UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMACOLOGIA I QUÍMICA TERAPÈUTICA

REACCIONS INTRAMOLECULARS DE RADICALS 2-INDOLILACIL: APLICACIÓ A LA SÍNTESI DE COMPOSTOS INDÒLICS

Francesc Ferrando i Ruana

Barcelona, abril de 2006

FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMACOLOGIA I QUÍMICA TERAPÈUTICA

PROGRAMA DE DOCTORAT: QUÍMICA ORGÀNICA I FARMACÈUTICA

BIENNI 2001-2003

REACCIONS INTRAMOLECULARS DE RADICALS 2-INDOLILACIL: APLICACIÓ A LA SÍNTESI DE COMPOSTOS INDÒLICS

Memòria presentada per Francesc Ferrando i Ruana per optar al títol de doctor per la Universitat de Barcelona

Dirigida per:

Dra. Lluïsa Bennasar i Fèlix

Dr. Tomàs Roca i Estrem

Francesc Ferrando i Ruana

Barcelona, abril de 2006

Vull donar gràcies a tots els qui m'heu acompanyat d'una manera o d'una altra durant aquests més de quatre anys. Tots vosaltres, cadascú a la seva manera, m'heu fet créixer com a persona.

Ara penso:

En la Lluïsa Bennasar a qui agraeixo la seva confiança i consell. En el Tomàs Roca, sempre atent a la feina del dia a dia i disposat a ajudar. En el Xavi Urb., perquè qualsevol nit pot sortir el sol. En la Sandra Díaz, gràcies per la teva petjada. En l'Eva Ricou, sempre disposada a acollir. En la Marisa, plena d'iniciativa i vida. En l'Arantxa, gràcies per l'esperança que transmets. En l'Oscar, per la teva bondat i humor. En el Robert, gràcies per com parles i t'expreses. En el Nolo, tot simpatia. En l'Oriol, sempre discret i ferm. En la Faïza, gràcies per les converses entranyables i profundes (seguim buscant!). En la Cris, gràcies per la teva tendresa. En la Mar gràcies per l'abraçada que encara segueix. En la Sandra R., gràcies pel teu silenci i serenitat. En el Lluís, gràcies per les teves llàgrimes. En la Rosa Griera, gràcies per aquelles paraules (em fan feliç). En el Xavi Vila sempre atent i disposat a escoltar. En la Mercè V., gràcies per obrir-me la porta des del primer dia. En la Marta Marfil, perquè segueixin les coincidències. En la Marta Huguet, gràcies pel teu somriure. En l'Abdu, tot humilitat. En la Davinia, gràcies per la teva alegria. En el Ben, ple d'ironia. En el Gorka, segueix amb aquesta empenta. En l'Olga, gràcies per la teva simpatia i escolta atenta. En l'Alex, sempre amb les mans obertes. En la Sara, gràcies per l'energia que dones. En la Neus, plena de vitalitat. En la Maria Bosch, gràcies per la teva ajuda sincera. En la Tania, plena de simpatia. En la Laura Paloma, gràcies per aquesta espontaneïtat. En la Sandra A., gràcies per les converses al final del Lab A. En la Bego, gràcies per punxar-me amb la teva simpatia. En la Maria Santos, sempre atenta i disposada a acollir. En la Núria Ll., maquíssima. En la Danica, per la teva escolta i les estones compartides. En l'Antònia, per les estones de conversa atenta. En el Carlos Ayala, gràcies per la teva fortalesa malgrat les adversitats. En el Carlos, gràcies per acollir-me sempre amb un somriure. En el Guillerm, sempre amb un gest agradable. En la Carme C., per la teva bondat. En la Carmen E., per fer-me despertar quan calia. En la Montse, plena de bondat i servei. En l'Anna L., gràcies per l'atenta bondat. En la Marina, gràcies pel teu ajut. En la Mari, gràcies per rebre'm. En l'Eva, gràcies per l'agradable salutació. En el Dani S., gràcies per les converses sobre llibres i sobre d'altres coses. En la Josefina, gràcies per ser propera i amable. En l'Asensio, gràcies per les converses en busca de sentit. En l'Ester Z., per l'amabilitat atenta. En l'Anna D., gràcies per la teva simpatia i sinceritat. En la Imma, gràcies per la teva mirada agradable. En la Lluïsa P., gràcies per la salutació sincera. En el Josep, gràcies per encaminar-me a Dinamarca. En el Joan, gràcies per l'atenta salutació. En la Merche, gràcies per l'amabilitat. En la Viviane, gràcies per la parla agradable. En el Slavo, sempre tranquil. En el Sven, de tracte agradable. En el Yohann, gràcies per acceptar la invitació. En l'Aureliant, per les ganes de conèixer. En la Nana, gràcies per la simpatia de cor. En la Luisa, pel "buenos días" de cada dia. En la Georgeta, sempre rient. En la Laia, per la simpàtica timidesa. En la Marta, per la simpàtica rialla. En l'Ariadna, pel seu rigor en la feina. En l'Eduard, sempre amb pressa. En la Isabel, sempre apunt per saludar. En la Eli, gràcies

pel silenci. En el Dani, gràcies per les ganes de participar. En la Marta Ecija, gràcies per recordar-me Tarragona. En el Josep Mª, amb un somriure espectant. En la Núria C., gràcies pel misteri. En l'Ermitas, gràcies pel somriure amb paraules. En la Nati, gràcies per la salutació oberta. En el Sergio C., per encaminar-me a Barcelona.

En el Xavi Formosa, gràcies per estar sempre aquí, al costat (pels Arubes). En la Laura S., gràcies per les ganes de viure. En l'Elena, gràcies per l'entranyable energia. En el Jose, gràcies per la bondat i els comentaris sorprenents. En la Rosa, gràcies per l'acollida incondicional. En l'Eva, gràcies pel teu rigor serè. En la Loli, gràcies pel teu somriure simpàtic. En el Carles Ayats, pel perdó. En la Ivana, per la búsqueda. En el Xavi B., gràcies pel teu camí. En el Jordi T., gràcies per l'acollida elegant. En el Carles G., gràcies per les ganes de ser. En la Núria, gràcies per la dolça bondat. En la Paramjit, gràcies pel diàleg. En el Santi, gràcies per remoure'm si cal. En el Diego, gràcies pel rigor bondadós. En la Manolita, per l'instint maternal. En el Pelayo, gràcies per la salutació constant. En el Javier, per la rebuda atenta.

En el Troels S., l'Anders, el Kasper, la Sine, la Signe, el Rolf, la Tina, la Heidi, la Lavinia, la Maria, la Lisbeth, el Karl, la Marie Louise, el Jakob, la Laura, la Lone, l'Anna Mette, la Mette, el JP, gràcies a tots. M'heu fet sentir Dinamarca com la meva segona casa. En l'Oscar López., gràcies per la teva bondat i l'exemple de treball. En el Fernando, gràcies per l'humor. En l'Aitor, per saber-se-les totes. En tothom qui vaig conèixer aquells mesos.

En els que vam fer el curs de danès. En els amics de Tarragona. En el Jordi P. i la Paloma, us tinc com a exemple. En el Josep Mª, sempre buscant l'estiu. En la Marta Cabré, gràcies per l'acollida. En la Tere, gràcies per l'equilibri. En la Margarita i la Montse pels esmorzars i "l'embolcall". En tots els qui em deixo per anomenar i que hem coincidit en el Camí.

Finalment, vull donar gràcies als meus pares (Ramon i Montse) i a la meva germana (Núria) pel suport i l'estimació que em doneu sempre i que han fet possible que arribés aquí. Gràcies també a tota la resta de la família, us porto dins meu.

Francesc Ferrando i Ruana

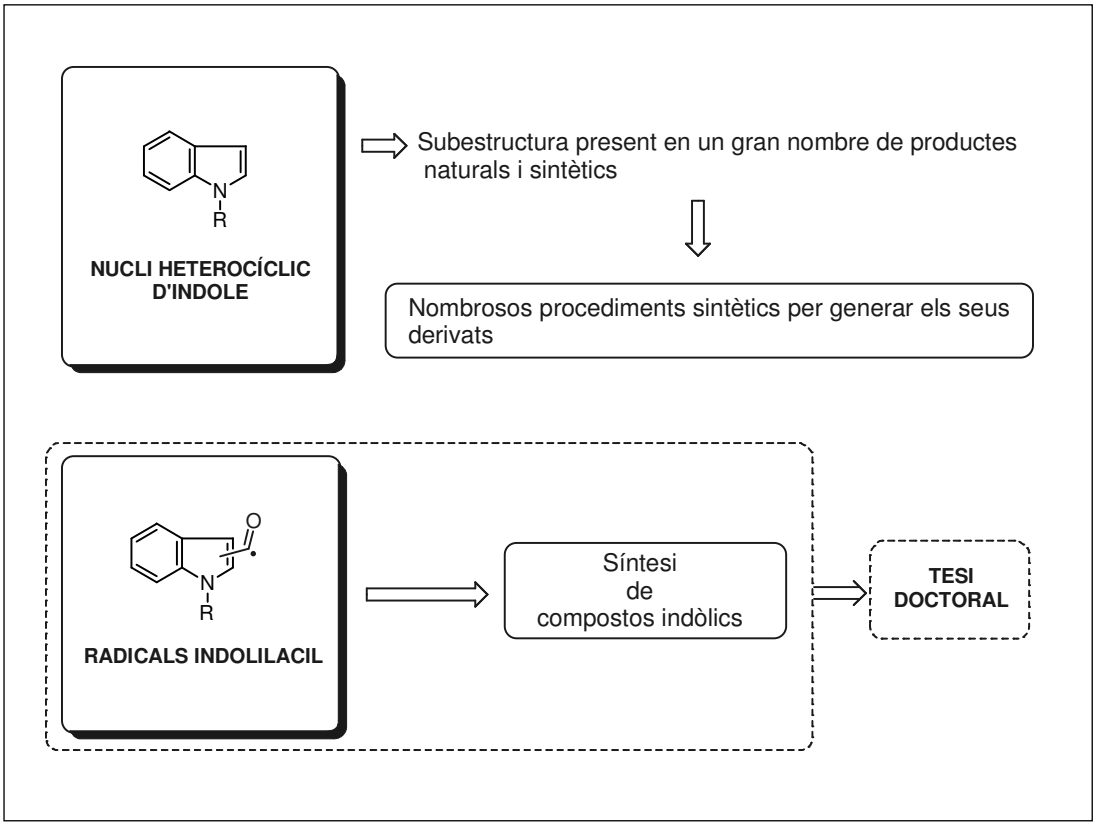
Barcelona, 18 de Maig de 2006

La present Tesi Doctoral ha estat possible gràcies a la concessió d'una beca pre-doctoral de Formació en la Recerca i la Docència, concedida per la Universitat de Barcelona.
D'altra banda, el treball d'investigació ha estat finançat pel Ministerio de Educación y Ciencia (projectes BQU 2000-0785 i BQU2003-04967).

La Memòria d'aquesta Tesi Doctoral es presenta com a *Compendi de publicacions*, en estar ja publicats els resultats que es descriuen. D'acord amb la normativa vigent, després de l'apartat d'*Introducció* es presenta un *Resum global* dels resultats obtinguts amb la seva discussió, agrupats en cinc subapartats que corresponen a les cinc publicacions aparegudes.

Després d'un apartat de *Conclusions*, s'inclou com a *Annex*, la còpia completa dels treballs.

1. INTRODUCCIÓ I OBJECTIUS



Els sistemes heterocíclics són considerats freqüentment subestructures *privilegiades*[1] des del punt de vista de la Química Mèdica, donada la seva capacitat d'unió a una gran varietat de receptors amb elevada afinitat. Això és particularment cert en el cas de l'indole, un nucli present en molts productes bioactius tant naturals com sintètics.[2] La ubiquïtat de l'indole a la natura és fonamentalment conseqüència de la seva presència a l'aminoàcid triptòfan, del qual en deriven molts productes rellevants com ara el alcaloides indòlics.[3] Per tots aquests motius, si bé es coneixen des del punt de vista sintètic nombrosos procediments per generar derivats de l'indole,[2,4] el desenvolupament de nous mètodes que permetin modificar els seu patró de substitució continua sent d'interès. El nostre grup de recerca centra des de fa uns anys els seus esforços en desenvolupar les possibilitats que ofereixen les reaccions dels radicals 2- i 3-indolilacil en la síntesi de compostos indòlics de diferent complexitat. La present Tesi Doctoral s'inclou en aquest context.

[1] (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930. (b) Vegeu també: (b) Schnur, D. M.; Hermsmeier, M. A.; Tebben, A. J. *J. Med. Chem.* **2006**, *49*, 2000-2009.

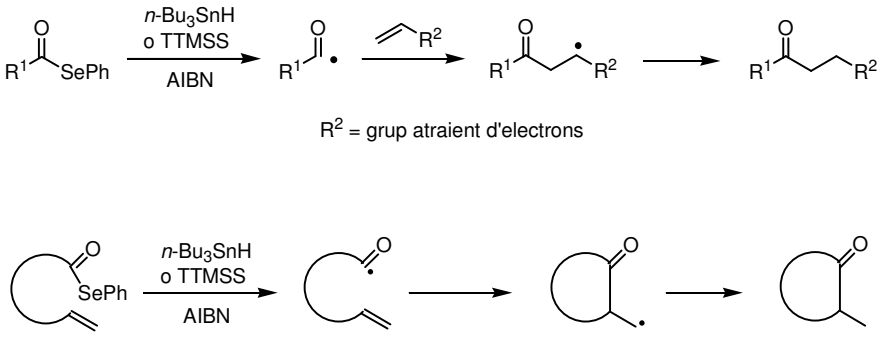
[2] (a) Sundberg, R. J. *Indoles*; Academic Press: New York, **1996**. (b) Joule, J. A. *Science of Synthesis* (*Houben-Weyl, Methods of Molecular Transformations*); Georg Thieme Verlag: Stuttgart, **2000**; Vol. 10, pp 361-652.

[3] Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73-103 i 761-793 i articles precedents de la mateixa sèrie.

[4] Per a revisions recents, vegeu: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873-2920. (b) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583-593.

Antecedents

Radicals acil: addició a enllaços múltiples



Les reaccions radicalàries han esdevingut unes eines imprescindibles en Síntesi Orgànica i constitueixen freqüentment les etapes clau en la síntesi de productes naturals complexos.[5] En particular, l'ús de radicals intrínsecament funcionalitzats com ara els radicals acil[6] en reaccions d'addició a enllaços múltiples carboni-carboni és un mètode útil per a la síntesi de cetones. La reacció de selenoèsters amb hidrur de tributilestany (*n*-Bu_3SnH) o tris(trimetilsilil)silà (TTMSS), en presència d'azo-bis(isobutironitril) (AIBN) o altres azo compostos com a iniciadors (condicions reductores), és una de les vies més pràctiques per a la generació d'aquests intermedis, encara que també es poden emprar altres protocols.[7]

Els radicals acil presenten propietats nucleòfiles[8] i, per tant, els anomenats efectes polars són especialment importants en les reaccions intermoleculars, les quals usualment només són productives quan l'enllaç múltiple acceptor està substituït per grups atraients d'electrons. La versió intramolecular, menys subjecte a aquest tipus de requeriment electrònic, s'ha emprat per a la

construcció d'una gran varietat d'estructures cícliques carboníliques, tant carbo-[5,6,9] com heterocícliques.[10]

[5] (a) Curran, D. P. En *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; vol. 4, pp. 715-777 i 779-831. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React*. **1996**, *48*, 301-856. (c) *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., eds; Wiley-VCH: Weinheim, 2001.

[6] (a) Ryu, I.; Sonoda, N.; Curran D. P. *Chem. Rev*. **1996**, *96*, 177-194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991-2069.

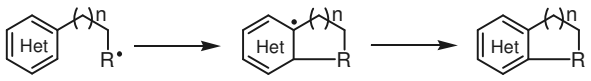
[7] Per a exemples de la generació de radicals acil a partir d'èsters de tiol, vegeu: (a) Crich, D.; Yao, Q. *J. Org. Chem*. **1996**, *61*, 3566-3570. (b) Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem*. **2003**, *68*, 4586-4589. (c) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett*. **2003**, *5*, 1313-1316. (d) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem*. **2006**, *71*, 000. A partir d'acilhidrazides, vegeu: (d) Braslau, R.; Anderson, M. O.; Rivera, F.; Jiménez, A.; Haddad, T.; Axon, J. R. *Tetrahedron* **2002**, *58*, 5513-5523. (e) Bath, S.; Laso, N. M.; López-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun*. **2003**, 204-205.

[8] Per a una discusió, vegeu: Daasbjerg, K.; Pedersen, S. U.; Kund, H. En *General Aspects of the Chemistry of Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, UK, **1999**; pp 385-427.

[9] Vegeu, entre d'altres: (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem*. **1992**, *57*, 1429-1443. Per a un exemple més recent, vegeu: (b) Wong, L. S.-M.; Sherburn, M. S. *Org. Lett.* **2003**, *5*, 3603-3606.

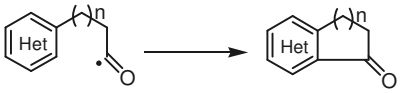
[10] Per a revisions específiques, vegeu: (a) Zhang, W. *Tetrahedron* **2001**, *57*, 7237-7262. (b) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747-2762. (c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377-10441. (d) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603-10642.

Reaccions intramoleculars amb sistemes aromàtics



Radicals aril o alquil

Het = Azoles
Indoles
Piridines
Quinolines



ACILACIÓ HOMOLÍTICA

D'altra banda, les reaccions intramoleculars de radicals amb sistemes aromàtics han rebut una considerable atenció sintètica per a la construcció de compostos policíclics complexes.[11] Generalment són processos de substitució homolítica aromàtica, és a dir, els productes obtinguts són completament aromàtics després de l'oxidació *in situ* dels radicals tipus ciclohexadienil formats. Aquesta oxidació té lloc fins i tot en condicions aparentment reductores (*n*-Bu_3SnH-AIBN), les quals són les emprades majoritàriament quan es treballa amb radicals nucleòfils. La natura exacta de l'agent oxidant i el mecanisme per el qual té lloc aquesta oxidació són actualment motiu de controvèrsia, encara que les evidències més recents apunten al paper preponderant de l'iniciador en el procés oxidatiu.[12]

Es coneixen exemples de ciclacions de radicals aril i, en menor extensió, alquil sobre arens[11,13] i nuclis heteroaromàtics, com ara azoles o altres heterocicles pentagonals,[14] indoles,[15,16] piridines[17] i quinolines.[18] No obstant això, els procesos similars en els quals intervenen radicals acil, és a dir, procesos d'acilació homolítica, han estat comparativament molt menys estudiats.[19]

[11] Studer, A.; Bossart, M. En *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., eds; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62-80.

[12] (a) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765-2770. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed*. **2004**, *43*, 95-98, i referències citades.

[13] Referències recents: (a) Fiumana, A.; Jones, K. *Tetrahedron Lett*. **2000**, *41*, 4209-4211. (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed*. **2000**, *39*, 731-733. (c) Harrowven, D. C.; L'Helias, N.; Moseley, J. D.; Blumire, N. J.; Flanagan, S. R. *Chem. Commun*. **2003**, 2658-2659.

[14] (a) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111-8128. (b) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453-1464. (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2002**, *43*, 4191-4193. (d) Gagosz, F.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 4345-4348. (e) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689-2696. (f) Crich, D.; Patel, M. *Org. Lett*. **2005**, *7*, 3625-3628.

[15] (a) Kraus, G. A.; Kim, H. *Synth. Commun*. **1993**, *23*, 55-64. (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem*. **1994**, *59*, 2456-2466. (c) Wang, S.-F.; Chuang, C.-P. *Tetrahedron Lett*. **1997**, *38*, 7597-7598. (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2639-2643. (e) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465-473. (f) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem*. **2004**, *69*, 4001-4004.

[16] Obtenció de dihidroderivats de l'indole: (a) Ziegler, F. E. Jeroncic, L. O. *J. Org. Chem*. **1991**, *56*, 3479-3486. (b) Gribble, G. W.; Fraser, H. L.; Badenock J. C. *Chem. Commun.* **2001**, 805-806. (c) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett*. **2003**, *44*, 1795-1798.

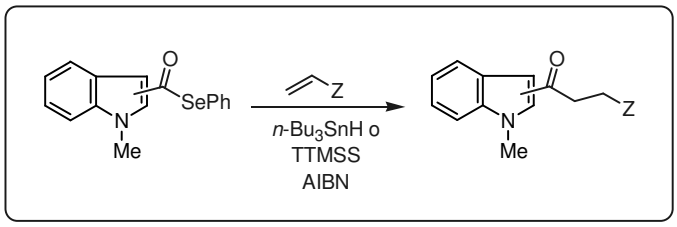
[17] (a) Harrowven, D. C.; Sutton, B. J. En *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2004; Vol. 16, pp. 27-53. (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett*. **2004**, *6*, 3671-3674. (c) Crich, D.; Patel, M. *Heterocycles* **2004**, *64*, 499-504. (d) Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217-6224. (e) Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem*. **2005**, *70*, 10615-10618. (f) Storey, J. M. D.; Ladwa, M. M. *Tetrahedron Lett*. **2006**, *47*, 381-383.

[18] (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*. **2001**, *42*, 2907-2910. (b) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387-3400.

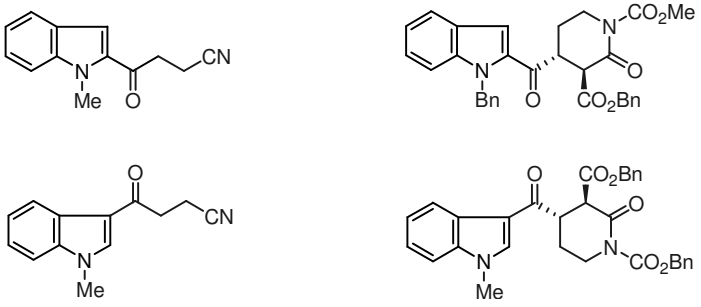
[19] *Sobre arens*: (a) Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett*. **2000**, *41*, 9667-9671, i referències citades. (b) *Sobre indoles*: Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett*. **1999**, *40*, 7153-7157. *Sobre azoles*: (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2001**, *42*, 7887-7890.

Objectius de la Tesi Doctoral

Reaccions intermoleculars dels radicals 2- i 3-indolilacil



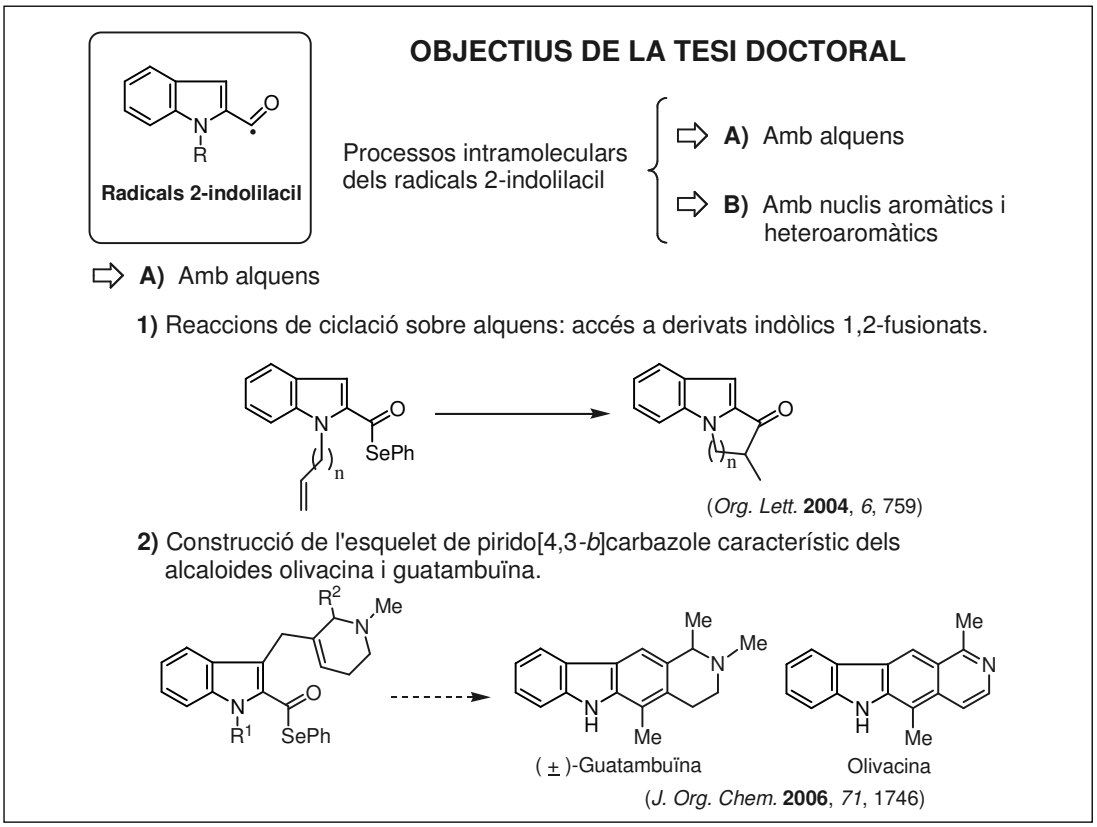
Org. Lett. **2001**, *3*, 1687
J. Org. Chem. **2002**, *67*, 6268



Amb la intenció de desenvolupar una metodologia sintètica vàlida per a la síntesi de compostos indòlics, el nostre grup de treball ha descrit la generació de radicals 2-[20] i 3-indolilacil[21] a partir dels corresponents fenil selenoèsters en condicions reductores (*n*-Bu_3SnH o TTMSS, AIBN) i l'abast de la seva participació en reaccions intermoleculars d'addició a alquens. A la figura es representen alguns dels compostos 2- i 3-acilindòlics sintetitzats emprant acceptors de diferent complexitat.

[20] (a) Bennasar, M.-L.; Roca, T.; Griera, R.; M.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697-1700. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; M.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547-7551.

[21] Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268-6271.



En aquesta Tesi Doctoral ens proposàrem avaluar les possibilitats sintètiques dels radicals 2-indolilacil en processos intramoleculars, emprant com a acceptors tant alquens com nuclis aromàtics o heteroaromàtics.

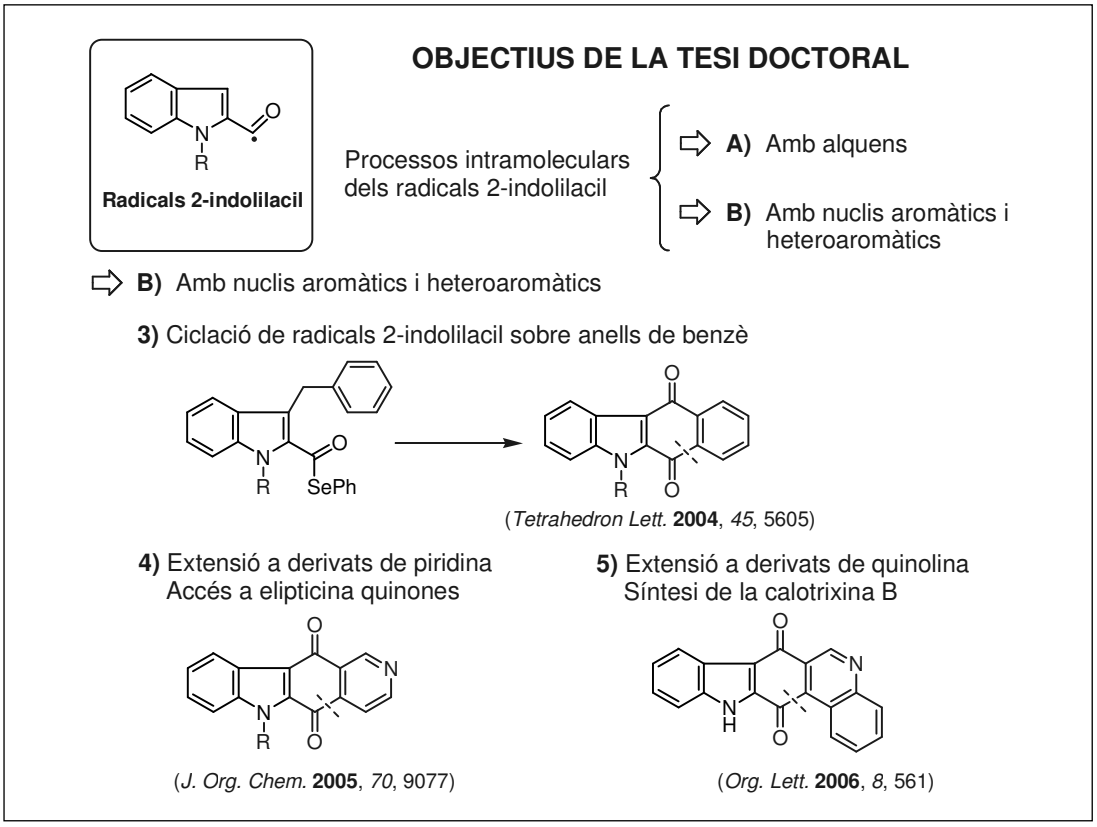
En el primer cas, els objectius concrets han estat:

1) Estudi general de l'abast i les limitacions de les reaccions de ciclació d'aquests intermedis sobre alquens en condicions reductores. Degut a la major accessibilitat dels productes de partida, en aquest estudi s'han emprat substrats en els quals l'acceptor radicalari estava unit al nitrogen de l'indole, possibilitant-se així l'accés a derivats indòlics 1,2-fusionats.

(Resultats publicats a: *Org. Lett*. **2004**, *6*, 759-762)

2) Desenvolupament d'una aplicació sintètica concreta: la construcció de l'esquelet de pirido[4,3-*b*]carbazole característic dels alcaloides olivacina i guatambuïna per ciclació de radicals 2-indolilacil sobre dobles enllaços inclosos en un anell de tetrahidropiridina.

(Resultats publicats a: *J. Org. Chem*. **2006**, *71*, 1746-1749)



En el segon cas, els objectius concrets han estat:

3) Estudi del comportament dels radicals 2-indolilacil en processos de ciclació sobre anells de benzè situats en cadenes unides a la posició 1 o bé a la posició 3 del nucli indòlic.

(Resultats publicats a: *Tetrahedron Lett*. **2004**, *45*, 5605-5609)

4) i 5) Extensió de les anteriors ciclacions a derivats de piridina i quinolina, la qual cosa ha permès desenvolupar una entrada sintètica a elipticina quinones i portar a terme una síntesi de l'alcaloide calotrixina B, respectivament.

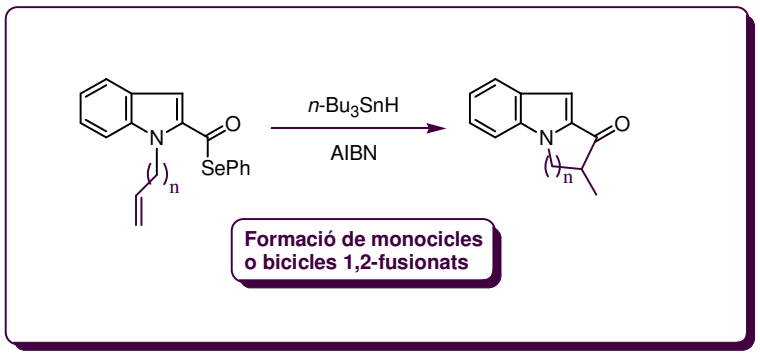
(Resultats publicats a: *J. Org. Chem*. **2005**, *70*, 9077-9080 i *Org. Lett*. **2006**, *8*, 561-564)

2. RESUM DE LES PUBLICACIONS

2.1. REACCIONS INTRAMOLECULARS DE RADICALS 2-INDOLILACIL: ACCÉS A DERIVATS INDÒLICS 1,2-FUSIONATS

(*Org. Lett.* **2004**, *6*, 759-762)

Reaccions intramoleculars de radicals 2-indolilacil

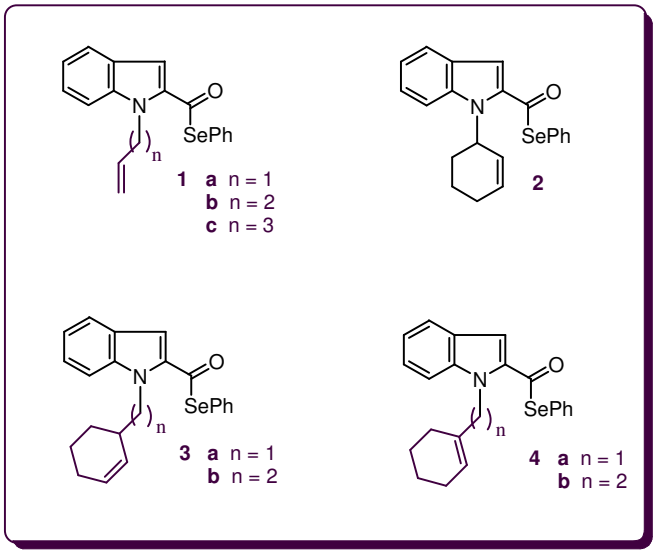


D'acord amb els nostres objectius, en primer lloc centràrem la nostra atenció en avaluar les possibilitats que oferien els radicals 2-indolilacil en processos intramoleculars en condicions reductores.

Inicialment, s'estudià aquest nou procediment de ciclació en substrats en els quals l'alquè, actuant com a acceptor radicalari, estava unit al nitrogen de l'indole.[1] Aquesta característica ens permetria accedir a estructures amb monocicles o bicicles 1,2-fusionats amb el nucli indòlic.

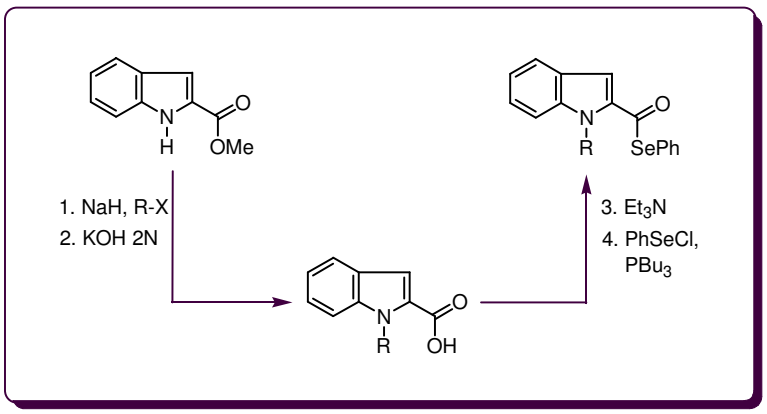
[1] Per a exemples relacionats de ciclacions de radicals 2-indolil, vegeu: Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149-2160.

Precursors radicalaris



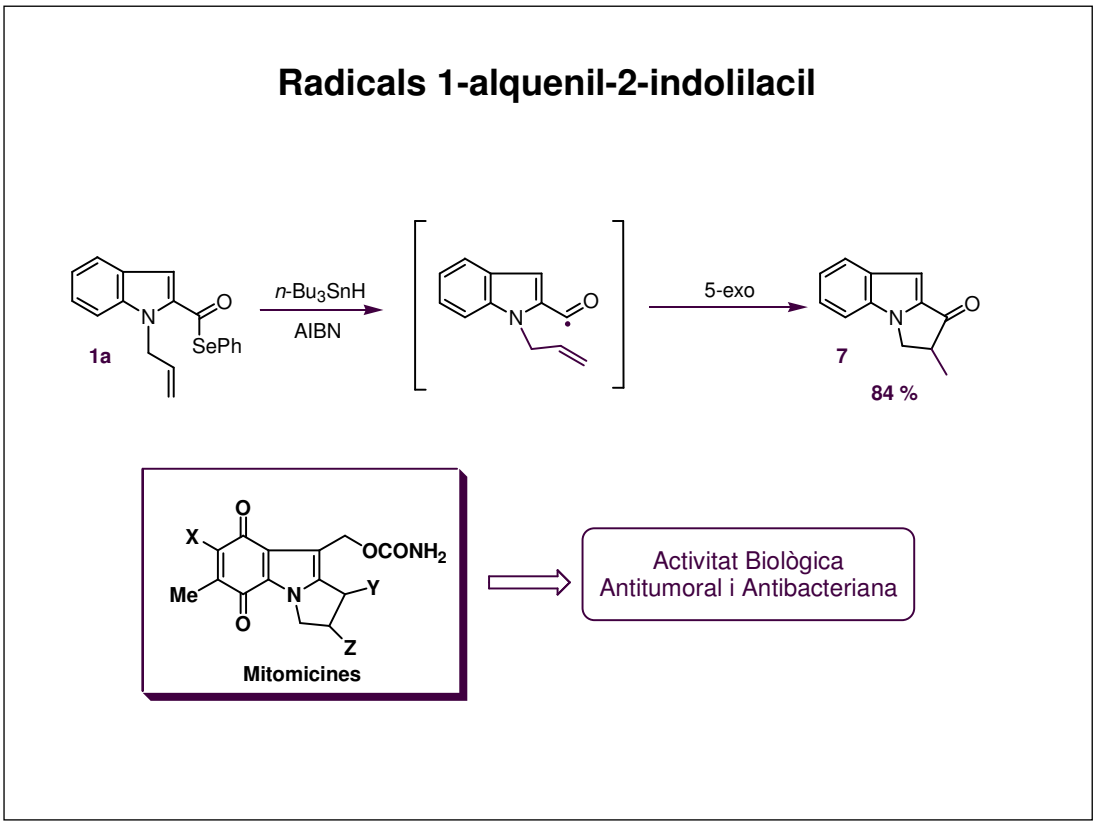
Per tal de conèixer d'una manera directa el comportament dels radicals 2-indolilacil en el procés de ciclació esmentat, es prepararen els selenoèsters **1-4** com a precursors radicalaris. Aquests compostos es diferencien en el tipus de substituent unit a l'àtom de nitrogen indòlic. Així, els compostos **1a-c** tenen en comú una cadena alquenílica amb un doble enllaç separat per un, dos o tres àtoms de carboni respectivament. D'altra banda, els selenoèsters **2** i **3a-b** estan substituits per un grup 2-ciclohexenil, unit directament al nitrogen o bé separat per un o dos àtoms de carboni. Anàlogament, els precursors **4a-b** presenten un substituent 1-ciclohexenil separat per un o dos carbonis.

Preparació dels selenoèsters



Tots aquests compostos foren accessibles a partir del 2-indolecarboxilat de metil mitjançant procediments convencionals d'*N*-alquilació seguida d'hidròlisi de la funció èster. La conversió dels àcids resultants en els selenoèsters es dugué a terme emprant el protocol experimental descrit per Batty i Crich,[2] que implica el tractament dels corresponents carboxilats d'amoni amb clorur de fenilseleni i tributilfosfina.

[2] Batty, D.; Crich, D. *Synthesis* **1990**, 273-275.



Els assajos realitzats amb aquests selenoèsters es dugueren a terme en les condicions reductores estàndard, utilitzant AIBN com a iniciador i addició lenta d'hidrur de tributilestany a la temperatura de reflux de benzè.

Com era previsible tant a partir de les regles empíriques de ciclació de radicals alquil[3] com dels resultats prèviament descrits per a radicals benzoïl,[4] l'espècie radicalària de tipus 5-hexenoïl provinent d'**1a** mostrà una elevada preferència per a la formació de l'anell de cinc baules a través d'una ciclació 5-exo, per donar el compost **7** com a producte únic amb un 84% de rendiment.

És d'interès assenyalar que **7** presenta l'esquelet de pirrolo[1,2-*a*]indole característic de les mitomicines,[5] un grup de metabòlits presents en diverses espècies bacterianes del gènere *Streptomyces* i que han atret especialment l'atenció degut a la seva elevada activitat antitumoral i antibacteriana.

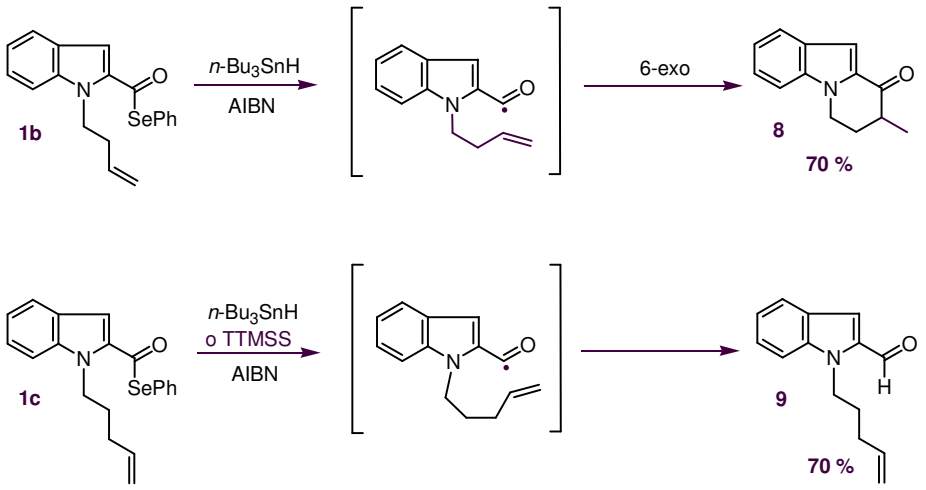
---

3 Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301-856.

4 Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429-1443.

5 Remers, W.A.; Dorr, R. T. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; Wiley: New York, 1988; Vol 6, pp. 1-74.

Radicals 1-alquenil-2-indolilacil

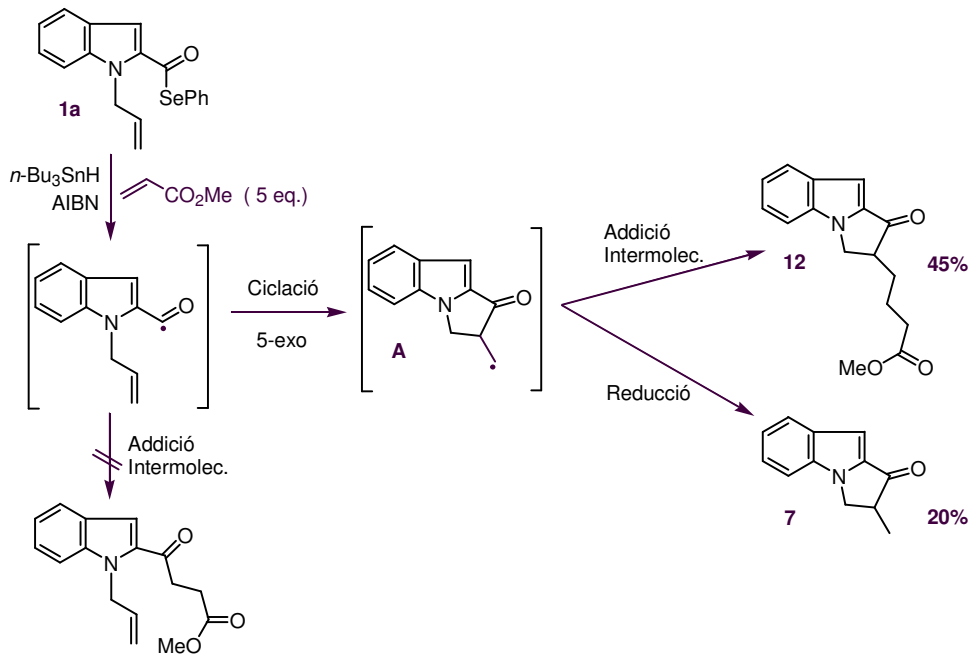


Anàlogament, la ciclació del radical 6-heptenoïl provinent d'**1b** fou totalment regioselectiva 6-exo i s'obtingué com a únic producte el pirido[1,2-*a*]indole **8** amb un 70% de rendiment. De manera significativa, en aquest últim cas no hi hagué evidència de la reducció del radical acil intermedi mitjançant l'abstracció d'hidrogen, ja sigui directament per part de l'hidrur o bé a través d'una transferència [1,5] d'hidrogen.

En canvi, contrastant amb els resultats obtinguts per a les sèries benzoïl, la formació de l'anell de set baules a partir d'**1c** no tingué lloc. Així, únicament s'obtingué l'aldehid **9** amb un 70% de rendiment, fins i tot quan s'emprà un donador d'hidrogen més dèbil com ara el tris(trimetilsilil)silà (TTMSS)[6] com a mediador radicalari per tal de minimitzar la reducció del radical acil.

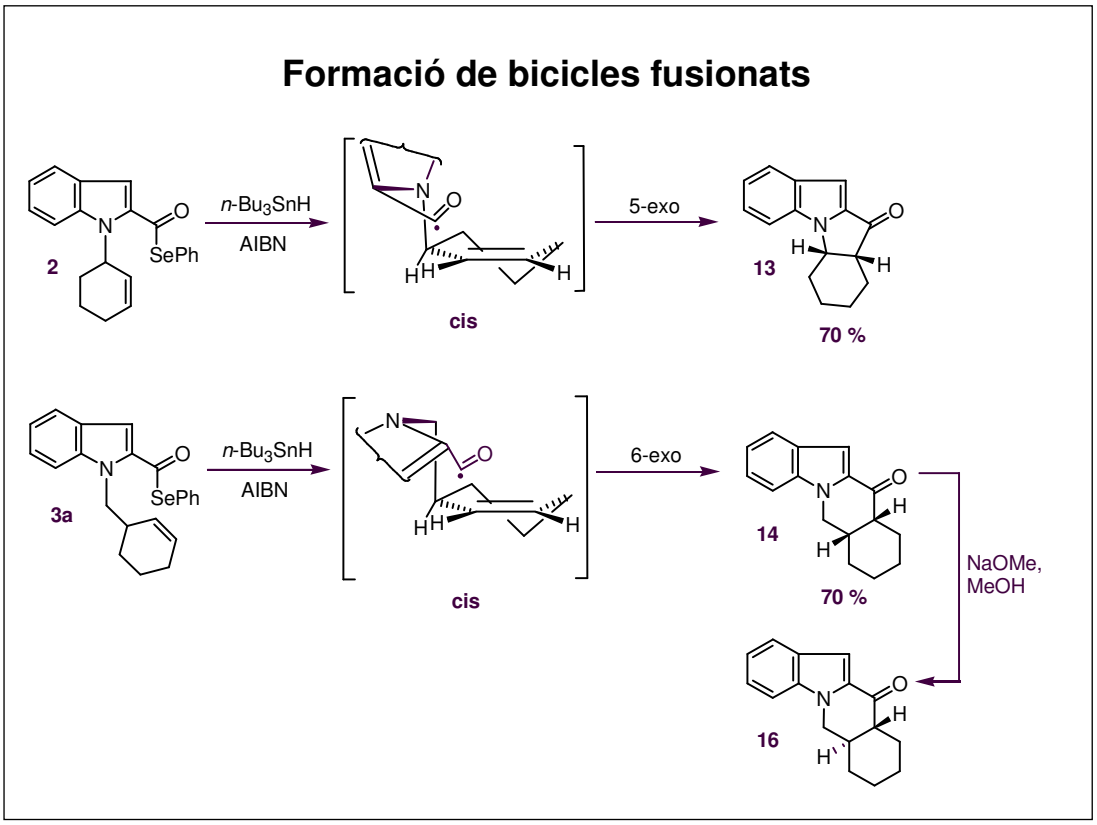
[6] Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188-194.

Radical 1-al.lil-2-indolilacil:
Reacció tàndem ciclació-addició intermolecular



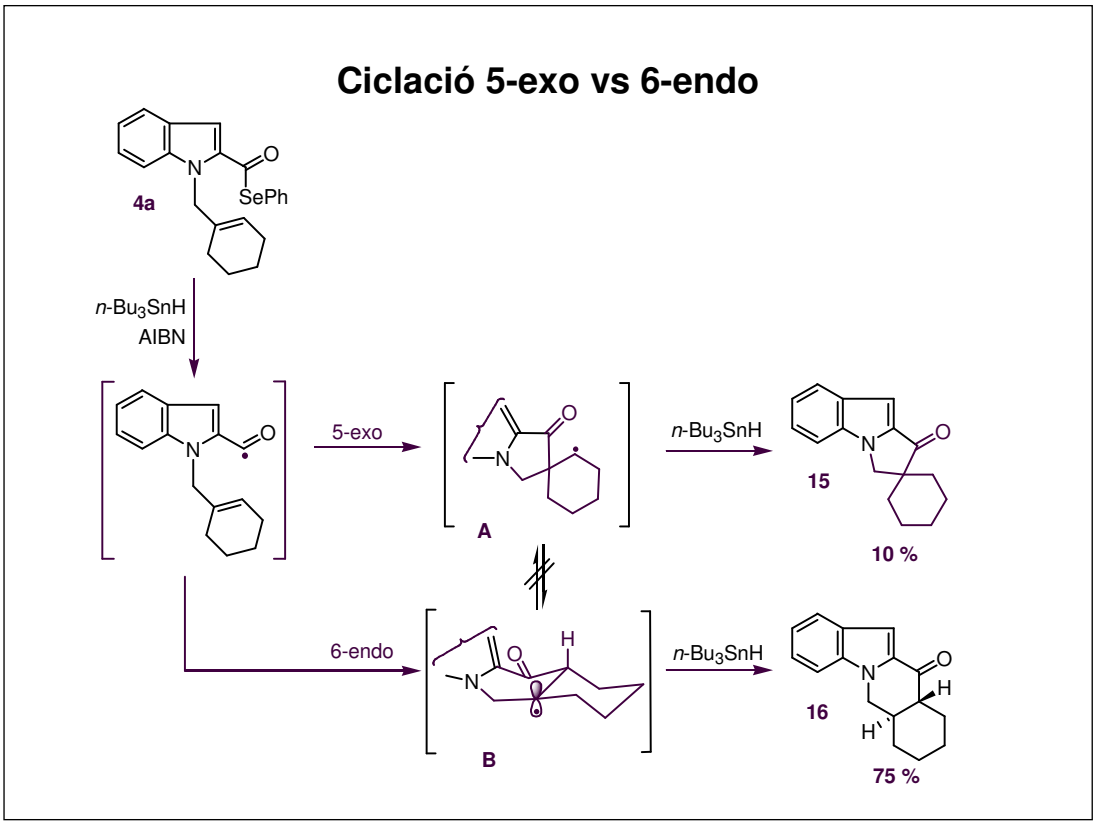
En aquest punt, el nostre interès es centrà en la possibilitat de dur a terme una reacció tàndem a partir del selenoèster **1a**, definida per un procés de ciclació seguit d'una addició intermolecular del radical intermedi **A** a un alquè extern deficient electrònicament, com ara l'acrilat de metil.[7] Amb aquesta finalitat, **1a** es tractà amb *n*-Bu_3SnH-AIBN en presència de diferents quantitats d'acceptor extern. Els millors rendiments del producte desitjat **12** (45%) s'obtingueren quan la reacció de ciclació s'efectuà en presència de 5 equivalents d'acrilat de metil. No obstant això, en aquestes condicions es formaven també quantitats significatives (20%) del producte de reducció **7**. En cap cas, s'observà la formació del producte d'addició directa del radical 2-indolilacil sobre l'acrilat de metil, fet que posa de manifest la major velocitat de ciclació 5-exo respecte de l'addició intermolecular.

[7] Per a exemples semblants de ciclacions 5-exo seguides d'addició intermolecular, vegeu: (a) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003-4008. (b) Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249-1251.



La formació de bicicles fusionats a través de ciclacions exo tingué lloc amb èxit a partir dels selenoèsters **2** i **3a**, els quals incorporen una agrupació de 2-ciclohexenil unida directament al nitrogen indòlic o bé separada per un grup metilè. Tal com era d'esperar, en ambdós casos l'addició del radical acil al doble enllaç tingué lloc en disposició cis, com a conseqüència de les restriccions estèriques imposades pel sistema cíclic.[8] La posterior reducció del radical resultant, situat a la posició α de la condensació, donà lloc als productes finals **13** i **14**, de configuració cis, amb bons rendiments. El compost tetracíclic **14** es pogué transformar de manera pràcticament quantitativa en el corresponent isòmer trans-fusionat **16**, termodinàmicament més estable, per tractament amb metòxid sòdic en el si de metanol.

[8] Curran, D. P.; Porter, N. A. Giese, B. *Stereochemistry of Radical Reactions*; WCH: Weinheim, 1996.



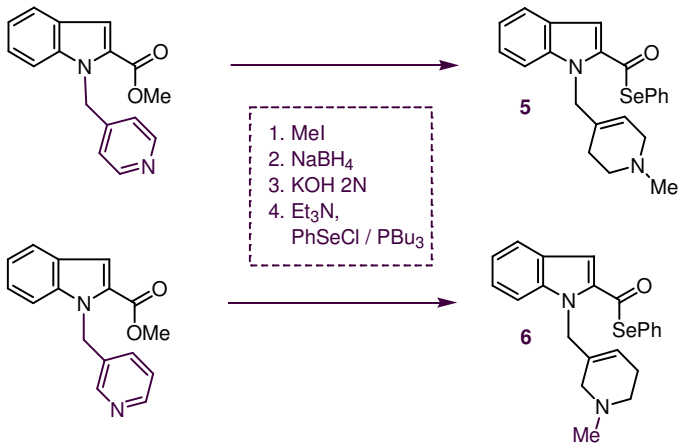
A partir del compost **4a** s'avaluà l'efecte que podria tenir el major grau de substitució del doble enllaç acceptor en el procés de ciclació. D'acord amb els precedents, la ciclació 6-endo fou el procés predominant en detriment del 5-exo, usualment afavorit, en donar el compost fusionat **16** com a producte majoritari (75%), acompanyat de quantitats minoritàries (10%) del compost espiràni c **15**. Donat que aquesta proporció endo-exo no es modificava significativament quan es variava la concentració d'hidrur, assumírem que reflectia la composició cinètica dels radicals inicialment formats **A** i **B** més que una possible equilibració entre aquests intermedis mitjançant una transposició intramolecular.[9] D'altra banda, el compost tetracíclic **16** s'obtingué exclusivament en configuració trans, degut a l'abstracció estereoselectiva axial[8,10]de l'àtom d'hidrogen de l'hidrur per part del radical **B**.

---

9 Per a una discussió, vegeu: Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J*. **1997**, *3*, 376-387. Vegeu també la referència 4.

10 Beckwith, A. L. J; Gream, G. E.; Struble, D. L. *Aust. J. Chem*. **1972**, *25*, 1081-1105.

Ciclació 5-exo vs 6-endo: tetrahidropiridines



Amb la intenció d'estendre l'anterior ciclació regioselectiva 6-endo a la construcció de sistemes azacíclics fusionats, centrarem la nostra atenció en els selenoèsters **5** i **6**. Aquests compostos presenten un doble enllaç amb el mateix grau de substitució que el compost **4a**, inclòs ara en un anell d'1,2,5,6-tetrahidropiridina 4- o 3- substituïda. Els selenoèsters **5** i **6** foren accessibles a partir de les corresponents piridines, mitjançant quaternització, reducció parcial amb borohidrur sòdic i fenilselenació.

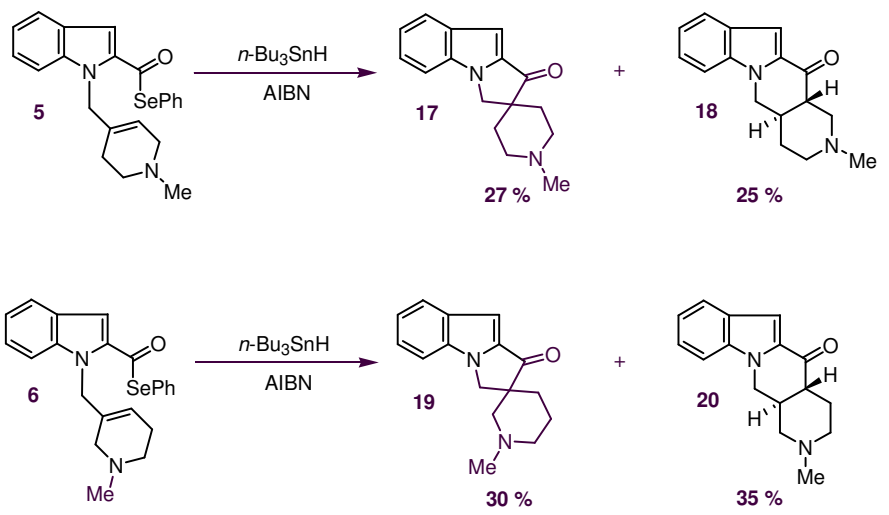
Cal esmentar que les reaccions radicalàries s'han emprat extensivament per a la construcció d'heterocicles nitrogenats. En aquest context, a la literatura s'han descrit alguns exemples de ciclacions sobre tetrahidropiridines, les quals majoritàriament condueixen a estructures on l'àtom de nitrogen també forma part del nou anell format.[11,12]

---

[11] (a) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349-10362. (b) Della, E. W.; Smith, P. A. *J. Org. Chem.* **2000**, *65*, 6627-6633. (c) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009-3018. (d) Bressy, C.; Menant, C. Piva, O. *Synlett* **2005**, 577-582.

[12] Per a ciclacions radicalàries sobre tetrahidropiridines en les quals es crea un nou carbocicle, vegeu: (a) Jenkinson, J. J.; Parsons, P. J. Eyley, S. C. *Synlett* **1992**, 679-680. (b) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84-91. (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503-8507.

Ciclació 5-exo vs 6-endo: tetrahidropiridines



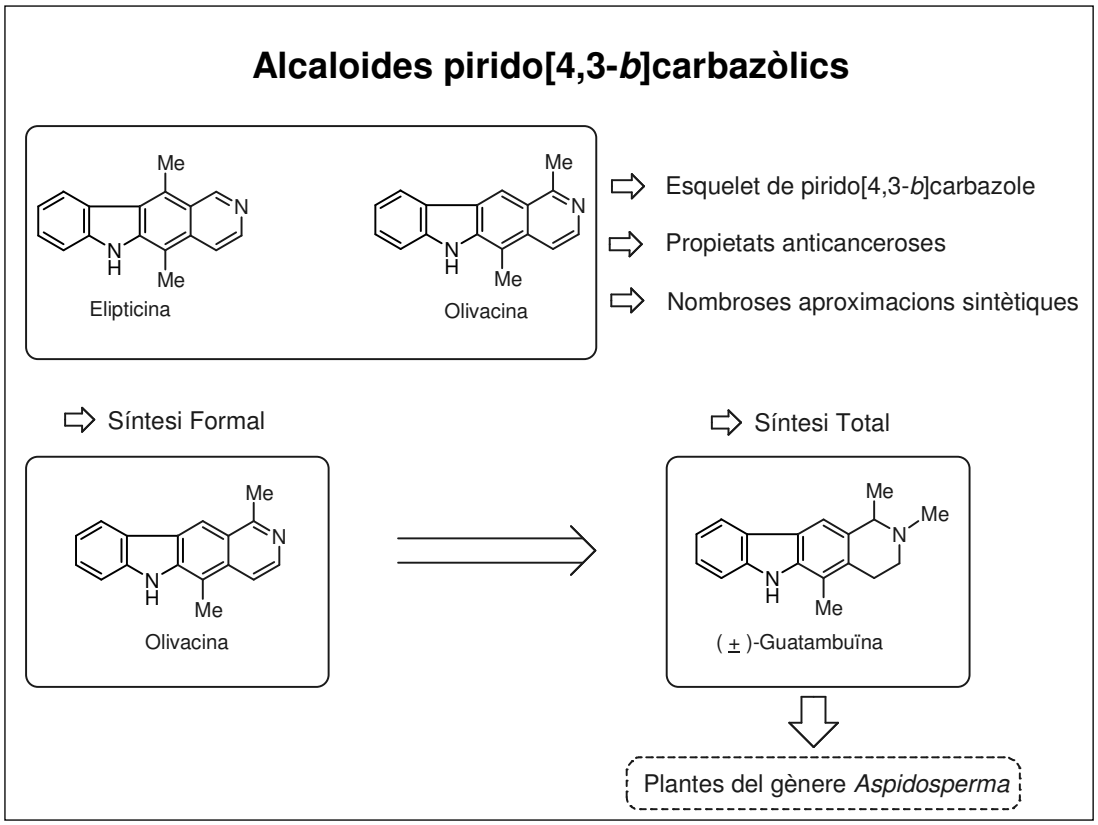
De manera sorprenent, el tractament dels selenoèsters **5** i **6** amb n-Bu_3SnH-AIBN proporcionà una mescla pràcticament equimolecular dels corresponents compostos espiràncis (**17** i **19**) i fusionats (**18** i **20**) amb rendiments globals moderats. De manera anàloga a l'anterior sèrie, els compostos **18** i **20** s'obtingueren esclusivament en configuració trans degut a la reducció estereoselectiva del radical intermedi.

La diferent regioselectivitat exo-endo observada en les reaccions de **5** i **6** respecte del compost carbocíclic **4a** sembla indicar que, com a conseqüència de la inclusió d'un àtom de nitrogen a l'anell acceptor, la via endo que condueix a un anell de sis baules fusionat per la cara a de l'indole es veu cinèticament desaccelerada.

Com a resum, els resultats descrits en aquest capítol estableixen un nou procediment d'anulació indòlica basat en les reaccions intramoleculars de radicals 2-indolilacil. Quan s'utilitzen acceptors alquenílics situats sobre el nitrogen indòlic, el procediment permet l'obtenció de cetones cícliques 1,2-fusionades amb l'indole, les quals presenten interès en la síntesi de productes naturals i altres compostos bioactius.

2.2. CICLACIONS REGIOSELECTIVES 6-ENDO DE RADICALS 2-INDOLILACIL: SÍNTESI TOTAL DE L'ALCALOIDE PIRIDO[4,3-*b*]CARBAZÒLIC GUATAMBUÏNA

(*J. Org. Chem.* **2006**, *71*, 1746-1749)



L'elipticina i l'olivacina són els compostos més representatius dels alcaloides pirido[4,3-*b*]carbazòlics, els quals constitueixen un petit subgrup de productes naturals bioactius coneguts des de fa més de quaranta anys.[1] Degut a les seves propietats anticanceroses ben establertes, l'elipticina i, en menor extensió, l'olivacina han estat objecte d'un gran nombre de síntesis totals emprant una gran varietat d'estratègies.[1-3] No obstant això, les metodologies radicalàries s'han utilitzat escassament per a la construcció de l'esquelet lineal de piridocarbazole característic d'aquests alcaloides.[4,5]

Amb la nostra experiència prèviament adquirida en les reaccions intramoleculars de radicals 2-indolilacil en condicions reductores, visualitzàrem una nova aproximació sintètica a l'esquelet de l'olivacina, que es concretà en una síntesi total de l'alcaloide (±)-guatambuïna, un tetrahidro derivat de l'olivacina aïllat de diverses espècies del gènere *Aspidosperma*.[6,7]

---

[1] (a) Sainsbury, M. *Synthesis* **1977**, 437-448. (b) Joule, J. A. *Indoles, The Monoterpenoid Indole Alkaloids*. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Weissberger. A.; Taylor, E. C., Eds.; Wiley: New York, 1983, Part 4, pp 275-286. (c) Gribble, G. W. *The Alkaloids*; Brosi, A., Ed.; Academic Press: New York, 1990; Vol. 39, pp 239-352.

[2] Per a una revisió, vegeu: Knölker, H.-J.; Reddy, K. R. *Chem. Rev*. **2002**, *102*, 4303-4427, i referències citades.

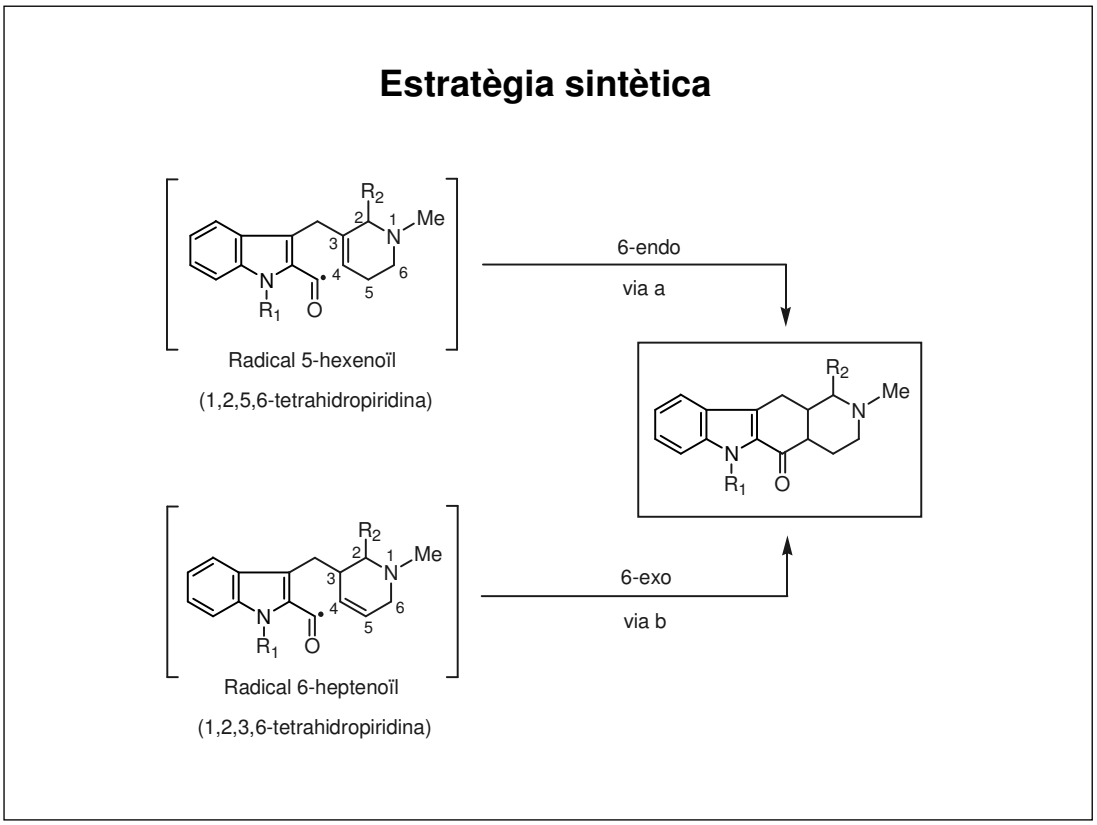
[3] Per a síntesis representatives de l'olivacina des de 1990, vegeu: (a) Bäckvall, J.-E.; Plobeck, N. A. *J. Org. Chem*. **1990**, *55*, 4528-4531. (b) Hogan, I.; Jenkins, P. D.; Sainsbury, M. *Tetrahedron* **1990**, *46*, 2943-2964. (c) Hibino, S.; Sugino, E. *J. Heterocycl. Chem*. **1990**, *27*, 1751-1755. (d) Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. *J. Chem. Soc. Perkin Trans 1* **1990**, 1319-1329. (e) Hall, R. J.; Marchant, J.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *J. Chem. Soc. Perkin Trans 1* **1992**, 3439-3450. (f) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem*. **1992**, *57*, 5891-5899. (g) Miki, Y.; Tsuzaki, Y.; Hibino, H.; Aoki, Y. *Synlett* **2004**, 2206-2208.

[4] Per a un exemple de protocol radicalari en cascada que condueix a l'elipticina, vegeu: Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem*. **2005**, *70*, 10615-10618.

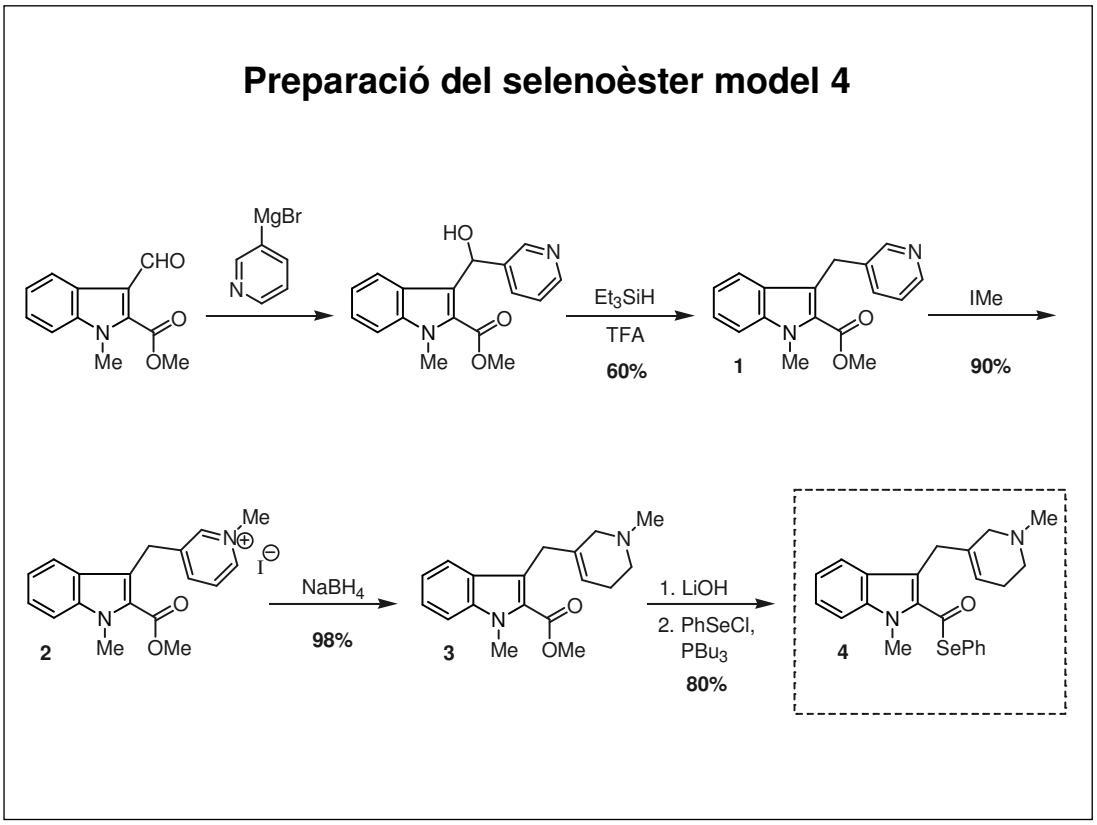
[5] Per a la síntesi d'elipticina quinones mitjançant acilació homolítica intramolecular de piridines, vegeu: Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem*. **2005**, *70*, 9077-9080. (Capítol 2.4).

[6] La guatambuïna fou aïllada en les formes (+), (–), i (±): (a) Ondetti, M. A.; Deulofeu, V. *Tetrahedron* **1961**, *15*, 160-166. (b) Burnell, R. H.; Della Casa, D. *Can. J. Chem*. **1967**, *45*, 89-92.

[7] Per a síntesis prèvies de la (±)-guatambuïna, vegeu: (a) Besselièvre, B.; Husson, H.-P. *Tetrahedron* **1981**, *37*, supplement No.1, 241-246. A través de l'olivacina: (b) Kutney, J. P.; Noda, M.; Lewis, N. G.; Monteiro, B.; Mostowicz, D.; Worth, B. R. *Can. J. Chem*. **1982**, *60*, 2426-2430.

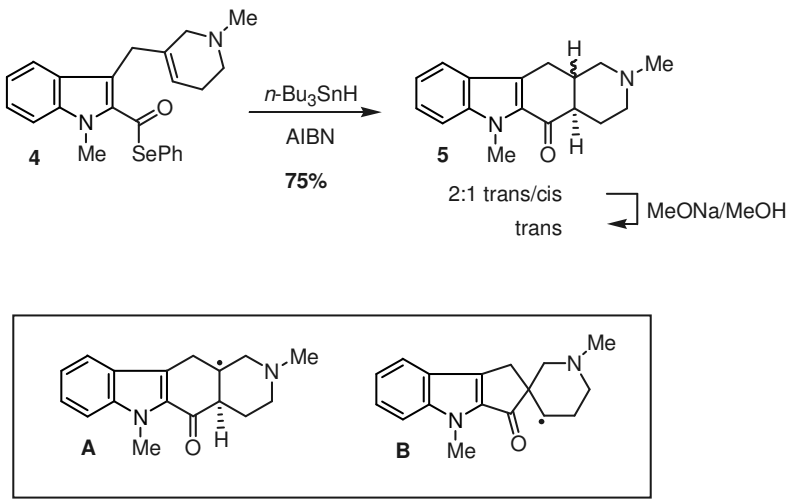


La nostra aproximació sintètica a l'esquelet de l'olivacina implicava l'elaboració de l'anell carbocíclic central per ciclació d'un radical 2-indolilacil sobre una tetrahidropiridina connectada a la posició 3 de l'indole. Per dur a terme aquest objectiu hi havien dues possibilitats: promoure una ciclació 6-endo d'un radical tipus 5-hexenoïl emprant una 1,2,5,6-tetrahidropiridina, de manera anàloga al capítol anterior, o bé promoure una ciclació 6-exo d'un radical tipus 6-heptenoïl emprant una 1,2,3,6-tetrahidropiridina. Degut a que els substrats de partida semblaven més accessibles mitjançant protocols convencionals de reducció de substrats piridínics, decidírem centrar inicialment la nostra atenció en la primera de les aproximacions esmentades (via a). Novament esperàvem que el major grau de substitució de l'alquè a la posició 3 de l'anell alentís la ciclació competitiva 5-exo, afavorint la formació de l'anell de sis baules fusionat ara per la cara b de l'indole.



Per tal de comprovar la viabilitat de la proposta decidírem estudiar la ciclació d'un compost model, el selenoèster **4**, que incorpora la unitat d'1,2,5,6-tetrahidropiridina. Aquest compost es preparà fàcilment segons la seqüència sintètica que es mostra a la figura. Així, la reacció entre el bromur de 3-piridilmagnesi i l'aldehid indòlic representat, seguida de reducció del carbinol resultant proporcionà el piridilmetilindole **1**, el qual es pogué transformar en **4** per quaternització amb iodur de metil, reducció amb borohidrur sòdic i fenilselenació de l'èster metílic tetrahidropiridínic **3** a través del corresponent àcid carboxílic.

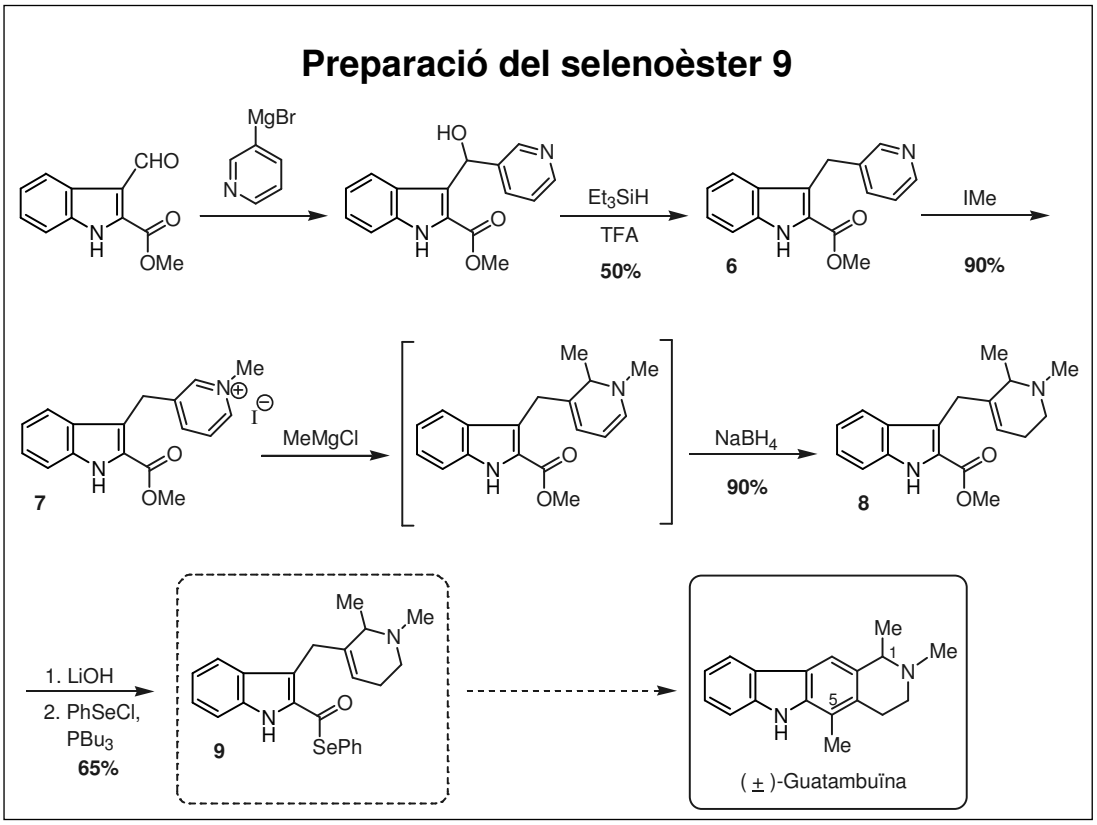
Ciclació del selenoèster model 4



Satisfactòriament, quan el selenoèster **4** es sotmeté a les condicions reductores de ciclació estàndard (*n*-Bu_3SnH-AIBN) s'obtingué el pirido[4,3-*b*]carbazole esperat **5** com una mescla 2:1 d'estereoisòmers trans-cis amb un rendiment del 75%. Cal esmentar que no es detectà per RMN la formació del corresponent producte de ciclació 5-exo.

Aquest resultat regioquímic és probablement conseqüència d'una ciclació directa 6-endo del radical acil format inicialment per donar el radical fusionat **A**, encara que un atac parcial 5-exo, seguit d'expansió d'anell del radical altament tensionat **B** no es pot descartar en les condicions de reacció (concentració 0.06 M).[8] A continuació, l'abstracció d'hidrogen del radical **A** d'una manera no completament estereoselectiva justificaria la formació de la mescla d'estereoisòmers trans-cis **5**. Aquesta mescla es pogué transformar en l'isòmer trans, termodinàmicament més estable, mitjançant el tractament amb metòxid sòdic en metanol.

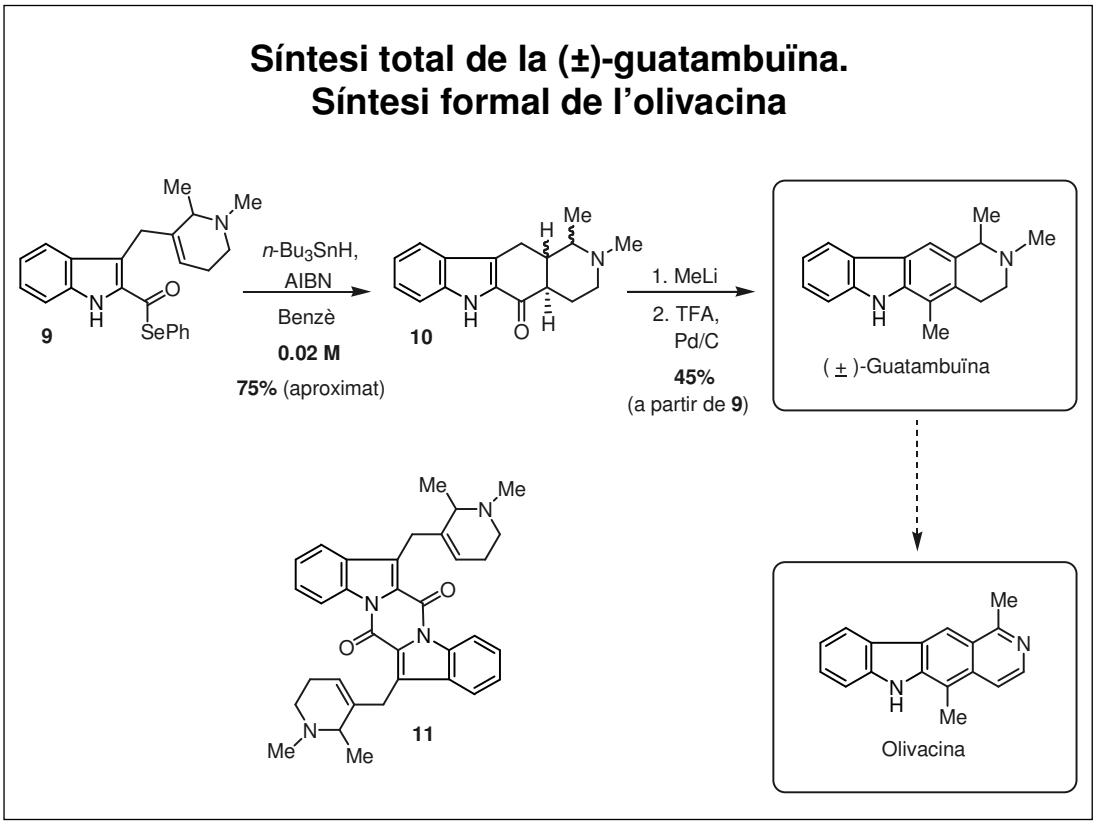
[8] Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J.* **1997**, *3*, 376-387.



La síntesi de l'alcaloide piridocarbazòlic (±)-guatambuïna requeria l'extensió de la seqüència sintètica anterior a substrats relacionats, no substituïts al nitrogen indòlic. A més, havíem de ser capaços d'introduir, en algun estadi del procés, els grups metil situats a les posicions 1 i 5 de l'alcaloide.

Amb aquesta finalitat, centrarem la nostra atenció en el piridilmetilindole **6**, el qual es preparà com a l'anterior sèrie model a partir de l'aldehid-èster representat i es convertí en la sal de piridini **7** per reacció amb iodur de metil. La reacció de **7** amb clorur de metilmagnesi permeté la introducció del grup metil de la posició 1. Significativament, l'addició de l'organometàl.lic tingué lloc d'una manera totalment regioselectiva al carboni 2 de l'anell[9] per donar, després de la reducció de la 1,2-dihidropiridina intermèdia amb $NaBH_4$, la tetrahidropiridina **8** com a únic producte amb un 90% de rendiment. La seva hidròlisi seguida de la posterior fenilselenació donà lloc al selenoèster **9**.

[9] Per a una discussió sobre l'origen d'aquesta regioselectivitat, vegeu: (a) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem*. **1986**, *51*, 3672-3679. Per a un exemple recent, vegeu: (b) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett*. **2004**, *6*, 3517-3520.



El selenoèster **9** es sotmeté al protocol radicalari reductiu prèviament utilitzat a la sèrie model, amb l'esperança de que el radical 2-acilindòlic generat iniciés la ciclació 6-endo desitjada sense interferència del grup NH indòlic. Satisfactòriament, quan es treballà en el si de benzè a una concentració 0.02 M s'obtingué el piridocarbazole **10** com una mescla d'estereoisòmers amb un rendiment aproximat del 75%. No obstant això, cal esmentar que quan, degut a la baixa solubilitat del selenoèster **9,** s'utilitzaren mescles 1:1 de benzè en un dissolvent més polar com l'acetonitril tenia lloc una ràpida dimerització[10] del substrat per donar la dicetopiperazina **11** com a producte únic.[11]

Sense purificació addicional, la mescla **10** es feu reaccionar amb metil-liti, la qual cosa aconseguí la introducció del segon grup metil de la posició 5 de l'alcaloide. A continuació, el tractament amb Pd/C en el si de TFA promogué la deshidratació del carbinol resultant i la deshidrogenació, per donar lloc a la (±)-guatambuïna amb un rendiment global del 45% (a partir de **9**).

Les dades de RMN del nostre producte sintètic foren concordants amb les descrites per a l'alcaloide.[6,7] A més, tenint en compte que la guatambuïna havia

estat transformada en l'olivacina per aromatització desalquilant,[6a,7a] la síntesi efectuada també constitueix una síntesi formal d'aquest alcaloide.

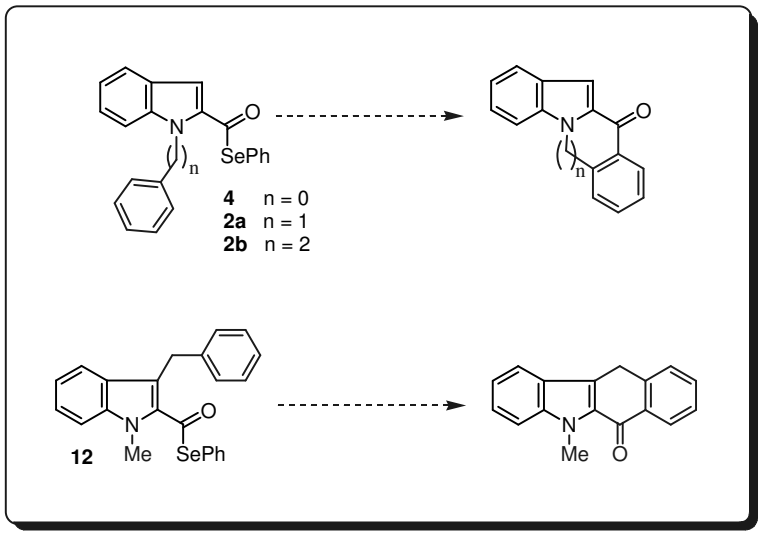
[10] Per a exemples de dimerització semblants amb clorurs de 2-indolilacil, vegeu: Boger, D. L.; Fink, B. E.; Hedrick, M. P. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1019-1020.

[11] L'escalfament del selenoèster **9** en benzè-acetonitril 1:1 durant 3 h donà una mescla 3:1 de **9** i **11**. En canvi, l'escalfament de **9** en benzè durant 6 h donà una mescla 10:1 de **9** i **11**.

2.3. REACCIONS INTRAMOLECULARS DE RADICALS 2-INDOLILACIL: CICLACIÓ SOBRE NUCLIS AROMÀTICS

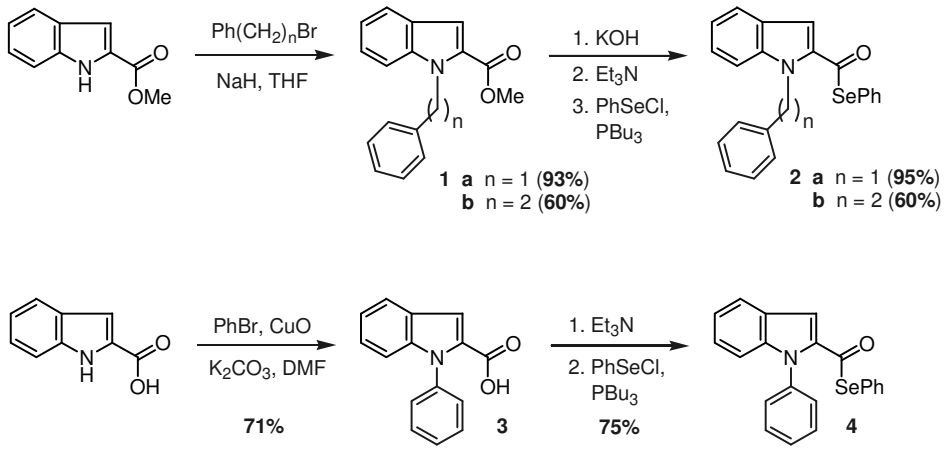
(*Tetrahedron Lett.* **2004**, *45*, 5605-5609)

Radicals 2-indolilacil: ciclació sobre anells aromàtics carbocíclics



En el context de les reaccions intramoleculars de radicals 2-indolilacil amb anells aromàtics s'estudià, en primer lloc, el comportament d'aquests intermedis radicalaris en processos de ciclació sobre anells de benzè situats en cadenes unides a la posició 1 o bé a la posició 3 del nucli indòlic. Inicialment, s'estudiaren processos de ciclació per a l'obtenció de derivats indòlics amb bicicles 1,2-fusionats. Per aquest motiu, es prepararen els selenoèsters **2a**, **2b** i **4**, els quals tenen l'anell de benzè unit directament a l'àtom de nitrogen de l'indole, o bé separat per un o dos metilens.

Preparació dels precursors *N*-substituïts

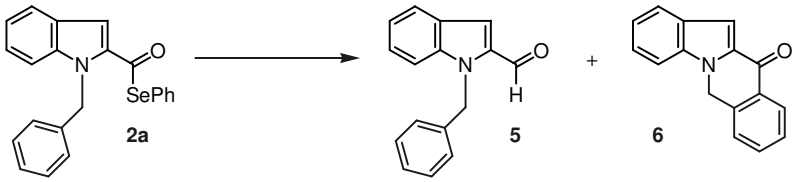


La preparació dels selenoèsters **2a** i **2b** es realitzà de manera eficient a partir del 2-indolecarboxilat de metil. Així, l'*N*-alquilació de la sal sòdica d'aquest èster amb bromur de benzil o bé de 2-feniletil donà lloc als compostos **1a** i **1b** amb bons rendiments. Aquests èsters es transformaren en **2a** i **2b** per hidròlisi i posterior fenilselenació dels àcids carboxílics resultants seguint el procediment usual.

D'altra banda, el selenoèster **4** s'obtingué utilitzant com a producte de partida l'àcid 2-indolecarboxílic. La reacció d'Ullman d'aquest àcid amb bromobenzè permeté obtenir **3**,[1] el qual es convertí per fenilselenació en el selenoèster **4** amb un rendiment del 75%.

[1] Olgen, S.; Akaho, E.; Nebioglu, D. *Eur. J. Med. Chem.* **2001**, *36*, 747-770.

Selenoèster 2a:
Condicions reductores



Assaig	Condicions Reductores	Dissolvent	Productes	Rendiment
1	*n*-Bu_3SnH-AIBN	Benzè	**5**	90%
2	*n*-Bu_3SnH-AIBN	ACN-Hexà	**5**	90%
3	*n*-Bu_3SnH-AIBN, Ph_2Se_2	Benzè	**5** + **2a** (1:1)	-
4	TTMSS-AIBN	Benzè	**5** + **6** (4:1)	-

Ens proposàrem examinar diverses condicions experimentals de ciclació partint del selenoèster **2a**. Tenint en compte els precedents descrits a la bibliografia,[2] les condicions reductores estàndard (*n*-Bu_3SnH-AIBN) foren les primeres que s'empraren. En els assajos 1 i 2, malgrat que la quantitat d'iniciador i el dissolvent foren diferents en cada cas, únicament s'obtingué l'aldehid **5** com a producte de la reducció del radical 2-indolilacil format inicialment. Aquesta reducció també s'observà en l'assaig 3, el qual es realitzà en presència de fenilselenol, emprant el protocol experimental descrit per Crich i Hwang.[3] En aquest cas s'aïllaren quantitats significatives del selenoèster de partida **2a** fins i tot després de vint hores de reacció.

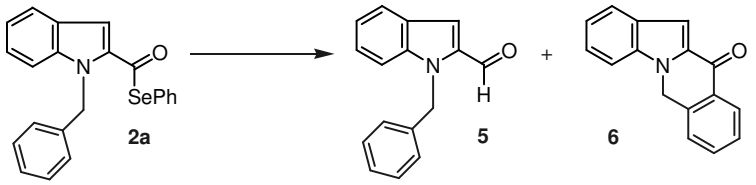
D'altra banda, emprant un donador d'hidrogen més dèbil com ara el tris(trimetilsilil)silà com a mediador radicalari s'obtingué un cru de reacció en el qual el producte majoritari fou l'aldehid **5**, acompanyat de quantitats minoritàries del tetracicle **6** desitjat.

---

[2] Studer, A.; Bossart, M. En *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., eds; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62-80.

[3] Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765-2770.

Selenoèster 2a:
Condicions no reductores



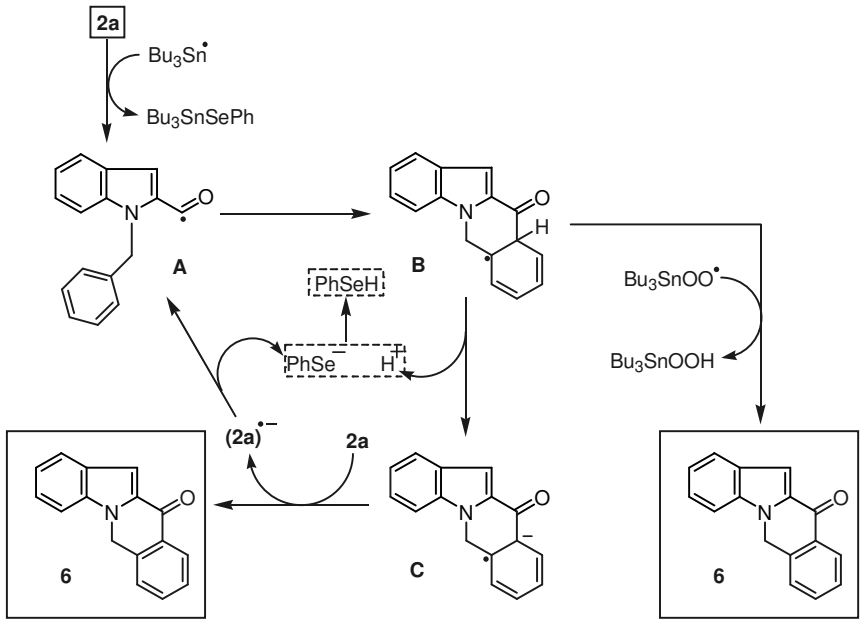
Assaig	Condicions no Reductores	Dissolvent	Productes i Rendiment
1	*n*-Bu_6Sn_2 (0.2 eq.), 300W	Benzè	**6** (40%)+**2a** (25%)+**5** (10%)
2	*n*-Bu_6Sn_2 (2.2 eq.), 300W	Benzè	**6** (65%)

Els resultats obtinguts en condicions reductores posaren de manifest que la reducció del radical 2-indolilacil intermedi era una etapa clarament competitiva. Per aquest motiu ens proposàrem estudiar la ciclació de **2a** en condicions no reductores (*n*-Bu_6Sn_2, 300W).[4] En aquest cas s'esperava que el procés de ciclació estés més afavorit degut al major temps de vida mitja efectiu del radical 2-indolilacil.

El tractament de **2a** amb quantitats subestequiomètriques de *n*-Bu_6Sn_2 (assaig 1) donà lloc al producte de ciclació desitjat **6** amb un 40% de rendiment. S'aïllaren també quantitats significatives del producte de partida **2a** (25%), fet indicatiu d'una reacció en cadena poc eficaç, i de l'aldehid **5** (10%). De manera satisfactòria, la conversió de **2a** es completà quan s'empraren 2.2 equivalents de mediador radicalari (assaig 2), per donar el tetracicle **6** amb un 65% de rendiment sense la presència de traces del producte de reducció.

[4] (a) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67-83. (b) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181-10184. (c) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765-768. (d) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547-7551.

Mecanisme proposat per a la ciclació del selenoèster 2a en condicions no reductores



Aquests resultats es poden raonar a través de l'esquema mecanístic que es mostra a la figura. El radical tributilestany generat inicialment mitjançant llum o calor reacciona amb el selenoèster **2a** per formar el radical 2-indolilacil intermedi **A**, el qual en absència de reaccions competitives pot reaccionar intramolecularment amb l'anell de benzè per generar el radical ciclohexadienil **B**.[5] Quan s'empren quantitats subestequiomètriques del mediador radicalari la conversió de **B** en **6** transcorre, com a mínim en part, a través d'un mecanisme en cadena, el qual probablement implica la reacció de S_{RN1} representada, semblant a la proposada per Bowman per a reaccions similars.[6] Així, la desprotonació del radical **B** i la posterior transferència electrònica (SET) del radical resultant **C** al selenoèster **2a** generaria el tetracicle **6** i un nou anió radical, el qual donaria lloc al radical **A** per pèrdua de l'anió fenilselenolat, propagant així la cadena. El fenilselenol format podria reduir el radical **A**, fet que explicaria la formació de l'aldehid **5**.

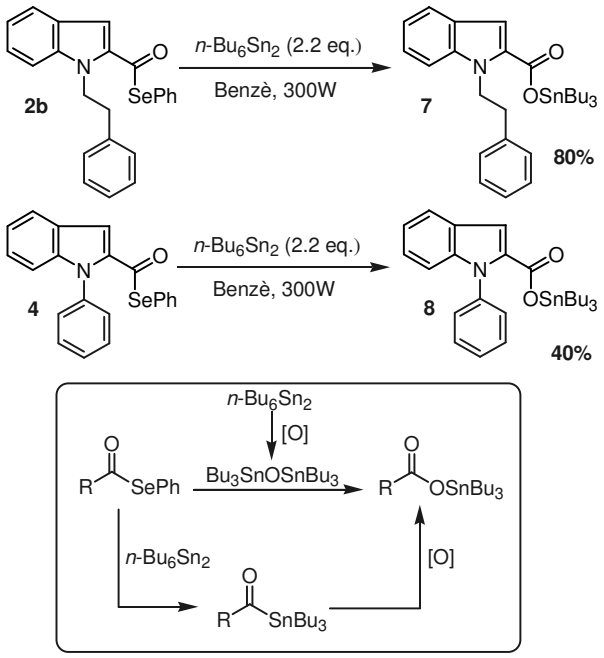
---

5 El fet de no observar ciclació després d'escalfar i irradiar (làmpara solar 300W) **2a** sense la presència de *n*-Bu_6Sn_2 exclou la possibilitat d'un mecanisme de substitució electròfila.

6 Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119-10128.

En canvi, quan s'empren 2.2 equivalents de *n*-Bu_6Sn_2, l'etapa d'oxidació també pot ser descrita a través d'una senzilla abstracció d'hidrogen, per exemple, per part del radical *n*-$Bu_3SnOO^{\cdot}$, el qual provindria de la reacció del radical tributilestany amb l'oxigen present al medi de reacció.

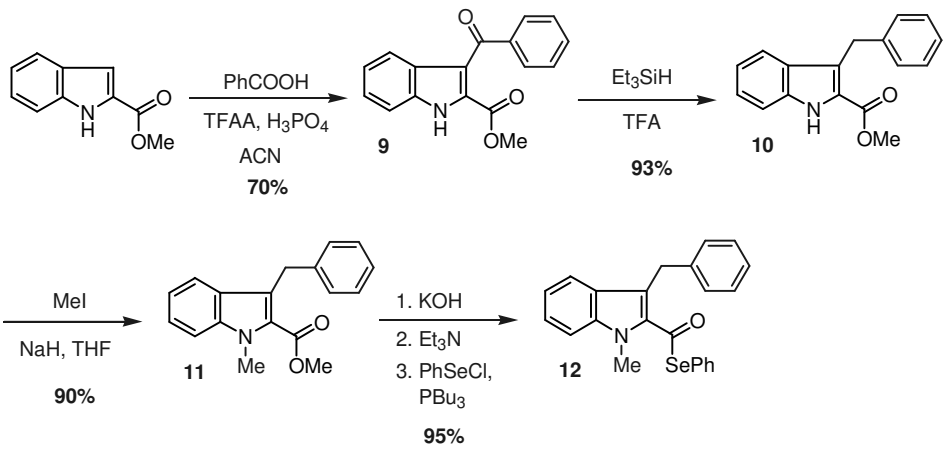
Selenoèsters 2b i 4:
Condicions no reductores



El mètode de ciclació amb el qual s'havia preparat de manera eficient l'isoquinolinoindole **6** s'aplicà als selenoèsters **2b** i **4**. Malauradament, el tractament de **2b** i **4** amb 2.2 equivalents de *n*-Bu_6Sn_2 donà lloc als èsters d'estany **7** (80%) i **8** (40%) com a productes únics. Aquests compostos provindrien de la reacció dels selenoèsters corresponents amb òxid d'hexabutildiestannà generat en el medi de reacció o bé per reacció amb el propi hexabutildiestannà, seguida de l'oxidació dels acilestannans resultants.[7]

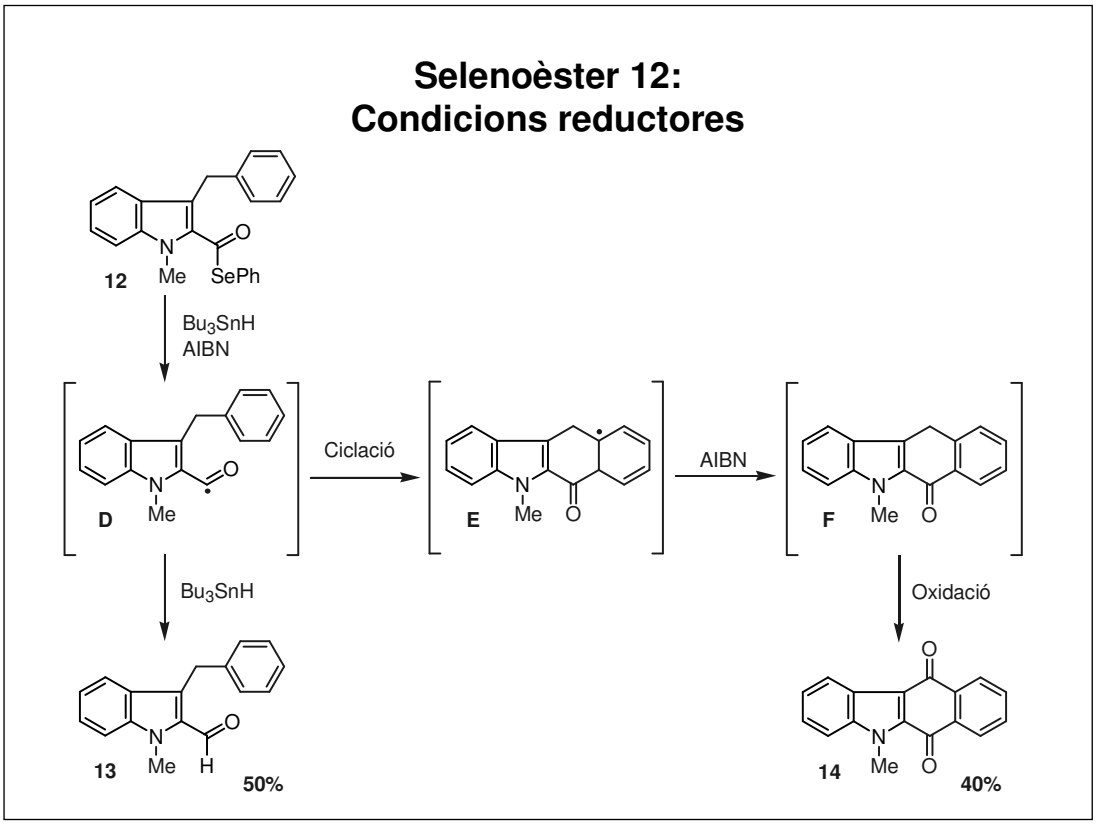
[7] Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3462-3464.

Preparació del selenoèster 12



A continuació, centrarem la nostra atenció en les ciclacions per a l'obtenció de derivats indòlics amb carbocicles fusionats per la cara b. Amb aquesta finalitat, el selenoèster **12**, amb un grup benzil a la posició 3 del nucli indòlic, es preparà a partir del 2-indolecarboxilat de metil. L'acilació de Friedel-Crafts de l'èster de partida amb àcid benzoic[8] i la posterior reducció del 2,3-diacilindole **9** amb trietilsilà donà l'èster **10,** el qual després d'*N*-metilació es convertí en **12** utilitzant el mateix procediment emprat prèviament per a l'obtenció dels selenoèsters **2** i **4**.

[8] Murakami, Y.; Tani, M.; Suzuki, M.; Sudoh, K.; Uesato, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull*. **1985**, *33*, 4707-4715.

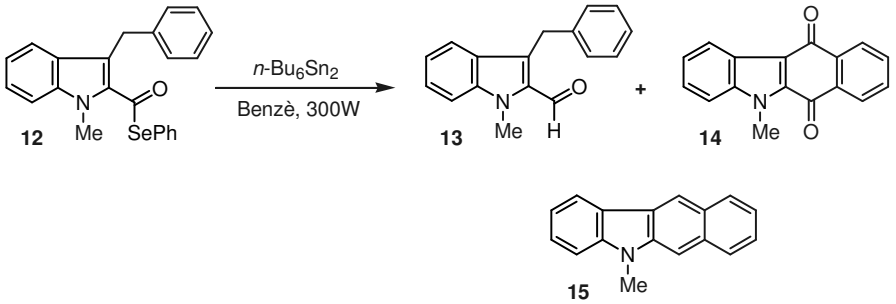


Al contrari del que havia succeït a l'anterior sèrie, el selenoèster **12** sí experimentà ciclació en les condicions reductores usuals (*n*-Bu_3SnH-AIBN) per donar la benzocarbazolodiona **14**[9] amb un 40% de rendiment, acompanyada de quantitats significatives de l'aldehid **13** (50%). Aquests resultats indicaven que la ciclació del radical acil **D** per donar el radical ciclohexadienil **E** estava ara més afavorida, encara que la reducció a **13** continuava sent una via competitiva. Considerant les darreres investigacions mecanístiques,[10] l'AIBN present en quantitats estequiomètriques seria el responsable de la regeneració de l'aromaticitat de l'anell benzènic. No obstant això, el tetracicle **F** que s'hauria format inicialment no s'aïllà en cap cas, en experimentar una sobreoxidació a la posició benzílica per donar la quinona **14**.

9 Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J. *Tetrahedron* **1994**, *50*, 4811-4 828.

10 Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 95-98, i les referències citades.

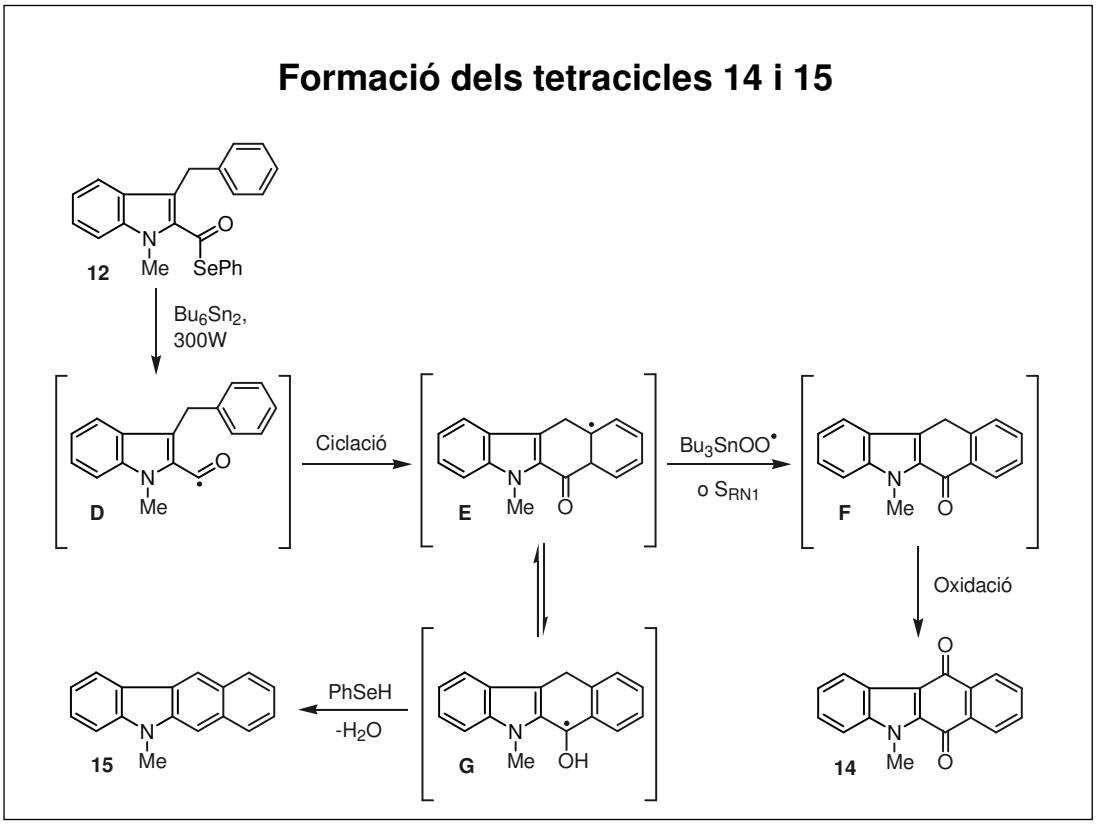
Selenoèster 12: Condicions no reductores



Assaig	Condicions no Reductores	Productes i Rendiment
1	*n*-Bu_6Sn_2 (0.2 eq.), 300W	**12**(25%)+**13** (14%)+**14**(30%)+**15**(5%)
2	*n*-Bu_6Sn_2 (2.2 eq.), 300W	**14**(50%)+**15**(10%)

Els resultats de la ciclació del selenoèster **12** en condicions no reductores foren similars als del selenoèster **2a**. Així, quan s'utilitzaren quantitats subestequiomètriques de *n*-Bu_6Sn_2 s'obtingué el tetracicle **14** amb un 30% de rendiment, acompanyat de quantitats minoritàries de dos productes de reducció: l'aldehid **13** (14%) i el compost **15** (5%).[11] Satisfactòriament, quan s'empraren 2.2 equivalents de mediador radicalari el rendiment de **14** pujà fins a un 50%, encara que s'aïllà també una petita quantitat del compost **15**.

[11] Markgraf, J.-H.; Patterson, D.-E. *J. Heterocycl, Chem*. **1986**, *33*, 109-111.



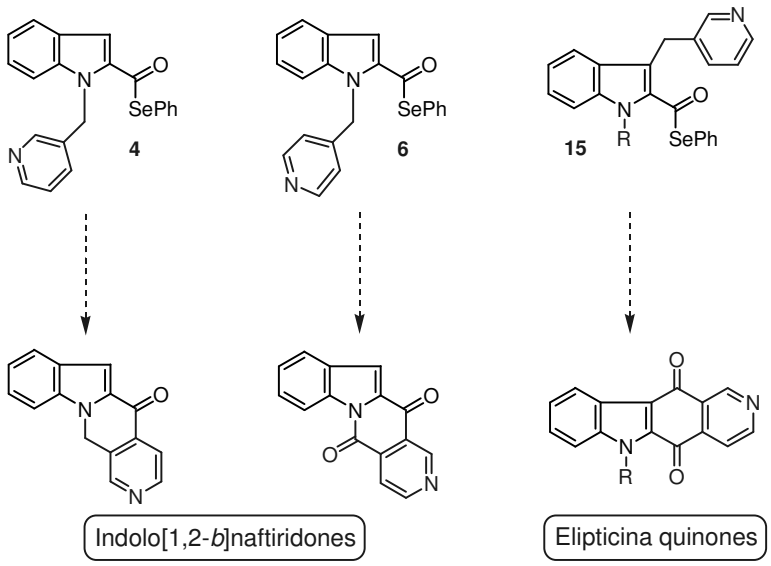
Des del punt de vista mecanístic, la regeneració de l'aromaticitat a partir del radical ciclohexadienil **E** pot ser descrita, com a la sèrie 1-benzil, mitjançant l'abstracció d'hidrogen per part del radical $Bu_3SnOO^{\cdot}$ o bé a través d'una reacció en cadena de tipus S_{RN1} per donar en ambdós casos el compost tetracíclic **F**, el qual és oxidat finalment a la quinona **14**.

D'altra banda, la formació de **15** es produiria a través d'una etapa competitiva de reducció del radical **E,** (a través de la forma tautomèrica **G**) promoguda pel fenilselenol,[3] seguida de deshidratació.

2.4. REACCIONS INTRAMOLECULARS REGIOSELECTIVES DE RADICALS 2-INDOLILACIL AMB PIRIDINES: ENTRADA SINTÈTICA A ELIPTICINA QUINONES

(*J. Org. Chem.* **2005**, *70*, 9077-9080)

Radicals 2-indolilacil: ciclació sobre piridines



Les anteriors ciclacions s'estengueren a substrats piridínics anàlegs com ara els selenoèsters **4**, **6** i **15**, que contenen una agrupació piridilmetil connectada al nitrogen o bé a la posició 3 de l'indole. En el primer cas, les ciclacions donarien accés a sistemes d'indolo[1,2-*b*]naftiridona, els quals constitueixen intermedis avançats en les primeres síntesis de Gribble de l'elipticina i compostos relacionats.[1,2] En el segon cas, s'accediria a elipticina quinones, compostos que presenten un interès intrínsec per la seva activitat anticancerosa[3] i també són importants intermedis en la síntesi de la pròpia elipticina.[4]

---

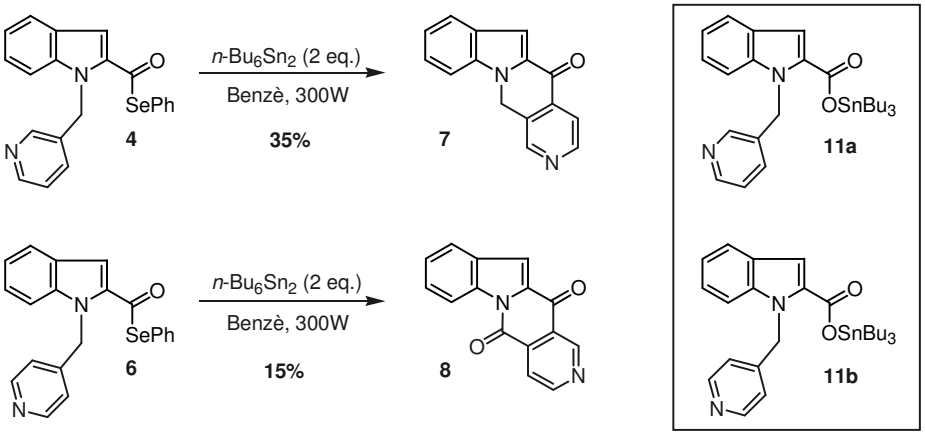
1 (a) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2810-2812. (b) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891-5899.

2 Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690-2695.

3 Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958-4963.

4 Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303-4427, i les referències citades.

Selenoèsters 4 i 6:
Condicions no reductores



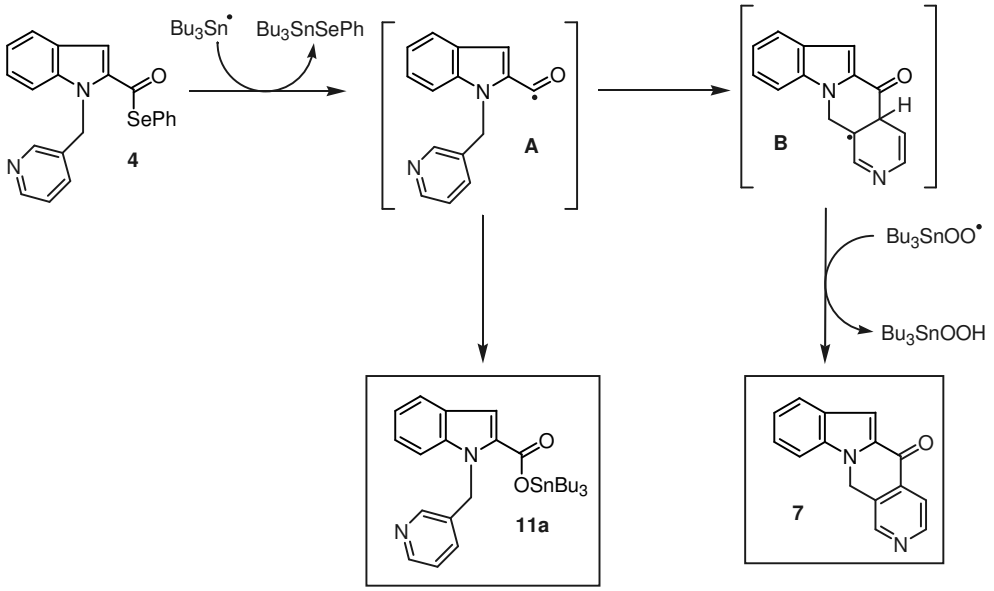
Anàlogament als resultats previs obtinguts a les sèries fenil, els selenoèsters **4** i **6** proporcionaren els corresponents productes de reducció quan es sotmeteren a ciclació en condicions reductores stàndard (*n*-Bu_3SnH-AIBN). En canvi, la ciclació desitjada sí tingué lloc quan els selenoèsters es tractaren amb 2 equivalents de *n*-Bu_6Sn_2 sota irradiació, encara que els rendiments foren clarament més baixos. A partir de **4**, l'acilació de l'anell piridínic tingué lloc de manera totalment regioselectiva per la posició 4 per donar el compost tetracíclic **7** amb un 35% de rendiment. Aquesta regioselectivitat C-4 contrasta amb els resultats descrits pels radicals aril, els quals normalment reaccionen amb el nucli piridínic proporcionant mescles regioisomèriques.[5]

A partir de **6**, l'acilació de la posició 3 de l'anell fou menys eficient i proporcionà, després de la sobreoxidació del metilè interanular, el compost tetracíclic **8** només amb un 15% de rendiment. En ambdós casos s'observà la formació de quantitats significatives dels èsters d'estany corresponents **11a** i **11b**.

---

[5] Harrowven, D. C.; Sutton, B. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2004; Vol. 16, pp. 27-53.

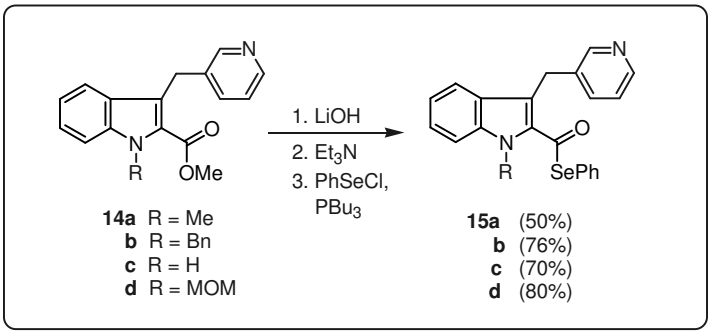
Mecanisme proposat per a la ciclació



El curs mecanístic d'aquestes ciclacions, representat a la figura per al selenoèster **4**, es pot interpretar a través d'un procés d'addició-oxidació, anàleg al postulat per a les sèries fenil. La relativa ineficiència d'aquestes ciclacions fou quelcom inesperat ja que estava descrit[6] que els perfils de reactivitat de les piridines no protonades amb radicals carbonats nucleòfils són similars als dels derivats benzènics. Aquestes diferències podrien ser atribuïdes a la presència de l'agrupació piridilmetil amb caràcter atraient d'electrons a l'àtom de nitrogen indòlic, fet que disminuiria la reactivitat del radical acil intermedi. Com a conseqüència, la concentració d'aquest radical augmentaria, facilitant així la formació de productes secundaris com els èsters d'estany **11**.

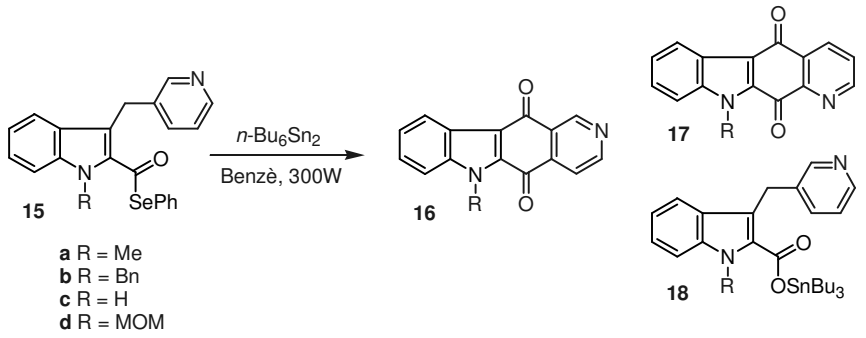
[6] (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489-519.

Preparació dels selenoèsters 15a-d



A continuació centràrem la nostra atenció en la sèrie 3-piridil. Tenint en compte que el substituent present al nitrogen indòlic podria modular la reactivitat del radical 2-indolilacil, es prepararen els selenoèsters **15a-d**, substituïts per grups metil, benzil o metoximetil, a partir del corresponents piridilmetilindoles **14** utilitzant procediments convencionals.

Selenoèsters 15: condicions no reductores



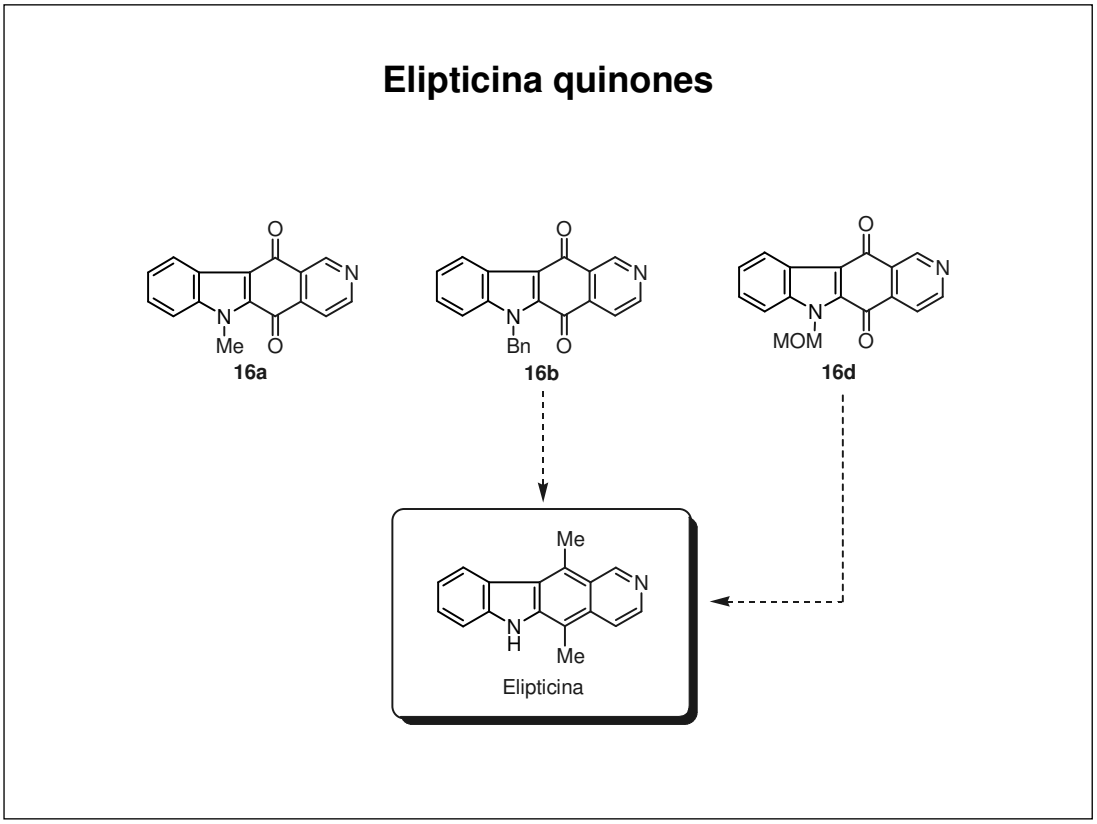
Assaig	Selenoèster	Elipticina quinona (rendiment)	Altres productes (rendiment)
1	**15a**	**16a** (60%)	**17a** (5%), **18a** (10%)
2	**15b**	**16b** (42%)	**17b** (8%)
3	**15c**	-	**18c** (85%)
4	**15d**	**16d** (10%)	**17d** (2%), **18d** (65%)

Els resultats obtinguts en la ciclació dels selenoèsters **15** en condicions no reductores es resumeixen a la taula representada a la figura. De manera satisfactòria, a partir dels derivats *N*-metil i *N*-benzil substituïts **15a** i **15b** (entrades 1 i 2) la ciclació tingué lloc de manera regioselectiva sobre la posició 4 de l'anell per donar, després de la sobreoxidació de la posició benzílica, les elipticina quinones **16a**[7] i **16b**[8] amb rendiments moderats. No obstant això es formaren també quantitats minoritàries dels corresponents regioisòmers **17** i dels èsters d'estany **18**.

Com era previsible, el radical acil derivat de **15d** (entrada 4) mostrà ser menys reactiu, probablement per la presència del grup metoximetil atraient d'electrons, en proporcionar la corresponent quinona **16d**[7] amb un rendiment molt baix. De manera inesperada, la ciclació no va tenir lloc a partir del selenoèster no substituït **15c** (entrada 3). Probablement el grup NH interfereix a l'etapa d'oxidació del radical azaciclohexadienil format inicialment, fet que inhibiria la reacció.[9] Significativament, en els dos darrers casos el producte majoritari o bé únic de la reacció fou l'èster d'estany **18**.

---

7 Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457-1460.



Com era d'esperar, les propietats físiques i espectroscòpiques de les elipticina quinones **16a**, **16b** i **16d** foren concordants amb les prèviament descrites per aquests compostos.[3,7,8] Tenint en compte que tant **16b**[7,8,10] com **16d**[7] s'havien transformat prèviament en l'alcaloide elipticina, la síntesi descrita constitueix una síntesi formal d'aquest producte natural.

Com a conclusió, es pot afirmar que la ciclació de radicals 2-indolilacil sobre piridines mediada per *n*-Bu_6Sn_2-hν té lloc amb una regioselectivitat notable per donar indolil 4-piridil cetones tetracícliques. L'efectivitat d'aquest protocol radicalari queda demostrada per una entrada sintètica directa a elipticina quinones.

---

8 Miki, Y.; Tada, Y.; Matsushita, K. *Heterocycles* **1998**, *48*, 1593-1597.

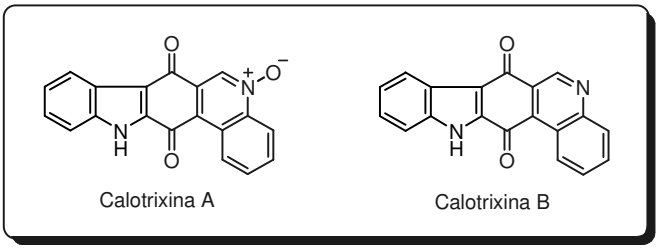
9 Per a la inhibició de radicals per part de la difenilamina i d'altres amines aromàtiques, vegeu: MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem*. **1996**, *61*, 1316-1321.

10 Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. *J. Chem. Soc., Perkin Trans.1*, **1990**, 1319-1329.

2.5. UNA NOVA RUTA SINTÈTICA CAP A LA CALOTRIXINA B A TRAVÉS DE RADICALS

(*Org. Lett.* **2006**, *8*, 561-564)

Calotrixines A i B



- Aïllats l'any 1999 de cianobacteris *Calothrix*
- Esquelet d'indolo[3,2-*j*]fenantridina
- Propietats antimalàriques i anticanceroses

La calotrixina B i el seu derivat *N*-òxid (calotrixina A) són dos productes naturals aïllats l'any 1999 de cianobacteris del gènere *Calothrix*,[1] caracteritzats per presentar una unitat de carbazole-1,4-quinona inclosa en un sistema pentacíclic d'indolo[3,2-*j*]fenantridina, inèdit entre els productes naturals.[2] Degut a les seves interessants propietats antimalàriques i anticanceroses,[3] aquests alcaloides han atret l'atenció sintètica de diversos grups de recerca.

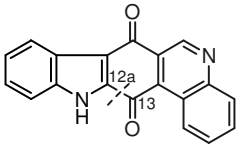
---

1 Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Saliba, K. J.; Smith, G. D. *Tetrahedron* **1999**, *55*, 13513-13520.

2 Per una aproximació sintètica a l'esquelet d'indolo[3,2-*j*]fenantridina, anterior a l'aïllament de les calotrixines, vegeu: Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem*. **1995**, *60*, 1939-1946.

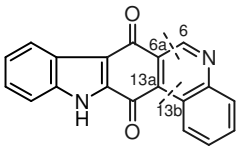
3 Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Simith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem*. **2004**, *47*, 4958-4963, i les referències citades.

Síntesis prèvies



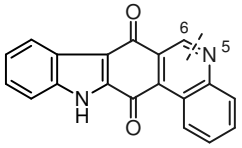
Kelly et al. *Org. Lett.* **2000**, *2*, 3735-3737.
Chai et al. *Tetrahedron Lett.* **2002**, *43*, 2939-2940.

⇨ Tècniques de metal.lació: enllaç format C_{12a}-C_{13}



Guingant et al. *Synlett* **2004**, 2612-2614.

⇨ Reacció d'hetero-Diels-Alder: enllaç format C_6-C_{6a} i C_{13a}-C_{13b}



Hibino et al. *Tetrahedron Lett.* **2005**, *46*, 5263-5264.

⇨ Construcció final de l'anell de quinolina: enllaç format C_5-C_6

S'han descrit 4 síntesis totals per a les calotrixines emprant les diferent estratègies sintètiques que s'esquematitzen a la figura. Així, l'any 2000 Kelly[4] i, 2 anys més tard, Chai[5] sintetitzaren les calotrixines A i B connectant els anells d'indole i quinoline mitjançant tècniques de metal.lació[6] (darrer enllaç format C_{12a}-C_{13}).

Més recentment, Guingant[7] i Hibino[8] sintetitzaren la calotrixina B emprant estratègies totalment diferents: una reacció d'hetero-Diels-Alder, que implica la formació dels enllaços C_6-C_{6a} i C_{13a}-C_{13b}, i la construcció final de l'anell de quinolina per formació de l'enllaç C_5-C_6, respectivament.

---

4 Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735-3737.

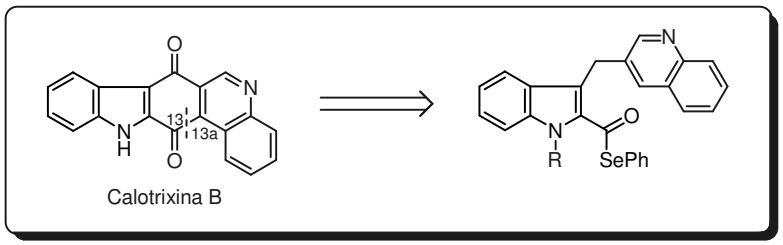
5 (a) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939-2940. (b) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906-8909.

6 S'havien emprat tècniques de metal.lació similars en el context de la síntesi d'elipticina quinones: (a) Watanabe, M.; Snieckus, V. *J. Am. Chem.* Soc. **1980**, *102*, 1457-1460. (b) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451-5457.

7 Sissouma, D.; Collet, S. C.; Guingant, A. Y. *Synlett* **2004**, 2612-2614.

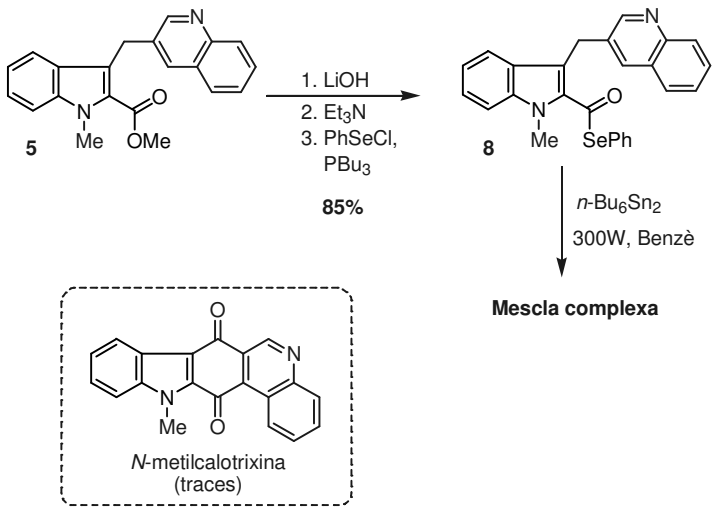
8 Tohyama, S.; Choschi, T.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2005**, *46*, 5263-5264.

Estratègia sintètica



Amb la nostra experiència prèvia, visualitzàrem una aproximació alternativa a l'esquelet pentacíclic de la calotrixina B basada en el tancament de l'anell carbocíclic central en les últimes etapes de la síntesi per acilació homolítica de la posició 4 de la quinolina (enllaç format C_{13}-C_{13a}). En aquesta aproximació, l'anell π-deficient de quinolina reaccionaria amb un radical acil nucleòfil, fet que es podria considerar com l'*umpolung* de la reacció intramolecular de Friedel-Crafts.

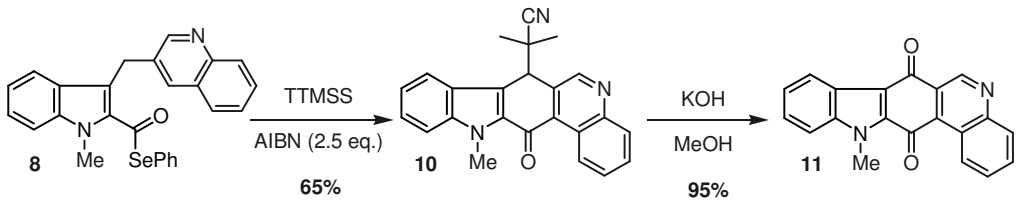
Sèrie model: ciclació del selenoèster 8



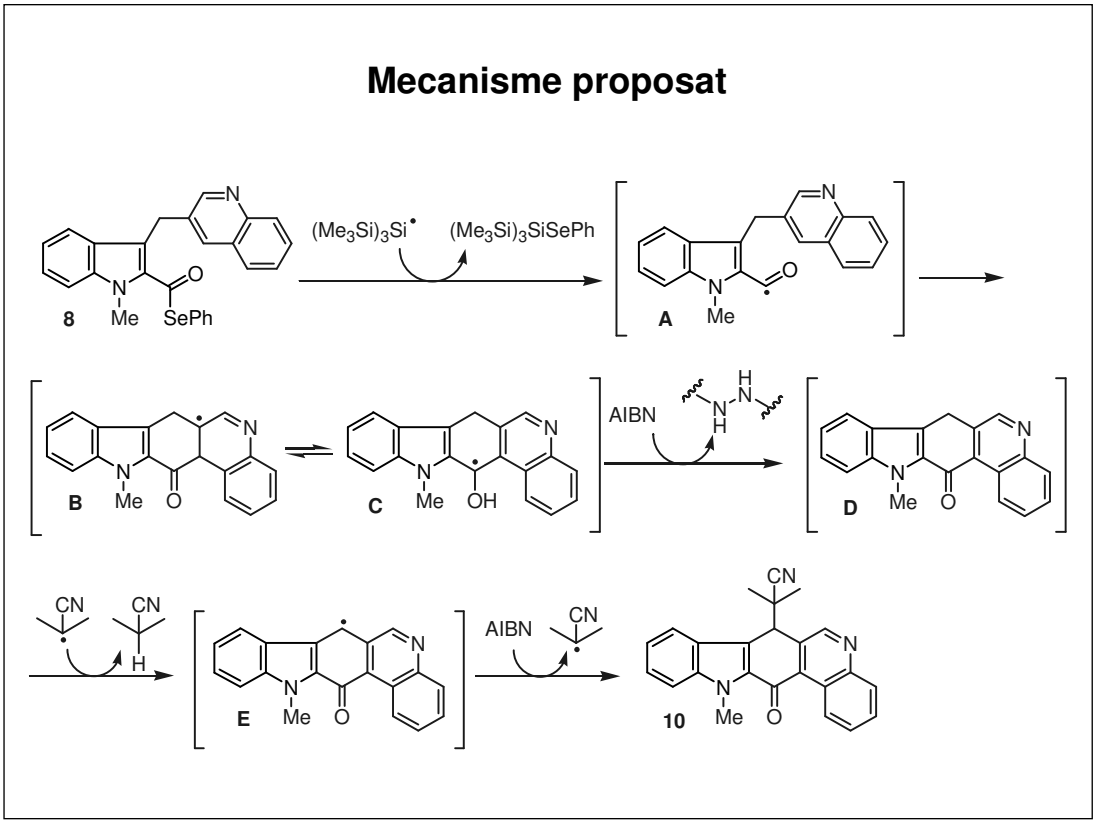
La nostra investigació s'inicià amb el selenoèster **8**, com a precursor radicalari model que incorporava la agrupació de (3-quinolil)metil connectada a la posició 3 de l'indole. Aquest compost fou assequible a partir de l'èster metílic **5** a través de reaccions anàlogues a les emprades a la sèrie piridina.

De manera anàloga a les anteriors sèries, el selenoèster **8** es sotmeté a ciclació en condicions no reductores (*n*-Bu_6Sn_2, 300W). Sorprenentment, en aquest cas la reacció proporcionà una mescla complexa de productes, de la qual només es pugué aïllar l'*N*-metilcalotrixina en quantitat de traces.

Selenoèster 8:
Ciclació en condicions reductores



Donat que aquest resultat decebedor podria estar relacionat amb un augment de la reactivitat de l'anell de quinolina en relació al de piridina o benzè, centrarem la nostra atenció en les condicions reductores, esperant que la ciclació fos ara suficientment ràpida com per evitar la reducció prematura del radical acil. De manera satisfactòria, el tractament de **8** amb TTMSS i AIBN (2.5 equivalents) proporcionà el compost pentacíclic relacionat amb la calotrixina **10** amb un 65% de rendiment. Aquest compost, que incorpora l'agrupació de 2-ciano-2-propil de l'iniciador, es convertí en l'*N*-metilcalotrixina **11** per tractament amb KOH en el si de metanol, a través d'un procés que implica una substitució nucleòfila tipus gramina, seguida de l'oxidació espontània del carbinol inicialment format.



La formació del compost **10** es podria explicar a través de la seqüència d'addició-rearomatització-sobreoxidació representada a la figura. Així, el radical indolilacil **A** format inicialment experimentaria ciclació regioselectiva sobre la posició 4 de la quinolina per donar el radical azaciclohexadienil **B**. Considerant els precedents descrits de reaccions de substitució homolítica en condicions reductores, aquest radical, o el radical tipus benzhidril tautomèric **C**, seria oxidat per l'iniciador AIBN mitjançant l'abstracció d'un àtom d'hidrogen.[9,10] A continuació, una nova abstracció d'hidrogen a la posició doblement benzílica de **D**, per exemple per part de radicals 2-ciano-2-propil, proporcionaria el radical **E**, que seria interceptat finalment per l'iniciador.[11]

Com es pot observar en aquest esquema, el mediador radicalari TTMSS només participa en la generació inicial del radical acil. Aquet fet ens feu plantejar la possibilitar de promoure una seqüència homolítica en absència de mediador,[12] en la qual l'AIBN actuaria d'oxidant i la homòlisi inicial de l'enllaç C-Se tindria lloc sota una simple irradiació.[13]

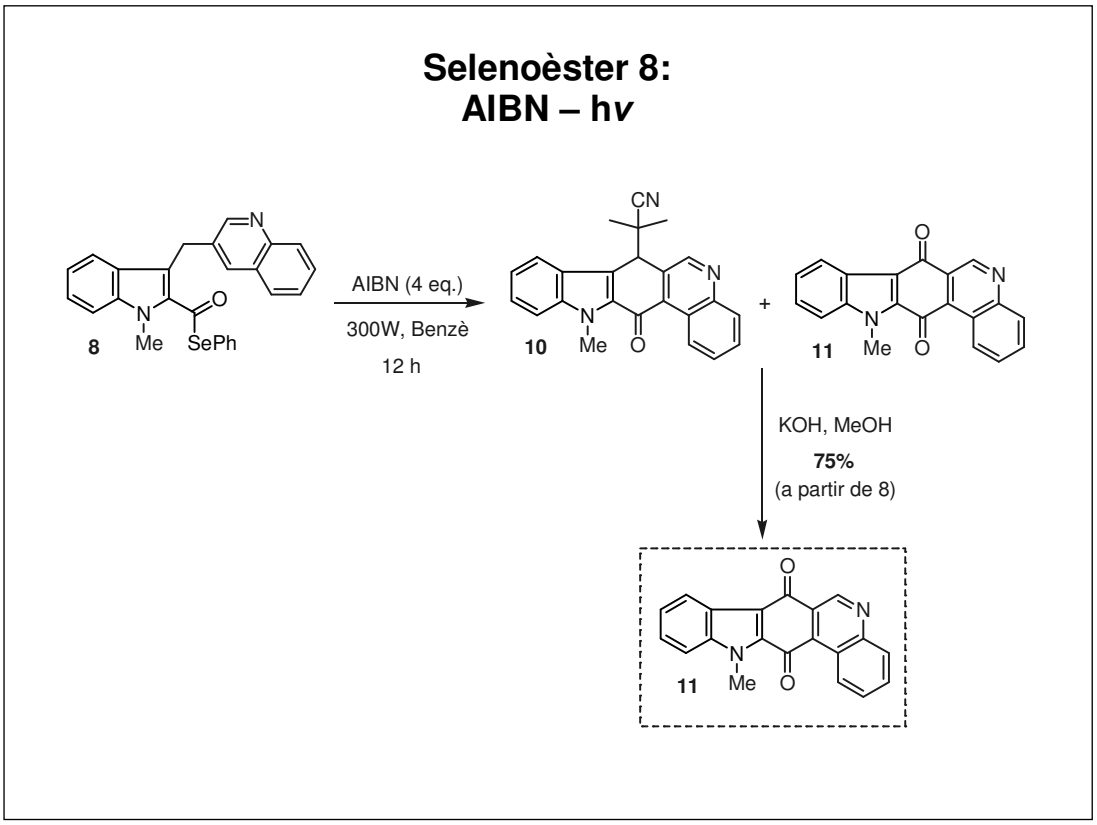
[9] Per a una discussió, vegeu: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed*. **2004**, *43*, 95-98, i les referències citades.

[10] És sabut que els azo compostos poden abstreure hidrogen dels radicals benzhidril per a donar benzofenona i hidrazines: Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc*. **1989**, *111*, 1830-1835.

[11] Per a exemples de ciclacions radicalàries en les quals té lloc la formació de subproductes que contenen la unitat 2-ciano-2-propil provinent de l'AIBN, vegeu: (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268-6271. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem*. **2001**, *66*, 7547-7551.

[12] Es tractaria d'una seqüència homolítica metal free: Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed*. **1998**, *37*, 3072-3082.

[13] Per a la generació de radicals acil per fotòlisi de teluroèsters, vegeu: Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc*. **1994**, *116*, 8937-8951.

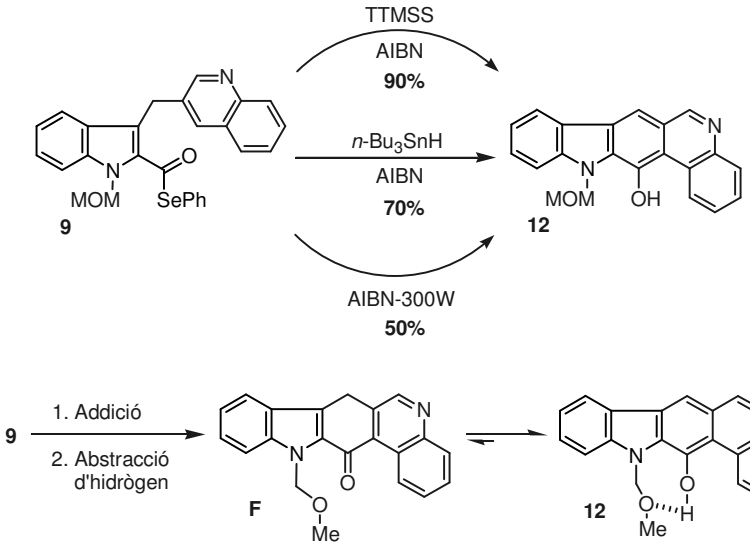


D'acord amb aquest plantejament, la ciclació desitjada tingué lloc quan el selenoèster **8** s'irradià (300 W) en presència d'AIBN a la temperatura de reflux de benzè.[14] No obstant això, la desaparició del producte de partida requerí temps de reacció més llargs i l'addició lenta de quantitats majors d'AIBN (fins a 4 equivalents).[15] S'obtingué així una mescla 1:1 del compost **10** i l'*N*-metilcalotrixina **11**, resultat que indicava que en aquestes condicions sí es produia, encara que parcialment, la completa oxidació al sistema de quinona. Com era d'esperar, el tractament d'aquesta mescla amb KOH en metanol proporcionà **11** com a producte únic amb un 75% de rendiment (a partir de **8**).

[14] No s'observà ciclació quan el selenoèster **8** s'irradià a 80ºC sense AIBN ni quan s'escalfà en presència d'AIBN sense irradiació.

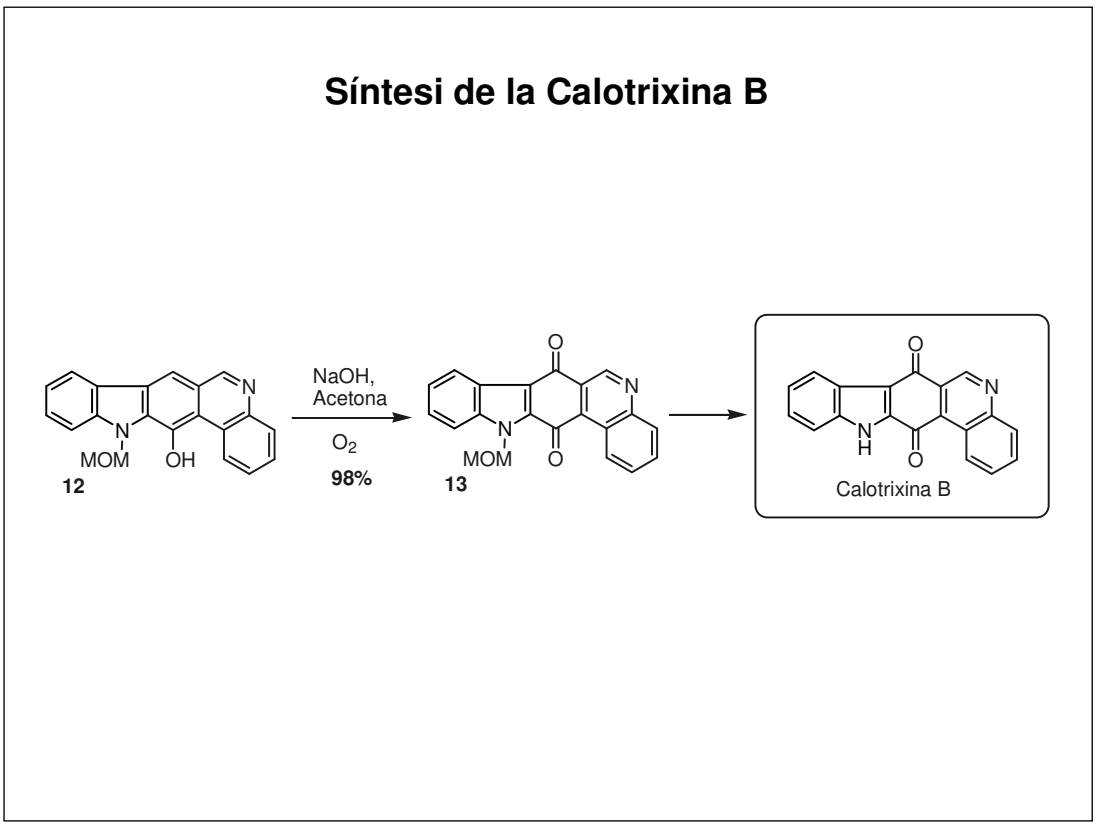
[15] El temps de vida mitja per a la descomposició de l'AIBN és de 2 h a 80ºC: Walling, C. *Tetrahedron* **1985**, *41*, 3887-3900.

Ciclació del selenoèster 9



En aquest punt, l'accés a l'alcaloide calotrixina B requeria l'extensió de la química anterior a un precursor radicalari convenientment protegit al nitrogen indòlic, com ara l'*N*-metoximetil selenoèster **9**. La ciclació de **9** en condicions reductores utilitzant TTMSS com a mediador radicalari tingué lloc de manera més eficient que a la sèrie *N*-metil proporcionant el fenol **12** amb un 90% de rendiment. El mateix fenol **12** s'obtingué emprant altres protocols (*n*-Bu_3SnH-AIBN o AIBN sota irradiació), encara que els rendiments foren més baixos (70 i 50% respectivament).

Cal esmentar que el fenol **12**, un tautòmer completament aromàtic de la cetona **F**, seria resistent a la sobreoxidació observada a la sèrie *N*-metil. Aquesta forma tautomèrica estaria ara afavorida degut a l'establiment d'un pont d'hidrogen intramolecular entre el grup hidroxi i el grup metoxi.



Des del punt de vista sintètic, l'oxidació desitjada al sistema quinònic tingué lloc amb un rendiment pràcticament quantitatiu per tractament de **12** amb oxigen en medi bàsic,[16] per donar l'*N*-metoximetil calotrixina **13** , un conegut precursor per desprotecció de la calotrixina B.

Com a conclusió, la ciclació de radicals 3-(3-quinolil)metil-2-indolilacil mediada per TTMSS-AIBN proporciona de manera eficaç compostos pentacíclics relacionats amb la calotrixina, els quals s'obtenen en diferents graus d'oxidació depenent del substituent situat al nitrogen indòlic. Les reaccions es poden efectuar també emprant un nou protocol radicalari que il.lustra el paper determinant de l'AIBN en les reaccions de substitució homolítica.

A partir del selenoèster **9** s'ha portat a terme una nova síntesi de la calotrixina B, posant de manifest el potencial sintétic de les ciclacions de radicals 2-indolilacil sobre nuclis heteroaromàtics per a la construcció de compostos indòlics policíclics.

---

[16] Per a oxidacions en medi bàsic relacionades, vegeu: (a) Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem*. **2005**, *13*, 819-837. (b) Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett*. **2005**, *46*, 7615-7618.

3. CONCLUSIONS

La present Tesi Doctoral es situa en el context de les reaccions intramoleculars de radicals 2-indolilacil i està constituïda, d'acord amb els objectius inicials, per dues parts.

La primera part centra l'atenció en les ciclacions de radicals 2-indolilacil en condicions reductores, emprant alquens com a acceptors radicalaris per a l'obtenció d'estructures que formen part de productes naturals i d'altres compostos bioactius.

En aquest context s'ha aconseguit:

- El desenvolupament d'un nou procediment d'anulació indòlica que permet accedir a cetones cícliques 1,2-fusionades amb l'indole.
- La síntesi total de l'alcaloide (±)-guatambuïna i la síntesi formal de l'alcaloide olivacina.

La segona part es situa en el context de les reaccions intramoleculars de radicals 2-indolilacil amb sistemes aromàtics.

Els principals aconseguiments en aquesta part són:

- La ciclació de radicals 2-indolilacil sobre anells de benzè en condicions no reductores (*n*-Bu_6Sn_2-hν) per donar de manera eficient indolil fenil cetones tetracícliques.
- La ciclació regioselectiva de radicals 2-indolilacil sobre piridines en condicions no reductores (*n*-Bu_6Sn_2-hν) per donar indolil 4-piridil cetones tetracícliques. L'efectivitat d'aquest protocol radicalari permet el fàcil accés a elipticina quinones.
- La ciclació de radicals 3-(3-quinolil)metil-2-indolilacil en condicions reductores (TTMSS-AIBN) per donar pentacicles relacionats amb la calotrixina, l'estat d'oxidació dels quals varia depenent del tipus de substituent del nitrogen indòlic. A partir d'un substrat convenientment substituït s'ha assolit la síntesi de l'alcaloide calotrixina B.

- El desenvolupament d'un protocol *metal free* per a la ciclació de radicals 3-(3-quinolil)metil-2-indolilacil, en el qual es fa evident la importància del paper de l'AIBN en les reaccions de substitució homolítica aromàtica.

4. ANNEX: PUBLICACIONS

ORGANIC LETTERS

2004
Vol. 6, No. 5
759−762

Intramolecular Reactions of 2-Indolylacyl Radicals: Access to 1,2-Fused Ring Indole Derivatives

M.-Lluïsa Bennasar,* Tomàs Roca, and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@ub.edu

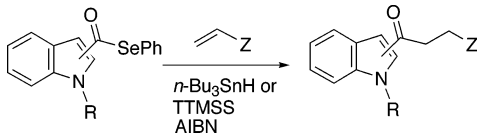
Received December 18, 2003

ABSTRACT

The generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters under reductive conditions and their behavior in intramolecular addition reactions to carbon–carbon double bonds located at the indole nitrogen have been studied.

Radical reactions have long been recognized as important tools in organic synthesis,[1] often being used as key steps in the construction of complex natural products.[2] In particular, the addition of *functionalized* acyl radicals[3] to multiple C−C bonds constitutes a useful method for the synthesis of acyclic and cyclic ketones. The reaction of selenoesters with stannyl and tris(trimethylsilyl)silyl radicals is one of the most practical ways to generate these radical intermediates,[3] although other protocols and precursors can be used.[4] Our interest in the chemistry of functionalized indoles as common substructures of many natural and medicinal compounds[5] led us to explore the reactivity and synthetic possibilities of indolylacyl radicals. Thus, with Boger's work on benzoyl radicals in mind,[6] 2- and 3-indolylacyl radicals were generated from the corresponding phenyl selenoesters under reductive conditions and allowed to intermolecularly react with alkene acceptors, providing easy access to 2-[7] and 3-acylindoles[8] (Scheme 1). Our efforts were then focused on the *intramolecular* version of the above radical reactions, as a general approach to a great variety of polycyclic indolyl ketones.[9] We herein report our preliminary results concerning this new indole annulation procedure, using 2-indolylacyl

Scheme 1



(1) (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715−777 and 779−831. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React*. **1996**, *48*, 301−856. (c) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

(2) (a) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 405−407. (b) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.

(3) For reviews on acyl radical chemistry, see: (a) Ryu, I.; Sonoda, N.; Curran D. P. *Chem. Rev*. **1996**, *96*, 177−194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991−2069.

(4) For recent examples of the generation of acyl radicals from thiolesters, see: (a) Crich, D.; Yao, Q. *J. Org. Chem*. **1996**, *61*, 3566−3570. (b) Ozaki, S.; Adachi, M.; Sekiya, S.; Kamikawa, R. *J. Org. Chem*. **2003**, *68*, 4586−4589. (c) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett*. **2003**, *5*, 1313−1316. From acyl hydrazides, see: (d) Braslau, R.; Anderson, M. O.; Rivera, F.; Jiménez, A.; Haddad, T.; Axon, J. R. *Tetrahedron* **2002**, *58*, 5513−5523. (e) Bath, S.; Laso, N. M.; López-Ruiz, H.; Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun*. **2003**, 204−205.

(5) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996; pp 105−134.

(6) Boger, D. L.; Mathvink, R. J. *J. Org. Chem*. **1992**, *57*, 1429−1443.

(7) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett*. **2001**, *3*, 1697−1700.

(8) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 6268−6271.

10.1021/ol036455l CCC: $27.50
Published on Web 01/30/2004

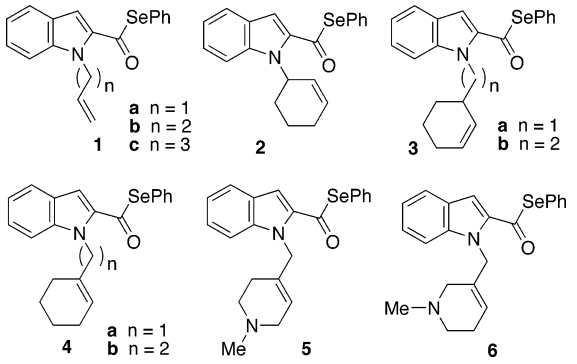


Figure 1.

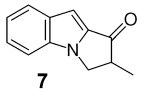
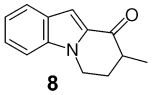
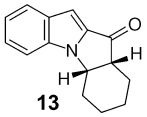
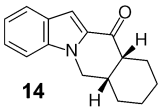
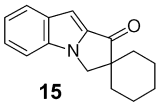
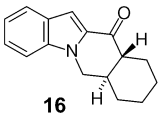
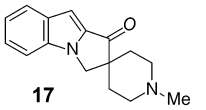
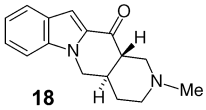
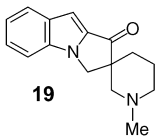
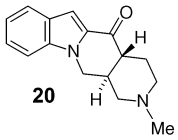
radicals in cyclization reactions upon alkene acceptors located at the indole nitrogen.[10]

With the aim of studying the scope of this cyclization process for the construction of isolated or fused rings, indole selenoesters **1**−**6** (Figure 1), which carry different alkenyl, cyclohexenyl, or tetrahydropyridyl moieties at the nitrogen, were selected as radical precursors. These compounds were prepared from the respective carboxylic acids,[11] following the procedure reported by Batty and Crich.[12] The results of the radical reactions, performed in all cases under standard reductive conditions (*n*-Bu_3SnH, AIBN, benzene, reflux, slow addition), are depicted in Table 1.

Consistent with empirical rules for alkyl radical cyclizations,[1b] as well as previous results with benzoyl radicals,[6] the 5-hexenoyl radical derived from **1a** showed a strong preference for the formation of the five-membered ring through the exo mode to give **7** as the only isolable product in 84% yield (entry 1).[13] Compound **7** has the pyrrolo[1,2-*a*]indole skeleton characteristic of mytomycins,[14] a group of metabolites from *Streptomyces* that have attracted much attention due to their antitumoral and antibacterial activity. Significantly, cyclization of the 6-heptenoyl radical[15] derived from **1b** was also totally exo regioselective, leading to pyrido[1,2-*a*]indole **8** in 70% yield (entry 2). No evidence of radical reduction (i.e., formation of an aldehyde) coming from direct hydrogen abstraction from the hydride or an eventual [1,5]-hydrogen atom transfer was observed. In contrast to the benzoyl series, the formation of a seven-membered ring did not occur from **1c**, only aldehyde **9** (Figure 2) being isolated in 70% yield. Reduction to **9** was also observed when the poorer hydrogen-atom donor tris(trimethylsilyl)silane[16] was used as the radical mediator.

We were also interested in the possibility of promoting a cascade reaction from selenoester **1a**, involving a cyclization process followed by an intermolecular addition of the intermediate cyclopentylmethyl radical **A** to an external electron-deficient alkene (Scheme 2).[17] To this end, **1a** was treated with *n*-Bu_3SnH-AIBN in the presence of different

Table 1. Radical Cyclization of Indoles **1**−**6**[a]

entry	indole	products	cyclization mode	yield[b]
1	**1a**	 **7**	5-exo	84
2	**1b**	 **8**	6-exo	70
3	**2**	 **13**	5-exo	70
4	**3a**	 **14**	6-exo	70
5	**4a**	 **15**	5-exo	10
		 **16**	6-endo	75
6	**5**	 **17**	5-exo	27
		 **18**	6-endo	25
7	**6**	 **19**	5-exo	30
		 **20**	6-endo	35

[a] *n*-Bu_3SnH (1.1 mol), AIBN (10 mol %), C_6H_6, 0.06 M, reflux, syringe pump. [b] Isolated yield of chromatographically pure material.

(9) For recent examples of intramolecular reactions of acyl radicals generated from *alkyl* phenyl selenoesters, see: (a) Double, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2005−2007. (b) Evans, P. A.; Raina, S.; Ahsan, K. *Chem. Commun.* **2001**, 2504−2505 and references therein. (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887−7890.

(10) For related cyclizations involving 2-indolyl radicals, see: Dobbs, A. P.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149−2160.

(11) See the Supporting Information for complete details.

(12) Batty, D.; Crich, D. *Synthesis* **1990**, 273−275.

(13) Tetracycle **7** has been prepared by cyclization of a 2-indolylacyl radical generated from an alkynylthiol ester. See ref 4c.

(14) Remers, W. A.; Dorr, R. T. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, pp 1−74.

(15) For a recent study on cyclization of 6-heptenyl radicals, see: Bailey, W.; Longstaff, S. C. *Org. Lett.* **2001**, *3*, 2217−2219.

(16) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

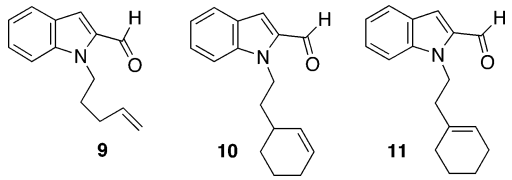
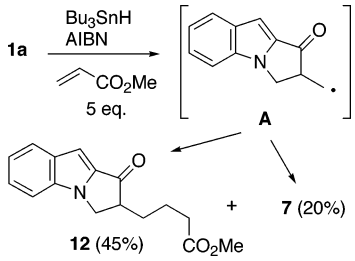


Figure 2.

amounts of methyl acrylate. The best yields (45%) of the desired 2-substituted pyrrolo[1,2-*a*]indole **12** were obtained when the reaction was performed in the presence of 5 equivalents of alkene. However, minor amounts (20%) of **7**, coming from the direct reduction of the radical **A**, were also formed. Confirming the fast 5-exo cyclization, the simple alkene-addition product was not detected in any assay.

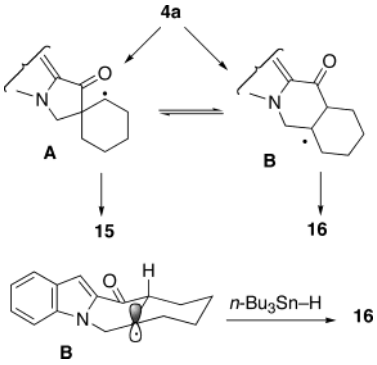
Scheme 2. Radical Cyclization−Intermolecular Addition Cascade Reaction



The formation of fused rings via an exo cyclization mode was investigated from selenoesters **2** and **3a**,**b**, bearing a 2-cyclohexenyl moiety directly attached to the indole nitrogen or separated by one or two methylene groups. In these series, we expected the cyclization of the 2-acyl radical to the cyclic alkene to occur in a cis manner owing to steric constraints imposed by the ring system.[18] Subsequent reduction of the cyclic radical adduct at the α-position of the ring junction would account for the formation of the final products. Indeed, clean 5- and 6-exo cyclizations took place from **2** and **3a** to give stereoselectively the cis-fused tetracycles **13** and **14** (entries 3 and 4, 70%). Tetracycle **14** could be quantitatively transformed into the thermodynamically more stable trans-fused tetracycle **16** (see below) by treatment with MeONa in MeOH. In contrast, 7-exo cyclization did not occur from **3b**, and only aldehyde **10** (Figure 2) was isolated from the reaction mixtures.

The higher alkene substitution present in the 2-indolylacyl radical derived from **4a** retarded the usually favored 5-exo cyclization mode in benefit of the 6-endo mode. Thus, the trans-fused tetracycle **16** was isolated as the major product in 75% yield along with minor amounts (10%) of the spiro compound **15** (entry 5). As the exo-endo product ratio was not significantly affected by the hydride concentration, we assumed that it reflected the kinetic composition of the initially formed radical adducts **A** and **B** rather than the equilibration between these intermediates through an intramolecular rearrangement (Scheme 3).[19] On the other hand, the trans configuration of **16** is the result of the stereoselective axial hydrogen abstraction of the bridgehead radical **B** from the hydride.[18,20]

Scheme 3



Disappointingly, the 2-indolylacyl radical derived from **4b**, with an additional carbon atom in the connecting chain, underwent reduction to aldehyde **11** (Figure 2) under the reaction conditions, thus indicating that both 6-exo and 7-endo ring closure were too slow for the radical chain to be productive.

With the aim of extending the above regioselective 6-endo cyclizations to the construction of fused azacyclic systems, we next turned our attention to selenoesters **5** and **6**, in which a double bond of the same substitution pattern as **4a** is included in a 4- or 3-substituted 1,2,5,6-tetrahydropyridine moiety.[21]

Rather surprisingly, in both cases the crude cyclization product was shown by ^{1}H NMR to be a nearly equimolecular mixture of the corresponding spiro (**17** and **19**) and fused piperidine compounds (**18** and **20**), from which pure regioisomers were isolated in yields depicted in Table 1 (entries 6 and 7). As in the above carbocyclic series, the 6-endo cyclization products **18** and **20** were exclusively obtained

(17) For similar 5-exo cyclizations−intermolecular additions, see: (a) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc*. **1990**, *112*, 4003−4008. (b) Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett* **1995**, 1249−1251.

(18) Curran, D. P.; Porter, N. A. Giese, B. *Stereochemistry of Radical Reactions*; WCH: Weinheim, 1996.

(19) For a discussion, see: Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J.* **1997**, *3*, 376−387. See also ref 6.

(20) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem*. **1972**, *25*, 1081−1105.

(21) In the literature, there are several reports of alkyl and aryl radical cyclizations upon azacyclic systems, most of them 1,4,5,6-tetrahydropyridines, to give heterocycles bearing the nitrogen atom in the new ring formed. See inter alia: (a) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349−10362. (b) Zhang, W. *Tetrahedron* **2001**, *57*, 7237−7262. (c) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009−3018. For radical cyclizations upon 1,4,5,6-tetrahidropyridines where a carbocycle is created, see: (d) Ripa, L.; Hallberg, A. *J. Org. Chem*. **1998**, *63*, 84−91. (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8507.

as trans-fused stereoisomers due to the stereoselective reduction of the intermediate radical adducts. The different exo-endo regioselectivity exhibited by 2-indolylacyl radicals derived from **5** and **6** with respect to **4a** deserves comment. It seems reasonable to assume that, as a consequence of the inclusion of a nitrogen atom in the preexisting ring, the 6-endo pathway is kinetically decelerated.

In summary, a new indole annulation procedure based on intramolecular reactions of 2-indolylacyl radicals has been developed. When appropriate carbon−carbon double bonds connected to the indole nitrogen are used as acceptors, the procedure provides straightforward access to cyclic ketones fused to the 1,2-position of the indole nucleus, which should be of interest for the synthesis of natural products and medicinal compounds.

Acknowledgment. Financial support from the "Ministerio de Ciencia y Tecnología" (MCYT), Spain (Project No. BQU2000-0785), and MCYT-FEDER (Project No. BQU2003-04967-C02-02) is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant No. 2001SGR00084. F.F. thanks the University of Barcelona for a grant.

Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036455L

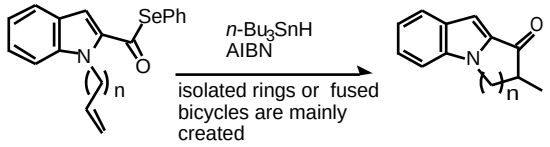
Supporting Information

Intramolecular Reactions of 2-Indolylacyl Radicals: Access to 1,2-Fused Ring Indole Derivatives

M.-Lluïsa Bennasar, Tomàs Roca, and Francesc Ferrando*

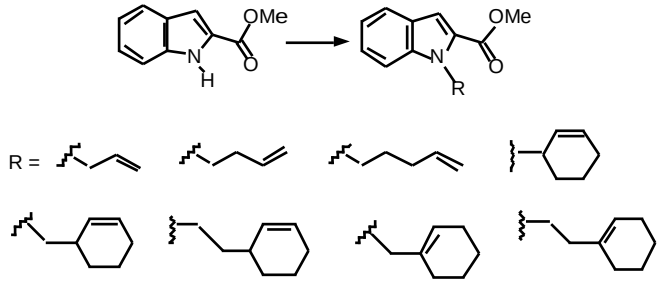
Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

bennasar@ub.edu



Contents:

A. Methyl 1-Alkyl-2-indolecarboxylates. General Procedure



A solution of methyl 2-indolecarboxylate (1 g, 5.71 mmol) in anhydrous DMF (10 mL) was added dropwise under Ar to a suspension of NaH (6.85 mmol) in anhydrous THF (5 mL). After stirring at rt for 1 h, the mixture was cooled to 0 ºC and the appropriate alkylating agent (see below, 6.85 mmol) was added. The mixture was allowed to warm to rt overnight, then was quenched with cold water and extracted with Et_2O (3 x 40 mL). The organic extracts were washed with H_2O (5 x 100 mL), dried and concentrated to give crude esters, which were purified by flash chromatography (SiO_2). Eluent, yields and NMR data ($CDCl_3$) are given below.

Methyl 1-Allyl-2-indolecarboxylate: alkylating agent, allyl bromide; 80% yield; elution with 2:8 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 3.86 (s, 3H), 4.86 (dddd, *J* = 1.4, 1.6, 1.6, 17 Hz, 1H), 5.07 (dddd, *J* = 1.4, 1.6, 1.6, 10.2 Hz, 1H), 5.19 (m, 1H), 5.98 (m, 1H), 7.13 (m, 1H), 7.32 (m, 3H), 7.62 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 46.8 (CH_2), 51.7 (CH_3), 110.6 (CH), 110.8 (CH), 116.0 (CH_2), 120.7 (CH), 122.7 (CH), 125.1 (CH), 126.0 (C), 127.0 (C), 133.8 (CH), 139.1 (C), 162.3 (C).

Methyl 1-(3-Butenyl)-2-indolecarboxylate: alkylating agent, 3-butenyl bromide; 40% yield; elution with 3:7 hexanes-AcOEt.

Spectroscopic data of the corresponding carboxylic acid (see below): ^{1}H NMR (200 MHz) δ 2.58 (d, *J* = 7.2 Hz, 2H), 4.60 (t, *J* = 7.2 Hz, 2H), 5.02 (m, 2H), 5.50 (br s, 1H), 5.80 (m, 1H), 7.16 (m, 1H), 7.35 (m, 2H), 7.42 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 34.9 (CH_2), 44.1 (CH_2), 110.5 (CH), 111.9 (CH), 116.9 (CH_2), 120.5 (CH), 122.7 (CH), 125.1 (CH), 125.9 (C), 128.0 (C), 134.8 (CH), 139.2 (C), 167.0 (C).

Methyl 1-(4-Pentenyl)-2-indolecarboxylate: alkylating agent, 4-pentenyl bromide; 45% yield; elution with 9:1 hexanes-CH_2Cl_2; ^{1}H NMR (300 MHz) δ 1.88 (m, 2H), 2.10 (q, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 4.54 (t, *J* = 7.2 Hz, 2H), 5.0 (m, 2H), 5.82 (m, 1H), 7.12 (m, 1H), 7.28 (s, 1H), 7.32 (m, 2H), 7.65 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 29.6 (CH_2), 31.1 (CH_2), 44.2 (CH_2), 51.5 (CH_3), 110.4 (CH), 110.6 (CH), 115.2 (CH_2), 120.5 (CH), 122.7 (CH), 124.9 (CH), 126.0 (C), 127.0 (C), 137.6 (CH), 139.0 (C), 162.2 (C).

Methyl 1-(2-Cyclohexenyl)-2-indolecarboxylate: alkylating agent**,** 2-cyclohexenyl bromide; 40% yield; elution with 5:5 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.8-2.2 (m, 6H), 3.90 (s, 3H), 5.95 (m, 2H), 6.25 (m,1H), 7.12 (m, 1H), 7.28 (m, 3H), 7.68 (d, *J* = 8 Hz, 1H).

Methyl 1-(2-Cyclohexenylmethyl)-2-indolecarboxylate: alkylating agent, (2-cyclohexenyl)methyl methanesulfonate; 45% yield; elution with 9:1 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 1.4-1.8 (m, 4H), 2.0 (m, 2H), 2.70 (m, 1H), 3.91 (s, 3H), 4.47 (m, 2H), 5.46 (dd, *J* = 2.2, 10.4 Hz, 1H), 5.75 (m, 1H), 7.14 (m, 1H), 7.32 (m, 1H), 7.33 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 20.9 (CH_2), 25.4 (CH_2), 26.8 (CH_2), 37.0 (CH), 49.4 (CH_2), 51.7 (CH_3), 110.9 (CH), 111.0 (CH), 120.4 (CH), 122.6 (CH), 124.8 (CH), 125.8 (C), 127.2 (C), 128.1 (CH), 128.7 (CH), 139.6 (C), 162.4 (C).

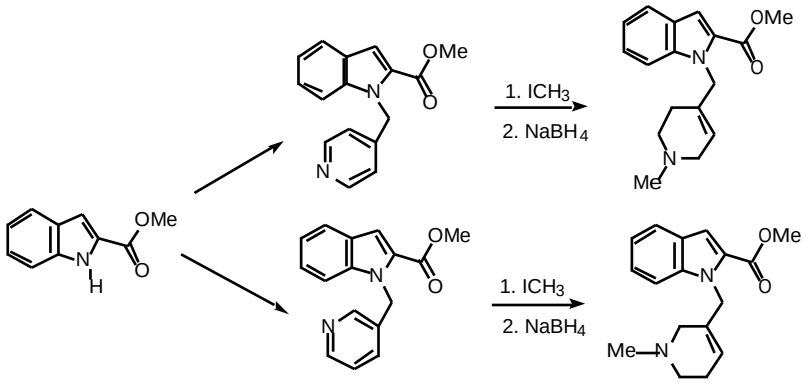
Methyl 1-[2-(2-Cyclohexenyl)ethyl)]-2-indolecarboxylate: alkylating agent, 2-(2-cyclohexenyl)ethyl methanesulfonate; 70% yield; elution with 95:5 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 1.4-2.0 (m, 8H), 2.10 (m, 1H), 3.88 (s, 3H), 4.59 (t, *J* = 8 Hz, 2H), 5.63 (d, *J* = 12.2 Hz, 1H), 5.72 (m, 1H), 7.12 (m, 1H), 7.30 (m, 2H), 7.35 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 1H);

^{13}C NMR (50.3 MHz) δ 21.5 (CH_2), 25.3 (CH_2), 29.0 (CH_2), 33.4 (CH), 36.7 (CH_2), 42.8 (CH_2), 51.6 (CH_3), 110.3 (CH), 110.6 (CH), 120.5 (CH), 122.7 (CH), 124.9 (CH), 126.0 (C), 126.9 (C), 127.7 (CH), 130.9 (CH), 138.8 (C), 162.3 (C).

Methyl 1-(1-Cyclohexenyl)methyl)-2-indolecarboxylate: alkylating agent, (1-cyclohexenyl)methyl bromide; 75% yield; elution with 8:2 hexanes-CH_2Cl_2; ^{1}H NMR (300 MHz) δ 1.52 (m, 4H), 1.87 (m, 4H), 3.86 (s, 3H), 5.09 (s, 2H), 5.19 (m, 1H), 7.12 (m, 1H), 7.28 (m, 1H), 7.30 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 22.2 (CH_2), 22.4 (CH_2), 24.7 (CH_2), 26.0 (CH_2), 49.9 (CH_2), 51.5 (CH_3), 110.4 (CH), 111.0 (CH), 120.4 (CH), 121.9 (CH), 122.3 (CH), 124.7 (CH), 125.7 (C), 127.3 (C), 133.9 (C), 139.4 (C), 162.2 (C).

Methyl 1-[2-(1-Cyclohexenyl)ethyl)]-2-indolecarboxylate: alkylating agent, 2-(1-cyclohexenyl)ethyl methanesulfonate; 45% yield; elution with 8:2 hexanes-AcOEt. Spectroscopic data of the corresponding carboxylic acid (see below): ^{1}H NMR (200 MHz) δ 1.55 (m, 4H), 1.95 (m, 4H), 2.38 (t, *J* = 7.2 Hz, 2H) 4.65 (t, *J* = 7.2 Hz, 2H), 5.32 (br s,1H), 7.16 (m, 1H), 7.42 (m, 2H), 7.45 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H).

B. Methyl 1-Alkyl-2-indolecarboxylates. Tetrahydropyridine Series



A solution of methyl 2-indolecarboxylate (1.5 g, 8.57 mmol) in anhydrous DMF (20 mL) was added dropwise under Ar to a suspension of NaH (22.3 mmol) in anhydrous THF (10 mL). After stirring at rt for 1 h, the mixture was cooled to 0 ºC and 3 or 4-chloromethylpyridine hydrochloride (1.74 g, 10.3 mmol) was added in portions. The mixture was allowed to warm to rt overnight, then was quenched with cold H_2O and extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were washed with H_2O (5 x 100 mL), dried and concentrated, and the resulting residue was chromatographed (SiO_2, 1.1 hexanes-AcOEt) to give methyl 1-(pyridylmethyl)-2-indolecarboxylates.

Iodomethane (1 mL, 16.64 mmol) in anhydrous benzene (1 mL) was added to a solution of the above esters (1.10 g, 4.16 mmol) in anhydrous acetone (6 mL). After stirring at rt for 5 h, the precipitated pyidiridinium salts were collected by filtration.

$NaBH_4$ (145 mg, 3.85 mmol) was added in two portions to an ice-cooled suspension of the above pyridinium salts (1.57 g, 3.85 mmol) in EtOH (40 mL). After stirring at rt for 5 h, the solvent was removed and the resulting residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried, filtered and concentrated to give the corresponding tetrahydropyridines.

Methyl 1-(1-Methyl-1,2,5,6-tetrahydro-4-pyridylmethyl)-2-indolecarboxylate: 48% overall yield; ^{1}H NMR (200 MHz) δ 2.09 (m, 2H), 2.29 (s, 3H), 2.49 (t, *J* = 5.8 Hz, 2H), 2.82 (m, 2H), 3.88 (s, 3H), 5.10 (m, 1H), 5.15 (s, 2H), 7.14 (m, 1H), 7.33 (m, 2H), 7.31 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 27.1 (CH_2), 45.6 (CH_3), 49.0 (CH_2), 51.6 (CH_2), 51.6 (CH_3), 54.0 (CH_2), 110.7 (CH), 111.0 (CH), 119.7 (CH), 120.6 (CH), 122.4 (CH), 125.0 (CH), 125.7 (C), 127.3 (C), 132.6 (C), 139.4 (C), 162.2 (C).

Methyl 1-(1-Methyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-2-indolecarboxylate: 52% overall yield; ^{1}H NMR (200 MHz) δ 2.10 (m, 2H), 2.31 (s, 3H), 2.43 (t, *J* = 6 Hz, 2H), 2.81 (m, 2H),

3.90 (s, 3H), 5.15 (br s, 2H), 5.24 (m, 1H), 7.14 (m, 1H), 7.32 (s, 1H), 7.35 (m, 2H), 7.68 (d, J = 7.6 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 25.2 (CH_2), 45.4 (CH_3), 47.7 (CH_2), 51.4 (CH_2), 51.6 (CH_3), 54.8 (CH_2), 110.8 (CH), 110.9 (CH), 120.2 (CH), 120.6 (CH), 122.4 (CH), 125.1 (CH), 125.8 (C), 127.1 (C), 132.4 (C), 139.4 (C), 162.2 (C).

C. Hydrolysis to 1-Alkyl-2-indolecarboxylic Acids.

A solution of the corresponding methyl 1-alkyl-2-indolecarboxylate (4 mmol) in a 1:1:1 mixture of aqueous 2N KOH:MeOH:dioxane (15 mL) was refluxed for 2 h. The reaction mixture was concentrated and acidified with aqueous 2N HCl. The precipitated carboxylic acid was collected by filtration.

D. Phenyl Selenoesters 1-6. General Procedure.

A suspension of the above carboxylic acid (4 mmol) in anhydrous CH_2Cl_2 (15 mL) was treated with a solution of Et_3N (4 mmol for selenoesters **1**-**4**; 8 mmol for selenoesters **5** and **6**) in CH_2Cl_2 (5 mL). After stirring at rt for 10 min, the mixture was concentrated to give the corresponding triethylammonium salts.

In another flask, tributylphosphine (6 mmol) was added under Ar to a solution of PhSeCl (6 mmol) in anhydrous THF (15 mL), and the mixture was stirred at rt for 10 min (yellow solution). To this solution, the above triethylammonium salt in THF (15 mL) was added and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O (40 mL) and H_2O (40 mL) and extracted with Et_2O (3 x 25 mL). The solvent was removed and the crude product was purified by flash chromatography (SiO_2, unless otherwise indicated). Eluents, yields and NMR data ($CDCl_3$) are given below.

***Se*-Phenyl 1-Allyl-2-indolecarboselenoate (1a):** 90% yield; elution with 9:1 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 4.86 (d, J = 17.2 Hz, 1H), 5.07 (m, 3H) 5.95 (m, 1H), 7.20 (m, 1H), 7.35-7.45 (m, 5H), 7.60 (s, 1H), 7.62 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 47.1 (CH_2), 110.8 (CH), 112.3 (CH), 116.2 (CH_2), 121.2 (CH), 122.9 (CH), 125.8 (C), 126.0 (C), 126.3 (CH), 129.0 (CH), 129.3 (CH), 133.2 (CH), 134.3 (C), 136.3 (CH), 139.5 (C), 184.4 (C). Anal. Calcd for $C_{18}H_{15}NOSe$: C, 63.26; H, 4.51; N, 4.08. Found: C, 63.20; H, 4.48; N, 4.09.

***Se*-Phenyl 1-(3-Butenyl)-2-indolecarboselenoate (1b):** 75% yield; elution with 9:1 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 2.45 (q, J = 7.2 Hz, 2H), 4.47 (t, J = 7.2 Hz, 2H), 5.0 (m, 2H), 5.75 (m, 1H), 7.19 (m, 1H), 7.36-7.44 (m, 5H), 7.57 (s, 1H), 7.62 (m, 2H), 7.70 (d, J = 8.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 34.8 (CH_2), 44.5 (CH_2), 110.8 (CH), 112.4 (CH), 117.3 (CH_2), 121.1 (CH), 123.0 (CH), 126.0 (C), 126.1 (C), 126.2 (CH), 129.1 (CH), 129.4 (CH), 134.3 (C), 134.5 (CH), 136.4 (CH), 139.5 (C), 184.5 (C). Anal. Calcd for $C_{19}H_{17}NOSe$: C, 64.41; H, 4.84; N, 3.95. Found: C, 64.27; H, 4.50; N, 4.01.

***Se*-Phenyl 1-(4-Pentenyl)-2-indolecarboselenoate (1c):** 65% yield; elution with 9:1 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 1.86 (m, 2H), 2.05 (m, 2H), 4.43 (t, J = 7.4 Hz, 2H), 5.0 (m, 2H), 5.79 (m, 1H), 7.17 (m, 1H), 7.37-7.45 (m, 5H), 7.59 (s, 1H), 7.64 (m, 2H), 7.74 (d, J = 8.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 29.4 (CH_2), 30.8 (CH_2), 44.5 (CH_2), 110.6 (CH), 112.2 (CH), 115.1 (CH_2), 120.9 (CH), 122.9 (CH), 125.9 (C), 126.1 (C), 126.1 (CH), 128.9 (CH), 129.2 (CH), 134.2 (C), 136.3 (CH), 137.4 (CH), 139.4 (C), 184.2 (C). Anal. Calcd for $C_{20}H_{19}NOSe$: C, 65.22; H, 5.20; N, 3.80. Found: C, 65.12; H, 5.03; N, 3.76.

***Se*-Phenyl 1-(2-Cyclohexenyl)-2-indolecarboselenoate (2):** 70% yield; elution with 8:2 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.6-1.9 (m, 2H), 2.20 (m, 4H), 5.7-6.0 (m, 3H), 7.18 (m, 1H), 7.25 (m, 1H), 7.45 (m, 3H), 7.60-7.75 (m, 5H); ^{13}C NMR (50.3 MHz) δ 22.1 (CH_2), 24.6 (CH_2), 28.9 (CH_2), 53.9 (CH), 112.8 (CH), 114.0 (CH), 120.8 (CH), 123.0 (CH), 125.4 (CH), 126.2 (C), 126.8 (C), 128.9 (CH), 129.1 (CH), 129.4 (CH), 129.7 (CH), 134.3 (C), 136.4 (CH), 139.2 (C), 185.3 (C); HRMS calcd for $C_{21}H_{19}NOSe$ 381.0632, found 381.0625.

***Se*-Phenyl 1-(2-Cyclohexenylmethyl)-2-indolecarboselenoate (3a):** 86% yield; elution with 7:3 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.2-1.8 (m, 4H), 1.97 (br s, 2H), 2.65 (br s, 1H), 4.33 (m, 2H), 5.38 (d, J = 11.6 Hz, 1H), 5.72 (m, 1H), 7.16 (m, 1H), 7.40 (m, 5H), 7.61 (s, 1H), 7.62 (m, 2H), 7.71 (d, J = 7.8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 20.9 (CH_2), 25.4 (CH_2), 26.7

(CH_2), 36.8 (CH), 49.7 (CH_2), 111.4 (CH), 112.6 (CH), 121.0 (CH), 122.9 (CH), 126.0 (C), 126.1 (C), 126.1 (CH), 128.9 (CH), 129.1 (2 CH), 129.4 (CH), 134.6 (C), 136.4 (CH), 140.1 (C), 184.3 (C); HRMS calcd for $C_{22}H_{21}NOSe$ 395.0788, found 395.0794.

***Se*-Phenyl 1-[2-(2-Cyclohexenyl)ethyl)]-2-indolecarboselenoate (3b):** 65% yield; elution with 7:3 hexanes-CH_2Cl_2; pale yellow solid, mp 79-81 °C; ^{1}H NMR (200 MHz) δ 1.3-2.0 (m, 8H), 2.10 (m, 1H), 4.48 (t, *J* = 7.6 Hz, 2H), 5.56 (dd, *J* = 1.8, 12.4 Hz, 1H), 5.70 (m, 1H), 7.17 (m, 1H), 7.38-7.46 (m, 5H), 7.58 (s, 1H), 7.64 (m, 2H), 7.73 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 21.5 (CH_2), 25.3 (CH_2), 29.0 (CH_2), 33.2 (CH), 36.6 (CH_2), 43.2 (CH_2), 110.6 (CH), 112.3 (CH), 121.0 (CH), 123.1 (CH), 126.2 (2C), 126.2 (CH), 127.7 (CH), 129.1 (CH), 129.4 (CH), 130.8 (CH), 134.4 (C), 136.4 (CH), 139.4 (C), 184.2 (C). Anal. Calcd for $C_{23}H_{23}NOSe$: C, 67.65; H, 5.65; N, 3.43. Found: C, 67.10; H, 5.70; N, 3.27.

***Se*-Phenyl 1-(1-Cyclohexenyl)methyl)-2-indolecarboselenoate (4a):** 76% yield; elution with 8:2 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.50 (m, 4H), 1.78 (m, 2H), 1.89 (m, 2H). 4.96 (s, 2H), 5.21 (m, 1H), 7.16 (m, 1H), 7.35 (m, 2H), 7.42 (m, 3H), 7.58 (s, 1H), 7.62 (m, 2H), 7.71 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 22.3 (CH_2), 22.4 (CH_2), 24.8 (CH_2), 25.9 (CH_2), 50.5 (CH_2), 111.5 (CH), 112.1 (CH), 121.0 (CH), 122.5 (CH), 122.8 (CH), 126.0 (C), 126.0 (CH), 126.1 (C), 129.0 (CH), 129.3 (CH), 133.6 (C), 134.9 (C), 136.3 (CH), 140.0 (C), 184.3 (C); HRMS calcd for $C_{22}H_{21}NOSe$ 395.0788, found 395.0801.

***Se*-Phenyl 1-[2-(1-Cyclohexenyl)ethyl)]-2-indolecarboselenoate (4b):** 65% yield; elution with 8:2 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.50 (m, 4H), 1.85 (m, 4H), 2.30 (t, *J* = 7.2 Hz, 2H) 4.51 (t, *J* = 7.2 Hz, 2H), 5.21 (br s,1H), 7.16 (m, 1H), 7.37 (m, 2H), 7.43 (m, 3H), 7.57 (s, 1H), 7.63 (m, 2H), 7.72 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 22.2 (CH_2), 22.8 (CH_2), 25.3 (CH_2), 28.6 (CH_2), 38.4 (CH_2), 44.0 (CH_2), 110.8 (CH), 112.1 (CH), 120.9 (CH), 122.9 (CH), 123.6 (CH), 126.0 (C), 126.0 (CH), 126.1 (C), 129.0 (CH), 129.3 (CH), 134.1 (C), 134.5 (C), 136.3 (CH), 139.5 (C), 184.1 (C); HRMS calcd for $C_{22}H_{23}NOSe$ 409.0945, found 409.0955.

***Se*-Phenyl 1-(1-Methyl-1,2,5,6-tetrahydro-4-pyridylmethyl)-2-indolecarboselenoate (5):** 34% yield; elution with 8:2 hexanes-AcOEt (Al_2O_3); ^{1}H NMR (200 MHz) δ 2.05 (m, 2H), 2.31 (s, 3H), 2.51 (t, *J* = 5.8 Hz, 2H), 2.87 (m, 2H), 5.02 (s, 2H), 5.09 (m, 1H), 7.17 (m, 1H), 7.34 (m, 2H), 7.44 (m, 3H), 7.60 (s, 1H), 7.62 (m, 2H), 7.72 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 26.6 (CH_2), 45.1 (CH_3), 49.3 (CH_2), 51.3 (CH_2), 53.6 (CH_2), 111.2 (CH), 112.4 (CH), 119.5 (CH), 121.2 (CH), 122.8 (CH), 125.9 (C), 126.3 (CH), 126.3 (C), 129.0 (CH), 129.3 (CH), 132.2 (C), 134.6 (C), 136.3 (CH), 139.9 (C), 184.3 (C); HRMS calcd for $C_{22}H_{22}N_2OSe$ 410.0897, found 410.0905.

***Se*-Phenyl 1-(1-Methyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-2-indolecarboselenoate (6):** 40% yield; elution with 8:2 hexanes-AcOEt (Al_2O_3); ^{1}H NMR (200 MHz) δ 2.24 (m, 2H), 2.44 (s, 3H), 2.64 (t, *J* = 5.6 Hz, 2H), 3.02 (s, 2H), 5.02 (s, 2H), 5.35 (m, 1H), 7.19 (m, 1H), 7.37 (m, 2H), 7.44 (m, 3H), 7.61 (s, 1H), 7.62 (m, 2H), 7.73 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 23.8 (CH_2), 44.1 (CH_3), 47.6 (CH_2), 50.5 (CH_2), 53.5 (CH_2), 110.8 (CH), 112.3 (CH), 120 .2 (CH), 121.1 (CH), 122.6 (CH), 125.6 (C), 125.7 (C), 126.3 (CH), 128.8 (CH), 129.0 (CH), 130.4 (C), 134.1 (C), 136.0 (CH), 139.7 (C), 184.1 (C); HRMS calcd for $C_{22}H_{22}N_2OSe$ 410.0897, found 410.0901.

E. General Procedure for Cyclization Reactions of Phenyl Selenoesters 1-6.

n-Bu_3SnH (0.52 mmol) in C_6H_6 (2 mL) was added over a period of 1h (syringe pump) to a heated (reflux) solution of selenoesters **1-6** (0.4 mmol) and AIBN (0.04 mmol) in C_6H_6 (4 mL). After additional 2-3 h at reflux, the solution was concentrated and the residue was chromatographed (SiO_2). Yields, eluents and NMR data ($CDCl_3$) are given below.

2,3-Dihydro-2-methyl-1*H*-pyrrolo[1,2-*a*]indol-1-one (7): 84% yield; elution with 7:3 hexanes-AcOEt; mp 100-102 °C; ^{1}H NMR (200 MHz) δ 1.45 (d, *J* = 7.8 Hz, 3H), 3.28 (ddddd, *J* = 4.6, 7.8, 7.8, 7.8, 8.0 Hz, 1H), 3.97 (dd, *J* = 4.6, 11 Hz, 1H), 4.66 (dd, *J* = 8, 11 Hz, 1H), 7.02 (s, 1H), 7.21 (m, 1H), 7.40 (m, 2H), 7.76 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 15.6 (CH_3), 45.5 (CH), 47.9 (CH_2), 99.2 (CH), 110.5 (CH), 121.4 (CH), 124.1 (CH), 125.0 (CH), 132.1 (C), 135.0 (C), 135.1 (C), 196.1 (C); HRMS calcd for $C_{12}H_{11}NO$ 185.0841, found

185.0842. Anal. Calcd for $C_{12}H_{11}NO.1/3H_2O$: C, 75.39; H, 6.15; N, 7.33. Found: C, 75.30; H, 5.90; N, 7.23.

6,7,8,9-Tetrahydro-8-methylpyrido[1,2-*a*]indol-9-one (8): 70% yield; elution with 9:1 hexanes-AcOEt; mp 145-147 °C; ^{1}H NMR (200 MHz) δ 1.35 (d, *J* = 6.8 Hz, 3H), 2.18 (m, 1H), 2.44 (dddd, *J* = 4.1, 4.4, 4.5, 13.8 Hz, 1H), 2.74 (m, 1H), 4.15 (ddd, *J* = 4.1, 10.6, 12.5 Hz, 1H), 4.41 (ddd, *J* = 4.4, 4.5, 12.5 Hz, 1H), 7.16 (m, 1H), 7.30 (s, 1H), 7.36 (m, 2H), 7.72 (d, *J* = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 14.9 (CH_3), 31.1 (CH_2), 40.9 (CH_2), 41.1 (CH), 105.6 (CH), 110.2 (CH), 121.0 (CH), 123.3 (CH), 125.4 (CH), 126.9 (C), 133.4 (C), 137.1 (C), 192.8 (C); Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.93; H, 6.69; N, 6.96.

***cis*-2,3,4,4a,11,11a-Hexahydro-1*H*-indolo[1,2-*a*]indol-11-one (13)**: 70% yield; elution with 9:1 hexanes-AcOEt; mp 93-94 °C; ^{1}H NMR (300 MHz) δ 1.2-1.8 (m, 6H), 2.40 (m, 2H), 3.29 (ddd, *J* = 3.2, 6.8, 7.2 Hz, 1H), 4.91 (ddd, *J* = 7.2, 7.2, 8.1 Hz, 1H), 7.00 (d, *J* = 0.8 Hz, 1H), 7.17 (ddd, *J* = 0.8, 6.8, 8 Hz, 1H), 7.35 (ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.47 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.77 (dd, *J* = 1.2, 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 20.6 (CH_2), 21.5 (CH_2), 22.4 (CH_2), 30.2 (CH_2), 51.0 (CH), 53.1 (CH), 99.1 (CH), 111.0 (CH), 121.2 (CH), 124.3 (CH), 124.8 (CH), 132.0 (C), 134.8 (C), 135.0 (C), 195.1 (C); Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.21. Found: C, 79.92; H, 6.75; N, 6.30.

***cis*-6,6a,7,8,9,10,10a,11-Octahydroisoquinolino[2,3-*a*]indol-11-one (14)**: 70% yield; elution with 6:4 hexanes-AcOEt; mp 98-100 °C; ^{1}H NMR (400 MHz) δ 1.45-1.70 (m, 7H), 2.37 (m, 1H), 2.59 (m, 1H), 2.83 (q, *J* = 4.8 Hz, 1H), 4.21 (dd, *J* = 4.8, 12.4 Hz, 1H), 4.25 (dd, *J* = 4.8, 12.4 Hz, 1H), 7.15 (m, 1H), 7.31 (s, 1H), 7.37 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 22.9 (CH_2), 24.3 (CH_2), 25.2 (CH_2), 27.9 (CH_2), 36.1 (CH), 45.4 (CH_2), 46.9 (CH), 105,4 (CH), 110.2 (CH), 120.9 (CH), 123.2 (CH), 125.3 (CH), 126.9 (C), 133.0 (C), 137.3 (C), 192.2 (C). This compound was quantitatively converted into **16** (see below) by treatment with MeONa (2 equivalents) in MeOH.

Spiro Compound (15): 10% yield; elution with 1:1 hexanes-CH_2Cl_2; ^{1}H NMR (200 MHz) δ 1.35-1.90 (m, 10H), 4.28 (s, 2H), 7.02 (d, *J* = 0.6 Hz, 1H), 7.18 (m, 1H), 7.37 (m, 1H), 7.44 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 23.1 (CH_2), 25.0 (CH_2), 33.0 (CH_2), 54.8 (C), 51.4 (CH_2), 99.4 (CH), 110.4 (CH), 121.3 (CH), 124.1 (CH), 124.9 (CH), 132.1 (C), 134.9 (C), 135.1 (C), 198.3 (C); HRMS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1312.

***trans*-6,6a,7,8,9,10,10a,11-Octahydroisoquinolino[2,3-*a*]indol-11-one (16)**: 75% yield; obtained directly from the crude by trituration with hexanes; mp 180-182 °C; ^{1}H NMR (300 MHz) δ 1.35 (m, 4H), 1.87 (m, 1H), 2.0 (m, 2H), 2.20 (m, 1H), 2.28 (ddd, *J* = 4, 12, 12 Hz, 1H), 2.51 (d, *J* = 13.2 Hz, 1H), 3.78 (dd, *J* = 4.5, 12 Hz, 1H), 4.38 (dd, *J* = 11.7, 12 Hz, 1H), 7.16 (m, 1H), 7.28 (s, 1H), 7.36 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 25.1 (CH_2), 25.2 (CH_2), 25.5 (CH_2), 30.8 (CH_2), 39.5 (CH), 47.6 (CH_2), 50.4 (CH), 105,2 (CH), 110.1 (CH), 120.9 (CH), 123.3 (CH), 125.3 (CH), 126.7 (C), 133.4 (C), 137.0 (C), 191.8 (C); Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.05; H, 7.17; N, 5.85.

Spiro Compound (17): 27% yield; elution with 95:4:1 CH_2Cl_2-MeOH-DEA; ^{1}H NMR (300 MHz) δ 1.33 (m, 1H), 1.72 (m, 2H), 2.17 (m, 3H), 2,38 (s, 3H), 3.02 (m, 2H), 4.27 (s, 2H), 7.03 (d, *J* = 0.6, 1H), 7.19 (m, 1H), 7.37 (m, 1H), 7.43 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 32.9 (CH_2), 46.3 (CH_3), 51.3 (CH_2), 51.9 (C), 52.4 (CH_2), 99.7 (CH), 110.4 (CH), 121.4 (CH), 124.1 (CH), 125.1 (CH), 132.1 (C), 134.7 (C), 135.1 (C), 197.1 (C); HRMS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1460.

***trans*-1,2,3,4,4a,5,12,12a-Octahydro-2-methylpyrido[3',4':4,5]pyrido[1,2-*a*]indol-12-one (18)**: 25% yield; elution with 95:4:1 CH_2Cl_2-MeOH-DEA; ^{1}H NMR (300 MHz) δ 1.81 (dddd, *J* = 3.9, 12.3, 12.3, 12.3 Hz, 1H), 1.92 (m, 1H), 1.95 (m, 1H), 2.01 (dd, *J* = 11.7, 12.3 Hz, 1H), 2.17 (ddddd, *J* = 3.9, 4.5, 10.8, 12, 12.3 Hz, 1H), 2.42 (s, 3H), 2.69 (ddd, *J* = 3.9, 10.8, 12.3 Hz, 1H), 3.01 (dddd, *J* = 1.2, 1.8, 1.8, 11.7 Hz, 1H), 3.59 (ddd, *J* = 1.2, 3.9, 12.3 Hz, 1H), 3.83 (t, *J* = 12 Hz, 1H), 4.45 (dd, *J* = 4.5, 12 Hz, 1H), 7.16 (ddd, *J* = 1.8, 6, 8.1 Hz, 1H), 7.31 (s, 1H), 7.36 (m, 2H), 7.73 (ddd, *J* = 0.9, 1.2, 7.8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 29.6 (CH_2), 37.5 (CH), 46.4 (CH_3), 47.1 (CH_2), 49.0 (CH), 54.5 (CH_2), 54.6 (CH_2), 105,6 (CH), 110.1 (CH), 121.1 (CH), 123.4 (CH), 125.6 (CH), 126.6 (C), 130.3 (C), 137.0 (C), 189.6 (C); HRMS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1424.

Spiro Compound (19): 30% yield; elution with 95:5 CH_2Cl_2-MeOH; ^{1}H NMR (400 MHz) δ 1.80 (m, 4H), 2.05 (m, 1H), 2.30 (m, 1H), 2.32 (br s, 3H), 2.75 (m, 1H), 2.95 (m, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.65 (br s 1H), 6.97 (s, 1H), 7.12 (ddd, *J* = 1.2, 6.8, 8 Hz, 1H), 7.31 (ddd, *J* = 0.8, 6.8, 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 22.8 (CH_2), 30.6 (CH_2), 46.6 (CH_3), 51.5 (CH_2), 55.08 (C), 55.14 (CH_2), 61.7 (CH_2), 99.6 (CH), 110.6 (CH), 121.4 (CH), 124.1 (CH), 125.2 (CH), 132.1 (C), 134.8 (C), 135.2 (C), 196.0 (C). **19.HCl**; mp 166-168 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.8-2.0 (m, 4H), 2.73 and 2.76 (2s, 3H), 3.03 (m, 1H), 3.16 (t, *J* = 10.6 Hz, 1H), 3.38 (m, 1H), 3.64 (d, *J* = 12.6 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.89 (d, *J* = 11.8 Hz, 1H), 7.11 (d, *J* = 0.8 Hz, 1H), 7.19 (ddd, *J* = 1, 6.8, 8 Hz, 1H), 7.41 (ddd, *J* = 1.2, 6.8, 8.2 Hz, 1H), 7.53 (dd, *J* = 0.8, 8.2 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 10.57 (br s, 1H); Anal. Calcd for $C_{16}H_{18}N_2O$.HCl.1/2H_2O: C, 64.32; H, 6.41; N, 9.38. Found: C, 64.12; H, 6.53; N, 9.44.

***trans*-1,2,3,4,4a,5,12,12a-Octahydro-2-methylpyrido[4',3':4,5]pyrido[1,2-*a*]indol-5-one (20)**: 35% yield; elution with 95:4:1 CH_2Cl_2-MeOH-DEA; mp 155-157 °C; ^{1}H NMR (300 MHz) δ 1.71 (dddd, *J* = 4.2, 11.4, 11.4, 12.6 Hz, 1H), 2.05 (dd, *J* = 10.8, 11.4 Hz, 1H), 2.08 (ddd, *J* = 2.4, 11.4, 11.4 Hz, 1H), 2.26 (ddd, *J* = 3.9, 11.1, 11.4 Hz, 1H), 2.38 (s, 3H), 2.43 (m, 1H), 2.54 (ddddd, *J* = 3.9, 4.8, 11.1, 11.4, 11.7 Hz, 1H), 3.09 (m, 1H), 3.13 (m, 1H), 3.80 (t, *J* = 11.7 Hz, 1H), 4.39 (dd, *J* = 4.8, 11.7 Hz, 1H), 7.17 (ddd, *J* = 1.5, 6.3, 8.1 Hz, 1H), 7.31 (s, 1H), 7.35 (m, 2H), 7.73 (ddd, *J* = 0.9, 1.2, 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 24.9 (CH_2), 38.4 (CH), 45.0 (CH_2), 46.2 (CH_3), 48.2 (CH), 55.5 (CH_2), 59.0 (CH_2), 105,6 (CH), 110.1 (CH), 121.1 (CH), 123.4 (CH), 125.6 (CH), 126.8 (C), 133.2 (C), 137.1 (C), 190.4 (C). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.27; H, 7.15; N, 10.80.

F. Cyclization-Intermolecular Addition Cascade Reaction from Phenyl Selenoester 1a.

n-Bu_3SnH (0.1 mL, 0.38 mmol) in C_6H_6 (2 mL) was added over a period of 1h (syringe pump) to a heated (reflux) solution of selenoester **1a** (0.1 g, 0.29 mmol), methyl acrylate (0.13 mL, 1.45 mmol) and AIBN (5 mg, 0.03 mmol) in C_6H_6 (29 mL). After additional 2 h at reflux, the solution was concentrated and the residue was chromatographed (SiO_2, 8:2 hexanes-AcOEt) to give **12** (35 mg, 45%) and **7** (11 mg, 20%).

Methyl 4-[2,3-Dihydro-1-oxo-1*H*-pyrrolo[1,2-*a*]indole]-2-butanoate (12): mp 75-77 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.79 (m, 2H), 2.10 (m, 2H), 2.40 (t, *J* = 7 Hz, 2H), 3.24 (m, 1H), 3.68 (s, 3H), 4.12 (dd, *J* = 4.2, 11 Hz, 1H),), 4.65 (dd, *J* = 8, 11 Hz, 1H), 7.01 (s, 1H), 7.19 (m, 1H), 7.40 (m, 2H), 7.76 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.5 (CH_2), 30.3 (CH_2), 33.7 (CH_2), 46.0 (CH_2), 50.5 (CH), 51.7 (CH_3), 99.3 (CH), 110.5 (CH), 121.4 (CH), 124.1 (CH), 125.1 (CH), 132.1 (C), 135.1 (C), 135.2 (C), 173.5 (C), 195.0 (C). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.58; H, 6.30; N, 5.14.

JOC*Note*

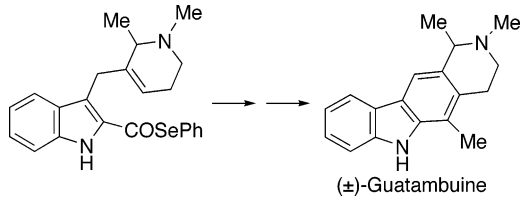
Regioselective 6-Endo Cyclizations of 2-Indolylacyl Radicals: Total Synthesis of the Pyrido[4,3-*b*]carbazole Alkaloid Guatambuine

M.-Lluïsa Bennasar,* Tomàs Roca, and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@ub.edu

Received November 24, 2005



A regioselective 6-endo reductive cyclization of 2-indolylacyl radicals constitutes the key step of a straightforward synthetic entry to the olivacine skeleton, illustrated by a total synthesis of the tetrahydropyridine alkaloid guatambuine.

The pyrido[4,3-*b*]carbazole alkaloids, exemplified by the fully aromatic components ellipticine and its isomer olivacine (Figure 1), constitute a small subgroup of naturally occurring biologically active compounds that have been known for more than 40 years.[1] Owing to their well-established anticancer properties, ellipticine and, to a lesser extent, olivacine have been the objective of many total syntheses using a great variety of approaches.[1−3] However, despite the intensive synthetic work, radical methodologies have been scarcely used to assemble the linear pyridocarbazole skeleton of these alkaloids.[4,5]

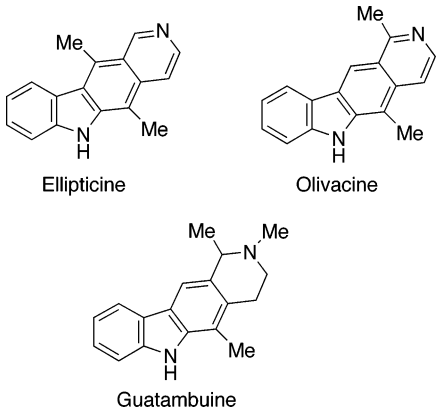
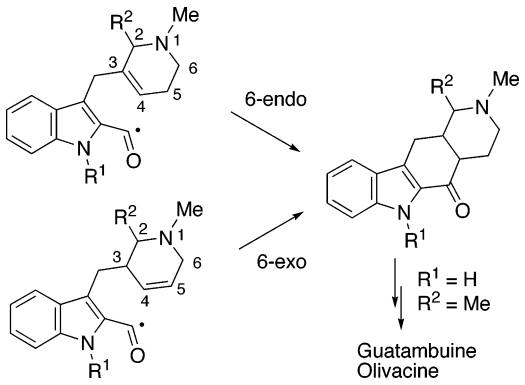


FIGURE 1. Pyrido[4,3-*b*]carbazole alkaloids.

SCHEME 1. Synthetic Strategy



Our previous experience in the inter-[6] and intramolecular[7] reactions of 2-indolylacyl radicals with alkenes under reductive conditions led us to envisage a straightforward approach to the olivacine skeleton hinging on the cyclization of 3-(tetrahydro-3-pyridylmethyl)-2-indolylacyl radicals (Scheme 1). This paper deals with our work in this area, including a concise total synthesis of the pyridocarbazole alkaloid (±)-guatambuine, a tetrahydro derivative of olivacine isolated from several *Aspidosperma* species.[8,9]

Radical reactions have become an important tool for the construction of nitrogen heterocycles.[10,11] In this context, there are several reports in the literature concerning radical cyclizations upon tetrahydropyridines, most of them leading to structures with the nitrogen atom in the newly formed ring.[12,13]

* To whom correspondence should be addressed. Tel: 34 934 024 540. Fax: 34 934 024 539.

(1) (a) Sainsbury, M. *Synthesis* **1977**, 437−448. (b) Joule, J. A. Indoles, The Monoterpenoid Indole Alkaloids. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Weissberger. A.; Taylor, E. C., Eds.; Wiley: New York, 1983; Part 4, pp 275−286. (c) Gribble, G. W. *The Alkaloids*; Brosi, A., Ed.; Academic Press: New York, 1990; Vol. 39, pp 239−352.

(2) For a review, see: Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427 and references therein.

(3) For representative syntheses of olivacine since 1990, see: (a) Bäckvall, J.-E.; Plobeck, N. A. *J. Org. Chem.* **1990**, *55*, 4528−4531. (b) Hogan, I.; Jenkins, P. D.; Sainsbury, M. *Tetrahedron* **1990**, *46*, 2943−2964. (c) Hibino, S.; Sugino, E. *J. Heterocycl. Chem.* **1990**, *27*, 1751−1755. (d) Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1319−1329. (e) Hall, R. J.; Marchant, J.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3439−3450. (f) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891−5899. (g) Miki, Y.; Tsuzaki, Y.; Hibino, H.; Aoki, Y. *Synlett* **2004**, 2206−2208.

(4) For a radical cascade protocol leading to ellipticine, see: Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615−10618.

(5) For the synthesis of ellipticine quinones by intramolecular homolytic acylation of pyridines, see: Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem.* **2005**, *70*, 9077−9080.

(6) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697−1700.

(7) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759−762.

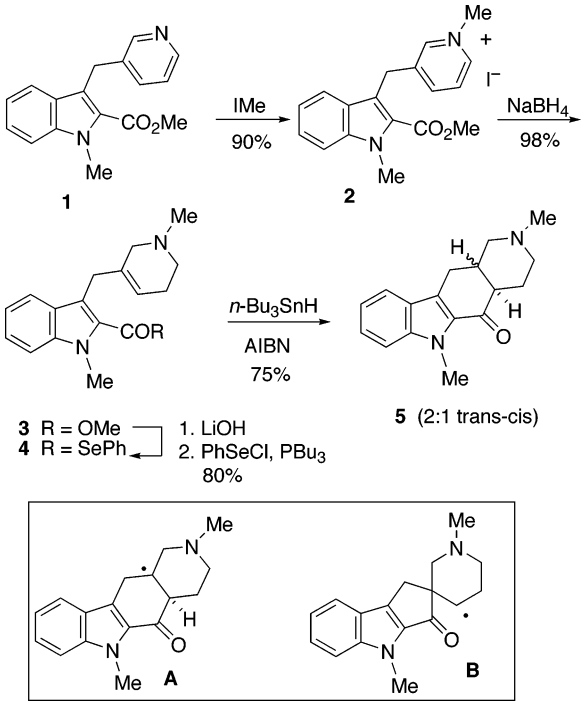
(8) Guatambuine was isolated as the (+)-, (−)-, and (±)-forms: (a) Ondetti, M. A.; Deulofeu, V. *Tetrahedron* **1961**, *15*, 160−166. (b) Burnell, R. H.; Della Casa, D. *Can. J. Chem.* **1967**, *45*, 89−92.

(9) For previous syntheses of (±)-guatambuine, see: (a) Besselièvre, B.; Husson, H.-P. *Tetrahedron* **1981**, *37*, Suppl. No. 1, 241−246. Through olivacine: (b) Kutney, J. P.; Noda, M.; Lewis, N. G.; Monteiro, B.; Mostowicz, D.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 2426−2430.

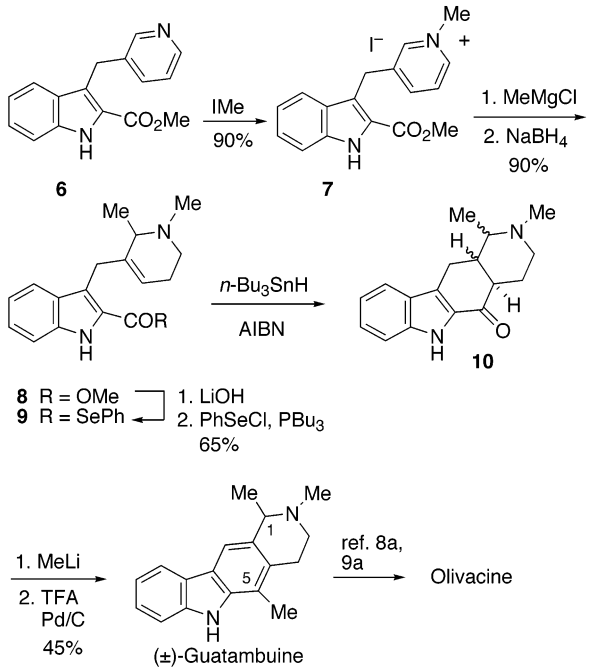
(10) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (b) Zhang, W. *Tetrahedron* **2001**, *57*, 7237−7262. (c) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (d) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377−10441. (e) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603−10642.

10.1021/jo052428s CCC: $33.50
Published on Web 01/12/2006

SCHEME 2. Model Studies



SCHEME 3. Synthesis of (±)-Guatambuine



In our initial design there were two distinct ways to close the central carbocyclic ring, namely, a 6-endo cyclization of a 5-hexenoyl radical (1,2,5,6-tetrahydropyridine) or a 6-exo cyclization of a 6-heptenoyl radical (1,2,3,6-tetrahydropyridine). As the required starting substrates appeared to be more accessible from pyridine derivatives through conventional reductive protocols, we focused our attention on the first approach. Considering the precedents on related cyclizations involving acyl radicals,[7,14] we expected that the higher alkene substitution at the 3-position of the ring would probably retard the competitive 5-exo cyclization mode, thus favoring the desired formation of the 6-membered ring.

We first carried out a model study to probe the feasibility of the proposal using selenoester **4**, which incorporated the required 1,2,5,6-tetrahydropyridine moiety, as the radical precursor (Scheme 2). As anticipated, this compound was easily accessible from the known pyridylmethylindole **1**[5] by quaternization with methyl iodide, reduction of the resulting pyridinium salt **2** with $NaBH_4$ in a protic solvent (EtOH), and the subsequent phenylselenation of the tetrahydropyridine methyl ester **3** through the corresponding carboxylic acid. We were pleased to find that selenoster **4** upon exposure to the standard reductive conditions (tributyltin hydride−AIBN, benzene, reflux, slow addition, final concentration 0.06 M) led to the expected pyrido[4,3-*b*]carbazole **5** as a 2:1 mixture of trans−cis stereoisomers in 75% yield. No 5-exo cyclization product was detected by NMR.

This regiochemical outcome is probably the result of a direct 6-endo cyclization of the initially formed acyl radical to give the fused radical adduct **A**, although a partial 5-exo attack followed by ring expansion of the highly strained radical adduct **B** cannot be completely ruled out under the reaction conditions.[15] Further hydrogen abstraction of the bridgehead radical **A** from tributyltin hydride in an incompletely stereoselective way would account for the formation of the trans−cis mixture **5**. This mixture could be quantitatively transformed into the thermodynamically more stable trans-fused piperidine compound by treatment with sodium methoxide in methanol.

At this point, the synthesis of the pyridocarbazole alkaloid guatambuine required the extension of the chemistry outlined above to related substrates unsubstituted at the indole nitrogen. Additionally, at some stage, we had to be able to introduce the C-1 and C-5 methyl groups of the alkaloid. To this end, we focused our attention on pyridylmethylindole **6**[5] (Scheme 3), which was converted as above into *N*-methylpyridinium salt **7**. Reaction of **7** with methylmagnesium chloride efficiently accomplished the introduction of the first (C-1) methyl group. Significantly, the addition of the organometallic reagent took place in a totally regioselective manner at the C-2 position of the ring[16] to give, after reduction of the intermediate 2,3-disubstituted 1,2-dihydropyridine with $NaBH_4$, tetrahydropyridine **8** as the sole product in a yield as high as 90%. Its subsequent hydrolysis followed by phenylselenation led to

(11) For recent examples of the synthesis of fused azacycles: (a) Miranda, L. D.; Zard, S. *Org. Lett*. **2002**, *4*, 1135−1138. (b) Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett*. **2004**, 45, 4661−4664. (c) Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. *J. Org. Chem*. **2005**, *70*, 519−528. (d) Taniguchi, T.; Tamura, O.; Uchiyama, M.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Synlett* **2005**, 1179−1181.

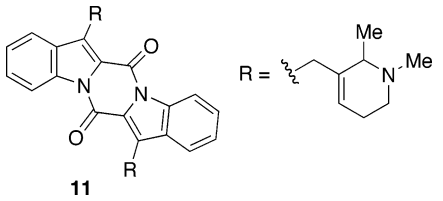
(12) See inter alia: (a) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349−10362. (b) Della, E. W.; Smith, P. A. *J. Org. Chem*. **2000**, *65*, 6627−6633. (c) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009−3018. (d) Bressy, C.; Menant, C.; Piva, O. *Synlett* **2005**, 577−582.

(13) For radical cyclizations upon tetrahydropyridines where a carbocycle is created, see: (a) Jenkinson, J. J.; Parsons, P. J.; Eyley, S. C. *Synlett* **1992**, 679−680. (b) Ripa, L.; Hallberg, A. *J. Org. Chem*. **1998**, *63*, 84−91. (c) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8506. (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem*. **1992**, *57*, 1429−1443. (b) For a review, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991−2069.

(14) For a recent example, see: (b) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett*. **2004**, *6*, 3517−3520.

(15) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem.—Eur. J.* **1997**, *3*, 376−387.

(16) For a discussion on the origin of this regioselectivity, see: (a) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672−3679.



11

FIGURE 2. Diketopiperazine **11**.

selenoester **9**, which was subjected to the radical protocol previously used in the model series (tributyltin hydride, AIBN, slow addition) with the hope that the initially formed 2-indolylacyl radical would initiate the desired 6-endo cyclization without interference from the indole NH group.[17]

Owing to the lower solubility of **9** in benzene, the first attempts were performed using a 1:1 mixture of benzene−acetonitrile as the solvent system. However, under these conditions, a fast dimerization of the substrate took place, most likely through a ketene intermediate, to give diketopiperazine **11** (Figure 2) as the only product in 63% yield.[18] The presence of the polar solvent was clearly responsible for this unwanted process[19] since when we worked with more diluted benzene solutions of **9** (final concentration 0.02 M) the radical reaction took place satisfactorily, giving access to pyridocarbazole **10** (mixture of stereoisomers) in approximately 75% yield. Without further purification, **10** was elaborated into (±)-guatambuine by reaction with methyllithium, which accomplished the introduction of the second (C-5) methyl group, followed by TFA−Pd/C promoted dehydration of the resulting carbinol with concomitant dehydrogenation to the carbazole ring. The overall yield from selenoester **9** was 45%.

Our synthetic material displayed ^{1}H NMR data identical to those previously reported,[8,9] and its ^{13}C NMR and analytical data were in full agreement with the proposed structure. Considering that guatambuine had been transformed into olivacine by further dealkylative aromatization,[8a,9a] the synthesis reported here also constitutes a formal synthesis of this fully aromatic alkaloid.

In conclusion, we have shown that the cyclization of 3-(tetrahydro-3-pyridylmethyl)-2-indolylacyl radicals under reductive conditions takes place with total 6-endo regioselectivity, providing a novel synthetic entry to the pyrido[4,3-*b*]carbazole skeleton characteristic of olivacine.

Experimental Section

2,6-Dimethyl-1,2,3,4,4a,6,11,11a-octahydropyrido[4,3-*b*]carbazole-5-one (5). *n*-Bu_3SnH (0.16 mL, 0.61 mmol) and AIBN (8 mg, 0.05 mmol) in C_6H_6 (3 mL) were added over a period of 1 h (syringe pump) to a heated (reflux) solution of selenoester **4** (0.20 g, 0.47 mmol) and AIBN (8 mg, 0.05 mmol) in C_6H_6 (5 mL). After an additional 2 h at reflux, the solution was concentrated, the resulting residue was partitioned between hexanes (10 mL) and acetonitrile (10 mL), and the polar layer was washed with hexanes (3 × 10 mL). The solvent was removed, and the crude product was chromatographed (96:3:1 CH_2Cl_2−MeOH−diethylamine) to give **5** as an oil: 94 mg (75%, 2:1 mixture of trans−cis stereoisomers). This mixture was quantitatively converted into the pure trans compound by treatment with MeONa (38 mg, 0.70 mmol) in MeOH (5 mL): ^{1}H NMR (400 MHz) δ 1.62 (qd, J = 4, 12.4, 12.4, 12.4 Hz, 1H), 1.98 (m, 2H), 2.14 (td, J = 2.7, 12, 12 Hz, 1H), 2.31 (m, 2H), 2.32 (s, 3H), 2.62 (dd, J = 11.6, 16, Hz, 1H), 3.05 (m, 2H), 3.06 (dd, J = 3.6, 16 Hz, 1H), 4.06 (s, 3H), 7.13 (ddd, J = 1.2, 7.2, 8 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.38 (ddd, J = 1.2, 7.2, 8 Hz, 1H), 7.61 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 25.5 (CH_2), 26.1 (CH_2), 31.3 (CH_3), 41.1 (CH), 46.2 (CH_3), 50.1 (CH), 55.7 (CH_2), 62.1 (CH_2), 110.2 (CH), 120.0 (CH), 121.0 (CH), 124.5 (C), 126.5 (CH), 127.0 (C), 129.8 (C), 139.7 (C), 192.5 (C). Anal. Calcd for $C_{17}H_{20}N_2O\cdot{}^1/_2H_2O$: C, 73.61; H, 7.63; N, 10.09. Found: C, 73.24; H, 7.39; N, 9.74.

Methyl 3-(1,2-Dimethyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-1*H*-2-indolecarboxylate (8). Pyridinium salt **7** (0.62 g, 1.50 mmol) was added under Ar to a cooled (−78 °C) solution of MeMgCl (3 M in THF, 1.75 mL, 5.25 mmol) in THF (35 mL), and the mixture was stirred at −78 °C for 20 min and at 0 °C for 6 h. The reaction mixture was poured into a 1:1 mixture of 20% NH_4OH and a saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were concentrated to dryness, and the resulting residue (0.47 g) was dissolved in MeOH (35 mL). $NaBH_4$ (0.16 g, 3.95 mmol) was added to the solution, and the mixture was stirred at rt for 4 h. The solvent was removed, and the resulting residue was partitioned between CH_2Cl_2 (30 mL) and a saturated aqueous Na_2CO_3 solution (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were dried and concentrated to give **8** as a brown oil: 0.40 g (90%); ^{1}H NMR (200 MHz) δ 1.28 (d, J = 6.6 Hz, 3H), 1.95−2.10 (m, 2H), 2.34 (s, 3H), 2.44 (dt, J = 5.6, 5.6, 11.8 Hz, 1H), 2.81 (ddd, J = 5.4, 7.2, 12.8 Hz, 1H), 2.94 (q, J = 6.2 Hz, 1H), 3.82 (br s, 2H), 3.93 (s, 3H), 5.27 (m, 1H), 7.10 (ddd, J = 1.8, 6.6, 8.2 Hz, 1H), 7.30−7.35 (m, 2H), 7.66 (d, J = 8 Hz, 1H), 8.91 (br s, 1H); ^{13}C NMR (75.4 MHz) δ 15.5 (CH_3), 24.0 (CH_2), 29.8 (CH_2), 42.4 (CH_3), 46.7 (CH_2), 51.7 (CH_3), 58.4 (CH), 111.7 (CH), 119.6 (CH), 120.0 (CH), 121.5 (CH), 121.6 (C), 123.5 (C), 125.5 (CH), 128.4 (C), 135.9 (C), 139.1 (C), 162.7 (C). Anal. Calcd for $C_{18}H_{22}N_2O_2\cdot H_2O$: C, 68.33; H, 7.64; N, 8.85. Found: C, 68.39; H, 7.26; N, 8.61.

***Se*-Phenyl 3-(1,2-Dimethyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-1*H*-2-indolecarboselenoate (9).** A solution of methyl ester **8** (0.30 g, 1 mmol) and $LiOH\cdot H_2O$ (50 mg, 1.20 mmol) in a 3:1 mixture of THF−H_2O (8 mL) was stirred at 65 °C for 5 h. The reaction mixture was concentrated, acidified with aqueous 1 N HCl until pH = 4, and concentrated to dryness. The resulting residue was digested with anhydrous MeOH. The methanolic solution was concentrated to give the crude carboxylic acid hydrochloride. A suspension of the above carboxylic acid in anhydrous CH_2Cl_2 (7 mL) was treated with Et_3N (2 mmol). After 15 min at rt, the mixture was concentrated under reduced pressure to give the triethylammonium salt.

In another flask, tributylphosphine (1.24 mL, 5 mmol) was added under Ar to a solution of PhSeCl (0.96 g, 5 mmol) in anhydrous THF (7 mL), and the mixture was stirred at rt for 10 min (yellow solution). Then, the above triethylammonium salt in THF (7 mL) was added to this solution, and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O (25 mL) and H_2O (25 mL) and extracted with Et_2O (3 × 15 mL). The solvent was removed, and the crude product was chromatographed (CH_2Cl_2 and 90:9:1 CH_2Cl_2−MeOH−diethylamine) to give selenoester **9** as a brown oil: 0.27 g (65%); ^{1}H NMR (200 MHz) δ 1.39 (d, J = 6.6 Hz, 3H), 2.05 (m, 2H), 2.45 (s, 3H), 2.51 (dd, J = 6, 12 Hz, 1H), 2.87 (dt, J = 5.8, 5.8, 12.2 Hz, 1H), 3.10 (q, J = 6.2 Hz, 1H), 3.79 (br d, J = 17.6 Hz, 1H), 3.96 (br d, J = 16.8 Hz, 1H), 5.17 (br s, 1H), 7.03 (d, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.45 (m, 3H), 7.65 (m, 3H), 9.82 (br s, 1H); ^{13}C NMR (75.4 MHz) δ 16.2 (CH_3), 24.1 (CH_2),

(17) We had observed that the indole NH group inhibited the radical cyclization of a related selenoester upon pyridines, probably by interfering at the rearomatization step: see ref 5.

(18) For a related dimerization involving 2-indolylacyl chlorides, see: Boger, D. L.; Fink, B. E.; Hedrick, M. P. *Biorg. Med. Chem. Lett.* **2000**, *10*, 1019−1020.

(19) Simple heating of selenoester **9** in 1:1 benzene−acetonitrile for 3 h led to a 3:1 mixture of **9** and **11**. In contrast, heating of **9** in benzene for 6 h led to a 10:1 mixture of **9** and **11**.

30.4 (CH_2), 42.7 (CH_3), 47.5 (CH_2), 59.5 (CH), 112.5 (CH), 120.4 (2 CH), 121.2 (C), 121.4 (CH), 125.4 (C), 126.5 (CH), 128.5 (C), 129.1 (CH), 129.4 (CH), 132.5 (C), 136.5 (C), 136.6 (CH), 137.8 (C), 184.4 (C). Anal. Calcd for $C_{23}H_{24}N_2OSe\cdot{}^3/_2H_2O$: C, 61.33; H, 6.04; N, 6.23. Found: C, 61.29; H, 5.66; N, 5.97.

(±) Guatambuine. *n*-Bu_3SnH (0.10 mL, 0.35 mmol) and AIBN (5 mg, 0.03 mmol) in C_6H_6 (5 mL) were added over a period of 2 h (syringe pump) to a heated (reflux) solution of selenoester **9** (115 mg, 0.27 mmol) and AIBN (5 mg, 0.03 mmol) in C_6H_6 (10 mL). After an additional 1 h at reflux, the solution was concentrated, and the resulting residue was partitioned between hexanes (10 mL) and acetonitrile (10 mL). The polar layer was washed with hexanes (3 × 10 mL) and concentrated to give ketone **10**.

A solution of crude **10** in anhydrous THF (7 mL) was added dropwise under Ar to a cooled (−10 °C) solution of MeLi (1.6 M in Et_2O, 2.50 mL, 4.0 mmol) in anhydrous THF (7 mL), and the resulting mixture was stirred at rt for 3 h. The reaction mixture was poured into an ice-cold saturated aqueous NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were dried and concentrated. 10% Pd/C (85 mg) was added to the resulting residue dissolved in TFA (4 mL), and the suspension was stirred at rt for 3 h. The reaction mixture was filtered through Celite, the cake was washed with CH_2Cl_2 (20 mL), and the organic solution was washed with a saturated aqueous $NaHCO_3$ solution (3 × 20 mL). The organic extracts were concentrated, and the crude product was chromatographed (92:7:1 CH_2Cl_2−MeOH−diethylamine) to give (±)-guatambuine: 32 mg (45%); ^{1}H NMR (300 MHz, HSQC and HMBC) δ 1.52 (d, J = 6.3 Hz, 3H, Me), 2.41 (s, 3H, Me), 2.54 (s, 3H, NMe), 2.79 (ddd, J = 5.7, 6, 11.7 Hz, 1H, 3-H), 2.94 (m, 2H, 4-H), 3.19 (ddd, J = 5.7, 6, 11.7 Hz, 1H, 3-H), 3.89 (q, J = 6.3 Hz, 1H, 1-H), 7.19 (ddd, J = 1.2, 6.6, 7.8 Hz, 1H, 9-H), 7.37 (ddd, J = 1.2, 6.6, 8.1 Hz, 1H, 8-H), 7.42 (dd, J = 1.2, 8.1 Hz, 1H, 7-H), 7.70 (s, 1H, 11-H), 7.85 (br s, 1H, NH), 8.00 (d, J = 7.8 Hz, 1H, 10-H); ^{13}C NMR (100.6 MHz, HSQC and HMBC) δ 12.9 (Me), 20.3 (Me), 25.0 (C-4), 42.0 (NMe), 48.1 (C-3), 59.7 (C-1), 110.6 (C-7), 115.9 (C-11), 116.9 (C-5), 119.2 (C-9), 120.1 (C-10), 121.3 (C-10b), 123.7 (C-10a), 125.5 (C-8), 128.8 (C-4a), 130.0 (C-11a), 138.1 (C-5a), 139.9 (C-6a); HRMS calcd for $C_{18}H_{20}N_2$ 264.1626, found 264.1628. Anal. Calcd for $C_{18}H_{20}N_2\cdot$HCl: C, 71.86; H, 7.04; N, 9.31. Found: C, 71.63; H, 6.85; N, 9.08.

Acknowledgment. Financial support from the Ministerio de Ciencia y Tecnología (MCYT-FEDER, Spain) through project BQU2003-04967-C-02-02 is gratefully acknowledged. F.F. also thanks the University of Barcelona for a grant.

Supporting Information Available: General experimental protocols and detailed experimental procedures for the preparation of synthetic intermediates **2**, **3**, **4**, and **7**. Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

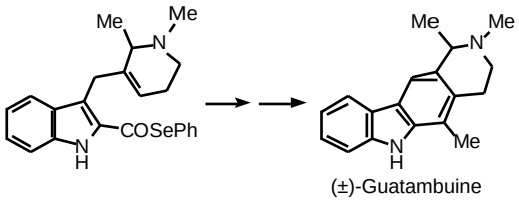
JO052428S

Supporting Information

Regioselective 6-Endo Cyclizations of 2-Indolylacyl Radicals: Total Synthesis of the Pyrido[4,3-*b*]carbazole Alkaloid Guatambuine

M.-Lluïsa Bennasar, Tomàs Roca, and Francesc Ferrando*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain



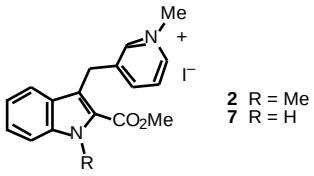
Total pages: 17

Contents:

General

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} 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 rotatory 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.

***N*-Methylpyridinium Iodides 2,7**

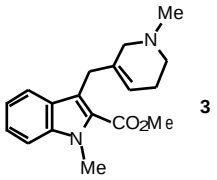


Iodomethane (1 mL, 16.64 mmol) in anhydrous benzene (1 mL) was added to a solution of pyridines **1, 6**[1] (4.16 mmol) in anhydrous acetone (6 mL). After stirring at rt for 5 h, the precipitated pyidinium salt was collected by filtration. Yields and NMR data are given below.

3-[(2-(Methoxycarbonyl)-1-methyl-3-indolylmethyl]-1-methylpyridinium Iodide (2): 90%; mp 212–214°C; ^1H NMR (CD_3OD, 200 MHz) δ 3.91 (s, 3H), 4.06 (s, 3H), 4.35 (s, 3H), 4.69 (s, 2H), 7.18 (dd, *J* = 7, 8 Hz, 1H), 7.41 (dd, *J* = 7, 8.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.91 (dd, *J* = 5.8, 7.6 Hz, 1H), 8.35 (d, *J* = 8 Hz, 1H), 8.69 (d, *J* = 5.8 Hz, 1H), 8.77 (s, 1H). Anal. Calcd for $C_{18}H_{16}IN_2O_2 \cdot 1/2H_2O$: C, 50.48; H, 4.00; N, 6.54. Found: C, 50.69; H, 4.36; N, 6.33.

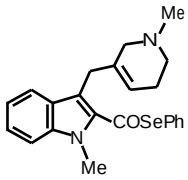
3-[(2-(Methoxycarbonyl)-1*H*-3-indolylmethyl]-1-methylpyridinium Iodide (7): 90%; mp 216-218°C; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.89 (s, 3H), 4.30 (s, 3H), 4.62 (s, 2H), 7.08 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.29 (td, *J* = 1.2, 7.2, 7.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.97 (dd, *J* = 5.7, 7.8 Hz, 1H), 8.36 (d, *J* = 8.1 Hz, 1H), 8.78 (d, *J* = 5.7 Hz, 1H), 8.89 (s, 1H), 11.90 (s, 1H). Anal. Calcd for $C_{17}H_{17}IN_2O_2$: C, 50.02; H, 4.20; N, 6.86. Found: C, 50.14; H, 4.44; N, 6.48.

Methyl 1-Methyl-3-(1-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-2-indolecarboxylate (3)



$NaBH_4$ (0.16 g, 3.95 mmol) was added in two portions to a suspension of pyridinium salt **2** (0.64 g, 1.52 mmol) in EtOH (15 mL) at rt. After stirring at rt for 4 h, the solvent was removed and the resulting residue was partitioned between CH_2Cl_2 (15 mL) and saturated Na_2CO_3 (15 mL), and extracted with CH_2Cl_2 (2x10 mL). The organic extracts were dried and concentrated to give **3** as a brown oil: 0.44 g (98%); ^1H NMR (200 MHz) δ 2.11 (m, 2H), 2.29 (s, 3H), 2.41 (t, *J* = 5.8 Hz, 2H), 2.84 (br s, 2H), 3.77 (br s, 2H), 3.92 (s, 3H), 4.01 (s, 3H), 5.37 (m, 1H), 7.14 (m, 1H), 7.35 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 26.1 (CH_2), 30.9 (CH_2), 32.1 (CH_3), 45.9 (CH_3), 51.4 (CH_3), 51.8 (CH_2), 57.4 (CH_2) 110.0 (CH), 119.1 (CH), 119.8 (CH), 121.2 (CH), 121.4 (C), 124.9 (C), 125.1 (CH), 127.0 (C), 135.2 (C), 138.7 (C), 163.2 (C); HRMS (CI) calcd for $C_{18}H_{23}N_2O_2$ 299.1759 (M+1), found 299.1758.

***Se*-Phenyl 1-Methyl-3-(1-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl)-2-indolecarboselenoate (4)**

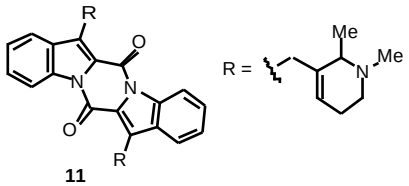


4

A solution of the methyl ester **3** (0.30 g, 1 mmol) and $LiOH \cdot H_2O$ (50 mg, 1.20 mmol) in a 3:1 mixture of THF-H_2O (8 mL) was stirred at 65°C for 5 h. The reaction mixture was concentrated, acidified with aqueous 1 N HCl until pH = 4, and concentrated to dryness. The resulting residue was digested with anhydrous MeOH. The methanolic solution was concentrated to give the crude carboxylic acid hydrochloride. A suspension of the above carboxylic acid in anhydrous CH_2Cl_2 (7 mL) was treated with Et_3N (2 mmol). After 15 min at rt, the mixture was concentrated to give the corresponding triethylammonium salt.

In another flask, tributylphosphine (0.62 g, 2.50 mmol) was added under Ar to a solution of PhSeCl (0.48 g, 2.50 mmol) in anhydrous THF (7 mL), and the mixture was stirred at rt for 10 min (yellow solution). Then, the above triethylammonium salt in THF (7 mL) was added to this solution and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O (25 mL) and H_2O (25 mL) and extracted with Et_2O (3x15 mL). The solvent was removed and the crude product was chromatographed (96:4 CH_2Cl_2-MeOH) to give selenoester **4**.HCl: 0.37 g (80%); mp 148-50°C; ^{1}H NMR (200 MHz) δ 2.50 (m, 2H), 2.78 (s, 3H), 3.13 (t, *J* = 6 Hz, 2H), 3.60 (br s, 2H), 3.91 (s, 3H), 3.94 (s, 2H), 5.62 (m, 1H), 7.19 (m, 1H), 7.35-7.50 (m, 5H), 7.55-7.65 (m 3H); ^{13}C NMR (50.3 MHz) δ 21.2 (CH_2), 30.4 (CH_2), 32.5 (CH_3), 41.7 (CH_3), 49.5 (CH_2), 53.6 (CH_2) 110.5 (CH), 116.7 (C), 120.4 (CH), 120.8 (CH), 121.0 (CH), 125.7 (C), 126.3 (CH), 126.8 (C), 129.3 (CH), 129.4 (C), 129.5 (CH), 134.4 (C), 136.0 (CH), 138.4 (C), 185.5 (C). Anal. Calcd for $C_{23}H_{24}N_2OSe \cdot HCl \cdot H_2O$: C, 57.81; H, 5.69; N, 5.86. Found: C, 58.12; H, 5.48; N, 5.82.

Diketopiperazine 11

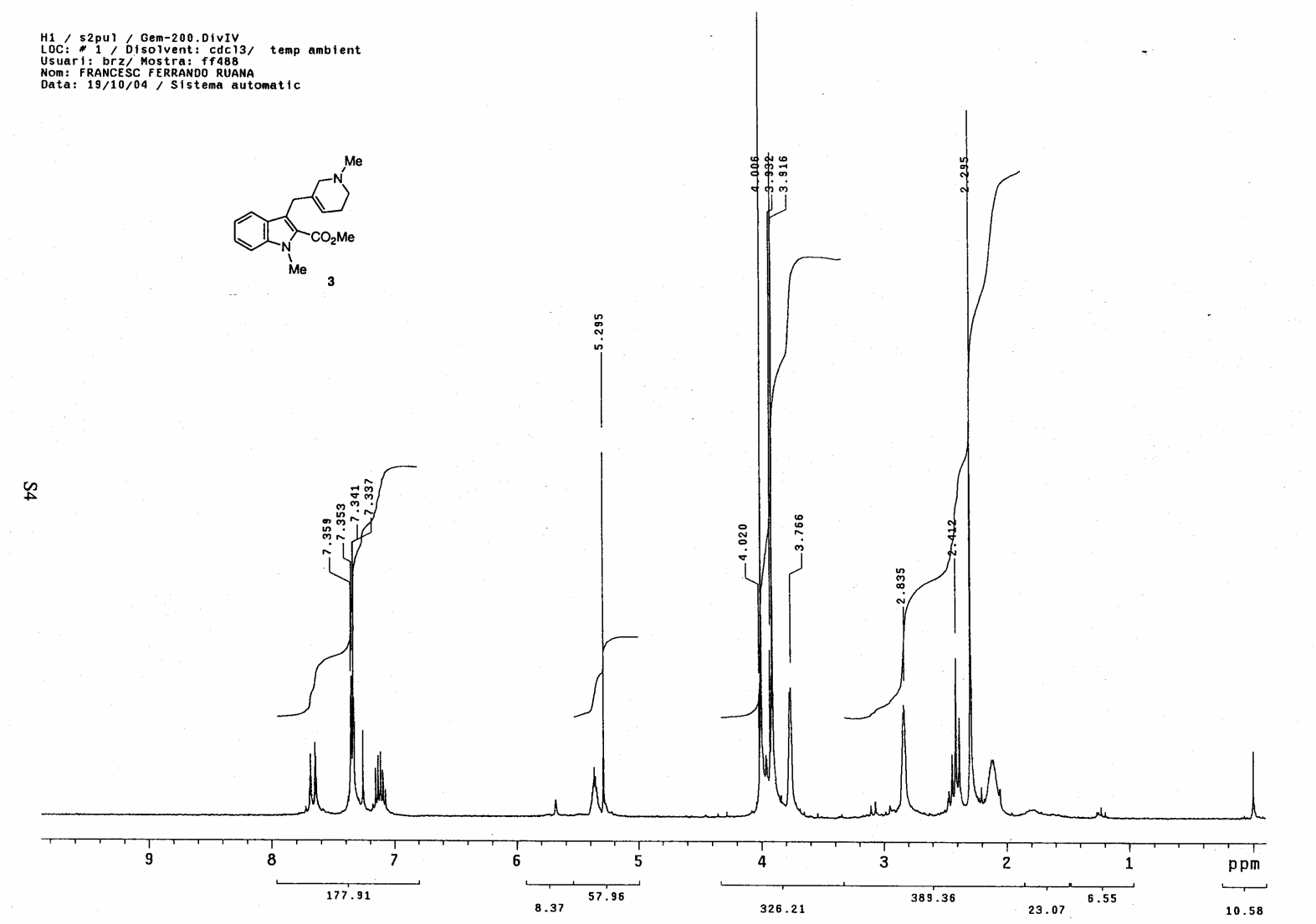


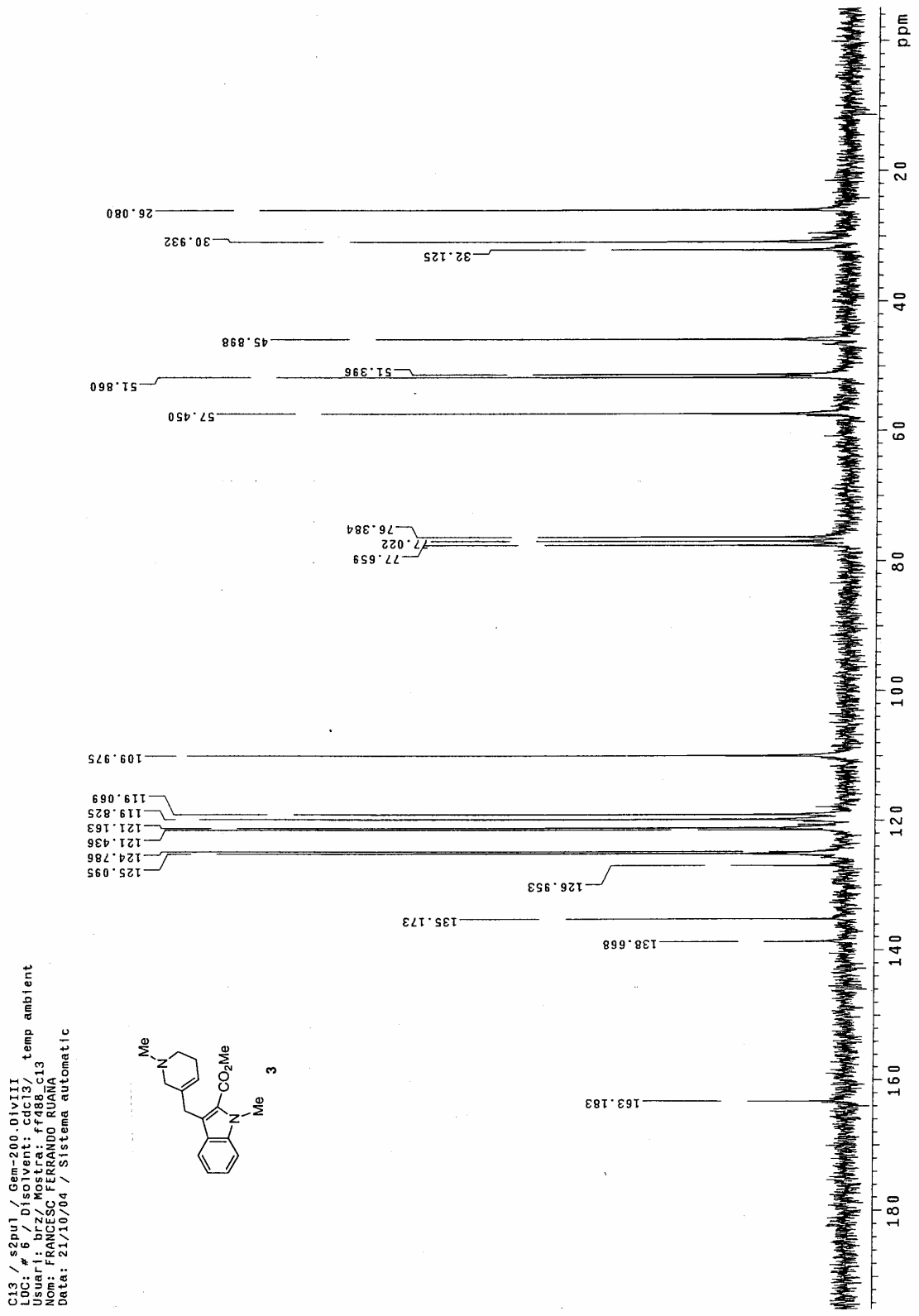
11

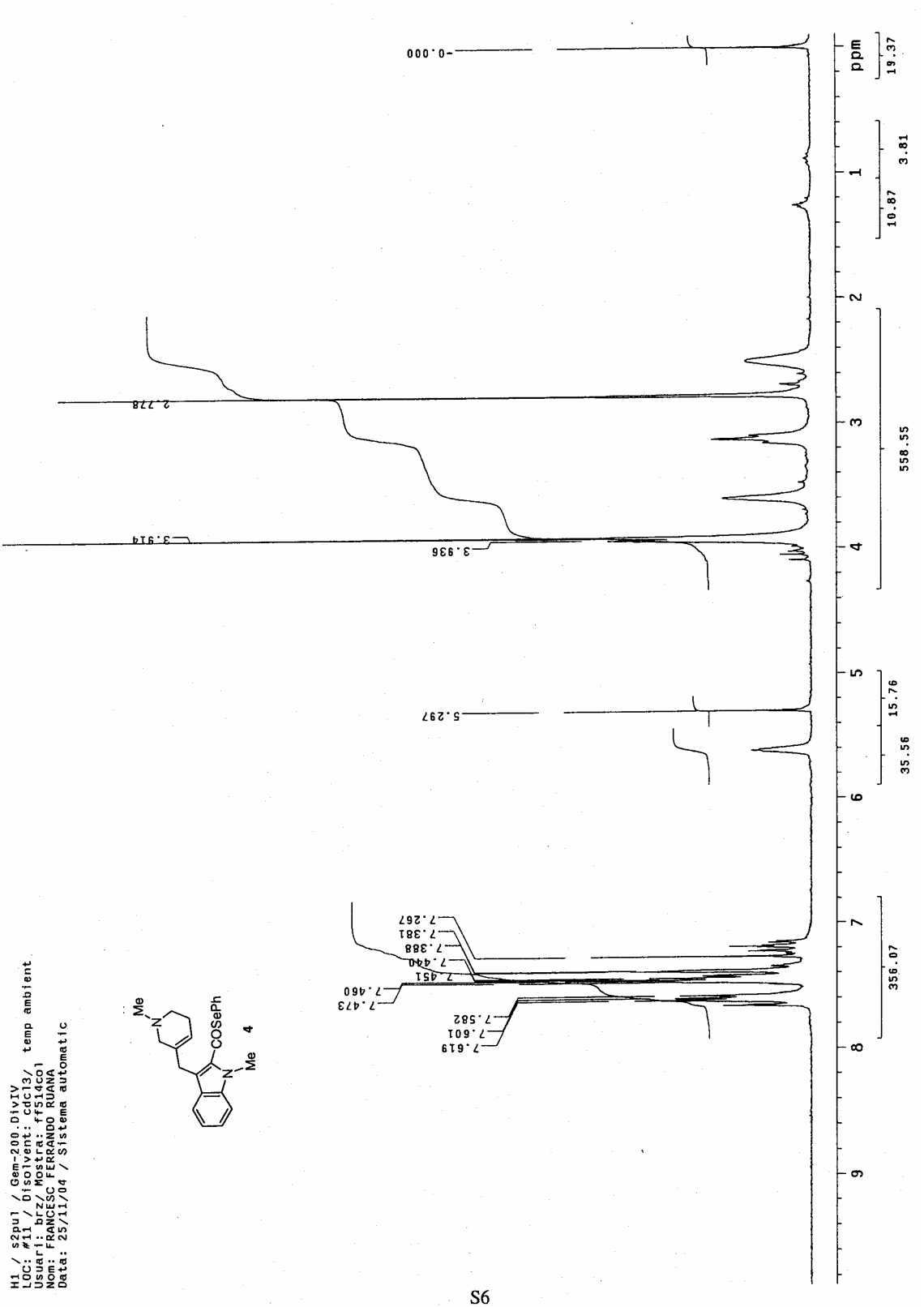
^{1}H NMR (300 MHz) δ 1.36 (d, *J* = 6.6 Hz, 6H), 1.95-2.15 (m, 4H), 2.37 (s, 6H), 2.46 (dt, *J* = 5.1, 5.1, 12 Hz, 2H), 2.81 (m, 2H), 3.02 (q, *J* = 6.6 Hz, 2H), 3.99 (d, *J* = 15.6 Hz, 2H), 4.17 (d, *J* = 15.3 Hz, 2H), 5.42 (broad s, 2H), 7.34 (ddd, *J* = 1.2, 7.2, 7.8 Hz, 2H), 7.53 (ddd, *J* = 1.2, 7.3, 8.4 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 8.62 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75.4 MHz) δ 15.5 (CH_3), 24.2 (CH_2), 29.6 (CH_2), 42.4 (CH_3), 46.7 (CH_2), 58.5 (CH), 117.0 (CH), 120.8 (CH), 121.8 (CH), 123.4 (C), 124.9 (CH), 129.2 (CH), 130.2 (C), 132.6 (C), 135.4 (C), 138.0 (C), 154.3 (C); FAB-MS *m/z* 533 (M+1).

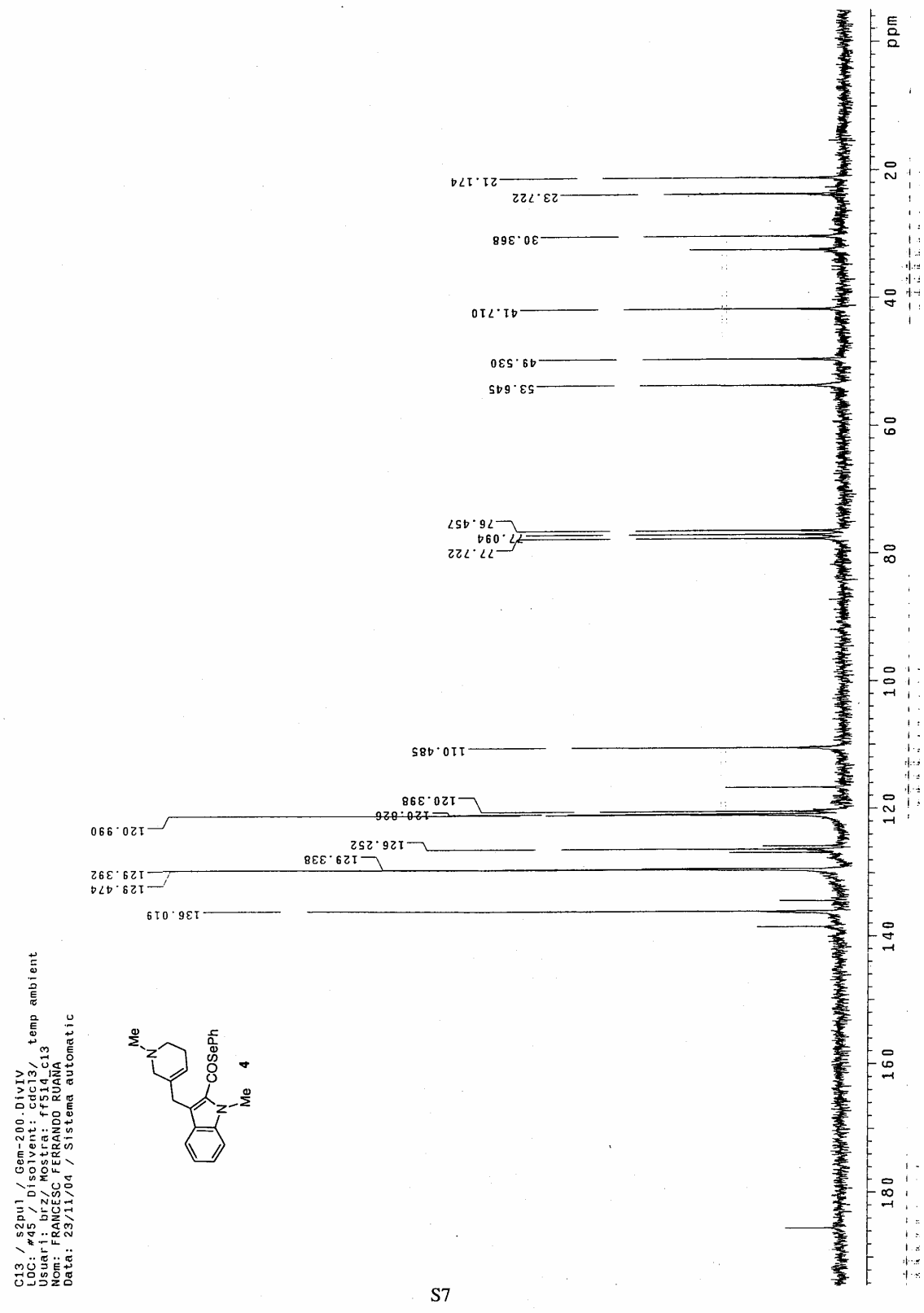
References

1. Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem.* **2005**, *70*, 9077-9080.


H1 / s2pul / Gem-200.DivIV
LOC: # 1 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff488
Nom: FRANCESC FERRANDO RUANA
Data: 19/10/04 / Sistema automatic
Me
N
CO2Me
N
Me
3
S4
7.359
7.353
7.341
7.337
5.295
4.006
3.932
3.916
4.020
3.766
2.835
2.412
2.295
9
8
7
6
5
4
3
2
1
ppm
177.91
8.37
57.96
326.21
389.36
23.07
6.55
10.58


C13 / s2pul / Gem-200.DivIII
LOC: # 6 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff488_c13
Nom: FRANCESC FERRANDO RUANA
Data: 21/10/04 / Sistema automatic
Me
N
CO2Me
N
Me
3
163.183
138.668
135.173
126.953
125.095
124.786
121.436
121.163
119.825
119.069
109.975
77.659
77.022
76.384
57.450
51.860
51.396
45.898
32.125
30.932
26.080
ppm
20
40
60
80
100
120
140
160
180


H1 / s2pul / Gem-200.DivIV
LOC: #11 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff514col
Nom: FRANCESC FERRANDO RUANA
Data: 25/11/04 / Sistema automatic
Me
N
COSePh
N
Me
4
7.619
7.601
7.582
7.473
7.460
7.451
7.440
7.388
7.381
7.267
5.297
3.936
3.914
2.728
0.000
ppm
356.07
35.56
15.76
558.55
10.87
3.81
19.37


C13 / s2pul / Gem-200.DivIV
LOC: #45 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff514_c13
Nom: FRANCESC FERRANDO RUANA
Data: 23/11/04 / Sistema automatic
Me
N
COSePh
N
Me
4
136.019
129.474
129.392
129.338
126.252
120.826
120.990
120.398
110.485
77.722
77.094
76.457
53.645
49.530
41.710
30.368
23.722
21.174
ppm

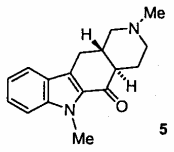
NIVERSITAT DE BARCELONA

RVEIS CIENTIFICO-TECNICS

UNITAT DE RMN D ALT CAMP

H1 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40004-1213
Usuari: brz / Mostra: ff527
Nom: FRANCESC FERRANDO RUANA
Data:20/12/04 / Sist automatic

Pulse Sequence: s2pul



5

S8

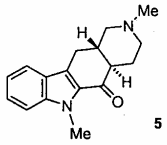
UNIVERSITAT DE BARCELONA

SERVEIS CIENTIFICO-TECNICS

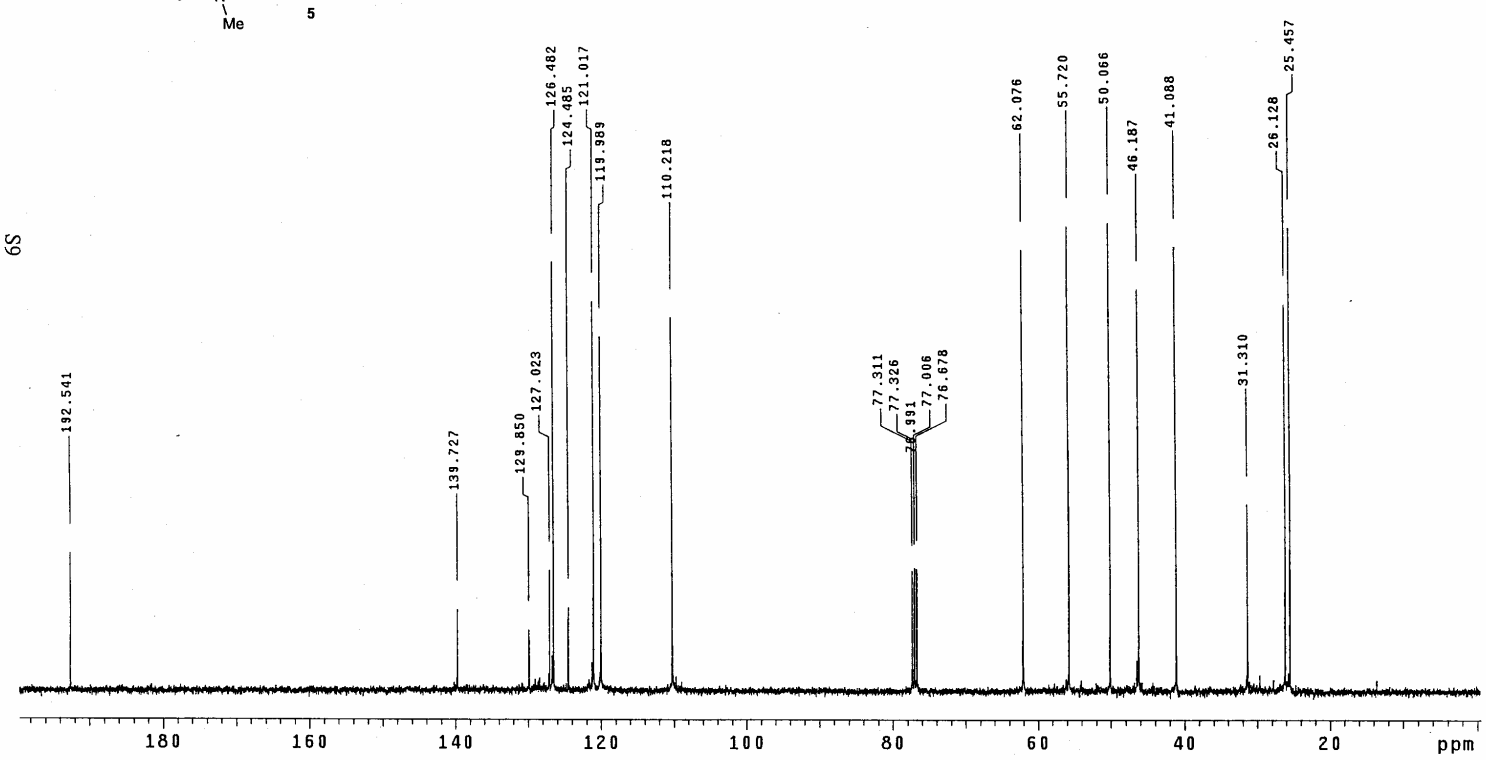
UNITAT DE RMN D ALT CAMP

C13 / s2pul / Mercury-400_qui
cdcl3/Temp: 25C /N reg: M40004-1213
Usuari: brz / Mostra: ff527
Nom: FRANCESC FERRANDO RUANA
Data:20/12/04 / Sist automatic

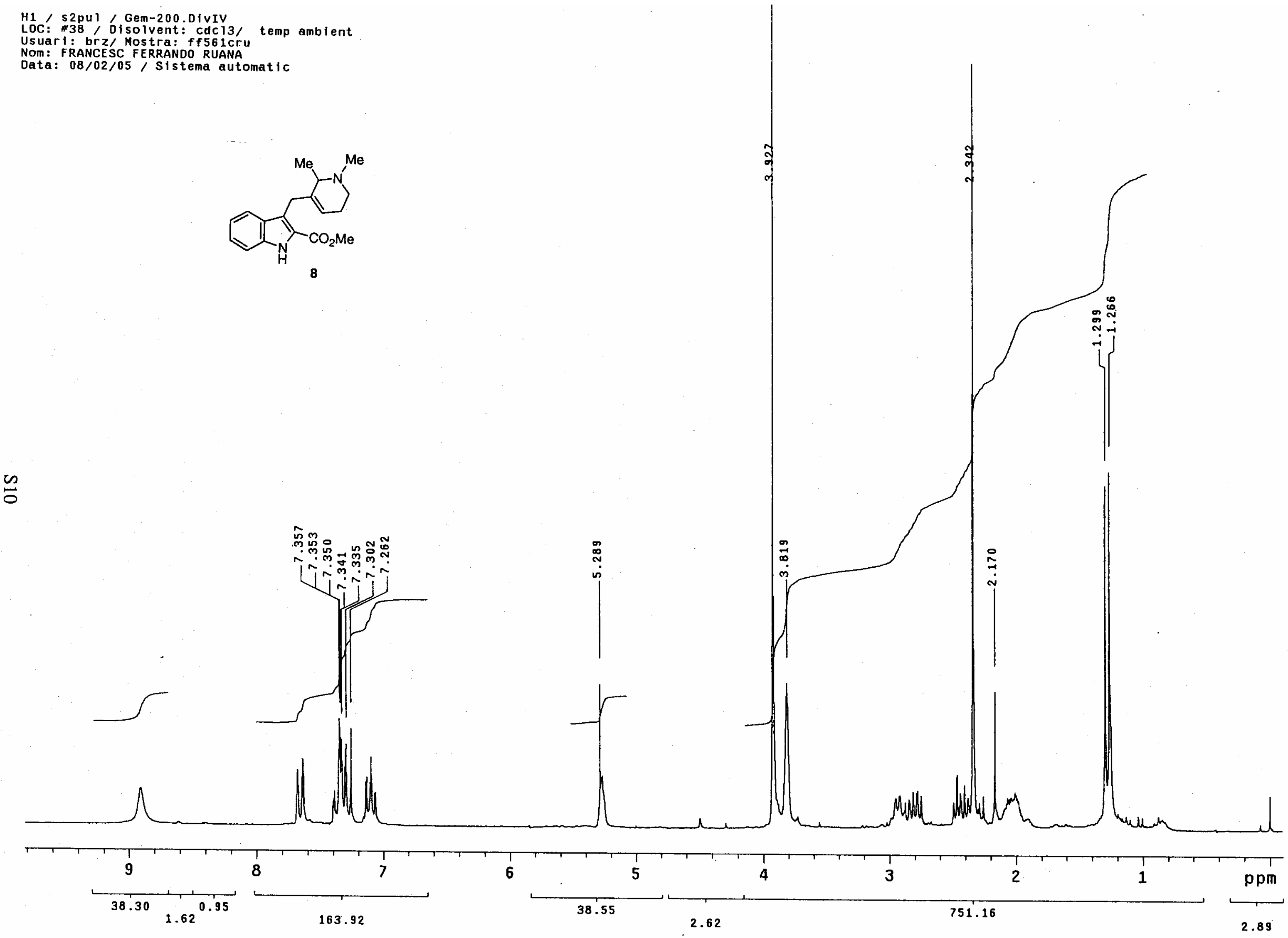
Pulse Sequence: s2pul

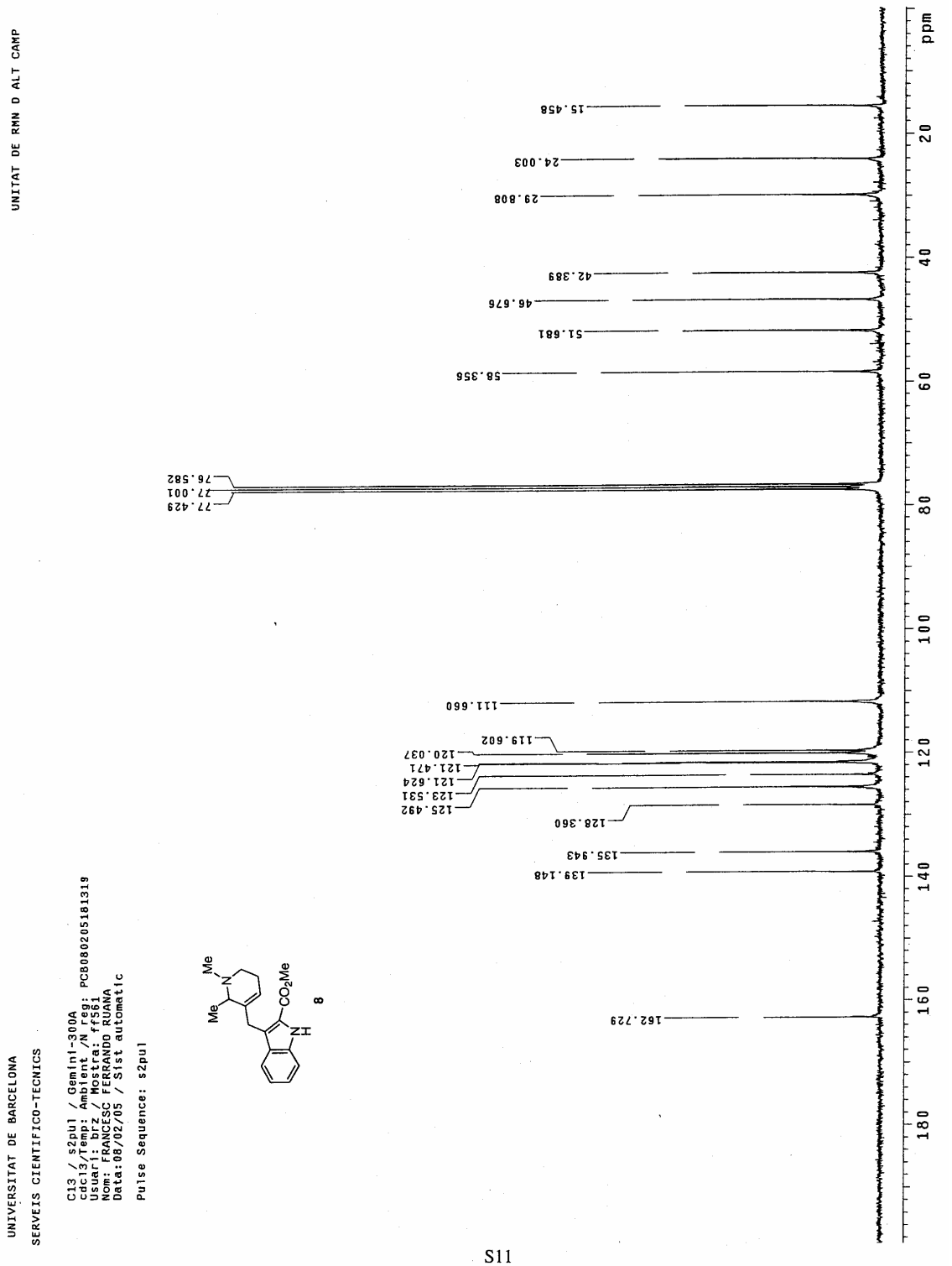


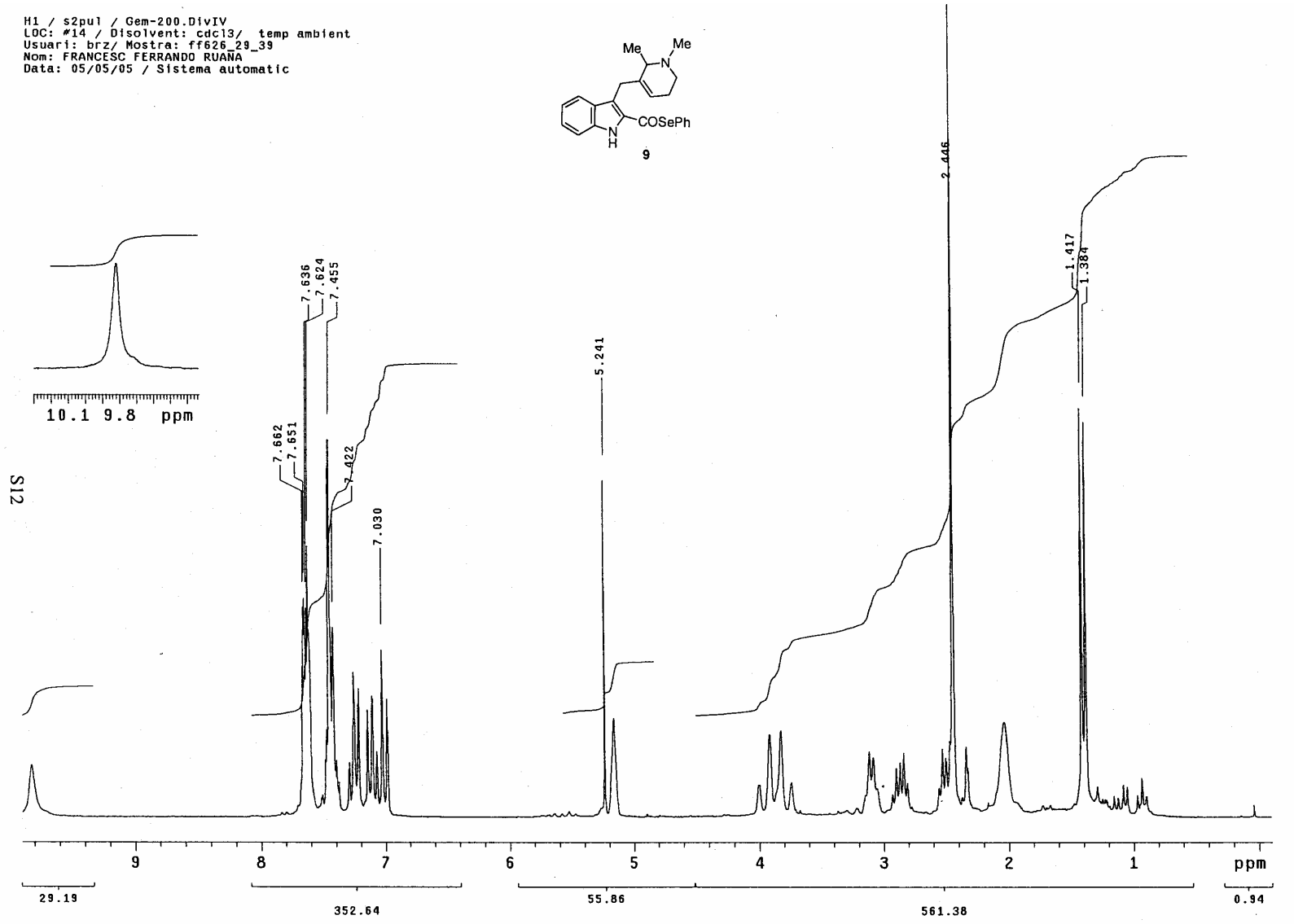
5

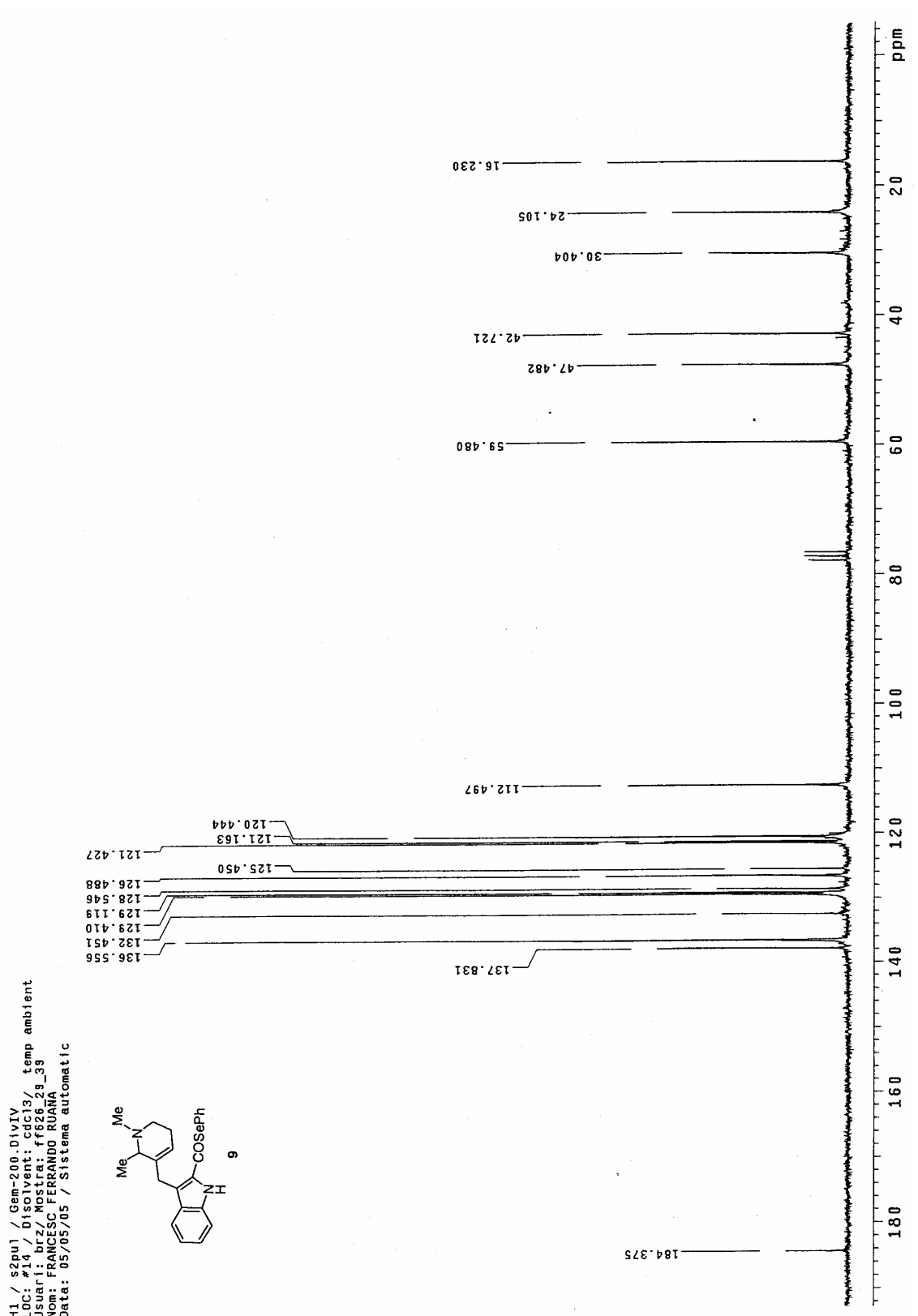


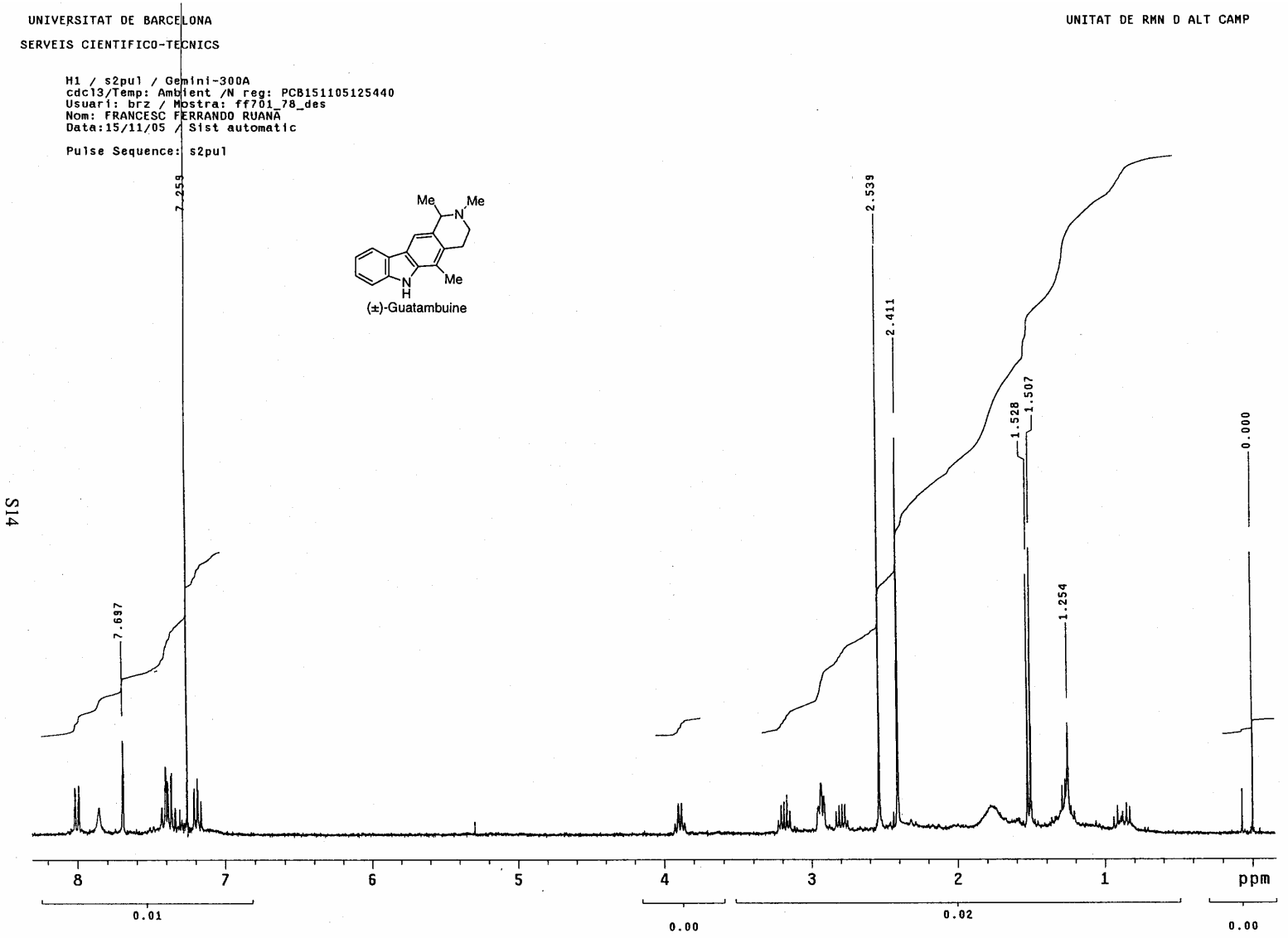
6S

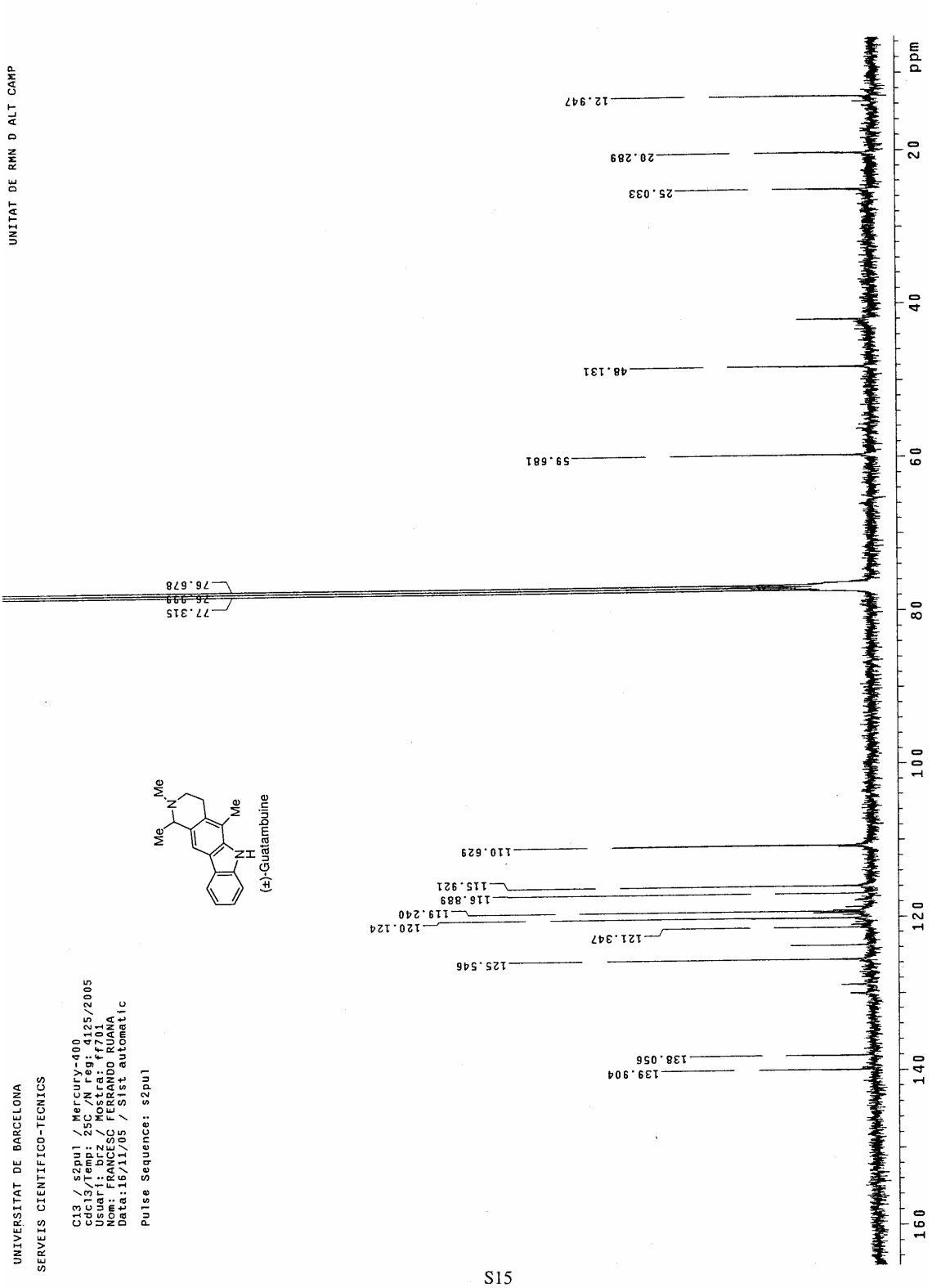

H1 / s2pul / Gem-200.DivIV
LOC: #38 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff561cru
Nom: FRANCESC FERRANDO RUANA
Data: 08/02/05 / Sistema automatic
Me
Me
N
CO2Me
N
H
8
3.927
2.342
1.299
1.266
7.357
7.353
7.350
7.341
7.335
7.302
7.262
5.289
3.819
2.170
9
8
7
6
5
4
3
2
1
ppm
38.30
1.62
0.95
163.92
38.55
2.62
751.16
2.89

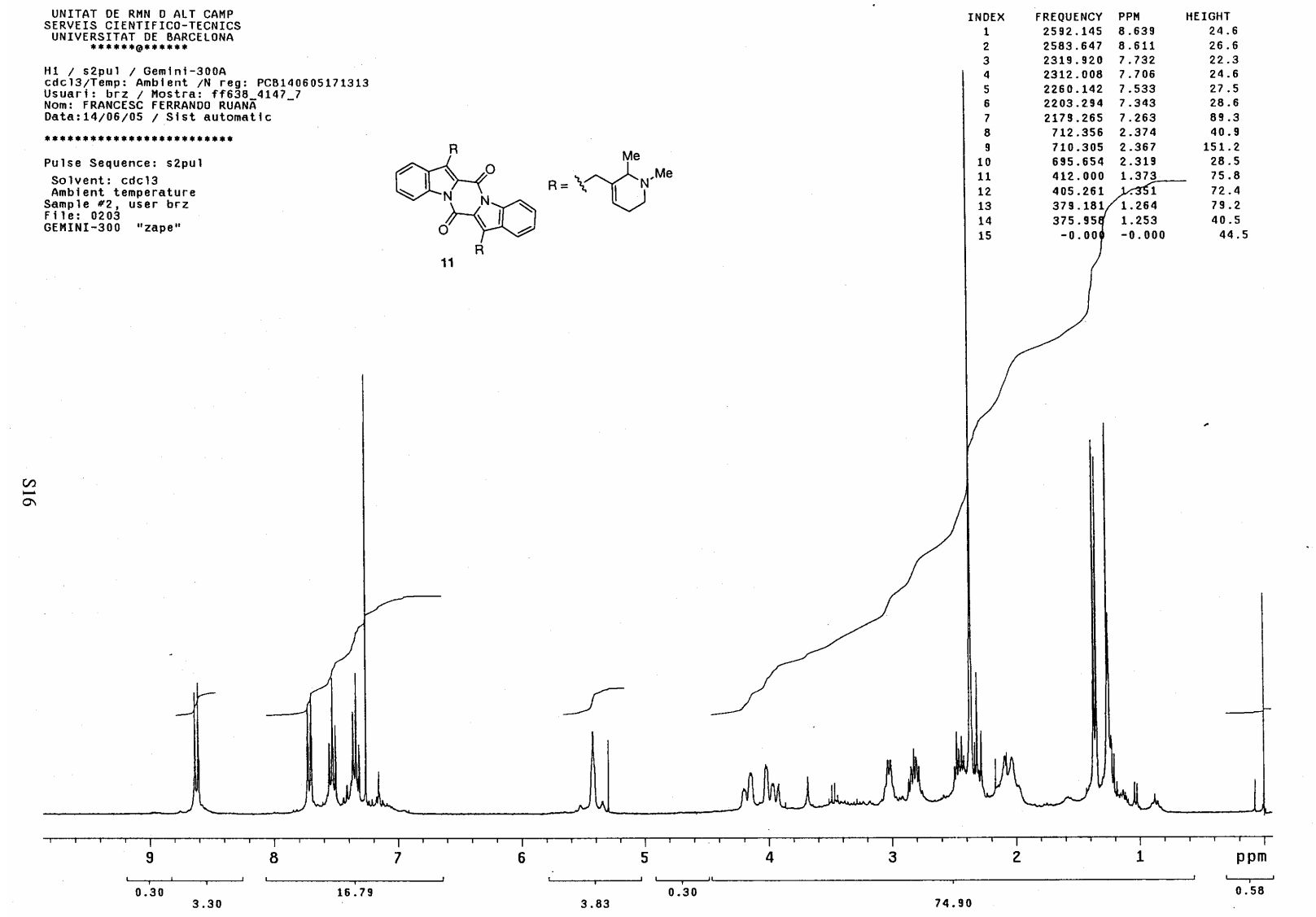

UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB08020518131g
Usuari: brz / Mostra: ff561
Nom: FRANCESC FERRANDO RUANA
Data:08/02/05 / Sist automatic
Pulse Sequence: s2pul
Me
N
Me
CO2Me
H
8
162.729
139.148
135.943
128.360
125.492
123.531
121.624
121.471
120.037
119.602
111.660
77.429
77.001
76.582
58.356
51.681
46.676
42.389
29.808
24.003
15.458
ppm

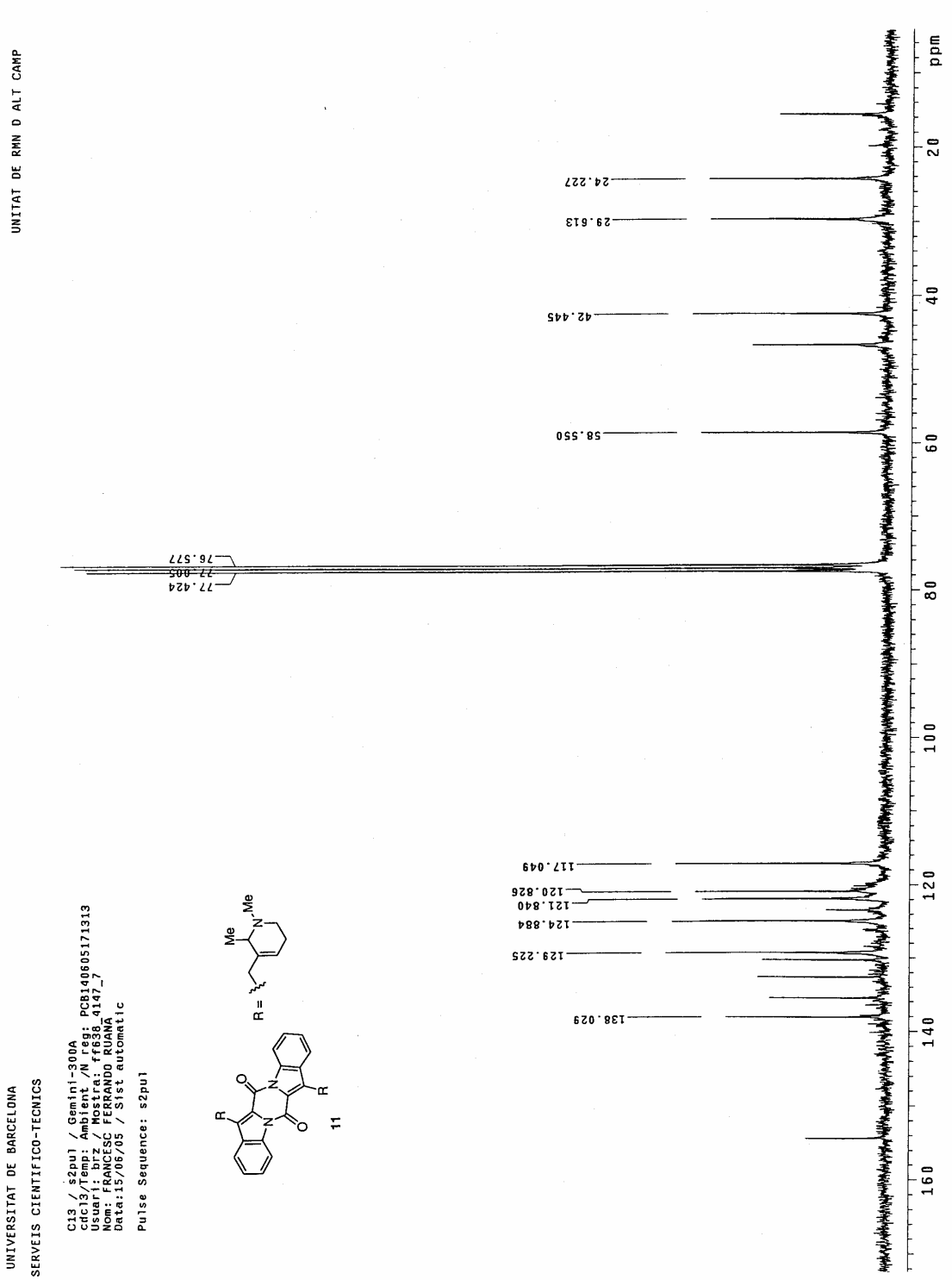

H1 / s2pul / Gem-200.DivIV
LOC: #14 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff626_29_39
Nom: FRANCESC FERRANDO RUANA
Data: 05/05/05 / Sistema automatic
Me
Me
N
COSePh
N
H
9
S12
10.1 9.8 ppm
7.662
7.651
7.636
7.624
7.455
7.422
7.030
5.241
2.446
1.417
1.384
9
8
7
6
5
4
3
2
1
ppm
29.19
352.64
55.86
561.38
0.94


H1 / s2pul / Gem-200.DivIV
LOC: #14 / Disolvent: cdcl3/ temp ambient
Usuari: brz/ Mostra: ff626_29_39
Nom: FRANCESC FERRANDO RUANA
Data: 05/05/05 / Sistema automatic
Me
N
Me
COSePh
N
H
9
184.375
137.831
136.556
132.451
129.410
129.119
128.546
126.488
125.450
121.427
121.163
120.444
112.497
59.480
47.482
42.721
30.404
24.105
16.230
ppm
180
160
140
120
100
80
60
40
20


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB151105125440
Usuari: brz / Mostra: ff701_78_des
Nom: FRANCESC FERRANDO RUANA
Data:15/11/05 / Sist automatic
Pulse Sequence: s2pul
7.259
2.539
2.411
1.528
1.507
1.254
0.000
7.697
Me
Me
Me
N
H
(±)-Guatambuine
8
7
6
5
4
3
2
1
ppm
0.01
0.00
0.02
0.00


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Mercury-400
cdcl3/Temp: 25C /N reg: 4125/2005
Usuari: brz / Mostra: ff701
Nom: FRANCESC FERRANDO RUANA
Data:16/11/05 / Sist automatic
Pulse Sequence: s2pul
Me
N
Me
Me
NH
(±)-Guatambuine
12.947
20.289
25.033
48.131
59.681
76.678
77.315
110.629
115.921
116.889
119.240
120.124
121.347
125.546
138.056
139.904
ppm
20
40
60
80
100
120
140
160


UNITAT DE RMN D ALT CAMP
SERVEIS CIENTIFICO-TECNICS
UNIVERSITAT DE BARCELONA
******@******
H1 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB140605171313
Usuari: brz / Mostra: ff638_4147_7
Nom: FRANCESC FERRANDO RUANA
Data:14/06/05 / Sist automatic
****
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #2, user brz
File: 0203
GEMINI-300 "zape"
R
O
N
N
O
R
11
R =
Me
N
Me
INDEX FREQUENCY PPM HEIGHT
1 2592.145 8.639 24.6
2 2583.647 8.611 26.6
3 2319.920 7.732 22.3
4 2312.008 7.706 24.6
5 2260.142 7.533 27.5
6 2203.294 7.343 28.6
7 2179.265 7.263 89.3
8 712.356 2.374 40.9
9 710.305 2.367 151.2
10 695.654 2.319 28.5
11 412.000 1.373 75.8
12 405.261 1.351 72.4
13 379.181 1.264 79.2
14 375.956 1.253 40.5
15 -0.000 -0.000 44.5
9
8
7
6
5
4
3
2
1
ppm
0.30
3.30
16.79
3.83
0.30
74.90
0.58


UNIVERSITAT DE BARCELONA
SERVEIS CIENTIFICO-TECNICS
UNITAT DE RMN D ALT CAMP
C13 / s2pul / Gemini-300A
cdcl3/Temp: Ambient /N reg: PCB140605171313
Usuari: Nom / Mostra: ff038_4147_7
Nom: FRANCESC / FERRANDO RUANA
Data:15/06/05 / Sist automatic
Pulse Sequence: s2pul
R =
Me
N
Me
R
R
O
N
N
O
11
ppm
20
40
60
80
100
120
140
160
24.227
29.613
42.445
58.550
76.577
77.005
77.424
117.049
120.826
121.840
124.884
129.225
138.029

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5605–5609
Tetrahedron Letters

Intramolecular reactions of 2-indolylacyl radicals: cyclisation upon aromatic rings

M.-Lluïsa Bennasar,* Tomàs Roca and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

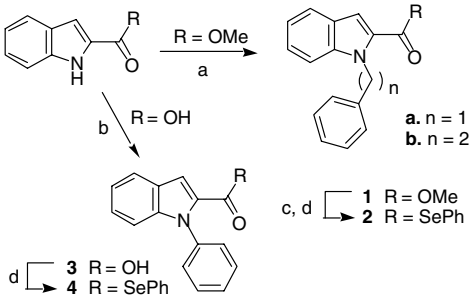
Received 5 May 2004; accepted 26 May 2004
Available online 15 June 2004

Abstract—The generation of 2-indolylacyl radicals from the corresponding selenoesters under reductive (tributyltin hydride–AIBN) and nonreductive (hexabutylditin, 300 W) conditions and their behaviour in cyclisation reactions upon benzene rings attached either to the indole nitrogen or the C-3 ring position have been studied.

Intramolecular reactions of nucleophilic carbon-centred radicals with aromatic systems have received considerable synthetic attention for the construction of complex polycyclic molecules incorporating aromatic rings.[1] Fully aromatic products are generally obtained after the in situ oxidation of the initially formed cyclohexadienyl radicals, which occurs even under the apparently reductive tributyltin hydride–AIBN conditions.[2] Most of the examples reported in the literature deal with cyclisations of aryl and, to a lesser extent, alkyl radicals upon arenes[1,3] and heteroarenes,[1] including pyridines,[4] quinolines,[5] azoles,[6] or indoles.[7,8] However, similar processes involving acyl radicals, which have an enhanced synthetic potential due to their intrinsic functionalisation,[9] have scarcely been studied.[10]

In the last few years we have been actively studying the generation of 2- and 3-indolylacyl radicals from the corresponding phenyl selenoesters and their reactions with alkene acceptors under reductive conditions.[11] Our continuing interest in this area led us to explore intramolecular reactions of these radical intermediates with aromatic and heteroaromatic rings, as a general approach to polycyclic aryl or heteroaryl indolyl ketones. We herein report our preliminary results using 2-indolylacyl radicals in cyclisation reactions upon benzene rings located in chains attached either to the indole nitrogen or the C-3 ring position.

Selenoesters **2a**,**b** and **4**, bearing a phenyl moiety separated by one or two methylene groups or directly attached to the indole nitrogen, were selected as radical precursors for cyclisations leading to 1,2-fused ring indole derivatives. These compounds were efficiently prepared from simple starting products as shown in Scheme 1. Thus, *N*-alkylation of the sodium salt of methyl indole 2-carboxylate with benzyl or 2-phenylethyl bromide gave esters **1a** and **1b**, which were converted into **2a** and **2b** by hydrolysis and subsequent reaction of the resulting carboxylic acids with Et_3N, PhSeCl and PBu_3.[12] On the other hand, Ullman reaction of indole 2-carboxylic acid with bromobenzene gave acid **3**,[13] which was converted as above into selenoester **4**.

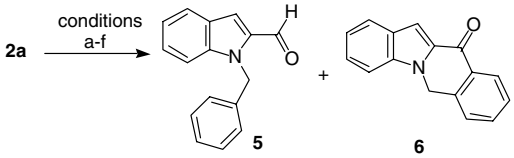


Scheme 1. Reagents and conditions: (a) $Ph(CH_2)_nBr$, NaH, THF, rt, 93% (**1a**), 60% (**1b**); (b) PhBr, K_2CO_3, CuO, DMF, reflux, 71%; (c) 2 N KOH, MeOH–dioxane, reflux, then, 2 N HCl; (d) Et_3N, then PhSeCl, PBu_3, THF, rt, 95% (**2a** from **1a**), 80% (**2b** from **1b**), 75% (**4**).

Keywords: Radicals; Radical cyclisation; Aromatic polycyclic compounds.
* Corresponding author. Tel.: +34-934024540; fax: +34-934024539; e-mail: bennasar@ub.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.133

Table 1. Radical cyclisation of selenoester **2a**



Entry	Radical mediator	Conditions[a]	Products (yields, %)[b]
1	*n*-Bu_3SnH	a or b	**5** (90)
2	*n*-Bu_3SnH	c	**5** + **2a** (1:1)[c]
3	TTMSS	d	**5** + **6** (4:1)[c]
4	*n*-Bu_6Sn_2	e	**5** (10), **2a** (25), **6** (40)
5	*n*-Bu_6Sn_2	f	**6** (65)

[a] Conditions a: *n*-Bu_3SnH (1.5 mol), AIBN (0.1 mol), benzene, 0.03 M, reflux, syringe pump, 2 h; b: *n*-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN–hexane, 0.06 M, reflux, syringe pump, 4 h; c: *n*-Bu_3SnH (1.2 mol), AIBN (0.1 mol), Ph_2Se_2 (cat), benzene, 0.01 M reflux, syringe pump, 20 h; d: TTMSS (1.2 mol), AIBN (2 mol), benzene, 0.03 M, reflux, syringe pump, 4 h; e: *n*-Bu_6Sn_2 (0.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h; f: *n*-Bu_6Sn_2 (2.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h.

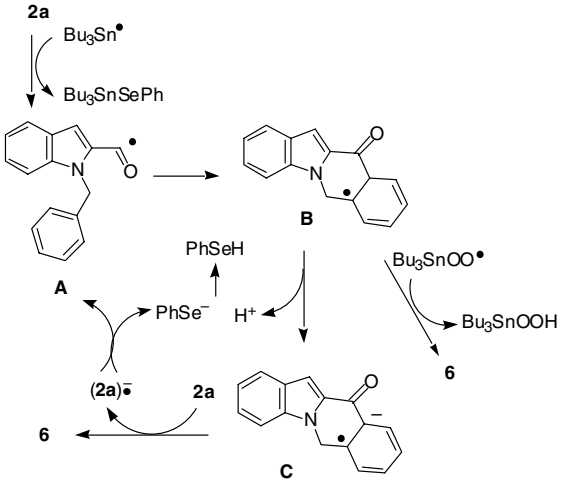
[b] Isolated yields.

[c] Ratio determined by ^1H NMR analysis of the reaction mixtures.

We set out to examine several experimental conditions from selenoester **2a** to achieve the desired cyclisation (Table 1). Considering the literature precedents,[1] the use of standard reductive (tributyltin hydride–AIBN) conditions was first investigated. Unsatisfactorily, using different amounts of the initiator either in benzene (entry 1, conditions a) or in acetonitrile–hexane[10d] (entry 1, conditions b) aldehyde **5**, coming from simple reduction of the initially formed 2-indolylacyl radical, was isolated in high yield as the only product. This premature reduction was also observed in the presence of catalytic phenylselenol under conditions reported by Crich and Hwang,[14] although significant amounts of the starting substrate **2a** were also recovered even after 20 h reaction (entry 2). On the other hand, the use of the poorer hydrogen-atom donor tris(trimethylsilyl)silane (TTMSS, entry 3)[15] as the radical mediator gave a reaction mixture, in which aldehyde **5** could be identified as the major product along with minor amounts of the desired tetracycle **6**.

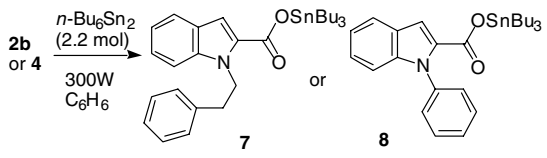
The above results prompted us to investigate the cyclisation of **2a** under non reductive conditions (*n*-Bu_6Sn_2, 300 W sun lamp, entries 4 and 5).[16] We expected that this process was now favoured due to the comparatively longer effective lifetime of the indolylacyl radical. Our first experiments were promising, as treatment of **2a** with a substoichiometric amount of *n*-Bu_6Sn_2 gave the cyclised product **6**[17] in 40% yield. However, significant amounts of recovered **2a** (25%), indicative of a poor chain, and aldehyde **5** (10%, see below) were also formed. Satisfactorily, complete conversion of the substrate **2a** was achieved using 2.2 mol of the radical mediator to give tetracycle **6** (65% isolated yield) with no trace of reduction product.

The above results can be rationalised as depicted in Scheme 2. After cleavage of *n*-Bu_6Sn_2 under the influence of heat and/or light, the resulting tributyltin radical generates the 2-indolylacyl radical **A**, which in absence of competitive reactions can intramolecularly react upon the benzene ring to give the cyclohexadienyl radical **B**.[18] When substoichiometric amounts of the radical mediator are used, conversion of **B** into **6** must be described, at least in part, through a chain propagation mechanism, which may involve a $S_{RN}1$ type reaction very similar to the one first proposed by Bowmann for tributyltin hydride–AIBN mediated aromatic substitutions.[19] Thus, deprotonation of radical **B**, followed by a SET reaction from the resulting radical anion **C** to selenoester **2a** would generate tetracycle **6** and a new radical anion, which would lose phenylselenolate anion to give radical **A** to propagate the chain. Phenylselenol thus formed could reduce radical **A**, thereby accounting for the formation of aldehyde **5**. However, under conditions of Table 1, entry 5, this oxidative step can also occur by a simple hydrogen abstraction,[16] for instance, by peroxy radical *n*-$Bu_3SnOO^{\cdot}$ coming from reaction of tin radicals with oxygen, which was not rigorously excluded from the reaction mixture.

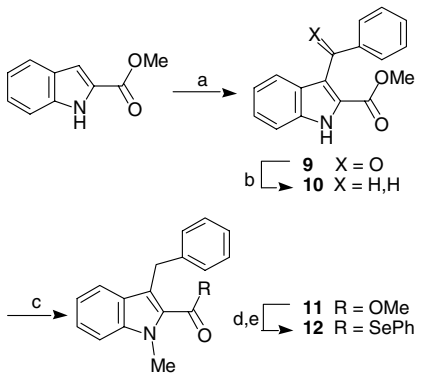


Scheme 2. Proposed mechanism for the *n*-Bu_6Sn_2-mediated cyclisation of selenoester **2a**.

The cyclisation method that had allowed the efficient preparation of isoquinolinoindole **6** was next extended to selenoesters **2b** and **4**, having a different tether between the phenyl ring and the radical centre (Scheme 3). However, all attempts to create a seven-membered or a strained benzo fused five-membered ring met with failure. Thus, when **2b** or **4** were treated with 2.2 mol of *n*-Bu_6Sn_2 under sun lamp irradiation tributyltin esters **7**[20] (80%) or **8** (40%) were isolated as the only reaction products. These compounds probably are formed by



Scheme 3.



Scheme 4. Reagents and conditions: (a) benzoic acid, trifluoroacetic anhydride, H_3PO_4, CH_3CN, rt, 70%; (b) Et_3SiH, TFA, rt, 93%; (c) MeI, NaH, THF, 0 °C to rt, 90%; (d) 2 N KOH, reflux, then, 2 N HCl; (e) Et_3N, then PhSeCl, PBu_3, THF, rt, 95%.

reaction of the starting selenoesters with *n*-Bu_6Sn_2, followed by oxidation of resulting 2-indolylacyltin with molecular oxygen.[21]

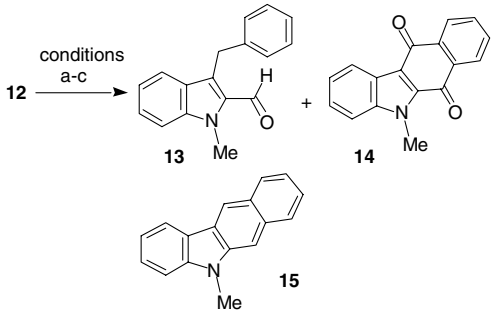
Attention was next turned to cyclisations leading to 2,3-fused ring indole derivatives. For this purpose, selenoester **12**, which incorporates a benzyl group at the 3-position of the indole ring, was prepared from methyl indole 2-carboxylate as depicted in Scheme 4. Friedel–Crafts acylation with benzoic acid[22] followed by reduction of the resulting 2,3-diacylindole **9** with triethylsilane gave ester **10**, which, after *N*-methylation, was converted into **12** following the same procedure previously used for selenoesters **2** and **4**.

We examined the behaviour of **12** in both reductive and non reductive conditions (Table 2). In contrast to the above 1-benzyl series, the desired cyclisation did take place when *n*-Bu_3SnH was used as the radical mediator to give tetracycle **14**[23] in 40% yield along with significant amounts of aldehyde **13** (50% yield, entry 1). These results clearly indicated that intramolecular reaction of the 2-indolylacyl radical **D** (Scheme 5) to give the cyclohexadienyl radical **E** is now more favoured, although reduction to **13** is still a competing pathway. Considering the recent mechanistic findings on the *n*-Bu_3SnH-mediated homolytic aromatic substitutions,[2] the initiator AIBN, which is present in stoichiometric amounts, is probably responsible for the regeneration of the aromaticity of the phenyl ring. Nevertheless, the initially formed tetracycle **F** was not observed since an additional oxidation at the benzylic position spontaneously occurred to give **14**.

Under nonreductive conditions the cyclisation course of selenoester **12** was similar to that of **2a**. As can be observed in Table 2, entry 2, exposure of **12** to a substoichiometric amount of *n*-Bu_6Sn_2 resulted in incomplete conversion to give the overoxidised tetracycle **14** in a modest 30% yield and minor amounts of two reduction products: aldehyde **13** (14% yield) and tetracycle **15**[24] (5%). Satisfactorily, the yield of **14** increased to 50% when 2.2 mol of the radical mediator were used (entry 3), neither the starting product **12** nor aldehyde **13** being observed.[25] Significantly, tetracycle **15** was again formed in 10% yield. From the mechanistic point of view, regeneration of the aromaticity from the cyclised cyclohexadienyl radical **E** can be described as in the 1-benzyl series, by hydrogen abstraction or via a $S_{RN}1$ type chain reaction to initially produce tetracycle **F**, which would now undergo an additional oxidation to give tetracycle **14** (Scheme 6). However, in this series reduction of radical **E** (or **G**), probably by phenylselenol[14] produced from the chain reaction (see Scheme 2), partially competes with the oxidative step to give **15** after dehydration.

In summary, the intramolecular homolytic acylation of benzene rings has been studied from several indolyl selenoesters. This reaction efficiently occurs from selenoesters **2a** and **12** under nonreductive conditions (*n*-Bu_6Sn_2, 300 W) to give tetracyclic phenyl indolyl

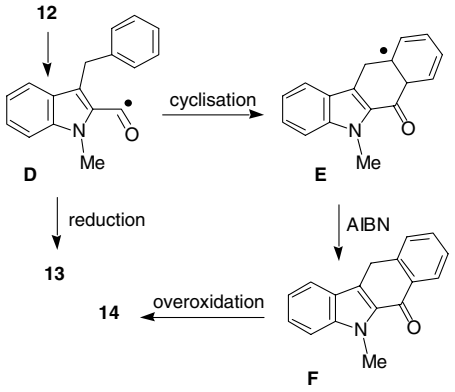
Table 2. Radical cyclisation of selenoester **12**



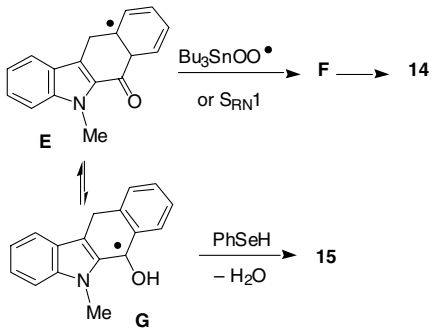
Entry	Radical mediator	Conditions[a]	Products (yields, %)[b]
1	*n*-Bu_3SnH	a	**13** (50), **14** (40),
2	*n*-Bu_6Sn_2	b	**12** (25), **13** (14), **14** (30), **15** (5)
3	*n*-Bu_6Sn_2	c	**14** (50), **15** (10)

[a] Conditions a: *n*-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN–hexane, 0.06 M, reflux, 4 h, syringe pump; b: *n*-Bu_6Sn_2 (0.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h; c: *n*-Bu_6Sn_2 (2.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h.

[b] Isolated yields.



Scheme 5. Probable mechanism for the *n*-Bu_3SnH–AIBN mediated cyclisation of **12**.



Scheme 6. Proposed mechanism for the formation of tetracycles **14** and **15** under *n*-Bu_6Sn_2–hν conditions.

ketones **6** and **14**, which deserve interest due to their potential pharmacological activities.[26] Further extension of this reaction to heterocyclic systems is currently underway in our laboratory.

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología', Spain, and the 'Fondo Europeo de Desarrollo Regional' (FEDER) through project BQU2003-04967-C02-02 is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084. F.F. thanks the University of Barcelona for a grant.

References and notes

1. Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62–80.
2. For a recent discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95–98, and references cited therein.
3. For recent leading references, see: (a) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209–4211; (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731–733; (c) Harrowven, D. C.; L'Helias, N.; Moseley, J. D.; Blumire, N. J.; Flanagan, S. R. *Chem. Commun.* **2003**, 2658–2659.
4. For instance, see: (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489–519; (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077–4088; (c) Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron* **2001**, *57*, 4447–4454; (d) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett.* **2001**, *42*, 9061–9064.
5. Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387–3400.
6. (a) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111–8128; (b) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453–1464; (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, 4191–4193.
7. For instance, see: (a) Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55–64; (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456–2466; (c) Wang, S.-F.; Chuang, C.-P. *Tetrahedron Lett.* **1997**, *38*, 7597–7598; (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639–2643; (e) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465–473; See also: (f) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209–210.
8. For the isolation of dihydro derivatives of indole, see: (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479–3486; (b) Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805–806; (c) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795–1798.
9. For reviews on acyl radical chemistry, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194; (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2069.
10. Upon arenes: (a) Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett.* **2000**, *41*, 9667–9671, and references cited therein; Upon pyridines: (b) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866–2869; Upon indoles and pyrroles: (c) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153–7157; (d) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887–7890; Upon pyridines: (e) Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372–1374.
11. (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697–1700; (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268–6271; (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759–762.
12. Batty, D.; Crich, D. *Synthesis* **1990**, 273–275.
13. Olgen, S.; Akaho, E.; Nebioglu, D. *Eur. J. Med. Chem.* **2001**, *36*, 747–770.
14. Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765–2770.
15. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.
16. (a) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67–83; (b) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181–10184; (c) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765–768; (d) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547–7551.
17. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.46 (s, 2H), 7.23 (m, 1H), 7.40–7.55 (m, 4H), 7.51 (s, 1H), 7.66 (ddd, $J = 1.6$, 7.6, 7.8 Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 8.38 (dd, $J = 1.6$, 7.8 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 44.4 (CH_2), 105.9 (CH), 110.1 (CH), 121.5 (CH), 123.4 (CH), 125.6 (CH), 126.3 (CH), 127.2 (C), 127.3 (CH), 128.0 (CH), 130.6 (C), 132.6 (C), 133.2 (CH), 136.3 (C), 137.4 (C), 177.3 (CO); HRMS calcd for $C_{16}H_{11}NO$ 233.0841, found 233.0834.
18. An electrophilic substitution mechanism can be excluded as no cyclisation was observed after heating **2a** under 300 W sunlamp irradiation without *n*-Bu_6Sn_2.
19. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128, See also Ref. 6a.
20. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 9H), 1.39 (m, 12H), 1.68 (m, 6H), 3.05 (t, $J = 7.8$ Hz, 2H), 4.81 (t, $J = 7.8$ Hz, 2H), 7.13 (m, 1H), 7.35–7.55 (m, 8H), 7.65 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.7 (CH_3), 16.8 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 37.1 (CH_2), 46.1 (CH_2), 110.2 (CH), 110.6 (CH), 120.1 (CH), 122.3 (CH), 124.2 (CH), 126.1 (C), 126.3 (CH), 128.4 (CH), 128.8 (CH), 129.4 (C), 138.6 (C), 139.2 (C), 166.2 (CO); CI-MS m/z 556 (MH^+).
21. Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3462–3464.

22. Murakami, Y.; Tani, M.; Suzuki, M.; Sudoh, K.; Uesato, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4707–4715.
23. Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J. *Tetrahedron* **1994**, *50*, 4811–4828.
24. Markgraf, J.-H.; Patterson, D.-E. *J. Heterocycl. Chem.* **1986**, *33*, 109–111.
25. However, no cyclisation was observed when a selenoester related to **12**, having a 3-benzoyl instead of a 3-benzyl substituent, was subjected to the experimental conditions of Table 2, entry 3.
26. For instance, see: Fernández, M.; Barcia, C.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Synlett* **2004**, 267–270, and references cited therein.

JOC*Note*

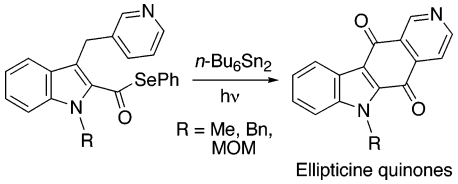
Regioselective Intramolecular Reactions of 2-Indolylacyl Radicals with Pyridines: A Direct Synthetic Entry to Ellipticine Quinones

M.-Lluïsa Bennasar,* Tomàs Roca, and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@ub.edu

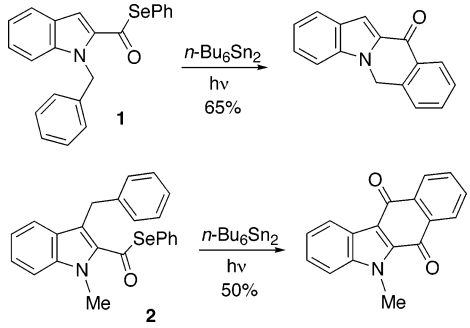
Received July 19, 2005



2-Indolylacyl radicals generated from the corresponding selenoesters under hexabutylditin−*hν* conditions undergo regioselective intramolecular reaction with unprotonated pyridines to give polycyclic indolylpyridyl ketones. For substrates bearing a (3-pyridyl)methyl moiety connected to the 3-position of the indole ring, the cyclization provides easy access to ellipticine quinones.

Intramolecular reactions of nucleophilic carbon-centered radicals with aromatic systems are often of synthetic value for the construction of polycyclic compounds incorporating aromatic rings.[1] Fully aromatic products are generally obtained after the oxidation of the initially formed cyclohexadienyl radical,[2] which takes place even under the most commonly used tributyltin hydride−AIBN *reductive* conditions.[3] In this context, cyclizations of aryl and alkyl radicals upon heteroaromatic substrates such as azoles,[4] indoles,[5,6] pyridines,[7] or quinolines[7a] have become increasingly important for the synthesis of otherwise quite inaccessible substituted heterocycles. However, similar processes involving acyl radicals, which have a high synthetic potential due to their intrinsic functionalization,[8] have scarcely been investigated.[9]

SCHEME 1



In the past few years, we have been studying the generation of 2- and 3-indolylacyl radicals from the corresponding phenyl selenoesters and their reactions with alkene acceptors under reductive conditions.[10] Our interest in this area led us to envisage intramolecular reactions of these radical intermediates with aromatic rings as a general approach to polycyclic aryl indolyl ketones, which are common substructures of many natural and medicinal compounds.[11] Thus, we have recently reported how 2-indolylacyl radicals, such as those derived from selenoesters **1** and **2** (Scheme 1), undergo cyclization upon phenyl rings under nonreductive (hexabutylditin, *hν*) conditions.[12] We believed that the extension of the above reactions to analogous pyridine substrates would be of interest, complementing the classical protocol of Minisci for the homolytic acylation of protonated pyridines under oxidative conditions,[13] mainly developed in its intermolecular version.[14] We herein report our work on this subject presenting as the

* Tel: 34 934 024 540. Fax: 34 934 024 539.

(1) Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 62−80.

(2) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765−2770.

(3) For a recent discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed*. **2004**, *43*, 95−98 and references therein.

(4) (a) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111−8128. (b) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453−1464. (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2002**, *43*, 4191−4193. (d) Gagosz, F.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 4345−4348. (e) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689−2696. See also: (f) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (g) Crich, D.; Patel, M. *Org. Lett*. **2005**, *7*, 3625−3628.

(5) For instance, see: (a) Kraus, G. A.; Kim, H. *Synth. Commun*. **1993**, *23*, 55−64. (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem*. **1994**, *59*, 2456−2466. (c) Wang, S.-F.; Chuang, C.-P. *Tetrahedron Lett*. **1997**, *38*, 7597−7598. (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639−2643. (e) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465−473. (f) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem*. **2004**, *69*, 4001−4004.

(6) For the isolation of dihydro derivatives of indole, see: (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem*. **1991**, *56*, 3479−3486. (b) Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805−806. (c) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett*. **2003**, *44*, 1795−1798.

(7) (a) Harrowven, D. C.; Sutton, B. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2004; Vol. 16, pp 27−53. For more recent work, see: (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett*. **2004**, *6*, 3671−3674. (c) Crich, D.; Patel, M. *Heterocycles* **2004**, *64*, 499−504. (d) Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217−6224.

(8) For reviews on acyl radicals, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev*. **1996**, *96*, 177−194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991−2069.

(9) For cyclization of acyl radicals upon indoles, see: (a) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett*. **1999**, *40*, 7153−7157. Upon pyrroles, see: (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2001**, *42*, 7887−7890.

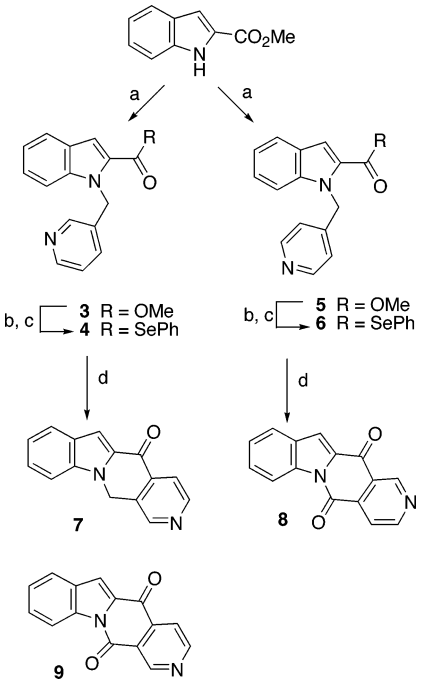
(10) (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett*. **2001**, *3*, 1697−1700. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 6268−6271. (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett*. **2004**, *6*, 759−762.

(11) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996; pp 105−134.

(12) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron Lett*. **2004**, *45*, 5605−5609.

10.1021/jo0514974 CCC: $30.25
Published on Web 10/04/2005

SCHEME 2[a]



[a] Reagents and conditions: (a) NaH, THF, 3- or 4-(chloromethyl)pyridine, HCl, rt, overnight, 70% (**3**), 65% (**5**); (b) 2 N KOH, MeOH-dioxane, reflux, 2 h, then 2 N HCl; (c) Et_3N, then PhSeCl, PBu_3, THF, rt, overnight, 82% (**4**), 83% (**6**); (d) *n*-Bu_6Sn_2, 300 W, C_6H_6, reflux, 24 h, 35% (**7**), 15% (**8**).

most significant result a straightforward synthetic entry to ellipticine quinones, which have an intrinsic interest as antitumor agents,[15] and are important intermediates in the synthesis of ellipticines.[16]

Selenoesters **4** and **6**, bearing 3- or 4-pyridylmethyl moieties connected to the indole nitrogen, were selected as substrates to study 2-indolylacyl radical cyclizations leading to indolo[1,2-*b*]naphthyridinones (Scheme 2), which constitute advanced intermediates in the earliest Gribble syntheses of ellipticine and analogues.[17,18] As expected, these radical precursors were easily accessible by N-alkylation of methyl indole-2-carboxylate with the appropriate (chloromethyl)pyridine, followed by hydrolysis of the resulting methyl esters **3** and **5**, and subsequent phenylselenation.

In analogy to our previous results for selenoester **1**,[12] we observed only premature reduction of the intermediate acyl radical to aldehyde **10** (Figure 1) when selenoesters **4** and **6** were submitted to standard reductive (*n*-Bu_3SnH o $(SiMe_3)_3SiH$−AIBN) conditions. However, the desired cyclization did take place upon treatment with *n*-Bu_6Sn_2 (2 mol, 300 W sun lamp), although the yields were lower than in the phenyl series. For selenoester **4**, the acylation took place exclusively at the 4-position of the pyridine ring to give tetracycle **7**, a deoxoderivative of the known ellipticine precursor **9**,[17] in 35% yield. No trace of the regioisomeric product coming from the alternative radical attack at the 2-position was detected. This regiochemical outcome is noteworthy, being in clear contrast with that observed in related reactions involving aryl radicals, which usually provide regioisomeric mixtures.[7] On the other hand, the 2-indolylacyl radical derived from selenoester **6** reacted at the 3-position of the pyridine ring in a less efficient way, ultimately leading to the overoxidized keto lactam **8**, a synthetic precursor of isoellipticine,[18] in 15% yield. In both cases, significant amounts (20−30%) of tin esters **11** (Figure 1) were also obtained.

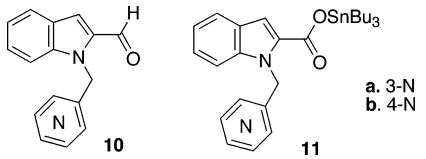
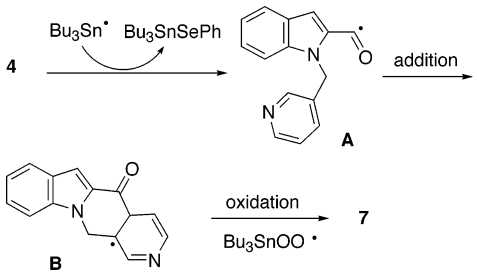


FIGURE 1. Other reaction products.

SCHEME 3



The cyclization process can be understood by studying the radical reactions depicted in Scheme 3 for selenoester **4**. After cleavage of *n*-Bu_6Sn_2 under the influence of heat and/or light, the resulting tributyltin radical generates the 2-indolylacyl radical **A**, which reacts at the 4-position of the pyridine ring to give the azacyclohexadienyl radical **B**. Subsequent oxidation would lead to **7**, probably by a simple hydrogen abstraction[19] by the peroxy radical *n*-$Bu_3SnOO^{\bullet}$ coming from the reaction of tin radicals with oxygen, which was not rigorously excluded from the reaction mixture. A similar addition−rearomatization mechanism followed by an additional oxidation at the interannular methylene group could account for the formation of keto lactam **8** from selenoester **6** (not shown).

The relative inefficiency of the above cyclizations with respect to the phenyl series (Scheme 1) was somewhat

(13) (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489−519. (b) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866−2869. (c) Minisci, F.; Recupero, F.; Ceccheto, A.; Punta, C.; Gambarotti, C.; Fontana, F.; Pedulli, G. F. *J. Heterocycl. Chem.* **2003**, *40*, 325−328. See also: (d) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937−1940.

(14) For an isolated example of the intramolecular version, see: Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372−1374.

(15) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958−4963.

(16) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427 and references therein.

(17) (a) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2810−2812. (b) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891−5899.

(18) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690−2695.

(19) For discussions, see: (a) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem.—Eur. J.* **1998**, *4*, 67−83. (b) Wang, C.; Russell, G. A.; Trahanovsky, W. S. *J. Org. Chem.* **1998**, *63*, 9956−9959. (c) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181−10184. (d) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765−768.

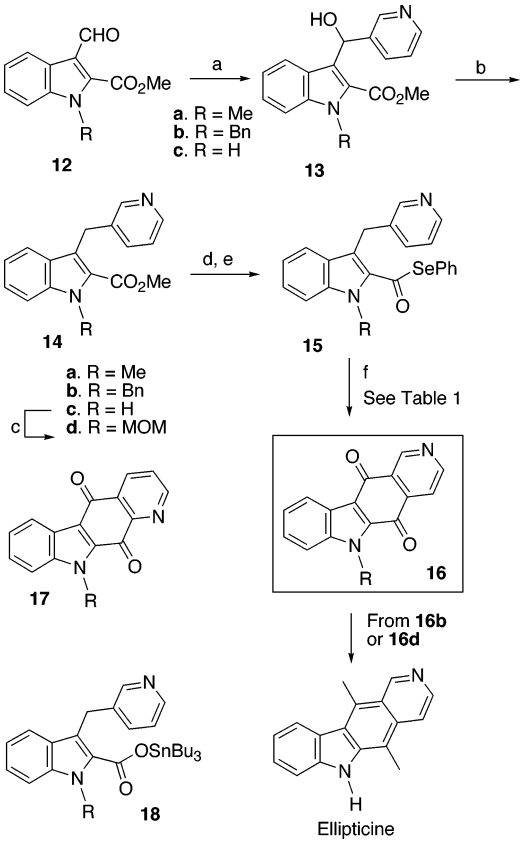
unexpected, as unprotonated pyridines have been reported to exhibit reactivity profiles toward most nucleophilic carbon-centered radicals that are similar to benzene derivatives.[13a] Nevertheless, these differences can be attributed to the presence of pendant electron-withdrawing 3- or, in particular, 4-pyridylmethyl moieties at the indole nitrogen, which would diminish the reactivity of the intermediate acyl radical. This would lead to a buildup of radical concentration, allowing undesired secondary reactions such as conversion into tin ester **11** to take place.[20]

We next turned to radical precursors in which the 3-pyridylmethyl moiety was attached at the indole 3-position. In this series, the hope was that the reaction would follow the same regiochemical course as described above for selenoester **4**, giving access to the pyrido[4,3-*b*]-carbazole skeleton characteristic of the indole alkaloid ellipticine. Considering that the substituent installed at the indole nitrogen could modulate the reactivity of the intermediate acyl radical and, consequently, determine the efficiency of the process, we decided to study the cyclization from a variety of N-substituted selenoesters **15a**−**d** (Scheme 4, Table 1).

Their preparation was a bit more laborious than in the above series, and required the use of 2,3-disubstituted indoles **12** as the starting products. Thus, reaction of **12a**−**c** with 3-pyridylmagnesium bromide, followed by triethylsilane reduction of the resulting carbinols **13a**−**c**, provided methyl esters **14a**−**c** in acceptable yields. *N*-(Methoxymethyl) ester **14d** was prepared by N-alkylation of the unsubstituted derivative **14c**, as triethylsilane reduction of carbinol **13** (R = MOM) resulted in the concomitant reduction of the N-substituent to give the *N*-methyl derivative **14a**. Subsequent hydrolysis of **14a**−**d**, followed by phenylselenation of the respective carboxylic acids, gave the target selenoesters **15a**−**d**.

To our delight, 2-indolylacyl radicals derived from *N*-methyl selenoesters **15a** and **15b** (entries 1 and 2) efficiently underwent regioselective cyclization upon the 4-position of the pyridine ring and, after the in situ oxidation at the interannular methylene group, gave the known ellipticine quinones **16a**[21] and **16b**[21,22] in 60 and 42% yield, respectively. Only minor amounts of regioisomers **17a** (5%) and **17b** (8%) were formed. However, the acyl radical derived from **15d** (entry 4) displayed diminished reactivity compared to that of those derived from **15a** and **15b**, probably due to the presence of the methoxymethyl group, which acts as an electron-withdrawing moiety. Thus, quinone **16d**[21] was isolated in a poor 10% yield along with trace amounts of the C-2 regioisomer **17d**. Attempts to improve this result using dicumyl peroxide[5f] were unsuccessful, as they led to the recovery of the starting selenoester.

SCHEME 4[a]



[a] Reagents and conditions: (a) 3-pyridylmagnesium bromide, −40°C to room temperature, 12 h; (b) Et_3SiH, TFA, rt, 7 h, **14a** (60%), **14b** (55%), **14c** (50%); (c) NaH, THF, MOMCl, 0 °C to room temperature, 12 h, 85%; (d) LiOH, 3:1 THF/H_2O, 65 °C, 5 h; (e) Et_3N, then PhSeCl, PBu_3, THF, rt, overnight, **15a** (80%), **15b** (76%), **15c** (70%), **15d** (80%); (f) *n*-Bu_6Sn_2, 300 W, C_6H_6, reflux, 24 h, see Table 1.

TABLE 1. *n*-Bu_6Sn_2-Mediated Radical Cyclization of Selenoesters 15

entry	selenoester	ellipticine quinone (yield, %)[a]	other products (yield, %)[a]
1	**15a**	**16a** (60)	**17a** (5), **18a** (10)
2	**15b**	**16b** (42)	**17b** (8)[b]
3	**15c**		**18c** (85)
4	**15d**	**16d** (10)	**17d** (2), **18d**[c]

[a] Isolated yields. [b] Minor amounts of the product coming from cyclization upon the benzene ring were also detected. [c] Not isolated. Major product in the reaction mixture (6:1 with respect to **16d** + **17d**).

Quite unexpectedly, cyclization did not occur for the unsubstituted selenoester **15c** (entry 3), indicating that the radical reaction was somehow inhibited by the presence of the indole NH group.[23] In the last two cases, it is somewhat significant that the undesired formation of tin esters **18c**,**d**, a minor process in the productive series, was the predominant pathway.[20]

As expected, ellipticine quinones **16a**, **16b**, and **16d** showed physical and spectroscopic data identical to those

(20) Formation of tin esters **11** and **18** can be explained by the reaction of the corresponding selenoesters with hexabutylditin oxide, which would be formed in the reaction mixture on exposure of hexabutylditin to light. Alternatively, they can be formed by reaction of the selenoesters with hexabutylditin, followed by oxidation of the resulting 2-indolylacyltin: Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3462−3464.

(21) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457−1460.

(22) Miki, Y.; Tada, Y.; Matsushita, K. *Heterocycles* **1998**, *48*, 1593−1597.

(23) For the radical inhibitory properties of diphenylamine and other aromatic amines, see: MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem*. **1996**, *61*, 1316−1321.

previously described.[15,21,22] Because both **16b**[21,22,24] and **16d**[21] were transformed into ellipticine, the synthesis reported here constitutes a formal synthesis of this natural product.

In conclusion, we have shown that the cyclization of 2-indolylacyl radicals upon pyridines under *n*-Bu_6Sn_2–*hν* conditions takes place with notable regioselectivity to give tetracyclic indolyl 4-pyridyl ketones. The effectiveness of this radical protocol is illustrated by a fast synthetic entry to ellipticine quinones.

Experimental Section

General Procedure for the Radical Cyclization of Phenyl Selenoesters 4, 6, and 15. A solution of the appropriate selenoester (0.50 mmol) and *n*-Bu_6Sn_2 (0.51 mL, 1 mmol) in C_6H_6 (30 mL) was refluxed under Ar under sun lamp irradiation (300 W) for 24 h. The solution was concentrated under reduced pressure. The resulting residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes (3 × 15 mL). The solvent was removed, and the crude product was purified by flash chromatography (SiO_2). For **15b**, the crude product was treated with a 0.5 M solution of KOH in MeOH (10 mL) at room temperature for 2 h before the chromatography. Yields, methods of purification, and NMR data are given below.

12*H*-Indolo[1,2-*b*][2,7]naphthyridin-5-one (**7**): 35% yield; elution with 99:1 CH_2Cl_2/MeOH; mp 190−192 °C; ^{1}H NMR (500 MHz) δ 5.45 (s, 2H), 7.22 (ddd, J = 1.5, 7, 8.5 Hz, 1H), 7.46 (m, 2H), 7.52 (s, 1H), 7.77 (dt, J = 1, 1, 7 Hz, 1H), 8.08 (d, J = 5 Hz, 1H), 8.79 (d, J = 5 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 42.2 (CH_2), 107.3 (CH), 110.2 (CH), 119.3 (CH), 122.0 (CH), 123.7 (CH), 126.5 (CH), 127.2 (C), 129.9 (C), 132.0 (C), 136.2 (C), 137.7 (C), 148.8 (CH), 149.6 (CH), 175.9 (C); HRMS calcd for $C_{15}H_{10}N_2O$ 234.0793, found 234.0798.

Indolo[1,2-*b*][2,6]naphthyridin-5,12-dione (**8**):[17] 15% yield; elution with 99:1 CH_2Cl_2/MeOH; ^{1}H NMR (200 MHz) δ 7.43 (t, J = 8 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 8.25 (d, J = 5.2 Hz, 1H), 8.62 (d, J = 8.4 Hz, 1H), 9.13 (d, J = 5 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 117.2 (CH), 117.4 (CH), 121.3 (CH), 124.1 (CH), 125.9 (CH), 126.5 (C), 128.6 (C), 130.4 (CH), 133.1 (C), 137.1 (C), 137.4 (C), 149.3 (CH), 155.5 (CH), 157.7 (C), 174.7 (C); HRMS calcd for $C_{15}H_8N_2O_2$ 248.0586, found 248.0596.

(24) Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1319−1329.

6-Methyl-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16a**):[21] 60% yield; elution with 5:5 hexanes/AcOEt; mp 240−242 °C (lit.[21] 245 °C); ^{1}H NMR (500 MHz, assignment aided by HSQC and HMBC) δ 4.29 (s, 3H, NMe), 7.46 (ddd, J = 1, 6.5, 8 Hz, 1H, 9-H), 7.51 (d, J = 8.5 Hz, 1H, 7-H), 7.55 (ddd, J = 1, 6.5, 8 Hz, 1H, 8-H), 7.98 (d, J = 5 Hz, 1H, 4-H), 8.49 (d, J = 8.5 Hz, 1H, 10-H), 9.05 (d, J = 5 Hz, 1H, 3-H), 9.47 (s, 1H, 1-H); ^{13}C NMR (100.6 MHz, assignment aided by HSQC and HMBC) δ 32.2 (NMe), 111.1 (C-7), 118.7 (C-4), 119.4 (C-10b), 123.8 (C-10a), 124.3 (C-10), 125.3 (C-9), 126.6 (C-11a), 128.3 (C-8), 134.6 (C-5a), 139.2 (C-4a), 140.5 (C-6a), 148.5 (C-1), 155.1 (C-3), 178.3 (C-5), 180.7 (C-11).

6-Benzyl-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16b**):[21,22] 42% yield; elution with 7:3 hexanes/AcOEt; mp 256−258 °C (lit.[21] 268 °C); ^{1}H NMR (300 MHz) δ 6.00 (s, 2H), 7.18 (dd, J = 1.8, 8.1 Hz, 2H), 7.29 (m, 3H), 7.42−7.52 (m, 3H), 7.94 (dd, J = 0.6, 5.1 Hz, 1H), 8.52 (br d, J = 7.8 Hz, 1H), 9.03 (d, J = 5.1 Hz, 1H), 9.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 47.8 (CH_2), 112.6 (CH), 118.2 (C), 118.6 (CH), 122.8 (CH), 123.0 (C), 125.1 (CH), 126.1 (C), 126.8 (CH), 127.6 (CH), 128.0 (CH), 128.7 (CH), 134.5 (C), 136.7 (C), 139.0 (C), 139.5 (C), 147.2 (CH), 155.2 (CH), 177.4 (C), 180.3 (C). Anal. Calcd for $C_{22}H_{14}N_2O_2 \cdot 3/2H_2O$: C, 72.42; H, 4.69; N, 7.67. Found: C, 72.15; H, 4.33; N, 7.39.

6-(Methoxymethyl)-6*H*-pyrido[4,3-*b*]carbazole-5,11-dione (**16d**):[15,21] 10% yield; elution with 6:4 hexanes/AcOEt; mp 190−193 °C (lit.[21] 196−197 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.40 (s, 3H), 6.16 (s, 2H), 7.25−7.60 (m, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 4.8 Hz, 1H), 8.50 (d, J = 8 Hz, 1H), 9.07 (d, J = 5.2 Hz, 1H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 56.6 (CH_3), 75.4 (CH_2), 112.0 (CH), 118.6 (CH), 120.3 (C), 123.8 (C), 124.1 (CH), 125.4 (CH), 126.0 (C), 128.7 (CH), 134.5 (C), 139.0 (C), 140.2 (C), 148.4 (CH), 155.1 (CH), 177.8 (C), 181.0 (C).

Acknowledgment. Financial support from the Ministerio de Ciencia y Tecnología (MCYT-FEDER, Spain) through Project BQU2003-04967-C-02-02 is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084. F.F. thanks the University of Barcelona for a grant.

Supporting Information Available: General experimental protocols and detailed experimental procedures for the preparation of all synthetic intermediates. Characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0514974

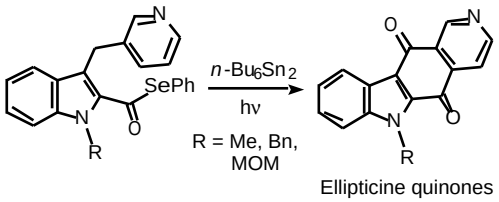
Supporting Information

Regioselective Intramolecular Reactions of 2-Indolylacyl Radicals with Pyridines: a Direct Synthetic Entry to Ellipticine Quinones

M.-Lluïsa Bennasar, Tomàs Roca, and Francesc Ferrando*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@ub.edu



Total pages: 21

Contents:

A. EXPERIMENTAL PROCEDURES

General.
Reactions courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} 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 rotatory 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.

Methyl Esters 3 and 5.
A solution of methyl 1*H*-2-indolecarboxylate (1.5 g, 8.57 mmol) in anhydrous DMF (20 mL) was added dropwise under Ar to a suspension of NaH (22.3 mmol) in anhydrous THF (10 mL). After stirring at rt for 1h, the mixture was cooled to 0°C, 3- or 4-(chloromethyl)pyridine hydrochloride (1.74 g, 10.3 mmol) was added dropwise and the mixture was allowed to warm to rt overnight. The reaction mixture was quenched with cold H_2O and extracted with CH_2Cl_2 (3x40 mL). The organic extracts were washed with H_2O (5x100 mL), dried and concentrated, and the resulting residue was chromatographed. Yields, eluents, and NMR data are given below.
Methyl 1-(3-Pyridylmethyl)-2-indolecarboxylate (3): 70%; 5:5 hexanes-AcOEt; mp 94-96°C; ^1H NMR (200 MHz) δ 3.88 (s, 3H), 5.86 (s, 2H), 7.10-7.20 (m, 2H), 7.20-7.35 (m, 3H), 7.40 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 8.48 (m, 2H); ^{13}C NMR (50.3 MHz) δ 45.6 (CH_2), 51.8 (CH_3), 110.4 (CH), 111.5 (CH), 121.1 (CH), 122.9 (CH), 123.5 (CH), 125.6 (CH), 126.1 (C), 127.0 (C), 133.7 (C), 134.1 (CH), 139.2 (C), 148.2 (CH), 148.7 (CH), 162.3 (C). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.24; H, 5.35; N, 10.59.
Methyl 1-(4-Pyridylmethyl)-2-indolecarboxylate (5): 65%; 5:5 hexanes-AcOEt; mp 76-78°C; ^1H NMR (200 MHz) δ 3.86 (s, 3H), 5.84 (s, 2H), 6.91 (d, *J* = 6.4 Hz, 2H), 7.20 (ddd, *J* = 1.6, 6.6, 8.2 Hz, 1H), 7.42 (d, *J* = 0.6 Hz, 1H), 7.28-7.35 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H), 8.48 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$-CD_3OD, 50.3 MHz) δ 46.7 (CH_2), 51.6 (CH_3), 110.0 (CH), 111.5 (CH), 121.1 (CH), 121.4 (CH), 122.7 (CH), 125.7 (CH), 125.9 (C), 126.8 (C), 139.1 (C), 148.3 (C), 149.0 (CH), 162.2 (C). Anal. Calcd for $C_{16}H_{14}N_2O_2$.HCl: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.26; H, 5.05; N, 9.12.

Selenoesters 4 and 6.
A solution of methyl esters **3** or **5** (0.53 g, 2 mmol) in a 1:1:1 mixture of 2N aqueous KOH/MeOH/dioxane (30 mL) was refluxed for 2 h. The reaction mixture was concentrated and acidified with aqueous 2N HCl until pH=5. The precipitated carboxylic acid hydrochloride was collected by filtration.
A suspension of the above carboxylic acid (1 mmol) in anhydrous CH_2Cl_2 (8 mL) was treated with Et_3N (0.29 mL, 2 mmol). After stirring at rt for 15 min, the mixture was concentrated to give the corresponding triethylammonium salt.
In another flask, tributylphosphine (0.66 mL, 2.60 mmol) was added under Ar to a solution of PhSeCl (0.5 g, 2.60 mmol) in anhydrous THF (15 mL), and the mixture was stirred at rt for 10 min (yellow solution). The above triethylammonium salt in THF (15 mL) was added to this solution and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O (40 mL) and H_2O (40 mL) and extracted with Et_2O (3x25 mL). The solvent was removed and the crude product was purified by flash chromatography. Yields, eluents, and NMR data are given below.
***Se*-Phenyl 1-(3-Pyridylmethyl)-2-indolecarboselenoate (4):** 82%; hexanes and 98:2 CH_2Cl_2-MeOH; mp 94-96°C; ^1H NMR (200 MHz) δ 5.60 (s, 2H), 7.02 (dd, *J* = 4.8, 8 Hz, 1H), 7.12-7.28 (m, 4H), 7.35 (m, 3H), 7.55 (m, 2H), 7.62 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 8.39 (m, 2H); ^{13}C NMR (50.3 MHz) δ 45.9 (CH_2), 110.7 (CH), 113.0 (CH), 121.7 (CH), 123.3 (CH), 123.5 (CH), 125.7 (C), 126.3 (C), 126.9 (CH), 129.2 (CH), 129.4 (CH), 133.1 (C), 134.2 (CH), 134.4 (C), 136.4 (CH), 139.6 (C), 148.2 (CH), 148.8 (CH), 184.8 (C). Anal. Calcd for $C_{21}H_{16}N_2OSe$: C, 64.45; H, 4,12; N, 7,16. Found: C, 64.45; H, 4.04; N, 7.02.

***Se*-Phenyl 1-(4-Pyridinylmethyl)-2-indolecarboselenoate (6):** 83%; elution with hexanes and 99:1 CH_2Cl_2-MeOH; mp 100-102°C; ^{1}H NMR (200 MHz) δ 5.70 (s, 2H), 6.86 (d, *J* = 5.6 Hz, 2H), 7.24 (m, 2H), 7.40 (m, 4H), 7.56 (m, 2H), 7.70 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (50.3 MHz) δ 47.3 (CH_2), 110.6 (CH), 113.0 (CH), 121.1 (CH), 121.8 (CH), 123.2 (CH), 125.5 (C), 126.2 (C), 126.8 (CH), 129.2 (CH), 129.4 (CH), 134.5 (C), 136.3 (CH), 139.7 (C), 146.6 (C), 149.9 (CH), 184.9 (C). Anal. Calcd for $C_{21}H_{16}N_2OSe$: C, 64.45; H, 4,12; N, 7,16. Found: C, 64.44; H, 4.30; N, 7.05.

Methyl 3-Formyl-2-indolecarboxylate (12c).[1]
$POCl_3$ (0.55 mL, 6 mmol) was added dropwise to cooled (ice-bath) DMF (1.62 mL, 21 mmol). A solution of methyl 1*H*-2-indolecarboxylate (1 g, 5.71 mmol) in DMF (2 mL) was added and the resulting mixture was stirred at rt for 30 min and at 60°C for 4 h. The reaction mixture was poured into ice (20 mL) and neutralized with 2 M aqueous NaOH. The yellow precipitate was collected by filtration to give **12c**: 1.04 g (90%); mp 199-201ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.98 (s, 3H), 7.29 (m, 1H), 7.39 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 10.59 (s, 1H), 12.85 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 52.9 (CH_3), 113.3 (CH), 118.6 (C), 122.5 (CH), 123.6 (CH), 124.8 (C), 126.0 (CH), 132.5 (C), 135.9 (C), 160.7 (C), 187.6 (CH); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 52.9 (CH_3), 113.3 (CH), 118.6 (C), 122.5 (CH), 123.6 (CH), 124.8 (C), 126.0 (CH), 132.5 (C), 135.9 (C), 160.7 (C), 187.6 (CH).

Methyl 3-Formyl-1-methyl-2-indolecarboxylate (12a).[1]
A solution of **12c** (2.03 g, 10 mmol) in anhydrous THF (40 mL) was added dropwise under Ar to an ice-cooled suspension of NaH (11 mmol) in anhydrous THF (20 mL). After stirring at 0ºC for 1 h, iodomethane (2.81 mL, 45 mmol) was added dropwise and the mixture was allowed to warm to rt overnight. The mixture was concentrated under reduced pressure, the residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic extracts were dried and concentrated to give aldehyde **12a** as a pale yellow solid: 2.1 g (97%); mp 145-146°C (Lit[1]: 150-152°C); ^{1}H NMR (200 MHz) δ 3.89 (s, 3H), 3.92 (s, 3H), 7.25 (m, 3H), 8.37 (d, *J* = 7.2 Hz, 1H), 10.40 (s, 1H); ^{13}C NMR (50.3 MHz) δ 32.4 (CH_3), 52.6 (CH_3), 110.3 (CH), 119.7 (C), 123.6 (CH), 124.0 (CH), 124.3 (C), 126.1 (CH), 133.1 (C), 138.1 (C), 161.3 (C), 188.2 (CH).

Methyl 1-Benzyl-3-Formyl-2-indolecarboxylate (12b).
$POCl_3$ (0.55 mL, 6 mmol) was added dropwise to cooled (ice-bath) DMF (1.62 mL, 21 mmol). A solution of methyl 1-benzyl-2-indolecarboxylate (1.51 g, 5.71 mmol) in DMF (3 mL) was added and the mixture was stirred at rt for 30 min and at 60°C for 4 h. The reaction mixture was poured into ice (20 mL), neutralized with 2 M aqueous NaOH and extracted with CH_2Cl_2 (3x20 mL). The organic extracts were washed with H_2O (6x40 mL), dried and concentrated to give aldehyde **12b** as a pale yellow solid: 1.40 g (84%); mp 106-108°C; ^{1}H NMR (200 MHz) δ 3.98 (s, 3H), 5.83 (s, 2H), 7.05 (m, 2H), 7.25 (m, 3H), 7.40 (m, 3H) 8.55 (m, 1H), 10.60 (s, 1H); ^{13}C NMR (50.3 MHz) δ 48.6 (CH_2), 52.7 (CH_3), 110.9 (CH), 120.4 (C), 123.8 (CH), 124.2 (CH), 124.6 (C), 126.1 (CH), 126.5 (CH), 127.6 (CH), 128.7 (CH), 132.9 (C), 136.6 (C), 138.1 (C), 161.2 (C), 188.3 (CH). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4,78. Found: C, 73.88; H, 5.25; N, 4.70

Methyl Esters 14a-c.
i-PrMgCl (2 M in THF, 1.20 mmol for **12a,b**, 2.40 mmol for **12c**) was added at rt to a solution of 3-bromopyridine (1.10 mmol for **12a,b**, 2.20 mmol for **12c**) in dry THF (2 mL) and the resulting mixture was stirred at rt for 1 h. After the mixture was cooled to –40°C, a solution of aldehydes **12a-c** (1mmol) in dry THF (7 mL) was added, and the mixture was allowed to slowly warm to rt for 12 h. The reaction mixture was poured into H_2O (5 mL) and extracted with CH_2Cl_2 (3x10 mL). The organic extracts were concentrated to give crude carbinols **13a-c**.
Et_3SiH (0.54 mL, 3.30 mmol) was added to a cooled (0°C) solution of the above carbinols in TFA (3 mL). After stirring at rt for 7 h, the solution was concentrated to dryness. The residue

was dissolved in CH_2Cl_2 (15 mL) and the organic solution was washed with 2 M Na_2CO_3 (3x10 mL), dried and concentrated. The crude product was chromatographed. Yields, elution and NMR data are given below.

Methyl 1-Methyl-3-[(3-pyridyl)methyl]-2-indolecarboxylate (14a): 60%; elution with 4:6 hexanes-AcOEt; mp 82-84°C; ^{1}H NMR (200 MHz) δ 3.88 (s, 3H), 4.03 (s, 3H), 4.44 (s, 2H), 7.13 (m, 2H), 7.37 (m, 2H), 7.45 (m, 1H), 7.63 (d, *J* = 8 Hz, 1H), 8.38 (d, *J* = 4.8 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (50.3 MHz) δ 28.5 (CH_2), 32.3 (CH_3), 51.5 (CH_3), 110.3 (CH), 120.4 (CH), 120.6 (CH), 121.6 (C), 123.2 (CH), 125.1 (C), 125.5 (CH), 126.4 (C), 135.6 (CH), 136.7 (C), 138.7 (C), 147.1 (CH), 149.6 (CH), 162.7 (C). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.45; H, 5.69; N, 9.62.

Methyl 1-Benzyl-3-[(3-pyridyl)methyl]-2-indolecarboxylate (14b): 55%; 7:3 hexanes-AcOEt; mp 90-92°C; ^{1}H NMR (300 MHz) δ 3.80 (s, 3H), 4.49 (s, 2H), 5.79 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.10-7.35 (m, 7H), 7.45 (ad, *J* = 7.2 Hz, 1H), 7.65 (dt, *J* = 0.9, 0.9, 5.6 Hz, 1H), 8.40 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.57 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 28.5 (CH_2), 48.3 (CH_2), 51.5 (CH_3), 110.8 (CH), 120.7 (2 CH), 122.4 (C), 123.2 (CH), 124.8 (C), 125.8 (CH), 126.0 (CH), 126.7 (C), 127.1 (CH), 128.5 (CH), 135.5 (CH), 136.6 (C), 138.3 (C), 138.8 (C), 147.2 (CH), 149.7 (CH), 162.5 (C). Anal. Calcd. For $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.52; H, 5.64; N, 7.73.

Methyl 3-[(3-Pyridyl)methyl]-1*H*-2-indolecarboxylate (14c): 50%; elution with 4:6 hexanes-AcOEt; mp 170-172°C; ^{1}H NMR (200 MHz) δ 3.92 (s, 3H), 4.50 (s, 2H), 7.12 (m, 2H), 7.32 (ddd, *J* = 1, 7.6, 8 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 8.41 (br s, 1H), 8.62 (br s, 1H), 9.27 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 27.9 (CH_2), 51.9 (CH_3), 111.9 (CH), 120.5 (CH), 120.7 (CH), 121.3 (C), 123.3 (CH), 123.5 (C), 125.8 (CH), 127.6 (C), 135.9 (CH), 136.5 (C), 147.1 (CH), 149.5 (CH), 162.4 (C), pyridine C-3 not observed. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.20; H, 5.37; N, 10.43.

Methyl 1-(Methoxymethyl)-3-[(3-Pyridyl)methyl]-2-indolecarboxylate (14d).

A solution of **14c** (0.27 g, 1.01 mmol) in anhydrous THF (8 mL) was added dropwise under Ar to an ice-cooled suspension of NaH (1.11 mmol) in anhydrous THF (2 mL). After stirring at 0°C for 1 h, chloromethyl methyl ether (0.10 mL, 1.32 mmol) was added and the mixture was allowed to warm to rt overnight. The reaction mixture was poured into H_2O (5 mL) and extracted with AcOEt (3x10 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (2:8 hexanes-AcOEt) to give **14d**: (0.27 g, 85% yield); ^{1}H NMR (200 MHz) δ 3.27 (s, 3H), 3.90 (s, 3H), 4.46 (s, 2H), 5.94 (s, 2H), 7.12 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.18 (m, 1H), 7.41 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8 Hz, 1H), 8.40 (d, *J* = 4.8 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (50.3 MHz) δ 28.5 (CH_2), 51.7 (CH_3), 56.0 (CH_3), 75.0 (CH_2), 111.0 (CH), 120.7 (CH), 121.3 (CH), 123.3 (CH), 123.6 (C), 124.7 (C), 126.1 (CH), 127.0 (C), 135.6 (CH), 136.3 (C), 139.0 (C), 147.2 (CH), 149.5 (CH), 162.4 (C); HRMS(CI) calcd for $C_{18}H_{19}N_2O_3$ 311.1395 (M+1), found 311.1392.

Selenoesters 15.

A solution of the respective methyl ester **14** (1.42 mmol) and $LiOH \cdot H_2O$ (71 mg, 1.70 mmol) in a 3:1 mixture of THF:H_2O (8 mL) was stirred at 65°C for 5 h. The reaction mixture was concentrated and acidified with aqueous 0.5 N HCl until pH= 6 (for **14c**,**d**) or pH= 5 (for **14a**). The precipitated carboxylic acid (from **14c**,**d**) or carboxylic acid hydrochloride (from **14a**) was collected by filtration.

A suspension of the above carboxylic acid (1 mmol) in anhydrous CH_2Cl_2 (7 mL) was treated with Et_3N (1 mmol for series **c,d**; 2 mmol for series **a**). After 15 min at rt, the mixture was concentrated under reduced pressure to give the respective triethylammonium salt.

In another flask, tributylphosphine (2.50 mmol for series **a,d**; 5 mmol for series **c**) was added under Ar to a solution of PhSeCl (2.50 mmol for series **a,d**; 5 mmol for series **c**) in anhydrous THF (7 mL) and the mixture was stirred at rt for 10 min (yellow solution). The above triethylammonium salt in THF (7 mL) was added to this solution and the resulting mixture was

stirred overnight. The reaction mixture was partitioned between Et_2O (25 mL) and H_2O (25 mL) and extracted with Et_2O (3 x 15 mL). The solvent was removed and the crude product was purified. Yields, methods of purification, and NMR data are given below.

***Se*-Phenyl 1-Methyl-3-[(3-pyridyl)methyl]-2-indolecarboselenoate (15a):** 80%; flash chromatography, elution with 7:3 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 3.91 (s, 3H), 4.66 (s, 2H), 7.15 (m, 2H), 7.40 (m, 5H), 7.54 (m, 4H), 8.46 (br s, 1H), 8.63 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 28.8 (CH_2), 32.4 (CH_3), 110.5 (CH), 119.0 (C), 120.8 (CH), 121.0 (CH), 123.3 (CH), 125.8 (C), 126.2 (CH), 126.8 (C), 129.3 (CH), 129.4 (CH), 134.4 (C), 135.9 (CH), 136.1 (CH), 138.6 (C), 147.3 (CH), 149.6 (CH), 185.7 (C), pyridine C-3 not observed; HRMS(CI) calcd for $C_{22}H_{19}N_2OSe$ 407.0662 (M+1), found 407.0669.

***Se*-Phenyl 1-Benzyl-3-[(3-pyridyl)methyl]-2-indolecarboselenoate (15b):** 76%; hexanes and 5:5 hexanes-AcOEt; mp 130-132°C; ^{1}H NMR (200 MHz) δ 4.68 (s, 2H), 5.60 (s, 2H), 7.0-7.5 (m, 16H), 8.45 (d, *J* = 3.8 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR (50.3 MHz) δ 28.8 (CH_2), 48.4 (CH_2), 111.1 (CH), 119.3 (C), 121.0 (CH), 121.1 (CH), 123.4 (CH), 125.8 (C), 126.2 (CH), 126.4 (CH), 127.1 (C), 127.3 (CH), 128.5 (CH), 129.2 (CH), 129.4 (CH), 134.6 (C), 135.7 (CH), 136.0 (CH), 137.5 (2 C), 138.4 (C), 147.5 (CH), 149.8 (CH), 186.2 (C). Anal. Calcd for $C_{28}H_{22}N_2OSe$: C, 69.85; H, 4.61; N, 5.82. Found: C, 70.01; H, 4.70; N, 5.73.

***Se*-Phenyl 3-[(3-Pyridyl)methyl]-1*H*-2-indolecarboselenoate (15c):** 70%; flash chromatography, elution with 6:4 hexanes-AcOEt; mp 190-192°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.40 (s, 2H), 7.10 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H), 7.23 (dd, *J* = 4.5, 7.8 Hz, 1H), 7.36 (ddd, *J* = 1.2, 7.2, 8.7 Hz, 1H), 7.50-7.60 (m, 7H), 7.73 (d, *J* = 7.8 Hz, 1H), 8.33 (d, *J* = 4.5 Hz, 1H), 8.49 (s, 1H), 11.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 27.5 (CH_2), 113.4 (CH), 120.0 (CH), 120.3 (C), 121.3 (CH), 123.6 (CH), 125.4 (C), 126.6 (CH), 127.4 (C), 129.4 (CH), 129.8 (CH), 131.1 (C), 135.8 (CH), 136.2 (C), 136.4 (CH), 137.6 (C), 147.4 (CH), 149.6 (CH), 183.2 (C). Anal. Calcd for $C_{21}H_{16}N_2OSe$: C, 64.45; H, 4.12; N, 7.16. Found: C, 64.47; H, 4.11; N, 7.22.

***Se*-Phenyl 1-(Methoxymethyl)-3-[(3-pyridyl)methyl]-2-indolecarboselenoate (15d):** 80%; flash chromatography, elution with 6:4 hexanes-AcOEt; ^{1}H NMR (200 MHz) δ 3.26 (s, 3H), 4.66 (s, 2H), 5.73 (s, 2H), 7.20 (m, 2H), 7.40-7.45 (m, 5H), 7.50-7.55 (m, 4H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR (50.3 MHz) δ 28.7 (CH_2), 56.1 (CH_3), 75.2 (CH_2), 111.3 (CH), 120.4 (C), 121.1 (CH), 121.7 (CH), 123.5 (CH), 125.8 (C), 126.6 (CH), 127.3 (C), 129.3 (CH), 129.5 (CH), 134.3 (C), 135.6 (C), 135.9 (CH), 136.0 (CH), 138.6 (C), 147.4 (CH), 149.6 (CH), 186.2 (C); HRMS calcd for $C_{23}H_{21}N_2O_2Se$ 437.0768, found 437.0770. Anal. Calcd for $C_{23}H_{20}N_2O_2Se.1/2H_2O$: C, 62.16; H, 4.76; N, 6.30. Found: C, 62.05; H, 4.88; N, 6.11.

B. ADDITIONAL SPECTROSCOPIC DATA

(Tributyltin) 1-(3-Pyridylmethyl)-2-indolecarboxylate (11a). ^{1}H NMR (200 MHz) δ 0.89 (t, *J* = 7.2 Hz, 9H), 1.33 (m, 12H), 1.60 (m, 6H), 5.90 (s, 2H), 7.15 (m, 3H), 7.32 (m, 2H), 7.39 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 8.44 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.60 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 14.3 (CH_3), 17.5 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 45.9 (CH_2), 110.9 (CH), 111.8 (CH), 121.3 (CH), 123.1 (CH), 124.2 (CH), 125.4 (CH), 127.0 (C), 130.1 (C), 135.3 (C), 135.4 (CH), 139.4 (C), 148.1 (CH), 148.2 (CH), 166.4 (C); HRMS calcd for $C_{27}H_{38}N_2O_2Sn$ 542.1955, found 5421966.

(Tributyltin) 1-Methyl-3-[(3-pyridyl)methyl]-2-indolecarboxylate (18a): ^{1}H NMR (200 MHz) δ 0.89 (t, *J* = 7 Hz, 9H), 1.32 (m, 12H), 1.60 (m, 6H), 4.06 (s, 3H), 4.54 (s, 2H), 7.15 (m, 2H), 7.35 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 4 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (100.6 MHz) δ 13.8 (CH_3), 17.0 (CH_2), 27.2 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 32.3 (CH_3), 110.5 (CH), 120.3 (CH), 120.6 (CH), 123.7 (CH), 125.1 (CH), 126.8 (C), 136.8 (CH), 138.0 (C), 138.8 (C), 146.4 (CH), 149.3 (CH), 167.5 (C), indole C-3 and C-3a not observed; CI-MS *m/z* 557 (MH^+).

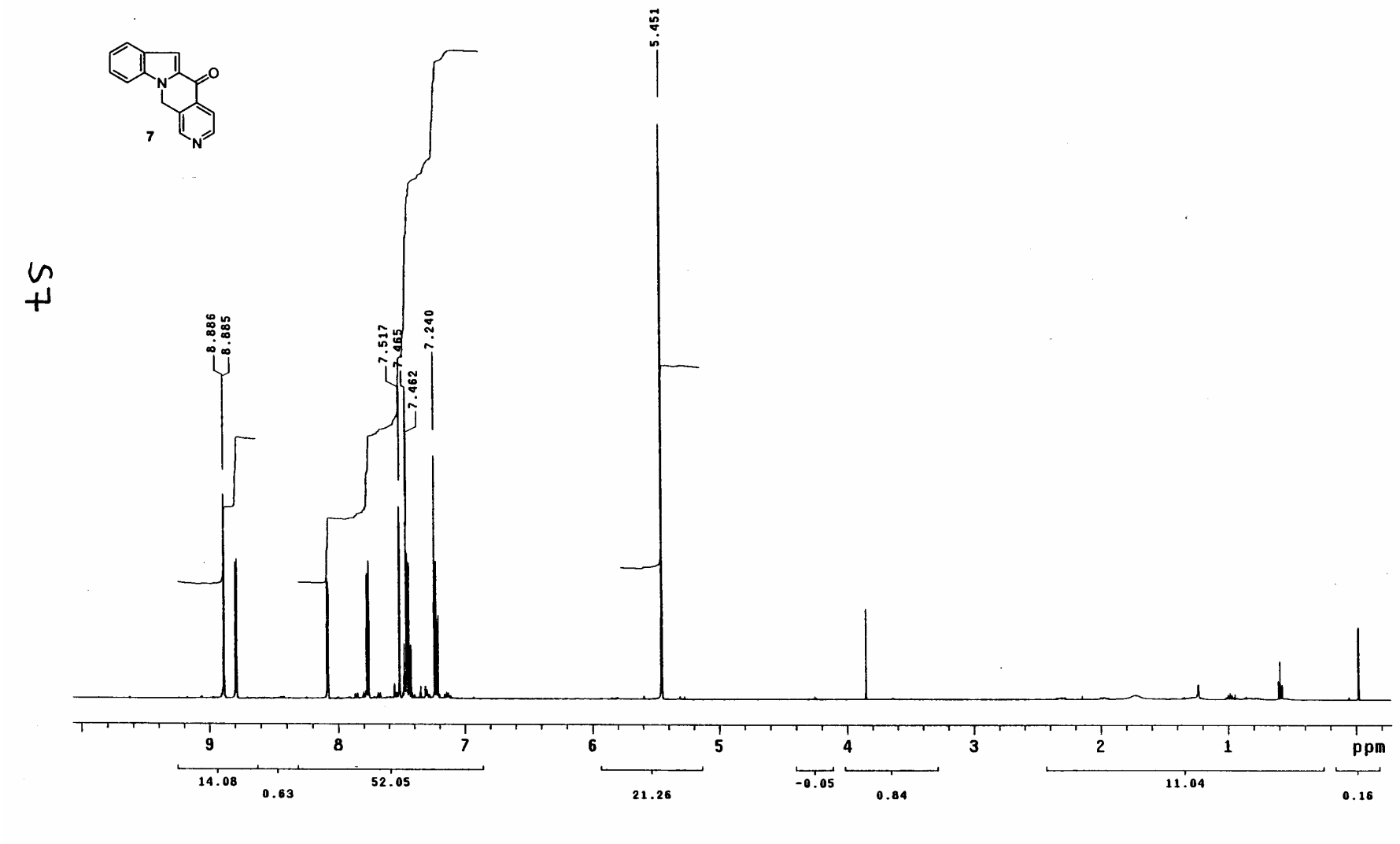
(Tributyltin) 3-[(3-Pyridyl)methyl]-1*H*-2-indolecarboxylate (18c): mp 119-121°C; ^{1}H NMR (200 MHz) δ 0.87 (t, *J* = 7 Hz, 9H), 1.33 (m, 12H), 1.61 (m, 6H), 4.53 (s, 2H), 7.08 (m, 2H), 7.25-7.35 (m, 2H), 7.54 (ad, 2H), 8.35 (d, *J* = 5.1 Hz, 1H), 8.60 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (75.4 MHz) δ 13.6 (CH_3), 16.8 (CH_2), 27.0 (CH_2), 27.8 (CH_2), 28.8 (CH_2), 111.7 (CH), 119.5 (C), 120.0 (CH), 120.4 (CH), 123.1 (CH), 124.9 (CH), 126.1 (C), 127.8 (C), 135.5 (C), 135.9 (CH), 137.0 (C), 146.8 (CH), 149.6 (CH), 166.8 (C); HRMS calcd for $C_{27}H_{39}N_2O_2Sn$ 543.2033, found 543.2011.

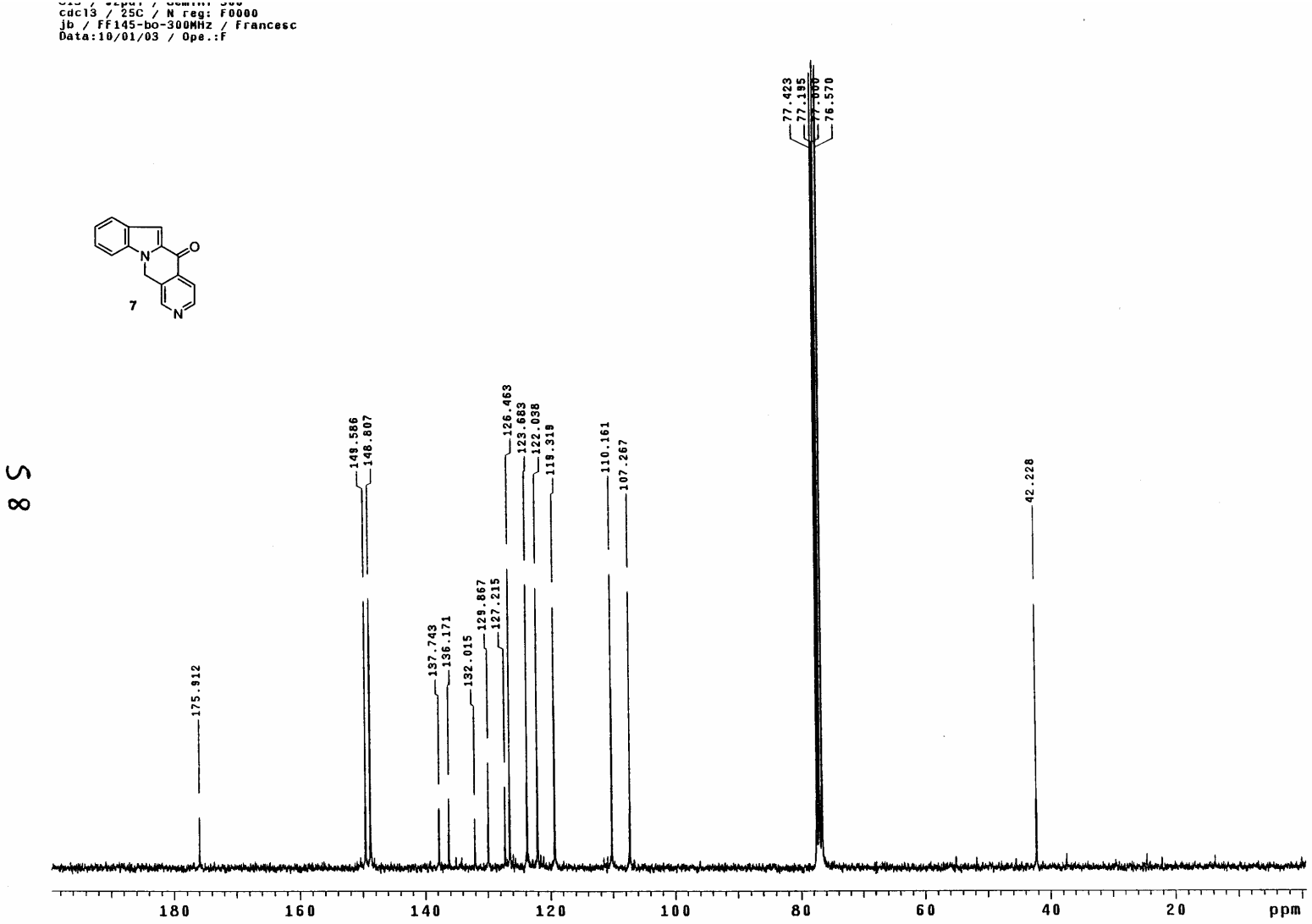
6-Methyl-6*H*-pyrido[2,3-*b*]carbazole-5,11-dione (17a): ^{1}H NMR (200 MHz) δ 4.33 (s, 3H), 7.40-7.60 (m, 3H), 7.68 (dd, *J* = 4.8, 8 Hz, 1H), 8.46 (d, *J* = 8 Hz, 1H), 8.56 (dd, *J* = 1.8, 7.8 Hz, 1H), 9.00 (dd, *J* = 1.8, 4.8 Hz, 1H).

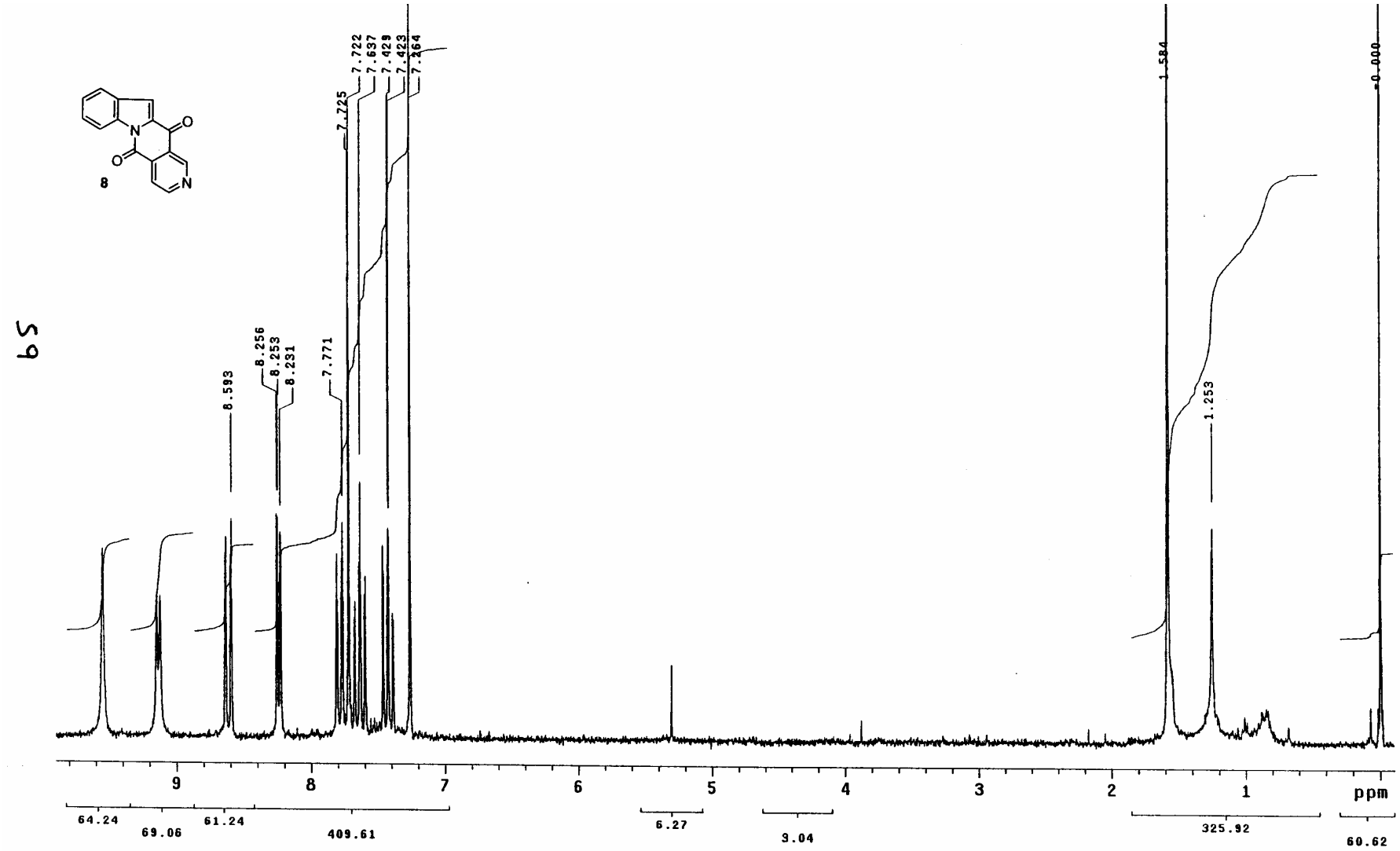
6-Benzyl-6*H*-pyrido[2,3-*b*]carbazole-5,11-dione (17b): ^{1}H NMR (200 MHz) δ 6.03 (s, 2H), 7.25 (m, 3H), 7.40-7.60 (m, 4H), 7.70 (m, 2H), 8.50 (d, *J* = 8 Hz, 1H), 8.57 (dd, *J* = 1.8, 7.8 Hz, 1H), 8.94 (dd, *J* = 1.8, 4.8 Hz, 1H).

6-(Methoxymethyl)-6*H*-pyrido[2,3-*b*]carbazole-5,11-dione (17d): ^{1}H NMR (300 MHz) δ 3.42 (s, 3H), 6.24 (s, 2H), 7.47 (m, 1H), 7.56 (m, 1H), 7.70 (m, 2H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.59 (d, *J* = 7.8 Hz, 1H), 9.02 (d, *J* = 3.6 Hz, 1H).

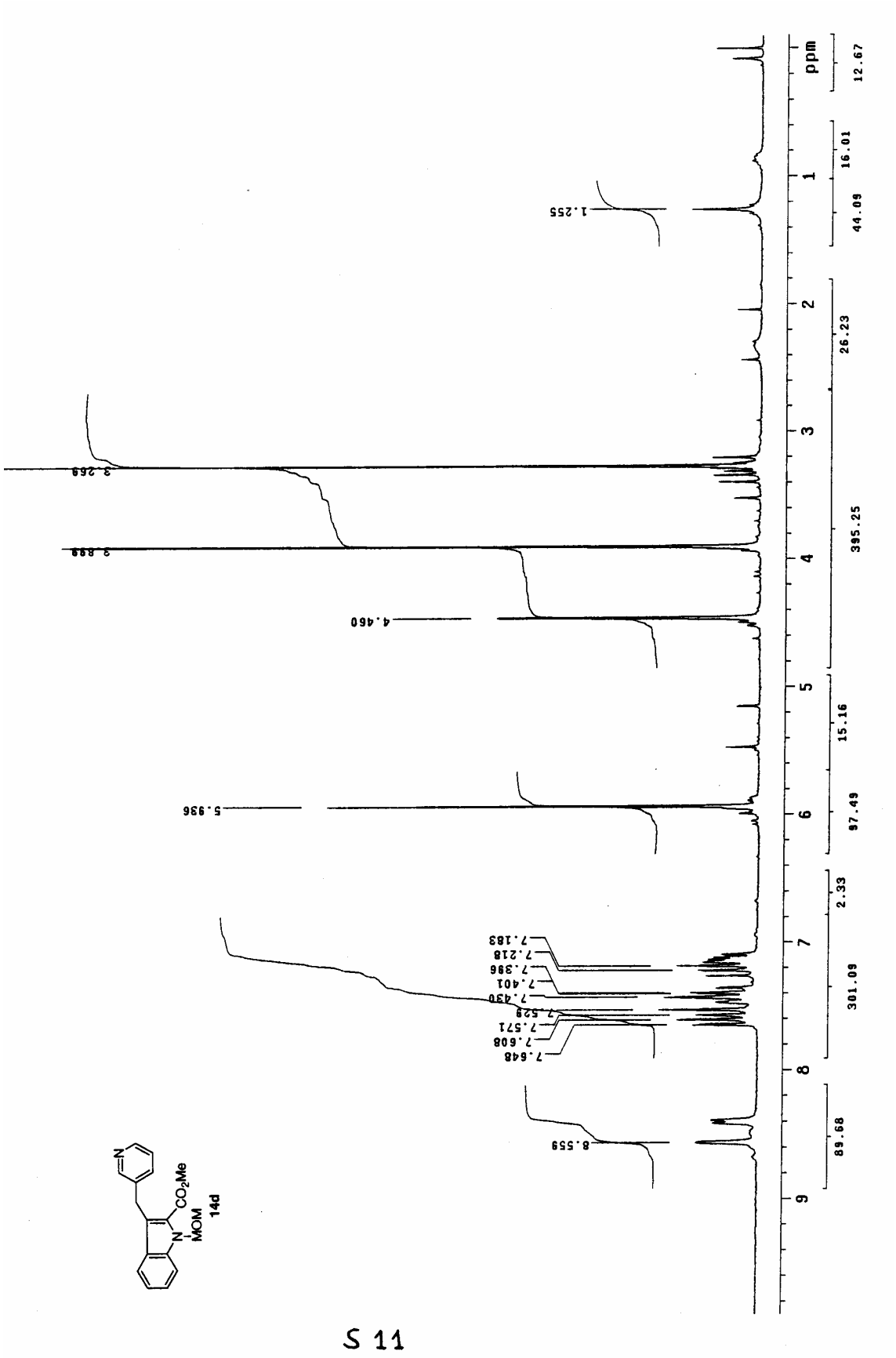
1. Bourlot, A. S.; Desarbre, E.; Mérour, J. Y. *Synthesis* **1994**, 411-416.

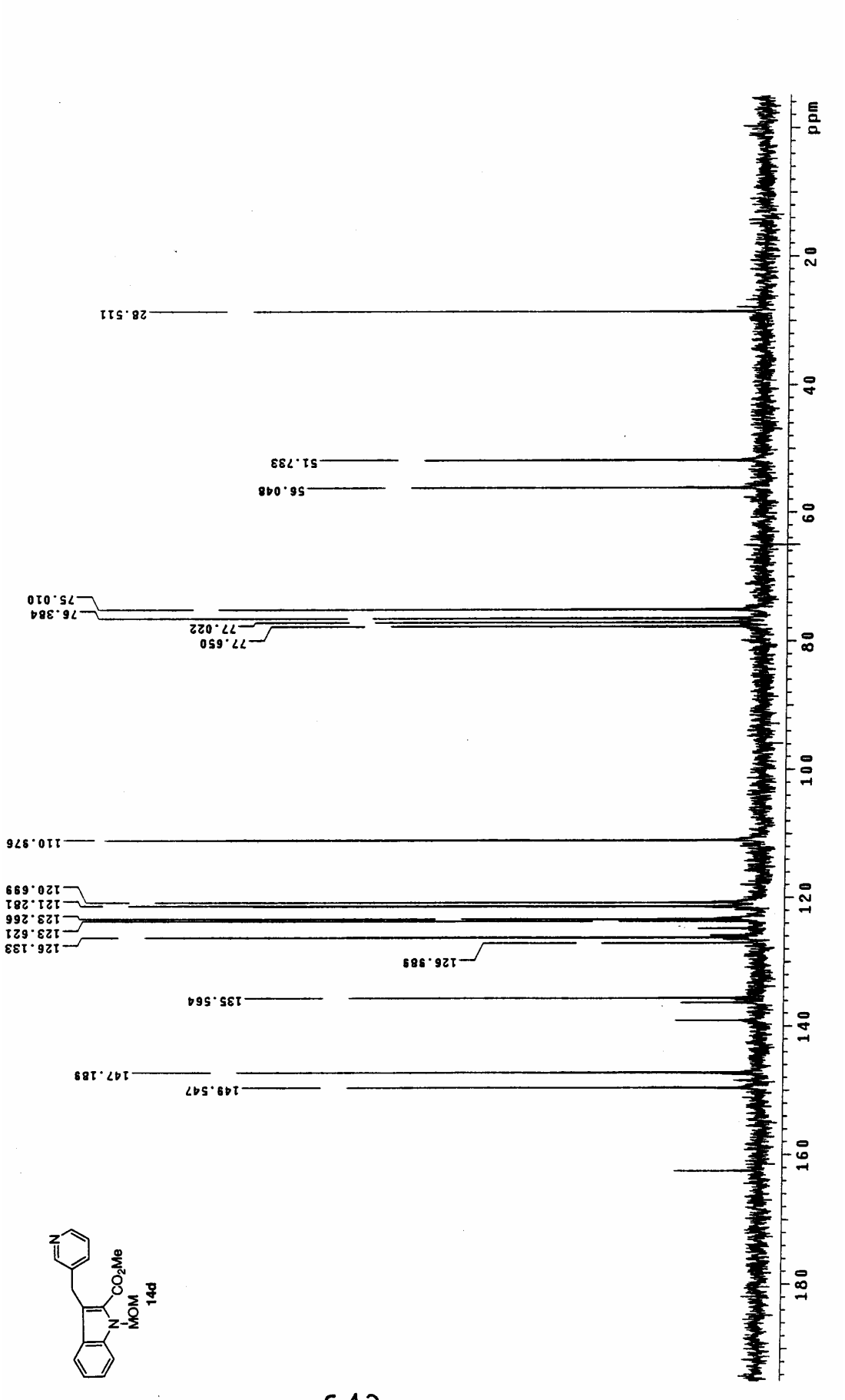

7
8.886
8.885
7.517
7.465
7.462
7.240
5.451
9
8
7
6
5
4
3
2
1
ppm
14.08
0.63
52.05
21.26
-0.05
0.84
11.04
0.16

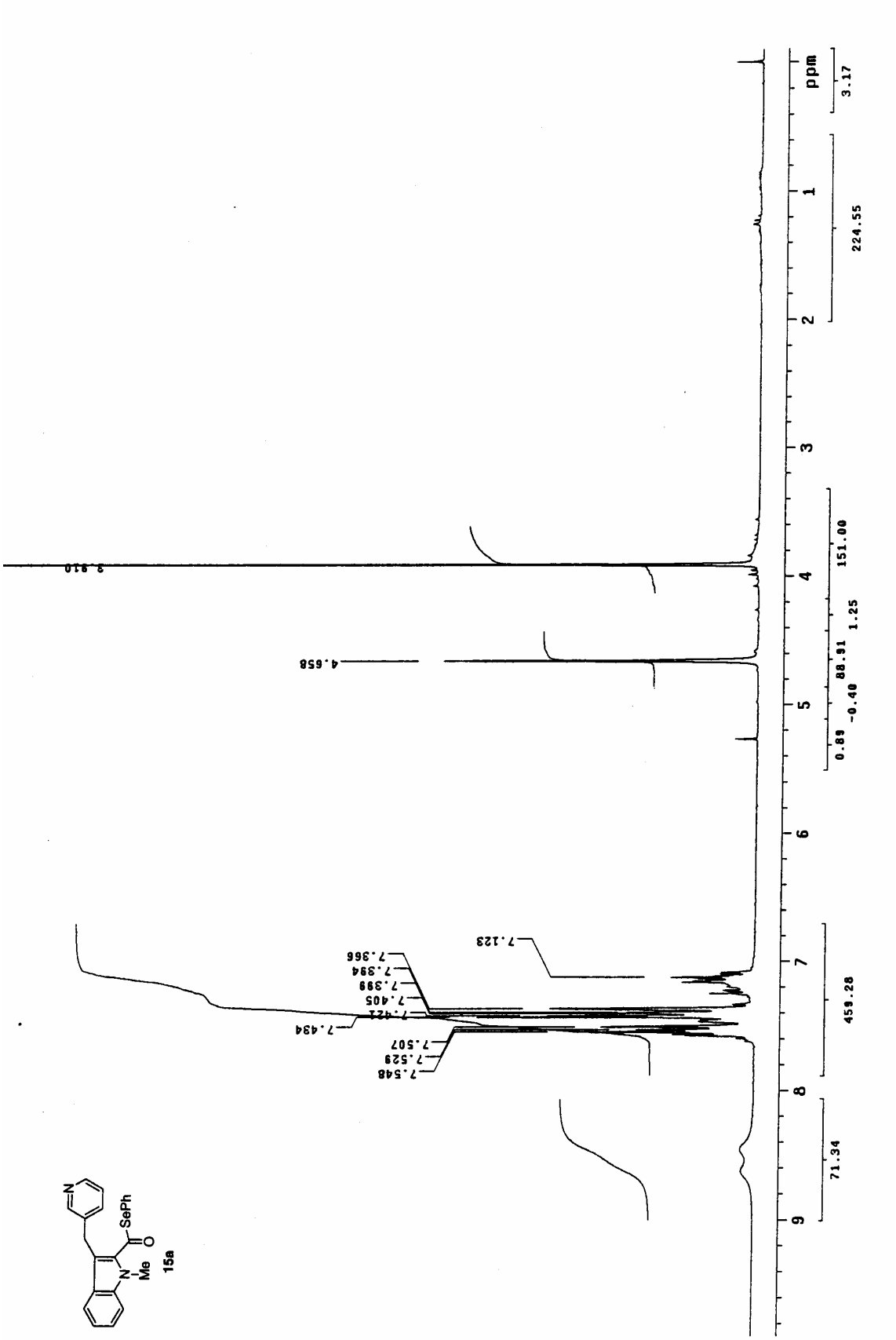

cdcl3 / 25C / N reg: F0000
jb / FF145-bo-300MHz / Francesc
Data:10/01/03 / Ope.:F
7
77.423
77.195
76.570
149.586
148.807
137.743
136.171
132.015
129.867
127.215
126.463
123.683
122.038
119.319
110.161
107.267
175.912
42.228
180
160
140
120
100
80
60
40
20
ppm


8
8.593
8.256
8.253
8.231
7.771
7.725
7.722
7.637
7.429
7.423
7.264
1.584
1.253
0.000
9
8
7
6
5
4
3
2
1
ppm
64.24
69.06
61.24
409.61
6.27
3.04
325.92
60.62

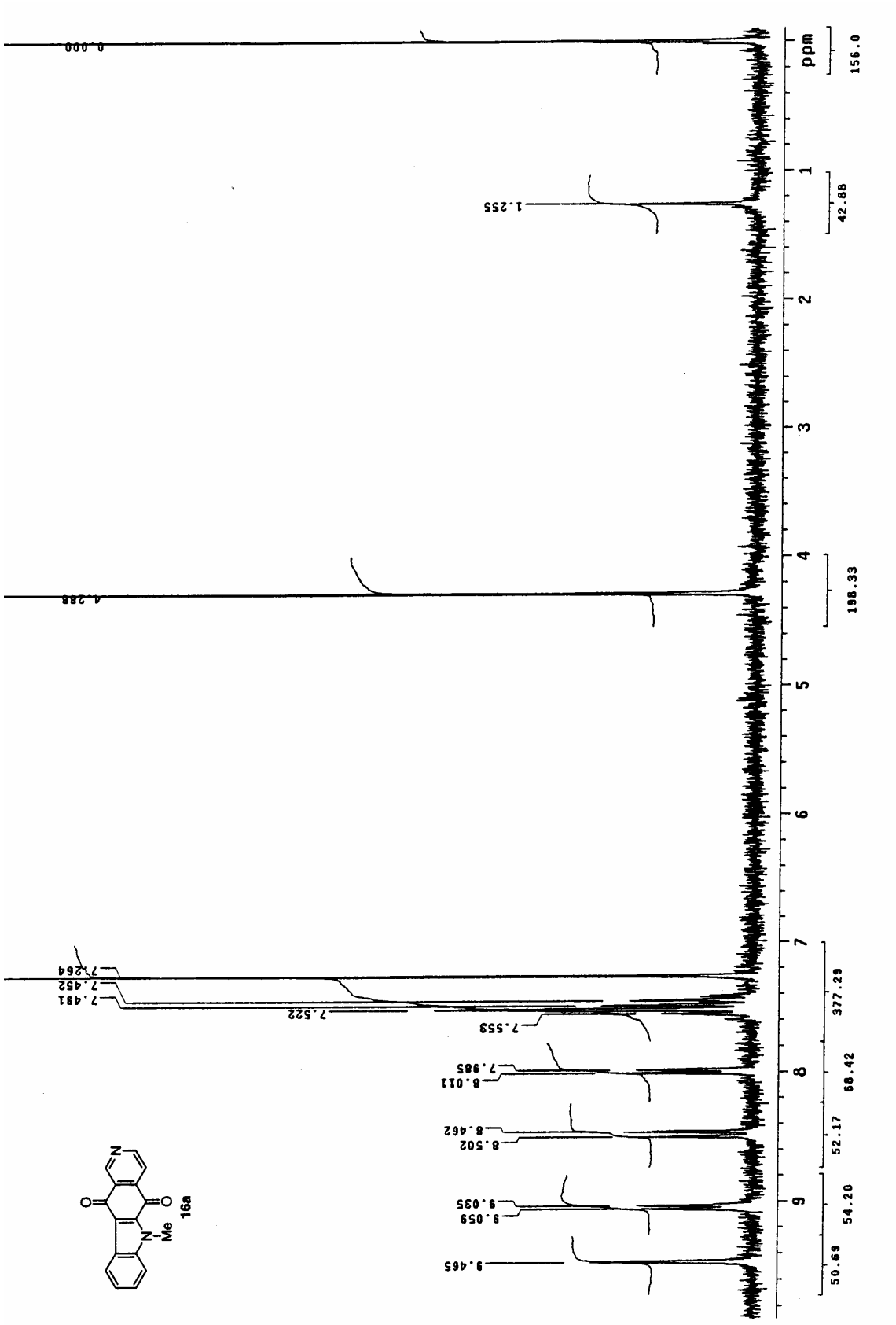
0.036
77.423
77.201
77.000
76.577
117.211
117.412
121.318
124.052
125.912
126.483
128.591
130.404
133.130
137.360
137.051
149.324
155.521
157.683
174.657
ppm
20
40
60
80
100
120
140
160
180
8

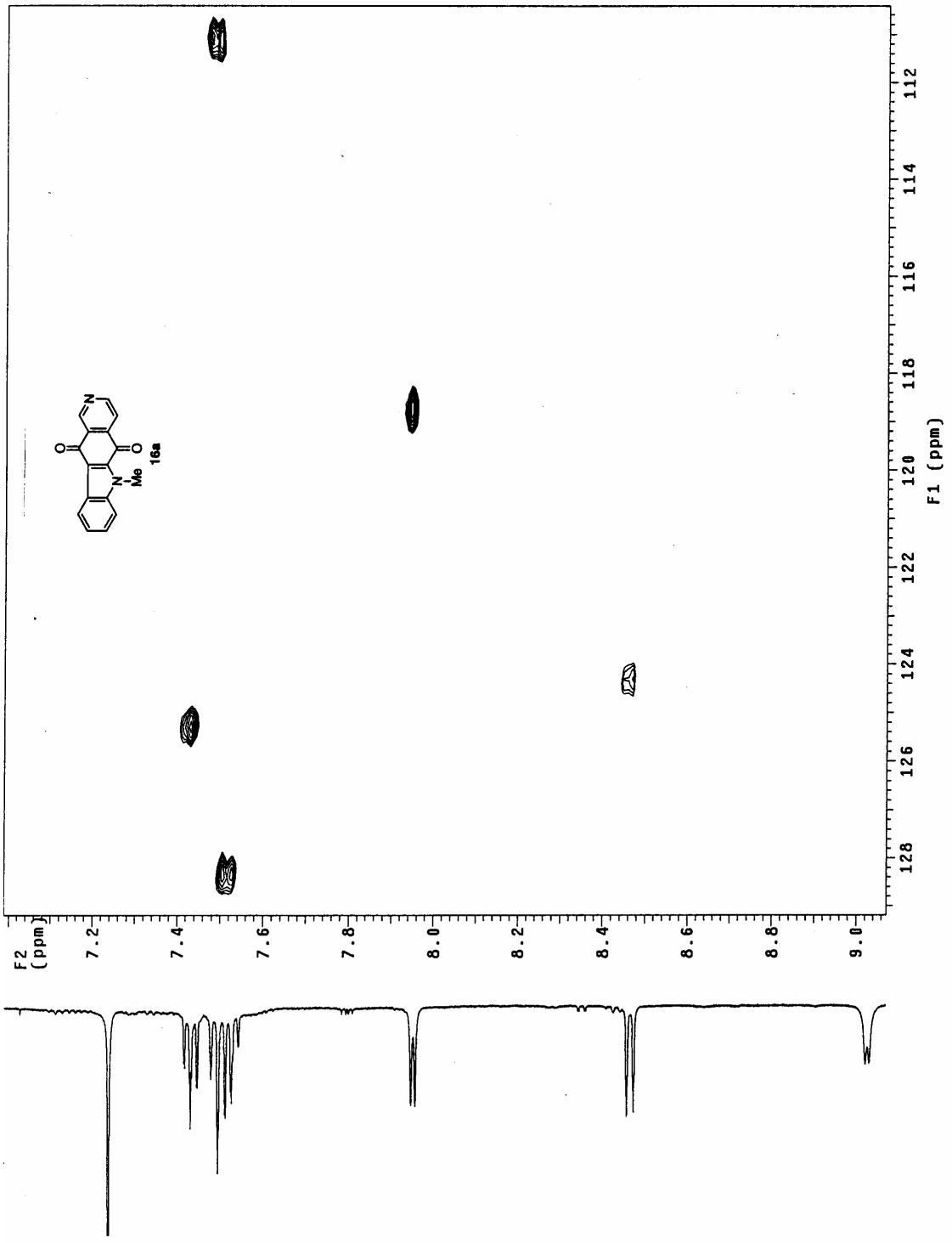

14d
MOM
CO2Me
N
N
8.559
7.648
7.608
7.571
7.529
7.430
7.401
7.396
7.218
7.183
5.936
4.460
3.899
3.269
1.255
ppm
89.68
301.09
2.33
97.49
15.16
395.25
26.23
44.09
16.01
12.67

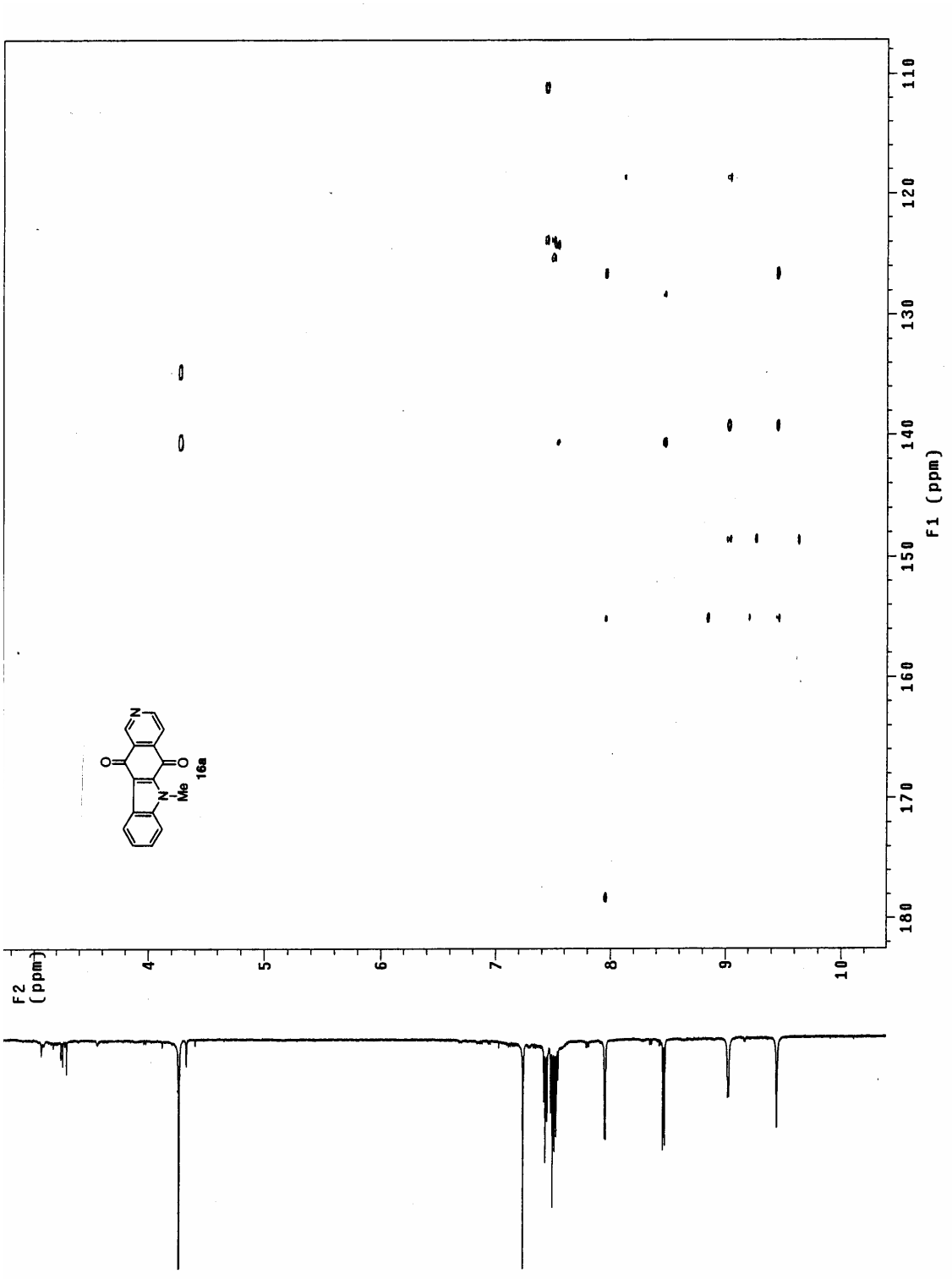

28.511
51.733
56.048
75.010
76.384
77.022
77.650
110.976
120.699
121.281
123.266
123.621
126.133
126.989
135.564
147.189
149.547
ppm
20
40
60
80
100
120
140
160
180
N
CO2Me
N
MOM
14d

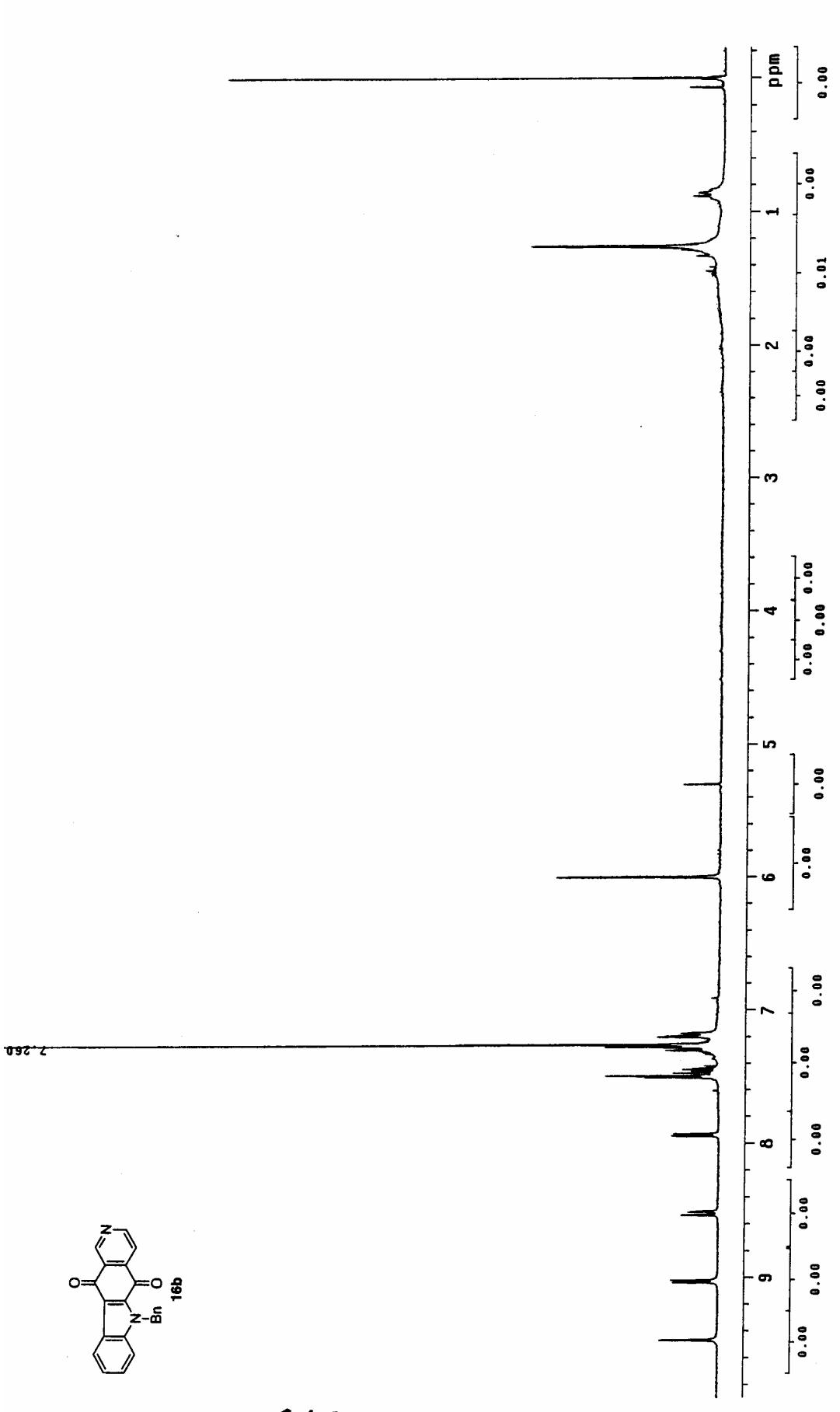

9.910
4.658
7.548
7.529
7.507
7.484
7.421
7.405
7.399
7.394
7.366
7.123
ppm
3.17
224.55
151.00
88.91
1.25
-0.40
0.89
459.28
71.34
SePh
N
Me
O
15a

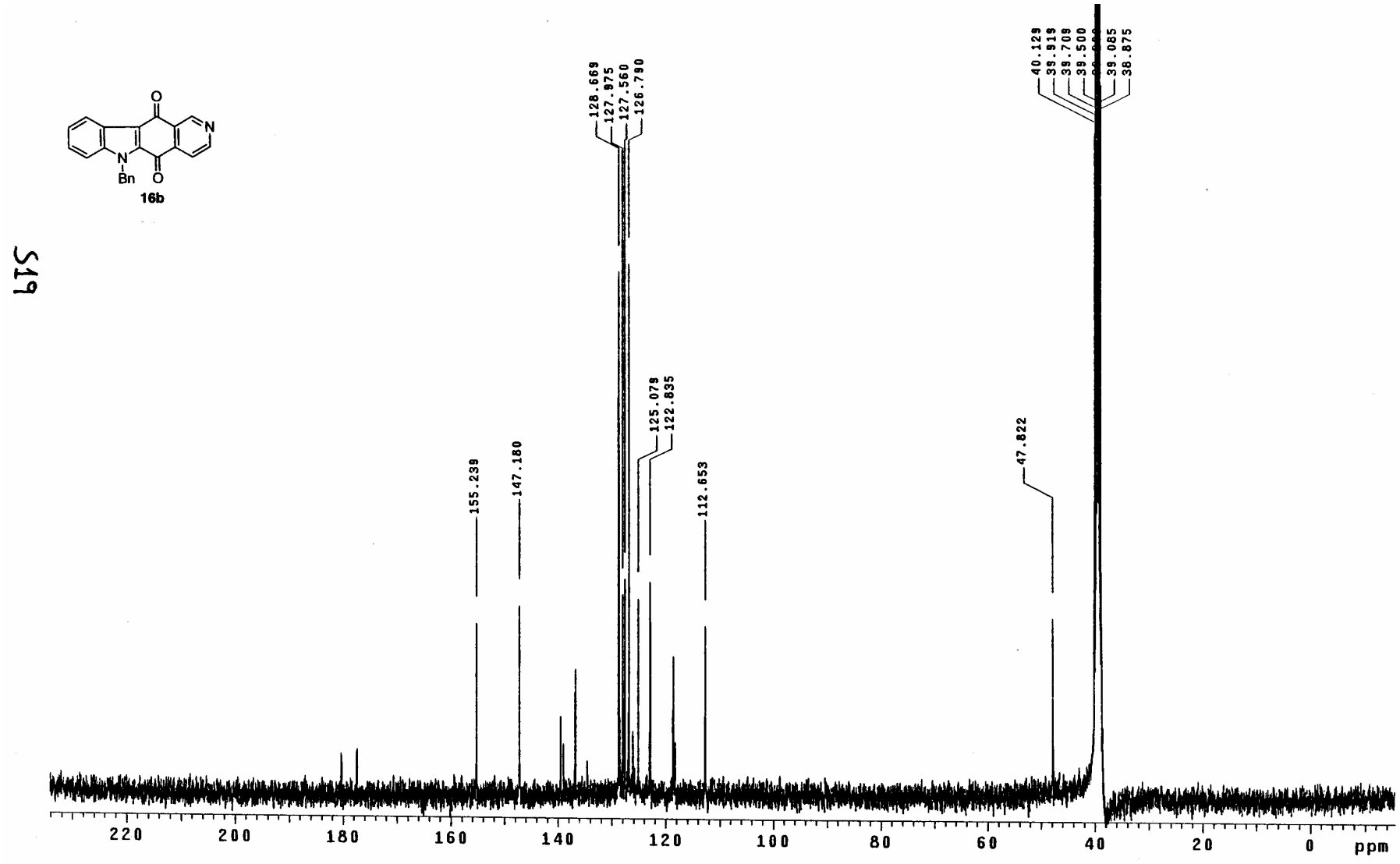
28.756
32.425
76.412
77.049
77.686
110.467
118.987
120.790
120.991
126.151
126.825
129.265
129.421
135.901
136.061
147.271
149.638
ppm
20
40
60
80
100
120
140
160
180
SePh
O
N
Me
15a

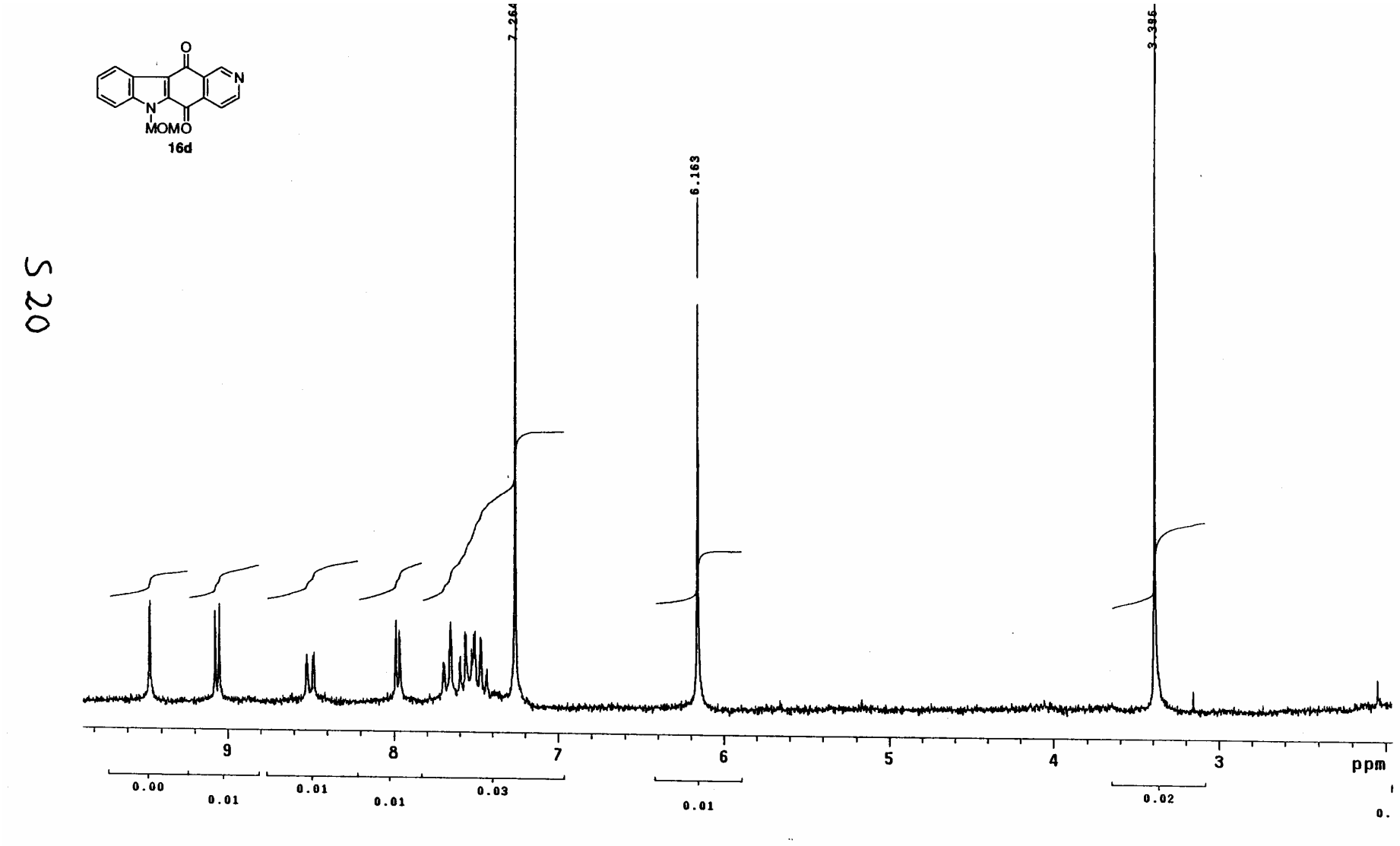

0.000
1.255
4.288
7.264
7.452
7.491
7.522
7.559
7.985
8.011
8.462
8.502
9.035
9.059
9.465
ppm
156.0
42.88
198.33
377.29
68.42
52.17
54.20
50.69
N
O
O
N
Me
16a

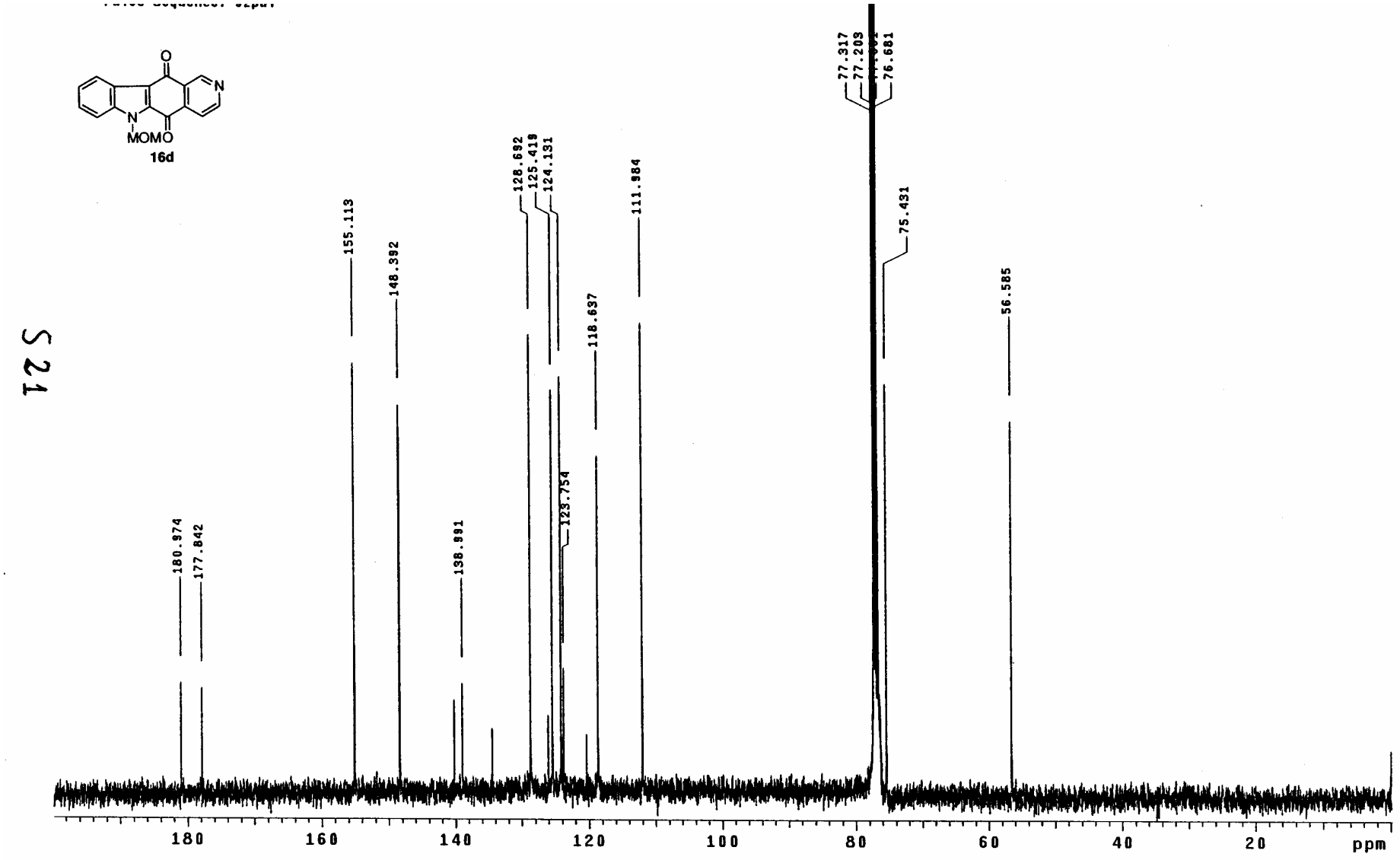

F2 (ppm)
7.2
7.4
7.6
7.8
8.0
8.2
8.4
8.6
8.8
9.0
F1 (ppm)
112
114
116
118
120
122
124
126
128
N
O
O
N
Me
16a


F2 (ppm)
F1 (ppm)
16a


7.260
ppm
16b
N-Bn


O
N
Bn
O
O
16b
128.669
127.975
127.560
126.790
125.079
122.835
112.653
155.239
147.180
47.822
40.129
39.919
39.709
39.500
39.085
38.875
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
N
N
MOMO
16d
7.264
6.163
3.386
9
8
7
6
5
4
3
ppm
0.00
0.01
0.01
0.01
0.03
0.01
0.02


O
N
N
MOMO
16d
180.974
177.842
155.113
148.392
138.991
128.682
125.419
124.131
123.754
118.637
111.984
77.317
77.203
76.681
75.431
56.585
180
160
140
120
100
80
60
40
20
ppm

ORGANIC LETTERS

2006
Vol. 8, No. 4
561−564

A New Radical-Based Route to Calothrixin B

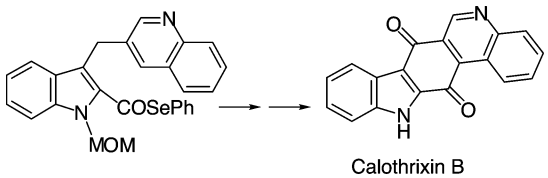
M.-Lluïsa Bennasar,* Tomàs Roca, and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@ub.edu

Received October 27, 2005

ABSTRACT

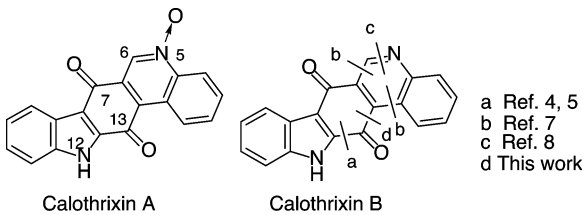


Calothrixin B

A high-yielding totally regioselective intramolecular homolytic acylation of a quinoline ring constitutes the key step in a new synthesis of the pentacyclic indolo[3,2-*j*]phenanthridine alkaloid calothrixin B.

Calothrixin B and its *N*-oxide derivative (calothrixin A) are quinone-based natural products isolated in 1999 from the cyanobacteria *Calothrix*[1] that display potent antimalarial and anticancer properties.[2] Owing to their striking biological activities as well as their pentacyclic indolo[3,2-*j*]phenanthridine skeleton, unprecedented among natural products,[3] calothrixins have attracted the synthetic interest of several research groups. Thus, four syntheses of calothrixins have been reported to date relying on the strategies depicted in Figure 1. In 2000, Kelly et al.[4] and two years later Chai et al.[5] synthesized calothrixin B and A by taking advantage of elegant metalation techniques, inspired in earlier syntheses of ellipticine quinones,[6] to assemble the indole and the quinoline nucleus (last bond formed $C_{12a}-C_{13}$, bond a). More recently, Guingant et al.[7] and Hibino et al.[8] accomplished the synthesis of calothrixin B by means of completely different strategies, such as a hetero-Diels−Alder reaction (bonds C_6-C_{6a} and $C_{13a}-C_{13b}$, bonds b) and a final formation of the quinoline ring from an appropriately substituted carbazole (bond C_5-C_6, bond c), respectively. In this context, we envisaged an alternative approach to the pentacyclic skeleton of calothrixin B, in which the central carbocyclic ring would be closed in the last synthetic steps by homolytic acylation of the 4-position of the quinoline ring (bond formed $C_{13}-C_{13a}$, bond d). In this manner, an electron-deficient quinoline ring would react with a nucleophilic acyl radical,[9] which could be considered as the umpolung of the intramolecular Friedel−Crafts acylation.

Intramolecular homolytic aromatic substitutions by nucleophilic carbon-centered radicals have become an important



Calothrixin A Calothrixin B

Figure 1. Calothrixins. Synthetic strategies.

(1) Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Saliba, K. J.; Smith, G. D. *Tetrahedron* **1999**, *55*, 13513−13520.
(2) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Simith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958−4963 and references therein.
(3) For a previous approach to the pentacyclic system of calothrixins, see: Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939−1946.
(4) Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735−3737.
(5) (a) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939−2940. (b) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906−8909.
(6) (a) Watanabe, M.; Snieckus, V. *J. Am. Chem.* Soc. **1980**, *102*, 1457−1460. (b) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451−5457.

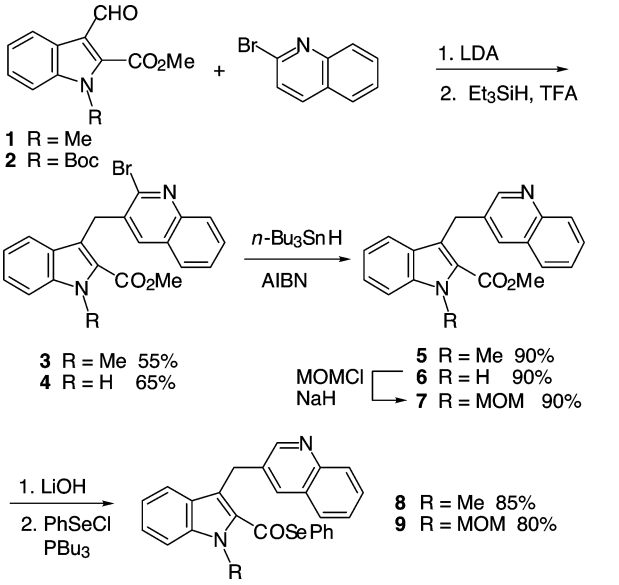
10.1021/ol052600e CCC: $33.50
Published on Web 01/25/2006

tool for the construction of otherwise quite inaccessible substituted heterocycles.[10,11] However, to our knowledge, the use of quinolines as substrates in intramolecular processes has been limited to the reaction with aryl radicals under reductive (tributyltin hydride) conditions.[12] In fact, most reported examples deal with intermolecular reactions conducted in acidic media under oxidative protocols.[13]

In the past few years, we have been studying the generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters and their reaction with alkenes under reductive conditions.[14] Cyclization upon aromatic rings was also possible,[15] but under nonreductive (hexabutylditin/*hν*) conditions, producing benzocarbazoledione[16] and ellipticine quinones[17] in moderate yields. Based on these results, we expected that the related quinoline-containing radicals would participate in similar cyclizations, ultimately leading to the carbazoledione moiety characteristic of calothrixin B.

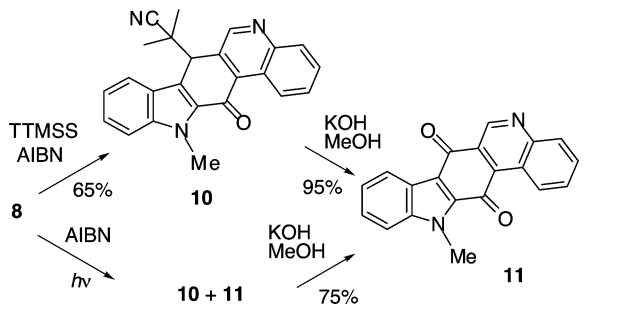
Our investigation began with the preparation of selenoester **8**, a model radical precursor bearing the required (3-quinolyl)methyl moiety connected to the indole 3-position.[18] This compound was easily accessible from *N*-methylindole **1** as depicted in Scheme 1. Chemoselective reaction with 3-lithio-2-bromoquinoline, followed by triethylsilane reduction of the resulting carbinol provided 2-bromoquinoline **3**, which was converted into methyl ester **5** upon reduction. Subsequent hydrolysis of **5**, followed by phenylselenation of the respective carboxylic acid gave the target compound **8**.

Scheme 1. Preparation of the Radical Precursors



N-Methylselenoester **8** was first allowed to react under conditions similar to those reported in our earlier work, i.e., with *n*-Bu_6Sn_2 under 300 W sun lamp irradiation. However, after irradiation and heating at 80 °C for 24 h, we obtained a complex reaction mixture of unidentified products, the expected quinone only being detected in trace amounts. As this disappointing result might be related with an increased reactivity of the quinoline with respect to the pyridine or phenyl rings, we turned to reductive conditions, hoping that the cyclization would now be fast enough to avoid the premature reduction of the initially formed acyl radical. We were pleased to find that treatment of selenoester **8** with tris(trimethylsilyl)silane[19] (TTMSS) and azobisisobutyronitrile (AIBN, 2.5 molar equiv) at 80 °C for 8 h led to the calothrixin-related pentacycle **10** in 65% isolated yield (Scheme 2). The rather surprising structure of **10**, incorporating the 2-cyano-2-propyl moiety of the initiator, was

Scheme 2. Cyclization in the *N*-Methyl Series



(7) Sissouma, D.; Collet, S. C.; Guingant, A. Y. *Synlett* **2004**, 2612−2614.

(8) Tohyama, S.; Choschi, T.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett*. **2005**, *46*, 5263−5264.

(9) For reviews on acyl radicals, see: (a) Ryu, I.; Sonoda, N.; Curran D. P. *Chem. Rev*. **1996**, *96*, 177−194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev*. **1999**, *99*, 1991−2069.

(10) For reviews, see: (a) Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62−80. (b) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762.

(11) For more recent representative leading references, see: (a) Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem*. **2004**, *69*, 4001−4004. (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett*. **2004**, *6*, 3671−3674. (c) Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217−6224. (d) Ohno, H.; Iwasaki, H.; Eguchi, T.; Tanaka, T. *Chem. Commun*. **2004**, 2228−2229. (e) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689−2696. (f) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett*. **2005**, *7*, 3287−3289. (g) Crich, D.; Patel, M. *Org. Lett*. **2005**, *7*, 3625−3628. (h) Taniguchi, T.; Iwasaki, K.; Uchiyama, M.; Tamura, O.; Ishibashi, H. *Org. Lett*. **2005**, *7*, 4389−4390.

(12) (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*. **2001**, *42*, 2907−2910. (b) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387−3400. For a review, see: (c) Harrowven, D. C.; Sutton, B. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2004; Vol. 16, pp 27−53.

(13) (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489−519. (b) Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y. M. *J. Org. Chem*. **1993**, *58*, 4207−4211. (c) Minisci, F.; Recupero, F.; Ceccheto, A.; Punta, C.; Gambarotti, C.; Fontana, F.; Pedulli, G. F. *J. Heterocycl. Chem*. **2003**, *40*, 325−328.

(14) (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett*. **2001**, *3*, 1697−1700. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem*. **2001**, *66*, 7547−7551. (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett*. **2004**, *6*, 759−762.

(15) For previous cyclizations of acyl radicals upon indoles and pyrroles under *n*-Bu_3SnH−AIBN conditions, see: (a) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett*. **1999**, *40*, 7153−7157. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2001**, *42*, 7887−7890.

(16) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron. Lett*. **2004**, *45*, 5605−5609.

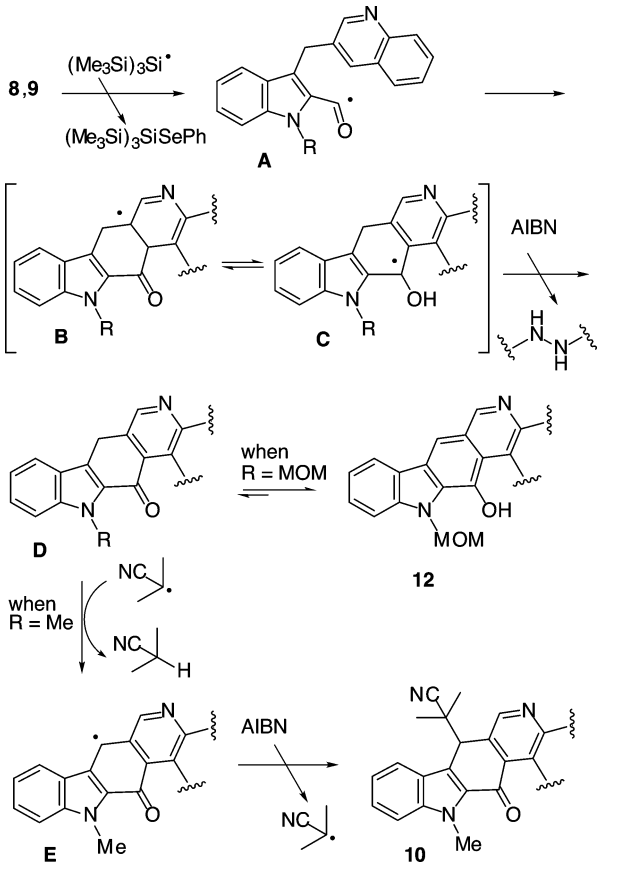
(17) Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem*. **2005**, *70*, 9077−9080.

(18) The placement of a carbonyl group in the tether chain was discarded as it would probably diminish the reactivity of the acyl radical.

established by a combination of HSQC and HMBC experiments. As expected, **10** could be converted into *N*-methylcalothrixin (**11**) by treatment with KOH in MeOH, through a process involving a gramine-type nucleophilic substitution (elimination−addition via a 3-alkylideneindolenine) and the spontaneous oxidation of the resulting carbinol (95% yield).

Formation of pentacycle **10** was consistent with the radical addition−rearomatization−overoxidation sequence depicted in Scheme 3. Thus, the initially formed radical **A**, coming

Scheme 3. Probable Mechanism



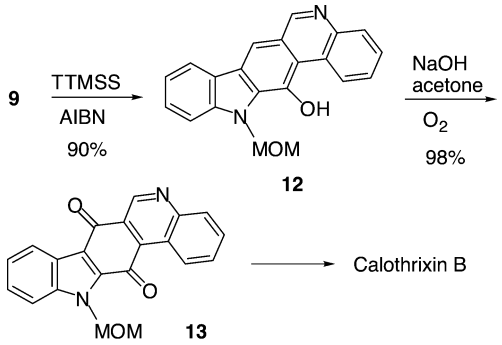
from the abstraction of the phenylseleno group by the silyl radical, undergoes regioselective cyclization upon the 4-position of the quinoline ring to give the azacyclohexadienyl radical **B**. Considering the numerous precedents of homolytic aromatic substitutions under apparently reductive conditions,[10,11] this radical (or the tautomeric benzhydryl radical **C**) is probably oxidized by hydrogen-atom abstraction at the hands of the initiator AIBN.[20,21] A new hydrogen-atom abstraction at the doubly benzylic position of pentacycle **D**, for instance by 2-cyano-2-propyl radicals, would lead to the radical **E**, which would be intercepted by AIBN.[22]

In the above sequential events leading to **10**, TTMSS would only participate in the initial generation of the 2-indolylacyl radicals. So, we wondered if we could promote a metal-free[23] homolytic sequence in the presence of AIBN acting as the oxidant, accomplishing the initial homolysis of the C−Se bond under simple irradiation.[9,24] Our reasoning proved to be correct as cyclization did take place when selenoester **8** and AIBN were irradiated (300 W sun lamp) at 80 °C in benzene.[25] Consumption of the starting product required longer reaction times (12 h) than under the above reductive conditions and the slow addition of higher amounts of the reagent (0.5 molar equiv every 1.5 h up to a total of 4 molar equiv).[26] Interestingly, after the extractive workup the crude reaction product was shown by ^{1}H NMR to be a 1:1 mixture of the pentacycle **10** and *N*-methylcalothrixin (**11**), thus indicating that complete oxidation to the quinone system had taken place under the reaction conditions. Treatment of this mixture with KOH in MeOH as above allowed the isolation of **11** in 75% overall yield from **8**.

At this point, access to the natural product calothrixin B required the extension of the chemistry outlined above to a radical precursor suitably protected at the indole nitrogen. To this end, we focused our attention on *N*-(methoxymethyl)-selenoester **9**, which was prepared from indole **2** by a synthetic route parallel to that previously used in the model series (Scheme 1). The overall yield through synthetic intermediates **4**, **6**, and **7** was 42%.

To our delight, *N*-MOM-substituted 2-indolylacyl radicals generated from selenoester **9** under reductive conditions (TTMSS, AIBN, 2 molar equiv, 80 °C, 4 h) underwent cyclization with an even higher efficiency than their *N*-methyl counterparts. Nevertheless, the reaction followed a different course since pentacyclic phenol **12**, a fully aromatic tautomeric form of **D** (R = MOM, Scheme 3) was isolated in a yield as high as 90% (Scheme 4).[27] The reaction was clean

Scheme 4. Synthesis of Calothrixin B



and showed no indication of byproducts coming from either the alternative mode of addition at the quinoline 2-position or overoxidation. On the other hand, upon application of the

(19) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

(20) For a discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98 and references therein.

(21) Azo compounds have been shown to abstract hydrogen from the benzhydryl radical to yield benzophenone and hydrazines: Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc.* **1989**, *111*, 1830−1835.

(22) For the isolation of AIBN-containing byproducts in related radical cyclizations, see: (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268−6271. (b) See also ref 14b.

AIBN/sun lamp irradiation protocol phenol **12** was also isolated as the only product, although in a lower yield (50%).

Clearly, AIBN (or 2-cyano-2-propyl radicals) is not able to overoxidize the initially formed cyclization product in this series, i.e., phenol **12**, which would be in the most favored tautomeric form, perhaps because of the establishment of a hydrogen bond between the hydroxy and methoxy group. From the synthetic standpoint, this was not a serious limitation since phenol **12** could be converted in a nearly quantitative yield into *N*-MOM calothrixin (**13**), a known immediate precursor of calothrixin B,[4,5] by mild oxidation with molecular oxygen in basic medium.[28]

(23) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.

(24) For the generation of acyl radicals by photolysis of acyl tellurides, see: Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937−8951.

(25) No cyclization was observed when selenoester **8** was irradiated at 80 °C without AIBN or when heated in the presence of AIBN without irradiation.

(26) The half-life for decomposition of AIBN is 2 h at 80 °C: Walling, C. *Tetrahedron* **1985**, *41*, 3887−3900.

(27) The use of *n*-Bu_3SnH instead of TTMSS led to phenol **12** in a lower yield (70%).

(28) For related oxidations in basic medium, see: (a) Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem.* **2005**, *13*, 819−837. (b) Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett.* **2005**, *46*, 7615−7618.

In conclusion, we have shown that the cyclization of 3-(3-quinolyl)methyl-2-indolylacyl radicals under TTMSS−AIBN conditions provides an efficient synthetic entry to calothrixin-related pentacycles, which are obtained in a different oxidation state depending on the substitution at the indole nitrogen. The reactions can also be performed under a new metal-free protocol that illustrates the determinant role of AIBN in homolytic aromatic substitutions. Starting from *N*-MOM substrates, we have accomplished a new synthesis of calothrixin B, thus highlighting the strong potential of cyclizations of 2-indolylacyl radicals upon aromatic systems for the construction of polycyclic indole compounds.

Acknowledgment. Financial support from the Ministerio de Ciencia y Tecnología (MCYT-FEDER, Spain) through Project No. BQU2003-04967-C-02-02 is gratefully acknowledged. F.F. also thanks the University of Barcelona for a grant.

Supporting Information Available: Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

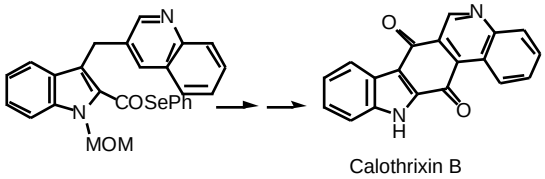
OL052600E

Supporting Information

A New Radical-Based Route to Calothrixin B

M.-Lluïsa Bennasar, Tomàs Roca, and Francesc Ferrando*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

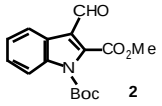


Total pages: 6

Contents:

General.
Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} 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 rotatory 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.

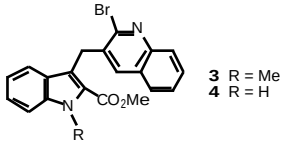
Methyl 1-(*t*-Butoxycarbonyl)-3-formyl-2-indolecarboxylate (2).



2

A solution of 3-formyl-1*H*-2-indolecarboxylate[1] (1.20 g, 5.91 mmol), $(Boc)_2O$ (1.55 g, 7.10 mmol), DMAP (0.14 g, 1.15 mmol) and Et_3N (0.82 mL, 5.91 mmol) in dry CH_2Cl_2 (60 mL) was stirred at rt for 5 h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The organic extracts were dried and concentrated, and the crude product was purified by flash chromatography (8:2 hexanes-AcOEt) to give **2** as a yellow solid: 1.72 g (96%); mp 90-2°C; ^1H NMR (200 MHz) δ 1.67 (s, 9H), 4.04 (s, 3H), 7.45 (m, 2H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 8 Hz, 1H), 10.20 (s, 1H); ^{13}C NMR (50.3 MHz) δ 27.8 (CH_3), 53.2 (CH_3), 86.6 (C), 114.7 (CH), 120.9 (C), 122.8 (CH), 124.6 (C), 125.1 (CH), 127.3 (CH), 135.6 (C), 137.5 (C), 148.1 (C), 161.4 (C), 185.8 (CH). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.71; H, 5.60; N, 4.48.

Methyl Esters 3,4.

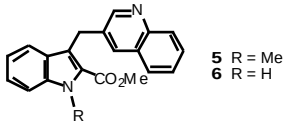


3 R = Me
4 R = H

n-BuLi (1.6 M in hexane, 0.79 mL, 1.27 mmol) was added under Ar to a cooled (–78ºC) solution of diisopropylamine (0.17 mL, 1.21 mmol) in dry THF (3 mL), and the resulting solution was stirred at –78°C for 0.5 h. Then, 2-bromoquinoline[2] (0.23 g, 1.10 mmol) in dry THF (3 mL) was added, and the resulting mixture was stirred at –78ºC for 2 h. A solution of aldehydes **1**[1] or **2** (1.10 mmol) in dry THF (10 mL) was added, and the mixture was allowed to slowly warm to 0ºC. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL).The organic extracts were concentrated to give the crude carbinols.
Et_3SiH (0.87 mL, 5.28 mmol) was added to a cooled (0ºC) solution of above carbinols in TFA (7 mL). After stirring at rt for 5 h, the solution was concentrated to dryness. The residue was dissolved with CH_2Cl_2 (25 mL), and the organic solution was washed with 2M Na_2CO_3 (3 x 20 mL), dried and concentrated. The crude product was chromatographed. Yields, elution and NMR data are given below.
Methyl 3-[(2-Bromo-3-quinolyl)methyl]-1-methyl-2-indolecarboxylate (3): 55%; elution with 8:2 hexanes-AcOEt; mp 194-6°C; ^1H NMR (200 MHz) δ 3.80 (s, 3H), 4.14 (s, 3H), 4.67 (s, 2H), 7.14 (m, 1H), 7.35-7.65 (m, 7H), 8.02 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 31.0 (CH_2), 32.3 (CH_3), 51.7 (CH_3), 110.4 (CH), 119.8 (C), 120.6 (CH), 120.7 (CH), 125.7 (CH), 125.8 (C), 126.7 (C), 126.8 (CH), 127.3 (CH), 127.6 (C), 128.1 (CH), 129.5 (CH), 135.1 (C), 136.0 (CH), 138.9 (C), 144.9 (C), 146.9 (C), 162.8 (C). Anal. Calcd for $C_{21}H_{17}BrN_2O_2$: C, 61.63; H, 4.19; N, 6.84. Found: C, 61.65; H, 4.36; N, 6.75.
Methyl 3-[(2-Bromo-3-quinolyl)methyl]-1*H*-2-indolecarboxylate (4): 65%; elution with 6:4 hexanes-AcOEt; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.80 (s, 3H), 4.64 (s, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.50 (m, 3H), 7.59 (s, 1H), 7.73 (ddd, *J* = 1.2, 6.8, 8.4 Hz,

1H), 7.77 (d, *J* = 8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 11.95 (br s, 1H); ^{13}C NMR (100.6 MHz) δ 30.1 (CH_2), 51.9 (CH_3), 112.9 (CH), 118.3 (C), 120.2 (CH), 120.4 (CH), 124.3 (C), 125.3 (CH), 127.2 (C), 127.3 (C), 127.4 (CH), 127.6 (CH), 127.9 (CH), 130.2 (CH), 134.9 (C), 136.3 (CH), 136.7 (C), 144.7 (C), 146.5 (C), 162.0 (C). Anal. Calcd for $C_{22}H_{19}BrN_2O_3$: C, 60.15; H, 4.36; N, 6.38. Found: C, 60.32; H, 4.54; N, 6.20.

Methyl Esters 5,6.



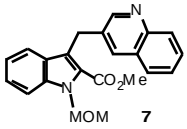
5 R = Me
6 R = H

A solution of the bromo derivative **3** or **4** (1.50 mmol), *n*-Bu_3SnH (1 mL, 3.77 mmol) and AIBN (25 mg, 0.15 mmol) in C_6H_6 (15 mL) was stirred at reflux for 2 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was partitioned between hexanes (20 mL) and acetonitrile (20 mL) and the polar layer was washed with hexanes (3 x 20 mL). The solvent was removed, and the crude product was purified by flash chromatography. Yields, elution and NMR data are given below.

Methyl 1-Methyl-3-[(3-quinolyl)methyl]-2-indolecarboxylate (5): 90%; elution with 7:3 hexanes-AcOEt; mp 93-5°C; ^{1}H NMR (200 MHz) δ 3.87 (s, 3H), 4.05 (s, 3H), 4.63 (s, 2H), 7.13 (m, 1H), 7.35-7.45 (m, 3H), 7.55-7.70 (m, 3H), 7.80 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.92 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 28.7 (CH_2), 32.3 (CH_3), 51.6 (CH_3), 110.3 (CH), 120.4 (CH), 120.6 (CH), 121.5 (C), 125.5 (CH), 126.4 (CH), 126.5 (C), 127.4 (CH), 128.1 (C), 128.5 (CH), 128.9 (CH), 133.9 (CH), 134.1 (C), 138.8 (C), 146.6 (C), 151.7 (CH), 162.8 (C). Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.31; H, 5.53; N, 8.27.

Methyl 3-[(3-Quinolyl)methyl]-1*H*-2-indolecarboxylate (6): 90%; elution with CH_2Cl_2 and then 98:2 CH_2Cl_2-MeOH; ^{1}H NMR (200 MHz) δ 3.94 (s, 3H), 4.68 (s, 2H), 7.13 (ddd, *J* = 1.6, 6.6, 8.2 Hz, 1H), 7.30-7.50 (m, 3H), 7.55-7.70 (m, 3H), 7.88 (s, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.85 (br s, 1H), 8.95 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 28.0 (CH_2), 51.8 (CH_3), 112.0 (CH), 120.5 (CH), 120.6 (CH), 120.9 (C), 125.7 (CH), 126.5 (CH), 126.6 (C), 127.4 (CH), 128.1 (C), 128.4 (CH), 128.8 (CH), 133.9 (C), 134.5 (CH), 136.1 (C), 146.2 (C), 151.4 (CH), 162.5 (C). Anal. Calcd for $C_{20}H_{16}N_2O_2 \cdot 1/2H_2O$: C, 73.83; H, 5.27; N, 8.61. Found: C, 73.64; H, 5.06; N, 8.41.

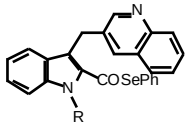
Methyl 1-(Methoxymethyl)-3-[(3-quinolyl)methyl]-2-indolecarboxylate (7).



7

A solution of **6** (0.31 g, 1 mmol) in dry THF (8 mL) was added dropwise under Ar to an ice-cooled suspension of NaH (1.30 mmol) in dry THF (2 mL). After stirring at 0°C for 1 h, chloromethyl methyl ether (0.12 mL, 1.53 mmol) was added and the mixture was allowed to warm to rt for 5 h. The reaction mixture was poured into H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried and concentrated and the resulting residue was chromatographed (7:3 hexanes-AcOEt) to give **7** as an oil: 0.32 g (90%); ^{1}H NMR (200 MHz) δ 3.29 (s, 3H), 3.89 (s, 3H), 4.64 (s, 2H), 5.97 (s, 2H), 7.18 (t, *J* = 8 Hz, 1H), 7.40 (m, 2H), 7.55-7.70 (m, 4H), 7.81 (d, *J* = 1.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.93 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 28.7 (CH_2), 51.8 (CH_3), 56.1 (CH_3), 75.1 (CH_2), 111.0 (CH), 120.7 (CH), 121.4 (CH), 123.4 (C), 124.8 (C), 126.2 (CH), 126.5 (CH), 127.0 (C), 127.4 (CH), 128.1 (C), 128.6 (CH), 128.7 (CH), 133.7 (C), 134.2 (CH), 139.1 (C), 146.3 (C), 151.4 (CH), 162.4 (C). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.79; H, 5.73; N, 7.68.

Selenoesters 8,9.



8 R = Me
9 R = MOM

A solution of methyl ester **5** or **7** (1.30 mmol) and $LiOH \cdot H_2O$ (65 mg, 1.56 mmol) in a 3:1 mixture of THF-H_2O (10 mL) was stirred at 65°C for 5 h. The reaction mixture was concentrated and acidified with aqueous 1 N HCl until pH= 6. The precipitated carboxylic acid was collected by filtration.

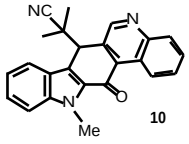
A suspension of the above carboxylic acid (1 mmol) in anhydrous CH_2Cl_2 (7 mL) was treated with Et_3N (2 mmol). After 15 min at rt, the mixture was concentrated under reduced pressure to give the respective triethylammonium salt.

In another flask, tributylphosphine (2.50 mmol) was added under Ar to a solution of PhSeCl (2.50 mmol) in anhydrous THF (7 mL), and the mixture was stirred at rt for 10 min (yellow solution). The above triethylammonium salt in THF (7 mL) was added to this solution and the resulting mixture was stirred overnight. The reaction mixture was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The solvent was removed and the crude product was purified. Yields, methods of purification and NMR data are given below.

***Se*-Phenyl 1-Methyl-3-[(3-quinolyl)methyl]-2-indolecarboselenoate (8):** 85%; oil that crystallizes on standing, washed with cold hexanes; mp 158-60°C; ^{1}H NMR (200 MHz) δ 4.00 (s, 3H), 4.87 (s, 2H), 7.15 (m, 1H), 7.40-7.45 (m, 5H), 7.50-7.65 (m, 4H), 7.76 (m, 2H), 8.09 (s, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR (75.4 MHz) δ 28.9 (CH_2), 32.5 (CH_3), 110.6 (CH), 118.3 (C), 120.8 (CH), 121.0 (CH), 125.8 (C), 126.3 (CH), 126.8 (C), 127.1 (CH), 127.5 (CH), 127.8 (CH), 128.1 (C), 129.3 (CH), 129.4 (CH), 129.6 (CH), 133.4 (C), 134.6 (C), 135.9 (CH), 136.0 (CH), 138.7 (C), 145.1 (C), 150.2 (CH), 185.6 (C). Anal. Calcd for $C_{26}H_{20}N_2OSe$: C, 68.57; H, 4.43; N, 6.15. Found: C, 68.53; H, 4.42; N, 6.05.

***Se*-Phenyl 1-(Methoxymethyl)-3-[(3-quinolyl)methyl]-2-indolecarboselenoate (9):** 80%; flash chromatography, elution with 6:4 hexanes-AcOEt; yellow oil; ^{1}H NMR (300 MHz) δ 3.29 (s, 3H), 4.85 (s, 2H), 5.77 (s, 2H), 7.16 (ddd, *J* = 0.9, 6.9, 7.8 Hz, 1H), 7.40-7.44 (m, 5H), 7.45-7.60 (m, 4H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.82 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.99 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 29.0 (CH_2), 56.1 (CH_3), 75.3 (CH_2), 111.4 (CH), 120.3 (C), 121.1 (CH), 121.7 (CH), 125.9 (C), 126.7 (CH), 127.4 (C), 127.5 (CH), 128.1 (C), 128.9 (CH), 129.0 (CH), 129.3 (CH), 129.5 (2 CH), 132.8 (C), 134.5 (CH), 136.0 (CH), 138.7 (C), 146.7 (C), 151.5 (CH), 186.3 (C); HRMS (ESI) calcd for $C_{27}H_{23}N_2O_2Se$ 487.0919 (M+1), found 487.0922.

Radical Cyclization of Selenoester 8 under TTMSS-AIBN Conditions.

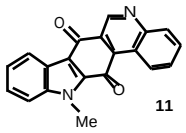


10

A solution of selenoester **8** (74 mg, 0.16 mmol), TTMSS (0.10 mL, 0.33 mmol) and AIBN (54 mg, 0.33 mmol) in C_6H_6 (6 mL) was added over a period of 5 h to heated (reflux) C_6H_6 (10 mL). After an additional 1 h at reflux, TTMSS (24 μL, 0.080 mmol) and AIBN (14 mg, 0.080 mmol) were added, and the reaction mixture was stirred at reflux for 2 h more. The solution was concentrated and the resulting residue was partitioned between acetonitrile (10 mL) and hexanes (10 mL) and the polar layer was washed with hexanes (3 x 10 mL). The solvent was removed and the crude product was chromatographed (hexanes and 7:3 hexanes-AcOEt) to give pentacycle **10** as a yellow solid: 38 mg (65%); mp 222-4 °C; ^{1}H NMR (500 MHz, assignment aided by HSQC and HMBC) δ 1.26 (s, 3H, Me), 1.47 (s, 3H, Me), 4.22 (s, 3H, NMe), 4.80 (s, 1H, 7-H), 7.25 (m, 1H, 9-H), 7.43 (ad, 2H, 10-H, 11-H), 7.73 (ddd, *J* = 1.5, 7, 8.5 Hz, 1H, 2-H),

7.78 (ddd, *J* = 1.5, 7, 8.5 Hz, 1H, 3-H), 7.84 (d, *J* = 8.5 Hz, 1H, 8-H), 8.18 (dd, *J* = 1, 8.5 Hz, 1H, 4-H), 9.30 (s, 1H, 6-H), 9.68 (dd, *J* = 1, 8.5 Hz, 1H, 1-H); ^{13}C NMR (100.6 MHz, assignment aided by HSQC and HMBC) δ 24.6 (Me), 26.7 (Me), 31.5 (NMe), 40.7 (*C*-CN), 44.9 (C-7), 110.8 (C-11), 121.3 (C-9), 121.6 (C-7a), 122.5 (C-8), 123.5 (CN), 124.5 (C-13b), 124.8 (C-7a), 126.5 (C-1), 126.8 (C-10), 129.0 (C-2), 129.8 (C-3), 130.0 (C-4), 133.7 (C-6a), 133.8 (C-12a), 136.3 (C-13a), 139.5 (C-11a), 148.8 (C-4a), 151.2 (C-6), 180.7 (C-13); CI-MS *m/z* 366 (MH^+), 299. Anal. Calcd for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50: Found: C, 78.52; H, 5.22; N, 11.23.

12-Methyl-12*H*-indolo[3,2-*j*]phenanthridine-7,13-dione (*N*-methylcalothrixin, 11).

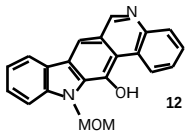


11

Tetracycle **10** (36 mg, 0.10 mmol) was treated with a 0.5 M solution of KOH in MeOH (3 mL) at rt for 8 h. The solvent was removed and the resulting 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 pure **11** as an orange solid: 29 mg (95%); mp 260-2°C; ^{1}H NMR (DMSO-d_6, 300 MHz, assignment aided by HSQC and HMBC) δ 4.24 (s, 3H, NMe), 7.45 (t, *J* = 7.8 Hz, 1H, 9-H), 7.55 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H, 10-H), 7.82 (d, *J* = 9 Hz, 1H, 11-H), 7.88 (t, *J* = 8.4 Hz, 1H, 2-H), 7.95 (t, *J* = 6.9 Hz, 1H, 3-H), 8.17 (d, *J* = 7.8 Hz, 1H, 4-H), 8.25 (d, *J* = 7.8 Hz, 1H, 8-H), 9.51 (d, *J* = 8.7 Hz, 1H, 1-H), 9.61 (s, 1H, 6-H); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.29 (s, 3H), 7.40-7.50 (m, 3H), 7.80 (m, 2H), 8.20 (d, *J* = 8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 9.59 (d, *J* = 8 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz, assignment aided by HSQC and HMBC) δ 32.2 (NMe), 112.3 (C-11), 122.2 (C-7b), 122.3 (C-8), 122.4 (C-13b), 124.2 (C-6a), 124.9 (C-9), 127.1 (C-10), 127.4 (C-1), 129.9 (C-4), 130.1 (C-2), 131.5 (C-3), 133.6 (C-13a), 136.2 (C-12a), 139.7 (C-11a), 147.1 (C-6), 151.2 (C-4a), 180.3 (C-7); C-7a and C-13, not observed. Anal. Calcd for $C_{20}H_{12}N_2O_2 \cdot 2H_2O$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.53; H, 4.83; N, 8.47.

Radical Cyclization of Selenoester 8 under AIBN-Sun Lamp Conditions. AIBN (66 mg, 0.40 mmol) was added in eight portions (0.05 mmol every 1.5 h) to a refluxed solution of selenoester **8** (45 mg, 0.10 mmol) in C_6H_6 (5 mL) under 300 W sun lamp irradiation. The solvent was removed and the resulting residue was treated with a 0.5 M solution of KOH in MeOH (3 mL) at rt for 8 h. The solvent was removed and the resulting residue was partitioned between CH_2Cl_2 and H_2O, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (6:4 hexanes-AcOEt) to give **11**: 23 mg (75%).

Radical Cyclization of Selenoester 9 under TTMSS-AIBN Conditions.

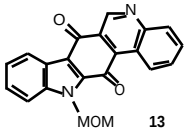


12

A solution of selenoester **9** (40 mg, 0.082 mmol), TTMSS (50 μL, 0.164 mmol) and AIBN (27 mg, 0.164 mmol) in C_6H_6 (3 mL) was added over a period of 4 h to heated (reflux) C_6H_6 (5 mL). After an additional 1 h at reflux, the solution was concentrated and the resulting residue was partitioned between acetonitrile (5 mL) and hexanes (5 mL) and the polar layer was washed with hexanes (3 x 5 mL). The solvent was removed and the crude product was chromatographed (1:1 hexanes-AcOEt) to give phenol **12** as an orange oil: 24 mg (90%); ^{1}H NMR (200 MHz) δ 3.65 (s, 3H), 5.86 (s, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.4 Hz,

1H), 7.70 (m, 2H), 8.20 (m 2H), 8.31 (s, 1H), 9.33 (s, 1H), 9.77 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 56.0 (CH_3), 76.2 (CH_2), 108.6 (CH), 112.8 (CH), 119.8 (C), 121.0 (CH), 121.3 (CH), 123.6 (C), 123.9 (C), 125.1 (C), 126.4 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 129.3 (CH), 131.3 (C), 140.7 (C), 142.4 (C), 144.1 (C), 154.3 (CH), indole C-3, not observed; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_2$ 329.1285 (M+1), found 329.1282.

12-(Methoxymethyl)-12*H*-indolo[3,2-*j*]phenanthridine-7,13-dione (*N*-MOM calothrixin 13).



13

Phenol **12** (20 mg, 0.060 mmol) in a 5:1 mixture of acetone-5% NaOH (5 mL) was stirred at rt under O_2 for 24 h. The mixture was concentrated, H_2O (5 mL) was added and the orange precipitate was collected by filtration to give **13**: 20 mg (98%); mp 231-3°C (Lit[3]: 234-5°C); ^{1}H NMR (300 MHz, assignment aided by HSQC and HMBC) δ 3.45 (s, 3H, OMe), 6.18 (s, 2H, NCH_2), 7.47 (ddd, *J* = 1.2, 6.9, 7.8 Hz, 1H, 9-H), 7.55 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H, 10-H), 7.67 (dt, *J* = 0.9, 0.9, 8.4 Hz, 1H, 11-H), 7.79 (ddd, *J* = 1.5, 6.9, 8.4 Hz, 1H, 2-H), 7.87 (ddd, *J* = 1.5, 6.6, 8.1 Hz, 1H, 3-H), 8.22 (d, *J* = 8.4 Hz, 1H, 4-H), 8.47 (d, *J* = 7.5 Hz, 1H, 8-H), 9.61 (d, *J* = 8.4 Hz, 1H, 1-H), 9.81 (s, 1H, 6-H); ^{13}C NMR (100.6 MHz, assignment aided by HSQC and HMBC) δ 56.7 (OMe), 75.5 NCH_2), 111.9 (C-11), 123.2 (C-13b), 123.3 (C-7b), 123.9 (C-8), 124.4 (C-6a), 125.4 (C-9), 127.7 (C-1), 128.3 (C-10), 130.2 (C-2), 130.4 (C-4), 131.5 (C-3), 133.4 (C-13a), 135.6 (C-12a), 140.4 (C-11a), 147.8 (C-6), 152.3 (C-4a), 181.4 (C-13), 182.2 (C-7), C-7a, not observed; HRMS (ESI) calcd for $C_{21}H_{15}N_2O_3$ 343.1077 (M+1), found 343.1080. Anal. Calcd for $C_{21}H_{14}N_2O_3 \cdot H_2O$: C, 69.99; H, 4.47; N, 7.77. Found: C, 69.92; H, 4.09; N, 7.82.

Radical Cyclization of Selenoester 9 under AIBN-Sun Lamp Conditions. AIBN (66 mg, 0.40 mmol) was added in eight portions (0.05 mmol every 1.5 h) to a heated (reflux) solution of selenoester **9** (48 mg, 0.10 mmol) in C_6H_6 (5 mL) under sun-lamp irradiation (300 W). After 12 h, the solvent was removed and the resulting residue was treated with a 0.5 M solution of KOH in MeOH (3 mL) at rt for 8h. The solvent was removed and the resulting residue was partitioned between CH_2Cl_2 and H_2O, 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 **12**: 17 mg (50%).

References:

1. Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem.* **2005**, *70*, 9077-9080.
2. Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120-5121.
3. Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735-3737.