kannadasan, S.; Srinivasan, P. C. *Tetrahedron Lett*. **2002**, *43*, 3149-3150.

[9] Per a la preparació de carbolines per reacció d'imines amb alquins catalitzades per pal·ladi (0), vegeu: Zhang, H; Jarock, R. C. *J. Org. Chem*. **2003**, 68, 5132-5138.

Com es pot observar, aquestes reaccions presenten trets diferencials respecte de la nostra anulació, ja que les temperatures de reacció són usualment elevades (>100ºC) i els productes obtinguts són sistemes de carbazole o carbolina totalment aromàtics. De fet, no hi ha precedents a la literatura de ciclacions electrocícliques seguides d'un procés de reducció per donar lloc a tetrahidrocarbazoles o tetrahidrocarbolines. Tenint en compte, a més, les condicions suaus de la nostra reacció i el fet que la imina intermèdia no es detectés en el cru de reacció quan el protocol experimental es reproduí en absència d'hidrur, considerarem una interpretació mecanística alternativa en la qual l'anell de tetrahidrocarbolina es formaria per addició conjugada a l'agrupació d'aldehid γ,δ-insaturat del substrat.[10] Aquesta etapa reversible aniria seguida d'un procés d'aminació intramolecular per donar un catió imini, que evolucionaria irreversiblement al nucli de carbolina per reducció.



A fi de confirmar aquesta proposta mecanística i disposar de més dades sobre el procés d'anulació, s'estudià el comportament d'altres amines primàries vers l'aldehid **1** i el seu derivat més senzill **2**[11] en les mateixes condicions de reacció. Els resultats d'aquest estudi es recullen a la Taula 1.

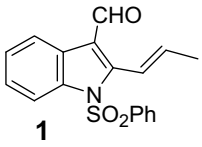
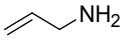
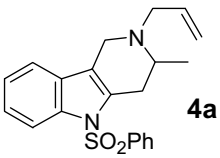
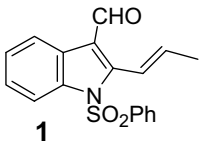
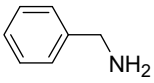
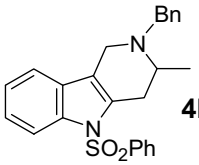
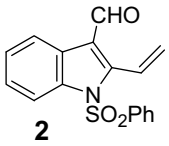
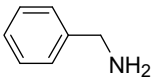
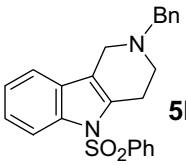
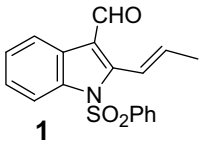
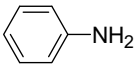
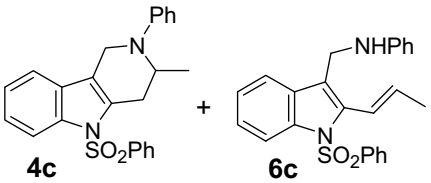
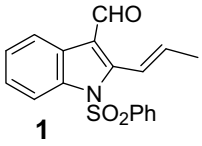
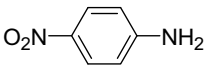
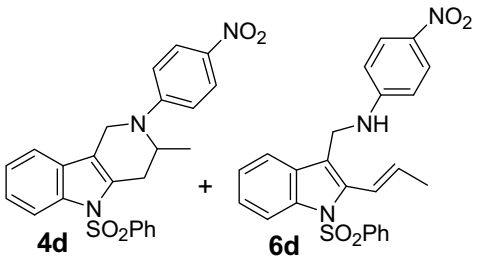
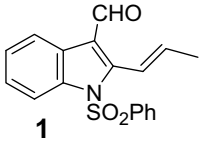
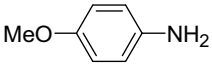
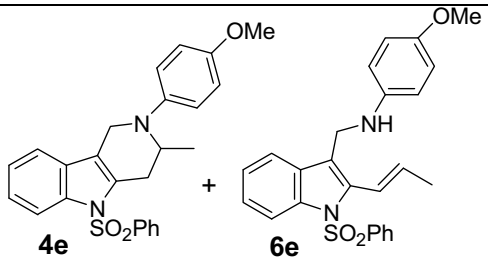
Com es pot observar, la reacció amb benzilamina procedeix de manera anàloga a la reacció amb al·lilamina per donar les corresponents tetrahidro-γ-carbolines **4b** o **5b** com a únics productes (entrades 2 i 3). En canvi, l'anilina mostrà un perfil de reactivitat diferent, probablement per la seva menor tendència a experimentar addició conjugada. Així, el procés d'aminació reductora competeix amb el procés d'anulació i condueix a una mescla pràcticament equimolecular de la γ-carbolina **4c** i l'amina secundària **6c** (entrada 4). De manera significativa, la substitució a l'anell aromàtic de l'anilina per un grup atraient d'electrons com el grup nitro condueix a

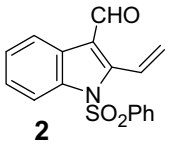
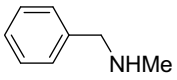
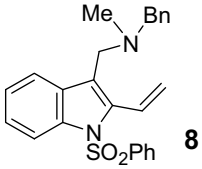
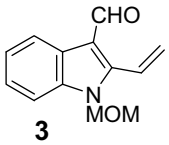
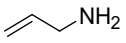
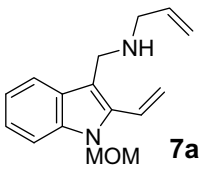
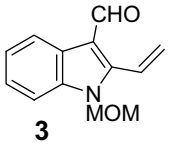
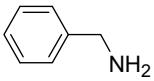
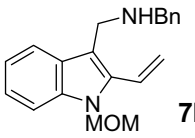
[10] Si bé la química normal de l'indole implica la reacció amb electròfils, es coneixen alguns exemples d'addicions o substitucions nucleòfiles en les quals intervenen indoles deficitaris electrònicament, tot i que l'atac nucleòfil es produeix directament sobre l'anell: (a) Joule, J. A. *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 1999; Vol. 11, pp 45-65. (b) Gribble, G. W. *Pure Appl. Chem*. **2003**, *75*, 1417-1432. Vegeu també: (c) Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett*. **2004**, *6*, 609-611.

[11] Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull*. **2001**, *49*, 881-886.

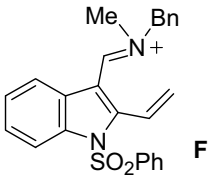
l'amina secundària **6d** com a producte majoritari (entrada 5), mentre que la substitució per un grup donador d'electrons com el grup metoxi proporcionà majoritàriament la γ-carbolina **4e** (entrada 6).

Taula 1. Reacció dels aldehids **1**-**3** amb amines en condicions reductores

	Aldehid	Amina	Productes	R
1	 **1**		 **4a**	90%
2	 **1**		 **4b**	85%
3	 **2**		 **5b**	80%
4	 **1**		 **4c** **6c**	(1:1) 70%
5	 **1**		 **4d** **6d**	(1:15) 90%
6	 **1**		 **4e** **6e**	(9:1) 70%

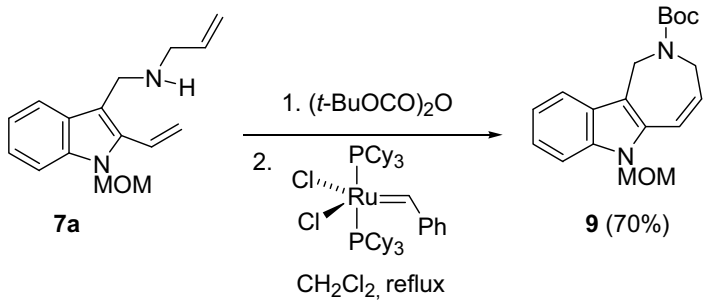
7	 **2**		 **8**	90%
8	 **3**		 **7a**	65%
9	 **3**		 **7b**	65%

S'estudià també la reacció de l'aldehid **2** amb una amina secundària, com ara l'*N*-metilbenzilamina (entrada 7). Tal com esperàvem d'acord amb les consideracions mecanístiques anteriors, el procés d'aminació reductora a través del catió imini **F** fou l'únic camí productiu i proporcionà l'amina terciària **8** amb un 90% de rendiment.

 **F**

En aquest punt raonàrem que el grup fenilsulfonil a l'àtom de nitrogen indòlic podria afavorir el procés d'anulació a carbolina, ja que augmentaria la capacitat del substrat d'actuar com a acceptor de Michael. Per tant, la substitució d'aquest grup protector per un altre de menor caràcter atraient d'electrons afavoriria el procés d'aminació reductora. D'acord amb aquest raonament, les amines secundàries **7a** i **7b** s'obtingueren com a únics productes quan l'aldehid **3**, protegit al nitrogen per un grup MOM, es féu reaccionar amb al·lilamina o benzilamina en les condicions usuals d'aminació reductora (entrades 8 i 9).

Finalment, el compost **7a** un cop protegit en forma de carbamat, resultà ser un precursor per RCM del sistema d'azepino[4,3-*b*]indole **9** per tractament amb el catalitzador de Grubbs de primera generació.[12]



Pot concloure's que la reacció de 2-vinil-3-indolecarbaldehids amb amines primàries en condicions d'aminació reductora segueix vies diferents depenent del tipus de substituent present en el nitrogen indòlic. Així, les tetrahidro-γ-carbolines es formen a partir dels *N*-(fenilsulfonil)indoles **1** i **2**, mentre que les amines secundàries s'obtenen a partir de l'*N*-(MOM)indole **3**.

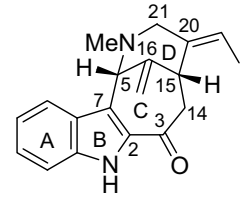
[12] Al capítol 3.2 es descriu la preparació de precursors diènics d'azocino[4,3-*b*]indoles per aminació reductora de *N*-MOM-2-vinil-3-indolecarbaldehids.

3. SEQÜÈNCIA DE RCM I CICLACIÓ DE HECK D'HALURS VINÍLICS: APLICACIÓ A LA SÍNTESI D'ESTRUCTURES INDÒLIQUES AMB PONT

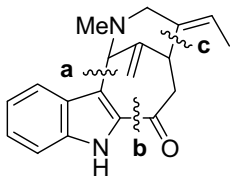
3.1. CONSTRUCCIÓ DEL SISTEMA TETRACÍCLIC DE L'ALCALOIDE ERVITSINA

(*Synlett* **2008**, 667-670)

L'ervitsina[1] és un alcaloide indòlic minoritari aïllat l'any 1977 de *Pandaca boiteaui* (Apocinàcies),[2] amb un esquelet tetracíclic únic que conté un sistema de 2-azabiciclo[4.3.1]decà fusionat amb el nucli indòlic i dos substituents alquilidè exocíclics, 16-metilè i 20*E*-etilidè (numeració biogenètica). L'elevada complexitat estructural d'aquest alcaloide ha atret l'atenció de diversos grups de recerca i, com a resultat, s'han descrit algunes aproximacions sintètiques a l'estructura tetracíclica[3] així com també una síntesi total.[4]



Ervitsina
(numeració biogenètica)



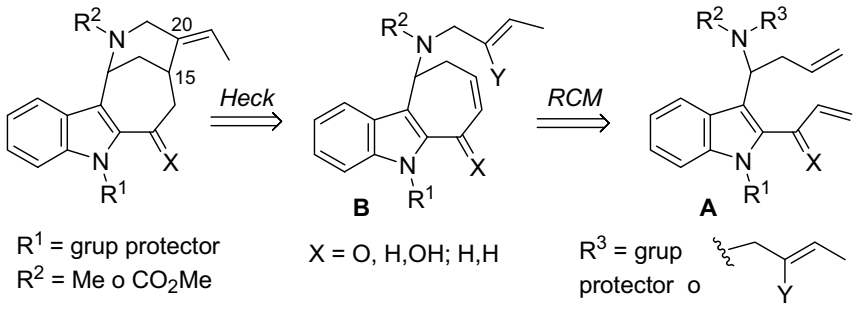
Ervitsina
(aproximacions sintètiques)

a enllaç C_5-C_7 (refs 3a, 3d, 4)
b enllaç C_2-C_3 (refs 3b, 3c, 3e)
c enllaç C_{15}-C_{20} (tesi doctoral)

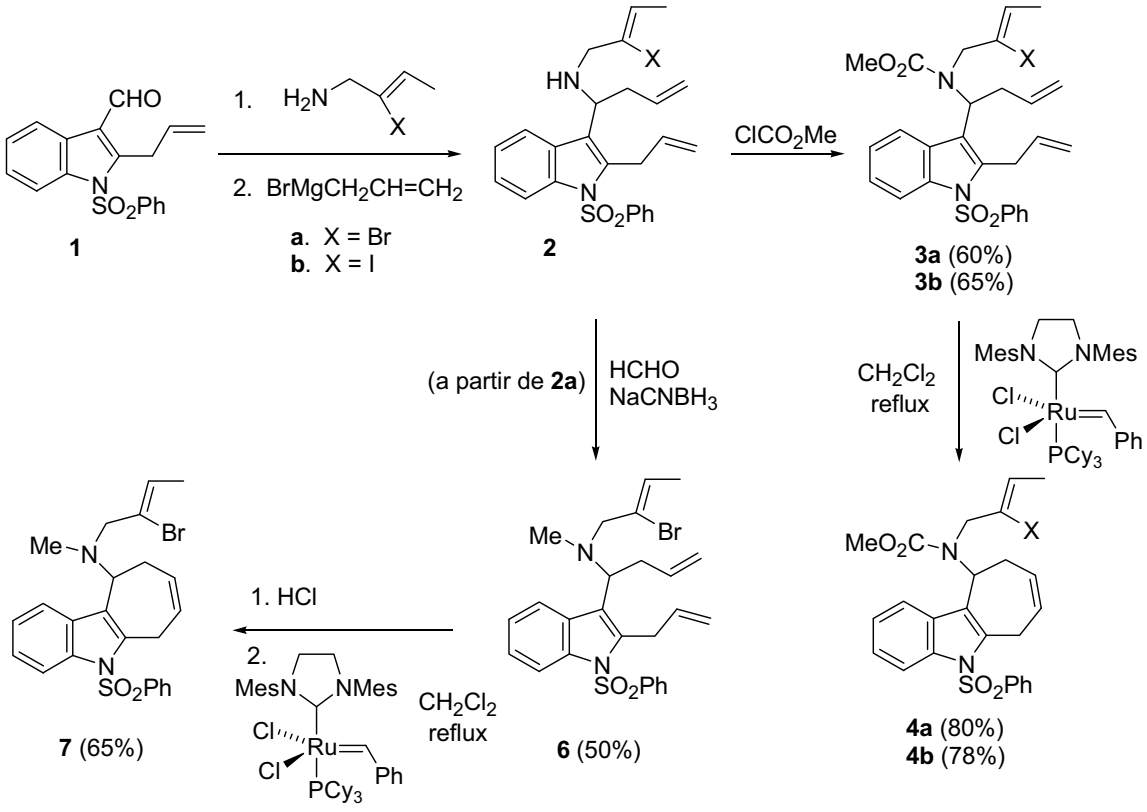
[1] Joule, J. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, pp 232-239.
[2] Andriantsiferana, M.; Besselièvre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587-2590.
[3] (a) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683-3694. (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem*. **1985**, *50*, 1516-1522. (c) Bosch, J.; Rubiralta, M.; Bolós, J. *Tetrahedron* **1987**, *43*, 391-396. (d) Salas, M.; Joule, J. A. *J. Chem. Res. (M)* **1990**, 664-673. (e) Rubiralta, M.; Marco, M.-P.; Bolós, J.; Trapé, J. *Tetrahedron* **1991**, *47*, 5585-5602.
[4] (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc*. **1993**, *115*, 5340-5341. (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem*. **1997**, *62*, 3597-3609. Per a una versió enantioselectiva, vegeu: (c) Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 469-479.

Malgrat la varietat d'estratègies emprades, totes les vies sintètiques descrites es fonamenten en la formació de l'anell carbocíclic central en les últimes etapes, ja sigui mitjançant la ciclació d'un ió de tipus imini sobre la posició 3 de l'indole (enllaç format C_5-C_7 **a**),[3a,3d,4] o bé per acilació de Friedel-Crafts sobre la posició 2 de l'indole (enllaç format C_2-C_3, **b**).[3b,3d,3e]

D'acord amb els nostres objectius, ens proposàrem avaluar les possibilitats sintètiques de la combinació d'una reacció de RCM d'un diè indòlic i una reacció de Heck d'un halur vinílic per a la construcció del sistema tetracíclic amb pont de l'alcaloide ervitsina. En concret, la reacció de RCM d'un diè indòlic d'estructura general **A** proporcionaria un anell de cicloheptà 2,3-fusionat amb l'indole (**B**), amb un doble enllaç C-C que s'empraria per a la posterior reacció de Heck intramolecular amb l'halur vinílic, connectat al sistema anular a través d'un àtom de nitrogen. En relació a les aproximacions sintètiques precedents, la nostra proposta implica el tancament de l'anell de piperidina en les darreres etapes de la síntesi per formació de l'enllaç C_{15}-C_{20} a partir d'un sistema tricíclic que conté els anells ABC de l'alcaloide.



Per tal de valorar la viabilitat de la metodologia, els nostres esforços inicials es dirigiren a la preparació de compostos tricíclics no funcionalitzats a la posició α-benzílica de l'indole (**B**, X = H, H), a priori més fàcilment accessibles. Escollírem com a producte de partida el 2-al·lil-3-indolecarbaldehid **1**, protegit a l'àtom de nitrogen amb un grup fenilsulfonil, a partir del qual ens plantejàrem introduir l'agrupació d'homoal·lilamina mitjançant una seqüència d'aminació seguida d'imino-al·lilació. Per tal d'evitar l'ús de grups protectors que necessàriament allargarien la seqüència sintètica, decidírem incorporar l'agrupació d'haloalquenil en l'etapa inicial d'aminació, esperant que fos suficientment inerta en la reacció de RCM subsegüent. La ruta sintètica que desenvolupàrem amb èxit es representa a continuació.



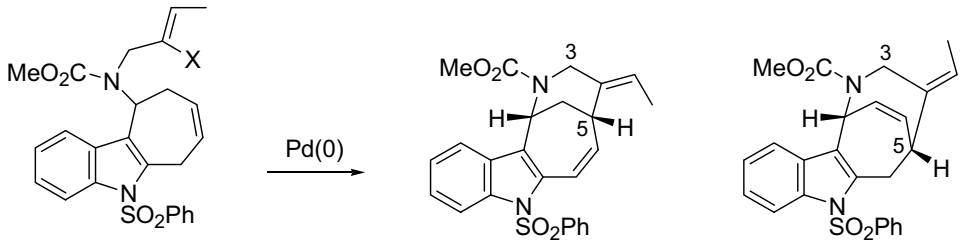
La reacció de l'aldehid **1** amb (*Z*)-2-bromo- o (*Z*)-2-iodo-2-butenilamina seguida d'alquilació de les imines resultants amb bromur d'al·lilmagnesi proporcionà les amines secundàries **2a** o **2b**, les quals s'acilaren directament amb cloroformat de metil per donar el carbamats trièn ics **3a** o **3b** amb rendiments globals del 60% i 65%. D'altra banda, es considerà també d'interès disposar d'un substrat trièn ic amb un àtom de nitrogen de tipus amina terciària com ara **6**, el qual s'obtingué amb un rendiment global del 50% per aminació de l'aldehid **1** i tractament de l'amina secundària **2a** amb formaldehid i cianoborohidrur sòdic.

A continuació centrarem els nostres esforços en la reacció de RCM. Com hem comentat, esperàvem que la diferent naturalesa electrònica dels dobles enllaços dels triens **3** o **6** determinés la formació preferent de l'anell carbocíclic de set baules fusionat amb l'indole. En efecte, el tractament de **3a** i **3b** amb el catalitzador de Grubbs de segona generació a la temperatura de reflux de diclorometà proporcionà els carbamats tricíclics desitjats **4a** i **4b** com a únics productes amb rendiments del 80% i 78%, respectivament. Per la seva banda, l'amina terciària **7** s'obtingué amb un rendiment lleugerament inferior (65%) per reacció de RCM del substrat **6**, prèviament convertit en el seu hidroclorur. [5]

[5] Per a una revisió recent de la reacció de RCM en aminodiens, vegeu: Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829-1846.

Un cop disposàvem d'una via eficient per a la construcció de la subestructura tricíclica ABC de l'alcaloide ervitsina, iniciàrem l'estudi de la reacció de Heck. Els resultats més significatius obtinguts a partir del carbamats **4** es recullen a la Taula 1.

Taula 1. Reacció de Heck dels halurs vinílics **4.**



4a X = Br
4b X = I

5

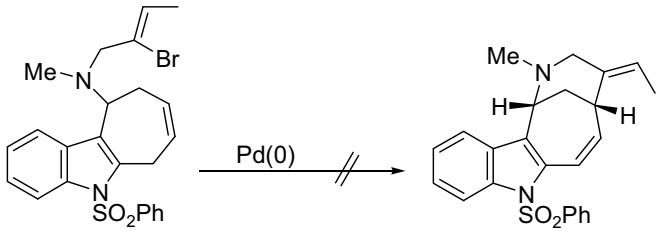
8

	Substrat	Condicions	Productes
1	**4a**	$Pd(OAc)_2$ (16%), Ph_3P (50%), Et_3N (2 equiv.), CH_3CN, reflux, 3 h	**4a** (33%)
2	**4a**	$Pd(OAc)_2$ (5%), K_2CO_3 (5 equiv), TBACl (1 equiv.), DMF, 60℃, 4 h	——
3	**4a**	$Pd(OAc)_2$ (5%), PPh_3 (20%), proton-sponge® (0.5 equiv.), K_2CO_3 (1.1 equiv.), toluè, reflux, 4h	**5** (30%) **4a** (16%)
4	**4a**	$Pd(PPh_3)_4$ (5%), proton-sponge® (0.1equiv.), K_2CO_3 (2.5 equiv.), toluè, tub tancat, 2.5 dies	**5** (30%) **4a** (5%)
5	**4b**	$Pd(OAc)_2$ (10%), Ph_3P (40%), proton-sponge® (0.3 equiv.), K_2CO_3 (1.5 equiv.), toluè, reflux, 24h	**5** (45%) **4b** (10%)
6	**4b**	$Pd(PPh_3)_4$ (10%), K_3PO_4 (3 equiv), Et_3N (6 equiv.), **fenol** (0.2 equiv.), toluè, reflux, 12 h	**5** (65%)
7*	**4b**	$Pd(OAc)_2$ (10%), Ph_3P (30%), **Ag_2CO_3** (3 equiv.), toluè, reflux, 40 min	**5** (45%) **8** (15%)
8*	**4b**	$Pd(OAc)_2$ (10%), Ph_3P (30%), **Ag_2CO_3** (3 equiv.), toluè, 80℃, 1 h	**5** (19%) **8** (43%)
9*	**4b**	$Pd(OAc)_2$ (10%), **dppe**[1] (12%), **Ag_2CO_3** (3 equiv.), DIPEA (2 equiv.), toluè, reflux, 2h	**5** (25%) **8** (25%)

* Resultats no publicats
[1]1,2-Bis(difenilfosfino)età.

Els primers assaigs realitzats a partir del bromo derivat **4a** foren descoratjadors, ja que en les condicions polars que havia utilitzat Rawal[6] per ciclacions similars [$Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, entrada 1] únicament es recuperà el producte de partida amb un rendiment baix. D'altra banda, en les condicions de Jeffery,[7,8] en absència de lligands fosfina i en presència de sals d'amoni, s'observà la descomposició total del material de partida (entrada 2). De manera més satisfactòria, la ciclació de **4a** tingué lloc en condicions no polars,[9] utilitzant el catalitzador de pal·ladi en presència de proton-sponge®, Ph_3P i K_2CO_3 en el si de toluè a reflux, per donar el compost tetracíclic esperat **5**, amb un substituent etilidè de configuració *E* (entrades 3 i 4). No obstant això, encara que l'anàlisi espectroscòpica de les mescles de reacció indicava que els rendiments de conversió eren alts, després de la purificació cromatogràfica el compost **5** s'obtenia amb rendiments moderats (30%), sempre acompanyat de producte de partida, fins i tot després de temps de reacció llargs.

S'ha d'esmentar que l'amina terciària **7** no fou un bon substrat de la reacció de Heck atès que proporcionà exclusivament mescles de reacció complexes quan es tractà en qualsevol de les condicions anteriors. Aquest fet semblava indicar que la presència d'un àtom de nitrogen bàsic en la cadena d'halobutè era incompatible amb les condicions dràstiques de ciclació, probablement degut a un procés competitiu de desalquilació.[8c]

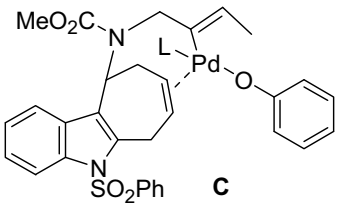


7

[6] Rawal, V. H.; Michoud, C. *Tetrahedron Lett*. **1991**, *32*, 1695-1698.
[7] (a) Jeffery, T. *Tetrahedron Lett*. **1985**, *26*, 2667-2670. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113-10130.
[8] Per a exemples relacionats, vegeu: (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc*. **1993**, *115*, 3030-3031. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686. (c) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc*. **2001**, *123*, 9324-9337. (d) Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219-7222.
[9] Birman, V. B.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 9146-9147.

En aquest punt dirigírem la nostra atenció al iodo derivat **4b**, un substrat a priori més reactiu. En efecte, quan **4b** es sotmeté a les condicions de reacció que havien proporcionat els millors resultats a partir del bromo derivat **4a**, el compost tetracíclic **5** s'obtingué amb un rendiment lleugerament superior (45%), encara que novament acompanyat de quantitats minoritàries de producte de partida (entrada 5).

Per tal de millorar l'eficiència de la ciclació estudiàrem l'efecte d'altres additius, com ara fenol o Ag_2CO_3. Satisfactòriament, quan la reacció es dugué a terme en presència d'una quantitat subestequiomètrica de fenol en combinació amb K_3PO_4 el compost tetracíclic **5** s'obtingué com a únic producte amb un rendiment superior (65%, entrada 6). Si bé no coneixem cap precedent de l'ús de fenol com a additiu en reaccions de Heck, s'ha descrit el seu paper beneficiós en algunes arilacions o alquenilacions d'enolats catalitzades per pal·ladi.[10,11] D'acord amb la proposta de Buchwald,[10] aquest additiu podria actuar estabilitzant els diferents intermedis de pal·ladi de la reacció per formació d'espècies de fenòxid de pal·ladi (per exemple, **C**).

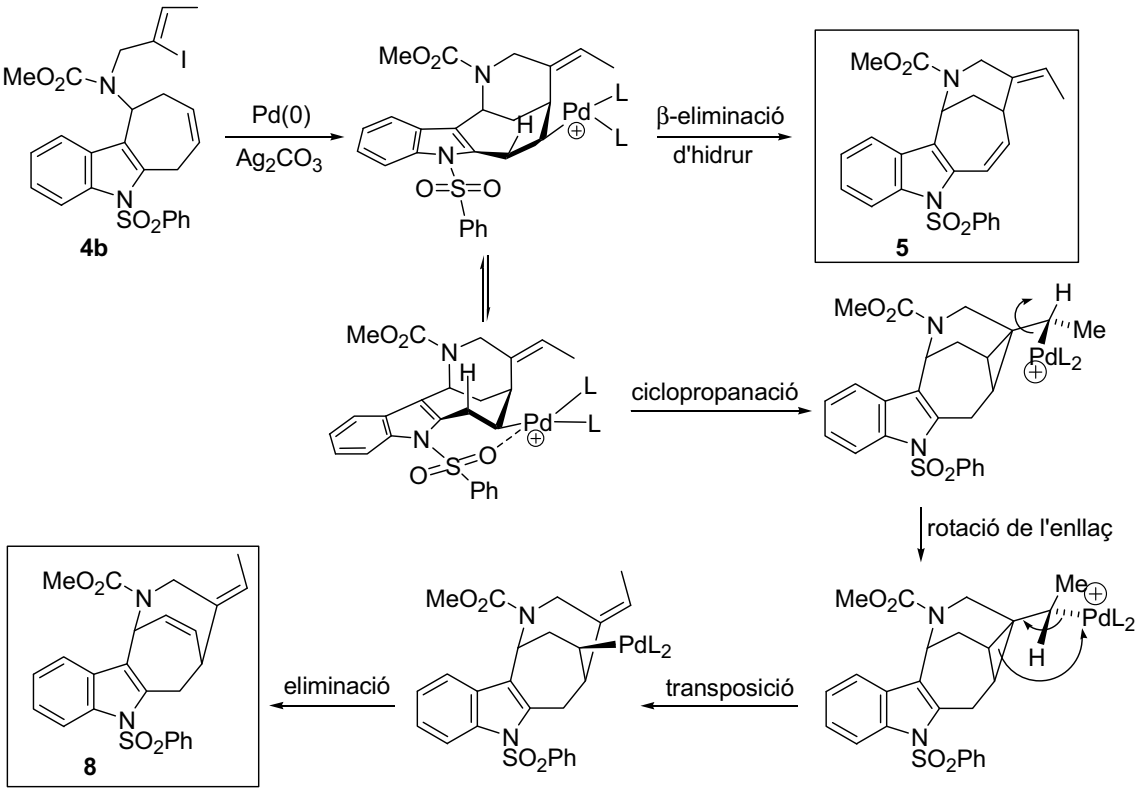


C

Mereixen un comentari especial els resultats obtinguts en la ciclació de Heck de **4b** en presència de Ag_2CO_3. Si bé en aquestes condicions catiòniques el producte de partida es consumia ràpidament, la ciclació seguí un curs diferent, produïnt-se el compost esperat **5** juntament amb quantitats variables de **8**, un compost isomèric derivat aparentment d'una ciclació 7-*endo* amb inversió de la configuració del grup etilidè.[12] Com es pot observar a la Taula 1, el compost **5** fou el producte majoritari quan la reacció es realitzà a la temperatura de reflux de toluè, mentre que el compost **8** es formà en una proporció més gran quan es treballà a temperatures més baixes (entrada 8) o bé en presència d'una fosfina bidentada (dppe) enlloc de Ph_3P (entrada 9).

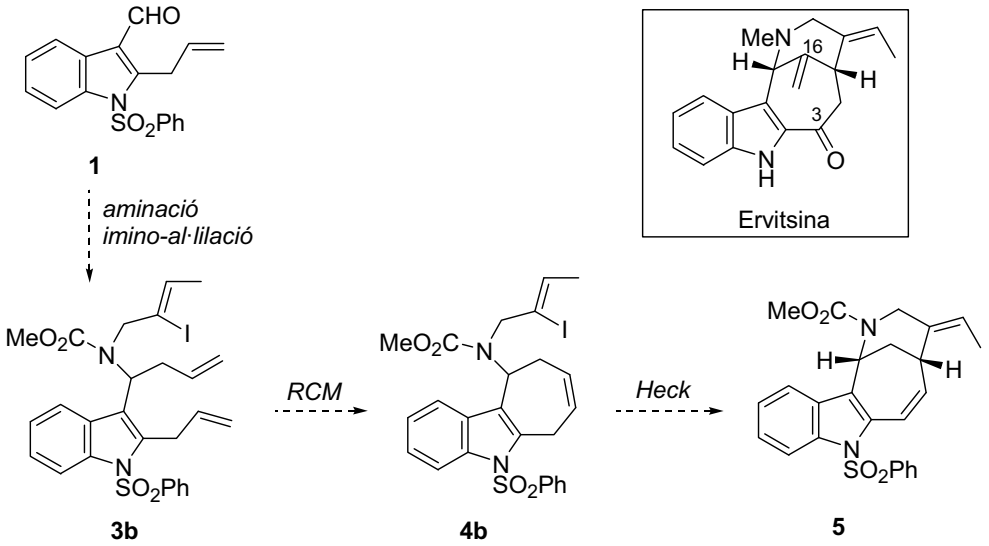
[10] Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 15618-15619.
[11] (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Tetrahedron Lett*. **2004**, *45*, 3131-3135. (b) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal*. **2004**, *346*, 1646-1650. (c) Solé, D.; Serrano, O. *J. Org. Chem*. **2008**, *73*, 2476-2479. (d) Solé, D.; Serrano, O. *J. Org. Chem*. **2008**, *73*, 9372-9378.
[12] La configuració *Z* del compost **8** s'establí per comparació dels desplaçaments químics del C-3 (δ41.0) i del C-5 (δ42.2) amb els corresponents al compost **5** (C-3 δ45.6 i C-5 δ35.7).

La formació de productes inusuals com **8** en el decurs de ciclacions de Heck d'halurs vinílics és un procés conegut,[13] que s'ha racionalitzat[14] considerant que l'intermedi σ-alquilpal·ladi resultant de la carbopal·ladació inicial 6-*exo* no evoluciona per β-eliminació d'hidrur cap el producte esperat (en el nostre cas, **5**), sinó que experimenta carbopal·ladació intramolecular amb el grup etilidè exocíclic. El ciclopropà resultant experimentaria transposició, amb inversió concomitant de la configuració de l'alquè, seguida de β-eliminació final d'hidrur. En el nostre cas, aquesta via competitiva només s'observaria en presència de Ag_2CO_3, ja que en aquestes condicions catiòniques el grup fenilsulfonil seria capaç de coordinar dèbilment amb l'intermedi σ-alquilpal·ladi catiònic, generant un pal·ladacicle de 7 baules.[15] Aquesta coordinació obstaculitzaria la β-eliminació d'hidrur i alhora afavoriria la ciclopropanació intramolecular, particularment quan la reacció es realitza a baixa temperatura o en presència d'una fosfina quelant com la dppe.



[13] (a) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583-5584. (b) Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans 1* **2000**, 1129-1137.
[14] Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091-10092.
[15] Un pal·ladacicle de set baules, format per coordinació d'un àtom d'oxigen d'un grup sulfonil, s'ha proposat com a estat de transició d'algunes reaccions de Suzuki: Broutin, P.-E.; Colobert, F. *Org. Lett.* **2005**, *7*, 3737-3740.

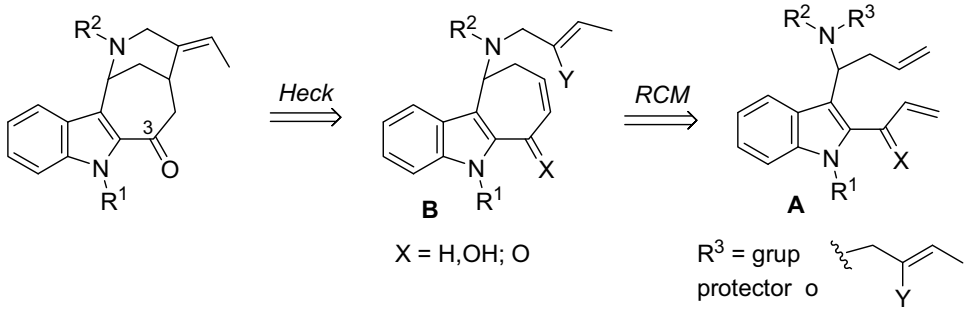
En resum, la ruta sintètica representada a continuació, que implica la seqüència d'aminació seguida d'imino-al·lilació a partir de l'aldehid **1**, la reacció de RCM quimioselectiva del triè **3b** i la ciclació de Heck del iodur vinílic **4b**, constitueix una via directa d'accés a l'estructura tetracíclica amb pont de l'alcaloide ervitsina a partir de precursors indòlics fàcilment accessibles.



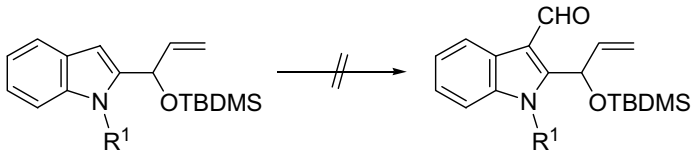
Encara que resultava evident que aquesta estratègia de doble anulació RCM-Heck difícilment permetria l'establiment d'una síntesi total per a aquest alcaloide, principalment per la dificultat d'introduir el substituent metilè de la posició 16, estudiàrem sense èxit la preparació d'anàlegs tetracíclics funcionalitzats addicionalment a la posició 3 amb un grup carbonil. El resultats d'aquest estudi, no publicats, s'exposen breument a continuació.

Intents de preparació d'anàlegs tetracíclics funcionalitzats en C-3.

La preparació de compostos tetracíclics funcionalitzats a la posició 3 amb un grup carbonil requeria disposar de diens de tipus **A**, funcionalitzats a les dues posicions benzíliques. La reacció de RCM d'aquests diens permetria accedir a substrats tricíclics de tipus **B**, a partir dels quals es promouria el tancament de l'anell de piperidina mitjançant una reacció de Heck clàssica (quan X = H, OH) o bé reductora (quan X = O).



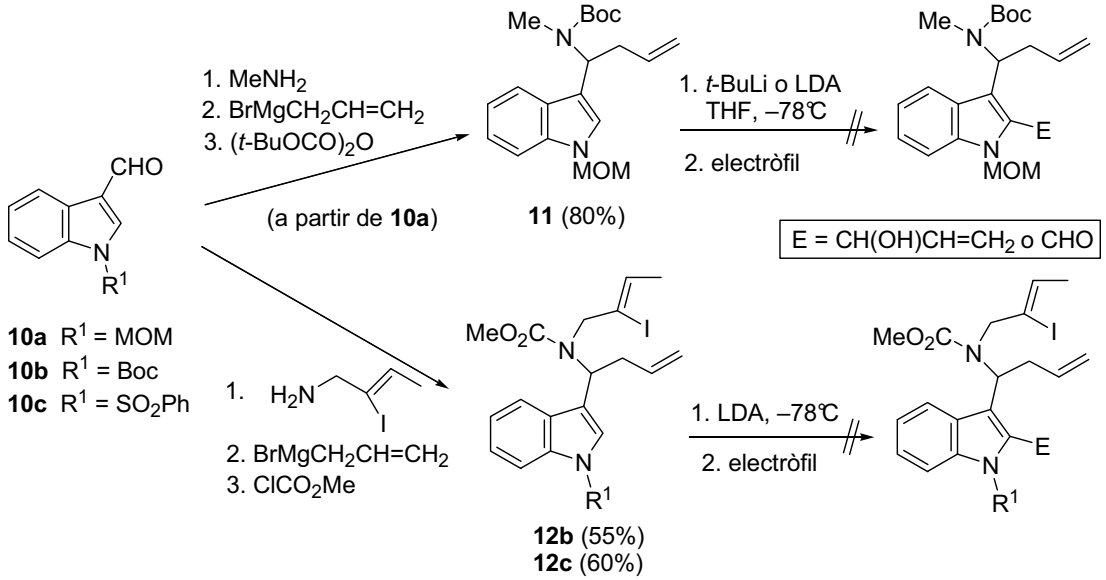
Per a la preparació dels precursors dièn ics **A** considerarem en primer lloc la preparació d'un 2-alquenil-3-indolecarbaldehid, a partir del qual s'introduiria l'agrupació d'homoal·lilamina de manera anàloga a la sèrie model. Malauradament, no fou possible dur a terme la formilació de la posició 3 dels 2-alquenilindoles **9**, tant en condicions de Friedel-Crafts (per **9a**, vegeu capítol 2.1) com de Vilsmeier (DMF, $POCl_3$, per **9b**).



9a $R^1 = SO_2Ph$ (capítol 2.1)
9b R^1 = MOM

Estudiarem a continuació una estratègia alternativa que implicava promoure la funcionalització de la posició 2 a partir d'indoles que ja incorporessin l'agrupació d'homoal·lilamina a la posició 3.

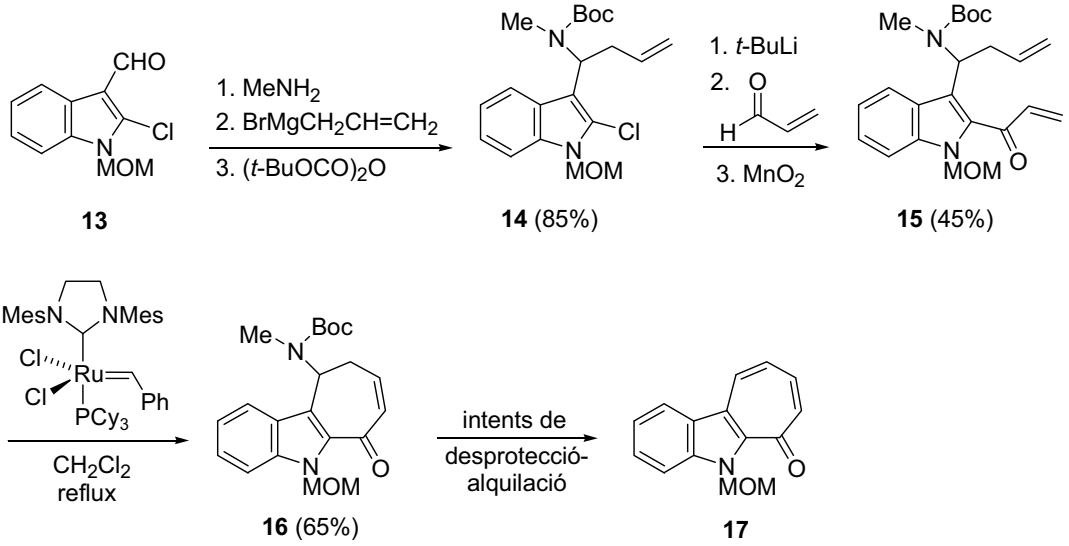
Amb aquesta finalitat es prepararà l'indole **11** per reacció de l'aldehid **10a**[16] amb metilamina, seguida d'imino-al·lilació i protecció final de l'amina secundària amb un grup Boc. A partir de l'indole **11** no fou possible introduir la cadena alquenílica a la posició 2, ja que tots els intents de promoure la metal·lació d'aquesta posició amb bases com ara *tert*-butil-liti o LDA conduïren a la recuperació del producte de partida després del tractament amb acroleïna o dimetilformamida. Aquesta transformació tampoc tingué lloc a partir dels indoles **12b** i **12c**, preparats com a la sèrie model a partir dels respectius indole-3-carbaldehids **10b**[17] i **10c**,[18] per reacció seqüencial amb (*Z*)-2-iodo-2-butenilamina, bromur d'al·lilmagnesi i cloroformat de metil. En aquest cas, després del tractament amb LDA a -78ºC i reacció amb l'electròfil, a més del producte de partida inalterat s'observà la formació de subproductes amb un triple enllaç carboni-carboni, procedents de l'eliminació del grup iodovinil.



Finalment, la metal·lació de la posició 2 sí fou possible per intercanvi halogen-metall del 2-cloro derivat **14**, preparat de manera anàloga a **11** per reacció de l'aldehid **13**[19] amb metilamina, seguida d'imino-al·lilació i protecció amb un grup Boc. El tractament de **14** amb *tert*-butil-liti seguit de reacció de l'intermedi 2-litioindole amb acroleïna proporcionà l'alcohol esperat, el qual resultà ser un compost bastant inestable i s'oxidà immediatament amb diòxid de manganès per donar la cetona **15**.

[16] Comins, D. L.; Killpack, M. O. *J. Org. Chem*. **1987**, *52*, 104-109.
Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem*. **1992**, *57*, 5878-5891.
[17] Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem*. **2005**, *75*, 5840-5851.
[18] Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem*. **1992**, *57*, 5878-5891.
[19] Hagiwara, H., Choshi, T.; Nobuhiro, H.; Hibino, S. *Chem. Pharm. Bull*. **2001**, *49*, 881-886.

La reacció de RCM de **15** tingué lloc en les condicions usuals, en presència del catalitzador de Grubbs de segona generació a la temperatura de reflux de diclorometà, per donar el ciclohepta[*b*]indole desitjat **16**. A partir d'aquest compost tricíclic intentàrem sense èxit la manipulació de l'àtom de nitrogen exocíclic per tal d'introduir la cadena d'haloalquenil necessària per a la ciclació de Heck. En totes les condicions assajades per desprotegir l'amina secundària s'observà l'eliminació ràpida del grup carbamat per donar el compost tricíclic aromàtic **17**, amb un anell de tropona.



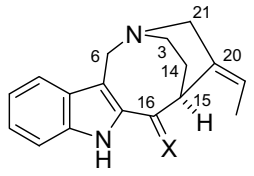
13 **14** (85%) **15** (45%)

16 (65%) **17**

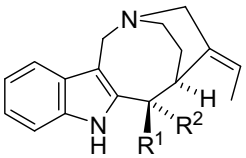
3.2. PRIMERA SÍNTESI TOTAL DE L'ALCALOIDE APARICINA

(*Chem. Commun*. **2009**, 3372-3374)
(*J. Org. Chem*. **2009**, *74*, 8359-8368)

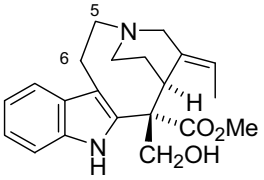
L'aparicina és un alcaloide indòlic relativament abundant, el qual fou aïllat per primera vegada d'*Aspidosperma dasycarpon* fa més de 40 anys.[1] La seva elucidació estructural,[2] duta a terme mitjançant degradació química i tècniques espectroscòpiques pioneres, revelà un esquelet tetracíclic particular amb un sistema d'1-azabiciclo[4.2.2]decà fusionat amb el nucli indòlic i dos substituents alquilidè exocíclics, 16-metilè i 20*E*-etilidè (numeració biogenètica).[3] El mateix sistema anular es trobà en la vallesamina[4] i posteriorment en un nombre reduït d'alcaloides, com ara la 16(*S*)-hidroxi-16,22-dihidroaparicina[5] o l'ervaticina,[6] els quals es diferencien de l'aparicina en la substitució de la posició 16.[7]



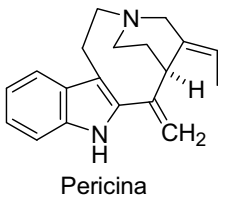
X = CH_2 Aparicina
X = O Ervaticina
(numeració biogenètica)



R^1 = CH_2OH, R^2 = CO_2Me
Vallesamina
R^1 = CH_3, R^2 = OH
16(*S*)-Hidroxi-16,22-dihidroaparicina



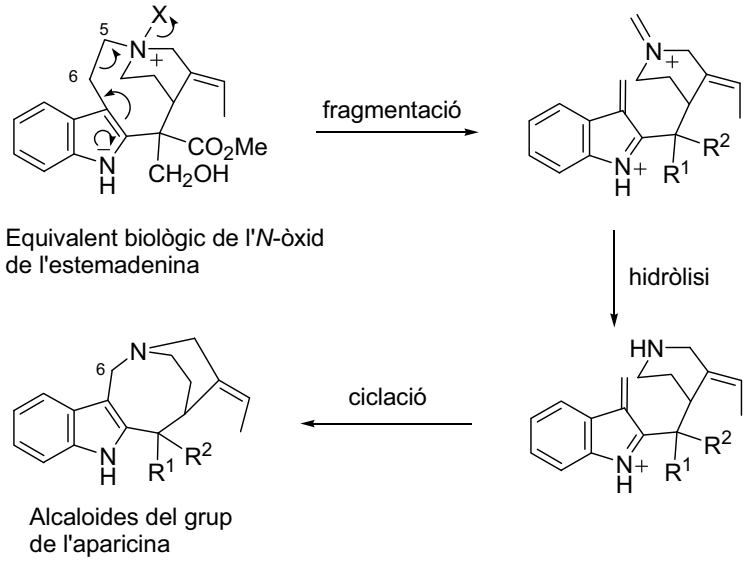
Estemadenina



Pericina
(Subincanadina E)

[1] Gilbert, B.; Duarte, A. P.; Nakagawa, Y.; Joule, J. A.; Flores, S. E.; Brissolese, J. A.; Campello, J.; Carrazzoni, E. P.; Owellen, R. J.; Blossey, E. C.; Brown Jr., K. S.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1141-1166.
[2] Joule, J. A.; Monteiro, H.; Durham, L. J.; Gilbert, B.; Djerassi, C. *J. Chem. Soc*. **1965**, 4773-4780.
[3] La configuració *E* del grup etilidè s'establí alguns anys més tard: Akhter, L.; Brown, R. T.; Moorcroft, D. *Tetrahedron Lett*. **1978**, *19*, 4137-4140.
[4] (a) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391-404. (b) Atta-ur-Rahman, Alvi, A. A.; Abbas, S. A.; Voelter, W. *Heterocycles* **1987**, *26*, 413-419.
[5] Perera, P.; van Beek, T. A.; Verpoorte, R. *J. Nat. Prod*. **1984**, *47*, 835-838.
[6] (a) Atta-ur-Rahman; Muzaffar, A. *Heterocycles* **1985**, *23*, 2975-2978. (b) Kam, T.-S.; Pang, H.-S.; Choo, Y.-M.; Komiyama, K. *Chemistry and Biodiversity* **2004**, *1*, 646-656.
[7] Per a una revisió, vegeu: Alvarez, M.; Joule, J. A. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, Capítol 4.

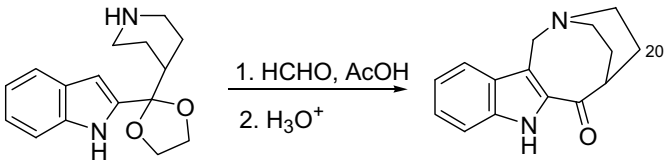
Els alcaloides del grup de l'aparicina es defineixen biogenèticament per la presència d'un únic àtom de carboni (C-6) entre la posició 3 de l'indole i l'àtom de nitrogen alifàtic, com a conseqüència de l'expulsió del C-5 del pont de triptamina de l'alcaloide estemadenina.[8] Aquesta interconversió biogenètica s'ha racionalitzat considerant la intervenció d'un equivalent biològic de la reacció de Polonovski modificada,[9] que implica la fragmentació d'una espècie equivalent a l'*N*-òxid de l'estemadenina. El catió imini resultant de la fragmentació experimentaria hidròlisi a una amina secundària, la qual conduiria a la nova estructura tetracíclica per ciclació sobre l'agrupació de 3-metilenindolenina.[10] Corroborant la hipòtesi biogenètica, l'estemadenina[11] i posteriorment la pericina (subincanadina E)[12] s'han transformat *in vitro* en els respectius C-5 nor-alcaloides, vallesamina i aparicina, per tractament dels *N*-òxids corresponents amb anhídric trifluoroacètic.



Si bé l'estructura d'aquests alcaloides es pot considerar un repte des del punt de vista sintètic, el treball en aquesta àrea s'ha limitat a l'aproximació sintètica desenvolupada per Joule a finals dels anys 70. L'aproximació, basada en la formació final de l'anell central de 8 baules mitjançant una reacció intramolecular de tipus Mannich, permeté la construcció de l'esquelet tetracíclic bàsic de l'aparicina (20-

[8] Kutney, J.-P. *Heterocycles* **1976**, *4*, 429-451.
[9] Potier, P. *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds; Academic Press: London, 1980; Capítol 8.
[10] Ahond, A.; Cavé, A.; Kan-Fan, C.; Langlois, Y.; Potier, P. *J. Chem. Soc., Chem. Commun*. **1970**, 517.
[11] Scott, A. I.; Yeh, C.-L.; Greenslade, D. *J. Chem. Soc., Chem. Commun*. **1978**, 947-948.
[12] Lim, K.-H.; Low, Y.-Y.; Kam, T.-S. *Tetrahedron Lett*. **2006**, *47*, 5037-5039.

desetilidenervaticina) però demostrà ser inviable per a la síntesi total de l'alcaloide.[13] De fet, a l'inici del nostre treball cap alcaloide del grup de l'aparicina havia estat produït per síntesi total.



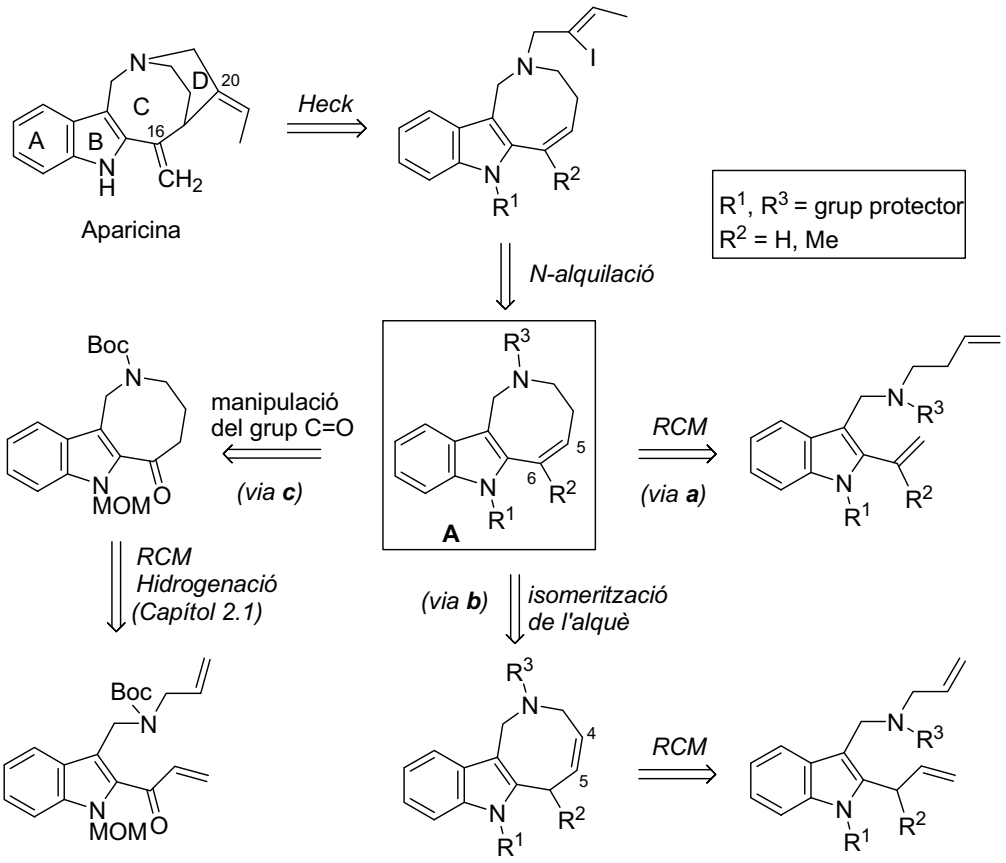
20-Desetilidenervaticina

En aquest context, ens proposàrem dur a terme la primera síntesi total de l'alcaloide aparicina posant a prova la nostra estratègia de doble anulació RCM-Heck. Per desenvolupar aquest objectiu, identificàrem els azocino[4,3-*b*]indoles d'estructura general **A** com a subestructures amb el sistema d'anells ABC de l'alcaloide, a partir de les quals es completaria l'esquelet tetracíclic amb pont per inserció de l'agrupació d'etilidenetà entre l'àtom de nitrogen alifàtic i la posició 5. En concret, després de la introducció de la cadena d'haloalquenil sobre l'àtom de nitrogen, la reacció de Heck intramolecular sobre l'agrupació de 2-vinilindole aconseguiria el tancament de l'anell de piperidina, incorporant al mateix temps els dos substituents exocíclics, 20*E*-etilidè i, quan R^2 = Me, 16-metilè.

Lògicament, decidírem aprofitar la nostra experiència prèvia en la síntesi d'azocinoindoles mitjançant RCM per a la construcció dels intermedis clau **A** i alhora instal·lar el doble enllaç entre les posicions 5 i 6, ja sigui directament (via **a**) o bé després d'una etapa d'isomerització (via **b**). També considerarem d'interès avaluar les possibilitats de crear la insaturació a partir d'una cetona tricíclica (via **c**), la preparació de la qual per RCM s'ha descrit al capítol 2.1.[14]

[13] (a) Scopes, D. I. C.; Allen, M. S.; Hignett, G. J.; Wilson, N. D. V.; Harris, M.; Joule, J. A. *J. Chem. Soc., Perkin 1* **1977**, 2376-2385. (b) Joule, J. A.; Allen, M. S.; Bishop, D. I.; Harris, M.; Hignett, G. J.; Scopes, D. I. C.; Wilson, N. D. V. *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic: London, 1980; pp 229-247.

[14] Per a una aproximació diferent a aquestes subestructures tricícliques, vegeu: (a) Street, J. D.; Harris, M.; Bishop, D. I.; Heatley, F.; Beddoes, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans*. *1* **1987**, 1599-1606. (b) Vegeu també la referència 13b.



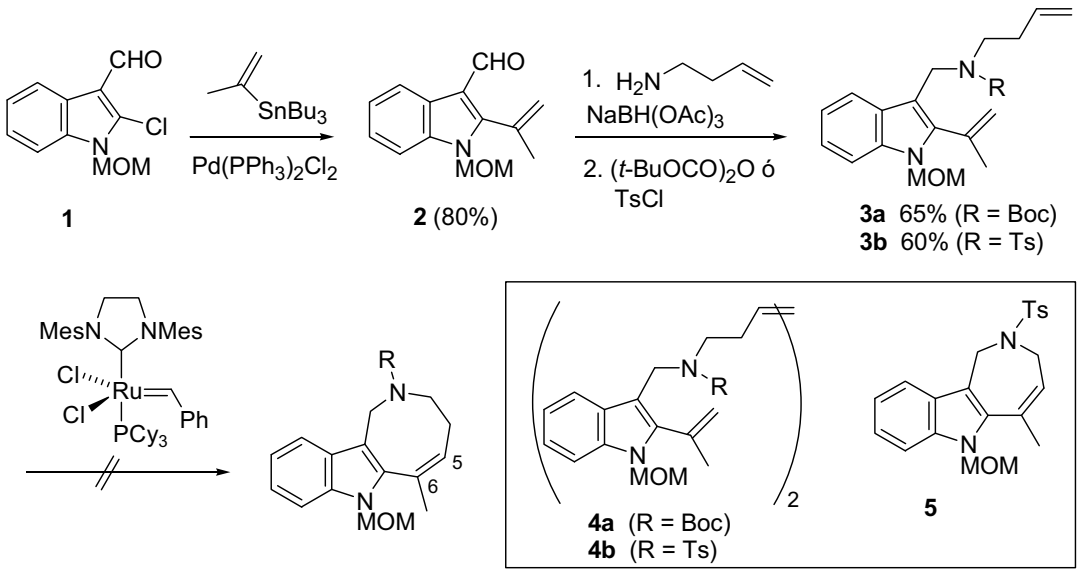
Estudis inicials (via a)

Començarem aquest estudi abordant la reacció de RCM per a la construcció directa de 6-metilazocino[4,3-*b*]indoles (**A**, R^2 = Me), amb el doble enllaç trisubstituït entre les posicions 5 i 6 necessari per l'acoblament final de Heck. Amb aquesta finalitat, escollírem com a precursors dièn ics els 2-isopropenilindoles **3**, protegits amb un grup Boc o tosil a l'àtom de nitrogen alifàtic i amb un grup MOM a l'àtom de nitrogen indòlic. Aquests compostos es prepararen de manera eficaç a partir del 2-cloroindole-3-carbaldehid **1,**[15] per reacció d'acoblament d'Stille amb isopropeniltributilestannà, aminació reductora de l'aldehid **2** amb 3-butenilamina i acilació o sulfonilació subsegüent de l'amina secundària resultant amb dicarbonat de di-*tert*-butil o clorur de tosil.

Malauradament, el tractament dels diens **3** amb el catalitzador de Grubbs de segona generació en dissolució de diclorometà o toluè no proporcionà els azocinoindoles esperats. En comptes d'evolucionar per RCM, el carbamat **3a** experimentà principalment reaccions de metàtesi intermolecular per donar, entre d'altres, el dímer **4a**, fins i tot quan es treballava en condicions d'elevada dilució

[15] Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull*. **2001**, *49*, 881-886.

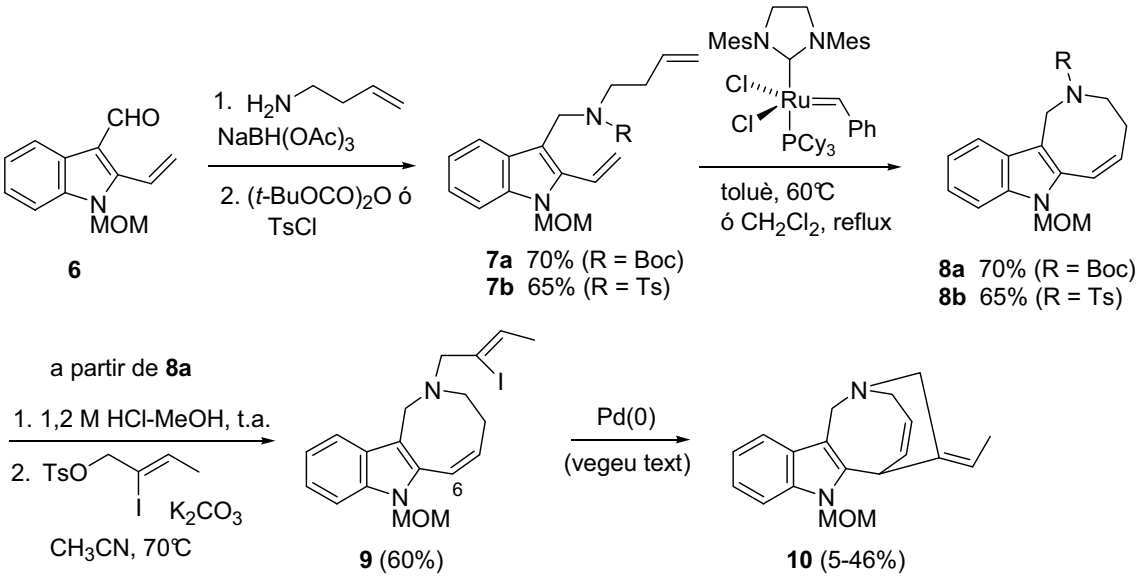
(0,007M). En canvi, la sulfonamida **3b** proporcionà el corresponent dímer **4b** acompanyat de quantitats variables del producte de contracció d'anell **5**, el qual procedia de la isomerització competitiva del doble enllaç terminal seguida de RCM amb alliberament de propè. L'azepinoindole **5** fou l'únic producte aïllat (75%) quan la ciclació de **3b** es realitzà a reflux de toluè. En ambdós substrats, l'ús d'altres catalitzadors de ruteni (Grubbs de primera generació, Hoveyda-Grubbs de segona generació) o de molibdè (catalitzador de Schrock) no millorà els resultats.



Atès que aquest resultat negatiu era degut molt probablement a la presència en els diens **3** d'un doble enllaç terminal disubstituït geminalment, dirigírem la nostra atenció a azocinoindoles que mancaven del grup metil a la posició 6 (**A**, R^2 = H), els quals havien de ser a priori més fàcilment accessibles per RCM. A partir d'aquestes estructures model també seria possible estudiar el tancament de l'anell de piperidina, ja sigui per ciclació de Heck en condicions reductores o bé per un procès tàndem de ciclació de Heck-captura, mitjançant el qual també es podria introduir l'àtom de carboni restant de la posició 16 de l'alcaloide.

El desenvolupament d'aquesta nova aproximació requeria disposar dels 2-vinilindoles **7a** i **7b** com a substrats de la RCM. Aquests compostos es prepararen a partir de l'aldehid **6**,[15] per aminació reductora amb 3-butenilamina seguida d'acilació o sulfonilació de les amines secundàries resultants. Com havíem previst, la reacció de RCM del diens **7a** i **7b**, que implicava ara la participació de dos dobles enllaços terminals no substituïts, tingué lloc en presència del catalitzador de Grubbs de segona generació en les condicions usuals (0,01 M, toluè, 60ºC o CH_2Cl_2, reflux) per donar els azocinoindoles **8a** i **8b** amb rendiments acceptables.

En aquest punt, l'accés a l'intermedi sintètic més avançat **9** requeria la desprotecció de l'àtom de nitrogen alifàtic de **8a** o **8b** per tal d'instal·lar la cadena de iodoalquenil necessària per a la reacció de Heck. Atès que els primers intents de promoure la desulfonilació del compost **8b** en condicions reductores (Mg, NH_4Cl, MeOH o Na/naftalè, THF) proporcionaren el producte de partida inalterat o bé mescles complexes de reacció, ens centràrem en el carbamat **8a**. L'eliminació del grup Boc en les condicions àcides usuals (TFA, Me_3SiI, $ZnBr_2$) també fou problemàtica, ja que s'observà la descomposició parcial del producte. Satisfactòriament, la desprotecció tingué lloc de forma eficient quan **8a** es tractà en condicions àcides suaus (1,2 M HCl en MeOH a temperatura ambient). L'amina secundària resultant s'alquilà directament amb tosilat de (*Z*)-2-iodo-2-butenil en dissolució d'acetonitril per donar l'amina terciària **9** amb un rendiment global del 60% a partir de **8a**.



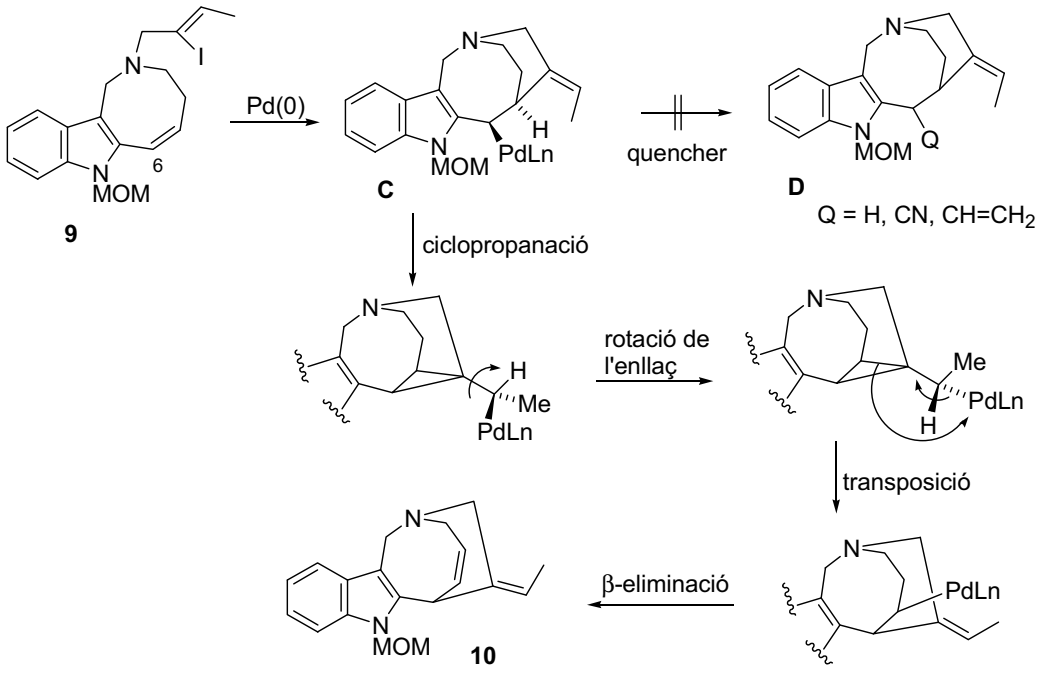
A continuació estudiàrem la ciclació catalitzada per pal·ladi de l'halur vinílic sobre l'agrupació de 2-vinilindole. Esperàvem que l'intermedi σ-alquilpal·ladi **C**, en no poder experimentar fàcilment β-eliminació d'hidrur,[16] fos suficientment estable per ser reduït o atrapat per un "quencher". No obstant això, quan **9** es sotmeté a diferents condicions utilitzades prèviament per altres autors per promoure reaccions de Heck reductores, el tetracicle desitjat **D** (Q = H) mai fou detectat. Quan la reacció es realitzà en absència de lligand fosfina [$Pd(OAc)_2$, K_2CO_3, TBACl, HCO_2Na, DMF, 80ºC], en

[16] Si bé el sistema sembla prou flexible conformacionalment per possibilitar la disposició *syn* de l'agrupació σ-alquilpal·ladi amb l'hidrogen de la posició cap de pont, la formació subsegüent del doble enllaç no estaria afavorida por motius geomètrics.

condicions similars a les que havia emprat amb èxit Overman en substrats relacionats,[17] l'únic procés observat fou l'*N*-desalquilació.

S'examinà a continuació l'efecte a la reacció d'una gran varietat de catalitzadors [$Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$], lligands (Ph_3P, dppe) i dissolvents (toluè, CH_3CN, THF), en presència de Et_3N o diisopropiletilamina com a reductors potencials.[18] Mentre que en temps de reacció curts es recuperava el producte de partida inalterat, quan augmentàrem el temps de reacció s'observà la formació del compost tetracíclic **10** amb un rendiment baix (5-10%). El rendiment de **10** augmentà fins al 30% quan **9** es tractà amb $Pd(PPh_3)_4$ en THF-Et_3N (1:1) en un tub tancat durant 24 hores a 90ºC.

D'altra banda, quan la reacció es realitzà en condicions catiòniques [$Pd(OAc)_2$, Ph_3P, Ag_2CO_3, toluè-Et_3N (1:1), 90ºC] el compost tetracíclic **10** s'obtingué amb un 46% de rendiment. Significativament, aquest resultats no es modificaren quan la reacció es realitzà en presència de HCO_2Na com a reductor, o bé en presència d'agents d'atrapada com ara KCN, $K_4[Fe(CN)_6]$, TMSCN o tributilvinilestannà.



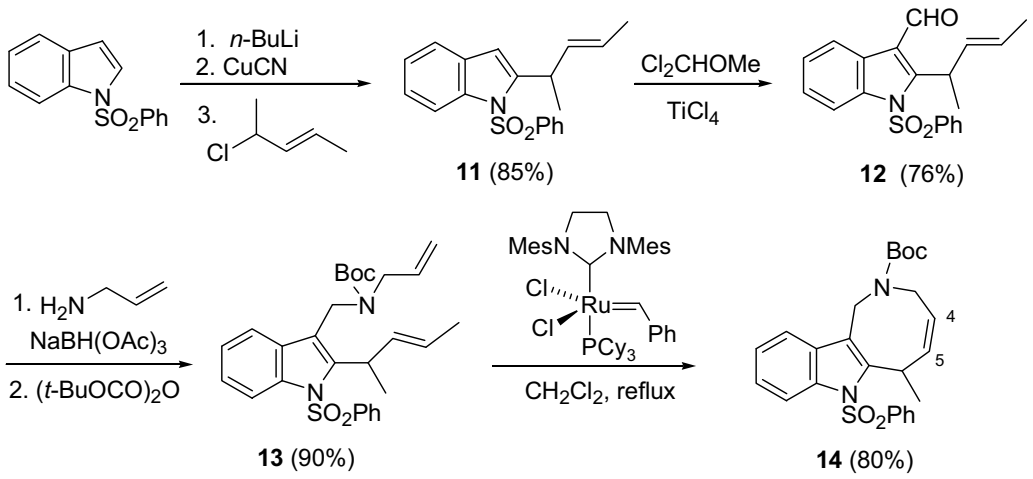
[17] Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. **2008**, *130*, 5368-5377.
[18] (a) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J*. **2000**, *6*, 655-665. (b) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem*. **2007**, *72*, 9253-9258.

El compost tetracíclic **10**, derivat aparentment d'una ciclació 7-*endo* amb inversió de la configuració del grup etilidè,[19] és el resultat d'un procés de ciclopropanació-transposició-eliminació anàleg al descrit al Capítol 3.1 per a la formació del compost tetracíclic **8**. En aquest cas, el procés seria suficientment ràpid com per impedir que l'intermedi σ-alquilpal·ladi **C** format inicialment fos interceptat per qualsevol dels "quenchers" emprats.

Aquests resultats posaven de manifest que la presència d'un grup metil a la posició 6 del substrat de la reacció de Heck era crucial per poder accedir a l'estructura amb pont de l'aparicina, ja que asseguraria la β-eliminació ràpida de l'intermedi σ-alquipal·ladi, evitant així la via competitiva no desitjada. Per tant, dirigírem un altre cop els nostres esforços a la síntesi de 6-metilazocino[4,3-*b*]indoles (**A**, R^2 = Me), abordant novament el problema de la reacció de RCM.

RCM seguida d'isomerització (via b)

Considerant que no havíem pogut formar el doble enllaç trisubstituït inclòs en l'anell de 8 baules directament per RCM, decidírem canviar el lloc de ciclació de la posició 5-6 a la posició 4-5, menys impedida, utilitzant com a diè un 3-(al·lilaminometil)-2-al·lilindole com ara **13**. En conseqüència, l'accés al precursor de la reacció de Heck requeriria una etapa addicional d'isomerització del doble enllaç resultant.



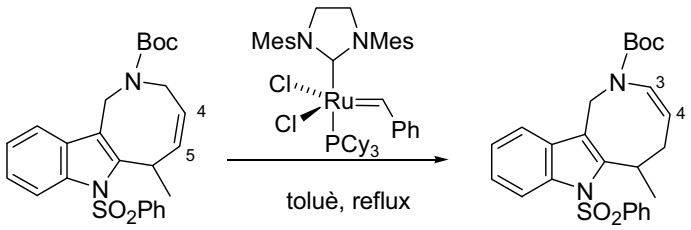
Per introduir la cadena α-metilal·lílica en la posició 2 de l'indole optàrem per emprar una reacció de substitució nucleòfila al·lílica a partir d'un derivat organometàl·lic de l'heterocicle. L'1-(fenilsulfonil)indole es féu reaccionar amb *n*BuLi i

[19] La configuració *Z* del substituent etilidè s'establí mitjançant experiments de NOESY.

CuCN i, tot seguit, el derivat d'organocoure intermedi es tractà amb (*E*)-4-cloro-2-pentè. L'indole **11** resultant es convertí en el substrat de la RCM **13** mitjançant formilació de Friedel-Crafts seguida d'aminació reductora de l'aldehid **12** amb al·lilamina i protecció de l'amina secundària amb dicarbonat de di-*tert*-butil. El rendiment global de les quatre etapes fou del 58%. Satisfactòriament, la reacció de RCM del diè **13** tingué lloc amb facilitat en presència del catalitzador de Grubbs de segona generació en les condicions usuals (0,07 M, CH_2Cl_2, reflux) per proporcionar el 6-metilazocinoindole **14** amb un rendiment del 80%.

A continuació, centrarem la nostra atenció en l'etapa d'isomerització del doble enllaç. Durant els darrers anys s'han descrit alguns exemples d'isomeritzacions post-RCM mediades pels mateixos catalitzadors de Grubbs convenientment modificats, ja sigui per la presència d'additius[20] o bé per l'ús de toluè a reflux.[21] Aquestes condicions afavoririen la generació d'espècies d'hidrur de ruteni, les quals serien responsables del procés d'isomerització.[22] Tenint en compte la simplicitat d'aquests protocols, decidírem en primer lloc examinar la seva viabilitat pel nostre propòsit.

Malauradament, el tractament de l'azocinoindole **14** amb el catalitzador de Grubbs de segona generació a reflux de toluè,[21] provocà la isomerització lenta del doble enllaç cap a la posició 3-4, conjugada amb l'àtom de nitrogen, en comptes de la posició 5-6, conjugada amb l'indole, per donar l'encarbamat **16** amb un rendiment no optimitzat del 50%.



14 **16** (50%)

De manera significativa, l'efecte dirigent exercit pel nitrogen de l'agrupació carbamat també fou decisiu, encara que en menor extensió, en la isomerització catalitzada per ruteni de l'anàleg 6-desmetilat **17a**,[23] ja que en aquest cas s'obtingué

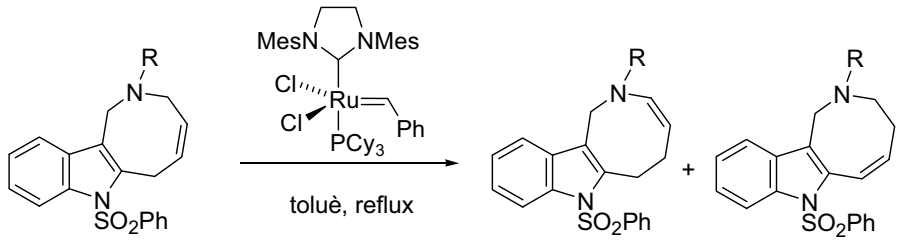
[20] (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc*. **2002**, *124*, 13390-13391. (b) Schmidt, B. *J. Org. Chem*. **2004**, *69*, 7672-7687. Per a un exemple més recent, vegeu: (c) Schmidt, B.; Biernat, A. *Chem. Eur. J.* **2008**, *14*, 6135-6141.

[21] Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem*. **2006**, *71*, 2706-2714.

[22] Per a reviews sobre el comportament no metatètic dels catalitzadors de Grubbs, vegeu: (a) Schmidt, B. *Eur. J. Org. Chem*. **2004**, 1865-1880. (b) Alcaide, A.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817-3858.

[23] La preparació d'aquest compost per RCM s'ha descrit al Capítol 2.1

una mescla aproximadament 3:1 de l'encarbamat **18a** i del vinilindole **19a**. En canvi, la isomerització de **17b**[23] proporcionà el vinilindole **19b** com a únic producte, fet que posava de manifest que l'àtom de nitrogen de l'agrupació sulfonamida no exercia cap influència en la isomerització.[24]

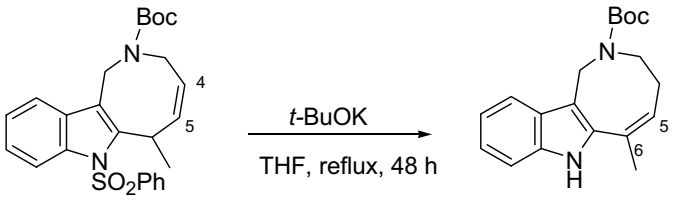


17a (R = Boc)
17b (R = Ts)

18a (35%)
18b (—)

19a (10%)
19b (40%)

Observàrem de manera fortuïta que el doble enllaç de l'azocinoindole **14** isomeritzava cap a la posició conjugada amb l'anell aromàtic en les condicions bàsiques requerides per eliminar el grup *N*-sulfonil. Aquesta observació fou útil des del punt de vista sintètic, ja que el tractament de **14** amb *t*-BuOK a la temperatura de reflux de THF durant 48 hores provocà, a més de la desprotecció de l'indole, la isomerització completa del doble enllaç per donar l'azocinoindole **15** amb un rendiment alt (90%). Emprant temps de reacció més curts i analitzant les mescles de reacció per RMN, poguérem determinar que la migració del doble enllaç tenia lloc després de la desprotecció, fet que suggereix que la isomerització induïda per base només és compatible amb la presència de l'àtom de nitrogen indòlic no substituït.



14

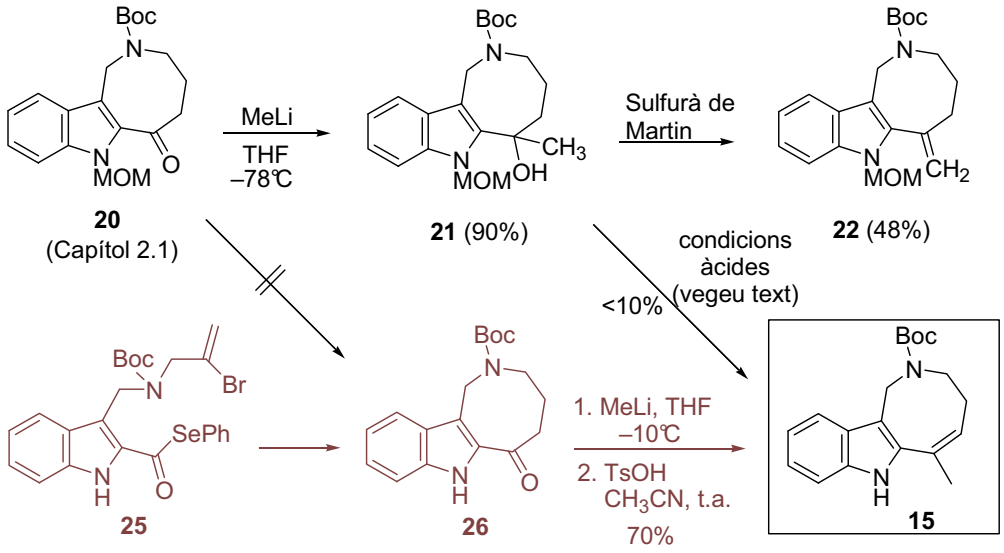
15 (90%)

[24] No s'observà isomerització quan els azocinoindoles **14** i **17** es tractaren amb el catalitzador de Grubbs en dissolució de metanol a reflux. Vegeu: Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett*. **2006**, *8*, 5481-5484.

Aproximació alternativa a l'azocinoindole 15 (via c)

Tot i que la seqüència sintètica de RCM-isomerització permetia accedir a l'intermedi clau de l'apericina **15** amb un rendiment global del 41% a partir de l'1-(fenilsulfonil)indole, a través de només quatre intermedis sintètics aïllats, explorarem també la possibilitat d'instal·lar el doble enllaç trisubstituït per manipulació del grup carbonil de la cetona tricíclica **20** (Capítol 2.1).

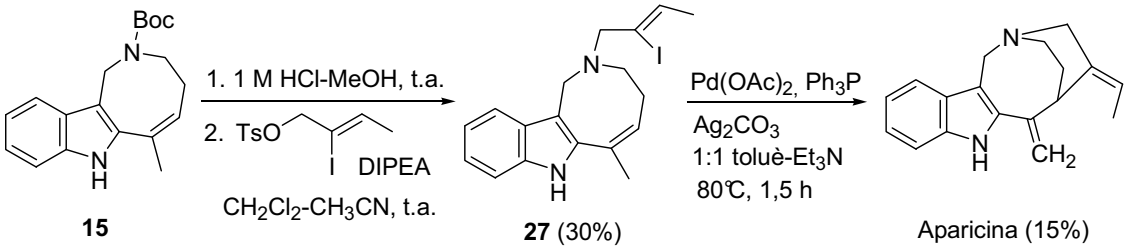
La reacció de **20** amb MeLi proporcionà l'alcohol terciari **21**, el qual es sotmeté a una gran varietat de protocols per promoure la seva deshidratació. El tractament en diverses condicions àcides (H_2SO_4 3M en acetona o TsOH en benzè) provocà, a més de la deshidratació desitjada, la desprotecció concomitant de l'indole per donar l'alquè endocíclic **15** amb un rendiment baix. D'altra banda, la deshidratació promoguda pel sulfurà de Martin fou més eficient però conduí a l'alquè exocíclic **22**, amb el grup *N*-MOM inalterat.



És important esmentar que la seqüència d'addició de MeLi seguida de deshidratació en medi àcid per donar l'alquè endocíclic **15** fou molt més eficient (70%) a partir del substrat anàleg **26**, no substituït a l'àtom de nitrogen indòlic. Si bé no fórem capaços de desprotegir selectivament la cetona **20**, fora del context d'aquesta Tesi Doctoral s'ha preparat la cetona **26** per una ruta alternativa, que implica com a etapa clau la ciclació radicalària del selenoèster **25**.

Desenllaç de la síntesi de l'aparicina

Un cop disposaven de l'azocinoindole **15**, el següent pas consistí en la desprotecció de l'àtom de nitrogen alifàtic per tal d'introduir posteriorment la cadena de iodoalquenil necessària per a la reacció de Heck. Tal com havia succeït amb l'anàleg desmetilat **8a**, l'eliminació del grup *N*-Boc de **15** requerí l'ús de condicions àcides suaus per evitar la formació de productes de descomposició. L'amina secundària resultant demostrà ser bastant inestable i s'alquilà directament amb tosilat de (*Z*)-2-iodo-2-butenil per donar l'amina terciària **27** amb un rendiment global del 30%. Tots el intents realitzats per incorporar novament el grup fenilsulfonil sobre l'àtom de nitrogen indòlic de **15** amb la intenció d'augmentar l'estabilitat d'aquests intermedis foren infructuosos.



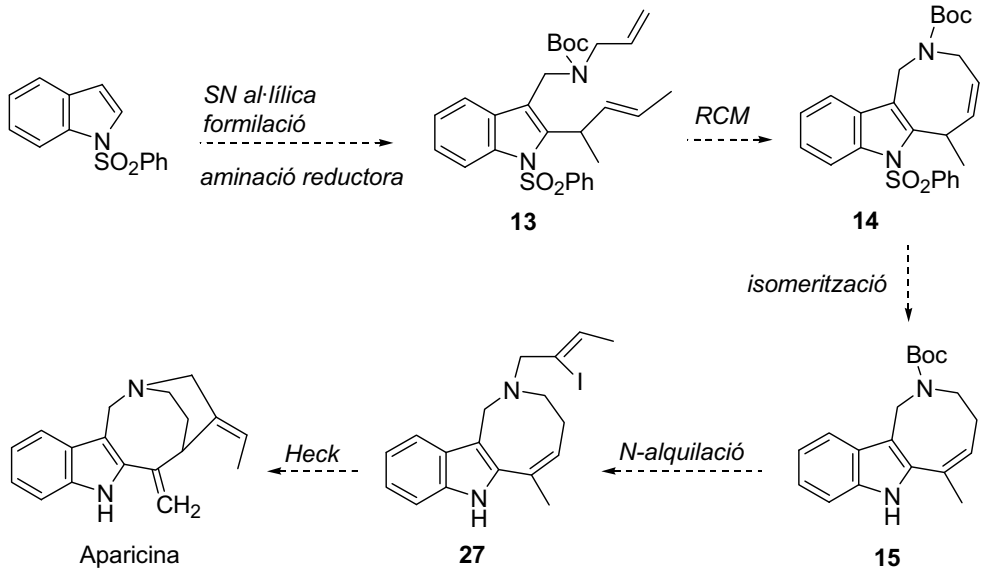
Estudiàrem, finalment, l'acoblament intramolecular de Heck entre el iodur vinílic i el doble enllaç trisubstituït de **27**. Després de nombrosos assaigs negatius emprant diferents catalitzadors de pal·ladi, dissolvents i additius, observàrem que el tancament del sistema tensionat d'1-azabiciclo[4.2.2]decà de l'aparicina amb la incorporació dels dos substituents exocíclics tenia lloc en condicions catiòniques, encara que la pèrdua de matèria era molt abundant. Aplicant un protocol específic [$Pd(OAc)_2$/Ph_3P (0,2:0,6 equiv.), Ag_2CO_3 (2 equiv.), toluè-Et_3N (1:1), 80ºC, 1.5 h], l'aparicina s'obtingué amb un rendiment reproduïble del 15%.

Les dades espectroscòpiques d'^1H i ^{13}C RMN de l'aparicina sintètica foren concordants amb les descrites a la literatura per al producte natural.[2,7,25] A més, el comportament cromatogràfic (capa fina) del producte sintetitzat fou idèntic al d'una mostra autèntica de l'alcaloide.[26]

[25] (a) Massiot, G.; Zèches, M.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. *J. Chem. Soc., Chem. Commun*. **1982**, 768-769. (b) van Beek, T. A.; Verpoorte, R.; Kinh, P. Q. *Planta Med*. **1985**, *51*, 277-279. (c) Atta-ur-Rahman; Fatima, T.; Mehrum-Nisa; Ijaz, S.; Crank, G.; Wasti, S. *Planta Med*. **1987**, *53*, 57-59.

[26] Agraïm al Professor John A. Joule la donació d'una mostra d'aparicina.

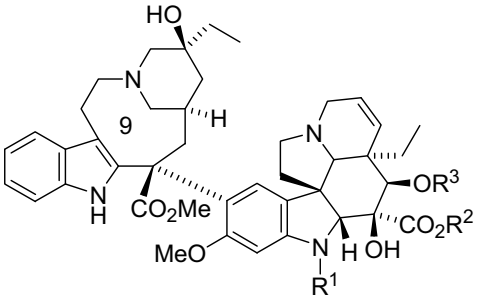
En resum, s'ha aconseguit la primera síntesi total de la (±)-apariciina a partir de l'1-(fenilsulfonil)indole, mitjançant una via sintètica concisa que implica com a etapas clau: (i) la reacció de RCM del diè indòlic **13** per construir l'anell central de 8 baules; (ii) la isomerització promoguda per base de **14**, amb desprotecció concomitant de l'indole; i (iii) la ciclació de Heck de l'halur vinílic **27** per completar la formació de l'esquelet amb pont.



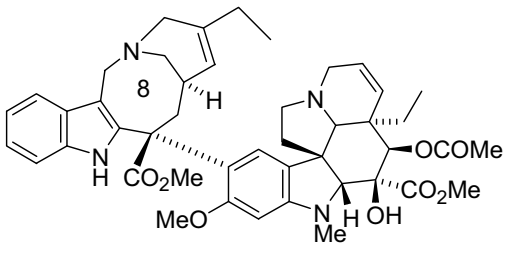
3.3. ACCÉS A LA UNITAT SUPERIOR DE LA VINORELBINA

(Resultats no publicats)

Els alcaloides indòlics *Vinca* constitueixen un grup de més de cent productes naturals aïllats de diverses espècies del gènere *Catharantus*, caracteritzats per presentar estructures dimèriques complexes associades a una notable activitat antimitòtica.[1] Els components més representatius del grup són la vinblastina i la vincristina, constituïts per una unitat superior de tipus cleavamina i una unitat inferior de tipus vindolina. Aquests dos productes naturals, juntament amb altres derivats semisintètics com ara la vindesina i la vinorelbina, són emprats avui en dia en la quimioteràpia del càncer.[2]



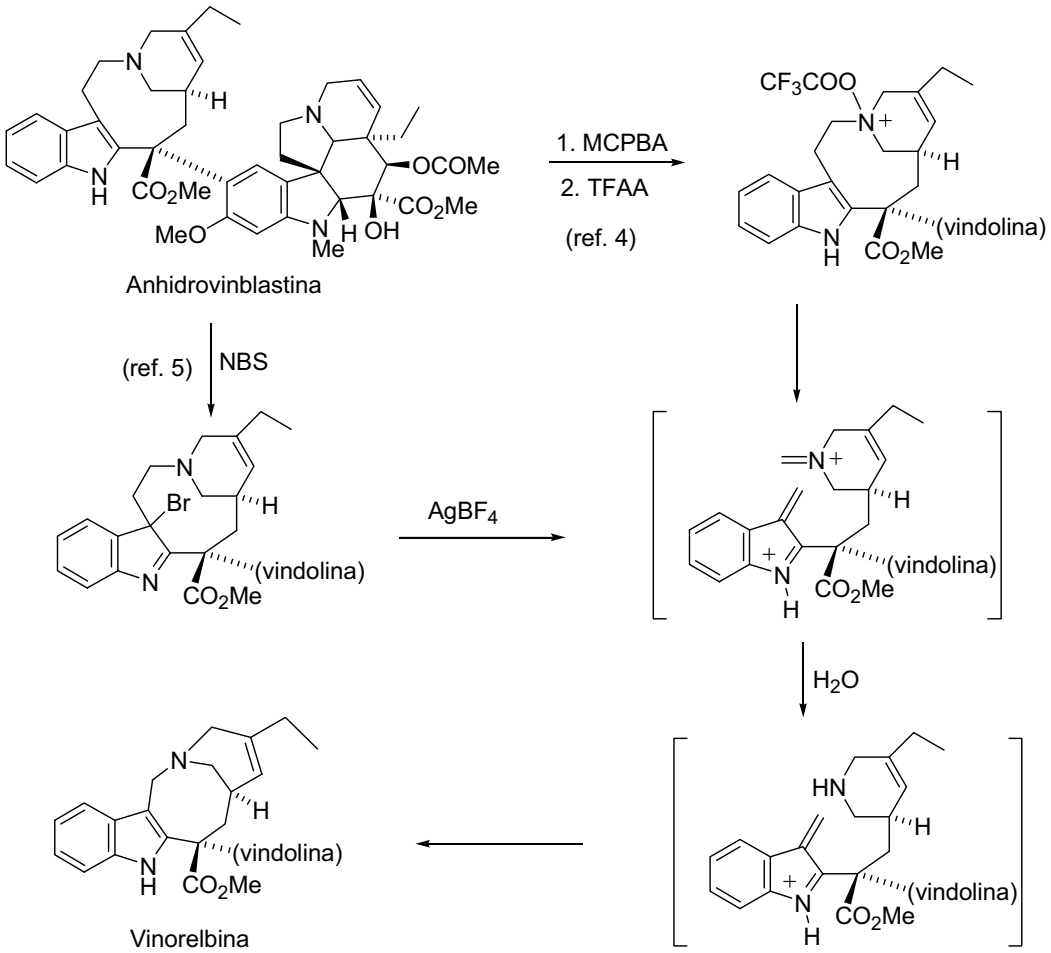
Vinblastina: R^1 = Me; R^2 = Me; R^3 = COMe
Vincristina: R^1 = CHO; R^2 = Me; R^3 = COMe
Vindesina: R^1 = Me; R^2 = NH_2; R^3 = H



Vinorelbina

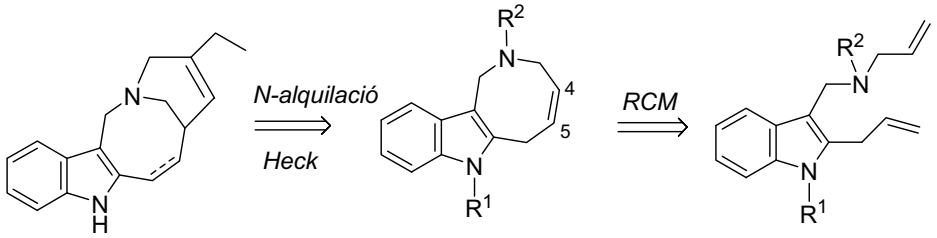
[1] Brossi, A.; Suffness, M., Eds; *The Alkaloids*, vol. 37; Academic Press: San Diego, 1990.
[2] Cuendet, M.; Pezzuto, J. M. *Modern Alkaloids: Structure Isolation and Biology*; Fattorusso, E.; Taglialatela-Scafati, O., Eds; Wiley-VCH: Weinheim, 2008; pp. 25-52.

La vinorelbina (navelbina®) representa una modificació estructural respecte dels altres membres dels grup, atès que la unitat superior conté un anell central de 8 baules en comptes de 9.[3] De fet, la vinorelbina es prepara per contracció d'anell del derivat semisintètic anhidrovinblastina, ja sigui mitjançant una reacció de Polonovski modificada del corresponent *N*-òxid[4] o bé per tractament amb $AgBF_4$ de la corresponent 3-haloindolenina.[5] En ambdós casos la reacció transcorreria a través del mateix catió imini, el qual experimentaria hidròlisi i ciclació de manera anàloga a allò que es descriu a l'apartat anterior per a la transformació entre els alcaloides de tipus estemadenina i de tipus aparicina.

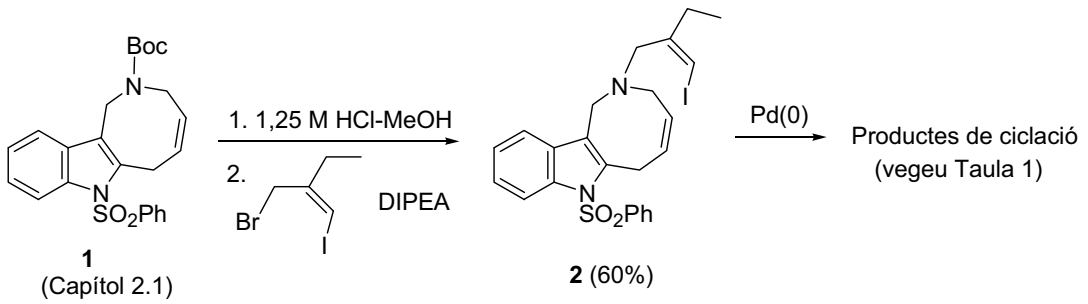


[3] Fahy, J. *Curr. Pharm. Des.*, **2001**, *7*, 1181-1197.
[4] (a) Mangeney, P.; Andriamialisoa, R. Z.; Lallemand, J. Y.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron.* **1979**, *35*, 2175-2179. (b) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Org. Chem.* **1979**, *44*, 3765-3768.
[5] (a) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron.* **1980**, *36*, 3053-3060. (b) Fahy, J.; Thillaye de Boullay, V.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 505-507. (c) Ngo, Q. A.; Roussi, F.; Cormier, A.; Thoret, S.; Knossow, M.; Guénard, D.; Guéritte, F. *J. Med. Chem*. **2009**, *52*, 134-142.

D'acord amb els nostres objectius, el sistema d'1-azabiciclo[5.3.1]undecà, característic de la unitat superior de la vinorelbina, es podria construir d'una manera similar al sistema bicíclic de l'alcaloide aparicina, combinant una reacció de RCM d'un diè indòlic i una ciclació de Heck d'un halur vinílic. En aquest cas, havíem de disposar d'un azocino[4,3-*b*]indole que incorporés un doble enllaç entre les posicions 4 i 5, a partir del qual s'inseriria l'agrupació de 2-etilpropè entre l'àtom de nitrogen alifàtic i la posició 4 mitjançant una reacció d'*N*-alquilació seguida d'acoblament intramolecular de Heck.



Escollírem com a substrat de partida l'azocinoindole **1**, protegit amb un grup fenilsulfonil a l'àtom de nitrogen indòlic i un grup Boc a l'àtom de nitrogen alifàtic, la preparació del qual per RCM s'ha descrit al capítol 2.1. Per tal d'eliminar el grup protector Boc, l'azocinoindole **1** es tractà en les condicions àcides suaus que ja havíem utilitzat a les sèries anteriors. A continuació, l'amina secundària resultant es féu reaccionar amb 3-bromo-2-etil-1-iodo-1-propè[6] per donar l'halur vinílic **2** amb un rendiment acceptable (60% per les dues etapes). A partir de **2** estudiàrem el tancament de l'anell de piperidina per reacció intramolecular de Heck. Els resultats més significatius d'aquest estudi es recullen a la Taula 1.

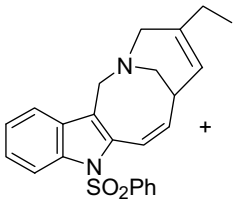
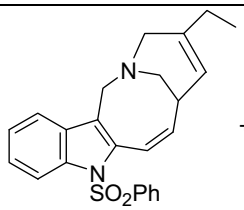
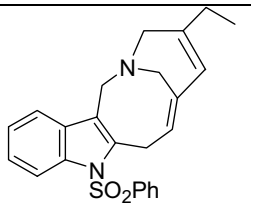
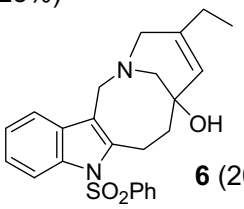


1
(Capítol 2.1)

2 (60%)

[6] Zhang, Y.; Herndon, J. W. *Org. Lett*. **2003**, *5*, 2043-2045.

Taula 1. Ciclació de Heck del iodur vinílic 2

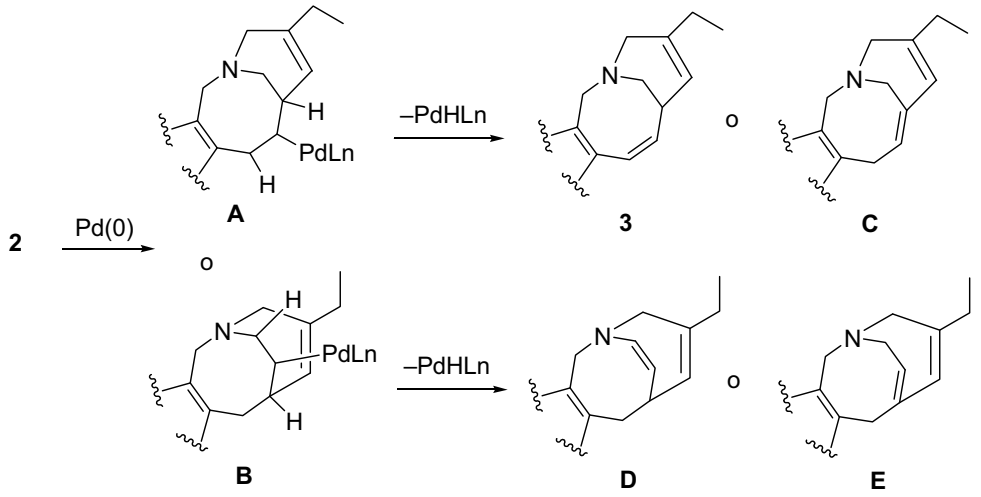
	Condicions	Productes
1	$Pd(OAc)_2$ (10%), Ph_3P (30%), Ag_2CO_3 (2 equiv.), toluè o CH_3CN, reflux, 24 h	Producte de partida (**2**)
2	$Pd(OAc)_2$ (10%), Ph_3P (40%), proton-sponge® (0.3 equiv.), K_2CO_3 (1.5 equiv.), toluè, reflux, 24 h	Producte de partida (**2**, 45%)  + **4 (?)** **3** 1:1 (24%)
3	$Pd(PPh_3)_4$ (15%), proton-sponge® (0.1 equiv.), K_2CO_3 (1.5 equiv.), toluè, reflux 24 h	**3** + **4** (3:1, 60%) **3** (40%)
4	$Pd(OAc)_2$ (10%), **BINAP**[1] (15%), proton-sponge® (0.3 equiv.), K_2CO_3 (1.5 equiv), toluè, reflux, 15 h	**3** + **4** (1:1, 75%) **3** (35%)
5	$Pd_2(dba)_3$ (7.5%), **xantphos**[2] (15%), proton-sponge® (0.3 equiv.), K_2CO_3 (1.5 equiv.), toluè, reflux, 24h	 +  **3** (25%) **5** (24%)  **6** (20%)

[1] (±)-2,2'-Bis(difenilfosfino)-1,1'-binaftalè.
[2] 4,5-Bis(difenilfosfino)-9,9-dimetilxantè.

En primer lloc, l'halur vinílic **2** es tractà amb $Pd(OAc)_2$ i Ph_3P en presència de Ag_2CO_3, en condicions catiòniques similars a les que s'havien emprat per tancar el sistema tensionat de l'aparicina. Malauradament, de la mescla de reacció únicament es recuperà el producte de partida inalterat, tant a la temperatura de reflux de toluè com d'acetonitril (entrada 1).

De manera significativa, la supressió de l'additiu Ag_2CO_3 i la inclusió de proton-sponge® com a base donà lloc a una mescla equimolecular de dos compostos, encara que amb un baix rendiment (24 %, entrada 2): el compost tetracíclic **3**, que presenta el sistema esperat d'1-azabiciclo[5.3.1]undecà resultant de la ciclació *exo* amb formació final d'un doble enllaç disubstituït, i un altre compost (**4**), d'estructura desconeguda. La utilització del protocol especificat a l'entrada 3 permeté aïllar el compost **3** amb un 40% de rendiment, a partir d'una mescla 3:1 de **3** i **4**.

L'estructura de **4** no es pogué determinar amb certesa degut a que el compost descomposava durant la purificació cromatogràfica o durant l'enregistrament de l'espectre de ^{13}C RMN. No obstant això, les dades de l'espectre de masses d'alta resolució indicaven que es tractava d'un regioisòmer de **3** mentre que l'espectre d'^1H RMN mostrava la presència d'únicament dos hidrogens vinílics.[7] Aquesta informació ens portà a considerar una estructura tetracíclica de tipus **C** o **E**, amb un doble enllaç en posició cap de pont. Mentre que l'estructura **C** procediria d'una ciclació 6-*exo* seguida de β-eliminació de l'hidrur en posició cap de pont de l'intermedi σ-alquilpal.ladi **A**, l'estructura **E** procediria d'una ciclació 7-*endo* seguida d'un procés d'eliminació anàleg a partir de l'intermedi **B.** Donat que posteriorment, l'estructura **C** fou assignada a un compost diferent (compost **5**, vegeu més endavant), l'estructura **E** semblaria la més probable.



[7] Compost **4**: ^1H RMN ($CDCl_3$, 400 MHz) δ 0.50 (t, *J* = 6.8 Hz, 3H), 1.71 (q, *J* = 6.8 Hz, 2H), 2.56 (td, *J* = 12.4 and 4.4 Hz, 1H), 2.67 (broad d, *J* = 12.4 Hz, 1H), 2.85 (broad t, *J* = 12 Hz, 1H), 3.20 (broad d, *J* = 13.8 Hz, 1H), 3.46 (d, *J* = 14.8 Hz, 1H), 3.69 (d, *J* = 12 Hz, 1H), 3.80 (d, *J* = 13.8 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.89 (s, 1H), 5.89 (s, 1H), 7.17-7.24 (m, 2H), 7.33-7.41 (m, 3H), 7.51 (m, 1H), 7.72 (m, 2H), 8.14 (d, *J* = 7.6 Hz, 1H); ESI-HRMS $[M + H]^+$ calculat per a $C_{24}H_{25}N_2O_2S$ 405.1631, trobat 405.1627.

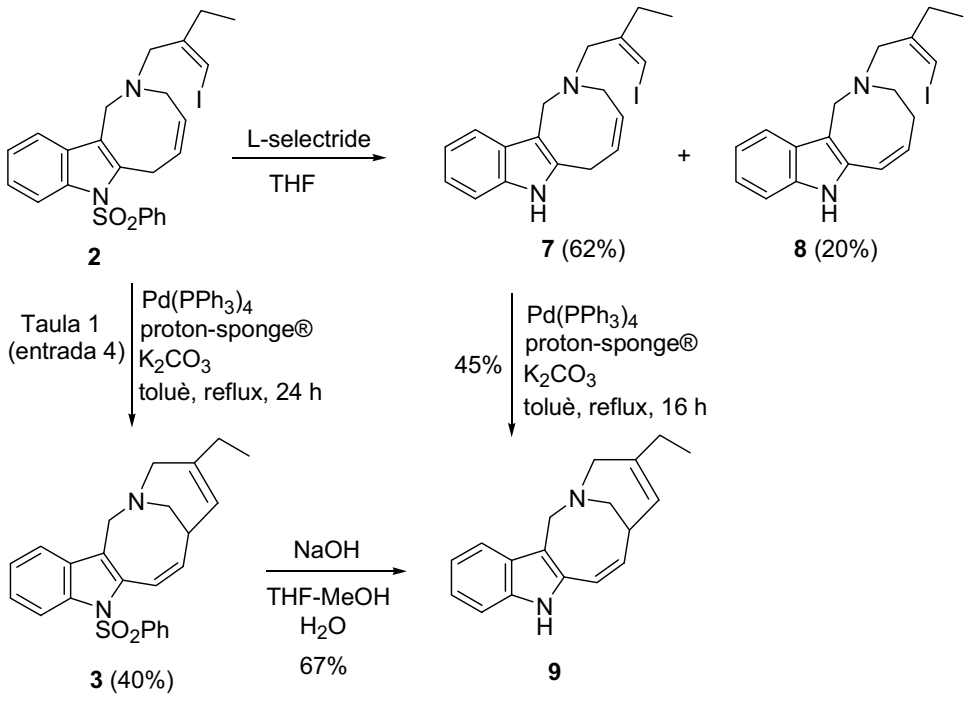
En aquest punt del treball decidírem estudiar la ciclació en presència de fosfines bidentades, ja que és conegut que augmenten l'eficiència de les reaccions catalitzades per pal·ladi i, en ocasions, en modifiquen la regioselectivitat. Mentre que en presència de dppe s'obtingué una mescla de reacció complexa formada, entre d'altres, pel producte de partida i els productes de ciclació **3** i **4** (resultat no recollit a la Taula 1), en presència de BINAP tingué lloc la formació d'una mescla equimolecular de **3** i **4** amb un rendiment elevat (75%, entrada 4).

D'altra banda, el curs de la ciclació es modificà sensiblement amb l'ús de la fosfina bidentada xantphos (entrada 5). En aquest cas, no es detectà la formació del compost d'estructura desconeguda **4** sinó que s'obtingueren quantitats equimoleculars del diè **3** i d'altres dos compostos amb el mateix esquelet carbonat: el diè **5**, amb un doble enllaç trisubstituït en posició cap de pont i, per tant, amb l'estructura **C**, i el carbinol **6**, procedent de la hidratació de l'anterior. Aquest resultat confirma que el sistema d'1-azabiciclo[5.3.1]undecà és prou flexible conformacionalment com per possibilitar la disposició *syn* de l'agrupació σ-alquilpal·ladi no només amb l'hidrogen de la posició benzílica sinó també amb l'hidrogen de la posició cap de pont. La presència de xantphos,[8] una fosfina bidentada amb un *bite angle* més gran (108º) que el BINAP (93º) i amb capacitat quelant tant en *cis* com en *trans*,[9] probablement disminueix la velocitat de l'etapa de β-eliminació i alhora afavoreix l'eliminació cap a la posició cap de pont per motius estèrics.

Finalment, es considerà d'interès estudiar la ciclació de Heck a partir d'un substrat no protegit a l'àtom de nitrogen indòlic. Per accedir a aquest compost, la opció més senzilla era promoure l'eliminació del grup fenilsulfonil de **2**, sabent que havíem d'evitar els protocols en medi bàsic per la previsible isomerització del doble enllaç C-C cap a la posició conjugada amb l'indole. D'acord amb els nostres interessos, quan l'halur vinílic **2** es tractà amb L-selectride s'obtingué l'halur vinílic desitjat **7** amb un rendiment acceptable (62%), acompanyat de quantitats minoritàries dels corresponent producte d'isomerització **8**.

A partir de **7** s'assajà la ciclació de Heck en les condicions que havien proporcionat un millor rendiment aïllat del producte de ciclació *N*-protegit **3** (Taula 1, entrada 4). Satisfactòriament, el tractament de **7** amb $Pd(PPh_3)_4$ en presència de proton-sponge® i K_2CO_3 a la temperatura de reflux de toluè proporcionà el compost tetracíclic **9** amb un rendiment del 45%. El mateix compost s'obtingué per desprotecció en medi bàsic del compost tetracíclic **3**.

[8] Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev*. **2009**, *38*, 1099-1118.
[9] Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644-12645.



Aquests resultats posen de manifest que la reacció de Heck d'un halogenur vinílic sobre un doble enllaç inclòs en un sistema d'azocino[4,3-*b*]indole constitueix un bon procediment per a la formació del sistema bicíclic amb pont característic de la unitat superior de la vinorelbina. No obstant això, és necessari dur a terme nous experiments per tal d'esbrinar alguns aspectes de la reacció, com ara la naturalesa del compost **4** o la possibilitat de modular completament la regioselectivitat de l'etapa d'eliminació.

A continuació es relacionen algunes dades d'interès referents a la determinació estructural dels productes de ciclació. La part experimental corresponent a aquest treball no publicat es relaciona al Capítol 5 (Annex).

1. Determinació estructural del diè 3:

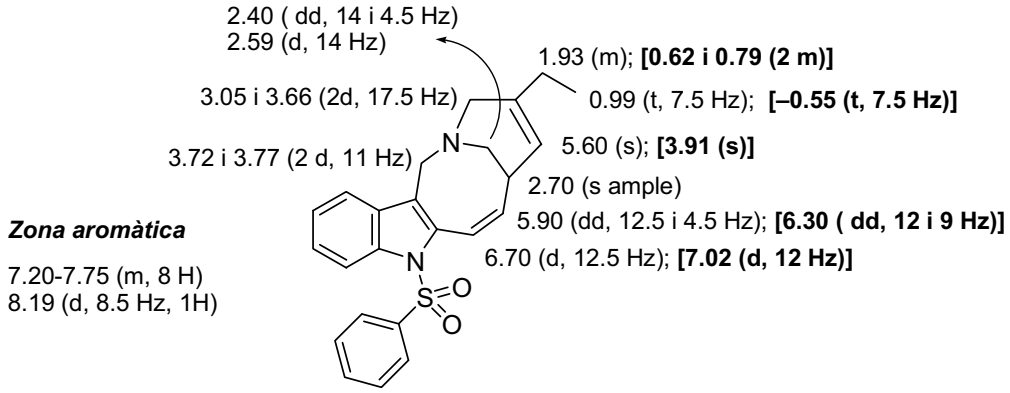
L'espectre d'^{1}H RMN (400 MHz) del diè **3**, enregistrat en $CDCl_3$, mostrà senyals molt amples, alguns d'ells duplicats, que indicaven l'existència de dues conformacions amb una barrera alta per a la interconversió. Quan s'enregistrà l'espectre d'^{1}H RMN a 50℃, la temperatura més alta compatible amb el dis solvent deuterat, els senyals encara eren massa amples per a la seva assignació, si bé s'observà la coalescència d'alguns dels senyals duplicats en senzills. Finalment, l'assignació estructural fou possible quan s'enregistrà l'espectre d'^{1}H RMN a -30℃, el qual mostrà senyals clars de dos confòrmers en proporció 2:1. L'espectre de ^{13}C RMN, enregistrat a -10℃, fou

concordant amb l'estructura proposada. L'estructura de **3** es confirmà completament mitjançant anàlisi per difracció de raigs X del corresponent picrat. Finalment, s'enregistrà també l'espectre de d'^{1}H RMN d'aquest picrat, el qual mostrà senyals clars de dos confòrmers en proporció 5:1.

Dades espectroscòpiques:

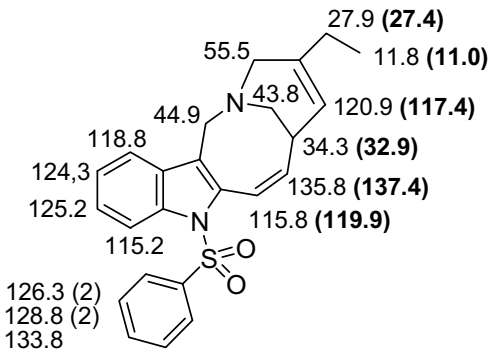
ESI-HRMS $[M + H]^+$ calculat per a $C_{24}H_{25}N_2O_2S$: 405.1631. Trobat: 405.1628.

^{1}H RMN ($CDCl_3$, 500 MHz, -30ºC, entre claudàtors i en negreta, de splaçaments químics del confòrmer minoritari):



(Assignació efectuada mitjançant ^{1}H-^{1}H g-COSY i HSQC)

^{13}C RMN ($CDCl_3$, 100.6 MHz, –10ºC, entre parèntesis i en negreta, desplaçaments químics del confòrmer minoritari):

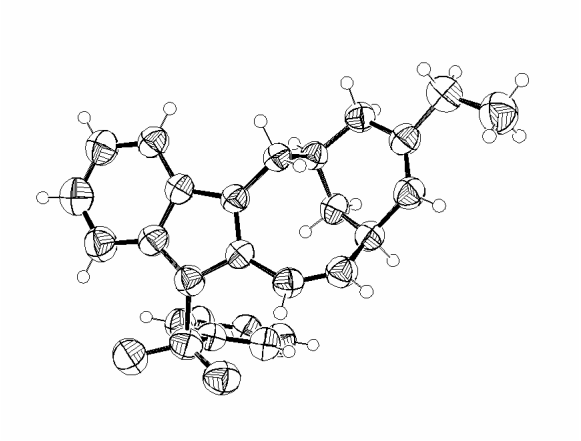


Carbonis quaternaris visibles

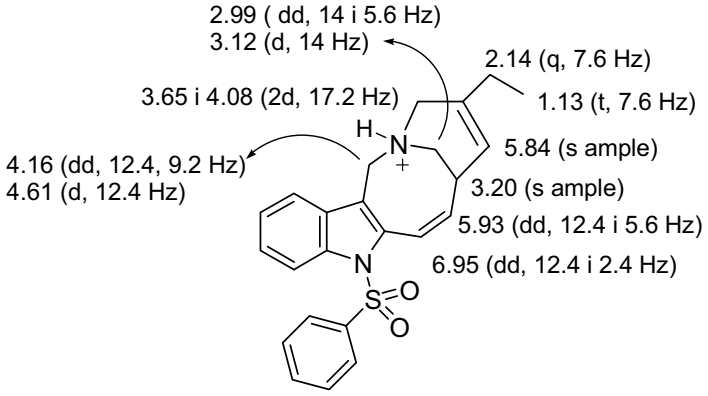
116.9
118.6
130.0
135.3
136.5
136.9

(Assignació efectuada mitjançant HSQC).

Representació **ORTEP** de **3.picrat** (l'anió no es representa):



^{1}H RMN (**3.picrat**, $CDCl_3$, 400 MHz, confòrmer majoritari):

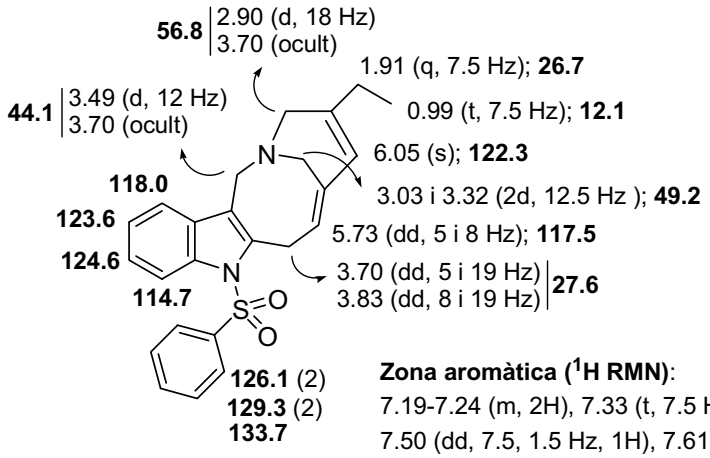


(Assignació efectuada mitjançant HSQC).

2. Dades espectroscòpiques del diè 5:

ESI-HRMS $[M + H]^+$ calculat per a $C_{24}H_{25}N_2O_2S$: 405.1631. Trobat: 405.1630.

^{1}H RMN ($CDCl_3$, 500 MHz) i **^{13}C RMN** ($CDCl_3$, 125.7 MHz, valors de δ en negreta):



Carbonis quaternaris visibles

128.9
131.0
133.5
136.4
137.6
139.2

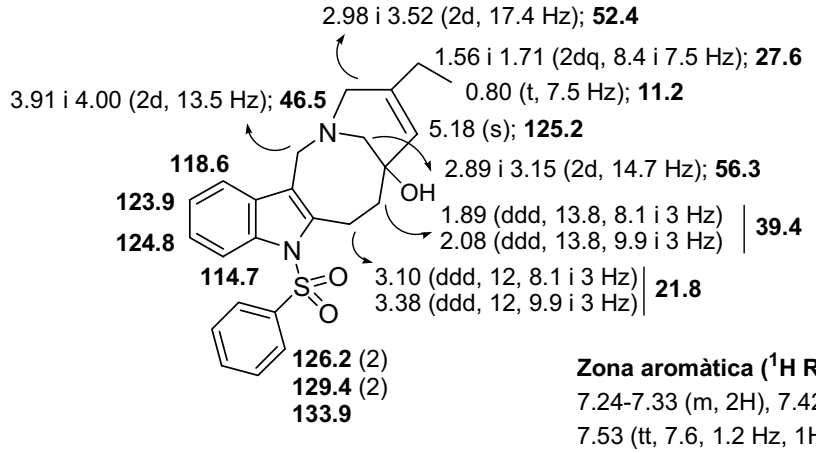
Zona aromàtica (^{1}H RMN):
7.19-7.24 (m, 2H), 7.33 (t, 7.5 Hz, 2H), 7.45 (tt, 7.5, 1.5 Hz, 1H), 7.50 (dd, 7.5, 1.5 Hz, 1H), 7.61 (m, 2H), 8.16 (d, 7.5 Hz, 1H)

(Assignació efectuada mitjançant ^{1}H-^{1}H g-COSY i HSQC.)

3. Dades espectroscòpiques del carbinol tetracíclic 6:

ESI-HRMS $[M + H]^+$ calculat per a $C_{24}H_{27}N_2O_3S$: 423.1737. Trobat: 423.1735.

^{1}H RMN ($CDCl_3$, 300 MHz) i **^{13}C RMN** ($CDCl_3$, 125.7 MHz, valors de δ en negreta):



Carbonis quaternaris visibles

128.8
136.3
139.1

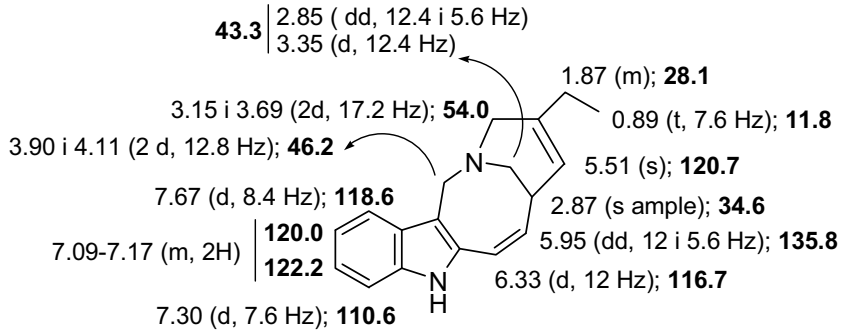
Zona aromàtica (^{1}H RMN):
7.24-7.33 (m, 2H), 7.42 (dd, 7.6, 1.2 Hz, 2H), 7.53 (tt, 7.6, 1.2 Hz, 1H), 7.57 (d, 8 Hz, 1H), 7.76 (m, 2H), 8.21 (dd, 7.2, 1.2 Hz, 1H)

(Assignació efectuada mitjançant ^{1}H-^{1}H g-COSY i HSQC)

4. Dades espectroscòpiques del diè 9:

ESI-HRMS $[M + H]^+$ calculat per a $C_{18}H_{21}N_2$: 265.1699. Trobat: 265.1698.

^{1}H RMN ($CDCl_3$, 400 MHz) i **^{13}C RMN** ($CDCl_3$, 100.5 MHz, valors de δ en negreta):



Carbonis quaternaris visibles

117.7
128.2
135.3
135.9
136.5

(Assignació efectuada mitjançant ^{1}H-^{1}H g-COSY i HSQC)

4. CONCLUSIONS

La present Tesi Doctoral es situa en el context de l'estudi d'estratègies sintètiques per a la formació d'anells en l'àrea heterocíclica. En particular, s'han avaluat les possibilitats sintètiques de la combinació de dues reaccions d'eficàcia prou reconeguda per a la formació d'enllaços carboni-carboni, la reacció de RCM i la reacció intramolecular de Heck d'halurs vinílics, per a la construcció de les estructures policícliques amb pont característiques dels alcaloides ervitsina i aparicina, així com també de la unitat superior de la vinorelbina. Els principals aconseguiments del treball i les conclusions més significatives que se'n deriven s'exposen a continuació:

- La reacció de RCM de diens indòlics ha mostrat ser un bon procediment per a la formació d'anells de 8 baules fusionats amb el nucli indòlic. L'eficiència de la ciclació, combinada amb la facilitat de preparació dels substrats diènics a partir de compostos indòlics senzills, determina que l'estratègia pugui ser emprada com a via d'accés a les subestructures tricícliques tant de l'alcaloide aparicina com de la unitat superior de la vinorelbina.

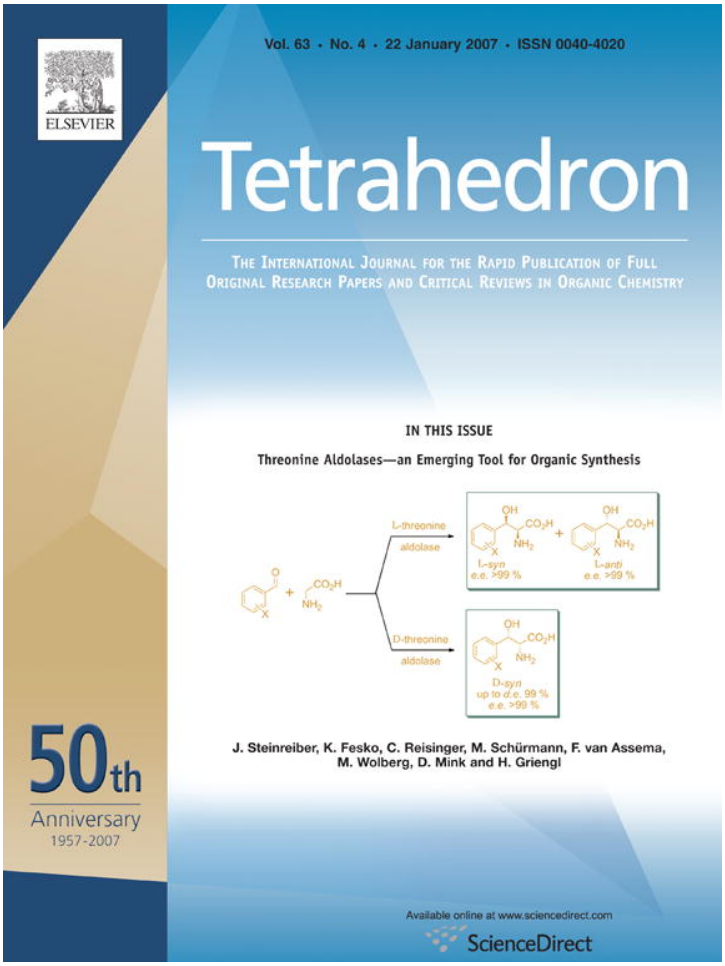
- L'aminació reductora d'indole-3-carbaldehids amb alquenilamines permet instal·lar cadenes d'alquenilaminometil a la posició 3 de l'heterocicle, d'interès per la preparació dels substrats diènics precursors de diversos azacicles per RCM. En el cas particular de 2-vinil-3-indolecarbaldehids, el procés d'aminació reductora no és compatible amb la presència d'un grup fenilsulfonil a l'àtom de nitrogen indòlic, ja que en comptes d'obtenir-se la corresponent amina secundària, s'observa la formació ràpida del nucli de tetrahidro-γ-carbolina. L'anulació és el resultat de l'addició conjugada de l'amina primària a l'agrupació d'aldehid γ,δ-insaturat del substrat, seguida d'un procés d'aminació reductora intramolecular.

- La metodologia de doble anulació RCM-Heck possibilita l'accés al sistema amb pont de 2-azabiciclo[4.3.1]decà característic de l'alcaloide ervitsina. En concret, la reacció de RCM quimioselectiva d'un triè indòlic genera un ciclohepta[*b*]indole, amb un doble enllaç adequat per al tancament subsegüent de l'anell de piperidina mitjançant un acoblament intramolecular de Heck amb l'halur vinílic, connectat al sistema anular a través de l'àtom de nitrogen. Si bé s'ha accedit al sistema tetracíclic de l'alcaloide que incorpora el substituent *E*-etilidè a la posició 20, l'estratègia no s'ha pogut estendre a la preparació de compostos tetracíclics funcionalitzats a la posició 3.

- S'ha dut a terme la primera síntesi total de l'alcaloide aparicina mitjançant una via sintètica concisa que implica com a etapas clau: (i) la reacció de RCM d'un diè indòlic per construir l'anell central de 8 baules; (ii) la isomerització promoguda per base del doble enllaç resultant de la ciclació, amb desprotecció concomitant de l'àtom de nitrogen indòlic; i (iii) la ciclació de Heck d'un halur vinílic per completar la formació de l'esquelet amb pont d'1-azabiciclo[4.2.2]decà i al mateix temps introduïr els dos dobles enllaços exocíclics de l'alcaloide.

- La inserció de l'agrupació de 2-etilpropè entre l'àtom de nitrogen alifàtic i la posició 4 d'un azocino[4,3-*b*]indole mitjançant una seqüència d'*N*-alquilació seguida de ciclació de Heck permet la formació del sistema amb pont d'1-azabiciclo[5.3.1]undecà característic de la unitat superior de la vinorelbina. Aquest resultat, juntament amb l'obtingut en el context de la síntesi de l'aparicina, posa de manifest la validesa dels acoblaments intramoleculars de Heck en els quals intervenen dobles enllaços inclosos en anells mitjans.

5. ANNEX: PUBLICACIONS



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Facile synthesis of azocino[4,3-*b*]indoles by ring-closing metathesis

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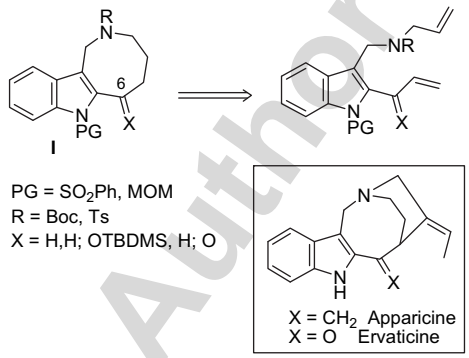
Abstract—The azocino[4,3-*b*]indole system, tricyclic substructure of the indole alkaloids apparicine and ervaticine, is efficiently assembled by ring-closing metathesis of 2-allyl-3-(allylaminomethyl)indoles. The metathesis sites are introduced into the indole nucleus by reductive amination of a 3-formyl derivative with allylamine, followed by α-lithiation with subsequent electrophilic trapping with acrolein.

1. Introduction

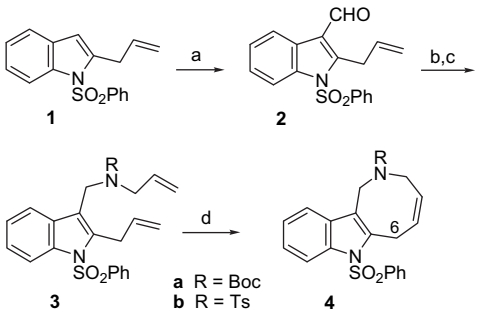
Ruthenium-catalyzed ring-closing metathesis (RCM)[1] has emerged as a powerful tool for the construction of a great variety of carbo- and heterocycles from acyclic precursors.[2] In particular, the RCM methodology has turned out to be very useful for the synthesis of medium-sized rings,[3] which is generally problematic due to disfavored entropic factors and transannular interactions. Our interest in the development of indole annulation methodologies led us to consider RCM reactions of indole-containing dienes[4,5] for the efficient construction of medium-sized indolo 2,3-fused carbo- and azacycles, which are common structural arrangements in many natural and synthetic bioactive compounds.[6] In this paper we report a direct synthetic approach to the azocino[4,3-*b*]indole system **I** by RCM of appropriate 2,3-dialkenylindoles incorporating a nitrogen atom in the tether linking the two double bonds (Scheme 1). It should be noted that **I** constitutes the tricyclic substructure of apparicine,[7] an indole alkaloid known for 40 years but still awaiting its first total synthesis,[8] and also the unprecedented 2-acylindole analogue ervaticine.[9]



Scheme 1. Synthetic plan.

2. Results and discussion

We set out to explore the feasibility of the protocol using model RCM precursors unfunctionalized at the benzylic indole α-position, such as 2-allyl-3-(allylaminomethyl)-indoles **3**.[10] For the preparation of these substrates, a fast formylation–reductive amination sequence starting from the known 2-allylindole **1**[11] was envisaged (Scheme 2). A strong electron-withdrawing benzenesulfonyl group was placed at the indole nitrogen to guarantee the stability of the proposed gramine-type intermediates. Thus, Friedel–Crafts reaction of **1** with Cl_2CHOMe in the presence of $TiCl_4$ gave the aldehyde **2** (90%), which was subjected to reductive amination with allylamine, followed by reaction of the resulting secondary amine with $(t\text{-BuOCO})_2O$ or TsCl. In this manner, the required RCM substrates **3a** or **3b**, bearing different



Scheme 2. Reagents and conditions: (a) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, −78 °C, 2 h, 90%; (b) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (c) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 65% (**3a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight 65% (**3b**); (d) $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 60% (**4a**), 89% (**4b**).

Keywords: Ring-closing metathesis; Indole; Indole alkaloids.
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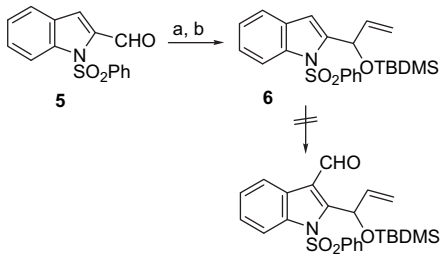
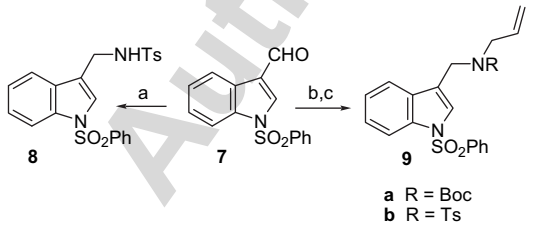
protecting groups at the aliphatic nitrogen, were obtained in 65% overall yield from **2**. Satisfactorily, ring closure of the *N*-Boc diene **3a** took place in refluxing dichloromethane in the presence of the first generation Grubbs catalyst to give the azocino[4,3-*b*]indole **4a** in 60% yield. The *N*-tosyl derivative **3b** proved to be a better substrate as it led to **4b** in a higher yield (89%).

With model azocino[4,3-*b*]indoles in hand, we sought to elaborate C-6 functionalized derivatives simply by extending the chemistry outlined above to an *O*-protected 2-(1-hydroxyallyl)indole. To this end, we selected silyl ether **6**, which was easily prepared from aldehyde **5**,[12] by reaction with vinylmagnesium bromide followed by protection of the resulting alcohol with *tert*-butyldimethylsilyl chloride (63% overall yield, Scheme 3). Disappointingly, we were not able to introduce the formyl group needed for the reductive amination step since **6** gave only a complex mixture upon subjection to the above Friedel–Crafts protocol.



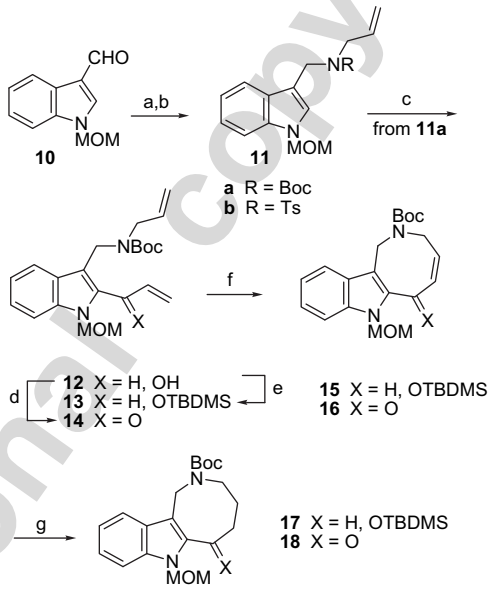
Scheme 3. Reagents and conditions: (a) $BrMgCH{=}CH_2$, THF, −78 °C–rt, overnight; (b) TBDMSCl, DMF, imidazole, 55 °C, overnight, 63%.

This unsuccessful result prompted us to change the order of the synthetic steps. Functionalization at the 2-position of a properly 3-substituted indole by α-metalation followed by electrophilic trapping seemed to be the logical solution. With this aim, we focused our attention on 3-(aminomethyl)-indoles **8** and **9**, which were available from indole-3-carbaldehyde **7**[13] through reductive amination techniques, using tosylamine or, as above, allylamine followed by acylation (Scheme 4). Unfortunately, treatment of these substrates with either LDA, *sec*-BuLi or *tert*-BuLi in THF under a variety of experimental conditions, followed by addition of DMF, HCOOMe, or acrolein led to the recovery of the starting product.



Scheme 4. Reagents and conditions: (a) $TsNH_2$, toluene, reflux, 24 h, then $NaBH_4$, MeOH, rt, 24 h, 70%; (b) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (c) $(t\text{-}BuOCO)_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 68% (**9a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight 67% (**9b**).

We reasoned that the replacement of the indole protecting group by a methoxymethyl (MOM) group could facilitate the α-lithiation, despite a probable reduction in stability of some synthetic intermediates due to the lower electron-withdrawing character of this moiety. Thus, we turned to aldehyde **10**[14] (Scheme 5), which was converted into the allylaminomethyl derivatives **11** under the usual conditions. As the tosyl compound **11b** partially decomposed under chromatographic purification, we decided to continue the synthesis only with the more stable *N*-Boc derivative **11a**, which could be isolated in a reproducible 72% yield.



Scheme 5. Reagents and conditions: (a) allylamine, $NaBH(OAc)_3$, AcOH, rt, overnight; (b) $(t\text{-}BuOCO)_2O$, 4:1 MeOH–Et_3N, reflux, 4 h, 72% (**11a**) or TsCl, Et_3N, CH_2Cl_2, rt, overnight (**11b**); (c) *t*-BuLi, THF, −78 °C, 2 h, then acrolein, −78 °C, 3.5 h, 79%; (d) MnO_2, CH_2Cl_2, rt, 60 h, 64%; (e) TBDMSCl, DMF, imidazole, 55 °C, overnight, 64%; (f) $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 85% (**15**) or $(Im)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, rt, overnight, 86% (**16**); (g) H_2, Pd/C, MeOH, 12 h, 80% (**17**), 82% (**18**).

We were pleased to find that the desired α-lithiation did take place from **11a** upon treatment with *tert*-BuLi in THF at −78 °C. After quenching with acrolein, the unstable alcohol **12** was isolated (79%) and immediately protected as the *tert*-butyldimethylsilyl ether **13** (64%) or, alternatively, oxidized with MnO_2 (64%) to the ketone **14**. Satisfactorily, when **13** was subjected to the previously used RCM conditions (first generation Grubbs catalyst in refluxing dichloromethane) the expected tricyclic compound **15** was obtained in good yield (85%). However, no cyclization was observed from ketone **14** under the above protocol, probably due to the presence of an electron-poor double bond, and only dimeric products coming from intermolecular metathesis reactions were formed. This problem was circumvented simply by using the more efficient second generation Grubbs catalyst at room temperature, leading to tricyclic ketone **16** in 86% yield. Finally, the saturated forms of the eight-membered heterocycles **17** and **18** were obtained by catalytic hydrogenation over Pd/C.

3. Conclusion

We have developed a new synthetic route to the azocino[4,3-*b*]indole system[15,16] relying on RCM of 2-allyl-3-(allylaminomethyl)indoles. The efficiency of the cyclization

combined with the easy preparation of the dienic precursors from simple indolic derivatives make this strategy attractive for the construction of medium-sized indolo 2,3-fused carbo- and azacycles, which are scaffolds found in many bioactive compounds.

4. Experimental

4.1. General methods

All nonaqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts was carried out over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure with a rotary evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 300 MHz (^{1}H) or 75.4 MHz (^{13}C) using Me_4Si as an internal reference.

4.1.1. 2-Allyl-1-(phenylsulfonyl)-3-indolecarbaldehyde (2). 2-Allylindole **1**[11] (0.7 g, 2.3 mmol) in CH_2Cl_2 (6 mL) was added to a solution of $TiCl_4$ (0.51 mL, 4.7 mmol) and Cl_2CHOCH_3 (0.4 mL, 4.7 mmol) in CH_2Cl_2 (6 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 2 h. The reaction mixture was diluted with H_2O, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (9:1 hexanes–AcOEt) to give aldehyde **2**: 0.69 g (90%); ^{1}H NMR δ 4.22 (m, 2H), 5.05 (dm, J=17.0, 1.1 Hz, 1H), 5.12 (dm, J=10.0, 1.1 Hz, 1H), 6.05 (m, 1H), 7.34–7.65 (m, 5H), 7.86 (m, 2H), 8.17 (m, 1H), 8.22 (m, 1H), 10.26 (s, 1H); ^{13}C NMR δ 29.5 (CH_2), 114.3 (CH), 117.6 (CH_2), 119.5 (C), 121.4 (CH), 125.1 (CH), 125.6 (CH), 126.0 (C), 126.6 (2CH), 129.4 (2CH), 134.2 (CH), 134.4 (CH), 135.9 (C), 138.4 (C), 148.8 (C), 185.6 (CO). Anal. Calcd for $C_{18}H_{15}NO_3S\cdot 1/4H_2O$: C, 65.52%; H, 4.73%; N, 4.24%. Found: C, 65.81%; H, 4.86%; N, 4.12%.

4.1.2. 2-Allyl-3-[(*N*-allyl-*N*-*tert*-butoxycarbonylamino)-methyl]-1-(phenylsulfonyl)indole (3a). Allylamine (0.15 mL, 2.0 mmol), $NaBH(OAc)_3$ (0.64 g, 3.0 mmol), and AcOH (0.06 mL, 1.1 mmol) were successively added to aldehyde **2** (0.33 g, 1.0 mmol) in CH_2Cl_2 (8 mL), and the mixture was stirred at rt overnight. The reaction mixture was diluted with H_2O, basified with solid Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the resulting residue was purified by flash chromatography (98:2 CH_2Cl_2–MeOH) to give the secondary amine: 0.32 g. This compound was dissolved in MeOH (8 mL), treated with Et_3N (2 mL) and (t-BuOCO)$_2$O (0.32 g, 1.46 mmol), and the resulting mixture was heated at reflux for 4 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 (15 mL) and washed successively with 1 N HCl and brine. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (CH_2Cl_2) to give **3a**: 0.30 g (65%); ^{1}H NMR (5:1 mixture of rotamers, major rotamer) δ 1.49 (s, 9H), 3.40 (br s, 2H), 3.83 (br d, J=6.0 Hz, 2H), 4.55 (s, 2H), 4.90 (m, 2H), 5.01 (m, 2H), 5.60 (m, 1H), 5.95 (m, 1H), 7.20–7.65 (m, 6H), 7.70 (m, 2H), 8.20 (d, J=7.5 Hz, 1H); ^{13}C NMR (major rotamer) δ 28.4 ($3CH_3$), 29.9 (CH_2), 38.5 (CH_2), 47.0 (CH_2), 79.9 (C), 115.0 (CH), 115.9 (CH_2), 116.2 (CH_2), 119.3 (CH), 123.7 (CH), 124.5 (CH), 126.2 (2CH), 129.0 (2CH), 129.8 (C), 133.4 (CH), 133.5 (CH), 134.9 (CH), 136.5 (C), 136.9 (C), 138.7 (C), 155.5 (CO); HRMS calcd for $C_{26}H_{30}N_2O_4S$ 466.1926, found 466.1932.

4.1.3. 2-Allyl-3-[(*N*-allyl-*N*-tosylamino)methyl]-1-(phenylsulfonyl)indole (3b). Aldehyde **2** (0.33 g, 1.0 mmol) was allowed to react as above with allylamine and the resulting secondary amine (0.32 g) was dissolved in CH_2Cl_2 (10 mL) and treated with tosyl chloride (0.19 g, 1.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic extracts were dried and concentrated and the residue was chromatographed (flash, CH_2Cl_2) to give **3b**: 0.34 g (65%); mp 118 °C (Et_2O); ^{1}H NMR δ 2.44 (s, 3H), 3.52 (d, J=6.3 Hz, 2H), 3.76 (dm, J=6.0 Hz, 2H), 4.36 (s, 2H), 4.66 (dd, J=17.0, 1.5 Hz, 1H), 4.72 (dd, J=10.0, 1.5 Hz, 1H), 4.92 (dd, J=17.0, 1.5 Hz, 1H), 4.99 (dd, J=10.0, 1.5 Hz, 1H), 5.23 (m, 1H), 5.93 (m, 1H), 7.25–7.75 (m, 12H), 8.20 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 21.5 (CH_3), 29.9 (CH_2), 41.5 (CH_2), 49.4 (CH_2), 114.9 (CH), 115.5 (C), 116.3 (CH_2), 118.1 (CH_2), 119.5 (CH), 123.8 (CH), 124.7 (CH), 126.2 (2CH), 127.2 (2CH), 129.0 (2CH), 129.1 (C), 129.7 (2CH), 132.4 (CH), 133.6 (CH), 134.7 (CH), 136.5 (C), 137.2 (C), 139.2 (C), 139.7 (C), 143.4 (C). Anal. Calcd for $C_{28}H_{28}N_2O_4S_2$: C, 64.59%; H, 5.41%; N, 5.38%. Found: C, 64.67%; H, 5.43%; N, 5.35%.

4.1.4. 2-(*tert*-Butoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (4a). $(PCy_3)_2(Cl)_2Ru$=CHPh (first generation Grubbs catalyst, 10 mol %) was added under Ar to a solution of amine **3a** (90 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (5 mL) and the resulting mixture was heated at reflux overnight. The reaction mixture was filtered and concentrated. Flash chromatography of the crude residue (1:1 hexanes–AcOEt) gave **4a**: 50 mg (60%); ^{1}H NMR (1:1 mixture of rotamers) δ 1.25 and 1.44 (2s, 9H), 3.82 (m, 2H), 3.88 and 4.02 (2br s, 2H), 4.55 and 4.68 (2s, 2H), 5.60 and 5.71 (2m, 1H), 5.85 (m, 1H), 7.22–7.53 (m, 7H), 7.73 (m, 1H), 8.20 (m, 1H); ^{13}C NMR δ 23.4 (CH_2), 28.3 ($3CH_3$), 42.6 (CH_2), 45.9 and 46.5 (CH_2), 79.9 (C), 114.8 (CH), 117.8 (CH), 118.6 (C), 123.3 (CH), 124.2 (CH), 126.2 (2CH), 127.1 (CH), 128.2 (CH), 129.0 (C), 129.1 (2CH), 133.5 (CH), 136.0 (2C), 139.0 (C), 155.0 (CO). Anal. Calcd for $C_{24}H_{26}N_2O_4S\cdot 1/2H_2O$: C, 64.36%; H, 6.08%; N, 6.25%. Found: C, 64.36%; H, 5.94%; N, 6.12%.

4.1.5. 7-(Phenylsulfonyl)-2-tosyl-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (4b). Operating as above, from amine **3b** (0.1 g, 0.19 mmol) **4b** was obtained: 80 mg (89%); ^{1}H NMR (^{1}H COSY) δ 2.40 (s, 3H, Me), 3.76 (d, J=6.6 Hz, 2H, 3-H), 3.98 (d, J=6.9 Hz, 2H, 6-H), 4.51 (s, 2H, 1-H), 5.42 (m, 1H, 4-H), 5.92 (m, 1H, 5-H), 7.20–7.70 (m, 12H, Ar), 8.20 (d, J=7.5 Hz, 1H, 8-H); ^{13}C NMR (Hetcor) δ 21.5 (CH_3), 25.0 (C-6), 42.1 (C-1), 45.0 (C-3), 114.8 (C-8), 115.3 (C-11b), 117.9 (C-11), 123.6 (C-10), 124.6 (C-9), 125.2 (C-4), 126.1 (2CH), 127.0 (2CH), 129.0 (C-11a), 129.2 (2CH), 129.6 (2CH), 129.8 (C-5), 133.7 (CH), 136.0 (2C), 136.4 (C), 138.8 (C), 143.3 (C); HRMS calcd for $C_{26}H_{24}N_2O_4S_2$ 492.6118, found 492.6110.

4.1.6. 2-[1-(*tert*-Butyldimethylsilyloxy)-2-propenyl]-1-(phenylsulfonyl)indole (6). $BrMgCH{=}CH_2$ (1 M solution in THF, 2.96 mmol) was added to a solution of aldehyde **5**[12] (0.65 g, 2.28 mmol) in THF (15 mL) at −78 °C and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with 10% aqueous NH_4Cl and extracted with Et_2O. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (9:1 hexanes–AcOEt) to give 1-(phenylsulfonyl)-2-(1-hydroxy-2-propenyl)indole (0.57 g). This compound was dissolved in DMF (5 mL) and treated with TBDMSCl (0.40 g, 2.7 mmol) and imidazole (0.30 g, 4.5 mmol) at 55 °C overnight. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (95:5 hexanes–AcOEt) of the residue gave **6**: 0.61 g (63%); ^{1}H NMR δ −0.01 and 0.10 (2s, 6H), 0.95 (s, 9H), 5.15 (d, J=10.0 Hz, 1H), 5.40 (d, J=15 Hz, 1H), 5.90 (br s, 1H), 6.20 (m, 1H), 6.85 (s, 1H), 7.25–7.50 (m, 6H), 7.60 (m, 2H), 8.15 (d, J=7.5 Hz, 1H); ^{13}C NMR δ −4.93 and −4.78 ($2CH_3$), 18.3 (C), 25.8 ($3CH_3$), 69.5 (CH), 109.8 (CH), 114.5 (CH_2), 115.0 (CH), 120.8 (CH), 123.8 (CH), 124.3 (CH), 126.3 (2CH), 129.0 (2CH), 129.9 (C), 133.6 (CH), 137.7 (C), 138.6 (C), 139.8 (CH), 144.4 (C); HRMS calcd for $C_{23}H_{29}NO_3SSi$ 427.1637, found 427.1640.

4.1.7. 1-(Phenylsulfonyl)-3-(tosylaminomethyl)indole (8). A solution of aldehyde **7**[13] (0.5 g, 1.75 mmol) and tosylamine (0.9 g, 5.25 mmol) in dry toluene (15 mL) was heated at reflux (Dean–Stark) for 24 h. The solvent was removed and the residue was dissolved in MeOH (10 mL) and treated with $NaBH_4$ (66 mg, 1.75 mmol) at rt for 24 h. The solvent was removed and the residue was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and concentrated and the resulting residue was purified by flash chromatography (6:4 hexanes–AcOEt) to give tosylamine **8**: 0.54 g (70%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 4.22 (d, J=6.0 Hz, 1H), 5.04 (br s, 2H), 7.20–7.90 (m, 13H); ^{13}C NMR δ 21.5 (CH_3), 38.6 (CH_2), 113.4 (CH), 117.6 (C), 119.6 (CH), 123.3 (CH), 124.5 (CH), 125.0 (CH), 126.3 (2CH), 126.6 (2CH), 129.2 (2CH), 129.6 (2CH, C), 133.8 (CH), 136.1 (C), 137.8 (C), 138.9 (C), 143.4 (C); HRMS calcd for $C_{22}H_{20}N_2O_4S_2$ 440.0864, found 440.0857.

4.1.8. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(phenylsulfonyl)indole (9a). Allylamine (0.34 mL, 4.6 mmol), $NaBH(OAc)_3$ (1.46 g, 6.9 mmol), and AcOH (0.13 mL, 2.3 mmol) were successively added to aldehyde **7** (0.65 g, 2.3 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with H_2O, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated. Flash chromatography of the residue (98:2 CH_2Cl_2–MeOH) gave the secondary amine (0.5 g). This compound was dissolved in MeOH (16 mL) and treated with $(t\text{-BuOCO})_2O$ (0.57 g, 2.65 mmol) and Et_3N (7.4 mL, 5.3 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed and the residue was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic extracts were dried and concentrated and the resulting residue was chromatographed (flash, 95:5 hexanes–AcOEt) to give **9a**: 0.66 g (68%); ^{1}H NMR δ 1.48 (s, 9H), 3.70 (br s, 2H), 4.52 (br s, 2H), 5.10 (m, 2H), 5.65 (m, 1H), 7.20–7.65 (m, 7H), 7.85 (m, 2H), 8.05 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 28.3 ($3CH_3$), 40.8 (CH_2), 48.0 (CH_2), 79.9 (C), 113.5 (CH), 116.3 (CH_2), 119.6 (CH), 120.3 (CH), 123.2 (CH), 124.6 (CH), 124.8 (CH), 126.5 (2CH), 128.8 (C), 129.1 (2CH), 133.4 (CH), 133.7 (CH), 135.3 (C), 137.9 (C), 155.3 (CO); HRMS calcd for $C_{23}H_{26}N_2O_4S$ 426.1613, found 426.1610.

4.1.9. 3-[(*N*-Allyl-*N*-tosyl)aminomethyl]-1-(phenylsulfonyl)indole (9b). Aldehyde **7** (0.65 g, 2.3 mmol) was allowed to react as above with allylamine and the resulting secondary amine was dissolved in CH_2Cl_2 (12 mL) and treated with tosyl chloride (0.33 g, 1.75 mmol) and Et_3N (0.25 mL, 1.75 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine prior to drying and solvent evaporation. The resulting residue was purified by flash chromatography (1:1 hexanes–CH_2Cl_2) to give **9b**: 0.74 g (67%); mp 108 °C (Et_2O); ^{1}H NMR δ 2.44 (s, 3H), 3.70 (d, J=6.3 Hz, 2H), 4.43 (s, 2H), 4.90 (m, 2H), 5.37 (m, 1H), 7.25–7.95 (m, 13H), 8.01 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 21.4 (CH_3), 41.8 (CH_2), 49.5 (CH_2), 113.3 (CH), 117.2 (C), 118.9 (CH_2), 120.1 (CH), 123.4 (CH), 125.0 (CH), 125.3 (CH), 126.4 (2CH), 126.9 (2CH), 129.1 (2CH), 129.5 (C), 129.6 (2CH), 131.9 (CH), 133.7 (CH), 135.1 (C), 136.7 (C), 137.7 (C), 143.4 (C). Anal. Calcd for $C_{25}H_{24}N_2O_4S_2$: C, 62.48%; H, 5.03%; N, 5.82%. Found: C, 62.58%; H, 5.21%; N, 5.69%.

4.1.10. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)indole (11a). Aldehyde **10**[14] (1.75 g, 9.2 mmol) in CH_2Cl_2 (30 mL) was allowed to react with allylamine (1.41 mL, 18.8 mmol) and then with $(t\text{-BuOCO})_2O$ (3.67 g, 16.8 mmol) as described in Section 4.1.8. After work-up and flash chromatography (7:3 hexanes–AcOEt), **11a** was obtained: 2.20 g (72%); ^{1}H NMR (50 °C) δ 1.50 (s, 9H), 3.21 (s, 3H), 3.74 (br s, 2H), 4.59 (s, 2H), 5.10 (m, 2H), 5.47 (s, 2H), 5.73 (m, 1H), 7.08 (s, 1H), 7.10–7.30 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H); ^{13}C NMR (50 °C) δ 28.5 ($3CH_3$), 40.6 (CH_2), 47.9 (CH_2), 55.8 (CH_3), 77.3 (CH_2), 79.6 (C), 109.8 (CH), 113.0 (C), 116.0 (CH_2), 119.6 (CH), 120.1 (CH), 122.4 (CH), 127.1 (CH), 128.2 (C), 134.1 (CH), 136.9 (C), 155.4 (CO). Anal. Calcd for $C_{19}H_{26}N_2O_3\cdot 1/4H_2O$: C, 68.14%; H, 7.97%; N, 8.36%. Found: C, 68.30%; H, 8.07%; N, 8.26%.

4.1.11. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-2-(1-hydroxy-2-propenyl)-1-(methoxymethyl)indole (12). *tert*-BuLi (1.7 M in pentane, 0.87 mmol) was slowly added under Ar to a solution of indole **11a** (0.22 g, 0.72 mmol) in anhydrous THF (10 mL) at −78 °C, and the resulting solution was stirred for 2 h at −78 °C. Then, acrolein (0.11 mL, 1.8 mmol) was added and the mixture was stirred at −78 °C for 3.5 h. The reaction mixture was poured into 10% aqueous NH_4Cl and extracted with Et_2O. The organic extracts were dried and concentrated and the residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give alcohol **12**: 0.22 g (79%, unstable oil); ^{1}H NMR (gHSQC,) δ 1.49 (s, 9H, $3CH_3$), 3.26 (s, 3H, OMe), 3.75 (m, 2H, $NCH_2CH{=}$), 4.68 and 4.73 (2d, J=15.3 Hz, 2H, indCH_2N), 5.09 (m, 1H, $CH_2{=}$), 5.13 (m, 1H, $CH_2{=}$), 5.24 (dm, J=10.8 Hz, 1H, $CH_2{=}$), 5.35 (dm, J=17.0 Hz, 1H, $CH_2{=}$), 5.47 and 5.62 (2d, J=10.8 Hz, 2H, CH_2OMe),

5.72 (m, 2H, CHOH, CH═), 6.15 (m, 1H, CH═), 7.15 (m, 1H, ind 5-H), 7.24 (m, 1H, ind 6-H), 7.41 (d, J=8.1 Hz, 1H, ind 7-H), 7.68 (dm, J=8.1 Hz, 1H, ind 4-H); ^{13}C NMR δ 28.5 ($3CH_3$), 39.3 (CH_2), 47.9 (CH_2), 55.8 (CH_3), 66.6 (CH), 74.5 (CH_2), 80.0 (C), 109.5 (CH), 111.6 (C), 115.1 (CH_2), 115.9 (CH_2), 119.5 (CH), 120.5 (CH), 122.8 (CH), 128.0 (C), 134.0 (CH), 137.6 (C), 137.9 (C), 139.0 (CH), 155.7 (CO).

4.1.12. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-2-[1-(*tert*-butyldimethylsilyloxy)-2-propenyl]-1-(methoxymethyl)indole (13). A solution of alcohol **12** (0.21 g, 0.5 mmol), TBDMSCl (0.25 g, 1.6 mmol), and imidazole (0.15 g, 2.1 mmol) in DMF (3 mL) was heated under Ar at 55 °C overnight. The reaction mixture was partitioned between 10% aqueous Na_2CO_3 and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (9:1 hexanes–AcOEt) of the residue gave **13**: 0.18 g (64%); IR (film) 1690; ^{1}H NMR δ 0.19 (s, 6H), 0.93 (s, 9H), 1.55 (s, 9H), 3.32 (s, 3H), 3.60 (br s, 2H), 4.77 (br s, 2H), 5.14 (m, 2H), 5.20 (dm, J=9.0 Hz, 1H), 5.40 (d, J=15.0 Hz, 1H), 5.54 and 5.76 (2d, J=10.0 Hz, 2H), 5.77 (m, 2H), 6.20 (m, 1H), 7.18 (m, 1H), 7.27 (m, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H); ^{13}C NMR δ −4.6 ($2CH_3$), 18.6 (C), 26.1 ($3CH_3$), 28.8 ($3CH_3$), 38.7 (CH_2), 47.3 (CH_2), 56.0 (CH_3), 68.1 (CH), 75.8 (CH_2), 80.0 (C), 109.9 (C), 110.8 (CH), 114.6 (CH_2), 116.0 (CH_2), 119.5 (CH), 120.6 (CH), 122.8 (CH), 128.4 (C), 134.1 (CH), 137.6 (CH), 138.3 (C), 139.9 (C), 155.8 (CO); HRMS calcd for $C_{28}H_{44}N_2O_4Si$ 500.3070, found 500.3062.

4.1.13. 3-[(*N*-Allyl-*N*-*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)-2-propenoylindole (14). Alcohol **12** (39 mg, 0.1 mmol) and MnO_2 (87 mg, 1.0 mmol) in CH_2Cl_2 (6 mL) were stirred at rt for 60 h. The reaction mixture was filtered through Celite and the filtrate was concentrated. The resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give ketone **14**: 25 mg (64%); ^{1}H NMR δ 1.50 (s, 9H), 3.19 (s, 3H), 3.55 (br s, 2H), 4.86 (s, 2H), 4.90 (dm, J=15.0 Hz, 1H), 5.05 (dm, J=9.6 Hz, 1H), 5.60 (br s, 1H), 5.64 (s, 2H), 5.99 (dd, J=10.5, 1.5 Hz, 1H), 6.30 (dd, J=17.1, 1.5 Hz, 1H), 6.89 (dd, J=17.1, 10.5 Hz, 1H), 7.22 (m, 1H), 7.40 (m, 1H), 7.50 (d, J=7.8 Hz, 1H), 7.80 (br d, J=7.8 Hz, 1H); ^{13}C NMR δ 28.7 ($3CH_3$), 40.0 (CH_2), 47.5 (CH_2), 56.3 (CH_3), 75.4 (CH_2), 80.0 (C), 111.1 (CH), 116.6 (CH_2), 119.4 (C), 121.8 (CH), 122.2 (CH), 126.2 (CH), 127.3 (C), 131.2 (CH_2), 133.8 (CH), 135.2 (C), 137.3 (CH), 138.9 (C), 155.8 (CO), 187.7 (CO); HRMS calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2033.

4.1.14. 2-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsilyloxy)-7-(methoxymethyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (15). Diene **13** (0.17 g, 0.33 mmol) was allowed to react with $(PCy_3)_2(Cl)_2Ru$═CHPh (10 mol %) in CH_2Cl_2 (9 mL) as described in Section 4.1.4. After work-up and flash chromatography (95:5 hexanes–AcOEt), compound **15** was obtained: 0.135 g (85%); ^{1}H NMR (400 MHz, gHSQC, 1:1 mixture of rotamers) δ 0.07 (s, 6H, CH_3), 0.91 (s, 9H, CH_3), 1.46 and 1.49 (2s, 9H, CH_3), 3.18 (s, 3H, OCH_3), 3.50, 3.75, and 3.96 (3m, 2H, 3-H), 4.52, 4.68, 4.87, and 5.10 (4d, J=16.0 Hz, 2H, 1-H), 5.45 and 5.63 (2m, 1H, 5-H), 5.63 and 5.83 (2m, 2H, OCH_2), 5.91 and 6.03 (2m, 1H, 4-H), 6.18 (br s, 1H, 6-H), 7.16 (t, J=8.0 Hz, 1H, 10-H), 7.21 (t, J=8.0 Hz, 1H, 9-H), 7.45 (d, J=8.0 Hz, 1H, 8-H), 7.57 (d, J=8.0 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, gHSQC, 1:1 mixture of rotamers) δ −4.6 ($2CH_3$), 18.4 (C), 26.0 ($3CH_3$), 28.7 and 28.8 ($3CH_3$), 41.2 and 41.6 (C-1), 43.9 and 44.3 (C-3), 55.9 (OCH_3), 66.4 and 66.5 (C-6), 75.2 and 75.4 (CH_2O), 79.8 and 80.2 (C), 109.5 and 109.6 (C), 110.2 and 110.3 (C-8), 118.4 and 118.5 (C-11), 120.3 and 120.4 (C-10), 122.3 and 122.4 (C-9), 126.1 and 126.5 (C-5), 127.8 and 127.9 (C), 136.1 and 136.3 (C-4), 136.9 (C), 137.3 (C), 155.3 and 155.4 (CO); HRMS calcd for $C_{26}H_{40}N_2O_4Si$ 472.2757, found 472.2750.

4.1.15. 2-(*tert*-Butoxycarbonyl)-7-(methoxymethyl)-6-oxo-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (16). (Im)-$(PCy_3)(Cl)_2Ru$═CHPh (second generation Grubbs catalyst, 10 mol %) was added under Ar to a solution of ketone **14** (25 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was filtered, the filtrate was concentrated, and the resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give **16**: 20 mg (86%); ^{1}H NMR (400 MHz) δ 1.48 (br s, 9H), 3.27 (s, 3H), 3.91 (br s, 2H), 4.83 (s, 2H), 5.99 (s, 2H), 6.44 (m, 1H), 6.63 (d, J=11.7 Hz, 1H), 7.26 (m, 1H), 7.43 (m, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.90 (m, 1H); ^{13}C NMR (100.6 MHz) δ 28.8 ($3CH_3$), 37.2 (CH_2), 39.6 (CH_2), 56.3 (CH_3), 75.4 (CH_2), 81.1 (C), 111.6 (CH), 121.4 (CH, C), 122.0 (CH), 126.5 (C), 127.6 (CH), 133.7 (C), 135.7 (CH), 138.4 (C), 139.9 (CH), 154.6 (CO), 184.2 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_4\cdot 1/2H_2O$: C, 65.74%; H, 6.90%; N, 7.67%. Found: C, 65.85%; H, 6.66%; N, 7.65%.

4.1.16. 2-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsilyloxy)-7-(methoxymethyl)-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (17). Compound **15** (63 mg, 0.13 mmol) dissolved in MeOH (6 mL) was hydrogenated over Pd/C (5%, 3.5 mg) for 12 h. The catalyst was filtered, the filtrate was concentrated, and the resulting residue was purified by flash chromatography (8:2 hexanes–AcOEt) to give azocinoindole **17**: 51 mg (80%); ^{1}H NMR (400 MHz) δ 0.08 (s, 3H), 0.93 (s, 9H), 1.46 and 1.55 (2s, 9H), 1.8 (m, 2H), 2.15 (m, 1H), 2.90 (m, 1H), 3.23 (s, 3H), 3.50 and 3.85 (2m, 2H), 4.85 (m, 2H), 5.51 (m, 1H), 5.56 and 5.68 (2d, J=14.4 Hz, 2H), 7.10–7.26 (m, 2H), 7.42 (d, J=8.0 Hz, 1H), 7.75 (m, 1H); ^{13}C NMR (1:1 mixture of rotamers) δ −4.64 ($2CH_3$), 18.5 (C), 24.0 and 24.1 (CH_2), 26.2 ($3CH_3$), 29.0 ($3CH_3$), 36.9 and 37.3 (CH_2), 39.4 and 39.7 (CH_2), 43.9 and 44.2 (CH_2), 56.0 (CH_3), 67.4 (CH), 74.6 (CH_2), 79.9 (C), 109.5 and 109.7 (CH), 110.4 and 110.5 (C), 119.1 and 119.5 (CH), 120.3 and 120.5 (CH), 122.4 (CH), 127.99 and 128.5 (C), 137.5 (C), 139.5 (C), 155.4 (CO); HRMS calcd for $C_{26}H_{42}N_2O_4Si$ 474.7083, found 474.7078.

4.1.17. 2-(*tert*-Butoxycarbonyl)-6-oxo-7-(methoxymethyl)-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (18). Operating as above, from **16** (0.28 g, 0.78 mmol) azocinoindole **18** was obtained after flash chromatography (6:4 hexanes–AcOEt): 0.23 g (82%); ^{1}H NMR (1:1 mixture of rotamers) 1.19 and 1.45 (2s, 9H), 2.10 (br, 2H), 2.95 (br, 2H), 3.21 (s, 3H), 3.55 and 3.65 (2m, 2H), 4.80 and 4.90 (2br s, 2H), 5.73 (br, 2H), 7.20 (t, J=8.0 Hz, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.50 (br d, J=8.0 Hz, 1H), 7.70 (m, 1H); ^{13}C NMR (1:1 mixture of rotamers) 25.3 and 25.6 (CH_2),

28.2 and 28.3 ($3CH_3$), 41.7 and 41.9 (CH_2), 43.4 and 44.1 (CH_2), 46.1 and 47.9 (CH_2), 55.8 (CH_3), 74.7 (CH_2), 80.0 (C), 110.7 and 110.9 (CH), 120.2 and 120.5 (CH), 121.3 and 121.4 (CH), 122.3 (C), 125.8 and 126.0 (CH, C), 132.5 (C), 137.8 (C), 155.4 (CO), 197.6 and 198.2 (CO); HRMS calcd for $C_{20}H_{26}N_2O_4$ 358.1892, found 358.1887.

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References and notes

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Preparation of RCM substrates for azepinoindole synthesis: reductive amination versus tetrahydro-γ-carboline formation

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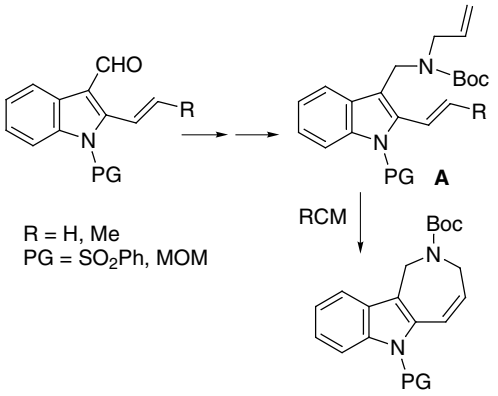
Dedicated to Professor Joaquín Plumet on the occasion of his 60th Birthday

Abstract—Treatment of *N*-(phenylsulfonyl)-2-vinyl-3-indolecarbaldehydes with primary aliphatic amines under mild reductive amination conditions leads to tetrahydro-γ-carbolines in high yield. The process can be suppressed by changing the protecting group at the indole nitrogen for a methoxymethyl group, thus allowing the preparation of RCM substrates for azepinoindole synthesis.

Ruthenium-catalysed ring-closing metathesis (RCM) reactions[1] are well-established processes for the construction of a great variety of nitrogen heterocycles.[2] In this context, cyclisations of indole-containing dienes[3] are particularly interesting as the resulting heterocyclic systems constitute structural arrangements present in many natural and medicinal compounds.[4] Our interest in the synthesis of azacycles fused to the 2,3-position of the indole ring[5] led us to study RCM reactions of 2-vinyl-3-(allylaminomethyl)indoles (for instance **A**, Scheme 1) as a synthetic entry to azepino[4,3-*b*]indoles. We planned to prepare the required RCM substrates from the corresponding *N*-protected (phenylsulfonyl or methoxymethyl) 3-indolecarbaldehydes, using simple reductive amination techniques followed by acylation of the aliphatic nitrogen.



Scheme 1. Synthetic plan to azepino[4,3-*b*]indoles.

Our attention was first focused on the indole *N*-phenylsulfonyl series as this strong electron-withdrawing substituent would guarantee the stability of the proposed gramine-type intermediates. Rather surprisingly, when 3-indolecarbaldehyde **1**[6] was treated with allylamine and $NaBH(OAc)_3$ in the presence of acetic acid in dichloromethane at room temperature, tetrahydro-γ-carboline **4a**[7] was isolated in high yield (90%, Scheme 2). No trace of the expected secondary amine **6a** was detected in the reaction mixture.

Initially, this unexpected result was rationalised considering that the imine **B** (Scheme 3), coming from the reaction of the primary amine with the aldehyde carbonyl group, would not be reduced by the hydride. Instead it would undergo cyclisation upon the alkene moiety, most probably through an electrocyclic reaction involving the indole 2,3-bond. Subsequent reduction of the resulting tetracycle **C** (for instance, through iminium cation **E**) would account for the formation of the tetrahydro-γ-carboline nucleus. In fact, we were aware that thermal

Keywords: Reductive amination; Tetrahydro-γ-carbolines; Ring-closing metathesis; Azepinoindoles.
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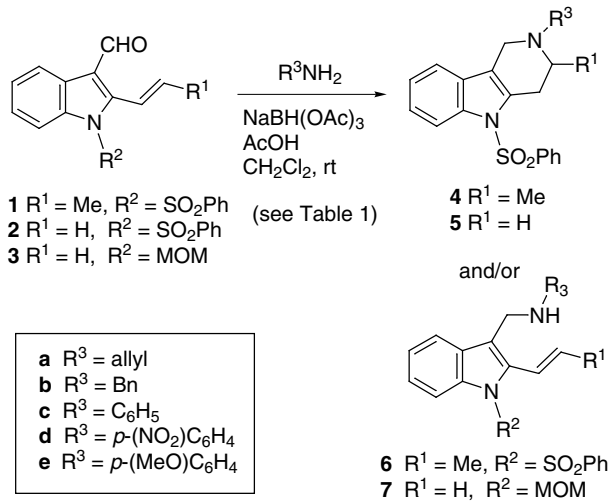
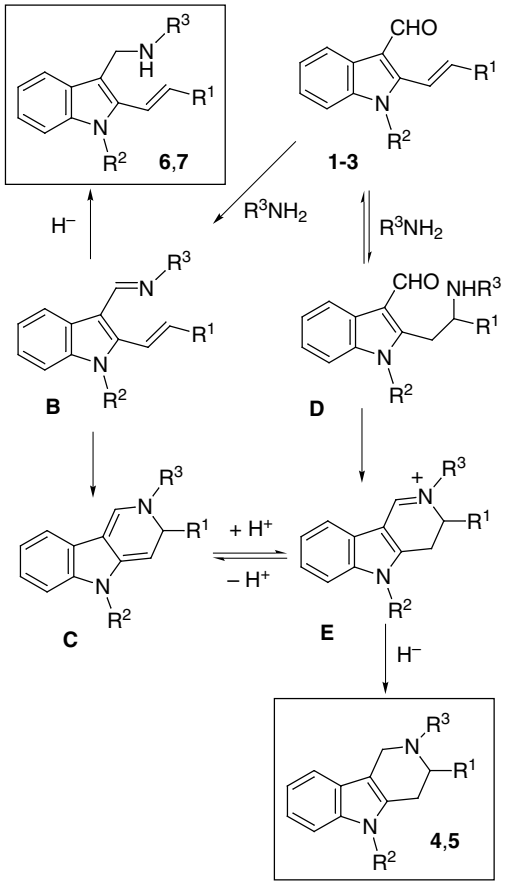


Scheme 2.

electrocyclic ring closures from the related indole-containing 1,3,5-hexatriene systems are common in the literature.[8–11] However, these substrates can be generally isolated and so the required temperatures for their cyclisation are usually high (>100 °C). From 2,3-divinylindoles, fully aromatic carbazoles are obtained after the in situ oxidation of the initially formed dihydro derivatives.[8] Closely related to our work, Hibino has exploited the cyclisation of vinyl oximes for the construction of β-[9] as well as γ-carbolines,[10] the aromaticity being achieved after dehydration. Cyclisations of vinyl imines, although less common, are also known.[11,12] To the best of our knowledge, no examples of electrocyclisations leading to tetrahydrocarbazoles or tetrahydrocarbolines after reduction have been reported.

Taking into account the mildness of our reaction conditions and the fact that the proposed imine intermediate was not present in the crude reaction mixture when the above experimental protocol was reproduced *without* $NaBH(OAc)_3$,[13] we envisaged an alternative mechanistic interpretation in which the tetrahydrocarboline ring would be produced by the initial conjugate addition of the primary amine to the γ,δ-unsaturated aldehyde.[14] This reversible step would be followed by the intramolecular reductive amination of the resulting secondary amine (**D**, Scheme 3), which would drive the reaction to completion.

With the aim of gaining more insight into the above annulation process, we examined the behaviour of other primary amines towards aldehyde **1** or the simpler derivative **2**[15] under the same set of conditions.[16] As can be observed in Table 1, the reaction with benzylamine proceeded along the same lines as described previously with allylamine, either from **1** or **2**, to give tetrahydro-γ-carbolines **4b**[17] or **5b**[18] as the only products (entries 2 and 3). Nevertheless, aniline exhibited a different reactivity profile towards aldehyde **1**, probably reflecting a lower tendency to undergo the aforementioned conjugate addition. Thus, the *normal* reductive amination pathway competed with the γ-carboline annulation and gave a



Scheme 3.

Table 1. Reaction of vinyl aldehydes **1**–**3** with primary amines[a]

Entry	Aldehyde	Primary amine	Product	Yield[b] (%)
1	**1**	Allylamine	**4a**	90
2	**1**	Benzylamine	**4b**	85
3	**2**	Benzylamine	**5b**	80
4	**1**	Aniline	**4c** + **6c** (1:1)	70
5	**1**	*p*-Nitroaniline	**4d** + **6d** (1:15)	90
6	**1**	*p*-Methoxyaniline	**4e** + **6e** (9:1)	70
7	**3**	Allylamine	**7a**	65
8	**3**	Benzylamine	**7b**	65

[a] Experimental conditions: see Ref. 16.
[b] Isolated yield.

nearly equimolecular mixture of the γ-carboline **4c** and the secondary amine **6c** (entry 4). Significantly, the substitution by an electron-withdrawing nitro group at the amine phenyl ring led to the secondary amine **6d** as the major product (entry 5), whereas the substitution by an electron-releasing methoxy group led to the γ-carboline **4e** as the main product (entry 6).

The reaction of aldehyde **2** with a secondary amine such as *N*-methylbenzylamine was also investigated. As could have been expected from the above mechanistic considerations, the reductive amination through iminium cation **F** was the only productive pathway, giving the tertiary amine **8** in 90% yield (Fig. 1).

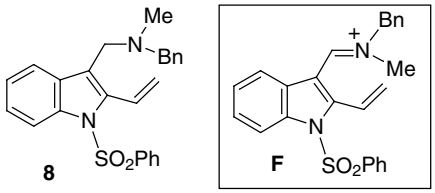
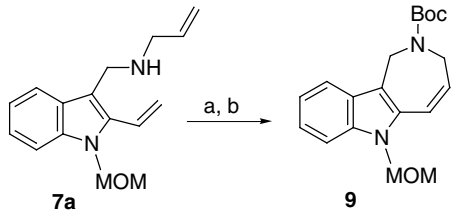


Figure 1.



Scheme 4. Reagents and conditions: (a) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h; (b) 5 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 70%.

At this point, we reasoned that the indole *N*-phenylsulfonyl group could benefit the γ-carboline annulation, enhancing the ability of 2-vinylindole to act as a Michael acceptor. Thus, in order to make the reductive amination of 2-vinyl-3-indolecarbaldehydes with primary aliphatic amines feasible, it would be better to place a less electron-withdrawing group, such as methoxymethyl, at the indole nitrogen. Our reasoning proved to be correct as secondary amines **7a** or **7b** were obtained as the only products by treatment of the *N*-MOM protected aldehyde **3**[15] with allylamine or benzylamine under mild reductive amination conditions (Table 1, entries 7 and 8). As expected, reaction of **7a** with di-*tert*-butyl dicarbonate followed by RCM reaction of the resulting carbamate with the first generation Grubbs catalyst gave the azepino[4,3-*b*]indole **9**[19] in good yield (Scheme 4).

In conclusion, the reaction of 2-vinyl-3-indolecarbaldehydes with primary amines under mild reductive amination conditions follows a different course depending on the substituent located at the indole nitrogen. Whereas tetrahydro-γ-carbolines are formed from *N*-(phenylsulfonyl)indoles **1** and **2** and aliphatic amines (and also the highly nucleophilic *p*-methoxyaniline), the initially expected secondary amines are formed from *N*-MOM indole **3**. Further work is currently underway to more fully establish the scope of this smooth γ-carboline annulation.

Acknowledgements

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7. Tetrahydro-γ-carboline **4a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, $J = 6$ Hz, 3H, Me), 2.90 (dm, $J = 11$ Hz, 1H, 4-H), 3.23 (m, 4H, 3-H, 4-H and CH_2), 3.65 (s, 2H, 1-H), 5.16 (m, 2H, $=CH_2$), 5.92 (m, 1H, CH=), 7.10–7.60 (m, 6H), 7.75 (d, $J = 7.5$ Hz, 2H), 8.15 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.7 (Me), 31.1 (C-4), 44.4 (C-1), 51.8 (C-3), 55.8 (CH_2), 114.5 (C-6), 115.6 (C-9b), 117.7 (C-9), 117.8 ($=CH_2$), 123.2 (C-8), 123.8 (C-7), 126.0, 128.9, 132.4, 133.3 (Ph), 128.3 (C-9a), 134.8 (CH=), 136.6 (C-4a), 138.5 (C-5a).
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13. Unfortunately, we were not able to isolate any definite compound under these conditions. However the subsequent reduction of the complex reaction mixture gave **4a**, although in a low yield (25%).
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16. General procedure: To a 0.1 M solution of the appropriate aldehyde in CH_2Cl_2 the primary amine (2 equiv), acetic acid (1 equiv) and $NaBH(OAc)_3$ (2 equiv) were added, and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2, washed with 10% aqueous Na_2CO_3, dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, 1:1 hexanes–AcOEt).
17. Tetrahydro-γ-carboline **4b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, $J = 6$ Hz, 3H, Me), 2.90 (dm, $J = 11$ Hz, 1H, 4-H), 3.25 (m, 2H, 3-H and 4-H), 3.61 (m, 2H, 1-H), 3.65 and 3.72 (2d, $J = 13$ Hz, 2H, CH_2), 7.17–7.52 (m, 11H), 7.78 (d, $J = 8$ Hz, 2H), 8.14 (d, $J = 8.4$ Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 15.0 (Me), 31.3 (C-4), 44.9 (C-1), 52.3 (C-3), 57.2 (CH_2), 114.8 (C-6), 116.2 (C-9b), 118.3 (C-9), 123.7 (C-8), 124.4 (C-7), 127.4 (C-9a), 126.6, 128.7, 133.2, 133.9 (Ph), 136.7 (C-4a), 139.3 (C-5a).
18. Tetrahydro-γ-carboline **5b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85 (m, 2H, 3-H), 3.13 (m, 2H, 4-H), 3.57 (s, 2H, 1-H), 3.73 (s, 2H, CH_2), 7.15–745 (m, 10H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 2H), 8.13 (d, $J = 8.4$ Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.8 (C-4), 49.5 (C-1), 50.5 (C-3), 62.5 (CH_2), 114.6 (C-6), 118.2 (C-9), 123.6 (C-8), 124.4 (C-7), 126.7, 127.6, 128.7, 129.3, 129.6, 133.8 and 133.9 (Ph), 136.5 (C-4a), 138.4 (C-5a).
19. Azepino[4,3-*b*]indole **9**: ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 1.29 and 1.45 (2s, 9H, Me), 3.22 (s, 3H, OMe), 4.12 and 4.31 (2s, 2H, 3-H), 4.74 and 4.92 (2s, 2H, 1-H), 5.46 (s, 2H, OCH_2), 6.06 (m, 1H, 4-H), 6.65 (d, $J = 10$ Hz, 1H, 5-H), 7.15 (t, $J = 7.8$ Hz, 1H, 9-H), 7.22 (t, $J = 8$ Hz, 1H, 8-H), 7.40 (d, $J = 8.4$ Hz, 1H, 7-H), 7.53 (d, $J = 7.8$ Hz, 1H, 10-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, major rotamer) δ 28.6 (Me), 44.7 (C-1), 48.9 (C-3), 56.0 (OMe), 73.8 (OCH_2), 80.1 (C), 109.7 (C-7), 116.4 (C-10b), 118.5 (C-10), 118.6 (C-5), 120.6 (C-9), 123.0 (C-8), 126.1 (C-10a), 131.4 (C-4), 133.5 (C-5a), 137.4 (C-6a), 155.8 (CO).

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Rapid Synthesis of the Ervitsine Alkaloid Skeleton by a Sequential RCM–Heck Cyclization Approach

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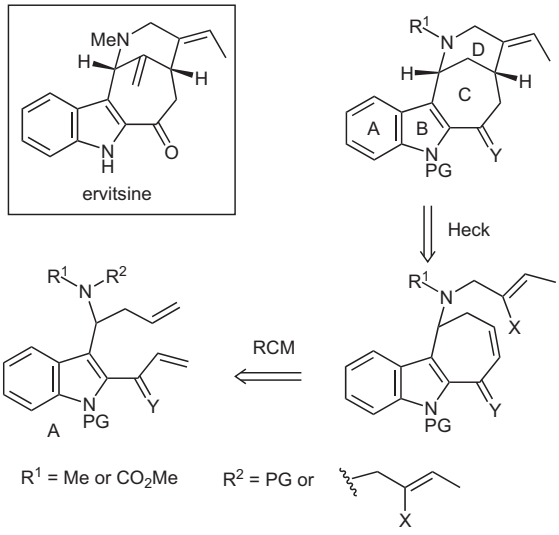
Abstract: An efficient approach to the bridged framework of the indole alkaloid ervitsine, featuring a ring-closing metathesis reaction from a 2,3-disubstituted indole followed by a vinyl halide Heck cyclization upon the resulting cycloheptene ring, is described.

Key words: indoles, annulation, metathesis, Heck reaction, alkaloids

Annulation methodologies involving the indole nucleus are of particular value for synthetic chemists as this heterocyclic moiety represents a common substructure of many biologically active compounds.[1] Our continuing interest in this area led us to investigate the synthetic possibilities of combining an indole-templated ring-closing metathesis (RCM)[2] and a vinyl halide Heck cyclization[3] to rapidly assemble complex bridged structures fused to the indole nucleus, which are present in some indole alkaloids. In this Letter we report the application of this double annulation methodology to the construction of the tetracyclic framework of ervitsine,[4] a unique alkaloid embodying a 2-azabicyclo[4.3.1]decane system fused to the indole ring and two exocyclic alkylidene substituents.[5]



Scheme 1 Synthetic strategy

As shown in Scheme 1, the metathetic ring closure of an indole-containing diene[6] (**A**) would provide an indolo 2,3-fused cycloheptene ring, with the appropriate functionality for the subsequent intramolecular Heck reaction with the amino-tethered vinyl halide.[7,8] Similar Heck couplings of vinyl halides and alkenes have proved to be useful for the closure of the piperidine ring in the synthesis of *Strychnos* alkaloids,[9] including strychnine[10] and minfiensine,[11] as well as in approaches to the geissoschizine[12] and apogeissoschizine[13] skeletons.

To establish the feasibility of our proposal for the ervitsine construction, we targeted indolic precursors unfunctionalized at the benzylic α-position (Y = H, H), knowing that this methylene group could be eventually oxidized at a later stage of the synthesis.[14] Protection of the indole nitrogen with a strong electron-withdrawing group was considered critical to guarantee the stability of the gramine [3-(aminomethyl)indole] moiety of the proposed intermediates. Our synthetic route began with the known 2-allyl-3-indolecarbaldehyde **1**[6c] (Scheme 2), from which an amination–imine allylation sequence was devised to install the homoallylic amine required for the RCM step. Faced with several possibilities, some of them requiring protecting groups, we chose a direct route and incorporated the additional haloalkenyl appendage at the amination step, with the hope that it would be sufficiently inert under the RCM conditions. Thus, reaction of aldehyde **1** with (*Z*)-2-bromo-2-butenylamine,[15] followed by alkylation of the resulting imine with allylmagnesium bromide (–78 °C to r.t.) led to the unstable secondary amine **2a** (not isolated), which was subsequently acylated with methyl chloroformate to give bromo triene **3a** in 60% overall yield. Similarly, iodo triene **3b** was prepared in 65% overall yield starting from **1** and (*Z*)-2-iodo-2-butenylamine.[15,16]

Attention was then directed to the RCM reaction. It was expected that, considering the different substitution and electronic nature of the double bonds of trienes **3**, the indole-templated cyclization leading to a fused seven-membered ring would be the preferred RCM event. Our expectations were confirmed when **3a** and **3b** on exposure to the second-generation Grubbs catalyst $(Im)(PCy_3)_2(Cl)_2Ru{=}CHPh$ (7 mol%) in refluxing CH_2Cl_2 gave the desired cyclohepta[*b*]indoles **4a** and **4b** as the only products in 80% and 78% yields, respectively.

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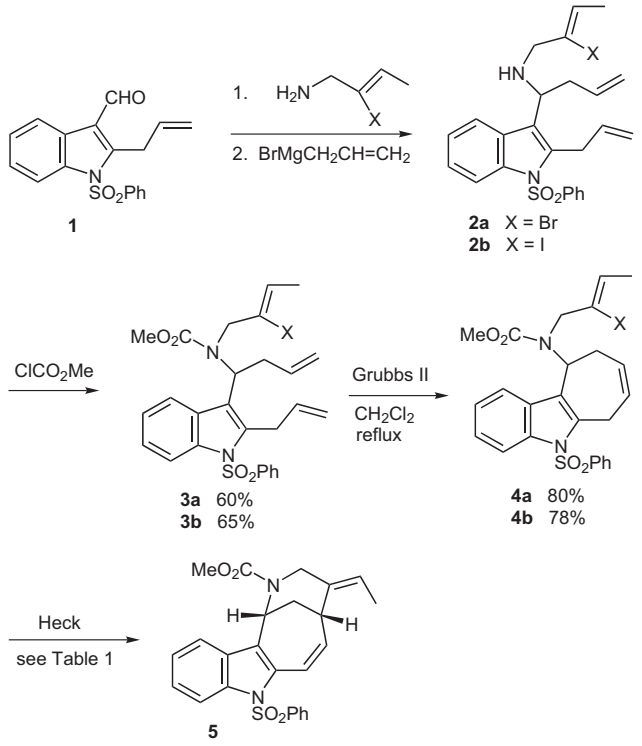
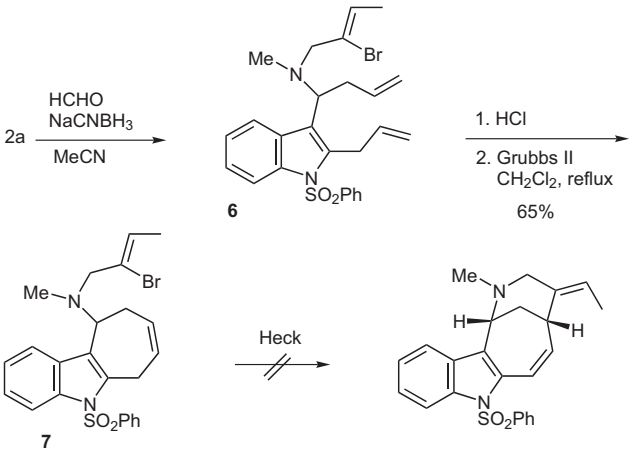


Scheme 2



Scheme 3

With a reliable and efficient route to suitably functionalized tricyclic ABC ervitsine substructures, a detailed investigation into the Heck reaction was then performed (Table 1). Our first assays using vinyl bromide **4a** as the substrate were discouraging since under classical polar conditions[9a] [$Pd(OAc)_2$, Ph_3P, Et_3N, MeCN, entry 1] only the starting product was recovered in low yield. On the other hand, the use of ligand-free conditions introduced by Jeffery[17] [$Pd(OAc)_2$, K_2CO_3, TBACl, DMF, entry 2], which had proven successful for the synthesis of related azapolycyclic structures,[9b,10a,c,12] resulted in the total decomposition of the material. More satisfactorily, the desired cyclization did proceed upon treatment of **4a** under nonpolar conditions[13] (palladium catalyst, Ph_3P, proton sponge, K_2CO_3, toluene, entries 3 and 4). However, although the conversion yields were good as evidenced by the NMR analysis of the crude reaction mixtures, the isolated yields of the (*E*)-ethylidene tetracycle **5** after column chromatography were only moderate (30%), **4a** being invariably recovered even under longer reaction times.

It should be mentioned that the analogous *N*-methyl derivative **7** (Scheme 3), prepared by methylation of the secondary amine **2a** followed by RCM of the resulting tertiary amine **6**, led to complex reaction mixtures under any of the above Heck conditions. This result seemed to indicate that the presence of a basic nitrogen in the halobutene chain is not compatible with the harsh cyclization conditions, probably due to a competitive dealkylation process.[10c]

We proceeded to focus on the more reactive vinyl iodide **4b**. When it was subjected to the same nonpolar protocol (entry 5), tetracycle **5** was obtained only in a slightly better yield (45%) along with minor amounts of recovered starting product. Interestingly, we were pleased to find that the addition of 20 mol% phenol in combination with K_3PO_4 resulted in a cleaner cyclization, giving the ervitsine tetracycle **5** as the only product in 65% yield (entry 6). As far as we know, the use of phenol as a catalytic additive in the Heck reaction is unprecedented, although its positive role in some palladium-catalyzed arylations of ketone enolates has been previously observed by Buchwald.[18,19] We believe that, according to Buchwald's proposal,[18] the intermediacy of a palladium phenoxide (e.g. **B**, Figure 1), which would stabilize an otherwise unstable intermediate, could account for the beneficial effect of the added phenol.

In summary, the RCM–Heck double annulation strategy described here gives short access to the bridged framework of ervitsine from easily accessible indolic precur-

Table 1 Heck Cyclization of Vinyl Halides **4**

Entry	X	Reaction conditions	Products (yield, %)[a]
1	Br	$Pd(OAc)_2$ (16%), Ph_3P (50%), Et_3N (2 equiv), MeCN, reflux, 3 h	**4a** (33)
2	Br	$Pd(OAc)_2$ (5%), K_2CO_3 (5 equiv), TBACl (1 equiv), DMF, 60 °C, 4 h	–
3	Br	$Pd(OAc)_2$ (5%), Ph_3P (20%), proton sponge (0.5 equiv), K_2CO_3 (1.1 equiv), toluene, reflux, 4 h	**5** (30), **4a** (16)
4	Br	$Pd(Ph_3P)_4$ (5%), proton sponge (0.1 equiv), K_2CO_3 (2.5 equiv), toluene, sealed tube, 2.5 d	**5** (30), **4a** (5)
5	I	$Pd(OAc)_2$ (10%), Ph_3P (40%), proton sponge (0.3 equiv), K_2CO_3 (1.5 equiv), toluene, reflux, 24 h	**5** (45), **4b** (10)
6	I	$Pd(Ph_3P)_4$ (10%), K_3PO_4 (3 equiv), Et_3N (6 equiv), PhOH (0.2 equiv), toluene, reflux, 12 h	**5** (65)

[a] Isolated yields after column chromatography.

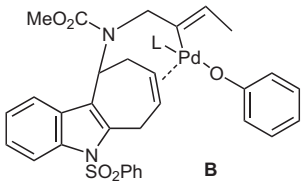


Figure 1 Role of the phenol additive

sors. The application of this approach to closer analogues of this natural product and other polycyclic indole alkaloids is being actively pursued in our laboratory.

Typical Procedure for the RCM Step: Synthesis of Cyclohepta[*b*]indole 4b

(Im)(PCy_3)(Cl_2)Ru=CHPh (second-generation Grubbs catalyst, 7 mol%) was added under Ar to a solution of carbamate **3b** (0.3 g, 0.5 mmol) in CH_2Cl_2 (2.5 mL) and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was concentrated and the residue was chromatographed (SiO_2, flash, 96:4 hexanes–EtOAc) to give **4b**: 0.22 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer): δ = 1.51 (d, *J* = 6.0 Hz, 3 H), 2.59 (br, 1 H), 2.74 (br, 1 H), 3.49 (d, *J* = 16.0 Hz, 1 H), 3.71 (d, *J* = 16.0 Hz, 1 H), 3.78 (br s, 3 H), 3.99 (m, 2 H), 5.25 (q, *J* = 6 Hz, 1 H), 5.72 (m, 1 H), 5.86 (m, 1 H), 5.95 (m, 1 H), 7.22 (m, 1 H), 7.29 (m, 2 H), 7.44 (m, 2 H), 7.54 (m, 1 H), 7.71 (m, 2 H), 8.23 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (74.5 MHz, $CDCl_3$): δ = 21.6 (CH_3), 25.6 (br, CH_2), 30.9 (br, CH_2), 52.4 (br, CH), 53.1 (br, CH_3), 55.1 (br, CH_2), 106.9 (br, C), 115.2 (CH), 118.6 (br, CH), 119.7 (br, C), 124.1 (CH), 124.8 (CH), 126.1 (2 CH), 126.4 (C), 128.9 (CH), 129.0 (CH), 129.4 (2 CH), 130.2 (CH); 133.9 (CH), 136.1 (C), 137.2 (br, C), 138.8 (C), 156.9 (CO). ESI-HRMS $[M + Na]^+$: *m/z* calcd for $C_{25}H_{25}IN_2NaO_4S$: 599.0472; found: 599.0474.

Heck Cyclization of 4b

$Pd(Ph_3P)_4$ (17 mg, 0.015 mmol), K_3PO_4 (96 mg, 0.45 mmol), PhOH (3.5 mg, 0.04 mmol), and Et_3N (0.1 mL, 0.75 mmol) were successively added to a solution of vinyl iodide **4b** (87 mg, 0.15 mmol) in toluene (11 mL), and the resulting mixture was heated at reflux for 12 h. The reaction mixture was diluted with Et_2O and washed with a sat. aq Na_2CO_3 solution and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed (SiO_2, flash, hexanes and 5% hexanes–EtOAc) to give 4-(*E*)-ethylidene-2-(methoxycarbonyl)-8-(phenylsulfonyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (**5**): 43 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$, assignment aided by gHSQC, 2:1 mixture of rotamers): δ = 1.70 (dm, *J* = 6.4 Hz, 3 H), 1.91 (d, *J* = 13.0 Hz, 1 H, 13-H), 2.25 (m, 1 H, 13-H), 2.94 and 3.10 (major) (2 d, *J* = 13.5 Hz, 1 H, 3-H), 3.67 (major) and 3.81 (2 s, 3 H, OCH_3), 3.81 (masked, 1 H, 5-H), 4.04 (major) and 4.17 (d, *J* = 13.5 Hz, 1 H, 3-H), 5.37 (major) and 5.42 (2 q, *J* = 6.4 Hz, 1 H), 5.73 and 5.91 (major) (2 br s, 1 H, 1-H), 6.05 (m, 1 H), 7.31 (m, 1 H), 7.34 (m, 1 H), 7.36 (m, 2 H), 7.49 (m, 2 H), 7.67 (m, 2 H), 7.85 (d, *J* = 8 Hz, 1 H), 8.25 (d, *J* = 8 Hz, 1 H). ^{13}C NMR (74.5 MHz, $CDCl_3$, assignment aided by gHSQC, major rotamer): δ = 12.5 (CH_3), 29.3 (C-13), 35.7 (C-5), 45.1 (C-1), 45.6 (C-3), 52.7 (OCH_3), 115.7 (CH), 118.6 (C-7), 119.3 (C), 120.2 (CH), 120.3 (CH), 124.5 (CH), 125.6 (CH), 126.2 (C), 126.3 (2 CH), 129.1 (2 CH), 133.3 (C), 133.6 (CH), 134.8 (C-6), 136.1 (C), 136.9 (C), 138.2 (C), 155.1 (CO). ESI-HRMS $[M + H]^+$: *m/z* calcd for $C_{25}H_{25}N_2O_4S$: 449.1529; found: 449.1523.

Acknowledgment

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(3) For general reviews, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-WCH: New York, **2004**, 217. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644.

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(13) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146.

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(15) Prepared from (*Z*)-1,2-dibromo-2-butene or (*Z*)-1-bromo-2-iodo-2-butene.
(16) Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177.
(17) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
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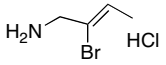
PART EXPERIMENTAL CORRESPONENT AL CAPÍTOL 3.1

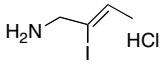
(*Z*)-2-Bromo-2-butenylamine Hydrochloride



Following a reported protocol for the preparation of closely related products,[1] (*Z*)-1,2-dibromo-2-butene[2] (3.12 g, 14.6 mmol) was added dropwise (1 h) to a solution of hexamethylenetetramine (2.25 g, 16 mmol) in $CHCl_3$ (18 mL) heated at reflux. The resulting mixture was heated at reflux for 4 h and then allowed to stand in the refrigerator overnight. The mixture was cooled in an ice bath and the quaternary salt was collected by filtration. The crude salt was dissolved in a warm solution, prepared from H_2O (6 mL), EtOH (29 mL), and 37% HCl (8 mL). The mixture was stirred for 4 h and then allowed to stand overnight. A precipitate of NH_4Cl was formed, which was removed by filtration washing carefully with ethanol. The filtrate was concentrated to a quarter of the volume and the resulting solid was removed by filtration. The filtrate was concentrated to dryness and the solid residue was carefully dried. The residue was digested with MeOH (15 mL) and the resulting solid was removed by filtration. The filtrate was concentrated to dryness to give (*Z*)-2-bromo-2-butenylamine hydrochloride (2.75 g, quantitative), which was used in the next reaction without purification.

[1]Bottini, A. T.; Dev, V. *J. Org. Chem.* **1962**, *27*, 968-973.
[2]Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett*. **1992**, *33*, 2571-2574.

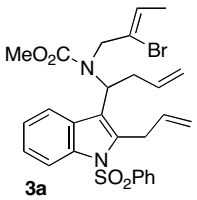
(*Z*)-2-Iodo-2-butenylamine Hydrochloride[3]



Operating as above, starting from (*Z*)-1-bromo-2-iodo-2-butene[4] (3.8 g, 14.6 mmol), (*Z*)-2-iodo-2-butenylamine hydrochloride (3.5 g, quantitative) was obtained.

[3]Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177-10184.
[4](a) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404-408. (b) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695-1698. (c) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230-7240.

Triene 3a



3a

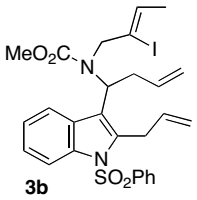
Et_3N (0.31 mL, 2.23 mmol) was added to a solution of (*Z*)-2-bromo-2-butenylamine hydrochloride (0.29 g, 1.5 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at rt for 10 min. Aldehyde **1**[5] (0.34 g, 1.0 mmol) in CH_2Cl_2 (5 mL) and AcOH (0.06 mL, 1.0 mmol) were successively added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), basified with a saturated aqueous Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were dried and concentrated to give the crude imine (480 mg).

Allylmagnesium bromide (1M in Et_2O, 1.6 mL, 1.6 mmol) was added under Ar to a cooled (–78ºC) solution of the above imine in anhydrous THF (30 mL), and the resulting mixture was stirred at rt for 2h. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (5 mL) and extracted with Et_2O (3 x 10 mL). The ethereal extracts were dried and concentrated to give the crude amine **2a** (342 mg).

A solution of the above amine **2a** in anhydrous THF (12 mL) was added under Ar to a suspension of NaH (60%, 56 mg, 1.4 mmol) in THF (2 mL) cooled at –20ºC, and the mixture was stirred at –20 °C for 20 min. A solution of methyl chloroformate (0.16 mL, 2.1 mmol) in THF (1 mL) was then added and the mixture was stirred at rt overnight. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried and concentrated. The resulting residue was chromatographed (SiO_2, flash, 97:3 hexanes-AcOEt) to give bromo triene **3a**: (0.35 g, 60%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, *J* = 6.4 Hz, 3H), 2.90 (m, 2H), 3.72 (s, 3H), 3.89 (m, 2H), 3.96 (br s, 2H), 4.95 (m, 2H), 5.03 (m, 2H), 5.41 (q, *J* = 6.4 Hz, 1H), 5.56 (m, 1H), 5.60 (m, 1H), 5.96 (m, 1H), 7.26 (m, 2H), 7.41 (m, 2H), 7.53 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.73 (m, 2H), 8.21 (dm, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 16.1 (CH_3), 30.2 (CH_2), 36.9 (CH_2), 51.4 (CH_2), 52.9 (CH_3), 53.2 (CH), 115.1 (CH), 116.3 (CH_2), 117.5 (CH_2), 118.8 (C), 120.1 (CH), 123.2 (CH), 123.6 (CH), 124.2 (CH), 124.3 (C), 126.4 (2CH), 129.2 (2CH), 129.4 (C), 133.7 (CH), 134.4 (CH), 134.8 (CH), 136.5 (C), 138.3 (C), 138.9 (C), 156.6 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{27}H_{30}BrN_2O_4S$ 557.1110, found 557.1104.

[5]Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861-866.

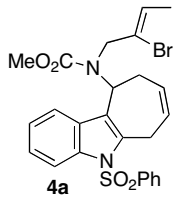
Triene 3b



3b

Operating as above, from aldehyde **1** (0.20 g, 0.6 mmol) and (*Z*)-2-iodo-2-butenylamine hydrochloride (0.25 g, 1.0 mmol), carbamate **3b** was obtained: 0.24 g (65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, *J* = 6.4 Hz, 3H), 2.82 (m, 2H), 3.63 (s, 3H), 3.81 (m, 2H), 3.90 and 3.95 (2d, *J* = 16 Hz, 2H), 4.82 (d, *J* = 10.4 Hz, 1H), 4.90 (br s, 1H), 4.95 (m, 2H), 5.18 (q, *J* = 6.4 Hz, 1H), 5.47 (m, 2H), 5.90 (m, 1H), 7.16 (m, 2H), 7.30 (m, 2H), 7.42 (m, 1H), 7.58 (dm, *J* = 8 Hz, 1H), 7.65 (m, 2H), 8.12 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 21.3 (CH_3), 30.4 (CH_2), 36.7 (CH), 52.9 (CH_3), 53.2 (CH), 54.7 (CH_2), 105.5 (C), 115.0 (CH), 116.3 (CH_2), 117.6 (CH_2), 118.7 (C), 120.2 (CH), 123.7 (CH), 124.2 (CH), 126.4 (2CH), 129.0 (CH), 129.2 (2CH), 129.3 (C), 133.8 (CH), 134.4 (CH), 134.9 (CH), 136.4 (C), 138.2 (C), 138.9 (C), 156.6 (CO).

10-[*N*-((*Z*)-2-Bromo-2-butenyl)-*N*-(methoxycarbonyl)amino]-5-(phenylsulfonyl)-9,10-dihydro-6*H*-cyclohepta[*b*]indole (4a)

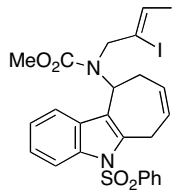


4a

(Im)(PCy_3)$(Cl)_2$Ru=CHPh (second generation Grubbs catalyst, 7 mol %) was added under Ar to a solution of carbamate **3a** (100 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was concentrated and the residue was chromatographed (SiO_2, flash, 96:4 hexanes-AcOEt) to give **4a**: 76 mg (80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (dm, *J* = 6.5 Hz, 3H), 2.55 (br, 1H), 2.65 (br, 1H), 3.40 (d, *J* = 16.8 Hz, 1H), 3.78 (br s, 3H), 4.05 (m, 3H), 5.36 (q, *J* = 6.5 Hz, 1H), 5.75 (m, 1H), 5.88 (m, 1H), 5.95 (m, 1H), 7.26 (m, 3H), 7.43 (m, 2H), 7.53 (m, 1H), 7.70 (m, 2H), 8.23 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 16.3 (CH_3), 25.5 (br, CH_2), 30.4 (br, CH_2), 51.4 (br, CH), 51.9 (br, CH_2), 53.0 (br,

CH_3), 115.3 (CH), 118.7 (br, CH), 120.0 (C), 123.0 (br, CH), 124.1 (CH), 124.8 (CH), 124.9 (C), 125.0 (C), 126.1 (2CH), 128.9 (CH), 129.3 (2CH), 130.3 (CH), 133.8 (CH), 136.1 (C), 137.2 (br, C), 138.7 (C), 156.7 (br, CO); ESI-HRMS $[M+Na]^+$ calcd for $C_{25}H_{25}BrN_2NaO_4S$ 551.0616, found 551.0591.

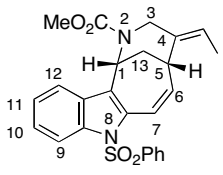
10-[*N*-((*Z*)-2-Iodo-2-butenyl)-*N*-(methoxycarbonyl)amino]-5-(phenylsulfonyl)-9,10-dihydro-6*H*-cyclohepta[*b*]indole (4b)



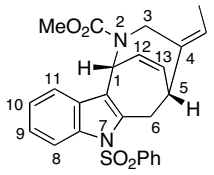
4b

Operating as above, from carbamate **3b** (0.30 g, 0.5 mmol), **4b** was obtained after column chromatography (SiO_2, flash, 96:4 hexanes-AcOEt): 0.22 g (78%); ^{1}H NMR ($CDCl_3$, 400 MHz, major rotamer) δ 1.51 (d, *J* = 6.0 Hz, 3H), 2.59 (br, 1H), 2.74 (br, 1H), 3.49 (d, *J* =16 Hz, 1H), 3.71 (d, *J* = 16 Hz, 1H), 3.78 (br s, 3H), 3.99 (m, 2H), 5.25 (q, *J* = 6 Hz, 1H), 5.72 (m, 1H), 5.86 (m, 1H), 5.95 (m, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.44 (m, 2H), 7.54 (m, 1H), 7.71 (m, 2H), 8.23 (d, *J* = 8,4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 21.6 (CH_3), 25.6 (br, CH_2), 30.9 (br, CH_2), 52.4 (br, CH), 53.1 (br, CH_3), 55.1 (br, CH_2), 106.9 (br, C), 115.2 (CH), 118.6 (br, CH), 119.7 (br, C), 124.1 (CH), 124.8 (CH), 126.1 (2CH), 126.4 (C), 128.9 (CH), 129.0 (CH), 129.4 (2CH), 130.2 (CH); 133.9 (CH), 136.1 (C), 137.2 (br, C), 138.8 (C), 156.9 (CO); ESI-HRMS $[M+Na]^+$ calcd for $C_{25}H_{25}IN_2NaO_4S$ 599.0472, found 599.0474.

Heck Cyclization of Vinyl Iodide 4b



5



8

Method A (Table 1, entry 6). $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), K_3PO_4 (96 mg, 0.45 mmol), phenol (3.5 mg, 0.04 mmol), and Et_3N (0.1 mL, 0.75 mmol) were successively added to a solution of vinyl iodide **4b** (87 mg, 0.15 mmol) in toluene (11 mL), and the resulting mixture was heated at reflux for 12 h. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous Na_2CO_3 solution and brine. The organic

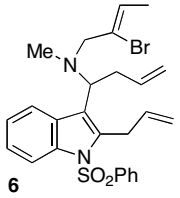
layer was dried and concentrated. The resulting residue was chromatographed (SiO_2, flash, hexanes and 5% hexanes-EtOAc) to give **4-(*E*)-ethylidene-2-(methoxycarbonyl)-8-(phenylsulfonyl)-2,3,4,5-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (5)**: 43 mg (65%); ^{1}H NMR ($CDCl_3$, 400 MHz, assignment aided by gHSQC, 2:1 mixture of rotamers) δ 1.70 (dm, *J* = 6.4 Hz, 3H), 1.91 (d, *J* = 13 Hz, 1H, 13-H), 2.25 (m, 1H, 13-H), 2.94 and 3.10 (major) (2d, *J* = 13.5 Hz, 1H, 3-H), 3.67 (major) and 3.81 (2s, 3H, OCH_3), 3.81 (masked, 1H, 5-H), 4.04 (major) and 4.17 (d, *J* = 13.5 Hz, 1H, 3-H), 5.37 (major) and 5.42 (2q, *J* = 6.4 Hz, 1H), 5.73 and 5.91 (major) (2 br s, 1H, 1-H), 6.05 (m, 1H), 7.31 (m, 1H), 7.34 (m, 1H), 7.36 (m, 2H), 7.49 (m, 2H), 7.67 (m, 2H), 7.85 (d, *J* = 8 Hz, 1H), 8.25 (d, *J* =8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz, assignment aided by gHSQC, major rotamer) δ 12.5 (CH_3), 29.3 (C-13), 35.7 (C-5), 45.1 (C-1), 45.6 (C-3), 52.7 (OCH_3), 115.7 (CH), 118.6 (C-7), 119.3 (C), 120.2 (CH), 120.3 (CH), 124.5 (CH), 125.6 (CH), 126.2 (C), 126.3 (2CH), 129.1 (2CH), 133.3 (C), 133.6 (CH), 134.8 (C-6), 136.1 (C), 136.9 (C), 138.2 (C), 155.1 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4S$ 449.1529, found 449.1523.

Method B (Table 1, entry 8). PPh_3 (13 mg, 0.05 mmol), Ag_2CO_3 (142 mg, 0.51 mmol), and $Pd(OAc)_2$ (4 mg, 0.017 mmol) were successively added to a solution of vinyl iodide **4b** (98 mg, 0.17 mmol) in toluene (9 mL), and the resulting mixture was stirred at 80 ºC for 1 h. The solvent was removed and the resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (SiO_2, flash, from cyclohexane to 6% cyclohexane-CH_2Cl_2) to give **5** (14 mg, 19%) and **8** (33 mg, 43%).

4-(*Z*)-Ethylidene-2-(methoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,4,5,6-hexahydro-1,5-ethenoazocino[4,3-*b*]indole (8): ^{1}H NMR ($CDCl_3$, 400 MHz, assignment aided by gCOSY and gHSQC, 2:1 mixture of rotamers) δ 1.58 (major) and 1.65 (2d, *J* = 6.4 Hz, 3H, CH_3), 3.27 (br s, 1H, 5-H), 3.30 (m, 2H, 6-H), 3.70 (major) and 3.76 (2s, 3H, OCH_3), 3.72 (m, 1H, 3-H), 4.43 and 4.67 (2d, *J* = 15.2 Hz, 1H, 3-H), 5.39 (m, 1H, CH= ethylidene), 5.79 and 6.01 (major) (2d, *J* = 7.6 or 8 Hz, 1H, 1-H), 6.16 (t, *J* = 8.8 Hz, 1H, 13-H), 6.30 (m, 1H, 12-H), 7.26 (m, 2H), 7.40 (m, 2H), 7.53 (m, 1H), 7.70 (m, 3H), 8.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz, assignment aided by gHSQC, major rotamer) δ 13.2 (CH_3), 32.8 (C-6), 41.0 (C-3), 42.2 (C-5), 46.5 (C-1), 52.8 (OCH_3), 114.4 (CH), 117.0 (C), 118.7 (CH), 123.0 (CH ethylidene), 123.7 (CH), 124.5 (CH),

126.2 (2CH), 129.2 (2CH), 129.5 (C), 132.0 (C-12), 133.4 (C-13), 133.6 (CH), 134.9 (C), 135.9 (C), 138.4 (C), 139.1 (C), 156.1 (CO); ESI-HRMS $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4S$ 449.1529, found 449.1527.

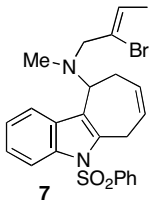
Triene 6



6

Aldehyde **1** (0.17 g, 0.5 mmol) was allowed to react with (*Z*)-2-bromo-2-butenylamine hydrochloride and allylmagnesium bromide as described in the preparation of carbamates **3**. The resulting crude amine **2a** (170 mg) was dissolved in CH_3CN (1.5 mL) and the resulting solution was treated with 37% aqueous formaldehyde (1.7 mmol) and $NaBH_3CN$ (34 mg, 0.55 mmol) for 45 min at rt. The acidic pH was maintained with regular addition of AcOH. The reaction mixture was basified with 2N NaOH (5 mL), diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layer was washed with 2N NaOH (2 x 10 mL), dried and concentrated. The resulting residue was chromatographed (SiO_2, flash, 90:10 hexanes-AcOEt) to give **6**: 134 mg, (50%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.71 (d, *J* = 6.4 Hz, 3H), 2.11 (s, 3H), 2.58 (m, 1H), 2.76 (m, 1H), 3.11 (br s, 2H), 3.54 (dd, *J* = 9.6 and 4.8 Hz, 1H), 3.82 (m, 2H), 4.63 (d, *J* =9.6 Hz, 1H), 4.72 (d, *J* =18.4 Hz, 1H), 5.07 (m, 2H), 5.20 (m, 1H), 5.86 (q, *J* = 6.4 Hz, 1H), 5.99 (m, 1H), 7.20 (m, 1H), 7.24 (m, 1H), 7.32 (m, 2H) 7.46 (m, 1H), 7.61 (m, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 16.6 (CH_3), 30.6 (CH_2), 37.0 (CH_2), 39.6 (CH_3), 61.7 (CH), 63.8 (CH_2), 115.2 (CH), 116.4 (CH_2), 116.7 (CH_2), 121.7 (CH), 122.6 (C), 123.5 (CH), 124.4 (CH), 125.6 (CH), 126.2 (2CH), 126.8 (C), 128.9 (2CH), 129.4 (C), 133.4 (CH), 135.2 (CH), 135.3 (CH), 136.0 (C), 137.1 (C), 138.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{26}H_{30}BrN_2O_2S$ 513.1205, found 513.1200.

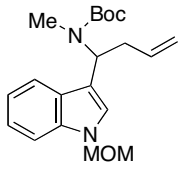
10-[*N*-(*(Z)*-2-bromo-2-butenyl)-*N*-methylamino]-5-(phenylsulfonyl)-9,10-dihydro-6*H*-cyclohepta[*b*]indole (7)



7

The hydrochloride of amine **6** (84 mg, 0.16 mmol) in CH_2Cl_2 (2.4 mL, 0.07 M) was heated at reflux in the presence of $(Im)(PCy_3)(Cl)_2Ru{=}CHPh$ (second generation Grubbs catalyst, 7 mol %) for 2 h. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (SiO_2, flash, 97:3 hexanes-AcOEt) to give **7**: 52 mg (65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (d, *J* = 6 Hz, 3H), 2.03 (s, 3H), 2.40 (m, 1H), 2.60 (m, 1H), 3.12 and 3.22 (2d, *J* = 14.0 Hz, 2H), 3.95 (m, 3H), 5.84 (m, 3H), 7.23 (m, 2H), 7.33 (m, 2H), 7.46 (m, 1H), 7.62 (m, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 16.6 (CH_3), 25.3 (CH_2), 25.9 (CH_2), 36.9 (CH_3), 58.5 (CH), 63.2 (CH_2), 115.4 (CH), 120.8 (CH), 123.6 (CH), 124.1 (C), 124.3 (CH), 125.5 (CH), 126.1 (2CH), 126.9 (C), 128.6 (CH), 128.7 (CH), 128.9 (2CH), 131.4 (C), 133.5 (CH), 136.5 (C), 136.6 (C), 138.2 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{26}BrN_2O_2S$ 485.0892, found 485.0873.

3-[1-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3-butenyl]-1-(methoxymethyl)indole (11)



11

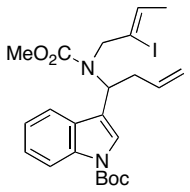
Methylamine (8M in EtOH, 1.32 mL, 10.6 mmol) and AcOH (0.06 mL, 1.06 mmol) were successively added to a solution of aldehyde **10a**[6] (0.2 g, 1.06 mmol) in CH_2Cl_2 (8 mL). After being stirred at rt overnight, the reaction mixture was diluted with CH_2Cl_2 (5 mL), basified with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried and concentrated to give the crude imine.

Allylmagnesium bromide (1M in Et_2O, 1.59 mL, 1.59 mmol) was added under Ar to a cooled (–78°C) solution of the above material in anhydrous THF (25 mL), and the mixture was stirred at rt overnight. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 10 mL). The organic extracts were dried and concentrated to give the crude secondary amine.

Et_3N (0.85 mL, 6.08 mmol) and $(Boc)_2O$ (0.46 g, 2.12 mmol) were successively added to a solution of the above material in MeOH (30 mL) and the mixture was heated at reflux for 5 h. The solvent was removed and the residue was diluted with CH_2Cl_2 (30 mL) and washed with 1N HCl (2 x 20 mL) and brine (2 x 20 mL). The organic solution was dried and concentrated and the residue was chromatographed (SiO_2, 85:15 hexanes-AcOEt) to give carbamate **11**: 0.29 g (80%); ^1H NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 1.50 and 1.57 (2 broad s, 9H), 2.50 (broad, 3H), 2.71 (m, 2H), 3.24 (s, 3H), 5.08 (broad d, *J* = 10.5 Hz, 1H), 5.17 (dm, *J* = 17.1 Hz, 1H), 5.43 (s, 2H), 5.60 and 5.86 (2 broad m, 2H), 7.08 (s, 1H), 7.14 (td, *J* = 7.5 and 1 Hz, 1H), 7.25 (td, *J* = 7.5 and 1 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.64 (broad d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, mixture of rotamers) δ 27.9 (CH_3), 28.5 (CH_3), 35.5 (CH_2), 49.9 and 51.5 (CH), 55.9 (CH_3), 77.3 (CH_2), 79.1 (C), 109.7 (CH), 115.9 (C), 116.8 and 117.1 (CH_2), 119.8 (CH), 120.3 (CH), 122.7 (CH), 126.0 (CH), 128.0 (C), 134.9 (CH), 136.9 (C), 155.9 (C).

[6]Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104-109.

Indole 12b



12b

Et_3N (0.4 mL, 2.86 mmol) was added to a solution of (*Z*)-2-iodo-2-butenylamine hydrochloride (0.4 g, 1.71 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 20 min. Aldehyde **10b**[7] (250 mg, 1.02 mmol) in CH_2Cl_2 (5.5 mL) and AcOH (0.06 mL, 1.05 mmol) were successively added and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL), basified with a

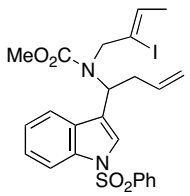
saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were dried and concentrated to give the crude imine (444 mg).

Allylmagnesium bromide (1M in Et_2O, 1.53 mL, 1.53 mmol) was added under Ar to a cooled (–78°C) solution of the above imine in anhydrous THF (23 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was quenched with a 10% aqueous NH_4Cl solution (6 mL) and extracted with Et_2O (3 x 15 mL). The organic extracts were dried and concentrated to give the crude secondary amine (390 mg).

A solution of the above amine in anhydrous THF (15 mL) was added under Ar to a suspension of NaH (60%, 1.66 mmol) in anhydrous THF (20 mL) cooled at –20ºC, and the mixture was stirred at –20°C for 20 min. A solution of methyl chloroformate (0.15 mL, 1.99 mmol) in THF (1 mL) was then added and the mixture was stirred at rt overnight. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3x15 mL). The combined organic extracts were dried and concentrated to give indole **12b**: 293 mg (55%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, *J* = 6 Hz, 3H), 1.69 (s, 9H), 2.77 (t, *J* = 7.2 Hz, 2H), 3.77 (broad, 3H), 3.96 (broad, 2H), 5.08 (dd, *J* = 10.4 and 1.6 Hz, 1H), 5.17 (dd, *J* = 17.2 and 1.6 Hz, 1H), 5.34 (broad, 1H), 5.55 and 5.75 (2 broad, 1H), 5.85 (m, 1H), 7.22 (td, *J* = 7.4 and 1.2 Hz, 1H), 7.30 (td, *J* = 7.4 and 1.2 Hz, 1H), 7.52 (broad singlet, 1H), 7.58 (broad, 1H), 8.08 (broad d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz, gHSQC) δ 21.5 (CH_3), 28.4 (CH_3), 36.4 (CH_2), 51.7 (CH), 53.2 (CH_3), 54.3 (CH_2), 84.2 (C), 105.0 (C), 115.3 (CH), 117.9 (CH_2), 119.2 (C), 119.9 (CH), 123.0 (CH), 124.6 (CH), 125.0 (CH), 129.8 (C), 130.2 (CH), 134.9 (CH), 135.5 (C), 149.9 (C), 157.3 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{23}H_{30}IN_2O_4$ 525.1244, found 525.1244; $[M+Na]^+$ calcd for $C_{23}H_{29}IN_2NaO_4$ 547.1064, found 547.1065.

[7]Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *75*, 5840-5851.

Indole 12c



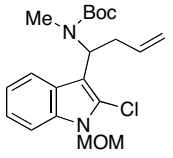
12c

Operating as above, from aldehyde **10c**[8] (0.5 g, 1.75 mmol) and (*Z*)-2-iodo-2-butenylamine hydrochloride (0.7 g, 2.99 mmol) carbamate **12c** was obtained: 0.59 g

(60%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, *J* = 6.4 Hz, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 3.65 (broad, 3H), 3.80 (broad, 2H), 4.98 (d, *J* = 10.4 Hz, 1H), 5.07 (dd, *J* = 17.2 and 1.6 Hz, 1H), 5.18 (broad, 1H), 5.42 and 5.64 (2 broad, 1H), 5.68 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 8 Hz, 2H), 7.43 (m, 2H), 7.50 (broad m, 1H), 7.78 (d, *J* = 8 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 21.4 (CH_3), 36.0 (CH_2), 51.0 (CH), 53.2 (CH_3), 54.1 (CH_2), 104.5 (C), 113.5(CH), 117.8 (CH_2), 120.1 (CH), 121.1 (C), 123.6 (CH), 124.7 (CH), 125.2 (CH), 126.7 (2 CH), 129.4 (2 CH), 130.3 (CH), 133.9 (CH), 134.4 (C), 134.9 (C), 137.9 (C), 157.0 (C); ESI-HRMS $[M+H]^+$calcd for $C_{24}H_{26}IN_2O_4S$ 565.0652, found 565.0640; $[M+Na]^+$ calcd for $C_{24}H_{25}IN_2O_4NaS$ 587.0472, found 587.0467.

[8]Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem*. **1992**, *57*, 5878-5891.

3-[1-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3-butenyl]-2-chloro-1-(methoxymethyl)indole (14)

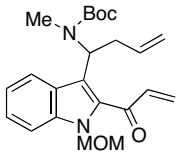


14

Operating as described for carbamate **11**, from aldehyde **13**[9] (0.3 g, 1.28 mmol) carbamate **14** was obtained after chromatography (SiO2, 85:15 hexanes-AcOEt): 412 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.69 (s, 3H), 2.82-3.08 (m, 2H), 3.28 (s, 3H), 5.04 (dm, *J* = 9 Hz, 1H), 5.16 (dm, *J* = 15 Hz, 1H), 5.53 (s, 2H), 5.72-5.90 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.8 (CH_3), 29.2 (CH_3), 35.5 (CH_2), 52.1 (CH), 56.3 (CH_3), 74.1 (CH_2), 79.8 (C), 110.1 (CH), 111.2 (C), 117.4 (CH_2), 119.8 (CH), 121.4 (CH), 123.1 (CH), 124.9 (C), 127.5 (C), 135.4 (CH), 136.0 (C), 155.7 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{20}H_{27}ClN_2NaO_3$ 401.1602, found 401.1619.

[9]Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull*. **2001**, *49*, 881-886.

3-[1-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-3-butenyl]-1-(methoxymethyl)-2-(1-oxo-2-propenyl)indole (15)

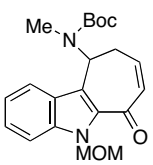


15

t-Buli (1.7 M in pentane, 0.6 mL, 1.02 mmol) was slowly added to a solution of 2-chloroindole **14** (254 mg, 0.67 mmol) in THF (12 mL) cooled at –78°C and the resulting mixture was stirred at –78°C for 30 min. Acroleine (0.13 mL, 1.92 mmol) was added and the mixture was stirred at –78°C for 20 min. The reaction mixture was quenched with 10% aqueous NH_4Cl (15 mL) and extracted with Et_2O (3 x 15 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (SiO_2, 1:1 hexanes-AcOEt) to give the crude carbinol.

A solution of the above material in CH_2Cl_2 (15 mL) was treated with MnO_2 (0.58 g, 6.7 mmol) at rt overnight. The reaction mixture was filtered through celite and the filtrate was concentrated to give ketone **15**: 120 mg (45%); ^{1}H NMR ($CDCl_3$, 300 MHz, major rotamer) δ 1.47 (s, 9H), 2.75 (s, 3H), 2.80 (m, 2H), 3.16 (s, 3H), 4.95 (dm, *J* = 9 Hz, 1H), 5.15 (dm, *J* = 15 Hz, 1H), 5.46 (d, *J* = 8.8 Hz, 1H), 5.53 (d, *J* = 8.8 Hz, 1H), 5.57 (m, 2H), 6.08 (d, *J* = 9 H, 1H), 6.18 (d, *J* = 15 Hz, 1H), 6.81 (dd, *J* = 15 and 8.8 Hz), 7.22 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, major rotamer) δ 28.8 (CH_3), 29.8 (CH_3), 36.4 (CH_2), 52.3 (CH), 56.2 (CH_3), 75.4 (CH_2), 79.9 (C), 111.2 (CH), 117.6 (CH_2), 118.1 (C), 121.7 (CH), 122.4 (CH), 124.9 (CH), 127.2 (C), 132.3 (CH_2), 135.0 (CH), 135.4 (C), 138.0 (CH), 139.3 (C), 155.5 (C), 197.0 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{23}H_{30}N_2NaO_4$ 421.2097, found 421.2089.

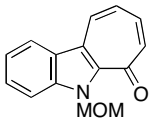
10-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-5-(methoxymethyl)-9,10-dihydro-*5H*-cyclohepta[*b*]indole-6-ona (16)



16

(Im)(PCy_3)$(Cl)_2$Ru=CHPh (second generation Grubbs catalyst, 30 mg, 7 mol %) was added under Ar to a solution of ketone **15** (0.2 g, 0.50 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was heated at reflux overnight. The reaction mixture was concentrated and the residue was chromatographed (SiO_2, 9:1 hexanes-AcOEt) to give **16**: 120 mg (65%); ^{1}H NMR ($CDCl_3$, 300 MHz, major rotamer) δ 1.54 (s, 9H), 2.66 (s, 3H), 2.85-3.05 (m, 2H), 3.32 (s, 3H), 6.01 (d, *J* =10.5 Hz, 1H), 6.10 (d, *J* = 10.5 Hz, 1H), 6.32 (d, *J* = 11 Hz, 1H), 6.65 (m, 1H), 7.18-7.30 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, major rotamer) δ 28.8 (CH_3), 31.7 (CH_3), 33.3 (CH_2), 49.7 (CH), 56.4 (CH_3), 75.9 (CH_2O), 80.1 (C), 111.5 (CH), 121.9 (CH), 122.2 (CH), 123.6 (C), 126.4 (C), 127.6 (CH), 134.8 (CH), 139.4 (CH), 140.2 (C), 155.5 (C), 185.4 (C). One quaternary C was not observed; ESI-HRMS calcd for $C_{21}H_{26}N_2O_4$ 370.1892, found 370.1910.

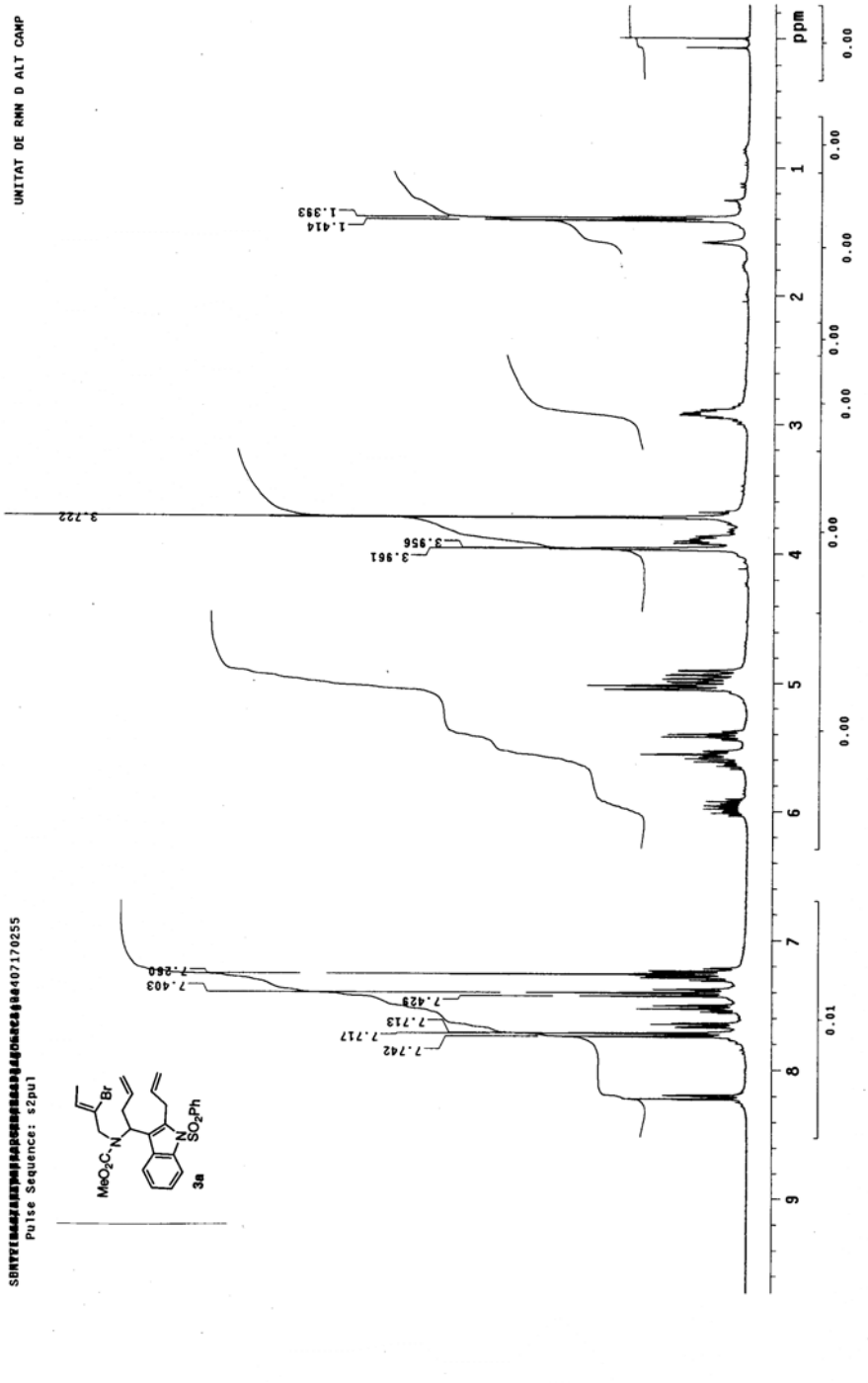
5-(Methoxymethyl)cyclohepta[*b*]indol-6-ona (17)

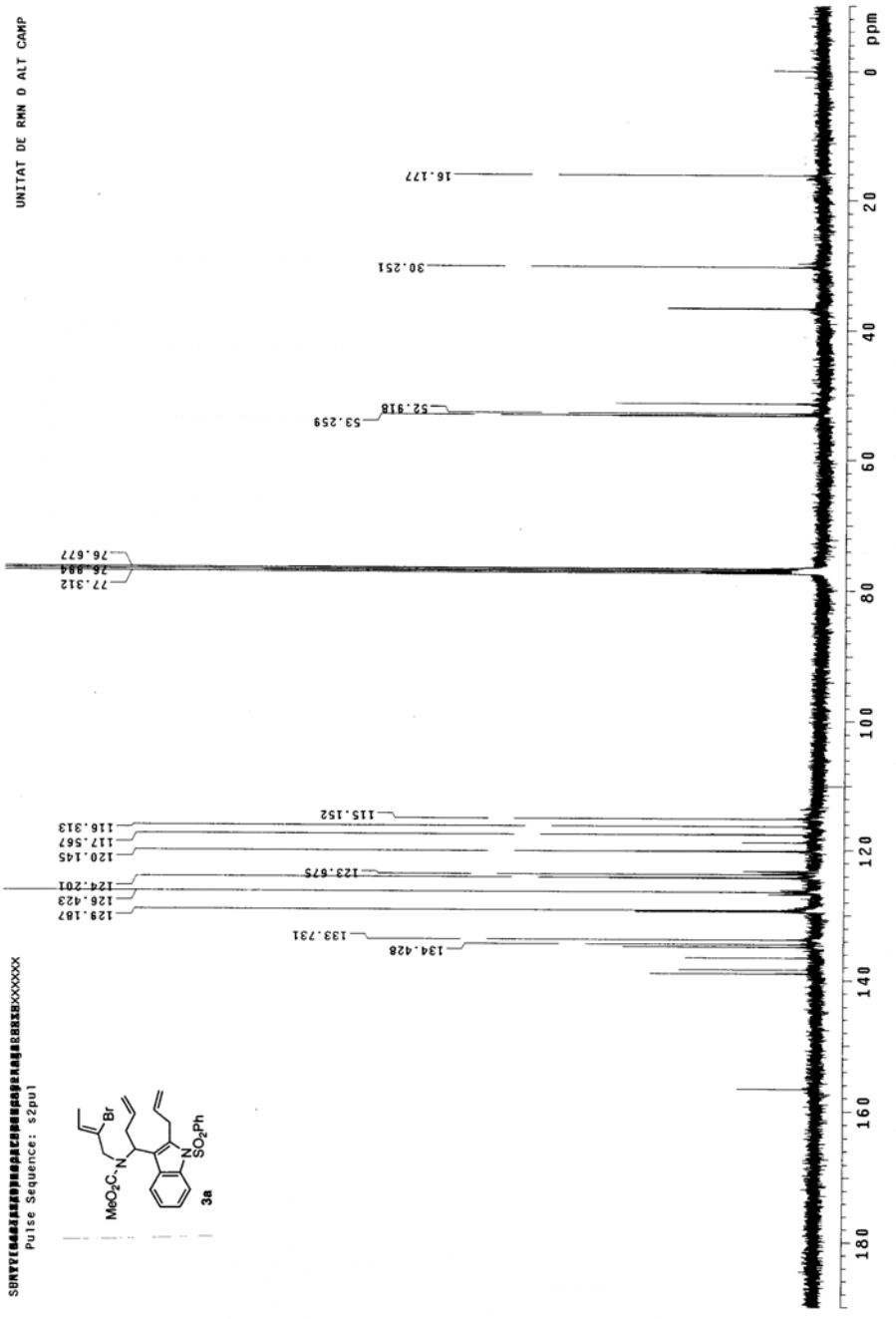


17

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.37 (s, 3H), 6.52 (s, 2H), 7.01 (m, 1H), 7.24-7.38 (m, 2H), 7.42 (tm, *J* = 8 Hz, 1H), 7.62 (tm, *J* = 8 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 56.2 (CH_3), 75.6 (CH_2), 112.2 (CH), 120.8 (CH), 122.7 (CH), 124.9 (CH), 125.1 (C), 126.0 (C), 128.4 (CH), 129.3 (CH), 135.3 (CH), 138.0 (CH), 140.3 (C), 140.5 (C), 179.7 (C); ESI-HRMS calcd for $C_{15}H_{13}NO_2$ 239.0946, found 239.0944.

^{1}H and ^{13}C NMR Spectra

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Br
N
SO2Ph
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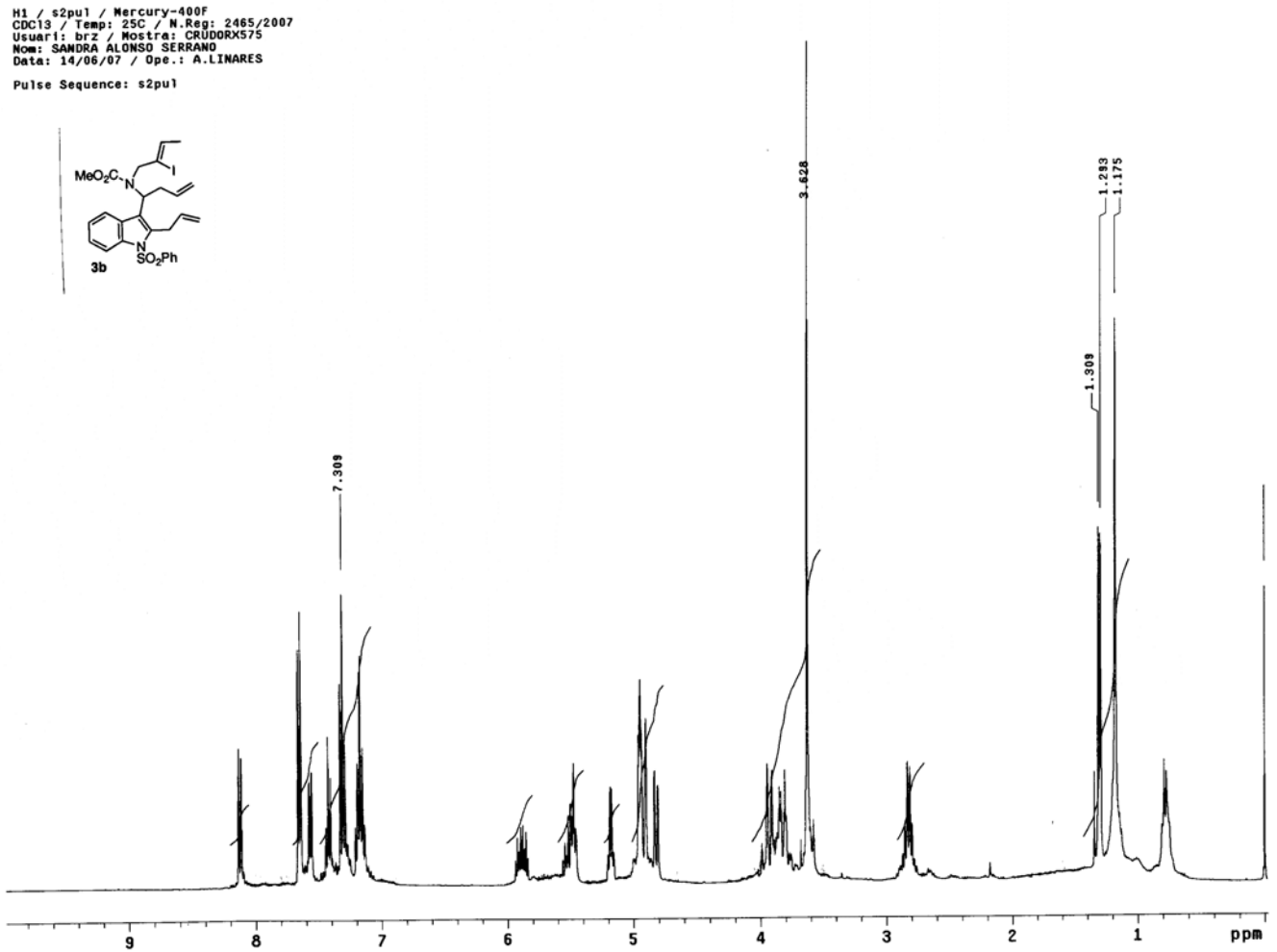
30.251
52.918
53.259
76.677
76.884
77.312
115.152
116.313
117.567
120.145
123.675
124.201
126.423
129.187
133.731
134.428
0
20
40
60
80
100
120
140
160
180
ppm


H1 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: 2465/2007
Usuari: brz / Mostra: CRUDORX575
Nom: SANDRA ALONSO SERRANO
Data: 14/06/07 / Ope.: A.LINARES
Pulse Sequence: s2pul
MeO2C
N
I
N
SO2Ph
3b
7.309
3.628
1.303
1.293
1.175
9
8
7
6
5
4
3
2
1
ppm

3b
C13 / S2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: 2465/2007
Usuario: brz / Nombre: CRUDORX575
Nom: SANDRA ALONSO SERRANO
Data: 14/06/07 // Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
Sample #6, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
512 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
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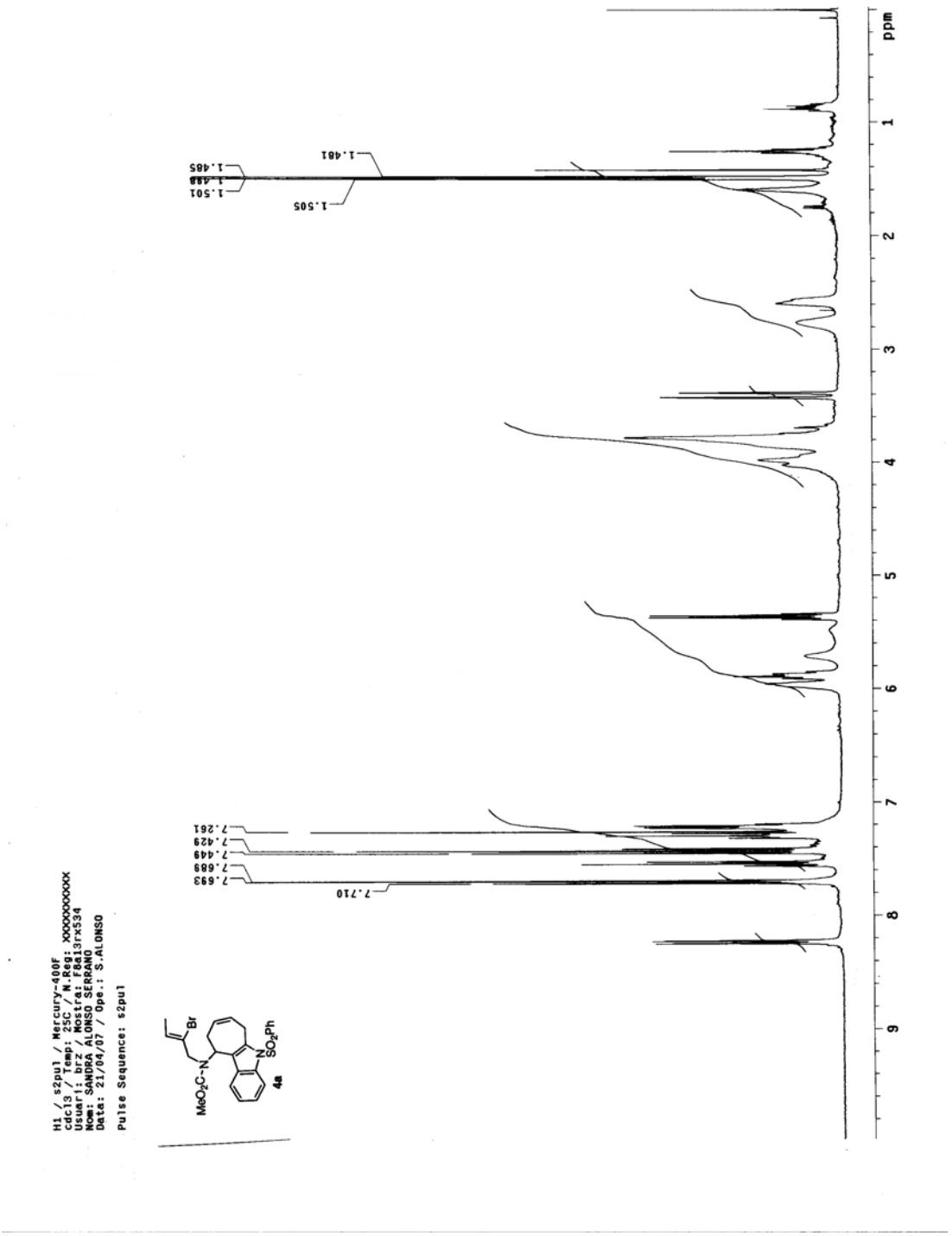
160
140
120
100
80
60
40
20
0
ppm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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F8a13rx534
Nom: SANDRA ALONSO SERRANO
Data: 21/04/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
MeO2C-N
Br
N
SO2Ph
4a
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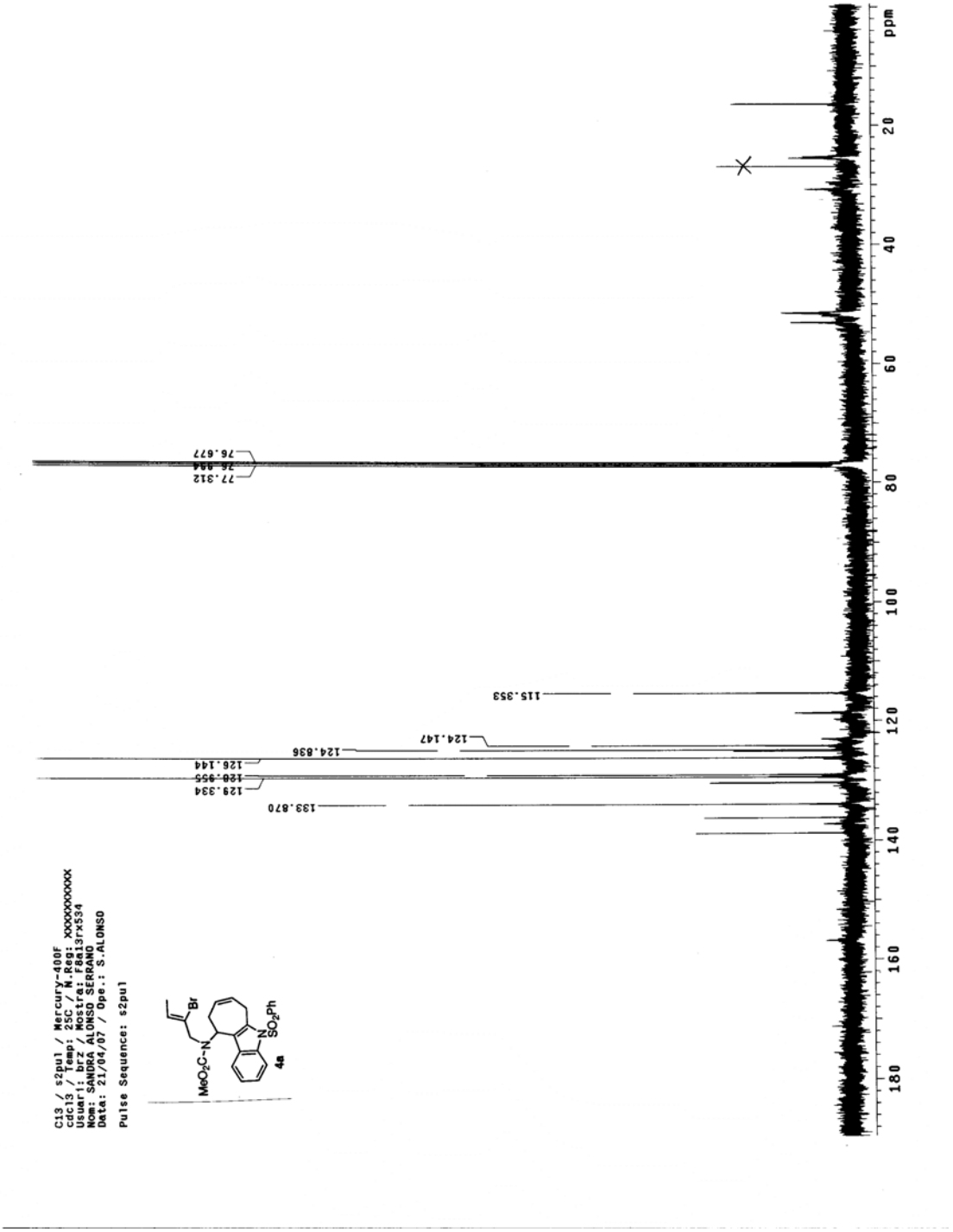
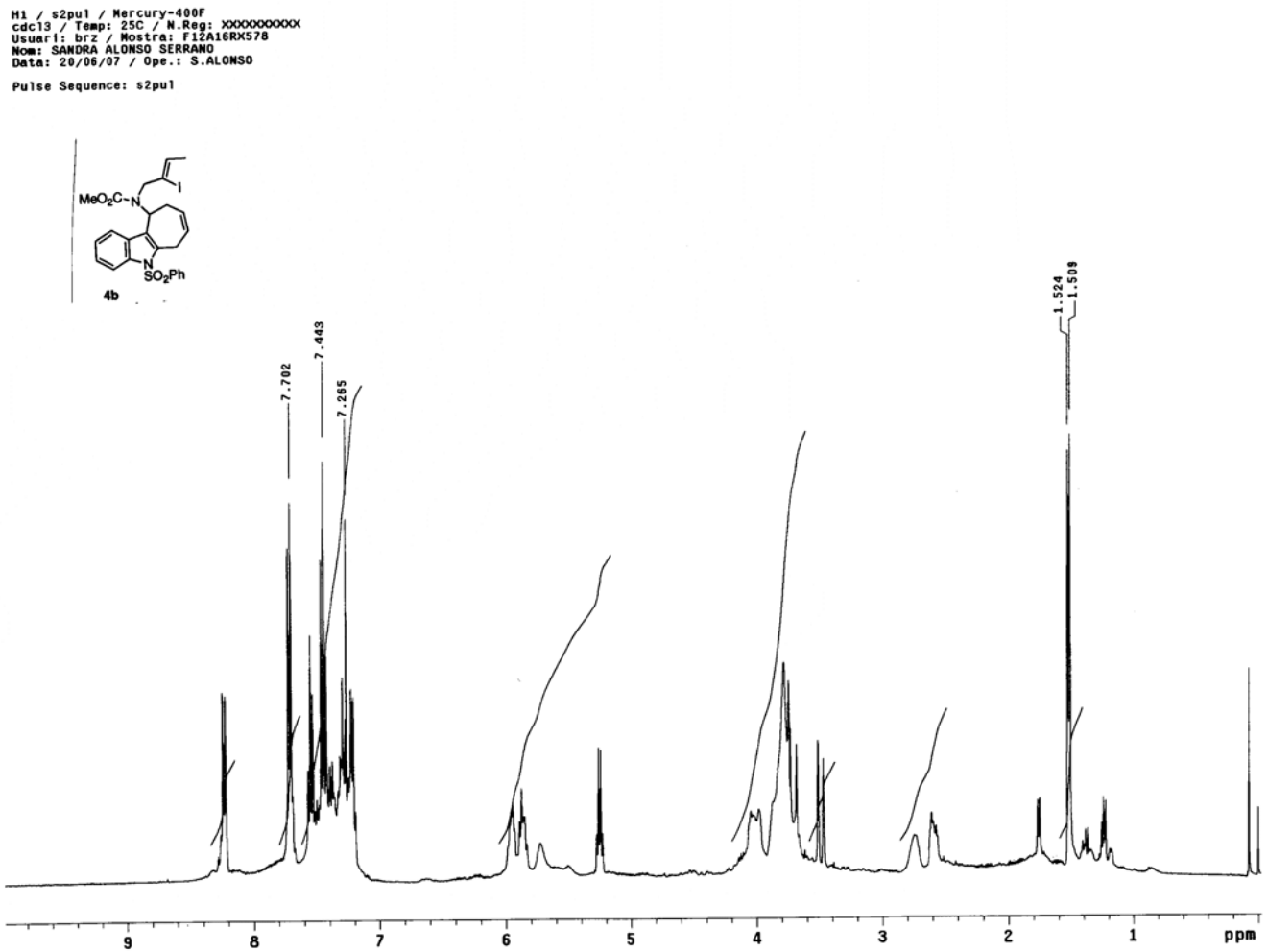
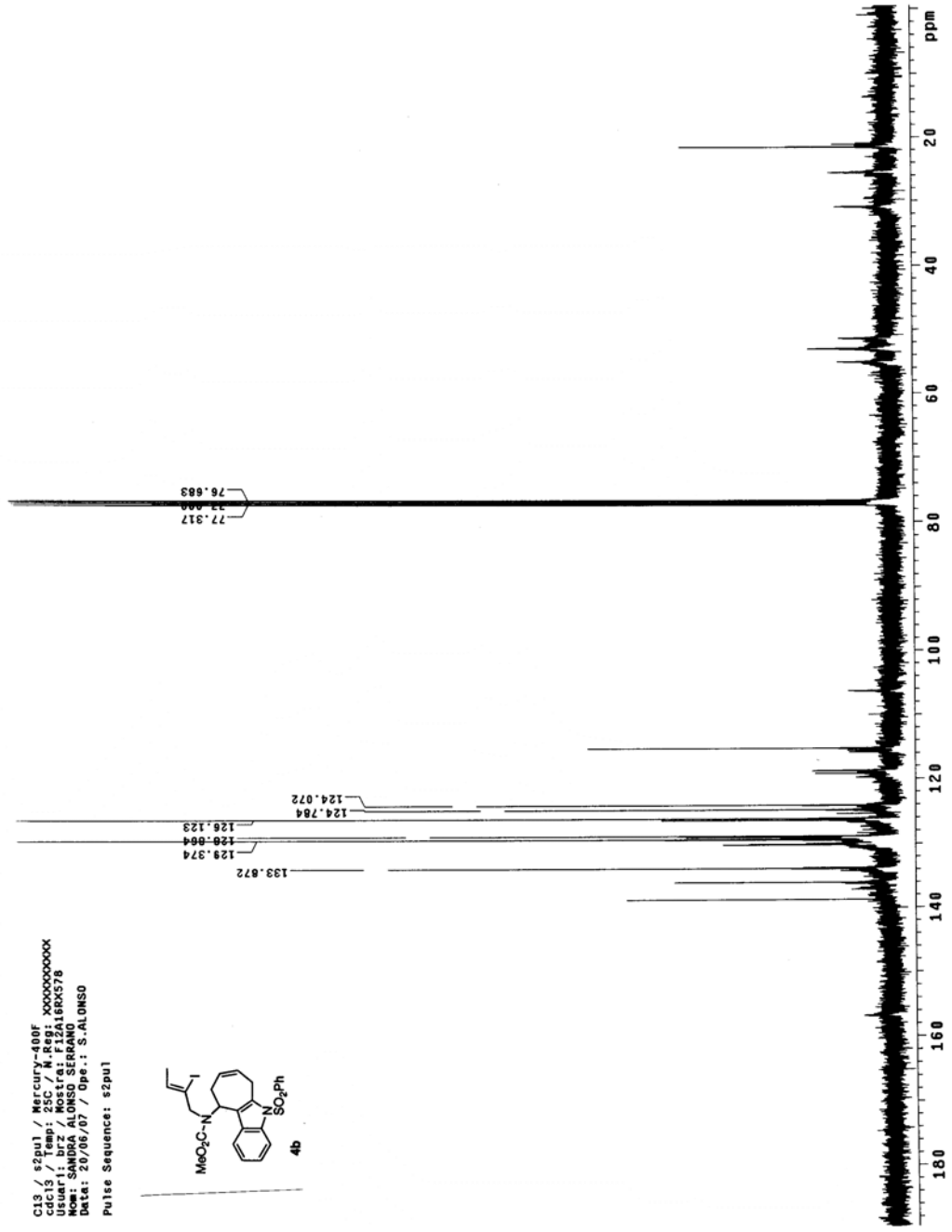
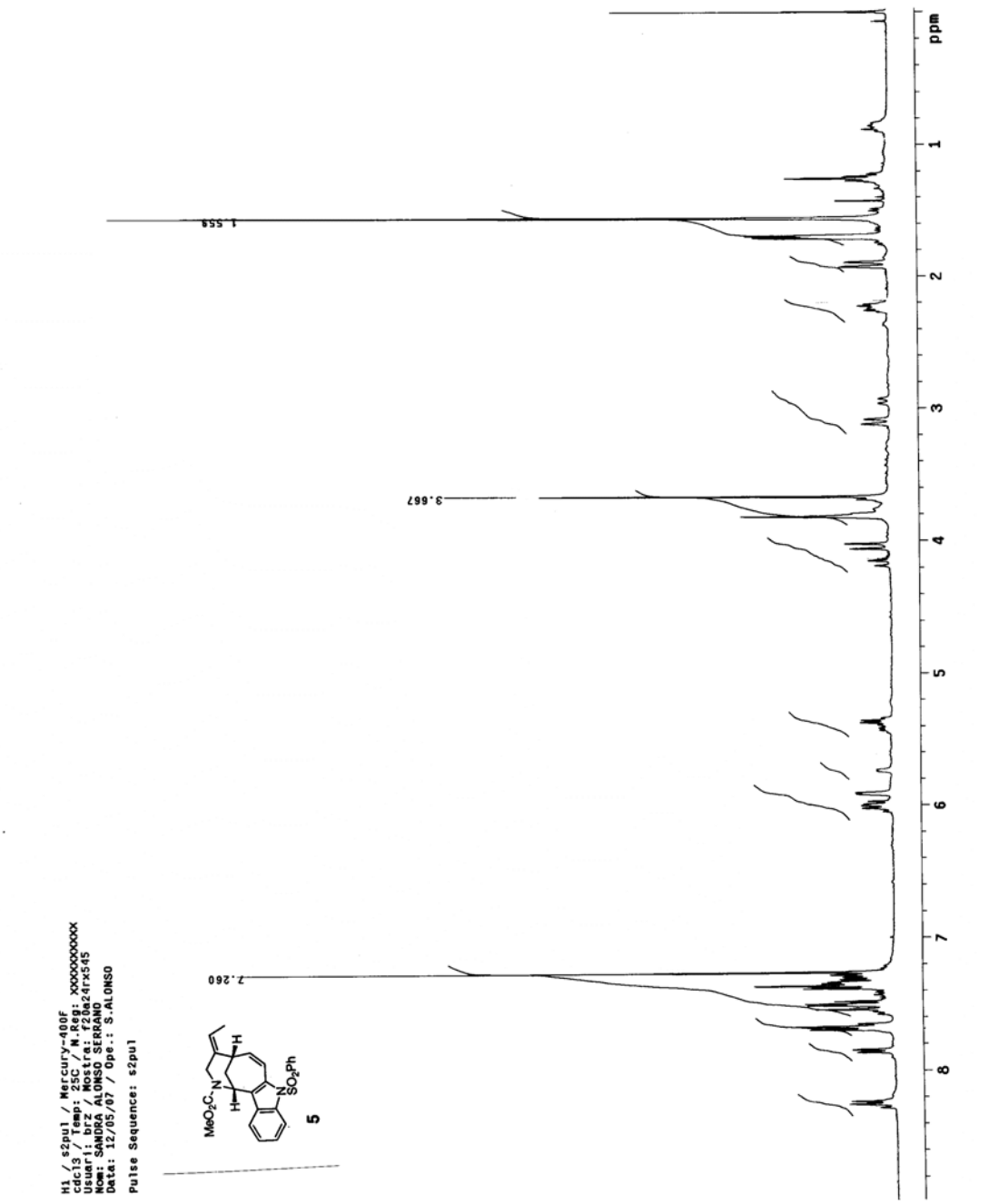
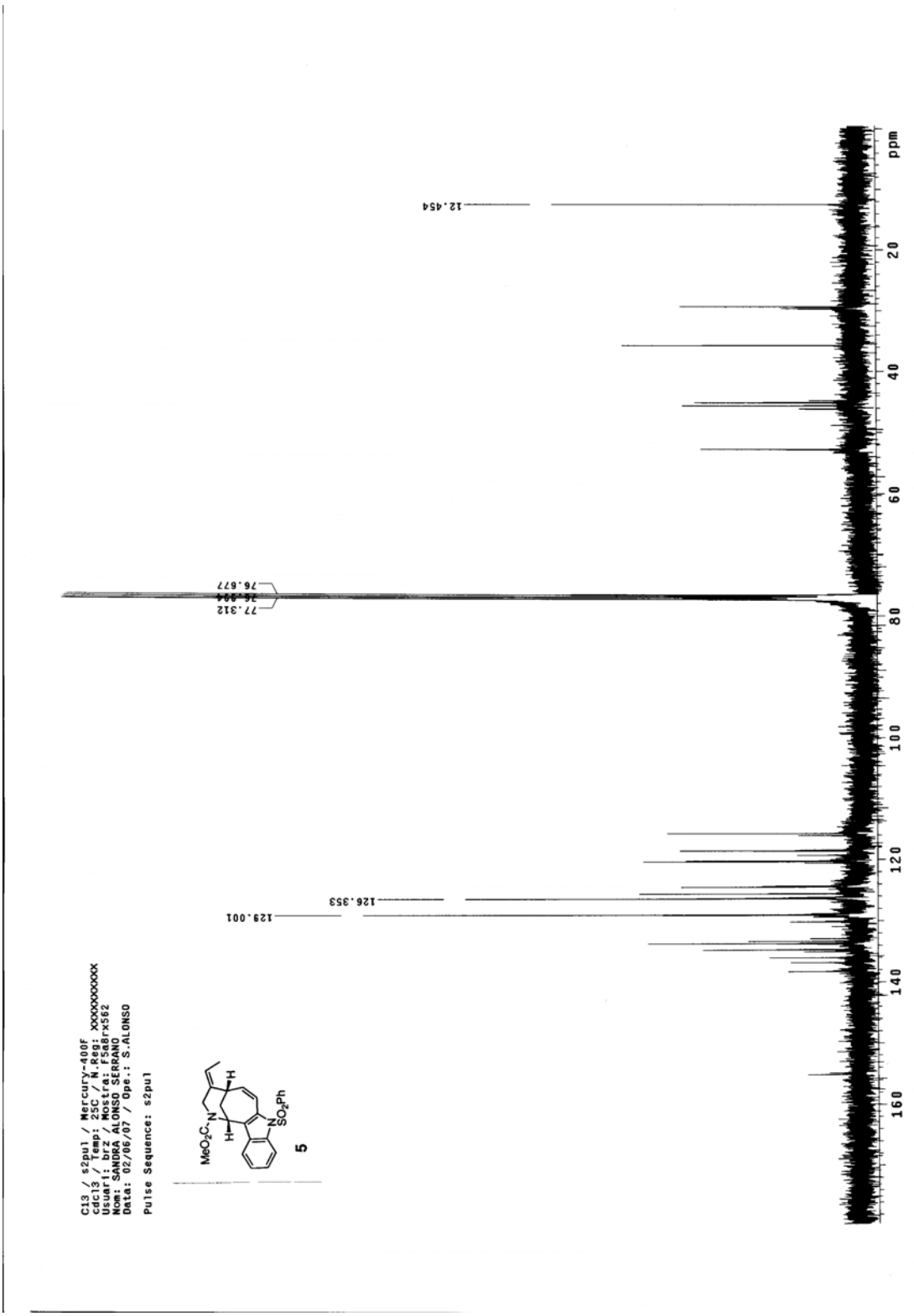
7.449
7.429
7.261
7.710
1.505
1.501
1.488
1.485
1.481
ppm


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: brz / Mostra: F8a13rx534
Nom: SANDRA ALONSO SERRANO
Data: 21/04/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
MeO2C-N
Br
N
SO2Ph
4a
133.870
129.334
128.955
126.144
124.836
124.147
115.353
77.312
76.994
76.677
ppm
180
160
140
120
100
80
60
40
20


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F12A16RX578
Nom: SANDRA ALONSO SERRANO
Data: 20/06/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
MeO2C-N
I
N
SO2Ph
4b
7.702
7.443
7.265
1.524
1.508
9
8
7
6
5
4
3
2
1
ppm


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: br2 / Mostra: F12A16RX578
Nom: SAMDRA ALONSO SERRANO
Data: 20/06/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
MeO2C-N
I
N
SO2Ph
4b
133.872
129.374
128.864
126.123
124.784
124.072
77.317
76.683
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: brz / Mostra: f20a24rx545
Nom: SANDRA ALONSO SERRANO
Data: 12/05/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
7.260
3.667
1.559
ppm
MeO2C
N
H
H
N
SO2Ph
5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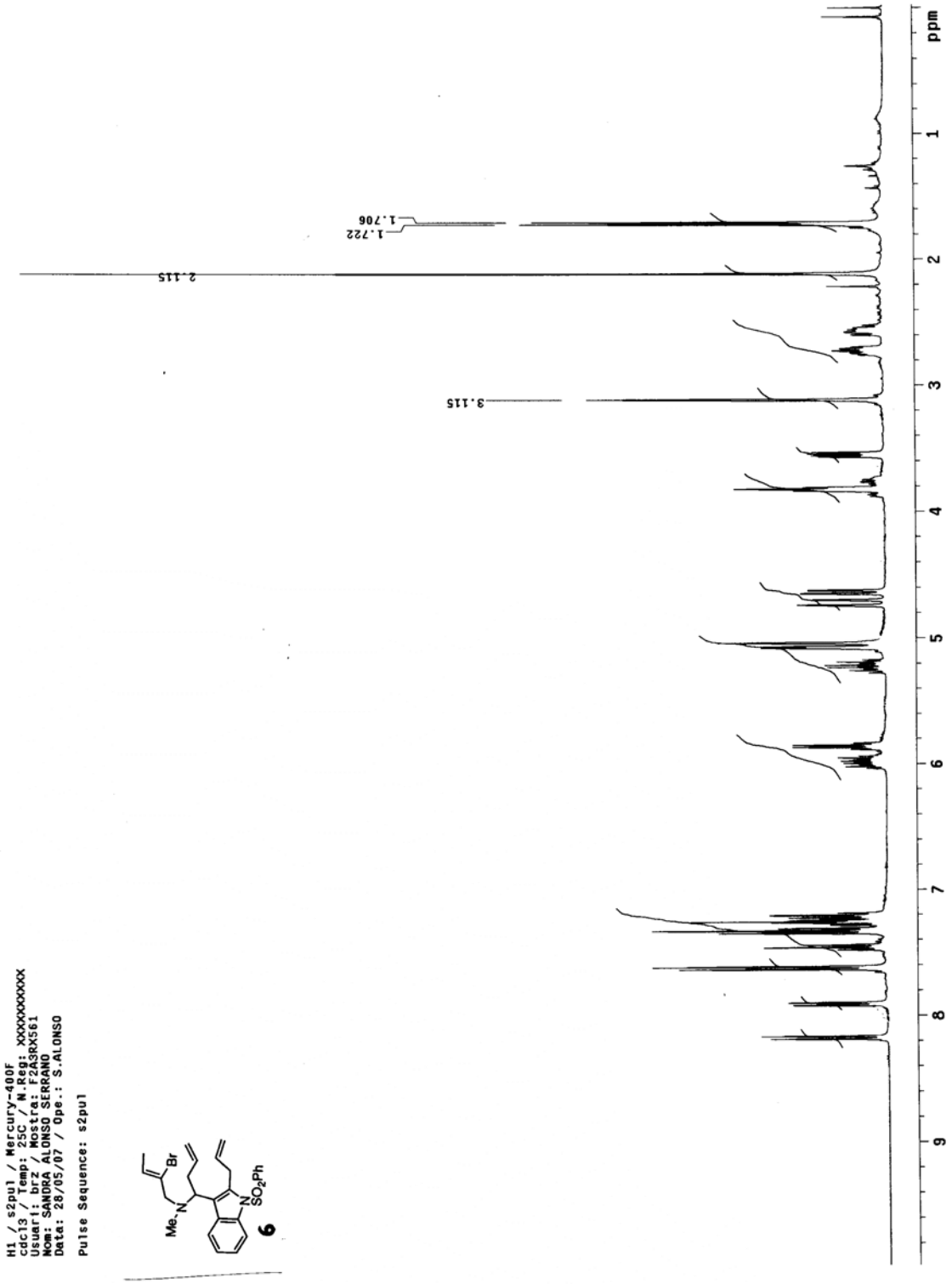
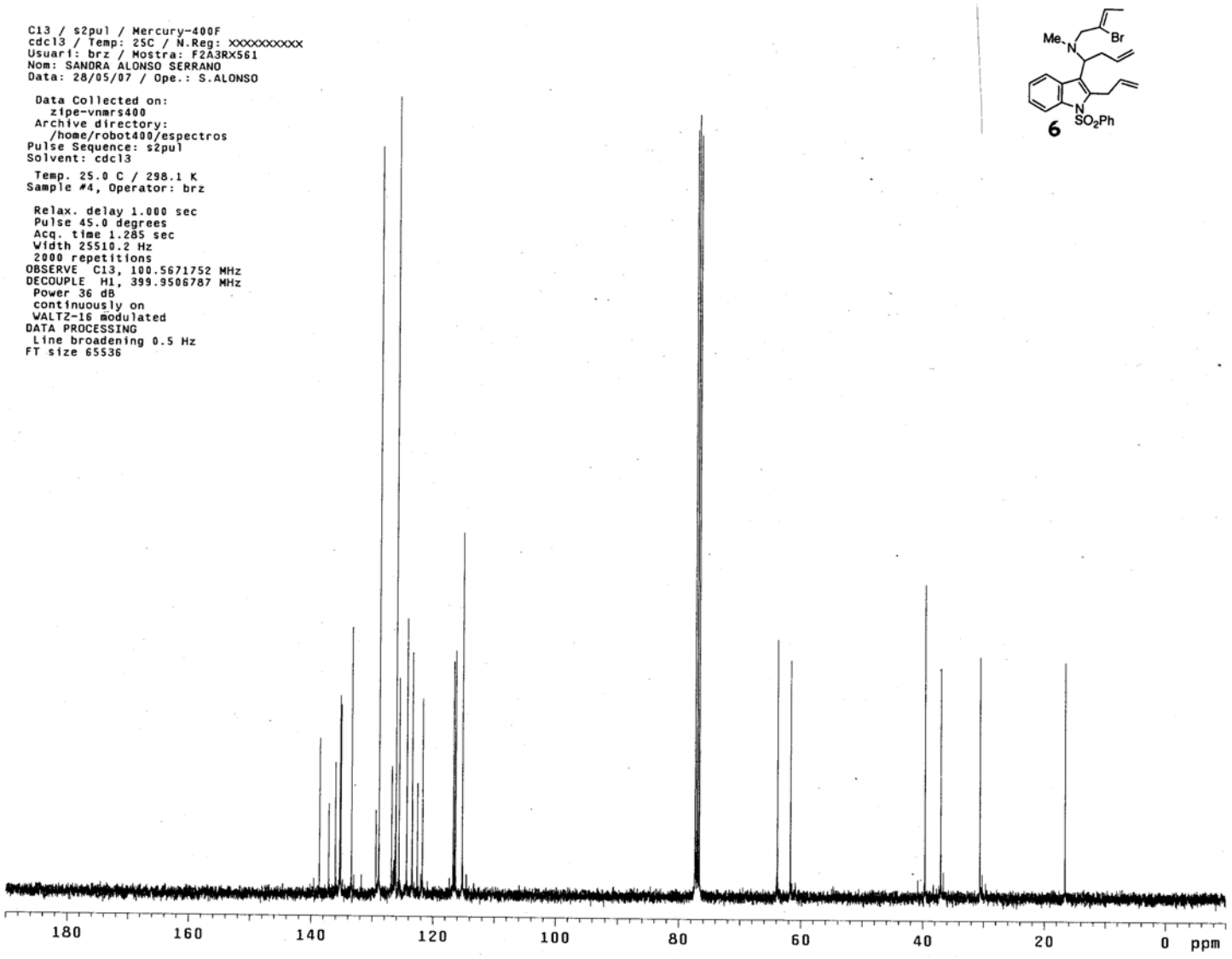
cdcl3 / Temp: 25°C / N° : XXXXXXXXXX
User: / bzz / Astra: FSA8rx562
Nom: SANDRA ALONSO SERRANO
Data: 02/06/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
MeO2C
SO2Ph
5
12.454
76.677
77.312
126.353
129.001
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brZ / Mostra: F2A3RX561
Nom: SANDRA ALONSO SERRANO
Data: 28/05/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
Me
N
Br
N
SO2Ph
6
1.706
1.722
2.115
3.115
ppm


C13 / s2pul / Mercury-400F
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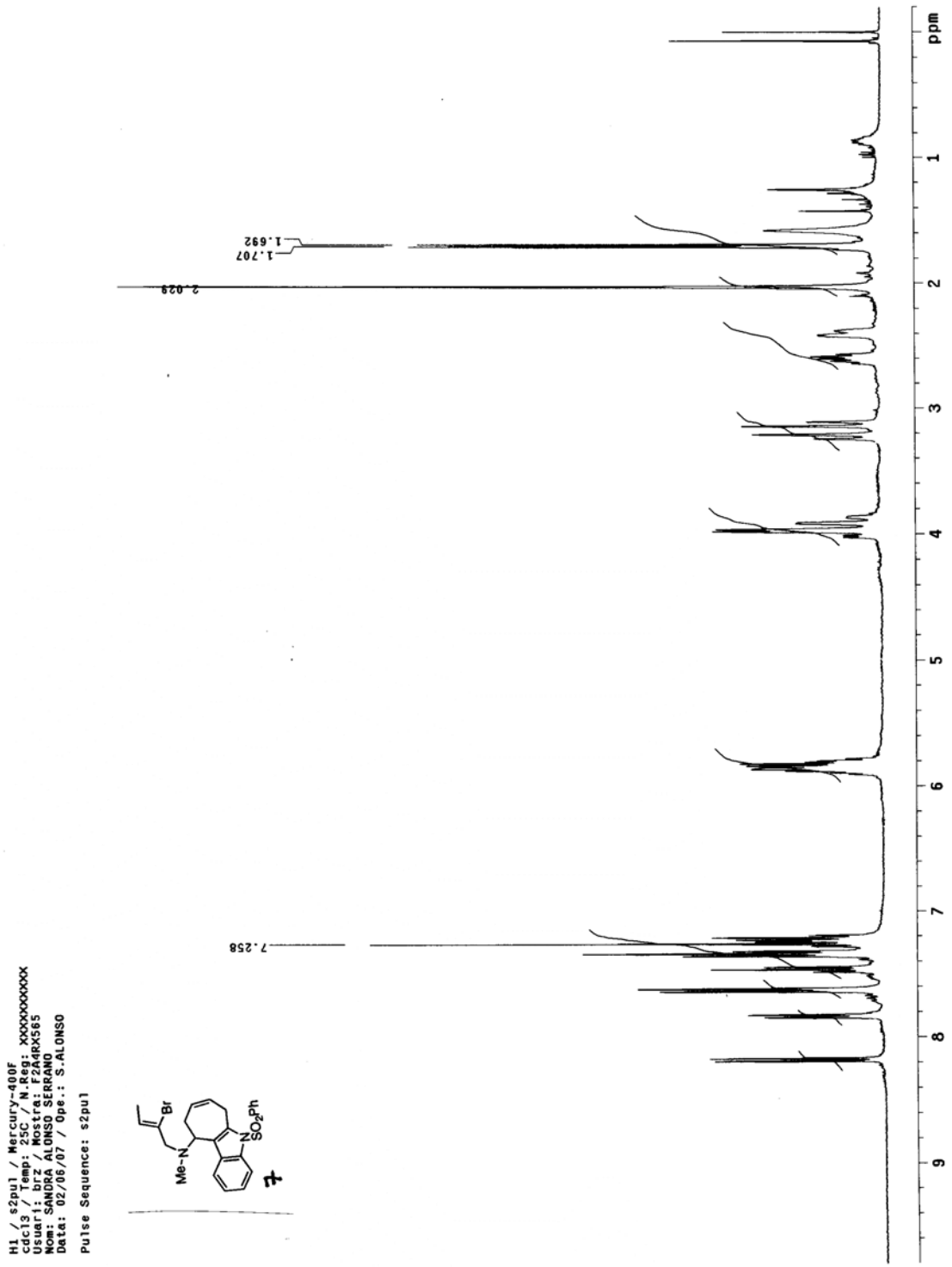
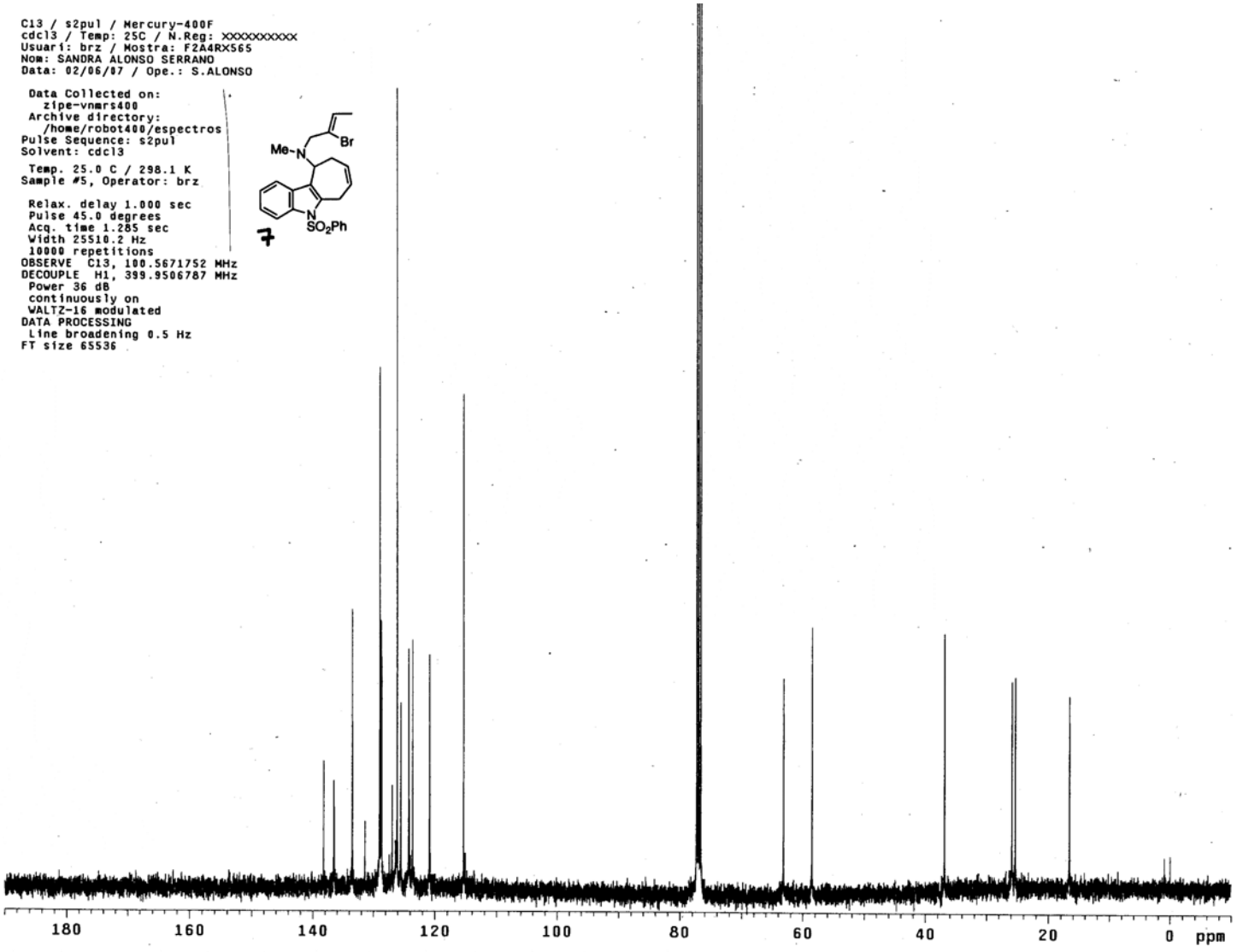
Nom: SANDRA ALONSO SERRANO
Data: 28/05/07 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #4, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
2000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Me
N
Br
N
SO2Ph
6
180
160
140
120
100
80
60
40
20
0
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F2A4RX565
Nom: SANDRA ALONSO SERRANO
Data: 02/06/07 / Ope.: S.ALONSO
Pulse Sequence: s2pul
7.258
2.029
1.707
1.692
Me-N
Br
N
SO2Ph
4
ppm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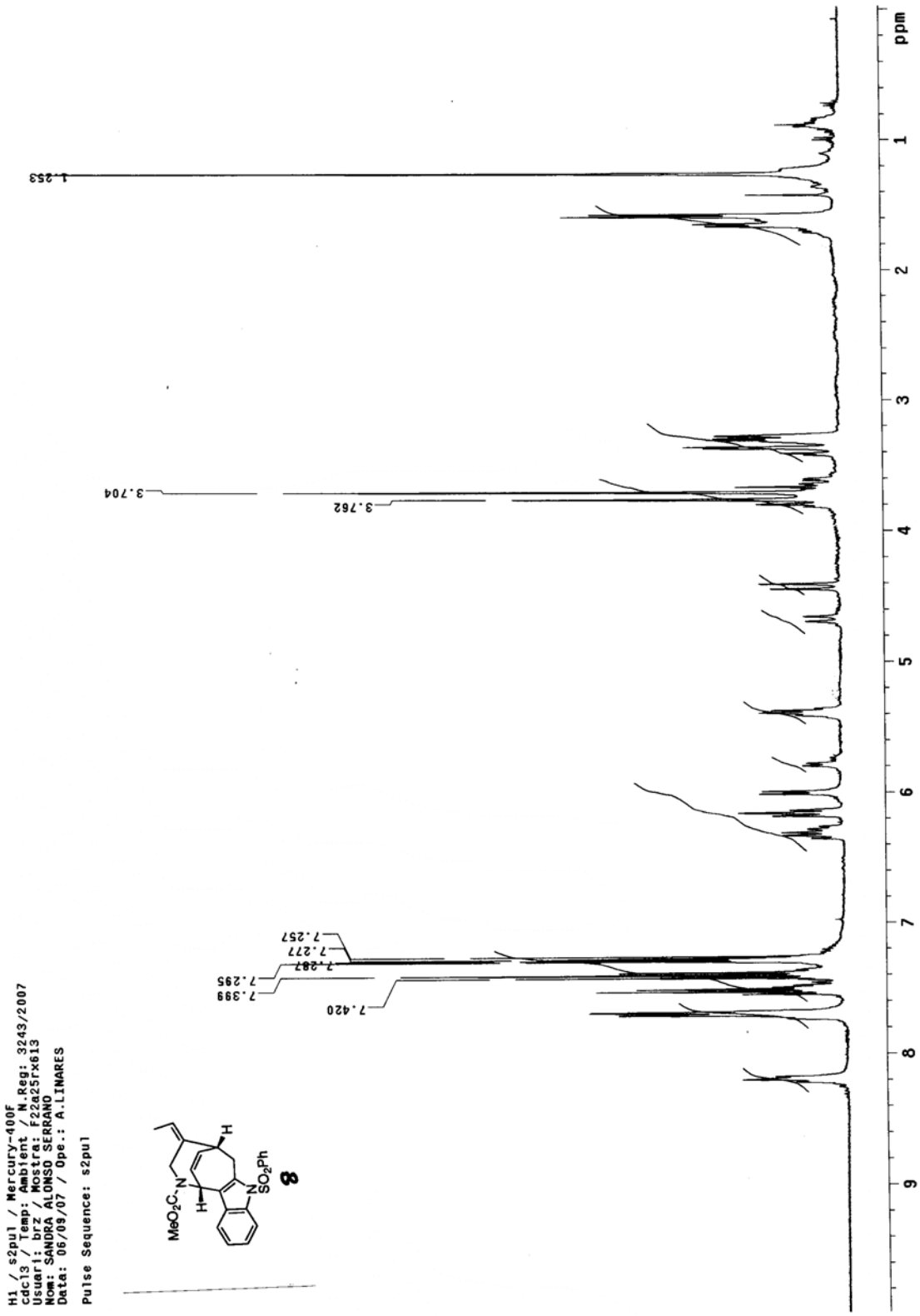
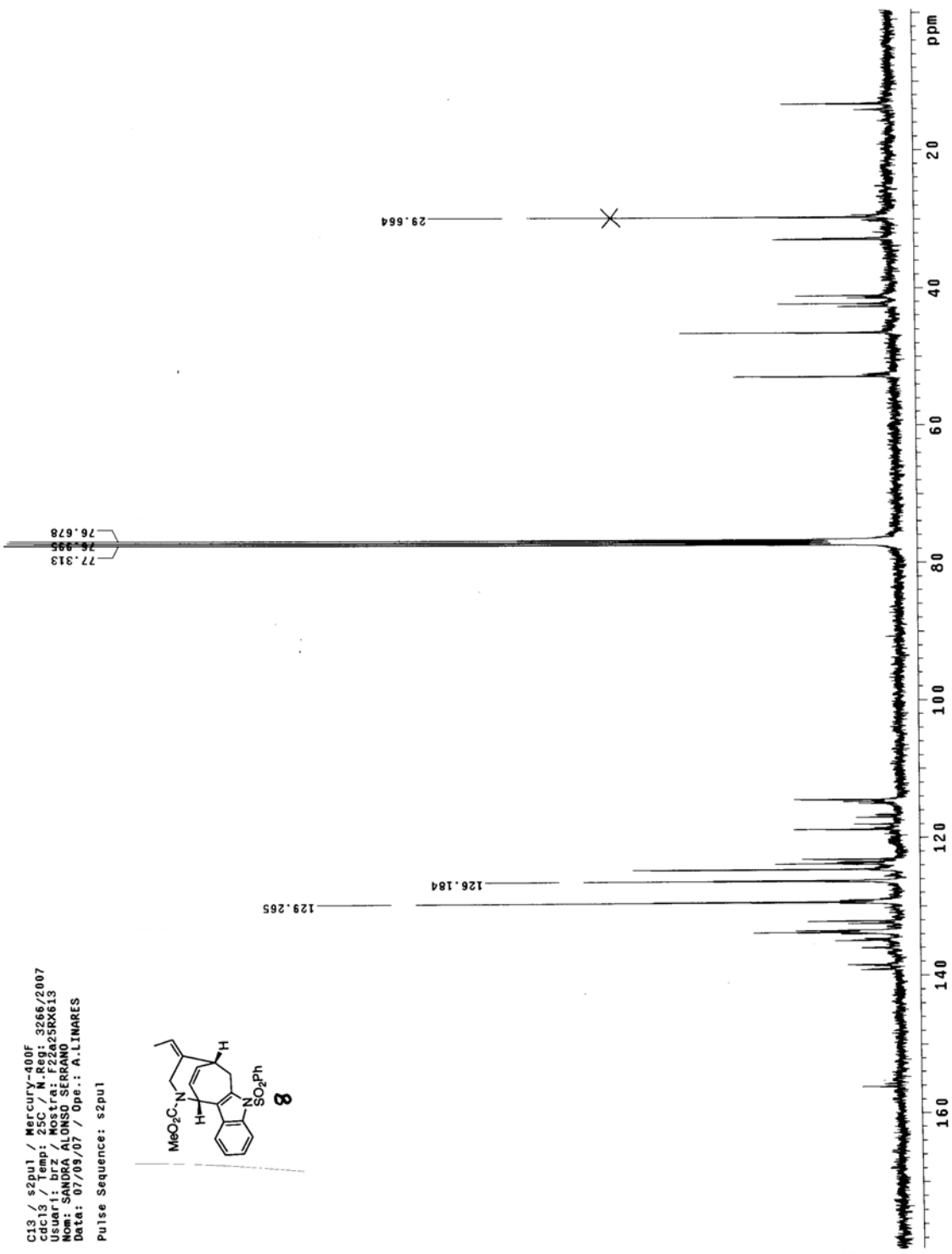
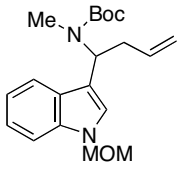
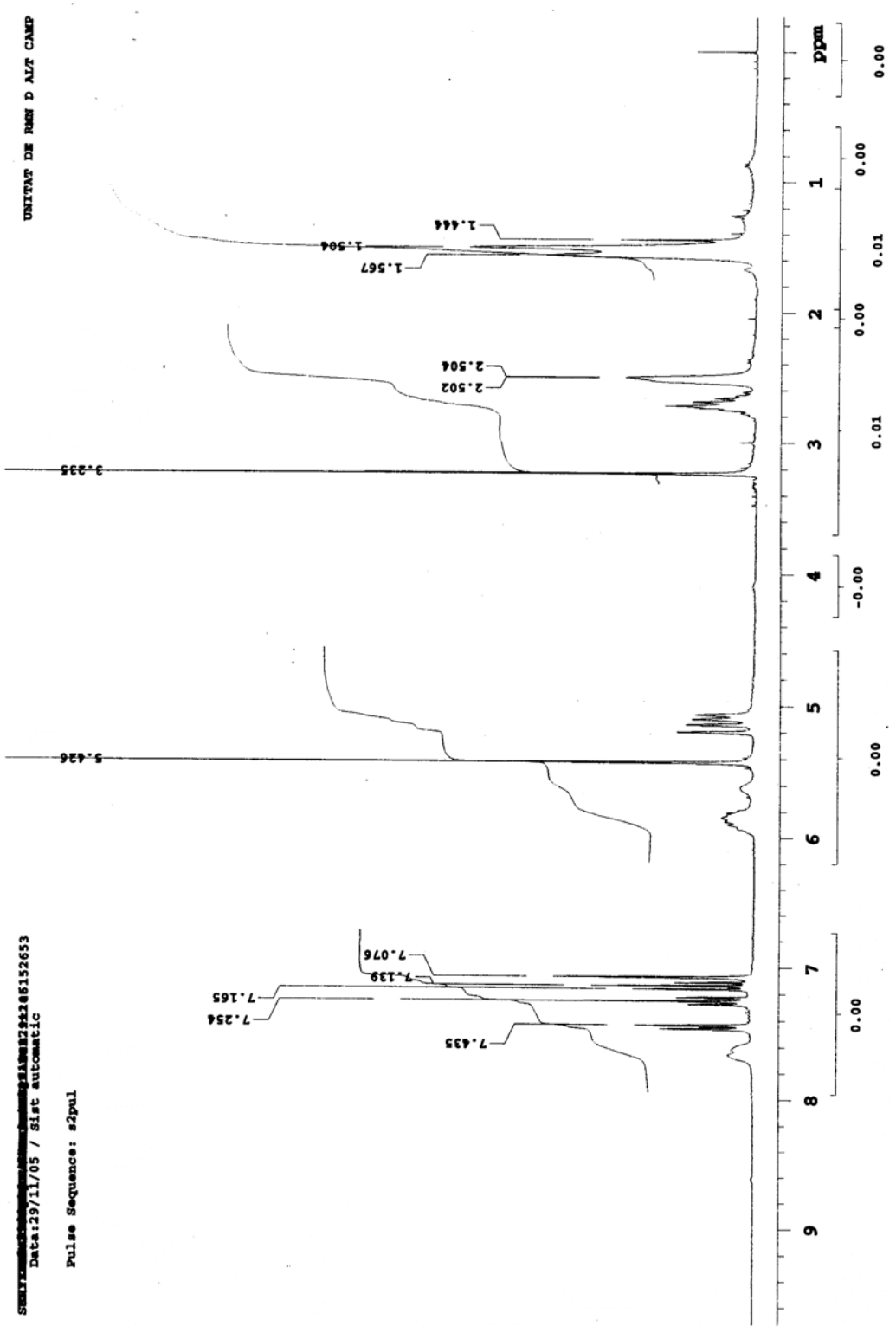
cdcl3 / Temp: 25C / N.Reg: xxxxxxxxxx
Usuari: brz / Mostra: F2A4RX565
Nom: SANDRA ALONSO SERRANO
Data: 02/06/07 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #5, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
10000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Me-N
Br
N
SO2Ph
7
180
160
140
120
100
80
60
40
20
0
ppm

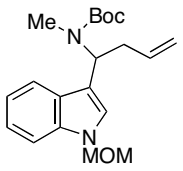

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3243/2007
Usuari: brZ / Mostra: F22a25fx613
Nom: SANDRA ALONSO SERRANO
Data: 06/09/07 / Ope.: A.LINARES
Pulse Sequence: s2pul
MeO2C
N
H
H
N
SO2Ph
8
1.253
3.704
3.762
7.257
7.277
7.287
7.295
7.399
7.420
ppm


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 3266/2007
Usuari: brz / Mostra: F22a25RX613
Nom: SANDRA ALONSO SERRANO
Data: 07/09/07 / Ope.: A.LINARES
Pulse Sequence: s2pul
MeO2C
N
H
H
N
SO2Ph
8
29.664
76.678
77.313
126.184
129.265
ppm
20
40
60
80
100
120
140
160

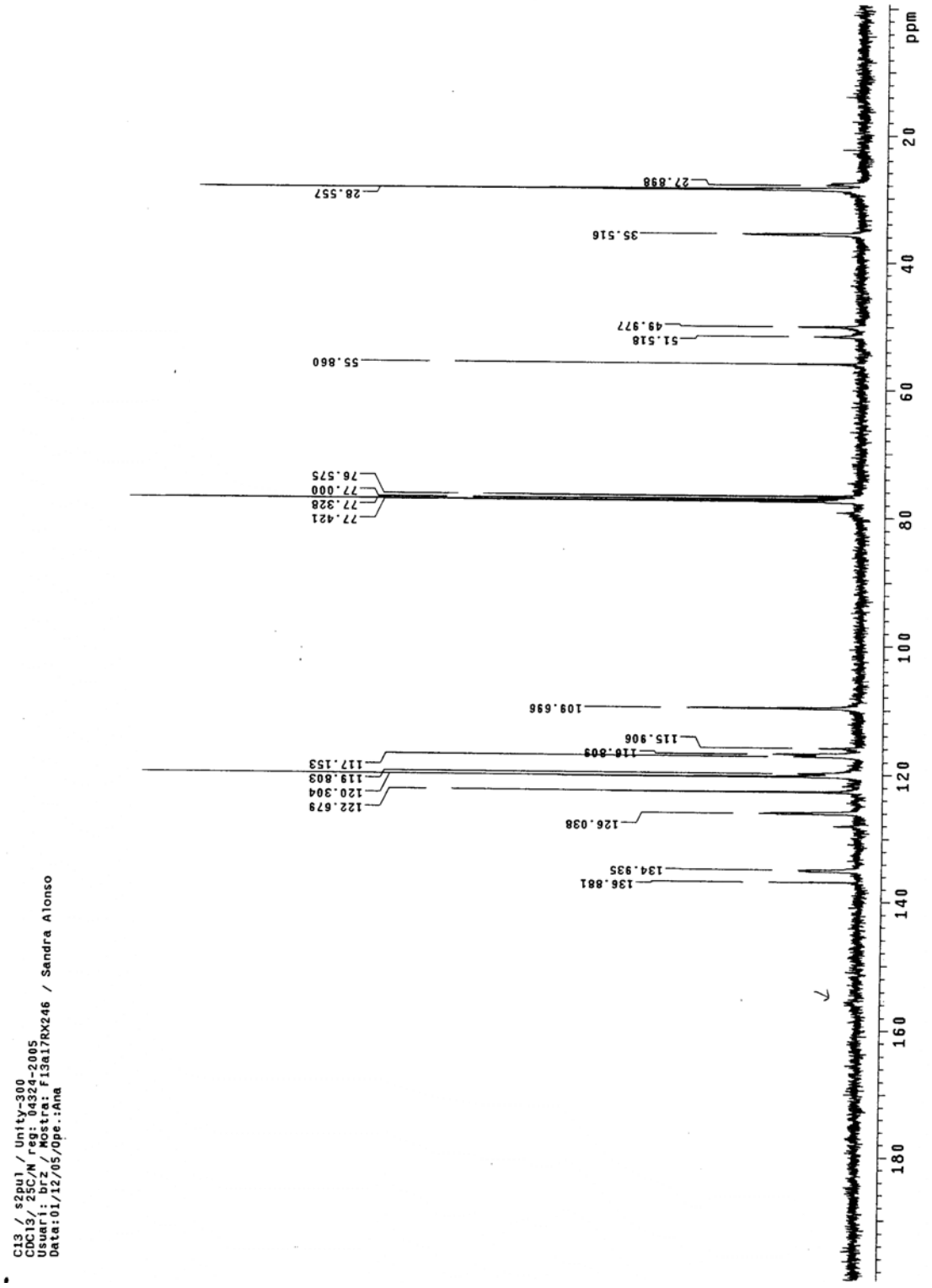

Me
N
Boc
N
MOM

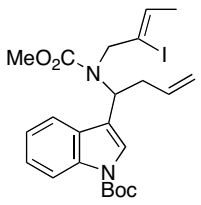
11


UNITAT DE RMN D AL/T CAMP
Data:29/11/05 / Sist automatic
Pulse Sequence: s2pul
1.444
1.504
1.567
2.502
2.504
3.235
5.436
7.076
7.139
7.165
7.254
7.435
ppm

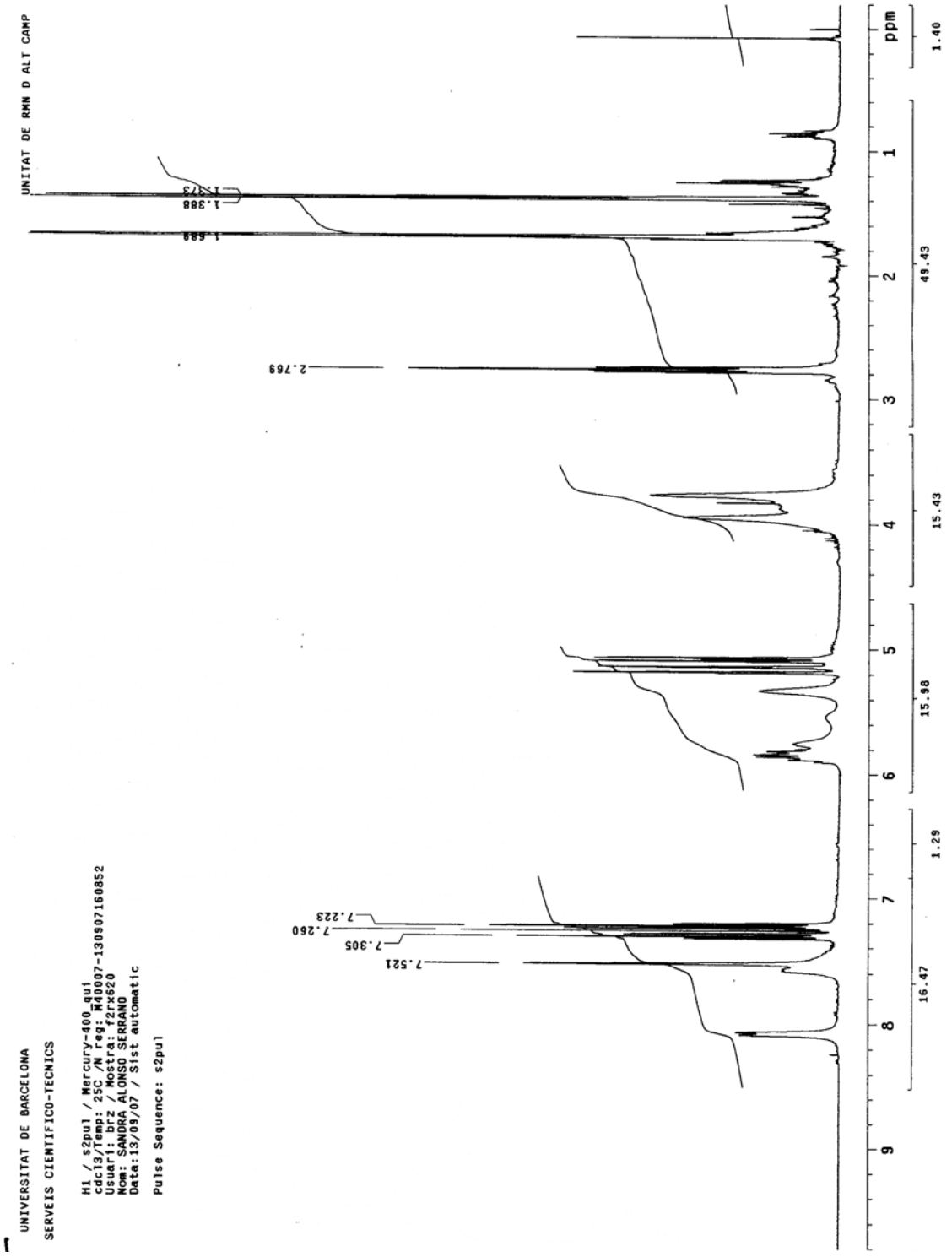

Me
N
Boc
N
MOM

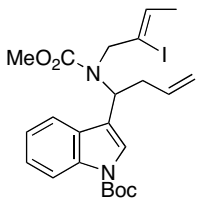
11


C13 / s2pul / Unity-300
CDCl3/ 25C/N reg: 04324-2005
Usuari: brz / Mostra: F13a17RX246 / Sandra Alonso
Data:01/12/05/Ope.:Ana
27.898
28.557
35.516
49.977
51.518
55.860
76.575
77.000
77.328
77.421
109.696
115.906
116.809
117.153
119.603
120.304
122.679
126.038
134.935
136.881
ppm
20
40
60
80
100
120
140
160
180

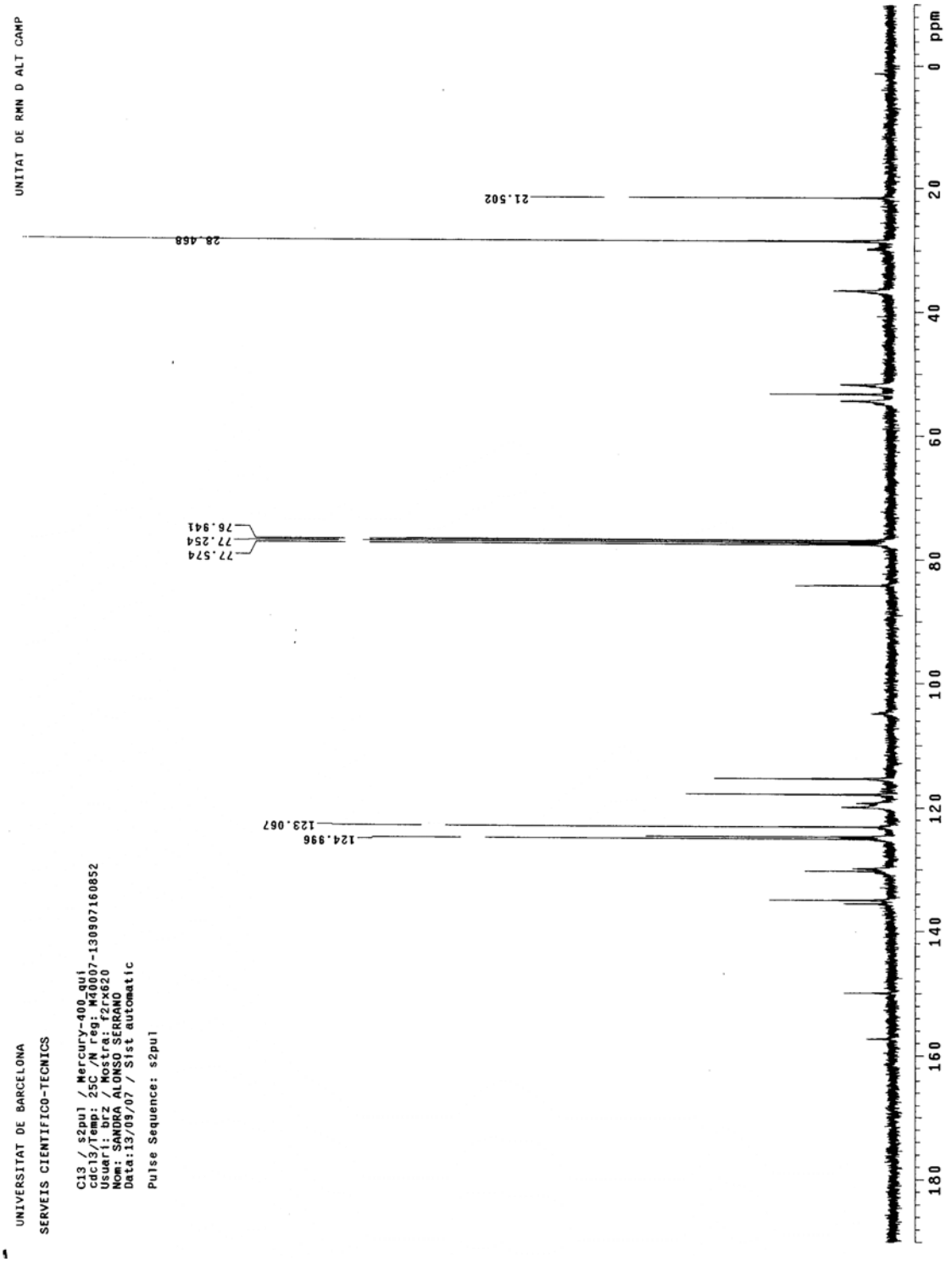

MeO2C
N
I
N
Boc

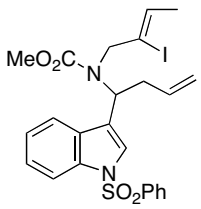
12b


UNITAT DE RMN D ALT CAMP
UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400_qu1
cdcl3/Temp: 25C /N reg: M40007-130907160852
Usuari: brz / Mostra: f2rx620
Nom: SANDRA ALONSO SERRANO
Data:13/09/07 / Sist automatic
Pulse Sequence: s2pul
1.373
1.388
1.689
2.769
7.223
7.260
7.305
7.521
ppm
16.47
1.29
15.98
15.43
49.43
1.40

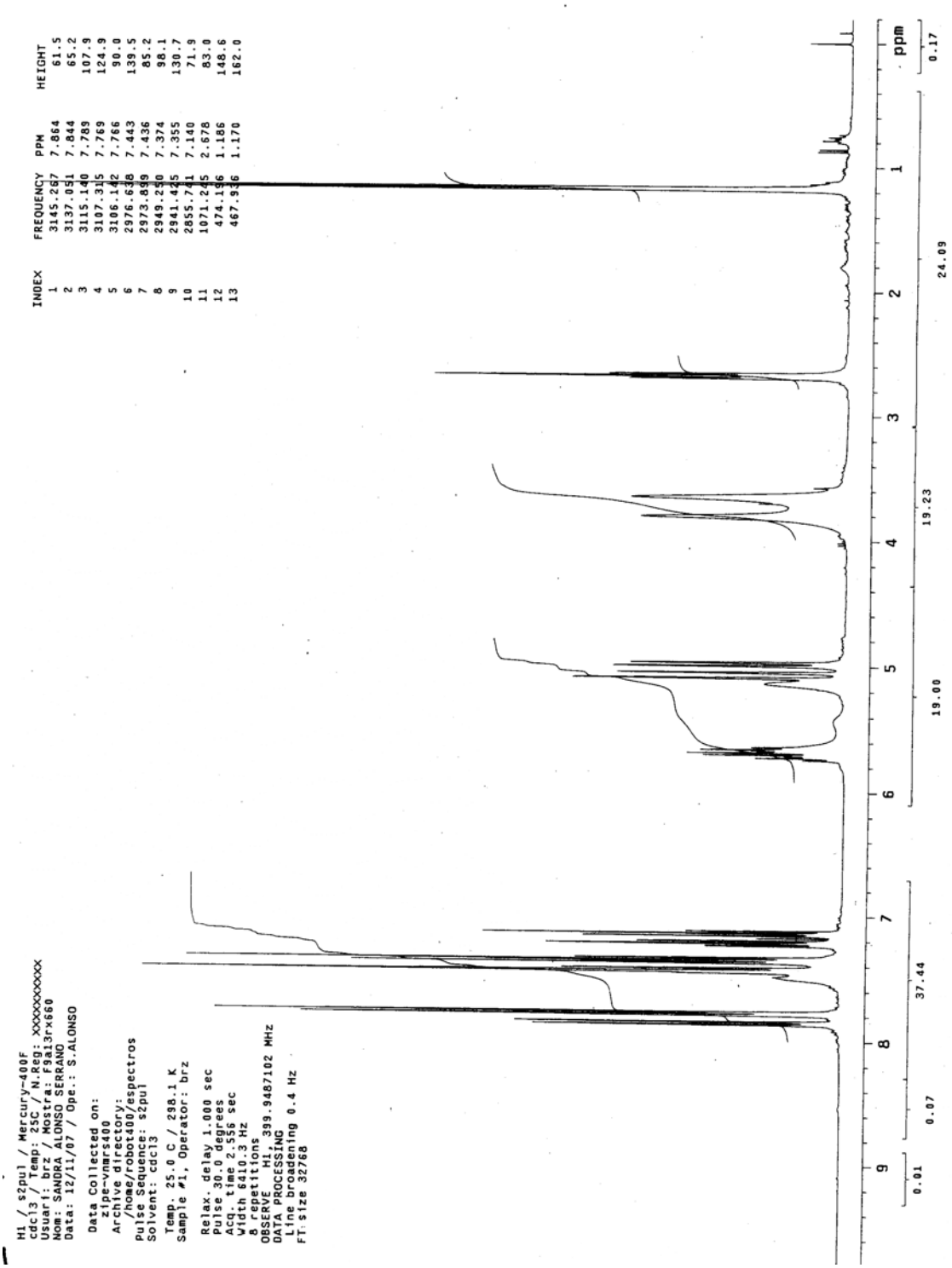

MeO2C
N
I
N
Boc

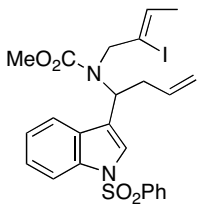
12b


UNITAT DE RMN D ALT CAMP
UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400.gui
cdcl3/Temp: 25C /N reg: MG0007-130907160852
Usuari: BRZ / Nostra: f2rx620
Nom: SANDRA ALONSO SERRANO
Data:13/09/07 / Sist automatic
Pulse Sequence: s2pul
21.502
28.468
76.941
77.254
77.574
123.067
124.996
0 ppm
20
40
60
80
100
120
140
160
180

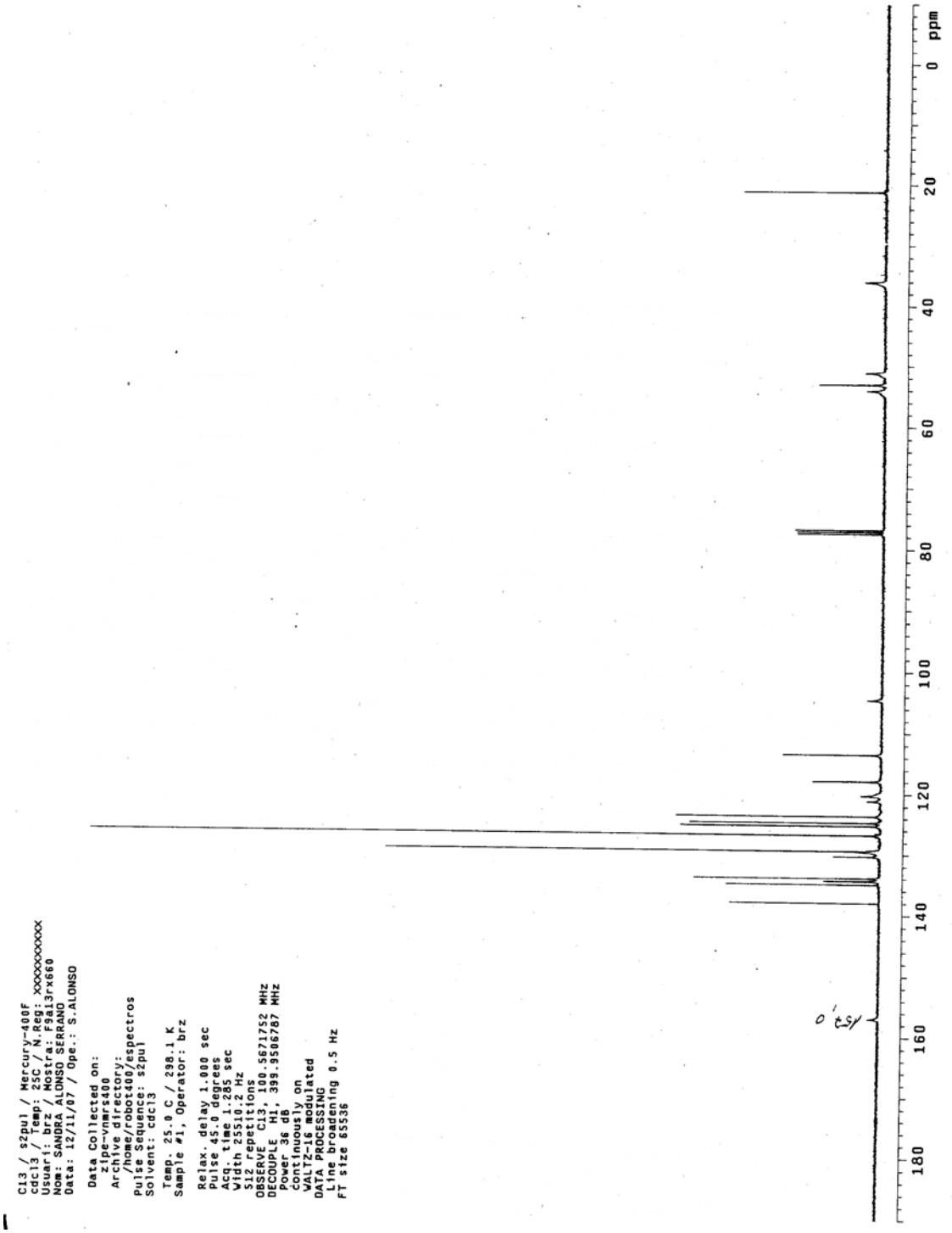

MeO2C
N
I
N
SO2Ph

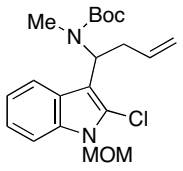
12c


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: brz / Mostra: F9813rx660
Nom: SANDRA ALONSO SERRANO
Data: 12/11/07 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: brz
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9487102 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
INDEX FREQUENCY PPM HEIGHT
1 3145.287 7.864 61.5
2 3137.051 7.844 65.2
3 3115.140 7.789 107.9
4 3107.315 7.769 124.9
5 3106.142 7.766 90.0
6 2976.638 7.443 139.5
7 2973.859 7.436 85.2
8 2949.250 7.374 98.1
9 2941.425 7.355 130.7
10 2855.741 7.140 71.9
11 1071.245 2.678 83.0
12 474.196 1.186 148.6
13 467.936 1.170 162.0
ppm
0.01
0.07
37.44
19.00
19.23
24.09
0.17


MeO2C
N
I
N
SO2Ph

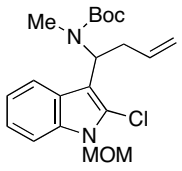
12c


C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: FB13rx660
Nom: SANDRA ALONSO SERRANO
Data: 12/11/07 / Ope.: S.ALONSO
Data Collected on:
z1pe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
512 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
ppm
0
20
40
60
80
100
120
140
160
180

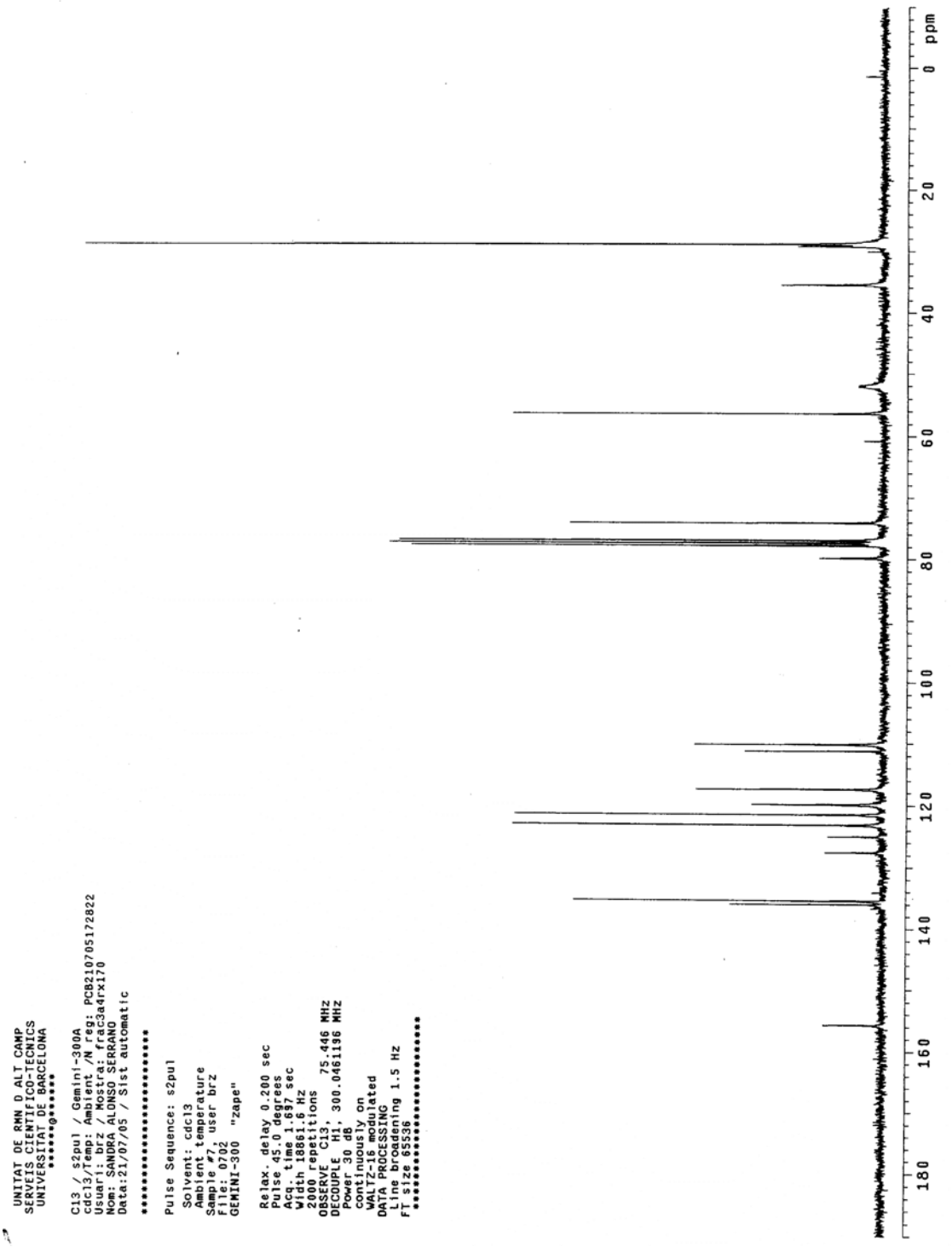

Me
N
Boc
Cl
N
MOM

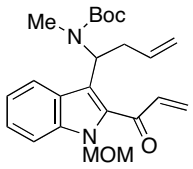
14

UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB210705172822
Usuari: brz / Mostra: freC3a4rx170
Nom: SANDRA ALONSO SERRANO
Data:21/07/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #7, user brz
File: 0701 "zape"
GEMINI-300 "zape"
Relax. delay 1.000 sec
Pulse 20.0 degrees
Acq. time 3.000 sec
Width 4800.7 Hz
32 repetitions
OBSERVE H1, 300.045 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 32768
INDEX FREQUENCY PPM HEIGHT
1 2177.214 7.256 13.9
2 2176.628 7.254 22.3
3 1659.723 5.532 74.7
4 984.581 3.281 156.7
5 808.763 2.695 56.3
6 612.140 2.040 18.1
7 453.025 1.510 60.9
8 376.544 1.255 14.8
9 22.856 0.076 12.5
0.11
3.46
11.04
13.52
7.39
0.71
27.15
1.38
33.42
0.75
1.06
ppm

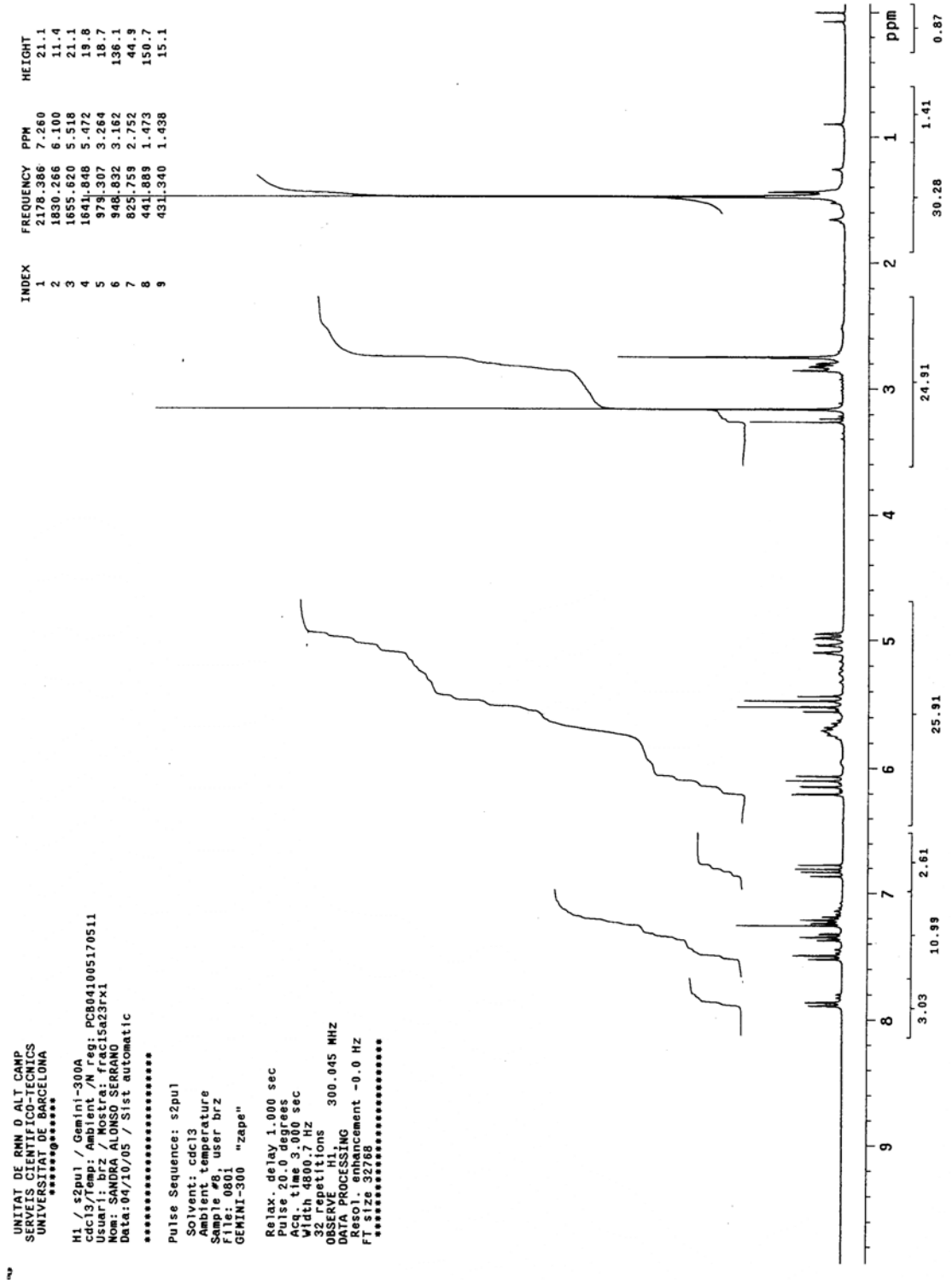

Me
N
Boc
Cl
N
MOM

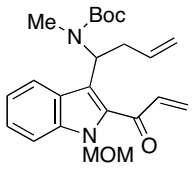
14


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB21070517282
Usuari: brz / Mostra: frac3a4rx170
Nom: SANDRA ALONSO SERRANO
Data:21/07/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #7, user brz
File: 0702 "zape"
GEMINI-300
Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.637 sec
Width 18861.6 Hz
2000 repetitions
OBSERVE C13, 75.446 MHz
DECOUPLE H1, 300.0461136 MHz
Power 30 dB
continuously on
WALTZ16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
180
160
140
120
100
80
60
40
20
0 ppm

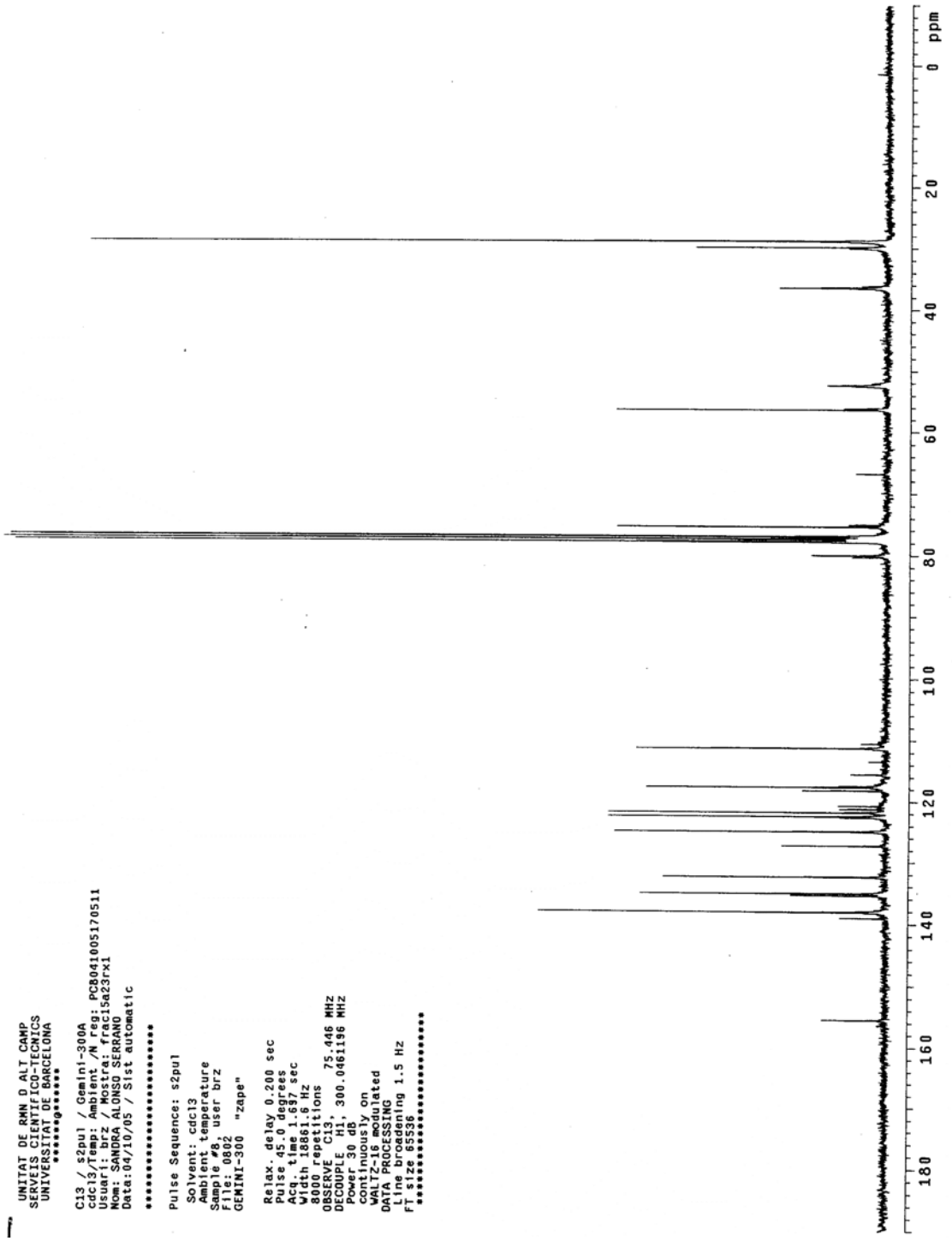

Me
N
Boc
N
MOM
O

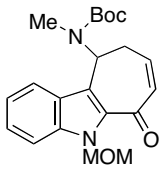
15


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB041005170511
Usuari: brz / Mostra: frac15a23rx1
Nom: SANDRA ALONSO SERRANO
Data:04/10/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #8, user brz
File: 0801 "zape"
Relax. delay 1.000 sec
Pulse 20.0 degrees
Acq. time 3.000 sec
Width 4800.7 Hz
32 repetitions
OBSERVE H1, 300.045 MHz
DATA PROCESSING
Resol enhancement -0.0 Hz
FT size 32768
INDEX FREQUENCY PPM HEIGHT
1 2178.386 7.260 21.1
2 1830.266 6.100 11.4
3 1655.620 5.518 21.1
4 1641.848 5.472 19.8
5 979.307 3.264 18.7
6 948.832 3.162 136.1
7 825.759 2.752 44.9
8 441.889 1.473 150.7
9 431.340 1.438 15.1
3.03
10.99
2.61
25.91
24.91
30.28
1.41
0.87
ppm

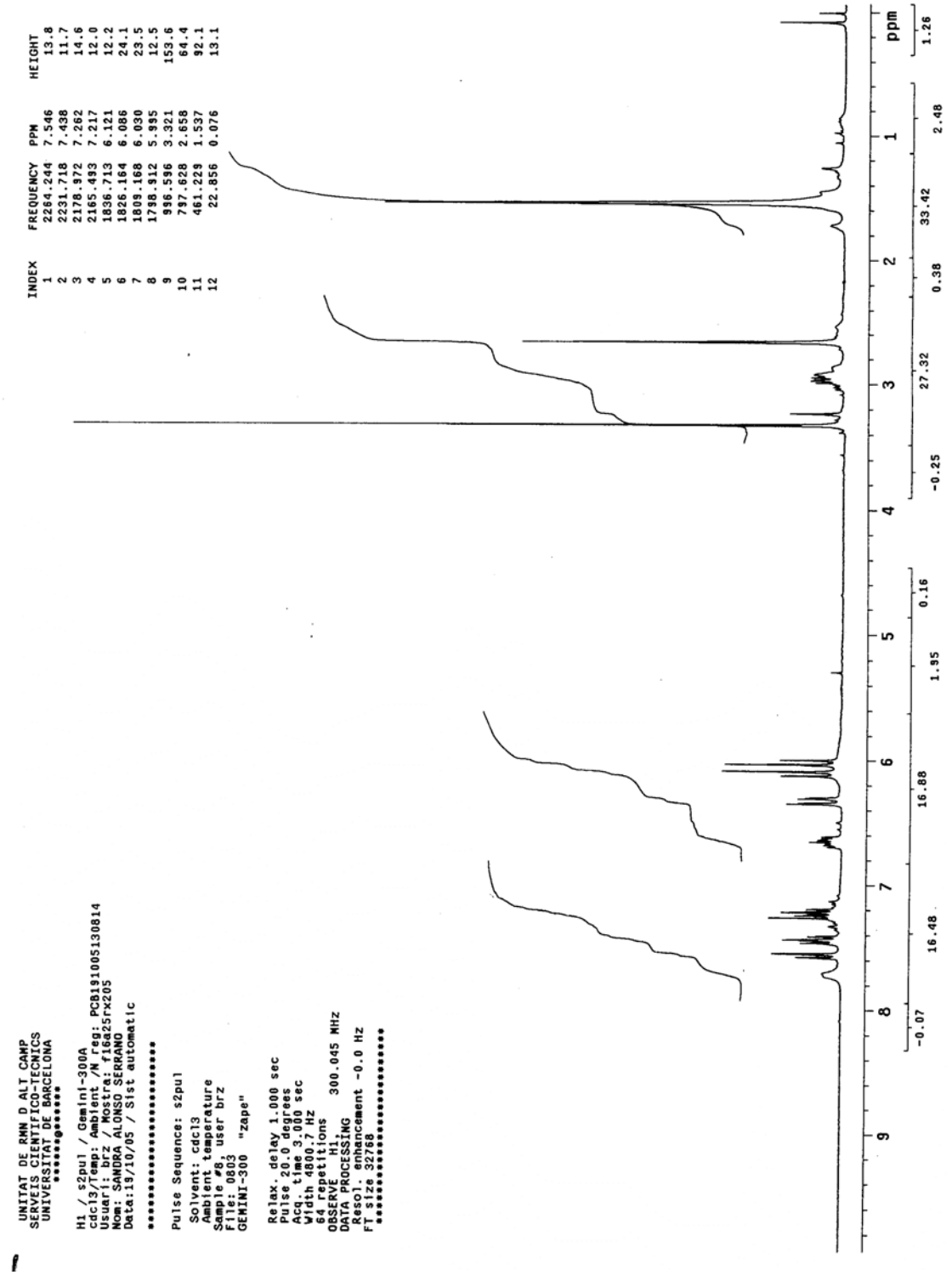

Me
N
Boc
N
MOM
O

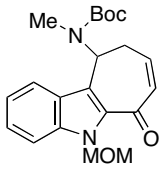
15


UNITAT DE RMN D'ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB041005170511
Usuari: brz / Mostra: fraci5a23fx1
Nom: SANDRA ALONSO SERRANO
Data:04/10/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #8, user brz
File: 0802 "zape"
Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.637 sec
Width 18861.6 Hz
8000 repetitions
OBSERVE C13, 75.446 MHz
DECOUPLE H1, 300.0461196 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
180
160
140
120
100
80
60
40
20
0 ppm

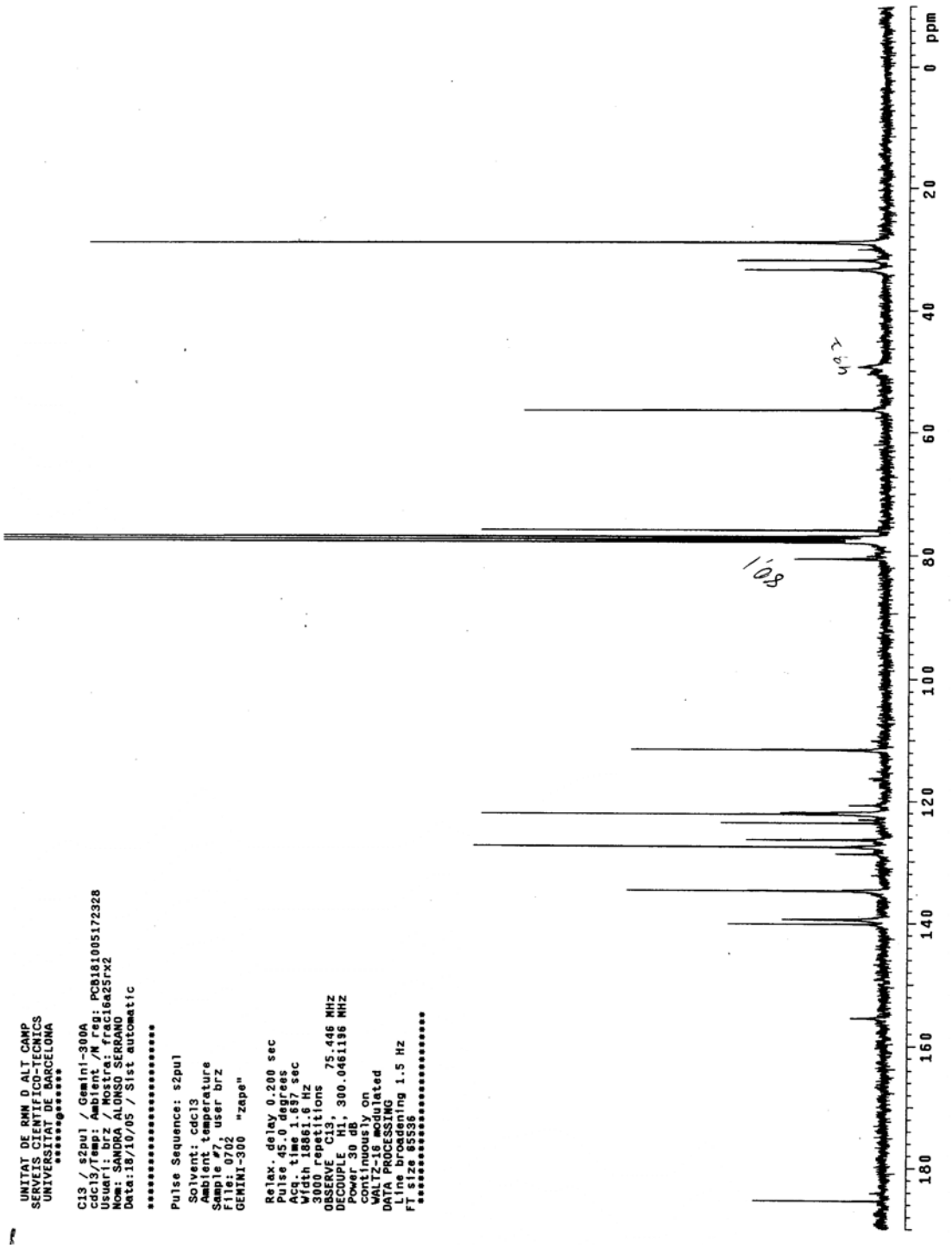

Me
N
Boc
N
MOM
O

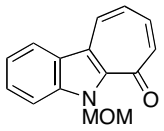
16


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB19100513081
Usuari: brz / Nom: fila25rx205
Nom: SANDRA ALONSO SERRANO
Data:19/10/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #8, user brz
File: 0803
GEMINI-300 "zape"
Relax. delay 1.000 sec
Pulse 20.0 degrees
Acq. time 3.000 sec
Width 4800.7 Hz
64 repetitions
OBSERVE H1, 300.045 MHz
DATA PROCESSING
Resol: enhancement -0.0 Hz
FT size 32768
INDEX FREQUENCY PPM HEIGHT
1 2264.244 7.546 13.8
2 2231.718 7.438 11.7
3 2178.972 7.262 14.6
4 2165.493 7.217 12.0
5 1836.713 6.121 12.2
6 1826.164 6.086 24.1
7 1809.168 6.030 23.5
8 1798.912 5.995 12.5
9 996.596 3.321 153.6
10 797.628 2.658 64.4
11 461.229 1.537 92.1
12 22.856 0.076 13.1
ppm

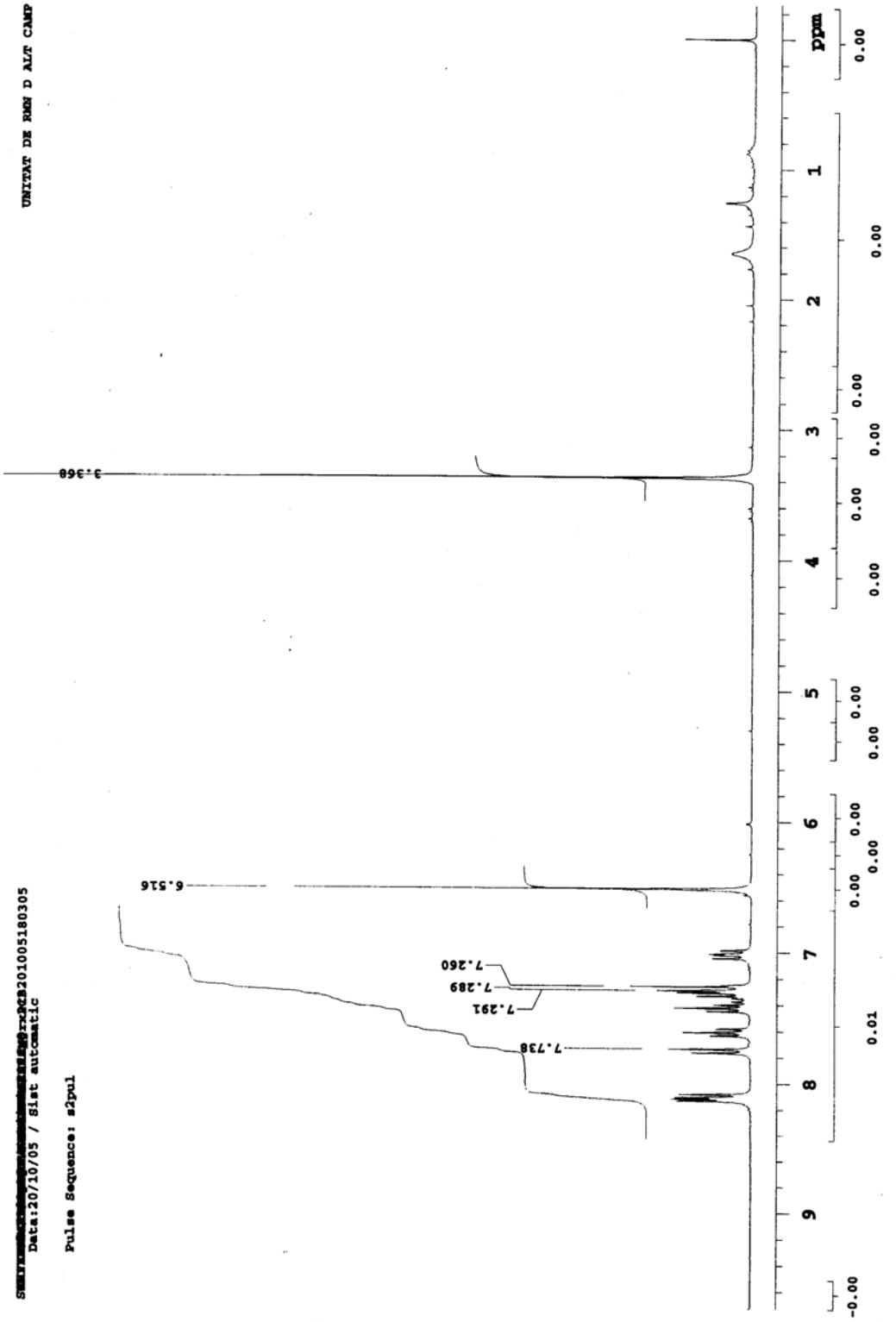

Me
N
Boc
N
MOM
O

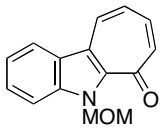
16


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB181005172328
Usuari: brz / Mostra: fraci6a25rx2
Nom: SANDRA ALONSO SERRANO
Data:18/10/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #7, user brz
File: 0702
GEMINI-300 "zpe"
Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.657 sec
Width 18861.6 Hz
3000 repetitions
OBSERVE C13, 75.446 MHz
DECOUPLE H1, 300.0461196 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536
168
49.7
180
160
140
120
100
80
60
40
20
0 ppm

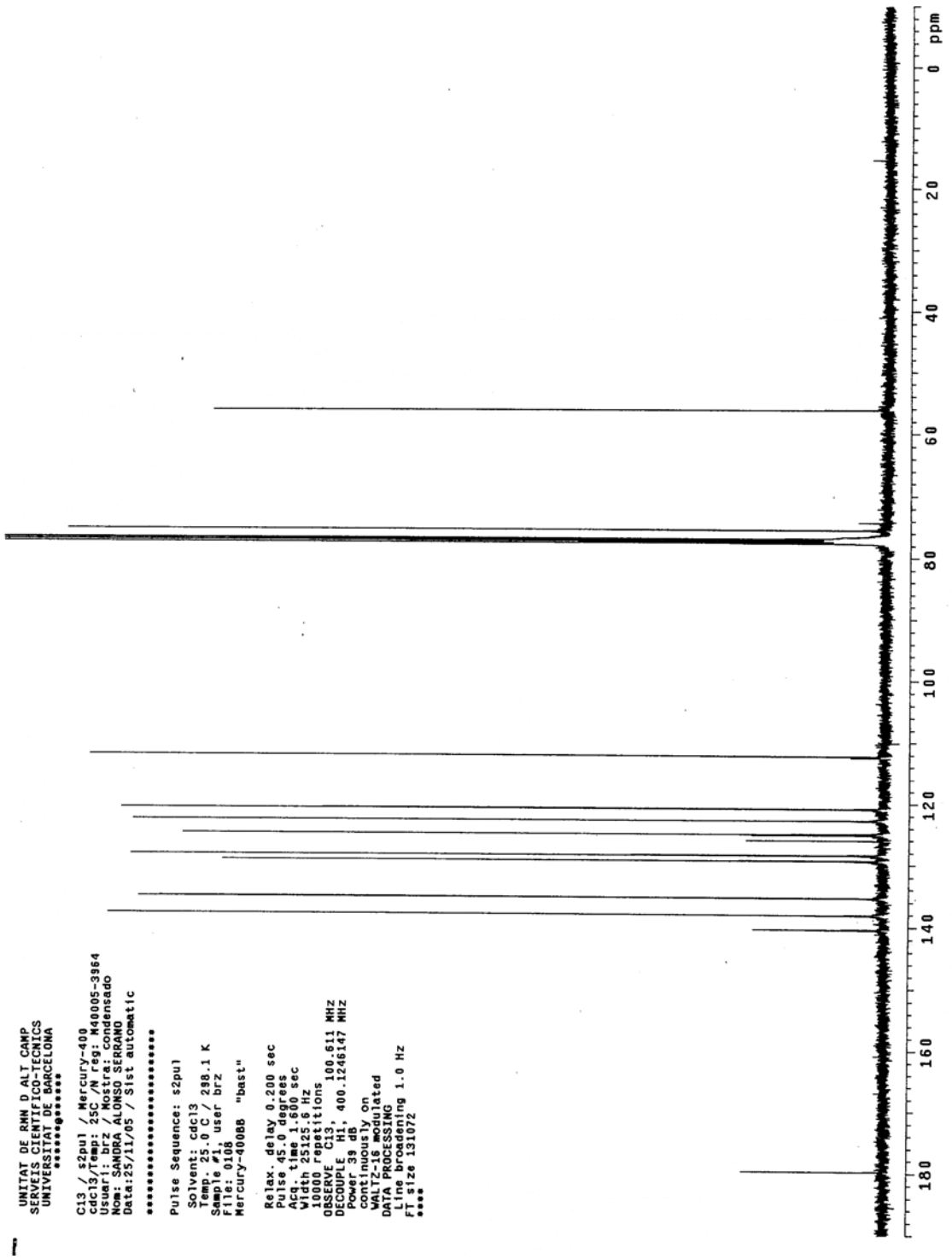

N
MOM
O

17


UNITAT DE RMN D ALT CAMP
Data:20/10/05 / Sist automatic
Pulse Sequence: s2pul
3.368
6.516
7.260
7.289
7.291
7.738
ppm


N
MOM
O

17


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
C13 / s2pul / Mercury-400
cdcl3/Temp: 25C/N reg: M40005-3964
Usuari: br2 / Mostra: condensado
Nom: SAMDRA ALONSO SERRANO
Data:25/11/05 / Sist automatic
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, user br2
File: 0108
Mercury-400B "bast"
Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 25125.6 Hz
10000 repetitions
OBSERVE C13, 100.611 MHz
DECOUPLE H1, 400.124147 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
180
160
140
120
100
80
60
40
20
0 ppm

The first total synthesis of (±)-apparicine†‡

M.-Lluïsa Bennasar,* Ester Zulaica, Daniel Solé and Sandra Alonso

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First published as an Advance Article on the web 27th April 2009
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The first total synthesis of the indole alkaloid apparicine has been developed through a sequence that includes an indole-templated ring-closing metathesis and a vinyl halide Heck cyclization.

Apparicine (Fig. 1) is a fairly widespread monoterpenoid indole alkaloid, first isolated from *Aspidosperma dasycarpon* more than forty years ago.[1] It is the main representative of a small group of alkaloids (*e.g.*, vallesamine and ervaticine) that are structurally defined by the presence of only one carbon (C-6) connecting the indole 3-position with the aliphatic nitrogen.[2] This particular architecture, embodying a 1-azabicyclo[4.2.2]decane framework, is probably the biogenetic result of the C-5 tryptamine atom being excised from the alkaloid stemmadenine.[3] Some *in vitro* transformations of stemmadenine-type to apparicine-type alkaloids have provided further support for this biogenetic model.[4,5]

From a synthetic standpoint, the pioneering route by Joule's group, which resulted in a synthesis of the ring skeleton of apparicine (*i.e.*, 20-deethylideneervaticine),[6] proved unsuitable for the total synthesis of the alkaloid. Indeed, neither apparicine itself, nor any member of this structural class of alkaloids, have been produced by total synthesis to date.

We herein report the first total synthesis of (±)-apparicine. Our approach hinges on the combination of an indole-templated ring-closing metathesis (RCM) to build the tricyclic ABC substructure and a vinyl halide Heck cyclization to close the piperidine ring, the latter process also installing the requisite exocyclic alkylidene (16-methylene and 20*E*-ethylidene) appendages. Although the RCM methodology has turned out to be a powerful tool for the synthesis of medium-sized rings,[7] the construction of eight-membered rings can be a challenging problem.[8] In this regard, we expected to take advantage of our recent synthesis of azocino[4,3-*b*]indoles by the RCM of 2,3-dialkenyl indoles.[9] On the other hand, Heck couplings of vinyl halides and elaborated cycloalkenes similar to our proposed intermediate have proved to be useful for the assembly of the bridged core of several indole alkaloids, including pentacyclic Strychnos alkaloids,[10] strychnine,[10c,11] minfiensine,[12] apogeissoschizine[13] and ervitsine.[14] However, to the best of our knowledge, this is the first example of a vinyl halide Heck reaction at an (aza)cyclooctene ring producing a strained bridged system.[15]

Our initial efforts were focused on developing a straightforward route in which 6-methylazocino[4,3-*b*]indoles with the trisubstituted 5,6-double bond functionality, required for the Heck reaction, would be directly assembled by the RCM of a suitable 3-(butenylaminomethyl)-2-vinylindole (**A**; $n = 2$, $m = 0$; Scheme 1).[16] To this end, we targeted dienes **3** (Scheme 2), which are equipped with Boc or Ts groups at the aliphatic nitrogen and a robust MOM group at the indole nitrogen. These compounds were efficiently prepared from the known 2-chloroindole-3-carbaldehyde **1**[17] by a Stille coupling with (isopropenyl)tributylstannane, followed by reductive amination of aldehyde **2** with 3-butenylamine and subsequent acylation or sulfonylation of the resulting secondary amine with di-*tert*-butyl dicarbonate or tosyl chloride, respectively. Unfortunately, the exposure of dienes **3** to second-generation Grubbs' catalyst **B** in dichloromethane or toluene did not deliver the expected eight-membered ring. Instead, depending on the reaction temperature or concentration, dimeric products **4**, resulting from intermolecular metathesis reactions, isomerized dienes **5** or ring-contracted products **6**, resulting from the RCM of **5** with liberation of propene, were formed.§

Since this unsuccessful result was probably due to the presence of a geminal disubstituted terminal alkene moiety in dienes **3**, we decided to change the cyclization site from the 5,6-position to the less crowded 4,5-position by using a 3-(allylaminomethyl)-2-allylindole (**A**; $n = 1$, $m = 1$; Scheme 1) as the RCM precursor. Consequently, the synthesis of the Heck precursor would now require an additional isomerization step of the resulting double bond.

It was planned to install the α-methyl-substituted allyl-type chain at the indole 2-position by taking advantage of an allylic nucleophilic substitution reaction using a suitable organometallic derivative of indole. Thus, 1-(phenylsulfonyl)indole was allowed to react with *n*-BuLi and CuCN, and the

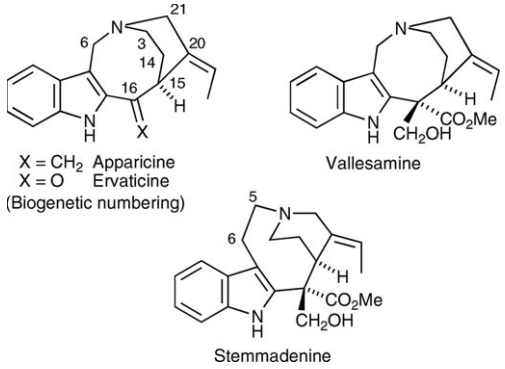

Fig. 1 Apparicine and related alkaloids.

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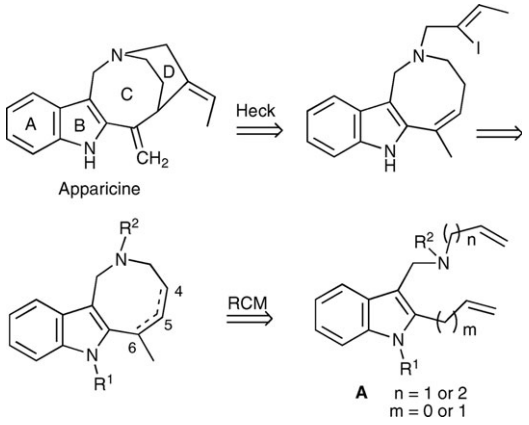
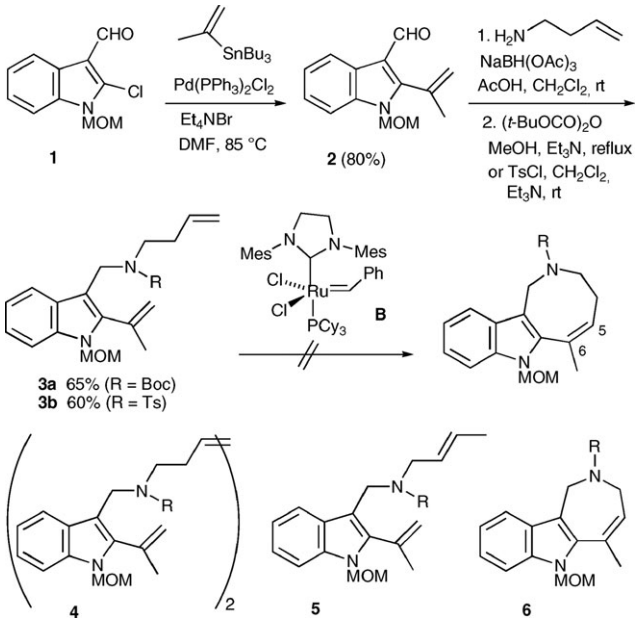
† Dedicated to Professor Josep Font on the occasion of his 70th birthday.

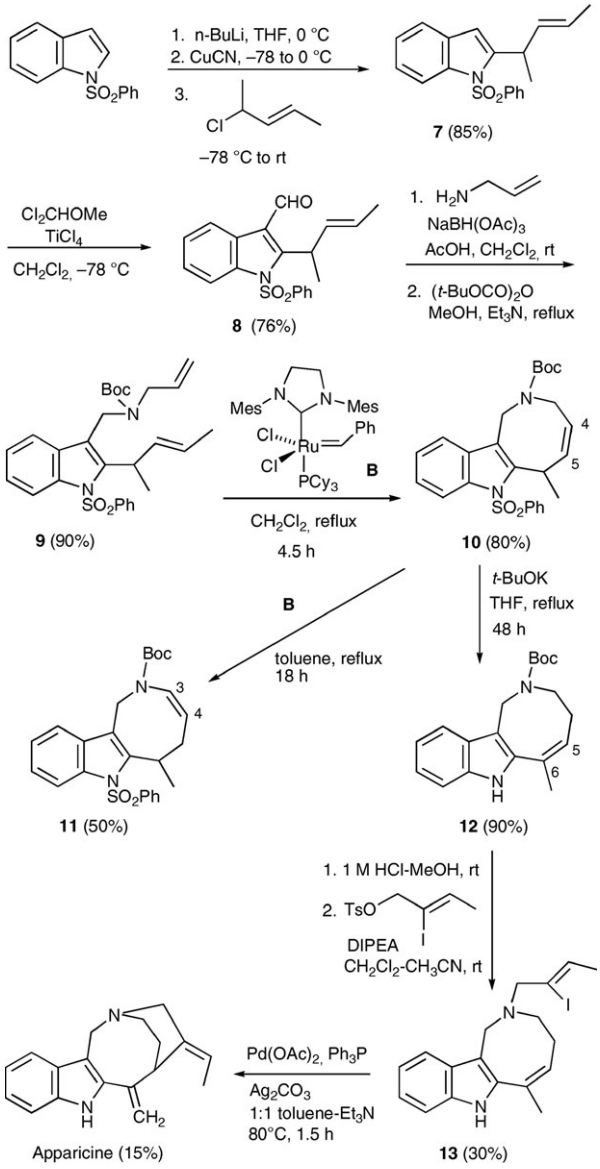
‡ Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b903577j



Scheme 1 Synthetic strategy.



Scheme 2 Attempted RCM synthesis of 6-methyl-1,2,3,4-tetrahydroazocino[4,3-*b*]indoles.



Scheme 3 Synthesis of (±)-apparicine.

intermediate organocopper derivative was treated with (*E*)-4-chloro-2-pentene. The resulting indole, **7**, was then uneventfully converted into RCM precursor **9** by a Friedel–Crafts formylation, reductive amination of aldehyde **8** with allylamine and subsequent protection of the aliphatic nitrogen with a Boc group (Scheme 3). The overall yield of the four steps was 58%. Satisfactorily, ring closure of diene **9** did take place with second-generation Grubbs' catalyst **B** under standard conditions (CH_2Cl_2, reflux, 0.07 M) to give the desired 6-methylazocinoindole, **10**, in 80% yield.

Attention was then focused on the isomerization step. Considering recent reports dealing with post-RCM alkene isomerizations mediated by suitably-modified ruthenium metathesis catalysts,[18] we first examined the reaction of azocinoindole **10** with catalyst **B** in refluxing toluene.[19] Interestingly, under these conditions, a slow isomerization of the double bond took place to its *N*-conjugated counterpart (3,4-position), providing enamide **11** in 50% yield (not optimized). However, we discovered that long exposure of **10** to *t*-BuOK in refluxing THF brought about the desired isomerization towards the opposite side of the bond, along with the anticipated removal of the indole phenylsulfonyl group, affording **12** in 90% yield. By using shorter reaction times and following the reaction by NMR techniques, we found that the migration of the double bond into conjugation with the aromatic ring took place after the initial indole *N*-deprotection step. This result suggests that the base-induced isomerization is only compatible with the presence of a free indole NH group.

With azocinoindole **12** in hand, we next sought to manipulate the aliphatic nitrogen to install the haloalkenyl chain for the eventual Heck reaction. Initial experiments to remove the *N*-Boc group in **12** under standard conditions (TFA, Me_3SiI, $ZnBr_2$) led to extensive decomposition of the skeleton, but the deprotection proceeded cleanly by the treatment of **12** with 1M HCl in MeOH at room temperature for 4.5 h. The resulting

secondary amine proved to be unstable and was directly subjected to alkylation with (*Z*)-2-iodo-2-butenyl tosylate to give **13** in 30% isolated yield over the two steps.

The stage was now set for the completion of the synthesis by intramolecular coupling of the vinyl iodide and the alkene. A variety of experimental conditions were screened, including different solvents, Pd sources and additives, resulting only in the recovery of the starting material or decomposition products. However, to our satisfaction, the critical closure of the strained 1-azabicyclo[4.2.2]decane framework, with concomitant incorporation of the exocyclic alkylidene substituents, took place in the presence of silver carbonate as the additive in toluene. Under these cationic conditions, the conversion yields were moderate but the loss of material was still extensive. Thus, when vinyl iodide **13** was subjected to a specific protocol, using $Pd(OAc)_2/PPh_3$ (0.2 : 0.6 equiv.) and Ag_2CO_3 (2 equiv.) in 1 : 1 toluene–Et_3N at 80 °C for a short reaction time, apparicine was obtained in a consistent, reproducible 15% isolated yield. The ^1H and ^{13}C NMR spectroscopic data of our synthetic apparicine essentially matched that described in the literature for the natural product.[1,2,20] Additionally, the chromatographic behavior of the synthetic apparicine was identical to that of an authentic sample.¶

In summary, the first total synthesis of (±)-apparicine has been accomplished from 1-(phenylsulfonyl)indole by a concise route that proceeds by way of only six isolated intermediates. It features: (1) an indole-templated RCM step to create the central eight-membered ring, (2) a base-promoted double bond isomerization, with concomitant indole deprotection, and (3) a challenging vinyl halide Heck cyclization to finally assemble the bridged skeleton.

This work was supported by the ''Ministerio de Ciencia e Innovación'', Spain (project CTQ2006-00500/BQU). Thanks are also due to the University of Barcelona for a pre-doctoral grant to S. A.

Notes and references

§ The use of other commercially available metathesis catalysts, either based on ruthenium (first-generation Grubbs' or second-generation Hoveyda–Grubbs' catalysts) or molybdenum (Schrock's catalyst) led to no improvement.

¶ We thank Prof. John Joule for an authentic sample of apparicine.

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Total Synthesis of the Bridged Indole Alkaloid Apparicine

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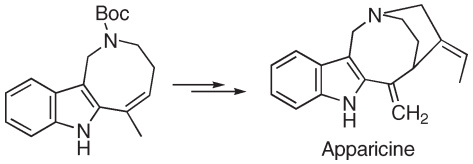

An indole-templated ring-closing metathesis or a 2-indolylacyl radical cyclization constitute the central steps of two alternative approaches developed to assemble the tricyclic ABC substructure of the indole alkaloid apparicine. From this key intermediate, an intramolecular vinyl halide Heck reaction accomplished the closure of the strained 1-azabicyclo[4.2.2]decane framework of the alkaloid with concomitant incorporation of the exocyclic alkylidene substituents.

Introduction

Apparicine (Figure 1) is a fairly widespread monoterpenoid indole alkaloid, first isolated from *Aspidosperma dasycarpon* more than 40 years ago.[1,2] Its structural elucidation,[2] carried out by chemical degradation and early spectroscopic techniques, revealed a particular skeleton with a bridged 1-azabicyclo[4.2.2]decane framework fused to the indole ring and two exocyclic alkylidene (16-methylene and 20*E*-ethylidene) substituents.[3] The same arrangement was also found in vallesamine[4] and later in a small number of alkaloids, including 16(*S*)-hydroxy-16,22-dihydroapparicine[5] or ervaticine,[6] which differ from apparicine in the substitution at C-16.[7]

The apparicine alkaloids are biogenetically defined by the presence of only one carbon (C-6) connecting the indole 3-position and the aliphatic nitrogen, which is the result of the C-5 excision from the original two-carbon tryptamine bridge of the alkaloid stemmadenine.[8] The fragmentation−iminium hydrolysis−recyclization route depicted in Scheme 1, which involves the operation of a stemmadenine *N*-oxide equivalent,[9] has been proposed to rationalize this biogenetic relationship. Such a route appears to be likely since stemmadenine itself[10] and, more

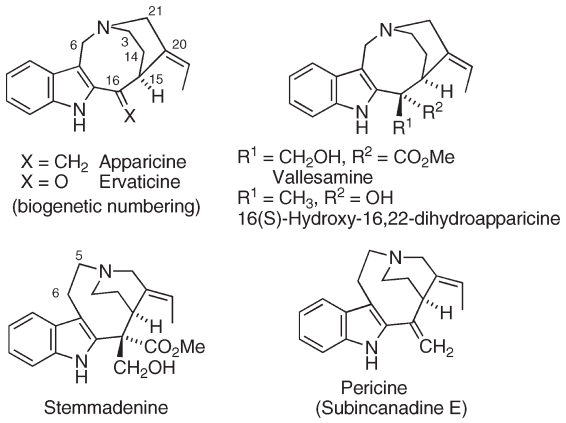

FIGURE 1. Apparicine and related alkaloids.

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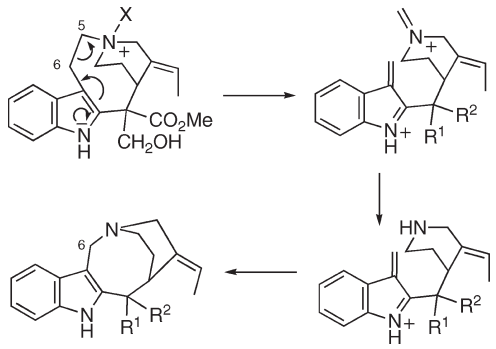
recently, pericine (subincanadine E)[11] have been transformed *in vitro* into the respective C-5 nor-alkaloids (vallesamine and apparicine) by treatment of the *N*-oxides with trifluoroacetic anhydride (modified Polonovski reaction).[12]

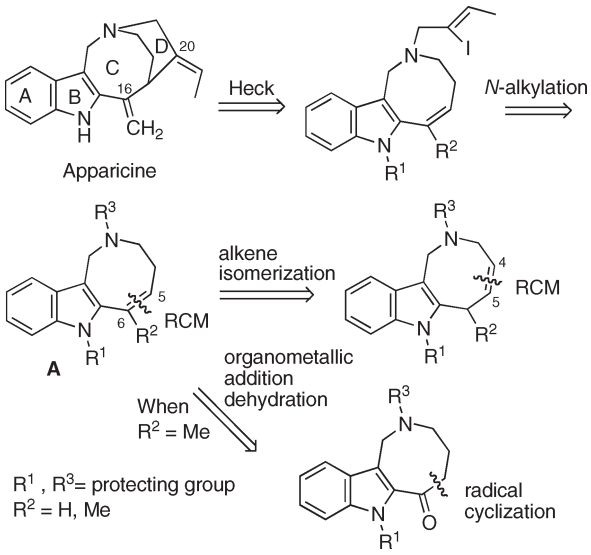
SCHEME 1. Biosynthesis of Apparicine Alkaloids



Their synthetically challenging structures make apparicine alkaloids attractive targets for synthesis. However, progress in this area has been limited to the approach developed by Joule's group in the late 1970s, which allowed the construction of the ring skeleton of apparicine (i.e., 20-deethylideneervaticine) but proved unsuitable for the total synthesis of the alkaloid.[13]

We envisaged apparicine to be accessible via tricyclic ABC substructures containing the central eight-membered ring (e.g., azocinoindoles **A**, Scheme 2), from which the carbon skeleton would be completed by inserting an ethylideneethano unit between the aliphatic nitrogen and C-5. In particular, it was planned that after *N*-alkylation with the appropriate haloalkenyl halide, an intramolecular Heck reaction[14] upon a 2-vinylindole moiety would serve to close the piperidine ring and at the same time install the requisite 20*E*-ethylidene and (when R^2 = Me) 16-methylene appendages. It should be noted that similar Heck couplings of vinyl halides and elaborated cycloalkenes have proved to be useful for the assembly of the bridged core of several indole alkaloids, including pentacyclic *Strychnos* alkaloids,[15] strychnine,[15c,16] minfiensine,[17] apogeissoschizine,[18] and ervitsine.[19] However, to the best of our knowledge, there are no reported vinyl halide Heck reactions involving (aza)cyclooctene rings to produce strained bridged systems.[20]

SCHEME 2. Synthetic Strategy



The power of ring-closing metathesis (RCM)[21] to synthesize medium-sized rings[22] and our own work on RCM of indole-containing dienes[23] made it our method of choice to assemble the indolo fused eight-membered ring of the key intermediates **A** and also to install the double bond required for the Heck reaction, either directly or after an isomerization step. In the course of our work, an alternative approach to **A** based on 2-indolylacyl radical cyclization[24] and manipulation of the resulting ketone was also investigated.[25] This Article deals with the development of the above indole annulation chemistry and its application to complete the first total synthesis of (±)-apparicine.[26]

Resuts and Discussion

Initial Studies. We set out to study the indole-templated RCM en route to apparicine, directly targeting 6-methylazocino[4,3-*b*]indoles (**A**, R^2 = Me, Scheme 2) with the trisubstituted 5,6-double bond functionality required for the Heck coupling. To this end, 2-isopropenylindoles **3**, which are equipped with Boc or Ts groups at the aliphatic nitrogen

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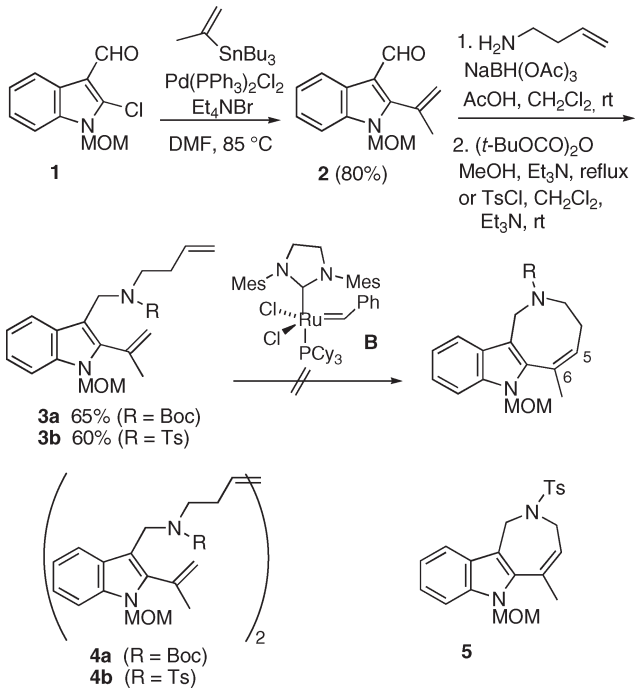
(22) For reviews, see: (a) Maier, M. E. *Angew. Chem., Int. Ed*. **2000**, *39*, 2073–2077. (b) Yet, L. *Chem. Rev*. **2000**, *100*, 2963–3007. (c) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed*. **2006**, *45*, 5740–5750.
(23) (a) Bennasar, M.-L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett*. **2004**, *45*, 6283–6285. (b) Bennasar, M.-L.; Zulaica, E.; Alonso, S. *Tetrahedron Lett*. **2005**, *46*, 7881–7884. (c) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866.
(24) Bennasar, M.-L.; Roca, T. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds; Elsevier: Amsterdam, 2009; Chapter 1, pp 1−19.
(25) For a previous different approach to apparicine ABC substructures, see: (a) Street, J. D.; Harris, M.; Bishop, D. I.; Heatley, F.; Beddoes, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1599–1606. (b) See also ref 13b.
(26) For a preliminary communication, see: Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun*. **2009**, 3372–3374.

and a robust MOM group at the indole nitrogen, were selected as the starting dienes (Scheme 3). These compounds were efficiently prepared from the known 2-chloroindole-3-carbaldehyde **1**[27] by a Stille coupling with (isopropenyl)tributylstannane, followed by reductive amination of aldehyde **2** with 3-butenylamine and subsequent acylation or sulfonylation of the resulting secondary amine with di-*tert*-butyl dicarbonate or tosyl chloride, respectively. Unfortunately, exposure of dienes **3** to the second-generation Grubbs catalyst **B** in CH_2Cl_2 or toluene did not deliver the expected eight-membered ring. Instead, carbamate **3a** mainly underwent an intermolecular metathesis reaction leading to dimer **4a**, even when working under high dilution conditions (0.007 M). Sulfonamide **3b**, in turn, led to the respective dimer **4b** along with variable amounts of the ring-contracted product **5**, coming from the competitive isomerization of the terminal double bond followed by RCM with liberation of propene. Azepinoindole **5** was the only isolated product (75%) when cyclization of **3b** was performed in refluxing toluene. In both cases, the use of other metathesis catalysts, either based on ruthenium (first-generation Grubbs or second-generation Hoveyda-Grubbs catalysts) or molybdenum (Schrock's catalyst) did not lead to any improvement.

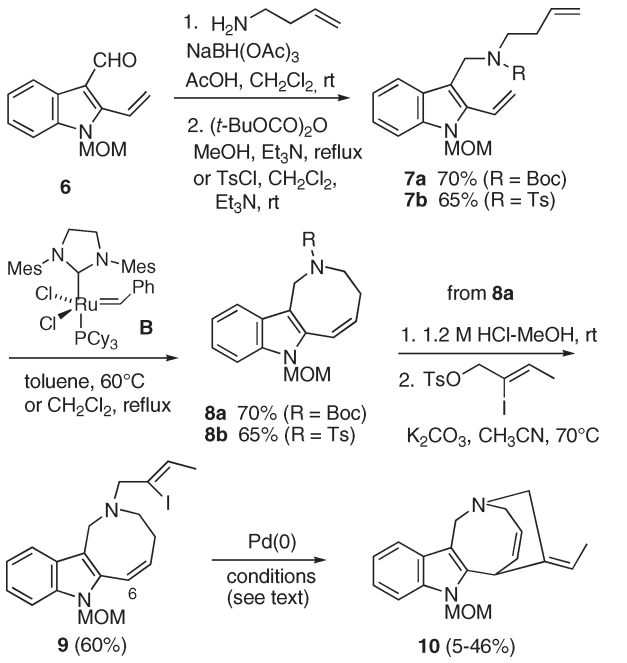
SCHEME 3. Attempted Direct RCM Synthesis of 6-Methyl-1,2,3,4-tetrahydroazocino[4,3-*b*]indoles



Because this unsuccessful result was probably due to the presence of a geminal disubstituted terminal alkene moiety in dienes **3**, we turned our attention to more easily available 6-demethyl tricyclic substructures (**A**, $R^2 = H$, Scheme 2). These model azocinoindoles would also serve as precursors for closing the piperidine ring of apparicine by a reductive Heck cyclization or a tandem Heck cyclization-capture, which could also allow the introduction of the remaining carbon atom at C-16. The implementation of this new synthetic plan is depicted in Scheme 4.

Thus, the required RCM substrates **7a** and **7b** were uneventfully prepared from 2-vinylindole-3-carbaldehyde **6**[27] by reductive amination with 3-butenylamine followed by *N*-acylation or sulfonylation, as in the above isopropenyl series. As anticipated, RCM of dienes **7a** or **7b**, involving two terminal monosubstituted alkene units, took place with the use of ruthenium complex **B** under standard conditions (0.01 M, toluene, 60 °C or CH_2Cl_2, reflux) to give azocinoindoles **8a** or **8b** in acceptable yields. At this point, access to the more advanced synthetic intermediate **9** required the manipulation of the aliphatic nitrogen of **8a** or **8b** to install the iodoalkenyl chain for eventual cyclization. As our first attempts to induce *N*-desulfonylation of **8b** under reductive conditions (Mg, NH_4Cl, MeOH or Na/naphthalenide, THF) proved problematic, affording the unchanged starting product or complex reaction mixtures, we focused on the more labile carbamate function of **8a**. Removal of the Boc group under standard acidic conditions (TFA, Me_3SiI, $ZnBr_2$) was also troublesome, leading to partial decomposition, but the deprotection took place cleanly upon exposure of **8a** to a mild acidic protocol (1.2 M HCl in MeOH at rt). The resulting secondary amine was directly subjected to alkylation with (*Z*)-2-iodo-2-butenyl tosylate in hot acetonitrile in the presence of K_2CO_3 to give **9** in 60% isolated yield over the two steps.

SCHEME 4. Studies in the 6-Demethyl Series



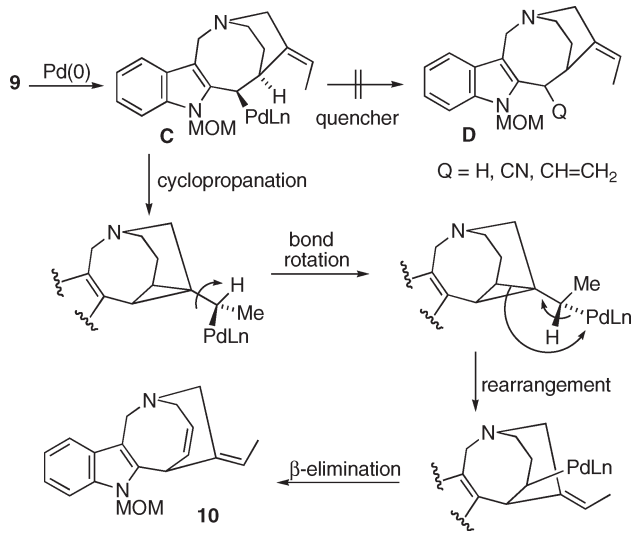
We next studied the key formation of the piperidine ring by Pd-catalyzed cyclization of the vinyl iodide upon the 2-vinylindole moiety. Our expectation was that the initially formed alkylpalladium intermediate **C** (Scheme 5), in which no β-hydrogen is available for elimination, would be stable enough to be reduced or trapped with a suitable quencher. However, when **9** was subjected to a number of standard conditions for reductive Heck reactions, the desired tetracyclic system **D** (Q = H) was never detected. The only observed process under the phosphine-free conditions[28] [$Pd(OAc)_2$,

(27) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881–886.

(28) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

K_2CO_3, TBACl, HCO_2Na, DMF, 80 °C] previously used by Overman[17a] on a related substrate was *N*-dealkylation. After this unsuccessful result, a variety of palladium precatalysts [$Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$], ligands (PPh_3, dppe), and cosolvents (toluene, CH_3CN, THF) were examined in the presence of Et_3N or diisopropylethylamine as the potential reductants.[16b,29] Whereas short reaction times left the starting product unchanged, prolonged heating gave low yields (5−10%) of the unexpected tetracycle **10**, coming from an apparent 7-*endo* cyclization with inversion of the ethylidene configuration.[30] The yield of **10** was raised to 30% on exposure of **9** to $Pd(PPh_3)_4$ in 1:1 THF−Et_3N in a sealed tube at 90 °C for 24 h. On the other hand, under cationic conditions [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, 1:1 toluene−Et_3N, 90 °C] the cyclization proceeded readily to give tetracycle **10** in 46% isolated yield. Significantly, this result was not substantially altered when the reaction was carried out in the presence of HCO_2Na as the reductant or KCN, $K_4[Fe(CN)_6]$, TMSCN, or tributylvinylstannane as trapping agents.

SCHEME 5



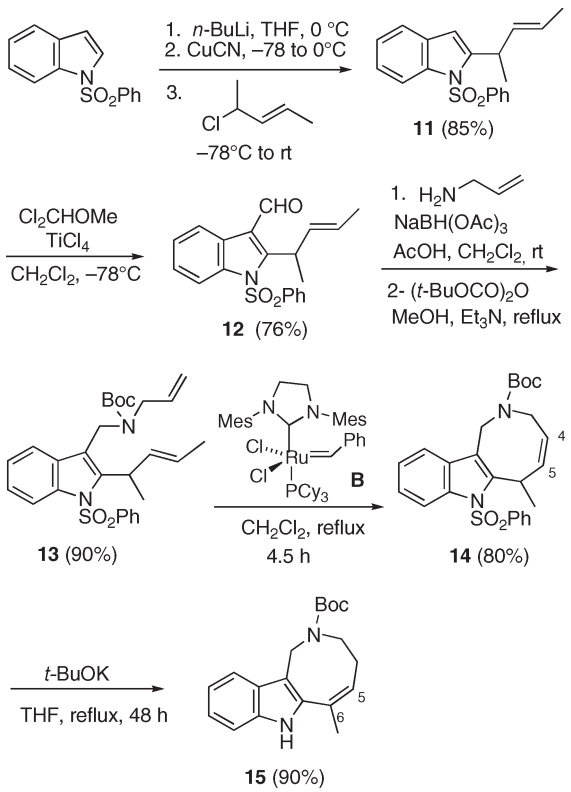
The formation of unusual Heck cyclization products like **10** has been previously observed[31] and rationalized[32] by considering that the initial 6-*exo* cyclization is followed by an intramolecular carbopalladation on the exocyclic alkene. The resulting cyclopropane intermediate would undergo rearrangement, with concomitant inversion of the alkene geometry, and final β-hydride elimination. In our case, the cyclopropanation−rearrangement route depicted in Scheme 5 would be fast enough to prevent the quenchers from intercepting the initially formed alkylpalladium intermediate **C**.

It now became apparent that the presence of a 6-methyl group in the Heck cyclization substrate was crucial to assemble the bridged framework of apparicine, as it would guarantee the β-elimination of the alkylpalladium intermediate arising from cyclization, thus hampering the above undesired route. Hence, we renewed our efforts to synthesize 6-methylazocino[4,3-*b*]indoles (**A**, R^2 = Me, Scheme 2), once again tackling the problem of RCM and ready to explore new routes.

RCM−Isomerization Route to Azocinoindole 15. Given that we were unable to directly form the trisubstituted double bond included in the azocine ring by RCM, we decided to change the cyclization site from the 5,6-position to the less crowded 4,5-position by using a 3-(allylaminomethyl)-2-allylindole such as **13** (Scheme 6) as the diene. Consequently, the synthesis of the Heck precursor would now require an additional isomerization step of the resulting double bond.

It was planned to install the α-methyl-substituted allyl-type chain at the indole 2-position taking advantage of an allylic nucleophilic substitution reaction using a suitable organometallic derivative of indole. Thus, 1-(phenylsulfonyl)indole was allowed to react with *n*-BuLi and CuCN, and the intermediate organocopper derivative was treated with (*E*)-4-chloro-2-pentene. The resulting indole **11** was then converted into the RCM precursor **13** by Friedel−Crafts formylation, reductive amination of aldehyde **12** with allylamine, and the subsequent protection of the aliphatic nitrogen with a Boc group. The overall yield of the four steps was 58%. Satisfactorily, ring closure of diene **13** took place with the second-generation Grubbs catalyst **B** under standard conditions (0.07 M, CH_2Cl_2, reflux) to give the desired 6-methylazocinoindole **14** in 80% yield.

SCHEME 6. RCM−Isomerization Route to 6-Methylazocinoindole 15

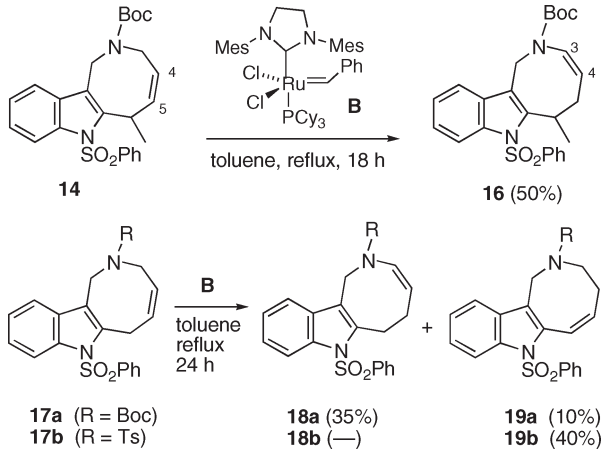


Attention was then focused on the isomerization step. Considering recent reports on alkene isomerizations mediated

(29) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253–9258.
(30) The configuration of the ethylidene substituent was established by NOESY experiments.
(31) (a) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583–5584. (b) Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1129–1137.
(32) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091–10092.

by suitably modified ruthenium-metathesis catalysts,[33−36] we sought to examine if such a protocol could be synthetically useful for our purpose (Scheme 7). Unfortunately, when azocinoindole **14** was treated with catalyst **B** in refluxing toluene,[35] a slow isomerization of the double bond took place to its *N*-conjugated counterpart (3,4-position), providing the enecarbamate **16** in 50% yield (not optimized). The directing effect of the carbamate nitrogen was also decisive, although to a lesser extent, in the ruthenium-catalyzed isomerization of the 6-demethyl analogue **17a**,[23c] which led to the enamide **18a** as the major product along with minor amounts of vinylindole **19a**. Significantly, the influence of the heteroatom was suppressed in the *N*-tosyl analogue **17b**,[23c] which underwent isomerization to afford vinylindole **19b** as the only product. Finally, no isomerization was observed upon exposure of azocinoindoles **14** or **17** to catalyst **B** in hot methanol.[36]

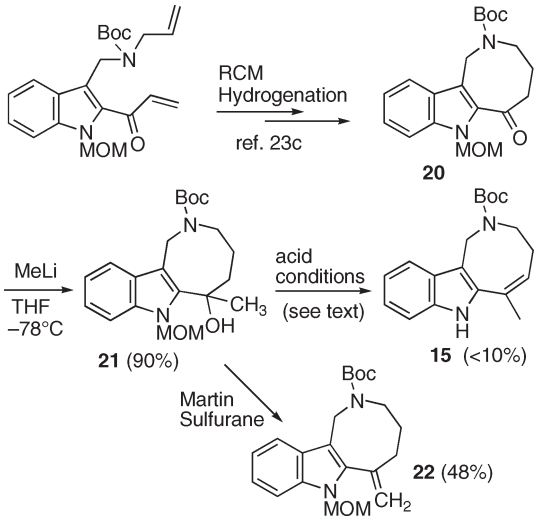
SCHEME 7. Isomerization Studies



Satisfactorily, we fortuitously discovered that the double bond of azocinoindole **14** moved into conjugation with the aromatic ring under the basic conditions used to remove the phenylsulfonyl group. Thus, long exposure of **14** to *t*-BuOK in refluxing THF brought about the anticipated indole deprotection along with alkene isomerization, affording **15** in 90% yield (Scheme 6). By using shorter reaction times and using NMR spectroscopy, we found that the migration of the double bond took place after the initial indole *N*-deprotection step, which suggests that the base-induced isomerization is only compatible with the presence of a free indole NH group.

Alternative Synthesis of 15. Although the RCM−isomerization route depicted in Scheme 6 allowed an efficient synthesis of the key apparicine intermediate **15** [41% overall yield from 2-(phenylsulfonyl)indole by way of four isolated intermediates], we explored the possibility of installing the trisubstituted double bond required for the Heck reaction from a ketone carbonyl group. To this end, the first substrate examined was the *N*-MOM tricyclic ketone **20** (Scheme 8), since it had already been prepared by RCM followed by removal of the resulting double bond by hydrogenation.[23c] Reaction of **20** with MeLi smoothly provided tertiary alcohol **21**, which was subjected to several dehydration protocols without success. Thus, the acid-catalyzed dehydration using 3 M H_2SO_4 in acetone or TsOH in benzene was complicated by the competitive indole deprotection, affording low yields of the endocyclic alkene (**15**). On the other hand, the use of Martin sulfurane resulted in a cleaner dehydration to the exocyclic alkene **22**, in which the *N*-MOM group remained unaffected.

SCHEME 8



In search of a more efficient approach, we decided to extend the above organometallic addition−dehydration sequence to an analogous indole unprotected ketone (i.e., **26**, Scheme 9). After unsuccessful attempts to remove the *N*-MOM group of **20**, the substrate was efficiently prepared by a more direct route free of indole protecting groups, based on an 8-*endo* cyclization of a 2-indolylacyl radical upon an amino tethered alkene.[24,37] The synthesis began with the preparation of selenoester **25** as the radical precursor, equipped with a bromovinyl chain to increase both the efficiency and the *endo* regioselectivity of the ring closure.[37] Thus, reductive amination of aldehyde **23** with 2-bromo-2-propenylamine followed by standard protection of the resulting secondary amine with a Boc group led to ester **24**, which was converted into **25** by phenylselenation through the corresponding carboxylic acid.[38] Treatment of selenoester **25** with *n*-Bu_3SnH as the radical mediator and Et_3B as the initiator achieved the desired ring closure affording ketone **26** in moderate yield (54%). Finally, to our satisfaction, reaction of **26** with methyllithium followed by dehydration of the resulting tertiary alcohol under mild acid conditions (TsOH, CH_3CN, rt) smoothly provided the target alkene **15**. Using this alternative route, the synthesis of **15** was accomplished from aldehyde **23** in 26% overall yield by way of only three isolated intermediates.

(33) For intentional post-RCM isomerizations, see: (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391. (b) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. For a recent example, see: (c) Schmidt, B.; Biernat, A. *Chem.—Eur. J.* **2008**, *14*, 6135–6141.

(34) For reviews on the nonmetathetic behavior of Grubbs ruthenium catalysts, see: (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880. (b) Alcaide, A.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817–3858.

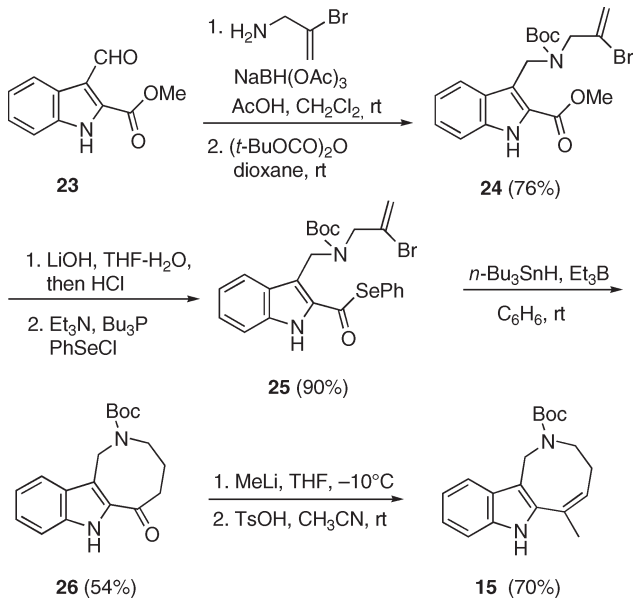
(35) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714.

(36) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481–5484.

(37) Bennasar, M.-L.; Roca, T.; García-Díaz, D. *J. Org. Chem.* **2007**, *72*, 4562–4565.

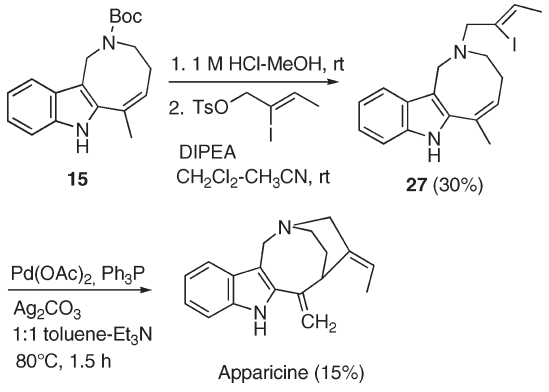
(38) Batty, D.; Crich, D. *Synthesis* **1990**, 273–275.

SCHEME 9. Radical Route to 6-Methylazocinoindole 15



Completion of the Synthesis of Apparicine. With azocinoindole **15** in hand, we next sought to manipulate the aliphatic nitrogen to install the haloalkenyl chain for the subsequent Heck reaction. As occurred with the C-6 demethyl analogue **8a** (Scheme 4), removal of the *N*-Boc group of **15** required a mild acid protocol to avoid decomposition. The resulting secondary amine proved to be highly unstable and was directly subjected to alkylation with (*Z*)-2-iodo-2-butenyl tosylate to give **27** in 30% isolated yield over the two steps (Scheme 10). Attempts to place a phenylsulfonyl group at the indole nitrogen of **15** in order to improve the yield were unsucccessful.

SCHEME 10. Completion of the Synthesis of Apparicine



The stage was now set for the completion of the synthesis by intramolecular coupling of the vinyl iodide and the trisubstituted alkene. A variety of experimental conditions were screened, including different solvents, palladium precatalysts, and additives, resulting only in the recovery of the starting material or decomposition products. However, the critical closure of the strained 1-azabicyclo[4.2.2]decane framework with concomitant incorporation of the exocyclic alkylidene substituents took place under cationic conditions, although loss of material was still extensive. Thus, when vinyl iodide **27** was subjected to a specific protocol, using $Pd(OAc)_2/PPh_3$ (0.2:0.6 equiv) and Ag_2CO_3 (2 equiv) in 1:1 toluene−Et_3N at 80 °C for a short reaction time (1.5 h), apparicine was obtained in a consistent, reproducible 15% isolated yield. The ^1H and ^{13}C NMR spectroscopic data of synthetic apparicine essentially matched those described in the literature for the natural product.[2,7,39] Additionally, the chromatographic (TLC) behavior of synthetic apparicine was identical to an authentic sample.

Conclusion

In summary, the first total synthesis of (±)-apparicine has been accomplished by a concise route employing a vinyl halide Heck cyclization to close the bridged piperidine ring in the last synthetic step. The key azocinoindole intermediate **15** has been successfully assembled by developing two alternative procedures, namely, an indole-templated RCM followed by base-induced isomerization and an acyl radical cyclization followed by ketone−alkene functional group interconversion.

Experimental Section

2-Isopropenyl-1-(methoxymethyl)indole-3-carbaldehyde (2). Tetraethylammonium bromide (0.42 g, 2.01 mmol), $Bu_3Sn(CH_3)C{=}CH_2$ (1.33 g, 4.02 mmol), and $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) were successively added to a solution of aldehyde **1**[27] (0.45 g, 2.01 mmol) in DMF (30 mL), and the mixture was stirred at 85 °C overnight. The reaction mixture was diluted with AcOEt and washed with brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (9:1 hexanes−AcOEt) to give **2** as an oil: 0.37 g (80%); IR (film) 3057, 2934, 1663 cm^{-1}; ^1H NMR (400 MHz) δ 2.25 (s, 3H), 3.31 (s, 3H), 5.35 (s, 1H), 5.44 (s, 2H), 5.76 (s, 1H), 7.33 (m, 2H), 7.49 (dm, $J = 7.5$ Hz, 1H), 8.35 (dm, $J = 7.5$ Hz, 1H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.0 (CH_3), 56.3 (CH_3), 75.2 (CH_2), 110.4 (CH), 115.2 (C), 122.1 (CH), 123.4 (CH), 123.9 (CH_2), 124.3 (CH), 125.2 (C), 133.4 (C), 136.8 (C), 153.3 (C), 186.8 (CH); ESI-HRMS $[M + H]^+$ calcd for $C_{14}H_{16}NO_2$ 230.1175, found 230.1183.

3-[*N*-(3-Butenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-2-isopropenyl-1-(methoxymethyl)indole (3a). 3-Butenylamine (0.24 mL, 2.60 mmol), $NaBH(OAc)_3$ (0.82 g, 3.90 mmol), and AcOH (0.08 mL, 1.36 mmol) were successively added to aldehyde **2** (0.30 g, 1.30 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.30 g). This compound was dissolved in MeOH (10 mL) and treated with $(t\text{-BuOCO})_2O$ (0.45 g, 2.06 mmol) and Et_3N (0.58 mL, 4.12 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed, and the residue was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the residue was chromatographed (8:2 hexanes−AcOEt) to give carbamate **3a** as a pale yellow oil: 0.33 g (65%); IR (film) 1689, 1462, 1415 cm^{-1}; ^1H NMR (400 MHz) δ 1.53 (br s, 9H), 2.12 (s, 3H), 2.13 (m, 2H), 3.10 (m, 2H) 3.26 (s, 3H), 4.66 (s, 2H), 4.96 (m, 2H), 5.15 (s, 1H), 5.38 (s, 2H), 5.60 (s, 1H), 5.65 (m, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.40 (d,

(39) (a) Massiot, G.; Zèches, M.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. *J. Chem. Soc., Chem. Commun.* **1982**, 768–769. (b) van Beek, T. A.; Verpoorte, R.; Kinh, Q. *Planta Med.* **1985**, *51*, 277–279. (c) Atta-ur-Rahman; Fatima, T.; Mehrum-Nisa; Ijaz, S.; Crank, G.; Wasti *Planta Med.* **1987**, *53*, 57–59.

J = 7.8 Hz, 1H), 7.75 (m, 1H); ^{13}C NMR (100.6 MHz) δ 24.5 (CH_3), 28.5 ($3CH_3$), 32.6 (CH_2), 39.7 (CH_2), 44.2 (CH_2), 55.7 (CH_3), 74.7 (CH_2), 79.2 (C), 109.8 (CH), 116.1 (CH_2), 120.1 (C), 120.4 (CH), 121.5 (CH_2), 122.4 (CH), 122.5 (CH), 127.9 (C), 135.5 (CH), 135.6 (C), 136.9 (C), 141.3 (C), 155.7 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_3$ 385.2485, found 385.2477.

3-[*N*-(3-Butenyl)-*N*-(tosyl)aminomethyl]-2-isopropenyl-1-(methoxymethyl)indole (3b). Aldehyde **2** (0.25 g, 1.09 mmol) was allowed to react as above with 3-butenylamine and $NaBH(OAc)_3$. The resulting secondary amine (0.25 g) was dissolved in CH_2Cl_2 (12 mL) and treated with TsCl (0.20 g, 1.05 mmol) and Et_3N (0.15 mL, 1.05 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (9:1 hexanes−AcOEt) to give sulfonamide **3b** as a pale yellow solid: 0.29 g (60%); mp 88 °C (Et_2O); IR (KBr) 1463, 1332, 1158 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.92 (m, 2H), 2.06 (s, 3H), 2.44 (s, 3H), 3.04 (m, 2H), 3.28 (s, 3H), 4.48 (s, 2H), 4.70 (dm, J = 17 Hz, 1H), 4.78 (dm, J = 10 Hz, 1H), 5.09 (s, 1H), 5.36 (s, 2H), 5.40 (m, 1H), 5.53 (br s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.33 (m, 2H), 7.43 (d, J = 8 Hz, 1H), 7.78 (m, 3H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 24.5 (CH_3), 32.9 (CH_2), 43.4 (CH_2), 46.7 (CH_2), 55.7 (CH_3), 74.7 (CH_2), 107.1 (C), 109.8 (CH), 116.3 (CH_2), 120.1 (CH), 120.7 (CH), 121.9 (CH_2), 122.7 (CH), 127.3 (2 CH), 127.7 (C), 129.2 (2 CH), 134.8 (CH), 135.2 (C), 136.9 (2C), 141.4 (C), 143.0 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3S$ 439.2049, found 439.2039; $[M + Na]^+$ calcd for $C_{25}H_{30}NaN_2O_3S$ 461.1869, found 461.1866. Anal. Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.88; N, 6.38. Found: C, 68.22; H, 6.43; N, 6.25.

3-[*N*-(3-Butenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)-2-vinylindole (7a). 3-Butenylamine (0.39 mL, 4.20 mmol), $NaBH(OAc)_3$ (1.33 g, 6.30 mmol), and AcOH (0.12 mL, 2.10 mmol) were successively added to aldehyde **6**[1] (0.45 g, 2.10 mmol) in CH_2Cl_2 (13 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.50 g). This compound was dissolved in MeOH (20 mL) and treated with $(t\text{-BuOCO})_2O$ (0.52 g, 2.40 mmol) and Et_3N (0.68 mL, 4.85 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give carbamate **7a** as a pale yellow oil: 0.55 g (70%); IR (film) 1687 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.54 (br s, 9H), 2.19 (br s, 2H), 3.10 (m, 2H), 3.11 (s, 3H), 4.79 (br s, 2H), 4.94 (s, 1H), 4.96 (dd, J = 8.4 and 1.6 Hz, 1H), 5.46 (s, 2H), 5.64 (d, J = 12 Hz, 1H), 5.65 (masked, 1H), 5.70 (d, J = 17 Hz, 1H), 6.90 (dd, J = 17 and 12 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.45 (br m, 1H); ^{13}C NMR (100.6 MHz) δ 28.5 (3 CH_3), 32.7 (CH_2), 39.4 (CH_2), 44.3 (CH_2), 55.7 (CH_3), 74.4 (CH_2), 79.4 (C), 109.4 (CH), 111.9 (C), 116.2 (CH_2), 119.9 (CH), 120.6 (CH), 120.7 (CH_2), 123.0 (CH), 125.2 (CH), 127,9 (C), 135.7 (CH), 136.6 (C), 137.7 (C), 155.6 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{22}H_{30}N_2O_3Na$ 393.2148, found 393.2139.

3-[*N*-(3-Butenyl)-*N*-(tosyl)aminomethyl]-1-(methoxymethyl)-2-vinylindole (7b). Aldehyde **6** (0.45 g, 2.10 mmol) was allowed to react as above with 3-butenylamine (0.39 mL, 4.20 mmol) and $NaBH(OAc)_3$ (1.33 g, 6.30 mmol). The resulting secondary amine was dissolved in CH_2Cl_2 (30 mL) and treated with TsCl (0.48 g, 2.52 mmol) and Et_3N (0.36 mL, 2.52 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (8:2 hexanes−AcOEt) to give sulfonamide **7b** as a white solid: 0.58 g (65%); mp 105 °C (Et_2O); IR (KBr) 1335, 1462, 1598 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.90 (m, 2H), 2.45 (s, 3H), 3.01 (m, 2H), 3.30 (s, 3H), 4.57 (s, 2H, CH_2), 4.68 (d, J = 17 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 5.38 (m, 1H), 5.45 (s, 2H), 5.60 (d, J = 12 Hz, 1H), 5.73 (d, J = 18 Hz, 1H), 6.80 (dd, J = 18 and 12 Hz, 1H), 7,12 (t, J = 7.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 33.1 (CH_2), 42.9 (CH_2), 46.9 (CH_2), 55.7 (CH_3), 74.4 (CH_2), 109.0 (C), 109.4 (CH), 116.4 (CH_2), 119.8 (CH), 120.8 (CH), 121.7 (CH_2), 123.3 (CH), 124.7 (CH), 127.3 (2CH), 129.7 (2CH), 127.8 (C), 134.8 (CH), 136.5 (C), 137.1 (C), 137.6 (C), 143.2 (C). Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.80; H, 6.63; N, 6.58; S; 7.68. Found: C, 67.62; H, 6.65; N, 6.52; S, 7.70.

2-(*tert*-Butoxycarbonyl)-7-(methoxymethyl)-1,2,3,4-tetrahydroazocino[4,3-*b*]indole (8a). The second-generation Grubbs catalyst (33 mg, 10 mol %) was added under Ar to a solution of diene **7a** (150 mg, 0.40 mmol) in toluene (40 mL), and the resulting mixture was heated at 60 °C for 2.5 h. The reaction mixture was concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give azocinoindole **8a** as a colorless oil: 97 mg (70%); IR (film) 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, assignment aided by gHSQC, mixture of rotamers) δ 1.30 and 1.44 (2 s, 9H, Boc), 2.48 (m, 2H, 4-H), 3.19 and 3.21 (2s, 3H, OCH_3), 3.59 and 3.68 (2 apparent t, J = 5.6 Hz, 2H, 3-H), 4.62 and 4.64 (2s, 2H, 1-H), 5.37 and 5.40 (2s, 2H, OCH_2), 6.09 (m, 1H, 5-H), 6.63 (m, 1H, 6-H), 7.13 (t, J = 7.6 Hz, 1H, 10-H), 7.22 (m, 1H, 9-H), 7.35 and 7.39 (2d, J = 8 Hz, 1H, 8-H), 7.56 and 7.70 (2 d, J = 8 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC, major rotamer) δ 28.4 ($3CH_3$), 28.6 (CH_2, C-4), 43.2 (CH_2, C-1), 45.8 (CH_2, C-3), 55.4 (CH_3), 73.8 (CH_2), 79.4 (C), 109.2 (CH, C-8), 112.3 (C), 118.7 (CH, C-11), 119.8 (CH, C-10), 120.6 (CH, C-6), 122.5 (CH, C-9), 127.0 (C), 132.5 (CH, C-5), 132.6 (C), 137.4 (C), 156.2 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_3$ 343.2016, found 343.2005; $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_3Na$ 365.1835, found 365.1837.

7-(Methoxymethyl)-2-tosyl-1,2,3,4-tetrahydroazocino[4,3-*b*]-indole (8b). The second-generation Grubbs catalyst (24 mg, 7 mol %) was added under Ar to a solution of diene **7b** (170 mg, 0.40 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was heated at reflux overnight. The reaction mixture was concentrated, and the residue was chromatographed (8:2 hexanes−AcOEt) to give azocinoindole **8b** as a white solid: 103 mg (65%); mp 154 °C (Et_2O); IR (KBr) 1157, 1330, 1462 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.30 (m, 2H), 2.37 (s, 3H), 3.16 (s, 3H), 3.36 (m, 2H), 4.47 (s, 2H), 5.30 (s, 2H, CH_2), 6.07 (m, 1H), 6.58 (d, J = 11 Hz, 1H), 7.19 (d, J = 8 Hz, 2H), 7.22 (m, 1H), 7.26 (m, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.4 (CH_3), 28.8 (CH_2), 43.4 (CH_2), 45.5 (CH_2), 55.6 (CH_3), 74.3 (CH_2), 109.4 (CH), 110.8 (C), 119.6 (CH), 120.2 (CH), 120.6 (CH), 122.9 (CH), 127.2 (2CH), 129.5 (2CH), 127.4 (C), 133.5 (CH), 135.3 (C), 137.0 (C), 137.3 (C), 142.9 (C). Anal. Calcd for $C_{22}H_{24}N_2O_3S$. 2/3H_2O: C, 64.67; H, 6.25; N, 6.86. Found: C, 64.19; H, 6.47; N, 6.49.

2-(2-Iodo-2-(*Z*)-butenyl)-7-(methoxymethyl)-1,2,3,4-tetrahidroazocino[4,3-*b*]indole (9). A solution of carbamate **8a** (0.31 g, 0.90 mmol) in 1.2 M HCl in MeOH (3.7 mL) was stirred at rt for 18 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.18 g). K_2CO_3 (0.16 g, 1.15 mmol) and (*Z*)-2-iodo-2-butenyl tosylate[15a,16c] (0.26 g, 0.74 mmol) were added to a solution of the above material (0.18 g, 0.74 mmol) in acetonitrile (20 mL), and the resulting mixture was stirred at 70 °C for 1.5 h. The solvent was removed, and the residue was dissolved in Et_2O and washed with H_2O. The organic solution was dried and concentrated to give the crude product. After chromatography

(9:1 hexanes−AcOEt) the pure tertiary amine **9** was obtained as a yellow oil: 0.23 g (60%); IR (film) 1323, 1461, 1659 cm^{-1}; ^1H NMR (400 MHz) δ 1.81 (d, J = 6.4 Hz, 3H), 2.30 (m, 2H), 2.79 (m, 2H), 3.23 (s, 3H), 3.32 (br s, 2H), 4.04 (br s, 2H), 5.44 (s, 2H), 5.80 (q, J = 6.4 Hz, 1H), 6.12 (m, 1H), 6.56 (d, J = 11.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.7 (CH_3), 26.9 (CH_2), 47.6 (CH_2), 49.3 (CH_2), 55.9 (CH_3), 65.4 (CH_2), 74.5 (CH_2), 109.4 (CH), 110.5 (C), 110.6 (C), 117.9 (CH), 118.8 (CH), 120.3 (CH), 122.5 (CH), 129.0 (C), 131.8 (CH), 135.6 (CH), 136.0 (C), 137.3 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{24}N_2OI$ 423.0927, found 423.0941.

12-(*Z*)-Ethylidene-7-(methoxymethyl)-1,2,3,6-tetrahydro-2,66-ethanoazocino[4,3-*b*]indole (10). Method A. $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) was added under Ar to a solution of amine **9** (45 mg, 0.107 mmol) in 1:1 THF−Et_3N (5 mL), and the mixture was heated at 90 °C in a sealed tube for 24 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 8:2 hexanes−AcOEt) to give **10** as a yellow oil: 10 mg (30%); ^1H NMR (400 MHz, assignment aided by gCOSY and gHSQC) δ 1.53 (d, J = 7.2 Hz, 3H, =CHC$\underline{H}_3$), 3.23 (s, 3H, OCH_3), 3.67 (d, J = 19.2 Hz, 1H, 3-H), 3.86 (dt, $\underline{J}$ = 19.2, 3, and 2.2 Hz, 1H, 3-H), 3.89 (d, J = 17.6 Hz, 1H, 13-H), 3.95 (d, J = 17.6 Hz, 1H, 13-H), 4.24 (d, J = 9.2 Hz, 1H, 6-H), 4.28 (d, J = 17.2 Hz, 1H, 1-H), 4.41 (d, J = 17.2 Hz, 1H, 1-H), 5.34 (qt, J = 7.2 and 2.2 Hz, 1H, =C$\underline{H}$CH$_3$), 5.45 (d, J = 11.6 Hz, 1H, OCH_2), 5.50 (d, J = 11.6 Hz, $\underline{1}$H, OCH_2), 5.59 (dt, J = 10.4 and 3 Hz, 1H, 4-H), 6.07 (ddt, J = 10.4, 9.2, and 3 Hz, 1H, 5-H), 7.08 (t, J = 7.6 Hz, 1H, 10-H), 7.16 (t, J = 7.6 Hz, 1H, 9-H), 7.36 (d, J = 8.4 Hz, 1H, 8-H), 7.39 (d, J = 8 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, assignment aided by gHSQC) δ 13.0 (=CH$\underline{C}$H$_3$), 44.0 (CH, C-6), 52.5 (CH_2, C-1), 53.0 (CH_2, C-13), 56.0 ($\underline{O}CH_3$), 57.0 (CH_2, C-3), 73.5 (OCH_2), 109.0 (CH, C-8), 112.4 (C), 118.0 (CH, C-11), 118.5 (CH, =$\underline{C}$HCH$_3$), 120.0 (CH, C-10), 121.5 (CH, C-9), 127.0 (C), 129.0 ($\underline{C}$H, C-5), 132.0 (CH, C-4), 136.9 (C), 139.0 (C), 143.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}N_2O$ 295.1804, found 295.1803.

Method B. $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (7 mg, 0.027 mmol), and Ag_2CO_3 (50 mg, 0.18 mmol) were added under Ar to a solution of amine **9** (40 mg, 0.095 mmol) in 1:1 toluene−Et_3N (5 mL), and the resulting mixture was heated at 90 °C for 1 h 45 min. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 8:2 hexanes−EtOAc) to give **10**: 13 mg (46%).

2-(1-Methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole (11). *n*-BuLi (1.6 M in hexane, 5.83 mL, 9.33 mmol) was slowly added to a cooled (0 °C) solution of 1-(phenylsulfonyl)indole (2 g, 7.78 mmol) in THF (20 mL), and the solution was stirred at 0 °C for 2 h and then cooled to −78 °C. CuCN (0.84 g, 9.38 mmol) was added and the reaction mixture was allowed to warm to rt (2−3 h) and then cooled again to −78 °C. (*E*)-4-Chloro-2-pentene (0.98 g, 9.38 mmol) was added, and the stirring was continued at rt for 12 h. The reaction mixture was diluted with 20% NH_4OH and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (hexanes and 95:5 hexanes−AcOEt) to give indole **11** as an oil: 2.15 g (85%); IR (neat) 1448, 1367, 1173 cm^{-1}; ^1H NMR (400 MHz, signals due to a minor isomer are omitted) δ 1.45 (d, J = 6.8 Hz, 3H), 1.67 (d, J = 6.0 Hz, 3H), 4.34 (m, 1H), 5.52 (m, 1H), 5.66 (m, 1H), 6.49 (s, 1H), 7.24−7.50 (m, 6H), 7.72 (m, 2H), 8.23 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 17.9 (CH_3), 21.7 (CH_3), 35.0 (CH), 108.6 (CH), 115.3 (CH), 120.3 (CH), 123.7 (CH), 124.0 (CH), 124.9 (CH), 126.2 (2CH), 129.0 (2CH), 129.9 (C), 133.5 (CH), 134.0 (CH), 137.5 (C), 139.0 (C), 147.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{20}NO_2S$ 326.1209, found 326.1212.

2-(1-Methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole-3-carbaldehyde (12). Indole **11** (1 g, 3.07 mmol) in CH_2Cl_2 (20 mL) was added to a cooled (− 78 °C) solution of $TiCl_4$ (1 M in CH_2Cl_2, 6.15 mL, 6.15 mmol) and Cl_2CHOCH_3 (0.55 mL, 6.15 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at −78 °C for 4 h. The reaction mixture was diluted with H_2O, basified with a saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 95:5 hexanes−AcOEt) to give aldehyde **12** as an amorphous solid: 0.83 g (76%); IR (film) 1666, 1449, 1382, 1174 cm^{-1}; ^1H NMR (400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 1.61 (dm, J = 6.4 Hz, 3H), 4.76 (m, 1H), 5.40 (m, 1H), 5.61 (dm, J = 15 Hz, 1H), 7.37 (m, 2H), 7.49 (m, 2H), 7.62 (m, 1H), 7.82 (d, J = 7.8 Hz, 2H), 8.32 (m, 2H), 10.45 (s, 1H); ^{13}C NMR (100.6 MHz) δ 17.7 (CH_3), 22.5 (CH_3), 33.8 (CH), 114.7 (CH), 119.3 (C), 122.1 (CH), 125.2 (CH), 125.7 (CH), 125.9 (CH), 126.3 (C), 126.5 (2CH), 129.6 (2CH), 133.1 (CH), 134.4 (CH), 136.4 (C), 139.4 (C), 155.3 (C), 187.5 (CH); ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{20}NO_3S$ 354.1158, found 354.1165.

3-[*N*-Allyl-*N*-(*tert*-butoxycarbonyl)aminomethyl]-2-(1-methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole (13). Allylamine (0.21 mL, 2.83 mmol), $NaBH(OAc)_3$ (0.90 g, 4.25 mmol), and AcOH (0.08 mL, 1.41 mmol) were successively added to aldehyde **12** (0.50 g, 1.41 mmol) in CH_2Cl_2 (17 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (540 mg). This compound was dissolved in MeOH (5 mL) and treated with $(t\text{-BuOCO})_2O$ (0.54 g, 2.47 mmol) and Et_3N (0.70 mL, 4.94 mmol). After the mixture was heated at reflux for 5 h, the solvent was removed, and the residue was diluted with CH_2Cl_2 and washed with 2 N HCl and brine. The organic extracts were dried and concentrated to give the crude product. After chromatography (hexanes and 95:5 hexanes−AcOEt) diene **13** was obtained as a pale yellow oil: 0.63 g (90%); IR (film) 1690, 1450, 1368, 1173 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (d, J = 7.2 Hz, 3H), 1.42 (s, 9H), 1.52 (d, J = 6.4 Hz, 3H), 3.38 (br s, 2H), 4.44 (m, 1H), 4.57 (m, 2H), 4.83 (dd, J = 17.2 and 1.5 Hz, 1H), 4.92 (dd, J = 10.4 and 1.5 Hz, 1H), 5.28 (m, 1H), 5.44 (dm, J = 15.2 Hz, 1H), 5.50 (m, 1H), 7.20 (m, 2H), 7.32 (m, J = 2H), 7.43 (m, 2H), 7.60 (dm, J = 8.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 18.1 (CH_3), 20.1 (CH_3), 28.6 ($3CH_3$), 33.5 (CH), 40.0 (CH_2), 46.8 (CH_2), 80.1 (C), 115.4 (CH_2), 115.6 (CH), 117.2 (C), 119.7 (CH), 123.9 (CH), 124.7 (CH), 125.2 (CH), 126.5 (2CH), 129.2 (C), 129.3 (2CH), 132.8 (CH), 133.8 (CH), 133.9 (CH), 137.1 (C), 139.7 (C), 142.9 (C), 156.1 (CO); ESI-HRMS $[M + Na]^+$ calcd for $C_{28}H_{34}N_2O_4NaS$ 517.2131, found 517.2144.

2-(*tert*-Butoxycarbonyl)-6-methyl-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (14). The second-generation Grubbs catalyst (24 mg, 7 mol %) was added under Ar to a solution of diene **13** (200 mg, 0.40 mmol) in CH_2Cl_2 (5.7 mL), and the resulting mixture was heated at reflux for 4.5 h. The reaction mixture was concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give azocinoindole **14** as a white foam: 146 mg (80%); IR (KBr) 1689, 1450, 1370, 1172 cm^{-1} ^1H NMR (400 MHz, assignments aided by gHSQC and ^1H gCOSY, mixture of rotamers) δ 1.42 (br s, 9H, Boc), 1.47 (br s, 3H, CH_3), 2.85 (m, 1H, 3-H), 3.81 and 4.03 (2m, 1H, 3-H), 4.37 (br s, 1H, 1-H), 4.65 (m, 1H, 6-H), 4.89 and 5.01 (2m, 1H, 1-H), 5.44 (br s, 1H, 4-H), 5.80 (br d, J = 11 Hz, 1H, 5-H), 7.29 (m, 3H), 7.38 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 8.28 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC) δ 24.3 (CH_3), 28.4 ($3CH_3$), 32.5 (CH, C-6), 37.0 (CH_2, C-1), 38.0 (CH_2, C-3), 79.90 (C), 115.6

(CH, C-8), 118.7 (CH, C-11), 118.9 (C), 121.0 (CH, C-4), 123.8 (CH, C-10), 124.8 (CH, C-9), 126.0 (2CH, Ph), 129.2 (2CH, Ph), 130.8 (C), 133.8 (CH, Ph), 136.9 (C), 137.6 (CH, C-5), 138.8 (C), 142.2 (C), 155.0 (CO); ESI-HRMS $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_4S$ 453.1842, found 453.1851; $[M + Na]^+$ calcd for $C_{25}H_{28}N_2O_4NaS$ 475.1662, found 475.1670.

Methyl 3-[*N*-(2-Bromo-2-propenyl)-*N*-(*tert*-butoxycarbonyl)-aminomethyl]indole-2-carboxylate (24). A solution of methyl 3-formylindole-2-carboxylate (**23**, 2.34 g, 11.52 mmol), 2-bromo-2-propenylamine (1.88 g, 13.82 mmol), $NaBH(OAc)_3$ (7.32 g, 35.0 mmol), and AcOH (1.32 mL, 23.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was stirred at rt overnight. The reaction mixture was washed with a saturated aqueous Na_2CO_3 solution. The solvent was removed, and the resulting residue (3.72 g, crude secondary amine) was dissolved in anhydrous dioxane (100 mL) and treated with $(t\text{-BuOCO})_2O$ (3.92 g, 17.96 mmol) at rt overnight. The reaction mixture was diluted with H_2O and concentrated. The residue was partitioned between Et_2O and brine and extracted with Et_2O. The organic extracts were dried and concentrated and the crude product was chromatographed (85:15 hexanes−AcOEt) to give **24** as a white solid: 3.71 g (76%); ^{1}H NMR (300 MHz, major rotamer) δ 1.49 (s, 9H), 3.89 (s, 2H), 3.96 (s, 3H), 5.11 (s, 2H), 5.49 (s, 1H), 5.57 (s, 1H), 7.16 (ddd, J = 1.5, 6.6, 8.1 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100.6 MHz, major rotamer) δ 28.2 (CH_3), 39.1 (CH_2), 52.0 (CH_3), 52.6 (CH_2), 80.2 (C), 111.7 (CH), 115.1 (CH_2), 118.8 (C), 120.8 (CH), 122.0 (CH), 124.8 (C), 125.9 (CH), 127.6 (C), 129.6 (C), 136.0 (C), 155.2 (C), 162.6 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{19}H_{23}BrN_2NaO_4$ 445.0733, found 445.0738. Anal. Calcd for $C_{19}H_{23}BrN_2O_4$: C, 53.91; H, 5.48; N, 6.62. Found: C, 53.85; H, 5.46; N, 6.56.

***Se*-Phenyl 3-[*N*-(2-Bromo-2-propenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-indole-2-carboselenoate (25).** A solution of carboxylic ester **24** (2.30 g, 5.44 mmol) and $LiOH \cdot H_2O$ (0.27 g, 6.43 mmol) in a 3:1 mixture of THF−H_2O (45 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated, acidified with 1 N HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the crude carboxylic acid (2.20 g). A suspension of this material in anhydrous CH_2Cl_2 (40 mL) was treated with Et_3N (1.50 mL, 10.88 mmol). After 15 min at rt, the mixture was concentrated to give the corresponding triethylammonium salt. In another flask, tributylphosphine (6.70 mL, 27.16 mmol) was added under Ar to a solution of PhSeCl (5.20 g, 27.16 mmol) in anhydrous THF (40 mL) and the mixture was stirred at rt for 10 min (yellow solution). The above triethylammonium salt in THF (40 mL) was added to this solution, and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O and H_2O and extracted with Et_2O. The organic extracts were dried and concentrated and the crude product was chromatographed (hexanes and 9:1 hexanes−AcOEt) to give **25** as a yellow solid: 2.68 g (90%); ^{1}H NMR (300 MHz, major rotamer) δ 1.51 (s, 9H), 3.93 (s, 2H), 5.13 (s, 2H), 5.44 (s, 1H), 5.54 (s, 1H), 7.18 (m, 1H), 7.39 (m, 2H), 7.46 (m, 3H), 7.62 (m, 2H), 7.94 (d, J = 7.8 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR (75.4 MHz, major rotamer) δ 28.3 (CH_3), 39.8 (CH_2), 53.0 (CH_2), 80.5 (C), 112.1 (CH), 115.8 (CH_2), 118.4 (C), 121.3 (CH), 122.4 (CH), 125.0 (C), 126.8 (CH), 127.8 (C), 129.4 (CH), 129.5 (CH), 132.8 (C), 136.3 (CH), 136.4 (C), 155.2 (C), 184.1 (C), (one missing quaternary carbon); HRMS $[M + Na]^+$ calcd for $C_{24}H_{25}BrN_2NaO_3Se$ 571.0105, found 571.0102. Anal. Calcd for $C_{24}H_{25}BrN_2O_3Se$: C, 52.57; H, 4.60; N, 5.11. Found: C, 52.57; H, 4.52; N, 5.11.

2-(*tert*-Butoxycarbonyl)-6-oxo-1,2,3,4,5,6-hexahydroazocino-[4,3-*b*]indole (26). *n*-Bu_3SnH (2.50 mL, 9.42 mmol) and Et_3B (1 M in hexanes, 9.50 mmol) were added to a solution of phenyl selenoester **25** (2.07 g, 3.78 mmol, previously dried azeotropically with anhydrous C_6H_6) in anhydrous C_6H_6 (135 mL). The reaction mixture was stirred at rt for 2 h with dry air constantly supplied by passing compressed air through a short tube of Drierite. Then, additional *n*-Bu_3SnH (0.50 mL, 1.89 mmol) and Et_3B (1 M in hexanes, 1.90 mmol) were added, and the reaction mixture was stirred under dry air at rt for 2 h. The reaction mixture was concentrated, and the resulting residue was partitioned between hexanes and acetonitrile. The polar layer was washed with hexanes and concentrated to give the crude product. Flash chromatography (8:2 hexanes−AcOEt) gave ketone **26** as an orange solid: 0.64 g (54%); ^{1}H NMR (400 MHz, assignment aided by gHSQC, mixture of rotamers) δ 1.30 and 1.50 (2s, 9H, Me), 1.96 and 2.04 (2m, 2H, 4-H), 2.97 (m, 2H, 5-H), 3.48 and 3.62 (2m, 2H, 3-H), 4.88 and 5.01 (2s, 2H, 1-H), 7.16 (t, J = 7.2 Hz, 1H, 10-H), 7.35 (ddd, J = 8.4, 7.2, 0.9 Hz, 1H, 9-H), 7.41 (d, J = 8.4 Hz, 1H, 8-H), [7.72 (d, J = 8.4 Hz), and 7.77 (d, J = 8 Hz), 1H, 11-H], 9.42 and 9.47 (2s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, gHSQC, mixture of rotamers) δ 23.9 and 25.1 (CH_2, C-4), 28.3 (CH_3), 38.7 and 39.5 (CH_2, C-5), 42.5 and 42.6 (CH_2, C-1), 43.0 and 46.1 (CH_2, C-3), 80.3 (C), 112.1 (CH, C-8), 117.3 and 119.3 (C), 120.3 and 120.7 (CH, C-10), 120.9 (CH, C-11), 126.4 and 126.6 (CH, C-9), 127.5 and 127.8 (C), 132.7 and 133.9 (C), 135.8 and 136.0 (C), 155.1 and 155.2 (C), 192.7 and 193.4 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{18}H_{22}N_2NaO_3$ 337.1522, found 337.1524. Anal. Calcd for $C_{18}H_{22}N_2O_3.1/2\ H_2O$ C, 66.85; H, 7,17; N, 8.66. Found: C, 67.24; H, 7.00; N, 8.33.

2-(*tert*-Butoxycarbonyl)-6-methyl-1,2,3,4-tetrahydroazocino-[4,3-*b*]indole (15). From Azocinoindole 14. *t*-BuOK (0.55 g, 4.90 mmol) was added to a solution of **14** (0.22 g, 0.49 mmol) in THF (14 mL), and the resulting solution was heated at reflux for 48 h. The reaction mixture was partitioned between a saturated aqueous NH_4Cl solution and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated to give azocinoindole **15** as a yellow foam: 138 mg (90%). An analytical sample was obtained by chromatography (hexanes and 8:2 hexanes−AcOEt); IR (film) 3321, 1670 cm^{-1}; ^{1}H NMR (400 MHz, assignments aided by gHSQC, mixture of rotamers) δ 1.35 and 1.45 (2s, 9H, Boc), 2.13 (s, 3H, CH_3), 2.37 (m, 2H, 4-H), 3.60 (m, 2H, 3-H), 4.64 (br s, 2H, 1-H), 5.69 and 5.75 (2t, J = 8 Hz, 1H, 5-H), 7.15 (m, 2H, 9-H, 10-H), 7.28 and 7.31 (2 d, J = 8 Hz, 1H, 8-H), 7.56 and 7.62 (2d, J = 8 Hz, 1H, 11-H), 7.85 and 7.89 (2 br s, 1H, NH); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC,) δ 22.7 and 22.8 (CH_3), 28.4 and 28.5 ($3CH_3$, Boc), 28.7 (CH_2, C-4), 43.4 and 43.5 (CH_2, C-1), 46.0 and 46.7 (CH_2, C-3), 79.1 and 79.3 (C), 110.3 and 110.4 (CH, C-8), 110.8 and 111.0 (C), 118.5 and 119.0 (CH, C-11), 119.3 and 119.4 (CH, C-10), 122.1 and 122.2 (CH, C-9), 126.5 and 127.1 (CH, C-5), 127.2 and 127.3 (C), 128.9 and 129.5 (C), 132.8 and 133.4 (C), 135.7 and 135.9 (C), 156.1 and 156.5 (C); ESI-HRMS calcd for $C_{19}H_{24}N_2O_2$ 312.1837, found 312.1837.

From Ketone 26. Ketone **26** (0.52 g, 1.66 mmol) in anhydrous THF (35 mL) was added under Ar to a cooled (−10 °C) solution of MeLi (1.6 M in Et_2O, 10.40 mL, 16.60 mmol) in anhydrous THF (35 mL). After stirring at rt for 2 h, the reaction mixture was quenched with ice−water and extracted with AcOEt. Concentration of the organic extracts gave the crude carbinol (0.45 g). *p*-Toluenesulfonic acid monohydrate (25 mg, 0.13 mmol) was added to a suspension of the above material in acetonitrile (25 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated, and the resulting residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous Na_2CO_3 solution. Concentration of the organic solution gave **15**: 0.36 g (70%).

2-(2-Iodo-2-(*Z*)-butenyl)-6-methyl-1,2,3,4-tetrahydroazocino-[4,3-*b*]indole (27). A solution of carbamate **15** (224 mg, 0.72 mmol) in 1.2 M HCl in MeOH (3.2 mL) was stirred at rt for 4.5 h. 20% NH_4OH was added and the organic solvent was removed. The residue was partitioned between CH_2Cl_2 and H_2O

and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the secondary amine (127 mg), which was directly used in the next step. Diisopropylethylamine (0.15 mL, 0.89 mmol) and (*Z*)-2-iodo-2-butenyl tosylate[15a,16c] (230 mg, 0.65 mmol) were added to a solution of the above amine (127 mg, 0.59 mmol) in 1:1 CH_2Cl_2−acetonitrile (21 mL). After the reaction mixture was stirred at rt for 2 h, $MeNH_2$ (2 M in MeOH, 1.5 mL, 3 mmol) was added and the stirring was continued for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution. The organic solution was dried and concentrated, and the residue was chromatographed (hexanes and 9:1 hexanes−EtOAc) to give pure tertiary amine **27** (yellow oil): 70 mg (30%); IR (film) 3408, 2923, 1612, 1460, 742 cm^{-1}; ^1H NMR (400 MHz) δ 1.79 (dd, J = 6.2 and 1.2 Hz, 3H), 2.11 (s, 3H), 2.14 (br s, 2H), 2.77 (br s, 2H), 3.35 (br s, 2H), 3.99 (br s, 2H), 5.81 (q, J = 6.2 Hz, 1H), 5.85 (t, J = 7.8 Hz, 1H), 7.15 (m, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.95 (br s, 1H); ^{13}C NMR (100.6 MHz) δ 21.7 (CH_3), 22.5 (CH_3), 26.0 (CH_2), 48.0 (CH_2), 50.6 (CH_2), 65.3 (CH_2), 110.1 (C), 110.5 (CH), 110.6 (C), 118.9 (CH), 119.5 (CH), 121.9 (CH), 126.9 (C), 128.8 (C), 130.0 (CH), 131.3 (CH), 135.8 (C), 136.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{22}IN_2$ 393.0822, found 393.0831.

(±)-Apparicine. $Pd(OAc)_2$ (7.6 mg, 0.034 mmol), PPh_3 (26 mg, 0.10 mmol) and Ag_2CO_3 (93 mg, 0.34 mmol) were added under Ar to a solution of amine **27** (65 mg, 0.17 mmol) in 1:1 toluene−Et_3N (17 mL) and the mixture was heated at 80 °C for 1.5 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (SiO_2, flash, CH_2Cl_2 to 9:1 CH_2Cl_2−MeOH). An additional chromatography (SiO_2, 0.5% Et_2O−diethylamine) gave pure (±)-apparicine as an amorphous solid: 6.6 mg (15%); ^1H NMR ($CDCl_3$, 400 MHz, assignments aided by gHSQC) δ 1.46 (dd, J = 6.8 and 2.4 Hz, 3H, 18-H), 1.89 (ddt, J = 13.6, 6.8, and 2.4 Hz, 1H, 14-H), 2.16 (dddd, J = 13.6, 11.2, 8, and 5.6 Hz, 1H, 14-H), 3.07 (dddd, J = 13.2, 11.2, 6.8, and 1.2 Hz, 1H, 3-H), 3.20 (d, J = 16 Hz, 1H, 21-H), 3.42 (ddd, J = 13.2, 8, and 2 Hz, 1H, 3-H), 3.82 (dt, J = 16 and 2 Hz, 1H, 21-H), 3.92 (broad s, 1H, 15-H), 4.28 (d, J = 17.8 Hz, 1H, 6-H), 4.51 (d, J = 17.8 Hz, 1H, 6-H), 5.25 (q, J = 6.8 Hz, 1H, 19-H), 5.26 (s, 1H, 17-H), 5.39 (s, 1H, 17-H), 7.06 (ddd, J = 7.6, 7.2, and 1.2 Hz, 1H, 10-H), 7.18 (ddd, J = 8, 7.2, and 1.2 Hz, 1H, 11-H), 7.28 (d, J = 8 Hz, 1H, 12-H), 7.42 (d, J = 7.6 Hz, 1H, 9-H), 7.84 (broad s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, assignment aided by gHSQC) δ 12.6 (CH_3, C-18), 29.6 (CH_2, C-14), 41.2 (CH, C-15), 45.3 (CH_2, C-3), 54.2 (CH_2, C-6), 54.3 (CH_2, C-21), 110.2 (CH, C-12), 111.5 (C, C-7), 112.2 (CH_2, C-17), 118.6 (CH, C-9), 119.3 (CH, C-10), 120.1 (CH, C-19), 123.0 (CH, C-11), 129.0 (C, C-8), 131.3 (C, C-20), 135.6 (C, C-16), 137.4 (C, C-13), 145.2 (C, C-2); ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}N_2$ 265.1699, found 265.1705.

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Supporting Information Available: General protocols, additional experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Supporting Information:

Total Synthesis of the Bridged Indole Alkaloid Apparicine

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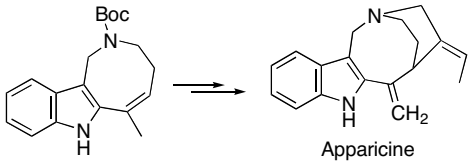


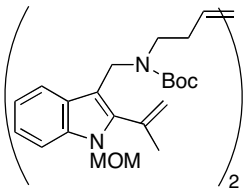
Contents

General

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F254 Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure with a rotary evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm). Melting points are uncorrected. Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using TMS as an internal reference.

Spectroscopic Data of Metathesis Products from Dienes 3:

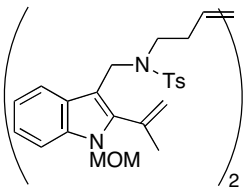
Dimer 4a



4a

^1H NMR (400 MHz, mixture of rotamers) δ 1.60 (br s, 9H), 1.98 (m, 2H), 2.06 (s, 3H), 2.94 (m, 2H), 3.28 (s, 3H), 4.59 (m, 2H), 5.12 (s, 1H), 5.20 (m, 1H), 5.43 (s, 2H), 5.58 (s, 1H, CH_2), 7.11 (m, 1H), 7.27 (m, 1H), 7.46 (m, 1H), 7.65 (m, 1H); ^{13}C NMR (100.6 MHz) δ 24.5 (CH_3), 28.5 ($3CH_3$), 32.1 (CH_2), 39.7 (CH_2), 44.5 (CH_2), 56.1 (CH_3), 74.6 (CH_2), 79.1 (C), 109.7 (CH), 119.5 (C), 120.0 (CH), 120.4 (CH), 120.9 (CH_2), 122.4 (CH), 127.4 (C), 127.6 (CH), 135.5 (C), 136.7 (C), 141.1 (C), 155.6 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{44}H_{60}N_4O_6Na$ 763.4405, found 763.4402.

Dimer 4b (mixture of *E*/*Z* isomers)

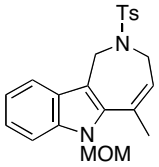


4b

Major isomer: ^1H NMR (400 MHz) δ 1.69 (m, 2H), 1.99 (s, 3H), 2.43 (s, 3H), 2.85 (m, 2H), 3.20 (s, 3H), 4.39 (s, 2H), 4.69 (m, 1H), 5.01 (s, 1H), 5.32 (s, 2H), 5.47 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.30 (m, 2H), 7.39 (d, *J* = 8 Hz, 1H),

7.80 (m, 3H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 24.5 (CH_3), 31.8 (CH_2), 43.4 (CH_2), 47.0 (CH_2), 55.7 (CH_3), 74.7 (CH_2), 107.0 (C), 109.7 (CH), 120.1 (CH), 120.7 (CH), 121.8 (CH_2), 122.6 (CH), 127.2 (2CH), 129.6 (2CH), 129.5 (CH), 127.7 (C), 135.0 (C), 136.9 (2C), 141.3 (C), 143.0 (C); ESI-HRMS $[M+H]^+$calcd for $C_{48}H_{57}N_4O_6S_2$ 849.3714, found 849.3704; $[M+Na]^+$ calcd for $C_{48}H_{56}NaN_4O_6S_2$ 871.3533, hallado 871.3528.

5-Methyl-6-(methoxymethyl)-2-tosyl-2,3-dihydro-1*H*-azepino[4,3-*b*]indole (5)

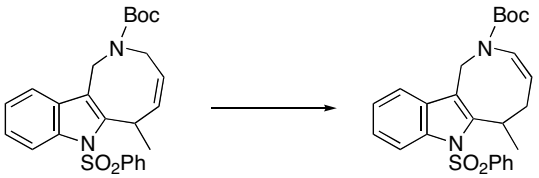


5

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 2.34 (s, 3H), 3.15 (s, 3H), 3.57 (d, *J* = 6.5 Hz, 2H), 4.36 (s, 2H), 5.40 (s, 2H), 6.00 (t, *J* = 6.5 Hz, 1H), 7.20 (m, 3H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 20.8 (CH_3), 21.3 (CH_3), 40.9 (CH_2), 44.5 (CH_2), 55.7 (CH_3), 75.2 (CH_2), 109.8 (CH), 112.5 (C), 118.5 (CH), 120.8 (CH), 123.2 (CH), 126.3 (C), 126.4 (CH), 127.4 (2CH), 129.5 (2CH), 135.7 (C), 136.1 (C), 138.1 (C), 139.5 (C), 142.9 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_3S$ 397.1580, found 397.1578.

Isomerizations Studies

2-(*tert*-Butoxycarbonyl)-6-methyl-7-(phenylsulfonyl)-1,2,5,6-tetrahydroazocino[4,3-*b*]indole (16).

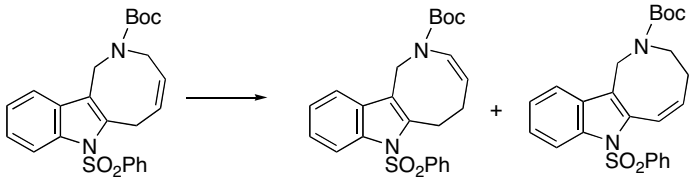


14 **16**

The second-generation Grubbs catalyst (4.5 mg, 10 mol %) was added under Ar to a solution of azocinoindole **14** (23 mg, 0.05 mmol) in toluene (5.5 mL) and the resulting mixture was heated at reflux for 18 h. The reaction mixture was concentrated and the residue was chromatographed (5% hexanes-AcOEt) to give enamide **16**: 12 mg (50%);

IR (film) 1700, 1650, 1450, 1363, 1173 cm^{-1}; ^1H NMR (400 MHz, assignments aided by gHSQC and gCOSY, mixture of rotamers) δ 1.44 and 1.46 (2s, 9H, Boc), 1.58 (s, 3H, CH_3), 2.16 (m, 1H, 5-H), 3.03 (m, 1H, 5-H), 3.82 (m, 1H, 6-H), 4.45 (m, 1H, 4-H), 4.75 and 4.90 (2d, *J* = 15.0 Hz, 1H, 1-H), 5.30 and 5.52 (2d, *J* = 15.0 Hz, 1H, 1-H), 6.10 and 6.26 (2d, *J* = 9.0 Hz, 1H, 3-H), 7.26 (m, 2H), 7.32 (m, 2H), 7.50 (m, 1H), 7.60 (m, 3H), 8.22 (br s, 1H); ^{13}C NMR (100.6 MHz, gHSQC, only CH_3, CH_2 and CH signals are listed) δ 24.0 (CH_3), 28.3 ($3CH_3$), 32.8 (CH_2, C-5), 34.3 (CH, C-6), 38.7 (CH_2, C-1), 107.8 (CH, C-4), 115.4 (CH, C-8), 118.4 (CH, C-11), 124.1 (2CH, C-9, C-10), 126.8 (2CH, Ph), 127.4 (CH, C-3), 129.1 (2CH, Ph), 133.6 (CH, Ph). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43%; H, 6.40%; N, 6.36%. Found: C, 65.58%; H, 6.24%; N, 5.94%.

Isomerization of Azocinoindole 17a

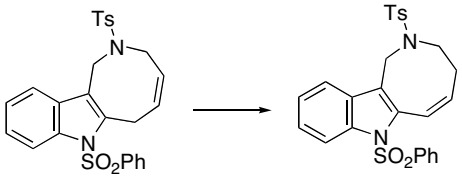


17a **18a** **19a**

Azocinoindole **17a**[1] (31 mg, 0.07 mmol) in toluene (7 mL) was treated as above with the second-generation Grubbs catalyst (5.5 mg, 10 mol %) at reflux temperature for 24 h. After workup, a 3:1 mixture of azocinoindoles **18a** and **19a** was obtained. Both compounds were separated by flash chromatography (9:1 hexanes-AcOEt). **2-*(tert*-Butoxycarbonyl)-7-(phenylsulfonyl)-1,2,5,6-tetrahydroazocino[4,3-*b*]indole (18a)**: 11 mg (35%); IR (neat) 1699, 1653, 1455, 1363, 1162 cm^{-1}; ^1H NMR (400 MHz, mixture of rotamers) δ 1.43 (br s, 9H), 2.76 (m, 2H), 3.32 (t, *J* = 6.5 Hz, 2H), 4.59 and 4.70 (2 m, 1H), 5.05 and 5.12 (2 br s, 2H), 6.40 and 6.45 (2 br d, *J* = 10 Hz, 1H), 7.23 (m, 2H), 7.37 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.68 (m, 3H), 8.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, major rotamer) δ 22.8 (CH_2), 28.1 ($3CH_3$), 29.5 (CH_2), 37.6 (CH_2), 81.2 (C), 106.5 (CH), 114.3 (CH), 116.6 (C), 118.8 (CH), 123.5 (CH), 124.3 (CH), 126.2 (2CH), 127.3 (CH), 129.8 (2CH), 133.6 (CH), 130.0 (C), 136.5 (C); 139.0 (C), 152.9 (C), (one missing quaternary carbon); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_4S$ 439.1686, found 439.1684. **2-*(tert*-Butoxycarbonyl)-7-(phenylsulfonyl)-1,2,3,4-tetrahydroazocino[4,3-*b*]indole (19a)**: 3 mg (10%); IR (neat) 1683, 1448, 1418, 1367

cm^{-1}; ^1H NMR (400 MHz, mixture of rotamers) δ 1.34 and 1.40 (2s, 9H), 2.15 (m, 2H), 3.50 (m, 2H), 4.41 (br s, 2H), 6.10 (m, 1H), 6.99 (m, 1H), 7.30 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.52 and 7.75 (2 m, 1H), 7.68 (d, *J* = 7.5 Hz, 2 H), 8.22 and 8.35 (2m, 1H); ^{13}C NMR (100.6 MHz, major rotamer) δ 28.3 ($3CH_3$), 28.7 (CH_2), 42.8 (CH_2), 44.5 (CH_2), 80.2 (C), 115.3 (CH), 119.0 (CH), 122.5 (CH), 123.6 (CH), 125.0 (CH), 126.5 (2CH), 128.8 (2CH), 131.7 (CH), 133.2 (CH), 136.9 (C), 138.4 (C), 155.5 (C), (three quaternary carbons missing); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_4S$ 439.1686, found 439.1685.

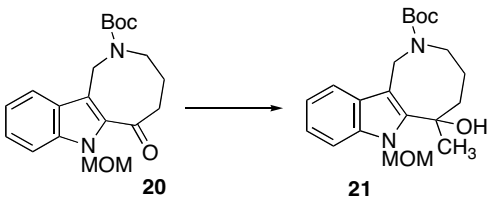
7-(Phenylsulfonyl)-2-tosyl-1,2,3,4-tetrahydroazocino[4,3-*b*]indole (19b).



17b **19b**

Operating as above, from azocinoindole **17b**[1] (134 mg, 0.27 mmol) azocinoindole **19b** was obtained after flash chromatography (7:3 hexanes-AcOEt): 54 mg (40%); mp 215 °C (CH_2Cl_2); IR (KBr) 1450, 1370, 1337, 1159 cm^{-1}; ^1H NMR (400 MHz) δ 2.08 (m, 2H), 2.46 (s, 3H), 3.11 (m, 2H), 4.24 (m, 2H), 6.06 (dt, *J* = 10.8 and 9 Hz, 1H), 6.97 (d, *J* = 10.8 Hz, 1H), 7.20-7.92 (m, 11H), 7.97 (dd, *J* =8.3 and 1.5 Hz, 1H), 8.22 (d, *J* = 8.3 and 1.5 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 28.4 (CH_2), 36.8 (CH_2), 44.5 (CH_2), 114.6 (CH), 118.7 (C), 120.5 (CH), 122.5 (CH), 124.3 (CH), 125.5 (CH), 126.5 (2CH), 127.1 (2CH), 129.0 (2CH), 129.7 (2CH), 132.9 (CH), 133.8 (CH), 135.3 (C), 135.7 (C), 136.6 (C), 138.3 (C), 143.3 (C), one quaternary carbon missing. Anal. Calcd. for $C_{26}H_{24}N_2O_4S_2.1/2\ H_2O$: C, 59.49%; H, 4.71%; N, 5.24%; S, 11.98%. Found: C, 59.41%; H, 4,61%; N, 5.23%; S, 11.61%.

2-*(tert*-Butoxycarbonyl)-6-hydroxy-7-(methoxymethyl)-6-methyl-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (21).

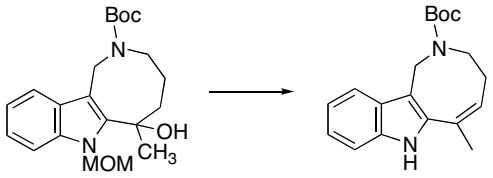


20 **21**

Ketone **20**[1] (40 mg, 0.11 mmol) in anhydrous THF (1.5 mL) was added under Ar to a cooled (–78 °C) solution of MeLi (1.6 M in Et_2O, 0.1 mL, 0.16 mmol) and the mixture was stirred at –78 °C for 1.5 h. Continuing the stirring, additional MeLi solution was added three times at 30 min intervals (3 x 0.035 mL, 0.17 mmol). The reaction mixture was partitioned between 10% NH_4Cl and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated to give essentially pure carbinol **21**: 37 mg (90%); IR (film) 3422, 2973, 1666 cm^{-1}; ^1H NMR (400 MHz, mixture of rotamers) δ 1.49 and 1.54 (2s, 9H), 1.64 (s, 3H), 1.83 (m, 1H), 2.02 (m, 2H), 2.47 (m, 1H), 2.99 (m, 1H), 3.23 (m, 1H), 3.36 (s, 3H), 3.51 and 3.63 (2 dm, J = 12 Hz, 1H), 4.52 (d, J = 14.4 Hz, 1H), 5.04 (br d, J = 14.4 Hz, 1H), 5.83 (s, 2H), 7.16 (td, J = 8 and 1.2 Hz, 1H), 7.25 (td, J = 8 and 1.2 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.57 and 7.64 (2d, J = 7.5 Hz, 1H); ^{13}C NMR (100.6 MHz, major rotamer) δ 24.1 (CH_2), 28.5 ($3CH_3$), 31.8 (CH_3), 39.9 (CH_2), 40.2 (CH_2), 41.6 (CH_2), 55.8 (CH_3), 72.4 (C), 75.5 (CH_2), 79.4 (C), 107.2 (C), 109.3 (CH), 118.7 (CH), 120.6 (CH), 122.9 (CH), 128.2 (C), 137.7 (C), 142.0 (C), 155.6 (C); ESI-HRMS $[M+Na]^+$ calcd for $C_{21}H_{30}N_2NaO_4$ 397.2098, found 397.2084.

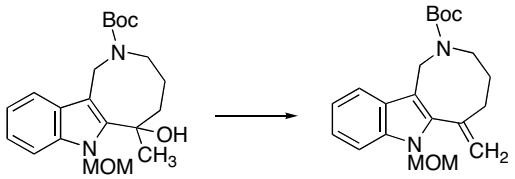
[1]Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861-866.

Dehydration of Carbinol 21.



21 **15**

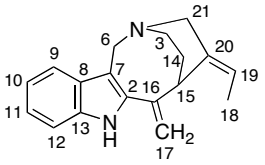
Method A. 3 M H_2SO_4 (0.25 mL) was added to carbinol **21** (35 mg, 0.093 mmol) in acetone (2.5 mL) and the solution was stirred at rt for 2 days. The reaction mixture was diluted with H_2O, basified with solid Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated. Flash chromatography of the residue (complex mixture) allowed the isolation of azocinoindole **15**: 2.6 mg (9%).



21 **22**

Method B. Martin sulfurane (0.22 g, 0.33 mmol) was added to carbinol **21** (41 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at rt for 1h. The reaction mixture was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the resulting residue was chromatographed (8:2 hexanes-AcOEt) to give 2-(*tert*-butoxycarbonyl)-7-(methoxymethyl)-6-methylene-1,2,3,4,5,6-hexahydroazocino[4,3-*b*]indole (**22**): 19 mg (48%); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 1.36 and 1.45 (2s, 9H), 1.82 (m, 2H), 2.51 (m, 2H), 3.18 and 3.20 (2s, 3H), 3.58 and 3.61 (2m, 2H), 4.63 and 4.67 (2s, 2H), 4.99 and 5.10 (2s, 1H), 5.40 (s, 2H), 5.48 and 5.53 (2s, 1H), 7.17 (m, 1H), 7.21 (m, 1H), 7.45 (m, 1H), 7.61 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100.6 MHz, mixture of rotamers) δ 25.4 and 26.7 (CH_2), 28.8 ($3CH_3$), 35.8 and 36.4 (CH_2), 43.9 and 44.2 (CH_2), 48.0 and 48.9 (CH_2), 55.8 (CH_3), 73.9 and 74.0 (CH_2), 79.3 (C), 110.1 and 110.2 (CH), 112.6 and 113.3 (C), 118.3 and 118.5 (CH_2), 118.6 (CH), 120.2 (CH), 122.3 (CH), 126.4 (C), 135.2 and 135.4 (C), 137.3 and 137.4 (C), 144.8 (C), 155.3 and 155.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{21}H_{29}N_2O_3$ 357.2172, found 357.2169; $[M+Na]^+$ calcd for $C_{21}H_{28}N_2O_3Na$ 379.1992, found 379.1989.

Comparison of the NMR data of synthetic apparicine with those reported for the natural product



Apparicine
(biogenetic numbering)

^{1}H NMR Data:

H	Synthetic Apparicine	Natural Product[2]
NH	7.84 (br s)	7.88 (br s)
3-H	3.07 (dddd, *J* = 13.2, 11.2, 6.8, 1.2 Hz) 3.42 (ddd, *J* = 13.2, 8, 2 Hz)	3.06 (dddd, *J* = 13.2, 11.4, 7.0, 1.2 Hz) 3.40 (ddd, *J* = 13.3, 8, 2.2 Hz)
6-H	4.28 (d, *J* = 17.8 Hz) 4.51 (d, *J* = 17.8 Hz)	4.26 (d, *J* = 17.7 Hz) 4.49 (d, *J* = 17.7 Hz)
9-H	7.42 (d, *J* = 7.6 Hz)	7.42 (dd, *J* = 7.7, 1.2 Hz)
10-H	7.06 (ddd, *J* = 7.6, 7.2, 1.2 Hz)	7.05 (ddd, *J* = 7.7, 7.3, 1.2 Hz)
11-H	7.18 (ddd, *J* = 8, 7.2, 1.2 Hz)	7.17 (ddd, *J* = 8.1, 7.3, 1.2 Hz)
12-H	7.28 (d, *J* = 8 Hz)	7.28 (dd, *J* = 8.1, 1.2 Hz)
14-H	1.89 (ddt, *J* = 13.6, 6.8, 2.4 Hz); 2.16 (dddd, *J* = 13.6, 11.2, 8, 5.6 Hz)	1.88 (dddd, *J* = 13.6, 7, 2.6, 2.2 Hz) 2.15 (dddd, *J* = 13.6, 11.4, 8, 5.4 Hz)
15-H	3.92 (br s)	3.91 (dd, *J* = 5.4, 2.6 Hz)
17-H	5.26 (s) 5.39 (s)	5.25 (s) 5.38 (s)
18-H	1.46 (dd, *J* = 6.8, 2.4 Hz)	1.45 (dd, *J* = 7, 2.3 Hz)
19-H	5.25 (q, *J* = 6.8 Hz)	5.23 (q, *J* = 7 Hz)
21-H	3.20 (d, *J* = 16 Hz) 3.82 (dt, *J* = 16, 2 Hz)	3.18 (dd, *J* = 16, 1.2 Hz) 3.80 (dd, *J* = 16, 2.3 Hz)

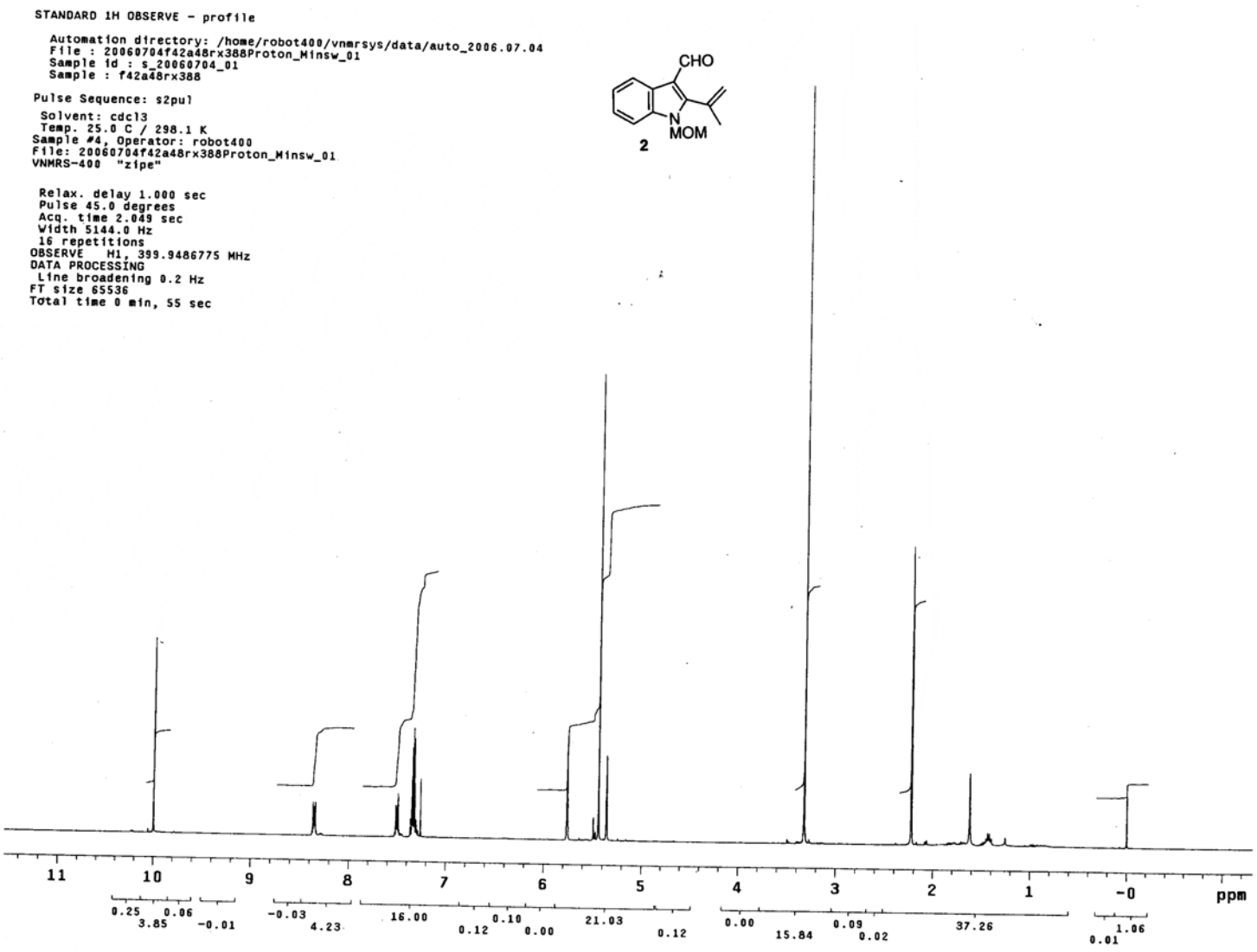
[2] van Beek, T. A.; Verpoorte, R.; Kinh, P. Q. *Planta Med.* **1985**, *51*, 277-279.

^{13}C NMR Data:

C	Synthetic Apparicine	Natural Product[3,4]	
		reference 3	reference 4
C-2	145.2	142.6	144.7
C-3	45.3	45.3	45.2
C-6	54.2	54.3	53.8
C-7	111.5	111.1	109.9[b]
C-8	129.0	129.0	129.0
C-9	118.6	118.6	118.6
C-10	119.3	119.3[a]	119.6
C-11	123.0	123.0[a]	123.2[c]
C-12	110.2	110.2	110.4[d]
C-13	137.4	137.8	136.6
C-14	29.6	29.6	29.1
C-15	41.2	41.3	41.1
C-16	135.6	135.7	135.8
C-17	112.2	112.2	112.6[b]
C-18	12.6	12.5	12.6
C-19	120.1	120.3	121.4[e]
C-20	131.3	131.3	131.6
C-21	54.3	54.3	54.2

[a] Exchanged assignments in ref. 3
[b] Exchanged assignments in ref. 4
[c] Signal assigned as C-12 in ref. 4
[d] Signal assigned as C-19 in ref. 4
[e] Signal assigned as C-11 in ref. 4

[3] Massiot, G.; Zèches, M.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. *J. Chem. Soc., Chem. Commun*. **1982**, 768-769.
[4] Atta-ur-Rahman; Fatima, T.; Mehrun-Nisa; Ijaz, S.; Crank, G.; Wasti, S. *Planta Med*. **1987**, *53*, 57-59.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Sample : f42a48rx388
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
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Width 5144.0 Hz
16 repetitions
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DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 0 min, 55 sec
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10
9
8
7
6
5
4
3
2
1
-0
ppm
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3.85
-0.01
-0.03
4.23
16.00
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0.10
0.00
21.03
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0.00
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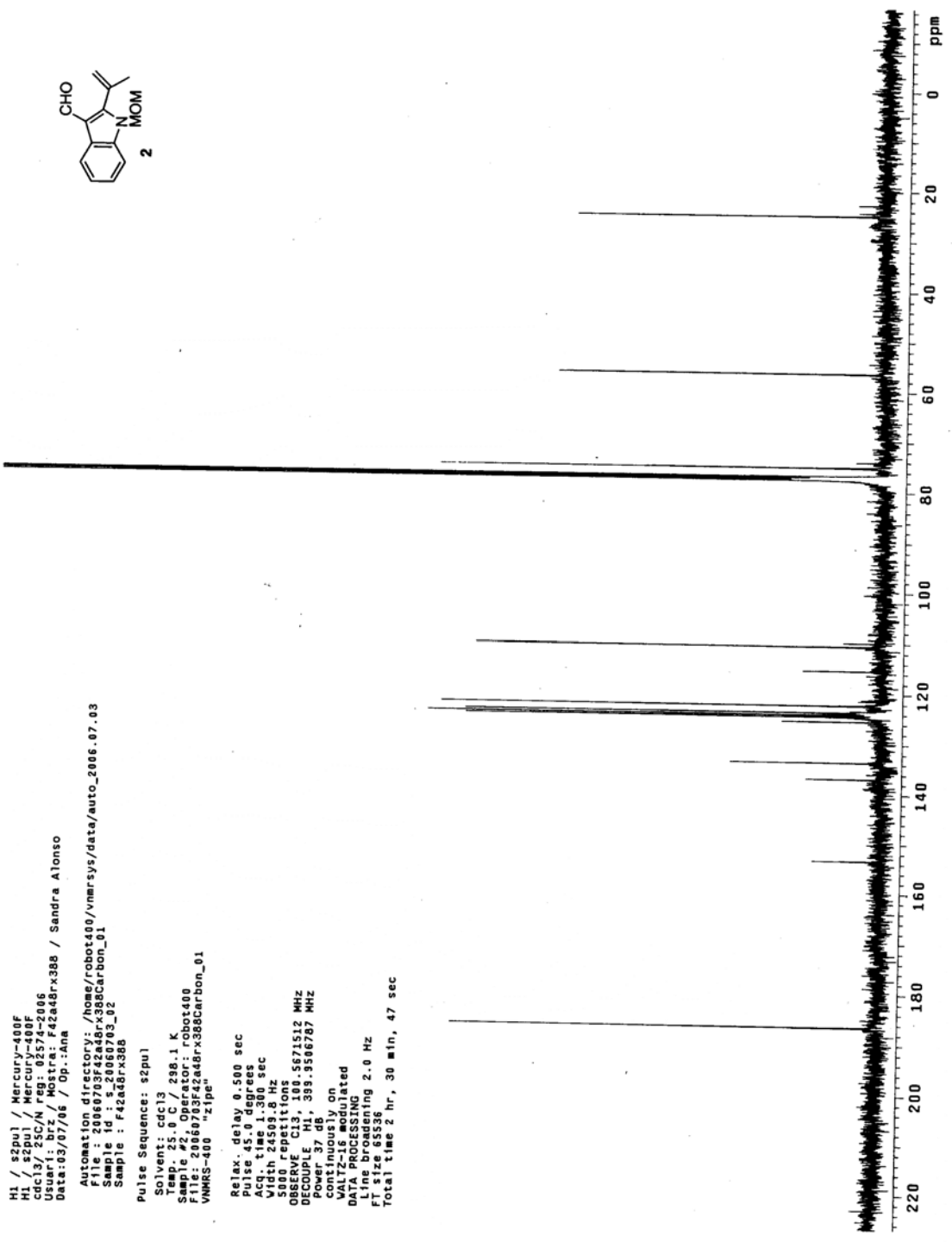
0.09
0.02
37.26
1.06
0.01


H1 / s2pul / Mercury-400F
H1 / s2pul / Mercury-400F
cdcl3/ 25c/N reg: 02574-2006
Usuari: brz / Mostra: F42a48rx388 / Sandra Alonso
Data:03/07/06 / Op.:Ana
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Sample : F42a48rx388
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #2, Operator: robot400
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DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
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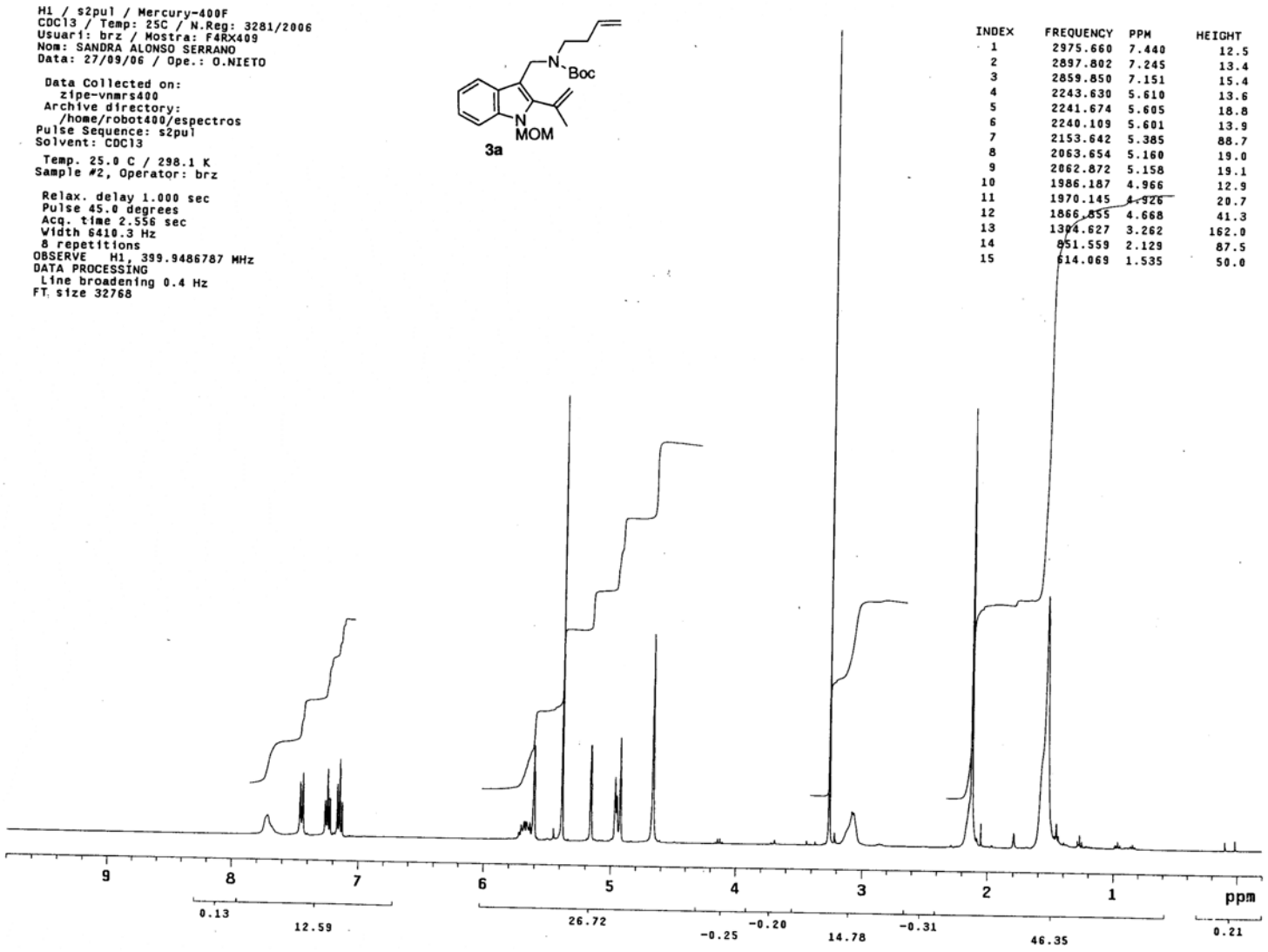
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CDCl3 / Temp: 25C / N.Reg: 3281/2006
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Data: 27/09/06 / Ope.: O.NIETO
Data Collected on:
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Archive directory:
/home/robot400/espectros
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Width 6410.3 Hz
8 repetitions
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DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
Boc
N
MOM
3a
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4 2243.630 5.610 13.6
5 2241.674 5.605 18.8
6 2240.109 5.601 13.9
7 2153.642 5.385 88.7
8 2063.654 5.160 19.0
9 2062.872 5.158 19.1
10 1986.187 4.966 12.9
11 1970.145 4.926 20.7
12 1866.855 4.668 41.3
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7
6
5
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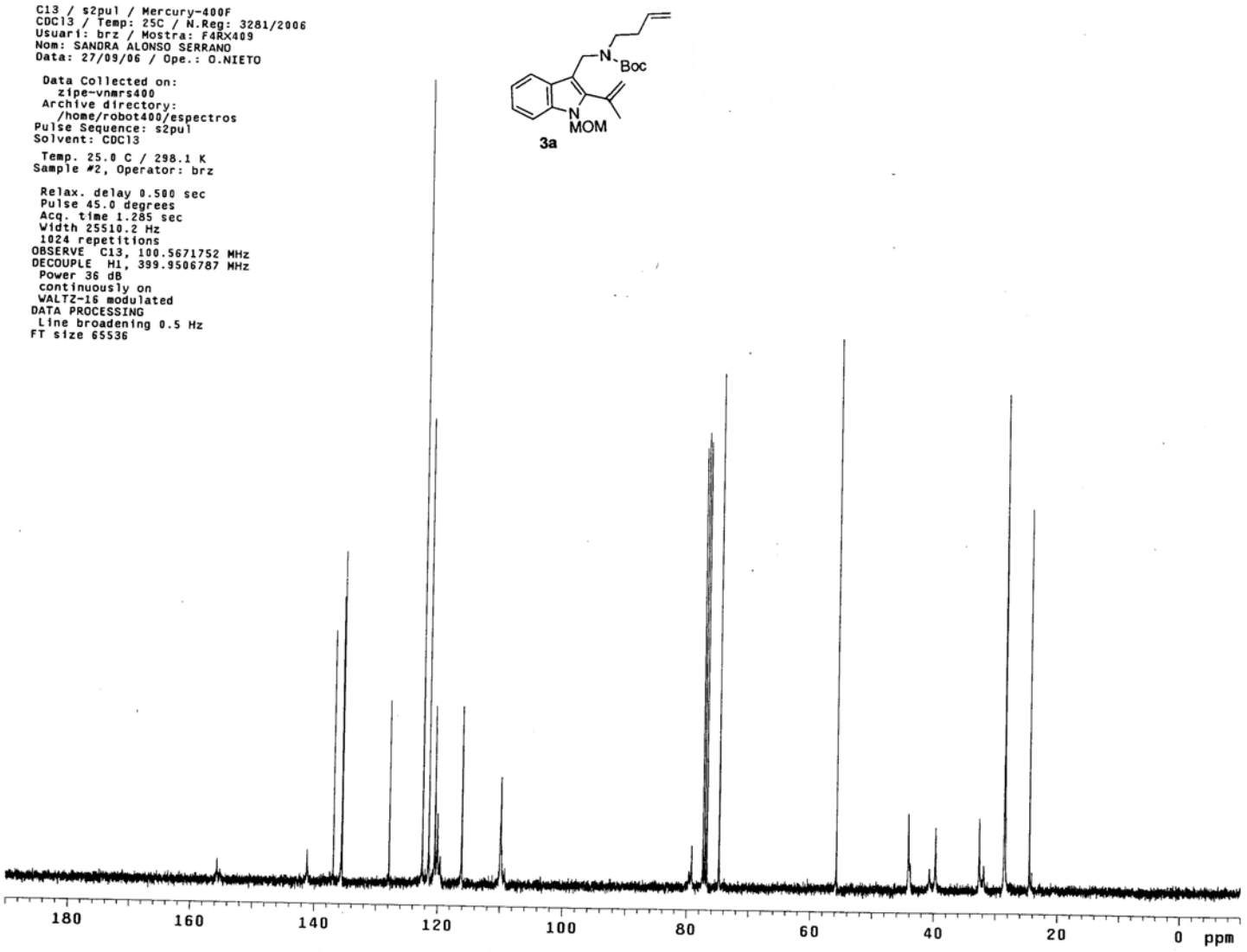
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Usuari: brz / Mostra: F4RX409
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Data: 27/09/06 / Ope.: O.NIETO
Data Collected on:
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Archive directory:
/home/robot400/espectros
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Solvent: CDCl3
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DECOUPLE H1, 399.9506787 MHz
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continuously on
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Line broadening 0.5 Hz
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Boc
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MOM
3a
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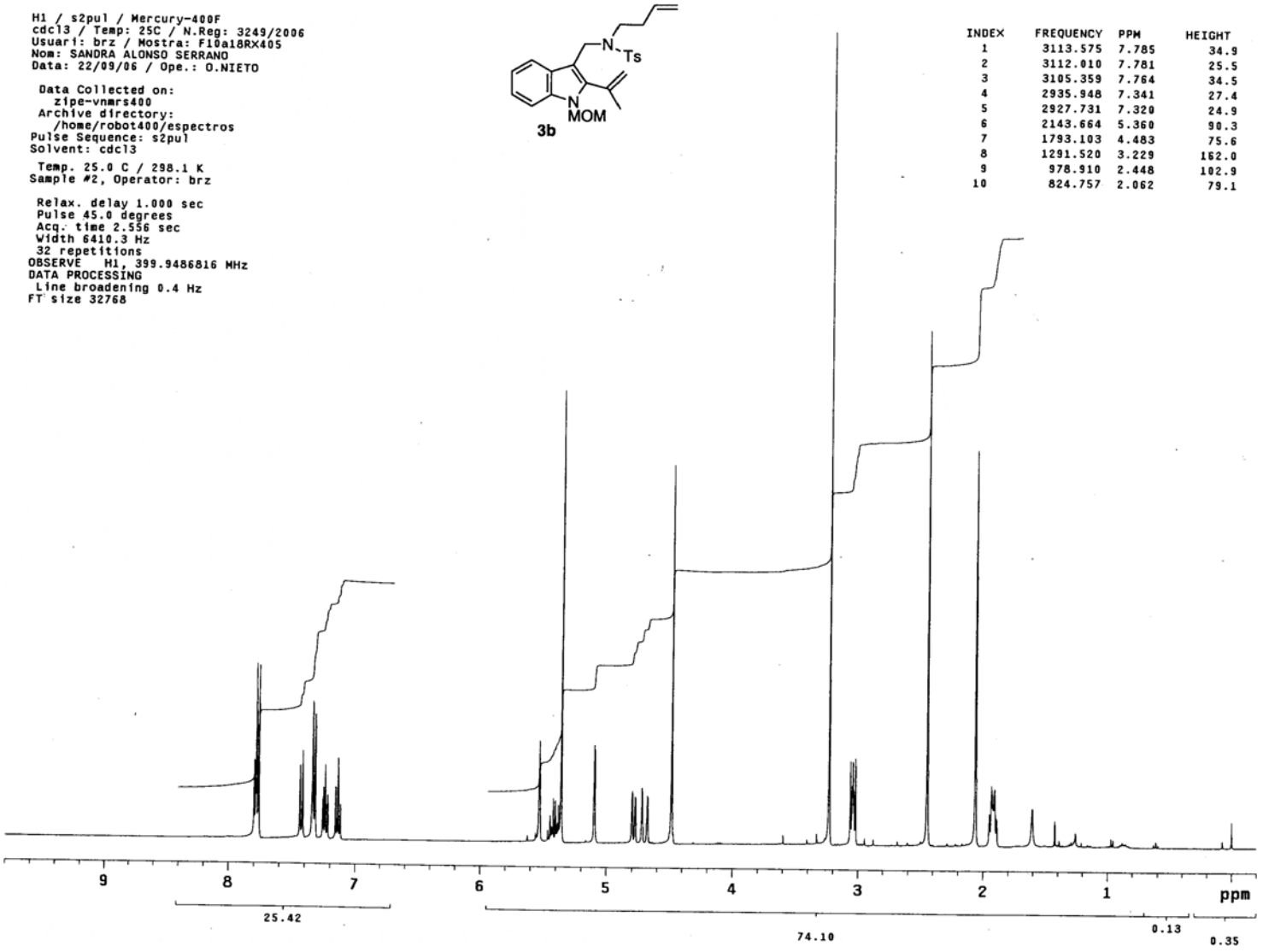
ppm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cdcl3 / Temp: 25C / N.Reg: 3249/2006
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Data: 22/09/06 / Ope.: O.NIETO
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Archive directory:
/home/robot400/espectros
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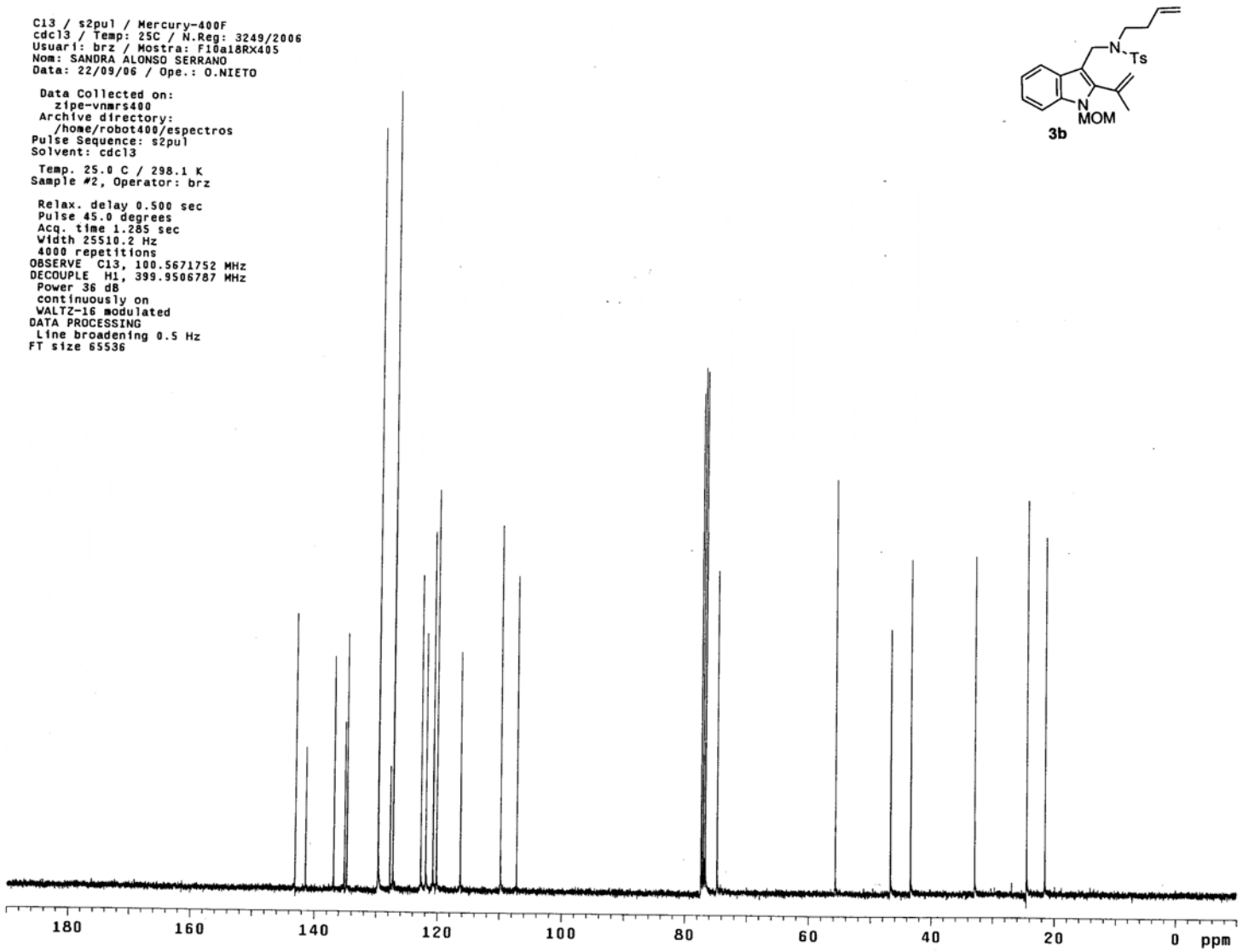
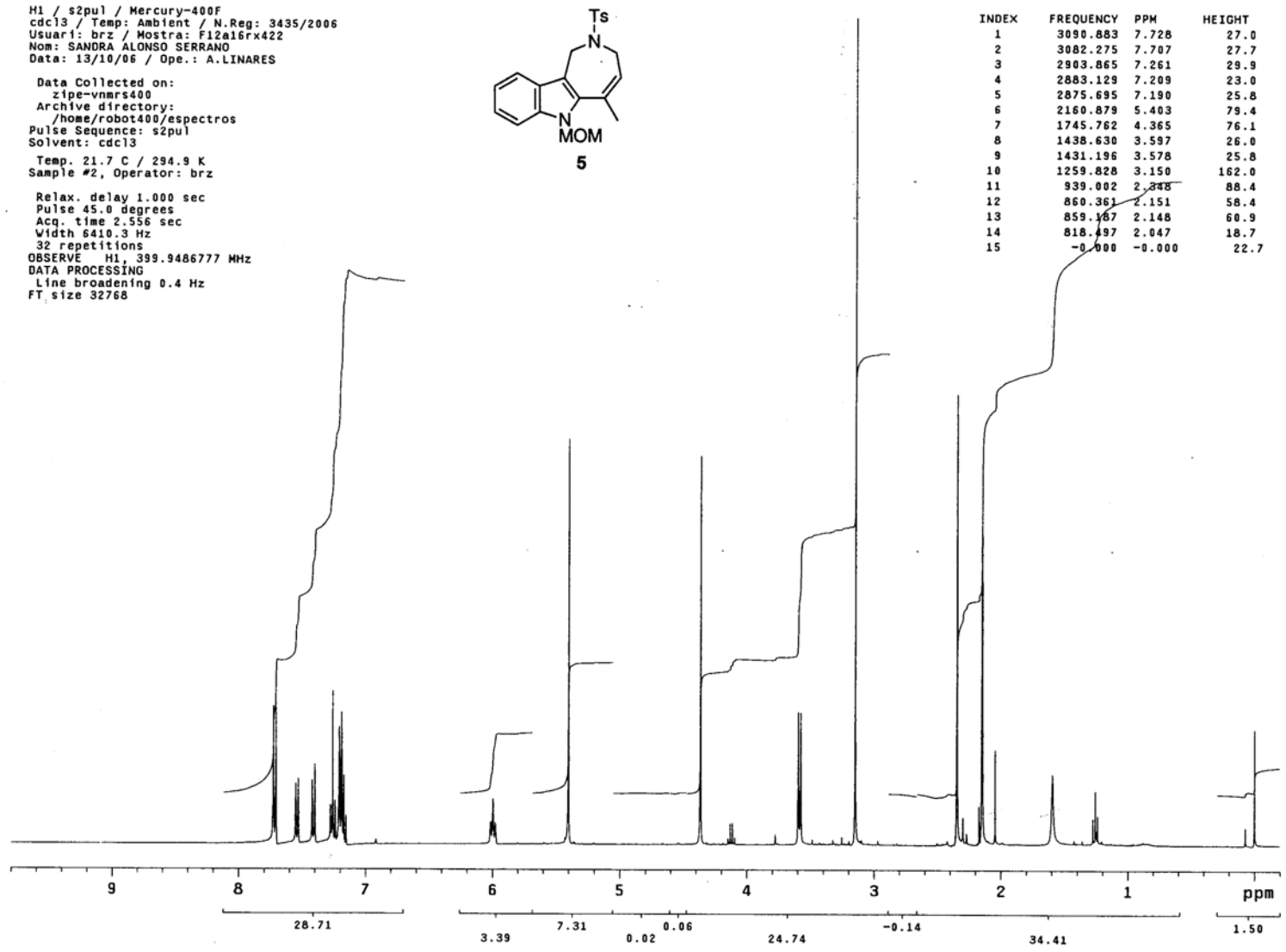
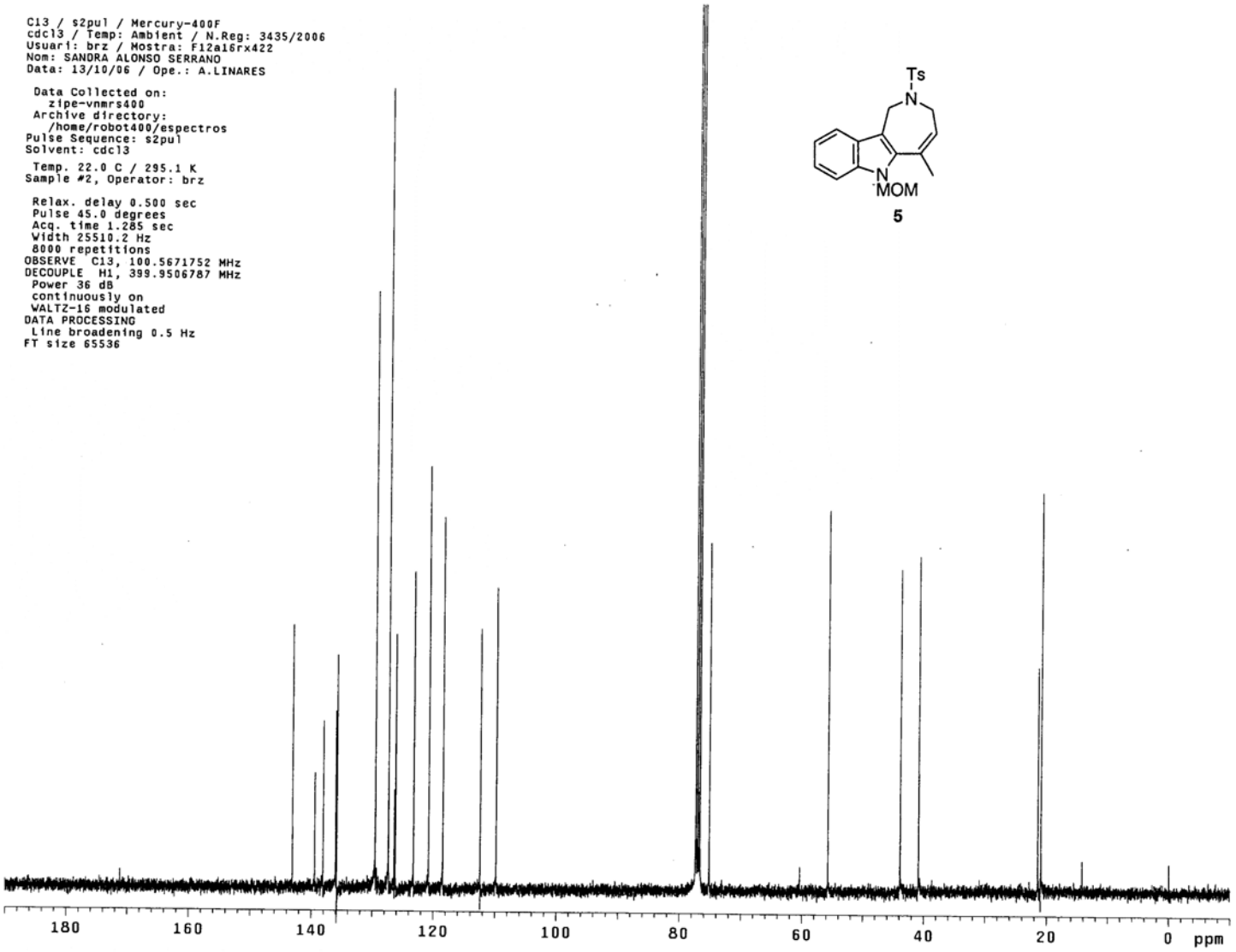
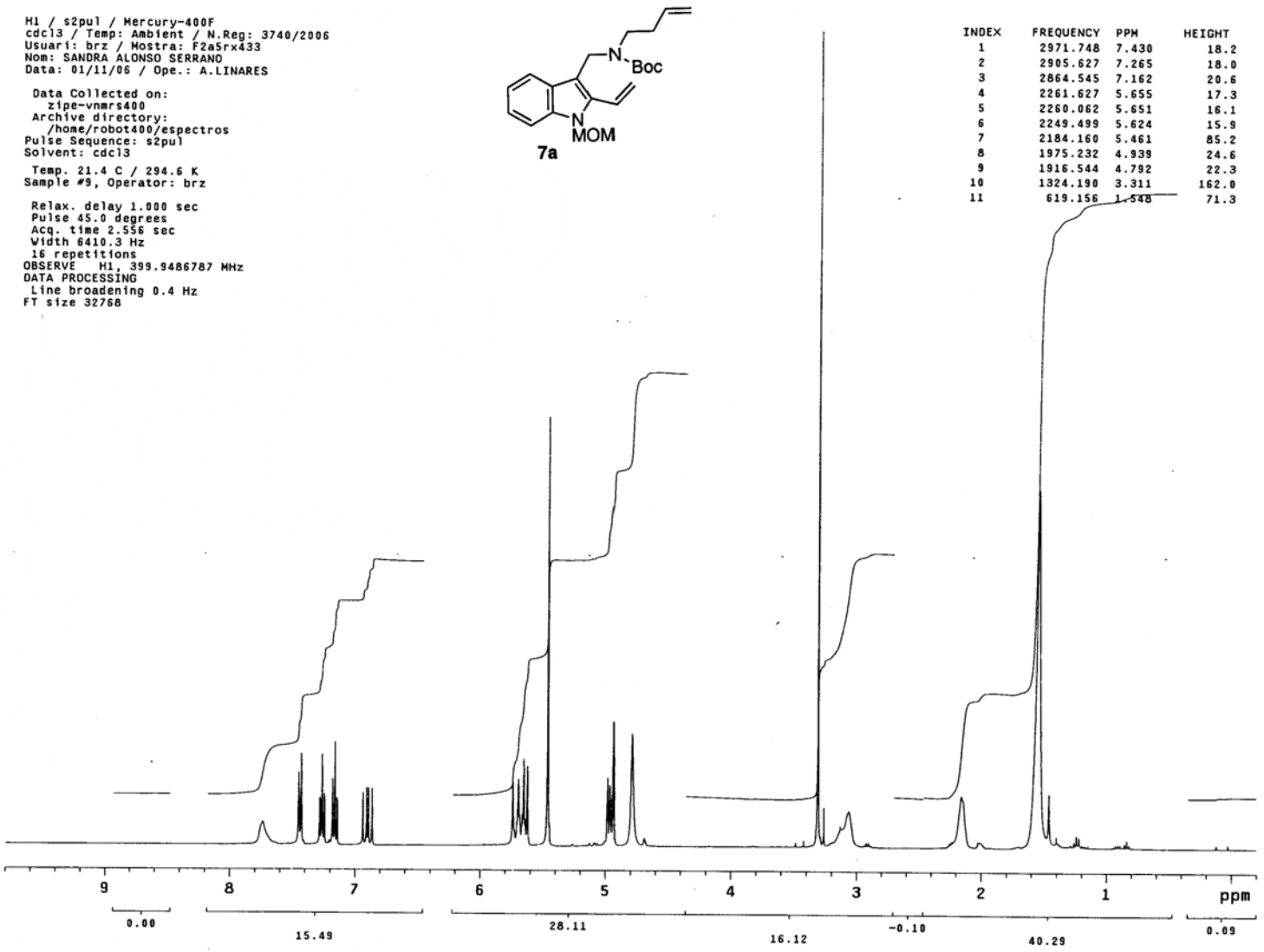
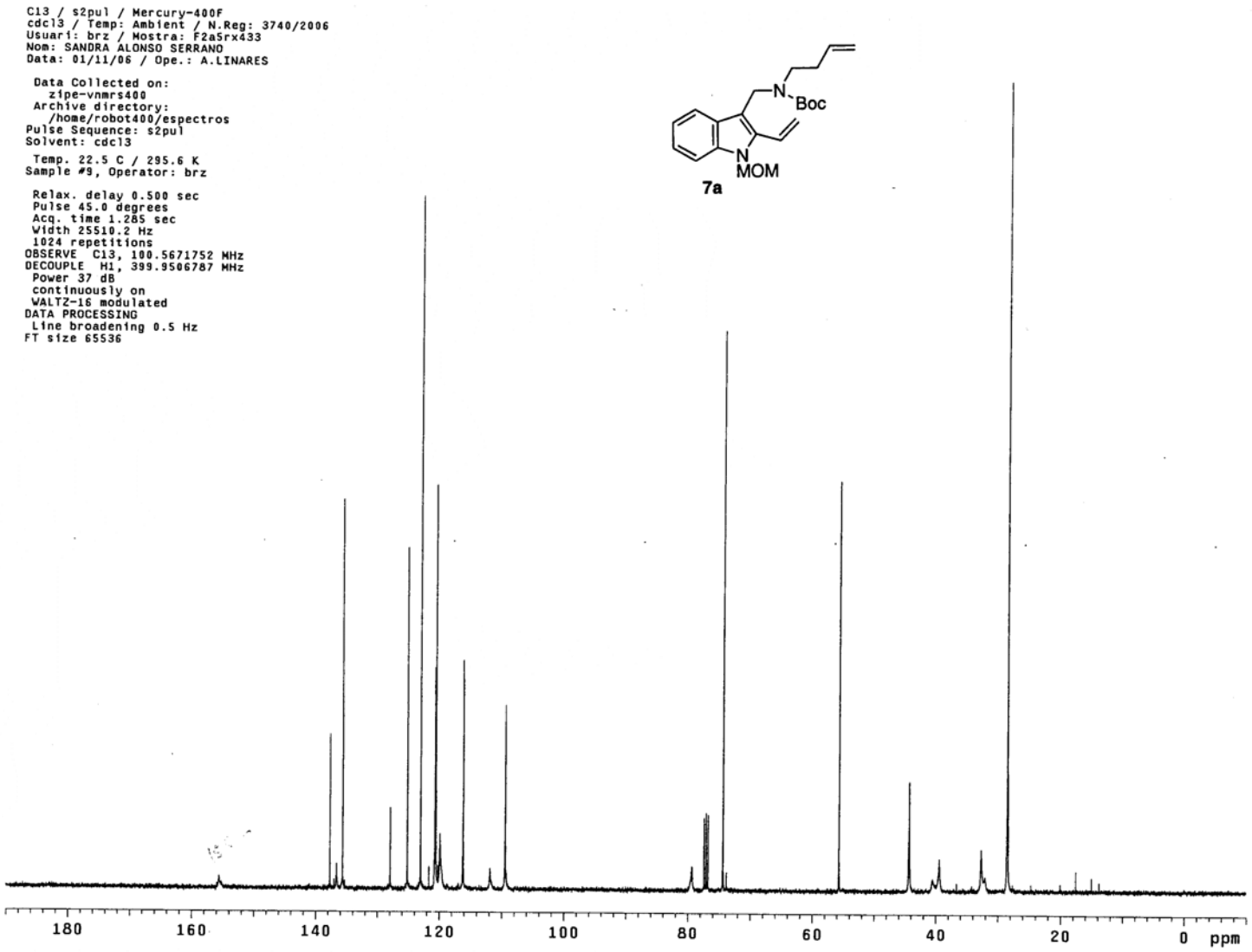
Temp. 25.0 C / 298.1 K
Sample #2, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.9486816 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
Ts
N
MOM
3b
INDEX FREQUENCY PPM HEIGHT
1 3113.575 7.785 34.9
2 3112.010 7.781 25.5
3 3105.359 7.764 34.5
4 2935.948 7.341 27.4
5 2927.731 7.320 24.9
6 2143.664 5.360 90.3
7 1793.103 4.483 75.6
8 1291.520 3.229 162.0
9 978.910 2.448 102.9
10 824.757 2.062 79.1
9
8
7
6
5
4
3
2
1
ppm
25.42
74.10
0.13
0.35

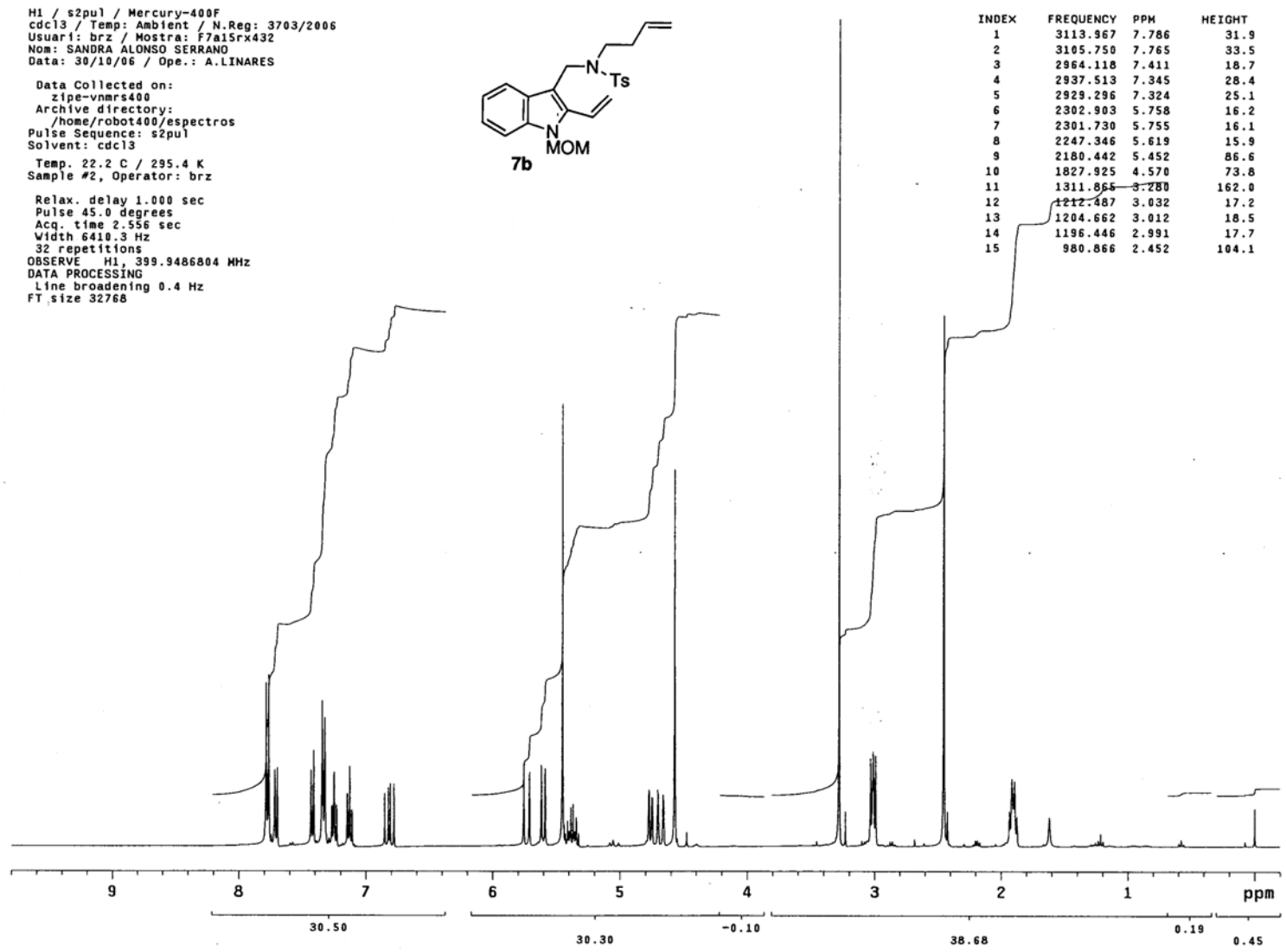

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 3249/2006
Usuari: brz / Mostra: F10a18RX405
Nom: SANDRA ALONSO SERRANO
Data: 22/09/06 / Ope.: O.NIETO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #2, Operator: brz
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
4000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
N
Ts
N
MOM
3b
180
160
140
120
100
80
60
40
20
0
ppm

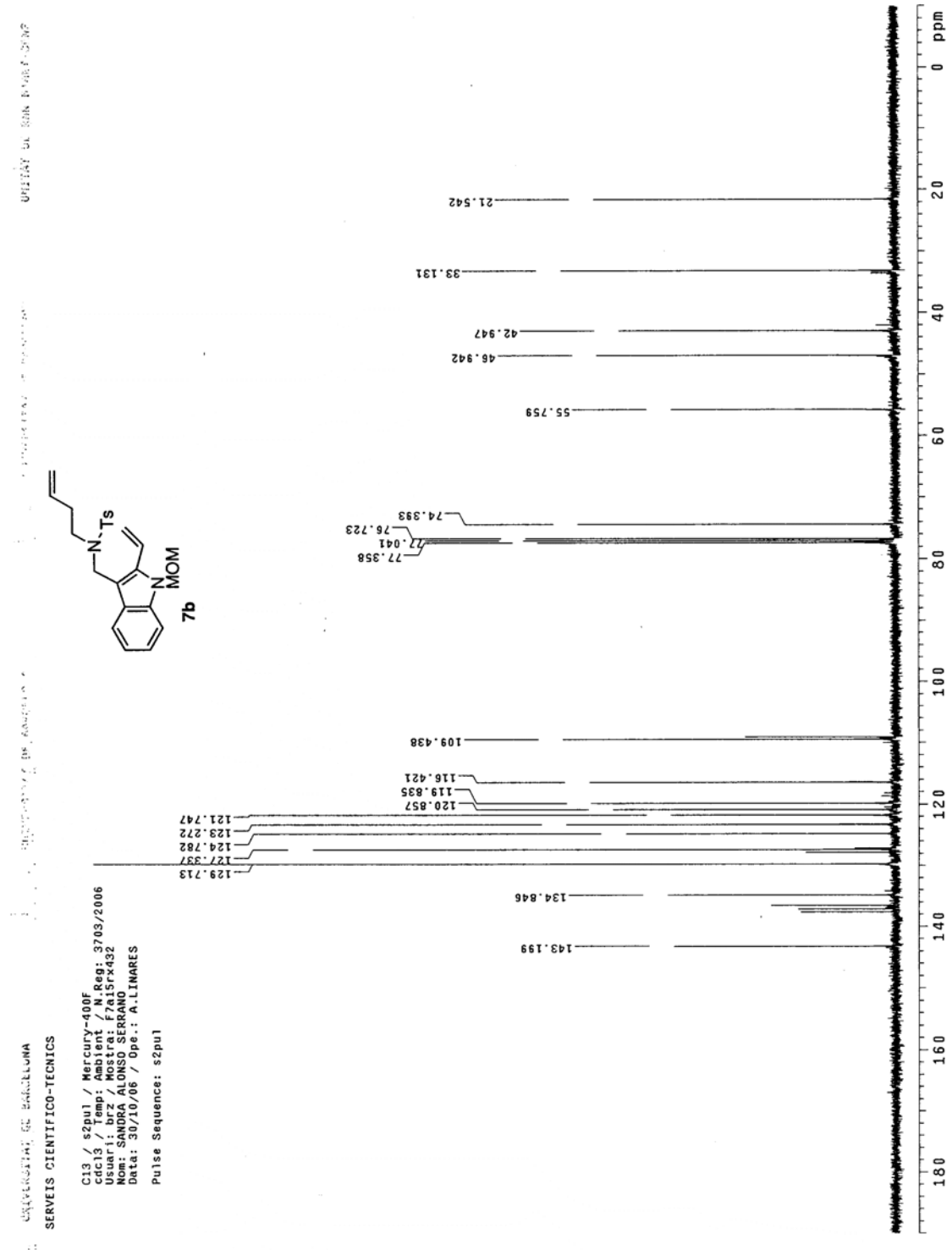

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3435/2006
Usuari: brz / Mostra: F12a16rx422
Nom: SANDRA ALONSO SERRANO
Data: 13/10/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.7 C / 294.9 K
Sample #2, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.9486777 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Ts
N
N
MOM
5
INDEX FREQUENCY PPM HEIGHT
1 3090.883 7.728 27.0
2 3082.275 7.707 27.7
3 2903.865 7.261 29.9
4 2883.129 7.209 23.0
5 2875.695 7.190 25.8
6 2160.879 5.403 79.4
7 1745.762 4.365 76.1
8 1438.630 3.597 26.0
9 1431.196 3.578 25.8
10 1259.828 3.150 162.0
11 939.002 2.348 88.4
12 860.361 2.151 58.4
13 859.187 2.148 60.9
14 818.497 2.047 18.7
15 -0.000 -0.000 22.7
9
8
7
6
5
4
3
2
1
ppm
28.71
3.39
7.31
0.02
0.06
24.74
-0.14
34.41
1.50

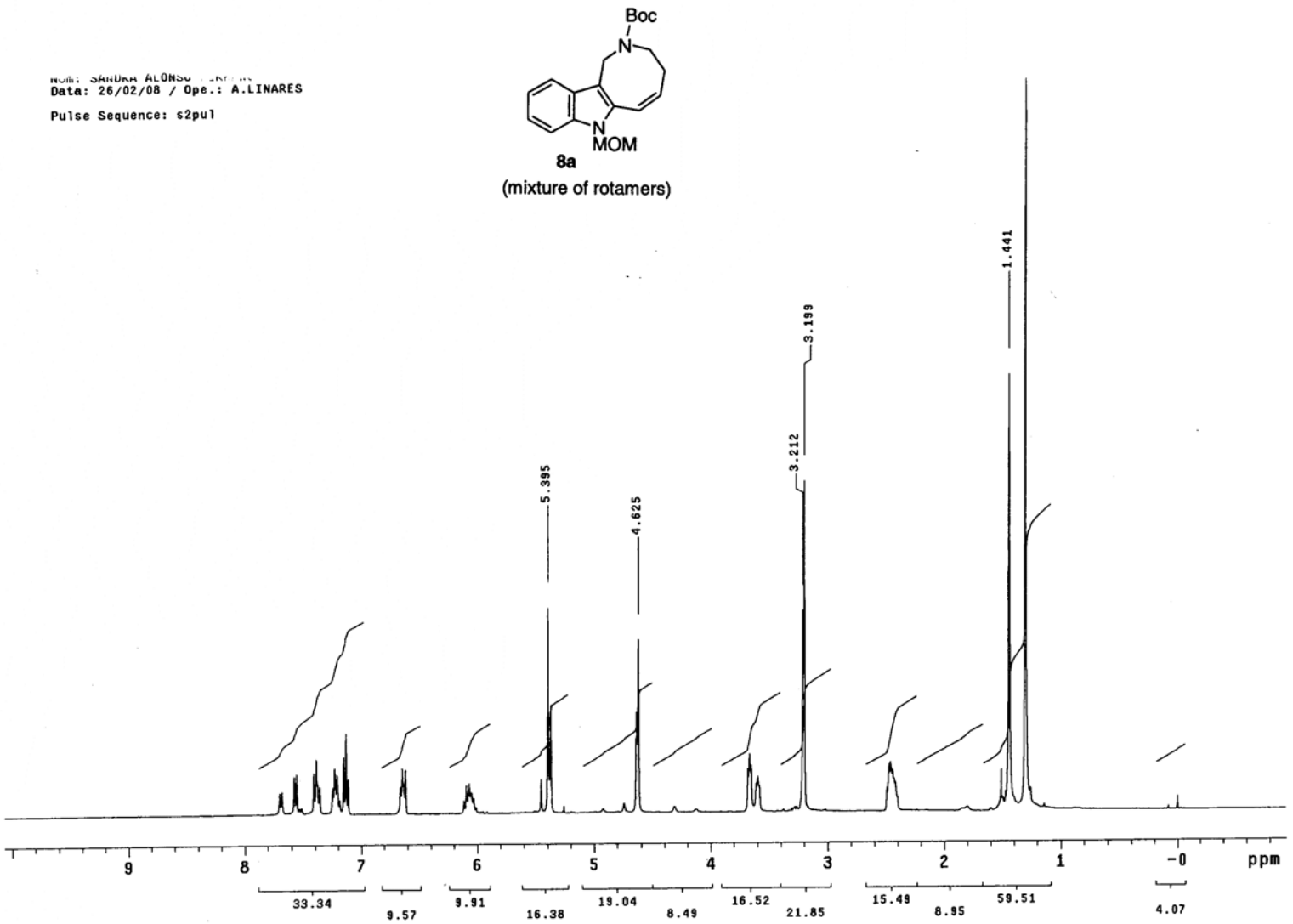

C13 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3435/2006
Usuari: brz / Mostra: F12a16rx422
Nom: SANDRA ALONSO SERRANO
Data: 13/10/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Sample #2, Operator: brz
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
8000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Ts
N
N
MOM
5
180
160
140
120
100
80
60
40
20
0
ppm

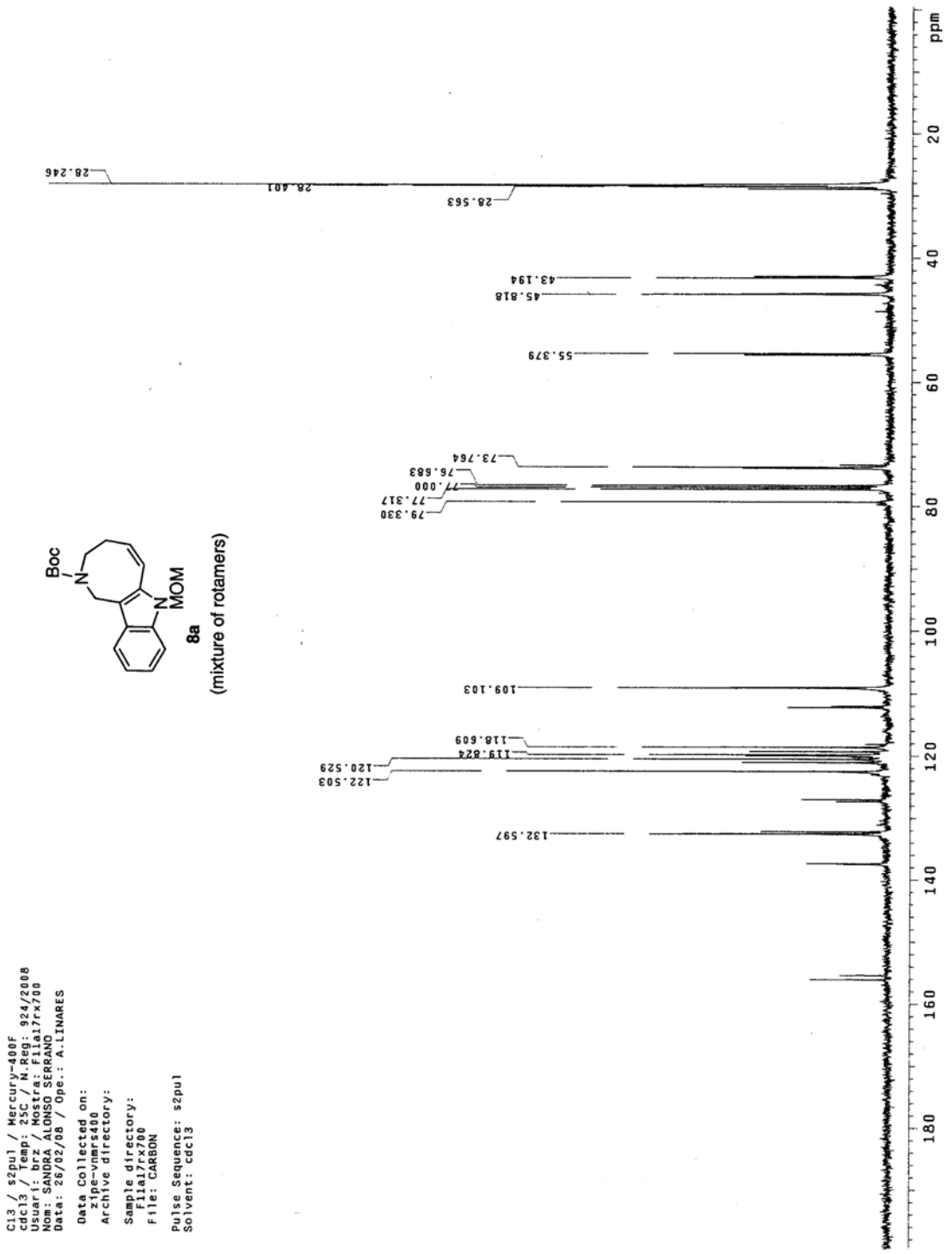

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3740/2006
Usuari: brz / Mostra: F2a5rx433
Nom: SANDRA ALONSO SERRANO
Data: 01/11/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.4 C / 294.6 K
Sample #9, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.9486787 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
Boc
N
MOM
7a
INDEX FREQUENCY PPM HEIGHT
1 2971.748 7.430 18.2
2 2905.627 7.265 18.0
3 2864.545 7.162 20.6
4 2261.627 5.655 17.3
5 2260.062 5.651 16.1
6 2249.499 5.624 15.9
7 2184.160 5.461 85.2
8 1975.232 4.939 24.6
9 1916.544 4.792 22.3
10 1324.190 3.311 162.0
11 619.156 1.548 71.3
9
8
7
6
5
4
3
2
1
ppm
0.00
15.49
28.11
16.12
-0.10
40.29
0.09

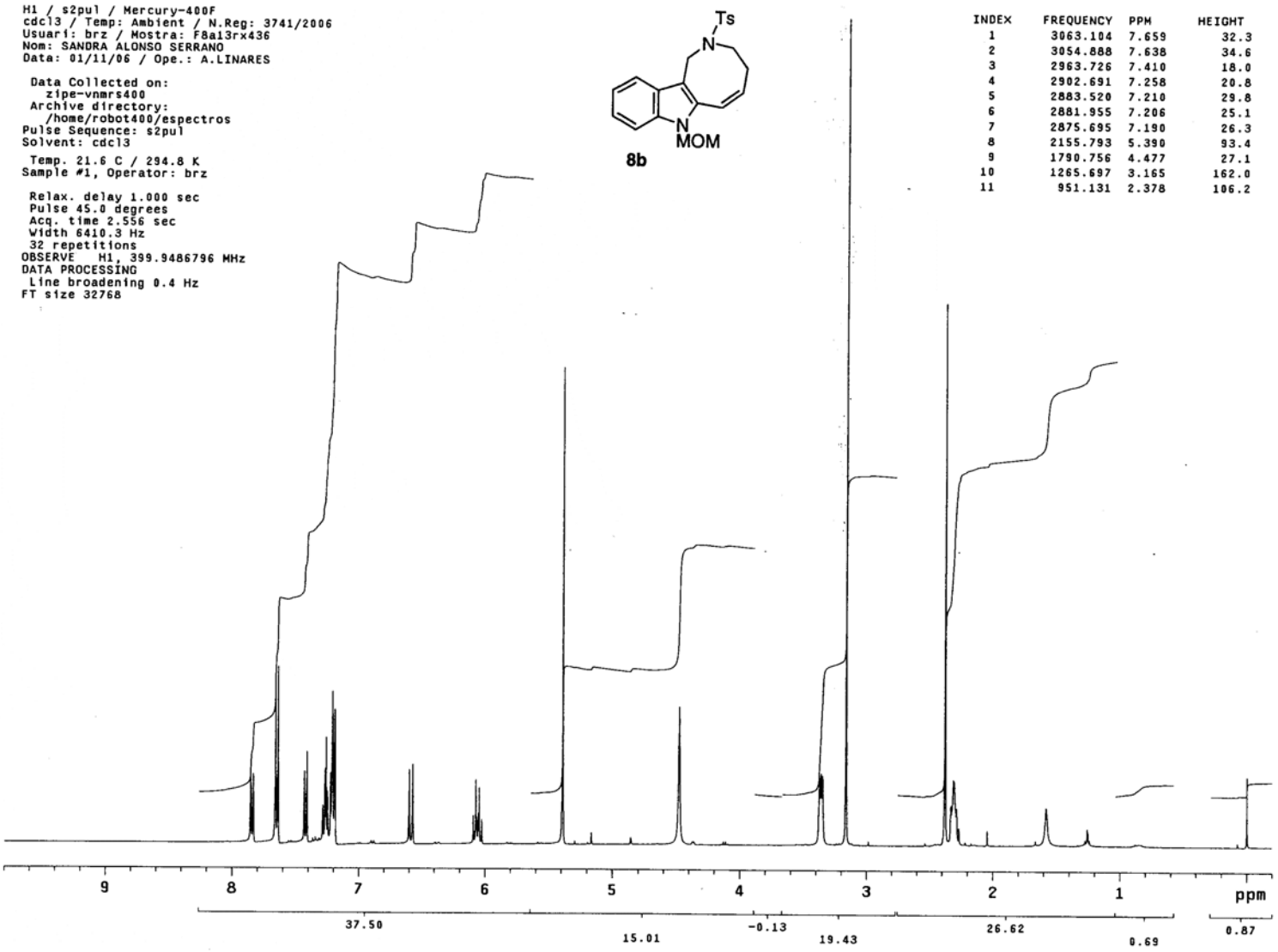

C13 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3740/2006
Usuari: brz / Mostra: F2a5rx433
Nom: SANDRA ALONSO SERRANO
Data: 01/11/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.5 C / 295.6 K
Sample #9, Operator: brz
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
1024 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
N
Boc
N
MOM
7a
180
160
140
120
100
80
60
40
20
0 ppm

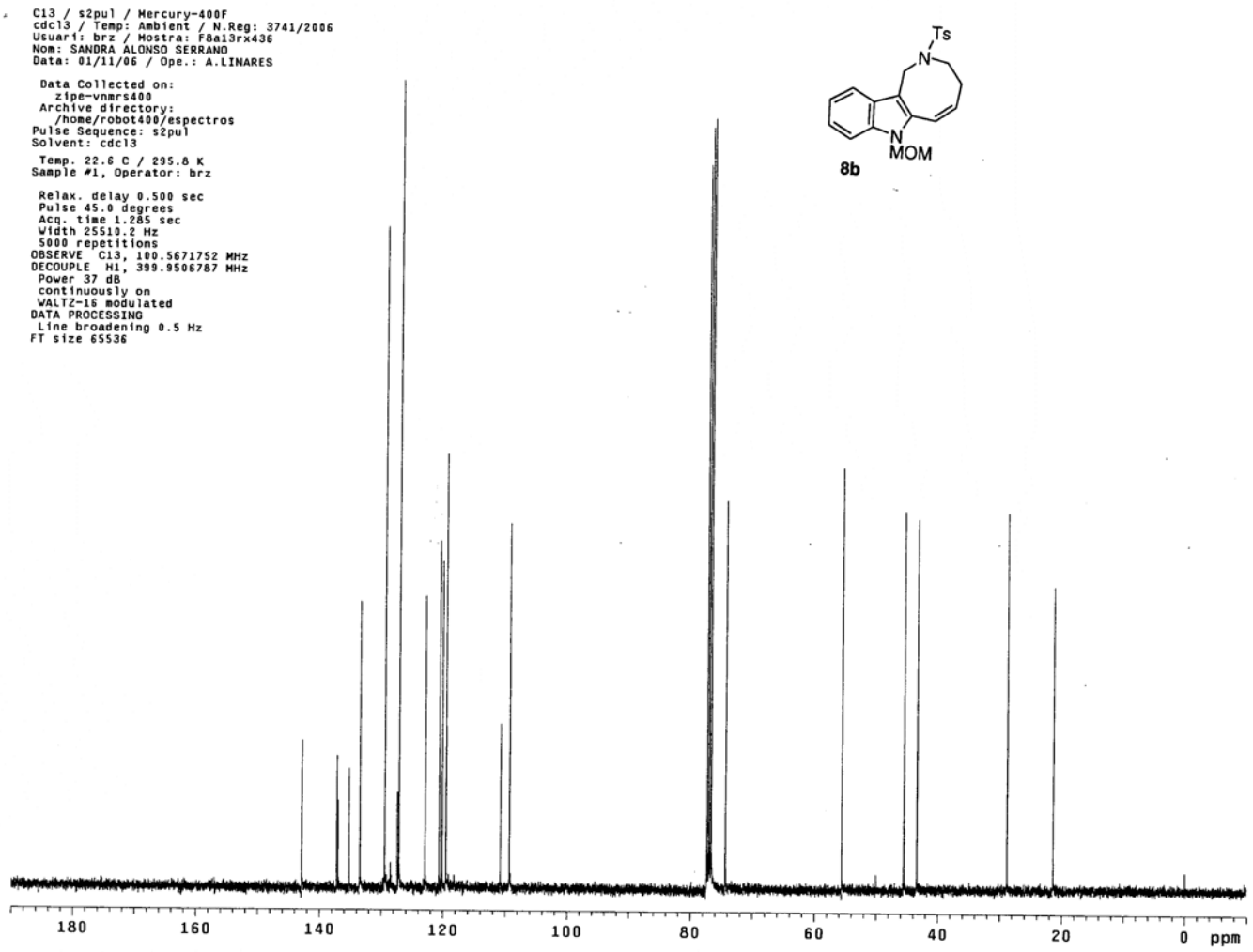

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3703/2006
Usuari: brz / Mostra: F7a15rx432
Nom: SANDRA ALONSO SERRANO
Data: 30/10/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.2 C / 295.4 K
Sample #2, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.9486804 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
Ts
N
MOM
7b
INDEX FREQUENCY PPM HEIGHT
1 3113.967 7.786 31.9
2 3105.750 7.765 33.5
3 2964.118 7.411 18.7
4 2937.513 7.345 28.4
5 2929.296 7.324 25.1
6 2302.903 5.758 16.2
7 2301.730 5.755 16.1
8 2247.346 5.619 15.9
9 2180.442 5.452 86.6
10 1827.925 4.570 73.8
11 1311.865 3.280 162.0
12 1212.487 3.032 17.2
13 1204.662 3.012 18.5
14 1196.446 2.991 17.7
15 980.866 2.452 104.1
9
8
7
6
5
4
3
2
1
ppm
30.50
30.30
-0.10
38.68
0.19
0.45

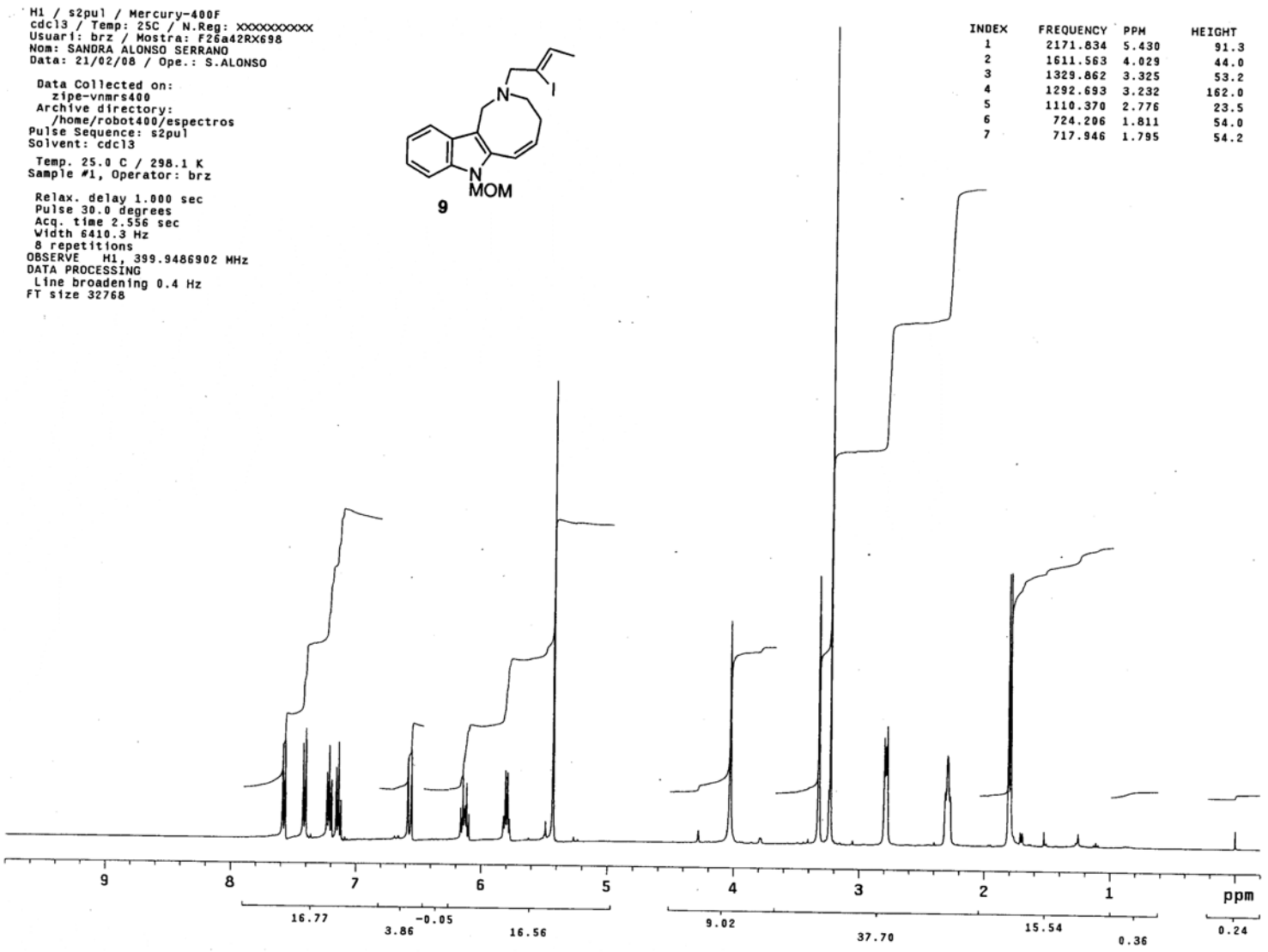

SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3703/2006
Usuari: brz / Mostra: F7a15rx432
Nom: SANDRA ALONSO SERRANO
Data: 30/10/06 / Ope.: A.LINARES
Pulse Sequence: s2pul
N
Ts
N
MOM
7b
143.199
134.846
129.713
127.337
124.782
123.272
121.747
120.857
119.835
116.421
109.438
77.358
77.041
76.723
74.393
55.759
46.942
42.947
33.131
21.542
180
160
140
120
100
80
60
40
20
0 ppm

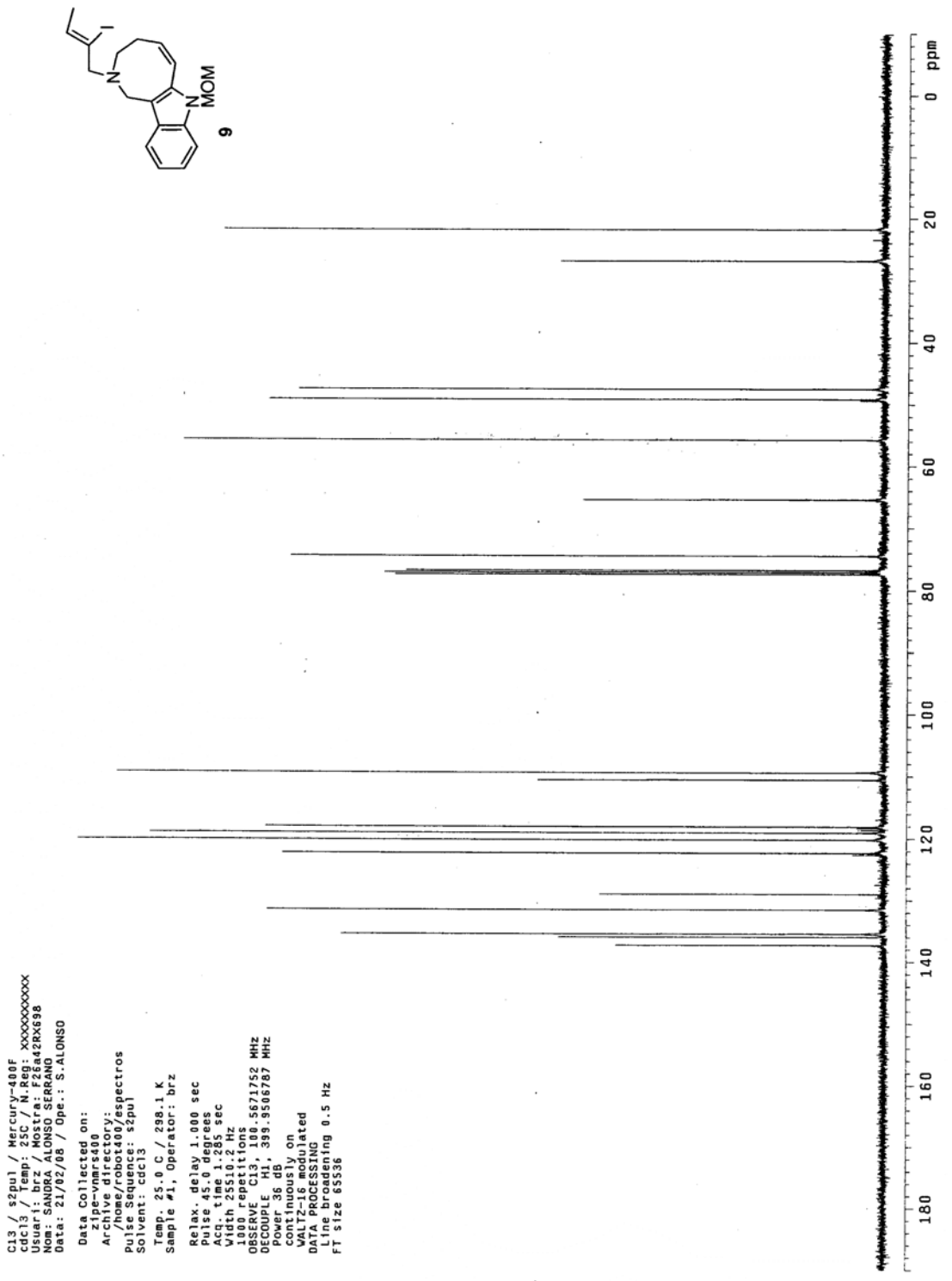

Data: 26/02/08 / Ope.: A.LINARES
Pulse Sequence: s2pul
Boc
N
N
MOM
8a
(mixture of rotamers)
1.441
3.199
3.212
4.625
5.395
9
8
7
6
5
4
3
2
1
-0
ppm
33.34
9.57
9.91
16.38
19.04
8.49
16.52
21.85
15.49
8.95
59.51
4.07

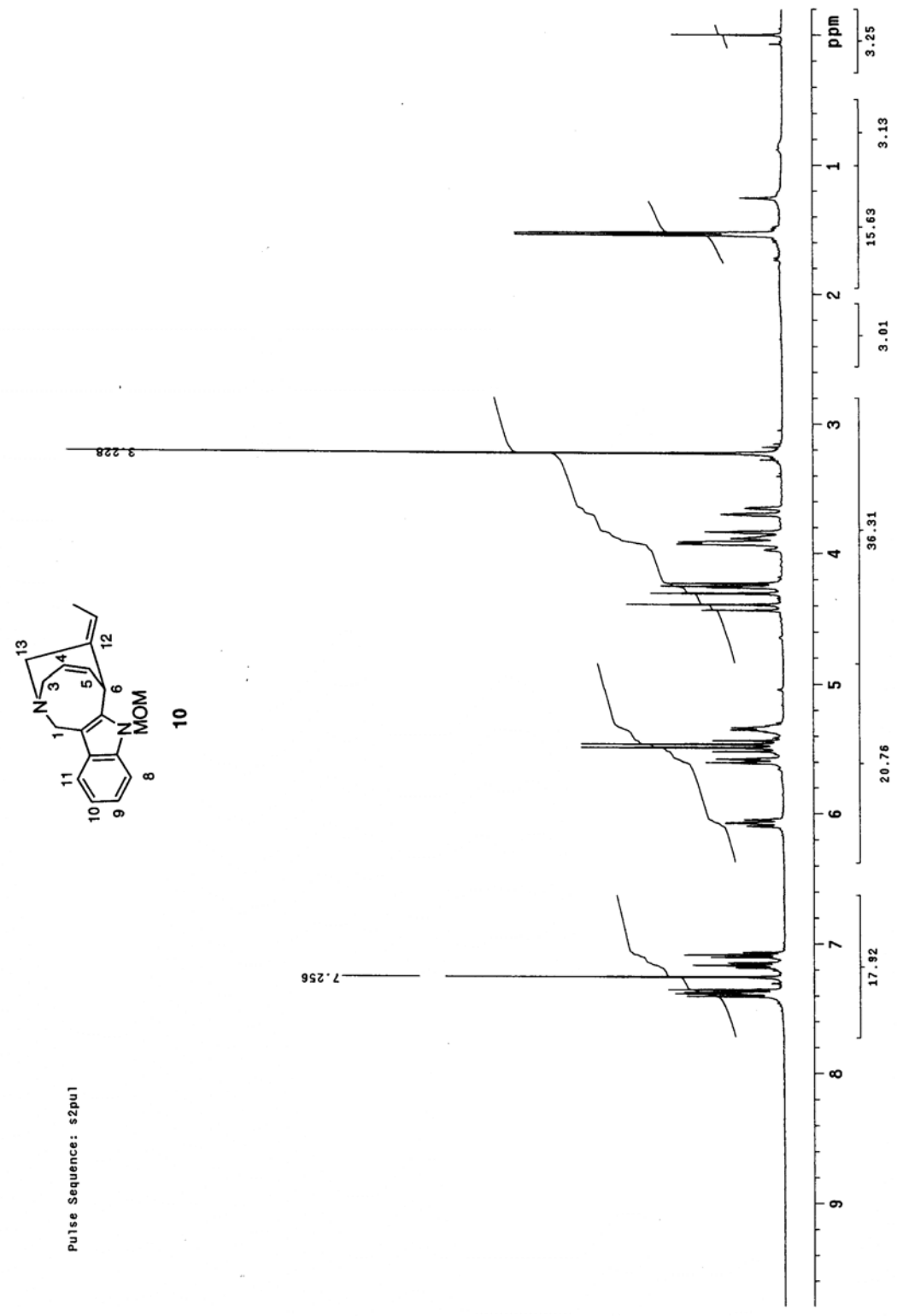

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 924/2008
Usuari: bra / Nostra Fila17rx700
Nom: SANDRA ALONSO SERRANO
Data: 26/02/08 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
Sample directory:
Fila17rx700
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
Boc
N
N
MOM
8a
(mixture of rotamers)
28.246
28.401
28.563
43.194
45.818
55.379
73.764
76.683
77.000
77.317
79.330
109.103
118.609
119.824
120.529
122.503
132.597
ppm

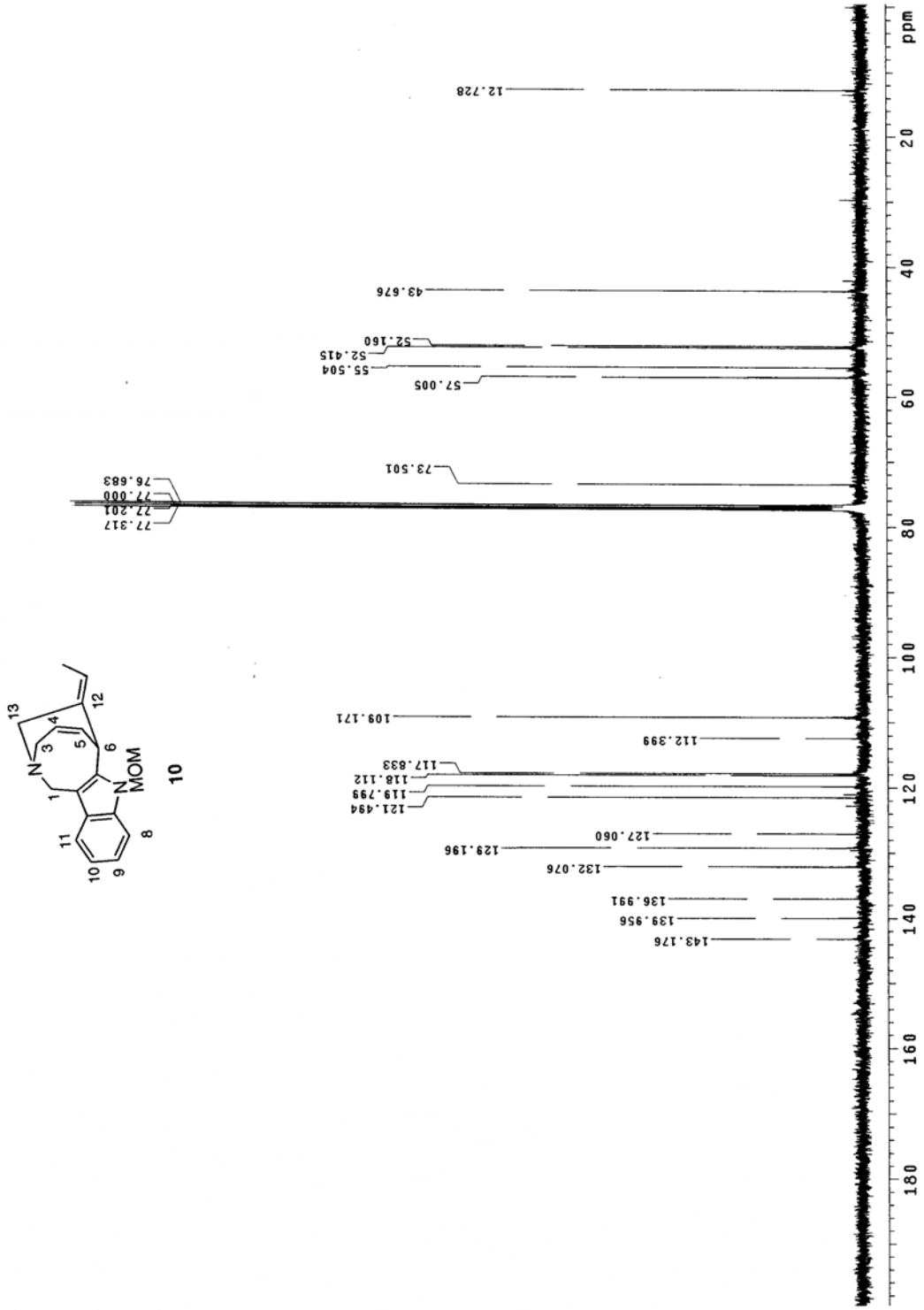

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3741/2006
Usuari: brz / Mostra: F8a13rx436
Nom: SANDRA ALONSO SERRANO
Data: 01/11/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.6 C / 294.8 K
Sample #1, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
32 repetitions
OBSERVE H1, 399.9486796 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Ts
N
N
MOM
8b
INDEX FREQUENCY PPM HEIGHT
1 3063.104 7.659 32.3
2 3054.888 7.638 34.6
3 2963.726 7.410 18.0
4 2902.691 7.258 20.8
5 2883.520 7.210 29.8
6 2881.955 7.206 25.1
7 2875.695 7.190 26.3
8 2155.793 5.390 93.4
9 1790.756 4.477 27.1
10 1265.697 3.165 162.0
11 951.131 2.378 106.2
9
8
7
6
5
4
3
2
1
ppm
37.50
15.01
-0.13
19.43
26.62
0.69
0.87

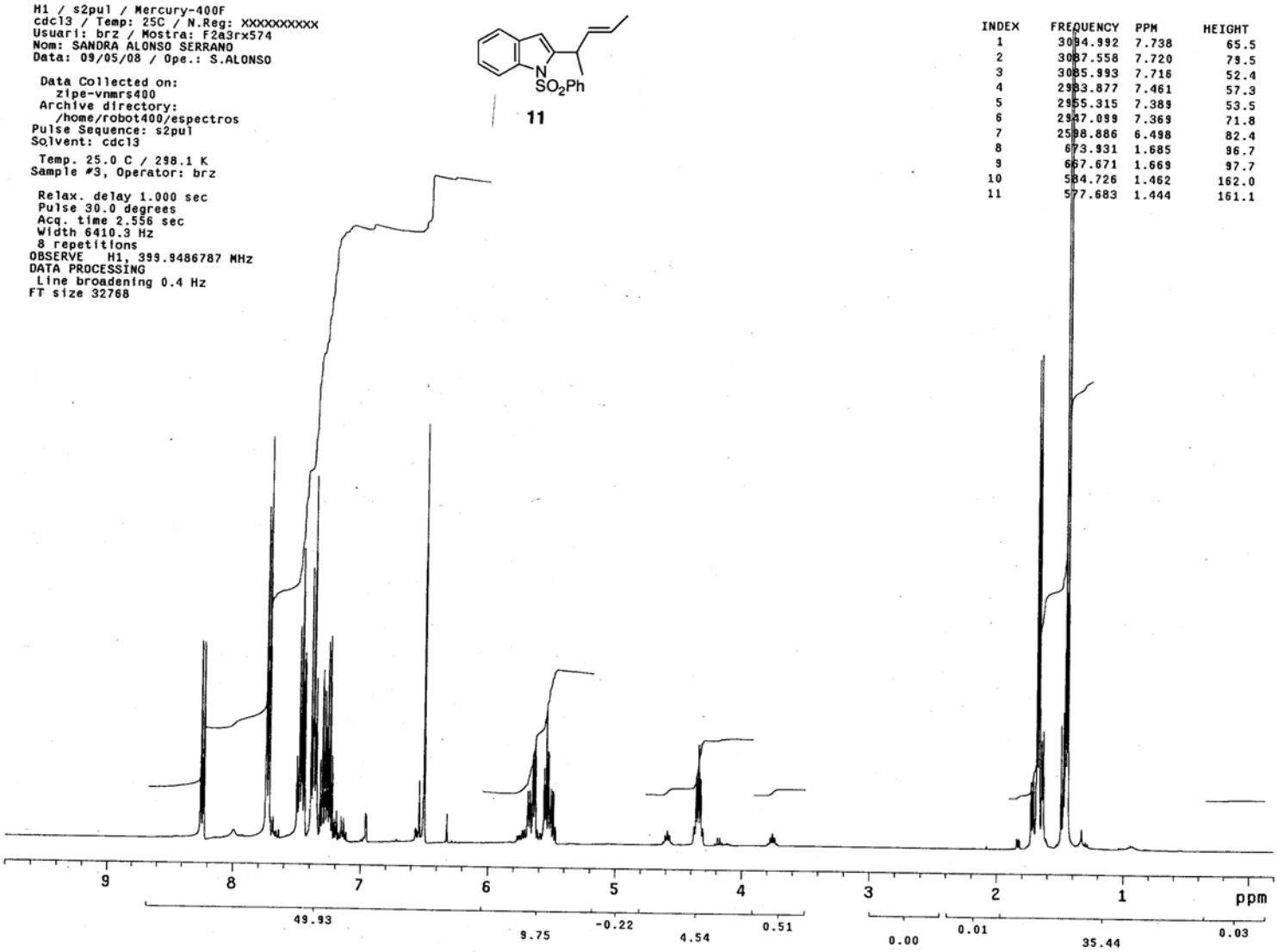

C13 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 3741/2006
Usuari: brz / Mostra: F8a13rx436
Nom: SANDRA ALONSO SERRANO
Data: 01/11/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.6 C / 295.8 K
Sample #1, Operator: brz
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
5000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Ts
N
N
MOM
8b
180
160
140
120
100
80
60
40
20
0
ppm

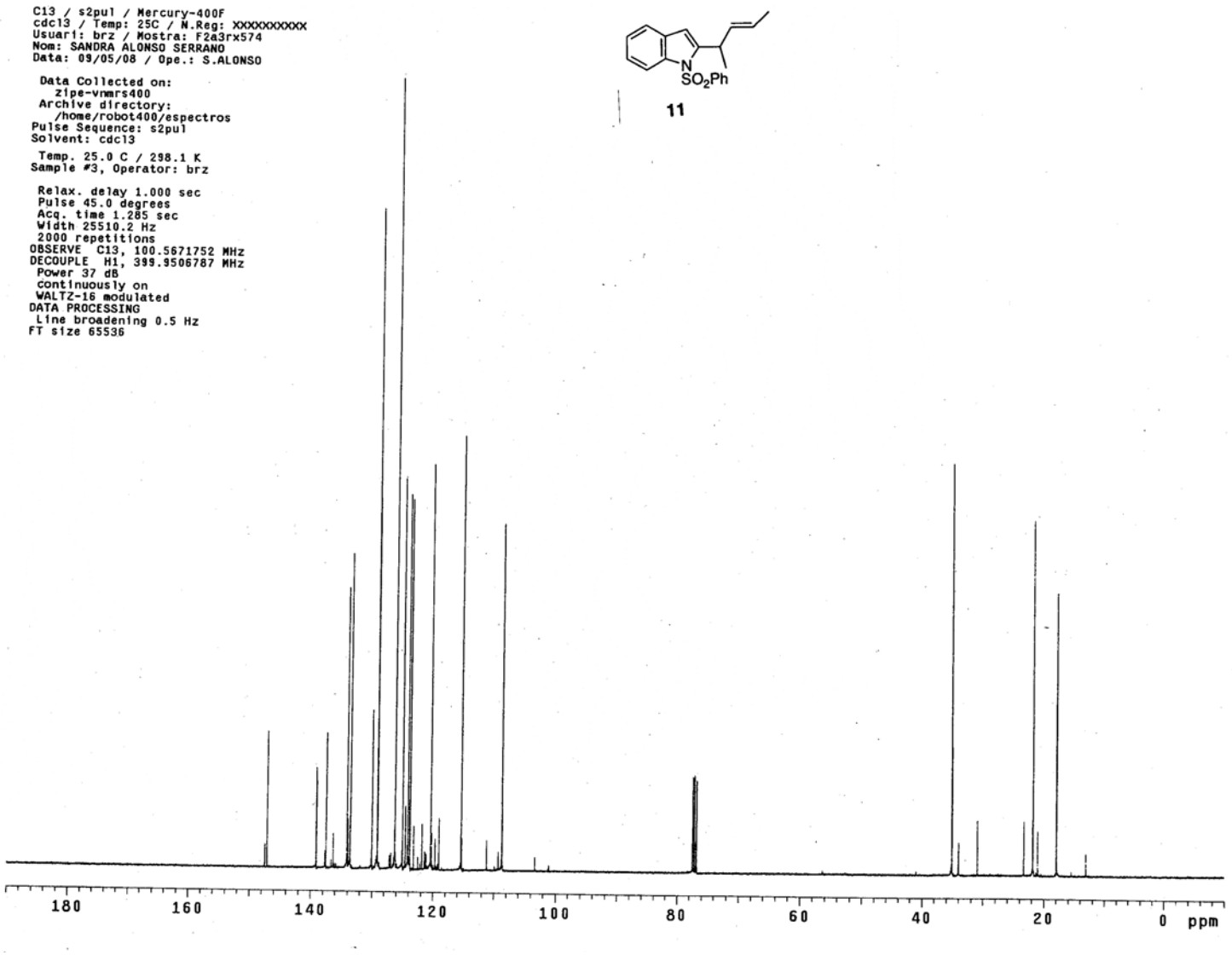

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: xxxxxxxxxx
Usuari: brz / Mostra: F26a42RX698
Nom: SANDRA ALONSO SERRANO
Data: 21/02/08 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: brz
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9486902 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
I
N
MOM
9
INDEX FREQUENCY PPM HEIGHT
1 2171.834 5.430 91.3
2 1611.563 4.029 44.0
3 1329.862 3.325 53.2
4 1292.693 3.232 162.0
5 1110.370 2.776 23.5
6 724.206 1.811 54.0
7 717.946 1.795 54.2
9
8
7
6
5
4
3
2
1
ppm
16.77
3.86
-0.05
16.56
9.02
37.70
15.54
0.36
0.24

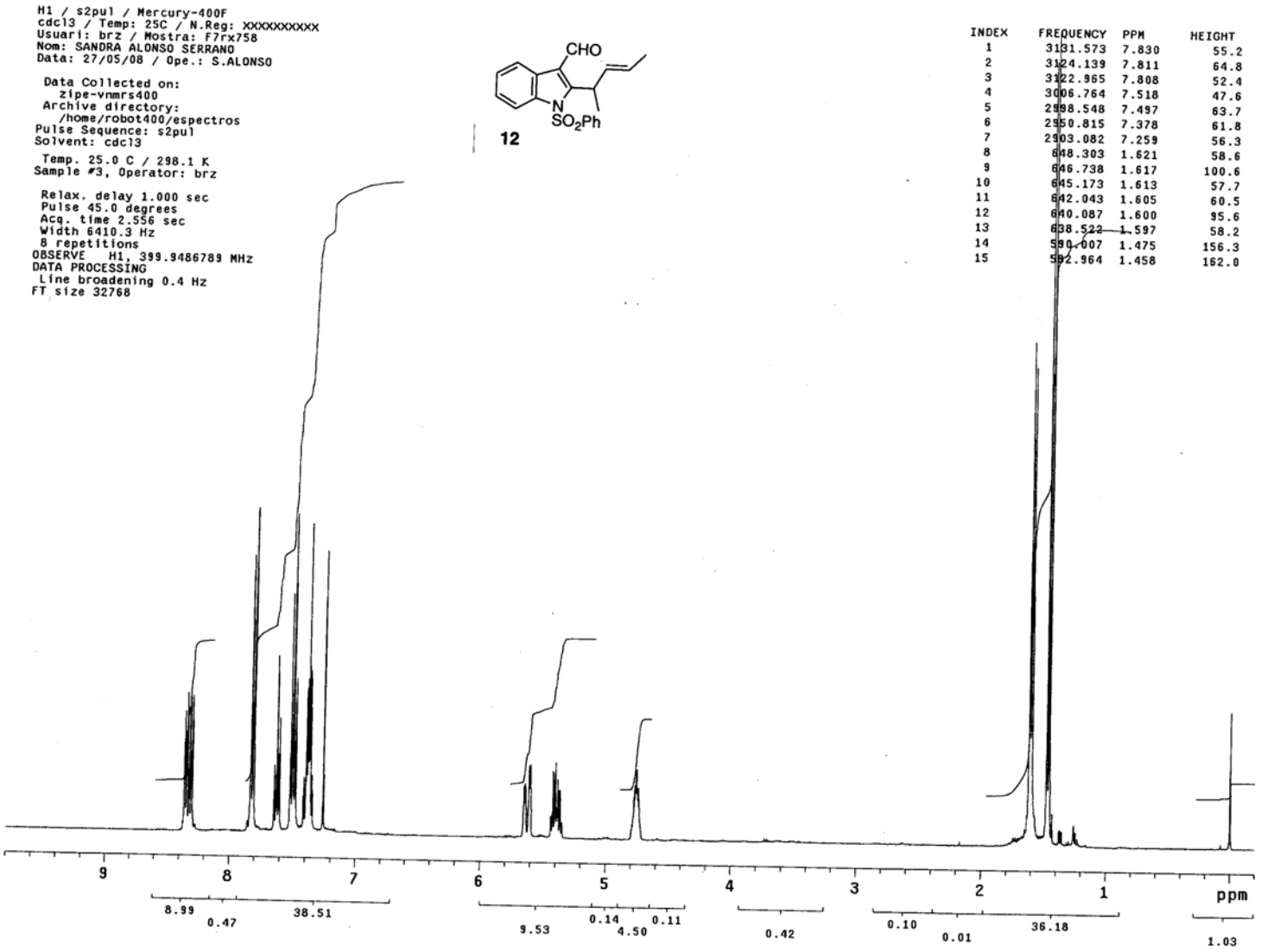

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuarf: brz / Nostra:F26a42RX698
Nom: SANDRA ALONSO SERRANO
Data: 21/02/08 / Ope.: S.ALONSO
Data Collected on:
z1pe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #1, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
1000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
N
MOM
9
180
160
140
120
100
80
60
40
20
0 ppm

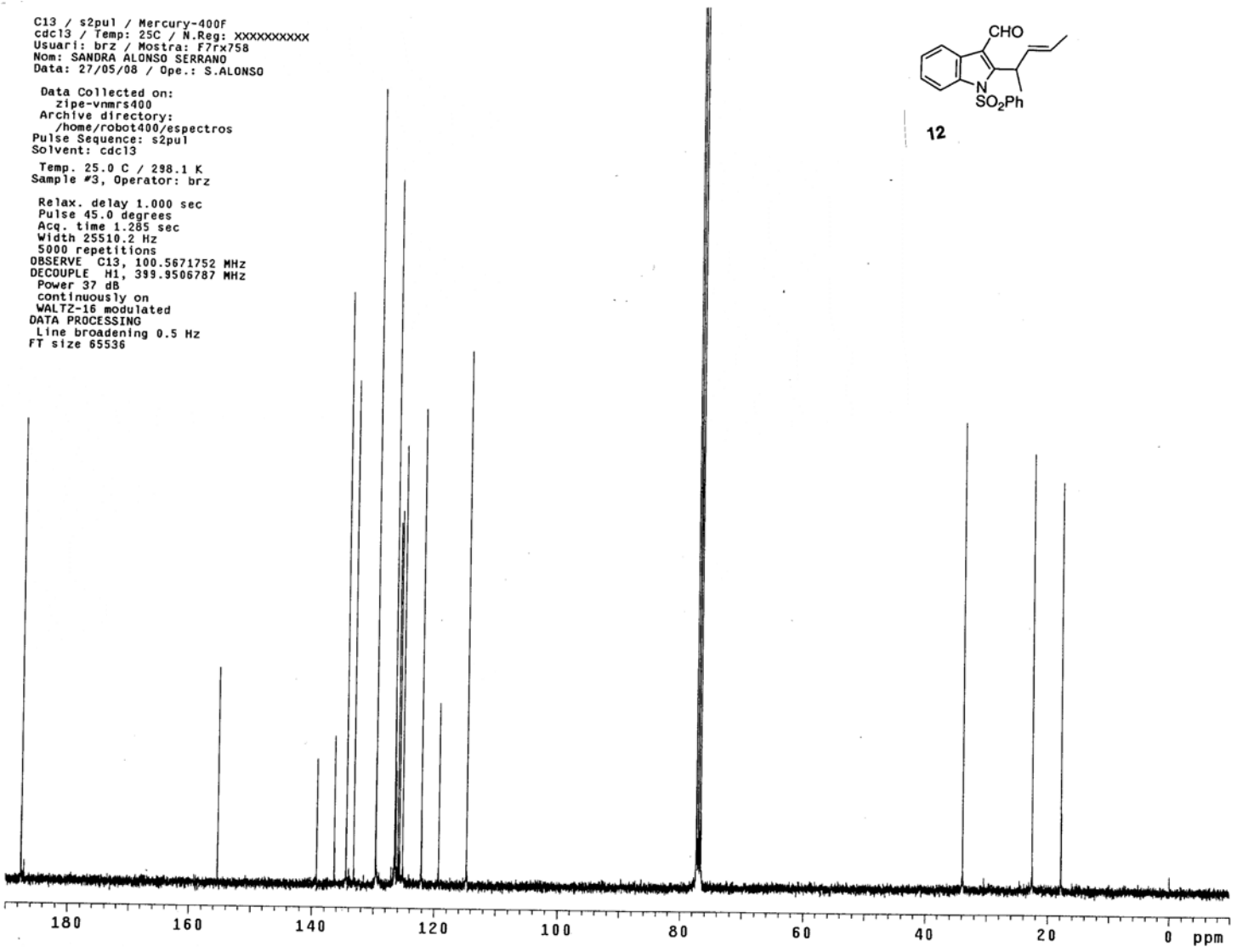

Pulse Sequence: s2pul
7.256
3.228
ppm
17.92
20.76
36.31
3.01
15.63
3.13
3.25
MOM
10

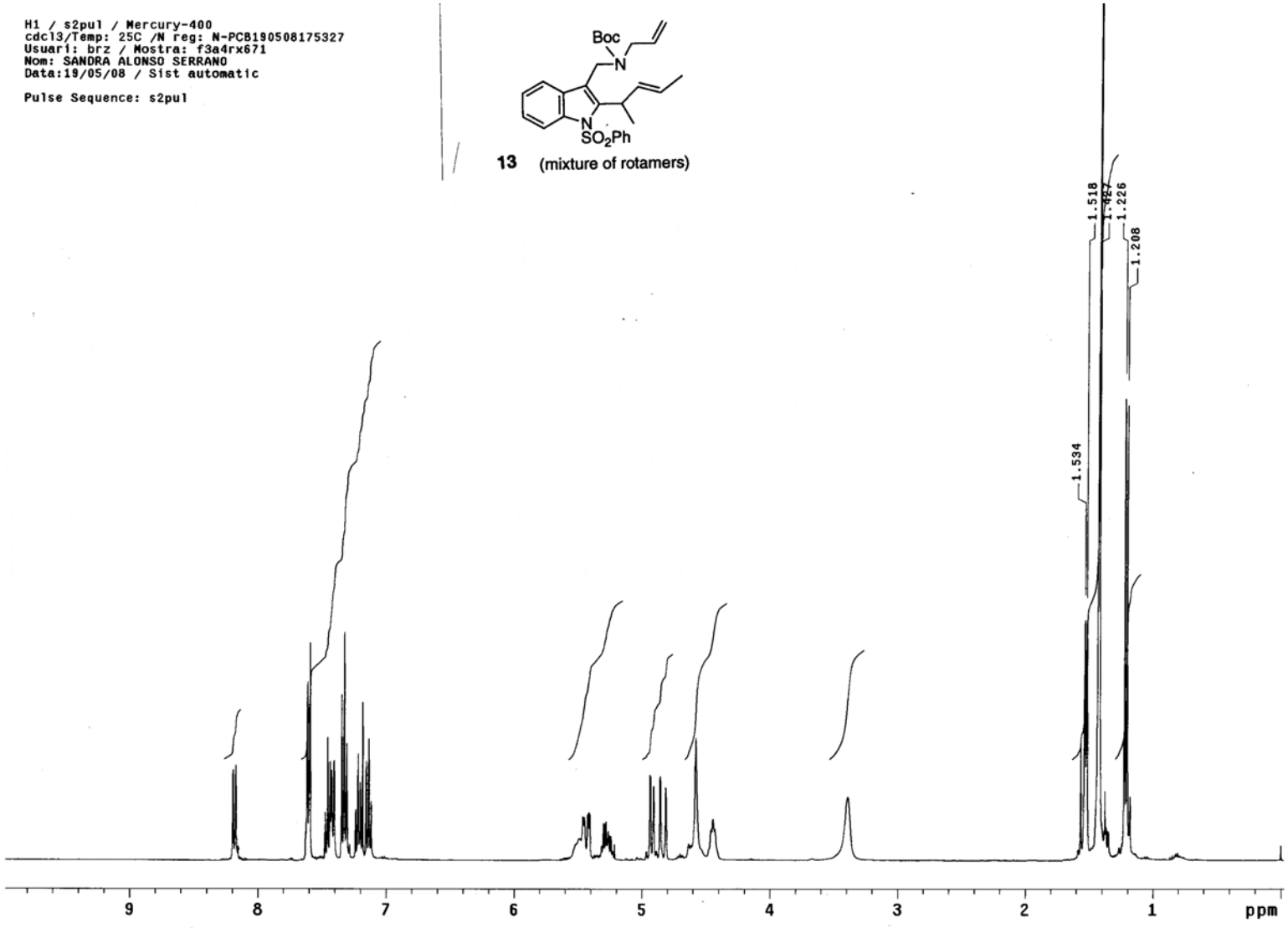

12.728
43.676
52.160
52.415
55.504
57.005
73.501
76.683
77.000
77.201
77.317
109.171
112.399
117.833
118.112
119.799
121.494
127.060
129.196
132.076
136.991
139.956
143.176
ppm
20
40
60
80
100
120
140
160
180
MOM
10

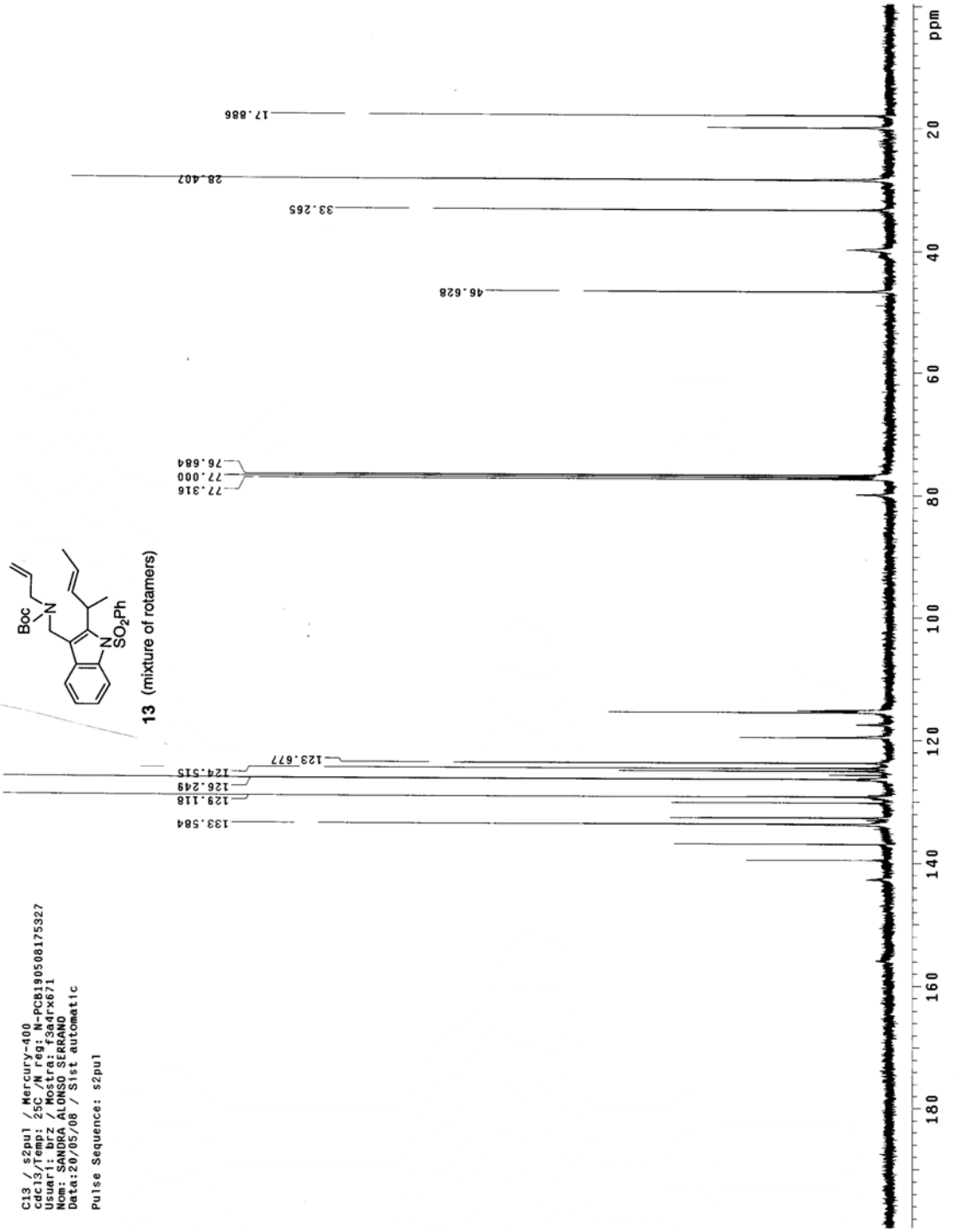

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F2a3rx574
Nom: SANDRA ALONSO SERRANO
Data: 09/05/08 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #3, Operator: brz
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9486787 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
N
SO2Ph
11
INDEX FREQUENCY PPM HEIGHT
1 3094.992 7.738 65.5
2 3087.558 7.720 79.5
3 3085.993 7.716 52.4
4 2983.877 7.461 57.3
5 2955.315 7.389 53.5
6 2947.099 7.369 71.8
7 2598.886 6.498 82.4
8 673.931 1.685 96.7
9 667.671 1.669 97.7
10 584.726 1.462 162.0
11 577.683 1.444 161.1
9
8
7
6
5
4
3
2
1
ppm
49.93
9.75
-0.22
4.54
0.51
0.00
0.01
35.44
0.03

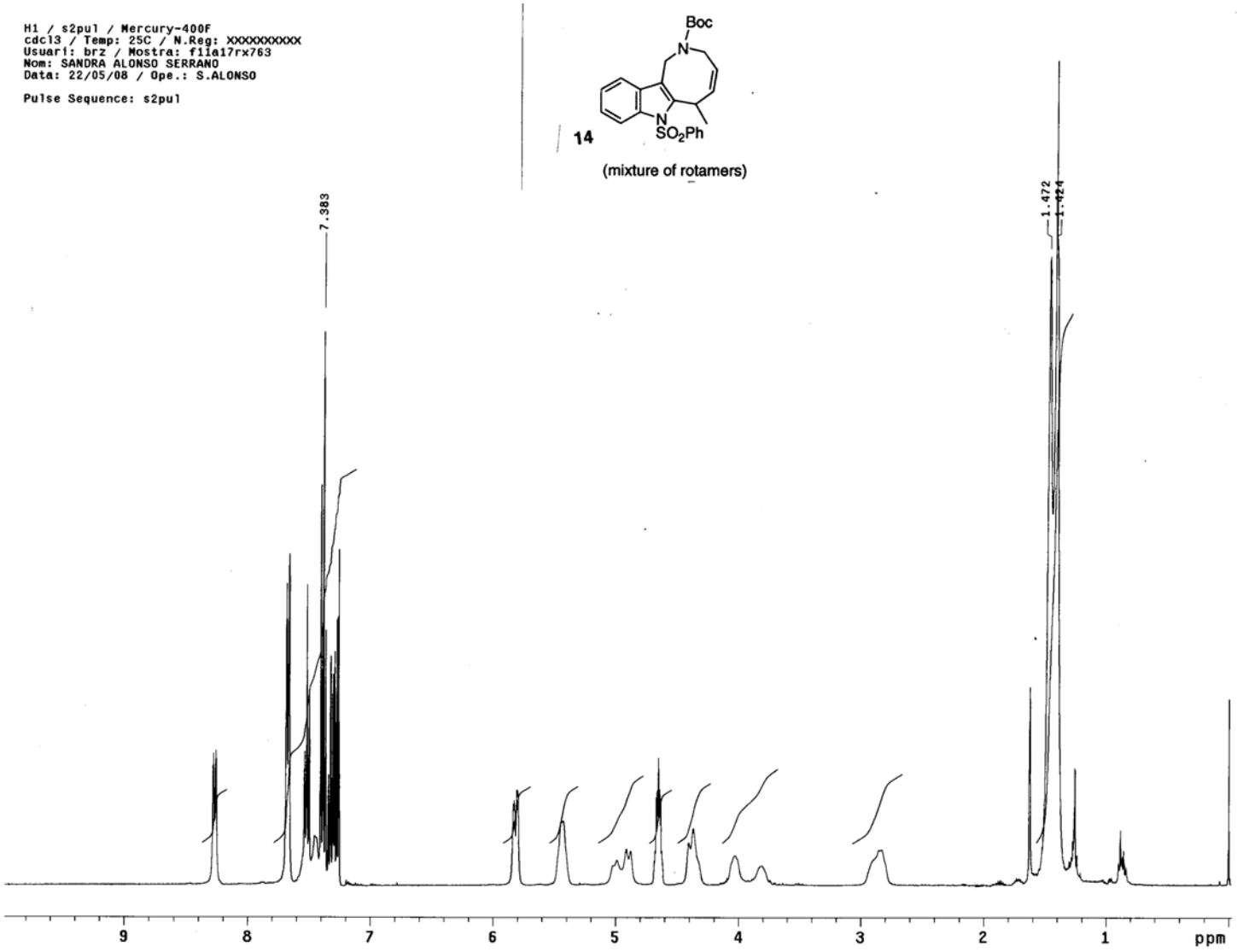

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F2a3rx574
Nom: SANDRA ALONSO SERRANO
Data: 09/05/08 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #3, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
2000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
N
SO2Ph
11
180
160
140
120
100
80
60
40
20
0
ppm

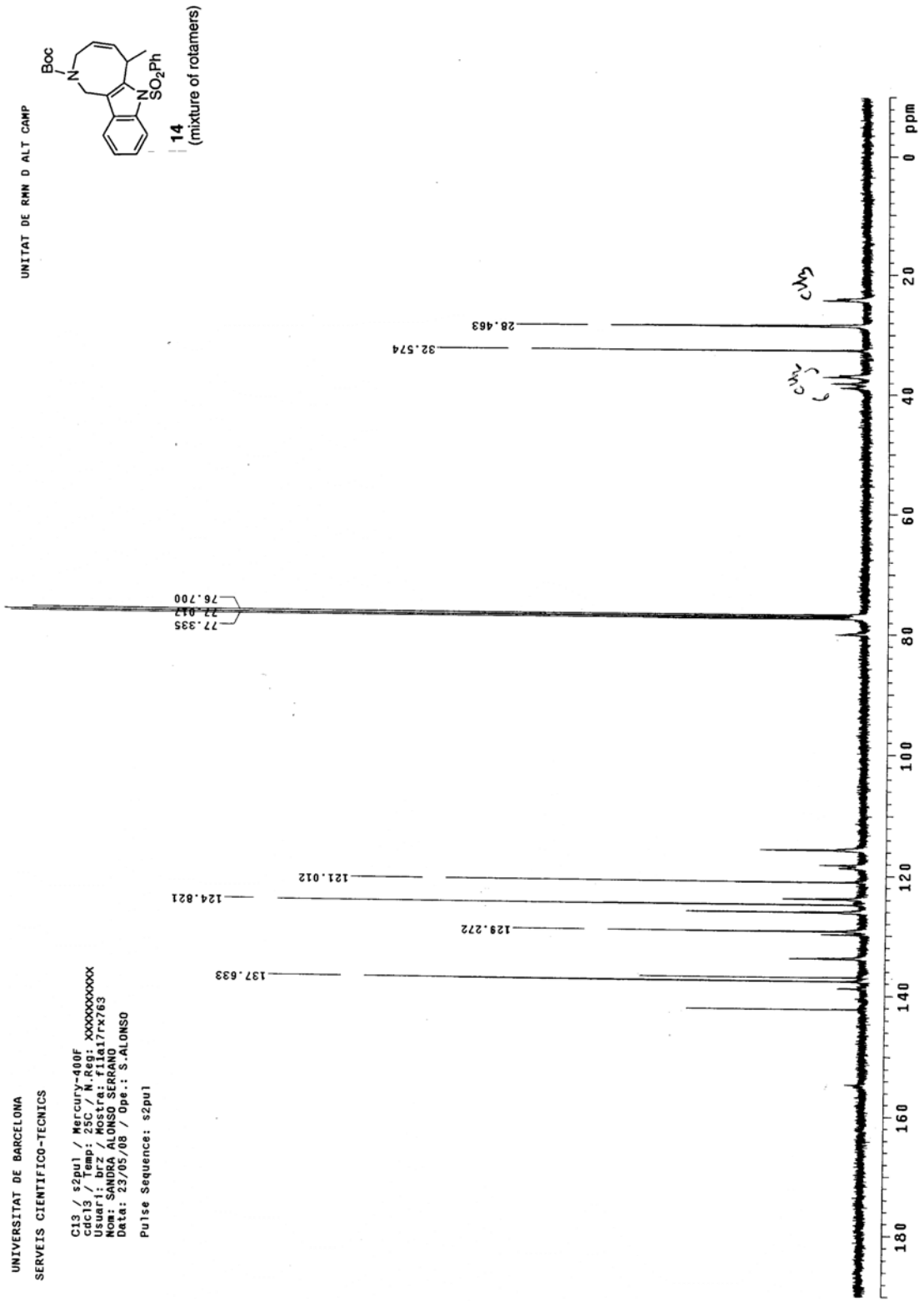

H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F7rx758
Nom: SANDRA ALONSO SERRANO
Data: 27/05/08 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #3, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.9486789 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
CHO
N
SO2Ph
12
INDEX FREQUENCY PPM HEIGHT
1 3131.573 7.830 55.2
2 3124.139 7.811 64.8
3 3122.965 7.808 52.4
4 3006.764 7.518 47.6
5 2998.548 7.497 63.7
6 2950.815 7.378 61.8
7 2903.082 7.259 56.3
8 648.303 1.621 58.6
9 646.738 1.617 100.6
10 645.173 1.613 57.7
11 642.043 1.605 60.5
12 640.087 1.600 95.6
13 638.522 1.597 58.2
14 590.007 1.475 156.3
15 582.964 1.458 162.0
9
8
7
6
5
4
3
2
1
ppm
8.99
0.47
38.51
9.53
0.14
4.50
0.11
0.42
0.10
0.01
36.18
1.03

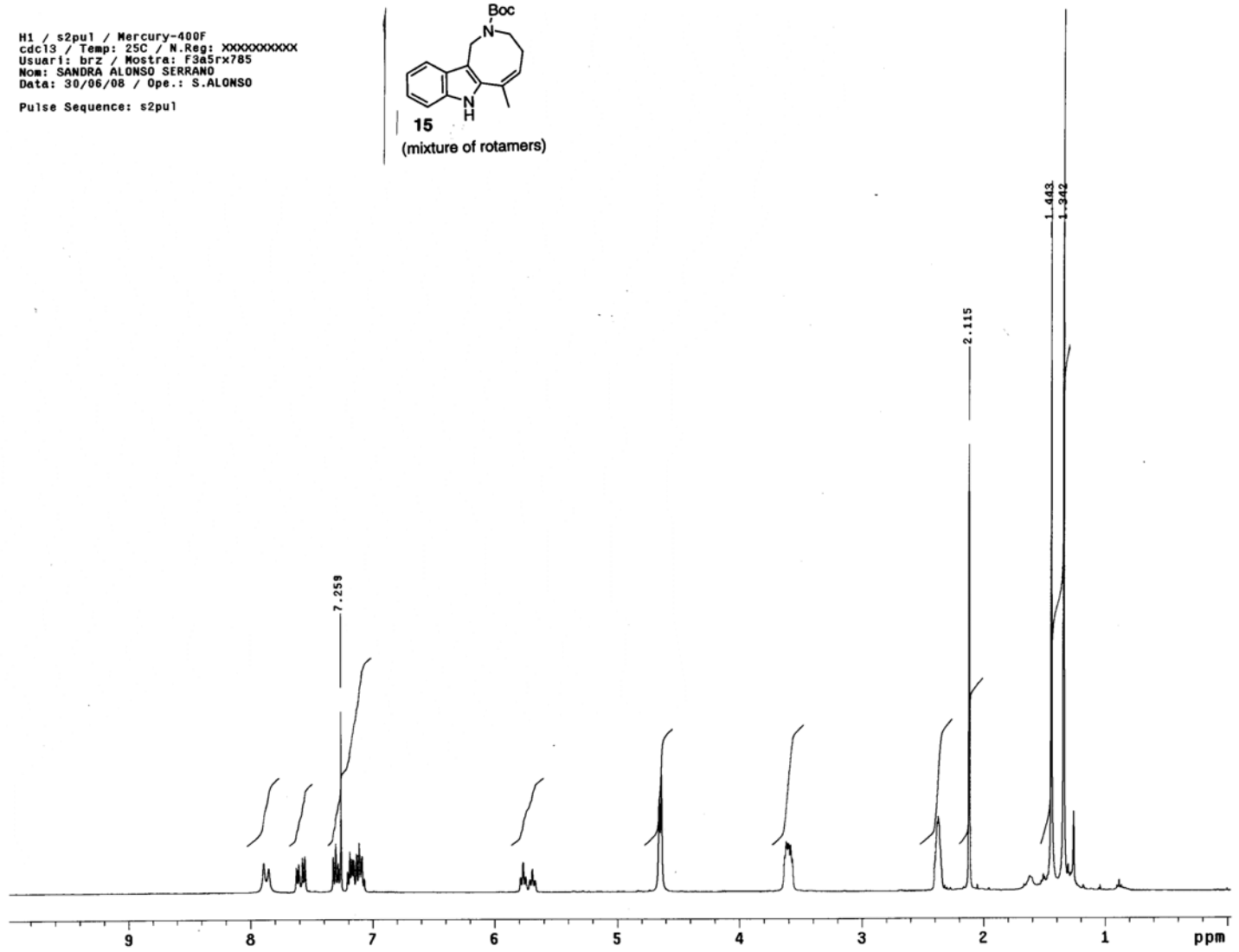

C13 / s2pul / Mercury-400f
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F7rx758
Nom: SANDRA ALONSO SERRANO
Data: 27/05/08 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #3, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
5000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
CHO
N
SO2Ph
12
180
160
140
120
100
80
60
40
20
0
ppm

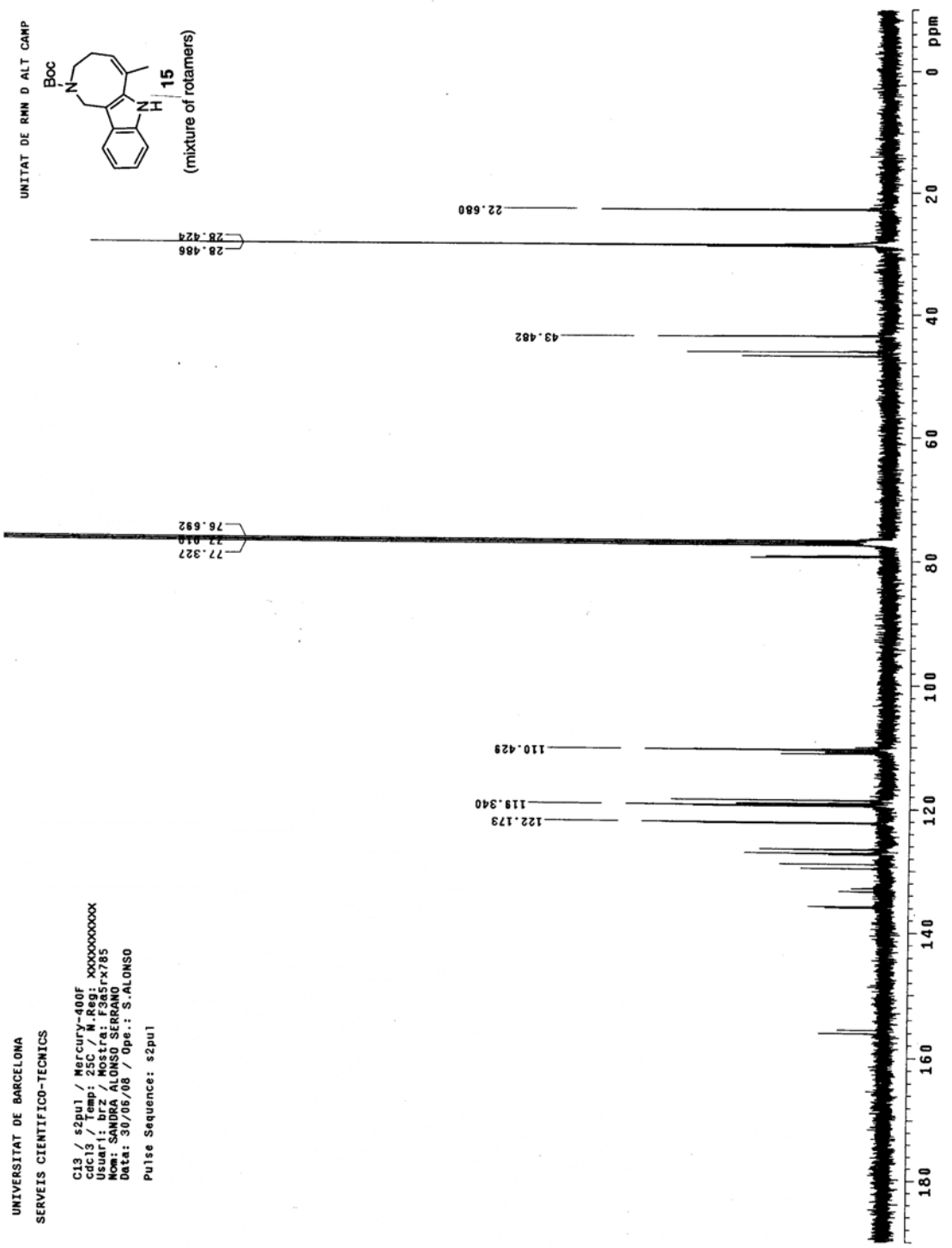

H1 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: N-PCB190508175327
Usuari: brz / Mostra: f3a4rx671
Nom: SANDRA ALONSO SERRANO
Data:19/05/08 / Sist automatic
Pulse Sequence: s2pul
Boc
N
N
SO2Ph
13 (mixture of rotamers)
1.534
1.518
1.427
1.226
1.208
9
8
7
6
5
4
3
2
1
ppm

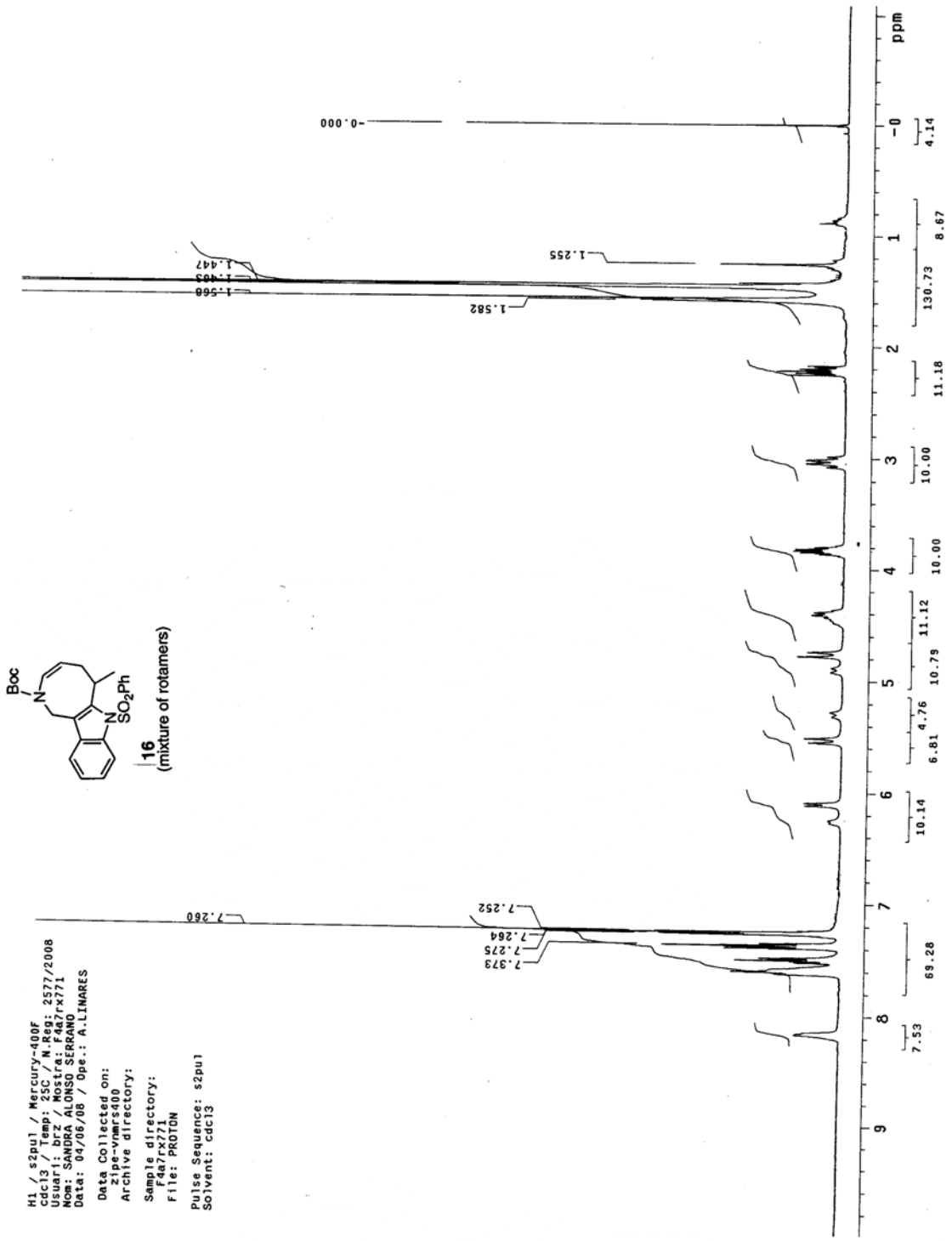

C13 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: N-PCB190508175327
Usuari: brz / Mostra: f3a4rx671
Nom: SANDRA ALONSO SERRANO
Data:20/05/08 / Sist automatic
Pulse Sequence: s2pul
13 (mixture of rotamers)
Boc
N
N
SO2Ph
17.886
28.407
33.265
46.628
76.684
77.000
77.316
123.677
124.515
126.249
129.118
133.584
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: f11a17rx763
Nom: SANDRA ALONSO SERRANO
Data: 22/05/08 / Ope.: S.ALONSO
Pulse Sequence: s2pul
Boc
N
N
SO2Ph
14
(mixture of rotamers)
7.383
1.472
1.424
9
8
7
6
5
4
3
2
1
ppm

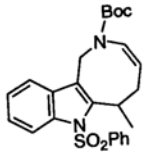

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: fila17rx763
Nom: SANDRA ALONSO SERRANO
Data: 23/05/08 / Ope.: S.ALONSO
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Boc
N
N
SO2Ph
14
(mixture of rotamers)
137.633
129.272
124.821
121.012
77.335
77.017
76.700
32.574
28.463
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F3a5rx785
Nom: SANDRA ALONSO SERRANO
Data: 30/06/08 / Ope.: S.ALONSO
Pulse Sequence: s2pul
Boc
N
N
H
15
(mixture of rotamers)
7.259
2.115
1.443
1.342
9
8
7
6
5
4
3
2
1
ppm

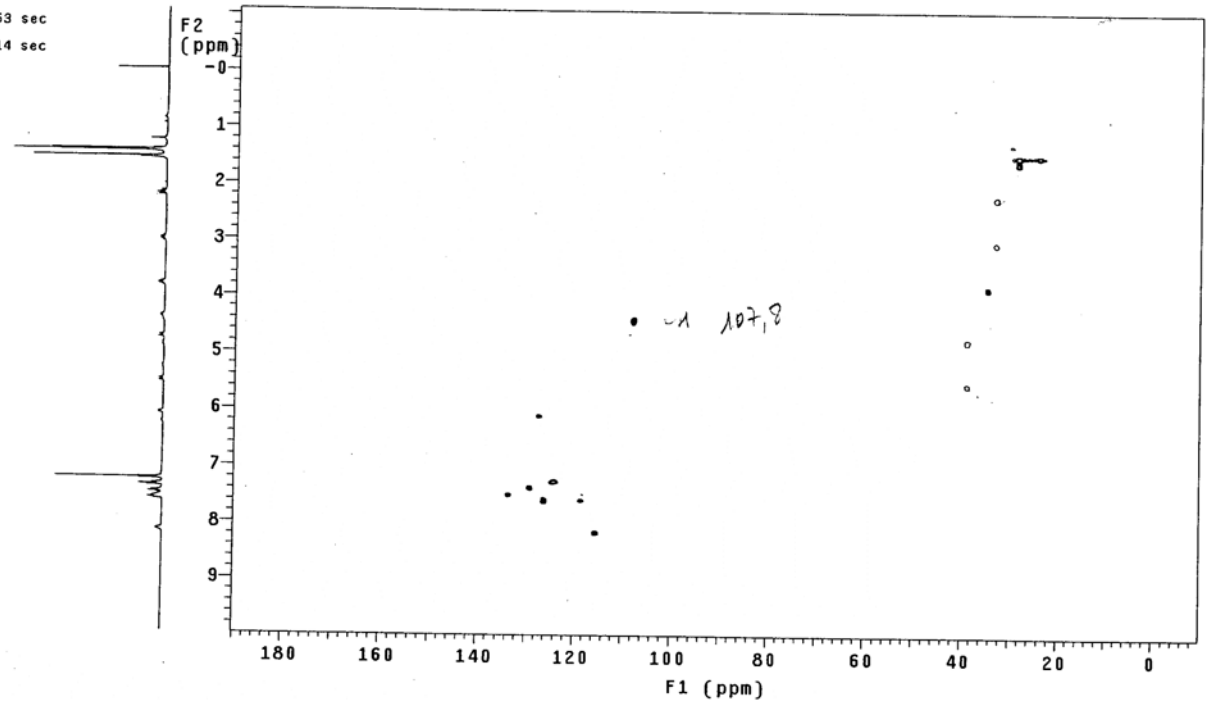

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F XXXXXXXXXX
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F3a5rx785
Nom: SANDRA ALONSO SERRANO
Data: 30/06/08 / Ope.: S.ALONSO
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Boc
N
N
H
15
(mixture of rotamers)
22.680
28.486
28.424
43.462
77.327
77.010
76.692
110.429
119.340
122.173
ppm

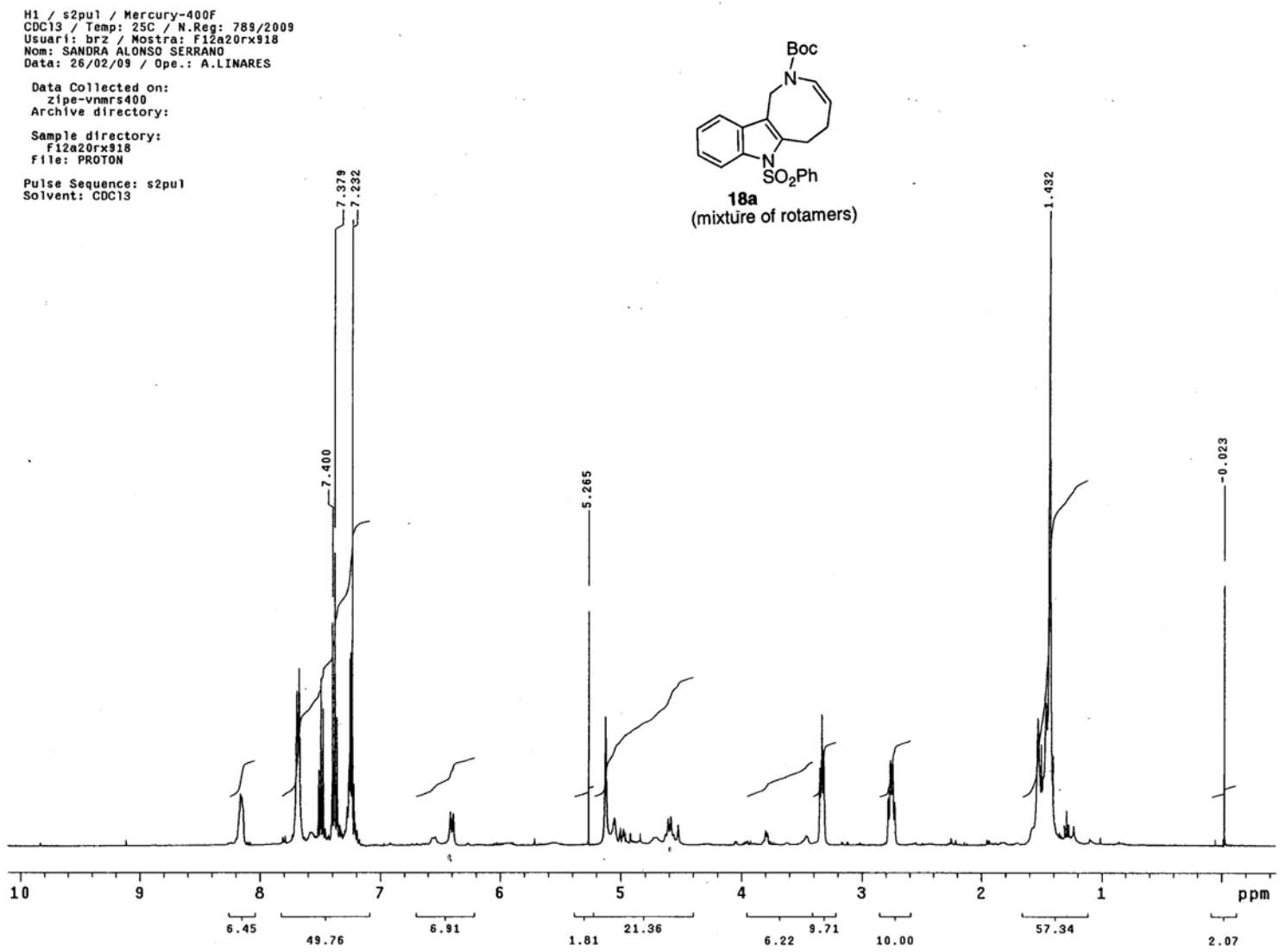

H1 /s2pul / Mercury-400F
Cdcl3 / Temp: 25C / N.Reg: 2577/2008
Usuari: brz / Mostra: F4a7rx771
Nom: SANDRA ALONSO SERRANO
Data: 04/06/08 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
Sample directory:
F4a7rx771
File: PROTON
Pulse Sequence: s2pul
Solvent: cdcl3
Boc
N
N
SO2Ph
16
(mixture of rotamers)
7.260
7.373
7.275
7.264
7.252
1.582
1.568
1.483
1.447
1.255
0.000
ppm
7.53
69.28
10.14
6.81
4.76
10.79
11.12
10.00
10.00
11.18
130.73
8.67
4.14

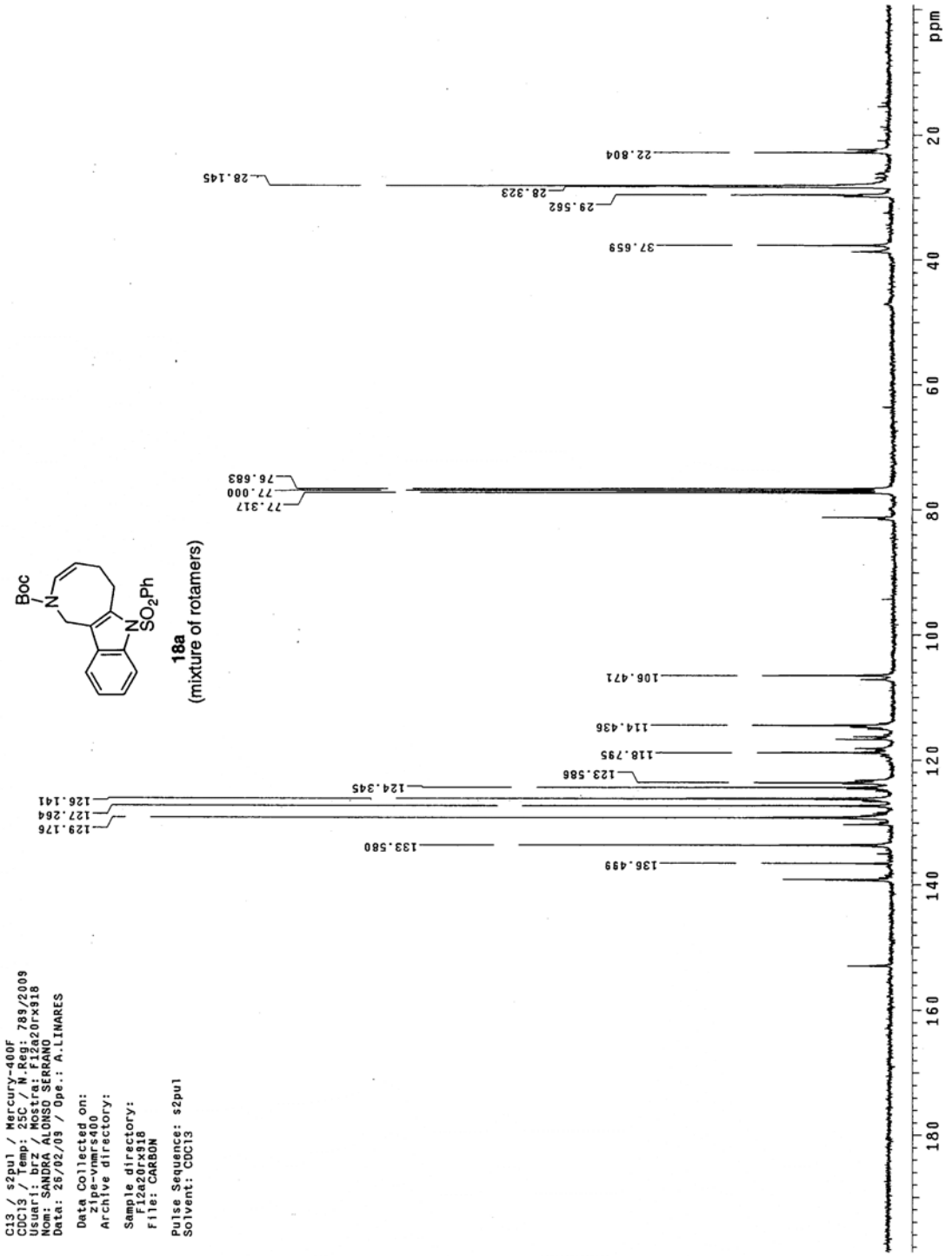
```
H1 / gHSQC / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 2577/2008
Usuari: brz / Mostra: F4a7rx771
Nom: SANDRA ALONSO SERRANO
Data: 04/06/08 / Ope.: A.LINARES

 Data Collected on:
   zipe-vnmrs400
 Archive directory:

Pulse Sequence: gHSQC
Solvent: cdcl3

 Temp. 25.0 C / 298.1 K
Operator: robot400

 Relax. delay 1.000 sec
 Acq. time 0.150 sec
 Width     4432.6 Hz
 2D Width 20115.7 Hz
 8 repetitions
 2 x 128 increments
OBSERVE    H1, 399.9486789 MHz
DECOUPLE C13, 100.5762263 MHz
 Power 33 dB
 on during acquisition
 off during delay
 W40_asw modulated
DATA PROCESSING
 Gauss apodization 0.053 sec
F1 DATA PROCESSING
 Gauss apodization 0.014 sec
FT size 1024 x 2048
```

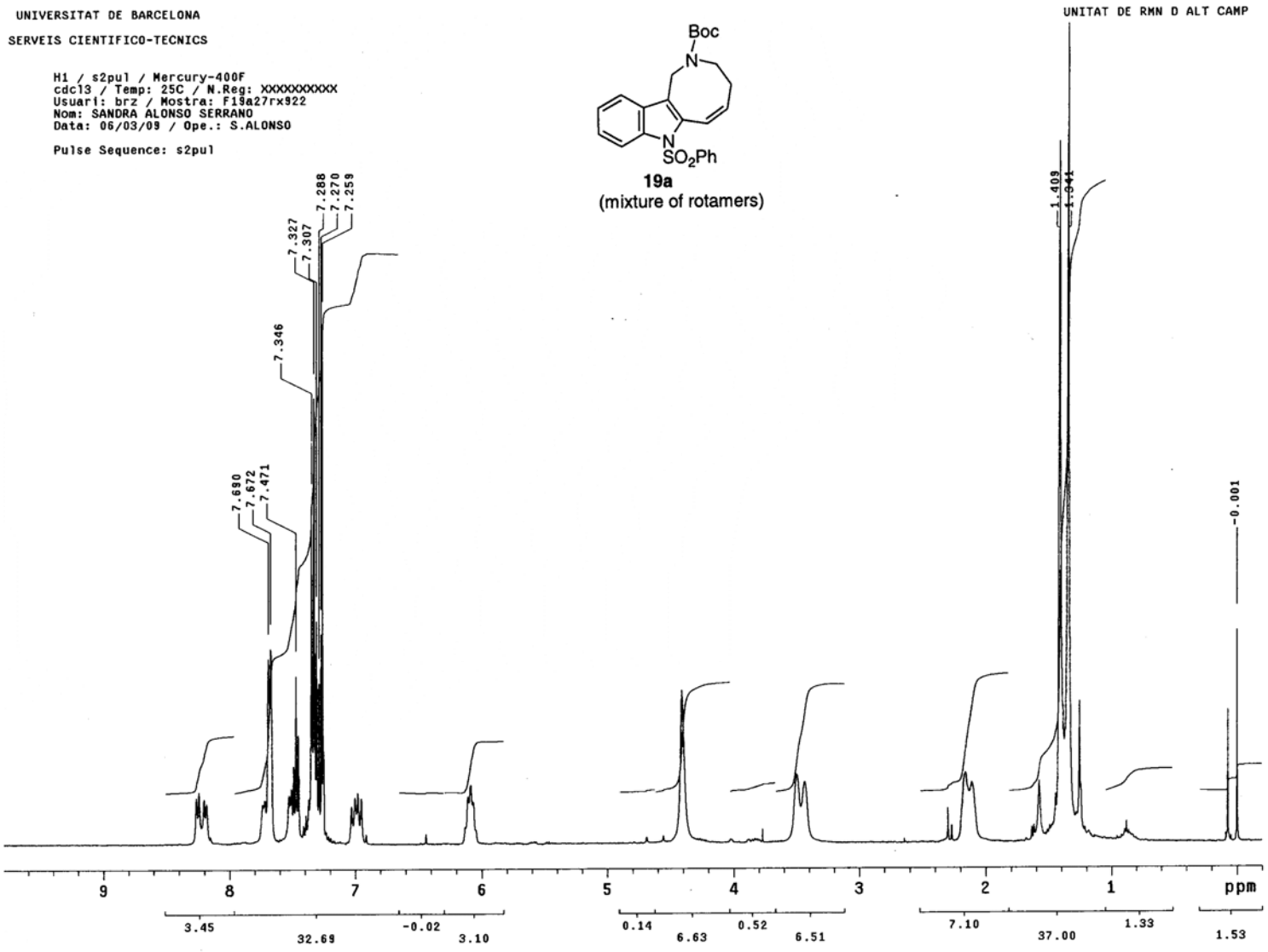


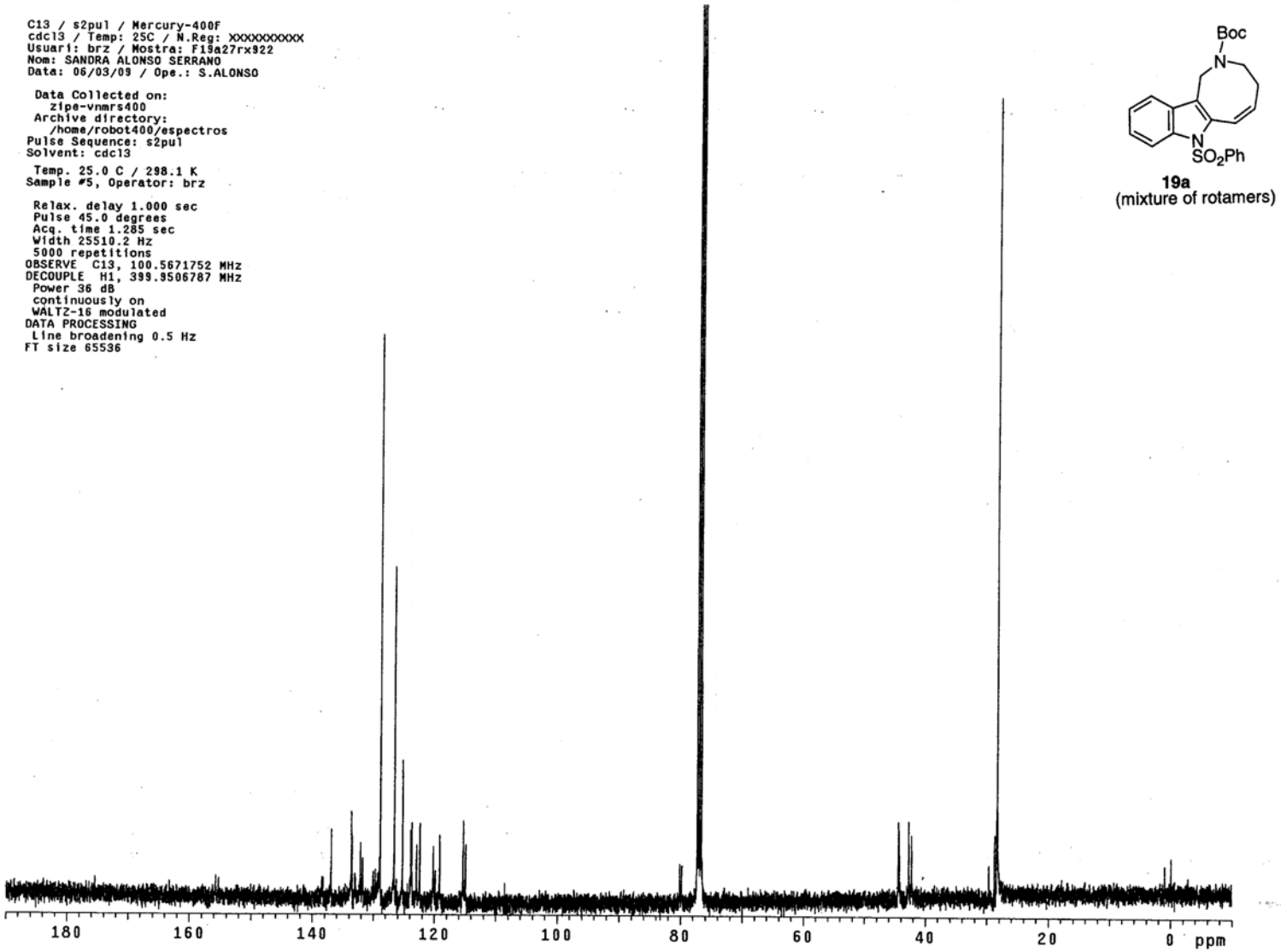
16
(mixture of rotamers)

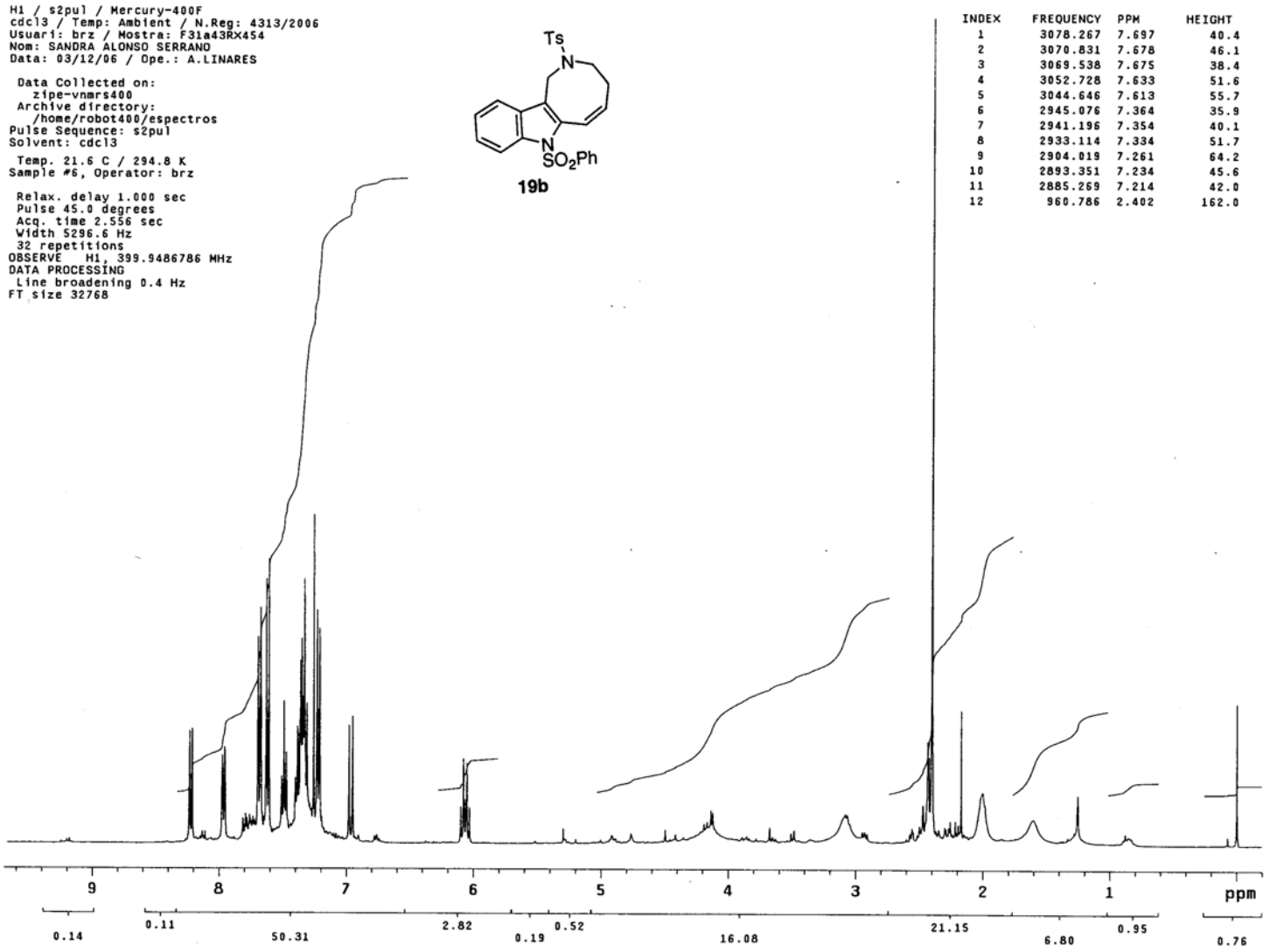


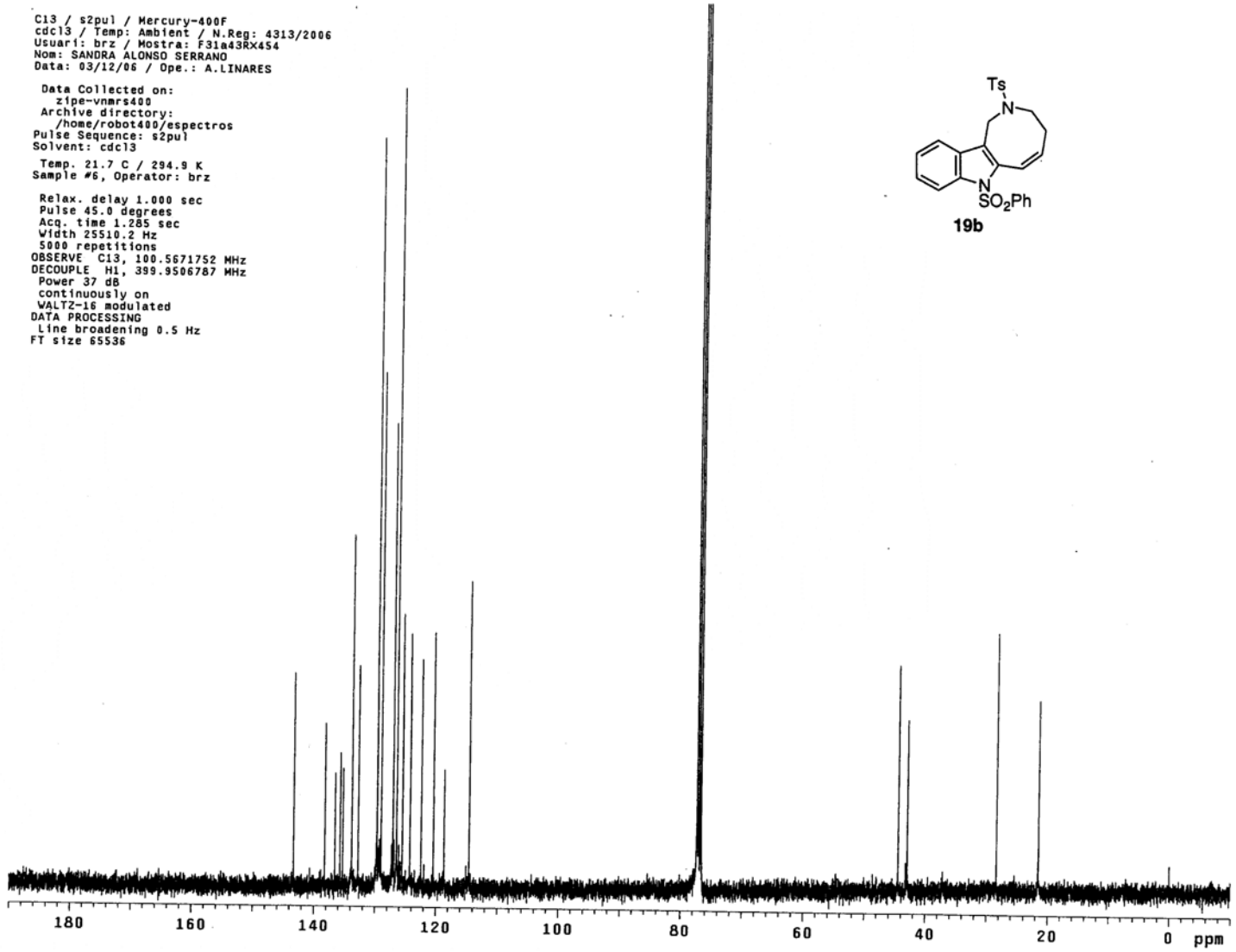

H1 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: 789/2009
Usuari: brz / Mostra: F12a20rx918
Nom: SANDRA ALONSO SERRANO
Data: 26/02/09 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
Sample directory:
F12a20rx918
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Boc
N
N
SO2Ph
18a
(mixture of rotamers)
7.379
7.232
7.400
5.265
1.432
-0.023
10
9
8
7
6
5
4
3
2
1
ppm
6.45
49.76
6.91
1.81
21.36
6.22
9.71
10.00
57.34
2.07

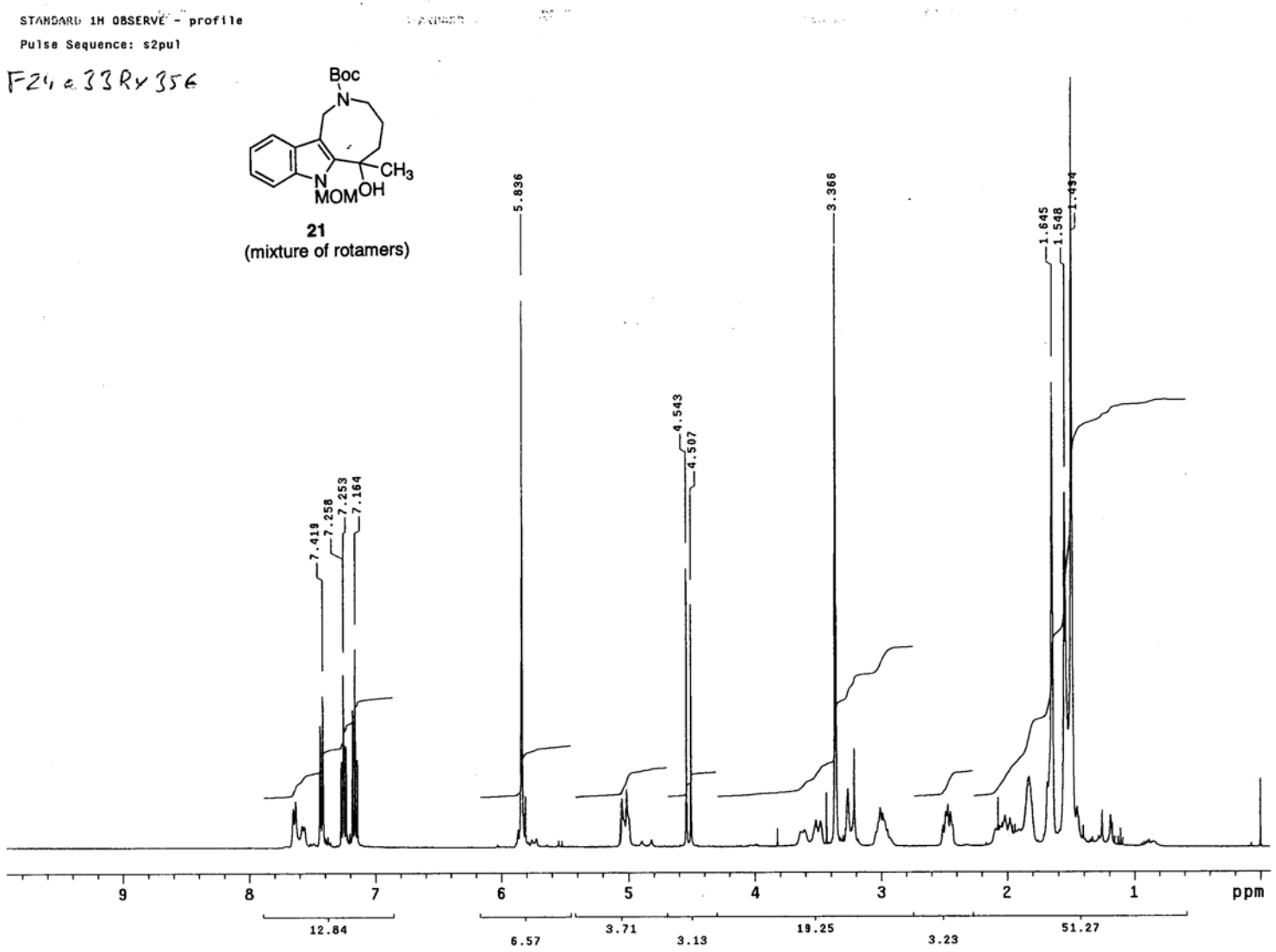

C13 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: 789/2009
Usuari: brz / Mostra: F12a20rx918
Nom: SANDRA ALONSO SERRANO
Data: 26/02/09 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
Sample directory:
F12a20rx918
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Boc
N
N
SO2Ph
18a
(mixture of rotamers)
129.176
127.264
126.141
124.345
123.586
118.795
114.436
106.471
133.580
136.499
77.317
77.000
76.683
37.659
29.562
28.323
28.145
22.804
ppm

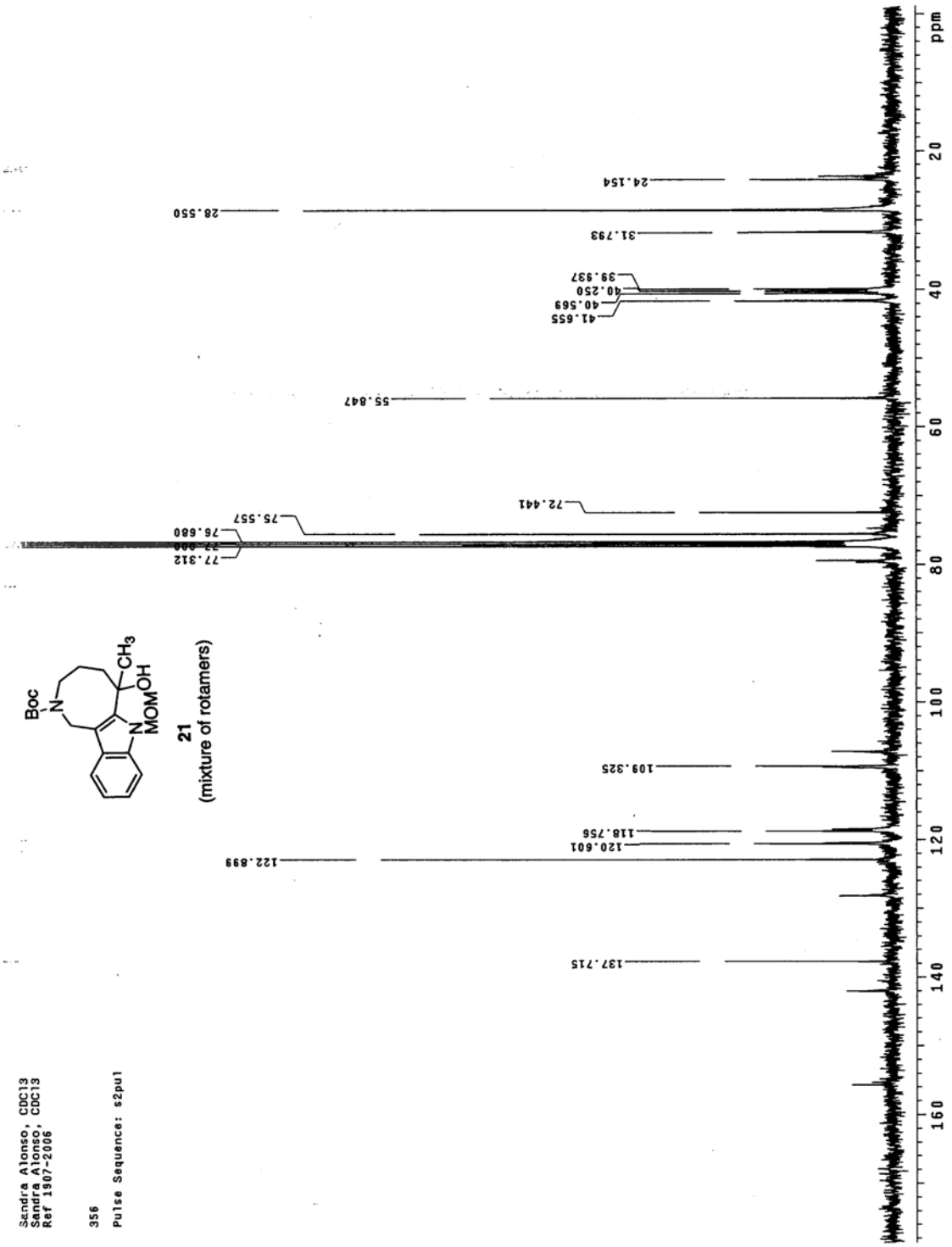

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F19a27rx922
Nom: SANDRA ALONSO SERRANO
Data: 06/03/09 / Ope.: S.ALONSO
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
Boc
N
N
SO2Ph
19a
(mixture of rotamers)
7.690
7.672
7.471
7.346
7.327
7.307
7.288
7.270
7.259
1.409
1.041
-0.001
9
8
7
6
5
4
3
2
1
ppm
3.45
32.69
-0.02
3.10
0.14
6.63
0.52
6.51
7.10
37.00
1.33
1.53

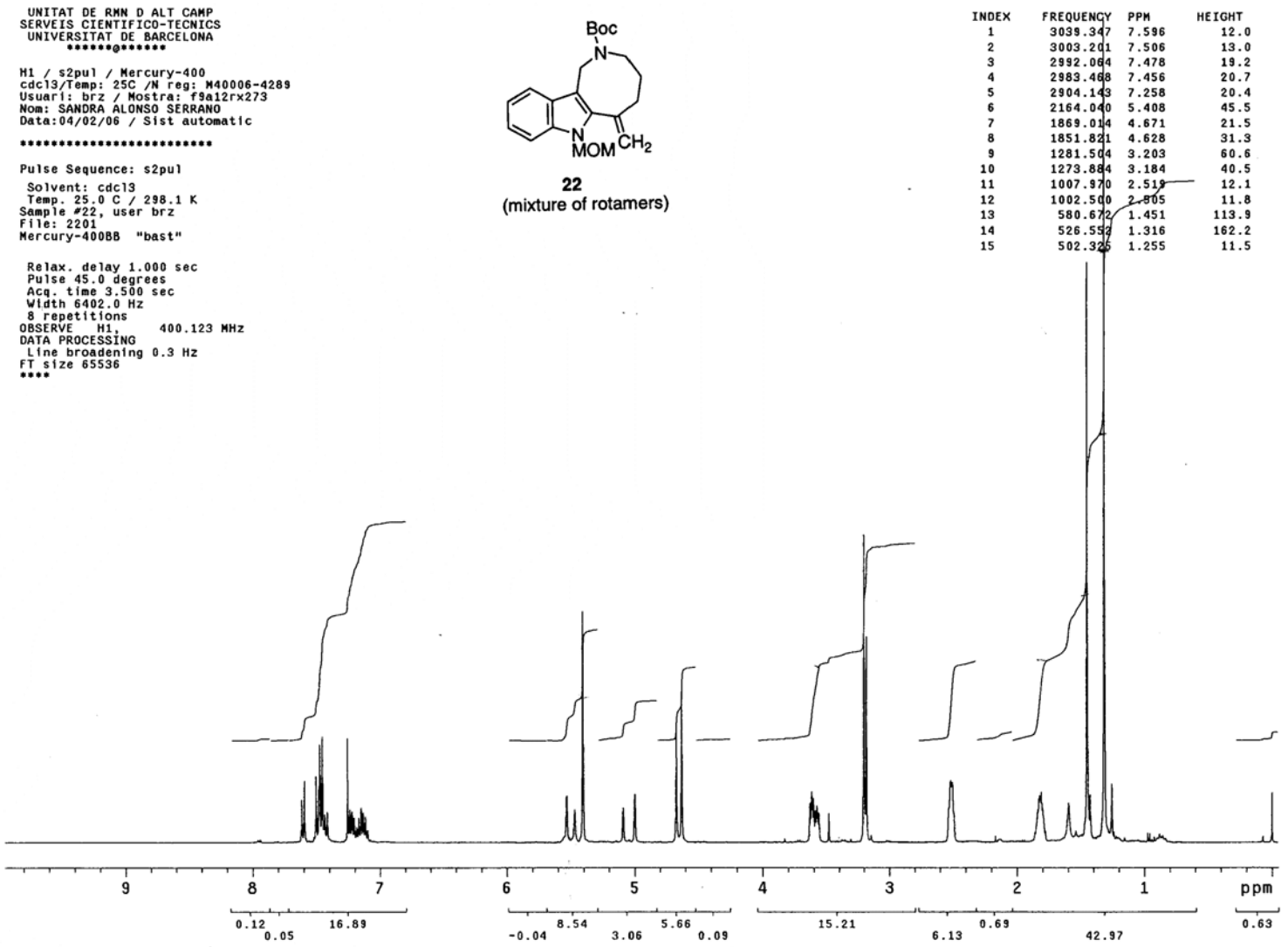

C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F19a27rx922
Nom: SANDRA ALONSO SERRANO
Data: 06/03/09 / Ope.: S.ALONSO
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #5, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
5000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Boc
N
N
SO2Ph
19a
(mixture of rotamers)
180
160
140
120
100
80
60
40
20
0
ppm

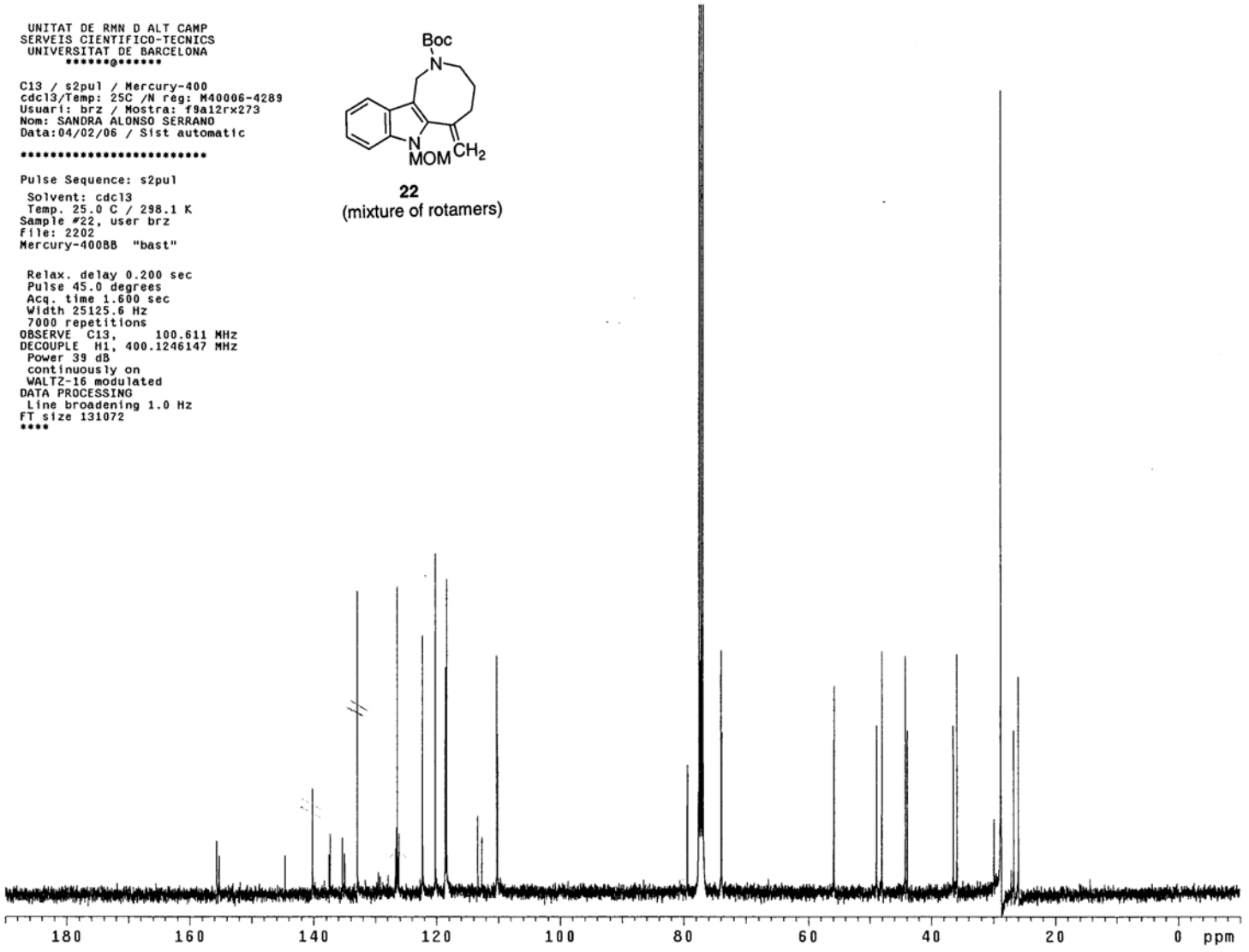

H1 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 4313/2006
Usuari: brz / Mostra: F31a43RX454
Nom: SANDRA ALONSO SERRANO
Data: 03/12/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.6 C / 294.8 K
Sample #6, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 5296.6 Hz
32 repetitions
OBSERVE H1, 399.9486786 MHz
DATA PROCESSING
Line broadening 0.4 Hz
FT size 32768
Ts
N
N
SO2Ph
19b
INDEX FREQUENCY PPM HEIGHT
1 3078.267 7.697 40.4
2 3070.831 7.678 46.1
3 3069.538 7.675 38.4
4 3052.728 7.633 51.6
5 3044.646 7.613 55.7
6 2945.076 7.364 35.9
7 2941.196 7.354 40.1
8 2933.114 7.334 51.7
9 2904.019 7.261 64.2
10 2893.351 7.234 45.6
11 2885.269 7.214 42.0
12 960.786 2.402 162.0
9
8
7
6
5
4
3
2
1
ppm
0.14
0.11
50.31
2.82
0.19
0.52
16.08
21.15
6.80
0.95
0.76

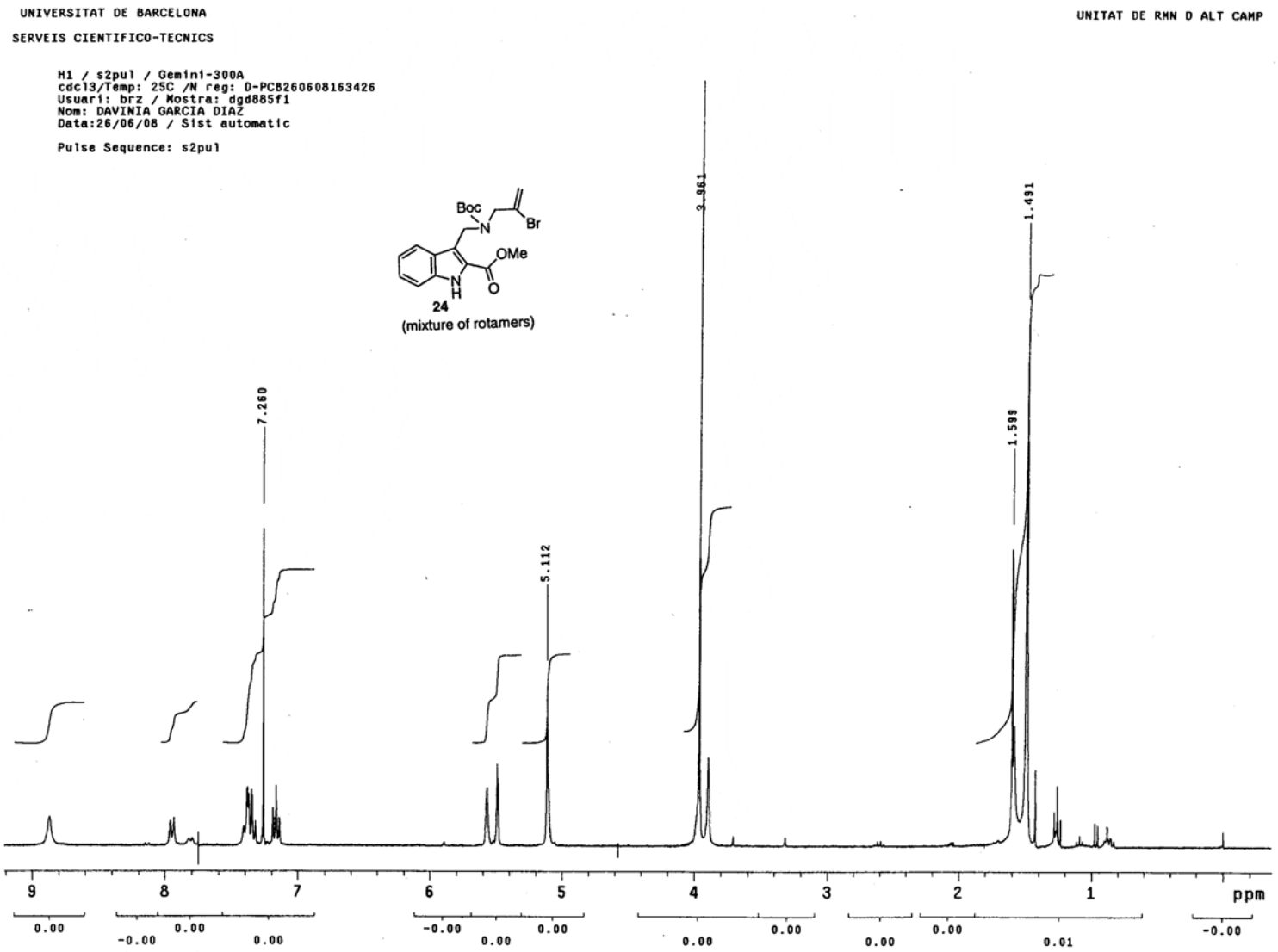

C13 / s2pul / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 4313/2006
Usuari: brz / Mostra: F31a43RX454
Nom: SANDRA ALONSO SERRANO
Data: 03/12/06 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
/home/robot400/espectros
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.7 C / 294.9 K
Sample #6, Operator: brz
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
5000 repetitions
OBSERVE C13, 100.5671752 MHz
DECOUPLE H1, 399.9506787 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Ts
N
N
SO2Ph
19b
180
160
140
120
100
80
60
40
20
0
ppm

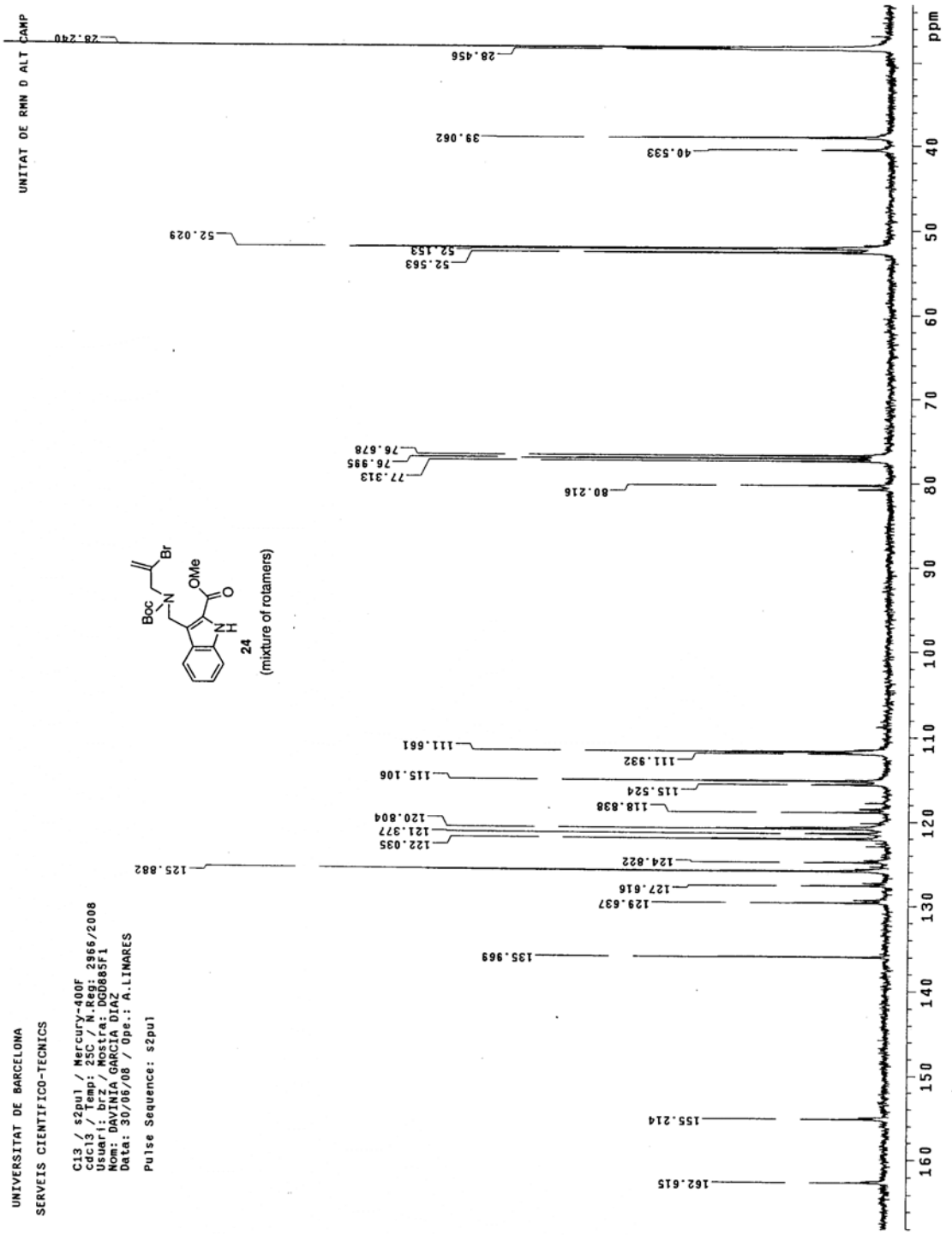

STANDARD 1H OBSERVE - profile
Pulse Sequence: s2pul
F24e33Ry356
Boc
N
N
MOM
OH
CH3
21
(mixture of rotamers)
5.836
3.366
4.543
4.507
1.645
1.548
1.494
7.419
7.258
7.253
7.164
9
8
7
6
5
4
3
2
1
ppm
12.84
6.57
3.71
3.13
19.25
3.23
51.27

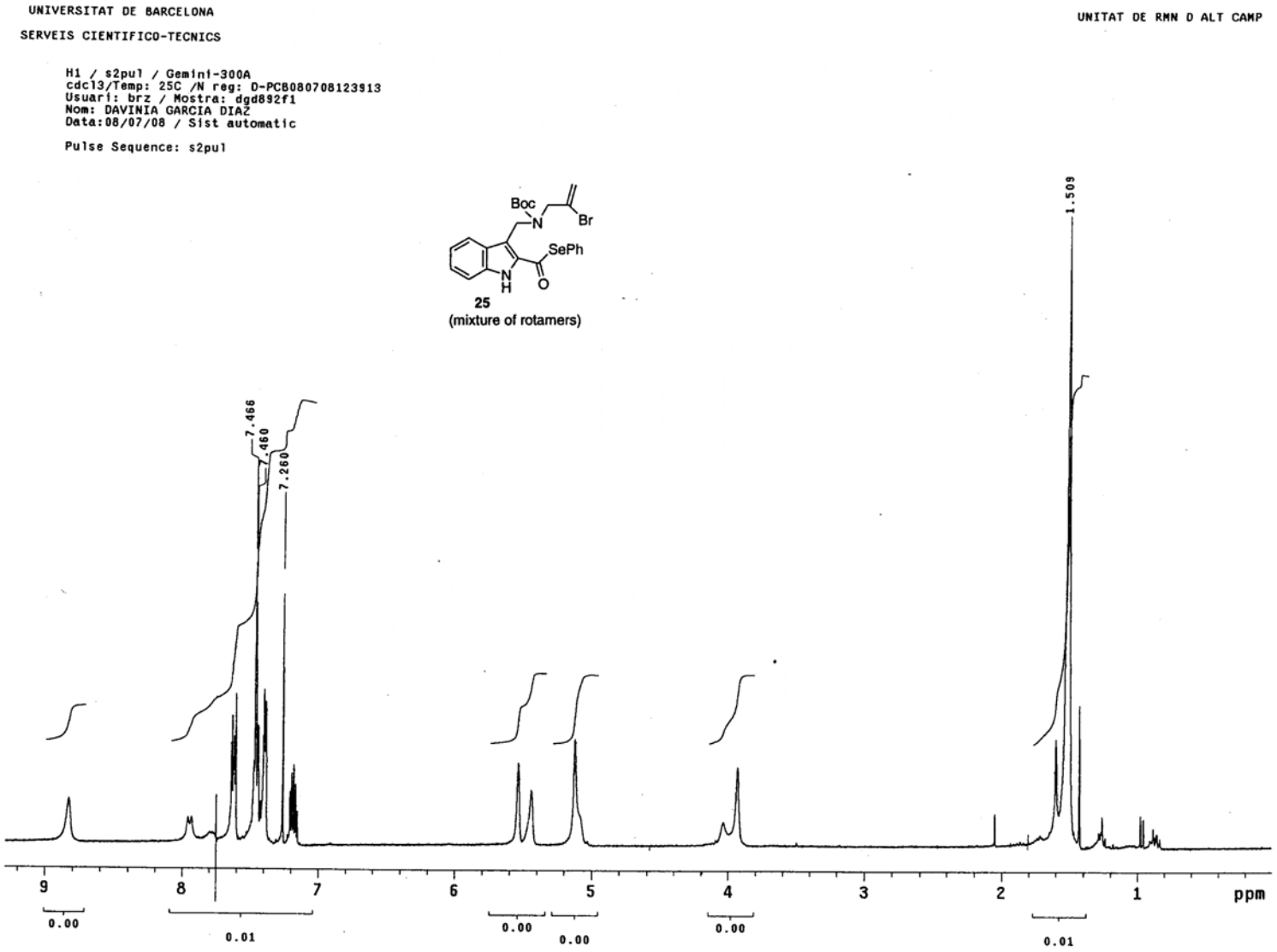

Sandra Alonso, CDCl3
Sandra Alonso, CDCl3
Ref 1907-2006
356
Pulse Sequence: s2pul
Boc
N
N
MOM
OH
CH3
21
(mixture of rotamers)
77.312
76.680
75.557
72.441
55.847
41.655
40.569
40.250
39.937
31.793
28.550
24.154
122.899
120.601
118.756
109.325
137.715
ppm
20
40
60
80
100
120
140
160


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
******@******
H1 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: M40006-4289
Usuari: brz / Mostra: f9a12rx273
Nom: SANDRA ALONSO SERRANO
Data:04/02/06 / Sist automatic
****
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #22, user brz
File: 2201
Mercury-400BB "bast"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.500 sec
Width 6402.0 Hz
8 repetitions
OBSERVE H1, 400.123 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 65536
****
Boc
N
N
MOM
CH2
22
(mixture of rotamers)
INDEX FREQUENCY PPM HEIGHT
1 3039.347 7.596 12.0
2 3003.201 7.506 13.0
3 2992.064 7.478 19.2
4 2983.468 7.456 20.7
5 2904.143 7.258 20.4
6 2164.040 5.408 45.5
7 1869.014 4.671 21.5
8 1851.821 4.628 31.3
9 1281.504 3.203 60.6
10 1273.884 3.184 40.5
11 1007.970 2.519 12.1
12 1002.500 2.505 11.8
13 580.672 1.451 113.9
14 526.552 1.316 162.2
15 502.325 1.255 11.5
9
8
7
6
5
4
3
2
1
ppm
0.12
16.89
0.05
-0.04
8.54
3.06
5.66
0.09
15.21
6.13
0.69
42.97
0.63


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
******@******
C13 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: M40006-4289
Usuari: brz / Mostra: f9a12rx273
Nom: SANDRA ALONSO SERRANO
Data:04/02/06 / Sist automatic
****
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #22, user brz
file: 2202
Mercury-400BB "bast"
Relax. delay 0.200 sec
Pulse 45.0 degrees
Acq. time 1.600 sec
Width 25125.6 Hz
7000 repetitions
OBSERVE C13, 100.611 MHz
DECOUPLE H1, 400.1246147 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
****
Boc
N
N
MOM
CH2
22
(mixture of rotamers)
180
160
140
120
100
80
60
40
20
0
ppm


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
H1 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: D-PCB260608163426
Usuari: brz / Mostra: dgd885f1
Nom: DAVINIA GARCIA DIAZ
Data:26/06/08 / Sist automatic
Pulse Sequence: s2pul
Boc
N
Br
OMe
N
H
O
24
(mixture of rotamers)
7.260
5.112
3.961
1.599
1.491
9
8
7
6
5
4
3
2
1
ppm
0.00
-0.00
0.00
0.00
-0.00
0.00
0.00
0.00
0.00
0.00
0.00
0.01
-0.00


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 2966/2008
Usuari: brz / Mostra: DG0885F1
Nom: DAVINIA GARCIA DIAZ
Data: 30/06/08 / Ope.: A.LINARES
Pulse Sequence: s2pul
UNITAT DE RMN D ALT CAMP
28.240
28.456
39.062
40.533
52.029
52.153
52.563
76.678
76.985
77.313
80.216
111.661
111.932
115.106
115.524
118.838
120.804
121.377
122.035
124.822
125.882
127.616
129.637
135.969
155.214
162.615
Br
OMe
Boc
N
H
O
24
(mixture of rotamers)
ppm


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
H1 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: D-PCB080708123913
Usuari: brz / Mostra: dgd892f1
Nom: DAVINIA GARCIA DIAZ
Data:08/07/08 / Sist automatic
Pulse Sequence: s2pul
Boc
N
Br
SePh
N
H
O
25
(mixture of rotamers)
7.466
7.460
7.260
1.509
9
8
7
6
5
4
3
2
1
ppm
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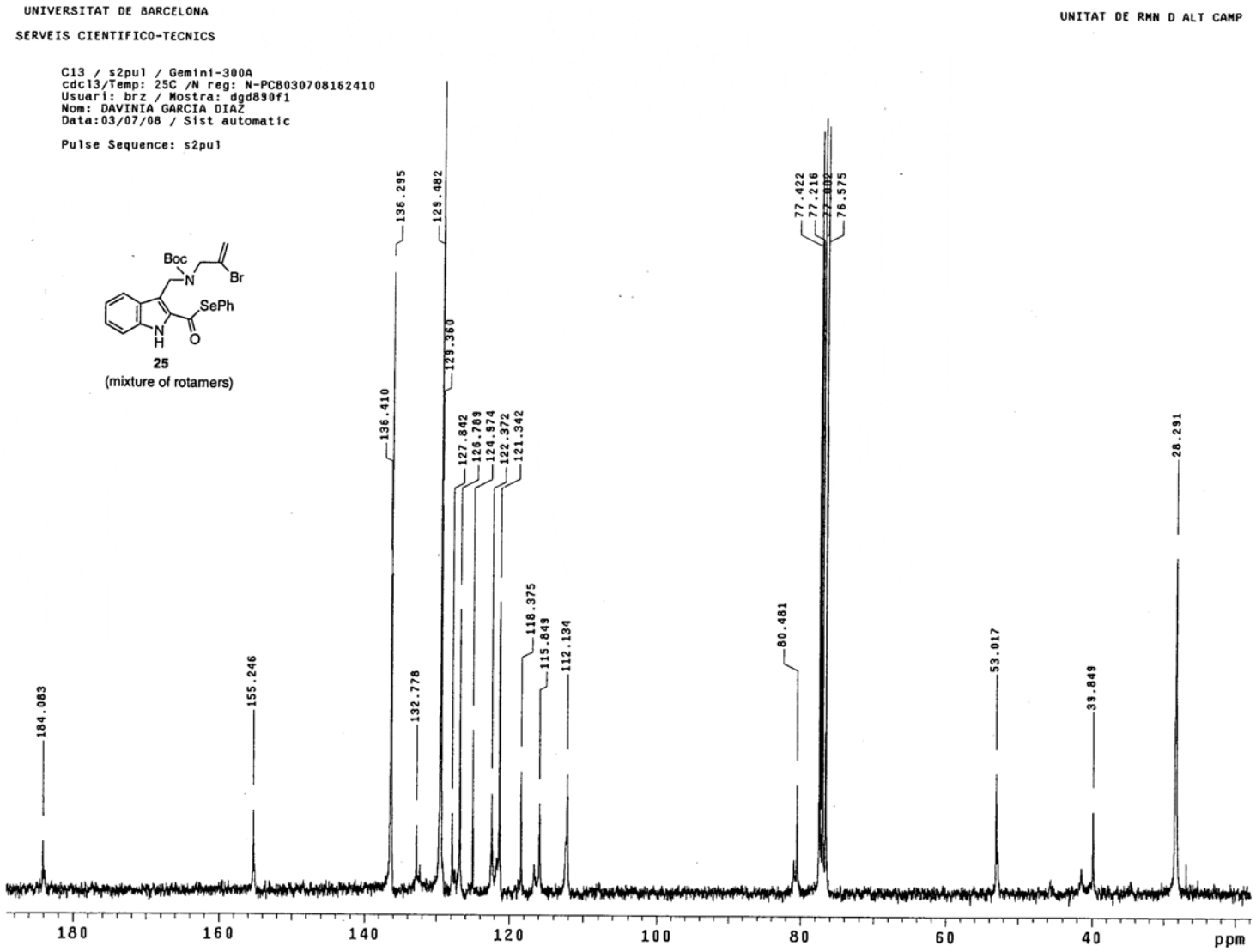
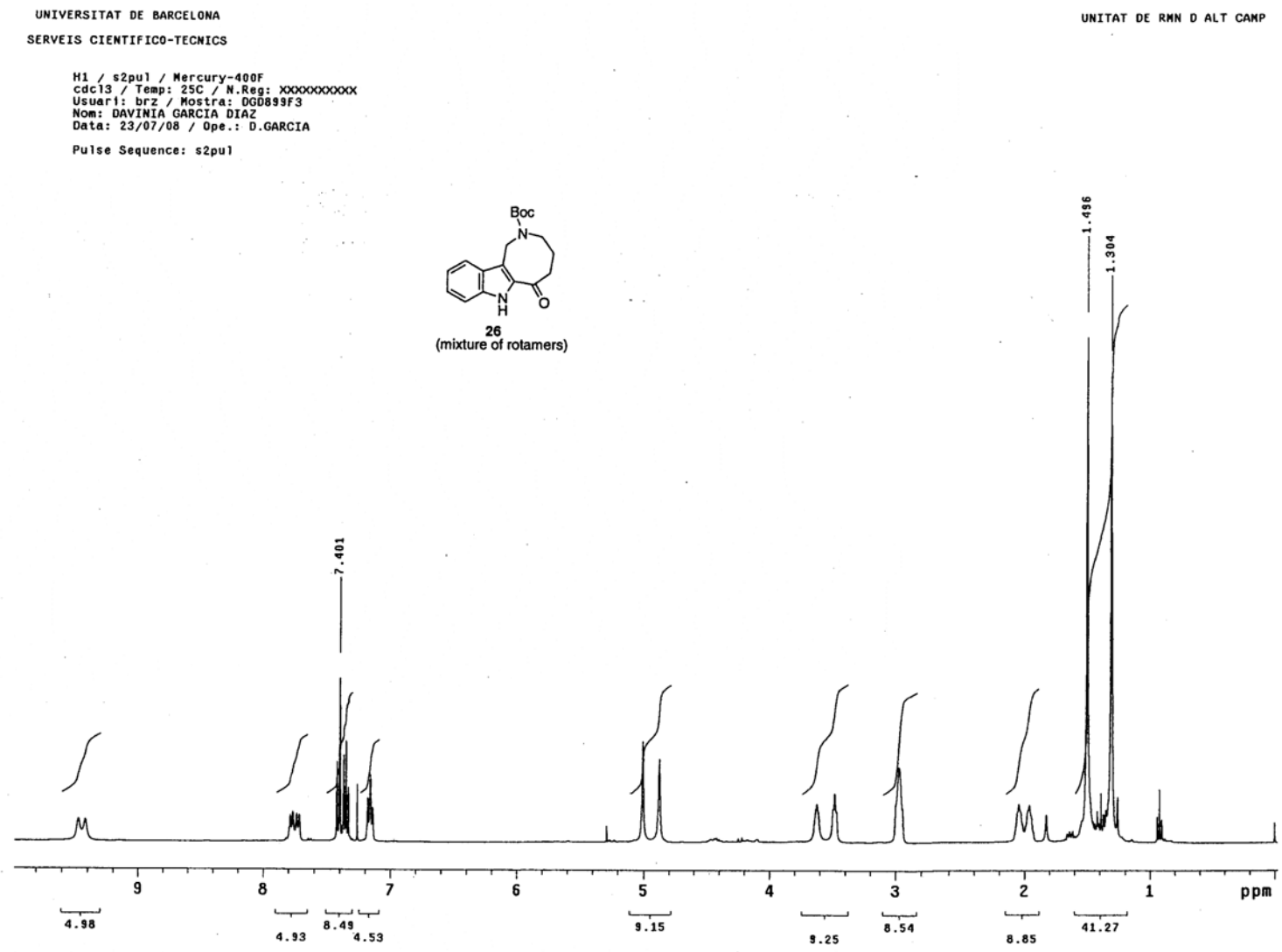
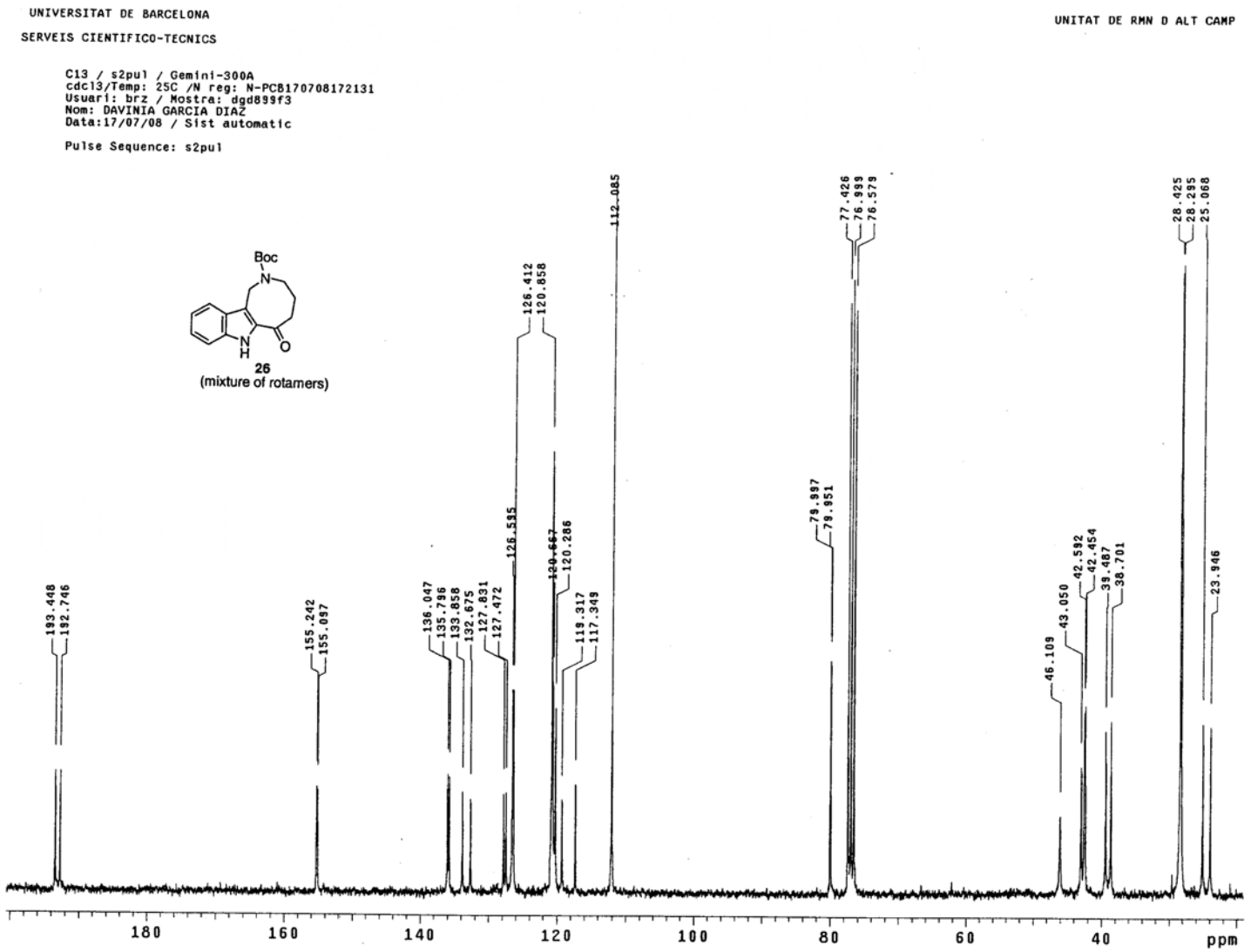
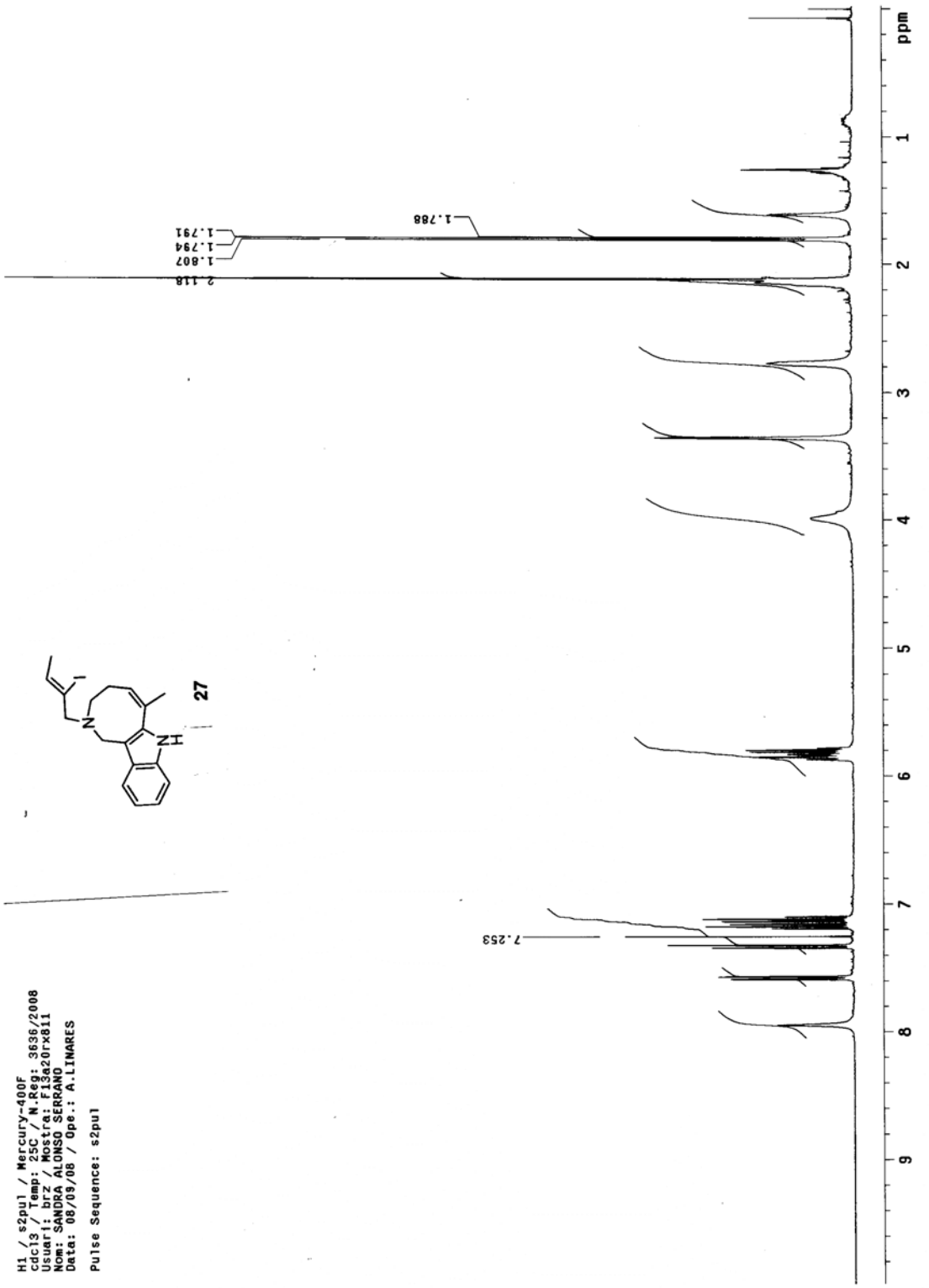
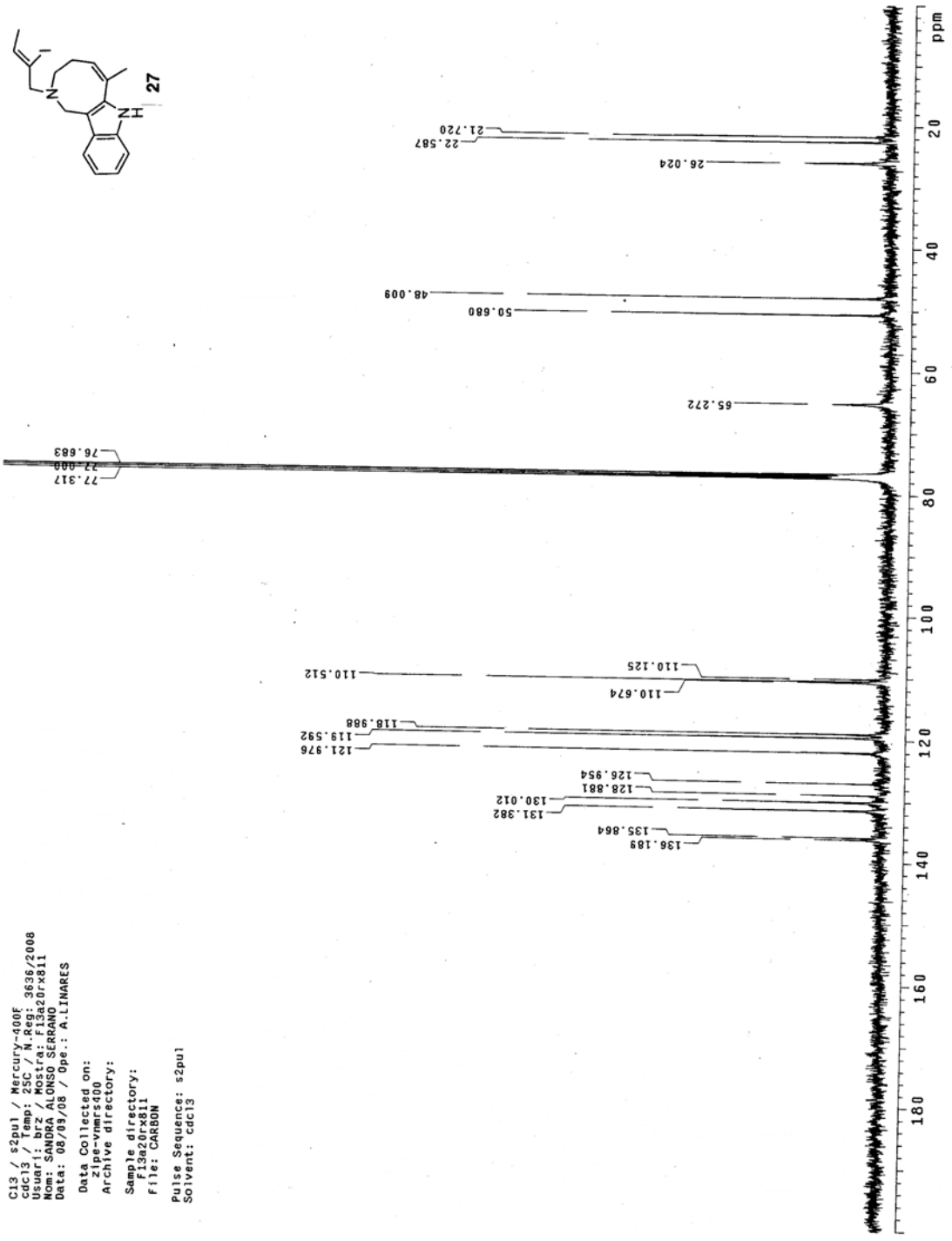
0.01
0.00
0.00
0.00
0.01


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: N-PCB030708162410
Usuari: brz / Mostra: dgd890f1
Nom: DAVINIA GARCIA DIAZ
Data:03/07/08 / Sist automatic
Pulse Sequence: s2pul
Boc
N
Br
SePh
N
H
O
25
(mixture of rotamers)
184.083
155.246
136.410
136.295
132.778
129.482
129.360
127.842
126.789
124.974
122.372
121.342
118.375
115.849
112.134
80.481
77.422
77.216
77.002
76.575
53.017
39.849
28.291
180
160
140
120
100
80
60
40
ppm


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: DGD899F3
Nom: DAVINIA GARCIA DIAZ
Data: 23/07/08 / Ope.: D.GARCIA
Pulse Sequence: s2pul
Boc
N
N
H
O
26
(mixture of rotamers)
1.496
1.304
7.401
9
8
7
6
5
4
3
2
1
ppm
4.98
4.93
8.49
4.53
9.15
9.25
8.54
8.85
41.27

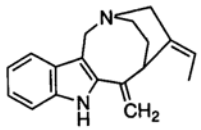

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Gemini-300A
cdcl3/Temp: 25C /N reg: N-PCB170708172131
Usuari: brz / Mostra: dgd899f3
Nom: DAVINIA GARCIA DIAZ
Data:17/07/08 / Sist automatic
Pulse Sequence: s2pul
Boc
N
N
H
O
26
(mixture of rotamers)
193.448
192.746
155.242
155.097
136.047
135.796
133.858
132.675
127.831
127.472
126.535
126.412
120.858
120.667
120.286
119.317
117.349
112.085
79.997
79.951
77.426
76.999
76.579
46.109
43.050
42.592
42.454
39.487
38.701
28.425
28.295
25.068
23.946
180
160
140
120
100
80
60
40
ppm


H1 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 3636/2008
Usuari: brz / Mostra: F13a20rx811
Nom: SANDRA ALONSO SERRANO
Data: 08/09/08 / Ope.: A.LINARES
Pulse Sequence: s2pul
27
7.253
2.118
1.807
1.794
1.791
1.788
ppm

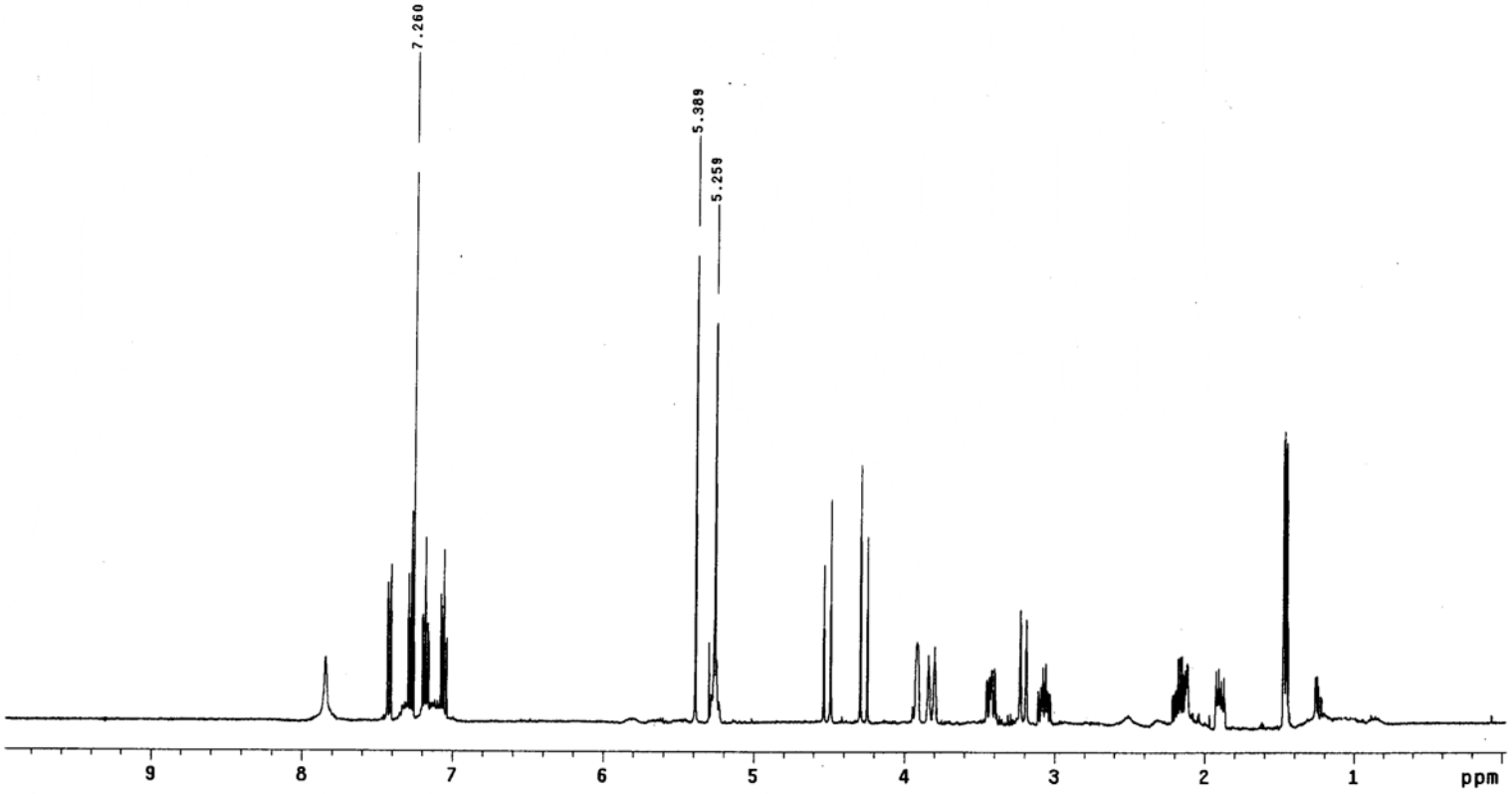

27
21.720
22.587
26.024
48.009
50.680
65.272
76.683
77.000
77.317
110.125
110.512
110.674
118.988
119.592
121.976
126.954
128.881
130.012
131.382
135.864
136.189
ppm
20
40
60
80
100
120
140
160
180
C13 / s2pul / Mercury-400E
cdcl3 / Temp: 25C / N.Reg: 3636/2008
Usuari: brz / Mostra: f13a20rx811
Nom: SANDRA ALONSO SERRANO
Data: 08/09/08 / Ope.: A.LINARES
Data Collected on:
zipe-vnmrs400
Archive directory:
Sample directory:
f13a20rx811
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3

Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 90/2009
Usuari: brz / Mostra: Dani4
Nom: DANIEL SOLE ARJO
Data: 14/01/09 10:08:17 h./ Ope.: ANA LINARES

Pulse Sequence: s2pul



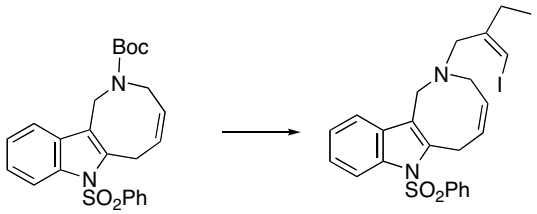
Apparicine



Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 90/2009
Usuari: brz / Mostra: Dan14
Nom: DANIEL SOLE ARJO
Data: 15/01/09 08:32:05 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
Apparicine
ppm
12.550
29.556
41.230
45.332
54.296
54.211
76.683
77.317
110.224
112.236
118.599
118.335
120.124
122.950
134.343
135.616
144.140
145.453

PART EXPERIMENTAL CORRESPONENT AL CAPÍTOL 3.3

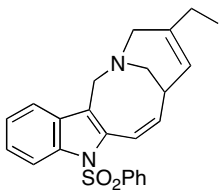
2-(2-Ethyl-3-iodo-2-propenyl*)*-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (2)



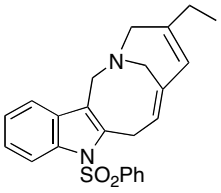
1 **2** (60%)

A solution of carbamate **1** (450 mg, 1.03 mmol) in 1.25 M HCl in MeOH (4.2 mL) was stirred at rt for 18 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (278 mg). Diisopropylethylamine (0.2 mL, 1.16 mmol) and 3-bromo-2-ethyl-1-iodo-1-propene (235 mg, 0.82 mmol) were added to a solution of the above amine (278 mg, 0.82 mmol) in 1:1 CH_2Cl_2–acetonitrile (16 mL) and the resulting mixture was stirred at rt overnight. The solvent was removed and the residue was dissolved in CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$. The organic solution was dried and concentrated to give the crude product. After chromatography (SiO_2, 8:2 hexanes-AcOEt) the pure tertiary amine **2** was obtained: 327 mg (60%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, *J* = 7.6 Hz, 3H), 2.29 (q, *J* = 7.6 Hz, 2H), 3.07 (d, *J* = 6.8 Hz, 2H); 3.26 (s, 2H), 3.90 (s, 2H), 4.05 (d, *J* = 6 Hz, 2H), 5.60 (m, 1H), 5.99 (m, 1H), 6.04 (br s, 1H), 7.28 (m, 2H), 7.40 (m, 3H), 7.54 (dd, *J* = 7.6 and 7.2 Hz, 1H), 7.76 (dd, *J* = 8.8 and 1.2 Hz, 2H), 8.23 (dd, *J* = 8.4 and 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 12.6 (CH_3), 26.6 (CH_2), 29.5 (CH_2), 47.0 (CH_2), 49.1 (CH_2), 60.6 (CH_2), 76.7 (CH), 115.0 (CH), 117.0 (C), 118.0 (CH), 123.7 (CH), 124.3 (CH), 126.2 (2CH), 126.6 (CH), 129.0 (C), 129.2 (2CH), 129.5 (CH), 133.6 (CH), 136.4 (C), 137.1 (C), 139.0 (C), 150.6 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{24}H_{26}IN_2O_2S$ 533.0754, found 533.0757.

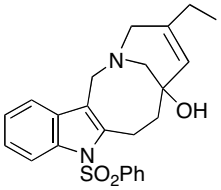
Heck Cyclization of Azocinoindole 2



3



5



6

Table 1, entry 3: To a solution of vinyl iodide **2** (45 mg, 0.085 mmol) in toluene (8.5 mL) were added under argon $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), proton-sponge® (5.5 mg, 0.025 mmol), and K_2CO_3 (18 mg, 0.13 mmol). The solution was heated at reflux for 24 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2-MeOH) to give a 3:1 mixture of **3** and **4** (21 mg, 60%), which was submitted to a second chromatographic purification (SiO_2, from Et_2O to 99:1 Et_2O-diethylamine) to give pure tetracycle **3**: 14 mg (40%); ^1H NMR ($CDCl_3$, 500 MHz, -30°C, **major conformer**) δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.93 (m, 2H), 2.40 (dd, *J* = 14 and 4.5 Hz, 1H), 2.59 (d, *J* = 14 Hz, 1H), 2.70 (broad s, 1H), 3.05 (d, *J* = 17.5 Hz, 1H), 3.66 (d, *J* = 17.5 Hz, 1H), 3.72 (d, *J* = 11 Hz, 1H), 3.77 (d, *J* = 11 Hz, 1H), 5.60 (s, 1H), 5.90 (dd, *J* = 12.5 and 4.5 Hz, 1H), 6.70 (d, *J* = 12.5 Hz, 1H), 7.20-7.75 (m, 8H), 8.19 (d, *J* = 8.5 Hz, 1H); **minor conformer**: -0.55 (t, *J* = 7.5 Hz, 3H), 0.62 (m, 1H), 0.79 (m, 1H), 2.59 (masked, 1H), 2.78 (d, *J* = 18 Hz, 1H), 3.00-3.10 (m, 3H), 3.20 (d, *J* = 15 Hz, 1H), 3.91 (s, 1H), 4.61 (d, *J* = 15 Hz, 1H), 6.30 (dd, *J* = 12 and 9 Hz, 1H), 7.02 (d, *J* = 12 Hz, 1H), 7.20-7.75 (m, 7H), 7.85 (d, *J* = 8 Hz, 1H), 8.21 (d, *J* = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, -10°C, **major conformer**) δ 11.8 (CH_3), 27.9 (CH_2), 34.3 (CH), 43.8 (CH_2), 44.9 (CH_2), 55.5 (CH_2), 115.2 (CH), 115.8 (CH), 116.9 (C), 118.6 (C), 118.8 (CH), 120.9 (CH), 124.3 (CH), 125.2 (CH), 126.3 (2 CH), 128.8 (2 CH), 130.0 (C), 133.8 (CH), 135.3 (C), 135.8 (CH), 136.5 (C), 136.9 (C); **minor conformer**: 11.0 (CH_3), 27.4 (CH_2), 32.9 (CH), 48.9 (CH_2), 49.1 (CH_2), 53.5 (CH_2), 114.1 (CH), 117.4 (CH), 119.9 (CH), 123.4 (CH), 124.5 (CH), 126.0 (CH), 127.1 (2 CH), 129.2 (2 CH), 130.7 (C), 131.9 (CH), 134.0 (C), 137.4 (CH), 138.6 (C), three quaternary C were not observed; ESI-HRMS $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_2S$ 405.1631, found 405.1628.

3 (picrate): ^{1}H NMR ($CDCl_3$, 400 MHz, **major conformer**) δ 1.13 (t, *J* = 7.6 Hz, 3H), 2.14 (q, *J* = 7.6 Hz, 2H), 2.99 (dd, *J* = 14 and 5.6 Hz, 1H), 3.12 (d, *J* = 14 Hz, 1H), 3.20 (broad s, 1H), 3.65 (d, *J* = 17.2 Hz, 1H), 4.08 (d, *J* = 17.2 Hz, 1H), 4.16 (dd, *J* = 12.4 and 9.2 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 5.84 (broad s, 1H), 5.93 (dd, *J* = 12.4 and 5.6 Hz, 1H), 6.95 (dd, *J* = 12.4 and 2.4 Hz, 1H), 7.04 (ddd, *J* = 8, 7.2, and 0.8 Hz, 1H), 7.34 (ddd, *J* = 8.8, 7.2, and 1.2 Hz, 1H), 7.40 (d, *J* = 8 Hz, 1H), 7.44 (tm, *J* = 8 Hz, 2H), 7.60 (tm, *J* = 8 Hz, 1H), 7.70 (dm, *J* = 8 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.82 (s, 2H), 11.46 (broad, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz, HSQC, **major conformer**) δ 11.6 (CH_3), 27.5 (CH_2), 33.7 (CH), 43.4 (CH_2), 45.6 (CH_2), 53.7 (CH_2), 111.7 (C), 115.3 (CH), 117.2 (CH), 118.8 (CH), 121.5 (CH), 124.7 (CH), 126.3 (2CH), 126.4 (2CH), 126.5 (CH), 128.0 (C), 128.5 (C), 129.4 (2CH), 131.4 (C), 132.2 (CH), 134.6 (CH), 137.0 (C), 137.8 (C), 138.1 (C), 141.5 (2C), 162.0 (C).

Table 1, entry 4: To a solution of vinyl iodide **2** (95 mg, 0.18 mmol) in toluene (18 mL) were added under argon $Pd(OAc)_2$ (4 mg, 0.018 mmol), (±)-BINAP (17 mg, 0.027 mmol), proton-sponge® (11.5 mg, 0.054 mmol) and K_2CO_3 (37 mg, 0.27 mmol). The solution was heated at reflux for 15 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2-MeOH) to give a 1:1 mixture of tetracycles **3** and **4** (55 mg, 75%), which was submitted to a second chromatographic purification (SiO_2, from Et_2O to 99:1 Et_2O-diethylamine) to give tetracycle **3**: 26 mg (35%).

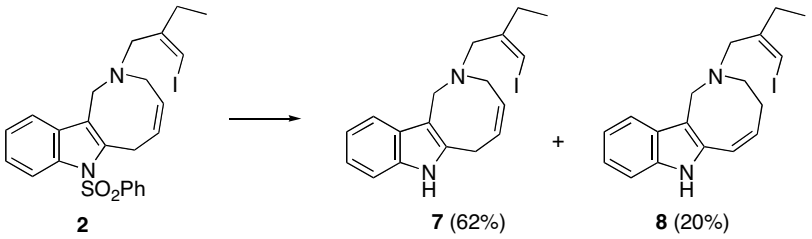
Table 1, entry 5: To a solution of vinyl iodide **2** (42 mg, 0.079 mmol) in toluene (8 mL) were added under argon $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), xantphos (7 mg, 0.012 mmol), proton-sponge® (5 mg, 0.023 mmol), and K_2CO_3 (16.5 mg, 0.12 mmol). The solution was heated at reflux for 24 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated. The residue was purified by chromatography (SiO_2, from CH_2Cl_2 to 94:6 CH_2Cl_2-MeOH) to give **5** (7.7 mg, 24%), **3** (8 mg, 25%), and **6** (6.7 mg, 20%).

5: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.91 (q, *J* = 7.5 Hz, 2H), 2.90 (d, *J* = 18 Hz, 1H), 3.03 (d, *J* = 12.5 Hz, 1H), 3.32 (d, *J* = 12.5 Hz, 1H), 3.49 (d, *J* = 12 Hz, 1H), 3.70 (dd, *J* = 19 and 5.5 Hz, 1H), 3.70 (m, 2H), 3.83 (dd, *J* = 19 and 8 Hz, 1H),

5.73 (dd, J = 8 and 5 Hz, 1H), 6.05 (s, 1H), 7.19-7.24 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.45 (tt, J = 7.5 and 1.5 Hz, 1H), 7.50 (dd, J = 7.5 and 1.5 Hz, 1H), 7.61 (m, 2H), 8.16 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, HSQC) δ 12.1 (CH_3), 26.7 (CH_2), 27.6 (CH_2), 44.1 (CH_2), 49.2 (CH_2), 56.8 (CH_2), 114.7 (CH), 117.5 (CH), 118.0 (CH), 122.3 (CH), 123.6 (CH), 124.6 (CH), 126.1 (2 CH), 128.9 (C), 129.3 (2 CH), 131.0 (C), 133.5 (C), 133.7 (CH), 136.4 (C), 137.6 (C), 139.2 (C), one quaternary C was not observed; ESI-HRMS $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_2S$ 405.1631, found 405.1630.

6: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 7.5 Hz, 3H), 1.56 (dq, J = 8.4 and 7.5 Hz, 1H), 1.71 (dq, J = 8.4 and 7.5 Hz, 1H), 1.89 (ddd, J = 13.8, 8.1, and 3 Hz, 1H), 2.08 (ddd, J = 13.8, 9.9, and 3 Hz, 1H), 2.89 (d, J = 14.7 Hz, 1H), 2.98 (d, J = 17.4 Hz, 1H), 3.10 (ddd, J = 12, 8.1, and 3 Hz, 1H), 3.15 (d, J = 14.7 Hz, 1H), 3.38 (ddd, J = 12, 9.9, and 3 Hz, 1H), 3.52 (d, J = 17.4 Hz, 1H), 3.91 (d, J = 13.5 Hz, 1H), 4.00 (d, J = 13.5 Hz, 1H), 5.18 (s, 1H), 7.24-7.33 (m, 2H), 7.42 (dd, J = 7.6 and 1.2 Hz, 2H), 7.53 (tt, J = 7.6 and 1.2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.76 (m, 2H), 8.21 (dd, J = 7.2 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, HSQC) δ 11.2 (CH_3), 21.8 (CH_2), 27.6 (CH_2), 39.4 (CH_2), 46.5 (CH_2), 52.4 (broad CH_2), 56.3 (CH_2), 67.7 (C), 114.7 (CH), 118.6 (CH), 123.9 (CH), 124.8 (CH), 125.2 (CH), 126.2 (2 CH), 128.8 (C), 129.4 (2 CH), 133.9 (CH), 136.3 (C), 139.1 (C), three quaternary C were not observed; ESI-HRMS $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3S$ 423.1737, found 423.1735.

Indole Deprotection of Azocinoindole 2



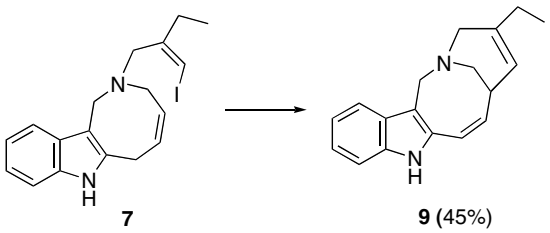
To a solution of azocinoindole **2** (35 mg, 0.066 mmol) in THF (5 mL) was added under Ar L-selectride (0.66 mL of 1M solution in THF, 0.66 mmol). After the resulting solution was refluxed for 1 h, the reaction was quenched with MeOH, diluted with H_2O and extracted with AcOEt. The organic extracts were washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, from CH_2Cl_2

to 97:3 CH_2Cl_2-MeOH) to give **2-(2-ethyl-3-iodo-2-propenyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole** (**7**, 16 mg, 62%) and its isomer **8** (5 mg, 20%).

7: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, *J* = 7.6 Hz, 3H), 2.41 (qd, *J* = 7.6 and 1.2 Hz, 2H), 3.14 (d, *J* = 7.6 Hz, 2H), 3.35 (s, 2H), 3.70 (d, *J* = 4.8 Hz, 2H), 3.97 (s, 2H), 5.79 (q, *J* = 7.6 Hz, 1H), 6.00-6.12 (m, 2H), 7.07-7.15 (m, 2H), 7.27 (dd, *J* = 6 and 1.6 Hz, 1H), 7.50 (dd, *J* = 6.8 and 1.6 Hz, 1H), 7.87 (broad, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 12.6 (CH_3), 27.7 (CH_2), 29.5 (CH_2), 45.9 (CH_2), 48.0 (CH_2), 60.7 (CH_2), 77.2 (CH), 110.0 (CH), 117.7 (CH), 119.6 (CH), 121.3 (CH), 126.9 (broad CH), 128.8 (broad CH), 129.5 (C), 134.8 (C), 135.3 (C), 150.5 (C), one quaternary C was not observed; ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{22}IN_2$ 393.0822, found 393.0823.

8: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, *J* = 7.6 Hz, 3H), 2.35 (qd, *J* = 7.6 and 1.2 Hz, 2H), 2.43 (m, 2H), 2.77 (m, 2H), 3.35 (s, 2H), 3.94 (s, 2H), 5.99 (dt, *J* = 11.2 and 7.2 Hz, 1H), 6.02 (d, *J* = 1.2 Hz, 1H), 6.44 (d, *J* = 11.2 Hz, 1H), 7.11 (ddd, *J* = 7.6, 6.8, and 0.8 Hz, 1H), 7.16 (ddd, *J* = 7.6, 6.8, and 0.8 Hz, 1H), 7.30 (dd, *J* = 7.6 and 0.8 Hz, 1H), 7.53 (dd, *J* = 7.6 and 0.8 Hz, 1H), 7.81 (broad, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 12.6 (CH_3), 27.5 (CH_2), 29.7 (CH_2), 49.1 (CH_2), 50.9 (CH_2), 60.9 (CH_2), 75.8 (CH), 110.5 (CH), 110.8 (C), 118.5 (CH), 119.6 (CH), 120.0 (CH), 122.0 (CH), 128.7 (C), 133.4 (C), 133.6 (CH), 135.9 (C), 151.1 (C); ESI-HRMS $[M+H]^+$ calcd for $C_{18}H_{22}IN_2$ 393.0822, found 393.0818.

Heck Cyclization of Azocinoindole 7

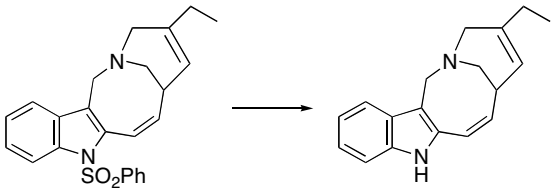


7 **9** (45%)

To a solution of **7** (20 mg, 0.05 mmol) in toluene (4.5 mL) were added under Ar $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol), proton-sponge® (2.1 mg, 0.01 mmol) and K_2CO_3 (10 mg, 0.075 mmol). The solution was heated at reflux for 16 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried and concentrated. The residue was purified by chromatography (SiO_2, from Et_2O to 98:2 Et_2O-diethylamine) to give

tetracycle **9**: 6 mg (45%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 7.6 Hz, 3H), 1.87 (m, 2H), 2.85 (dd, *J* = 12.4 and 5.6 Hz, 1H), 2.87 (broad s, 1H), 3.15 (d, *J* = 17.2 Hz, 1H), 3.35 (d, *J* = 12.4 Hz, 1H), 3.69 (d, *J* = 17.2 Hz, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 5.51 (s, 1H), 5.95 (dd, *J* = 12 and 5.6 Hz, 1H), 6.33 (d, *J* = 12 Hz, 1H), 7.09-7.17 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 8.07 (broad, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 11.8 (CH_3), 28.1 (CH_2), 34.6 (CH), 43.3 (CH_2), 46.2 (CH_2), 54.0 (CH_2), 110.6 (CH), 116.7 (CH), 117.7 (C), 118.6 (CH), 120.0 (CH), 120.7 (CH), 122.2 (CH), 128.2 (C), 135.3 (C), 135.8 (CH), 135.9 (C), 136.5 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}N_2$ 265.1699, found 265.1698.

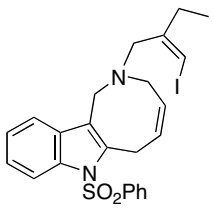
Indole Deprotection of Tetracycle 3



3 **9** (67%)

H_2O (1 mL) and 50% aqueous NaOH solution (1 mL) were added to a solution of tetracycle **3** (18 mg, 0.044 mmol) in a 1:3 mixture of THF-MeOH (6 mL). The mixture was heated at 85 ºC for 3 h and then poured into a saturated aqueous NH_4Cl solution. The organic solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and brine. The organic layer was dried and concentrated and the residue was chromatographed (SiO_2, from Et_2O to 98:2 Et_2O-diethylamine) to give tetracycle **9**: 8 mg (67%).

^{1}H and ^{13}C NMR Spectra



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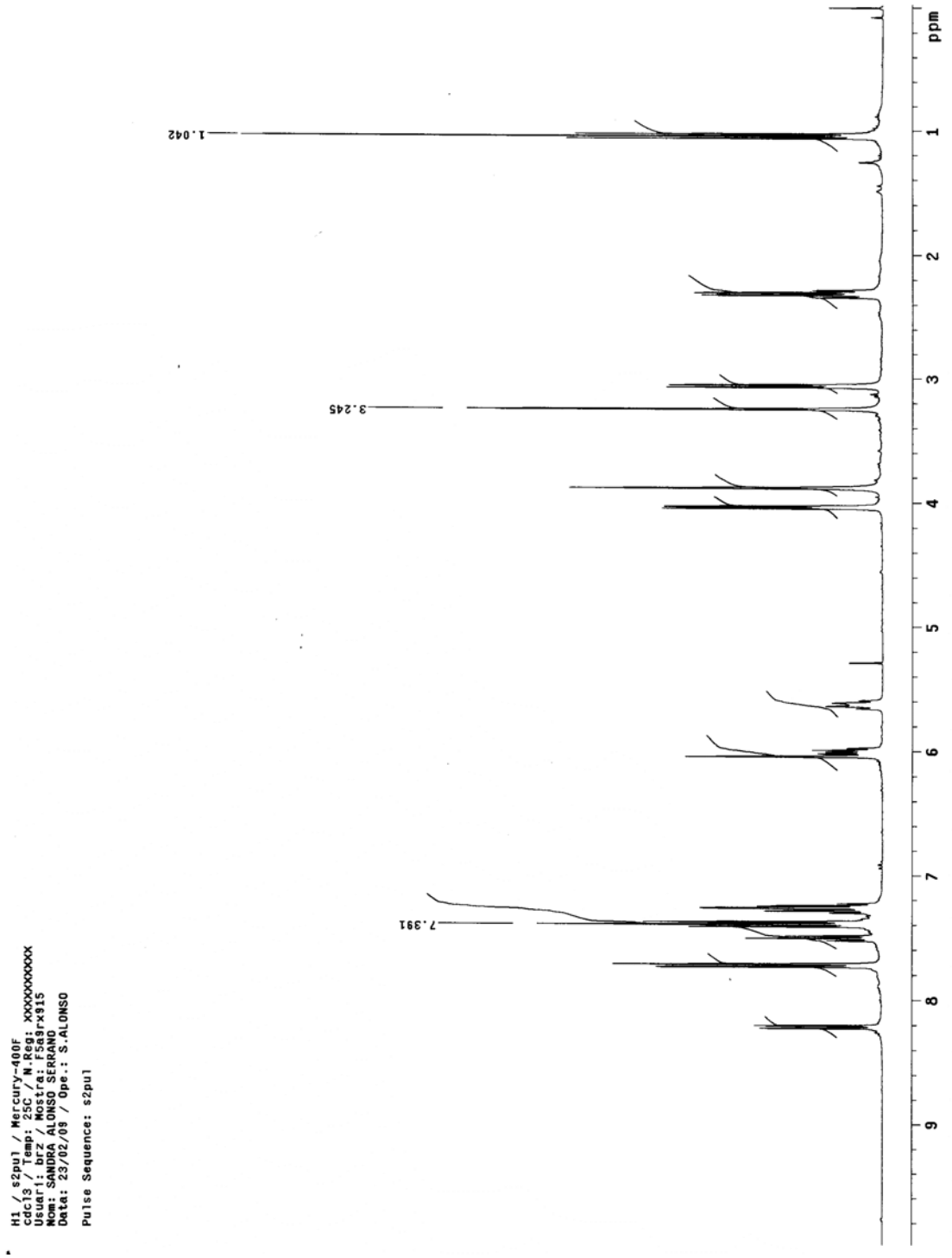

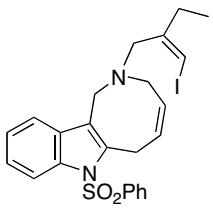
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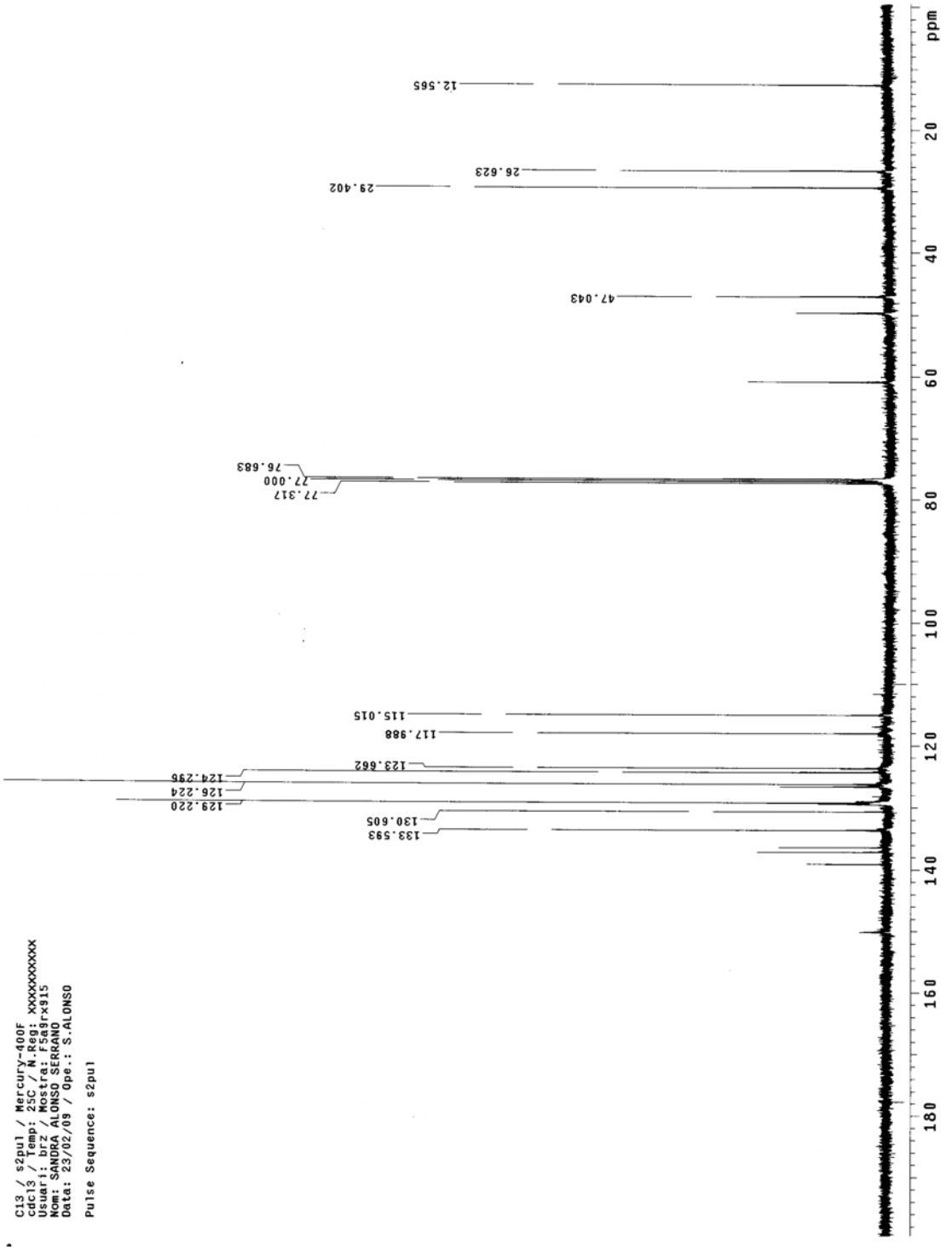
I
N
SO2Ph

2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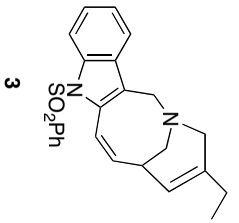
123.662
124.296
126.224
129.220
130.605
133.593
ppm
20
40
60
80
100
120
140
160
180
C13 / s2pul / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: brz / Mostra: F5a9rx915
Nom: SANDRA ALONSO SERRANO
Data: 23/02/09 / Ope.: S.ALONSO
Pulse Sequence: s2pul

H1 / zg/ Bruker DMX500
F11-16-RX931/ 243 K / N reg.:1531_2009
brz / CDCl3/ SAlonso
Data:11/05/09 / Op.: MA Molins
Comprovacio p360 H1
>24.8us >25.2us >26us >26.8 =27.2
p90 (H1)= 6.8us a 0dB a 243K



3

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PROCNO	1
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FIDRES	0.145340 Hz
AQ	3.4402499 sec
RG	64
DW	100.000 usec
DE	6.50 usec
TE	243.1 K
D1	0.20000000 sec
TD0	1
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P1	6.80 usec
PL1	0.00 dB
SFO1	500.1319432 MHz
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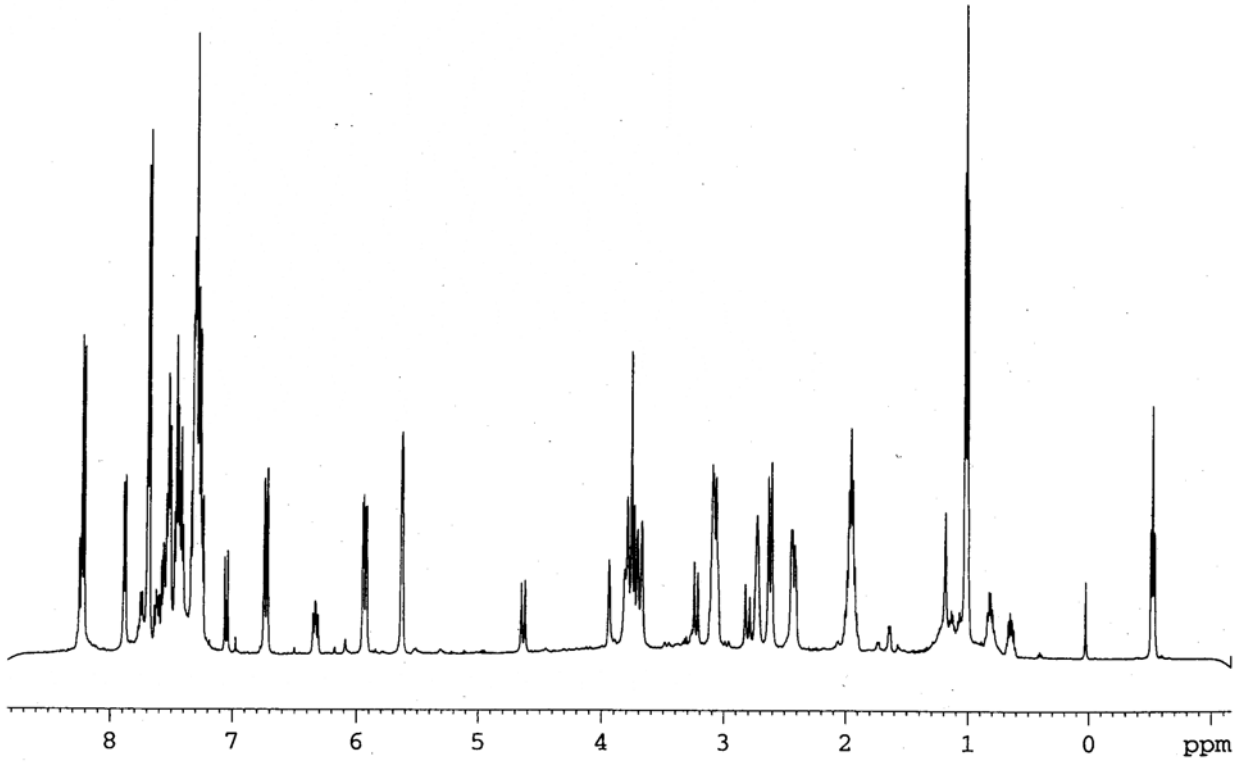
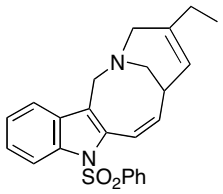
GB	0
PC	0.50

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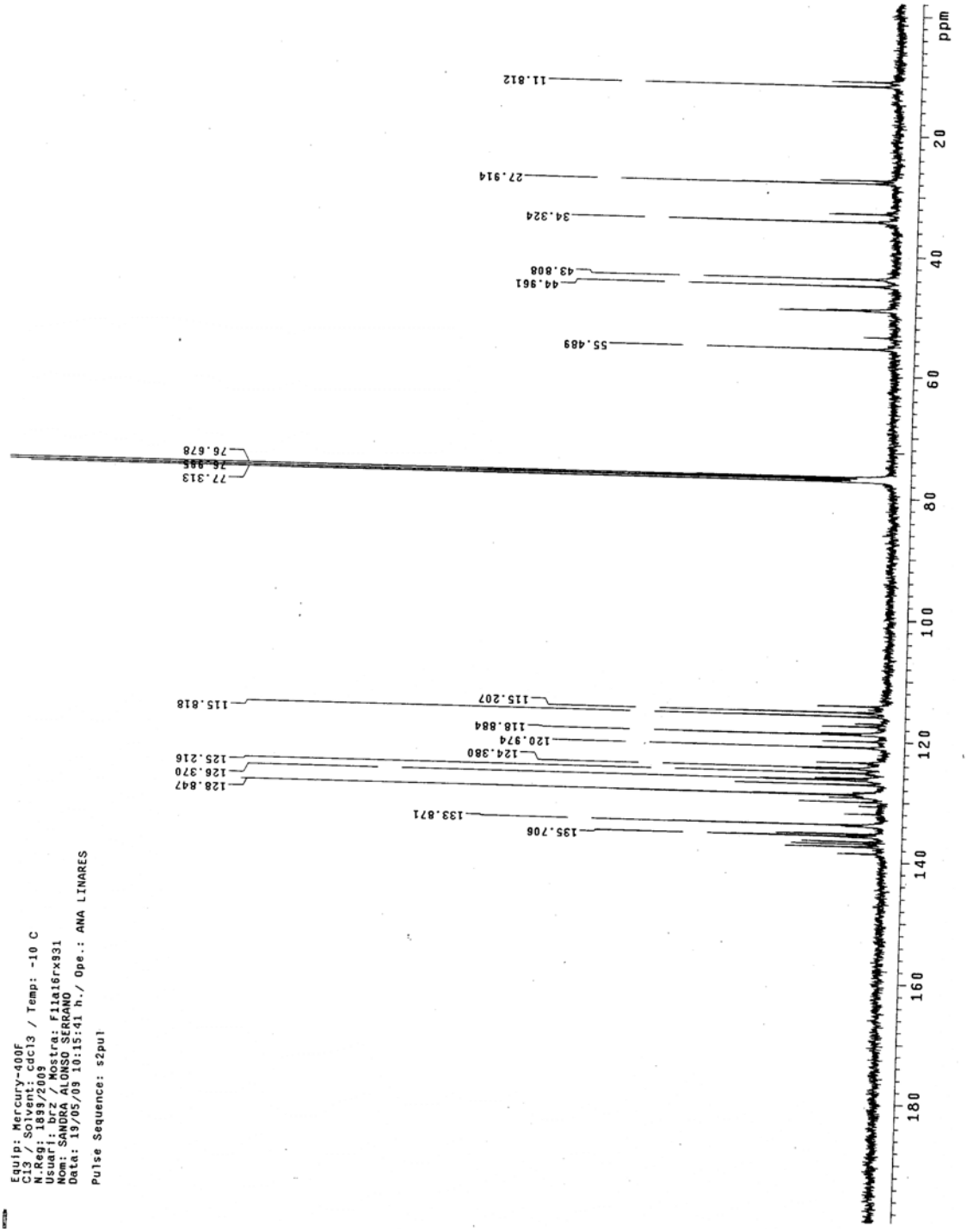
3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133.871
135.706
ppm
20
40
60
80
100
120
140
160
180
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C13 / Solvent: cdcl3 / Temp: -10 C
N.Reg: 1899/2009
Usuari: brz / Mostra: Flia16rx931
Nom: SANDRA ALONSO SERRANO
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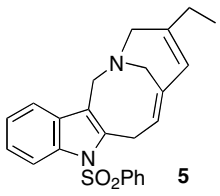
Pulse Sequence: s2pul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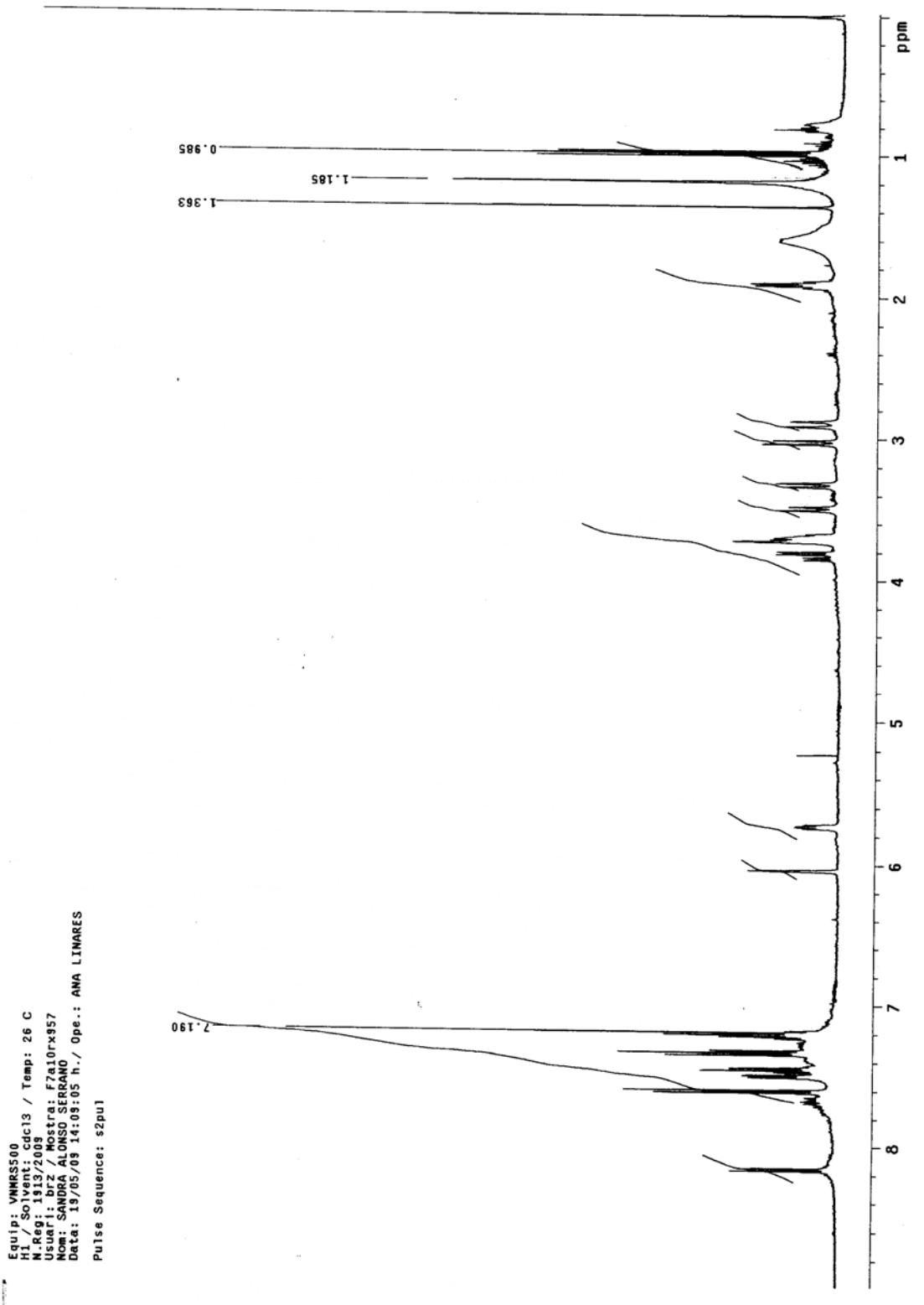
N
SO2Ph

5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H1 / Solvent: cdcl3 / Temp: 26 C
N.Reg: 1913/2009
Usuari: brz / Mostra: F7a10rx957
Nom: SANDRA ALONSO SERRANO
Data: 19/05/09 14:09:05 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
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ppm
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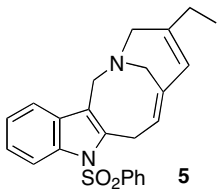
2
3
4
5
6
7
8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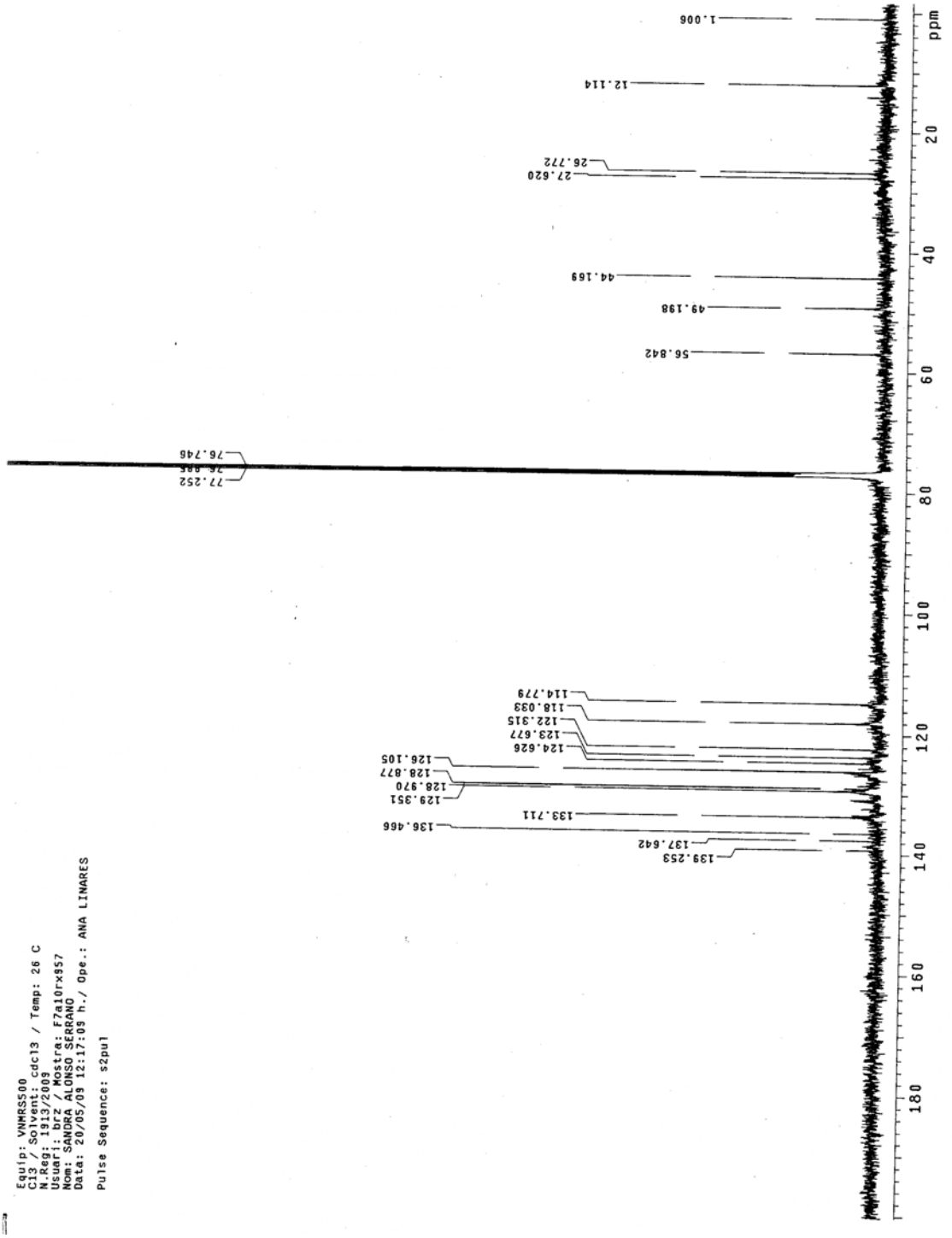
N
SO2Ph

5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C13 / Solvent: cdcl3 / Temp: 26 C
N.Reg: 1913/2009
Usuari: brz / Mostra: F7a10rx957
Nom: SANDRA ALONSO SERRANO
Data: 20/05/09 12:17:09 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
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27.620
44.169
49.138
56.842
76.746
77.252
114.779
118.033
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128.877
128.970
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ppm
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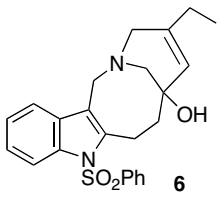
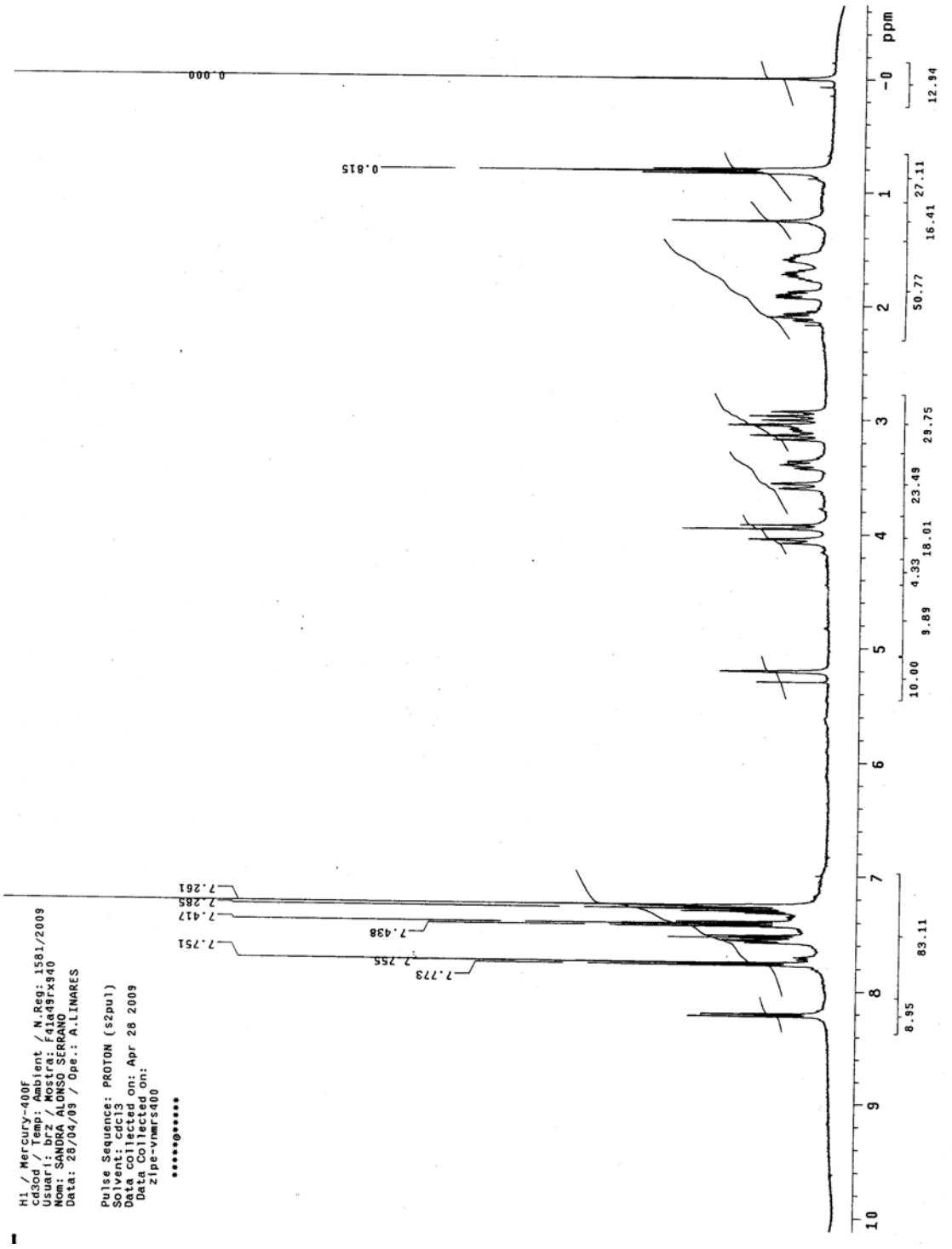
160
140
120
100
80
60
40
20


N
OH
N
SO2Ph

6


H1 / Mercury-400F
cd3od / Temp: Ambient / N.Reg: 1581/2009
Usuari: brz / Mostra: F41a49rx940
Nom: SANDRA ALONSO SERRANO
Data: 28/04/09 / Ope.: A.LINARES
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Apr 28 2009
Data Collected on:
zipe-vnmrs400
0.000
0.815
7.261
7.285
7.417
7.438
7.751
7.755
7.773
ppm
12.94
27.11
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50.77
29.75
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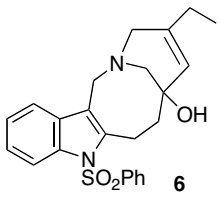
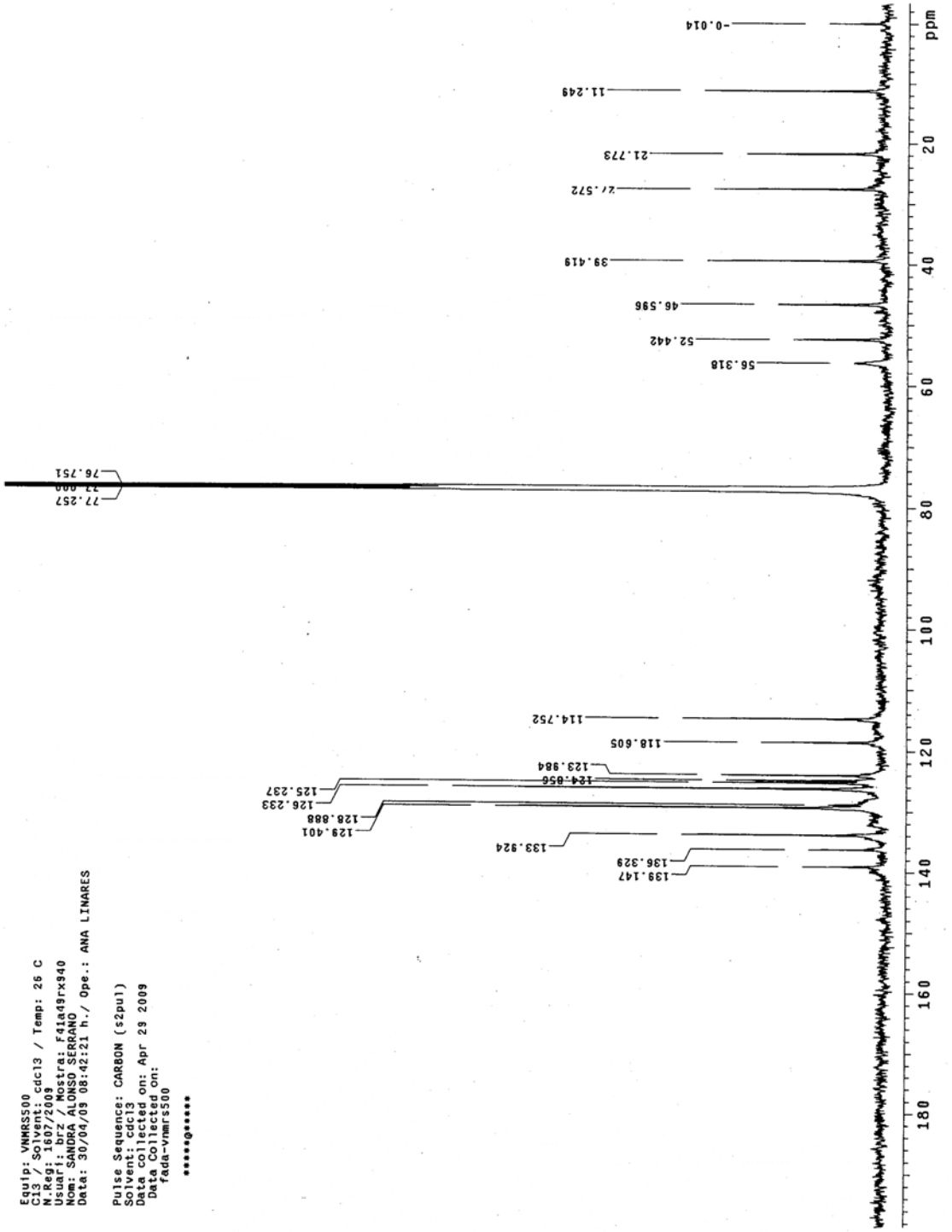
18.01
4.33
9.89
10.00
83.11
8.95


N
OH
N
SO2Ph

6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52.442
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125.237
126.233
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129.401
133.924
136.329
139.147
ppm
20
40
60
80
100
120
140
160
180
Equip: VNMRS500
C13 / Solvent: cdcl3 / Temp: 26 C
N.Regi: 1607/2009
Usuari: brz / Mostra: f41a49rx940
Nom: SANDRA ALONSO SERRANO
Data: 30/04/09 08:42:21 h./ Ope.: ANA LINARES
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Solvent: cdcl3
Data collected on: Apr 29 2009
Data Collected On:
fada-vmrs500
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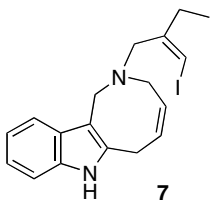
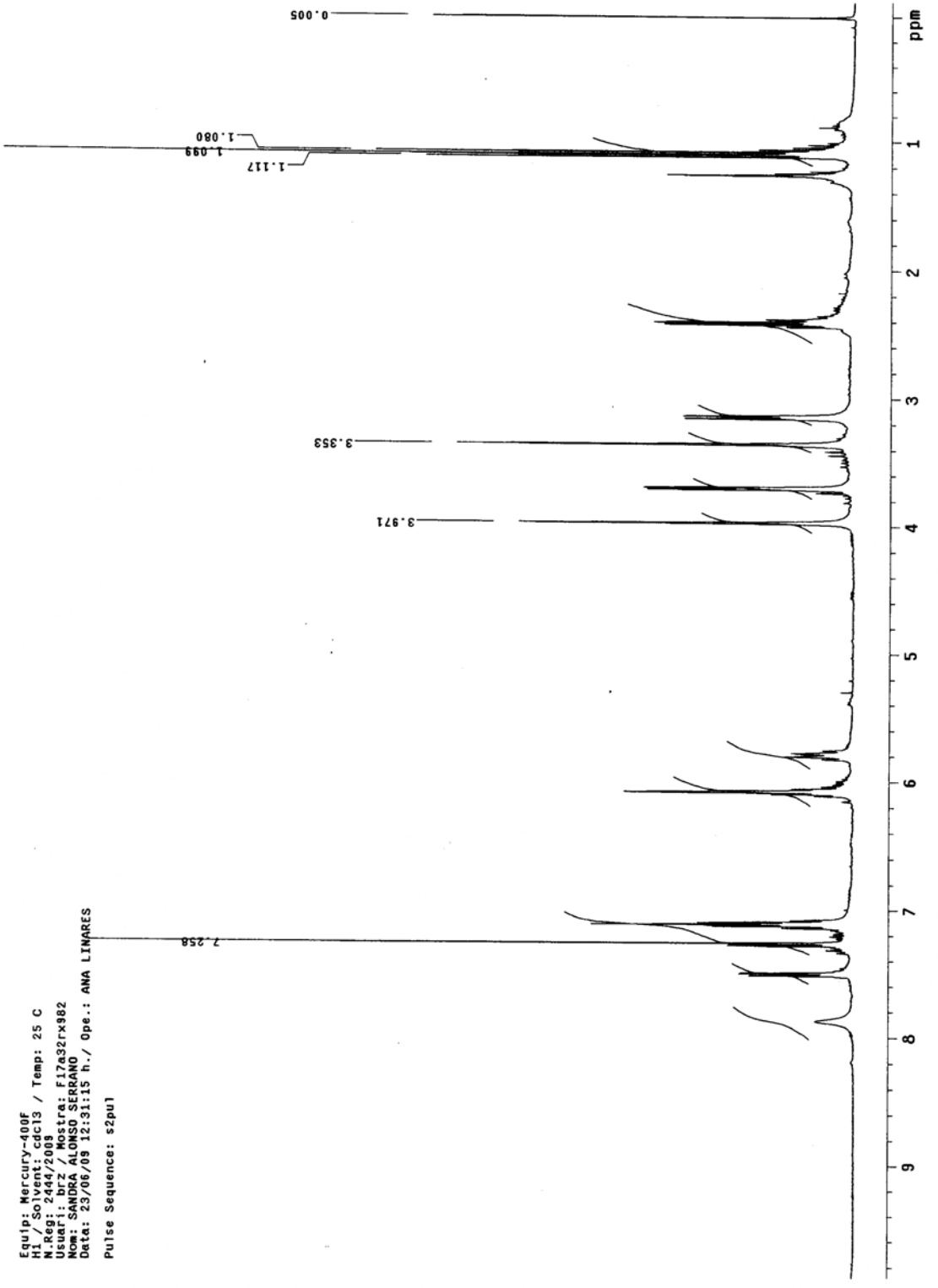

N
I
N
H

7


Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 2444/2009
Usuari: brz / Mostra: F17a32rx982
Nom: SANDRA ALONSO SERRANO
Data: 23/06/09 12:31:15 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
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1.080
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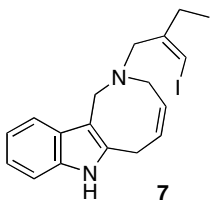
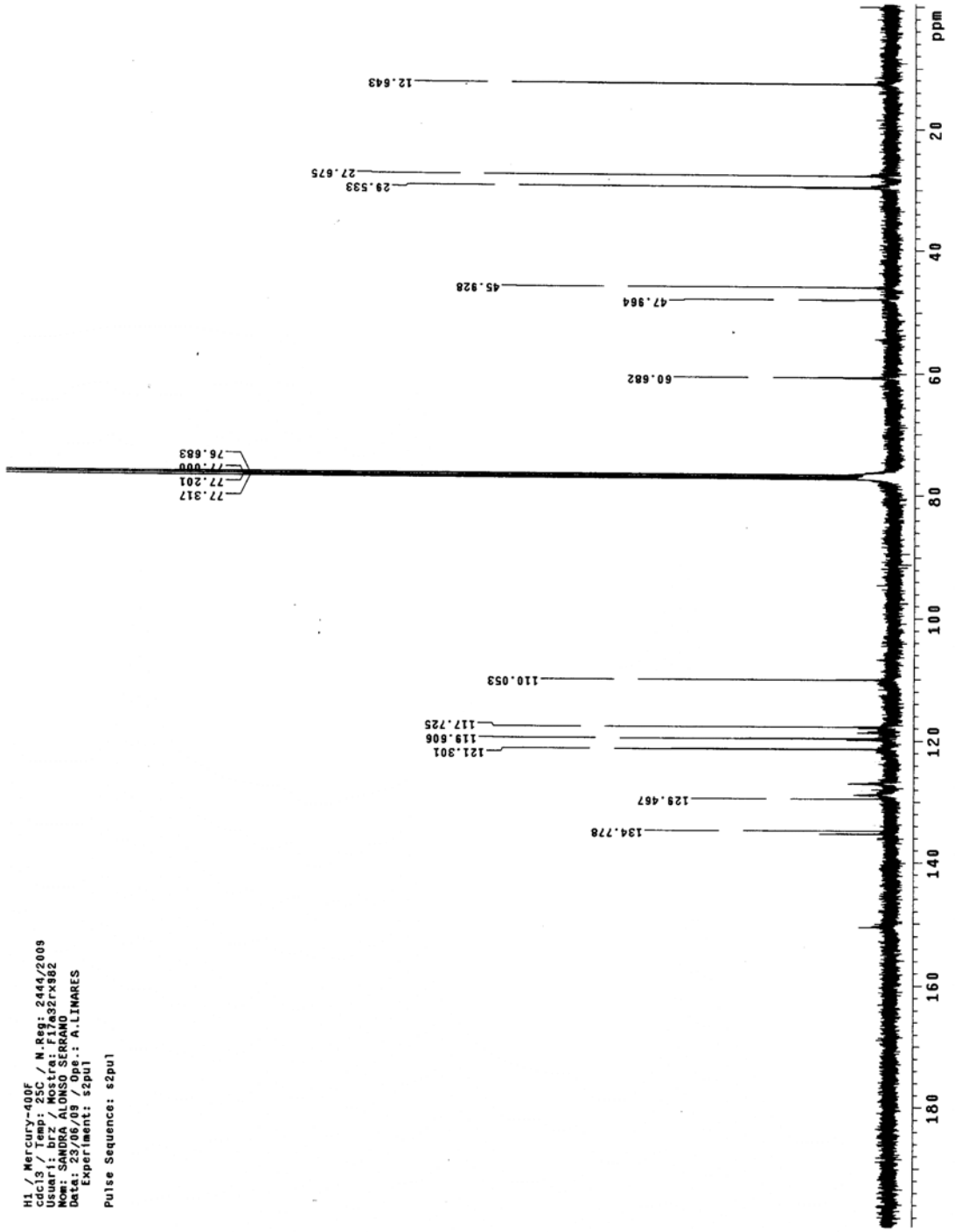
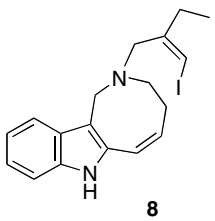
ppm

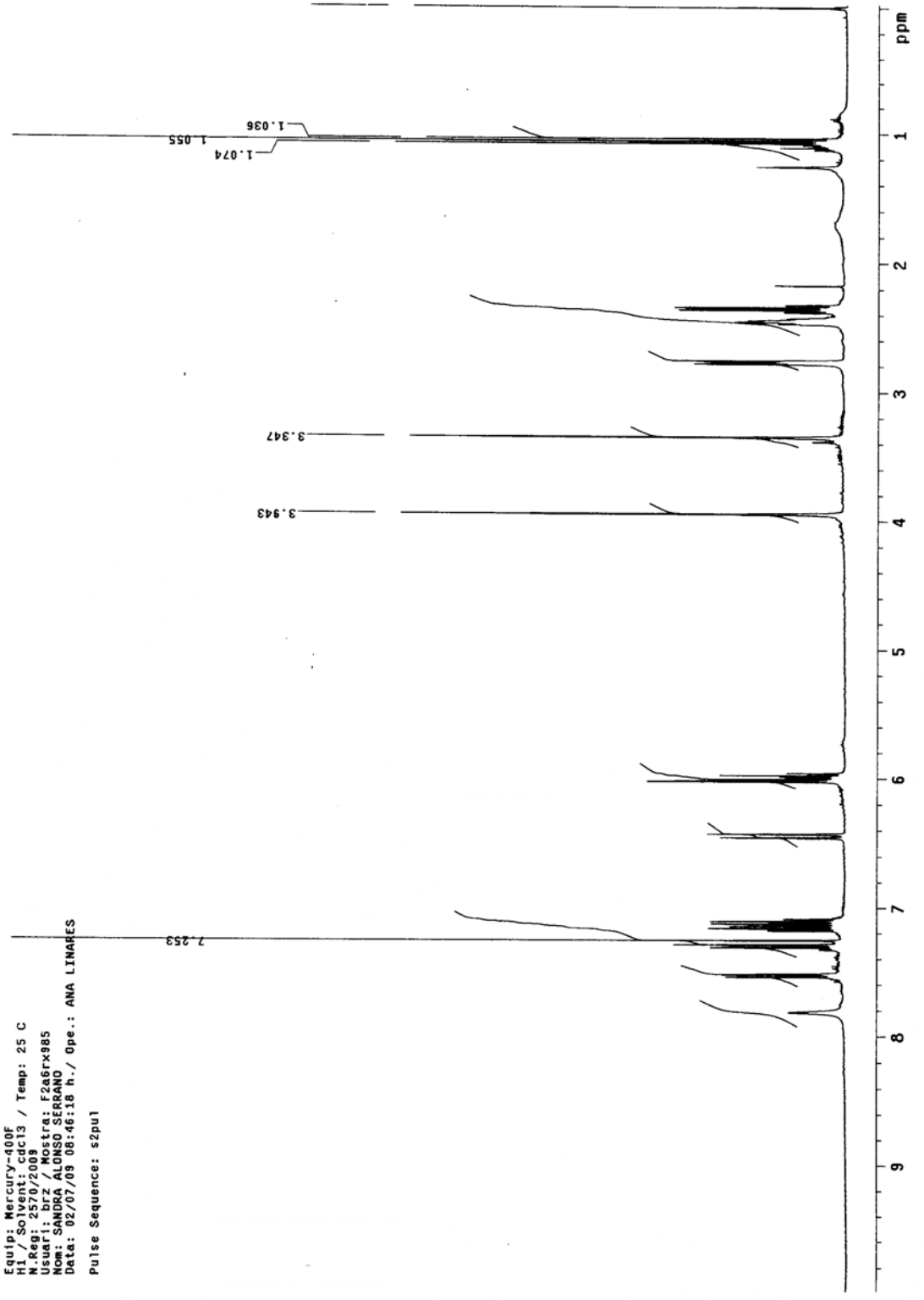

N
I
N
H

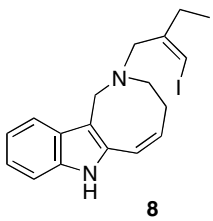
7


12.643
27.675
29.533
45.928
47.864
60.682
76.683
77.000
77.201
77.317
110.053
117.725
119.606
121.301
129.467
134.778
ppm
20
40
60
80
100
120
140
160
180
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: 2444/2009
Usuari: brz / Mostra: F17a32rx982
Nom: SANDRA ALONSO SERRANO
Data: 23/06/09 / Ope.: A.LINARES
Experiment: s2pul
Pulse Sequence: s2pul

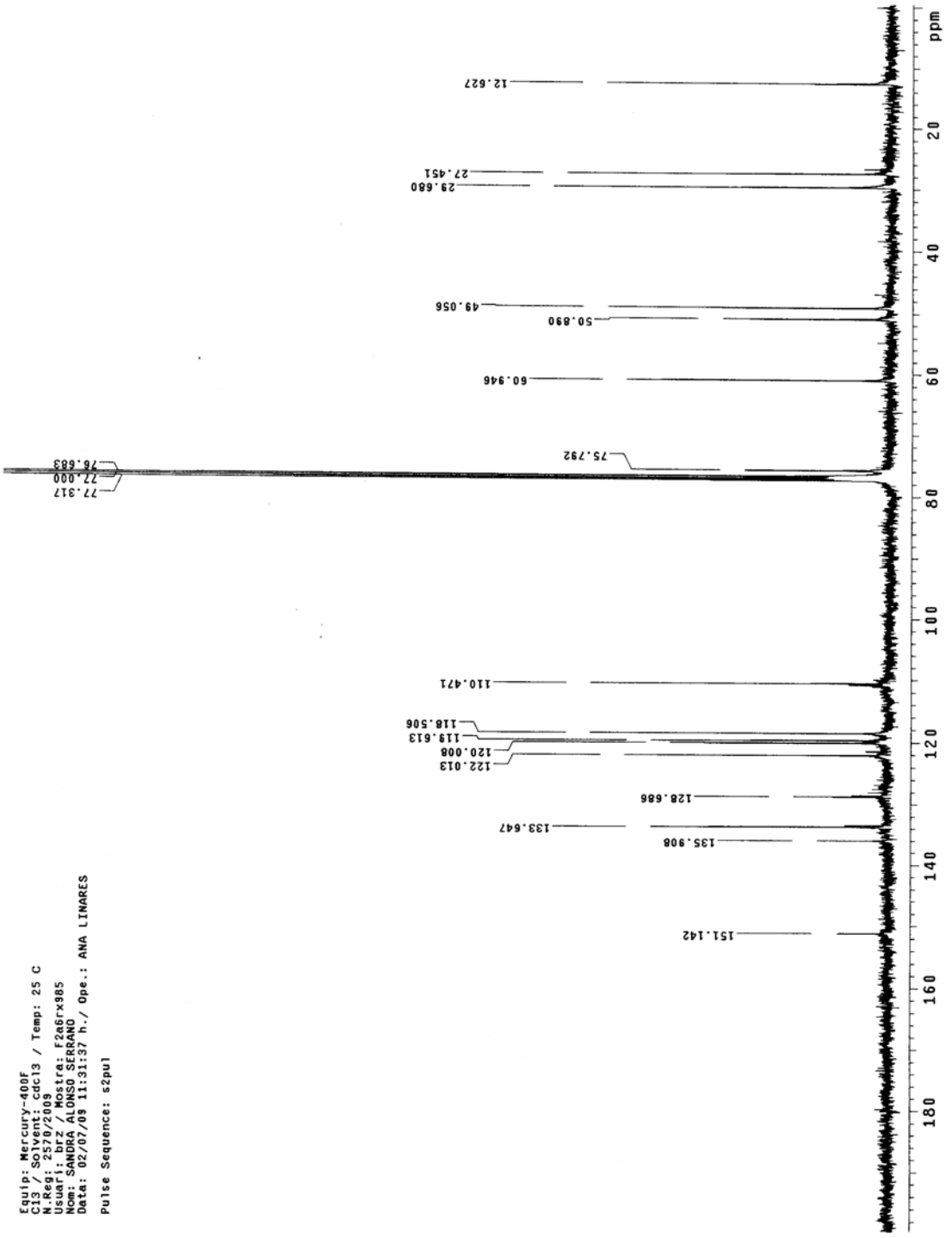

N
I
N
H

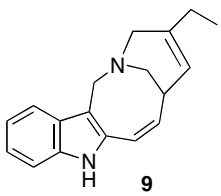
8


1.036
1.055
1.074
3.347
3.943
7.253
ppm
1
2
3
4
5
6
7
8
9
Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 2570/2009
Usuari: brz / Mostra: F2a6rx985
Nom: SANDRA ALONSO SERRANO
Data: 02/07/09 08:46:18 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul

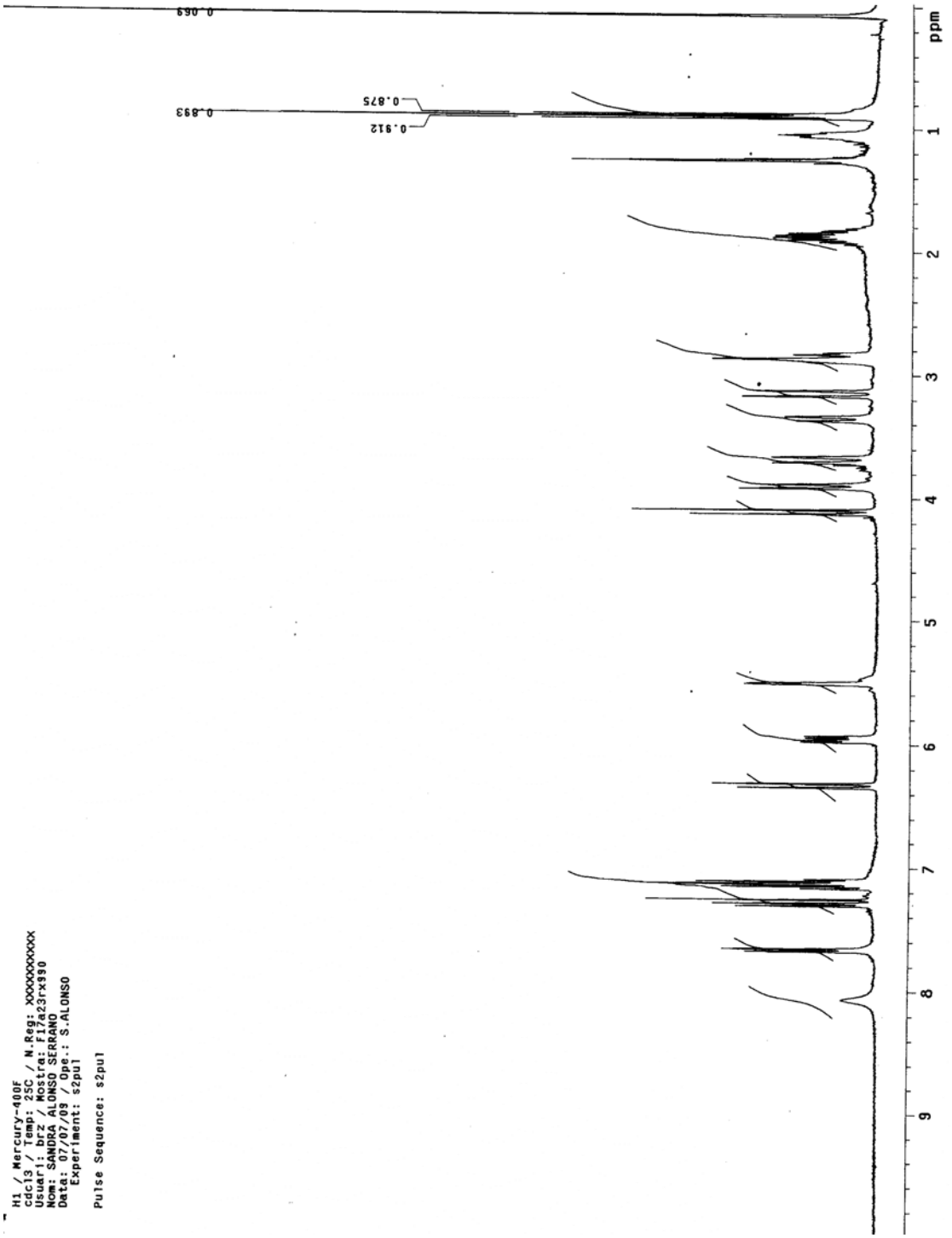

N
I
N
H

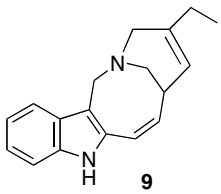
8


Equip: Mercury-400f
C13 / Solvent: cdcl3 / Temp: 25 C
N.Regi: 2570/2008
Usuari: bz / Mostra: f2a6rx985
Nom: SANDRA ALONSO SERRANO
Data: 02/07/09 11:31:37 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
12.627
27.451
29.680
49.056
50.890
60.946
75.792
76.683
77.000
77.317
110.471
118.506
119.613
120.008
122.013
128.686
133.647
135.908
151.142
ppm
20
40
60
80
100
120
140
160
180

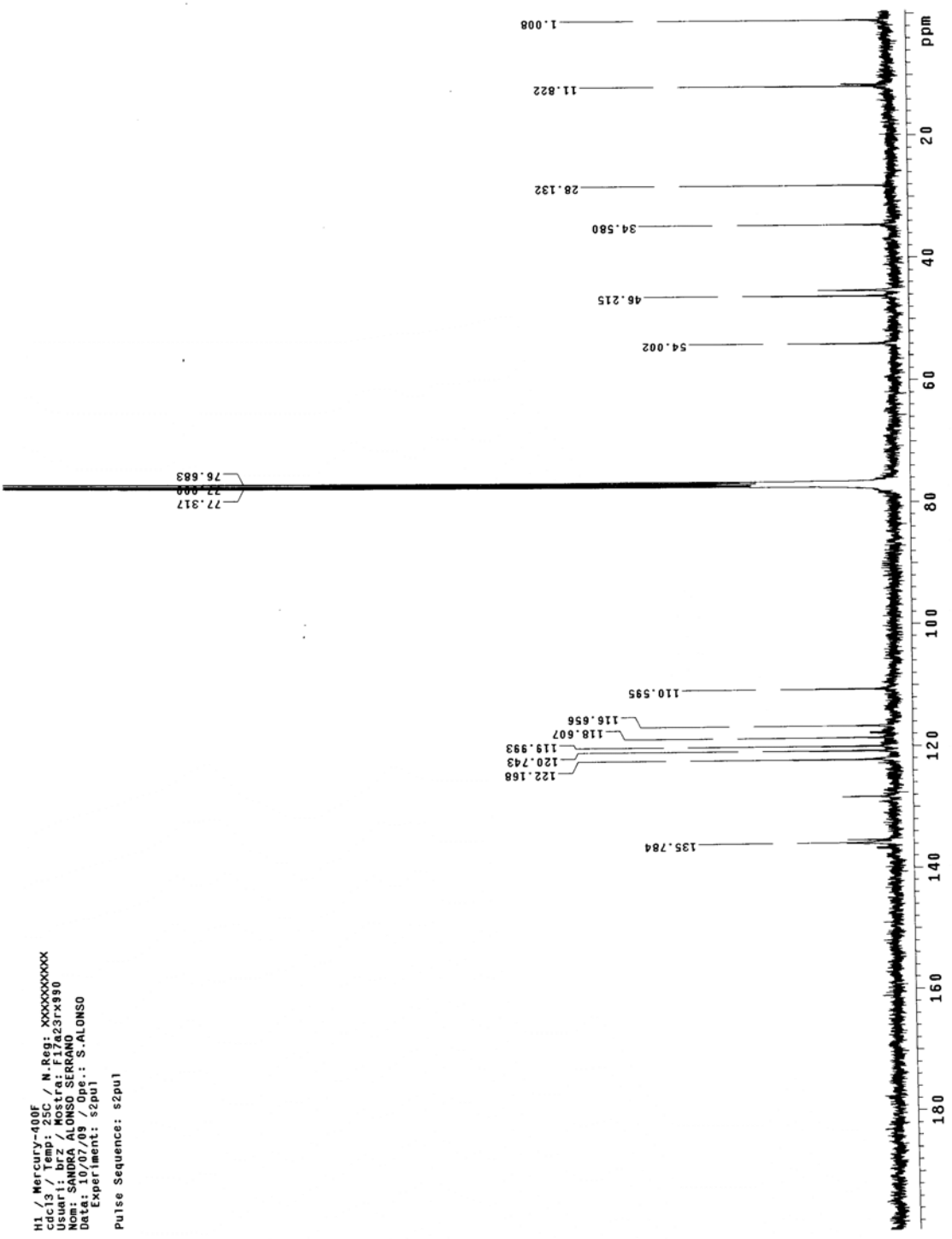


9


0.069
0.893
0.875
0.912
ppm
1
2
3
4
5
6
7
8
9
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: brz / Mostra: F17a23rx990
Nom: SANDRA ALONSO SERRANO
Data: 07/07/09 / Ope.: S.ALONSO
Experiment: s2pul
Pulse Sequence: s2pul



9


1.008
11.822
28.132
34.580
46.215
54.002
76.683
77.000
77.317
110.595
116.656
118.607
119.993
120.743
122.168
135.784
ppm
20
40
60
80
100
120
140
160
180
H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: brz / Nostra: F17a23rx990
Nom: SANDRA ALONSO SERRANO
Date: 10/07/09 / Ops.: S.ALONSO
Experiment: s2pul
Pulse Sequence: s2pul