A small portion was evaporatively distilled (120 °C/0.02 mm) for elemental analysis: $[\alpha]^{23}_D$ −23.2° (*c* 1.16, $CHCl_3$); R_f 0.27 (70% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.16 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.18 (s, 3 H, $C(OCH_3)(CH_3)CH_3$), 1.23–1.53 (m, line spacing = 7.1, 7.1, 4.4, 7.3, 7.8, 7.3, 6.8 Hz, 5 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$), 1.53–2.06 (m, 6 H, $OCH_2CH_2CH_2CH_3$, $NCH_2CH_2CH_2$), 2.83–3.08 (m, 1 H, NCHH), 3.19 (s, 3 H, OCH_3), 3.26–3.47 (m, 1 H, NCHH), 3.66–3.85 (m, 1 H, $NCHC(OCH_3)(CH_3)_2$), 3.89–4.11 (m, 4 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$); IR (neat) 2960 (s), 1268 (s), 1245 (s), 1062 (vs), 1024 (vs), 980 (m), 957 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{30}NO_4P$: C, 54.71; H, 9.84; N, 4.56. Found: C, 54.99; H, 10.11; N, 4.47.

(*R*)-Butyl Ethyl Methyl Phosphate [(*R*)-33] via Protic Acid Catalyzed Methanolysis of 30. Representative Procedure. Phosphate (*R*)-**33** was prepared from phosphoramidate **30** (459 mg, 1.48 mmol) by the method described for the preparation of phosphate **20**. Purification by flash chromatography using 50% ethyl acetate in hexanes as the eluent followed by evaporative distillation (95 °C/0.8 mm) afforded 136 mg (47%) of (*R*)-**33** as a colorless liquid. ^1H NMR spectral analysis in the presence of $Eu(hfc)_3$ indicated 71% ee, the high-field enantiomer being in excess: $[\alpha]^{23}_D$ −0.07° (*c* 9.84, acetone); R_f 0.12 (40% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.28–1.52 (m, 5 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$), 1.58–1.75 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 3.76 (d, *J* = 11.2 Hz, OCH_3), 3.97–4.21 (m, 4 H, OCH_2CH_3, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 13.58, 16.12, 16.18, 18.69, 32.29, 32.34, 54.06, 54.11, 63.83, 63.88, 67.57, 67.62; IR (neat) 2960 (s), 1463 (w), 1270 (vs), 1030 (vs), 836 (s) cm^{-1}; MS (CI, CH_4) *m/z* (relative intensity) 197 (MH^+, 20.8), 169 (12.9), 141 (100), 113 (35). Anal. Calcd for $C_7H_{17}O_4P$: C, 42.86; H, 8.73. Found: C, 41.85; H, 8.97.

(*R*)-33 via Sodium *n*-Butoxide Displacement of Phosphate 24. Representative Procedure. A 0.34 M solution of sodium butoxide was prepared from 1-butanol (0.20 mL, 2.2 mmol) and sodium hydride (50.8 mg, 2.12 mmol) in 6 mL of dry THF under N_2 at room temperature. To a stirred solution of phosphate **24** (115 mg, 0.405 mmol) in 3 mL of dry THF at room temperature under N_2 was then added sodium butoxide (2.4 mL, 8.2 mmol) over 30 min. After allowing the reaction mixture to stir for 2.5 h, it was quenched by partitioning between 10 mL of saturated $NaHCO_3$ and 30 mL of CH_2Cl_2. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 layer was thoroughly dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography using 45% ethyl acetate in hexanes as the eluent followed by evaporative distillation afforded 27.4 mg (55%) of a colorless liquid possessing identical ^1H NMR, IR, and TLC characteristics with that of **33** prepared from **30**. ^1H NMR spectral analysis in the presence of $Eu(hfc)_3$ indicated 87% ee, the high-field enantiomers being in excess.

Recovery of Chiral Auxiliary 11. Representative Procedure. Aqueous HCl layers from several phosphoramidate methanolysis reactions were combined and basified with 20% NaOH. This aqueous solution was extracted with ether (5 × 100 mL), and the ethereal layer dried over N_2SO_4, filtered, and concentrated to a yellow liquid. This material was evaporatively distilled to afford 1.32 g (60% recovery) of aminoether **11**, identical in bp, NMR and IR characteristics with those of freshly prepared sample: $[\alpha]^{23}_D$ −24.8° (*c* 2.94, MeOH).

Recovery of chiral auxiliary reagents **3** and **6** were carried out in analogous fashion to also provide unchanged materials in satisfactory yields.

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Supplementary Material Available: General experimental details, method of preparation, and spectral data for compounds not included in the Experimental Section; tables of data for X-ray diffraction study, bond angles, interatomic distances, positional parameters, isotropic temperature factors, and anisotropic temperature factors of compound **14** (32 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Isolobophytolide and (±)-Crassin by Titanium-Induced Carbonyl Coupling

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Contribution from the Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853. *Received February 5, 1990*

Abstract: Syntheses of the antitumor cembrane lactones (±)-crassin (**1**) and (±)-isolobophytolide (**2**) are reported. The key steps are the titanium-induced pinacol coupling of lactone keto aldehydes **3c** and **3t** to yield macrocyclic diols without harming the lactone rings also present in the molecules. Compound **3t** yields a diol (**18a**) that is converted into isolobophytolide by epoxide formation and methylenation. Compound **3c** yields a diol (**21a**) that is converted into crassin by double stereochemical inversion of the hydroxyl groups, translactonization, and methylenation. The syntheses demonstrate an important extension of the titanium-induced carbonyl-coupling reaction by showing that complex, polyoxygenated macrocycles can be produced.

The cembrene diterpenes are a large and varied class of natural products characterized by the presence of a 14-membered carbocyclic ring.[1] Cembranes have been detected in plants, insects, and animals and have been found in terrestrial as well as marine environments. The majority of known cembranes have come from pine trees and tobacco plants,[2] but many others have come from marine organisms.[3] Simple marine invertebrates, particularly the Caribbean gorgonians (sea fans and sea whips, order *Gorgonacea*) and the Pacific soft corals (true soft corals, order *Alcyonacea*) have provided a rich selection of highly oxygenated

(1) Reviews: (a) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 285–387. (b) Fenical, W. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; pp 187–200. (c) Manchand, P. S.; White, J. D. In *Contemporary Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978. (d) Kashman, Y.; Groweiss, A.; Carmely, S.; Kinamoni, Z.; Czarkie, D.; Rotem, M. *Pure Appl. Chem.* **1982**, *54*, 1995–2010. (e) Krebs, H. C. *Fortschr. Chem. Org. Naturst.* **1986**, *49*, 231–247.

(2) For a review of the isoprenoids found in tobacco plants, see: Wahlberg, I.; Enzell, C. R. *Nat. Prod. Rep.* **1987**, *4*, 237–247.

(3) Reviews on the chemistry of marine natural products: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613–663 and preceding issues. (b) Fenical, W. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2, pp 187–200. (c) Tursch, B.; Braekman, J. C.; Daloze, D.; Kaisin, M. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2, pp 247–296.

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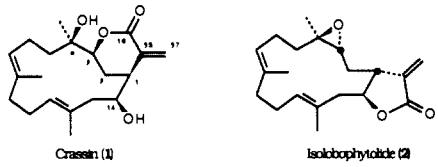
cembranes, including crassin (**1**) and isolobophytolide (**2**).



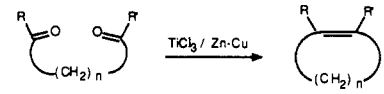
Crassin acetate (**1** acetate) was isolated in 1960 by Ciereszko, Sifford, and Weinheimer from the Caribbean gorgonian *Pseudoplexaura porosa* (*Plexaura crassa*), in which it comprises up to 2% of the dry weight of the organism.[4] It has subsequently been found in lesser amounts in other species of this genus[5] and appears to be a widespread metabolite in these gorgonians. Its structure was originally determined through a combination of chemical degradation studies, IR, low-field ^{1}H NMR, and mass spectrometry,[1a] and an X-ray analysis of the *p*-iodobenzoate derivative was published in 1969.[6] Crassin acetate has antibiotic activity,[4] and the free alcohol itself shows in vitro activity against human epidermoid carcinoma of the nasopharynx (KB) at a concentration of 1 μg/mL.[1a] Related cinnamoyl esters also show in vitro antileukemic activity.[5]

Isolobophytolide (**2**) was isolated as the major terpenoid component from the Pacific soft coral *Lobophytum crassum* in 1977 by Coll and co-workers.[7] Through an elegant series of ^{1}H NMR experiments, Coll was able to determine the skeletal framework of isolobophytolide, including the relative positioning of the lactone and epoxide functions. He then proposed a structure that turned out to be epimeric to the true material at C1 on the ring (the lactone bridgehead carbon). Marshall's later conversion of crassin to 1-epiisolobophytolide, a compound whose spectral data were not in agreement with those published for isolobophytolide, implied that Coll's structure was incorrect.[8] A subsequent X-ray analysis confirmed that isolobophytolide was indeed a trans fused γ-lactone,[9] and the compound was subsequently synthesized by Marshall.[9,10] Like crassin acetate, isolobophytolide is almost surely a defense secretion of *L. crassum*. It displays significant activity against murine P-338 lymphocytic leukemia, but a complete screening of its biological action does not appear to have been published.

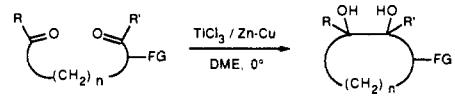
Note that crassin and isolobophytolide represent members of the β and α series of the cembranoids, respectively. This designation refers to the stereochemistry at C1 when drawn as above in accordance with previously established conventions.[1a] To date, virtually all cembranolides isolated from Caribbean gorgonians have the β-configuration at C1, while those from Pacific soft corals have the α-configuration at this center.

A substantial amount of synthetic work has been done on cembranoids in the last decade, and a review has been published.[11] Not surprisingly, most synthetic work has been aimed at simpler target molecules with relatively light functionalization. Most of the biologically important compounds, however, contain fused or bridged lactone rings in addition to furan, epoxide, and/or alcohol functions, and few of these so-called cembranolides have yet yielded to laboratory total synthesis. Crassin, in particular, has been the object of work in several research groups during the past decade[8,12,13] but has not yet been prepared.[14]

General Synthetic Considerations. Some years ago, we found that open-chain diketones, dialdehydes, or keto aldehydes undergo a carbonyl-coupling reaction on treatment with $TiCl_3$/Zn/Cu in refluxing dimethoxyethane to give good yields of large-ring cycloalkenes.[15,16]

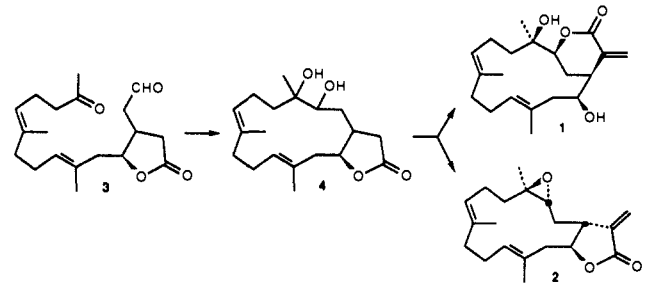


Although the carbonyl-coupling reaction works well when a hydrocarbon product is formed, the strong reducing conditions and extended reaction times normally used make the process incompatible with the presence elsewhere in the molecule of easily reducible functional groups. In particular, the presence of other carbonyl groups is troublesome, making doubtful the applicability of the coupling reaction to cembranolide synthesis. We have found[17] in recent work, however, that many otherwise troublesome groups are often stable to titanium-induced cyclization if the coupling reaction is carried out below O °C rather than at higher temperatures. The products of this low-temperature coupling are cyclic 1,2-diols (pinacols) rather than cycloalkenes.



The yields of this low-temperature, titanium-induced pinacol-coupling reaction are high, and the stereochemistry of the diol product is predictable when dialdehyde substrates are used.[17] Eight-membered rings and smaller are formed with predominant cis diol stereochemistry, while ten-membered rings and larger are formed with predominant trans diol stereochemistry.

Our overall plan for the synthesis of both crassin and isolobophytolide was based on the hypothesis that these compounds might arise from a precursor such as **3** (cis lactone for crassin; trans lactone for isolobophytolide) by low-temperature, titanium-induced carbonyl coupling, followed by further manipulation of the diol product. The macrocyclization reaction is thus the crucial step in the synthesis, and its success relies on the ability of the titanium reagent to effect the desired keto aldehyde coupling in preference to any side reactions involving the lactone group.



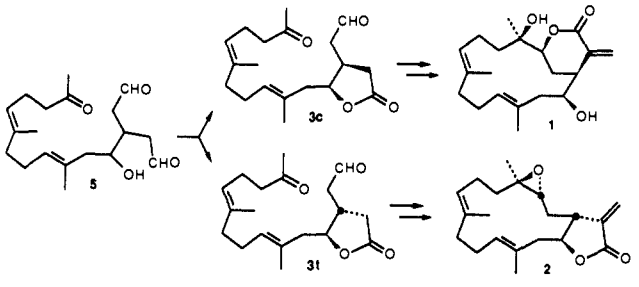
There are at least two potential drawbacks to this plan. The first problem, which affects only the crassin synthesis, is that, if we start with a *five*-membered lactone ring as in **3**, it may be difficult to isomerize to a *six*-membered lactone ring in the product. Fortunately, Marshall had previously demonstrated that isocrassin alcohol **26** can be converted into crassin by saponification and acidification of the resulting hydroxy carboxylate salt.[8] It was not known, however, whether the exo methylene substituent

(4) Ciereszko, L. S.; Sifford, D. S.; Weinheimer, A. J. *Ann. N.Y. Acad. Sci.* **1960**, *90*, 917–919.
(5) Weinheimer, A. J.; Matson, J. A. *Lloydia* **1975**, *38*, 378–382.
(6) Hossain, M. B.; van der Helm, D. *Recl. Trav. Chim. Pays-Bas.* **1969**, *88*, 1413–1423.
(7) Bowden, B. F.; Brittle, J. A.; Coll, J. C.; Liyanage, N.; Mitchell, S. J.; Stokie, G. J. *Tetrahedron Lett.* **1977**, *41*, 3661–3662.
(8) Marshall, J. A.; Karas, L. J.; Coghlan, M. J. *J. Org. Chem.* **1982**, *47*, 699–701.
(9) Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378–2388.
(10) Marshall, J. A.; Andrews, R. C. *Tetrahedron Lett.* **1986**, *43*, 5197–5200.
(11) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719–732.
(12) Dauben, W. G.; Saugier, R. K.; Fleischauer, I. *J. Org. Chem.* **1985**, *50*, 3767–3774.
(13) (a) Marshall, J. A.; Royce, R. D. *J. Org. Chem.* **1982**, *47*, 693–698. (b) Marshall, J. A.; Coghlan, M. J.; Watanabe, M. *J. Org. Chem.* **1984**, *49*, 747–753.
(14) A preliminary account of this work has been published: McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928–8929.
(15) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655.
(16) Reviews: (a) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405–411. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524. (c) Welzel, P. *Nachr. Chem. Tech. Lab.* **1983**, *31*, 814–816. (d) Lenoir, D. *Synthesis* **1989**, 883–897.
(17) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169–1172.

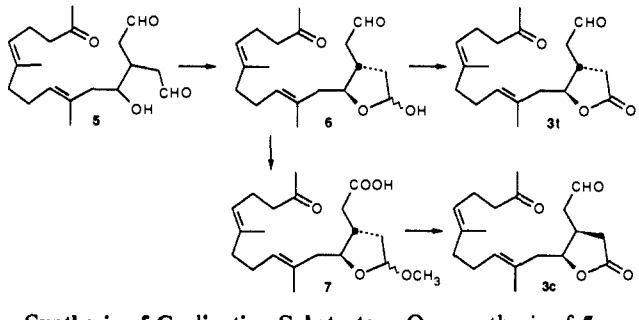
was required for this translactonization reaction to take place, or whether the translactonization might proceed in its absence.

A second and more serious problem that affects both crassin and isolobophytolide is that we have no stereocontrol over the cyclization reaction—a mixture of four stereoisomeric diols might result in each case. There are numerous methods for changing diol stereochemistry to convert an incorrect isomer to the correct one, however, and we only hoped that the cyclizations would at least give rise to a single major diol product.

The two cyclization substrates necessary for the preparation of crassin and isolobophytolide differ only in the stereochemistry of their lactone rings: cis for crassin and trans for isolobophytolide. In our initial planning, therefore, we sought a method by which both isomers might be prepared from a common precursor. A clue as to how this might be done came by realizing that the problem was one of controlling the stereochemistry of lactone formation. That is, if we were to prepare a symmetrical intermediate such as **5** closure to one of the nearby carbonyl groups would provide a cis fusion, and closure to the other would provide a trans fusion.



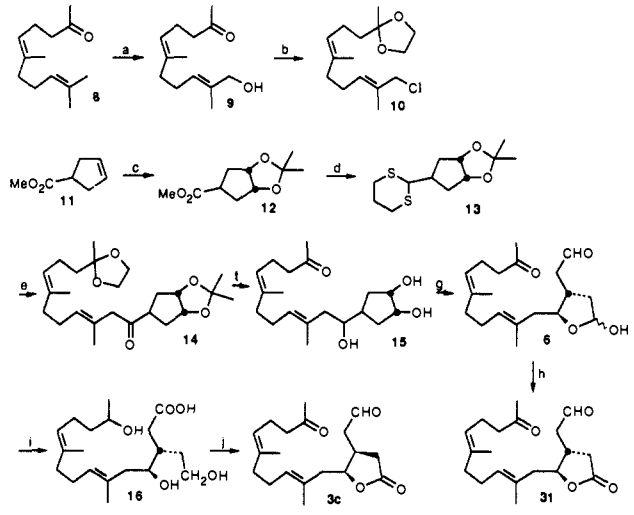
The trans isomer **3t** necessary for isolobophytolide is less strained than the cis isomer and would presumably result by spontaneous closure of hydroxy dialdehyde **5** to a trans lactol (**6**), followed by oxidation. The cis isomer necessary for crassin must be prepared by distinguishing between the two aldehyde carbonyl groups and oxidizing only the desired one to an acid. It should be possible to accomplish this distinction by conversion of the trans lactol **6** to its corresponding acetal on treatment with acidic methanol. Oxidation of the free aldehyde group to a carboxylic acid, hydrolysis of the acetal, and lactonization should then effectively interchange the acid and aldehyde carbons, resulting in an "isomerization" of the trans fusion to a cis fusion and the production of **3c**.



Synthesis of Cyclization Substrates. Our synthesis of **5** was based on the idea that the 1,5-dialdehyde function could result from oxidative cleavage of a four-substituted 1,2-cyclopentanediol such as **15**, whose synthesis is shown in Scheme I. Alcohol **9** was prepared in 76% yield from geranylacetone by selective oxidation of the terminal methyl group with SeO_2/*t*-BuOOH according to the Sharpless procedure.[18] Protection of the ketone carbonyl group as its ethylene acetal and reaction with the insoluble complex of *N*-chlorosuccinimide and triphenylphosphine in tetrahydrofuran[19] gave the clean chloro acetal **10** in yields of 80–90%.

Dithiane acetal **13** was prepared as a 1:6 mixture of syn and anti isomers from the known[20] methyl 3-cyclopentenecarboxylate

Scheme I[a]



[a](a) SeO_2, *t*-BuOOH, CH_2Cl_2, 76%; (b) $HOCH_2CH_2OH$, $(COOH)_2$, benzene, 100%; then Ph_3P, NCS, THF, 85%; (c) OsO_4, NMO, H_2O, *t*-BuOH, THF; then 2,2-dimethoxypropane, amberlyst-15; 71%; (d) $LiAlH_4$, THF; then PCC, CH_2Cl_2; then 1,3-propanedithiol, *p*-TSA; 62% from **12**; (e) **13**, BuLi, THF, HMPA; then **13**; then NCS, $AgNO_3$, H_2O, CH_3CN; (f) $NaBH_4$, EtOH, 60% from **10**; then H_2O, CH_3COOH; (g) $NaIO_4$, H_2O, THF, 75%; (h) PCC, CH_2Cl_2, 75%; (i) $AgNO_3$, NaOH, H_2O; then $NaBH_4$; (j) *p*-TSA, benzene; then DMSO, $(COCl)_2$, TEA, 56% from **6**.

(**11**). Osmium tetraoxide oxidation[21] (catalytic OsO_4, *N*-methylmorpholine *N*-oxide) gave the crude ester diol which was immediately treated with acetone in the presence of amberlyst and 2,2-dimethoxypropane to provide ester **12**. Reduction with $LiAlH_4$, oxidation with pyridinium chlorochromate (PCC), and reaction with 1,3-propanedithiol in the presence of *p*-toluenesulfonic acid gave the desired thioacetal **13**.

Alkylation of the anion of dithiane **13** with allylic chloride **10** took place smoothly in mixed THF/HMPA solvent at −78 °C, and the dithiane group was oxidatively removed from the product without damage to the rest of the molecule by treatment with *N*-chlorosuccinimide and $AgNO_3$[22] in aqueous acetonitrile at −10 °C to give **14**. Reduction of the free ketone carbonyl group with $NaBH_4$ and removal of both acetal protecting groups by hydrolysis with hot aqueous acetic acid then gave keto triol **15**. Periodate cleavage of the diol function by $NaIO_4$ took place smoothly and was immediately followed by spontaneous cyclization to provide an anomeric mixture of trans lactols **6**. Oxidation of this lactol mixture with PCC gave a single pure trans lactone product, **3t**.

Synthesis of cis lactone **3c** proved more difficult than anticipated but was eventually accomplished in a straightforward, though experimentally exacting, manner. Tollens oxidation of **6** with $AgNO_3$ in aqueous ethanolic NaOH gave a carboxylic acid, which was immediately reduced in the same vessel by addition of excess $NaBH_4$ to provide trihydroxy acid **16** after quenching with HCl. Treatment with a catalytic amount of *p*-toluenesulfonic acid in CH_2Cl_2 solution at room temperature effected lactonization with almost exclusive formation of the desired γ lactone isomer rather than the alternative δ isomer in 60% yield. Twofold oxidation with oxalyl chloride in dimethyl sulfoxide under Swern[23] conditions then gave the cis keto aldehyde lactone **3c**.

Completion of the Isolobophytolide Synthesis. With both cis and trans lactones **3c** and **3t** available, we next turned to the key steps in the projected syntheses—the titanium-induced carbonyl couplings. Working first with the more readily available trans lactone, slow addition over a 45-h period of **3t** in DME at room

(18) Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.
(19) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937–3940.
(20) Depres, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928–931.
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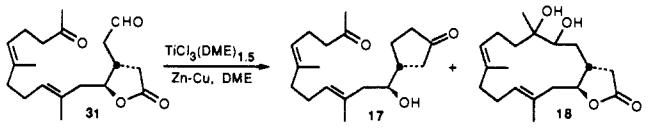
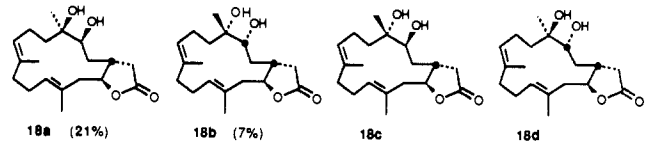
(22) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

temperature to a stirred slurry of low-valent titanium reagent prepared by reduction of $TiCl_3(DME)_{1.5}$ with Zn–Cu gave a complex mixture of products, which could be separated into two crude fractions by rapid chromatography. The less polar material, isolated in 10–15% yield, appeared to have lost its lactone function and to have gained a cyclopentanone carbonyl group. It was therefore spectroscopically identified as ketone **17**, the product of intramolecular aldehyde-lactone coupling. The more polar material, isolated in 55–60% yield, retained a lactone carbonyl group but had lost both ketone and aldehyde carbonyls. It therefore appeared to be a mixture of the desired diols **18**.



Separation of the diol mixture could be accomplished either directly (with some difficulty) by HPLC on a Waters Radial-Pak silica column or indirectly (with relative ease) by conversion to their acetonides followed by HPLC chromatography. All four possible diol products were found, in amounts of 21%, 19%, 11%, and 7% (58% total yield), and structure determination became the next problem. Fortunately, the desired diol **18a** was a known compound (as its acetonide derivative), having previously been prepared by Marshall in the course of his own isolobophytolide synthesis.[9]

Comparison of published[9] spectral data of the acetonide derivative with those we recorded for our four isolated diol acetonides indicated that the major product (21% yield) was the known erythro isomer **18a**. We were subsequently able to show that the minor product (7% yield) was erythro isomer **18b**, but we were unable to assign stereochemistry to the remaining two threo isomers **18c** and **18d** (19% and 11% yields).

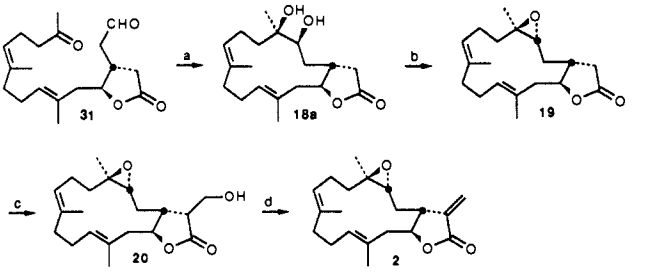


Several points about the coupling reaction deserve comment. First, of course, is that the reaction works. Formation of a 14-membered ring by keto-aldehyde coupling occurs in preference to formation of a five-membered ring by alternative aldehyde-lactone coupling, showing the relative stability of lactone carbonyl groups toward low-temperature titanium reactions. Second, the major product has erythro (cis) stereochemistry, although the reaction is much less stereoselective than that found in the previous model work. This erosion of stereoselectivity is undoubtedly due to the fact that a *keto* aldehyde rather than a dialdehyde is undergoing coupling. Third, although a mixture is formed, the major diol product **18a** has the correct stereochemistry needed for conversion into isolobophytolide, as previously demonstrated by Marshall.[9]

Reaction of **18a** with an excess of methanesulfonyl chloride in ether/pyridine at 0 °C gave a monomesylate that was dissolved in THF and treated with benzyltrimethylammonium hydroxide to give epoxide **19**, spectroscopically identical with the substance reported by Marshall.[9] Methylenation by reaction with LDA and formaldehyde, followed by dehydration of the hydroxymethylated aldol product **20** with 1-cyclohexyl-3-2(2-morpholinoethyl)-carbodiimide (morpho CDI) according to published conditions[9] completed the synthesis and gave (±)-isolobophytolide. The route is summarized in Scheme II.

Completion of the Crassin Synthesis. Turning next to the cis keto aldehyde **3c**, we began the final steps in the crassin synthesis. Slow addition of **3c** in DME over 45 h at room temperature to a slurry of low-valent titanium reagent resulted in a coupling reaction almost identical with that previously observed for **3t**. Again, rapid chromatography of the product gave two crude fractions, one of which (10% yield) was identified as a cyclopentanone resulting from aldehyde-lactone coupling and the other

Scheme II[a]



[a] (a) $TiCl_3(DME)_{1.5}$, Zn–Cu, DME, 45 h, room temperature; 21%; (b) MsCl, ether, pyridine, 0 °C; benzyltrimethylammonium hydroxide, THF, −20 °C; (c) LDA, THF, −78 °C; then CH_2O; (d) morpho CDI, $CuCl_2$, CH_3CN.

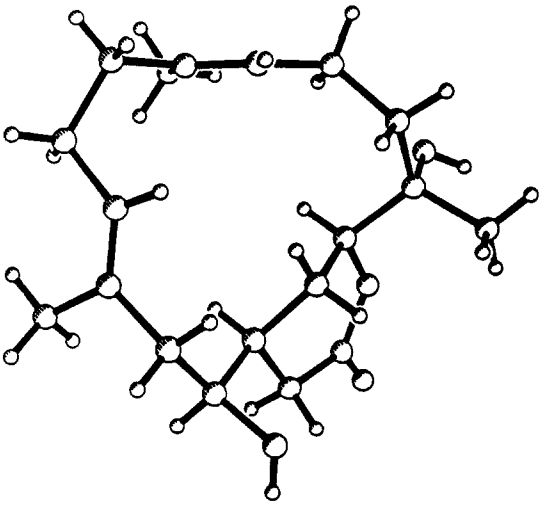
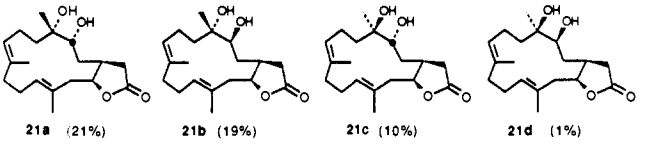
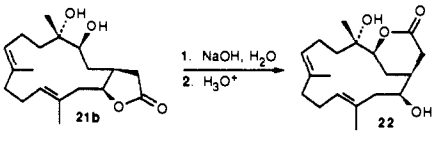


Figure 1. X-ray crystal structure of lactone **22**.

of which (50% yield) was a mixture of cyclic diols. Separation of the diol mixture could be accomplished either directly by a combination of HPLC and crystallization or indirectly by HPLC on the mixture of acetonide derivatives. All four possible diols were again present in the mixture in the approximate amounts 21%, 18%, 10%, and 1%. The major diol (21% yield) proved to be **21a**, a known compound previously prepared by Marshall.[9] Note that this major product is again an erythro diol as in the isolobophytolide work and that it has the same stereochemistry relative to the carbon atom of the lactone ring. It is, however, isomeric with crassin at both C3 and C4.

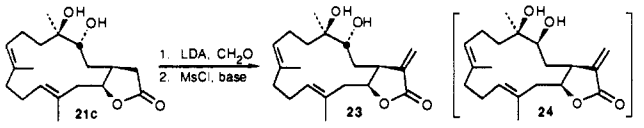


Assignment of stereochemistry to the remaining diols proved difficult but was ultimately accomplished through a variety of circumstances. The second diol (18%) was shown to be **21b** when it was found that it could be converted into a highly crystalline δ lactone (**22**) by saponification with aqueous NaOH followed by reacidification. X-ray crystallography (Figure 1) showed the stereochemistry of **22** unequivocally, implying that the second diol was isomeric with crassin at C4.



The third diol (10%) was identified as **21c** by conversion to its α-methylene derivative **23** and comparison with **24**, a known compound previously prepared from natural crassin.[8] The two

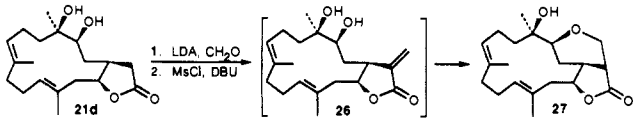
compounds were not identical, implying that the third diol isomer was isomeric with crassin at C3. Further proof was obtained when the material failed to undergo translactonization on saponification followed by reacidification.



With three diols proved not to have the crassin stereochemistry, the fourth and minor diol (1% yield) must correspond to crassin (**21d**). To obtain this material in quantity, however, it is obviously necessary to find a method of inverting stereochemistry in one or more of the other products. Starting with **21a**, the major product whose stereochemistry is incorrect at both C3 and C4, a double inversion is necessary to convert it into **21d**. Inversion at C3, a secondary center, should be possible by monomesylation and formation of an epoxide as in the isolobophytolide work, but inversion at C4, a tertiary center, looks more difficult. In principle, what is needed is an epoxide opening with S_N1-like regiochemistry (cleavage of the tertiary rather than the secondary C–O bond) but with S_N2-like stereochemistry (inversion rather than retention of configuration).[24]

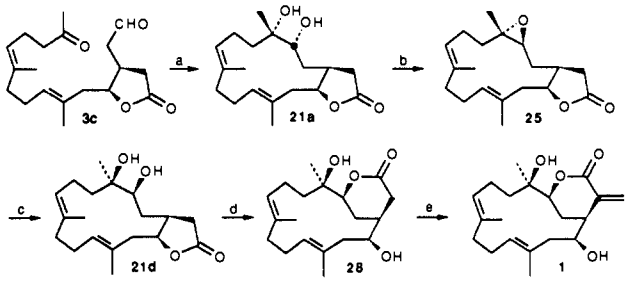
We were unable to find a good literature analogy for the proposed opening of our macrocyclic secondary/tertiary epoxide,[25] but we nevertheless proceeded on the hypothesis that some acidic conditions might be found that could effect the desired reaction. Treatment of **21a** with an excess of methanesulfonyl chloride in ether/pyridine at 0 °C, followed by reaction of the resultant monomesylate with benzyltrimethylammonium hydroxide in THF, gave epoxide **25**. In our first attempt, reaction of **25** in THF for 1 h with 10% aqueous $HClO_4$ at room temperature gave a new isomeric diol in 77% yield, along with several minor byproducts that appeared to be the result of transannular epoxyolefin cyclizations. That this new diol was **21d** was ultimately shown by its conversion into (±)-crassin.

Our first attempt at the conversion of **21d** into crassin was to introduce an α-methylene group next to the lactone carbonyl to yield isocrassin **26**. Isocrassin might then translactonize into crassin by analogy with similar transformations previously reported by Marshall.[8] We were unable to test the hypothesis, however, because isocrassin proved too reactive to isolate under our conditions. α-Methylenation of **21d** yielded only the intramolecular Michael adduct **27**, a substance previously isolated by Weinheimer in his original structural elucidation work.[5] Attempted saponification and reacidification of **27** yielded only recovered starting material.



The successful conversion was ultimately accomplished by reversing the order of methylenation and translactonization steps. We discovered that **21d** underwent nearly quantitative translactonization when first saponified with aqueous ethanolic NaOH and then acidified by treatment with dilute HCl at 0 °C. The resultant material, 17-norcrassin (**28**), was methylenated by reaction with LDA and formaldehyde, followed by dehydration of the hydroxymethyl intermediate by treatment with methanesulfonyl chloride and DBU. Synthetic (±)-crassin was obtained in 53% overall yield as fine white needles, mp 174–176 °C. Direct comparison of the synthetic material with an authentic sample of natural crassin established the identity of the two. A summary of the synthesis in shown in Scheme III.

Scheme III[a]



[a] (a) $TiCl_3(DME)_{1.5}$, Zn–Cu, DME, 45 h, room temperature; 20%; (b) MsCl, pyridine; then benzyltrimethylammonium hydroxide, benzene; 68%; (c) H_2O, $HClO_4$, THF; 77%; (d) NaOH; H_2O, EtOH; then H_3O^+, 0 °C, 1 h; 95%; (e) LDA, then CH_2O; then methanesulfonyl chloride, pyridine; then DBU, benzene; 53%.

Summary and Conclusions. Prior to this work, the value of titanium-induced carbonyl-coupling reactions for the synthesis of macrocyclic hydrocarbons had been amply demonstrated, but there was real doubt that the reaction could be used for the preparation of highly oxygenated products. Target molecules with an epoxide or carbonyl group present seemed particularly difficult. By carrying out the coupling reaction at low temperature and isolating the intermediate 1,2-diol product, however, we have been able to demonstrate that large rings can still be formed in good yield but that otherwise reducible functional groups are not affected. We believe that the findings demonstrated in this paper make possible the synthesis of a vastly increased number of compound types by carbonyl-coupling reactions.

Experimental Section

General Methods. Melting points were recorded on a Thomas-Hoover apparatus. The following were used to record spectra: IR, Perkin-Elmer Model 298 (samples run as neat films or Nujol mulls), Polaris Fourier transform (samples run as dilute solutions in CH_2Cl_2 in matching cells); NMR, Varian VXR-200 (200 MHz), Varian VXR-400 (400 MHz, 100 MHz ^{13}C); GC, Hewlett Packard 5830A; prep-GC, Varian 3300; MS, Finnigan MS-902 or Kratos MS890MS. All reactions were conducted under an atmosphere of argon unless otherwise noted. All solvents were distilled prior to use. Tetrahydrofuran (THF) and dimethoxyethane (DME) were doubly distilled from potassium. Acetonitrile, *tert*-butyl alcohol (*t*-BuOH), methylene chloride (CH_2Cl_2), triethylamine, dimethyl sulfoxide (DMSO), and diisopropylamine were distilled from calcium hydride. Dimethylformamide (DMF) was distilled under reduced pressure from $CuSO_4$. Anhydrous diethyl ether was purchased from Mallinckrodt or Fischer Scientific and was used without further drying.

(5*E*,9*E*)-11-Hydroxy-6,10-dimethyl-5,9-undecadien-2-one (9). Geranylacetone (**8**, 5.0 g, 0.026 mol) was added to an ice-cold solution of selenium dioxide (1.15 g, 0.010 mol) and *tert*-butyl hydroperoxide (90%, 9.0 mL) in CH_2Cl_2 (25 mL). The mixture was stirred under argon at 0 °C for 3.5 h, then diluted with ethyl acetate (200 mL), and washed successively with water (2 × 100 mL), saturated $NaHCO_3$ (100 mL), water (100 m), and brine (100 mL). The solution was then dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed over silica gel (100 g). Elution with 33–50% ethyl acetate in hexanes gave 3.4 g (76% based on recovered starting material) of the desired allylic alcohol **9** as a clear colorless oil used directly in the next step: IR (film) 3400, 2900, 2850, 1700, 1360, 1235, 1165, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.33 (t, J = 6.8 Hz, 1 H), 5.05 (t, J = 6.8 Hz, 1 H), 3.96 (d, J = 6.1 Hz, 2 H), 2.43 (t, J = 7.4 Hz, 2 H), 2.25 (m, 2 H), 2.10 (s, 3 H), 2.00 (m, 2 H), 1.63 (s, 3 H), 1.60 (s, 3 H).

(5*E*,9*E*)-11-Chloro-6,10-dimethyl-5,9-undecadien-2-one Ethylene Acetal (10). A solution of keto alcohol **9** (2.9 g, 0.014 mol), ethylene glycol (20 mL), and oxalic acid dihydrate (200 mg) in benzene (125 mL) was refluxed under argon overnight with azeotropic removal of water. The mixture was then cooled and washed successively with saturated $NaHCO_3$ (50 mL) and water (50 mL). Aqueous washes were back extracted with ether (2 × 50 mL), and pooled organics were washed with brine, dried ($MgSO_4$), and evaporated to give 3.5 g (100%) of protected alcohol (5*E*,9*E*)-11-hydroxy-6,10-dimethyl-5,9-undecadien-2-one ethylene acetal as a clear colorless oil. This material was used directly without further purification: IR (film) 3420, 3000, 2930, 1450, 1370, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.37 (t, J = 7.3 Hz, 1 H), 5.13 (t, J =

(24) Review of epoxide ring-opening reactions: Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737–799.

(25) The primary/secondary epoxide (+)-1,2-epoxyphenylethane undergoes acid-catalyzed methanolysis to give 2-methoxy-2-phenylethanol with inversion of configuration: Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* **1971**, 71–74.

(26) For the synthesis and use of this material in carbonyl couplings, see: McMurry, J. E.; Rico, J. G.; Lectka, T. C. *J. Org. Chem.* **1989**, *54*, 3748–3749.

7.3 Hz, 1 H), 3.98 (m, 2 H), 3.94 (m, 4 H), 1.97–2.17 (m, 6 H), 1.67 (s, 3 H), 1.62 (s, 3 H), 1.55–1.79 (m, 2 H), 1.32 (s, 3 H).

Triphenylphosphine (3.9 g, 0.015 mol, 1.14 equiv) in 15 mL of THF was added dropwise to a stirring solution of *N*-chlorosuccinimide (2.0 g, 0.015 mol, 1.14 equiv) in THF (15 mL) under an atmosphere of argon. After 30 min, protected allylic alcohol (3.3 g, 0.013 mol) in THF (15 mL) was added dropwise over 5 min to the resulting suspension of solids, and the mixture was stirred at room temperature until it became clear and homogeneous (2 h). The resulting dark mixture was diluted with ether (100 mL), washed successively with saturated aqueous $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography over silica gel (80 g, elution with 2% ethyl acetate in hexanes) gave 3.0 g (85%) of allylic chloride **10** as a clear colorless oil: IR (film) 3000, 2950, 1450, 1390, 1275, 1065, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.45 (t, J = 6.8 Hz, 1 H), 5.08 (t, J = 6.9 Hz, 1 H), 3.95 (s, 2 H), 3.88 (m, 4 H), 1.94–2.12 (m, 6 H), 1.68 (s, 3 H), 1.60 (m, 2 H), 1.56 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.26, 131.61, 130.51, 124.62, 109.84, 64.55, 52.32, 39.02, 38.76, 26.54, 23.72, 22.59, 15.79, 13.99.

Methyl 6*t*-*cis*-2,2-Dimethyl-1,3-dioxabicyclo[3.3.0]octanecarboxylate (12). Osmium tetraoxide (2.5% in *tert*-butyl alcohol 1.0 mL) was added to a stirring solution of methyl 3-cyclopentenecarboxylate (**11**, 7.60 g, 0.060 mol) and *N*-methylmorpholine *N*-oxide (14.1 g, 0.120 mol, 2.0 equiv) in THF (50 mL), *tert*-butyl alcohol (30 mL), and water (15 mL). The mixture was stirred under argon at room temperature for 4 h, then diluted with brine (50 mL), and extracted with ethyl acetate (6 × 100 mL). Pooled organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give the crude diol. This material was taken up in dry acetone (80 mL) and stirred for 6 h at room temperature in the presence of Amberlyst-15 (2.5 g) and 2,2-dimethoxypropane (20 mL, 0.16 mol, 2.7 equiv). The mixture was then filtered and evaporated to dryness. The resulting dark oil was taken up in ethyl acetate (150 mL), washed with saturated aqueous $NaHCO_3$ (80 mL), water (80 mL), and brine, then dried ($MgSO_4$), concentrated, and distilled to give 8.6 g (71%) of **12** as a clear colorless oil: bp 73–75 °C (1.2 mmHg). This material was a 6:1 ratio of the anti/syn isomers by integration of relevant peaks in the ^1H NMR spectrum: anti isomer, IR (film) 2990, 2950, 1740, 1375, 1215, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.62 (dd, J = 1.4, 3.7 Hz, 2 H), 3.63 (s, 3 H), 2.98 (tt, J = 6.0, 12.2 Hz, 1 H), 2.08 (dd, J = 6.0, 14.2 Hz, 2 H), 1.67 (m, 2 H), 1.38 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.60, 108.48, 79.59, 51.12, 40.25, 36.57, 25.69, 23.30; syn isomer, IR (film) 2990, 2950, 1740, 1375, 1215, 1050 cm^{-1}: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.57 (m, 2 H), 3.64 (s, 3 H), 2.75 (m, 1 H), 2.41 (dd, J = 3.1, 14.1 Hz, 2 H), 2.82 (m, 2 H), 1.32 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.73, 109.84, 80.10, 41.93, 34.52, 25.53, 23.65.

6*t*-*cis*-2,2-Dimethyl-1,3-dioxabicyclo[3.3.0]octanecarbaldehyde. A solution of ester acetonide **12** (7.5 g, 0.038 mol) in THF (40 mL) was added to an ice-cold suspension of $LiAlH_4$ (1.77 g, 0.47 mol, 1.25 equiv) in THF (150 mL). The mixture was stirred under argon for 15 min and then heated to reflux for 2.5 h. The reaction was then cooled to 0 °C, treated successively with water (1.6 mL) and 25% aqueous NaOH (6.4 mL), stirred 10 min, and filtered through a small pad of Celite. Evaporation of the filtrate left 6.0 g (93%) of *cis*-2,2-dimethyl-6*t*-(hydroxymethyl)-1,3-dioxabicyclo[3.3.0]octane, which was carried on directly without further purification: IR (film) 3420, 2920, 1380, 1210, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.63 (dd, J = 3.6, 1.1 Hz, 2 H), 3.61 (m, 2 H), 2.39 (m, 1 H), 1.92 (dd, J = 5.8, 14.0 Hz, 2 H), 1.42 (s, 3 H), 1.3–1.5 (m 2 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.70, 80.32, 64.99, 38.76, 36.16, 55.95, 23.63.

The crude alcohol (5.9 g, 0.034 mol) in CH_2Cl_2 (15 mL) was added to a stirring suspension of pyridinium chlorochromate (13.3 g, 0.062 mol, 1.8 equiv), $NaCO_3$ (11.3 g, 0.106 mol, 3.1 equiv), and powdered 4Å molecular sieves (17 g, 0.5 g/mmol) in CH_2Cl_2 (200 mL). The mixture was stirred under argon at room temperature for 1.0 h, diluted with ether (80 mL), filtered through a short pad of Florisil, and evaporated. The resulting dark oil was passed through a column of silica gel (12 g, eluted with 200 mL of 1:1 ethyl acetate–hexanes). Evaporation of the solvent left 5.3 g (91%) of 6*t*-*cis*-2,2-dimethyl-1,3-dioxabicyclo[3.3.0]octanecarboxaldehyde of purity suitable for use in the following reaction; IR (film) 2980, 2950, 2745, 1720, 1210, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.70 (d, J = 2.3 Hz, 1 H), 4.68 (m, 2 H), 3.07 (m, 1 H), 2.07 (dd, J = 6.0, 14.3 Hz, 2 H), 1.65 (m, 2 H), 1.42 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.16, 108.87, 79.52, 46.68, 33.75, 25.73, 23.36.

6*t*-2-(1,3-Propanediyldithiomethyl)-*cis*-2,2-dimethyl-1,3-dioxabicyclo[3.3.0]octane (13). 1,3-Propanedithiol (3.6 mL, 3.9 g, 0.036 mol, 1.15 equiv) was added to a suspension of crude aldehyde (5.3 g, 0.031 mol), *p*-toluenesulfonic acid monohydrate (300 mg), and $MgSO_4$ (3g) in $CHCl_3$ (80 mL), and the mixture was stirred overnight under argon at room temperature. Filtration, concentration, and chromatography over silica gel (115 g, elution with 200 mL of hexanes, followed by 1 L of 10% ethyl acetate in hexanes) gave 6.0 g (62% from **12**) of **13** as a clear viscous oil: IR (film) 2980, 2910, 1375, 1215, 1050, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.54 (dd, J = 1.3, 3.8 Hz, 2 H), 3.95 (d, J = 7.8 Hz, 1 H), 2.78 (m, 4 H), 2.45 (m, 1 H), 2.05 (m, 1 H), 2.01 (dd, J = 5.7, 14.2 Hz, 2 H), 1.79 (m, 1 H), 1.37 (m, 2 H), 1.34 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 108.64, 79.22, 51.35, 40.71, 37.21, 30.35, 25.95, 25.89, 23.62.

6*t*-1-((3*E*,7*E*)-3,7-Dimethyl-11-ethylenedioxy-1-oxo-3,7-dodecadienyl)-*cis*-2,2-dimethyl-1,3-dioxabicyclo[3.3.0]octane (14). *n*-Butyllithium (1.6 M in hexanes, 10.6 mL, 16.9 mmol, 1.38 equiv) was added to a solution of dithiane acetonide **13** (3.20 g, 12.3 mmol) in THF (25 mL) under an atmosphere of argon at −78 °C. The mixture was allowed to warm to 0 °C and maintained at ice temperature for 2 h before being recooled to −78 °C. Hexamethylphosphoramide (5.10 mL, 2.38 equiv) was added, followed by the dropwise addition of allylic chloride **10** (3.65 g, 13.5 mmol) in THF (25 mL). The mixture was allowed to warm to room temperature, then diluted with a saturated solution of NH_4Cl (50 mL), and extracted with ether (3 × 75 mL). Ether extracts were washed with water (2 × 100 mL) and brine (100 mL), then dried ($MgSO_4$), and evaporated to give 6.8 g of crude alkylation product suitable for use in the next reaction: ^1H NMR ($CDCl_3$, 200 MHz) δ 5.21 (t, J = 7 Hz, 1 H), 5.03 (t, J = 7 Hz, 1 H), 4.62 (m, 2 H), 3.95 (m, 4 H), 2.75–3.06 (overlapping m, 4 H), 2.73 (s, 2 H), 1.95–2.12 (overlapping m, 4 H), 1.82 (s, 3 H), 1.70 (m, 1 H), 1.62 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.29 (s, 3 H).

An ice-cold solution of crude dithiane alkylation adduct (6.8 g, 85% pure, 11.65 mmol) in acetonitrile (25 mL) was added to a solution of *N*-chlorosuccinimide (2.79 g, 20.9 mmol) and $AgNO_3$ (4.08 g, 24.0 mmol) in 80% aqueous acetonitrile (65 mL) at −5 °C. The resulting mixture was stirred at −5 °C for 5 min, and then saturated solutions of $NaHSO_3$ (5.3 mL), Na_2CO_3 (5.3 mL), and NaCl (5.3 mL) were sequentially added at 1-min intervals. The mixture was allowed to warm toward room temperature for 10 min, and a 1:1 mixture of hexanes and CH_2Cl_2 (70 mL) and Celite (3 g) was added. The resulting mixture was filtered through Florisil (1:1 hexanes–CH_2Cl_2), and the filtrate was dried ($MgSO_4$) and evaporated to give the crude keto acetonide dioxolane **14** as a yellow oil. Purification was performed by adsorption onto silica (15 g) and filtration through a short column of silica gel (15 g, eluted with 20% ethyl acetate in hexanes) to afford 3.68 g of material suitable for use in the following step. An analytical sample was purified by chromatography over silica gel (15% ethyl acetate in hexanes elution): IR (film) 2980, 2920, 1708, 1375, 1215, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 20 (t, J = 6.5 Hz, 1 H), 5.08 (t, J = 6.9 Hz, 1 H), 4.61 (dd, J = 4.2, 8.6 Hz, 2 H), 3.88 (m, 4 H), 3.20 (m, 1 H), 3.05 (s, 2 H), 1.92–2.11 (m, 8 H), 1.57–1.64 (m, 4 H), 1.56 (s, 6 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.32, 134.71, 129.63, 128.47, 124.30, 109.87, 108.93, 80.11, 64.58, 53.61, 47.19, 39.19, 39.06, 36.54, 26.77, 26.16, 23.75, 22.62, 16.45, 15.87; mass spectrum (chemical ionization, i-BuH) m/z (rel intensity) 407 (28.4), 345 (100), 169 (52.6), 161 (93.3), 121 (71.1), 87 (63.3).

(*R*,*S*)-*trans*-(6*E*,10*E*)-6,10-Dimethyl-4-hydroxy-1,14-dioxo-3-(2-oxoethyl)-6,10-pentadecadiene Hemiacetal (6). A solution of crude ketone **14** (3.68 g, 9.06 mmol) in ethanol (25 mL) at 0 °C under an atmosphere of argon was treated with $NaBH_4$ (0.86 g, 22.7 mmol, 2.5 equiv). The mixture was allowed to warm to room temperature over 1 h and was then diluted with brine (35 mL) and extracted with ethyl acetate (3 × 50 mL). Pooled extracts were washed with water (85 mL) and brine, then dried ($MgSO_4$), and evaporated to give the crude alcohol. This material was purified by chromatography over silica gel (80 g, elution with 25% ethyl acetate in hexanes) to give 3.0 g (60% from **13**) of clean product: IR (film) 3500, 2990, 2920, 1375, 1210, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.14 (t, J = 6.8 Hz, 1 H), 5.06 (t, J = 6.6 Hz, 1 H), 4.57 (m, 2 H), 3.87 (m, 4 H), 3.45 (m, 1 H), 1.88–2.19 (m, 8 H), 1.72–1.79 (m, 2 H), 1.58–1.62 (m, 2 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.65, 131.80, 128.38, 124.47, 109.84, 108.64, 80.39, 80.23, 70.06, 64.51, 47.04, 42.00, 39.38, 38.93, 36.01, 34.91, 26.34, 26.08, 23.75, 23.69, 22.56, 15.89, 15.70.

The alcohol (3.0 g, 7.35 mmol) was heated under argon to 80 °C in 80% aqueous acetic acid (70 mL) for 1.25 h, then poured onto ice (150 g), and extracted with ethyl acetate (4 × 100 mL). The organic extracts were washed with ice-cold 20% aqueous NaOH (250 mL), the basic wash was back extracted with ethyl acetate (100 mL), and the pooled organics were washed successively with saturated NH_4Cl (150 mL), water (150 mL), and brine (150 mL). Evaporation left the crude wet triol **15**, which was taken up in 1:1 THF–water (35 mL) and treated with $NaIO_4$ (2.24 g, 10.5 mmol, 1.43 equiv). After stirring for 1.5 h at room temperature, the mixture was diluted with water (30 mL) and extracted with ethyl

acetate–ether (1:1, 3 × 75 mL). These extracts were washed with saturated $NaHCO_3$ (50 mL), water (50 mL), and brine. Drying ($MgSO_4$), evaporation, and chromatography over silica gel (50 g, elution with 40% ethyl acetate in hexanes) gave 1.72 g (73%) of the desired keto aldehyde hemiacetal **6** as a 1:1 mixture of anomers: IR (film) 3420, 2940, 2750, 1720, 1708, 1450, 1360, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1 H), 5.50 (m, 0.5 H), 5.44 (m, 0.5 H), 5.16 (m, 1 H), 5.04 (t, J = 6.8 Hz, 1 H), 3.96 (m, 0.5 H), 3.76 (m, 0.5 H), 2.59–2.68 (m, 2.40 (m, 2 H), 2.17–2.26 (m, 4 H), 2.10 (s, 3 H), 1.96–2.07 (m, 4 H), 1.61 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.74, 200.94, 200.41, 136.00, 131.73, 131.67, 127.01, 126.95, 122.72, 98.06, 97.93, 82.99, 81.01, 65.68, 47.95, 46.98, 46.56, 44.52, 43.63, 40.19, 39.25, 37.15, 36.60, 29.72, 26.40, 22.44, 16.44, 15.87; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 305 (20.5, M + 1 − H_2O), 287 (35.9), 269 (19.2), 247 (27.3), 243 (29.0), 151 (100).

(*R*,*S*)-*trans*-5-(11-[(5*E*,9*E*)-6,10-Dimethyl-2-oxo-5,9-undecadienyl])-4-(2-oxoethyl)-dihydro-2-(3*H*)-furanone (3t). A solution of the keto aldehyde hemiacetal **6** (250 mg, 0.776 mmol) in CH_2Cl_2 (2 mL) was added to a stirring suspension of pyridinium chlorochromate (300 mg, 1.39 mmol, 1.8 equiv), Na_2CO_3 (250 mg, 2.40 mmol, 3 equiv), and powdered 4Å molecular sieves (390 mg, 0.5 g/mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature under argon for 1.5 h, then diluted with ether (2 mL), filtered through a short pad of Florisil, and evaporated to dryness. Chromatography of the resulting crude oil over silica gel (3 g, elution with 35% ethyl acetate in hexanes) gave 186 mg (75%) of trans lactone keto aldehyde **3t** as a clear colorless oil: IR (film) 2910, 2840, 1780, 1720, 1715, 1370, 1170, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1 H), 5.19 (t, J = 6.3 Hz, 1 H), 5.03 (t, J = 7.0 Hz, 1 H), 4.22 (ddd, J = <1, 5.9, 12.7 Hz, 1 H), 2.81 (dd, J = 8.3, 17.5 Hz, 1 H), 2.52–2.75 (m, 2 H), 2.42 (t, J = 7 Hz, 2 H), 2.30 (m, 1 H), 2.21 (m, 2 H), 2.09 (s, 3 H), 1.92–2.13 (m, 4 H), 1.62 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.20, 198.86, 175.25, 135.61, 129.81, 128.52, 122.90, 83.25, 46.79, 44.10, 43.49, 39.02, 34.49, 34.40, 29.58, 26.31, 22.35, 16.41, 15.74; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 321 (100), 303 (64.8), 285 (19.2), 245 (15.6), 243 (18.7), 151 (98.7), 139 (46.3).

(*R*,*S*)-*cis*-5-(11-[(5*E*,9*E*)-6,10-Dimethyl-2-oxo-5,9-undecadienyl])-4-(2-oxoethyl)-dihydro-2-(3*H*)-furanone (3c). A solution of hemiacetal **6** (500 mg, 1.55 mmol) and $AgNO_3$ (316 mg, 1.86 mmol) in ethanol (8 mL) was treated with a solution of 5 N aqueous NaOH in ethanol (1:5, 6.7 mL, 5.6 mmol of NaOH). After 5 min, the mixture was filtered, the precipitate was washed with a minimal amount of ethanol, and the filtrate was concentrated to a volume of about 10 mL. This mixture was cooled to 0 °C, and $NaBH_4$ (230 mg, 6.1 mmol, 4.0 equiv) was added. The reaction was stirred under argon (0 °C to room temperature) for 45 min, water (4 mL) was added to homogenize the mixture, and stirring was continued at room temperature for an additional 20 min. The resulting clear solution was cooled to 0 °C and acidified to pH 3 by slow addition of ice-cold 5% HCl. Extraction of this mixture with CH_2Cl_2 (4 × 15 mL), washing of the extracts with brine (20 mL), and drying (Na_2SO_4) gave a solution of the crude carboxylic acid triol **16**. This solution was concentrated to a volume of about 10 mL and stirred at room temperature under argon in the presence of *p*-toluenesulfonic acid monohydrate (50 mg) for 1 h. This mixture was then washed with saturated $NaHCO_3$, water, and brine. Drying (Na_2SO_4) and evaporation left 500 mg of crude lactone as a mixture of diastereomers that was used directly in the next step without purification. An analytical sample was purified by chromatography over a column of silica gel: IR (film) 3380, 2960, 2905, 1765, 1260, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.17 (t, J = 6 Hz, 1 H), 5.12 (t, J = 7 Hz, 1 H), 4.64 (ddd, J = <1, 6.3, 13.1 Hz, 1 H), 3.57–3.80 (m, 2 H), 2.68 (m, 1 H), 2.58 (dd, J = 7.8, 17 Hz, 1 H), 2.34 (dd, J = 6.8, 17 Hz, 1 H), 2.22 (br d, J = 7 Hz), 2.07 (m, 2 H), 1.99 (t, J = 7 Hz, 2 H), 1.76 (m, 1 H), 1.62 (s, 3 H), 1.57 (s, 3 H), 1.46 (m, 2 H), 1.15 (d, J = 6.1 Hz, 3 H).

Dimethyl sulfoxide (1.0 mL, 1.1 g, 14 mmol, 9.0 equiv) in CH_2Cl_2 (2 mL) was added to a solution of oxalyl chloride (608 μL, 885 mg, 6.97 mmol, 4.50 equiv) in CH_2Cl_2 (12 mL) at −60 °C under an atmosphere of argon. After 2 min, a solution of the crude cis lactone diol (500 mg) in CH_2Cl_2 (5 mL) was added, and the mixture was allowed to warm to −10 °C and was then maintained at that temperature for 15 min. The reaction was then recooled to −30 °C, triethylamine (4.25 mL) was added, and the solution was allowed to warm to 10 °C. The solution was diluted with CH_2Cl_2 (25 mL), washed successively with water (15 mL), dilute HCl (2%, 15 mL), water (3 × 15 mL), and brine (15 mL), then dried ($MgSO_4$), and evaporated to give a crude oil. This material was purified by chromatography over silica gel (3 g, elution with 30% ethyl acetate in hexanes) to give 280 mg (56% from the hemiacetal) of **3c** as a clear slightly tinted oil: IR (film) 2910, 2840, 2730, 1775, 1720, 1715, 1370, 1175, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1 H), 5.15 (t, J = 6.4 Hz, 1 H), 5.03 (t, J = 6.6 Hz, 1 H), 4.71 (ddd, J = 5.5, 5.7, 8.9 Hz, 1 H), 3.03 (m, 1 H), 2.76 (m, 1 H), 2.70 (m, 1 H), 2.55 (dd, J = 8.7, 18.5 Hz, 1 H), 2.43 (t, J = 7 Hz, 2 H), 2.22 (m, 4 H), 2.10 (s, 3 H), 1.92–2.14 (m, 4 H), 1.61 (s, 3 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.96, 135.81, 128.11, 123.03, 80.39, 43.65, 42.87, 40.08, 39.15, 34.91, 32.90, 29.71, 26.40, 22.49, 16.25, 15.89; mass spectrum (chemical ionization, *i*-BuH m/z (rel intensity) 321 (18.6), 85 (18.0), 83 (25.6), 81 (33.9), 69 (67.6), 61 (100).

Coupling of Trans Lactone Keto Aldehyde 3t. Zn–Cu couple (1.37 g, 21.1 mmol, 45 equiv) was added to a suspension of $TiCl_3$·$(DME)_{1.5}$[26] (2.35 g, 7.03 mmol, 15 equiv) in DME (50 mL), and the mixture was refluxed with efficient stirring under an argon atmosphere for 1.5 h. Upon cooling to room temperature, trans lactone keto aldehyde **3t** (150 mg, 0.47 mmol) in DME (150 mL) was added via syringe pump over a period of 45 h. After an additional 5 h, aqueous K_2CO_3 (20%, 35 mL) was added, the mixture was allowed to stir at room temperature for 6 h, and the resulting suspension was extracted with ethyl acetate (4 × 75 mL). The pooled extracts were washed with cold HCl (2%, 100 mL), water (75 mL), and brine (75 mL), then dried ($MgSO_4$), and concentrated. The resulting oil was passed through a short pad of silica and then subjected to HPLC separation (Waters radial-pak silica cartridge, 60% ethyl acetate in hexanes elution). This provided the known macrocyclic diol **18a** (32 mg, 21%) and three other isomeric diols (10.5 mg, 7%; 28 mg, 19%; and 16 mg, 11%). The identity of the desired product **18a** was verified by conversion into the known acetonide derivative by the published methods.[9] Our acetonide **18a** gave a ^1H NMR spectrum in complete agreement with that published and was indistinguishable from an authentic spectrum provided by Professor J. A. Marshall.

Diol 18a: IR ($CHCl_3$) 3400, 2915, 1775, 1460, 1210, 1200, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.09 (br d, J = 9.3 Hz, 1 H), 4.97 (br d, J = 9.8 Hz, 1 H), 4.31 (ddd, J = 3.3, 7.7, 10.8 Hz, 1 H), 3.15 (t, J = 10.9 Hz, 1 H), 2.90 (br s, 1 H), 2.76 (dd, J = 8.9, 17.4 Hz, 1 H), 2.46 (m, 2 H), 2.28 (m, 1 H), 1.99–2.25 (overlapping m), 1.70 (s, 3 H), 1.63 (s, 3 H), 1.56–1.79 (m, 2 H), 1.34 (m, 1 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.24, 137.78, 130.62, 129.83, 125.14, 82.37, 73.56, 73.71, 46.13, 37.73, 37.43, 36.68, 35.84, 27.42, 24.11, 18.37, 17.20; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (16.6), 306 (19.3), 305 (100), 287 (13.3), 109 (12.8).

Diol 18b: IR ($CHCl_3$) 3500, 2910, 1770, 1450, 1380, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.09 (m, 1 H), 4.9 (t, J = 6.9 Hz, 1 H), 4.25 (ddd, J = 3.1, 6.8, 9.7 Hz, 1 H), 3.38 (m, 1 H), 2.85 (dd, J = 8.9, 18.0 Hz, 1 H), 2.58 (br d, J = 13.5 Hz, 1 H), 2.40 (dd, J = 8.9, 18 Hz), 1.98–2.30 (overlapping m), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.43 (m, 1 H), 1.23 (s, 3 H); mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (23.7), 306 (17.5), 305 (100), 287 (17.5), 109 (22.7), 95 (21.6).

17-Norisolobophytolide (19). Methanesulfonyl chloride (38 μL, 57 mg, 0.50 mmol, 20 equiv) was added to an ice-cold solution of diol **18a** (8 mg, 0.025 mmol) in ether (0.5 mL), CH_2Cl_2 (0.1 mL), and pyridine (0.5 mL), and the mixture was maintained at 0 °C under argon for 25 h. The mixture was then warmed to room temperature for 3 h, diluted with water, acidified (diluted HCl), and extracted with ethyl acetate (4 × 15 mL). The pooled extracts were washed with brine, then dried (Na_2SO_4), and concentrated. The resulting oil was passed through silica and concentrated to give about 10 mg of the crude hydroxy mesylate.

The above crude mesylate was dissolved in THF (1 mL), cooled to −20 °C, and treated with benzyltrimethylammonium hydroxide (2.39 M in methanol, 16 μL, 0.037 mmol, 1.5 equiv). After 5 min the mixture was passed through silica, concentrated, and purified by chromatography over silica (15% ethyl acetate in hexanes) to give 5 mg (68%) of the known epoxide **19** as an oil.[9] This material gave a ^1H NMR spectrum indistinguishable from one provided by Professor J. A. Marshall: IR ($CHCl_3$) 2910, 1770, 1450, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (t, J = 6.3 Hz, 1 H), 4.98 (m, 1 H), 4.20 (ddd, J = 9.1, 9.0, 4.7 Hz, 1 H), 2.81 (dd, J = 17, 8.2 Hz, 1 H), 2.62 (t, J = 5.5 Hz, 1 H), 2.41 (m, 1 H), 2.26 (dd, J = 17.1, 8.8 Hz, 1 H), 2.21 (m, 1 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.52–1.74 (m, 2 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.73, 134.65, 130.09, 129.63, 124.62, 82.85, 62.63, 59.88, 43.31, 39.38, 37.87, 37.24, 36.08, 32.33, 24.71, 24.00, 17.45, 16.99, 15.33.

The conversion of this material to (±)-isolobophytolide has been published.[9]

Coupling of Cis Lactone Keto Aldehyde 3c. Zn–Cu couple (0.96 g, 14.0 mmol, 45 equiv) was added to a suspension of $TiCl_3$·$(DME)_{1.5}$ (1.56 g, 4.68 mmol, 15 equiv) in DME (35 mL), and the mixture was refluxed with efficient stirring under an argon atmosphere for 1.5 h. Upon cooling to room temperature, keto aldehyde **3** (100 mg, 0.31 mmol) in DME (100 mL) was added via syringe pump over a period of 45 h. After an additional 5 h, aqueous K_2CO_3 (20%, 25 mL) was added, the mixture was allowed to stir at room temperature for 6 h, and the resulting suspension was extracted with ethyl acetate (4 × 75 mL). Pooled extracts were washed with cold HCl (2%, 100 mL), water (75 mL), and brine (75 mL),

then dried ($MgSO_4$), and concentrated. The resulting oil was passed through a short pad of silica and then subjected to HPLC separation (Waters radial-pak silica cartridge, 67% ethyl acetate in hexane elution) to provide a pure macrocyclic diol subsequently identified as **21b** (19 mg, 19%) and an inseparable mixture of the remaining isomers (28 mg, 28%) in a ratio of about 0.1 (**21d**):2 (**21a**):1(**21c**). Careful fractional crystallization (using 50% ethyl acetate in hexane) of this mixture gave clean crystals (plates) of a diol identified as **21c** (3-*epi*-17-norisocrassin) and the mother liquor enriched in diol **21a**. Repeated crystallization of this mother liquor (20% ethyl acetate in hexanes) then gave clean **21a** as colorless needles (20 mg, 21%). The identity of this material was verified by conversion to the acetonide derivative and comparison with an authentic spectrum provided by Professor J. A. Marshall. The fourth isomer (**21d**) could not be purified from the remaining mother liquors.

4-*epi*-17-Norisocrassin (21b): Plates grown from ether–hexanes gave mp 135 °C; IR ($CHCl_3$) 3450, 2910, 1770, 1440, 1380, 1160, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.04 (t, J = 7.6 Hz, 1 H), 4.92 (br t, J = 6.5 Hz, 1 H), 4.72 (ddd, J = 4.0, 5.1, 11.7 Hz, 1 H), 3.55 (br d, J = 10.4 Hz, 1 H), 3.19 (d, J = 17.2 Hz, 1 H), 2.66 (dd, J = 7.9, 17.3 Hz, 1 H), 2.59 (m, 1 H), 2.46 (br s, 1 H), 2.27 (m, 1 H), 2.15 (m, 2 H), 1.93 (m, 1 H), 1.84 (m, 1 H), 1.64 (s, 3 H), 1.56 (s, 3 H), 1.40 (m, 1 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.63, 134.43, 129.16, 125.99, 81.53, 75.52, 75.03, 39.35, 38.87, 37.64, 37.44, 35.86, 26.97, 24.66, 22.89, 20.94, 17.28, 15.78; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (14.3), 321 (5.2), 306 (26.9), 305 (100), 287 (18.3), 167 (23.7), 129 (22.3).

3-*epi*-17-Norisocrassin (21c): Fine needles grown from ethyl acetate–hexanes gave mp 167–169 °C; IR ($CHCl_3$) 3500, 2920, 1765, 1450, 1375, 1180, 1080, 1020, 950 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (overlapping m, 2 H), 4.73 (ddd, J = 2.9, 7.2, 7.2 Hz, 1 H), 3.42 (m, 1 H), 2.55 (dd, J = 8.2, 16.9 Hz, 1 H), 2.48 (m, 1 H), 2.44 (m, 1 H), 2.34 (dd, J = 9.9, 16.9 Hz, 1 H), 2.15–2.29 (overlapping m), 2.12 (m, 1 H), 1.94 (m, 1 H), 1.86 (m, 1 H), 1.69 (s, 3 H), 1.59 (s, 3 H) 1.58 (t, J = 8.6 Hz, 2 H), 1.46 (m, 1 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.28, 135.42, 131.05, 129.47, 128.98, 82.21, 75.45, 73.83, 40.20, 39.20, 38.81, 35.95, 28.39, 24.56, 23.97, 21.39, 17.19, 15.31; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (31.2), 306 (28.9), 305 (100), 287 (21.0), 167 (23.1), 137 (19.3), 123 (29.9), 109 (54.01), 95 (31.2).

3,4-*diepi*-17-Norisocrassin (21a): Needles grown from ethyl acetate–hexanes gave mp 144–146 °C; IR ($CHCl_3$) 3450, 2940, 1765, 1370, 1250, 1180, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.22 (t, J = 7.1 Hz, 1 H), 5.09 (t, J = 6.6 Hz, 1 H), 4.80 (ddd, J = 4.3, 6.3, 10.9 Hz, 1 H), 3.26 (t, J = 8.8 Hz, 1 H), 2.87 (m, 1 H), 2.69 (dd, J = 8.2, 17.4 Hz, 1 H), 2.64 (m, 1 H), 2.54 (s, 1 H), 1.95–2.41 (overlapping m), 1.80 (m, 1 H), 1.77 (d, J = 8.7 Hz, 1 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.27 (m, 2 H), 1.12 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.48, 135.31, 129.71, 127.79, 127.55, 80.82, 76.34, 74.08, 39.18, 38.43, 38.05, 34.55, 34.15, 28.16, 27.60, 24.33, 21.80, 16.88, 16.27; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (4.4), 305 (17.7), 164 (17.7), 136 (100).

17-Norisocrassin (21d). Methanesulfonyl chloride (130 μL, 192 mg, 1.67 mmol, 22 equiv) was added to an ice-cold solution of a 2:1 mixture of diols **21a** and its C3 epimer (25 mg, 0.077 mmol) in ether (1 mL), CH_2Cl_2 (0.3 mL), and pyridine (0.3 mL). The mixture was maintained at 0 °C for 25 h, then warmed to room temperature, diluted with water (5 mL), acidified (diluted HCl), and extracted with ethyl acetate (4 × 10 mL). The pooled organics were washed with water (10 mL) and brine (15 mL), then dried ($MgSO_4$), concentrated, and passed through a short pad of silica gel (1 g, eluted with 50% ethyl acetate in hexanes) to provide a mixture of crude hydroxy mesylates. The mixture of mesylates was taken up in THF (2 mL), cooled to −20 °C, and treated with benzyltrimethylammonium hydroxide (2.39 M in methanol, 53 μL, 0.13 mmol, 1.5 equiv). After 5 min, the mixture was passed through silica gel (50% ethyl acetate in hexanes), concentrated, and chromatographed (1 g of silica gel, 15% ethyl acetate in hexanes) to give 16 mg (68%) of a mixture of isomeric epoxides.

A solution of this epoxide mixture (12 mg, 0.039 mmol) in THF (1.5 mL) and water (0.5 mL) was treated at room temperature with aqueous perchloric acid (10%, 0.5 mL). The mixture was stirred for 1.0 h, basified (saturated aqueous $NaHCO_3$), saturated with NaCl, and extracted with ethyl acetate (4 × 10 mL). Pooled organics were washed with brine (15 mL), then dried (Na_2SO_4), concentrated, and chromatographed to give 10.3 mg (81%) of a mixture of diols. Separation by HPLC (Waters radial-pak silica cartridge, 67% ethyl acetate in hexanes) gave clean samples of 4-*epi*-17-norisocrassin and 17-norisocrassin (**21d**). Small white needles of the latter, grown from mixtures of ethyl acetate and hexanes gave mp 151–152 °C: IR ($CHCl_3$) 3500, 2920, 1765, 1375, 1220, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.03 (t, J = 7.7 Hz, 1 H), 4.93 (t, J = 6.6 Hz, 1 H), 4.74 (ddd, J = 5.1, 5.6, 10.7 Hz, 1 H), 3.37 (br t, J = 8 Hz, 1 H), 3.04 (dd, J = 2.7, 17.4 Hz, 1 H), 2.68 (dd, J = 7.9, 17.4 Hz, 1 H), 2.60 (m, 1 H), 2.55 (m, 1 H), 2.10–2.33 (overlapping m, 4 H), 1.98 (m, 1 H), 1.90 (m, 1 H), 1.80 (br d, J = 14 Hz, 2 H), 1.72 (dd, J = 2.4, 8.5 Hz, 1 H), 1.65 (s, 3 H), 1.61 (m, 1 H), 1.55 (s, 3 H), 1.31 (m, 1 H), 1.25 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.34, 134.81, 129.79, 126.24, 124.91, 81.66, 76.79, 76.20, 39.30, 38.63, 38.00, 37.64, 36.00, 27.22, 24.94, 24.59, 22.84, 17.16, 15.83; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 323 (16.6), 321 (14.9), 305 (100), 287 (38.2), 120 (43.2).

17-Norcrassin (28). The mixture of 4-epimeric diols (10 mg, 0.031 mmol) obtained from the epoxide ring opening was saponified in 3% aqueous KOH (1 mL) by heating for 1 h to 100 °C. The mixture was then cooled to ice temperature, acidified (diluted HCl), and stirred for 1 h at 0 °C. Extraction with ethyl acetate (4 × 5 mL), washing with brine, drying (Na_2SO_4), and evaporation left a mixture of epimeric δ-lactones (10 mg, 100%) that was easily separated by chromatography (40% ethyl acetate in hexanes) to give 6.0 mg of 17-norcrassin (**28**) and 4.0 mg of 4-*epi*-15-norcrassin (**22**). Compound **28** was crystallized form ethyl acetate–hexanes to give fine needles, mp 157 °C: IR ($CHCl_3$) 3450, 2920, 1730, 1450, 1375, 1250, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (m, 1 H), 5.09 (t, J = 7.5 Hz, 1 H), 4.00 (dd, J = 1.5, 11.4 Hz, 1 H), 3.79 (m, 1 H), 2.68 (m, 1 H), 2.58 (dd, J = 8.1, 21.0 Hz, 1 H), 2.43 (m, 1 H), 1.87–2.35 (overlapping m), 1.80 (dd, J = 8.9, 14.3 Hz, 1 H), 1.60 (m, 2 H), 1.57 (s, 6 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.06, 134.86, 130.52, 127.83, 125.32, 84.10, 74.27, 70.23, 45.80, 39.71, 38.36, 32.96, 32.75, 24.96, 23.82, 22.36, 19.86, 15.03, 14.83; mass spectrum (chemical ionization, CH_4) m/z (rel intensity) 305 (M + 1 − H_2O, 72.8), 306 (45.7), 165 (64.0), 123 (72.8), 109 (100).

(±)-Crassin (1). Lithium diisopropylamide (0.81 M in 1:1 THF–hexane, 300 μL, 0.24 mmol, 7.8 equiv) was added to a solution of the δ-lactone diol **28** (10 mg, 0.031 mmol) in THF (1.5 mL) at −78 °C. The mixture was slowly warmed to −30 °C over 30 min, and formaldehyde (20 mg) was added in a stream of argon (cracked at 160 °C). After 1 min, the mixture was quenched with saturated NH_4Cl (2.5 mL) and extracted with ethyl acetate (4 × 5 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated, leaving a mixture of isomeric hydroxy lactones. The hydroxy lactone mixture was taken up in ether (1 mL), CH_2Cl_2 (0.2 mL), and pyridine (0.2 mL), cooled to 0 °C, and treated with a solution of methanesulfonyl chloride in CH_2Cl_2 (0.5 M, 74 μL, 0.037 mmol, 1.2 equiv). After stirring at 0 °C overnight, the mixture was passed through a short pad of silica and concentrated to leave a crude mixture of mesylates. This mesylate mixture was taken up in dry benzene (1 mL) and treated with DBU (12 μL, 0.078 mmol, 2.5 equiv). After stirring at room temperature for 10 min, the mixture was passed through silica, concentrated, and purified by chromatography (0.5 g silica, 30–50% ethyl acetate in hexanes) to give 5.5 mg (53%) of crystalline synthetic crassin that was identical by TLC, IR, ^1H NMR, and ^{13}C NMR with natural material prepared by alkaline hydrolysis of natural crassin acetate.[8] Fine white needles grown from ethyl acetate–hexanes gave mp 174–176 °C: IR ($CHCl_3$) 3550, 2950, 1720, 1460, 1300, 1200, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.54 (d, J = 2.1 Hz, 1 H), 5.70 (d, J = 2.1 Hz, 1 H), 5.23 (m, 1 H), 5.05 (t, J = 7.8 Hz, 1 H), 4.20 (m, 1 H), 3.92 (d, J = 11.5 Hz, 1 H), 2.55 (m, 1 H), 2.44 (dd, J = 4.3, 12.9 Hz, 1 H), 2.02–2.38 (overlapping m), 1.72–1.95 (overlapping m), 1.65 (s, 3 H), 1.58 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.82, 138.49, 135.54, 130.54, 127.75, 127.64, 125.27, 82.50, 74.06, 72.01, 44.59, 40.14, 39.27, 28.65, 24.82, 24.03, 22.09, 19.32, 14.96, 14.49.

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Registry No. (±)-**1**, 123484-44-6; (±)-**2**, 108147-41-7; (±)-**3t**, 128524-22-1; (±)-**3c**, 123412-05-5; (±)-**3c** (lactone diol, isomer 1), 128414-06-2; (±)-**3c** (lactone diol, isomer 2), 128524-25-4; (±)-**6** (isomer 1), 123484-35-5; (±)-**6** (isomer 2), 123412-03-3; **8**, 3796-70-1; **9**, 93525-18-9; **9** ethylene acetal, 104476-98-4; **10**, 123411-95-0; **11**, 58101-60-3; **12**, 39798-12-4; **12** alcohol, 77714-61-5; **12** aldehyde, 123411-97-2; **13**, 123411-98-3; **14**, 123412-00-0; (±)-**14** alcohol, 123412-01-1; (±)-**15**, 123412-02-2; (±)-**16** (isomer 1), 123412-04-4; (±)-**16** (isomer 2), 123484-36-6; (±)-**189**, 108210-91-9; (±)-**18a** mesylate, 108119-96-6; (±)-**18b**, 128524-94-7; (±)-**18c**, 128524-23-2; (±)-**18d**, 128524-24-3; (±)-**19**, 108147-40-6; (±)-**20**, 108104-53-6; (±)-**21a**, 108104-48-9; (±)-**21b**, 123484-37-7; (±)-**21c**, 123484-38-8; (±)-**21d**, 123484-42-4; (±)-**22**, 123484-43-5; (±)-**25**, 108104-52-5; (±)-**28**, 123412-06-6.