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A new concise stereoselective method for the preparation of a β-hydroxyfurfurylamine derivative and synthesis of 1-deoxyazasugar isomers

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Abstract

A new method to prepare a chiral building block, a β-hydroxyfurfurylamine derivative, is achieved and 1-deoxyazasugar isomers are synthesized.

1. Introduction

Polyhydroxylated piperidine alkaloids, such as (+)-1-deoxynojirimycin **1**[1] and (−)-1-deoxymannojirimycin **2**[2] (Fig. 1) can be regarded as 1-deoxyazasugars. Owing to the variety of their biological activities, many efforts have been devoted in recent years to develop appropriate synthetic methods.[3]

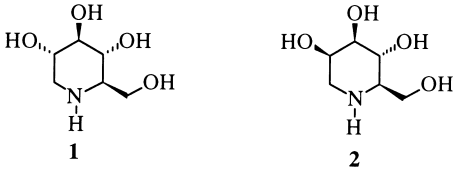

Figure 1.

In connection with our previous work on the kinetic resolution of racemic α-furfurylamine by using a modified Sharpless epoxidation reagent,[4] recently, Zhou et al. applied the chiral dihydropyridone **4** (R=Me) obtained from the kinetic resolution of the racemic β-hydroxyfurfurylamine derivative **3a** to synthesize (−)- and (+)-1-deoxymannojirimycin as well as (−)- and (+)-deoxyaltronojirimycin.[5] In the meanwhile, Altenbach and Wischnat[6] synthesized a protected mannojirimycin derivative through

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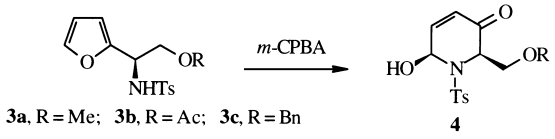
the racemic dihydropyridone **4** (R=Ac) obtained from the racemic β-hydroxyfurfurylamine derivative **3b** which was prepared from furfuryl glycine (Scheme 1). In addition, very recently, Zhou et al.[7a] and O'Doherty et al.[7b] employed independently the Sharpless asymmetric aminohydroxylation[7c] of vinylfuran for the preparation of a useful chiral building block, β-hydroxyfurfurylamine derivative.

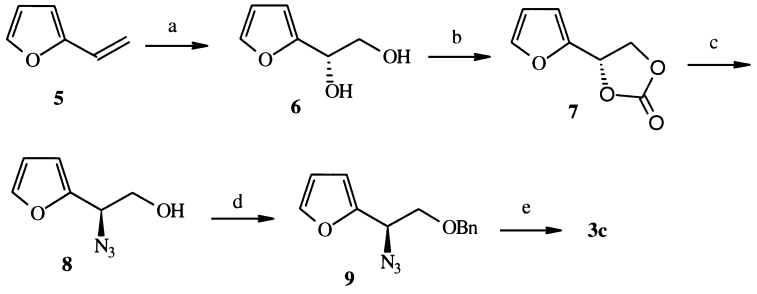


3a, R = Me; **3b**, R = Ac; **3c**, R = Bn **4**

Scheme 1.

2. Results and discussion

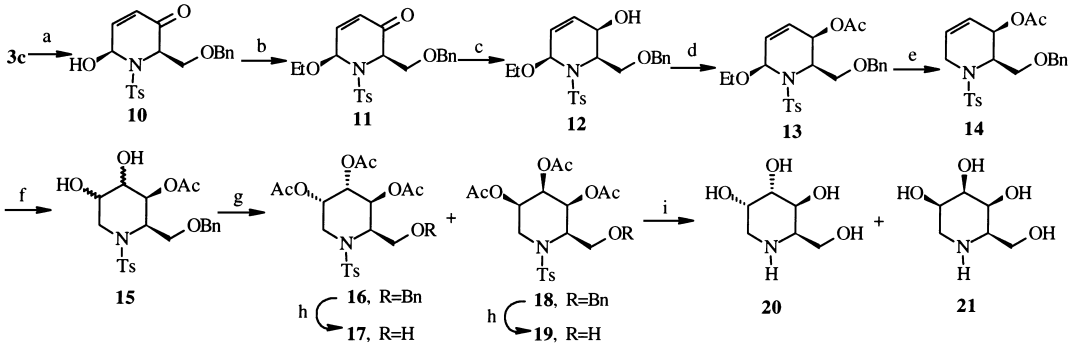
A new concise method to prepare chiral β-hydroxyfurfurylamine derivative **3c** by using Sharpless asymmetric dihydroxylation (AD)[8] as the key step with high chemical yield and high enantioselectivity is described. This new method has advantages over the above mentioned kinetic resolution, not only because of its convenient manipulation, but also its suitability for large scale preparation. As depicted in Scheme 2, furfuryl glycol **6**[9] was obtained by Sharpless AD[8] from vinyl furan **5**[10] with $(DHQD)_2$–PHAL as a ligand, in 92% yield. Then the dihydroxyl group was protected with dimethyl carbonate by heating in the presence of a catalytic amount of NaOH to give **7** in 94% yield and 92% e.e.[11] Compound **7** was treated with NaN_3 in the presence of 1 equiv. H_2O in DMF to give **8** in 91% yield and 91% e.e.[11] The azido-compound **8** was produced stereospecifically with inversion.[12] The β-hydroxyfurfurylamine derivative **3c** (R=Bn) was then obtained by protection of the primary hydroxyl group of **8** with a benzyl group, then reduction with $LiAlH_4$ in THF and final protection of the primary amino group with *p*-toluenesulfonyl chloride in pyridine in 74% yield from **8** and 94% e.e.[11] (after recrystallization with petroleum ether–ethyl acetate). The overall yield is 59% in five steps (Scheme 2).



5 **6** **7** **8** **9**

Scheme 2. Reagents and conditions: (a) $(DHQD)_2$–PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, 0°C, 10 h, 92%; (b) $(MeO)_2CO$, KOH, 60° → 90°C, 94%, 92% e.e.; (c) NaN_3, DMF, H_2O, 120°C, 10 h, 91%, 91% e.e.; (d) NaH, BnBr, 80.7%; (e) (i) $LiAlH_4$, THF, reflux; (ii) TsCl, Py, 0°C, 93% (two steps), 94%, e.e. (after recrystallization)

Synthesis of the target molecules starting from **3c** was carried out as shown in Scheme 3. The procedure for preparation of these target molecules was similar to that prepared previously by Zhou et al.[5] Compound **10** was obtained by oxidation of β-hydroxyfurfurylamine derivative **3c** with *m*-CPBA leading to the *cis*-stereochemistry[13] of 2H and 6H in **10** which was confirmed by X-ray[14] diffraction (Fig. 2). The hydroxyl group of **10** was then protected with triethylorthoformate in the presence of $BF_3 \cdot Et_2O$[15] to give **11** which was reduced with $NaBH_4$ in the presence of $CeCl_3$ to give solely the C_3-β-hydroxyl compound **12**. The configuration of this hydroxyl group was assigned by 2D-NOESY spectroscopic analysis.[5b]



Scheme 3. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 82.4%; (b) $HC(OEt)_3$, $BF_3 \cdot Et_2O$, 4 Å sieves, THF, 0°C, 4 h, 90%; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −30°C, 2 h, 97%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 2 h, 86%; (e) $NaBH_4$, HCOOH, 0°C, 85.9%; (f) $(DHQD)_2$–PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O (1:1), 0°C, 94%; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 2 h, 86% in the ratio of 4:1; (h) Pd/C, H_2, EtOAc, rt, 4 h, 82.0% for **17**, 84.0% for **19**; (i) Na/NH_3(l), −78°C, 4 h, 52% for **20**, 55% for **21**

Compound **12** was protected by Ac_2O in the presence of Et_3N and catalytic amount of DMAP. The ethoxy group in **13** was removed by using $NaBH_4$ in formic acid to give **14**. However, removal of ethoxy group of **12** without protection of C_3-OH group under the same conditions as for **13** gave a complex mixture. Compound **14** was subjected to the Sharpless asymmetric dihydroxylation with $(DHQD)_2$–PHAL as a ligand to give the mixture of **15**, which was separated through flash column chromatography on silica gel to afford **16** and **18** after acetylation in the ratio of 4:1. The major isomer is the α-hydroxy compound. Debenzylation of **16** and **18** with Pd–C gave **17** and **19**, respectively. The configurations of **16** and **18** were distinguished by 2D–^{1}H NOESY spectrum as shown in Fig. 3. Deprotection of **17** and **19** with sodium and liquid ammonia[16] gave 1-deoxyazasugar isomer **20** along with minor isomer **21**, respectively.

In summary, a new method to prepare the chiral building block, β-hydroxyfurfurylamine derivative **3c**, the e.e. value of which is 94%, was achieved in five steps in an overall yield of 58%. The chiral β-hydroxyfurfurylamine derivative **3c** is a useful building block, since it could be easily transformed into chiral dihydropyridone derivatives which are used for synthesis of the polyhydroxylated alkaloids,[5,17] such as azasugars, by conversion of α,β-unsaturated ketone into the desired functional groups with various methods. 1-Deoxyazasugar isomers **20** and **21** were prepared in overall yields of 16% and 3.5%, respectively.

3. Experimental

3.1. General

Melting points were determined with a Büchi 535 melting point apparatus and were uncorrected. All additions were made by syringes. Reactions were monitored by using thin layer chromatography (TLC). The silica gel used in flash chromatography was silica gel H (10–40 μ) which was produced by the Qingdao Chemical Plant, China. IR spectra were measured on a Schimadzu IR 400 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) with $CDCl_3$ as solvent and values were reported in ppm using TMS or residual $CHCl_3$ as internal standard. MS spectra were conducted on a Finnigan 4021 GC–MS instrument and JMS-01U spectrometer. The optical rotations, $[\alpha]_D^{20}$, were measured on a Perkin–Elmer 241 MC automatic polarimeter in a 1 dm cell and recorded in units of 10^{-1}deg cm^2 g^{-1}. Element analysis were performed by the Analytical Department of this

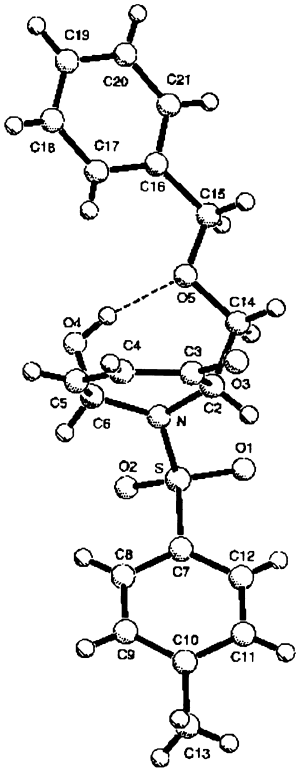
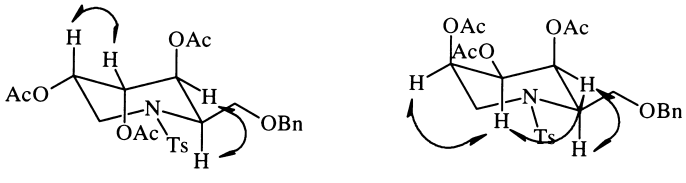


Figure 2. The molecule structure of **10**



NOE correlation in **16** NOE correlation in **18**

Figure 3.

institute. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was freshly distilled from Na–benzophenone.

*3.2. (S)-1-(α-Furyl)-1,2-ethanediol **6***

A 2 l round bottom flask was charged with *tert*-butyl alcohol (0.8 l), water (0.8 l), $K_3Fe(CN)_6$ (157.5 g, 0.48 mol), K_2CO_3 (66.1 g, 0.48 mol) and $(DHQD)_2$–PHAL (248 mg, 2% equiv.). After the resulting mixture was cooled to 0°C, compound **5** (15.0 g, 0.16 mol) and $K_2OsO_2(OH)_4$ (117 mg, 2% equiv.) were added to the resulting heterogeneous slurry which was then vigorously stirred at 0°C for 4 h. The reaction was quenched by addition of Na_2SO_3 (60.6 g, 0.48 mol) to the mixture and stirred for 1 h. The salt added caused the organic layer separation. The aqueous layer was separated and extracted with ethyl acetate (3×250 ml). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (20:10)] to afford an oil **6** (19.2 g, 94%). $[\alpha]_D^{20}=-32.8$ (c=2.8, $CHCl_3$)

[lit.[9]: $[\alpha]_D^{20}$=−34.2, (c=0.4, $CHCl_3$)]; ^{1}H NMR δ: 3.84 (d, 2H, J=5.9 Hz, CH_2OH), 4.78 (t, 1H, J=5.5 Hz, CHOH), 6.30 (d, 1H, J=3.2 Hz, furyl 3-H), 6.34 (dd, 1H, J=1.9, 3.2 Hz, furyl 4-H), 7.37 (d, 1H, J=1.3 Hz, furyl 5-H); IR: 3400 cm^{-1}; MS *m/z*: 128 (M^+), 111 (M^++1−H_2O).

3.3. (S)-4-(α-Furyl)-1,3-dioxolane-2-one **7**

A 250 ml round bottom flask was charged with compound **6** (19.2 g, 0.15 mol), dimethyl carbonate (100 ml) and solid KOH (8.4 g). After the mixture was heated at 60°C for 2 h, the resulting methanol and unreacted dimethyl carbonate were distilled out at 95°C and 110°C, respectively. After the residue was cooled to rt, ethyl acetate (100 ml) and water (50 ml) were added. The aqueous layer was separated and extracted with ethyl acetate (3×100 ml). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **7** (19.6 g, 84%). $[\alpha]_D^{20}$=+63.4 (c=1.1, EtOH); ^{1}H NMR δ: 4.70 (dd, 2H, J=2.1, 8.2 Hz, CH_2O), 5.70 (t, 1H, J=8.0 Hz), 6.44 (dd, 1H, J=1.8, 3.2 Hz, furyl 4-H), 6.60 (d, 1H, J=3.2 Hz, furyl 3-H), 7.53 (d, 1H, J=1.8 Hz, furyl 5-H); IR: 1736 cm^{-1}; MS *m/z*: 154 (M^+), 110 (M^+−CO_2); HRMS (M^+) for $C_7H_6O_4$: calcd: 154.0268; found: 154.0270.

3.4. (R)-2-(α-Furyl)-2-triazo-1-ethanol **8**

A 250 ml round bottom flask was charged with DMF (50 ml), NaN_3 (3.25 g, 0.15 mol), distilled water (0.9 ml, 0.05 mol) and compound **7** (7.70 g, 0.05 mol). After reaction for 12 h at 120°C, ethyl acetate (100 ml) and water (50 ml) were added. The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **8** (6.96 g, 91%). $[\alpha]_D^{20}$=+95.3 (c=1.3, EtOH); ^{1}H NMR δ: 3.92 (d, 2H, J=6.3 Hz, CH_2OH), 4.65 (t, 1H, J=6.2 Hz, CHN_3), 6.39 (m, 2H), 7.44 (d, 1H, J=1.4 Hz, furyl 5-H); IR: 2176, 3400 cm^{-1}; MS *m/z*: 153 (M^+), 111 (M^+−N_3) 122 (M^+−CH_2OH); HRMS (M^+) for $C_6H_7N_3O_2$: calcd: 153.0518; found: 153.0498.

3.5. (R)-2-((1-Triazo-2-phenylmethoxy)ethyl)furan **9**

To sodium hydride (1.33 g, 0.055 mol) in 100 ml of DMF at 0°C was added **8** (7.65 g, 0.05 mol) for 0.5 h, then benzyl bromide (5.8 ml, 0.055 mol) was added slowly for another 0.5 h. After being stirred for 2 h, 20 ml of aqueous NH_4Cl and 20 ml of water were added sequentially. The mixture was extracted with ethyl acetate and the combined organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (90:10)] to afford an oil **9** (9.8 g, 80.7%). $[\alpha]_D^{20}$=+26.3 (c=1.5, EtOH); ^{1}H NMR δ: 3.84 (m, 2H), 4.62 (d, 2H J=4.0 Hz, $PhCH_2$), 4.70 (m, 1H), 6.36 (m, 2H), 7.41 (m, 6H); IR: 2100 cm^{-1}; MS *m/z*: 243 (M^+), 152 (M^+−Bn). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.12. Found: C, 64.25; H, 5.41; N, 17.56.

3.6. (R)-1-(α-Furyl)-2-phenylmethoxy-N-tosylethylamine **3c**

To $LiAlH_4$ (0.62 g, 0.016 mol) in THF (10 ml) at 0°C was added a solution of **9** (2.38 g, 0.010 mol) in THF (2 ml) for 0.5 h. After being stirred for 0.5 h, the mixture was warmed up to rt and stirred at rt for 1 h, and then reluxed for 4 h. The reaction was quenched by addition of water. The mixture was filtered and the filtrate was dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil. To the

solution of the crude oil in pyridine (15 ml) was added *p*-toluenesulfonyl chloride (1.95 g, 10.8 mmol) at 0°C. After being stirred for 0.5 h, 20 ml of water was added. Working up as usual afforded a solid which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (90:10)] to afford **3c** (3.2 g, 93%) as a solid. M.p. 72–74°C, $[\alpha]_D^{20}$=+7.5 (c=0.6, EtOH); ^{1}H NMR δ: 2.39 (s, 3H, Ts-CH_3), 3.62 (m, 1H), 3.74 (m, 1H), 4.47 (s, 2H, PhCH_2), 4.63 (m, 1H), 5.21 (d, 1H, J=7.4 Hz, N-H), 6.13 (d, 1H, J=3.2 Hz, furyl 3-H), 6.21 (dd, 1H, J=1.8, 3.1 Hz, furyl 4-H), 7.18–7.39 (m, 8H), 7.65 (d, 2H, J=8.1 Hz, Ph); IR: 3256 cm^{-1}; MS *m/z*: 371 (M^+), 250 (M^+−BnOCH_2), 216 (M^+−Ts). Anal. calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.35; H, 5.63; N, 3.47.

*3.7. (2*R*,6*S*)-1,6-Dihydro-1-tosyl-6-hydroxy-2-phenylmethoxymethyl-3(2*H*)-pyridinone **10***

The procedure was the same as that of our previous paper.[18]

*3.8. (2*R*,6*S*)-1,6-Dihydro-1-tosyl-6-ethoxy-2-phenylmethoxymethyl-3(2*H*)-pyridinone **11***

The procedure was the same as that of our previous paper.[18]

*3.9. (2*R*,3*R*,6*S*)-1-Tosyl-6-ethoxy-2-phenylmethoxymethyl-1,2,3,6-tetrahydropyridin-3-ol **12***

To a solution of compound **11** (0.971 g, 2.34 mmol) in MeOH (10 ml) was added $CeCl_3$ (0.288 g, 1.17 mmol). $NaBH_4$ (0.267 g, 7.02 mmol) was added in portions at −30°C to the mixture which was then stirred at the same temperature for 2 h. Water (5 ml) was added at −10°C to the mixture which was filtered. MeOH was evaporated from the filtrate under reduced pressure and the aqueous residue was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **9** (0.95 g, 97.4%). $[\alpha]_D^{20}$=−34.3 (c=0.53, EtOH); ^{1}H NMR δ: 1.16–1.26 (m, 3H), 2.41 (s, 3H, CH_3 of Ts), 3.64–3.70 (m, 4H), 4.22 (m, 2H), 4.48 (s, 2H, PhCH_2), 5.40 (m, 1H), 5.74 (m, 2H), 7.24–7.32 (m, 7H), 7.69 (d, 2H, J=8.3 Hz); IR: 3400 cm^{-1}; MS *m/z*: 372 (M^+−EtO), 262 (M^+−Ts), 155 (Ts), 91 (Bn). Anal. calcd for $C_{22}H_{27}NO_5S$: C, 63.29; H, 6.51; N, 3.35. Found: C, 63.47; H, 6.03; N, 3.07.

*3.10. (2*R*,3*R*,6*S*)-1-Tosyl-6-ethoxy-2-phenylmethoxymethyl-1,2,3,6-tetrahydro-3-pyridyl acetate **13***

To a solution of compound **12** (0.720 g, 1.73 mmol) in CH_2Cl_2 (15 ml) were added triethylamine (0.48 ml, 3.46 mmol) and DMAP (42 mg, 0.346 mmol) at 0°C. After being stirred for 0.5 h, acetic anhydride (0.33 ml, 3.46 mmol) was added at the same temperature. The mixture was then stirred at 0°C for another 2 h. Water (5 ml) was added and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **13** (0.674 g, 86%). $[\alpha]_D^{20}$=−96.1 (c=1.33, EtOH); ^{1}H NMR δ: 1.16 (t, 3H, J=7.0 Hz, CH_3CH_2O), 1.84 (s, 3H, AcO), 2.41 (s, 3H, CH_3 of Ts), 3.47–3.87 (m, 4H), 4.38–4.57 (m, 4H), 4.75 (d, 1H, J=1.9 Hz), 5.47–5.85 (m, 2H), 7.25–7.30 (m, 7H), 7.76 (d, 2H, J=8.3 Hz, Ph); MS *m/z*: 458 (M^+−1), 414 (M^+−EtO), 155 (Ts), 91 (Bn). Anal. calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.04. Found: C, 62.83; H, 6.48; N, 2.64.

3.11. (2R,3R)-1-Tosyl-2-phenylmethoxymethyl-1,2,3,6-tetrahydro-3-pyridyl acetate **14**

To a solution of **13** (200 mg, 0.436 mmol) in 88% formic acid (2 ml) at 0°C was added $NaBH_4$ (49 mg, 1.3 mmol) in portions. After being stirred for 4 h, the mixture was evaporated under reduced pressure and water (4 ml) was added to the residue. The resulting mixture was extracted with ethyl acetate and the combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **14** (155 mg, 86%). $[\alpha]_D^{20}$=−47 (c=0.67, EtOH); ^{1}H NMR δ: 1.97 (s, 3H, OAc), 2.38 (s, 3H, Ts-CH_3), 3.38–3.57 (m, 3H), 4.07 (m, 1H), 4.33, (d, 1H, J=12.0 Hz, CH_aH_bPh), 4.45 (d, 1H, J=12.0 Hz, CH_aH_bPh), 4.76 (m, 1H), 5.30 (m, 1H), 5.54 (m, 1H), 5.71 (m, 1H), 7.20–7.35 (m, 7H), 7.75 (d, 2H, J=8.2 Hz); IR: 1750 cm^{-1}; MS *m/z*: 414 (M^++1), 356 (M^+−OAc), 260 (M^+−Ts), 294 (M^+−CH_2OBn). Anal. calcd for $C_{22}H_{25}NO_5S$: C, 63.59; H, 6.06; N, 3.37. Found: C, 63.11; H, 6.03; N, 3.22.

3.12. (2R,3R)-1-Tosyl-4,5-dihydroxy-2-phenylmethoxymethyl-3-piperidyl acetate **15**

A 25 ml round bottom flask was charged with *tert*-butyl alcohol (4 ml), water (4 ml), $K_3Fe(CN)_6$ (0.713 g, 2.17 mmol), K_2CO_3 (0.299 g, 2.17 mmol) and $(DHQD)_2$–PHAL (28 mg, 5% equiv.). After the resulting mixture was cooled to 0°C, compound **14** (0.300 g, 0.722 mmol) and $K_2OsO_2(OH)_4$ (13 mg, 5% equiv.) were added to the resulting heterogeneous slurry which was then vigorously stirred at 0°C for 4 h. The reaction was quenched by addition of Na_2SO_3 (0.270 g, 2.17 mmol) to the mixture and stirred for 1 h. The salt added caused layer separation. The aqueous layer was separated and extracted with ethyl acetate (3×25 ml). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (20:10)] to afford a mixture of **15** (0.302 g, 93%).

3.13. (2R,3S,4S,5S)-1-Tosyl-3,4,5-triacetoxy-2-phenylmethoxymethyl piperidine **16** and (2R,3S,4R,5R)-1-Tosyl-3,4,5-triacetoxy-2-phenylmethoxymethyl piperidine **18**

To a solution of compound **15** (0.260 g, 0.579 mmol) in CH_2Cl_2 (10 ml) were added triethylamine (0.097 ml, 0.70 mmol) and DMAP (7 mg, 0.058 mmol) at 0°C. After being stirred for 0.5 h, acetic anhydride (0.13 ml, 1.4 mmol) was added at the same temperature. The mixture was then stirred at 0°C for another 2 h. Water (5 ml) was added and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **16** (0.220 g, 71%) and **18** (0.054 g, 17%). Compound **16**: $[\alpha]_D^{20}$=+5.9 (c=1.7, EtOH); ^{1}H NMR δ: 1.97, 1.967, 2.009 (s, each 3H, OAc), 2.38 (s, 3H, CH_3 of Ts), 3.067 (dd, 1H, J=14.1, 11.5Hz, H_{6a}), 3.634 (dd, 1H, J=11.1, 9.2 Hz, H_e of CH_2OBn), 3.812 (dd, 1H, J=11.1, 3.1 Hz, H_a of CH_2OBn), 3.830 (dd, 1H, J=14.1, 5.4 Hz, H_{6e}), 4.431, 4.523 (ab, 2H, J=12 Hz, CH_2Ph), 4.661 (ddd, 1H, J=9.2, 6.5, 3.1 Hz, H_{2a}), 4.687 (ddd, 1H, J=11.5, 5.4, 2.7 Hz, H_{5a}), 4.846 (dd, 1H, J=6.5, 2.7 Hz, H_{3e}), 5.441 (dd, 1H, J=2.7, 2.6 Hz, H_{4e}), 7.223, 7.810 (d, each 2H, J=8.4 Hz, each Ts-aromatic), 7.259–7.343 (m, 5H, benzyl-aromatic) (their assignments were made by COSY and NOESY spectrum run at 600 MHz NMR); IR: 1750 cm^{-1}; MS *m/z*: 378 (M^+−Ts), 426 (M^+−BnO), 155 (Ts), 91 (Bn). Anal. for ($C_{26}H_{31}NO_9S$) calcd: C, 58.52; H, 5.85; N, 2.62; found: C, 58.43; H, 5.94; N, 2.09. **18**: $[\alpha]_D^{20}$ +33.4 (c=0.3, EtOH); ^{1}HNMR δ (ppm): 1.85 (s, 3H, AcO), 1.93 (s, 3H, AcO), 1.97 (s, 3H, AcO), 2.39 (s, 3H, CH_3 of Ts), 3.65 (d, 1H, J=3.2 Hz), 3.69 (d, 1H, J=14.9 Hz), 3.93 (d, 1H, J=14.9 Hz), 4.37

(d, 1H, J=12.2 Hz), 4.51 (d, 1H, J=12.2 Hz), 4.53 (m, 2H), 5.19 (m, 2H), 5.63 (dd, 1H, J=3.4, 10.9 Hz), 7.25–7.37 (m, 7H), 7.74 (d, 2H, J=8.3 Hz); IR: 1750 cm^{-1}; MS *m/z*: 378 (M^+−Ts), 426 (M^+−BnO), 155 (Ts), 91 (Bn). Anal. calcd for $C_{26}H_{31}NO_9S$: C, 58.52; H, 5.85; N, 2.62. Found: C, 58.34; H, 5.90; N, 2.06.

*3.14. (2R,3S,4S,5S)-1-Tosyl-3,4,5-triacetoxy-2-hydroxymethyl piperidine **17***

To a solution of **16** (0.110 g, 0.210 mmol) in ethyl acetate (15 ml) was added 10% Pd on carbon (0.100 g), and the mixture was placed under an atmosphere of H_2 and stirred at rt. After 8 h, the reaction mixture was filtered and the solvent was removed under reduced pressure to give a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (10:10)] to afford **17** (0.076 g, 82%) as an oil. $[\alpha]_D^{20}$=−4.0 (c=2.0, EtOH); ^{1}H NMR δ: 1.85 (s, 3H, AcO), 1.96 (s, 3H, AcO), 2.06 (s, 3H, AcO), 2.43 (s, 3H, Ts-CH_3), 3.49 (m, 1H), 3.62 (dd, 1H, J=1.6, 13.8 Hz), 3.88 (m, 1H), 3.98–4.04 (m, 1H), 4.49 (m, 1H), 5.21 (m, 1H), 5.24 (dd, 1H, J=4.5, 6.4 Hz), 5.30 (dd, 1H, J=3.4, 7.6 Hz), 7.34 (d, 2H, J=8.3 Hz) 7.80 (d, 2H, J=8.3 Hz); IR: 3500, 1750 cm^{-1}; MS *m/z*: 444 (M^++1), 426 (M^++1−H_2O), 412 (M^+−CH_2OH). HRMS (M^+−CH_2OH) for $C_{18}H_{22}NO_8S$: calcd: 412.1075; found: 412.1066.

*3.15. (2R,3S,4R,5R)-1-Tosyl-3,4,5-triacetoxy-2-hydroxymethyl piperidine **19***

To a solution of **18** (0.150 g, 0.281 mmol) in ethyl acetate (15 ml) was added 10% Pd on carbon (0.120 g), and the mixture was placed under an atmosphere of H_2 and stirred at rt. After 6 h, the reaction mixture was treated in the way as described for **17** to afford **19** (0.105 g, 84%) as an oil. $[\alpha]_D^{20}$=+36.2 (c=2.5, EtOH); ^{1}H NMR δ: 1.99 (s, 3H, AcO), 2.04 (s, 3H, AcO), 2.09 (s, 3H, AcO), 2.45 (s, 3H, Ts-CH_3), 3.27 (m, 1H), 3.76 (dd, 1H, J=2.0, 10.1 Hz), 4.12 (dd, 1H, J=7.2, 14.3 Hz), 4.32 (m, 1H), 4.52 (m, 1H), 4.58 (dd, 1H, J=2.7, 6.6 Hz), 5.36 (t, 1H, J=2.7 Hz), 7.38 (d, 2H, J=8.3 Hz, Ph), 7.84 (d, 2H, J=8.3 Hz, Ph); IR: 3500, 1750 cm^{-1}; MS *m/z*: 444 (M^++1), 426 (M^++1−H_2O), 412 (M^++1−CH_2OH). Anal. calcd for $C_{19}H_{25}NO_9S$: C, 51.45; H, 5.68; N, 3.15. Found: C, 51.27; H, 5.57; N, 2.75.

*3.16. (2R,3S,4S,5S)-3,4,5-Trihydroxy-2-hydroxymethyl piperidine **20***

To the liquid ammonia (15 ml) at −78°C was added **17** (0.060 g, 0.135 mmol) (dissolved in 5 ml of THF) and sodium to keep the solution a blue color. After being stirred for 3.5 h, the sat. NH_4Cl was added. Warming up to rt under N_2, liquid ammonia was evaporated. The residue was purified by column chromatography on ion exchange resin (Dowex 50) to afford a colorless solid **20** (9 mg, 41%). M.p.: 148–149.6°C; $[\alpha]_D^{20}$=−16.2 (c=0.3, EtOH); ^{1}H NMR δ (D_2O): 3.07 (dd, 1H, J=4.7, 7.1 Hz), 3.33 (dd, 1H, J=4.7, 7.1 Hz), 3.64 (m, 1H), 3.98–4.15 (m, 2H), 4.33 (m, 1H), 4.42 (m, 1H), 4.60 (m, 1H); IR: 3500 cm^{-1}; MS (ESI) *m/z*: 164 (M+H), 186 (M+Na).

*3.17. (2R,3S,4R,5R)-3,4,5-Trihydroxy-2-hydroxymethyl piperidine **21***

To the liquid ammonia (15 ml) at −78°C was added **19** (0.080 g, 0.135 mmol) (dissolved in 5 ml of THF) and sodium to keep the solution a blue color. The reaction solution was treated in the way as described for **20** to afford a colorless solid **21** (12 mg, 41%). M.p. 150–151°C; $[\alpha]_D^{20}$=+30.4 (c=0.3, EtOH); ^{1}H NMR δ (ppm) (D_2O): 2.79 (m, 1H), 2.95 (dd, 1H, J=4.8, 12.3 Hz), 3.10 (dd, 1H, J=8.9, 8.4Hz), 3.61–3.66 (m, 2H), 3.92–4.01 (m, 3H); IR: 3500 cm^{-1}; MS (ESI) *m/z*: 164 (M+H), 186 (M+Na).

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