dimethyl ester **8c** (0.025 g, 24%), which can be quantitatively recycled to ester-acid **15b**. On the basis of this recovery, the conversion of **15b** to the protected protetrone **14b** is 34%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3 H, CH_3), 3.70 (s, 5 H, OCH_3, $ArCH_2COOR$), 3.89 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.12 (s, 2 H, $COCH_2CO$), 5.63 (br s, 1 H, NH), 6.55 (d, 1 H, J = 2.2 Hz), 6.95 (d, 1 H, J = 2.2 Hz), 7.19 (br s, 1 H, NH), 7.60 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.48 (CH_3), 38.83 ($ArCH_2COOR$), 51.02 (ester OCH_3), 52.19 ($ArCOCH_2CO$), 55.18 (ether OCH_3), 56.44 (ether OCH_3), 64.03 (ether OCH_3), 64.12 (ether OCH_3), 94.02 (CH), 98.98 (CH), 116.20 (C), 116.89 (C), 123.21 (CH), 123.30 (C), 128.13 (C), 129.22 (C), 133.26 (C), 135.34 (C), 153.39 (COOR), 157.22 (COR), 158.41 (COR), 158.88 (COR), 169.01 ($CONH_2$), 172.24 (COOR), 203.43 (C=O); EI-MS, m/z (relative intensity) 469 ($M^{\cdot+}$, 52), 451 (57), 424 (33), 423 (100), 411 (24), 393 (31), 383 (67), 367 (28), 354 (28); IR (KBr) 3355 (br), 2948, 1745, 1710, 1668, 1608, 1428, 1323, 1209, 1163, 1038 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 430 (1180), 386 (1930), 331 (5780), 274 (16 200), 239 (19 400); HRMS calcd for $C_{25}H_{27}NO_8$ m/z 469.1737, found m/z 469.1735.

10-Dehydroxy-6-methylpretetramide (12). A slurry of anthracene **9** (8.4 mg, 0.021 mmol) in acetic acid (10 mL) was treated with aqueous HBr (10 mL, 49%, freshly distilled from red phosphorus) for 7 h at 40 °C under N_2. The mixture was then stored at 4 °C. Crystals deposited and were collected and washed with H_2O, MeOH, CH_2Cl_2, $CHCl_3$, Et_2O, and EtOAc to yield naphthacene **12** (5.9 mg, 82%): mp (vac) 200-300 °C dec; too insoluble to obtain NMR spectra; EI-MS, m/z (relative intensity) 349 ($M^{\cdot+}$, 55), 332 (100), 318 (91), 306 (82), 292 (73), 291 (86), 263 (23), 262 (23), 189 (50), 176 (32); IR (KBr) 3470, 3410, 1655, 1595 cm^{-1}; UV (1:9 AcOH/EtOH) λ_{max} nm (ϵ) 435 (4800), 350 (5200), 315 (6800), 265 (11 200); HRMS calcd for $C_{20}H_{15}NO_5$ m/z 349.0950, found m/z 349.0955.

6-Methylpretetramide (1). Protetrone **14a** (0.025 g, 0.057 mmol) was refluxed for 3 h in 2 mL of a 50% mixture of acetic and hydriodic acids (47% aqueous, distilled from red P, 123-124 °C, stabilized with 1.5% H_3PO_2). After cooling to room temperature, the reaction mixture was poured over 10 g of crushed ice and filtered. The brick red solid was washed with H_2O, acetone, EtOAc, and Et_2O to give 6-methylpretetramide (**1**; 10 mg, 50%): mp (vac) 220-240 °C dec (lit.[2a] mp 200-300 °C dec); EI-MS, m/z (relative intensity) 365 ($M^{\cdot+}$ 42), 348 (100); UV [98% H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 505 (9600), 403 (11 200), 343 (sh, 3900), 328 (4600), 293 (7200), 275 (8200), 263 (8800) [lit.[3] 512 (15 100), 398 (17 650), 339 (16 200), 295 (22 900), 276 (23 900), 262 (24 700), 233 (20 200)]; HRMS calcd for $C_{20}H_{15}NO_6$ m/z 365.0876, found m/z 365.0893.

8-Hydroxy-6-methylpretetramide (4). A solution of protetrone **14b** (0.014 g, 0.030 mmol) in acetic acid (0.4 mL) under an argon atmosphere was treated with hydriodic acid (0.4 mL, 47% aqueous, distilled from red P, 123-124 °C, stabilized with 1.5% H_3PO_2) at reflux for 3 h. The orange suspension was poured over crushed ice (15 g), and the precipitate was collected by suction filtration and washed with H_2O (6 mL), cold acetone (0.5 mL), cold EtOAc (2 mL), and Et_2O (2 mL) to yield 8-hydroxy-6-methylpretetramide (**4**) as a brick-orange solid (0.006 g, 53%): mp (vac) 330-338 °C dec; ^{1}H NMR insufficiently soluble in DMSO-d_6/1% $Mg(OCOCD_3)_2$ to obtain a satisfactory spectrum at 400 MHz; EI-MS, m/z (relative intensity) 381 ($M^{\cdot+}$, 10), 364 (26), 339 (31), 338 (100), 324 (39), 323 (95), 309 (24), 295 (21); IR (KBr) 3434 (br), 1726 (w), 1709 (w), 1689 (w), 1655, 1638, 1627, 1609, 1600, 1411, 1400, 1390, 1381, 1350, 1290, 1170 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 438 (14 700), 326 (17 000), 296 (20 100), 280 (20 500), 259 (19 500); HRMS calcd for $C_{20}H_{15}NO_7$ m/z 381.0849, found m/z 381.0852.

Extraction of the aqueous filtrate with EtOAc yielded anthrone **18** as an orange solid (3.0 mg, 33%): 300-MHz ^{1}H NMR (acetonitrile-d_3) δ 1.50 (d, 3 H, CH_3, J = 7 Hz), 3.63 (s, 2 H, CH_2), 4.21 (q, 1 H, C-10 CH, J = 7 Hz), 6.27 (d, 1 H, J = 2 Hz), 6.48 (d, 1 H, J = 2 Hz), 6.75 (d, 1 H, J = 1.8 Hz), 6.90 (d, 1 H, J = 1.8 Hz), 8.03 (s, 1 H, isolated phenol OH), 12.29 (s, 1 H, H-bonded phenol OH), 12.42 (s, 1 H, H-bonded phenol OH); EI-MS, m/z (relative intensity) 314 ($M^{\cdot+}$, 100), 299 (90), 271 (25), 270 (20), 268 (50), 204 (60); IR (KBr) 3260 (br), 2580, 1700, 1655, 1602, 1457, 1418, 1363, 1282, 1258, 1220, 1162 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 429 (2120), 362 (4540), 270 (5130), 244 (7660), 226 (9820), 198 (20 150); HRMS calcd for $C_{17}H_{14}O_6$ m/z 314.0790, found m/z 314.0786.

Acknowledgment. We wish to thank Drs. Ian Blair and Brian Sweetman for mass spectra and the US Public Health Service (Grant GM-12848) for generous financial support.

Stereocontrolled Construction of an Ingenol Prototype Having a Complete Array of Oxygenated and Unsaturated Centers

Leo A. Paquette,* Robert J. Ross,[1] and James P. Springer[2]

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and the Merck Institute for Therapeutic Research, Rahway, New Jersey 07065. *Received January 22, 1988*

Abstract: The keto tetrol **3**, a close prototype of ingenol, has been synthesized in highly stereoselective fashion. Starting with β-diketone **9**, the allylic alcohol **13** was first crafted. The stage was thereby set for Sharpless oxidation and introduction of the ring A double bond. Subsequent regiospecific opening of epoxy alcohol **16** with titanium isopropoxide in the presence of ammonium benzoate followed by acetonide formation delivered **21**. Once the benzoyloxy group in this intermediate was transformed into a carbonyl, conversion to **34** was readily accomplished. Selenoxide elimination and adjustment of the oxidation level at two centers followed by removal of the acetonide functionalities delivered **3**. This target molecule can be cleanly acylated at its 3- and 3,5-positions with palmitoyl chloride.

Euphorbia, the largest genus (ca. 1600 species) of the family *Euphorbiaceae* (290 genera),[3] occur as succulent or nonsucculent plants in most parts of the world. Although the lattices of most of these species are widely known to be highly irritating, various parts have nonetheless seen extensive use in folk medicine against all kinds of diseases.[4] The types that grow as weeds have often been held responsible for the poisoning of livestock.[5] Of special medicinal relevance are the various esters of phorbol (**1**) and ingenol (**2**) that are contained therein.[6] Detailed investigations

(1) National Science Foundation Graduate Fellow, 1982-1985; Amoco Graduate Fellow, 1985-1986.

(2) Merck Institute. Author to whom all inquiries regarding the X-ray crystallographic analysis should be addressed.

(3) Engler, A. *Syllabus der Pfanzenfamilien*; Nikolassee: Berlin, 1964; Gebr. Borntrager.

(4) (a) Watt, J. M.; Breyer-Brandwijk, M. G. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*; E. and S. Livingstone: Edinburgh, 1962. (b) Hartwell, J. L. *Lloydia* **1969**, *32*, 157. (c) Morton, J. F. In *Atlas of Medicinal Plants of Middle America. Bahamas to Yucatan*; Thomas, C. C., Ed.; Springfield, IL, 1981.

(5) Forsyth, A. A. *British Poisonous Plants*; Her Majesty Stationary Office: London, 1968; pp 73-75.

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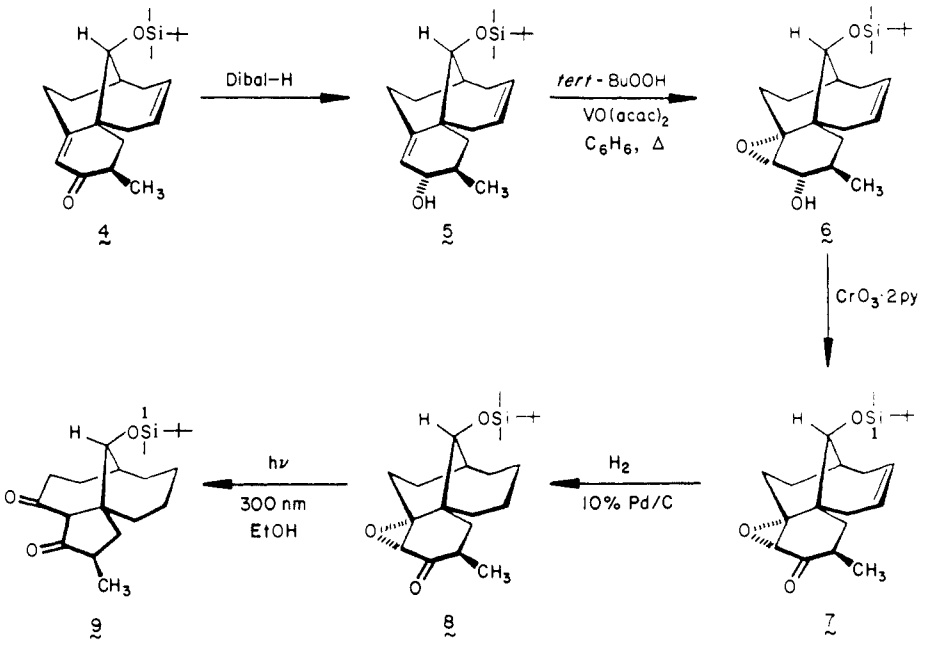
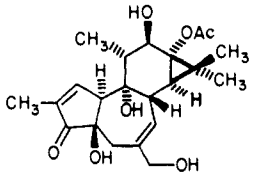
Scheme I

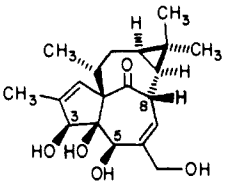


4 5 6 7 8 9

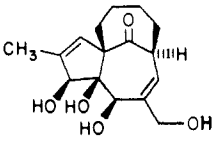
have confirmed that esters of **1** and **2** do possess striking tumor-promoting properties.[6,7]



1



2



3

Ingenol (**2**), the parent diterpene of the ingenane family, is itself ineffective in promoting tumors, but its 3-hexadecanoyloxy derivative constitutes one of the most potent compounds (active at 10^{-7} M) yet studied for inducing Epstein–Barr virus in lymphoblastoid cells.[8] The molecular basis for induction of oncogenic herpes virus by these esters is not fully understood. Recent work does suggest, however, that the initial action of tumor promoters may be associated with perturbation of the organization of membrane phospholipids[9] as well as with binding to, and activation of, protein kinase C.[10]

We[11] and others[12] have been concerned with developing a total synthesis of ingenol and related molecules, since the availability of these substances holds considerable promise as tools for understanding the mechanism of viral and chemical carcinogenesis. Although several ingenious routes to the carbocyclic ABC ring system of **2** and its less strained C-8 epimer have been devised, no progress toward full elaboration of the imposing array of hydroxyl groups and double bonds found in ingenol has yet been disclosed. Herein is described the full details of a completely stereocontrolled synthesis of the prototype **3**.[13] We also report the preparation of its 3-hexadecanoyloxy and 3,5-bis(hexadecanoyloxy) derivatives and provide preliminary in vitro data relating to their biological activity.

Results

Construction of an Appropriately Functionalized ABC Framework. Although the readily available tricyclic α,β-unsaturated ketone **4** had previously been transformed into **7**,[11a] it became imperative for large-scale work to devise an alternative to its direct alkaline peroxidation. The latter reaction proceeds in the desired direction only when relatively small quantities are involved. Furthermore, the efficiency is invariably low.[14] Dibal-H reduction

(6) (a) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (b) Hecker, E. In *Carcinogenesis, Vol. 2. Mechanism of Tumor Promotion and Carcinogenesis*; Slaga, T. S., Sivak, A., Boutwell, R. K., Eds.; Raven: New York, 1978; p 11. (c) Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193. (d) Adolf, W.; Hecker, E. *Tetrahedron Lett.* **1980**, *21*, 2887. (e) Falsone, G.; Crea, A. E. G.; Noack, E. A. *Arch. Pharm.* **1982**, *315*, 1026. (f) Sorg, B.; Hecker, E. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37B*, 1640. (g) Gotta, H.; Adolf, W.; Opferkuch, H. J.; Hecker, E. *Ibid.* **1984**, *39B*, 683. (h) Rizk, A. M.; Hammouda, F. M.; El-Missiry, M. M.; Radwan, H. M.; Evans, F. J. *Phytochemistry* **1985**, *24*, 1605.

(7) (a) Berenblum, E.; Shubik, P. *Br. J. Cancer* **1947**, *1*, 379. (b) Hecker, E. *Cancer Res.* **1968**, *28*, 2338. (c) Adolf, A.; Opferkuch, H.; Hecker, E. *Fette Seifen Anstrichm.* **1968**, *70*, 850. (d) Furstenberger, G.; Hecker, E. *Planta Med.* **1972**, *22*, 241. (e) Hecker, E.; Friesel, H.; Schmidt, R.; Siebert, D.; Marquardt, H. *Advances in Medical Oncology, Research and Education, Vol. 1, Carcinogenesis*; Margison, G. P., Ed.; Pergamon: New York, 1969; p 207. (f) Fujiki, H.; Mori, M.; Sugimura, T.; Ohigashi, H.; Hirota, M.; Koshimizu, K. In *Cocarcinogenesis and Biological Effects of Tumor Promoters*; Hecker, E., et al., Eds.; Raven: New York, 1965; p 65. (g) Blumberg, P. M. *CRC Crit. Rev. Toxicol.* **1980**, 153. (h) Hergenhahn, M.; Hecker, E. *Carcinogenesis* **1981**, *2*, 1277. (i) Schmidt, R.; Hecker, E. *Ibid.* **1982**, *7*, 57. (j) Pecar, S.; Sentjurc, M.; Schara, M.; Nemec, M.; Sorg, B.; Hecker, E. *Ibid.* **1982**, *7*, 541. (k) Hecker, E.; Lutz, D.; Weber, J.; Goerttler, K.; Morton, J. F. *Biol. Cancer* **1983**, *1*, 219. (l) Schmidt, R.; Hecker, E. *Periodicum Biologorum* **1983**, *85*, Suppl. 2, 155. (m) Hergenhahn, M.; Hecker, E. *Ibid.* **1983**, *85*, 240. (n) Schmidt, R.; Adolf, W.; Marston, A.; Roeser, H.; Sorg, B.; Fujiki, H.; Sugimura, T.; Moore, R. E.; Hecker, E. *Carcinogenesis* **1983**, *4*, 77. (o) Hecker, E. *Arzneim. Forsch.* **1985**, *35*(II), 12a, 1890.

(8) (a) Keller, R.; Keist, R.; Adolf, W.; Opferkuch, H. J.; Schmidt, R.; Hecker, E. *Exp. Cell Biol.* **1982**, *50*, 121. (b) Kinsel, V.; Kreilbich, G.; Hecker, E.; Suss, R. *Cancer Res.* **1979**, *39*, 2743. (c) Terada, M.; Adolf, M.; Opferkuch, W.; Schmidt, H. J.; Hecker, E.; Sugimura, T. *Cancer Res. Chem. Oncol.* **1982**, *103*, 17.

(9) (a) Shuyab, M. *NATO Adv. Sci. Inst. Ser. A.* **1983**, *57*, 307. (b) Shuyab, M.; Todaro, E. I. *Nature (London)* **1980**, *288*, 451.

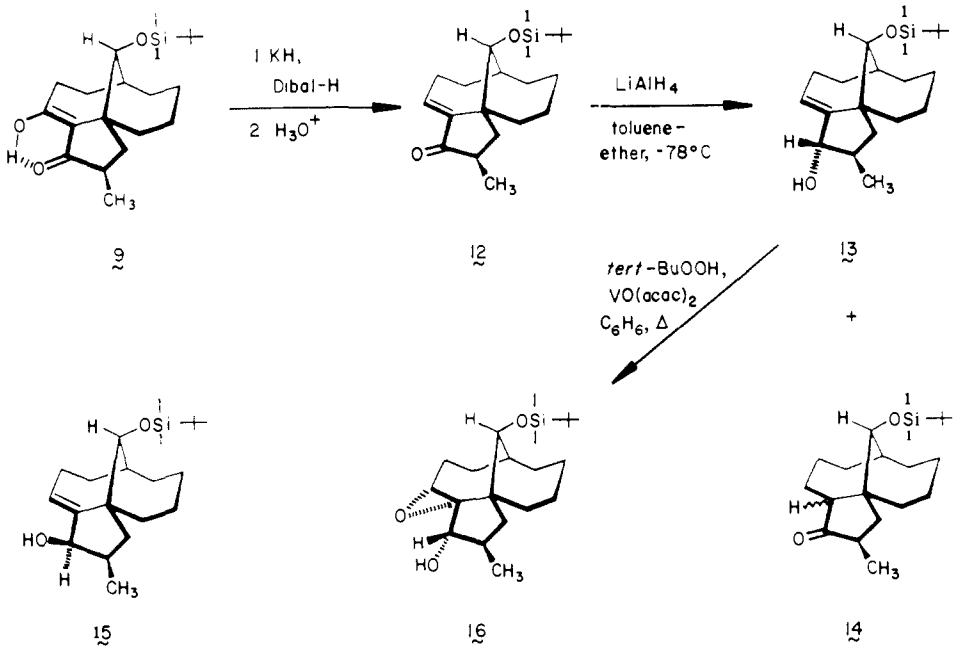
(10) (a) Jeffrey, A. M.; Liskamp, R. M. S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 241. (b) Wender, P. A.; Kochler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Ibid.* **1986**, *83*, 4214.

(11) (a) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (b) Ross, R. J.; Paquette, L. A. *J. Org. Chem.* **1987**, *52*, 5497.

(12) (a) Wender, P. A.; Hilleman, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205. (b) Satoh, T.; Okuda, T.; Kaneko, Y.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 1401. (c) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398. (d) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (e) Winkler, J. D.; Henegar, K. E.; Williard, P. G. *Ibid.* **1987**, *109*, 2850. (f) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (g) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390.

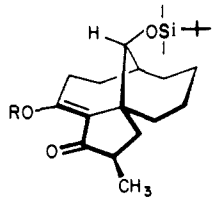
(13) For a preliminary communication of these results, consult ref 11b.

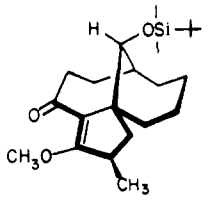
Scheme II



of **4** occurs with high stereoselectivity from the less hindered π surface to furnish **5** in 98% yield (Scheme I). With secure supplies of **5** in hand, it proved an easy matter to achieve stereocontrolled epoxidation of this allylic alcohol with *tert*-butyl hydroperoxide and vanadyl bis(acetylacetonate) in refluxing benzene (96%).[15] Subsequent Collins oxidation[16] delivered **7**. For reasons delineated earlier, saturation of the double bond in **7** was accomplished prior to photoisomerization and generation of β-diketone **9**.[11a]

More sophisticated functionalization of the B and C rings required that the pair of carbonyl groups in **9** be chemically differentiated. In view of the generally substantive enolic character of 1,3-diketones, the selective formation of enol derivatives was initially examined. Methanolic diazomethane proved to be too harsh a reagent for this substrate, affording a mixture of **10a** and **11** in 10% and 7% yields, respectively. No unreacted starting material could be recovered. In contrast, treatment of **9** with acetic anhydride in pyridine containing (4-(dimethylamino)pyridine or with *tert*-butyldimethylsilyl triflate and 2.6-lutidine in ether led regiospecifically to **10b** (77%) and **10c** (87%).





10a, R=CH_3
b, R=$COCH_3$
c, R=$SiMe_2$*tert*-Bu

11

Notwithstanding these successes, no additional study of intermediates **10b** and **10c** was pursued following the almost simultaneous discovery that Dibal-H reduction of the potassium enolate of **9** delivered **12** efficiently (85%, Scheme II). This direct conversion likely materializes by 1,4-hydride addition to the dominant enolic form of **9**[11a] and elimination of hydroxide ion (or its equivalent) from the intervening β-hydroxy enolate during the ensuing acid hydrolysis.

Attention was next focused on carbonyl group reduction within **9** for the purpose of properly introducing the A-ring hydroxyl group. Recourse to cerium trichloride doped sodium borohydride[17] provided the desired allylic alcohol **13** in reasonable yield (57%), but the quantities of epimeric alcohol **15** (22%) and fully saturated carbinol (11%) were too great. Dibal-H, often the reagent of choice for this type of reduction,[18] gave a preponderance of ketone **14**. The best conditions uncovered for controlled 1,2-reduction consisted in the use of lithium aluminum hydride in toluene–ether solution at −78 °C.[19] In this fashion, **13** could be isolated in 65% yield. Some degree of 1,4-reduction leading to **14** (22%) remained operational, but chromatographic separation of these products was easily achieved.

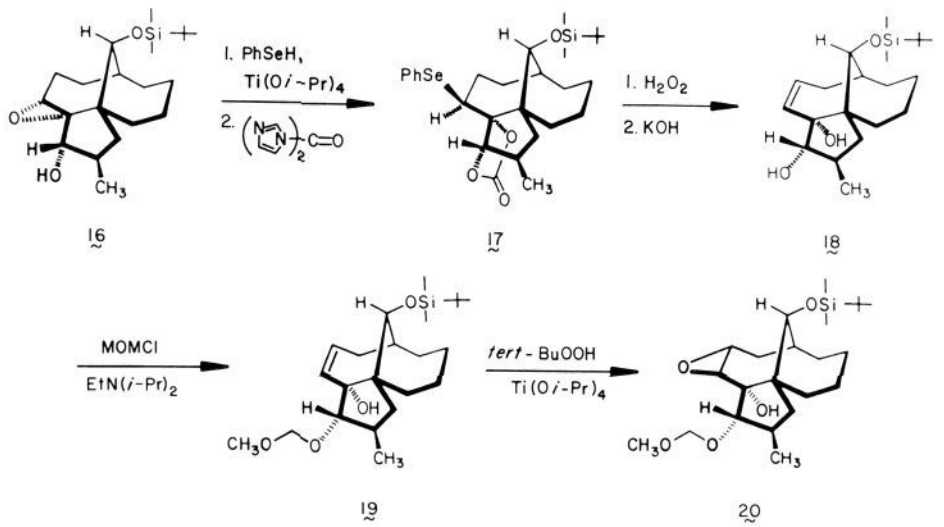
The relative stereochemistries of the hydroxyl groups in **13** and **15** were established by comparative lanthanide-induced shifting of their ^1H NMR spectra. The focus of the study was the impact of incremental amounts of $Eu(fod)_3$ on the relative position of the signal stemming from the syn-oriented proton at C-9. For the β-hydroxyl epimer, complexation with europium on the "top" side should give rise to appreciable downfield shifting of the H-9 proton, while the α-isomer should exert much less of an effect at this site. The clear cut results are displayed graphically in Figure 1. A similar phenomenon was encountered for the adjoining methyl group. For **13**, the relevant double was already shifted completely out of the spectral range examined following addition of 5% $Eu(fod)_3$. The corresponding signal for **15** was much less strongly influenced.

As observed previously in the case of **5**, the response of **13** to *tert*-butyl hydroperoxide and $VO(acac)_2$ in refluxing benzene was stereospecific epoxidation, providing **16** in 96% yield.

Crystallographic Verification of Fully Stereocontrolled Advanced Oxygenation. By this stage, it had become quite evident that the surface of the A and B rings that is syn to the C-9 bridge happens to be appreciably more accessible sterically. Consequently, the epoxidation of **13** that leads to **16** has taken place from the more encumbered direction. Because the structural features of the target molecule mandate more extensive oxygenation of these intermediates, some concern arose about the continued stereochemical efficacy of metal template directed oxygenations as the number of functional groups on the already more congested face was increased.

(14) Ross, R. J. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1986.
(15) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(16) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379.
(17) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(18) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972.
(19) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206.

Scheme III



16 17 18 19 20

The decision was therefore made to clarify the state of affairs while simultaneously developing a workable synthetic protocol.

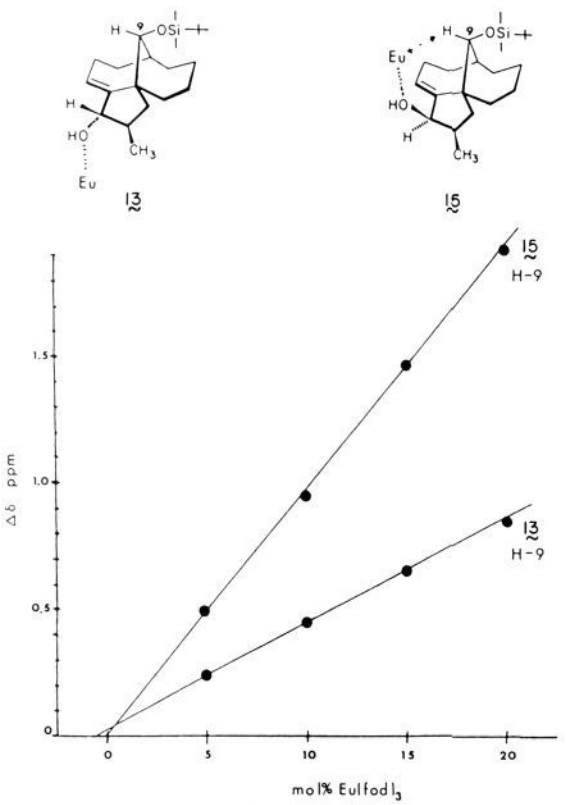


Figure 1. Lanthanide shift study on alcohols **13** and **15**.

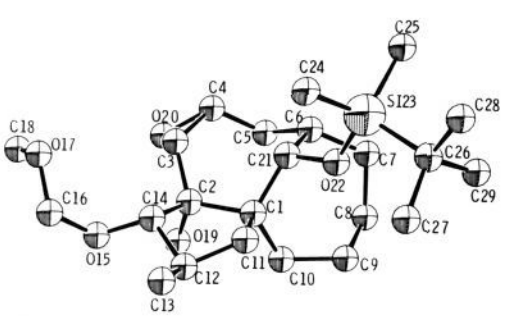


Figure 2. A computer-generated drawing of **20** derived from the X-ray coordinates with hydrogens omitted for clarity.

To this end, **16** was treated with benzeneselenol in benzene solution containing titanium(IV) isopropoxide[20] to afford a *cis*-1,2-diol that was promptly converted in 71% overall yield to cyclic carbonate **17** (Scheme III). This intermediate was in turn exposed to hydrogen peroxide and subsequently to potassium hydroxide in order to generate **18**. This white crystalline substance was obtained in 81% yield without need for chromatographic purification.

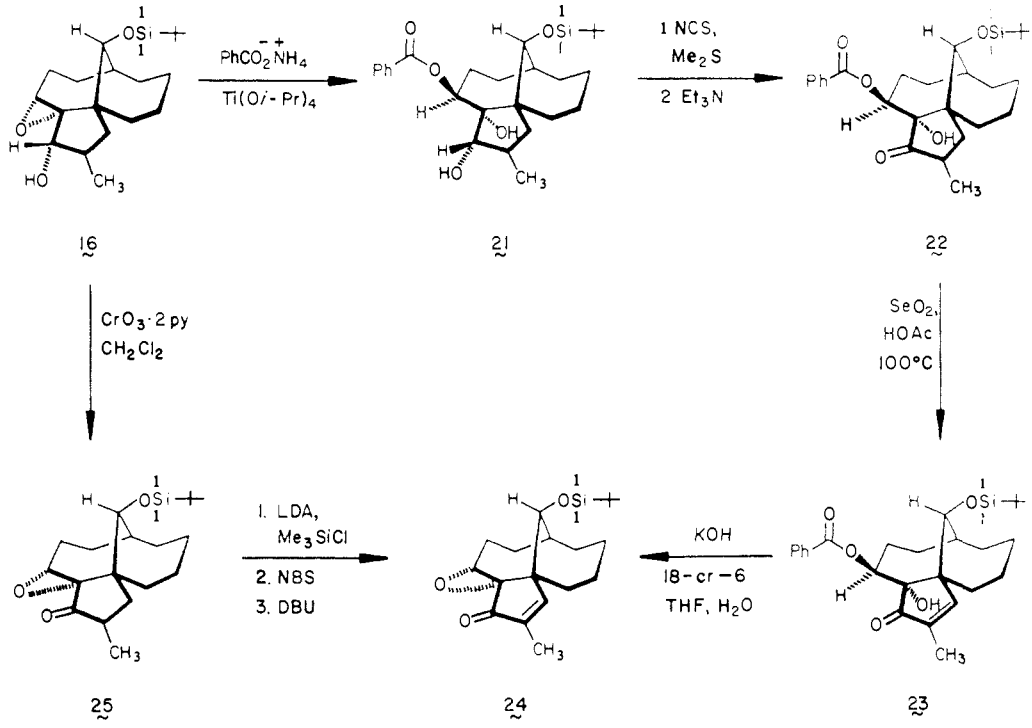
The response of **18** to Sharpless epoxidation proved to be problematic. With $VO(acac)_2$ as catalyst, decomposition was evidenced. Although the diol was stable to titanium isopropoxide, epoxidation with this reagent proceeded at an unusually slow rate, requiring several days to realize approximately 30% conversion to an epoxy diol. A probable reason for this sluggishness was deemed to be sufficiently strong coordination of the titanium cation to the diol to render it less reactive than usual. To test this hypothesis, **18** was transformed regioselectively into MOM ether **19**.[21] To our delight, the response of **19** to the action of titanium isopropoxide and *tert*-butyl hydroperoxide at −35 °C was to deliver **20** in 87% yield after only 2 h. Furthermore, X-ray crystallographic analysis of **20** (see Figure 2) confirmed that epoxidation had once again occurred from below (as drawn) without obvious steric complications.

Introduction of the A Ring Double Bond. Since the objective of stereospecific hydroxylation of ring B was now regarded as attainable, we turned to *prior* introduction of the ring A double bond. The intent was to be opportunistic. Installation of the needed site of unsaturation at this stage should preclude later excessive use of blocking–deblocking maneuvers and thereby streamline the overall synthesis. Epoxy ketone **24** was therefore targeted as the next immediate goal (Scheme IV).

Reaction of **16** with ammonium benzoate and titanium isopropoxide[22] proceeded regiospecifically as expected. Selective oxidation of the secondary hydroxyl group in diol **21** took place without carbon–carbon bond cleavage[23] in the presence of the Corey–Kim reagent.[24] The conversion of **22** to enone **23** could not be accomplished with benzeneseleninic anhydride. From among the various conditions examined for implementing oxidation with selenium dioxide, that involving simply the use of hot (100 °C) acetic acid as solvent[25] culminated in the highest yield (60%) of **23**. It should be pointed out here that the use of basic oxidants had to be avoided in the present context because of the need to circumvent intramolecular S_N2 displacement of benzoate and

(20) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1530.
(21) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(22) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(23) Rocek, J.; Westheimer, F. H. *J. Am. Chem. Soc.* **1962**, *84*, 2241.
(24) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1974**, 287.
(25) Engel, C. R.; Rakhit, S.; Huculak, W. W. *Can. J. Chem.* **1962**, *40*, 921.

Scheme IV



16 21 22 25 24 23

premature epoxide formation. The latter process was of particular value once **23** was in hand. Its treatment with potassium hydroxide and 18-crown-6 in aqueous tetrahydrofuran led efficiently (88%) to the targeted intermediate **24**.

Despite the success of this venture, the length and overall inefficiency of the scheme were such that improvements were called for. For this reason, **16** was oxidized to **25** with the Collins reagent. The conversion of **25** to its silyl enol ether proved problematic until recourse was made to premixing the LDA and Me_3SiCl prior to introduction of the ketone.[26] Quite unexpectedly, subsequent exposure to DDQ, $PdCl_2$, or $Pd(OAc)_2$ was not effective in delivering **24**. Selenium reagents were not examined because of the high risk of competing selenoxide elimination toward the methyl group. However, the loss of HBr should exhibit that regiochemical preference encompassed by the Saytzeff rule. Indeed, bromination of the silyl enol ether of **25** with NBS[27] followed by treatment of the α-bromo ketone with DBU[28] at room temperature provided **24** in 70% overall yield. In our experience, this "three-pot" procedure represents the most efficacious route to **24**.

Complete Assembly of 3. It now appeared that **3** would be in hand if three tactical problems were solved: (1) introduction of an hydroxymethyl group at C-6; (2) installation of the C-6–C-7 double bond; and (3) stereocontrolled reduction of the carbonyl group at C-5 in order to provide proper stereodisposition to the hydroxyl substituent at that site. Of these, item (3) was viewed with the least concern because of earlier findings relevant to steric access to ring B. The topological and diastereofacial facets of processes (1) and (2), although inextricably linked, could be brought under proper control either by implementing (1) before (2), or vice-versa. Ultimately, both options were investigated for reasons discussed below.

The low-temperature lithium aluminum hydride reduction of **24** gave **26** (84%) and **27** (11%), the stereochemical outcome implicating a somewhat greater proclivity for "above-plane" attack in this example relative to **12**. Following Ti(IV)-promoted opening of the epoxide ring in **26** with benzoate ion,[22] the pair of cis-vicinal hydroxyl groups were ketalized to make **28** available (Scheme V). Brief saponification of **28** and subsequent pyridinium chlorochromate oxidation furnished **29**, thereby setting the stage for one-carbon homologation.

Despite the fact that the enolate anion of **29** forms readily, its condensation with chloromethyl benzyl ether produced only difficultly separable mixtures in inferior yield. Also, subsequent conversion to the silyl enol ether was not successful. Clarification of the questions associated with these unproductive processes was not pursued when it was discovered that SEM chloride reacted smoothly with **29** to give **30** (89%). The single epimer to result was assigned the indicated stereochemistry solely on the basis of the examination of molecular models, since this chiral center was to experience loss of its stereogenicity in the very next step. The silyl enol ether derived from **30** reacted readily with benzeneselenenyl chloride,[29,30] and subsequent selenoxide elimination[31] introduced the intraannular double bond.

Low-temperature hydride reduction of **31** proceeded to give **32** (95% isolated) as expected from the prevailing steric contributions. That the hydride had indeed entered syn to the C-9 bridge was ascertained by difference NOE spectroscopy (see formula **32**). Unfortunately, all attempts to remove the (trimethylsilyl)ethyl ("short-SEM") blocking group from **32** were to no avail.

This negative insight suggested to us that our purposes would likely be better served if the hydroxymethyl group were originally introduced in unmasked condition. The simplest implementation of this concept involves execution of tactic (2) prior to (1). Consequently, **29** was selenenylated to provide **33** (Scheme VI), thereby enhancing the acidity of the remaining α-carbonyl proton. When treated with 37% aqueous formaldehyde and potassium hydroxide in methanol,[32] **33** was stereospecifically transformed in 80% yield to the hydroxymethyl derivative **34**. Selenoxide

(26) For earlier uses of this methodology, see: (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (c) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. (d) Paquette, L. A.; Schaefer, A. G. *Tetrahedron*, in press.

(27) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

(28) Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591.

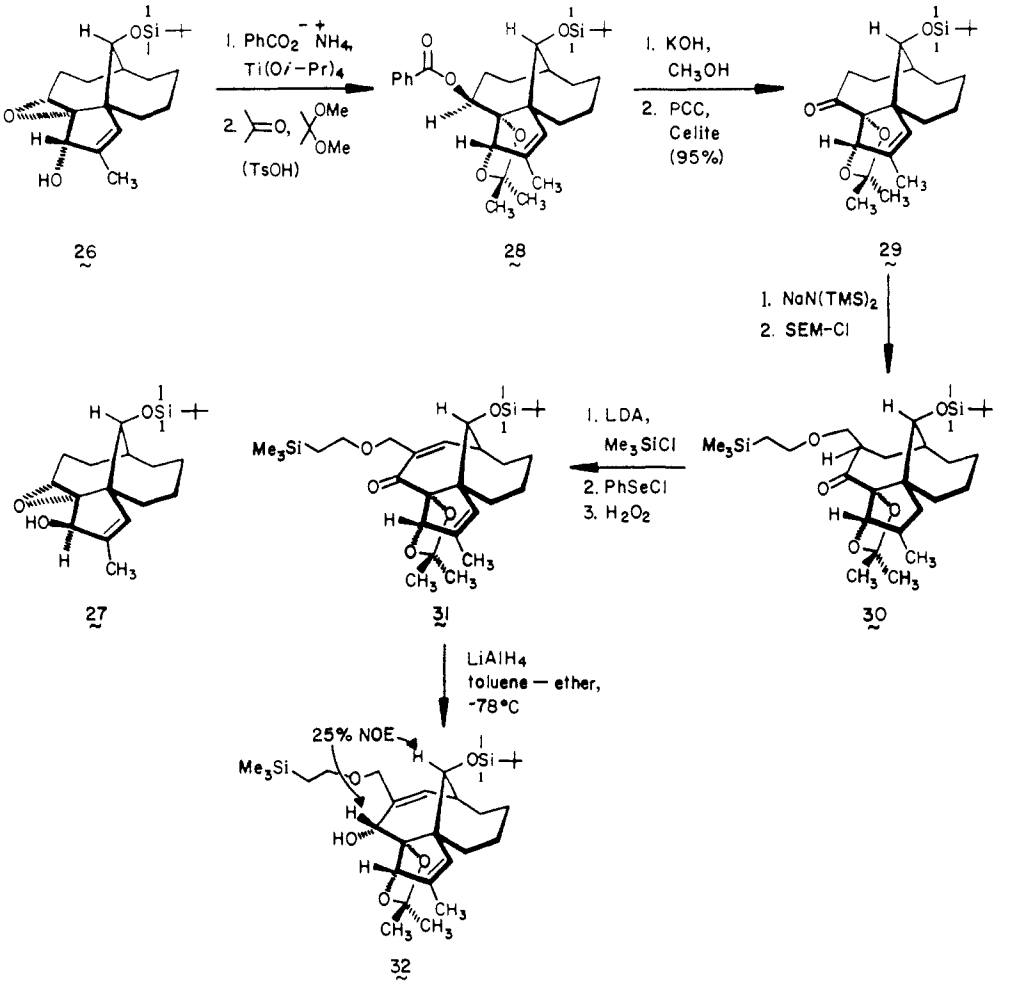
(29) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699.

(30) In this instance, there was no need to premix the LDA and Me_3SiCl, although the latter does work well. An inverse quench into sodium bicarbonate solution was performed. Direct phenylselenenylation of the enolate anion proceeded poorly. Interestingly, use of di-2-pyridyldiselenide worked well in the first two steps, but elimination proceeded in the wrong direction (to deliver a very unstable keto aldehyde following hydrolysis).

(31) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(32) (a) Ho, P.-T. *Tetrahedron Lett.* **1978**, 1623. (b) Ono, N.; Miyake, H.; Fujii, M.; Kaji, A. *Ibid.* **1983**, 3477.

Scheme V



elimination within **34** then led to **35**.[33]

In this instance, **35** was reduced with sodium borohydride–cerium trichloride in order to curtail 1,4-addition.[17] This proved particularly effective as well as stereochemically selective, since the derived ketal (99% overall yield) exhibited a 25% NOE enhancement between the newly introduced carbinol proton and the syn-hydrogen positioned at C-9.

The *tert*-butyldimethylsilyl group, which had served us so well to this point, was now removed with tetra-*n*-butylammonium fluoride to allow for subsequent oxidation. Arrival at **37** was uncomplicated, as was the subsequent liberation of all four hydroxyl groups with 7% perchloric acid in methanol.[34]

The ^1H NMR spectrum of **3** (see the Experimental Section) is fully consistent with the structural formulation and is distinctly different from that of ingenol below δ 2.0.[34] The presence of several hydroxyl groups is evidenced by the very intense broad infrared absorption observed in the 3700–3100-cm^{-1} region and by the low solubility of the colorless solid in such solvents as chloroform. The carbonyl absorption for **3** (1675 cm^{-1}) differs somewhat from that for ingenol (1705 cm^{-1}) presumably as a result of the unequal ground-state strain energy present in the two systems. MM2 calculations performed on the basic ingenane and 8-isoingenane hydrocarbon frameworks indicate their respective strain energies to be 51.1 and 48.6 kcal/mol.[35] A breakdown of the energy contributions is given in Table I. The approximately 2.5 kcal/mol thermodynamic advantage enjoyed by the C-8 epimer

Table I. Summary of MM2 Calculations[a]

energy contributions[b]	ingenane	8-isoingenane
compression	3.2469	2.3362
bending	16.8490	19.0450
stretch–bend	0.0000	0.0000
van der Waals		
1,4-energy	12.2848	11.8123
other	−0.4212	−2.5225
torsional	18.9734	17.7821
dipole	0.1840	0.1734

[a] The steric energies of the two hydrocarbons were minimized to within 0.0030 kcal/mol. [b] All values are in kcal/mol.

can be expected to increase somewhat when a carbonyl group is introduced at C-9 and this site becomes sp^2-hydridized.

The successful transformation of **4** to **3** has constituted a major synthetic undertaking in that 25 steps were utilized to accomplish the multiple functionalization. The overall efficiency of the necessarily linear approach documented here is 1.6%.

Preparation of Fatty Acid Esters. In order to investigate possible tumor-promoting activity in our ingenol congener, it was necessary to protect the C-16 primary hydroxyl group. It is well recognized in the ingenane series that a free OH group at this site is a mandatory prerequisite for biological activity.[36] Conversion to the appropriate monosilyl ether was easily accomplished with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide solution. Once this had been accomplished, introduction of the fatty acid ester groups at C-3 and/or C-5 could be realized simply by condensation with the appropriate amount of hexadecanoyl (palmitoyl) chloride in the presence of catalytic 4-(di-

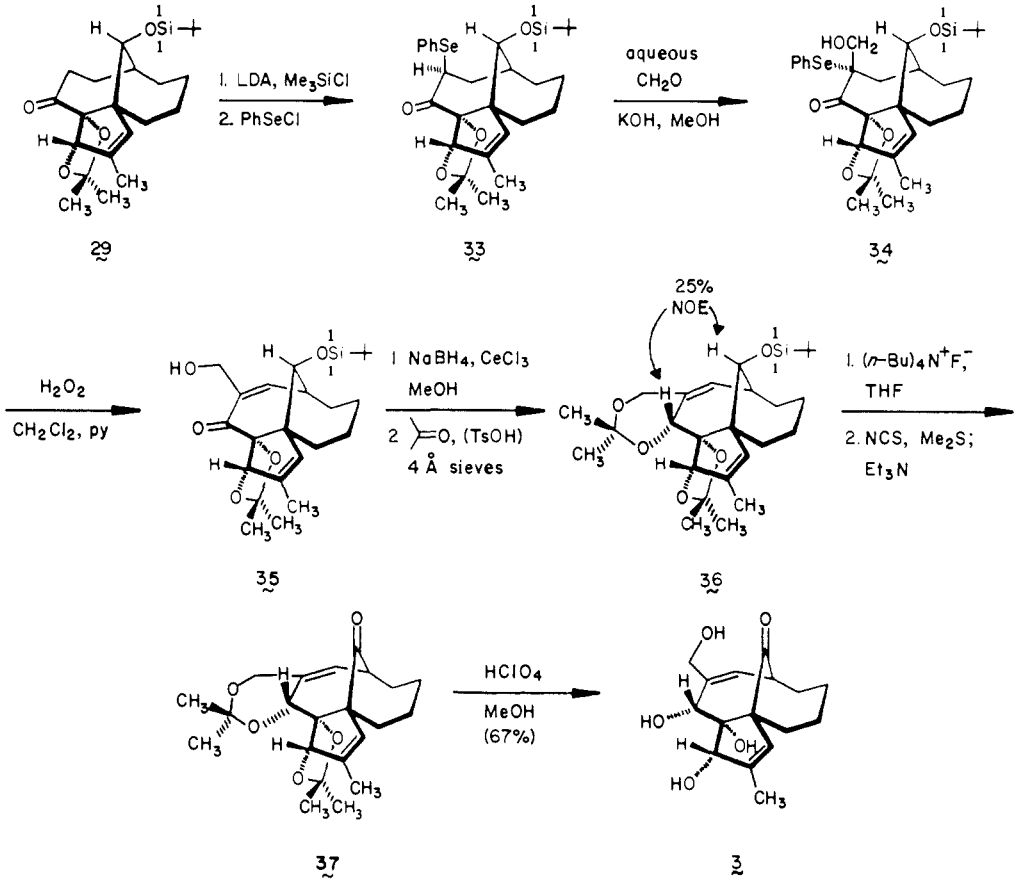
(33) The best conditions uncovered involve the two-phase system shown. Sodium periodate, *m*-chloroperbenzoic acid, and *t*-BuOOH/$Mo(CO)_6$ were less effective.

(34) Opferkuch, H. J.; Adolf, W.; Sorg, B.; Kusumoto, S.; Hecker, E. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1981**, *36B*, 878.

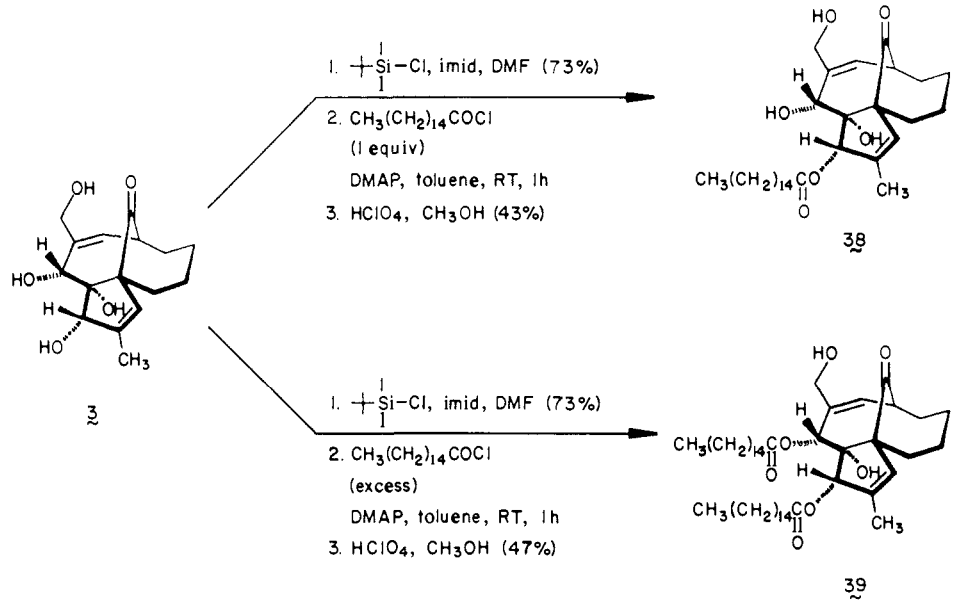
(35) Williams, E. (Monsanto Corp., St. Louis, MO), private communication.

(36) Sorg, B.; Hecker, E. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37B*, 748, 1640.

Scheme VI



Scheme VII



methylamino)pyridine (Scheme VII). Hydrolytic removal of the C-16 protecting group then made both **38** and **39** available in reasonable amounts for appropriate bioassay.

Unfortunately, the dipalmitoylated derivative proved insufficiently soluble to permit in vitro assays to be performed on it. Data for **38** were generated in two assays:[37] (a) the CEM cytotoxicity assay, which determines the ability of a compound to inhibit the growth of the human leukemic cell line CCRF-CEM relative to control growth over a 72-h incubation period, and (b) the arachidonate release assay, which determines the ability of a compound to either mimic or inhibit the ability of phorbol diesters to stimulate the release of arachidonic acid from a fibroblast cell line. In the first screen, the IC_{50} (the dose level that inhibits growth to 50% of control values) for **38** was 5.4 μg/mL. This value does not rate as particularly toxic in our experience. The monopalmitoylated compound also exhibited no inhibition to arachidonate release. Rather, in the arm of the assay which receives no phorbols, **38** stimulated release by 50% at about 25 μM.

(37) The following library of crystallographic programs was used: MULTAN 80, P. Main et al., University of York, York, England, 1980; ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1970; SDP PLUG V1.1, Y. Okaya et al., B. A. Frenz and Associates, College Station, TX, 1984. Dr. Jeffrey Howbert of Eli Lilly Co. has overseen this testing, and we thank him for his efforts.

Because this is a rather high dose, it is difficult to exclude the possibility of nonspecific membrane perturbation in this instance. Despite these unimpressive results, whole animal in vivo studies have been deemed important and are soon to be implemented.[38] (See the Noted Added in Proof.)

Experimental Section

(2*S,3*R**,4a*S**,9*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-2,3,4,5,8,9,10,11-octahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2-ol (5).** To a cooled (−78 °C) solution of **4** (5.00 g, 14.4 mmol) in tetrahydrofuran (100 mL) was added 1.0 M diisobutylaluminum hydride (22.5 mL, 22.5 mmol in hexane) over 5 min. After 15 min, the reaction mixture was quenched with 40 mL of a saturated solution of Rochelle salt and stirred overnight at 25 °C. The mixture was diluted with water (100 mL) and extracted with ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried, and concentrated to provide 5.00 g (98%) of **5** as a colorless solid, mp 109–111 °C (from petroleum ether): IR (neat, cm^{-1}) 3005, 2930, 2890, 2850, 1460, 1360, 1250, 1080, 1035, 900, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80–5.69 (m, 1 H), 5.60–5.51 (m, 1 H), 5.35 (s, 1 H), 3.67 (d, *J* = 9 Hz, 1 H), 3.58 (d, *J* = 5 Hz, 1 H), 3.08–2.92 (m, 1 H), 2.84–2.72 (br d, *J* = 15 Hz, 1 H), 2.72–2.60 (m, 1 H), 2.14 (dd, *J* = 15, 8 Hz, 1 H), 2.03–1.90 (m, 2 H), 1.91–1.74 (m, 2 H), 1.74–1.40 (m, 5 H), 1.05 (d, *J* = 6.3 Hz, 3 H), 0.92 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 145.72 (s), 131.54 (d), 129.36 (d), 126.11 (d), 82.60 (d), 74.62 (d), 45.68 (t), 44.15 (s), 37.82 (d), 34.95 (t), 33.99 (d), 32.14 (t), 31.50 (t), 29.45 (t), 26.07 (q), 19.04 (q), 18.40 (s), −3.88 (q), −4.78 (q); MS, *m/z* ($M^+ - H_2O$) calcd 330.2379, obsd 330.2353. Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.35; H, 10.41. Found: C, 72.17; H, 10.54.

(1*S,2*S**,4a*S**,9*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxy-1,2,3,4,5,8,9,10,11,11a-decahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2-ol (6).** To a refluxing solution of **5** (5.00 g, 14.3 mmol) in benzene (14 mL) containing vanadyl bis(acetylacetonate) (60 mg) was added *tert*-butyl hydroperoxide (2.8 g, 15 mmol, 70%) over 30 min. After an additional 30 min at the reflux temperature, the solution was cooled, diluted with ether (20 mL), and washed with 10% sodium sulfite solution (10 mL). The aqueous layer was extracted with ether (10 mL), and the combined organic layers were washed with brine, dried, and concentrated to provide 5.10 g (96%) of **6** as a colorless solid: IR (neat, cm^{-1}) 3300, 2950, 2860, 1460, 1375, 1250, 1090, 1035, 990, 875, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.74 (m, 1 H), 5.74–5.60 (m, 1 H), 3.74 (d, *J* = 5 Hz, 1 H), 3.42 (m, 1 H), 3.02 (s, 1 H), 2.80–2.40 (m, 3 H), 2.17–2.09 (dd, *J* = 15, 8 Hz, 1 H), 2.08–1.88 (m, 2 H), 1.80–1.68 (m, 2 H), 1.68–1.45 (m, 3 H), 1.16–1.10 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.91 (s, 9 H), 0.90–0.70 (m, 1 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 131.81 (d), 129.11 (d), 82.87 (d), 75.53 (d), 68.68 (d), 67.22 (s), 47.20 (t), 41.54 (s), 37.00 (d), 31.22 (t), 30.74 (t), 30.15 (d), 28.26 (t), 27.99 (t), 25.89 (q), 18.22 (s), 18.01 (q), −3.89 (q), −4.91 (q); MS, *m/z* ($M^+ - C_4H_9$) calcd 307.1729, obsd 307.1723.

(1*R,3*R**,4a*S**,9*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxy-3,4,5,8,9,10,11,11a-octahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (7).** A solution of **6** (5.30 g, 14.4 mmol) in methylene chloride (40 mL) was added in one batch to a stirring solution of chromium trioxide (7.2 g, 72 mmol) and pyridine (11.4 mL, 144 mmol) in 160 mL of dry methylene chloride at 0 °C. After 0.5 h, the solution was allowed to warm to room temperature and stirred vigorously for 5 h. At this point, the reaction mixture was poured onto a column of silica gel (100 g) and eluted with methylene chloride (500 mL). After removal of the solvent in vacuo, the resulting clear oil was chromatographed further on silica gel (elution with 10% ether in petroleum ether) to furnish 3.5 g (70%) of **7** as a white solid, mp 74.5–75.5 °C (lit.[11a] mp 74.5–75.5 °C).

(2*R,3a*S**,8*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-2,3a,5,6,7,8,9,10-octahydro-11-hydroxy-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-1(4*H*)-one (9).** The sequential conversion of 7 to **8** (100%) and then to **9** (65% yield alongside 25% of recovered epoxy ketone) was performed as previously described. In each instance, the spectral properties were identical with those reported earlier.

O-Methylation of 9. A solution of diazomethane (14.3 mmol, from 5.2 g of Diazald) in ether (60 mL) was added to a solution of **9** (1.18 g, 3.24 mmol) in methanol (50 mL) at room temperature. After 4 h, the excess diazomethane was decomposed with solid magnesium sulfate, the reaction mixture was filtered, and the solvent was removed. Purification by MPLC (elution with 50% ethyl acetate in petroleum ether) provided 100 mg (10%) of **10a** as a clear oil and 70 mg (7%) of **11** as a white solid.

For **10a**: IR (neat, cm^{-1}) 2960, 2920, 2860, 1694, 1585, 1460, 1255, 1145, 1070, 1020, 910, 880, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (d, *J* = 6.2 Hz, 1 H), 3.72 (s, 3 H), 2.71–2.64 (m, 1 H), 2.50–1.10 (series of m, 15 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.03 (s, 6 H).

For **11**: IR ($CHCl_3$, cm^{-1}) 2930, 2850, 1680, 1580, 1460, 1250, 1210, 1110, 1070, 830; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, *J* = 6.1 Hz, 1 H), 3.71 (s, 3 H), 2.77–2.60 (m, 1 H), 2.50–1.20 (series of m, 15 H), 0.97 (d, *J* = 6 Hz, 3 H), 0.95 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 210.55 (s), 164.88 (s), 126.55 (s), 81.58 (d), 57.62 (q), 49.00 (t), 48.17 (s), 43.32, 42.80, 29.90, 29.58, 27.60, 27.15, 26.13 (q), 24.41, 23.00, 18.41 (s), −3.69 (q), −5.10 (q), one signal not observed.

Enol Acetylation of 9. A solution of **9** (100 mg, 0.3 mmol) in pyridine (5 mL), and acetic anhydride (0.5 mL) containing 4-(dimethylamino)-pyridine (10 mg) was allowed to stand at 25 °C for 24 h. Solvent was removed in vacuo, and the residue was purified by MPLC (elution with 5% ethyl acetate in petroleum ether) to provide 80 mg (77%) of **10b** as a white solid, mp 97–98 °C (from petroleum ether): IR (film, cm^{-1}) 2960, 2860, 1760, 1725, 1630, 1470, 1360, 1255, 1190, 1080, 1020, 950, 910, 880, 835, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (d, *J* = 6.2 Hz, 1 H), 2.60–2.45 (m, 1 H), 2.45–2.30 (m, 2 H), 2.21 (s, 3 H), 2.21–2.10 (m, 3 H), 2.10–1.80 (m, 2 H), 1.80–1.20 (series of m, 8 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.93 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 204.93, 167.98, 154.28, 133.16, 81.14, 49.39, 43.12, 42.89, 40.44, 39.76, 32.68, 27.62, 27.44, 26.28, 24.13, 23.90, 20.84, 18.48, 14.86, −3.79, −5.17; MS, *m/z* ($M^+ - C_4H_9$) calcd 349.1835, obsd 349.1833. Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 68.19; H, 9.53.

Enol Silylation of 9. To a cold (0 °C) solution of **9** (630 mg, 1.73 mmol) and 2,6-lutidine (376 mg, 3.5 mmol) in ether (20 mL) was added *tert*-butyldimethylsilyl triflate (927 mg, 3.5 mmol) in ether (10 mL) over 5 min. The reaction mixture was poured onto cold (0 °C) 10% potassium bisulfate solution (75 mL) and shaken vigorously. The layers were separated, and the organic layer was quickly washed with 5% sodium bicarbonate solution (70 mL) and brine (50 mL). Solvent was removed under reduced pressure to provide 720 mg (87%) of **10c** as a clear oil: IR (neat, cm^{-1}) 2950, 2925, 2860, 1695, 1580, 1460, 1250, 1070, 945, 905, 825, 765; ^1H NMR (300 MHz, C_6D_6) δ 3.92 (d, *J* = 6.7 Hz, 1 H), 2.40–1.72 (series of m, 10 H), 1.55–1.36 (m, 3 H), 1.38–1.2 (m, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 1.07 (s, 9 H), 0.99 (s, 9 H), 0.30 (s, 6 H), 0.01 (s, 3 H), −0.01 (s, 3 H); MS, *m/z* ($M^+ - C_4H_9$) calcd 421.2594, obsd 421.2545.

Regioselective Reductive Deoxygenation of 9. A solution of diketone **9** (4.0 g, 11 mmol) in anhydrous tetrahydrofuran (45 mL) was added dropwise during 45 min to a suspension of potassium hydride (480 mg, 12 mmol) in the same solvent (12 mL) at 0 °C. After addition was complete, the solution was cooled to −45 °C, Dibal-H (12 mL, 1.0 M, 12 mmol) was added during 20 min, and the solution was stirred for an additional 30 min. The reaction mixture was diluted with 10% hydrochloric acid (100 mL), stirred at room temperature overnight, diluted with water (50 mL), and extracted with ether (5 × 100 mL). The combined organic phases were washed with brine (100 mL) and dried. High-pressure liquid chromatography (elution with 2% ethyl acetate in petroleum ether) provided 3.3 g (85%) of **12** as a white solid, mp 93–94 °C: IR (KBr, cm^{-1}) 2950, 2920, 2850, 1715, 1635, 1425, 1245, 1065, 890, 870, 825, 765; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80–6.60 (m, 1 H), 3.86 (d, *J* = 6.5 Hz, 1 H), 2.29–2.17 (m, 6 H), 2.14–1.94 (m, 3 H), 1.94–1.59 (m, 5 H), 1.59–1.40 (m, 2 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.94 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 208.97, 147.008 136.01, 81.20, 50.53, 43.37, 39.76, 39.37, 27.33, 27.14, 26.82, 26.66, 26.08, 23.81, 18.31, 14.36, −3.85, −5.11, one signal not observed. Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.36; H, 10.41. Found: C, 72.06; H, 10.36.

(1*S,2*R**,3a*S**,8*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,2,3,4,5,6,7,8,9,10-decahydro-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-1-ol (13).** To a cold (−78 °C) solution of **12** (1.0 g, 2.85 mmol) in toluene (25 mL) was added a solution of lithium aluminum hydride (2.85 mL, 2.85 mmol; 1.0 M in ether) dropwise over 15 min. The reaction mixture was stirred for an additional 30 min, quenched with saturated Rochelle salt solution (20 mL), and stirred overnight at room temperature. The solution was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried. Removal of solvent in vacuo provided 1.05 g of a clear oil. Purification by MPLC (elution with 12% ethyl acetate in petroleum ether) afforded 650 mg (65%) of alcohol **13**. In addition, 220 mg (22%) of ketone **14** was obtained.

For **14**: IR (neat, cm^{-1}) 2960, 2870, 1740, 1475, 1260, 1080, 1040, 1010, 900, 840, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, *J* = 6.6 Hz,

(38) This study is to be overseen by Professor Erich Hecker of the German Cancer Institute in Heidelberg, West Germany.

1 H), 2.35–2.05 (m, 5 H), 2.05–1.60 (series of m, 5 H), 1.50–1.15 (series of m, 9 H), 1.11 (d, J = 7 Hz, 3 H), 0.96 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H); MS, m/z ($M^+ - C_4H_9$) calcd 293.1937, obsd 293.1930.

For **13**: mp 109–110 °C; IR (CCl_4, cm^{-1}) 3620, 2960, 2930, 2860, 1470, 1435, 1250, 1200, 1070, 1000, 900, 830; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69–5.66 (m, 1 H), 3.85 (br d, J = 6 Hz, 1 H), 3.80 (d, J = 6 Hz, 1 H), 2.40–1.80 (series of m, 10 H), 1.80–1.30 (series of m, 7 H), 1.07 (d, J = 6.5 Hz, 3 H), 0.92 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 154.45, 126.47, 83.82, 80.99, 53.58, 46.51, 43.63, 40.36, 39.07, 27.56, 27.37, 27.23, 26.83, 26.10, 23.84, 18.28, 18.20, −3.84, −5.03. Anal. Calcd for $C_{21}H_{38}O_2Si$: C, 71.92; H, 10.93. Found: C, 72.01; H, 11.00.

(1*S,2*R**,3a*R**,8*S**,11*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-11,11a-epoxydodecahydro-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-1-ol (16).** To a refluxing solution of **13** (390 mg, 1.15 mmol) in benzene (5 mL) containing $VO(acac)_2$ (5 mg) was added 70% *tert*-butyl hydroperoxide (0.25 g, 1.95 mmol) over 10 min. The solution was heated at the reflux temperature for 2 h, cooled to room temperature, diluted with ether (10 mL), and extracted with saturated sodium sulfite solution (20 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried. Solvent was removed in vacuo to provide 380 mg (96%) of **16** as a clear oil: IR (neat, cm^{-1}) 3500, 2950, 2880, 1470, 1460, 1390, 1370, 1255, 1075, 1030, 1010, 990, 920, 870, 840, 775, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (d, J = 6 Hz, 1 H), 3.28 (d, J = 6 Hz, 1 H), 3.06 (d, J = 3 Hz, 1 H), 2.36–2.25 (m, 1 H), 2.20 (d, J = 7 Hz, 1 H), 2.17–1.40 (series of m, 13 H), 1.32–1.17 (m, 2 H), 1.09 (d, J = 6 Hz, 3 H), 0.93 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 78.80 (d), 77.59 (d), 71.09 (s), 61.08 (d), 48.29 (s), 43.97 (t), 43.15 (t), 38.01 (t), 36.97 (t), 27.89 (d), 26.72 (t), 26.25 (d), 26.09 (q), 23.14 (t), 20.73 (t), 18.33 (s), 16.96 (q), −3.76 (q), −5.18 (q); MS, m/z ($M^+ - C_4H_9$) calcd 309.1886, obsd 309.1877.

Cyclic (1*S,2*R**,3a*R**,8*S**,11*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)decahydro-2-methyl-11-(phenylselenyl)-3a,8-methano-3a*H*-cyclopentacyclodecen-1,11a(1*H*)-ylene Carbonate (17).** A solution of epoxy alcohol **16** (400 mg, 1.10 mmol), benzeneselenol (0.80 mL, 5.00 mmol), and titanium isopropoxide (0.94 mL, 3.3 mmol) in dichloromethane (20 mL) was stirred for 48 h at room temperature. The reaction mixture was quenched with saturated sodium bicarbonate solution (50 mL) and stirred for 1 h. The layers were separated, and the aqueous phase was extracted with ether (5 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried. The solvent was removed in vacuo, and the residue was purified by MPLC (elution with 9% ethyl acetate in petroleum ether) to provide 493 mg (87%) of diol: IR ($CHCl_3$, cm^{-1}) 3400, 2950, 2920, 2850, 1575, 1530, 1470, 1450, 1430, 1250, 1060, 1040, 960, 935, 910, 880, 850, 830, 800, 770, 730, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.51 (m, 2 H), 7.28–7.24 (m, 3 H), 4.01 (d, J = 8.4 Hz, 1 H), 3.83 (s, 1 H), 3.24–3.18 (m, 1 H), 2.80–2.65 (m, 1 H), 2.22–2.15 (m, 1 H), 2.00–1.35 (m, 16 H), 1.12 (d, J = 6.5 Hz, 3 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); MS, m/z (M^+) calcd 524.2225, obsd 524.2227.

A solution of the diol (400 mg, 0.80 mmol) and carbonyldiimidazole (146 mg, 0.9 mmol) in benzene (20 mL) was heated at reflux for 16 h. Solvent was removed in vacuo, and cyclic carbonate **17** (330 mg, 82%) was isolated by chromatography on Florisil (10 g, (elution with 2% ethyl acetate in petroleum ether) as a white solid, mp 139–140 °C: IR (neat, cm^{-1}) 2960, 2930, 2860, 1800, 1470, 1340, 1250, 1220, 1165, 1040, 990, 885, 865, 775, 745, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2 H), 7.34–7.26 (m, 3 H), 4.54 (d, J = 5.6 Hz, 1 H), 3.85 (s, 1 H), 3.28 (br d, J = 3.1 Hz, 1 H), 2.65–2.53 (m, 1 H), 2.41–2.30 (m, 1 H), 2.30–2.15 (m, 2 H), 2.05–1.92 (m, 2 H), 1.90–1.50 (m, 8 H), 1.24 (d, J = 6.3 Hz, 3 H), 0.93 (s, 9 H), 0.88–0.82 (m, 2 H), 0.14 (s, 3 H), 0.09 (s, 3 H). Anal. Calcd for $C_{28}H_{42}O_4SeSi$: C, 61.18; H, 7.70. Found: C, 61.27; H, 7.68.

(1*S,2*R**,3a*R**,8*S**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-2,3,4,5,6,7,8,9-octahydro-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecene-1,11a(1*H*)-diol (18).** Hydrogen peroxide (115 mg, 30%, 1 mmol) was added to a solution of **17** (100 mg, 0.19 mmol) in tetrahydrofuran (3 mL) at 0 °C and warmed to reflux (66 °C) where it was kept for 1 h. The solution was diluted with dichloromethane (40 mL) and extracted with water (5 mL). The organic layer was separated and dried. Solvent was removed under reduced pressure to provide the elimination product (75 mg, 98%) as a clear oil: IR (neat, cm^{-1}) 2960, 2940, 2850, 1800, 1465, 1375, 1260, 1120, 1070, 1045, 835, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02–5.94 (m, 1 H), 5.58 (dd, J = 10.8, 1.5 Hz, 1 H), 4.08 (d, J = 8.1 Hz, 1 H), 3.70 (d, J = 5.5 Hz, 1 H), 2.50–2.35 (m, 1 H), 2.20–2.00 (m, 3 H), 2.00–1.85 (m, 3 H), 1.85–1.70 (m, 4 H), 1.70–1.45 (m, 3 H), 1.13 (d, J = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 154.16, 135.10, 128.45, 94.22, 92.95, 80.33, 53.87, 48.28, 38.47, 36.47, 34.79, 30.86, 29.07, 26.02, 25.84, 25.23, 17.98, 16.75, −3.98, −5.15; MS, m/z ($M^+ - C_4H_9$) calcd 335.1679, obsd 335.1677.

A solution of the unsaturated cyclic carbonate (120 mg, 0.30 mmol) in tetrahydrofuran (10 mL) and water (1 mL) containing potassium hydroxide (100 mg, 1.8 mmol) was heated at the reflux temperature for 18 h. The solution was diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried. Solvent evaporation yielded 100 mg (84%) of **18** as a white solid: IR ($CHCl_3$, cm^{-1}) 3400, 2940, 2920, 2860, 1470, 1460, 1255, 1070, 1045, 895, 860, 835, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89–5.74 (m, 2 H), 3.60 (d, J = 6.2 Hz, 1 H), 3.05 (d, J = 10.4 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.15–1.20 (series of m, 15 H), 1.02 (d, J = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); MS, m/z (M^+) calcd 366.2590, obsd 366.2615.

(1*S,2*R**,3a*R**,8*S**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-2,3,4,5,6,7,8,9-octahydro-1-(methoxymethoxy)-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-11a(1*H*)-ol (19).** To a cold (0 °C) solution of **18** (150 mg, 0.41 mmol) and diisopropylethylamine (318 mg, 2.46 mmol) in dichloromethane (5 mL) was added chloromethyl methyl ether (255 mg, 2.05 mmol) in five portions of 51 mg (1 equiv) each at 0.5-h intervals. Thin-layer chromatography indicated the presence of mono-MOM ether **19**, the corresponding bis(MOM) ether, and some starting diol. The solution was diluted with ether (10 mL), and water (5 mL) was added. The organic layer was separated and dried, and solvent was removed in vacuo to provide 150 mg of a yellow oil. MPLC (elution with 5% ethyl acetate in petroleum ether) provided 90 mg (67%) of **19** as a clear crystalline solid, mp 75–76.5 °C, and 25 mg (13%) of the bis-MOM ether as a colorless oil.

For **19**: IR ($CHCl_3$, cm^{-1}) 3400, 2960, 2920, 2860, 1470, 1375, 1260, 1070, 880, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74–5.71 (m, 2 H), 4.74 (s, 2 H), 3.68 (d, J = 5.6 Hz, 1 H), 3.41 (s, 3 H), 3.31 (d, J = 9.7 Hz, 1 H), 2.58 (s, 1 H), 2.45–2.39 (m, 1 H), 2.20–2.05 (m, 5 H), 1.85–1.45 (m, 7 H), 1.40–1.27 (m, 1 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.93 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 135.69, 128.13, 97.19, 91.29, 81.29, 79.32, 55.83, 52.31, 44.76, 39.50, 35.35, 33.95, 28.91, 28.80, 26.75, 26.07, 23.81, 18.32, 17.77, −3.64, −5.04. Anal. Calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31. Found: C, 66.89; H, 10.24.

For the bis(MOM) ether: IR (neat, cm^{-1}) 2950, 2920, 2860, 1470, 1460, 1255, 1210, 1145, 1070, 1050, 1030, 920, 890, 860, 835, 775; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06–5.97 (m, 1 H), 5.79 (dd, J = 10.9, 1.9 Hz, 1 H), 4.86 (d, J = 6.7 Hz, 1 H), 4.71 (s, 2 H), 4.69 (d, J = 6.7 Hz, 1 H), 3.61 (d, J = 6.4 Hz, 1 H), 3.42 (s, 3 H), 3.38 (s, 3 H), 3.06 (d, J = 10.6 Hz, 1 H), 2.60–2.43 (m, 1 H), 2.22–1.92 (m, 5 H), 1.90–1.60 (m, 3 H), 1.58–1.40 (m, 4 H), 1.36–1.26 (m, 1 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.91 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); MS ($M^+ - C_2H_4O$) calcd 410.2852, obsd 410.2849.

(1*S,2*R**,3a*R**,8*S**,10*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-10,11-epoxydecahydro-1-(methoxymethoxy)-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-11a(1*H*)-ol (20).** *tert*-Butyl hydroperoxide (38.6 mg, 0.43 mmol) was added to a solution of **19** (100 mg, 0.24 mmol) and titanium isopropoxide (69 mg, 0.24 mmol) in dichloromethane (5 mL) at −20 °C. After 2 h, the solution was diluted with ether (10 mL) and the reaction mixture was quenched with saturated sodium bicarbonate solution (5 mL). The organic layer was separated and dried, and the solvent was removed in vacuo to yield 90 mg (87%) of **20** as a colorless solid, mp 108–109 °C: IR ($CHCl_3$, cm^{-1}) 3500, 2940, 2850, 1470, 1440, 1250, 1140, 1070, 1030, 960, 940, 905, 830, 770, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (m, 2 H), 3.90 (d, J = 6.8 Hz, 1 H), 3.42 (s, 3 H), 3.24 (quint, J = 4.7 Hz, 1 H), 3.14 (d, J = 5.2 Hz, 1 H), 3.12 (s, 1 H), 2.76 (s, 1 H), 2.36–2.22 (m, 1 H), 2.18–1.82 (m, 4 H), 1.80–1.65 (m, 2 H), 1.57–1.22 (m, 6 H), 1.20–1.10 (m, 1 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.93 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 96.73, 92.18, 77.73, 76.38, 58.37, 56.11, 55.70, 52.17, 45.00, 39.28, 37.83, 33.76, 29.44, 28.24, 28.09, 25.97, 23.25, 18.20, 16.48, −3.71, −5.25. Anal. Calcd for $C_{23}H_{42}O_5Si$: C, 64.75; H, 9.92. Found: C, 64.90; H, 9.94.

X-ray Crystal Structure Analysis of 20. Suitable crystals of **20** ($C_{23}H_{42}SiO_5$) for X-ray diffraction studies formed with space group symmetry of $P1$ and cell constants of a = 12.108 (3) Å, b = 13.440 (2) Å, c = 8.524 (2) Å, α = 106.16 (1)°, β = 93.46 (2)°, and γ = 72.58 (2)° with Z = 2 and a calculated density of 1.121 g/cm^3. Of the 3397 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 3016 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[37] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum W(|F_o| - |F_c|)^2$ with $W = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.056. One intermolecular hydrogen bond exists between O19 and O20 of length

2.86 Å. Tables I–III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 2 is a computer generated perspective drawing of **20** from the final X-ray coordinates showing the relative stereochemistry.

Ring Opening of 16 with Ammonium Benzoate. Ammonium benzoate (500 mg, 4.10 mmol) was added to a solution of **16** (900 mg, 2.46 mmol) in tetrahydrofuran (20 mL), and the reaction vessel was flushed with nitrogen. Titanium isopropoxide (1.22 mL, 4.1 mmol) was added via syringe, and the resulting yellow solution was stirred under nitrogen for 28 h. The reaction mixture was diluted with ether (50 mL) and quenched by addition of 5% aqueous sulfuric acid (50 mL). Vigorous stirring was maintained until two clear layers formed. The aqueous phase was extracted with ether (3 × 100 mL), and the combined organic layers were washed with saturated sodium bicarbonate solution (2 × 100 mL) and brine (50 mL) prior to drying. Solvent was removed to provide 950 mg (80%) of **21** as a white solid, mp 144–146 °C (from petroleum ether): IR (thin film, cm^{-1}) 3430, 2950, 2820, 1720, 1698, 1450, 1335, 1270, 1110, 1050, 970, 910, 880, 835, 770, 710 (carbonyl region is one peak at 1720 in ether solution); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08–8.04 (m, 2 H), 7.64–7.59 (m, 1 H), 7.48 (t, J = 7.4 Hz, 2 H), 5.00 (d, J = 5.7 Hz, 1 H), 4.26 (s, 1 H), 3.27 (d, J = 9.3 Hz, 1 H), 3.24–3.20 (m, 1 H), 2.50–2.38 (m, 1 H), 2.35–2.25 (m, 1 H), 2.00–1.75 (m, 7 H), 1.75–1.50 (m, 6 H), 1.50–1.40 (m, 1 H), 1.20 (t, J = 12.6 Hz, 1 H), 0.94 (s, 9 H), 0.92 (d, J = 7 Hz, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H). Anal. Calcd for $C_{28}H_{44}O_5Si$: C, 68.81; H, 9.07. Found: C, 68.68; H, 9.03.

Oxidation of 21. Dimethyl sulfide (31 μL, 0.42 mmol) was added to a solution of *N*-chlorosuccinimide (56 mg, 0.42 mmol) in toluene (1.5 mL) at 0 °C and stirred for 0.5 h. The resulting suspension was then cooled to −25 °C, and a solution of **21** (100 mg, 0.21 mmol) in toluene (0.5 mL) was added dropwise. The white suspension was stirred at −25 °C for 3 h. A solution of triethylamine (78 μL, 0.56 mmol) in toluene (0.3 mL) was next added, and after 5 min the cooling bath was removed and the solution was allowed to warm to room temperature. The solution was diluted with ether (20 mL) and washed with ice-cold 2% hydrochloric acid solution (2 × 20 mL) and brine (10 mL) prior to drying. Solvent removal provided 95 mg (95%) of **22** as a white solid, mp 185–186.5 °C (from petroleum ether–ethyl acetate): IR (thin film, cm^{-1}) 3480, 2860, 2820, 2750, 1740, 1715, 1470, 1460, 1260, 1175, 1120, 1070, 1055, 835, 770, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.7 Hz, 2 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 2 H), 5.19 (d, J = 4.1 Hz, 1 H), 4.47 (s, 1 H), 2.55–2.24 (m, 5 H), 2.10–1.85 (m, 5 H), 1.80–1.42 (m, 7 H), 0.99 (s, 9 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.19 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 225.19, 164.47, 133.24, 129.54, 128.52, 84.55, 82.11, 79.52, 53.25, 47.05, 44.67, 38.68, 33.39, 29.72, 28.85, 28.20, 26.00, 23.98, 21.92, 18.22, 14.21, −3.60, −4.43. Anal. Calcd for $C_{28}H_{42}O_5Si$: C, 69.10; H, 8.70. Found: C, 68.98; H, 8.65.

Selenium Dioxide Oxidation of 22. A solution of selenium dioxide (113 mg, 1.02 mmol) and **22** (240 mg, 0.51 mmol) in glacial acetic acid (10 mL) and dioxane (1.5 mL) was heated at 105 °C for 2 h. After being cooled to room temperature, the solution was diluted with water (20 mL) and extracted with ether (5 × 50 mL). The combined organic layers were filtered to remove elemental selenium and washed with water (3 × 50 mL) and brine (50 mL) before drying. Removal of solvent and chromatography on TLC grade silica (elution with 4% ethyl acetate in petroleum ether) provided 150 mg (69%) of **23** as a white solid: IR (thin film, cm^{-1}) 3450, 2950, 2920, 2860, 1725 (broad), 1625 (weak), 1450, 1380, 1330, 1310, 1260, 1110, 1060, 1000, 910, 880, 835, 770, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.87 (m, 2 H), 7.55–7.53 (m, 1 H), 7.44–7.37 (m, 3 H), 5.02 (d, J = 5.3 Hz, 1 H), 4.44 (s, 1 H), 2.76 (s, 1 H), 2.55–2.40 (m, 1 H), 2.25–2.15 (m, 1 H), 2.10–1.75 (m, 4 H), 1.65–1.60 (m, 3 H), 1.60 (d, J = 1.2 Hz, 3 H), 1.45–1.37 (m, 2 H), 1.20–1.10 (m, 1 H), 1.00 (s, 9 H), 0.90–0.80 (m, 1 H), 0.17 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 211.25, 167.38, 164.28, 134.49, 133.13, 129.73, 129.31, 128.37, 81.98, 78.26, 77.58, 57.52, 43.58, 34.11, 29.80, 29.24, 27.63, 26.02, 23.69, 21.29, 18.15, −3.61, −4.78, one carbon not observed; MS, m/z (M^+) calcd 484.2644, obsd 484.2691.

Recyclization of 23. A solution of **23** (25 mg, 0.052 mL), 18-crown-6 (5 mg), and potassium hydroxide in tetrahydrofuran–water (9:1, 5 mL) was stirred at room temperature for 2 h. The solution was diluted with water (10 mL) and was extracted with ether (3 × 20 mL). The combined organic phase were washed with brine (10 mL) and dried. Solvent was removed under reduced pressure to afford 16.2 mg (88%) of **24** as a white solid, mp 115–116 °C: IR (thin film, cm^{-1}) 2950, 2920, 2860, 1710, 1630, 1470, 1460, 1440, 1260, 1250, 1080, 1050, 1025, 1010, 965, 935, 910, 895, 885, 860, 840, 775, 750, 730, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 1.2 Hz, 1 H), 3.75 (d, J = 6.6 Hz, 1 H), 3.51 (d, J = 2.8 Hz, 1 H), 2.47–2.35 (m, 1 H), 2.17–2.00 (m, 3 H), 2.00–1.90 (m, 1 H), 1.82 (d, J = 1.2 Hz, 3 H), 1.80–1.40 (m, 5 H), 1.40–1.25 (m, 2 H), 0.97 (s, 9 H), 0.95–0.90 (m, 1 H), 0.01 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 203.95, 168.17, 136.53, 78.33, 66.80, 63.90, 49.18, 43.70, 34.69, 27.59, 27.43, 25.99, 22.96, 19.99, 18.22, 10.39, −4.48, −5.10, one signal not observed. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.54; H, 9.46. Found: C, 69.55; H, 9.50.

(2*R,3a*R**,8*S**,11*R**,11a*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-11,11a-epoxydecahydro-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-1(4*H*)-one (25).** A solution of **16** (280 mg, 0.76 mmol) in dichloromethane (1.5 mL) was added to a solution of chromium trioxide (360 mg, 3.6 mmol) and pyridine (0.5 mL, 7.20 mmol) in dichloromethane (7 mL) at 0 °C and then stirred at 22 °C for 2 h. The solution was decanted, and the solid residue was washed well with dichloromethane. The combined organic phases were filtered through a short column of silica gel (10 g), and the solvent was removed in vacuo to yield 240 7g (85%) of **25** as a white solid: IR ($CDCl_3$, cm^{-1}) 2980, 2940, 2860, 1745, 1460, 1450, 1415, 1265, 1060, 850, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (d, J = 6.5 Hz, 1 H), 3.62 (d, J = 3.5 Hz, 1 H), 2.50–2.24 (m, 3 H), 2.18–1.60 (m, 8 H), 1.60–1.32 (m, 3 H), 1.30–1.18 (m, 2 H), 1.11 (d, J = 6.4 Hz, 3 H), 0.94 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 216.14 (s), 79.88 (d), 67.15 (s), 63.53 (d), 45.00 (s), 43.67 (d), 42.37 (t), 39.78 (d), 35.12 (t), 27.78 (t), 26.05 (q), 25.85 (t), 23.16 (t), 19.36 (t), 18.32 (s), 13.01 (q), −3.68 (q), −5.28 (q), one signal not observed; MS, m/z ($M^+ - C_4H_9$) calcd 307.1729, obsd 307.1719.

Conversion of 25 to 24. A solution of **25** (200 mg, 0.55 mmol) in tetrahydrofuran (2 mL) was added dropwise over 35 min to a premixed solution of lithium diisopropylamide (1.37 mmol, from 138 mg of diisopropylamine and 0.87 mL of 1.57 M *n*-butyllithium) and chlorotrimethylsilane (297 mg, 2.75 mmol) at −78 °C. The resulting solution was kept at −78 °C for 6 h, allowed to warm to room temperture overnight, and poured onto a rapidly stirring mixture of ether (50 mL) and saturated sodium bicarbonate solution (50 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (30 mL) and brine (30 mL). Drying and solvent evaporation provided 250 mg of an orange oil. The crude silyl enol ether was dissolved in tetrahydrofuran (8 mL), and *N*-bromosuccinimide (107 mg, 0.60 mmol) was added. The solution was stirred for 20 min, and diazabicycloundecene (1.5 mL) was added. After 10 min, a white precipitate formed. The solution was filtered, and the filtrate was diluted with ether (120 mL) and washed with 2% aqueous hydrochloric acid (3 × 30 mL). The organic layer was washed with saturated sodium bicarbonate solution (30 mL) and dried. Solvent was removed under reduced pressure to provide 210 mg of an orange oil. Chromatography (MPLC, elution with 7% ethyl acetate in petroleum ether) provided 140 mg (70%) of **24** as a white solid, identical in all respects with the material prepared above by all the usual spectroscopic criteria (IR, ^1H NMR, ^{13}C NMR).

Hydride Reduction of 24. A solution of lithium aluminum hydride in ether (0.34 mL, 1.0 M, 0.34 mmol) was added dropwise to a solution of **24** (124 mg, 0.34 mmol) in toluene (10 mL) at −78 °C over 0.5 h. The mixture was stirred for an additional 0.5 h and quenched with a saturated solution of Rochelle salt (30 mL). Ether was added (30 mL), and the resulting two-phase mixture was stirred vigorously for 18 h. The layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried. Solvent was removed to provide 119 mg of a clear oil. Chromatography on TLC grade silica gel (elution with 7% ethyl acetate in petroleum ether) afforded 100 mg (84%) of **26**, followed by 13 mg (11%) of **27**, both as white foams.

For **26**: mp 78–80 °C (from ethyl acetate–petroleum ether); IR (film, cm^{-1}) 3430, 2925, 2860, 1470, 1440, 1255, 1085, 1060, 925, 915, 900, 835, 775; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, J = 1.2 Hz, 1 H), 4.19 (s, 1 H), 3.75 (d, J = 6.6 Hz, 1 H), 3.31 (d, J = 2.9 Hz, 1 H), 2.40–2.28 (m, 1 H), 2.15–1.79 (m, 6 H), 1.79 (s, 3 H), 1.78–1.56 (m, 3 H), 1.55–1.40 (m, 2 H), 1.35–1.17 (m, 2 H), 0.94 (s, 9 H), −0.01 (s, 3 H), −0.04 (s, 3 H); MS, m/z ($M^+ - C_4H_9$) calcd 307.1729, obsd 307.1734. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.29; H, 10.07.

For **27**: mp 115–116.5 °C (from petroleum ether); IR (thin film, cm^{-1}) 3400, 2960, 2940, 2860, 1470, 1460, 1445, 1255, 1120, 1085, 1065, 1005, 965, 940, 890, 835, 775, 740, 675; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1 H), 4.37 (s, 1 H), 3.81 (d, J = 6.7 Hz, 1 H), 3.61 (d, J = 3.2 Hz, 1 H), 2.40–2.30 (m, 1 H), 2.15–1.90 (m, 3 H), 1.75 (s, 3 H), 1.70–1.40 (m, 6 H), 1.30–1.15 (m, 3 H), 0.95 (s, 9 H), 0.93–0.85 (m, 1 H), 0.00 (s, 6 H); MS, m/z ($M^+ - C_4H_9$) calcd 307.1729, obsd 307.1723. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.15; H, 9.98.

Conversion of 26 to 28. Titanium isopropoxide (236 mg, 0.830 mmol) was added to a suspension of ammonium benzoate (115 mg, 0.825 mmol) and **26** (100 mg, 0.275 mmol) in tetrahydrofuran (5 mL) under nitrogen at 22 °C. The colorless solution which formed immediately was stirred

at 22 °C for 27 h. Ether (10 mL) and 10% hydrochloric acid (10 mL) were added, and the resulting mixture was stirred vigorously for 0.5 h. The layers were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (3 × 30 mL), water (10 mL), and brine (10 mL). After drying, solvent was removed in vacuo and the residue was dissolved in acetone (10 mL) and 2,2-dimethoxypropane (1 mL). *p*-Toluenesulfonic acid (50 mg) was introduced, and the solution was left to stand for 3 h at room temperature. Pyridine (0.05 mL) was added, and the solvent was removed in vacuo. The residue was partitioned between ether (60 mL) and water (50 mL). The ether layer was washed with brine (20 mL) and dried. Removal of solvent under reduced pressure provided 131 mg (91%) of **28** as a white solid: IR (thin film, cm^{-1}) 3050, 2950, 2920, 1720, 1470, 1460, 1450, 1380, 1270, 1210, 1110, 1050, 1025, 1000, 830, 775, 740, 715; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.97 (m, 2 H), 7.57 (t, J = 5.5 Hz, 1 H), 7.42 (t, J = 7.4 Hz, 2 H), 5.67 (d, J = 1.4 Hz, 1 H), 5.35 (d, J = 6.1 Hz, 1 H), 4.57 (s, 1 H), 4.29 (s, 1 H), 2.45–2.30 (m, 1 H), 2.30–2.17 (m, 1 H), 2.10–1.83 (m, 4 H), 1.80–1.64 (m, 3 H), 1.63 (s, 3 H), 1.61–1.56 (m, 1 H), 1.55 (s, 3 H), 1.45 (s, 3 H), 1.43–1.35 (m, 2 H), 0.96 (s, 9 H), 0.94–0.85 (m, 1 H), 0.11 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 165.43, 141.95, 133.03, 131.26, 130.04, 129.55, 128.36, 113.59, 94.29, 92.43, 80.44, 78.76, 61.61, 44.00, 34.68, 30.44, 28.63, 27.36, 26.95, 26.36, 26.02, 23.77, 23.08, 18.12, 14.69, −3.81, −4.77; MS, m/z ($M^+ - C_4H_9$) calcd 469.2410, obsd 469.2383.

Saponification–Oxidation of 28. A solution of **28** (130 mg, 0.25 mmol) in tetrahydrofuran (3 mL) was added to a magnetically stirred solution of potassium hydroxide (300 mg) and 18-crown-6 (50 mg) in methanol (7 mL), and the resulting mixture was stirred at room temperature for 18 h. Solvent was reduced to ca. 2 mL, and the mixture was partitioned between water (30 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 × 30 mL), and the combined organic phases were washed with brine (30 mL) and dried. Solvent was removed in vacuo to afford 100 mg (95%) of hydroxy ketal as a white foam: IR (thin film, cm^{-1}) 3470, 2910, 2850, 1460, 1380, 1250, 1180, 1165, 1130, 1090, 1040, 1000, 940, 875, 835, 770, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 1.2 Hz, 1 H), 4.79 (s, 1 H), 4.09 (d, J = 1.8 Hz, 1 H), 4.07 (dd, J = 6, 1.4 Hz, 1 H), 2.30–2.10 (m, 2 H), 1.97–1.77 (m, 3 H), 1.77 (s, 3 H), 1.76–1.48 (m, 6 H), 1.48 (s, 3 H), 1.40 (s, 3 H), 1.40–1.30 (m, 1 H), 1.25 (s, 1 H), 0.93 (s, 9 H), 0.94–0.84 (m, 1 H), 0.05 (s, 3 H), 0.01 (s, 3 H); MS, m/z ($M^+ - C_4H_9$) calcd 365.2148, obsd 365.2153.

Pyridinium chlorochromate (80 mg, 0.48 mmol) was added to a magnetically stirred suspension of hydroxy ketal (100 mg, 0.24 mmol), Celite (150 mg), and sodium acetate (90 mg) in dichloromethane (8 mL) at room temperature. After 1 h, the reaction mixture was diluted with ether (20 mL) and vacuum filtered through a fritted funnel filled with silica gel (20 g). The filter pad was washed with ether (60 mL), and the filtrate was evaporated under reduced pressure to provide 100 mg (100%) of **29** as a white solid, mp 96–98 °C (from petroleum ether): IR (thin film, cm^{-1}) 3040, 2950, 2880, 1705, 1470, 1435, 1410, 1380, 1365, 1295, 1260, 1215, 1165, 1090, 1065, 1035, 990, 945, 900, 840, 775, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (m, 1 H), 5.34 (s, 1 H), 3.54 (d, J = 5.9 Hz, 1 H), 2.87–2.75 (m, 1 H), 2.45–2.30 (m, 3 H), 2.22–1.85 (m, 4 H), 1.77 (d, J = 1 Hz, 3 H), 1.69–1.48 (m, 3 H), 1.49 (s, 3 H), 1.48–1.35 (m, 2 H), 1.23 (s, 3 H), 0.92 (s, 9 H), −0.04 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 210.34, 138.64, 132.14, 113.22, 95.54, 88.14, 77.57, 59.40, 43.14, 39.15, 36.03, 28.66, 27.08, 26.78, 26.00, 25.51, 24.56, 24.18, 18.17, 14.45, −4.41, −5.17; MS, m/z (M^+) calcd 420.2695, obsd 420.2688.

Alkylation of 29 with SEM Chloride. A 1.0 M tetrahydrofuran solution of sodium hexamethyldisilazide (0.31 mL, 0.31 mmol) was added to a solution of **29** (100 mg, 0.24 mmol) in the same solvent (5.5 mL) at −78 °C, and the mixture was stirred at that temperature for 0.5 h. SEM chloride (80 mg, 0.48 mmol) was introduced, and the mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature over an additional hour. The solution was diluted with water (10 mL) and extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (10 mL) and dried. Removal of solvent in vacuo afforded 118 mg (89%) of **30** as a slightly yellow viscous oil: IR (neat, cm^{-1}) 2950, 2920, 2860, 1700, 1470, 1460, 1450, 1380, 1370, 1360, 1255, 1210, 1170, 1090, 1035, 900, 860, 840, 780, 740, 700, 670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, J = 1.6 Hz, 1 H), 5.36 (s, 1 H), 3.61–3.42 (m, 5 H), 2.81–2.72 (m, 1 H), 2.36 (dd, J = 14.3, 11.2 Hz, 1 H), 2.30–1.95 (m, 3 H), 1.95–1.85 (m, 1 H), 1.76 (d, J = 1 Hz, 3 H), 1.76–1.74 (m, 1 H), 1.73–1.45 (m, 4 H), 1.45 (s, 3 H), 1.44–1.30 (m, 1 H), 1.20 (s, 3 H), 1.00–0.85 (m, 11 H, large singlet at 0.91), 0.01 (s, 9 H), −0.05 (s, 3 H), −0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 209.13, 138.74, 132.12, 113.40, 96.31, 88.61, 77.75, 73.17, 68.02, 59.97, 52.92, 42.41, 36.34, 28.91, 27.83, 27.37, 27.06, 26.02, 24.11, 18.31, 18.20, 14.34, −1.34, −4.41, −5.14, one signal not observed; MS, m/z ($M^+ - C_4H_9$) calcd 493.2805, obsd 493.2798.

Oxidation of 30. A 1.53 M solution of *n*-butyllithium (1.17 mL, 1.78 mmol) was added dropwise to a solution of diisopropylamine (0.253 mL, 1.78 mmol) in tetrahydrofuran (12 mL) at 0 °C and stirred at that temperature for 15 min. The solution was cooled at −78 °C, and chlorotrimethylsilane (0.45 mL, 3.55 mmol) was added. The resulting mixture was stirred at −78 °C for 1 h. A solution of **30** (300 mg, 0.55 mmol) in tetrahydrofuran (4 mL) was next added dropwise over 30 min. The solution was stirred at −78 °C for 5 h, allowed to warm to room temperature overnight, and poured onto a stirring mixture of ether (50 mL) and saturated sodium bicarbonate solution (50 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL) prior to drying. Removal of solvent in vacuo provided 350 mg of the silyl enol ether as a slightly yellow oil; MS, m/z (M^+ for $C_{33}H_{62}O_5Si_3$ by FAB) calcd 622.39, obsd 622.46.

Phenylselenenyl chloride (35 mg, 0.18 mmol) was added to a solution of the silyl enol ether (100 mg, 0.16 mmol) in tetrahydrofuran (4 mL) containing 0.025 mL of di-*tert*-butylpyridine. The mixture was stirred at room temperature for 48 h, diluted with ether (120 mL), washed with saturated sodium bicarbonate solution (50 mL), and dried. After removal of solvent in vacuo, the resulting yellow oil was dissolved in dichloromethane (4 mL) and cooled to 0 °C. Pyridine (0.1 mL) was added, followed by 30% hydrogen peroxide (0.10 mL). The mixture was stirred vigorously, allowed to warm to room temperature over 40 min, diluted with ether (50 mL), and washed with water (2 × 30 mL) and brine (20 mL). The organic phase was dried, and the solvent was removed under reduced pressure to provide 90 mg of a clear oil. Chromatography (elution with 1.5% ethyl acetate in petroleum ether, 5 g TLC grade silica gel) provided 27 mg (31%) of **31** as a clear oil, which later solidified: IR (thin film, cm^{-1}) 3020, 2940, 2915, 2840, 1735, 1680, 1465, 1450, 1375, 1360, 1250, 1155, 1090, 1060, 1005, 925, 885, 855, 835, 775, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15–6.12 (m, 1 H), 5.47 (d, J = 1.0 Hz, 1 H), 5.41 (s, 1 H), 4.24–4.19 (m, 1 H), 4.08–4.04 (m, 1 H), 3.75 (d, J = 5.4 Hz, 1 H), 3.65–3.47 (m, 2 H), 2.90 (br s, 1 H), 2.37–2.20 (m, 1 H), 2.10–2.00 (m, 1 H), 1.97–1.56 (m, 7 H, including a large singlet at 1.77), 1.55–1.25 (m, 8 H, including large singlets at 1.31 and 1.28), 1.05–0.91 (m, 2 H), 0.90 (s, 9 H), 0.01 (s, 9 H), −0.07 (s, 3 H), −0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 200.95, 138.47, 136.28, 135.34, 134.86, 113.42, 96.69, 87.92, 76.03, 71.27, 67.61, 57.39, 46.65, 34.90, 29.69, 29.24, 28.53, 28.06, 27.75, 25.93, 23.13, 18.17, 13.34, −1.38, −4.59, −5.30; MS, m/z (M^+) calcd 548.3365, obsd 548.3359.

Hydride Reduction of 31. A 1.0 M solution of lithium hydride in ether (0.086 mL, 0.086 mmol) was added to a solution off **31** (47 mg, 0.086 mmol) in toluene (5.5 mL) at −78 °C. The solution was stirred for 20 min at −78 °C and quenched with 3 mL of saturated Rochelle salt solution. The mixture was warmed to room temperature, stirred for 3 h, diluted with ether (50 mL), and washed with water (2 × 10 mL). The organic layer was dried, and the solvent was evaporated to provide 45 mg (95%) of **32** as a clear colorless oil, which later solidified: IR (thin film, cm^{-1}) 3480, 2960, 2940, 2870, 1475, 1465, 1455, 1380, 1365, 1250, 1210, 1170, 1075, 1055, 1010, 950, 935, 870, 840, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 1 H), 5.51 (s, 1 H), 4.94 (br d, J = 7.9 Hz, 1 H), 4.89 (s, 1 H), 4.22 (d, J = 11 Hz, 1 H), 4.19 (d, J = 7 Hz, 1 H), 3.95 (d, J = 11.5 Hz, 1 H), 3.67 (qt, J = 8 Hz, 1 H), 3.66 (d, J = 7.9 Hz, 1 H), 3.43 (qt, J = 8 Hz, 1 H), 2.95 (br s, 1 H), 2.27–2.16 (m, 1 H), 2.05–1.76 (m, 2 H), 1.75 (s, 3 H), 1.74–1.50 (m, 2 H), 1.49 (s, 3 H), 1.49–1.32 (m, 2 H), 1.31 (s, 3 H), 1.04–0.93 (m, 3 H), 0.92 (s, 9 H), 0.01 (s, 9 H), −0.02 (s, 3 H), −0.05 (s, 3 H); MS, m/z ($M^+ - C_4H_9$) calcd 493.2893, obsd 493.2850.

Selenenylation of 29. A solution of *n*-butyllithium (0.73 mL, 1.5 M, 1.1 mmol) was added to a solution of diisopropylamine (154 μL, 1.1 mmol) in tetrahydrofuran (8 mL) at 0 °C. After 15 min, the solution of LDA was cooled to −60 °C and a solution of **29** (150 mg, 0.36 mmol) in tetrahydrofuran (2 mL) was added dropwise. The resulting mixture was stirred at −60 °C for 20 min, and chlorotrimethylsilane (140 μL, 1.1 mmol) was added. The solution was stirred for an additional 10 min at −60 °C and transferred via cannula to a rapidly stirred saturated solution of sodium bicarbonate (50 mL) at room temperature. The solution was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (20 mL) before drying. Solvent was removed in vacuo to provide 200 mg of a slightly yellow oil, which was dissolved in methylene chloride (15 mL). Di-*tert*-butylpyridine (200 μL) was added, followed by a solution of phenylselenenyl chloride (72 mg, 0.38 mmol) in methylene chloride (1 mL). The mixture was next diluted ether (120 mL) and washed with saturated sodium bicarbonate solution (2 × 50 mL) and brine (50 mL) prior to drying. Removal of solvent under reduced pressure and chromatography (TLC grade silica gel, elution with 2% ether in petroleum ether) afforded 186 mg (90%) of **33** as a white

solid: IR (thin film, cm^{-1}) 3050, 2960, 2925, 2860, 1695, 1475, 1440, 1385, 1380, 1270, 1215, 1170, 1095, 1045, 1030, 920, 900, 845, 785, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.64 (m, 2 H), 7.32–7.28 (m, 3 H), 5.65 (d, J = 1.5 Hz, 1 H), 5.38 (s, 1 H), 3.63 (dd, J = 8.9, 3.8 Hz, 1 H), 3.61 (d, J = 6.1 Hz, 1 H), 2.77 (qt, J = 13.5 Hz, 1 H), 2.44 (dd, J = 14.9, 12.1 Hz, 1 H), 2.20–1.85 (m, 3 H), 1.80 (s, 3 H), 1.75–1.60 (m, 2 H), 1.53 (s, 3 H), 1.45 (s, 3 H), 1.40–1.25 (m, 2 H), 0.91 (s, 9 H), 0.90–0.80 (m, 2 H), –0.07 (s, 3 H), –0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.69, 138.57, 134.12, 132.23, 131.37, 129.17, 127.96, 114.10, 95.67, 88.37, 76.63, 60.15, 49.80, 43.36, 36.53, 32.92, 28.19, 27.85, 26.89, 26.49, 25.97, 23.66, 18.17, 14.57, –4.39, –5.24; MS, m/z (M^+) calcd 576.2174, obsd 576.2191.

Hydroxymethylation of 33. A solution of **33+** (186 mg, 0.32 mmol), aqueous formaldehyde (3.1 mL, 37%), and sodium hydroxide (0.31 mL, 4 N) in methanol (14 mL) was stirred at room temperature for 6 h. The solution was diluted with water (30 mL) and brine (30 mL) and extracted with ether (5 × 60 mL). The combined organic phases were washed with brine (50 mL) and dried. Solvent was removed in vacuo, and the residue was chromatographed (TLC grade silica gel, elution with 4% ethyl acetate in petroleum ether) to provide 154 mg (80%) of **34** as a colorless crystalline solid, mp 150–151.5 °C: IR (thin film, cm^{-1}) 3480, 2990, 2960, 2940, 2860, 1690, 1470, 1440, 1375, 1255, 1215, 1170, 1095, 1075, 1050, 905, 895, 880, 845, 780, 750, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.1 Hz, 2 H), 7.44–7.34 (m, 1 H), 7.33–7.30 (m, 2 H), 5.64 (d, J = 1.5 Hz, 1 H), 5.42 (s, 1 H), 3.88 (d, J = 11.6 Hz, 1 H), 3.69 (d, J = 6.7 Hz, 1 H), 3.46 (d, J = 11.6 Hz, 1 H), 2.90–2.72 (m, 1 H), 2.45 (dd, J = 15.4, 13.1 Hz, 1 H), 2.31 (dd, J = 14.7, 11.1 Hz, 1 H), 2.25–2.05 (m, 1 H), 2.00–1.85 (m, 1 H), 1.79 (s, 3 H), 1.78–1.65 (m, 1 H), 1.65–1.48 (m, 2 H), 1.47 (s, 3 H), 1.46–1.31 (m, 1 H), 1.30 (s, 3 H), 1.17–1.05 (m, 1 H), 0.96 (s, 9 H), 0.92–0.80 (m, 2 H), 0.16 (s, 3 H), –0.01 (s, 3 H); MS, m/z (M^+) calcd 606.2266, obsd 606.2261. Anal. Calcd for $C_{31}H_{46}O_5SeSi$: C, 61.47; H, 7.65. Found: C, 61.41; H, 7.68.

Oxidative Elimination of 34. A solution of 30% hydrogen peroxide (0.70 mL) in water (5.5 mL) was added to a magnetically stirred solution of **34** (154 mg, 0.25 mmol) and pyridine (0.70 mL) in methylene chloride (27 mL) at 0 °C. After 30 min, the solution was allowed to warm to room temperature and stirred vigorously for 45 min. The reaction mixture was diluted with 10% sodium thiosulfate solution (70 mL) and extracted with ether (5 × 80 mL). The combined organic layers were washed with brine (50 mL) and dried. Solvent was removed in vacuo, and the residue was chromatographed (TLC grade silica gel, elution with 8% ethyl acetate in petroleum ether) to provide 51 mg (46%) of **35** as a colorless oil that solidified on standing: IR (thin film, cm^{-1}) 3420, 3000, 2960, 2930, 2860, 1685, 1460, 1380, 1370, 1250, 1165, 1100, 1070, 1015, 935, 900, 870, 845, 780; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 3 Hz, 1 H), 5.49 (s, 1 H), 5.44 (s, 1 H), 4.34 (d, J = 12.3 Hz, 1 H), 4.20 (d, J = 12.3 Hz, 1 H), 3.77 (d, J = 5.4 Hz, 1 H), 2.94 (br s, 1 H), 2.28 (tt, J = 14, 4 Hz, 1 H), 2.05–1.96 (m, 1 H), 1.79 (s, 1 H), 1.78–1.60 (m, 5 H), 1.50–1.33 (m, 1 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.29–1.16 (m, 1 H), 0.91 (s, 9 H), –0.07 (s, 3 H), –0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 201.86, 139.89, 138.12, 135.51, 134.82, 113.74, 96.41, 87.86, 75.87, 65.94, 57.31, 46.67, 35.04, 29.28, 28.44, 28.04, 27.79, 25.93, 23.06, 18.18, –4.56, –5.27; MS, m/z ($M^+ - C_4H_9$) calcd 391.1941, obsd 391.1926.

Reduction and Ketalization of 35. Sodium borohydride (10 mg, 0.25 mmol) was added to a magnetically stirred solution of **35** (31 mg, 0.069 mmol) and cerium trichloride (20 mg, 0.081 mmol) in methanol (9 mL) and tetrahydrofuran (2 mL) at 0 °C. The solution was diluted with ether (20 mL), and 4 N sodium hydroxide solution was added. After 5 min, water (20 mL) and brine (20 mL) were added. The layers were separated, and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried. The solvent was removed in vacuo, the residue was dissolved in acetone (8 mL), *p*-toluenesulfonic acid (10 mg) and 4-Å molecular sieves (ca. 30) were added, and the mixture was left to stand at room temperature for 24 h. A drop of pyridine was then added to neutralize the acid, and the solution was diluted with ether (80 mL). The sieves were removed by filtration, and the filtrate was washed with brine (20 mL) and dried. Removal of solvent under reduced pressure afforded 34 mg (99%) of **36** as a colorless oil: ^1H NOE Difference NMR (300 MHz, $CDCl_3$) indicated a 25% NOE enhancement between the singlet at δ 4.83 and the doublet at δ 4.20, and an 8% NOE between the doublet at δ 4.2 and the broad singlet at δ 3.02; IR (thin film, cm^{-1}) 3060, 2940, 2860, 1460, 1380, 1370, 1250, 1220, 1160, 1070, 935, 900, 875, 840, 780, 675; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, J = 1 Hz, 1H), 5.39 (s, 1 H), 4.83 (s, 1 H), 4.79 (s, 1 H), 4.42 (dd, J = 11.2, 1.2 Hz, 1 H), 4.20 (d, J = 6.9 Hz, 1 H), 3.80 (d, J = 11.3 Hz, 1 H), 3.02 (br s, 1 H), 2.25–2.14 (m, 1 H), 2.00–1.85 (m, 1 H), 1.75 (s, 3 H), 1.74–1.65 (m, 1 H), 1.54 (s, 3 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.31 (s, 3 H), 0.93 (s, 9 H), 0.92–0.79 (m, 5 H), 0.005 (s, 3 H), –0.04 (s, 3 H); MS, m/z ($M^+ - CH_3$) calcd 475.2880, obsd 475.2914.

Desilylation–Oxidation of 36. A solution of **36** (34 mg, 0.069 mmo6) and tetra-*n*-butylammonium fluoride trihydrate (160 mg, 0.5 mmol) in tetrahydrofuran (5 mL) was stirred at room temperature for 7 h. The solution was diluted with saturated sodium bicarbonate solution (30 mL) and extracted with ether (4 × 50 mL). The combined organic phases were washed with brine (30 mL) and dried. Solvent was removed in vacuo to provide 26 mg (99%) of the alcohol as a colorless oil: IR (thin film, cm^{-1}) 3480, 2990, 2920, 2860, 1465, 1370, 1245, 1215, 1160, 1065, 900, 880, 745; ^1H NMR (300 MHz, C_6D_6) δ 5.42 (s, 1 H), 5.09 (s, 1 H), 4.81 (s, 1 H), 4.67 (s, 1 H), 4.55 (dd, J = 11.2, 1.3 Hz, 1 H), 3.82 (d, J = 11.2 Hz, 1 H), 3.71 (d, J = 6.8 Hz, 1 H), 2.84 (br s, 1 H), 2.83–2.21 (m, 1 H), 2.11 (d, J = 14.3, 10.7 Hz, 1 H), 1.95–1.74 (m, 2 H), 1.73 (s, 3 H), 1.71 (s, 3 H), 1.51 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.34–1.20 (m, 1 H), 1.10–0.80 (m, 4 H); MS molecular ion too transient to allow determination of exact mass.

Dimethyl sulfide (8.25 μL, 0.112 mmol) was added to a magnetically stirred solution of *N*-chlorosuccinimide (15 mg, 0.112 mmol) in toluene (320 μL) at 0 °C. After 30 min, the resulting suspension was cooled to –25 °C and a solution of the above alcohol (16 mg, 0.043 mmol) in toluene (300 μL) was added dropwise over 25 min. After 3 h of stirring at –25 °C, triethylamine (20 μL) in toluene (90 μL) was added, and the mixture was stirred for 5 min. The solution was warmed to room temperature, diluted with ether (60 mL), and washed with saturated sodium bicarbonate solution (20 mL) and brine (20 mL) prior to drying. Solvent was removed in vacuo, and the residue was chromatographed (TLC grade silica gel, elution with 8% ethyl acetate in petroleum ether) to provide 12 mg (75%) of **37** as a white solid: IR (thin film, cm^{-1}) 3050, 2990, 2940, 2860, 1693, 1450, 1380, 1370, 1245, 1160, 1130, 1110, 1085, 1065, 1030, 985, 945, 925, 895, 865, 835, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (d, J = 1.8 Hz, 1 H), 5.33 (s, 1 H), 4.88 (s, 1 H), 4.54 (br d, J = 11.3 Hz, 1 H), 4.48 (d, J = 1.4 Hz, 1 H), 4.01 (d, J = 11.3 Hz, 1 H), 3.68 (br s, 1 H), 2.24 (dd, J = 14.6, 11.6 Hz, 1 H), 2.05–1.98 (m, 1 H), 1.83 (s, 3 H), 1.81–1.58 (m, 3 H), 1.57 (s, 3 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.31–1.25 (m, 1 H), 1.03 (qt, J = 12 Hz, 1 H), 0.88 (t, J = 7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 214.92, 139.95, 137.27, 129.89, 121.31, 113.26 (2 C), 100.06, 95.99, 90.43, 72.69, 69.27, 65.17, 54.44, 33.79, 32.08, 28.32, 27.77, 27.66, 25.43, 24.37, 13.50; MS, m/z (M^+) calcd 374.2093, obsd 374.2084.

Acid-Catalyzed Hydrolysis of 37. Ketone **37** (32 mg, 0.086 mmol) was dissolved in methanol (9 mL), and 70% perchloric acid (1 mL) was added at room temperature (*CAUTION*: alcoholic solutions of perchloric acid should never be heated due to possible formation of explosive perchlorate esters). After 70 h, the reaction mixture was poured onto saturated sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (10 mL) and brine (10 mL) prior to drying. Removal of solvent under reduced pressure and chromatography of the residue (TLC grade silica gel, elution with 5% methanol in ethyl acetate) afforded 17 mg (67%) of **3** as a white solid, mp 173–176 °C, which was only sparingly soluble in chloroform: IR (thin film, cm^{-1}) 3700–3100 (broad, with peaks at 3480, 3410, 3330, 3260), 2940, 2860, 1675, 1455, 1435, 1380, 1370, 1330, 1280, 1220, 1115, 1055, 1025, 1005, 970, 925, 875, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.26 (s, 1 H), 4.61 (s, 1 H), 4.58 (s, 1 H), 4.56 (br s, 1 H), 4.47 (br d, J = 11 Hz, 1 H), 4.12 (d, J = 11 Hz, 1 H), 3.79 (br s, 1 H), 3.53 (s, 1 H), 3.41 (br s, 1 H), 3.17 (br s, 1 H), 2.23 (dd, J = 14.9, 11.7 Hz, 1 H), 2.00–1.92 (m, 1 H), 1.81 (s, 3 H), 1.80–1.50 (m, 5 H), 1.07 (qt, J = 12 Hz, 1 H); MS, m/z (M^+) calcd 294.1467, obsd 294.1449.

Monoesterification of 3. A solution of *tert*-butyldimethylsilyl chloride (44 mg, 0.29 mmol), tetrol **3** (16 mg, 0.054 mmol), and imidazole (33 mg, 0.48 mmol) in dimethylformamide (0.5 mL) was stirred at room temperature for 1 h. The solution was diluted with ethyl acetate (50 mL) and washed with saturated sodium bicarbonate solution (20 mL). The layers were separated, and the organic phase was washed with water (2 × 10 mL) and brine (10 mL) prior to drying. Solvent was removed in vacuo to provide 16 mg (73%) of the monosilylated derivative as a slightly yellow oil, which was used without purification in subsequent reactions: ^1H NMR (300 MHz, C_6D_6) δ 5.29 (d, J = 2 Hz, 1 H), 5.25 (t, J = 1.7 Hz, 1 H), 4.86 (s, 1 H), 4.67 (s, 1 H), 4.44 (br d, J = 10 Hz, 1 H), 4.43 (d, J = 1.7 Hz, 1 H), 3.96 (d, J = 10 Hz, 1 H), 3.40 (br s, 1 H), 3.08 (br s, 1 H), 2.87–2.80 (m, 1 H), 2.21 (dd, J = 15, 11.6 Hz, 1 H), 1.80 (d, J = 1 Hz, 3 H), 1.60–1.10 (m, 7 H), 0.93 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); MS, m/z (FAB, $M^+ + H$) calcd 409.2410, obsd 409.2386.

Palmitoyl chloride (11 mg, 0.040 mmol) was added to a solution of the above triol (16 mg, 0.039 mmol) and 4-(dimethylamino)pyridine (10 mg, 0.055 mmol) in toluene (1.5 mL) and stirred at room temperature for 1 h. The mixture was diluted with 0.1 M phosphate buffer (20 mL, pH 8) and extracted with ethyl acetate (4 × 25 mL). The organic layers

were washed with brine (20 mL) and dried. Removal of solvent in vacuo provided 26 mg of a white solid, which was dissolved in methanol-tetrahydrofuran (5 mL/2 mL) and treated with perchloric acid (2 drops). After 15 min, the solution was diluted with pH 8 phosphate buffer (30 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried, the solvent was removed under reduced pressure, and the residue was chromatographed (TLC grade silica gel, 18% ethyl acetate in petroleum ether) to yield 9 mg (43%) of 3-palmitate ester **38** as a white solid and 4 mg (13%) of 3,5-dipalmitate ester **39**.

For **38**: mp 120-125 °C; IR (thin film, cm^{-1}) 3550-3250 (broad), 2920, 2860, 1745, 1695, 1470, 1455, 930, 875; ^1H NMR (300 MHz, C_6D_6) δ 5.75 (d, J = 1.5 Hz, 1 H), 5.39 (t, J = 1.6 Hz, 1 H), 5.23 (s, 1 H), 4.51 (s, 1 H), 4.35 (d, J = 11.5 Hz, 1 H), 3.97 (d, J = 11.5 Hz, 1 H), 3.95-3.85 (m, 2 H), 3.38 (br s, 1 H), 2.44 (br s, 1 H), 2.23 (dd, J = 15.2, 11.7 Hz, 1 H), 2.16 (t, J = 7.6 Hz, 2 H), 1.75 (t, J = 8 Hz, 1 H), 1.67 (d, J = 1.1 Hz, 3 H), 1.62-1.50 (m, 5 H), 1.50-1.15 (m, 26 H), 0.91 (t, J = 6.6 Hz, 3 H), 0.88-0.82 (m, 1 H); MS, m/z (FAB, M^+ + H) calcd 533.3842, obsd 533.3837.

Diesterification of 3. By use of the procedure described above, but with 13 mg (0.032 mmol) of **3**, 16 mg (0.06 mmol) of palmitoyl chloride, and 28 mg (0.154 mmol) of 4-(dimethylamino)pyridine in 1 mL of toluene, there was isolated exclusively the dipalmitate **39** (11.4 mg, 47%) after chromatography (TLC grade silica gel, 12% ethyl acetate in petroleum ether): mp 80-83 °C; IR (thin film, cm^{-1}) 3530, 3420, 2920, 2850, 1740, 1720, 1695, 1470, 1450, 1390, 1170, 1155, 915, 725; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (s, 1 H), 5.76 (s, 1 H), 5.56 (s, 1 H), 5.40 (s, 1 H), 4.00 (s, 2 H), 3.70 (s, 1 H), 2.45-2.20 (m, 5 H), 2.05-1.97 (m, 1 H), 1.81-1.50 (m, 13 H, including CH_3 singlet at 1.68), 1.40-1.20 (br s, 48 H), 1.15-0.93 (m, 2 H), 0.88 (t, J = 6.5 Hz, 6 H); MS, m/z (FAB, M^+ + H) calcd 772, obsd 772.

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Note Added in Proof. The results of the irritant assays involving **38** and **39** on the mouse ear have now been completed courtesy of Professor Hecker (Heidelberg). Following a standard 24-h wait after administration, no irritant unit with 5 μg/mouse ear was seen with either ester. Thus, the IU^{24} values are necessarily larger, and the $ID_{50}{}^{24}$'s are expected to be even higher. In comparison, the IU^{24} of 3-*O*-hexadecanoylingenol is 0.1 μg/ear and its $ID_{50}{}^{24}$ is 0.050 μg/ear. Although the PKC-binding activity of **38** and **39** and their capability of stimulating Epstein-Barr-Virus synthesis are currently being determined, past correlations would suggest a prognosis that is not favorable.

Supplementary Material Available: Tables containing fractional coordinates, temperature factors, bond distances, and bond angles of **20** (5 pages). Ordering information is given on any current masthead page.

Molecular Recognition in Aqueous Media. Conformationally Restricted Water-Soluble Cyclophanes Derived from 6*H*,12*H*-5,11-Methanodibenzo[*b*,*f*][1,5]diazocine

Marlon D. Cowart, Irving Sucholeiki, Rudolf R. Bukownik, and Craig S. Wilcox*

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received January 13, 1988*

Abstract: Two new water-soluble cyclophanes, which incorporate the Tröger's base structural unit, have been prepared. The two macrocycles are very similar and differ only by two (geminal) methyl groups. NMR data reveal that these macrocycles form complexes in aqueous solution with benzenoid substrates. Analysis of the titration binding curves indicates dissociation constants ranging from 3 to 23 mM. Computer-aided molecular modeling studies of these hosts were carried out, and probable conformations for the macrocycles are discussed. Association energies for the host based on the diphenylmethane structural unit are always stronger (by 0.1-0.4 kcal/mol) than the binding energies measured for the host based on 2,2-diphenylpropane. Although the differences in association energies for the two hosts with a given substrate are small (0.1-0.4 kcal/mol), the average structures of the two complexes are believed to differ. Host-induced changes of guest chemical shifts are larger for the host derived from diphenylmethane and indicate that introduction of the geminal dimethyl group inhibits deep complexation, while shallow host-guest interactions are less affected.

Several water-soluble cyclophanes are known to be effective receptors for small, neutral organic molecules. Pioneering experiments by Koga, Tabushi, and Whitlock have demonstrated that water-soluble cyclophanes prepared from 1,4-disubstituted benzene derivatives can bind to benzenoid and naphthalenoid substrates in aqueous solution.[1] Diederich has carefully investigated a number of new water-soluble cyclophanes based on 4,4-diarylpiperidinium ions.[2] We have shown that derivatives of 6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine (which we refer to as "Tröger's base derivatives") are easily prepared in good yield.[3,4] The bridged dibenzodiazocine ring system is sharply

(1) (a) Odashima, K.; Itai, A.; Iitaka, Y.; Arata, Y.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4347-4350. (b) Soga, T.; Odashima, K.; Koga, K. *Ibid.* **1980**, *21*, 4351-4354. (c) Odashima, K.; Itai, A.; Itaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504-2505. (d) Odashima, K.; Koga, K. In *Cyclophanes*; Kheen, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983; Vol. II. (e) Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* **1983**, *113*, 145-182. (f) Tabushi, I.; Kimura, Y.; Yamamura, K. In *Chemical Approaches to Understanding Enzyme Catalysis: Biomimetic Chemistry and Transition State Analogs*; Ashani, B. S. Y., Chipman, D., Eds.; Elsevier: Amsterdam, 1981. See also (g) Tabushi, I.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727-5728. (h) Tabushi, I.; Yamamura, K. *Ibid.* **1978**, *100*, 1304-1306. (i) Tabushi, I.; Kimura, Y. *Tetrahedron Lett.* **1976**, 3327-3330. (j) Jarvi, E. T.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 657-662. (k) Whitlock, B. J.; Jarvi, E. T.; Whitlock, H. W., Jr. *J. Org. Chem.* **1981**, *46*, 1832-1835. (l) Adams, S. P.; Whitlock, H. W., Jr. *Ibid.* **1981**, *46*, 3474-3478. (m) Adams, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 1602-1611. (n) Jarvi, E. T.; Whitlock, H. W., Jr. *Ibid.* **1982**, *104*, 7196-7204. (o) Sheridan, R. E.; Whitlock, H. W., Jr. *Ibid.* **1986**, *108*, 7120-7121.

(2) (a) Diederich, F.; Dick, K. *Tetrahedron Lett.* **1982**, *23*, 3167-3170. (b) Diederich, F.; Dick, K. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 715-716. (c) Diederich, F.; Dick, K. *Angew. Chem. Suppl.* **1983**, 957-972. (d) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024-8036. (e) Diederich, F.; Dick, K. *Ibid.* **1984**, *106*, 8037-8046. (f) Diederich, F.; Dick, K.; Griebel, D. *Chem. Ber.* **1985**, *118*, 3588-3619. (g) Diederich, F.; Dick, K. *Ibid.* **1985**, *118*, 3817-3829. (h) Lutter, H.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125-1127. (i) Ferguson, S. B.; Diederich, F. *Ibid.* **1986**, *25*, 1127-11229. (j) Schurmann, G.; Diederich, F. *Tetrahedron Lett.* **1986**, *27*, 4249-4252. (k) Rubin, Y.; Dick, K.; Diederich, F.; Georgiadis, T. M. *J. Org. Chem.* **1986**, *51*, 3270-3278.

(3) (a) Wilcox, C. S. *Tetrahedron Lett.* **1985**, 5749-5752. (b) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865-1867. (c) Larson, S. B.; Wilcox, C. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 224-227. (d) Wilcox, C. S.; Cowart, M. D. *Carbohydr. Res.* **1987**, *171*, 141-160. (e) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463-471. (f) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. *Ibid.* **1988**, *53*, 98-104.

0002-7863/88/1510-6204$01.50/0