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THE TOTAL SYNTHESIS OF *RAC*-O-METHYLJOUBERTIAMINE

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Abstract—The Claisen-Eschenmoser[3.3]sigmatropic rearrangement[1] of appropriately functionalized 3-aryl-2-cyclohexenols provides a ready synthesis of mesembrane alkaloids.[2,3] Herein we describe the total synthesis of *rac*-O-methyljoubertiamine[4]† (1) as part of the development of a general synthetic route to these alkaloids, involving the aforementioned rearrangement as the key synthetic step.

Gradual heating of **2a** (*vide infra*) and N,N-dimethylacetamide dimethylacetal during 2 hr to 120° with continuous removal of the ensuing methanol in a nitrogen stream, afforded **3a** after silica gel chromatography in 71% yield. Enone amide **3b** was obtained in 75% yield after dethioacetalization in refluxing methyl iodide/aq. acetone.[5] Subsequent reduction of **3b** with LAH in ether afforded the allylic alcohol **4a**, which was smoothly oxidized to the title compound **1** in high yield with activated manganese dioxide in petroleum ether-chloroform. The spectral properties of synthetic O-methyljoubertiamine were identical in all respects with those of the natural product.[4]‡

The key allylic alcohol **2a** was readily synthesized as follows: hydroxymethylenation of 3 - (4 - methoxyphenyl)cyclohex - 2 - en - 1 - one[6] (**5a**) in benzene in the presence of an excess of sodium hydride,[7] afforded **5b** in 95% yield. Conversion of **5b** into **5c** with propane-1,3-dithiol ditosylate in refluxing ethanol containing potassium acetate,[8] was accomplished in 86% yield. Finally LAH reduction of **5c** in tetrahydrofurane gave **2a** quantitatively.

Initially a more direct synthesis of **1** was attempted: allylic alcohol **2b** (obtained by LAH reduction of enone **5a**) was heated with N,N-dimethylacetamide dimethylacetal as before, to yield amide **3c** in 85% yield, after silica gel chromatography. Allylic functionalization of amide **3c**, however, proved to be difficult. Enone amide **3b** could be obtained in only 21% yield after oxidation with an excess of pyridinium chromate in dichloromethane[9] for 115 hr (68% if based on recovered starting material). Attempted functionalization of **3c** with t-butyl chromate,[10] mercury-II-bromide in hexane under UV-irradiation,[11] N-bromosuccinimide and benzoyl-peroxide in refluxing carbon tetrachloride,[12] or manganese-III-acetate in acetic acid[13] failed completely, and only starting material or a complex reaction mixture (in the latter case) could be recovered. Also, α-acetoxylation of enone **5a** with lead tetraacetate in refluxing benzene,[14] under neutral or acidic conditions, or with Lewis acid catalysis[14] proved unsuccessful. In all instances only starting material was recovered.

An alternative route, involving the functionalization of the unsaturated acetal **6** (*vide infra*) at C-2 also met with difficulty. Phenyltrimethylammonium perbromide, which is claimed to α-brominate acetals without concomitant addition to double bonds, reacted with the double bond of acetal **6**. Attempted allylic bromination of **6** with NBS and benzoyl-peroxide in carbon tetrachloride[12] or allylic oxidation with manganese-III-acetate in acetic acid,[13] gave complex reaction mixtures. Eventually, enone acetal **5d** was obtained in a mere 8% yield (13% yield if recovered starting material is accounted for) on treatment of **6** with an excess of pyridinium chromate in dichloromethane.[9] The subsequent synthesis of *rac*-O-methyljoubertiamine from enone acetal **5d** followed readily: LAH-reduction of **5d** in ether afforded allylic alcohol **2c**, which was subjected to the amide-acetal Claisen-type rearrangement by heating with N,N-dimethylacetamide dimethylacetal as before, to afford the unsaturated amide acetal **3d** in 89% yield. Amino acetal **4b** was obtained on LAH reduction of **3d**. Subsequent deacetalization of **4b** with 8% aq. hydrochloric acid afforded **1**.

The unsaturated acetal **6** was obtained by dehydration of the hydroxy acetal **7** with *p*-toluenesuphonic acid in refluxing benzene, with azeotropic removal of water. Hydroxy acetal **7**, in turn, was synthesized in excellent yield by reaction of 4-methoxyphenyl lithium[15] (prepared from n-butyllithium and p-bromoanisole) with cyclohexane - 1,4 - dione monoethyleneacetal[16] (**8**).

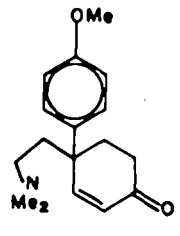
EXPERIMENTAL

IR spectra were obtained on a Unicam SP200 or Beckman 4250 spectrometer; the spectra were recorded in the solvent stated or as a solid suspension in KBr (KBr-wafer). PMR spectra were determined with a Varian HA100 spectrometer in the solvent stated with TMS as internal reference. Mass spectra were determined with an AEI model MS-9 spectrometer with direct probe insertion and operated with an ionising 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 parentheses. M.ps were obtained on a Kofler micro hot stage and are reported uncorrected.

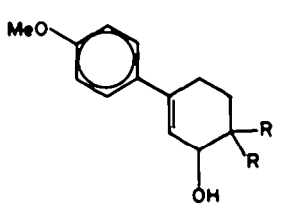
(±) - N,N - *Dimethyl* - 4 - (4 - *methoxyphenyl*) - 1,1 - (*propane* - 1,3 - *dithio*)*cyclohex* - 2 - *ene* - 4 - *acetamide* (**3a**). A soln of 3 - (4 - methoxyphenyl) - 6,6 - (propane - 1,3 - dithio)cyclohex - 2 - en - 1 - ol (200 mg, 0.65 mmole) in N,N-dimethylacetamidedimethylacetal (3 ml) was gradually heated (0.5 hr) to 100° and then (1.5 hr) to 120°, whilst a N_2 stream was passed over the soln surface. The mixture was cooled, diluted with benzene (5 ml) and concentrated under reduced pressure. The resulting oil was chromatographed over silica to afford the crystalline product (175 mg, 71%), m.p. 112–113° (EtOH–pet. ether), ν_{max} (KBr-

†The total synthesis of *rac*-O-methyljoubertiamine has been accomplished by Stevens *et al.*[3a]

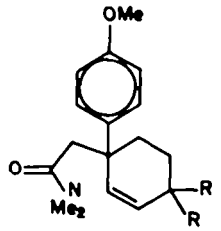
‡We thank Prof. R. R. Arndt and Dr. J. J. Nieuwenhuis for the spectra (NMR, IR, UV, ms) of authentic O-methyljoubertiamine.



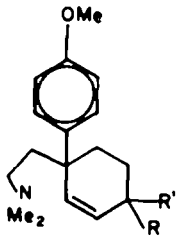
1



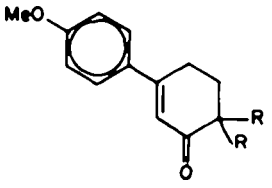
2a : R,R = S S
b : R,R = H,H
c : R,R = O O



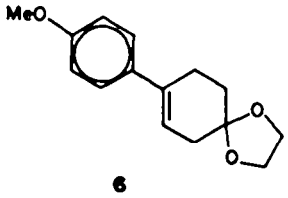
3a : R,R = S S
b : R,R = O
c : R,R = H,H
d : R,R = O O



4a : R' = OH, R = H
b : R,' R = O O



5a : R,R = H,H
b : R,R = CHOH
c : R,R = S S
d : R,R = O O



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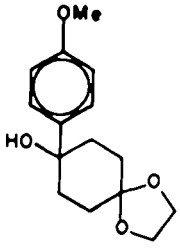

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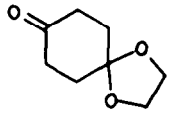

8

wafer) 1645 cm^{-1} (amide CO); $\delta(CDCl_3)$ 1.76–2.47 and 2.71–3.02 (m's, 12H, $-CH_2-$), 2.84 (s, 6H, -NMe), 3.80 (s, 3H, -OMe), 6.09 (d, 1H, J 10 Hz, =CH-), 6.39 (d, 1H, J 10 Hz, =CH-), 6.86 (BB', 2H, J 9 Hz, Ar-H) and 7.25 (AA', 2H, J 9 Hz, Ar-H); *m/e* (100°) 377 (M^+, 4; $C_{20}H_{27}NO_2S_2$ requires 377.149; found 377.148), 290 (100) and 216 (22); Calc. for $C_{20}H_{27}NO_2S_2$: C, 63.66; H, 7.16; N, 3.71; S, 16.97. Found: C, 63.72; H, 7.16; N, 3.74; S, 16.80.

(±) - N,N - *Dimethyl* - 4 - (4 - *methoxyphenyl*)*cyclohex* - 2 - *en* - 1 - *one* - 4 - *acetamide* (3b). A soln of (±) - N,N - dimethyl - 4 - (4 - methoxyphenyl) - 1,1 - (propane a 1,3 - dithio)cyclohex - 2 - ene - 4 - acetamide (100 mg, 0.35 mmole) in acetone (6 ml) containing water (0.3 ml) and MeI (3 ml) was heated under reflux for 7 hr. The mixture was cooled and the solvent evaporated under reduced pressure. Water (5 ml) was added and the product extracted with ether (2 × 5 ml) and chloroform (2 × 25 ml). The combined extracts were dried (K_2CO_3) and evaporated. Chromatography over silica yielded the pure product (55 mg, 72%) as a colourless oil, ν_{max} (CCl_4) 1680 (enone CO) and 1655 (amide CO) cm^{-1}; $\delta(CCl_4)$ 2.03–2.44 (m, 4H, ring $-CH_2-$), 2.66–2.93 (overlapping system, 8H, $-CH_2-CONMe_2$), 3.75 (s, 3H, -OMe), 5.98 (d, 1H J 10 Hz, -CH=), 6.77 (BB', 2H, J 9 Hz, Ar-H), 7.16 (AA', 2H, J 9 Hz, Ar-H) and 7.50 (d, 1H, J 10 Hz, =CH-); *m/e* (130°) 287 (M^+, 49 $C_{17}H_{21}NO_3$ requires: 287.152. Found: 287.150), 201 (100).

(±)-O-*Methyljoubertiamine* (1). A soln of (±) - N,N - dimethyl - 4 - (4 - methoxyphenyl) - 2 - cyclohexenone - 4 - acetamide (150 mg, 0.52 mmole) in dry THF (8 ml) was added dropwise over 10 min to a stirred suspension of LAH (111 mg, 2.9 mmole) in THF (8 ml) at room temp. After an additional 20 min the excess reducing agent was decomposed with EtOAc (2 ml) and water (1 ml). The mixture was filtered (filter aid) and EtOH (2 × 10 ml) and benzene (2 × 10 ml) added prior to evaporation under reduced pressure. The crude mixture of the two diastereomeric racemic allylic alcohols (4a), ν_{max} (CCl_4) 3580 and 3350 (-OH) and 1640 (C=C) cm^{-1}; $\delta(CCl_4)$ 1.14–2.27 (m, 8H, $-CH_2-$), 2.06 and 2.08 (s's, 6 H, $-NMe_2$), 2.19–2.40 (m, 1H, -OH, exchanges with D_2O), 3.74 (s, 3H, -OMe), 3.90–4.19 (m, 1H, $W_{1/2}$ 16 Hz, >CH-OH), 5.80 and 5.89 (s's, 2H, -CH=CH-) and 6.62–7.24 (irregular pattern, 4H, Ar-H); $C_{17}H_{23}NO_3$ requires 175.189; found 275.186 was thus obtained in near quantitatative yield.

The mixture of allylic alcohols was dissolved in a mixture of chloroform and petroleum ether (1 : 1 (v/v), 10 ml) and stirred at room temp. in the presence of activated MnO_2 (320 mg) in a stoppered flask. After 2, 3 and 4 hr additional amounts of MnO_2 (100, 50 and 50 mg respectively) were added. After 5.5 hr the mixture was filtered (filter aid) and the MnO_2-filter cake extracted with boiling chloroform (10 ml). Chromatography on alumina afforded 107 mg (75% from 3b) of a colourless oil, ν_{max} ($CHCl_3$) 1675 (enone CO) cm^{-1}; $\delta(CCl_4)$ 1.83–2.41 (m, 8H, $-CH_2-$), 2.10 (s, 6H, $-NMe_2$), 3.78 (s, 3H, -OMe), 6.03 (d, 1H, J 10 Hz, =CH-), 6.81 (BB', 2H, J 9 Hz, Ar-H), 7.07 (d, 1H, J 10 Hz, -CH=), and 7.17 (AA', 2H, J 9 Hz, Ar-H); *m/e* (130°) 273 (M^+, 16; $C_{17}H_{23}NO_2$ requires: 273.173. Found: 273.170), 58 (100), identical with those of the authentic alkaloid.

3 - (4 - *Methoxyphenyl*) - 6 - *hydroxymethylenecyclohex* - 2 - *en* - 1 - *one* (5b). To a soln of 3 - (4 - methoxyphenyl)cyclohex - 2 - en - 1 - one (202 mg, 1.0 mmole) and ethylformate (5 ml, freshly

distilled) in dry benzene (75 ml) was added NaH (500 mg, 21 mmole) in one portion at 0° under argon. The mixture was stirred for 2 hr at room temp. and excess reagent was quenched with MeOH (2 ml). The mixture was diluted with benzene (20 ml) and 20% aq. acetic acid (15 ml). The acid phase was separated and the organic phase washed with sat. $NaHCO_3$aq (10 ml) and water (10 ml). Drying ($MgSO_4$) and concentration *in vacuo* at 30° furnished the crude product of high purity. Recrystallization from ether afforded yellow–brownish crystals (219 mg, 95%), m.p. 92–93°, ν_{max} (KBr-wafer) 3450 (br., –OH), 1645 (enone CO) cm^{-1}; δ ($CDCl_3$) 2.45–2.87 (m, 4H, $-CH_2-$), 3.83 (s, 3H, –OMe), 6.42 (t, 1H, J 1.2 Hz, =CH–CO–), 6.92 (BB', 2H, J 9 Hz, Ar–H), 7.50 (AA', 2H, J 9 Hz, Ar–H), 7.60 (br. s, 1H, $=CH_2$–OH) and 13.96 (br. m, 1H, –OH, exchanges with D_2O); *m/e* (60°) 230 (M^+, 100; $C_{14}H_{14}O_3$ requires: 230.094. Found: 230.095, 212 (77), and 201 (82); Calc. for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09. Found: C, 72.78; H, 6.20.

3 - (4 - *Methoxyphenyl*) - 6,6 - (*propane* - 1,3 - *dithio*)*cyclohex* - 2 - *en* - 1 - *one* (5c). 3 - (4 - Methoxyphenyl) - 6 - hydroxymethylenecyclohex - 2 - en - 1 - one (3.1 g, 13.5 mmole) in abs. EtOH (50 ml) was added dropwise during 2 hr to a mixture of propane - 1,3 - dithiol ditosylate (7.0 g, 17 mmole) and dry KOAc (8 g) in EtOH (120 ml) at reflux temp. After an additional 5 hr the mixture was concentrated in vacuum to about half its original volume, diluted with water (200 ml) and extracted with ether (2 × 100 ml). The combined ether extract was washed with water (1 × 25 ml), dried ($MgSO_4$) and solvent was removed under reduced pressure. Recrystallization from EtOH afforded the crystalline product (3.3 g, 80%). Chromatography of the mother liquor on silica afforded an additional 0.25 g product. Combined yield: 86%. An analytical sample had m.p. 137–138°, ν_{max} (KBr-wafer) 1660 cm^{-1} (enone CO); δ($CDCl_3$) 1.76–2.76 and 3.37–3.70 (m's, 4H and 2H resp., thioacetal $-CH_2-$) 2.40 (t, 2H, J 6 Hz, C_5 $-CH_2-$), 2.88 (t, 2H, J 6 Hz, C_4 $-CH_2-$), 3.83 (s, 3H, –OMe), 6.30 (t, 1H, J 1.3 Hz, =CH–) 6.90 (BB', 2H, J 9 Hz, Ar–H), 3.83 (s, 3H, –OMe), 6.30 (t, 1H, J 1.3 Hz, =CH–) 6.90 (BB', 2H, J 9 Hz, Ar–H) and 7.48 (AA', 2H, J 9 Hz, Ar–H); *m/e* 306 (M^+, 33; $C_{16}H_{18}O_2S_2$ requires 306.075; found 306.076), 174 (100); Calc. for $C_{16}H_{18}O_2S_2$: C, 62.74; H, 5.88; S, 20.91. Found: C, 62.72; H, 5.87; S, 20.82.

(±) - 3 - (4 - *Methoxyphenyl*) - 6,6 - (*propane* - 1,3 - *dithio*)*cyclohex* - 2 - *en* - 1 - *ol* (2a). 3 - (4 - Methoxyphenyl) - 6,6 - (propane - 1,3 - dithio)cyclohex - 2 - en - 1 - one (1.1 g, 3.6 mmole) in dry THF (30 ml) was added dropwise over 0.5 hr at room temp. to a stirred suspension of LAH (213 mg, 5.7 mmole) in THF (25 ml). 15 min after complete addition excess reagent was quenched with EtOAc (3 ml) and water (0.5 ml). The mixture was vacuum filtered (filter aid), benzene (10 ml) and EtOH (5 ml) added and solvent rotary evaporation under reduced pressure to yield an essentially pure (tlc) colourless oil (1.1 g, 99%). Crystallization from ether pet. ether afforded white crystals, m.p. 98–99°, ν_{max} (KBr-wafer) 3440 (–OH) and 1628 (C=C) cm^{-1}; δ($CDCl_3$) 1.80–3.10 (m's, 11 H, $-CH_2-$ and –OH, one proton exchanges with D_2O), 3.78 (s, 3H, –OMe), 4.45 (m, 1H, $W_{1/2}$ 9 Hz, > CH–OH; d, J 4.2 Hz after D_2O exchange), 6.06 (t of d, 1H, J 4.2 and 1.6 Hz, =CH–), 6.83 (BB', 2H, J 9 Hz, Ar–H) and 7.34 (AA', 2H, J 9 Hz, Ar–H); *m/e* (100°) 308 (M^+, 79; $C_{16}H_{20}O_2S_2$ requires: 308.090. Found: 308.093) and 176 (100); Calc. for $C_{16}H_{20}O_2S_2$: C, 62.34; H, 6.49; S, 20.78. Found: C, 62.39; H, 6.54; S, 20.40.

(±) - 3 - (4 - *Methoxyphenyl*)*cyclohex* - 2 - *en* - 1 - *ol* (2b). A soln of 3 - (4 - methoxyphenyl)cyclohex - 2 - en - 1 - one (1.0 g, 4.95 mmole) in dry THF (10 ml) was added dropwise at room temp. with stirring to a suspension of LAH (0.2 g, 5.25 mmole) in THF (5 ml). Stirring was extended for 10 min. The excess reducing agent was reacted with EtOAc (0.5 ml) and decomposed with water (1 ml). The mixture was filtered (filter aid) and evaporated *in vacuo* (< 40°) to yield the allylic alcohol (0.9 g, 89%) as a white solid, m.p. 83–84°, ν_{max} (KBr-wafer) 3370 (–OH) and 1640 (C=C) cm^{-1} δ($CDCl_3$) 1.49–2.10 and 2.28–2.51 (m's, 4H and 2H respectively, $-CH_2-$), 1.74 (s, 1H, –OH, D_2O– exchangeable), 3.79 (s, 3H, –OMe), 4.24–4.47 (m, 1H, $W_{1/2}$ 10 Hz, > CH–OH), 6.01–6.13 (m, 1H olefinic H), 6.86 (BB', 2H, J 9 Hz, Ar–H), and 7.34 (AA', 2H, J 9 Hz, Ar–H); *m/e* (80°) 204 (M^+, 84 $C_{13}H_{16}O_2$ requires: 204.115. Found: 204.118), 186 (100); Calc. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.18; H, 8.01.

(±) - N,N - *Dimethyl* - 3 - (4 - *methoxyphenyl*)*cyclohex* - 1 - *ene* - 3 - *acetamide* (3c). A soln of 3 - (4 - methoxyphenyl)cyclohex - 2 - en - 1 - ol (1.1 g, 5.5 mmole) in N,N-dimethylacetamide dimethylacetal (10 ml) was gradually heated with stirring whilst a stream of dry N_2 was passed over the surface of the soln. Heating was continued until the vapour temp. registered 110° (*ca.* 1 hr bath temp. 140°). The mixture was cooled, diluted with benzene (5 ml) and concentrated *in vacuo*. Chromatography on silica afforded the oily amide (1.25 g, 85%), ν_{max} ($CHCl_3$) 1635 (amide CO) cm^{-1}; δ(CCl_4) 1.27–1.74 and 1.90–2.15 (m's, 2H and 4H resp., ring $-CH_2-$), 2.57 and 2.59 (s's, 2H, $-CH_2-$ $CONMe_2$), 2.73 (br. s, 6H, $-NMe_2$), 3.75 (s, 3H, –OMe), 5.80 (t of d, 1H, J 10 and 3.5 Hz, =CH–), 6.17 (br. d, 1H, J 10 Hz, –CH=), 6.73 (BB', 2H, J 9 Hz, Ar–H), and 7.17 (AA', 2H, J 9 Hz, Ar–H); *m/e* (75°) 273 (M^+, 64; $C_{17}H_{23}NO_2$ requires: 273.173. Found: 273.174) and 187 (100).

(±) - N,N - *Dimethyl* - 4 - (4 - *methoxyphenyl*)*cyclohex* - 2 - *en* - 1 - *one* - 4 - *acetamide* (3b). To a stirred suspension of CrO_3-pyridine complex (4 g, 15.4 mmole; prepared and isolated as reported by Dauben[9]) in dry dichloromethane (50 ml) was added a soln of N,N - dimethyl - 3 - (4 - methoxyphenyl)cyclohexene - 3 - acetamide (240 mg, 0.88 mmole) in dichloromethane (5 ml) in one portion under dry, O_2-free argon at room temp. After 30, 60 and 90 hr additional amounts of oxidant (1 g) were added. The solvent had to be replenished intermittently. Stirring was discontinued after 115 hr. The mixture was filtered and the filtercake washed with CH_2Cl_2 (2 × 20 ml). The combined filtrate was concentrated *in vacuo* to *ca.* 5 ml and filtered through neutral alumina. Subsequent chromatography on silica afforded starting material (165 mg) and the required product (54 mg, 21%–68% if accounted for recovered starting material) as a colourless oil, with the same spectral properties as reported before (*vide supra*).

4 - (4 - *Methoxyphenyl*)*cyclohex* - 3 - *ene* - 1,2 - *dione* - 1 - *ethyleneacetal* (5d). To a stirred suspension of CrO_3-pyridine complex[9] (4.9 g, 18.9 mmole) in CH_2Cl_2 (60 ml), a soln of 4 - (4 - methoxyphenyl) cyclohex - 3 - en - 1 - one ethyleneacetal (450 mg, 1.83 mmole) in CH_2Cl_2 (1 ml) was added in one portion. A tarry ppt gradually started to form. After 40 hr the soln was decouted from residual tar, the tarry residue washed with ether (2 × 20 ml) and the washings combined with the CH_2Cl_2-solution. The resulting soln was washed with sat. $NaHCO_3$aq (5 × 20 ml), followed by water (25 ml). The solvents were rotary evaporated and the residue chromatographed on silica, to yield starting material (151 mg) and the required oxidation product (39 mg, 8%–13% if accounting for recovered starting material) as white crystals, m.p. 86.5–87.5° (ether), ν_{max} (CCl_4) 1675 (enone CO) cm^{-1}; δ(CCl_4) 2.23 (t, 2H, J 6 Hz, ring–CH_2- α to acetal), 2.90 (d of t, 2H, J 1 and 6 Hz, C_5-CH_2-), 3.82 (s, 3H, –OMe), 2.44–2.99 (symm. m, 4H, $-O-CH_2-CH_2-O-$), 6.21 (t, 1H, J 1 Hz, =CH–), 6.86 (BB', 2H, J 9 Hz, Ar–H), and 7.46 (AA', 2H, J 9 Hz, Ar–H); *m/e* (130°) 260 (M^+, 25 $C_{15}H_{16}O_4$ requires: 260.105. Found: 260.105) and 174 (100); Calc. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.27; H, 6.24.

(±) - 4 - (4 - *Methoxyphenyl*) - 2 - *hydroxycyclohex* - 3 - *en* - 1 - *one* - *ethyleneacetal* (2c). A soln of 4 - (4 - methoxyphenyl)-cyclohex - 3 - ene - 1,2 - dione 1-ethyleneacetal (279 mg, 1.07 mmole) in dry ether (15 ml) was added dropwise with stirring to a suspension of LAH (50 mg, 1.33 mmole) in ether (5 ml) at room temp. The excess of LAH was quenched after 10 min with EtOAc (1 ml) and water (0.5 ml). The resulting mixture was filtered (filter aid), concentrated *in vacuo* and recrystallized from ether–pet. ether to yield the hydroxy acetal (263 mg, 94%), m.p. 93–95°, ν_{max} ($CHCl_3$) 3580 (–OH) and 1640 (C=C) cm^{-1}; δ(CCl_4) 1.74–2.12 and 2.50–2.73 (m's, 2H each, ring $-CH_2-$), 2.12–2.34 (m, 1H, –OH), 3.79 (s, 3H, –OMe), 3.96–4.14 (m, 4H, acetal $-CH_2-$), 4.11–4.26 (m, 1H, $W_{1/2}$ 8 Hz, methine H), 5.85–5.94 (m, 1H, =CH–), 6.81 (BB', 2H, J 9 Hz, Ar–H), and 7.31 (AA', 2H, J 9 Hz, Ar–H); *m/e* (200°) 262 (M^+, 14 $C_{15}H_{18}O_4$ requires: 262.121. Found: 262.121) and 87 (100); Calc. for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.70; H, 6.99.

(±) - N,N - *Dimethyl* - 4 - (4 - *methoxyphenyl*) - 1 - *ethylenedioxycyclohex* - 2 - *ene* - 4 - *acetamide* (3d). A soln of 4 - (4 - methoxyphenyl) - 2 - hydroxycyclohex - 3 - en - 1 - one ethyleneacetal (210 mg, 0.63 mmole) in N,N-dimethylacetamide

dimethylacetal (3.5 ml) was gradually heated whilst a nitrogen stream was passed over the solution surface. The bath temp. reached 140° after 1.5 hr and was kept at this temp. for 1.5 hr. The mixture was cooled, diluted with benzene and evaporated *in vacuo*. Subsequent chromatography afforded the crystalline product, (235 mg, 89%), m.p. 114–115° (ether), ν_{max} (CCl_4) 1659 (amide CO) cm^{-1}; δ(CCl_4) 1.53–1.70 and 1.98–2.18 (m's, 2H each, ring $-CH_2-$), 2.62 and 2.70 (s's, 2H, $-CH_2-CONMe_2$), 2.75 (s, 6H, $-NMe_2$), 3.74 (s, 3H, –OMe), 3.82–3.96 (m, 4H, $-O-CH_2-O-$), 5.63 (d, 1H, J 10 Hz, =CH–), 6.46 (d, 1H, J 10 Hz, –CH=), 6.74 (BB', 2H, J 9 Hz, Ar–H), and 7.16 (AA', 2H, J 9 Hz, Ar–H); *m/e* (90°) 331 (M^+, 19; $C_{19}H_{25}NO_4$ requires: 331.178. Found: 331.177) and 173 (100); Calc. for $C_{19}H_{25}NO_4$: C, 68.88; H, 7.55; N, 4.23. Found: C, 68.87; H, 7.56; N, 4.26.

(±) - 4 - (4 - *Methoxyphenyl*) - 4 - (2 - *dimethylaminoethyl*)-*cyclohex* - 2 - *en* - 1 - *one ethyleneacetal* (4b). A soln of N,N - dimethyl - 4 - (4 - methoxyphenyl) - 1 - ethylenedioxycyclohex - 2 - ene - 4 - acetamide (20 mg, 0.06 mmole) in dry ether (1 ml) was reduced with LAH (8 mg, 0.21 mmole as described for 3b (*vide supra*) to yield the amine acetal (18 mg, 94%) as a colourless oil, ν_{max} (CCl_4) 1650 (C=C) cm^{-1}; δ(CCl_4) 1.52–2.26 (m, 8H, ring and sidechain $-CH_2-$), 2.11 (s, 6H, $-NMe_2$), 3.76 (s, 3H, –OMe), 3.82–4.00 (m, 4H, $-O-CH_2-CH_2-O-$), 5.67 (d, 1H, J 10 Hz, =CH–), 5.97 (d, 1H, J 10 Hz, –CH=), 6.77 (BB', 2H, J 9 Hz, Ar–H), and 7.17 (AA', 2H, J 9 Hz, Ar–H); *m/e* (100°) 317 (M^+, 3; $C_{19}H_{27}NO_3$ requires: 317.199. Found: 317.199), 58 (100).

(±) - O - *Methyljoubertiamine* (1). A soln of O-methyljoubertiamine ethyleneacetal (18 mg) in ether (2 ml) was extracted with HClaq. (8%, 1.5 ml). The acid phase was basified with solid $NaHCO_3/K_2CO_3$ and re-extracted with ether (3 × 2 ml). The combined extract was dried (K_2CO_3), filtered and evaporated *in vacuo* to afford O-methyljoubertiamine (14 mg, 94%) having spectral data identical with those reported before.

4 - *Hydroxy* - 4 - (4 - *methoxyphenyl*)*cyclohexan* - 1 - *one ethyleneacetal* (7). To a stirred soln of 4-bromoanisole (1.859 g, 9.95 mmole, freshly vacuum distilled from basic activity I alumina) in dry hexane (9 ml) was injected (needle and syringe) under dry argon a 1.9 M soln of *n*-BuLi in hexane (5.4 ml, 10.2 mmole) at room temp. The mixture turned turbid after 0.25 hr and crystals of *p*-anisyllithium started to precipitate. The mixture was filtered under argon after 1.5 hr and the ppt washed with hexane (7 ml) under argon. The solid Li was suspended in fresh hexane (5 ml) and a soln of cyclohexane - 1,4 - dione mono ethyleneacetal (0.785 g, 5.03 mmole) in dry THF (5 ml) was added dropwise over 2 min under argon at room temp. The mixture was stirred for an additional 0.3 hr and the excess reagent quenched with water (5 ml). The resulting two-phase system was separated, the organic phase dried (K_2CO_3), filtered and evaporated *in vacuo* to afford the tertiary alcohol (1.223 g, 92%) as white crystals, m.p. 124.5° (acetone–ether) ν_{max} (KBr-wafer) 3440 (–OH) cm^{-1}; δ($CDCl_3$), 1.43–2.24 (m, 8H, ring $-CH_2-$), 1.62 (s, 1H, –OH, exchanges with D_2O), 3.66 (s, 3H, –OMe), 3.83 (s, 4H, $-O-CH_2-CH_2-O-$), 6.74 (BB', 2H, J 8.5 Hz, Ar–H), and 7.30 (AA', 2H, J 8.5 Hz, Ar–H); *m/e* (160°) 264 (M^+, 3 $C_{15}H_{20}O_4$ requires: 264.136. Found: 264.137) and 150 (100); Calc. for $C_{15}H_{20}O_4$: C, 68.19; H, 7.58. Found: C, 68.36; H, 7.63.

4 - (4 - *Methoxyphenyl*)*cyclohex* - 3 - *en* - 1 - *one ethyleneacetal* (6). *p*-Toluene sulphonic acid (72 mg, 0.38 mmole) and dry benzene (70 ml) were heated under reflux for 15 min. The mixture was cooled somewhat and 4 - hydroxy - 4 - (4 - methoxyphenyl)-cyclohexan - 1 - one ethyleneacetal (2.294 g, 9.45 mmole) was added in one portion. Refluxing was resumed while the water which formed was removed with a Dean Stark separator. Heating was terminated after 10 min and the mixture cooled, washed with sat. $NaHCO_3$aq (20 ml) and water (10 ml). Drying (K_2CO_3), evaporation of the solvent, and recrystallization from ether-pet. ether yielded 2.034 g (87%) of the unsaturated acetal as white crystals, m.p. 96–96.5°, ν_{max} (KBr-wafer) 1632 (C=C) cm^{-1}; δ(CCl_4) 1.84 (t, 2H, J 6 Hz, C_6 $-CH_2-$), 2.30–2.44 (m, 2H, $W_{1/2}$ 8 Hz, C_2 $-CH_2-$), 2.44–2.71 (m, 2H, $W_{1/2}$ 12 Hz, C_5 $-CH_2-$), 3.77 (s, 3H, –OMe), 3.93 (s, 4H, $-O-CH_2-CH_2-O-$) 5.72–5.86 (m, 1H, $W_{1/2}$ 8 Hz, =CH–), 6.75 (BB', 2H, J 9 Hz, Ar–H), and 7.23 (AA', 2H, J 9 Hz, Ar–H); *m/e* (80°) 246 (M^+, 32 $C_{15}H_{18}O_3$ requires: 246.126. Found: 246.128) and 160 (100); Calc. for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.25; H, 7.41.

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