Double Intramolecular S_N' *O*-Cyclization for Stereoselective Synthesis of Bistetrahydrofuran Core of Acetogenins

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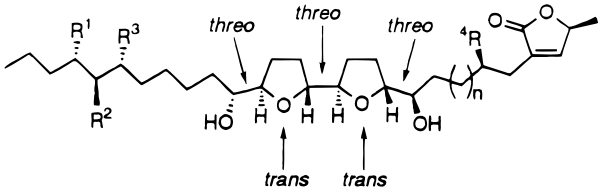
A C_2-symmetric bistetrahydrofuran core of acetogenins has been prepared via double intramolecular S_N' *O*-cyclization reactions. Approaches using readily prepared both *E*- and *Z*-olefin substrates are investigated. The cyclization of *E*-olefins gave a mixture of two diastereomers with low selectivity, while the corresponding *Z*-olefins predominantly provided a desired *trans*,*trans*-bistetrahydrofuran product. The high diastereoselectivity is presumably controlled by a hydrogen-bonding transition state. An efficient enantioselective synthesis of this C_2-symmetric bistetrahydrofuran is also described. Sharpless asymmetric dihydroxylation was used for this approach.

Introduction

Over 200 acetogenins have been isolated from the plant Annonacea and many of them contain one or more 2,5-disubstituted tetrahydrofuran rings as a core unit. This acetogenin family exhibits a diverse array of biological properties: antitumor, antiprotozoal, antifeedant, immunosuppressive, pesticidal, anthelminitic, and microbial activities.[1,2] It is believed that the primary mode of action for these acetogenins is inhibition of the mitochondrial NADH:ubiquinone oxidoreductase, an essential enzyme for ATP production.[3] The structure−activity relationships (SARs) of acetogenins suggest that Parviflorin (**1**) and the Asimicin subgroup (**2**−**5**), both of which are comprised of a core containing *trans*,*threo*,*trans*-bistetrahydrofuran moiety, showed promise in the inhibition of oxygen uptake in mitochondrial assays of rat liver.[4] The interesting structural features and biological activity of acetogenins have attracted considerable attention. The research groups of Trost,[5a] Marshall,[5b,c,e] Hoye,[5f,g] Sinha,[5d,h] and Sasaki[5i] have all reported elegant syntheses for this *trans*,*threo*,*trans*-bistetrahydrofuran system. As an application of our S_N' *O*-cyclization strategy for the construction of substituted tetrahydrofurans,[6] we were intrigued with the possibility of using this strategy for the efficient preparation of bistetrahydrofuran systems which could be used to synthesize a sufficient amount of the naturally occurring acetogenins and/or the isomers with various side chains for the evaluation of biological activity (SARs).

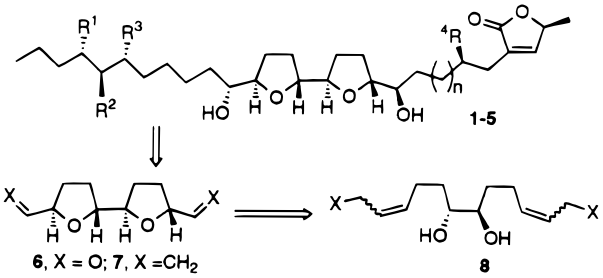


$R^1 = R^2 = R^3 = H$, $R^4 = OH$, n = 7 Parviflorin (**1**)
$R^1 = R^2 = R^3 = H$, $R^4 = OH$, n = 9 Asimicin (**2**)
$R^1 = R^2 = R^4 = H$, $R^3 = OH$, n = 9 Asiminacin (**3**)
$R^1 = R^3 = R^4 = H$, $R^2 = OH$, n = 9 Asiminecin (**4**)
$R^2 = R^3 = R^4 = H$, $R^1 = OH$, n = 9 Asiminocin (**5**)

Results and Discussion

Retrosynthetic Analysis. Our retrosynthetic analysis is outlined in Scheme 1. The hidden symmetry of

Scheme 1



acetogenins (**1**−**5**) suggests that they could easily be prepared from a C_2-symmetric bistetrahydrofuran, such as **6** or **7**. Compound **7** could be prepared from the S_N' *O*-cyclization of compound **8**. Once cyclized, the two vinyl groups on **7** could be exploited to further functionalize the two side chains. Epoxidation, dihydroxylation, ozo-

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(4) (a) Landolt, J. L.; Ahammadsahib, K. I.; Hollingworth, R. M.; Barr, R.; Crane, F. L.; Buerck, N. L.; McCabe, G. P.; McLaughlin, J. L. *Chem.-Biol. Interact.* **1995**, *98*, 1. (b) Alfonso, D.; Johnson, H. A.; Colman-Saizarbitoria, T.; Presley, C. P.; McCabe, G. P.; McLaughlin, J. L. *Nat. Toxins* **1996**, *4*, 181.

(5) Selected recent syntheses (after 1995): (a) Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632. (b) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996. (c) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989. (d) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423. (e) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247. (f) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (g) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (h) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257. (i) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.

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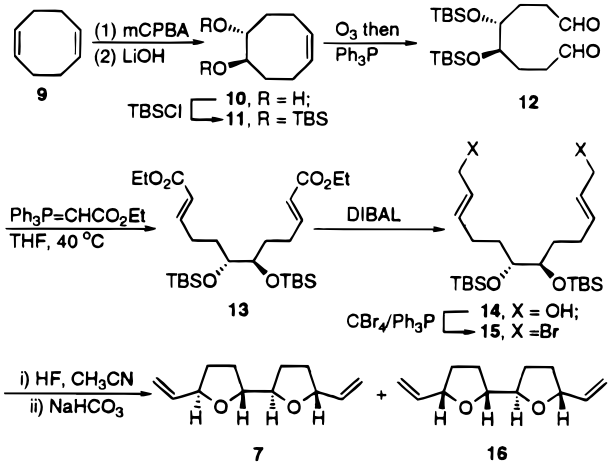
nolysis, and hydroboration can be envisioned as processes to effect this functionalization. For example, a hydroxyl group of the side chains, which is adjacent to THF rings, can be introduced diastereoselectively from the corresponding THF carbaldehyde with a Grignard reagent by using literature procedures.[7]

S_N' Cyclization of *E*-Olefins. Our racemic approach to the bistetrahydrofuran **7** is illustrated in Scheme 2.

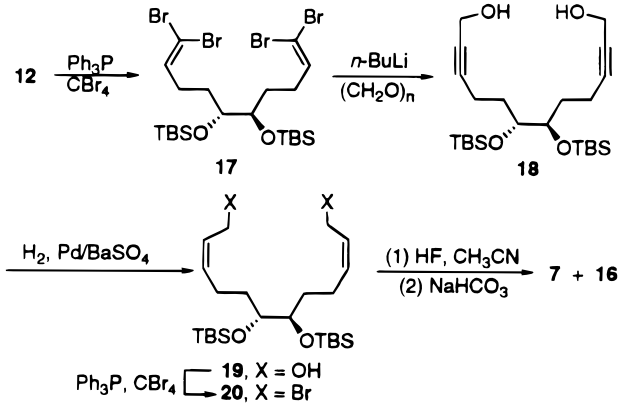
Scheme 2



The commercially available 1,5-cyclooctadiene (**9**) served as the starting material for this synthesis, and the two double bonds in this compound have proved the possibility of partial oxidation.[8] Treatment of **9** with 1 equiv of *m*-chloroperoxybenzoic acid (mCPBA) provided a monoepoxide which was subjected to an aqueous LiOH solution at 100 °C to produce the *trans*-diol **10** in 74% overall yield. Protection of the hydroxyl groups with TBSCl and ozonolysis[9] of the remaining double bond provided the corresponding dialdehyde **12**. Reaction of the dialdehyde with a readily available Wittig reagent in THF at 40 °C gave the *E*-alkene (**13**) exclusively. Compound **13** was reduced with DIBAL in CH_2Cl_2 at −78 °C to produce trans allylic diol **14**, which was treated with Ph_3P and CBr_4 in diethyl ether to brominate the hydroxyl groups. The double S_N' *O*-cyclization was first attempted by treating compound **15** with HF to deprotect the silyl groups[10] followed by subsequent treatment with base. Using this scheme, a mixture of two bistetrahydrofurans (**7**:**16** = 2:1) was obtained in 69% yield. Another possible diastereoisomer (cis, cis) was not detected.

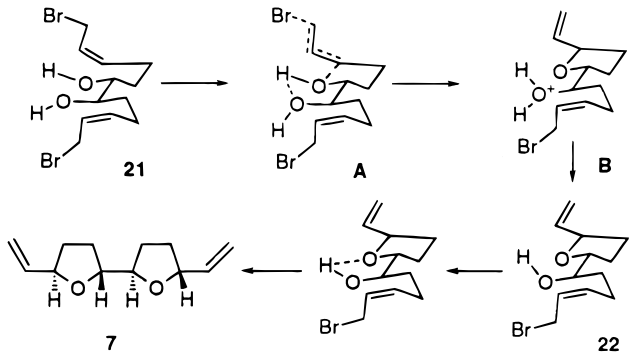
S_N' Cyclization of *Z*-Olefins. Scheme 3 illustrates an alternative approach to bistetrahydrofuran **7** by using *Z*-olefin **20**. Following the procedure described by Marshall,[11] the *Z*-olefin **20** was obtained from the dialdehyde **12** in four steps. Treatment of dialdehyde **12** with Ph_3P and CBr_4 in methylene chloride gave a tetrabromide

Scheme 3



derivative **17** in excellent yield (96%). This tetrabromide was then converted to a propargyl alcohol derivative **18** in 90% yield by reaction with *n*-BuLi and formaldehyde at −78 °C in anhydrous THF. Hydrogenation with Lindlar's catalyst[12] in ethyl acetate gave exclusively *Z*-allylic alcohol **19**, which was converted to the *Z*-allylic dibromide **20** by reaction with Ph_3P and CBr_4 in anhydrous diethyl ether in 77% yield from **18**. The key S_N' *O*-cyclization was carried out following the same conditions as described in Scheme 2. Under these conditions, the desired *trans*,*trans*-bistetrahydrofuran derivative **7** was obtained in 88% yield together with 7% of the *cis*,*trans*-isomer **16**. Although it is unclear why a good selectivity (12.6:1) was observed by using *Z*-olefin, a rigid transition state could result from hydrogen bonding between the two hydroxyl groups under the nonbasic conditions. The transition state for this cyclization can be imagined as chelated structures (**A**−**B**) (Scheme 4).

Scheme 4



Hydrogen bonding between the two OH groups provided five-membered-ring systems **A**−**B**, where nucleophilic attack of the oxygen atoms to the double bonds forms rigid cyclic transition states resulting in the stereoselective S_N' cyclization product. To confirm this hypothesis, a solution of **21** in THF was heated at 50 °C with no base present and the monocyclized product **22**[13] was isolated in high selectivity (>20:1).

Enantioselective Synthesis of 7. Based on this strategy, we have designed a route to the enantioselective

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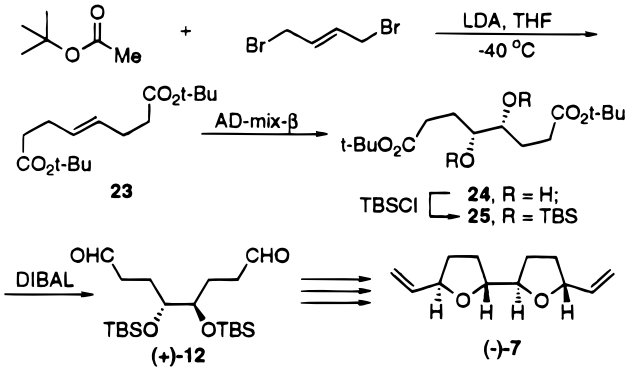
(13) ^{1}H NMR (200 MHz, $CDCl_3$) for the monocyclized intermediate **22**: δ 5.71 (3H, m), 5.16 (2H, m), 4.36 (1H, dt, J = 7.1, 6.8 Hz), 4.01 (2H, d, J = 8.0 Hz), 3.88 (1H, m), 3.39 (1H, m), 2.71 (1H, br), 2.30 (2H, dt, J = 7.4, 7.1 Hz), 2.04 (2H, m), 1.60 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.2, 135.5, 126.5, 115.9, 82.9, 80.7, 73.7, 33.4, 33.2, 29.0, 27.9, 23.7.

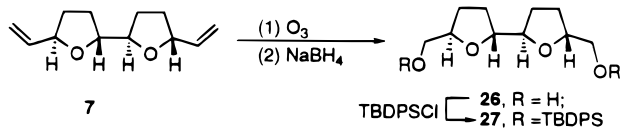
Scheme 5



synthesis of **7** as described in Scheme 5. Double alkylation of *tert*-butyl acetate with (*E*)-1,4-dibromo-2-butene under LDA conditions afforded a diester **23** in 74% yield.[14] Sharpless asymmetric dihydroxylation[15] with AD-mix-β in *t*-BuOH and H_2O introduced the (*R*,*R*)-dihydroxyl groups on the *E*-olefin with 89% yield and high enantiomeric excess (ee > 98%).[16] Protection of the diol with TBS followed by DIBAL reduction provided the optically active dialdehyde **12** in 40% overall yield. Following the procedures described in Scheme 3, we successfully isolated the enantiomeric pure isomer **7**.

The relative stereochemistry of compound **7** was established by comparison to a known compound **27** (Scheme 6) which was reported by Koert's group.[7b]

Scheme 6



Ozonolysis[9] of **7** gave a dialdehyde which was transformed to alcohol **26** by reduction with sodium borohydride. TBDPS protection of the dihydroxyl groups on **26** provided **27**. The ^{1}H and ^{13}C NMR data we obtained matched the reported data.

Conclusion

We have developed a convenient synthesis of the C_2-symmetric bistetrahydrofuran core of acetogenins via our previously reported S_N' *O*-cyclization strategy. The requisite starting materials for the desired cyclization reactions can be easily prepared in both racemic and enantiomerically pure forms. The double S_N' intramolecular cyclization products were achieved with high stereoselectivity. The newly formed terminal double bonds can serve as functional groups for the stepwise elaboration to secondary hydroxyl derivatives.[17]

Experimental Section[18]

1,2-*trans*-Dihydroxy-5-cyclooctene (10). To a solution of 1,5-cyclooctadiene (**9**) (20 g, 185 mmol) in methylene chloride (600 mL) was slowly added 3-chloroperoxybenzoic acid (mCPBA) (70%, 46 g, 186 mmol) at 10 °C. The reaction mixture was stirred at room temperature overnight, washed with aqueous $NaHCO_3$ (200 mL) and 10% NaOH (200 mL), and evaporated under reduced pressure. The crude product was obtained and used in the next step without further purification.

To the solution of the resulting monoepoxide (17 g, 137 mmol) in water (450 mL) was added $LiOH\cdot H_2O$ (17 g, 405 mmol) at room temperature. The reaction mixture was refluxed for 14 h, cooled to room temperature, and extracted with ethyl acetate (4 × 250 mL). The combined organic layers were dried over $MgSO_4$. Following evaporation under reduced pressure the crude product was purified by flash silica gel chromatography (eluting with 50−90% ethyl acetate in petroleum ether) to give pure 1,2-*trans*-dihydroxy-5-cyclooctene (**10**) (19 g, 135 mmol, 74% overall) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.58 (2 × 1H, m), 3.64 (2 × 1H, m), 3.19 (2 × 1H, br), 2.33 (2 × 1H, m), 2.10 (2 × 2H, m), 1.57 (2 × 1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 129.6, 74.3, 34.0, 23.3. MS: *m*/*e* (relative intensity), 142 (3.7, M^+), 124 (2.9), 114 (9.2), 96 (22), 81 (41), 54 (94), 39 (100). Anal. Calcd for $C_8H_{14}O_2\cdot 0.2H_2O$: C, 65.90; H, 9.95. Found: C, 65.64; H, 9.61.

***trans*-1,2-Bis(*tert*-butyldimethylsilyl)oxy-5-cyclooctene (11).** To a solution of *trans*-1,2-dihydroxy-5-cyclooctene (**10**) (13.0 g, 91.4 mmol) in anhydrous DMF (150 mL) was added *tert*-butyldimethylsilyl chloride (TBSCl) (41.0 g, 272.1 mmol) at 0 °C followed by addition of imidazole (37.0 g, 543.3 mmol). The reaction mixture was stirred at 0 °C for 4 h and maintained at room temperature overnight. The product was extracted with diethyl ether (3 × 100 mL), and the combined extracts were washed with water (3 × 100 mL) and dried over $MgSO_4$. After removal of solvents under reduced pressure, the crude *trans*-1,2-bis(*tert*-butyldimethylsilyl)oxy-5-cyclooctene (**11**) was purified by silica gel flash column chromatography (eluting with pure petroleum ether) (33.5 g, 90.4 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.60 (2 × 1H, m), 3.92 (2 × 1H, m), 2.32 (2 × 1H, m), 2.08 (2 × 2H, m), 1.64 (2 × 1H, m), 0.90 (2 × 9H, s), 0.048 (2 × 3H, s), 0.027 (2 × 3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 130.3, 74.4, 33.8, 26.5, 22.7, 18.7, −3.97, −4.17. MS: *m*/*e* (relative intensity), 370 (0.004, M^+), 313 (1.2), 181 (4), 147 (45), 73 (100). Anal. Calcd for $C_{20}H_{42}O_2Si_2$: C, 64.80; H, 11.42. Found: C, 64.84; H, 11.47.

4,5-Bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde (12). A solution of 1,2-bis(*tert*-butyldimethylsilyl)oxy-5-cyclooctene (**11**) (4.4 g, 11.9 mmol) in methanol (50 mL) and methylene chloride (50 mL) was ozonized at −78 °C. After 40 min, the solution turned blue to indicate the completed ozonolysis (excess ozone was removed by bubbling argon into the solution). To this mixture was added triphenyl phosphine (5.0 g, 19.1 mmol), and the mixture was stirred at room temperature for 5 h. After removal of solvents by evaporation, the residue was dissolved in pure petroleum ether to filter off the byproduct triphenylphosphine oxide. The filtrate was evaporated, and the crude product was purified by flash silica gel chromatography (eluting with 10% ethyl acetate in petroleum ether) to give 4,5-bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde (**12**) (4.5 g, 11.2 mmol, 94%) as a white solid, mp 58−60 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.77 (2 × 1H, t, J = 1.6 Hz), 3.61 (2 × 1H, m), 2.48 (2 × 2H, m), 2.00 (2 × 1H, m), 1.65 (2 × 1H, m), 0.88 (2 × 9H, s), 0.05 (2 × 6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 202.6, 74.7, 41.6, 26.4, 23.3, 18.5, −3.46, −4.09.

Diethyl 6,7-Bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadienedioate (13). To a solution of 4,5-bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde (**12**) (14 g, 34.8 mmol) in dry THF (170 mL) was added carbethoxymethylene triphenylphosphorane ($Ph_3P{=}CHCOOEt$) (30 g, 86.2 mmol). The mixture

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was stirred at 40 °C for 6 h. After removal of solvents by evaporation, the residue was dissolved in pure petroleum ether to filter off the byproduct triphenylphosphine oxide. The filtrate was evaporated, and the crude product was purified by flash silica gel chromatography (eluting with 5% ethyl acetate in petroleum ether) to give diethyl 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadienedioate (**13**) (17.4 g, 32.1 mmol, 92%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.97 (2 × 1H, dt, J = 15.8, 7.0 Hz), 5.82 (2 × 1H, d, J = 15.7 Hz), 4.19 (2 × 2H, q, J = 7.2 Hz), 3.56 (2 × 1H, m), 2.37 (2 × 1H, m), 2.13 (2 × 1H, m), 1.79 (2 × 1H, m), 1.45 (2 × 1H, m), 1.29 (2 × 3H, t, J = 7.1 Hz), 0.88 (2 × 9H, s), 0.055 (2 × 3H, s), 0.045 (2 × 3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.9, 149.4, 121.9, 75.0, 60.6, 29.8, 29.3, 26.4, 18.6, 14.9, −3.39, −3.97. HRMS: calcd, for $C_{28}H_{55}O_6Si_2$ (MH^+) 543.3537; found, 543.3549.

6,7-Bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadiene-1,12-diol (14). To a solution of diethyl 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadienedioate (**13**) (17 g, 31 mmol) in dry methylene chloride (160 mL) was added dropwise a solution of DIBAL-H in cyclohexane (1.0 M, 180 mL, 180 mmol) at −78 °C. The reaction mixture was stirred for 3 h and then quenched with 10% NaOH solution (100 mL). After stirring at room temperature for 40 min, the mixture was extracted with methylene chloride (3 × 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was subjected to silica gel flash column chromatography (eluting with 70% ethyl acetate in petroleum ether) to give 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadiene-1,12-diol (**14**) (11 g, 24 mmol, 78%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.67 (2 × 2H, m), 4.08 (2 × 2H, d, J = 4.4 Hz), 3.54 (2 × 1H, m), 2.20 (2 × 1H, m), 1.98 (2 × 1H, m), 1.71 (2 × 1H, m), 1.39 (2 × 1H, m), 1.34 (2 × 1H, bs), 0.89 (2 × 9H, s), 0.056 (2 × 3H, s), 0.041 (2 × 3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.9, 129.5, 75.2, 64.4, 30.4, 29.8, 26.4, 18.6, −3.38, −3.88. HRMS: calcd, for $C_{24}H_{51}O_4Si_2$ (MH^+) 459.3326; found, 459.3337. Anal. Calcd for $C_{24}H_{50}O_4Si_2 \cdot 0.2H_2O$: C, 62.34; H, 10.99. Found: C, 62.39; H, 11.03.

6,7-Bis(*tert*-butyldimethylsilyl)oxy-1,12-dibromo-2(*E*),10(*E*)-dodecadiene (15). To a solution of 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*E*),10(*E*)-dodecadiene-1,12-diol (**14**) (6.5 g, 14.2 mmol) in anhydrous diethyl ether (140 mL) was added triphenyl phosphine (15 g, 57.2 mmol) in one portion. The reaction mixture was stirred for 10 min until all the PPh_3 was dissolved. Carbon tetrabromide (19.0 g, 57.3 mmol) was then added. After stirring at room temperature for 6 h, the precipitate was filtered off through Celite. The filtrate was concentrated under reduced pressure. The crude residue was subjected to silica gel flash column chromatography (eluting with 1% ethyl acetate in petroleum ether) to give 6,7-bis(*tert*-butyldimethylsilyl)oxy-1,12-dibromo-2(*E*),10(*E*)-dodecadiene (**15**) (7.4 g, 12.6 mmol, 89%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74 (2 × 2H, m), 3.95 (2 × 2H, d, J = 6.4 Hz), 3.54 (2 × 1H, m), 2.23 (2 × 1H, m), 2.01 (2 × 1H, m), 1.71 (2 × 1H, m), 1.41 (2 × 1H, m), 0.89 (2 × 9H, s), 0.061 (2 × 3H, s), 0.051 (2 × 3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.0, 126.9, 75.0, 33.9, 30.0, 29.6, 26.5, 18.6, −3.34, −3.85. HRMS: calcd, for $C_{24}H_{47}Br_2O_2Si_2$ ($M^+ - H$) 581.1481; found, 581.1490. Anal. Calcd for $C_{24}H_{48}Br_2O_2Si_2$: C, 49.31; H, 8.28; Br, 27.34. Found: C, 49.29; H, 8.27; Br, 27.32.

3,6:7,10-Diepoxy-1,11-dodecadiene (7 and 16). To a solution of 6,7-bis(*tert*-butyldimethylsilyl)oxy-1,12-dibromo-2(*E*),10(*E*)-dodecadiene (**15**) (4 g, 6.8 mmol) in acetonitrile (68 mL) was added HF (48%, 1.2 mL, 33 mmol). The mixture was stirred at room temperature for 2 h. Excess HF was removed by aspirator, and the mixture was heated at 50 °C overnight to complete the monocyclization. Following addition of $NaHCO_3$, the mixture was stirred at room temperature for 2 h and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue (**7**:**16** = 2:1 by GC/MS) was subjected to silica gel flash column chromatography (eluting with 10% ethyl acetate in petroleum ether) to give 3,6:7,10-diepoxy-1,11-dodecadiene (**7** + **16**) (820 mg, 3.2 mmol, 69%) as a colorless oil. For minor product **16**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.85 (2H, m), 5.13 (4H, m), 4.42 (1H, m), 4.32 (1H, m), 3.97 (1H, m), 3.88 (1H, m), 2.18−1.60 (8H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.8, 139.7, 115.6, 115.4, 82.5, 82.4, 81.9, 81.3, 33.1, 32.4, 29.0, 28.4. For major product **7**, ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.84 (2 × 1H, ddd, J = 6.4, 10.2, 17.0 Hz), 5.19 (2 × 1H, dt, J = 1.6, 17.0 Hz), 5.05 (2 × 1H, dt, J = 1.6, 10.3 Hz), 4.23 (2 × 1H, m), 3.98 (2 × 1H, m), 2.05 (2 × 2H, m), 1.68 (2 × 2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.8, 115.5, 82.0, 81.0, 33.1, 29.0. HRMS: calcd, for $C_{12}H_{18}O_2$ 194.1306; found, 194.1304.

5,6-Bis(*tert*-butyldimethylsilyl)oxy-1,1,10,10-tetrabromo-1,9-decadiene (17). To a solution of triphenyl phosphine (23.4 g, 89.2 mmol) in anhydrous methylene chloride (60 mL) was added CBr_4 (15.0 g, 45.2 mmol) in portions at 0 °C over 20 min. The reaction mixture was stirred at room temperature for 30 min, cooled to 0 °C, and added to a solution of 4,5-bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde (**12**) (4.5 g, 11.2 mmol) in methylene chloride (5 mL). After stirring at room temperature overnight, most of the solvent was removed by evaporation. Petroleum ether (60 mL) was added to precipitate out the byproducts, which were filtered off through Celite. The filtrate was concentrated under reduced pressure. The crude residue was subjected to silica gel flash column chromatography (eluting with petroleum ether) to give 5,6-bis(*tert*-butyldimethylsilyl)oxy-1,1,10,10-tetrabromo-1,9-decadiene (**17**) (7.7 g, 10.8 mmol, 96%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.41 (2 × 1H, t, J = 7.2 Hz), 3.54 (2 × 1H, m), 2.23 (2 × 1H, m), 2.03 (2 × 1H, m), 1.75 (2 × 1H, m), 1.37 (2 × 1H, m), 0.90 (2 × 9H, s), 0.08 (2 × 3H, s), 0.07 (2 × 3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.0, 89.5, 75.2, 31.0, 29.0, 26.4, 18.6, −3.37, −3.99.

6,7-Bis(*tert*-butyldimethylsilyl)oxy-2,10-dodecadiyne-1,12-diol (18). To a solution of 5,6-bis(*tert*-butyldimethylsilyl)-oxy-1,1,10,10-tetrabromo-1,9-decadiene (**17**) (7.7 g, 10.8 mmol) in anhydrous THF (110 mL) was slowly added a solution of *n*-BuLi in hexanes (1.4 M, 32 mL, 44.8 mmol) at −78 °C. After stirring for 1 h, the solution was allowed to warm to room temperature over 35 min and then cooled to −78 °C, at which time, dry paraformaldehyde (1.3 g, 43.3 mmol) was added. The mixture was warmed to room temperature gradually over 1 h, stirred overnight, and quenched with aqueous NH_4Cl solution (100 mL). After extraction by ethyl acetate (3 × 100 mL), the combined extracts were dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel (eluting with 6% ethyl acetate in petroleum ether) gave 6,7-bis(*tert*-butyldimethylsilyl)oxy-2,10-dodecadiyne-1,12-diol (**18**) (4.4 g, 9.7 mmol, 90%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.23 (2 × 2H, t, J = 2.1 Hz), 3.76 (2 × 1H, m), 2.28 (2 × 2H, m), 1.85 (2 × 1H, m), 1.54 (2 × 1H, br), 1.45 (2 × 1H, m), 0.90 (2 × 9H, s), 0.09 (2 × 6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 86.9, 79.3, 73.7, 51.9, 29.5, 26.4, 18.6, 16.2, −3.47, −4.08.

6,7-Bis(*tert*-butyldimethylsilyl)oxy-2(*Z*),10(*Z*)-dodecadiene-1,12-diol (19). A solution of 6,7-bis(*tert*-butyldimethylsilyl)oxy-2,10-dodecadiyne-1,12-diol (**18**) (2.0 g, 4.4 mmol) in a flask with ethyl acetate (22 mL), quinoline (0.5 mL, 4.2 mmol), and Lindlar's catalyst (200 mg, 10% w/w) was stirred under an atmosphere of H_2. After consumption of 1 molar equiv of H_2 the mixture was filtered through Celite to remove the catalyst. The filtrate was evaporated and purified by silica gel flash column chromatography (eluting with 15% ethyl acetate in petroleum ether) to give 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*Z*),10(*Z*)-dodecadiene-1,12-diol (**19**) (2.0 g, 4.3 mmol, 99%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.55 (2 × 2H, m), 4.18 (2 × 2H, d, J = 5.2 Hz), 3.54 (2 × 1H, m), 2.22 (2 × 1H, m), 1.97 (2 × 1H, m), 1.77 (2 × 1H, br), 1.65 (2 × 1H, m), 1.32 (2 × 1H, m), 0.88 (2 × 9H, s), 0.05 (2 × 6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.1, 129.2, 75.4, 59.1, 31.1, 26.4, 25.3, 18.6, −3.40, −3.95. Anal. Calcd for $C_{24}H_{50}O_4Si_2 \cdot 0.2H_2O$: C, 62.34; H, 10.99. Found: C, 62.33; H, 11.08.

6,7-Bis(*tert*-butyldimethylsilyl)oxy-1,12-dibromo-2(*Z*),10(*Z*)-dodecadiene (20). To a solution of 6,7-bis(*tert*-butyldimethylsilyl)oxy-2(*Z*),10(*Z*)-dodecadiene-1,12-diol (**19**) (2.0 g, 4.3 mmol) in anhydrous diethyl ether (50 mL) was added

triphenyl phosphine (4.6 g, 17.5 mmol) in one portion. The reaction mixture was stirred for 10 min until all the PPh_3 was dissolved. Carbon tetrabromide (5.8 g, 17.5 mmol) was then added. After stirring at room temperature for 6 h, the precipitate was filtered off through Celite. The filtrate was concentrated under reduced pressure. The crude residue was subjected to silica gel flash column chromatography (eluting with 2% ethyl acetate in petroleum ether) to give 6,7-bis(*tert*-butyldimethylsilyl)oxy-1,12-dibromo-2(*Z*),10(*Z*)-dodecadiene (**20**) (2.0 g, 3.4 mmol, 79%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.67 (2 × 2H, m), 3.98 (2 × 2H, d, J = 7.7 Hz), 3.58 (2 × 1H, m), 2.30 (2 × 1H, m), 2.05 (2 × 1H, m), 1.71 (2 × 1H, m), 1.40 (2 × 1H, m), 0.90 (2 × 9H, s), 0.07 (2 × 6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.2, 125.9, 75.4, 30.5, 27.6, 26.5, 24.8, 18.6, −3.32, −3.90. HRMS: calcd for $C_{24}H_{47}Br_2O_2Si_2$ (M^+ − H) 581.1481; found, 581.1465. Anal. Calcd for $C_{24}H_{48}Br_2O_2Si_2$: C, 49.31; H, 8.28; Br, 27.34. Found: C, 49.38; H, 8.33; Br, 27.28.

Di-*tert*-butyl *trans*-4-Octenedioate (23). To a solution of diisopropylamine (6.6 mL, 47 mmol) in anhydrous THF at −78 °C (80 mL) was slowly added a solution of *n*-butyllithium in hexanes (1.4 M, 32 mL, 45 mmol), and the mixture was stirred for 40 min. To the above mixture was added *tert*-butyl acetate (5.8 mL, 43 mmol), and the reaction mixture was stirred for another 40 min. After HMPA (8.2 mL, 47 mmol) was added, the reaction was warmed to −60 °C and a solution of *trans*-1,4-dibromo-2-butene (5.5 g, 26 mmol) in THF (20 mL) was added. The resulting mixture was stirred at −40 °C for 1 h, quenched with 2 N HCl solution, and extracted with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of all the solvents under reduced pressure gave crude di-*tert*-butyl *trans*-4-octenedioate (**23**) (4.5 g, 16 mmol, 74%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.42 (2 × 1H, br), 2.22 (2 × 4H, s), 1.41 (2 × 9H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 129.8, 80.6, 36.0, 28.7, 28.6.

Di-*tert*-butyl 4(*R*),5(*R*)-Dihydroxyoctanedioate (24). To a solution of di-*tert*-butyl *trans*-4-octenedioate (**23**) (4.4 g, 15.5 mmol) in *tert*-butyl alcohol (75 mL) and water (75 mL) was added AD-mix-β (32 g, 22.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and maintained at room temperature overnight. After workup with $NaHCO_3$ and ethyl acetate, the combined solvents were removed under reduced pressure. The crude di-*tert*-butyl 4(*R*),5(*R*)-dihydroxyoctanedioate (**24**) was purified by silica gel flash column chromatography (4.4 g, 13.8 mmol, 89%, ee > 98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.40 (2 × 1H, m), 3.01 (2 × 1H, d, J = 5.0 Hz), 2.40 (2 × 2H, t, J = 7.2 Hz), 1.77 (2 × 2H, m), 1.43 (2 × 9H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.1, 81.1, 74.3, 32.5, 29.2, 28.7.

Di-*tert*-butyl 4(*R*),5(*R*)-Bis(*tert*-butyldimethylsilyl)oxyoctanedioate (25). Di-*tert*-butyl 4(*R*),5(*R*)-bis(*tert*-butyldimethylsilyl)oxyoctanedioate (**25**) was prepared (75% yield) from di-*tert*-butyl 4(*R*),5(*R*)-dihydroxyoctane dioate (**24**) according to the similar procedures as described for the preparation of compound **11**, white solid, mp 101−103 °C. $[\alpha]^{25}_D$ = +64.9° (c = 1.1, ethanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.55 (2 × 1H, m), 2.37−1.82 (2 × 3H, m), 1.55 (2 × 1H, m), 1.40 (2 × 9H, s), 0.86 (2 × 9H, s), 0.027 (2 × 6H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3, 80.3, 74.8, 33.1, 28.7, 26.4, 18.5, −3.53, −4.10.

4(*R*),5(*R*)-Bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde [(+)-12]. To a solution of di-*tert*-butyl 4(*R*),5(*R*)-bis(*tert*-butyldimethylsilyl)oxyoctanedioate (**25**) (4.9 g, 9.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added DIBAL (1.0 M, 27 mL, 27.0 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, quenched with aqueous NaOH solution, and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over $MgSO_4$. After removal of solvents under reduced pressure, the crude 4(*R*),5(*R*)-bis(*tert*-butyldimethylsilyl)oxyoctadialdehyde [**(+)-12**] was purified by silica gel flash column chromatography (52%), white solid, mp 58−60 °C.

3(*R*),6(*R*):7(*R*),10(*R*)-Diepoxy-1,11-dodecadiene [(−)-7]: $[\alpha]^{25}_D$ = − 22.9° (c = 2.0, CH_2Cl_2).

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Supporting Information Available: A synthetic procedure for compound **27** and 300 MHz ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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