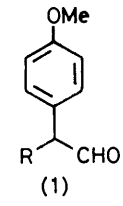
Applications of Substituted Arylacetaldehydes in the Total Synthesis of *seco*-Mesembrane Alkaloids. Part 1. The Total Synthesis of (±)-*O*-Methyljoubertiamine

By **Craig P. Forbes,* Wentzel J. Schoeman, Heinrich F. Strauss, Elize M. M. Venter, George L. Wenteler, and Adriaan Wiechers,** Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

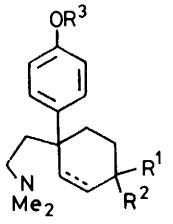
The substituted arylacetaldehyde 2-(*p*-methoxyphenyl)-5-dimethylaminobutanol (1a) is shown to serve as a precursor in the total synthesis of the *seco*-mesembrane alkaloid (±)-*O*-methyljoubertiamine (2; R^1R^2 = O, R^3 = Me, Δ^7 unsaturation).

THE substituted arylacetaldehyde (1a) can be used as a precursor in the total synthesis of *seco*-mesembrane alkaloids (2).[1] Hitherto, several alkaloids of the mesembrane series have been synthesized by routes involving the annelation of 3-aryl-2-pyrrolines (3) with vinyl ketones, a method developed largely by Stevens.[2] This versatile synthetic route has been used in the total synthesis of (±)-mesembranone [2a,c] (4; R = OMe) and

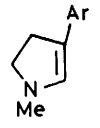


(1)

(a) R = $CH_2CH_2NMe_2$
(b) R = $CH_2CH{=}CH_2$



(2)



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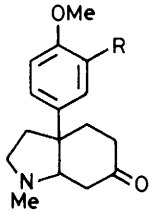
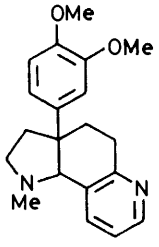


(4)



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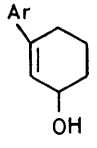


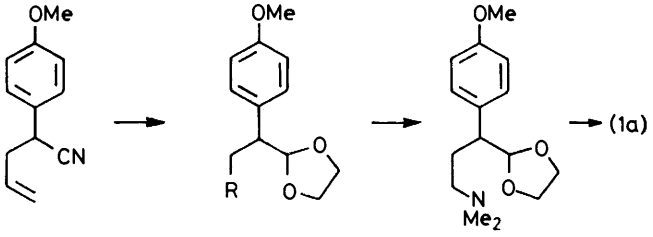
(6)

of (±)-sceletium alkaloid A_4 (5).[2c,3] Recently, the total synthesis of the *seco*-mesembrane alkaloid (±)-joubertiamine [4] (2; R^1R^2 = O, R^3 = H, Δ^7 unsaturation) was reported.[2b] This compound was obtained by the annelation of 3-(4-methoxyphenyl)-2-pyrroline (3; Ar = 4-methoxyphenyl) with methyl vinyl ketone to produce (±)-3-demethoxymesembranone (4; R = H) which was converted into (±)-joubertiamine by Hofmann elimination of the derived methiodide followed by demethylation of the methoxy-group in hot hydrobromic acid. Until recently this was the only reported total synthesis of a *seco*-mesembrane alkaloid. We have subsequently shown that the Claisen–Eschenmoser [3,3] sigmatropic rearrangement of functionalized 3-arylcyclohex-2-enols (6) provides a general route to *seco*-mesembrane alkaloids.[5]

Further studies directed towards these synthetic ends have indicated that the substituted arylacetaldehyde (1a) can also be used as a general precursor in the total synthesis of *seco*-mesembrane alkaloids. We present here the total synthesis of (±)-*O*-methyljoubertiamine (2; R^1R^2 = O, R^3 = Me, Δ^7 unsaturation) to illustrate the principle. Three different routes to the intermediate (1a) were investigated.

RESULTS AND DISCUSSION

Pathway (a) involved the monoallylation [6] of 4-methoxyphenylacetonitrile with allyl bromide in tetrahydrofuran (THF) containing hexamethylphosphorotriamide (HMPTA) at −78 °C using lithium di-isopropylcyclohexylamide as base to produce the nitrile (7) in 70% yield. Reduction [7] of (7) with DIBAL in benzene at room temperature produced the substituted arylacetaldehyde (1b), which was acetalized with ethylene glycol in benzene to produce the acetal (8a) in 82% overall yield. Oxidative cleavage [8] of the allyl side chain of (8a) with OsO_4–$NaIO_4$ to give the monoprotected dialdehyde (8b), followed by reductive amination [9] with dimethylamine hydrochloride and sodium



(7) (8) (9) (1a)

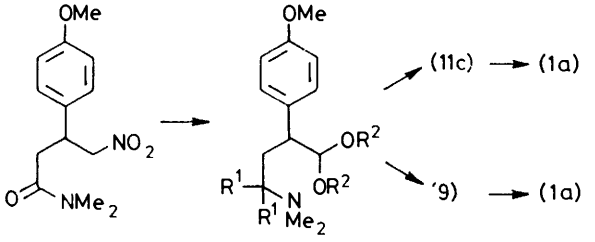
(a) R = $CH{=}CH_2$
(b) R = CHO

Pathway (a)

cyanoborohydride gave the amino-acetal (9) in 60% yield. Hydrolysis of (9) with toluene-*p*-sulphonic acid in aqueous dioxan gave the required intermediate (1a) in 26% overall yield.

Pathway (b) proceeded *via* the nitroamide (10). Conjugate addition of *NN*-dimethyl-α-lithioacetamide [10]

to 4-methoxyphenyl-β-nitrostyrene at −78 °C in THF gave (10) in 77% yield. Conversion of the methylene-nitro-group of (10) into an aldehyde was problematical. The rather drastic conditions of the classical Nef [11]

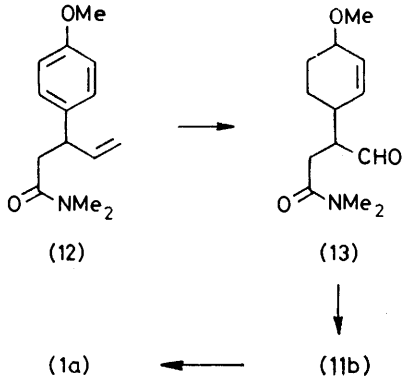


(10) (11)

(a) $R^1R^1=O; R^2=Me$
(b) $R^1R^1=O; R^2R^2=-CH_2CH_2-$
(c) $R^1R^1=H,H; R^2=Me$

Pathway (b)

reaction prompted us to try the direct methylene-nitro→dimethyl acetal transformation recently reported by Jacobson.[12] Despite several attempts, this reaction produced the amide-substituted acetal (11a) in only 15% yield. However the Ti^{3+} reduction [13] of the *aci*-nitro-form of (10), followed by acetalization of the resulting aldehyde with ethylene glycol in refluxing benzene, gave (11b) in 52% for the two steps. Reduction of (11a) and (11b) with $LiAlH_4$ produced the amines (11c) and (9) in good yield. Acetal hydrolysis with 8% aqueous HCl for (11c), or with toluene-*p*-sulphonic acid in 87% aqueous dioxan for (9) produced (1a) in 79% and 75% yields respectively. Despite this apparent success the Ti^{3+} reduction was unreliable and the above-mentioned yields



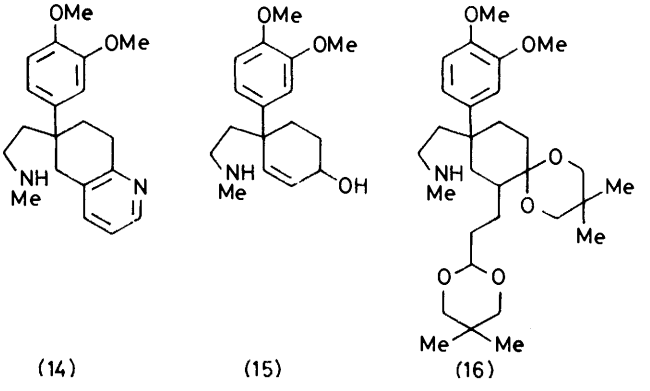
Pathway (c)

were the best obtained. Yields ranged between 20 and 65% for different runs.

Pathway (c) proved to be the most efficient. Treatment of 4-methoxycinnamyl alcohol with the dimethyl acetal of *NN*-dimethylacetamide in refluxing benzene for 1 h produced the unsaturated amide (12) *via* a [3,3]-sigmatropic rearrangement [14] in 93% yield. Oxidative cleavage of the allyl side chain with OsO_4–$NaIO_4$ as before [8] produced the aldehyde (13) in 94% yield. Aldehyde protection, reduction, and hydrolysis as before gave (1a) in 46% overall yield.

Intermediate (1a) was converted into (±)-*O*-methyljoubertiamine in 47% yield by Robinson annulation with methyl vinyl ketone in refluxing 95% aqueous ethanolic KOH. The synthetic product was spectrally identical with an authentic specimen. This general approach is presently being extended.*

Recent work from these laboratories has indicated that substituted arylacetaldehydes can also be used in the total synthesis of mesembrane alkaloids. The recently characterized *seco*-mesembrane alkaloid joubertiamine (15),[16] totally synthesized by a different route, was readily converted into mesembranone (4; R = OMe) by oxidation with MnO_2, indicating that a suitable choice



(14) (15) (16)

of substituents in the *seco*-mesembrane precursor can lead to the mesembrane series.[17] Work is at present under way to further investigate this principle.

EXPERIMENTAL

I.r. spectra were obtained on a Unicam SP 200 or Beckman 4250 spectrophotometer; the spectra were recorded in the solvent stated, neat or as a solid suspension in KBr (KBr-wafer). ^1H N.m.r. spectra were determined with a Varian HA100 spectrometer in the solvent stated with $SiMe_4$ as internal reference. Mass spectra and accurate mass measurements were made on a Du Pont 21.492B or A.E.I. model MS-9 mass spectrometer. Melting points were obtained on a Kofler micro hot stage.

(±)-α-*Allyl*-α-(p-*methoxyphenyl*)*acetonitrile* (7).—4-Methoxyphenylacetonitrile (10 g, 67.9 mmol, 1 equiv.) was added dropwise to a 1M-solution of lithium isopropylcyclohexylamide in THF–hexane (1 : 1) (71 ml, 1.05 equiv.) at −78 °C under N_2. The resulting solution was treated dropwise over 5 min with a mixture of allyl bromide (8.6 g, 71.3 mmol, 1.05 equiv.) and HMPTA (4.3 g, 27.1 mmol, 0.4 equiv.). The mixture was stirred for 2 h at −78 °C and then permitted to warm to room temperature. It was

*A projected total synthesis of tortuosamine [15] (14) *via* intermediate (1b) led to the diprotected keto-aldehyde (16) in the penultimate step. However simultaneous hydrolysis and pyridine ring formation with an excess of hydroxylamine hydrochloride in aqueous ethanol [3] produced, instead of the expected product tortuosamine, the ring-closed sceletium alkaloid A_4 (5).[2c,3] This unexpected result is under investigation and will form the subject of a later communication.

diluted with 10% aqueous HCl saturated with NaCl (100 ml) and extracted with ether (10 × 100 ml). The organic phase was washed (saturated aqueous $NaHCO_3$–NaCl), dried ($MgSO_4$), and concentrated to an oil. Distillation afforded starting material (1.09 g; 11%) (b.p. 104 °C at 0.5 Torr) and (±)-α-allyl-α-(*p*-methoxyphenyl)acetonitrile (7) (8.59 g; 70%) (b.p. 112 °C at 0.5 Torr), n_D^{20} 1.5297; $\nu_{max.}$ (neat) 3 010, 2 840, 2 240, 1 640, 1 610, 1 584, 1 520, 998, 930, and 840 cm^{-1}; $\lambda_{max.}$ (MeOH) 226, 275.5, and 282 nm (log $\varepsilon_{max.}$ 2.875, 2.813, and 2.756); δ($CDCl_3$) 2.59 (t, 2 H, *J* 7 Hz, $-CH_2-CH=CH_2$), 3.8 [t, 1 H, *J* 7 Hz, Ar–*CH*(CN)], 3.79 (s, 3 H, OMe), 5.02—5.27 (m, 2 H, $CH=CH_2$), 5.58—6.02 (m, 1 H, $CH=CH_2$), 6.88—7.22 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: C, 76.80; H, 7.0; N, 7.5. $C_{12}H_{13}NO$ requires C, 76.97; H, 6.99; N, 7.48%).

(±)-α-*Allyl*-α-(p-*methoxyphenyl*)*acetaldehyde* (1b).—α-Allyl-α-(4-methoxyphenyl)acetonitrile (7) (5.8 g, 31 mmol, 1 equiv.) dissolved in dry benzene (40 ml) was treated dropwise with DIBAL (4.97 g, 35 mmol, 1.05 equiv.) in dry benzene (45 ml) over 20 min at room temperature. The mixture was stirred for 1 h, added with stirring to 5% aqueous H_2SO_4 (200 ml), stirred for 2 h, and extracted (3 × 50 ml) with ether. The ether phase was washed with water (10 ml), dried ($MgSO_4$), and concentrated. Distillation of the residual oil produced (±)-α-allyl-α-(*p*-methoxyphenyl)acetaldehyde (1b) (4.82 g, 83%), b.p. 85 °C (bath temp.) at 0.08 Torr, n_D^{20} 1.5310; $\nu_{max.}$ (neat) 3 000, 2 850, 2 750, 2 640, 1 710, 1 625, 1 600, 1 570, 1 505, 1 455, 1 435, 1 290, 1 240, 1 160, 1 100, 1 020, 980, 910, and 820 cm^{-1}; $\lambda_{max.}$ (MeOH) 205.5, 223, 275, and 281.5 nm (log $\varepsilon_{max.}$ 3.8, 3.85, 3.38, and 3.35); δ($CDCl_3$) 2.62 (m, 2 H, CH_2), 3.53 (m, 1 H, benzylic-H), 3.78 (s, 3 H, OMe), 4.88—5.28 (m, 1 H, $CH=CH_2$), 6.88—7.07 (AA'BB', 4 H, *p*-methoxyphenyl ring protons), and 9.61 (d, 1 H, *CH*O) (Found: C, 75.7; H, 7.4. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%).

2-[1-(p-*Methoxyphenyl*)*but*-3-*enyl*]-1,3-*dioxolan* (8a).—The aldehyde (1b) (2.0 g, 10 mmol, 1 equiv.), ethylene glycol (1.24 g, 20 mmol, 2 equiv.), and toluene-*p*-sulphonic acid monohydrate (180 mg, 1 mmol, 0.1 equiv.) were refluxed in benzene (50 ml) for 5 h with constant azeotropic water removal. The resulting solution was diluted with benzene (20 ml), extracted with saturated aqueous $NaHCO_3$ (2 × 10 ml), and brine (2 × 20 ml), dried ($MgSO_4$), and concentrated. The resulting oil was filtered through neutral alumina [benzene–chloroform (2 : 3)] to give the dioxolan (8a) (2.3 g, 99%); $\nu_{max.}$ (neat) 2 850, 1 640, 1 610, 1 590, 1 520, 1 250, 1 180, 1 150, 1 120, 1 040, 945, 920, and 835 cm^{-1}; δ(CCl_4) 2.34—2.62 (m, 2 H, $CH_2-CH=CH_2$), 2.72—2.96 (m, 1 H, benzylic-H), 3.68 (s, 4 H, $-OCH_2CH_2O-$), 3.70 (s, 3 H, OMe), 4.76—5.86 (m, 3 H, $CH=CH_2$), 4.91 (d, 1 H, dioxolan CH), and 6.72—7.09 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: C, 71.7; H, 7.7. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%).

2-[1-(p-*Methoxyphenyl*)-3-*oxopropyl*]-1,3-*dioxolan* (8b).—The allyl-substituted aldehyde (8a) (0.5 g, 2 mmol, 1 equiv.) was partitioned between ether (12 ml) and distilled water (12 ml). Osmium tetraoxide (51 mg, 0.2 mmol, 0.02 equiv.) was added to the vigorously stirred solution, producing the black osmate ester. Sodium metaperiodate (5 g, 23 mmol, 11.5 equiv.) was added in portions during 20 min and the mixture stirred for 20 h. The phases were separated, the aqueous phase extracted with ether (2 × 10 ml), and the combined organic phase was dried ($MgSO_4$) and concentrated. The resulting oil, filtered through neutral Al_2O_3 [5 g; benzene–chloroform (2 : 3)] gave the mono-protected dialdehyde (8b) (0.4 g, 80%); $\nu_{max.}$ (neat) 2 940, 2 860, 2 720, 1 720, 1 618, 1 588, 1 525, 1 255, 1 185, 1 150, 1 120, 1 090, 1 040, and 842 cm^{-1}; δ(CCl_4) 2.56 and 2.80 (dd, 2 H, *J* 3.7 and 16 Hz, CH_2CHO), 3.44 (m, 1 H, benzylic-H), 3.74 (s, 4 H, $-OCH_2CH_2O-$), 3.79 (s, 3 H, OMe), 4.90 (d, 1 H, *J* 4 Hz, dioxolan CH), 6.74—7.14 (AA'BB', 4 H, *p*-methoxyphenyl ring protons), and 9.55 (t, 1 H, *J* 3 Hz, CHO) (Found: C, 66.0; H, 6.6. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.8%).

2-[1-(p-*Methoxyphenyl*)-3-NN-*dimethylamino*]*propyl*-1,3-*dioxolan* (9).—*Pathway* (*a*). The mono-protected dialdehyde (8b) (236 mg, 1 mmol, 1 equiv.) in dry methanol (50 ml) was treated with dry dimethylammonium chloride (0.86 g, 10 mmol; 10 equiv.) and sodium cyanoborohydride (95 mg, 1.5 mmol, 1.5 equiv.) and stirred at room temperature for 40 min. Solid Na_2CO_3 (1 g) was added and the mixture refluxed for 30 min. Filtration and concentration gave an oil which was filtered through neutral Al_2O_3 [2 g; benzene–chloroform (2 : 3)] to yield the amino-acetal (9) (0.2 g, 75%); $\nu_{max.}$ (neat) 2 940, 2 880, 2 765, 1 615, 1 585, 1 520, 1 250, 1 180, 1 140, 1 040, and 840 cm^{-1}; δ(CCl_4) 1.56—2.20 (m, 4 H, $CH_2CH_2NMe_2$), 2.08 (s, 6 H, NMe_2), 2.74—2.96 (m, 1 H, benzylic-H), 3.72 (s, 3 H, OMe), 3.74 (s, 4 H, $-OCH_2CH_2O-$), 4.85 (d, 1 H, *J* 4 Hz, dioxolan CH), 6.71—7.09 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: C, 67.7; H, 8.55; N, 5.3%; M^+, 265.1675. $C_{15}H_{23}NO_3$ requires C, 67.89; H, 8.70; N, 5.27%; *M*, 265.1679).

Pathway (*b*). The amide (11b) (72.8 mg, 0.26 mmol, 1 equiv.) reduced by the same method used for (11a) (see below) produced the pure amino-acetal (9) (47 mg; 71%) identical with the specimen obtained previously.

2-(p-*Methoxyphenyl*)-4-(NN-*dimethylamino*)*butanal* (1a).—*Pathway* (*a*). The amino-acetal (9) (0.20 g, 75 mmol, 1 equiv.) and toluene-*p*-sulphonic acid monohydrate (0.142 g, 8.25 mmol, 0.11 equiv.) in dioxan–water (8 ml, 7 : 1 v/v) were refluxed under N_2 for 1.25 h. The mixture was neutralised with solid $NaHCO_3$, filtered, and concentrated. The resulting oil was filtered through neutral Al_2O_3 (2 g, $CHCl_3$) to afford the amino-aldehyde intermediate (1a) (156 mg; 75%); δ($CDCl_3$) 1.82—2.68 (m, 4 H, $CH_2CH_2NMe_2$), 2.40 (s, 6 H, NMe_2), 3.50—3.72 (m, 1 H, benzylic-H), 3.79 (s, 3 H, OMe), 6.90—7.16 (AA'BB', 4 H, *p*-methoxyphenyl ring protons), and 9.92 (d, *J* 3 Hz, *CH*O). This compound was used directly without any further purification.

Pathways (*b*) *and* (*c*). The dimethyl acetal (11c) (58 mg, 0.2 mmol) in ether (3 ml) was extracted with 8% aqueous HCl (3 ml). The acid phase was neutralized with solid $NaHCO_3$ and re-extracted with $CHCl_3$ (6 × 5 ml). The organic phase was dried ($MgSO_4$) and concentrated to afford (1a) (38 mg; 79%), identical with the previous sample.

(±)-NN-*Dimethyl*-3-(p-*methoxyphenyl*)-4-*nitrobutyramide* (10).—*NN*-Dimethylacetamide (6.5 g, 75 mmol, 1.5 equiv.) was added dropwise over 10 min to a 0.43M solution of lithium isopropylcyclohexylamide in THF–hexane (10 : 3) (140 ml, 1.4 equiv.) at −78 °C. The mixture was stirred for 1 h and treated dropwise with 4-methoxynitrostyrene (8.9 g, 50 mmol, 1 equiv.) in THF (100 ml) over 50 min. The mixture was stirred at −78 °C for 2 h, quenched with acetic acid (15 ml), and warmed to room temperature. Dilution with water (60 ml) and concentration gave a residue which was extracted (2 × 20 ml) with methylene chloride. The extract was washed with saturated aqueous

$NaHCO_3$ (2 × 10 ml), dried (Na_2SO_4), and evaporated. Crystallisation of the residue (ethanol–water) gave the desired nitrobutyramide (10) (10.1 g; 77%), m.p. 82 °C; $\nu_{max.}$ (KBr disc) 1 650, 1 530, 1 255, and 845 cm^{-1}; δ($CDCl_3$) 2.68 and 2.75 (2 × s, each 1 H, CH_2CONMe_2), 2.90 (s, 6 H, NMe_2), 3.76 (s, 3 H, Me), 4.0 (quintet, 1 H, methine H), 4.72 and 4.79 (2 × overlapping ABq, 2 H, J_{AB} 12 Hz, CH_2NO_2), and 6.84—7.15 (AA'BB', 4 H, J 8.5 Hz, *p*-methoxyphenyl ring protons) (Found: C, 58.85; H, 7.0; N, 10.55. $C_{13}H_{18}N_2O_4$ requires C, 58.64; H, 6.77; N, 10.53%).

(±)-NN-*Dimethyl*-4,4-*dimethoxy*-3-(p-*methoxyphenyl*)-*butyramide* (11a).—The nitroamide (10) (243 mg, 0.91 mmol, 1 equiv.) in methanolic NaOMe (2.5 ml, 1.25 mmol 1.4 equiv.) was added dropwise to concentrated H_2SO_4 (2.4 ml) in absolute methanol (10 ml) at −35 °C at a rate of 1 drop per second. The resulting blue mixture was stirred for a further 5 min, added to CH_2Cl_2 (50 ml), washed with ice water (25 ml) and then 5% aqueous NaOH (18 ml) and dried (K_2CO_3). Concentration gave an oil (90 mg) which, on chromatography over basic alumina [grade II—III (10 g) hexane–ethyl acetate (4 : 1)] afforded the desired pure acetal (11a) (38 mg; 15%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 660, 1 255, and 840 cm^{-1}; δ(CCl_4) 2.42—2.66 (m, 2 H, CH_2CONMe_2), 2.77 and 2.85 (2 × br s, 6 H, $CONMe_2$), 3.24 and 3.29 [2 × s, 2 × Me, $CH(OMe)_2$], 3.31—3.49 (m, 1 H, benzylic-H), 3.71 (s, 3 H, ArO*Me*), 4.31 [d, 1 H, J 5 Hz, $-CH(OMe)_2$], and 6.68—8.09 (AA'BB', 4 H, *p*-methoxyphenyl ring protons). This compound was used without further purification in the following step of the synthesis.

(±)-NN-*Dimethyl*-4-(*ethylenedioxy*)-3-(p-*methoxyphenyl*)-*butyramide* (11b).—The oxo-amide (13) (128 mg, 0.54 mmol, 1 equiv.), dry ethylene glycol (124 mg, 2.0 mmol, 3.7 equiv.) and toluene-*p*-sulphonic acid (9.5 mg, 0.05 mmol, 0.9 equiv.) in dry benzene (10 ml) were refluxed for 15 min with azeotropic removal of water. Three fresh portions of dry benzene (3 × 2 ml) were added during the reaction. The reaction mixture was cooled, diluted with benzene (10 ml), washed with saturated aqueous $NaHCO_3$ (5 ml), dried ($MgSO_4$), and concentrated to produce the pure acetal (11b) (122 mg; 80%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 658, 1 512, 1 248, 1 135, and 1 040 cm^{-1}; δ(CCl_4) 2.55—2.75 (m, 2 H, $COCH_2$), 2.80—3.03 (2 × s, 6 H, 2 × NMe), 3.40—3.63 (m, 1 H, benzylic-H), 3.82 (s, 7 H, ArO*Me* and $-OCH_2CH_2O-$), 5.04 (d, 1 H, dioxolan CH), and 6.70—7.40 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: M^+, 279.1467. $C_{15}H_{21}NO_4$ requires M, 279.1471). This compound was used without purification in the following step of the reaction.

(±)-4-(*Dimethylamino*)-1,1-*dimethoxy*-2-(p-*methoxyphenyl*)*butane* (11c).—The amide (11a) (80 mg, 0.28 mmol, 1 equiv.) in dry THF (3 ml) was added dropwise with stirring to $LiAlH_4$ (14 mg, 0.36 mmol, 5.1 equiv.) in THF (2 ml) at room temperature under N_2. After 10 min, excess of reagent was decomposed with ethyl acetate (5 ml), water (2 ml), and 0.07% HCl (3 drops). The resulting mixture was filtered through Hyflo Supercel and concentrated *in vacuo* at 40 °C. Azeotropic removal of residual water with ethanol (2 × 5 ml) at 40 °C and chromatography over basic alumina (grade II—III, 11 g, $CHCl_3$) gave the required amino-acetal (11c) as an oil (64 mg; 84%); $\nu_{max.}$ ($CHCl_3$) 1 479, 1 458, 1 256, 1 082, and 842 cm^{-1}; δ(CCl_4) 1.40—2.34 (m, 4 H, $CH_2CH_2NMe_2$), 2.07 (s, 6 H, NMe_2), 2.72—2.99 (m, 1 H, ArCH), 3.15—3.29 [2 × s, $CH(OMe)_2$], 3.75 (s, 3 H, ArO*Me*), 4.25 [d, 1 H, J 6.5 Hz, $-CH(OMe)_2$], and 6.72—7.03 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: C, 67.4; H, 9.1; N, 5.15. $C_{15}H_{25}NO_3$ requires C, 67.3; H, 9.4; N, 5.23%).

(±)-NN-*Dimethyl*-3-(p-*methoxyphenyl*)*pent*-4-*enamide* (12).—3-(*p*-Methoxyphenyl)propenol (7.0 g, 42.6 mmol) dissolved in *NN*-dimethylacetamide dimethyl acetal (30 ml) was heated under N_2 with stirring for 1 h (bath temperature 140 °C, vapour temperature 108 °C). The mixture was cooled, diluted with benzene (60 ml), and concentrated. The resulting crude product (9.46 g) chromatographed over silica (1 200 g, increasing concentration of ethyl acetate in light petroleum) gave the enamide (12) as an oil (6.4 g; 93%); $\nu_{max.}$ (neat) 2 910, 1 640, 1 518, 1 400, 1 250, 1 170, and 1 030 cm^{-1}; δ(CCl_4) 2.54 (d, 2 H, J 7 Hz, CH_2CONMe_2), 2.80 (2 × s, 2 × 3 H, $CONMe_2$), 3.68 (s, 3 H, OMe), 3.82 (m, 1 H, benzylic-H), 4.90 (m, 2 H, CH_2=CH), 6.0 (m, 1 H, CH_2=C*H*), and 6.67—7.12 (AA'BB', 4 H, *p*-methoxyphenyl ring protons) (Found: C, 72.6; H, 8.2; N, 5.95. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%).

(±)-NN-*Dimethyl*-4-*oxo*-3-(p-*methoxyphenyl*)*butyramide* (13).—The enamide (12) (101.3 mg, 0.43 mmol, 1 equiv.) in 1 : 1 t-butyl alcohol–H_2O (2 ml) was treated with OsO_4 (19.6 mg, 0.07 mmol; 0.16 equiv.) and stirred for 1 h; the black osmate ester formed. The mixture was cooled to 0 °C and treated over 3 h with solid $NaIO_4$ in three portions (103.4 mg, 0.48 mmol, 1.1 equiv.). The reaction mixture was stirred for a further 1 h. The mixture was extracted with ether (10 × 1 ml). The ether extracts were dried ($MgSO_4$) and concentrated, and the residue was filtered through neutral alumina (grade II, 1 g, ethyl acetate) to afford the aldehyde (13) (95.6 mg; 94%); $\nu_{max.}$ (CCl_4) 2 860, 1 735, 1 655, 1 505, 1 240, and 1 037 cm^{-1}; δ($CDCl_3$) 2.82 and 2.92 (2 × s, 2 × 3 H, $CONMe_2$), 3.70 (s, 3 H, OMe), 4.12 (m, 1 H, benzylic-H), 6.70—7.20 (AA'BB', 4 H, *p*-methoxyphenyl ring protons), and 9.55 (s, 1 H, CHO), which formed a 2,4-dinitrophenylhydrazone, m.p. 146—151 °C (EtOH) (Found: C, 54.9; H, 5.15; N, 16.7. $C_{19}H_{20}N_5O_6$ requires C, 54.94; H, 5.09; N, 16.85%).

(±)-O-*Methyljoubertiamine* (2; R^1R^2 = O, R^3 = Me, Δ^7-*unsaturation*).—Intermediate (1a) (37.6 mg, 0.17 mmol, 1 equiv.) was dissolved in 95% aqueous ethanol (3 ml) containing methyl vinyl ketone (48 mg, 0.69 mmol, 4 equiv.) and the resulting solution was added dropwise during 5 min to a refluxing solution of KOH (33 mg, 0.59 mmol, 3.5 equiv.) in 95% aqueous ethanol (3 ml) under N_2. The mixture was refluxed for 35 min and concentrated. The resulting oil was dissolved in $CHCl_3$ (10 ml) and extracted with 4% aqueous HCl (2 × 5 ml). The aqueous acidic phase was neutralized with solid $NaHCO_3$ and extracted with chloroform (4 × 6 ml). The organic phase was dried ($MgSO_4$) and concentrated to an oil which on filtration through neutral alumina (grade II—III, 2 g, $CHCl_3$) gave (±)-*O*-methyljoubertiamine (26 mg; 47%) identical with an authentic specimen.[5]

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REFERENCES

[1] A. Popelak and G. Lettenbauer in ' The Alkaloids,' vol. IX, ed. R. H. F. Manske, Academic Press, New York, N.Y., 1968.

[2] (*a*) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, 1968, **90**, 5580; (*b*) R. V. Stevens and J. T. Lai, *J. Org. Chem.*, 1972, **37**, 2138; (*c*) R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, 1975, **40**, 3495.

[3] C. P. Forbes, G. L. Wenteler, and A. Wiechers, *Tetrahedron*, 1978, **34**, 487.

[4] R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.
[5] H. F. Strauss and A. Wiechers, *Tetrahedron*, 1978, **34**, 127.
[6] For related monalkylations of nitriles see D. S. Watt, *Tetrahedron Letters*, 1974, 707, and references cited therein.
[7] *For related* nitrile reduction see (*a*) S. Trofimento, *J. Org. Chem.*, 1964, **29**, 3046; (*b*) A. E. G. Miller, J. W. Biss, and L. H. Schwartzman, *ibid.*, 1959, **24**, 627.
[8] R. Pappa, D. S. Allen, R. H. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.
[9] R. F. Borch, M. B. Bernstein, and H. D. Hurst, *J. Amer. Chem. Soc.*, 1971, **93**, 2898.
[10] D. Seebach, H. F. Leitz, and V. Ehrig, *Chem. Ber.*, 1975, **108**, 1924.
[11] W. E. Noland, *Chem. Rev.*, 1955, **55**, 137.
[12] R. M. Jacobson, *Tetrahedron Letters*, 1974, 3215.
[13] J. E. McMurray and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.
[14] D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, 1969, **52**, 1030.
[15] F. O. Snyckers, F. Strelow, and A. Wiechers, *Chem. Comm.*, 1971, 1467.
[16] K. Psotta, F. Strelow, and A. Wiechers, *J.C.S. Perkin I*, 1979, 1063.
[17] K. Psotta and A. Wiechers, *Tetrahedron*, 1979, **35**, 255.