Stereocontrolled synthesis of orthogonally protected 2-substituted 4-aminopiperidines†

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Received 11th March 2009, Accepted 23rd April 2009
First published as an Advance Article on the web 27th May 2009
DOI: 10.1039/b904948g

Expedient and highly stereoselective routes to orthogonally protected chiral 2-substituted 4-aminopiperidines have been developed. Diastereoselective nucleophilic substitution of the hydroxy group of (2*R*,4*S*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-hydroxy-1-[(*S*)-1-phenylethyl]piperidine using sodium azide afforded the corresponding azido derivative, which could be reduced and selectively protected to give (2*R*,4*R*)-1-*tert*-butoxycarbonyl-2-[(*S*)-1,2-dibenzyloxyethyl]-4-acetylaminopiperidine. This compound was easily converted into optically active 2-substituted 4-aminopiperidines using different synthetic methodologies such as epoxide nucleophilic ring opening reactions and Wittig olefination reactions among others.

Introduction

Compounds containing 4-aminopiperidine as a structural motif have shown a wide variety of biological activities. Fentanyl and its analogues are extensively used for anesthesia and analgesia due to their exceptional analgesic potency.[1] 4-Aminopiperidines with different substitution patterns have been evaluated as serotonin and norepinephrine re-uptake inhibitors[2] to treat neurological diseases, as CCR5 chemokine receptor ligands[3] to be used as anti-HIV agents, as melanin concentrating hormone agonists[4] for treatment of obesity, as potent antimalarial compounds effective against *Plasmodium falciparum*,[5] or as N-type calcium channel blockers[6] to treat neuropathic pain. This structural motif is also present in selective inhibitors of protein kinases,[7] platelet activation factor receptor antagonists,[8] selective agonist of the human β_3-adrenergic receptor[9] or useful drugs for treatment of diseases associated with dipeptidyl peptidase IV[10] among others.

Although different approaches to the stereoselective synthesis of substituted piperidines have been developed[11] most of them involve approaches specific to the synthesis of a target molecule and the development of general synthetic methodologies in which preformed chiral non-racemic building blocks are used for the construction of a wide variety of simple or complex structures is less common. So the development of new and general routes for the synthesis of these classes of molecules from a single precursor is of considerable importance.

In this manuscript we wish to illustrate the potential of the chiral intermediate (*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (**1**) for the synthesis of diversely 2-substituted *trans* 4-aminopiperidines in enantiomerically pure form using different synthetic strategies.

Results and discussion

Synthetic strategy

As part of a programme aimed at the design and preparation of polyfunctionalised chiral building blocks that are useful for the asymmetric synthesis of biologically active nitrogen-containing compounds, in recent years we have studied the behaviour of (*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]-2,3-dihydro-4(1*H*)-pyridone (**1**) as a synthetic precursor. Under optimised reaction conditions [low temperature, acetonitrile as solvent, ZnI_2 as Lewis acid] enaminone **1** is easily obtained as a single diastereomer on a gram scale from inexpensive D-mannitol,[12] which comes from renewable sources.

This chiral compound has proven to be a versatile intermediate in the synthesis of enantiomerically pure pipecolic acid derivatives,[13] (*R*)- and (*S*)-2-substituted-4-alkylidenepiperidines,[14] *cis*- and *trans*-2,4-disubstituted piperidines[15] and *cis*- and *trans*-2,3-disubstituted-2,3-dihydro-4(1*H*)-pyridones.[16]

Compound **1** can be stereoselectively reduced to (2*R*,4*S*)-2-[(S)-1,2-dibenzyloxyethyl]-4-hydroxy-1-[(S)-1-phenylethyl]piperidine (**2**) using sodium borohydride,[13b] so the introduction of an azido group could be achieved by nucleophilic substitution of the 4-hydroxy group in compound **2**. The resulting 4-azido compound could be used as a precursor in the synthesis of chiral 2-substituted 4-aminopiperidines (Fig. 1).

Highly stereoselective introduction of the acetamido moiety at C4

The introduction of the acetamido moiety at C4 was performed by nucleophilic substitution and subsequent reduction. The target azido derivative **4** was obtained in enantiomerically pure form from compound **2** in a two-step procedure similar to that described by Machetti *et al.* for related racemic substrate.[17] The hydroxy group at the C4 position was first converted into a good leaving group by treatment with methanesulfonyl chloride in a basic

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† Electronic supplementary information (ESI) available: Characterisation spectra for compounds **3**, **4**, **5**, **6**, **7**, **8**, **10**, **11**, **12**, **13**, **14** and **15**; noesy spectra for compounds **4** and **5**; crystal structure data for compound **3**. CCDC reference number 723555. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904948g

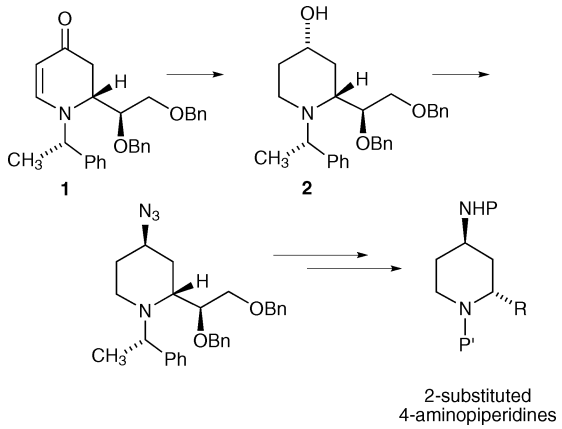
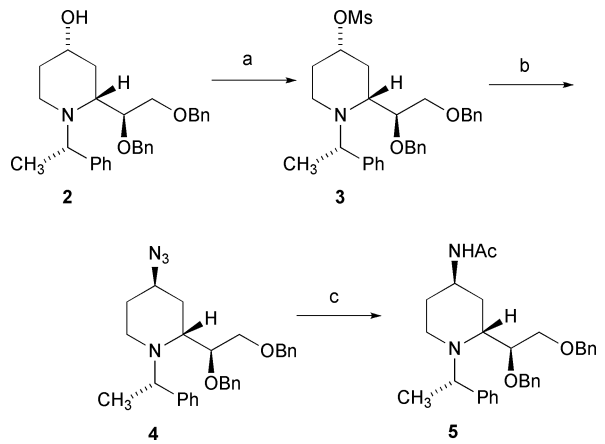


Fig. 1 Synthetic strategy for chiral 2-substituted 4-aminopiperidines.

medium. The configuration of the resulting mesylate **3** was found by X-ray crystallography† to be that shown in Scheme 1. Subsequent reaction of compound **3** with sodium azide in dry DMF at 85 °C led to azido compound **4** with inversion of configuration at C4 in *ca* 72% yield for the two steps.



Scheme 1 *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 5 h, rt (80%); (b) NaN_3, DMF, 12 h, 85 °C (89%); (c) Ac_2O, Et_3N, H_2, Pd/C, AcOEt, 12 h, rt, 1 atm. (70%).

Finally, exposure of **4** to an atmosphere of hydrogen in the presence of acetic anhydride, using palladium on charcoal as catalyst, caused simultaneous azide reduction/*N*-acetylation to give the desired compound **5** as a single diastereomer in 70% yield. These reactions are shown in Scheme 1

Both the ^{1}H NMR and ^{13}C NMR spectra of compounds **4** and **5** showed only one set of signals and these corresponded to two chair conformers in rapid equilibrium. The assignment of the relative stereochemistry of compounds **4** and **5** was made on the basis of their ^{1}H NMR spectra and the *trans* disposition of the two substituents in these compounds was deduced on the basis of noesy experiments‡ (Fig. 2).

‡ NOESY spectra were acquired in the phase sensitive mode with gradient pulses in the mixing time as 2048 × 256 hypercomplex files with 8 transients for 256 time increments. A mixing time of 600 ms was used and processing was carried out using a sine-bell squared function shifted by π/2 and a states-TPPI method. Special precautions such as degassing of the sample were not taken.

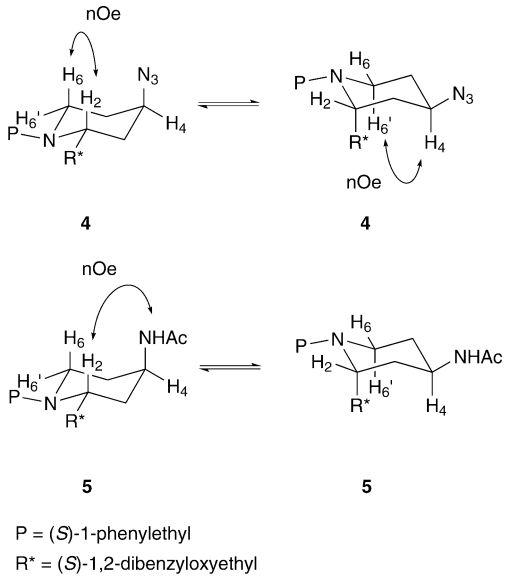


Fig. 2 Diagnostic nOe cross-peaks for the unambiguous determination of the configurations of compounds **4** and **5**.

In the ^{1}H NMR spectrum of compound **4** it is possible to unambiguously assign the H_6 and $H_{6'}$ resonances as those at *ca* 2.60 and 2.50 ppm, respectively, as the resonance due to H_6 clearly shows a cross-peak with the H_2 resonance (*ca* 3.20 ppm) in the noesy spectrum. In turn, $H_{6'}$ shows a clear cross-peak with the H_4 resonance (*ca* 3.90 ppm), indicating the *cis* relationship between these two nuclei and the *trans* disposition of the C2 and C4 substituents on the piperidine ring. On the other hand, in the noesy spectrum of compound **5** the cross-peak observed between H_2 and the NH resonance clearly shows the *cis* relationship between these two nuclei. This situation results from a *trans* disposition between the C2 and C4 substituents on the piperidine ring.

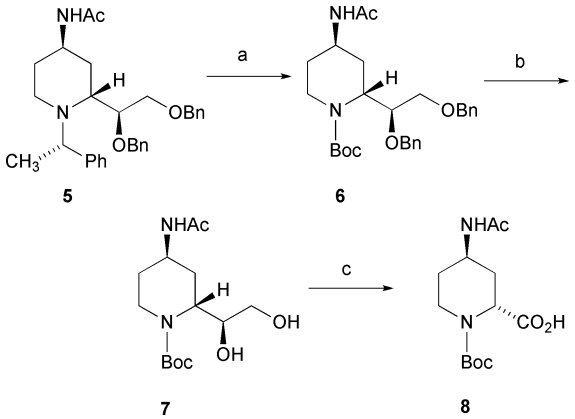
Transformation of the 1,2-dihydroxy moiety into achiral C2 substituents

The synthetic potential of substrate **5** is derived from manipulation of the 1,2-dibenzyloxy moiety at C2 as this can be easily transformed into a wide variety of functional groups.

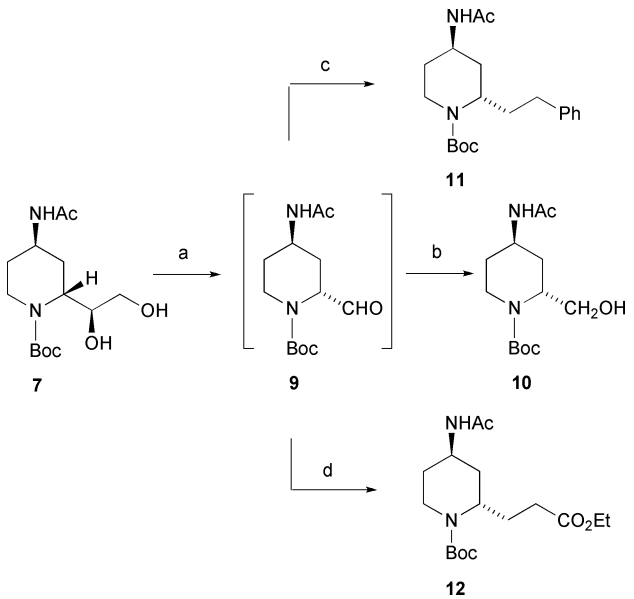
Selective *N*-debenzylation/*N*-*tert*-butoxycarbonylation of compound **5** was performed by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate using palladium hydroxide on charcoal as the catalyst.

This protocol gave compound **6**, which was subsequently *O*-debenzylated by hydrogenolysis in the presence of a catalytic amount of palladium hydroxide to afford diol **7** in 98% yield. The oxidative cleavage of the diol moiety in compound **7** to the carboxylic acid was performed under similar conditions to those described previously for the synthesis of pipecolic acid derivatives.[13] In this way, treatment of **7** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ provided the pipecolic acid derivative **8** in 65% yield, as shown in Scheme 2.

Oxidative cleavage of diol **7** with $NaIO_4$ led to the formation of aldehyde **9** and this was used without purification. Firstly, reduction of the carbonyl group with sodium borohydride cleanly afforded 4-acetamido-*N*-*tert*-butoxycarbonyl-2-hydroxymethylpiperidine **10** in excellent 98% yield (Scheme 3).



Scheme 2 *Reagents and conditions*: (a) Boc_2O, EtOH, H_2, $Pd(OH)_2/C$, 3 h, rt, 1 atm. (83%); (b) H_2, $Pd(OH)_2/C$, EtOH, 17 h, rt, 1 atm. (98%); (c) $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$, 2 h, rt. (65%).



Scheme 3 *Reagents and conditions*: (a) $NaIO_4$, CH_3OH, 45 min, rt; (b) $NaBH_4$, EtOH, 30 min, rt (98% from **7**); (c) (i) Ph_3PCH_2PhCl, $NaOCH_3$, 1 h, rt (ii) H_2, Pd/C, EtOH, 30 min, rt, 1 atm. (86% from **7**); (d) (i) $Ph_3PCH_2CO_2EtCl$, $NaOCH_3$, 2 h, rt (ii) H_2, Pd/C, EtOH, 30 min, rt, 1 atm. (53% from **7**).

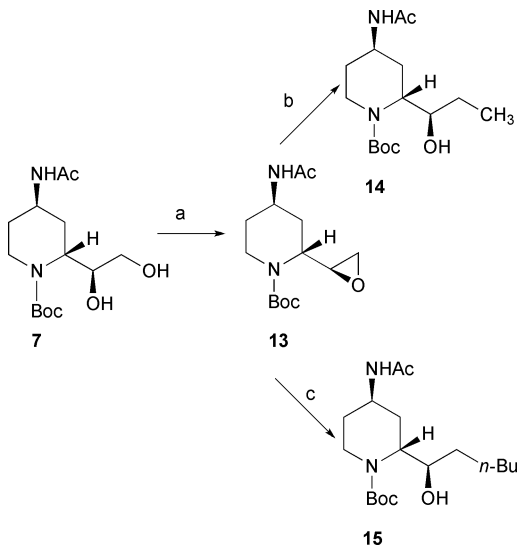
Wittig olefination is widely recognized as one of the most useful synthetic methodologies for the creation of C–C bonds from carbonyl compounds. The behavior of aldehyde **9** towards several phosphoranes was studied in order to evaluate the versatility of this methodology to gain access to new 2-substituted 4-aminopiperidines. The reaction of **9** with the semi-stabilized ylide benzylidenetriphenylphosphorane involved treatment of benzylidenetriphenylphosphonium chloride with sodium methoxide in benzene at room temperature and subsequent addition of the carbonyl compound to the reaction mixture. This protocol gave the corresponding unsaturated compound as a 67/33 mixture of *E*/*Z* diastereomers, which was cleanly hydrogenated at room temperature and atmospheric pressure in the presence of a catalytic amount of palladium on charcoal to afford compound **11** in 86% yield from diol **7**.

The reaction of aldehyde **9** with the stabilized ylide ethoxycarbonyltriphenylphosphorane under identical reaction conditions led to an 85/15 mixture of *E*/*Z* diastereomers which, upon hydrogenation at room temperature and atmospheric pressure in the presence of a catalytic amount of palladium on charcoal, afforded compound **12** in acceptable yield, 53%, from diol **7** (Scheme 3). In all cases the spatial disposition of stereogenic centers remained unchanged under the different reaction conditions and **6–12** were obtained as enantiomerically pure compounds.

Transformation of the 1,2-dihydroxy moiety into chiral C2 substituents

The 1,2-dibenzyloxy moiety at C2 can be considered as a masked oxirane ring that can be opened with organometallic compounds to provide a variety of chiral hydroxylated substituents. With this aim in mind, diol **7** was treated with triphenylphosphine and diethyl azodicarboxylate under Mitsunobu reaction conditions[18] but, unfortunately, diol **7** was recovered unchanged. Finally, diol **7** was converted into epoxide **13** in a two-step procedure consisting of activation of the primary hydroxy group by reaction with *p*-toluenesulfonyl chloride and subsequent cyclization in a basic medium.

In order to prove the versatility of the proposed synthetic strategy, the reaction of epoxide **13** with some lithium dialkylcuprate reagents was tested. Treatment of **13** with lithium dimethylcuprate gave rise to the regioselective cleavage of the epoxide ring to provide alcohol **14** in 89% yield. Alternatively, regioselective cleavage of the epoxide ring in compound **13** with lithium di-*n*-butylcuprate gave compound **15** as a single product in 60% yield. These reactions are represented in Scheme 4. This synthetic protocol allows the preparation of enantiomerically pure 4-aminopiperidines bearing a chiral 1-hydroxyalkyl chain at C2. This structural feature is present in many biologically active alkaloids derived from piperidine.



Scheme 4 *Reagents and conditions*: (a) (i) $^nBu_2SnO$, Et_3N, TsCl, CH_2Cl_2, 7 h, rt (ii) K_2CO_3, CH_3OH, 0 °C, then 1 h, rt (85%); (b) $(CH_3)_2CuLi$, Et_2O, 1 h, −35 °C (89%) (c) $(n\text{-Bu})_2CuLi$, Et_2O, 1 h, −35 °C (60%).

Conclusions

In summary, the chemistry described above provides a convenient, efficient and versatile method for the stereoselective synthesis of orthogonally protected chiral *trans*-2-substituted-4-aminopiperidines and such compounds are potentially biologically active. Changes in the configuration of stereogenic centers generally induce significant changes in the specificity or potency of biologically active compounds and so the extension of the synthetic methodologies described here to the stereoselective synthesis of *cis* 2-substituted-4-aminopiperidines is now in progress and will be published in due course.

Experimental

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 thin layer chromatography (TLC). TLC was performed on pre-coated silica gel polyester plates and products were visualised using UV light (254 nm) and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed using silica gel (Kiesegel 60, 230–400 mesh). (2*R*,4*S*)-2-[(*S*)-1,2-dibenzyloxyethyl]-4-hydroxy-1-[(*S*)-1-phenylethyl]piperidine (**2**) was prepared according to the previously described procedures.[12,13b]

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. Microanalyses were determined using a Perkin-Elmen 2400 CHNS elemental analyser. ^{1}H 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 ^{1}H NMR and 100 or 75 MHz for ^{13}C NMR at room temperature or 333 K in $CDCl_3$ using a 5 mm probe. The chemical shifts (δ) are reported in parts per million and were referenced to the residual solvent peak The coupling constants (*J*) are quoted in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal; bd, broad doublet; dd, doublet of doublets, ddd, doublet of doublet 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 a four circle Siemens P-4 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 1.6 to 28.3°. The structure was solved by direct methods using SIR92[19] and refinement was performed using SHELXL 97[20] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. 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 (1.5 for the methyl protons).

Colourless single crystals of **3** were obtained by slow evaporation from an ethanol solution. Crystallographic data: crystal size 0.44 × 0.40 × 0.36 mm^3. M = 523.67, crystal system monoclinic, unit cell dimensions a = 10.0148(6), b = 10.6959(7), c = 12.9949(8) Å, α = 90°, β = 102.575(10)°, γ = 90°, V = 1358.59(15) $Å^3$, T = 293(2) K, space group P21, absorption coefficient μ (Mo-Kα) = 0.159 mm^{-1}, 16360 reflections collected 6243 unique [R(int) = 0.0223] which were used in all calculations. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0401, $wR2$ = 0.1018 R indices (all data) $R1$ = 0.0418, $wR2$ = 0.1028.

(2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-4-mesyloxy-1-[(*S*)-1-phenylethyl]piperidine (3). A solution of methanesulfonyl chloride (0.87 mL, 1.29 g, 11.24 mmol) in dry CH_2Cl_2 (7 mL) was added dropwise to a solution of compound **2** (4.17 g, 9.37 mmol) and Et_3N (1.57 mL (1.14 g), 11.24 mmol) in dry CH_2Cl_2 (60 mL) at 0 °C under argon. The solution was allowed to warm up to room temperature and, after stirring for 5 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (Eluent: Et_2O/hexane; 1:1) gave 3.93 g (80% yield) of compound **3** as a white solid; mp 99–101 °C; $[\alpha]^D_{23}$ = −2.9 (*c* 1.0 $CHCl_3$); IR absorption (nujol) 1353, 1175 cm^{-1}; ^{1}H NMR (400 MHz, room temperature, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 3H), 1.40–1.56 (m, 2H), 1.88–1.95 (m, 1H), 2.08 (ddd, J = 12,1 Hz, J = 12,1 Hz, J = 2.4 Hz, 1H), 2.45 (ddd, J = 12,1 Hz, J = 3.6 Hz, J = 3.6 Hz, 1H), 2.44–2.50 (m, 1H), 2.79 (ddd, J = 11.2 Hz, J = 4.5 Hz, J = 2.4 Hz, 1H), 2.97 (s, 3H), 3.67 (dd, J = 10.5 Hz, J = 7.5 Hz, 1H), 4.03 (dd, J = 10.5 Hz, J = 1.2 Hz, 1H), 4.06–4.13 (m, 2H), 4.47–4.57 (m, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 7.26–7.42 (m, 15H); ^{13}C NMR (75 MHz, room temperature, $CDCl_3$) δ 8.2, 32.7, 32.8, 39.0, 42.6, 53.8, 57.6, 70.8, 72.8, 73.6, 76.9, 80.3, 126.6, 127.4, 127.7, 127.8, 128.1, 128.4, 128.4, 138.1, 138.6, 143.1, Elemental analysis calcd (%) for $C_{30}H_{37}NO_5S$: C, 68.81; H, 7.12; N, 2.67; S, 6.12; found: C, 68.96; H, 7.21; N, 2.64; S, 6.23.

(2*R*,4*R*)-4-Azido-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine (4). NaN_3 (831 mg, 12.79 mmol) was added to a solution of **3** (3.345 g, 6.39 mmol) in dry DMF (50 mL) and the mixture was stirred at 85 °C for 12 h. The reaction mixture was allowed to cool, then EtOAc (100 mL) was added and the resulting solution was washed with saturated aqueous NaCl solution (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification of the residue by flash chromatography (Eluent: Et_2O/hexane; 1:4) gave 2.67 g (89% yield) of compound **4** as an oil; $[\alpha]^D_{24}$ = +7.6 (*c* 1.0 $CHCl_3$); IR absorption (nujol) 2094 cm^{-1}; ^{1}H NMR (400 MHz, room temperature, $CDCl_3$) δ 1.26 (d, J = 6.8 Hz, 3H), 1.45–1.58 (m, 3H), 2.04 (ddd, J = 13.2 Hz, J = 6.5 Hz, J = 3.8 Hz, 1H), 2.48 (ddd, J = 12.7 Hz, J = 6.1 Hz, J = 4.3 Hz, 1H), 2.60 (ddd, J = 12.7 Hz, J = 7.6 Hz, J = 4.3 Hz, 1H), 3.08–3.14 (m, 1H), 3.64 (dd, J = 10.5 Hz, J = 6.8 Hz, 1H), 3.83 (dd, J = 10.5 Hz, J = 2.3 Hz, 1H), 3.85–3.91 (m, 1H), 3.96–4.01

(m, 1H), 4.05 (c, $J = 6.8$ Hz, 1H), 4.50 (d, $J = 12.1$ Hz, 1H), 4.57 (d, $J = 12.1$ Hz, 1H), 4.68 (d, $J = 11.7$ Hz, 1H), 4.80 (d, $J = 11.7$ Hz, 1H), 7.18–7.42 (m, 15H); ^{13}C NMR (100 MHz, room temperature, $CDCl_3$) δ 13.5, 28.8, 29.8, 40.5, 54.4, 56.2, 56.2, 71.4, 72.9, 73.4, 78.4, 126.6, 127.4, 127.5, 127.5, 127.6, 127.9, 128.0, 128.3, 128.4, 138.2, 138.7, 144.7, HRMS (ESI+): m/z [M + H$^+$] calcd for $C_{29}H_{35}N_4O_2$: 471.2754; found 471.2728.

(2*R*,4*R*)-4-Acetamido-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine (5). Et_3N (1.2 mL, 0.86 g, 8.53 mmol), Ac_2O (0.64 mL, 0.695 g, 6.80 mmol) and Pd/C (130 mg) was added successively to a solution of **4** (2.67 g, 5.67 mmol) in EtOAc (65 mL) and the resulting mixture was stirred at room temperature under hydrogen at atmospheric pressure for 12 h. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluents: CH_2Cl_2; CH_2Cl_2/EtOH; 9:1) gave 1.94 g (70% yield) of compound **5** as an oil; $[\alpha]^D_{22} = -27.1$ (*c* 1.0 $CHCl_3$); IR absorption (nujol) 3293, 1645 cm^{-1}; ^{1}H NMR (400 MHz, room temperature, $CDCl_3$) δ 1.29 (d, $J = 6.6$ Hz, 3H), 1.32–1.42 (m, 1H), 1.56–1.63 (m, 1H), 1.63–1.72 (m, 1H), 1.72–1.79 (m, 1H), 1.95 (s, 3H), 2.44–2.53 (m, 1H), 2.57 (ddd, $J = 12.1$ Hz, $J = 8.6$ Hz, $J = 3.3$ Hz, 1H), 3.13–3.20 (m, 1H), 3.64 (dd, $J = 10.8$ Hz, $J = 5.7$ Hz, 1H), 3.84 (dd, $J = 10.8$ Hz, $J = 2.2$ Hz, 1H), 4.02–4.13 (m, 3H), 4.51 (d, $J = 12.1$ Hz, 1H), 4.56 (d, $J = 12.1$ Hz, 1H), 4.62 (d, $J = 11.8$ Hz, 1H), 4.82 (d, $J = 11.8$ Hz, 1H), 5.30 (bs, 1H), 7.14–7.45 (m, 15H); ^{13}C NMR (75 MHz, room temperature, $CDCl_3$) δ 17.7, 23.4, 30.5, 32.0, 41.9, 44.0, 55.1, 58.8, 71.3, 72.9, 73.5, 78.6, 126.6, 127.3, 127.4, 127.4, 127.6, 127.9, 128.1, 128.2, 128.3, 138.6, 139.2, 146.1, 169.1, HRMS (ESI+): m/z [M + H$^+$] calcd for $C_{31}H_{39}N_2O_3$: 487.2955; found 487.2952.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-[(*S*)-1,2-dibenzyloxyethyl]piperidine (6). 20% $Pd(OH)_2$/C (200 mg) was added to a solution of **5** (1.90 g, 3.90 mmol) and di-*tert*-butyl dicarbonate (2.55 g, 11.7 mmol) in absolute EtOH (35 mL) and the mixture was stirred at room temperature under hydrogen at atmospheric pressure for 3 h. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluents: EtOAc/hexane; 1:4; EtOAc) gave 1.56 g (83% yield) of compound **6** as an oil; $[\alpha]^D_{23} = -6.5$ (*c* 1.0 $CHCl_3$); IR absorption (nujol) 3303, 1683 cm^{-1}; ^{1}H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.11–1.23 (m, 1H), 1.32–1.42 (m, 1H), 1.42 (s, 9H), 1.84–1.91 (m, 1H), 1.93 (s, 3H), 1.94–2.01 (m, 1H), 2.78–2.89 (m, 1H), 3.64 (dd, $J = 10.7$ Hz, $J = 5.0$ Hz, 1H), 3.72 (dd, $J = 10.7$ Hz, $J = 3.6$ Hz, 1H), 3.80 (ddd, $J = 8.5$ Hz, $J = 5.0$ Hz, $J = 3.6$ Hz, 1H), 3.94–4.08 (m, 1H), 4.09–4.23 (m, 1H), 4.50–4.56 (m, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.58 (d, $J = 12.0$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 5.11 (bd, $J = 7.3$ Hz, 1H), 7.21–7.35 (m, 10H); ^{13}C NMR (75 MHz, 333 K, $CDCl_3$) δ 23.3, 28.4, 32.3, 33.6, 39.3, 43.7, 52.1, 71.0, 72.7, 73.5, 77.9, 79.5, 127.4, 127.5, 127.6, 128.2, 128.3, 138.4, 138.5, 155.2, 169.1, HRMS (ESI+): m/z [M + Na$^+$] calcd for $C_{28}H_{38}N_2NaO_5$: 505.2673; found 505.2691.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-[(*S*)-1,2-dihydroxyethyl]piperidine (7). 20% $Pd(OH)_2$/C (150 mg) was added to a solution of **6** (1.32 g, 2.74 mmol) in absolute EtOH (30 mL) and the mixture was stirred at room temperature under hydrogen at atmospheric pressure for 17 h. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo* to give 0.81 g (98% yield) of compound **7** as a white solid; mp 103–105 °C; $[\alpha]^D_{26} = +67.1$ (*c* 1.0 $CHCl_3$); IR absorption (nujol) 3440, 3323, 1674, 1651 cm^{-1}; ^{1}H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.18–1.32 (m, 1H), 1.40–1.48 (m, 1H), 1.47 (s, 9H), 1.89–1.96 (m, 1H), 1.95 (s, 3H), 2.01–2.07 (m, 1H), 2.87 (bs, 2H), 3.06–3.20 (m, 1H), 3.56 (dd, $J = 11.6$ Hz, $J = 5.2$ Hz, 1H), 3.69 (dd, $J = 11.6$ Hz, $J = 5.2$ Hz, 1H), 3.95 (ddd, $J = 7.0$, $J = 5.2$ Hz, $J = 5.2$ Hz,1H), 4.04–4.15 (m, 1H), 4.16–4.28 (m, 1H), 4.34–4.43 (m, 1H), 5.30 (bd, $J = 6.5$ Hz, 1H); ^{13}C NMR (75 MHz, 333 K, $CDCl_3$) δ 23.3, 28.4, 32.1, 33.6, 40.1, 43.7, 51.8, 64.2, 73.1, 80.4, 156.3, 169.6, Elemental analysis calcd (%) for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.26; found: C, 55.82; H, 8.79; N, 9.31.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonylpipecolic acid (8). Small portions of $NaIO_4$ (207 mg, 0.97 mmol) were added to a stirred solution of **7** (75 mg, 0.248 mmol) in $CH_3CN/CCl_4/H_2O$ (2:2:3, 7 mL). After being vigorously stirred for 5 min following completion of the addition, the mixture was treated with $RuCl_3 \cdot H_2O$ (2 mg, 0.01 mmol) and stirring was continued for 2 h. CH_2Cl_2 (20 mL) was then added, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 2:9) gave 46 mg (65% yield) of compound **8** as a white solid; mp 107–108 °C; $[\alpha]^D_{25} = +18.1$ (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.24–1.31 (m, 1H), 1.42–1.50 (m, 1H), 1.47 (s, 9H), 1.94–2.00 (m, 1H), 1.97 (s, 3H), 2.49–2.56 (m, 1H), 3.09–3.22 (m, 1H), 3.83–3.95 (m, 1H), 3.97–4.15 (m, 1H), 4.80–5.05 (bs, 1H), 5.40–5.50 (m, 1H); ^{13}C NMR (75 MHz, 333 K, $CDCl_3$) δ 23.2, 28.4, 31.6, 32.9, 40.7, 44.7, 53.7, 80.7, 155.7, 170.4, 172,6, Elemental analysis calcd (%) for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78; found: C, 54.76; H, 7.87; N, 9.83.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-hydroxymethylpiperidine (10). $NaIO_4$ (64 mg, 0.298 mmol) was added to a solution of **7** (75 mg, 0.248 mmol) in CH_3OH (2 mL). After 45 min at room temperature the reaction mixture was filtered, extracted with CH_2Cl_2 and concentrated *in vacuo.* The crude product was dissolved in CH_2Cl_2, filtered and evaporated under reduced pressure to give aldehyde **9**, which was used in the next step without further purification. $NaBH_4$ (8 mg, 0.215 mmol) was added to a solution of compound **9** in EtOH (3 mL) and the resulting mixture was stirred at room temperature for 30 min. H_2O (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 4:1) gave 66 mg (98% yield) of compound **10** as a white solid; mp 41–43 °C; $[\alpha]^D_{22} = +37.8$ (*c* 0.5 $CHCl_3$); IR absorption (nujol) 3305, 1650 cm^{-1}; ^{1}H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.15–1.28 (m, 1H), 1.36 (ddd, $J = 12.8$ Hz, $J = 12.8$ Hz, $J = 6.0$ Hz, 1H), 1.43 (s, 9H), 1.87–1.92 (m, 1H), 1.92 (s, 3H), 1.99–2.06 (m, 1H), 2.65 (bs, 1H), 2.88–2.97 (m, 1H), 3.66 (dd, $J = 11.0$ Hz, $J = 7.0$ Hz, 1H), 3.71 (dd, $J = 11.0$ Hz, $J = 7.6$ Hz, 1H), 3.96–4.08 (m, 2H), 4.33–4.42 (m, 1H), 5.62 (bd, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 23.2, 28.4, 31.9, 32.1, 38.9, 43.2, 52.3, 61.5, 80.0, 155.5, 169.5, Elemental analysis calcd (%) for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29; found: C, 57.22; H, 8.62; N, 10.41.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-(2-phenylethyl)-piperidine (11). A 30% solution of $NaOCH_3$ in CH_3OH (0.082 mL, 78 mg, 0.43 mmol) was added dropwise to a suspension of benzyltriphenylphosphonium chloride (193 mg, 0.496 mmol) in benzene (2 mL) at room temperature and the mixture was stirred for 10 min at the same temperature. A solution of aldehyde **9** (obtained as above) in benzene/CH_2Cl_2 (1:0.5, 1.5 mL) was added and stirring was continued for 1 h. H_2O (5 mL) was added and the solution was concentrated *in vacuo* until the organic solvents were removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a 67/33 mixture of alkenes. The residue was chromatographed (Eluent: EtOAc/hexane; 3:1), dissolved in EtOH (5 mL) and hydrogenated with Pd/C (10 mg) as catalyst at room temperature and atmospheric pressure for 30 min. When the reaction was complete the catalyst was removed by filtration through a Celite pad and the mixture was concentrated *in vacuo* to afford compound **11**. Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 9.5:0.5) gave 74 mg (86% yield) of pure compound **11** as a white solid; mp 31–32.5 °C; $[\alpha]^D_{22}$= +28.6 (*c* 1.1 $CHCl_3$); IR absorption (nujol) 3290, 1650 cm^{-1}; ^1H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.14–1.26 (m, 1H), 1.35–1.43 (m, 1H), 1.46 (s, 9H), 1.77–1.90 (m, 1H), 1.88–1.98 (m, 2H), 1.94 (s, 3H), 1.98–2.08 (m, 1H), 2.51–2.69 (m, 2H), 2.84–2.93 (m, 1H), 4.05–4.18 (m, 2H), 4.34–4.46 (m, 1H), 5.20 (bd, J = 5.8 Hz, 1H), 7.13–7.20 (m, 3H), 7.23–7.29 (m, 2H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 23.3, 28.4, 32.4, 32.6, 32.7, 35.4, 37.9, 43.0, 50.6, 79.6, 125.9, 128.3, 128.4, 141.7, 154.9, 169.1, Elemental analysis calcd (%) for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09; found: C, 69.62; H, 8.59; N, 8.31.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-(2-ethoxycarbonylethyl)piperidine (12). A 30% solution of $NaOCH_3$ in CH_3OH (0.082 mL, 78 mg, 0.43 mmol) was added dropwise to a suspension of 80% (ethoxycarbonylmethyl)triphenylphosphonium chloride (238 mg, 0.496 mmol) in benzene (2 mL) at room temperature and the mixture was stirred for 10 min at the same temperature. A solution of aldehyde **9** (obtained as above) in benzene/CH_2Cl_2 (1:0.5, 1.5 mL) was added and stirring was continued for 2 h. H_2O (5 mL) was added and the solution was concentrated *in vacuo* until the organic solvents were removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford an 85/15 mixture of alkenes. The residue was chromatographed (Eluent: EtOAc/hexane; 3:1), dissolved in EtOH (5 mL) and hydrogenated with Pd/C (10 mg) as catalyst at room temperature and atmospheric pressure for 30 min. When the reaction was complete the catalyst was removed by filtration through a Celite pad and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluent: EtOAc/EtOH; 9.5:0.5) gave 45 mg (53% yield) of compound **12** as a white solid; mp 55–57 °C; $[\alpha]^D_{22}$= +19.5 (*c* 1.68 $CHCl_3$); IR absorption (nujol) 3291, 1731, 1658 cm^{-1}; ^1H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.10–1.21 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.34–1.42 (m, 1H), 1.42 (s, 9H), 1.71–1.80 (m, 1H), 1.80–1.87 (m, 1H), 1.88–1.95 (m, 1H), 1.91 (s, 3H), 1.98–2.10 (m, 1H), 2.18–2.33 (m, 2H), 2.80–2.90 (m, 1H), 4.00–4.10 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.30–4.40 (m, 1H), 5.37 (bs, 1H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 14.1, 23.2, 25.8, 28.4, 31.2, 32.5, 35.6, 37.7, 42.9, 50.3, 60.3, 79.7, 154.7, 169.1, 172.8, Elemental analysis calcd (%) for $C_{17}H_{30}N_2O_5$: C, 59.63; H, 8.83; N, 8.18; found: C, 59.52; H, 8.62; N, 8.00.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-[(*S*)-oxiranyl]-piperidine (13). $^nBu_2SnO$ (6.6 mg, 0.026 mmol), Et_3N (0.22 mL (161 mg), 1.59 mmol) and *p*-toluenesulfonyl chloride (303 mg, 1.59 mmol) were added to a solution of **7** (400 mg, 1.32 mmol) in dry CH_2Cl_2 (8 mL) and the mixture was stirred at room temperature for 7 h. Brine was added (10 mL) and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* The residue was passed through a short pad of silica gel (Eluents: Et_2O; CH_2Cl_2/EtOH; 9:1) to give the corresponding tosylate. K_2CO_3 (219 mg, 1.59 mmol) was added to a stirred solution of tosylate in CH_3OH (10 mL) at 0 °C and the solution was allowed to warm up to room temperature. After stirring for an additional 1 h, saturated aqueous NH_4Cl (10 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 9:1) gave 320 mg (85% yield) of compound **13** as an oil; $[\alpha]^D_{23}$= +41.4 (*c* 1 $CHCl_3$); IR absorption (nujol) 3310, 1743, 1662 cm^{-1}; ^1H NMR (400 MHz, room temperature, $CDCl_3$) δ 1.16–1.28 (m, 1H), 1.42–1.53 (m, 1H), 1.45 (s, 9H), 1.92–1.98 (m, 1H), 1.96 (s, 3H), 2.03–2.10 (m, 1H), 2.57 (dd, J = 4.4 Hz, J = 2.8 Hz, 1H), 2.78 (dd, J = 4.4 Hz, J = 4.1 Hz, 1H), 3.14 (ddd, J = 4.1 Hz, J = 4.0 Hz, J = 2.8 Hz, 1H), 4.00–4.14 (m, 1H), 4.14–4.25 (m, 1H), 4.26–4.49 (m, 1H), 5.28 (bd, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, room temperature, $CDCl_3$) δ 23.4, 28.3, 31.8, 33.7, 40.1, 43.7, 44.8, 50.4, 53.2, 80.1, 154.9, 169.4, HRMS (ESI+): m/z [M + H^+] calcd for $C_{14}H_{24}N_2NaO_4$: 307.1628; found 307.1634.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-[(*R*)-1-hydroxypropyl]piperidine (14). A 1.4M solution of CH_3Li in Et_2O (2.51 mL, 3.52 mmol) was added dropwise to a suspension of CuI (335 mg, 1.76 mmol) in dry Et_2O (10 mL) at –35 °C under argon. After stirring for 30 min at –35 °C, a solution of compound **13** (100 mg, 0.352 mmol) in dry Et_2O (1.3 mL) was added and the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was diluted with EtOAc (20 mL) and carefully quenched at –35 °C with saturated NH_4Cl (10 mL). After the addition of H_2O (10 mL) the reaction mixture was allowed to warm up to room temperature with vigorous stirring. The organic layer was separated and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 9:1) gave 94 mg (89% yield) of compound **14** as a white solid; mp 158–160 °C; $[\alpha]^D_{23}$= +42.7 (*c* 0.88 $CHCl_3$); IR absorption (nujol) 3282, 1691, 1640 cm^{-1}; ^1H NMR (400 MHz, 333 K, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.16–1.30 (m, 1H), 1.32–1.46 (m, 2H), 1.45 (s, 9H), 1.64–1.75 (m, 1H), 1.88–1.95 (m, 1H), 1.92 (s, 3H), 1.95–2.10 (m, 1H), 2.06 (bs, 1H), 2.97–3.07 (m, 1H), 3.79 (ddd, J = 8.6 Hz, J = 8.5 Hz, J = 3.2 Hz, 1H), 4.00–4.12 (m, 2H), 4.12–4.20 (m, 1H), 5.35 (bd, J = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 9.2, 23.2, 27.5, 28.5, 32.3, 33.1, 39.4, 43.6, 55.8, 71.6, 80.2, 156.3, 169.1, Elemental analysis calcd (%) for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33; found: C, 60.20; H, 9.61; N, 9.55.

(2*R*,4*R*)-4-Acetamido-1-*tert*-butoxycarbonyl-2-[(*R*)-1-hydroxyhexyl]piperidine (15). A 1.6M solution of BuLi in hexane (2.70 mL, 4.32 mmol) was added dropwise to a suspension of CuI (412 mg, 2.16 mmol) in dry Et_2O (10 mL) at −35 °C under argon. After stirring for 30 min at −35 °C, a solution of compound **13** (115 mg, 0.40 mmol) in dry Et_2O (1.5 mL) was added and the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was diluted with EtOAc (20 mL) and carefully quenched at −35 °C with saturated NH_4Cl (10 mL). After the addition of H_2O (10 mL) the reaction mixture was allowed to warm up to room temperature with vigorous stirring. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the residue by flash chromatography (Eluent: CH_2Cl_2/EtOH; 9:1) gave 83 mg (60% yield) of the compound **15** as a yellowish solid; mp 46–47 °C; $[\alpha]^{D}_{23}$= +45.5 (*c* 0.83 $CHCl_3$); IR absorption (nujol) 3307, 1691, 1659 cm^{-1}; ^{1}H NMR (400 MHz, 333 K, $CDCl_3$) δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.18–1.48 (m, 8H), 1.45 (s, 9H), 1.48–1.56 (m, 1H), 1.56–1.65 (m, 1H), 1.88–1.96 (m, 2H), 1.91 (s, 3H), 1.96–2.03 (m, 1H), 3.02 (ddd, *J* = 13.9 Hz, *J* = 13.8 Hz, *J* = 2.5 Hz, 1H), 3.80–3.87 (m, 1H), 4.03–4.12 (m, 2H), 4.13–4.18 (m, 1H), 5.27 (bs, 1H); ^{13}C NMR (100 MHz, 333 K, $CDCl_3$) δ 13.8, 22.5, 23.2, 24.8, 28.4, 31.9, 32.2, 33.0, 34.8, 39.3, 43.4, 56.0, 70.4, 80.1, 156.2, 169.1, Elemental analysis calcd (%) for $C_{18}H_{34}N_2O_4$: C, 63.13; H, 10.01; N, 8.18; found: C, 63.33; H, 9.87; N, 7.98.

Acknowledgements

The financial support of the Spanish Ministry of Science and Innovation and European Regional Development Fund (CTQ2008-00187/BQU) and the Government of Aragón (GA E-71) is acknowledged.

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