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Synthesis of 3,4-Dihydro- and 1,2,3,4-Tetrahydroisoquinolines

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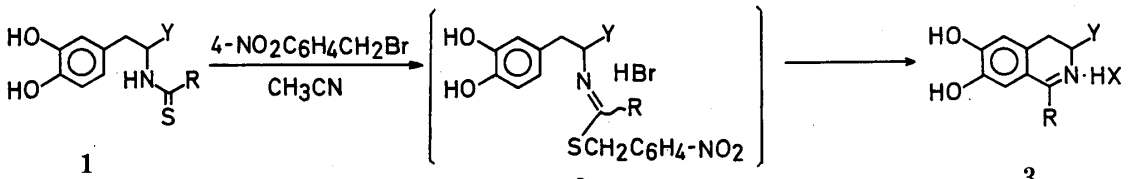
N-Alkylthiocarbonyldopa (**1a—e**) and dopamine (**1f—h**) derivatives can be converted into the corresponding 3,4-dihydroisoquinolines (**3**) by treatment with 4-nitrobenzyl bromide. The $NaBH_4$ reduction of 1,3-disubstituted 3,4-dihydroisoquinolines (**3a—e**) gave 1,3-*cis*-1,2,3,4-tetrahydroisoquinolines (**4a—e**). Hydrogenation of **3a—e** over PtO_2 also gave **4a—e** in good yields. The synthesis of optically active **3a, i** and **4a, i** is also described.

Keywords——*N*-thioacyldopa; 3,4-dihydroisoquinoline; 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1-substituted); 4-nitrobenzyl bromide; alkylthioiminium salt; Lawesson's reagent; X-ray analysis

We have recently reported on the cyclization of N^{α}-thioacyltryptophans to 3,4-dihydro-β-carbolines *via* the thioiminium salts by the use of alkylating agents, and the reduction of the resulting 1,3-disubstituted 3,4-dihydro-β-carbolines to *cis*- or *trans*-1,2,3,4-tetrahydro-β-carbolines with satisfactory stereoselectivity.[1] In this paper, we describe the synthesis of 1-substituted 6,7-dihydroxy-3,4-dihydroisoquinolines (**3**) by the similar cyclization reaction of the *N*-alkylthiocarbonyl derivatives (**1**) of 3,4-dihydroxyphenylalanine (dopa) and 2-(3,4-dihydroxyphenyl)ethylamine (dopamine), and the reduction of **3a—e** to 1,3-*cis*-disubstituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines (**4a—e**).



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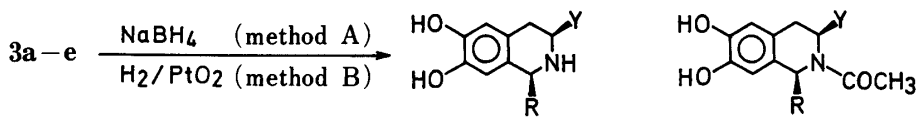


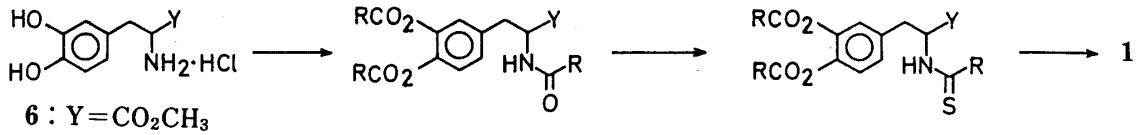
4a—e 5a—c

a: $R=CH_3$, $Y=CO_2CH_3$
b: $R=C_2H_5$, $Y=CO_2CH_3$
c: $R=CH_2C_6H_5$, $Y=CO_2CH_3$
d: $R=CH_2CH_2C_6H_5$, $Y=CO_2CH_3$
e: $R=C_6H_5$, $Y=CO_2CH_3$
f: $R=CH_3$, $Y=H$
g: $R=C_2H_5$, $Y=H$
h: $R=C_6H_5$, $Y=H$
i: $R=CH_3$, $Y=CO_2C_2H_5$

Chart 1

N-Alkylthiocarbonyl derivatives (**1**) were readily prepared from dopa and dopamine by a three-step reaction sequence as shown in Chart 2. Acylation and thionation with Lawesson's

reagent gave thioamides (**10**), which were converted to **1** by treatment with pyrrolidine (or HCl) in CH_3OH. The overall yields of **1** were approximately 75—85% from the starting amines (**6**—**8**).



6 : Y=CO_2CH_3
7 : Y=$CO_2C_2H_5$
8 : Y=H

9 **10**

R=CH_3, C_2H_5, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, C_6H_5

Chart 2

The cyclization was examined using **1a** as a substrate (Entries 1—5 in Table I). After screening various alkylating agents, we found that 4-nitrobenzyl bromide was most effective for the cyclization of **1** to **3** *via* the thioiminium salts (**2**). As can be seen in Table I, treatment of **1a**—**d** with 4-nitrobenzyl bromide in refluxing CH_3CN gave the corresponding 3,4-dihydroisoquinolines (**3a**—**d**) in reasonable to good yields. However the reactions of **1e**—**h** were very slow in refluxing CH_3CN[2] and required a higher reaction temperature. At 130 °C in a sealed tube, compounds **1f**—**h** gave the cyclization products (**3f**—**h**) in moderate yields. In the case of the phenylthiocarbonyl derivative (**1e**) only, the reactions at higher temperatures (at 107 °C in iso-BuCN, 115 °C in BuCN, and 130 °C in CH_3CN in a sealed tube) were always accompanied by decarboxylation to result in the formation of a mixture of **3e** and **3h**, from which only *ca.* 20% of **3e** was isolated in pure form.

TABLE I. The Cyclization of *N*-Thioacyl Derivatives (**1**) to 3,4-Dihydroisoquinolines (**3**) with Alkyl Halides in Acetonitrile

Entry	1	Alkyl halide	Reaction conditions		Product (3)[a]	
			Temperature	Time (h)	Yield (%)	mp °C (dec.)
1	**1a**	CH_3I	Refl.	24	9[b]	Foam
2	**1a**	$C_6H_5CH_2Br$	Refl.	72	64	201—203
3	**1a**	4-$CH_3OC_6H_4CH_2Br$	Refl.	72	18	201—203
4	**1a**	4-$ClC_6H_4CH_2Br$	Refl.	48	60	201—203
5	**1a**	4-$NO_2C_6H_4CH_2Br$	Refl.	24	85	201—203
6	**1b**	4-$NO_2C_6H_4CH_2Br$	Refl.	48	73	164—166
7	**1c**	4-$NO_2C_6H_4CH_2Br$	Refl.	72	65	194—195
8	**1d**	4-$NO_2C_6H_4CH_2Br$	Refl.	72	57	108—109
9	**1e**	4-$NO_2C_6H_4CH_2Br$	115 °C[c]	60	22	Foam
10	**1f**	4-$NO_2C_6H_4CH_2Br$	130 °C[d]	24	75	218—220
11	**1g**	4-$NO_2C_6H_4CH_2Br$	130 °C[d]	24	50	223—224
12	**1h**	4-$NO_2C_6H_4CH_2Br$	130 °C[d]	48	76	273—275

a) The hydrobromides unless otherwise stated. *b*) Isolated as a free base. *c*) In refluxing BuCN. *d*) In a sealed tube.

Conversion of **3** into 1,2,3,4-tetrahydroisoquinolines (**4**) was conducted by method A (reduction with $NaBH_4$) and method B (catalytic hydrogenation over PtO_2).

The reduction of **3** with $NaBH_4$ proceeded in stereospecific manner at −78 °C to give **4** as air-sensitive free bases, which, to avoid coloration and decomposition during work-up, were converted to the hydrochlorides and purified by recrystallization to give the pure hydrochlorides (**4**·HCl) in moderate yields (method A in Table II).[3]

The catalytic hydrogenation of **3** (method B) was carried out at room temperature in CH_3OH under 1 atm of hydrogen. The usual work-up, including separation from the catalyst, removal of the solvent, and purification by recrystallization, gave the 1,3-*cis* isomers (**4**) in good yields as the stable salts (**4a—d** as the hydrobromides, **4e** as the hydrochloride).[3] The results are summarized in Table II. The better results in method B than in method A are considered to be due to the simplicity of work-up.

For characterization, the reduction products (**4a—c**) were converted into the corresponding *N*-acetyl tetrahydroisoquinolines (**5**) in high yields.

TABLE II. The Reduction of 3,4-Dihydroisoquinolines (**3a—e**)

Entry	Product	Method A (HCl salt)[a]		Method B (HBr salt)[a]	
		Yield (%)	mp °C (dec.)	Yield (%)	mp °C (dec.)
13	**4a**	62	227—229	85	214—215
14	**4b**	60	183—185	85	202—204
15	**4c**	62	207—209	79	194—195
16	**4d**	63	179—181	78	Powder
17	**4e**	49	234—236	72[b]	234—236

a) Method A, reduction with $NaBH_4$; method B, hydrogenation over PtO_2. *b*) HCl salt.

The stereochemistry of **4a** was deduced from a comparison of its spectral data with those of an optically active authentic 1,3-*cis* isomer.[4] The 1,3-*cis* relationship for compounds **4e**, and **5c** (*N*-acetyl derivative of **4c**) was unambiguously defined by X-ray crystallographic analysis (Figs. 1, 2). As regards the configurations of **4b** and **4d**, we postulate the 1,3-*cis* relationship from the analogy of the mode of reduction.

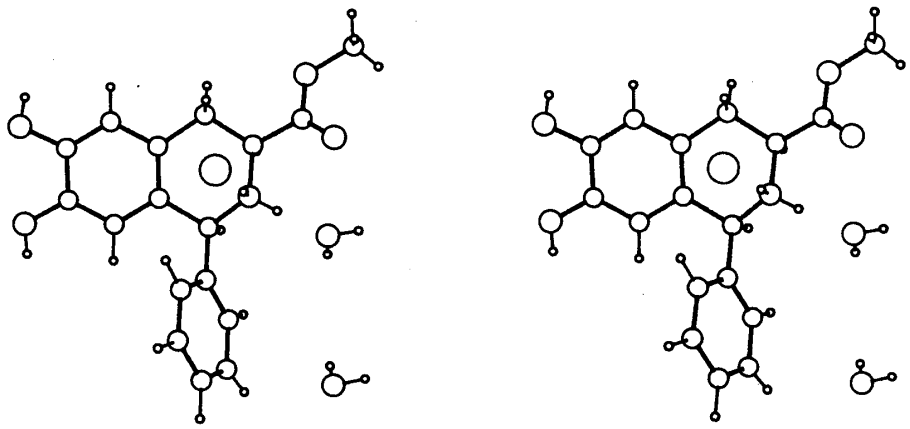


Fig. 1. Stereoview of the Structure of **4e**

This cyclization–reduction method was applied to the synthesis of optically active 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic esters, (1*S*, 3*S*)-**4a** and (1*S*, 3*S*)-**4i**.

Optically active thioamides, (*S*)-**1a** and (*S*)-**1i**, were prepared from the corresponding L-dopa esters ((*S*)-**6** and (*S*)-**7**) in the same manner as used for the preparation of *dl*-**1a**.[1,5] The optical purity of (*S*)-**1a** was confirmed by reconverting it into the amide, (*S*)-**9a**; treatment of (*S*)-**1a** with methyl iodide in CH_3OH, followed by acetylation with acetic anhydride gave (*S*)-**9a** in 87% yield; the optical rotation of the product coincided with that of the original (*S*)-**9a**.

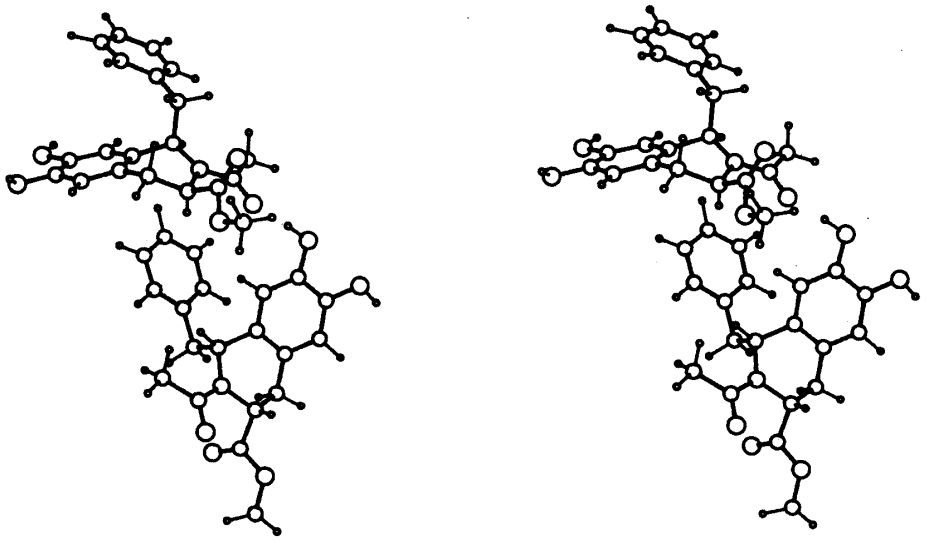


Fig. 2. Stereoview of the Structure of **5c**

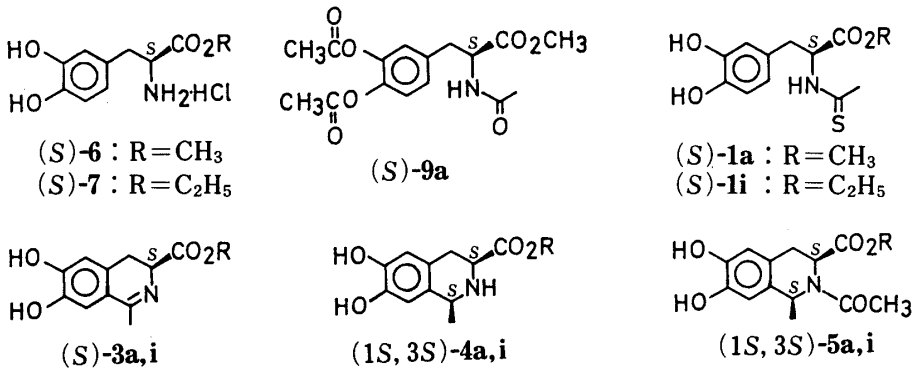
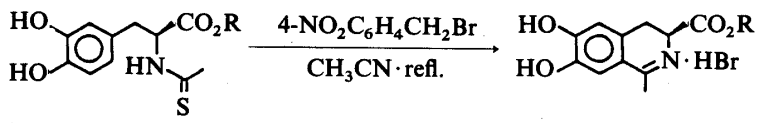


Chart 3

The cyclization was examined under reflux in CH_3CN. Treatment of (*S*)-**1a** and (*S*)-**1i** with 4-nitrobenzyl bromide gave optically active (*S*)-**3a** and (*S*)-**3i** in good yields, respectively. It should be noted, however, that, as can be seen in Table III, partial racemization of the products took place in this cyclization reaction during prolonged refluxing.

TABLE III. The Cyclization of the Optically Active Isomers



(*S*)-**1a**, **i** (*S*)-**3a**, **i**

Thioamide	Reaction time (h)	Yield of (*S*)-**3** (%)	$[\alpha]_D^{20}$ (c=1.0, CH_3OH)
(*S*)-**1a**	16	73	+167.9°
(*S*)-**1a**	24	87	+166.8°
(*S*)-**1a**	48	82	+124.0°
(*S*)-**1i**	18	78	+158.6°
(*S*)-**1i**	48	82	+123.7°

The cyclized products, (*S*)-**3a** and (*S*)-**3i**, were stereoselectively converted into the 1,3-*cis* isomers, (1*S*, 3*S*)-**4a** and (1*S*, 3*S*)-**4i**, by $NaBH_4$ reduction (Table IV). Hydrogenation also

gave the 1,3-*cis* isomers, (1*S*, 3*S*)-**4a**·HBr and (1*S*, 3*S*)-**4i**·HBr, in good yields, and these were readily converted into the corresponding *N*-acetyl derivatives, (1*S*, 3*S*)-**5a** and (1*S*, 3*S*)-**5i**, in high yields. Specific rotation values of the 1,3-*cis* products ((1*S*, 3*S*)-**4a**·HCl, (1*S*, 3*S*)-**4i**·HCl, (1*S*, 3*S*)-**5a**, and (1*S*, 3*S*)-**5i**) were consistent with those of authentic samples.[4,6,7]

TABLE IV. The Reduction of the Optically Active Isomers

(*S*)-**3a**, **i** (1*S*,3*S*)-**4a**, **i**

3[a]	Method[b]	Product	Yield (%)	$[\alpha]_D^{20}$ (c=1.0, CH_3OH)
(*S*)-**3a**	A	(1*S*,3*S*)-**4a**·HCl	62	−105.6°[c]
(*S*)-**3a**	B	(1*S*,3*S*)-**4a**·HBr	84	−100.8°
(*S*)-**3i**	A	(1*S*,3*S*)-**4i**·HCl	80	−106.3°[d]
(*S*)-**3i**	B	(1*S*,3*S*)-**4i**·HBr	85	−102.4°

a) (*S*)-**3a**, $[\alpha]_D^{20}$ +166.8°; (*S*)-**3i**, $[\alpha]_D^{20}$ +158.6°. *b*) Method A, reduction with $NaBH_4$; method B, hydrogenation over PtO_2. *c*) Authentic (1*S*,3*S*)-**4a**·HCl[4a]: $[\alpha]_D^{20}$ −112.4° (c=1.0, CH_3OH). *d*) Authentic (1*S*,3*S*)-**4i**·HCl[4b,d]: $[\alpha]_D$ −110.5° (c=1.0, CH_3OH).

Experimental

Melting points were determined with a Yanaco MP-J2 hot stage microscope and a Yamato MP-21 melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 260-10 or an FX-6200 FT-IR spectrophotometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were measured with a JEOL JNM-PMX 60 or a JEOL FX-100 S spectrometer. Mass spectra (MS) were recorded on a Hitachi RMU-6M mass spectrometer. Optical rotations were recorded with an automatic digital polarimeter (PM-201, Union Giken).

Preparation of Thioamide (1)——Thioamides (**1**) were prepared from dopa ester (**6**) and dopamine (**8**). The general procedure is exemplified by the preparaion of **1a**.

***N*-Methylthiocarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (1a)**——A solution of **6** (9.90 g, 40 mmol) and Ac_2O (13.5 g, 132 mmol) in pyridine (40 ml) was stirred for 20 h at room temperature. The pyridine was removed at 40 °C. The residual oil was dissolved in AcOEt, washed with dil.HCl, saturated $NaHCO_3$ solution and brine, and dried. Evaporation of the AcOEt gave 13.5 g (quant.) of **9a** as an oil. IR ($CHCl_3$) cm^{-1}: 3320, 1750, 1650. MS *m/e*: 337 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.0 (3H, s), 2.27 (6H, s), 3.15 (2H, d), 3.72 (3H, s), 4.9 (1H, m), 6.15 (1H, br d), 6.9—7.3 (3H, m). This oil was dissolved in dimethoxyethane (DME) (110 ml), then Lawesson's reagent (9.70 g, 24 mmol) was added and the mixture was stirred for 24 h at room temperature. The DME was removed under reduced pressure. The residue was taken up in AcOEt and the solution was washed with saturated $NaHCO_3$ solution and H_2O, then dried. Removal of the AcOEt gave a crude product (**10a**), which was purified by column chromatography on silica gel. Elution with hexane–AcOEt (1 : 1, v/v) gave 12.71 g (90%) of **10a**, mp 109—111 °C. IR (Nujol) cm^{-1}: 3280, 1770, 1710. MS *m/e*: 353 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (6H, s), 2.55 (3H, s), 3.85 (2H, m), 3.74 (3H, s), 5.45 (1H, m), 6.9—7.4 (3H, m), 7.7 (1H, br). This compound **10a** (12.71 g) was dissolved in CH_3OH (150 ml), and pyrrolidine (6.4 g, 90 mmol) was added at 0 °C. The mixture was stirred for 20 min at the same temperature. In order to neutralize excess pyrrolidine, HCl–CH_3OH was added to the reaction mixture and the solvent was evaporated off. The residue was chromatographed on silica gel (hexane–AcOEt (1 : 2, v/v) as an eluent) to give 8.72 g (81% yield from **6**) of **1a**, mp 139—141 °C. This *O*-deacetylation can also be achieved with HCl in CH_3OH; treatment of **10a** with excess anhydrous HCl in CH_3OH (*ca.* 10% solution) for 1 h at room temperature gave **1a** in 90% yield. IR (Nujol) cm^{-1}: 3480, 3280, 1710, 1600. MS *m/e*: 269 (M^+), 194. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.55 (3H, s), 3.12 (2H, m), 3.73 (3H, s), 5.30 (1H, m), 6.35—6.8 (3H, m), 7.6 (2H, br), 8.17 (1H, br d). An analytically pure sample, mp 141—142 °C, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.90. Found: C, 53.41; H, 5.55; N, 5.03; S, 11.79.

***N*-Ethylthiocarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (1b)**——This compound **1b** was obtained from **6** in 79% yield, mp 101—102 °C (recrystallized from ether–hexane). IR (Nujol) cm^{-1}: 3420, 3280, 1720, 1600. MS *m/e*: 283 (M^+), 194. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.00 (3H, t), 2.10 (2H, q), 3.80 (2H, m), 3.65 (3H, s), 4.50 (1H, quasi-

t), 6.3—7.1 (5H, m), 7.75 (1H, br d). *Anal.* Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 55.21; H, 6.04; N, 4.99; S, 11.07.

***N*-Phenylmethylthiocarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (1c)**——Phenylacetyl chloride (24.7 g, 160 mmol) was added slowly to a stirred mixture of **6** (9.90 g, 40 mmol) in H_2O (150 ml), ether (150 ml), and K_2CO_3 (27.6 g, 200 mmol) at 0 °C. After stirring for 2 h at room temperature, the ether layer was separated and washed with dil.HCl, saturated $NaHCO_3$ solution, and brine, then dried over anhydrous $MgSO_4$. Evaporation of the ether gave 21.47 g (95%) of **9c**. IR (Nujol) cm^{-1}: 3380, 1760, 1750, 1730, 1650, 1610. MS *m/e*: 565 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.98 (2H, d), 3.4—3.6 (6H), 3.60 (3H, s), 4.80 (1H, quasi-q), 5.85 (1H, br d), 6.6—7.5 (18H, m). Thionation of **9c** (21.47 g) with Lawesson's reagent (9.70 g, 24 mmol) gave 19.29 g (83%) of **10c** as an oil. MS *m/e*: 581 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.13 (2H, quasi-t), 3.52 (4H, s), 3.59 (3H, s), 3.99 (2H, s), 5.29 (1H, quasi-q), 6.5—7.5 (9H, m), 7.2 (10H, s). This oil was dissolved in HCl–CH_3OH (*ca.* 10% solution, 150 ml) and the solution was stirred for 1 h at room temperature. Evaporation of the solvent gave an oil which was chromatographed on silica gel (hexane–AcOEt (1 : 1) as an eluent) to give 9.87 g (75% yield from **6**) of **1c**, mp 118—119 °C (recrystallized from ether). IR (Nujol) cm^{-1}: 3400, 3260, 3060, 1710, 1600. MS *m/e*: 345 (M^+). ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.06 (2H, quasi-t), 3.67 (3H, s), 4.03 (2H, s), 5.22 (1H, quasi-t), 6.1—6.7 (3H, m), 7.2 (5H, s), 7.5 (2H, br s), 7.9 (1H, br d). *Anal.* Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.51; H, 5.44; N, 4.31; S, 9.11.

***N*-2-(Phenyl)ethylthiocarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (1d)**——This compound **1d** was obtained from **6** in 74% yield as a foam. IR ($CHCl_3$) cm^{-1}: 3250, 3050, 1720, 1600. MS *m/e*: 359 (M^+), 194. ^{1}H-NMR ($CDCl_3$) δ: 3.05 (6H, m), 3.70 (3H, s), 5.35 (1H, m), 5.7 (2H, br), 6.2—6.8 (3H), 7.22 (5H, s), 7.55 (1H, br d).

***N*-Phenylthiocarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (1e)**——This compound **1e** was obtained from **6** in 77% yield, mp 166—167 °C (recrystallized from ether). IR (Nujol) cm^{-1}: 3460, 3300, 3210, 1740, 1605. MS *m/e*: 331 (M^+), 194. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.26 (2H, t), 3.76 (3H, s), 5.50 (1H, quasi-t), 6.4—6.8 (3H, m), 7.2—7.8 (7H, m), 8.20 (1H, br d). *Anal.* Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23; S, 9.67. Found: C, 61.59; H, 5.18; N, 4.41; S, 9.92.

***N*-[2-(3,4-Dihydroxyphenyl)ethyl]thioacetamide (1f)**——This compound **1f** was obtained from **8** in 84% yield, mp 104—105 °C (recrystallized from AcOEt–hexane). IR (Nujol) cm^{-1}: 3360, 3240, 3160, 1600. MS *m/e*: 211 (M^+), 136. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.40 (3H, s), 2.75 (2H, m), 3.65 (2H, m), 6.4—6.8 (3H, s), 8.61 (2H, br s), 9.90 (1H, br). *Anal.* Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.17. Found: C, 56.86; H, 6.13; N, 6.71; S, 14.96.

***N*-[2-(3,4-Dihydroxyphenyl)ethyl]propanethioamide (1g)**——This compound **1g** was obtained from **8** in 81% yield, mp 103—104 °C (recrystallized from AcOEt–hexane). IR (Nujol) cm^{-1}: 3420, 3280, 1610. MS *m/e*: 225 (M^+), 136. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.20 (3H, t), 2.60 (2H, q), 2.75 (2H, q), 3.80 (2H, q), 6.5—6.9 (3H, m), 7.68 (2H, br s), 8.36 (1H, br). *Anal.* Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.61; H, 6.68; N, 6.11; S, 14.27.

***N*-[2-(3,4-Dihydroxyphenyl)ethyl]thiobenzamide (1h)**——This compound **1h** was obtained from **8** in 80% yield, mp 126—127 °C (recrystallized from ether–hexane). IR (Nujol) cm^{-1}: 3300, 1600. MS *m/e*: 273 (M^+), 136. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.95 (2H, t), 4.00 (2H, quasi-q), 6.5—7.1 (3H, m), 7.2—7.8 (7H, m), 8.41 (1H, br). *Anal.* Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53; N, 5.12; S, 11.72. Found: C, 65.82; H, 5.45; N, 5.29; S, 11.47.

Preparation of 3: Cyclization of 1 with 4-Nitrobenzyl Bromide——All the reactions were carried out under an argon atmosphere with protection from light.

Methyl 6,7-Dihydroxy-1-methyl-3,4-dihydroisoquinoline-3-carboxylate Hydrobromide (3a, X = Br)——A solution of **1a** (3.23 g, 12 mmol) and 4-nitrobenzyl bromide (3.88 g, 18 mmol) in CH_3CN (70 ml) was refluxed for 24 h. Evaporation of the CH_3CN gave an oil, which was crystallized from acetone–ether. The crystals were rinsed with the same solvent and recrystallized from CH_3OH–ether to give 3.22 g (85%) of **3a** (X = Br), mp 201—203 °C (dec.). IR (Nujol) cm^{-1}: 3490, 3000—3400, 1730, 1630, 1610. MS *m/e*: 253 (M^+), 176. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 2.75 (3H, s), 3.30 (2H, d), 3.70 (3H, s), 5.05 (1H, t), 6.90 (1H, s), 7.40 (1H, s). *Anal.* Calcd for $C_{12}H_{13}NO_4 \cdot HBr$: C, 45.59; H, 4.46; N, 4.43; Br, 24.99. Found: C, 45.47; H, 4.52; N, 4.39; Br, 25.28. This compound **3a** was also obtained from **1a** by the use of other alkylating agents (as shown in Table I) under conditions similar to those described above.

Methyl 6,7-Dihydroxy-1-ethyl-3,4-dihydroisoquinoline-3-carboxylate Hydrobromide (3b, X = Br)——A solution of **1b** (3.40 g, 12 mmol) and 4-nitrobenzyl bromide (3.88 g, 18 mmol) in CH_3CN (70 ml) was refluxed for 48 h. The CH_3CN was evaporated off and the residue was extracted with H_2O (50 ml). The aqueous layer was lyophilized to give 3.17 g (80%) of crude **3b**. Recrystallization from iso-PrOH–ether gave 2.87 g (73%) of **3b** (X = Br), mp 164—166 °C (dec.). IR (Nujol) cm^{-1}: 3250, 3210, 1740, 1610. MS *m/e*: 249 (M^+), 190. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 1.30 (3H, t), 3.15 (2H, q), 3.35 (2H, br d), 3.72 (3H, s), 5.05 (1H, br t), 6.90 (1H, s), 7.45 (1H, s). *Anal.* Calcd for $C_{13}H_{15}NO_4 \cdot HBr$: C, 47.29; H, 4.89; N, 4.24; Br, 24.20. Found: C, 47.51; H, 4.92; N, 4.15; Br, 23.99.

Methyl 6,7-Dihydroxy-1-phenylmethyl-3,4-dihydroisoquinoline-3-carboxylate Hydrobromide (3c, X = Br)——This compound **3c** was obtained from **1c** in a manner similar to that described for **3b**. Cyclization of **1c** (2.06 g, 6 mmol) with 4-nitrobenzyl bromide (1.94 g, 9 mmol) in CH_3CN gave 1.53 g (65%) of **3c** (X = Br), mp 194—195 °C (dec.) (recrystallized from iso-PrOH–iso-Pr_2O). IR (Nujol) cm^{-1}: 3260, 3120, 1740, 1630. MS *m/e*: 311 (M^+), 252. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 3.35 (2H, br d), 3.75 (3H, s), 4.55 (2H, br s), 5.15 (1H, t), 6.90 (1H, s), 7.45 (6H, br s). *Anal.*

Calcd for $C_{18}H_{17}NO_4 \cdot HBr$: C, 55.12; H, 4.63; N, 3.57; Br, 20.37. Found: C, 55.04; H, 4.66; N, 3.55; Br, 20.29.

Methyl 6,7-Dihydroxy-1-(2-phenyl)ethyl-3,4-dihydroisoquinoline-3-carboxylate Hydrobromide (3d, X=Br)——This compound **3d** was obtained from **1d** in a manner similar to that described for **3b**. Cyclization of **1d** (2.23 g, 6.2 mmol) with 4-nitrobenzyl bromide (1.94 g, 9 mmol) in CH_3CN gave 1.44 g (57%) of **3d** (X=Br), mp 108—109 °C (dec.) (recrystallized from acetone–hexane). IR (Nujol) cm^{-1}: 3000—3400, 1740, 1600. MS *m/e*: 325 (M^+), 266. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 3.05 (4H, m), 3.35 (2H, br d), 3.70 (3H, s), 5.10 (1H, t), 6.90 (1H, s), 7.30 (5H, s), 7.55 (1H, s). *Anal.* Calcd for $C_{19}H_{19}NO_4 \cdot HBr$: C, 56.17; H, 4.96; N, 3.45; Br, 19.67. Found: C, 56.39; H, 4.88; N, 3.25; Br, 19.41.

Methyl 6,7-Dihydroxy-1-phenyl-3,4-dihydroisoquinoline-3-carboxylate Hydrochloride (3e, X=Cl)——A solution of **1e** (2.0 g, 6 mmol) and 4-nitrobenzyl bromide (1.94 g, 9 mmol) in BuCN (50 ml) was stirred for 60 h at 115 °C. The BuCN was evaporated off and the residue was extracted with H_2O (50 ml). The aqueous layer was lyophilized to give a hardly separable mixture of **3e**, **3h**, and unknown products as a foam. In order to isolate **3e**, the mixture was acetylated once with Ac_2O (0.7 ml) and pyridine (25 ml) under stirring for 2 h at room temperature. The reaction mixture was concentrated *in vacuo*, taken up in $CHCl_3$, washed with saturated $NaHCO_3$ solution, and dried. After evaporation of $CHCl_3$, the resulting oil was chromatographed on silica gel. Elution with hexane–AcOEt (1 : 2) gave 504 mg (22%) of methyl 6,7-diacetoxy-1-phenyl-3,4-dihydroisoquinoline-3-carboxylate (**11**), mp 57—59 °C. IR ($CHCl_3$) cm^{-1}: 1780, 1740 (sh), 1610. MS *m/e*: 381 (M^+), 322. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.30 (3H, s), 3.05 (2H, quasi-d), 3.81 (3H, s), 4.40 (1H, quasi-t), 7.1—7.7 (7H, m). *Anal.* Calcd for $C_{21}H_{19}NO_6$: C, 66.12; H, 5.02; N, 3.68. Found: C, 65.94; H, 5.16; N, 3.41. Solvolysis of **11** by treatment with HCl–CH_3OH gave pure **3e** (X=Cl) as a foam in a quantitative yield. IR (Nujol) cm^{-1}: 3000—3600, 1740. MS *m/e*: 297 (M^+), 238. ^{1}H-NMR ($CDCl_3$–DMSO-d_6–D_2O) δ: 3.50 (2H, m), 3.73 (3H, s), 5.05 (1H, m), 6.9 (1H, s), 7.0 (1H, s), 7.72 (5H, s). Isolation of **3h**, which was clearly detectable by thin-layer chromatography (TLC), was unsuccessful even as the acetate. Unambiguous preparation of **3h** from **1h** is described later in this section.

6,7-Dihydroxy-1-methyl-3,4-dihydroisoquinoline Hydrobromide (3f, X=Br)——A solution of **1f** (1.06 g, 5 mmol) and 4-nitrobenzyl bromide (1.72 g, 8 mmol) in CH_3CN (40 ml) was heated at 130 °C in a sealed tube. After 24 h, the reaction mixture was cooled and the resulting precipitates were collected by filtration. Recrystallization from C_2H_5OH–iso-Pr_2O gave 0.97 g (75%) of **3f** (X=Br), mp 218—220 °C (dec.) (lit.[8] mp 216 °C (dec.)). IR (Nujol) cm^{-1}: 3370, 3170, 3140, 1650, 1600. MS *m/e*: 177 (M^+), 176. ^{1}H-NMR (D_2O) δ: 2.65 (3H, br s), 2.96 (2H, quasi-t), 3.75 (2H, quasi-t), 6.76 (1H, s), 7.23 (1H, s).

6,7-Dihydroxy-1-ethyl-3,4-dihydroisoquinoline Hydrobromide (3g, X=Br)——Cyclization of **1g** (1.13 g, 5 mmol) with 4-nitrobenzyl bromide (1.72 g, 8 mmol) in CH_3CN gave 0.68 g (50%) of **3g** (X=Br), mp 223—224 °C (dec.) (recrystallized from iso-PrOH–iso-Pr_2O). IR (Nujol) cm^{-1}: 3350, 3220, 3150, 1640, 1600. MS *m/e*: 191 (M^+). ^{1}H-NMR (D_2O) δ: 1.25 (3H, t), 3.05 (4H, m), 3.81 (2H, t), 6.76 (1H, s), 7.24 (1H, s). *Anal.* Calcd for $C_{11}H_{13}NO_2 \cdot HBr$: C, 48.55; H, 5.18; N, 5.15; Br, 29.36. Found: C, 48.39; H, 5.17; N, 5.18; Br, 29.57.

6,7-Dihydroxy-1-phenyl-3,4-dihydroisoquinoline Hydrobromide (3h, X=Br)——Cyclization of **1h** (1.37 g, 5 mmol) with 4-nitrobenzyl bromide (1.72 g, 8 mmol) in CH_3CN gave 1.21 g (76%) of **3h** (X=Br), mp 273—274 °C (dec.) (recrystallized from CH_3OH). IR (Nujol) cm^{-1}: 3400, 3200, 3100, 1620, 1580. MS *m/e*: 329 (M^+), 328. ^{1}H-NMR (DMSO-d_6–D_2O) δ: 3.05 (2H, quasi-t), 3.85 (2H, quasi-t), 6.78 (1H, s), 6.94 (1H, s), 7.6 (5H, s). *Anal.* Calcd for $C_{15}H_{13}NO_2 \cdot HBr$: C, 56.27; H, 4.41; N, 4.38; Br, 24.96. Found: C, 56.18; H, 4.35; N, 4.33; Br, 25.14.

Preparation of 4: Conversion of 3 into 4 by Method A (Reduction with $NaBH_4$) and Method B (Catalytic Hydrogenation over PtO_2)——The general procedure is exemplified by the preparation of **4a**.

Methyl *cis*-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (4a)——Method A: $NaBH_4$ (190 mg, 5 mmol) was added to a stirred solution of **3a** (1.58 g, 5 mmol) in CH_3OH (200 ml) at −78 °C. The mixture was stirred for 1 h at −78 °C, and the reaction was quenched by addition of acetone (1 ml). After concentration, the resulting oil was dissolved in $CHCl_3$–CH_3OH (10 : 1), washed with saturated $(NH_4)_2SO_4$ solution, and dried. Removal of the solvent and treatment of the residue with HCl–CH_3OH gave colorless crystals, which were recrystallized from CH_3OH–ether to give 0.85 g (62%) of **4a**·HCl, mp 227—229 °C (dec.). IR (Nujol) cm^{-1}: 3240, 3060, 3000, 1750. MS *m/e*: 237 (M^+), 222. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.68 (3H, d, J=6.6 Hz, CH_3), 3.12 (2H, quasi-d, on irradiation at 4.28, br s), 3.85 (3H, s), 4.28 (1H, dd, J=7.3, 9.8 Hz, C_3-H), 4.49 (1H, quasi-q, C_1-H, on irradiation at 1.68, br s), 6.62 (1H, s), 6.69 (1H, s), 7.59 (3H, br). ^{13}C-NMR ($CDCl_3$–DMSO-d_6) δ: 18.2 (q), 28.1 (t), 52.0 (d), 52.9 (q), 53.9 (d), 112.2 (d), 115.0 (d), 120.5 (s), 123.4 (s), 144.8 (s), 145.1 (s), 168.8 (s). *Anal.* Calcd for $C_{12}H_{15}NO_4 \cdot HCl$: C, 52.66; H, 5.89; N, 5.12; Cl, 12.95. Found: C, 52.37; H, 5.91; N, 5.04; Cl, 13.02.

Method B: A solution of **3a** (632 mg, 2 mmol) in CH_3OH (70 ml) was hydrogenated over PtO_2 catalyst (130 mg) at room temperature for 30 min under atmospheric pressure of hydrogen. After removal of the catalyst, the filtrate was evaporated, and the residue was recrystallized from CH_3OH–ether to give 540 mg (85%) of **4a**·HBr, mp 214—215 °C (dec.). *Anal.* Calcd for $C_{12}H_{15}NO_4 \cdot HBr$: C, 45.30; H, 5.06; N, 4.40; Br, 25.12. Found: C, 45.02; H, 5.02; N, 4.34; Br, 25.12.

Methyl *cis*-6,7-Dihydroxy-1-ethyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (4b)——Method A: $NaBH_4$ reduction of **3b** (1.65 g, 5 mmol), followed by treatment with HCl–CH_3OH gave 0.86 g (60%) of **4b**·HCl, mp 183—185 °C (dec.) (recrystallized from CH_3OH–ether). IR (Nujol) cm^{-1}: 3230, 3100, 1740. MS *m/e*: 251 (M^+), 222. ^{1}H-

NMR ($CDCl_3$–DMSO-d_6) δ: 1.21 (3H, t, J=7.5 Hz), 2.09 (2H, m), 3.02 (1H, dd, J=16.5, 6.5 Hz, C_4-H), 3.22 (1H, dd, J=16.5, 10.3 Hz, C_4-H), 3.85 (3H, s), 4.20 (1H, dd, J=6.5, 10.3 Hz, C_3-H), 4.40 (1H, quasi-t, C_1-H, on irradiation at 2.09, br s), 6.63 (1H, s), 6.71 (1H, s), 7.0—9.0 (3H, br). ^{13}C-NMR ($CDCl_3$–DMSO-d_6) δ: 9.6 (q), 25.7 (t), 28.0 (t), 52.9 (q), 54.4 (d), 57.1 (d), 112.4 (d), 115.1 (d), 121.0 (s), 122.0 (s), 144.8 (s), 145.0 (s), 168.6 (s). *Anal.* Calcd for $C_{13}H_{17}NO_4 \cdot HCl$: C, 54.26; H, 6.31; N, 4.87; Cl, 12.32. Found: C, 54.53; H, 6.61; N, 4.60; Cl, 12.33.

Method B: Hydrogenation of **3b** (330 mg, 1 mmol) gave 280 mg (85%) of **4b**·HBr, mp 202—204 °C (dec.) (recrystallized from CH_3OH–ether). *Anal.* Calcd for $C_{13}H_{17}NO_4 \cdot HBr$: C, 47.00; H, 5.46; N, 4.22; Br, 24.05. Found: C, 47.09; H, 5.58; N, 4.15; Br, 23.77.

Methyl *cis*-6,7-Dihydroxy-1-phenylmethyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (4c)——Method A: $NaBH_4$ reduction of **3c** (1.57 g, 4 mmol) followed by treatment with HCl–CH_3OH gave 0.87 g (62%) of **4c**·HCl, mp 207—209 °C (dec.) (recrystallized from CH_3OH–ether). IR (Nujol) cm^{-1}: 3480, 3220, 3000, 1730. MS *m/e*: 313 (M^+), 222. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.02 (1H, dd, J=16.0, 6.5 Hz, C_4-H), 3.24 (1H, dd, J=16.0, 10.0 Hz, C_4-H), 3.37 (2H, d, J=6.5 Hz), 3.84 (3H, s), 4.18 (1H, dd, J=10.0, 6.5 Hz, C_3-H), 4.71 (1H, quasi-t, C_1-H, on irradiation at 3.37, br s), 6.64 (1H, s), 6.72 (1H, s), 7.24—7.5 (5H, m), 7.5—10 (3H, br). ^{13}C-NMR ($CDCl_3$–DMSO-d_6) δ: 28.2 (t), 39.7 (t), 52.9 (t), 54.6 (d), 57.0 (d), 112.7 (d), 115.1 (d), 121.0 (s), 122.2 (s), 127.1 (d), 2×128.6 (d), 2×129.6 (d), 136.1 (s), 144.8 (s), 145.3 (s), 168.9 (s). *Anal.* Calcd for $C_{18}H_{19}NO_4 \cdot HCl$: C, 61.80; H, 5.76; N, 4.00; Cl, 10.13. Found: C, 61.61; H, 5.70; N, 3.92; Cl, 10.18.

Method B: Hydrogenation of **3c** (392 mg, 1 mmol) gave 319 mg (79%) of **4c**·HBr, mp 194—195 °C (dec.) (recrystallized from C_2H_5OH–iso-Pr_2O). *Anal.* Calcd for $C_{18}H_{19}NO_4 \cdot HBr$: C, 54.84; H, 5.11; N, 3.55; Br, 20.27. Found: C, 54.99; H, 5.12; N, 3.54; Br, 19.98.

Methyl *cis*-6,7-Dihydroxy-1-(2-phenyl)ethyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (4d)——Method A: $NaBH_4$ reduction of **3d** (810 mg, 2 mmol), followed by treatment with HCl–CH_3OH gave 461 mg (63%) of **4d**·HCl, mp 179—181 °C (dec.) (recrystallized from iso-PrOH–iso-Pr_2O). IR (Nujol) cm^{-1}: 3550, 3120, 1750. MS *m/e*: 327 (M^+), 222. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.2—2.5 (2H, m), 2.8—3.0 (2H, m), 3.00 (1H, dd, J=16.0, 6.5 Hz, C_4-H), 3.22 (1H, dd, J=16.0, 10.0 Hz, C_4-H), 3.89 (3H, s), 4.24 (1H, dd, J=10.0, 6.5 Hz, C_3-H), 4.52 (1H, quasi-t, C_1-H), 6.64 (1H, s), 6.76 (1H, s), 7.1—7.4 (5H), 7.7—9.5 (3H, br). ^{13}C-NMR ($CDCl_3$–DMSO-d_6) δ: 28.2 (t), 31.0 (t), 35.0 (t), 53.0 (q), 54.5 (d), 55.9 (d), 112.4 (d), 115.2 (d), 121.2 (s), 122.2 (s), 126.0 (d), 2×128.2 (d), 2×128.3 (d), 140.9 (s), 144.9 (s), 145.1 (s), 168.8 (s). *Anal.* Calcd for $C_{19}H_{21}NO_4 \cdot HCl$: C, 62.72; H, 6.09; N, 3.85; Cl, 9.74. Found: C, 62.98; H, 6.31; N, 3.57; Cl, 9.49.

Method B: Hydrogenation of **3d** (365 mg, 0.9 mmol) gave 286 mg (78%) of **4d**·HBr as a powder. *Anal.* Calcd for $C_{19}H_{21}NO_4 \cdot HBr$: C, 55.89; H, 5.43; N, 3.43; Br, 19.57. Found: C, 55.61; H, 5.70; N, 3.18; Br, 19.29.

Methyl *cis*-6,7-Dihydroxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (4e)——Method A: $NaBH_4$ reduction of **3e** (1.00 g, 3 mmol), followed by treatment with HCl–CH_3OH gave 0.49 g (49%)of **4e**·HCl, mp 234—236 °C (dec.) (recrystallized from iso-PrOH–iso-Pr_2O). IR (Nujol) cm^{-1}: 3500, 3150, 1750. MS *m/e*: 299 (M^+), 240, 222. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 3.15 (1H, dd, J=16.5, 6.0 Hz, C_4-H), 3.42 (1H, dd, J=16.5, 11.5 Hz, C_4-H), 3.82 (3H, s), 4.42 (1H, dd, J=11.5, 6.0 Hz, C_3-H), 5.58 (1H, br s, C_1-H), 6.09 (1H, s), 6.69 (1H, s), 7.3—7.7 (5H, m), 7.7—10 (3H, br). ^{13}C-NMR ($CDCl_3$–DMSO-d_6) δ: 27.9 (t), 52.8 (q), 54.9 (d), 61.0 (d), 114.3 (d), 115.0 (d), 121.7 (s), 122.2 (s), 2×128.3 (d), 129.3 (d), 2×130.6 (d), 136.4 (s), 144.5 (s), 145.5 (s), 168.2 (s). *Anal.* Calcd for $C_{17}H_{17}NO_4 \cdot HCl$: C, 60.81; H, 5.43; N, 4.17; Cl, 10.56. Found: C, 60.73; H, 5.34; N, 4.16; Cl, 10.62.

Method B: Hydrogenation of **3e** (200 mg, 0.6 mmol) gave 145 mg (72%) of **4e**·HCl, mp 234—236 °C (dec.).

Preparation of 5——*N*-Acetyl derivatives (**5**) were prepared by acetylation of **4** with Ac_2O in pyridine and subsequent treatment with HCl–CH_3OH. The general procedure is exemplified by the preparation of **5a**.

Methyl *cis*-2-Acetyl-6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5a)——i) From **4a**·HCl: A solution of **4a**·HCl (350 mg, 1.3 mmol) and Ac_2O (522 mg, 5.1 mmol) in pyridine (5 ml) was stirred for 24 h at room temperature. The pyridine was removed *in vacuo*. The residue was taken up in $CHCl_3$, washed with saturated $NaHCO_3$ solution and brine, and dried. Evaporation of the $CHCl_3$ gave an oil (460 mg). This oil was dissolved in HCl–CH_3OH (10% solution, 10 ml) and stirred for 2 h at room temperature. After evaporation of the solvent, the residue was chromatographed on silica gel ($CHCl_3$–CH_3OH (20:1) as an eluent) to give 314 mg (88%) of **5a**, mp 164—166 °C. IR (Nujol) cm^{-1}: 3480, 1740, 1620. MS *m/e*: 279 (M^+), 264. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.41 (3H, d, J=7.0 Hz), 2.14 (3H, s), 2.97 (2H, quasi-d), 3.67 (3H, s), 4.65 (1H, quasi-t), 4.96 (1H, br), 6.61 (2H, s), 7.92 (2H, br s). An analytically pure sample, mp 170—171 °C, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.05; H, 6.09; N, 4.94.

ii) From **4a**·HBr: Acetylation of **4a**·HBr in a similar manner gave **5a** in 89% yield, mp 164—166 °C.

Methyl *cis*-2-Acetyl-6,7-dihydroxy-1-ethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5b)——This compound **5b** was obtained from **4b**·HCl and **4b**·HBr in 90% and 89% yields, respectively. mp 196—197 °C (dec.) (recrystallized from AcOEt). IR (Nujol) cm^{-1}: 3460, 1740, 1620, 1600. MS *m/e*: 293 (M^+), 264. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 0.96 (3H, t, J=7.0 Hz), 1.70 (2H, m), 2.10 (3H, s), 2.96 (2H, quasi-d, on irradiation at 4.40, s), 3.69 (3H, s), 4.40 (1H, quasi-t, on irradiation at 2.96, s), 4.45 (1H, br), 6.60 (1H, s), 6.64 (1H, s), 7.0—9.0 (2H, br). *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.44; H, 6.53; N, 4.74.

Methyl *cis*-2-Acetyl-6,7-dihydroxy-1-phenylmethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5c)——This

compound **5c** was obtained from **4c**·HCl and **4c**·HBr in 88% and 83% yield, respectively. mp 185—186 °C (dec.) (recrystallized from AcOEt). IR (Nujol) cm^{-1}: 3440, 1750, 1590. MS *m/e*: 355 (M^+), 264. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.87 (3H, s), 2.84 (1H, quasi-q, on irradiation at 4.81, d), 3.04 (2H, quasi-d), 3.24 (1H, quasi-q, on irradiation at 4.81, d), 3.75 (3H, s), 4.39 (1H, quasi-t, on irradiation at 3.04, br s), 4.81 (1H, br), 6.25 (1H, br s), 6.67 (1H, s), 7.20 (5H, s), 7.8—8.0 (2H, br). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.55; H, 5.92; N, 3.78.

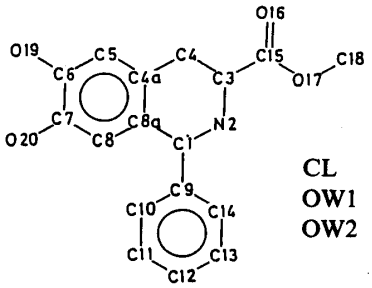
Preparation of (*S*)-1a and (*S*)-1i——These compounds were obtained from the corresponding L-dopa ester hydrochloride ((*S*)-**6**, **7**) in the same manner as described for *dl*-**1**. (*S*)-**1a**: 81% yield from (*S*)-**6**. mp 127—128 °C (recrystallized from ether–hexane). $[\alpha]_D^{20}$ +112.8° (*c*=1.0, CH_3OH). *Anal.* Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.90. Found: C, 53.51; H, 5.53; N, 5.18; S, 12.05. (*S*)-**1i**: 79% yield from (*S*)-**7**. mp 114—115 °C (recrystallized from AcOEt–hexane). IR (Nujol) cm^{-1}: 3460, 3260, 3050, 1700, 1600. MS *m/e*: 283 (M^+), 208. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.24 (3H, t), 2.52 (3H, s), 3.06 (2H, m), 4.16 (2H, q), 5.22 (1H, quasi-q), 6.4—6.8 (3H, m), 7.95 (1H, br), 8.07 (1H, br), 9.26 (1H, br d). $[\alpha]_D^{20}$ +111.4° (*c*=1.0, CH_3OH). *Anal.* Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 55.07; H, 6.19; N, 5.13; S, 11.04.

Reconversion of (*S*)-1a into (*S*)-9a——A solution of (*S*)-**1a** (1.00 g, 3.7 mmol) and methyl iodide (2 ml) in CH_3OH (100 ml) was stirred for 24 h at room temperature under an argon atmosphere with protection from light. Removal of the solvent gave a mixture of (*S*)-**6a** (HI salt) and a small amount of *N*-acetyldopa methyl ester. This mixture was dissolved in pyridine (20 ml) and Ac_2O (1.51 g, 14.8 mmol). The solution was stirred for 17 h at room temperature and the pyridine was removed under reduced pressure. The residue was taken up in AcOEt, washed with saturated $NaHCO_3$ solution and brine, and dried. Removal of the AcOEt, followed by recrystallization from ether gave 1.09 g (87%) of (*S*)-**9a**, mp 120—121 °C. $[\alpha]_D^{20}$ +21.0° (*c*=1.0, CH_3OH).

Preparation of (*S*)-9a——Ac_2O (48.0 g, 0.4 mol) was added to a solution of (*S*)-**6** (30.0 g, 0.12 mol) in pyridine (100 ml) at 0 °C. The mixture was stirred for 17 h at room temperature. After usual work-up, the crude product was recrystallized from ether to give 38.7 g (95%) of (*S*)-**9a**, mp 119—120 °C, $[\alpha]_D^{20}$ + 20.8° (*c*=1.0, CH_3OH). Spectral data were consistent with those of *dl*-**9a**.

Preparation of (*S*)-3a and (*S*)-3i——Cyclization of (*S*)-**1a** was carried out under conditions similar to those described for the preparation of *dl*-**3a**. After refluxing of a solution of (*S*)-**1a** and 4-nitrobenzyl bromide in CH_3CN for 24 h, the CH_3CN solution was concentrated under reduced pressure. The resulting precipitates were collected by filtration, rinsed with acetone and dried to give (*S*)-**3a**·HBr in 87% yield, mp 188—190 °C (dec.). *Anal.* Calcd for $C_{12}H_{13}NO_4$·HBr: C, 45.59; H, 4.46; N, 4.43; Br, 24.99. Found: C, 45.44; H, 4.57; N, 4.21; Br, 24.69. Similarly, (*S*)-**3i**·HBr was obtained as powder by cyclization of (*S*)-**1i**. IR (Nujol) cm^{-1}: 3000—3500, 1740, 1610. MS *m/e*: 250 (M^+), 176. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.24 (3H, t), 2.80 (3H, s), 3.30 (2H, m), 4.20 (2H, q), 4.78 (1H, t), 6.85 (1H, s), 7.40 (1H, s), 8.0—10.0 (2H, br). *Anal.* Calcd for $C_{13}H_{15}NO_4$·HBr·H_2O: C, 44.84; H, 5.21; N, 4.02; Br, 22.95. Found: C, 45.09; H, 5.19; N, 3.89; Br, 23.25.

TABLE V. Bond Lengths (Å) of **4e**

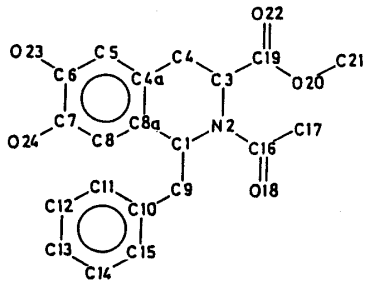


C(1)–N(2)	1.506 (3)	C(7)–C(8)	1.382 (3)
C(1)–C(8a)	1.523 (3)	C(7)–O(20)	1.362 (2)
C(1)–C(9)	1.514 (3)	C(8)–C(8a)	1.396 (2)
N(2)–C(3)	1.490 (3)	C(9)–C(10)	1.396 (4)
C(3)–C(4)	1.525 (3)	C(9)–C(14)	1.378 (3)
C(3)–C(15)	1.510 (3)	C(10)–C(11)	1.392 (5)
C(4)–C(4a)	1.508 (3)	C(11)–C(12)	1.371 (5)
C(4a)–C(5)	1.401 (3)	C(12)–C(13)	1.381 (5)
C(4a)–C(8a)	1.395 (3)	C(13)–C(14)	1.383 (4)
C(5)–C(6)	1.376 (3)	C(15)–O(16)	1.184 (3)
C(6)–C(7)	1.405 (4)	C(15)–O(17)	1.321 (3)
C(6)–O(19)	1.365 (3)	O(17)–C(18)	1.453 (3)

TABLE VI. Bond Angles (Å) of **4e**

N(2)–C(1)–C(8a)	109.2 (2)	C(6)–C(7)–C(8)	119.2 (2)
N(2)–C(1)–C(9)	109.2 (2)	C(8a)–C(8)–C(7)	121.5 (2)
C(8a)–C(1)–C(9)	115.1 (1)	C(4a)–C(8a)–C(8)	119.3 (2)
C(3)–N(2)–C(1)	110.9 (2)	C(4a)–C(8a)–C(1)	121.5 (2)
N(2)–C(3)–C(4)	109.4 (1)	C(8)–C(8a)–C(1)	119.2 (2)
N(2)–C(3)–C(15)	108.9 (2)	C(10)–C(9)–C(1)	119.9 (2)
C(4)–C(3)–C(15)	113.3 (2)	C(10)–C(9)–C(14)	119.2 (2)
C(4a)–C(4)–C(3)	112.0 (2)	C(1)–C(9)–C(14)	120.9 (2)
C(8a)–C(4a)–C(4)	122.3 (2)	C(9)–C(10)–C(11)	119.5 (3)
C(5)–C(4a)–C(4)	118.8 (2)	C(10)–C(11)–C(12)	120.6 (3)
C(4a)–C(5)–C(6)	121.6 (2)	C(13)–C(12)–C(11)	119.9 (3)
C(7)–C(6)–C(5)	119.4 (2)	C(14)–C(13)–C(12)	120.0 (3)
C(7)–C(6)–O(19)	116.9 (2)	C(9)–C(14)–C(13)	120.8 (3)
C(5)–C(6)–O(19)	123.7 (2)	O(17)–C(15)–C(3)	110.2 (2)
O(20)–C(7)–C(6)	117.4 (2)	O(17)–C(15)–O(16)	125.0 (2)
O(20)–C(7)–C(8)	123.4 (2)	C(3)–C(15)–O(16)	124.7 (2)

TABLE VII. Bond Lengths (Å) of **5c**



	A[a]	B[a]		A[a]	B[a]
C(1)–N(2)	1.48 (1)	1.45 (1)	C(7)–O(24)	1.34 (1)	1.38 (1)
C(1)–C(8a)	1.51 (1)	1.50 (1)	C(8)–C(8a)	1.38 (1)	1.39 (1)
C(1)–C(9)	1.56 (1)	1.56 (1)	C(9)–C(10)	1.49 (1)	1.51 (1)
N(2)–C(3)	1.49 (1)	1.49 (1)	C(10)–C(11)	1.39 (1)	1.37 (1)
N(2)–C(16)	1.35 (1)	1.34 (1)	C(10)–C(15)	1.40 (1)	1.39 (1)
C(3)–C(4)	1.51 (1)	1.54 (1)	C(11)–C(12)	1.38 (2)	1.43 (2)
C(3)–C(19)	1.55 (1)	1.51 (1)	C(12)–C(13)	1.39 (2)	1.36 (2)
C(4)–C(4a)	1.49 (1)	1.51 (1)	C(13)–C(14)	1.36 (2)	1.38 (2)
C(4a)–C(5)	1.39 (1)	1.37 (1)	C(14)–C(15)	1.35 (2)	1.38 (2)
C(4a)–C(8a)	1.39 (1)	1.38 (1)	C(16)–C(17)	1.53 (1)	1.49 (1)
C(5)–C(6)	1.39 (1)	1.40 (1)	C(16)–O(18)	1.23 (1)	1.23 (1)
C(6)–C(7)	1.39 (1)	1.36 (1)	C(19)–O(20)	1.33 (1)	1.34 (1)
C(6)–O(23)	1.37 (1)	1.38 (1)	C(19)–O(22)	1.19 (1)	1.20 (1)
C(7)–C(8)	1.41 (1)	1.39 (1)	O(20)–C(21)	1.49 (1)	1.46 (1)

a) A and B refer to molecules A and B in the asymmetric unit.

Preparation of (1*S*,3*S*)-4a·HCl and (1*S*,3*S*)-4i·HCl——$NaBH_4$ reduction of (*S*)-**3a**·HBr was carried out under conditions similar to those described for the preparation of *dl*-**4a**·HCl. (1*S*,3*S*)-**4a**·HCl was obtained from (*S*)-**3a** in 62% yield, mp 226—228 °C (dec.) (recrystallized from CH_3OH–ether). *Anal.* Calcd for $C_{12}H_{15}NO_4$·HCl: C, 52.66; H, 5.89; N, 5.12; Cl, 12.95. Found: C, 52.39; H, 6.03; N, 5.11; Cl, 12.76. Similarly, (1*S*,3*S*)-**4i**·HCl was obtained from (*S*)-**3i** in 80% yield, mp 219—221 °C (dec.) (lit[4d] mp 220—221 °C (dec.)). Spectral data of (1*S*,3*S*)-**4i**·HCl were consistent with those reported in the literature.[4b,d]

Preparation of (1*S*,3*S*)-4a·HBr and (1*S*,3*S*)-4i·HBr——Hydrogenation of (*S*)-**3**·HBr was carried out under conditions similar to those described for the preparation of *dl*-**4**·HBr. (1*S*,3*S*)-**4a**·HBr: mp 212—213 °C (dec.) (recrystallized from CH_3OH–ether). *Anal.* Calcd for $C_{12}H_{15}NO_4$·HBr: C, 45.30; H, 5.06; N, 4.40; Br, 25.12. Found:

TABLE VIII. Bond Angles (°) of **5c**

	A	B		A	B
N(2)–C(1)–C(8a)	110.7 (6)	112.7 (7)	C(7)–C(8)–C(8a)	119.7 (7)	119.2 (8)
N(2)–C(1)–C(9)	110.7 (7)	112.0 (7)	C(1)–C(8a)–C(4a)	118.6 (7)	119.2 (8)
C(8a)–C(1)–C(9)	112.3 (7)	111.3 (7)	C(1)–C(8a)–C(8)	120.3 (7)	121.3 (7)
C(1)–N(2)–C(3)	120.6 (6)	120.3 (6)	C(4a)–C(8a)–C(8)	121.1 (7)	119.5 (8)
C(1)–N(2)–C(16)	123.7 (7)	125.0 (7)	C(1)–C(9)–C(10)	110.1 (8)	111.0 (8)
C(3)–N(2)–C(16)	114.8 (7)	114.1 (7)	C(9)–C(10)–C(11)	122.2 (8)	118.1 (8)
N(2)–C(3)–C(14)	111.6 (7)	111.6 (7)	C(9)–C(10)–C(15)	121.9 (8)	122.0 (9)
N(2)–C(3)–C(19)	108.8 (7)	112.4 (7)	C(11)–C(10)–C(15)	115.8 (9)	119.8 (9)
C(4)–C(3)–C(19)	106.7 (8)	105.7 (8)	C(10)–C(11)–C(12)	121.3 (10)	119.1 (10)
C(3)–C(4)–C(4a)	110.8 (8)	111.5 (8)	C(11)–C(12)–C(13)	119.5 (11)	119.1 (11)
C(4)–C(4a)–C(5)	122.5 (8)	121.3 (8)	C(12)–C(13)–C(14)	120.7 (11)	122.0 (11)
C(4)–C(4a)–C(8a)	118.2 (7)	117.5 (8)	C(13)–C(14)–C(15)	118.5 (12)	118.6 (10)
C(5)–C(4a)–C(8a)	119.3 (8)	121.2 (8)	C(10)–C(15)–C(14)	124.1 (10)	121.3 (10)
C(4a)–C(5)–C(6)	120.2 (8)	119.1 (8)	N(2)–C(16)–C(17)	119.6 (8)	119.5 (8)
C(5)–C(6)–C(7)	120.6 (8)	120.0 (8)	N(2)–C(16)–O(18)	120.7 (8)	120.5 (8)
C(5)–C(6)–O(23)	119.5 (7)	119.8 (8)	C(17)–C(16)–O(18)	119.6 (8)	119.9 (8)
C(7)–C(6)–O(23)	119.9 (8)	120.2 (8)	C(3)–C(19)–O(20)	110.0 (8)	109.9 (8)
C(6)–C(7)–C(8)	119.1 (8)	121.0 (8)	C(3)–C(19)–O(22)	123.8 (9)	125.2 (8)
C(6)–C(7)–O(24)	115.2 (7)	114.7 (8)	O(20)–C(19)–O(22)	125.8 (9)	124.8 (9)
C(8)–C(7)–O(24)	125.7 (7)	124.3 (8)	C(19)–O(20)–C(21)	114.1 (8)	116.3 (8)

TABLE IX. Fractional Coordinates ($\times 10^4$; for Cl $\times 10^5$) and Isotropic Thermal Parameters of **4e**

Atom	x	y	z	B_{eq} [a]
CL	37556 (6)	79355 (6)	6511 (7)	3.8
C(1)	3176 (2)	6210 (2)	4243 (3)	2.6
N(2)	4197 (2)	7490 (2)	4354 (2)	2.6
C(3)	5544 (2)	7369 (2)	4790 (3)	2.7
C(4)	5631 (2)	6336 (2)	3310 (3)	2.9
C(4a)	4430 (2)	5071 (2)	2588 (3)	2.6
C(5)	4459 (2)	3935 (2)	1423 (3)	3.0
C(6)	3387 (2)	2759 (2)	694 (3)	3.0
C(7)	2241 (2)	2682 (2)	1149 (3)	3.1
C(8)	2207 (2)	3798 (2)	2299 (3)	3.0
C(8a)	3282 (2)	5003 (2)	3012 (3)	2.6
C(9)	1828 (2)	6383 (2)	3827 (3)	2.9
C(10)	1269 (3)	6660 (3)	5098 (3)	4.0
C(11)	37 (3)	6835 (3)	4708 (5)	5.4
C(12)	−640 (3)	6715 (3)	3085 (5)	5.5
C(13)	−86 (3)	6443 (3)	1828 (4)	4.9
C(14)	1147 (2)	6290 (2)	2207 (3)	3.6
C(15)	6558 (2)	8758 (2)	5284 (3)	3.0
O(16)	6307 (2)	9774 (2)	5351 (3)	5.2
O(17)	7763 (2)	8680 (2)	5662 (3)	4.3
C(18)	8835 (3)	9967 (3)	6265 (5)	5.6
O(19)	3362 (2)	1638 (2)	−469 (2)	4.4
O(20)	1204 (2)	1499 (2)	392 (2)	4.3
OW1	4464 (2)	8920 (2)	7543 (2)	5.6
OW2	1139 (2)	8732 (2)	9079 (3)	5.6

a) $B_{eq} = 4/3 \sum_i \sum_j \beta_{ij} \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

TABLE X. Fractional Coordinates ($\times 10^4$) and Isotropic Thermal Parameters of **5c**

Atom	A				B			
	x	y	z	B_{eq}	x	y	z	B_{eq}
C(1)	4150 (5)	4412 (5)	−1740 (6)	3.9	6403 (5)	7341 (5)	6693 (7)	3.9
N(2)	3933 (4)	4581 (4)	−636 (5)	4.1	6168 (4)	7181 (4)	5617 (5)	4.0
C(3)	4588 (5)	4705 (5)	160 (7)	4.0	6808 (5)	7068 (5)	4802 (7)	4.1
C(4)	5418 (6)	4829 (6)	−346 (7)	4.6	7669 (5)	6965 (6)	5291 (8)	5.0
C(4a)	5597 (5)	4229 (5)	−1120 (6)	3.8	7842 (5)	7557 (5)	6106 (7)	4.1
C(5)	6364 (5)	3881 (5)	−1204 (7)	4.2	8598 (5)	7897 (6)	6176 (7)	4.5
C(6)	6503 (5)	3334 (5)	−1962 (6)	3.8	8736 (5)	8424 (6)	6971 (7)	4.4
C(7)	5876 (5)	3118 (5)	−2643 (7)	3.8	8115 (5)	8616 (5)	7633 (7)	4.0
C(8)	5091 (5)	3452 (5)	−2541 (6)	3.6	7338 (5)	8297 (5)	7533 (7)	4.1
C(8a)	4966 (5)	4007 (5)	−1801 (6)	3.6	7208 (5)	7753 (5)	6771 (6)	3.6
C(9)	4138 (5)	5142 (5)	−2413 (7)	4.4	6405 (6)	6617 (6)	7385 (7)	4.7
C(10)	4144 (6)	4947 (6)	−3549 (7)	4.7	6453 (6)	6814 (6)	8538 (7)	4.7
C(11)	4863 (6)	4933 (7)	−4134 (8)	6.0	5746 (7)	7046 (7)	9031 (8)	6.1
C(12)	4860 (8)	4717 (9)	−5175 (10)	7.7	5788 (7)	7290 (9)	10096 (9)	7.5
C(13)	4126 (8)	4493 (9)	−5639 (9)	7.9	6529 (9)	7298 (8)	10587 (8)	7.7
C(14)	3409 (8)	4497 (10)	−5089 (9)	9.1	7236 (7)	7037 (8)	10109 (8)	6.8
C(15)	3424 (6)	4739 (9)	−4083 (9)	7.8	7191 (6)	6802 (8)	9085 (9)	6.5
C(16)	3167 (6)	4509 (6)	−241 (7)	4.4	5401 (5)	7221 (6)	5241 (7)	4.5
C(17)	2442 (5)	4380 (7)	−983 (8)	5.5	4699 (6)	7333 (8)	5978 (8)	5.9
O(18)	3043 (4)	4566 (4)	702 (5)	4.9	5271 (4)	7155 (4)	4298 (5)	4.8
C(19)	4385 (6)	5427 (6)	784 (7)	4.8	6659 (6)	6371 (6)	4157 (7)	4.4
O(20)	4650 (5)	5360 (4)	1764 (5)	6.0	6925 (5)	6479 (4)	3179 (5)	5.3
C(21)	4523 (10)	6045 (7)	2413 (10)	8.5	6945 (9)	5818 (7)	2506 (10)	7.3
O(22)	4104 (5)	5981 (4)	399 (7)	6.8	6378 (5)	5790 (4)	4484 (6)	5.8
O(23)	7269 (4)	3011 (4)	−2045 (5)	5.0	9504 (4)	8749 (4)	7080 (5)	5.7
O(24)	6081 (4)	2580 (4)	−3335 (5)	4.5	8329 (4)	9130 (4)	8400 (5)	5.0

C, 45.59; H, 5.10; N, 4.26; Br, 24.83. (1*S*,3*S*)-**4i**·HBr: mp 199—201 °C (dec.) (recrystallized from C_2H_5OH–ether). *Anal.* Calcd for $C_{13}H_{17}NO_4$·HBr: C, 47.00; H, 5.46; N, 4.22; Br, 24.05. Found: C, 47.23; H, 5.69; N, 4.50; Br, 23.76.

Preparation of (1*S*,3*S*)-5a and (1*S*,3*S*)-5i——Conversion of (1*S*,3*S*)-**4**·HBr into (1*S*,3*S*)-**5** was carried out under conditions similar to those described for the preparation of *dl*-**5**. (1*S*,3*S*)-**5a**: 84% yield, mp 137—138 °C (dec.) (recrystallized from AcOEt–hexane). $[\alpha]_D^{20}$ −22.6° (c=1.0, CH_3OH). The spectral data and $[\alpha]_D$ value were consistent with those of an authentic sample [$[\alpha]_D^{20}$ −22.8° (c=1.0, CH_3OH)] prepared from the known (1*S*,3*S*)-6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.[6] (1*S*,3*S*)-**5i**: 90% yield, mp 185—186 °C (lit.[7] 185—187 °C). $[\alpha]_D^{20}$ −22.4° (c=1.0, CH_3OH) (lit.[7] $[\alpha]_D$ −21.6°). Spectral data were consistent with those reported in the literature.[7]

Crystal Data for 4e——$C_{17}H_{17}NO_4$·HCl·$2H_2O$, M_r=371.82, triclinic, P_T, a=11.0609 (9), b=10.7333 (8), c=8.6146 (7) Å, α=103.403 (6), β=104.367 (7), γ=104.764 (7)°, V=909.3 (1) Å^3, D_c=1.358 g/cm^3, Z=2.

Crystal Data for 5c——$C_{20}H_{21}NO_5$, M_r=355.39, orthorhombic, $Pn2_1a$, a=16.251 (3), b=17.785 (3), c=12.771 (2) Å, V=3691 (1) Å^3, D_c=1.279 g/cm^3, Z=8.

X-Ray Analysis——Single crystals of **4e** were obtained from aqueous methanol and of **5c** from ethanol by slow evaporation. The intensity data were collected by the 2θ-ω scanning technique using graphite-monochromated Cu$K\alpha$ radiation on a four-circle diffractometer (Rigaku AFC-5). In total, 3141 reflections for **4e** and 3240 for **5c** were measured, of which 2937 and 2515, respectively, were judged significant ($|F_o| \geqq 2.67\sigma(F_o)$). Both structures were solved by direct methods using MULTAN and refined by the block-diagonal least-squares method with anisotropic temperature factors for all non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final R values were 0.045 for **4e** and 0.075 for **5c**. The bond lengths and angles and the numbering system (used in the crystallographic analysis) of **4e** and **5c** are illustrated in Tables V—VIII. Fractional coordinates and thermal parameters for **4e** and **5c** are given in Tables IX and X.

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References and Notes

1) *a*) A. Ishida, T. Nakamura, K. Irie, and T. Oh-ishi, *Chem. Pharm. Bull.*, **30**, 4226 (1982); *b*) T. Nakamura, A. Ishida, K. Irie, and T. Oh-ishi, *ibid.*, **32**, 2859 (1984); *c*) A. Ishida, T. Nakamura, K. Irie, and T. Oh-ishi, *ibid.*, **33**, 3237 (1985).
2) Reaction of **1h** with 4-nitrobenzyl bromide in refluxing CH_3CN gave the thioiminium salt (**2h**) in 79% yield, mp 157—159 °C. IR (Nujol) cm^{-1}: 3100—3500, 1600. ^1H-NMR (DMSO-d_6) δ: 2.93 (2H, quasi-t), 3.96 (2H, quasi-t), 4.48 (2H, d), 6.3—8.3 (14H, m).
3) The crude reduction product seemed to contain a small amount of 1,3-*trans* isomer (on the thin-layer chromatogram).
4) *a*) The authentic sample, (1*S*,3*S*)-**4a**, was prepared by the esterification (HCl–CH_3OH) of known (1*S*,3*S*)-6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**12**)[4b] according to the literature[4b-d]; *b*) A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **55**, 15 (1972); *c*) M. Konda, T. Oh-ishi, and S. Yamada, *Chem. Pharm. Bull.*, **25**, 69 (1977); *d*) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 4183 (1978).
5) Lawesson's reagent was reported to be useful as a thionation reagent of peptides, without racemization (see reference 1*c*).
6) An authentic sample, (1*S*,3*S*)-**5a**, was obtained by acetylation of (1*S*,3*S*)-**4a**·HCl prepared from the known acid **12**. mp 137—138 °C. $[\alpha]_D^{20}$ −22.8° (*c* = 1.0, CH_3OH).
7) H. Bruderer, A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta*, **58**, 795 (1975).
8) H. Corrodi and N. A. Hillarp, *Helv. Chim. Acta*, **47**, 911 (1964).