An Efficient Bidirectional Approach to the C_2-Symmetric Stereoisomers of the Bistetrahydrofuran Core of the Acetogenins

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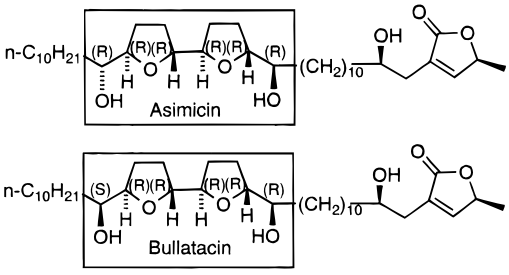
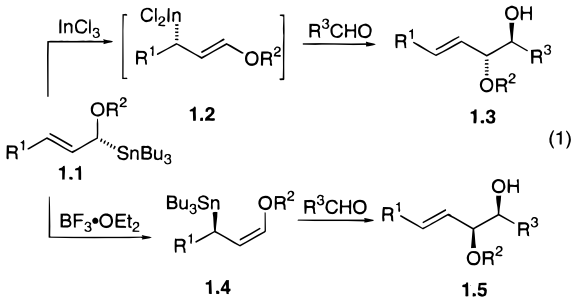
A bidirectional route to nonracemic C_2-symmetric bistetrahydrofuran units related to acetogenin natural products was developed starting from the (*S*,*S*)-tartrate-derived dialdehyde **3.3**. Bis-homologation with the (*R*)-α-OMOM crotylstannane (*R*)-**4.1** in the presence of $InCl_3$ afforded the *anti* adduct, diol **4.3**. The derived tosylate **4.4**, upon treatment with TBAF in THF, underwent sequential TBS cleavage and cyclization to the (*R*,*R*,*R*,*R*,*R*,*R*)-bis-OMOM bistetrahydrofuran **4.7**. The epimeric (*S*,*R*,*R*,*R*,*R*,*S*)-bis-OMOM bistetrahydrofuran **4.10** was prepared along similar lines, except that the (*R*)-α-OMOM crotylstannane (*R*)-**4.1** was first converted to the (*R*)-γ-isomer (*R*)-**4.2** with BF_3·OEt_2. Subsequent addition of dialdehyde **3.3** led to the diol adduct **4.5**, which after tosylation and treatment with TBAF, yielded the bistetrahydrofuran **4.10**. By repeating the aforementioned sequences, but starting with the (*S*)-α-OMOM-crotylstannane (*S*)-**4.1**, the (*S*,*S*-,*R*,*R*,*S*,*S*)- and the (*R*,*S*,*R*,*R*,*S*,*R*)-bistetrahydrofurans **5.5** and **5.8** were prepared. A variation on the foregoing sequence in which the OTBS grouping of the adduct was converted to a mesylate and the OH group was used to effect intramolecular displacement was also examined. Accordingly, adduct *ent*-**5.3** from BF_3-promoted addition of stannane (*R*)-**4.2** and *ent*-**3.3**, the enantiomer of aldehyde **3.3**, was acetylated. Cleavage of the TBS ether followed by mesylate formation and then concommitant acetate hydrolysis and cyclization with methanolic Triton B yielded the bis-OMOM bistetrahydrofuran **5.5**. An analogous sequence was used to convert adduct **4.3** to *ent*-**4.10**. In this case, acetate saponification was effected with methanolic K_2CO_3, and the resulting diol, **7.4**, was cyclized with NaH in THF.

In recent years, increasing attention has been directed toward acetogenins of the Annonacae family.[1] Numbering roughly 100 members, this large family of fatty-acid related natural products shows a range of potentially useful biological activities. Most contain one or more 2,5-disubstituted tetrahydrofuran rings as a central core unit. Asimicin and bullatacin exemplify a subgroup in which the central core is comprised of a 2,2′-linked 5,5′-bis(hydroxyalkyl)bistetrahydrofuran moiety. Several stereoisomeric variants of this core unit are known.



While considerable progress has been made in the design of synthetic routes to bistetrahydrofuran prototypes, and the natural products themselves, general and efficient schemes leading to core stereoisomers have only recently been explored.[2] It is of interest to access such isomers in order to evaluate structure−activity relationships with a view toward finding analogues with enhanced biological activity. In this connection, we have developed straightforward, direct bidirectional routes[3] to prototypes of the eight C_2-symmetric bistetrahydrofuran core units.

Our approach is based on recent findings that chiral nonracemic α-alkoxy allylic stannanes **1.1** undergo 1,3-isomerization or transmetalation and subsequent S_E2' addition to aldehydes leading to either *syn* or *anti* monoprotected 1,2-diols stereospecifically and with high diastereoselectivity (eq 1).[4]



(1)

We envisioned the use of a protected γ-hydroxy aldehyde **2.1** as the substrate for these additions. The differentially protected triol adducts **2.2** could then be converted to the tetrahydrofuran products **2.3** and **2.4**, after conversion of the OH or OR to a suitable leaving group, followed by base-initiated cyclization and hydro-

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(1) *Cf.* Zhao, G.-X.; Gu, Z.-M.; Zeng, L.; Chao, J.-F.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron* **1995**, *51*, 7149 and references cited therein. Wu, Y.-C.; Chang, F.-R.; Chen, K.-S.; Liang, S.-C.; Lee, M.-R. *Heterocycles* **1994**, *38*, 1475. Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447.

(2) *Cf.* Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. Sinha, S. C.; Sinha-Bagehi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, 36, 9257.

(3) *Cf.* Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

(4) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920.

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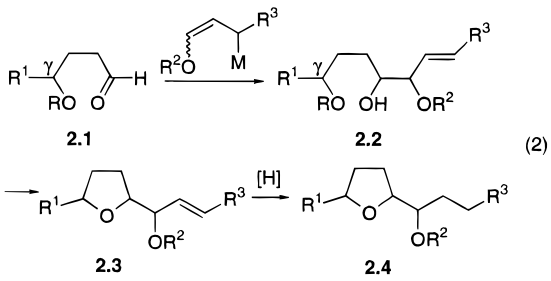
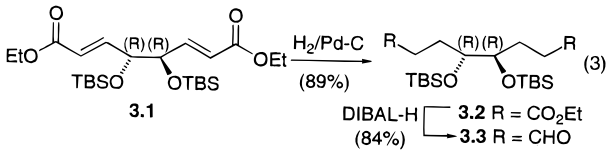
genation.[5] For these initial studies we elected to pursue a bidirectional approach[3] to various C_2-symmetric prototypes structures in order to establish the overall feasibility of the methodology and uncover possible limitations.



(2)

An appropriate dialdehyde, **3.3**, was prepared from the (*S*,*S*)-diethyl tartrate-derived diester **3.1**[6] through catalytic hydrogenation and subsequent reduction with DIBAL-H (eq 3).

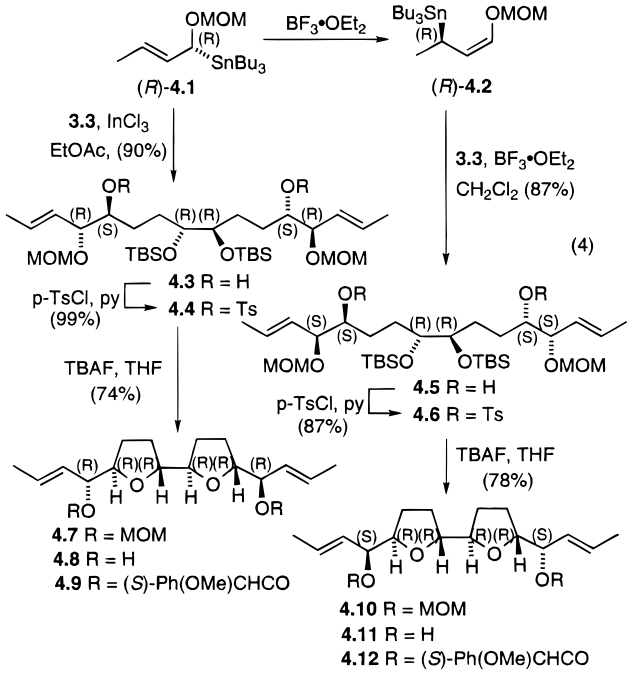


(3)

Treatment of the known α-OMOM-crotyl stannane (*R*)-**4.1**[7] with dialdehyde **3.3** in the presence of $InCl_3$ led to the bis-*anti* adduct **4.3** and a small amount (*ca.* 5%) of diastereomers in 90% yield. Presumably, this addition involves an *in situ* transmetalation of stannane (*R*)-**4.1** to the γ-OMOM indium reagent as depicted in eq 1.[4] Diastereomeric byproducts are presumed to arise from the small amount of enantiomeric stannane present in (*R*)-**4.1** (<5%), from minor amounts of epimerized (*meso*) diester **3.1** (0−5%), and from a small amount of *syn* adduct (<10% based on previous studies[4]). Treatment of diol **4.3** with *p*-TsCl in pyridine afforded the ditosylate **4.4** which yielded the (*R*,*R*,*R*,*R*,*R*,*R*)-bisfuran **4.7** upon exposure to TBAF in THF at 40 °C.

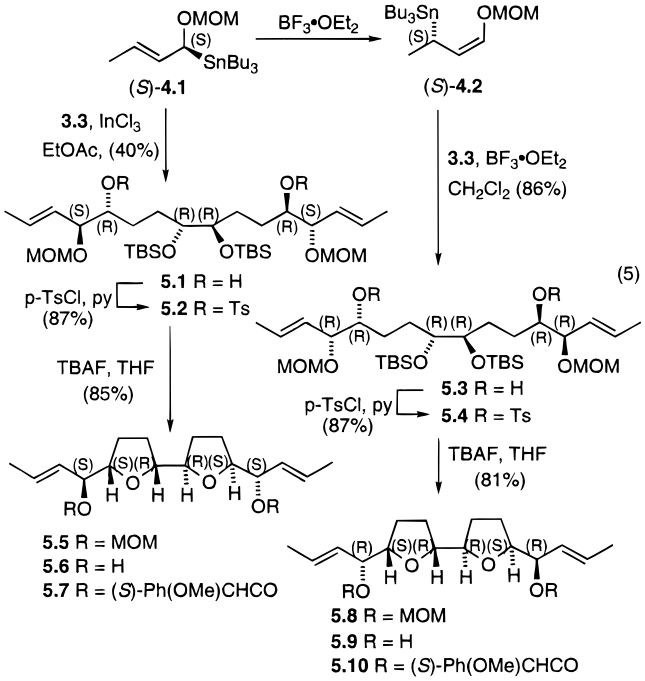
The γ-OMOM allylic stannane (*R*)-**4.2**, obtained by BF_3-catalyzed isomerization of (*R*)-**4.1**,[7] readily added to dialdehyde **3.3** in the presence of $BF_3{\cdot}OEt_2$ to afford the bis-*syn* adduct **4.5** along with *ca.* 10% of inseparable diastereomers in 87% yield. These byproducts are most likely derived as noted above.[8] Sequential treatment with *p*-TsCl in pyridine and TBAF in THF converted diol **4.5** to the (*S*,*R*,*R*,*R*,*R*,*S*)-bisfuran **4.10** in 68% overall yield, after separation from minor diastereomers by chromatography.

Repetition of the foregoing sequences with dialdehyde **3.3** starting from the enantiomeric α-OMOM-crotylstannane (*S*)-**4.1** led to the (*S*,*S*,*R*,*R*,*S*,*S*) and (*R*,*S*,*R*,*R*,*S*,*R*)-bisfurans **5.5** and **5.8**. In the former case, an appreciable amount of the monoadduct (∼50%) was isolated under



(4)

the normal reaction conditions in which the reactants were mixed at −78 °C, and the mixture was allowed to warm to room temperature overnight. However, notable improvement in the yield of diadduct **5.1** was realized when the reaction temperature was held at −20 °C. Presumably because the addition in this case is slow, competing decomposition of the transient allylindium reagent occurs at the more elevated temperatures. The addition did not take place at −78 °C.



(5)

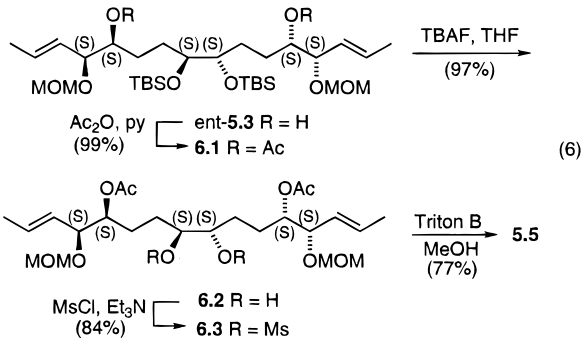
A complementary, albeit less direct, sequence to bisfuran **5.5** was effected as shown in eq 6. Here, the intial bis-*syn* adduct *ent*-**5.3**, from *ent*-**3.3** and stannane (*R*)-**4.2** (BF_3), was acetylated. Subsequent cleavage of the TBS ethers and treatment of the diol **6.2** with MsCl and Et_3N afforded the dimesylate **6.3**. Cleavage of the diacetate with Triton B in methanol led directly to the (*S*,*S*,*R*,*R*,*S*,*S*)-bistetrahydrofuran **5.5** in 77% yield.

(5) For a recent example of such a cyclization, see: Koert, U.; Wagner, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1873.

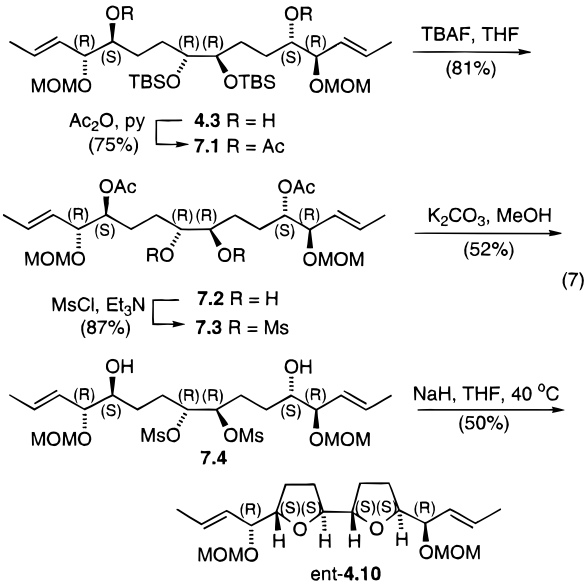
(6) Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T. Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292. Dialdehyde **3.3** was of >90% ee based on comparison of the optical rotation of the precursor **3.1** with the literature value.

(7) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647. The stannanes employed in these studies were of 90−95% ee according to comparison of optical rotations to those of samples whose ee's were determined independently.

(8) For a recent review, see: Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. Analogous BF_3-promoted additions to unbranched aldehydes typically yield *ca.* 95:5 mixtures of *syn* and *anti* adducts.



By a parallel (unoptimized) sequence, adduct **4.3** was converted to bistetrahydrofuran *ent*-**4.10** (eq 7). In this



case, the diacetate intermediate **7.3** was saponified with K_2CO_3 and then subjected to NaH to effect cyclization. The analogous diacetate **6.3** afforded inseparable elimination byproducts upon exposure to K_2CO_3, necessitating the development of the Triton B saponification protocol. Presumably, diacetate **7.3** could likewise be directly converted to bistetrahydrofuran *ent*-**4.10**. However, lack of material and time precluded our examination of this option.

The relative and absolute stereochemistry of adducts **4.3**, **4.5**, **5.1**, and **5.3** can be assigned from a knowledge of the configuration of stannanes (*R*)- and (*S*)-**4.1**, the dialdehyde **3.3**, and the reaction pathway as established by our prior studies.[4,7,8] These assignments were confirmed through conversion of these adducts to the *O*-methylmandelates.[9,10] Additional evidence was secured through ^{1}H NMR analysis of the *O*-methylmandelates **4.9**, **4.12**, **5.7**, and **5.10**.[10]

Although we have not done so, all eight of the C_2-symmetric bistetrahydrofuran prototype systems **4.7**, **4.10**, **5.5**, and **5.8** and their enantiomers should be available by the foregoing methodology from a single set of enantiomeric stannanes and dialdehydes. Application to the natural acetogenins would be most efficiently approached through mono reduction of diester **3.2** and addition of an appropriate long-chain allylic stannane, ester reduction, and addition of a second allylic stannane. Preliminary efforts along these lines have demonstrated the feasibility of such an approach.

Experimental Section[11]

General Procedure for $InCl_3$-Promoted Additions. One mol equiv (relative to aldehyde) of $InCl_3$ in enough EtOAc to make a 0.04 M solution was placed in a sonication bath at rt for 15 min to dissolve the $InCl_3$. The solution was removed from the bath, and the aldehyde was added with stirring. The solution was cooled to −78 °C followed by addition of the allylic stannane reagent (1.5 equiv). The reaction was allowed to slowly warm to rt as its progress was monitored by TLC. When the aldehyde was no longer present the reaction was quenched with cold 1 M HCl and extracted with ether. The organic extracts were dried over $MgSO_4$, and Et_3N (approximately 2 equivs)was added to remove tin byproducts. The solvent was distilled under reduced pressure and the product purified by column chromatography on silica gel with 35% EtOAc−hexanes as eluant.

General Procedure for BF_3·Et_2O-Promoted Additions. To 1.5 mol equiv (relative to aldehyde) of 0.04 M allylic stannane **3.1** in CH_2Cl_2 at −78 °C was added an equimolar quantity of BF_3·Et_2O. The solution was stirred for 1 h at −78 °C, and the aldehyde was then added as a 0.20 M solution in CH_2Cl_2. The progress of the reaction was monitored by TLC. When the aldehyde was no longer present the reaction was quenched at −78 °C with saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, and Et_3N (approximatley 2 equiv)was added to remove tin byproducts. The solvent was distilled under reduced pressure and the product purified by column chromatography on silica gel with 35% EtOAc−hexanes as eluant.

Diethyl (4*R*,5*R*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)-octanedioate (3.2) and Diethyl (4*S*,5*S*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)octanedioate (*ent*-3.2). To a solution of 2.8 g (5.7 mmol) of diene diester **3.1**[6] in 20 mL of EtOAc was added 0.60 g (0.57 mmol) of 10% palladium on carbon. The mixture was stirred under 1 atm of H_2 (balloon) for 12 h and then filtered through a pad of Celite with the aid of CH_2Cl_2. The solvent was removed under reduced pressure and the product purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant to afford 2.5 g (89%) of diester **3.2**: $[\alpha]_D$ 44.6 (*c* 1.7, CH_2Cl_2); IR (film), 1739 cm^{-1}; ^{1}H NMR δ 4.10 (dq, J = 7.3, 2.7 Hz, 4H), 3.62 (bd, J = 9.7 Hz, 2H), 2.49−2.38 (m, 2H), 2.30−2.19 (m, 2H), 2.02−1.92 (m, 2H), 1.67−1.57 (m, 2H), 1.25 (t, J = 7.3, 6H), 0.89 (s, 18H), 0.05 (s, 6H), 0.05 (s, 6H); ^{13}C NMR δ −4.8, −4.2, 14.2, 17.9, 25.5, 25.7, 31.3, 60.2, 74.1, 173.6. Anal. Calcd for $C_{24}H_{50}O_6Si_2$: C, 58.73; H, 10.27. Found: C, 58.83; H, 10.21.

The above procedure was employed with 2.28 g (4.6 mmol) of diene diester *ent*-**3.1** in 25 mL of EtOAc and 0.50 g (0.47 mmol) of 10% palladium on carbon. After 12 h the reaction was processed as described to afford 2.13 g (92%) of *ent*-**3.2**: $[\alpha]_D$ −42.7 (*c* 1.3, CH_2Cl_2).

(4*R*,5*R*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)octanedial (3.3) and (4*S*,5*S*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)octanedial (*ent*-3.3). To a solution of 0.52 g (1.0 mmol) of diester **3.2** in 20 mL of toluene at −78 °C was added 1.5 mL (2.3 mmol) of DIBAL-H in toluene (1.5 M). The progress of the reaction was monitored by TLC. Upon consumption of starting material the reaction was quenched at −78 °C with saturated aqueous Rochelle's salt and diluted with 100 mL of Et_2O. The solution was allowed to warm to rt over 3 h, and then it was extracted with Et_2O. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant to afford 0.36 g (84%) of dialdehyde **3.3**: mp 56−58 °C; $[\alpha]_D$ 41.3 (*c* 1.6, CH_2Cl_2); IR ($CHCl_3$) 1724 cm^{-1}; ^{1}H NMR δ 9.78 (s, 2H), 3.61 (bd, J = 8.9 Hz, 2H), 2.62−

(9) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(10) For an analysis of these spectra, see the supporting information.

(11) Unless otherwise stated, ^{1}H NMR spectra were measured at 300 MHz as dilute solutions in $CDCl_3$. For a summary of experimental protocols, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960.

2.51 (m, 2H), 2.46−2.35 (m, 2H), 2.05−1.95 (m, 2H), 1.71−1.63 (m, 2H), 0.88 (s, 18H), 0.05 (s, 6H), 0.05 (s, 6H); ^{13}C NMR δ −4.7, −4.1, 17.9, 22.7, 25.8, 41.1, 74.2, 202.3. Anal. Calcd for $C_{20}H_{42}O_4Si_2$: C, 59.65; H, 10.51. Found: C, 59.40; H, 10.59.

The above procedure was employed with 1.20 g (2.4 mmol) of diester *ent*-**3.2** in 35 mL of toluene and 3.56 mL (2.4 mmol) of DIBAL-H in toluene (1.5 M). After 1.5 h the reaction was processed as described to afford 0.74 g (75%) of *ent*-**3.3**: $[\alpha]_D$ −41.1 (*c* 1.2, CH_2Cl_2).

(2*E*,14*E*,4*R*,5*S*,8*R*,9*R*,12*S*,13*R*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol (4.3). The general procedure was employed with 0.21 g (0.95 mmol) of $InCl_3$ in 24 mL of EtOAc, 0.19 g (0.48 mmol) of dialdehyde **3.3**, and 0.62 g (1.5 mmol) of stannane (*R*)-**4.1**. After 5 h, the reaction was quenched at rt with 1 M HCl and processed as described, affording 0.29 g (90%) of adduct **4.3**: $[\alpha]_D$ −45.1 (*c* 1.5, CH_2Cl_2); IR (film) 3480, 1671 cm^{-1}; ^{1}H NMR δ 5.72 (dq, J = 15.4, 6.5 Hz, 2H), 5.41 (ddq, J = 15.4, 8.1, 1.5 Hz, 2H), 4.73, 4.56 (ABq, J = 7.0 Hz, 4H), 3.93 (dd, J = 8.1, 3.5 Hz, 2H), 3.64−3.61 (m, 2H), 3.55 (bd, J = 5.8, 2H), 3.37 (s, 6H), 2.10 (bs, 2H), 1.89−1.81 (m, 4H), 1.73 (dd, J = 6.5, 1.5 Hz, 6H), 1.70−1.62 (m, 4H), 0.87 (s, 18H), 0.04 (s, 6H), 0.04 (s, 6H); ^{13}C NMR δ −4.7, −4.1, 17.9, 18.0, 25.9, 26.7, 29.9, 55.5, 74.2, 75.9, 80.4, 93.7, 126.4, 131.8. Anal. Calcd for $C_{32}H_{66}O_8Si_2$: C, 60.52; H, 10.48. Found: C, 60.52; H, 10.53.

(2*E*,14*E*,4*R*,5*S*,8*R*,9*R*,12*S*,13*R*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol Bis(*p*-toluenesulfonate) (4.4). To a solution of 0.13 g (0.20 mmol) of diol **4.3** in 0.5 mL of pyridine was added 0.11 g (0.57 mmol) of *p*-toluenesulfonyl chloride. The progress of the reaction was monitored by TLC. After 12 h, when the diol was no longer present, the reaction was quenched at rt with H_2O and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, the solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel. Elution with 35% EtOAc−hexanes afforded 0.19 g (99%) of tosylate **4.4**: $[\alpha]_D$ −28.3 (*c* 1.5, CH_2Cl_2); IR (film) 1672 cm^{-1}; ^{1}H NMR δ 7.79 (d, J = 8.5 Hz, 4H), 7.31 (d, J = 8.1 Hz, 4H), 5.72 (dq, J = 15.4, 6.5 Hz, 2H), 5.23 (dd, J = 15.4, 7.7 Hz, 2H), 4.59, 4.42 (ABq, J = 6.5 Hz, 4H), 4.48−4.46 (m, 2H), 4.20 (bd, J = 8.1, 3.5 Hz, 2H), 3.34−3.31 (m, 2H), 3.30 (s, 6H), 2.43 (s, 6H), 1.77−1.71 (m, 4H), 1.70 (d, J = 6.5 Hz, 6H), 1.55−1.49 (m, 4H), 0.85 (s, 18H), 0.01 (s, 6H), −0.01 (s, 6H); ^{13}C NMR δ −4.8, −4.1, 17.8, 17.9, 21.6, 25.8, 26.4, 27.0, 55.4, 75.2, 77.6, 85.7, 93.6, 126.3, 127.8, 129.5, 131.9, 134.7, 144.1.

(2*E*,14*E*,4*S*,5*S*,8*R*,9*R*,12*S*,13*S*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol (4.5). The general procedure was employed with 0.62 g (1.5 mmol) of stannane (*R*)-**4.1** in 10 mL of CH_2Cl_2, 0.18 mL (1.5 mmol) of $BF_3{\cdot}Et_2O$, and 0.21 g (0.50 mmol) of dialdehyde **3.3**. After 3 h, the reaction was quenched at −78 °C with saturated aqueous NH_4Cl and processed as described, affording 0.28 g (87%) of diol **4.5**: $[\alpha]_D$ 92.0 (*c* 1.5, CH_2Cl_2); IR (film) 3488, 1672 cm^{-1}; ^{1}H NMR δ 5.72 (dq, J = 15.4, 6.6 Hz, 2H), 5.27 (ddq, J = 15.4, 8.1, 1.5 Hz, 2H), 4.74, 4.54 (ABq, J = 6.9 Hz, 4H), 3.78 (dd, J = 8.1, 7.7 Hz, 2H), 3.54−3.42 (m, 4H), 3.38 (s, 6H), 2.10 (bs, 2H), 1.85−1.76 (m, 4H), 1.71 (d, J = 6.6, 1.5 Hz, 6H), 1.20−1.16 (m, 4H), 0.87 (s, 18H), 0.03 (s, 6H), 0.02 (s, 6H); ^{13}C NMR δ −4.7, −4.1, 17.9, 18.0, 25.8, 26.5, 30.3, 55.6, 74.3, 75.8, 81.1, 93.4, 127.8, 131.9. Anal. Calcd for $C_{32}H_{66}O_8Si_2$: C, 60.52; H, 10.48. Found: C, 60.78; H, 10.55.

(2*E*,14*E*,4*S*,5*S*,8*R*,9*R*,12*S*,13*S*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol Bis(*p*-toluenesulfonate) (4.6). The procedure given above for tosylate **4.4** was employed with 0.26 g (0.42 mmol) of diol **4.5** in 2.0 mL of pyridine and 0.24 g (1.2 mmol) of *p*-toluenesulfonyl chloride. After 12 h, the reaction was quenched at rt with H_2O and processed as described, affording 0.34 g (87%) of tosylate **4.6**: $[\alpha]_D$ 50.7 (*c* 1.4, CH_2Cl_2); IR (film) 3844, 1672 cm^{-1}; ^{1}H NMR δ 7.80 (d, J = 8.1 Hz, 4H), 7.32 (d, J = 8.1 Hz, 4H), 5.70 (dq, J = 15.4, 6.2 Hz, 2H), 5.21 (dd, J = 15.4, 8.5 Hz, 2H), 4.56, 4.39 (ABq, J = 6.9 Hz, 4H), 4.56−4.52 (m, 2H), 4.05 (d, J = 8.1 Hz, 2H), 3.36 (bd, J = 9.1 2H), 3.26 (s, 6H), 2.44 (s, 6H), 1.93−1.89 (m, 4H), 1.68 (d, J = 6.2 Hz, 6H), 1.32−1.29 (m, 4H), 0.84 (s, 18H), −0.02 (s, 6H), −0.03 (s, 6H); ^{13}C NMR δ −4.8, −4.0, 17.8, 17.9, 21.6, 25.8, 26.4, 27.0, 55.4, 75.2, 77.6, 85.7, 93.6, 126.3, 127.9, 129.5, 131.9, 134.6, 144.1.

(2*E*,14*E*,4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-4,13-Bis(methoxymethoxy)-4,9-bistetrahydrofuran 4.7. To solution of 0.18 g (0.19 mmol) of bis-TBS ether **4.4** in 1.0 mL of THF at 40 °C was added 75 mL (0.39 mmol) of 1 M TBAF in THF. The progress of the reaction was monitored by TLC. During 6 h, a more polar spot appeared which was gradually replaced with a less polar one. The reaction was cooled to rt, quenched with H_2O, and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 35% EtOAc−hexanes as eluant, affording 51 mg (74%) of bistetrahydrofuran **4.7**: $[\alpha]_D$ −97.4 (*c* 1.3, CH_2Cl_2); IR (film) 1675 cm^{-1}; ^{1}H NMR δ 5.73 (dq, J = 15.4, 6.5 Hz, 2H), 5.36 (ddq, J = 15.4, 8.1, 1.5 Hz, 2H), 4.69, 4.58 (ABq, J = 6.6 Hz, 4H), 4.06−3.89 (m, 6H), 3.37 (s, 6H), 1.92−1.83 (m, 4H), 1.73 (dq, J = 6.5, 1.5 Hz, 10H); ^{13}C NMR δ 17.9, 27.9, 28.0, 55.2, 78.7, 81.2, 81.5, 93.6, 127.8, 130.3. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.68; H, 9.30.

(2*E*,14*E*,4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-5,9-Bistetrahydrofuran-4,13-diol 4.8. To a solution of 50 mg (0.14 mmol) of bistetrahydrofuran **4.7** in 0.3 mL of *tert*-butyl alcohol was added 0.14 g of pyridinium *p*-toluenesulfonate. The solution was heated to 85 °C and monitored by TLC. Upon consumption of all starting material (approximately 8 h), the reaction was allowed to cool to rt and quenched with H_2O. The product was extracted with Et_2O and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel with 95% EtOAc−5% MeOH as eluant to afford 14 mg (37%) of diol **4.8**: ^{1}H NMR δ 5.77 (dq, J = 15.4, 6.6 Hz, 2H), 5.40 (ddq, J = 15.4, 6.5, 1.5 Hz, 2H), 3.93−3.82 (m, 6H), 2.40 (bs, 2H), 2.06−1.85 (m, 4H), 1.70 (dq, J = 6.6, 1.5 Hz, 8H), 1.68−1.56 (m, 2H); ^{13}C NMR δ 17.9, 28.0, 28.7, 75.6, 81.7, 82.9, 129.2, 129.6.

(2*E*,14*E*,4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-5,9-Bistetrahydrofuran-4,13-diol Bis((*S*)-*O*-methylmandelate) 4.9. The Trost procedure[9] for *O*-methylmandelates was employed with 10 mg (0.04 mmol) of diol **4.8** in 0.3 mL of CH_2Cl_2, 23 mg (0.16 mmol) of (*S*)-methoxyphenylacetic acid, 26 mg (0.13 mmol) of dicyclohexylcarbodiimide, and 16 mg (0.13 mmol) of 4-(*N*,*N*-dimethylamino)pyridine. The reaction was monitored by TLC. After 10 min, all starting material was consumed, and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel with 35% EtOAc in hexanes as eluant to afford 10 mg (50%) of the diester **4.9**: ^{1}H NMR δ 7.46−7.42 (m, 4H), 7.37−7.30 (m, 6H), 5.50 (dq, J = 15.4, 6.6 Hz, 2H), 5.29 (ddq, J = 15.4, 7.3, 1.5 Hz, 2H), 5.29−5.17 (m, 2H), 4.79 (s, 2H), 4.05−4.00 (m, 2H), 3.89−3.83 (m, 2H), 3.42 (s, 6H), 2.01−1.85 (m, 6H), 1.69 (dq, J = 6.6, 1.5 Hz, 6H), 1.61−1.52 (m, 2H).

(2*E*,14*E*,4*S*,5*R*,8*R*,9*R*,12*R*,13*S*)-4,13-Bis(methoxymethoxy)-5,9-bistetrahydrofuran 4.10. The procedure described above for bistetrahydrofuran **4.7** was employed with 0.31 g (0.33 mmol) of bis-TBS ether **4.6** in 1.0 mL of THF and 1.3 mL (1.3 mmol) of TBAF. After 12 h, the reaction was quenched at rt with H_2O and processed as described affording 94 mg (78%) of bistetrahydrofuran **4.10**: $[\alpha]_D$ 147.9 (*c* 1.7, CH_2Cl_2); IR (film) 1681 cm^{-1}; ^{1}H NMR δ 5.70 (dq, J = 15.4, 6.5 Hz, 2H), 5.32 (ddq, J = 15.4, 7.7, 1.5 Hz, 2H), 4.70, 4.56 (ABq, J = 6.5 Hz, 4H), 4.09−3.90 (m, 6H), 3.35 (s, 6H), 2.05−1.80 (m, 4H), 1.72 (dq, J = 6.5, 1.5 Hz, 10H); ^{13}C NMR δ 17.9, 27.0, 28.0, 55.3, 78.8, 81.6, 81.9, 93.7, 127.8, 130.5. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.95; H, 9.29.

(2*E*,14*E*,4*S*,5*R*,8*R*,9*R*,12*R*,13*S*)-5,9-Bistetrahydrofuran-4,13-diol 4.11. The procedure for diol **4.8** was employed with 44 mg (0.11 mmol) of bistetrahydrofuran **4.10** in 0.3 mL of *tert*-butyl alcohol and 50 mg of pyridinium *p*-toluenesulfonate. After 8 h, the reaction was quenched and processed as described, with chromatography on silica gel with 35% EtOAc in hexanes as eluant affording 14 mg (42%) of diol **4.11**: ^{1}H NMR δ 5.75 (dq, J = 15.4, 6.6 Hz, 2H), 5.39 (ddq, J = 15.4, 6.9, 1.5 Hz, 2H), 4.34 (dd, J = 6.6,3.1 Hz, 2H), 4.02−3.87 (m,

4H), 2.30 (bs, 2H), 2.01−1.85 (m, 4H), 1.69 (dq, J = 6.6, 1.5 Hz, 6H), 1.61−1.52 (m, 2H); ^{13}C NMR δ 17.9, 25.0, 28.7, 72.7, 82.7, 83.2, 128.5, 128.9.

(2*E*,14*E*,4*S*,5*R*,8*R*,9*R*,12*R*,13*S*)-5,9-Bistetrahydrofuran-4,13-diol Bis((*S*)-*O*-methylmandelate) 4.12. The procedure for **4.9** was employed with 12 mg (0.05 mmol) of diol **4.11** in 0.3 mL of CH_2Cl_2, 30 mg (0.20 mmol) of (*S*)-methoxyphenylacetic acid, 34 mg (0.16 mmol) of dicyclohexylcarbodiimide, and 20 mg (0.16 mmol) of 4-(*N*,*N*-dimethylamino)pyridine. After 10 min, the reaction was processed as described and chromatographed on silica gel with 35% EtOAc in hexanes as eluant to afford 23 mg (92%) of the diester **4.12**: ^{1}H NMR δ 7.43−7.39 (m, 4H), 7.33−7.28 (m, 6H), 5.75 (dq, J = 15.4, 6.6 Hz, 2H), 5.40 (ddq, J = 15.4, 7.3, 1.5 Hz, 2H), 5.33−5.27 (m, 2H), 4.72 (s, 2H), 3.81−3.75 (m, 2H), 3.39 (s, 6H), 3.89−3.83 (m, 2H), 2.01−1.85 (m, 6H), 1.69 (dq, J = 6.6, 1.5 Hz, 6H), 1.61−1.52 (m, 2H).

(2*E*,14*E*,4*S*,5*S*,8*S*,9*S*,12*S*,13*S*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol (*ent*-5.3). The general procedure was employed with 0.75 g (1.8 mmol) of stannane (*R*)-**4.1** in 10 mL of CH_2Cl_2, 0.23 mL (1.8 mmol) of $BF_3{\cdot}Et_2O$, and 0.25 g (0.60 mmol) of dialdehyde *ent*-**3.3**. After 3 h, the reaction was quenched at −78 °C with saturated aqueous ammonium chloride and processed as described, affording 0.32 g (82%) of diol *ent*-**5.3**: $[\alpha]_D$ 28.7 (*c* 1.1, CH_2Cl_2); IR (film) 3496, 1672 cm^{-1}; ^{1}H NMR δ 5.73 (dq, J = 15.4, 6.6 Hz, 2H), 5.28 (ddq, J = 15.4, 8.5, 1.5 Hz, 2H), 4.74, 4.54 (ABq, J = 7.0 Hz, 4H), 3.79 (dd, J = 8.5, 7.7 Hz, 2H), 3.61−3.44 (m, 4H), 3.38 (s, 6H), 2.30 (bs, 2H), 1.77−1.72 (m, 2H), 1.72 (dd, J = 6.6, 1.5 Hz, 6H), 1.59−1.42 (m, 6H), 0.87 (s, 18H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR δ −4.6, −4.1, 17.9, 18.0, 25.8, 26.0, 29.8, 55.6, 73.4, 75.3, 81.1, 93.5, 127.7, 131.9. Anal. Calcd for $C_{32}H_{66}O_8Si_2$: C, 60.52; H, 10.48. Found: C, 60.62; H, 10.44.

(2*E*,14*E*,4*S*,5*S*,8*S*,9*S*,12*S*,13*S*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-5,12-diol Diacetate (6.1). To a solution of 0.21 g of diol *ent*-**5.3** (0.32 mmol) in 0.5 mL of pyridine was added 0.20 mL (1.9 mmol) of acetic anhydride and 25 mg (0.02 mmol) of 4-(*N*,*N*-dimethylamino)pyridine. The reaction was monitored by TLC, and after 2 h it was quenched with cold saturated aqueous $NaHCO_3$, washed with saturated aqueous $CuSO_4$, and extracted with ether. The product was purified by column chromatography on silica gel. Elution with 35% EtOAc−hexanes afforded 0.23 g (99%) of diacetate **6.1**: $[\alpha]_D$ 29.3 (*c* 1.3, CH_2Cl_2); IR (film) 1747, 1672 cm^{-1}; ^{1}H NMR δ 5.76 (dq, J = 15.4, 6.6 Hz, 2H), 5.25 (ddq, J = 15.4, 6.5, 1.5 Hz, 2H), 4.96−4.92 (m, 2H), 4.68, 4.51 (ABq, J = 6.6 Hz, 4H), 4.02 (dd, J = 7.3, 6.5 Hz, 2H), 3.47 (d, J = 8.1 Hz, 4H), 3.35 (s, 6H), 2.06 (s, 6H), 1.72 (dd, J = 6.6, 1.5 Hz, 6H), 1.67−1.48 (m, 6H), 1.28−1.23 (m, 2H), 0.86 (s, 18H), 0.02 (s, 6H), 0.02 (s, 6H); ^{13}C NMR δ −4.9, −4.4, 17.6, 17.7, 20.8, 25.1, 25.5, 27.5, 55.1, 74.8, 75.0, 76.3, 93.1, 126.5, 131.3, 170.2. Anal. Calcd for $C_{36}H_{70}O_{10}Si_2$: C, 60.13; H, 9.81. Found: C, 59.99; H, 9.73.

(2*E*,14*E*,4*S*,5*S*,8*S*,9*S*,12*S*,13*S*)-5,12-Diacetoxy-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-8,9-diol (6.2). To a solution of 0.33 g (0.46 mmol) of TBS ether **6.1** in 0.5 mL of THF was added two drops of H_2O as a buffer and 2.0 mL (2.0 mmol) of 1.0 M TBAF at rt. The reaction was monitored by TLC, and after 6 h it was quenched with water and extracted with CH_2Cl_2. The product was purified by column chromatography on silica gel. Elution with 75% EtOAc−hexanes afforded 0.22 g (97%) of diol **6.2**: $[\alpha]_D$ 55.3 (*c* 1.2, CH_2Cl_2); IR (film) 3480, 1738 cm^{-1}; ^{1}H NMR δ 5.75 (dq, J = 15.4, 6.6 Hz, 2H), 5.28 (ddq, J = 15.4, 8.5, 1.5 Hz, 2H), 4.99 (dt, J = 6.2, 5.8 Hz, 2H), 4.68, 4.51 (ABq, J = 6.9 Hz, 4H), 4.03 (dd, J = 8.5, 5.8 Hz, 2H), 3.43−3.37 (m, 4H), 3.35 (s, 6H), 2.08 (s, 6H), 1.77−1.63 (m, 4H), 1.72 (dd, J = 6.6, 1.5 Hz, 6H), 1.47−1.38 (m, 4H); ^{13}C NMR δ 17.9, 21.1, 26.6, 29.1, 55.4, 73.8, 74.7, 77.3, 93.2, 126.6, 131.9, 170.8. Anal. Calcd for $C_{24}H_{42}O_{10}$: C, 58.76, H, 8.63. Found: C, 58.60, H, 8.65.

(2*E*,14*E*,4*S*,5*S*,8*S*,9*S*,12*S*,13*S*)-5,12-Diacetoxy-4,13-bis(methoxymethoxy)-2,14-hexadecadiene-8,9-diol Dimesylate (6.3). To a solution of 0.21 g (0.43 mmol) of diol **6.2** in 3.0 mL of CH_2Cl_2 was added 0.36 mL (2.6 mmol) of Et_3N and 0.10 mL (1.3 mmol) of methanesulfonyl chloride at −78 °C. The reaction was monitored by TLC, and after 1 h it was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O, affording 0.22 g (84%) of mesylate **6.3**. The product was used in later experiments without further purification: IR (film) 1738, 1672 cm^{-1}; ^{1}H NMR δ 5.77 (dq, J = 15.4, 6.6 Hz, 2H), 5.30 (ddq, J = 15.4, 8.5, 1.5 Hz, 2H), 5.07−4.96 (m, 2H), 4.81−4.76 (m, 2H), 4.68, 4.50 (ABq, J = 6.6 Hz, 4H), 4.03 (dd, J = 8.5, 6.2 Hz, 2H), 3.35 (s, 6H), 3.07 (s, 6H), 2.10 (s, 6H), 1.82−1.63 (m, 8H), 1.73 (dd, J = 6.6, 1.5 Hz, 6H); ^{13}C NMR δ 17.8, 21.0, 25.8, 25.8, 38.5 ,55.4, 73.8, 77.2, 79.4, 93.2, 126.4, 132.2, 170.8.

(2*E*,14*E*,4*S*,5*S*,8*R*,9*R*,12*S*,13*S*)-4,13-Bis(methoxymethoxy)-5,9-bistetrahydrofuran (5.5). To 40 mg (0.06 mmol) of diacetate **6.3** was added 0.5 mL (1.1 mmol) of Triton B. The reaction was monitored by TLC, and after complete consumption of starting material it was quenched with H_2O and extracted with CH_2Cl_2. The product was extracted with Et_2O, and dried over $MgSO_4$ and the solvent distilled under reduced pressure. The product was purified by column chromatography on silica gel with 35% EtOAc in hexanes as eluant to afford 17 mg (77%) of bistetrahydrofuran **5.5**.

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Supporting Information Available: ^{1}H NMR spectra for all intermediates and selected ^{13}C NMR spectra, experimental procedures for **5.1**−**5.5**, **5.8**, **7.1**−**7.3**, and *ent*-**4.10**, and ^{1}H NMR spectra for *O*-methylmandelates (61 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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