Chem. Pharm. Bull.
29(10)2816—2824(1981)

Studies on 1,2,3,4-Tetrahydroisoquinolines. III.[1] Syntheses and β-Adrenoceptor Activities of Methyl Derivatives of Trimetoquinol

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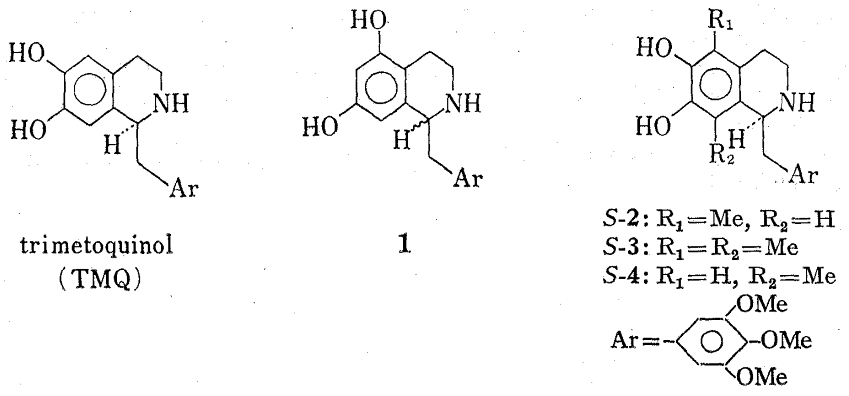
(Received March 24, 1981)

Three methyl derivatives (*S*-**2**, *S*-**3**, and *S*-**4**) of trimetoquinol (TMQ), in which one or both of the ring positions *ortho* to a phenolic group are substituted by a methyl group, were synthesized and evaluated for bronchodilating activity.

They were prepared by $NaBH_3CN$ reduction of the Mannich bases (*S*-**6**, *S*-**8**, and *S*-**23**) *via* the quaternary salts in a one-pot procedure followed by catalytic reduction on 10% Pd-C. A comparison of the 5-methyl derivative (*S*-**2**) with TMQ revealed that the duration of bronchodilating effect of *S*-**2** is considerably longer than that of TMQ on intraduodenal administration.

Keywords——1,2,3,4-tetrahydroisoquinolines; methyl derivatives of trimetoquinol; β-adrenoceptor activity; one-pot procedure; Mannich base; quaternary salt; reduction; β_2-selectivity; oral efficacy; intraduodenal administration

The previous paper[2] of this series described the synthesis of positional isomers of trimetoquinol (TMQ) with respect to its 6,7-dihydroxy group, and the 5,7-dihydroxy derivative (**1**) was shown to exhibit more potent β-adrenoceptor activity and longer duration of action than (±)-TMQ on intraduodenal administration. As another line of study on the structural modification of TMQ, we have synthesized three methyl derivatives of TMQ, in which one or both of the ring positions *ortho* to an OH group are substituted by a methyl group.



trimetoquinol (TMQ)

1

S-**2**: R_1=Me, R_2=H
S-**3**: R_1=R_2=Me
S-**4**: R_1=H, R_2=Me

Chart 1

Since the phenolic hydroxyl groups are considered to be one of the essential structural requisites for the β-adrenoceptor activity of TMQ, it was of interest to examine the effect of methyl substitution *ortho* to this functional group. In this paper, we describe the syntheses and β-adrenoceptor activities of the 5- and 8-methyl as well as the 5,8-dimethyl derivatives (*S*-**2**, *S*-**4**, and *S*-**3**) of TMQ. Because they were prepared from TMQ without affecting the stereochemical integrity of C_1, their absolute configurations are all 1*S*.[3]

Chemistry

Previously, we reported a facile conversion of Mannich bases *via* quaternary salts into the corresponding methyl compounds by treatment with $NaBH_3CN$ in HMPA in a one-pot procedure.[4] This method could be favorably applied to the preparation of the methyl derivatives (*S*-**2**, *S*-**3**, and *S*-**4**) of TMQ. The Mannich base (*S*-**6**), a suitable precursor of the 5-methyl derivative (*S*-**2**), was readily obtained from TMQ in 81% yield by N-benzyloxycarbonylation followed by Mannich reaction with N,N-dimethyl (methylene)ammonium chloride[5] and Et_3N in CH_3CN. Treatment of *S*-**6** with Me_2SO_4 followed by $NaBH_3CN$ in HMPA gave the 5-methyl derivative (*S*-**7**) in 68% yield, and on hydrogenolysis this gave the 5-methyl derivative of TMQ (*S*-**2**) (Chart 2).

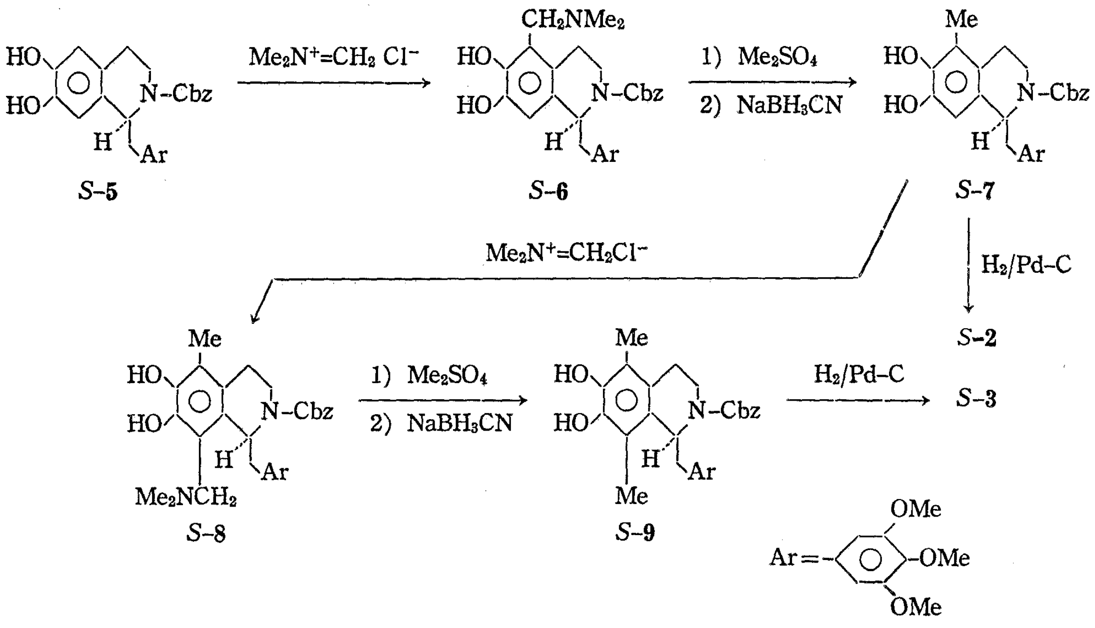


Chart 2

The position of the methyl group in the compound (*S*-**2**) was established in the following manner (Chart 3). The racemic N-benzyloxycarbonyl-5-methyl derivative [(±)-**7**] was similarly prepared in a comparable yield from (±)-TMQ. On the other hand, the 6-hydroxy-7-methoxy derivative [(±)-**10**],[6] a known metabolite of (±)-TMQ,[7] was converted to the 6,7-dimethoxy-5-methyl derivative [(±)-**13**] by the sequence of reactions outlined in Chart 3; the latter compound was proved to be identical with the sample prepared by O-methylation of (±)-**7**.

The Mannich reaction of *S*-**7** gave the 5-methyl-8-dimethylaminomethyl derivative (*S*-**8**), which was converted to the 5,8-dimethyl derivative (*S*-**3**) of TMQ by the usual method. Finally, to obtain the 8-methyl derivative of TMQ, the Mannich reaction of *S*-**15**, in which the 5-position is blocked by bromine, was attempted. The bromide (*S*-**15**) was prepared by N-benzyloxycarbonylation of the known dibromide (*S*-**14**).[8] Interestingly, the product of the Mannich reaction of (*S*-**15**) was found to be the 5-dimethylaminomethyl derivative (*S*-**17**) instead of the expected amine (*S*-**16**). The structure of *S*-**17** was deduced from its mass spectrum (presence of only one Br atom) and was unequivocally established by chemical conversion into the 5-methyl derivative (*S*-**2**) of TMQ described above (Chart 4). The mechanism in the formation of *S*-**17** from *S*-**15** is not clear at present.

To obtain the 8-methyl derivative of TMQ, therefore, the monobenzyloxy derivative (*S*-**19**) was employed as a starting material. Treatment of the N-benzyloxycarbonyl TMQ (*S*-**5**) with benzyl chloride (1.3 equiv) in the presence of K_2CO_3 in DMSO gave *S*-**19**, *S*-**20**, and *S*-**21** in

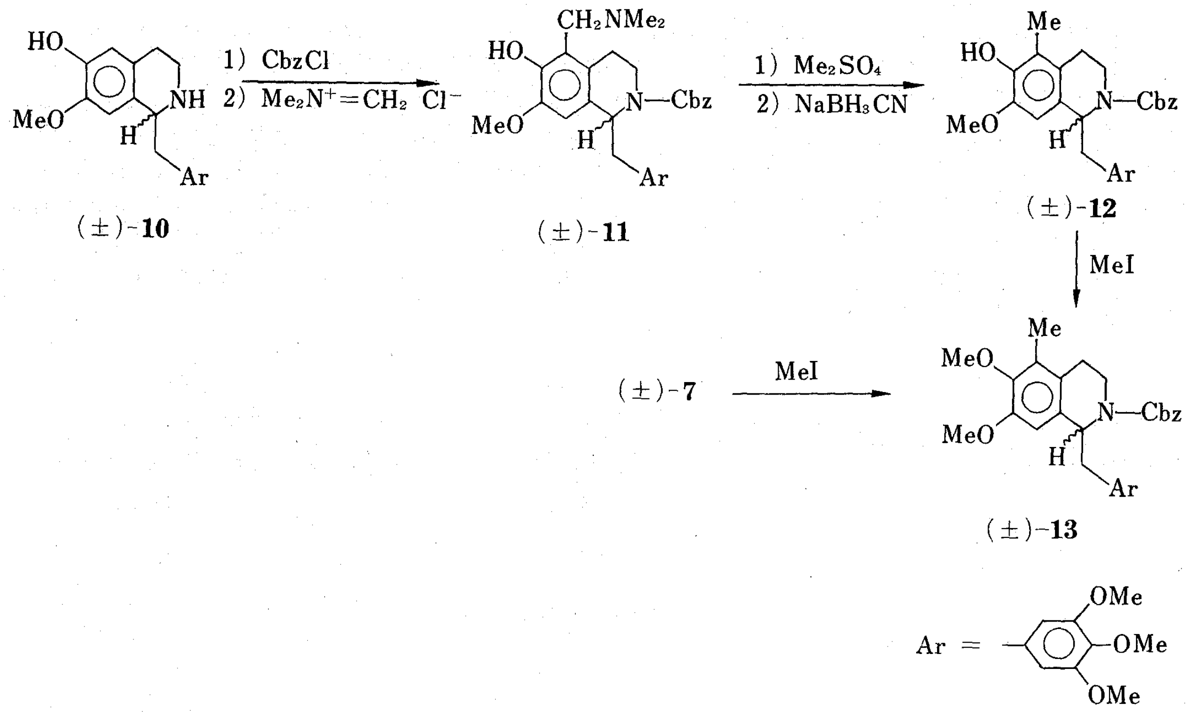


Chart 3

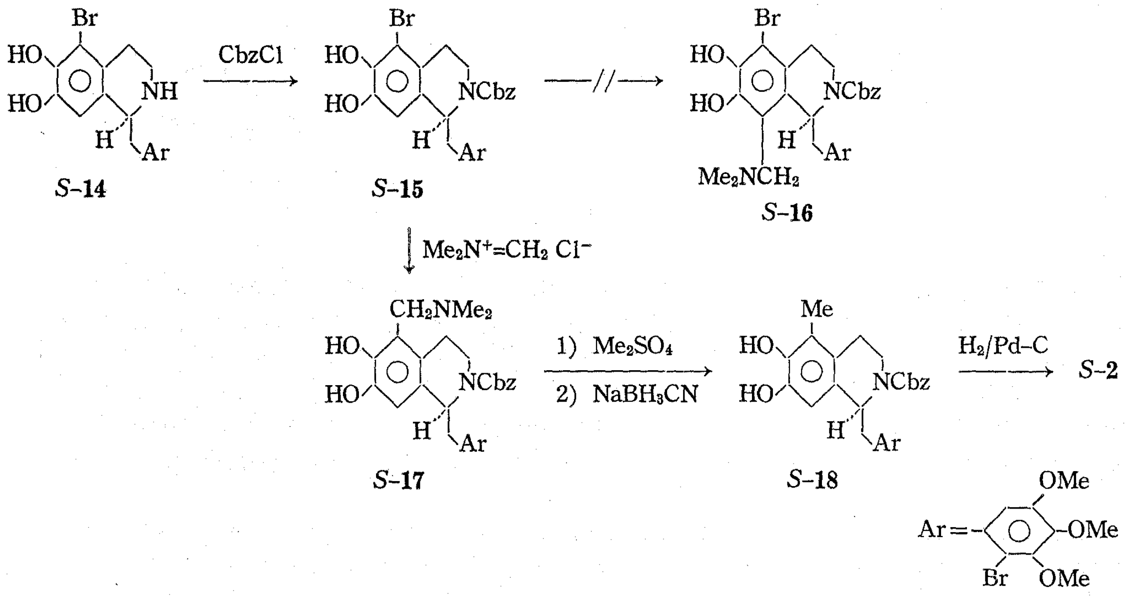


Chart 4

28%, 25%, and 35% yields, respectively. The structures of the monobenzyloxy derivatives (*S*-**19** and *S*-**20**) were established by chemically relating them to the known 6-hydroxy-7-methoxy and 6-methoxy -7-hydroxy derivatives [(±)-**10**⁶⁾ and (±)-**22**⁶⁾], respectively. The Mannich reaction of *S*-**19** with N,N-dimethyl(methylene)ammonium chloride and Et_3N in CH_3CN gave the 8-dimethylaminomethyl derivative (*S*-**23**) in 84% yield, and this was converted to the corresponding methyl derivative (*S*-**24**) by the usual method. Hydrogenolysis of *S*-**24** gave the 8-methyl derivative (*S*-**4**) of TMQ in 74% yield.

Physical data of the methyl derivatives of TMQ thus obtained are summarized in Table I.

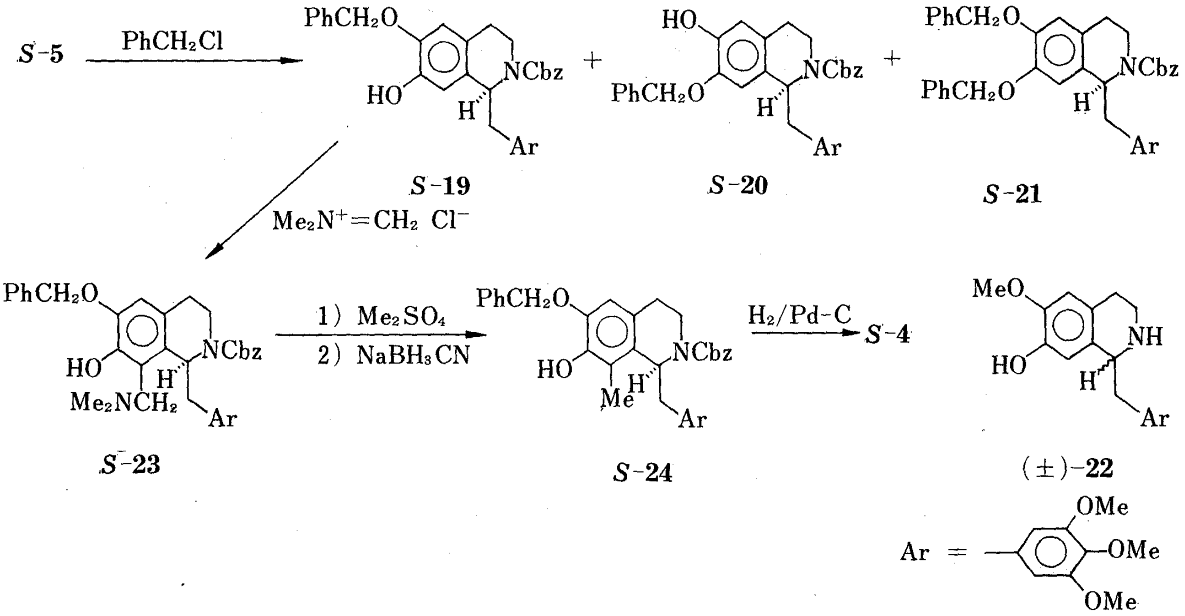


Chart 5

Table I

Compound No.	Appearance (Recryst. solvent)	mp (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
S-2·HCl	Colorless prisms	242—244°C	$C_{20}H_{25}O_5N \cdot HCl$	60.68	6.62	3.54	8.95
	(MeOH–H_2O)			(60.90	6.72	3.58	8.80)
S-3·HCl	Colorless prisms	217—220°C	$C_{21}H_{27}O_5N \cdot HCl$	60.21	6.74	3.34	8.46
	(EtOH–Et_2O)		0.5 H_2O	(60.38	6.89	3.35	8.65)
S-4·HCl	Colorless powder	140 (sint.)	$C_{20}H_{25}O_5N \cdot HCl$	60.37	6.86	3.41	8.62
	(EtOH–Et_2O)	145—165°C	1/3 EtOH	(60.16	6.80	3.41	8.81)

Table II. Geometric Mean ED Values[a] and Activity Ratio of Trimetoquinol and Its Methyl Derivatives on Bronchodilating and Positive Chronotropic Actions in Anesthetized Cats.

Drug	No. of experiments	Bronchodilation		Heart rate		Activity ratio A/B
		ED_{50}[a] (μg/kg, *i.v.*)	A P.R.[b]	HR_{20}[c] (μg/kg, *i.v.*)	B P.R.[b]	
Trimetoquinol	6	0.041	100	0.024	100	1
		(0.019—0.061)		(0.015—0.038)		
S-2·HCl	6	0.12	33	0.14	16	2.1
		(0.043—0.35)		(0.070—0.30)		
S-3·HCl	6	1.3	3.2	1.8	1.4	2.3
		(0.66—2.5)		(0.96—3.2)		
S-4·HCl	6	9.5	0.43	14	0.17	2.5
		(5.1—17.8)		(8.8—21)		

a) Dose, with 95% confidence limits, producing 50% inhibition of 5-HT-induced bronchoconstriction.
b) Potency ratio; trimetoquinol=100.
c) Dose, with 95% confidence limits, producing an increase in heart rate by 20 beats/min.

Biological Results

The bronchodilating activities of the methyl derivatives (*S*-**2**, *S*-**3**, and *S*-**4**) of TMQ in anethetized cats against serotonin-induced bronchoconnstriction were compared to that of TMQ.[2] On intravenous administration, the bronchodilating activities of *S*-**2** and *S*-**3** were approx. 1/3 and 1/30 of that of TMQ, respectively, while that of *S*-**4** was less than 1/250 of that of TMQ (Table II). As shown in Table II, however, the conversion of TMQ into the methyl derivatives (*S*-**2** and *S*-**3**) resulted in the generation of more β_2-selective bronchodilating compounds than TMQ.

In order to assess oral efficacy, compound *S*-**2**, which exhibited the most potent bronchondilating activity among the methyl derivatives, was given into the duodenum and the result was compared to that obtained with TMQ.

As shown in Fig. 1, the duration of bronchodilating effect of *S*-**2** was considerably longer than that of TMQ, which suggests that compound *S*-**2** may be orally more effective than TMQ.

From the above results, it can be assumed that the introduction of the methyl group at the 5-position of TMQ may exert some influence on the metabolic fate of the catechol group of the tetrahydroisoquinoline nucleus.

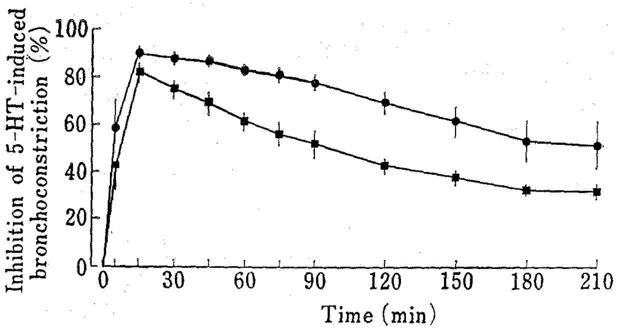


Fig. 1. Effects of Intraduodenal Administration of *S*-**2**·HCl and TMQ on the 5-HT-Induced Bronchoconstriction in Anesthetized Cats

Each point and vertical bar represents the mean ± S.E.
—●—: *S*-**2**·HCl 30 μg/kg ($n=4$); —■—: TMQ 30 μg/kg ($n=5$).

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi IR-215 spectrometer, NMR spectra with a JEOL MH-60, PMX-60, PS-100 or FX-100 spectrometer (with TMS as an internal standard), and mass spectra with a Hitachi RMU-6M spectrometer. Optical rotations were measured with a JASCO DIP-180 or Union Giken PM-201 polarimeter. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (preparative TLC) were carried out on Silica gel 60F-254 (Merck) and 60GF$_{254}$ (Merck), respectively. Column chromatography were performed on Silica gel 60 (70—230 mesh ASTM) (Merck).

(*S*)-N-Benzyloxycarbonyl-6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-5)——A solution of benzyloxycarbonyl chloride (2.51 g, 14.7 mmol) in $CHCl_3$ (10 ml) was added to a stirred mixture of TMQ[9] (5.00 g, 13.1 mmol), $NaHCO_3$ (2.70 g, 32.2 mmol), $CHCl_3$ (40 ml), and H_2O (30 ml) under cooling below 5°C. The mixture was stirred at 5°C for 1 h and then at room temperature for 2 h. The $CHCl_3$ layer was separated, washed successively with H_2O, 5% aq. HCl, and H_2O, dried (Na_2SO_4), and concentrated. The residual oil was solidified by trituration with a small amount of AcOEt to afford *S*-**5**·AcOEt (6.45 g, 87%) as a colorless solid, mp 71—75°C. Recrystallization from AcOEt–hexane gave colorless needles, mp 74—76°C, $[\alpha]_D^{15}$ +47.6° ($c=1.00$, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3525, 3250, 1720 (AcOEt), 1680. MS *m/e*: 479 (M^+), 298 (M^+-181, base). NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz, $CH_3CO_2CH_2C\underline{H}_3$), 2.04 (3H, s, $C\underline{H}_3CO_2CH_2CH_3$), 3.66 (6H, s, OMe × 2), 3.81 (3H, s, OMe), 4.15 (2H, q, $J=7$ Hz, $CH_3CO_2C\underline{H}_2CH_3$), 4.8—5.4 (3H, m), 6.22 (2H, s, H(2′) and H(6′)), 6.51 and 6.63 (1H each, s, H(5) and H(8)), 7.2—7.8 (5H, m, $-C_6H_5$). *Anal.* Calcd for $C_{27}H_{29}O_7N$·AcOEt: C, 65.59; H, 6.57; N, 2.47. Found: C, 65.56; H, 6.43; N, 2.47.

(±)-TMQ[10] (15.0 g, 39.2 mmol) was also treated as described above for the preparation of *S*-**5** to give (±)-**5** (16.1 g, 85%) as colorless prisms (from AcOEt–hexane), mp 97—100°C. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3380, 1690. *Anal.* Calcd for $C_{27}H_{29}O_7N$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.42; H, 6.13; N, 2.79.

(*S*)-N-Benzyloxycarbonyl-6,7-dihydroxy-5-dimethylaminomethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-6)——A solution of Et_3N (3.03 g, 30 mmol) in CH_3CN (5 ml) was added dropwise to a stirred suspension of *S*-**5**·AcOEt (17.0 g, 30 mmol) and N,N-dimethyl(methylene)ammonium chloride[5] (3.27 g, 35 mmol) in CH_3CN (90 ml) under cooling below 0°C. The mixture was stirred at 0°C for 1 h and then treated with H_2O. After removal of the solvent, the residue was dissolved in 5% aq. HCl (50 ml). The aqueous layer was washed with Et_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with 10%

ethanolic HCl to give *S*-**6**·HCl (16.0 g, 93%) as a colorless solid (from EtOH–Et_2O), mp 118—125°C (dec.). Recrystallization from EtOH–Et_2O gave colorless needles, mp 125—130°C (dec.), $[\alpha]_D^{20}$ +35.1° (c=1.00, MeOH). *Anal.* Calcd for $C_{30}H_{36}O_7N_2$·HCl: C, 62.88; H, 6.51; N, 4.89; Cl, 6.19. Found: C, 62.49; H, 6.48; N, 4.84; Cl, 6.05. *S*-**6** (free base): a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3549, 3400 (br), 1685. MS *m/e*: 355 (M^+-181, base). NMR ($CDCl_3$) δ: 2.34 (6H, s, NMe_2), 3.73 (6H, s, OMe×2), 3.82 (3H, s, OMe), 6.30 (2H, s, H(2′) and H(6′)), 6.63 (1H, s, H(8)), 7.1—7.4 (5H, m, $-C_6H_5$), 7.87 (2H, s, exchanges with D_2O).

(±)-**5** (4.80 g, 10 mmol) was also treated as described above for the preparation of *S*-**6** to give (±)-**6**·HCl (4.99 g, 87%) as colorless needles (from MeOH), mp 156—160°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3380 (br), 3200, 2720 (br), 1665. *Anal.* Calcd for $C_{30}H_{36}O_7N_2$·HCl: C, 62.88; H, 6.51; N, 4.89. Found: C, 62.45; H, 6.42; N, 4.92.

(*S*)-N-Benzyloxycarbonyl-6,7-dihydroxy-5-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-7)——Me_2SO_4 (390 mg, 3.10 mmol) was added to a solution of Mannich base *S*-**6** (1.59 g, 2.97 mmol) in HMPA (10 ml), and the mixture was heated at 50°C for 1.5 h. $NaBH_3CN$ (1.0 g, 15.8 mmol) was then added and the whole was heated at 70°C for 2 h. After cooling, the reaction mixture was treated with H_2O, and extracted with benzene. The benzene extracts were washed successively with H_2O, 10% aq. HCl, and H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [AcOEt–benzene (1: 3, v/v)] to afford *S*-**7** (1.00 g, 68%). Recrystallization from AcOEt–hexane gave *S*-**7**·1/2AcOEt as colorless needles, mp 130—131°C, $[\alpha]_D^{20}$ +47° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3495, 3185 (br), 1730 (AcOEt), 1660. MS *m/e*: 493 (M^+), 312 (M^+-181, base). NMR ($CDCl_3$) δ[11]: 1.25 (1.5H, t, J=7 Hz, $1/2CH_3CO_2CH_2\underline{CH_3}$), 2.03 (1.5H, s, $1/2\underline{CH_3}CO_2CH_2CH_3$), 2.11 (3H, s, 5-Me), 3.65 (6H, s, OMe×2), 3.78 (3H, s, OMe), 4.10 (1H, q, J=7 Hz, $1/2CH_3CO_2\underline{CH_2}CH_3$), 6.24 and 6.26 (2H, 2s, H(2′) and H(6′)), 6.41 and 6.44 (1H, 2s, H(8)), 7.2—7.4 (5H, m, $-C_6H_5$). *Anal.* Calcd for $C_{28}H_{31}O_7N$·1/2AcOEt: C, 67.02; H, 6.56; N, 2.61. Found: C, 66.90; H, 6.68; N, 2.55.

(±)-**6** (4.51 g, 8.45 mmol) was also treated as described above for the preparation of *S*-**7** to give (±)-**7** (2.88 g, 69%) as colorless prisms (from MeOH–AcOEt–hexane), mp 190—191°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3490, 3360, 1665. *Anal.* Calcd for $C_{28}H_{31}O_7N$: C, 68.14; H, 6.33; N, 2.84. Found: C, 67.79; H, 6.47; N, 3.05.

(*S*)-6,7-Dihydroxy-5-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-2)——A solution of *S*-**7** (780 mg, 1.45 mmol) in AcOH (15 ml) was hydrogenated on 10% Pd-C (0.3 g) at atmospheric pressure and room temperature for 1 h. After removal of the catalyst, the filtrate was treated with 10% ethanolic HCl, and concentrated *in vacuo*. The residue was crystallized from EtOH–Et_2O to give *S*-**2**·HCl (550 mg, 95%) as a colorless solid, mp 235—240°C (dec.). Recrystallization from MeOH–Et_2O gave an analytical sample as colorless prisms, mp 242—244°C (dec.), $[\alpha]_D^{20}$ −11.4° (c=0.5, H_2O). NMR ($CDCl_3$–CF_3CO_2H) δ: 2.10 (3H, s, 5-Me), 3.79 (6H, s, OMe×2), 3.91 (3H, s, OMe), 4.6—4.8 (1H, m, H(1)), 6.06 (1H, s, H(8)), 6.44 (2H, s, H(2′) and H(6′)).

***S*-2·HBr**——*S*-**2**·HCl (20 mg) was dissolved in 47% aq. HBr (2 ml). After removal of the solvent, the residue was recrystallized from H_2O–EtOH–Et_2O to afford *S*-**2**·HBr (12 mg) as colorless pillars, mp 256—259°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3475, 3150.

(*S*)-N-Benzyloxycarbonyl-6,7-dihydroxy-5-methyl-8-dimethylaminomethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (S-8)——A solution of Et_3N (505 mg, 5 mmol) in CH_3CN (5 ml) was added to a stirred suspension of *S*-**7** (2.685 g, 5 mmol) and N,N-dimethyl(methylene)ammonium chloride (611 mg, 6.5 mmol) in CH_3CN (20 ml). After being stirred at room temperature for 6 h, the reaction mixture was treated with H_2O, and concentrated. The residue was made alkaline with aq. $NaHCO_3$, and extracted with AcOEt. The AcOEt extracts were washed with sat. brine, dried (Na_2SO_4), and concentrated. The residue was treated with 10% ethanolic HCl to give *S*-**8**·HCl (2.84 g, 95%) as a colorless solid (from EtOH–Et_2O). Recrystallization from EtOH–Et_2O gave colorless needles, mp 176—177°C (dec.), $[\alpha]_D^{20}$ +13.8° (c=0.420, MeOH). *Anal.* Calcd for $C_{31}H_{38}O_7N_2$·1/2H_2O: C, 62.64; H, 6.76; N, 4.70; Cl, 5.95. Found: C, 62.78; H, 6.83; N, 4.65; Cl, 6.15. *S*-**8** (free base): a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1680. MS *m/e*: 550 (M^+), 369 (M^+-181, base), 324. NMR ($CDCl_3$) δ: 2.17 (3H, s, 5-Me), 2.22 (6H, s, NMe_2), 3.65, 3.69, and 3.79 (9H, 3s, OMe×3), 4.9—5.6 (3H, m), 6.14 (2H, s, H(2′) and H(6′)), 7.2—7.3 (5H, m, $-C_6H_5$), 8.1 (2H, br s, OH×2, exchanges with D_2O).

(*S*)-N-Benzyloxycarbonyl-6,7-dihydroxy-5,8-dimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-9)——A solution of *S*-**8** (2.44 g, 4.43 mmol) in Et_2O (25 ml) was added to Me_2SO_4 (2.79 g, 22 mmol) under ice-cooling. The mixture was stirred at room temperature for 2 h, and the resulting precipitates were collected by decantation, washed well with Et_2O, and dried *in vacuo*. This product was dissolved in HMPA (20 ml) followed by addition of $NaBH_3CN$ (1.20 g, 19 mmol), and the whole was heated at 70°C for 3 h. The reaction mixture was treated with H_2O and extraction was carried out with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [benzene–AcOEt (5: 1, v/v)] to afford *S*-**9** (1.06 g, 47%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 1680. MS *m/e*: 326 (M^+-181, base). NMR ($CDCl_3$) δ[11]: 1.95 and 2.03 (3H, 2s, 8-Me), 2.12 (3H, s, 5-Me), 3.67 (6H, s, OMe×2), 3.79 (3H, s, OMe), 6.19 (2H, s, H(2′) and H(6′)), 7.2—7.3 (5H, m, $-C_6H_5$).

(*S*)-6,7-Dihydroxy-5,8-dimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-3)——A solution of *S*-**9** (600 mg, 1.18 mmol) in EtOH (20 ml) containing 10% aq. HCl (1.5 ml) was hydrogenated on 10% Pd–C (120 mg) at atmospheric pressure and room temperature for 6 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH–Et_2O to give *S*-**3**·HCl (270 mg, 56%) as colorless prisms, mp 217—220°C (dec.), $[\alpha]_D^{20}$ +42.3° (c=0.5, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3550, 3500, 1650. MS *m/e*: 373 (M$^+$, faint), 192 (M$^+$−181, base). NMR ($CDCl_3$–CF_3CO_2H) δ: 2.00 (3H, s, 8-Me), 2.13 (3H, s, 5-Me), 3.80 (6H, s, OMe×2), 3.90 (3H, s, OMe), 4.9—5.2 (1H, m, H(1)), 6.37 (2H, s, H(2′) and H(6′)).

(±)-N-Benzyloxycarbonyl-6-hydroxy-7-methoxy-5-dimethylaminomethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-11]——The N-benzyloxycarbonyl derivative (4.20 g, 85%) of (±)-**10** was obtained from (±)-**10**·HCl[6] (3.96 g, 10 mmol) as described above for the preparation of *S*-**5**. Recrystallization from AcOEt–hexane gave colorless needles, mp 125—126°C. IR ν_{max}^{Nujol} cm^{-1}: 3230 (br), 1660. MS *m/e*: 312 (M$^+$−181, base). NMR ($CDCl_3$) δ[11]: 3.6—3.8 (12H, group of singlets, OMe×4), 5.66 (1H, s, OH, exchanges with D_2O), 6.13 and 6.17 (2H, 2s, H(2′) and H(6′)), 6.26 and 6.66 (1H each, s, H(5) and H(8)), 7.32 (5H, s, $-C_6H_5$). *Anal.* Calcd for $C_{28}H_{31}O_7N$: C, 68.14; H, 6.33; N, 2.84. Found: C, 67.96; H, 6.45; N, 2.70. A solution of Et_3N (202 mg, 2 mmol) in CH_3CN (5 ml) was added to a stirred suspension of this N-benzyloxycarbonyl derivative (986 mg, 2 mmol) of (±)-**10** and N,N-dimethyl(methylene)ammonium chloride (255 mg. 2.4 mmol) in CH_3CN (15 ml) under ice-cooling. After being stirred at room temperature for 2 h, the reaction mixture was treated with H_2O. After removal of the solvent, the residue was dissolved in 5% aq. HCl (20 ml). The aqueous layer was washed with Et_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine, dried (Na_2SO_4), and concentrated. The residue was treated with 10% ethanolic HCl to give (±)-**11**–HCl (1.06 g, 90%) as a colorless solid (from EtOH–Et_2O), mp 204—207°C (dec.). Recrystallization from EtOH–Et_2O gave colorless needles, mp 207—209°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3500—3100 (br), 2700—2450 (br), 1685 *Anal.* Calcd for $C_{31}H_{38}O_7N_2\cdot HCl$: C, 63.42; H, 6.70; N, 4.77. Found: C, 63.53; H, 6.93; N, 4.70. (±)-**11** (free base): a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 1685. MS *m/e*: 369 (M$^+$−181, base). NMR ($CDCl_3$) δ: 2.30 (6H, s, NMe_2), 3.68 (9H, s, OMe×3), 3.78 (3H, s, OMe), 6.23 (3H, s, H(2′), H(6′), and H(8)), 7.2—7.4 (5H, m, $-C_6H_5$), 8.1—8.6 (1H, m, OH, exchanges with D_2O).

(±)-N-Benzyloxycarbonyl-6-hydroxy-7-methoxy-5-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-12]——(±)-**11** (1.10 g, 2 mmol) was treated as described above for the preparation of *S*-**9** to afford (±)-**12** (792 mg, 78%) as a colorless solid. Recrystallization from EtOH–hexane gave colorless plates, mp 125—126°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3660, 3535, 1685. MS *m/e*: 326 (M$^+$−181, base). NMR ($CDCl_3$) δ[11]: 2.13 (3H, s, 5-Me), 3.67—3.87 (12H, group of singlets, OMe×4), 5.63 (1H, s, OH, exchanges with D_2O), 6.03 (1H, s, H(8)), 6.17 and 6.25 (2H, 2s, H(2′) and H(6′)), 7.2—7.4 (5H, m, $-C_6H_5$).

(±)-N-Benzyloxycarbonyl-6,7-dimethoxy-5-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-13]——A stirred mixture of (±)-**7** (494 mg, 1 mmol), CH_3I, 2.5 g, excess), K_2CO_3 (500 mg, 3.63 mmol) and DMF (10 ml) was heated at 80°C for 4 h. After cooling, the reaction mixture was treated with H_2O, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residual solid (±)-**13** (510 mg, 98%) was recrystallized from benzene–hexane to give colorless prisms, mp 115—117°C. IR ν_{max}^{Nujol} cm^{-1}: 1700. MS *m/e*: 340 (M$^+$−181, base). NMR ($CDCl_3$) δ[11]: 2.16 (3H, s, 5-Me), 3.55—3.8 (15H, group of singlets, OMe×5), 6.10 and 6.14 (1H, 2s, H(8)), 6.20 and 6.28 (2H, 2s, H(2′) and H(6′)), 7.2—7.4 (5H, m, $-C_6H_5$). *Anal.* Calcd for $C_{30}H_{35}O_7N$: C, 69.08; H, 6.76; N, 2.69. Found: C, 69.09; H, 6.77; N, 2.72.

Methylation of (±)-12——Compound (±)-**12** (507 mg) was methylated as described above for the methylation of (±)-**7** to give (±)-**13** (510 mg, 98%) as colorless prisms (from benzene–hexane), mp 115—117°C. This material was identical with a sample obtained by methylation of (±)-**7** (IR, mass, and NMR spectra and mixed melting point).

(*S*)-N-Benzyloxycarbonyl-5-bromo-1-(2-bromo-3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (*S*-15)——*S*-**14**·HBr·1/2H_2O[8] (4.0 g, 6.75 mmol) was treated in the manner described for the preparation of *S*-**5** to give *S*-**15** (4.25 g, 98%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3230 (br), 1675. MS *m/e*: 639, 637, and 635 (M$^+$), 378 and 376 (M$^+$−261, 259), 334 and 332, 261 and 259.

(*S*)-N-Benzyloxycarbonyl-1-(2-bromo-3,4,5-trimethoxybenzyl)-6,7-Dihydroxy-5-dimethylaminomethyl-1,2,3,4-tetrahydroisoquinoline (*S*-17)——A solution of Et_3N (404 mg, 4 mmol) in CH_3CN (5 ml) was added to a stirred suspension of *S*-**15** (2.55 g, 4.0 mmol) and N,N-dimethyl(methylene)ammonium chloride (564 mg, 6 mmol) in CH_3CN (20 ml) under ice-cooling. After being stirred at room temperature for 3 h, the reaction mixture was treated with H_2O. After removal of the solvent, the residue was dissolved in 5% aq. HCl (30 ml). The aqueous solution was washed with Et_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine, dried (Na_2SO_4), and concentrated. The residual oil (2.30 g) was purified by column chromatography [$CHCl_3$–MeOH (10: 1, v/v)] to give *S*-**17** (615 mg, 25%) as a pale brown viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1695. MS *m/e*: 355 (M$^+$−261, 259), 261 and 259. NMR ($CDCl_3$) δ[11]: 2.33 (6H, s, NMe_2), 3.6—4.0 (9H, group of singlets, OMe×3), 7.1—7.4 (5H, m, $-C_6H_5$), 7.8—8.0 (2H, m, OH). *Anal.* Calcd for $C_{30}H_{35}O_7N_2Br$: C, 58.54; H, 5.73; N, 4.55; Br, 12.98. Found: C, 59.09; H, 5.62; N, 4.43; Br, 13.19.

(*S*)-N-Benzyloxycarbonyl-1-(2-bromo-3,4,5-trimethoxybenzyl)-6,7-dihydroxy-5-methyl-1,2,3,4-tetrahydroisoquinoline (*S*-18)——*S*-**17** (338 mg, 0.55 mmol) was treated in the manner described for the preparation of *S*-**9**. The crude product was purified by preparative TLC [AcOEt–hexane (1: 1, v/v)] to give *S*-**18** (150 mg, 48%) as a colorless viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3280, 1690. MS *m/e*: 312 (M$^+$−261, 259), 268, 261, and 259. NMR ($CDCl_3$) δ[11]: 2.12 (3H, s, 5-Me), 3.60, 3.74, 3.76, 3.82, and 3.85 (9H, 5s, OMe×3), 6.34 and 6.38

(1H, 2s, H(6′) or H(8)), 6.56 and 6.68 (1H, 2s, H(6′) or H(8)), 7.2—7.4 (5H, m, $-C_6H_5$).

Hydrogenolysis of *S*-18——A solution of *S*-**18** (80 mg, 0.14 mmol) in EtOH (5 ml) and H_2O (1 ml) was hydrogenated on 10% Pd–C (60 mg) at 3.0 times atmospheric pressure and at 40—50°C for 1 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was recrystallized from H_2O–EtOH–Et_2O to give *S*-**2**·HBr (40 mg, 65%) as colorless pillars, mp 257—260°C (dec.). *Anal.* Calcd for $C_{20}H_{25}O_5N\cdot HBr$: C, 54.56; H, 5.95; N, 3.18; Br, 18.15. Found: C, 54.47; H, 5.96; N, 3.33; Br, 18.03. This material was identical with a sample (*S*-**2**·HBr) obtained by hydrogenolysis of *S*-**7** (IR, mass and NMR spectra and mixed melting point).

Benzylation of *S*-5——A mixture of *S*-**5** (567 mg, 1 mmol), benzyl chloride (165 mg, 1.3 mmol), K_2CO_3 (230 mg, 1.7 mmol), and DMSO (5 ml) was stirred at room temperature for 18 h under argon. The reaction mixture was diluted with AcOEt, and the organic layer was washed successively with 5% aq. HCl and H_2O, dried (Na_2SO_4), and concentrated. The residual oil (680 mg), which contained 3 major components having *Rf* 0.56, 0.59, and 0.65 on TLC [benzene–AcOEt (5: 3, v/v)], was fractionated by preparative TLC [repeated 4 times with benzene–AcOEt (9: 1, v/v)].

S-**19** (*Rf* 0.56) was obtained as a colorless viscous oil (160 mg, 28%), $[\alpha]_D^{20}$ +36.6° (c=1.79, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 3550, 1690. MS *m/e*: 569 (M^+, faint), 388 (M^+-181). NMR ($CDCl_3$) δ: 3.68 (6H, s, OMe×2), 3.80 (3H, s, OMe), 5.07 (2H, s, 6-O$\underline{H}_2C_6H_5$), 5.59 (1H, s, OH, exchanges with D_2O), 6.21 (2H, s, H(2′) and H(6′)), 6.58 and 6.63 (1H each, s, H(5) and H(8)), 7.2—7.4 (10H, m, $-C_6H_5\times2$).

S-**20** (*Rf* 0.59) was obtained as a colorless viscous oil (143 mg, 25%), $[\alpha]_D^{20}$ +45.7° (c=1.33, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3660, 3540, 1685. MS *m/e*: 569 (M^+, faint), 388 (M^+-181). NMR ($CDCl_3$) δ:[11] 3.6—3.8 (9H, group of singlets, OMe×3), 4.84 (2H, s, 7-OC$\underline{H}_2C_6H_5$), 5.62 (1H, s, OH, exchanges with D_2O), 6.16 (1H, s, H(8)), 6.20 (2H, s, H(2′) and H(6′)), 6.67 (1H, s, H(5)), 7.3—7.4 (10H, m, $-C_6H_5\times2$).

S-**21** (*Rf* 0.65) was obtained as a colorless viscous oil (233 mg, 35%), $[\alpha]_D^{20}$ +46.7° (c=0.974, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685. MS *m/e*: 478 (M^+-181). NMR ($CDCl_3$) δ: 3.66 (6H, s, OMe×2), 3.79 (3H, s, OMe), 4.95 and 5.11 (2H each, s, $-OC\underline{H}_2C_6H_5\times2$), 6.18 (2H, s, H(2′) and H(6′)), 6.39 (1H, s, H(8)), 6.69 (1H, s, H(5)), 7.2—7.4 (15H, m, $-C_6H_5\times3$).

(*S*)-6-Hydroxy-7-methoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-10)——A mixture of *S*-**19** (80 mg, 0.14 mmol), CH_3I (0.15 ml), K_2CO_3 (50 mg, 0.4 mmol), and DMSO (2 ml) was stirred at room temperature for 48 h. The reaction mixture was treated with H_2O, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to give the O-methyl derivative (85 mg, 100%) of *S*-**19** as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685. MS *m/e*: 583 (M^+). NMR ($CDCl_3$) δ: 3.67 (9H, s, OMe×3), 3.79 (3H, s, OMe), 5.09 (2H, s, 6-OC$\underline{H}_2C_6H_5$), 6.20 (1H, s, H(8)), 6.24 (2H, s, H(2′)and H(6′)), 6.64 (1H, s, H(5)), 7.3—7.4 (10H, m, $-C_6H_5\times2$). A solution of the O-methyl derivative (61 mg, 0.105 mmol) of *S*-**19** in EtOH (3 ml) containing 10% aq. HCl (0.5 ml) was hydrogenated on 10% Pd–C (30 mg) at atmospheric pressure and room temperature for 6 h. After removal of the catalyst by filtration, the filtrate was concentrated. The residual viscous oil was dissolved in H_2O, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4), and concentrated. The residual pale yellow solid was recrystallized from EtOH–hexane to give *S*-**10** (15 mg) as colorless prisms, mp 187—188°C. MS *m/e*: (M^+-181, base). NMR ($CDCl_3$) δ: 3.86 (12H, s, OMe×4), 6.45 (2H, s, H(2′) and H(6′)), 6.60 and 6.64 (1H each, s, H(5) and H(8)). This material was identical with (±)-**10**,[6] and was different from (±)-**22**[6] (TLC behavior and NMR spectrum).

(*S*)-7-Hydroxy-6-methoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-22)——*S*-**20** (65 mg) was methylated as described above for the preparation of *S*-**19** to give the O-methyl derivative (66 mg, 99%) of *S*-**20** as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685. MS *m/e*: 583 (M^+). NMR ($CDCl_3$) δ: 3.67 (6H, s, OMe×2), 3.79 and 3.83 (3H each, s, OMe×2), 4.92 (2H, s, 7-OC$\underline{H}_2C_6H_5$), 6.17 (2H, s, H(2′) and H(6′)), 6.32 (1H, s, H(8)), 6.62 (1H, s, H(5)), 7.3—7.4 (10H, m, $-C_6H_5\times2$). The O-methyl derivative (45 mg) of *S*-**20** was hydrogenated as described above for the preparation of *S*-**10** to give *S*-**22** (11 mg) as a pale yellow viscous oil. MS *m/e*: 178 (M^+-181, base). NMR ($CDCl_3$) δ: 3.84 (12H, s, OMe×4), 6.44 (2H, s, H(2′) and H(6′)), 6.56 and 6.82 (1H each, s, H(5) and H(8)). This material was identical with (±)-**22**[6] (TLC behavior and NMR spectrum).

(*S*)-N-Benzyloxycarbonyl-6-benzyloxy-7-hydroxy-8-dimethylaminomethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (*S*-23)——Et_3N (850 mg, 8.42 mmol) was added to a stirred suspension of *S*-**19** (4.80 g, 8.42 mmol) and N,N-dimethyl(methylene)ammonium chloride (1.18 g, 12.6 mmol) in CH_3CN (50 ml), and the whole was stirred at room temperature for 7 h. The reaction mixture was treated with H_2O, and concentrated *in vacuo*. The residue was treated with 10% aq. HCl (30 ml) and washed with Et_2O. The aqueous layer was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was treated with 10% ethanolic HCl to give *S*-**23**·HCl (4.68 g, 84%) as colorless prisms (from EtOH–Et_2O), mp 195—196°C (dec.). Recrystallization from EtOH–Et_2O gave colorless prisms, mp 199—200°C (dec.), $[\alpha]_D^{20}$ +23.0° (c=1.00, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2650, 1680. MS *m/e*: 445 (M^+-181, base). *Anal.* Calcd for $C_{37}H_{42}O_7N_2\cdot HCl$: C, 67.01; H, 6.54; N, 4.22. Found: C, 66.77; H, 6.67; N, 4.31. *S*-**23** (free base): a colorless viscous oil. NMR ($CDCl_3$) δ: 2.23 (6H, s, NMe_2), 3.68 (6H, s, OMe×2), 3.80 (3H, s, OMe), 6.1 (2H, br s, H(2′) and H(6′)), 6.7 (1H, br s, H(5)), 7.2—7.5 (10H, m, $-C_6H_5\times2$).

(S)-N-Benzyloxycarbonyl-6-benzyloxy-7-hydroxy-8-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (S-24)——A solution of S-23 (4.37 g, 6.97 mmol) in a mixture of Et_2O (20 ml) and THF (20 ml) was added to a stirred solution of Me_2SO_4 (8.82 g, 70 mmol) in Et_2O (30 ml). The whole was stirred at room temperature for 3 h, and the resulting oil was taken up by decantation, washed with Et_2O, and dried. The residue was dissolved in HMPA (30 ml), and $NaBH_3CN$ (1.90 g, 30 mmol) was added to this solution. The whole was heated at 70°C for 5 h. The reaction mixture was treated with H_2O, and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [AcOEt–hexane (1: 4—1: 2, v/v)] to afford S-**24** (2.88 g, 70%) as a colorless viscous oil, $[\alpha]_D^{20}$ $+12.6°$ (c=0.870, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545, 1685. MS m/e: 402 (M^+-181, base). NMR ($CDCl_3$) δ:11) 1.99 and 2.05 (3H, 2s, 8-Me), 3.66 (6H, s, OMe × 2), 3.79 (3H, s, OMe), 5.07 (2H, s, $-OC\underline{H}_2C_6H_5$), 5.71 (1H, s, OH, exchanges with D_2O), 6.16 (2H, s, H(2′) and H(6′)), 6.59 (1H, br s, H(5)), 7.2—7.4 (10H, m, $-C_6H_5\times 2$).

(S)-6,7-Dihydroxy-8-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (S-4)——A solution of S-**24** (2.60 g, 4.45 mmol) in EtOH (20 ml) containing 10% aq. HCl (4 ml) was hydrogenated on 10% Pd–C (0.3 g) at atmospheric pressure and room temperature for 6 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was treated with EtOH–Et_2O under reflux to afford S-**4**·HCl·1/3EtOH (1.30 g, 74%) as a colorless powder, mp 140°C (sint.), 145—165°C (dec.), $[\alpha]_D^{20}$ $+40.2°$ (c=0.5, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3410 (br), 3100 (br). MS m/e: 178 (M^+-181, base). NMR ($CDCl_3$–CF_3CO_2H) δ: 1.28 (1H, t, J=7 Hz, $1/3C\underline{H}_3CH_2OH$), 2.02 (3H, s, 8-Me), 3.78 (6H, s, OMe × 2), 3.84 (3H, s, OMe), 4.5—5.1 (1H, m, H(1)), 6.36 (2H, s, H(2′) and H(6′)), 6.48 (1H, s, H(5)).

Acknowledgement The authors are grateful to Dr. S. Sugasawa, Professor Emeritus of Tokyo University, for valuable discussions, and to Dr. S. Saito for his encouragement. Thanks are also due to the staff of the Analytical Center of this company for spectral measurements and elemental analyses.

References and Notes

1) Part II: K. Yamada, N. Itoh, K. Ikezawa, A. Kiyomoto, and T. Iwakuma, *Chem. Pharm. Bull.*, **29**, 1848 (1981).
2) K. Yamada, M. Ikezaki, N. Umino, H. Ohtsuka, N. Itoh, K. Ikezawa, A. Kiyomoto, and T. Iwakuma, *ibid.*, **29**, 744 (1981).
3) S. Yamamura, K. Oda, T. Mizoguchi, S. Saito, Y. Iwasawa, and A. Kiyomoto, *ibid.*, **27**, 858 (1979).
4) K. Yamada, N. Itoh, and T. Iwakuma, *Chem. Commun.*, **1978**, 1089.
5) G. Kinast and L.-F. Tietze, *Angew. Chem. Int. Ed. Engl.*, **15**, 239 (1976).
6) E. Yamato, Y. Miura, T. Nagao, and M. Kawanishi, *Japan. Patent Kokai*, 72-8308 (1972).
7) C. Satoh, T. Nagao, T. Kono, and A. Kiyomoto, *Chem. Pharm. Bull.*, **19**, 667 (1971).
8) T. Takahashi and Y. Sato, *Radioisotopes*, **17**, 374 (1968).
9) H. Hiramatsu, M. Senuma, and I. Ogawa, *Japan. Patent Kokai*, 72-14229 (1972).
10) E. Yamato, M. Hirakura, and S. Sugasawa, *Tetrahedron*, *Suppl.* **8**, *Part I*, 129 (1966).
11) Brossi *et al.* reported that the solution NMR spectra of the 1-benzyl-N-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinolines shows the presence of two rotomers. See K.C. Rice and A. Brossi, *J. Org. Chem.*, **45**, 592 (1980).