Synthetic Studies on the Ingenane Diterpenes. Construction of a Tetracyclic 8-Isoingenane Model

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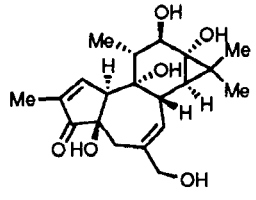
A thermally allowed tropone–diene [6π + 4π] cycloaddition is employed to produce a functionally rich BC ring building block for the construction of 8-isoingenol intermediates. Bridgehead enolate alkylation followed by aldol condensation is used to install the elements of the A-ring. Stereo- and regioselective bis-hydroxylation at C-13 and -14 of the C-ring followed by activation as the corresponding bis-mesyloxy derivative and treatment with diethyl sodiomalonate affords an advanced, functionalized isoingenol tetracyclic intermediate.

Introduction

Plant extracts from members of the family *Euphorbiaceae* have long been employed as folk medicines against a wide variety of diseases.[1] Interest in these materials intensified when the intriguing tumor-promoting properties of the seed oil from *Croton tiglium* were noted.[1b,c] As a result of these early investigations, as well as from further examination of the genus *Euphorbia*, a number of structurally complex and biologically potent diterpene esters have been identified.[1] Of these, various ester derivatives of phorbol (1) and ingenol (**2a**) are of particular medicinal significance.[2] For example, the 3-hexadecanoyl derivative of ingenol (**2a**) has been shown to be one of the most active compounds yet studied for inducing Epstein–Barr virus in lymphoblastoid cells,[3] and recent evidence has been accumulating that suggests that esters of phorbol and ingenol exert their influence by binding to, and activation of, protein kinase C.[4]



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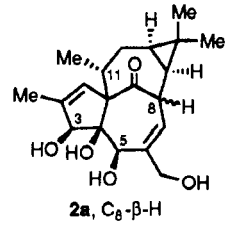

2a, C_8-β-H

2b, C_8-α-H

Considerable effort has been devoted recently to developing total synthetic approaches to both ingenol and phorbol.[5] These endeavors have resulted in two syntheses of the latter;[6] however, to date, no total synthetic entry into ingenol has been forthcoming. The obvious structural complexity of these natural products has certainly contributed to this state of affairs. One of the most noteworthy and synthetically challenging structural features exhibited by the naturally occurring ingenanes is the strained "in, out" intrabridgehead stereochemical relationship in the bicyclo[4.4.1]undecane moiety, which has been the subject of considerable synthetic attention.[5] In this account we describe the full details of an approach toward the less-strained 8-isoingenol species **2b**, which is epimeric to the natural series at one of the B–C bridgehead positions (C-8). This effort has culminated in the assembly of an advanced, functionally elaborate tetracyclic intermediate. Access to members of this class of compounds, which, to date, have not been isolated from natural sources, may provide further insight into the structure–activity relationships extant within the ingenane skeleton.[7]

Construction of a Functionalized ABC Ring Unit

Rapid assembly of a highly functionalized bicyclo[4.4.1]-undecanone intermediate via higher-order cycloaddition was envisioned to provide a suitable building block upon which the elements of the A and D rings could be installed. The basic features of this strategy are outlined in Scheme I.[8]

The centerpiece of this approach is the use of a thermally allowed [6π + 4π] cycloaddition reaction between a substituted tropone and an appropriate diene partner to provide a highly functionalized BC ring precursor. As initially envisioned, this operation employed a tropone 6π partner already endowed with the A-ring carbons possessing properly positioned latent functionalization for subsequent cyclopentannulation. Although the parent tropone (3) itself is known to be a reasonably effective 6π addend in higher-order cycloaddition reactions, formation

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(1) (a) Hartwell, J. L. *Lloydia*, **1969**, *32*, 153. (b) Hecker, E.; Schmidt, R. *Progr. Chem. Org. Nat. Prod.* **1974**, *31*, 377. (c) Evans, F. J.; Kinghorn, A. D. *Phytochemistry* **1974**, *13*, 1011. (d) Hecker, E. *Pure Appl Chem.* **1977**, *49*, 1423. (e) Evans, F. J.; Taylor, S. E. *Progr. Chem. Org. Nat. Prod.* **1983**, *44*, 1.

(2) (a) Hecker, E. in "Carcinogenesis," Vol. 2, "Mechanism of Tumor Promotion and Carcinogenesis," Slaga, T. S.; Sivak, A.; Boutwell, R. K. (Eds.); Raven Press: New York, 1978, p. 11. (b) Hecker, E.; Fusening, N. E.; Kunz, W.; Marks, F.; Thielmann, H. W. (Eds.) "Carcinogenesis," Vol. 7, "Cocarcinogenesis and Biological Effects of Tumor Promoters."•aven Press: New York, 1982. (c) Slaga, T. J. (Ed.) "Mechanism of Tumor Promotion," CRC Press, Boca Raton, FL, 1984, Vol. I-IV.

(3) (a) Kinzel, V.; Kreibich, G.; Hecker, E.; Süss, R. *Cancer Res.* **1979**, *39*, 2743. (b) Terada, M.; Adolf, M.; Opferkuch, W.; Schmidt, H. J.; Hecker, E.; Sugimura, T. *Cancer Res. Chem. Oncl.* **1982**, *103*, 17.

(4) (a) Nishizuka, Y. *Nature* **1988**, *334*, 661. (b) Nishizuka, Y. *Cancer* **1989**, *63*, 1892. (c) Jeffrey, A. M.; Liskamp, R. M. J. *Proc. Natl. Acad. Sci., USA* **1986**, *83*, 241. (d) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Ibid.* **1986**, *83*, 4214. (e) Lotter, H.; Hecker, E. *Fresenius' Z. Anal. Chem.* **1985**, *321*, 639.

(5) For a recent review of synthetic approaches to tumor-promoting diterpenes, see: Rigby, J. H. in "Studies in Natural Products Chemistry," Rahman, A.-u. (Ed); Elsevier: Amsterdam, 1993, Vol. 12, Stereoselective Synthesis (Part H), pp. 233–74.

(6) (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, Jr., J. D.; Wilhelm, R. S.; Williams, P. D. *Ibid.* **1989**, *111*, 8957. (c) Wender, P. A.; McDonald, F. E. *Ibid.* **1990**, *112*, 4956.

(7) Recent preliminary in vitro data suggest that the isoingenol series is substantially less active than natural derivatives: Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192.

(8) For an early effort in this area, see: Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398.

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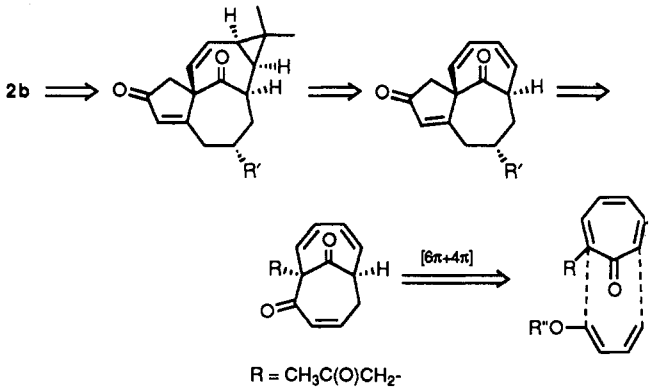
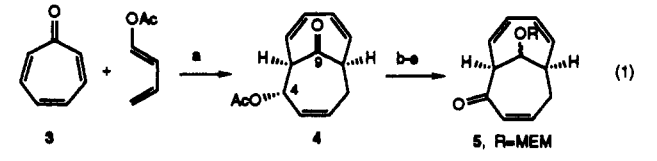
Scheme I



of the desired bicyclo[4.4.1]undecanone adduct was completely suppressed when a 1-substituted derivative was employed in early model studies from our laboratory. Only small quantities of products derived from alternative pericyclic processes were isolated in this instance. Capricious periselection as a function of substitution is a general characteristic of many higher-order cycloaddition reactions, a fact that has contributed to the paucity of synthetic applications for these reactions found in the chemical literature.[9,10]

The inability to directly access bridgehead substituted bicyclo[4.4.1]undecanone species via [6 + 4] cycloaddition required that unsubstituted tropone (**3**) serve as the 6π partner in the initial cycloaddition step. As a consequence, the viability of the entire strategy became critically dependent on the successful introduction of the A-ring carbons at a bridgehead position in the bicyclo[4.4.1]-undecanone system subsequent to the cycloaddition step. A likely candidate for achieving this objective would be alkylation of an appropriate bridgehead enolate species. While useful alkylation of bridgehead enolates is not unknown,[11] it does entail considerable risks and we proceeded to this phase of the synthesis with some concern. Unlike the more substituted series, the simplified BC ring precursor was accessed in straightforward fashion with reasonable efficiency. Heating the parent tropone (**3**) in the presence of a large surplus of 1-acetoxybutadiene (*E*/*Z* mixture) afforded adduct **4** as a single exo diastereomer in modest, but serviceable yield (59%) (eq (1)). Routine

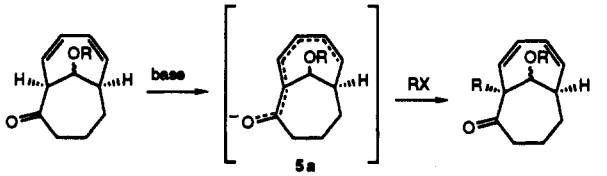


(1)

a) xylene, reflux (59%) b) $NaBH_4$, MeOH, 0°C (93%) c) MEMCl, $(i\text{-}Pr)_2EtN$ (97%) d) K_2CO_3, MeOH (94%) e) Swern ox (87%)

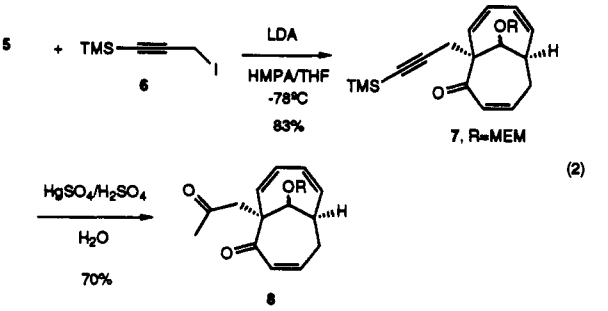
oxidation level adjustment followed to provide enone **5** as a mixture of C-9 epimers (ingenol numbering), which were separated and used independently in subsequent steps. This maneuver was necessitated by the ill-behaved nature of the enolate derived directly from compound **4**, which precluded its use in the projected alkylation step.

With reasonable quantities of enone **5** in hand, attention turned to fabricating the A-ring substructure. The enolate chemistry of enone **5** and related compounds proved to be surprisingly well-behaved and bridgehead alkylation emerged as a relatively routine aspect of these studies. The ease of generating and manipulating these carbanions apparently stems from interaction of the bridgehead enolate with the diene system in the adjacent ring via extended enolate **5a**. The requisite orbital alignments for



promoting effective delocalization of the anion are evident from molecular models. That this interaction, in fact, contributes substantially to the properties of this carbanion is evidenced by the observation that enolate **5a** prevails under both thermodynamic and kinetic conditions even when the more accessible α′ position is not blocked by the presence of a double bond.[12]

While a variety of functionalized alkylating agents have been examined previously for installing the A-ring elements,[8,12] the somewhat labile propargyl iodide **6**[13] ultimately proved to be the most effective source of the requisite three-carbon chain in functionalized form. In



(2)

the event, treatment of enone **5** with LDA at −78 °C resulted in the typically bright-red solution of the extended enolate, which, upon addition of **6**, afforded the bridgehead alkylated species **7** in 83% yield. Smooth hydration of the alkyne in **7** followed to provide the key dione **8**.[14] At this juncture, a number of options were considered for introducing the carbon substituent required at C-6 (ingenol numbering) of the final target. Several methods are available for introducing latent hydroxymethyl units via carbanion chemistry;[15] however, these have proven to be problematic transformations in our hands when attempted on this substrate. For the purposes of this model study,

(9) For an overview of higher-order cycloaddition reactions, consult: Rigby, J. H. in "Comprehensive Organic Synthesis," Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp. 617–43.

(10) The difficulties encountered during this study prompted an examination of metal-promoted higher-order cycloadditions and these results have been reported: (a) Rigby, J. H.; Ateeq, H. S. *J. Am. Chem. Soc.* **1990**, *112*, 6442. (b) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *Ibid.* **1993**, *115*, 1382.

(11) For some recent examples of bridgehead enolate alkylation, see: (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253. (b) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *Ibid.* **1988**, *110*, 4822. (c) Kende, A. S.; Kaldor, I.; Aslanian, R. *Ibid.* **1988**, *110*, 6265.

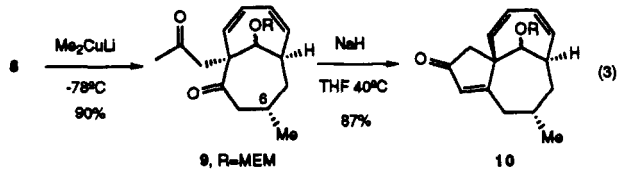
(12) Rigby, J. H.; Moore, T. L. *J. Org. Chem.* **1990**, *55*, 2959.

(13) Propargyl iodide **6** was prepared starting from propargyl alcohol using a series of literature steps: (a) Jones, T. K.; Denmark, S. E. *Org. Synth.* **1986**, *64*, 182. (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. I* **1980**, 2866. (c) Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett.* **1983**, *24*, 4883.

(14) McCrae, D. A.; Dolby, L. *J. Org. Chem.* **1977**, *42*, 1607.

(15) (a) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930. (b) Still, W. C. *Ibid.* **1978**, *100*, 1481.

a methyl group was employed in place of the hydroxymethyl carbon found at C-6 in the target molecule. This carbon was easily installed onto dione 8 in completely stereoselective fashion via organocopper chemistry, affording dione 9 in 90% yield. The exo nature of this



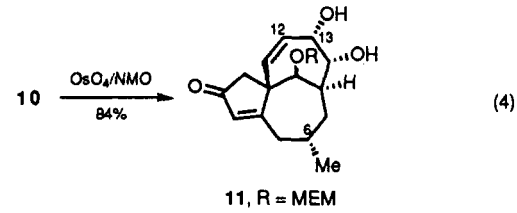
addition has been established previously by a single crystal X-ray analysis on a related bicyclic intermediate.[8] From recent investigations in this area, it has become increasingly clear that there exists a strong bias for reagent approach from the exo surface of the bicyclo[4.4.1]undecane ring system.[8,16]

The final objective of this phase of the synthesis was ring closure of compound 9 to complete construction of an intact ABC ring substructure. After exploring a number of conditions, it was found that warming 9 in the presence of sodium hydride promoted clean aldol condensation to provide the crucial tricyclic enone 10 in 87% yield. This species is particularly attractive as an (iso)ingenol precursor because actual or latent functionalization is present in each of the three ring units allowing for eventual manipulation of each sector of the molecule selectively.

Installation of the D-Ring Elements

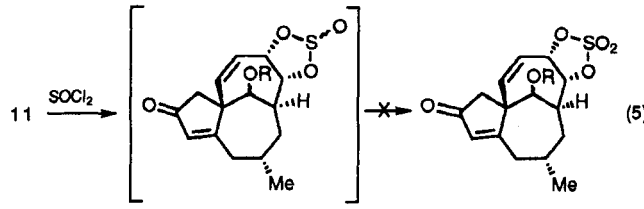
With an advanced ABC ring intermediate in hand, attention turned to the addition of the cyclopropane unit to the sterically less accessible endo face of the C-ring of compound 10. Crucial to the success of this endeavor was the ability to selectively manipulate one of the two double bonds comprising the diene in ring C. It was reasoned that the neopentyl nature of the C-11,12 unsaturation (ingenol numbering) would favor reaction at the alternative, less-hindered double bond. In support of this contention, reaction of a related tricyclic substrate with *m*-CPBA led to the production of a mixture of epoxide products with the less-hindered regioisomer prevailing. More important, attack of the oxidizing agent occurred exclusively from the anticipated exo-face as demonstrated by an X-ray crystal structure of the major product.[17] Achieving the requisite endo disposition of the D-ring assembly relative to the existing BC ring architecture demanded a tactic that would be capable of exploiting the facial bias inherent in the bicyclo[4.4.1]undecane array. An obvious and easily tested method for solving this problem would be to incorporate appropriately positioned leaving groups on the more accessible exo-surface of the substrate and then to displace them from the endo direction with a suitable carbon nucleophile.

The initial phase of this two-step operation was the selective elaboration of suitable leaving groups at C-13 and -14. The level of regioselectivity encountered during previous manipulations in this region of related tricycles was cause for encouragement. However, for our purposes bis-hydroxylation appeared to offer a number of advantages over epoxidation since the utility of a wider range of leaving group functions could be evaluated, affording greater tactical flexibility at this juncture in the sequence. Exposing compound 10 to a slight modification of the catalytic osmium tetroxide protocol provided a *single* diol in 84% yield.[18] Structure 11 was assigned to this material



based on the ^{1}H NMR multiplicity pattern of the unreacted C-ring unsaturation and the stereochemistry depicted was assumed based on the proclivity for exo-face delivery of reagents to these ring systems as alluded to earlier. Furthermore, the J_{12-13} value of 4.8 Hz was consistent with the presence of an α-disposed hydroxyl group at C-13.[19] The next objective was to activate the *cis*-diol for subsequent cyclopropane installation.

A particularly appealing strategy for accomplishing this task was to derivatize the diol in 11 as the corresponding cyclic sulfate. Sharpless has recently demonstrated the

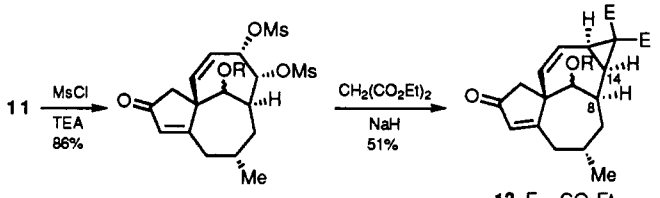


considerable utility of these intermediates for double nucleophilic displacement.[20] Treating 11 with thionyl chloride provided the intermediate sulfite as a mixture of epimers (1:1) at sulfur. This species was immediately subjected to the Sharpless catalytic RuO_4 oxidizing conditions; however, minimal reaction occurred after 1 h and extended reaction times resulted in complete decomposition of the substrate. Although cyclic sulfites are known to be less reactive than their more highly oxidized counterparts, there exist several reports of useful reactions with a variety of nucleophilic agents.[21] Unfortunately, even under relatively forcing conditions, no discernible reaction occurred between our cyclic sulfite and several carbon nucleophiles. In response to these obstacles, diol 11 was treated with *p*-toluenesulfonyl chloride in pyridine in an effort to activate the diol as the corresponding bis-tosyloxy derivative. Surprisingly, this reaction proved to be unacceptably slow in this substrate. Finally, the diol system was suitably derivatized by exposure of 11 to excess methanesulfonyl chloride/TEA in methylene chloride, which provided the requisite bis-mesyloxy compound 12 in excellent yield.

A number of candidate nucleophiles for introducing the elements of the *gem*-dimethyl cyclopropane unit were considered at this point. Cognizant of the well-established

(16) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.
(17) Cuisiat, S. V. and Heeg, M. J., Wayne State University unpublished results. Details of this X-ray crystallographic study will appear elsewhere.
(18) Baeckström, P.; Li, L.; Polec, I.; Unelius, C. R.; Wimalasiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358.
(19) Hall, L. D. *J. Org. Chem.* **1964**, *29*, 297.
(20) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655. (c) Lohray, B. B. *Synthesis*, **1992**, 1035.
(21) Gao, Y.; Zepp, C. M. *Tetrahedron Lett.* **1991**, *32*, 3155.

facial biases that prevail in the bicyclo[4.4.1]undecane system, our initial concern was identifying an agent that could effectively attack from the more sterically encumbered endo face of the C-ring. Although presenting possible difficulties for subsequent conversion into the requisite *gem*-dimethyl substituents, malonate anion appeared to offer several advantages for achieving these objectives and we elected to proceed with this nucleophile.[19,22] Reaction of the newly acquired bis-mesylate **12** with diethyl malonate in the presence of excess sodium hydride at 70 °C provided the desired tetracycle **13** as a single diastereomer in modest yields.[19,22] The assigned



(6)

stereochemistry of the cyclopropane ring is supported by the relatively small coupling between H-8 and H-14 (J = 3.0 Hz). A much larger coupling constant is characteristic of the corresponding trans relationship between these two protons as established in the natural ingenol series.[16] Compound **13** represents an advanced isoingenol intermediate with functionalization appropriately positioned throughout the tetracycle for further conversion into the target molecule. Efforts to transform the *gem*-bis(ethoxycarbonyl) groups on substrate **13** into the necessary methyls met with limited success due to difficulties encountered during attempted oxidation level adjustment. Unfortunately, most reducing conditions appeared to sever one of the bonds of the cyclopropane ring. Work on a modified strategy for circumventing this problem is currently being pursued.

The strategy into the ingenane diterpenes described in this report is particularly amenable to rapidly accessing advanced tri- and tetracyclic intermediates. Further work is currently underway on related entries into both the ingenane and 8-isoingenane series. Recent results on transition metal promoted [6π + 4π] cycloaddition reactions[10] suggest that functionalized bicyclo[4.4.1]undecane building blocks will become increasingly accessible, facilitating the construction of ingenane natural products.

Experimental Section[23]

7α-Acetoxy-(1Hα,6Hα)-bicyclo[4.4.1]undeca-2,4,8-trien-11-one (4). A solution of 2,4,6-cycloheptatrien-1-one (tropone) (**3**) (10 g, 0.094 mol) and 1-acetoxy-1,3-butadiene (15.8 g, 0.14 mol) in xylene (300 mL) was heated at reflux for 5 d. Removal of solvent *in vacuo* and chromatography (silica gel, hexanes/ethyl acetate, 4:1) afforded 12.1 g (59%) of the cycloadduct as a pale yellow oil: R_f = 0.35 (3:1 hexanes–ethyl acetate); IR (neat) ν 3031, 2937, 1735, 1707, 1437, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.56 (m, 2 H), 3.54 (brq, J = 6.3 Hz, 1 H), 3.67 (brt, J = 6.3 Hz, 1 H), 5.67 (m, 4 H), 5.78 (m, 1 H), 6.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.9, 29.1, 55.2, 60.5, 69.5, 125.1, 126.1, 127.6, 129.8, 130.5, 131.4, 170.2, 202.9; mass spectrum m/e (rel inten) 218 (2), 176 (4), 158 (11), 149 (11), 108 (9), 107 (100); HRMS calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0940. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; found: C, 71.14; H, 6.54.

7-Oxo-11(*R*)-[(2-methoxyethoxy)methoxy]-(1Hα,6Hα)-bicyclo[4.4.1]undeca-2,4,8-triene (5). Ketone **4** (12 g, 0.055 mol) was dissolved in methanol (79 mL) and cooled to 0 °C. Sodium dihydrogen phosphate (9.1 g, 0.066 mol) was added as a buffer. Sodium tetrahydridoborate (2.29 g, 0.061 mol) was then added in small portions and the reaction followed by TLC. When the reaction was complete as indicated by TLC, the mixture was reduced *in vacuo* to half its volume, poured into methylene chloride (400 mL), and washed with 5% aqueous hydrochloric acid solution (150 mL), water (150 mL), and brine (2 × 150 mL) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and chromatography (silica gel, hexanes/ethyl acetate, 4:1) afforded 5.81 g (48%) of the less-polar alcohol as a white solid: mp 71–72 °C (hexanes); R_f = 0.40 (hexanes/ethyl acetate, 2:1); IR ($CDCl_3$) ν 3560, 3017, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.21 (m, 1 H), 2.95 (m, 1 H), 3.00 (m, 1 H), 3.28 (m, 1 H), 3.33 (d, J = 9.6 Hz, 1 H), 4.52 (m, 1 H), 5.41 (m, 1 H), 5.49 (m, 1 H), 5.71 (m, 3 H), 5.86 (m, 1 H), 5.94 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 25.0, 45.3, 48.1, 72.1, 74.5, 124.2, 125.7, 127.1, 130.4, 133.4, 135.8, 169.1; mass spectrum m/e (rel inten) 220 (0.2), 160 (15.0), 142 (18.9), 131 (16.7), 107 (17.7), 91 (100.0); HRMS calcd for $C_{13}H_{16}O_3$ 220.10993, calcd – CH_3CO_2H 160.0888, found 160.0884. Also isolated was the more-polar alcohol (5.45 g, 45%) of as a pale yellow oil: R_f = 0.18 (hexanes/ethyl acetate, 2:1); IR (neat) ν 3467, 3016, 1735, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H), 2.36 (dd, J = 8.4, 5.8 Hz, 1 H), 2.44 (m, 1 H), 3.03 (m, 1 H), 3.32 (m, 1 H), 4.38 (m, 1 H), 5.36 (dd, J = 6.8, 5.3 Hz, 1 H), 5.59 (m, 1 H), 5.73 (m, 2 H), 5.88 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 27.5, 46.0, 49.5, 62.0, 68.0, 125.1, 127.6, 128.4, 129.6, 134.0, 134.5, 169.7; mass spectrum m/e (rel inten) (no M$^+$), 160 (51), 145 (13), 142 (14), 131 (21), 129 (16), 115 (11), 112 (11), 91 (100); HRMS calcd for $C_{13}H_{16}O_3$, calcd – CH_3CO_2H 160.0888, found 160.0883.

To a solution of the less-polar alcohol (5.3 g, 0.024 mol) in methylene chloride (30 mL) was added diisopropylethylamine (8.3 mL, 0.048 mol), followed by the dropwise addition of MEMCl (6.87 mL, 0.060 mol). The reaction was stirred for 15 h at rt, and then poured into methylene chloride (300 mL), washed consecutively with water (150 mL), 5% aqueous hydrochloric acid solution (150 mL) and saturated aqueous sodium bicarbonate solution (150 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* and chromatography (silica gel, hexanes/ethyl acetate, 2:1) afforded 7.19 g (97%) of the product as a yellow oil: R_f = 0.45 (hexanes/ethyl acetate, 2:1); IR (neat) ν 3019, 2963, 1734, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.12 (m, 1 H), 2.90 (m, 1 H), 3.07 (m, 1 H), 3.35 (s, 3 H), 3.40 (m, 1 H), 3.51 (m, 2 H), 3.67 (m, 2 H), 4.34 (t, J = 3.3 Hz, 1 H), 4.70 (dd, J = 13.5, 7.1 Hz, 2 H), 5.30 (dd, J = 6.8, 4.8 Hz, 1 H), 5.55 (m, 1 H), 5.69 (m, 4 H), 5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 25.8, 42.9, 45.2, 58.9, 66.8, 70.4, 71.7, 79.1, 94.4, 124.3, 126.7, 127.1, 129.7, 133.5, 135.5, 170.8; mass spectrum m/e (rel inten) 176 (4), 159 (3), 129 (10), 91 (17), 89 (56); HRMS calcd for $C_{17}H_{24}O_5$ 308,-16235, calcd – MEM 219.1021, found 219.1019.

The acetate (7.19 g, 0.023 mol) was placed in methanol (35 mL), and potassium carbonate (3.87 g, 0.028 mol) was added at rt. The resulting purple solution was stirred for 5 h at which time it was reduced to half its volume and poured into ether (300 mL). The organic layer was washed with water (2 × 150 mL) and brine (150 mL) and concentrated *in vacuo*. Chromatography (silica gel, hexanes/ethyl acetate, 3:1) afforded 5.83 g (94%) of the alcohol as a yellow oil: R_f = 0.23 (hexanes/ethyl acetate, 2:1); IR (neat) ν 3511, 3020, 2887, 1449 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (m, 1 H), 2.95 (m, 2 H), 3.36 (s, 3 H), 3.40 (m, 1 H), 3.53 (brt, J = 4.6 Hz, 2 H), 3.73 (m, 2 H), 4.29 (m, 1 H), 4.51 (d, J = 8.2 Hz, 1 H), 4.55 (brt, J = 3.7 Hz, 1 H), 4.81 (dd, J = 15.1, 7.2 Hz, 2 H), 5.45 (m, 1 H), 5.65 (m, 3 H), 5.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.6, 42.8, 48.6, 58.9, 67.4, 69.9, 71.6, 81.1, 94.6, 124.4, 125.7, 126.6, 132.3, 132.7, 134.7; mass spectrum m/e (rel inten) 160 (35), 145 (21), 143 (11), 129 (13), 117 (15), 91 (100); HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, calcd + H 267.1596, found 267.1597.

To a solution of oxalyl chloride (2.23 mL, 0.026 mol) in methylene chloride (39 mL) was added dropwise DMSO (3.88 mL, 0.055 mol) in methylene chloride (4.5 mL) at –78 °C. The reaction mixture was stirred for 20 min and the alcohol (5.8 g, 0.022 mol) in methylene chloride (10.9 mL) was added dropwise.

(22) Podder, R. K.; Sarkar, R. K.; Ray, S. C. *Indian J. Chem.* **1988**, *27B*, 530.

(23) For general experimental information, consult: Rigby, J. H.; Kotnis, A.; Kramer, J. *J. Org. Chem.* **1990**, *55*, 5078.

Stirring was continued for 1 h at −78 °C and triethylamine (15.2 mL, 0.11 mol) was then added dropwise to the yellow solution which turned red-brown. The reaction mixture was stirred for 20 min and then allowed to warm to room temperature. Water (50 mL) was added and the aqueous layer extracted with methylene chloride (3 × 100 mL). The organic phase was washed with 5% hydrochloric acid solution (150 mL), water (100 mL), saturated aqueous sodium bicarbonate solution (150 mL), and water (2 × 100 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a brown oil which was chromatographed (silica gel, hexanes/ethyl acetate, 4:1), providing 5.0 g (87%) of ketone **5** as a yellow oil: R_f = 0.57 (hexanes/ethyl acetate, 2:1); IR (neat) ν 3017, 2931, 2818, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (ddd, J = 16.6, 6.8, 1.1 Hz, 1 H), 2.76 (ddd, J = 16.6, 5.3, 1.4 Hz, 1 H), 3.10 (m, 1 H), 3.25 (s, 3 H), 3.50 (m, 2 H), 3.64 (m, 2 H), 3.96 (m, 1 H), 4.23 (brt, J = 4.0 Hz, 1 H), 4.65 (s, 2 H), 5.49 (dd, J = 10.6, 7.1 Hz, 1 H), 5.80 (m, 3 H), 6.05 (dd, J = 12.3, 0.88 Hz, 1 H), 6.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5, 43.8, 58.8, 61.6, 67.1, 71.5, 76.4, 94.6, 124.6, 124.9, 127.1, 133.5, 135.0, 142.5, 198.2; mass spectrum m/e (rel inten) 264 (1), 175 (10), 91 (100); HRMS calcd for $C_{15}H_{20}O_4$ 264.1361, calcd − MEM 175.0759, found 175.0763. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.41; H, 7.79.

1-Iodo-3-(trimethylsilyl)-2-propyne (6).[13b,c] To a 2-L flask equipped with a mechanical stirrer was added 3-(trimethylsilyl)-2-propyn-1-ol (25 g, 0.2 mol, prepared according to the literature[13a]) in a 3:1 mixture of diethyl ether/acetonitrile (1 L). To the solution (maintained at 0–5 °C by external cooling) was added successively triphenylphosphine (77 g, 0.3 mol), imidazole (20 g, 0.3 mol), and portions of iodine (74 g, 0.3 mol). The resultant yellow-brown suspension was stirred for 45 min during which time a white solid formed. Saturated aqueous sodium bicarbonate solution was added (700 mL) and the reaction mixture was stirred for another 5 min. The mixture was then extracted with ether (3 × 400 mL), washed with 10% aqueous sodium thiosulfate solution (300 mL) and water (300 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product containing the white solid was then dissolved in pentane, filtered, and concentrated *in vacuo*. Filtration through a pad of silica gel with pentane afforded 34.70 g (72%) of the labile alkyl iodide as a pale yellow oil: R_f = 0.86 (hexanes/ethyl acetate, 3:1); IR (neat) ν 2955, 2157 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9 H), 3.69 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ −15.5, −0.39, 90.7, 101.9.

6α-[3-(Trimethylsilyl)-2-propyn-1-yl]-11(*R*)-[(2-methoxyethoxy)methoxy]-7-oxo-(1Hα)-bicyclo[4.4.1]undeca-2,4,8-triene (7). To a solution of lithium diisopropylamide in tetrahydrofuran (16.8 mL) at −78 °C prepared from diisopropylamine (1.6 mL, 0.012 mol) and *n*-butyllithium (2.5 M in hexanes, 4.4. mL, 0.011 mol) was added dropwise the enone (2.6 g, 0.0098 mol) in tetrahydrofuran (9.8 mL). The resulting red solution was stirred for 5 min at −78 °C and HMPA (2.6 mL) was added, followed by alkyne **6** (4.6 g, 0.0196 mol). The reaction mixture was then warmed to rt and stirred until no starting material remained by TLC analysis (10 min). The mixture was quenched with saturated aqueous ammonium chloride solution (2 mL), poured into ether (200 mL), washed with water (2 × 100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography (silica gel, hexanes/ethyl acetate, 15:1) afforded 3.02 g (83%) of the product as a yellow oil: R_f = 0.70 (hexanes/ethyl acetate, 2:1); IR (neat) ν 3027, 2956, 2175, 1664, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 9 H), 2.39–2.50 (m, 1 H), 2.55–2.65 (m, 1 H), 2.79 (ABq, $\Delta\nu_{AB}$ = 74.6 Hz, J = 17 Hz, 2 H), 3.34 (s, 3 H), 3.36 (m, 1 H), 3.48–3.53 (m, 2 H), 3.55–3.61 (m, 1 H), 3.69–3.75 (m, 1 H), 4.40 (s, 1 H), 4.80 (d of ABq, $\Delta\nu_{AB}$ = 8.0 Hz, J = 7.2, 1.5 Hz, 2 H), 5.15 (d, J = 11.7 Hz, 1 H), 5.80–5.90 (m, 1 H), 5.90–6.10 (m, 3 H), 6.50–6.58 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.07, 27.8, 27.9, 42.8, 58.9, 64.1, 67.5, 71.6, 80.4, 87.7, 96.5, 104.1, 125.7, 128.0, 128.9, 135.0, 135.3, 142.6, 198.5; mass spectrum m/e (rel inten) 285 (4), 201 (51), 129 (7), 115 (3); HRMS calcd for $C_{21}H_{30}O_4Si$ 374.1913, calcd − MEM 285.1311, found 285.1306.

6α-(2-Oxopropyl)-11(*R*)-[(2-methoxyethoxy)methoxy]-7-oxo-(1Hα)-bicyclo[4.4.1]undeca-2,4,8-triene (8). A mixture of mercuric sulfate (0.14 g, 0.48 mmol), sulfuric acid (37 M, 2 drops), water (2 mL), and tetrahydrofuran (10 mL) were placed in a round-bottom flask and stirred for 5 min. Compound **7** (3.0 g, 8 mmol) was then added to the yellow suspension and stirred for 1 h. The solution was poured into water (10 mL) and extracted with methylene chloride (4 × 50 mL). The remaining aqueous phase was saturated with sodium chloride and extracted further with methylene chloride. The combined organic extracts were then washed with brine (100 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give a yellow oil. Chromatography (silica gel, hexanes/ethyl acetate, 8:1) afforded 1.79 g (70%) of diketone **8**: R_f = 0.23 (hexanes/ethyl acetate, 4:1); IR (neat) ν 3025, 2931, 2888, 1713, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 2.41 (m, 1 H), 2.74 (m, 1 H), 3.05 (ABq, $\Delta\nu_{AB}$ = 29.2 Hz, J = 16.7 Hz, 2 H), 3.37 (s, 3 H), 3.60 (m, 3 H), 3.72 (m, 2 H), 4.35 (d, J = 3.86 Hz, 1 H), 4.69 (ABq, $\Delta\nu_{AB}$ = 11.1 Hz, J = 6.99 Hz, 2 H), 5.45 (d, J = 12.0 Hz, 1 H), 5.92 (m, 3 H), 6.11 (dt, J = 12.2, 1.2 Hz, 1 H), 6.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.0, 31.5, 42.9, 48.6, 58.8, 63.1, 67.9, 71.5, 81.1, 96.8, 125.7, 126.3, 130.3, 134.5, 134.5, 141.9, 199.4, 206.7; mass spectrum m/e (rel inten) 320 (1), 231 (16), 147 (79), 129 (8), 105 (22); HRMS calcd for $C_{18}H_{24}O_5$ 320.16236, calcd − MEM 231.1021, found 231.1025.

6α-(2-Oxopropyl)-9α-methyl-11(*R*)-[(2-methoxyethoxy)methoxy]-7-oxo-(1Hα)-bicyclo[4.4.1]undeca-2,4-diene (9). Copper(I) iodide (1.88 g, 9.9 mmol) was placed in a flame-dried flask, anhydrous diethyl ether (11.4 mL) was added, and the slurry cooled to −20 °C. Methyllithium (1.4 M, 14.1 mL, 19 mmol) was injected dropwise via syringe and the clear solution was stirred for 30 min. The solution was then cooled to −78 °C and enone **8** (1.58 g, 4.9 mmol) in diethyl ether (11.5 mL) was added. The resultant yellow reaction mixture was stirred for 2 h, warmed to −20 °C, and stirred for an additional 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL), and dried over magnesium sulfate. The mixture was concentrated *in vacuo* and chromatography (silica gel hexanes/ethyl acetate, 4:1) afforded 1.49 g (90%) of diketone **9** as a yellow oil: R_f = 0.51 (hexanes/ethyl acetate, 2:1); IR (neat) ν 2959, 1724, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.4 Hz, 3 H), 1.56 (m, 1 H), 1.90 (m, 1 H), 1.98 (m, 1 H), 2.15 (s, 3 H), 2.46 (m, 2 H), 2.95 (ABq, $\Delta\nu_{AB}$ = 33.5 Hz, J = 17.3 Hz, 2 H), 3.17 (m, 1 H), 3.38 (s, 3 H), 3.54 (m, 2 H), 3.73 (m, 2 H), 4.15 (d, J = 5.2 Hz, 1 H), 4.70 (ABq, $\Delta\nu_{AB}$ = 16.8 Hz, J = 7.4 Hz, 2 H), 5.65 (m, 2 H), 5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.8, 26.1, 31.0, 35.8, 44.0, 48.3, 49.8, 58.9, 62.3, 68.2, 71.6, 79.9, 96.7, 125.2, 125.4, 131.8, 132.6, 205.9, 209.0; mass spectrum m/e (rel inten) 336 (0.6), 247 (66), 231 (13), 187 (9), 187 (9), 161 (9), 147 (57), 105 (25); HRMS calcd for $C_{19}H_{28}O_5$ 336.1936, calcd − MEM 247.1334, found 247.1330.

12(*R*)-[(2-methoxyethoxy)methoxy]-8a,9,10,11-tetrahydro-10α-methyl-3aα,8α-methano-3aα*H*-cyclopentacyclodecen-2(3*H*)-one (10). Sodium hydride (60% dispersion in oil, 0.36 g, 8.9 mmol, washed with pentane) was suspended in tetrahydrofuran (44 mL) and the slurry was warmed to 40 °C with an oil bath. Diketone **9** (1.49 g, 4.4 mmol) in tetrahydrofuran (12 mL) was then added via a syringe and the mixture gradually turned dark brown. The reaction mixture was stirred for 2 h at this temperature and then cooled to 0 °C. The solution was quenched carefully with water (3 mL), poured into ether (150 mL), washed with water (2 × 80 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Chromatography (silica gel, hexanes/ethyl acetate, 3:1) afforded 1.23 g (87%) of **10** as a white solid: mp 59–60 °C (hexanes); R_f = 0.43 (hexanes/ethyl acetate 1:1); IR ($CDCl_3$) ν 2920, 1705, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 3 H), 1.42 (m, 1 H), 1.71 (m, 1 H), 2.13 (m, 1 H), 2.35 (m, 1 H), 2.49 (ABq, $\Delta\nu_{AB}$ = 93.3 Hz, J = 17.7 Hz, 2 H), 2.75 (m, 1 H), 2.89 (m, 1 H), 3.35 (s, 3 H), 3.52 (m, 2 H), 3.66 (m, 2 H), 4.01 (d, J = 2.9 Hz, 1 H), 4.69 (ABq, $\Delta\nu_{AB}$ = 42.0 Hz, J = 7.9 Hz, 2 H), 5.25 (d, J = 12.4 Hz, 1 H), 5.77 (m, 2 H), 5.88 (m, 1 H), 5.95 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.2, 34.1, 40.2, 43.2, 51.6, 58.9, 59.7, 68.1, 71.6, 80.3, 95.3, 125.1, 125.4, 132.6, 132.9, 133.6, 179.0, 207.1; mass spectrum m/e (rel inten) 319 (8), 318 (3), 243 (5), 213 (10); HRMS calcd for $C_{19}H_{26}O_4$ 318.1831, found 318.1834. Anal. Calcd for $C_{19}H_{26}O_4$, C, 71.66; H, 8.24. Found: C, 71.55; H, 8.28.

6α,7α-Dihydroxy-12(*R*)-[(2-methoxyethoxy)methoxy]-10α-methyl-6,7,8,9,10,11-hexahydro-3aα,8α-methano-3aα*H*-cyclopentacyclodecen-2(3*H*)-one (11). To a stirred solution of compound **10** (0.403 g, 1.3 mmol) in acetone (0.46 mL) and water

(1.15 mL) was added *N*-methylmorpholine *N*-oxide (60% wt in water, 0.16 mL, 1.5 mmol) and osmium tetroxide (10 mg/mL THF, 0.96 mL, 0.038 mmol). The reaction mixture was stirred for 4 h at room temperature and sodium hydrosulfite, magnesium silicate, and water (10 mL) were added. The mixture was stirred for 20 min and filtered on Celite and the filtrate neutralized to pH 7 with 5% aqueous hydrochloric acid solution. The acetone was removed and the pH further adjusted to 2. The solution was saturated with sodium chloride and extracted with chloroform (3 × 30 mL) and the organic phase dried over anhydrous sodium sulfate and concentrated *in vacuo*. Chromatography (silica gel, chloroform/acetone, 7:3) afforded 0.363 g (84%) of the diol as a white solid: mp 62–63 °C (hexanes/ether, 6:1); R_f = 0.2 (hexanes/ethyl acetate 1:2); IR ($CDCl_3$) ν 3422, 2950, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.3 Hz, 3 H), 1.62 (d, J = 14.7 Hz, 1 H), 1.75 (dt, J = 14.7, 4.8 Hz, 1 H), 2.06 (brs, 1 H), 2.43 (dd, J = 18.3, 9.6 Hz, 1 H), 2.49 (ABq, $\Delta\nu_{AB}$ = 99.89 Hz, J = 17.4 Hz, 2 H), 2.57 (t, J = 3.6 Hz, 1 H), 2.79 (dd J = 18.3, 3.3 Hz, 1 H), 3.35 (s, 3 H), 3.41–3.59 (m, 4 H), 3.60–3.69 (m, 2 H), 3.87 (brs, 1 H), 4.30 (brs, 1 H), 4.70 (d, J = 3.3 Hz, 1 H), 4.72 (ABq, $\Delta\nu_{AB}$ = 35.88 Hz, J = 7.2 Hz, 2 H), 5.28 (d, J = 12.6 Hz, 1 H), 5.67 (dd, J = 12.6, 4.8 Hz, 1 H), 5.89 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.5, 34.9, 39.9, 44.9, 51.2, 58.7, 58.9, 67.6, 70.9, 71.6, 73.6, 77.6, 95.6, 128.7, 131.6, 135.6, 181.5, 207.5; mass spectrum *m/e* (rel inten) 352 (1), 263 (3), 199 (4), 162 (11); HRMS calcd for $C_{19}H_{28}O_6$ 352.1886, found 352.1891.

6α,7α-Bis[(methylsulfonyl)oxy]-12(*R*)-[(2-methoxyethoxy)-methoxy]-10α-methyl-6,7,8,9,10,11-hexahydro-3aα,8α-methano-3aα*H*-cyclopentacyclodecen-2(3*H*)-one (12). To a solution of diol 11 (0.126 g, 0.36 mmol) in methylene chloride (1.8 mL) at −5 °C was added dropwise triethylamine (0.15 mL, 1.1 mmol), followed by methanesulfonyl chloride (0.069 mL, 0.89 mmol). The reaction mixture was stirred at this temperature for 1 h and then was poured into methylene chloride (150 mL), washed with 5% aqueous hydrochloric acid solution (40 mL), water (40 mL), saturated aqueous sodium bicarbonate solution (40 mL), and brine (50 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by chromatography (silica gel, hexanes/ethyl acetate, 1:2) yielded 0.153 g (86%) of the product as a white solid: mp = 80–81 °C (hexanes/ether, 6:1); R_f = 0.17 (hexanes/ethyl acetate, 1:2); IR ($CDCl_3$) ν 3147, 3020, 2972, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.6 Hz, 3 H), 1.76 (dd, J = 7.2, 3.6 Hz, 2 H), 2.14 (m, 1 H), 2.45 (dd, J = 16.5, 6.3 Hz, 1 H), 2.51 (ABq, $\Delta\nu_{AB}$ = 136.4 Hz, J = 17.7 Hz, 2 H), 2.73 (m, 2 H), 3.13 (s, 3 H), 3.15 (s, 3 H), 3.36 (s, 3 H), 3.52 (m, 2 H), 3.66 (m, 2 H), 4.55 (d, J = 4.2 Hz, 1 H), 4.73 (ABq, $\Delta\nu_{AB}$ = 24.2 Hz, J = 7.2 Hz, 2 H), 4.99 (dd, J = 6.0, 2.4 Hz, 1 H), 5.42 (dd, J = 7.2, 2.4 Hz, 1 H), 5.75 (d, J = 12.0 Hz, 1 H), 5.89 (dd, J = 12.0, 7.5 Hz, 1H), 6.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.1, 26.4, 31.6, 37.6, 39.0, 39.1, 43.0, 50.1, 58.5, 59.1, 68.1, 71.7, 76.2, 76.6, 78.4, 95.7, 122.2, 133.6, 143.0, 176.9, 206.0 mass spectrum *m/e* (rel inten) 508 (0.4), 412 (3), 270 (4), 228 (4), 199 (8); HRMS calcd for $C_{21}H_{32}O_{10}S_2$ 352.1886, found 352.1891. Anal. Calcd for $C_{21}H_{32}O_{10}S_2$: C, 49.63, H, 6.31. Found: C, 49.87; H, 6.14.

Diethyl 1*H*-(2Hα)-2,8aα-Methano-11(*R*)-[2-(methoxyethoxy)methoxy]-2,3,4,5,7,8,10aα,1aα-octahydro-4α-methyl-7-oxo-cyclopenta[*a*]cyclopropa[*e*]cyclodecene-1,1-dicarboxylate (13). To a suspension of sodium hydride (118 mg, 2.95 mmol, 60% suspension in mineral oil washed with pentane) in THF (4.2 mL) was added at 0 °C a solution of diethyl malonate (0.15 mL, 1.48 mmol) in THF (0.5 mL). The mixture was stirred at this temperature for 40 min and the dimesylate **12** (150 mg, 0.30 mmol) in THF (0.6 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, at rt for 30 min, and finally at 70 °C for 1 h. The reaction mixture was then cooled to 0 °C, quenched with water (3 mL), and extracted with ether (2 × 100 mL). The organic layer was washed with brine (2 × 40 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by chromatography (silica gel, hexanes/ethyl acetate, 3:1) yielded 71.7 mg (51%) of **13** as a white solid: mp = 70 °C (hexanes); R_f = 0.64 (hexanes/ethyl acetate, 1:3); IR ($CDCl_3$) ν 2982, 1744, 1724, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 6.8 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.56 (dt, J = 14.7, 3.8 Hz, 1 H), 1.99 (dd, J = 2.8, 2.5 Hz, 1 H), 2.11 (m, 1 H), 2.24 (dd, J = 2.5, 0.8 Hz, 1 H), 2.26 (m, 1 H), 2.50 (m, 1 H), 2.72 (m, 1 H), 2.85 (m, 1 H), 3.28 (m, 1 H), 3.36 (s, 3 H), 3.39 (m, 1 H), 3.51 (m, 2 H), 3.62 (m, 2 H), 3.92 (s, 1 H), 4.16–4.28 (m, 4 H), 4.70 (ABq, $\Delta\nu_{AB}$ = 12.0 Hz, J = 6.8 Hz, 2 H), 5.21–5.25 (m, 2 H), 5.56 (ddd, J = 12.3, 2.1, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 22.3, 31.1, 36.5, 38.0, 39.0, 39.9, 45.0, 47.9, 54.8, 59.0, 61.7, 61.8, 67.2, 71.7, 76.3, 94.0, 121.5, 125.4, 129.8, 168.0, 168.1, 181.3, 204.3; mass spectrum *m/e* (rel inten) 476 (4), 371 (11), 211 (26); HRMS calcd for $C_{26}H_{36}O_8$ 476.2410, found 476.2417. Anal. Calcd for $C_{26}H_{36}O_8$: C, 65.57; H, 7.62. Found: C, 65.47; H, 7.72.

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Supplementary Material Available: Copies of NMR spectra of **6–9** and **11** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.