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THE TOTAL SYNTHESIS OF JOUBERTINAMINE

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Abstract—The recently described N-demethyl-seco-mesembrane alkaloid joubertinamine[1] (1) and the 3a-aryl-octahydroindole alkaloid mesembranone (17) are accessible via a common synthetic pathway.

Pharmacological evaluation of joubertinamine (1), which is the first N-demethyl-seco-mesembrane alkaloid to be isolated and characterized,[1] was hampered by the small quantities of natural product available.[1] We consequently undertook the synthesis of this compound.

The construction of the mesembrane carbon skeleton proceeded via our previously reported method:[2] the Grignard reaction of bromoveratrole with 3-ethoxy-2-cyclohexenone[3] afforded 3 in 66% purified yield. α-Hydroxymethylenation[4] of 3 afforded the intensely yellow α-hydroxymethylene cyclohexenone (4) in quantitative yield. The thioacetal-enone (5) was subsequently obtained in 50% yield by treating 4 with propane-1,3-dithiol ditosylate.[5] LAH reduction of 5 afforded a 93% yield of the allylic alcohol 6, which in turn was converted to the substituted acetamide 8 by the Claisen–Eschenmoser reaction[2,6] with N,N-dimethylacetamide dimethylacetal in 90% yield. The previously employed[2] Fetizon procedure[7] for the dethioacetalization of 8 (excess MeI in refluxing aqueous acetone) proved unsatisfactory (37% yield). However the use of aqueous methanol gave the enone-amide 9 in 73% yield.

Completion of the total synthesis, by simultaneous reduction of the tertiary amide and enone functions of 9 to afford 11, followed by the reductive amination of 11 to afford joubertinamine (1), proved to be challenging.

Preliminary experiments on the model amide 10 (readily obtained by LAH reduction of 3 to 7 followed by the Claisen–Eschenmoser reaction as described above) showed that diisobutylaluminium hydride (DIBAH) was superior to $LiAlH(OEt)_3$ for the reduction of amides to aldehydes.[8] Reduction of 10 with 2 equivalents of DIBAH in toluene gave 12 in 45% yield (57% if based on recovered starting material) whilst reduction with $LiAlH(OEt)_3$ gave a 28% yield (in addition $LiAlH(OEt)_3$ afforded a 36% yield of the overreduced product 13, and 14% of recovered starting material). This trend was also followed by the enone-amide 9. Reduction with 3 equivalents of DIBAH gave the desired hydroxy-aldehyde (11) in 38% yield whilst the attempted reduction with $LiAlH(OEt)_3$ was unsuccessful. The major products were the partially reduced alcohol-amide (14) and the alcohol amine (15), the yields of which varied with reaction conditions. Only traces of 11 could be detected.

The attempted reductive amination of 11 with methylammonium chloride and sodium cyanoborohydride according to Borch[9] failed, despite the successful reductive amination of the model aldehyde 12 and our previously successful reductive aminations of mesembrane alkaloid precursors.[10] However this transformation was successfully achieved by *in situ* formation of the imine 16 with methylamine in benzene in the presence of anhydrous magnesium sulphate,[11] followed by reduction with $NaBH_4$[12] to afford joubertinamine (1) in 61% yield. The spectral properties of this compound were identical with those reported previously for the natural product.[1] Oxidation of synthetic joubertinamine (1) with activated manganese dioxide[13] as before,[1] afforded mesembranone (17) in high yield.

While our previously reported synthetic approach[2] provided access only to N,N-dimethyl-seco-mesembrane alkaloids, both N-demethyl-seco-mesembranes and octahydroindole mesembrane alkaloids (e.g. mesembranone 17) are now accessible via a common reaction pathway.

EXPERIMENTAL

All m.ps were obtained on a Kofler micro hot-stage and are reported uncorrected. IR spectra were recorded on a Unicam SP-200 spectrophotometer in $CHCl_3$ (unless otherwise specified). PMR spectra were determined on a Varian HA-100 spectrometer in $CDCl_3$ (unless otherwise specified) with TMS as internal reference. Mass spectra were determined with a DuPont 21-492B mass spectrometer with direct probe insertion operated with an ionizing potential of 70 eV. The probe inlet temp. and the percentage abundances of peaks relative to the base peak (100%) in each spectrum are given in parenthesis. Elemental analyses were performed by Messrs. Pascher in Bonn, W. Germany. Solvents and reagents were dried and purified by standard procedures.

Experimental procedures for the syntheses of compounds 3, 4, 5, 6, 8 and 9 are similar to those reported for the corresponding 4-monomethoxyphenyl analogues.[2] Correct elemental analyses were obtained for all of these compounds.

(±) - 3 - (3',4' - *Dimethoxyphenyl)cyclohex* - 2 - *en* - 1 - *ol* (7). A soln of 3 - (3',4' - dimethoxyphenyl)cyclohex - 2 - en - 1 - one (10.0 g, 43.1 mmole) in anhyd THF (160 ml) was added dropwise over 40 min to a stirred suspension of LAH (3 g, 69.6 mmole) in anhyd THF (60 ml). After stirring for 5 min (tlc control), the mixture was quenched by addition of EtOAc (15 ml) and water (5 ml). The resulting slurry was stirred for 1.5 hr and filtered through celite. Evaporation of the solvent afforded the crude product as a light yellow solid. Recrystallization from acetone–petroleum ether (40–60°) afforded homogeneous 7 (8.1 g, 81%); m.p. 94.5–95.5°; ν_{max} 3610, 3450 cm^{-1} (OH); δ 1.5–2.6 (m, 6H, 3x-CH_2-), 2.32 (s, 1H, -OH; D_2O exchangeable), 3.87 and 3.88 (2xs, 6H, 2x $-OCH_3$), 4.3–4.5 (m, 1H, $W_{1/2}$ 15 Hz, methine proton), 6.08 (app s, $W_{1/2}$ 8 Hz, 1H, olefinic proton), and 6.7–7.1 (m, 3H, Ar-H); *m/e* (100°) 235 (4%), 234 (M^+, 26), 227 (19), 226 (100), 203 (14), 201 (18), 185 (23), 175 (15), and 69 (36); [Found, M^+ 234.1238. $C_{14}H_{18}O_3$ requires: M^+ 234.1256]; [Found, C, 71.77; H, 7.78%. $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74%].

(±) - N,N - *dimethyl* - 2 - [1' - (3",4" - *dimethoxyphenyl)cyclohex* - 2' - *ene]acetamide* (10). 3 - (3',4' - Dimethoxyphenyl)cyclohex - 2 - en - 1 - ol (100 mg, 0.43 mmole) was dissolved in N,N-dimethylacetamide dimethylacetal (3 ml). The soln was gradually heated, with stirring, to 145° (bath temp) over 1.5 hr whilst a

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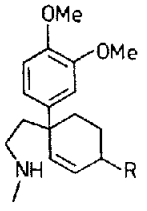
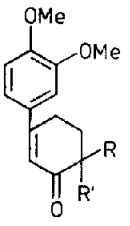
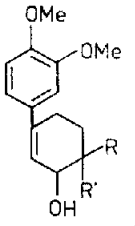


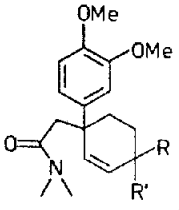
(1) R = OH
(2) R = H



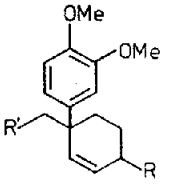
(3) R,R' = H,H
(4) R,R' = CHOH
(5) R,R' = S S



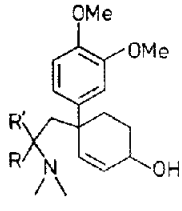
(6) R,R' = S S
(7) R,R' = H,H



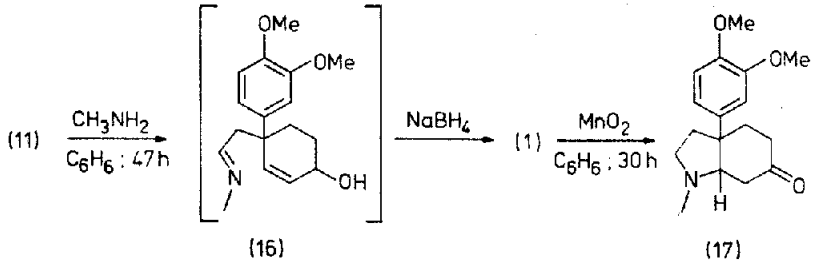
(8) R,R' = S S
(9) R,R' = O
(10) R,R' = H,H



(11) R = OH, R' = CHO
(12) R = H, R' = CHO
(13) R = H, R' = CH_2OH



(14) R,R' = O
(15) R,R' = H,H



(11) $\xrightarrow[C_6H_6 : 47h]{CH_3NH_2}$ (16) $\xrightarrow{NaBH_4}$ (1) $\xrightarrow[C_6H_6 : 30h]{MnO_2}$ (17)

stream of N_2 was directed over the surface. The ensuing MeOH and the excess of reagent were distilled off to afford a brown, oily residue, which was chromatographed over silica to afford homogeneous (±) - N,N - dimethyl - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]acetamide **10** (105 mg, 81% as a pale yellow oil; ν_{max} (neat) 1640 cm^{-1} (amide CO); δ 1.1–2.3 (m, 6H, 3x $-CH_2-$), 2.72 (s, 2H, $-CH_2-CO-NMe_2$), 2.76 and 2.85 (2xs, 6H, $-N(CH_3)_2$), 3.86 (s, 6H, 2x $-OCH_3$), 5.92 (dt, 1H, J_d 10 Hz and J_t 3.5 Hz, $-CH=CH-CH_2-$), 6.20 (d, 1H, J 10 Hz, $-CH=CH-CH_2-$), and 6.7–7.0 (m, 3H, Ar–H); *m/e* (70°) 304 (6%), 303 (M^+, 31), 218 (15), 217 (100), 216 (25), 151 (14), 79 (11), and 72 (10); [Found: C, 71.18; H, 8.26; N, 4.46. $C_{18}H_{25}NO_3$ requires: C, 71.26; H, 8.31; N, 4.62%].

(±) - 2 - [1' - (3",4" - *Dimethoxyphenyl)cyclohex - 2' - ene] - acetaldehyde* (**12**). (a) DIBAH (11.6 ml of a 0.7 M soln in toluene; 8.1 mmole) was added dropwise over 1 hr to a stirred soln of (±) - N,N - dimethyl - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2 - ene]acetamide (1.22 g, 4.05 mmole) in anhyd toluene (30 ml) at 0° under N_2. The mixture was immediately quenched with 20% H_2SO_4 aq (15 ml) and stirred for 1 hr. The two phases were separated. The aqueous phase was basified by cautiously adding satd Na_2CO_3 aq and extracted with $CHCl_3$ (6 × 10 ml). Drying ($MgSO_4$) of the combined $CHCl_3$ extract and solvent evaporation afforded the crude product which was chromatographed over silica to afford homogenous (±) - 2[1' - (3",4" - dimethoxyphenyl)cyclohex - 2 - ene]acetaldehyde **12** (0.48 g, 45%); ν_{max} 2850, 2740 (C–H, aldehyde) and 1715 cm^{-1} (C=O); δ 1–2.3 (m, 6H, 3x $-CH_2-$ of cyclohexene ring), 2.4–2.9 (m, 2H, $-CH_2-CHO$), 3.86 and 3.88 (2xs, 6H, 2x $-OCH_3$), 5.8–6.1 (m, 2H, olefinic protons), 6.7–7.0 (m, 3H, Ar–H), and 9.58 (t, 1H, J 3 Hz, –CHO); *m/e* (40°) 260 (M^+, 21%), 217 (100), 151 (16), and 79 (14); [Found: M^+ 260.1413. $C_{16}H_{20}O_3$ requires: M^+ 260.1412]; [Found: C, 73.31; H, 7.84. $C_{16}H_{20}O_3$ requires: C, 73.82; H, 7.74%]. In addition, 0.25 g (21%) of starting material was recovered. (b) EtOH (0.46 ml, 7.88 mmole) was added dropwise over 15 min to a standardized soln of LAH (2.64 mmole) in ether (20 ml) at 0° under N_2 and stirred for 30 min. A portion of the resulting soln of lithium triethoxyaluminium hydride (8.5 ml, 1.12 mmole) was added dropwise over 3 hr to a stirred soln of (±)N,N - dimethyl - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]acetamide (99 mg, 0.33 mmole) in ether (3 ml) at 0° under N_2. The mixture was stirred at 0° for 30 min (tlc control) and quenched by addition of EtOH (1 ml) and 20% H_2SO_4 aq (5 ml). The aqueous phase was extracted with ether (3 × 5 ml) and the combined ether extract was washed with satd $NaHCO_3$ aq (10 ml) and dried ($MgSO_4$). Evaporation of the solvent afforded a crude product which was chromatographed over silica to afford, as before (±) - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]acetaldehyde **12** (24 mg, 28%) and (±) - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]ethanol **13** (31 mg, 36%); ν_{max} 3490 cm^{-1} (OH); δ 1.0–2.5 (m, 7H, 3x $-CH_2-$ of cyclohexene ring, and –OH), 2.03 (t, 2H, J

7 Hz, HO–CH_2–CH_2–), 3.70 (t, 2H, J 7 Hz, HO–CH_2–CH_2–), 3.86 and 3.87 (2x S, 6H, 2x –OCH_3), 5.9 (app s, 2H, olefinic protons), and 6.7–7.0 (m, 3H, Ar–H); *m/e* (80°) 263 (3%), 262 (M^+, 15), 218 (15), 217 (100), 151 (13), and 79 (9); [Found: C, 73.58; H, 8.80. $C_{16}H_{22}O_3$ requires: C, 73.25; H, 8.48%]. In addition, 14 mg (14%) of starting material was recovered.

(±) - 2 - [l'(3",4" - *Dimethoxyphenyl)cyclohex - 2' - en - 4' - ol]acetaldehyde* (11). DIBAH (3.5 ml of a 0.286 M soln in toluene; 3eq) was added dropwise over 1 hr to a stirred soln of (±) - N,N - dimethyl - 2 - [1' - (3",4" - dimethoxyphenyl) - cyclohex - 2' - en - 4' - one]acetamide **9** (106 mg, 0.34 mmole) in toluene (5 ml) at 0° under N_2. After 80 min (tlc control), the mixture was quenched by adding 20% H_2SO_4 aq (5 ml), and stirring was extended for another 1.5 hr. Workup as before afforded homogeneous (±) - 2 - [l' - (3",4" - dimethoxyphenyl)cyclohex - 2' - en - 4' - ol]acetaldehyde **11** (35 mg, 38%); ν_{max} 3620 (OH monomer), 3430 (OH), 2850, 2750 (C–H, aldehyde), 1715 cm^{-1} (C=O); δ 1.0–3.0 (m, 5H, –CH_2–CH_2– and –OH), 2.72 (dd, 2H, J 8 Hz and 3 Hz, –CH_2–CHO), 3.82 and 3.84 (2xS, 6H, 2x –OCH_3), 4.2 (m, 1H, $W_{1/2}$ 16 Hz, methine proton), 5.9–6.1 (m, 2H, olefinic protons), 6.7–7.0 (m, 3H, Ar–H), and 9.52 (t, 1H, J 3 Hz, –CHO); *m/e* (100°) 277 (5%), 276 (M^+, 31), 234 (17), 233 (100), 215 (31), 151 (26), 138 (18), and 95 (20); [Found: C, 69.68; H, 7.20. $C_{16}H_{20}O_4$ requires: C, 69.55; H, 7.30%].

(±) - N - *methyl* - 2 - [l' - (3",4" - *dimethoxyphenyl)cyclohex* - 2' - *ene]ethylamine* (2). Methylamine hydrochloride (670 mg, 10.2 mmole; dried at 80° under vacuum for 15 hr) and 3A molecular sieves (1 g) were added to a soln of (±) - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]acetaldehyde (260 mg, 1 mmole) in anhyd MeOH (10 ml; distilled from Mg). The mixture was stirred at rt under N_2 for 25 min, whilst the pH of the mixture was adjusted from pH 5 to pH 8 by carefully adding methanolic NaOH. Subsequently, $NaBH_3CN$ (65 mg, 1 mmole; dried at 80° under vacuum for 15 hr) was added in one portion to the mixture and stirring was continued for 30 min (tlc control). Solid NaOH (one pellet) was added to the mixture which was refluxed for 30 min to decompose the excess $NaBH_3CN$. Filtration and evaporation of the solvent afforded a pale brown solid which was dissolved in $CHCl_3$ (2 ml). The $CHCl_3$ soln was chromatographed over alumina (III) to afford (±) - N - methyl - 2 - [l' - (3",4" - dimethoxyphenyl)cyclohex - 2' - ene]ethylamine **2** (130 mg, 47%); δ 1.2–2.2 (m, 8H, 4x –CH_2–), 1.45 (s, 1H, –NHMe, D_2O exchangeable), 2.3–2.7 (m, 2H, –CH_2–NHMe), 2.38 (s, 3H, –NH–CH_3), 3.87 and 3.89 (2xs, 6H, 2x –OCH_3), 5.9 (app s, 2H, olefinic protons), and 6.7–7.0 (m, 3H, Ar–H); *m/e* (100°) 276 (12%), 275 (M^+, 62), 218 (62), 217 (33), 187 (20), 151 (21), and 44 (100); [Found: M^+ 275.1885. $C_{17}H_{25}NO_2$ requires: M^+ 275.1879]; [Found: C, 74.31; H, 9.03; N, 4.96. $C_{17}H_{25}NO_2$ requires: C, 74.14; H, 9.15; N, 5.09%].

(±)-*Joubertinamine* (1). Anhyd $MgSO_4$ (1 g, dried at 400° for 24 hr) was added to a soln of (±) - 2 - [1' - (3",4" - dimethoxyphenyl)cyclohex - 2' - en - 4' - ol]acetaldehyde (100 mg, 0.36 mmole) in Na-dried benzene. The stirred suspension was saturated with anhyd methylamine gas. After 47 hr at rt, $NaBH_4$ (100 mg, 2.6 mmole) was added. MeOH (0.4 ml) was added to the mixture to facilitate the $NaBH_4$ dissolution and reduction. After 5 hr (tlc control) the mixture was quenched with MeOH (2 ml), NaOH (2 pellets) and water (1 ml). The mixture was refluxed for 30 min. The layers were separated and the aqueous layer was extracted with ether (3 × 10 ml). The combined ethereal extract was dried ($MgSO_4$). Solvent evaporation afforded a crude product which was chromatographed over alumina (III) to afford homogeneous (±)-**1** (64 mg, 61%), the spectral and chromatographical data of which exactly correspond to those of the natural alkaloid.[1]

(±)-*Mesembranone* (17). MnO_2 oxidation of (±)-joubertinamine as described for the natural product[1] afforded (±)-mesembranone, spectrally and chromatographically identical with an authentic sample.

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