

Preparation of Deoxygenated Derivatives of Neoanisatin, a Neurotoxic Sesquiterpenoid Having a β-Lactone

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Seven deoxygenated neoanisatin derivatives were prepared from anisatin and neoanisatin by utilizing methoxalyl ester/tributylstannane (n-Bu_3SnH) deoxygenation procedure coupled with a novel dehydration reaction of neoanisatin.

Anisatin (**1**)[1,2] and neoanisatin (**2**)[2] are convulsant principles isolated from the fruits of the toxic plant, *Illicium anisatum* L. (shikimi in Japanese) (Fig. 1). The intriguing structures of anisatin (**1**) and neoanisatin (**2**) characterized by a novel spiro β-lactone were determined by Yamada.[2] Recently we have achieved the total synthesis of natural enantiomers of anisatin (**1**) and neoanisatin (**2**),[3,4] establishing their absolute stereochemistry as depicted. The toxicity of neoanisatin (**2**) is almost identical with that of anisatin (**1**) [LD_{50} in mice (i.p.), 1 mg/kg].[2]

A neurochemical study has shown anisatin (**1**) to be a picrotoxane-type, non-competitive antagonist of an inhibitory neurotransmitter GABA (γ-aminobutyric acid).[5] Although the convulsant toxicities of **1** and **2** may be concerned with GABA antagonist activity, their precise modes of action are unclear. We are currently investigating the relationship between the convulsant activity and the functional group array in anisatin (**1**) and neoanisatin (**2**). As mentioned, the toxicity of neoanisatin (**2**) regarded as 3-deoxyanisatin is almost identical with that of anisatin (**1**), indicating that the 3-hydroxy group in **1** is not essential for the toxic activity. On the other hand, some derivatives of anisatin (**1**) such as noranisatin (**3**) and anisatic acid (**4**) are non-toxic, indicating that a certain spatial arrangement of oxygen-containing functional groups is an important structure requirement for toxicity. We believe that one of the important functional groups for toxic activity would be the hydroxy one placed on the 2-oxabicyclo[3.3.1]nonane skeleton in anisatin (**1**) and neoanisatin (**2**). Therefore we decided to study the relationship between toxic activities and a series of the deoxygenated derivatives of neoanisatin (**2**). Neoanisatin (**2**) has three hydroxy groups. Thus seven structures **5**–**11** (Fig. 2) are possible as the deoxygenated derivatives of neoanisatin (**2**). Described herein is the preparation of all possible deoxygenated neoanisatin derivatives **5**–**11** for biological study.

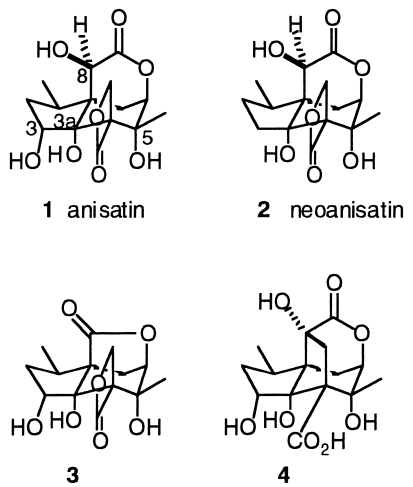


Fig. 1. Structures of anisatin (**1**), neoanisatin (**2**), and the related derivatives.

Results and Discussion

Reactivity of Anisatin (1) and Neoanisatin (2) to 1,1′-Thiocarbonyldiimidazole. A number of methods for deoxygenation of alcohols are available.[6] Some methods employed under strongly basic conditions are unsuitable for the deoxygenation of base-sensitive anisatin (**1**) and neoanisatin (**2**).[2] Therefore we first attempted imidazole-1-carbothioate/tributylstannane (n-Bu_3SnH) reduction methodology[7] for the deoxygenation of anisatin (**1**) and neoanisatin (**2**). However the conversion of anisatin (**1**) into the corresponding imidazole-1-carbothioate **12** by the reaction with 1,1′-thiocarbonyldiimidazole was unsatisfactory, owing to the preferential formation of thiocarbonate **13** (Scheme 1). In addition, the reaction of neoanisatin (**2**) with 1,1′-thiocarbonyldiimidazole did not take place at all.

Reactivity of Anisatin (1) and Neoanisatin (2) to Methyl Oxalyl Chloride. Previously we reported the conversion of anisatin (**1**) into neoanisatin (**2**),[4] in which methoxalyl ester/n-Bu_3SnH reduction methodology[8,9] was employed successfully. Therefore we decided to utilize this methodology for the systematic deoxygenation of neoanisatin (**2**). For the selective deoxygenation of a specific hydroxy group in **1** and **2** by using the methoxalyl ester/n-Bu_3SnH reduction methodology, the targeted hydroxy group should be selectively converted into the corresponding methoxalyl ester. For this purpose we examined the reactivity of the hydroxy groups in anisatin (**1**) and neoanisatin (**2**) toward methyl oxalyl chloride (Scheme 2).

As reported previously, anisatin (**1**) was converted smoothly into the corresponding 3-monooxalate **14** by treatment with an

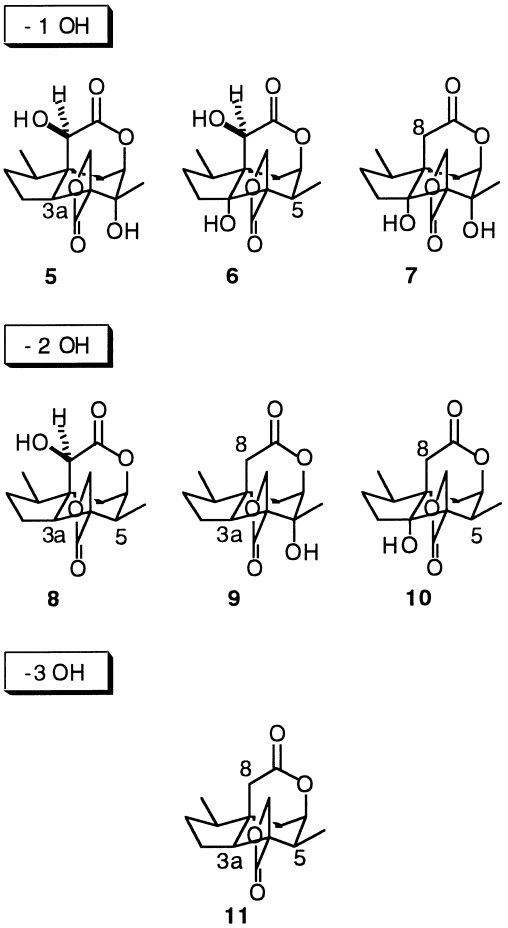
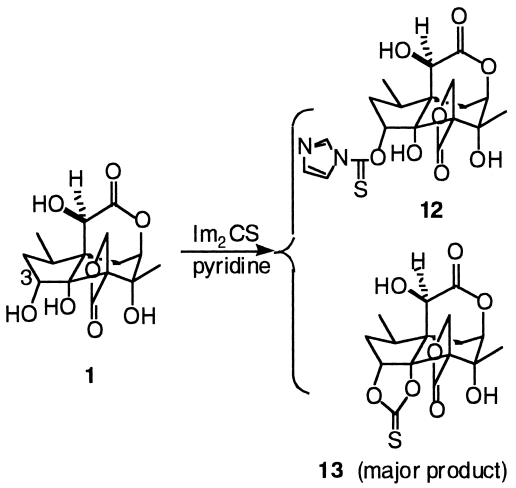
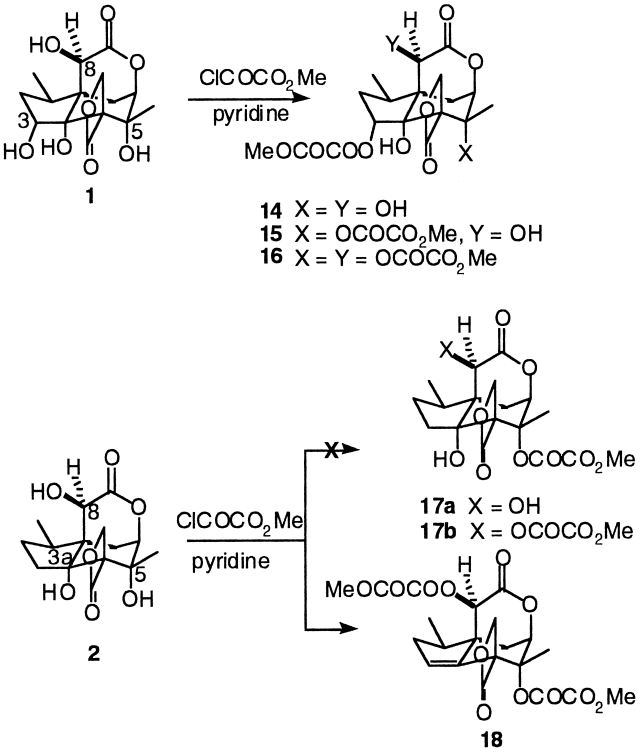


Fig. 2. Structures for deoxyneoanisatins **5**–**11**.

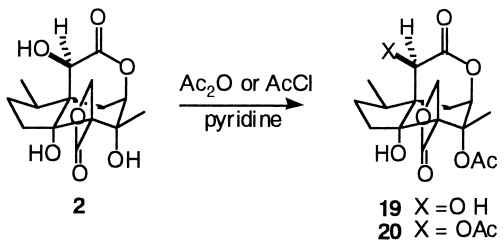


Scheme 1. Reaction of anisatin (**1**) with 1,1′-thiocarbonyldiimidazole.

equimolar amount of methyl oxalyl chloride in pyridine at room temperature.[4] Furthermore, treatment of **1** with 2.1 molar amounts or more than 3 molar amounts of methyl oxalyl chloride in pyridine at room temperature provided the corresponding desired 3,5-dimethoxalyl ester **15** or 3,5,8-trimethoxalyl ester **16** in moderate yields, respectively. However, the 3a-



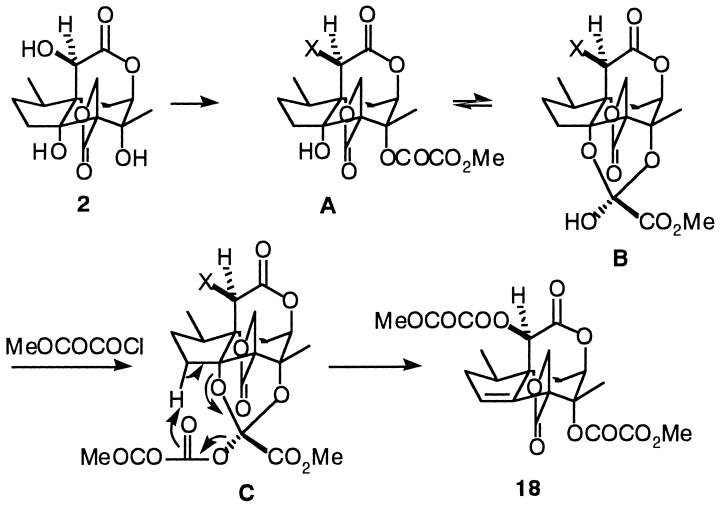
Scheme 2. Reaction of anisatin (**1**) and neoanisatin (**2**) with methyl oxalyl chloride.



Scheme 3. Acetylation of neoanisatin (**2**).

hydroxy group in **1** was never esterified under the conditions studied. The 5-oxalate groups in the derived **15** and **16** were easily cleaved by hydrolysis during purification by silica gel chromatography. On the other hand, the reaction of neoanisatin (**2**) with an equimolar amount of methyl oxalyl chloride gave a complex mixture mainly containing the recovered **2**, and none of the expected monooxalate **17a** was obtained. In contrast, the treatment of neoanisatin (**2**) with more than 3 molar amounts of methyl oxalyl chloride afforded, without any formation of the expected dimethoxalyl ester **17b**, the dehydrated dimethoxalyl ester **18** in high yield, from which we could prepare anisatin (**1**).[10] The 5-oxalate group in **18** was also hydrolyzed easily during purification by silica gel chromatography. Interestingly, acetylation of neoanisatin (**2**) with Ac_2O or AcCl proceeded smoothly to give the corresponding monoacetate **19** and diacetate **20**, and no dehydration took place (Scheme 3). Neither dehydration nor acylation took place on treatment of **20** with methyl oxalyl chloride in pyridine.

Although the actual dehydration mechanism is unclear so



Scheme 4. Plausible mechanism for the formation of the dehydrated product **18**.

far, we believe that the dehydration may take place from the initially formed **A**, in which X may be either OH, or $OCOCO_2Me$ (Scheme 4). Thus, **A** may be present as the ortho ester form **B** in an equilibrium concentration, which then may be acylated with methyl oxalyl chloride, giving the advanced intermediate **C**. The intramolecular *syn* elimination of methyl hydrogen oxalate from **C** may lead to the dehydrated product **18**. In the case of anisatin (**1**), the similar *syn* elimination from the intermediate corresponding to **A** is unable to proceed owing to the absence of hydrogen required for the *syn* elimination, leading to the normal acylation products, **15** and **16**, respectively. In the acetates **19** and **20**, the ortho ester formation corresponding to **B** may not occur.

The poor reactivity of the 3a-hydroxy group in neoanisatin (**2**) made this hydroxy group difficult to introduce directly suitable ester functional groups susceptible to deoxygenation reaction. However the position-selective dehydration of neoanisatin (**2**) into the dehydrated dimethoxalyl ester **18** coupled with hydrogenation reaction offered a novel route to the deoxygenation at the 3a-position in neoanisatin (**2**). Thus, starting with **15**, **16**, **18**, and **19**, the desired deoxygenated neoanisatin derivatives **5**–**11** could be prepared. The structures including stereochemistry of the derived **5**–**11** were assigned as depicted by extensive spectral analyses coupled with NOE experiments.

Preparation of Monodeoxyneoanisatins (Scheme 5).

3a-Deoxyneoanisatin (5). Treatment of neoanisatin (**2**) with 3 molar amounts of methyl oxalyl chloride in pyridine gave dehydrated product **18**.[10] Hydrolysis of **18** provided diol **21**. Alternatively, diol **21** was prepared from anisatin (**1**) via thiocarbonate **13**. Thus anisatin (**1**) was converted into thiocarbonate **13** by the reaction with 1,1′-thiocabonyldiimidazole in pyridine. Treatment of thiocarbonate **13** with *n*-Bu_3SnH in the presence of AIBN in refluxing toluene gave the desired diol **21** in 72% yield.[11] Hydrogenation of diol **21** over PtO_2 furnished the desired **5**.

5-Deoxyneoanisatin (6). Treatment of anisatin (**1**) with 2.1 molar amounts of methyl oxalyl chloride in pyridine gave unstable dimethoxalyl ester **15**. Without purification, dimethoxalyl ester **15** was reduced with *n*-Bu_3SnH in the presence of AIBN in refluxing toluene to give the desired **6**.

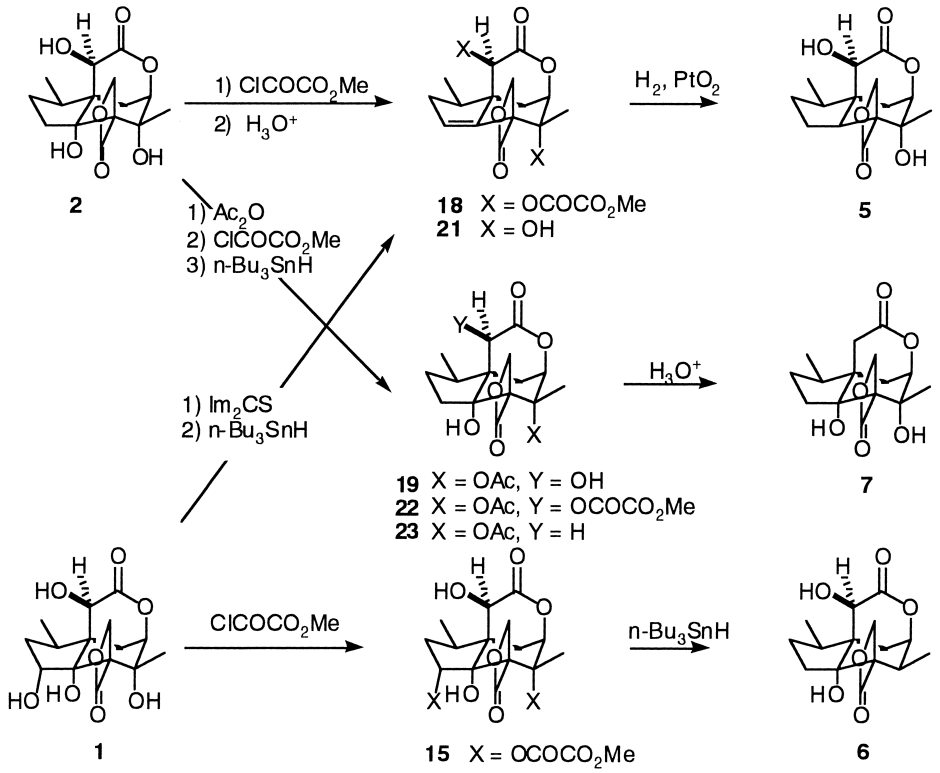
8-Deoxyneoanisatin (7). Acetylation of neoanisatin (**2**) with Ac_2O in pyridine at room temperature gave monoacetate **19**, which upon treatment with methyl oxalyl chloride afforded acetate–oxalate diester **22**. Reduction of **22** with *n*-Bu_3SnH in the presence of AIBN in refluxing toluene furnished acetate **23**, hydrolysis of which furnished the desired **7**.

Preparation of Dideoxyneoanisatins (Scheme 6). 3a,5-Dideoxyneoanisatin (8). On treatment with Ac_2O in pyridine, the secondary hydroxy group of the above-obtained diol **21** was selectively acetylated to give 8-acetate **24**, while the tertiary hydroxy group in neoanisatin (**2**) was smoothly acetylated under the similar conditions (Ac_2O–pyridine at room temperature) (Schemes 3 and 5). The abnormal high reactivity of the tertiary, 5-hydroxy group in **2** toward acylation may be attributed to intramolecular hydrogen bond formation between the H of 5-hydroxy group and the O of 3a-hydroxy one, increasing the nucleophilicity of the 5-hydroxy group. 8-Acetate **24** was then converted into 5-oxalate **25**. *n*-Bu_3SnH reduction of **25** gave 5-deoxy-8-acetate **26**, which upon hydrolysis furnished alcohol **27**. Hydrogenation of **27** over Pt/C provided the desired **8**.

3a,8-Dideoxyneoanisatin (9). The reactivity of 8-deoxyneoanisatin (**7**) to methyl oxalyl chloride was similar to that of neoanisatin (**2**). Thus treatment of **7** with methyl oxalyl chloride in pyridine gave dehydrated 5-oxalate **28**. The 5-oxalate group in **28** was then hydrolyzed by exposure to silica gel to provide olefinic alcohol **29**, which upon hydrogenation over PtO_2 provided the desired **9**.

5,8-Dideoxyneoanisatin (10). Treatment of anisatin (**1**) with excess methyl oxalyl chloride in pyridine gave unstable 3,5,8-trimethoxalyl ester **16**, as described above. Without purification, **16** was reduced with *n*-Bu_3SnH in the presence of AIBN in refluxing toluene to give the desired **10**.

Preparation of 3a,5,8-Trideoxyneoanisatin (11) (Scheme 6). Reduction of dimethoxalyl ester **18**, derived from neoanisatin (**1**) as described above, with *n*-Bu_3SnH in the presence of AIBN in refluxing toluene gave 5,8-deoxy derivative **30**, which upon hydrogenation over PtO_2 furnished the desired **11**.



Scheme 5. Preparation of monodeoxyneoanisatins **5**, **6**, and **7**.

Conclusion

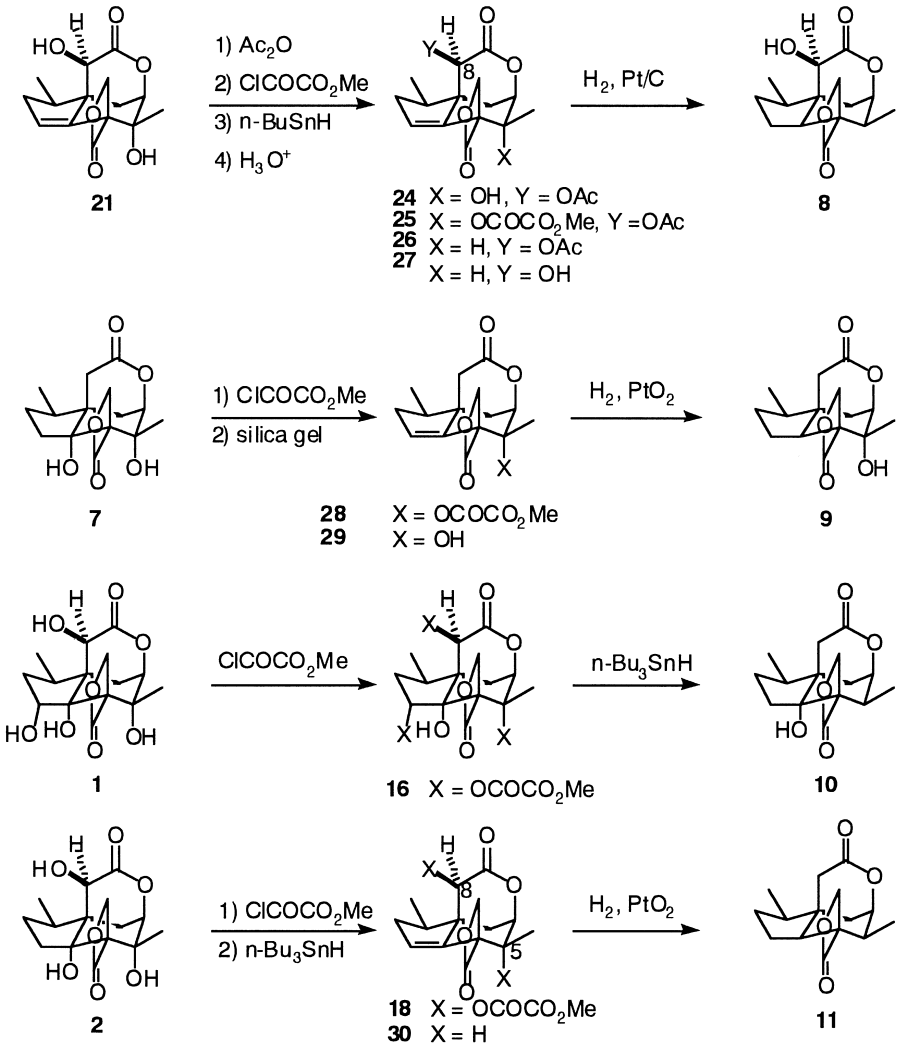
We achieved the preparation of seven deoxyneoanisatins **5**–**11** from anisatin (**1**) and neoanisatin (**2**) by utilizing methoxalyl ester/*n*-Bu_3SnH method coupled with a novel dehydration reaction of neoanisatin (**2**). The toxicity of the derived compounds is now under investigation.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were obtained on a JASCO Model IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL Lambda-270 (270 MHz) spectrometer in $CDCl_3$ or $(CD_3)_2CO$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS ($\delta = 0.0$) and coupling constants in Hz. Low-resolution electron impact mass spectra (EIMS) were recorded on a JEOL JMS-600 instrument operating at 70 eV for ionization energy. Low-resolution fast atom bombardment mass spectra (FABMS) were recorded on a Finnigan MAT TSQ-700 instrument using a Xe atom beam for ionization. High-resolution mass spectra (HREIMS) were recorded on a HITACHI M80B instrument operating at 70 eV for ionization energy. Merck silica gel 60 was used for column chromatography. Merck precoated silica gel 60 F_{254} plates with 0.25 mm or 0.5 mm thickness were used for analytical and preparative thin layer chromatography (TLC). Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl under nitrogen. Toluene, pyridine, and CH_2Cl_2 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.

Dehydrated Dimethoxalyl Ester 18. To a solution of **2** (195 mg, 0.625 mmol) in pyridine (2 mL) was added methyl oxalyl chloride (172 µL, 230 mg, 1.87 mmol) under Ar. The reaction mixture was stirred at room temperature for 3 h. Ice (ca. 1 g) was added to the reaction mixture for quenching the reaction. The mixture was stirred for a while and then diluted with EtOAc (20 mL). The mixture was washed successively with 1 M (= 1 mol dm^{-3}) HCl (1 mL) and with saturated brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a white solid. The solid was recrystallized from acetone–hexane to give **18** (217 mg, 74%) as colorless needles: mp 192–193 °C (acetone–hexane); IR (KBr) 1845, 1778, and 1765 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (3 H, d, J = 6.9 Hz), 1.96 (1 H, dd, J = 14.8, 1.6 Hz), 1.97 (3 H, s), 2.15 (1 H, ddd, J = 15.6, 9.9, 1.6 Hz), 2.30 (1 H, ddq, J = 9.9, 7.8, 6.9 Hz), 2.34 (1 H, dd, J = 14.8, 4.3 Hz), 2.58 (1 H, ddd, J = 15.6, 7.8, 3.4 Hz), 3.91 (3 H, s), 3.94 (3 H, s), 4.00 (1 H, d, J = 5.9 Hz), 4.30 (1 H, d, J = 5.9 Hz), 5.48 (1 H, dd, J = 4.3, 1.6 Hz), 5.49 (1 H, s), and 6.21 (1 H, dd, J = 3.4, 1.6 Hz); EIMS (70 eV) *m/z* (rel intensity) 466 (M^+, 0.2), 422 (1), 379 (0.2), 171 (10), 157 (100), and 143 (6); HREIMS, found: *m/z* 379.1030 [(M−COCOOMe)$^+$], calcd for $C_{18}H_{19}O_9$: 379.1028.

Diol 21. (a) From Neoanisatin (2). As described above, neoanisatin (**2**) (54.2 mg, 0.174 mmol) was converted into **18** with methyl oxalyl chloride (150 µL, 200 mg, 1.63 mmol) in pyridine (1 mL). To a solution of the crude **18** thus obtained in MeOH (5 mL) was added 6 M HCl (2 mL), and the mixture was stirred at 50 °C for 2 days. After cooling, the reaction mixture was diluted with water (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The extracts were combined, washed with saturated brine, and concentrated under reduced pressure. The residue was



Scheme 6. Preparation of dideoxyneoanisatins **8**, **9**, and **10**, and trideoxyneoanisatin **11**.

purified by TLC on silica gel [10 cm × 20 cm × 0.5 mm × 3 plates, benzene–acetone (2:1)] to give **21** (35.6 mg, 70% from **2**) as colorless needles; mp 80–83 °C (benzene–hexane); IR (KBr) 3570, 3420, 1824, and 1730 cm^{-1}; ^1H NMR (270 M Hz, $CDCl_3$) δ 1.19 (3 H, d, J = 6.6 Hz), 1.60 (3 H, s), 2.08 (1 H, dd, J = 14.2, 4.3 Hz), 2.15–2.27 (2 H, complex), 2.33 (1 H, dd, J = 14.2, 1.7 Hz), 2.44–2.53 (1 H, m), 2.71 (1 H, br s, OH), 3.08 (1 H, br s, OH), 4.06 (1 H, d, J = 5.3 Hz), 4.10 (1 H, s), 4.23 (1 H, d, J = 5.3 Hz), 4.40 (1 H, dd, J = 4.3, 1.7 Hz), and 6.01 (1 H, dd, J = 3.6, 1.6 Hz); EIMS (70 eV) *m/z* (rel intensity) 294 (M^+, 3), 250 (15), 219 (47), 175 (100), 157 (16), and 147 (20); HREIMS, found: *m/z* 294.1087 (M^+), calcd for $C_{15}H_{18}O_6$: 294.1102.

(b) From Anisatin (1) via Thiocarbonate 13. A mixture of **1** (126 mg, 0.383 mmol) and 1,1′-thiocarbonyldiimidazole (85 mg, 0.473 mmol) in pyridine (2 mL) was stirred at 60 °C for 12 h under Ar. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (10 mL) and the mixture was washed successively with 1 M HCl (1 mL) and with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a white solid. Purification by TLC on silica gel [20 cm × 20 cm × 1 mm × 1 plate, $CHCl_3$–acetone (5:1)] gave **13** (94 mg, 66%) as colorless needles; mp 180–182 °C (EtOAc–hexane); IR ($CHCl_3$) 3520, 3420, 1825, and 1750 cm^{-1}; ^1H NMR (270 M Hz, $CDCl_3$) δ 1.11 (3 H, d, J = 6.3 Hz), 1.63 (3 H, s), 2.07–2.16 (1 H, m), 2.18 (1 H, dd, J = 15.0, 3.6 Hz), 2.37–2.61 (2 H, m), 2.67 (1 H, dd, J = 15.0, 2.0 Hz), 3.39 (1 H, s, OH), 3.75 (1 H, br s, OH), 4.15 (1 H, d, J = 6.9 Hz), 4.20 (1 H, br s), 4.42 (1 H, d, J = 6.9 Hz), 4.44 (1 H, dd, J = 2.0, 3.6 Hz), and 5.33 (1 H, dd, J = 7.9, 1.3 Hz); EIMS (70 eV) *m/z* (rel intensity) 370 (M^+, 16), 310 (45), 266 (36), 247 (50), 205 (52), and 147 (100); HREIMS, found: *m/z* 370.0742 (M^+), calcd for $C_{16}H_{18}SO_8$: 370.0721.

A mixture of **13** (7 mg, 0.02 mmol), *n*-Bu_3SnH (30 µL, 0.095 mmol), and AIBN (2 mg) in toluene (5 mL) under Ar was heated under reflux for 30 min. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.5 mm × 2 plates, benzene–acetone (4:1)] to give **21** (4 mg, 72%), along with **31** (0.3 mg, 5%) as an amorphous solid. **31**: IR ($CHCl_3$) 3620, 3550, 1820, and 1740 cm^{-1}; ^1H NMR [270 M Hz, $(CD_3)_2CO$] δ 1.02 (3 H, d, J = 6.6 Hz), 1.39–1.79 (2 H, m), 1.54 (3 H, s), 1.73–1.84 (1 H, m), 2.08–2.14 (2 H, m), 2.81 (1 H, d, J = 4.9 Hz), 3.59 (1 H, d, J = 6.9 Hz, OH), 4.00 (1 H, d, J = 6.3 Hz), 4.14 (1 H, d, J = 3.0 Hz; s on D_2O addition), 4.21 (1 H, dd, J = 3.3, 2.6 Hz), 4.23 (1 H, s, OH), 4.46 (1 H, d, J = 6.3 Hz), 4.60–4.71 (1 H, m), and 4.84 (1 H, d, J = 3.0 Hz, OH); FABMS (positive, glycerol) *m/z* (rel intensity) 313 [(M

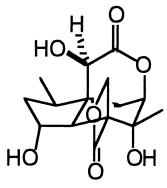


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Fig. 3. Structure of 3a-deoxyanisatin (**31**).

+ H)$^+$, 100], 295 (83), 265 (33), 250 (26), and 160 (100); HREIMS, found: *m/z* 276.0987 [(M − 2H$_2$O)$^+$], calcd for $C_{15}H_{16}O_5$: 276.0996.

The reduction of **13** with *n*-Bu$_3$SnH in refluxing hexane resulted in the formation of **31** (Fig. 3) exclusively.

3a-Deoxyneoanisatin (5). A mixture of **21** (18.4 mg, 0.0612 mmol) and PtO_2 (5 mg) in AcOH (1 mL) was vigorously stirred under hydrogen atmosphere at room temperature for 36 h. The reaction mixture was filtered through a pad of celite and the filter cake was washed thoroughly with EtOAc. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by TLC on silica gel [10 cm × 20 cm × 0.5 mm × 1 plate, benzene–acetone (2:1)] to give **5** (11.5 mg, 71% from **2**) as an amorphous solid; IR ($CHCl_3$) 3550, 1815, and 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.11 (3 H, d, J = 6.9 Hz), 1.34 (3 H, s), 1.63–1.79 (3 H, m), 1.83–1.96 (1 H, m), 2.05–2.20 (2 H, m), 2.38–2.45 (1 H, m), 2.73 (1 H, dd, J = 14.8, 1.6 Hz), 4.13 (1 H, d, J = 5.6 Hz), 4.18 (1 H, d, J = 2.6 Hz; s on D_2O addition), 4.39 (1 H, dd, J = 4.0, 1.6 Hz), 4.44 (1 H, d, J = 5.6 Hz), 4.54 (1 H, d, J = 2.6 Hz, OH), and 4.83 (1 H, s, OH); EIMS *m/z* (rel intensity) 296 (M$^+$, 100), 278 (30), 252 (20), 235 (40), and 189 (70); HREIMS, found: *m/z* 296.1210 (M$^+$), calcd for $C_{15}H_{20}O_6$: 296.1258.

5-Deoxyneoanisatin (6). To a solution of **1** (35 mg, 0.107 mmol) in pyridine (0.5 mL) was added methyl oxalyl chloride (21 µL, 27.5 mg, 0.225 mmol). The reaction mixture was stirred at room temperature for 2 h. Ice (ca. 0.5 g) was added to the reaction mixture for quenching the reaction and the mixture was diluted with EtOAc (10 mL). The mixture was washed successively with 1 M HCl (1 mL) and with saturated brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave the crude **15** (ca. 50 mg), which was used for the next reaction without further purification. **15**: IR ($CHCl_3$) 3550, 3450, 1835, 1770, and 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.07 (3 H, d, J = 7.3 Hz), 1.97 (3 H, s), 2.02–2.08 (2 H, m), 2.18 (1 H, ddd, J = 15.2, 9.4, 7.9 Hz), 2.60 (1 H, dd, J = 15.2, 2.0 Hz), 2.68–2.80 (1 H, m), 3.62 (2 H, br s, 2 OH), 3.91 (3 H, s), 3.94 (3 H, s), 4.13 (1 H, d, J = 7.3 Hz), 4.19 (1 H, s), 4.38 (1 H, d, J = 7.3 Hz), 5.58 (1 H, dd, J = 4.0, 2.0 Hz), and 6.02 (1 H, dd, J = 9.4, 5.3 Hz); EIMS *m/z* (rel intensity) 441 [(M−COOMe)$^+$, 4], 413 (10), 351 (66), and 177 (10).

A mixture of the crude **15** (ca. 50 mg), *n*-Bu$_3$SnH (118 µL, 116 mg, 0.4 mmol), and AIBN (2 mg) in toluene (5 mL) under Ar was heated under reflux for 1.5 h. After cooling, the mixture was concentrated under reduced pressure. The residue was repeatedly purified by TLC on silica gel [20 cm × 20 cm × 0.25 mm × 2 plates, benzene–acetone (3:1)] to give **6** (4 mg, 13%) as an amorphous solid; IR ($CHCl_3$) 3560, 3540, 1815, and 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.04 (3 H, d, J = 6.9 Hz), 1.25 (3 H, d, J = 7.3 Hz), 1.45–1.68 (2 H, m), 1.93 (1 H, dd, J = 14.0, 3.0 Hz), 2.05–2.15 (1 H, m), 2.11 (1 H, br s, OH), 2.33 (1 H, dd, J = 14.0, 2.3 Hz), 2.37–2.55 (2 H, m), 2.95 (1 H, dq, J = 2.0, 6.9 Hz), 2.96 (1 H, br s, OH), 4.07 (1 H, br s), 4.18 (1 H, d, J = 6.3 Hz), 4.33 (1 H, d, J = 6.3 Hz), and 4.52 (1 H, ddd, J = 4.0, 2.3, 2.3 Hz); EIMS *m/z* (rel intensity) 296 (M$^+$, 3), 278 (4), 252 (30), and 178 (100); HREIMS, found: *m/z* 296.1296 (M$^+$), calcd for $C_{15}H_{20}O_6$: 296.1258.

8-Deoxyneoanisatin (7). A mixture of **2** (60.5 mg, 0.194 mmol), pyridine (1 mL) and Ac_2O (0.1 mL) was stirred at room temperature for 3 days. The reaction mixture was concentrated azeotropically with toluene under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.5 mm × 4 plates, benzene–acetone (2:1)] to give **19** (34.4 mg, 50%) as an amorphous solid, along with the recovered **2** (28.1 mg, 46%). **19**: IR ($CHCl_3$) 3550, 1830, and 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.06 (3 H, d, J = 7.3 Hz), 1.51–1.73 (2 H, m), 1.92 (3 H, s), 1.92–1.98 (1 H, m), 2.06–2.25 (1 H, m), 2.13 (3 H, s), 2.36–2.51 (3 H, m), 3.23 (1 H, s, OH), 3.58 (1 H, s, OH), 4.12 (1 H, d, J = 6.9 Hz), 4.15 (1 H, m), 4.33 (1 H, d, J = 6.9 Hz), and 5.62 (1 H, dd, J = 4.0, 2.0 Hz); EIMS *m/z* (rel intensity) 354 (M$^+$, 7), 312 (5), 294 (7), 276 (9), 266 (18), 250 (64), and 176 (100).

To a solution of **19** (23.1 mg, 0.065 mmol) in pyridine (1 mL) was added methyl oxalyl chloride (30 µL, 0.33 mmol) under Ar. The mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of water (10 mL). The mixture was extracted with EtOAc (3 × 30 mL). The extracts were combined, washed with saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude **22**, which was used for the next reaction directly. To a solution of the crude **22** in toluene (5 mL) was added *n*-Bu$_3$SnH (150 µL, 0.55 mmol) and AIBN (2 mg) under Ar. The mixture was heated under reflux for 45 min. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [10 g, hexane–acetone (1:1)] followed by TLC on silica gel [10 cm × 20 cm × 0.5 mm × 2 plates, benzene–acetone (3:1)] to give **23** (18.5 mg, 84% from **19**) as an amorphous solid; IR ($CHCl_3$) 3540, 3450, 1835, and 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.93 (3 H, d, J = 6.9 Hz), 1.25–1.40 (2 H, m), 1.75–1.89 (3 H, m), 1.93 (3 H, s), 2.13 (3 H, s), 2.09 (1 H, d, J = 18.8, 2.6 Hz), 2.13–2.23 (1 H, m), 2.43–2.60 (1 H, m), 2.55 (1 H, d, J = 18.8 Hz), 3.88 (1 H, br s), 4.17 (1 H, d, J = 6.9 Hz), 4.26 (1 H, d, J = 6.9 Hz), and 5.65 (1 H, dd, J = 4.0, 1.6 Hz); EIMS *m/z* (rel intensity) 338 (M$^+$, 6), 278 (37), 234 (66), 175 (70), 149 (79), and 43 (100).

A solution of **23** (18.5 mg, 0.547 mmol) in 10% HCl–MeOH (5 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.5 mm ×2 plates, benzene–acetone (2:1)] to give **7** (15.5 mg, quantitative) as an amorphous solid; IR ($CHCl_3$) 3430, 1830, and 1730 cm^{-1}; ^{1}H NMR (270 M Hz, $CDCl_3$) δ 0.95 (3 H, d, J = 6.9 Hz), 1.34–1.45 (1 H, m), 1.61 (3 H, s), 1.63–1.77 (1 H, m), 1.86 (1 H, dd, J = 14.5, 4.0 Hz), 2.08 (1 H, dd, J = 19.1, 3.0 Hz), 2.09–2.24 (2 H, m), 2.39 (1 H, ddd, J = 14.5, 3.0, 2.0 Hz), 2.48–2.57 (1 H, m), 2.56 (1 H, d, J = 19.1 Hz), 3.37 (1 H, br s, OH), 4.16 (1 H, d, J = 6.9 Hz), 4.26 (1 H, d, J = 6.9 Hz), 4.38 (1 H, dd, J = 4.0, 2.0 Hz), and 5.00 (1 H, br s, OH); EIMS (70 eV) *m/z* (rel intensity) 296 (M$^+$, 6), 278 (19), 235 (49), 190 (41), 147 (31), and 43 (100); HREIMS, found: *m/z* 296.1312 (M$^+$), calcd for $C_{15}H_{20}O_6$: 296.1258.

3a,5-Dideoxyneoanisatin (8). A mixture of **21** (11 mg, 0.037 mmol), pyridine (0.5 mL), and Ac_2O (0.1 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated azeotropically with toluene under reduced pressure to give the

crude **24** (ca. 12 mg), which was used for the next reaction without purification. **24**: IR ($CHCl_3$) 3560, 1820, 1760 and 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (3 H, d, J = 6.9 Hz), 1.62 (3 H, s), 2.01 (1 H, ddd, J = 15.8, 10.4, 2.0 Hz), 2.16 (3 H, s), 2.17–2.24 (1 H, m), 2.25–2.32 (1 H, m), 2.41 (1 H, dd, J = 14.4, 1.5 Hz), 2.55 (1 H, ddd, J = 15.8, 7.9, 3.0 Hz), 4.00 (1 H, d, J = 5.4 Hz), 4.28 (1 H, d, J = 5.4 Hz), 4.40 (1 H, dd, J = 4.3, 1.5 Hz), 5.42 (1 H, s), and 6.03 (1 H, m); EIMS *m/z* (rel intensity) 336 (M^+, 18), 292 (10), 276 (19), and 175 (100).

To a solution of the crude **24** (ca. 12 mg) in pyridine (0.5 mL) was added methyl oxalyl chloride (10 µL, 13.2 mg, 0.108 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of saturated brine (1 mL), and the mixture was extracted with EtOAc (3 × 3 mL). The extracts were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude **25** (ca.14 mg), which was used for the next reaction without further purification. **25**: IR ($CHCl_3$) 1835, 1765, and 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (3 H, d, J = 6.9 Hz), 1.90 (1 H, dd, J = 15.8, 1.6 Hz), 1.96 (3 H, s), 2.04 (1 H, ddd, J = 14.8, 10.4, 2.0 Hz), 2.16 (3 H, s), 2.22–2.28 (1 H, m), 2.32 (1 H, dd, J = 14.8, 4.5 Hz), 2.59 (1 H, ddd, J = 15.8, 7.9, 3.0 Hz), 3.90 (3 H, s), 3.95 (1 H, d, J = 7.0 Hz), 4.32 (1 H, d, J = 7.0 Hz), 5.44 (1 H, dd, J = 4.5, 1.6 Hz), 5.45 (1 H, br s), and 6.14 (1 H, m); EIMS *m/z* (rel intensity) 422 (M^+, 7), 378 (10), 318 (12), 274 (66), 214 (98), and 169 (100).

A mixture of the crude **25** (ca. 14 mg), *n*-Bu_3SnH (18 µL, 19 mg, 0.066 mmol), and AIBN (1 mg) in toluene (5 mL) under Ar was heated under reflux for 1.5 h. After cooling, the mixture was concentrated under reduced pressure. The residue was repeatedly purified by TLC on silica gel [20 cm × 20 cm × 0.25 mm × 1 plate, benzene–acetone (5:1)] to give **26** (5 mg, 47%) as an amorphous solid; IR ($CHCl_3$) 1825, 1760 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (3 H, d, J = 7.3 Hz), 1.28 (3 H, d, J = 7.2 Hz), 1.58–1.68 (1 H, m), 1.74 (1 H, dd, J = 13.9, 1.6 Hz), 2.03 (1 H, dd, J = 15.5, 2.0 Hz), 2.14 (3 H, s), 2.24 (1 H, m), 2.47 (1 H, dd, J = 13.9, 4.6 Hz), 2.50 (1 H, ddd, J = 15.5, 7.6, 3.0 Hz), 3.90 (1 H, d, J = 5.3 Hz), 4.35 (1 H, d, J = 5.3 Hz), 4.60 (1 H, ddd, J = 4.6, 1.6, 1.3 Hz), 5.39 (1 H, br s), and 5.98 (1 H, dd, J = 3.0, 2.0 Hz); EIMS *m/z* (rel intensity) 320 (M^+, 1), 276 (23), 234 (8), and 159 (100).

To a solution of **26** (4 mg, 0.01 mmol) in DME (2 mL) was added 3 M HCl (1 mL) and the mixture was stirred at 80 °C for 3 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.25 mm × 1 plate, benzene–acetone (5:1)] to give **27** (2 mg, 58%) as an amorphous solid; IR ($CHCl_3$) 3550, 1825, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.18 (3 H, d, J = 6.6 Hz), 1.27 (3 H, d, J = 6.9 Hz), 1.69 (1 H, dd, J = 14.5, 1.3 Hz), 2.15–2.20 (2 H, m), 2.16–2.32 (1 H, m), 2.36 (1 H, dd, J = 7.6, 3.3 Hz), 2.50 (1 H, dd, J = 4.3, 2.0 Hz), 2.95 (1 H, br s, OH), 3.93 (1 H, d, J = 5.1 Hz), 4.07 (1 H, br s), 4.32 (1 H, d, J = 5.1 Hz), 4.40 (1 H, ddd, J = 4.3, 1.3, 1.0 Hz), and 5.96 (1 H, m); EIMS *m/z* (rel intensity) 278 (M^+, 12), 248 (10), 234 (46), and 203 (100).

A mixture of **27** (2 mg, 0.007 mmol) and 5% Pt/C (5 mg) in MeOH (1 mL) was vigorously stirred under hydrogen at room temperature for 3 days. The reaction mixture was filtered through a pad of celite and the filter cake was washed thoroughly with MeOH. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.25 mm × 1 plate, benzene–acetone (3:1)] to give **8** (1 mg, 50%) as an amorphous solid, along with the recovered **27** (1 mg, 50%). **8**: IR ($CHCl_3$) 3550, 1820, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.08 (3 H, d, J = 6.9 Hz), 1.28 (3 H, d, J = 6.9 Hz), 1.52–1.58 (1 H, m), 1.63–1.86 (2 H, m), 1.87–1.90 (1 H, m), 1.94–2.08 (2 H, m), 2.15–2.20 (2 H, m), 2.31 (1 H, dd, J = 14.3, 4.5 Hz), 2.98 (1 H, br s, OH), 4.09 (1 H, br s), 4.17 (1 H, d, J = 5.9 Hz), 4.40 (1 H, d, J = 5.9 Hz), and 4.56 (1 H, ddd, J = 4.0, 2.0, 2.0 Hz); EIMS *m/z* (rel intensity) 280 (M^+, 0.7), 236 (29), and 192 (100); HREIMS, found: *m/z* 280.1332 (M^+), calcd for $C_{15}H_{20}O_5$: 280.1309.

3a,8-Dideoxyneoanisatin (9). To a solution of 8-deoxyneoanisatin (**7**) (48.4 mg, 0.164 mmol) in pyridine (1 mL) was added methyl oxalyl chloride (45 µL, 60 mg, 0.49 mmol) under Ar. The reaction mixture was stirred at room temperature for 13 h. The reaction was quenched by the addition of saturated brine (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The extracts were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude **28**, which was used for the next reaction without further purification. The crude **28** was dissolved in EtOAc (5 mL), and the solution was loaded onto a column packed with silica gel for chromatography (10 g). The column was left at room temperature for 2 days, and then the products were eluted with MeOH. The eluted solution was concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.5 mm × 2 plates, benzene–acetone (4:1)] to give **29** (34.5 mg, 76%) as an amorphous solid; IR ($CHCl_3$) 3430, 1830, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.04 (3 H, d, J = 6.9 Hz), 1.62 (3 H, s), 1.96 (1 H, dd, J = 13.2, 4.6 Hz), 2.06 (1 H, ddd, J = 16.1, 9.6, 2.1 Hz), 2.17–2.29 (2 H, m), 2.34 (1 H, dd, J = 17.6, 2.6 Hz), 2.58 (1 H, d, J = 17.6 Hz), 2.62 (1 H, ddd, J = 16.1, 7.9, 3.0 Hz), 2.65 (1 H, OH), 3.93 (1 H, d, J = 5.6 Hz), 4.38 (1 H, d, J = 5.6 Hz), 4.45 (1 H, dd, J = 4.6, 1.7 Hz), and 5.85 (1 H, dd, J = 3.0, 1.6 Hz).

A mixture of **29** (17.5 mg, 0.063 mmol) and PtO_2 (5 mg) in AcOH (5 mL) was vigorously stirred under hydrogen at room temperature for 2 days. The reaction mixture was filtered through a pad of celite and the filter cake was washed thoroughly with EtOAc. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.5 mm × 1 plate, benzene–acetone (2:1)] to give **9** (10.5 mg, 57%) as an amorphous solid; IR ($CHCl_3$) 3560, 1815, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (3 H, d, J = 7.3 Hz), 1.26–1.37 (1 H, m), 1.56 (3 H, s), 1.55–1.63 (1 H, m), 1.84–1.94 (1 H, m), 1.97–2.19 (2 H, m), 2.28–2.43 (3 H, m), 2.51 (1 H, s, OH), 2.47–2.54 (1 H, m), 2.53 (1 H, d, J = 12.2 Hz), 3.94 (1 H, d, J = 5.9 Hz), 4.32 (1 H, d, J = 5.9 Hz), and 4.38 (1 H, dd, J = 4.3, 1.6 Hz); EIMS *m/z* (rel intensity) 280 (M^+, 70), 262 (100), 237 (95), 219 (66), 193 (85), and 176 (100); HREIMS, found: *m/z* 280.1307 (M^+), calcd for $C_{15}H_{20}O_5$: 280.1309.

5,8-Dideoxyneoanisatin (10). To a solution of **1** (15 mg, 0.046 mmol) in pyridine (0.5 mL) was added methyl oxalyl chloride (28 µL, 38 mg, 0.308 mmol). The reaction mixture was stirred at room temperature for 2 h. Ice (ca. 0.5 g) was added to the reaction mixture for quenching the reaction and the mixture was diluted with EtOAc (10 mL). The mixture was washed successively with 1 M HCl (1 mL) and with saturated brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave the crude **16** (ca. 30 mg), which was used for the next reaction without further purification. **16**: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3 H, d, J = 7.4 Hz), 1.95 (3 H, s), 1.98–2.08 (2 H, m), 2.17 (1 H, dd, J = 14.8, 4.0 Hz), 2.76 (1 H, dd, J = 14.8,

2.0 Hz), 2.77–2.92 (1 H, m), 3.93 (6 H, s), 4.05 (3 H, s), 4.16 (1 H, d, J = 7.5 Hz), 4.32 (1 H, d, J = 7.5 Hz), 5.46 (1 H, s), 5.73 (1 H, dd, J = 4.0, 2.0 Hz), and 6.12 (1 H, dd, J = 9.4, 5.9 Hz).

A mixture of the crude **16**, *n*-Bu_3SnH (270 µL, 291 mg, 1 mmol), and AIBN (2 mg) in toluene (5 mL) under Ar was heated under reflux for 3 h. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by TLC on silica gel [20 cm × 20 cm × 0.25 mm × 1 plate, benzene–acetone (3:1)] to give **10** (3 mg, 23% from **1**) as an amorphous solid; IR ($CHCl_3$) 3560, 1815, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3 H, d, J = 6.9 Hz), 0.94–1.07 (1 H, m), 1.27 (3 H, d, J = 7.4 Hz), 1.32–1.44 (1 H, m), 1.58–1.76 (1 H, m), 1.80–1.88 (1 H, m), 2.02–2.27 (4 H, m), 2.44–2.50 (2 H, m), 3.97 (1 H, br s, OH), 4.18 (1 H, d, J = 6.4 Hz), 4.35 (1 H, d, J = 6.4 Hz), and 4.58 (1 H, ddd, J = 4.0, 2.0, 2.0 Hz); EIMS *m*/*z* (rel intensity) 280 (M^+, 5), 262 (3), 236 (55), and 176 (100); HREIMS, found: *m*/*z* 280.1327 (M^+), calcd for $C_{15}H_{20}O_5$: 280.1309.

3a,5,8-Trideoxyneoanisatin (11). As described above, neoanisatin (**2**) (29.2 mg, 0.0935 mmol) was converted into **18** with methyl oxalyl chloride (150 µL, 200 mg, 1.63 mmol) in pyridine (1 mL). A mixture of the crude **18**, *n*-Bu_3SnH (200 µL, 216 mg, 0.74 mmol), and AIBN (2 mg) in toluene (5 mL) under Ar was heated under reflux for 45 min. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by TLC on silica gel [10 cm × 20 cm × 0.5 mm × 2 plates, benzene–acetone (2:1)] to give **30** (14.4 mg, 59% from **2**) as an amorphous solid; IR ($CHCl_3$) 1830, and 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.03 (3 H, d, J = 6.9 Hz), 1.29 (3 H, d, J = 7.3 Hz), 1.60 (1 H, ddd, J = 13.5, 2.6, 1.6 Hz), 2.06 (1 H, ddd, J = 15.8, 9.6, 2.0 Hz), 2.10–2.29 (1 H, m), 2.13–2.38 (1 H, m), 2.18–2.35 (1 H, m), 2.31 (1 H, dd, J = 17.8, 2.6 Hz), 2.54 (1 H, d, J = 17.8 Hz), 2.60 (1 H, ddd, J = 15.8, 7.6, 2.6 Hz), 3.87 (1 H, d, J = 5.3 Hz), 4.47 (1 H, d, J = 5.3 Hz), 4.66 (1 H, ddd, J = 4.0, 1.6, 1.6 Hz), and 5.80 (1 H, dd, J = 2.6, 2.0 Hz); EIMS *m*/*z* (rel intensity) 262 (M^+, 0.3), 232 (13), 218 (85), and 174 (100).

A mixture of **30** (14.4 mg, 0.055 mmol) and PtO_2 (3 mg) in AcOH (1 mL) was vigorously stirred under hydrogen atmosphere at room temperature for 22 h. The reaction mixture was filtered through a pad of celite and the filter cake was washed thoroughly with EtOAc. The filtrate and washings were combined and concentrated under reduced pressure. The residue was purified by TLC on silica gel [10 cm × 20 cm × 0.5 mm × 1 plate, benzene–acetone (2:1)] to give **11** (10.5 mg, 72%) as an amorphous solid; IR ($CHCl_3$) 1820, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3 H, d, J = 6.9 Hz), 1.29 (3 H, d, J = 7.3 Hz), 1.48 (1 H, ddd, J = 13.5, 2.3, 2.0 Hz), 1.27–1.40 (1 H, m), 1.53–1.65 (1 H, m), 1.67–1.91 (3 H, m), 1.97–2.25 (4 H, m), 2.35 (1 H, d, J = 17.8 Hz), 4.21 (1 H, d, J = 6.3 Hz), 4.27 (1 H, d, J = 6.3 Hz), and 4.62 (1 H, ddd, J = 3.6, 2.0, 1.6 Hz); EIMS *m*/*z* (rel intensity) 264 (M^+, 5) and 220 (100); HREIMS, found: *m*/*z* 264.1305 (M^+), calcd for $C_{15}H_{20}O_4$: 264.1360.

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