p-nitrophenyl phosphate at 0.85 M TEAB. The yield of N^2,3-ethenoguanosine 5'-phosphate was 20%, but the nucleotide was contaminated by some nucleoside. The nucleoside was recovered, and phosphorylation was repeated twice. The total yield of pure N^2,3-ethenoguanosine 5'-monophosphate after three runs and rechromatography of pooled nucleotide fractions on the same column was 370 A^{pH7}_{258nm} units (40%).

N^2,3-Ethenoguanosine 5'-Diphosphate. The general synthetic procedure was according to Hoard and Ott,[24] using triethylammonium phosphate instead of tributylammonium pyrophosphate. The products from the reaction of 370 A^{pH7}_{258nm} units (0.035 mmol) of N^2,3-ethenoguanosine 5'-phosphate were separated on a 2 × 16 cm column packed with DEAE Sephadex A-25 (HCO_3^- form) with a linear gradient from 600 mL of H_2O to 600 mL of 0.5 M TEAB and flow rate 4 mL/min. N^2,3-Ethenoguanosine 5'-phosphate, 90 A^{pH7}_{258nm} units (24%), appeared as a sharp peak at 0.40–0.42 M TEAB. Fractions containing ethenoguanosine 5'-diphosphate were evaporated three times with water. Without further treatment the aqueous solution of triethylammonium salt of N^2,3-ethenoguanosine 5'-diphosphate was used for the preparation of polynucleotides. The structure of N^2,3-ethenoguanosine 5'-diphosphate was confirmed by limited digestion by bacterial alkaline phosphatase, which hydrolyzed stepwise yielding the nucleoside 5'-diphosphate, 5'-monophosphate, and finally the nucleoside (R_f 0.43, 0.36, and 0.24, respectively, in system III).

Preparation and Analysis of Polynucleotides. N^2,3-Ethenoguanosine 5'-diphosphate was copolymerized with varying proportions of CDP or ADP as described by Singer et al.[28,29] Analyses, after enzymatic digestion to nucleosides,[30] were performed on a BioRad HPLC system, which will be described in detail in a paper on the properties of such polynucleotides (Singer et al., *Carcinogenesis*, in press).

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Synthetic Studies on Cembranolides. Stereoselective Total Synthesis of Isolobophytolide†

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The synthesis of (±)-isolobophytolide starting from diol **1**, the coupling product of the geraniol-derived sulfone IX and the epoxy alkoxide X, has been achieved. Macrocyclization was accomplished via the π-allyl palladium complex of the allylic pivalate **8**. The derived carboxylic acid **11** underwent carboxy inversion to the cis lactone **32**. Subsequent conversion to the trans lactone **42** followed by internal epoxidation to **44** and lactone α-methylenation completed the synthesis. Alternative methods were developed for carboxy inversion and α-methylenation.

Since their initial recognition some 25 years ago,[1a-c] the cembrane diterpenes have emerged as a major class of natural products with widespread origins in both the plant and animal kingdoms.[1d] In the latter category, Caribbean gorgonians and Pacific soft corals account for the greatest diversity of cembrane structures. These "cembranolides", with their characteristic fused and bridged lactone groupings, represent the most structurally complex and biologically interesting members of the entire family. To date, synthetic work has focused on the relatively simple cembranes.[2] Cembranolides have received only scant attention.[3]

One of our first efforts in the cembranolide area was directed toward isolobophytolide, the major terpenoid component of the soft coral *Lobophytum crassum*.[4] Bowden et al. initially proposed a cis-fused γ-lactone structure for isolobophytolide.[4] We succeeded in synthesizing this cis-fused lactone from the abundant natural cembranolide crassin acetate (Figure 1).[5] However, the spectral properties of our synthetic lactone clearly differed from those reported for natural isolobophytolide.[4] A major discrepancy was the chemical shift of the lactone carbinyl proton H14, which appeared at 4.7 ppm in our synthetic material vs. 4.1 ppm for natural isolobophytolide. It was subsequently found through single-crystal X-ray structure analysis that isolobophytolide is a trans-fused lactone with the relative stereochemistry depicted in I (Figure 2).[6]

† Dedicated to Prof. William G. Dauben in commemoration of the 25th anniversary of his structure elucidation of cembrene.

‡ To whom inquiries regarding X-ray structure analysis should be directed.

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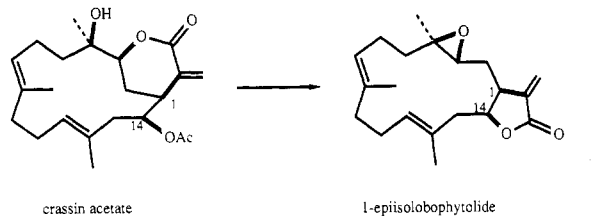


Figure 1. Chemical correlation of crassin acetate and isolobophytolide.[5]

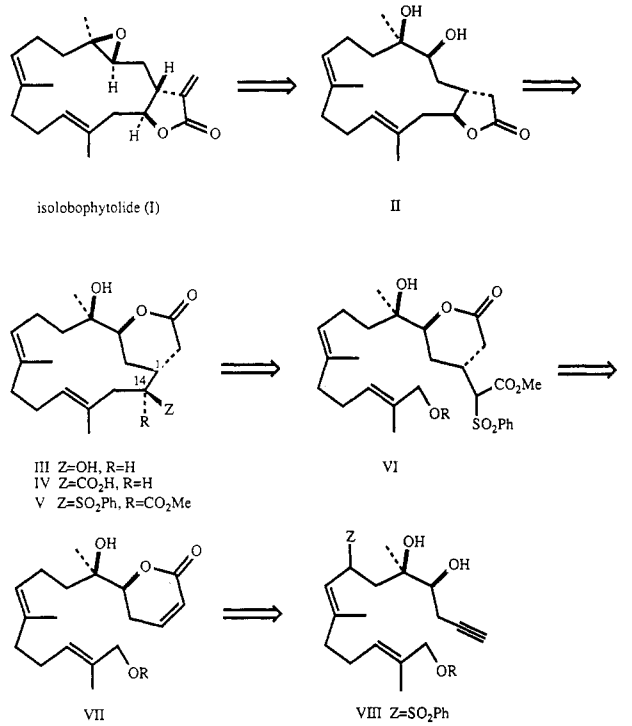
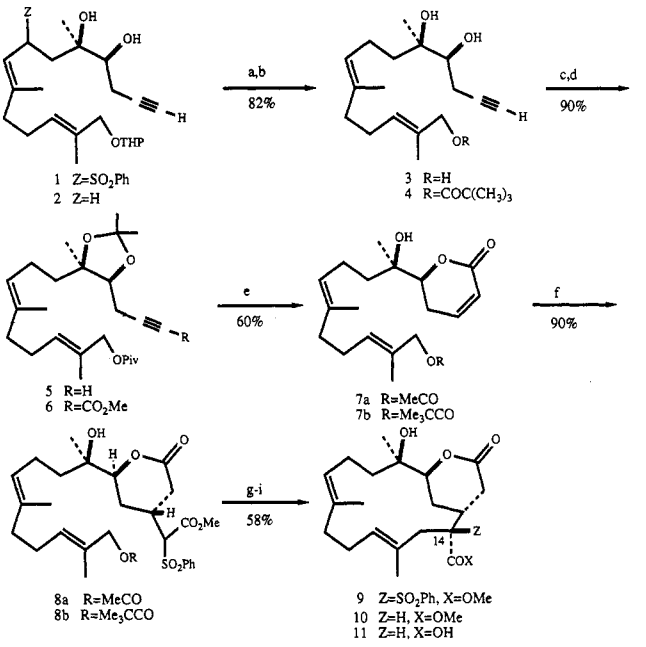


Figure 2. Retrosynthetic analysis of isolobophytolide.

Following our conversion of crassin acetate to 1-epiisolobophytolide, we developed an interest in the total synthesis of these natural products along the lines depicted in Figure 2. The plan entailed assemblage of a macrocyclic intermediate V via π-allyl palladium mediated cyclization[7] of an α-(phenylsulfonyl)acetate derived from an acyclic precursor such as lactone VI. This trans lactone would expectedly arise from conjugate addition of a sulfonylacetic ester to the pentenolide VII under kinetic conditions.[8] Presumably the more stable cis isomer of lactone VI, a possible crassin acetate precursor, might be obtained under equilibrating conditions.

The use of an acetic ester derivative as the nucleophilic partner in the cyclization step necessitates a subsequent oxidative decarboxylation to remove the extraneous carboxyliic acid (IV → III). The "carboxy inversion" sequence[9] was of special interest here because such "inversions" proceed with retention of stereochemistry.[10,11] Therefore the C14 stereochemistry of lactone acid IV should be directly transferable to the derived alcohol III, thus permitting potential access to both epimers through

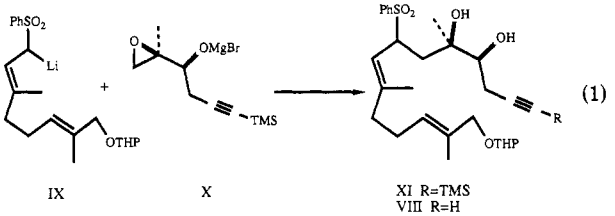
Scheme I[a,b]



[a] (a) MeOH, *p*-TsOH, 25 °C; (b) Me_3CCOCl, C_5H_5N, 0 °C; (c) CH_2=C(OMe)Me, $C_5H_5NH^+OTs^-$, CH_2Cl_2; (d) LiN(*i*-Pr)$_2$, THF, −78 °C; $ClCO_2Me$, −78 °C; (e) MeOH, H_2O, H_2SO_4; H_2/Pd-$BaSO_4$, C_5H_5; CSA, THF, reflux; (f) $PhSO_2CH_2CO_2Me$, KO-*t*-Bu, *t*-BuOH, Me_2SO; (g) BSA, THF, reflux; $Pd(PPh_3)_4$, $Ph_2PCH_2CH_2PPh_2$, THF, reflux; $Bu_4N^+F^-$, THF; (h) 6% Na(Hg), THF, MeOH, Na_2HPO_4, −78 °C; (i) NaOMe, MeOH; NaOH, H_2O, DME; H_2O, THF, HCl, Et_2O, inverse addition; C_6H_6, 80 °C. [b] THP = tetrahydropyranyl, Piv = $(CH_3)_3CCO$, CSA = camphor-10-sulfonic acid, BSA = *O*,*N*-bis(trimethylsilyl)acetamide.

epimerization of the carboxylic acid grouping of IV.[12] The ensuing trans-lactonization (III → II) and diol–epoxide conversion (II → I) closely parallel comparable steps in our earlier structure correlation work (Figure 1).[5]

Sulfone diol VIII, prepared via addition of the lithio sulfone IX to the magnesio alkoxide X, as described previously, was the effective starting point for the synthetic sequence shown in Scheme I.[13] Desulfonylation of sulfone



(1)

1 with sodium amalgam in methanol afforded diol **2** containing 8–10% of the disubstituted double bond isomer. Hydrolysis of the THP ether followed by selective esterification of triol **3** with pivaloyl chloride yielded the monopivalate **4**. The choice of pivalate over the more common acetate was made on the basis of its enhanced stability to the ensuing reaction conditions and its effectiveness in the ultimate cyclization step (**8** → **9**).

Diol **4** was protected as the acetonide **5**. Treatment with LDA in THF and carboxylation of the resulting lithio acetylide with methyl chloroformate gave rise to the acetonide ester **6**. Hydrolysis of this acetonide with methanolic *p*-toluenesulfonic acid, partial hydrogenation of the acetylene over palladium on barium sulfate, and treatment

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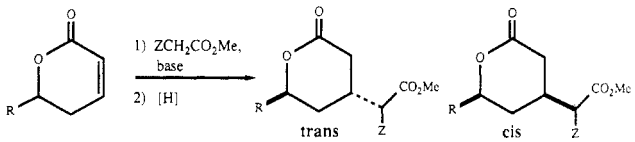
Table I. Conjugate Additions to Pentenolides



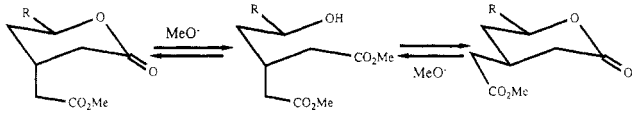
12 R=n-C_5H_{11}
13 R=i-Pr
7a[a]

14 R=n-C_5H_{11}
15 R=i-Pr
8a[a]

16 R=n-C_5H_{11}
17 R=i-Pr
18a[a]

						Z = H, trans:cis		
entry	R	Z	base[b]	yield, %	[H][b]	yield, %	kinetic[c]	equil[c]
1	n-C_5H_{11} (12)	$PhSO_2$	A	83	D	91	95:5	30:70
2	n-C_5H_{11} (12)	$PhSO_2$	B	76	D	92	80:20	30:70
3	n-C_5H_{11} (12)	CO_2Me	C	73	D		85:15[d]	30:70
4	i-Pr (13)	$PhSO_2$	A	76	D	75	85:15	25:75
5	7a	$PhSO_2$	A	81[e]	E	87	60:40[f]	10:90

[a] R = $CH_3COOCH_2C(CH_3)$=$CH(CH_2)_2C(CH_3)$=$CH(CH_2)_2C(CH_3)OH$. [b] A = KO-t-Bu, t-BuOH, Me_2SO; B = $KN(Me_3Si)_2$, THF, HMPA; C = KO-t-Bu, t-BuOH; D = W-2 Raney nickel in EtOAc; E = Na(Hg), MeOH, −78 °C. [c] Estimated from integration of the ^1H NMR spectrum. [d] Z = CO_2Me. [e] Estimated trans–cis ratio >90:10 according to ^1H NMR analysis. [f] Partial equilibration during desulfonylation.



14 R=n-C_5H_{11}
15 R=i-Pr
8 (see Table 1)

19

16 R=n-C_5H_{11}
17 R=i-Pr
18 (see Table 1)

Figure 3. Equilibration of lactone esters 14–18.

of the resulting hydroxy ester with camphorsulfonic acid in THF led to pentenolide **7b**, our pivotal intermediate, in 55% overall yield.[8]

Conjugate additions of organocopper reagents to pentenolides such as **7** have been shown to proceed via kinetically controlled axial attack.[8] We expected **7** to follow a similar course and yield the trans isomer **8** upon addition of methyl α-(phenylsulfonyl)acetate under appropriate nonequilibrating conditions. In order to define such conditions and ascertain the stereochemistry of the adducts, we examined the model pentanolides **12** and **13** shown in Table I. These lactones were prepared from hexanal and 2-methylpropanal via addition of propargylmagnesium bromide followed by methyl chloroformate, then partial hydrogenation, and acidic lactonization along the lines employed for **7**.[8]

The addition of potassium methyl α-(phenylsulfonyl)-acetate to the pentylpentenolide **12** under protic conditions (entry 1) afforded a 95:5 mixture of isomeric products (**14** and **16**, Z = SO_2Ph) according to ^1H NMR analysis. In fact, two new stereocenters are produced in the addition reaction. The α-sulfonyl center is a nearly 1:1 diastereomeric mixture readily discernible in the NMR spectrum. Desulfonylation with Raney nickel in ethyl acetate gave a consistent 95:5 mixture of stereoisomeric lactones **14** and **16** (Z = H). Confirmation of the assumed stereochemistry was secured via methoxide-promoted equilibration of this 95:5 mixture to a 30:70 mixture in which the more stable cis isomer **16** (Z = H) predominates. Although it was never detected, the symmetrical diester **19** (Figure 3) is the presumed intermediate in this equilibration process.

Under aprotic conditions, the addition of potassium methyl α-(phenylsulfonyl)acetate to pentenolide **12** yielded an 80:20 mixture of the trans and cis products **14** and **16** (Z = SO_2Ph) (Table I, entry 2). This ratio did not change with prolonged reaction time. Potassium dimethyl malonate gave rise to a similar 85:15 mixture of **14** and **16** (Z = CO_2Me) upon addition to pentenolide **12** (Table I, entry 3). The isopropyl-substituted pentenolide **13** showed analogous behavior with poassium methyl α-(phenylsulfonyl)acetate (Table I, entry 4). Attempts to carry out these Michael reactions in methanol led to 1,4-addition of methanol and subsequent methanolysis of the resulting saturated β-methoxy lactone. We were unable to find conditions favoring the cis (phenylsulfonyl)acetate adduct although, as noted above, the desulfonylated products **16**, **17**, and **18a** (Z = H) were readily secured through lactone equilibration.

Pentenolides **7a** and **7b**, upon treatment with potassium methyl α-(phenylsulfonyl)acetate in Me_2SO–*tert*-butyl alcohol, afforded the trans-1,4-adducts **8a** and **8b** in high yield and excellent stereoselectivity according to ^1H NMR analysis. Attempted confirmation of stereochemistry through Raney nickel desulfonylation of **8a** was thwarted by competing double bond reduction. Desulfonylation was therefore effected with sodium amalgam in methanol. However, the basic conditions of this reaction effected partial equilibration, even at −78 °C, giving rise to a 60:40 mixture favoring the trans lactone **8a**, Z = H (Table I, entry 5). Treatment of this mixture with methanolic sodium methoxide led to a 90:10 mixture favoring the cis isomer **18a**. Additional support for the structure of lactones **8a** and **8b** was gained from subsequent cyclization studies.

Intramolecular allylations of stabilized malonate, acetoacetate, and α-sulfonylacetate anions have previously been employed for the closure of medium- and large-ring carbocycles and lactones.[7] Although no example of a cembranolide cyclization has been recorded, there is no reason to doubt the probable success of such an application. Indeed, the allylic pivalate **8b** was smoothly converted to the cembranoid lactone ester **9** upon slow addition of the enol Me_3Si derivative to a solution of tetrakis(triphenylphosphine)palladium(0) in refluxing THF containing 1 equiv of 1,2-bis(diphenylphosphino)ethane, all at moderate dilution. The acetate counterpart, ester **8a**, gave equally satisfactory results, but as noted above, the pivalate showed less tendency to suffer cleavage in the conversions leading to **8**. Although yields as high as 60% were realized from small-scale reactions, in preparative runs 40–50% was the norm. Cyclizations of the sodio derivatives of esters **8a** and **8b** prepared via deprotonation with sodium hydride were only effective for small-scale reactions. Significant material losses were incurred on attempted scale-up.

The cyclized sulfonyl ester **9** was obtained as a single diastereoisomer, a nicely crystalline substance whose

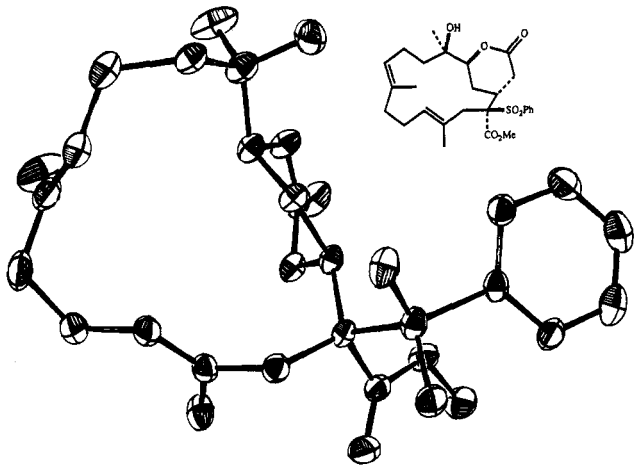


Figure 4. X-ray structure of lactone **9**.

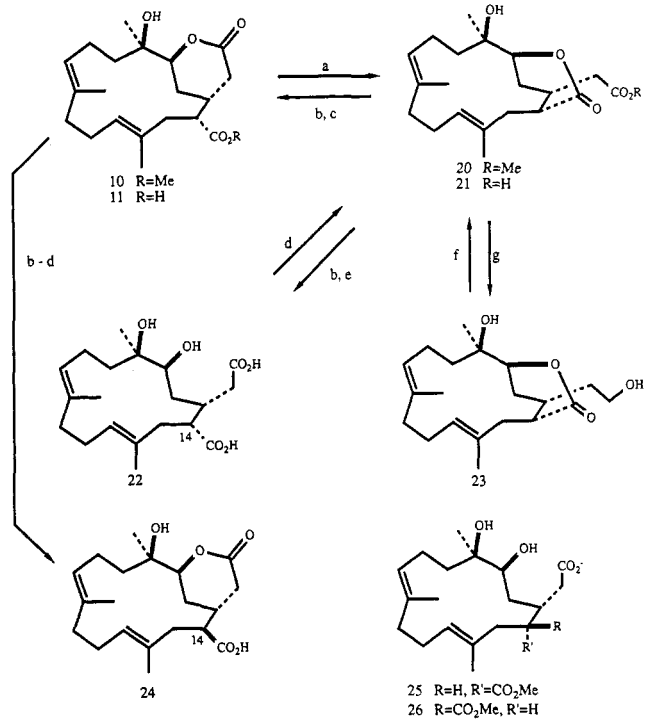
structure was confirmed through single-crystal X-ray analysis (Figure 4). The apparent steric preference at C14 must result from interactions in the cyclization transition state. Presumably, the bulky phenylsulfonyl grouping of the prochiral sulfonylacetate anion preferentially occupies a position external to the developing macrocyclic ring, leaving the alternative internal position to the smaller carboxylic substituent.

Desulfonylation of sulfonyl ester **9** with sodium amalgam in methanol at −78 °C afforded lactone ester **10** exclusively. At 0 °C, the same desulfonylation led to an isomeric lactone ester (**20**). This "thermodynamic" isomer, which could also be secured through treatment of ester **10** with methanolic sodium methoxide, was at first assumed to be the C14 epimer of **10**. Subsequent transformations outlined in Scheme II proved this assumption erroneous.

Saponification of the "thermodynamic" lactone ester **20** followed by careful stoichiometric acidification afforded diacid **22**. Addition of the foregoing saponification mixture to excess acid ("inverse addition") yielded the "kinetic" lactone acid **11**, identified through conversion to ester **10** by treatment with diazomethane. Addition of excess aqueous hydrochloric acid to the same saponification mixture ("normal addition") gave rise to a 1:3 mixture of the "kinetic" lactone acid **11** and a new lactone acid **21** presumed (incorrectly) to be the C14 epimer of **11**. Esterification with diazomethane converted this new lactone acid to the previously obtained "thermodynamic" lactone ester **20**. The structure of this ester (as **20**) and its related acid (**21**) was clarified through selective reduction of the ester function with lithium borohydride whereupon a lactone diol, identified as **23** through ^{1}H NMR analysis, was obtained as the major product. This same diol was also produced upon reduction of the "kinetic" lactone ester **10** with lithium borohydride. Evidently the small amount of lithium methoxide produced in this reaction must catalyze translactonization of **10** to the "thermodynamic" lactone ester **20** before significant reduction of the methyl ester has taken place. Oxidation of lactone diol **23** with chromic acid in aqueous acetone afforded the acid **21** identical with the "thermodynamic" lactone acid obtained via treatment of the lactone ester saponification reaction mixture with excess acid.

Saponification of the "kinetic" lactone ester **10** followed by "inverse" acidification at 0 °C afforded a 40:60 mixture of the "kinetic" lactone acid **11** and a diacid, not **22**. The latter gave rise to a new lactone acid, thought to be **24**, upon heating in benzene. In **10** the lactone is expectedly saponified more rapidly than the ester moiety. Hence the intermediate ester carboxylic acid salt **25** can epimerize

Scheme II[a]



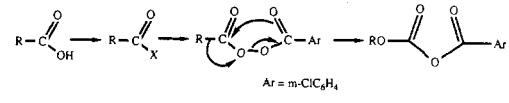
[a] (a) NaOMe, MeOH; (b) NaOH, H_2O, DME; (c) inverse HCl, THF; (d) C_6H_6, 80 °C; (e) stoichiometric HCl, THF; (f) $LiBH_4$, THF, 0 °C; (g) H_2CrO_4, H_2O, acetone.

to **26** under the basic saponification conditions. Lactone **20**, on the other hand, is not epimerized upon saponification. It can assume a favorable half-chair conformation with all substituents equatorially disposed. Therefore neither **20** nor the derived lactone carboxylic acid salt stands to gain from inversion at C14. Prior saponification of the lactone grouping would lead to an ester carboxylic acid salt, which would be obliged to form a carboxylic dianion in order to epimerize. Direct equilibration of **10** at C14 with alkoxide bases is precluded by its facile translactonization to **20**.

As noted above, the dicarboxylic acid salt derived from lactone ester **20** afforded the diacid **22** upon careful acidification with a stoichiometry quantity of mineral acid. This diacid yielded lactone acid **21** upon heating in benzene. Thus diacid **22** is also not readily epimerized.

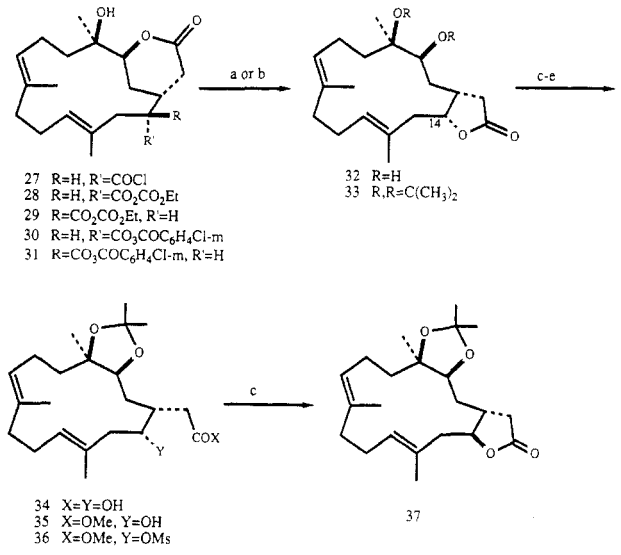
The epimeric lactone acids **11** and **24** were readily separated by flash chromatography on silica gel. Acid **11** was most efficiently prepared from the thermodynamic ester **20** via saponification and "inverse" acidification as described above. A more efficient route to acid **24** was not sought because of unfavorable developments, to be discussed. As we initially had no basis for assigning stereochemistry to lactone acids **11** and **24**, we employed the more accessible isomer **11** in our exploratory carboxy inversion experiments.

The thermal rearrangement of diacyl peroxides to mixed carbonic anhydrides has been studied by several investigators. Denney was the first to demonstrate that mixed acyl peroxides could be employed in a synthetically useful sequence.[9] The methodology effectively transforms a carboxylic acid into an alcohol by insertion of oxygen between the carbonyl grouping and the α-carbon (eq 2). It was found that the reaction rate parallels the ability of the



(2)

Scheme III[a]



[a] (a) *m*-$ClC_6H_4CO_3H$, Et_2O, 2,6-$Me_2C_5H_3N$, −78 to 25 °C; (b) *m*-$ClC_6H_4CO_3Na$, CH_2Cl_2, THF, −78 °C; NH_4Cl, H_2O; (c) NaOH, H_2O, DME; H_2O, HCl, 0 °C; (d) CH_2N_2, CH_2Cl_2, Et_2O, −20 °C; (e) MsCl, CH_2Cl_2, C_5H_5N, 0 °C.

migrating group R to tolerate electron deficiency, reminiscent of the Baeyer–Villiger oxidation of ketones. The question of stereochemistry was not addressed by Denney, but an earlier paper by Lau and Hart showed that the acyl peroxides derived from *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids each rearranged nearly quantitatively to the 4-*tert*-butylcyclohexyl esters with retention of stereochemistry.[10] Although the result was attributed to a radical cage phenomenon, the possibility of a Baeyer–Villiger-like carboxy inversion pathway seems equally plausible. Further evidence for the mechanism of the carboxy inversion reaction was reported by Kashiwagi et al.[11]

In 1973 Rosen disclosed the first synthetic application of the carboxy inversion process in connection with a total synthesis of prostaglandins.[14] Danishefsky subsequently employed the reaction in the total synthesis of widdrol.[15] In each case retention of stereochemistry was observed.

Following the general approach of Denney[9] with suitable modifications to accommodate its apparent instability, we prepared acid chloride **27** (Scheme III) by addition of lactone acid **11** to excess oxalyl chloride in a mixture of benzene and xylene at room temperature. The conditions employed in this step strongly influenced the yield and stereoselectivity of the overall process owing to the instability and stereochemical lability of the intermediate acid chloride **27**. Typically, most of the benzene and excess oxalyl chloride were removed at reduced pressure and the xylene solution of acid chloride was treated with purified *m*-chloroperoxybenzoic acid and 2,6-lutidine in ether or methylene chloride at −78 °C with gradual warming to room temperature. After several days, methanolic sodium methoxide was added to effect methanolysis of the intermediate mixed anhydride followed by aqueous acid to liberate any uninverted carboxylic acid. The product thus obtained contained varying amounts of cis and trans γ-lactones (**32**, **42**) and acid **11** and its C14 epimer **24**, depending upon the conditions employed for preparation of the acid chloride. In the worst case, when benzene alone

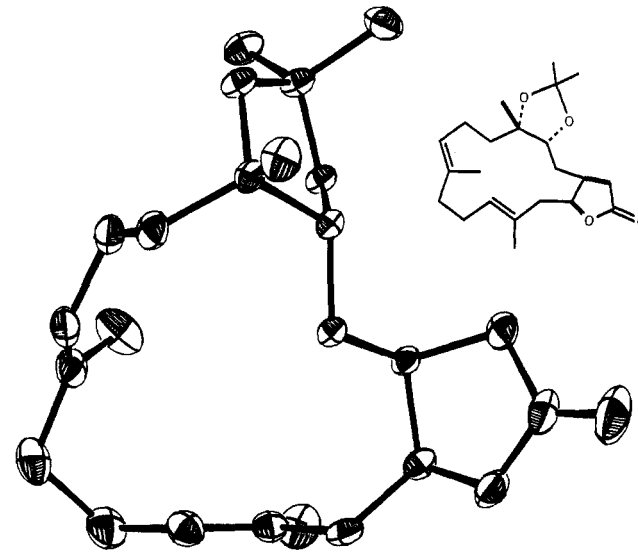


Figure 5. X-ray structure of lactone acetonide **33**.

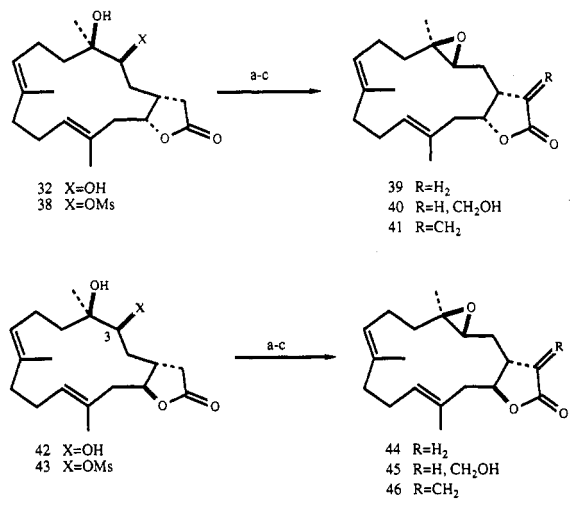
was used as the solvent and the crude acid chloride was taken to dryness, a 1:1 mixture of cis and trans lactones was isolated in only 15% yield. With careful control of temperature and dilution, conversion could be effected in 65% yield to an 87:13 mixture of cis and trans lactones with 10% of recovered acid **11**. The isomeric lactones proved inseparable by column chromatography, but purification could be conveniently effected through the highly crystalline acetonide derivative **33**. This derivative also proved amenable to single-crystal X-ray analysis (Figure 5), thus establishing the stereochemistry as shown. Surprisingly, attempts at carboxy inversion of the lactone acid **24** along the foregoing lines uniformly failed owing to extensive decomposition of the acid chloride and derived intermediates. The modification of Rosen[14] using DCC to form the mixed acyl peroxide proved unsuccessful as well, both with acid **24** and with its C14 epimer **11**.

Because of the erratic behavior of the foregoing acid chlorides, a more reliable route to the acyl peroxides was sought (Scheme III). Accordingly, the stable mixed carbonic anhydrides **28** and **29** were prepared from acids **11** and **24** with methyl chloroformate and triethylamine. Treatment of these anhydrides with the sodium salt of *m*-chloroperoxybenzoic acid in methylene chloride at −78 °C afforded the isolable acyl peroxides **30** and **31**. The former gave the cis lactone **32** of >90% isomeric purity in 40–50% yield reproducibly upon standing in ether–ethyl acetate at room temperature for 2 days. The latter peroxide decomposed under similar conditions to an intractable mixture of products containing 10% or less of the trans lactone **42**.

Unable to produce the trans lactone **42** efficiently from acid **24**, we turned our efforts to inversion of the crystalline cis lactone acetonide **33** at C14. To that end, the hydroxy acid **34** was prepared via saponification and careful acidification. Attempts at direct inversion–lactonization with DEAD gave a nearly 1:1 mixture of cis and trans lactones.[16] Better results were realized with the mesylate derivative **36** of hydroxy ester **35**. Saponification of **36** with NaOH in DME followed by acidification yielded the trans lactone acetonide **37** in 67% yield. It is presumed that this process occurs via intramolecular S_N2 displacement of the mesylate by the carboxylate grouping. Hydrolysis of the acetonide then gave the elusive trans lactone diol **42** (Scheme IV).

(14) Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440.
(15) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891.
(16) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme IV[a]



[a] (a) Triton B OH, MeOH, THF, −50 °C; (b) LDA, THF, −30 °C; CH_2O (g); (c) $O(CH_2CH_2)_2N^+(Me)CH_2CH_2N{=}C{=}NC_6H_{11}$, OTs^-, $CuCl_2$, CH_3CN, THF, 55 °C.

The final steps in our synthesis required conversion of the 3,4-diol grouping of **42** to the epoxide function with inversion at C-3 and ultimate α-methylenation of the γ-lactone moiety. These steps were first examined with the more accessible cis lactone diol **32**. Treatment of **32** with MsCl in pyridine–CH_2Cl_2 afforded the monomesylate **38**, which subsequently yielded the epoxide **39** upon exposure to Triton B hydroxide in THF at −20 °C.[5]

For α-methylenation of lactone epoxide **39** we devised a new two-step method based on the known DCC-promoted dehydration of β-hydroxy ketones and esters under neutral conditions.[17] This was motivated by concerns that the sensitive epoxide grouping of **39** and **44** might be adversely affected by the conventional sequence of hydroxymethylation–mesylation–elimination.[18] Accordingly, lactone **39** was hydroxymethylated by treatment with LDA in THF at −30 °C and subsequent addition of gaseous formaldehyde. The crude α-hydroxymethyl lactone **40** was then treated with excess 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate,[19] a water-soluble carbodiimide, in CH_3CN–THF containing $CuCl_2$ to promote addition to the diimide. The reaction mixture was filtered through silica gel to remove excess diimide and polar byproducts, whereupon the α-methylene lactone **41** was readily isolated in 53% yield. As expected, the ^1H NMR spectrum of this lactone differed from that of isolobophytolide, especially in the 4–5 ppm region. In particular, the C14 proton appeared at 4.96 ppm, indicative of the cis 1,14 ring fusion.

The trans lactone acetonide **37** when subjected to hydrolysis, monomesylation, and base treatment, as described for the cis isomer **33**, afforded the epoxide **44** in 41% overall yield (Scheme IV). α-Methylenation, as before, gave racemic isolobophytolide (**46**) in 40% yield for the two steps. The identity of this material with the natural substance was established by comparison of the high-field ^1H NMR spectrum and TLC mobility.

Thus we have completed the first total synthesis of isolobophytolide, a complex cembranolide natural product. Although racemic material was employed, we have prepared epoxide X in homochiral form through Sharpless epoxidation[20] so the synthesis of either enantiomer of isolobophytolide could be effected. The sequence permits complete control of all stereocenters. Its main shortcomings are the failure of acid **24** to undergo efficient carboxy inversion to the trans lactone **44** and our inability to effect thermodynamically controlled Michael additions to pentenolide **7** for production of a potential crassin acetate synthon. Nonetheless, we expect the concepts and methodology that evolved from the successful route to find additional applications in cembranolide and related natural product synthesis.

Experimental Section

The apparatus and methods described by G. W. Kramer, M. M. Midland, and A. B. Levy[21] were used to maintain an argon or nitrogen atmosphere in the reaction flask. Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and dioxane), calcium hydride (dichloromethane and hexamethylphosphoramide), or sodium (benzene and toluene). Infrared absorption maxima are reported in wavenumbers (cm^{-1}). Proton magnetic resonance samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; envelope, e; multiplet, m. Coupling constants (J) are reported in hertz (Hz). J_{Avic} and J_{Bvic} refer to vicinal couplings of the A and B protons of AB quartets with neighboring protons. Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. E. Merck silica gel 60 (230–400 ASTM mesh) was employed for chromatography according to the procedure of Still et al.[22]

***rel*-(4*R*,5*S*)-(8*E*,12*E*)-5,9,13-Trimethyltetradeca-8,12-dien-1-yne-4,5,14-triol (3).** A solution of 9.77 g (19.4 mmol) of diol **1** in 40 mL of MeOH and 40 mL of THF was chilled to −78 °C with mechanical stirring and then treated with 16.5 g (116 mmol) of Na_2HPO_4 and 41 g of powdered 6% sodium amalgam. After the mixture was stirred vigorously for 3.5 h at −78 °C, it was warmed to room temperature. The supernatant was decanted, and the solids were washed with water and ether. The layers were separated, and the aqueous layer was extracted with ether and dried over $MgSO_4$. Solvent evaporation under reduced pressure afforded the crude diol **2**, which was stirred in 40 mL of MeOH at room temperature as 180 mg (0.95 mmol) of *p*-TsOH was added. After 1 h, 1.0 mL of Et_3N was added and the mixture was concentrated at reduced pressure. Chromatography on silica gel (elution with 20% EtOAc–hexane followed by 50% EtOAc–hexane) gave 3.93 g (72%) of the triol **3** as an oil: IR (film) ν 3370, 3300, 2960, 2910, 2800, 1450, 1385, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, C5 Me), 1.57 (m, H6), 1.63 (s, C13 Me), 1.64 (s, C9 Me), 2.01 (m, H7), 2.04 (t, J = 2.5 Hz, H1), 2.78 (m, H10, H11), 2.35 (s, OH), 2.44 (dd of AB, J_{AB} = 18.2 Hz, $\Delta\nu$ = 42 Hz, J_{Avic} = 9.1, 2.5 Hz, J_{Bvic} = 3.6, 2.5 Hz, H3), 2.58 (d, J = 4.3 Hz, OH), 3.59 (ddd, J = 9.1, 3.6, 4.3 Hz, H4), 3.95 (d, J = 4.6 Hz, H14), 5.17 (t, J = 6.4 Hz, H12), 5.30 (t, J = 5.8 Hz, H8); ^{13}C NMR ($CDCl_3$) δ 135.3, 135.0, 125.3, 124.6, 82.0, 75.4, 74.4, 70.4, 68.5, 39.1, 36.7, 25.6, 22.6, 21.9, 21.8, 15.8, 13.6. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.07. Found: C, 72.56; H, 10.12.

***rel*-(10*R*,11*S*)-(2*E*,6*E*)-10,11-Dihydroxy-2,6,10-trimethyl-2,6-tetradecadien-13-ynyl Pivalate (4).** A solution of 5.771 g (20.58 mmol) of triol **3** in 20 mL of pyridine and 20 mL of CH_2Cl_2 was cooled to 0 °C as 3.45 mL (22.6 mmol) of pivaloyl chloride was added. The mixture was stirred for 40 min at 0 °C,

(17) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winger, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. Andrews, R. C.; Marshall, J. A.; DeHoff, B. S. *Synth. Commun.* **1986**, *16*, 1593.

(18) Cf.: Grieco, P. A.; Noquez, J. A.; Hiroi, K.; Nishizawa, M.; Rocsowsky, A.; Oppenheim, S.; Lazarus, H. *J. Med. Chem.* **1977**, *20*, 71.

(19) Available from Aldrich Chemical Co., Milwaukee, WI. For an analogous dehydration, see: Alexandre, G.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1973**, 1837.

(20) Cf.: Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. Andrews, R. C. Ph.D. Thesis, University of South Carolina, 1986, p 42.

(21) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975; pp 191–202.

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2933.

10 mL of MeOH was added, and stirring was continued for 10 min at 0 °C. The mixture was diluted with water and extracted with ether. The organic layers were washed with saturated aqueous $CuSO_4$, water, and brine and were dried over $MgSO_4$. Solvent removal at reduced pressure provided an oil, which was purified by chromatography on silica gel (elution with hexane followed by 60% ether–hexane) to give 6.161 g (87%) of pivalate **4** as an oil: IR (film) ν 3450, 3280, 2950, 1715, 1455, 1285, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, *t*-Bu), 1.25 (s, C10 Me), 1.42 (m, H9), 1.62 (s, C2 Me), 1.63 (s, C6 Me), 2.04 (m, H8), 2.09 (t, J = 2.6 Hz, H14), 2.13 (m, H4, H5), 2.15 (s, OH), 2.46 (dd of AB, J_{AB} = 16.7 Hz, $\Delta\nu$ = 36 Hz, J_{Avic} = 3.4, 2.6 Hz, J_{Bvic} = 8.9, 2.6 Hz, H12), 2.57 (d, J = 4.4 Hz, OH), 3.61 (ddd, J = 8.9, 4.4, 3.4 Hz, H11), 4.43 (s, H1), 5.13 (t, J = 6.0 Hz, H3), 5.40 (t, J = 5.7 Hz, H7); ^{13}C NMR ($CDCl_3$) δ 178.2, 134.8, 130.2, 128.3, 124.5, 81.8, 75.3, 73.9, 70.5, 69.7, 38.9, 38.7, 37.0, 27.1, 26.0, 22.8, 21.8, 15.8, 13.6. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.40; H, 9.97.

***rel*-(10*R*,11*S*)-(2*E*,6*E*)-10,11-(Isopropylidenedioxy)-2,6,10-trimethyltetradeca-2,6-dien-13-ynyl Pivalate (5).** A solution of 898 mg (2.46 mmol) of diol **4** in 5 mL of CH_2Cl_2 was stirred at 0 °C as 31 mg (0.12 mmol) of pyridinium *p*-toluenesulfonate was added, followed by 0.42 mL (4.9 mmol) of 2-methoxypropene. The mixture was stirred at 0 °C for 10 min and at room temperature for 7 h. It was then diluted with 20 mL of ether and washed twice with half-saturated brine and once with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was chromatographed on silica gel (elution with 10% EtOAc–hexane) to give 990 mg (99%) of acetonide **5**: IR (film) ν 3270, 2950, 2900, 2850, 1720, 1455, 1280, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, *t*-Bu), 1.33 (s, C10 Me), 1.37, 1.41 (2 s, acetonide Me), 1.53 (m, H9), 1.61 (s, C2 Me), 1.62 (s, C6 Me), 2.01 (m, H8), 2.03 (t, J = 2.7 Hz, H14), 2.48 (dd of AB, J_{AB} = 17.0 Hz, $\Delta\nu$ = 88 Hz, J_{Avic} = 6.6, 2.7 Hz, J_{Bvic} = 8.0, 2.7 Hz, H12), 3.91 (dd, J = 8.0, 6.6 Hz, H11), 4.42 (s, H1), 5.13 (t, J = 7.2 Hz, H3), 5.41 (t, J = 5.7 Hz, H7); ^{13}C NMR ($CDCl_3$) δ 178.1, 134.6, 130.2, 128.4, 124.5, 106.8, 81.7, 79.8, 70.3, 69.7, 39.0, 38.7, 34.4, 28.2, 27.1, 26.9, 26.2, 23.6, 21.7, 18.9, 15.9, 13.7; MS calcd for $C_{25}H_{40}O_4$ *m/e* 404.29, found ($M^+ - CH_3$) 389, (M^+) 404. Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.39; H, 10.01.

Methyl *rel*-(5*R*,6*S*)-(9*E*,13*E*)-5,6-(Isopropylidenedioxy)-15-(pivalyloxy)-6,10,14-trimethylpentadeca-9,13-dien-2-ynoate (6). A solution of 990 mg (2.44 mmol) of acetonide **5** was stirred in 2.5 mL of THF at −78 °C under nitrogen. In a separate vessel, 0.41 mL (2.9 mmol) of diisopropylamine in 2.5 mL of THF was chilled to 0 °C as 1.05 mL (2.68 mmol) of 2.55 M *n*-BuLi was added dropwise. After 15 min, the mixture was taken up into a dry syringe and added over 2 min to the cold alkyne solution. After 20 min at −78 °C, 0.56 mL (7.2 mmol) of methyl chloroformate was added. The mixture was stirred at −78 °C for 30 min, then warmed to 0 °C, quenched with 10% aqueous NH_4OH, and poured into water. The mixture was extracted with ether, and the ether layers were washed with water and brine and dried over $MgSO_4$. Solvent removal in vacuo was followed by chromatography on silica gel (elution with 5% EtOAc–hexane) to give 1.031 g (91%) of the ester **6** as an oil: IR (film) ν 2930, 2220, 1715, 1435, 1380, 1255, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, *t*-Bu), 1.34 (s, C6 Me), 1.37, 1.41 (2 s, acetonide Me), 1.56 (m, H7), 1.62 (s, C14 Me), 1.64 (s, C10 Me), 2.01 (m, H8), 2.13 (m, H11, H12), 2.64 (d of AB, J_{AB} = 17.2 Hz, $\Delta\nu$ = 86 Hz, J_{Avic} = 6.5 Hz, J_{Bvic} = 7.9 Hz, H4), 3.77 (s, MeO), 3.95 (dd, J = 7.9, 6.5 Hz, H5), 4.44 (s, H15), 5.14 (t, J = 7.1 Hz, H13), 5.42 (t, J = 5.7 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 178.1, 153.6, 134.8, 130.2, 128.3, 124.3, 107.2, 84.6, 80.9, 74.3, 69.7, 52.5, 39.0, 38.7, 34.5, 28.1, 27.1, 26.2, 23.4, 21.6, 19.2, 15.9, 13.7; MS calcd for $C_{27}H_{42}O_6$ *m/e* 462.24, found ($M^+ - CH_3$) 447, (M^+) 462.

***rel*-(5*R*,6*S*)-(2*Z*,9*E*,13*E*)-5,6-Dihydroxy-15-(pivalyloxy)-6,10,14-trimethylpentadeca-2,9,13-trienoic Acid δ-Lactone (7b).** A solution of 1.019 g (2.194 mmol) of ester **6** in 4 mL of MeOH and 0.4 mL of 2% aqueous H_2SO_4 was heated at reflux under nitrogen for 7 h. After the mixture was cooled to room temperature, it was diluted with water, extracted with ether, and dried over $MgSO_4$. Concentration in vacuo and chromatography on 20 g of silica gel (elution with 10% EtOAc–hexane) gave 661 mg (71%) of the diol methyl ester as an oil: IR (film) ν 3430, 2950, 2230, 1710, 1435, 1270, 1160, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, *t*-Bu), 1.19 (s, C6 Me), 1.38 (m, H7), 1.60 (s, C14 Me), 1.61 (s, C10 Me), 2.02 (m, H8), 2.10 (m, H11, H12), 2.17 (s, OH), 2.57 (d of AB, J_{AB} = 16.8 Hz, $\Delta\nu$ = 22 Hz, J_{Avic} = 3.2 Hz, J_{Bvic} = 9.2 Hz, H4), 2.86 (d, J = 5.0 Hz, OH), 3.68 (ddd, J = 9.2, 5.0, 3.2 Hz, H5), 3.74 (s, MeO), 4.41 (s, H15), 5.10 (t, J = 6.8 Hz, H13), 5.38 (t, J = 5.9 Hz, H9); Anal. Calcd for $C_{24}H_{39}O_6$: C, 68.05; H, 9.28. Found: C, 67.94; H, 9.29.

A suspension of 10 mg of 5% palladium on barium sulfate was stirred in 1 mL of pyridine under 1 atm of hydrogen for 0.5 h in a base-washed, oven-dried flask. The mixture was treated with 919 mg (2.18 mmol) of the diol methyl ester in 3 mL of pyridine. After 2.5 h the mixture was aspirated free of hydrogen and filtered through a column of Celite (elution with ether). The filtrate was washed once with water, and the aqueous phase was extracted once with ether. The combined organic layers were washed with saturated $CuSO_4$ solution, water, and brine and dried over $MgSO_4$. Solvent evaporation in vacuo and filtration through silica gel (elution with 15% EtOAc–hexane) gave 910 mg (99%) of the cis ester diol as an oil.

The cis ester was stirred in 4 mL of THF as 25 mg (0.11 mmol) of 10-camphorsulfonic acid was added. The mixture was heated at reflux for 2.5 h, then cooled to room temperature, treated with 0.2 mL of Et_3N, and filtered through a pad of Florisil (ether elution). Purification of the crude product by chromatography on silica gel (elution with 30% EtOAc–hexane) gave 781 mg (91% overall) of the pentenolide **7b** as an oil: IR (film) ν 3420, 2960, 1720, 1395, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, *t*-Bu), 1.28 (s, C6 Me), 1.50 (m, H7), 1.59 (s, C14 Me), 1.60 (s, C10 Me), 2.02 (m, H7, H11), 2.13 (m, H12), 2.25 (s, OH), 2.45 (dd of AB, J_{AB} = 18.9 Hz, $\Delta\nu$ = 97 Hz, J_{Avic} = 12.7, 2.0 Hz, J_{Bvic} = 6.2, 3.8 Hz, H4), 4.26 (dd, J = 12.7, 3.8 Hz, H5), 4.40 (s, H15), 5.17 (t, J = 8.1 Hz, H9), 5.37 (t, J = 5.4 Hz, H13), 5.98 (dt, J = 9.0, 2.0 Hz, H2), 6.92 (ddd, J = 9.0, 6.2, 2.0 Hz, H3); Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.19, H, 9.26.

***rel*-(3*R*,5*S*,6*R*)-(9*E*,13*E*)-15-Acetoxy-3-[(phenylsulfonyl)carbomethoxymethyl]-5,6-dihydroxy-6,10,14-trimethylpentadeca-9,13-dienoic Acid δ-Lactone (8a).** A solution of 205 mg (0.586 mmol) of lactone **7a** in 0.3 mL of *t*-BuOH and 0.8 mL of Me_2SO was stirred as 0.14 mL (0.12 mmol) of 0.85 M KO-*t*-Bu in *t*-BuOH was added, followed by 0.11 mL (0.66 mmol) of methyl (phenylsulfonyl)acetate. After 21 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl and water. The mixture was extracted with ether and dried over $MgSO_4$. Concentration under reduced pressure and chromatography on silica gel (elution with 40% EtOAc–hexane) gave 295 mg (89%) of the lactone **8a** as an oil: IR (film) ν 3430, 2910, 1730, 1458, 1250, 1155, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19, 1.22 (2 s, C6 Me), 1.43 (m, H7), 1.57 (2 s, C10 Me), 1.60 (s, C14 Me), 1.95 (m, H8), 2.01 (s, AcO), 2.05 (m, H11, H12), 2.20 (m, H4), 2.51 (d of AB, J_{AB} = 17.8 Hz, $\Delta\nu$ = 53 Hz, J_{Avic} = 6.7 Hz, J_{Bvic} = 10.0 Hz, H2), 2.63 (d of AB, J_{AB} = 12.8 Hz, $\Delta\nu$ = 25 Hz, J_{Avic} = 5.6 Hz, J_{Bvic} = 7.8 Hz, H2), 2.98 (m, H3), 3.24, 3.56 (2 s, OMe), 4.00, 4.02 (2 d, J = 10.0, 6.1 Hz, $PhSO_2CHRCO_2R$), 4.11 (dd, J = 8.9, 6.1 Hz, H5), 4.25 (dd, J = 10.6, 5.0 Hz, H5), 4.37 (s, H15), 5.04 (m, H9), 5.39 (br t, J = 7.8 Hz, H13), 7.35 (m, *m*-Ar), 7.43 (m, *p*-Ar), 7.83 (m, *o*-Ar); Anal. Calcd for $C_{29}H_{40}O_9S$: C, 61.68; H, 7.14. Found: C, 61.72; H, 7.15.

***rel*-(3*R*,5*S*,6*R*)-(9*E*,13*E*)-3-[(Phenylsulfonyl)carbomethoxymethyl]-5,6-dihydroxy-15-(pivalyloxy)-6,10,14-trimethylpentadeca-9,13-dienoic Acid δ-Lactone (8b).** In the manner described for lactone **8a**, 544 mg (1.39 mmol) of lactone **7b** in 1.6 mL of Me_2SO and 0.4 mL of *t*-BuOH was treated with 0.28 mL (1.68 mmol) of methyl (phenylsulfonyl)acetate and 0.40 mL (0.34 mmol) of 0.85 M KO-*t*-Bu in *t*-BuOH. After 16 h at room temperature, workup and purification in the manner described for **8a** gave 771 mg (92%) of the sulfone **8b** as an oil: IR (film) ν 3420, 2900, 1740, 1460, 1250, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, *t*-Bu), 1.28 (s, C6 Me), 152 (m, H7), 1.61 (br s, C10 Me, C14 Me), 2.01 (m, H8, H11), 2.12 (m, H12), 2.26 (m, H4), 2.58 (d of AB, J_{AB} = 16.1 Hz, $\Delta\nu$ = 50 Hz, J_{Avic} = 5.6 Hz, J_{Bvic} = 6.8 Hz, H2), 2.71 (d of AB, J_{AB} = 6.8 Hz, $\Delta\nu$ = 13 Hz, J_{Avic} = 5.7 Hz, J_{Bvic} = 6.8 Hz, H2), 3.03 (m, H3), 3.50, 3.56 (2 s, OMe), 4.01, 4.06 (2 d, J = 9.6, 7.9 Hz, $PhSO_2CHRCO_2R$), 4.17 (dd, J = 8.8, 6.1 Hz, H5), 4.32 (dd, J = 10.2, 4.5 Hz, H5), 4.43 (s, H15), 5.11 (m, H9), 5.40 (br t, J = 6.2 Hz, H13), 7.58 (m, *m*-Ar),

7.70 (m, *p*-Ar), 7.88 (m, *o*-Ar); MS calcd for $C_{32}H_{46}O_9S$ *m/e* 606.28, found ($M^+ - C_{16}H_{27}O_2$) 355, (M^+) 606. Anal. Calcd for $C_{32}H_{40}O_9S$: C, 63.34; H, 7.64. Found: C, 62.65; H, 7.70.

***rel*-(5*R*,6*S*)-(9*E*,12*E*)-15-Acetoxy-3-(carbomethoxymethyl)-5,6-dihydroxy-6,10,14-trimethylpentadeca-9,13-dienoic Acid δ-Lactone (8a/18a, Z = H).** A solution of 123 mg (0.218 mmol) of sulfone lactone **8a** in 1 mL of MeOH and 1 mL of THF was stirred under nitrogen at −78 °C as 310 mg (2.18 mmol) of Na_2HPO_4 and 200 mg of powdered 6% sodium amalgam were added. The mixture was stirred mechanically at −78 °C for 45 min, then acidified with 0.4 N aqueous tartaric acid, diluted with water, and extracted with ether. The organic solutions were washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure and chromatography on silica gel (elution with 45% EtOAc–hexane) gave 80 mg (87%) of lactones **8a/18a** (Z = H) as a 60:40 trans–cis mixture, as judged by ^1H and ^{13}C NMR analysis: IR (film) ν 3420, 2900, 1722, 1435, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23, 1.24 (2 s, C6 Me), 1.33 (m, H3), 1.42 (m, H3, H7), 1.60 (s, C14 Me), 1.63 (s, C10 Me), 1.67 (m, H4), 2.03 (m, H8, H11, H12), 2.05 (s, OAc), 2.28 (m, H2), 2.38 (d of AB, J_{AB} = 9.9 Hz, $\Delta\nu$ = 15 Hz, J_{Avic} = 7.6 Hz, J_{Bvic} = 8.7 Hz, H2), 2.60 (d of AB, J_{AB} = 6.4 Hz, $\Delta\nu$ = 22 Hz, J_{Avic} = 6.4 Hz, J_{Bvic} = 8.2 Hz, RCH_2CO_2R), 2.62 (d of AB, J_{AB} = 22.7 Hz, $\Delta\nu$ = 154 Hz, J_{Avic} = 7.6 Hz, J_{Bvic} = 6.2 Hz, RCH_2CO_2R), 3.68 (s, OMe), 4.17 (m, H5), 4.42 (s, H15), 5.11 (t, J = 6.4 Hz, H9), 5.41 (t, J = 7.0 Hz, H13); ^{13}C NMR ($CDCl_3$) δ 173.2, 173.0, 171.6, 171.5, 170.8, 135.0, 134.6, 129.9, 129.8, 129.2, 129.1, 124.8, 124.1, 85.4, 81.9, 75.7, 74.3, 73.0, 70.1, 51.6, 51.4, 39.1, 38.9, 37.5, 37.0, 35.8, 35.3, 34.7, 29.2, 28.1, 26.9, 26.1, 25.9, 22.9, 22.5, 21.8, 21.7, 20.8, 15.8, 13.8. Anal. Calcd for $C_{23}H_{36}O_7$: C, 65.07; H, 8.55. Found: C, 65.02; H, 8.58.

***rel*-(3*R*,5*S*,6*R*)-(9*E*,12*E*)-15-Acetoxy-3-(carbomethoxymethyl)-5,6-dihydroxy-6,10,14-trimethylpentadeca-9,13-dienoic Acid δ-Lactone (18a, Z = H).** A solution of 38 mg (0.090 mmol) of lactone (40:60 cis–trans) in 1 mL of MeOH was treated with 2 mg (0.04 mmol) of NaOMe at room temperature. After 3.5 h at room temperature, the mixture was treated with 1 mL of 3 N HCl and water. The mixture was extracted with ether and dried over $MgSO_4$. Solvent removal in vacuo gave the crude diol, which was stirred in 0.2 mL of CH_2Cl_2 and 0.1 mL of pyridine at 0 °C as 0.020 mL (0.22 mmol) of Ac_2O was added. After 1 h at 0 °C and 3.5 h at room temperature, the mixture was quenched with MeOH, diluted with water, and extracted with ether. The combined ether solutions were washed with water and brine and dried over $MgSO_4$. Solvent evaporation under reduced pressure and filtration through silica gel (elution with 50% EtOAc–hexane) gave 33 mg (87%) of lactones **8a/18a** (Z = H) as a 90:10 cis–trans mixture, as judged by ^1H and ^{13}C NMR analysis: IR (film) ν 3450, 2910, 1735, 1442, 1380, 1250, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, C6 Me), 1.25 (m, H3), 1.40 (m, H7), 1.57 (m, H4), 1.59 (s, C14 Me), 1.62 (s, C10 Me), 2.00 (m, H8, H11), 2.05 (s, AcO), 2.07 (m, H8), 2.38 (d of AB, J_{AB} = 9.9 Hz, $\Delta\nu$ = 10 Hz, J_{Avic} = 10.9 Hz, J_{Bvic} = 2.2 Hz, H2), 2.62 (d of AB, J_{AB} = 22.7 Hz, $\Delta\nu$ = 154 Hz, J_{Avic} = 7.6 Hz, J_{Bvic} = 6.2 Hz, RCH_2CO_2R), 3.68 (s, OMe), 4.16 (dd, J = 11.9, 3.0 Hz, H5), 4.42 (s, H15), 5.11 (t, J = 6.4 Hz, H9), 5.41 (t, J = 7.0 Hz, H13); ^{13}C NMR ($CDCl_3$) δ 173.5, 170.9, 170.1, 135.2, 130.1, 129.3, 124.2, 85.6, 73.2, 70.2, 51.7, 40.1, 39.0, 36.9, 35.8, 28.7, 28.2, 26.2, 22.4, 21.7, 20.9, 15.9, 13.9.

Methyl *rel*-(1*R*,2*S*,12*R*,13*S*)-(5*E*,9*E*)-12-(Phenylsulfonyl)-2-hydroxy-2,6,10-trimethyl-15-oxo-16-oxabicyclo[11.3.1]heptadeca-5,9-diene-12-carboxylate (9). A solution of 793 mg (1.31 mmol) of lactone **8b** in 4 mL of THF was stirred under argon at room temperature as 0.97 mL (3.96 mmol) of *O,N*-bis(trimethylsilyl)acetamide was added. The container was alternately evacuated (25 mmHg) and filled with argon five times, and then the mixture was heated to reflux under argon. After 4 h the mixture was cooled to room temperature, diluted to a volume of 6.5 mL with THF, and taken up into a dry syringe.

In a separate vessel, a solution of 316 mg (0.274 mmol) of $(Ph_3P)_4Pd$ and 113 mg (0.283 mmol) of $Ph_2PCH_2CH_2PPh_2$ in 27 mL of THF was stirred at room temperature as the container was alternately evacuated and filled with argon in the above manner. The mixture was refluxed for 15 min. To this catalyst system was added the lactone solution via syringe pump over 14 h. The mixture was allowed to reflux for an additional 1 h and then was cooled to room temperature as 2.0 mL (2 mmol) of 1 M Bu_4NF in THF was added. After 10 min the mixture was filtered through silica gel (elution with CH_2Cl_2). Concentration and chromatography on 45 g of silica gel (elution with 35% EtOAc–hexane) gave 383 mg (58%) of crystalline sulfone **9**. Recrystallization from CH_2Cl_2–ether (1:5) gave the analytical sample: mp 186–188 °C; IR ($CDCl_3$) ν 3450, 2905, 1740, 1458, 1320, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ 1.33 (s, C2 Me), 1.46 (s, C10 Me), 1.58 (s, C6 Me), 1.68 (s, OH), 1.83 (dd of AB, J_{AB} = 10.1 Hz, $\Delta\nu$ = 96 Hz, J_{Avic} = 9.2, 3.2 Hz, J_{Bvic} = 8.8, 3.3 Hz, H3), 2.15 (m, H7, H8, H4), 2.29 (m, H4), 2.39 (m, H17), 2.51 (d of AB, J_AB = 13.8 Hz, $\Delta\nu$ = 93 Hz, J_{Avic} = 13.9 Hz, J_{Bvic} = 5.1 Hz, H14), 3.15 (AB, J_{AB} = 14.5 Hz, $\Delta\nu$ = 235 Hz, H11), 3.16 (m, H13), 3.60 (s, OMe), 4.35 (dd, J = 5.2, 10.9 Hz, H1), 5.23 (br t, J = 7.5 Hz, H9), 5.42 (br s, H5), 7.56 (m, *m*-Ar), 7.69 (m, *p*-Ar), 7.75 (m, *o*-Ar); ^{13}C NMR ($CDCl_3$) δ 172.7, 167.5, 136.1, 134.5, 133.9, 133.0, 130.3, 130.0, 128.9, 126.6, 79.7, 78.8, 73.6, 52.9, 38.4, 37.9, 36.5, 32.0, 24.9, 24.6, 23.1, 22.1, 16.9, 15.5; MS calcd for $C_{27}H_{36}O_7S$ *m/e* 504.22, found ($M^+ - PhSO_2$) 363, (M^+) 504. Anal. Calcd for $C_{27}H_{36}O_7S$: C, 64.26; H, 7.19. Found: C, 64.15; H, 7.22.

Methyl *rel*-(1*R*,2*S*,12*S*,13*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-15-oxo-16-oxabicyclo[11.3.1]heptadeca-5,9-diene-12-carboxylate (10). A solution of 640 mg (1.27 mmol) of sulfone **9** in 4 mL of THF and 8 mL of MeOH was chilled to −78 °C under nitrogen as 1.44 g (10.1 mmol) of Na_2HPO_4 and 3.8 g of powdered 6% sodium amalgam were added. The mixture was stirred at −78 °C for 0.5 h and then warmed rapidly to 0 °C. The supernatant was decanted, and the solids were rinsed with ether and water. The mixture was diluted further with water, extracted with ether, and dried over $MgSO_4$. Concentration under reduced pressure was followed by chromatography on silica gel (elution with 25% EtOAc–hexane) to provide 355 mg (76%) of lactone **10** as a crystalline solid. Crystallization from benzene–hexane (1:5) gave the analytical sample: mp 137–138 °C; IR ($CDCl_3$) ν 3420, 2910, 1720, 1440, 1382, 1210, 1175, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, C2 Me), 1.61 (s, C6 Me), 1.65 (s, C10 Me), 1.69 (dd of AB, J_AB = 10.3 Hz, $\Delta\nu$ = 38 Hz, J_{Avic} = 10.9, 3.1 Hz, J_{Bvic} = 8.1, 3.5 Hz, H3), 1.72 (ddd, J = 16.0, 6.6, 3.5 Hz, H17), 2.04 (m, H17), 2.07 (m, H8, H7), 2.17 (m, H4), 2.26 (m, H13), 2.34 (m, H8, H11), 2.49 (d of AB, J_{AB} = 14.9 Hz, $\Delta\nu$ = 27 Hz, J_{Avic} = 14.8 Hz, J_{Bvic} = 4.0 Hz, H14), 2.77 (ddd, J = 9.4, 5.8, 2.9 Hz, H12), 3.68 (s, OMe), 4.08 (dd, J = 9.6, 6.6 Hz, H1), 5.02 (t, J = 7.2 Hz, H5), 5.14 (d, J = 9.4 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 174.3, 173.3, 135.1, 131.4, 129.0, 124.5, 82.2, 74.2, 51.8, 43.6, 38.7, 38.6, 37.2, 33.2, 30.3, 25.4, 25.2, 24.7, 23.7, 22.4, 16.2, 15.0. Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.22; H, 8.87.

Methyl 2-[*rel*-(1*R*,2*S*,12*S*,15*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-13-oxo-14-oxabicyclo[10.2.2]hexadeca-5,9-dien-16-yl]acetate (20).

A. Via Desulfonylation of 9. A solution of 397 mg (0.787 mmol) of sulfone **9** was stirred under nitrogen in 2 mL of MeOH and 2 mL of DME with cooling to 0 °C as 665 mg (4.68 mmol) of Na_2HPO_4 and 1.57 g of powdered 6% sodium amalgam were added. The mixture was stirred at 0 °C for 1 h, then diluted with water, and decanted. The solids were rinsed with ether, and the combined solutions were extracted with ether and dried over $MgSO_4$. Concentration under reduced pressure and chromatography on silica gel (elution with 25% EtOAc–hexane) gave 248 mg (87%) of the crystalline lactone **20**. Crystallization from CH_2Cl_2–ether (1:10) gave the analytical sample, mp 120–121 °C.

B. Via Isomerization of 10. A solution of 40.0 mg (0.109 mmol) of lactone **10** was stirred in 1 mL of MeOH as 0.40 mL (0.11 mmol) of 2.81 M NaOMe in MeOH was added. After 5 h at room temperature, the mixture was diluted with water, extracted with ether, and dried over $MgSO_4$. Solvent removal in vacuo and chromatography on 13 g of silica gel (elution with 25% EtOAc–hexane) gave 29.9 mg (75%) of crystalline ester lactone **20**: IR ($CDCl_3$) ν 3400, 2910, 1735, 1445, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, C2 Me), 1.32 (m, H15), 1.63 (s, OH, C10 Me) 1.81 (dd of AB, J_{AB} = 11.6 Hz, $\Delta\nu$ = 134 Hz, J_{Avic} = 11.3, 2.9 Hz, J_{Bvic} = 8.0, 1.4 Hz, H16), 2.09 (m, H8, H4), 2.16 (m, H11, H7), 2.24 (m, H4), 2.31 (m, H3), 2.42 (d of AB, J_{AB} = 4.4 Hz, $\Delta\nu$ = 96 Hz, J_{Avic} = 3.5 Hz, J_{Bvic} = 4.5 Hz, $R_2CHCH_2CO_2R$), 2.48 (m, H3), 2.86 (d, J = 15.1 Hz, H12), 3.69 (s, OMe), 4.25 (dd, J = 11.1, 1.4 Hz, H1), 5.03 (br t, J = 6.5 Hz, H5), 5.16 (br t, J = 7.2 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 173.6, 172.0, 132.9, 130.8, 127.8, 127.7, 79.8, 72.9, 51.6, 45.7, 39.5, 39.1, 37.8, 37.4, 31.1, 28.5, 24.7, 23.4,

22.3, 18.8, 15.0; MS calcd for $C_{21}H_{32}O_3$ m/e 364.23, found (M^+ − 18) 346, (M^+) 364. Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.22; H, 8.87.

2-[*rel*-(1*R*,2*S*,12*S*,15*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-13-oxo-14-oxabicyclo[10.2.2]hexadeca-5,9-dien-16-yl]acetic Acid (21). A. Via Oxidation of 23. A solution of 4.2 mg (0.012 mmol) of diol **23** in 0.5 mL of acetone was stirred at −40 °C as 3 drops of 2.60 M chromic acid in acetone was added. The mixture was warmed to 0 °C over 17 min and then quenched with 0.3 mL of *i*-PrOH. The mixture was extracted with ether and dried over $MgSO_4$. Solvent removal under reduced pressure and purification by chromatography on silica gel (elution with 30:68:2 EtOAc–C_6H_6–HOAc) gave 3.6 mg (86%) of acid **21**.

B. Via Hydrolysis of 20. To a solution of 157 mg (0.431 mmol) of lactone **20** in 1.5 mL of THF at room temperature were added 1.5 mL of water and 0.22 mL (2.2 mmol) of 10 N aqueous NaOH. The mixture was stirred for 17 h, then treated with 3 mL of 3 N HCl, and stirred for 3 h at room temperature. The mixture was extracted with ether and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the product on silica gel (elution with 30:68:2 EtOAc–C_6H_6–HOAc) provided, after one recycle of mixed fractions, 98 mg (65%) of acid **21** and 22 mg (15%) of acid **11**. Separate experiments identical with the above but with diazomethane treatment of the crude acid mixture and analysis of the resulting ester mixture by ^1H NMR revealed a **21**:**11** ratio of 75:25. **21**: IR ($CDCl_3$) ν 3360, 2900, 1720, 1715, 1442, 1385, 1280, 1238, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, C2 Me), 1.30 (m, H15), 1.55 (br s, OH), 1.66 (s, C6 Me, C10 Me), 1.84 (dd of AB, J_{AB} = 15.5 Hz, $\Delta\nu$ = 115 hZ, J_{Avic} = 12.3, 2.5 Hz, J_{Bvic} = 7.5, 0 Hz, H16), 2.12 (m, H8, H4), 2.18 (m, H7, H11), 2.26 (m, H4), 2.31 (m, H3), 2.44 (d of AB, J_{AB} = 4.5 Hz, $\Delta\nu$ = 10 Hz, J_{Avic} = 3.5 Hz, J_{Bvic} = 4.5 Hz, $R_2CHCH_2CO_2R$), 2.48 (m, H3), 2.88 (br d, J = 14.2 Hz, H12), 4.26 (br d, J = 12.3 Hz, H1), 5.04 (t, J = 6.8 Hz, H5), 5.17 (br t, J = 7.1 Hz, H9); ^{13}C NMR ($CDCl_3$) δ 175.9, 174.1, 133.1, 130.8, 127.8, 128.0, 80.0, 73.6, 45.7, 39.3, 37.4, 31.2, 28.4, 24.9, 23.3, 22.4, 19.0, 15.1. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.68.

2-[*rel*-(1*R*,2*S*,12*S*,15*R*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-13-oxo-14-oxabicyclo[10.2.2]hexadeca-5,9-dien-16-yl]ethanol (23). A. Via Reduction of 10. A solution of 16 mg (0.044 mmol) of ester lactone **10** in 1.2 mL of THF was stirred at 0 °C under nitrogen as 3.0 mg (0.14 mmol) of $LiBH_4$ was added under a stream of nitrogen. The mixture was stirred at 0 °C for 15 min and at room temperature for 20 h, and then MeOH and 1.5 N HCl were added. After the mixture was stirred at room temperature for 10 h, it was diluted with water, extracted with ether, and dried over $MgSO_4$. Concentration in vacuo and chromatography of the residue on silica gel (elution with 70% EtOAc–hexane) provided 11 mg (74%) of diol **23** as an oil.

B. Via Reduction of 20. In the manner described for reduction of **10**, 11.3 mg (0.0310 mmol) of lactone ester **20** was treated in 1.0 mL of THF with 3.0 mg (0.14 mmol) of $LiBH_4$ for 10 min at 0 °C and 17 h at room temperature. Workup and purification as for method A afforded 8.1 mg (77%) of diol lactone **23**, identical with material obtained as described above: IR (film) ν 3375, 2900, 1700, 1440, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, C2 Me), 1.27 (m, H15), 1.42 (m, CH_2CH_2OH), 1.57 (br s, OH), 1.61 (s, C10 Me), 1.63 (s, C6 Me), 1.77 (m, CH_2CH_2OH), 1.82 (dd of AB, J_{AB} = 11.3 Hz, $\Delta\nu$ = 120 Hz, J_{Avic} = 10.7, 2.5 Hz, J_{Bvic} = 7.8 Hz, H16), 2.08 (m, H8, H14), 2.18 (m, H11, H7), 2.30 (m, H4), 2.38 (m, H3), 2.86 (br dd, J = 14.9, 3.5 Hz, H12), 3.75 (m, CH_2CH_2OH), 4.22 (br d, J = 10.7 Hz, H1), 5.02 (t, J = 6.4 Hz, H9), 5.16 (t, J = 6.6 Hz, H5).

***rel*-(1*R*,2*S*,12*S*,13*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-15-oxo-16-oxabicyclo[11.3.1]heptadeca-5,9-diene-12-carboxylic Acid (11).** A solution of 295 mg (0.810 mmol) of lactone **20** in 1.5 mL of DME was stirred at room temperature as 1.5 mL of water and 0.49 mL (4.9 mmol) of 10 N aqueous NaOH were added. The mixture was stirred for 27 h at room temperature and then pipetted into a rapidly stirring, chilled mixture of 5 mL of 3 N HCl and 5 mL of THF at 0 °C. After 10 min the mixture was diluted with water and extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and concentrated in vacuo to afford a mixture of acid **11** and **22**, which was diluted with 5 mL of C_6H_6 and then heated at 80 °C for 20 min with stirring under nitrogen. The mixture was cooled to room temperature, and solvent was removed at reduced pressure. The residue was diluted with 0.5 mL of THF and chromatographed on silica gel (elution with 30:68:2 EtOAc–C_6H_6–HOAc) to give 258 mg (91%) of the crystalline acid **11**. Recrystallization from 1:10 THF–ether provided the analytical sample: mp 193–194 °C; IR ($CDCl_3$) ν 3410, 2900, 1710, 1435, 1378, 1250, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, C2 Me), 1.62 (s, C6 Me), 1.68 (s, C10 Me), 1.71 (dd of AB, J_{AB} = 10.2 Hz, $\Delta\nu$ = 40 Hz, J_{Avic} = 11.0, 3.3 Hz, J_{Bvic} = 8.1, 3.5 Hz, H3), 1.72 (ddd, J = 15.8, 6.4, 4.0 Hz, H17), 2.10 (m, H17, H8, H7, OH), 2.17 (m, H4), 2.25 (m, H13), 2.36 (m, H8), 2.38 (d of AB, J_{AB} = 15.7 Hz, $\Delta\nu$ = 39 Hz, J_{Avic} = 2.7 Hz, J_{Bvic} = 9.9 Hz, H11), 2.53 (d of AB, J_{AB} = 15.1, $\Delta\nu$ = 18 Hz, J_{Avic} = 15.7 Hz, J_{Bvic} = 4.1 Hz, H14), 2.81 (dt, J = 9.9, 2.7 Hz, H12), 4.10 (dd, J = 10.4, 6.4 Hz, H1), 5.00 (t, J = 7.0 Hz, H5), 5.17 (d, J = 7.5 Hz, H9). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.65; H, 8.67.

***rel*-(1*R*,2*S*,12*R*,13*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-15-oxo-16-oxabicyclo[11.3.1]heptadeca-5,9-diene-12-carboxylic Acid (24).** A solution of 214 mg (0.582 mmol) of ester **10** in 1.0 mL of THF was treated with 0.5 mL of water and 0.35 mL of 10 N aqueous NaOH. The mixture was stirred at room temperature for 40 h and then pipetted into a cold, stirring mixture of 3.5 mL of 3 N HCl and 3.5 mL of THF at 0 °C. Stirring was continued for 20 min, and then the mixture was diluted with water and extracted with CH_2Cl_2. Drying of the organic phases over $MgSO_4$ followed by solvent removal under reduced pressure afforded the crude mixture of acids **11** and **24** accompanied by varying amounts of the diacids. Lactonization in the manner described for acid **11** and chromatography of the mixture on silica gel (elution with 20:78:2 EtOAc–C_6H_6–HOAc) provided, in order of elution, 64 mg (31%) of crystalline acid **24**, and 104 mg (51%) of crystalline acid **11**. An analytical sample of **24**, mp 212–214 °C, was prepared by crystallization from 1:9 THF–cyclohexane: IR ($CDCl_3$) ν 3350, 2920, 1710, 1440, 1240, 1160, 1125, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, C2 Me), 1.38 (dd of AB, J_{AB} = 13.1 Hz, $\Delta\nu$ = 71 Hz, J_{Avic} = 12.5, 3.8 Hz, J_{Bvic} = 12.1, 5.9 Hz, H3), 1.40 (2 s, OH), 1.58 (s, C10 Me), 1.62 (ddd, J = 27.7, 9.7, 6.6 Hz, H17), 1.69 (s, C6 Me), 1.80 (dddd, J = 19.0, 12.1, 7.0, 3.8 Hz, H4), 1.96 (m, H11), 2.07 (m, H17, H8), 2.26 (m, H4), 2.35 (m, H11, H8, H12), 2.59 (d of AB, J_{AB} = 14.0 Hz, $\Delta\nu$ = 20 Hz, J_{Avic} = 4.2 Hz, J_{Bvic} = 5.3 Hz, H14), 2.68 (m, H7), 4.19 (dd, J = 6.6,3.1 Hz, H1), 5.22 (br d, J = 10.4 Hz, H9), 5.39 (br t, J = 7.0 Hz, H5). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.60; H, 8.66.

Methyl *rel*-(1*R*,2*S*,12*R*,13*S*)-(5*E*,9*E*)-2-Hydroxy-2,6,10-trimethyl-15-oxo-16-oxabicyclo[11.3.1]heptadeca-5,9-diene-12-carboxylate (24, Methyl Ester). A solution of 9.0 mg (0.026 mmol) of lactone acid **24** in 1 mL of THF was chilled to 0 °C as standard ethereal diazomethane was added via pipette. After 30 min at 0 °C, the mixture was quenched with 50 μL of HOAc. Solvent removal under reduced pressure and chromatography on 3 g of silica gel (elution with 30% EtOAc–hexane) gave 8.6 mg (91%) of the crystalline methyl ester of lactone acid **24**. Recrystallization from 1:5 ether–hexane afforded the analytical sample: mp 168–169 °C; IR ($CDCl_3$) ν 3400, 2900, 1720, 1440, 1380, 1250, 1105, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, C2 Me), 1.39 (dd of AB, J_{AB} = 14.4 Hz, $\Delta\nu$ = 69 Hz, J_{Avic} = 12.3, 3.4 Hz, J_{Bvic} = 12.3, 6.0 Hz, H3), 1.48 (m, H17), 1.56 (s, C10 Me), 1.67 (s, C6 Me), 1.71 (s, OH), 1.97 (m, H11), 2.05 (ddd of AB, J_{AB} = 17.9 Hz, $\Delta\nu$ = 87 Hz, J_{Avic} = 12.3, 8.0, 3.4 Hz, J_{Bvic} = 12.3, 8.0, 6.0 Hz, H4), 2.08 (m, H17, H18), 2.30 (m, H17), 2.37 (m, H8, H11), 2.38 (m, H12), 2.55 (dd of AB, J_{AB} = 4.9 Hz, $\Delta\nu$ = 55 Hz, J_{Avic} = 4.9 Hz, J_{Bvic} = 3.3 Hz, H14), 2.58 (m, H7), 3.66 (s, OMe), 4.17 (dd, J = 5.7, 2.8 Hz, H1), 5.21 (dd, J = 11.4, 1.5 Hz, H9), 5.38 (t, J = 8.0 Hz, H5). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.08; H, 8.88.

***rel*-(1*R*,3*S*,4*R*,14*R*)-(7*E*,11*E*)-3,4-Dihydroxy-4,8,12-trimethyl-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (32).** A solution of 52.0 mg (0.148 mmol) of acid **11** in 1.5 mL of CH_2Cl_2 and 0.3 mL of THF was chilled to −78 °C under nitrogen as 28 μL (0.29 mmol) of ethyl chloroformate and 42 μL (0.30 mmol) of Et_3N were added. The mixture was stirred at −78 °C for 2 h, then warmed rapidly to room temperature, and filtered through silica gel (elution with ether). Concentration under reduced pressure afforded the crude carbonic anhydride **28**, which was

diluted with 1 mL of THF and chilled to −78 °C under argon. In a separate vessel, 51 mg (0.30 mmol) of *m*-chloroperoxybenzoic acid in 2 mL of CH_2Cl_2 was chilled to −78 °C under nitrogen as 15 mg (0.63 mmol) of 97% NaH was added with vigorous stirring. After 10 min at −78 °C and 10 min at 0 °C, the thick slurry was taken up into a dry syringe and added to the chilled solution of carbonic anhydride. After 15 min at −78 °C, the mixture was treated with 2 mL of saturated aqueous NH_4Cl, diluted with water, and rapidly extracted with 1:1 ether–EtOAc. The organic phases were washed with 2% aqueous NaOH, water, and brine and were dried over $MgSO_4$. The drying agent was filtered, and the filtrate was allowed to stand at room temperature under nitrogen for 40 h.

The combined basic aqueous layers from the workup were acidified to pH 2 with 3 N HCl and extracted with CH_2Cl_2. Completion of the workup procedure and chromatography as for acid lactone **21** gave 4.5 mg (9%) of recovered crystalline acid **11**.

The carboxy inversion reaction mixture was concentrated under reduced pressure, and the residue was stirred in 1 mL of THF as 0.4 mL (1 mmol) of 2.5 N aqueous NaOH was added. After 3 h at room temperature, the mixture was chilled to 0 °C as 1 mL of 3 N HCl was added. The mixture was warmed to room temperature and then extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine and then dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel (elution with 25% EtOAc–hexane) gave 27.3 mg (42%) of the diol lactone **32** as an oil. Gas chromatographic and ^1H NMR analysis indicated a **32:42** ratio of 92:8: IR (film) ν 3450, 2910, 1765, 1440, 1380, 1180, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, C4 Me), 1.30 (m, H5), 1.59 (s, C8 Me), 1.67 (s, C12 Me), 1.71 (m, H5, H2), 2.04 (br s, OH), 2.00 (m, H6, H10, H9), 2.46 (d of AB, J_{AB} = 15.5 Hz, $\Delta\nu$ = 148 Hz, J_{Bvic} = 11.2 Hz, H13), 2.54 (d of AB, J_{AB} = 15.9 Hz, $\Delta\nu$ = 140 Hz, J_{Avic} = 7.8 Hz, J_{Bvic} = 3.0 Hz, H17), 2.87 (m, H1), 3.28 (br t, J = 8.1 Hz, H3), 4.82 (ddd, J = 11.2, 6.1, 3.9 Hz, H14), 5.11 (br t, J = 6.1 Hz, H7), 5.23 (br t, J = 7.0 Hz, H11); MS calcd for $C_{19}H_{30}O_4$ m/e 322.45, found ($M^+ - 2H_2O$) 286, ($M^+ - H_2O$) 304, (M^+) 322. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.60; H, 9.42.

***rel*-(1*R*,3*S*,4*R*,14*R*)-(7*E*,11*E*)-3,4-(Isopropylidenedioxy)-4,8,12-trimethyl-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (33).** A solution of 42.2 mg (0.131 mmol) of an 83:17 **32–42** lactone diol mixture was stirred in 1 mL of CH_2Cl_2 with cooling to 0 °C under nitrogen as 0.20 mL (2.1 mmol) of 2-methoxypropene and 0.5 mg (0.02 mmol) of pyridinium *p*-toluenesulfonate were added. After 10 min at 0 °C and 3 h at room temperature, the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (elution with 15% EtOAc–hexane) to give 38.0 mg (80%, 95%, corrected for starting **32**:42 ratio) of crystalline lactone **33**. Recrystallization from 1:5 CH_2Cl_2–cyclohexane at −25 °C afforded 30 mg of colorless prisms: mp 136–137 °C; IR ($CDCl_3$) ν 2910, 1765, 1380, 1210, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, C4 Me), 1.34 (m, H2, H5), 1.37, 1.45 (2 s, acetonide Me), 1.52 (s, C8 Me), 1.66 (s, C12 Me), 1.72 (ddd, J = 26.5, 9.6, 5.8 Hz, H5), 1.92 (td, J = 12.0, 4.4 Hz, H2), 2.11 (m, H9, H10), 2.26 (m, H6), 2.48 (d of AB, J_{AB} = 15.3 Hz, $\Delta\nu$ 109 Hz, J_{Avic} = 0 Hz, J_{Bvic} = 11.7 Hz, H13), 2.58 (d of AB, J_{AB} = 17.4 Hz, $\Delta\nu$ = 72 Hz, J_{Avic} = 8.0 Hz, J_{Bvic} = 4.4 Hz, H17), 2.80 (m, H1), 3.79 (dd, J = 12.0, 3.0 Hz, H2), 4.82 (ddd, J = 11.7, 5.9, 3.6 Hz, H14), 5.11 (br d, J = 7.2 Hz, H7), 5.15 (t, J = 6.3 Hz, H11); MS calcd for $C_{22}H_{34}O_4$ m/e 362.21, found ($M^+ - C_3H_6O$) 304, ($M^+ - CH_3$) 347, (M^+) 362. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.84; H, 9.49.

***rel*-(1*R*,3*R*,4*R*,14*R*)-(7*E*,11*E*)-3,4-Epoxy-4,8,12-trimethyl-15-oxabicyclo[12.3.0]hpetadeca-7,11-dien-16-one (39).** A solution of 26.0 mg (0.0713 mmol) of acetonide **33** in 0.5 mL of MeOH and 25 μL of water was stirred at room temperature as 15 mg of Amberlite IR-120 ion-exchange resin (H^+ form) was added. The mixture was heated at 80 °C under nitrogen for 19 h and then was cooled to room temperature. The solvent was pipetted away from the resin, and the resin was washed with ether. The combined solution was evaporated under reduced pressure with drying of the product by azeotropic distillation with toluene. The crude diol **32** was then stirred in 0.3 mL of CH_2Cl_2 and 1 mL of ether as 0.3 mL of pyridine was added. The mixture was chilled to 0 °C as 110 μL (1.42 mmol) of methanesulfonyl chloride was added. After 30 h at 0 °C, the mixture was warmed to room temperature, quenched with water, and extracted with CH_2Cl_2. Drying of the organic layers over $MgSO_4$ and concentration under reduced pressure gave the crude product, which was filtered through silica gel (elution with 40% EtOAc–hexane), giving the monomesylate as an oil.

The foregoing mesylate was stirred in 2.5 mL of THF and chilled to −20 °C as 38 μL (0.0714 mmol) of 1.88 M methanolic benzyltrimethylammonium hydroxide was added. After 5 min the mixture was filtered through silica gel (elution with CH_2Cl_2). Concentration under reduced pressure and chromatography on silica gel (elution with 10% EtOAc–hexane) provided 16.8 mg (77%) of the epoxy lactone **39** as an oil: IR (film) ν 2960, 2910, 1770, 1375, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, C4 Me), 1.21 (m, H2, H5), 1.59 (s, C8 Me), 1.71 (s, C12 Me) 1.63 (m, H2), 2.12 (m, H6, H9, H10), 2.43 (m, H13), 2.47 (d of AB, J_{AB} = 24.8 Hz, $\Delta\nu$ = 43 Hz, J_{Avic} = 7.7 Hz, J_{Bvic} = 9.9 Hz, H17), 2.50 (dd, J = 9.8, 1.6, Hz, H3), 2.79 (m, H1), 4.83 (ddd, J = 10.8, 6.5, 2.9 Hz, H14), 4.92 (t, J = 6.4 Hz, H7), 5.15 (d, J = 8.3 Hz, H11); MS calcd for $C_{19}H_{28}O_3$ m/e 304.43, found (M^+) 304. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.04; H, 9.30.

***rel*-(1*R*,3*R*,4*R*,14*R*)-(7*E*,11*E*)-3,4-Epoxy-4,8,12-trimethyl-17-methylene-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (41, 14-Epiisolobophytolide).** A solution of 6.9 mg (0.023 mmol) of epoxide **39** in 0.5 mL of THF was chilled to −78 °C under nitrogen as 125 μL (0.069 mmol) of 0.55 M lithium diisopropylamide in THF was added dropwise. The mixture was warmed to −25 °C over 20 min and stirred rapidly at this temperature as a stream of gaseous formaldehyde in nitrogen (generated by thermolysis of 15 mg (0.50 mmol) of paraformaldehyde at 160 °C) was passed over the surface of the stirring reaction mixture. After 1 min, 1 mL of saturated NH_4Cl was added and the mixture was diluted with water and extracted with CH_2Cl_2. Drying of the organic solution over $MgSO_4$ and concentration in vacuo gave the oily crude hydroxymethylated lactone **40**.

The aforementioned lactone was stirred in 0.2 mL of dry CH_3CN with 1 mg of anhydrous $CuCl_2$ as 10 mg (0.045 mmol) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Morpho CDI) was added. The mixture was heated under nitrogen for 4 h at 50 °C and cooled to room temperature. Filtration of the mixture through silica gel (elution with CH_2Cl_2) and concentration in vacuo gave the crude product. Chromatography on 7 g of silica gel (elution with 8% EtOAc–hexane followed by 10% EtOAc–hexane) provided 3.8 mg (53%) of 14-epiisolobophytolide (**41**) as an oil: IR (film) ν 2900, 1765, 1420, 1260, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (m, H5), 1.26 (s, C4 Me), 1.28 (m, H5), 1.42 (ddd, J = 15.1, 10.5, 4.0 Hz, H2), 1.60 (s, C8 Me), 1.67 (m, H2), 1.73 (s, C12 Me), 2.13 (m, H6, H9, H10), 2.40 (br d of AB, J_{AB} = 14.6 Hz, $\Delta\nu$ = 23 Hz, J_{Avic} = 0 Hz, J_{Bvic} = 9.7 Hz, H13), 2.57 (dd, J = 10.5, 1.5 Hz, H3), 3.36 (m, 1 H), 4.96 (m, H11, H14), 5.09 (br d, J = 7.7 Hz, H7), 5.51 (d, J = 3.0 Hz, C17 CH_2), 6.25 (d, J = 3.2 Hz, C17 CH_2); MS calcd for $C_{20}H_{28}O_3$ m/e 316.44, found ($M^+ - CH_3$) 301, (M^+) 316.

Methyl 2-[*rel*-(1*R*,3*S*,4*R*,14*R*)-(7*E*,11*E*)-3,4-(Isopropylidenedioxy)-14-(methylsulfonyl)-4,8,12-trimethylcyclotetradeca-7,11-dien-1-yl]acetate (36). A solution of 13.0 mg (0.0357 mmol) of lactone **33** in 0.3 mL of DME and 20 μL of water was treated with 31 μL (0.107 mmol) of 3.44 N aqueous NaOH. The mixture was heated to 50 °C for 3 h, cooled to room temperature, and diluted with ice water as 54 μL (0.112 mmol) of 2.08 N HCl was added. The mixture was extracted with CH_2Cl_2, and the organic phases were dried over $MgSO_4$ and concentrated under reduced pressure at 15 °C to a volume of 0.5 mL. This solution was chilled to −20 °C under nitrogen as dry standard ethereal diazomethane was added until a yellow color persisted. After 12 min the solvent was evaporated at 0 °C (30 mmHg). The resulting ester **35** was treated with 0.35 mL of pyridine and 0.2 mL of CH_2Cl_2 with cooling to 0 °C as 55 μL (0.71 mmol) of methanesulfonyl chloride was added. Stirring was maintained at 0 °C under nitrogen for 72 h, at which time 0.1 mL of water and 0.1 mL of 0.3 N HCl was added. The mixture was extracted with CH_2Cl_2, the organic phases were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (elution with 20% EtOAc–hexane followed by 40% EtOAc–hexane) gave 12.2 mg (71%) of the mesylate **36** as an oil: IR (film) ν 2920, 1440, 1380, 1125, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, C4 Me), 1.28 (m, H5),

1.32, 1.42 (2 s, acetonide Me), 1.54 (s, C8 Me), 1.65 (dd of AB, J_{AB} = 7.5 Hz, $\Delta\nu$ = 13 Hz, J_{Avic} = 6.8, 2.6 Hz, J_{Bvic} = 11.4, 3.1 Hz, H2), 1.72 (s, C12 Me), 1.91 (m, H1), 1.98 (m, H9), 2.15 (m, H10), 2.25 (m, H10), 2.54 (d of AB, J_{AB} = 15.8 Hz, $\Delta\nu$ = 22 Hz, J_{Avic} = 6.1 Hz, J_{Bvic} = 11.0 Hz, H13), 2.58 (m, CH_2CO_2R), 3.00 (s, $MeSO_2O$), 3.69 (s, MeO), 3.75 (dd, J = 11.4, 2.6 Hz, H3), 5.13 (br t, J = 8.2 Hz, H7, H11), 5.22 (ddd, J = 11.0, 6.1, 2.2 Hz, H14); MS calcd for $C_{24}H_{40}O_7S$ m/e 472.25, found ($M^+ - C_3H_6O$) 414, ($M^+ - CH_3$) 457, (M^+) 472, ($M^+ + 1$) 473, ($M^+ + 2$) 474.

***rel*-(1*R*,3*S*,4*R*,14*S*)-(7*E*,11*E*)-3,4-(Isopropylidenedioxy)-4,8,12-trimethyl-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (37).** A solution of 15.6 mg (0.0329 mmol) of mesylate **36** in 0.6 mL of DME was stirred under nitrogen as 0.29 mL (0.99 mmol) of 3.44 N aqueous NaOH was added. The mixture was heated at 55 °C for 19 h, chilled to 0 °C, and treated with 1 mL of 2.08 N HCl. The mixture was diluted with water and extracted with CH_2Cl_2. Drying of the organic solutions over $MgSO_4$ and solvent removal in vacuo gave the crude lactone. Chromatography on silica gel (elution with 5% EtOAc–hexane followed by 10% EtOAc–hexane) gave 8.1 mg (67%) of lactone **37** as an oil: IR (film) ν 2960, 2900, 1780, 1380, 1210, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, C4 Me), 1.26 (m, H5), 1.30, 1.43 (2 s, acetonide Me), 1.52 (s, C8 Me), 1.60 M, H2), 1.66 (s, C12 Me), 1.95 (m, H6, H10), 2.15 (m, H6, H10, H9), 2.22 (d of AB, J_{AB} = 12.3 Hz, $\Delta\nu$ = 20 Hz, J_{Avic} = 2.9 Hz, J_{Bvic} = 10.8 Hz, H13), 2.44 (m, H1), 2.70 (m, H17), 3.63 (dd, J = 11.3, 2.6 Hz, H3), 4.14 (ddd, J = 10.8, 8.6, 2.9 Hz, H14), 5.08 (br t, J = 6.2 Hz, H7), 5.17 (br t, J = 6.9 Hz, H11); MS calcd for $C_{22}H_{34}O_4$ m/e 362.25, found ($M^+ - C_3H_6O$) 304, ($M^+ - CH_3$) 347, (M^+) 362.

***rel*-(1*R*,3*R*,4*R*,14*S*)-(7*E*,11*E*)-3,4-Epoxy-4,8,12-trimethyl-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (44).** A solution of 26.1 mg (0.0720 mmol) of acetonide lactone **37** was stirred in 1.4 mL of dry MeOH under nitrogen as 26 mg of Amberlite IR-120 ion-exchange resin (H^+ form) was added. The mixture was heated at 60 °C for 4 h and then cooled to room temperature. The mixture was filtered through silica gel (CH_2Cl_2 elution), and the filtrate was concentrated under reduced pressure with drying by azeotropic distillation of benzene. The crude diol **42** thus obtained was stirred in 0.20 mL of dry pyridine at −20 °C as 60 μL (0.78 mmol) of methanesulfonyl chloride was added. After 14 h at −20 °C the mixture was warmed to 0 °C, quenched with 0.3 mL of 2.5 N aqueous NH_4OH, stirred for 30 s, and then treated with 1 mL of saturated NH_4Cl. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude mesylate **43**.

The mesylate was dissolved in 0.7 mL of dry THF and chilled to −50 °C under nitrogen as 40 μL (0.075 mmol) of 1.88 M methanolic benzyltrimethylammonium hydroxide was added dropwise. After 10 min, another 40-μL aliquot of base was added and the mixture was warmed to −20 °C over 10 min. Filtration of the mixture through silica gel (CH_2Cl_2 elution) and concentration of the filtrate under reduced pressure gave the crude epoxide. Chromatography on silica gel (elution with 2% EtOAc–C_6H_6 followed by 5% EtOAc–C_6H_6) gave 8.9 mg (41%) of the epoxide **44** as an oil: IR (film) ν 2900, 1770, 1430, 1370, 1260, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, C4 Me), 1.27 (m, H5), 1.59 (s, C8 Me), 1.62 (dd of AB, J_{AB} = 15.1 Hz, $\Delta\nu$ = 70 Hz, J_{Avic} = 6.5, 5.0 Hz, J_{Bvic} = 10.3, 6.9 Hz, H2), 1.68 (s, C12 Me), 2.10 (m, H7, H8), 2.25 (m, H4, H11), 2.41 (m, H1), 2.63 (d of AB, J_{AB} = 18.5 Hz, $\Delta\nu$ = 131 Hz, J_{Avic} = 8.8 Hz, J_{Bvic} = 6.1 Hz, H17), 2.64 (dd, J = 6.9, 5.0 Hz, H3), 4.21 (ddd, J = 10.2, 8.2, 4.8 Hz, H14), 4.98 (br t, J = 6.2 Hz, H7), 5.10 (t, J = 6.9 Hz, H11); MS calcd for $C_{19}H_{28}O_3$ m/e 304.20, found ($M^+ - CH_3$) 289, (M^+) 304.

***rel*-(1*R*,3*R*,4*R*,14*S*)-(7*E*,11*E*)-3,4-Epoxy-17-methylene-4,8,12-trimethyl-15-oxabicyclo[12.3.0]heptadeca-7,11-dien-16-one (46, Isolobophytolide).** A solution of 3.9 mg (0.0128 mmol) of epoxide **44** in 0.24 mL of THF was chilled to −78 °C under nitrogen as 72 μL (0.026 mmol) of 0.36 M lithium diisopropylamide in THF was added. The mixture was stirred, warming to −30 °C, over 25 min, and it was kept at −30 °C as a stream of gaseous formaldehyde in nitrogen (generated by thermolysis of 20 mg (0.60 mmol) of paraformaldehyde at 180 °C) was passed over the surface of the stirring reaction mixture. After 1 min the mixture was treated with 1 mL of saturated NH_4Cl, diluted with water, and extracted with CH_2Cl_2. Drying of the organic phases over $MgSO_4$ and concentration under reduced pressure gave the crude hydroxymethyl lactone **45**, which was dissolved in 0.8 mL of acetonitrile and treated at room temperature with 1 mg of $CuCl_2$ and 12 mg (0.028 mmol) of Morpho CDI. The mixture was stirred and heated at 50 °C under nitrogen for 3 h, then cooled to room temperature, and filtered through silica gel (ether elution). Concentration of the filtrate in vacuo and chromatography on silica gel (elution with 10% EtOAc–hexane) gave 1.6 mg (40%) of oily racemic isolobophytolide (**46**). Combination of the above sample with material from another run and chromatography on 5 g of silica gel (elution with 5% EtOAc–C_6H_6) gave racemic isolobophytolide (**46**) of purity comparable to a sample of natural (−)-isolobophytolide. Mass, ^1H NMR, and IR spectra and the TLC mobilities of synthetic and natural **46** were identical: IR (film) ν 2900, 1760, 1440, 1365, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, C4 Me), 1.30 (m, H5), 1.58 (s, C8 Me), 1.65 (dd of AB, J_{AB} = 15.8 Hz, $\Delta\nu$ = 77 Hz, J_{Avic} = 4.0, 3.7 Hz, J_{Bvic} = 6.5, 8.9 Hz, H2), 1.69 (s, C12 Me), 2.10 (m, H9, H10), 2.25 (m, H6), 2.48 (d of AB, J_{AB} = 13.2 Hz, $\Delta\nu$ = 80 Hz, J_{Avic} = 3.0 Hz, J_{Bvic} = 9.5 Hz, H13), 2.77 (dd, J = 6.5, 4.0 Hz, H3), 2.86 (m, H1), 4.12 (ddd, J = 9.5, 8.1, 3.0 Hz, H14), 5.00 (br t, J = 6.5 Hz, H7), 5.15 (br t, J = 7.0 Hz, H11), 5.92 (d, J = 2.8 Hz, C17 CH_2), 6.25 (d, J = 3.1 Hz, C17 CH_2); MS calcd for $C_{20}H_{28}O_3$ m/e 316.44, found ($M^+ - CH_3$) 301, (M^+) 316.

Epinigericin, a New Polyether Carboxylic Antibiotic. Structural Determination by 2D NMR Methods

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A new polyether carboxylic antibiotic, epinigericin (1), was isolated from *Streptomyces hygroscopicus* NRRL B-1865. Its structure and stereochemistry in comparison with nigericin are investigated by 1D and 2D ^1H and ^{13}C NMR spectrometry.

The majority of polyether carboxylic antibiotics[1] possess the ability to transport monovalent cations through biological membranes by forming lipophilic complexes. They are of considerable commercial importance as feed additives acting as anticoccidial agents and growth promoters in ruminants.

High-field NMR spectrometry and new pulse Fourier transform techniques allow the structure and conformation of ionophore–cation complexes in solution to be determined.

NMR conformational studies can help to understand the

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