α-Conidendrin as a Source for Preparation of Sikkimotoxin Derivatives

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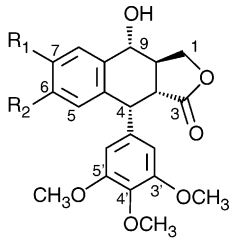
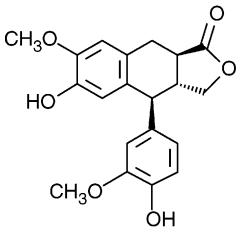
Oxidation of α-conidendrin (**3**) by Fremy's salt favored formation of an *o*-quinone (**4**) at the pendant aromatic ring as opposed to the fused aromatic ring. Quinone reduction and phenolic methylation, followed by lactone reduction, and subsequent oxidation by dichlorodicyanoquinone produced sikkimotoxin oxabicyclooctane (**7**), while oxidation with cupric sulfate/potassium persulfate gave sikkimotoxin dioxatricyclodecane (**8**).

Early structure determination for the tetrahydronaphthalene lignan sikkimotoxin (**1**) was facilitated by the conversion of podophyllotoxin (**2**) to sikkimotoxin derivatives.[1] More recently, **2** served as the precursor in preparations of different types of methyleneoxy-bridged derivatives of sikkimotoxin required for SAR studies.[2,3] These more recent studies also included the corresponding analogues of **2** as well as those of the tetrahydronaphthalene lignan α-conidendrin (**3**). Among the derivatives of **1** were the oxabicyclooctane **7** and the dioxatricyclodecane **8** (Scheme 1).



1: $R_1 = R_2 = OCH_3$

2: R_1-$R_2 = OCH_2O$



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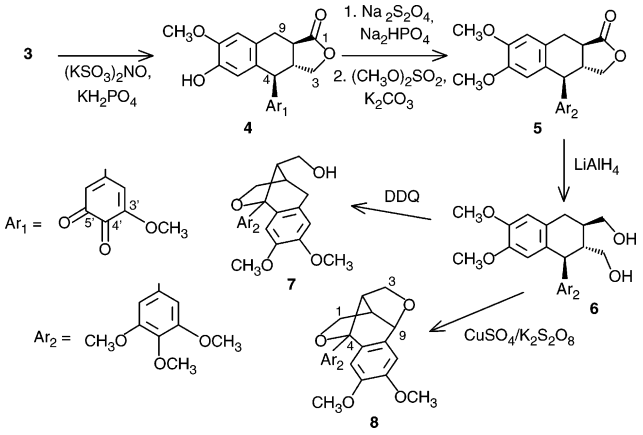
We now find that α-conidendrin can replace podophyllotoxin as the starting material for preparations of sikkimotoxin derivatives such as **7** and **8**, which can be obtained through the common intermediate 4-*epi*-9-deoxysikkimol, **6**. These more recent semisyntheses were initiated by oxidation of α-conidendrin's pendant aromatic ring, giving *o*-quinone **4** in 61% yield. This preference for the oxidation of the pendant ring of **3** has been achieved using $(KSO_3)_2NO$, often referred to as Fremy's salt,[4] which has been used in preparations of *o*- and *p*-benzoquinones, naphthoquinones, and some polycondensed quinones[4,5] and in the oxidation of indolines.[6] However, there appears to be only a single publication concerning the application of Fremy's salt to an oxidation of a tetrahydronaphthalene lignan; this was *β*-peltatin, whose fused, phenolic ring was converted to a *p*-benzoquinone.[7] The structure of the *o*-quinone **4** was determined by NMR analyses and was supported by the structure of the succeeding intermediate lactone, **5**, obtained from **4** in 74% yield by reduction with $Na_2S_2O_4$ followed by methylation by Me_2SO_4. Lactone **5** has the same substitution pattern of methoxy groups in fused and pendant aromatic rings as sikkimotoxin.[1] Possibly, C-5′ in the pendant aromatic ring of **3** undergoes oxidation, in preference to C-5 in the fused phenolic ring, as a result of greater steric accessibility of C-5′.

Scheme 1. Fremy's Salt Oxidation of α-Conidendrin (**3**), Reduction of *o*-Quinone **4** and Methylation Giving Lactone **5**, Reduction to Sikkimotoxin-diol **6**, and DDQ and $K_2S_2O_8/CuSO_4$ Oxidations to Oxabicyclooctane **7** and Dioxatricyclodecane **8**



Lithium aluminum hydride reduction of **5** gave 4-*epi*-9-deoxysikkimol, **6** (82%). Oxidation of **6** by dichlorodicyanoquinone (DDQ) produced oxabicyclooctane **7** (42%), while treatment of **6** with the oxidant couple $CuSO_4/K_2S_2O_8$ gave dioxatricyclodecane **8** (41%) and oxabicyclooctane **7** (9%), whose physical properties agreed with those reported earlier[3] for these two compounds. The DDQ oxidation of 4-*epi*-9-deoxysikkimol (**6**) to oxabicyclooctane **7** occurred in a slightly higher yield than the 33% yield of **7** from the DDQ oxidation of 9-deoxysikkimol.[3] These oxidations of **6** leading to **7** and **8** can be explained as one-electron processes followed by intramolecular coupling.[8−10] The configuration of the pendant, aromatic ring of methyleneoxy-bridged structures **7** and **8** is the same as that found in the tetrahydronaphthalene lignans podophyllotoxin and sikkimotoxin. In earlier work, low-level cytotoxicities of

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both oxabicyclooctane **7** and dioxatricyclodecane **8** had been observed[3] at 10^{-5} M, with 45 cell lines sensitive to **7** and 51 cell lines sensitive to **8** for the 56 cell lines representing nine different cell panels.

Hydrogenolyses of the α-conidendrin- and podophyllotoxin-derived oxabicyclooctane analogues of **7** have been directed to occur with retention or inversion at C-4 in the course of preparing a group of oxolanes, whose cytotoxicities were determined.[2] A single sikkimotoxin oxolane derivative having the same C-4 configuration as podophyllotoxin had been prepared from podophyllotoxin for this earlier study. While sikkimotoxin derivatives are not among the highly active cytotoxins, they have been important in comparing the relative cytotoxic responses resulting from various aromatic ring substituents.[2,3] The results of the present study indicate that α-conidendrin, a potentially less expensive source material than podophyllotoxin, could replace the latter lignan in the preparation of sikkimotoxin structural variants. α-Conidendrin was once recovered on a trial basis from softwood pulping for possible commercial uses.[11]

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher Scientific melting point apparatus using open capillary tubes and are uncorrected. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Bruker-Spectrospin 600 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as the internal references). Chemical shifts (δ) are in ppm, and coupling constants are in Hz. NMR assignments were assisted by DEPT and 2D NMR experiments (COSY, HMQC, and HMBC). HRMS were performed by the Nebraska Center for Mass Spectrometry, University of Nebraska−Lincoln, Lincoln, NE, and the University of Kansas Mass Spectrometry Laboratory, Lawrence, KS. THF was distilled from $LiAlH_4$ prior to use. Flash chromatography was performed using SG 2340 silica gel 60 (230−400 mesh). Purities of each of the two targets oxabicyclooctane **7** and dioxatricyclodecane **8** were determined by both isocratic (I, CH_3OH/H_2O, 0.65/0.35) and linear gradient (G, 15 min, 1 mL/min, CH_3CN/H_2O, 50/50−95/5) HPLC. α-Conidendrin was obtained from the Crown Zellerbach Corporation, Chemical Products Division, Camas, WA, and Raisio Chemicals, Raisio, Finland.

Fremy's Salt Oxidation of 3, Reduction of *o*-Quinone 4, and Methylation to Lactone 5. A solution of Fremy's salt (450 mg, 1.68 mmol) in H_2O (20 mL) containing aqueous KH_2PO_4 (170 mg in 6 mL of H_2O) was added in one portion to a stirred solution of α-conidendrin (**3**) (200 mg, 0.56 mmol) in acetone (14 mL). The solution was stirred at 25 °C for 4.25 h. The dark red solution was extracted with $CHCl_3$ and dried over $MgSO_4$. After the solvent was removed, the residue was separated by flash chromatography (CH_2Cl_2/EtOAc, 5/1) to give a red amorphous solid *o*-quinone **4** (126 mg, 61%) and starting **3** (44 mg, 22%). **4**: ^{1}H NMR δ 6.72 (1H, s, H-8), 6.64 (1H, s, H-5), 6.16 (1H, s, H-6′), 5.62 (1H, s, OH), 5.43 (1H, s, H-2′), 4.49 (1H, dd, J = 8.3, 5.7, H-3), 4.07 (1H, dd, J = 8.3, 5.9, H-3), 3.91 (3H, s, OCH_3), 3.82 (1H, d, J = 11.0, H-4), 3.63 (3H, s, OCH_3), 3.21 (1H, dd, J = 15.3, 3.5, H-9), 2.93 (1H, dd, J = 15.3, 13.1, H-9), 2.58 (1H, m, H-9a), 2.49 (1H, m, H-3a); ^{13}C NMR δ 178.1 (C-5′), 175.7 (C-4′), 175.4 (C-1), 156.6 (C-1′), 153.9 (C-3′), 146.5 (C-7), 144.9 (C-6), 126.9 (C-4a), 125.2 (C-8a), 122.0 (C-6′), 114.0 (C-5), 112.3 (C-8), 106.7 (C-2′), 70.9 (C-3), 56.1 (OCH_3), 56.0 (OCH_3), 51.0 (C-4), 43.0 (C-3a), 41.0 (C-9a), 28.9 (C-9).

To a solution of *o*-quinone **4** (55 mg, 0.15 mmol) in $CHCl_3$ (20 mL) was added a solution of $Na_2S_2O_4$ (123 mg, 0.60 mmol) and Na_2HPO_4 (45 mg) in H_2O (2 mL). The mixture was stirred at 25 °C for 0.5 h. The organic layer was separated. The aqueous layer was diluted with water (20 mL) and was extracted with EtOAc (3 × 10 mL). The combined EtOAc layers were washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue (51 mg) was methylated using Me_2SO_4 and K_2CO_3 in acetone. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1) to obtain lactone **5** (46 mg, 75%). **5**: mp 170−172 °C; $[\alpha]^{22}_D$ − 117.6° ($CHCl_3$, *c* 1.1); ^{1}H NMR δ 6.68 (1H, s, H-8), 6.33 (1H, s, H-5), 6.32 (2H, s, H-2′ and H-6′), 4.25 (1H, dd, J = 8.8, 6.5, H-3), 4.05 (1H, dd, J = 10.4, 8.8, H-3), 3.91 (1H, d, J = 11.0, H-4), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.80 (6H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.21 (1H, dd, J = 15.8, 5.0, H-9), 2.99 (1H, dd, J = 15.8, 12.7, H-9), 2.61−2.54 (1H, m, H-9a), 2.54−2.48 (1H, m, H-3a); ^{13}C NMR δ 176.7 (C-1), 153.6 (C-3′ and C-5′), 148.0 (C-6), 147.6 (C-7), 138.1 (C-4′), 137.2 (C-1′), 130.1 (C-8a), 127.3 (C-4a), 112.3 (C-8), 111.9 (C-5), 105.2 (C-2′ and C-6′), 71.7 (C-3), 60.8 (OCH_3), 56.2 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 50.7 (C-4), 47.6 (C-3a), 41.8 (C-9a), 29.2 (C-9); HRMS *m/z* 414.1679 (calcd for $C_{23}H_{26}O_7$, 414.1679).

Lactone Reduction in 5, Yielding Diol 6, and Oxidations of 6 to Oxabicyclooctane 7 and Dioxatricyclodecane 8. Following the general procedure for $LiAlH_4$ reduction, 6,4′,5′-tri-*O*-methyl-α-conidendrin **5** (42 mg, 0.10 mmol) was treated with $LiAlH_4$ (23 mg, 0.61 mmol) in dry THF (6 mL) at 25 °C for 4 h. The 4-epi-9-deoxysikkimol **6** (35 mg, 83%) was obtained after workup. **6**: mp 145−146 °C; $[\alpha]^{23}_D$ +15.0° ($CHCl_3$, *c* 0.5); ^{1}H NMR δ 6.58 (1H, s, H-8), 6.33 (2H, s, H-2′ and H-6′), 6.21 (1H, s, H-5), 3.86 (1H, d, J = 12.8, H-4), 3.83 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.78 (6H, s, OCH_3), 3.81−3.60 (3H, m, 2 × H-1 and H-3), 3.58 (3H, s, OCH_3), 3.49 (1H, dd, J = 11.0, 4.8, H-3), 2.90 (2H, bs, 2 × OH), 2.80−2.68 (2H, m, 2 × H-9), 2.00 (1H, m, H-9a), 1.85 (1H, m, H-3a); ^{13}C NMR δ 153.1 (C-3′ and C-5′), 147.3 (C-7), 147.1 (C-6), 141.0 (C-4′), 136.5 (C-1′), 131.5 (C-8a), 128.3 (C-4a), 113.0 (C-5), 110.9 (C-8), 106.4 (C-2′ and C-6′), 66.3 (C-1), 62.7 (C-3), 60.9 (OCH_3), 56.2 (OCH_3), 56.0 (OCH_3), 55.8 (OCH_3), 48.8 (C-4), 48.2 (C-3a), 39.9 (C-9a), 33.2 (C-9); HRCIMS *m/z* 419.2053 (calcd for $C_{23}H_{31}O_7$ [M + H], 419.2070).

Oxabicyclooctane 7. Following a known procedure,[2] diol **6** (35 mg, 0.084 mmol) was oxidized by DDQ (23 mg, 0.100 mmol) in CH_2Cl_2 (10 mL) for 4 h. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 2/1) to give 15 mg of pure oxabicyclooctane **7** (42%): HPLC (% purity) 98.6 (I); 98.7 (G); $[\alpha]^{23}_D$ +66.1° ($CHCl_3$, *c* 3.8); ^{1}H and ^{13}C NMR of **4** were identical with those obtained earlier.[2]

Dioxatricyclodecane 8. A solution of $CuSO_4 \cdot 5H_2O$ (44 mg, 0.177 mmol) and $K_2S_2O_8$ (96 mg, 0.354 mmol) in H_2O (10 mL) was added to a solution of **6** (74 mg, 0.177 mmol) in CH_3CN (25 mL), and the resulting mixture was heated to reflux for 0.5 h. H_2O was added, and the solution was extracted repeatedly with EtOAc. The combined EtOAc solution was washed with water and brine. Evaporation of the EtOAc left a residue, which was purified by flash chromatography (CH_2Cl_2/EtOAc, 3/1) to obtain dioxatricyclodecane **8** (30 mg, 41%) and oxabicyclooctane **7** (7 mg, 9%). **8**: HPLC (% purity) 99.0% (I); 100% (G); $[\alpha]^{23}_D$ +19.6° ($CHCl_3$, *c* 3.4); ^{1}H and ^{13}C NMR were identical with those obtained earlier.[2,3]

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