Synthesis of the Reported Structure of Herbolide I and Its C-11 Epimer from Artemisin

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Artemisin (1) was converted into 12 (the reported structure for herbolide I) and its C-11 epimer 19 via a synthetic pathway involving a functionality transfer from C-8 to C-9 and an A-ring refunctionalization. The ^1H and ^{13}C NMR data of synthetic products 12 and 19 reveal that the assigned structure of the natural herbolide I is erroneous.

Sesquiterpene lactones constitute a group of natural compounds widely distributed in the plant kingdom.[1] These lactones exhibit a remarkably broad range of biological activities, which include cytotoxic,[2] antibacterial, and antifungal effects[3] and antifeedant[4] properties against pest insects. Efficient total and partial synthesis of this class of compounds is a synthetic challenge that has received much attention in recent years.[5]

Herbolide I is a 9-oxyfunctionalized sesquiterpene lactone that was isolated by Segal from *Artemisia herba alba* growing in Israel.[6] On the basis of its spectroscopic properties this compound has been proposed to have structure 12. As part or our continuing research program on the synthesis of natural sesquiterpene lactones[7] we report in this paper our work concerning the chemical transformation of (−)-artemisin (1) into structure 12 and its C-11 epimer (19). Functionality transfer from C-8 in artemisin to C-9 in structure 12 is a key step in this synthesis.[8] Methodology for the functionalization of C-9 has not yet been reported, although a number of 9-oxyfunctionalized sesquiterpenes have been isolated from natural sources in recent years. Lactones, acids,[9] and other functional groups[10] in various oxidation states have been found in the eudesmane,[11] germacrane,[12] guiane,[13] and elemane[14] skeletal classes.

Results and Discussion

We had two plans for the functionality transfer from C_8 to C_9 in the eudesmane framework of artemisin (1). The first plan involved 1,2-carbonyl transposition methodology[15] from compound 5.[16] However, attempts to introduce a sulfur[17] or a selenium[18] substituent at C-9 were unsuccessful. The use of an enamine[19] or a hydrazone[20] to activate to the C_9-methylene were also unsuccessful, because preferential attack of the nucleophilic nitrogen on the lactone carbonyl group.

The alternative plan involved 8,9-epoxide 7 as a key intermediate and led, in acceptable yield, to the functionality transfer from C-8 to C-9. The starting material for this approach was 1,2-dihydroartemisin (2).

Attempts to effect dehydration of 2 via the chloride, sulfide–sulfoxide, or mesylate were unsuccessful, but elimination of the triflate[21] with Li_2CO_3/DMF[22] allowed us to isolate alkene 6 (35%) as well as 8-*epi*-1,2-dihydroartemisin (3) (21% yield) and its formate (21% yield). The formation of these latter two products involves nucleophilic attack of DMF on the triflate, and subsequent hydrolysis of the alkoxyformamidinium salt intermediate.[23] Consequently, in order to improve the yield of the dehydration product we carried out the elimination of the triflate with $LiCO_3$ in dimethylacetamide (DMA) as the solvent. Under these conditions, a 53% yield of alkene 6 was obtained as well as a 12 % yield of 8-*epi*-1,2-dihydroartemisin (3) and a 33% yield of its acetate 4. Initial attempts at epoxidation of alkene 6 with *m*-chloroperbenzoic acid,[24] hexafluoroacetone–H_2O_2,[25] or sodium perborate–acetic anhydride[26] were unsuccessful; the starting

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(1) Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105. Fraga B. M. *Nat. Prod. Rep.* **1985**, *2*, 147; **1986**, *3*, 273; **1987**, *4*, 473; **1988**, *5*, 497; **1990**, *7*, 61; **1990**, *7*, 515; **1992**, *9*, 217; **1992**, *9*, 515.

(2) Lee K. H.; Hall, I. H.; Mar, E. C.; Starnes, C. O.; El Gebaly, S. A.; Waddell, T. G.; Hadgraft, R. L.; Ruffner, C. G.; Weider, I. *Science* **1977**, *196*, 533.

(3) Picman, A. K. *Biochem. Syst. Ecol.* **1983**, *11*, 183.

(4) Van Beek, T. A.; De Groot, A. *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 513.

(5) (a) Heathcock, C. H. In *The total synthesis of natural products*; Apsimon, J., Ed., John Wiley & Sons: New York, 1973; Vol. 2, Chapter 2. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The total synthesis of natural products*; Apsimon, J., Ed., John Wiley & Sons: New York, 1983; Vol. 5. (c) Roberts, J. S. *Nat. Prod. Rep.* **1985**, *2*, 97.

(6) Segal, R.; Eden, L.; Danin, A.; Kaiser, M.; Duddeck, H. *Phytochemistry* **1984**, *23*, 2954.

(7) (a) Blay, G.; Cardona, L.; García, B.; Pedro J. R. *J. Org. Chem.* **1991**, *56*, 6172. (b) Blay, G.; Cardona, L.; García, B.; Pedro, J. R.; Serrano, A. *Tetrahedron* **1992**, *48*, 5265.

(8) A part of this work has been published in a preliminary communication. Blay, G.; Cardona, L.; García, B.; Pedro J. R. *Tetrahedron Lett.* **1992**, *33*, 5253.

(9) Bohlmann, F.; Jakupovic, J.; Schuster, A.; King, R. M.; Robinson, M. *Phytochemistry* **1984**, *23*, 1445.

(10) Ohmoto, T.; Ikeda, K.; Nomura, S.; Shimizu, M.; Saito, S. *Chem. Pharm. Bull.* **1987**, *35*, 2272.

(11) Bohlmann, F.; Ates, N.; Grenz, M. *Phytochemistry* **1982**, *21*, 1166.

(12) Adekenov, S. M.; Turmukhambetov, A. Zh.; Buketova, G. K. *Chem. Nat. Compd.* **1992**, *28*, 387.

(13) Wright, A. D.; König, G. M.; Sticher, O. *Tetrahedron* **1993**, *49*, 571.

(14) Serkerov, S. V.; Aleskerova, A. N. *Khim. Prir. Soed.* **1987**, 101.

(15) Kane, V. V.; Singh, V.; Martin, A.; Doyle, D. L. *Tetrahedron* **1983**, *39*, 345.

(16) Carda, M.; Arnó, M.; Marco, J. A. *Tetrahedron* **1986**, *42*, 3655.

(17) (a) Trost, B. M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* **1975**, *97*, 438. (b) Wilson, S. R.; Georgiadis, G. R.; Khatri, H. N.; Bartmess, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 3577.

(18) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(19) (a) Roelofsen, D. P.; van Bekkum, H. *Rec. Trav. Chim. Pays-Bas* **1972**, *91*, 605. (b) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

(20) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337.

(21) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3673.

(22) (a) Zehavi, U. *J. Org. Chem.* **1975**, *40*, 3870. (b) Corey, E. J.; Hortmann A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736.

(23) Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc. Perkin Trans. I* **1976**, 754.

(24) Pearson, A. J.; Hsu, S. Y. *J. Org. Chem.* **1986**, *51*, 2505.

(25) Heggs, R. P.; Ganem, B. *J. Am. Chem. Soc.* **1979**, *101*, 2484.

(26) Xie, G.; Xu, L.; Hu, J.; Ma, S.; Hou, W.; Tao, F. *Tetrahedron Lett.* **1988**, *29*, 2967.

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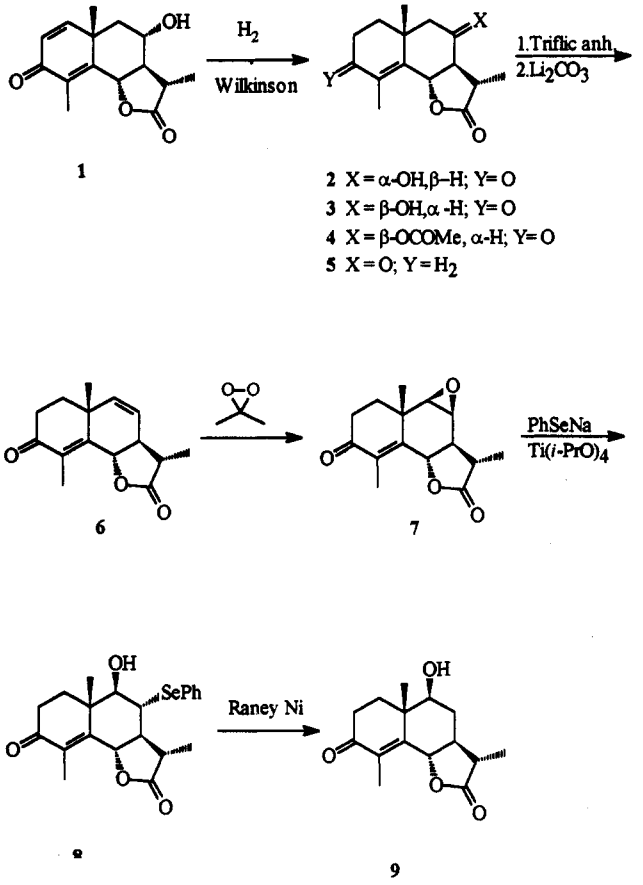
Scheme I



material was recovered unchanged. However, treatment of alkene **6** with dimethyldioxirane[27] provided epoxide **7** in excellent chemo- and stereoselectivity and yield (100%). From related work,[28] we expected that the epoxidation of **6** would take place on the less-hindered α-face. Fortunately, however, only the β-epoxide was obtained. This result can be readily explained through an examination of the stereostructure of alkene **6** obtained by molecular mechanics calculations.[29] In the minimum energy conformation, the B ring adopts a boat-like conformation that confers a convex shape to the molecule and hinders the α-face, thus making β-attack largely preferred in this molecule.

In order to open the oxirane ring, compound **7** was treated with different reagents [PhSH/HNa, PhSH/Ti(*i*-PrO$_4$].[30] Success was achieved with PhSeNa/Ti (*i*-PrO)$_4$/DMF[31] which yielded **8** (83%). Treatment of compound **8** with deactivated Raney Ni[32] effected the elimination of the phenylselenyl group and gave compound **9** (80%). With the desired functionality transfer from C_8 to C_9 accomplished, the final task for the synthesis of herbolide I involved the refunctionalization of the A ring. First, ketone **9** was transformed into **11** by thioketalization followed by

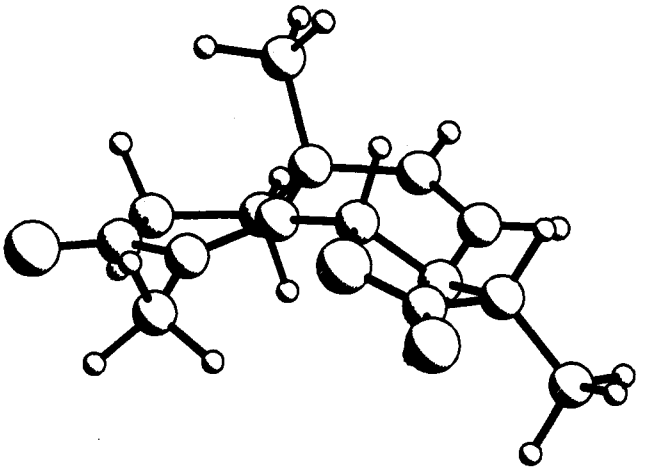
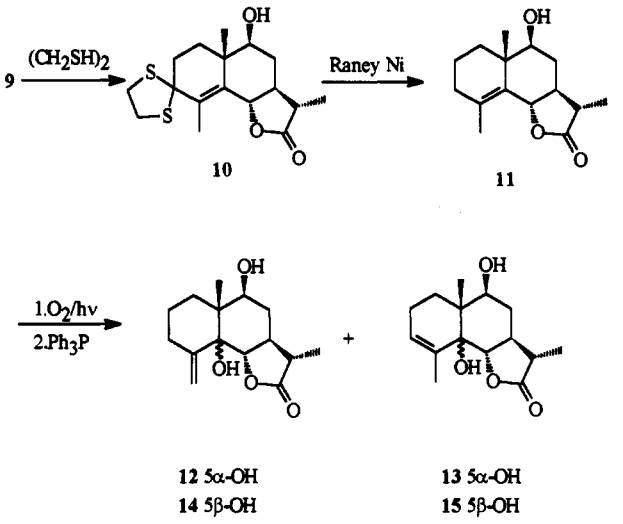


Figure 1. Computer-generated PLUTO representation of the minimum energy conformation of **9** obtained from force-field calculations.

Scheme II



desulfurization with Raney Ni. Afterwards, the introduction of the hydroxyl group at C-5 was achieved by a photochemical reaction, in which oxygen was bubbled through an irradiated ethanolic solution of **11** and deoxygenation of the resulting hydroperoxide with triphenylphosphine.[33] Although it has been reported that for related compounds[33] these conditions led to the migration of the double bond to the 4,15-position only, in our case this migration led also to the 3,4-double bond. Thus, compounds **12** and **13** were obtained in 25 and 13% yields, respectively. We could also isolate the corresponding 5-epimers,[34] **14** and **15**, in 6 and 5% yields respectively. The ^{1}H NMR spectrum of synthetic product **12** showed two broad singlets at 4.99 and 4.91 for H-15, a double doublet at 3.94 (*J* 11.0 and 4.6 Hz) for H-9, indicating the β-equatorial disposition of the hydroxyl group at this carbon and a doublet at 4.22 (*J* 10.5 Hz) for the lactonic proton H-6. The upfield shifts of H-6 and H-14 (δ 0.94) of **12** in relation with those of isomeric compound **14** (4.35 for H-6 and 1.05 for H-14) indicated the α-stereochemistry of the 5-hydroxyl group. As in artemisin and in all the

(27) Messeguer, A.; Sánchez-Baeza, F.; Casas, J.; Hammock, B. D. *Tetrahedron* **1991**, *47*, 1291.
(28) Yamakawa, K., Nishitani, K.; Murakami, A. *Chem. Pharm. Bull.* **1983**, *31*, 3411.
(29) The calculations were performed using the PCMODEL program with the MMX force field. Serena Software, Box 3076, Bloomington, IN 47402.
(30) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(31) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728.
(32) (a) Sevrin, M.; Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1976**, 2643. (b) Raney Ni W-2 was deactivated by heating the ethanolic suspension at 60 °C for 3–4 days.
(33) El-Feraly, F. S.; Benigni, D. A.; McPhail, A. T. *J. Chem. Soc. Perkin Trans. I* **1983**, 355.
(34) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408.

Table I. ^{13}C NMR Data of Compounds 2–4, 6–13, and 16–20 (δ, $CDCl_3$)

	2[a]	3	4[b]	6	7	8[c]	9[d]	10[e]	11	12[a]	13	16[c]	17	18	19[a]	20
C_1	39.0	38.2	38.3	35.0[f]	33.7[f]	35.0	34.1	35.8	36.7	32.5[f]	25.9[f]	36.6	36.6	36.8	32.1[f]	25.9
C_2	33.8	32.9	33.1	33.7[f]	32.9[f]	33.0	33.1	41.2	18.4	22.7	22.3[f]	18.5	18.5	18.5	22.5	22.3
C_3	198.3	199.0	195.2	197.9	197.1	198.2	199.2	72.4	34.2	32.2[f]	127.2	34.4	34.1	34.4	31.1[f]	127.2
C_4	128.2[f]	127.2[f]	129.0[f]	127.4[g]	127.5[g]	129.4[f]	129.1[f]	130.2[f]	127.9[f]	148.6	135.6	127.8[f]	127.9[f]	128.2[f]	148.5	
C_5	153.3[f]	154.9[f]	151.8[f]	153.1[g]	152.2[g]	149.1[f]	151.2[f]	133.2[f]	128.7[f]	76.8	73.5	129.3[f]	129.3[f]	129.0[f]	76.9	
C_6	79.2	76.3	76.3	80.7	75.3	80.2	81.0	81.9	82.4	81.7	81.8	80.1	82.5	81.4	80.6	80.6
C_7	59.3	56.3	54.3	50.7	51.3[h]	50.6[g]	47.8	48.8	49.2	43.5[g]	42.4[g]	53.6	46.3	44.7	38.8[f]	37.8[f]
C_8	69.2	64.1	67.3	120.9[h]	52.4[h]	52.0[g]	32.1	32.7	32.5	31.2[f]	31.4	30.2	31.1	29.6	29.8	28.9
C_9	52.4	48.2	45.2	138.9[h]	60.8	79.3	76.9	77.4	77.8	73.0	72.8	77.8	77.9	78.1	73.0	72.9
C_{10}	38.0	38.0	37.9	41.5	37.5	42.5	43.0	42.0	41.9	46.1	43.7	42.0	42.0	41.8	45.7	
C_{11}	41.1	35.7	36.3	40.9	38.4	41.4	40.7	40.9	40.9	41.1[g]	40.8[g]	48.8	138.5	37.9	38.6[f]	37.9[f]
C_{12}	178.2	178.3	176.7	177.6	176.2	176.7	177.8	178.2	178.9	177.4	179.1	175.9	170.2	179.5	179.9	
C_{13}	14.6	11.8	12.3	12.7	12.5	14.8	12.2	12.3	12.3	12.8	12.4	19.3[g]	118.4	9.7	9.6	9.5
C_{14}	25.1	26.1	26.0	25.5	21.5	18.0	17.6	19.3[g]	20.3	14.7	13.5	20.2[g]	19.4[g]	19.4[g]	14.5	13.4
C_{15}	11.2	10.8	11.1	10.7	10.5	10.9	11.0	16.6[g]	19.3	110.4	21.6	22.3[g]	20.0[g]	20.1[g]	110.4	21.6

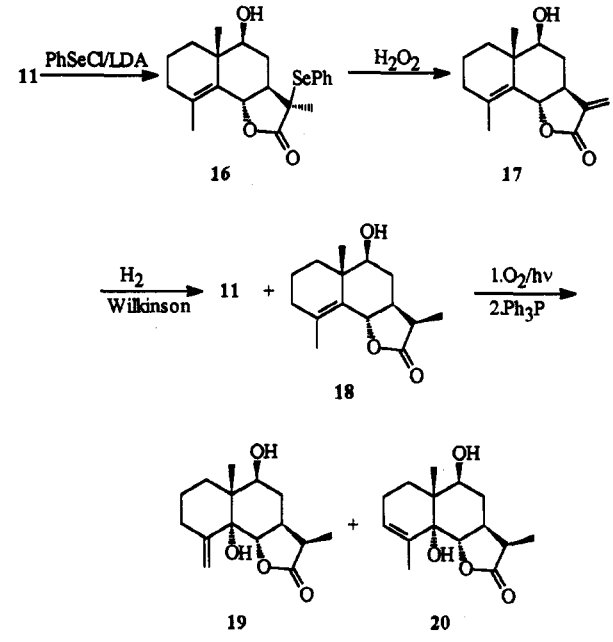
[a] In CD_3COCD_3 solution. [b] Acetate group: δ 21.0; 169.9. [c] Aromatic carbons for 8: δ 126.3, 128.3, 129.3, 134.6; for 16: 124.3, 129.1, 129.7, 138.2. [d] Assignment by heteronuclear ^1H–^{13}C NMR correlation. [e] $(CH_2S)_2$ group: δ 39.1, 40.1. [f–h] These signals may be interchanged within the corresponding spectrum.

products of the synthetic sequence, in 12 the C_{11}-methyl group is α. The α C_{11} methyl was verified from the coupling constant ($J_{7,11}$) observed for the signal of H-11, which appeared as a double quartet with coupling constants of 12 and 7 Hz, and from the chemical shift (*ca.* 12 ppm) of C-13 in the ^{13}C NMR spectra.

These data are consistent with structure 12, which had been proposed for herbolide I.[6] However, the ^1H and ^{13}C NMR spectra described for the natural product do not coincide with those of the synthetic product. The δ values of H-6 and H-9 appear at δ 4.22 and 3.94 in the synthetic product and at δ 4.48 and 4.16 in the natural product, and in the ^{13}C NMR, the value for C-13 is δ 12.8 in the synthetic product and δ 9.2 in the natural product. The values for the natural product are in good agreement with a β-methyl group at C-11,[35] and, therefore, we thought that the structure of the natural herbolide I might be C_{11}-epimer 19.

This data encouraged us to epimerize C-11. Initial attempts at epimerization via the lactone enolate[36] of 11 were unsuccessful; starting material was recovered unchanged. We also tried the epimerization via phenylseleno derivative 16, which was synthesized in good yield by allowing the lithium enolate of 11 to react with phenylselenyl chloride.[37] However the deselenization reaction with Raney Ni[32] afforded starting lactone 11. Finally, phenylselenide 16 was treated with 30% hydrogen peroxide in THF to afford dehydro derivative 17, which by hydrogenation over Wilkinson catalyst yielded a mixture of C-11 epimers 18 and 11. By photooxygenation of 18 and reduction of the resulting hydroperoxide, compounds 19 and 20 were obtained. The ^1H and ^{13}C NMR spectra of compounds 18, 19, and 20 clearly indicated a β-methyl group at C-11 (quint. at 2.6, J = 7.5 Hz for H-11 and signal at δ 9.6 for C-13). However, the ^1H and ^{13}C NMR spectra of synthetic product 19 also do not coincide with those described for the natural herbolide I; the δ value for H-9 is 3.97 for the synthetic product 19 and 4.16 for the natural product and C-9 and C-14 appear at δ 73.0 and 14.5 for 19 and at δ 71.0 and 12.8 for the natural product. In view of the ^1H and ^{13}C NMR data of synthetic products 12 and 19, we believe that the structure assigned to the natural product herbolide I is erroneous and must be revised.[38]

Scheme III



Experimental Section

All melting points are uncorrected. TLC was carried out on Merck 0.25-mm silica gel 60 HF_{254} analytical aluminum plates. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). HPLC was carried out on a Waters 590 HPLC pump using a Waters RCM cartridge (25 cm × 10 mm i.d.). IR spectra were recorded as liquid films for oils and as KBr disks for solids. Specific rotations were measured in $CHCl_3$. NMR spectra were run in $CDCl_3$ at 200.1, 299.95, or 399.95 MHz for ^1H and 50.3, 75.43, or 100.58 MHz for ^{13}C. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV.

3-Oxo-(7αH,6,11βH)-eudesma-4,8-dien-6,12-olide (6). A solution of dihydroartemisin (2)[16] (200 mg, 0.76 mmol) and pyridine (0.17 mL, 2.10 mmol) in CH_2Cl_2 (8 mL) was added dropwise with stirring over a 30-min period to a solution of triflic anhydride (0.19 mL, 1.13 mmol) in CH_2Cl_2 (10 mL) at −20 °C. After 15 min, the reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with brine, and dried over Na_2SO_4 containing a little of K_2CO_3. Filtration and solvent removal gave an unstable

(35) (a) Moss, G. P.; Pregosin, P. S.; Randall, E. W. *J. Chem. Soc. Perkin Trans. I* 1974, 1525. (b) Marco, J. A. *Phytochemistry* 1989, *28*, 3121.

(36) Miller, R. B.; Frinck, J. M. *J. Org. Chem.* 1981, *46*, 2972.

(37) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* 1974, *39*, 120.

(38) A sample of the natural herbolide I has not been available.

dark oil (305 mg), which was immediately employed in the next step without further purification.

A suspension of the resulting oil and Li_2CO_3 (460 mg, 6.2 mmol) in *N,N*-dimethylacetamide (10 mL) was heated under argon at 80 °C for 15 min. After this time, the reaction mixture was cooled in an ice bath, quenched with aqueous 10% HCl, and extracted with ethyl acetate (three times). The combined organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure followed by chromatography of the residue with hexane–ethyl acetate gave 6 (96 mg, 53%), acetate 4 (57 mg, 33%), and 8-*epi*-dihydroartemisin (3) (24 mg, 12%).

Compound 6: mp 116–117 °C (from hexane–CH_2Cl_2); $[\alpha]^{24}_D$ +42° (*c* 0.65); IR (KBr) 3050, 1780, 1660, 1010, 740 cm^{-1}; MS *m/e* 246 (M^+, 8), 231 (M^+ – Me, 7), 202 (47), 175 (30), 147 (43), 119 (37), 105 (42), 91 (100); HRMS 246.1256, $C_{15}H_{18}O_3$ required 246.1251; ^1H NMR δ 5.74 (dd, 1H, *J* = 1.3, 9.5 Hz, H-9), 5.46 (dd, 1H, *J* = 2.9, 9.5 Hz, H-8), 4.73 (dd, 1H, *J* = 1.2, 10.9 Hz, H-6), 2.67 (dddd, 1H, *J* = 1.3, 2.9, 10.9, 12.4 Hz, H-7), 2.42 (qd, 1H, *J* = 6.7, 12.5 Hz, H-11), 1.98 (d, 3H, *J* = 1.3, H-15), 1.80 (ddd, 1H, *J* =3.0, 5.8, 13.0, H-1β), 1.37 (s, 3H, H-14), 1.33 (d, 3H, *J* = 6.7, H-13).

Compound 4: mp 140–141 °C (from hexane–ethyl acetate); $[\alpha]^{24}_D$ +9° (*c* 2.6); IR (KBr) 3050, 1775, 1730, 1655, 1620, 1240, 1035 cm^{-1}; MS *m/e* 306 (M^+, 11), 264 (16), 146 (24), 218 (11), 203 (10), 190 (23), 175 (21), 43 (100); HRMS 306.1467, $C_{17}H_{22}O_5$ required 306.1461; ^1H NMR δ 5.32 (ddd, 1H, *J* = 2.5, 3.6, 5.8 Hz, H-8), 5.13 (dd, 1H, *J* = 1.4, 12.0 Hz, H-6), 2.44 (qd, 1H, *J* = 6.7, 12.9 Hz, H-11), 2.19 (dt, 1H, *J* = 2.5, 12.0 Hz, H-7), 2.13 (s, 3H, MeCO), 2.07 (dd, 1H, *J* = 2.5, 15.5, H-9β), 1.99 (d, 3H, *J* = 1.4 Hz, H-15), 1.68 (dd, 1H, *J* = 3.6, 15.5 Hz, H-9α), 1.42 (s, 3H, H-14), 1.25 (d, 3H, *J* = 6.7 Hz, H-13).

8-*epi*-Dihidroartemisin (3): mp 112–114 °C (hexane–CH_2Cl_2); $[\alpha]^{24}_D$ +29° (*c* 1.3); IR (KBr) 3400, 1775, 1650, 1610, 1040 cm^{-1}; MS *m/e* 264 (M^+, 100), 249 (M^+ – Me, 7), 246 (M^+ – H_2O, 5), 231 (5), 208 (45), 190 (10); HRMS 264.1361, $C_{15}H_{24}O_4$ required 264.1356; ^1H NMR δ 5.27 (dd, 1H, *J* = 1.4, 2.0 Hz, H-6), 4.31 (ddd, 1H, *J* = 2.5, 3.4, 5.3 Hz, H-8), 2.78 (qd, 1H, *J* = 7.2, 12.0 Hz, H-11), 2.57 (td, 1H, *J* = 6.2, 16.5 Hz, H-2β), 2.39 (td, 1H, *J* = 4.4, 16.5 Hz, H-2α), 2.00 (d, 3H, *J* = 1.4 Hz, H-15), 1.65 (dd, 1H, *J* = 3.4, 14.5 Hz, H-9α), 1.51 (s, 3H, H-14), 1.24 (3H, d, *J* = 7.2 Hz, H-13).

8β,9β-Epoxy-3-oxo-(7αH,6,11βH)-eudesm-4-en-6,12-olide (7). A 0.09 M solution of dimethyldioxirane in acetone (5.4 mL, 0.486 mmol) was added to a solution of compound 6 (94 mg, 0.382 mmol) in CH_2Cl_2 (2.7 mL) at 0 °C and the mixture stirred at this temperature for 9 h. After this time, the solvent was removed at reduced pressure to afford pure epoxide 7 (100 mg, 100%): mp 185–197 °C dec (hexane–EtOAc), $[\alpha]^{24}_D$ +41° (*c* 0.78); IR (KBr) 3020, 1780, 1665, 1630, 1190, 1230, 1020, 860 cm^{-1}, MS *m/e* 262 (M^+, 18), 247 (M^+ – Me, 9), 244 (11), 234 (9), 216 (58), 201 (35), 189 (43), 91 (100); HRMS 262.1204 $C_{15}H_{18}O_4$ required 262.1200; ^1H NMR δ 4.86 (dd, 1H, *J* = 1.0, 11.0 Hz, H-6), 3.54 (d, 1H, *J* = 3.8 Hz, H-8), 2.93 (d, 1H, *J* = 3.8 Hz, H-9), 2.81 (qd, 1H, *J* = 6.7, 12.7 Hz, H-11), 2.7–2.4 (m, 2H, 2H-2 overlapped with H-11), 2.32 (dd, 1H, *J* = 11.0, 12.7 Hz, H-7), 2.10 (dt, 1H, *J* = 6.0, 13.0 Hz, H-1α), 1.93 (d, 3H, *J* = 1.3 Hz, H-15), 1.9 (m, 1H, H-1β overlapped with H-15), 1.44 (s, 3H, H-14), 1.38 (d, 3H, *J* = 6.7 Hz, H-13).

8α-(Phenylseleno)-9β-hydroxy-3-oxo-(7αH,6,11βH)-eudesm-4-en-6,12-olide (8). Sodium borohydride (220 mg, 5.8 mmol) was added in portions to a solution of diphenyl diselenide (1.66 g, 5.0 mmol) in DMF (16 mL) under Ar at rt. The mixture was stirred at rt for 2 h, at which time no evolution of H_2 was observed. To the resulting mixture were added via syringe acetic acid (0.111 mL, 1.9 mmol), compound 10 (550 mg, 2.1 mmol) in DMF (25 mL), and titanium isopropoxide (0.66 mL, 2.2 mmol), and the mixture was stirred for 25 h. After this time, the reaction was quenched with water and extracted with ethyl acetate. Usual workup and chromatography (gradient elution 25–40% hexane–EtOAc) yielded hydroxy selenide 8 (736 mg, 83%). Compound 8: mp 167–168 °C (hexane–EtOAc), $[\alpha]^{22}_D$ +73° (*c* 1.4); IR (KBr) 3560–3300, 3060, 1780, 1670, 1620, 1580, 1030, 920, 735, 690 cm^{-1}; MS *m/e* 422, 420, 418, 417, 416 (M^+, 7, 28, 13, 5), 263 (25), 245 (45), 235 (28), 234 (25), 189 (68), 157 (87), 77 (100); ^1H NMR δ 7.58 (dd, 2H, *J* = 2.0, 7.5 Hz, aromatic), 7.4–7.2 (m, 3H, aromatic), 4.67 (dd, 1H, *J* = 1.0, 11.0 Hz, H-6), 3.22 (t, 1H, J = 11.0 Hz, H-8), 3.15 (d, 1H, *J* = 11.0 Hz, H-9 overlapped with H-8), 2.57 (qd, 1H, *J* = 6.8, 11.0 Hz, H-11), 2.5–2.4 (m, 2H, 2H-2), 2.25 (dt, 1H, *J* = 4.3, 13.5 Hz, H-1β), 2.03 (t, 1H, *J* = 11.0 Hz, H-7), 1.94 (d, 3H, *J* = 1.0 Hz, H-15), 1.61 (d, 3H, *J* = 6.8 Hz, H-13), 1.33 (s, 3H, H-14).

9β-Hydroxy-3-oxo-(7αH,6,11βH)-eudesm-4-en-6,12-olide (9). Hydroxy selenide 8 (315 mg, 0.752 mmol) in methanol (5 mL) was treated with deactivated ethanolic W-2 Raney Ni (5.5 mL, ca. 3 g) for 30 min at rt and protected from the light. After this time, the reaction mixture was filtered through a short plug of silica gel with ethyl acetate to remove the catalyst to yield compound 9 (167 mg, 85%): mp 167–169 °C (hexane–EtOAc); $[\alpha]^{24}_D$ –64° (*c* 1.3); IR (KBr) 3560–3200, 1775, 1660, 1620, 1025 cm^{-1}; MS *m/e* 264 (M^+, 66), 246 (M^+ – H_2O,10), 220 (15), 191 (14), 175 (20), 154 (100), 135 (39), 125 (53), HRMS 264.1361 $C_{15}H_{20}O_4$ required 146.1356); ^1H NMR δ 4.67 (dd, 1H, *J* = 1.2, 11.6 Hz, H-6), 3.60 (dd, 1H, *J* = 4.6, 11.5 Hz, H-9), 2.5–2.4 (m, 2H, 2H-2), 2.39 (qd, 1H, *J* = 7.2, 11.5 Hz, H-11), 2.15 (td, *J* = 4.8, 13.2 Hz, H-1β), 2.01 (d, 3H, *J* =1.2 Hz, H-15), 2.0–1.8 (1H, m, H-1α overlapped with H-7), 1.87 (dt, 1H, *J* = 3.4, 11.5 Hz, H-7), 1.72 (q, 1H, *J* = 11.5 Hz, H-8β), 1.30 (s, 3H, H-14), 1.28 (2H, 3H, *J* = 7.3 Hz, H-13).

3,3-(1,2-ethanediyldithio)-9β-hydroxy-(7αH,6,11βH)-eudesm-4-en-6,12-olide (10). A solution of compound 9 (111 mg, 0.42 mmol), 99% ethanedithiol (0,25 mL, 3.07 mmol), and boron trifluoride etherate (0.030 mL) in AcOH (1.5 mL) was stirred at rt for 8 h. After this time, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Solvent removal followed by chromatography with hexane–EtOAc (4:6) gave compound 10 (135 mg, 94%): mp 181–182 °C (hexane–EtOAc); $[\alpha]^{24}_D$ +55° (*c* 1.3), IR (KBr) 3580–3300, 1760, 1030 cm^{-1}; MS *m/e* 340 (M^+, 100), 322 (M^+ – H_2O, 1), 312 (12), 280 (58), 262 (3), 247 (12); HRMS 340.1166, $C_{17}H_{24}O_3S_2$ required 340.1161; ^1H NMR δ 4.53 (d, 1H, *J* = 11.0 Hz, H-6), 3.46 (dd, 1H, *J* = 4.7, 11.0 Hz), 3.4–3.1 (m, 4H, 2 CH_2S), 2.28 (qd, 1H, *J* = 6.9, 11.0 Hz, H-11), 2.2–2.1 (m, 1H, H-2 overlapped with H-8α), 2.13 (m, 1H, H-8α), 2.08 (s, 3H, H-15), 1.74 (dq, 1H, *J* = 2.9, 11.0 Hz, H-7), 1.57 (q, 1H, *J* = 11.0 Hz, H-8β), 1.21 (d, 3H, *J* = 6.9 Hz, H-13), 1.11 (s, 3H, H-14).

9β-Hydroxy-(7αH,6,11βH)-eudesm-4-en-6,12-olide (11). A solution of compound 10 (122 mg, 0.357 mmol) in MeOH (1.2 mL) was treated with W-2 Raney Ni (3 mL, ca. 1.7 g) for 20 min. After this time, the reaction mixture was worked up as described above and chromatographed with hexane–EtOAc (4:6) to yield compound 11 (80 mg 89%) as an oil; $[\alpha]^{24}_D$ +25° (*c* 0.85); IR (NaCl) 3580–3200, 1780, 1040, 990 cm^{-1}; MS *m/e* 250 (M^+, 38), 232 (M^+ – H_2O, 22), 217 (20), 206 (100), 189 (22), 178 (22), 137 (52); HRMS 250.1568, $C_{15}H_{22}O_3$ required 250.1563; ^1H NMR δ 4.52 (broad d, 1H, *J* = 10.5 Hz, H-6), 3.44 (dd, 1H, *J* = 4.7, 10.5 Hz, H-9), 2.28 (qd, 1H, *J* = 6.7, 10.5 Hz, H-11), 2.09 (ddd, 1H, *J* = 2.0, 4.7, 10.5 Hz, H-8α), 1.82 (broad s, 3H, H-15), 1.20 (d, 3H, *J* = 6.7 Hz, H-13), 1.08 (s, 3H, H-14).

5α,9β-Dihydroxy-(7αH,6,11βH)-eudesm-4(15)-en-6,12-olide (12). Compound 11 (83 mg, 0.332 mmol) was dissolved in absolute ethanol (34 mL), and methylene blue (3 mg) was added. Oxygen was gently bubbled through the solution. The reaction tube was submerged in a water bath (17 °C) thermostated by an external flow of cold methanol and irradiated by two lamps (Osram HQL, 400 W each) for 15.5 h. The solvent was removed, and chromatography of the residue on silica gel (hexane–EtOAc 1:1) afforded starting material (18 mg, 21%) and a mixture of four hydroperoxides (60.1 mg, 64%). The hydroperoxide mixture (57 mg) was dissolved in acetone (3.5 mL) and treated with triphenylphosphine (55 mg, 0.20 mmol). After 20 min, the mixture was concentrated in vacuo and chromatographed (hexane–EtOAc gradient elution) to give compound 13 (11.8 mg, 13%), compound 15 (4.5 mg, 5%), and a mixture of compounds 12 and 14 (29.3 mg). Compounds 12 and 14 were separated by preparative HPLC to afford compound 12 (23.1 mg, 25%) and compound 14 (5.0 mg, 6%).

Compound 12: mp 200–201 °C (hexane–EtOAc); $[\alpha]^{24}_D$ +192° (*c* 1.9); IR (KBr) 3580–3200, 1760, 1640, 1010, 900 cm^{-1}; MS *m/e* 266 (M^+, 100), 248 (M^+ – H_2O, 6), 233 (5), 220 (4), 205 (8), 193 (8), 175 (9); HRMS 266.1518 $C_{15}H_{22}O_4$ required 266.1512; ^1H NMR δ 4.99 (d, 1H, *J* = 0.9 Hz, H-15), 4.91 (s, 1H, s, H-15'), 4.22 (d,

1H, J = 10.5 Hz, H-6), 3.94 (dd, 1H, J = 4.6, 11.0 Hz, H-9), 2.55 (1H, dt, J = 6.0, 13.2 Hz, H-3), 2.4–2.3 (m, 2H, H-7, H-11); 2.10 (td, 1H, J = 3.7, 13.2 Hz, H-3β), 2.02 (ddd, 1H, J = 2.3, 4.6, 10.8 Hz, H-8α), 1.93 (dd, 1H, J = 4.5, 12.9 Hz, H-1), 1.8–1.5 (m, 4H, 2H-2, H-1β, H-8β), 1.22 (d, 3H, J = 6.1 Hz, H-13), 0.94 (s, 3H, H-14).

Compound **13**: an oil, $[\alpha]^{24}_D$ +32° (c 0.6), IR (NaCl) 3600–3180, 1760, 1650, 1000 cm^{-1}; MS m/e 266 (M^+, 7), 248 ($M^+ - H_2O$, 27), 233 (5), 215 (7), 204 (17), 187 (4), 175 (6); HRMS 266.1518 $C_{15}H_{22}O_4$, required 266.1512; ^{1}H NMR δ 5.52 (broad s, 1H, H-3), 4.04 (d, 1H, J = 10.3 Hz, H-6), 3.90 (dd, 1H, J = 4.6, 11.5 Hz, H-9), 2.4–2.1 (m, 3H, H-2, H-7, H-11), 2.01 (ddd, 1H, J = 2.5, 4.6, 11.5 Hz, H-8α), 1.85 (t, 3H, J = 1.8 Hz, H-15); 1.60 (q, 1H, J = 11.5 Hz, H-8β), 1.21 (d, 3H, J = 6.4 Hz, H-13), 0.93 (s, 3H, H-14).

Compound **14**: an oil, IR (NaCl) 3560–3200, 1760, 1640, 1010 cm^{-1}; ^{1}H NMR δ 5.03 (s, 1H, H-15), 4.97 (s, 1H, H-15′), 4.35 (d, 1H, J = 11.5 Hz, H-6), 3.89 (dd, 1H, J = 4.4, 11.1 Hz, H-9), 2.35 (m, 1H, H-11 overlapped with H-7), 2.30 (dt, 1H, J = 4.5, 13.5 Hz, H-7), 2.09 (td, 1H, J = 4.4, 14.1 Hz, H-3β), 1.23 (d, 3H, J = 6.4 Hz, H-13), 1.05 (s, 3H, H-14).

Compound **15**: an oil, IR (NaCl) 3560–3200, 1765, 1650, 1020 cm^{-1}; ^{1}H NMR δ 5.62 (broad s, 1H, H-3), 4.28 (d, 1H, J = 11.3 Hz, H-6), 3.76 (dd, 1H, J = 4.8, 10.8 Hz, H-9), 2.34 (qd, 1H, J = 6.9, 11.8 Hz, H-11), 2.2–2.0 (m, 3H, 2H-2, H-8α), 1.76 (q, 3H, J = 1.8 Hz, H-15), 1.7–1.5 (m, 4H, 2H-1, H-7, H-8β), 1.21 (d, 3H, J = 6.9, H-13), 1.07 (s, 3H, H-14).

9β-Hydroxy-11β-(phenylseleno)-(7αH,6,11β)-eudesm-4-en-6,12-olide (16). To a THF solution of lithium diisopropylamide prepared from diisopropylamine (0.13 mL, 0.91 mmol), 1.6 M n-BuLi in hexane (0.59 mL, 0.90 mmol), and 1 mL of dry THF at −78 °C was added compound **11** (67 mg, 0.27 mmol) in 1 mL of dry THF. After the solution was stirred at −78 °C for 1 h, phenylselenyl chloride (193 mg, 0.96 mmol) in 2.5 mL of dry THF and HMPA (0.16 mL) were added at −78 °C. The mixture was stirred at the same temperature for 1 h, then warmed to −30 °C, and kept at this temperature for 2 h. The reaction was quenched with 10% HCl (5 mL) at 0 °C. The product was treated as usual and chromatographed on silica gel to give 56.8 mg (52%) of compound **16** and 6.4 mg (9.6%) of starting material. Compound **16**: mp 172–174 °C (hexane–ether); $[\alpha]^{20}_D$ +31° (c 0.80); IR (KBr) 3500–3100, 1770, 1020, 730, 680 cm^{-1}; ^{1}H NMR δ 7.62 (dd, 2H, J = 1.8, 6.8 Hz, aromatic), 7.5–7.1 (m, 3H, aromatic), 4.94 (broad d, 1H, J = 9.2 Hz, H-6), 3.48 (dd, 1H, J = 4.7, 10.4 Hz, H-9), 2.06 (td, 1H, J = 4.7, 7.5 Hz, H-8α), 2.0–1.7 (m, 2H, H-7,H-8β), 1.83 (s, 3H, H-15), 1.53 (s, 3H, H-13), 1.09 (s, 3H, H-14).

9β-Hydroxy-(7αH,6βH)-eudesma-4,11(13)-dien-6,12-olide (17). To a 0 °C solution containing compound **16** (73 mg, 0.18 mmol) in 1.9 mL of THF was added 30% H_2O_2 (50 μL, 0.48 mmol). The mixture was stirred at rt for 1 h and then poured into brine. The usual procedure yielded 38.0 mg (85%) of compound **17** as an oil: $[\alpha]^{24}_D$ +28° (c 3.1); IR (NaCl) 3600–3100, 1750 cm^{-1}; MS m/e 248 (M^+, 2), 230 ($M^+ - H_2O$, 2), 204 (11), 161 (2), 159 (3), 145 (5), 139 (4), 131 (4), 109 (15), 53 (100); HRMS 248.1411, $C_{15}H_{20}O_3$ required 248.1407; ^{1}H NMR δ 6.13 (d, 1H, J = 3.4 Hz, H-13), 5.44 (d, J = 3.1 Hz, H-13′), 4.50 (dd, 1H, J = 1.3, 11.7 Hz, H-6), 3.51 (dd, 1H, J = 4.5, 11.2 Hz, H-9), 2.56 (ddddd, 1H, J = 3.1, 3.4, 3.7, 11.7, 12.2 Hz, H-7), 2.29 (ddd, 1H, J = 3.7, 4.6, 12.2 Hz, H-8α), 2.0–1.9 (m, 2H, 2H-3), 1.86 (broad s, 3H, H-15), 1.8–1.4 (m, 5H, 2H-1, 2H-2, H-8β), 1.08 (s, 3H, H-13).

9β-Hydroxy-3-oxo-(7,11αH,6βH)-eudesm-4-en-6,12-olide (18). A solution of fresh Wilkinson's catalyst (12 mg) in benzene (0.45 mL) was stirred under a H_2 atmosphere until it turned from red to yellow-orange (1 h). Then compound **17** (36 mg, 0.145 mmol) in 1.3 mL of benzene–EtOH (1:2) was introduced via syringe, and the mixture was hydrogenated for 4 h. After this time, the solvent was removed in vacuo, and the residue was chromatographed on silica gel with hexane–EtOAc (increasing polarity from 8:2) to give compound **11** (9.4 mg, 26%) and its C_{11} epimer **18** (13.8 mg, 38%). Compound **18**: an oil; $[\alpha]^{20}_D$ +62° (c 1.1); IR (NaCl) 3600–3100, 1765, 1650, 1010 cm^{-1}; MS m/e 250 (M^+, 24), 235 (M^+ – Me, 8), 232 ($M^+ - H_2O$, 9), 218 (7), 206 (38), 189 (9), 163 (7), 109 (37), 91 (54), 43 (100); HRMS 250.1568, $C_{15}H_{22}O_3$ required 250.1563; ^{1}H NMR δ 4.74 (broad d, 1H, J = 12.8 Hz, H-6), 3.48 (dd, 1H, J = 4.7, 11.0 Hz, H-9), 2.62 (quint, 1H, J = 7.6 Hz, H-11), 2.12 (ddt, 1H, J = 2.9, 7.6, 12.8 Hz, H-7), 2.0–1.7 (m, 3H, 2H-3, H-8α), 1.82 (s, 3H, H-15), 1.17 (d, 3H, J = 7.6 Hz, H-13), 1.07 (s, 3H, H-14).

5α,9β-Dihydroxy-(7,11αH,6βH)-eudesm-4(15)-en-6,12-olide (19). Compound **18** (12.0 mg, 0.048 mmol) was photooxygenated for 25 h as described above. After this time, the dye was removed by filtering the solution through a short plug of silica gel with EtOAc. After removal of the solvent, the residue (14.0 mg) without purification was diluted in acetone (1 mL) and treated with triphenylphosphine (11 mg) for 45 min. Then the solvent was removed, and the resulting residue was carefully chromatographed with EtOAc–hexane to give starting material (1.1 mg, 9%), compound **19** (5.2 mg, 41%), and compound **20** (3.0 mg, 23%). Compound **19**: mp 208–211 °C (hexane–acetone), $[\alpha]^{24}_D$ +83° (c 0.47); IR (KBr) 3530, 3600–3220, 1775, 995, 900 cm^{-1}; MS m/e 266 (M^+, 100), 248 ($M^+ - H_2O$), 233 (6), 219 (5), 205 (8), 193 (7), 175 (13); HRMS 266.1518 $C_{15}H_{22}O_4$, required 266.1512; ^{1}H NMR δ 5.01 (s, 1H, H-15), 4.94 (s, 1H, H-15′), 4.45 (1H, d, J = 11.3 Hz, H-6), 3.97 (dd, 1H, J = 4.9, 10.7 Hz, H-9), 2.85 (dddd, 1H, J = 3.8, 7.5, 11.3, 13.2 Hz, H-7), 2.66 (quint, 1H, J = 7.5Hz, H-11), 2.51 (dd, 1H, J = 6.9, 12.7 Hz, H-3α), 2.13 (broad d, 1H, J = 12.7 Hz, H-3β), 2.00 (dd, 1H, J = 5.1, 13.5 Hz, H-1α), 1.87 (ddd, 1H, J = 4.9, 7.7, 11.5 Hz; H-8α), 1.21 (d, 3H, J = 7.7 Hz, H-13), 0.93 (s, 3H, H-14).

Compound **20**: an oil; $[\alpha]^{24}_D$ +25° (c 0.31); IR (NaCl) 3570–3040, 1760, 1000, 800 cm^{-1}; MS m/e 266 (M+, 11), 249 (M^+ – OH, 14), 248 ($M^+ - H_2O$, 65), 230 (25), 221 (12), 215 (22), 204 (44), 43 (100); HRMS 266.1518 $C_{15}H_{22}O_4$ required 266.1512; ^{1}H NMR δ 5.54 (broad s, 1H, H-3), 4.27 (dd, 1H, J = 11.2 Hz, H-6), 3.93 (dd, 1H, J = 4.5, 10.8 Hz, H-9), 2.9–2.7 (m, 1H, H-7), 2.63 (q, 1H, J = 7.5 Hz, H-11), 1.55 (s, 3H, H-15), 1.18 (d, 3H, J = 7.5 Hz, H-13), 0.94 (s, 3H, H-14).

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Supplementary Material Available: Copies of ^{13}C NMR spectra of **3**, **4**, **6–13**, and **16–20** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.