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TOTAL SYNTHESIS OF (+)-ASTELTOXIN[1]

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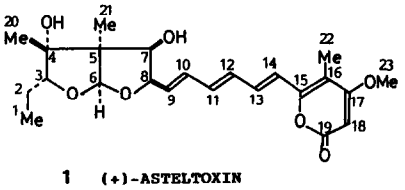
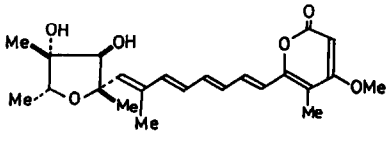
Abstract : A total synthesis of (+)-asteltoxin, a novel mycotoxin isolated from Aspergillus stellatus, has been achieved by using D-glucose as an enantiomerically pure starting material.

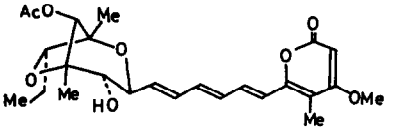
In 1979 Vleggaar and co-workers reported the isolation of a novel mycotoxin (+)-asteltoxin (1) from the toxic maize meal cultures of Aspergillus stellatus Curzi (MRC 277).[2] Based on a combination of the spectral analysis and a single-crystal X-ray crystallography, the relative stereochemistry of 1 was determined.[2] A notable structural characteristic of 1 is the bistetrahydrofuran moiety having six consecutive stereogenic centers. The structural similarity of 1 to the other mycotoxins such as (-)-citreoviridin (2)[3] and (-)-aurovertin B (3)[4], both potent inhibitors of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme systems, implicated similar bioactivity for 1. In fact, asteltoxin (1) was found to be a potent inhibitor of E. Coli. BF_1-ATPase activity.[5] Biosynthetic studies of the unusual bistetrahydrofuran moiety of 1 have been disclosed by Vlaggaar.[6] In the past several years efforts have resulted in the total syntheses of 1, 2,[7] 3,[8] and related mycotoxins.[9]



1 (+)-ASTELTOXIN



2 (-)-CITREOVIRIDIN



3 (-)-AUROVERTIN B

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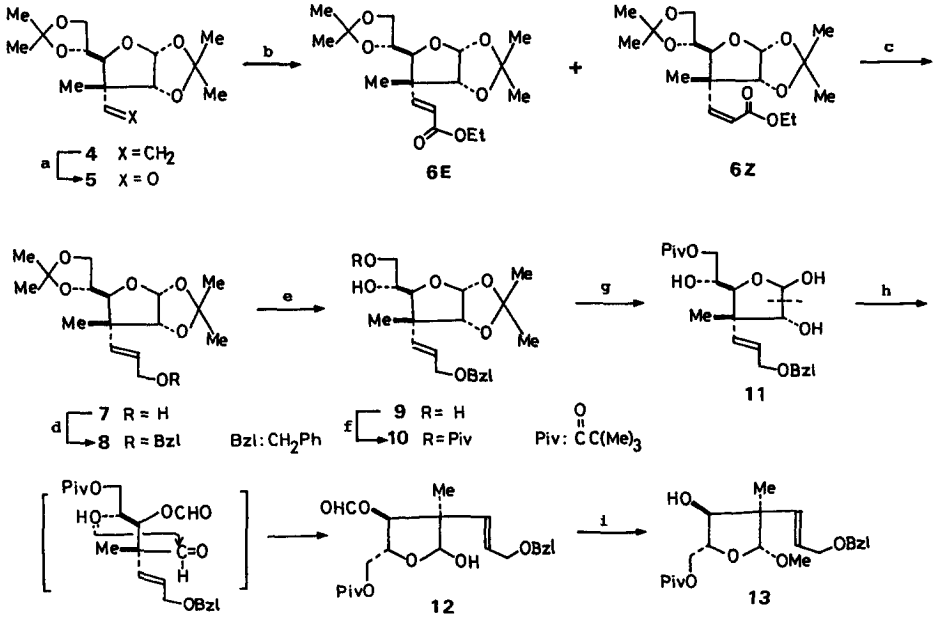
In 1983, the first synthesis of racemic bistetrahydrofuran moiety of **1** was reported by Schreiber and Satake.[10] Soon afterward, they completed the first total synthesis of (±)-**1**.[11] This total synthesis confirmed the relative configuration of **1**. They finally established the absolute stereochemistry of natural (+)-**1** in 1986 through an asymmetric synthesis of the bistetrahydrofuran moiety.[12] Herein, we report a total synthesis of natural (+)-**1**, which features a carbohydrate-mediated chiron approach.[13]

As an enantiomerically pure starting compound for our total synthesis of **1**, we used a derivative of tetrahydrofuran (**4**) which includes a stereochemically defined quaternary carbon atom. The compound **4** was prepared from D-glucose by employing the ortho ester Claisen rearrangement as a key reaction.[14] The quaternary carbon atom corresponds to the C-5 in **1** (asteltoxin numbering), and modification of the vinyl group in **4** would afford the C-7 through C-9 carbon framework. For this purpose, the vinyl group in **4** was cleaved by ozonolysis to afford an aldehyde (**5**) (Scheme 1). Wittig reaction of **5** with Ph_3P=CHCOOEt in refluxing benzene afforded the (E)-α,β-unsaturated ester (**6E**) in 90% yield along with a 4% yield of **6Z** (J=18 Hz for the vinyl protons of **6E**). The predominant isomer **6E** possesses the proper double bond geometry for functionalization in



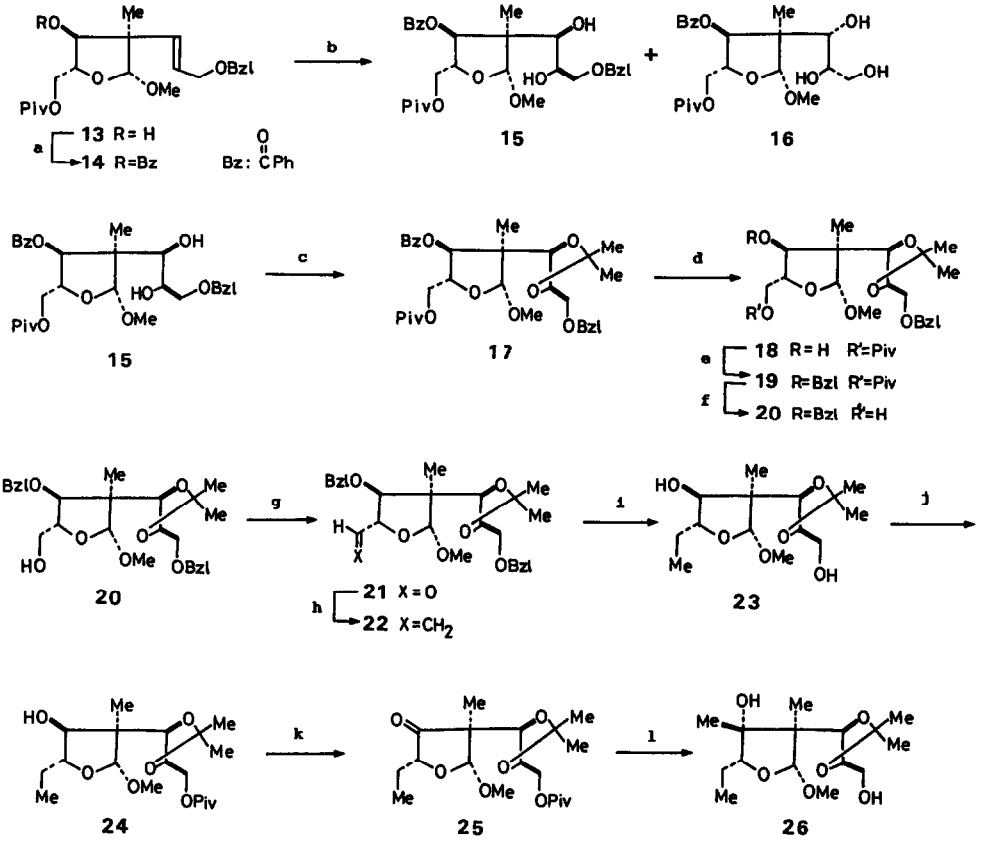
a. O_3, CH_2Cl_2, -78 °C; then Ph_3P, -78 °C to r.t.. **b.** Ph_3P=CHCOOEt, benzene, reflux. **c.** Dibal-H, CH_2Cl_2, -40 °C. **d.** BzlBr, NaH, DMF, r.t.. **e.** 50% aqueous AcOH, r.t.. **f.** $Me_3CC(O)Cl$, pyridine, DMAP, CH_2Cl_2, r.t.. **g.** 60% aqueous CF_3COOH, 5 °C, 64 h. **h.** $NaIO_4$, H_2O/MeOH, r.t.. **i.** MeOH, Amberlite IR-120 (H^+), reflux.

Scheme 1

later stages. Diisobutylaluminum hydride (Dibal-H) reduction of **6E** followed by benzylation of the allyl alcohol (**7**) gave the benzyl ether (**8**) in 94% yield. Hydrolysis of **8** with 50% AcOH afforded the diol (**9**) which was then selectively acylated to give the mono-pivaloyl ester (**10**) in 89% yield. The isopropylidene group in **10** was removed upon exposure to 60% CF_3COOH at 5 °C to give a diastereomeric mixture of hemiacetal (**11**) in 78% yield. $NaIO_4$ oxidation of **11** for glycol cleavage afforded a pentasubstituted tetrahydrofuran (**12**), which was converted to the diastereomerically single methyl glycoside (**13**) in 80% yield by heating in MeOH in the presence of (H^+)- type resin. The formyl group in **12** was removed under these glycosidation conditions. The anomeric configuration of **13** was determined based on the n.O.e. experiment of the advanced compound **17**.[15]

Introduction of a cis-diol to the double bond in **13** was next executed. (Scheme 2). The hydroxy group in **13** was protected to give the benzoate (**14**) quantitatively. Osmium tetroxide oxidation of **14** under the Kelly's conditions[16] [catalytic OsO_4 in the presence of N-methylmorpholine N-oxide (NMO)] provided the cis-diol (**15**) in 68% yield along with the diastereomer (**16**) in 15% yield.[17] The stereochemistry of the cis-diol in the main product **15** was confirmed to be the desired R,R-configuration by some chemical transformations.[18] The steric environment of **14** seems to be the major factor for this stereoselective cis-dihydroxylation. The hydroxyl groups in **15** were protected to be an acetonide (**17**), which was then exposed to MeONa briefly at 0 °C affording the debenzoyl derivative (**18**) in 62% yield. The liberated hydroxyl group was then benzylated, and the pivaloyl group in the resulting benzyl ether (**19**) was removed with excess MeONa at room temperature to afford the primary hydroxyl derivative (**20**) in 83% yield. Swern oxidation[19] of **20** smoothly gave an aldehyde (**21**), which was subjected to Wittig methylenation under the standard conditions affording the adduct (**22**) in 87% yield. Simultaneous saturation of the vinyl group and removal of the benzyl groups in **22** under a prolonged hydrogenation in the presence of Raney Ni resulted in the formation of **23** (78%). For functionalization of the secondary hydroxyl group in **23**, the primary hydroxyl group was protected to be the pivaloyl ester (**24**) in 87% yield. Pyridinium chlorochromate (PCC) oxidation[20] of **24** gave a tetrahydrofuranone derivative (**25**). Grignard addition of MeMgBr to **25** in THF at 0 °C proceeded highly stereoselectively, to our delight, to afford one diastereomer (**26**) in 95% yield. The homogeneity of the adduct was confirmed by the ^1H NMR (400 MHz) analysis. The stereochemistry of the newly introduced stereogenic center was establised to be (S) as that of natural **1** through the transformation of **26** to the bistetrahydrofuran moiety of **1**, Schreibers's key intermediate for their total synthesis, by acid-catalyzed cyclization.[21] One plausible account for this exclusively stereoselective addition of the Grignard reagent is that the reagent is directed to the β-face of the tetrahydrofuranone ring by chelation with one of the isopropylidene ketal oxygens. As a result, the attack of the reagent took place from the β-face.

The final stage of the total synthesis was effected as follows (Scheme 3). PCC oxidation of **26** followed by Wittig-Horner reaction of the resulting aldehyde (**27**) with triethyl 4-phosphonocrotonate provided (*E*,*E*)-αβ,γδ-unsaturated ester (**28**) in 72% yield. Acid hydrolysis (60% aqueous CF_3COOH) of **28** smoothly gave a bistetrahydrofuran (**29**) in 89% yield. Dibal-H reduction of **29** provided the allyl alcohol (**30**) in 78% yield.

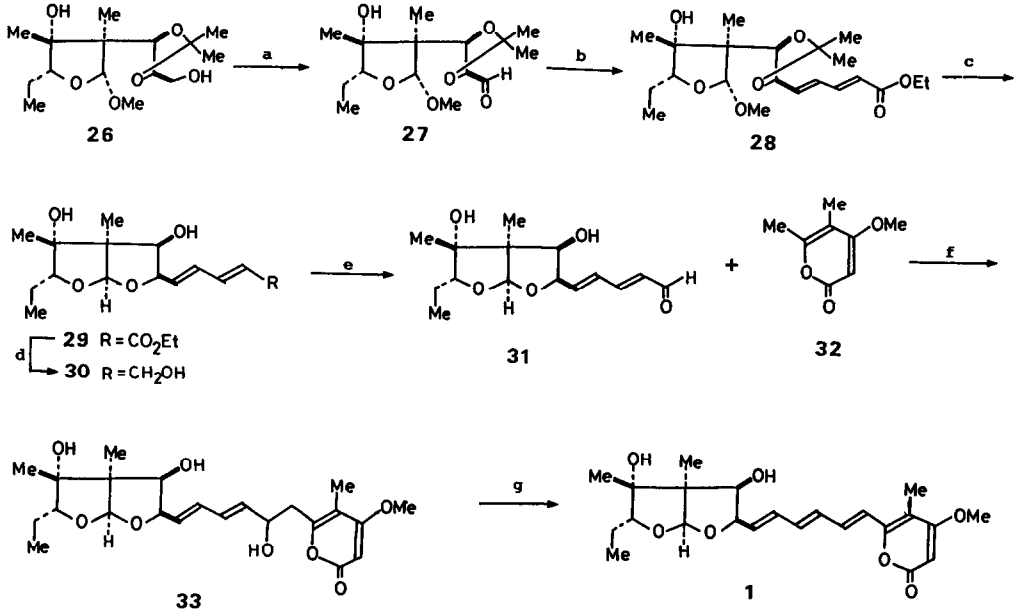


a. BzCl, pyridine, 60 °C. **b.** OsO_4 in 2-methyl-2-propanol, NMO, aqueous acetone, r.t.. **c.** 2,2-dimethoxypropane, acetone, CSA, r.t.. **d.** MeONa, MeOH, 0 °C, 90 min. **e.** NaH, BzlBr, DMF, r.t.. **f.** MeONa, MeOH, r.t., 20 h. **g.** DMSO, $(COCl)_2$, CH_2Cl_2, - 78 °C; then Et_3N, -78 °C to r.t.. **h.** $Ph_3P^+MeBr^-$, $NaNH_2$, THF, reflux; then added **21**, THF, r.t.. **i.** H_2, Raney Ni, EtOH, r.t., 4 days. **j.** $Me_3CC(O)Cl$, pyridine, DMAP, CH_2Cl_2, r.t.. **k.** PCC, MS, CH_2Cl_2, r.t. **l.** MeMgBr, THF, 0 °C.

Scheme 2

Active MnO_2 oxidation of **30** gave (*E*,*E*)-α,β,γ,δ-unsaturated aldehyde (**31**), an advanced intermediate for the Schreiber's total synthesis of **1**, in 86% yield. The aldol condensation protocol previously reported[11] was used for our final two steps. The aldol reaction of **31** and 4-methoxy-5,6-dimethyl-2-pyrone (**32**)[22] with LDA (lithium diisopropylamide) provided a diastereomeric mixture (**33**) in 28% yield (the aldehyde **32** was recovered in 32% yield, however, this reaction was not optimized). By treatment of this mixture **33** with excess p-toluenesulfonyl chloride in the presence of Et_3N and 4-dimethylaminopyridine (DMAP) gave (+)-asteltoxin (**1**) in 73% yield. The ^1H (400 MHz) and ^{13}C (100 MHz) NMR, and MS of the synthetic **1** were superimposable with those of natural and racemic ones. The TLC behavior in several solvent systems revealed that the synthetic **1** was identical with natural source. The specific rotation of **1** [$[\alpha]_D$ +20° (c 0.1, MeOH)] well matched with that for natural product [$[\alpha]_D$+20° (c 1.15, MeOH)].

In conclusion, we completed the total syntheis of (+)-**1**. Through the present synthesis, the utility of the D-glucose derived synthon **4** was embodied.



a. PCC, MS, CH_2Cl_2, r.t.. **b.** $(EtO)_2P(O)CH_2CH{=}CHCOOEt$, LDA, THF, -78 °C; then added **27**, -78 °C to r.t.. **c.** 60% aqueous CF_3COOH, r.t.. **d.** Dibal-H, CH_2Cl_2, -78 °C. **e.** MnO_2, CH_2Cl_2, r.t.. **f.** LDA, THF, HMPA, -78 °C, added **32**; then added **31**, -78 °C, 15 min. **g.** TsCl, DMAP, Et_3N, CH_2Cl_2, r.t..

Scheme 3

EXPERIMENTAL

Melting points are uncorrected. Specific rotations in $CHCl_3$ were measured by using JASCO Model DIP-4 polarimeter in a 10 mm cell. IR spectra (neat) were recorded on a JASCO Model A-202 spectrometer. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) and JEOL JNM GX-400 (400 MHz) spectrometers in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a JEOL JNM GX-400 (100 MHz) spectrometer. High resolution mass spectra (HRMS) were measured by using a Hitachi M-80 spectrometer (EI method). Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF_{254} (Merck). Each crude product was chromatographed on a silica gel (Katayama Chemicals, K070) column. Unless otherwise specified, reactions were carried out at room temperature. Reactions involving organometallic reagents were performed under argon atmosphere. Solvents were removed by concentration using an evaporator.

(2*R*,3*R*,4*R*,5*S*)-4-[(*E*)-2-(Ethoxycarbonyl)ethenyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-methyltetrahydrofuran (6E). To a solution of **4** (5.02 g, 17.7 mmol) in CH_2Cl_2 (40 mL) was bubbled a stream of O_3 (ca. 3% in O_2) at −78 °C until blue color of the solution was sustained. A CH_2Cl_2 solution (40 mL) of Ph_3P (9.27 g, 35.5 mmol) was added to the mixture, and gradually warmed to room temparature. After stirring for 1 h, the mixture was concentrated. The residue was rapidly chromatographed on silica gel (AcOEt/hexane 1:15) to give an aldehyde **5** (5.16 g), which was subjected to the Wittig reaction directly: TLC R_f 0.40 (AcOEt/hexane 1:3); ^1H NMR (90 MHz) δ 1.12 (3H, s), 1.30, 1.31, 1.38, 1.59 (3H x 4, 4s), 4.09 (2H, d, J=3 Hz), 4.10 (1H, ddd, J=8, 3, 3 Hz), 4.40 (1H, d, J=4 Hz), 4.54 (1H, d, J=8 Hz), 5.84 (1H, d, J=4 Hz), 9.74 (1H, s).

A solution of **5** (5.16 g) and Ph_3P=CHCOOEt (24.6 g, 70.6 mmol) in benzene (100 mL) was refluxed for 12 h. The mixture was concentrated in vacuo, and the residue was stirred with petroleum ether. After cooling at 5 °C overnight, the precipitated Ph_3PO was removed by filtration, washed well with petroleum ether. The combined filtrate and washings were concentrated. The residue was chromatographed on silica gel (AcOEt/hexane 1:20, 1:10, then 1:5) to give **6Z** (239 mg, 4%) and **6E** (5.64 g, 90%). **6Z** as a colorless oil: TLC R_f 0.55 (AcOEt/hexane 1:3): $[\alpha]_D^{26}$ +108.9° (c 1.63); IR 3000, 2950, 2880, 1725, 1645, 1460, 1420, 1380, 1375 cm^{-1}; ^1H NMR (90 MHz) δ 1.3-1.5 (18H, m), 3.9-4.3 (6H, m), 5.01 (1H, d, J=5 Hz), 5.72 (1H, d, J=4 Hz), 5.85 (1H, d, J=13 Hz), 6.35 (1H, d, J=13 Hz); HRMS calcd for $C_{17}H_{25}O_7$: m/z 341.1597 ($M^+ - CH_3$). Found: m/z 341.1602. **6E** as a colorless oil: TLC R_f 0.46 (AcOEt/hexane 1:3): $[\alpha]_D^{25}$ +93.0° (c1.11); IR 2980, 2930, 2870, 1715, 1655, 1450, 1370, 1300 cm^{-1}; ^1H NMR (90 MHz) δ 1.1-1.6 (18H, m), 3.9-4.3 (7H, m), 5.79 (1H, d, J=4 Hz), 5.94 (1H, d, J=18 Hz), 7.12 (1H, d, J=18 Hz); HRMS calcd for $C_{17}H_{25}O_5$: m/z 341.1597 (M^+-CH_3). Found: m/z 341.1593.

(2*R*,3*R*,4*R*,5*S*)-4-[(*E*)-3-(Benzyloxy)-1-propenyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-methyltetrahydrofuran (8). To a stirred solution of **6E** (5.45 g, 15.3 mmol) in CH_2Cl_2 (100 mL) was added Dibal-H (25 wt% in toluene, 30.9 mL, 45.9 mmol) at − 40 °C. After stirring at −40 °C for 30 min, the mixture was quenched with 10 mL of H_2O. After warming to room temperature, the resulting gels were removed by filtration, washed well with CH_2Cl_2. The combined filtrate and washings were washed with H_2O (150 mL). The aqueous phase was extracted with CH_2Cl_2 (100 mL x 4). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give **7** (4.90 g), which was benzylated directly. In a separate experiment, the crude **7** was purified by silica gel chromatography (AcOEt/hexane 1:3): TLC R_f 0.20 (AcOEt/hexane 1:2): $[\alpha]_D^{26}$ +67.1° (c 0.98); IR 3470, 2980, 2940, 2880, 1450, 1370, 1245, 1215 cm^{-1}; ^1H NMR (90 MHz) 1.02 (3H, s), 1.26, 1.38, 1.48 (6H, 3H, 3H, 3s), 2.0-2.2 (1H, br s), 3.9-4.1 (7H, m), 5.6-5.8 (3H, m); HRMS calcd for $C_{16}H_{25}O_6$: m/z 313.1649 (M^+-H). Found: m/z 313.1648.

To a suspension of NaH (734 mg, 30.6 mmol) in DMF (20 mL) were added a DMF solution (40 mL) of **7** (4.90 g) and benzyl bromide (3.6 mL, 30.6 mmol) at 0 °C. After stirring for 4 h, 5 mL of EtOH was added to the mixture. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was partitioned between AcOEt (300 mL) and H_2O (100 mL). The aqueous phase was extracted with AcOEt (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed

on silica gel (AcOEt/hexane 1:15) to give **8** (5.80 g, 94%) as a colorless oil: TLC R_f 0.74 (AcOEt/hexane 1:2); $[\alpha]_D^{26}$ +47.5° (c 1.04); IR 2980, 2930, 2870, 1490, 1450, 1375, 1365, 1210 cm^{-1}; ^1H NMR (90 MHz) δ 1.09 (3H, s), 1.30, 1.35, 1.54 (6H, 3H, 3H, 3s), 4.0–4.2 (7H, m), 4.53 (2H, s), 5.78 (1H, d, J=4.5 Hz), 5.8–6.1 (2H, m), 7.36 (5H, s); HRMS calcd for $C_{23}H_{32}O_6$: m/z 404.2196 (M^+). Found: m/z 404.2176.

(2*R*,3*R*,4*R*,5*S*)-4-[(*E*)-3-(Benzyloxy)-1-propenyl]-5-[(1*R*)-[1-hydroxy-2-(2,2-dimethylpropionyl)oxy]ethyl]-2,3-(isopropylidenedioxy)-4-methyltetrahydrofuran (10). A solution of **8** (5.80 g, 14.3 mmol) in 50% aqueous AcOH (300 mL) was stirred for 22 h, and then concentrated in vacuo with an aid of EtOH to give crude **9** which was acylated directly. In a separate experiment, the crude **9** was purified by silica gel chromatography. **9** as a colorless oil: TLC R_f 0.11 (AcOEt/hexane 1:2); $[\alpha]_D^{25}$ +75.0° (c 1.29); IR 3440, 3000, 2950, 2880, 1680, 1500, 1460, 1390, 1380 cm^{-1}; ^1H NMR (90 MHz) δ 1.15 (3H, s), 1.33, 1.58 (3H x 2, 2s), 2.6 (2H, br s), 3.6–4.2 (7H, m), 4.57 (2H, s), 5.8–6.2 (3H, m), 7.40 (5H, s); HRMS calcd for $C_{20}H_{28}O_6$: m/z 364.1884 (M^+). Found: m/z 364.1879.

To a solution of **9** obtained above in CH_2Cl_2 (150 mL) were added pyridine (50 mL), pivaloyl chloride (3.5 mL, 28.7 mmol), and DMAP (526 mg, 4.3 mmol). The mixture was stirred for 10 h, during which 2 mL of Et_3N and each 1.8 mL of pivaloyl chloride were added after 5 and 8 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (200 mL x 1, 100 mL x 1). The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (AcOEt/hexane 1:10 then 1:5) to give **10** (5.71 g, 89%) as a colorless oil: TLC R_f 0.65 (AcOEt/hexane 1:2); $[\alpha]_D^{25}$ +62.2° (c 1.31); IR 3500, 2980, 2940, 2870, 1710, 1480, 1460 cm^{-1}; ^1H NMR (90 MHz) δ 1.08 (3H, s), 1.18 (9H, s), 1.24, 1.48 (3H x 2, 2s), 2.03 (1H, br s), 4.0–4.3 (7H, m), 4.46 (2H, s), 5.7–6.1 (3H, m), 7.30 (5H, s); LRMS m/z 433 ($M^+ - CH_3$).

(2*R*,3*R*,4*S*,5*R*)-3-[(*E*)-3-(Benzyloxy)-1-propenyl]-5-[[(2,2-dimethylpropionyl)oxy]methyl]-4-hydroxy-2-methoxy-3-methyltetrahydrofuran (13). A solution of **10** (5.71 g, 12.7 mmol) in 60% aqueous CF_3COOH (83 mL) was stirred at 5 °C for 64 h. The solution was neutralized with 10 M aqueous NaOH (ca. 60 mL) and diluted with H_2O (100 mL). This was extratced with CH_2Cl_2 (200 mL x 2, 100 mL x 4). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (AcOEt/hexane 1:2 then 2:3) to give an anomeric mixture of **11** (4.07 g, 78%) as a colorless oil: IR 3430, 2970, 2930, 2910, 2870, 1720, 1480, 1450 cm^{-1}; ^1H NMR (90 MHz) δ 1.21 (9H, s), 1.30 (3H, s), 2.2–2.6 (3H, m), 3.0–4.7 (7H, m), 4.53 (2H, s), 5.1–5.2 (1H, m), 5.8–6.2 (2H, m), 7.36 (5H, s).

To a stirred solution of **11** (4.07 g, 9.9 mmol) in MeOH (200 mL) was added an aqueous solution (80 mL) of $NaIO_4$ (6.37 g, 29.8 mmol). The mixture was stirred for 2 h, and the precipitated solids were removed by filtration, washed well with MeOH. The combined filtrate and washings were concentrated in vacuo. The residue was dissolved in H_2O (200 mL), and extracted with CH_2Cl_2 (200 mL x 2, 100 mL x 3). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give crude **12** which was used directly. In a separate experiment, the crude **12** was purified by silica gel chromatography. **12** as a colorless oil: TLC R_f 0.75 (AcOEt/hexane 2:3); IR 3450, 2980, 2930, 2870, 1730, 1480, 1455, 1360, 1280, 1160 cm^{-1}; ^1H NMR (90 MHz) δ 1.22 (9H, s), 1.25 (3H, s), 3.6 (1H, br s), 4.0–4.1 (2H, m), 4.2–4.3 (3H, m), 4.51 (2H, s), 5.0–5.4 (2H, m), 5.7–6.1 (2H, m), 7.33 (5H, s), 8.02 (1H, s).

A solution of **12** obtained above in MeOH (80 mL) was heated at 60 °C for 7 h in the presence of Amberlite IR-120 (H^+) (ca. 6 g). The resin was removed by filtration and washed well with MeOH. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:10) to give **13** (2.59 g, 67%) as a colorless oil. The unreacted **12** (705 mg, 17%) was also recovered, which was recyclized for the acetalization to give **13** (520 mg). Total amount of **13** was 3.11 g (80 %) after one recycle. **13**: TLC R_f 0.46 (AcOEt/hexane 1:3); $[\alpha]_D^{26}$ −0.5°(c 0.80); IR 3450, 2970, 2940, 1730, 1720, 1480, 1285, 1160 cm^{-1}; ^1H NMR (90 MHz) δ 1.17 (3H, s), 1.22 (9H, s), 2.0 (1H, br s), 3.33 (3H, s), 3.8–4.3 (6H, m), 4.51 (2H, s), 4.56 (1H, s), 5.8–5.9 (2H, m), 7.33 (5H, s); HRMS calcd for $C_{22}H_{32}O_6$: m/z 392.2196 (M^+). Found: m/z 392.2187.

(2*R*,3*R*,4*S*,5*R*)-4-(Benzoyloxy)-3-[(*E*)-3-(benzyloxy)-1-propenyl]-5-[[(2,2-dimethylpropionyl)oxy]methyl]-2-methoxy-3-methyltetrahydrofuran (14). To a solution of **13** (2.51 g, 6.4 mmol) in pyridine (100 mL) was added benzoyl chloride (1.5 mL, 12.8 mmol). The mixture was heated at 60 °C for 6 h, and concentrated in vacuo with an aid of toluene. The residue was partitioned bewteen CH_2Cl_2 (300 mL) and H_2O (200 mL). The aqueous phase was extracted with CH_2Cl_2 (150 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:15) to give **14** (3.34 g, quantitatively) as a colorless oil: TLC R_f 0.55 (AcOEt/hexane 1:5); $[\alpha]_D^{23}$ -25.6°(c 1.07); IR 2970, 2930, 2880, 1730, 1600, 1580, 1480, 1450, 1270, 1160 cm^{-1}; ^1H NMR (90 MHz) δ 1.18 (9H, s), 1.27 (3H, s), 3.39 (3H, s), 4.06 (2H, d, J=4.5 Hz), 4.2-4.3 (3H, m), 4.49 (2H, s), 4.63 (1H, s), 5.4-5.5 (1H, m), 5.8-6.1 (2H, m), 7.30 (5H, s), 7.3-7.5 (5H, m); HRMS calcd for $C_{28}H_{33}O_6$: m/z 465.2275 (M^+-OCH_3). Found: m/z 465.2246.

(2*R*,3*R*,4*S*,5*R*)-4-(Benzoyloxy)-3-[(1*R*,2*R*)- and (1*S*,2*S*)-[3-(benzyloxy)-1,2-dihydroxy]propyl]-5-[[(2,2-dimethylpropionyl)oxy]methyl]-2-methoxy-3-methyltetrahydrofuran (15 and 16). To a solution of NMO (6.91 g, 51.1 mmol) in an aqueous acetone (1:1 v/v, 100 mL) were added OsO_4 (0.02 M solution in 2-methyl-2-propanol, 32.0 mL, 0.64 mmol) and an acetone solution (100 mL) of **14** (3.34 g, 6.7 mmol). The mixture was stirred for 23 h, and then $NaHSO_3$ (2.16 g, 20.8 mmol) was added. This was stirred for 30 min, and 1 M aqueous HCl (ca. 10 mL) was added for neutralization. The mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The aqueous phase was extracted with CH_2Cl_2 (200 mL x 3). The combined organic phases were washed with saturated brine (100 mL x 2), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:6, 1:5, then 1:4) to give **15** (2.44 g, 68%) and **16** (0.52 g, 15%). **15** as a colorless oil: TLC R_f 0.44 (AcOEt/hexane 1:2); $[\alpha]_D^{21}$ -48.9° (c 0.97); IR 3480, 2970, 2940, 1730, 1600, 1580, 1480, 1450, 1270 cm^{-1}; ^1H NMR (90 MHz) δ 1.01 (12 H, s), 2.62 (1H, d, J=5 Hz), 2.88 (1H, d, J=9 Hz), 3.23 (3H, s), 3.4-4.3 (7H, m), 4.34 (2H, s), 5.37 (1H, s), 5.51 (1H, d, J=7 Hz), 7.29 (5H, s), 7.4-7.6, 8.0-8.1 (5H, m); HRMS calcd for $C_{28}H_{34}O_8$: m/z 498.2250 (M^+-CH_3OH). Found: m/z 498.2243. **16** as a colorless oil: TLC R_f 0.48 (AcOEt/hexane 1:2); $[\alpha]_D^{21}$ -50.6°(c 0.63); IR 3480, 2970, 2930, 2870, 1730, 1600, 1580, 1450, 1270 cm^{-1}; ^1H NMR (90 MHz) δ 1.17 (9H, s), 1.31 (3H, s), 2.8 (1H, br s), 3.3 (1H, br s), 3.40 (3H, s), 3.59 (2H, d, J=6 Hz), 3.8-4.4 (5H, m), 4.57 (2H, s), 5.3-5.6 (1H, m), 7.32 (5H, s), 7.2-7.6, 7.9-8.1 (5H, m); HRMS calcd for $C_{28}H_{34}O_8$: m/z 498.2250 (M^+ - CH_3OH). Found: m/z 498.2250.

(2*R*,3*S*,4*S*,5*R*)-3-[(1*R*,2*R*)-[3-(Benzyloxy)-1,2-(isopropylidenedioxy)propyl]-5-[[(2,2-dimethylpropionyl)oxy]methyl]-4-hydroxy-2-methoxy-3-methyltetrahydrofuran (18). A solution of **15** (1.06 g, 2.0 mmol) in a mixture of acetone (40 mL) and 2,2-dimethoxypropane (1.2 mL, 10.0 mmol) was stirred for 42 h in the presence of camphorsulfonic acid (87 mg). The solution was neutralized with saturated aqueous $NaHCO_3$ and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL), and the aqueous phase was extracted with CH_2Cl_2 (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated to give crude **17** (1.17 g), which was used for the next step directly. In a separate experiment, the crude **17** was purified by silica gel chromatography. **17** as a colorless oil: TLC R_f 0.66 (AcOEt/hexane 1:3); $[\alpha]_D^{28}$ -10.0° (c 1.21); IR 2990, 2950, 1740, 1600, 1480, 1460, 1400, 1380, 1370, 1320, 1270 cm^{-1} ; ^1H NMR (400 MHz) δ 1.06 (3H, s), 1.18 (9H, s), 1.39, 1.48 (3H x 2, 2s), 3.41 (3H, s), 3.49-3.61, 4.09-4.47 (2H, 5H, 2m), 4.49, 4.54 (1H x 2, 2d, J=12.4 Hz), 4.94 (1H, s), 5.44 (1H, d, J=6.8 Hz), 7.26-7.60, 8.03-8.06 (10H, m); HRMS calcd for $C_{31}H_{39}O_9$: m/z 555.2590 (M^+-CH_3). Found: m/z 555.2583.

To a solution of **17** (1.17 g) in MeOH (40 mL) was added MeONa (1 M solution in MeOH, 0.8 mL, 0.8 mmol) at 0 °C. The mixture was stirred for 90 min, and neutralized with Amberlite IR-120 (H^+). The resin was removed by filtration, washed well with MeOH. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:7) to give **18** (577 mg, 62%) as a colorless oil: TLC R_f 0.34 (AcOEt/hexane 1:3); $[\alpha]_D^{30}$ -24.2° (c 1.23); IR 3430, 2980, 2960, 2870, 1730, 1480, 1460, 1380, 1360, 1280 cm^{-1}; ^1H NMR (90 MHz) δ 1.06 (3H, s), 1.22 (9H, s), 1.36, 1.42 (3H x 2, 2s), 3.2 (1H, br s), 3.32 (3H, s), 3.5-4.4 (8H, m), 4.58 (2H, s), 4.80

(1H, s), 7.32 (5H, s); HRMS calcd for $C_{24}H_{35}O_8$: m/z 451.2329 (M^+-CH_3). Found: m/z 451.2325.

(2*R*,3*S*,4*S*,5*R*)-4-(Benzyloxy)-3-[(1*R*,2*R*)-[3-(benzyloxy)-1,2-(isopropylidenedioxy)-propyl]-5-(hydroxymethyl)-2-methoxy-3-methyltetrahydrofuran (20). To a solution of 18 (553 mg, 1.2 mmol) in DMF (20 mL) were added dried NaH (57 mg, 2.4 mmol) and benzyl bromide (0.4 mL, 3.6 mmol). The mixture was stirred for 15 h and 0.2 mL of MeOH was added. The mixture was diluted with AcOEt (200 mL) and washed with H_2O (50 mL x 3). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give crude 19 which was deacylated directly. In a separate experiment, the crude 19 was purified by PTLC to give pure 19: TLC R_f 0.57 (AcOEt/hexane 1:4); $[\alpha]_D^{30}$ +6.3°(c 1.16); IR 2990, 2960, 2940, 2870, 1730, 1500, 1460, 1400, 1380, 1360, 1280, 1250, 1170 cm^{-1}; ^1H NMR (90 MHz) δ 1.02 (3H, s), 1.19 (9H, s), 1.31, 1.37 (3H x 2, 2s), 3.24 (3H, s), 3.4-4.4 (12H, m), 4.67 (1H, s), 7.23 (10H,s); HRMS calcd for $C_{31}H_{41}O_8$: m/z 541.2798 (M^+-CH_3). Found: m/z 541.2788.

To a solution of 19 obtained above in MeOH (15 mL) was added MeONa (1 M solution in MeOH, 5.9 mL, 5.9 mmol). The mixture was stirred for 20 h, and neutralized with Amberlite IR-120 (H^+). The resin was removed by filtration, washed well with MeOH. The combined filtrate and washings were concentrated. The residue was chromatographed on silica gel to give 20 (465 mg, 83%) as a colorless oil: TLC R_f 0.45 (AcOEt/hexane 1:2); $[\alpha]_D^{31}$ +8.6° (c 0.80); IR 3480, 2990, 2910, 2880, 1500, 1450, 1380, 1370, 1260 cm^{-1}; ^1H NMR (90 MHz) δ 1.05 (3H, s), 1.37, 1.43 (3H x 2, 2s), 2.0 (1H, br s), 3.38 (3H, s), 3.4-4.5 (12H, m), 4.75 (1H, s), 7.30 (10H, s); HRMS calcd for $C_{27}H_{37}O_7$: m/z 473.2537 (M^++H). Found: m/z 473.2511.

(2*R*,3*S*,4*S*,5*R*)-4-(Benzyloxy)-3-[(1*R*,2*R*)-[3-(benzyloxy)-1,2-(isopropylidenedioxy)]-propyl]-2-methoxy-3-methyl-5-vinyltetrahydrofuran (22). A mixture of DMSO (0.6 mL, 9.0 mmol), oxalyl chloride (0.8 mL, 9.0 mmol), and CH_2Cl_2 (12 mL) was stirred at -78 °C for 10 min. To the mixture was added a CH_2Cl_2 solution (18 mL) of 20 (430 mg, 0.91 mmol). After stirring for 90 min at -78 °C, Et_3N (2.5 mL) was added to the mixture. This was gradually warmed to room temperature and stirred for further 1 h. The solution was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL x 3). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 21 which was used to the Wittig reaction directly. In a separate experiment, pure 21 was obtained by PTLC purification: TLC R_f 0.71 (AcOEt/hexane 1:2); $[\alpha]_D^{27}$ -29.3° (c 1.11); IR 2990, 2940, 2910, 2870, 1730, 1500, 1450, 1390, 1370, 1250, 1210 cm^{-1}; ^1H NMR (90 MHz) δ 1.00 (3H, s), 1.37, 1.43 (3H x 2, 2s), 3.41 (3H, s), 3.4-4.5 (10H, m), 4.90 (1H, s), 7.30 (10H, s), 9.56 (1H, s).

To a solution of 21 obtained above in benzene (20 mL) was added $Ph_3P{=}CH_2$ [754 mg (2.7 mmol), prepared from Ph_3PCH_3Br by treatment with fresh $NaNH_2$ in refluxing THF for 4 h followed by concentration of the supernatant part of the reaction mixture]. The mixture was stirred for 10 min and H_2O (100 mL) was added, then extracted with Et_2O (100 mL x 1, 50 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:30) to give 22 (370 mg, 87%) as a colorless oil: TLC R_f 0.67 (AcOEt/hexane 1:4); $[\alpha]_D^{25}$ -19.2° (c 1.00); IR 2990, 2940, 2910, 2870, 2830, 1640, 1500, 1450, 1390, 1370, 1250, 1210 cm^{-1}; ^1H NMR (90 MHz) δ 1.07 (3H, s), 1.37, 1.45 (3H x 2, 2s), 3.38 (3H, s), 3.5-4.5 (10H, m), 4.78 (1H, s), 5.1-5.4 (2H, m), 5.7-6.0 (1H, m), 7.30 (10H, s); HRMS calcd for $C_{27}H_{33}O_6$: m/z 453.2274 (M^+-CH_3). Found: m/z 453.2273.

(2*R*,3*S*,4*S*,5*R*)-5-Ethyl-4-hydroxy-3-[(1*R*,2*R*)-[3-hydroxy-1,2-(isopropylidenedioxy)]-propyl]-2-methoxy-3-methyltetrahydrofuran (23). A solution of 22 (370 mg, 0.8 mmol) in EtOH (5 mL) was stirred for 4 days under atmospheric hydrogen in the presence of Raney nickel. The catalyst was removed by filtration through a Celite-pad, washed well with EtOH. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:4 then 1:2) to give 23 (178 mg, 78%) as colorless needles, mp 59.5-61 °C: TLC R_f 0.20 (AcOEt/hexane 1:2); $[\alpha]_D^{29}$ -31.1° (c 1.10); IR 3400, 2990, 2970, 2940, 2890, 2840, 1460, 1380, 1370, 1250, 1210 cm^{-1}; ^1H NMR (400 MHz) δ 1.02 (3H, t, J=7.3 Hz), 1.06 (3H, s), 1.40 , 1.45 (3H x 2, 2s), 1.57-1.74 (2H, m), 2.32 (1H, br s), 2.90 (1H, br s), 3.42 (3H, s), 3.53-3.58 (1H, m), 3.66-3.74 (2H,

m), 3.84 (1H, d, J=11.7 Hz), 4.13-4.19 (2H, m), 4.86 (1H, s). Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 58.27; H, 9.00.

(2*R*,3*S*,4*S*,5*R*)-3-[(1*R*,2*R*)-3-[(2,2-Dimethylpropionyl)oxy]-1,2-(isopropylidenedioxy)-propyl]-5-ethyl-4-hydroxy-2-methoxy-3-methyltetrahydrofuran (24). To a solution of **23** (173 mg, 0.6 mmol)in CH_2Cl_2 (15 mL) were added pyridine (3 mL), pivaloyl chloride (0.3 mL, 2.3 mmol), and DMAP (147 mg, 1.2 mmol). The mixture was stirred for 1 h, and pivaloyl chloride (0.3 mL) and Et_3N (0.5 mL) were added. The mixture was stirred more 1 h. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with H_2O (50 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:20 then 1:10) to give **24** (194 mg, 87%) as a colorless oil: TLC R_f 0.74 (AcOEt/hexane 1:2); $[\alpha]_D^{31}$ -17.3° (c 1.62); IR 3480, 2980, 2940, 2880, 2840, 1730, 1720, 1480, 1460, 1400, 1380, 1340, 1290, 1250 cm^{-1}; ^1H NMR (90 MHz) δ 1.0-1.6 (24H, m), 3.34 (3H, s), 3.4-3.8, 4.0-4.4 (6H, m), 4.73 (1H, s); HRMS calcd for $C_{19}H_{35}O_7$:m/z 375.2381 (M+H). Found:m/z 375.2390.

(2*R*,3*S*,5*R*)-3-[(1*R*,2*R*)-3-[(2,2-Dimethylpropionyl)oxy]-1,2-(isopropylidenedioxy)-propyl]-5-ethyl-2-methoxy-3-methyltetrahydrofuran-4-one (25). A mixture of **24** (193 mg, 0.5 mmol), PCC (444 mg, 2.1 mmol), and molecular sieves (4A, powder, 412 mg) in CH_2Cl_2 (10 mL) was stirred for 2 h. The reaction mixture was charged on a silica gel column (20 g) and eluted with Et_2O to give **25** (188 mg, 98%) as a colorless oil: TLC R_f 0.53 (AcOEt/hexane 1:5); $[\alpha]_D^{26}$ -2.9° (c 1.17); IR 2980, 2940, 2920, 2880, 1760, 1480, 1460, 1400, 1380, 1370, 1280, 1250, 1220 cm^{-1}; ^1H NMR (90 MHz) δ1.00 (3H, s), 1.22 (9H, s), 1.36, 1.40 (3H x 2, 2s), 1.4-2.0 (5H, m), 3.45 (3H, s), 3.84 (1H, dd, J=6, 9 Hz), 4.0-4.3 (4H, m), 5.09 (1H, s); HRMS calcd for $C_{18}H_{29}O_7$: m/z 357.1911 ($M^+ - CH_3$). Found: m/z 357.1893.

(2*R*,3*R*,4*R*,5*R*)-5-Ethyl-4-hydroxy-3-[(1*R*,2*R*)-3-hydroxy-1,2-(isopropylidenedioxy)-propyl]-2-methoxy-3,4-dimethyltetrahydrofuran (26). To a solution of **25** (186 mg, 0.5 mmol) in THF (10 mL) was added MeMgBr (2.5 M solution in THF, 4.0 mL, 10.0 mmol)at 0 °C. After stirring at 0 °C for 1 h and then at room temperature for 2 h, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) then diluted with H_2O (80 mL). This aqueous solution was extracted with AcOEt (100 mL x 1, 60 mL x 4). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:4 then 1:2) to give **26** (144 mg, 95%) as a colorless oil: TLC R_f 0.18 (AcOEt/hexane 1:2); $[\alpha]_D^{25}$ +0.2° (c 1.08); IR 3470, 2970, 2930, 2860, 1460, 1400, 1380, 1370, 1340, 1320, 1290, 1250, 1220 cm^{-1}; ^1H NMR (400 MHz)δ 0.92 (3H, s), 1.04 (3H, t, J=7.3 Hz), 1.15 (3H, s), 1.38, 1.44 (3H x 2, 2s), 1.51-1.63 (2H, m), 2.03 (1H, t, J=6.1 Hz), 2.71 (1H, s), 3.38 (3H, s), 3.66-3.71 (1H, m), 3.77-3.82 (1H, m), 3.85 (1H, d, J=6.8 Hz), 3.95 (1H, dd, J=4.9, 8.8 Hz), 4.04 (1H, dt, J=6.8, 2.9 Hz), 4.76 (s, 1H); HRMS calcd for $C_{14}H_{25}O_6$: m/z 289.1649 ($M^+ - CH_3$). Found: m/z 289.1651.

(2*R*,3*R*,4*R*,5*R*)-3-[(1*R*,2*R*,3*E*,5*E*)-[6-(Ethoxycarbonyl)-1,2-(isopropylidenedioxy)]hexa-3,5-dienyl]-5-ethyl-4-hydroxy-2-methoxy-3,4-dimethyltetrahydrofuran (28). To a solution of **26** (17.6 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) were added PCC (100 mg, 0.46 mmol) and molecular sieves (4A, powder, 95 mg). The mixture was stirred for 1 h, and then charged on a silica gel column (2 g). The column was eluted with Et_2O, and the fractions having R_f 0.58 (AcOEt/hexane 1:2) were combined and concentrated to give **27** (17.5 mg) as a colorless oil which was used to the next step: IR 3510, 2980, 2950, 2880, 1740, 1460, 1405, 1380, 1260, 1215 cm-1; ^1H NMR (90 MHz) δ 1.06 (3H, t, J=7 Hz), 1.20 (3H, s), 1.25 (3H, s), 1.25, 1.51 (3H x 2, 2s), 1.3-1.7 (2H, m), 3.0 (1H, br s), 3.37 (3H, s), 3.8-3.9 (2H, m), 4.3-4.4 (1H, m), 4.75 (1H, s), 9.87 (1H, s). To a stirred solution of diisopropylamine (0.08 mL, 0.58 mmol) in THF (1.5 mL) was added n-BuLi (1.64 M solution in hexane, 0.28 mL, 0.46 mmol) at 0 °C. After the solution was stirred for 10 min at 0 °C, $(EtO)_2P(O)CH_2CH{=}CHCOOEt$ (0.13 mL, 0.58 mmol) was added to this solution at - 78 °C. The solution was stirred at - 78 °C for 1 h, and a THF solution (2 mL) of **27** (17.5 mg) was added. The mixture was stirred at -78 °C for 20 min and at room temperature for 40 min. Then, 2 mL of saturated aqueous NH_4Cl was added, diluted with AcOEt (30 mL). This was washed with H_2O (10 mL x 2). The organic phase

was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (AcOEt/hexane 1:4) to give **28** (16.6 mg, 72%) as a colorless oil: TLC R_f 0.60 (AcOEt/hexane 1:2); $[\alpha]_D^{22}$ +55.4°(c 0.83); IR 3520, 2980, 2940, 2880, 1720, 1645, 1460, 1450, 1380, 1370, 1310, 1260, 1230 cm^{-1}; ^1H NMR (400 MHz) δ 0.92 (3H, s), 1.05 (3H, t, J=7.3 Hz), 1.12 (3H, s), 1.30 (3H, t, J=7.3 Hz), 1.36, 1.45 (3H x 2, 2s), 1.53-1.60 (2H, m), 2.74 (1H, s), 3.39 (3H, s), 3.83 (1H, d, J=6.8 Hz), 3.93 (1H, dd, J=4.9, 8.3 Hz), 4.21 (2H, q, J=7.3 Hz), 4.41 (1H, t, J=6.8 Hz), 4.80 (1H, s), 5.93 (1H, d, J=15.1 Hz), 6.11 (1H, dd, J=6.8, 15.1 Hz), 6.45 (1H, dd, J=10.7, 15.1 Hz), 7.28 (1H, dd, J=10.7, 15.1 Hz); HRMS calcd for $C_{20}H_{31}O_7$: m/z 383.2068 (M^+-CH_3). Found: m/z 383.2095.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-7-[(1*E*,3*E*)-4-(Ethoxycarbonyl)buta-1,3-dienyl]-3-ethyl-4,6-dihydroxy-4,5-dimethyl-2,8-dioxabicylo[3.3.0]octane (29). A solution of **28** (15.5 mg, 0.04 mmol) in 60% aqueous CF_3COOH (2 mL) was stirred for 41 h. To the solution was added saturated aqueous $NaHCO_3$ (15 mL), and this was extracted with AcOEt (20 mL x 4). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (AcOEt/hexane 1:1) to give **29** (11.3 mg, 89%) as a colorless oil: TLC R_f 0.39 (AcOEt/hexane 1:1); $[\alpha]_D^{20}$ +30.9° (c 0.57); IR 3460, 2970, 2930, 2830, 1700, 1640, 1620, 1460, 1370, 1310, 1270, 1240 cm^{-1}; ^1H NMR (400 MHz) δ 1.06 (3H, t, J=7.3 Hz), 1.19 (3H, s), 1.30 (3H, t, J=7.0 Hz), 1.38 (3H, s), 1.53-1.61 (3H, m), 1.68 (1H, d, J=5.4 Hz), 3.77 (1H, dd, J=2.9, 5.4 Hz), 4.21 (2H, q, J=7.0 Hz), 4.27 (1H, dd, J=4.9, 7.8 Hz), 4.76 (1H, br s), 5.30 (1H, s), 5.96 (1H, d, J=15.6 Hz), 6.12 (1H, dd, J=4.9, 15.1 Hz), 6.67 (1H, ddd, J=1.0, 11.2, 15.1 Hz), 7.30 (1H, dd, J=11.2, 15.6 Hz); HRMS calcd for $C_{17}H_{26}O_6$: m/z 326.1727 (M^+). Found: m/z 326.1714.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-Ethyl-4,6-dihydroxy-7-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]-4,5-dimethyl-2,8-dioxabicyclo[3.3.0]octane (30). To a solution of **29** (11.0 mg, 0.03 mmol) in CH_2Cl_2 (1.5 mL) was added Dibal-H (25 wt% in toluene, 0.23 mL, 0.03 mmol) at -78 °C. The mixture was stirred at -78 °C for 2 h during which 0.23 mL of Dibal-H was added after 1 h. The mixture was quenched with H_2O (0.1 mL), and warmed to room temperature. Then, 5 mL of THF and 2 g of Na_2SO_4 were added. The inorganic solids were removed by filtration, and washed well with AcOEt. The combined filtrate and washings were concentrated in vacuo. The residue was purified by PTLC (EtOH/toluene 1:6) to give **30** (7.5 mg, 78%) as a colorless oil: TLC R_f 0.25 (EtOH/toluene 1:5); $[\alpha]_D^{23}$ +30.0° (c 0.38); IR 3400, 2970, 2930, 2880, 2860, 1660, 1630, 1460, 1380, 1355, 1290, 1260, 1200 cm^{-1}; ^1H NMR (400 MHz) δ 1.06 (3H, t, J=7.3 Hz), 1.18 (3H, s), 1.38 (3H, s), 1.52-1.60 (4H, m), 1.75 (1H, d, J=4.9 Hz), 3.69 (1H, dd, J=2.9, 4.9 Hz), 4.20-4.23 (2H, m), 4.29 (1H, dd, J=4.9, 7.3 Hz), 4.68-4.72 (1H, m), 5.27 (1H, s), 5.72 (1H, dd, J=5.4, 15.1 Hz), 5.91-5.97 (1H, m), 6.32 (1H, dd, J=10.7, 15.1 Hz), 6.56 (1H, dd, J=10.7, 15.1 Hz); HRMS calcd for $C_{15}H_{22}O_4$: m/z 266.1517 (M^+-H_2O). Found: m/z 266.1521.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-Ethyl-7-[(1*E*,3*E*)-4-formylbuta-1,3-dienyl]-4,6-dihydroxy-4,5-dimethyl-2,8-dioxabicyclo[3.3.0]octane (31). A solution of **30** (7.3 mg, 0.03 mmol) in CH_2Cl_2 (1.5 mL) was stirred in the presence of active MnO_2 (97 mg) for 1 h. The inorganic materials were removed by passing the mixture through a short silica gel column (0.5 g, Et_2O elution). The etheral eluate was concentrated in vacuo. The residue was purified by PTLC (EtOH/toluene 1:5) to give **31** (6.2 mg, 86%) as a colorless oil: TLC R_f 0.40 (EtOH/toluene 1:5); $[\alpha]_D^{23}$ +35.5° (c 0.31); IR 3450, 2970, 2930, 2880, 2850, 1680, 1640, 1430, 1380, 1260 cm^{-1}; ^1H NMR (400 MHz) δ 1.07 (3H, t, J=7.3 Hz), 1.20 (3H, s), 1.40 (3H, s), 1.51-1.62 (3H, m), 1.68 (1H, d, J=6.1 Hz), 3.82 (1H, dd, J=3.1, 6.1 Hz), 4.25 (1H, dd, J=4.9, 7.9 Hz), 4.79-4.81 (1H, m), 5.32 (1H, s), 6.20-6.30 (2H, m), 6.80 (1H, dd, J=11.0, 15.3 Hz), 7.14 (1H, dd, J=11.0, 15.3 Hz), 9.60 (1H, d, J=7.9 Hz); HRMS calcd for $C_{15}H_{22}O_5$: m/z 282.1465 (M^+). Found: m/z 282.1482.

Mixture of (1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-Ethyl-4,6-dihydroxy-7-[(1*E*,3*E*,5*R* and *S*)-5-hydroxy-6-(4-methoxy-5-methyl-2-pyron-6-yl)hexa-1,3-dienyl]-4,5-dimethyl-2,8-dioxabicyclo[3.3.0]octane (33). To a solution of diisopropylamine (0.04 mL, 0.26 mmol) in THF (0.8 mL) was added n-BuLi (1.64 M solution in hexane, 0.13 mL, 0.22 mmol). After the solution was stirred at 0 °C for 10 min, HMPA (0.05 mL, 0.26 mmol) was added. The solution was stirred at 0 °C for 10 min, and cooled to -78 °C. To this was added a THF solution (0.5 mL) of **32** (33.9 mg, 0.22 mmol), and the resulting yellow solution was stirred at

−78 °C for 5 min. A THF solution (2 mL) of **31** (6.2 mg, 0.02 mmol) was then added. After the mixture was stirred at −78 °C for 15 min, saturated aqueous NH_4Cl (2 mL) was added. The mixture was warmed to room temperature, and diluted with H_2O (10 mL). This was extracted with AcOEt (10 mL x 6). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by PTLC (EtOH/toluene 1:3) to give **33** (2.7 mg, 28%) as a colorless oil. The aldehyde **31** (2.0 mg, 32%) was recovered. **33**: TLC R_f 0.45 (EtOH/toluene 1:4); IR 3300, 2950, 2930, 2880, 2850, 1705, 1645, 1565, 1460, 1405, 1300, 1245, 1200 cm^{-1}; ^1H NMR (400 MHz) δ 1.06 (3H, t, J=7.3 Hz), 1.18 (3H, s), 1.38 (3H, s), 1.52-1.60 (3H, m), 1.71-1.78 (3H, m), 1.91 (3H, s), 2.80-2.87 (1H, m), 3.69-3.71 (1H, m), 3.83 (3H, s), 4.30 (1H, dd, J=5.2, 7.6 Hz), 4.64-4.69 (2H, m), 5.27 (1H, s), 5.46 (1H, s), 5.72-5.84 (2H, m), 6.27-6.35 (1H, m), 6.50 (1H, dd, J=11.0, 15.9 Hz); HRMS calcd for $C_{23}H_{30}O_7$: m/z 418.1990 (M^+-H_2O). Found: m/z 418.1991.

(1*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-3-Ethyl-4,6-dihydroxy-7-[(1*E*,3*E*,5*E*)-6-(4-methoxy-5-methyl-2-pyron-6-yl)hexa-1,3,5-trienyl]-4,5-dimethyl-2,8-dioxabicyclo[3.3.0]octane, (+)-Asteltoxin (1). A mixture of **33** (2.7 mg, 0.006 mmol), p-toluenesulfonyl chloride (31.0 mg, 0.16 mmol), DMAP (8.3 mg), and Et_3N (0.1 mL) in CH_2Cl_2 (2 mL) was stirred for 18 h. The resulting yellow solution was concentrated in vacuo. The residue was purified by PTLC (EtOH/toluene 1:5) to give **1** (1.9 mg, 73%) as yellow powders: TLC R_f 0.47 (EtOH/toluene 1:5); $[\alpha]_D^{23}$ +20.0°(c 0.10, MeOH); IR 3440, 3010, 2970, 2930, 2880, 2860, 1700, 1625, 1565, 1540, 1460, 1410, 1250, 1210, 1180 cm^{-1}; ^1H NMR (400 MHz) δ 1.07 (3H, t, J=7.3 Hz), 1.19 (3H, s), 1.39 (3H, s), 1.51-1.59 (2H, m), 1.61 (1H, br s), 1.72 (1H, d, J=4.9 Hz), 1.99 (3H, s), 3.73 (1H, dd, J=2.9, 4.9 Hz), 3.84 (3H, s), 4.30 (1H, dd, J=5.1, 7.6 Hz), 4.74-4.76 (1H, m), 5.29 (1H, s), 5.51 (1H, s), 5.86 (1H, dd, J=4.9, 15.1 Hz), 6.39 (1H, d, J=15.1 Hz), 6.42 (1H, dd, J=10.7, 14.6 Hz), 6.52 (1H, dd, J=10.7, 14.6 Hz), 6.66 (1H, ddd, J=1.5, 10.7, 15.1 Hz), 7.19 (1H, dd, J=10.7, 15.1 Hz); ^{13}C NMR (100 MHz) δ 8.9, 11.2, 16.0, 17.9, 21.6, 56.2, 62.2, 78.6, 81.0, 82.9, 89.0, 89.7, 107.9, 111.7, 120.2, 129.1, 132.9, 134.0, 135.3, 136.2, 154.1, 164.0, 170.7; , HRMS calcd for $C_{23}H_{30}O_7$: m/z 418.1989 (M^+). Found: m/z 418.1983.

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18. The major diastereomer **15** was converted to the bistetrahydrofuran derivative in 70% yield by exposure to 60% aqueous CF_3COOH at 5 °C for 4 days. Exhaustive deacylation (MeONa, r.t.) of this product followed by isopropylidenation resulted in the formation of the isopropylidene ketal in 87% yield. The spectral evidence that the ketal was formed between two secondary hydroxyl groups verified the structures of **15** and the bistetrahydrofuran derivative.

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