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PAPER

Switch in regioselectivity of epoxide ring-opening by changing the organometallic reagent†

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The regio- and stereoselective ring-opening of a 2-(2′-oxiranyl)-1,2,3,6-tetrahydropyridine using organometallic reagents is reported. The choice of the organometallic reagent determines the formation of either 2-[(*R*)-1-hydroxyalkyl]- or 2-[(*S*)-2-hydroxy-1-alkyl]-1,2,3,6-tetrahydropyridines. The formation of 2-[(*S*)-2-hydroxy-1-alkyl]-1,2,3,6-tetrahydropyridines is a rare example of epoxide ring-opening with retention of configuration. The process has been applied to the asymmetric synthesis of β-(+)-conhydrine and to the formal synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate from a common precursor. Extension of the structural diversity of the process has allowed the synthesis of several β-(+)-conhydrine analogs.

Introduction

Many structurally diverse alkaloids and compounds with therapeutically interesting biological activities possess a piperidine ring in their structures.[1] Among them, piperidines with a hydroxyalkyl substituent at C2 are abundant in nature and are of special interest due to their potent antiviral, antitumor and anti-HIV activities.[2]

In particular, 2-(1-hydroxyethyl)piperidines, conhydrines (Fig. 1), which are isolated from the seeds and leaves *Conium maculatum* L. (a poisonous plant, the extracts of which have been used throughout history to murder individuals), have attracted considerable interest from a synthetic point of view.[3]

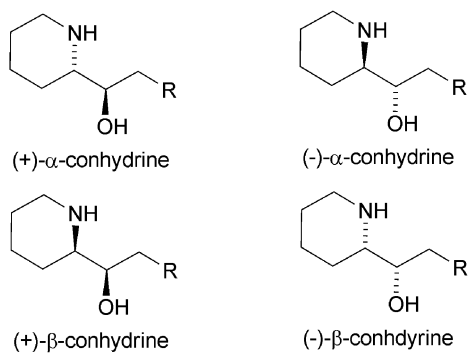

Fig. 1 Structures of the four conhydrine stereoisomers.

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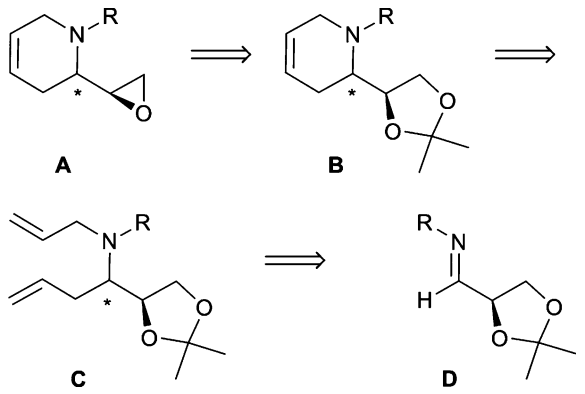
† Electronic supplementary information (ESI) available: Characterisation spectra for compounds **2–10** and crystal structure data for compound **9e**. CCDC reference number 837207. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06216f

Epoxide ring-opening using carbon nucleophiles is a common synthetic methodology for the preparation of hydroxyalkyl-substituted compounds.[4] In this context, (2*S*,2′*S*)-1-benzyloxycarbonyl-2-(2′-oxiranyl)piperidine has proven to be a useful intermediate in the asymmetric synthesis of (+)-α-conhydrine,[5] and (2*R*,4*R*,2*S*′)-4-acetamido-1-*tert*-butoxycarbonyl-2-(2′-oxiranyl)piperidine has proven to be a useful intermediate in the asymmetric synthesis of orthogonally protected 2-substituted 4-aminopiperidines.[6]

In the course of our research into the development of new stereocontrolled and versatile approaches to the synthesis of bioactive molecules from the chiral pool, we showed that easily accessible *N*-benzylimines derived from D-glyceraldehyde are excellent synthetic precursors to obtain compounds with very different structures.[6,7] We wish to discuss here the stereoselective synthesis of 2-(2′-oxiranyl)-1,2,3,6-tetrahydropiperidine derivatives from *N*-benzyl imines derived from D-glyceraldehyde acetonide. We also investigated the nucleophilic ring-opening of the epoxide with C-nucleophiles under different reaction conditions in an effort to achieve the asymmetric synthesis of piperidines with a hydroxyalkyl substituent at C2.

Results and discussion

Based on our previous results on the diastereoselective addition of allylmagnesium bromide to *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde[8] and the potential of the 2,2-dimethyl-1,3-dioxolan-4-yl moiety in the installation of different functional groups,[6] the proposed synthesis of the 2-(2′-oxiranyl)-1,2,3,6-tetrahydropyridine derivative **A** with a well defined stereochemistry relies on the following key steps: (a) diastereoselective addition of allylmagnesium bromide to *N*-benzylimines derived from D-glyceraldehyde acetonide **D**, (b) ring-closing metathesis to construct the piperidine ring and (c) appropriate stereoselective



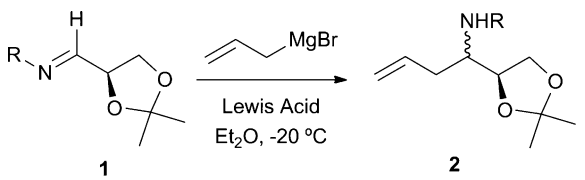
Scheme 1 Retrosynthesis approach to 2-(2′-oxiranyl)-1,2,3,6-tetrahydropyridine derivatives.

manipulation of the substituent at C2 in **B** (Scheme 1). Starting *N*-benzylimines can be obtained from D-glyceraldehyde acetonide, which is readily available on a gram scale from the inexpensive precursor D-mannitol,[9] according to previously described procedures.[10]

The first step of the proposed synthetic route involved a study of the nucleophilic addition of allylmagnesium bromide to imine **1a** under different reaction conditions (Table 1). This reaction allowed the creation of the stereogenic center at C2 in the target molecule.

When the reaction was performed in diethyl ether at –20 °C, homoallylamine ***syn*-2a** was obtained preferentially (*syn*/*anti* = 80/20). The presence of Lewis acids had a noticeable influence on the stereochemical course of the reaction. The presence of ZnI_2 in the reaction medium was detrimental in terms of diastereoselectivity (*syn*/*anti* = 68/32). When imine **1a** was pre-complexed with $BF_3{\cdot}OEt_2$ before the addition of the organometallic reagent, the opposite stereochemical course was observed and ***anti*-2a** was the major product (*syn*/*anti* = 13/87). This observation is consistent with previous results for $BF_3{\cdot}OEt_2$ precomplexation of the imine.[7e,10]

Table 1 Addition of allylmagnesium bromide to imine **1**



1 **2**

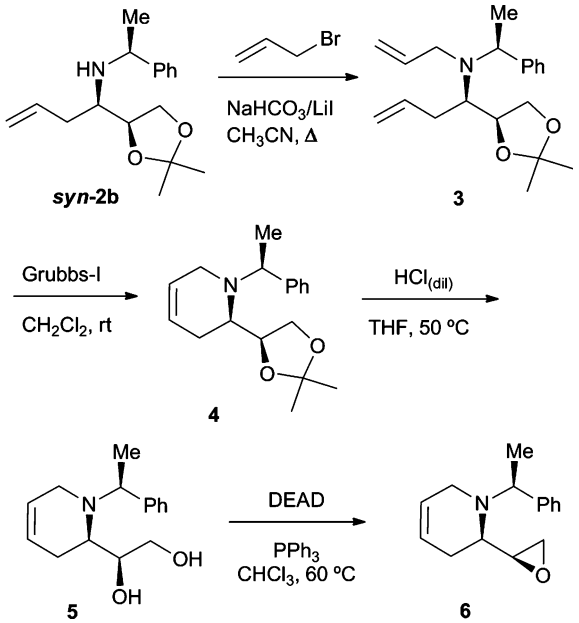
a: R = Bn
b: R = (*S*)-CH(CH$_3$)Ph
c: R = (*R*)-CH(CH$_3$)Ph

Imine	Lewis Acid	Product	Yield[a] (%)	*syn*/*anti*[b]
1a	none	**2a**	70	80/20
1a	ZnI_2	**2a**	60	68/32
1a	$BF_3{\cdot}OEt_2$	**2a**	72	13/87
1b	none	**2b**	80	>98/2
1b	$BF_3{\cdot}OEt_2$	**2b**	55	<2/98
1c	none	**2c**	70	80/20
1c	$BF_3{\cdot}OEt_2$	**2c**	53	9/91

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.

The use of imines **1b** and **1c** derived from chiral (*S*)-phenylethylamine and (*R*)-phenylethylamine, respectively, gave excellent (matched pair) to good (mismatched pair) diastereoselectivities. The use of imine **1b** as substrate gave diastereomerically pure ***syn*-2b** on addition of allylmagnesium bromide in diethyl ether at –20 °C. On the other hand, the addition of allylmagnesium bromide to the $BF_3{\cdot}OEt_2$ pre-complexed imine led to homoallylamine ***anti*-2b** with total diastereoselectivity. At this point compound ***syn*-2b** (isolated in 80% yield) was selected to proceed with the proposed synthetic route.

Ring-closing metathesis is nowadays a well-established synthetic strategy for the construction of nitrogen heterocycles[11] and it has already been applied to the formation of the piperidine ring in several previously described syntheses of conhydrines.[3,12] The required dialkene **3** was cleanly obtained in 87% yield by reaction of ***syn*-2b** with allyl bromide in acetonitrile using sodium hydrogen carbonate as base in the presence of lithium iodide. RCM performed on **3** using Grubbs' first generation catalyst led to tetrahydropyridine **4** in 87% yield. From this compound 2-(2′-oxiranyl)-1,2,3,6-tetrahydropyridine **6** was obtained in *ca.* 51% yield by deprotection of the diol moiety with HCl in THF–water followed by formation of the epoxide ring (Scheme 2).

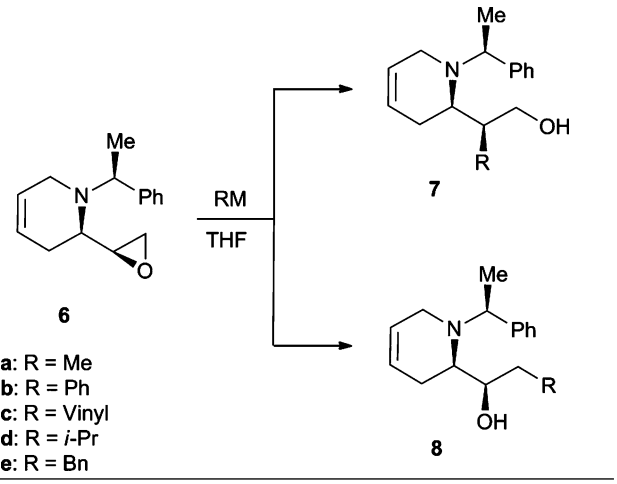


Scheme 2 Synthesis of 2-(2′-oxiranyl)-1,2,3,6-tetrahydropyridine **6**.

Deprotection smoothly led to diol **5** in nearly quantitative yield, but epoxide ring formation proved problematic. All attempts to perform the cyclization of tosylate or mesylate intermediates were unsuccessful and under Mitsunobu conditions;[13] the use of chloroform as solvent proved necessary to obtain epoxide **6**. When THF or toluene were used as reaction medium, the cyclization did not occur and the use of methylene chloride as solvent preferentially gave 2-(1,2-dichloroethyl)-1,2,3,6-tetrahydropyridine.

With diastereomerically pure **6** in hand we focused our attention on its use as a synthetic intermediate to obtain a range of stereochemically well defined 2-(1-hydroxalkyl)piperidines from a common precursor. To this end, regioselective cleavage of the epoxide ring with methyl organometallic reagents was first tested.

Table 2 Regioselective epoxide ring-opening



Entry	Nucleophilic system	Product	7/8[a]	Yield[b] (%)
1	MeMgBr	**7a**	>98/2	73
2	MeMgBr/CuBr(cat)	**8a**	<2/98	82
3	Me_2CuLi	**8a**	<2/98	61
4	PhMgBr	**7b**	>98/2	77
5	PhMgBr/CuBr(cat)	**8b**	<2/98	97
6	VinylMgBr	**7c**	>98/2	87
7	*i*-PrMgBr/CuBr(cat)	**8d**	<2/98	86
8	BnMgBr/CuBr(cat)	**8e**	<2/98	78

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

To our surprise, the reaction of epoxide **6** with methylmagnesium bromide—a strong nucleophile—yielded regioselectively 2-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridine derivative **7a**, which resulted from the nucleophile attacking the more substituted end of the epoxide with retention of configuration (entry 1, Table 2). In combination with a catalytic amount of cuprous bromide the attack of methylmagnesium bromide occurred as expected on the less substituted end of the epoxide (entry 2, Table 2) and the same behavior was observed when lithium dimethyl cuprate was used as the nucleophilic system (entry 3, Table 2). This was a general trend when organomagnesium reagents were used in combination with or in the absence of catalytic cuprous bromide (entries 4 and 6 *vs.* 5, 7 and 8, Table 2).

Examples of epoxide ring-opening with a strong nucleophile proceeding at the more substituted end of the epoxide are rare and retention of configuration in the attack is very unusual. A similar behavior has been observed in the reaction of epoxy sulfides,[14] epoxy selenides[15] and epoxy amines[16] with organoaluminium reagents or epoxy sulfides with phenylboronic acid,[17] but as far as we know, retention of configuration in the attack of organomagnesium reagents has not been described previously.

It has been previously reported[18] that under Lewis acidic conditions 2,3-epoxyamines can generate reactive aziridinium ions. To explain the formation of compounds **7a–c** we propose the formation of an intermediate aziridinium ion—by coordination of the organomagnesium reagent to the epoxide oxygen and attack of the nitrogen on the C2 of the epoxide from the back side—followed by the intramolecular attack of the nucleophile on the C2 of the aziridinium ion from the coordinated magnesium reagent from the back side. This mechanism would account for the formation

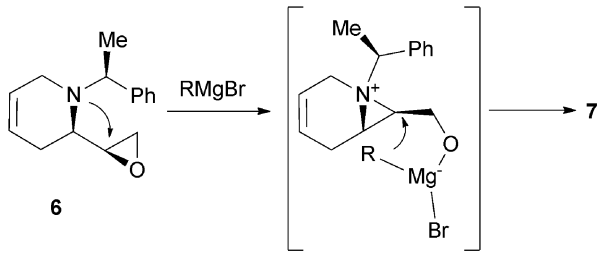
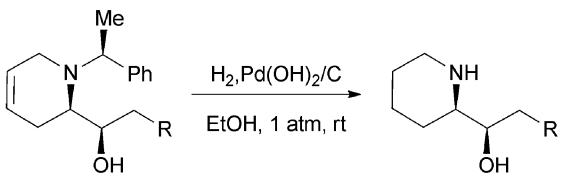


Fig. 2 Proposed model for epoxide ring-opening by organomagnesium reagents.

of compounds **7a–c** with neat retention of configuration (Fig. 2). This proposal is in accordance with that of Saigo *et al.*[16] for the reaction of 2,3-epoxyamines with organoaluminium reagents.

Exposure of compound **8a** to molecular hydrogen in the presence of catalytic $Pd(OH)_2/C$ led to enantiomerically pure β-(+)-conhydrine **9a** in 82% yield by hydrogenation of the unsaturated moiety with concomitant *N*-deprotection (Scheme 3). This methodology was extended to the synthesis of (+)-β-conhydrine analogs **9b** (81%), **9d** (80%) and **9e** (82%), which incorporate the 2-(1-hydroxyalkyl)piperidine pattern. The stereochemistry of the products was confirmed by physical and spectroscopic data for compound **9a** and also by single-crystal X-ray diffraction analysis of compound **9e**.



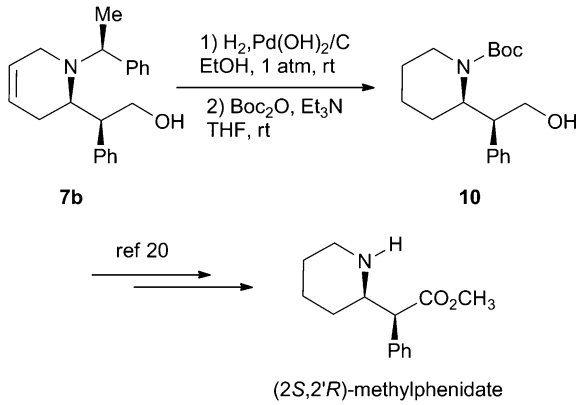
a: R = Me, 82%; **b**: R = Ph, 81%; **d**: R = *i*-Pr, 80%; **e**: R = Bn, 82%

Scheme 3 Synthesis of β-(+)-conhydrine and its analogs.

Some approaches to the synthesis of the psychostimulant drug for the treatment of attention-deficit hyperactivity disorder, (2*R*,2′*R*)-(+)-*threo*-methylphenidate (Ritalin®), are based on the enantioselective synthesis of (2*S*,2′*R*)-methylphenidate followed by epimerization.[19] Compound **7b** was transformed into compound **10**—a formal precursor of (2*S*,2′*R*)-methylphenidate[20]—by exposure to molecular hydrogen in the presence of catalytic $Pd(OH)_2/C$ followed by *tert*-butoxycarbonylation of the piperidine nitrogen by treatment with di-*tert*-butyl dicarbonate in the presence of a catalytic amount of triethylamine (Scheme 4). The physical and spectroscopic data for compound **10** are consistent with those previously described for the (2*S*,2′*R*)-diastereoisomer[20] and proved that epoxide ring-opening had occurred with retention of configuration.

Summary

In summary, we have developed a stereoselective and flexible methodology for the synthesis of structurally diverse 2-(1-hydroxyalkyl)- and 2-(2-hydroxyalkyl)piperidines with a well defined stereochemistry from a common precursor, epoxide **6**.



Scheme 4 Formal synthesis of (2*S*,2′*R*)-methylphenidate.

Epoxide ring-opening using Grignard-derived organocuprates exclusively occurred at the less substituted carbon of the epoxide ring whereas attack of Grignard reagents on the epoxide ring only took place at the more hindered carbon and with complete retention of configuration. Moreover, a wide variety of compounds can be easily obtained from epoxide **6** by changing the hydrocarbon chain of the organometallic reagent.

Experimental section

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Reactions were carried out using anhydrous solvents. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualized using UV light (254 nm), ninhydrin and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed using silica gel (Kiesegel 60, 230–400 Mesh). *N*-Benzylimines **1a–c** were prepared according to previously described procedures.[10]

Melting points were determined in open capillaries using a Gallenkamp capillary melting point apparatus and are not corrected. FTIR spectra of oils were recorded as thin films on NaCl plates and FTIR spectra of solids were recorded as nujol dispersions on NaCl plates using a Thermo Nicolet Avatar 360 FT-IR spectrometer, ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco 1020 polarimeter at λ 589 nm and 25 °C in a cell with 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} deg cm g^{-1} and concentrations are given in g/100 mL. ^1H NMR and ^{13}C NMR spectra were acquired on a Bruker AV-400 spectrometer or a Bruker AV-300 spectrometer operating at 400 or 300 MHz for ^1H NMR and 100 or 75 MHz for ^{13}C NMR at room temperature unless otherwise stated using a 5 mm probe. The chemical shifts (δ) are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. Coupling constants (J) are quoted in hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; m, multiplet; bs, broad singlet; ddd, doublet of doublets of doublets; dddd, doublet of doublet of doublets of doublets. High resolution mass spectra were recorded using a Bruker Daltonics MicroToF-Q instrument from methanolic solutions using the positive electrospray ionization mode (ESI+).

X-Ray diffraction

The X-ray diffraction data were collected at room temperature on an Oxford XCalibur diffractometer, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Reflections were measured in the $\theta/2\theta$-scan mode in the θ range 2.85 to 29.02°. The structure was solved by direct methods using SHELXS 97 and refinement was performed using SHELXL 97 by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. The hydrogen atom bonded to nitrogen was located on the difference Fourier map and refined with an isotropic thermal factor, all other hydrogen atoms were calculated at idealized positions, and during refinement they were allowed to ride on their carrying atom with an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom.

Colourless single crystals of **9e** were obtained by slow evaporation from an ethanol solution. Crystallographic data: crystal size $0.35 \times 0.15 \times 0.14$ mm^3. M = 219.32, crystal system orthorhombic, unit cell dimensions a = 6.3355(6) Å, b = 7.4390(8) Å, c = 26.291(2) Å, V = 1239.1(2) $Å^3$, T = 293(2) K, space group $P212121$, Z = 4, absorption coefficient μ(Mo-Kα) = 0.073 mm^{-1}, 21730 reflections measured, 2988 independent reflections (R_{int} = 0.1681) which were used in all calculations. Final R indices [$I > 2\sigma(I)$] R_1 = 0.0520, w$R(F^2)$ = 0.0762, R indices (all data) R_1 = 0.0944, w$R(F^2)$ = 0.0836.

General procedure for the addition of allylmagnesium bromide to chiral imines

Method A. A solution of the starting chiral imine **1a–c** (1.0 mmol) in dry Et_2O (1 mL) was slowly added to a stirred 1.0 M solution of allylmagnesium bromide in Et_2O (2 mL, 2.0 mmol) diluted with dry Et_2O (5 mL) under argon at –20 °C, and stirring was continued for 12 h at the same temperature. The reaction mixture was then quenched with water (5 mL), the organic phase separated and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the corresponding allylamine **2a–c**.

Method B. A solution of the starting chiral imine **1a–c** (1.0 mmol) in dry Et_2O (1 mL) was slowly added to a stirred solution of the corresponding Lewis acid (1.0 mmol) in dry Et_2O (5 ml) under argon at –20 °C. After stirring for 5 min at –20 °C a 1.0 M solution of allylmagnesium bromide in Et_2O (2 mL, 2.0 mmol) was slowly added under argon at –20 °C and stirring was continued for 12 h at the same temperature. The reaction mixture was then quenched with water (5 mL), the organic phase separated and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography yielded the corresponding allylamine **2a–c**.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-buten-1-amine (*syn*-2b). Following procedure A, treatment of imine **1b** (5.13 g, 22.0 mmol) with a 1.0 M solution of allylmagnesium bromide in Et_2O (44 mL, 4.0 mmol) yielded compound ***syn*-2b** as a single diastereoisomer. Purification of the crude product by silica gel column chromatography (eluent:

Et_2O/hexanes, 1 : 2) yielded compound ***syn*-2b** (4.85 g, 80%) as an oil. $[\alpha]^{D}_{25} = -10.5$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3340, 1639, 1602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.26 (d, *J* = 6.6, 3H), 1.27 (s, 3H), 1.71 (bs, 1H), 2.03–2.12 (m, 1H), 2.16–2.24 (m, 1H), 2.36 (ddd, *J* = 6.2, *J* = 6.2, *J* = 4.9, 1H), 3.60 (dd, *J* = 7.9, *J* = 7.3, 1H), 3.78 (dd, *J* = 7.9, *J* = 6.5, 1H), 3.85 (q, *J* = 6.6, 1H), 3.89–3.94 (m, 1H), 4.95–4.98 (m, 1H), 4.98–5.30 (m, 1H), 5.72 (dddd, *J* = 17.5, *J* = 10.3, *J* = 7.2, *J* = 7.2, 1H), 7.11–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (CH_3), 25.3 (CH_3), 26.4 (CH_3), 34.9 (CH_2), 54.8 (CH), 55.8 (CH), 66.4 (CH_2), 77.6 (CH), 108.7 (C), 117.2 (CH_2), 126.6 (CH), 126.7 (CH), 128.3 (CH), 135.1 (CH), 145.6 (C); HRMS (FAB$^+$) calcd for $C_{17}H_{26}NO_2$ (MH^+) 276.1958; found 276.1963.

(*S*)-*N*-[(*S*)-1-Phenylethyl]-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-buten-1-amine (*anti*-2b). Following procedure B, treatment of imine **1b** (233 mg, 1.0 mmol) precomplexed with $BF_3{\cdot}OEt_2$ (127 µL, 1.0 mmol) with a 1.0 M solution of allylmagnesium bromide in Et_2O (2 mL, 2.0 mmol) yielded compound ***anti*-2b** as a single diastereoisomer. Purification of the crude product by silica gel column chromatography (eluent: Et_2O/hexanes, 1 : 2) yielded compound ***anti*-2b** (151 mg, 55%) as an oil. $[\alpha]^{D}_{25} = +3.3$ (*c* 0.50, $CHCl_3$); IR absorptions (pure) ν_{max} 3332, 1639, 1602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.6, 3H), 1.27 (s, 3H), 1.36 (s, 3H), 2.00–2.14 (m, 2H), 2.57–2.62 (m, 1H), 3.74–3.81 (m, 1H), 3.82 (q, *J* = 6.6, 1H), 3.90–3.98 (m, 2H), 4.92–5.00 (m, 2H), 5.58 (dddd, *J* = 16.7, *J* = 10.5, *J* = 7.3, *J* = 7.3, 1H), 7.11–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2 (CH_3), 25.2 (CH_3), 26.6 (CH_3), 35.4 (CH_2), 55.7 (CH), 55.9 (CH), 66.8 (CH_2), 77.5 (CH), 108.7 (C), 117.8 (CH_2), 126.6 (CH), 126.8 (CH), 128.3 (CH), 135.1 (CH), 146.1 (C); HRMS (FAB$^+$) calcd for $C_{17}H_{26}NO_2$ (MH^+) 276.1958; found 276.1958.

(*R*)-*N*-Allyl-*N*-[(*S*)-1-phenylethyl]-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-buten-1-amine (3)

A mixture of ***syn*-2b** (3.30 g, 12.0 mmol), allyl bromide (2.18 g, 18.0 mmol), $NaHCO_3$ (2.52 g, 30.0 mmol) and LiI (160 mg, 1.2 mmol) in CH_3CN (30 mL) was heated under reflux for 36 h. Then the resulting reaction mixture was evaporated *in vacuo* and the residue partitioned between Et_2O (50 mL) and water (30 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by silica gel column chromatography (eluent: Et_2O/hexanes, 1 : 4) yielded compound **3** (3.53 g, 87%) as an oil. $[\alpha]^{D}_{25} = -6.2$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 1639; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.31 (d, *J* = 6.9, 3H), 1.33 (s, 3H), 1.74–1.82 (m, 1H), 1.89–1.97 m, 1H), 2.85 (ddd, *J* = 8.4, *J* = 6.6, *J* = 6.5, 1H), 3.11 (dddd, *J* = 15.1, *J* = 6.8, *J* = 1.2, *J* = 1.2, 1H), 3.50 (dddd, *J* = 15.1, *J* = 5.6, *J* = 1.7, *J* = 1.7, 1H), 3.72 (dd, *J* = 7.5, *J* = 5.9, 1H), 3.82 (dd, *J* = 7.5, *J* = 6.1, 1H), 4.01 (q, *J* = 6.9, 1H), 4.10 (ddd, *J* = 8.4, *J* = 6.1, *J* = 5.9, 1H), 4.79–4.86 (m, 1H), 4.83–4.89 (m, 1H), 4.98 (dddd, *J* = 10.2, *J* = 1.6, *J* = 1.6, *J* = 1.6, 1H), 5.08 (dddd, *J* = 17.1, *J* = 1.7, *J* = 1.7, *J* = 1.7, 1H), 5.61 (dddd, *J* = 17.0, *J* = 10.3, *J* = 7.1, *J* = 7.1, 1H), 5.82 (dddd, *J* = 17.1, *J* = 10.2, *J* = 6.8, *J* = 5.6, 1H), 7.11–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3), 25.4 (CH_3), 26.6 (CH_3), 33.2 (CH_2), 50.6 (CH_2), 57.2 (CH), 57.3 (CH), 67.1 (CH_2), 77.5 (CH), 108.3 (C), 115.4 (CH_2), 116.0 (CH_2), 126.6 (CH), 127.6 (CH), 128.0(CH), 136.7 (CH), 139.2 (CH), 144.6 (C); HRMS (FAB$^+$) calcd for $C_{20}H_{30}NO_2$ (MH^+) 316.2271; found 316.2259.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,2,3,6-tetrahydropyridine (4)

A solution of **3** (1.0 mmol) in CH_2Cl_2 (50 mL) was slowly added to a solution of Grubbs' first generation catalyst (823 mg, 1.0 mmol) in CH_2Cl_2 (200 mL) at room temperature. The resulting solution was stirred for 12 h at the same temperature and then evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (eluent: Et_2O/hexanes, 1 : 4) yielded compound **4** (2.67 g, 87%) as an oil. $[\alpha]^{D}_{25} = -17.2$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 1659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.42 (d, *J* = 6.5, 3H), 1.44 (s, 3H), 1.64–1.73 (m, 1H), 2.43–2.51 (m, 1H), 3.00–3.13 (m, 2H), 3.35–3.41 (m, 1H), 3.59 (dd, *J* = 8.0, *J* = 8.0, 1H), 3.98 (dd, *J* = 8.0, *J* = 6.2, 1H), 4.02 (q, *J* = 6.5, 1H), 4.48 (ddd, *J* = 8.1, *J* = 8.0, *J* = 6.2, 1H), 5.56–5.62 (m, 1H), 5.64–5.71 (m, 1H), 7.18–7.25 (m, 1H), 7.26–7.34 (m, 2H), 7.35–7.44 (m, 2H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 25.6 (CH_3), 26.6 (CH_3), 27.0 (CH_2), 45.4 (CH_2), 53.7 (CH), 61.0 (CH), 67.9 (CH_2), 74.5 (CH), 108.7 (C), 123.1 (CH), 126.1 (CH), 126.5 (CH), 127.2 (CH), 128.2 (CH), 146.8 (C); HRMS (FAB$^+$) calcd for $C_{18}H_{26}NO_2$ (MH^+) 288.1958; found 288.1962.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-1,2-dihydroxyethyl]-1,2,3,6-tetrahydropyridine (5)

A solution of **4** (2.58 g, 9.0 mmol) in THF (15 mL) was treated with a 2 N aqueous solution of HCl (15 mL) and stirred for 2 h at 50 °C. The reaction mixture was then evaporated *in vacuo* and the residue dissolved in Et_2O (50 mL). The organic solution was washed with 2 N aqueous solution of NaOH (20 mL) and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by silica gel column chromatography (1st eluent: Et_2O, 2nd eluent Et_2O/EtOH, 4 : 1) yielded compound **5** (2.20 g, 99%) as an oil. $[\alpha]^{D}_{25} = -21.9$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3373, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.6, 3H), 1.61–1.69 (m, 1H), 2.25–2.32 (m, 1H), 2.86 (dd, *J* = 10.2, *J* = 7.0, 1H), 3.33 (dd, *J* = 11.7, *J* = 3.9, 1H), 3.33–3.47 (m, 2H), 3.61 (ddd, *J* = 10.2, *J* = 3.9, *J* = 2.9, 1H), 3.70 (dd, *J* = 11.7, *J* = 2.8, 1H), 3.95 (q, *J* = 6.6, 1H), 5.67–5.75 (m, 1H), 5.73–5.80 (m, 1H), 7.21–7.29 (m, 1H), 7.27–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (CH_2), 21.6 (CH_3), 40.3 (CH_2), 52.9 (CH), 59.9 (CH), 63.2 (CH_2), 69.4 (CH), 124.1 (CH), 124.9 (CH), 127.1 (CH), 127.2 (CH), 128.5 (CH), 144.5 (C); HRMS (FAB$^+$) calcd for $C_{15}H_{22}NO_2$ (MH^+) 248.1645; found 248.1635.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-oxiran-2-yl]-1,2,3,6-tetrahydropyridine (6)

A solution of compound **5** (741 mg, 3.0 mmol), PPh_3 (943 mg, 3.6 mmol) and 40% solution in toluene of diethyl azodicarboxylate (1.57 g, 3.6 mmol) in dry $CHCl_3$ (60 mL) was stirred under argon at 60 °C until complete disappearance of **5** (monitored by TLC). In the event that some of starting material remained unaltered after 2 days a solution of PPh_3 (471 mg, 1.8 mmol) and 40% solution

in toluene of diethyl azodicarboxylate (785 mg, 1.8 mmol) in dry $CHCl_3$ (5 mL) was added at room temperature and the resulting reaction mixture stirred under argon at 60 °C for an additional 12h. Upon completion solvent was evaporated *in vacuo*. Purification of the crude product by silica gel column chromatography (eluent: Et_2O/hexanes) yielded compound **6** (350 mg, 51%) as an oil. $[\alpha]^D_{25} = -18.9$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 1666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.5, 3H), 1.95–2.02 (m, 1H), 2.28–2.35 (m, 1H), 2.44 (dd, J = 5.0, J = 2.7, 1H), 2.70 (dd, J = 5.0, J = 4.4, 1H), 2.78–2.85 (m, 1H), 2.87–3.02 (m, 2H), 3.14 (ddd, J = 7.2, J = 4.1, J = 2.8, 1H), 4.10 (q, J = 6.5, 1H), 5.48–5.55 (m, 1H), 5.58–5.66 (m, 1H), 7.11–7.20 (m, 1H), 7.18–7.28 (m, 2H), 7.29–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH_3), 28.5 (CH_2), 44.0 (CH_2), 45.6 (CH_2), 51.7 (CH), 55.0 (CH), 60.5 (CH), 123.0 (CH), 125.6 (CH), 126.6 (CH), 127.4 (CH), 128.2 (CH), 145.5 (C); HRMS (FAB$^+$) calcd for $C_{15}H_{20}NO$ (MH$^+$) 230.1539; found 230.1539.

General procedure for the addition of Grignard reagents to epoxide 6

A solution of the corresponding Grignard reagent (1.0 mmol) was slowly added to a solution of compound **6** (115 mg, 0.5 mmol) in dry THF (10 mL) under argon at room temperature and the mixture was stirred for 20 h. The reaction mixture was then quenched with water (10 mL) and extracted with diethyl ether Et_2O (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude products by silica gel column chromatography (eluent: Et_2O/hexanes, 1 : 1) yielded the corresponding tetrahydropyridine **7**.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-1-hydroxypropen-2-yl]-1,2,3,6-tetrahydropyridine (7a). Following the general procedure described above, **7a** (90 mg, 73%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with a 3 M solution of methylmagnesium bromide in dry THF (0.34 mL, 1.0 mmol). Oil, $[\alpha]^D_{25} = -10.2$ (*c* 0.78, $CHCl_3$); IR absorptions (pure) ν_{max} 3363; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 7.0, 3H), 1.26 (d, J = 6.7, 3H), 1.86–1.96 (m, 1H), 2.02–2.12 (m, 1H), 2.12–2.22 (m, 1H), 2.72 (ddd, J = 5.5, J = 5.5, J = 5.5, 1H), 2.94–3.11 (m, 2H), 3.49 (dd, J = 10.9, J = 5.4, 1H), 3.60 (dd, J = 10.9, J = 6.3, 1H), 4.20 (q, J = 6.7, 1H), 5.50–5.57 (m, 1H), 5.67–5.74 (m, 1H), 7.11–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3), 16.1 (CH_3), 23.2 (CH_2), 35.5 (CH), 42.6 (CH_2), 56.7 (CH), 57.9 (CH), 66.7 (CH_2), 124.6 (CH), 125.2 (CH), 126.8 (CH), 127.6 (CH), 128.2 (CH), 144.6 (C); HRMS (FAB$^+$) calcd for $C_{16}H_{24}NO$ (MH$^+$) 246.1852; found 246.1852.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-2-hydroxy-1-phenylethyl]-1,2,3,6-tetrahydropyridine (7b). Following the general procedure described above, **7b** (354 mg, 77%) was obtained by treatment of **6** (345 mg, 1.5 mmol) with a 3 M solution of phenylmagnesium bromide in dry Et_2O (1.00 mL, 3.0 mmol). Oil, $[\alpha]^D_{25} = +49.8$ (*c* 0.88, $CHCl_3$); IR absorptions (pure) ν_{max} 3398, 1652; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.6, 3H), 1.90–1.99 (m, 1H), 2.00 (bs, 1H), 2.21–2.32 (m, 1H), 2.90–2.98 (m, 1H) 2.98–3.09 (m, 2H), 3.15 (ddd, J = 8.1, J = 8.0, J = 5.3, 1H), 3.62 (dd, J = 10.9, J = 7.8, 1H), 3.82 (dd, J = 10.9, J = 5.3, 1H), 3.87 (q, J = 6.6, 1H), 5.55–5.62 (m, 1H), 5.66–5.74 (m, 1H), 7.03–7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1 (CH_3), 23.3 (CH_2), 41.9 (CH_2), 48.3 (CH), 55.2 (CH), 59.0 (CH), 65.0 (CH_2), 124.1 (CH), 126.1 (CH), 126.5 (CH), 126.7 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 141.5 (C), 145.2 (C); HRMS (FAB$^+$) calcd for $C_{21}H_{26}NO$ (MH$^+$) 308.2009; found 308.2020.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*S*)-1-hydroxy-3-buten-2-yl]-1,2,3,6-tetrahydropyridine (7c). Following the general procedure described above **7c** (112 mg, 87%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with a 1 M solution of vinylmagnesium bromide in dry THF (1.00 mL, 1.0 mmol). Oil, $[\alpha]^D_{25} = +4.9$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3405, 1852; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.6, 3H), 1.67–1.77 (m, 1H), 2.14–2.25 (m, 1H), 2.36–2.47 (m, 1H), 2.78 (ddd, J = 7.0, J = 7.0, J = 2.8, 1H), 3.02–3.19 (m, 2H), 3.25 (bs, 1H), 3.31 (dd, J = 10.8, J = 6.9, 1H), 3.59 (dd, J = 10.8, J = 4.8, 1H), 3.94 (q, J = 6.6, 1H), 5.02–5.07 (m, 1H), 5.06–5.11 (m, 1H), 5.48–5.56 (m, 1H), 5.60–5.69 (m, 1H), 5.72–5.83 (m, 1H), 7.08–7.16 (m, 1H), 7.15–7.24 (m, 2H), 7.22–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (CH_3), 23.3 (CH_2), 42.2 (CH_2), 47.8 (CH), 54.4 (CH), 59.0 (CH), 64.0 (CH_2), 116.7 (CH_2), 124.3 (CH), 125.3 (CH), 126.8 (CH), 127.4 (CH), 128.3 (CH), 138.6 (CH), 145.3 (C); HRMS (FAB$^+$) calcd for $C_{17}H_{24}NO$ (MH$^+$) 258.1852; found 258.1838.

General procedure for the addition of Grignard-derived organocuprate reagents to epoxide 6

A solution of the corresponding Grignard reagent (1.0 mmol) was added to a suspension of CuBr (14 mg, 0.1 mmol) in dry THF (4 mL) under argon at 0 °C and the mixture was stirred for 10 min at the same temperature. Then a solution of compound **6** (115 mg, 0.5 mmol) in dry THF (10 mL) was slowly added under argon at 0 °C and the mixture was stirred for 14 h at room temperature. The reaction mixture was quenched with water (10 mL) and extracted with diethyl ether Et_2O (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude products by silica gel column chromatography (eluent: Et_2O/hexanes, 1 : 1) yielded the corresponding tetrahydropyridine **8**.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*R*)-1-hydroxypropyl]-1,2,3,6-tetrahydropyridine (8a). Following the general procedure described above, **8a** (101 mg, 82%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with the organocuprate reagent obtained from catalytic CuBr and a 3 M solution of methylmagnesium bromide in dry THF (0.34 mL, 1.0 mmol). Oil, $[\alpha]^D_{25} = -10.4$ (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3399, 1602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3, 3H), 0.93–1.07 (m, 1H), 1.32 (d, J = 6.5, 3H), 1.35–1.49 (m, 1H), 1.52–1.64 (m, 1H), 2.06–2.18 (m, 1H), 2.44 (dd, J = 9.9, J = 7.1, 1H), 3.22–3.38 (m, 2H), 3.34–3.42 (m, 1H), 3.84 (q, J = 6.5, 1H), 4.01 (bs, 1H), 5.57–5.65 (m, 1H), 5.63–5.71 (m, 1H), 7.11-7.20 (m, 1H), 7.18-7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0 (CH_3), 20.4 (CH_2), 21.9 (CH_3), 26.8 (CH_2), 40.2 (CH_2), 57.1 (CH), 59.7 (CH), 69.7 (CH), 124.3 (CH), 124.8 (CH), 127.0 (CH), 127.2 (CH), 128.5 (CH), 144.8 (C); HRMS (FAB$^+$) calcd for $C_{16}H_{24}NO$ (MH$^+$) 246.1852; found 246.1841.

(*R*)-*N*-[(*S*)-1-Phenylethyl]-2-[(*R*)-2-phenyl-1-hydroxyethyl]-1,2,3,6-tetrahydropyridine (8b). Following the general procedure described above, **8b** (149 mg, 97%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with the organocuprate reagent obtained

from catalytic CuBr and a 3 M solution of phenylmagnesium bromide in dry Et_2O (0.34 mL, 1.0 mmol). Oil, $[\alpha]^D_{25}$ = +30.7 (*c* 1.00, $CHCl_3$); IR absorptions (pure) ν_{max} 3344, 1604;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.5, 3H), 1.69–1.79 (m, 1H), 2.17–2.29 (m, 1H), 2.38 (dd, *J* = 14.1, *J* = 8.1, 1H), 2.56 (dd, *J* = 9.6, *J* = 7.3, 1H), 2.75 (dd, *J* = 14.1, *J* = 2.7, 1H), 3.24–3.41 (m, 2H), 3.76 (ddd, *J* = 9.6, *J* = 8.1, *J* = 2.7, 1H), 3.87 (q, *J* = 6.5, 1H), 4.01 (bs, 1H), 5.62–5.69 (m, 1H), 5.70–5.78 (m, 1H), 7.09–7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_2), 21.7 (CH_3), 40.4 (CH_2), 40.5 (CH_2), 57.1 (CH), 59.8 (CH), 69.7 (CH), 124.1 (CH), 125.0 (CH), 125.9 (CH), 127.0 (CH), 127.1 (CH), 128.1 (CH), 128.5 (CH), 129.2 (CH), 139.1 (C), 144.6 (C); HRMS (FAB$^+$) calcd for $C_{21}H_{26}NO$ (MH^+) 308.2009: found 308.2012.

(*R*)-*N*-[(*S*)-1-1-Phenylethyl]-2-[(*R*)-1-hydroxy-3-methylbutyl]-1,2,3,6-tetrahydropyridine (8d). According to the general procedure described above **8d** (117 mg, 86%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with the organocuprate reagent obtained from catalytic CuBr and a 2 M solution of isopropylmagnesium bromide in dry Et_2O (0.50 mL, 1.0 mmol). Oil, $[\alpha]^D_{25}$ = –8.6 (*c* 0.50, $CHCl_3$); IR absorptions (pure) ν_{max} 3400, 1653;^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.7, 3H), 0.81 (d, *J* = 6.7, 3H), 0.95–1.05 (m, 2H), 1.32 (d, *J* = 6.5, 3H), 1.53–1.63 (m, 1H), 1.73–1.85 (m, 1H), 2.10–2.21 (m, 1H), 2.38 (dd, *J* = 9.8, *J* = 7.1, 1H), 3.22–3.38 (m, 2H), 3.44–3.51 (m, 1H), 3.84 (q, *J* = 6.5, 1H), 5.59–5.64 (m, 1H), 5.65–5.71 (m, 1H), 7.12–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_2), 21.6 (CH_3), 21.8 (CH_3), 24.1 (CH_3), 25.0 (CH), 40.2 (CH_2), 44.0 (CH_2), 58.2 (CH), 59.7 (CH), 66.7 (CH), 124.3 (CH), 124.9 (CH), 127.0 (CH), 127.2 (CH), 128.5 (CH), 144.8 (C); HRMS (FAB$^+$) calcd for $C_{18}H_{27}NO$ (MH^+) 274.2165; found 274.2153.

(*R*)-*N*-[(*S*)-1-1-Phenylethyl]-2-[(*R*)-1-hydroxy-3-methylbutyl]-1,2,3,6-tetrahydropyridine (8e). According to the general procedure described above **8e** (125 mg, 78%) was obtained by treatment of **6** (115 mg, 0.5 mmol) with the organocuprate reagent obtained from catalytic CuBr and a 1 M solution of benzylmagnesium bromide in dry Et_2O (1.00 mL, 1.0 mmol). Oil, $[\alpha]^D_{25}$ = –6.1 (*c* 0.70, $CHCl_3$); IR absorptions (pure) ν_{max} 3392, 1602;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.36 (m, 1H), 1.31 (d, *J* = 6.5, 3H), 1.50–1.59 (m, 1H), 1.59–1.69 (m, 1H), 2.06–2.17 (m, 1H), 2.45 (dd, *J* = 9.9, *J* = 7.0, 1H), 2.52 (ddd, *J* = 13.7, *J* = 11.0, *J* = 5.7, 1H), 2.75 (ddd, *J* = 13.7, *J* = 11.3, *J* = 5.0, 1H), 3.21–3.37 (m, 2H), 3.45–3.52 (m, 1H), 3.82 (q, *J* = 6.5, 1H), 4.04 (bs, 1H), 5.56–5.62 (m, 1H), 5.61–5.68 (m, 1H), 7.01–7.08 (m, 3H), 7.10–7.18 (m, 3H), 7.20–7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (CH_2), 21.8 (CH_3), 32.2 (CH_2), 36.4 (CH_2), 40.1 (CH_2), 57.4 (CH), 59.6 (CH), 68.3 (CH), 124.2 (CH), 124.8 (CH), 125.5 (CH), 127.1 (CH), 127.2 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 142.6 (C), 144.7 (C); HRMS (FAB$^+$) calcd for $C_{22}H_{28}NO$ (MH^+) 322.2165; found 322.2153.

General procedure for the hydrogenation of tetrahydropyridines 8

A solution of the corresponding tetrahydropyridines **8** (0.35 mmol) in EtOH (5 mL) was hydrogenated with molecular hydrogen for 14 h at atmospheric pressure and room temperature in the presence of 20% $Pd(OH)_2$/C (20 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad and the solvent evaporated *in vacuo* to afford the corresponding piperidine **9**.

(*R*)-2-[(*R*)-1-Hydroxypropyl]piperidine (9a). Following the general procedure described above, **9a** (41 mg, 82%) was obtained by hydrogenation of **8a** (86 mg, 0.35 mmol). Oil, $[\alpha]^D_{25}$ = +8.1 (*c* 1.00, EtOH) {lit[12e] $[\alpha]^D_{25}$ = +7.9 (*c* 0.6, EtOH), $[\alpha]^D_{25}$ = +8.3 (*c* 0.9, EtOH)}; IR absorptions (pure) ν_{max} 3316; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.4, 3H), 1.10–1.50 (m, 4H), 1.50–1.70 (m, 3H), 1.75–1.84 (m, 1H), 2.41 (ddd, *J* = 10.7, *J* = 7.9, *J* = 2.7, 1H), 2.59 (ddd, *J* = 12.1, *J* = 12.0, *J* = 2.8, 1H), 3.09–3.17 (m, 1H), 3.27 (ddd, *J* = 8.4, *J* = 8.4, *J* = 3.2, 1H), 3.99 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (CH_3), 23.9 (CH_2), 25.5 (CH_2), 26.3 (CH_2), 28.4 (CH_2), 46.0 (CH_2), 60.9 (CH), 74.8 (CH); HRMS (FAB$^+$) calcd for $C_8H_{18}NO$ (MH^+) 144.1383; found 144.1389.

(*R*)-2-[(*R*)-1-Hydroxy-2-phenylethyl]piperidine (9b). Following the general procedure described above, **9b** (58 mg, 81%) was obtained by hydrogenation of **8b** (107 mg, 0.35 mmol). M.p. 119 °C, $[\alpha]^D_{25}$ = +35.2 (*c* 1.20, $CHCl_3$); IR absorptions (pure) ν_{max} 3320; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.48 (m, 3H), 1.44–1.56 (m, 1H), 1.67–1.84 (m, 2H), 2.43–2.56 (m, 2H), 2.58 (dd, *J* = 13.8, *J* = 8.9, 1H), 2.87 (dd, *J* = 13.8, *J* = 3.4, 1H), 2.99–3.07 (m, 1H), 3.61 (ddd, *J* = 8.9, *J* = 8.8, *J* = 3.4, 1H), 4.37 (bs, 2H), 7.16–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (CH_2), 24.8 (CH_2), 28.0 (CH_2), 39.9 (CH_2), 45.7 (CH_2), 60.6 (CH), 74.2 (CH), 126.2 (CH), 128.3 (CH), 129.5 (CH), 138.6 (C); HRMS (FAB$^+$) calcd for $C_{13}H_{20}NO$ (MH^+) 206.1539; found 206.1547.

(*R*)-2-[(*R*)-1-Hydroxy-3-methylbutyl]piperidine (9d). Following the general procedure described above, **9d** (48 mg, 80%) was obtained by hydrogenation of **8d** (96 mg, 0.35 mmol). Oil, $[\alpha]^D_{25}$ = +34.4 (*c* 1.70, $CHCl_3$); IR absorptions (pure) ν_{max} 3314; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.6, 3H), 0.87 (d, *J* = 6.7, 3H), 0.97–1.40 (m, 5H), 1.48–1.55 (m, 1H), 1.55–1.63 (m, 1H), 1.68–1.76 (m, 1H), 1.76–1.87 (m, 1H), 2.21 (ddd, *J* = 10.3, *J* = 7.6, *J* = 2.4, 1H), 2.50 (ddd, *J* = 11.8, *J* = 11.7, *J* = 2.5, 1H), 2.98–3.05 (m, 1H), 3.29 (ddd, *J* = 10.0, *J* = 7.6, *J* = 2.5, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 24.0 (CH_3), 24.3 (CH_2), 24.5 (CH), 26.1 (CH_2), 29.1 (CH_2), 43.0 (CH_2), 46.4 (CH_2), 61.8 (CH), 71.9 (CH); HRMS (FAB$^+$) calcd for $C_{10}H_{22}NO$ (MH^+) 144.1383; found 144.1389.

(*R*)-2-[(*R*)-1-Hydroxy-3-phenylpropyl]piperidine (9e). Following the general procedure described above, **9e** (63 mg, 82%) was obtained by hydrogenation of **8e** (112 mg, 0.35 mmol). M.p. 117 °C, $[\alpha]^D_{25}$ = +24.6 (*c* 0.95, $CHCl_3$); IR absorptions (pure) ν_{max} 3312, 3171; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.37 (m, 3H), 1.45–1.64 (m, 3H), 1.67–1.82 (m, 2H), 2.28 (ddd, *J* = 10.3, *J* = 8.0, *J* = 2.3, 1H), 2.50 (ddd, *J* = 11.8, *J* = 11.7, *J* = 2.3, 1H), 2.59 (ddd, *J* = 13.8, *J* = 9.9, *J* = 6.7, 1H), 2.83 (ddd, *J* = 14.6, *J* = 10.1, *J* = 4.8, 1H), 2.98–3.06 (m, 1H), 3.22 (ddd, *J* = 9.9, *J* = 7.7, *J* = 2.5, 1H), 7.07–7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3 (CH_2), 26.3 (CH_2), 29.0 (CH_2), 32.1 (CH_2), 35.4 (CH_2), 46.4 (CH_2), 61.3 (CH), 73.3 (CH), 125.7 (CH), 128.3 (CH), 128.4 (CH), 142.3 (C); HRMS (FAB$^+$) calcd for $C_{14}H_{22}NO$ (MH^+) 220.1696; found 220.2691.

(*R*)-*N*-[*tert*-Butoxycarbonyl]-2-[(*S*)-2-hydroxy-1-phenylethyl]piperidine (10)

A solution of compound **8b** (307 mg, 1.0 mmol) in EtOH (15 mL) was hydrogenated with molecular hydrogen for 14 h at atmospheric pressure and room temperature in the presence of

20% $Pd(OH)_2/C$ (60 mg) as a catalyst. The catalyst was removed by filtration through a Celite® pad, washed with ethanol (2 × 10 mL) and the solvent was evaporated *in vacuo*. The resulting compound, triethylamine (121 mg, 1.2 mmol) and di-*tert*-butyl dicarbonate (436 mg, 2.0 mmol) were dissolved in THF (10 mL) and the mixture was stirred for 16 h at room temperature. The reaction mixture was evaporated *in vacuo* and the crude product was purified by column chromatography (eluent: Et_2O/hexanes, 3 : 2) to yield compound **10** (259 mg, 85%) as an oil. $[\alpha]^{D}_{25}$ = +52.7 (*c* 1.06, CH_2Cl_2) {lit[20] $[\alpha]^{D}_{25}$ = +52.3 (*c* 1.06, CH_2Cl_2)}; IR absorptions (pure) ν_{max} 3340, 1685, 1664; ^{1}H NMR (300 MHz, 333 K, $CDCl_3$) δ 1.32 (s, 9H), 1.20–1.98 (m, 6H), 2.61 (ddd, J = 13.7, J = 12.8, J = 3.7, 1H), 3.24 (ddd, J = 9.8, J = 7.4, J = 5.6, 1H), 3.72–3.92 (m, 3H), 4.52–4.61 (m, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 19.2 (CH_2), 25.1 (CH_2), 26.9 (CH_2), 28.3 (3 × CH_3), 39.4 (CH_2), 48.5 (CH), 51.6 (CH), 65.0 (CH_2), 79.1 (C), 126.9 (CH), 128.3 (CH), 129.0 (CH), 139.7 (C), 154.9 (C); HRMS (FAB$^+$) calcd for $C_{18}H_{28}NO_3$ (MH^+) 328.1883; found 328.1883.

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