diastereostereomeric mixture) δ -5.09, -4.31, -0.42, 13.55, 17.78, 22.42, 24.00, 24.55, 24.72, 25.59, 26.88, 27.63, 28.33, 28.65, 31.64, 32.91, 38.30, 44.23, 73.33, 73.49, 104.44, 104.62, 131.54, 134.94, 155.29. The relative intensities of three pairs of signals at (i) -5.09 and -4.31, (ii) 73.33 and 73.49, and (iii) 104.44 and 104.62 indicate that the material is a ca. 50:50 mixture of two diastereomers.

Methyl (5*Z*,8α,12β,13*E*)-15-(*tert*-Butyldimethylsiloxy)-9-oxo-5,13-prostadienoate (8). To a solution of 3-[(*E*)-3'-(*tert*-butyldimethylsiloxy)oct-1-enyl]-1-(trimethylsiloxy)cyclopent-1-ene (1.01 g, 2.54 mmol) in 10 mL of THF was added dropwise 1.2 mL (3 mmol) of 2.5 M *n*-BuLi under nitrogen at 0 °C. After the reaction mixture had been stirred for 10 min at 0 °C, it was cooled to -78 °C, and 0.7 mL (0.49 g, 5 mmol) of neat BEt_3 was slowly added to it. The mixture was warmed to 0 °C over 20 min. A solution of methyl (*Z*)-7-acetoxy-5-heptenoate (0.51 g, 2.54 mmol) and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) in 5 mL of THF was slowly added to the reaction mixture. The cooling bath was removed, and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was quenched by the addition of 50 mL of water, and the product was extracted with 3 × 50 mL of ether. The organic extract was washed with 50 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, concentrated, and passed through a 10 cm column (silica gel, 60-200 mesh, 5 g, *n*-hexane). Removal of the solvent under reduced pressure afforded 0.87 g (74%) of methyl (5*Z*, 8α, 12β, 13*E*)-15-(*tert*-butyldimethylsiloxy)-9-oxo-5,13-prostadienoate and its 15-epimer, which appeared to be present in approximately equal amounts as judged by the relative intensities of ^{13}C NMR signals at δ 126.98 and 127.57 as well as those at δ 131.33 and 131.68. The diastereomeric mixture showed the following ^{13}C NMR signals whose relative intensities were ≥10%: δ -5.21, -4.55, 13.65, 17.77, 22.36, 24.56, 25.51, 26.30, 27.62, 31.54, 32.62, 36.97, 38.15, 43.61, 43.96, 50.43, 54.08, 72.83, 126.98, 127.57, 129.86, 131.33, 131.68, 131.77, 134.25, 134.43, 172.14, 215.33. In addition to these signals there were minor (<5%) signals two of which appeared at δ 115.42 and 139.44. The IR and ^1H NMR spectral data of the title compound were as follows: IR (neat) 1740 (br, s), 1250 (m), 1150 (m), 1060 (m), 965 (m), 825 (m), 770 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.86 (m, 12 H), 1.0-2.5 (m, 22 H), 3.54 (s, 3 H), 3.9-4.2 (m, 1 H), 5.1-5.6 (m, 4 H).

Methyl (5*Z*,8α,12β,13*E*)-15-Hydroxy-9-oxo-5,13-prostadienoate (11-Deoxy-PGE$_2$ Methyl Ester and 11-Deoxy-15-epi-PGE$_2$ Methyl Ester) (1). A modification of a known procedure[7] was used to prepare the title compound. A solution of 0.50 g (1.07 mmol) of methyl (5*Z*,8α,12β,13*E*)-15-(*tert*-butyldimethylsiloxy)-9-oxo-5,13-prostadienoate in 1 mL of THF was added to 10 mL of acetic acid-water-THF (10:3.3:1) at room temperature. The resulting solution was heated to 50 °C for 1.5 h and cooled. The product was extracted with 3 × 50 mL of ether. The combined ether layers were washed with saturated sodium bicarbonate solution and water and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 0.33 g (89%) of 11-deoxy-PGE_2 methyl ester and 11-deoxy-15-epi-PGE_2 methyl ester. These two compounds appeared to be present in equal amounts as indicated by the ^{13}C NMR spectrum. The IR and ^1H NMR spectra are indistinguishable from those in the literature,[2a,7] and are as follows: IR (neat) 3500 (s), 1740 (s), 1725 (s), 1150 (bs) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, *J* = 7 Hz, 3 H), 1.1-2.6 (m, 22 H), 3.00 (br s, 1 H), 3.66 (s, 3 H), 3.9-4.2 (m, 1 H), 5.3-5.5 (m, 2 H), 5.5-5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.10, 22.68, 24.69, 24.82, 25.21, 26.69, 27.95, 31.87, 33.31, 37.54, 37.80, 44.14, 44.52, 51.42, 54.72, 72.18, 72.36, 127.14, 127.65, 130.50, 131.96, 132.16, 132.31, 132.48, 134.72, 173.96, 218.88.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for support of this research. We also thank Hoffmann-La Roche, Inc., for additional support and Engelhard Industries for a loan of $PdCl_2$. Professor P. L. Fuchs of our department has facilitated our literature survey.

Total Synthesis of Tetracyclic Triterpenes. 1. The (±)-5-*epi*-Euphane Ring System

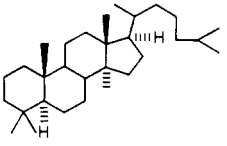
Lawrence Kolaczkowski and William Reusch*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

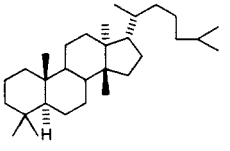
Received April 23, 1985

An A + CD Diels-Alder approach to the synthesis of tetracyclic triterpenes generated a lanostane-like configuration of the tetracyclic adduct. An efficient two-step photoepimerization at C-10 provided an equivalent euphane-like intermediate. This intermediate has been converted to the butyrospermol ring system, but unexpectedly, this proved to be a C-5 epimer (AB-cis) of the natural ring system. The configuration of the final product, 13, was established by X-ray diffraction analysis.

Of the tetracyclic triterpenes having a perhydrocyclopentaphenathrene skeleton, the lanostanes, the euphanes, and the cucurbitanes all bear transorientated methyl groups at C-13 and C-14 (CD ring fusion carbons).[1] Although the structures of the lanostane and euphane families have been known since the early 1950s, efforts to effect their total synthesis have been remarkably sparse. A landmark synthesis of lanosterol by Woodward et al. in 1954[2] and van Tamelen's polyene cyclization studies in the early 1970s[3] are the only noteworthy examples of lanostane total synthesis. No equivalent synthesis has yet been reported for any member of the large euphane family.



lanostane skeleton



euphane skeleton

The most challenging aspect of designing and executing a synthesis of these natural products lies in fixing the relative configurations of the angular methyl groups. Furthermore, the tendency of the euphane skeleton to undergo acid-catalyzed rearrangement to the more stable isoeuphane system[1] restricts the tactical options that may

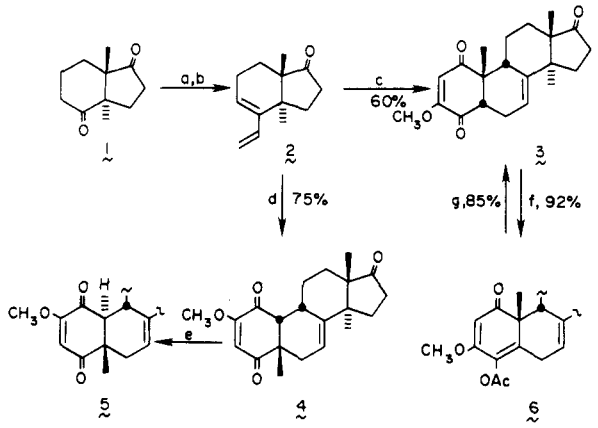
(1) Ourisson, G.; Crabbe, P.; Rodig, O. "Tetracyclic Triterpenes"; Holden-Day: San Francisco, 1964.

(2) Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D.; Kelley, R. *J. Am. Chem. Soc.* **1954**, *76*, 2852; *J. Chem. Soc.* **1957**, 1131.

(3) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1979**, *94*, 8225.

0022-3263/85/1950-4766$01.50/0

Scheme I[a]



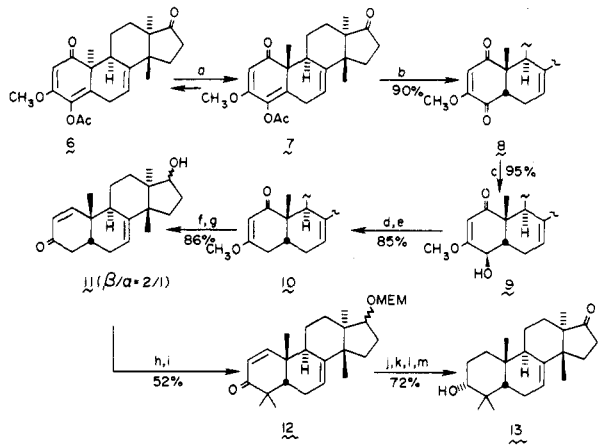
[a] (a) CH_2=CHMgCl; (b) BF_3·THF, C_6H_6; (c) 2-methoxy-5-methyl-1,4-benzoquinone, BF_3·ether, CH_2Cl_2, −16 °C; (d) 2-methoxy-5-methyl-1,4-benzoquinone, $SnCl_4$, CH_2Cl_2, 0 °C; (e) $NaHCO_3$, CH_3OH, reflux; (f) Ac_2O, NaOAc, DMAP, C_6H_6, reflux; (g) K_2CO_3, CH_3OH.

be exercised and has thus far limited the polyene cyclization approach to products having lanostane, protosterane, and isoeuphane structures.[3] Indeed, the euphanes may be yet another example of what E. J. Corey calls the "fiercely defiant" resistance of some well-known natural products to conventional synthesis.[4]

Our discovery of a facile two-step synthesis of bicyclic diketone **1** from the Wieland–Miescher ketone,[5] and its subsequent conversion to the useful diene **2** (Scheme I), provided a promising solution to configurational control of the CD ring fusion. However, our ability to transmit this control in a selective manner during construction of the AB portion of the tetracyclic target molecules remained uncertain. Fortunately, Diels–Alder cycloaddition reactions of **2** with a number of dienophiles under both thermal and acid-catalyzed conditions always gave α-endo adducts as shown in Scheme I. Since the regioselectivity of cycloaddition to 2-methoxy-5-methyl-1,4-benzoquinone could be controlled by selective Lewis acid catalysis,[6] an efficient (five-step) synthesis of lanostane intermediate **3** was in hand.[7]

In this paper, we describe a simple, high-yield method for converting **3** into its euphane-like analogue **8**, followed by transformations of **8** that give the 5-epibutyrospermol ring system **13**. We were led to this, in part, by our inability to epimerize **3** to the AB-trans isomer under conditions that gave facile isomerization of regioisomer **4** to **5**. Although bicyclic enediones analogous to the AB portion of **3** and **4** are reported to epimerize easily to their trans-fused analogues,[8a] a similar difference in behavior for a pair of regioisomeric tetracyclic quinone adducts was noted recently by Das et al.[8b] Since an enol acetate derivative, **6**, returned **3** on solvolysis, it followed that the AB-cis configuration here was more stable than the 5α-trans epimer.[9] Furthermore, recognition that **6** was a

Scheme II[a]

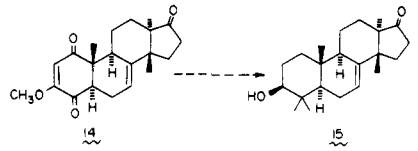


[a] (a) hν (365 nm), CH_3CN, 15 °C; (b) K_2CO_3, CH_3OH; (c) Zn, HOAc/H_2O; (d) CH_3SO_2Cl, pyridine; (e) Zn, NaI, glyme, reflux; (f) $(i\text{-Bu})_2AlH$, CH_2Cl_2; (g) HCl (4 drops), THF/H_2O; (h) $CH_3OCH_2CH_2OCH_2Cl$, $C_2H_5(i\text{-}C_3H_7)_2N$; (i) $2(CH_3)_3COK$, THF, $2CH_3I$; (j) $TiCl_4$, CH_2Cl_2; (k) H_2, Pt(Adams); (l) PDC; (m) $NaBH_4$.

cyclohexadienone that might undergo photoepimerization at C-10 provided the key to its transformation to **8**.

A careful study of the photoepimerization of 2,4-androstadien-1-one and its C-10 epimer was reported recently by G. Quinkert et al.[10] In acetonitrile solution, a clean equilibrium between these epimers was established on irradiation with 365-nm light; the natural epimer (10β) predominanted by ca. 6.5:1. Since the 9,10-anti configuration was favored in this case, we speculated that an equivalent photoepimerization of enol ether **6** would generate the euphane-like isomer **7**, assuming of course that the polar substituents at C-3 and C-4 and the Δ^7 double bond do not divert the reaction to other products. In the event, photolysis of **6** under identical conditions proceeded smoothly to a 1:6 mixture of **6** and **7** (note that the arbitrary configurations used in Scheme II are the mirror image of those in Scheme I in order to emphasize their relationship to the euphane triterpenes). In practice, these epimers are most easily separated (flash chromatography[11]) after solvolysis to a mixture of **8** and **3**. In this fashion, **8** is obtained from **3** in an overall yield of 73% (82% based on recovered **3**).

Because all previous experience indicated that the tetracyclic enedione derived from **7** would have an AB-trans configuration,[7-9] we planned the remainder of this synthesis on the assumption that the product from base-catalyzed solvolysis of **7** was **14**. Therefore, the reactions



outlined in Scheme II were expected to give the butyrospermol derivative **15**. Surprisingly, this product stubbornly resisted all our efforts to isomerize the Δ^7 double bond to the more stable $\Delta^{8(9)}$ location,[1] a transformation which would have allowed its direct comparison with a euphol degradation product obtained recently by Audouin and Levisalles.[13] Consequently, we were obliged to test our structural assignment by X-ray analysis[12] and thus found

(4) Corey, E. J.; Pearce H. *J. Am. Chem. Soc.* **1979**, *101*, 5841.
(5) Reusch, W.; Grimm, K.; Karoglan, J.; Martin, J.; Subrahamanian, K. P.; Venkataramani, P. S.; Yordy, J. *J. Am. Chem. Soc.* **1977**, *99*, 1958.
(6) Reusch, W.; Tou, J. S. *J. Org. Chem.* **1980**, *45*, 5012.
(7) Tou, J. S. Ph.D. Thesis, Michigan State University, East Lansing, 1980.
(8) (a) Bohlmann, F.; Mather, W.; Schwarz, H. *Chem. Ber.* **1977**, *110*, 2028. (b) Das, J.; Kubela, R.; MacAlpine, G.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308.
(9) This configurational preference may be due to the trans-like BC fusion in **3**. Conformational analysis demonstrates a thermodynamic advantage for cis-syn-trans perhydrophenanthrenes vs. their trans-syn-trans isomers. Johnson, W. S. *Experientia* **1951**, *7*, 315; *J. Am. Chem. Soc.* **1953**, *75*, 1493.
(10) Quinkert, G.; Englert, H.; Cech, F.; Stegk, A.; Haupt, E.; Liebfritz, D.; Rehm, D. *Chem. Ber.* **1979**, *112*, 310.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

that the AB ring fusion was cis (**13**), as shown throughout Scheme II. A careful study of molecular models of **8** and **14** has failed to disclose an explanation for the unexpected predominance of the former at equilibrium.

To effect transformation of **8** to a form suitable for geminal-dimethylation at C-4, we used a reaction sequence patterned after that developed by Speziale et. al.[14a] for the preparation of a key CD synthon in the Woodward cholesterol synthesis.[14b] Thus, zinc dust reduction of **8**, followed by mesylation and further reduction, gave the crystalline methoxy enone **10** in over 80% yield. Reduction of **10** (DIBAH) gave, after careful acid hydrolysis, a mixture of epimeric 17-alcohols (**11**) having the desired 1-en-3-one function in ring A. The Δ^1 double bond served to block enolization to C-2, and following protection of the 17-hydroxyl group as a MEM ether[15] and exhaustive methylation to a mixture of 4,4-dimethyl-17-MEM ether epimers (**12**), this superfluous function was removed by catalytic hydrogenation. Dimethylation of **11** or its MEM derivative proved to be very sluggish. The best conditions developed thus far involve treatment with excess potassium *tert*-butoxide in THF, followed by addition of excess methyl iodide. Oxidation of the deprotected epimer mixture by pyridinium dichromate (PDC)[16] yielded a diketone, which was reduced selectively to the crystalline butyrospermol derivative **13**, mp 192.5–194.5 °C, in 72% overall yield from **12**.

The X-ray crystal structure of **13** shows that ring A assumes a chair conformation in which the 3-hydroxyl group is equatorial. Even though the 4α-methyl group suffers serious crowding by the 9α-hydrogen atom and the 13α-methyl group, this conformation seems to persist in solution, as evidenced by the ^{1}H NMR signal[21] from the carbinol (C-3) proton at δ 3.31 (doublet of doublets, J apparent = 6.4 and 9.5 Hz).

Although the failure of this synthesis to give the natural euphane configuration was both surprising and disappointing, we believe that our approach to tetracyclic triterpene synthesis is potentially the most versatile and efficient yet reported. Our reasons are the following. First, the problem of AB ring fusion control can be solved in several ways. Indeed, by a small modification of Scheme II, we have made good progress to this end; and both lanostanes and euphanes should be accessible by this method. Second, the syntheses of racemic **3** and **8** described here can be modified to give pure enantiomers. The only chiral reactant (diketone **1**) comes from the Wieland–Miescher ketone, which can be prepared enantiomerically pure by using either (*R*)- or (*S*)-proline as a catalyst for the final aldol cyclization.[17] Finally, side chain attachment at the C-17 carbonyl function can in principle be effected in several different ways.[18] We have demonstrated one such method using a bicyclic model system,[19] and other promising approaches have been described.[20] Since most structural variations among lanostane and euphane triterpenes occur in the side chain, it makes sense to construct the tetracyclic core before proceeding to elaborate this feature.

Experimental Section

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere using solvents distilled from appropriate drying agents. Small-scale chromatographic separations were accomplished with the use of 2-mm silica plates (Merck F-254, 20 × 20 cm). Larger scale separations were effected by flash chromatography (40–63-nm silica gel, Merck 9385). Melting points were determined on either a Thomas-Hoover capillary melting point apparatus or a Reichert hot stage microscopic apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Mass spectra (MS) were obtained with a Finnigan 4000 GC/MS spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were taken in deuterochloroform solution with either a Varian T-60 or a Bruker WM 250 spectrometer and are calibrated in parts per million (δ) from tetramethylsilane (Me_4Si) as an internal standard. Carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker WM 250 spectrometer at 69.8 MHz using deuterochloroform as solvent and are calibrated in parts per million (δ) from Me_4Si as internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, MI.

Diels–Alder Adduct 3. To a solution of 2-methoxy-5-methyl-1,4-benzoquinone (15.2 g, 0.1 mol) in 500 mL of methylene chloride at 0 °C was added 10 mL (0.09 mol) of boron trifluoride etherate. The resulting orange-colored solution was stirred for 15 min and cooled to −15 °C, and a solution of diene **2**[21] (11.8 g, 0.062 mol) in 15 mL of methylene chloride was added slowly with stirring. After 4 h, water and methylene chloride were added, and the organic layer was washed, dried, and then condensed. This residue was stirred with aqueous sodium bisulfite solution for 1 h and then extracted with methylene chloride. The combined organic fractions were washed and dried. Evaporation of the solvent gave an off-white solid, which on trituration with ether yielded a white solid (14.0 g, 66%), identified as adduct **3** (contaminated with less than 5% isomer **4**). The minor adduct (**4**) was removed by recrystallization from cyclohexane/methylene chloride solution. Pure **3** displayed the following properties: mp 260–261 °C; mass spectrum (70 eV), m/e (relative intensity) 342 (1), 314 (15), 299 (9), 189 (11), 155 (10), 154 (100), 145 (12), 119 (15), 105 (17), 69 (10); IR ($CHCl_3$) 2950, 1740, 1710, 1675, 1605, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 3 H), 1.15 (d, 3 H, J = 0.9 Hz), 1.39 (s, 3 H), 1.40–2.80 (m, 11 H), 2.99 (dd, 1 H, J = 7.9, 10.1 Hz), 3.78 (s, 3 H), 5.29 (dd, 1 H, J = 3.1, 6.4 Hz), 5.67 (s, 1 H); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 219.54, 201.54, 196.02, 159.11, 145.15, 115.74, 109.54, 56.31, 56.10, 50.90, 50.66, 46.75, 42.31, 34.20, 30.76, 27.58, 25.94, 25.35, 24.55, 23.38, 17.58. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.37; H, 7.70.

Diels–Alder Adduct 4. To a solution of 0.152 g (1 mmol) of 2-methoxy-5-methyl-1,4-benzoquinone in 8 mL of methylene chloride at 0 °C was added 0.8 mL (0.8 mmol) of a 1 M solution of stannic chloride in methylene chloride, and this mixture was stirred for 1 h. A solution of 0.114 g (0.6 mmol) of diene **2** in 9 mL of methylene chloride was then added, and after being stirred at this temperature for about 1.5 h, the reaction mixture was decomposed by the addition of 10 mL of water. The organic layer was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were worked up in the same manner as the corresponding boron trifluoride catalyzed reaction. The product was triturated with ether, and the resulting colorless solid was recrystallized from methylene chloride/ether to give 0.152 g (74%) of **4**. Pure **4** displayed the following properties: mp 239.5–241.0 °C; IR (KBr) 2950, 1740, 1710, 1665, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.2 (s, 3 H), 1.5 (s, 3 H), 1.6–3.0 (m, 12 H), 3.7 (s, 3 H), 5.2 (dd, 1 H), 5.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 217.8, 201.4, 194.1, 161.8, 143.8, 115.5, 108.3, 56.3, 55.8, 51.0, 50.3, 46.8, 34.9, 34.2, 31.7, 30.6, 26.5, 25.0, 23.8,

(12) X-ray analyses were conducted by Professor Paul Williard, Department of Chemistry, Brown University, Providence, RI 02912.
(13) Audouin, M.; Levisalles, J. *Tetrahedron* **1983**, *39*, 2799.
(14) (a) Speziale, A. J.; Stephens, J.; Thompson, Q. E. *J. Am. Chem. Soc.* **1954**, *76*, 5011. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamer, W. *J. Am. Chem. Soc.* **1951**, *73*, 1547, 1548, 2403; **1952**, *74*, 4223.
(15) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(16) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(17) (a) Gutzwiller, J.; Buchschacher, P.; Furst, A. *Synthesis* **1977**, 167. (b) Hajos, Z. G.; Parrish, D. *J. Org. Chem.* **1974**, 1615. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.
(18) (a) Piatak, D.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. (b) Redpath, J.; Zeelen, F. *Chem. Soc. Rev.* **1983**, *12*, 75.
(19) Gibson, J. R.; Reusch, W. *Tetrahedron* **1983**, *39*, 55.
(20) (a) Krief, A.; Schauder, J. *Tetrahedron Lett.* **1982**, *23*, 4389. (b) Midland, M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725.
(21) LaBlance-Combier, a.; Levisalles, J.; Pete, J.-P.; Rudler, H. *Bull. Soc. Chim. Fr.* **1963**, 1689.

21.3, 20.9; UV λ_{max} (EtOH) 268 nm (ϵ 1.5 × 10^4); mass spectrum (70 eV), m/e (relative intensity) 342 (1), 327 (4), 314 (100), 299 (69), 281 (14), 105 (33), 91 (33), 69 (56). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.75; H, 7.75.

Epimerization of 4 to 5. To a solution of 0.025 g of sodium bicarbonate in 7 mL of methanol was added 100 mg (0.29 mmol) of **4**, and the resulting solution was refluxed overnight. The cooled reaction mixture was diluted with water and extracted with methylene chloride. The combined organic extracts were washed, dried, and evaporated. Crystallization of the residue from methylene chloride/cyclohexane gave 80 mg (80%) of **5**, mp 218–220 °C. Pure **5** displayed the following properties: IR ($CHCl_3$) 2920, 1750, 1725, 1665, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.24 (s, 3 H), 1.39 (s, 3 H), 1.49–2.95 (m, 11 H), 2.51 (ddd, 1 H, J = 1.8, 9.8, 19.2 Hz), 3.77 (s, 3 H), 5.27 (dd, 1 H, J = 2.7, 7.0 Hz), 5.78 (s, 1 H); mass spectrum (70 eV), m/e (relative intensity) 342 (1), 327 (1), 314 (33), 299 (27), 145 (23), 131 (31), 126 (22), 125 (26), 119 (25), 105 (46), 91 (48), 79 (22), 77 (27), 69 (100).

Enol Acetate 6. A mixture of triketone **3** (8.4 g, 24.6 mmol), anhydrous sodium acetate (4.03 g, 49.2 mmol), and 4-(dimethylamino)pyridine (DMAP) (20 mg, 0.16 mmol) was added to 300 mL of 2:1 (v/v) benzene and acetic anhydride. After heating under reflux for 4 days, the mixture was cooled to room temperature and filtered to remove sodium acetate. The solvent was removed under vacuum and the resulting solid dissolved in methylene chloride, washed with water and brine, and dried over sodium sulfate. Removal of solvent yielded a solid, which on separation by flash chromatography (silica, 40% methylene chloride/ether) yielded 8.7 g (92%) of **6** as the lower R_f components and 0.4 g (5%) of unreacted **3** as the higher R_f component. An analytical sample of **6** was prepared by crystallization from ethyl acetate/petroleum ether. Characterization properties are as follows: mp 195–197 °C; mass spectrum (70 eV), m/e (relative intensity) 384 (3), 342 (24), 327 (15), 324 (22), 299 (11), 129 (11), 128 (10), 119 (11), 115 (11), 105 (18), 91 (16), 69 (20), 55 (13), 43 (100), 41 (13); IR ($CDCl_3$) $\bar{\nu}_{max}$ 2950, 1760, 1740, 1675, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) ± 0.97 (s, 3 H), 1.26 (s, 3 H), 1.50 (s, 3 H), 2.26 (s, 3 H), 1.60–3.10 (m, 11 H), 3.75 (s, 3 H), 5.43 (s, 1 H), 5.56 (q, 1 H).

Treatment of **6** (20 mg) with methanolic potassium carbonate (5 mL of methanol containing 10 mg of K_2CO_3) for 10 min gave a brown solution, which on workup and TLC yielding triketone **3** (12 mg).

Enol Acetate 7. A solution of **6** (1.5 g, 3.9 mmol) in 1 L of dry acetonitrile was deoxygenated by bubbling a stream of dry argon through it for 15 min. The solution was then irradiated for 1.5 h with a Hanovia medium-pressure mercury lamp (450 W) filtered by a saturated copper(II) sulfate solution. The filter solution was cooled by an ice–calcium chloride bath and circulated through a jacketed vessel surrounding the lamp. Removal of the solvent yielded 1.5 g of a gummy yellow solid. Separation of products was difficult but was accomplished on a small scale (150 mg) by preparative TLC (silica, ether, four passes). Three components were isolated: R_f 0.58 (8.4 mg), not identified; R_f 0.50 (109 mg), **7**; R_f 0.44 (19 mg), **6**. Characteristic properties of **7** are as follows: mp 176–177.5 °C; mass spectrum (70 eV), m/e (relative intensity) 384 (8), 342 (42), 207 (16), 204 (14), 181 (20), 167 (35), 166 (83), 161 (18), 119 (20), 105 (17), 69 (21), 43 (100); IR ($CDCl_3$) 2990, 1785, 1755, 1645, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.97 (s, 3 H), 1.06 (s, 3 H), 1.27 (s, 3 H), 2.27 (s, 3 H), 0.80–3.30 (m, 11 H), 3.77 (s, 3 H), 5.43 (d, 1 H, J = 3.9 Hz), 5.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 218.87, 200.72, 199.10, 168.67, 164.85, 143.50, 142.41, 117.59, 99.92, 56.25, 51.14, 50.25, 46.73, 43.11, 34.14, 31.08, 26.88, 26.23, 24.17, 23.25, 20.23, 17.35, 15.09; high-resolution mass spectrometry (performed at Dow Chemical Co.), calcd for $C_{23}H_{28}O_5$ m/e 384.1937, found m/e 384.1950.

Triketone 8. The mixture of enol acetates **6** and **7** (2.0 g, 5.2 mmol) from the photoequilibrium was dissolved in 100 mL of dry methanol. Potassium carbonate (0.5 g, 3.6 mmol) was then added in one portion, and the mixture was stirred for 10 min. Filtration followed by solvent removal yielded a brown solid, which was dissolved in methylene chloride and washed with 10% aqueous acetic acid, water, and brine. The aqueous phase was extracted with methylene chloride. The combined organic phases were dried over sodium sulfate and evaporation of the solvent yielded a brown solid. Trituration with ether gave 1.5 g of a light yellow solid, which on flash chromatography (silica gel, 5% methylene chloride/ether) yielded two products, **3** (0.25 g) and **8** (1.25 g). Characteristic properties of **8** are as follows: mp 229–232 °C; mass spectrum (70 eV), m/e (relative intensity) 342 (19), 299 (10), 211 (15), 171 (16), 138 (12), 119 (16), 114 (100), 105 (29), 91 (19), 86 (32), 69 (28), 55 (12), 44 (15); IR (CH_2Cl_2) 2990, 1750, 1725, 1680, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.91 (s, 3 H), 0.97 (s, 3 H), 1.34 (s, 3 H), 1.30–3.15 (m, 12 H), 3.81 (s, 3 H), 5.46 (q, 1 H, 5.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 218.5, 201.5, 201.5, 193.3, 162.1, 141.8, 117.9, 109.5, 56.3, 53.5, 52.1, 50.5, 46.6, 40.1, 34.1, 30.7, 26.9, 24.5, 23.7, 21.1, 19.2, 14.3.

Alcohol 9. Triketone **8** (1.5 g, 4.39 mmol) and zinc dust (0.5 g) were added to 60 mL of 2:1 (v/v) acetic acid/water. After the mixture was stirred at room temperature for 1.5 h, the unreacted zinc was removed by filtration, washed several times with hot methanol, and discarded. The combined organic and aqueous phases were extracted with ether (five times), and the combined ether phases were then washed with saturated sodium bicarbonate, water, and brine. After drying over sodium sulfate, the ether solution was evaporated to give 1.43 g (95%) of **9** as a white solid. An analytical sample was prepared by recrystallization from methanol. Characteristic properties of **9** are as follows: mp 256.5–257 °C; mass spectrum (70 eV), m/e (relative intensity) 344 (10), 155 (17), 154 (100), 123 (13), 56 (8); IR ($CDCl_3$) 3585 (s), 3545 (br), 2240, 1724, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.00 (s, 3 H), 1.02 (s, 3 H), 1.08 (s, 3 H), 1.20–2.75 (m, 12 H), 2.99 (d, 1 H, J = 2.8 Hz), 3.78 (s, 3 H), 4.34 (dd, 1 H, J = 2.4, 10.0 Hz), 5.31 (s, 1 H), 5.49 (q, 1 H, J = 3.1 Hz); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 202.0, 189.0, 173.7, 143.4, 118.3, 100.2, 68.1, 56.1, 50.5, 47.6, 46.8, 46.2, 36.5, 34.2, 30.9, 27.2, 24.6, 24.1, 24.0, 18.6, 14.3. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.39; H, 8.16.

Methoxy Enone 10. Alcohol **9** (1.36 g, 3.95 mmol) was dissolved in 50 mL of dry pyridine and cooled to 0 °C. Mesyl chloride (0.62 mL, 0.91 g, 6.3 mmol) was added with stirring, and this mixture was stored in the freezer overnight. Pyridine hydrochloride was removed by filtration, and after removal of the solvent under vacuum, the residue was dissolved in methylene chloride and washed with water and brine and dried over sodium sulfate. Removal of solvent by rotary evaporation yielded 1.56 g (94%) of the corresponding mesylate. Recrystallization from methylene chloride/heptane gave a white crystalline solid: mp 196–198 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.01 (s, 3 H), 1.05 (s, 3 H), 1.12 (s, 3 H), 1.25–2.65 (m, 12 H), 3.17 (s, 3 H), 3.82 (s, 3 H) 5.34 (d, 1 H, J = 9.5 Hz), 5.41 (d, 1 H, J = 1.2 Hz, 5.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 200.3, 189.4, 168.8, 143.5, 117.6, 102.3, 78.1, 56.4, 48.4, 44.8, 39.1, 36.6, 34.1, 30.9, 27.2, 24.6, 24.1, 18.6, 14.0. Anal. Calcd for $C_{22}H_{30}O_6S$: C, 62.54; H, 7.16; S, 7.59. Found: C, 62.71; H, 7.14; S, 7.51.

The mesylate (1.0 g, 2.37 mmol), sodium iodide (1.78 g, 11.8 mmol), and zinc dust (1.54 g, 23.6 mmol) were added to 20 mL of dry glyme and heated under reflux for 3 h. After cooling to room temperature and filtering, the solution was diluted with water and extracted with ether. The combined ether extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent yielded 0.698 g (89%) of **10** as a white powdery solid. An analytical sample of **10** was prepared by recrystallization from ether (white needles). Characteristic properties of **10** are as follows: mp 215–217 °C; mass spectrum (70 eV), m/e (relative intensity) 328 (47), 313 (14), 230 (17), 215 (19), 213 (23), 139 (95), 138 (100), 119 (37), 105 (38), 99 (19), 91 (19), 40 (20); IR ($CDCl_3$) 2975, 1740, 1620, 1390, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.01 (s, 3 H), 1.05 (s, 3 H, 1.06 (s, 3 H), 1.35–2.80 (m, 14 H), 3.70 (s, 3 H), 5.28 (d, 1 H, J = 1.4 Hz), 5.44 (dd, 1 H, J = 2.8, 6.5 Hz); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 202.94, 189.26, 175.42, 143.87, 117.50, 100.41, 55.53, 50.57, 46.84, 46.13, 38.25, 34.67, 34.14, 32.99, 30.87, 28.70, 27.11, 24.64, 23.94, 18.41, 14.20. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.89; H, 8.44.

Enones 11β and 11α. Compound **10** (1.10 g, 3.35 mmol) was dissolved in 20 mL of dry methylene chloride and cooled to 0 °C. To this solution was added 10 mL of 1 M diisobutylaluminum hydride (DIBAL) in hexane (10 mmol). After the mixture was stirred for 1.25 h, excess hydride was destroyed by the addition of 10 mL of saturated sodium potassium tartrate. The reaction mixture was then extracted with ether, and these extracts yielded

1.10 g (99%) of a white solid, which slowed a single spot on TLC (silica, ether). This product was dissolved in 100 mL of 4:1 (v/v) THF/water along with 4 drops of concentrated HCl. The resulting solution was stirred at room temperature overnight, diluted with water, and then extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and brine and dried over sodium sulfate. Evaporate of solvent yielded a light yellow solid, which by TLC (silica, ether) proved to be a mixture of three products. Flash chromatography (silica, ether) gave 11β (R_f 0.43; 578 mg, 58%), 11α (R_f 0.35; 278 mg, 28%), and a small amount of material which was not identified. The total yield (11β + 11α) was 86%.

Characteristic properties of 11β are as follows: mp 181–183 °C; mass spectra (70 eV), m/e (relative intensity) 300 (1), 285 (7), 267 (4), 192 (67), 174 (49), 159 (96), 109 (100), 105 (58), 91 (49), 79 (39), 41 (46); IR (CH_2Cl_2) 3625 (sh), 3490 (br, 2975, 2910, 1700, 1325 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.77 (s, 3 H), 1.06 (s, 3 H), 1.22 (s, 3 H), 1.20–2.80 (m, 15 H), 3.78 (dd, 1 H, J = 1.7, 7.5 Hz), 5.31 (q, 1 H, J = 3.1 Hz), 5.96 (d, 1 H, J = 10.1 Hz), 6.97 (d, 1 H, J = 10.1 Hz); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 200.42, 162.72, 146.08, 128.15, 116.57, 79.44, 49.74, 46.64, 41.81, 39.93, 39.75, 37.76, 35.22, 33.22, 29.22, 28.34, 27.99, 25.24, 19.64, 18.99. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.95; H, 9.31.

Characteristic properties of 11α are as follows: mp 168–169 °C; mass spectrum (70 eV), m/e (relative intensity) 300 (3), 285 (9), 192 (56), 177 (18), 159 (25), 133 (32), 119 (37), 109 (100), 91 (58), 79 (52), 41 (48); IR (CH_2Cl_2) 3610 (s), 3465 (br), 2965, 2890, 1680, 1665, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.88 (s, 3 H), 1.04 (s, 6 H), 1.40–2.80 (m, 15 H), 4.10 (dd, 1 H, J = 6.9, 8.7 Hz), 5.28 (q, 1 H, J = 3.1 Hz), 5.96 (d, 1 H, J = 10.1 Hz), 6.96 (d, 1 H, J = 10.1 Hz); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 201.12, 162.38, 145.20, 127.91, 116.40, 80.20, 48.54, 43.92, 41.49, 39.40, 39.31, 37.43, 33.30, 30.16, 29.81, 28.87, 27.05, 20.67, 19.40, 18.37. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.92; H, 9.29.

MEM Ether Derivatives. This procedure will be illustrated for a single C-17 epimer (11β). Normally, mixtures of β- and α-epimers were used.

11β (700 mg, 2.33 mmol) was dissolved in 3 mL of methylene chloride in a dry 10-mL pear-shaped flask with a side arm. To this solution was added (β-methoxyethoxy)methyl chloride (MEMCl) (400 μL, 3.5 mmol), followed by diisopropylethylamine (610 μL, 3.5 mmol). After the mixture was stirred at room temmpature for 3 h, the starting material was no longer evident by TLC analysis (silica, ether) and the reaction was halted. After addition of 5 mL of water, the organic phase was separated, and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed with brine and dried over sodium sulfate. Removal of the solvent by rotary evaporation yielded 783 mg of the corresponding MEM ether (87%) as a yellow oil: mass spectrum (70 eV), m/e (relative intensity) 389 (2), 283 (28), 175 (25), 137 (9), 109 (17), 89 (100); IR ($CDCl_3$) 2900, 2240, 1660, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.80 (s, 3 H), 1.05 (s, 3 H), 1.16 (s, 3 H), 0.80–2.80 (m, 15 H), 3.39 (s, 3 H), 3.56 (m, 2 H), 3.67 (m, 2 H), 4.61 (d, 1 H, J = 6.7 Hz), 4.72 (d, 1 H, J = 6.7 Hz), 5.30 (dd, 1 H, J = 3.1, 6.4 Hz), 5.95 (d, 1 H, J = 10.1 Hz), 6.95 (d, 1 H, J = 10.1 Hz).

Dimethyl Enones 12β and 12α. To a 100-mL pear-shaped flask containing 1.22 g (10 mmol) of potassium *tert*-butoxide (Aldrich) was added a mixture of MEM ether derivatives (905 mg, 2.33 mmol) as a solution in 50 mL of THF. The yellow-orange solution turned brown on contact with the base. After this mixture was stirred for 10 min, methyl iodide (0.62 mL, 1.42 g, 10 mmol) was added in one portion. The solution immediately turned a milky white, and the flask became warm to the touch. Stirring was continued for two days; an additional portion of methyl iodide was added, and following an additional 2 days, the reaction mixture was diluted with 100 mL of water and 100 mL of ether. The aqueous phase was separated and extracted twice with ether, and the combined ether extracts were washed and dried over sodium sulfate. Removal of the solvent yielded 946 mg of product as a dark yellow oil. Preparative TLC (silica, 50% ether/hexanes) yielded two products, 12β (R_f 0.62; 362 mg) and 12α (R_f 0.53; 180 mg). The total yield of these isomers was 56%.

Characteristic properties of 12β are as follows: mass spectrum (70 eV), m/e (relative intensity) 416 (4), 372 (4), 340 (4), 320 (4), 311 (1), 174 (7), 159 (7), 145 (4), 137 (15), 89 (77), 56 (100); IR (neat) 2932, 2880, 1660, 1460, 1370, 1111, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.76 (s, 3 H), 1.06 (s, 3 H), 1.08 (s, 3 H), 1.15 (s, 3 H), 1.17 (s, 3 H), 0.80–2.80 (m, 13 H), 3.39 (s, 3 H), 3.56 (m, 2 H), 3.67 (m, 2 H, 4.62 (d, 1 H, J = 6.7 Hz), 4.73 (d, 1 H, J = 6.7 Hz), 5.38 (q, 1 H, J = 3.1 Hz), 5.93 (d, 1 H, J = 10.1 Hz), 6.89 (d, 1 H, J = 10.1 Hz).

Characteristic properties of 12α are as follows: mass spectrum (70 eV), m/e (relative intensity) 372 (1), 340 (1), 311 (1), 280 (1), 280 (1), 174 (7), 159 (7), 137 (15), 89 (77), 59 (100); IR (neat) 2946, 2884, 1664, 1457, 1350, 1105, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.84 (s, 3 H), 1.04 (s, 3 H), 1.05 (s, 3 H), 1.10 (s, 3 H), 1.15 (s, 3 H), 0.75–2.80 (m, 13 H), 3.40 (2, 3 H), 3.55 (m, 2 H), 3.68 (m, 2 H), 3.99 (dd, 1 H, J = 6.4, 9.2 Hz), 4.70 (s, 2 H), 5.35 (q, 1 H, J = 3.1 Hz), 5.94 (d, 1 H, J = 10.1 Hz), 6.88 (d, 1 H, J = 10.1 Hz).

Cleavage and Oxidation of MEM Ethers 12. This procedure will be illustrated for a single C-17 epimer 12β. A solution of 12β (271 mg, 0.65 mmol) in 3 mL of methylene chloride was cooled to 0 °C. Pyridine (40 μL, 0.5 mmol) was added, followed by titanium(IV) chloride (215 μL, microliters, 1.95 mmol). The solution turned dark brown, and after 30 min, the starting material was no longer evident by TLC analysis (silica, ether). The reaction was quenched by the addition of 2 mL of concentrated ammonium hydroxide solution and then diluted with 5 mL of water. After separation of the organic phase, the aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed with water until the aqueous phase was neutral and finally dried over sodium sulfate. Removal of the solvent gave a brown oil, which was chromatographed (silica) to give 171 mg (80%) of the 17β-alcohol as a yellowish solid.

A portion of this alcohol (40 mg, 0.12 mmol) was added to a stirred solution of pyridinium dichromate (PDC) in 2 mL of dimethylformamide (DMF). The initial bright orange solution turned brown as the reaction proceeded. After being stirred overnight (16 h) at room temperature, the solution was diluted with water and extracted (three times) with ether. The combined ether extracts were washed with water, brine, and dried over sodium sulfate. Evaporation of the solvent yielded 32 mg of a brown oil. Passage through a short silica column gave the expected ketone as a colorless oil: mass spectrum (70 eV), m/e (relative intensity) 327 (1), 311 (1), 190 (1), 175 (14), 137 (97), 133 (24), 44 (43), 40 (100); IR (neat) 2960, 2880, 1735, 1665, 1455, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.98 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 1.17 (s, 3 H), 0.70–2.40 (m, 10 H), 2.42–2.56 (ddd, 1 H, J = 1.8, 9.5, 19.2 Hz), 2.66–2.80 (m, 1 H), 5.53 (q, 1 H, J = 3.1 Hz), 5.96 (d, 1 H, J = 10.1 Hz), 6.88 (d, 1 H, J = 10.1 Hz).

Ketol 13. The unsaturated diketone generated by the previous operation was reduced by hydrogen (1 atm) in the presence of finely divided platinum (Adam's catalyst). The resulting dihydro product exhibited the following characteristic properties: IR (neat) 2960, 1745, 1700, 1465, 1375, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.92 (s, 3 H), 1.02 (d, 3 H, J = 0.85 Hz), 1.06 (s, 3 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 0.80–2.40 (m, 13 H), 2.43–2.58 (ddd, 1 H, J = 1.8, 9.5, 19.2 Hz), 2.59–2.75 (ddd, 1 H, J = 5.2, 14.8, 9.6 Hz), 2.93–3.08 (m, 1 H), 5.51 (dd, 1 H, J = 3.4, 6.7 Hz).

The reduced product (35 mg, 0.11 mmol) was dissolved in 3 mL of 95% aqueous ethanol and cooled to 0 °C. To this pale yellow solution was added 1 mL of 0.1 M sodium borohydride in 3 N aqueous sodium hydroxide. This mixture was stirred at 0 °C, and the reaction progress was monitored by TLC (silica, ether). After 3 h, the solution was diluted with 5 mL of water and extracted three times with ether. The combined ether extracts were washed with water and brine and dried over sodium sulfate. Removal of the solvent by rotary evaporation produced 32 mg (91%) of 13 as an oil, which crystallized on standing. An analytical sample was prepared by recrystallization (methylene chloride/petroleum ether) to yield 13 as a colorless crystalline solid: mp 192.5–194.5 °C; mass spectrum (70 eV), m/e (relative intensity) 330 (4), 297 (29), 230 (21), 133 (22), 119 (37), 107 (24), 105 (39), 91 (41), 79 (26), 57 (36), 55 (62), 43 (92), 41 (100); IR ($CDCl_3$) 3670, 3600, 2920, 2220, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.82 (s, 3 H), 0.89 (s, 3 H), 0.97 (d, 3 H, J = 0.92 Hz), 1.04 (s, 3 H), 1.05 (s, 3 H), 0.80–2.40 (m, 15 H), 2.41–2.55 (ddd, 1 H, J = 1.8, 9.5, 19.2 Hz), 2.74–2.87 (m, 1 H), 3.31 (dd, 1 H, J = 6.4, 9.5 Hz), 5.43 (q, 1 H, 3.2 Hz); ^{13}C NMR ($CDCl_3$, 69.8 MHz) δ 219.82, 143.28,

119.70, 79.33, 50.65, 50.24, 46.63, 39.86, 35.63, 34.65, 34.60, 34.37, 30.95, 29.51, 27.08, 24.99, 24.70, 23.75, 23.52, 17.59, 14.81. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.06; H, 10.32.

Acknowledgment. We thank Professor Paul Williard (Brown University) for conducting the X-ray analysis of 13, Mr. Ernest Oliver for his assistance in obtaining mass spectra, and Union Carbide Corporation for providing a Summer Term Fellowship for L.K.

Registry No. (±)-1, 84551-60-0; (±)-2, 75476-24-3; (±)-3, 75476-25-4; (±)-4, 75476-26-5; (±)-5, 98717-57-8; (±)-6, 98653-35-1; (±)-7, 98717-58-9; (±)-8, 98717-59-0; (±)-9, 98653-36-2; (±)-9 (mesylate), 98653-40-8; (±)-10, 98653-37-3; (±)-10 (1,17α-diol), 98677-73-7; (±)-10 (1,17β-diol), 98653-48-6; (±)-11α, 98677-48-6; (±)-11α (MEM deriv), 98653-42-0; (±)-11β, 98653-41-9; (±)-11β (MEM deriv), 98677-72-6; (±)-12α, 98653-38-4; (±)-12α (alcohol), 98653-44-2; (±)-12β, 98653-43-1; (±)-12β (alcohol), 98653-45-3; (±)-12 (3,17-dione), 98653-46-4; (±)-13, 98653-39-5; (±)-13 (dione), 98653-47-5; (±)-5-*epi*-euphane, 98717-60-3; 2-methoxy-5-methyl-1,4-benzoquinone, 614-13-1.

Supplementary Material Available: Crystallographic data for 13: atom coordinates, temperature factors, bond lengths, bond angles, and hydrogen coordinates (20 pages). Ordering information is given on any masthead page.

Herbasterol, an Ichthyotoxic 9,11-Secosterol from the Sponge *Dysidea herbacea*

Robert J. Capon and D. John Faulkner*

Scripps Institution of Oceanography (A-012F), La Jolla, California 92093

Received May 7, 1985

A specimen of the marine sponge *Dysidea herbacea* contained the known metabolite dysidin (1) and a new ichthyotoxic 9,11-secosterol, herbasterol (2). The structure of herbasterol was elucidated by interpretation of spectral data. Treatment of herbasterol (2) with either acid or base caused a retro-aldol reaction resulting in the formation of 19-norherbasterol (4).

An unusually diverse array of metabolites has been isolated from various specimens of *Dysidea herbacea*.[1] A reason for the unusual diversity could be that some of the metabolites are produced by the symbiotic microorganisms known to coexist with *D. herbacea*. Alternatively, the species, as presently defined, may not be homogeneous. The metabolites reported to date include polybrominated biphenyl ethers,[2] chlorinated nitrogenous metabolites[3] that are reminiscent of certain blue-green algal metabolites, and sesquiterpenes[4] that are almost certainly true sponge metabolites.

We have examined three samples of *D. herbacea* from different depths and locations on Bowl Reef near Townsville, Australia. We had hoped to find qualitative or quantitative differences in the secondary metabolites from each sample but the composition of the three crude extracts was identical within experimental error. The dichloromethane extracts all contained dysidin (1), as previously reported by Hofheinz and Oberhänsli,[3a] suggesting that this variety of *D. herbacea* had already been studied. We were, therefore, surprised to find that the methanolic extracts of each sample contained a single ichthyotoxic and antimicrobial metabolite. In this paper we describe the structural elucidation of herbasterol (2), a polyhydroxylated 9,11-secosterol responsible for the observed biological activities.

Chromatography of the methanol-soluble material on Sephadex LH-20 with 1:1 dichloromethane/methanol as eluant gave herbasterol (2, 8.6% dry wt) as an off-white solid, mp 113–5 °C. The molecular formula, $C_{27}H_{48}O_6$, was established from a combination of measurements: the highest peak in the mass spectrum gave a molecular formula of $C_{26}H_{46}O_5$ (M – CH_2O) but the ^{13}C NMR spectrum required 27 carbon atoms, including one ketone carbonyl (δ 215.2), and acetylation produced a pentaacetate 3. The ^{13}C NMR spectrum also contained two hydroxymethylene signals at δ 58.9 and 71.4 and three hydroxymethine signals at δ 71.4, 72.6, and 75.3. The infrared spectrum contained bands at 3400 cm^{-1} (broad) and 1700 cm^{-1} due to the hydroxyl and ketone functionalities. The ^1H NMR spectrum gave the first data that indicated a sterol structure. The methyl signals at δ 0.77 (s, 3 H), 1.00 (d, 3 H, J = 6.5 Hz), and 0.88 (d, 6 H, J = 6.5 Hz), could be assigned to carbons 18, 21, 26 and 27 of a "cholestane" skeleton. The absence of a C-19 methyl signal and the presence of two hydroxymethylene proton signals at δ 3.52 (d, 1 H, J = 11.2 Hz) and 4.64 (d, 1 H, J = 11.2 Hz) allowed a hydroxymethylene group to be placed at C-10. The facile loss of a one carbon unit in the mass spectrum and under both acidic or basic conditions can readily be explained by a retro-aldol reaction if the ketone group is at C-9 of a 9,11-secosterol. The remaining hydroxymethylene group that gives rise to a ^1H NMR signal at δ 3.58 (t, 2 H, J = 8.0 Hz) can be assigned to C-11 of a 9,11-secosterol. The mutually coupled (J = 13.4 Hz) signals at δ 3.28 (m, 1 H, J = 13.4, 9.4, 4.7 Hz)

(1) Faulkner, D. J. *Natural Product Reports* **1984**, *1*, 551.

(2) (a) Norton, R. S.; Wells, R. J. *Tetrahedron Lett.* **1980**, *21*, 3801. (b) Cartê, B.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 2335. (c) Sharma, G. M.; Vig, B.; Burkholder, P. R. *Food, Drugs, Sea, Proc. Conf. Drugs, Sea, 2nd* **1969**, 307. (d) Sharma, G. M.; Vig, B. *Tetrahedron Lett.* **1969**, 1715. (e) Norton, R. S.; Croft, K. D.; Wells, R. J. *Tetrahedron* **1981**, *37*, 2341.

(3) Von Hofheinz, W.; Oberhänsli, W. E. *Helv. Chim. Acta* **1977**, *60*, 660. (b) Kazlauskas, R.; Lidgard, R. O.; Wells, R. J.; Vetter, W. *Tetrahedron Lett.* **1977**, 3183. (c) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Karlsson, R. *Tetrahedron Lett.* **1978**, 1519. (d) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B. *Tetrahedron* **1980**, *36*, 2133. (d) Erickson, K. L.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 31. (f) Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1984**, *25*, 2935. (g) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4945.

(4) (a) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4949. (b) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Declerq, J. P.; Germain, G.; Van Meerssche, M. *Bull. Soc. Chim. Belg.* **1978**, *87*, 481. (c) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J.; Schönholzer, P. *Tetrahedron Lett.* **1978**, 4951. (d) Dunlop, R. W.; Kazlauskas, R.; March, G.; Murphy, P. T.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 95.

0022-3263/85/1950-4771$01.50/0