# TOTAL SYNTHESIS OF (+)-ASTELTOXIN<sup>1</sup>

Kin-ichi Tadano,<sup>\*</sup> Hirohiko Yamada, Yoko Idogaki, Seiichiro Ogawa, and Tetsuo Suami<sup>†</sup> Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama, 223, Japan

(Received in Japan 13 November 1989)

Abstract : A total synthesis of (+)-asteltoxin, a novel mycotoxin isolated from <u>Aspergillus stellatus</u>, 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 <u>Aspergillus</u> <u>stellatus</u> Curzi (MRC 277).<sup>2</sup> Based on a combination of the spectral analysis and a single-crystal X-ray crystallography, the relative stereochemistry of 1 was determined.<sup>2</sup> 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)<sup>3</sup> and (-)-aurovertin B (3)<sup>4</sup>, both potent inhibitors of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme systems, implicated similar bio-activity for 1. In fact, asteltoxin (1) was found to be a potent inhibitor of <u>E</u>. <u>Coli</u>. BF<sub>1</sub>-ATPase activity.<sup>5</sup> Biosynthetic studies of the unusual bistetrahydrofuran moiety of 1 have been disclosed by Vlaggaar.<sup>6</sup> In the past several years efforts have resulted in the total syntheses of 1, 2, <sup>7</sup> 3, <sup>8</sup> and related mycotoxins.<sup>9</sup>



+ Present address: Department of Chemistry, Meisei University, Hino, Tokyo 191, Japan

In 1983, the first synthesis of racemic bistetrahydrofuran moiety of 1 was reported by Schreiber and Satake.<sup>10</sup> Soon afterward, they completed the first total synthesis of  $(\pm)-1$ .<sup>11</sup> 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.<sup>12</sup> Herein, we report a total synthesis of natural (+)-1, which features a carbohydrate-mediated chiron approach.<sup>13</sup>

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.<sup>14</sup> 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<sub>3</sub>P=CHCOOEt in refluxing benzene afforded the (E)- $\alpha$ , $\beta$ -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.**  $Me_3CC(0)Cl$ , pyridine, DMAP,  $CH_2Cl_2$ , r.t.. **g.** 60% aqueous  $CF_3COOH$ , 5 °C, 64 h. **h.** NaIO<sub>4</sub>,  $H_2O/MeOH$ , r.t.. **i.** MeOH, Amberlite IR-120 (H<sup>+</sup>), reflux.

2354

later stages. Dissobutylaluminum 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<sub>3</sub>COOH at 5 °C to give a diastereomeric mixture of hemiacetal (11) in 78% yield. NaIO<sub>4</sub> 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<sup>+</sup>)- 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.<sup>15</sup>

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<sup>16</sup>[catalytic OsO, 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.<sup>17</sup> The stereochemistry of the cis-diol in the main product 15 was confirmed to be the desired  $\underline{R}, \underline{R}$ -configuration by some chemical transformations.<sup>18</sup> 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  $^\circ$ 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<sup>19</sup> 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 N1 resulted in the formation of 23 For functionalization of the secondary hydroxyl group in 23. (78%). the primary hydroxyl group was protected to be the pivaloyl ester (24) in 87% yield. Pyridinium chlorochromate (PCC) oxidation<sup>20</sup> of 24 gave a tetrahydrofuranone derivative (25). Grignard addition of MeMqBr to 25 in THF at 0  $^{\circ}$ C proceeded highly stereoselectively, to our delight, to afford one diastereomer (26) in 95% yield. The homogeneity of the adduct was confirmed by the <sup>1</sup>H 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.<sup>21</sup> One plausible account for this exclusively stereoselective addition of the Grignard reagent is that the reagent is directed to the  $\beta\text{-face}$  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  $\beta$ -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  $(E,E)-\alpha\beta,\gamma\delta$ -unsaturated ester (28) in 72% yield. Acid hydrolysis (60% aqueous CF<sub>3</sub>COOH) 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.  $0sO_4$  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<sub>3</sub>N, -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.  $Me_3CC(0)Cl$ , pyridine, DMAP,  $CH_2Cl_2$ , r.t.. k. PCC, MS,  $CH_2Cl_2$ , r.t. 1. MeMgBr, THF, 0 °C.

Active MnO<sub>2</sub> oxidation of **30** gave  $(E,E)-\alpha\beta$ ,  $\gamma\delta$ -unsaturated aldehyde (31), an advanced intermediate for the Schreiber's total synthesis of **1**, in 86% yield. The aldol condensation protocol previously reported <sup>11</sup> was used for our final two steps. The aldol reaction of **31** and 4-methoxy-5,6-dimethyl-2-pyrone (**32**)<sup>22</sup> 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<sub>3</sub>N and 4-dimethylaminopyridine (DMAP) gave (+)-asteltoxin (1) in 73% yield. The <sup>1</sup>H (400 MHz) and <sup>13</sup>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 [[ $\alpha$ ]<sub>D</sub> +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.  $(EtO)_2P(0)CH_2CH=CHCOOEt$ , 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<sub>3</sub>N,  $CH_2Cl_2$ , r.t.,

Scheme 3

## K. TADANO et al.

#### EXPERIMENTAL

Melting points are uncorrected. Specific rotations in CHCl<sub>3</sub> 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. <sup>1</sup>H NMR spectra were recorded on a Varian EM-390 (90 MHz) and JEOL JNM GX-400 (400 MHz) spectrometers in CDCl<sub>3</sub> solution with tetramethyl-silane as an internal standard. <sup>13</sup>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<sub>254</sub> (Merck). Each crude product was chromatographed on a silica gel (Katayama Chemicals, K070) column. Unless otherwise specified, reactions were performed under argon atmosphere. Solvents were removed by concentration using an evaporator.

 $(2R, 3R, 4R, 5S)-4-[(E)-2-(Ethoxycarbony])etheny]]-2.3-(isopropylidenedioxy)-5-[(1R)-1.2-(isopropylidenedioxy)ethy]]-4-methyltetrahydrofuran (6E). To a solution of 4 (5.02 g, 17.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was bubbled a stream of O<sub>3</sub> (ca. 3% in O<sub>2</sub>) at -78 °C until blue color of the solution was sustained. A CH<sub>2</sub>Cl<sub>2</sub> solution (40 mL) of Ph<sub>3</sub>P (9.27 g, 35.5 mmol) was added to the mixture, and gradually warmed to room temparature. After stirring for 1 h, the mixture was concentrated. The residue was rapidly chromatographed on silica gel (AcOEt/hexane 1:15) to give an aldehyde 5 (5.16 g), which was subjected to the Wittig reaction directly: TLC R<sub>f</sub> 0.40 (AcOEt/hexane 1:3); <sup>1</sup>H NMR (90 MHz) <math display="inline">\delta$  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<sub>3</sub>P=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<sub>3</sub>PO 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<sub>f</sub> 0.55 (AcOEt/hexane 1:3):  $[\alpha]_{2}^{26}$  +108.9° (c 1.63); IR 3000, 2950, 2880, 1725, 1645, 1460, 1420, 1380, 1375 cm<sup>-1</sup>: 1H NMR (90 MHz)  $\delta$  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<sub>17</sub>H<sub>25</sub>O<sub>7</sub>: m/z 341.1597 (M<sup>+</sup>-CH<sub>3</sub>). Found: m/z 341.1602. 6E as a colorless oil: TLC R<sub>f</sub> 0.46 (AcOEt/hexane 1:3):  $[\alpha]_{2}^{25}$  +93.0° (c1.11); IR 2980, 2930, 2870, 1715, 1655, 1450, 1370, 1300 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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<sub>25</sub>O<sub>5</sub>: m/z 341.1597 (M<sup>+</sup>-CH<sub>3</sub>). Found: m/z 341.1593.

 $(2R, 3R, 4R, 5S)-4-[(E)-3-(Benzyloxy)-1-propenyl]-2, 3-(isopropylidenedioxy)-5-[(1R)-1,2-(isopropylidenedioxy)ethyl]-4-methyltetrahydrofuran (8). To a stirred solution of 6E (5.45 g, 15.3 mmol) in CH_2Cl_2 (100 mL) was added Dibal-H (25 wt% in toluene, 30.9 mL, 45.9 mmol) at - 40 °C. After stirring at -40 °C for 30 min, the mixture was quenched with 10 mL of H_2O. After warming to room temperature, the resulting gels were removed by filtration, washed well with CH_2Cl_2. The combined filtrate and washings were washed with H_2O (150 mL). The aqueous phase was extracted with CH_2Cl_2 (100 mL x 4). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give 7 (4.90 g), which was benzylated directly. In a separate experiment, the crude 7 was purified by silica gel chromatography (AcOEt/hexane 1:3): TLC R_f 0.20 (AcOEt/hexane 1:2): [\alpha]_2^{6} +67.1° (c 0.98): IR 3470. 2980, 2940, 2880, 1450, 1370, 1245, 1215 cm^{-1}: <sup>1</sup>H NMR (90 MHz) 1.02 (3H, s), 1.26, 1.38, 1.48 (6H, 3H, 3H, 3s), 2.0-2.2 (1H, br s), 3.9-4.1 (7H, m), 5.6-5.8 (3H, m); HRMS calcd for C1_6H_25O_6: m/z 313.1649 (M<sup>+</sup>-H). Found: m/z 313.1648. To a suspension of NAH (734 mg, 30.6 mmol) in DMF (20 mL) were added a DMF solution (40 mL) of 7 (4.90 g) and benzyl bromide (3.6 mL, 30.6 mmol) at 0 °C. After stirring for 4 h, 5 mL of EtOH was added to the mixture. The mixture was stirred for 30 min and then concentrated in vacuo. The residue was partitioned between AcOEt (300 mL) and H_2O (100 mL). The aqueous phase was extracted with AcOEt (100 mL x 2). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed$ 

on silica gel (AcOEt/hexane 1:15) to give 8 (5.80 g, 94%) as a colorless oil: TLC R<sub>f</sub> 0.74 (AcOEt/hexane 1:2);  $[\alpha]_D^{26} + 47.5^{\circ}$  (c 1.04); IR 2980, 2930, 2870, 1490, 1450, 1375, 1365, 1210 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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<sub>23</sub>H<sub>32</sub>O<sub>6</sub>: m/z 404.2196 (M<sup>+</sup>). Found: m/z 404.2176.

(2R, 3R, 4R, 5S)-4-[(E)-3-(Benzyloxy)-1-propenyl]-5-[(1R)-[1-hydroxy-2-(2,2-dimethyl-propionyl)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 Rf 0.11 (AcOEt/hexane 1:2);  $[\alpha]_D^{25}$  +75.0° (c 1.29); IR 3440, 3000, 2950, 2880, 1500, 1500, 1460, 1390, 1380 cm<sup>-1</sup>; 1H NMR (90 MHz)  $\delta$  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 C20H2806: m/z 364.1884 (M<sup>+</sup>). 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 H20 (200 mL x 1, 100 mL x 1). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.65 (AcOEt/hexane 1:2);  $[\alpha]_D^{25}$  +62.2° (c 1.31); IR 3500, 2980, 2940, 2870, 1710, 1480, 1460 cm<sup>-1</sup>; 1H NMR (90 MHz)  $\delta$  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<sup>+</sup> -CH<sub>3</sub>).

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<sub>4</sub> (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<sub>2</sub>SO<sub>4</sub>) 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 Rf 0.75 (AcOEt/hexane 2:3); IR 3450, 2980, 2930, 2870, 1730, 1480, 1455, 1360, 1280, 1160 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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<sup>+</sup>) (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<sub>f</sub> 0.46 (AcOEt/hexane 1:3); [ $\alpha$ ]<sup>26</sup> -0.5° (c 0.80); IR 3450, 2970, 2940, 1730, 1720, 1480, 1285, 1160 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MH2) <sup>D</sup> $_{\circ}$  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<sub>22</sub>H<sub>32</sub>O<sub>6</sub>: m/z 392.2196 (M<sup>+</sup>). Found: m/z 392.2187.

 $(2R, 3R, 4S, 5R)-4-(Benzoyloxy)-3-[(B)-3-(benzyloxy)-1-propenyl]-5-[[(2,2-dimethyl-propionyl)oxy]methyl]-2-methoxy-3-methyltetrahydrofuran (14). To a solution of 13 (2.51 g, 6.4 mmol) in pyridine (100 mL) was added benzoyl chloride (1.5 mL, 12.8 mmol). The mixture was heated at 60 °C for 6 h, and concentrated in vacuo with an aid of toluene. The residue was partitioned bewteen CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and H<sub>2</sub>O (200 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (150 mL × 2). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/hexane 1:15) to give 14 (3.34 g, quantitatively) as a colorless oil: TLC R<sub>f</sub> 0.55 (AcOEt/hexane 1:5); [<math>\alpha$ ]<sub>6</sub><sup>23</sup> -25.6°(c 1.07); IR 2970, 2930, 2880, 1730, 1600, 1580, 1480, 1450, 1270, 1160 cm-1; IH NMR (90 MHz) \delta 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<sub>28</sub>H<sub>33</sub>O<sub>6</sub>: m/z 465.2275 (M<sup>+</sup>-OCH<sub>3</sub>). Found: m/z 465.2246.

(2R, 3R, 4S, 5R)-4-(Benzoyloxy)-3-[(1R, 2R)- and (1S, 2S)-[3-(benzyloxy)-1,2-dihydroxy]-propy]]-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 0s0<sub>4</sub> (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<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> (200 mL) and saturated aqueous NaHCO<sub>3</sub> (200 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL x 3). The combined organic phases were washed with saturated brine (100 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.44 (AcOEt/hexane 1:2);  $[\alpha]_{21}^{21}$  -48.9° (c 0.97); IR 3480, 2970, 2940, 1730, 1600, 1580, 1480, 1450, 1270 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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<sub>28</sub>H<sub>34</sub>O<sub>8</sub>: m/z 498.2250 (M<sup>+</sup>-CH<sub>3</sub>OH). Found: m/z 498.2243. 16 as a colorless oil: TLC R<sub>f</sub> 0.48 (AcOEt/hexane 1:2);  $[\alpha]_{21}^{21}$  -50.6° (c 0.63); IR 3480, 2970, 2930, 2870, 1730, 1600, 1580, 1450, 130 (MHz)  $\delta$  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<sub>28</sub>H<sub>34</sub>O<sub>8</sub>: m/z 498.2250 (M<sup>+</sup> - CH<sub>3</sub>OH). Found: m/z 498.2250.

(2R, 3S, 4S, 5R)-3-[(1R, 2R)-[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<sub>3</sub> and concentrated in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and H<sub>2</sub>O (200 mL), and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL x 2). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>F</sub> 0.66 (AcOEt/hexane 1:3); [ $\alpha$ ]<sub>D</sub><sup>2B</sup> -10.0° (c 1.21); IR 2990, 2950, 1740, 1600, 1480, 1460, 1400, 1380, 1370, 1320, 1270 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$  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<sub>31</sub>H<sub>39</sub>O<sub>9</sub>: 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<sup>+</sup>). 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<sub>f</sub> 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<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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

2360

(1H, s), 7.32 (5H, s); HRMS calcd for  $C_{24}H_{35}O_{8}$ : m/z 451.2329 (M<sup>+</sup>-CH<sub>3</sub>). Found: m/z 451.2325.

(2R, 3S, 4S, 5R)-4-(Benzyloxy)-3-[(1R, 2R)-[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<sub>2</sub>O (50 mL x 3). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 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<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$ 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<sub>31</sub>H<sub>41</sub>O<sub>8</sub>: m/z 541.2798 (M<sup>+</sup>-CH<sub>3</sub>). 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 mL, 5.9 mmol). The mixture was stirred for 20 h, and neutralized with Amberlite IR-120 (H<sup>+</sup>). 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);  $[\alpha]_{3}^{31}$  +8.6° (c 0.80); IR 3480, 2990, 2910, 2880, 1500, 1450, 1380, 1370, 1260 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  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.

To a solution of 21 obtained above in benzene (20 mL) was added Ph\_P=CH\_ [754 mg (2.7 mmol), prepared from Ph\_3PCH\_3Br by treatment with fresh NaNH<sub>2</sub> 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<sub>2</sub>O (100 mL) was added, then extracted with Et<sub>2</sub>O (100 mL × 1, 50 mL × 2). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.67 (AcOEt/hexane 1:4); [ $\alpha$ ]<sup>25</sup> -19.2° (c 1.00); IR 2990, 2940, 2910, 2830, 1640, 1500, 1450, 1390, 1370, 1250, <sup>1</sup>210 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$  1.07 (3H, s), 1.37, 1.45 (3H × 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<sub>27</sub>H<sub>33</sub>O<sub>6</sub>: m/z 453.2274 (M<sup>+</sup>-CH<sub>3</sub>). 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<sub>f</sub> 0.20 (AcOEt/hexane 1:2);  $[\alpha]_2^{29}$ -31.1 (c 1.10); IR 3400, 2990, 2970, 2940, 2890, 2840, 1460, 1380, 1370, 1250, 1210 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$  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.

 $\begin{array}{l} (2R,3S,5R)-3-[(1R,2R)-3-[(2,2-Dimethylpropionyl)oxy]-1,2-(isopropylidenedioxy)-\\ propyl]-5-ethyl-2-methoxy-3-methyltetrahydrofuran-4-one (25). A mixture of 24 (193 mg, 0.5 mmol), PCC (444 mg, 2.1 mmol), and molecular sieves (4A, powder, 412 mg) in CH_2Cl_2 (10 mL) was stirred for 2 h. The reaction mixture was charged on a silica gel column (20 g) and eluted with Et_0 to give 25 (188 mg, 98%) as a colorless oil: TLC R_f 0.53 (AcOEt/hexane 1:5); [<math>\alpha$ ]<sup>26</sup> -2.9° (c 1.17); IR 2980, 2940, 2920, 2880, 1760, 1480, f 1460, 1400, 1380, 1370, 1280, 1250, 1220 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz)  $\delta$ 1.00 (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<sub>18</sub>H<sub>29</sub>O<sub>7</sub>; m/z 357.1911 (M<sup>+</sup> -CH<sub>3</sub>). Found: m/z 357.1893.

(2R, 3R, 4R, 5R)-5-Ethyl-4-hydroxy-3-[(1R, 2R)-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<sub>4</sub>Cl (10 mL) then diluted with H<sub>2</sub>O (80 mL). This aqueous solution was extracted with AcOEt (100 mL x 1, 60 mL x 4). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.18 (AcOEt/hexane 1:2);  $[\alpha]_{2}^{25}$  +0.2° (c 1.08); IR 3470, 2970, 2930, 2860, 1460, 1400, 1380, 1370, 1340, 1320, 1290, 1250, 1220 cm<sup>-1</sup>; <sup>1</sup>H 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 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<sup>+</sup>-CH<sub>3</sub>). Found: m/z 289.1651.

(2R, 3R, 4R, 5R)-3-[(1R, 2R, 3E, 5E)-[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<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O, 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; <sup>1</sup>H NMR (90 MHz)  $\delta$  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)<sub>2</sub>P(O)CH<sub>2</sub>CH=CHCODEt (0.13 mL, 0.58 mmol) was added to this solution at - 78 °C. The solution was stirred at -78 °C for 20 min and at room temperature for 40 min. Then, 2 mL of saturated aqueous NH<sub>4</sub>Cl was added, diluted with AcOEt (30 mL). This was washed with H<sub>2</sub>O (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<sub>f</sub> 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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) & 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<sub>20</sub>H<sub>31</sub>O<sub>7</sub>: m/z 383.2068 (M<sup>+</sup>-CH<sub>3</sub>). Found: m/z 383.2095.

(1R, 3R, 4R, 5R, 6R, 7R)-7-[(1E, 3E)-4-(Ethoxycarbony1)buta-1,3-dieny1]-3-ethy1-4,6-dihydroxy-4,5-dimethy1-2,8-dioxabicy10[3.3.0]octane (29). A solution of 28 (15.5 mg, 0.04 mmo1) in 60% aqueous CF<sub>3</sub>COOH (2 mL) was stirred for 41 h. To the solution was added saturated aqueous NaHCO<sub>3</sub> (15 mL), and this was extracted with AcOEt (20 mL x 4). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.39 (AcOEt/hexane 1:1); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +30.9° (c 0.57); IR 3460, 2970, 2930, 2830, 1700, 1640, 1620, 1460, 1370, 1310, 1270, 1240 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz) & 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 C1<sub>7</sub>H<sub>26</sub>O<sub>6</sub>: m/z 326.1727 (M<sup>+</sup>). Found: m/z 326.1714.

(1R. 3R. 4R. 5R. 6R. 7R)-3-Ethyl-4. 6-dihydroxy-7-[(1E, 3E)-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<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O (0.1 mL), and warmed to room temperature. Then, 5 mL of THF and 2 g of Na<sub>2</sub>SO<sub>4</sub> 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<sub>f</sub> 0.25 (EtOH/toluene 1:5); [ $\alpha$ ] $\beta^3$  +30.0° (c 0.38); IR 3400, 2970, 2930, 2880, 2860, 1660, 1630, 1460, 1380, 1355, 1290, 1260, 1200 cm<sup>-1</sup>; 1H NMR (400 MHz)  $\delta$  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); 6.66 (1H, dd, J=10.7, 15.1 Hz); HRMS calcd for C<sub>15</sub>H<sub>22</sub>O<sub>4</sub>: m/z 266.1517 (M<sup>+</sup>-H<sub>2</sub>O). Found: m/z 266.1521.

(1R, 3R, 4R, 5R, 6R, 7R)-3-Ethy]-7-[(1E, 3E)-4-formy]buta-1, 3-dieny]]-4, 6-dihydroxy-4, 5-dimethy]-2, 8-dioxabicyclo[3.3.0]octane (31). A solution of 30 (7.3 mg, 0.03 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was stirred in the presence of active MnO<sub>2</sub> (97 mg) for 1 h. The inorganic materials were removed by passing the mixture through a short silica gel column (0.5 g, Et<sub>2</sub>O 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<sub>F</sub> 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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$  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), 9.60 (1H, d, J=7.9 Hz); HRMS calcd for C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>: m/z 282.1465 (M<sup>+</sup>). Found: m/z 282.1482.

Mixture of (1R, 3R, 4R, 5R, 6R, 7R)-3-Ethyl-4,6-dihydroxy-7-[(1E, 3E, 5R 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

# K. TADANO et al.

-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<sub>4</sub>Cl (2 mL) was added. The mixture was warmed to room temperature, and diluted with H<sub>2</sub>O (10 mL). This was extracted with AcOEt (10 mL x 6). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>f</sub> 0.45 (EtOH/toluene 1:4); IR 3300, 2950, 2930, 2880, 2850, 1705, 1645, 1565, 1460, 1405, 1300, 1245, 1200 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz)  $\delta$  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<sup>+</sup>-H<sub>2</sub>O). Found: m/z 418.1991.

(1R, 3R, 4R, 5R, 6R, 7R)-3-Ethyl-4, 6-dihydroxy-7-[(1E, 3E, 5E)-6-(4-methoxy-5-methyl-2-pyron-6-yl)hexa-1, 3, 5-trienyl]-4, 5-dimethyl-2, 8-dioxabicyclo[3, 3, 0]octane, (+)-Astel-toxin (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<sub>3</sub>N (0.1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (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); [ $\alpha$ ] $\beta^3$  +20.0° (c 0.10, MeOH); IR 3440, 3010, 2970, 2930, 2880, 2860, 1700, 1625, 1565, 1540, 1460, 1410, 1250, 1210, 1180 cm-1; <sup>1</sup>H NMR (400 MHz)  $\delta$  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), 6.66 (1H, ddd, J=1.5, 10.7, 15.1 Hz), 7.19 (1H, dd, J=10.7, 15.1 Hz); <sup>13</sup>C NMR (100 MHz)  $\delta$  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<sub>23</sub>H<sub>30</sub>O<sub>7</sub>; m/z 418.1989 (M<sup>+</sup>). Found: m/z 418.1983.

Acknowlegments. We express our cordial gratitudes to Professor Stuart L. Schreiber (Harvard University) for sending us precious samples and copies of the spectra  $(^{1}H, ^{13}C)$  NMR, MS, and IR) of compound 1 and some synthetic intermediates, and to Dr. Robert Vleggaar (National Chemical Research Laboratory, CSIR, South Africa) for sending us natural asteltoxin.

## **References and Notes**

- This work was presented at 16th International Symposium on the Chemistry of Natural Products, Kyoto, Japan, May 1988. Abstract PB166.
- Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J., <u>J. Chem. Soc.</u>, <u>Chem.</u> <u>Commun</u>. 1979, 441.
- (a)Sakabe, N.; Goto, T.; Hirata, Y., <u>Tetrahedron Lett.</u> 1964, 1825; Idem, <u>Tetrahedron</u> 1977, <u>33</u>, 3077 (b) Franck, B.; Gehrken, H.-P., <u>Angew. Chem. Int. Ed. Engl.</u> 1980, <u>19</u>, 461.
- (a) Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Psselton, M. D., J. <u>Chem.</u> <u>Soc.</u>, <u>Chem.</u> <u>Commun.</u> 1974, 874. (b) Norestam, R., <u>Acta</u> <u>Crystallgr.</u>, <u>Sect.</u> <u>A</u>: <u>Cryst.</u> <u>Phys.</u> <u>Diffr.</u> <u>Theor</u>. <u>Gen.</u> <u>Crystallogr.</u> 1978, <u>A34</u>. <u>s79</u>.
- 5. Satre, M., <u>Biochem</u>. <u>Biophys</u>. <u>Res</u>. <u>Commun</u>, 1981, <u>100</u>, 267.
- A leading article for biosynthesis of polyene mycotoxins, see: (a) Vleggaar, R. <u>Pure Appl. Chem.</u> 1986, <u>58</u>, 239. On the biosynthesis of (+)-asteltoxin, see: (b) Steyn, P. S.; Vleggaar, R. J. <u>Chem. Soc.</u>, <u>Chem. Commun</u>, 1984, 977. On the biosynthesis of citreoviridin, see: (c) Steyn, P. S.; Vleggaar, R.; Wessels, P. L.; Woundenberg, M., J. <u>Chem. Soc.</u>, <u>Perkin Trans.</u> 1 1982, 2175. On the biosynthesis of

aurovertins, see: Steyn, P. S.; Vleggaar, R.; Wessels, P. L., J. <u>Chem.</u> <u>Soc.</u>, <u>Chem.</u> <u>Commun</u>. **1979**, 1041; Idem, <u>J. Chem. Soc.</u>, <u>Perkin</u> <u>Trans</u>. <u>1</u> **1981**, 1298.

- Total syntheses of (-)-2 have been achieved: (a) Nishiyama, S.; Shizuri, Y.; Yamamura, S., <u>Tetrahedron Lett</u>. 1985, <u>26</u>, 231. (b) Suh, H.; Wilcox, C. S., J. <u>Am</u>. <u>Chem</u>. <u>Soc</u>. 1988, <u>110</u>, 470. Total synthesis of racemic-2, see: (c) Williams, D. R.; White, F. H., J. <u>Org</u>. <u>Chem</u>. 1987, <u>52</u>, 5067.
- Nishiyama, S.; Toshima, H.; Kanai, H.; Yamamura, S., <u>Tetrahedron Lett</u>. 1986, <u>27</u>, 3463; idem, <u>Tetrahedron</u> 1988, <u>44</u>, 6315.
- Total syntheses of racemic citreoviral, see: (a) Shizuri, Y.; Nishiyama, S.: Shigemori, H.; Yamamura, S., J. <u>Chem. Soc.</u>, <u>Chem. Commun.</u> 1985, 292. (b) Williams, D. R.; White, F. H., <u>Tetrahedron Lett</u>. 1985, <u>26</u>, 2529. Ibid., 1986, <u>27</u>, 2195 and and also see ref. 7c. (c) Bowden, M. C.; Patel, P.; Pattenden, G., <u>Tetrahedron</u> 9. Lett. 1985, 26, 4793; Bowden, M. C.; Pattenden, G., Ibid., 1988, 29, 711. Total syntheses of (+)-citreoviral and synthetic approaches: (d) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S., <u>Tetrahedron Lett</u>. 1985, <u>26</u>, 6485. (e) Trost, B. M.; Lynch, J. K.; Angle, S. R., Tetrahedron Lett. 1987, 28, 375. See (f) also refs 7a and b. Isolation and structure determination of verrucosidin: Wilson, B. J.; Byerly, C. S.; Burka, L. T., <u>J</u>. <u>Am. Vet. Med. Assoc</u>. 1**98**1, <u>179</u>, 480; Burka, L. T.; Ganguli, M.; Wilson, B. J., J. Chem. Soc., Chem. Commun. 1983, 544; Ganguli, M.; Burka, L. T.; Harris, T. M., J. Org. Chem. 1984, 49, 3762. Total synthesis of (+)-verrucosidin: (g) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S., J. Am. Chem. Soc. 1988, 110, 5201. Synthetic studies of verrucosidin: (h) Nishiyama, S.; Shizuri, Y.; Shigemori, H.; Yamamura, S., <u>Tetrahedron Lett</u>. 1986, <u>27</u>, 723. (i) Klein, L. L., <u>Tetrahedron Lett</u>. 1986, <u>27</u>, 4545. (j) Cha, J. K.; Cooke, R. J., <u>Tetrahedron Lett</u>. 1987, 28, 5473. Isolation and structure determination of citreomontanin: (k) Rebuffat, S.; Davoust, D.; Molho, L.; Molho, D., <u>Phytochemistry</u> **1980**, <u>19</u>, 427. Total synthesis of citreomontanin: (1) Patel, P.; Pattenden, G., <u>Tetrahedron Lett</u>. **1985**, <u>26</u>, 4789. (m) Venkataraman, H.; Cha, J. K., Tetrahedron Lett. 1987, 28, 2455. Isolation and stereostructures of citreoviral, citreodiol and epicitreodiol:(n) Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S.; Furukawa, H.; Kawai, K.; Okuda, N., <u>Tetrahedron Lett</u>. **1984**, <u>25</u>, 4771. Structures of citreoviridinol and isocitreoviridinol: (o) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S.; Terada, Y.; Niwa, H.; Kawai, K.; Furukawa, H., <u>Tetra-</u> <u>hedron</u> <u>Lett</u>. **1985**, <u>25</u>, 3243. Isolation and stereostructures of neocitreoviridinol and epicitreoviridinol: (p) Nishiyama, S.; Shizuri, Y.; Yamamura, S.; Terada, Y.; Kawai, K.; Furukawa, H., Tetrahedron Lett. 1985, 26, 6239. Total syntheses of citreoviridinol and neocitreoviridinol: (q) Nishiyama, S.; Toshima, H.; Yamamura, Chem. Lett. 1986, 1973.
- 10. Schreiber, S. L.; Satake, K., J. Am. Chem. Soc. 1983, 105, 6723.
- 11. Schreiber, S. L.; Satake, K., J. Am. Chem. Soc. 1984, 106, 4186.
- 12. Schreiber, S. L.; Satake, K., Tetrahedron Lett. 1986, 27, 2575.
- The synthesis of the bistetrahydrofuran moiety of 1 was reported preliminarily, see: Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T., <u>Tetrahedron Lett</u>. 1988, <u>29</u>, 655.
- Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T., <u>Chem. Lett</u>. 1985, 1925; Idem, <u>J. Org. Chem.</u> 1987, <u>52</u>, 1201.
- 15. The n. O. .e. experiment of 17 verified the configuration of the anomeric carbon as depicted. When the quaternary methyl group was irradiated, 14% and 25% enhancements of the signals of OCH<sub>3</sub> at the acetal carbon and of the methine proton at the carbon bearing benzoyloxy group were observed, respectively.

- 16. VanRheenen, V.; Kelly, R. C.; Cha, D. Y., Tetrahedron Lett. 1976, 1973.
- 17. The following  $0sO_4$  oxidations were examined: (1) catalytic  $0sO_4$  in t-BuOH in the presence of 35% aqueous  $H_2O_2$  (the formation of an  $\alpha$ -keto hydroxy derivative); (2) 1.1 mol eq. of  $0sO_4$  in pyridine followed by aqueous NaHSO<sub>3</sub> work-up (the formation of 2:1 mixture of 15 and 16 in a combined yield of 90%).
- 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.
- 19. Mancuso, A. J.; Huang, S. L.; Swern, D., J. Org. Chem. 1978, 43, 2480.
- 20. Corey, E. J.; Suggs, J. W., Tetrahedron Lett. 1975, 2647.
- 21. Compound 26 was transformed to the bistetrahydrofuran moiety of 1 and its diacetate as follows: 1) pivaloylation of the primary hydroxyl group, 2) deprotection of the isopropylidene ketal accompanied by the bistetrahydrofuran ring formation (50% aqueous CF<sub>3</sub>COOH, r.t. 20 h), 3) depivaloylation, and 4) acetylation. These compounds were completely identical with the racemic samples synthesized by Schreiber's group in all respects.
- 22. Compound 32 was prepared from 2,4-pentanedione according to the reported procedures: (a) Johnson, A. W.; Markham, E.; Price, R., "Organic Synthesis". Wiley: New York; 1973, Collect. Vol. V, p.785. (b) Harris, T.; Harris, C. M., J. Org. Chem. 1966, 31. 1032; Harris, T. M.; Harris, C. M.; Wachter, M. P., <u>Tetrahedron 1968, 24</u>, 6897; (c) Ohta, S.; Tsujimura, A.; Okamaoto, M., <u>Chem. Pharm. Bull</u>.1981, 29, 2762; (d) Bu'Lock, J. D.; Smith, H. G., J. Chem. Soc. 1960, 502; Suzuki, E.; Katsuragawa, B.; Inoue, S., J. Chem. Research (S) 1982, 244.