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Novel asymmetric total synthesis of the natural (+)-6-epicastanospermine

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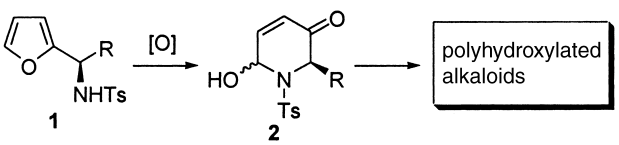
Abstract—An efficient noncarbohydrate-based enantioselective synthesis of (+)-6-epicastanospermine has been developed utilizing the Sharpless asymmetric aminohydroxylation of furyl acrylate and oxidation of α-furfurylamine derivative **17** as key steps.

1. Introduction

We have been interested in exploiting dihydropyridones **2**, which are produced by oxidation of α-furfuryl amines **1**, as key intermediates in the asymmetric total syntheses of a variety of polyhydroxylated alkaloids (Scheme 1). The application of this strategy has resulted in syntheses of (+)-azimic acid, (+)-desoxoprosophylline, prosophylline swainsonine and azasugars.[1] As an extension of this work, we were intrigued by the possibility of using this strategy to realize polyhydroxylated alkaloids of the indolizidine family.[2] Among the polyhydroxylated indolizidine alkaloids, castanospermine **3** and its derivatives have been the most popular targets for synthetic investigations. Castanospermine **3** (Fig. 1), isolated from the seeds of the Australian legume *Castanospermum australe*[3] and the dried pod of *Alexa leiopetala*,[4] has been shown to be a potent competitive and reversible inhibitor of various glycosidases.[5] It has potential for the treatment of diabetes,[6] obesity,[7] cancer,[6b,8] and viral infections.[9,10] (+)-6-Epicastanospermine **4**, coexisting with castanospermine in the Australian legume *Castanospermum australe*,[11] is a



Scheme 1.

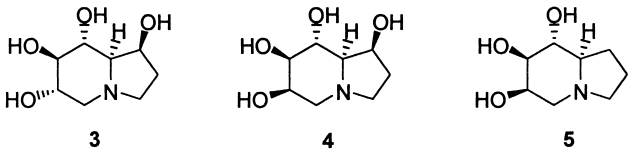


Figure 1.

powerful inhibitor of amyloglucosidase (an exo-1,4-α-glucosidase) but does not inhibit either α-mannosidase or β-glucosidase.[11]

During the studies of structure–activity relationships, a number of natural and unnatural derivatives of castanospermine have been synthesized,[12] utilizing a common synthetic approach in which appropriate carbohydrate precursors were used. With the advancement in technologies for enantioselective synthesis, non-carbohydrate derived syntheses are becoming increasingly popular. We recently reported the use of α-furfurylamine as a precursor for the synthesis of 1-deoxy-6-epicastanospermine **5**.[13] Recently, we have extended the approach to the synthesis of 6-epicastanospermine[14] by using β-hydroxy-α-furfurylamine **9** as a precursor. Herein, we wish to report our result in details.

As shown in the retrosynthetic analysis (Scheme 2), the key intermediate of our approach is the enantiopure β-hydroxy-α-furfurylamine **9** that could be prepared from the Sharpless asymmetric aminohydroxylation of furyl acrylate.[15] One of the attractive features of this approach lay in its inherent flexibility since the stereoselectivity of Sharpless asymmetric aminohydroxylation of furyl acrylate could be controlled by employing different ligands.

Keywords: total synthesis; castanospermine; 6-epicastanospermine; dihydropyridone; α-furfurylamine.

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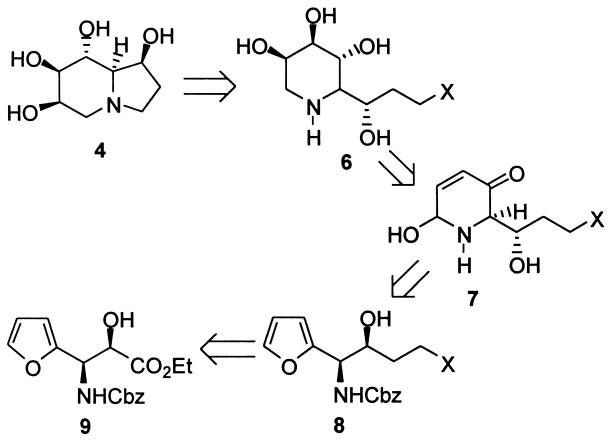
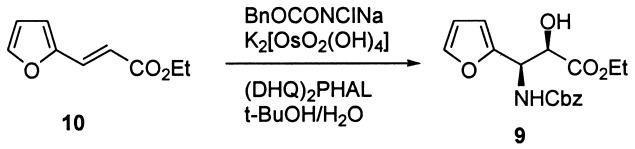


Scheme 2.

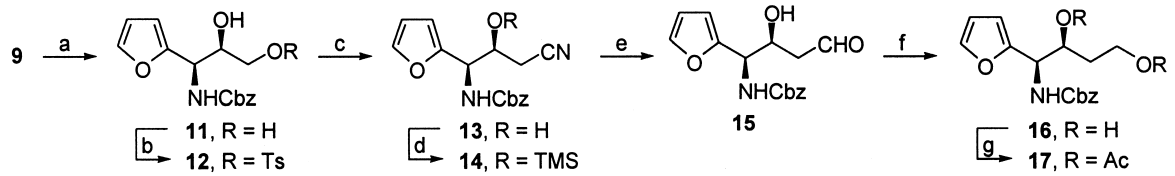


Scheme 3.

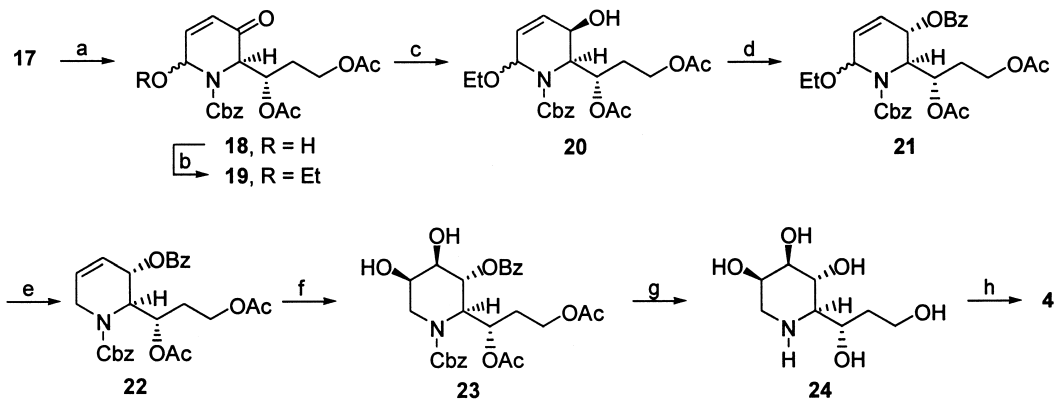
2. Results and discussion

Asymmetric aminohydroxylation of furyl acrylate **10** by the reported procedure[15] using $(DHQ)_2PHAL$ as the chiral ligand yielded β-hydroxy-α-furfurylamine **9** in 62% yield and 87% ee (Scheme 3).[15a] Homologation of the side chain of compound **9** began with its reduction with an excess of sodium borohydride at room temperature to give diol **11**[16] (Scheme 4). Selective tosylation of the primary hydroxyl group of **11** with TsCl in pyridine gave tosylate **12** in 94% yield. Reaction of **12** with KCN in $EtOH/H_2O$ (3:2) at room temperature gave probably an epoxide as a white solid and then nitrile **13**. After we failed to reduce nitrile **13** with Raney Ni in the presence of $Et_3NH^+H_2PO_2^-\cdot 1.5H_2O$[17] to give aldehyde **15**, we turned to use diisobutylaluminum hydride (DIBAL-H) as the reducing agent. The reduction of nitrile **13** with an excess of DIBAL-H proceeded very slowly at −65°C. Considering the likely complexation of the naked hydroxyl group with DIBAL-H would retard the reduction, we tried to protect the hydroxyl group with BnBr/NaH, $BnBr/Ag_2O$ and MOMCl, but failed because of low yield as well as the formation of complex byproducts. After the hydroxyl group was protected by trimethylsilyl chloride successfully, the silyl ether **14** was reduced smoothly with DIBAL-H. Without further separation, the resulted aldehyde **15** was further reduced by sodium borohydride to give the diol **16**. It should be noted that reduction of nitrile **13** with DIBAL-H in toluene or THF failed because of low solubility or low reactivity. Modification of the DIBAL-H reduction conditions by changing the solvent to *tert*-butyl methyl ether and working up with 30% $HOAc-H_2O$[18] increased the yield up to 70% for two steps. Working up with 30% $HOAc-H_2O$ not only decomposed the aluminum complex for a smooth extraction, but also deprotected the trimethylsiyl group at the same time. The diol **16** was protected by Ac_2O to give diacetate **17**.

Construction of the piperidine ring of **4** began with the oxidation of compound **17** by *m*-CPBA to give dihydropyridone **18** (Scheme 5). After protecting the hydroxyl group of **18** with triethyl orthoformate, the dihydropyridone **19** was stereoselectively reduced by sodium borohydride in the presence of cerium chloride heptahydrate ($CeCl_3\cdot 7H_2O$) to give **20**, in which the configuration of the newly formed stereocenter was assigned by NOESY spectroscopic



Scheme 4. *Reagents and conditions*: (a) $NaBH_4$, EtOH, rt, 94%; (b) TsCl, pyridine, 94%; (c) KCN, EtOH, H_2O, 96%; (d) Me_3SiCl, Et_3N, CH_2Cl_2, 99%; (e) (i) DIBAL-H, $(CH_3)_3COCH_3$, −78°C; (ii) $HOAc/H_2O$; (f) $NaBH_4$, MeOH, 70% from **14**; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%.



Scheme 5. *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2, 16 h, 88%; (b) $HC(OEt)_3$, $BF_3\cdot OEt_2$, 4 Å MS, THF, 0°C, 94%; (c) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, −78°C, 99%; (d) $PhCO_2H$, PPh_3, DEAD, THF, 92%; (e) $NaBH_4$, HCO_2H, 88%; f) $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, K_2CO_3, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 79%; g) (i) H_2, 10% Pd–C, EtOH, 3 h; (ii) K_2CO_3, MeOH, rt 10 h; (h) Ph_3P, CCl_4, Et_3N, DMF, 62% from **23**.

analysis to be of *R*-form, which is opposite to that in the target molecule. Thus, Mitsunobu reaction[19] was employed to invert the configuration of this hydroxyl group and as a result benzoate **21** was obtained. After reductive deethoxylation of **21** by using $NaBH_4$ in formic acid,[1c] Sharpless asymmetric dihydroxylation[20] was used to introduce two hydroxyl groups which afforded 1,2-glycol **23** with indicated configuration as deduced by 2D-^{1}H NOESY study.

Having introduced the three desirable hydroxyl groups to the six-membered ring, all that remained was the construction of the final bicyclic skeleton of **4**. The protecting groups in **23** were removed by catalytic hydrogenation on 10% Pd–C followed by hydrolysis (K_2CO_3, H_2O). Treatment of **24** with 2 equiv. of $PPh_3/CCl_4/Et_3N$ (1:1:1)[21] in anhydrous DMF at room temperature in the darkness resulted in the complete conversion of monocyclic **24** into the expected bicyclic (+)-6-epicastanospermine **4** in 87% yield (62% yield from **23**). The ^{1}H and ^{13}C NMR spectral data matched those reported in the literature[11,22] {$[\alpha]_D^{26}$=+3.0 (*c*=1.3, MeOH); lit.,[22] $[\alpha]_D^{20}$=+2.2 (*c*=0.7, MeOH), lit.[11] $[\alpha]_D^{24}$=+8 (*c*=1.09, MeOH)}.

In conclusion, the asymmetric total synthesis of the natural (+)-6-epicastanospermine **4** was achieved in 15 steps and 19% overall yield starting from β-hydroxy-α-furfurylamine derivative. Most significantly, the generality of this approach would allow us to synthesize other polyhydroxylated indolizidines.

3. Experimental

3.1. General

Melting points were determined with a Büchi 535 melting point apparatus and were uncorrected. Reactions were monitored by using thin layer chromatography (TLC). The silica gel H (10–40 μm) used in flash chromatography was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Shimadzu IR 400 spectrometer. ^{1}H NMR and ^{13}C 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 institute. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was freshly distilled from Na-benzophenone.

3.1.1. (2*R*,3*R*)-3-(carbobenzoxyamino)-3-(2′-furyl)-1,2-propanediol (11). To a solution of **9** (1.67 g, 5.00 mmol) in absolute EtOH (15 mL) was added $NaBH_4$ (284 mg, 7.5 mmol) in small portions. After the solution was stirred at room temperature for 30 min, the solvent was evaporated, and water (10 mL) was added. The resulting solution was extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (hexane/AcOEt, 10:10) to afford a colorless solid **11** (1.37 g, 94%). Mp 92–93°C; $[\alpha]_D^{17}$=+42.5 (*c*=0.8, $CHCl_3$); ^{1}H NMR δ: 2.48–2.56 (m, 2H, OH), 3.59 (m, 2H, H-1), 4.12 (s, 1H, NH), 5.02 (m, 1H, H-2), 5.14 (m, 2H, CH_2Ph), 5.48 (d, 1H, *J*=7.16 Hz, H-3), 6.31 (s, 1H, H-3′), 6.35 (m, 1H, H-4′), 7.33–7.38 (m, 6H, Ph, H-5′); IR: 3526 (OH), 3327 (NH), 1686 (C=O) cm^{-1}; MS *m*/*z*: 292 (M^++1), 230 (M^+−CCHOHCH$_2$OH), 91 (CH_2Ph); Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.86; H, 5.80; N, 4.72.

3.1.2. (2*R*,3*R*)-3-(Carbobenzoxyamino)-3-(2′-furyl)-1-(*p*-tolylsulfonyloxy)-2-propanol (12). To a solution of diol **11** (673 mg, 2.3 mmol) in dry pyridine (4 mL) at 0°C was added a solution of TsCl (529 mg, 2.8 mmol) in pyridine (3 mL) dropwise. After the addition, the solution was stirred at 0°C for 4.5 h and then poured into a mixture of ethyl acetate (100 mL) and cold water (20 mL). The layers were separated, and the organic layer was washed with water (20 mL), 2N HCl (20 mL) and saturated NaCl (20 mL) in turn, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (hexane/AcOEt, 30:10–10:10) to afford **12** (0.967 g, 94%) as a colorless oil. $[\alpha]_D^{20}$=+18.3 (*c*=0.9, $CHCl_3$); ^{1}H NMR δ: 2.45 (s, 1H, Ts-CH_3), 2.74 (br s, 1H, OH), 4.08 (m, 2H, H-1), 4.28 (br s, 1H, NH), 4.91 (dd, 1H, *J*=4.00, 9.01 Hz, H-2), 5.10 (s, 2H, CH_2Ph), 5.43 (br s, 1H, H-3), 6.25 (d, 1H, *J*=2.80 Hz, H-3′), 6.32 (dd, 1H, *J*=1.79, 3.21 Hz, H-4′), 7.24–7.35 (m, 8H, H-5′ and Ph), 7.79 (d, 2H, *J*=8.14 Hz, Ph); IR: 3381 (NH, OH), 1702 (C=O) cm^{-1}; MS *m*/*z*: 354 (M^+−CH_2Ph), 257 (M^+−OH−OTs), 230 (M^+−CHOHCH$_2$OTs), 91 (CH_2Ph); Anal. calcd for $C_{22}H_{23}NO_7S$: C, 59.31; H, 5.20; N, 3.14. Found: C, 59.21; H, 5.38; N, 2.86.

3.1.3. (3*S*,4*R*)-4-(Carbobenzoxyamino)-4-(2′-furyl)-3-hydroxybutanenitrile (13). To a solution of **12** (6.85 g, 15.4 mmol) in ethanol (34 mL) was added water (23 mL). The resulting suspension was cooled to 0°C and KCN (5.0 g, 76.8 mmol) was added. After the solution was stirred at room temperature for 10 min, the epoxide was formed as white precipitate, which disappeared gradually to give a purple solution. After 10 h, ethanol was evaporated in vacuo, and water (50 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate (3×100 mL). The combined organic layer was washed with saturated NaCl (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (hexane/AcOEt, 20:10–10:10) to afford **13** (4.45 g, 96%) as a pale yellow solid. Mp 105–106°C; $[\alpha]_D^{16}$=+22.6 (*c*=1.3, $CHCl_3$); ^{1}H NMR δ: 2.55 (m, 2H, H-2), 3.03 (br s, 1H, OH), 4.36 (br s, 1H, NH), 4.91 (m, 1H, H-3), 5.14 (s, 2H, CH_2Ph), 5.48 (m, 1H, H-4), 6.34 (m, 1H, H-3′), 6.36 (m, 1H, H-4′), 7.56 (m, 5H, Ph), 7.39 (m, 1H, H-5′); IR: 3408 (OH), 3319 (NH), 2260 (CN), 1690 (C=O) cm^{-1}; MS *m*/*z*: 301 (M^++1), 230 (M^-−CH_2OHCH_2CN), 91 (CH_2Ph); Anal. calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.19; H, 5.39; N, 9.37.

3.1.4. (3*S*,4*R*)-4-(Carbobenzoxyamino)-4-(2′-furyl)-3-trimethylsilyloxybutanenitrile (14). To a solution of **13**

(2.23 g, 7.43 mmol) in CH_2Cl_2 (20 mL) and Et_3N (4.14 mL, 29.7 mmol) at 0°C was slowly added Me_3SiCl (1.88 mL, 14.8 mmol). The resulting solution was allowed to warm to room temperature and stirred for 3 h. The mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with saturated NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by flash chromatography on silica gel (hexane:AcOEt, 60:10) to afford **14** (2.75 g, 99%) as a yellow oil. $[\alpha]_D^{19}$=+1.0 (c=1, $CHCl_3$); ^{1}H NMR δ: −0.02 (m, 9H, TMS), 2.57 (m, 2H, H-2), 4.45 (br s, 1H, NH), 4.89 (d, 1H, J=9.47 Hz, H-3), 5.15 (s, 2H, CH_2Ph), 5.48 (d, 1H, J=9.10 Hz, H-4), 6.20 (d, 1H, J=3.27 Hz, H-3′), 6.34 (dd, 1H, J=2.02, 3.24 Hz, H-4′), 7.38 (m, 6H, H-5′ and Ph); IR: 3332 (NH), 2251 (CN), 1723 (C=O) cm^{-1}; MS m/z: 373 (M^++1), 230 (M^+−$CH_2OTMSCH_2CN$), 91 (CH_2Ph); Anal. calcd for $C_{19}H_{24}N_2O_4Si$: C, 61.26; H, 6.49; N, 7.52. Found: C, 60.99; H, 6.74; N, 7.45.

3.1.5. (3*S*,4*R*)-4-(Carbobenzoxyamino)-4-(2′-furyl)-1,3-butanediol (16). To a solution of **14** (1.26 g, 3.39 mmol) in $(CH_3)_3COCH_3$ (25 mL) at −78°C was added dropwise the toluene solution of DIBAL-H (1.0 M, 7.5 mL) over 1 h, maintaining the temperature between −78 and −65°C. After the solution was stirred at −78°C for an additional 2.5 h, MeOH (0.2 mL) was added to terminate the reaction. The mixture was poured into acetic acid solution (30%, 25 mL) and stirred for 0.5 h. The layers were separated, and the aqueous layer was extracted with ether (5×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×10 mL), saturated NaCl (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give aldehyde **15** (974 mg) as a colorless oil. To the solution of the crude aldehyde **15** in MeOH (20 mL) at room temperature was added $NaBH_4$ (188 mg, 4.97 mmol) in portions. After being stirred at room temperature for 20 min, the mixture was concentrated. The residue was partitioned between ethyl acetate (30 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with saturated NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 10:10) to afford **16** (727 mg, 70% from **14**) as colourless prisms. Mp 74–76°C; $[\alpha]_D^{16}$=+37.1 (c=1, $CHCl_3$); ^{1}H NMR δ: 1.70–1.90 (m, 2H, H-2), 2.17 (br s, 1H, OH), 2.93 (br s, 1H, OH), 3.88 (m, 2H, H-1), 4.29 (m, 1H, NH), 4.84 (d, 1H, J=6.70 Hz, H-3), 5.13 (s, 2H, CH_2Ph), 5.55 (m, 1H, H-4), 6.27 (d, 1H, J=2.90 Hz, H-3′), 6.34 (dd, 1H, J=2.02, 3.24 Hz, H-4′), 7.37 (m, 6H, H-5′ and Ph); IR: 3343 (NH), 1689 (C=O) cm^{-1}; MS m/z: 306 (M^++1), 230 (M^+−$CH_2OHCH_2CH_2OH$), 91 (CH_2Ph); Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.96; H, 6.24; N, 4.35.

3.1.6. (3*S*,4*R*)-4-(Carbobenzoxyamino)-4-(2′-furyl)-1,3-butanediol, diacetate (17). To a solution of **16** (636 mg, 2.08 mmol), DMAP (20 mg) and Et_3N (0.87 mL, 6.25 mmol) in CH_2Cl_2 (8 mL) was added Ac_2O (0.29 mL, 3.12 mmol) slowly. The mixture was stirred at room temperature for 1 h and then poured into ice water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with saturated NaCl (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 40:10) to afford **17** (771 mg, 95%) as a yellow oil. $[\alpha]_D^{16}$=+15.1 (c=1, $CHCl_3$); ^{1}H NMR δ: 1.92 (m, 2H, H-2), 1.96 (s, 3H, Ac), 2.04 (s, 3H, Ac), 4.08 (m, 2H, H-1), 5.04 (m, 1H, NH), 5.12 (m, 2H, CH_2Ph), 5.33 (d, 1H, J=9.11 Hz, H-3), 5.41 (m, 1H, H-4), 6.23 (br s, 1H, H-3′), 6.32 (br s, 1H, H-4′), 7.36 (br s, 6H, H-5′ and Ph); IR: 3335 (NH), 1741 (C=O) cm^{-1}; MS m/z: 330 (M^+−OAc), 230 (M^+−$CHOAcCH_2CH_2OAc$), 91 (CH_2Ph); Anal. calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.80; H, 6.13; N, 3.49.

3.1.7. (2*R*,6ξ,1′*S*)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-6-hydroxy-1,2,3,6-tetrahydropyridin-3-one (18). To a solution of **17** (820 mg, 2.10 mmol) in CH_2Cl_2 (20 mL) was added 3-chloroperoxybenzoic acid (*m*-CPBA, 417 mg, 2.42 mmol). After the solution was stirred for 16 h at room temperature, the solvent was evaporated under reduced pressure to give a solid which was purified by flash chromatography on silica gel (hexane/AcOEt, 40:10 and 20:10) to afford **18** (753 mg, 88%) as a yellow oil. $[\alpha]_D^{16}$=+25.8 (c=1.5, $CHCl_3$); ^{1}H NMR δ: 1.85–2.00 (m, 5H, H-2′ and Ac), 2.05 (s, 3H, Ac), 3.75–4.08 (m, 2H, H-3′), 4.97 (m, 1H, H-1′), 5.24 (s, 2H, CH_2Ph), 5.33–5.52 (m, 1H, H-2), 6.10 (m, 1H, H-6), 6.18 (d, 1H, J=10.35 Hz, H-4), 6.95 (m, 1H, H-5), 7.37 (m, 5H, Ph); IR: 3458 (OH), 1741, 1709, 1692 (C=O), 1640 (C=C) cm^{-1}; MS m/z: 388 (M^++1−H_2O), 328 (M^++2−H_2O−OAc), 289 (M^++2−2OAc), 91 (CH_2Ph); Anal. calcd for $C_{20}H_{23}NO_8$: C, 59.25; H, 5.72; N, 3.45. Found: C, 58.95; H, 5.91; N, 3.27.

3.1.8. (2*R*,6ξ,1′)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-6-ethoxy-1,2,3,6-tetrahydropyridin-3-one (19). To a suspension solution of 4 Å molecular sieves (160 mg) in THF (10 mL) at 0°C were sequentially added 18 (930 mg, 2.29 mmol), triethylorthoformate (0.95 mL, 5.7 mmol) and $BF_3{\cdot}Et_2O$ (50 μl). After 3 h at 0°C, 10 mL of water was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 40:10) to afford **19** (0.940 g, 94%) as an oil. $[\alpha]_D^{15}$=+21.7 (c=2, $CHCl_3$); ^{1}H NMR δ: 1.20 (m, 3H, EtO−CH_3), 1.85–2.00 (m, 5H, H-2′and Ac), 2.05 (s, 3H, Ac), 3.74 (m, 2H, EtO−CH_2), 4.11 (m, 2H, H-3′), 4.87–5.03 (m, 1H, H-1′), 5.16 (m, 1H, H-2), 5.31 (m, 2H, CH_2Ph), 5.96 (m, 1H, H-5), 6.11 (d, 1H, J=10.29 Hz, H-4), 6.96 (m, 1H, H-6), 7.33 (m, 5H, Ph); IR: 1745, 1710 (C=O) cm^{-1}; MS m/z: 434 (M^++1), 388 (M^+−EtO), 374 (M^+−OAc), 91 (CH_2Ph); Anal. calcd for $C_{22}H_{27}NO_8$: C, 60.96; H, 6.29; N, 3.23. Found: C, 60.96; H, 6.35; N, 3.05.

3.1.9. (2*R*,3*R*,6ξ,1′)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-6-ethoxy-3-hydroxy-1,2,3,6-tetrahydropyridine (20). To a solution of **19** (531 mg, 1.22 mmol) in methanol (12 mL) was added $CeCl_3{\cdot}7H_2O$ (228 mg, 0.61 mmol). After the solution was cooled to −78°C, $NaBH_4$ (46 mg,

1.2 mmol) was added in small portions. The resulting mixture was stirred for 10 min, and water (7 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 30:10) to afford an oil **20** (531 mg, 99%). $[\alpha]_D^{15}=-57.3$ (c=1.4, $CHCl_3$); ^{1}H NMR δ: 1.14 (m, 3H, EtO–CH_3), 1.95 (s, 3H, Ac), 2.04 (m, 5H, H-2′and Ac), 3.50–3.75 (m, 2H, EtO–CH_2), 4.12 (m, 2H, H-3′), 4.24 (m, 1H, H-2), 4.30, (br s, 1H, OH), 4.60 (m, 1H, H-3), 5.19 (m, 3H, H-1′and CH_2Ph), 5.59 (m, 2H, H-4 and H-5), 5.72 (m, 1H, H-6), 7.37 (m, 5H, Ph); IR: 3456 (OH), 1740, 1709 (C═O) cm^{-1}; MS *m/z*: 390 (M^+−EtO), 300 (M^+−Cbz), 346 (M^++1−OAc−Et), 91 (CH_2Ph); Anal. calcd for $C_{22}H_{29}NO_8$: C, 60.68; H, 6.71; N, 3.22. Found: C, 60.48; H, 6.71; N, 3.19.

3.1.10. (2*R*,3*S*,6ξ,1′)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-6-ethoxy-3-benzoyloxy-1,2,3,6-tetrahydropyridine (21). To a solution of **20** (483 mg, 1.11 mmol) in dry THF (12 mL) at room temperature were added triphenyl phosphine (582 mg, 2.22 mmol), benzoic acid (271 mg, 2.22 mmol) and diethylazodicarboxylate (DEAD) (0.35 mL, 2.22 mmol). After the mixture was stirred for 2 h, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/AcOEt, 50:10) to give **21** (550 mg, 92%) as a colourless oil. $[\alpha]_D^{15}=+152.4$ (c=1, $CHCl_3$); ^{1}H NMR δ: 1.20 (m, 3H, EtO–CH_3), 1.74 (m, 1H, H-2′), 1.99 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.25 (m, 1H, H-2′), 3.49–3.70 (m, 2H, EtO–CH_2), 4.19 (m, 3H, H-3′ and H-2), 4.87–5.00 (m, 1H, H-1′), 5.11 (m, 2H, CH_2Ph), 5.48 (m, 1H, H-3), 5.63–5.78 (m, 1H, H-6), 6.16 (m, 2H, H-4 and H-5), 7.23–7.57 (m, 8H, Ph), 7.94 (m, 2H, Ph); IR: 1743, 1713 (C═O) cm^{-1}; MS *m/z*: 540 (M^++1), 494 (M^+−EtO), 480 (M^+−OAc), 450 (M^++1−Et−OAc), 434 (M^+−OBz), 91 (CH_2Ph); Anal. calcd for $C_{29}H_{33}NO_9$: C, 64.55; H, 6.16; N, 2.60. Found: C, 64.51; H, 6.24; N, 2.75.

3.1.11. (2*R*,3*S*,1′*S*)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-3-benzoyloxy-1,2,3,6-tetrahydropyridine (22). To a solution of **21** (523 mg, 0.97 mmol) in 88% formic acid (3 mL) was added $NaBH_4$ (93 mg, 2.46 mmol) in portions at 0°C. After being stirred for 0.5 h at 0°C, the mixture was diluted with ethyl acetate (10 mL). The resulting mixture was neutralized with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 40:10) to afford an oil **22** (421 mg, 88%). $[\alpha]_D^{15}=+22.6$ (c=1.2, $CHCl_3$); ^{1}H NMR δ: 1.75 (m, 1H, H-2′), 1.90 (s, 3H, Ac), 2.05 (m, 4H, H-2′ and Ac), 3.80 (m, 1H, H-2), 4.15 (m, 2H, H-3′), 4.50 (m, 1H, H-6), 4.76 (dd, 1H, J=7.01, 32.80 Hz, H-6), 5.20 (m, 3H, H-1′ and CH_2Ph), 5.50 (m, 1H, H-3), 5.98 (m, 1H, H-4), 6.15 (m, 1H, H-5), 7.23–7.57 (m, 8H, Ph), 7.93 (m, 2H, Ph); IR: 1743, 1714 (C═O) cm^{-1}; MS *m/z*: 495 (M^+), 436 (M^+−OAc), 390 (M^+−Bz), 91 (CH_2Ph); Anal. calcd for $C_{27}H_{29}NO_8$: C, 65.44; H, 5.90; N, 2.83. Found: C, 65.43; H, 5.87; N, 2.69.

3.1.12. (2*R*,3*S*,4*R*,5*R*,1′*S*)-2-((1′,3′-Diacetoxy)propyl)-1-carbobenzoxy-3-benzoyloxy-4,5-dihydroxypiperidine (23). To a solution of **22** (124 mg, 0.25 mmol) in *tert*-butyl alcohol (2 mL) and water (2 mL) at 0°C were added $K_3[Fe(CN)_6]$ (247 mg, 0.75 mmol), $(DHQ)_2PHAL$ (10 mg, 5% equiv.), K_2CO_3 (104 mg, 0.75 mmol), $CH_3SO_2NH_2$ (24 mg, 0.25 mmol) and $K_2OsO_2(OH)_4$ (5 mg, 5% equiv.). After the mixture was stirred at 0°C for 2 h, the reaction was quenched by addition of Na_2SO_3 (0.094 g). Water (10 mL) was added after 30 min and the resulting mixture was extracted with ethyl acetate (3×30 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/AcOEt, 10:10) to afford a colorless oil **23** (105 mg, 79%). $[\alpha]_D^{14}=-36.9$ (c=1, $CHCl_3$); ^{1}H NMR δ: 1.83 (s, 3H, Ac), 2.00 (s, 3H, Ac), 2.10 (m, 1H, H-2′), 2.30 (m, 1H, H-2′), 3.29 (m, 2H, H-6), 4.08–4.20 (m, 4H, H-3′ and H-2, H-4), 4.49 (m, 1H, H-5), 5.06–5.20 (m, 2H, CH_2Ph), 5.39 (m, 1H, H-1′), 5.82 (m, 1H, H-3), 7.10–7.1 (m, 2H, Ph), 7.32–7.43 (m, 4H, Ph), 7.58 (m, 2H, Ph), 7.90 (d, 2H, J=7.35 Hz, Ph); IR: 1743, 1714 (C═O) cm^{-1}; MS *m/z*: 530 (M^++1), 470 (M^+−OAc), 424 (M^+−Bz), 91 (CH_2Ph); IR: 3451, 1739, 1722 cm^{-1}; Anal. calcd for $C_{27}H_{31}NO_{10}$: C, 61.24; H, 5.90; N, 2.65. Found: C, 61.24; H, 5.83; N, 2.50.

3.1.13. (1*S*,6*R*,7*R*,8*S*,8a*R*)-1,6,7,8-Tetrahydroxy-indolizidine (6-epicastanospermine) (4). To a solution of **23** (120 mg, 0.23 mmol) in ethanol (3 mL) was added catalytic amount of 10% Pd/C (12 mg). After being stirred under H_2 atmosphere (1 atm) at room temperature for 5 h, the mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (3 mL), and then K_2CO_3 (96 mg, 0.69 mmol) was added. After the resulting solution was stirred at room temperature for 24 h, the solvent was evaporated under reduced pressure. The residue was purified by chromatography on Dowex-50 (H^+) (first elution with MeOH, then with strong aqueous ammonia) to afford **24** (41.5 mg). The crude **24** was dissolved in dry DMF (0.5 mL), and then triphenyl phosphine (3.5 mg) and CCl_4 (0.033 mL) were added. After 10 min, Et_3N (0.044 mL) was added, and the mixture was stirred at room temperature for 20 h. Methanol (0.3 mL) was added to quench the reaction. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel ($CHCl_3$–MeOH, 2:1) to give a yellow oil **4** (26.3 mg, 62%). $[\alpha]_D^{26}=+3.0$ (c 1.3, MeOH); ^{1}H NMR (D_2O) δ: 1.74 (m, 1H, H-2), 2.01 (dd, 1H, J=4.20, 9.70 Hz, H-8a), 2.21 (m, 1H, H-3), 2.31–2.40 (m, 2H, H-5 and H-2), 3.12 (m, 2H, H-3 and H-5), 3.54 (dd, 1H, J=3.45, 9.52 Hz, H-7), 3.89 (t, 1H, J=9.65 Hz, H-8), 4.02 (m, 1H, H-6), 4.41 (m, 1H, H-1); ^{13}C NMR (D_2O) δ: 35.3 (C2), 54.4 (C3), 57.9 (C5), 69.8 (C8), 71.4 (C6), 72.7 (C1), 74.4 (C8a), 77.9 (C7).

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