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Polyhydroxylated indolizidine alkaloids—synthesis of dideoxycastanospermine

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ABSTRACT

The key transformation developed in this work is the anti-Kishi selective dihydroxylation, which proceeds by way of intramolecular participation of the nitrogen protecting group to furnish the desired stereochemistry required for castanospermine like structures. In this paper, we completed a first synthesis of a novel dideoxycastanospermine **6**.

1. Introduction

Castanospermine is an indolizidine alkaloid first isolated from the seeds of the tree *Castanospermum australe*[1] and later also from the tree *Alexa leiopetale*.[2] Castanospermine analogues attract continued interest by synthetic and medicinal chemists for their potent inhibitory action towards various glucosidase enzymes.[3] Castanospermine was first synthesized by Ganem and Bernotas in 1984,[4] and subsequent syntheses have been reviewed.[5,6]

In connection with our program to develop chiroselective synthesis protocols utilizing amino acid derived α′-chiral β-ketophosphonates,[7] we specifically aimed at utilizing proline-derived β-ketophosphonates as chiral building blocks in the synthesis of indolizidine alkaloids.[8,9]

We have previously reported the synthesis of a 7-*epi*-deoxycastanospermine derivative.[8] The reported route did not allow for the introduction of the *anti* stereochemistry at C7/8 required for the castanospermine structure. In this paper we wish to report our progress in this regard.

Creation of the stereogenic centres was planned to occur by way of internal asymmetric induction, where the initial chiral information is derived from L-proline (Fig. 1). The β-ketophosphonate chemistry followed by HWE-olefination, developed in our laboratory will allow for transfer of the chirality from the proline centre to the new carbinol centre by diastereoselective reduction. The next stereogenic centre (C-7 in castanospermine numbering) was envisaged to be created by diastereoselective oxidation of the allylic alkoxy compounds. In most cases, however, convenient access is possible only for compounds where the relative stereochemistry between the pre-existing alkoxy group and the newly introduced hydroxyl groups follows the Kishi rule.[10] An integral part of our program was, therefore, to find solutions for an anti-Kishi selective oxidation.[11] In this paper we describe a highly selective method for the introduction of the hydroxyl group with the correct stereochemistry for castanospermine structures based on an intramolecular Prevost–Woodward type oxidation.[12]

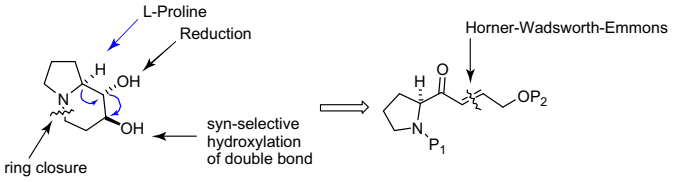
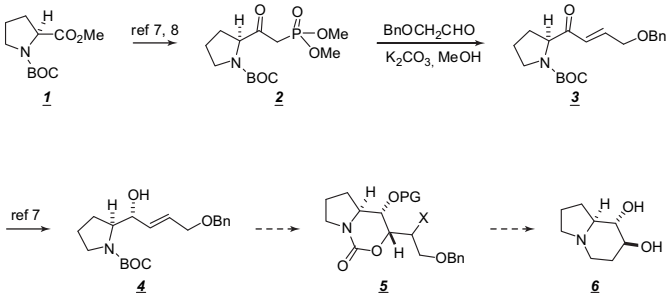


Figure 1. Strategic disconnections and key transformations.

2. Results and discussion

2.1. Synthetic plan (Scheme 1)

A more detailed view of the synthesis is presented in Scheme 1. Fully protected proline **1** is commercially available in both



Scheme 1.

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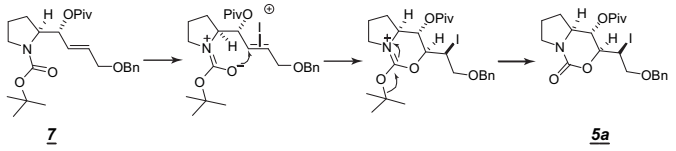
enantiomeric forms but also easily prepared from L/D-proline via esterification and *N*-Boc protection. Preparation of β-ketophosphonate **2** is also reported in the literature.[8,13]

Horner–Wadsworth–Emmons reaction under mild conditions has been shown to give enone **3** with *E*-configuration with high enantiopurity.[8] We have also earlier developed diastereoselective reductions of the enone **3** to selectively access the *anti* allylic alcohol **4**.[8]

In this work, *syn* selective introduction of oxygen would give **5** with the desired relative stereochemistry between carbons C-8 and C-7 (castanospermine numbering) thus facilitating the synthesis of dihydroxyindolizidine **6**.

2.2. Woodward oxidation (Scheme 2)

Our previous model experiments indicated that protection of the alcohol moiety followed by oxidation under Woodward conditions would result in cis hydroxylation *syn* to the pre-existing hydroxyl group.[11] In addition, in the case of a trans double bond the large size of the protecting group improves the selectivity. Accordingly the alcohol **4** was protected as pivaloate ester **7** and oxidized.



Scheme 2.

However, instead of cis hydroxylation, cyclocarbamation took place. Internal nucleophile attacked the π-complex to form the cyclic carbamate **5a**. As confirmed by inspection of NMR spectra, the stereoselectivity followed the same pattern as the oxidation. Informative coupling constants are presented in Figure 2.

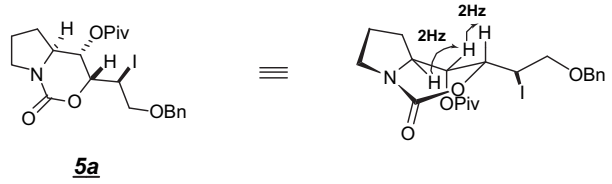


Figure 2. Informative coupling constants in carbamate **5a**.

The reaction was carried out under standard conditions. After all iodine had been added, TLC indicated that all alcohol had been consumed. Purification of the crude product was first attempted by flash chromatography, but as considerable loss of material occurred, only a quick filtration through a short silica pad was done prior to the next reaction step. The yield of the reaction remained consistently below 60%, probably due to the instability of the iodocarbamate.

2.3. Origin of the selectivity

Oxidation of **7** probably follows the mechanism of halolactonization.[14] In halolactonization, protection of the alcohol does affect the stereoselectivity: *syn* attack is preferred in all cases. It has been suggested that the stereoselectivity in electrophilic attack of iodine on a double bond is dependent on how far along the reaction coordinate (π-complex to onium ion) the transition state actually lies. The internal nucleophile traps the initially formed π-complex before it collapses to onium ion. The favoured π-complex A gives *syn* addition (see Fig. 3). Acyl derivatives would give *syn* addition via transition state B.

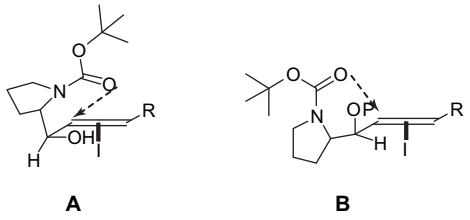
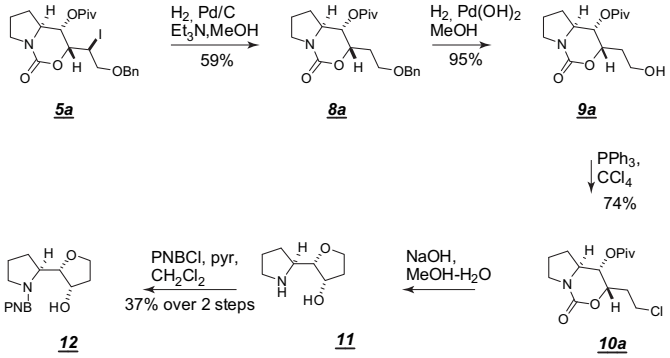


Figure 3. Favoured π-complexes for cyclocarbamation.

2.4. Proof of absolute and relative stereochemistry (Scheme 3)

The reaction sequence was continued with the iodocarbamate **5a**. The cyclic carbamate serves as a protecting group for nitrogen during the rest of the synthesis. Our first attempts to convert carbamate to the indolizidine resulted in the formation of tetrahydrofuranylpyrrolidine **11** as shown in Scheme 3, which allowed us to confirm the stereochemical assignments through X-ray analysis of the derived *p*-nitrobenzamide **12**.



Scheme 3.

Reductive removal of iodine by catalytic hydrogenation (Pd/C, H_2) in the presence of Et_3N[15] gave **8a** (59%), which was again exposed to catalytic hydrogenation to give free alcohol **9a** (95%). Standard reaction conditions with Pd/C catalyst did not induce cleavage of the benzyl group even under elevated H_2 pressure. Changing the catalyst to $Pd(OH)_2$ with an otherwise similar protocol gave a smooth reaction. Hydrolysis of the carbamate would require basic conditions, and that rules out the mesylate mediated cyclization used earlier in the synthesis of trihydroxyindolizidine.[8] Instead, a Mitsunobu-type cyclization[16] was attempted. The primary alcohol was converted to chloride **10a** (74%) by treatment with $PPh_3/K_2CO_3/CCl_4$ in MeCN. Hydrolysis of the cyclic carbamate should then result in cyclization in situ. When chloride **10a** was treated with NaOH in $MeOH/H_2O$, cleavage of the pivaloate occurred first and cyclization took place to C-8 to form **11**. X-ray structure of the derived *p*-nitrobenzoyl derivative (PNB) **12** confirmed the relative stereochemistry between C-8 and C-7 (Fig. 4).[17,18]

2.5. Concluding steps in the synthesis of (7*S*,8*S*,8a*S*)-7,8-dihydroxyindolizidine (Scheme 4)

Since the oxidation involved intramolecular participation of the carbamate group, it was feasible that the role of the protecting group in stereoselectivity is diminished. Thus, it was

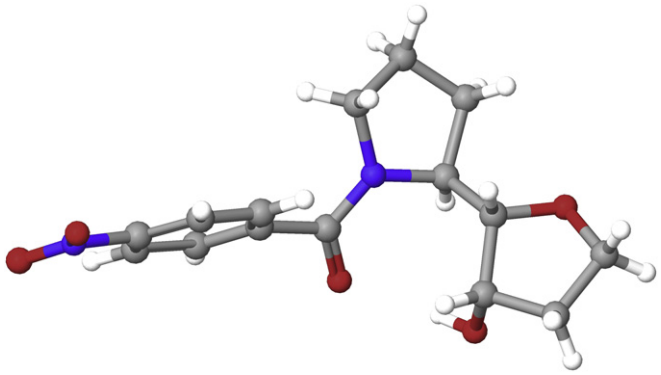
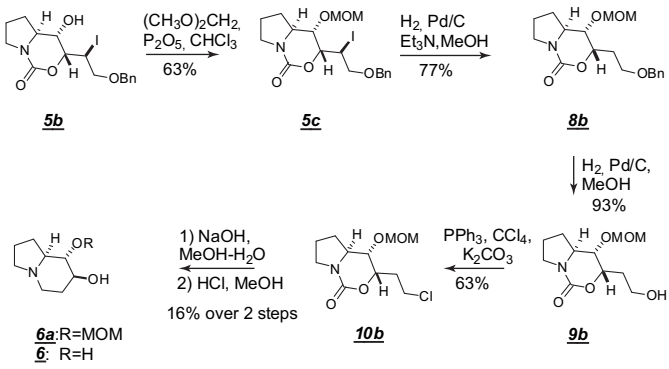


Figure 4. X-ray structure of **12**.



Scheme 4.

possible to replace the pivaloate to a hydrolytically stable protecting group. The synthesis of dihydroxyindolizidine **6** was finally accomplished with methoxy-methyl (MOM) derivative as shown in Scheme 4.

Compound **5b** was obtained by treatment of free alcohol **4** with iodine/silver acetate in acetic acid (55%). Alcohol **5b** was protected as MOM-ether **5c** by treatment with $(CH_3O)_2CH_2/P_2O_5$ in chloroform (63%). Essentially identical reaction conditions as in the sequence with pivaloate **5a** furnished chloride **10b** in comparable yields. Thus, reduction of the iodide **5c** gave **8b** (77%), followed by cleavage of the benzyl group to give the primary alcohol **9b** (93%), which was converted to the primary chloride **10b** (63%).

As with compound **10a**, the chloride **10b** was treated with NaOH in MeOH/H_2O. The mixture was heated to reflux for 16 h to give indolizidine **6a** in only 20% yield. In part, the low yield can be explained by decomposition of the product caused by the long reaction time at high temperature, which was seen as the formation of polar baseline impurities on TLC. Treatment of **6a** in HCl/MeOH gave (7*S*,8*S*,8a*S*)-octahydroindolizine-7,8-diol **6** quantitatively and a total yield of 1.1% over 10 steps.

3. Conclusions

Amino acids provide a valuable source of enantiopure starting materials for the synthesis of complex bioactive compounds. In this paper, we have described a useful route to dihydroxylated indolizidine alkaloids based on the utilization of L-proline-derived β-ketophosphonate. Horner–Wadsworth–Emmons olefination followed by diastereoselective reduction gives the key allylic alcohol. The key transformation developed in this work is the anti-Kishi selective dihydroxylation, which proceeds by way of intramolecular participation of the nitrogen protecting group to furnish the desired stereochemistry required for castanospermine like structures. In this paper, we completed a first synthesis of a novel dideoxyastanospermine **6**.

4. Experimental section

4.1. General

THF was distilled prior to use from sodium/benzophenone, MeCN from phosphorus pentoxide, MeOH from magnesium methoxide, CH_2Cl_2 from CaH_2 and toluene was distilled from Na. Diethyl ether was distilled from $LiAlH_4$ and stored over sodium flakes. Triethylamine and pyridine were fractionally distilled and stored over molecular sieves. Other solvents and reagents were used as obtained from the supplier without further purification.

All air and moisture sensitive reactions were carried out under positive argon atmosphere with magnetic stirring. Evaporation of the solvents was performed with a Büchi rotavapor (water aspirator) followed by static evaporation with an oil pump.

Analytical thin-layer chromatography was performed using precoated aluminium plates (Merck Kieselgehl 60 F254). The chromatograms were visualized with UV and/or polyphosphomolybdic acid in 90% EtOH (10 g/100 mL) or anisaldehyde/glacial acetic acid/H_2SO_4/EtOH (5:1:5:90) or 10% sulfuric acid/H_2O or ninhydrin in *i*-PrOH (1 g/100 mL, 3–5 drops of glacial acetic acid). The flash chromatography was performed using silica gel 60 (E. Merck) as a stationary phase. HPLC was performed using the following columns: Shandon Hypersil Silica Column with Waters Guard-Pak™ precolumn fitted with Resolve™ silica inserts for normal phase chromatography and Daicel chiralcel OD 25 cm×0.46 cm with Daicel chiralcel OD 5 cm×0.46 cm precolumn for chiral chromatography.

Melting points were determined with Gallenkamp melting point apparatus MFB-595 and are uncorrected. Optical rotations were determined on a Perkin–Elmer digital polarimeter in a 1 dm/1 mL cell (*c*=g/100 mL).

The mass spectra were measured by the Mass Spectrometry Laboratory in the University of Oulu on a Kratos MS 80. Elemental analyses were performed by the Trace Element Laboratory in the University of Oulu. NMR spectra were recorded on Bruker AM200 (^{1}H 200.13 MHz, ^{13}C 50.32 MHz), or Bruker DX400 (^{1}H 400.13 MHz, ^{13}C 100.62 MHz) or Bruker DPX 500 (^{1}H NMR 500.13 MHz, ^{13}C 125.77 MHz). Chemical shifts are reported in parts per million (δ) with respect scale calibrated to internal reference tetramethylsilane (TMS) or solvent residual signal.

4.2. (*S*)-*tert*-Butyl 2-((*R*,*E*)-4-(benzyloxy)-1-(pivaloyloxy)but-2-enyl)pyrrolidine-1-carboxylate 7

To a solution of **4** (1.35 g, 3.9 mmol, 100 mol %) in pyridine (15 mL), pivaloyl chloride (1.0 mL, 7.8 mmol, 200 mol %) and dimethylaminopyridine (10 mg, cat) were added. The resulting mixture was stirred at room temperature under argon for 18 h. The mixture was evaporated to dryness in a rotary evaporator and dissolved in Et_2O (40 mL). The organic phase was washed with 10 wt % citric acid (20 mL), water (20 mL) and brine (20 mL) and dried over Na_2SO_4. Filtration, evaporation and chromatography (silica, 30% EtOAc in hexanes) gave **7** (1.43 g, 83%) as a clear oil. R_f (25% EtOAc/hex)=0.5. $[\alpha]_D^{20}$ −33.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.22 (2s, 9H), 1.45, 1.50 (2s, 9H), 1.60–2.28 (m, 4H), 3.20–3.60 (m, 2H), 3.80–4.04 (m, 1H), 4.02 (d, 2H, *J*=4.0 Hz), 4.50, 4.51 (2s, 2H), 5.67 (dt, 1H, *J*=6.4 Hz, 14.8 Hz), 5.60–5.80 (m, 2H), 7.15–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ major rotamer 23.5, 26.4, 27.2, 28.3, 38.7, 46.8, 59.7, 69.7, 72.2, 73.2, 79.8, 127.7, 128.3, 128.6, 128.8, 129.1, 138.0, 154.1, 177.3. HRMS *m*/*z* calcd for $C_{25}H_{37}NO_5$ (M+1) 432.2750, found 432.2782.

4.3. (3*S*,4*S*,4a*S*)-3-((*S*)-2-(Benzyloxy)-1-iodoethyl)-1-oxohexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-4-yl pivalate 5a

To a solution of **7** (1.38 g, 3.1 mmol, 100 mol %) in glacial acetic acid (20 mL), AgOAc (1.16 g, 7.0 mmol, 225 mol %) and I_2 (0.824 g, 3.25 mmol, 105 mol %), respectively, were added and the resulting mixture was stirred at room temperature for 5 h. The mixture was filtered and the filtrate was washed with toluene. The solution was evaporated to dryness in rotary evaporator and dried further in vacuo. The resulting brownish thick oil was chromatographed (silica, 25% EtOAc in hexanes) to give **5a** (0.714 g, 55%) as a clear oil. R_f (75% EtOAc/hex)=0.8. $[\alpha]_D^{20}$ −5.8 (*c* 0.54, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.65–2.05 (m, 4H), 2.36 (m, 1H), 3.28 (ddd, 1H, *J*=1.9 Hz, 5.4 Hz, 11.8 Hz), 3.39 (m, 1H), 3.59 (m, 1H), 3.85 (dd, 1H, *J*=2.7 Hz, 10.8 Hz), 4.04 (dd, 1H, *J*=4.6 Hz, 10.8 Hz), 4.33 (ddd, 1H, *J*=2.7 Hz, 4.6 Hz, 10.5 Hz), 4.41 (dd, 1H, *J*=2.4 Hz, 10.5 Hz), 4.65 (dd, 2H, *J*=12.1 Hz, 21.2 Hz), 5.41 (t, 1H, *J*=2.2 Hz), 7.28–7.36 (m, 5H). ^{13}C NMR (100 MHz) δ 21.2, 25.2, 27.0, 27.2, 30.6, 38.8, 44.6, 62.3, 70.9, 72.6, 75.6, 127.7, 128.3, 152.6, 177.6. HRMS *m*/*z* calcd for $C_{21}H_{28}INO_5$ (M+1) 502.1091, found 502.1109.

4.4. (3*S*,4*S*,4a*S*)-3-(2-(Benzyloxy)ethyl)-1-oxohexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-4-yl pivalate 8a

Compound **5a** (682 mg, 1.33 mmol, 100 mol %) was dissolved in MeOH (50 mL). Air was evacuated from the reaction vessel and replaced by argon. Triethylamine (382 mL, 2.66 mmol, 200 mol %) and 10% Pd/C (68.2 mg, 10 wt %) were added. Argon was evacuated from the reaction vessel and replaced with H_2. The mixture was allowed to stir under H_2 pressure for 18 h. The mixture was filtered through a short Celite pad and evaporated to dryness. The resulting yellowish oil was chromatographed (silica, 50% EtOAc/hex) to give **8a** (301 mg, 59%) as a clear oil. R_f (75% EtOAc/hex)=0.63. $[\alpha]_D^{20}$ −90.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.52–2.20 (m, 6H), 3.36–3.71 (m, 5H), 4.5 (m, 3H), 4.95 (dd, 1H, *J*=6.8 Hz, 4.3 Hz), 7.3 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 26.9, 29.8, 31.3, 38.8, 46.2, 58.0, 65.7, 69.9, 72.9, 73.1, 127.5, 127.8, 128.3, 138.0, 152.3, 177.2. HRMS *m*/*z* calcd for $C_{21}H_{29}NO_5$ (M+1) 376.2124, found 376.2118.

4.5. (3*S*,4*S*,4a*S*)-3-(2-Hydroxyethyl)-1-oxohexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-4-yl pivalate 9a

Compound **8a** (298 mg, 0.79 mmol, 100 mol %) was dissolved in MeOH (25 mL). Air was evacuated from the reaction vessel and replaced by argon after which $Pd(OH)_2$ (20%, 47 mg, 15 wt %) was added. Argon was evacuated from the reaction vessel and replaced with H_2. The mixture was allowed to stir under H_2 pressure for 18 h. The mixture was filtered through a short Celite pad and evaporated to dryness to give **9a** (216 mg, 95%) as a clear oil. R_f (75% EtOAc/hex)=0.1. $[\alpha]_D^{20}$ −81.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.54–2.18 (m, 6H), 2.85 (br s, 1H), 3.35–3.64 (m, 3H), 3.8 (m, 2H), 4.52, (ddd, 1H, *J*=4.7 Hz, 4.7, 9.0 Hz), 4.94, (dd, 1H, *J*=3.8 Hz, 6.8 Hz). ^{13}C (50 MHz, $CDCl_3$) δ 22.1, 26.9, 31.3, 31.9, 38.8, 46.3, 58.1, 58.2, 70.0, 73.2, 152.6, 177.3. HRMS *m*/*z* calcd for $C_{14}H_{23}NO_5$ (M+1) 286.1654, found 286.1640.

4.6. (3*S*,4*S*,4a*S*)-3-(2-Chloroethyl)-1-oxohexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-4-yl pivalate 10a

To a solution of **9a** (216 mg, 0.75 mmol, 100 mol %) in MeCN (10 mL) were successively added K_2CO_3 (207 mg, 1.5 mmol, 200 mol %), PPh_3 (492 mg, 1.88 mmol, 250 mol %) and CCl_4 (342 mg, 2.25 mmol, 300 mol %). The resulting mixture was stirred at 40 °C for 3 h after which the reaction mixture was evaporated to dryness. The brownish thick residue was washed thoroughly several times with hot EtOAc (100 mL in all). The organic solvents were combined and evaporated to dryness. The resulting brownish oil was chromatographed (silica, 30% EtOAc/hex) to give **10a** (170 mg, 74%) as a clear oil. R_f (75% EtOAc/hex)=0.38. $[\alpha]_D^{20}$ −64.8 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.50–2.25 (m, 6H), 3.35–3.76 (m, 5H), 4.54 (ddd, 1H, *J*=10.2 Hz, 2.5 Hz, 7.2 Hz), 4.96 (dd, 1H, *J*=4.2 Hz, 7.2 Hz,). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 27.0, 31.5, 32.6, 38.9, 40.4, 46.5, 57.9, 69.6, 72.8, 151.9, 177.2.

4.7. (2*S*,3*S*)-2-((*S*)-Pyrrolidin-2-yl)tetrahydrofuran-3-ol 11

To a solution of **10a** (170 mg, 0.56 mmol, 100 mol %) in MeOH/H_2O (5 mL/5 mL) was added NaOH (174 mg, 4.46 mmol, 800 mol %). The mixture was heated to reflux for 8 h after which it was evaporated to dryness. The residue was dissolved in EtOAc and filtered. The filtrate was evaporated to give **11** as yellowish oil, which was used in the next step without purification. R_f (50% EtOAc/hex)=0.04. ^{1}H NMR (400 MHz, d_5-pyridine) δ 2.71 (ddd, 1H, *J*=9.6 Hz, 6.3 Hz, 7.9 Hz,), 2.87 (m, 1H,), 3.61 (dd, 1H, *J*=3.4 Hz, 6.0 Hz), 3.69 (dd, 1H, *J*=7.4 Hz, 13.6 Hz,), 3.83 (ddd, 1H, *J*=11.8 Hz, 7.8 Hz, 4.0 Hz,), 4.17 (ddd, 1H, *J*=8.0 Hz, 7.8 Hz,), 4.61 (ddd, 1H, *J*=1.6 Hz, 3.2 Hz, 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 27.5, 36.3, 45.3, 59.3, 66.7, 72.5, 81.4. HRMS *m*/*z* calcd for $C_8H_{15}NO_2$ (M+1) 158.1181, found 158.1085.

4.8. ((*S*)-2-((2*S*,3*S*)-3-Hydroxytetrahydrofuran-2-yl)-pyrrolidin-1-yl)(4-nitrophenyl)methanone 12

To a solution of **11** from the previous reaction (0.56 mmol, 100 mol %) in dichloromethane (10 mL) were added pyridine (362 mL, 4.48 mmol, 800 mol %) and *p*-nitrobenzoylchloride (418 mg, 2.24 mmol, 400 mol %). The resulting mixture was stirred at room temperature for 6 h after which 10 mL saturated $NaHCO_3$ in brine (50:50) was added. The layers were separated and the organic phase was successively washed with 10 wt % citric acid (10 mL) and brine (10 mL) and dried over Na_2SO_4. Filtration and evaporation gave a yellowish oil, which was chromatographed to give **12** (64 mg, 37%).

Compound **12**: R_f (75% EtOAc/hex)=0.32. $[\alpha]_D^{20}$ −75.6 (*c* 0.345, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.8–2.21 (m, 6H), 3.32 (m, 1H), 3.45 (m, 1H), 3.9 (m, 1H), 4.1 (q, 1H, *J*=8.4 Hz), 4.18 (s, 1H), 4.5 (ddd, 1H, *J*=3.6 Hz, 6.0 Hz, 7.2 Hz), 7.63 (d, 2H, *J*=8.8 Hz), 8.25 (d, 2H, *J*=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.2, 34.2, 50.5, 55.7, 66.3, 70.4, 83.8, 123.7, 128.0, 142.1, 148.5, 169.6, HRMS *m*/*z* calcd for $C_{15}H_{18}N_2O_5$ (M+1) 307.1294, found 307.1321.

4.9. (3*R*,4*S*,4a*S*)-3-((*S*)-2-(Benzyloxy)-1-iodoethyl)-4-hydroxyhexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 5b

To a solution of alcohol **4** (1.3 g, 3.76 mmol, 100 mol %) in glacial acetic acid (55 mL) was added AgOAc (4.13 g, 24.75 mmol, 450 mol %) and then I_2 (2.93 g, 11.55 mmol, 210 mol %) in portions. The resulting mixture was stirred at room temperature for 2 h after which NaCl was added and the solids were filtered off. The filtrate was evaporated to dryness and the residue was dissolved in EtOAc (20 mL). The organic phase was washed with water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave the crude product, which was purified by flash chromatography (15% *i*-PrOH/hex) to give **5b** (855 mg, 55%) as a yellowish oil. R_f (*i*-PrOH/hex)=0.31. $[\alpha]_D^{20}$ −35.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (m, 1H), 1.83 (m, 1H), 2.0 (m, 1H), 2.19 (m, 1H), 3.01 (broad d, 1H, *J*=8.0 Hz) 3.40 (ddd, 1H, *J*=4.0 Hz, 9.9 Hz, 11.3 Hz), 3.46 (ddd, 1H, *J*=3.7 Hz, 5.5 Hz, 11.2 Hz), 3.61 (dt, 1H, *J*=8.1 Hz, 11.3 Hz), 3.91 (dd, 1H, *J*=4.6 Hz, 10.6 Hz), 3.98 (dd, 1H, *J*=4.6 Hz, 10.6 Hz), 4.35 (ddd, 1H, *J*=3.3 Hz, 7.7 Hz), 4.39 (dd, 1H, *J*=3.0 Hz, 8.5 Hz), 4.40 (dt, 1H, *J*=4.6 Hz, 8.4 Hz), 4.65 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 26.0, 31.0, 45.7, 63.1, 71.1, 71.4, 73.8, 78.7, 128.3, 128.9, 137.7, 153.1. HRMS *m*/*z* calcd for $C_{16}H_{20}INO_4$ (M+1) 418.0515, found 418.0507.

4.10. (3*R*,4*S*,4a*S*)-3-((*S*)-2-(Benzyloxy)-1-iodoethyl)-4-(methoxymethoxy)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 5c

To a solution of **5b** (314 mg, 0.75 mmol, 100 mol %) in $CHCl_3$ (8 mL), $(CH_3O)_2CH_2$ (6.7 mL, 75 mmol, 10,000 mol %) and P_2O_5 (4.5 g) were added. The mixture was stirred at room temperature for 1 h and then poured into the ice/$NaHCO_3$ solution (15 mL). The resulting mixture was extracted with diethyl ether (3×15 mL) and the combined organic phase was successively washed with water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave crude **5c** (220 mg, 63%), which was used in the next step without further purification. R_f (20% *i*-PrOH/hex)=0.60. $[\alpha]_D^{20}$ −39.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (m, 1H), 1.81 (m, 1H), 1.97 (m, 1H), 2.21 (m, 1H), 3.37 (m, 1H), 3.44 (s, 3H), 3.49–3.62 (m, 2H), 3.87 (dd, 1H, *J*=3.2 Hz, 10.7 Hz), 4.01 (dd, 1H, *J*=5.1 Hz, 10.7 Hz), 4.3 (t, 1H, *J*=2.8 Hz), 4.41 (dd, 1H, *J*=2.7 Hz, 9.9 Hz), 4.50 (ddd, 1H, *J*=3.2 Hz, 4.8 Hz, 9.9 Hz), 4.64 (m, 2H), 4.74 (d, 1H, *J*=7.3 Hz), 4.82 (d, 1H, *J*=7.3 Hz), 7.25–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 26.7, 31.2, 45.5, 56.9, 61.7, 71.7, 73.6, 76.4, 77.5 (under $CDCl_3$), 97.8, 128.2, 128.8, 138.2, 153.1. HRMS *m*/*z* calcd for $C_{18}H_{24}INO_5$ (M+1) 462.0777, found 462.0779.

4.11. (3*S*,4*S*,4a*e*)-3-(2-(Benzyloxy)ethyl)-4-(methoxymethoxy)-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 8b

To a solution of **5c** (143 mg, 0.31 mmol, 100 mol %) in MeOH (10 mL) was added triethylamine (86.4 mL, 0.62 mmol, 200 mol %). The reaction mixture was flushed with Ar. 10% Pd/C (20 mg) was added after which Ar was evacuated from the vessel and H_2 was introduced. The mixture was allowed to stir under H_2 balloon for 5 h and then filtered through a short pad of Celite. Evaporation of the solvent followed by chromatography (silica, 15% *i*-PrOH in hexanes) gave **8b** (80 mg, 77%) as a clear oil. R_f (*i*-PrOH/hex)=0.44. $[\alpha]_D^{20}$ −101.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (m, 1H), 1.81 (m, 2H), 2.02 (m, 1H), 2.16 (dddd, 1H, *J*=1.9 Hz, 7.3 Hz, 9.1 Hz, 14.5 Hz), 2.28 (dt, 1H, *J*=5.8 Hz, 11.6 Hz), 3.35 (s, 3H), 3.39–3.50 (m, 1H), 3.58 (ddd, 1H, *J*=7.9 Hz, 10.6 Hz), 3.72 (m, 3H), 4.52 (m, 2H), 4.60 (ddd, 1H, *J*=1.9 Hz, 4.8 Hz, 11.0 Hz), 4.67 (m, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 29.7, 32.5, 47.6, 56.5, 57.3, 66.5, 73.6, 74.5, 74.6, 96.8, 128.0, 128.8, 138.7, 152.4. HRMS *m*/*z* calcd for $C_{18}H_{25}NO_5$ (M+1) 336.1811, found 336.1810.

4.12. (3*S*,4*S*,4a*S*)-3-(2-Hydroxyethyl)-4-(methoxymethoxy)-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 9b

Compound **8b** (133 mg, 0.40 mmol, 100 mol %) was dissolved in MeOH (5 mL) and the reaction vessel was flushed with argon. Pd/C (10%; 24 mg) was added. Argon was evacuated from the vessel and H_2 was introduced. The mixture was allowed to stir under H_2 balloon for 48 h after which the mixture was filtered through a Celite pad to give alcohol **9b** (90 mg, 93%) as a clear oil. R_f (75% EtOAc/hex)=0.13. $[\alpha]_D^{20}$ −90.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (m, 1H), 1.72–1.85 (m, 2H), 1.98–2.10 (m, 2H), 2.24–2.30 (m, 1H), 2.95 (br s, 1H), 3.84 (s, 3H), 3.34–3.48 (m, 2H), 3.54–3.60 (m, 1H), 3.72 (dd, *J*=4.9 Hz, 9.1 Hz), 3.83 (m, 2H), 4.58 (ddd, 1H, *J*=2.4 Hz, 4.8 Hz, 10.7 Hz), 4.67 (d, *J*=6.8 Hz), 4.71 (d, 1H, *J*=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 32.0, 32.4, 47.5, 56.4, 56.5, 57.4, 58.9, 74.9, 96.8, 152.5. HRMS *m*/*z* calcd for $C_{11}H_{19}NO_6$ (M+1) 246.1341, found 246.1347.

4.13. (3*S*,4*S*,4a*S*)-3-(2-Chloroethyl)-4-(methoxymethoxy)-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one 10b

To a solution of **9b** (133 mg, 0.54 mmol, 100 mol %) in MeCN (10 mL) were successively added PPh_3 (356 mg, 1.36 mmol, 250 mol %), K_2CO_3 (149 mg, 1.08 mmol, 200 mol %) and CCl_4 (155 mL, 1.63 mmol, 300 mol %). The mixture was heated to 60 °C and stirred for 40 min. The solids were filtered off and the filtrate was poured into water (10 mL). The mixture was extracted with $CHCl_3$ (3×10 mL) and the organic phases were combined and washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave the crude product, which was quickly purified by flash chromatography (silica, 50% EtOAc in hexanes) to give **10b** (90 mg, 63%) as a clear oil. R_f (75% EtOAc/hex)=0.50. $[\alpha]_D^{20}$ −109.7 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (m, 1H), 1.79 (m, 1H), 2.05 (m, 2H), 2.20 (m, 1H), 2.28 (m, 1H), 3.39 (s, 3H), 3.32–3.49 (m, 2H), 3.58 (ddd, 1H, *J*=7.9 Hz, 10.5 Hz), 3.72–3.78 (m, 3 H), 4.62 (ddd, 1H, *J*=1.9 Hz, 5.0 Hz, 10.7 Hz), 4.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 32.47, 32.53, 41.2, 47.6, 56.6, 57.4, 74.4 (2C), 96.9, 151.9.

4.14. (7*S*,8*S*,8a*S*)-8-(Methoxymethoxy)octahydroindolizin-7-ol 6a

To a solution of **10b** (60 mg, 0.23 mmol, 100 mol %) in MeOH/H_2O (2 mL/0.2 mL) was added NaOH (100 mg, 2.5 mmol, 108 mol %). The mixture was heated to 80 °C and stirred for 15 h. The mixture was evaporated to dryness and dissolved in EtOAc (10 mL) and poured into water (5 mL). The mixture was extracted with EtOAc (3×10 mL) and the organic phases were combined and washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave crude product, which was purified by flash chromatography (silica, 30% EtOH/$CHCl_3$) to give pure **6a** (10 mg, 18%) as a clear oil. R_f (30% EtOH/$CHCl_3$)=0.47. ^{1}H NMR (400 MHz, C_6D_6) δ 1.52–1.68 (m, 2H), 1.64–1.75 (m, 1H), 1.88–2.20 (m, 6H), 2.84 (ddd, 1H, *J*=2.0 Hz, 3.6 Hz, 10.4 Hz), 2.97 (dt, 1H, *J*=2.0 Hz, 8.4 Hz), 3.28 (t, 1H, *J*=8.4 Hz), 3.65 (ddd, 1H, *J*=5.3 Hz, 8.4 Hz, 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 28.5, 32.0, 49.3, 53.6, 55.8, 66.4, 73.0, 89.3, 98.0. HRMS *m*/*z* calcd for $C_{10}H_{19}NO_3$ (M+1) 202.1443, found 202.1463.

4.15. (7*S*,8*S*,8a*S*)-Octahydroindolizine-7,8-diol 6

To a solution of **6a** (10 mg, 0.04 mmol, 100 mol %) in MeOH (1 mL) was added a catalytic amount of HCl. The resulting mixture was heated to reflux for 3 h after which the solvent was evaporated. The residue was chromatographed (75% EtOH/$CHCl_3$) to give **6** (6 mg, 96%) as a clear oil. R_f (50% $CDCl_3$/MeOH)=0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4–2.3 (m, 9H), 3.04 (ddd, 1H, *J*=2.3 Hz, 4.6 Hz, 11.4 Hz), 3.08 (dt, 1H, *J*=2.3 Hz, 8.7 Hz), 3.28 (7, 1H, *J*=8.7 Hz), 3.47 (ddd, 1H, *J*=5.1 Hz, 8.6 Hz, 11.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 28.2, 32.5, 49.5, 53.6, 67.6, 74.9, 78.7. HRMS *m*/*z* calcd for $C_8H_{15}NO$ 157.1103, found 157.1121.

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