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Asymmetric Synthesis of 1-Benzyltetrahydroisoquinolines Using Chiral Oxazolo[2,3-*a*]tetrahydroisoquinolines

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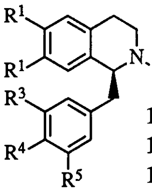
A novel synthetic route to enantiomerically pure 1-benzyltetrahydroisoquinolines (1) was developed *via* the reaction of oxazolo[2,3-*a*]tetrahydroisoquinoline (5) with benzyltriisopropoxytitanium compounds (10). This method was applied to the synthesis of (*S*)-trimetoquinol (1c; a bronchodilator).

Keywords oxazolo[2,3-*a*]tetrahydroisoquinoline; 1-benzyltetrahydroisoquinoline; 1-chloroisochroman; phenylglycinol; (*S*)-norarmepavine; (*S*)-tetrahydropapaverine; (*S*)-trimetoquinol; asymmetric synthesis

Chiral 1-benzyltetrahydroisoquinoline alkaloids are widely distributed among plants, and have interesting biological activities.[1] Fujii *et al.*[1a] reported that *dl*-1-(*p*-alkoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines inhibit the collagen-induced activation (aggregation and adenosine triphosphate (ATP) secretion) of rabbit platelets. Akasu *et al.*[1b] found that *dl*-1-benzyloxybenzyl-1,2,3,4-tetrahydroisoquinoline derivatives have antitumor activity, while Fujiya *et al.*[1c] reported that armepavine (**1a**), laudanosine (**1b**), and related compounds have inhibitory activity against co-carcinorgens. In addition, (*S*)-trimetoquinol [**1c**; (*S*)-6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline][2] has been used as a bronchodilator in Japan (Fig. 1).



1a: (*S*)-armepavine (R^1=OMe, R^2=Me, R^3, R^5=H, R^4=OH)
1b: (*S*)-laudanosine (R^1, R^3, R^4=OMe, R^2=Me, R^5=H)
1c: (*S*)-trimetoquinol (R^1=OH, R^2=H, R^3, R^4, R^5=OMe)

Fig. 1

Since 1-benzyltetrahydroisoquinolines (**1**) are also useful as intermediates for the synthesis of isoquinoline alkaloids, the development of a convenient method for the asymmetric synthesis of **1** is very important. Recently, several methods[3] for the highly stereoselective synthesis of 1-alkyltetrahydroisoquinolines have been developed and applied to the asymmetric synthesis of 1-benzyltetrahydroisoquinolines (**1**).

We have previously succeeded in the synthesis of enantiomerically pure (*S*)-1-alkyltetrahydroisoquinolines [(*S*)-**1**] *via* the stereoselective alkylation of chiral oxazolo[2,3-*a*]tetrahydroisoquinolines (**5**) (Chart 1). The chiral key intermediate (**5**) was synthesized by the diastereoselective cyclization of the chiral isoquinolinium salt (**4**) prepared by the reaction of 2-(2-haloethyl)benzaldehyde (**3**) with (*R*)-phenylglycinol.[4] Compound **5**, which is regarded as a cyclic *N*,*O*-acetal, undergoes diastereoselective nucleophilic substitution by a variety of Grignard reagents (**7**), except benzylmagnesium halide, to give the corresponding (*S*)-1-alkylated tetrahydroisoquinoline derivatives (**8**). Removal of the chiral auxiliary moiety of **8** by hydrogenolysis gives

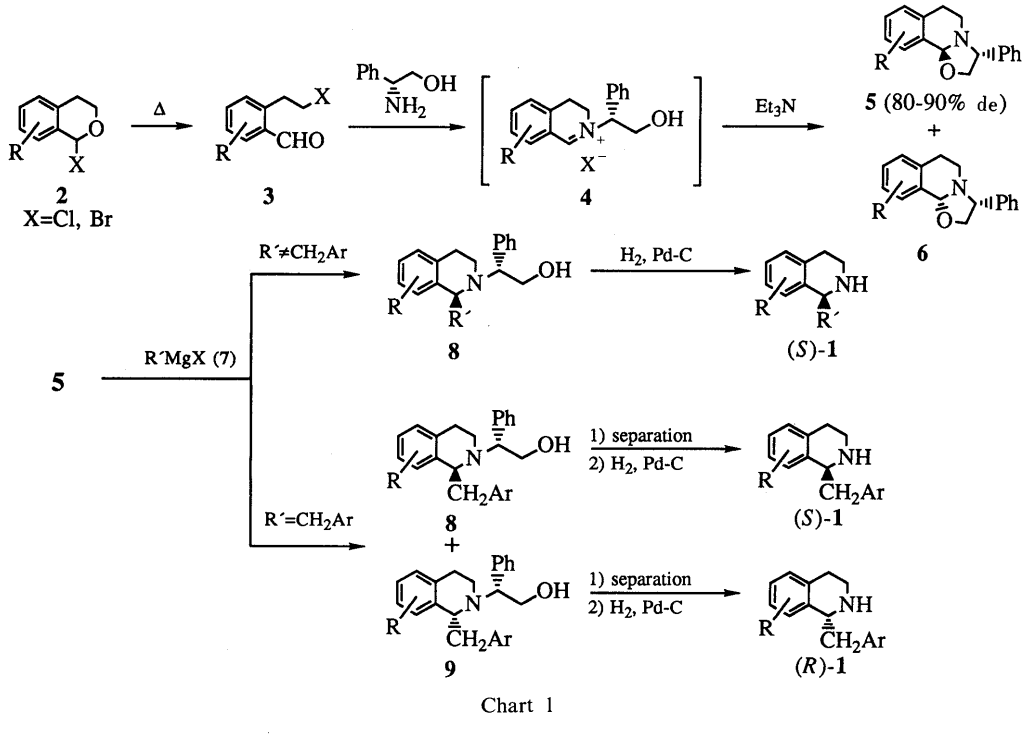


Chart 1

(*S*)-1-alkyltetrahydroisoquinolines (**1**). This method has been applied to the asymmetric syntheses of some natural products, *e.g.* salsolidine, homolaudanosine, and cryptostyline II.[4b)]

At that time, we found that the reaction of **5** with benzylmagnesium halide (**7**) proceeds with exceptionally low diastereoselectivity, affording a separable mixture of (1*S*)- and (1*R*)-1-benzyl derivatives (**8** and **9**). As an extension of this work, we describe here an improved method for the synthesis of enantiomerically pure 1-benzyltetrahydroisoquinolines (**1**) *via* the reaction of **5** with benzyltriisopropoxytitanium compounds (**10**) and its application to the asymmetric synthesis of (*S*)-trimetoquinol (**1c**).

Results and Discussion

The chiral (3*R*,10b*S*)-oxazolo[2,3-*a*]tetrahydroisoquinolines, **5a** (R = H) and **5b** (R = OMe), were prepared with 84 and 100% de, respectively, according to the method previously reported (Chart 1). In general, the cyclization of the isoquinolinium salt **4** to **5** proceeds with 80—90% de. When the cyclized product **5** and its diastereoisomer (**6**) are oils, the separation of **5** from **6** by column chromatography is difficult. On the other hand, when they are solids, pure **5** can be obtained by recrystallization of the mixture of **5** and **6** from ethanol.[4b)]

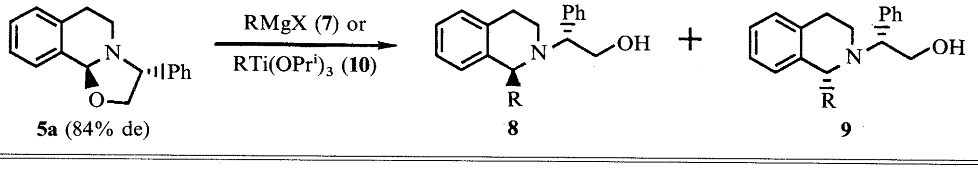
In earlier work,[4b)] we examined asymmetric alkylation of **5a**, which had the diastereoisomeric purity of 82% de, with methyl-, butyl-, phenyl-, benzyl-, and phenethylmagnesium halides at −78 °C and found that the diastereoselectivity of the reaction of **5a** with benzylmagnesium chloride was exceptionally lower than the diastereoisomeric purity of **5a**. We have now reinvestigated the reaction of benzylmagnesium chloride (**7d**) with **5a** at −78 °C (Table I, run 8). The reproducibility was found to be poor with respect to the diastereoselectivity of the Grignard reaction of **5a** with **7d**. We therefore investigated stereoselective benzylation of **5** with another benzyl metal reagent. Benzyltriisopropoxytitanium compound (**10d**) was selected as a benzylating agent, because alkyltriisopropoxytitanium compounds (**10**) are known to react highly selectively with a carbonyl group.[5)]

First, we examined the reaction of **5a** (84% de) with a variety of alkyltriisopropoxytitanium compounds (**10a—d**) (Table I). In order to compare the diastereoselectivity, the reaction of **5a** with the corresponding Grignard reagent under the same reaction condition was undertaken. The reaction (run 3) of **5a** with methyltriisopropoxytitanium (**10a**) occurred at room temperature to give a 59 : 41 mixture of **8a** and **9a**. The diastereoisomeric excess of **8a** was found to be 18% de, which is low as compared with that of the reaction (run 2) of **5a** with methylmagnesium iodide (**7a**). The reaction (run 5 or 7) of **5a** with butyltriisopropoxytitanium (**10b**) or phenyltriisopropoxytitanium (**10c**) did not take place even in refluxing benzene. In contrast with those reactions, the reaction (run 10) of **5a** with benzyltriisopropoxytitanium (**10d**) occurred at −5 °C to give an 18 : 82 mixture of **8d** and **9d**. The diastereoisomeric excess of **8d** was found to be 63% de. Although the major product was the reverse of that in the reaction of **5a** with **7d**, the diastereoisomeric excess was relatively high.

Since the benzylation of **5a** with benzyltriisopropoxytitanium (**10d**) smoothly proceeded with good diastereoselectivity, we then examined the generality of this method using diastereoisomerically pure **5b** and a variety of benzyltitanium reagents (**10d, f—i**) (Table II, method B). In order to compare the diastereoselectivity, the reactions of **5b** with the corresponding Grignard reagents (**7d, f—i**) were undertaken (method A). In method A, the diastereoisomeric excess in each reaction was found to be low. On the other hand, in method B, the benzylation proceeded with relatively high diastereoselectivity, affording **9** with approximately 65—90% de. Compound **8** accompanied with **9** was easily purified by column chromatography and subsequently converted to enantiomerically pure **9** by hydrogenolysis on palladium–carbon (Pd–C).

In the above reactions, the diastereoisomeric excess was determined by high performance liquid chromatography (HPLC) analysis. The structures of the major products, **8g** and **8h**, in the reaction of **5b** with Grignard reagent (method

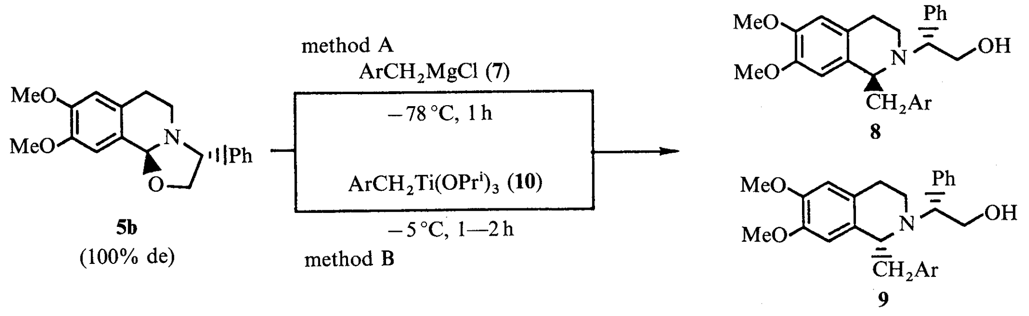
TABLE I. Reaction of **5a** with Alkylmetal Reagents

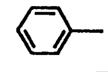
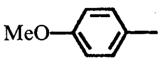
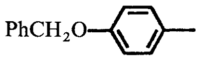
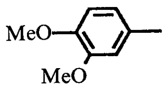
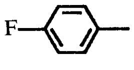


Run	Alkylating agent		Reaction condition			Product (8+9)		
	No.	R	Temperature (°C)	Time (h)	Solvent	Yield (%)	Major product	% de
1[a)]	**7a**	Me	−78	1	Et_2O	98	**8a**	82
2	**7a**	Me	r.t.	1	Et_2O	84	**8a**	65
3	**10a**	Me	r.t.	16	Et_2O	69	**8a**	18
4[a)]	**7b**	Bu	−78	1	Et_2O	81	**8b**	100
5	**10b**	Bu	Reflux	10	Benzene	No reaction		
6[a)]	**7c**	Ph	−78	1	Et_2O	80	**8c**	100
7	**10c**	Ph	Reflux	6	Benzene	No reaction		
8	**7d**	$PhCH_2$	−78	1	Et_2O	85—95	**8d**	5—35
9	**7d**	$PhCH_2$	−5	1	THF	92	**9d**	8
10	**10d**	$PhCH_2$	−5	2	Et_2O–THF	95	**9d**	63

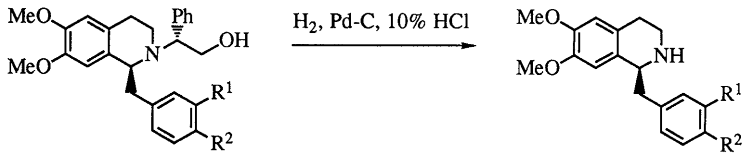
a) See reference 4*b*. r.t. = room temperature.

TABLE II. Benzylation of **5b**



Alkylating agent		Method	Product (8+9)		
No.	Ar		Yield (%)	Major product	% de
7d		A	84	**8e**	15
10d		B	90	**9e**	77 (74)[a]
7f		A	90	**8f**	18
10f		B	91	**9f**	65 (72)[a]
7g		A	92	**8g**	24
10g		B	86	**9g**	90 (75)[a]
7h		A	83	**8h**	21
10h		B	73	**9h**	79 (54)[a]
7i		A	78	**8i**	13
10i		B	79	**9i**	77 (70)[a]

a) Isolated yield of **9**.



8g : $R^1 = H, R^2 = OCH_2Ph$
8h : $R^1, R^2 = OMe$

(*S*)-norarmepavine (**1g**) : $R^1 = H, R^2 = OH$
(*S*)-tetrahydropapaverine (**1h**) : $R^1, R^2 = OMe$

Chart 2

A) were assigned after their conversion to known alkaloids, (*S*)-norarmepavine[6] (**1g**) and (*S*)-tetrahydropapaverine[7] (**1h**) (Chart 2). The structures of other compounds, **8e**, **8f**, and **8i**, were identified based on the similarities of the thin layer chromatography (TLC), HPLC, and nuclear magnetic resonance (NMR) spectral patterns not to those of **9g** and **9h**, but to those of **7g** and **7h**.

Since the above results seemed to indicate that method B is effective, we next attempted asymmetric synthesis of (*S*)-trimetoquinol (**1c**), which is currently obtained by optical resolution on an industrial scale. In order to obtain **1c** according to method B, (3*S*,10b*R*)-oxazolo[2,3-*a*]tetrahydroisoquinoline (**16**) was required as a chiral intermediate. Compound **16** was synthesized as follows. 3,4-Dibenzyloxyphenethyl alcohol[8] (**11**), on treatment with triethyl orthoformate in the presence of boron trifluoride etherate ($BF_3 \cdot Et_2O$) at room temperature, gave 6,7-dibenzyloxy-1-ethoxyisochroman (**12**) accompanied with several by-products, purification of which by recrystallization from hexane afforded pure **12** in 40% yield. Compound **12** was allowed to reflux in acetyl chloride for 2 h to give 2-(2-chloroethyl)benzaldehyde (**14**) in 72% yield. Treatment of **14** with (*S*)-phenylglycinol in ethanol at room temperature gave crude isoquinolium chloride (**15**), which, on treatment with triethylamine in methylene chloride at −5 °C, afforded **16** in 93% yield as an oily product. The diastereoisomeric excess of **16** was determined to be 85% by 500 MHz NMR spectral analysis. Compound **16** was, without further separation, treated with (3,4,5-trimethoxybenzyl)triisopropoxytitanium (**17**) at −5 °C in tetrahydrofuran (THF) to give an 80 : 20 (60% de) mixture of **18** and **19**. The major product **18** was separated from **19** by column chromatography on silica gel in 50% yield based on **16**. Hydrogenolysis of **18** in the presence of Pd–C in acidic ethanol gave enantiomerically pure (*S*)-trimetoquinol hydrochloride[9] (**1c**·HCl).

The synthetic strategy *via* the reaction of chiral oxazolo[2,3-*a*]tetrahydroisoquinolines, easily prepared using (*R*)- and (*S*)-phenylglycinol, with benzyltriisopropoxytitaniums (**10**) provides a general and useful method for the synthesis of enantiomerically pure (*R*)- and (*S*)-1-benzyltetrahydroisoquinolines (**1**). Investigations on further applications of

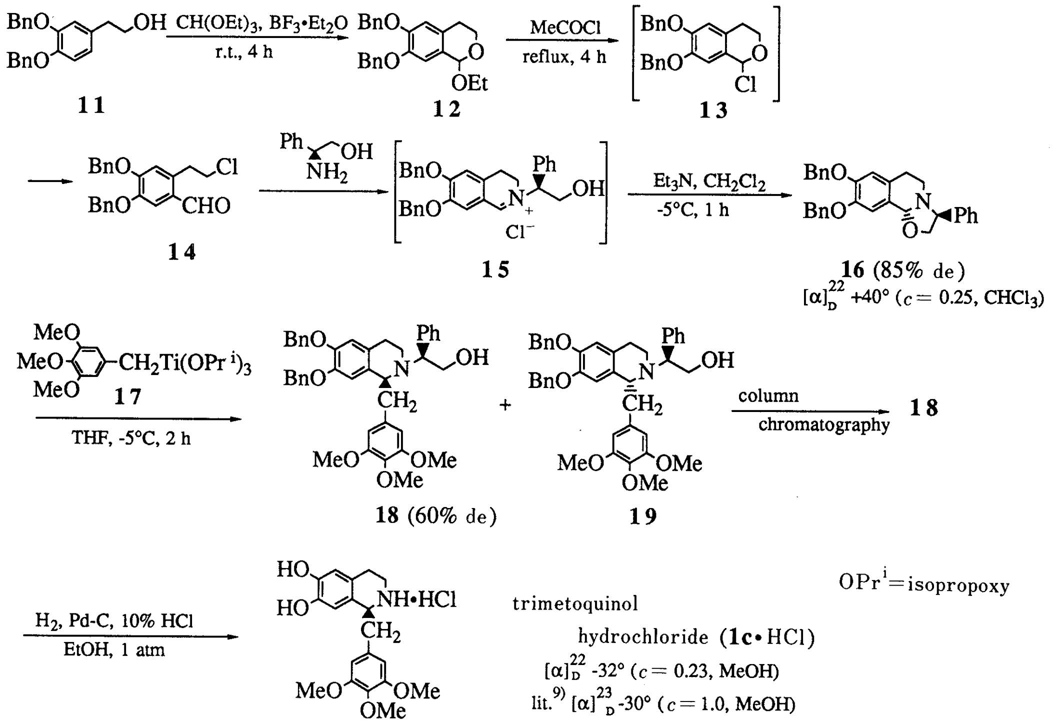


Chart 3

this strategy and on the reaction mechanism of stereoselective alkylation of the chiral intermediate **4** are in progress.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a Shimadzu LKB 9000 spectrometer and fast atom bombardment mass spectra (FAB-MS) were recorded on a VG-70SE spectrometer. ^{1}H-NMR spectra were run on a Hitachi R-24 spectrometer or on a Varian VXR-500 instrument. Optical rotations were measured on a JASCO DIP-4 spectrometer. Analytic HPLC was performed with a Shimadzu SPD-6A instrument on a chiral phase column, Chiralcel OD (Daisel) or a Chemcosorb 5Si-U (Chemco) fitted with an ultraviolet (254 nm) detector. Merck Silica gel 60 (230—400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over anhydrous $MgSO_4$.

Reaction of 5a with MeMgI (7a) at Room Temperature A solution of **5a** (0.15 g, 0.6 mmol) in dry Et_2O (5 ml) was added dropwise to a solution of MeMgI (2.4 mmol) in dry Et_2O (20 ml). After being stirred for an additional 1 h at room temperature, the reaction mixture was quenched with aqueous NH_4Cl solution and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) to give 0.13 g of a mixture of (1*S*,1′*R*)-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline[4b] (**8a**) and (1*R*,1′*R*)-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (**9a**) in a combined chemical yield of 84%. The diastereomeric excess of **8a** was determined to be 65% by HPLC analysis.

Reaction of 5a with Triisopropoxymethyltitanium (10a) A solution of 95% ClTi(OPr^i)$_3$ (4.8 mmol) in dry hexane (10 ml) was added dropwise to a solution of MeMgI (4.8 mmol) in dry Et_2O (20 ml) at −5 °C and the mixture was stirred for 2 h at −5 °C. After a precipitate was formed, the supernatant was added dropwise to a solution of **5a** (0.3 g, 1.2 mmol) in dry Et_2O (10 ml) at −5 °C. The reaction mixture was stirred at room temperature for 16 h and then quenched with aqueous NH_4Cl solution. The resulting precipitate was filtered off and the filtrate was extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) to give 0.22 g of a mixture of **8a** and **9a** in a combined chemical yield of 69%. The diastereomeric excess of **8a** was determined to be 18% by HPLC analysis.

(1*R*,1′*R*)-2-(2-Hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (9a) Viscous oil; IR (neat): 3430 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.48 (3H, d, J = 8 Hz), 2.24—3.36 (4H, m), 2.66 (1H, s), 3.36—4.25 (4H, m), 6.87—7.67 (4H, m), 7.26 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 268 (M^+ + 1). $[\alpha]_D^{17}$ −9.7° (c = 0.7, $CHCl_3$).

Reaction of 5a with PhCH$_2$MgCl (7d) at −78 °C Mg turnings (192 mg, 8 mmol) and dry Et_2O (30 ml) were placed in a 3-necked flask, fitted with a reflux condenser and septum rubber and continuously maintained with a flow of argon. A trace of iodine was added and stirring was continued until the iodine color disappeared. Benzyl chloride (0.92 ml, 8 mmol) was then added dropwise at room temperature. Stirring was continued at room temperature for 1 h. Finally the mixture was diluted with Et_2O to get the Grignard reagent in 0.1 molar concentration. The flask was cooled to −78 °C and 500 mg (2 mmol) of **5a** (84% de), dissolved in dry THF (10 ml), was added dropwise at −78 °C. After being stirred for an additional 1 h at −78 °C, the reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) to give 0.58 g of a mixture of (1*S*,1′*R*)-1-benzyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline[4b] (**8d**) and (1*R*,1′*R*)-1-benzyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (**9d**) in a combined chemical yield of 84%. The diastereomeric excess of **8d** was determined to be 34% by HPLC analysis. The mixture of **8d** and **9d** was chromatographed on an open column of silica gel (hexane : AcOEt = 2 : 1) to give pure **8d** and **9d**.

(1*R*,1′*R*)-1-Benzyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (8d) Oil. *Anal.* Calcd for $C_{24}H_{25}NO$: C, 83.92; H, 7.34; N, 4.08. Found: C, 84.12; H, 7.40; N, 4.11. IR (neat): 3450 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.98 (1H, s), 2.21—3.38 (6H, m), 3.41—4.34 (4H, m), 6.65—7.35 (4H, m), 7.10 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 344 (M^+ + 1). $[\alpha]_D^{24}$ −21.50° (c = 0.2, EtOH).

Reaction of 5a with PhCH$_2$MgCl (7d) at −5 °C A solution of **4a** (0.2 g, 0.8 mmol) in dry THF (20 ml) was added dropwise to a solution of $PhCH_2MgCl$ (3.2 mmol) in dry THF (10 ml) at −5 °C. After being stirred for an additional 1 h at room temperature, the reaction mixture was quenched with aqueous NH_4Cl solution and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) to give 0.25 g of a mixture of **7d** and **8d** in a combined chemical yield of 92%. The diastereomeric excess of **8d** was determined to be 8% by HPLC analysis.

Reaction of 5a with Benzyltriisopropoxytitanium (10d) A solution of 95% ClTi(OPr^i)$_3$ (4.8 mmol) in dry hexane (10 ml) was added dropwise to a solution of $PhCH_2MgCl$ (4.8 mmol) in dry Et_2O (20 ml) at −5 °C, and the mixture was stirred for an additional 2 h at −5 °C. After a precipitate was formed, the supernatant was added dropwise to a solution of **4a** (0.3 g, 1.2 mmol) in dry Et_2O (10 ml) at -5 °C. The reaction mixture was then stirred at -5 °C for 2 h. Work-up as described above and purification by chromatography on a column of silica gel (hexane : AcOEt = 1 : 1) gave 0.39 g of a mixture of **7d** and **8d** in a combined chemical yield of 95%. The diastereomeric excess of **8d** was determined to be 63% by HPLC analysis.

General Procedure for Reaction of 5b with Benzylmagnesium Halide (7d, f—i) (Method A) Grignard reagent, **7i**, was prepared as described for the reaction of **5a** with **7i**. The other Grignard reagent, **7f**, **7g**, or **7h**, was prepared as follows. Mg turnings (1.2 g, 50 mmol) were placed in a 3-necked flask fitted with a reflux condenser and septum rubber and continuously maintained with a flow of argon. Dry THF (20 ml) was added to cover the magnesium surface. A few crystals of iodine were added and the flask was kept undisturbed for 10 min. Stirring was started and a few drops of 1,2-dibromoethane were added. Stirring was continued until the iodine color disappeared. The flask was cooled to -10 °C and the corresponding benzyl chloride (13 mmol) dissolved in dry THF (50 ml) was added dropwise over a period of 1 h with vigorous stirring. After completion of the addition, dry THF (40 ml) was added. The reaction mixture was stirred for a further 30 min at -10 °C.

Next, 0.2 g (0.64 mmol) of **5b** was added dropwise at -78 °C to the flask containing Grignard reagent (**7**; 2.56 mmol) prepared by the above procedure. After being stirred for an additional 1 h at -78 °C, the reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried. The solvent was evaporated off and the residue was purified by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) to give a mixture of **8e—i** and **9e—i** in the combined chemical yield as shown in Table II. The diastereomeric excess of **8e—i** (Table II) was determined by HPLC analysis. The mixture of **8e—i** and **9e—i** was separated by chromatography on an open column of silica gel (hexane : AcOEt = 2 : 1) to give pure **8e—i** and **9e—i**.

(1*S*,1′*R*)-1-Benzyl-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8e) Hygroscopic solid. IR (neat): 3540 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.02 (1H, s), 2.47—3.38 (6H, m), 3.44—4.02 (4H, m), 3.51, 3.81 (3H × 2, each s), 5.86, 6.50 (1H × 2, each s), 6.84—7.37 (10H, m). FAB-MS (positive ion mode) *m*/*z*: 404 ($M^+ + 1$). $[\alpha]_D^{22}$ $+27°$ ($c = 0.3$, EtOH).

(1*R*,1′*R*)-1-Benzyl-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9e) Hygroscopic solid. IR (neat): 3500 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.04 (1H, s), 2.24—3.39 (6H, m), 3.43—3.85 (4H, m), 3.60, 3.79 (3H × 2, each s), 6.10, 6.40 (1H × 2, each s), 6.85—7.31 (4H, m), 7.15 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 404 ($M^+ + 1$). $[\alpha]_D^{22}$ $-89°$ ($c = 0.1$, EtOH).

(1*S*,1′*R*)-2-(2-Hydroxy-1-phenylethyl)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (8f) Hygroscopic solid. IR (neat): 3540 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.19—3.41 (6H, m), 3.24 (1H, s), 3.45—4.12 (4H, m), 3.54, 3.77, 3.79 (3H × 3, each s), 5.90, 6.50 (1H × 2, each s) 6.62—7.40 (4H, m), 7.12 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 434 ($M^+ + 1$). $[\alpha]_D^{22}$ $+44.9°$ ($c = 0.21$, EtOH).

(1*R*,1′*R*)-2-(2-Hydroxy-1-phenylethyl)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (9f) Hygroscopic solid. IR (neat): 3540 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.27—3.40 (6H, m), 2.29 (1H, s), 3.56—3.95 (4H, m), 3.65, 3.75, 3.78 (3H × 3, each s), 6.22, 6.48 (1H × 2, each s), 6.66—7.10 (4H, m), 7.23 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 434 ($M^+ + 1$). $[\alpha]_D^{22}$ $-48.5°$ ($c = 0.24$, EtOH).

(1*S*,1′*R*)-1-(4-Benzyloxybenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8g) Hygroscopic solid. IR (neat): 3450 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.35 (1H, s), 2.45—3.41 (6H, m), 3.50—4.09 (4H, m), 3.53, 3.82 (3H × 2, each s), 5.04 (2H, s), 5.90, 6.58 (1H × 2, each s), 6.90 (5H, s), 7.03—7.60 (4H, m), 7.40 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 510 ($M^+ + 1$). $[\alpha]_D^{18}$ $+66°$ ($c = 0.3$, $CHCl_3$).

(1*S*,1′*R*)-1-(4-Benzyloxybenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9g) Hygroscopic solid. IR (neat): 3460 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.21—3.45 (6H, m), 2.49 (1H, s), 3.59—4.20 (4H, m), 3.62, 3.81 (3H × 2, each s), 5.09 (2H, s), 6.20, 6.50 (1H × 2, each s), 6.98 (4H, s), 7.31 (5H, s), 7.42 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 510 ($M^+ + 1$). $[\alpha]_D^{18}$ $-96°$ ($c = 0.1$, $CHCl_3$).

(1*S*,1′*R*)-1-(3,4-Dimethoxybenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8h) Hygroscopic solid. IR (neat): 3525 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.10—3.40 (6H, m), 2.47 (1H, s), 3.41—4.02 (4H, m), 3.56, 3.71, 3.79, 3.80 (3H × 4, each s), 5.90, 6.43 (1H × 2, each s), 6.55—6.91 (3H, m), 7.15 (5H, br s). FAB-MS (positive ion mode) *m*/*z*: 464 ($M^+ + 1$). $[\alpha]_D^{22}$ $+28°$ ($c = 0.27$, $CHCl_3$).

(1*R*,1′*R*)-1-(3,4-Dimethoxybenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9h) Hygroscopic solid. IR (neat): 3530 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.19—3.30 (6H, m), 2.42 (1H, s), 3.32—4.39 (4H, m), 3.63, 3.70, 3.76, 3.80 (3H × 4, each s), 6.19, 6.46 (1H × 2, each s), 6.32—6.86 (3H, m), 7.26 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 464 ($M^+ + 1$). $[\alpha]_D^{22}$ $-77°$ ($c = 0.12$, $CHCl_3$).

(1*S*,1′*R*)-1-(4-Fluorobenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8i) Oil. IR (neat): 3540 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.45—3.42 (6H, m), 2.85 (1H, s), 3.50—4.20 (4H, m), 3.58, 3.82 (3H × 2, each s), 5.90, 6.50 (1H × 2, each s), 6.61—7.52 (9H, m). FAB-MS (positive ion mode) *m*/*z*: 422 ($M^+ + 1$). $[\alpha]_D^{23}$ $+23.4°$ ($c = 0.20$, EtOH).

(1*R*,1′*R*)-1-(4-Fluorobenzyl)-2-(2-hydroxy-1-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9i) Oil. IR (neat): 3540 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.24—3.18 (6H, m), 2.39 (1H, s), 3.39—4.29 (4H, m), 3.64, 3.77 (3H × 2, each s), 6.19, 6.47 (1H × 2, each s), 6.75—7.19 (4H, m), 7.23 (5H, s). FAB-MS (positive ion mode) *m*/*z*: 422 ($M^+ + 1$). $[\alpha]_D^{23}$ $-41.5°$ ($c = 0.21$, EtOH).

General Procedure for Reaction of 5b with Benzyltriisopropoxytitanium Compounds (10d, f—i) (Method B) A solution of 95% $ClTi(OPr^i)_3$ (1 ml, 4 mmol) in dry hexane (10 ml) was added dropwise at -5 °C to a solution of $ArCH_2MgCl$ (4 mmol) prepared as described above (method A) in dry THF (20 ml), and the mixture was stirred for 2 h at -5 °C. After a precipitate was formed the supernatant was added dropwise to a solution of **5b** (0.3 g, 0.96 mmol) in dry THF (10 ml) at -5 °C. The reaction mixture was then stirred at -5 °C for 1—2 h, until **5b** disappeared. Work-up as described above and subsequent purification by flash chromatography on silica gel (hexane : AcOEt = 1 : 1) gave a mixture of **8e—i** and **9e—i**. The diastereomeric excess of **9e—i** was determined by HPLC analysis. Rechromatography of the mixture of **8e—i** and **9e—i** gave pure **9e—i**. The chemical yield, diastereomeric excess of **8e—i** , and isolated yield of **8e—i** are given in Table II.

(*S*)-1-(4-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-Norarmepavine; 1g] A solution of **8g** (0.3 g, 0.87 mmol) in EtOH was hydrogenated in the presence of 10% Pd–C (0.3 g) and 10% HCl (2 ml). After the completion of hydrogen absorption, the solvent was evaporated off and 10% HCl (20 ml) was added to the residue. The acidic solution was washed with Et_2O, made basic with saturated $KHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried, then the solvent was evaporated off. The resulting crude product was crystallized from Me_2CO to give 0.24 g (80%) of **1g**. Spectral data were in good agreement with the literature values.6) mp 155—157 °C (lit.6) mp 152—153 °C). $[\alpha]_D^{24}$ $-24°$ ($c = 0.2$, $CHCl_3$) (lit.6) $[\alpha]_D^{25}$ $-23°$ ($c = 1.53$, $CHCl_3$)).

(*S*)-6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(*S*)-Tetrahydropapaverine; 1h] Compound **8h** was hydrogenated as described for **1g** to **1h** in 85% yield. Spectral data were in good agreement with the literature values.7) $[\alpha]_D^{24}$ $-24°$ ($c = 0.22$, $CHCl_3$) [lit.7) $[\alpha]_D$ $-21°$ ($c = 1.0$, $CHCl_3$)]. **1h**·HCl: mp 162—164 °C (lit.7) mp 167 °C).

6,7-Dibenzyloxy-1-ethoxyisochroman (12) $BF_3 \cdot Et_2O$ (5 ml, 41 mmol) was added quickly to a solution of 3,4-dibenzyloxyphenethyl alcohol8) (**11**, 9 g, 27 mmol) in triethyl orthoformate (45 ml, 270 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature, made basic with saturated $KHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was washed with water and dried. Evaporation of the solvent gave a brown oily mass, which was crystallized from hexane to give **12** (4.2 g, 40%). mp 99—102 °C. *Anal.* Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found C, 76.94; H, 6.76. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.28 (3H, t, $J = 6.4$ Hz), 2.22—2.97 (2H, m), 3.50—4.19 (4H, m), 5.10 (4H, s), 5.46 (1H, s), 6.70 (1H, s), 6.85 (1H, s), 7.37 (10H, br s). EI-MS *m*/*z*: 390 (M^+).

2-(2-Chloroethyl)-4,5-dimethoxybenzaldehyde (14) A solution of **13** (1.7 g, 4.36 mmol) in acetyl chloride (3.5 ml, 49.2 mmol) was refluxed for 2.5 h. The excess acetyl chloride was distilled off and the residue was heated at 90—100 °C for 1 h. The volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (hexane : AcOEt = 8 : 1) to give **14** (1.2 g, 72%). mp 75—77 °C (from Et_2O). *Anal.* Calcd for $C_{23}H_{21}ClO_3$: C, 72.59; H, 5.56. Found: C, 72.62; H, 5.61. IR (Nujol): 1668 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.15—3.78 (4H, m), 5.11 (2H, s), 5.19 (2H, s), 6.77 (1H, s), 7.30 (1H, s), 10.05 (1H, s). EI-MS *m*/*z*: 382 ($M^+ + 2$), 380 (M^+).

(3*S*,10b*R*)-8,9-Dibenzyloxy-3-phenyl-2,3,5,6-tetrahydro-10b*H*-oxazolo-[2,3-*a*]isoquinoline (16) A solution of **14** (1.0 g, 2.6 mmol), (*S*)-phenylglycinol (0.43 g, 3.2 mmol) and AcOH (2.6 mmol) in EtOH (50 ml) was stirred for 10 h at room temperature. The solvent was evaporated off under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 ml). Triethylamine (0.45 g, 3.2 mmol) was added dropwise to the resulting solution at -5 °C. After being stirred at -5 °C for an additional 1 h, the reaction mixture was washed with water and dried. The solvent was chromatographed on alumina (hexane : AcOEt = 3 : 1) to give an inseparable mixture (1.15 g, 94%) of **16** (85% de) and (3*S*,10b*S*)-8,9-dibenzyloxy-3-phenyl-2,3,5,6-tetrahydro-10b*H*-oxazolo[2,3-*a*]isoquinoline (**17**) as a viscous oil. The diastereoisomeric excess of **16** was determined from the 500 MHz NMR spectrum of the oily mixture. *Anal.* Calcd for $C_{31}H_{29}NO_3$: C, 80.82; H, 6.31; N, 3.02. Found: C, 80.86; H, 6.35; N, 3.06. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.59—3.11 (4H, m), 3.61—3.91 (1H, m), 4.10—4.45 (2H, m), 5.12 (4H, s), 5.36 (1H, s), 6.77 (1H, s), 7.06 (1H, s), 7.40 (15H, br s). FAB-MS (positive ion mode) *m/z*: 464 ($M^+ + 1$). $[\alpha]_D^{22}$ +40° (c = 0.25, $CHCl_3$).

(1*S*,1′*S*)-6,7-Dibenzyloxy-2-(2-hydroxy-1-phenylethyl)-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (18) A solution of 95% $ClTi(OPr^i)_3$ (2.4 ml, 9.6 mmol) in dry hexane (10 ml) was added dropwise at −5 °C to a solution of 3,4,5-trimethoxybenzylmagnesium chloride (8 mmol) prepared as described for **7f**—**h** (method A) in dry THF (50 ml), and the mixture was stirred for 2 h at −5 °C. A solution of **4b** (0.92 g, 2 mmol) in dry THF (10 ml) was added dropwise to the mixture at −5 °C. The reaction mixture was then stirred at −5 °C for 1.5 h. Work-up as described above and subsequent purification by flash chromatography on silica gel (hexane : AcOEt = 2 : 1) gave 1.23 g (95%) as a mixture of **18** and (1*R*,1′*S*)-6,7-dibenzyloxy-2-(2-hydroxy-1-phenylethyl)-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**19**). The diastereoisomeric excess of **18** was determined to be 60% by HPLC analysis. The mixture was separated by chromatography on an open column of silica gel (hexane : AcOEt = 3 : 1) to give 0.65 g (50%) of **18**. Hygroscopic solid. IR (Nujol): 3480 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.19—3.09 (6H, m), 2.42 (1H, s), 3.65, 3.75, 3.79 (3H × 3, each s), 3.56—4.20 (4H, m), 4.89, 5.05 (2H × 2, each s), 6.08 (2H, s), 6.30, 6.58 (1H × 2, each s), 7.10—7.59 (15H, m). FAB-MS (positive ion mode) *m/z*: 646 ($M^+ + 1$). $[\alpha]_D^{18}$ +26.4° (c = 0.21, EtOH).

(*S*)-(−)-Trimetoquinol Hydrochloride (1c · HCl) Hydrogenolysis of **18** was carried out as described for **1g**. After absorption of hydrogen was complete, the catalyst was filtered off. The filtrate was concentrated to give the hydrochloride of (*S*)-trimetoquinol (**1c** · HCl, yield 86%). Spectral data of **1c** · HCl were in good agreement with literature values.[9] **1c** · HCl: mp 155—156 °C (lit.[9] mp 151—153 °C). $[\alpha]_D^{22}$ −32° (c = 0.23, MeOH) [lit.[9] $[\alpha]_D^{23}$ −30° (c = 1.0, MeOH)].

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