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Synthesis of Optically Active Hexahydrofuro[2,3-*b*]furan, A Nonchromophore Moiety of Asteltoxin

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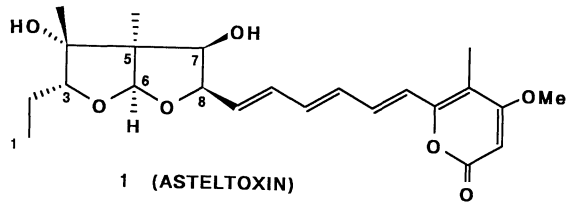
An optically active nonchromophore moiety of asteltoxin carrying a hexahydrofuro[2,3-*b*]furan structure has been successfully synthesized from a branched-chain D-xylohexofuranose derivative.

Of mycotoxins possessing inhibitory activities to mitochondrial ATPase, asteltoxin (**1**) was isolated from cultures of *Aspergilus stellatus* Curzi, and its structure has been established by spectroscopic data and an X-ray crystallographic analysis.[1] In addition to the absolute configuration, asteltoxin (**1**) containing the characteristic hexahydrofuro[2,3-*b*]furan has served an interesting target to synthetic chemists, and up to now two research groups have presented total synthesis of this mycotoxin in (±)- and (+)-forms.[2] We have also been interested in the absolute configuration which should be as depicted in Fig. 1, from view points of our extensive investigation on isolation, structural determination and synthesis of the metabolites of *Penicillium citreoviride* B. and related mycotoxins.[3] Therefore, we have independently started the synthetic study on **1**, in which an optically active tetrahydrofuran derivative (**2**) could be synthesized. As anticipated, comparison of the optical rotation value with a natural product indicated that **1** has the same absolute configuration as those of citreoviridin class mycotoxins, which have been formed from sugars carrying D-configurations. We describe herein our research process.[4]

Results and Discussion

The known branched chain sugar (**3**)[3] was chosen as the starting material in which the carbon sequence from C-1 to C-4 in **1** has already been set up. Thus,



1 (ASTELTOXIN)

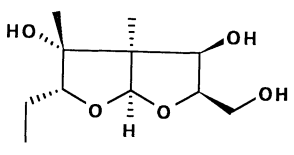


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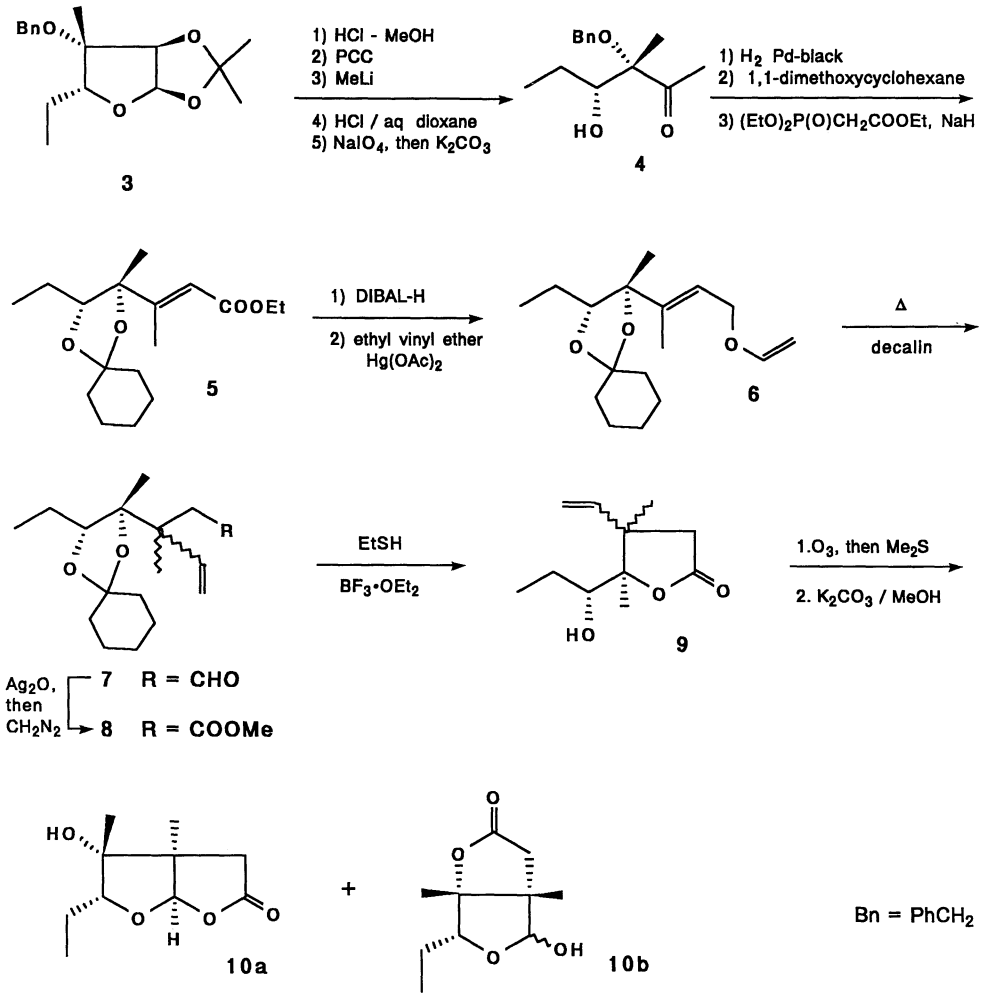
Fig. 1.

compound **3** was transformed into the corresponding glycoside to modify the C-2 OH group. After oxidation of the methyl glycoside, the resulted carbonyl group was methylated (MeLi) to give a tertiary alcohol, and then a vicinal diol obtained by acid-hydrolysis was oxidized with $NaIO_4$, followed by treatment with K_2CO_3 to give an acyclic methyl ketone (**4**) (62% yield from **3**). After removal of the benzyl group in **4**, the vicinal diol was again protected with that of the cyclohexylidene group. Carbon chain elongation was accomplished with Horner–Emmons reaction to afford an α,β-unsaturated ester (**5**) in 99% yield. In the following step, Claisen rearrangement (**6**→**7**) might be available to construct the quaternary carbon at C-5 position in **1**. To realize this strategy, **5** was subjected to DIBAL reduction and the resulted allyl alcohol was reacted with ethyl vinyl ether to give **6**. Reaction of **6** in decalin at 200 °C gave rise to the expected rearrangement to ca. 1:1 mixture of aldehydes (**7**) in 89% yield. Unfortunately, the stereoselectivity of the reaction products could not be improved, therefore the following steps were performed without further separation. The aldehyde function in **7** was transformed into the corresponding methyl esters (**8**) in two steps. Treatment of **8** with EtSH–$BF_3 \cdot OEt_2$ effected deprotection of the acetal group and concomitant ring rearrangement to γ-lactone (**9**) having the IR absorption band at 1770 cm^{-1}. Conversion of **9** to a mixture of **10a** and **10b** was effected with ozonization, followed by exposure to K_2CO_3 in MeOH. The resulted **10a** and **10b** could be separated after acetylation.

As indicated in Scheme 2, under hydrogen chloride in MeOH conditions, the γ-lactone moiety in **10a** was opened to give a methyl glycoside (**11**), from which a reaction process was started to introduce two new chiral centers at C-6 and 7 positions in **1** or **2**. Compound **11** was reacted with $LiAlH_4$ to give an alcohol, which could be converted to a vinyl derivative (**12**) by *o*-nitrobenzeneselenenyl cyanide. Ozonization of **12**, followed by Horner–Emmons olefination underwent the desired C-1 unit elongation to **13**, which was also obtained from **10b** as follows.

Conversion of **10b** to a methyl glycoside (**14**) was smoothly effected in three steps. Compound **14** so far obtained was transformed into an acyclic triol (**15**).



Scheme 1.

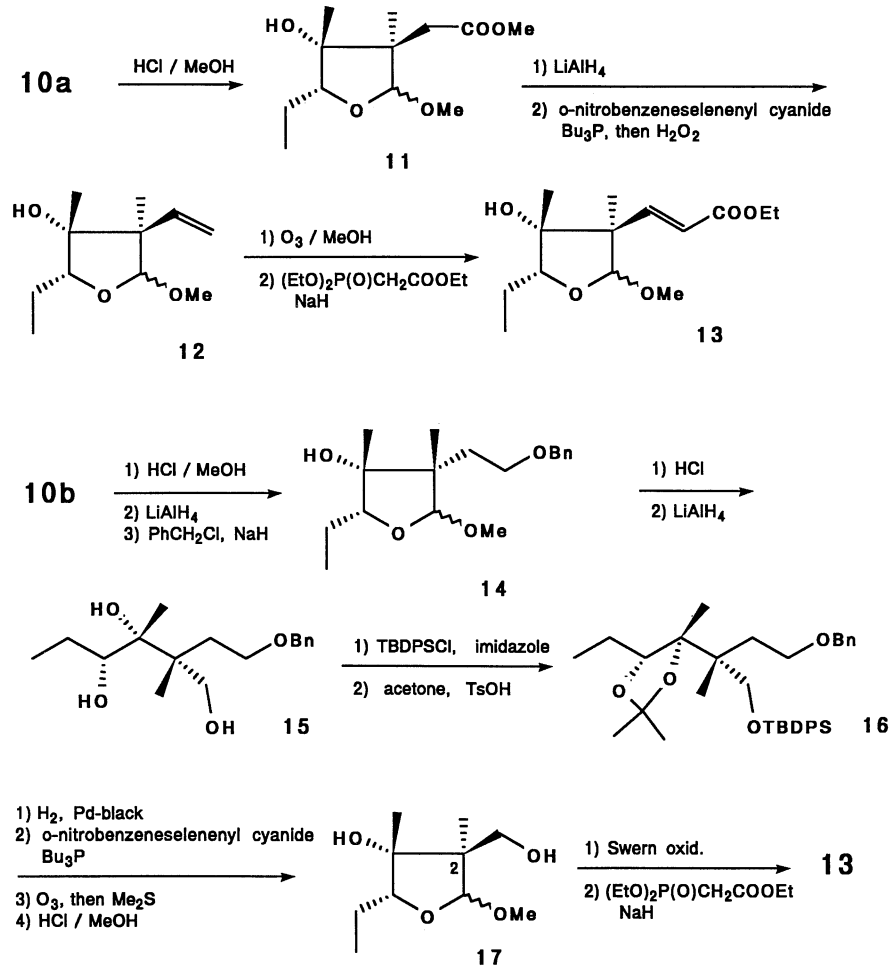
Selective protection of **15** afforded **16** in 84% yield, and then the C-1 unit was cleaved in four steps to give **17**, in which the stereochemistry of C-3 — C-5 positions in **1** has set as the required configuration. Successive Swern oxidation and Horner–Emmons reaction effected carbon-chain elongation of **17** to yield **13**.

Compound **13** so far obtained was converted to an allyl benzyl ether (**18**) in two steps. Treatment of **18** with OsO_4 afforded a mixture of vicinal diols, which was subjected to acidic conditions [catalytic camphorsulfonic acid (CsOH) in benzene] to give a chromatographically separable mixture of **19a** and **19b**. The desired **19a** could be readily distinguished from **19b** by comparison of the optical rotations (**19a**: $[\alpha]_D$+55.2°; **19b**: $[\alpha]_D$+2.8°). Finally, catalytic hydrogenation of **19a** provided the hexahydrofuro[2,3-*b*]furan (**2**), the structure of which was supported under full range of spectral data. Particularly, the optical rotation of the synthetic **2** ($[\alpha]_D$ +53°) was in good agreement with that of an authentic sample ($[\alpha]_D$ +52.9°)[2c] derived from asteltoxin (**1**).

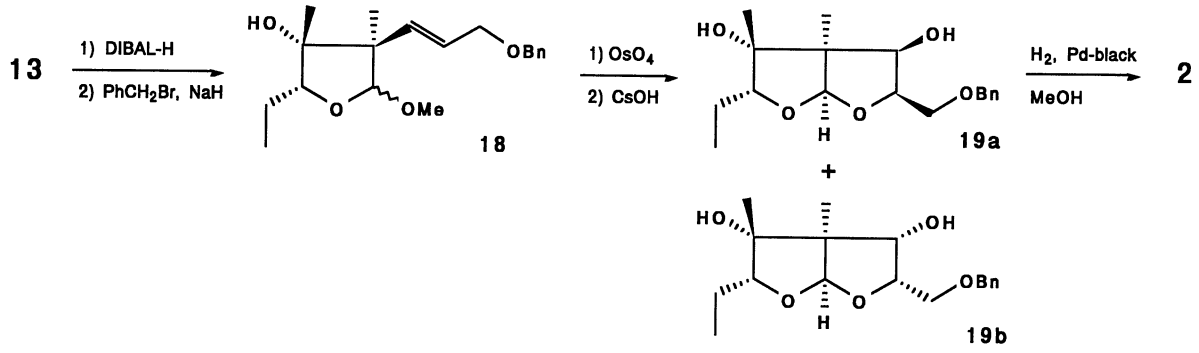
Experimental

All the melting points were obtained on a Mitamura Riken melting point apparatus and uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR spectra were obtained on a Varian EM-390 (90 MHz) or a JEOL JNM GX-400 (400 MHz) NMR spectrometer in deuteriochloroform solution using tetramethylsilane as an internal standard, unless otherwise stated. High resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating with an ionization energy (70 eV). Optical rotations were measured on a JASCO DIP-360 polarimeter in chloroform, unless otherwise stated. Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merck A. C. West Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Katayama silica-gel (K 070) was used for column chromatography.

Conversion of 3 to the Acyclic Ketone (4). A solution of 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-xylohexofuranose (**3**)[3] (4.66 g) in 0.75 M hydrogen chloride (1 M=1 mol dm^{-3}) in MeOH (60 ml) was stirred at room temperature for 5 h. The resulted reaction mixture was



Scheme 2.



Scheme 3.

evaporated to give a residue, which on purification by silica-gel column chromatography [40 g, hexane–EtOAc (4:1)] afforded a methyl glycoside (4.30 g), which was directly oxidized at reflux temperature for 2 h with pyridinium chlorochromate (PCC) (10 g) in benzene (300 ml) in the presence of excess Celite to yield 3.63 g of the desired ketone derivative. To a solution of the ketone (750 mg) in THF (50 ml) was added MeLi (4.3 ml, 0.99 M hexane solution) at −78 °C under Ar. The mixture was stirred at the same temperature for 1.5 h, and quenched in a usual manner to give a crude product which was purified by preparative TLC [hexane–EtOAc (3:1)] to give a methyl derivative (780 mg). The methyl glycoside (700 mg) was hydrolyzed at room temperature for 6 d in 12 M HCl (4 ml) – dioxane

(3 ml) – H_2O (10 ml) to give a 1,2-diol derivative (490 mg). A mixture of the diol (2.08 g) and $NaIO_4$ (3.4 g) in MeOH (120 ml) – H_2O (120 ml) was stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated to give a residue which was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to yield a crude product, which was treated with catalytic K_2CO_3 in MeOH at room temperature for 1 h to afford an oily methyl ketone (**4**) (1.84 g): $[\alpha]_D^{24}$ −32.5° (*c* 0.81); IR (film) 3480 and 1710 cm^{-1}; ^1H NMR δ=0.98 (3H, t, *J*=7.5 Hz), 1.33 (3H, s), 1.2—1.6 (2H, complex), 2.20 (3H, s), 2.45 (1H, broad s), 3.67 (1H, dd, *J*=4.5, 8 Hz), 4.37 (1H, d, *J*=12 Hz), 4.50 (1H, d, *J*=12 Hz), and 7.34 (5H, s). Found: *m/z* 237.1480. Calcd for $C_{14}H_{21}O_3$: M+1, 237.1489.

Synthesis of the α,β-Unsaturated Ester (5). Compound **4** (1.86 g) was hydrogenated at room temperature for 5 h in MeOH (50 ml) in the presence of catalytic Pd-black to give a diol (1.17 g): mp 56—57 °C (from hexane–EtOAc); $[\alpha]_D^{23}$ +65.2° (*c* 0.67). A solution of the diol (1.17 g) and 1,1-dimethoxycyclohexane (3.5 g) in DMF (50 ml) in the presence of catalytic TsOH was heated at 60 °C (20 torr) for 2 d. The reaction mixture was partitioned between EtOAc and H_2O. The EtOAc layer was washed with sat. aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified on a silica-gel column [50 g, hexane/EtOAc (15:1)] to afford an oily cyclohexylidene derivative (1.35 g): $[\alpha]_D^{25}$ −19.5° (*c* 1.02). Ethyl diethoxyphosphinylacetate [$(EtO)_2P(O)CH_2COOEt$] (7.84 g) in anhydrous THF (5 ml) was treated with NaH (1.58 g, 60% dispersion in mineral oil) at 0 °C for 5 min under Ar. To this mixture was added the cyclohexylidene derivative (1.49 g) in THF, and the reaction mixture was stirred at room temperature overnight. The resulted solution was partitioned between EtOAc and H_2O, and the EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which on purification by silica-gel column chromatography [60 g, hexane–EtOAc (1:1)] yielded an oily α,β-unsaturated ester (**5**) (1.93 g): $[\alpha]_D^{26}$ +8.9° (*c* 1.31); IR (film) 1720 and 1640 cm^{-1}; ^1H NMR δ=1.03 (3H, t, *J*=7.5 Hz), 1.21 (3H, s), 1.30—1.80 (12H, complex), 2.15 (3H, s), 3.73 (1H, dd, *J*=4.5, 7.5 Hz), 4.13 (2H, q, *J*=7.5 Hz), and 6.05 (1H, broad s). Found: *m/z* 296.1981. Calcd for $C_{17}H_{28}O_4$: M, 296.1985.

Conversion of 5 to the Vinyl Ether (6). To a solution of **5** (1.89 g) in dry THF (25 ml) was added diisobutylaluminum hydride (DIBAL-H) (13 ml, 1.5 M toluene solution) at −72 °C, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of EtOAc and aqueous Rochelle salt, and the resulted mixture was stirred for another 30 min, and filtered. The filtrate was partitioned between EtOAc and H_2O, and the EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified on a silica-gel column [50 g, hexane–EtOAc (3:1)] to give an allylic alcohol (1.60 g). A mixture of the allylic alcohol (40 mg) and $Hg(OAc)_2$ (10 mg) in ethyl vinyl ether (2 ml) was refluxed for 7 h under Ar. The reaction mixture was partitioned between benzene and H_2O, and the organic layer was washed with sat. aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then evaporated. Chromatographic purification [Florisil 1 g, hexane–EtOAc (10:1)] of the crude product afforded a vinyl ether (**6**) (41 mg): $[\alpha]_D^{25}$ +10.3° (*c* 1.94); IR (film) 1630 and 1610 cm^{-1}; ^1H NMR δ=1.00 (3H, t, *J*=7.5 Hz), 1.18 (3H, s), 1.25—1.65 (12H, complex), 1.70 (3H, s), 3.73 (1H, dd, *J*=4.5, 11 Hz), 4.00 (2H, complex), 4.27 (2H, broad d, *J*=7.5 Hz), 5.68 (1H, broad t, *J*=7.5 Hz), and 6.45 (1H, dd, *J*=7.5, 15 Hz). Found: *m/z* 280.2030. Calcd for $C_{17}H_{28}O_3$: M, 280.2036.

Claisen Rearrangement of 6. A decalin solution of **6** (70 mg in 5 ml) under Ar in a sealed tube was heated at 200 °C for 2 h. The mixture was charged on a silica-gel column (10 g) and eluted successively with hexane and hexane–EtOAc (10:1) to give a ca. 1:1 mixture of the desired aldehydes (**7**) (62 mg): IR (film) 1720 and 1620 cm^{-1}; ^1H NMR δ=9.70 (1H, complex). This mixture was used for the next reaction without separation.

Synthesis of the Methyl Esters (8). To a stirred solution of **7** (1.20 g) and $AgNO_3$ (1.54 g) in EtOH (60 ml) and H_2O (6 ml) was gradually added aq NaOH solution (1.44 g in 24 ml) over 5 min, and then the resulted mixture was stirred at room temperature for an additional hour. The reaction mixture was filtered, and the filtrate was evaporated to give a residue, which was extracted with EtOAc. The EtOAc solution was successively washed with H_2O, 2 M HCl, and brine. After being dried over anhydrous Na_2SO_4, the solution was evaporated to give a crude product, which was dissolved in EtOAc (10 ml), and then treated with CH_2N_2 (10 ml, ether solution) at room temperature for 10 min. After evaporation, the resulted product was separated by preparative TLC [hexane–EtOAc (10:1)] to give 1.11 g of **8**: IR (film) 1740 and 1640 cm^{-1}; ^1H NMR δ=3.57 (3H, s). This mixture was subjected to the next reaction without further purification.

Formation of the γ-Lactone (9). A mixture of **8** (1.15 g), EtSH (2.1 ml) and $BF_3 \cdot OEt_2$ (1.4 ml) in CH_2Cl_2 (40 ml) was stirred at 0 °C, and then gradually warmed up to room temperature during 5 h. The resulted mixture was partitioned between $CHCl_3$ and H_2O, and the $CHCl_3$ layer was washed with saturated aq $NaHCO_3$, dried over anhydrous Na_2SO_4, and then evaporated to give a residue, which on purification by preparative TLC [hexane–EtOAc (2:1)] afforded a 1:1 mixture of **9** (670 mg): IR (film) 3480, 1770, and 1640 cm^{-1}; ^1H NMR δ=1.22 (3H, broad s), 1.27 (3H, broad s), 2.33 (0.5 H, d, *J*=18 Hz), 2.38 (0.5 H, d, *J*=18 Hz), 2.85 (0.5 H, d, *J*=18 Hz), and 2.92 (0.5 H, d, *J*=18 Hz). This mixture was used for the next ozonization without further separation.

Synthesis of the Hexahydrofuro[2,3-b]furan (10a) and Its Isomer (10b). Ozone was passed through a solution of **9** (580 mg) in MeOH (30 ml) at −75 °C for 15 min. After excess ozone was purged with Ar, Me_2S (3 ml) was added to the stirred solution, which was gradually warmed up to room temperature during 30 min. The mixture was evaporated, and the resulted syrup was treated with catalytic K_2CO_3 in MeOH (40 ml) at room temperature for 2 h. After being neutralized by adding AcOH, the mixture was evaporated to give a crude mixture of **10a** and **10b**, which on acetylation yielded a chromatographically separable mixture [preparative TLC, benzene–acetone (5:1)] of **10a** (269 mg) and monoacetylated **10b** (307 mg).

10a: $[\alpha]_D^{24}$ +52.8° (*c* 0.59); IR (film) 3470 and 1780 cm^{-1}; ^1H NMR δ=1.05 (3H, t, *J*=7.5 Hz), 1.17 (3H, s), 1.30 (3H, s), 1.57 (2H, complex), 1.88 (1H, broad s), 2.27 (1H, d, *J*=18 Hz), 2.67 (1H, d, *J*=18 Hz), 3.83 (1H, dd, *J*=4.5, 6 Hz), and 5.55

(1H, s). Found: *m/z* 200.1037. Calcd for $C_{10}H_{16}O_4$: M, 200.1047.

10b (as acetate): IR (film) 1790 and 1750 cm^{-1}; ^1H NMR δ=1.02 (3H, t, J=7.5 Hz), 1.15 (3H, s), 1.40 (3H, s), 1.65 (2H, complex), 2.08 (3H, s), 2.45 (1H, d, J=18 Hz), 2.83 (1H, d, J=18 Hz), 3.81 (1H, t, J=6 Hz), and 6.08 (1H, s). Treatment of this anomeric mixture with K_2CO_3 in MeOH effected deacylation, and the crude product was used for the next step without purification.

Conversion of 10a to the α,β-Unsaturated Ester (13). A solution of **10a** (16 mg) in 0.75 M hydrogen chloride in MeOH (1 ml) was kept at room temperature for 2 d. The mixture was neutralized with $NaHCO_3$ and then evaporated. The residue so far obtained was separated by preparative TLC [hexane–EtOAc (2:1)] to afford **11** (16 mg) and the recovered starting material (1 mg).

11: IR (film) 3500 and 1730 cm^{-1}; ^1H NMR δ=3.40 (3H, s), 3.70 (3H, s), 4.50 (0.25H, s), and 5.05 (0.75H, s).

Compound **11** (96 mg) was treated with $LiAlH_4$ (45 mg) in dry ether (5 ml) at room temperature for 1 h. The reaction was quenched in a usual manner to give an alcohol (85 mg), which was dissolved in dry THF (5 ml). To this solution under Ar were added *o*-nitrobenzeneselenenyl cyanide (170 mg) and Bu_3P (0.19 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The resulted residue was purified by preparative TLC [hexane–EtOAc (2:1)] to give a selenenyl derivative (162 mg). The selenenyl derivative (242 mg) was dissolved in THF (12 ml), and 35% aq H_2O_2 (0.75 ml) was added to this solution. After being stirred at room temperature overnight, the reaction mixture was partitioned between EtOAc and H_2O. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give a residue, which on purification by preparative TLC [hexane–EtOAc (3:1)] afforded an anomeric mixture (**12**) (117 mg). Treatment of **12** (68 mg) with ozone as the case of **9** gave a crude aldehyde, which was dissolved in dry THF (3 ml). To this solution were added $(EtO)_2P(O)CH_2COOEt$ (0.33 ml) and NaH (67 mg, 60% dispersion in mineral oil), and then the mixture was stirred at room temperature for 2 h. After usual work-up, the crude product was purified by preparative TLC [hexane–EtOAc (2:1)] to afford a ca. 2:1 mixture of esters (**13**) (64 mg): IR (film) 3520, 1720, and 1650 cm^{-1}; ^1H NMR δ=3.37 (3H, s), 3.78 (0.36H, t, J=6 Hz), 3.83 (0.64H, t, J=6 Hz), 4.17 (0.72H, q, J=6 Hz), 4.22 (1.28H, q, J=6 Hz), 4.55 (0.64H, s), 4.60 (0.36H, s), 5.92 (1H, d, J=15 Hz), 6.85 (0.36H, d, J=15 Hz), and 7.28 (0.36H, d, J=15 Hz). This mixture was used for the next step without separation.

Conversion of 10b to 16 via the Glycoside (15). A solution of **10b** (82 mg) in 0.75 M hydrogen chloride in MeOH (3 ml) was stirred at room temperature overnight. After being neutralized with $NaHCO_3$, the mixture was evaporated and purified on a silica-gel column (1 g, EtOAc) to yield a methyl glycoside (83 mg), which was reduced with $LiAlH_4$ (45 mg) in ether (5 ml) at room temperature for 1 h. Usual work-up afforded a crude product, which was chromatographed on a silica-gel column (1 g, EtOAc) to give an alcohol (84 mg). A mixture of the alcohol (84 mg), benzyl chloride (0.053 ml) and NaH (37 mg, 60% dispersion in mineral oil) in DMF (3 ml) was stirred at room temperature for 1 h. The reaction mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by preparative TLC [hexane–EtOAc (3:1)] to give a benzyl derivative (**14**) (111 mg): IR (film) 3500, 1600, and 1580 cm^{-1}. Compound **14** (91 mg) was then hydrolyzed in 1 M HCl in dioxane (4 ml) at room temperature for 4 h. After being neutralized, the reaction mixture was evaporated to give a residue, which was extracted with EtOAc. The EtOAc solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was separated by preparative TLC [hexane–EtOAc (2:1)] to give a hemiacetal (72 mg) as well as 10 mg of the starting material. The hemiacetal (72 mg) so far obtained was treated with $LiAlH_4$ (48 mg) in ether (4 ml) at room temperature for 2 d. Usual work-up followed by preparative TLC purification [hexane–EtOAc (1:1)] afforded an oily triol (**15**) (22 mg) and the unreacted hemiacetal (13 mg).

15: $[\alpha]_D^{23}$ +23.2° (*c* 1.12); IR (film) 3400 cm^{-1}; ^1H NMR δ=0.77 (3H, s), 1.00 (3H, t, J=7.5 Hz), 1.02 (3H, s), 4.50 (2H, s), and 7.32 (5H, broad s).

A mixture of **15** (22 mg), *t*-butyldiphenylsilyl chloride (TBDPSCl) (0.03 ml) and imidazole (8 mg) in DMF (1 ml) was stirred at room temperature overnight. Extractive work-up followed by preparative TLC purification [hexane–EtOAc (2:1)] yielded a monosilylated derivative (35 mg), which was dissolved in acetone (1 ml), and kept at room temperature for 6 h in the presence of catalytic TsOH. After neutralization, the mixture was filtered, and the filtrate was evaporated to give a residue, which on purification by preparative TLC [hexane–EtOAc (4:1)] gave an acetonide (**16**) (36 mg): $[\alpha]_D^{22}$ −2.36° (*c* 1.52); IR (film) 1580 cm^{-1}; ^1H NMR δ=0.93 (3H, s), 0.95—1.20 (15H, complex), 1.33 (3H, s), 1.40—1.60 (2H, complex), 1.76 (2H, dd, J=7.5, 9 Hz), 3.30—3.70 (3H, complex), 3.85 (2H, q, J=7.5 Hz), 4.40 (2H, s), 7.26 (5H, broad s), and 7.30—7.80 (10H, complex). Found: *m/z* 559.3242. Calcd for $C_{35}H_{47}O_4Si$: M–Me, 559.3241.

Conversion of 16 to 13 via the Glycoside (17). Compound **16** (36 mg) was hydrogenated in MeOH (2 ml) in the presence of catalytic Pd-black at room temperature for 2 h to give an alcohol (28 mg), which was converted to the corresponding vinyl derivative (23 mg) as the case of **12**. The vinyl derivative so far obtained was ozonized in MeOH (1 ml) at −78 °C for 5 min. After reductive quenching with Me_2S, a crude product was dissolved in 0.75 M hydrogen chloride in MeOH (1 ml), and kept at room temperature for 4 d to give a methyl glycoside (**17**) (6.3 mg): IR (film) 3440 cm^{-1}. To a stirred solution of $(COCl)_2$ (0.013 ml) and DMSO (0.022 ml) in dry CH_2Cl_2 (1 ml) at −63 °C under Ar was added **17** (6.3 mg) in dry CH_2Cl_2 (1 ml), and the temperature was elevated to −30 °C during 30 min. After addition of Et_3N (0.13 ml), the reaction mixture was stirred at the same temperature for another 5 min. The resulted mixture was partitioned between $CHCl_3$ and H_2O, and the $CHCl_3$ layer was dried over anhydrous Na_2SO_4, followed by evaporation to give a yellow syrup. After co-evaporation with benzene, the product was dissolved in dry THF (1 ml), and reacted with $(EtO)_2P(O)CH_2COOEt$ (0.036 ml) in the presence of NaH (7.2 mg, 60% dispersion in mineral oil) at room temperature overnight. Extractive work-up followed by preparative TLC purification [hexane–EtOAc (4:1)] gave **13**

(4.8 mg).

Synthesis of the Hexahydrofuro[2,3-b]furan Derivatives (19a, 19b). A mixture of **13** (64 mg) in dry THF (5 ml) under Ar was treated with DIBAL-H (0.79 ml, 1.5 M toluene solution) at −78 °C for 3 h. After usual work-up, the crude product was purified by preparative TLC [hexane–EtOAc (1:2)] to give an allylic alcohol (34 mg) and the unreacted starting material (8 mg). To a solution of the allylic alcohol (34 mg) in DMF (2 ml) were added benzyl bromide (0.09 ml) and NaH (30 mg, 60% dispersion in mineral oil) at 0 °C, and then the reaction mixture was stirred at room temperature for 1 d. Usual work-up followed by preparative TLC purification [hexane–EtOAc (4:1)] yielded a benzyl derivative (**18**) (45 mg). A mixture of **18** (34 mg) and OsO_4 (42 mg) in dioxane (1.5 ml) and pyridine (0.02 ml) was stirred at room temperature for 2.5 h, and an excess amount of aq $NaHSO_3$ was added to the mixture. After being stirred overnight, the resulted mixture was partitioned between EtOAc and H_2O, and the EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by preparative TLC [hexane–EtOAc (2:1)] to give an oily diol. The diol so far obtained was dissolved in benzene (2 ml), and the solution in the presence of catalytic CsOH was stirred at room temperature for 2.5 h. The reaction mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with saturated aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was separated by preparative TLC [hexane–EtOAc (2:1)] to give **19a** (7 mg) and **19b** (18 mg).

19a: $[\alpha]_D^{24}$ +55.4° (*c* 1.01); IR (film) 3430, 1600, and 1580 cm^{-1}; ^1H NMR δ=1.04 (3H, t, *J*=7.5 Hz), 1.16 (3H, s), 1.50—1.65 (2H, complex), 1.57 (3H, s), 1.60 (1H, m), 1.73 (1H, m), 3.51 (1H, d, *J*=5 Hz), 3.87—3.95 (3H, complex), 4.32 (2H, complex), 4.56 (1H, d, *J*=12 Hz), 4.61 (1H, d, *J*=12 Hz), 4.66 (1H, d, *J*=12 Hz), 4.71 (1H, d, *J*=12 Hz), 5.39 (1H, s), and 7.31—7.36 (10H, complex). Found: *m/z* 413.2355. Calcd for $C_{25}H_{33}O_5$: M+1, 413.2326.

19b: $[\alpha]_D^{24}$ +2.8° (*c* 1.39); IR (film) 3470, 1600, and 1580 cm^{-1}; ^1H NMR δ=1.03 (3H, t, *J*=7.5 Hz), 1.18 (3H, s), 1.49 (3H, s), 1.68 (1H, m), 1.90 (1H, m), 3.71 (1H, dd, *J*=4, 10 Hz), 3.79 (1H, dd, *J*=7, 10 Hz), 3.87 (1H, dd, *J*=4, 10 Hz), 4.14 (1H, d, *J*=5.5 Hz), 4.46 (1H, m), 4.51 (1H, d, *J*=11 Hz), 4.54 (1H, d, *J*=11 Hz), 4.63 (1H, d, *J*=11 Hz), 4.68 (1H, d, *J*=11 Hz), 5.04 (1H, s), and 7.30 (10H, complex). Found: *m/z* 413.2333. Calcd for $C_{25}H_{33}O_5$: M+1, 413.2326.

Synthesis of 2. Compound **19a** (6 mg) was hydrogenated in MeOH (1 ml) in the presence of catalytic Pd-black at room temperature for 1 h to give 4 mg of **2**: $[\alpha]_D^{22}$ +53° (*c* 0.36, MeOH); IR (film) 3420 cm^{-1}; ^1H NMR δ=1.04 (3H, t, *J*=7.5 Hz), 1.11 (3H, s), 1.40 (3H, s), 1.55 (2H, complex), 3.99 (2H, complex), 4.09 (1H, dd, *J*=4, 12.5 Hz), 4.28 (2H, complex), and 5.34 (1H, s). Found: *m/z* 232.1281. Calcd for $C_{11}H_{20}O_5$: M, 232.1309.

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