ARYL RADICAL CYCLIZATION OF CHIRAL 3-ALLYL-2-(2-BROMOPHENYL)-1,3-OXAZOLIDINES WITH TRIBUTYL Tin HYDRIDE

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Abstract—Stereoselective radical cyclization of (4R)-3-allyl-2-(2-bromophenyl)-4-phenyl-1,3-oxazolidine promoted by the initiator/tributyltin hydride system constructed the chiral oxazolo[2,3-a]tetrahydroisoquinoline skeleton. These tricyclic compounds were transformed into 4-alkyl-1,2,3,4-tetrahydroisoquinolines and 1,4-dialkyl-1,2,3,4-tetrahydroisoquinolines.

INTRODUCTION

The development of radical cyclizations offers tremendous opportunities in organic chemistry. It is difficult to control the regio- and stereochemistry of cyclizations based on construction of a heterocyclic skeleton. Nevertheless, a potential methodology for the synthesis of natural products such as alkaloids has been developed. 1,2,3,4-Tetrahydroisoquinolines are of considerable interest in organic and medicinal chemistry. These compounds inhibit serotonin, dopamine and norepinephrine uptake in the central nervous system. Therefore much effort has been expended toward synthesis of various substituted 1,2,3,4-tetrahydroisoquinolines. Despite the utility of the chiral 4-substituted derivatives in biologically interesting syntheses there have been few reports of their use. Recently, a method for asymmetric synthesis of 4-substituted 1,2,3,4-tetrahydroisoquinolines was developed by Pedrosa, in which radical cyclization employed (−)-8-aminomenthol as chiral auxiliary. We have devoted considerable effort for the past few years to the development of diastereoselective addition of Grignard reagents to 1,3-oxazolidines derived from (R)-phenylglycinol as chiral auxiliary. Herein we describe asymmetric synthesis of enantiomerically pure 4- and 1,4-substituted 1,2,3,4-tetrahydroisoquinolines based on aryl radical cyclization of chiral 1,3-oxazolidines derived from (R)-phenylglycinol.
RESULTS AND DISCUSSION

The preparation of aryl radical cyclization precursors (2) was easily produced in either two or three steps from (R)-phenylglycinol (Scheme 1, Table 1). Condensation of (R)-phenylglycinol with the corresponding allyl aldehyde, followed by reduction with NaBH₄, provided 1a and 1b. The formation of 1c was effected by allylation of (R)-phenylglycinol with allyl bromide in the presence of base. Treatment of 1a-c with 2-bromobenzaldehyde afforded the corresponding oxazolidines in good yield. The ratio of diastereomers at 2 position in 2a-c was determined by ¹H NMR spectrometry, and X-Ray analysis of similar compounds gives supporting evidence for their absolute configurations.

\[
\text{(R)-Phenylglycinol} \xrightarrow{i, ii \text{ or } iii} 1a-c \xrightarrow{iv} 2a-c
\]

Scheme 1. Reagents and conditions: (i) MeRC=CHCHO, CH₂Cl₂, MS 3A, 2 h; (ii) NaBH₄, MeOH, 2 h; (iii) allyl bromide, K₂CO₃, THF, 16 h; (iv) 2-bromobenzaldehyde, benzene, reflux, 2 h.

<table>
<thead>
<tr>
<th>Run</th>
<th>R₁</th>
<th>R₂</th>
<th>Method</th>
<th>Yield of 1ᵃ (%)</th>
<th>Ratio of 2ᵇ Yield of 2ᵇ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(a)</td>
<td>Me</td>
<td>Me</td>
<td>i, ii</td>
<td>91</td>
<td>96 : 4</td>
</tr>
<tr>
<td>2(b)</td>
<td>Me</td>
<td>H</td>
<td>i, ii</td>
<td>85</td>
<td>96 : 4</td>
</tr>
<tr>
<td>3(c)</td>
<td>H</td>
<td>H</td>
<td>iii</td>
<td>75</td>
<td>95 : 5</td>
</tr>
</tbody>
</table>

ᵃIsolated yield.ᵇEstimated by ¹H NMR (270 MHz) spectrum.

The crucial aryl radicals were generated from the corresponding bromides as illustrated in Scheme 2. The results of these experiments are summarized in Table 2. A 25 mM solution of each bromide in its appropriate solvent was added to tributyltin hydride in the presence of one of three initiators. The aryl radical cyclization of 2a and 2b attained exclusive formation of 6-exo tricyclic products (3a, b) and (4a, b) without formation of a 7-endo addition product. However, the cyclization of 2c gave three inseparable diastereomers and 7-endo product (5). The two diastereomers (3a-c) were confirmed to be inseparable thermodynamic mixtures at the 10b position of N, O-acetal, and 4a-c was a single diastereomer. The stereochemistry of 10b in the tricycle (3a-c) might arise by thermodynamic equilibration of the final products.
Some reaction conditions were evaluated to study the influence of the stereoselectivity on the radical cyclization. The choice of initiators was determined by the reaction temperature. When 2a or 2b was boiled with tributyltin hydride and AIBN in a solvent such as benzene or toluene, cyclic additions proceeded smoothly with moderate selectivity (Runs 1, 2, 6, 7, 9). 2, 2'-Azobis(2,4-dimethyl-4-methoxy-valeronitrile) (V-70) as initiator was used for radical cyclization, with various solvents, at room temperature (Runs 3, 4, 8, 10). CH2Cl2 prevented the reaction at room temperature (Run 3). Poor conversion of substrate was a drawback with Et3B/O2 as initiator (Run 5). As expected, the reduced speed of the tributyltin hydride reaction did not influence diastereoselectivity (Runs 1, 2, 6, 7, 9). The factors that influence the 6-exo versus 7-endo modes of intramolecular addition could be a result of some steric and electric interactions at the allylic position. The cause for the diastereoselectivity of additional
cyclization was inferred in a former communication.\textsuperscript{11} When the reaction temperature was decreased, it lowered reactivity and yield. However, the diastereoselectivity of the aryl radical cyclization did not change.

Conversion to 4-substituted 1,2,3,4-tetrahydroisoquinolines (9a-c) was then done (Scheme 3). Treatment of the tricycles (3a-c, 4a, 4b, and 5) with a small excess of NaBH\textsubscript{4} afforded the corresponding tetrahydroisoquinolines (6a-c, 7a, 7b, and 8) in good yields, although separation of diastereomers (6c) was incomplete. Subsequently, the auxiliary part was efficiently removed by hydrogenation of 6a-c on 10% Pd/C in methanol in the presence of 10% HCl\textsuperscript{12} to give the desired 9a-c.

We next examined alkylation and arylation of Grignard reagents to tricycles (3a-c) (Scheme 4, Table 3). Addition of three equivalents of Grignard reagent in THF proceeded with good yield and moderate diastereoselectivity. A temperature-dependence study of the diastereoselective addition revealed increasing diastereoselectivity with decreasing temperature. The absolute configuration of the major isomers (10a-c) and the minor isomers (11a-c) was determined to be based on the known configuration of phenylglycinol, and confirmation of the relative configuration was achieved by an X-Ray structure.

\textbf{Scheme 3}. \textit{Reagents and conditions}: (i) NaBH\textsubscript{4}, MeOH, 2 h; (ii) 10% Pd-C, H\textsubscript{2}, HCl, MeOH, 16 h.
analysis of 10c and 11a (Figures 1, 2). The hydrogenation of 10a-c afforded the 1,4-dialkylated
tetrahydroisoquinolines (12a-c).

**Scheme 4.** Reagents and conditions: (i) R₃MgBr, THF, 15 h; (ii) 10% Pd-C, H₂, HCl, MeOH, 16 h.

**Table 3.** Diastereoselective Addition of Grignard Reagents to 3a-c

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>R₃</th>
<th>Temp. (°C)</th>
<th>Ratio (10 : 11)</th>
<th>Yield of 10+11 (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Me</td>
<td>0</td>
<td>68 : 32</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Me</td>
<td>−50</td>
<td>79 : 21</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>Me</td>
<td>0</td>
<td>67 : 33</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>Me</td>
<td>−50</td>
<td>73 : 27</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>Me</td>
<td>0</td>
<td>64 : 36</td>
<td>91</td>
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<td>6</td>
<td>3c</td>
<td>Me</td>
<td>−50</td>
<td>79 : 21</td>
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<td>7</td>
<td>3a</td>
<td>Et</td>
<td>0</td>
<td>76 : 24</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>Ph</td>
<td>0</td>
<td>85 : 15</td>
<td>89</td>
</tr>
</tbody>
</table>

A plausible explanation for the effect of reactivity on diastereoselectivity is proposed (Figure 3). According to our previous model,⁸g,h,i,⁹ the diastereoselective addition of 1,3-oxazolidine derived from (R)-phenylglycinol to Grignard reagent should resemble the most preferable iminium complex. Unexpectedly, the diastereoselectivity was poor. It is reasonable that the C6 substituent could adopt a pseudo-axial position to minimize steric interactions between C7-H and the C6 substituents. However, owing to the steric repulsion of the axial C6 substituent, the reagent prefers to attack the carbon of the C=N bond from the si face.
In summary, we have developed a concise method for asymmetric synthesis of 4- and 1,4-disubstituted 1,2,3,4-tetrahydroisoquinolines starting from (R)-phenylglycinol. The stereoselective synthesis of (3R, 6R)-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinolines has been achieved by aryl radical cyclization of 2-(2-bromophenyl)-3-allyl-1,3-oxazolidines with Bu3SnH in the presence of initiator.

**EXPERIMENTAL**

Melting point is uncorrected. 1H and 13C NMR spectra were measured with JEOL GSX 270 instrument for solutions in CDCl3. IR spectra were recorded on a JASCO FT/IR-200 and major absorption is listed in cm⁻¹. MS and High-resolution MS were measured with a JEOL JMS 600 spectrometer in the chemical ionization (CI) with isobutane and electron impact (EI) method. Optical rotations were performed on a
JASCO-DIP–1000 polarimeter. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Column chromatography was performed on silica gel (45–75 µm, Wakogel C-300). TLC was carried out on glass plates coated with silica gel F254 (Merck). Spot detection was performed with UV 254 nm, iodine vapor, or with a solution mixture of p-anisaldehyde, sulfuric acid, acetic acid and ethanol (2.5:3.5:1:93). All solvents were freshly distilled before use.

(R)-2-(3-Methylbut-2-enylamino)-2-phenylethanol (1a): To a solution of (R)-phenylglycinol (6.75 g, 50 mmol) in CH2Cl2 (300 mL) was added 3-methyl-2-butenal (4.63 g, 55 mmol) and 3A molecular sieves (10 g) at rt. After being stirred overnight, the reaction mixture was filtered through Celite, and evaporated under reduced pressure. The residue was dissolved in methanol (50 mL), and to the solution was portionwise added NaBH4 (3.78 g, 100 mmol) at rt. After being stirred for 2 h, the mixture was quenched with water and extracted with CH2Cl2. The combined extracts were washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The crude product was recrystallized from benzene to give 1a (9.33 g, 91%) as colorless needles; mp 76 °C. [α]24D −92.7° (c 1.03, CHCl3). 1H NMR (CDCl3) δ 1.53 (s, 3H), 1.71 (s, 3H), 2.05 (br, 2H), 3.05 (dd, 1H, J = 12.9, 6.6 Hz), 3.15 (dd, 1H, J = 6.6, 12.9), 3.54 (dd, 1H, J = 8.6, 10.6 Hz), 3.71 (dd, 1H, J = 4.6, 10.6 Hz), 3.78 (dd, 1H, J = 4.6, 8.6 Hz), 5.25 (t, 1H, J = 6.6 Hz), 7.26–7.38 (m, 5H). 13C NMR (CDCl3) δ 17.75, 25.64, 44.63, 64.14, 66.54, 122.51, 127.36, 127.41, 128.41, 128.62, 140.51. IR (CHCl3) 3390, 3090, 3070, 2830, 1670, 1600, 1460, 1050, 870, 760, 700 cm−1. MS m/z: EI, 174 (M+–CH2OH); CI, 206 (M++1). Anal. Calcd for C13H19NO: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.83; H, 9.34; N, 6.77.

(R)-2-(But-2-enylamino)-2-phenylethanol (1b): Following the above procedure, (R)-phenylglycinol (6.75 g, 50 mmol) was treated with crotonaldehyde (3.85 g, 55 mmol) in the presence of 3A molecular sieves (10 g). After workup, the crude material was distilled by bulb-to-bulb to give 1b (8.12 g, 85%) as colorless oil; oven temperature 110 °C / 5 mmHg. [α]24D −86.1° (c 0.96, CHCl3). 1H NMR (CDCl3) δ 1.66 (d, 1H, J = 4.4 Hz), 2.14 (br, 1H), 3.01 (dd, 1H, J = 4.0, 12.2 Hz), 3.15 (dd, 1H, J = 4.0, 12.2 Hz), 3.55 (dd, 1H, J = 8.7, 10.5 Hz), 3.71 (dd, 1H, J = 4.4, 10.5 Hz), 4.79 (dd, 1H, J = 4.4, 8.7 Hz), 5.54 (m, 2H), 7.24–7.38 (m, 5H). 13C NMR (CDCl3) δ 17.70, 48.99, 63.80, 66.46, 127.34, 127.41, 128.41, 140.51. IR (CHCl3) 3390, 3090, 3070, 2830, 1670, 1600, 1460, 1050, 870, 760, 700 cm−1. MS m/z: EI, 174 (M+–CH2OH); CI, 206 (M++1). Anal. Calcd for C12H17NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.14; H, 8.96; N, 7.36.

(R)-2-Allylamino-2-phenylethanol (1c): To a solution of phenylglycinol (6.75 g, 50 mmol) in THF (400 mL) was added K2CO3 (10 g, 72 mmol) and allyl bromide (4.33 mL, 50 mmol). After being stirred overnight at rt, the reaction mixture was diluted with water (300 mL) and extracted with AcOEt (150 mL × 3). The combined organic layer was washed with water and brine, dried over Na2SO4, concentrated under reduced pressure. The residue was chromatographed on silica gel (CH2Cl2/CH3OH, 10:1) to give 1c (6.64 g, 75%) as pale yellow oil. [α]24D −79.7° (c 0.48, CHCl3). 1H NMR (CDCl3) δ 2.48 (br, 2H), 3.08 (dd, 1H,
\[ J = 6.4, 14.0 \text{ Hz}, 3.22 (\text{dd}, 1H, J = 5.6, 14.0 \text{ Hz}), 3.58 (\text{dd}, 1H, J = 8.6, 10.7 \text{ Hz}), 3.72 (\text{dd}, 1H, J = 4.4, 10.7 \text{ Hz}), 3.82 (\text{dd}, 1H, J = 4.4, 8.6 \text{ Hz}), 5.09 (\text{d}, 1H, J = 10.2 \text{ Hz}), 5.14 (\text{d}, 1H, J = 18.1 \text{ Hz}), 5.88 (\text{m}, 1H), 7.25–7.38 (\text{m}, 5H). \]

\[^{13}\text{C NMR } (\text{CDCl}_3) \delta 49.49, 63.69, 66.26, 116.03, 126.35, 127.22, 128.26, 136.11, 140.12. \]

IR (CHCl\textsubscript{3}) 3290, 1490, 1450, 1030 cm\textsuperscript{-1}. MS \textit{m/z} \textit{EI}, 146 (M+–CH\textsubscript{2}OH); CI, 178 (M\textsuperscript{+}+1).

Anal. Calcd for C\textsubscript{11}H\textsubscript{15}NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.32; H, 8.59; N, 7.90.

**General Procedure for the Preparation of 2a–c:** A mixture of 1a–c (10 mmol) and 2-bromobenzaldehyde (1.92 g, 10 mmol) in benzene (40 mL) was refluxed for 2 h with a Dean-Stark trap. After being cooled, the reaction mixture was concentrated under reduced pressure. The residue was distilled by bulb-to-bulb to give 2a–c as pale yellow oil.

\((4R)-2-(2\text{-Bromophenyl})-3-(3\text{-methylbut}-2\text{-enyl})-4\text{-phenyl}-1,3\text{-oxazolidine} \text{ (2a): Yield 90%; oven temperature 210 °C / 3 mmHg; } [\alpha]^{25}_{\text{D}} -45.7° (c 1.03, \text{CHCl}_3). ^{1}\text{H NMR (CDCl}_3) \delta 1.40 (\text{s}, 1H), 1.45 (\text{s}, 1H), 3.14 (\text{d}, 1H, J = 7.3 \text{ Hz}), 3.84 (\text{dd}, 1H, J = 7.6, 8.6 \text{ Hz}), 4.10 (\text{d}, 1H, J = 7.2, 8.6 \text{ Hz}), 4.26 (\text{dd}, 1H, J = 7.2, 7.6 \text{ Hz}), 4.94 (\text{t}, 1H, J = 7.3 \text{ Hz}), 5.63 (\text{s}, 1H), 7.16–7.64 (\text{m}, 8H), 7.96 (\text{dd}, 1H, J = 1.8, 7.7 \text{ Hz}). \]

\[^{13}\text{C NMR (CDCl}_3) \delta 17.58, 25.47, 46.12, 66.42, 73.71, 94.28, 119.43, 124.47, 127.23, 127.57, 127.61, 128.32, 129.86, 130.08, 132.46, 135.31, 138.96, 139.33. \text{ MS } \textit{m/z} \textit{EI}, 148; \textit{CI}, 372, 374 (M\textsuperscript{+}+1). \]

Anal. Calcd for C\textsubscript{20}H\textsubscript{22}NOBr: C, 64.52; H, 5.96; N, 3.76. Found: C, 64.22; H, 5.89; N, 3.62. The \(^{1}\text{H NMR spectrum showed it to contain a trace amount of diastereomer due to the 2 position of oxazolidine.} \]

\((4R)-2-(2\text{-Bromophenyl})-3-(\text{but}-2\text{-enyl})-4\text{-phenyl}-1,3\text{-oxazolidine} \text{ (2b): Yield 89%; oven temperature 200 °C / 3 mmHg; } [\alpha]^{23}_{\text{D}} +39.9° (c 1.15, \text{CHCl}_3). ^{1}\text{H NMR (CDCl}_3) \delta 1.45 (\text{d}, 1H, J = 6.1 \text{ Hz}), 3.05 (\text{dd}, 1H, J = 7.4, 13.8 \text{ Hz}), 3.14 (\text{dd}, 1H, J = 6.2, 13.8 \text{ Hz}), 3.86 (\text{t}, 1H, J = 7.4 \text{ Hz}), 4.10 (\text{t}, 1H, J = 7.4 \text{ Hz}), 4.27 (\text{t}, 1H, J = 7.4 \text{ Hz}), 5.25 (\text{m}, 1H), 5.38 (\text{m}, 1H), 5.63 (\text{s}, 1H), 7.16–7.56 (\text{m}, 8H), 7.94 (\text{dd}, 1H, J = 1.6, 7.7 \text{ Hz}). \]

\[^{13}\text{C NMR (CDCl}_3) \delta 17.51, 51.09, 66.25, 73.85, 94.32, 124.48, 126.17, 127.43, 127.71, 128.51, 129.22, 130.03, 132.46, 135.31, 138.96, 139.33. \text{ MS } \textit{m/z} \textit{EI}, 272, 274; \textit{CI}, 358, 360 (M\textsuperscript{+}+1). \]

Anal. Calcd for C\textsubscript{19}H\textsubscript{20}NOBr: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.79; H, 5.89; N, 3.65. The \(^{1}\text{H NMR spectrum showed it to contain a trace amount of diastereomer due to the 2 position of oxazolidine.} \]

\((4R)-3\text{-Allyl}-2-(2\text{-bromophenyl})-4\text{-phenyl}-1,3\text{-oxazolidine} \text{ (2c): Yield 99%; oven temperature 200 °C / 5 mmHg; } [\alpha]^{24}_{\text{D}} -24.7° (c 1.07, \text{CHCl}_3). ^{1}\text{H NMR (CDCl}_3) \delta 3.14 (\text{dd}, 1H, J = 7.4, 13.8 \text{ Hz}), 3.87 (\text{dd}, 1H, J = 7.7, 8.4 \text{ Hz}), 4.12 (\text{dd}, 1H, J = 7.2, 8.4 \text{ Hz}), 4.28 (\text{dd}, 1H, J = 7.2, 7.7 \text{ Hz}), 4.90 (\text{d}, 1H, J = 10.9 \text{ Hz}), 4.98 (\text{d}, 1H, J = 16.9 \text{ Hz}), 5.64 (\text{m}, 1H), 5.65 (\text{s}, 1H), 7.18–7.57 (\text{m}, 8H), 7.95 (\text{dd}, 1H, J = 1.8, 7.7 \text{ Hz}). \]

\[^{13}\text{C NMR (CDCl}_3) \delta 52.23, 66.33, 73.70, 94.33, 117.79, 124.43, 127.38, 127.74\times2, 128.49\times2, 130.12, 132.62, 133.46, 138.62, 139.13. \text{ MS } \textit{m/z} \textit{EI}, 188; \textit{CI}, 344, 346 (M\textsuperscript{+}+1). \]

Anal. Calcd for C\textsubscript{18}H\textsubscript{18}NOBr: C, 62.80; H, 5.27; N, 4.07. Found: C, 62.58; H, 5.37; N, 4.08.
General Procedure for Radical Cyclization of 2a–c with Bu$_3$SnH: To a solution of diastereomers (2a–c, 95:5 or 96:4) (5 mmol) in toluene (250 mL) was added Bu$_3$SnH (2.02 mL, 20 mmol) in the presence of initiator at appropriate temperature. After being stirred for appropriate time, the mixture was evaporated under reduced pressure. The residue was dissolved in AcOEt (120 mL), treated with saturated aqueous KF (2 × 60 mL), and filtered off a white solid (Bu$_3$SnF). The organic layer was separated, washed with H$_2$O and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane, 1:3). All obtained compounds were unstable and measured of $^1$H NMR spectrum only.

(3$R,6R$)-6-Isopropyl-3-phenyl-2,3,6,10$\textit{b}$-tetrahydro-5$\textit{H}$-oxazolo[2,3-$\textit{a}$]isoquinoline (3a): Pale yellow oil, inseparable diastereomers (62:38) by the configuration of 10$\textit{b}$ position; Major component, $^1$H NMR (CDCl$_3$) $\delta$ 0.79 (d, 3H, $J= 6.9$ Hz), 1.14 (d, 3H, $J= 6.9$ Hz), 2.64 (m, 1H), 2.77 (dd, 1H, $J= 10.1, 11.4$ Hz), 2.98 (dd, 1H, $J= 4.3, 10.1$ Hz), 3.06 (dt, 1H, $J= 4.3, 11.4$ Hz), 3.79 (dd, 1H, $J= 5.8, 7.9$ Hz), 4.34 (dd, 1H, $J= 5.8, 7.4$ Hz), 4.50 (dd, 1H, $J= 7.4, 7.9$ Hz), 5.34 (s, 1H), 7.26–7.45 (m, 9H). Minor component, $^1$H NMR (CDCl$_3$) $\delta$ 0.79 (d, 3H, $J= 6.8$ Hz), 0.89 (d, 3H, $J= 6.8$ Hz), 2.14 (m, 1H), 2.50 (m, 1H), 2.65 (m, 2H), 4.02 (dd, 1H, $J= 7.4, 9.7$ Hz), 4.23 (t, 1H, $J= 7.4$ Hz), 4.44 (dd, 1H, $J= 7.4, 9.7$ Hz), 5.31 (s, 1H), 7.26–7.45 (m, 9H). The $^1$H NMR spectrum showed it to contain minor component due to the 10$\textit{b}$ position $\delta$ 5.30 (s, 1H).

(3$R,6S$)-6-Isopropyl-3-phenyl-2,3,6,10$\textit{b}$-tetrahydro-5$\textit{H}$-oxazolo[2,3-$\textit{a}$]isoquinoline (4a): Pale yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 0.95 (d, 3H, $J= 6.8$ Hz), 1.04 (d, 3H, $J= 6.8$ Hz), 2.12 (m, 1H), 2.40 (ddd, 1H, $J= 2.5, 3.0, 8.4$ Hz), 2.92 (dd, 1H, $J= 3.0, 10.5$ Hz), 3.17 (dd, 1H, $J= 2.5, 10.5$ Hz), 3.72 (dd, 1H, $J= 7.1, 7.9$ Hz), 4.24 (dd, 1H, $J= 7.1, 7.3$ Hz), 4.47 (dd, 1H, $J= 7.3, 7.9$ Hz), 5.41 (s, 1H), 7.15–7.47 (m, 9H).

(3$R,6R$)-6-Ethyl-3-phenyl-2,3,6,10$\textit{b}$-tetrahydro-5$\textit{H}$-oxazolo[2,3-$\textit{a}$]isoquinoline (3b): Pale yellow oil, inseparable diastereomers (88:12) by the configuration of 10$\textit{b}$ position; Major component, $^1$H NMR (CDCl$_3$) $\delta$ 1.00 (t, 3H, $J= 7.5$ Hz), 1.66 (m, 2H), 2.71 (m, 1H), 3.03 (m, 2H), 3.79 (dd, 1H, $J= 5.9, 7.9$ Hz), 4.32 (dd, 1H, $J= 5.9, 7.3$ Hz), 4.49 (dd, 1H, $J= 7.3, 7.9$ Hz), 5.37 (s, 1H), 7.15–7.45 (m, 9H). Minor component, $^1$H NMR (CDCl$_3$) $\delta$ 0.87 (t, 3H, $J= 7.4$ Hz), 2.10 (m, 1H), 2.71 (m, 2H), 4.06 (dd, 1H, $J= 7.4, 9.8$ Hz), 4.24 (dd, 1H, $J= 7.4, 7.6$ Hz), 4.50 (m, 1H), 5.33 (s, 1H), 7.15–7.45 (m, 9H). The $^1$H NMR spectrum showed it to contain minor component due to the 10$\textit{b}$ position $\delta$ 5.34 (s, 1H).

(3$R,6S$)-6-Ethyl-3-phenyl-2,3,6,10$\textit{b}$-tetrahydro-5$\textit{H}$-oxazolo[2,3-$\textit{a}$]isoquinoline (4b): Pale yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 1.02 (t, 3H, $J= 7.5$ Hz), 1.84 (m, 2H), 2.67 (m, 1H), 3.03 (m, 2H), 3.75 (dd, 1H, $J= 6.3, 7.9$ Hz), 4.37 (dd, 1H, $J= 6.3, 7.7$ Hz), 4.82 (dd, 1H, $J= 7.7, 7.9$ Hz), 5.33 (s, 1H), 7.17–7.45 (m, 9H).

(3$R,6R$)-6-Methyl-3-phenyl-2,3,6,10$\textit{b}$-tetrahydro-5$\textit{H}$-oxazolo[2,3-$\textit{a}$]isoquinoline (3c): Pale yellow oil, inseparable diastereomers (92:8) by the configuration of 10$\textit{b}$ position; Major component, $^1$H NMR (CDCl$_3$) $\delta$ 1.33 (d, 3H, $J= 6.9$ Hz), 2.69 (dd, 1H, $J= 10.1, 11.4$ Hz), 2.96 (dd, 1H, $J= 4.6, 10.1$ Hz), 3.15
(1H, m), 3.80 (dd, 1H, J = 5.8, 8.1 Hz), 4.30 (dd, 1H, J = 5.8, 7.6 Hz), 4.48 (dd, 1H, J = 7.6, 8.1 Hz), 5.38 (s, 1H), 7.23–7.45 (m, 9H). Minor component, ^1^H NMR (CDCl$_3$) δ 1.27 (d, 3H, J = 7.1 Hz), 5.24 (s, 1H).

The ^1^H NMR spectrum showed it to contain minor component due to the 10b position δ 5.24 (s, 1H).

(3R)-3-Phenyl-2,3,4,5,6,10b-hexahydro-1-oxa-3a-azabenzo[e]azulene (5): Pale yellow oil; ^1^H NMR (CDCl$_3$) δ 1.27 (d, 3H, J = 7.1 Hz), 5.24 (s, 1H).

General Procedure for Reduction of 3a-c with NaBH$_4$: To a solution of 3a-c (5.0 mmol) in MeOH (50 mL) was portionwise added NaBH$_4$ (378 mg, 10 mmol) at rt. After being stirred for 2 h, the mixture was quenched with water and extracted with CH$_2$Cl$_2$. The combined extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/hexane, 1:3) to give 6a-c.

(1'R,4R)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (6a): Yield 96%. Colorless needles, mp 64 °C (hexane/Et$_2$O). [α]$^D_{29}$ −13.4° (c 1.46, CHCl$_3$). ^1^H NMR (CDCl$_3$) δ 0.82 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 6.8 Hz), 2.27 (m, 1H), 2.64–2.77 (m, 3H), 2.82 (dd, 1H, J = 3.9, 10.1 Hz), 3.45 (d, 1H, J = 14.5 Hz), 3.75 (d, 1H, J = 14.5 Hz), 3.76 (dd, 1H, J = 5.1, 10.1 Hz), 4.13 (dd, 1H, J = 10.1 Hz), 6.96–7.40 (m, 9H). ^13^C NMR (CDCl$_3$) δ 18.67, 21.21, 31.45, 43.99, 48.48, 51.60, 60.85, 69.98, 125.35, 125.67, 126.33, 126.8, 128.06, 128.12 × 2, 128.69 × 2, 135.04, 135.72, 137.37. MS m/z EI, 295 (M$^+$), 264 (M$^+$–CH$_2$OH). IR (CHCl$_3$) 3420 cm$^{-1}$. HRMS Calcd for C$_{20}$H$_{25}$NO: 295.1936. Found: 295.1915.

(1'R,4R)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (7a): Yield 91%. Pale yellow oil. [α]$^D_{29}$ −33.0° (c 1.19, CHCl$_3$). ^1^H NMR (CDCl$_3$) δ 0.83 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.9 Hz), 1.62 (br, 1H), 2.21 (m, 1H), 2.49 (dd, 1H, J = 4.7, 11.4 Hz), 2.68 (m, 1H), 2.88 (dd, 1H, J = 5.4, 11.5 Hz), 3.70 (s, 2H), 3.78 (dd, 1H, J = 4.9, 10.5 Hz), 3.78 (dd, 1H, J = 4.9, 11.9 Hz), 4.09 (dd, 1H, J = 10.5, 11.9 Hz), 6.98–7.40 (m, 9H). ^13^C NMR (CDCl$_3$) δ 18.67, 21.21, 31.05, 44.25, 48.26, 52.69, 61.09, 70.02, 125.46, 125.52, 126.35, 127.81, 128.16×2, 128.51, 128.90×2, 134.96, 136.04, 137.23. MS m/z EI, 295 (M$^+$), 264 (M$^+$–CH$_2$OH). IR (CHCl$_3$) 3420 cm$^{-1}$. HRMS Calcd for C$_{20}$H$_{25}$NO: 295.1936. Found: 295.1941.

(1'R,4R)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (6b): Yield 87%. Pale yellow oil; oven temperature 250 °C / 3 mmHg. [α]$^D_{29}$ −12.1° (c 1.83, CHCl$_3$). ^1^H NMR (CDCl$_3$) δ 0.99 (t, 3H, J = 7.5 Hz), 1.71–1.86 (m, 2H), 2.65 (dd, 1H, J = 4.8, 11.0 Hz), 2.74 (m, 2H), 2.86 (dd, 1H, J = 4.1, 11.0 Hz), 3.43 (d, 1H, J = 14.7 Hz), 3.74 (d, 1H, J = 14.7 Hz), 3.76 (dd, 1H, J = 5.1, 9.7 Hz), 3.86 (dd, 1H, J = 5.1, 8.4 Hz), 4.11 (dd, 1H, J = 8.4, 9.7 Hz), 6.94–7.45 (m, 9H). ^13^C NMR (CDCl$_3$) δ 11.93, 28.33, 40.19, 51.37, 51.53, 60.83, 69.97, 125.48, 126.02, 126.38, 127.88, 128.03, 128.23×2, 128.74×2, 134.48, 135.75, 138.60. MS m/z EI, 281 (M$^+$), 250 (M$^+$–CH$_2$OH). IR (CHCl$_3$) 3410 cm$^{-1}$. HRMS Calcd for
C_{19}H_{23}NO: 281.1780. Found: 281.1765.

(1'R,4S)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (7b): Yield 93%. Pale yellow oil. [α]_{D}^{29} = -26.0° (c 0.95, CHCl_{3}). \text{H NMR (CDCl}_{3} \delta 0.98 (t, J = 7.4 Hz), 1.68–1.80 (m, 2H), 2.05 (br, 1H), 2.35 (dd, 1H, J = 4.2, 11.7 Hz), 2.66 (m, 1H), 2.91 (dd, 1H, J = 3.8, 11.7 Hz), 3.36–3.88 (m, 4H), 4.08 (m, 1H), 6.95–7.40 (m, 9H). \text{C NMR (CDCl}_{3} \delta 12.20, 28.87, 40.33, 48.81, 53.60, 61.03, 69.67, 125.63, 126.07, 126.37, 128.00, 128.32, 128.46, 128.97, 134.49, 135.90, 138.92. MS m/z EI, 281 (M^+), 250 (M^+–CH_{2}OH); CI, 282 (M^{+1}). IR (CHCl_{3}) 3390 cm^{-1}. HRMS calcd for C_{19}H_{23}NO: 281.1780. Found: 281.1765.

(1'R,4S)-2-(2'-Hydroxy-1'-phenylethyl)-4-methyl-1,2,3,4-tetrahydroisoquinoline (6c): Yield 75%. Pale yellow oil; oven temperature 250 °C / 3 mmHg. \text{H NMR (CDCl}_{3} \delta 1.31 (d, J = 6.9 Hz), 2.30 (dd, J = 6.2, 11.0 Hz), 3.01 (m, 2H), 3.59 (d, J = 14.4 Hz), 3.77 (d, J = 14.4 Hz), 3.75–3.85 (m, 2H), 4.12 (dd, J = 7.9, 9.4 Hz), 6.97–7.40 (m, 9H). \text{C NMR (CDCl}_{3} \delta 20.36, 33.16, 52.61, 54.32, 60.97, 69.65, 125.43, 126.13, 126.25, 127.24, 127.75, 128.14, 128.65, 134.25, 135.96, 139.31. MS m/z EI, 267 (M^+), 236 (M^+–CH_{2}OH); CI, 268 (M^{+1}). IR (CHCl_{3}) 3430 cm^{-1}. Anal. Calcd for C_{18}H_{21}NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.58; H, 7.91; N, 5.15.

(R)-2-(2'-Hydroxy-1'-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (8): Yield 94%. Colorless solid, mp 92 °C (hexane/Et_{2}O). [α]_{D}^{26} +27.6° (c 1.19, CHCl_{3}). \text{H NMR (CDCl}_{3} \delta 1.76 (m, 3H), 2.83 (m, 2H), 2.94 (m, 1H), 3.13 (m, 1H), 3.60 (d, 1H, J = 13.9 Hz), 3.76 (m, 2H), 3.90 (d, 1H, J = 13.9 Hz), 3.93 (dd, 1H, J = 12.0, 9.4 Hz), 7.02–7.40 (m, 9H). \text{C NMR (CDCl}_{3} \delta 27.62, 35.53, 56.65, 57.53, 61.73, 68.40, 125.99, 127.16, 127.75, 128.30, 128.51, 128.80, 129.37, 137.55, 139.45, 142.71. MS m/z EI, 267 (M^+), 236 (M^+–CH_{2}OH). IR (CHCl_{3}) 3420 cm^{-1}. Anal. Calcd for C_{18}H_{21}NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.77; H, 8.02; N, 5.22.

General Procedure for the Preparation of (4R)-4-Substituted 1,2,3,4-Tetrahydroisoquinolines (9a-c): A solution of amino alcohol (0.5 mmol) in MeOH (10 mL) and 10% HCl (1 mL) was hydrogenated over 10% palladium on carbon (30 mg) at atmospheric pressure. After being stirred for 14 h, the mixture was filtered, evaporated under reduced pressure. The residue was dissolved in 10% HCl and washed with ether twice. The acidic solution was basified with 10% NaOH, extracted with CH_{2}Cl_{2} twice, and the extract was dried over Na_{2}SO_{4}, and evaporated under reduced pressure.

(R)-4-Isopropyl-1,2,3,4-tetrahydroisoquinolines (9a): Yield 74%. Pale yellow oil. [α]_{D}^{26} +27.6° (c 0.47, CHCl_{3}). [lit., \text{α}]_{D}^{25} +29.8° (c 1.19, CHCl_{3}). \text{H NMR (CDCl}_{3} \delta 0.84 (d, J = 6.9 Hz), 2.83 (m, 2H), 2.94 (m, 1H), 3.13 (m, 1H), 3.60 (d, 1H, J = 13.9 Hz), 3.76 (m, 2H), 3.90 (d, 1H, J = 13.9 Hz), 3.93 (dd, 1H, J = 12.0, 9.4 Hz), 7.02–7.40 (m, 9H). \text{C NMR (CDCl}_{3} \delta 27.62, 35.53, 56.65, 57.53, 61.73, 68.40, 125.99, 127.16, 127.75, 128.30, 128.51, 128.80, 129.37, 137.55, 139.45, 142.71. MS m/z EI, 267 (M^+), 236 (M^+–CH_{2}OH). IR (CHCl_{3}) 3420 cm^{-1}. Anal. Calcd for C_{18}H_{21}NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.77; H, 8.02; N, 5.22.
(R)-4-Ethyl-1,2,3,4-tetrahydroisoquinolines (9b): Yield 68%. Pale yellow oil. [α]$_D^{28}$ +21.2° (c 0.50, CHCl$_3$) [lit. 7 [α]$_D^{28}$ +6.7° (c 1.1, CHCl$_3$)]. ¹H NMR (270 MHz, CDCl$_3$) δ 1.01 (t, 3H, J = 7.5 Hz), 1.76 (m, 2H), 2.74 (m, 1H), 2.86 (br, 1H), 3.09 (dd, 1H, J = 5.3, 12.9 Hz), 3.23 (dd, 1H, J = 4.8, 12.9 Hz), 4.09 (s, 2H), 7.02–7.21 (m, 4H). ¹³C NMR (270 MHz, CDCl$_3$) δ 11.62, 27.49, 37.76, 46.27, 47.09, 126.11, 126.20, 126.68, 128.46, 133.04, 138.07. MS m/z EI, 161 (M$^+$). IR (film) 3340 cm$^{-1}$. HRMS calcd for C$_{11}$H$_{15}$N; 161.1204. Found; 161.1229.

(R)-4-Methyl-1,2,3,4-tetrahydroisoquinolines (9c): Yield 94%. Pale yellow oil. ¹H NMR (270 MHz, CDCl$_3$) δ 1.28 (t, 3H, J = 6.8 Hz), 2.02 (br, 1H), 2.80 (dd, 1H, J = 6.0, 12.0 Hz), 2.87 (m, 1H), 3.20 (dd, 1H, J = 4.4, 12.0 Hz), 3.99 (s, 2H), 6.98–7.25 (m, 4H). ¹³C NMR (270 MHz, CDCl$_3$) δ 20.49, 32.00, 48.71, 51.10, 125.63, 125.92, 126.18, 128.12, 135.52, 140.05. MS m/z EI, 147 (M$^+$). IR (film) 3330 cm$^{-1}$. HRMS calcd for C$_{10}$H$_{13}$N; 147.1048. Found; 147.1108.

General Procedure for the Preparation of (1'R,4R)-2-(2'-Hydroxy-1'-phenylethyl)-1,4-disubstituted 1,2,3,4-Tetrahydroisoquinoline (10a-c): To the solution of tricycles in THF was added Grignard reagents (3 eq) at appropriate temperature under nitrogen. After being stirred for 15 h, the reaction mixture was quenched with saturated aqueous NH$_4$Cl, extracted with CH$_2$Cl$_2$ for three times. The combined organic layer was washed with water and brine, dried over Na$_2$SO$_4$, concentrated reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane, 1:3) to give title products.

(1S,1'R,4R)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (10a): Yellow oil. [α]$_{25}D$ –17.3° (c 1.53, CHCl$_3$). ¹H NMR (CDCl$_3$) δ 0.69 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz), 1.32 (d, 3H, J = 6.6 Hz), 2.40 (m, 2H), 2.85–3.00 (m, 3H), 3.78–3.91 (m, 3H), 3.95 (q, 1H, J = 6.6 Hz), 6.89–7.31 (m, 9H). ¹³C NMR (CDCl$_3$) δ 16.80, 20.55, 20.84, 29.56, 40.22, 40.27, 55.00, 62.96, 66.12, 125.22, 125.85, 127.13, 127.29, 127.40, 128.32×4, 137.25, 140.60×2. MS m/z EI, 278 (M$^+$–CH$_2$OH); Cl, 310 (M$^+$+1). IR (CHCl$_3$) 3390 cm$^{-1}$. HRMS Calcd for C$_{21}$H$_{27}$NO: 309.2093. Found: 309.2084.

(1R,1'R,4R)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (11a): Colorless needle, mp 80 °C (hexane). [α]$_{28}D$ +37.5° (c 0.53, CHCl$_3$). ¹H NMR (CDCl$_3$) δ 0.73 (d, 3H, J = 6.9 Hz), 1.13 (d, 3H, J = 6.9 Hz), 1.38 (d, 3H, J = 6.6 Hz), 2.40 (m, 2H), 2.85–3.00 (m, 3H), 3.78–3.91 (m, 3H), 3.95 (q, 1H, J = 6.6 Hz), 6.89–7.31 (m, 9H). ¹³C NMR (CDCl$_3$) δ 16.80, 20.55, 20.84, 29.56, 40.22, 40.27, 55.00, 62.96, 66.12, 125.22, 125.85, 127.13, 127.29, 127.40, 128.32×4, 137.25, 140.60×2. MS m/z EI, 278 (M$^+$–CH$_2$OH); Cl, 310 (M$^+$+1). IR (CHCl$_3$) 3390 cm$^{-1}$. HRMS Calcd for C$_{21}$H$_{27}$NO: 309.2093. Found: 309.2087.

(1S,1'R,4R)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (10b): Yellow oil. [α]$_{26}D$ –16.7° (c 1.07, CHCl$_3$). ¹H NMR (CDCl$_3$) δ 0.85 (t, 3H, J = 7.6 Hz), 1.33 (d, 3H, J = 6.8
Hz), 1.54 (m, 1H), 1.95 (m, 1H), 2.14 (br, 1H), 2.85 (m, 2H), 3.08 (m, 1H), 3.82–3.96 (m, 3H), 4.01 (q, 1H, J = 6.8 Hz), 6.92–7.37 (m, 9H). 13C NMR (CDCl3) δ 10.69, 20.34, 26.24, 35.98, 44.75, 55.01, 63.02, 66.05, 125.30, 125.93, 127.09, 127.20, 127.36, 128.27×4, 137.75, 140.20, 140.66. MS m/z EI, 295 (M+), 278 (M+–CH2OH). IR (CHCl3) 3410 cm⁻¹. HRMS Calcd for C20H25NO: 295.1936. Found: 295.1941.

(1R,1’R,4R)-4-Ethyl-2-(2’-hydroxy-1’-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (11b): Yellow oil. [α]26D +18.3° (c 0.95, CHCl3). 1H NMR (CDCl3) δ 1.02 (t, 3H, J = 7.4 Hz), 1.34 (d, 3H, J = 6.4 Hz), 1.67 (m, 1H), 1.90 (m, 1H), 2.27 (br, 1H), 2.43 (dd, 1H, J = 6.6, 11.5 Hz), 2.76 (m, 1H), 3.09 (dd, 1H, J = 4.1, 11.5 Hz), 3.81 (dd, 1H, J = 4.8, 10.1 Hz), 3.98 (q, 1H, J = 6.4 Hz), 3.99 (dd, 1H, J = 7.6, 10.1 Hz), 4.07 (dd, 1H, J = 4.8, 7.6 Hz), 6.96–7.36 (m, 9H). 13C NMR (CDCl3) δ 11.81, 19.19, 26.84, 40.19, 44.07, 54.23, 62.05, 64.44, 125.49, 125.63, 126.91, 126.95, 127.73, 128.30×2, 128.78×2, 137.60, 138.73, 140.45. MS m/z EI, 295 (M+), 278 (M+–CH2OH). IR (CHCl3) 3430 cm⁻¹. HRMS Calcd for C20H25NO: 295.1936. Found: 295.1941.

(1S,1’R,4R)-1,4-Dimethyl-2-(2’-hydroxy-1’-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (10c): Colorless needle, mp 100 °C (hexane). [α]27D –17.5° (c 0.71, CHCl3). 1H NMR (CDCl3) δ 1.22 (d, 3H, J = 6.4 Hz), 1.32 (d, 3H, J = 6.8 Hz), 2.18 (br, 1H), 2.76 (dd, 1H, J = 12.5, 14.7 Hz), 2.98–3.08 (m, 2H), 3.80–3.94 (m, 3H), 4.05 (q, 1H, J = 6.8 Hz), 6.92–7.38 (m, 9H). 13C NMR (CDCl3) δ 18.45, 19.55, 29.51, 47.69, 54.85, 63.36, 66.16, 125.31, 125.95, 126.69, 127.11, 127.25, 128.19×4, 138.87, 139.60, 140.96. MS m/z EI, 250 (M+–CH2OH); CI, 282 (M++1). IR (CHCl 3) 3410 cm -1. Anal. Calcd for C 19H23NO: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.05; H, 8.30; N, 4.92.

(1S,1’R,4R)-1-Ethyl-2-(2’-hydroxy-1’-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (10d): Yellow oil. [α]24D –34.6° (c 0.98, CHCl3). 1H NMR (CDCl3) δ 0.72 (d, 3H, J = 6.9 Hz), 0.94 (t, 3H, J = 7.1 Hz), 1.54 (m, 1H), 1.76 (m, 1H), 2.05 (br, 1H), 2.47 (m, 1H), 3.01 (m, 1H), 3.14 (m, 2H), 3.38 (m, 1H), 3.74 (dd, 1H, J = 4.0, 5.6 Hz), 3.83 (dd, 1H, J = 4.0, 10.9 Hz), 3.99 (dd, 1H, J = 5.6, 10.9 Hz), 6.77 (dd, 1H, J = 7.6 Hz), 7.01–7.36 (m, 8H). 13C NMR (CDCl3) δ 11.20, 16.56, 20.43, 29.11, 29.78, 32.13, 39.75, 60.31, 63.47, 65.14, 124.98, 125.91, 126.97, 127.28, 127.72, 128.08, 128.47, 137.23, 138.90, 140.90. MS m/z EI, 323 (M+), 292 (M+–CH2OH). IR (CHCl3) 3410 cm⁻¹. HRMS Calcd for C22H29NO: 323.2249. Found: 323.2262.

(1R,1’R,4R)-1-Ethyl-2-(2’-hydroxy-1’-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (11d): Yellow oil. [α]24D +34.5° (c 1.00, CHCl3). 1H NMR (CDCl3) δ 0.65 (d, 3H, J = 7.3 Hz), 1.06 (d, 3H, J = 7.1 Hz), 1.54 (m, 1H), 1.76 (m, 1H), 2.05 (br, 1H), 2.47 (m, 1H), 3.01 (m, 1H), 3.14 (m, 2H), 3.38 (m, 1H), 3.74 (dd, 1H, J = 4.0, 5.6 Hz), 3.83 (dd, 1H, J = 4.0, 10.9 Hz), 3.99 (dd, 1H, J = 5.6, 10.9 Hz), 6.77 (dd, 1H, J = 7.6 Hz), 7.01–7.36 (m, 8H). 13C NMR (CDCl3) δ 11.20, 16.56, 20.43, 29.11, 29.78, 32.13, 39.75, 60.31, 63.47, 65.14, 124.98, 125.91, 126.97, 127.28, 127.72, 128.08, 128.47, 137.23, 138.90, 140.90. MS m/z EI, 323 (M+), 292 (M+–CH2OH). IR (CHCl3) 3410 cm⁻¹. HRMS Calcd for C22H29NO: 323.2249. Found: 323.2262.
Calcd for C_{22}H_{29}NO: 323.2249. Found: 323.2224.

(1S,1’R,4R)-2-(2’-Hydroxy-1’-phenylethyl)-4-isopropyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (10e): Yellow oil. [α]_{25}^D +55.0° (c 1.58, CHCl_3). \(^1\)H NMR (CDCl_3) δ 0.59 (d, J = 6.8 Hz), 0.94 (d, J = 6.9 Hz), 2.34 (m, 1H), 2.67 (m, 1H), 2.97 (dd, 1H, J = 4.8, 13.0 Hz), 3.08 (dd, 1H, J = 4.9, 13.0 Hz), 3.88 (dd, 1H, J = 4.9, 6.9 Hz), 3.94–4.08 (m, 2H), 4.88 (s, 1H), 6.70–7.39 (m, 14H). \(^1\)C NMR (CDCl_3) δ 18.72, 21.10, 30.61, 41.75, 43.19, 61.02, 63.99, 64.49, 125.52, 125.64, 126.99, 127.38, 128.09, 128.20, 128.32, 128.69, 129.16, 129.31, 137.16, 138.11, 139.88, 144.70. MS m/z EI, 371 (M^+), 340 (M^+–CH_2OH). IR (CHCl_3) 3450 cm–1. HRMS Calcd for C_{26}H_{29}NO: 371.2249. Found: 371.2242.

(1R,1’R,4R)-2-(2’-Hydroxy-1’-phenylethyl)-4-isopropyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (11e): Yellow oil. [α]_{26}^D –117.9° (c 0.11, CHCl_3). \(^1\)H NMR (CDCl_3) δ 0.65 (d, J = 6.9 Hz), 1.22 (d, 3H, J = 6.9 Hz), 2.15 (t, 1H, J = 11.0 Hz), 2.83 (m, 1H), 3.22 (m, 1H), 3.36 (dd, 1H, J = 4.7, 11.0 Hz), 3.44 (dd, 1H, J = 4.7, 10.2 Hz), 3.94 (dd, 1H, J = 4.7, 11.0 Hz), 4.09 (dd, 1H, J = 10.2, 11.0 Hz), 4.77 (s, 1H), 6.57–7.80 (m, 14H). \(^1\)C NMR (CDCl_3) δ 16.42, 21.07, 28.25, 42.02, 43.64, 60.13, 62.73, 66.53, 125.30, 125.80, 127.58, 127.99, 128.08, 128.23, 128.78, 129.20, 129.36, 129.68, 134.58, 137.14, 139.88, 144.26. MS m/z EI, 371 (M^+), 340 (M^+–CH_2OH); CI, 372 (M^+1). IR (CHCl_3) 3410 cm–1. HRMS Calcd for C_{26}H_{29}NO: 371.2249. Found: 371.2269.

Syntheses of 1,4-Disubstituted 1,2,3,4-Tetrahydroisoquinoline: The 1,4-disubstituted 1,2,3,4-tetrahydroisoquinolines (12a-c) were synthesized following the same procedure as for the 4-substituted 1,2,3,4-tetrahydroisoquinolines (9a-c).

(1S,4R)-4-Isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (12a): Yield 80%. [α]_{24}^D –23.9° (c 1.11, CHCl_3). \(^1\)H NMR (270 MHz, CDCl_3) δ 0.93 (d, J = 6.8 Hz), 1.02 (d, J = 6.8 Hz), 1.46 (d, J = 6.8 Hz), 1.99 (br, 1H), 2.09 (m, 1H), 2.43 (m, 1H), 2.98 (dd, 1H, J = 4.6, 13.3 Hz), 3.25 (dd, 1H, J = 4.1, 13.3 Hz), 4.11 (q, 1H, J = 6.8 Hz), 7.11–7.32 (m, 4H). \(^1\)C NMR (270 MHz, CDCl_3) δ 19.36, 21.46, 23.07, 31.28, 42.56, 43.61, 51.63, 125.46, 125.87, 125.99, 129.38, 137.89, 140.34. MS m/z EI, 189 (M^+). IR (film) 3320 cm–1. HRMS calcd for C_{13}H_{19}N; 189.1517. Found; 189.1518.

(1S,4R)-4-Ethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (12b): Yield 92%. [α]_{28}^D +27.4° (c 2.47, CHCl_3). \(^1\)H NMR (270 MHz, CDCl_3) δ 0.97 (t, J = 7.5 Hz), 1.48 (d, J = 6.8 Hz), 1.65 (m, 1H), 1.82 (m, 1H), 2.56 (br, 1H), 2.76 (m, 1H), 2.87 (m, 1H), 3.33 (dd, 1H, J = 5.1, 12.9 Hz), 4.14 (q, 1H, J = 6.8 Hz), 7.09–7.29 (m, 4H). \(^1\)C NMR (270 MHz, CDCl_3) δ 19.36, 24.69, 27.26, 38.59, 41.43, 51.41, 125.68, 125.81, 126.11, 128.04, 138.40, 139.57. MS m/z EI, 175 (M^+). IR (film) 3320 cm–1. HRMS calcd for C_{12}H_{17}N; 189.1517. Found; 189.1518.

(1S,4R)-1,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline (12c): Yield 67%. [α]_{25}^D –30.0° (c 0.93, CHCl_3). \(^1\)H NMR (270 MHz, CDCl_3) δ 1.31 (d, J = 7.1 Hz), 1.46 (d, J = 6.8 Hz), 1.87 (br, 1H), 2.81 (m, 1H), 2.92 (dd, 1H, J = 3.3, 12.9 Hz), 3.13 (dd, 1H, J = 4.6, 12.9 Hz), 4.06 (q, 1H, J = 6.4 Hz), 7.10–7.16 (m,
$^13$C NMR (270 MHz, CDCl$_3$) $\delta$ 21.45, 22.69, 32.60, 48.34, 51.70, 125.69, 125.77, 125.99, 128.44, 140.14×2. IR (film) 3340 cm$^{-1}$. MS m/z EI, 161 (M$^+$). HRMS calcd for C$_{11}$H$_{15}$N; 161.1204. Found; 161.1188.

**Crystal Structure of 10c:** (C$_{19}$H$_{23}$NO)$_2$, M=562.79, orthorhombic, space group $P2_12_12_1$ (#19) with $a=17.559(2)$, $b=24.372(2)$, $c=7.504(1)$ A, $V=3211.4(6)$ A$^3$, $Z=4$, $D_c=1.164$ g/cm$^3$, $R=0.056$ and $R_w=0.028$ for 1401 reflections with $I>3.00\sigma(I)$. A crystal of 0.20×0.20×0.40 mm was used. Data were collected on a Rikaku AFC7R diffractometer with filtered Cu-K$\alpha$. No. of variables were 379. The structure was solved by direct method (SAPI91) and expanded using Fourier techniques (DIRDIF99).

**Crystal Structure of 11a:** (C$_{21}$H$_{27}$NO)$_4$, M=1237.80, triclinic, space group $P1$ (#1) with $a=11.862(2)$, $b=16.095(3)$, $c=9.632(2)$ A, $\alpha=97.72(2)$, $\beta=90.35(2)$, $\gamma=99.46(1)$, $V=1796.5(6)$ A$^3$, $Z=1$, $D_c=1.144$ g/cm$^3$, $R=0.099$ and $R_w=0.100$ for 6078 reflections with $I>3.00\sigma(I)$. A crystal of 0.30×0.30×0.40 mm was used. Data were collected on a Rikaku AFC7R diffractometer with filtered Cu-K$\alpha$. No. of variables were 829. The structure was solved by direct method (SIR92) and expanded using Fourier techniques (DIRDIF99).

This paper is dedicated to Professor A. I. Meyers in celebration of his 70th birthday.

**REFERENCES AND NOTES**


