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The synthesis of (1*S*,8a*S*)-1-hydroxyindolizidine using a stereoselective Grignard addition to an *N*-benzyl-3-deoxy sugar imine derived from D-Glucose

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ABSTRACT

A highly stereoselective approach to 1-hydroxyindolizidine is described using a Grignard reaction on *N*-benzyl imine derived from 3-deoxy-1,2-*O*-isopropylidine-α-D-xylo-pentodialdofuranose and reductive cyclization as key steps.

1. Introduction

Polyhydroxylated indolizidine alkaloids are frequently encountered in nature in a variety of sources. Some of the important members of this family are castanospermine **1**, swainsonine **2**, lentiginosine **3**, and slaframine **4**. Compounds **1**–**3** are specific inhibitors of glycosidases and have shown activity against HIV, cancer, and diabetes.[1,2] Slaframine **4** is a neurotoxin fungus metabolite that has potent use in the treatment of diseases involving cholinergic dysfunction.[3] Due to their interesting biological activity and structural features, these indolizidine alkaloids have attracted the attention of both biologists and synthetic chemists.[4] As part of an ongoing program for the synthesis of azasugars,[5,6] we recently developed an approach for the synthesis of (5, 6), (6, 6), (6, 7) bicyclic iminosugars using a highly stereoselective Grignard addition onto a sugar imine.[6] Herein we report an extension of this methodology for the stereoselective synthesis of (1*S*,8a*S*)-1-hydroxyindolizidine **5**, which is a key precursor in the biosynthesis of indolizidine alkaloids, such as swainsonine **2** and slaframine **4** in the fungus *Rhizoctonia legumniola* (Fig. 1).[7] Although several approaches are known in the literature for **5**, to the best of our knowledge none of them have utilized carbohydrates as the starting materials.[8] The key aspect of the present synthesis is to find the stereoselectivity in the Grignard addition to an *N*-benzyl-3-deoxy sugar imine derived from D-glucose (Scheme 1).

2. Results and discussions

Our synthesis starts from aldehyde **6**, which can be prepared from commercially available D-glucose using a literature procedure.[9] Condensation of aldehyde **6** with benzylamine in the presence of 4 Å molecular sieves afforded chiral imine **7**, which was used as such without any purification for the next step. Treatment of imine **7** with homoallyl magnesium bromide in THF at 0 °C gave *syn*-amino olefin **8** as the exclusive isomer by ^{1}H NMR. The absolute configuration of the newly created stereogenic center was not known at this stage (Scheme 1). However, based on our earlier observation we presumed it to be a *syn* isomer, because the ring oxygen chelates with the Grignard reagent and helps the nucleophile to undergo addition with high stereoselectivity.[6,10] It was thought that the presence of an alkoxy group at the C-3 position also helped in getting exclusive stereoselectivity, however the formation of **8** clearly shows that the chelation of ring oxygen is the only essential factor for the selectivity (Fig. 2).

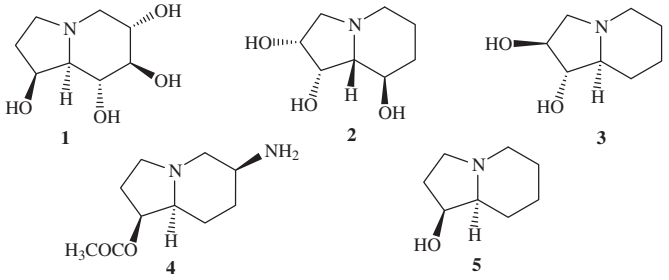

Figure 1.

In order to construct the piperidine ring, the amino compound **8** was treated with benzyloxy carbonyl chloride in the presence of $NaHCO_3$ in MeOH to afford compound **9** in 92% yield. Hydroboration of **9** with BH_3·DMS at 0 °C gave amino alcohol **10**. Both **9** and **10** exist as rotational isomers as seen by the ^{1}H and ^{13}C NMR because of the hindered rotation of N–C bond of the *N*-Cbz group.[5b,11] Debenzylation of **10** with Pd/C in the presence of ammonium formate in methanol for 3 h at 60 °C gave the free amine, which was immediately protected as the Cbz derivative

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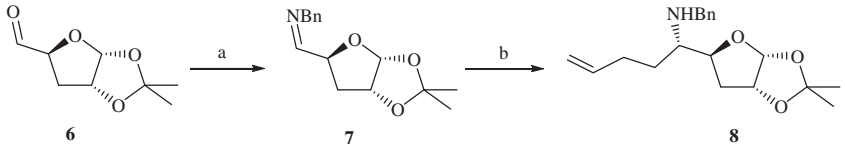


Scheme 1. Reagents and conditions: (a) $BnNH_2$, 4 Å molecular sieves, DCM; (b) homoallyl magnesium bromide, THF, 0 °C, 12 h.

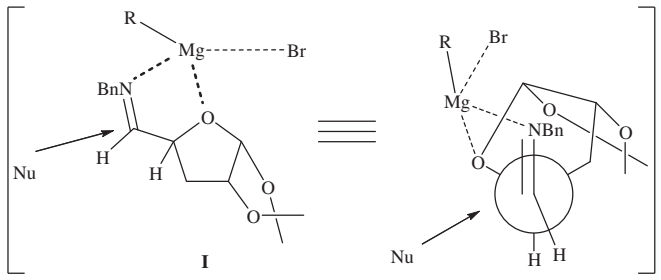


Figure 2.

11 in 86% yield. For the construction of the piperidine ring, compound **11** was treated with MsCl and Et_3N in CH_2Cl_2 at 0 °C to give the mesyl derivative, which was used as such without purification. The cyclization was carried out on the crude mesyl derivative using KO^{t}Bu in THF to yield compound **12** in 80% yield. The next stage was to construct the pyrrolidine unit; for this the acetonide moiety in **12** was removed using TFA–H_2O to give hemiacetal **13** in 85% yield. Oxidative cleavage of **13** with $NaIO_4$ in methanol-water gave the eliminated α,β-unsaturated aldehyde **14** in 82% yield. The formation of **14** can be explained through β-formyloxy elimination of the aldehyde derived from **13** during oxidative cleavage (Scheme 2).[12]

To circumvent the elimination problem, hemiacetal **13** was treated with $NaBH_4$ in methanol to give triol **15** in 80% yield. The subsequent oxidative degradation of compound **15** with $NaIO_4$ gave the aldehyde, which was used as such in the next step without any purification. Deprotection of Cbz and simultaneous reductive amino cyclization under Pd/C and an H_2 atmosphere in methanol gave 1-hydroxyindolizidine **5** in 73% yield, whose NMR and physical properties were in perfect agreement with the reported values (Scheme 3).[8j,l,13]

3. Conclusion

In conclusion, a highly stereoselective Grignard addition reaction onto a 3-deoxy sugar imine derived from D-glucose was utilized for the synthesis of 1-hydroxyindolizidine. This approach is also helpful for the preparation of other indolizidine and quinolizidine alkaloids. Work is currently in progress in our laboratory.

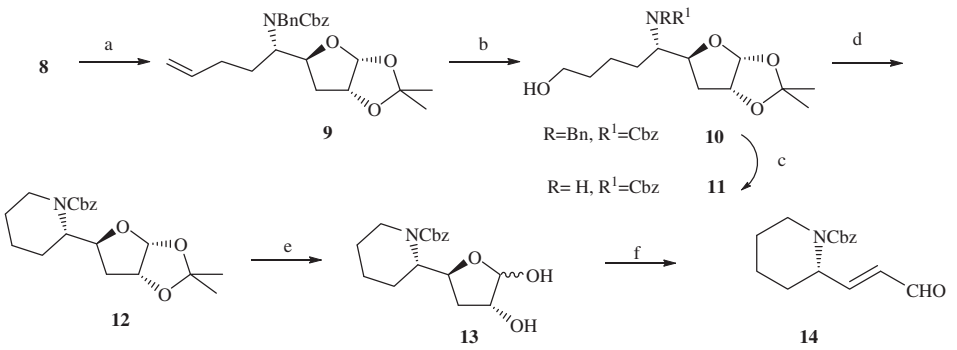
4. Experimental

4.1. General

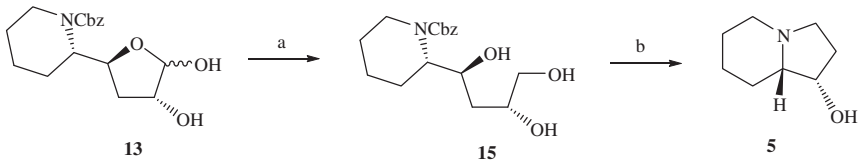
TLC was performed on Merck Kiesel Gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance-300 MHz, Varian-400 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet), number of proton(s) and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA). Due to the isomerization by the restricted rotation around C=N with the presence of *N*-Cbz group, the ^{1}H and ^{13}C NMR spectra's of compounds **9** and **10** showed doubling of the signals and were thus assigned as rotamers.[5b,11]

4.1.1. (*S*)-*N*-Benzyl-1-((3*aR*,5*S*,6*aR*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)pent-4-en-1-amine (8)

To a solution of aldehyde **6** (1.60 g, 9.3 mmol) in dry CH_2Cl_2 (20 mL) and molecular sieves 4 Å (200 mg) was added benzylamine (1 mL, 9.3 mmol) at room temperature and kept at 0 °C for 4 h. The reaction mixture was filtered and concentrated to give crude imine **7**, which was used as such for the next step. To the solution of homoallyl magnesium bromide prepared from Mg (1.11 g, 46.3 mmol) and homoallyl bromide (4.6 mL, 46.3 mmol) in THF (30 mL) was added a solution of chiral imine **7** (2.42 g, 9.3 mmol) in THF over 10 min at 0 °C under nitrogen. After stirring overnight at room temperature, the mixture was poured into



Scheme 2. Reagents and conditions: (a) CbzCl, $NaHCO_3$, MeOH, rt, 4 h; (b) BH_3.DMS, THF, 0 °C, 2 h; (c) (i) Pd/C, ammonium formate, 60 °C, 2 h, (ii) CbzCl, $NaHCO_3$, MeOH, rt, 4 h; (d) (i) MsCl, TEA, DMAP, CH_2Cl_2, 30 min, (ii) KO^{t}Bu, THF, 0 °C to rt, 3 h; (e) TFA: H_2O (3:2), rt, 3 h; (f) $NaIO_4$, MeOH–H_2O, 2 h.



13 15 5

Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 1 h; (b) $NaIO_4$, MeOH–H_2O, 2 h, then H_2, Pd/C, MeOH, 12 h.

saturated NH_4Cl (50 mL) and extracted into ethyl acetate (3 × 50 mL). The collected organic layers were combined, washed with water, brine, then dried over Na_2SO_4, concentrated under reduced pressure, and purified through column chromatography (hexane/ethyl acetate = 8:2) to afford the corresponding amino olefin **8** as a yellow oil (2.1 g, 72% for two steps). $[\alpha]_D^{28} = -9.6$ (*c* 1.51, $CHCl_3$); IR (neat) ν_{max} 2983, 2933, 1640, 1453, 1375, 1214, 1062, 1021, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 1.47 (s, 3H), 1.5–1.67 (m, 2H), 1.67–1.8 (m, 1H), 1.98 (dd, 1H, *J* = 4.15, 12.84 Hz), 2.06–2.25 (m, 2H), 2.5–2.6 (m, 1H), 3.72 (d, 1H, *J* = 13.2 Hz), 3.85 (d, 1H, *J* = 13.2 Hz), 4.15–4.25 (m, 1H), 4.66 (dd, 1H, *J* = 4.1 Hz), 4.9–5.03 (m, 2H), 5.69–5.84 (m, 1H), 5.72 (d, 1H, *J* = 3.4 Hz), 7.12–7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.7, 29.6, 29.8, 35.6, 51.2, 58.9, 80.0, 80.4, 105.2, 110.8, 114.6, 126.7, 128.1, 128.2, 138.5, 140.7; ESI/MS (*m/z*) 318 (M^++H); HRMS calcd for $C_{19}H_{28}NO_3$ 318.2069, found 318.2057.

4.1.2. Benzyl((*S*)-1-((3*aR*,5*S*,6*aR*)-2,2-dimethyl-tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)pent-4-eny-l)carbamate (9)

To a stirred solution of **8** (1.9 g, 6 mmol) in dry methanol was added sodium bicarbonate (1 g, 12 mmol) followed by benzyloxycarbonyl chloride (1.5 mL, 9 mmol) at 0 °C. The mixture was stirred at rt for 3 h. Methanol was evaporated under reduced pressure and reaction mixture was extracted with ethyl acetate and water. The collected organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate = 9:1) to give **9** (2.5 g, 92%) as a thick liquid. $[\alpha]_D^{28} = -23.33$ (*c* 0.9, $CHCl_3$); IR (neat) ν_{max} 2982, 2934, 1697, 1454, 1415, 1216, 1162, 1020, 914, 848, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.38 (s, 3H), 1.28–1.63 (m, 4H), 1.68–2.06 (m, 3H), 4.08–4.3 (m, 1H), 4.3–4.71 (m, 3H), 4.75–4.94 (m, 2H), 5.07–5.25 (m, 2H), 5.31–5.73 (m, 2H), 7.1–7.4 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.6, 28.3 and 28.8*, 29.0 and 29.6*, 30.2 and 30.3*, 36.2, 67.2 and 67.4*, 78.6, 78.9, 80.1 and 80.2*, 104.7 and 104.8*, 110.8, 115.0, 126.6, 127.2, 127.9, 128.1, 128.2, 128.3, 136.3, 137.4, 139.1, 157.4; ESI/MS (*m/z*) 452 (M^++H); HRMS calcd for $C_{27}H_{33}NO_5Na$ 474.2256, found 474.2265.

* Rotamers.

4.1.3. Benzyl((*S*)-1-((3*aR*,5*S*,6*aR*)-2,2-dimethyl-tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)-5-hydroxy-pentyl)carbamate (10)

To a solution of **9** (2.4 g, 5.3 mmol) in dry THF (30 mL), BH_3·DMS (1.5 mL, 16 mmol) was added at 0 °C. Stirring was continued for 3 h at room temperature. The reaction mixture was quenched by the addition of 10% NaOH (8.16 mL) followed by 30% H_2O_2 (2.4 mL) at 0 °C and stirring was continued at room temperature for another 1 h. The reaction mixture was extracted with ethyl acetate and water and the combined organic layers were washed with brine dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate = 7:3) to give alcohol **10** (2.3) in 93% yield as a thick liquid. $[\alpha]_D^{28} = -27.7$ (*c* 1.55, $CHCl_3$); IR (neat) ν_{max} 3452, 2936, 1693, 1454, 1417, 1242, 1214, 1161, 1055, 1019, 848, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.38 (s, 3H), 1.3–2.05 (m, 8H), 3.29–3.54 (m, 2H), 4.06–4.30 (m, 2H), 4.33–4.66 (m, 3H), 5.09–5.22 (br d, 2H, *J* = 16.9 Mz), 5.36–5.5 (m, 1H), 7.10–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3 and 22.4*, 26.1, 26.6, 29.1, 29.6, 32.2, 36.3, 42.5, 62.3, 67.3 and 67.4*, 78.7 and 79.0*, 80.1 and 80.2*, 104.7 and 104.8*, 110.9, 126.7, 127.3, 127.7, 128.1, 128.2, 128.4, 136.3, 139.2, 157.5; ESI/MS (*m/z*) 470 (M^++H); HRMS calcd for $C_{27}H_{35}NO_6Na$ 492.2362, found 492.2333.

* Rotamers.

4.1.4. Benzyl(*S*)-1-((3*aR*,5*S*,6*aR*)-2,2-dimethyl-tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)-5-hydrox-ypentylcarbamate (11)

A solution of **10** (2.2 g, 4.7 mmol) in dry methanol (20 mL) was hydrogenated in the presence of 10% Pd–C and ammonium formate (0.9 g, 14.1 mmol) at 60 °C for 3 h. The catalyst was filtered through a Celite pad and the collected filtrate was concentrated to give the free amine. This crude amine was dissolved in dry DCM and to it were added sodium bicarbonate (1.13 g, 13.5 mmol) and benzyloxycarbonyl chloride (1.12 mL, 6.7 mmol) at 0 °C and stirred at rt for overnight. The reaction mixture was washed with saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined and washed with brine then dried over Na_2SO_4 and concentrated in vacuo and purified through silica gel column chromatography (hexane/ethyl acetate = 8:2) to give **11** (1.45 g) in 86% as a syrup. $[\alpha]_D^{28} = -40.2$ (*c* 0.55, $CHCl_3$); IR (neat) ν_{max} 3441, 2936, 1704, 1528, 1455, 1376, 1299, 1219, 1161, 1051, 1018, 847, 754, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.47 (s, 3H), 1.34–1.73 (m, 7H), 2.0 (dd, 1H, *J* = 4.2, 13.2 Hz), 3.48–3.65 (m, 2H), 3.65–3.8 (m, 1H), 4.13–4.23 (m, 1H), 4.62 (dd, 1H, *J* = 4.2 Hz), 4.79 (d, 1H, *J* = 10.2 Hz), 5.03 (d, 1H, *J* = 12.5 Hz), 5.08 (d, 1H, *J* = 12.5 Hz), 5.69 (d, 1H, *J* = 3.8 Hz), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 26.0, 26.7, 32.3, 33.7, 35.1, 42.6, 62.5, 66.8, 79.3, 80.3, 105.2, 111.2, 128.0, 128.1, 128.5, 136.3, 156.6; ESI/MS (*m/z*) 380 (M^++H); HRMS calcd for $C_{20}H_{29}NO_6Na$ 402.1892, found 402.1881.

4.1.5. (*S*)-Benzyl 2-((3*aR*,5*S*,6*aR*)-2,2-dimethyl-tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)piperidine-1-carboxylate (12)

To a solution of **11** (1.2 g, 3.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added methanesulphonylchloride (0.3 mL, 3.8 mmol) followed by triethylamine (1.34 mL, 9.6 mmol). After 30 min stirring at this temperature, the reaction mixture was poured into water (25 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. To this mesylate derivative in dry THF (15 mL) was added KO^tBu (1.06, 9.5 mmol) and the resulting yellow solution was stirred at room temperature for 3 h. The reaction mixture was quenched with NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate = 9:1) to give the title compound **12** as a colorless oil (0.9 g) in 80% yield. $[\alpha]_D^{28} = -60.7$ (*c* 2.57, $CHCl_3$); IR (neat) ν_{max} 2938, 1696, 1426, 1376, 1318, 1249, 1214, 1163, 1077, 1021, 908, 848, 761, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 1.28 (s, 3H), 1.47 (s, 3H), 1.57–1.8 (m, 7H), 1.9–2.1 (m, 1H), 3.06 (dd, 1H, J = 12.5 Hz), 4.01–4.31 (m, 2H), 4.32–4.48 (m, 1H), 4.62 (dd, 1H, J = 3.97 Hz), 5.04 (d, 1H, J = 12.5 Hz), 5.15 (d, 1H, J = 12.5 Hz), 5.67–5.77 (br s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 25.0, 25.9, 26.5, 26.8, 36.5, 40.3, 52.8, 66.8, 77.3, 79.9, 105.0, 110.6, 127.5, 127.6, 128.2, 136.7, 155.6; ESI/MS (m/z) 362 (M^++H); HRMS calcd for $C_{20}H_{27}NO_5Na$ 384.1786, found 384.1767.

4.1.6. (*S*)-Benzyl 2-((2*S*,4*R*)-4,5-dihydroxy-tetrahydrofuran-2-yl)piperidine-1-carboxylate (13)

The cyclic compound **12** (0.8 g) was treated with 2 mL of TFA/H_2O (3:2) at 0 °C; then the reaction mixture was warmed to room temperature and stirred for 3 h. The solvents were removed by three co-evaporations with toluene (3 × 10 mL), and the residual product was dissolved in water and neutralized with $NaHCO_3$ extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated in vacuo and the crude product purified by column chromatography (hexane/ethyl acetate = 6:4) to give the lactol in 85% yield as a syrup. $[\alpha]_D^{28} = -47.6$ (c 1.48, $CHCl_3$); IR (neat) ν_{max} 3399, 2931, 1671, 1433, 1353, 1260, 1145, 1071, 1030, 955, 856, 757, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–2.1 (m, 10H), 3.0 (m, 1H), 3.95–4.32 (m, 3H), 4.55–4.67 (m, 1H), 4.97–5.27 (m, 3H), 7.20–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 19.3, 24.9, 25.0, 25.9, 36.0, 39.9, 57.4, 67.0, 67.3, 75.1, 102.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 136.6, 157.6; ESI/MS (m/z) 344 (M^++Na); HRMS calcd for $C_{17}H_{23}NO_5Na$ 344.1473, found 344.1472.

4.1.7. (*S*,*E*)-Benzyl 2-(3-oxoprop-1-enyl)piperidine-1-carboxylate (14)

Lactol **13** (0.2 g, 0.73 mmol) was dissolved in methanol (5 mL) and was added to $NaIO_4$ (0.31 g, 1.46 mmol in 3 mL H_2O) at 0 °C. The reaction mixture was stirred at rt for 1 h. After completion of the reaction, methanol was removed under reduced pressure and extracted with ethyl acetate. The combined organic layers were washed with aq $NaHCO_3$, dried, concentrated, and purified by column chromatography (hexane/ethyl acetate = 8:2) to give α,β-unsaturated aldehyde **14** (0.14 g) in 82% yield as a colorless oil. $[\alpha]_D^{28} = -21.5$ (c 0.58, $CHCl_3$); IR (neat) ν_{max} 2923, 2854, 1696, 1460, 1420, 1262, 1173, 1083, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36–1.55 (m, 2H), 1.68 (m, 2H), 1.77–1.95 (m, 2H), 2.86 (t, 1H, J = 12.5 Hz), 4.10 (d, 1H, J = 12.8 Hz), 5.14 (s, 2H), 5.07–5.23 (m, 1H), 6.06–6.17 (ddd, 1H, J = 2.2, 7.5, 15.8 Hz), 6.75 (dd, 1H, J = 4.0, 15.8 Hz), 7.28–7.40 (m, 5H), 9.58 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 25.1, 28.6, 40.7, 52.2, 67.4, 127.9, 128.1, 128.5, 133.0, 136.4, 155.6, 156.2, 193.0; ESI/MS (m/z) 296 (M^++Na).

4.1.8. (*S*)-Benzyl 2-((1*S*,3*R*)-1,3,4-trihydroxybutyl)piperidine-1-carboxylate (15)

The lactol **13** (0.35 g, 1.1 mmol) was dissolved in dry methanol (10 mL) and to it was added $NaBH_4$ (0.082 g, 2.2 mmol) at 0 °C and stirred for 1 h. The reaction mixture was quenched by adding satd NH_4Cl and MeOH was removed in vacuo and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate = 3:7) to afford the triol **15** (0.23 g) in 80% yield as a liquid. $[\alpha]_D^{28} = -43.33$ (c 0.40, $CHCl_3$); IR (neat) ν_{max} 3391, 2935, 1672, 1432, 1351, 1262, 1174, 1081, 1035, 741, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.80 (m, 8H), 2.92–3.12 (m, 1H), 3.43 (dd, 1H, J = 6.0, 11.1 Hz), 3.56 (dd, 1H, J = 2, 11.1 Hz), 3.78–4.2 (m, 4H), 4.34 (br s, 1H), 5.06 (d, 1H, J = 12.5 Hz), 5.1 (d, 1H, J = 12.5 Hz), 7.22–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 25.0, 25.7, 36.5, 40.4, 56.5, 66.5, 67.3, 69.7, 71.8, 127.6, 127.9, 128.4, 136.5, 157.1; ESI/MS (m/z) 346 (M^++Na); HRMS calcd for $C_{17}H_{25}NO_5Na$ 346.1630, found 346.1624.

4.1.9. (1*S*,8a*S*)-Octahydroindolizin-1-ol (5)

To a stirred solution of compound triol **15** (0.17 g, 0.53 mmol) in methanol (5 mL) was added $NaIO_4$ (0.224 g, 1.05 mmol in 3 mL water) and stirring was continued for 1 h. After completion of the reaction, methanol was evaporated under reduced pressure and the crude slurry was dissolved in ethyl acetate, organic layer was washed with $NaHCO_3$ and brine then dried over Na_2SO_4, and concentrated to give the crude aldehyde (0.1 g), which was used as such for the next reaction immediately without any purification. A solution of the aldehyde in methanol (5 mL) was added to 10% Pd/C (0.01 g) and then the flask was purged with H_2 and the solution hydrogenated for 24 h. The catalyst was filtered and washed with methanol and the filtrate was concentrated to give a crude product, which upon purification by column chromatography (chloroform/methanol = 7:3) gave **5** (0.035 g, 73%) as a liquid. $[\alpha]_D^{28} = +23.5$ (c 0.80, EtOH), {lit.[8j], $[\alpha]_D^{25} = +22.5$ (c 1, EtOH)}; IR (neat) ν_{max} 3359, 2926, 2854, 1653, 1547, 1447, 1264, 1133,830, 754 cm^{-1}; The NMR spectroscopic values are in good agreement with the earlier reports.[8j,l] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.3 (m, 2H), 1.46–1.75 (m, 5H), 1.80–2.0 (m, 3H), 2.17 (m, 1H), 2.5 (br s, OH, 1H), 3.13 (m, 2H), 4.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 25.0, 25.1, 33.2, 52.7, 53.5, 69.0, 72.8; ESI/MS (m/z) 142 (M^++H); HRMS calcd for $C_8H_{16}NO$ 142.1231, found 142.1239.

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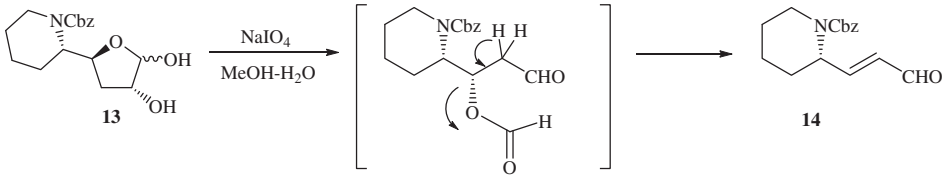
12. Formation of **14**:



13. The NMR spectral pattern of synthetic compound **5** is superimposable with the spectra available in the Supplementary data given by Wee et al.[8l]