Further Chemical Studies on Anisatin, a Neurotoxic Sesquiterpenoid Having a β-Lactone

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Synopsis. By a series of chemical reactions, anisatin was efficiently converted into the key intermediate employed in the synthesis of anisatin.

Anisatin (**1**) is a convulsant sesquiterpenoid isolated from the seeds of Japanese star anise (*Illicium anisatum* L.; shikimi in Japanese).[1,2] The structure of anisatin (**1**) was based on extensive chemical and spectroscopic studies.[2] The unique structure particularly characterized by a novel spiro β-lactone has made anisatin (**1**) a challenging synthetic target. Recently we have achieved the first total synthesis of anisatin (**1**) in the stereocontrolled manner.[3] In the course of synthetic studies of anisatin (**1**), we further investigated the reactivity of the uniquely arranged functional groups in anisatin (**1**) and the derivatives.[4] Described herein is the successful transformation of anisatin (**1**) into lactone **2**, the key intermediate employed in our recent synthesis of anisatin (**1**).[3]

First, we converted anisatin (**1**) into noranisatin acetonide (**4**). Thus, reaction of anisatin (**1**) with 2-methoxypropene in the presence of (+)-10-camphorsulfonic acid in *N*,*N*-dimethylformamide furnished anisatin acetonide (**3**) in 91% yield. Subsequent oxidation of **3** with $KMnO_4$ in AcOH–H_2O provided noranisatin acetonide (**4**) in 89% yield.

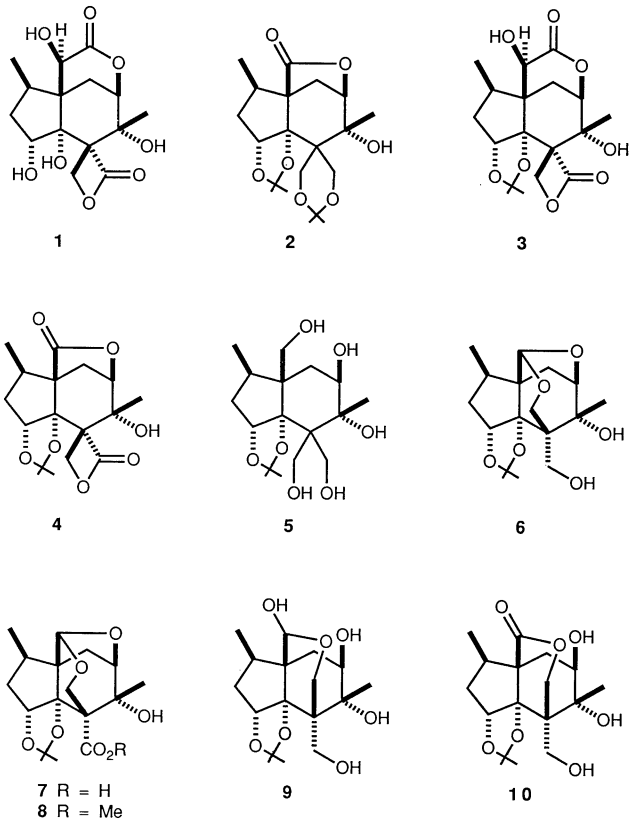
Next, we performed reduction of **4** with $LiAlH_4$ under various conditions and the results are summarized in Table 1. Reduction of **4** in tetrahydrofuran (THF) at reflux temperature yielded pentol **5** and acetal **6** in 30% and 25% yield, respectively. Reduction of **4** in THF at 0°C gave carboxylic acid **7** in 29% yield (isolated and characterized as methyl ester **8**). On reduction of **4** in ether at reflux temperature, **5** and **6** were obtained in 44% and 32% yield, respectively, together with a small amount of hemiacetal **9**[5] (13%). When reduction of **4** was performed in ether at −20°C, **9** was obtained as the major product (60%) along with lactone **10** (21%) and **7** (10%).

Oxidation of **9** wtih I_2–$CaCO_3$ in H_2O–MeOH furnished **10** in 78% yield. Finally, reaction of **10** with 2-methoxypropene in the presence of (+)-10-camphorsulfonic acid in benzene afforded rearranged lactone **2** in 90% yield. Spectral and chiroptical properties of **2** [$[\alpha]_D^{21}$ +14.5° (*c* 0.444, $CHCl_3$)] derived from natural anisatin (**1**) were identical with those of **2** [$[\alpha]_D^{21}$ +14.8° (*c* 0.446, $CHCl_3$)] synthesized from (*R*)-(+)-pulegone.[3]

Table 1. Reduction of **4** with $LiAlH_4$

Entry	Solvent	Temperature	Product[a]/%				
			5	**6**	**7**	**9**	**10**
1	THF	Reflux	30	25			
2	THF	0°C			29[b]		
3	Ether	Reflux	44	32		13	
4	Ether	−20°C			10	60	21

a) Isolated yield. b) Yield refers to the derived methyl ester **8**.



Experimental

Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-181 polarimeter. Infrared (IR) spectra were obtained on a JASCO Model IR-810 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM-C675 (270 MHz) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ=0.0) and coupling constants in Hz. The low-resolution (CIMS and EIMS) and high-resolution (HRCIMS and HREIMS) mass spectra were recorded on a JEOL JMS-LG2000 instrument using methane as the reagent gas for CIMS. Fuji-Davison silica gel BW-820MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, were used for analytical thin-layer chromatography. Benzene was distilled from Na under nitrogen. Tetrahydrofuran (THF) and ether were distilled from Na-benzophenone ketyl under

nitrogen. *N,N*-Dimethylformamide and pyridine were distilled from CaH_2 under nitrogen. Unless otherwise stated, organic solutions obtained by extractive workup were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure by a rotary evaporator.

Anisatin Acetonide (3). To a solution of anisatin (**1**) (515 mg, 1.6 mmol) in *N,N*-dimethylformamide (8 ml) were added 2-methoxypropene (0.22 ml, 2.4 ml) and (+)-10-camphorsulfonic acid (19 mg, 0.080 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Pyridine (ca. 0.1 ml) was added for quenching the reaction and the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel [30 g, benzene–acetone (5:1)] to give **3** (527 mg, 91%) as colorless needles; mp 206—208 °C (benzene); $[\alpha]_D^{23}$ +6.6° (*c* 0.14, $CHCl_3$); IR ($CHCl_3$) 3500, 3420, 1830, 1735, 1370, and 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.03 (3H, d, *J*=6.6 Hz), 1.54 (3H, s), 1.56 (3H, s), 1.75 (3H, s), 1.87 (1H, ddd, *J*=14.5, 8.2, 1.0 Hz), 2.02 (1H, dd, *J*=14.8, 3.6 Hz), 2.29 (1H, ddd, *J*=14.5, 11.9, 8.6 Hz), 2.44—2.53 (1H, m), 2.57 (1H, dd, *J*=14.8, 2.3 Hz), 3.26 (1H, s, –OH), 4.03 (1H, d, *J*=6.6 Hz), 4.12 (1H, br s), 4.33 (1H, dd, *J*=3.6, 2.3 Hz), 4.52 (1H, d, *J*=6.6 Hz), 4.90 (1H, dd, *J*=8.6, 1.0 Hz), and 5.44 (1H, d, *J*=1.0 Hz, –OH); CIMS *m/z* (rel intensity) 369 [$(M+H)^+$, 90], 353 (67), 339 (30), 323 (39), and 311 (100). Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57%. Found: C, 58.51; H, 6.54%.

Noranisatin Acetonide (4). To a solution of **3** (1.1 g, 3.0 mmol) in acetic acid (25 ml) was added a solution of $KMnO_4$ (1.0 g, 6.6 mmol) in H_2O (25 ml). The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution (5 ml) and the mixture was extracted with ethyl acetate (3×5 ml). The combined organic layers were washed with saturated NaCl solution (50 ml), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [50 g, hexane–ether (6:1→4:1)] to give **4** (0.90 g, 89%) as colorless needles; mp 125.5—126.5 °C (benzene–hexane); $[\alpha]_D^{18}$ +55° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 3480, 1830, 1775, 1385, 1375, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.09 (3H, d, *J*=6.6 Hz), 1.51 (3H, s), 1.54 (3H, s), 1.59 (3H, s), 2.02 (1H, dd, *J*=13.5, 5.9 Hz), 2.29—2.52 (3H, m), 2.75 (1H, d, *J*=12.5 Hz), 3.99 (1H, d, *J*=7.1 Hz), 4.27 (1H, br s, –OH), 4.28 (1H, d, *J*=7.1 Hz), 4.38 (1H, d, *J*=5.9 Hz), and 4.89 (1H, d, *J*=7.1 Hz); EIMS *m/z* (rel intensity) 338 (M^+, 10), 323 (100), 281 (15), and 263 (31). Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55%. Found: C, 59.99; H, 6.51%.

$LiAlH_4$ Reduction of Noranisatin Acetonide (4) (Table 1).

(a) Reduction in THF at Reflux Temperature (Entry 1). To a solution of **4** (19 mg, 0.056 mmol) in THF (1 ml) was added a 1M (1M=1 mol dm^{-3}) solution of $LiAlH_4$ in THF (0.12 ml, 0.12 mmol). The reaction mixture was heated under reflux for 2 h. After the reaction mixture was cooled to room temperature, NaF (104 mg, 2.48 mmol) was added and the mixture was vigorously stirred for a while. To the ice-cooled mixture was added dropwise 10% H_2O–THF (1.5 ml). The mixture was stirred for 30 min at room temperature and filtered through a pad of Celite. The filter cake was washed thoroughly with THF. The combined organic solutions were concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [4 g, benzene–acetone (4:1→1:10→0:1)] to give pentol **5** (5.7 mg, 30%) and acetal **6** (4.1 mg, 25%) as a colorless oil, respectively.

5: $[\alpha]_D^{21}$ +1.2° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3450, 1390, 1150, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.02 (3H, d, *J*=6.6 Hz), 1.21 (3H, s), 1.50—1.60 (1H, m), 1.62 (3H, s), 1.68 (3H, s), 1.78 (1H, dd, *J*=14.0, 8.0 Hz), 2.08 (1H, dd, *J*=14.8, 4.0 Hz), 2.20—2.38 (1H, m), 2.49 (1H, ddd, *J*=14.0, 10.8, 8.0 Hz), 3.57—3.65 (1H, m, –OH), 3.63 (1H, d, *J*=14.0 Hz), 3.69 (1H, dd, *J*=4.0, 2.0 Hz), 3.88 (1H, d, *J*=12.0 Hz), 3.90—4.00 (1H, m, –OH), 4.18 (1H, d, *J*=13.0 Hz), 4.60—4.98 (2H, m), 4.83 (1H, d, *J*=14.0 Hz), 5.23 (1H, br s, –OH), and 5.25 (1H, d, *J*=8.0 Hz); EIMS *m/z* (rel intensity) 328 [$(M-H_2O)^+$, 43], 310 (38), 292 (21), and 55 (100). HREIMS. Found: *m/z* 310.1776. Calcd for $C_{17}H_{26}O_5$: M−2×H_2O, 310.1780.

6: $[\alpha]_D^{21}$ −31.2° (*c* 0.511, $CHCl_3$); IR ($CHCl_3$) 3500, 1385, 1160, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.01 (3H, d, *J*=6.9 Hz), 1.27 (3H, s), 1.52 (3H, s), 1.56 (3H, s), 1.80 (1H, ddd, *J*=14.8, 12.8, 8.4 Hz), 1.89 (1H, dd, *J*=12.4, 5.0 Hz), 1.96 (1H, ddd, *J*=14.8, 8.4, 2.0 Hz), 2.28 (1H, d, *J*=12.4 Hz), 2.35—2.46 (1H, m), 2.46—2.55 (1H, m, –OH), 3.48 (1H, dd, *J*=12.9, 10.9 Hz), 3.64 (1H, br s, –OH), 3.82 (1H, d, *J*=5.0 Hz), 3.87 (1H, d, *J*=11.4 Hz), 4.10—4.16 (1H, m), 4.14 (1H, d, *J*=11.4 Hz), 4.98 (1H, dd, *J*=8.4, 2.0 Hz), and 5.31 (1H, s); EIMS *m/z* (rel intensity) 326 (M^+, 0.5), 311 (20), 308 (18), and 265 (100). HREIMS. Found: *m/z* 326.1709. Calcd for $C_{17}H_{26}O_6$: M, 326.1729.

(b) Reduction in THF at 0 °C (Entry 2). Reduction of **4** (19 mg, 0.056 mmol) with $LiAlH_4$ (0.12 mmol) was performed in THF at 0 °C for 20 min. After workup as described above, the crude product containing acid **7** was treated with ethereal CH_2N_2 and subjected to column chromatography on silica gel [3 g, benzene–acetone (10:1→5:1→1:1)] to give methyl ester **8** (5.5 mg, 29%) as a colorless oil: $[\alpha]_D^{21}$ −27.3° (*c* 0.134, $CHCl_3$); IR ($CHCl_3$) 3500, 1715, 1435, 1380, 1240, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.00 (3H, d, *J*=6.9 Hz), 1.24 (3H, s), 1.45 (3H, s), 1.48 (3H, s), 1.79 (1H, dd, *J*=11.8, 5.0 Hz), 1.82—1.92 (2H, m), 2.34—2.50 (1H, m), 2.56 (1H, d, *J*=11.8 Hz), 3.79 (3H, s), 3.90 (1H, d, *J*=5.0 Hz), 3.99 (1H, d, *J*=11.2 Hz), 4.45 (1H, d, *J*=11.2 Hz), 4.68 (1H, s, –OH), 5.09 (1H, dd, *J*=8.1, 1.0 Hz), and 5.29 (3H, s); EIMS *m/z* (rel intensity) 354 (M^+, 62), 339 (100), 311 (71), and 295 (63). HREIMS. Found: *m/z* 354.1675. Calcd for $C_{18}H_{26}O_7$: M, 354.1678.

(c) Reduction in Ether at Reflux Temperature (Entry 3). To a vigorously stirred suspension of $LiAlH_4$ (31 mg, 0.82 mmol) in ether (0.5 ml) was added dropwise a solution of **4** (16 mg, 0.047 mmol) in ether (1.5 ml). The reaction mixture was heated under reflux for 3 h. After workup as described above, the crude product was subjected to column chromatography on silica gel [2 g, benzene–acetone (4:1→3:1)] to give **5** (7.2 mg, 44%), **6** (5.1 mg, 32%), and hemiacetal **9**[5] (2.2 mg, 13%) as a colorless oil, respectively.

9: IR ($CHCl_3$) 3600, 3450, 1480, 1385, 1085, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz; signals for the major diastereomer) δ=1.02 (3H, d, *J*=6.9 Hz), 1.28 (3H, s), 1.56 (3H, s), 1.60 (3H, s), 1.88 (1H, ddd, *J*=15.8, 12.2, 8.2 Hz), 2.02 (1H, ddd, *J*=15.8, 8.5, 2.0 Hz), 2.08 (1H, dd, *J*=15.2, 4.9 Hz), 2.24 (1H, d, *J*=15.2 Hz), 2.20—2.35 (1H, m), 2.50—2.80 (1H, m, –OH), 3.52—3.70 (3H, m; 2H, m on addition of D_2O), 3.80 (1H, d, *J*=13.2 Hz), 3.93 (1H, d, *J*=13.2 Hz), 4.33 (1H, d, *J*=13.2 Hz), 4.58 (1H, br s), 4.65—4.80 (1H, m, –OH), 4.89 (1H, br s, –OH), and 5.13 (1H, dd, *J*=8.2, 2.0 Hz); EIMS *m/z* (rel intensity) 344 (M^+, 2), 326 (15), 311 (22), and 255 (100). HREIMS. Found: *m/z* 326.1733. Calcd for $C_{17}H_{26}O_6$: M−H_2O, 326.1730.

(d) Reduction in Ether at −20 °C (Entry 4). Reduction of **4** (43 mg, 0.13 mmol) with $LiAlH_4$ (1.3 mmol) was performed in ether at −20 °C for 3 h. After workup as described above, the crude product was subjected to column chromatography on silica gel [5 g, benzene–acetone (10:1→6:1→4:1)] to give **7** (4.3 mg, 10%; characterized as **8**), **9** (26 mg, 60%), and lactone **10** (9.1 mg, 21%) as a colorless oil, respectively.

10: $[\alpha]_D^{21}$ −85.4° (*c* 0.856, MeOH); IR ($CHCl_3$) 3600, 3460, 1735, 1455, 1385, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.21 (3H, d, *J*=6.9 Hz), 1.30 (3H, s), 1.56 (3H, s), 1.63 (3H, s), 1.60—1.70 (1H, m), 1.90 (1H, dd, *J*=14.5, 6.2 Hz), 2.20 (1H, dd, *J*=11.6, 2.7 Hz), 2.28 (1H, dd, *J*=11.6, 2.7 Hz), 2.41 (1H, dq, *J*=6.2, 6.9 Hz), 2.82—2.95 (1H, m, –OH), 3.48—3.60 (1H,

m), 3.76 (1H, dd, J=2.7, 2.7 Hz), 4.33 (1H, d, J=13.2 Hz), 4.43 (1H, d, J=11.9 Hz), 4.63 (1H, d, J=11.9 Hz), 4.78 (1H, br s, -OH), and 4.98 (1H, d, J=7.9 Hz); EIMS m/z (rel intensity) 342 (M^+, 60), 327 (81), 324 (40), 298 (46), and 294 (100). HREIMS. Found: m/z 342.1661. Calcd for $C_{17}H_{26}O_7$: M, 342.1678.

Oxidation of Hemiacetal 9 to Lactone 10. A mixture of **9** (27 mg, 0.079 mmol), I_2 (209 mg, 0.83 mmol), and $CaCO_3$ (252 mg, 2.52 mmol) in 50% H_2O–MeOH (2 ml) was stirred at 50 °C for 3 d in the dark. After cooling, the reaction mixture was filtered through a pad of Celite. The filter cake was washed thoroughly with MeOH. The filtrate and washings were combined and the solution was concentrated under reduced pressure. The residue was dilute with H_2O (5 ml) and extracted with EtOAc (4×5 ml). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution and saturated NaCl solution, dried, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel [1 g, benzene–acetone (8:1→4:1→1:1)] to give **10** (21 mg, 78%) along with the recovered **9** (2.8 mg, 10%).

Conversion of Lactone 10 into Lactone 2. A mixture of **10** (45 mg, 0.13 mmol), 2-methoxypropene (15 mg, 0.21 mmol), and (+)-10-camphorsulfonic acid (3 mg, 0.013 mmol) in benzene (3.5 ml) was stirred at room temperature for 2 h. The reaction was quenched by the addition of 2 drops of pyridine and the mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [2 g, benzene–acetone (20:1→1:1)] to give **2** (45 mg, 90%) as an amorphous solid: $[\alpha]_D^{21}$ +14.5° (c 0.444, $CHCl_3$) [synthetic **2**,[3] $[\alpha]_D^{21}$ +14.8° (c 0.446, $CHCl_3$)]; IR ($CHCl_3$) 3500, 1770, 1450, and 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.03 (3H, d, J=6.6 Hz), 1.32 (3H, s), 1.33 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.91 (1H, dd, J=12.8, 5.0 Hz), 2.22 (1H, dd, J=12.5, 5.3 Hz), 2.28 (1H, dd, J=12.8, 6.2 Hz), 2.32—2.47 (1H, m), 2.58 (1H, d, J=12.5 Hz), 3.25 (1H, br s, -OH), 3.55 (1H, d, J=13.2 Hz), 3.99 (1H, d, J=13.2 Hz), 3.98 (2H, s), 4.23 (1H, d, J=5.3 Hz), and 5.28 (1H, d, J=6.2 Hz); EIMS m/z (rel intensity) 382 (M^+, 1), 367 (100), 324 (87), 306 (41), and 279 (84). HRCIMS. Found: m/z 383.2069. Calcd for $C_{20}H_{31}O_7$: M+H, 383.2070.

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4) Previous chemical studies: Ref. 2; see also, K. Yamada, S. Takada, and Y. Hirata, *Tetrahedron*, **24**, 1255 (1968).

5) This material was an 8:1 mixture concerning the hydroxyl group in the hemiacetal moiety.