Formal synthesis of the bisbenzylisoquinoline alkaloid berbamunine by asymmetric substitution of chiral organolithium compounds

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Dedicated to Professor Bill Bailey on the occasion of his 65th birthday

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Abstract

Asymmetric alkylation of enantiomeric tetrahydroisoquinolyl oxazolines was achieved with 96-97% diastereoselectivity. Removal of the oxazoline chiral auxiliary and further transformations provide a straightforward synthesis of the two synthetic intermediates that were previously synthesized by resolution, and which comprise a formal synthesis of berbamunine by Ullman coupling.

Keywords: Oxazoline auxiliary

Introduction

The bisbenzylisoquinoline alkaloids are a class of compounds having two benzylisoquinoline subunits, which may be similar or dissimilar, joined by one or more ether bridges. One group of structurally identical bisbenzylisoquinolines, of which there are four diastereomers, is shown in Figure 1. Of these, three were first isolated from natural sources: magnoline from the leaves of *Magnolia fuscata*,[1] berbamunine from *Berberis amurensis*,[2] and guattegaumerine from *Guatteria gaumeri*,

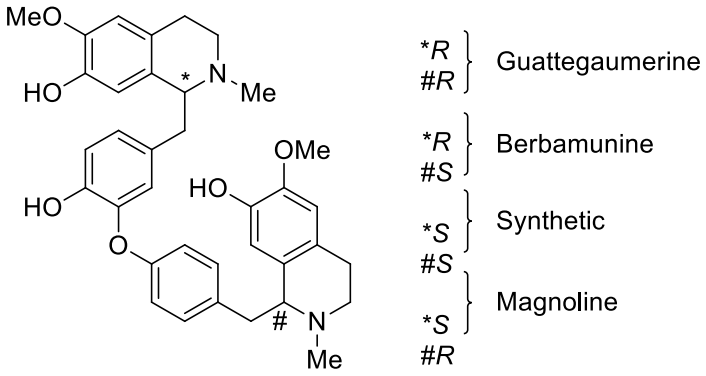
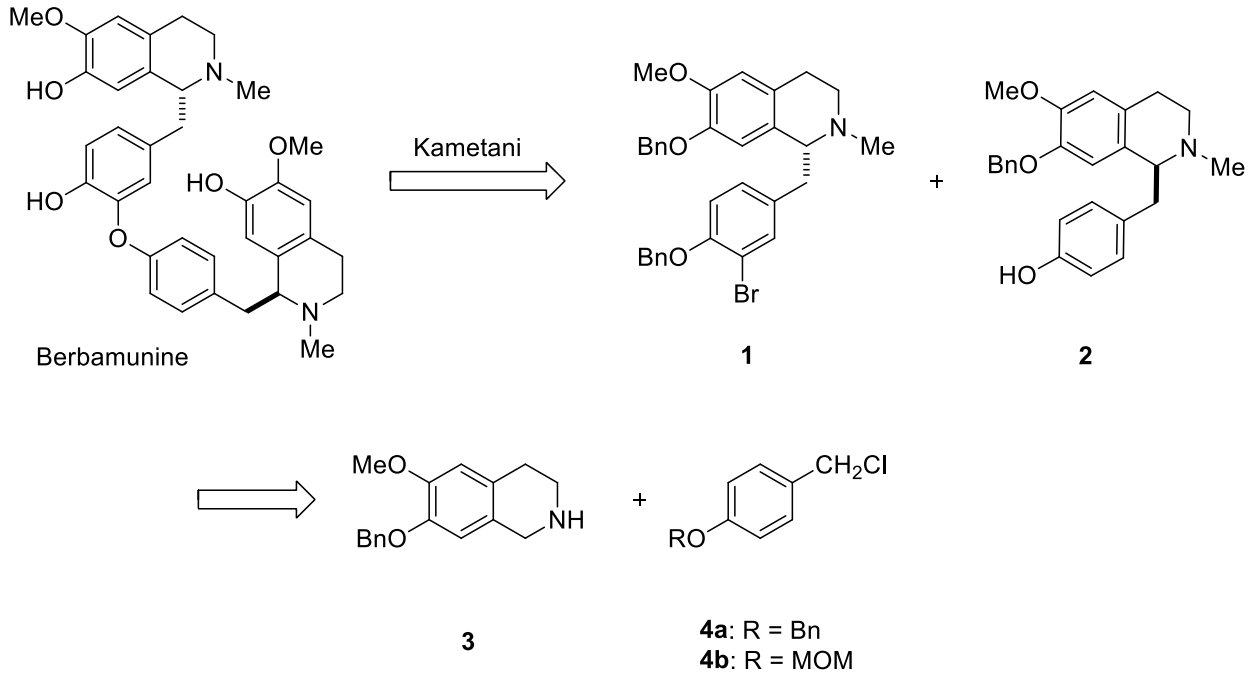


Figure 1. Stereoisomeric bisbenzylisoquinoline alkaloids.

a medicinal plant in southeast Mexico.[3] The fourth has yet to be isolated from natural sources, but has been synthesized,[4] Some of the bisbenzylisoquinoline alkaloids have shown antitumor activity.

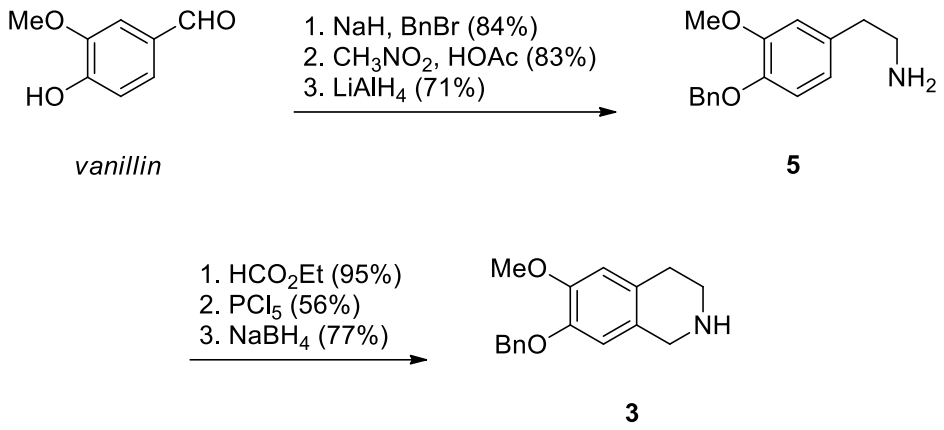
Results and Discussion

The synthesis of berbamunine by Ullman ether coupling of the two fragments **1** and **2**, shown in Scheme 1, was reported by Kametani in 1969.[4-5] These two fragments were obtained either by resolution of synthetic material or by modification of natural coclaurine. Our goal was simply to prepare these two species by asymmetric synthesis, as shown by the second retrosynthetic arrow. Particularly appealing is that both **1** and **2** are derived from the same compound, **3**. Control of the absolute configuration is dependent on the absolute configuration of the chiral auxiliary. The pioneer in the auxiliary-mediated alkylation of tetrahydroisoquinolines using formamidines was Meyers;[6] in this work, we use an oxazoline auxiliary developed in our group.[7]



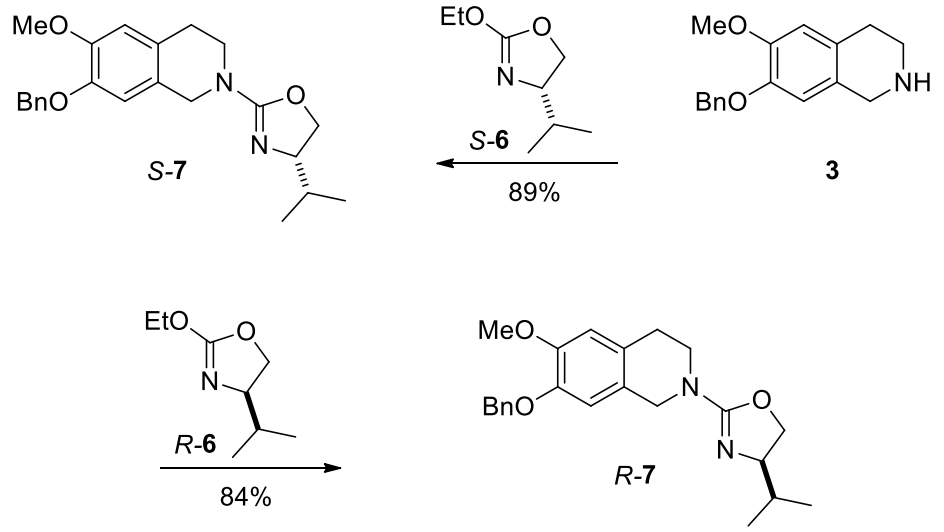
Scheme 1. Retrosynthetic plan for synthesis of berbamunine.

Tetrahydroisoquinoline **3** was prepared in six routine steps, as illustrated in Scheme 2. The phenolic hydroxyl group of vanillin was protected as its benzyl ether, and the aldehyde function was then condensed with nitromethane in a Henry reaction. Reduction of the double bond and nitro groups afforded phenyethyl amine **5**. Formylation of **5** was followed by Bischler-Napieralski cyclization using PCl_5. Reduction of the resulting imine hydrochloride gave tetrahydroisoquinoline **3** in 20% overall yield for the 6 steps.



Scheme 2. Tetrahydroisoquinoline synthesis.

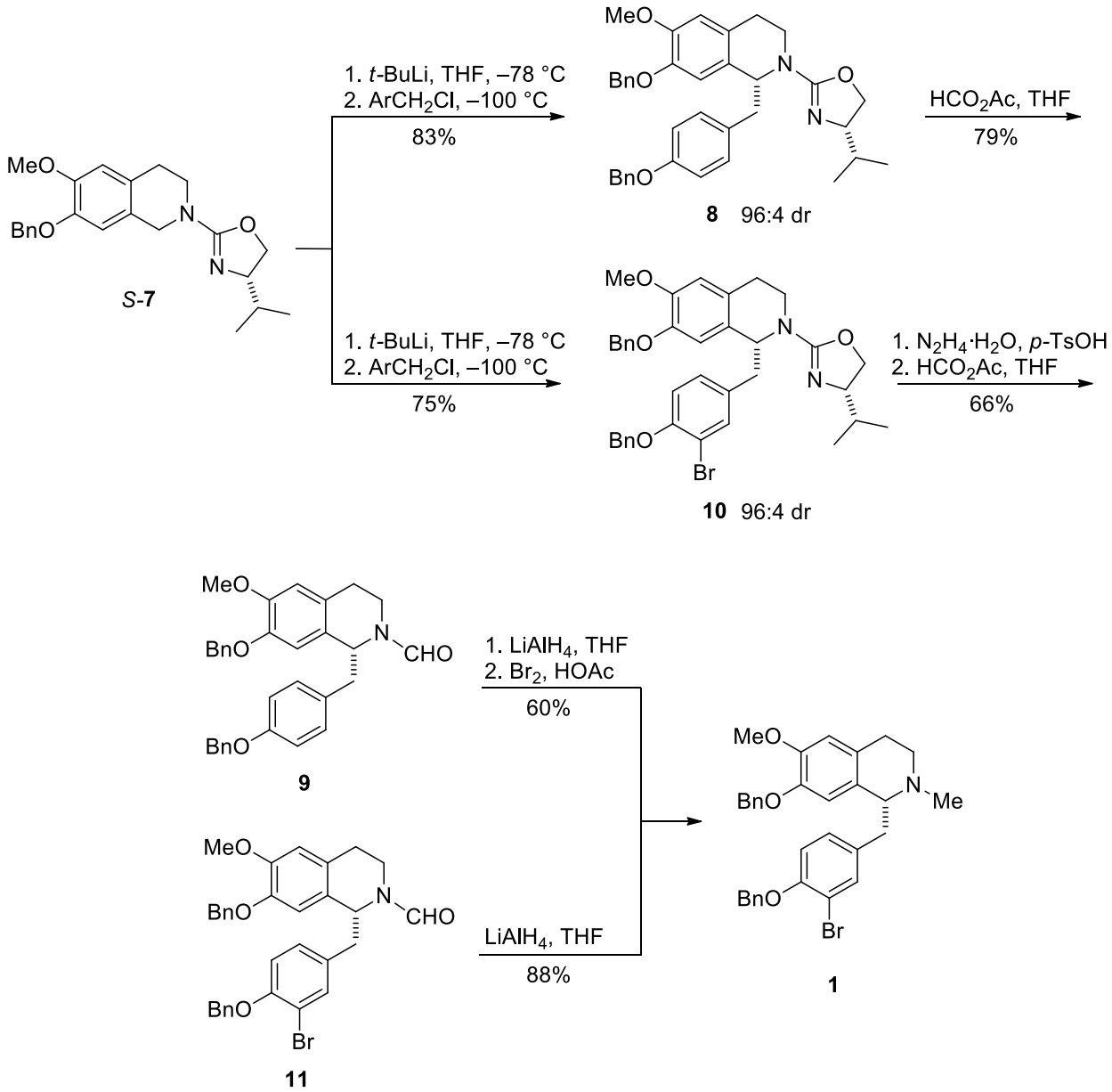
Since compounds **1** and **2** differ in their absolute configuration, enantiomeric chiral auxiliaries were appended, as illustrated in Scheme 3. Ethoxyoxazolines *S*-**6** and *R*-**6** are readily available from the corresponding oxazolidinone by O-alkylation with triethyloxonium tetrafluoroborate.[7] Refluxing the 2-ethoxyoxazolines with tetrahydroisoquinoline **3** in benzene with a catalytic amount of *p*-TsOH afforded *S*-**7** and *R*-**7** in excellent yield.



Scheme 3. Chiral auxiliary attachment.

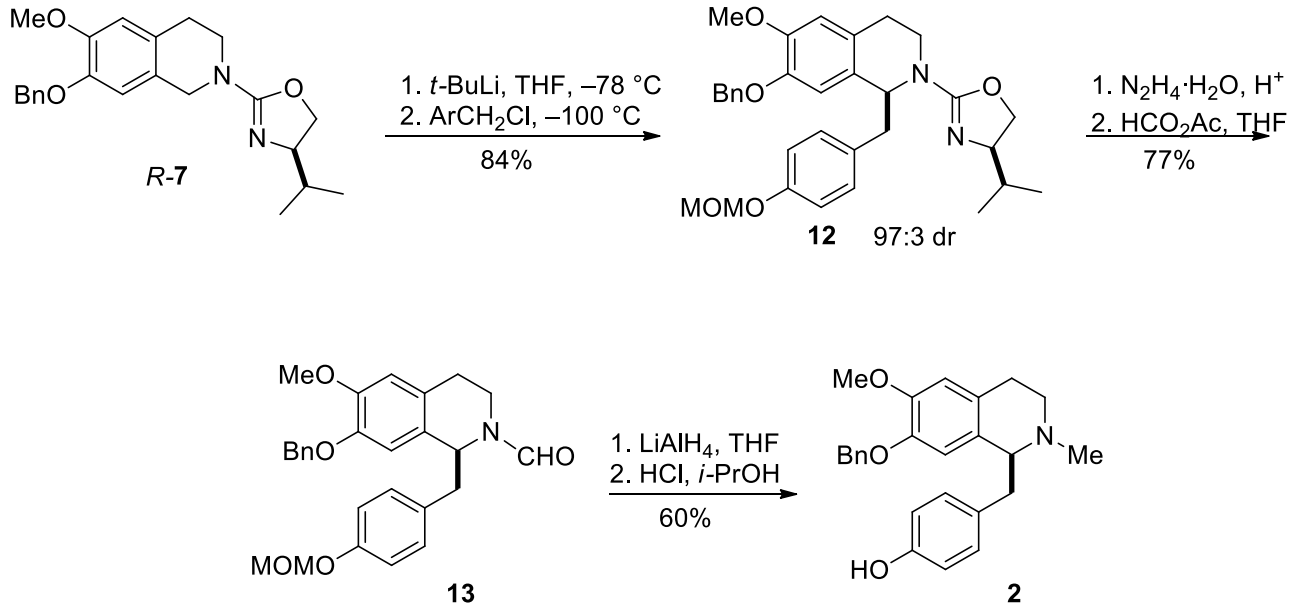
Fragment **1** was synthesized in either of two ways, illustrated in Scheme 4, which differ only in the sequence of steps. In the first path, alkylation of *S*-**7** with 4-benzyloxybenzyl chloride gave compound **8** in 83% yield and 96% diastereoselectivity. The stereoisomer ratio was determined by chiral stationary phase chromatography after removal of the oxazoline auxiliary and acylation with 1-naphthoyl chloride, which provides both the enantiomer ratio and the absolute configuration.[8] Treatment of **8** with acetic formic anhydride removed the auxiliary and formylated the nitrogen in a single step,[9] giving *N*-formyl tetrahydroisoquinoline **9** in 79% yield. Reduction and bromination

then afforded **1** in 60% yield for the two steps. Alternatively, *S*-**7** could be alkylated with 3-bromo-4-benzyloxybenzyl chloride in 75% yield and 96% diastereoselectivity. The oxazoline was removed from **10** by hydrazinolysis and the nitrogen was formylated with acetic formic anhydride to give *N*-formyltetrahydroisoquinoline **11** in 66% yield for the two steps. After hydrazinolysis, the enantiomer ratio, er, and absolute configuration were determined as above. Reduction then yields **1** in 86% yield. The overall yield via **8** and **9** is 39%, and via **10** and **11** is 43%, while each route requires 4 steps. The identity of this compound was established by comparison of the melting point of the free base and its di-*p*-tolyltartrate salt, as well as the optical rotations of each, with literature values.[10]



Scheme 4. Synthesis of fragment **1**.

The synthesis of fragment **2** was accomplished as shown in Scheme 5. The *R* enantiomer of **7** was alkylated with 4-methoxymethoxybenzyl chloride in 84% yield and 97% diastereoselectivity. The stereoisomer ratio and absolute configuration were again established by hydrazinolysis and acylation with 1-naphthoyl chloride, followed by chiral stationary phase HPLC.[8] Hydrazinolysis and formylation with acetic formic anhydride gave *N*-formyl tetrahydroisoquinoline **13** in 77% yield for the two steps. Reduction and deprotection afforded fragment **2** in 60% yield. The preparation of **2** therefore proceeded in 38% overall yield for the 5 steps.



Scheme 5. Synthesis of fragment **2**.

In conclusion, the asymmetric synthesis of fragments **1** and **2** constitute a formal synthesis of the bisbenzylisoquinoline alkaloid berbamunine, a route which could also be adapted to the synthesis of its diastereomers.

Experimental Section

General. Tetrahydrofuran and diethyl ether were distilled immediately prior to use from sodium benzophenone ketyl. Tetramethylethylene diamine (TMEDA) was distilled from CaH_2 immediately before use. All other solvents used during the synthetic procedures were purified by distillation; other commercial reagents were used as received. All reactions were run under a nitrogen atmosphere. Infrared spectra were obtained as neat films or as a methylene chloride solution. Proton NMR spectra were recorded at either 60 or 400 MHz, and carbon NMR spectra were recorded at 20 MHz; chemical shifts are reported in ppm, relative to TMS. Chiral stationary phase chromatography employed a Bakerbond *(R)*-DNBPG (covalent) Pirkle column. All melting and boiling points are

reported in °C and are uncorrected. Radial chromatography was performed on a Harrison Research Model 7924 Chromatron using silica gel 60 PF254 (E. Merck) containing gypsum. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia.

3-Methoxy-4-(benzyloxy)benzaldehyde. Vanillin (**4**, 30.0 g, 197.0 mmol) was added slowly to a stirred, cooled (10 °C) suspension of sodium hydride (50% oil dispersion: 10.44 g, 217.0 mmol) in THF (500 mL). The suspension was warmed to room temperature and stirred 0.5 h. Tetrabutylammonium iodide (3.0 g) and benzyl bromide (24.60 mL, 207.0 mmol) were added, the reaction refluxed 18 h, cooled, washed with water (2 x 200 mL) and brine (200 mL), the organic phase dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallization from 10% THF/hexanes gave 40.30 g (84%) of an off-white solid; mp 62-64 °C (lit. mp 63-65 °C).[11] ^{1}H NMR ($CDCl_3$): 3.93 (s, 3H), 5.24 (s, 2H), 6.93-7.07 (m, 3H), 7.40 (bs, 5H), 9.84 (s, 1H).

1-(Benzyloxy)-2-methoxy-4-(2-nitroethenyl)benzene. A solution of the above aldehyde (20.0 g, 83.0 mmol), nitromethane (11.0 mL, 203.0 mmol) and ammonium acetate (7.0 g, 91.0 mmol) in glacial acetic acid (150 mL) was refluxed 5 h. The hot solution was poured on to crushed ice (700g), the precipitate filtered, washed with water, air dried and recrystallized from 20% EtOAc/hexanes to give the nitrostyrene (19.52 g, 83%) as yellow needle-like crystals; mp 124-125 °C (lit. mp 126-128 °C).[12]

2-[3-Methoxy-4-(benzyloxy)phenyl]ethylamine (5). The above nitrostyrene (21.0 g, 74.0 mmol) was added slowly to a stirred, cooled (10 °C) suspension of LAH (4.19 g, 110.0 mmol) in THF (300 mL). The reaction mixture was warmed to room temperature, refluxed 16 h, cooled, diluted with ether (150 mL) and quenched with water (4 mL), 15% NaOH (4 mL) and water (12 mL). The mixture was stirred 30 min, filtered, the filtrate washed with brine (300 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 10% HCl (100 mL) and washed with ether (2 x 75 mL). The aqueous phase was made basic and extracted with ether (3 x 100 mL). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the phenethylamine (13.50 g, 71 %); mp 59-61 °C (lit. mp 60-62 °C).[13]

***N*-Formyl-2-[3-methoxy-4-(benzyloxy)phenyl]ethyl amine.** A solution of phenethylamine **5** (17.35 g, 67.0 mmol) and ethyl formate (20.0 mL, 247.0 mmol) was refluxed 12 h, cooled, and concentrated *in vacuo*. The organic residue was dissolved in methylene chloride (150 mL), washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the formamide (18.33 g, 95%) as an orange oil that was used directly in the next step. IR (Neat): 3370, 3070, 2980, 2800, 1690, 1630, 1610 cm^{-l}; ^{1}H NMR ($CDCl_3$): 2.68 (t, 2H, J = 12Hz), 3.39 (t, 2H, J = l1Hz), 3.82 (s, 3H), 5.07 (s, 2H), 6.18 (bs, 1H), 6.69-6.75 (m, 3H), 7.34 (s, 5H), 7.98 (s, 1H); ^{13}C ($CDCl_3$) ppm: 161.1, 149.7, 146.8, 137.1, 131.6, 128.4, 127.7, 127.2, 120.6, 114.3, 112.4, 71.1, 55.9, 39.1, 35.0.

6-Methoxy-7-benzyloxy-3,4-dihydroisoquinoline. Phosphorus pentachloride (10.51g, 50.0 mmol) was added slowly added to a stirred, cooled (–78 °C) solution of the above formamide (7.20g, 25.0 mmol) in chloroform (150 mL). The reaction mixture was warmed to room temperature slowly, stirred 24 h and poured into cooled (–78 °C) ether (600 mL). The precipitate was filtered, washed with ether (3 x 100 mL), dried and recrystallized from ethanol to give the HCl salt (4.31g, 56%) as a

yellow solid; mp 181-183°C. The salt was partitioned between chloroform (50 mL) and 10% NaOH (50 mL), the aqueous phase was extracted once with chloroform (30 mL), the organic phases were combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallization from 5% EtOAc/hexanes gave 3.65g (54%) of a white solid; mp 181- 183°C; Methiodide mp 193-195°C; IR ($CHCl_3$): 1650, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$): 2.64 (t, 2H, *J* = 12Hz), 3.72 (t, 2H, *J* = 12Hz), 3.91 (s, 3H), 5.14 (s, 2H), 6.69 (s, 1H), 6.85 (s, 1H), 7.40 (s, 5H), 8.16 (s, 1H); ^{13}C ($CDCl_3$): 157.9, 150.4, 145.3, 135.3, 128.8, 126.9, 126.3, 125.7, 119.9, 111.7, 109.2, 73.8, 69.7, 54.4, 45.6, 23.1. Methiodide Anal. Calc. for $C_{18}H_{20}INO_2$: C, 52.82; H, 4.92. Found: C, 52.69; H, 4.93.

6-Methoxy-7-benzyloxy-l,2,3,4-tetrahydroisoquinoline, (3). Sodium borohydride (0.56g, 15.0 mmol) was added to a stirred, cooled (15 °C) solution of the above HCl salt (3.0g, 10.0 mmol) in ethanol (25 mL). The reaction mixture was warmed to room temperature, stirred 3 h, quenched with water (10 mL) and concentrated *in vacuo* to one-third the original volume. The residue was dissolved in chloroform (50 mL), washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallization from 10% THF/ether gave (2.05g, 77%) of a white solid; mp 124-126 °C (lit. mp 125-126 °C).[14]

General synthetic procedures

General procedure A. Condensation of tetrahydroisoquinolines with the chiral oxazolines A solution of the tetrahydroisoquinoline (1 equivalent), the chiral auxiliary (1.1 equivalent) and a catalytic amount of *p*-toluenesulfonic acid, in benzene (10 mL/eq) were refluxed 6-8 h. The reaction mixture was then washed with saturated bicarbonate (10 mL/eq) and brine (10 mL/eq) solutions. The organic phase was dried (Na_2CO_3) and concentrated *in vacuo*. The crude product was then purified by radial chromatography (2% MeOH/CH_2Cl_2), followed by bulb-to-bulb distillation from calcium hydride.

General procedure B. Metalation and alkylation of tetrahydroisoquinolinyl-oxazolines

The base, t-butyllithium (1.7M solution in pentane, 1.2 equivalents) was added slowly to a 0.2 M solution of the tetrahydroisoquinolinyloxazoline (1 equivalent) in THF at -78 °C. The reaction mixture was stirred at –78 °C for 330 minutes, cooled to –100 °C and quenched with a 0.3 M solution of the electrophile (1.5 equiv) in THF. The reaction temperature was maintained at –100 °C for 30 min and then allowed to warm to room temperature slowly. The mixture was then quenched with brine (10 mL/eq), the organic phase extracted with $CHCl_3$ (10 mL/eq), washed with brine, dried (Na_2CO_3) and concentrated *in vacuo*. The crude product was purified via radial chromatography (2% MeOH/CH_2Cl_2) and/or by kugelrohr distillation from calcium hydride.

General procedure C. Removal of the chiral auxiliary

A solution of the 1-alkyl-tetrahydroisoquinolyloxazoline (1 equiv), hydrazine hydrate (5 equiv) and p-toluenesulfonic acid in 95% ethanol (10 mL/eq) was refluxed 6 h. The reaction mixture was concentrated *in vacuo*, the residue dissolved in CH_2Cl_2 (10 mL/eq), washed with water (5 x 10

mL/eq) and brine (10 mL/eq), dried (Na_2CO_3) and concentrated *in vacuo*. The crude product was then purified by radial chromatography (5% MeOH/CH_2Cl_2).

General procedure D. Optical purity determination *via* Pirkle column

A solution of the l-alkyltetrahydroisoquinoline (1 equiv), 1-naphthoyl chloride (1.5 equiv) and triethylamine (3 equiv) in methylene chloride (10 mL/eq) was stirred one-half hour at room temperature. The reaction mixture was diluted with methylene chloride (20 mL/eq), washed with saturated bicarbonate (10 mL/eq) and brine (l0 mL/eq), dried (anhy. K_2CO_3) and concentrated *in vacuo*. The crude product was purified by radial chromatography (2% MeOH/CH_2C1_2). The naphthamide derivative was then subjected to HPLC analysis using a *R*-DNBPG Pirkle column, according to the published procedure.[8] General conditions for each run were: solvent, 20 to 25% isopropanol in hexane; flow rate 2.0 mL/min; detection at 240 nm.

Synthesis of fragment (1)

2-[4,5-Dihydro-4-((*S*)-1-methylethy1)2-oxazolyl]-6-methoxy-7-benzyloxy-l,2,3,4-tetrahydroisoquinoline (*S*-7). A solution of **3** (1.0 g, 3.71 mmol) and ethoxyoxazoline (*S*-**6**) (0.64 g, 4.08 mmol) were reacted according to General procedure A. Recrystallization from hexanes afforded 79 (0.90 g, 64%) as a white solid; mp 77-78 °C; $[\alpha]_D^{20}$ –30.4 (c=0.5, benzene); IR ($CHCl_3$): 2920, 2860, 1660, 1625, 1610 cm^{-1}; ^1H NMR ($CDC1_3$): 0.88 (t, 6H, *J* = 10Hz), 1.64 (m, 1H), 2.76 (t, 2H, *J* = 10Hz), 3.60 (t, 2H, *J* = 10Hz), 3.84 (s, 4H), 4.01-4.29 (m, 2H), 4.42 (s, 2H), 5.09 (s, 2H), 6.61 (s, 2H), 7.38 (s, 5H); ^{13}C ($CDCl_3$) ppm: 160.8, 148.2, 146. 7, 137.1, 128.4, 127.7, 127.1, 126.8, 112.1, 112.0, 71.1, 70.4, 70.1, 56.0, 46.9, 42.8, 33.2, 28.1, 18.8, 17.5. Anal. Calc. for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42. Found: C, 72.67; H, 7.44

2-[4,5-Dihydro-4((*S*)-1-methylethyl)-2-oxazolyl]-(R)-1-(4-benzyloxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4- tetrahydroisoquinoline (8). Isoquinolyloxazoline *S*-**7** (0.20 g, 0.52 mmol), tert-butyllithiun (0.37 mL, 0.63 mmol) and 4-benzyloxybenzyl chloride (0.18 g, 0.79 mmol) were reacted according to General procedure B. Radial chromatography (2.5% MeOH/ CH_2C1_2) gave 80 (0.25 g, 88%) as a glass. IR ($CHCl_3$): 3370, 3040, 2980, 1660, 1630, 1610 cm^{-1}; ^1H NMR ($CDC1_3$): 0.84 (m, 6H), 1.60 (m, 1H), 2.60 (m, 2H), 2.80 (m, 2H), 3.64 (m, 1H), 3.82 (s, 3H), 3.93-4.20 (m, 4H), 4.93 (s, 2H), 4.99 (s, 2H), 5.73 (m, 1H), 6.41 (s, 1H), 6.57 (s, 1H), 6.91 (m, 2H), 7.34 (bs, 12H); ^{13}C ($CDCl_3$) ppm: 160.0, 157.2, 148.3, 146.0, 136.8, 130.6, 129.9, 129.2, 128.2, 128.0,127.6,127.1, 126.0, 121.2, 114.4, 112.9, 111.6, 70.8, 69.6, 57.4, 55.7, 32.3, 18.1. HRMS calc. for $C_{37}H_{40}N_2O_4$: M^+ = 576.2988. Found $M–H^+$ = 575.2919.

(*R*)-1-(4-Benzyloxybenzyl)-6-methoxy-7-benzyloxy-l,2,3,4-tetrahydroisoquinoline. A solution of **8** (0.69 g, 1.20 mmol) and hydrazine hydrate (0.60 mL, 12.0 mmol) were reacted following General procedure C. Radial chromatography (7% MeOH/CH_2C1_2) gave 0.46 g (82%) as a pale yellow oil that was used directly in the next step. IR (Neat): 3380, 3060, 2945, 1625, 1600 cm^{-l}; ^1H NMR ($CDC1_3$): 2.72 (m, 2H), 2.89 (m, 3H), 3.82 (s, 5H), 5.03 (m, 5H), 6.59-6.67 (m, 2H), 6.97-7.05 (m, 2H), 7.36 (bs, 12H); ^{13}C ($CDCl_3$) ppm: 157.3, 148.1, 145.9, 137.2, 136.9, 131.1, 130.4, 130.1, 128.3, 128.0, 127.7, 127.6, 127.2, 114.7, 112.7, 112.3, 71.2, 69.8, 56.6, 55.7, 41.5, 29.3. Following

experimental guidelines given in General procedure D, the major isomer was found to be *R* (96:4 er).

(*R*)-1-(4-Benzyloxybenzyl)-2-formyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydro-isoquinoline (9). Method A. A solution of the above secondary amine (0.46 g, 1.0 mmol) and acetic formic anhydride (0.43 g, 5.0 mmol) in THF (10 ml) was refluxed 6 h, cooled and concentrated *in vacuo*. The residue was dissolved in methylene chloride (25 mL), washed with water (25 mL), saturated bicarbonate (25 mL) and brine (25 mL) solutions, dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (2% MeOH/ CH_2C1_2) gave **9** (0.41 g, 83%) as a yellow oil which was used directly in the following step. IR (Neat): 3060, 2960, 1690, 1630, 1600 cm^{-l}; ^1H NMR ($CDCl_3$): 2.65-3.10 (m, 4H), 3.82 (s, 5H), 4.99 (s, 2H), 5.07 (s, 2H), 5.38 (m, IH), 6.59 (s, 2H), 6.91 (d, 2H, J = 8Hz), 7.36 (bs, 12H), 8.06 (s, 1H); ^{13}C ($CDCl_3$) ppm: 160.9, 157.4, 136.6, 130.4, 130.1, 129.8, 129.4, 129.1, 128.1, 127.5, 127.0, 126.4, 114.7, 114.5, 114.3, 114.2, 111.8, 75.4, 69.5, 55.6, 40.5.

Method B. A solution of **8** (0.54 g, 93.0 mmol) and acetic formic anhydride (l.64 g, 18.62 mmol) in THF (8 mL) was refluxed 18 h, cooled and concentrated *in vacuo*. The residue was dissolved in chloroform (50 mL), washed with water (50 mL), saturated bicarbonate (50 mL) and brine (50 mL) solutions, dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (2% MeOH/ CH_2C1_2) gave **9** (0.36 g, 79%) as a yellow oil. Spectral data identical to that from method A.

(*R*)-1-(4-Benzyloxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline. The formamide **9** (0.29 g, 0.59 mmol) was added dropwise to a stirred suspension of LAH (0.045 g, 1.17 mmol) in THF (5 mL). The reaction mixture was refluxed 12 h, cooled, diluted with ether (10 mL) and quenched with water (0.05 mL), 15% NaOH (0.05 mL) and water (0.15 mL). The solution was filtered, the filtrate dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (2.5% MeOH/ CH_2C1_2) afforded 0.24 g (85%) of a pale yellow oil. $[\alpha]_D^{20}$ –37.6 (c=0.9, $CHCl_3$); IR (Neat): 3440, 3060, 2960, 2820, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 2.48 (8, 3H), 2.66-3.03 (m, 4H), 3.60 (m, 2H), 3.80 (s, 3H), 3.99 (m, 1H), 4.77 (s, 2H), 4.97 (s, 2H), 6.08 (s, 1H), 6.55 (s, 1H), 6.89 (s, 2H), 7.31 (bs, 12H); ^{13}C ($CDCl_3$) ppm: 157.2, 157.1, 147.8, 145.4, 137.1, 137.0, 131.9, 130.6, 128.8, 128.3, 127.9, 127.7, 127.4, 127.2, 127.1, 126.4, 126.3, 114.3, 113.8, 113.7, 111.7, 111.6, 70.7, 69.8, 64.6, 55.7, 46.7, 42.4, 25.4.

(*R*)-1-(3-Bromo-4-benzyloxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (1). A solution of bromine (0.033 g, 0.21 mmol) in glacial acetic acid (1 mL) was added over 30 min to a stirred, cooled (10 ºC) solution of the above compound (0.10 g, 0.21 mmol) in 8% acetic acid (6 mL). The reaction mixture was warmed to room temperature, stirred 1 h then made basic with 10% NaOH. The solution was extracted with ether (3 x 20 mL), the combined extracts washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (5% MeOH/ CH_2C1_2) afforded **1** (0.083 g, 71 %) as a yellow oil. This was converted to the tartrate by reaction with di-*p*-tolyltartaric acid (0.058 g, 0.15 mmol) in acetone (2 mL). The solution was refrigerated overnight, diluted with hexane (1 mL), the crystals filtered and recrystallized from methanol to give a white solid; mp 155-156 °C (lit. mp 157.5-158 ºC).[10] $[\alpha]_D^{20}$ –82.3, c = l, $CHCl_3$ (lit. $[\alpha]_D^{20}$ –84.6, c = 2.8, $CHC1_3$).[10] The salt was suspended in chloroform (10 mL) and made alkaline with 10% NH_4OH. The organic phase was washed with brine (20 mL), dried

(Na_2SO_4) and concentrated *in vacuo* to give **1** (0.067g) as a pale yellow oil; $[\alpha]_D^{20}$ –40.92, c = 3.35, $CHCl_3$ (lit. $[\alpha]_D^{20}$ –41.8, $CHCl_3$;[4] $[\alpha]_D^{4}$ –43.0, c = 5.3 in $CHCl_3$.[10]). IR (neat); 3060, 2960, 1630, 1600, 1525 cm^{-1}; ^1H NMR ($CDCl_3$): 2.47 (s, 3H), 2.65-2.80 (m, 2H), 2.95-3.15 (m, 2H), 3.58 (t, 1H), 3.80 (d, 2H), 3.83 (s, 3H), 4.78-4.90 (ABq, 2H, *J* = 12Hz), 5.08 (s, 2H), 6.13 (s, 1H), 6.55 (s, 1H), 6.72-6.87 (m, 2H), 7.23-7.44 (m, 11H); ^{13}C ($CDCl_3$) ppm: 157.1, 147.9, 145.5, 137.2, 137.1, 132.2, 130.7, 129.1, 128.4, 128.3, 127.8, 127.6, 127.3, 127.2, 126.5, 114.4, 113.8, 111.7, 70.8, 67.0, 64.7, 55.8, 47.0, 42.5, 40.0, 25.6.

2-[4,5-Dihydro-4-((*S*)-1-methylethyl)-2-oxazolyl]-(*R*)-1-(3-bromo-4-benzyloxy-benzyl)-6-methoxy-7-benzyloxy-l,2,3,4-tetrahydroisoquinoline (10). The isoquinolyloxazoline *S*-**7** (0.75 g, 1.97 mmol), tert-butyllithium (1.62 ml, 2.76 mmol) and 3-bromo-4-benzyloxybenzyl chloride (0.92 g, 2.96 mmol) were reacted according to General Procedure B. Radial chromatography (2.0% MeOH/CH_2C1_2) gave **10** (0.97 g, 75%) as a viscous yellow oil. IR (Neat): 3000, 2950, 1680, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 0.84 (m, 6H), 1.45 (m, 1H), 2.50-2.93 (m, 4H), 3.58 (m, 1H), 3.76 (s, 3H), 3.95-4.27 (m, 4H), 4.89 (s, 2H), 5.03 (s, 2H), 5.83 (m, 1H), 6.32 (s, 1H), 6.53 (s, 1H), 6.85-6.81 (m, 2H), 7.30 (bs, 10H), 7.81 (s, 1H); ^{13}C ($CDCl_3$) ppm: 160.1, 153.3, 148.2, 145.9, 136.9, 136.4, 134.3, 132.5, 129.6, 128.3, 127.9, 127.6, 127.0, 126.7, 113.3, 113.1, 111.7, 70.9, 70.6, 69.6, 56.9, 55.8, 33.1, 17.6. HRMS calc. for $C_{37}H_{39}BrN_2O_4$: M^+ = 654.2093. Found M+ = 654.2060.

(*R*)-1-(3-Bromo-4-benzyloxybenzyl)-2-formyl-6-methoxy-7-benzyloxy-l,2,3,4-tetrahydroiso-quinoline (11). A solution of **10** (0.90 g, 1.37 mmol) and hydrazine hydrate (0.69 ml, 13.73 mmol) were reacted following General Procedure C. Radial chromatography (7% MeOH/ CH_2C1_2) gave 0.61 g (81 %) of a pale yellow oil which was used directly in the next step. IR (Neat): 3310, 3030, 2980, 2860, 1630, 1600 cm^{-1}. Following experimental guidelines given in General Procedure D, the major isomer was found to be *R* (96:4 er). A solution of this amine (0.60 g, 1.10 mmol) and acetic formic anhydride (0.50 g, 5.68 mmol) was refluxed 6 h, cooled and concentrated *in vacuo*. The residue obtained was dissolved in methylene chloride (30 mL), washed with water (30 mL), saturated bicarbonate (30 mL) and brine (30 mL) solutions, dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (2.0% MeOH/ CH_2C1_2) gave **11** (0.52 g, 82%) as a dark yellow oil that was used directly in the next step. IR (Neat): 3060, 3010, 2980, 2880, 1690, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 2.58-2.95 (m, 4H), 3.80 (8, 5H), 4.91 (s, 2H), 5.03 (s, 2H), 5.40 (m, 1H), 6.32 (s, 1H), 6.54 (s, 1H), 6.83-6.97 (m, 2H), 7.35 (bs, 10H), 7.67 (s, 1H), 8.06 (s, 1H); ^{13}C ($CDCl_3$) ppm: 161.1, 153.6, 148.9, 148.4, 146.4, 146.2, 136.8, 136.7, 136.2, 131.4, 131.1, 121.5, 128.3, 127.6, 127.1, 127.0, 126.8, 126.6, 126.3, 125.8, 113.6, 113.0, 112.4, 111.8, 71.1, 70.6, 58.1, 55.8.

(*R*)-1-(3-Bromo-4-benzyloxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-l,2,3,4-tetrahydroisoquinoline (1). A solution of **11** (0.50 g, 0.87 mmol) in THF (2 mL) was added dropwise to a stirred suspension of LAH (0.033 g, 0.87 mmol) in THF (10 mL). The reaction mixture was stirred 15 min at room temperature, refluxed 14 h, cooled, diluted with ether (10 mL) and quenched with water (0.03 mL), 15% NaOH (0.03 mL) and water (0.09 mL). The mixture was then filtered and the filtrate concentrated *in vacuo*. Radial chromatography (2.0% MeOH/ CH_2C1_2) gave **1** (0.43 g, 88%) as a pale yellow oil. The tartrate salt was prepared following the procedure outlined previously; mp 155-156 °C (lit. mp 157.5-158°C).[10] $[\alpha]_D^{20}$ –83.11 (c = 1.0, MeOH).

Neutralization of the salt with NH_4OH afforded **1** (0.353 g) as a yellow oil. $[\alpha]_D^{20}$ **–**41.44, c=3.35, $CHCl_3$ (lit. $[\alpha]_D^{20}$ **–**41.8, $CHCl_3$;[4] $[\alpha]_D^{4}$ –43.0, c = 5.3 in $CHCl_3$.[10]). NMR spectral data were identical to that obtained previously.

Synthesis of fragment (2)

2-[4,5-Dihydro-4-((*R*)-1-methylethyl)-2-oxazolyl]-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (*R*-7). A solution of **3** (1.0 g, 3.71 mmol) and *R*-**6** (0.64 g, 4.08 mmol) were reacted following General Procedure A. The viscous residue obtained was dissolved in hot hexanes and slowly cooled to afford *R*-**7** (1.14 g, 81 %) of a white solid; mp 75-77°C. $[\alpha]_D^{20}$ +29.6 (c = 0.5, benzene). Spectral data identical to *S*-**7**.

2-[4,5-Dihydro-4-((*R*)-1-methylethyl)-2-oxazolyl]-(*S*)-1-(4-methoxymethoxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (12). Isoquinolyloxazoline *R*-**7** (0.75 g, 1.97 mmol), tert-butyllithium (1.51 mI, 2.56 mmol) and 4-methoxymethoxybenzyl chloride (0.51 g, 2.76 mmol) were reacted according to General Procedure B. Radial chromatography (2.5% MeOH/ CH_2C1_2) gave **12** (0.84 g, 84%) as a viscous yellow oil. IR (Neat): 3000, 2950, 1680, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 0.84 (m, 6H), 1.56 (m, 1H), 2.72-2.97 (m, 4H), 3.39 (s, 3H), 3.58 (m, 1H), 3.82 (s, 3H), 3.95-4.27 (m, 4H), 4.89 (s, 2H), 5.09 (s, 2H), 5.83 (m, 1H), 6.32 (s, 1H), 6.55 (s, 1H), 6.95 (m, 2H),7.32 (bs, 7H); ^{13}C ($CDCl_3$) ppm: 160.2, 155.6, 148.2, 145.8, 136.9, 130.6, 129.6, 129.0, 128.2, 127.7, 127.5, 127.0, 126.4, 115.8, 113.1, 111.7, 94.3, 70.8, 70.3, 55.6, 32.7, 18.3, 17.3. HRMS calc. for $C_{32}H_{35}N_2O_5$: M^+ = 530.2781, Found: M–H^+ 529.2726

(*S*)-l-(4-Methoxymethoxybenzyl)-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydro-isoquinoline. A solution of **12** (0.65 g, 1.22 mmol) and hydrazine hydrate (0.60 mL, 12.25 mmol) were reacted following General Procedure C. Radial chromatography (7% MeOH/ CH_2C1_2) gave 0.41 g (81 %) of a pale yellow oil that was used directly in the next step. IR (Neat): 3310, 3030, 2980, 2860, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 2.70-2.80 (m, 5H), 3.39 (s, 3H), 3.77 (s, 5H), 4.50 (m, 1H), 5.01 (s, 2H), 5.09 (s, 2H), 6.57-6.70 (m, 2H), 7.01 (s, 2H), 7.33 (bs, 7H); ^{13}C ($CDCl_3$) ppm: 155.0, 147.4, 145.2, 136.6, 131.5, 129.7, 129.5, 127.5, 127.3, 126.8, 126.5, 115.5,115.2, 112.1, 111.7, 93.5, 70.4, 54.9, 47.3, 39.9, 29.9. Following experimental guidelines given in General Procedure D, the major isomer was found to be *S* (97:3 er).

(*S*)-1-(4-Methoxymethoxybenzyl)-2-formyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (13). A solution of the above compound (0.20 g, 0.48 mmol) and acetic formic anhydride (0.21 g, 2.38 mmol) was refluxed 6 h, cooled and concentrated *in vacuo*. The residue obtained was dissolved in methylene chloride (30 mL), washed with water (30 mL), saturated bicarbonate (30 mL) and brine (30 mL) solutions, dried (Na_2SO_4) and concentrated *in vacuo*. Radial chromatography (2.5% MeOH/CH_2C1_2) gave **13** (0.202g, 95%) as a pale yellow oil which was used directly in the following step. $[\alpha]_D^{20}$ +39.0 (c = 2.02, $CHCl_3$). IR (Neat): 3060, 3010, 2980, 2880, 1690, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 2.66-3.03 (m, 4H), 3.45 (s, 3H), 3.82 (s, 5H), 5.09 (s, 2H), 5.13 (s, 2H), 5.40 (m, IH), 6.61 (s, 2H), 6.95 (d, 2H, *J* = 8Hz), 7.36 (bs, 7H), 8.10 (s, IH).

(*S*)-1-(4-Methoxymethoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline. A solution of **13** (0.20 g, 0.45 mmol) in THF (3 mL) was added dropwise to a stirred suspension of LAH (0.025 g, 0.67 mmol) in THF (10 mL). The reaction mixture was stirred 15 min at room temperature, refluxed 14 h, cooled, diluted with ether (10 mL) and quenched with water (0.025 mL), 15% NaOH (0.025 mL) and water (0.075 mL). The mixture was then filtered and the filtrate concentrated *in vacuo*. Radial chromatography (2.5% MeOH/ CH_2C1_2) gave 0.15 g (80%) as a pale yellow oil which was used directly in the following step. $[\alpha]_D^{20}$ +39.79 (c = 3.75, $CHCl_3$); IR (Neat): 3060, 2980, 2860, 2810, 1630, 1525 cm^{-1}; ^1H NMR ($CDCl_3$): 2.50 (s, 3H), 2.66-3.03 (m, 4H), 3.19 (m, 2H), 3.43 (s, 3H), 3.64 (m, 1H), 3.84 (s, 3H), 4.81 (s, 2H), 5.13 (s, 2H), 6.10 (s, 1H), 6.57 (s, 1H), 6.95-7.03 (m, 2H), 7.32 (s, 7H); ^{13}C ($CDCl_3$) ppm: 155.5, 147.9, 145.5, 137.3, 133.2, 130.6, 129.1, 128.3, 127.5, 127.1, 126.5, 115.9, 113.8, 111.7, 94.5, 70.7, 64.7, 55.8, 46.9, 42.5, 40.0, 25.5.

(*S*)-1-(4-Hydroxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydro-isoquinoline (2). A solution of the above compound (0.075 g, 0.17 mmol) and 18% HCl (0.9 mL) in 50% *i*-PrOH/THF was stirred at room temperature 14 h, made alkaline with concentrated NH_4OH and concentrated *in vacuo*. The residue obtained was partitioned between methylene chloride (10 mL) and water (10 mL), the aqueous phase was separated, extracted with methylene chloride (2 x 10 mL), the organic extracts were combined, washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Radial chromatography (5% MeOH/ CH_2C1_2) gave **2** (0.048 g, 73%) as a pale yellow oil $[\alpha]_D^{16}$ +129.7, c = 2.5, MeOH (lit. $[\alpha]_D^{15}$ +135.5 in MeOH).[15] IR (Neat): 3300, 3040, 2960, 2810, 1635, 1610, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.49 (s, 3H), 2.57-2.72 (m, 2H), 2.75-2.90 (m, 2H), 3.00-3.25 (m, 2H), 3.67 (t, 1H), 3.82 (s, 3H), 4.74-4.85 (ABq, 2H, *J* = 12Hz), 6.06 (s, 1H), 6.56 (s, 1H), 6.65 (d, 2H, *J* = 8Hz), 6.84 (d, 2H, *J* = 8Hz), 7.20-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) ppm: 154.8, 148.1, 145.7, 137.2, 130.7, 130.6, 128.6, 128.4, 127.6, 127.3, 125.9, 115.4, 114.0, 111.8, 70.8, 64.8, 55.9, 46.2, 42.0, 40.2, 24.7.

References and Notes

1. Proskurnina, N. F.; Orekhoff, A. P. *Bull. Soc. Chim. Fr.* **1938**, *5*, 1357.
2. Tomita, M.; Kugo, T. *Yakugaku Zasshi* **1957**, *77*, 1075.
3. Dehaussy, H.; Tits, M.; Angenot, L. *Planta Med.* **1983**, *49*, 25.
4. Kametani, T.; Iida, H.; Sakurai, K.; Kano, S.; Ihara, M. *Chem. Pharm. Bull.* **1969**, *17*, 2120.
5. Kametani, T.; Iida, H.; Sakurai, K. *J. Chem. Soc. C* **1969**, 500.
6. (a) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59; (b) Highsmith, T. K.; Meyers, A. I. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: Greenwich, CT, 1991; Vol. 1, p 95; (c) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.
7. (a) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076; (b) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211.

8. Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504.
9. This surprising transformation was discovered by accident when formylation with acetic formic anhydride was conducted on a mixture of the secondary amine produced after only partial removal of the oxazoline auxiliary.
10. Kametani, T.; Takano, S.; Masuko, K. *Yakugaku Zasshi* **1966**, *86*, 976.
11. Farkas, L.; Wolfner, A.; Olechnow.V *Acta Chim. Acad. Sci. Hung.* **1972**, *74*, 367.
12. Kessar, S. V.; Jogi, R. R.; Rampal, A. L.; Kumar, K. *Indian J. Chem.* **1964**, *2*, 240.
13. Falco, M. R.; Vries, J. X. D.; Marchell.E; Lorenzo, H. C. D.; Mann, G. *Tetrahedron* **1972**, *28*, 5999.
14. Hara, H.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* **1985**, *33*, 2705.
15. Kametani, T.; Yagi, H. *Chem. Pharm. Bull.* **1967**, *15*, 1283.

