Selective and Potent β_2-Adrenoceptor Agents within the Tetrahydroisoquinoline Class: Effect of Methyl Substitution at the Benzylic Carbon of the 1-(3,4,5-Trimethoxybenzyl) Group of Trimetoquinol

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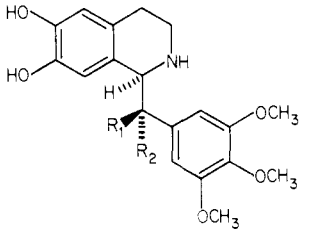
A systematic series of methyl (2 and 3) and dimethyl (4) analogues of trimetoquinol (1) were synthesized and evaluated for their β_1 (atria) and β_2 (trachea) adrenoceptor activities. Structural assignments for the erythro (2) and the threo (3) diastereoisomers of 1-(3,4,5-trimethoxy-α-methylbenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline were based on NMR spectra of the 6,7-dibenzyl precursors 15 and 16, respectively, and on the synthetic derivatives of *cis*- and *trans*-13-methyl-2,3-bis(benzyloxy)-9,10,11-trimethoxytetrahydroprotoberberine (18 and 17). The rank order of β_2-agonist activity for these compounds was 3 > 1 > 2 > 4. The rank order of activity as β_1 agonists on the guinea pig atria is 1 > 3 > 2, and 4 was inactive. The methylated analogues show selectivity for β_2 receptors in our preliminary pharmacological studies. The threo isomer 3 is the most potent and selective β_2 stimulant reported to date in the tetrahydroisoquinoline class.

In our studies to better characterize the optimum structural requirements of tetrahydroisoquinolines (THIs) for β-adrenoceptor stimulant activity, we have examined a systematic set of analogues of trimetoquinol (1).[1-5] One



1, $R_1 = R_2 = H$
2, $R_1 = H$; $R_2 = CH_3$
3, $R_1 = CH_3$; $R_2 = H$
4, $R_1 = R_2 = CH_3$

of our initial approaches was to examine fragmented analogues of the THI ring system, and with such analogues we found a considerable reduction in the β-adrenoceptor agonist activity;[1,2] this has been confirmed by studies reported during the same time period by Iwasawa and coworkers.[6]

We have more recently concentrated on the additon of functional groups to 1 and the effect such groups have on β-adrenoceptor activity.[3,5] The addition of a methyl or a benzyl group to the 1 position of 1 provided unusual results in that the 1-benzyl congener possessed selective β_1-adrenoceptor antagonist properties while the 1-methyl congener was shown to be a partial agonist in β_1-adrenoceptor systems.[3] The addition of a hydroxyl group to the benzylic carbon of the 3,4,5-trimethoxybenzyl substituent of 1 provided a set of diastereomeric analogues that possess significant but less β_1- and β_2-adrenoceptor agonist activity as compared to the parent compound.[5,7] In an attempt to investigate the effect of lipophilic substituents on the α carbon of the 3,4,5-trimethoxybenzyl substituent of 1, we report the synthesis and structural assignments of the diastereomeric methyl analogues 2 and 3 of 1 along with the dimethyl analogue 4 and the preliminary β-adrenoceptor activity of these analogues. Such modifications have provided a compound that is more active and selective for β_2-receptors than 1.

Chemistry. The synthetic sequence outlining the preparation of 2-4 is shown in Scheme I. Initially, the 2-substituted propionic acid 6 was prepared from the ester 5 using the procedure of Shamma and Jones.[8] The acid 6 was then converted to the acid chloride and it was allowed to react with 3,4-bis(benzyloxy)phenethylamine (10) to give the desired amide 11.[1] The amide 11 was allowed to undergo a Bischler-Napieralski reaction using $POCl_3$ in acetonitrile to give the intermediate dihydroisoquinoline 13, which was in turn reduced to give a mixture of the diastereomeric THIs 15 and 16. Reduction of 13 with $NaBH_4$ afforded a mixture of 15 and 16 in a 90:10 ratio based on the integrals of the NMR doublets of the C-methyl moiety at δ 1.33 and 1.06, respectively. Isolation of the predominate isomer 15 could be achieved by successive recrystallizations of the HCl salt of 15 from $MeOH/Et_2O$. Reduction of 13 with $LiAlH_4$ in THF afforded a higher yield of the minor isomer 16, but isomer 15 still predominated in a 70:30 ratio. The diastereoisomers could be separated using column chromatography. The compound assigned the erythro configuration (15) had a methyl doublet at δ 1.33, while the threo compound (16) had a methyl doublet at δ 1.06 which is consistent with literature values of δ 1.39 and 0.91 for the erythro (19) and threo (20) isomers of 1-[α-methyl-3,4-bis(benzyloxy)-benzyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, respectively.[8]

(1) D. D. Miller, P. Osei-Gyimah, J. Bardin, and D. R. Feller, *J. Med. Chem.*, 18, 454 (1975).
(2) D. D. Miller, P. F. Kador, R. Venkatraman, and D. R. Feller, *J. Med. Chem.*, 19, 763 (1976).
(3) D. D. Miller, P. Osei-Gyimah, R. V. Raman, and D. R. Feller, *J. Med. Chem.*, 20, 1502 (1977).
(4) P. F. Kador, R. Venkatraman, D. R. Feller, and D. D. Miller, *J. Med. Chem.*, 20, 891 (1977).
(5) P. Osei-Gyimah, M. T. Piascik, J. W. Fowble, D. R. Feller, and D. D. Miller, *J. Med. Chem.*, 21, 1173 (1978).
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(7) M. T. Piascik, M. F. Piascik, D. D. Miller, and D. R. Feller, *Life Sci.*, 24, 2433 (1979).
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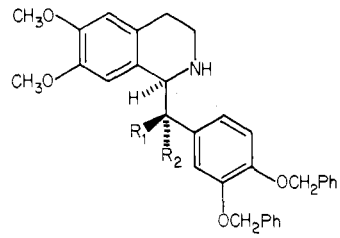
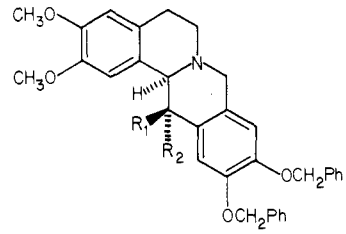


19, $R_1 = H$; $R_2 = CH_3$
20, $R_1 = CH_3$; $R_2 = H$



21, $R_1 = H$; $R_2 = CH_3$
22, $R_1 = CH_3$; $R_2 = H$

Since several authors[5,8-10] have previously reported successful assignments of the relative configurations of the C-13 and C-14 protons of C-13 substituted tetrahydroprotoberberines, we treated **15** and **16** under Mannich conditions to afford the tetrahydroprotoberberines **17** and **18**, respectively. In the 300-MHz NMR spectrum, the C-13 methyl doublet for **17** and **18** appeared at δ 1.30 (J = 6.7 Hz) and 0.87 (J = 6.9 Hz), respectively, and this is in agreement with the absorptions shown for the methyl doublets of **21** and **22** at δ 1.39 and 0.91 as reported by Shamma and Jones.[8] Cushman and co-workers[10] have also shown similar absorptions for *cis*- and *trans*-13-methyltetrahydroprotoberberine systems. In the NMR spectrum, the C-13 proton doublet at δ 2.48 (J = 8.4 Hz) established the trans relative configuration for **17**, while the C-13 proton doublet at δ 3.62 (J = 2.7 Hz) established the cis relative configuration for **18**. The absence of Bohlmann bands in the infrared spectrum of **17** indicates this molecule exists in a *cis*-quinolizidine conformation, and the appearance of such bands in the spectrum of **18** indicates that it exists in a *trans*-quinolizidine conformation.[10]

The desired analogues **2** and **3** of **1** were prepared by catalytic reduction of the protected THIs **15** and **16**, respectively. The synthesis of the dimethyl analogue **4** of **1** was carried out in a similar manner to that described for **2** and **3**, except that 2-methyl-2-(3,4,5-trimethoxyphenyl)propionic acid (**7**) was prepared and converted to amide **12** and utilized as outlined in Scheme I.

Biological Results

The parent compound (**1**) and analogues **2–4** were examined for their comparative β-adrenoceptor activities in guinea pig atrial (Figure 1) and tracheal (Figure 2) tissues, which were selected as representative β_1- and β_2-receptor systems, respectively. As shown in Figure 1, two of these analogues (**2** and **3**) gave the same maximal increase in heart rate as **1** but were considerably less active than the parent compound in this β_1 system. Although **4** was inactive as an agonist, a significant reduction in basal heart rate of 21 and 32% was observed with **4** at 10^{-4} and 3×10^{-4} M, respectively. Other experiments using 10^{-4} M **4** showed that this compound was ineffective as an antagonist of the chronotropic response to isoproterenol (unpublished observation, 1980). In summary, the rank order of chronotropic potency among these THIs was **1** > **3** > **2**, whereas **4** was inactive as a β_1-adrenoceptor agonist or antagonist at doses up to 10^{-4} M.

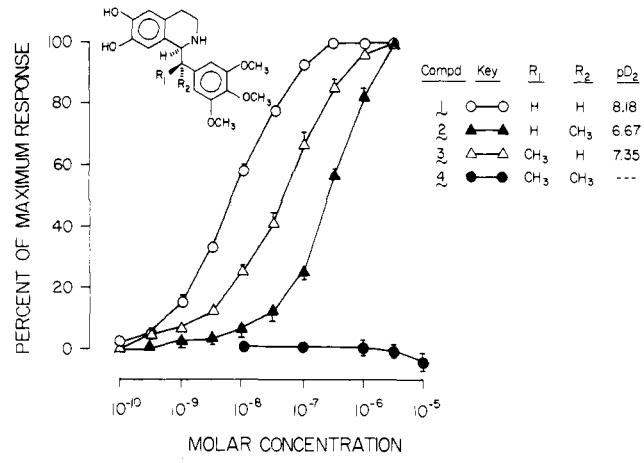


Figure 1. Dose–response curves for (±)-trimetoquinol (**1**), the monomethyl erythro (**2**) and threo (**3**) analogues, and the dimethyl (**4**) analogue on the spontaneously beating guinea pig right atrium. Values are represented as the mean ± SEM of n = 4–8.

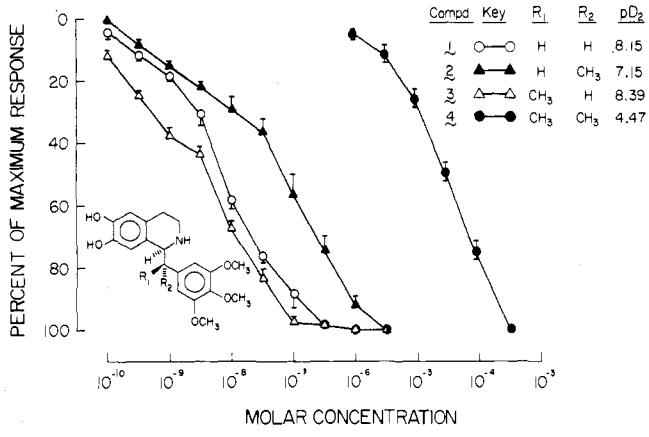


Figure 2. Dose–response curves for (±)-trimetoquinol (**1**), the monomethyl erythro (**2**) and threo (**3**) analogues, and the dimethyl (**4**) analogue on the relaxation of guinea pig tracheal smooth muscle. Values are represented as the mean ± SEM of n = 4–8.

The β_2-adrenergic activities of these compounds in guinea pig trachea (Figure 2) differed significantly from their chronotropic effects. In trachea, the rank order of potency for **1** and analogues was **3** > **1** > **2** > **4**. A biphasic relaxation curve was observed for the α-methyl substituted analogues (**2** and **3**) which was more evident than that for **1**. The existence of a biphasic pattern of dose–response relationships for **1** on β-adrenoceptor systems has been reported, but the origin of this phenomenon remains unresolved.[11,12] It is noteworthy that (a) **3** is more potent as a bronchial relaxant than **1** while **2** and **4** are less active and that (b) **4** is active in this β_2-adrenoceptor system. When the relative potencies of **2–4** in trachea vs. atria are compared to the potency of **1** (see Figures 1 and 2), these analogues show a pattern of β_2 selectivity, whereas **1** was equally effective in these β-receptor systems (pD_2 values of **1** were 8.18 and 8.15 in trachea and atria, respectively).

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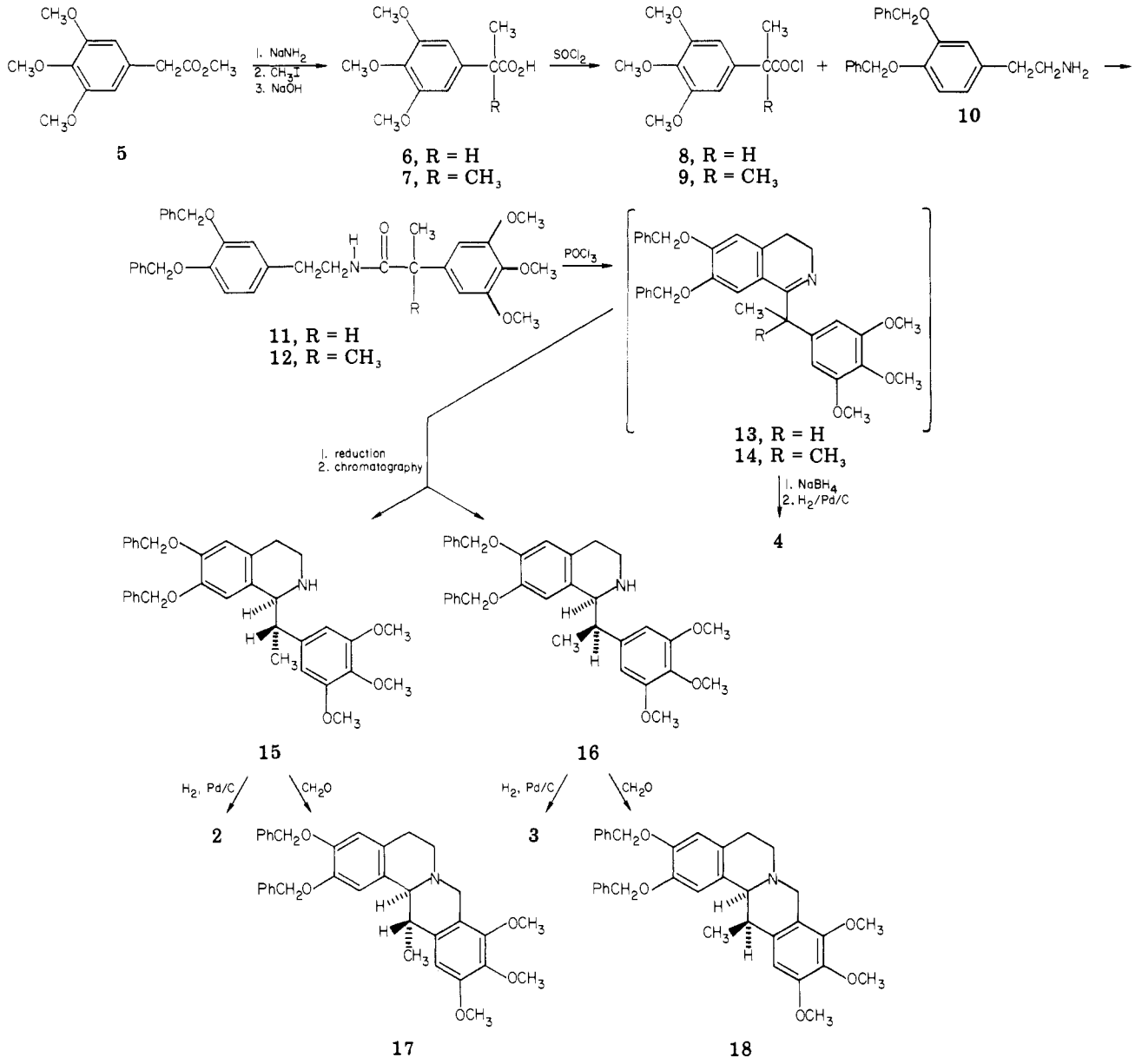
Scheme I



Discussion

The data reported herein clearly demonstrate that methyl or dimethyl substitution of the α-carbon atom of the 1-(3,4,5-trimethoxybenzyl) substituent of 1 has a significant effect upon β-adrenergic potency and tissue selectivity. Specifically, the *threo*-α-methyl analogue (3) was more potent and β_2 selective as an adrenoceptor stimulant than 1. The remaining analogues (3 and 4) also exhibited a greater β_2 selectivity than 1 but possessed a reduced potency when compared to 1 or 3. In contrast, we previously reported that the presence of a hydroxyl group at the α-benzyl carbon atom of 1 gave compounds which were less potent and nonselective as compared to 1 in guinea pig atrial and tracheal preparations.[5] Yamamura et al.[13] also have prepared a set of hexahydrobenzo[*d*,*e*]quinoline analogues of 1 which may be visualized as having an alkyl substituent at the α-benzyl carbon atom. In their studies,[13] the compounds were found to be less active than 1 but, nevertheless, exhibited a greater selectivity for β_2-receptor systems. Taken together, these results suggest that the addition of lipophilic alkyl groups to the benzylic carbon of the 1-(3,4,5-trimethoxybenzyl) substituent of 1 affords compounds which possess an increased degree of β_2 selectivity. To our knowledge, the threo analogue (3) as synthesized and evaluated in this paper represents the most potent bronchoselective adrenoceptor stimulant within the THI class reported to date.

(13) S. Yamamura, K. Oda, T. Mizoguchi, S. Saito, Y. Iwasawa, and A. Kiyomoto, *Chem. Pharm. Bull.*, **27**, 858 (1979).

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 spectrophotometer. The NMR spectra were recorded on a Varian A-60A or a Bruker Model HX-90E, WH-270, or WM-300 NMR spectrometer utilizing Me_4Si as the internal standard. The mass spectra were determined on a DuPont Model 491 or AEI MS-30 mass spectrometer. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN.

2-(3,4,5-Trimethoxyphenyl)propionic Acid (6). 3,4,5-Trimethoxyphenylacetic acid (10 g, 0.044 mol) was dissolved in 75 mL of absolute methanol containing several drops of concentrated HCl. After the solution was stirred for 24 h at room temperature, the solvent was removed in vacuo to yield a yellow oil, which was distilled [138–139 °C (0.5 mm)] to yield 8.5 g (80%) of a methyl ester. The oil solidified upon standing to give crystalline material: mp 40.5–41.5 °C; IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (s,

2 H, ArCH_2), 3.70 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 OCH_3), 6.50 (s, 2 H, aromatic).

Utilizing the alkylation procedure of Shamma and Jones[8,14] we converted 10 g (0.042 mol) of ester **5** to give 8.2 g (77%) of methyl 2-(3,4,5-trimethoxyphenyl)propionate as a light yellow oil: bp 118–120 °C (0.3 mm); IR (neat) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (d, 3 H, ArCHCH_3), 3.66 (s, 3 H, OCH_3), 3.65 (m, 1 H, ArCH), 3.81 (s, 3 H, OCH_3), 3.85 (s, 6 H, 2 OCH_3), 6.51 (s, 2 H, aromatic). Anal. ($C_{13}H_{18}O_5$) C, H.

To a solution of 10.1 g (0.040 mol) of methyl 2-(3,4,5-trimethoxyphenyl)propionate in MeOH was added 25 mL of 15% NaOH. After the solution was stirred at room temperature overnight, the MeOH was removed in vacuo and the resulting basic layer was transferred to a separatory funnel. After acidifying with 50% HCl, the product was extracted with several portions of $CHCl_3$, dried with $MgSO_4$, and collected via an in vacuo solvent removal to yield 9.6 g (100%) of a pale yellow oil which solidified upon standing. It was recrystalized from $CHCl_3$–hexane: mp 85–86 °C; IR (neat) 3200 (br d, OH), 1710 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 1.48 (d, 3 H, ArCHCH_3) 3.5–3.8 (m, 1 H, ArCH), 3.80 (s, 9 H, 3 ArOCH_3), 6.50 (s, 2 H, aromatic). Anal. ($C_{12}H_{16}O_5$) C, H.

***N*-[3,4-Bis(benzyloxy)phenethyl]-2-(3,4,5-trimethoxyphenyl)propionamide (11).** The acid **6** was quantitatively converted to the acid chloride **8** by stirring the acid in 120 mL of dry THF and 6.2 g (0.052 mol) of $SOCl_2$ for 2 h. The THF and excess $SOCl_2$ were removed in vacuo to yield the acid chloride as a yellow oil: IR (neat) 1795 cm^{-1}. To a mechanically stirred solution of 17.0 g (0.051 mol) of 3,4-bis(benzyloxy)phenethylamine (**10**) in 100 mL of $CHCl_3$ was added 6.3 g (0.045 mol) of anhydrous K_2CO_3 in 100 mL of H_2O. Then 10.5 g (0.038 mol) of the 2-(3,4,5-trimethoxyphenyl)propionyl chloride in 125 mL of $CHCl_3$ was added dropwise and the solution was allowed to stir for 3 h. The $CHCl_3$ layer was then separated from the aqueous phase, washed with 10% HCl, saturated $NaHCO_3$, and H_2O and dried (Na_2SO_4). Solvent removal under reduced pressure afforded a light brown oil which solidified upon trituration with Et_2O. Recrystallization of the solid from benzene–ether afforded 16.4 g (78%) of the amide **11**: mp 101–103 °C; IR (KBr) 3305, 1650 cm^{-1} (amide); NMR ($CDCl_3$) δ 1.48 (d, 3 H, ArCHCH_3), 2.58 (br t, 2 H, CH_2, J = 7 Hz), 3.15–3.60 (m, 3 H, CH_2 and CH), 3.75 (s, 6 H, 2 ArOCH_3), 3.78 (s, 3 H, ArOCH_3), 5.03 (s, 4 H, 2 PhCH_2O), 6.30–6.55 (m, 3 H, aromatic), 6.61–7.9 (m, 2 H, aromatic), 7.10–7.50 (m, 10 H, aromatic). Anal. ($C_{34}H_{37}NO_6$) C, H, N.

***erythro*-1-(α-Methyl-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-bis(benzyloxy)isoquinoline (15).** To a solution of 8.5 g (0.016 mol) of the amide **11** in 100 mL of dry acetonitrile was added 5.0 mL of $POCl_3$, and the solution allowed to reflux under nitrogen for 1.5 h. After the solution was cooled the solvent and excess $POCl_3$ were removed under reduced pressure. The resulting oil was taken up in $CHCl_3$ and rapidly washed with 10% $NaHCO_3$ and H_2O. After drying with Na_2SO_4, the solvent was removed in vacuo to yield 6.5 g (75%) of the desired product imine **13** as an oil (R_f 0.84 in 2:1 CH_2Cl_2–MeOH), which was used without further purification.

To a solution of 3.0 g (5.6 mmol) of the imine **13** in 70 mL of MeOH was added 3.4 g of $NaBH_4$ in methanol dropwise over a 0.5-h period. The solution was then allowed to stir overnight. The solvent was then removed in vacuo, and the white residue was suspended in H_2O and extracted with several portions of Et_2O. The combined Et_2O layers were washed with H_2O and dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded 2.8 g (90%) of **15** and **16** in a 90:10 diastereoisomeric mixture, as indicated by the NMR integrals of the doublet at δ 1.39 and 1.08, respectively. Preparation of the HCl salt afforded a white solid which could be recrystallized from MeOH–Et_2O. After several recrystallizations, only the predominant isomer (**15**) was observed in the NMR spectra: mp 166–168.5 °C; NMR ($CDCl_3$, free base) δ 1.33 (d, 3 H, ArCHCH_3, J = 7 Hz), 1.92 (br d, 1 H, NH), 2.30–3.40 (m, 5 H, ArCH_2CH_2N and ArCHCH), 3.70 (s, 6 H, 2 ArOCH_3), 3.80 (s, 3 H, ArOCH_3), 4.00 (d, 1 H, ArCHN, J = 6 Hz), 5.10 (s, 4 H, 2 PhCH_2O), 6.25 (s, 2 H, aromatic), 6.55 (s, 1 H, aromatic), 6.72 (s, 1 H, aromatic), 7.15–7.50 (m, 10 H, aromatic). Anal. ($C_{34}H_{38}NO_5Cl$) C, H, N.

***threo*-1-(α-Methyl-3,4,5-trimethoxybenzyl)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (16).** Under nitrogen atmosphere, 2.5 g of $LiAlH_4$ was suspended in 40 mL of dry THF. Then 5.0 g (9.33 mmol) of the imine **13** as a slurry in 20 mL of dry THF was added dropwise over 90 min. The solution was then allowed to stir at room temperature overnight. The excess $LiAlH_4$ was decomposed by the slow addition of 30 mL of H_2O followed by 30 mL of 15% NaOH and an additional 40 mL of H_2O. The aluminum salt was removed by filtration and leached with several portions of THF. The THF portions were combined and evaporated to yield an aqueous and oily residue. The residue was extracted with several portions of $CHCl_3$. The organic layers were combined, washed with H_2O, and dried with Na_2SO_4. Removal of solvent in vacuo afforded a mixture of the diastereomeric amines **15** and **16** in a 70:30 ratio as indicated by the NMR integrals. The minor isomer **16** could be isolated via chromatography on silica gel using a three-component solvent system of toluene, ethyl acetate, and 2-propanol (65:25:10, 1% NH_4OH). The HCl salt was prepared: mp 236–238 °C, NMR (90 MHz, $CDCl_3$, free base) δ 1.06 (d, 3 H, ArCHCH_3), 1.61 (br s, 1 H, NH), 2.70–3.30 (m, 5 H, ArCH_2CH_2N and ArCH), 3.85 (br s, 9 H, 3 ArOCH_3), 4.00 (d, 1 H, ArCHN, J = 4.7 Hz), 5.05 (s, 2 H, PhCH_2O), 5.12 (s, 2 H, PhCH_2O), 6.48 (s, 2 H, aromatic), 6.64 (s, 1 H, aromatic), 6.68 (s, 1 H, aromatic), 7.20–7.50 (m, 10 H, aromatic). Anal. ($C_{34}H_{38}NO_5Cl$) C, H, N.

***trans*-13-Methyl-2,3-bis(benzyloxy)-9,10,11-trimethoxytetrahydroprotoberberine (17).** To a solution of 0.4 g (0.68 mmol) of **15** as the HCl salt in 6 mL of hot EtOH and 12 mL of hot H_2O was added 1.5 mL of 37% formaldehyde solution. The solution was heated to reflux for 6 h and then allowed to cool. The solution was extracted with several portions of $CHCl_3$, and the combined organic phases were washed with H_2O and dried with Na_2SO_4. Solvent removal in vacuo afforded a yellow oil which solidified on standing. Recrystallization from methanol yielded 0.3 g (75%) of **17** as a white crystalline solid: mp 146–148.5 °C, NMR (300 MHz, $CDCl_3$, free base) δ 1.30 (d, 3 H, ArCHCH_3, J = 6.7 Hz), 2.68–2.76 (m, 1 H), 2.84–2.92 (m, 3 H), 3.01–3.09 (m, 1 H), 2.48 (d, 1 H, ArCHN, J = 8.4 Hz), 3.79–3.85 (m, 10 H), 3.95 (d, 1 H, NCH_2Ar, J_{gem} = 15.8 Hz), 5.10 (d, 1 H, PhCH_2O, J_{gem} = 11.9 Hz), 5.12 (s, 2 H, PhCH_2O), 5.20 (d, 1 H, PhCH_2O), 6.47 (s, 1 H), 6.69 (s, 1 H), 6.77 (s, 1 H), 7.25–7.46 (m, 10 H). Anal. ($C_{34}H_{38}NO_5Cl$) C, H, N.

***cis*-13-Methyl-2,3-bis(benzyloxy)-9,10,11-trimethoxytetrahydroprotoberberine (18).** To a solution of 0.4 g (0.68 mmol) of **16** as the HCl salt in 6 mL of hot EtOH and 12 mL of hot H_2O was added 1.5 mL of 37% CH_2O. The solution was heated at reflux for 3 h and cooled. The solution was then extracted with several portions of $CHCl_3$, and the combined organic layers were washed with H_2O and dried with Na_2SO_4. Evaporation of the $CHCl_3$ solution afforded the desired product as a yellow oil. The oil was purified by column chromatography on silica gel using absolute ether (R_f 0.86) as the mobile phase. Addition of pentane to the ethereal solution afforded 100 mg (25%) of a yellow solid after several hours: mp 88–90 °C; NMR (300 MHz, $CDCl_3$, free base) δ 0.87 (d, 3 H, ArCHCH_3, J = 6.9 Hz), 2.48–2.60 (m, 2 H), 3.02–3.15 (m, 3 H), 3.05 (d, 1 H, NCH_2Ar, J = 15.5 Hz), 3.62 (d, ArCHN, J = 2.7 Hz), 4.38 (d, 1 H, NCH_2Ar), 5.14 (s, 4 H, PhCH_2O), 6.45 (s, 1 H), 6.70 (s, 1 H), 6.74 (s, 1 H), 7.30–7.48 (m, 10 H). Anal. ($C_{35}H_{37}NO_5$) C, H, N.

***erythro*-1-(α-Methyl-3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (2).** A suspension of 500 mg of 10% Pd/C in 50 mL of absolute ethanol was hydrogenated at 40 psi for 1 h to saturate the catalyst. Then 1.80 g (0.18 mmol) of the protected compound **15** as the HCl salt in 25 mL of absolute EtOH was added, and the mixture hydrogenated at 40 psi at room temperature overnight. The solution was then suction filtered through Celite, and the solution was concentrated to about 4 mL in vacuo. Trituration yielded a white hydrochloride salt, which was crystallized from MeOH–Et_2O to afford 530 mg (76%) of a white solid (**2**): mp 236–238.5 °C; IR (KBr, HCl salt) 3380 cm^{-1} (br d, OH and NH). Anal. ($C_{20}H_{26}NO_5Cl$) C, H, N.

***threo*-1-(α-Methyl-3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (3).** A solution of 300 mg of 10% Pd/C catalyst in 50 mL of absolute EtOH was hy-

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 1034.

drogenated for 1 h at 40 psi to saturate the catalyst. Then 1.20 g (0.12 mmol) of **16** as the HCl salt in 25 mL of absolute EtOH was added, and the mixture was hydrogenated at 40 psi overnight at room temperature. The solution was then filtered through Celite, and the solvent was reduced to about 2 mL in vacuo. Trituration with Et_2O in the cold for 2 days afforded 350 mg (88%) of the desired product **3** as the HCl salt: mp 227–229 °C. Anal. ($C_{20}H_{26}NO_5Cl$) C, H, N.

2-Methyl-2-(3,4,5-trimethoxyphenyl)propionic Acid (7). Using the procedure of Shamma and Jones,[8] 12 g (0.05 mol) of ester **5** was alkylated twice with methyl iodide to give 7.54 g (56%) of ester **7**: mp 83–84 °C (recrystalized from ether); IR (KBr) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.55 [s, 6 H, $ArC(CH_3)_2$], 3.63 (s, 3 H, $COOCH_3$), 3.81 (s, 9 H, 3 $ArOCH_3$), 6.48 (s, 2 H, aromatic). Anal. ($C_{14}H_{20}O_5$) C, H.

A solution of 6 g (0.022 mol) of the ester and 1.25 g (0.022 mol) of KOH in 50% aqueous MeOH was refluxed overnight. The solvent was evaporated in vacuo, and the resulting basic layer was transferred to a separatory funnel, washed with Et_2O, and then acidified with 10% HCl. The product was extracted with several portions of $CHCl_3$, dried with $MgSO_4$, and evaporated in vacuo to give a pale yellow oil which solidified upon standing. It was recrystallized from $CHCl_3$–hexane to give the acid **7** as needles: yield 4.1 g (72%); IR (KBr) 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.60 [s, 6 H, $ArC(CH_3)_2$], 3.84 (s, 3 H, $ArOCH_3$), 3.86 (s, 6 H, 2 $ArOCH_3$), 6.62 (5, 2 H, aromatic). Anal. ($C_{13}H_{18}O_5$) C, H.

***N*-[3,4-Bis(benzyloxy)phenethyl]-2-methyl-2-(3,4,5-trimethoxyphenyl)propionamide (12).** The acid **7**, 3.5 g (0.0138 mol), was converted to the acid chloride by stirring the acid in 10 mL of dry THF, 1.64 g (0.0138 mol) of thionyl chloride, and a few drops of pyridine overnight. The precipitate was filtered. The filtrate was evaporated in vacuo to yield the acid chloride as an oil. The acid chloride was used without further purification.

To a mechanically stirred solution of 5.09 g (0.0138 mol) of the phenethylamine **10** in 100 mL of $CHCl_3$ was added 2.56 g (0.024 mol) of anhydrous K_2CO_3 in 100 mL of H_2O. Then the acid chloride described above in 10 mL of $CHCl_3$ was added dropwise to the two-phase mixture and allowed to stir for 3 h. The $CHCl_3$ layer was then separated from the aqueous phase, washed with 10% HCl, saturated $NaHCO_3$, and H_2O, and dried with Na_2SO_4. Solvent removal under reduced pressure afforded a colorless oil, which was chromatographed on silica gel (300 g). Elution with ethyl acetate afforded the amide **12**, 7.1 g (90%), as a clear oil: IR (neat) 3400, 1650 cm^{-1} (amide); NMR ($CDCl_3$) δ 1.50 [s, 6 H, $ArC(CH_3)_2$], 1.58 (s, 1 H, $NHCO$), 2.60 (t, 2 H, $ArCH_2$, J = 6.5 Hz), 3.37 (q, 2 H, CH_2NH, J = 6.5 Hz), 3.80 (s, 6 H, 2 $ArOCH_3$), 3.84 (s, 3 H, $ArOCH_3$), 5.10 (s, 2 H, $PhCH_2O$), 5.12 (s, 2 H, $PhCH_2O$), 6.35–7.00 (m, 5 H, aromatic), 7.10–7.50 (m, 10 H, aromatic). Anal. ($C_{35}H_{39}NO_6$) C, H, N.

1-(α,α-Dimethyl-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (4). To a solution of 4.87 g (0.0086 mol) of the amide **12** in 100 mL of dry acetonitrile was added 3.94 g (0.0257 mol) of $POCl_3$, and the solution was allowed to reflux under Ar for 5 h. After the solution was cooled, the solvent and excess $POCl_3$ were removed in vacuo. The resulting oil was taken up in $CHCl_3$ and rapidly washed with 10% $NaHCO_3$ and H_2O. After drying with Na_2SO_4, the solvent was removed in vacuo to yield imine **14** as an oil (IR 3390, 1580 cm^{-1}), which was used without further purification. To a solution of the imine **14** in 50 mL of MeOH was added 3.24 g of $NaBH_4$ portionwise over 0.5 h. The solution was then allowed to stir for 1 h. The solvent was then removed in vacuo. The white residue was suspended in H_2O and extracted with several portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with H_2O and dried with $MgSO_4$. Removal of the solvent under reduced pressure yielded 4.55 g (96%) of the 1-(α,α-dimethyl-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-bis(benzyloxy)isoquinoline. Preparation of the HCl salt afforded a white crystalline solid which was recrystallized from MeOH: mp 223–224 °C dec; NMR ($CDCl_3$, free base) δ 1.23 (s, 3 H, $ArCCH_3$), 1.27 (s, 3 H, $ArCCH_3$), 2.06 (br, 1 H, NH), 2.30–3.30 (m, 4 H, $ArCH_2CH_2$), 3.78 (s, 6 H, 2 $ArOCH_3$), 3.82 (s, 3 H, $ArOCH_3$), 4.33 (s, 1 H, $ArCHNH$), 4.82 (s, 2 H, $PhCH_2O$), 5.10 (s, 2 H, $PhCH_2O$), 6.24 (s, 1 H, aromatic), 6.45 (s, 2 H, aromatic), 6.61 (s, 1 H, aromatic), 7.25–7.55 (m, 10 H, aromatic). Anal. ($C_{35}H_{40}NO_5Cl$) C, H, N.

A mixture of 0.3 g (0.81 mmol) of 1-(α,α-dimethyl-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-bis(benzyloxy)isoquinoline hydrochloride and 110 mg of 10% Pd/C in 100 mL of anhydrous MeOH was hydrogenated at 40 psi for 5 h. The solution was then filtered through Celite, and the filtrate was evaporated in vacuo. The resulting glassy residue was triturated in dry Et_2O to yield a white solid, which was crystallized from MeOH–Et_2O to afford 140 mg of white solid **4**: mp 253–255 °C dec. Anal. ($C_{21}H_{28}NO_5Cl$) C, H, N.

Pharmacological Testing. Guinea pigs of either sex (weighing 300–500 g) were employed in all experiments. The isolation and procedures for testing of each compound in isolated guinea pig atria and trachea were identical with those described previously.[1] In all biological experiments, dose–response curves (DRC) were obtained with each drug (10^{-10} to 10^{-4} M range) and the data were expressed in terms of the percent of the maximal effect obtained with each drug. pD_2 values (negative logarithm of molar ED_{50}) were determined from the DRC of each test compound. In these experiments, each point on the DRC represented the mean of at least four observations. All drug solutions were freshly prepared in normal saline containing 0.05% sodium metabisulfite.

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