A NEW SHORT STEREOSELECTIVE SYNTHESIS OF RACEMIC LYCORAMINE

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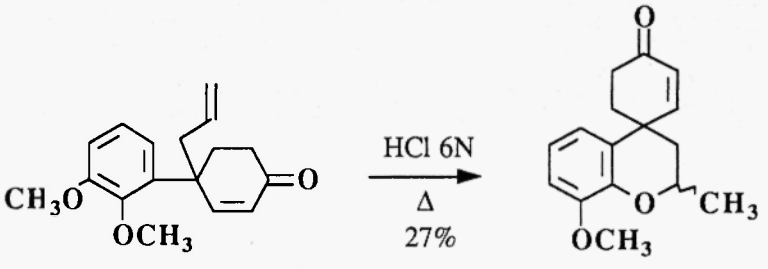
Abstract : A new short stereoselective synthesis of racemic lycoramine is described starting from an allylcyclohexenylveratrole.

Introduction

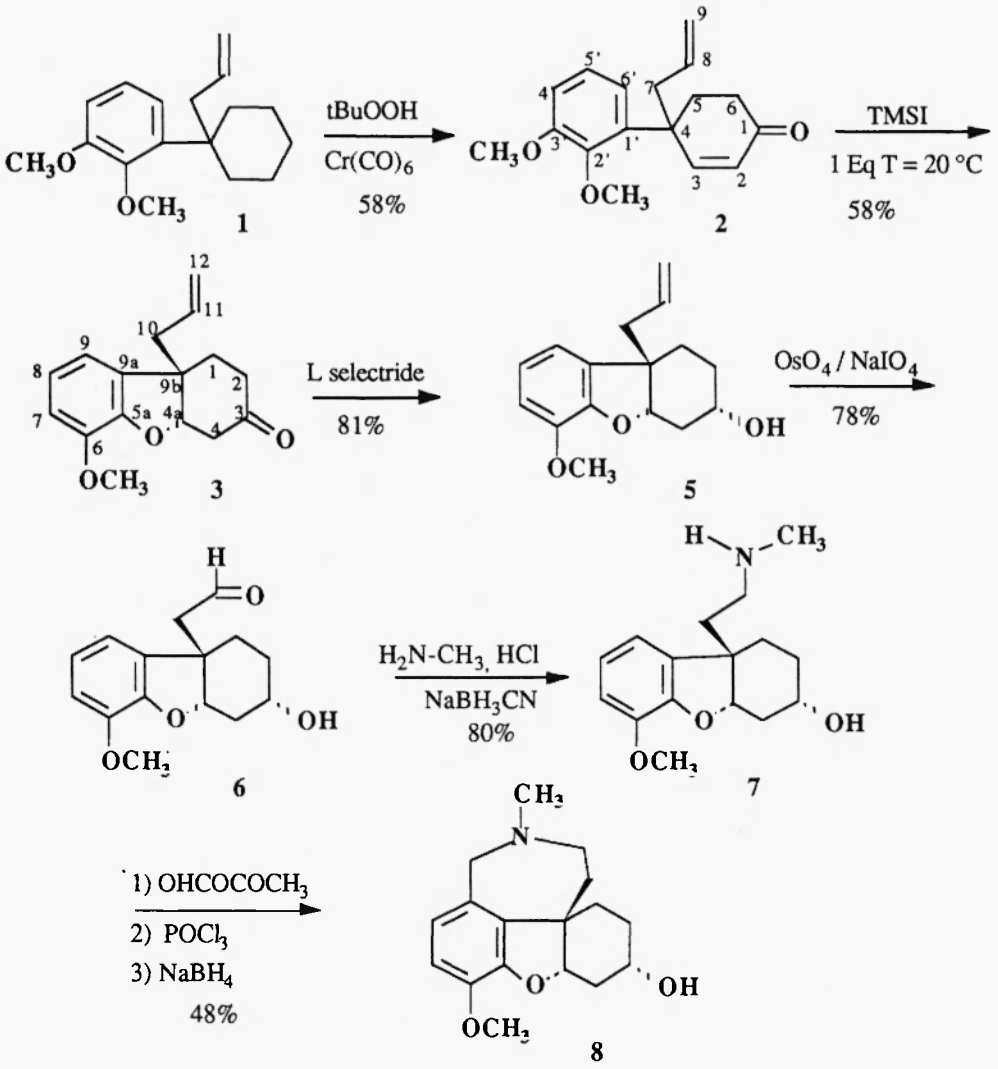
In connection with our research toward the development of a new shorter stereoselective synthesis of dibenzofuran derivatives such as morphine and Amaryllidaceae alkaloids (1), we synthesised the 3-(1-allylcyclohex-2-en-1-yl)veratrole **1** (2) .We now report the route to lycoramine from this compound in a seven steps synthesis.

Results

After examination of a variety of methods, it was found that reaction of **1** with hexacarbonylchromium and *t*.butyl hydroperoxide (3) gave as sole product the conjugated ketone **2**. In the following steps, deprotection of the phenol was effected to promote ring closure to the dibenzofuran **3**. In this context, reactions of **2** with aluminium trichloride (4), lithium chloride or iodide in DMF (5), borane trichloride (6) in CH_2Cl_2 led to either recovery of the starting material or to complex mixture. However, treatment of **2** with warm HCl (7) resulted in selective demethylation of the more hindered methoxy group and formation of the spirocyclohexylbenzopyran **4** as a mixture of two isomers.



2 **4**



Ultimately it was found that reaction of **2** with trimethylsilyl iodide provided the desired dibenzofuranone **3** in a 50% yield. Under these conditions, starting material could be recycled. Ketone **3** was stereospecifically reduced using L.selectride, whereas with $LiAlH_4$ 10% of the unwanted alcohol was obtained. Oxidation of alcohol **5** with osmium tetroxide-sodium metaperiodate (8) gave the aldehyde **6** in 75% yield. Reductive amination of this aldehyde with methylamine hydrochloride and sodium cyanoborohydride (9) followed by acid treatment afforded **7** in 80% yield. The last two steps were identical to those described by S.F. Martin and al. (10). The spectral and physical data of the isolated compound were coincident with those of the (*R*, *S*) alkaloid in the literature (1).

Experimental

Thin layer chromatography was performed on Kieselgel 60F Merck or Riedel-DeHaen . Flash chromatography was done with Merck 9385 40-63 mm or Riedel-DeHaen 31607 silicagel. Mass spectrum were performed on a V.G 70-70 apparatus and elementary analysis

on a Perkin Elmer 240 apparatus. ^{1}H NMR spectra were recorded on a Bruker AC 200 P (200 MHz) in deuterated chloroform and tetramethylsilane (TMS) used as internal reference. Chemical shifts were expressed in ppm et coupling constants in Hz.

4-allyl-4-(2',3'-dimethoxyphenyl)-cyclohex-2-en-1-one 2

To 2.58 g (0.01 mol) of ethylenic **1**, 1.2 equivalent of tertiobutyl hydroperoxide and 0.25 equivalent of hexacarbonylchromium was added 5 ml of freshly distillated acetonitrile and the mixture stirred 6 hours at room temperature and 30 hours under reflux. The solvent was evaporated and the residue extracted with ether. .The organic layer was dried over sodium sulfate and evaporated. The oily residue was chromatographied on silicagel (petroleum ether-ethyl acetate 70/30) to give 1.56 g (oily liquid, yield = 58%) of **2.**

Anal. $C_{17}H_{20}O_3$ (272); Calc. C : 74.97; H : 7.40. found C : 74.75; H : 7.51.

^{1}H nmr (δ, ppm) : 7.25 (dd, J_1 = 10.4 Hz, J_2 = 1.8 Hz, 1 H, H_3), 7.0-6.6 (m, Ar H), 5.95 (d, J = 10.4 Hz, 1 H, H_2), 5.5 (m, 1H, H_8), 5.0 (m, 2 H, 2 H_9), 3.8 and 3.75 (2s, 2 OCH_3), 2.8-1.9 (d + m, 6 H). ^{13}C nmr (δ, ppm) : 199.9 (s, C_1), 157.4 (d, C_3), 153.4 (s, $C_{3'}$), 147.9 (s, $C_{2'}$), 135.3 (s, $C_{1'}$), 133.8 (d, C_8), 127.1 (d, C_2), 123.1 (d, $C_{5'}$), 120.6 (d, $C_{6'}$), 118.2 (t, C_9), 111.5 (d, $C_{4'}$), 60.1 (q, OCH_3), 55.6 (q, OCH_3), 44.7 (t, C_7), 43.6 (s, C_4), 34.8 (t, C_6), 33.6 (t, C_5).

9b-β-allyl-6-methoxy-1,2,3,4,9b-hexahydrodibenzofuran-3-one 3

To a solution under argon of 2.72 g (0.01 mol) of compound **2** in 30 ml of anhydrous chloroform was added dropwise via a syringe 1.7 ml (0.01 mol) of iodotrimethylsilane and the mixture agitated for 3 hours at room temperature. 3 ml of methanol was added and agitation maintained for 1 hour. The solvent was evaporated and the residue extracted with 3x10 ml of ethyl acetate.The organic layer was dried over sodium sulfate and evaporated. The oily residue was chromatographied on silicagel (petroleum ether-ethyl acetate 70/30) to give 1.28 g (yield = 58%) of **3** (1.3 g of unreacted starting product was recovered).

Anal. $C_{16}H_{18}O_3$ (258); Calc. C : 74.41; H : 6.9. found C : 74.52; H : 7.01.

^{1}H nmr (δ, ppm) : 6.9-6.7 (m, Ar H), 5.7 (m, 1 H, H_{11}), 5.1 (m, 2H, 2 H_{12}), 4.95 (t, J = 3.3 Hz,1 H, H_4a), 3.85 (s, OCH_3), 2.95 (dd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, 1 H, H_4), 2.6 (dd, J_1 = 17.2 Hz, J_2 = 3.5 Hz, 1 H, H_4), 2.55-1.9 (m, 6 H). ^{13}C nmr (δ, ppm) : 209.0 (s, C_3), 147.5 (s, C_6), 144.3 (s, C_{5a}), 133.1 (s, C_{9a}), 132.7 (d, C_{11}), 121.8 (d, C_8), 119.6 (t, C_{12}), 115.3 (d, C_9), 111.5 (d, C_7), 85.1 (d, C_{4a}), 55.8 (q, OCH_3), 47.7 (s, C_{9b}), 44.2 (t, C_{10}), 41.6 (t, C_4), 35.7 (t, C_2), 32.2 (t, C_1).

Spiro-(2,3-dihydro-8-methoxy-2-methylbenzo-4H-pyrane)-4-1'-(4'-oxo-cyclohexen-2'-ene) 4

272 mg (0.001 mol) of compound **2** and 10 ml of a 6N solution of hydrochloric acid were refluxed for a night. After cooling, the mixture was extracted with ether, the organic layer washed with water, dried over sodium sulfate and evaporated. The residue was

chromatographied on silicagel (petroleum ether-ethyl acetate 70/30) to give 70 mg (yield = 27%) of **4.**

SM : m/e 258 (M^+), 201.

^1H nmr (δ, ppm) : 6.9-6.5 (m, ArH + H_2), 6.1 and 5.95 (2d, J = 10 Hz, H_3),4.3 and 4.15 (2m, $H_{2'}$), 3.0 (s, OCH_3), 2.5 (m, 2H), 2.3 (m, 2 H), 2.1-1.7 (m, 2 H), 1.5 (2d, 3H). ^{13}C nmr (δ, ppm) : 198.9 (s, C_4), 156.2 and 156.9 (2d, $C_{2'}$), 148.4 (s, C_8), 143.8 (s, C_{8a}), 128.8 and 126.8 (2d, $C_{3'}$), 127.1 (s, C_{4a}), 120.2 and 120.4 (2d, C_6), 120.1 and 119.4 (2d, C_5), 110.0 and 109.0 (2d, C_7), 69.6 and 68.4 (2d, C_2), 55.9 (q, OCH_3), 42.5 (s, C_4), 37.4 and 37.7 (2t, C_3), 36.0 (t, $C_{5'}$), 33.4 and 34.5 (2t, $C_{6'}$), 21.6 and 21.7 (2q, CH_3).

9b-β-allyl-6-methoxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-α-ol 5

20 ml of anhydrous THF and 15 ml of a 1N solution of l-selectride in THF (1.5 mmol) were chilled to -78 °C and 258 mg (1 mmol) of ketone **3** in 10 ml of anhydrous THF were added. The mixture was agitated for 3 hours at -78 °C and for one night at room temperature. 2 ml of methanol wad added. The solvent was evaporated and the oily residue was chromatographied on silicagel (hexane-ethyl acetate 70/30) to give 210 mg (yield = 80%) of the alcohol **5.**

Anal. $C_{16}H_{20}O_3$ (260); Calc. C : 73.8; H : 7.6. found C : 73.6; H : 8.2.

^1H nmr (δ, ppm) : 6.9-6.6 (m, Ar H), 5.6 (m, 1 H, H_{11}), 4.9 (m, 2H, 2 H_{12}), 4.5 (t, 1 H, H_4a), 3.8 (s, OCH_3), 3.6 (m, 1 H, H_3), 2.5 (s, OH), 2.2 (d, 2 H, H_{10}), 2.1-1.2 (m, 6 H). ^{13}C nmr (δ, ppm) : 146.1 (s, C_6), 145.0 (s, C_{5a}), 135.0 (s, C_{9a}), 133.4 (d, C_{11}), 121.2 (d, C_8), 118.1 (t, C_{12}), 115.0 (d, C_9), 111.1 (d, C_7), 86.4 (d, C_{4a}),65.9 (d, C_3), 55.6 (q, OCH_3), 47.1 (s, C_{9b}), 43.2 (t, C_{10}), 35.3 (t, C_1), 29.7 (t, C_4), 28.5 (t, C_2).

9b-β-(2-oxoethyl)-6-methoxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-3α-ol 6

95 mg of osmium tetroxide were added to 2.6 g (0.01 mol) of compound **5** in 19 ml of dioxane and the mixture agitated for 15 minutes at room temperature. 5 ml of water were added, then during one hour 5.4 g (0.025 mol) of sodium periodate in 10 ml of water. The mixture was agitated for a night and filtrated on celite. Celite was washed three times with ether. The organic layer was washed with a sodium chloride saturated solution, dried over sodium sulfate and evaporated. The residue was chromatographied on silicagel (petroleum ether-ethyl acetate 60/40) to give 2.05 g (yield = 78%) of **6.**

Anal. $C_{15}H_{18}O_3$ (262); Calc. C : 68.6; H : 6.9. found C : 68.4; H : 7.0.

^1H nmr (δ, ppm) : 9.7 (t, 1 H, H_{11}), 6.8 (m, Ar H), 4.6 (t, 1 H, H_{4a}), 3.85 (s, OCH_3), 3.6 (m, 2 H, H_3 + OH), 2.7 (d, 1H, H_{10}), 2.6 (d, 1 H, H_{10}), 2.3-1.3 (2m, 6 H). ^{13}C nmr (δ, ppm) : 201.0 (d, C_{11}), 145.9 (s, C_6), 145.3 (s, C_{5a}), 132.9 (s, C_{9a}), 121.6 (d, C_8), 114.7 (d, C_9), 111.9 (d, C_7), 86.3 (d, C_{4a}), 65.6 (d, C_3), 55.6 (q, OCH_3), 52.2 (t, C_{10}), 45.9 (s, C_{9b}), 36.0 (t, C_1), 29.7 (t, C_4), 28.4 (t, C_2).

6-methoxy -9b-β-(2-methylaminoethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-3α-ol (1) **7**

30 ml of methanol under argon, 262 mg (1 mmol) of aldehyde **6**, 130 mg (2 mmol) of $NaBH_3CN$ and 2 g of molecular sieve (4 A°) were stirred for 48 hours. After filtration on celite, the solvent was evaporated. The residue was taken up with a 2N hydrochloric acid solution, which was washed three times with 30 ml of ethyl acetate. The solution was made aalcaline with NaOH up to pH 13 and extracted three times with 30 ml of ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated to give 220 mg (yield = 80%) of **7.**

Anal. $C_{16}H_{23}NO_3$ (277); Calc. C : 69.3; H : 8.3; N : 5.0. found C : 69.5; H : 8.0; N : 4.9.

^1H nmr (δ, ppm) : 6.8-6.4 (m, ArH), 4.4 (t, H_{4a}), 3.7 (s, OCH_3 + OH), 3.5 (m, H_3), 2.8 (NH), 2.4-1.8 (s + m, 7H), 1.7-1.2 (m, 6H). ^{13}C nmr (δ, ppm) : 146.5 (s, C_6), 145.4 (s, C_{5a}), 134.3 (s, C_{9a}), 121.7 (d, C_8), 115.1 (d, C_9), 111.7 (d, C_7), 87.0 (d, C_{4a}), 66.0 (d, C_3), 55.9 (q, OCH_3), 52.5 (s, C_{9b}), 46.7 (q, NCH_3), 41.7 (t, C_{11}), 35.5 and 35.1 (2t, C_1 and C_{10}), 29.9 and 29.7 (2t, C_4 and C_2).

dl lycoramine 8

Prepared according to S.F. Martin (10).

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