Regioselective Total Synthesis of (±)-Berberastine

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The title compound has been synthesized in 37% overall yield from methyl 6-chloromethyl-2,3-dimethoxybenzoate (**8**) through the following six steps: Reformatsky-type condensation of (**8**) with 3,4-methylenedioxybenzaldehyde gave 3,4-dihydro-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)-isocoumarin (**10**), which was transformed into 2,3-dimethoxy-6-(3,4-methylenedioxyphenacyl)-benzaldehyde (**6**) by reduction with lithium aluminium hydride followed by Swern oxidation; reductive amination of compound (**6**) with aminoacetaldehyde dimethyl acetal afforded 2-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-3-(3,4-methylenedioxyphenyl)isoquinoline (**3**); acid-catalysed cyclization of the acetal (**3**) gave 5-hydroxytetrahydroberberines (**2**), from which berberastine iodide (**1**) was obtained by iodine oxidation. All attempts to oxidize compounds (**2**) to the corresponding ketone have so far failed.

The total synthesis of (±)-berberastine (**1**) involves the resolution of problems frequently encountered in the preparation of berbine derivatives *i.e.* (i) the construction of the dibenzo[*a*,*g*]quinolizine system with a 9,10-dioxy substitution pattern, which therefore contain a benzene ring with four contiguous substituents (ring A), (ii) the manipulaton of intermediates often unstable in strong acidic conditions, due to the presence in their molecules of a methylenedioxy-substituted benzene ring, and (iii) the need for accurate control of the oxidation level of the quinolizine moiety (rings B and C).

Although the use of the *ortho*-lithiation reaction in the elaboration of the appropriate synthetic intermediates has greatly contributed to the development of regioselective syntheses of 9,10-dioxyberbines,[1] and although several methods are available both for redox transformations of the etherocyclic portion and for the introduction of hydroxy functions at C-5[2] and C-13,[3] an efficient regioselective synthesis of compound (**1**) and, more generally, of 9,10-dioxy-5-hydroxyberbines is still lacking. On the other hand, compounds exhibiting these structural features are interesting since the oxygenated function at C-5 may be an important centre for further elaboration, thus securing access to potentially useful alkaloid analogues. Furthermore, 5-hydroxyberbines can be considered as rigid models of epinephrine, to which compound (**1**) is also biosynthetically related.[2b]

In this paper we report the first regioselective total synthesis of (±)-berberastine (**1**). This synthesis is shorter and more efficient than the only other synthesis, described about ten years ago by Dyke and Tiley in connection with their structure elucidation of berberastine.[4]

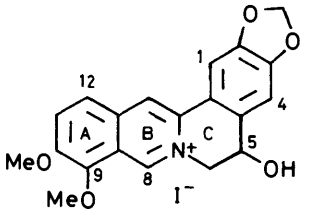
In their extensive study on the preparation of 5-hydroxyberbines, the aforementioned authors outlined some important features of this specific synthetic problem. In particular, they showed that the acid-catalysed cyclization of acetal (**3**) to alcohol (**2**) is an excellent method for ring-C formation with concomitant introduction of a hydroxy group at C-5, and they demonstrated that keto ester (**4**), in contrast with the behaviour of other analogues used in previous syntheses, cannot be used as an obvious direct precursor for the construction of ring B. This unexpected difficulty led them to make use of an alternative mode of construction of ring B, consisting in the non-regioselective cyclofunctionalization of the phenolic phenethylamine (**7**).[4]

The facility with which we expected to obtain compounds (**5**) and (**6**), by employing recent methods of elaboration of aromatic substrates and functional groups, led us to investigate these still obvious precursors for the synthesis of (**3**) by etherocyclic ring-B annulation. In particular, the possibility of obtaining acetal (**3**) from aminoacetaldehyde dimethyl acetal by direct rhodium-catalysed alkylation[5] with diol (**5**) or by reductive alkylation[6] with keto aldehyde (**6**) appeared encouraging.

Results and Discussion

The appropriate aromatic 1,5-difunctionalized intermediates (**4**), (**5**), and (**6**) required for our synthesis were easily prepared by means of the known method for carbon–carbon bond formation involving dithianes.[7] Thus, chloro ester (**8**) was condensed with 2-lithio-2-(3,4-methylenedioxyphenyl)-1,3-dithiane to afford compound (**9**), from which keto ester (**4**) was formed by acid hydrolysis in the presence of glyoxylic acid. Compound (**4**), on reduction with lithium aluminium hydride, cleanly gave diol (**5**). A more convenient and better yielding procedure for the preparation of compound (**5**) consisted of the Reformatsky-type reductive coupling of chloride (**8**) with 3,4-methylenedioxybenzaldehyde (piperonal) to give the 3,4-dihydroisocoumarin derivative (**10**), which, on reduction with lithium aluminium hydride, afforded the desired product. Carefully selected conditions were required for obtaining satisfactory results from the Reformatsky reaction, optimum yields (75—80%) being achieved with the use of active zinc prepared by reduction of zinc chloride with lithium and naphthalene in 1,2-dimethoxyethane.[8] The use of either different solvents [tetrahydrofuran (THF), ether], or of zinc produced by reduction of zinc chloride with potassium,[9] led to much lower yields. No reaction took place on using commercial zinc powder activated with a variety of methods,[10] in different solvents, and with ultrasonic irradiation.[11]

Unfortunately, attempts to alkylate aminoacetaldehyde dimethyl acetal with diol (**5**) in the presence of rhodium complexes[5] did not give the expected product (**3**). Although no attempt has been made to optimize the reaction conditions with respect to our substrate, steric factors may be responsible for the hitherto unsuccessful results. Diol (**5**) was thus smoothly converted into keto aldehyde (**6**) by Swern oxidation.[12] This compound reacted cleanly with ammonia to give the 3-phenylisoquinoline (**11**). In agreement with the results obtained from similar compounds,[13] no *N*-alkylated product was formed by heating (**11**) either with methyl bromoacetate or with allyl bromide, thus precluding other possible routes for ring-C construction. Finally, our target compound (**3**) was obtained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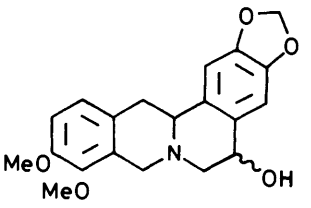
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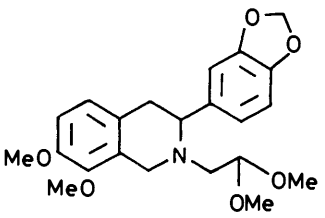
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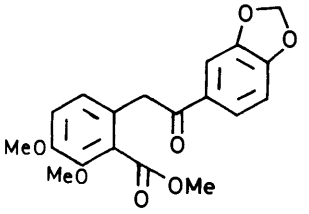
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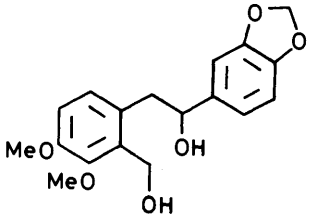
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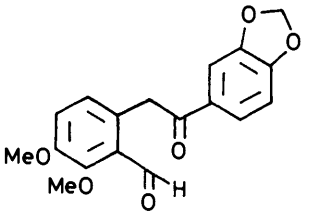
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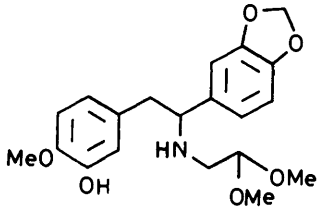
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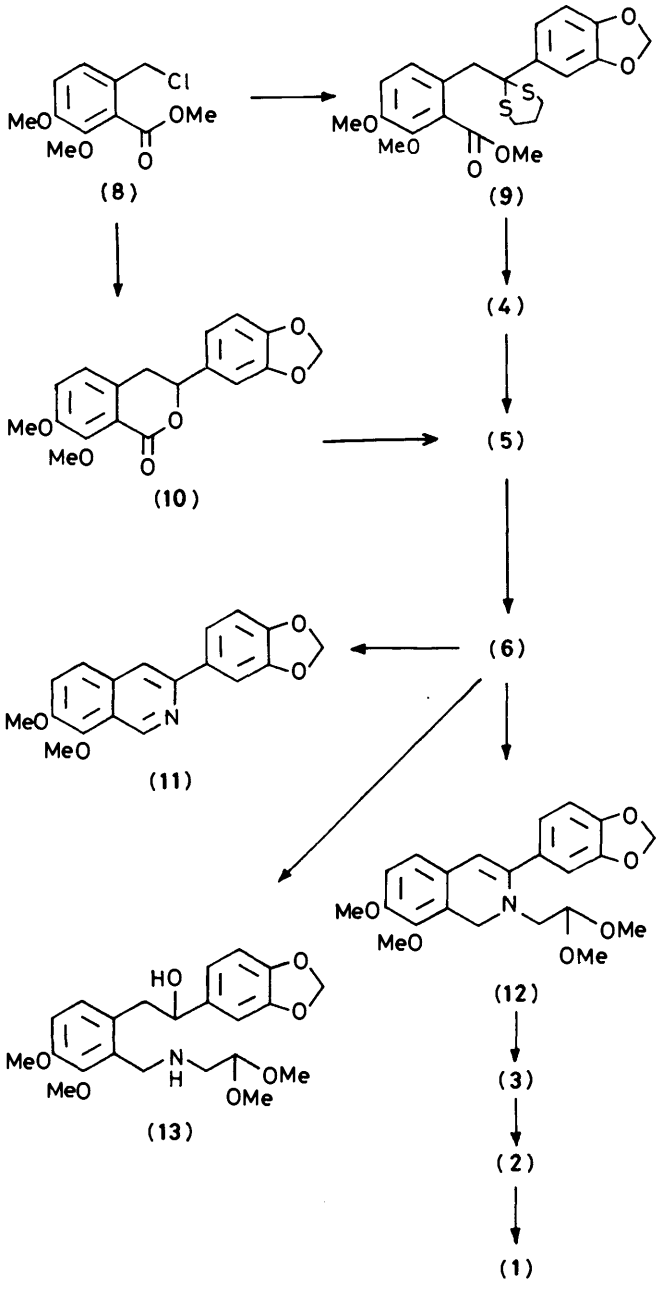
by reductive amination consisting of condensation of keto aldehyde (**6**) with aminoacetaldehyde dimethyl acetal followed by treatment with sodium cyanoborohydride and methanol–acetic acid in the presence of methyl orthoformate in order to minimize possible hydrolytic cleavage of the acetal function. When the addition of acetic acid to the reaction mixture was carefully controlled, it was also possible to isolate the intermediate enamine (**12**). The use of sodium borohydride in methanol as reducing agent gave the open-chain amino alcohol (**13**) as the main product. Conversion of the amino acetal (**3**) into the amino alcohols (**2**) and into (±)-berberastine iodide (**1**) was accomplished by following a previously reported procedure.[4] No attempt was made to separate diastereoisomeric amino alcohols (**2**). Instead, several attempts were made to oxidize compound (**2**) to the corresponding ketone. Straightforward application of literature methods for oxidation of amino alcohols [Oppenauer oxidation,[14] or chromium(VI) oxidation[15]] failed to give the expected product.

Experimental

M.p.s were determined with a Kofler apparatus and are uncorrected; i.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 197 spectrophotometer, and the most intense and/or representative absorption bands are given; n.m.r. spectra were recorded in part with a Varian EM360A, in part with a Varian CFT-20 instrument, and the most significant signals are quoted as δ-values in p.p.m. downfield from $SiMe_4$ as internal standard; evaporation of solvents was performed on a rotary evaporator under diminished pressure. Dry ethereal solvents were obtained by distillation from sodium–benzophenone under nitrogen.

Methyl 2,3-*Dimethoxy*-6-{[2-(3,4-*methylenedioxyphenyl*)-1,3-*dithian*-2-*yl*]*methyl*}*benzoate* (**9**).—To a stirred solution of 2-(3,4-methylenedioxyphenyl)-1,3-dithiane[16] (5.4 g, 22.5 mmol) in dry THF (100 ml) at −78 °C was added butyl-lithium (14.1 ml of a 1.6M-solution in hexane, 22.5 mmol) dropwise under nitrogen. One hour after the end of the addition, a solution of compound (**8**)[17] (5.0 g, 20.5 mmol) in THF (30 ml) was added dropwise and the reaction mixture was allowed to return to room temperature during 3 h. Acetic acid (3 ml) was added and most of the solvent was evaporated off. The residue was partitioned between water and dichloromethane, and the organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The oily residue, triturated with diethyl ether, afforded the *title compound* (**9**) (6.0 g, 65%), which crystallized from dichloromethane–diethyl ether as needles, m.p. 77—79 °C (Found: C, 58.9; H, 5.3. $C_{22}H_{24}O_6S_2$ requires C, 58.9; H, 5.3%); $\nu_{max.}$ 1 700 cm^{-1}; $\delta_H(CDCl_3)$ 1.70—2.13 (2 H, m, SCH_2CH_2), 2.46—2.83 (4 H, m, SCH_2CH_2), 3.35 (2 H, s, $ArCH_2$), 3.75, 3.78, and 3.83 (each 3 H, s, OMe), 6.00 (2 H, s, OCH_2O), and 6.81—7.13 (5 H, m, ArH).

Methyl 2,3-*Dimethoxy*-6-(3,4-*methylenedioxyphenacyl*)-*benzoate* (**4**).—A mixture of compound (**9**) (4.7 g, 10.5 mmol), glyoxylic acid hydrate (5.0 g, 54.3 mmol), acetic acid (50 ml), and conc. hydrochloric acid (1 ml) was heated on a steam-bath for 20 min and left for 18 h at room temperature. The solvent was then evaporated off and the residue was partitioned between



Scheme.

water and ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to afford the *title keto ester* (**4**) (3.1 g, 85%), which crystallized from dichloromethane–diethyl ether as prisms, m.p. 107—109 °C (Found: C, 63.5; H, 5.0. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.0%); $\nu_{max.}$ 1 700 and 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 3.81, 3.86, and 3.88 (each 3 H, s, OMe), 4.21 (2 H, s, $ArCH_2$), 6.05 (2 H, s, OCH_2O), and 6.75—7.73 (5 H, m, ArH).

3,4-*Dihydro*-7,8-*dimethoxy*-3-(3,4-*methylenedioxyphenyl*)*isocoumarin* (**10**).—Anhydrous zinc chloride (1.5 g, 10.9 mmol), dry 1,2-dimethoxyethane (15 ml), naphthalene (0.3 g, 2.3 mmol), and lithium (0.15 g, 22.9 mmol) were stirred under nitrogen for 24 h after the appearance of a dark precipitate. (The lithium surface should be scratched if no precipitate is formed within 15 min after the reagents have been mixed.) To the resulting black mixture was added a solution of the chloride (**8**)[17] (2.0 g, 9.4 mmol) and 3,4-methylenedioxybenzaldehyde (piperonal) (1.4 g, 9.4 mmol) in dry 1,2-dimethoxyethane (15 ml) dropwise. A slight exothermic reaction ensued. After the mixture had been stirred for 1 h, 10% hydrochloric acid (10 ml) was added, and the mixture was stirred until most of the black precipitate had dissolved. The mixture was then diluted with dichloromethane, washed with saturated brine, dried ($MgSO_4$), and evaporated. The residue was triturated with diethyl ether to give *title isocoumarin* (**10**) (2.5 g, 79%), which crystallized from dichloromethane-diethyl ether as plates, m.p. 148—149 °C (Found: C, 65.9; H, 4.8. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%); $\nu_{max.}$ 1 720 cm^{-1}; δ_H ($CDCl_3$; 60 MHz) 2.80, 2.90, 3.00, 3.02, 3.07, 3.12, 3.20, and 3.47 (2 H, *ABX* pattern, CH_2CH), 3.88 and 3.96 (each 3 H, s, OMe), 5.20, 5.27, 5.37, and 5.43 (1 H, AB*X* pattern, CH_2CH), 5.96 (2 H, s, OCH_2O), and 6.83—7.26 (5 H, m, ArH).

2-(2-*Hydroxymethyl*-3,4-*dimethoxyphenyl*)-1-(3,4-*methylenedioxyphenyl*)*ethanol* (**5**).—A mixture of the isocoumarin (**10**) (2.5 g, 7.0 mmol), lithium aluminium hydride (0.3 g, 8.0 mmol), and dry THF (30 ml) was refluxed under nitrogen for 5 h, cooled, diluted with diethyl ether (50 ml), and treated dropwise and successively with water (0.3 ml), 10% aqueous sodium hydroxide (0.3 ml), and water (1.0 ml). The precipitate was filtered off and extracted with several portions of hot dichloromethane. The extracts and the ethereal filtrate were combined, dried ($MgSO_4$), and evaporated to give the *diol* (**5**) (2.24 g, 97%), which crystallized from dichloromethane–diethyl ether as needles, m.p. 122—123 °C (Found: C, 65.2; H, 6.0. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.1%); $\nu_{max.}$ 3 310 and 3 200 cm^{-1}; $\delta_H(CDCl_3$–$D_2O)$ 2.95 (2 H, d, *J* 6 Hz, CH_2CH), 3.83 and 3.85 (each 3 H, s, OMe), 4.43—4.91 (3 H, m, $CHOH$ and CH_2OH), 5.93 (2 H, s, OCH_2O), and 6.78—6.86 (5 H, m, ArH). Analogous results were obtained from compound (**4**).

2,3-*Dimethoxy*-6-(3,4-*methylenedioxyphenacyl*)*benzaldehyde* (**6**).—To a solution of oxalyl dichloride (0.87 ml, 10.0 mmol) in dichloromethane (25 ml), stirred at −60 °C under nitrogen was added dropwise a solution of dimethyl sulphoxide (DMSO) (1.5 ml, 21.1 mmol) in dichloromethane (10 ml) during 5 min. A solution of diol (**5**) (1.5 g, 4.5 mmol) in dichloromethane (10 ml) containing DMSO (1 ml) was then added dropwise after 10 min; after being stirred for 15 min, the mixture was treated with triethylamine (6.3 ml, 45 mmol), added during 5 min. The cooling bath was removed and the solution, having warmed to room temperature, was washed with water, dried ($MgSO_4$), filtered through alumina, and evaporated. The residue, triturated with diethyl ether, afforded the *title aldehyde* (**6**) (1.26 g, 85.7%), which crystallized from dichloromethane–diethyl ether as prisms, m.p. 131—133 °C (Found: C, 65.6; H, 4.7. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%); $\nu_{max.}$ 1 680 cm^{-1}; $\delta_H(CDCl_3)$ 3.30 and 3.97 (each 3 H, s, OMe), 4.51 (2 H, s, $ArCH_2$), 6.03 (2 H, s, OCH_2O), 6.92—7.73 (5 H, m, ArH), and 10.48 (1 H, s, CHO).

7,8-*Dimethoxy*-3-(3,4-*methylenedioxyphenyl*)*isoquinoline* (**11**).—A mixture of keto aldehyde (**6**) (0.2 g, 0.6 mmol), dioxane (10 ml), and conc. ammonia (5 ml) was heated on a steam-bath for 10 min and left at 4 °C for 18 h. Compound (**11**) (0.16 g, 89%), which separated as a solid, was crystallized from ethyl acetate as *needles*, m.p. 138—139 °C (Found: C, 69.6; H, 4.7; N, 4.4. $C_{18}H_{15}NO_4$ requires C, 69.9; H, 4.65; N, 4.5%); $\nu_{max.}$ 1 600 and 1 520 cm^{-1}; $\delta_H(CDCl_3)$ 4.03 and 4.11 (each 3 H, s, OMe), 6.06 (2 H, s, OCH_2O), 6.88—7.75 (5 H, m, homocyclic ArH), 7.90 (1 H, s, 4-H), and 9.72 (1 H, s, 1-H).

2-(2,2-*Dimethoxyethyl*)-1,2-*dihydro*-7,8-*dimethoxy*-3-(3,4-*methylenedioxyphenyl*)*isoquinoline* (**12**) *and* 2-(2,2-*Dimethoxyethyl*)-1,2,3,4-*tetrahydro*-7,8-*dimethoxy*-3-(3,4-*methylenedioxy*-

phenyl)isoquinoline (**3**).—A solution of keto aldehyde (**6**) (1.0 g, 3.0 mmol) and aminoacetaldehyde dimethyl acetal (0.6 ml, 5.5 mmol) in dioxane (30 ml) was heated on a steam-bath for 15 min and was then evaporated. The oily residue was dissolved in methanol (20 ml) containing methyl orthoformate (0.6 ml, 5.5 mmol), sodium cyanoborohydride (0.36 g, 6.0 mmol), and methyl red as indicator. To the stirred solution was added a mixture of acetic acid (1 ml) and methanol (5 ml) dropwise, so that a light red colour was maintained. When the addition was stopped at the appearance of turbidity, *compound* (**12**) separated as a solid, which was collected by suction, washed with methanol, and dried *in vacuo* (0.6 g, 50% unoptimized), prisms, m.p. 102—105 °C (Found: C, 65.8; H, 6.2; N, 3.3. $C_{22}H_{25}NO_6$ requires C, 66.2; H, 6.3; N, 3.5%); $\nu_{max.}$ 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 3.02 (2 H, d, *J* 6 Hz, NCH_2CH), 3.08 [6 H, s, $CH(OMe)_2$], 3.85 (6 H, s, 2 × ArOMe), 4.15 (1 H, t, *J* 6 Hz, NCH_2CH), 4.51 (2 H, s, $ArCH_2$), 5.97 (2 H, s, OCH_2O), 6.02 (1 H, s, ArCH), and 6.75—7.13 (5 H, m, ArH).

Alternatively, on addition of all the acetic acid, the precipitate redissolved. After 3 h at room temperature, the solution was made alkaline with 10% aqueous sodium hydroxide (10 ml) and most of the solvent was evaporated off. The residue was taken up in dichloromethane, and the organic phase was washed with water, dried (Na_2CO_3), and evaporated to afford compound (**3**) (1.2 g, 100%) as a pale yellow thick oil; δ_H ($CDCl_3$;80 MHz) 2.23, 2.30, 2.40, 2.46, 2.62, 2.69, 2.79, and 2.86 (2 H, *ABX* pattern NCH_2CH), 2.97 (2 H, br d, *J* 7 Hz, $ArCH_2CH$), 3.27 and 3.32 [each 3 H, s, together $CH(OMe)_2$], 3.53, 3.73, 4.17, and 4.38 (2 H, ABq, $ArCH_2N$), 3.65 (1 H, t, *J* 7 Hz, $ArCH_2CH$), 3.84 (6 H, s, ArOMe), 4.46, 4.53, and 4.59 (1 H, AB*X* pattern, NCH_2CH), 5.93 (2 H, s, OCH_2O), and 6.70—6.90 (5 H, m, ArH) [lit.,[4] 2.48 (1 H, d, *J* 5 Hz), 2.67 (1 H, d, *J* 5 Hz), 2.98 (2 H, br d, *J* 7 Hz), 3.28 (3 H, s), 3.32 (3 H, s), 3.45—4.00 (2 H, m), 3.86 (6 H, s), 4.10—4.70 (2 H, m), 5.95 (2 H, s), and 6.60—7.00 (5 H, m)]. Hydrochloride, m.p. 130—133 °C (lit.,[4] 130—132 °C).

2-[2-(2,2-*Dimethoxyethylaminomethyl*)-3,4-*dimethoxyphenyl*]-1-(3,4-*methylenedioxyphenyl*)*ethanol* (**13**).—A solution of keto aldehyde (**6**) (1.0 g, 3.0 mmol) and aminoacetaldehyde dimethyl acetal (0.38 ml, 9.5 mmol) in dioxane (20 ml) was heated for 1 h on a steam-bath and was then evaporated to dryness. The residue was dissolved in methanol, and the stirred solution, cooled with ice, was treated with sodium borohydride (0.19 g, 5.0 mmol). After 15 min, 10% aqueous sodium hydroxide (10 ml) was added and most of the methanol was evaporated off on a steam-bath at atmospheric pressure. The residue was partitioned between water and dichloromethane, and the organic phase was dried (Na_2CO_3), and then evaporated, to give a viscous oil (1.29 g). T.l.c. (silica gel; diethyl ether–isopropyl alcohol 95:5 v/v) showed the presence of two major components, of R_F 0.3 and 0.6, respectively, which were separated by flash chromatography.[18] The first eluted compound was shown to be (**3**) (0.13 g, 10%) and the second was the *title compound* (**13**), oil (1.0 g, 80%) (Found: C, 62.6; H, 6.8; N, 3.1. $C_{22}H_{29}NO_7$ requires C, 63.0; H, 6.9; N, 3.3%); $\nu_{max.}$ 3 700—2 900 cm^{-1}; δ_H ($CDCl_3$; 80 MHz) 2.82—2.95 (4 H, m, NCH_2CH and $ArCH_2CH$), 3.38 and 3.42 [each 3 H, s, together $CH(OMe)_2$], 3.54, 3.68, 4.00, and 4.14 (2 H, ABq, $ArCH_2N$), 3.83 and 3.85 (each 3 H, s, ArOMe), 4.50—4.78 (2 H, m, NCH_2CH and $ArCH_2CH$), 5.94 (2 H, s, OCH_2O), and 6.73—7.00 (5 H, m, ArH).

(±)-Tetrahydroberberastine hydrochloride (**2**)·HCl and (±)-berberastine iodide (**1**) were prepared from compound (**3**) as described in the literature.[4]

Acknowledgements

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