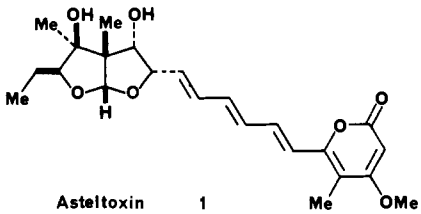
Total Synthesis of (±)-Asteltoxin†

Stuart L. Schreiber*[1] and Kunio Satake

Contribution from Yale University, Sterling Chemistry Laboratory, New Haven, Connecticut 06511. *Received December 27, 1983*

Abstract: A convergent synthesis of (±)-asteltoxin has been achieved in 16 steps (3.0% overall yield) from 3,4-dimethylfuran. The attachment of the triene pyrone side chain to the bis(tetrahydrofuran) skeleton proceeds by way of the addition of the Corey equivalent to anion **3** to the aldehyde **2** and a subsequent aldol condensation–dehydration reaction of pyrone **4**.

The investigation of toxic maize cultures of *Aspergillus stellatus* Curzi by Vleggaar and co-workers led to the isolation and structure determination of the trienic α-pyrone asteltoxin,[2] **1**. This mycotoxin is structurally related to aurovertin[3] and citreoviridin,[4] compounds which have been used extensively as inhibitors of oxidative phosphorylation.[5] Later studies have indicated that asteltoxin has a similar inhibitory effect on the activity of E. coli BF_1-ATPase.[6] Herein we report our studies of this class of compounds which have resulted in the first total synthesis of asteltoxin.[7]



Asteltoxin 1

The synthesis of asteltoxin proceeds in a convergent manner along the lines indicated in Scheme I. The preparation of the aldehyde **2** from the Paterno–Büchi photocycloaddition of 3,4-dimethylfuran and β-benzyloxypropanal, and subsequent functionalization, has been previously reported[7b] (Scheme II). We required a synthetic equivalent to the anion of 4-formyl-1,3-butadiene (**3**) to be stereoselectively coupled to aldehyde **2**. Aldol condensation of pyrone **4** to the resultant dienal, and dehydration, would complete the asteltoxin synthesis.

The preparation of pyrone **4** was achieved in analogy to known literature methods[8] (Scheme III). Methylation of the monoanion of 2,4-pentanedione provided 3-methyl-2,4-pentanedione[9] which was carboxylated via the dianion.[10] Cyclization of the carboxlic acid was achieved through the action of carbonyl diimidazole,[11] and subsequent methylation with dimethyl sulfate[12] produced α-pyrone **4**. A suitable equivalent to the side chain anion **3** can be found in a recent report by Corey and Hoover, who employed the α-lithio carbanion from pentadienyl sulfoxide, **5**, in their synthesis of 5-desoxyleukotriene D.[13] We chose to prepare **5**[14] by the sulfenate-to-sulfoxide rearrangement,[15] beginning with divinyl carbinol. Metalation of **5** with *n*-butyllithium and addition to aldehyde **2** followed by double [2,3] sigmatropic rearrangement at room temperature (3 h)[13] furnished a 3:1 mixture[7b] of the diol **6**[16] and the corresponding α-epimer[16] (Scheme IV). The desired diol **6**, which could be separated from the undesired epimer by flash chromatography,[17] was cyclized to the bis(tetrahydrofuran) **7**[16] upon treatment with camphorsulfonic acid in methylene chloride.[7b] Pummerer rearrangement and hydrolysis were carried out in the manner described by Corey and Hoover[13,18] to afford dienal **8**.[16]

Attachement of the α-pyrone was achieved by a crossed aldol condensation with dienal **8** to provide triol **9**.[16] Selective dehydration of the less hindered alcohol with tosyl chloride and triethylamine furnished (±)-asteltoxin which exhibited UV, infrared, ^1H NMR (500 MHz), ^{13}C NMR (62.9 MHz), and mass spectra and chromatographic properties identical with those of an authentic sample of asteltoxin generously provided by Dr. Vleggaar.

Further studies in the application of the furan–carbonyl photocycloaddition reaction and the coupling procedure outlined above to the synthesis of other members of this class of compounds are in progress.

Experimental Section

General. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride, triethylamine, diisopropylamine, 2,6-lutidine, and HMPA were distilled from CaH_2. Acetic anhydride was purified by distillation from toluene (to effect the azeotropic removal of acetic acid). Dimethyl sulfide was purified by distillation. *p*-Toluenesulfonyl chloride was recrystallized from benzene. All distillations were performed under nitrogen atmosphere. All reactions were carried out under nitrogen atmosphere and were monitored by analytical thin-layer chromatographic methods (TLC) using E. Merck silica gel 60F-24 glass plates (0.25 mm). Flash chromatography[17] was carried out by using E. Merck silica gel 60 (23–400 mesh).

8(*R*,*S*)-Ethyl-7(*R*,*S*)-hydroxy-5(*R*,*S*)-(1(*R*,*S*)-hydroxy-6-(phenylsulfinyl)-(*E*,*E*)-hexa-2,4-dien-1-yl)-3,3,6(*R*,*S*),7-tetramethyl-1(*R*,*S*)-2,4,9-trioxabicyclo[4.3.0]nonane (6). Ozone was introduced to a solution of the vinyl precursor of **2**[7b] (158 mg; 0.617 mmol) and $NaHCO_3$ (50 mg) in CH_2CL_2 (10 mL) and MeOH (0.2 mL) at −78 °C until the blue color persisted. Excess ozone was removed by passing nitrogen through the solution. The clear reaction mixture was treated with dimethyl sulfide (3 mL; excess), warmed to room temperature, stirred for 3 h, and filtered through Celite. After evaporation of solvent, the crude aldehyde **2** (200 mg) was obtained which was used in the next step without further purification.

Dropwise addition of *n*-butyllithium (1.9 M in hexane, 0.77 mL; 1.46 mmol) to a THF solution of **5** (280 mg; 1.46 mmol) at −78 °C resulted in the formation of a pale yellow solution. After 10 min, a THF solution (3 mL) of the crude aldehyde **2** (200 mg) was added to the mixture at

† Dedicated to the memory of Professor Kunio Sakan.

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(16) All new compounds reported gave ^{13}C NMR (62.9 MHz), ^1H NMR (500 or 250 MHz), FT-IR, and mass spectra (low resolution) in accord with the structure given. Exact mass measurements were obtained for compounds **6**, **7**, **9** and (±)-**1**.
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(18) The experimental details of this transformation were supplied by Dr. Dennis Hoover of Pfizer, Inc., to whom we are grateful.

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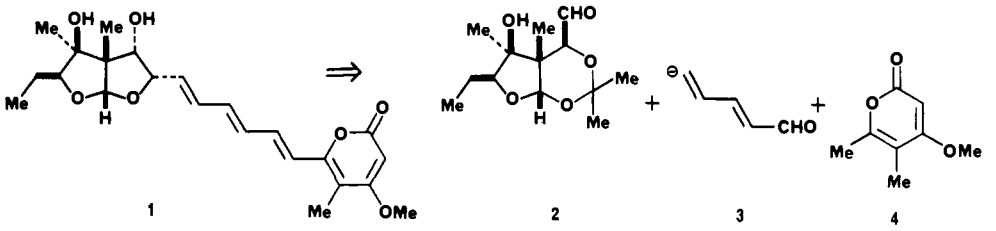
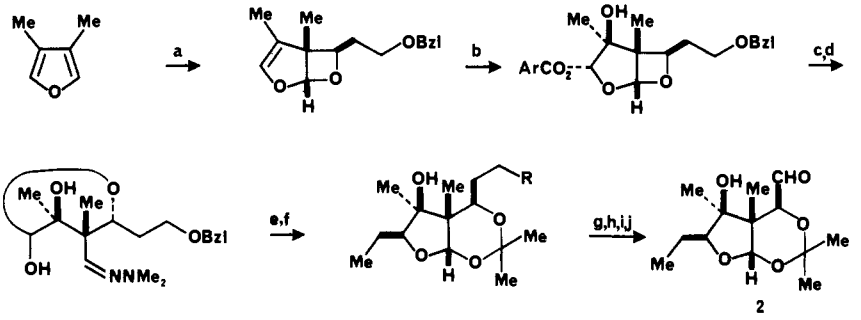
Scheme I

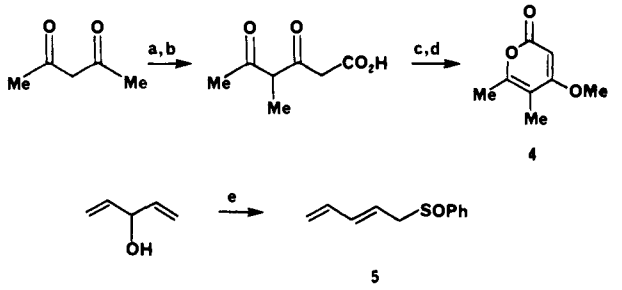


Scheme II[a]



[a] a: Benzene, Et_2O, $h\nu$ (Vycor), 6 h, 63%. b: MCPBA, $NaHCO_3$, CH_2Cl_2, 80%. c: THF, 3 N HCl (3:1). d: Me_2NNH_2, CH_2Cl_2, $MgSO_4$, 72%. e: EtMgBr, THF, room temperature, 48 h. f: acetone, $CuSO_4$, CSA, 55%. g: Li, NH_3, Et_2O, 98%. h: *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF. i: H_2O_2, THF, 81%. j: O_3, CH_2Cl_2, MeOH, DMS, 92%.

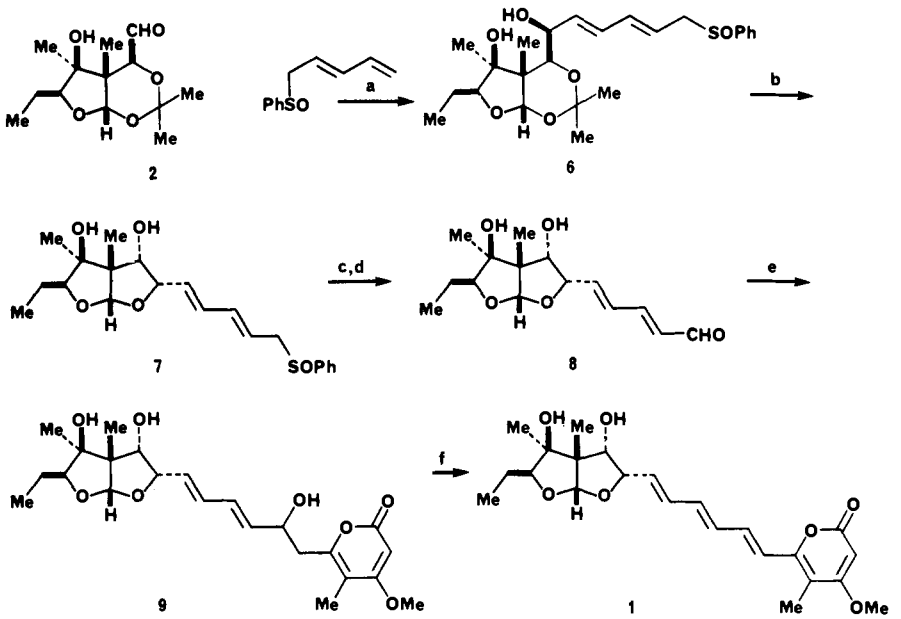
Scheme III[a]



[a] a: MeI, K_2CO_3, acetone. b: $NaNH_2$, NH_3, Et_2O, CO_2. c: $(im)_2CO$, THF. d: $(MeO)_2SO_2$, K_2CO_3, acetone. e: *n*-BuLi, THF, −78 °C, PhSCl, −50 °C → 0 °C.

−78 °C. After being stirred for 30 min at −78 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The THF was removed by rotary evaporation, and the resultant solution was diluted with ether and extracted. The combined organic extracts were dried over $MgSO_4$ and concentrated. After the mixture was left standing for 2–3 h, double sigmatropic rearrangement was complete and provided a mixture of **6** and the corresponding epimer. Flash chromatography (50% ether/hexane, then 50% EtOAc/ether) provided 6 (185 mg) and the corresponding α-epimer (58 mg) in a combined yield of 88%: TLC (EtOAc) R_f 0.37; IR (CH_2Cl_2) 3420, 1048 cm^{-1}; MS (EI, 20 eV) *m/e* (relative intensity) 309 (0.6), 267 (14), 171 (35), 125 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (3 H, t, *J* = 7.4 Hz), 1.20 (3 H, s), 1.23 (3 H, s), 1.43 (3 H, s), 1.46 (3 H, s), 3.50–3.68 (2 H, m), 3.73 (1 H, m), 3.88 (1 H, t, *J* = 6.4 Hz), 4.28 (1 H, br t, *J* = 7.0 Hz), 5.02 (1 H, s), 5.51 (1 H, m), 5.73 (1 H, d d, *J* = 6.3, 14.5 Hz), 6.20 (2 H, m), 7.48–7.67 (5 H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 11.2, 13.2, 21.9, 24.9, 26.2, 52.3, (60.2, 60.7)*, 70.0, 71.9, 79.1, 87.7, 99.4, 104.8, (120.0,

Scheme IV[a]



[a] a: **5**, *n*-BuLi, THF, −78 °C; then **2**, NH_4Cl (aq), room temperature, 3 h, 88% (3:1 β/α). b: CSA, CH_2Cl_2, 77%. c: $CF_3CO_2COCH_3$, Ac_2O, 2,6-lutidine. d: $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, (3:1), 60%. e: **4**, LDA, HMPA, THF, −78 °C; then **8**, −78 °C, 80%. f: TsCl, DMAP, Et_3N, CH_2Cl_2, 82%.

120.2)*, 124.3, 129.0, 129.6, 131.1, 135.2, 137.8, 143.0 (diastereomeric sulfoxides)*; HRMS (CI, NH_3) calculated for $C_{24}H_{35}O_6S$ ($M^+ + H$) 451.2154, found 451.2177.

4(*R*,*S*),6(*R*,*S*)-Dihydroxy-5(*R*,*S*),6-dimethyl-7(*R*,*S*)-ethyl-3(*R*,*S*)(5-phenylsulfinyl)-(*E*,*E*)-penta-1,3-dien-1-yl)-1(*S*,*R*)-2,8-dioxabicyclo[3.3.0]octane (7). Compound 6 (112 mg; 0.249 mmol) was treated with camphorsulfonic acid (40 mg; 0.17 mmol) in CH_2Cl_2 (10 mL) and stirred for 8 h at room temperature. The reaction mixture was quenched with triethylamine (1 mL; excess) and evaporated. The residue was purified by flash chromatography (15% hexane/ether, then 33% EtOAc/ether) to provide 7 (75 mg; 0.19 mmol) in 77% yield: TLC (EtOAc) R_f 0.26; IR (CH_2Cl_2) 3605, 3570 cm^{-1}; MS (EI, 20 eV) *m/e* (relative intensity) 267 (11), 171 (32), 125 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (3 H, t, J = 7.4 Hz), 1.15 (3 H, s), 1.36 (3 H, s), 1.54 (2 H, m), 3.57 (2 H, m), 3.68 (1 H, d, J = 2.8 Hz) (minor trans epimer exhibited a corresponding signal at 3.76 (1 H, d, J = 5.9 Hz)), 4.30 (1 H, d d, J = 5.6, 7.2 Hz), 4.62 (1 H, m), 5.24 (1 H, s), 5.49 (1 H, m), 5.73 (1 H, d d, J = 5.5, 15.5 Hz), 6.15 (1 H, m), 6.43 (1 H, br d d, J = 10.6, 15.5 Hz), 7.50 (5 H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 11.2, 16.0, 18.0, 21.7, (60.1, 60.6)*, 62.0, 78.8, 80.9, 83.2, 89.6, 111.8, (120.6, 120.9)*, 124.3, 129.1, 131.2, 132.8, 137.6, 142.7, 142.8 (diastereomeric sulfoxides)*; HRMS (CI, NH_3) calculated for $C_{21}H_{29}O_5S$ ($M^+ + H$) 393.1735, found 393.1730.

4(*R*,*S*),6(*R*,*S*)-Dihydroxy-5(*R*,*S*),6-dimethyl-7(*R*,*S*)-ethyl-3(*R*,*S*)-(5-hydroxy-6-(4-methoxy-5-methyl-α-pyron-6-yl)-(*E*,*E*)-hexa-1,3-dien-1-yl)-1(*S*,*R*)-2,8-dioxabicyclo[3.3.0]octane (9). A stock solution (ca. 1.6 M) of acetic trifluoracetic anhydride in acetic anhydride was prepared from trifluoroacetic anhydride (1.4 mL; 10 mmol), sodium acetate (820 mg; 10 mmol), and acetic anhydride (5 mL).[18]

Bis(tetrahydrofuran) 7 (40 mg, 0.092 mmol) was dissolved in acetic anhydride (0.20 mL) at room temperature. To this mixture was added the mixed anhydride solution (0.83 mL; 1.3 mmol), followed by 2,6-lutidine (0.24 mL; 2.1 mmol). After 1 h, the reaction mixture was quenched with excess sodium acetate powder and concentrated in vacuo. The residue was partitioned between ether and aqueous $NaHCO_3$, and the organic layer was dried over $MgSO_4$. Evaporation of solvent provided the crude acetoxy sulfide, which was dissolved in acetonitrile–water (3:1). $CaCO_3$ (0.1 g; excess) and $HgCl_2$ (72 mg; 0.27 mmol) were added, and the solution was stirred for 2 h at room temperature. The reaction mixture was filtered through Celite, which was washed with ether. The filtrate was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. The crude dienal was purified by flash chromatography (25% hexane/ether, then ether) to provide dienal 8 (16 mg; 0.056 mmol; 60%), which was used immediately for the next reaction.[18]

A solution of 4 (47 mg; 0.31 mmol) in THF (1 mL) was added dropwise at −78 °C to LDA–HMPA in THF (5 mL) prepared from diisopropylamine (0.051 mL; 0.36 mmol), HMPA (0.063 mL; 0.36 mmol), and *n*-BuLi (0.125 mL, 2.5 M in hexane; 0.31 mmol). After the mixture was stirred for 5 min, dienal 8 (17.5 mg; 0.062 mmol) in THF (2 mL) was added dropwise to the resultant yellow solution. After 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, evaporated, and extracted with EtOAc to give the crude aldol, which was purified by flash chromatography (20% hexane/ether, then 33% ether/EtOAc) to provide 9 (21.5 mg; 0.045 mmol; 80%) as a mixture of aldol epimers: TLC (EtOAc) R_f 0.21; IR (CH_2Cl_2) 3605, 1708, 1567, 1406, 1246 cm^{-1}; MS (EI, 20 eV) *m/e* (relative intensity) 418 (0.3), 368 (1), 154 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (3 H, t, J = 7.5 Hz), 1.19 (3 H, s), 1.40 (3 H, s), 1.92 (3 H, s), 3.71 (1 H, d d, J = 2.9, 4.6 Hz), 3.84 (3 H, s), 4.31 (1 H, d d, J = 5.7, 7.1 Hz), 4.62–4.73 (3 H, m), 5.28 (1 H, s), 5.47 (1 H, s), 5.68–5.88 (2 H, m), 6.32 (1 H, m), 6.53 (1 H, d d d, J = 1.2, 10.7, 15.2 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 9.6, 11.2, 16.1, 18.0, 21.7, 38.8, 56.2, 62.2 (70.1, 70.2)*, 78.8, 81.0, 83.2, 88.2, 89.7, 109.2, 111.8, 127.8, (128.9, 130.0)*, 133.4, 135.8, 157.2, 164.6, 171.1 (diastereomeric aldols)*; HRMS CI(NH_3) $C_{23}M_{33}O_8$ ($M^+ + H$) calculated 437.2175, found 437.2168.

(±)-Asteltoxin (1). *p*-Toluenesulfonyl chloride (18 mg; 0.094 mmol) was added to a mixture of 9 (13.5 mg; 0.031 mmol), 4-dimethylaminopyridine (4 mg; 0.032 mmol), and triethylamine (45 mL; 0.32 mmol) in CH_2Cl_2 (20 mL). After the mixture was stirred for 12 h, the resultant yellow solution was concentrated and purified by flash chromatography (20% hexane/ether, then 50% EtOAc/ether) to give (±)-asteltoxin (1) (10.5 mg; 82%): TLC (EtOAc) R_f 0.46. IR (CH_2Cl_2) 3600 (br), 1705, 1627, 1627, 1542, 1454, 1406, 1248, 1093, 1003 cm^{-1}; MS (EI, 20 eV) *m/e* (relative intensity) 418 (14, M^+), 354 (6), 298 (21), 276 (27), 260 (39), 248 (92), 247 (86), 219 (100), 171 (33), 154 (65), 139 (83), 136 (81), 125 (70); UV (MeOH) 367, 274, 269 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (3 H, t, J = 7.5 Hz), 1.20 (3 H, s), 1.40 (3 H, s), 1.56 (2 H, m), 1.72 (1 H, d, J = 4.8 Hz, sec-OH), 1.99 (3 H, s), 3.74 (1 H, d d, J = 3.0, 4.8 Hz), 3.84 (3 H, s), 4.31 (1 H, d d, J = 4.9, 7.9 Hz), 4.76 (1 H, m), 5.30 (1 H, s), 5.51 (1 H, s), 5.87 (1 H, d d, J = 4.8, 15.2 Hz), 6.40 (1 H, d, J = 15.0 Hz), 6.43 (1 H, d d, J = 11.0, 14.8 Hz), 6.53 (1 H, d d, J = 10.7, 14.8 Hz), 6.66 (1 H, ddd, J = 1.5, 10.7, 15.2 Hz), 7.20 (1 H, d d, J = 11.0, 15.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 9.0, 11.3, 16.1, 18.1, 21.8, 56.2, 62.3, 78.8, 81.0, 83.1, 89.1, 89.8, 108.4, 111.9, 120.3, 129.5, 132.9, 134.0, 135.4, 136.4, 154.3, 163.6, 170.7; HRMS (EI) calculated for $C_{23}H_{30}O_7$ (M^+) 418.1991, found 418.1993.

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Supplementary Material Available: Spectroscopic data for synthetic asteltoxin (9 pages). Ordering information is given on any current masthead page.