JOC*Article*

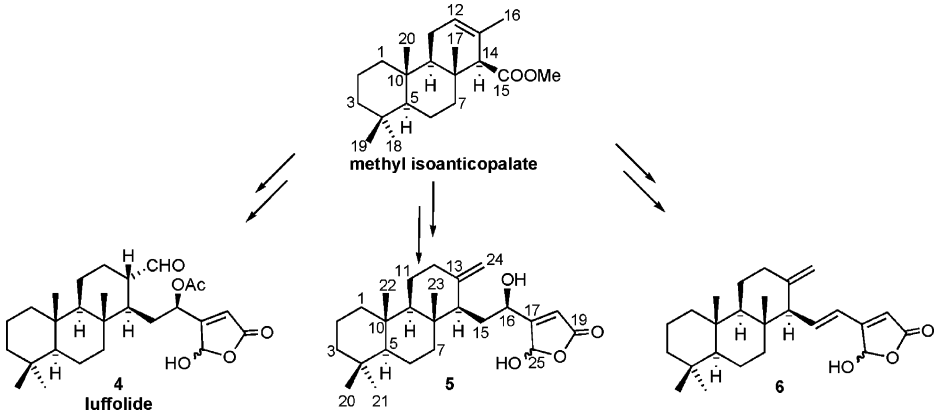
Synthesis of Three Marine Natural Sesterterpenolides from Methyl Isoanticopalate. First Enantioselective Synthesis of Luffolide

P. Basabe,* S. Delgado, I. S. Marcos, D. Diez, A. Diego, M. De Román, and J. G. Urones

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain

pbb@usal.es

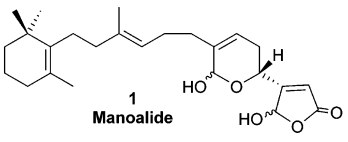
Received July 26, 2005



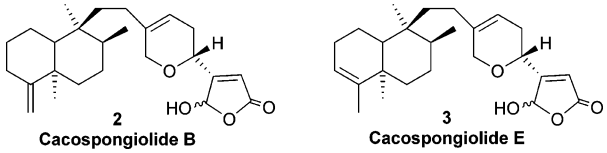
The synthesis of three marine sponge metabolites, luffolide (**4**), **5**, and **6**, are described for the first time, establishing the absolute configuration of these compounds. The key intermediate, aldehyde **17**, was obtained from methyl isoanticopalate, **11**. The addition of 3-furyllithium to **17** and subsequent photochemical oxidation give the γ-hydroxybutenolide **5** and its epimer at C-16. Sesterterpenolide **6** is obtained by dehydration of **5**. From the key aldehyde **17**, luffolide (**4**) was obtained in six steps.

Introduction

Various kinds of terpenoids bearing a γ-hydroxybutenolide moiety have been isolated from marine sources, and some of them, represented by manoalide (**1**), have received considerable attention because of their antiinflammatory activity.[1]



This compound is a potent inhibitor of the enzyme phospholipase A_2, which is intimately involved in the initial step of the inflammatory response. A number of bicarbocyclic sesterterpenoides with a carbon skeleton reminiscent of the carbon skeleton of clerodane diterpenoids, such as cacospongiolide B (**2**) and E (**3**), have biological properties that include antimicrobial, cytotoxic, and antiinflammatory activities.[2] They have the pyranofuranone moiety, present in manoalide, as part of their structures.



Recently Snapper et al.[3] described the total synthesis of cacospongiolides B and E and the initial study of the mechanism of the antiinflammatory activity. Tricarbocyclic sesterpenoides with cheilanthane skeleton have been obtained from *Spongia* species. They are exemplified by luffolide (**4**), the natural compounds **5** and **6** and petrosaspongiolides **M**−**R** (**7**−**10**) (Figure 1).

* To whom correspondence should be addressed. Fax: 34 923 294574.

10.1021/jo0515529 CCC: $30.25
Published on Web 10/15/2005

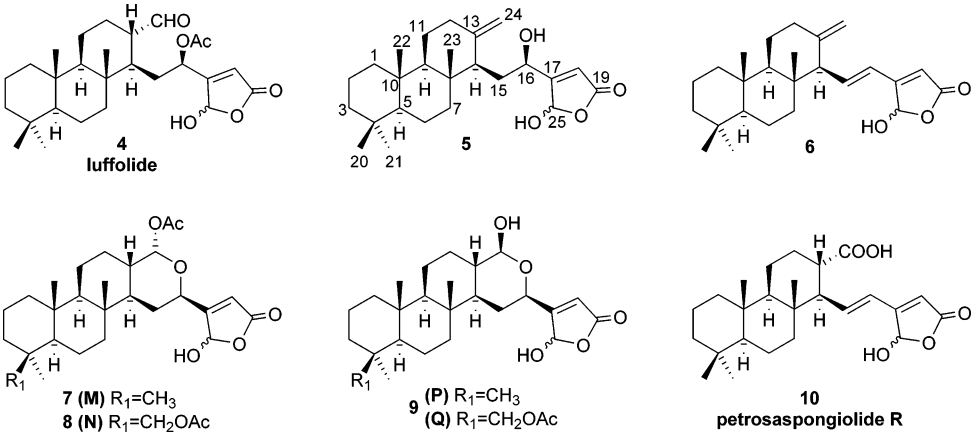


FIGURE 1. Several sesterterpenolides with a cheilanthane skeleton.

Luffolide (**4**) is a minor metabolite of the sponge *Luffariella* sp. from Palau.[4] The structure of luffolide was determined by single-crystal X-ray analysis. Sponges of the genus *Luffariella* have provided a series of sesterterpenes that are potent antiinflammatory agents;[5] luffolide also inhibits hydrolysis of phosphatidylcholine by bee venom PLA_2. However the lack of a natural compound had limited the study of the pharmacological properties of luffolide.

The sesterterpenolides **5** and **6** were isolated from marine sponge *Ircinia* sp.[6] and show a protein kinase inhibitor activity. Selective inhibitors of MSK 1 and MAPKAPK-2 protein kinase are most likely to exhibit highly specific cellular effects.

The absolute configuration was not established for compound **5** at C-16 and furthermore was isolated as inseparable 1:1 mixture of C-25 epimers.

Petrosaspongiolides **M**−**R** have been isolated from the New Caledonian marine sponge *Petrosaspongia nigra* Bergaquist.[7] Their chemical structures were determined from spectral studies. Petrosaspongiolides are potent and selective phospholipase A_2 inhibitors. They have shown an in vitro and in vivo potent antiinflammatory activity, mediated by specific inhibition of secretor phospholipase A_2.[8]

Results and Discussion

When nature provides sufficient quantity of homochiral material, which can be used as starting material for the synthesis of active compounds, enantioselective semisynthesis is a reasonable and cheap alternative to total synthesis. Several routes leading to a variety of enantiopure bioactive terpene compounds has been developed starting from natural chiral building blocks such as carvone,[9] sclareol,[10] sclareolide,[11] ent-halimic acid,[12] and zamoranic acid,[13] among others.

Methyl isoanticopalate, **11**, obtained from sclareol[14] is an excellent precursor for the synthesis of bioactive

(1) (a) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett*. **1980**, *21*, 1611−1614. (b) de Freitas, J. C.; Blankmeier, L. A.; Jacobs, R. S. *Experientia* **1984**, *40*, 864−865. (c) Glaser, K. B.; Jacobs R. S. *Biochem. Pharmacol*. **1986**, *35*, 449−453. (d) Glaser, K. B.; Jacobs R. S. *Biochem. Pharmacol*. **1987**, *36*, 2079−2086. (e) Jacobs, R. S.; Culver, P.; Langdon, R.; O'Brien, T.; White, S. *Tetrahedron* **1985**, *41*, 981−984. (f) Lombardo, D.; Dennis, E. A. *J. Biol. Chem*. **1985**, *260*, 7234−7240. (g) Deems, R. A.; Lombardo, D.; Morgan, D. P.; Mihelich, E. D.; Dennis, E. A. *Biochim. Biophys. Acta* **1987**, *917*, 258−268. (h) Kernan, M. R.; Faulkner, D. J.; Jacobs, R. S. *J. Org. Chem*. **1987**, *52*, 3081−3083.

(2) (a) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Pronzato, R.; Zavodnik, N. *J. Nat. Prod*. **1995**, *58*, 1776−1780. (b) García Pastor, P.; De Rosa, S.; De Giulio, A.; Payá, M.; Alcaraz, M. J. *Brit. J. Pharm*. **1999**, *126*, 301−311. (c) De Rosa, M.; Giordano, S.; Scettri, A.; Sodano, G.; Soriente, A.; García Pastor, P.; Alcaraz, M. J.; Payá, M. *J. Med. Chem*. **1998**, *41*, 1, 3232−3238.

(3) Cheung, A. K.; Murelli, R.; Snapper, M. L. *J. Org. Chem*. **2004**, *69*, 5712−5719.

(4) Kernan, M. R.; Faulkner, D. J.; Parkanyi, L.; Clardy, J.; Carvalho, M. S.; Jacobs, R. S. *Experientia* **1989**, *45*, 388−390.

(5) Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2004**, *67*, 1216−1238.

(6) Buchanan, M. S.; Edser, A.; King, G.; Whitmore, J.; Quinn, R. J. *J. Nat. Prod*. **2001**, *64*, 300−303.

(7) Randazzo, A.; Debitus, C.; Minale, L.; García Pastor, P.; Alcazar, M. J.; Payá, M.; Gómez Paloma, L. *J. Nat. Prod*. **1998**, *61*, 571−575.

(8) Monti, M. C.; Casapullo, A.; Riccio, R.; Gómez Paloma, L. *Bioorg. Med. Chem.* **2004**, *12*, 1467−1474.

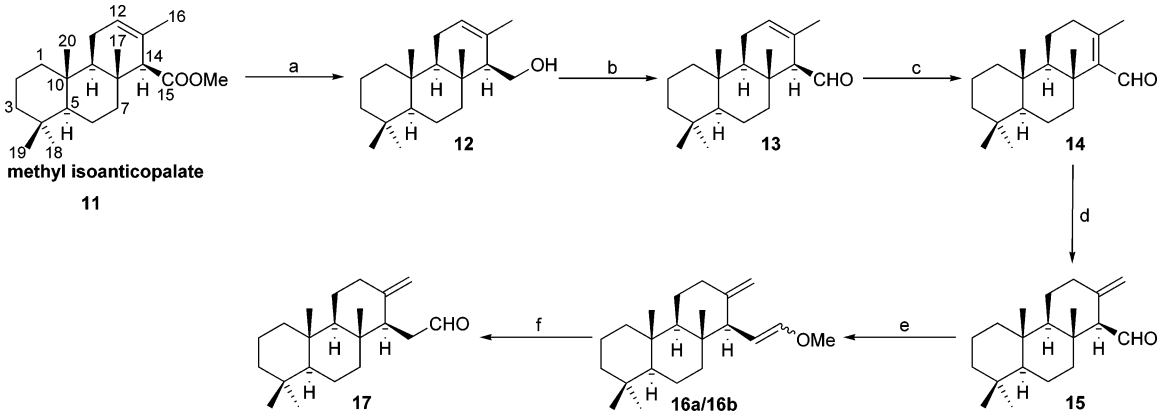
(9) (a) Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996−6000. (b) Shing, T. K. M.; Zhu, X. Y.; Yeung, Y. Y. *Chem. Eur. J.* **2003**, *9*, 5489−5500. (c) Nicolau, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, T.; Ohshima, D.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661−8673. (d) Shing, T. K. M.; Lee, C. M.; Lo, H. Y. *Tetrahedron* **2004**, *60*, 9179−9197. (e) Meulemans T. M.; Stork, G. A.; Jansen, B. J. M.; Groot, A. *Tetrahedron Lett*. **1998**, *39*, 6565−6568. (f) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *Synlett* **1994**, *2*, 733−735. (g) González, M. A.; Ghosh, S.; Rivas, F.; Fischer, D.; Theodorakis, E. A. *Tetrahedron Lett*. **2004**, *45*, 5039−5041. (h) Srikrishna, A.; Satyanarayana, G. *Org. Lett*. **2004**, *6*, 2337−2339. (i) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165−168. (j) Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B.; Giménez-Saiz, C. *Tetrahedron* **2003**, *59*, 9523−9536.

(10) (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; González Diaz, V. *Synlett* **2000**, *11*, 1561−1564. (b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181−15208. (c) Utenova, B. T.; Gundersen, L. L. *Tetrahedron Lett.* **2004**, *45*, 4233−4235. (d) Basabe, P.; Diego, A.; Díez, D.; Marcos, I. S.; Urones, J. G. *Synlett* **2000**, *12*, 1807−1809. (e) Basabe, P.; Diego, A.; Díez, D.; Marcos, I. S.; Mollinedo, F.; Urones, J. G. *Synthesis* **2002**, *11*, 1523−1529. (f) Basabe, P.; Diego, A.; Delgado, S.; Díez, D.; Marcos, I. S.; Urones, J. G. *Tetrahedron* **2003**, *59*, 9173−9177.

(11) (a) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Org. Chem.* **2003**, *68*, 6611−6618. (b) Hua, D. H.; Huang, X.; Chen, Y.; Battina, S. K.; Tamura, M.; Noh, S. K.; Koo, S. I.; Namatame, I.; Tomada, H.; Perchellet, E. M.; Perchellet, J.-P. *J. Org. Chem.* **2004**, *69*, 6065−6078. (c) Fráter, G.; Helmlinger, D.; Kraft, P. *Helv. Chim. Acta* **2003**, *86*, 678−696. (d) de la Torre, M. C.; García, I.; Sierra, M. A. *Tetrahedron Lett*. **2002**, *43*, 6351−6353. (e) Poigny, S.; Nouri, S.; Chiaroni, A.; Guyot, M.; Samadi, M. *J. Org. Chem.* **2001**, *66*, 7263−7269. (f) de la Torre, M. C.; García, I.; Sierra, M. A.*Chem. Eur. J.* **2005**, *11*, 3659−3667.

(12) (a) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Díez, D.; Basabe, P.; García, N.; Moro, R. F.; Broughton, H. B.; Mollinedo, F.; Urones, J. G. *J. Org. Chem.* **2003**, *68*, 7496−7504. (b) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Díez, D.; Basabe, P.; Hernández, F. A.; Broughton, H. B.; Urones, J. G. *Synlett* **2002**, *1*, 105−109. (c) Marcos, I. S.; Hernández, F. A.; Sexmero, M. J.; Díez, D.; Basabe, P.; Pedrero, A. B.; García, N.; Sanz, F.; Urones, J. G. *Tetrahedron Lett.* **2003**, *43*, 1243−1245. (d) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Díez, D.; Basabe, P.; Hernández, F. A.; Urones, J. G. *Tetrahedron* Lett. **2003**, *44*, 369−372.

SCHEME 1. Synthesis of Aldehyde 17[a]



[a] Reagents and conditions: (a) DIBAL-H, DCM, −78 °C, 2 h, 60%; (b) TPAP, NMO, DCM, sieves 4 Å, rt, 1 h, 98%; (c) *p*-TsOH, benzene, 80 °C, 2 h, 98%; (d) (i) LDA, HMPA, THF, −78 °C, 20 min, (ii) H_2O/THF 1:3, 70%; (e) $(MeOCH_2Ph_3)^+Cl^-$, HMDSNa, THF, −78 °C, 1 h, 80%; (f) *p*-TsOH, acetone/H_2O 45:1, rt,12 h, 97%.

natural compounds due to its tricycle framework and the stereochemistry of its chiral centers.

In this work, methyl isoanticopalate, **11**, has been transformed for the first time into luffolide (**4**) and the natural sesterterpenolides **5** and **6**. In this way, a new, easily obtained chiral starting material can be added to the chiral pool for the synthesis of marine natural products.

Synthesis of Aldehyde 17. The synthetic plan for the synthesis of the above compounds was the transformations of methyl isoanticopalate, **11**, into a key aldehyde, **17**. This aldehyde will be the starting material for the three compounds.

The synthesis of the aldehyde was accomplished in six steps from methyl isoanticopalate, **11**, as depicted in Scheme 1. Reduction of the methoxycarbonyl with DIBAL gave the alcohol **12**, thence oxidized with TPAP, Ley's oxidant,[15] to aldehyde **13**. The key isomerization of the 12,13-double bond, in aldehyde **13**, to the 13-16 position in aldehyde **15** was carried out from aldehyde **14** following the methodology of Arnó et al.[16] The aldehyde **14** was obtained by treatment of **13** with *p*-TsOH/C_6H_6 at 80 °C. When the kinetic enolate of **14**, which had been generated with LDA/HMPA at −78 °C, was treated with a 1:3 mixture of cold water/THF the aldehyde **15** was obtained in a 70%. The stereochemistry of aldehyde **15** was confirmed by NOE experiments. The experimental results indicated a clear NOE between the aldehydic proton and Me-17 and also with one of the terminal methylenic protons.

Reaction of **15** with methoxymethylenetriphenyl-phosphonium chloride in the presence of NaHMDS gave a mixture of **16a/16b** at 80%. The synthesis of **17** from **16a/16b** could be achieved with *p*-TsOH in acetone/water. In this way we have access to the key aldehyde **17**, in an easy repeated and scalable way.

Synthesis of Sesterterpenolides 5 and 6 from Aldehyde 17. Once aldehyde **17** had been obtained, the synthesis for the three natural compounds was initiated. First of all we described the synthesis of the natural sesterterpenolides **5** and **6**.

Treatment of **17** with an excess of 3-furyllithium[17] obtained by reaction of 3-bromofuran with BuLi gives a 1:1 mixture of diastereoisomers **18** and **19**, which were separated by column chromatography, as illustrated in Scheme 2.

To determine the C-16 absolute configuration of the furanoderivatives **18** and **19**, the modified Mosher's method[18] was applied. Compound **18** and **19** were treated with (+)-MTPA to afford esters **18a** and **19a**, respectively. Comparison between the NMR spectra of each parent compound and its derivative, specially the δ of H-18, confirmed the (*R*)-configuration for **18** at C-16 and the (*S*)-configuration for **19** at the same center (Scheme 2).

The oxidation of a furan ring to a γ-hydroxybutenolide following the Faulkner methodology[19] has been used by our group for the synthesis of several sesterterpenolides.[12a,b] This reaction is easy to carry out and gives excellent yields.

The application of this reaction to compound **18** gave **5** in 75% yield, whose properties were identical to those

(13) (a) Marcos, I. S.; Laderas, M.; Díez, D.; Basabe, P.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 5419−5422. (b) Marcos, I. S.; Cubillo, M. A.; Moro, R. F.; Díez, D.; Basabe, P.; Sanz, F.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 8831−8835. (c) Marcos, I. S.; Cubillo, M. A.; Moro, R. F.; Carballares, S.; Díez, D.; Basabe, P.; Llamazares, C. F.; Beneitez, A.; Sanz, F.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 977−1003. (d) Marcos, I. S.; Moro, R. F.; Carballares, S.; Urones, J. G. *Tetrahedron Lett.***1999**, *40*, 2615−2618. (e) Marcos, I. S.; Moro, R. F.; Carballares, S.; Urones, J. G. *Synlett* **2000**, *4*, 541−543.

(14) (a) Urones, J. G.; Sexmero, M. J.; Lithgow, A.; Basabe, P.; Estrella, A.; Gómez, A.; Marcos, I. S.; Díez, D.; Carballares, S.; Broughton, H. B. *Nat. Prod. Lett.* **1995**, *6*, 285−290. (b) Urones, J. G.; Marcos, I. S.; Basabe, P.; Gómez, A.; Estrella, A. *Nat. Prod. Lett.* **1994**, *5*, 217−220.

(15) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *2*, 639−666.

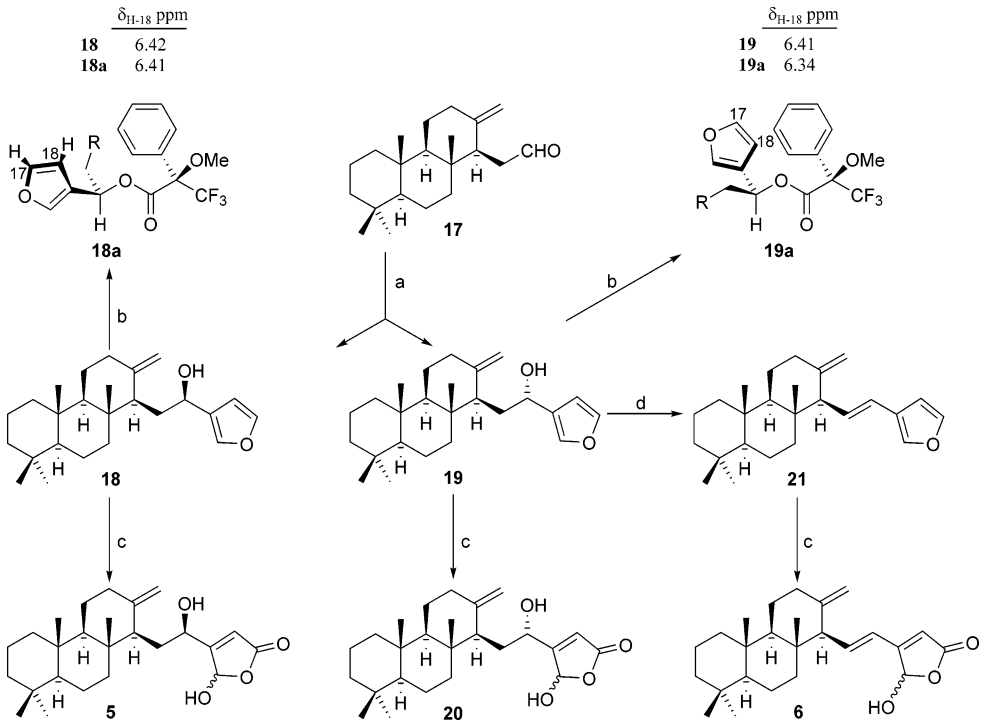
(16) Arnó, M.; González, M. A.; Zaragozá, R. J. *Tetrahedron* **1999**, *55*, 12419−12428.

(17) (a) Marcos, I. S.; Hernández, F. A.; Sexmero, M. J.; Díez, D.; Basabe, P.; Pedrero, A. B.; García, N.; Urones, J. G. *Tetrahedron* **2003**, *59*, 685−694. (b) Zoretic, P. A.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1156−1161. (c) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615−1616.

(18) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (c) Ohtami, I.; Hotta, K.; Ichikawa, Y.; Isobe, M. *Chem. Lett.* **1995**, 513. (d) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Nat. Prod.* **2002**, *65 (5)*, 661−668. (e) Seco, J. M.; Quiñoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

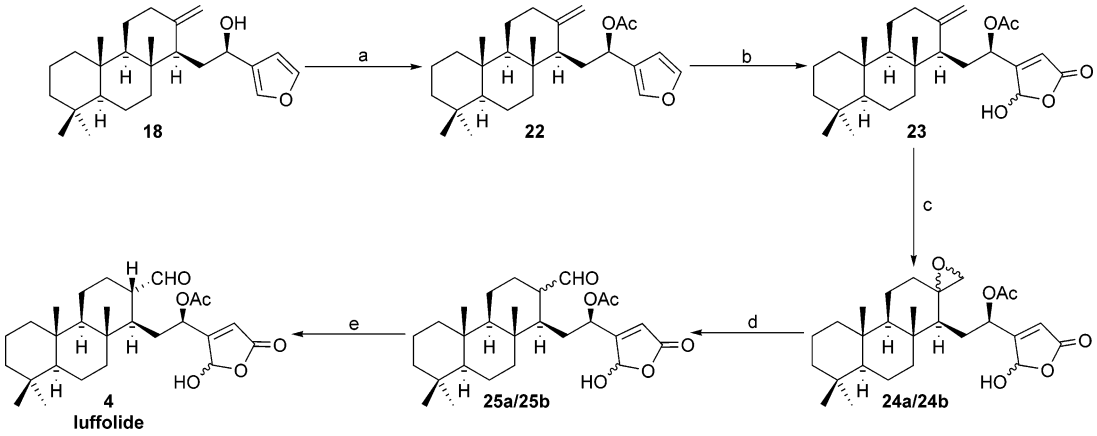
(19) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773−2776.

SCHEME 2. Synthesis of 5 and 6[a]



[a] Reagents and conditions: (a) 3-bromofurane, *n*-BuLi, −78 °C, 1 h, **18**(41%), **19** (30%); (b) (+)-MTPA, DMAP, DCC, DCM, 12 h, 99% (**18a**), 82% (**19a**); (c) $^1O_2$ *hν*, Rose Bengal, DCM, −78 °C, 3 h, 75% (**5**), 74% (**20**), 73% (**6**); (d) $POCl_3$, Py, 0 °C to rt, 4 h, 26%.

SCHEME 3. Synthesis of Luffolide[a]



[a] Reagents and conditions: (a) Ac_2O, Py, rt, 12 h, 99%; (b) $^1O_2$ *hν*, Rose Bengal, DCM, −78 °C, 3 h, 77%; (c) m-CPBA, DCM, rt, 1 h, 84%; (d) $BF_3{\cdot}Et_2O$, benzene, 10 °C, 5 min, 50%; (e) *p*-TsOH, benzene, rt, 12 h, 50%.

of the natural compound, establishing the absolute stereochemistry for this compound, which was hitherto unknown.

When the photochemical oxidation was carried out with alcohol **19** gave the product **20**, the epimer of **5** at C-16, was obtained in 77% yield.

Finally, dehydration of **19** with phosphorus oxychloride in pyridine gave the intermediate **21**, which by photochemical oxidation yields the butenolide **6** with properties identical to those of natural sesterterpenolide.

Synthesis of Luffolide 4. Finally we described the synthesis of luffolide as illustrated in Scheme 3. The alcohol **18** was converted in two steps to hydroxybutenolide **23**. The epoxidation of **23** with *m*-CPBA yielded a mixture of epoxides **24a/24b**. The key in the synthesis of luffolide is the epoxide rearrangement (**24a/24b**) in order to obtain the aldehydic function.

Even though the epoxidation reaction is not stereoselective, this step does not present a problem in our synthetic strategy, because the final step is an equilibration reaction of the aldehyde mixture leading to the thermodynamically stable one, in which the formyl group is equatorial, avoiding any 1,3 diaxial interaction with Me-23.

The treatment of epoxides **24a/24b** with $BF_3{\cdot}Et_2O$ results in rearrangement[20] to form the aldehyde **25a/25b**.

(20) (a) Trost, B. M.; Shen, H. C.; Surivet, J. P. *Angew. Chem., Int. Ed*. **2003**, *42*, 3943−3947. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 741. (c) Fracheboud, M. G.; Shimomura, O.; Hill, R. K.; Johnson, F. H. *Tetrahedron Lett*. **1969**, *10*, 3951−3952.

The equilibration reaction of the aldehyde mixture **25a/25b** with p-TsOH yielded the aldehyde **4** (50%). Comparison of the ^{1}H NMR of **4** with the ^{1}H NMR spectra reported in the literature[4] for luffolide clearly shows that they are identical. We reported the ^{13}C NMR data for luffolide and its optical rotation.

In conclusion, we have accomplished a diastereoselective synthesis of luffolide from methylisoanticopalate that establishes this compound as an excellent source for the synthesis of marine natural products. The usefulness of the aldehyde **17** in marine natural γ-hydroxybutenolide synthesis has also been demostrated.

Experimental Section

17,18,19,25-Tetranor-cheilanth-13(24)-en-16-al (17). To a 0.03 M solution of **16a/16b** (102 mg, 0.33 mmol) in acetone (11 mL) and water (0.3 mL) was added *p*-TsOH (330 mg, 1.7 mmol) at room temperature. After being stirred for 15 h, the reaction mixture was diluted with water and extracted with Et_2O. The extracts were washed with 6% aqueous $NaHCO_3$ solution and water. Evaporation of the solvent yielded the aldehyde **17** (97 mg, 97%). IR (film): 2929, 2846, 1727, 1648, 1459,1386, 1095, 1040, 893 cm^{-1}. ^{1}H NMR δ: 9.62 (1H, dd, J = 2.6, 1.2 Hz), 4.79 (1H, s), 4.37 (1H, s), 2.50−1.10 (19H, m), 0.85, 0.81, 0.80 and 0.70 (3H, s each). ^{13}C NMR δ: 203.2, 148.0, 107.3, 59.5, 56.0, 50.8, 41.5, 40.5, 39.6, 39.3, 38.7, 37.3, 39.6, 32.9, 32.8, 22.3, 21.0, 18.6, 18.2, 15.8, 15.1. EIMS *m/z* (%) 302 (M)$^+$ (18), 285 (10), 149 (20), 109 (65), 69 (100). HRMS (EI) *m/z* calcd for $C_{21}H_{34}O$ (M)$^+$ 302.2610, found 302.2614.

19,25-Epoxy-cheilantha-13(24),17(25),18-trien-(16*R*)-ol (18) and 19,25-Epoxy-cheilantha-13(24),17(25),18-trien-(16*S*)-ol (19). A solution of 3-bromofuran (0.3 mL, 3.3 mmol) in THF (7 mL) was treated dropwise with *n*-BuLi (1.6 M in hexane, 1.96 mL, 3.3 mmol) at −78 °C. After the reaction mixture was stirred for 30 min at this temperature, a solution of aldehyde **17** (100 mg, 0.33 mmol) in dry THF (9 mL) was added and stirred for an additional 45 min. The reaction mixture was treated with saturated NH_4Cl aqueous solution, warmed to room temperature and extracted with Et_2O. The organic layer was washed with brine and water and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by chromatography (Hex/EtOAc 9/1, 85/15) to yield the diastereoisomer alcohols **18** (50 mg, 41%, *R*) and **19** (37 mg, 30%, *S*). **Data for 18.** $[\alpha]^{22}_D = -11$ (c = 0.19, $CHCl_3$). IR (film): 3357, 2928, 2847, 1644, 1503, 1461, 1386, 1157, 1025, 874 cm^{-1}. ^{1}H NMR δ: 7.41 (1H, s), 7.35 (1H, s), 6.42 (1H, s), 4.87 (1H, s), 4.71 (1H, s), 4.70 (1H, t, J = 4.8 Hz), 2.35 (1H, ddd, J = 12.6, 4.0, 2.5 Hz), 1.95−0.80 (17H, m), 0.84 (3H, s), 0.80 (6H, s), 0.70 (3H, s). ^{13}C NMR δ: 148.9, 145.5, 139.6, 128.8, 108.2, 106.3, 66.2, 59.4, 56.2, 53.3, 42.0, 40.4, 39.9, 39.7, 38.1, 37.7, 33.2, 33.2, 31.8, 23.1, 21.4, 19.0, 18.6, 16.2, 15.6. EIMS *m/z* (%) 370 (M)$^+$ (27), 337 (7), 259 (23), 191 (69), 137 (33), 197 (61), 69 (100). HRMS (EI): *m/z* calcd for $C_{25}H_{38}O_2$ (M)$^+$ 370.2872, found 370. 2876. **Data for 19.** $[\alpha]^{22}_D = -48$ (c = 0.1, $CHCl_3$). IR (film): 3397, 3076, 2929, 2849, 1644, 1458, 1386, 1160, 1025, 878 cm^{-1}. ^{1}H NMR δ: 7.38 (2H, s), 6.41 (1H, s), 4.85 (1H, s), 4.67 (1H, d, J = 8.8 Hz), 4.47 (1H, s), 2.42 (1H, ddd, J = 12.6, 4.0, 2.5 Hz), 2.10−0.90 (17H, m), 0.85 (3H, s), 0.83 and 0.81 (3H, s each), 0.69 (3H, s). ^{13}C NMR δ: 148.9, 143.2, 138.4, 130.2, 108.4, 106.1, 65.2, 60.1, 56.3, 52.7, 42.0, 40.7, 40.1, 39.4, 38.1, 37.7, 33.3, 33.2, 32.6, 23.3, 21.4, 19.0, 18.6, 16.1, 15.6. EIMS *m/z* (%) 370 (M)$^+$ (13), 256 (11), 191 (17), 153 (52), 107 (55), 77 (100). HRMS (EI): *m/z* calcd for $C_{25}H_{38}O_2$ (M)$^+$ 370.2872, found 370. 2869.

(16*R*),(25*R/S*)-Dihydroxy-cheilantha-13(24),17-dien-19,-25-olide (5). Rose Bengal (3 mg) was added to a solution of **18** (16 mg, 0.04 mmol) and DIPEA (0.07 mL, 0.42 mmol) in dry CH_2Cl_2 (4 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 3 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (5 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (benzene/EtOAc 9/1) to yield **5** (45 mg, 75%) as a colorless oil. $[\alpha]^{22}_D$ = −15.5 (c = 0.45, $CHCl_3$), lit.[6] $[\alpha]^{25}_D$ = −118.65 (c = 0.44, $CHCl_3$), (personal communication from the authors state that the natural compounds could be decomposed). IR (film): 3364, 2931, 2846, 1751, 1645, 1458, 1387, 1131, 1040, 948, 908, 878 cm^{-1}. ^{1}H NMR δ **major**: 6.16 (1H, s), 6.00 (1H, s), 4.91 (1H, s), 4.77 (1H, br s), 4.68 (1H, s), 4.65 (1H, br t, J = 6.8 Hz), 2.68 (1H, br s), 2.40 (1H, br d, J = 11.8 Hz), 2.0−1.0 (17H, m), 0.86 (3H, s), 0.83 (6H, s), 0.69 (3H, s). ^{1}H NMR δ **minor**: 6.24 (1H, s), 6.00 (1H, s), 4.91 (1H, s), 4.77 (1H, br s), 4.68 (1H, s), 4.65 (1H, br t, J = 6.8 Hz), 2.73 (1H, br s), 2.40 (1H, br d, J = 11.8 Hz), 2.0−1.0 (17H, m), 0.86 (3H, s), 0.83 (6H, s), 0.70 (3H, s). ^{13}C NMR δ **major**: 169.9, 167.8, 149.5, 117.8, 106.9, 98.0, 68.6, 60.0, 56.2, 53.8, 41.9, 40.5, 40.2, 40.1, 38.1, 37.8, 33.3, 33.3, 30.0, 23.2, 21.4, 19.0, 18.6, 16.2, 15.5. ^{13}C NMR δ **minor**: 170.6, 170.4, 149.1, 118.9, 106.9, 97.5, 68.4, 60.0, 56.2, 53.7, 41.9, 40.7, 40.2, 40.1, 38.1, 37.8, 33.3, 33.3, 29.8, 23.2, 21.4, 19.0, 18.6, 16.2, 15.5. EIMS *m/z* (%) 402 (M)$^+$ (2), 362 (4), 307 (12), 154 (100), 77 (38). HRMS (EI): *m/z* calcd for $C_{25}H_{38}O_4$ (M)$^+$ 402.2770, found 402.2776.

(16*S*),(25*R/S*)-Dihydroxy-cheilantha-13(24),17-dien-19,-25-olide (20). Rose Bengal (1 mg) was added to a solution of **19** (8 mg, 0.02 mmol) and DIPEA (0.04 mL, 0.27 mmol) in dry CH_2Cl_2 (2.5 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 3 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (5 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (benzene/EtOAc 9/1) to yield **20** (6 mg, 74%). $[\alpha]^{22}_D = -54$ (c = 0.30, $CHCl_3$). IR (film): 3365, 2928, 2851, 1721, 1462, 1389, 1131, 1058 cm^{-1}. ^{1}H NMR δ **major**: 6.15 (1H, s), 6.08 (1H, s), 4.89 (1H, s), 4.67 (1H, d, J = 8.0 Hz), 4.51 (1H, s), 2.40 (1H, br d, J = 11.8 Hz), 2.0−0.85 (18H, m), 0.86, 0.82, 0.80 and 0.70 (3H, s each). ^{1}H NMR δ **minor**: 6.22 (1H, s), 6.03 (1H, s), 4.86 (1H, s), 4.60 (1H, d, J = 6.4 Hz), 4.46 (1H, s), 2.40 (1H, br d, J = 11.8 Hz), 2.10−0.85 (18H, m), 0.86, 0.82, 0.80 and 0.70 (3H, s each). ^{13}C NMR δ **major**: 171.4, 170.0, 148.3, 117.3, 106.5, 97.1, 66.7, 60.1, 56.3, 52.1, 41.9, 40.7, 40.1, 39.6, 38.0, 37.8, 33.3, 33.3, 30.3, 23.1, 21.4, 18.9, 18.6, 16.2, 15.6. ^{13}C NMR δ **minor**: 171.4, 169.9, 148.4, 117.7, 106.3, 97.5, 66.7, 60.1, 56.3, 52.2, 41.9, 40.7, 40.1, 39.6, 38.0, 37.8, 33.3, 33.3, 30.1, 23.1, 21.4, 18.9, 18.6, 16.2, 15.6. EIMS *m/z* (%) 402 (M)$^+$ (12), 384 (42), 362 (35), 154 (100), 77 (65). HRMS (EI): *m/z* calcd for $C_{25}H_{38}O_4$ (M)$^+$ 402.2770, found 402.2765.

25-Hydroxy-cheilantha-13(24),15,17-trien-19,25-olide (6). Rose Bengal (2 mg) was added to a solution of **21** (8 mg, 0.023 mmol) and DIPEA (0.05 mL, 0.24 mmol) in dry CH_2Cl_2 (3 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 3 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (5 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (Hex/EtOAc 8/2) to yield **6** (6.5 mg,

73%) as a colorless oil. $[\alpha]^{22}_D = -36.4$ ($c = 0.25$, $CHCl_3$), lit.[6] $[\alpha]^{25}_D = -36.09$ ($c = 0.53$, $CHCl_3$). UV (EtOH) λ_{max} (log ϵ) 202 (3.50), 264 (3.80) nm. IR (film): 3357, 2925, 2851, 1747, 1645, 1458, 1387, 1129, 969 cm^{-1}. ^1H NMR δ: 6.59 (1H, dd, $J = 16.0$, 10.2 Hz), 6.31 (1H, d, $J = 16.0$ Hz), 6.26 (1H, s), 5.86 (1H, s), 4.77 (1H, s), 4.40 (1H, s), 2.47 (1H, br d, $J = 10.2$ Hz), 2.45 (1H, br d, $J = 18.0$ Hz), 2.06 (1H, td, $J = 18.0$, 4.8 Hz), 1.85−1.00 (14H, m), 0.87 (3H, s), 0.85 (6H, s), 0.80 (3H, s). ^{13}C NMR δ: 170.9, 161.1, 149.1, 144.4, 123.0, 116.0, 108.7, 97.5, 62.9, 59.7, 57.2, 42.9, 42.4, 40.4, 40.3, 38.4, 36.9, 33.7, 33.8, 22.5, 21.9, 19.2, 19.0, 16.8, 16.5; HRMS (EI): *m/z* calcd for $C_{25}H_{36}O_3$ $(M)^+$ 384.2656, found 384.2650.

(16*R*)-Acetoxy-(25*R*/*S*)-hydroxy-cheilantha-13(24)17-dien-19,25-olide (23). Rose Bengal (8 mg) was added to a solution of **22** (41 mg, 0.099 mmol) and DIPEA (0.26 mL, 1.03 mmol) in dry CH_2Cl_2 (15 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 3 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (8 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (Hex/EtOAc 8/2) to yield **23** (34 mg, 77%) as a colorless oil. $[\alpha]^{22}_D = -9.05$ ($c = 0.53$, $CHCl_3$). IR (film): 3367, 2928, 2847, 1744, 1647, 1458, 1386, 1234, 1129, 1025, 950, 889 cm^{-1}. ^1H NMR δ **major**: 6.04 (1H, s), 5.90 (1H, d, $J = 9.4$ Hz), 5.38 (1H, dd, $J = 9.2$, 6.2 Hz), 5.06 (1H, d, $J = 9.4$ Hz), 4.93 (1H, s), 4.62 (1H, s), 2.39 (1H, br d, $J = 11.8$ Hz), 2.11 (3H, s), 2.0−0.96 (17H, m), 0.86 (3H, s), 0.79 (6H, s), 0.69 (3H, s). ^1H NMR δ **minor**: 6.12 (1H, m), 6.09 (1H, s), 5.51 (1H, dd, $J = 9.2$, 6.2 Hz), 4.87 (1H, s), 4.62 (1H, s), 2.38 (1H, br d, $J = 11.8$ Hz), 2.08 (3H, s), 2.0−0.96 (17H, m), 0.86 (3H, s), 0.79 (6H, s), 0.69 (3H, s). ^{13}C NMR δ **major**: 171.6, 170.4, 168.2, 147.6, 119.6, 107.6, 99.3, 69.3, 60.2, 56.3, 52.8, 42.1, 40.7, 40.2, 40.1, 38.2, 38.0, 33.7, 33.5, 28.9, 23.3, 21.6, 21.2, 19.2, 18.8, 16.4, 15.6. ^{13}C NMR δ **minor**: 171.6, 170.4, 168.2, 148.1, 120.2, 107.2, 98.6, 69.3, 60.1, 56.3, 52.4, 42.1, 40.7, 40.2, 40.1, 38.2, 38.0, 33.5, 33.5, 28.9, 23.3, 21.6, 21.2, 19.2, 18.8, 16.4, 15.6. EIMS *m/z* (%) 445 $(M + 1)^+$ (8), 427 (10), 367 (18), 289 (12), 191 (22), 154 (98), 69 (100). HRMS (EI): *m/z* calcd for $C_{27}H_{40}O_5$ $(M + 1)^+$ 445.2909, found 445.2911.

(13*S*),(16*R*)-Acetoxy-(25*R*,*S*)-hydroxy-16-oxo-cheilanth-17-en-19,25-olide (4). To an ice-cooled solution of **23** (11 mg, 0.026 mmol) in dry CH_2Cl_2 (0.7 mL) was added *m*-CPBA (18 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with water and extracted with Et_2O. The organic layer was washed successively with 10% aqueous solution of Na_2SO_3, 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the dried extract gave the mixture of epoxides derivatives **24a/24b** (10 mg, 84%). IR (film): 3337, 2933, 1744, 1657, 1579, 1458, 1388, 1236, 1129, 1048, 951, 897 cm^{-1}. ^1H NMR δ: 6.13−6.04 (2H, m), 5.58 (1H, m), 2.76 (1H, br s), 2.58 (1H, m) 2.11 (3H, s), 1.96−1.00 (19H, m), 0.88 (3H, s), 0.82 (6H, s), 0.77 (3H, s). EIMS *m/z* (%) 461 $(M + 1)^+$ (3), 307 (18), 154 (100), 89 (31).

To a stirred solution of **24a/24b** (15 mg, 0.032 mmol) in dry benzene (3 mL) at 10 °C was added $BF_3{\cdot}Et_2O$ (0.001 mL) under argon. The mixture was stirred up to 10 °C over 5 min and was poured into water (2 mL). This solution was removed by extraction with Et_2O (3 × 100 mL). The organic layer was washed with an aqueous solution of $NaHCO_3$ 10% and water, dried over Na_2SO_4 and concentrated under reduced pressure to give **25a/25b** (7.5 mg, 50%). IR (film): 2925, 2853, 1801, 1719, 1657, 1459, 1374, 1226, 1155, 1048, 998, 878 cm^{-1}. ^1H NMR δ: 9.97 (1H, s), 9.44 (1H, d, $J = 4$ Hz), 6.15−5.95 (2H, m), 5.50 (1H, m), 2.13 (3H, s), 2.15−0.90 (20H, m), 0.87 (3H, s), 0.85 (3H, s), 0.83 (3H, s), 0.81 (3H, s). EIMS *m/z* (%) 461 $(M + 1)^+$ (5), 284 (22), 256 (42), 185 (15), 129 (28).

To a solution of aldehyde **25a/25b** (4 mg, 0.0086 mmol) in dry benzene (0.6 mL) was added *p*TsOH (20 mg, 0.11 mmol), and the mixture was stirred 12 h. Then, saturated aqueous $NaHCO_3$ was added. The organic phase was separated and the aqueous phase was extracted with EtOAc. Extracts were washed with brine and dried. Evaporation of the solvent yielded the aldehyde **4** (2 mg, 50%) as an amorphous white solid, mp 130−132 °C, lit.[4] mp 123 °C ($CDCl_3$). $[\alpha]^{22}_D = -4.3$ ($c = 0.25$, $CHCl_3$). IR (film): 3367, 2925, 2851, 1751, 1720, 1459, 1372, 1232, 1133, 1040, 963, 736 cm^{-1}. ^1H NMR δ: 9.45 (1H, d, $J = 4.4$ Hz), 6.06 (1H, br s), 5.97 (1H, s), 5.29 (1H, dd, $J = 10.8$, 2.7 Hz), 2.35−0.80 (20H, m), 2.12 (3H, s), 0.87 (3H, s), 0.85 (3H, s), 0.83 (3H, s), 0.81 (3H, s). ^{13}C NMR δ: 204.2, 171.1, 168.9, 166.2, 118.8, 97.7, 70.6, 58.9, 56.3, 52.7, 47.3, 41.9, 40.3, 39.8, 38.3, 37.5, 33.3, 33.2, 32.3, 26.8, 21.4, 20.8, 18.6, 18.5, 18.2, 16.2, 14.8. EIMS *m/z* (%) 461 $(M + 1)^+$ (12), 282 (35), 289 (56), 185 (15), 154 (12). HRMS (EI): *m/z* calcd for $C_{27}H_{40}O_6$ $(M + 1)^+$ 461.2858, found 461.2860.

Acknowledgment. The authors thank the CICYT for financial support (BQU 2002-02049) and Junta de Castilla y Leon for a doctoral fellowship to S.D. and M.D.R. The authors also thank to Dr. Stephen Marsden (University of Leeds) for NMR spectra of the compound **6**.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra This material is available free of charge via the Internet at http://pubs.acs.org.

JO0515529