ORGANIC LETTERS

2005
Vol. 7, No. 10
2039−2042

Short Asymmetric Synthesis of (−)- and (+)-*cis*-Lauthisan

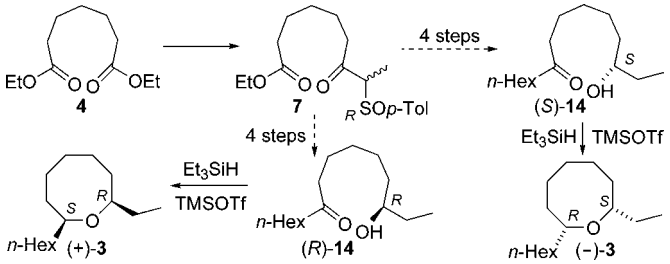
M. Carmen Carreño,*,† Renaud Des Mazery,†,‡ Antonio Urbano,† Françoise Colobert,*,‡ and Guy Solladié*,‡

Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain, and Laboratoire de Stéréochimie associé au CNRS, Université Louis Pasteur, E.C.P.M., 25 rue Becquerel, 67087 Strasbourg Cedex 2, France

carmen.carrenno@uam.es

Received March 22, 2005

ABSTRACT



The asymmetric synthesis of both enantiomers of *cis*-lauthisan (3) is achieved in only six steps from diethyl pimelate (4), the key steps being the diastereodivergent reduction of *β*-ketosulfoxide 7 and the highly cis-stereoselective Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure hydroxy sulfinyl ketones (*S*)-14 and (*R*)-14.

Medium-ring ethers constitute important structural features present in a number of biologically active marine natural products, particularly from *Laurencia* red algae.[1] Many compounds of this class contain an eight-membered oxocane or oxocene ring usually with cis stereochemistry in the alkyl substituents at C-2 and C-8. Among them, (+)-laurencin (**1**), isolated from the extracts of *Laurencia glandulifera* by Irie and Masamune in 1965,[2] and (+)-laurenyne (**2**), first isolated from a sample of the alga *Laurencia obtusa* collected in the Aegean Sea off the coast of Turkey by Thomson and co-workers in 1980,[3] are representative examples that have been the subject of significant synthetic efforts within the past decade.[4] The difficulty of the eight-membered ring construction from acyclic precursors, due to entropy factors and developing transannular repulsions as the ring is formed, is well-known.[5] Thus, the development of efficient and ste-

† Universidad Autónoma de Madrid.

‡ Université Louis Pasteur.

(1) For reviews concerning marine natural products including medium-ring ethers, see: (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*, Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, pp 131−257. (c) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15−61 and earlier reviews in the same series.

(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091−1099.

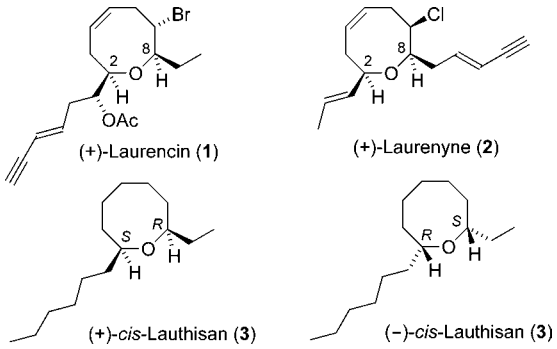
(3) Falshaw, C. P.; King, T. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951−4954.

(4) Total syntheses of (+)-laurencin: (a) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75−77. (b) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032. (c) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483−7498. (d) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. (e) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345−43484. Formal syntheses of (+)-laurencin: (f) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 1, 5653−5660. (g) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728−9738. (h) Krüger, J.; Hoffman, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499−7500. (i) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983−984. Total syntheses of (+)-laurenyne: (j) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639−8642. (k) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891−3894. Total synthesis of (−)-laurenyne: (l) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256.

(5) (a) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrik, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3−12. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

10.1021/ol050620a CCC: $30.25
Published on Web 04/19/2005

reoselective approaches to cis-2,8-disubstituted oxocenes and oxocanes[6] has been an important challenge to synthetic organic chemists.



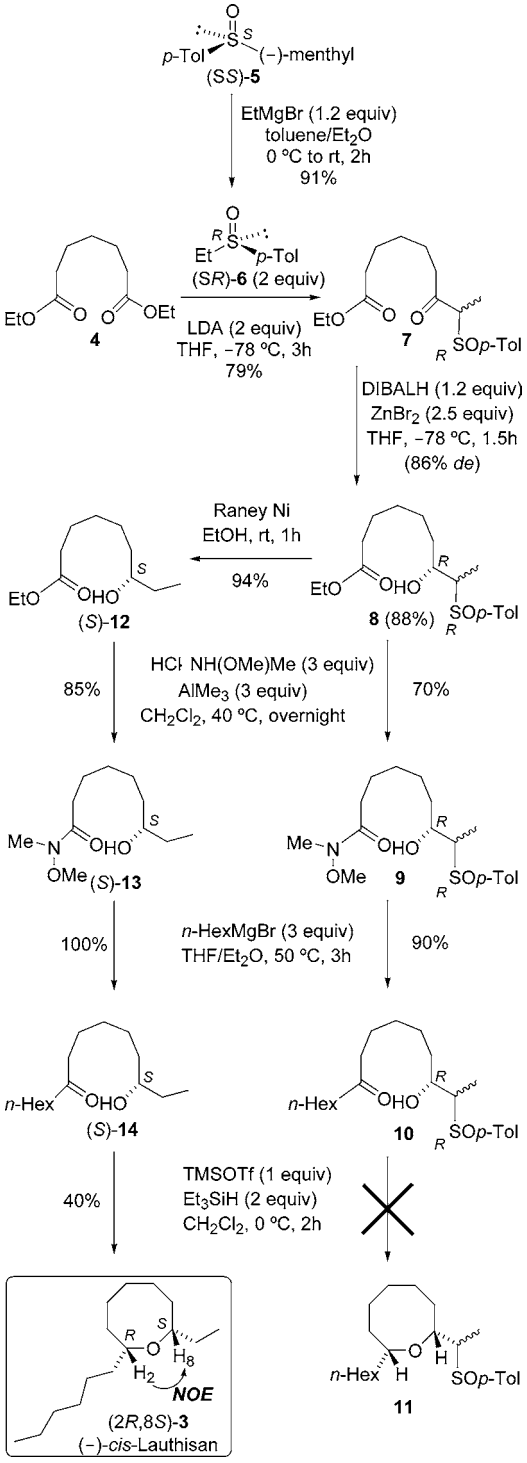
(+)-*cis*-Lauthisan (**3**), the fully saturated core of the natural derivative (+)-**1**, has been often used as a target to check the validity of a particular synthetic methodology for efficient oxocane construction. Although several strategies have been employed for the stereoselective preparation of racemic[7] and enantioenriched[8] *cis*-lauthisan, most of them require multistep synthesis or take place with moderate cis selectivities. For example, the last synthesis of racemic *cis*-lauthisan, published in 2002 by De Voss et al.,[7a] was achieved in seven steps from commercially available precursors but with a moderate 2.3:1 cis selectivity. On the other hand, Kim et al.[8a] reported in 2004 the last preparation of (+)-*cis*-lauthisan with an excellent 21:1 cis selectivity, but they needed 18 steps to accomplish the asymmetric synthesis.

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[9] we have recently described a highly stereoselective approach to different sized cis-disubstituted cyclic ethers based on the Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure hydroxy sulfinyl ketones.[10] This method had first been reported by Olah for the synthesis of acyclic ethers from alcohols and ketones[11a,b] and was later applied by Nicolaou for the preparation of racemic oxepanes.[11c,d]

In this communication, we extend the scope of our methodology, for the first time, to the efficient construction of eight-membered cyclic ethers as illustrated by the short enantioselective total synthesis of both enantiomers of the 2,8-disubstituted oxocane, (−)- and (+)-*cis*-lauthisan (**3**).

The asymmetric synthesis of the (−)-enantiomer of *cis*-lauthisan (**3**) is depicted in Scheme 1 and started with

Scheme 1. Asymmetric Synthesis of (−)-*cis*-Lauthisan (**3**)



commercially available diethyl pimelate (**4**). Thus, the addition of 2 equiv of the LDA-generated anion of enantiomerically pure (S*R*)-ethyl-*p*-tolylsulfoxide (**6**) to the diester **4** gave rise to the corresponding β-ketosulfoxide **7**, as a 50:50 mixture of epimers at the α-carbon with respect to the sulfinyl group, in 79% yield. (S*R*)-Ethyl-*p*-tolylsulfoxide (**6**) was prepared by condensation of ethylmagnesium bromide and (S*S*)-(−)-menthyl-*p*-toluenesulfinate (**5**), following the method reported by one of us[12] for the methyl derivative,

(6) For reviews on the construction of medium-ring ethers, see: (a) Holmes, A. B.; Stephenson, G. R. *Chem. Ind.* **2001**, 187−189. (b) Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457−474. For recent references, see: (c) Kadota, I.; Uyehara, H.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7361−7365. (d) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238−10240. (e) Saitoh, T.; Suzuki, T.; Onodera, N.; Sekiguchi, H.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 2709−2712. (f) Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148−149. (g) Martín, M.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **2001**, 117−119. (h) Edwards, S. D.; Lewis, T.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 4267−4270. (i) Mújica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728−9738. (j) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919−6920. (k) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−7649.

with 91% yield. The highly stereoselective reduction of the ketone functionality of **7** using DIBALH in the presence of $ZnBr_2$ afforded a 93:7 mixture (86% de) of the (*R*)- and (*S*)-epimeric carbinols at the newly created stereogenic center.[13] After flash chromatography, major stereoisomer **8**, bearing the (*R*)- absolute configuration at C-7, was obtained with 88% yield in optically pure form (>97% ee).

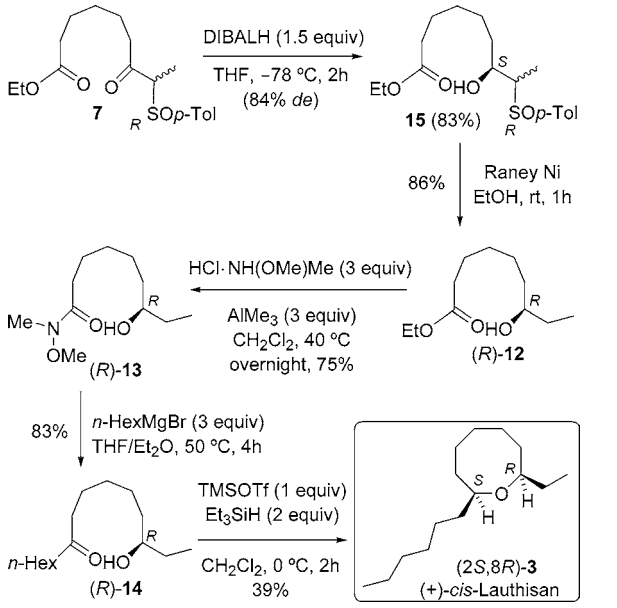
At this point, we decided to transform the hydroxy sulfinyl ester **8** into the corresponding hydroxy ketone **10**, bearing the sulfinyl group, and submit it to the reductive cyclization conditions we have previously reported for smaller cyclic ethers. Thus, the treatment of **8** with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum[14] afforded, in 70% yield, the Weinreb amide **9**, which, after reaction with *n*-hexylmagnesium bromide, gave rise to ketone **10** in 90% yield. Nevertheless, when the hydroxy sulfinyl ketone **10** was treated with Et_3SiH in the presence of TMSOTf, formation of the oxocane cyclic ether **11** was not observed.

We reasoned that, in this case, the difficulty of formation of the eight-membered ring from the acyclic precursor could be enhanced due to the presence of the bulky sulfinyl group in the starting hydroxy ketone **10**. Therefore, we decided to follow the same synthetic pathway but using the derivatives lacking the sulfoxide.

Thus, the treatment of the sulfinyl-substituted hydroxy ester **8** with Raney nickel in ethanol at room temperature for 1 h afforded the hydroxy ester **12** bearing the (*S*)- absolute configuration at the unique stereogenic center, as demonstrated after transformation into the corresponding Mosher esters,[13] in enantiomerically pure form (>97% ee). The Weinreb amide (*S*)-**13** was obtained from ester (*S*)-**12** as above in 85% yield. After addition of *n*-hexylmagnesium bromide, (*S*)-**13** was transformed into the corresponding ketone (*S*)-**14** in quantitative yield. In this case, when hydroxy ketone (*S*)-**14** was submitted to the reductive cyclization conditions (TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 2 h), we observed formation of the desired eight-membered cyclic ether **3** together with a byproduct resulting from the reduction of the carbonyl of **14** to a methylene group. After SiO_2 flash chromatography, we isolated, as the only cyclic diastereoisomer, the oxocane (−)-*cis*-lauthisan (**3**) {$[\alpha]^{20}_D = -4.0$ (*c* 0.15, $CHCl_3$)},[15] in 40% yield. This reductive cyclization was completely cis stereoselective, and the corresponding diastereoisomer, *trans*-lauthisan, was not detected in the crude reaction mixture. The relative cis stereochemistry of derivative **3** was determined after a NOESY experiment, which demonstrated the close spatial proximity between the two protons H_2 and H_8 situated on the carbons adjacent to the oxygen atom (Scheme 1).

The asymmetric synthesis of (+)-*cis*-lauthisan (**3**), shown in Scheme 2, started with the common intermediate keto sulfinyl ester **7** and followed a synthetic pathway similar to

Scheme 2. Asymmetric Synthesis of (+)-*cis*-Lauthisan (**3**)



(7) (a) Coster, M. J.; De Voss, J. J. *Org. Lett.* **2002**, *4*, 3047−3050. (b) Udding, J. H.; Giesselink, J. P. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 6671−6682. (c) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83−94. (d) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263−6276. (e) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504−2506.

(8) (+)-*cis*-Lauthisan: (a) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019−8022. (b) Kim, H.; Ziani-Cherif, Ch.; Oh, J.; Cha, J. K.; *J. Org. Chem.* **1995**, *60*, 792−793. (c) Paquette, L. A.; Sweeney, T. J. *Tetrahedron* **1990**, *46*, 4487−4502. (d) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761−764. (e) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703−1704. (f) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153−5161. (g) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565−567. (−)-*cis*-Lauthisan: (h) Suh, Y.-G.; Koo, B.-A.; Kim, E.-N.; Choi, N.-S. *Tetrahedron Lett.* **1995**, *36*, 2089−2092.

(9) Overview: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *7*, 328−401. (c) Carreño, M. C.; Urbano, A. *Synlett* **2005**, 1−25. Recent work: (d) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, A.; Urbano, A. *Org. Lett.* **2005**, *7*, 1419−1422. (e) Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, 1113−1128. (f) Carreño, M. C.; González-López, M.; Urbano, A. *Chem. Commun.* **2005**, 611−613. (g) Lanners, S.; Khiri, N.; Solladié, G.; Hanquet, G. *Tetrahedron Lett.* **2005**, *46*, 619−622. (h) Broutin, P.-E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419−4422. (i) Brinkmann, Y.; Carreño, M. C.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 4335−4338. (j) Carreño, M. C.; Sanz-Cuesta, M. J.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 3537−3540.

(10) (a) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 297−299. (b) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *J. Org. Chem.* **2003**, *68*, 7779−7787.

(11) (a) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **1988**, *44*, 3371−3380. (b) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314−4319. (c) Nicolaou, K. C. Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4137. (d) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **1995**, *117*, 10227−10238.

(12) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173−175.

(13) Both the diastereoisomeric excess and the absolute configuration of carbinols **8** and **15** were determined after desulfuration with Raney Ni followed by formation of the corresponding Mosher esters: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(14) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 916−917.

(15) Reported values for the optical rotation of (+)-*cis*-lauthisan (see ref 8) ranged from 5.0 to 13.9, and its enantiomeric excess has never been determined. We have tried different methods to check the optical purity of **3** (chiral HPLC, chiral lanthanide shift reagents), but we never observed separation between diastereomers using racemic *cis*-lauthisan.

that described for the (−)-enantiomer. In this case, the diastereodivergent reduction of the ketone functionality of **7** in the presence of DIBALH furnished, in a highly stereoselective way, a 92:8 mixture (84% de) of the corresponding (*S*)- and (*R*)- epimeric carbinols at the newly created stereogenic center.[13] After SiO_2 flash chromatography, major stereoisomer **15**, bearing the (*S*)- absolute configuration at C-7, was obtained with 83% yield in optically pure form (>97% ee).

Elimination of the sulfinyl group of derivative **15** was performed using Raney nickel and gave rise to the hydroxy ester **12** with an (*R*)- absolute configuration, as demonstrated after transformation into the corresponding Mosher esters,[13] in enantiomerically pure form (>97% ee). The transformation of ester (*R*)-**12** into ketone (*R*)-**14** was achieved after reaction with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum (75%) and condensation of the resulting Weinreb amide (*R*)-**13** with *n*-hexylmagnesium bromide (83%). Finally, the treatment of hydroxy ketone (*R*)-**14** with Et_3SiH and TMSOTf afforded, in 39% yield, (+)-*cis*-lauthisan (**3**) {$[\alpha]^{20}_D = +4.0$ (*c* 0.15, $CHCl_3$)}.[15]

In summary, we have described a short asymmetric synthesis of both enantiomers of the eight-membered cyclic ether *cis*-lauthisan (**3**) in only six steps from commercially available diethyl pimelate (**4**) with 22 and 14% overall yields for the (−)- and (+)-enantiomers, respectively.

Acknowledgment. We thank Ministerio de Ciencia y Tecnología (Grant BQU2002-03371) and Centre Nationale de la Recherche Scientifique (PICS 537) for financial support. R.D.M. wishes to thank the Ministère Français de l'Enseignement et de la Recherche for a fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and copies of ^1H NMR and ^{13}C NMR spectra for selected derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050620A