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Synthesis of (-)-Neoanisatin, a Neurotoxic Sesquiterpenoid Having a Novel Spiro β-Lactone

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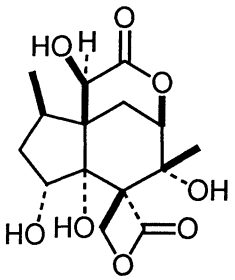
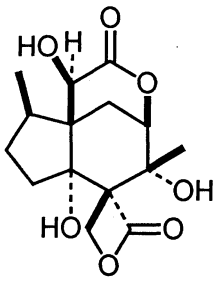
(-)-Anisatin can be converted into (-)-neoanisatin, which accomplishes the total synthesis of the natural enantiomer of neoanisatin.

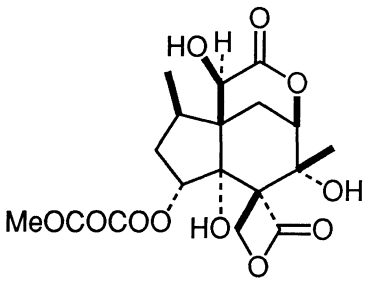
Anisatin (**1**) and neoanisatin (**2**) are neurotoxic sesquiterpenoids isolated from the seeds of Japanese star anise (*Illicium anisatum* L., shikimi in Japanese).[1,2] Toxicity of neoanisatin (**2**) [LD_{50} in mice (i. p.), 1.6 mg/kg][3] is almost identical with that of anisatin (**1**) [LD_{50} in mice (i. p.), 1 mg/kg].[2] Thus, anisatin (**1**) and neoanisatin (**2**) are regarded as the most powerful poisons of plant origin. Recent neurochemical studies have shown anisatin (**1**) to be one of the specific antagonists of GABA.[4] The intriguing biological activities and the unique structures characterized by the presence of a novel spiro β-lactone have made anisatin (**1**) and neoanisatin (**2**) particularly attractive synthetic targets. We have recently described stereocontrolled total synthesis of (-)- anisatin (**1**), and confirmed the absolute stereostructure of natural anisatin to be as depicted in formula **1**.[5] In connection with our continuing studies in this field, we report herein the conversion of (-)-anisatin (**1**) to (-)-neoanisatin (**2**), which accomplishes the total synthesis of the natural enantiomer of neoanisatin (**2**).



1 anisatin



2 neoanisatin



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The conversion of (-)-anisatin (**1**) to (-)-neoanisatin (**2**) involves a deoxygenation process, for which methyl oxalate **3** is requisite as an intermediate.[6] Thus, reaction of (-)-anisatin (**1**) with methyl oxalyl chloride (1.2 equiv.) in dry pyridine at room temperature for 2 days furnished the desired methyl oxalate **3** in 95% yield.[7] Subsequent reduction of methyl oxalate **3** was effected by the slow addition (over a 30 min period) of a solution of tri-*n*-butyltin hydride (2 equiv.) in toluene containing AIBN (0.05 equiv.), into a refluxing solution of **3** in toluene.[8,9] After being refluxed for an additional 2 h, the reaction mixture was concentrated and the residue was purified directly by column chromatography on silica gel to give (-)-neoanisatin (**2**) in 70% yield, along with recovered (-)-anisatin (**1**) (10%). Chromatographic and spectral properties of synthetic neoanisatin (**2**) [mp 212-213 °C (acetone-hexane); $[\alpha]_D^{16}$ -29.7° (*c* 0.135, MeOH)] were identical with those of natural neoanisatin (**2**) [mp 213-214 °C (acetone-hexane); $[\alpha]_D^{16}$ -31.9° (*c* 0.185, MeOH)] in all respects.

In conclusion, we achieved the total synthesis of the natural enantiomer of neoanisatin (**2**).

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References

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6) Attempts to convert anisatin (**1**) into neoanisatin (**2**) through the corresponding thioimidazolide (D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574) were unsatisfactory owing to the preferential formation of the unpleasant thiocarbonate during the preparation of the thioimidazolide.
7) Satisfactory spectral (IR, ^{1}H NMR, and mass) and exact mass spectral data were obtained for this compound. The yield refers to the material purified by column chromatography on silica gel.
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