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Abnormal Reactivity of Anisatin and Neoanisatin to Samarium Iodide-Hexamethylphosphorictriamide

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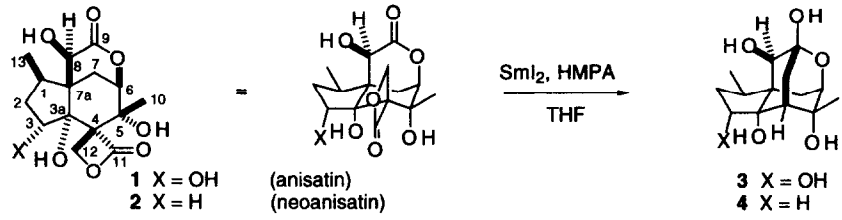
Abstract: Reactions of anisatin and neoanisatin with SmI_2 in the presence of HMPA give novel products having an oxaadamanthane skeleton accompanied by decarboxylation from the spiro β-lactone functionality. © 1997 Elsevier Science Ltd.

Anisatin (**1**) and neoanisatin (**2**) are convulsant principles isolated from the fruits of the toxic plant, *Illicium anisatum L.* (shikimi in Japanese).[1] Their structures characterized by an unusual spiro β-lactone were determined on the bases of extensive spectral and chemical studies.[1] A neurochemical study indicated **1** to be a non-competitive antagonist of an inhibitory neurotransmitter GABA (γ-aminobutyric acid).[2] Although the convulsant activity of **1** and **2** may be concerned with this GABA antagonist activity, their presice modes of the biological function are unclear. Recently we have achieved the total synthesis of natural enantiomer of **1** and **2**, establishing their absolute stereochemistry.[3] We are currently undergoing to study on the relationship between the functional group array in **1** and **2** and the convulsant activity, using a series of thier deoxygenated derivatives such as 8-deoxyanisatin and 8-deoxyneoanisatin. Described herein are novel reactions of **1** and **2** with SmI_2-HMPA providing **3** and **4**, respectively (Scheme **1**).



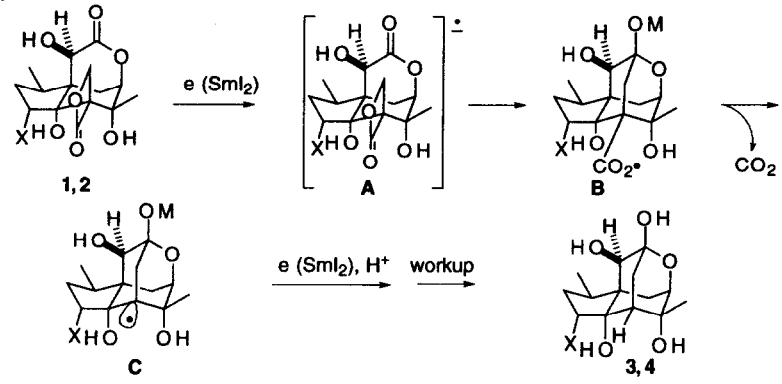
1 X = OH (anisatin)
2 X = H (neoanisatin)

3 X = OH
4 X = H

Scheme 1

As well known, a reagent system SmI_2-HMPA-RCO_2H (as a proton source) takes place deoxygenation of α-hydroxy esters to give the corresponding esters.[4] We therefore expected that the α-hydroxy-δ-lactone group in **1** and **2** would be reduced similarly with this reagent system, yielding 8-deoxyanisatin and 8-deoxyneoanisatin, respectively. However, reaction of **1** with SmI_2 (5 equiv) in the presence of HMPA (50 equiv) in THF at room temperature under argon proceeded within few minutes to give an unexpected product **3**[5] having an oxaadamantane skeleton in 83% yield after isolation. Similarly, reaction of **2** under essentially the same conditions gave the corresponding derivative **4**[6] in 83% yield after isolation. The structures of **3** and **4** were established by the extensive analysis of their spectral data. In contrast, reactions of **1** and **2** with SmI_2 in the absence of HMPA resulted in the complete recovery of **1** and **2**. Thus the coordination of HMPA to the Sm ion is essential for proceeding with this decarboxylative C-C bond formation reaction.

Although the precise reaction mechanism for the formation of **3** and **4** is unclear, we believe that the reaction may proceed as shown in Scheme **2**.



Scheme 2

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References and Notes

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5. **3**: colorless glass; IR ($CHCl_3$) 3680, 3360, 1600, 1450, 1290, 1258 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 0.99 (3 H, d, J = 7.1 Hz, H_{13}), 1.47 (3 H, s, H_{10}), 1.61–1.70 (2 H, m, H_2, H_7), 4.87 (1 H, ddd, J = 2.3, 3.5, 13.5 Hz, H_{12}), 1.84–1.89 (2 H, m, H_4, H_7), 2.07–2.11 (1 H, m, H_2), 2.16–2.26 (2 H, m, H_1, H_{12}), 3.54 (1 H, dd, J = 3.5, 3.5 Hz; 1 H, d, J = 3.5 Hz by the addition of D_2O, H_8), 3.62 (1 H, ddd, J = 2.3, 4.1, 4.1 Hz, H_6), 3.86 (1 H, d, J = 3.5 Hz, –OH), 4.38 (1 H, d, J = 5.3 Hz, –OH), 4.87 (1 H, ddd, J = 5.3, 5.3, 9.6 Hz; 1 H, dd, J = 5.3, 9.6 Hz by the addition of D_2O, H_3), 5.15 (1 H, d, J = 6.0 Hz, –OH), 5.79 (1 H, brs, –OH), 5.93 (1 H, brs, –OH); ^{13}C NMR (67.5 MHz, acetone-d_6) δ 12.9 (q, C_{13}), 26.9 (q, C_{10}), 31.7 (t, C_7), 31.9 (t, C_{12}), 37.8 (d, C_1), 42.2 (t, C_2), 42.7 (d, C_4), 49.8 (s, C_{7a}), 72.4 (d, C_3), 73.1 (s, C_5), 76.3 (d, C_8), 79.2 (d, C_6), 85.9 (s, C_{3a}), 96.2 (s, C_9); EIMS (70 eV) *m/z* (relative intensity) 286 (M^+, 2), 268 (2), 250 (3), 225 (5), 207 (7), 163 (17), 135 (12), 91 (44), 43 (100). HREIMS: found *m/z* 286.1416 (M^+); calcd for $C_{14}H_{22}O_6$ 286.1415.
6. **4**: colorless glass; IR ($CHCl_3$) 3700, 3400, 1460, 1380, 1108 cm^{-1}; ^1H NMR (270 MHz, acetone-d_6) δ 1.06 (3 H, d, J = 7.2 Hz, H_{13}), 1.41 (3 H, s, H_{10}), 1.51 (1 H, m, H_2), 1.61 (1 H, dd, J = 4.0, 13.4 Hz, H_7), 1.81 (1 H, ddd, J = 2.0, 4.0, 13.4 Hz, H_{12}), 1.93–2.00 (2 H, m, H_3, H_4), 2.05–2.20 (3 H, m, H_1, H_2, H_7), 2.21 (1 H, dd, J = 3.0, 13.4 Hz, H_{12}), 2.49 (1 H, ddd, J = 5.0, 11.5, 16.8 Hz, H_3), 3.41 (1 H, dd, J = 2.5, 2.5 Hz; 1 H, d, J = 2.5 Hz by the addition of D_2O, H_8), 3.45 (1 H, d, J = 2.5 Hz, –OH), 3.47 (1 H, ddd, J = 2.0, 4.0, 4.0 Hz, H_6), 4.94 (1 H, brs, –OH), 5.08 (1 H, brs, –OH), 5.87 (1 H, brs, –OH); ^{13}C NMR (67.5 MHz, acetone-d_6) δ 12.9 (q, C_{13}), 27.1 (q, C_{10}), 31.9 (t, C_7), 32.1 (t, C_2), 32.6 (t, C_{12}), 35.3 (t, C_3), 38.7 (d, C_1), 45.4 (d, C_4), 50.1 (s, C_{7a}), 73.6 (s, C_5), 76.4 (d, C_8), 78.2 (d, C_6), 86.7 (s, C_{3a}), 96.3 (s, C_9); EIMS (70 eV) *m/z* (relative intensity) 270 (M^+, 1), 252 (3), 234 (5), 209 (2), 191 (5), 165 (25), 123 (16), 105 (13), 91 (20), 43 (100). HREIMS: found *m/z* 252.1357 [$(M-H_2O)^+$]; calcd for $C_{14}H_{20}O_4$ 252.1360.

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