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ASYMMETRIC SYNTHESIS OF 1-ALKYLTETRAHYDROISOQUINOLINES USING CHIRAL OXAZOLO[2,3-a]TETRAHYDROISOQUINOLINES

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Abstract: A new method of synthesizing enantiomerically pure (S)- and (R)-alkyl- and 1-aryltetrahydroisoquinolines has been achieved starting from isochroman with (R)- or (S)-phenylglycinol.

Chiral 1-alkyltetrahydroisoquinolines (VI) are useful as key intermediates for the synthesis of isoquinoline alkaloids. Several reports[1a-d] on the highly stereoselective synthesis of 1-alkyltetrahydroisoquinolines have recently been reported. Meyers et al.[1a] have reported the efficient diastereoselective alkylation of 1-lithiated tetrahydroisoquinolines containing the chiral formamidine auxiliary. Noyori et al.[1b] have accomplished asymmetric hydrogenation of N-acyl-1-alkylidenetetrahydroisoquinolines using chiral BINAP catalyst. However, these methodologies can not be applied to the asymmetric synthesis of 1-aryltetrahydroisoquinolines.

We have previously communicated the synthesis of chiral oxazolo[2,3-a]-tetrahydroisoquinolines (V) and their utility in the asymmetric syntheses of isoquinoline alkaloids,(S)-(-)- and (R)-(+)-salsolidines[2,3] (16 and 18) (Chart 4). The idea of synthesizing the chiral oxazoloisoquinolines (V)

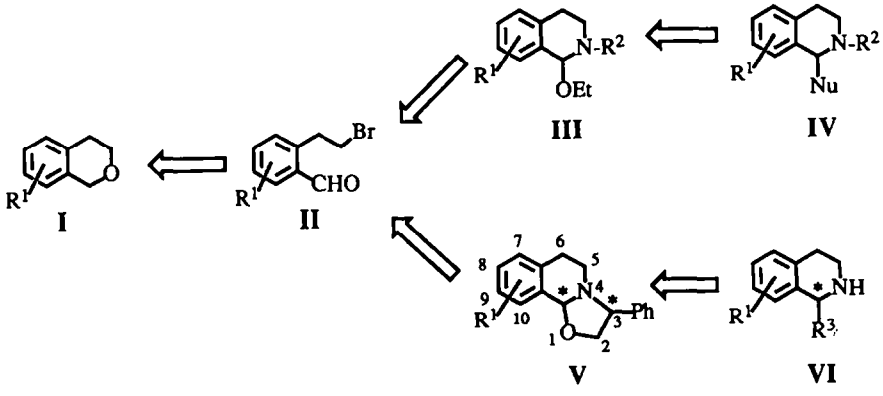


Chart 1

was obtained during our investigation on the reactivity of 1-ethoxy-2-methyltetrahydroisoquinoline[4] (III) which is considered as a N,O-acetal. Compound III was found to undergo facile substitution by nucleophilic reagents such as active methylene compounds[4] or Grignard reagents to give the 1-substituted compounds (IV). This finding drew our attention towards the synthesis of cyclic chiral 1-alkoxytetrahydroisoquinoline, namely oxazoloisoquinolines (V). Compound V has been easily prepared using (R)- or (S)-phenylglycinol and converted to (S)- or (R)-salsolidine in 100% ee by the Grignard reaction followed by hydrogenolysis. As a further extension, we have investigated the scope and limitation of this method.

We report here the complete details of our study including the syntheses of 1-alkyl and 1-aryltetrahydroisoquinoline alkaloids {(S)- and (R)-salsolidines (16 and 18), (S)-homolaudanosine (21), and (S)-cryptostyline II (22)}.

Results and Discussion

SYNTHESIS OF CHIRAL OXAZOLOISOQUINOLINES

(3R,10bS)-Oxazolo[2,3-a]tetrahydroisoquinoline (5a) was obtained as shown in Chart 2. Bromination of isochroman (1a) in the presence of sunlight gives 1-bromoisochroman which, upon heating, gives 2-(2-bromoethyl)benzaldehyde.

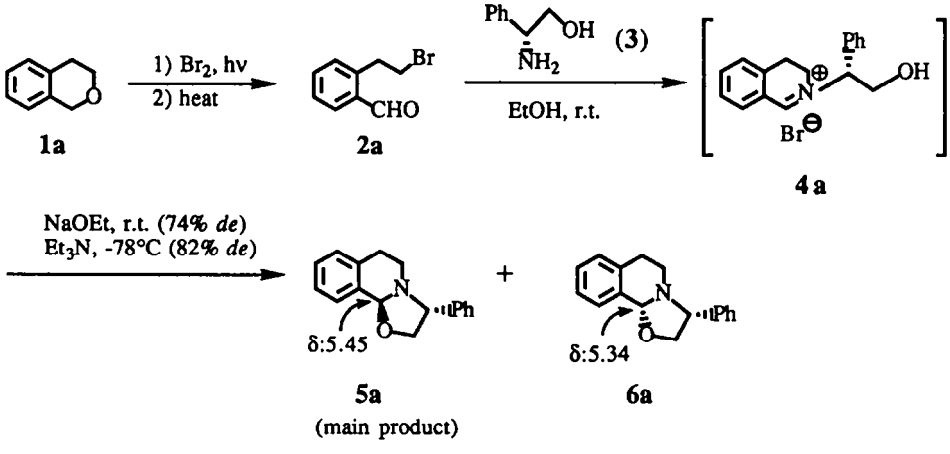


Chart 2

aldehyde[6] (2a). Treatment of 2a with D-(R)-phenylglycinol (3) gave (R)-3,4-dihydroisoquinolinium bromide (4a) which was then cyclized to the oxazoloisoquinoline using sodium ethoxide at room temperature. As expected, the cyclization of 4a took place diastereoselectively due to the asymmetric center at the 1'-position of 4a to give an inseparable 6.8:1 (74% de) diastereomeric mixture of 5a and 6a. The structures of 5a and 6a were assigned by X-ray crystal structure and 500 MHz ^{1}H-NMR analyses (vide infra). The diastereomeric excess was determined by integration of the single peaks of the 10bH protons of the diastereomers.

We tried to synthesize 5a in high diastereomeric excess under various conditions. The most highly stereoselective cyclization of 4a was achieved using triethylamine in CH_2Cl_2 at -78°C, the major product being 5a with 82% diastereoselection.

In the case of the synthesis of the analogous 6,7-dimethoxy compound (5b) (Chart 3), bromination of 6,7-dimethoxyisochroman (1b) with bromine or NBS was unsuccessful due to the formation of a polymer.[6] The desired 2b was obtained in 28% yield by heating the 1-ethoxyisochroman (9b) with acetyl bromide. When acetyl chloride was used in a similar reaction, compound 8b was obtained in 70% yield. Compound 8b was then converted to the (R)-isoquinolinium salt by the reaction with D-(R)-phenylglycinol (3). The resulting crude salt, upon treatment with triethylamine in CH_2Cl_2 at -78°C, gave cyclized product as a 19:1 (90% de) mixture of 5b and 6b. Recrystallization of the mixture from ethanol gave pure 5b in 93% yield. The absolute configration of 5b was determined by X-ray crystal structure analysis and found to be 3R, 10bS.[7]

The structures of 5a and 6a (Chart 2), which are inseparable, were assigned by comparison of their signals for 10bH protons with those of 5b and 6b. The signal for 10bH of 5b appears at δ:5.40 as a single peak. The $\Delta\delta$ value of the 10bH signal for the pair of 5b and 6b is 0.1 ppm. In the case of the inseparable mixture of 5a and 6a, the 10bH proton for the major product is deshielded and $\Delta\delta$ value is 0.1 ppm. From this great similarity, the structure of the major product was determined to be 5a.

Consequently, it was found that the configuration of the asymmetric carbon created in the cyclization was the S-configuration.

The enantiomer of 5b, (3S, 10bR)-oxazoloisoquinoline (11b) was also prepared from 8b using L-(S)-phenylglycinol (10).

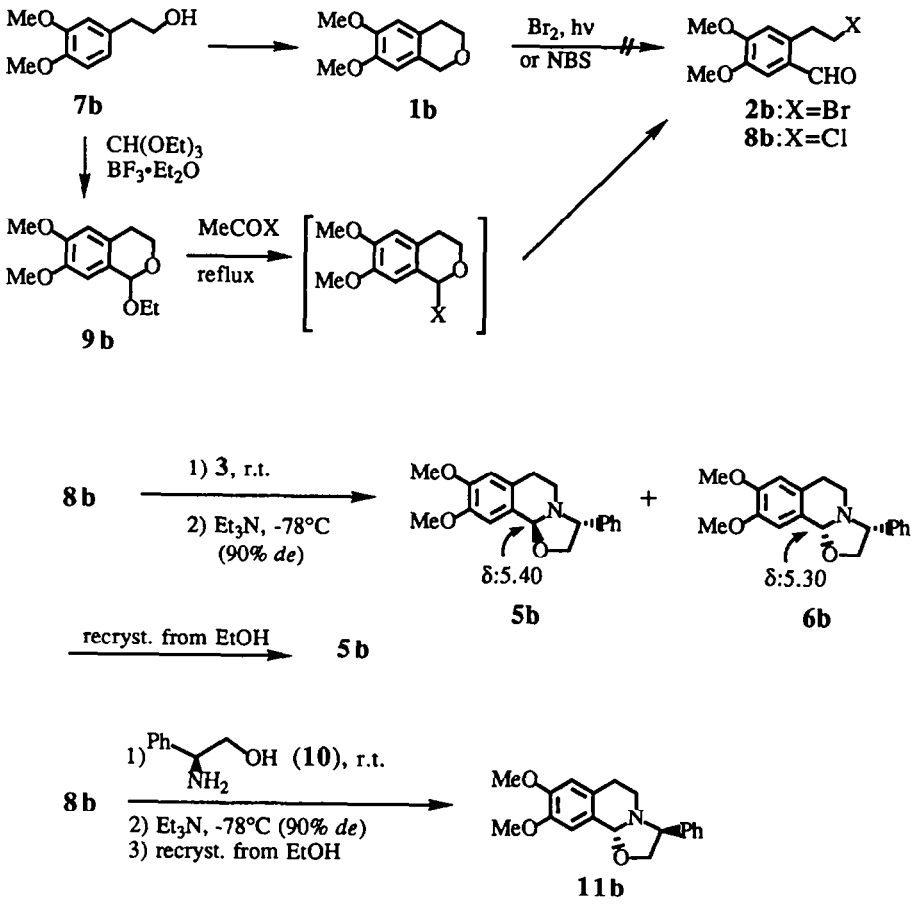

MeO
MeO
OH
7b
1b
Br2, hv
or NBS
X
CHO
2b:X=Br
8b:X=Cl
CH(OEt)3
BF3•Et2O
MeCOX
reflux
OEt
9b
8b
1) 3, r.t.
2) Et3N, -78°C
(90% de)
Ph
δ:5.40
δ:5.30
5b
6b
recryst. from EtOH
5b
1)
OH (10), r.t.
NH2
2) Et3N, -78°C (90% de)
3) recryst. from EtOH
11b

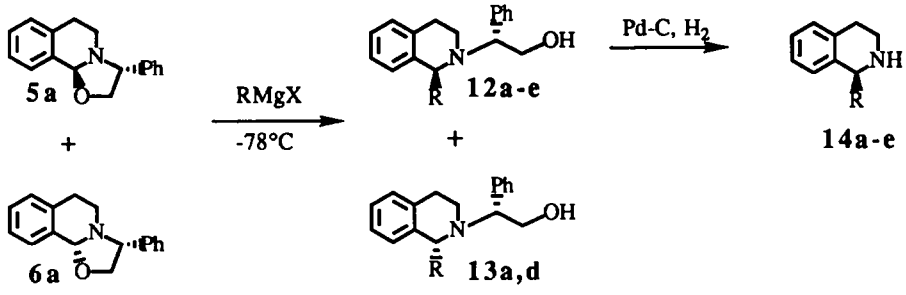
Chart 3

GRIGNARD REACTION OF 5a

Asymmetric alkylation of oxazoloisoquinoline 5a was examined using the Grignard reagents listed in Table I in ether at -78°C. Since chromatographic separation of an oily mixture of 5a and 6a was difficult, we used a 10:1 (82% de) mixture of 5a and 6a as a starting material. It was found that 4 equivalent of the Grignard reagent was necessary to completely alkylate 5a.

As we would expect, the reaction of methylmagnesium iodide gave a 10:1 (82% de) mixture of 12a and 13a. The diastereomeric excess was determined by 500 MHz NMR spectroscopy and found to be similar to the diastereomeric purity of the starting material, 5a. Later, the mixture of 12a and 13a was separated by column chromatography on alumina to give pure 12a in 80% yield. In the case of butyl-, phenethyl-, or phenylmagnesium halide, the reaction gave only one diastereoisomer, 12b, 12c, or 12e, respectively. However, the reaction of benzylmagnesium chloride gave a separable 8:1 (78% de) mixture of 12d and 13d. The diastereomeric excess was exceptionally lower than the diastereomeric purity of 5a.

Table I. Grignard Reaction of 5a[a)]



RMgX		Product Yield (%)[b)]	Ratio (12:13)	% *de*
MeMgI	a	98 (88)[c)]	10:1	82
BuMgBr	b	81	only **12b**	100
PhMgBr	c	80	only **12c**	100
$PhCH_2MgCl$	d	88 (78)[c)]	9:1	78
$PhCH_2CH_2MgCl$	e	84	only **12e**	100

a) A 10:1 (82% *de*) mixture of **5a** and **6a** was used as a starting material. b) The yield was calculated based on a mixture of **5a** and **6a**. c) The value in parenthesis shows the isolated yield of **12** after column chromatography.

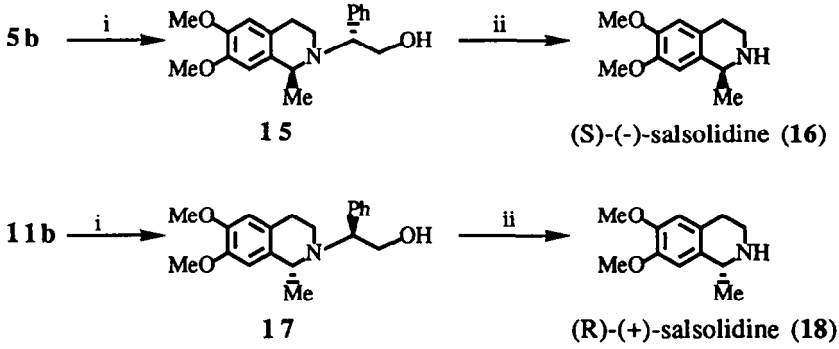
The structures of 12a-e were assigned as follows: compounds 12a-e were hydrogenated with Pd-carbon in acidic ethanol solution to give 1-alkyl-tetrahydroisoquinolines. Their absolute configurations were elucidated as the S-configuration by comparison of the optical rotation values with those reported[8] of the authentic samples.

Consequently, the asymmetric carbon created in the Grignard reaction

SYNTHESIS OF (S)-(-)- and (R)-(+)-SALSOLIDINE

Based on the previously described finding, the synthesis of the simple natural isoquinoline alkaloid, salsolidine, was synthesized using pure 5b (Chart 4). Methylmagnesium iodide in ether was used to alkylate 5b at -78°C. The TLC analysis of the resulting methylated compound (15) showed that only one diastereoisomer was produced. This observation was also confirmed from the signal of the methyl proton on the 500 MHz ^{1}H-NMR spectrum. Hydrogenolysis of 15 on Pd-carbon in acidic ethanol furnished the natural (S)-(-)-salsolidine (16) in 92% yield. Its optical rotation and chiral HPLC analysis showed that the synthetic salsoldine (16) was produced in 100% ee.

In a similar way, (R)-(+)-salsolidine (18) was synthesized from (3S,10bR)-oxazoloisoquinoline (11b) in 100% ee.



Reagent : i) MeMgI, -78°C, Et_2O; ii) Pd-C, H_2, EtOH, r.t.

Chart 4

SYNTHESES OF (S)-(-)-HOMOLAUDANOCINE (21) and (S)-(+)-CRYPTOSTYLINE II (22)

In a similar way as described for the synthesis of (S)-salsolidine, 1-phenyl- (19) and 1-phenethyl- (20) isoquinoline alkaloides were synthesized from 5b in 73 and 75% yields (based on 5b), respectively. N-Methylation of 19 and 20 by the reaction with formaldehyde and formic acid gave (S)-(-)-

homolaudanosine (21) and (S)-(+)-cryptostyline II (22) in 41 and 80% yields, respectively. Their chiral HPLC analysis revealed a single peak, implying that the natural alkaloids, 21 and 22, were obtained in 100% ee. This was also supported by comparison of their optical rotation with those reported.

From the present results, it can be concluded that a facile method has been developed for the asymmetric synthesis of 1-alkyl and 1-aryltetrahydroisoquinoline alkaloids.

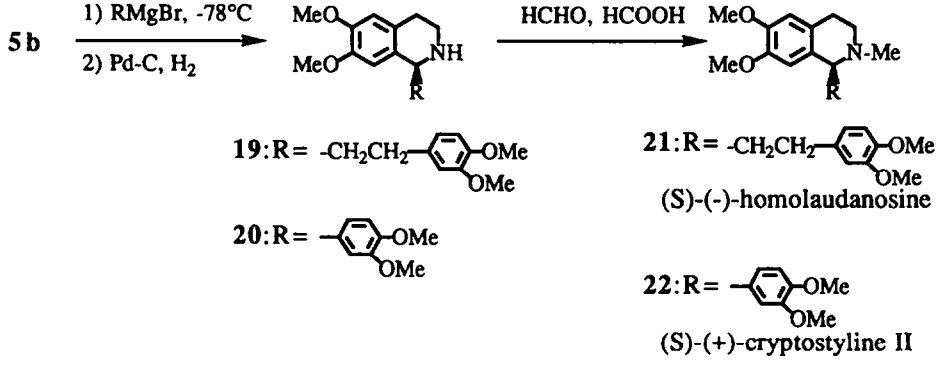


Chart 5

Acknowledgement

We are grateful to The SC-NMR Laboratory of Okayama University for 500-MHz proton-NMR experiments.

Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra were recorded on a Schimadzu LKB 9000 spectrometer and FAB-Mass spectra were recorded on a VG-70SE spectrometer. NMR spectra 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 Shimadzu SPD-6A instrument on a DAICEL chiral phase column (Chiralcel OD) fitted with an ultraviolet (254 nm) detector.

Wako C-300 silica gel (200-300 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over $MgSO_4$.

(3R,10bS)-3-Phenyl-2,3,5,6-tetrahydro-10bH-oxazolo[2,3-a]isoquinoline (5a)

A solution of 2-(2-bromoethyl)benzaldehyde[6] (2a; 1 g 4.7 mmol) and D-(R)-phenylglycinol (0.66 g, 4.7 mmol) in dry EtOH (4 ml) was stirred for 4 h at room temperature. The solvent was evaporated under reduced pressure to give (1'R)-2-(2-hydroxy-1-phenylethyl)-3,4-dihydroisoquinolinium bromide (4a) as a solid, which was used in the following reaction without further purification. The crude 4a (1.56 g, 4.68 mmol) was dissolved in dry CH_2Cl_2 (150 ml), and then Et_3N (0.86 g, 9.4 mmol) was added dropwise at -78°C. The mixture was then stirred for 1 h at -78°C, washed with H_2O, and dried. The solvent was evaporated and the residue was column chromatographed on alumina (AcOEt:hexane; 1:16) to give an inseparable 10:1 (82% de) mixture (1.1 g, 94%) of 5a and (3R,10bR)-3-phenyl-2,3,5,6-tetrahydro-10bH-oxazolo-[2,3-a]isoquinoline (6a) as a viscous oil. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.00; H, 6.94; N, 5.54. MS m/z: 251 (M^+). NMR (60 MHz, $CDCl_3$) δ: 2.75-3.12 (4H, m), 3.77 (1H, dd, J = 5 and 6 Hz), 4.10-4.60 (2H, m), 5.40 (1H, s), 7.05-7.59 (9H, m). The diastereomeric excess of 5a was determined by 500 MHz NMR spectrum of the oily mixture. For 5a: 5.44 (0.91H, s, 10bH); for 6a: 5.34 (0.09H, s, 10bH).

6,7-Dimethoxy-1-ethoxyisochroman (9b)

To a solution of 3,4-dimethoxyphenethyl alcohol (7b; 8.6 g, 44 mmol) in ethyl orthoformate (73 ml, 440 mmol), $BF_3.Et_2O$ (5.5 ml, 44 mmol) was added quickly at 0°C. The reaction mixture was stirred for 2.5 h at room temperature, made basic with saturated $KHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried. Evaporation of the solvent gave brown oily mass which was purified by column chromatography on silica gel (hexane:AcOEt; 8:1) to give 9b (4.92 g, 47%), mp 64-66°C. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.89; H, 7.89. NMR (60 MHz, $CDCl_3$) δ: 1.24 (3H, t, J = 7.6 Hz), 2.52-2.99 (2H, m), 3.47-4.18 (4H, m), 3.80, (3H, s), 3.82 (3H, s), 5.49 (1H, s), 6.56 (1H, s), 6.69 (1H, s).

2-(2-Chloroethyl)-4,5-dimethoxybenzaldehyde (8b)

A solution of 9b (6 g, 25.2 mmol) in acetyl chloride (18 ml) 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 crude reaction mixture was then chromatographed on silica gel (hexane:AcOEt; 8:1) to give 8b (4.02 g, 70%), which was recrystallized from Et_2O, mp 62-64°C. Anal. Calcd for $C_{11}H_{13}ClO_3$: 57.76; H, 5.70. Found: C, 57.83; H, 5.74. IR (Nujol) cm^{-1}: 1668. NMR (60 MHz, $CDCl_3$) δ: 3.35-3.93 (4H, m), 3.98 (3H, s), 4.00 (3H, s), 6.84 (1H, s), 7.41 (1H, s), 10.17 (1H, s).

2-(2-Bromoethyl)-4,5-dimethoxybenzaldehyde (2b)

Compound 2b was similarily obtained from 9b and acetyl bromide in 28% yield, mp 62-64°C (from hexane-AcOEt). Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 47.94; H, 4.72. Found: C, 48.40; H, 4.80. IR (Nujol) cm^{-1}: 1668. NMR (60 MHz, $CDCl_3$) δ: 3.50(4H, s), 3.90(3H, s), 3.92 (3H, s), 6.72 (1H, s), 7.29 (1H, s), 10.12 (1H, s).

(3R,10bS)-8,9-Dimethoxy-3-phenyl-2,3,5,6-tetrahydro-10bH-oxazolo[2,3-a]isoquinoline (5b)

A solution of 8b (0.2 g, 0.88 mmol), D-(R)-phenylglycinol (0.12 g,

0.88 mmol) and AcOH (53 mg, 0.88 mmol) in EtOH (5 ml) was stirred for 5 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (20 ml). Triethylamine (0.18 g, 1.76 mmol) was added dropwise at -78°C. After being stirred at -78°C for an additional 1 h, the reaction mixture was washed with saturated $KHCO_3$ solution and H_2O. Evaporation of the solvent gave a 19:1 (90% de) mixture of 5b and (3R,10bR)-8,9-dimethoxy-3-phenyl-2,3,5,6-tetrahydro-10bH-oxazolo-[2,3-a]isoquinoline (6b) as a solid, which was recrystallized from EtOH to give optically pure 5b (0.254 g, 93%), mp 115-116°C. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C,73.25; H, 6.77; N, 4.51. MS m/z: 311 (M^+). NMR (60 MHz, $CDCl_3$) δ: 2.30-3.20 (4H, m), 3.33-3.67 (1H, m) 3.88 (6H, s), 4.10-4.58 (2H, m), 5.41 (1H, s), 6.66 (1H, s), 6.91 (1H, s), 6.97-7.55 (5H, m). $[\alpha]^{22}_D$ -38° (c, 0.1, EtOH)

(3S,10bR)-8,9-Dimethoxy-3-phenyl-2,3,5,6-tetrahydro-10bH-oxazolo[2,3-a]isoquinoline (11b)

Compound 11b was prepared from 8b (0.2 g, 0.73 mmol) and L-(S)-phenylglycinol (10) by the procedure described for the preparation of 5b, mp 114-115°C. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.21; H, 6.75; N, 4.52. MS m/z: 311 (M^+). $[\alpha]^{28}_D$ +34.2° (c, 0.1, EtOH).

General Procedure for the Alkylation of 5a with Grignard Reagent

To a 3-necked flask, fitted with a reflux condenser and septum rubber and continuously maintained with a flow of argon, Mg turning (192 mg, 8 mmol) and dry Et_2O (30 ml) were placed. Alkyl halide (8 mmol) was added dropwise with occasional heating to initiate reaction. Stirring was continued at room temperature for 1 h with occationally heating. Finally it 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 (82% 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 solution. The organic layer was separated. Further extraction with CH_2Cl_2 was performed. The combined organic layer were washed with H_2O and dried. The solvent was evaporated off under reduced pressure. The residue was purified by flash chromatography on alumina.

The diastereomeric excess of the pure products was determined by 500 MHz NMR spectroscopy.

(1S,1'R)-2-(2-Hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (12a)

The reaction of 5a (82% de, 2 mmol) with MeMgI afforded a 10:1 (82% de) mixture of 12a and (1R,1'R)-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,-3,4-tetrahydroisoquinoline (13a) in 98% yield. The mixture was then separated by column chromatography on alumina (AcOEt:hexane; 2:3) to give optically pure 12a (88%), as a viscous oil. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.88; H, 7.99; N, 5.20. NMR (60 MHz, $CDCl_3$) δ: 1.31 (3H, d, J = 6.5 Hz), 2.10 (1H, s), 2.60-3.16 (4H, m), 3.50-4.30 (4H, m), 7.09 (4H, s), 7.34 (5H, s). $[\alpha]^{29}_D$ -20° (c, 0.17, $CHCl_3$)

(1S,1'R)-1-Butyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (12b)

The reaction of 5a (82% de, 2 mmol) with BuMgBr afforded only 12b in 81% yield, as a viscous oil. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.29; H, 8.75; N, 4.60. IR (Neat) cm^{-1}: 3435. NMR (60 MHz, $CDCl_3$) δ: 0.71-1.55 (10H, m), 2.09 (1H, br), 2.15-3.14 (1H, m), 3.16- 4.10 (6H, m). 6.90-7.41 (4H, m), 7.27 (5H, s). FAB-MS (positive ion mode) m/z 310 (M^+ + 1). $[\alpha]^{26}_D$ -34° (c, 0.1, EtOH).

(1S,1'R)-2-(2-Hydroxy-1-phenylethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (12c)

The reaction of 5b (82% de, 1.2 mmol) with PhMgBr afforded only 12c in 80% yield. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.25; H, 7.04; N, 4.25. Found: C, 83.59; H, 6.99; N,4.21. IR (Neat) cm^{-1}: 3420. NMR (60 MHz, $CDCl_3$) δ: 2.06 (1H, s), 2.64-3.21 (4H, m), 3.73-4.11 (3H, m), 4.82 (1H, s), 6.50-7.37 (14H, m). FAB-MS (positive ion mode) m/z 330 (M^+ + 1).$[\alpha]^{20}_D$ +13° (c, 0.1,

EtOH).

(1S,1'R)-1-Benzyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (12d)

The reaction of 5a (82% de, 2 mmol) with $PhCH_2MgCl$ afforded a 9:1 (78% de) mixture of 12d and (1R,1'R)-1-benzyl-2-(2-hydroxy-1-phenethyl)-1,2,3,4-tetrahydroisoquinoline (13d) in 88% yield. The mixture was separated by column chromatography on alumina (AcOEt:hexane, 1:4) to give opticaly pure 13d as an oil in 78% yield. Anal Calcd for $C_{24}H_{25}NO$: C, 83.92; H, 7.34; N, 4.08. Found: C, 84.06; H, 7.59; N, 4.11. IR (Neat) cm^{-1}: 3495. NMR (60 MHz, $CDCl_3$) δ: 2.08-3.19 (7H, m), 3.29-4.03 (4H, m), 6.79-7.43 (14H, m). FABMS (possitive ion mode) m/z: 344 (M^+ + 1). $[\alpha]^{26}_D$ -26° (c, 0.11, $CHCl_3$).

(1S,1'R)-2-(2-Hydroxy-1-phenylethyl)-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (12e)

The reaction of 5a (82% de, 2 mmol) with $PhCH_2CH_2MgBr$ afforded only 12e in 84% yield, mp 168-170°C (decomp.) (from Et_2O). Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.59; H, 7.45; N, 4.01. IR (Nujol) cm^{-1}: 3450. NMR (60 MHz, $CDCl_3$) δ: 2.37-2.92 (5H, m), 3.58-4.87 (8H, m), 7.11 (4H, s), 7.35 (5H, s). FABMS (positive ion mode) m/z: 356 (M^+ + 1). $[\alpha]^{25}_D$ +23.0° (c, 0.16, EtOH).

General Procedure for Hydrogenolysis

A solution of 12a-e (0.81 mmol) was hydrogenated in EtOH in the presence of 10% Pd-carbon (300 mg) and 10% HCl (2 ml). After the completion of H_2 absorption, the solvent was evaporated and 10% HCl (20 ml) was added. 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 oil was purified by molecular distillation to give optically pure (S)-1-alkyltetrahydroisoquinoline (14a-e). The chiral HPLC analysis of the free base (14a-e) showed their enantiomeric purities to be 100%.

(S)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (14a)

Oil, yield 98%. Optical rotation of the free amine was in good agreement with that reported. $[\alpha]^{23}_D$ -71.3° (c, 11.0, EtOH), Lit[a] $[\alpha]^{25}_D$ -71.3° (c, 0.64, THF). NMR (60 MHz, $CDCl_3$) δ: 1.41 (3H, d, J = 7 Hz), 2.08 (1H, s), 2.60-3.32 (4H, m), 4.06 (1H, q, J = 7 Hz), 7.03 (4H, s). Hydrochloride salt: mp 211-213°C; Lit[a] 208°C.

(S)-1-Butyl-1,2,3,4-tetrahydroisoquinoline (14b)

Oil, yield 95%. Optical rotation of the free amine was in good agreement with that reported. $[\alpha]^{24}_D$ -78° (c, 0.1, THF); Lit[a] $[\alpha]^{25}_D$ -78.4° (c, 0.61, THF). IR (Neat) cm^{-1}: 3310. NMR (60 MHz, $CDCl_3$) δ: 0.89 (3H, t, J = 6 Hz), 1.13-2.03 (6H, m), 2.63-3.30 (5H, m), 3.95 (1H, t, J = 7Hz), 7.04 (4H, s). Hydrochloride salt: mp 146-148°C. lit[a] mp 142-143°C.

(S)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (14c)

Mp 82-84°C (decomp), yield 86%. Anal. Calcd for $C_{15}H_{15}N$: C, 86.06; H, 7.22; N, 6.69. Found: C, 86.01; H, 7.25; N, 6.65. IR (Nujol) cm^{-1}: 3260. NMR (60 MHz, $CDCl_3$) δ: 2.12 (1H, s), 2.64-3.26 (4H, m), 4.95 (1H, s), 6.99 (4H, s), 7.14 (5H, s). FABMS (positive ion mode) m,/z: 210 (M^+ + 1). $[\alpha]^{24}_D$ -10.2° (c, 0.17, $CHCl_3$).

(S)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline (14d)

Oil, yield 92%. Optical rotation of the free base was in good agreement with that reported. $[\alpha]^{25}_D$ -63.1° (C, 0.6, THF); Lit[a] $[\alpha]^{25}_D$ -62.2° (c, 1.24, THF). IR (Neat) cm^{-1}: 3350. NMR (60 MHz, $CDCl_3$) δ: 2.70-3.43 (7H, m), 4.25 (1H, dd, J = 5 and 10 Hz), 7.11 (4H, s), 7.25 (5H, s). Hydrochloride salt: mp 184-186°C; Lit[a] mp 187°C.

(S)-1-Phenethyl-1,2,3,4-tetrahydroisoquinoline (14e)

Oil, yield 91%. Optical rotation of the free base was in good agreement with that reported. $[\alpha]^{22}_D$ -24° (c, 0.1, THF); Lit[a] $[\alpha]^{25}_D$

-23.5° (c, 5.71, THF). IR (Neat) cm^{-1}: 3350. NMR (60 MHz, $CDCl_3$) δ: 1.83-2.91 (3H, m), 2.59-3.41 (6H, m), 4.01 (1H, t, J = 6 Hz), 7.09 (4H, s), 7.22 (5H, s). Hydrochloride salt: mp 204-205°C; Lit[14] mp 200°C.

(1S,1'R)-6,7-Dimethoxy-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (15)

Methylmagnesium iodide (5.2 mmol) was used to alkylate optically pure 5b (2.6 mmol) according to the general procedure for the preparation of 14. After column chromatography of the crude product on alumina (AcOEt:hexane, 2:3), 0.79 g (93%) of 15 was obtained as an oil with 100% de. The optical purity was determined by TLC and 500 MHz NMR analyses. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.26; H, 7.70; N, 4.28. Found: C, 73.29; H, 7.54; N, 4.10. IR (Neat) cm^{-1}: 3530. NMR (60 MHz, $CDCl_3$) δ: 1.31 (3H, d, J = 7 Hz), 2.21 (1H, s), 2.50-3.28 (4H, m), 3.60-4.20 (4H, m), 3.81 (3H, s), 3.85 (3H, s), 6.42 (1H, s), 6.56 (1H, s), 7.36 (5H, s). $[\alpha]^{20}_D$ -6.4 ° (c, 1.0, EtOH).

(S)-(-)-Salsolidine (16)

Compound 15 (0.5 g, 1.5 mmol) was hydrogenated according to the general procedure for the hydrogenolysis. The crude product was purified by molecular distillation to give (S)-(-)-salsolidine (0.2 g, 92%). Chiral HPLC analysis of the free base showed its enantiomeric purity to be 100%. Spectroscopic properties were in good agreement with literature values. $[\alpha]^{24}_D$ -62.5° (c, 0.1, EtOH); Lit[8] $[\alpha]^{22}_D$ -59.5° (c, 4.39, EtOH). Hydrochloride salt mp 234-236°C; Lit[9] 235-236°C.

(1R,1'S)-6.7-Dimethoxy-2-(2-hydroxy-2-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (17)

Methylmagnesium iodide (5.2 mmol) was used to alkylate of optically pure 17 (2.6 mmol) according to the general procedure for the preparation of 14. Column chromatography on alumina (AcOEt:hexane, 2:3) of the crude product gave 17 in 93% yield (100% de). The optical purity was determined by TLC and 500 MHz NMR analyses. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70, N, 4.8. Found: C, 73.45 H, 7.82; N, 4.30. $[\alpha]^{20}_D$ +6.1° (c, 1.0, EtOH). The NMR spectrum was identical to that of 15.

(R)-(+)-Salsolidine (18)

Compound 17 (0.5 g, 1.5 mmol) was hydrogenated according to the general procedure for the hydrogenolysis. The crude product was purified by molecular distillation to give 18. The chiral HPLC analysis of the free base showed its enantiomeric purity to be 100%. $[\alpha]^{22}_D$ +62.8° (c, 0.1, EtOH); Lit[9] $[\alpha]^{16}_D$ 59.9° (C, 2.5, EtOH). Hydrochloride salt: mp 234-235°C; Lit[9] 235-236°C.

(S)-(-)-Norhomolaudanosine (19)

A solution of 3,4-dimethoxyphenetylmagnesium bromide (13 mmol) in THF was used to alkylate optically pure 5b (3.2 mmol) according to the general prcedure for the preparation of 14. The crude product was purified by flash chromatography on alumina (AcOEt:CH_2Cl_2, 9:1) to give (1S,1'R)-6,7-dimethoxy-(3,4-dimethoxyphenethyl)-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline as a hygroscopic solid in 81% yiled (100% de). The optical purity was determined to be 100% by its TLC and 500 MHz NMR analyses. IR (Nujol) cm^{-1}: 3550. NMR (60 MHz, $CDCl_3$) δ: 1.66-2.14 (5H, m), 2.43-4.02 (7H, m), 3.73 (12H, s), 6.11 (1H, s), 6.43-7.75 (4H, m), 7.19 (5H, s). FABMS (positive ion mode) m/z 478 (M^+ + 1). $[\alpha]^{21}_D$ -7.3° (c, 0.22, EtOH).

After hydrogenolysis according to the general procedure, 19 was obtained in 81% yield as an oil. The chiral HPLC analysis of the free base showed its enantiomeric purity to be 100%. IR (neat) cm^{-1}: 3350. NMR(60 MHz, $CDCl_3$) δ: 1.92 (1H, s), 1.91-2.30 (2H, m), 2.43-2.87 (4H, m), 2.89-3.30 (2H, m), 3.79 (12H, s), 3.71-4.05 (1H, m), 6.47 (2H, s), 6.68 (3H, s). FABMS (positive ion mode) m/z: 356 (M^+ + 1). $[\alpha]^{21}_D$ -17.7° (c, 0.23, EtOH).

(S)-(+)-Homolaudanosine (21)

A mixture of 19 (470 mg, 1.3 mmol), 37% formaline (1.8 ml), and formic acid (2.8 ml) was heated at 90-95°C for 2.5 h. The volatile components were removed in vacuo and the residue was made basic with

saturated $KHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried over K_2CO_3 and the solvent was evaporated. The residue was column chromatographed on alumina (AcOEt:hexane:CH_2Cl_2, 6:2:1) to give (S)-(+)-homolaudanosine (21) (200 mg, 41%) as a yellow oil. Spectroscopic properties were in good agreement with literature values. $[\alpha]^{22}_D$ +10.8° (c, 0.17, EtOH), Lit[10] $[\alpha]^{25}_D$ +11° (c, 0.21, EtOH).

(S)-(-)-Norcryptostyline II (20)

A solution of 3,4-dimethoxyphenylmagnesium bromide (13 mmol) in THF was used to alkylate optically pure 5b (3.2 mmol) according to the procedure for the preparation of 14. The crude product was purified by flash chromatography on alumina (AcOEt:CH_2Cl_2, 9:1) to give (1S,1'R)-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline in 84% yield (100% de) as a yellow solid. The optical purity was determined by TLC and 500 MHz NMR analyses. IR (Nujol) cm^{-1}: 3520. NMR (60 MHz, $CDCl_3$) δ: 2.02 (1H, s), 2.42-2.98 (4H, m), 2.99-3.98 (m, 3H), 3.65, 3.77, 3.83, 3.88 (each 3H, each s), 4.73 (1H, s), 6.23 (1H, s), 6.49-6.89 (4H, m), 7.33 (5H, s). FABMS (positive ion mode) m/z: 450 (M^+ + 1). $[\alpha]^{22}_D$ +31° (c, 0.15, $CHCl_3$).

After hydrogenolysis according to the general procedure, (S)-(-)-norcryptostyline II (20) was obtained in 95% yield, mp 113-114°C; Lit[11] mp 115-116°C. The chiral HPLC analysis of the free base showed its enantimeric purity to be 100%. The optical rotation was in agreement with that reported. $[\alpha]^{18}_D$ -37° (c, 0.26, $CHCl_3$); Lit[11] $[\alpha]_D$ -34° ($CHCl_3$). NMR (60 MHz, $CDCl_3$) δ: 2.50-3.35 (5H, m), 3.65, (3H, s), 3.86 (9H, s), 5.01 (1H, s), 6.31 (1H, s), 6.66 (1H, s), 6.72-7.01 (3H, m). FABMS (positive ion mode) m/z: 330 (M^+ + 1).

(S)-(+)-Cryptstyline II (22)

Compound 22 was prepared from 20 (300 mg, 0.91 mmol) according to the procedure for the synthesis of 21 in 80% yield. Spectroscopic properties were in good agreement with litereture values.[11] mp 116-118°C ; Lit[12] 117-118°C. $[\alpha]^{22}_D$ +59.6° (c, 0.28, $CHCl_3$); Lit[11] $[\alpha]^{25}_D$ +58.0° (c, 0.28, $CHCl_3$).

References and Notes

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