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Asymmetric Synthesis of *cis*-4- and *trans*-3-Hydroxypipecolic Acids

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Enantioselective syntheses of *cis*-4- and *trans*-3-hydroxypipecolic acids from 2,3-epoxy-5-hexen-1-ol (**7**) are described. Regioselective C-3 or C-2 ring opening of the epoxide by the appropriate nitrogen nucleophile is the key step in each route. As enantiomerically enriched epoxy alcohols are readily available in any configuration by Sharpless epoxidation, both enantiomers are equally accessible. This approach was also employed to synthesize the natural product baikiain and the important synthetic intermediate *trans*-3-hydroxy-2-hydroxymethylpiperidine.

Introduction

Functionalized chiral piperidines are ubiquitous in nature and are also pharmacologically important synthetic products.[1] Hydroxylated piperidine alkaloids in organisms possess a wide range of biological activities, mainly due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[2] Cyclic α-amino acids are also present in many biologically important compounds.[3] In particular, hydroxypipecolic acids can be considered as expanded hydroxylated homoprolines or as constrained serine derivatives. As such, replacement of natural amino acids in bioactive compounds with this fragment may affect the physiological and pathological processes in which they are involved.[4] Therefore, it is not surprising that much effort has been directed towards the development of efficient syntheses of pipecolic acid derivatives.[5]

(–)-*cis*-4-Hydroxypipecolic acid [(–)-**1**] (Figure 1), isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[6] has been identified as a constituent of cyclopeptide antibiotics such as virginiamycin S_2.[7] It has also been employed as a precursor in the preparation of selective *N*-methyl-D-aspartate (NMDA) receptor antagonists[8] and in the synthesis of palinavir, a potent peptidomimetic-based HIV protease inhibitor (Figure 2).[9]

(–)-*trans*-3-Hydroxypipecolic acid [(–)-**2**] is a nonnatural cyclic β-hydroxy-α-amino acid that has been used as a precursor in the synthesis of (–)-swainsonine, a potent and specific inhibitor of α-D-mannosidase.[10] Its enantiomer (+)-**2** is found in (+)-febrifugine, a potent antimalarial agent,[11]

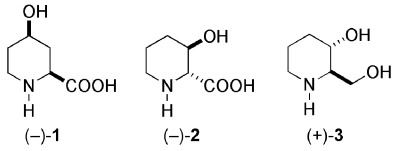

Figure 1. Structures of *cis*-4-hydroxypipecolic acid (**1**), *trans*-3-hydroxypipecolic acid (**2**) and *trans*-3-hydroxy-2-hydroxymehtylpiperidine (**3**).

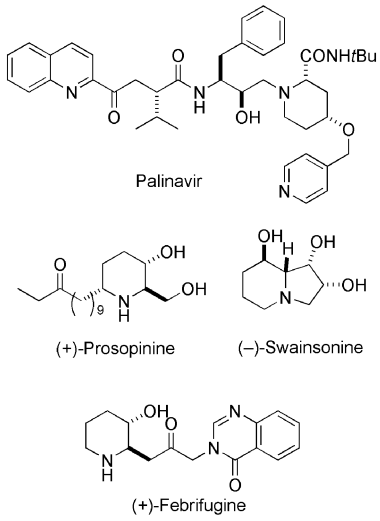

Figure 2. The structures of palinavir, febrifugine, prosopinine and swainsonine.

and its reduced derivative (+)-**3** has been used for the preparation of (+)-prosopinine, which exhibits analgesic, anaesthetic and antibiotic activities.[12] Both *cis*-4-hydroxypipecolic[8b,13] and *trans*-3-hydroxypipecolic[4b,11,14] acids, as well as several N- and/or O-protected analogues of **3**,[11,12,14a–d,15] have been the target of several synthetic strategies. However, the majority of these are racemic syntheses or require either chiral building blocks or enzymatic resolu-

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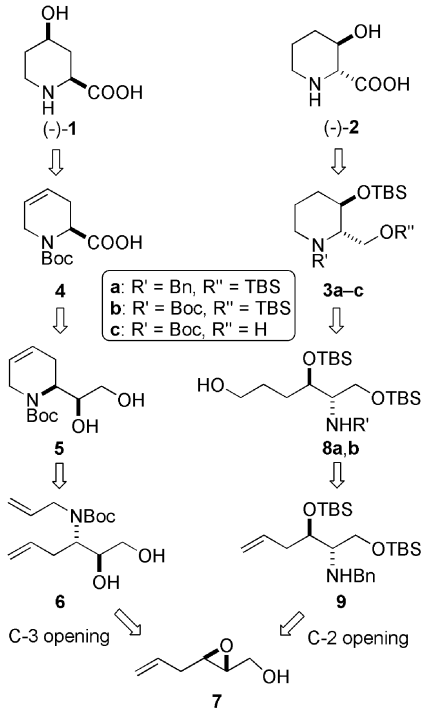
tion. Indeed, only a few stereoselective syntheses in which all the stereogenic centres are constructed by asymmetric synthesis have been reported for **1**,[13l] **2** and **3**.[14a–14d,14o,15e]

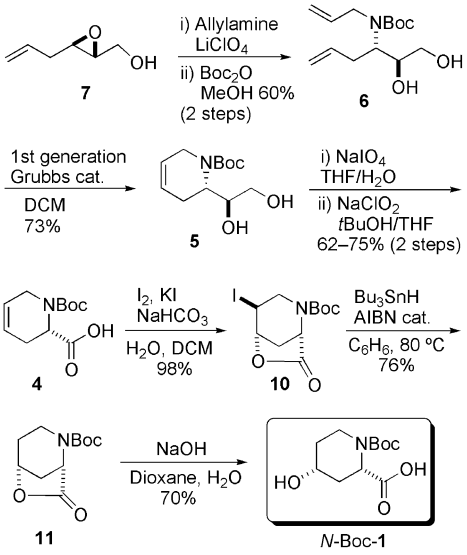
During the past few years our research group has worked towards the synthesis of several types of amino acids and cyclic amino alcohols by using epoxy alcohols as a source of chirality,[16,17] because they are readily available in any configuration through Sharpless epoxidation.[18] The C-2 ring opening of an epoxy alcohol leads to 2-amino-1,3-diols with *anti* stereoselectivity, which is ideally suited for the preparation of *trans*-3-hydroxypipecolic acids by appropriate cyclization. Alternatively, C-3 ring opening leads to 3-amino-1,2-diols, which are amenable to the preparation of pipecolic acids or derivatives through the use of ring-closing metathesis (RCM).[19] We describe here the syntheses of *cis*-4- and *trans*-3-hydroxypipecolic acids from 2,3-epoxy-5-hexen-1-ol according to the retrosynthetic analysis outlined in Scheme 1.



Scheme 1. Retrosynthetic analysis of pipecolic acid derivatives **1** and **2**.

Results and Discussion

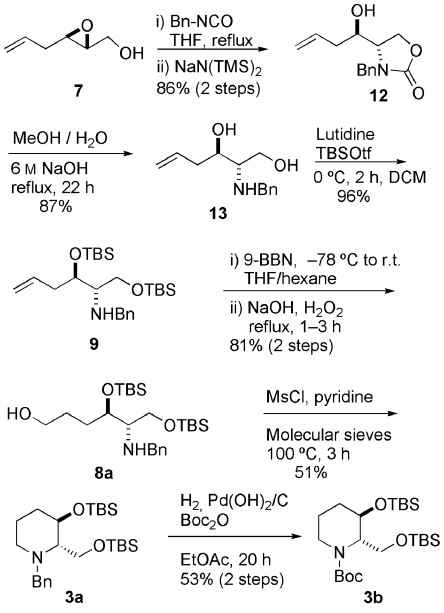
Our syntheses started from 2,3-epoxy-5-hexen-1-ol (**7**), which was readily available by Sharpless epoxidation of 2,5-hexadien-1-ol (prepared from propargyl alcohol and allyl bromide by using a modified literature procedure).[20] Enantiomerically enriched **7** was obtained in 63% overall yield (three steps) and 93%*ee* by working on a 50-g scale. It was then subjected to the five-step procedure shown in Scheme 2, which we developed in our preliminary communication, to yield *N*-Boc-protected baikiain (**4**).[17] The sequence involves regioselective (10:1) C-3 ring opening with allylamine by using the conditions of Crotti,[21] followed by Boc protection, RCM (2 × 4 mol-% of first generation Grubbs' catalyst) and two-step oxidative cleavage of the diol ($NaIO_4$ to yield the aldehyde, which is then oxidized with sodium chlorite)[22] to avoid oxidation of the double bond. *N*-Boc baikiain (**4**)[23] was thus obtained in 99%*ee* after recrystallization. Iodolactonization of **4** by standard procedures proceeded with excellent yield.[24] Iodide elimination followed by lactone hydrolysis afforded the desired *N*-protected *cis*-4-hydroxypipecolic acid (*N*-Boc-**1**) in good yield and excellent enantiomeric purity (Scheme 2).



Scheme 2. Synthesis of *N*-Boc-*cis*-4-hydroxypipecolic acid (*N*-Boc-**1**).

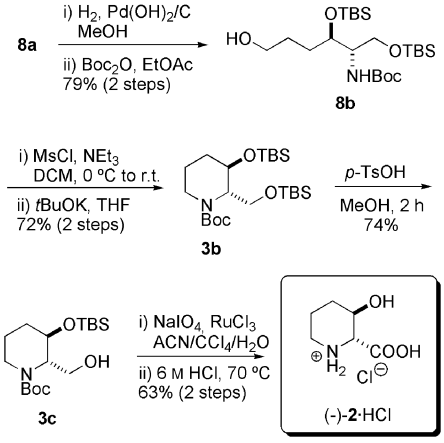
Epoxy alcohol **7** was subjected to a completely regioselective C-2 ring opening to afford **12** (Scheme 3) in excellent overall yield (86% over two steps).[25] Only 7% of the transacylated isomer was observed by ^1H NMR spectroscopy. Cyclic carbamate **12** was deprotected under basic conditions, and the resulting diol was protected by using TBSOTf in high yield. Subsequent regioselective, oxidative hydroboration of the terminal olefin by using 9-BBN to afford **8a** also proceeded with good yield and high selectivity (95:5). At this point, we explored two different pathways, depending on the N-protecting group used prior to the cyclization. With a benzyl protecting group, direct cyclization under Mitsunobu conditions[26] yielded **3a** (40%), but only in moderate yield. This yield was improved by mesylation of the primary alcohol and in situ cyclization. Subsequent hydrogenation of the benzyl group and simultaneous protection of the free amine with Boc_2O gave compound **3b**.[27]

Alternatively, compound **3b** was also obtained by changing the protecting group before cyclization. Hydrogenation of the benzyl group of **8a**, followed by protection of the free amine with Boc_2O, yielded compound **8b**. Higher yields were obtained by performing these two reactions separately, because of the formation of an *N*-Bn–*N*-Boc byproduct, which was not hydrogenated under the reaction conditions. With compound **8b** in hand, the primary alcohol was acti-



Scheme 3. Synthesis of piperidines **3**.

vated with MsCl so that it could undergo cyclization. Although the use of NEt_3 or catalytic 4-DMAP did not promote cyclization, treatment with stronger bases afforded piperidine **3b** in moderate-to-good yields (61–69% by using NaH in THF/DMF or 72% by using *t*BuOK in THF). Finally, selective deprotection of the primary alcohol with catalytic *p*-TsOH, followed by oxidation of the free alcohol and total acidic hydrolysis, gave the *trans*-3-hydroxypipecolic acid hydrochloride [(–)-**2**·HCl] in good yield[14c] (Scheme 4).



Scheme 4. Synthesis of (–)-**2**·HCl.

Conclusions

We developed two enantioselective entries to *cis*-4- and *trans*-3-hydroxypipecolic acids with complete control of the stereochemistry of both stereogenic centres. Diversely protected piperidines **3**, key intermediates for a variety of biologically active products, were also synthesized.

Experimental Section

General Methods: Dry solvents were distilled before use (DCM over CaH; toluene, Et_2O and THF over Na). All reagents were used as received. All reactions were performed in flame-dried glassware under an atmosphere of nitrogen. Optical rotations were measured at room temperature (23 °C), and concentrations are reported in g per 100 mL. Infrared spectra were recorded by using NaCl films. ^{1}H NMR spectra were obtained at 400 MHz with tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained at 100.6 MHz and referenced to the solvent signal. Chemical shifts are recorded in ppm. Signals marked with an asterisk correspond to rotamers. Chromatographic separations were performed with SiO_2 (70–230 mesh) pretreated with NEt_3 (2.5% v/v) by eluting with increasing polarity mixtures of hexane/ethyl acetate. Compound **7** was prepared according to a literature procedure.[20]

(2*S*,3*S*)-*N*-Allyl-*N*-*tert*-butoxycarbonyl-3-amino-5-hexen-1,2-diol (6): To a solution of epoxy alcohol [(+)-**7**, 1.50 g, 13.2 mmol] in acetonitrile (35 mL) was added $LiClO_4$ (21.0 g, 195 mmol) with stirring. After 15 min, allylamine (9.8 mL, 132 mmol) was added, and the reaction was warmed to 65 °C. After 16 h, the solution was cooled to room temperature and water (100 mL) was added. The mixture was extracted with DCM (3 × 100 mL). The combined organic layer was dried with $MgSO_4$, and concentrated in vacuo and then redissolved in MeOH (70 mL). To this solution was added $NaHCO_3$ (3.27 g, 39.6 mmol) and Boc_2O (3.38 g, 15.5 mmol) in acetonitrile (8 mL). After 16 h, the reaction mixture was filtered and then concentrated in vacuo. The crude product was dissolved in Et_2O (60 mL), filtered again and concentrated in vacuo. Column chromatography yielded **6** (2.11 g, 60% yield over 2 steps) as a colourless oil. R_f (hexane/EtOAc, 1:1) = 0.44. $[\alpha]_D$ = +1.6 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3424, 2932, 2979, 1694, 1667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, O*t*Bu), 2.40–2.54 (m, 1 H, 4-H^a), 2.58–2.71 (m, 1 H, 4-H^b), 3.10 (br. s, 1 H, OH), 3.30 (br. s, 1 H, OH), 3.50–3.66 (m, 3 H, 1-H and 2-H), 3.70 (d, $^3J_{H,H}$ = 6.1 Hz, 2 H, NC*H*$_2$CHCH$_2$), 3.73–3.85 (m, 1 H, 3-H), 5.03–5.20 (m, 4 H, C*H*$_2$=CH-C), 5.69–5.82 (m, 2 H, CH$_2$=C*H*-C) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5 (OC*Me*$_3$), 32.2 (CH$_2$-2), 48.5 (NCH$_2$CHCH$_2$), 58.4 (CH-3), 63.4 (CH$_2$-1), 73.6 (CH-2), 81.0 (O*C*Me$_3$), 117.1 (*C*H$_2$=CH-C), 117.3 (*C*H$_2$=CH-C), 135.1 (CH$_2$=*CH*-C), 135.5 (CH$_2$=*CH*-C), 157.5 (N*C*=O) ppm. HRMS (CI+): calcd. for $C_{14}H_{26}NO_4$ 272.1862; found 272.1858.

(*S*)-*N*-*tert*-Butoxycarbonyl-1-[(*S*)-1′,2′,3′,6′-tetrahydropyridin-2-yl]-ethan-1,2-diol (5): To a stirring solution of a **6** (1.00 g, 3.71 mmol) in dry DCM (400 mL) at room temperature was added the first generation Grubbs catalyst (0.091 g, 3 mol-%) in dry DCM (10 mL). After 4 h, the first generation Grubbs catalyst (0.091 g, 3 mol-%) in dry DCM (10 mL) was added again. After 15 h, the solvent was evaporated in vacuo, and the crude product was purified by column chromatography to yield **5** (0.658 g, 73%) as a white solid. Recrystallization of this solid from hot hexane gave **5** in 99% *ee* (determined by HPLC of a subsequently formed derivative). R_f (hexane/EtOAc, 1:1) = 0.20. $[\alpha]_D$ = +39.5 (*c* = 1.0, $CHCl_3$). M.p. 92–93 °C. IR (film): $\tilde{\nu}$ = 3418, 2975, 2931, 1693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, O*t*Bu), 2.26–2.40 (m, 1 H, 6′-H^a), 2.62 (dd, $^2J_{H,H}$ = 16.7 Hz, $^3J_{H,H}$ = 5.0 Hz, 1 H, 6′-H^b), 3.34–3.80 (m, 4 H, 3′-H^a, 1-H and 2-H), 4.05–4.23 (m, 2 H, 1′-H and 3′-H^b), 5.58–5.86 (m, 1 H, C*H*=CH), 5.76–5.86 (m, 1 H, CH=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH$_2$-6′), 28.5 (OC*Me*$_3$), 41.5 (CH$_2$-3′), 48.6 (CH-1′), 62.7 (CH$_2$-2), 69.8 (CH-1), 81.1 (O*C*Me$_3$), 122.2 (*CH*=CH), 123.5 (CH=*CH*), 157.0 (N*C*=O) ppm. MS (FA+): *m*/*z* (%) = 266 (30) [M + Na]$^+$, 244 (40)

$[M + H]^+$, 188 $[(M - 55)]^+$, 100. HRMS (CI+): calcd. for $C_{12}H_{22}NO_4$ 244.1549; found 244.1555.

(*S*)-*N*-*tert*-Butoxycarbonylbaikiain (4): To a solution of **5** (6.05 g, 24.9 mmol) in THF/H_2O (1:3, 75 mL) whilst stirring was added $NaIO_4$ (7.98 g, 37.3 mmol). After 2 h at room temperature (TLC monitoring), H_2O (50 mL) and EtOAc (50 mL) were added. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was used in subsequent chemistry without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ =1.50 (s, 9 H, O*t*Bu), 2.40–2.60 (m, 2 H, 3-H), 3.60–4.00 (m, 2 H, 6-H), 4.66 (m, 1 H, 2-H), 4.89* (d, $^3J_{H,H}$ = 6.8 Hz, 1 H, 2-H), 5.60–5.81 (m, 2 H, 4-H and 5-H), 9.54 (s, 1 H, COH) ppm.

The crude reaction of the aforementioned aldehyde was dissolved in a mixture of THF (52 mL) and *t*BuOH (120 mL). To this solution was then added 2-methyl-2-butene (15.8 mL, 149 mmol) plus an aqueous solution of NaH_2PO_4 (3.88 g, 32.3 mmol) and $NaClO_2$ (80%, 3.65 g, 32.3 mmol) in water (17 mL). After 15 h, a solution of aqueous $NaHSO_3$ (5%, 120 mL) was added. The aqueous layer was extracted with EtOAc (2 × 70 mL), and the combined organic layer was dried with $MgSO_4$ and then concentrated in vacuo. The crude product was recrystallized from hot hexane to afford pure **4** (3.50 g, 62%) as a white solid in 99%*ee* [HPLC of the methyl ester saturated derivative, methyl (*S*)-*N*-*tert*-butoxycarbonylpipecolate; Chiracel OD]. R_f (hexane/EtOAc, 2:1) = 0.14. $[a]_D$ = +7.6 (*c* = 1.2, $CHCl_3$). M.p. 113–115 °C. IR (film): $\tilde{\nu}$ = 2929, 1705, 1645 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, O*t*Bu), 1.49* (s, 9 H, O*t*Bu), 2.46–2.58 (m, 1 H, 3-H^a), 2.59–2.72 (m, 1 H, 3-H^b), 3.77 (d, $^2J_{H,H}$ = 19.6 Hz, 1 H, 6-H^a), 3.82* (d, $^2J_{H,H}$ = 18.5 Hz, 1 H, 6-H^a), 4.06 (d, $^2J_{H,H}$ = 17.1 Hz, 1 H, 6-H^b), 4.11* (d, $^2J_{H,H}$ = 17.9 Hz, 1 H, 6-H^b), 4.92 (d, $^3J_{H,H}$ = 6.4 Hz, 1 H, 2-H), 5.10* (d, $^3J_{H,H}$ = 5.9 Hz, 1 H, 2-H), 5.62–5.83 (m, 2 H, 4-H and 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.5 (CH_2-3), 26.7* (CH_2-3), 28.4 (OC*Me*$_3$), 28.5* (OC*Me*$_3$), 41.6 (CH_2-C6), 42.3* (CH_2-C6), 50.9 (CH-C1), 52.3* (CH-C1), 80.8 (O*C*Me$_3$), 121.9 (*CH*=CH), 122.4* (*CH*=CH), 124.3 (CH=*CH*), 124.7* (CH=*CH*), 156.1 (N*C*=O), 177.4 (COOH), 177.5* (COOH) ppm. HRMS (CI+): calcd. for $C_{11}H_{18}NO_4$ 228.1236; found 228.1225.

(1*S*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-4-iodo-6-oxa-7-oxo-2-azabicyclo-[3.2.1]octane (10): To a solution of **4** (2.60 g, 11.4 mmol) in DCM (50 mL) and water (100 mL) was added $NaHCO_3$ (1.92 g, 22.9 mmol), iodide (8.71 g, 34.3 mmol) and KI (11.33 g, 68.6 mmol) whilst stirring. After 72 h, the reaction mixture was cooled to 0 °C and $Na_2S_2O_3$ was gradually added until the yellow colour of the solution disappeared. The aqueous layer was extracted with DCM (3 × 100 mL), and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was run through a short silica plug to afford **10** (3.96 g, 98%) as a white solid. R_f (hexane/EtOAc, 3:1) = 0.50. M.p. 88–89 °C (ref.[22] 89–90 °C). IR (film): $\tilde{\nu}$ = 1799, 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = (s, 9 H, O*t*Bu), 2.23–2.31 (m, 1 H, 8-H^a), 2.94 (d, $^2J_{H,H}$ = 12.8 Hz, 1 H, 8-H^b), 3.70–3.86 (m, 1 H, 3-H^a), 4.18–4.32 (m, 1 H, 3-H^b), 4.33–4.45 (m, 1 H, 4-H), 4.61–4.87 (m, 1 H, 1-H), 4.96 (t, $^3J_{H,H}$ = 4.8, Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (br. s, CH-4), 20.3* (br. s, CH-4) 28.3 (OC*Me*$_3$), 34.0 (br. s, CH_2-8), 34.2* (br. s, CH_2-8), 47.7 (br. s, CH_2-3), 48.9* (br. s, CH_2-3), 53.4 (br. s, CH-1), 54.1* (br. s, CH-1), 80.1 (br. s, CH-5), 81.9 (O*C*Me$_3$), 153.6 (N*C*=O), 172.4 (*C*OOC) ppm.

(1*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-6-oxa-7-oxo-2-azabicyclo[3.2.1]-octane (11): To a solution of **10** (0.400 g, 0.65 mmol) in benzene (6 mL) was added tributyltin hydride (0.192 mL, 0.72 mmol) and a small amount of AIBN whilst stirring. After 5 h at 85 °C (TLC monitoring), the reaction mixture was cooled to room temperature, and DCM (5 mL) and a solution of aqueous KF (10%, 10 mL) were added. After 30 min, the reaction mixture was filtered through Celite. The aqueous layer was extracted with DCM, and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to yield **11** (0.195 g, 76%) as a white solid. R_f (hexane/EtOAc, 3:1) = 0.47. $[a]_D$ = –133.0 (*c* = 0.8, $CHCl_3$) [ref.[13m] –136.9 (*c* = 1.075, $CHCl_3$)]. M.p. 142–144 °C (ref.[13m] 144–145 °C). IR (film): $\tilde{\nu}$ = 1775, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, O*t*Bu), 1.88 (dddd, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 0.7 Hz, 1 H, 4-H^a), 1.95 (d, $^2J_{H,H}$ = 12.1 Hz, 1 H, 8-H^a), 2.01–2.12 (m, 1 H, 4-H^b), 2.26–2.35 (m, 1 H, 8-H^b), 3.12–3.29 (m, 1 H, 3-H^a), 3.95–4.18 (m, 1 H, 3-H^b), 4.59–4.90 (m, 1 H, 1-H), 4.97 (t, $^3J_{H,H}$ = 5.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (OC*Me*$_3$), 28.8 (CH_2-4), 36.8 (CH_2-8), 38.1 (br. s, CH_2-3), 38.7* (br. s, CH_2-3), 53.2 (br. s, CH-1), 53.9* (CH-1), 77.1 (CH-5), 81.3 (O*C*Me$_3$), 153.9 (N*C*=O), 173.6 (*C*OOC) ppm.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxypipecolic Acid (*N*-Boc-1): To a solution of **11** (0.050 g, 0.22 mmol) in dioxane (5 mL) was added NaOH (0.010 g, 0.24 mmol) in water (2.5 mL). After 24 h whilst stirring at room temperature, the reaction mixture was extracted with DCM, and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to obtain *N*-Boc-**1** (0.038 g, 70%) as a white solid. $[a]_D$ = –67.3 (*c* = 0.25, $CHCl_3$). M.p. 142–144 °C. IR (film): $\tilde{\nu}$ = 3423, 2976, 2898, 1697, 1668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, O*t*Bu), 1.47* (s, 9 H, O*t*Bu), 1.57–1.84 (m, 2 H, 3-H^a and 5-H^a), 1.89 (dd, $^2J_{H,H}$ = 13.8 Hz, $^3J_{H,H}$ = 6.3 Hz, 1 H, 5-H^b), 2.36–2.50 (m, 1 H, 2-H^b), 3.31 (dd, $^2J_{H,H}$ = 12.7 Hz, $^3J_{H,H}$ = 11.7 Hz, 1 H, 6-Ha), 3.42* (dd, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 11.7 Hz, 1 H, 6-H^a), 3.78 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, 6-H^b), 3.85* (d, $^2J_{H,H}$ = 10.1 Hz, 1 H, 6-H^b), 4.18 (br. s, 1 H, 4-H), 4.63 (br. s, 1 H, 2-H), 4.80* (br. s, 1 H, 2 H), 5.93 (br. s, 2 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.4 (OC*Me*$_3$), 28.5* (OC*Me*$_3$), 30.7 (CH_2-5), 30.9* (CH_2-5), 33.5 (CH_2-3), 35.0 (CH_2-6), 36.2* (CH_2-6), 50.3 (CH-2), 51.4* (CH-2), 63.4 (CH-4), 80.5 (O*C*Me$_3$), 155.9 (N*C*=O), 156.3* (N*C*=O), 176.9 (COOH) ppm. MS (CI): *m*/*z* (%) = 246 (30) $[M + H]^+$, 190 $[M - 55]^+$, 70, 146 $[M - 99]^+$, 100. HRMS (CI+): calcd. for $C_{11}H_{20}NO_5$ 246.1341; found 2446.1339. $C_{11}H_{19}NO_5$ (245.27): calcd. C 53.87, N 5.71, H 7.81; found C 54.25, N 5.47, H 7.88.

(4*S*)-3-Benzyl-4-[(1*R*)-1-hydroxy-3-buthenyl]oxazolidin-2-one (12): NEt_3 (3.6 mL, 24.9 mmol) was added dropwise to a solution of epoxide (+)-**7** (1.32 g, 11.6 mmol) in Et_2O (100 mL). After 15 min stirring, benzyl isocyanate (2.1 mL, 17.4 mmol) was added, and the reaction mixture was warmed to reflux. After 16 h, the reaction was cooled to 0 °C, and a saturated solution of NH_4Cl (100 mL) was added. The organic layer was washed with a saturated solution of NaCl (200 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to obtain (2*R*,3*R*)-*N*-Benzyl-5-hexen-2,3-epoxy-1-carbamate (2.69 g, 95%) as a white solid. R_f (hexane/EtOAc, 2:3) = 0.45. M.p. 43–46 °C. $[a]_D$ = +23.4 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3334, 2981, 2927, 1708, 1529, 1242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (dd, $^3J_{H,H}$ = 5.5 Hz, $^3J_{H,H}$ = 5.5 Hz, 2 H, 4-H), 2.94 (dt, $^3J_{H,H}$ = 5.0 Hz, $^3J_{H,H}$ = 1.6 Hz, 1 H, $CH_2CHOCHCH_2$), 2.99–3.04 (m, 1 H, $CH_2CHOCHCH_2$), 3.95 (dd, $^2J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 6.2 Hz, 1 H, 1-H^a), 4.37 (d, $^3J_{N,H}$ = 6.0 Hz, 2 H, NHCH_2Ph), 4.42 (dd, $^2J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 3.1 Hz, 1 H, 1-H^b), 5.01–5.20 (m, 2 H, 6-H), 5.80 (tdd, $^3J_{H,H}$ = 17.0 Hz, $^3J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 6.6 Hz, 1 H, 5-H), 7.25–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7 (CH_2-4), 45.3 (NH*C*H_2Ph), 55.3 (CH_2CHO*C*HCH$_2$), 55.4

($CH_2CHOCHCH_2$), 65.1 (CH_2-1), 118.0 (CH_2-6), 127.6 (CH_{ar}), 127.7 (CH_{ar}), 128.8 (CH_{ar}), 132.7 (CH-5), 138.4 (C_{ar}), 156.2 (OCONH) ppm. HRMS (CI+): calcd. for $C_{14}H_{18}NO_3$ 248.1287; found 248.1282.

To a solution of the aforementioned epoxycarbamate (2.64 g, 10.69 mmol) in THF (250 mL) was added sodium bis(trimethylsilyl)amide (2.15 g, 11.76 mmol) in THF (50 mL). After 15 min stirring, DCM (40 mL) was added, and the reaction mixture was washed with a saturated solution of NH_4Cl (40 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to afford a 12.7:1 regioisomeric mixture with **12** as the major isomer (2.40 g, 91%) as a colourless oil. R_f (hexane/EtOAc, 2:3) = 0.45. $[\alpha]_D$ = +5.14 (c = 0.56, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3418, 2922, 2857, 1731, 1435 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (ddd, $^2J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 6.2 Hz, $^3J_{H,H}$ = 6.2 Hz, 1 H, 2′-H^a), 2.15 (ddd, $^2J_{H,H}$ = 15.1 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H, 2′-H^b), 2.53 (br. s, 1 H, OH), 3.65 (ddd, $^3J_{H,H}$ = 8.8 Hz, $^3J_{H,H}$ = 6.5 Hz, $^3J_{H,H}$ = 1.8 Hz, 1 H, 4-H), 3.90 (ddd, $^3J_{H,H}$ = 5.8 Hz, $^3J_{H,H}$ = 5.8 Hz, $^3J_{H,H}$ = 1.8 Hz, 1 H, 1′-H), 4.20 (dd, $^2J_{H,H}$ = 8.9 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, 5-H^a), 4.28 (d, $^2J_{H,H}$ = 15.3 Hz, 1 H, NC*H*HPh), 4.36 (dd, $^2J_{H,H}$ = 8.6 Hz, $^3J_{H,H}$ = 6.4 Hz, 1 H, 5-H^b), 4.73 (d, $^2J_{H,H}$ = 15.3 Hz, 1 H, NCH*H*Ph), 5.04–5.13 (m, 2 H, 4′-H), 5.72 (tdd, $^3J_{H,H}$ = 17.6 Hz, $^3J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 7.0 Hz, 1 H, 3′-H), 7.28–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8 (CH_2-2′), 46.6 (NCH_2Ph), 58.4 (CH-4), 62.2 (CH_2-5), 67.1 (CH-1′), 118.7 (CH_2-4′), 128.2 (CH_{ar}), 128.2 (CH_{ar}), 129.1 (CH_{ar}), 133.4 (CH-3′), 136.2 (C_{ar}), 159.3 (OCONH) ppm. HRMS (CI+): calcd. for $C_{14}H_{18}NO_3$ 248.1287; found 248.1282.

(2*S*,3*R*)-*N*-Benzyl-2-amino-5-hexen-1,3-diol (13): Compound **12** (1.56 g, 6.33 mmol) was dissolved in MeOH/water (9:1, 125 mL). A solution of aqueous NaOH (6 M, 30 mL) was added, and the reaction mixture was stirred under reflux overnight. After 22 h, the reaction mixture was cooled to room temperature and then concentrated in vacuo. The aqueous mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. Compound **13** (1.22 g, 87%) was thus obtained as a colourless oil, which was used in the next step without further purification. R_f (hexane/EtOAc, 2:3) = 0.20. IR (film): $\tilde{\nu}$ = 3407, 2889, 1640, 1453, 1045 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.37 (m, 2 H, 4-H), 2.66 (dd, $^3J_{H,H}$ = 9.5 Hz, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-H), 3.69–3.78 (m, 2 H, 1-H), 3.72 (dd, $^2J_{H,H}$ = 11.0 Hz, $^3J_{N,H}$ = 5.4 Hz, 1 H, NC*H*HPh), 3.75 (dd, $^2J_{H,H}$ = 11.0 Hz, $^3J_{N,H}$ = 4.3 Hz, 1 H, NCH*H*Ph), 3.79–3.91 (m, 1 H, 3-H), 5.10–5.19 (m, 2 H, 6-H), 5.82 (tdd, $^3J_{H,H}$ = 17.1 Hz, $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 7.23–7.30 (m, 2 H, $CH_{ar}C_{ar}CH_{ar}$), 7.30–7.35 (m, 3 H, $CH_{ar}CH_{ar}CH_{ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6 (CH_2-4), 51.6 (HNCH_2Ph), 60.6 (CH_2-1), 60.9 (CH-2), 71.0 (CH-3), 118.2 (CH_2-6), 127.4 (CH_{ar}), 128.4 (CH_{ar}), 128.7 (CH_{ar}), 134.9 (CH-5), 140.2 (C_{ar}) ppm.

(2*S*,3*R*)-*N*-Benzyl-2-amino-1,3-bis(*tert*-butyldimethylsilyloxy)-5-hexene (9): A solution of diol **13** (0.97 g, 4.38 mmol), lutidine (1.5 mL, 13.15 mmol) and *tert*-butyldimethylsilyl triflate (2.52 mL, 10.96 mmol) in DCM (35 mL) was stirred for 2 h (TLC monitoring). Water (35 mL) was then added, and the resulting mixture was washed with a saturated aqueous solution of $NaHCO_3$ (35 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to yield compound **9** (1.90 g, 96%) as a colourless oil. R_f (hexane/EtOAc, 4:1) = 0.95. $[\alpha]_D$ = +9.8 (c = 1.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2929, 2857, 1471, 1255, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, $SiMe_2$), 0.05 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si*t*Bu), 0.89 (s, 9 H, Si*t*Bu), 2.24–2.35 (m, 1 H, 4-H^a), 2.40 (ddd, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 7.1 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, 4-H^b), 2.73 (dd, $^3J_{H,H}$ = 10.5 Hz, $^3J_{H,H}$ = 5.7 Hz, 1 H, 2-H), 3.66 (m, 2 H, 1-H), 3.77 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, NC*H*HPh), 3.82 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H, NCH*H*Ph), 3.83–3.89 (m, 1 H, 3-H), 4.98–5.10 (m, 2 H, 6-H), 5.84 (tdd, $^3J_{H,H}$ = 17.3 Hz, $^3J_{H,H}$ = 10.1 Hz, $^3J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 7.20–7.26 (m, 1 H, *p*-Ph), 7.27–7.35 (m, 4 H, *o*-Ph and *m*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (SiMe), –5.2 (SiMe), –4.3 (SiMe), –4.2 (SiMe), 18.3 (SiCMe_3), 18.4 (SiCMe_3), 26.1 (SiCMe_3), 26.1 (SiCMe_3), 37.1 (CH_2-4), 52.9 (HNCH_2Ph), 62.2 (CH_2-1), 63.2 (CH-2), 72.4 (CH-3), 116.8 (CH_2-6), 126.9 (CH-*p*-Ph), 128.3 (CH_{ar}), 128.4 (CH_{ar}), 136.2 (CH-5), 141.2 (C_{ar}) ppm. MS (CI): *m*/*z* (%) = 450 (100) [M + H]$^+$, 434 [M – 15]$^+$, 50, 392 [M – 57]$^+$, 40. HRMS (CI+): calcd. for $C_{25}H_{48}NO_2Si_2$ 450.3224; found 450.3229.

(2*S*,3*R*)-*N*-Benzyl-2-amino-1,3-bis(*tert*-butyldimethylsilyloxy)hexan-6-ol (8a): To a solution of **9** (0.240 g, 0.545 mmol) in THF (1 mL) at –78 °C was added 9-BBN (0.4 M in hexane, 4.1 mL, 1.63 mmol) dropwise. The reaction mixture was then warmed to room temperature over 4 h and then left to stir overnight. After 24 h, EtOH (0.3 mL), a solution of aqueous NaOH (6 M, 0.1 mL) and H_2O_2 (33%, 9.2 mL) were added, and the reaction mixture was warmed to 50 °C and stirred for 1 h. After that, the reaction was allowed to cool to room temperature, and it was then dried with K_2CO_3 and concentrated. The crude product was purified by column chromatography to afford compound **8a** (0.206 g, 81% over 2 steps) as a colourless oil. R_f (hexane/EtOAc, 1:1) = 0.53. $[\alpha]_D$ = +13.9 (c = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2953, 2928, 2856, 1471, 1255, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.89 (s, 9 H, Si*t*Bu), 0.89 (s, 9 H, Si*t*Bu), 1.50–1.80 (m, 4 H, 4-H and 5-H), 2.74 (dd, $^3J_{H,H}$ = 10.8 Hz, $^3J_{H,H}$ = 5.4 Hz, 1 H, 2-H), 3.61 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, 6-H), 3.67 (dd, $^2J_{H,H}$ = 17.3 Hz, $^3J_{H,H}$ = 10.4 Hz, 1 H, 1-H^a), 3.69 (dd, $^2J_{H,H}$ = 16.9 Hz, $^3J_{H,H}$ = 10.3 Hz, 1 H, 1H^b), 3.74 (d, $^2J_{H,H}$ = 12.8 Hz, 1 H, NC*H*HPh), 3.82 (d, $^2J_{H,H}$ = 12.8 Hz, 1 H, NCH*H*Ph), 3.85–3.88 (m, 1 H, 3-H), 7.20–7.27 (m, 1 H, *p*-Ph), 7.27–7.35 (m, 4 H, *o*-Ph and *m*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (SiMe), –5.2 (SiMe), –4.3 (SiMe), –4.3 (SiMe), 18.2 (SiCMe_3), 18.3 (SiCMe_3), 26.1 (SiCMe_3), 28.5 (CH_2CH_2), 28.8 (CH_2CH_2), 52.9 (HNCH_2Ph), 61.7 (CH_2-1), 63.0 (CH-6), 63.1 (CH-2), 71.8 (CH-3), 127.1 (CH-*p*-Ph), 128.4 (CH_{ar}), 128.5 (CH_{ar}), 140.8 (C_{ar}) ppm. MS (CI): *m*/*z* (%) = 468 (95) [M + H]$^+$, 452 [M – 15]$^+$, 36, 264 [M – 203]$^+$, 100. HRMS (CI+): calcd. for $C_{25}H_{50}NO_3Si_2$ 468.3329; found 468.3326.

(2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-2-amino-1,3-bis(*tert*-butyldimethylsilyloxy)hexan-6-ol (8b): A mixture of **8a** (0.200 g, 0.428 mmol) and $Pd(OH)_2$ (20 wt.-% on carbon, 0.020 g, 10 wt.-%) in MeOH (3 mL) was stirred under an atmosphere of H_2. After 24 h, the mixture was filtered through Celite and then concentrated in vacuo. The crude product was dissolved in EtOAc (3 mL) and Boc_2O (0.121 g, 0.556 mmol) was added. The resulting solution was stirred at room temperature for 16 h and then concentrated. The crude product was purified by flash chromatography to afford **8b** (0.161 g, 79% over 2 steeps) as a colourless oil. R_f (hexane/EtOAc, 3:1) = 0.45. $[\alpha]_D$ = –2.3 (c = 0.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3452, 2955, 2930, 2858, 1721, 1706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.89 (s, 9 H, Si*t*Bu), 0.90 (s, 9 H, Si*t*Bu), 1.43 (s, 9 H, O*t*Bu), 1.54–1.58 (m, 4 H, 4-H and 5-H), 3.55–3.71 (m, 4 H, 2-H, 1-H^a and 6-H), 3.74–3.80 (m, 1 H, 1-H^b), 3.83–3.89 (m, 1 H, 3-H), 4.71 (br. d, $^3J_{N,H}$ = 7.5 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 (SiMe), –5.1 (SiMe), –4.7 (SiMe), –4.1 (SiMe), 18.2 (SiCMe_3), 18.4 (SiCMe_3), 26.0 (SiCMe_3), 26.1 (SiCMe_3), 27.6

(CH_2CH_2), 28.6 (OCMe_3), 29.4 (CH_2CH_2), 54.6 (CH-2), 61.7 (CH_2-1), 63.1 (CH_2-6), 71.0 (CH-3), 79.4 (SiCMe$_3$), 156.0 (NC=O) ppm. MS (CI): *m*/*z* (%) = 478 (15) [M + H]$^+$, 378 [M – 99]$^+$, 100. HRMS (CI+): calcd. for $C_{23}H_{52}NO_5Si_2$ 478.3384; found 478.3366.

(2*S*,3*R*)-*N*-Benzyl-2-*tert*-butyldimethylsilyloxymehtyl-3-*tert*-butyldimethylsilyloxypiperidine (3a)

Procedure A: To a solution of alcohol **8a** (0.090 g, 0.192 mmol) and PPh_3 (0.101 g, 0.385 mmol) in toluene (1 mL) at 0 °C was added DIAD (0.075 mL, 0.385 mmol) dropwise. The mixture was then warmed to room temperature and left to stir overnight. Et_2O (1 mL) was then added, and the resulting solution was washed with a saturated solution of $NaHCO_3$ (2 × 1 mL), dried with $MgSO_4$ and concentrated. The crude product was dissolved in Et_2O (1 mL) and treated with hexane, and the resulting mixture was filtered to remove the triphenylphosphane oxide. The solvent was evaporated off, and the crude product was purified by flash chromatography to yield **3a** (0.035 g, 40%) as a colourless oil.

Procedure B: A mixture of alcohol **8a** (0.100 g, 0.214 mmol) and activated, powdered, 4-Å molecular sieves (0.40 g) in pyridine (2.1 mL) was stirred at room temperature for 10 min. MsCl (0.025 mL, 0.321 mmol) was then added, and the reaction mixture was warmed to 100 °C and stirred for 3 h (TLC monitoring). The mixture was then diluted with DCM (2 mL), filtered through Celite and concentrated. The crude product was purified by flash chromatography to yield **3a** (0.049 g, 51%) as a colourless oil. R_f (hexane/EtOAc, 3:1) = 0.89. $[\alpha]_D$ = +3.2 (c = 1.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2954, 2928, 2856, 1727, 1462, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, SiMe), 0.04 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.89 (s, 9 H, Si*t*Bu), 0.91 (s, 9 H, Si*t*Bu), 1.30–1.42 (m, 2 H, 4-H^a and 5-H^a), 1.59–1.71 (m, 1 H, 4-H^b or 5-H^b), 1.85–1.94 (m, 1 H, 4-H^b or 5-H^b), 2.02 (dd, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 9.6 Hz, 1 H, 6-H^a), 2.28–2.38 (m, 1 H, 2-H), 2.62–2.71 (m, 1 H, 6-H^b), 3.36 (d, $^2J_{H,H}$ = 13.9 Hz, 1 H, C*H*HOTBS), 3.60–3.68 (m, 1 H, 3-H), 3.79 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{N,H}$ = 5.2 Hz, 1 H, NC*H*HPh), 4.04 (dd, $^2J_{H,H}$ = 10.7 Hz, $^3J_{N,H}$ = 3.5 Hz, 1 H, NCH*H*Ph), 4.29 (d, $^2J_{H,H}$ = 13.8 Hz, 1 H, CH*H*OTBS), 7.20 (t, $^3J_{H,H}$ = 7.1 Hz, 1 H, *p*-Ph), 7.28 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, *o*-Ph), 7.36 (dd, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 7.2 Hz, 2 H, *m*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2 (SiMe), –5.2 (SiMe), –4.4 (SiMe), –3.9 (SiMe), 18.2 (SiCMe$_3$), 18.3 (SiCMe$_3$), 26.1 (SiCMe_3), 26.1 (SiCMe_3), 29.4 (CCH_2CH$_2$C), 33.1 (CCH$_2$$CH_2$C), 50.9 ($CH_2$-6), 58.6 ($CH_2$OTBS), 62.3 (N$CH_2$Ph), 68.7 (CH-3), 69.9 (CH-2), 126.6 (CH-*p*-Ph), 128.2 (CH-*m*-Ph), 129.0 (CH-*o*-Ph), 140.8 (C_{ar}) ppm. MS (CI): *m*/*z* (%) = 450 (45) [M + H]$^+$, 434 [M – 15]$^+$, 40, 304 [M – 145]$^+$, 100. HRMS (CI+): calcd. for $C_{25}H_{48}NO_2Si_2$ 450.3224; found 450.3224.

(2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-*tert*-butyldimethylsilyloxypiperidine (3b)

Procedure A: A mixture of **3a** (0.048 g, 0.107 mmol), Boc_2O (0.030 g, 0.139 mmol) and $Pd(OH)_2$ (20 wt.-% on carbon, 0.005 g) in EtOAc (1 mL) was stirred under an atmosphere of H_2. After 20 h (TLC monitoring), the mixture was filtered through Celite and then concentrated in vacuo. The crude product was purified by flash chromatography to afford **3b** (0.026 g, 53% over 2 steeps) as a colourless oil.

Procedure B: To a mixture of alcohol **8b** (0.041 g, 0.086 mmol) and NEt_3 (0.024 mL, 0.171 mmol) in DCM (1.5 mL) at 0 °C was added MsCl (0.010 mL, 0.128 mmol). After 30 min at this temperature the reaction mixture was allowed to warm to room temperature over 30 h (TLC monitoring). A mixture of water/Et_2O (1:1, 2 mL) was then added, and the organic layer was extracted with Et_2O (2 × 2 mL). The combined organic layer was dried with $MgSO_4$ and then concentrated in vacuo. The crude product was purified by flash chromatography to provide the desired mesylate (0.048 g, 99%), which was used immediately. To a mixture *t*BuOK (0.023 g, 0.207 mmol) in THF (0.7 mL) at 0 °C was added a solution of the aforementioned mesylate (0.048 g, 0.086 mmol) in THF (0.7 mL). After 10 min, the reaction mixture was allowed to warm to room temperature over 1.5 h (TLC monitoring). Water was then added (1 mL), and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layer was dried with $MgSO_4$ and then concentrated in vacuo. The crude product was purified by flash chromatography to yield **3b** (0.029 g, 73%) as a colourless oil. R_f (hexane/EtOAc, 3:1) = 0.89. $[\alpha]_D$ = +12.5 (c = 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2954, 2929, 2857, 1697, 1415 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, SiMe), 0.05 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.88 (s, 9 H, Si*t*Bu), 0.89 (s, 9 H, Si*t*Bu), 1.25–1.37 (m, 1 H, 5-H^a), 1.45 (s, 9 H, O*t*Bu), 1.53–1.71 (m, 2 H, 4-H), 1.85–1.99 (m, 1 H, 5-H^b), 2.66 (dd, $^2J_{H,H}$ = 13.0 Hz, $^3J_{H,H}$ = 12.0 Hz, 1 H, 6-H^a), 3.52–3.61 (m, 1 H, NC*H*HPh), 3.66 (dd, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, NCH*H*Ph), 3.87–4.25 (m, 3 H, 2-H and 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2 (SiMe$_2$), –4.8 (SiMe$_2$), 18.2 (SiCMe$_3$), 18.3 (SiCMe$_3$), 19.0 (CH_2-5), 25.9 (SiCMe_3), 26.0 (SiCMe_3), 27.4 (CH_2-4), 28.6 (OCMe_3), 39.5 (CH_2-6), 59.5 (CH-2), 61.3 (CH_2OTBS), 64.7 (CH-3), 79.4 (OCMe$_3$), 155.8 (NC=O) ppm. MS (ES+): *m*/*z* (%) = 461 (100) [M + H]$^+$, 361 [M – 99]$^+$, 80. HRMS (ESI+): calcd. for $C_{23}H_{50}NO_4Si_2$ 460.3273; found 460.3269.

(2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-*tert*-butyldimethylsilyloxypiperidine (3c): A mixture of **3b** (0.061 g, 0.136 mmol) and *p*-toluenesulfonic acid (10 mol-%, 0.003 g, 0.014 mmol) in MeOH (3 mL) was stirred at room temperature for 2 h (TLC monitoring). DCM (6 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) were then added, and the aqueous layer was extracted with DCM (3 × 2 mL). The combined organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography to yield **3c** (0.035 g, 74%) as a colourless oil. R_f (hexane/EtOAc, 3:1) = 0.32. $[\alpha]_D$ = +24.3 (c = 0.7, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3445, 2953, 2929, 2857, 1694, 1668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.89 (s, 9 H, Si*t*Bu), 1.30–1.38 (m, 1 H, 5-H^a), 1.45 (s, 9 H, O*t*Bu), 1.55–1.65 (m, 2 H, 4-H), 1.92 (dtd, $^2J_{H,H}$ = 17.1 Hz, $^3J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 4.5 Hz, 1 H, 5-H^b), 2.84 (dd, $^2J_{H,H}$ = 12.8 Hz, $^3J_{H,H}$ = 12.4 Hz 1 H, 6-H^a), 3.63 (dd, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 6.3 Hz, 1 H, C*H*HOH), 3.71 (dd, $^2J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, CH*H*OH), 3.86–3.90 (m, 1 H, 3-H), 3.98 (d, $^2J_{H,H}$ = 11.4 Hz, 1 H, 6-H^b), 4.17 (dd, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 6.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 (SiMe), –4.7 (SiMe), 18.1 (SiCMe$_3$), 19.4 (CH_2-5), 25.9 (SiCMe_3), 28.4 (CH_2-4), 28.6 (OCMe_3), 39.8 (CH_2-6), 60.2 (CH-2), 60.9 (CH_2OH), 65.4 (CH-3), 79.8 (OCMe$_3$), 156.4 (NC=O) ppm. MS (CI): *m*/*z* (%) = 346 (71) [M + H]$^+$, 290 [M – 55]$^+$, 80, 246 [M – 99]$^+$, 100. HRMS (CI+): calcd. for $C_{17}H_{36}NO_4Si$ 346.2414; found 346.2408.

(2*R*,3*R*)-3-Hydroxypipecolic Acid Hydrochloride [(–)-2·HCl]: A mixture of $NaIO_4$ (0.037 g, 0.174 mmol) and $RuCl_3$·H_2O (0.002 g, 0.009 mmol, 10% mol.) in acetonitrile/CCl_4/H_2O (1:1:10, 1 mL) was stirred at room temperature. After 45 min, **3c** (0.030 g, 0.087 mmol) in acetonitrile (0.5 mL) was added. $NaIO_4$ (0.019 g, 0.087 mmol) was then added, and the reaction mixture was left to stir for 30 min (TLC monitoring). The reaction mixture was filtered through Celite, washed with EtOAc, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (SiO_2). The O-protected hydroxy acid was treated with aqueous HCl (6 M, 2 mL) at 70 °C for 2 h. The reaction mixture was then

extracted with Et_2O (2 mL), dried with $MgSO_4$ and concentrated to yield (–)-**2**·HCl (0.010 g, 63% over 2 steps) as a solid. $[\alpha]_D$ = –13.5 (c = 0.3, H_2O) [ref.[14c] +14.2 for (+)-**2**·HCl (c = 0.95, H_2O)]. ^{1}H NMR (400 MHz, D_2O): δ = 1.64–1.83 (m, 2 H, 4-H^a and 5-H^a), 1.96–2.10 (m, 2 H, 4-H^b and 5-H^b), 3.07–3.15 (m, 1 H, 6-H^a), 3.36–3.43 (m, 1 H, 6-H^b), 3.81 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, 2-H), 4.16 (dt, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 3.0 Hz, 1 H, 3-H) ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of *N*-Boc-**1**, **2**·HCl, **3a**–**c**, **4**–**6**, **8a**,**b** and **9**–**13**.

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[1] For recent reviews on the synthesis of substituted piperidines, see: a) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 3551; b) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953; c) S. Laschat, T. Dickner, *Synthesis* **2000**, *13*, 1781.

[2] a) E. S. H. El Ashry, N. Rashed, A. H. S. Shobier, *Pharmazie* **2000**, *55*, 331; b) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645; c) M. J. Schneider, "Pyridine and Piperidine Alkaloids: An Update" in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Pergamon, Oxford, **1996**, vol. 10, pp. 155–299; d) G. B. Fodor, B. Colasanti, "The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology" in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Wiley-Interscience, New York, **1985**, vol. 3, pp. 1–90.

[3] See, for example: a) M. Yasuda, M. Ueda, H. Muramatsu, M. Mihara, N. Esaci, *Tetrahedron: Asymmetry* **2006**, *17*, 1775; b) S. N. Osipov, P. Dixneuf, *Russ. J. Org. Chem.* **2003**, *39*, 1211; c) M. Pohlman, U. Kazmaier, *Org. Lett.* **2003**, *5*, 2631; d) K. Park, M. J. Kurth, *Tetrahedron* **2002**, *58*, 8629; e) E. Bunuel, A. Jimenez, M. D. Diaz-de-Villegas, C. Cativiela, *Targets Heterocycl. Syst.* **2001**, *5*, 79–111; f) M. Petersen, M. Sauter, *Chimia* **1999**, *53*, 608.

[4] a) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron* **1997**, *53*, 12789; b) G. M. Sahara, G. R. Marshall, *Tetrahedron Lett.* **1997**, *38*, 5069.

[5] For recent reviews of asymmetric syntheses of pipecolic acids and their derivatives, see: a) C. Kadouri-Puchot, S. Comesse, *Amino Acids* **2005**, *29*, 101; b) F. Couty, *Amino Acids* **1999**, *16*, 297.

[6] a) J. T. Romeo, L. A. Swain, A. B. Bleecker, *Phytochemistry* **1983**, *22*, 1615; b) V. W. Schenk, H. R. Schutte, *Flora* **1963**, *153*, 426; c) J. W. Clark-Lewis, P. I. Mortimer, *J. Chem. Soc.* **1961**, 189.

[7] H. Vanderhaeghe, G. Janssen, F. Compernolle, *Tetrahedron Lett.* **1971**, *28*, 2687.

[8] a) R. Pellicciari, B. Natalini, R. Luneia, M. Marinozzi, R. Marinella, G. C. Rosato, B. M. Sadeghpour, J. P. Snyder, J. B. Monahan, F. Moroni, *Med. Chem. Res.* **1992**, *2*, 491; b) S. J. Hays, T. C. Malone, G. Johnson, *J. Org. Chem.* **1991**, *56*, 4084 and references cited therein.

[9] a) P. L. Beaulieu, P. Lavalleé, A. Abraham, P. C. Anderson, C. Boucher, Y. Bousquet, J. S. Duceppe, J. Gillard, V. Gorys, C. Grand-Maitre, L. Grenier, Y. Guindon, I. Guse, L. Plamondom, F. Soucy, S. Valois, D. Wernic, C. Yoakim, *J. Org. Chem.* **1997**, *62*, 3440; b) D. Lamarre, G. Croteau, L. Bourgon, D. Thibeault, E. Wardrop, C. Clouette, M. Vaillancourt, E. Cohen, C. Pargellis, C. Yoakim, P. C. Anderson, *Antimicrob. Agents Chemother.* **1997**, *41*, 965; c) P. C. Anderson, F. Soucy, C. Yoakim, P. Lavalleé, P. L. Beaulieu, U. S. Patent 5614533, **1997**; d) P. L. Beaulieu, I. Guse, U. S. Patent 5545640, **1996**.

[10] F. Ferreira, C. Greck, J. P. Genet, *Bull. Soc. Chim. Fr.* **1997**, *134*, 615.

[11] A. Jourdant, J. Zhu, *Tetrahedron Lett.* **2000**, *41*, 7033 and references cited therein.

[12] I. Ojima, E. S. Vidal, *J. Org. Chem.* **1998**, *63*, 7999.

[13] a) J. C. Jung, M. A. Avery, *Tetrahedron: Asymmetry* **2006**, *17*, 2479; b) F. M. Cordero, S. Bonollo, F. Machetti, A. Brandi, *Eur. J. Org. Chem.* **2006**, 3235; c) J. Marin, C. Didierjean, A. Aubry, J. R. Casimir, J. P. Briand, G. Guichard, *J. Org. Chem.* **2004**, *69*, 130; d) R. C. Lloyd, M. E. B. Smith, D. Brick, S. J. C. Taylor, D. A. Chaplin, R. McCague, *Org. Process Res. Dev.* **2002**, *6*, 762; e) P. Celestini, B. Danieli, G. Lesma, A. Sacchetti, A. Silvani, D. Passarella, A. Virdis, *Org. Lett.* **2002**, *4*, 1367; f) M. Sabat, C. R. Johnson, *Tetrahedron Lett.* **2001**, *42*, 1209; g) C. Agami, F. Bisaro, S. Comesse, S. Guesné, C. Kadouri-Puchot, R. Morgentin, *Eur. J. Org. Chem.* **2001**, 2385; h) F. A. Davis, T. Fang, B. Chao, D. M. Burns, *Synthesis* **2000**, *14*, 2106; i) C. A. Brooks, D. L. Comins, *Tetrahedron Lett.* **2000**, *41*, 3551; j) M. Haddad, M. Larcheveque, *Tetrahedron: Asymmetry* **1999**, *10*, 4231; k) C. Di Nardo, O. Varela, *J. Org. Chem.* **1999**, *64*, 6119; l) R. Chênevert, M. P. Morin, *J. Org. Chem.* **1999**, *64*, 3178; m) Y. Bousquet, P. C. Anderson, T. Bogri, J. S. Duceppe, L. Grenier, I. Guse, *Tetrahedron* **1997**, *53*, 15671; n) J. Gillard, A. Abraham, P. C. Anderson, P. L. Beaulieu, T. Bogri, Y. Bousquet, L. Grenier, I. Guse, P. Lavalleé, *J. Org. Chem.* **1996**, *61*, 2226; o) A. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* **1995**, *36*, 2037; p) A. P. Nin, O. Varela, R. M. de Lederkremer, *Tetrahedron* **1993**, *49*, 9459; q) P. L. Orstein, D. D. Schoepp, M. B. Arnold, J. D. Leander, D. Lodge, J. W. Paschal, T. Elzey, *J. Med. Chem.* **1991**, *34*, 90; r) P. M. Esch, R. F. de Boer, H. Hiemstra, I. M. Boska, W. N. Speckamp, *Tetrahedron* **1991**, *47*, 4063; s) P. M. Esch, I. M. Boska, H. Hiemstra, W. N. Speckamp, *Synlett* **1989**, 38; t) G. Jolles, G. Poiget, J. Robert, B. Terlain, J. P. Thomas, *Bull. Soc. Chim. Fr.* **1965**, 2252.

[14] a) I. S. Kim, J. S. Oh, O. P. Zee, Y. H. Jung, *Tetrahedron* **2007**, *63*, 2622; b) I. S. Kim, Y. J. Ji, Y. H. Jung, *Tetrahedron Lett.* **2006**, *47*, 7289; c) P. Kumar, M. S. Bodas, *J. Org. Chem.* **2005**, *70*, 360; d) M. S. Bodas, P. Kumar, *Tetrahedron Lett.* **2004**, *45*, 8461; e) N. Liang, A. Datta, *J. Org. Chem.* **2005**, *70*, 10182; f) M. Quibell, A. Benn, N. Flinn, T. Monk, M. Ramjee, Y. Wang, J. Watts, *Bioorg. Med. Chem.* **2004**, *12*, 5689; g) S. D. Koulocheri, P. Magiatis, A. L. Skaltsounis, S. A. Haroutounian, *Tetrahedron* **2002**, *58*, 6665; h) M. Haddad, M. Larcheveque, *Tetrahedron Lett.* **2001**, *42*, 5223; i) J. D. Scott, R. M. Williams, *Tetrahedron Lett.* **2000**, *41*, 8413; j) M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843; k) J. D. Scott, T. N. Tippie, R. M. Williams, *Tetrahedron Lett.* **1998**, *39*, 3659; l) C. H. Sugisaki, P. J. Carroll, C. R. D. Correia, *Tetrahedron Lett.* **1998**, *39*, 3413; m) L. Battistini, F. Zanardi, G. Rassu, P. Spanu, G. Pelosi, G. G. Fava, M. B. Ferrari, G. Casiraghi, *Tetrahedron: Asymmetry* **1997**, *8*, 2975; n) C. Agami, F. Couty, H. Mathieu, *Tetrahedron Lett.* **1996**, *37*, 4001; o) C. Greck, F. Ferreira, J. P. Genet, *Tetrahedron Lett.* **1996**, *37*, 2031; p) D. W. Knight, N. Lewis, A. C. ShareDavidHaigh, *Tetrahedron: Asymmetry* **1993**, *4*, 625; q) R. C. Roemmele, H. Rapoport, *J. Org. Chem.* **1989**, *54*, 1866.

[15] a) H. Takahata, Y. Banda, M. Sasatani, H. Nemoto, A. Kato, I. Adachi, *Tetrahedron* **2004**, *60*, 8199; b) S. Furegati, W. Ganci, F. Gorla, U. Ringeisen, P. Rueedi, *Helv. Chim. Acta* **2004**, *87*, 2629; c) H. Takahata, Y. Banda, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527; d) H. Takahata, Y. Banda, H. Ouchi, H. Nemoto, A. Kato, I. Adachi, *J. Org. Chem.* **2003**, *68*, 3603; e) M. H. Haukaas, G. A. O'Doherty, *Org. Lett.* **2001**, *3*, 401; f) Y. Banda, C. Abe, H. Nemoto, A. Kato, I. Adachi, H. Takahata, *Tetrahedron: Asymmetry* **2001**, *12*, 817; g) D. Enders, U. Jegelka, *Synlett* **1992**, 999; h) M. Mocerino, R. V. Stick, *Aust. J. Chem.* **1990**, *43*, 1183.

[16] See inter alia: a) C. Alegret, F. Santacana, A. Riera, *J. Org. Chem.* **2007**, *72*, 7688; b) C. Murruzzu, A. Riera, *Tetrahedron: Asymmetry* **2007**, *18*, 149; c) C. Alegret, J. Benet-Buchholz, A. Riera, *Org. Lett.* **2006**, *8*, 3069; d) M. Alonso, F. Santacana, L. Rafecas, A. Riera, *Org. Process Res. Dev.* **2005**, *9*, 690; e) R. Martín, C. Murruzzu, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2005**, *70*, 2325; f) N. García-Delgado, K. S. Reddy, L. Solà, A. Riera, M. A. Pericàs, X. Verdaguer, *J. Org. Chem.* **2005**, *70*, 7426; g) X. Ginesta, M. Pastó, M. A. Pericàs, A. Riera, *Org. Lett.* **2003**, *5*, 3001; h) M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369; i) R. Martín, M. Alcón, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2002**, *67*, 6896.

[17] X. Ginesta, M. A. Pericàs, A. Riera, *Tetrahedron Lett.* **2002**, *43*, 779.

[18] a) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; b) V. S. Martín, T. Katsuki, *Org. React.* **1996**, *48*, 1–299.

[19] a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; b) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; c) K. J. Ivin, *J. Mol. Catal., A Chem.* **1998**, *133*, 1; d) M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036; e) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446.

[20] M. Alcón, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron: Asymmetry* **1999**, *10*, 4639.

[21] a) M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E. Giovani, F. Macchia, M. J. Pineschi, *J. Org. Chem.* **1993**, *58*, 1221–1227; b) M. Chini, P. Crotti, F. Macchia, *J. Org. Chem.* **1991**, *56*, 5939–5942.

[22] a) T. Q. Dinh, X. Du, C. D. Smith, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 6773–6783; b) B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.

[23] Baikiain is a natural product isolated from *Baikiaea plurijuga*. F. E. King, T. J. King, A. J. Warwick, *J. Chem. Soc.* **1950**, 3590.

[24] Lactonization of racemic **4**: G. J. Hanson, M. A. Russell, *Tetrahedron Lett.* **1989**, *30*, 5751.

[25] X. Ginesta, M. A. Pericàs, A. Riera, *Synth. Commun.* **2005**, *35*, 289.

[26] a) T. Tsunoda, F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto, S. Itô, *Tetrahedron Lett.* **1996**, *37*, 2463; b) D. L. Hughes, "The Mitsunobu Reaction" in *Organic Reactions* (Ed.: P. Beak et al.), John Wiley & Sons, Inc., New York, **1992**, vol. 42, pp. 335–656; c) O. Mitsunobu, *Synthesis* **1981**, 1.

[27] Spectroscopic data of **3b** do not mach the description found in ref.[12] We believe that this compound was erroneously described.

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