Total Synthesis of (±)-Lubimin and (±)-Oxylubimin. II. Transformation of (±)-15-Norsolavetivanes into (±)-Lubimin, (±)-Oxylubimin, and Related Compounds[1)]

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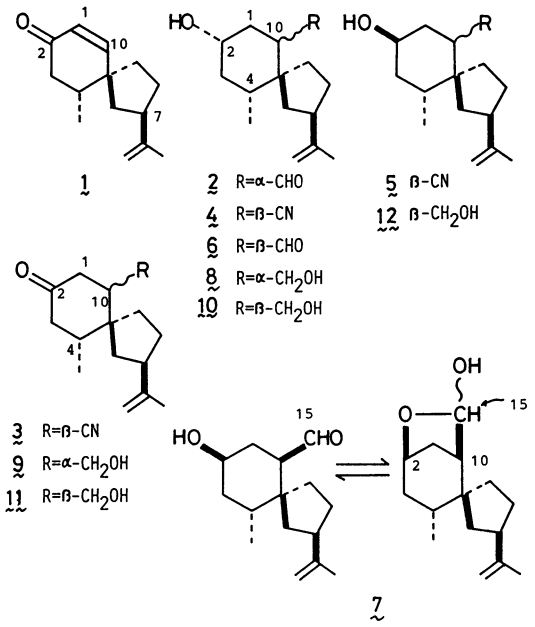
The transformation of (±)-15-norsolavetivone and related compounds, into (±)-lubimin and (±)-oxylubimin, which constitutes the total synthesis of these highly oxygenated spirovetivane phytoalexins, is described.

In the preceding paper we reported the synthesis of (±)-15-norsolavetivone and its oxygenated derivatives from orcinol dimethyl ether. Transformation of these compounds into the title natural compounds has recently been completed, and the result was published in a preliminary communication.[2)] In the present paper details of the transformation are described.

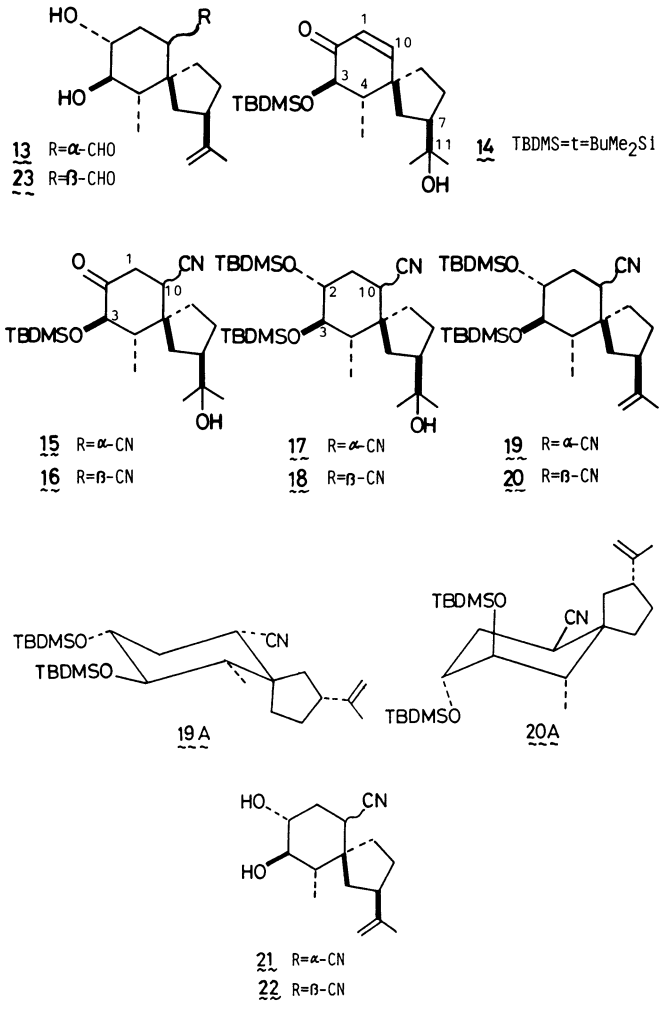
Conversion of (±)-15-norsolavetivone (**1**) into (±)-lubimin (**2**) was commenced with hydrocyanation by a modification of Nagata's conditions.[3)] The reaction proceeded regio- and stereo-selectively, giving 10-cyano-15-norsolavetiv-11-en-2-one (**3**) as the sole isolable product in 81% yield. The NMR spectrum of **3** [δ 2.61 (2H, d, J=6 Hz, 1-H) and 3.10 (1H, t, J=6 Hz, 10-H)] indicated that the cyano ketone (**3**) is a mixture of rapidly equilibrating conformers, and hence the 10-cyano and 4-methyl groups are oriented *trans* each other. Reduction of **3** with the ammonia-borane complex in aqueous mixture[4)] afforded a 2:1 mixture of 2-*equatorial*- (**4**) and 2-*axial*-hydroxy-10-*axial*-cyano-15-norsolavetivenes (**5**), which were easily separated by chromatography in 60 and 30% yields, respectively. In accordance with the assigned structures, the compounds (**4**) and (**5**) exhibited the following NMR spectra: **4**, δ 2.74 (1H, t, J=4 Hz, 10-H) and 3.97 (1H, br m, W_H=25 Hz, 2-H); **5**, δ 2.77 (1H, t, J=4 Hz) and 3.92 (1H, br m, W_H=12 Hz). These nitriles (**4**) and (**5**), when treated with diisobutylaluminium hydride in ether, were converted into the corresponding aldehydes (**6**) and (**7**) in 93 and 74% yields, respectively. The latter (**7**) was isolated as a 1:3 inseparable mixture of the hydroxy aldehyde and its acetal, as revealed by the IR and NMR spectra: IR, 3630, 3450, 2730, and 1719 cm^{-1}; NMR, δ 4.02 (0.25H, m, W_H=10 Hz, 2-H), 4.33 (0.75H, m, W_H= 16 Hz, 2-H), 5.18 (0.75H, br s, 15-H), and 9.73 (0.25H, br s, W_H=6 Hz, 15-H). These compounds (**6**) and (**7**) were identified as (±)-10-epilubimin[5)] and (±)-2-epi-10-epilubimin[6)] by direct comparison of the synthetic and natural samples (MS, IR, NMR, and TLC). After repeated epimerization[5)] of **6** with base, (±)-lubimin (**2**) was isolated in an overall yield of 2.1% from orcinol dimethyl ether. Since lubimin (**2**) has been transformed into lubiminol[5b,7)] (**8**) and isolubimin[5b,7,8)] (**9**), 10-epilubimin (**6**) into 10-epilubiminol[5)] (**10**) and 10-epiisolubimin[5,6,9)] (**11**), and 2-epi-10-epi-lubimin (**7**) into 2-epi-10-epilubiminol[5b,6)] (**12**), respectively, the present transformation implies the synthesis of these natural spirovetivane stress metabolites.

The synthesis of (±)-oxylubimin (**13**) was performed in the same manner as that of (±)-lubimin (**2**), starting with the 3-*t*-butyldimethylsilyl ether (**14**) of



(3*SR*,4*RS*,7*SR*)-3,11-dihydroxy-15-norspirovetiv-1(10)-en-2-one, which had been prepared previously.[1,10)] Hydrocyanation of **14** under the same conditions[3a)] as that of 15-norsolavetivone (**1**) led only to regioselective formation of a mixture of the corresponding 10-*equatorial*- (**15**) and 10-*axial*-cyano-15 norsolavetivenes (**16**), which were separated easily by chromatogarphy in 44 and 32% yields, respectively. The NMR spectra of these compounds [**15**, δ 2.88 (1H, dd, J=12 and 4.5 Hz, 10-H) and 3.77 (1H, d, J=11 Hz, 3-H); **16**, δ 3.05 (1H, t, J=5 Hz) and 3.76 (1H, d, J=11 Hz)] supported the assigned configurations. Reduction of the cyano ketones (**15**) and (**16**) with the ammonia-borane complex[4)] proceeded stereoselectively, in contrast with that of **3**, giving the corresponding 2-alcohols, which were converted into the respective 2,3-bis(*t*-butyldimethylsilyl) ethers (**17**) and (**18**) in 80 and 58% yields. The NMR spectra of these ethers [**17**, δ 2.58 (1H, dd, J=9 and 4 Hz, 10-H), 3.26 (1H, t, J=7 Hz, 3-H), and 3.50 (1H, m, W_H=20 Hz, 2-H); **18**, 3.10 (1H, dd, J=12 and 4 Hz), 3.52 (1H, t, J=4 Hz), and 3.72 (1H, m, W_H=12 Hz)] suggested that the A ring of **17** would probably take a deformed chair conformation with 2,3-diequatorial hydroxyl and 10-equatorial cyano groups, while **18** would adopt a slightly deformed one with 2,3-diaxial hydroxyl and 10-equatorial cyano groups owing to the bulkiness of the silyl groups. This assignment to the conformation was revealed clearly for the following compounds. Compounds **17** and **18**, when treated with

pyridine-modified alumina[10] at 220°C underwent dehydration to give the corresponding isopropenyl derivatives (**19**) and (**20**) in 74 and 75% yields, respectively. The NMR spectra [**19**, δ 2.48 (1H, dd, J=12 and 4 Hz, 10-H), 3.16 (1H, t, J=9 Hz, 3-H), and 3.44 (1H, m, W_H=20 Hz, 2-H); **20**, δ 3.05 (1H, dd, J=12 and 4 Hz), 3.50 (1H, t, J=4 Hz), and 3.69 (1H, m, W_H=14 Hz)] indicated that these compounds would be represented by conformations **19A** and **20A**. Removal of the silyl groups of **19** and **20** with hydrofluoric acid[12] afforded 10-*equatorial*- (**21**) and 10-*axial*-cyano-2,3-di-(*equatorial*-hydroxy)-15-norsolvetiv-11-enes (**22**) in 91 and 63% yields, respectively: **21**, δ 2.53 (1H, dd, J=12 and 4 Hz, 10-H), 2.97 (1H, t, J=11 Hz, 3-H), and 3.36 (1H, W_H=24 Hz); **22**, δ 2.66 (1H, t, J=4 Hz), 2.99 (1H, t, J=11 Hz), and 3.74 (1H, m, W_H=21 Hz). The compounds (**21**) and (**22**), when treated with diisobutylaluminium hydride in 1,2-dimethoxyethane, was converted into the corresponding aldehydes in 58 and 68% yields, which were identified as (±)-oxylubimin[12] (**13**) and (±)-10-epioxylubimin[12] (**23**), respectively, by direct comparison of the synthetic and natural samples. After repeated epimerization of **23**, the overall yield of (±)-oxylubimin amounted to 0.82% from orcinol dimethyl ether. The present result constitutes the first total synthesis of highly oxygenated spirovetivane phytoalexins.



Experimental

A general procedure was described in the preceding paper.[1]

10-Cyano-15-norsolavetiv-11-en-2-one (3). To a solution of **1** (68 mg) in tetrahydrofuran (THF) (2 ml) at 0°C was added a solution of hydrogen cyanide (HCN) and triethylaluminium (Et_3Al), prepared from Et_3Al in hexane (15% w/w, Tokyo-Kasei) (1.5 ml) and 0.91 M† HCN in THF (1.2 ml) at 0°C for 5 min under stirring. The mixture was warmed to room temperature and stirred for 4 h. The mixture was mixed with 2 M hydrochloric acid (HCl) (2 ml) at 0°C and stirred for 20 min, and poured into saturated brine (30 ml), and extracted with ethyl acetate (4×40 ml). The acetate extracts were washed with 2 M aq sodium hydroxide (NaOH) (2×20 ml) and saturated brine, dried, evaporated, and separated by chromatography over silica gel (5 g) with benzene to afford **3** (58 mg), oil; MS, m/z 231 (M^+); IR, 3090, 2210, 1722, 1648, and 890 cm^{-1}; NMR, δ 0.99 (3H, d, J=6 Hz), 1.76 (3H, s), 2.61 (2H, d, J=6 Hz), 3.10 (1H, t, J=6 Hz), and 4.75 (2H, s). Found: m/z 231.1594. Calcd for $C_{15}H_{21}NO$: M, 231.1621.

10-Cyano-15-norsolavetiv-11-en-2-ols (4) and (5). To a mixture of **3** (30 mg) in methanol (3 ml) and water (1.5 ml) was added the ammonia-borane complex (5 mg). The mixture was stirred at 20°C for 2 h, poured into 2 M HCl (1 ml), and stirred for 20 min. The mixture was extracted with ethyl acetate (4×30 ml), dried, evaporated, and separated by chromatography over silica gel (3 g) with benzene–ethyl acetate (8:1) to give 2α-alcohol (**4**) (18 mg) and 2β-alcohol (**5**) (9 mg). **4**, oil; MS, m/z 233 (M^+); IR, 3460, 3096, 2215, 1650, and 890 cm^{-1}; NMR, δ 0.96 (3H, d, J=6 Hz), 1.71 (3H, s), 2.74 (1H, t, J=4 Hz), 3.97 (1H, br m, W_H=25 Hz), 4.66 (2H, s). Found: m/z 233.1755. Calcd for $C_{15}H_{23}NO$: M, 233.1776. **5**, oil; MS, m/z 233 (M^+); IR, 3460, 3090, 2215, 1648, and 888 cm^{-1}; NMR, δ 0.95 (3H, d, J=6 Hz), 1.71 (3H, s), 2.77 (1H, t, J=4 Hz), 3.92 (1H, br m, W_H=12 Hz), and 4.67 (2H, s). Found: m/z 233.1820. Calcd for $C_{15}H_{23}NO$: M, 233.1776.

(±)-2-Epi-10-epilubimin (7) and (±)-10-Epilubimin (6). To a solution of **5** (5 mg) in ether (4 ml) at 0°C was added 1.7 M diisobutylaluminium hydride in hexane (0.14 ml), and the mixture was stirred for 4 h at the temperature. The reaction was quenched by saturated brine, and extracted with ethyl acetate (4×200 ml). The extracts were washed with 2 M HCl and saturated brine, dried, evaporated and separated by chromatography to give **7** (3.7 mg), oil; MS, m/z 236 (M^+); IR, 3630, 3450, 3090, 2730, 1719, 1649, 1036, 1000, and 895 cm^{-1}; NMR (CCl_4), δ 0.87 (3H, d, J=6 Hz), 1.71 (3H, s), 4.02 (0.25H, m, W_H=10 Hz), 4.33 (0.75H, m, W_H=16 Hz), 4.63 (2H, s), 5.18 (0.75H, s), and 9.73 (0.25H, m, W_H=8 Hz). Found: m/z 236.1785. Calcd for $C_{15}H_{24}O_2$: M, 236.1777. Natural; NMR (CCl_4), δ 0.88 (3H, d, J=6 Hz), 1.72 (3H, s), 4.02 (0.25H, m, W_H=10 Hz), 4.32 (0.75H, br m, W_H=16 Hz), 4.64 (2H, s), 5.20 (0.75H, s), and 9.74 (0.25H, m, W_H=8 Hz).

Reduction of **4** (7 mg) was carried out under the same conditions as described above to give **6** (6.5 mg), oil; MS, m/z 236 (M^+), 218, and 205; IR, 3630, 3450, 3090, 1715, 1648, 1115, 1090, and 895 cm^{-1}; NMR, δ 0.95 (3H, d, J=7 Hz), 1.73 (3H, s), 3.72 (1H, m, W_H=24 Hz), 4.69 (2H, s), and 9.85 (1H, s). Found: m/z 236.1758. Calcd for $C_{15}H_{24}O_2$: M, 236.1777. Natural; NMR, δ 0.95 (3H, d, J=7 Hz), 1.73 (3H, s), 3.71 (1H, m, W_H=25 Hz), 4.69 (2H, s), and 9.85 (1H, s).

10-Cyano-3,10-dihydroxy-15-norsolavetiv-2-one 3-t-butyldimethylsilyl Ethers (15) and (16). To a solution of **14** (40 mg, 0.11 mmol) in THF (1 ml) at 0°C under nitrogen was added a solution of Et_3Al–HCN in THF, prepared from Et_3Al (0.55 mmol) in hexane (10% w/w) (0.55 ml) and 1.3 M

† 1 M=1 mol dm^{-3}.

HCN (0.33 mmol) in THF (0.25 ml) at 0°C for 5 min, and the mixture was stirred for 14 h at room temperature. The reaction mixture was poured into 2 M HCl (20 ml), and extracted with ethyl acetate (4×30 ml). The extracts were washed with 2 M aqueous NaOH (2×20 ml) and saturated brine (20 ml), dried, evaporated, and separated by chromatography over silica gel (4 g) with benzene–ethyl acetate (10:1) to give **15** (19 mg) and **16** (14 mg), respectively. **15**, mp 110—112°C (from hexane–diisopropyl ether) (1:1); MS, *m/z* 364 (M^+-15); IR, 3625, 3480, 2220, 1735, 1145, 865, and 840 cm^{-1}; NMR, δ 1.12 (3H, d, J=6 Hz), 1.23 (6H, s), 2.72 (1H, t, J=12 Hz), 2.75 (1H, dd, J=12 and 4.5 Hz), 2.88 (1H, dd, J=12 and 4.5 Hz), 3.77 (1H, d, J=11 Hz). Found: C, 66.57; H, 9.81; N, 3.91%. Calcd for $C_{21}H_{37}O_3NSi$: C, 66.44; H, 9.82; N, 3.69%. **16**, mp 132.5—133.5°C (from diisopropyl ether); MS, *m/z* 379 (M^+); IR, 3620, 3480, 2210, 1753, 1135, 860, and 840 cm^{-1}; NMR, δ 1.10 (3H, d, J=6 Hz), 1.23 (6H, s), 2.69 (2H, d, J=5 Hz), 3.05 (1H, t, J=5 Hz), and 3.76 (1H, d, J=11 Hz). Found: C, 66.16; H, 9.80; N, 3.84%. Calcd for $C_{21}H_{37}O_3NSi$: C, 66.44; H, 9.82; N, 3.69%.

(2SR,3SR,4RS,7SR,10RS)-10-Cyano-15-norsolavetivane-2,3,10-triol 2,3-Bis(t-butyldimethylsilyl) ether (17) and its 10-Epimer (18). i) A mixture of **15** (149 mg) and the ammonia–borone complex (14 mg) in methanol (6 ml) and water (3 ml) was stirred at room temperature for 2 h under nitrogen. To the mixture was added 2 M HCl (4 ml), and the whole mixture was concentrated *in vacuo*. The residue was extracted with ethyl acetate (4×30 ml), and the extracts were washed with 2 M HCl (1×20 ml) and saturated brine (20 ml), dried, and evaporated. The residue was separated by chromatography over silica gel (10 g) with benzene–ethyl acetate (2:1) to give triol (120 mg), mp 139—140°C (from hexane–ether, 1:1); MS, *m/z* 366 (M^+-15), and 348; IR, 3625, 3445, 2205, 1475, 1257, 1100, 1060, and 840 cm^{-1}; NMR, δ 1.00 (3H, d, J=6 Hz), 1.21 (6H, s), 2.53 (1H, dd, J=12 and 4 Hz), 3.01 (1H, t, J=11 Hz), and 3.34 (1H, br m, W_H=22 Hz).

A mixture of the triol (61 mg), *t*-butyldimethylchlorosilane (96 mg), and imidazole (86 mg) in *N,N*-dimethylformamide (0.6 ml) was heated at 50°C under argon for 48 h. The reaction mixture was poured into saturated brine (20 ml), and extracted with ethyl acetate (4×40 ml). The combined extracts were washed with saturated brine, dried, evaporated, and separated by chromatography over silica gel (8 g) with benzene–ethyl acetate (15:1) to give **17** (70 mg), mp 129—130°C (from diisopropyl ether); MS, *m/z* 480 (M^+-15); IR, 3630, 3460, 2215, 1120, and 840 cm^{-1}; NMR, δ 1.10 (3H, d, J=6 Hz), 1.20 (6H, s), 2.58 (1H, dd, J=9 and 4 Hz), 3.26 (1H, t, J=7 Hz), and 3.50 (1H, m, W_H=20 Hz). Found: C, 65.73; H, 10.63; N, 2.62%. Calcd for $C_{27}H_{35}O_3NSi_2$: C, 65.40; H, 10.77; N, 2.82%.

ii) Reduction of **16** (136 mg) under the same conditions as described above afforded the epimeric triol (101 mg), mp 181—182°C (from ethyl acetate); MS, *m/z* 366 (M^+-15); IR, 3630, 3460, 2210, 1480, 1265, 1100, and 842 cm^{-1}; NMR, δ 0.98 (3H, d, J=6 Hz), 1.19 (6H, s), 2.69 (1H, t, J=4 Hz), 3.04 (1H, t, J=11 Hz), and 3.72 (1H, m, W_H=22 Hz).

Silylation of the triol (70 mg) was carried out under the same conditions as described above to give **18** (71 mg), mp 85—87°C (from hexane); MS, *m/z* 480 (M^+-15); IR, 3620, 3500, 2220, 1090, 870, and 840 cm^{-1}; NMR, δ 1.02 (3H, d, J=7.5 Hz), 1.21 (6H, s), 3.10 (1H, dd, J=12 and 4 Hz), 3.52 (1H, t, J=4 Hz), and 3.72 (1H, m, W_H=12 Hz). Found C, 65.73; H, 10.46; N, 2.70%. Calcd for $C_{27}H_{53}O_3NSi_2$: C, 65.40; H, 10.77; N, 2.82%.

(2SR,3SR,4RS,7SR,10RS)-10-Cyano-15-norsolavetiv-11-ene-2,3-diol 2,3-Bis(t-butyldimethylsilyl) ether (19) and its 10-Epimer (20). i) A suspension of **17** (41 mg) and pyridine-modified alumina (0.25 g) in 1,3,5-triisopropylbenzene (0.3 ml) was heated at 220°C under argon for 30 min. The mixture was dissolved in ether (40 ml) and triethylamine (5 ml), stirred at room temperature under nitrogen for 5 h, and filtered through Celite. The filtrate was concentrated, and purified by chromatography over silica gel (7 g) with hexane–benzene (1:5) to give **19** (23.5 mg) (74% based on the consumed starting material), amorphous; MS, *m/z* 462 (M^+-15); IR, 3090, 2210, 1648, 1263, 1120, 890, and 840 cm^{-1}; NMR, δ 1.05 (3H, d, J=6 Hz), 1.72 (3H, s), 2.48 (1H, dd, J=12 and 4 Hz), 3.16 (1H, t, J=9 Hz), 3.44 (1H, m, W_H=20 Hz) and 4.68 (2H, s).

ii) Dehydration of **18** (57 mg) was carried out under the same conditions as described above to give **20** (32 mg) (75% based on the recovered starting material), amorphous; MS, *m/z* 477 (M^+); IR, 3085, 2215, 1650, 1270, 1095, 1015, 870, and 840 cm^{-1}; NMR, δ 1.01 (3H, d, J=6 Hz), 1.72 (3H, s), 3.05 (1H, dd, J=12 and 4 Hz), 3.50 (1H, t, J=4 Hz), 3.69 (1H, m, W_H=14 Hz), and 4.66 (1H, br s, W_H=7 Hz).

(2SR,3SR,4RS,7SR,10RS)-10-Cyano-15-norsolavetiv-11-ene-2,3-diol (21) and its 10-Epimer (22). i) A mixture of **19** (19 mg) and 46% hydrofluoric acid (0.35 ml) in THF (0.6 ml) and acetonitrile (0.3 ml) was stirred at room temperature for 6 h. Triethylamine (0.5 ml) was then added to the reaction mixture. The whole mixture was concentrated, and purified by chromatography over silica gel (2 g) with benzene–ethyl acetate (1:1) to give **21** (9 mg), mp 159—160°C (from ether); MS, *m/z* 249 (M^+); IR, 3600, 3450, 3080, 2215, 1646, and 895 cm^{-1}; NMR, δ 1.07 (3H, d, J=6 Hz), 1.74 (3H, s), 2.53 (1H, dd, J=12 and 4 Hz), 2.97 (1H, t, J=11 Hz), 3.36 (1H, m, W_H=24 Hz), and 4.72 (2H, s). Found: C, 72.51; H, 9.19; N, 5.50%. Calcd for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.61%.

ii) Desilylation of **20** (31 mg) was carried out under the same conditions as described above to give **21** (10 mg), mp 102—103°C (from ether); MS, *m/z* 249 (M^+); IR, 3600, 3450, 3090, 2220, 1650, and 895 cm^{-1}; NMR, δ 1.07 (3H, d, J=6 Hz), 1.72 (3H, s), 2.66 (1H, t, J=4 Hz), 2.99 (1H, t, J=11 Hz), 3.74 (1H, m, W_H=21 Hz), and 4.70 (2H, s). Found: C, 72.53; H, 9.20; N, 5.43%. Calcd for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.61%.

(±)-Oxylubimin (13). To a solution of **21** (8.5 mg) in 1,2-dimethoxyethane (1 ml) was added 1.7 M diisobutylaluminium hydride in hexane (0.4 ml) at room temperature. The mixture was stirred for 12 h, mixed with 2 M HCl (2 ml) at 0°C, poured into saturated brine (10 ml), and extracted with ethyl acetate (4×30 ml). The combined acetate extracts were washed with 5% aqueous sodium hydrogencarbonate (10 ml), and saturated brine, dried, concentrated, and separated by chromatography over silica gel (2 g) with benzene–ethyl acetate (2:1) to give **13** (5 mg), mp 79—81°C (from diisopropyl ether); MS, *m/z* 252 (M^+) and 234; IR, 3600, 3440, 3080, 2725, 1720, 1645, and 894 cm^{-1}; NMR, δ 1.05 (3H, d, J=6 Hz), 1.68 (3H, s), 3.00 (1H, t, J=9 Hz), 3.42 (1H, m, W_H=22 Hz), 4.65 (2H, s), and 10.00 (1H, d, J=2 Hz). Found: C, 71.54; H, 9.67%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%. Natural, mp 85—86°C (from diisopropyl ether); IR, 3600, 3440, 3080, 2727, 1720, 1646, and 894 cm^{-1}; NMR, δ 1.05 (3H, d, J=6 Hz), 1.69 (3H, s), 3.00 (1H, t, J=9 Hz), 3.43 (1H, m, W_H=23 Hz), 4.66 (2H, s), and 10.02 (1H, d, J=2 Hz).

(±)-10-Epioxylubimin (23). Reduction of **22** (9.5 mg) was carried out under the same conditions as described above to give **23** (6.5 mg), mp 121—123°C (from diisopropyl ether); MS, *m/z* 252 (M^+) and 234; IR, 3600, 3445, 3085, 2730, 1720, 1648, and 897 cm^{-1}; NMR, δ 1.05 (3H, d, J=6 Hz), 1.70 (3H, s), 3.03 (1H, t, J=9 Hz), 3.40 (1H, m, W_H=20 Hz), 4.66 (2H, s), and 10.04 (1H, s). Found: C, 71.27; H, 9.65%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%. Natural, mp 123—124°C (from diisopropyl ether); IR, 3600, 3445, 3085, 2730, 1719, 1647, and 895 cm^{-1}; NMR, δ 1.06 (3H, d, J=6 Hz), 1.71 (3H, s), 3.02 (1H, t, J=9 Hz), 3.41 (1H, m, W_H=20 Hz), 4.66 (2H, s), and 10.04 (1H, s).

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