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SYNTHESIS OF CALYCOTOMINE AND *N*-METHYLCALYCOTOMINE USING A PETASIS REACTION — POMERANZ-FRITSCH-BOBBITT CYCLIZATION SEQUENCE

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Abstract – The use of aminoacetaldehyde acetals as the amine components in the one-step, three-component Petasis reaction followed by the Pomeranz-Fritsch-Bobbitt cyclization has been shown to be a convenient and simple method for the synthesis of tetrahydroisoquinoline alkaloids. Using this method two alkaloids, calycotomine and *N*-methylcalycotomine hydrochlorides, have been prepared in 61% overall yield.

INTRODUCTION

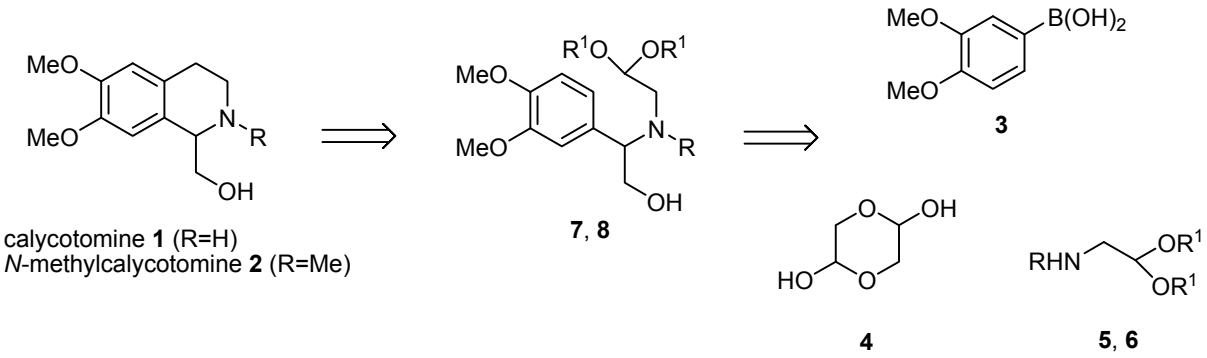
Recently, we have reported[1] a novel approach to the synthesis of tetrahydroisoquinoline-1-carboxylic acids based on a sequence of two reactions: the Petasis synthesis of α-amino acids[2] and the Pomeranz-Fritsch-Bobbitt synthesis of tetrahydroisoquinoline derivatives.[3] In our method, the Petasis three-component reaction (boronic acid, carbonyl derivative and amine), was modified by the use of aminoacetaldehyde acetals as the amine components, thus preparing key intermediates for the Pomeranz-Fritsch-Bobbitt cyclization in one single operation.

RESULTS AND DISCUSSION

Herein, we present results of experiments undertaken to adapt this approach to the synthesis of two isoquinoline alkaloids, calycotomine **1** and *N*-methylcalycotomine **2**, in which glycolaldehyde was used as the carbonyl component.

A retrosynthetic analysis of the planned synthesis is shown in Scheme 1.

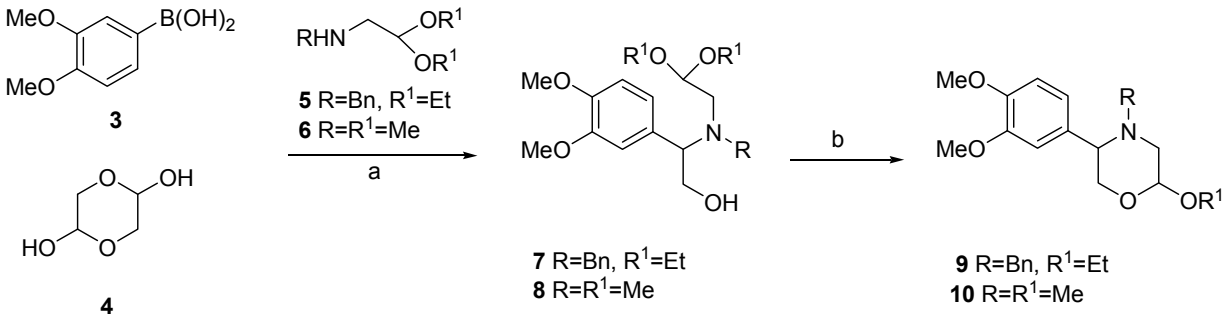
This paper is dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday.



Scheme 1

As illustrated in Scheme 1, the planned two-step synthesis involves a reaction between 3,4-dimethoxyphenylboronic acid **3**, glycolaldehyde dimer **4** and *N*-substituted aminoacetaldehyde acetals **5** and **6** to give the Petasis reaction products **7** and **8**, respectively. In the next step the latter ones are subjected to the Pomeranz-Fritsch-Bobbitt cyclization, leading to the final products, **1** and **2**.

The synthesis of calycotomine **1** started with the preparation of the Petasis addition product **7** (Scheme 2). A reaction of boronic acid **3**, glycolaldehyde dimer **4** and *N*-benzylaminoacetaldehyde diethyl acetal **5** in dichloromethane (DCM)/H_2O (3:2) at room temperature afforded hydroxy aminoacetal **7**, in 92% yield, as an oil. It was pure enough to be used in the next step of the synthesis without further purification since chromatographic purification caused partial decomposition and thus substantial reduction in the yield. The same situation was experienced with all others intermediates prepared in the course of the synthesis of **1** and **2**, which were oily compounds. Fortunately, they were pure enough to be used in the syntheses as crude products.



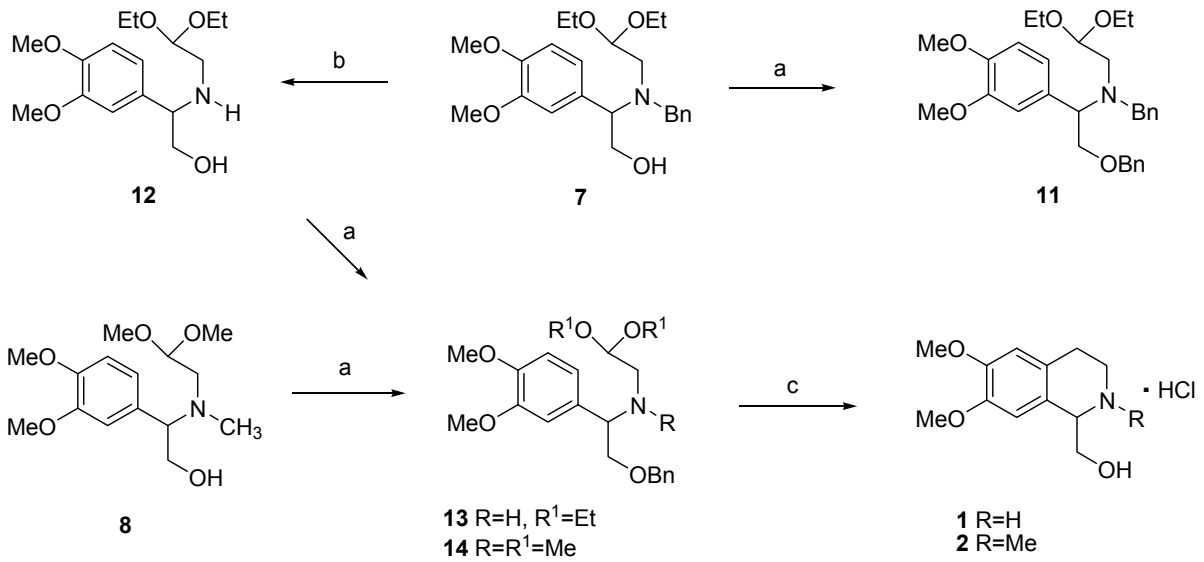
Reagents and conditions: (a) DCM/H_2O (3:2), rt, 72 h (92% for **7**, 81% for **8**); (b) 20% HCl, rt, 48 h (92% for **9**, 84% for **10**).

Scheme 2

Construction of the tetrahydroisoquinoline ring system via the acid-promoted Pomeranz-Fritsch-Bobbitt cyclization is usually carried out in various acids and various concentrations.[3b] When hydroxy

aminoacetal **7** was treated with 20% HCl for 48 h at room temperature (rt), that means, in the reaction conditions applied in our earlier experiments,[1] *N*-benzyl-2-ethoxy-5-(3,4-dimethoxyphenyl)morpholine **9** was produced in high yield as a mixture of diastereoisomers (66:34, HPLC), instead of the expected tetrahydroisoquinoline alkaloid (Scheme 2).

Obviously, the attack of a hydroxyl group on the liberating aldehyde became a competing process to the electrophilic aromatic substitution. To avoid this complication, *O*-benzyl protection of the hydroxyl group in **7** was introduced, by applying the very efficient KH(P)/THF/BnBr reagents system, recently developed by Taber *et al.*[4] (Scheme 3). *N*,*O*-Dibenzyl derivative **11**, obtained in quantitative yield, was then treated with 20% hydrochloric acid at rt for 72 h. However, instead of the expected tetrahydroisoquinoline derivative a complex mixture of products was formed, among which, the starting aminoacetal **11** (*ca* 25%) and morpholine **9** (*ca* 21%) were found (HPLC). Still more complicated mixture was produced when the 12N HCl/THF (1:1) at reflux was tested. On the other hand, when 4N hydrochloric acid was used, no progress of the reaction was observed, even after 48 h at rt.



Reagents and conditions: (a) KH(P)/THF, BnBr, 0 °C - rt (100% for **11**, 96% for **13**, 81% for **14**); (b) H_2/$Pd(OH)_2$, EtOH, 24 h (97% for **12**); (c) 12N HCl/THF (1:1), 30 min; H_2, 10% Pd/C (85% for **1**·**HCl**, 94% for **2**·**HCl**).

Scheme 3

Since the two-step synthesis of calycotomine **1** was unsuccessful, another route toward **1** was planned. It relied on the use of *O*-benzyl aminoacetal **13**, chosen as the key intermediate (Scheme 3). This compound was earlier prepared by Kaufman[5] in a four-step synthesis from veratraldehyde and was used with success in the synthesis of calycotomine **1** by the Pomeranz-Fritsch-Bobbitt methodology.

Initial attempts to prepare compound **13** directly by the Petasis reaction using *N*-unsubstituted aminoacetaldehyde acetal failed, a case met sometimes in this reaction with primary amines.[2a] *O*-Benzyl aminoacetal **13** was then easily prepared in two steps from *N*-benzyl derivative **7**, via *N*-debenzylation (H_2/$Pd(OH)_2$/EtOH) to give **12** in 97% yield, followed by *O*-benzylation [KH(P)/THF/BnBr], affording **13** in 96% yield (81% after chromatographic purification). Subjecting compound **13** to the cyclization/hydrogenolysis procedure described by Kaufman[5] (*1*. 4N HCl, overnight, *2*. 10% Pd/C, H_2, 1 atm) we were surprised to find *N*-debenzylated morpholine **9** as the only product, with no traces of calycotomine **1**.

To approach this problem, several experiments were carried out to find cyclization milieu in which hydrolysis of the *O*-benzyl protection would be prevented. Finally, 12N HCl/THF (1:1) hydrolysis system[6] turned out to be the best choice. Thus, when *O*-benzyl aminoacetal **13** was treated with 12N HCl/THF (1:1) at reflux for 30 min, and then hydrogenated in the presence of 10% palladium on carbon, calycotomine hydrochloride **1•HCl** was produced in 61% overall yield of four steps. Mp 196–198 ºC (lit.[5]: 194–196 ºC, lit.[7]: 196–198 ºC).

It should be mentioned that there are many synthetic methodologies proposed for the synthesis of calycotomine **1**. They were comprehensively reviewed by Kaufman[8] in 2005. Since that time several novel strategies have been developed,[9] some were realized in racemic,[9a,b] same others in the asymmetric[9c-e] version.

In a parallel series of experiments *N*-methylcalycotomine hydrochloride **2•HCl** was prepared in a three-step synthesis in 61% overall yield. It started with the 3,4-dimethoxyphenylboronic acid **3**/ glyceraldehyde dimer **4**/ *N*-methylaminoacetaldehyde dimethyl acetal **6** coupling to give the Petasis product **8** in 92% yield. It was then *O*-benzylated [KH(P)/THF/BnBr] to the *O*-benzyl derivative **14** in 81% yield. Cyclization/hydrogenolysis carried in the 12N HCl/THF (1:1)/ H_2, Pd(C) reagents system afforded crystalline *N*-methylcalycotomine hydrochloride **2•HCl**; mp 219–221 ºC (from ethanol).

In comparison with the great interest in the syntheses of calycotomine **1**, not much attention has been paid to the synthesis of its *N*-methyl analogue **2**. To our knowledge, only three syntheses of *N*-methylcalycotomine **2** in optically active form have been reported. They were based either on reductive *N*-methylation of (+)-calycotomine **1**,[10] or on a diastereoselective Pictet-Spengler cyclization.[11,12]

It should be added, that hydrolysis of *O*-unprotected derivative **8** in 12N HCl/THF (1:1) solution afforded *N*-methyl-2-methoxy-5-(3,4-dimethoxyphenyl)morpholine **10** in 84% yield, as a mixture of diastereoisomers (58:42, ^{1}H NMR), in a similar way to the formation of **9** from **7**.

In conclusion, a short and efficient method for the synthesis of isoquinoline alkaloids, calycotomine **1** and *N*-methylcalycotomine **2**, has been developed. It was based on a combination of two reactions: the Petasis synthesis of aminoalcohols, in which aminoacetaldehyde acetals were used as the amine components, and

the Pomeranz-Fritsch-Bobbitt cyclization to tetrahydroisoquinoline ring system. This approach offers a possibility for a new synthesis of other types of isoquinoline alkaloids, by a short and simple procedure, which in comparison with the two-step synthesis of tetrahydroisoquinoline-1-carboxylic acids[1] needed additional steps: *N*-benzylation/debenzylation and *O*-protection.

EXPERIMENTAL

Melting points were determined on a Koffler block and are uncorrected. NMR spectra: Varian Gemini 300, with TMS as the internal standard. Mass spectra: AM D402. Merck DC-Alufolien Kieselgel 60_{254} were used for TLC and Kieselgel 60 (70-230 mesh ASTM) for column chromatography. Analytical HPLC: Waters HPLC system with Daicel Chiralcel OD-H column; hexane/propan-2-ol (9:1), flow 0.5 mL/min. All compounds were purchased from Aldrich Chemical Co. and used as received.

***N*-Benzyl-*N*-(2,2-diethoxyethyl)-2-(3,4-dimethoxyphenyl)glycinol** (**7**). In a round-bottom flask 3,4-dimethoxyphenylboronic acid (**3**) (1.82 g, 10 mmol) and glycolaldehyde dimer (**4**) (0.60 g, 5 mmol) in DCM/H_2O (3:2, 15 mL) two-phase system were stirred for 10 min under the argon atmosphere before *N*-benzylaminoacetaldehyde diethyl acetal (**5**) (2.20 g, 10 mmol) was added. The mixture was then stirred at ambient temperature for 72 h (TLC) and after this time phases were separated and the aqueous one was extracted with DCM until Dragendorff test was negative. The combined organic extracts were washed with 15% sodium hydroxide, dried and the solvent was removed under reduced pressure. The oily product **7** (3.71 g, 92%) could be used for the next step of the synthesis without purification. An analytical sample was prepared by chromatographic purification over silicagel (1:10) using hexane/EtOAc (8:1) as eluents; ^{1}H NMR ($CDCl_3$) δ 1.78 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 2.45 (dd, *J* = 3.5, 14.0 Hz, 1H), 3.06 (dd, *J* = 7.2, 14.0 Hz, 1H), 3.38–3.84 (m, 6H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90–4.03 (m, 3H), 4.19 (dd, *J* = 3.5, 7.2 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.3, 52.3, 55.7, 55.8, 57.3, 61.5, 62.8, 63.4, 65.4, 102.3, 110.8, 111.9, 120.4, 127.2, 128.4, 128.5, 128.7, 129.5, 139.6, 148.4, 148.6; EI MS *m/z* 404 (M^++1, 0.6), 372 (80), 300 (21), 181 (100), 149 (12), 91 (22); HR-MS Calcd for $C_{23}H_{34}NO_5$: (M+1), 404.24371. Found: *m/z* 404.24097.

***N*-(2,2-Dimethoxyethyl)-*N*-methyl-2-(3,4-dimethoxyphenyl)glycinol** (**8**). Following the above procedure compound **8** was prepared from 3,4-dimethoxyphenylboronic acid (**3**), glycolaldehyde dimer (**4**) and *N*-methylacetaldehyde dimethyl acetal (**6**) in a 5 mmol scale in 81% yield. The TLC-pure oily product **8** was used for the next step of the synthesis without purification. An analytical sample was prepared by chromatographic separation over silicagel (1:10) using hexane/EtOAc (9:1) for elution; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.43 (dd, *J* = 4.5, 13.7 Hz, 1H), 2.76 (dd, *J* = 6.1, 13.7 Hz, 1H), 3.39 (s, 3H), 3.41 (s, 3H), 3.64 (dd, *J* = 5.0, 10.9 Hz, 1H), 3.74 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H),

3.86–3.96 (m, 1H), 4.47 (dd, *J* = 4.5, 6.1 Hz, 1H), 6.72–6.76 (m, 2H), 6.84 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.3, 53.7, 54.1, 54.4, 55.7, 55.8, 61.1, 68.9, 103.1, 110.7, 111.8, 120.6, 128.6, 148.5, 148.6; EI MS *m/z* 300 (M^++1, 0.3), 268 (49), 182 (12), 181 (100), 148 (16), 121 (11); HR-MS Calcd for $C_{15}H_{26}NO_5$: (M+1), 300.18365. Found: *m/z* 300.18109.

***N*-(2,2-Diethoxyethyl)-2-(3,4-dimethoxyphenyl)glycinol** (**12**). A solution of *N*-benzyl derivative **7** (1.38 g, 3.42 mmol) in 99% EtOH (38 mL) was hydrogenated with hydrogen from balloon in the presence of $Pd(OH)_2$ (0.68 g) for 24 h at rt. The catalyst was then removed by filtration and washed with 99% EtOH. The solvent was removed under reduced pressure to deposit pure oily amino alcohol **12** (1.03 g, 97%); ^{1}H NMR ($CDCl_3$) δ 1.17–1.25 (m, 6H), 2.65 (dd, *J* = 5.5, 12.1 Hz, 2H; + 2H, which disappear on treatment with D_2O), 3.46–3.74 (m, 7H), 3.87 (s, 3H), 3.88 (s, 3H), 4.58 (t, *J* = 5.5 Hz, 1H), 6.83 (s, 1H), 6.84 (s, 1H), 6.87 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2, 49.4, 55.7, 55.8, 61.8, 62.2, 64.2, 66.7, 101.9, 109.9, 110.9, 119.4, 132.9, 148.2, 149.0; EI MS *m/z* 314 (M^++1, 8), 283 (21), 282 (100), 237 (15), 236 (78), 222 (19), 207 (10), 190 (24), 182 (12), 181 (89), 176 (12), 164 (11), 150 (20), 149 (22), 138 (11), 121 (17), 103 (49), 75 (44); HR-MS Calcd for $C_{16}H_{28}NO_5$: (M+1), 314.19675. Found: *m/z* 314.19565.

***O*-Benzyl-*N*-(2,2-diethoxyethyl)-2-(3,4-dimethoxyphenyl)glycinol** (**13**). To a solution of aminoalcohol **12** (1.00 g, 3.2 mmol) in THF (18 mL) potassium hydride, 50 wt. % in paraffin, (0.51 g, 6.4 mmol) was slowly added with stirring at 0 ºC. After potassium hydride was consumed, benzyl bromide (1.10 g, 6.4 mmol) was introduced dropwise at 0 ºC and stirring was continued for 5 h at rt. Then 20% ammonium chloride (10 mL) was added and the aqueous phase was extracted with Et_2O until Dragendorff test was negative. The basic product was then taken into 10% hydrochloric acid and the acidic solution was basified with 20% sodium hydroxide and reextracted with Et_2O to afford oily *O*-benzyl derivative **13** (1.24 g, 96%), which was purified by column chromatography (silicagel, 1:10, hexane/EtOAc 9:1) to give 1.05 g (81%) of pure **13**; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.22 (s, br., 1H, disappears on treatment with D_2O), 2.55–2.63 (m, 2H), 3.46–3.72 (m, 6H), 3.86 (s, 3H), 3.89 (m, 4H), 4.53 (dd, *J* = 12.0, 14.9 Hz, 2H), 4.58 (dd, *J* = 5.0, 6.0 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.88 (dd, *J* = 1.9, 8.4 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 7.27–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.3, 49.6, 55.7, 55.8, 61.8, 62.1, 62.4, 73.0, 75.5, 101.9, 110.1, 110.8, 119.9, 127.5, 127.6, 128.3, 133.1, 138.1, 148.2, 148.9; EI MS *m/z* 404 (M^++1, 3), 283 (17), 282 (100), 237 (12), 236 (78), 190 (16), 103 (13), 91 (77), 75 (12); HR-MS Calcd for $C_{23}H_{34}NO_5$: (M+1), 404.24371. Found: *m/z* 404.24255.

***N*,*O*-Dibenzyl-*N*-(2,2-diethoxyethyl)-2-(3,4-dimethoxyphenyl)glycinol** (**11**). According to the above procedure *N*,*O*-dibenzyl derivative **11** was prepared in 83% yield as a TLC-pure oil from **7** (0.50 g, 1.2 mmol), potassium hydride, 50 wt. % in paraffin (0.19 g, 2.4 mmol) and benzyl bromide (0.41 g, 2.4 mmol) in THF (7 mL). Analytical sample was prepared by chromatographic purification (silicagel 1:10, hexane/EtOAc 19:1); ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 2.64 (dd, *J* =

5.0, 14.0 Hz, 1H), 2.83 (dd, *J* = 5.3, 14.1 Hz, 1H), 3.32–3.59 (m, 4H), 3.70 (d, *J* = 14.0 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.82–3.96 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.08 (t, *J* = 6.4 Hz, 1H), 4.37 (t, *J* = 5.3 Hz, 1H), 4.52 (dd, *J* = 2.7, 12.2 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.87 (dd, *J* = 1.8, 8.3 Hz, 1H), 6.91 (d, *J* = 1.9 Hz, 1H), 7.21–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.3, 53.5, 55.7, 55.8, 56.0, 61.9, 62.4, 62.6, 70.4, 73.0, 103.1, 110.5, 112.2, 120.3, 126.7, 127.4, 127.5, 128.0, 128.2, 128.7, 132.3, 138.3, 140.6, 147.9, 148.5; EI MS *m/z* 493 (M^+, 0.4), 373 (15), 372 (60), 271 (17), 253 (14), 165 (10), 91 (100); HR-MS Calcd for $C_{30}H_{39}NO_5$: M, 493.28284. Found: *m/z* 493.27968.

***O*-Benzyl-*N*-(2,2-dimethoxyethyl)-*N*-methyl-2-(3,4-dimethoxyphenyl)glycinol** (**14**). Following the above procedure *O*-benzyl derivative **14** was prepared in 81% yield in reaction between hydroxy acetal **8** (1.50 g, 5 mmol), potassium hydride, 50 wt. % in paraffin (0.80 g, 10 mmol) and benzyl bromide (1.70 g, 10 mmol) in THF (30 mL). The crude, oily product was purified by column chromatography (silicagel 1:10, hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.51 (dd, *J* = 5.2, 13.5 Hz, 1H), 2.67 (dd, *J* = 5.4, 13.5 Hz, 1H), 3.28 (s, 3H), 3.30 (s, 3H), 3.70–3.74 (m, 2H), 3.82–3.87 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.45 (t, *J* = 5.2 Hz, 1H), 4.51 (dd, *J* = 6.7, 12.2 Hz, 2H), 6.79–6.84 (m, 2H), 6.88 (s, br, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 40.3, 53.1, 53.4, 55.7, 56.0, 67.9, 71.5, 73.1, 103.3, 110.5, 111.6, 120.5, 127.5, 127.6, 128.2, 132.2, 138.1, 148.0, 148.6; EI MS *m/z* 389 (M^+, 0.6), 271 (11), 269 (15), 268 (94), 253 (10), 181 (26), 150 (10), 91 (100); HR-MS Calcd for $C_{22}H_{31}NO_5$: M, 389.22021. Found: *m/z* 389.21978.

***N*-Benzyl-2-ethoxy-5-(3,4-dimethoxyphenyl)morpholine** (**9**). Aminoacetal **7** (0.20 g, 0.5 mmol) was dissolved in 4N HCl (5 mL) and kept at rt for 24 h. After this time, the solution was basified with 5% NaOH and extracted with Et_2O until Dragendorff test was negative. The combined ethereal extracts were dried and the solvent evaporated under reduced pressure to give 0.11g (92%), TLC-pure **9** as a 66:34 mixture of diastereoisomers [HPLC, t_R 12.9 min (66%), 15.8 min (34%)]. An analytical sample was prepared by column chromatography purification using silicagel (1:10) and hexane/EtOAc (19:1); major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.07 (t, *J* = 10.0 Hz, 1H), 2.90–2.98 (m, 2H), 3.30–3.58 (m, 3H), 3.72–3.84 (m, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 3.85–3.96 (m, 1H), 4.63 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.96–7.10 (m, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 55.6, 55.8 (2C), 58.8, 62.8, 64.4, 65.8, 95.7, 110.6, 111.1 (2C), 120.6 (2C), 127.0, 128.1, 128.8, 131.3, 138.0, 149.0, 149.14; minor diastereoisomer (characteristic signals): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.39 (dd, *J* = 2.9, 11.9 Hz, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 3.87 (s, 3H), 3.91 (s, 3H), 4.77 (d, *J* = 1.9 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 54.6, 55.8, 55.9, 58.7, 65.6, 65.7, 70.9, 99.3, 110.8, 111.0 (2C), 120.6 (2C), 126.8, 128.0, 128.9, 131.9, 137.4, 148.4, 148.5; EI MS *m/z* (%) 357 (M^+, 34), 328 (5), 312 (9), 266 (26), 255 (68), 164 (100), 91 (82); HR-MS Calcd for $C_{21}H_{27}NO_4$: M, 357.19400. Found: *m/z* 357.19414.

Similar results as to the yield (87%) and diastereomeric composition (66:34) of compound **9** were obtained when aminoacetal **7** was hydrolyzed in 12N HCl/THF (1:1) at reflux for 15 min.

***N*-Methyl-2-methoxy-5-(3,4-dimethoxyphenyl)morpholine** (**10**). Following the above procedure morpholine **10** was prepared in 84% yield by refluxing hydroxyacetal **8** (0.60 g, 2 mmol) in a mixture of THF (10 mL) and 12N HCl (10 mL) for 20 min. The oily product was a 58:42 mixture of diastereoisomers. An analytical sample was prepared by column chromatography purification using silicagel (1:20) and hexane/EtOAc (9:1); major diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.13-2.19 (m, 1H), 2.98–3.05 (m, 2H), 3.48–3.54 (m, 1H), 3.54 (s, 3H), 3.78–3.97 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.61 (d, *J* = 6.9 Hz, 1H), 6.81–6.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 43.2, 55.0, 55.8, 55.9, 59.0, 67.6, 70.6, 100.2, 110.4, 110.9, 120.5, 131.3, 148.6, 149.1; minor diasteroisomer: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.45 (d, *J* = 11.4 Hz, 1H), 3.02–3.08 (m, 2H), 3.42–3.45 (m, 1H), 3.45 (s, 3H), 3.82–3.88 (m, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 4.72 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.89 (dd, *J* = 1.8, 8.2 Hz, 1H), 6.92 (s, 1H);^{13}C NMR ($CDCl_3$) δ 43.6, 55.0, 55.8, 56.1, 58.5, 65.2, 68.7, 96.9, 110.5, 110.8, 120.6, 131.2, 148.6, 149.1; EI MS *m/z* (%) 267 (M^+, 34), 237 (11), 179 (100), 164 (91), 148 (19), 133 (12), 91 (11); HR-MS Calcd for $C_{14}H_{21}NO_4$: M, 267.14706. Found: *m/z* 267.14687.

Calycotomine hydrochloride 1•HCl. Compound **13** (0.10 g, 0.25 mmol) dissolved in a mixture of THF (1.4 mL) and 12N HCl (1.4 mL) was heated at reflux for 30 min. Water (1.4 mL) was then added and THF was distilled off under reduced pressure. To this solution 10% palladium on carbon (0.10 g) was added at rt and it was hydrogenated with hydrogen from a baloon for 72 h. The catalyst was removed by filtration, washed with water (1.4 mL) and the filtrate was concentrated to give TLC-pure calycotomine hydrochloride **1•HCl** (66 mg, 85%); mp 196–198 ºC (lit.,[5] 194–196 ºC, lit.,[7] 196–198 ºC); ^{1}H NMR (D_2O) (TPS as internal standard) δ 3.09–3.13 (m, 2H), 3.50 (td, *J* = 3.0, 12.6 Hz, 1H), 3.67 (td, *J* = 6.4, 12.8 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.99 (dd, *J* = 8.3, 12.6 Hz, 1H), 4.22 (dd, *J* = 3.9, 12.6 Hz, 1H), 4.64 (dd, *J* = 3.8, 8.2 Hz, 1H), 6.91 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (D_2O) (TPS as internal standard) δ 27.3, 41.6, 58.6, 58.7, 58.9, 64.2, 112.1, 114.8, 123.2, 127.9, 150.2, 150.9; EI MS *m/z* 223 (M^+-HCl, 1.5), 222 (2.5), 192 (100), 177 (11), 176 (15), 147 (10); HR-MS Calcd for $C_{12}H_{17}NO_3$: (M-HCl), 223.12085. Found: *m/z* 223.11905.

***N*-Methylcalycotomine hydrochloride 2•HCl**. Following the above procedure, *N*-methylcalycotomine hydrochloride **2•HCl** was prepared by refluxing *O*-benzyl derivative **14** (0.21 g, 0.52 mmol) in a mixture of THF (2.45 mL) and 12N HCl (2.45 mL) for 30 min. followed by hydrogenolysis with hydrogen in the presence of 10% palladium on carbon for 72 h. Crystallization from EtOH gave a nicely crystalline **2•HCl** in 94% yield; mp 219–221 ºC; ^{1}H NMR (D_2O) (TPS as internal standard) δ 3.09 (s, 3H), 3.11–3.26 (m, 2H), 3.51 (td, *J* = 5.3, 12.8 Hz, 1H), 3.81 (td, *J* = 6.0, 13.0 Hz, 1H), 3.89 (s, 6H), 3.99 (dd, *J* = 8.1, 13.1 Hz, 1H), 4.22 (dd, *J* = 3.7, 13.0 Hz, 1H), 5.55 (dd, *J* = 3.9, 8.0 Hz, 1H), 6.93 (s, 1H), 6.97 (s, 1H);

^{13}C NMR (D_2O) (TPS as internal standard) δ 24.7, 42.8, 49.3, 58.6, 58.7, 64.3, 67.6, 112.9, 114.5, 122.0, 126.7, 150.4, 151.2; EI MS *m/z* 238 (M^+-Cl, 0.41), 237 (M^+-HCl, 0.36), 236 (0.69), 207 (14), 206 (100), 190 (16); HR-MS Calcd for $C_{13}H_{20}NO_3$: (M-Cl), 238.14432. Found: *m/z* 238.14561.

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