Synthesis of 10-*tert*-Butyl-5,10-dihydrophenophosphazine 10-Oxide (4). A suspension of 15 g (60 mmol) of 10-chloro-5,10-dihydrophenophosphazine 10-oxide (**5**)[8] in 250 mL of THF was stirred vigorously at −60 °C while 100 mL of 1.7 M *tert*-butyllithium in pentane was slowly added. The solution was warmed to room temperature and stirred for 4 h. It was cooled again to −60 °C and treated with 40 g of ice. The mixture was warmed to room temperature and the white solid (**4**) recovered by filtration. It was recrystallized from DMSO: yield, 12.6 g (77%); mp 360–363 °C; ^{13}C NMR, Table I; ^{31}P NMR, Table II.

Anal. Calcd for $C_{16}H_{18}NOP$: C, 70.83; H, 6.68; N, 5.16. Found: C, 70.67; H, 6.60; N, 5.08.

The same phosphine oxide (**4**) was formed by oxidation of phosphine **3** (2.55 g) with a mixture of acetone (4 mL) and 30% hydrogen peroxide (2 mL) at room temperature for 1 h. The yield was 2.6 g (96%), mp 366–367 °C; the product had NMR parameters identical with those of the product prepared from **5**.

Synthesis of 5,10-Dihydrophenophosphazine (6). A 4.3-g (20 mmol) sample of secondary phosphine oxide **2** and 1 mL of CCl_4[11] were heated rapidly to 200–220 °C in a Büchi-Kugelrohr apparatus at 0.05 mmHg. A yellow solid (**6**, 0.8 g, 38%) sublimed into the connecting bulb of the apparatus. Phosphinic acid **7**[8] (^{31}P δ +10.8 in DMSO) was isolated from the pot residue by extraction with 10% KOH in ethanol–water, followed by precipitation with 5% HCl. Spectral data for **6** are given in Tables I and II. The sensitivity of the phosphine to oxidation hindered its purification for analysis.

Synthesis of 10-Benzyl-5,10-dihydrophenophosphazine 10-Oxide (10). To a solution of secondary phosphine oxide **2** (2.15 g, 10 mmol) in 20 mL of dimethyl sulfoxide was added 1.6 g of a 50% KOH solution (12 mmol). Benzyl chloride (1.4 mL, 12 mmol) was added dropwise at room temperature and the mixture then heated for 1 h at 50 °C. The solution was diluted with an ice–water mixture and extracted with four 30-mL portions of methylene chloride. The extracts were washed with a saturated sodium chloride solution (two 10-mL portions), dried over sodium sulfate, and rotary-evaporated. The solid residue was chromatographed on silica gel with elution by CH_2Cl_2, and the recovered solid was then recrystallized from 95% ethanol to give 2.1 g (69%) of **9**: mp 216–219 °C; ^{13}C NMR, Table I; ^{31}P NMR, Table II.

Anal. Calcd for $C_{19}H_{16}NOP$: C, 74.74; H, 5.28; N, 4.58. Found: C, 74.57; H, 4.91; N, 4.56.

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Boron Triene Annulation. Substrate Structural Effects on Steroidal Annulation

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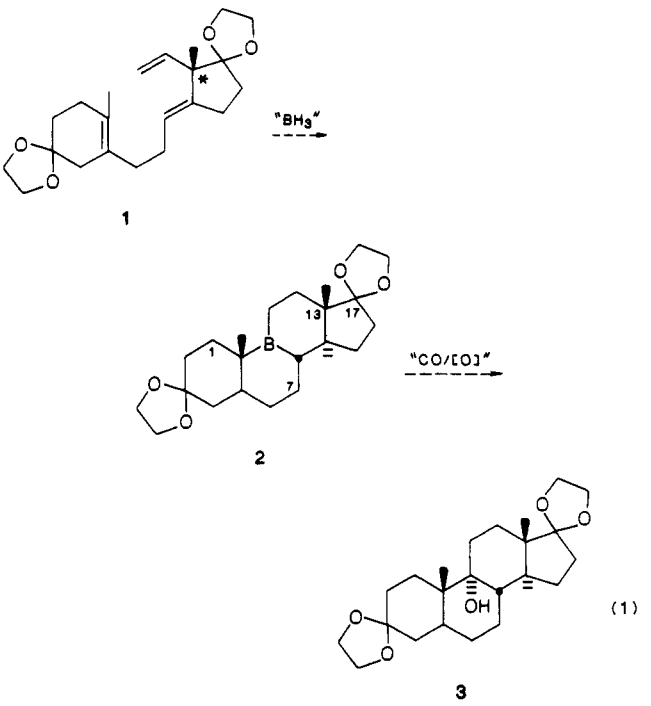
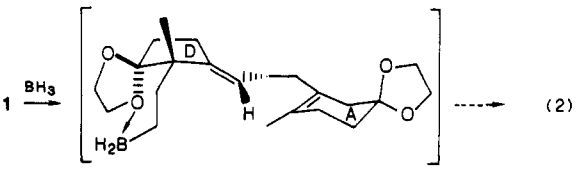
In principle boron annulation of trienes (e.g. **1**) is well-suited for the synthesis of steroids[1] and other carbocycles.[2] To illustrate, carborane **2** could be formed by successive inter- and intramolecular borane–olefin additions with **1** (eq 1). Carbonylation of boracyclane **2** followed by oxidation would provide the steroid nucleus (**3**) in which the stereochemistry is derived from the defined chiral center in substrate **1**. In practice, attempted boron annulations with variations of triene **1** have generally failed



with the implication that strong Lewis acid–base interactions between boron and the C-17 (steroid numbering system) appended acetal were the likely source of the problem as suggested in eq 2.[3] Variations of triene substrate **1** were sought that would disfavor any *cis*-hydrindane oxygen–boron interactions that could retard further intramolecular olefin additions.



4

negative annulation factor

Moving the ketal group by homologation (eq 3) of the D ring in substrate **1** would disfavor the proposed boron Lewis acid–base complex via an unfavorable pseudoring size while still maintaining the potential annulating stereochemical control at C-13.[4] Investigation of this hypothesis required a new approach to triene synthesis[5] centering on coupling of an allylic halide (**5**) and enone (**6**) as outlined in eq 3.

Attempts to directly alkylate the enolate of **6a** with allylic chlorides resulted in multiple alkylations in low yields. However β-keto sulfone **6b**, obtained from the reaction of the acetal of Hagemann's ester (**8**) and the

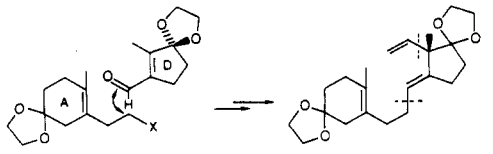
(1) Bryson, T. A.; Reichel, C. J. *Tetrahedron Lett.* **1980**, *21*, 2381–4. Pye, W. E.; Bryson, T. A. *J. Org. Chem.* **1977**, *42*, 3214–5.

(2) Bryson, T. A.; Reichert, C. F.; Pye, W. E. *Tetrahedron* **1981**, *37*, 2441–4. Welch, M. C.; Bryson, T. A. *Tetrahedron Lett.* **1988**, *29*, 521–4. Stevenson, J. W. S.; Bryson, T. A. *Chem. Lett.* **1984**, 5–9. Levine, E.; Bryson, T. A. *Heterocycles* **1982**, *18*, 271–5.

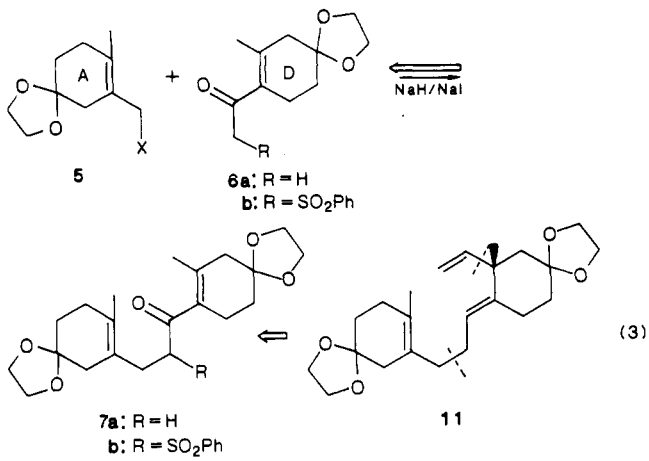
(3) Bonitz, G. H. Ph.D. Dissertation, University of South Carolina, Columbia, SC, 1982; p 125.

(4) Other trienes designed to remedy the proposed cyclic complexation theory added more chiral centers to the "D ring" of the steroid synthon complicating plausible asymmetric approaches to steroids.

(5) Fulmer, T. D. Ph.D. Dissertation, University of South Carolina, Columbia, SC, 1987. The standard approach has been some variation of organometallic A-ring unit addition to D-ring aldehyde, Claisen rearrangement, reduction, and elimination.



0022-3263/89/1954-3496$01.50/0



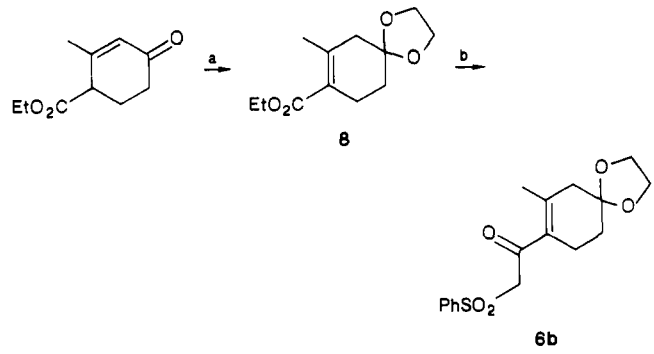
lithium anion of methyl phenyl sulfone,[6,7] proved to be an excellent coupling reagent (**6b**, NaH then **5a** with NaI) for triene synthesis (Scheme I).

The synthesis of the allylic chloride began with the Dieckmann cyclization[8] of the acetal of diethyl 4-oxopimelate. To avoid incomplete reaction of starting materials and difficult purification procedures, the ketalization and cyclization conditions of Gardner[9] and Thompson[10] were slightly modified as noted under the experimental procedures. Treatment of the sodium enolate of β-keto ester **9a** with diethyl chlorophosphate followed by reaction with lithium dimethylcuprate yielded α,β-unsaturated ester **9c**,[11] which was reduced by LAH to alcohol **5b**. The allylic chloride **5a** was obtained via the mesylate by in situ chloride ion displacement[12] on the allylic alcohol **5b** (Scheme II).

Alkylated β-keto sulfone **7b** was reduced[6] to the α,β-unsaturated ketone **7a** by using aluminum amalgam. Diisobutylaluminum hydride[13] reduction of **7a** afforded coupled allylic alcohol **7c**. Claisen rearrangement of **7c** was effected by treatment with *N,N*-dimethylacetamide dimethyl acetal to yield amide **10a**. Reduction of **10a** with LAH followed by oxidation of the resultant amine **10b** with *m*-chloroperbenzoic acid yielded the *N*-oxide **10c**. Thermally induced elimination of the *N*-oxide provided the monosubstituted olefin and completed the synthesis of triene **11** (see Scheme III).

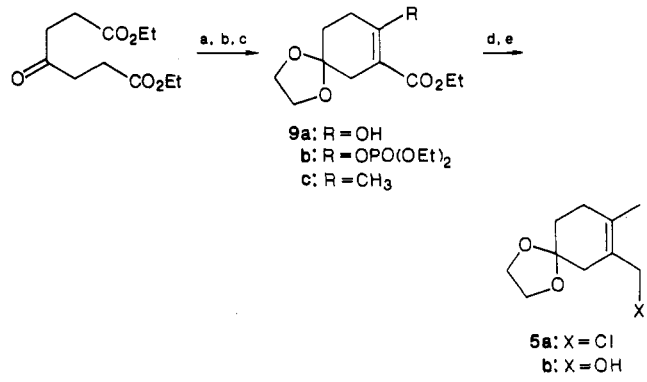
Standard hydroboration[14] reactions of triene **11** were disappointing. As is the case with substrate **1**, triene **11** sluggishly reacts with boron hydrides to give, following oxidation, varying amounts of nonolefinic intractable polar and nonpolar products along with trace amounts of starting material.[15] Attempts to force the hydroboration of tetrasubstituted olefinic system **11** using BH_3 followed by oxidation or carbonylation (or the equivalent process)

Scheme I[a]



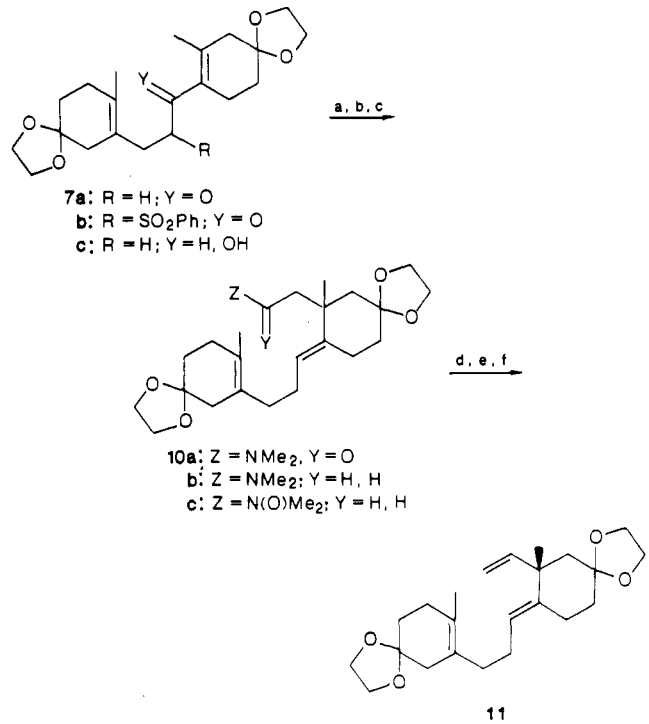
[a] (a) $HOCH_2CH_2OH$, TsOH, PhH; (b) $LiCH_2SO_2Ph$, THF.

Scheme II[a]



[a] (a) $HOCH_2CH_2OH$, PPTS, PhH, Δ; (b) NaH, DME; EtOH (cat.); (c) NaH, Et_2O; $(EtO)_2P(O)Cl$; Me_2CuLi; (d) LAH, ether; (e) LiCl, collidine, MsCl, DMF.

Scheme III[a]

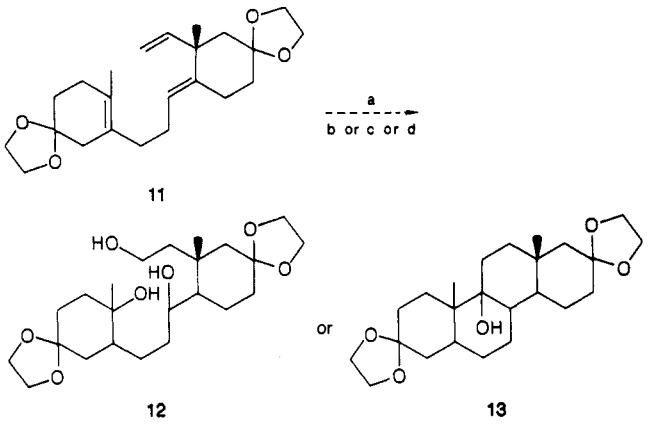


[a] (a) Al–Hg, THF (aq); (b) DIBAL, THF; (c) $(CH_3)_2NC(OCH_3)_2$-CH_3, xylene, Δ; (d) LAH, Et_2O; (e) MCPBA, CH_2Cl_2, −78 °C; (f) Δ.

resulted in loss of the triene[15] with none of the targeted compounds (**12** or **13**) being formed (Scheme IV). It should be noted that the monohydroboration product of **11**, i.e. dienol **14**,[16] was not formed as a detectable by-

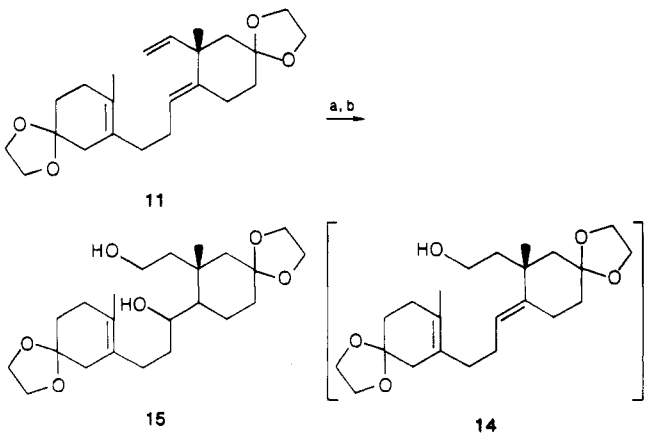
(6) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–53.
(7) Field, L.; Clark, R. D. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 674.
(8) Schaefer, J. P.; Bloomfield, J. J. *Organic Reactions*; Wiley: New York, 1967; Vol. 15, p 1.
(9) Gardner, P. D.; Rand, L.; Haynes, G. R. *J. Am. Chem. Soc.* **1956**, *78*, 3425–7.
(10) Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577–81.
(11) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1981**, *22*, 1337–40.
(12) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044–5.
(13) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213–4. Corey, E. J.; Broger, E. A. *Tetrahedron Lett.* **1969**, 1779–82.
(14) Brown, H. C. *Organic Synthesis via Boranes*; John Wiley & Sons: New York, 1975; Chapters 7 and 8.
(15) TLC and NMR analyses show disappearance of triene **11** on treatment with boron hydrides (BH_3, thexylborane, and H_2BCl) and formation of nondiscrete products (TLC, streaked; NMR, broad array of hydrocarbon resonances).

Scheme IV[a]



[a] (a) BH_3; (b) NaOH, H_2O_2; (c) DCME, base; NaOH, H_2O_2; (d) CO, 1000 psi; NaOH, H_2O_2.

Scheme V[a]



[a] (a) ThxylBH$_2$; (b) NaOH, H_2O_2.

product. However, results suggesting a partial solution to reoccurring triene boron annulation problems were gained by specifically employing thexylborane with **11** using low temperatures and extended reaction times to minimize retrohydroboration. This affords diol **15** following oxidation and separation form the usual array of hydrocarbon and polar products (see Scheme V).

The stark boron annulation contrast between model diene systems[1,2] and trienes (e.g. 1, **11**)[3,5] can be attributed to juxtaposed olefin and oxygen complexation sites within triene substrates and the sluggish addition of boron hydrides to tetrasubstituted olefins which affixes this ring-forming process. The formation of **15**, albeit in low yield, presents a strategy for abatement of internal substrate Lewis acid–base problems.[17] Attempts to enhance tetrasubstituted olefin participation in this annulation process are on going.[18]

Experimental Section

Proton NMR were recorded by a Varian EM-390 or a Bruker AM-300 ^{1}H spectrometer and ^{13}C NMR were recorded by an IBM NR-80 (20 MHz) spectrometer. All chemical shifts reported relative to TMS (ppm) while coupling constants are recorded in hertz. A Beckman Acculab I was used to obtain infrared spectral data (cm^{-1}); mass spectra were recorded on a Finnigan 4021-C GC/EI-CI spectrometer.

Ethyl 4,4-(Ethylenedioxy)-2-methyl-1-cyclohexenecarboxylate (8). A mixture of 4-carbethoxy-3-methyl-2-cyclohexen-1-one (50.0 g, 0.28 mol), ethylene glycol (31.2 g, 0.50 mol), *p*-toluenesulfonic acid (1.0 g, 5.0 mmol), and benzene (600 mL) was refluxed for 12 h by employing a Dean–Stark trap. The cooled reaction mixture was poured into $NaHCO_3$ (saturated) and extracted. The phases were separated, and the organics were washed with $NaHCO_3$ (saturated) and brine. The resulting organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield a yellow oil. The oil was distilled (bp 120 °C at 2 mmHg) and further purified on the Waters Prep LC/System 500A (10% ethyl acetate in hexane) to give **8** (52.0 g, 84%) as a colorless oil: IR (film) ν 2960, 2900, 1710, 1640; ^{1}H NMR (90 MHz) δ 4.17 (q, J = 7.2, 2 H, OCH_2), 3.98 (s, 4 H, OCH_2CH_2O), 2.64–2.27 (m, 4 H, $=CCH_2$), 2.0 (s, 3 H, CH_3), 1.70 (t, J = 6.8, 2 H, CH_2), 1.27 (t, J = 7.5, 3 H, OCH_2CH_3); MS 226 (M^+, 7), 99 ($C_5H_7O_2$, 100).

1-(2-(Phenylsulfonyl)-1-oxoethyl)-4,4-(ethylenedioxy)-2-methyl-1-cyclohexene (6b). Butyllithium (41.0 mL, 70.2 mmol) was added dropwise to a solution of methyl phenyl sulfone (10.95 g, 70.2 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred 1 h at 0 °C, and ester **8** (7.9 g, 35.1 mmol) in THF (10 mL) was added dropwise at 0 °C. The mixture was stirred for 1 h and poured into 20% NH_4OH. The aqueous layer was separated from the organic, washed twice with ether, acidified with cold concentrated HCl, and extracted three times with CH_2Cl_2. The combined chlorocarbon extracts were dried over $MgSO_4$ and concentrated under reduced pressure to yield **6b** (9.4 g, 80%). An analytical sample was prepared by recrystallization from CH_2Cl_2: mp 119–120 °C; IR (CH_2Cl_2) ν 2950, 2890, 1670, 1600; ^{1}H NMR (300 MHz) δ 7.91–7.90 (m, 2 H, ArH), 7.89–7.52 (m, 3 H, ArH), 4.33 (s, 2 H, $SCH_2C{=}O$), 3.95 (s, 4 H, OCH_2CH_2O), 2.54–2.49 (m, 2 H, $=CCH_2$), 2.34 (s, 2 H, $=CCH_2$), 1.81 (s, 3 H, CH_3), 1.73 (t, J = 6.48, 2 H, CH_2); ^{13}C NMR 191.0, 145.2, 139.2, 133.9, 130.5, 129.0, 128.3, 106.5, 64.8, 64.4, 43.5, 30.6, 25.7, 21.7; MS (direct probe) 336 (M^+, 10), 86 ($C_4H_6O_2$, 100). Anal. Calcd for $C_{17}H_{20}O_5S$: C, 60.69; H, 6.00. Found: C, 60.59; H, 6.03.

Diethyl 4,4-(Ethylenedioxy)pimelate. Diethyl 4-oxopimelate (14.4 g, 62.5 mmol), ethylene glycol (34.5 g, 0.56 mol), pyridinium *p*-toluenesulfonate (2.3 g, 9.2 mmol), and benzene (60 mL) were refluxed for 15 h using a Dean–Stark trap. The cooled reaction mixture was poured into $NaHCO_3$ (saturated), and the phases were separated. The organic phase was washed with $NaHCO_3$ (saturated), dried over $MgSO_4$, and concentrated under reduced pressure to yield the acetal of diethyl 4-oxopimelate (14.7 g, 85%) as a colorless oil: IR (film) ν 2980, 2890, 1730; ^{1}H NMR (300 MHz) δ 4.05 (q, J = 7.13, 4 H, OCH_2), 3.86 (s, 4 H, OCH_2CH_2O), 2.31–2.26 (m, 4 H, $CH_2C{=}O$), 1.90 (t, J = 7.3, 4 H, CH_2C), 1.18 (t, J = 7.1, 6 H, OCH_2CH_3); MS (methane chemical ionization) 275 (M^+ + 1, 20), 229 ($M^+ - OC_2H_5$, 100).

Ethyl 5,5-(Ethylenedioxy)-2-oxocyclohexanecarboxylate (9a). Absolute ethanol (0.18 mL) was added dropwise to 60% NaH (1.3 g, 31.0 mmol washed with hexane) in DME (7 mL). Diethyl 4,4-(ethylenedioxy)pimelate (5.0 g, 18.3 mmol) in DME (7 mL) was added over 15 min at 0 °C. After standing for 48 h at room temperature with no stirring, the reaction mixture was diluted with benzene (11 mL) and neutralized by addition of glacial acetic acid (1.9 g, 31.0 mmol). The reaction mixture was poured into brine and extracted. The phases were separated, and the organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 3.3 g of an orange oil. Purification by flash chromatography on silica gel (10% ethyl acetate in hexane) afforded **9a** (3.0 g, 73%) as an amorphous solid existing in the enol form: mp 49–50 °C; IR (CH_2Cl_2) ν 2950, 2880, 1650, 1610; ^{1}H NMR (300 MHz) δ 12.18 (s, 1 H, OH), 4.18 (q, J = 7.12, 2 H, OCH_2), 4.01–3.95 (m, 4 H, OCH_2CH_2O), 2.48–2.45 (m, 4 H, $=CCH_2$), 1.82 (t, J = 6.6, 2 H, CCH_2), 1.24 (t, J = 7.13, 3 H, OCH_2CH_3); ^{13}C NMR 171.98, 170.92, 107.12, 95.16, 64.41, 60.23, 32.61, 30.16, 27.76, 14.10; MS 228 (M^+, 10), 86 ($C_4H_6O_4$, 100). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.87; H, 7.08. Found: C, 57.97; H, 7.10.

Ethyl 5,5-(Ethylenedioxy)-2-methyl-1-cyclohexenecarboxylate (9c). Keto ester **9a** (7.1 g, 31.3 mmol) in ether (70 mL) was added dropwise to 60% NaH (1.6 g, 40.7 mmol, hexane washed) in ether (140 mL). The reaction mixture was refluxed

(16) Dienol **14** was previously characterized from triene **11** preparative studies.

(17) TMS and TBS ethers used in other terpene synthetic studies (e.g. ref 2, Welch) decrease oxygen participation in or complication of boron annulation.

(18) The NIH (Grant GM 34896) is acknowledged for support of this work.

for 2 h followed by dropwise addition of diethyl chlorophosphate (7.6 g, 43.8 mmol) at room temperature and stirring over night. In a separate flask, methyllithium complexed to lithium bromide (93.0 mL, 0.16 mol) was added dropwise to a slurry of copper(I) iodide (14.9 g, 78.2 mmol) in ether (210 mL) at 0 °C. After mixture was stirred for 15 min at 0 °C, the latter solution was transferred by cannula into the former reaction mixture at −78 °C. The mixture was stirred for 12 h at −10 °C, quenched by addition of aqueous NH_4Cl (saturated), diluted with 5% aqueous NH_4OH, and stirred until all salts dissolved. The phases were separated, and the organic phase was washed with aqueous NH_4Cl (saturated), dried over $MgSO_4$, and concentrated under reduced pressure. Ester **9c** (6.3 g, 89%) was obtained as an orange oil: IR (film) ν 2990, 2960, 1705, 1640; ^1H NMR (300 MHz) δ 4.12–4.00 (m, 2 H, OCH_2), 3.98–3.86 (m, 4 H, OCH_2CH_2O), 2.43 (m, 2 H, $=CCH_2$), 2.30 (t, J = 6.65, 2 H, $=CCH_2$), 1.98 (m, 3 H, CH_3), 1.70 (m, 2 H, CH_2), 1.20 (m, 3 H, OCH_2CH_3); ^{13}C NMR 167.6, 146.3 121.6, 107.5, 64.4, 59.9, 36.2, 33.1, 30.6, 21.3, 14.2; MS 226 (M^+, 10), 86 ($C_4H_6O_2$, 100). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.69; H, 8.03. Found: C, 63.59; H, 8.05.

(5,5-(Ethylenedioxy)-2-methyl-1-cyclohexenyl)methanol (5b). Ester **9c** (2.0 g, 8.8 mmol) in ether (25 mL) was added dropwise to an ether (125 mL) slurry of LAH (0.37 g, 8.8 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature, cooled to 0 °C, and quenched by sequential addition of water (0.33 mL), 15% sodium hydroxide (0.33 mL), and water (0.99 mL). The reaction mixture was stirred 12 h, dried over $MgSO_4$, and concentrated under reduced pressure to yield **5b** (1.4 g, 86%) as a colorless oil: IR (film) ν 3400, 2880; ^1H NMR (300 MHz) δ 4.05 (s, 2 H, CH_2O), 4.0–3.9 (m, 4 H, OCH_2CH_2O), 2.31 (s, 2 H, $=CCH_2$), 2.12 (t, J = 5.9, 2 H, $=CCH_2$), 2.00–1.68 (m, 6 H, OH, CH_3, CH_2); MS 184 (M^+, 5), 86 ($C_4H_6O_2$, 100).

2-(Chloromethyl)-4,4-(ethylenedioxy)-1-methyl-1-cyclohexene (5a). A solution of LiCl (3.13 g, 73.8 mmol) in DMF (65 mL) was added dropwise to allylic alcohol **5b** (13.6 g, 73.8 mmol) and collidine (9.39 g, 77.5 mmol). After cooling to 0 °C, methanesulfonyl chloride (8.45 g, 73.8 mmol) was added dropwise. The reaction mixture was stirred for 5 h at 0 °C, poured into ice water, and extracted with cold ether/hexane (1:1). The organic phase was washed with saturated copper sulfate and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **5a** (12.4 g, 83%): IR (film) ν 2960, 2890; ^1H NMR (300 MHz) δ 4.06 (s, 2 H, CH_2Cl), 4.0–3.94 (m, 4 H, OCH_2CH_2O), 2.34 (s, 2 H, $=CCH_2$), 2.23 (t, J = 6.6, 2 H, $=CCH_2$), 1.74–1.71 (m, 5 H, CH_3 and CH_2); MS 202 (M^+, 25), 86 ($C_4H_6O_2$, 100).

1-(4,4-(Ethylenedioxy)-2-methyl-1-cyclohexenyl)-3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)-2-(phenylsulfonyl)propan-1-one (7b). Keto sulfone **6b** (0.10 g, 0.30 mmol) was added to a THF (2 mL) slurry of 60% NaH (12.8 mg, 0.33 mmol) at 0 °C. The ice bath was removed, and the reaction mixture was stirred for 3 h. A THF (0.5 mL) solution of chloride **5a** was added dropwise followed by NaI (44.6 mg, 0.30 mmol). The reaction mixture was stirred for 12 h, poured into saturated sodium metabisulfite, and extracted. The aqueous phase was drained, and the organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the resulting foam was purified via silica gel column chromatography (7% ether in CH_2Cl_2) to give **7b** (0.12 g, 82%). An analytical sample was prepared by crystallization for ether: mp 118 °C; IR (CH_2Cl_2) ν 2900, 1680, 1590; ^1H NMR (300 MHz) δ 7.82–7.50 (env, 5 H, ArH), 4.61 (dd, J = 3.2, 11.2, 1 H, CH), 3.94 (s, 4 H, OCH_2CH_2O), 3.93 (s, 4 H, OCH_2CH_2O), 2.79–1.52 [env, 20 H, s at 1.80 ($O{=}CC{=}CCH_3$) and 1.52 ($=CCH_3$), CH_2]; ^{13}C NMR 195.2, 144.5, 137.4, 133.9, 131.4, 130.6, 129.4, 128.8, 121.6, 107.9, 106.6, 69.1, 64.3, 64.2, 43.6, 39.3, 32.1, 31.0, 30.8, 25.5, 21.5, 18.6; MS (direct probe) 502 (M^+, 10), 91 (B, 100). Anal. Calcd for $C_{27}H_{34}O_7S$: C, 64.51; H, 6.83. Found: C, 64.35; H, 6.87.

1-(4,4-(Ethylenedioxy)-2-methyl-1-cyclohexenyl)-3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)propan-1-one (7a). β-Keto sulfone **7b** (1.97 g, 3.91 mmol) was dissolved in a THF/H_2O (25 mL/4 mL) solution and cooled to 0 °C. Strips of aluminum foil (2.03 g, 75.29 mmol) were dipped into saturated mercuric chloride for 15 s, rinsed with ether, and cut into the reaction mixture over a period of 3 min. The resulting slurry was stirred for 30 min at 0 °C and filtered through a pad of Celite. The aluminum salts were washed with CH_2Cl_2 (150 mL), and the filtrate was poured into a separatory funnel containing water and extracted. The phases were separated, and the organic extracts were dried over $MgSO_4$. Removal of solvent under reduced pressure afforded a yellow oil, which was purified via silica gel column chromatography (50% ethyl acetate in hexane) to yield **7a** (0.97 g, 68%): IR (film) ν 2880, 1680; ^1H NMR (300 MHz) δ 3.95 (s, 4 H, OCH_2CH_2O), 3.94 (s, 4 H, OCH_2CH_2O), 2.55–1.19 [env, 22 H, m at 1.79 ($O{=}CC{=}CCH_3$), s at 1.61 ($=CCH_3$), CH_2]; MS (direct probe) 362 (M^+, 12), 86 ($C_4H_6O_2$, 100).

1-(4,4-(Ethylenedioxy)-2-methyl-1-cyclohexenyl)-3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)propan-1-ol (7c). Diisobutylaluminum hydride (4.8 mL, 4.8 mmol) was added to α,β-unsaturated ketone **7a** (0.79 g, 2.19 mmol) in THF (18 mL) at 0 °C. The reaction mixture was stirred for 1.25 h at 0 °C, quenched with saturated Rochelle's salt, and stirred overnight. The layers were separated, and the organic phase was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **7c** (0.78 g, 98%): IR (film) ν 3470, 2920; ^1H NMR (300 MHz) δ 4.55 (dd, J = 5.8, 7.9, 1 H, $CHOH$), 3.93 (s, 8 H, OCH_2CH_2O), 2.35–1.34 (env, 23 H, CH_2 and CH_3); ^{13}C NMR 131.7, 127.0, 126.2, 125.9, 108.5, 107.9, 70.1, 64.2, 42.1, 39.2, 33.0, 31.3, 31.1, 30.9, 29.6, 21.9, 18.5, 18.2; MS (direct probe) 364 (M^+, 50), 57 (C_3H_5O, 100).

(*E*)-*N*,*N*-Dimethyl-2-(5,5-(ethylenedioxy)-1-methyl-2-(3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)-propylidene)cyclohexyl)acetamide (10a). Allylic alcohol **7c** (0.66 g, 1.8 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (0.36 g, 2.7 mmol) were heated under reflux for 12 h in xylene (15 mL). The cooled mixture was poured into water, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash chromatography (75% hexane in ethyl acetate, neutral alumina III) affording **10a** (0.58 g, 74%): IR (CH_2Cl_2) ν 2935, 1640; ^1H NMR (300 MHz) δ 5.23–5.20 (m, 1 H, $=CH$), 4.00–3.83 (m, 8 H, OCH_2CH_2O), 2.97 (s, 3 H, NMe), 2.89 (s, 3 H, NMe), 2.70 and 2.39 (AB q, J = 14.87, 2 H, $O{=}CH_2$), 2.57–1.21 [env, 22 H, s at 1.62 ($=CCH_3$) and 1.19 (CCH_3), CH_2]; ^{13}C NMR 171.8, 142.6, 126.8, 125.4, 121.1, 108.5, 108.2, 63.9, 63.4, 44.1, 39.7, 39.4, 39.2, 37.6, 35.7, 35.0, 33.2, 31.0, 30.6, 25.7, 22.2, 18.2; MS (direct probe) 433 (M^+, 40), 87 ($C_4H_7O_2$, 100). Anal. Calcd for $C_{25}H_{39}NO_5$: C, 69.24; H, 9.08. Found: C, 69.13; H, 9.15.

Dimethyl(2-(5,5-(ethylenedioxy)-1-methyl-2-(3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)propylidene)-cyclohexyl)ethyl)amine (10b). A solution of amide **10a** (0.51 g, 1.2 mmol) in ether (5 mL) was added dropwise to an ether slurry (10 mL) of LAH (44.5 mg, 1.2 mmol). After being stirred for 5 h, the reaction was quenched by addition of 3 M NaOH (0.40 mL). The mixture was stirred 3 h, dried over $MgSO_4$, and filtered. Concentration under reduced pressure afforded **10b** (0.49 g, 81%): IR (film) ν 2950, 2780; ^1H NMR (300 MHz) δ 5.12 (t, J = 6.4, 1 H, $=CH$), 3.93–3.81 (m, 8 H, OCH_2CH_2O), 2.18 (s, 6 H, NMe_2), 2.47–1.00 [env, 26 H, s at 1.60 ($=CCH_3$) and 0.98 (CCH_3), CH_2]; MS (direct probe) 419 (M^+, 15), 58 (CH_2NMe_2, 100).

Dimethyl(2-(5,5-(ethylenedioxy)-1-methyl-2-(3-(5,5-(ethylenedioxy)-2-methyl-1-cyclohexenyl)propylidene)-cyclohexyl)ethyl)amine *N*-Oxide (10c). *m*-Chloroperbenzoic acid (72.3 mg, 0.42 mmol) in CH_2Cl_2 (2 mL) was added dropwise to amine **10b** (0.17 g, 0.40 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The reaction mixture was stirred for 10 min and poured onto an activity III alumina column (10% ethanol in CH_2Cl_2). Flash column chromatography followed by removal of solvent under reduced pressure afforded **10c**, which was used directly in the thermal elimination: IR (film) ν 3250 (broad), 2960, 1675; ^1H NMR (300 MHz) δ 5.14 (m, 1 H, $=CH$), 3.93–3.81 (m, 8 H, OCH_2CH_2O), 3.07 (s, 6 H, $ONMe_2$), 3.18–0.99 [env, 26 H, s at 1.56 ($=CCH_3$) and 0.99 (CCH_3), CH_2]; MS 374 ($M^+ - Me_2(O)NH$), 99 ($C_5H_7O_2$, 100).

1-(4,4-(Ethylenedioxy)-2-methyl-2-vinylcyclohexyl)-3-(5,5-(ethylenedioxy)-2-methylcyclohexenyl)-1-propene (11). Crude *N*-oxide **10c** was heated (140 °C, 1 mmHg) for 12 min. Silica gel column chromatography using 20% ethyl acetate in hexane afforded **11** (0.11 g, 71% yield from amine **10b**): IR (film) ν 2950, 2880, 1440; ^1H NMR (300 MHz) δ 6.00–5.21 (m, 1 H, $H_2C{=}CH$), 5.23–5.21 (m, 1 H, $=CH$), 4.95–4.85 (m, 2 H, $=CH_2$), 3.95 (s, 4 H, OCH_2CH_2O), 3.92 (s, 4 H, OCH_2CH_2O), 2.38–1.14 [env, 22 H, s at 1.62 ($=CCH_3$) and 1.14 (CCH_3), CH_2]; ^{13}C NMR

147.3, 141.5, 127.1, 125.7, 122.6, 110.8, 108.8, 108.6, 64.3, 64.00, 64.07, 47.3, 43.7, 39.5, 35.6, 33.6, 31.3, 30.9, 26.1, 26.0, 22.5, 18.5; MS 374 (M^+, 10), 99 ($C_5H_7O_2$, 100). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.75; H, 9.17. Found: C, 73.82; H, 9.22.

1-(4,4-(Ethylenedioxy)-2-(2-hydroxyethyl)-2-methylcyclohexyl)-3-(5,5-(ethylenedioxy)-2-methylcyclohexenyl)-1-propanol (15). Thexylborane–methyl sulfide complex (0.15 mmol) was prepared by adding borane–methyl sulfide complex (14.6 μL, 0.15 mmol) to 2,3-dimethyl-2-butene (0.02 mL, 0.15 mmol) in $DCCl_3$ (1 mL) at 0 °C. The resulting solution was stirred for 3 h and added dropwise to triene **11** (50 mg, 0.13 mmol) in $DCCl_3$ (0.5 mL) at −78 °C. The reaction mixture was allowed to warm gradually to room temperature, stirred 24 h, and quenched with absolute ethanol (1 mL). Crushed NaOH (32 mg, 0.80 mmol) was added, and the reaction mixture was cooled to 0 °C; 30% H_2O_2 (0.07 mL, 0.067 mmol) was added dropwise, and the oxidation mixture was stirred for 8 h at room temperature and for 3 h at 50 °C. After being cooled to room temperature and saturated with NaCl, the aqueous phase was washed three times with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 0.326 g of a yellow oil. Column chromatography on neutral activity III alumina (10% ethanol in ethyl acetate) afforded diol **15** (8.1 mg, 15%): IR (film) ν 3380, 2920; ^1H NMR (300 MHz) δ 3.95–3.75 (m, 8 H, OCH_2CH_2O), 3.75–3.52 (m, 3 H, CH_2OH), 2.18–0.74 [env, 27 H, s at 1.65 (=CCH_3) and 1.00 (CCH_3), CH_2, CH]; MS (direct probe) 410 (M^+, 32), 168 (B).

Structure Elucidation of a New Polyether Antibiotic *iso*-Dianemycin

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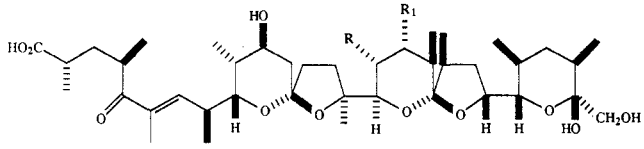
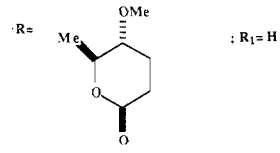
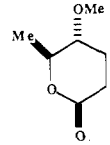
In the course of screening soil samples for new antibacterial agents,[1] we isolated a new polyether natural product (**1**) related to Dianemycin (**2**).[2] Herein, we describe the detailed structure of *iso*-Dianemycin (**1**) via NMR and high-resolution mass spectroscopic analyses, as well as solid-state techniques.





R= ; R_1= H *iso*-Dianemycin, **1**



R= H; R_1= Dianemycin, **2**

The structure elucidation of **1** was initiated by assigning a molecular formula. NMR analysis via the polarization

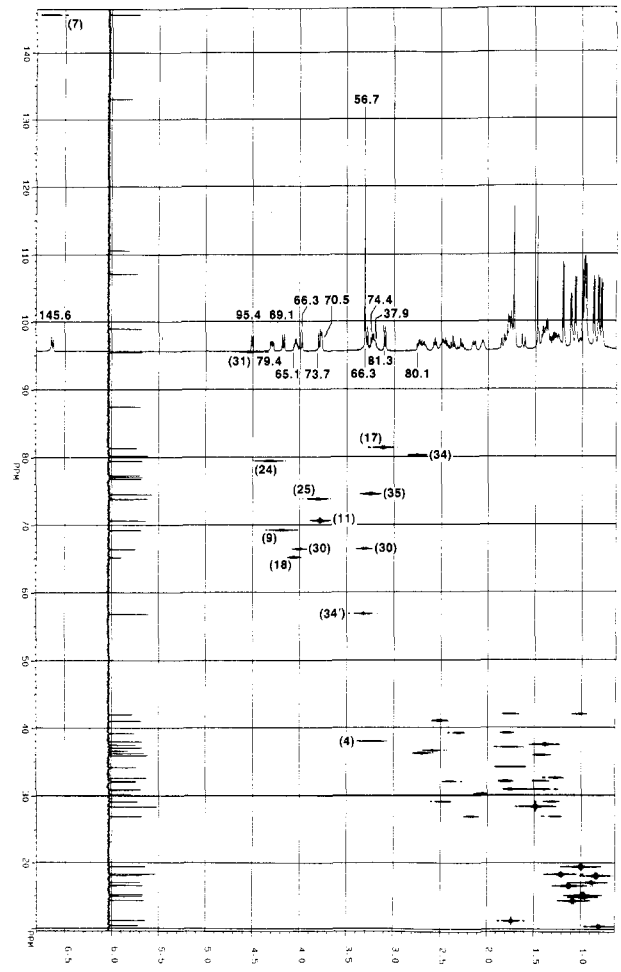


Figure 1. ^{13}C–^1H correlation spectrum of polyether **1**. The numbers in parentheses refer to the carbon numbering system, whereas the numbers appearing on the ^1H NMR spectrum are the actual chemical shifts of the correlated carbon resonances.

transfer (DEPT)[3] experiment supported a carbon number of 47 with 74 nonexchangeable protons directly bonded to carbon (see Table I). Furthermore, the number of exchangeable protons, and their corresponding vicinally attached carbons, was ascertained by the direct observation of vicinal deuterium isotope shifts for four carbon resonances;[4] namely, carbons 1, 11, 29, and 30 (see the figures for the numbering scheme) exhibiting chemical shifts of 183.8, 70.5, 98.8, and 66.3 ppm, respectively. Thus, the total number of protons was 78. The assignment of the molecular formula was completed by mass spectral experiments, since a molecular ion for the rubidium salt of **1** (M^+ − Rb = m/e 951.5779) was observed in the high-resolution FAB mass spectrum. Since the carbon and proton numbers were defined, the only heteroatom that permitted a reasonable fit of the high-resolution data was oxygen, which defined the molecular formula as $C_{47}H_{78}O_{14}$.

Support for the definition of oxygen as the only heteroatom was also derived from an assessment of the carbon functionality (Table I includes the carbon functionality), which was assigned by chemical shift analogy.[5] A total of 17 carbons (see Table I) contained oxygen as a sub-

(1) The fermentation and isolation of **1**, as well as the characterization of the producing organism, will appear elsewhere.

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