Specific C−C Bond Construction by Remote C−H Activation: Synthesis of (−)-*trans*-Cembranolide

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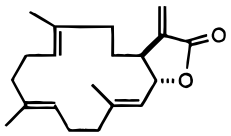
The first total synthesis of (−)-*trans*-cembranolide (**1**), isolated from *Sinularia mayi* Luttschw., is described. The key step in the synthesis is the diastereoselective Rh-mediated cyclization of the enantiomerically pure diazo ester **4** to the tetrahydrofuran **3a**.

Introduction

The 14-membered diterpenoid lactone[1] (−)-*trans*-cembranolide (**1**) was isolated from *Sinularia mayi* Luttschw. by Uchino *et al.*[2] in 1982. While two reports on the total synthesis of racemic **1** have appeared,[3,4] no synthesis of the natural enantiomer has been reported.



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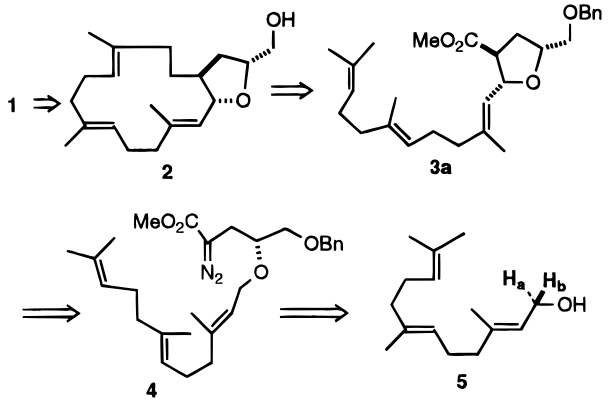
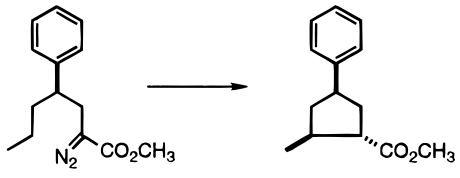
Our approach to **1** was based on the retrosynthetic analysis illustrated below. Formation of carbon−carbon bonds by C−H activation is one of the most difficult of all organic transformations.[5] In 1973, Breslow adumbrated principles that could guide C−C bond construction by remote C−H activation.[6] The Breslow group demonstrated that through conformational analysis of a pendant reactive group, it was possible to selectively activate specific C−H sites on the steroid skeleton. We have now extended this analysis to allow *enantioselectivity* in the insertion. From the perspective of *trans,trans*-farnesol (**5**), our hypothesis was that judicious consideration of conformational preferences should allow the design of an enantiomerically pure linker that, attached as an ether and bearing an α-diazo ester (**4**), should direct insertion to just *one* of the two enantiotopic C−H sites (**5**, H_a vs H_b) on the target methylene. We report here the reduction of this approach to practice and its practical application in the preparation of (−)-*trans*-cembranolide (**1**), starting from the inexpensive *trans,trans*-farnesol (**5**).



Computational Analysis

We have presented [5d,7] a computational model that accurately predicts the dominant diastereomer from the Rh-mediated cyclizations of simple α-diazo esters (e.g. **6** → **7**). Applying this model to the prospective cyclization



of **4**, the point of commitment to a particular diastereomer is represented by transition state **13** (Scheme 1), in which there is overlap between the C═Rh bond and the target C−H bond. There are four diastereomeric chairlike transition states (**13**) for the cyclization of **4**,

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(1) For a review of syntheses in the cembranolide series, see: (a) Tius, M. A. *Chem. Rev.* **1988**, 719. For biological activity of cembranolides, see: (b) Manchand, P. S.; White, J. D. *Contemporary Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic: New York, 1978; Vol. 2, p 337. (c) Tursch, B.; Braeckman, J. C.; Daloze, D.; Kaisin, M. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. II, p 247. (d) Culver, P.; Burch, M.; Potenza, C.; Wasserman, L.; Fenical, W.; Taylor, P. *Mol. Pharmacol.* **1985**, *28*, 436. For more recent syntheses in the cembranolide series, see: (e) Marshall, J. A.; DeHoff, B. S. *Tetrahedron* **1987**, *43*, 4849. (f) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616. (g) Nishitani, K.; Isozaki, M.; Yamakawa, K. *Chem. Pharm. Bull.* **1990**, *38*, 28. (h) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165. (i) Nishitani, K.; Konomi, T.; Okayo, K.; Yamakawa, K. *Heterocycles* **1994**, *37*, 679. (j) Rodriguez, A. D.; Pina, I. C.; Barnes, C. L. *J. Org. Chem.* **1995**, *60*, 8096. (k) Yue, X.; Li, Y. *Tetrahedron Lett.* **1996**, *37*, 671.

(2) Uchio, Y.; Eguchi, S.; Nakayama, M.; Hase, T. *Chem. Lett.* **1982**, 277.

(3) Kodama, M.; Takahashi, T.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 5175.

(4) Nishitani, K.; Konomi, T.; Okada, K.; Yamakawa, K. *Heterocycles* **1994**, *37*, 679.

(5) For C−C bond construction by intermolecular C−H activation, see: (a) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486. (b) Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986. For a review of diastereoselectivity and enantioselectivity in C−C bond construction by intramolecular C−H activation, see: (b) Taber, D. F. *Methods of Organic Chemistry*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag Stuttgart: New York, 1995; p 1127. For more recent references, see: (c) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983. (d) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (e) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (f) Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett.* **1996**, 85. (g) Wee, A. G. H.; Liu, B. *Tetrahedron Lett.* **1996**, *37*, 145.

(6) (a) Breslow, R.; Baldwin, S.; Fiechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251. (b) Breslow, R.; Corcoran, R. J.; Snider, B. B *J. Am. Chem. Soc.* **1974**, *96*, 6791. (c) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 1213.

(7) (a) Taber, D. F.; Song, Y. *Tetrahedron Lett.* **1995**, *36*, 2578. (b) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.

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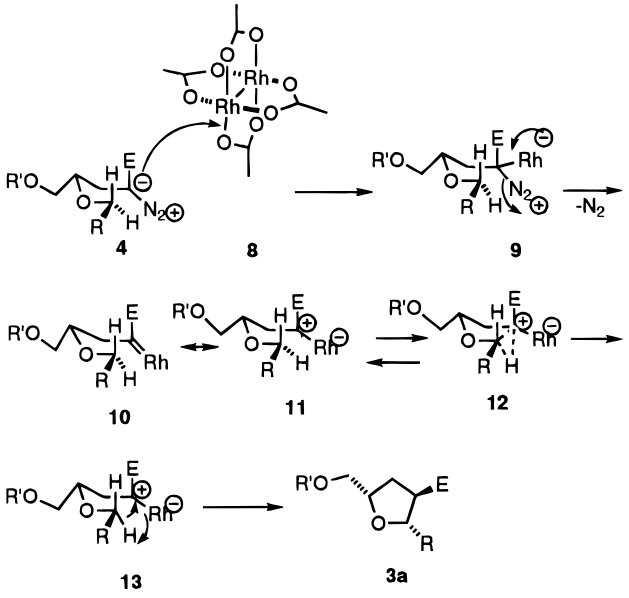
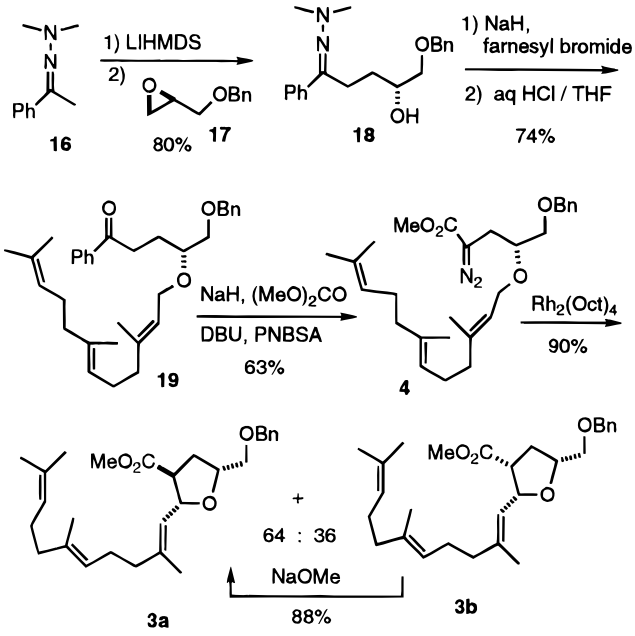
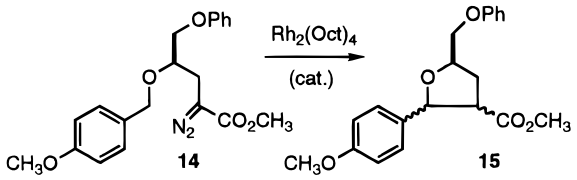
Scheme 1



Scheme 2



each leading to one of the four possible diastereomers of **3**. With the positions of the ligands on Rh locked and the angles and bonds defined as before,[5d,7] we minimized each of the four transition states with molecular mechanics. The transition state **13** in which both substituents are equatorial on the "chair" was found to be 3.5 kcal/mol lower in energy then the next most stable transition state. As **13** is the transition state that would lead to **3a**, we predicted that **3a** should be the dominant product from the cyclization.



There was one critical concern with this analysis. In a model study,[7] we had observed that the diastereoselectivity of the cyclization was substantially diminished if the target C−H site was particularly electron rich. Thus, cyclization of **14** led to a mixture of *all four* of the diastereomers of **15**, in a ratio of 56:33:4:4. As the target C−H bonds of **4** are particularly electron rich, there was a real concern whether the cyclization would indeed show sufficient selectivity for H_a.

Preparation of Diazo Ester 4. To prepare **4** (Scheme 2), it was necessary to develop a new strategy for the preparation of α-diazo esters. To this end, (−)-(*R*)-1,2-epoxy-3-(benzyloxy)propane **17**[8] was opened with the lithium enolate derived from hydrazone **16**,[9] in the presence of catalytic yttrium triflate.[10] The derived γ-hydroxy hydrazone **18** was then alkylated with *trans*,-*trans*-farnesyl bromide.[11] Exposure of the alkylated hydrazone to aqueous HCl then gave the aryl ketone **19**. Treatment of the ketone with methyl carbonate and NaH, followed by exposure to DBU[12] and 4-nitrobenzenesulfonyl azide (PNBSA) gave the α-diazo ester **4**. The debenzoylated methyl ester, a side product from this procedure, was converted to **5** by benzoylation[12] followed by diazo transfer.

Cyclization of Diazo Ester 4. Two stereogenic centers were to be formed in the cyclization of **4**. As outlined above, detailed conformational analysis[7] of the competing transition states for the cyclization led us to expect high selectivity for insertion into the desired H_a, rather than H_b. The likehood of control of the ester center was not so clear. As we reported previously,[7] diastereoselectivity at the center α to the ester is a function of the electron-withdrawing ability of the substitution on the target methylene. The diastereoselectivity decreases if the reactivity of the target C−H is activated by an electron-donating substituent. In diazo ester **4**, the disubstituted vinyl adjacent to the target C−H is very strongly electron-donating.

In the event, catalytic rhodium octanoate in CH_2Cl_2 at room temperature smoothly cyclized α-diazo ester **4** to a 64:36 mixture of **3a** and **3b**. As we had hoped, *exclusive* insertion into H_a was indeed observed. The lack of stereocontrol at the ester center was not an issue, as the minor ester **3b** was smoothly epimerized to **3a** with NaOMe in MeOH (**3a**:**3b** = 86:14 at equilibrium).[13]

Construction of the 14-Membered Ring. To close the 14-membered ring (Scheme 3), we next needed to specifically activate the terminal C−H site on the farnesyl skeleton. This was achieved by the Sharpless protocol,[14] oxidation of the sulfone **21**[15] with catalytic SeO_2. Bromination of the resulting allylic alcohol was

(8) (−)-(*R*)-1,2-epoxy-3-(benzyloxy)propane was provided by DAISO Co., Ltd.

(9) For the preparation of acetophenone dimethylhydrazone, see: (a) Fisher, M.; Fisher, L. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1969; Vol. 2; p 154. For the deprotonation of dimethylhydrazones, see: (b) Enders D.; Weuster, P. *Tetrahedron Lett.* **1978**, *19*, 2853.

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(11) Castro, A.; Spencer, T. A. *J. Org. Chem.* **1992**, *57*, 3496.

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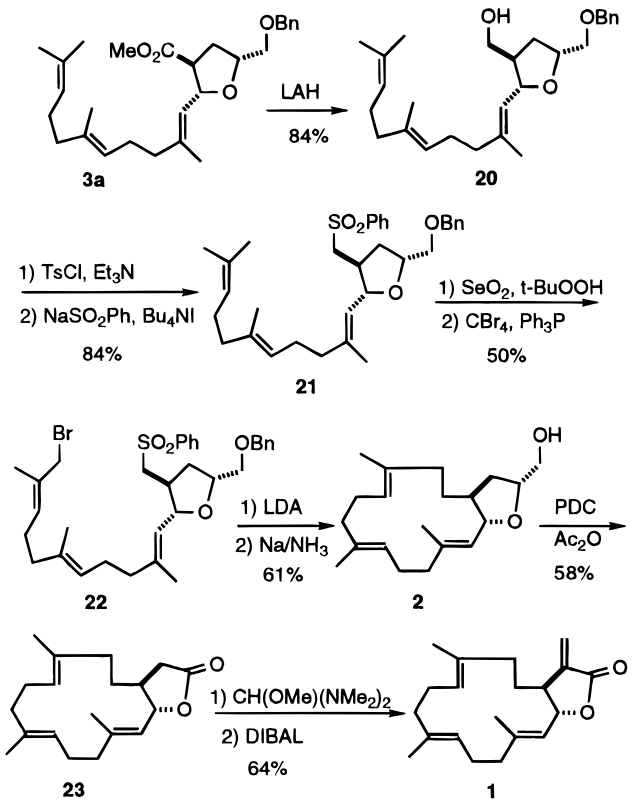
(13) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280. It is noteworthy that β-elimination/cyclization, which would lead to *all four* diastereomers of **3**, does not compete with this epimerization.

(14) Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(15) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.

Scheme 3



then effected with PPh_3-CBr_4, giving the *trans* allylic bromide **22**.

Sulfone **22** cyclized smoothly on exposure to LDA (−78 °C → rt),[16] giving the 14-membered ring. The intramolecular S_N2 displacement is probably made more efficient in this case by the templating effect of the already constructed 5-membered ring. Because of the newly formed stereogenic center at the sulfone, two diastereomers were found after the cyclization. Reduction of this diastereomeric mixture with dissolving metal (Na/NH_3)[17] removed both the phenylsulfonyl group and the benzyl group, to give the primary alcohol **2**.

Synthesis of (−)-*trans*-Cembranolide (1). To complete the synthesis of (−)-*trans*-cembranolide (**1**), we effected oxidative cleavage of **2** with PDC and acetic anhydride[18,19] to give the lactone **23**. Following the procedure of Ziegler,[20] treatment of **23** with bis(dimethylamino)methoxymethane followed by reduction of the resulting vinylogous carbamate with DIBAL then gave the α-methylene lactone **1**. The identity of the synthetic α-methylene lactone **1** with natural (−)-*trans*-cembranolide was confirmed by ^1H and ^{13}C NMR, HRMS, and $[\alpha]_D$ (observed = −31.0°, lit.[2] = −29.0°) comparison.

Conclusion

We have completed the first total synthesis of the natural enantiomer of (−)-*trans*-cembranolide (**1**), confirming the assigned absolute configuration. The strategy employed in this project, use of an initially constructed enantiomerically pure tetrahydrofuran as a template to guide further ring construction, should be of general utility in target-directed organic synthesis.

Experimental Section[21]

(*R*)-1-Phenyl 4-[(3,7,11-Trimethyl-2(*E*),6(*E*),10-tetradecatrienyl)oxy]-5-(phenylmethoxy)-1-pentanone (19). Neat hydrazone **16** and (*R*)-1,2-epoxy-3-(benzyloxy)propane were dried separately with 4A molecular sieve overnight. At 0 °C, the hydrazone **16** (25 g, 0.154 mol) in 30 mL of dry toluene was added dropwise over 10 min to a solution of LiHMDS (31.5 g) in 188 mL of toluene. After 30 min at 0 °C, the (*R*)-1,2-epoxy-3-(benzyloxy)propane (10.3 g, 62.8 mmol) in 20 mL of toluene was added over 5 min to the reaction mixture, and then $Y(OTf)_3$ (3.4 g, 6.28 mmol) was added all at once. After 18 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was partitioned between EtOAc and, sequentially, saturated aqueous NH_4Cl and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give 16.4 g of the γ-hydroxy hydrazone **18** (80% from (*R*)-1,2-epoxy-3-(benzyloxy)propane), TLC R_f (20% EtOAc/petroleum ether) = 0.21.

NaH (6.0 g, 0.15 mol, 60% in mineral oil) was added in portions to the γ-hydroxy hydrazone **18** (16.4 g, 50.3 mmol) in 120 mL of dry THF at 0 °C. Farnesyl bromide (22.8 g, 80 mmol) and Bu_4NI (200 mg) were then added. The reaction mixture was warmed up to rt. After 10 h, the reaction was cautiously quenched with 4 N aqueous HCl, to pH = 2. After 2 h, the mixture was partitioned between EtOAc and, sequentially, 4 N aqueous HCl and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the aryl ketone **19** (18.1 g, 59% from (*R*)-1,2-epoxy-3-(benzyloxy)propane). TLC R_f (20% EtOAc/petroleum ether) = 0.71. ^1H NMR (d): 7.95 (m, 2H), 7.52 (m, 1H), 7.41 (m, 2H), 5.32 (m, 1H), 5.08 (m, 2H), 4.55 (s, 2H), 4.16 (dd, *J* = 6.7, 11.6 Hz, 1H), 4.04 (dd, *J* = 6.7, 11.6 Hz), 3.6 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (d): u 200.1, 140.0, 138.3, 137.0, 135.2, 131.2, 73.3, 72.5, 66.4, 39.6, 39.5, 34.1, 26.7, 26.4, 26.3; d 132.8, 128.5, 128.3, 128.0, 127.6, 127.5, 124.3, 123.8, 121.0, 76.4, 25.6, 17.6, 15.9. IR (cm^{-1}): 2919, 1684, 1598, 1449, 1357, 1093. $[\alpha]$ = +10.9° (*c* 2.62, CH_2Cl_2).

Methyl (*R*)-2-Diazo-4-[(3,7,11-trimethyl-2(*E*),6(*E*),10-tetradecatrienyl)oxy]-5-(phenylmethoxy)pentanoate (4). At rt, NaH (2.5 g, 62.7 mmol, 60% in mineral oil) was added to **19** (10.2 g, 20.9 mmol) and dimethyl carbonate (3.93 g, 41.8 mmol) and methylene blue (3 mg) in 80 mL of dry DME. The reaction mixture was then heated to 70 °C for 3 h. The reaction was cautiously quenched with 1 N aqueous HCl, to pH = 4. The mixture was partitioned between EtOAc and, sequentially, 1 N aqueous HCl and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the β-keto ester (7.2 g), TLC R_f (20% EtOAc/petroleum ether) = 0.68, and the corresponding debenzoylated methyl ester (1.4 g), TLC R_f (20% EtOAc/petroleum ether) = 0.71.

At 0 °C, NaH (432 mg, 10.8 mmol, 60% in mineral oil) was added to the debenzoylated methyl ester (1.4 g, 3.2 mmol) and methylene blue (3 mg) in 12 mL of DME. After 10 min at 0 °C, methyl benzoate (979 mg, 7.2 mmol) was added all at once. The reaction mixture was then heated to reflux for 10 h. The reaction was cautiously quenched with 1 N aqueous HCl, to pH = 4. The mixture was partitioned between EtOAc and, sequentially, 1 N aqueous HCl and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated and chromatographed to give the β-keto ester (1.3 g).

DBU (4.7 g, 30.8 mmol) was added to a solution of combined β-keto ester (8.5 g, 15.5 mmol) in 40 mL of CH_2Cl_2 at 0 °C.

(16) (a) Kumagai, T.; Ise, F.; Uyehara, T.; Kato, T. *Chem. Lett.* **1981**, 25. (b) Takayanagi, H.; Uyehara, T.; Kato, T. *Chem. Commun.* **1978**, 359.

(17) (a) Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 858. (b) For a closely related cyclization/desulfonylation/debenzylation, see: Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107.

(18) Kim, J. N.; Ryu, E. K. *Tetrahedron Lett.* **1992**, *33*, 3141.

(19) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 7508.

(20) (a) Ziegler, F. E.; Fang, J. M. *J. Org. Chem.* **1981**, *46*, 825. (b) Ziegler, F. E.; Fang, J. M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174.

(21) For general experimental procedures, see: Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

After 10 min, 4-nitrobenzenesulfonyl azide (4.6 g, 20.2 mmol) was added. After warming to rt for 3 h, the reaction mixture was partitioned between 0.5 M aqueous phosphate buffer (pH = 7.0) and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **4** (6.2 g, 63% yield from **19**) as a bright yellow oil. TLC R_f (20% EtOAc/petroleum ether) = 0.66. ^{1}H NMR (d): 7.33 (m, 5H), 5.31 (m, 1H), 5.10 (m, 2H), 4.54 (s, 2H), 4.16 (dd, J = 6.8, 11.6 Hz, 1H), 4.02 (dd, J = 6.8, 11.6 Hz, 1H), 3.75 (s, 3H), 3.67 (m, 1H), 3.54 (d, J = 5.0 Hz, 2H), 2.5 (m, 2H), 2.11−1.70 (m, 8H0, 1.67 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (d): u 168.0, 140.4, 138.1, 135.2, 131.2, 73.4, 71.4, 66.6, 39.7, 39.6, 26.7, 26.3, 26.2; d 128.3, 127.6, 124.3, 123.8, 120.6, 76.6, 51.8, 25.6, 17.6, 16.4, 15.9. IR (cm^{-1}): 2916, 2088, 1694, 1436, 1341, 1128.

Methyl (*R*,*R*,*R*)-2-(2,6,10-Trimethyl-1(*E*),5(*E*),9-tridecatrienyl)-5-[(phenylmethoxy)methyl]-2,3,4,5-tetrahydro-3-furancarboxylate (3a) and Methyl (*R*,*S*,*R*)-2-(2,6,10-Trimethyl-1(*E*),5(*E*),9-tridecatrienyl)-5-[(phenylmethoxy)methyl]-2,3,4,5-tetrahydro-3-furancarboxylate (3b). Diazo ester **4** (6.2 g, 13.2 mmol) in a 250 mL round bottom flask containing a magnetic stir bar was evaporated with toluene (3 × 20 mL). Methylene chloride was then added by filtration through a pad of anhydrous K_2CO_3. Dirhodium tetraoctanoate (6 mg) was added with stirring. The reaction was complete in 20 min (TLC analysis). The reaction mixture was concentrated and the residue was chromatographed to give 3.41 g of **3a** (58% yield from **4**) and 1.90 g of **3b** (32% yield from **4**).

3a: TLC R_f (20% EtOAc/petroleum ether) = 0.63. ^{1}H NMR (d): 7.32 (m, 5H), 5.22 (d, J = 8.8 Hz, 1H), 5.08 (m, 2H), 4.73 (t, J = 8.4 Hz, 1H), 4.57 (s, 2H), 4.24 (m, 1H), 3.67 (s, 3H), 3.51 (d, J = 4.6 Hz, 2H), 2.77 (m, 1H), 2.31 (m, 1H), 2.09−1.71 (m, 8H), 1.68 (s, 3H), 1.67 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (d): u 173.7, 141.0, 138.2, 135.2, 131.2, 73.3, 72.2, 39.6, 39.5, 33.0, 26.7, 26.2. IR (cm^{-1}): 2915, 1738, 1455, 1366, 1098. MS (*m*/*z*): 440 (57), 349 (38), 317 (48), 289 (38), 202 (100). HRMS calcd for $C_{28}H_{40}O_4$ 440.2927, obsd 440.2926. [α] = +34.5° (*c* 2.00, CH_2Cl_2).

3b: TLC R_f (20% EtOAc/petroleum ether) = 0.56. ^{1}H NMR (d): 7.35 (m, 5H), 5.16 (d, J = 8.9 Hz), 1H), 5.09 (m, 2H), 4.87 (t, J = 8.4 Hz, 1H), 4.58 (dd, J = 12.2, 21 Hz, 2H), 4.10 (m, 1H), 3.64 (m, 2H), 3.61 (m, 3H), 3.22 (q, J = 8.2 Hz, 1H), 2.17−1.71 (m, 11H), 1.68 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (d): u 172.6, 140.6, 138.2, 135.2, 131.2, 73.3, 72.5, 39.6, 31.7, 26.6, 26.5; d 128.2, 127.7, 127.4, 124.2, 123.7, 121.4, 78.1, 77.3, 51.3, 48.1, 25.6, 17.6, 15.9. IR (cm^{-1}): 2919, 1740, 1453, 1169, 1101, 1028. MS (*m*/*z*): 440 (47), 349 (50), 317 (57), 202 (100). HRMS calcd for $C_{28}H_{40}O_4$ 440.2927, obsd 440.2909. [α] = −17.6° (*c* 2.58, CH_2Cl_2).

At rt, NaOMe (1 mL, 2.0 M in MeOH) was added to the minor diastereomer **3b** (88 mg, 0.20 mmol) in 1 mL of MeOH. After 8 h at rt, the reaction was partitioned between ether and, sequentially, 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the major diastereomer **3a** (68 mg, 88% from **3b**) and the minor diastereomer **3b** (11 mg).

(*S*,*R*,*R*)-2-(2,6,10-Trimethyl-1(*E*),5(*E*),9-tridecatrienyl)-5-[(phenylmethoxy)methyl]-2,3,4,5-tetrahydrofuran-3-methanol (20). $LiAlH_4$ (378 mg, 9.96 mmol) was added to **3a** (2.2 g, 5.0 mmol) in 40 mL of dry THF at 0 °C. After 10 h at rt, water (1.0 mL), aqueous 10% NaOH (1.0 mL), and water (3.0 mL) were added sequentially over 2 h, at which point the grayish reaction mixture had become a white paste. The mixture was filtered with EtOAc, and the filtrate was concentrated and chromatographed to give **20** as a colorless oil (96 mg, 84% from **3a**). TLC R_f (40% EtOAc/petroleum ether) = 0.40. ^{1}H NMR (d): 7.33 (m, 5H), 5.22 (d, J = 8.9 Hz, 1H), 5.09 (m, 2H), 5.56 (s, 2H), 4.35 (t, J = 8.2 Hz, 1H), 4.16 (m, 1H), 3.59 (m, 2H), 3.49 (m, 2H), 2.12−1.83 (m, 10H), 1.70 (s, 3H), 1.69 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (d): u 140.4, 138.3, 135.3, 131.2, 73.3, 73.0, 63.4, 39.6, 32.0, 26.7, 26.2; d 128.3, 127.6, 127.5, 124.8, 124.3, 123.7, 78.5, 77.1, 47.7, 25.6, 17.6, 16.7, 16.0. IR (cm^{-1}) 2915, 1654, 1540, 1452, 1376, 1098. MS (*m*/*z*): 412 (48), 351 (12), 325 (31), 243 (61), 203 (100). HRMS calcd for $C_{27}H_{40}O_3$ 412.2977, obsd 412.2957. [α] = +19.3° (*c* 2.96, CH_2Cl_2).

(*S*,*R*,*R*)-2-(2,6,10-Trimethyl-1(*E*),5(*E*),9-tridecatrienyl)-3-[(phenylsulfonyl)methyl]-5-[(phenylmethoxy)methyl]-2,3,4,5-tetrahydrofuran (21). Tosyl chloride (372 mg, 1.95 mmol) was added to a mixture of the primary alcohol **20** (501 mg, 1.22 mmol) and Et_3N (493 mg, 4.88 mmol) and DMAP (10 mg) at 0 °C. After 10 h at rt, the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the tosylate as a colorless oil (640 mg). TLC R_f (20% EtOAc/petroleum ether) = 0.54.

A mixture of the tosylate (640 mg, 1.12 mmol), Bu_4NI (2.1 g, 5.6 mmol), $NaSO_2Ph$ (1.2 g, 3.25 mmol), and copper powder (10 mg) was heated to reflux in 10 mL of THF. Additional portions of $NaSO_2Ph$ (0.4 g) were added after 3 h and after 6 h. After a total of 18 h at reflux, the mixture was cooled and then partitioned between water and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the sulfone **21** as a colorless oil (544 mg, 84% from **20**). TLC R_f (40% EtOAc/petroleum ether) = 0.56. ^{1}H NMR (d): 7.88 (m, 2H), 7.64 (m, 1H), 7.52 (m, 1H), 7.33 (m, 5H), 5.07 (m, 3H), 4.54 (s, 2H), 4.18 (m, 2H), 3.45 (d, J = 4.8 Hz, 2H), 3.07 (m, 2H), 2.21−1.84 (m, 10H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.58 (s,3H). ^{13}C NMR (d): u 142.9, 139.3, 138.2, 135.4, 131.3, 73.3, 72.7, 58.0, 39.6, 34.3, 26.7, 26.3; d 133.7, 129.3, 128.3, 127.9, 127.6, 127.5, 124.2, 123.6, 122.4, 80.2, 77.2, 39.7, 25.7, 17.7, 16.9. IR (cm^{-1}) 2915, 1448, 1308, 1148, 1086. MS (*m*/*z*): 536 (18), 395 (80), 243 (64), 203 (100). HRMS calcd for $C_{33}H_{44}O_4S$ 536.2960, obsd 536.2960. [α] = +14.7° (*c* 3.04, CH_2Cl_2).

(*S*,*R*,*R*)-2-(2,6,10-Trimethyl-11-bromo-1(*E*),5(*E*),9(*E*)-tridecatrienyl)-3-[(phenylsulfonyl)methyl]-5-[(phenylmethoxy)methyl]-2,3,4,5-tetrahydrofuran (22). Selenium dioxide (1.8 mg) and salicylic acid (11 mg) were dissolved in 0.7 mL of t-butyl hydroperoxide (4.4 M in CH_2Cl_2). The resulting solution was added to the sulfone **21** (428 mg, 0.8 mmol) in a 25 °C water bath. After 3 h, the mixture was partitioned between 10% aqueous NaOH and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the allylic alcohol as a colorless oil (174 mg), TLC R_f (30% EtOAc/petroleum ether) = 0.22, and recovered sulfone **21** (111 mg).

Triphenylphosphine (203 mg, 0.776 mmol) in 3 mL of CH_2Cl_2 was added dropwise over 10 min to a solution of the allylic alcohol (332 mg, 0.6 mmol) and CBr_4 (258 mg, 0.776 mmol) in 8 mL of CH_2Cl_2 at 0 °C. After 2 h at rt, 3 drops of methanol were added. The reaction mixture was concentrated and chromatographed to give the allylic bromide **12** as a light yellow oil (281 mg, 50% yield from **21**). TLC R_f (30% EtOAc/petroleum ether) = 0.56. ^{1}H NMR (d): 7.86 (m, 2H), 7.63 (m, 1H), 7.52 (m, 1H), 7.32 (m, 5H), 5.57 (m, 1H), 5.04 (m, 1H), 4.54 (s, 2H), 4.15 (m, 2H), 3.96 (s, 2H), 3.45 (d, J = 4.7 Hz, 2H), 3.07 (m, 2H), 2.28−1.76 (m, 10H), 1.74 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (d): u 142.5, 139.2, 138.1, 134.4, 131.8, 73.2, 72.6, 57.8, 41.7, 39.4, 38.5, 34.1, 26.6, 26.1; d 133.6, 131.0, 129.2, 128.2, 127.7, 127.5, 127.4, 124.1, 122.4, 80.1, 77.1, 39.6, 16.8, 15.8, 14.5. IR (cm^{-1}) 2916, 1447, 1307, 1146, 1086. MS (*m*/*z*): 534 (20), 395 (68), 345 (18), 303 (33), 243 (100). HRMS calcd for $C_{33}H_{43}O_4SBr$ (M − HBr) 534.2804, obsd 534.2469. [α] = +15.5° (*c* 1.10, CH_2Cl_2).

(1*R*,14*R*,16*R*)-(2*E*,6*E*,10*E*)-16-(Hydroxymethyl)-3,7,11-trimethyl-16-oxabicyclo[12.3.0]heptadeca-2,6,10-triene (2). LDA (2.6 mL, 0.2 M) was added to the allylic bromide **22** (230 mg, 0.37 mmol) in 9 mL of dry THF at −78 °C. After 2 h at −78 °C, the mixture was slowly warmed up to rt over 14 h. The reaction mixture was partitioned between H_2O and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give a diastereomeric mixture of the cyclized compound as a colorless oil (133 mg), TLC R_f (20% EtOAc/petroleum ether) = 0.44 and 0.48).

Sodium metal was added to a solution of the sulfone (133 mg, 0.25 mmol) in dry THF and EtOH (6 mL, 1:1 v/v) and condensed ammonia (15 mL) at −78 °C until the solution was dark blue. After 10 min at −78 °C, solid NH_4Cl was added

until the blue color disappeared. The reaction mixture was warmed to rt and then partitioned between H_2O and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **2** as a colorless oil (70 mg, 61% yield from **22**). TLC R_f (30% EtOAc/petroleum ether) = 0.34. ^{1}H NMR (d): 5.08 (d, J = 9.2 Hz, 1H), 4.95 (m, 2H), 4.26 (dd, J = 6.8, 9.2 Hz, 1H), 4.09 (m, 1H), 3.66 (m, 1H), 3.49 (m, 1H), 2.24 −1.84 (m, 15H), 1.68 (s, 3H), 1.58 (s, 6H). ^{13}C NMR (d): u 138.1, 133.6, 132.5, 65.3, 39.0, 38.6, 35.1, 34.8, 29.7, 24.3, 23.6; d 125.7, 122.3, 81.0, 43.5, 17.7, 16.6, 15.3. IR (cm^{-1}) 2924, 2340, 1443, 13484, 1049. MS (*m*/*z*): 304 (100), 299 (11), 207 (32), 167 (74). HRMS calcd for $C_{20}H_{32}O_2$ 304.2402, obsd 304.2395. [α] = −30.4° (*c* 0.54, CH_2Cl_2).

(1*R*,14*R*)-(2*E*,6*E*,10*E*)-17-Oxo-3,7,11-trimethyl-16-oxabicyclo[12.3.0]heptadeca-2,6,10-triene (23). Compound **2** (20 mg) was added to a refluxing solution of pyridinum dichromate (99 mg) and Ac_2O (81 mg) in 1 mL of CH_2Cl_2 and 0.5 mL of DMF. After 30 min, Et_2O (5 mL) and Florisil (2 g) were added. The mixture was filtered, and the residue was washed with ether. The combined filtrate was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give lactone **23** as a colorless oil (11 mg, 58% yield from **2**). TLC R_f (30% EtOAc/petroleum ether) = 0.56. ^{1}H NMR (d): 5.12 (d, J = 9.4 Hz, 1H), 4.93 (m, 2H), 4.82 (dd, J = 6.7, 9.4 Hz, 1H), 2.75 (dd, J = 7.3, 15.9 Hz, 1H), 2.29−1.94 (m, 14H), 1.71 (d, J = 1.0 Hz, 3H), 1.58 (s, 6H). ^{13}C NMR (d): u 177.3, 144.4, 134.3, 132.4, 39.4, 38.8, 36.3, 35.2, 30.2, 24.6, 24.1; d 125.9, 125.3, 123.2, 81.9, 40.5, 17.9, 17.2, 15.6. IR (cm^{-1}) 1777, 1435, 1384, 1171. MS (*m*/*z*): 288 (100), 260 (4), 232 (26), 219 (16), 191 (40). HRMS calcd for $C_{19}H_{28}O_2$: 288.2089, obsd 288.2105. [α] = −60.0° (*c* 0.20, CH_2Cl_2).

(−)-*trans*-Cembranolide (1). The lactone **23** (9.0 mg) in 1 mL of methoxybis(dimethylamino)methane was heated in an oil bath from 25 to 90 °C. After 18 h at 90 °C, the solvent was removed in vacuo. The residue was refluxed in 0.9 mL of MeOH and 0.5 mL of 20% aqueous K_2CO_3 for 30 min. The reaction mixture was neutralized with 2.5 mL of 50% aqueous NaH_2PO_4 at 0 °C and then partitioned between the aqueous solution and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give vinylogous carbamate as a yellowish semisolid (10.0 mg, 96%), TLC R_f (40% EtOAc/petroleum ether) = 0.46.

At −78 °C, DIBAL (0.3 mL, 1.0 M in hexanes) was added dropwisely to a solution of the vinylogous carbamate (5.1 mg) in 1.2 mL of dry THF. After 2 h at −78 °C, the mixture was slowly warmed up to rt and then stirred for 12 h. The reaction mixture was quenched with 0.3 mL of saturated aqueous NH_4Cl and stirred at 25 °C for 30 min. Solid $MgSO_4$ (0.7 g) was added, the mixture was filtered, and the residue was washed with ether. Evaporation of the the combined filtrate and chromatography of the residue afforded *trans*-cembranolide (**1**) as a colorless oil (2.0 mg) and the recovered vinylogous carbamate (2.1 mg). The calibrated yield from the lactone **23** is 64%. TLC R_f (20% EtOAc/petroleum ether) = 0.66. ^{1}H NMR (d): 6.23 (d, J = 2.6 Hz, 1H), 5.57 (d, J = 2.3 Hz, 1H), 5.08 (br d, J = 10.3 Hz, 1H), 5.08−4.80 (m, 2H), 4.86 (dd, J = 3.8, 9.8 Hz), 2.64 (m, 1H), 2.22−2.03 (m, 12H), 1.72 (d, J = 1.2 Hz), 3H), 1.61 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (d): u 1170.2, 141.3, 140.7, 133.6, 131.3, 121.5, 38.9, 38.4, 36.0, 32.1, 24.0, 23.8; d 125.9, 125.3, 123.4, 79.2, 43.0, 16.4, 15.6, 15.2. MS (*m*/*z*): 300 (100), 279 (61), 257.2 (28), 217 (36). HRMS calcd for $C_{20}H_{28}O_2$ 300.2089, obsd 300.2075. [α] = −31.0° (*c* 0.10, $CHCl_3$). This compound is identical with the natural product by ^{1}H NMR, ^{13}C NMR, and HRMS. The optical rotation reported for natural **1** is [α] = −29.0° (*c* 3.40, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds are available (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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