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A new asymmetric synthetic route to substituted piperidines☆

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Abstract—An asymmetric synthesis of substituted piperidines has been described. β-Cyclodextrin- or oxazaborolidine-catalyzed asymmetric reduction of α-azido aryl ketones to the corresponding alcohols has been employed as the key step along with ring closing metathesis and selective dihydroxylation.

1. Introduction

Substituted piperidines (polyhydroxy piperidines or azasugars) have been identified as an important class of therapeutic agents in the treatment of influenza infection,[1] cancer metastatis,[2] viral infections including AIDS,[3] and diabetes (Fig. 1).[4] As a result, numerous classes of inhibitors have been developed, some of which provide interesting insights into the mechanism of enzymatic glycoside hydrolysis. Amongst them, both naturally occurring and synthetic polyhydroxylated piperidines[5] (**1**–**4**) have been shown to be specific and potent inhibitors of glycosidases[6] and have been demonstrated to have great potential as drugs for treating a variety of carbohydrate mediated diseases.[7]

As a consequence of this, there has been a great deal of interest, not only in the synthesis of the natural products themselves, but also that of chemically modified analogues. However, most of the methodologies have been developed for the synthesis of compounds **1** and **4** and their stereoisomers,[8,9] which can be regarded as substituted piperidines, starting from the carbohydrates and, in general, require chiral starting materials to reach the specific target. Thus, the development of new methods from achiral precursors for the enantioselective synthesis of polyhydroxylated piperidines constitutes an area of current interest.[10] Herein, we wish to report the complete asymmetric synthesis of **1** and **4** starting from readily available achiral 4-methyl phenacyl bromide **5**.

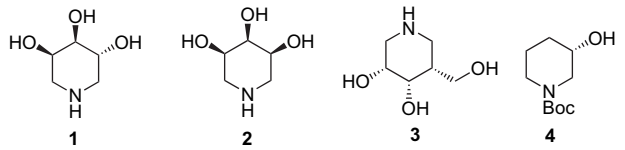

Figure 1.

2. Results and discussion

Our synthetic program (depicted in Scheme 1) starts from the readily available 4-methyl phenacyl bromide **5**, which on treatment with NaN_3 in the presence of β-cyclodextrin[11,12] in water at room temperature resulted in azide **6**. This is identical in all respects with the reported one.[13] Asymmetric reduction with azido aryl ketone **6**–β-cyclodextrin complex and sodium borohydride[12a] in water produced **7** in 95% yield and 80% ee. The same ketone **6**, when reduced with oxazaborolidine-catalyzed asymmetric borane[14a] yielded the alcohol **7** in 94% yield and 100% ee. There are certain advantages with both the reagents as the earlier one is easily accessible, inexpensive, and recyclable but the latter gives good ee %.

Alcohol **7** was protected as its MOM ether **8**, which on oxidative cleavage with $RuCl_3$ and $NaIO_4$ gave methyl ester **9**. Reduction of the azide group in **9** with β-cyclodextrin and TPP gave the corresponding amine, which on in situ protection with the Boc group produced **10**.[12e] $NaBH_4$ and LiCl mediated reduction[15] of the methyl ester group in **10** resulted in alcohol **11**. Alcohol **11** was oxidized under Swern conditions[16] to give the corresponding aldehyde, which, as a crude, on Wittig olefination with MeTPPI and *t*-BuOK in THF at 0 °C produced olefin **12**. *N*-Allylation of **12** was achieved by treating with allyl bromide in the presence of NaH and a catalytic amount of TBAI to furnish **13**, the precursor for the key reaction, ring closing metathesis (RCM).[17] Substrate

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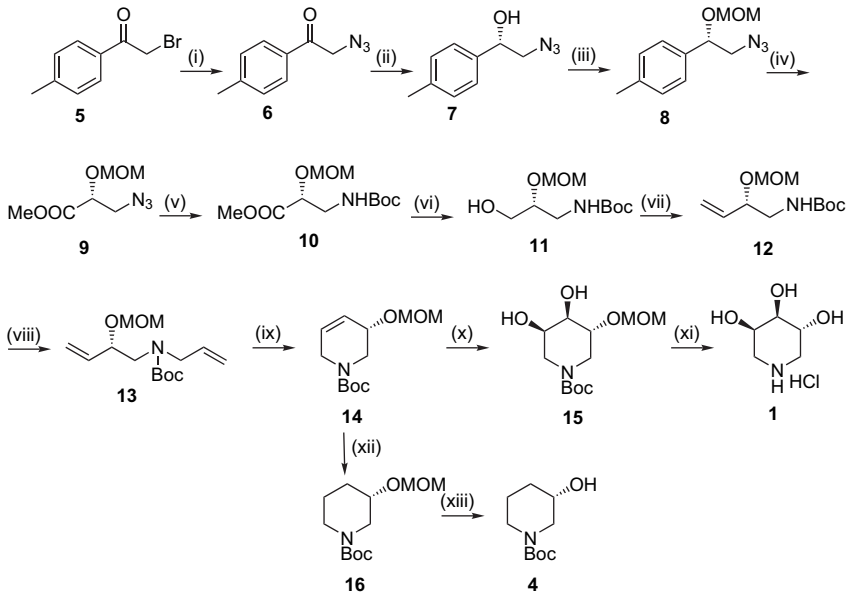

Scheme 1. Synthesis of substituted piperidines **1** and **4**. Reagents, conditions, and yields: (i) β-CD/H_2O, NaN_3, rt, 50 min, 99%; (ii) (*S*)-diphenyl prolinol, BH_3Me_2S, THF, 40 °C, 94%; (iii) MOMCl, DIPEA, DMAP, DCM, 0 °C–rt, 15 h, 94%; (iv) (a) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (1:1:1.5), rt, 8 h; (b) CH_2N_2, ether, 0 °C, 5 min, 85% for two steps; (v) β-CD/H_2O, TPP, rt, then $(Boc)_2O$, rt, 35 min, 91% for two steps; (vi) $NaBH_4$, LiCl, MeOH/THF, 0 °C–rt, 18 h, 90%; (vii) (a) DMSO, oxalyl chloride, TEA, DCM, −78 °C, 1.5 h; (b) MeTPPI, *t*-BuOK, 0 °C–rt, 1 h, 85% for two steps; (viii) NaH, allyl bromide, cat TBAI, THF, rt, 4 h, 84%; (ix) Grubbs' catalyst 1st generation, rt, 24 h, 92%; (x) 4% OsO_4, NMO, 82%; (xi) 6 N HCl, MeOH, rt, overnight, 90%; (xii) H_2/PtO_2, EtOAc, rt, 1 h, 98%; (xiii) (a) 6 N HCl, MeOH, rt, 7 h; (b) Et_3N, $(Boc)_2O$, rt, 30 min, 89%.

13 on treatment with Grubbs' 1st generation catalyst in DCM produced **14** in 24 h at room temperature. Dihydroxylation[9i] of **14** with OsO_4 and NMO in acetone and water medium gave **15**, which on treatment with 6 M HCl in MeOH at room temperature resulted in the hydrochloride salt of piperidine derivative **1**. Substrate **1** compared well with the reported data[9] proving that the dihydroxylation of **15** was performed on the expected *anti* face.

In another route, reduction of **14** using PtO_2 under an H_2 atmosphere resulted in piperidine derivative **16**. Substrate **16** on treatment with 6 M HCl in methanol resulted in *S*-3-hydroxy piperidine, which without purification was subjected to Boc-protection in the presence of TEA and Boc-anhydride to furnish *N*-Boc piperidine **4**, which was in good agreement with the reported data.[18,9d]

3. Conclusion

In summary, we have demonstrated the synthesis of substituted piperdines **1** and **4** from the compound **5** via asymmetric reduction of α-azido aryl ketone, oxidative cleavage of an aryl group, RCM, and dihydroxylation reactions in a highly stereoselective and efficient manner. Thus, a new synthetic route has been demonstrated to 1-aza sugars related to hydroxy piperidines that are highly potent and specific inhibitors of β-glycosidases.

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as internal standard. Coupling constants (J) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh). Mass spectra were obtained on Finnegan MAT 1020B or micro mass VG 70-70H spectrometers operating at 70 eV using a direct inlet system.

4.1.1. 2-Azido-1-*p*-tolylethanone (6). β-CD (17.02 g, 15.0 mmol) was suspended in distilled water (200 mL) and the resulting mixture was heated to 60 °C. To this clear solution, 4-methyl phenacyl bromide **5** (3.18 g, 15 mmol) in acetone (7 mL) was added dropwise over a period of 10 min. After complete addition, the mixture was brought to room temperature slowly. Then sodium azide (1.46 g, 22.5 mmol) was added to the reaction mixture and stirred for 50 min. The product was extracted with ethyl acetate (3×250 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product thus obtained was purified by column chromatography (SiO_2, 3% EtOAc in petroleum ether eluent) to afford **6** (2.59 g, 99%) as yellow solid. The aqueous layer was cooled to 5 °C to recover precipitated β-CD by filtration (95%). The recovered β-CD was reused number of times without change in the yield.

Mp 65–67 °C, (lit.[13] mp 63–65 °C); IR (neat): ν_{max} 2969.2, 2100.6, 1686.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, 2H, J=8.3 Hz, Ar-*H*), 7.28 (d, 2H, J=8.3 Hz, Ar-*H*), 4.48 (s, 2H, CH_2N), 2.45 (s, 3H, *Me*); MS (ESIMS): *m*/*z* 176 $[M+H]^+$.

4.1.2. (*S*)-2-Azido-1-*p*-tolylethanol (7). To a solution of (*S*)-diphenyl prolinol (0.253 g, 1 mmol) in dry THF (5 mL) was added a solution of $BH_3 \cdot Me_2S$ (5 mL, 2 M in toluene, 10 mmol) and stirred at 40 °C for 6 h under an N_2 atmosphere. To the resulting solution of oxazaborolidine, a solution of compound **6** (1.75 g, 10 mmol) dissolved in anhydrous THF (5 mL) was added dropwise by syringe, over a period of 20 min. After the addition was complete, the reaction mixture was stirred at the same temperature for another 10 min. It was then cooled to room temperature and cautiously quenched with MeOH (2 mL). The solvent was evaporated and the residue was purified by column chromatography (SiO_2, 15% EtOAc in petroleum ether eluent) to afford **7** (1.66 g, 94%) as a colorless oil.

$[\alpha]_D^{25}$ +104.0 (*c* 0.54, $CHCl_3$) (lit.[14] $[\alpha]_D^{20}$ +103.2 (*c* 1.46, $CHCl_3$)); IR (neat): ν_{max} 3421.0, 2922.6, 2104.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 2H, *J*=8.3 Hz, Ar-*H*), 7.11 (d, 2H, *J*=8.3 Hz, Ar-*H*), 4.78 (dd, 1H, *J*=7.5, 3.8 Hz, C*H*OH), 3.50–3.24 (m, 2H, CH_2N), 2.35 (s, 3H, *Me*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.9, 137.5, 129.2, 125.7, 73.0, 57.7, 21.0; MS (ESIMS): *m*/*z* 178.0 $[M+H]^+$.

4.1.3. 1-[(*S*)-2-Azido-1-(methoxymethoxy)ethyl]-4-methyl benzene (8). To a stirred solution of alcohol **7** (1.5 g, 8.4 mmol) in dry DCM (30 mL) under a nitrogen atmosphere was added di-isopropyl ethylamine (3.25 g, 25.2 mmol) at 0 °C. Methoxymethyl chloride (2.01 g, 25.2 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM (2×30 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude compound was purified by column chromatography (SiO_2, 0.6% EtOAc in petroleum ether eluent) to afford **8** (1.74 g, 94%) as a colorless oil.

$[\alpha]_D^{25}$ +111.98 (*c* 0.71, $CHCl_3$); IR (neat): ν_{max} 2932.8, 2101.7, 1026.7 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.21–7.10 (m, 4H, Ar-*H*), 4.72 (dd, 1H, *J*=8.7, 4.0 Hz, C*H*OCH_2), 4.54 (s, 2H, OCH_2O), 3.48 (dd, 1H, *J*=12.7, 8.7 Hz, C$H_A$$H_B$N), 3.39 (s, 3H, O*Me*), 3.13 (dd, 1H, *J*=12.6, 4.0 Hz, CH$_A$$H_B$N), 2.35 (s, 3H, *Me*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 135.2, 129.2, 126.7, 93.9, 76.8, 56.4, 55.5, 21.0; MS (ESIMS): *m*/*z* 244 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{15}N_3O_2$ $[M+Na]^+$: 244.1061, found: 244.1061.

4.1.4. (*R*)-Methyl 3-azido-(methoxymethoxy) propanoate (9). To a solution of **8** (1.7 g, 7.8 mmol) in CCl_4 (47 mL), MeCN (47 mL), and H_2O (71 mL) were added $NaIO_4$ (25 g, 117 mmol) and $RuCl_3 \cdot H_2O$ (83 mg, 0.4 mmol) and stirred vigorously for 8 h. Then the solution was filtered through Celite and the Celite was washed with DCM (2×250 mL). The combined organic phases were washed with water (2×50 mL), brine (2×50 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude acid. The crude acid was dissolved in ether, the solution cooled to 0 °C, and an ethereal solution of diazomethane was added and stirred for 5 min. The solvent was evaporated and the crude reaction mixture was chromatographed (SiO_2, 5% EtOAc in petroleum ether eluent) to afford **9** (1.25 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ +88.06 (*c* 0.37, $CHCl_3$); IR (neat): ν_{max} 2953.5, 2106.9, 1751.0, 1444.73, 1278.6, 1020.11 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.76 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.69 (d, 1H, *J*=6.8 Hz, OCH$_A$$H_B$O), 4.29–4.26 (m, 1H, C*H*OCH$_2$), 3.77 (s, 3H, *Me*OOC), 3.57–3.45 (m, 2H, CH_2N), 3.42 (s, 3H, O*Me*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 96.3, 74.5, 56.2, 52.6, 52.4; MS (ESIMS): *m*/*z* 212 $[M+Na]^+$; HRMS (ESI) calcd for $C_6H_{11}N_3O_4$ $[M+Na]^+$: 212.0642, found: 212.0647.

4.1.5. *tert*-Butyl (*R*)-2-(methoxycarbonyl)-2-(methoxymethoxy) ethyl carbamate (10). To a solution of β-CD (567 mg, 0.5 mmol) in distilled water (60 mL) at room temperature was added compound **9** (1.0 g, 5.3 mmol) in acetone (5 mL), followed by TPP (1.67 g, 6.36 mmol). The mixture was stirred at room temperature for 15 min. Then Boc_2O (1.11 mL, 5 mmol) was added to the reaction mixture and stirring was continued at the same temperature for another 20 min. The product was then extracted with ethyl acetate (3×100 mL) and washed with brine solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product thus obtained was purified by column chromatography (SiO_2, 14% ethyl acetate/hexane eluent) to afford **10** (1.26 g, 91%) as a colorless liquid. The aqueous layer was cooled to 5 °C to recover precipitated β-cyclodextrin by filtration (95%) and reused.

$[\alpha]_D^{25}$ +43.06 (*c* 0.54, $CHCl_3$); IR (neat): ν_{max} 3375.8, 2975.3, 1750.1, 1715.1, 1518.6, 1162.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83 (br s, 1H, N*H*), 4.69 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.65 (d, 1H, *J*=6.8 Hz, OCH$_A$$H_B$O), 4.20–4.18 (m, 1H, C*H*OCH$_2$), 3.75 (s, 3H, *Me*OOC), 3.55–3.42 (m, 2H, CH_2N), 3.37 (s, 3H, O*Me*), 1.43 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.9, 155.6, 96.0, 79.5, 74.2, 55.9, 52.0, 42.5, 28.2; MS (ESIMS): *m*/*z* 264 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{22}NO_6$ $[M+H]^+$: 264.1441, found: 264.1447.

4.1.6. *tert*-Butyl (*R*)-3-hydroxy-2-(methoxymethoxy) propyl carbamate (11). To a stirred solution of $NaBH_4$ (370 mg, 10.0 mmol) in dry EtOH (10 mL) at 0 °C was added LiCl (420 mg, 10.0 mmol) and stirred at the same temperature for 10 min. Then compound **10** dissolved in THF (15 mL) (1.0 g, 4.0 mmol) was cannulated into the reaction mixture and stirred at ambient temperature for 18 h. It was then quenched cautiously with saturated aqueous NH_4Cl solution (4 mL) slowly and extracted with EtOAc (2×100 mL). The organic extracts were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. After concentration in vacuo it was subjected to chromatographic purification (SiO_2, 32% EtOAc in petroleum ether eluent) to afford **11** (0.85 g, 90%) as a colorless oil.

$[\alpha]_D^{25}$ +8.6 (*c* 0.54, $CHCl_3$); IR (neat): ν_{max} 3363.3, 2974.9, 2934.5, 1694.1, 1525.4, 1170.7, 1035.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.87 (br s, 1H, N*H*), 4.66 (s, 2H, OCH_2O), 3.68–3.46 (m, 3H, C*H*OCH$_2$, CH_2N), 3.38 (s, 3H, O*Me*), 3.36–3.21 (m, 2H, CH_2OH), 1.44 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 96.3, 79.1, 78.4, 62.0, 55.5, 40.9, 28.2; MS (ESIMS): *m*/*z* 236 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_{22}NO_5$ $[M+H]^+$: 236.1506, found: 236.1497.

4.1.7. *tert*-Butyl (*S*)-2-(methoxymethoxy) but-3-enyl carbamate (12). To a solution of oxalyl chloride (0.56 mL, 6.8 mmol) in dry DCM (15 mL) at −78 °C, DMSO (0.72 mL, 10.2 mmol) was added dropwise with stirring under nitrogen. After stirring for 15 min, compound **11** (0.8 g, 3.4 mmol) in dry DCM (10 mL) was added to the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (2.86 mL, 20.4 mmol) was added and stirred for another 0.5 h at −78 °C and 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (2×100 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude compound was used in the next step without purification.

To methyltriphenylphosphonium iodide (13.7 g, 34 mmol) in dry THF (50 mL) under a nitrogen atmosphere at −78 °C was added *t*-BuOK (3.18 g, 28 mmol) and stirred for 30 min at room temperature. Then the orange yellow ylide solution was added to the above crude aldehyde in dry THF (5 mL) via a cannula and stirring was continued for 1 h, allowing the temperature to warm to 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL). The mixture was filtered over a sintered funnel and the residue was washed with ether (3×15 mL). The combined organic filtrates were evaporated after washing with water (25 mL), drying over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO_2, 8% EtOAc in petroleum ether eluent) afforded **12** (0.67 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ +17.69 (*c* 0.65, $CHCl_3$); IR (neat): ν_{max} 3366.0, 2977.0, 2931.0, 1714.0, 1529.0, 1171.0, 1033.0 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.79–5.56 (m, 1H, CH_2=C*H*), 5.42–5.18 (m, 2H, CH_2=CH), 4.81 (br s, 1H, N*H*), 4.67 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.54 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.18–4.01 (m, 1H, C*H*OCH_2), 3.42–3.23 (m, 1H, C$H_A$$H_B$N), 3.35 (s, 3H, O*Me*), 3.18–2.98 (m, 1H, C$H_A$$H_B$N), 1.43 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.9, 135.4, 118.5, 94.1, 79.2, 76.3, 55.4, 44.5, 28.3; MS (ESIMS): *m*/*z* 232 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{22}NO_4$ $[M+H]^+$: 232.1543, found: 232.1548.

4.1.8. *tert*-Butyl allyl (*S*)-2-(methoxymethoxy) but-3-enyl carbamate (13). A solution of compound **12** (0.6 g, 2.6 mmol) in dry THF (15 mL) was cooled to 0 °C and 60% NaH (208 mg, 5.2 mmol) was added portionwise with stirring under nitrogen atmosphere. After 15 min of stirring at 0 °C, allyl bromide was added to the reaction mixture followed by TBAI (96 mg, 0.26 mmol) and brought to ambient temperature and stirred for 4 h. It was then quenched cautiously with saturated aqueous NH_4Cl solution (5 mL) slowly and extracted with EtOAc (2×75 mL), brine (15 mL) and dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by column chromatography (SiO_2, 5% EtOAc in petroleum ether eluent) to afford **13** (592 mg, 84%) as a colorless liquid.

$[\alpha]_D^{25}$ +21.68 (*c* 0.56, $CHCl_3$); IR (neat): ν_{max} 3465.0, 2970.0, 1697.0, 1533.0, 1407.0, 1155.0, 1030.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.87–5.54 (m, 2H, 2×CH_2=C*H*), 5.36–5.20 (m, 2H, 2×C$H_A$$H_B$=CH), 5.13–5.02 (m, 2H, 2×C*H*$_A$H$_B$=CH), 4.61 (d, 1H, *J*=6.8 Hz, OC*H*$_A$H$_B$O), 4.54–4.40 (m, 1H, OCH$_A$*H*$_B$O), 4.37–4.20 (m, 1H, C*H*OCH$_2$), 4.15–3.88 (m, 1H, =CHC*H*$_A$CH$_B$), 3.78 (dd, 1H, *J*=15.9, 6.0 Hz, =CHCH$_A$C*H*$_B$), 3.42–3.19 (m, 4H, including s for O*Me*, C$H_A$$H_B$N), 3.10 (dd, 1H, *J*=14.4, 8.3 Hz, CH$_A$*H*$_B$N), 1.47 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 75 MHz) (rotamers): δ 157.1, 135.9, 134.0, 118.4, 118.2, 116.3, 115.7, 94.0, 93.7, 79.7, 79.5, 75.9, 55.2, 51.2, 50.7, 50.5, 29.7, 28.3; MS (ESIMS): *m*/*z* 272 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{26}NO_4$ $[M+H]^+$: 272.1854, found: 272.1861.

4.1.9. (*S*)-*tert*-Butyl 5,6-dihydro-5-(methoxymethoxy) pyridine-1-(2*H*)-carboxylate (14). Bis-(tricyclohexylphospine)benzylideneruthenium(IV) dichloride (Grubbs' catalyst) (91 mg, 0.11 mmol) was added to a solution of compound **13** (500 mg, 1.84 mmol) in DCM (300 mL) and stirred for 24 h at room temperature; when TLC revealed the complete consumption of the starting material, the solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, 6% EtOAc in petroleum ether eluent) to afford **14** (411 mg, 92%) as a colorless oil.

$[\alpha]_D^{25}$ +9.0 (*c* 0.74, $CHCl_3$), IR (neat): ν_{max} 3439.0, 2975.0, 2930.0, 1704.0, 1367.0, 1156.0, 1042.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.94–5.69 (m, 2H, C*H*=C*H*), 4.69 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.67 (d, 1H, *J*=6.8 Hz, OCH$_A$*H*$_B$O), 4.17–4.06 (m, 1H, C*H*OCH$_2$), 3.98–3.60 (m, 3H, 2×H_2, H_6), 3.37–3.21 (m, 4H, including s for O*Me*, H_6), 1.46 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 154.9, 131.2, 129.0, 95.3, 80.0, 68.6, 68.0, 55.5, 38.6, 28.4; MS (ESIMS): *m*/*z* 244 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{22}NO_4$ $[M+H]^+$: 244.1549, found: 244.1554.

4.1.10. (3*R*,4*R*,5*R*)-*tert*-Butyl 3,4-dihydroxy-5-(methoxymethoxy) piperidine-1-carboxylate (15). To a solution of compound **14** (121 mg, 0.5 mmol) in acetone (2 mL) was added aqueous 4% OsO_4 solution (65 μL, 0.01 mmol). After 10 min, aqueous 50% NMO solution (0.176 mL, 0.75 mmol) was added and the mixture was stirred overnight. To the solution were added Na_2SO_3 and Na_2SO_4. The mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, 50% EtOAc in petroleum ether eluent) to afford **15** (113 mg, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ −33.0 (*c* 0.44, $CHCl_3$); IR (neat): ν_{max} 3436.7, 2929.1, 1686.2, 1426.6, 1162.7, 1038.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.70 (d, 1H, *J*=6.8 Hz, OC$H_A$$H_B$O), 4.66 (d, 1H, *J*=6.8 Hz, OCH$_A$*H*$_B$O), 4.34–3.92 (m, 3H, H_3, H_4, H_5), 3.74–3.31 (m, 5H, including s for O*Me*, H_{2eq}, H_{6eq}), 3.17–2.83 (m, 2H, H_{2ax}, H_{6ax}), 2.75–2.55 (br s, 1H, O*H*), 2.32–2.12 (br s, 1H, O*H*), 1.45 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 50 MHz) (rotamers): δ 155.0, 96.1, 95.8, 79.5, 75.4, 74.8, 72.6, 72.2, 66.7, 55.1, 50.5, 46.4, 45.3, 44.4, 29.1, 27.7, 22.5; MS (ESIMS): *m*/*z* 278 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{24}NO_6$ $[M+H]^+$: 278.1592, found: 278.1603.

4.1.11. (*S*)-*tert*-Butyl 3-(methoxymethoxy) piperidine-1-carboxylate (16). To a solution of **14** (121 mg, 0.5 mmol) in ethyl acetate (5 mL) was added PtO_2 (6 mg,

0.025 mmol) and the reaction mixture was allowed to stir under an H_2 atmosphere for 1 h. The reaction mixture was filtered through Celite and evaporated to dryness under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 6% EtOAc in petroleum ether eluent) to afford **16** (120 mg, 98%) as a light yellow liquid.

$[\alpha]_D^{25}$ −34.8 (*c* 0.56, $CHCl_3$); IR (KBr): ν_{max} 3446.0, 2932.8, 1694.5, 1419.8, 1153.9, 1041.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.65 (d, 1H, *J*=6.8 Hz, OCH_AH_BO), 4.59 (d, 1H, *J*=6.8 Hz, OCH_AH_BO), 3.92–3.45 (m, 3H, $CHOCH_2$, H_2, H_6), 3.35 (s, 3H, O*Me*), 3.12–2.91 (m, 2H, H_2, H_6), 1.98–1.83 (m, 1H, H_4), 1.82–1.65 (m, 1H, H_5), 1.58–1.21 (m, 11H, including s for ^{t}Bu, H_4, H_5); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9, 94.7, 79.5, 76.4, 70.9, 55.2, 47.7, 30.7, 28.3, 22.6; MS (ESIMS): *m/z* 246 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{24}NO_4$ $[M+H]^+$: 246.1714, found: 246.1705.

4.1.12. (3*R*,5*R*)-Piperidine-3,4,5-triol hydrochloride (1). To a solution of **15** (100 mg, 0.36 mmol) in distilled MeOH (2 mL) was added 6 M HCl (0.04 mL) and the reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was passed through a short pad of Celite and the solvent was removed under reduced pressure to afford **1**·HCl (43 mg, 90%) as a white solid.

Mp=190–191 °C; $[\alpha]_D^{25}$ −15.0 (*c* 0.42, MeOH) (lit.[9a,d] mp 191–192 °C, $[\alpha]_D^{20}$ −16.0 (*c* 0.9, MeOH)); IR (neat): ν_{max} 3388.4, 3070.5, 2925.3, 1465.4, 1082.2 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 4.23–4.18 (m, 1H, H_5), 4.12–4.01 (m, 1H, H_3), 3.73 (dd, 1H, *J*=7.5, 2.7 Hz, H_4), 3.36 (dd, 1H, *J*=12.3, 4.1 Hz, H_{2eq}), 3.32–3.12 (m, 2H, H_{6eq}, H_{6ax}), 2.92 (dd, 1H, *J*=12.3, 8.2 Hz, H_{2ax}); ^{13}C NMR (D_2O, 75 MHz): δ 70.9, 65.2, 64.8, 46.3, 45.6; MS (ESIMS): *m/z* 134 $[M+H]^+$; HRMS (ESI) calcd for $C_5H_{12}NO_3$ $[M+H]^+$: 134.0821, found: 134.0817.

4.1.13. (*S*)-*tert*-Butyl 3-hydoxy piperidine-1-carboxylate (4). A solution of piperidine **16** (100 mg, 0.4 mmol) in distilled MeOH (2 mL) was treated with 6 M HCl (0.04 mL) and stirred at room temperature for 7 h. The reaction mixture was evaporated under reduced pressure. The resulting residue was dissolved in MeOH (4 mL) and Et_3N (0.11 mL, 2 mmol) and Boc_2O (0.11 mL, 0.48 mmol) were added successively and the reaction mixture was stirred at room temperature for 30 min. Then the solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate (3×15 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue thus obtained was purified by column chromatography (SiO_2, 25% ethyl acetate/hexane eluent) to afford **4** (72 mg, 89%) as a colorless liquid.

$[\alpha]_D^{25}$ +23.0 (*c* 0.65, EtOH) (lit.[18c,9d] $[\alpha]_D^{25}$ +23.5 (*c* 1.46, EtOH)); IR (neat): ν_{max} 3424.8, 2928.6, 2857.9, 1693.8, 1426.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.77–3.63 (m, 2H, H_2, H_6), 3.56–3.39 (m, 1H, $CHOH$), 3.23–2.99 (m, 2H, H_2, H_6), 1.91–1.66 (m, 2H, H_4, H_5), 1.59–1.33 (m, 11H, including s for ^{t}Bu, H_4, H_5); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.7, 77.8, 72.5, 51.5, 42.8, 33.3, 29.2, 22.5; MS (ESIMS): *m/z* 202 $[M+H]^+$; HRMS (ESI) calcd for $C_{10}H_{20}NO_3$ $[M+H]^+$: 202.1452, found: 202.1443.

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