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Extension of the Bobbitt Acetal Cyclization to the Elaboration of 1-Hydroxymethyl-Substituted Simple Tetrahydroisoquinolines. A New Synthesis of Calycotomine

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EXTENSION OF THE BOBBITT ACETAL CYCLIZATION TO THE ELABORATION OF 1-HYDROXYMETHYL-SUBSTITUTED SIMPLE TETRAHYDROISOQUINOLINES. A NEW SYNTHESIS OF CALYCOTOMINE

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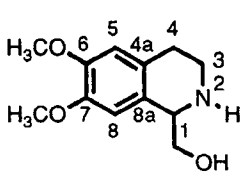
Abstract: Aromatic benzyloxymethyl ketones are convenient intermediates for the elaboration, *via* the Bobbitt acetal cyclization, of 1-hydroxymethyl-substituted simple tetrahydroisoquinolines, such as calycotomine and one bearing the 1,7,8-oxygenated substitution pattern of MY336-a.

The Bobbitt[1] modification of the Pomeranz-Fritsch isoquinoline synthesis has allowed the development of facile syntheses of various members of this family, providing an excellent route to certain otherwise inaccessible oxygenated tetrahydroisoquinolines. Although the range of substituted tetrahydroisoquinolines that can be produced is limited, applications of the Bobbitt procedure to the preparation of N-alkyl,[2] 4-hydroxy,[3,4] 4-benzyl,[5] 1-alkyl[6] and 3-alkyl[7] simple tetrahydroisoquinolines have been described.

Naturally occurring simple tetrahydroisoquinolines bearing a hydroxymethyl substituent at C_1 constitute a small group of molecules which include the widespread calycotomine (**1**),[8] deglucopterocereine (**2**)[9] and its N-oxide derivative (**3**),[10] hedycarine (**4**)[11] and the novel β-adrenergic receptor antagonist MY336-a (**5**).[12] A few more complex molecules sharing the same structural characteristic are also known, among them the novel antitumor agent quinocarcin (**6**)[13] and its derivatives.



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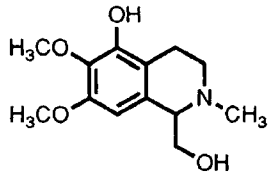

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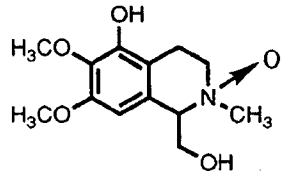

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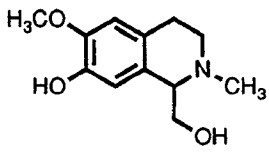

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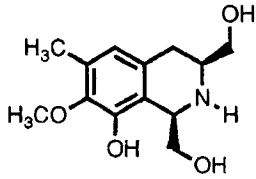

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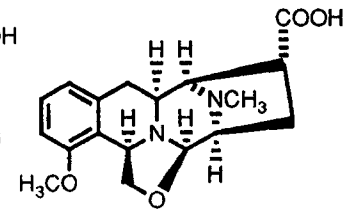


6

Several syntheses of calycotomine have been previously reported,[14-18] however, because they were based mainly on Bischler-Napieralski or Pictet-Spengler reaction schemes they

made use of the C_1-C_{8a} and/or C_1-N bond formation as the heterocyclic ring closure strategy. Other procedures involving the establishment of the C_1 substituent either by carbon-carbon bond formation[19] or by oxidative degradation of isoquinolinic starting materials[20] have also been described.

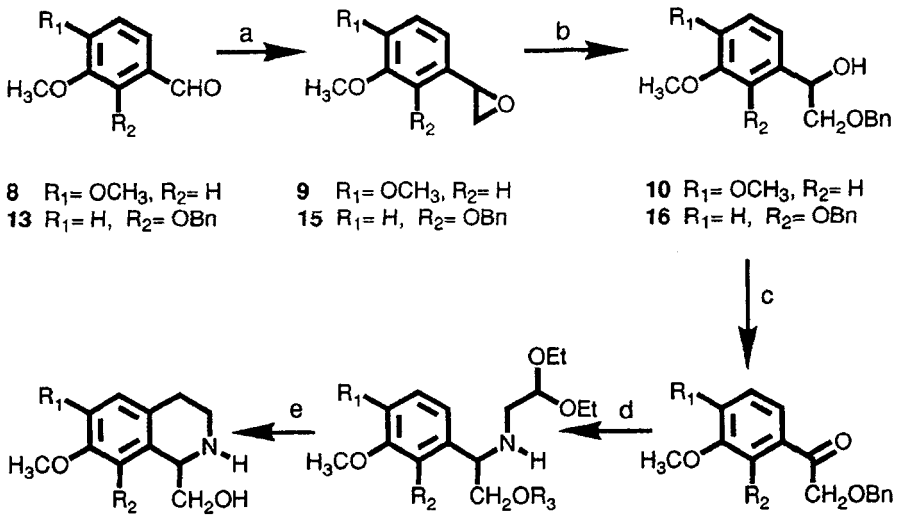
Reported in this communication is an extension of the Bobbitt protocol to the synthesis of tetrahydroisoquinolines bearing a 1-hydroxymethyl substituent, namely the known calycotomine (**1**) and the previously unreported 8-hydroxy-1-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**7**), which embodies the 1,7,8-oxygenated substitution pattern of the novel microbial metabolite MY336-a.

The new entry to the above compounds described here involves the closure of the heterocyclic ring by formation of the C_4-C_{4a} bond from appropriately substituted benzyloxymethyl aromatic ketones, key intermediates for the elaboration of the benzylamino acetals required as substrates for the Bobbitt cyclization.

As indicated in the Scheme, synthesis of calycotomine started from the readily available veratraldehyde (**8**), which was converted into epoxide **9** in almost quantitative yield after treatment with trimethylsulfonium hydrogen sulfate[21] under phase-transfer catalysis conditions.[22]

Then, opening of the oxirane ring was approached; the regioselective outcome of this process has been found to be

SCHEME



8 R_1= OCH_3, R_2= H
13 R_1= H, R_2= OBn

9 R_1= OCH_3, R_2= H
15 R_1= H, R_2= OBn

10 R_1= OCH_3, R_2= H
16 R_1= H, R_2= OBn

1 R_1= OCH_3, R_2= H
7 R_1= H, R_2= OH

12 R_1= OCH_3, R_2= H, R_3= Bn
17 R_1= H, R_2= OBn, R_3= Bn
18 R_1= H, R_2= OH, R_3= H

11 R_1= OCH_3, R_2= H
14 R_1= H, R_2= OBn

Reagents and Conditions: a. $(CH_3)_3S^+HSO_4^-$, cat. $(C_4H_9)_4N^+I^-$, CH_2Cl_2/50% NaOH, reflux, **8** → **9**: 99%, **13** → **15**: 98%; b. NaBnO, BnOH, 100°C, overnight, **9** → **10**: 61%, **15** → **16**: 66%; c. PCC/Al_2O_3, NaAcO, CH_2Cl_2, reflux, **10** → **11**: 90%, **16** → **14**: 85%; d. $H_2NCH_2CH(OCH_2CH_3)_2$, glacial AcOH, $NaCNBH_3$, $MgSO_4$, MeOH, reflux, **11** → **12**: 95%, **14** → **17**: 96%, **17** → **18**: HCl, 1 equiv./MeOH, H_2/10% Pd/C, 99%; e. 1. 4N HCl, overnight, 2. 10% Pd/C, H_2, 1 atm., **12** → **1**: 74%, **18** → **7**: 69%.

dependent on the reaction mechanism and highly sensitive to electronic as well as steric effects.[23] In neutral and basic solutions attack at the less hindered carbon atom is favored as a result of the influence of steric effects, while with electrophilic catalysis electronic effects increase the tendency

for attack at the more substituted carbon atom, which can better accommodate a positive charge.

Consequently, **9** was regioselectively opened with sodium benzyloxide in hot benzyl alcohol to afford 66% of glycol monoether **10** as the main product. Reaction conditions were selected by analogy with the recent observations of Chini *et al.* on the metal salt catalyzed aminolysis of styrene oxide. They reported that the use of a protic solvent, like an alcohol shifts the regiochemical outcome of the aminolysis toward the anti Markovnikov adduct. In addition, according to these authors, being a weak Lewis acid sodium cation favors nucleophilic attack on the less substituted oxirane carbon atom.[24]

Alcohol **10** was efficiently oxidized to the related ketone **11** in 90 % yield with pyridinium chlorochromate supported on alumina[25] in refluxing dichloromethane and this, in turn, was reductively aminated with aminoacetaldehyde diethyl acetal to afford secondary amine **12** in 92 % yield.

The sluggishness with which aromatic ketones undergo condensation with aliphatic primary amines and the retardatory effect on the reaction rate produced by the electron donating *para*-methoxy group of **11**, which might have resulted in the increased generation of side products,[26] were overcame by the use of an excess of the amine acetate

and cyanoborohydride-mediated *in situ* reduction of the imminium intermediate,[27] which formation was favored by the addition of calcined magnesium sulfate to the ethanolic reaction medium as a dehydrating agent.[28] The same strategy was recently reported as a key step in the synthesis of the cactus alkaloid arizonine.[29]

Finally, aqueous hydrochloric acid treatment of **12**, followed by palladized charcoal-catalyzed hydrogenation of the cyclization intermediates provided calycotomine without incidents. This final compound was characterized by comparison of its ^{1}H NMR spectrum and the melting point of its hydrochloride with published data, resulting in a complete agreement.

Similarly, the known aldehyde **13** was converted into ketone **14** in 55% overall yield, by homologation-epoxidation to yield **15**, followed by epoxide opening and pyridinium chlorochromate-mediated oxidation of the resulting benzylic alcohol **16**. Reductive amination of **14** afforded **17** in 96% yield. Contrasting with **12**, however, the amine was unable to dissolve properly in aqueous hydrochloric acid, disfavoring its direct cyclization into **7**.

Thus, a two-step process was used, where **17** was first subjected to catalytic hydrogenolysis in methanolic hydrochloric acid, allowing the selective removal of the more labile aromatic benzyl ether. This afforded **18** which, without

purification was smoothly transformed into **7** in 68% yield following the same hydrochloric acid-catalytic hydrogenation treatment employed for the obtention of **1**.

In conclusion, the use of aromatic benzyloxymethyl ketones as starting carbonyl units for the Bobbitt reaction scheme provides a suitable pathway toward 1-hydroxymethyl -substituted simple tetrahydroisoquinolines.

EXPERIMENTAL SECTION

Infrared spectra were measured with a Bruker IFS 25 FTIR spectrophotometer, melting points were determined on an Ernst Leitz hot-stage apparatus and NMR spectra were recorded on Bruker WP 80 SY or Bruker AC-200E spectrometers in $CDCl_3$, unless otherwise stated. The ^1H NMR spectra were measured either at 80.13 or at 200.15 MHz respectively, employing Me_4Si as an internal standard, chemical shifts are expressed in δ. The ^{13}C NMR spectra were determined at 20.15 or at 50.32 MHz and the chemical shift values are given in parts per million downfield from Me_4Si. ^{13}C NMR resonances corresponding to two carbon atoms are designated with "*" while those assigned to three carbons are marked with "#". High and low resolution mass spectral data were obtained from CERIDE (Santa Fe) and column chromatographies were performed with slurry-packed Silica Gel 60H, employing increasing amounts of ethyl acetate in hexane as solvent, unless otherwise noted.

(3,4-dimethoxyphenyl)oxirane (**9**): A solution of trimethyl sulfonium hydrogen sulfate (1.77 mL, 6.02 mmol) was added to a stirred, two-phase mixture of 50% NaOH (6 mL), veratraldehyde (500 mg, 3.01 mmol) and tetrabutylammonium iodide (7.5 mg) in CH_2Cl_2 (8 mL). The reaction was heated at 50°C until all the aldehyde was consumed, then it was allowed to cool to room temperature, diluted brine was added (15 mL) and the product was extracted with Et_2O (4 x 20 mL). The combined extracts were washed with brine (1 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Filtration through a short plug of basic alumina afforded **9** (535 mg, 2.98 mmol, 99%) as a solid, mp: 37.5-38°C (recryst. from hexane-Et_2O); IR ν 2937, 1609, 1520, 1465, 1396, 1273, 1236, 1140, 1027, 849 and 761 cm^{-1}; ^1H NMR δ 2.78 (dd, 1H, J= 5.3, 2.5 Hz), 3.12 (dd, 1H, J= 5.3, 4.1 Hz), 3.82 (dd, 1H, J= 4.1, 2.5 Hz), 3.88 (s, 6H), 6.76 (bs, 1H) and 6.85 (s, 2H); ^{13}C NMR δ 50.22, 51.66, 55.27*, 107.78, 110.81, 117.87, 129.57, 148.64 and 148.80.

(2-Benzyloxy-3-methoxyphenyl)oxirane (**15**): Application of the foregoing transformation to **13** (500 mg, 2.07 mmol) gave **15** (519 mg, 2.03 mmol, 98%) as an oil; IR ν 3020, 2950, 1590, 1490, 1370, 1290, 1080, 925, 795 and 710 cm^{-1}; ^1H NMR δ 2.54 (dd, 1H, J= 2.6, 5.5 Hz), 2.95 (dd, 1H, J= 4.0, 5.5 Hz), 3.90 (s, 3H), 4.09 (dd, 1H, J= 2.6, 4.0 Hz), 5.07 (s, 2H), 6.63-7.15 (m, 3H) and 7.27-7.51 (m, 5H); irradiation either at δ 2.50 or at δ 3.00 collapsed the δ 4.09 signal into a doublet and irradiation at δ 4.09 transformed the δ 2.54 and δ 2.95 resonances into two doublets; ^{13}C NMR δ 47.98, 50.14, 55.56, 74.93, 111.78, 116.32, 124.13, 127.80, 128.07*, 128.21*, 131.84, 137.30, 146.43 and 152.22; mass spectrum, m/e (relative intensity) 256 (M^+, 6), 227 (3), 165 (4), 137 (4), 91 (100) and 65 (8); found for M^+ m/e 256.10972 ($C_{16}H_{16}O_3$ requires m/e 256.10993).

1-(3,4-Dimethoxyphenyl)-2-(Benzyloxy)ethanol (**10**): A warm solution of sodium benzyloxide in benzyl alcohol (0.114 mL, 0.33 mmol) was added to **9** (120 mg, 0.66 mmol) dissolved in benzyl alcohol (1.2 mL). The mixture was heated

at 100°C overnight, then it was allowed to cool, 10% sodium citrate was added (10 mL) and the reaction products were extracted with Et_2O (4 x 20 mL). The extracts were washed with brine (10 mL), dried (Na_2SO_4), concentrated under reduced pressure and carefully chromatographed, yielding **10** (116 mg, 0.40 mmol, 61%); IR ν 3488, 3001, 2934, 1607, 1518, 1453, 1265, 1139, 1028, 740 and 699 cm^{-1}; ^1H NMR δ 2.74 (bs, 1H, $w_{1/2}$= 12 Hz), 3.53 (dd, 1H, J= 8.2, 9.7 Hz), 3.61 (dd, 1H, J= 4.2, 9.7 Hz), 3.86 (s, 3H), 3.87 (s, 3H), 4.60 (s, 2H), 4.87 (dd, 1H, J= 4.2, 8.2 Hz), 6.85-6.95 (m, 3H) and 7.33 (s, 5H); ^{13}C NMR δ 55.32*, 72.01, 72.75, 75.36, 109.16, 110.70, 118.03, 127.23#, 127.86*, 132.91, 137.43, 148.11 and 148.54; mass spectrum, m/e (relative intensity) 288 (M^+, 13), 167 (100), 139 (27), 124 (6), 108 (5) and 91 (24); found for M^+ m/e 288.13615 ($C_{17}H_{20}O_4$ requires m/e 288.13615).

1-(2-Benzyloxy-3-methoxyphenyl)-2-(Benzyloxy)ethanol (**16**): The foregoing experiment was repeated using **15** (1200 mg, 4.69 mmol) to give **16** (1125 mg, 3.09 mmol, 66%); IR ν 3450, 3040, 2940, 2860, 1595, 1485, 1290, 1095, 1065, 765 and 710 cm^{-1}; ^1H NMR δ 2.75 (bs, 1H, $w_{1/2}$= 6 Hz), 3.48 (dd, 1H, J= 8.0, 9.6 Hz), 3.56 (dd, 1H, J= 4.0, 9.6 Hz), 3.87 (s, 3H), 4.48 (s, 2H), 4.93 and 5.12 (ABq, 2H, J= 11.2 Hz), 5.20 (dd, 1H, J= 4.0, 8.0 Hz), 6.80-7.11 (m, 3H), 7.27 (s, 5H) and 7.35-7.47 (m, 5H); ^{13}C NMR δ 55.64, 67.87, 72.87, 74.50, 74.72, 111.62, 118.74, 124.13, 127.52*, 127.56, 127.62, 127.85, 128.01, 128.23*, 128.28*, 134.07, 137.51, 137.84, 144.70 and 152.19.

(Benzyloxy)methyl-3,4-dimethoxyphenyl ketone (**11**): Alcohol **10** (100 mg, 0.347 mmol) was dissolved in dry CH_2Cl_2 (4 mL) to which anhydrous sodium acetate (57 mg, 0.694 mmol) and PCC supported on alumina (857 mg, 2 equiv.) were added portionwise. The reaction mixture was stirred under reflux until all the starting material disappeared; then the suspension was poured over Celite contained in a Büchner funnel, filtered under vacuum and the solids repeatedly washed with CH_2Cl_2. Concentration and chromatography of the combined filtrates gave **11** (90 mg, 0.31 mmol, 90%) as a solid, mp: 67-69 °C (recryst. from Et_2O); IR ν 3005, 2935,

1685, 1517, 1419, 1267, 1169, 1124, 1023, 764 and 699 cm^{-1}; ^1H NMR δ 3.91 (s, 3H), 3.93 (s, 3H), 4.68 (s, 2H), 4.71 (s, 2H), 6.80-7.62 (m, 3H) and 7.35 (s, 5H); ^{13}C NMR δ 55.86*, 72.44, 73.18, 110.01, 110.22, 122.50, 127.86#, 128.08, 128.29*, 137.27, 149.07, 153.53 and 194.77.

(Benzyloxy)methyl-(2-Benzyloxy-3-methoxy)phenyl ketone (**14**): Repetition of the foregoing procedure with **11** (975 mg, 2.68 mmol) afforded **14** (826 mg, 2.28 mmol, 85%); IR ν 3040, 2980, 1700, 1590, 1485, 1325, 1280, 1145, 1015, 800, 760 and 710 cm^{-1}; ^1H NMR δ 3.88 (s, 3H), 4.51 (s, 2H), 4.59 (s, 2H), 5.05 (s, 2H), 6.94-7.22 (m, 3H) 7.28 (s, 5H) and 7.33 (s, 5H); ^{13}C NMR δ 55.96, 73.02, 75.68*, 116.17, 120.90, 124.20, 127.60, 127.81*, 128.04, 128.24#, 128.29#, 131.69, 136.63, 137.54, 147.16, 152.68 and 198.65; mass spectrum, m/e (relative intensity) 362 (M^+, 1), 271 (4), 256 (4), 241 (10), 213 (2), 181 (5), 164 (5), 151 (8), 123 (2), 91 (100) and 65 (7); found for M^+ m/e 362.15109 ($C_{23}H_{22}O_4$ requires m/e 362.15179).

4-(1-(N-(2,2-diethoxyethyl)amino)-2-(benzyloxy)ethyl)-1,2-dimethoxybenzene (**12**): Ketone **11** (30 mg, 0.11 mmol), aminoacetaldehyde diethyl acetal (0.072 mL, 0.52 mmol) and glacial acetic acid (0.027 mL, 0.47 mmol) were mixed in absolute EtOH (1 mL). Calcined magnesium sulfate (50 mg) and sodium cyanoborohydride (6.4 mg, 0.105 mmol) were added to the above solution and the mixture was stirred under reflux until the starting material was consumed. The reaction was quenched with 1 N NaOH (1 mL), brine was added (10 mL) and the reaction product was extracted with EtOAc (4 x 20 mL). The organic extract was washed with brine (10 mL), dried (Na_2SO_4), concentrated and chromatographed, affording **12** (40 mg, 0.1 mmol, 95%) as a colorless oil; IR ν 3030, 2974, 2860, 1606, 1517, 1464, 1357, 1235, 1137, 1030, 956, 809, 738 and 699 cm^{-1}; ^1H NMR δ 1.17 (t, 3H, J= 9.4 Hz), 1.20 (t, 3H, J= 9.4 Hz), 2.39 (bs, 1H, $w_{1/2}$= 8 Hz), 2.60 (d, 2H, J= 5.3 Hz), 3.40-3.80 (m, 6H), 3.86 (s, 6H), 3.87 (t, 1H, J= 4.0 Hz), 4.53 (s, 2H), 4.59 (t, 1H, J= 5.3 Hz), 6.84-6.97 (m, 3H) and 7.31 (s, 5H); ^{13}C NMR δ 15.15*, 49.53, 55.75*, 61.70, 61.91, 62.29,

72.97, 75.41, 101.93, 110.38, 111.02, 119.84, 127.44#, 128.13*, 133.18, 138.07, 148.27 and 149.02; mass spectrum, m/e (relative intensity) 403 (M^+, 0), 358 (M^+ - CH_3CH_2O, 1), 302 (2), 282 (57), 283 (9), 236 (37), 190 (5), 178 (5), 164 (6), 151 (10), 103 (16), 91 (100) and 75 (13); found for M^+ m/e 358.20195 ($C_{21}H_{28}O_4N$ requires m/e 358.20182).

1-(1-(N-(2,2-diethoxyethyl)amino)-2-(benzyloxy)ethyl)-3-methoxy-2-(benzyloxy)benzene (**17**): The foregoing procedure was applied to **15** (773 mg, 2.14 mmol), yielding **17** (980 mg, 2.05 mmol, 96%); IR ν 3000, 2960, 1600, 1505, 1395, 1305, 1285, 1080, 770 and 715 cm^{-1}; ^1H NMR δ 1.14 (t, 3H, J= 7.2 Hz), 1.17 (t, 3H, J= 7.2 Hz), 2.02 (bs, 1H, $w_{1/2}$= 4 Hz), 2.51 (d, 1H, J= 5.6 Hz), 3.23-3.80 (m, 6H), 3.87 (s, 3H), 4.36 (t, 1H, J= 4.8 Hz), 4.44 (s, 2H), 4.55 (t, 1H, J= 5.6 Hz), 5.00 (s, 2H), 6.77-7.12 (m, 3H), 7.26 (s, 5H) and 7.34-7.50 (m, 5H); irradiation at δ 3.50 transformed the δ 1.14, δ 1.17 and δ 4.36 resonances into singlets, while irradiation at δ 4.55 collapsed the δ 2.51 signal into a singlet; ^{13}C NMR δ 15.09*, 49.64, 55.54, 61.65, 61.86, 72.49, 74.14, 74.56, 101.93, 118.97, 119.57, 123.88, 127.23#, 127.60*, 127.97#, 128.08#, 134.35, 137.64, 138.23, 145.99 and 152.36.

1-Hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (calycotomine,**1**): An Et_2O-MeOH solution containing the amine **12** (49 mg, 0.122 mmol) was added to a stirred, cold 4N HCl solution (3 mL); after 30 min at 0°C, the organic solvent was removed under reduced pressure and the mixture was stirred overnight at room temperature. Then, 10% Pd/C (50 mg) was added and stirring was continued for 24 h at room temperature under atmospheric pressure of hydrogen. The catalyst was separated by centrifugation and thoroughly washed with water (3 x 2 mL). The combined aqueous phases were carefully concentrated *in vacuo* and the residue was chromatographed (CH_2Cl_2-EtOH) to give **1** (20 mg, 0.09 mmol, 74%); mp of the hydrochloride: 194-196°C (recryst. from MeOH-benzene, lit: 194-195°C[14,15] and 196-198°C[19]); IR ν 3483, 3403, 3342, 2920, 2832, 1616, 1523, 1470, 1384, 1266, 1124, 1060, 993, 858 and 627 cm^{-1}; ^1H

NMR (200 MHz, D_2O) δ 2.85-2.85 (m, 2H), 3.17-3.31 (m, 1H), 3.35-3.50 (m, 1H), 3.74 (s, 6H), 3.76 (dd, 1H, J= 8.0, 12.5 Hz), 4.00 (dd, 1H, J= 3.0, 12.5 Hz), 4.36 (dd, 1H, J= 3.0, 8.0 Hz), 6.77 (s, 1H) and 6.78 (s, 1H); ^{13}C NMR (50 MHz, D_2O) δ 26.10, 39.89, 56.83, 56.96, 57.13, 62.91, 110.51, 113.15, 122.61, 126.84, 148.29 and 149.07.

6-(1-(N-(2,2-dimethoxyethyl)amino)-2-(benzyloxy)ethyl) -2-methoxyphenol (**18**): 10% Pd/C (31 mg) was added to a solution of **17** (300 mg, 0.63 mmol) in hydrochloric (0.626 mmol) MeOH (5 mL) and the reaction was stirred overnight under hydrogen; the catalyst was removed by centrifugation, washed with MeOH (2 x 2 mL) and the methanolic solution was concentrated *in vacuo* giving **18** (242 mg, 0.62 mmol, 99%); IR ν 3328, 3031, 2929, 2864, 1588, 1475, 1373, 1254, 1116, 1069, 989, 833. 737 and 699 cm^{-1}; ^1H NMR (200 MHz) δ 1.15 (t, 6H, J= 6.8 Hz), 1.21 (t, 6H, J= 6.8 Hz), 2.72 (d, 2H, J= 5.0 Hz), 3.35-3.80 (m, 6H), 3.85 (s, 3H), 3.96-4.13 (m, 1H), 4.55 (s, 2H), 4.65 (t, 1H, J= 5.0 Hz), 6.48-6.82 (m, 3H) and 7.32 (s, 5H); ^{13}C NMR (50 MHz) δ 15.16, 15.20, 49.22, 55.63, 62.26, 62.66, 63.06, 71.84, 72.98, 101.12, 110.77, 118.55, 120.80, 121.12, 127.54*, 127.69, 128.30*, 137.56, 147.42 and 148.02.

8-Hydroxy-1-hydroxymethyl-7-methoxy-1,2,3,4-tetrahy droisoquinoline (**7**): HCl treatment of **18** followed by catalytic hydrogenation, as with **12**, afforded **7** (89 mg, 0.42 mmol, 69%); mp of the salicylate: 217°C, dec. (recryst. from EtOH-Et_2O); IR ν 3403, 2959, 2842, 1636, 1624, 1501, 1384, 1284, 1102, 1039 and 804 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 2.96-3.11 (m, 2H), 3.42-3.60 (m, 2H), 3.83 (dd, 1H, J= 8.8, 12.8 Hz), 3.87 (s, 3H), 4.18 (dd, 1H, J= 4.0, 12.8 Hz), 4.65 (dd, 1H, J= 4.0, 8.8 Hz), 6.81 and 7.05 (ABq, 2H, J= 8 Hz); ^{13}C NMR (50 MHz, D_2O) δ 23.63, 36.57, 52.43, 55.86, 58.30, 112.10, 115.42, 119.50, 124.66, 142.26 and 145.44; mass spectrum, m/e (relative intensity) 209 (M^+, 0), 208 (M^+ - H, 0.2), 178 (100), 163 (25), 150 (18), 135 (7), 91 (7) and 77 (4); found for M^+ m/e 208.09717 ($C_{11}H_{14}O_3N$ requires m/e 208.09735).

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