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

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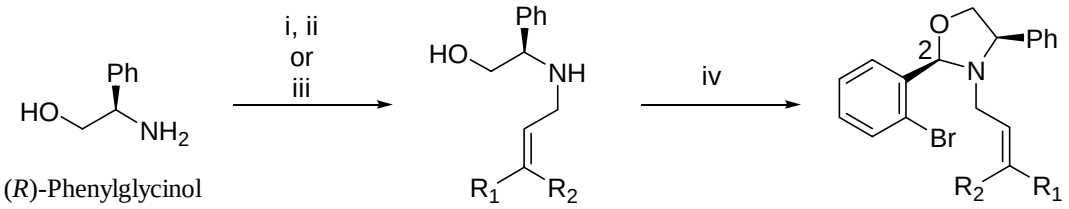
Abstract——Stereoselective radical cyclization of (4*R*)-3-allyl-2-(2-bromophenyl)-4-phenyl-1,3-oxazolidine promoted by the initiator/tributyltin hydride system constructed the chiral oxazolo[2,3-*a*]tetrahydroisoquinoline skeleton. These tricyclic compounds were transformed into 4-alkyl-1,2,3,4-tetrahydroisoquinolines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

INTRODUCTION

The development of radical cyclizations offers tremendous opportunities in organic chemistry.[1] 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.[2] 1,2,3,4-Tetrahydroisoquinolines are of considerable interest in organic and medicinal chemistry.[3] These compounds inhibit serotonin, dopamine and norepinephrine uptake in the central nervous system.[4] Therefore much effort has been expended toward synthesis of various substituted 1,2,3,4-tetrahydroisoquinolines.[5] Despite the utility of the chiral 4-substituted derivatives in biologically interesting syntheses there have been few reports of their use.[6] 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.[7] 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.[8] 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 $NaBH_4$, 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 ^{1}H NMR spectrometry, and X-Ray analysis[8a,9] of similar compounds gives supporting evidence for their absolute configurations.



(*R*)-Phenylglycinol

a; R_1=R_2=Me
b; R_1=Me, R_2=H
c; R_1=R_2=H

1a-c **2a-c**

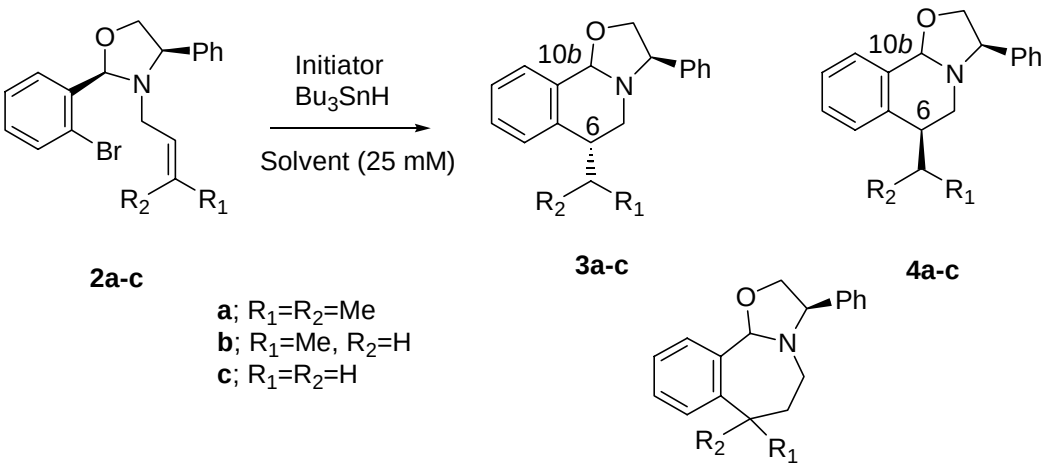
Scheme 1. *Reagents and conditions*: (i) MeRC=CHCHO, CH_2Cl_2, MS 3A, 2 h; (ii) $NaBH_4$, MeOH, 2 h; (iii) allyl bromide, K_2CO_3, THF, 16 h; (iv) 2-bromobenzaldehyde, benzene, reflux, 2 h.

Table 1. Results for the reactions shown in Scheme 1

Run	R_1	R_2	Method	Yield of **1**[a] (%)	Ratio of **2**[b] (2*R* : 2*S*)	Yield of **2**[a] (%)
1(**a**)	Me	Me	i, ii	91	96 : 4	90
2(**b**)	Me	H	i, ii	85	96 : 4	89
3(**c**)	H	H	iii	75	95 : 5	99

[a]Isolated yield. [b]Estimated by ^{1}H 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 10*b* position of *N*, *O*-acetal, and **4a-c** was a single diastereomer. The stereochemistry of 10*b* in the tricycle (**3a-c**) might arise by thermodynamic equilibration of the final products.



2a-c **3a-c** **4a-c**

a; R_1=R_2=Me
b; R_1=Me, R_2=H
c; R_1=R_2=H

5

Scheme 2

Table 2. Aryl Radical Cyclizations of **2a-c** with Bu_3SnH

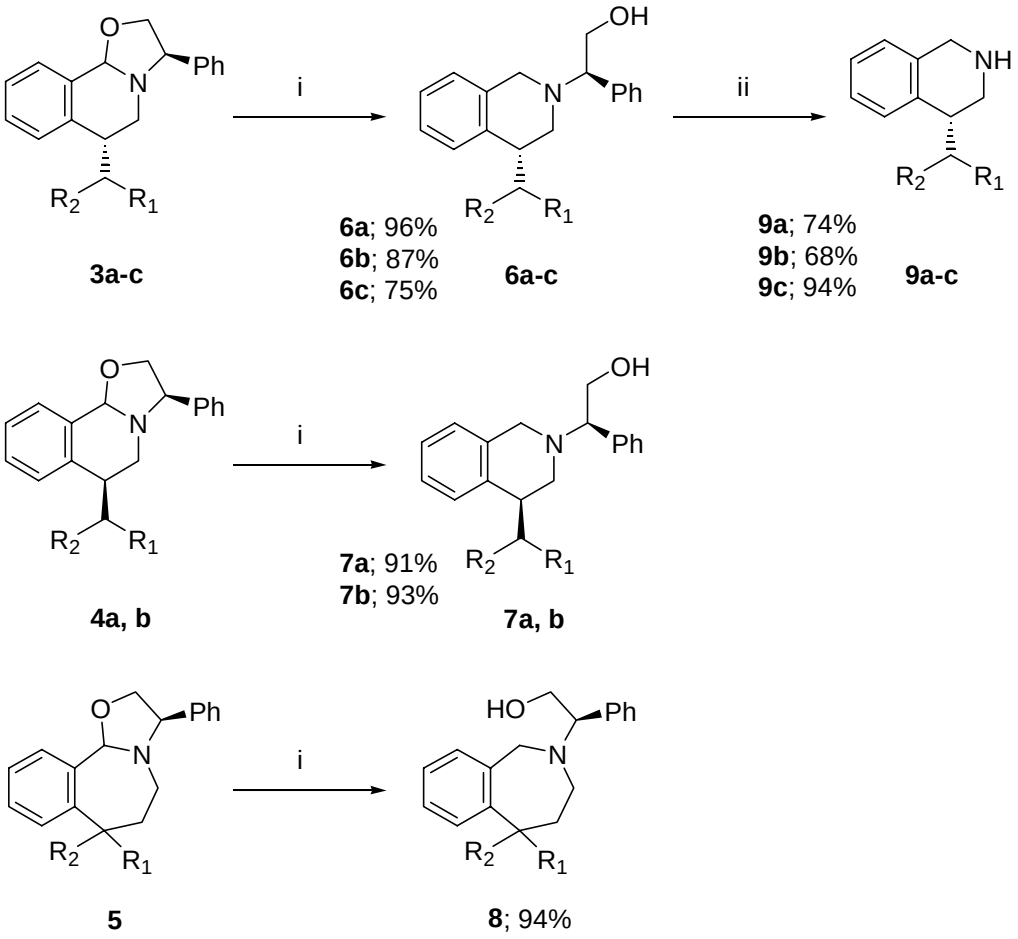
Run[a]	Substrate	Initiator (mol%)	Solvent	Temp. (ºC)	Time (d)	Ratio[b] (**3**[d] : **4** : **5**)	Yield[c] (%)
1	**2a**	AIBN (10)	toluene	reflux	1	74 : 26 : -	83
2	**2a**	AIBN (10)	benzene	reflux	1	75 : 25 : -	87
3	**2a**	V-70 (50)	CH_2Cl_2	rt	3	-	NR
4	**2a**	V-70 (50)	Et_2O	rt	3	81 : 19 : -	70
5	**2a**	Et_3B (100)	toluene	–20	9	79 : 21 : -	63[e]
6	**2b**	AIBN (10)	toluene	reflux	1	83 : 17 : -	85
7	**2b**	AIBN (10)	benzene	reflux	1	85 : 15 : -	86
8	**2b**	V-70 (50)	Et_2O	rt	3	88 : 12 : -	67
9	**2c**	AIBN (10)	benzene	reflux	1	57 : 23 : 20	77
10	**2c**	V-70 (50)	Et_2O	rt	3	57 : 29 : 14	71

[a]All reactions were carried out by adding *n*Bu_3SnH (1.5 equiv) to aryl bromide. [b]Estimated by ^1H NMR (270 MHz) spectrum. [c]Isolated yield. [d]Diastereomer ratio of 10*b*; **3a** (62:38), **3b** (69:31), **3c** (88:12). [e]Little starting substrate remained.

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, [10] with various solvents, at room temperature (Runs 3, 4, 8, 10). CH_2Cl_2 prevented the reaction at room temperature (Run 3). Poor conversion of substrate was a drawback with Et_3B/O_2 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.[11] When the reaction temperature was decreased, it lowered reactivity and yield. However, the diastereoselectivity of the aryl radical cyclization did not change.

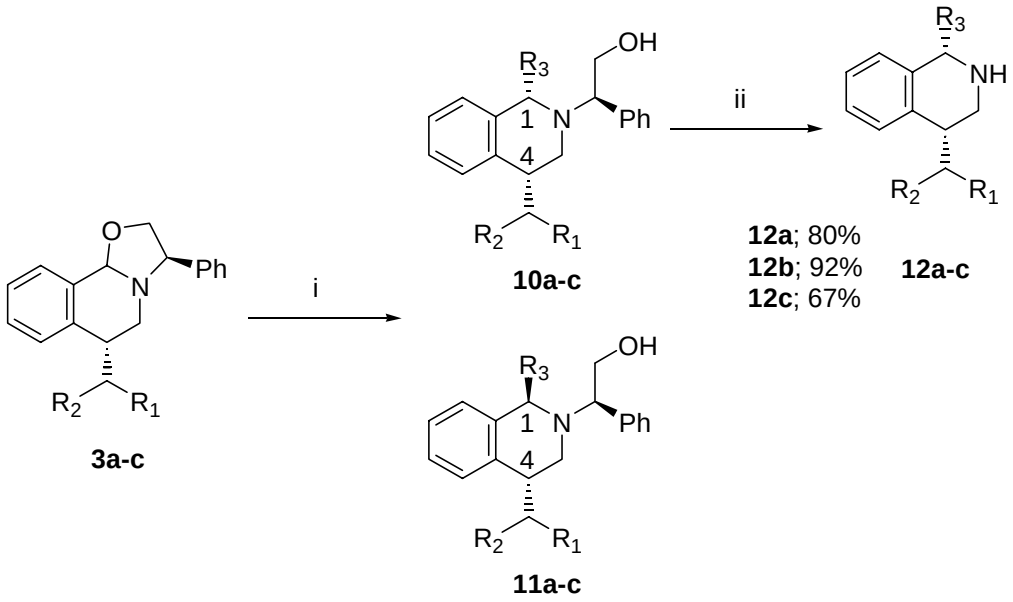
Convertion to 4-substituted 1,2,3,4-tetrahydroisoquinolines (**9a-c**) was then done (Scheme 3). Treatment of the tricycles (**3a-c**, **4a**, **4b**, and **5**) with a small excess of $NaBH_4$ afforded the corresponding tetrahydroisoquinolines (**6a-c**, **7a**, **7b**, and **8**) in good yields, although 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[12] to give the desired **9a-c**.



Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, MeOH, 2 h; (ii) 10% Pd-C, H_2, HCl, MeOH, 16 h.

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

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) R_3MgBr, THF, 15 h; (ii) 10% Pd-C, H_2, HCl, MeOH, 16 h.

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

Run	Substrate	R_3	Temp. (ºC)	Ratio (**10** : **11**)	Yield of **10**+**11** (%)
1	**3a**	Me	0	68 : 32	85
2	**3a**	Me	–50	79 : 21	91
3	**3b**	Me	0	67 : 33	91
4	**3b**	Me	–50	73 : 27	78
5	**3c**	Me	0	64 : 36	91
6	**3c**	Me	–50	79 : 21	77
7	**3a**	Et	0	76 : 24	99
8	**3a**	Ph	0	85 : 15	89

A plausible explanation for the effect of reactivity on diastereoselectivity is proposed (Figure 3). According to our previous model,[8g,h,j,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.

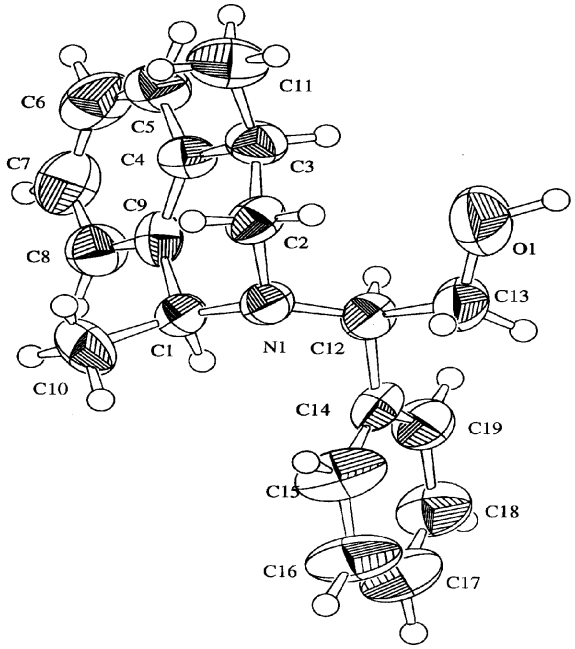


Figure 1. An ORTEP drawing of **10c**

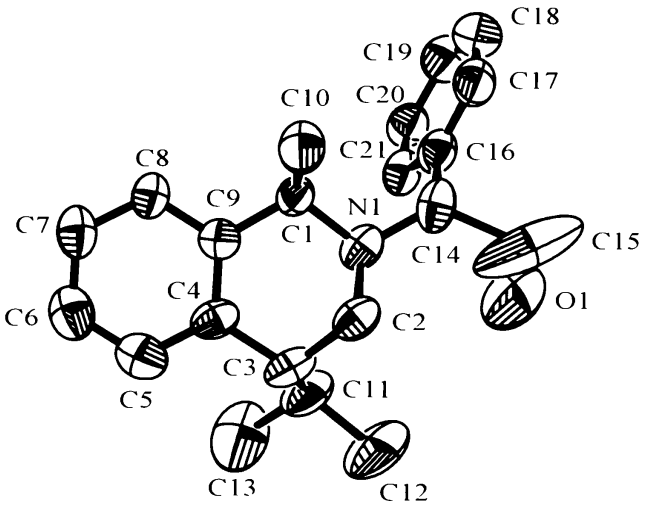


Figure 2. An ORTEP drawing of **11a**

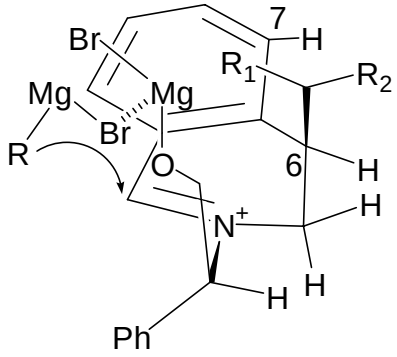


Figure 3. Preferential attack of Grignard reagent

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 (3*R*, 6*R*)-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinolines has been achieved by aryl radical cyclization of 2-(2-bromophenyl)-3-allyl-1,3-oxazolidines with Bu_3SnH in the presence of initiator.

EXPERIMENTAL

Melting point is uncorrected. ^1H and ^{13}C NMR spectra were measured with JEOL GSX 270 instrument for solutions in $CDCl_3$. 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 F_{254} (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 CH_2Cl_2 (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 $NaBH_4$ (3.78 g, 100 mmol) at rt. After beening stirred for 2 h, the mixture was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, 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. $[\alpha]^{24}_D$ −92.7° (*c* 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 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). ^{13}C NMR ($CDCl_3$) δ 17.75, 25.64, 44.63, 64.14, 66.54, 122.51, 127.36, 127.41, 128.41, 134.62, 140.51. IR ($CHCl_3$) 3390, 3090, 3070, 2830, 1670, 1600, 1460, 1050, 870, 760, 700 cm^{-1}. MS *m/z*: EI, 174 (M^+–CH_2OH); CI, 206 (M^++1). Anal. Calcd for $C_{13}H_{19}NO$: 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. $[\alpha]^{24}_D$ –86.1° (*c* 0.96, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 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). ^{13}C NMR ($CDCl_3$) δ 17.70, 48.99, 63.80, 66.46, 127.34, 127.41, 127.69, 128.46, 128.95, 140.41. IR ($CHCl_3$) 3290, 1450, 1040, 970, 700 cm^{-1}. MS *m/z* EI, 160 (M^+–CH_2OH); CI, 192 (M^++1). Anal. Calcd for $C_{12}H_{17}NO$: 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 K_2CO_3 (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 Na_2SO_4, concentrated reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/CH_3OH, 10:1) to give **1c** (6.64 g, 75%) as pale yellow oil. $[\alpha]^{24}_D$ –79.7° (*c* 0.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.48 (br, 2H), 3.08 (dd, 1H,

J= 6.4, 14.0 Hz), 3.22 (dd, 1H, *J*= 5.6, 14.0 Hz), 3.58 (dd, 1H, *J*= 8.6, 10.7 Hz), 3.72 (dd, 1H, *J*= 4.4, 10.7 Hz), 3.82 (dd, 1H, *J*= 4.4, 8.6 Hz), 5.09 (d, 1H, *J*= 10.2 Hz), 5.14 (d, 1H, *J*= 18.1 Hz), 5.88 (m, 1H), 7.25–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 49.49, 63.69, 66.26, 116.03, 126.35, 127.22, 128.26, 136.11, 140.12. IR ($CHCl_3$) 3290, 1490, 1450, 1030 cm^{-1}. MS *m/z* EI, 146 (M^+–CH_2OH); CI, 178 (M^++1). Anal. Calcd for $C_{11}H_{15}NO$: 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.

(4*R*)-2-(2-Bromophenyl)-3-(3-methylbut-2-enyl)-4-phenyl-1,3-oxazolidine (2a): Yield 90%; oven temperature 210 °C / 3 mmHg; $[\alpha]^{25}_D$ –45.7° (*c* 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 1H), 1.45 (s, 1H), 3.14 (d, 2H, *J*= 7.3 Hz), 3.84 (dd, 1H, *J*= 7.6, 8.6 Hz), 4.10 (dd, 1H, *J*= 7.2, 8.6 Hz), 4.26 (dd, 1H, *J*= 7.2, 7.6 Hz), 4.94 (t, 1H, *J*= 7.3 Hz), 5.63 (s, 1H), 7.16–7.64 (m, 8H), 7.96 (dd, 1H, *J*= 1.8, 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ 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. MS *m/z* EI, 148; CI, 372, 374 (M^++1). Anal. Calcd for $C_{20}H_{22}NOBr$: C, 64.52; H, 5.96; N, 3.76. Found: C, 64.22; H, 5.89; N, 3.62. The ^{1}H NMR spectrum showed it to contain a trace amount of diastereomer due to the 2 position of oxazolidine δ 4.50 (m, 1H, Me_2C=C*H*), 5.76 (s, 1H, NC*H*O).

(4*R*)-2-(2-Bromophenyl)-3-(but-2-enyl)-4-phenyl-1,3-oxazolidine (2b): Yield 89%; oven temperature 200 °C / 3 mmHg; $[\alpha]^{23}_D$ +39.9° (*c* 1.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 1H, *J*= 6.1 Hz), 3.05 (dd, 1H, *J*= 7.4, 13.8 Hz), 3.14 (dd, 1H, *J*= 6.2, 13.8 Hz), 3.86 (t, 1H, *J*= 7.4 Hz), 4.10 (t, 1H, *J*= 7.4 Hz), 4.27 (t, 1H, *J*= 7.4 Hz), 5.25 (m, 1H), 5.38 (m, 1H), 5.63 (s, 1H), 7.16–7.56 (m, 8H), 7.94 (dd, 1H, *J*= 1.6, 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ 17.51, 51.09, 66.25, 73.85, 94.32, 124.48, 126.17, 127.43, 127.71, 127.84, 128.51, 129.22, 130.03, 130.30, 132.60, 138.94, 139.32. MS *m/z* EI, 272, 274; CI, 358, 360 (M^++1). Anal. Calcd for $C_{19}H_{20}NOBr$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.79; H, 5.58; N, 3.65. The ^{1}H NMR spectrum showed it to contain a trace amount of diastereomer due to the 2 position of oxazolidine δ 1.55 (3H, d, *J*= 5.4 Hz, C*H*$_3$C=CH), 5.74 (1H, s, NC*H*O).

(4*R*)-3-Allyl-2-(2-bromophenyl)-4-phenyl-1,3-oxazolidine (2c): Yield 99%; oven temperature 200 °C / 5 mmHg; $[\alpha]^{24}_D$ –24.7° (*c* 1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.14 (dd, 1H, *J*= 7.6, 14.2 Hz), 3.24 (dd, 1H, *J*= 6.1, 14.2 Hz), 3.87 (dd, 1H, *J*= 7.7, 8.4 Hz), 4.12 (dd, 1H, *J*= 7.2, 8.4 Hz), 4.28 (dd, 1H, *J*= 7.2, 7.7 Hz), 4.90 (d, 1H, *J*= 10.9 Hz), 4.98 (d, 1H, *J*= 16.9 Hz), 5.64 (m, 1H), 5.65 (s, 1H), 7.18–7.57 (m, 8H), 7.95 (dd, 1H, *J*= 1.8, 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ 52.23, 66.33, 73.70, 94.33, 117.79, 124.43, 127.38, 127.74×2, 128.49×2, 130.12, 132.62, 133.46, 138.62, 139.13. MS *m/z* EI, 188; CI, 344, 346 (M^++1). Anal. Calcd for $C_{18}H_{18}NOBr$: 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_3SnH: To a solution of diastereomers (**2a–c**, 95:5 or 96:4) (5 mmol) in toluene (250 mL) was added Bu_3SnH (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_3SnF). The organic layer was separated, washed with H_2O and brine, dried over Na_2SO_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 ^1H NMR spectrum only.

(3*R*,6*R*)-6-Isopropyl-3-phenyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (3a): Pale yellow oil, inseparable diastereomers (62:38) by the configuration of 10*b* position; Major component, ^1H NMR ($CDCl_3$) δ 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, ^1H NMR ($CDCl_3$) δ 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 ^1H NMR spectrum showed it to contain minor component due to the 10*b* position δ 5.30 (s, 1H).

(3*R*,6*S*)-6-Isopropyl-3-phenyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (4a): Pale yellow oil; ^1H NMR ($CDCl_3$) δ 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*,6*R*)-6-Ethyl-3-phenyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (3b): Pale yellow oil, inseparable diastereomers (88:12) by the configuration of 10*b* position; Major component, ^1H NMR ($CDCl_3$) δ 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, ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J*= 7.4 Hz), 2.10 (m, 1H), 2.41 (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 ^1H NMR spectrum showed it to contain minor component due to the 10*b* position δ 5.34 (s, 1H).

(3*R*,6*S*)-6-Ethyl-3-phenyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (4b): Pale yellow oil. ^1H NMR ($CDCl_3$) δ 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*,6*R*)-6-Methyl-3-phenyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (3c): Pale yellow oil, inseparable diastereomers (92:8) by the configuration of 10*b* position; Major component, ^1H NMR ($CDCl_3$) δ 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 10*b* position δ 5.24 (s, 1H).

(3*R*)-3-Phenyl-2,3,4,5,6,10*b*-hexahydro-1-oxa-3*a*-azabenzo[*e*]azulene (5): Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 1H), 1.85 (m, 1H), 2.55 (dt, 1H, *J*= 2.6, 11.9 Hz), 2.79–2.97 (m, 2H), 3.16 (dt, 1H, *J*= 3.5, 12.0 Hz), 3.79–3.88 (m, 2H), 4.31 (m, 1H), 5.33 (s, 1H), 7.10–7.70 (m, 9H).

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_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/hexane, 1:3) to give **6a-c**.

(1'*R*,4*R*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (6a): Yield 96%. Colorless needles, mp 64 °C (hexane/Et_2O). $[\alpha]^{29}_D$ –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, 10.3 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), 3.85 (dd, 1H, *J*= 5.1, 9.1 Hz), 4.13 (dd, 1H, *J*= 9.1, 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, 127.75, 128.06, 128.12×2, 128.69×2, 135.04, 135.72, 137.37. MS *m/z* EI, 295 (M^+), 264 (M^+–CH_2OH). IR ($CHCl_3$) 3420 cm^{-1}. HRMS Calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1915.

(1'*R*,4*S*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (7a): Yield 91%. Pale yellow oil. $[\alpha]^{29}_D$ –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 19.16, 21.28, 31.05, 44.25, 48.36, 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_2OH). IR ($CHCl_3$) 3420 cm^{-1}. HRMS Calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1941.

(1'*R*,4*R*)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (6b): Yield 87%. Pale yellow oil; oven temperature 250 °C / 3 mmHg. $[\alpha]^{29}_D$ –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_2OH). IR ($CHCl_3$) 3410 cm^{-1}. HRMS Calcd for

$C_{19}H_{23}NO$: 281.1780. Found: 281.1765.

(1'*R*,4*S*)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (7b): Yield 93%. Pale yellow oil. $[\alpha]^{29}_D$ –26.0° (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, *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). ^{13}C NMR ($CDCl_3$) δ 12.20, 28.87, 40.33, 48.81, 53.60, 61.03, 69.67, 125.63, 126.07, 126.37, 128.00, 128.32×2, 128.46, 128.97×2, 134.49, 135.90, 138.92. MS *m/z* EI, 281 (M^+), 250 (M^+–CH_2OH); CI, 282 (M^++1). IR ($CHCl_3$) 3390 cm^{-1}. HRMS Calcd for $C_{19}H_{23}NO$: 281.1780. Found: 281.1788.

(1'*R*,4*S*)-2-(2'-Hydroxy-1'-phenylethyl)-4-methyl-1,2,3,4-tetrahydroisoquinoline (6c): Yield 75%. Pale yellow oil; oven temperature 250 °C / 3 mmHg. ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, *J*= 6.9 Hz), 2.30 (dd , 1H, *J*= 6.2, 11.0 Hz), 3.01 (m, 2H), 3.59 (d, 1H, *J*= 14.4 Hz), 3.77 (d, 1H, *J*= 14.4 Hz), 3.75–3.85 (m, 2H), 4.12 (dd, 1H, *J*= 7.9, 9.4 Hz), 6.97–7.40 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 20.36, 33.16, 52.61, 54.32, 60.97, 69.65, 125.43, 126.13, 126.25, 127.24, 127.75, 128.14×2, 128.65×2, 134.25, 135.96, 139.31. MS *m/z* EI, 267 (M^+), 236 (M^+–CH_2OH); 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-1*H*-benzo[*c*]azepine (8): Yield 94%. Colorless solid, mp 92 °C (hexane/Et_2O). $[\alpha]^{26}_D$ –29.8° (*c* 1.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 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). ^{13}C NMR ($CDCl_3$) δ 27.62, 35.53, 56.65, 57.53, 61.73, 68.40, 125.99, 127.16, 127.75, 128.30×2, 128.51×2, 128.80, 129.37, 137.55, 139.45, 142.71. MS *m/z* EI, 267 (M^+), 236 (M^+–CH_2OH). 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 (4*R*)-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 beening 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_2Cl_2 twice, and the extract was dried over Na_2SO_4, and evaporated under reduced pressure.

(*R*)-4-Isopropyl-1,2,3,4-tetrahydroisoquinolines (9a): Yield 74%. Pale yellow oil. $[\alpha]^{26}_D$ +27.6° (*c* 0.47, $CHCl_3$) {lit.,[7] $[\alpha]^{25}_D$ +27.6° (*c* 0.3, $CHCl_3$)}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J*= 6.9 Hz), 1.04 (d, 3H, *J*= 6.9 Hz), 1.66 (br, 1H), 2.22 (m , 1H), 2.62 (q , 1H, *J*= 5.8 Hz), 3.06 (dd, 1H, *J*= 5.8, 13.2 Hz), 3.12 (dd, 1H, *J*= 5.8, 13.2 Hz), 3.97 (s, 2H), 6.99–7.35 (m, 4H). ^{13}C NMR (270 MHz, $CDCl_3$) δ 18.27, 21.19, 31.17, 42.60, 44.40, 48.49, 125.51, 125.91, 126.04, 128.72, 136.25, 138.03. MS *m/z* EI, 175 (M^+). IR (film) 3340 cm^{-1}. HRMS calcd for $C_{12}H_{17}N$; 175.1361. Found; 175.1314.

(*R*)-4-Ethyl-1,2,3,4-tetrahydroisoquinolines (9b): Yield 68%. Pale yellow oil. $[\alpha]^{28}_{D}$ +21.2° (*c* 0.50, $CHCl_3$) {lit.,[7] $[\alpha]^{25}_{D}$ +6.7° (*c* 1.1, $CHCl_3$)}. ^{1}H 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). ^{13}C 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. ^{1}H 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). ^{13}C 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*,4*R*)-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_4Cl, extracted with CH_2Cl_2 for three times. The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane, 1:3) to give title products.

(1*S*,1'*R*,4*R*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (10a): Yellow oil. $[\alpha]^{25}_{D}$ –17.3° (*c* 1.53, $CHCl_3$). ^{1}H 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). ^{13}C 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_2OH); CI, 310 (M^++1). IR ($CHCl_3$) 3390 cm^{-1}. HRMS Calcd for $C_{21}H_{27}NO$: 309.2093. Found: 309.2084.

(1*R*,1'*R*,4*R*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (11a): Colorless needle, mp 80 °C (hexane). $[\alpha]^{28}_{D}$ +37.5° (*c* 0.53, $CHCl_3$). ^{1}H 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*= 6.4 Hz), 2.32 (dd, 1H, *J*= 7.9, 11.4 Hz), 2.44 (m, 2H), 2.80 (m, 1H), 3.07 (dd, 1H, *J*= 4.1, 11.4 Hz), 3.74 (dd, 1H, *J*= 4.6, 9.7 Hz), 3.98 (q, 1H, *J*= 6.4 Hz), 4.03–4.17 (m, 2H), 7.00–7.39 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 17.68, 20.52, 21.49, 29.40, 41.44, 44.14, 54.68, 61.40, 64.33, 125.47, 126.44, 127.08, 127.88, 128.37, 128.97, 137.60, 141.11. MS *m/z* EI, 278 (M^+–CH_2OH); CI, 310 (M^++1). IR ($CHCl_3$) 3390 cm^{-1}. HRMS Calcd for $C_{21}H_{27}NO$: 309.2093. Found: 309.2087.

(1*S*,1'*R*,4*R*)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (10b): Yellow oil. $[\alpha]^{26}_{D}$ –16.7° (*c* 1.07, $CHCl_3$). ^{1}H 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). ^{13}C NMR ($CDCl_3$) 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^+–CH_2OH). IR ($CHCl_3$) 3410 cm^{-1}. HRMS Calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1941.

(1*R*,1'*R*,4*R*)-4-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (11b): Yellow oil. $[\alpha]^{26}_D$ +18.3° (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 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). ^{13}C NMR ($CDCl_3$) 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^+–CH_2OH). IR ($CHCl_3$) 3430 cm^{-1}. HRMS Calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1941.

(1*S*,1'*R*,4*R*)-1,4-Dimethyl-2-(2'-hydroxy-1'-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (10c): Colorless needle, mp 100 °C (hexane). $[\alpha]^{27}_D$ –17.5° (*c* 0.71, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 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). ^{13}C NMR ($CDCl_3$) 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^+–CH_2OH); CI, 282 (M^++1). IR ($CHCl_3$) 3410 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.05; H, 8.30; N, 4.92.

(1*S*,1'*R*,4*R*)-1-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (10d): Yellow oil. $[\alpha]^{24}_D$ –34.6° (*c* 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 3H, *J*= 6.9 Hz), 0.94 (t, 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). ^{13}C NMR ($CDCl_3$) δ 11.20, 16.56, 20.43, 29.11, 29.85, 37.13, 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^+–CH_2OH). IR ($CHCl_3$) 3410 cm^{-1}. HRMS Calcd for $C_{22}H_{29}NO$: 323.2249. Found: 323.2262.

(1*R*,1'*R*,4*R*)-1-Ethyl-2-(2'-hydroxy-1'-phenylethyl)-4-isopropyl-1,2,3,4-tetrahydroisoquinoline (11d): Yellow oil. $[\alpha]^{24}_D$ +34.5° (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.65 (d, 3H, *J*= 7.3 Hz), 0.66 (t, 3H, *J*= 7.7 Hz), 1.16 (d, 3H, *J*= 6.9 Hz), 1.80 (m, 1H), 2.04 (t, 1H, *J*= 10.5 Hz), 2.12 (m, 1H), 2.52 (m, 1H), 2.84 (m, 1H), 3.13 (dd, 1H, *J*= 3.8, 10.5 Hz), 3.42 (br, 1H), 3.67 (dd, 1H, *J*= 4.3, 9.6 Hz), 4.03 (m, 1H), 4.11 (dd, 1H, *J*= 9.6, 10.4 Hz), 4.19 (dd, 1H, *J*= 4.3, 10.4 Hz), 6.99–7.32 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 7.63, 16.40, 21.28, 26.52, 27.30, 41.21, 4370, 59.74, 60.17, 63.97, 124.64, 125.25, 126.80, 127.72, 128.07, 128.99, 135.33, 138.70, 139.12. MS *m/z* EI, 323 (M^+), 292 (M^+–CH_2OH). IR ($CHCl_3$) 3430 cm^{-1}. HRMS

Calcd for $C_{22}H_{29}NO$: 323.2249. Found: 323.2224.

(1*S*,1'*R*,4*R*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (10e): Yellow oil. $[\alpha]^{25}_{D}$ +55.0° (*c* 1.58, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.59 (d, 3H, *J*= 6.8 Hz), 0.94 (d, 3H, *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*= 6.9, 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). ^{13}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.

(1*R*,1'*R*,4*R*)-2-(2'-Hydroxy-1'-phenylethyl)-4-isopropyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (11e): Yellow oil. $[\alpha]^{26}_{D}$ –117.9° (*c* 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.65 (d, 3H, *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). ^{13}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**).

(1*S*,4*R*)-4-Isopropyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (12a): Yield 80%. $[\alpha]^{24}_{D}$ –23.9° (*c* 1.11, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (d, 3H, *J*= 6.8 Hz), 1.02 (d, 3H, *J*= 6.8 Hz), 1.46 (d, 3H, *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). ^{13}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.

(1*S*,4*R*)-4-Ethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (12b): Yield 92%. $[\alpha]^{28}_{D}$ +27.4° (*c* 2.47, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J*= 7.5 Hz), 1.48 (d, 3H, *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). ^{13}C NMR (270 MHz, $CDCl_3$) δ 11.42, 22.50, 27.26, 38.59, 44.30, 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 $C_{12}H_{17}N$; 175.1361. Found; 175.1356.

(1*S*,4*R*)-1,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline (12c): Yield 67%. $[\alpha]^{25}_{D}$ –30.0° (*c* 0.93, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (d, 3H, *J*= 7.1 Hz), 1.46 (d, 3H, *J*= 6.6 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,

4H). ^{13}C NMR (270 MHz, $CDCl_3$) δ 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: $(C_{19}H_{23}NO)\times2$, *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, *Dc*=1.164 g/cm^3, *R*=0.056 and *Rw*=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-Kα. No. of variables were 379. The structure was solved by direct method (SAPI91) and expanded using Fourier techniqus (DIRDIF99).

Crystal Structure of 11a: $(C_{21}H_{27}NO)\times4$, *M*=1237.80, triclinic, space group *P*1(#1) with *a*=11.862(2), *b*=16.095(3), *c*=9.632(2) A, α=97.72(2), β=90.35(2), γ=99.46(1), *V*=1796.5(6) A^3, *Z*=1, *Dc*=1.144 g/cm^3, *R*=0.099 and *Rw*=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-Kα. No. of variables were 829. The structure was solved by direct method (SIR92) and expanded using Fourier techniqus (DIRDIF99).

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

REFERENCES AND NOTES

1. For reviews (a) A. J. McCarroll and J. C. Walton, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3215. (b) B. K. Banik, *Curr. Org. Chem.*, 1999, **3**, 469. (c) L. Yet, *Tetrahedron*, 1999, **55**, 9349.
2. For reviews (a) W. R. Bowman, M. O. Cloonan, and S. L. Krintel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2885. (b) J. Hartung, *Eur. J. Org. Chem.*, 2001, 619. (c) W. R. Bowman, C. F. Bridge, and P. Brookes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1. (d) J. Cossy, *Recent Res. Dev. Synth. Org. Chem.*, 1999, **2**, 23. (e) M. Ikeda, T. Sato, and H. Ishibashi, *Rev. Heteroat. Chem.*, 1998, **18**, 169.
3. (a) R. B. Herbert, 'The Chemistry and Biology of Isoquinoline Alkaloids,' ed. by J. D. Philipson, M. F. Roberts, and M. H. Zenk, Springer-Verlag, Berlin, 1985, p. 213. (b) M. Shamma, 'Isoquinoline Alkaloids, Chemistry and Pharmacology, 'Academic Press, New York, 1972.
4. (a) G. L. Grunewald, V. H. Dahanukar, B. Teoh, and W. B. Criscione, *J. Med. Chem.*, 1999, **42**, 1982. (b) T. Yamakawa and S. Ohta, *Biochem. Biophys. Res. Commun.*, 1997, **236**, 676. (c) U. Thull, S. Kneubühler, D. P. Gaillar, P.-A. Carrupt, B. Testa, C. Altomare, A. Carotti, P. Jenner, and K. S. P. McNaught, *Biochem. Pharmacol.*, 1995, **50**, 869. (d) B. E. Maryanoff, J. L. Vaught, R. P. Shank, D. F. McComsey, M. J. Costanzo, and S. O. Nortey, *J. Med. Chem.*, 1990, **33**, 2793. (e) J. Ulin, A. D. Gee, P. Malmborg, J. Tedroff, and B. Långström, *Appl. Radiat. Isot.*, 1989, **40**, 171. (f) B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, and P. E. Setler, *J. Med. Chem.*, 1987, **30**, 1433. (g) E. Z. Kaczián, L. György, G. Deák, A. Seregi, and M. Dóda,

J. Med. Chem., 1986, **29**, 1189. (h) M. Kohno, S. Ohta, and M. Hirobe, *Biochem. Biophys. Res. Commun.*, 1986, **140**, 448.

5. (a) T. Itoh, K. Nagata, M. Miyazaki, K. Kameoka, and A. Ohsawa, *Tetrahedron*, 2001, **57**, 8827. (b) M. Bois-Choussy, S. Cadet, M. D. Paolis, and J. Zhu, *Tetrahedron Lett.*, 2001, **42**, 4503. (c) A. R. Katritzky, H.-Y. He, R. Jiang, and Q. Long, *Tetrahedron: Asymmetry*, 2001, **12**, 2427. (d) V. Alezra, M. Bonin, L. Micouin, and H.-P. Husson, *Tetrahedron Lett.*, 2001, **42**, 2111. (e) T. Sano, *Trends in Heterocyclic Chemistry*, 2001, **7**, 117. (f) J. Czombos, W. Aelterman, A. Tkachev, J. C. Martins, D. Tourwe, A. Peter, G. Toth, F. Fulop, and N. De Kimpe, *J. Org. Chem.*, 2000, **65**, 5469. (g) F. A. Davis, P. K. Mohanty, D. M. Burns, and Y. W. Andemichael, *Org. Lett.*, 2000, **2**, 3901. (h) D. Taniyama, M. Hasegawa, and K. Tomioka, *Tetrahedron: Asymmetry*, 1999, **10**, 221. (i) A. Monsees, S. Laschat, I. Dix, and P. G. Jones, *J. Org. Chem.*, 1998, **63**, 10018. (j) T. Shinohara, A. Takeda, J. Toda, Y. Ueda, M. Kohno, and T. Sano, *Chem. Pharm. Bull.*, 1998, **46**, 918. (k) G. L. Grunewald, V. H. Dahanukar, P. Ching, and K. R. Criscione, *J. Med. Chem.*, 1996, **39**, 3539. (l) M. Kihara, M. Ikeuchi, S. Adachi, Y. Nagao, H. Moritoki, M. Yamaguchi, and Z. Taira, *Chem. Pharm. Bull.*, 1995, **43**, 1543.
6. (a) R. Pedrasa, C. Andrés, J. M. Iglesias, and A. Pérez-Encabo, *J. Am. Chem. Soc.*, 2001, **123**, 1817. (b) N. Philippe, V. Levacher, G. Dupas, G. Queguiner, and J. Bourguignon, *Org. Lett.*, 2000, **2**, 2185. (c) V. Jullian, J.-C. Quirion, and H.-P. Husson, *Eur. J. Org. Chem.*, 2000, 1319. (d) L. Belvisi, C. Gennari, G. Poli, C. Scolastico, and B. Salom, *Tetrahedron: Asymmetry*, 1993, **4**, 273.
7. R. Pedrasa, C. Andrés, J. M. Iglesias, and M. A. Obeso, *Tetrahedron*, 2001, **57**, 4005.
8. (a) T. Yamauchi, K. Higashiyama, and S. Ohmiya, *Heterocycles*, 2000, **53**, 2499. (b) T. Yamauchi, K. Higashiyama, H. Kubo, and S. Ohmiya, *Tetrahedron: Asymmetry*, 2000, **11**, 3003. (c) T. Yamauchi, H. Fujikura, K. Higashiyama, and S. Ohmiya, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2791. (d) T. Yamauchi, H. Takahashi, and K. Higashiyama, *Heterocycles*, 1998, **48**, 1813. (e) T. Yamauchi, H. Takahashi, and K. Higashiyama, *Chem. Pharm. Bull.*, 1998, **46**, 384. (f) K. Higashiyama, H. Kyo, and H. Takahashi, *Synlett*, 1998, 489. (g) H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, and S. Ohmiya, and H. Takahashi, *Tetrahedron*, 1998, **54**, 13955. (h) H. Poerwono, K. Higashiyama, and H. Takahashi, *J. Org. Chem.*, 1998, **63**, 2711. (i) H. Poerwono, K. Higashiyama, and H. Takahashi, *Heterocycles*, 1998, **47**, 263. (j) H. Poerwono, K. Higashiyama, T. Yamauchi, and H. Takahashi, *Heterocycles*, 1997, **46**, 385.
9. H. Takahashi, B. C. Hsieh, and K. Higashiyama, *Chem. Pharm. Bull.*, 1990, **38**, 2429.
10. (a) M. Matsugi, K. Gotanda, C. Ohira, M. Suemura, A. Sano, and Y. Kita, *J. Org. Chem.*,1999, **64**, 6928. (b) K. Gotanda, M. Matsugi, M. Suemura, C. Ohira, A. Sano, M. Oka, and Y. Kita, *Tetrahedron*, 1999, **55**, 10315. (c) Y. Kita, A. Sano, T. Yamaguchi, M. Oka, K. Gotanda, and M. Matsugi, *J. Org. Chem.*, 1999, **64**, 675. (d) Y. Kita, A. Sano, T. Yamaguchi, M. Oka, K. Gotanda, and M. Matsugi,

Tetrahedron Lett., 1997, **38**, 3549.

11. T. Yamauchi, J. Sugiyama, and K. Higashiyama, in contribution.
12. M. Yamato, K. Hashigaki, N. Qais, and S. Ishikawa, *Tetrahedron*, 1990, **46**, 5909.