Total Synthesis of (±)-Lubimin and (±)-Oxylubimin

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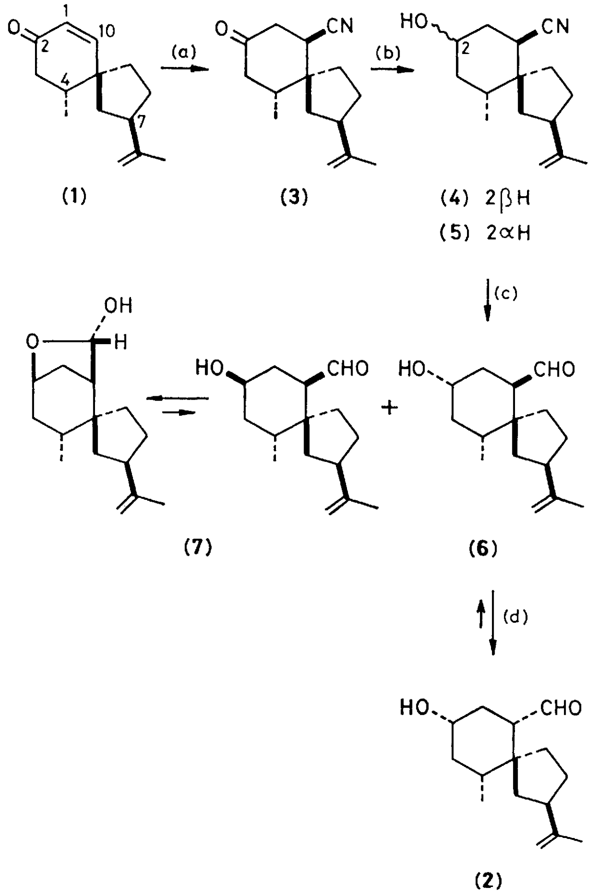
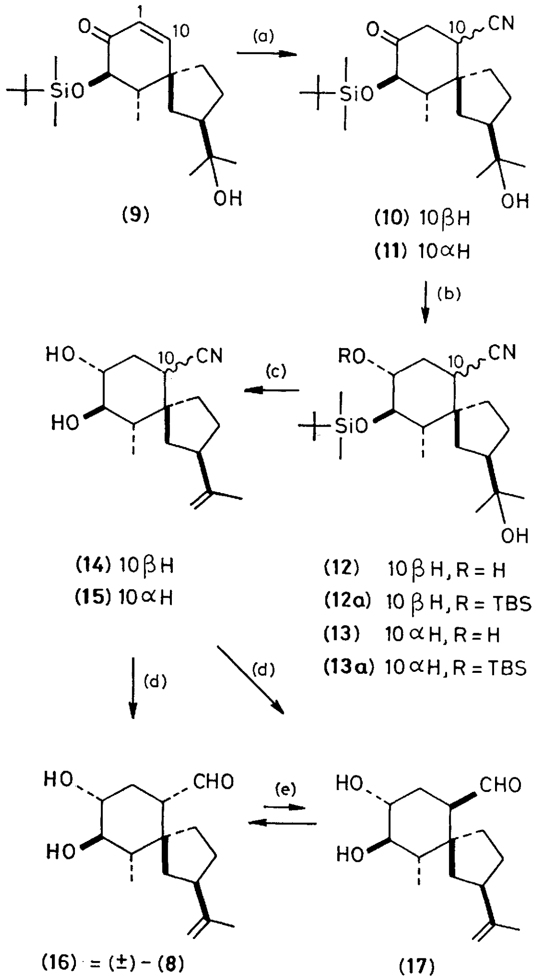
The total synthesis of the title compounds, examples of the spirovetivane type of phytoalexins in the genus *Solanum*, by transformation of (±)-15-norsolavetivone and its derivatives, is described.

The title compounds, described as phytoalexins, are members of a group of sesquiterpenes of the spirovetivane type, produced by plants of the *Solanum* genus.[1,2] These stress metabolites are biosynthetic intermediates in the major pathway from acetic acid to rishitin *via* solavetivone *in vivo*,[3,4] and are characterized structurally by the presence of five or six asymmetric centres in the spiro[4.5]decane system. In the preceding communication[5] we reported the total synthesis of (±)-15-norsolavetivone and related compounds. We describe herein transformation of these compounds into (±)-lubimin, (±)-oxylubimin, and related compounds, which constitutes the first synthesis of these highly oxygenated spirovetivane phytoalexins.

Conversion of (±)-15-norsolavetivone (**1**) into (±)-lubimin (**2**) (Scheme 1) commenced with hydrocyanation of (**1**) by a modification of Nagata's conditions.[6] The reaction proceeded regio- and stereo-selectively, giving 10-cyano-15-norsolavetivone (**3**) as the sole product (81%). The n.m.r. spectrum [δ 2.61 (2H, d, *J* 6 Hz, 1-H) and 3.10 (1H, t, *J* 6 Hz, 10-H)] indicated that (**3**) is a mixture of rapidly equilibrating conformers. Reduction of (**3**) with borane–ammonia complex[7] gave a mixture of 2-*eq*- (**4**) and 2-*ax*- (**5**) hydroxy-10-*ax*-cyano-15-norsolavetivones, which were easily separated by chromatography in 60 and 30% yields, respectively [(**4**), δ 2.74 (1H, t, *J* 4 Hz, 10-H) and 3.97 (1H, br. m, $W_{\frac{1}{2}}$ 25 Hz, 2-H); (**5**), δ 2.77 (1H, t, *J* 4 Hz) and 3.92 (1H, br. m, $W_{\frac{1}{2}}$ 12 Hz)]. Compounds (**4**) and (**5**), when treated with di-isobutylaluminium hydride in ether, were converted into 2-*eq*-hydroxy-10-*ax*-formyl-15-norsolavetivene (**6**) and its 2-*ax*-epimer (**7**) in 93 and 74% yields, respectively [(**6**), i.r., 1715 cm^{-1}, δ 9.85 (1H, s, 15-H); (**7**) (isolated as a 1 : 3 insepar-



Scheme 1. Reagents: (a) HCN (3 mol. equiv.) and Et_3Al (5 mol. equiv.) in tetrahydrofuran, room temp., 4 h. (b) BH_3–NH_3 complex in aqueous MeOH, room temp., 2 h. (c) Di-isobutylaluminium hydride in ether, 0 °C, 3 h. (d) 5% KOH in MeOH, room temp., 1 h.



Scheme 2. Reagents: (a) HCN (3 mol. equiv.) and Et_3Al (5 mol. equiv.) in tetrahydrofuran, room temp., 2 h. (b) BH_3–NH_3 complex in aqueous MeOH, room temp., 3.5 h; TBSCl–imidazole in dimethylformamide, 50 °C, 36 h. (c) Pyridine–Al_2O_3, 220 °C, 30 min; HF in tetrahydrofuran–MeCN, room temp., 6.5 h, (d) Di-isobutylaluminium hydride in dimethoxyethane, room temp., 12 h. (e) 5% KOH in MeOH, room temp., 1 h. TBS = Bu^tMe_2Si.

able mixture of the hydroxy aldehyde and its acetal), i.r., 3630, 3450, 2730, and 1719 cm^{-1}, δ 4.02 (0.25H, m, $W_{\frac{1}{2}}$ 10 Hz, 2-H), 4.33 (0.75H, m, $W_{\frac{1}{2}}$ 16 Hz, 2-H), 5.18 (0.75H, br. s, 10-H), and 9.73 (0.25H, m, $W_{\frac{1}{2}}$ 6 Hz, 10-H)]. Compounds (**6**) and (**7**) were identified as (±)-10-epilubimin[8] and (±)-2-epi-10-epilubimin[9] by direct comparison with natural samples. After repeated epimerization of (**6**),[8] (±)-lubimin (**2**)[2] was isolated in an overall yield of 37% from (±)- (**1**) (2.1% from orcinol dimethyl ether[5]).

The synthesis of (±)-oxylubimin (**8**) was performed in the same manner as that of (±)-(**2**), starting with the 3-t-butyldimethylsilyl ether (**9**) of (4*RS*, 7*SR*)-3,11-dihydroxy-15-norspirovetiv-1(10)-en-2-one[5] (Scheme 2). Hydrocyanation of (**9**) led to only regioselective formation of a mixture of the corresponding, easily separable 10-*eq*-(**10**) (44%) and 10-*ax*-(**11**) (32%) cyano-norsolavetivanes [(**10**), δ 2.88 (1H, dd, J 12 and 4.5 Hz, 10-H) and 3.77 (1H, d, J 11 Hz, 3-H); (**11**), δ 3.05 (1H, t, J 5 Hz) and 3.76 (1H, d, J 11 Hz)]. Reduction of (**10**) and (**11**) with borane–ammonia complex proceeded stereoselectively, in contrast with (**3**), giving the corresponding 2-alcohols (**12**) and (**13**), which on silylation formed the respective 2,3-disilyl ethers (**12a**) and (**13a**) in 80 and 58% yields [(**12a**), δ 3.26 (1H, t, J 7 Hz, 3-H) and 3.50 (1H, m, $W_{\frac{1}{2}}$ 20 Hz, 2-H); (**13a**), δ 3.52 (1H, t, J 4 Hz) and 3.72 (1H, m, $W_{\frac{1}{2}}$ 12 Hz)]. Dehydration of the isopropyl moieties of (**12a**) and (**13a**) by treatment with pyridine-modified alumina[10] followed by removal of the silyl groups[11] afforded 10-*eq*- (**14**) and 10-*ax*-(**15**) cyano-2,3-di-*eq*-hydroxy-15-norsolavetivenes in 67 and 47% yields, respectively. Treatment of (**14**) and (**15**) with di-isobutylaluminium hydride in dimethoxyethane gave the corresponding aldehydes (**16**), m.p. 79—81 °C, and (**17**), m.p. 121—123 °C, in 58 and 68% yields, which were identified as (±)-oxylubimin[2] and (±)-10-epioxylubimin,[8b,12] respectively, by direct comparison with natural samples. After repeated epimerization[8b,12] of (**17**), (±)-oxylubimin was isolated in an overall yield of 20% from (**9**) (0.82% from orcinol dimethyl ether[5]).

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