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Polyhydroxylated indolizidine alkaloids—an efficient synthesis of 1-deoxy-8,8a-di-*epi*-castanospermine

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Abstract—A new and efficient enantioselective total synthesis of the title deoxycastanospermine derivative has been developed, based on amino acid and β-ketophosphonate chemistry, as well as employment of internal asymmetric induction for the creation of the new chiral centers proved successful. With proper choice of reaction conditions, the approach can also be applied in selective preparation of several isomers of deoxycastanospermine. The length (9 steps) and overall yield of the title compound trihydroxyindolidine **1**, 7.3%, compares well with the literature syntheses of similar compounds.

1. Introduction

Aminosugar glycosidase inhibitors are structural analogs of monosaccharides in which the ring oxygen has been replaced by nitrogen. These alkaloids include polyhydroxylated derivatives of piperidine (A), pyrrolidine (B), pyrroline (C), indolizine (D) and pyrrolizidine (E) (Fig. 1).[1]

Castanospermine[2,3] has attracted continued interest by synthetic and medicinal chemists for its inhibitory action toward various glucosidase enzymes and promising effects against autoimmune diseases (e.g. HIV-infection and diabetes). More than 60 syntheses of castanospermine and its analogs have been published since the first one by Ganem and Bernotas in 1984.[4,5]

The work described in this paper is part of a broader program aimed at developing new synthetic methods based on amino acids, which are inexpensive and easily available chiral compounds in both enantiomeric forms. A specific goal in this program to develop methods to utilize internal asymmetric induction in such a way that chirality will be derived from pre-existing chiral centers in the molecule without the need to resort to external sources of chirality.

Specifically, this work aims at utilizing the proline-derived β-ketophosphonates as chiral building blocks in the synthesis of indolizine alkaloids. The continuous chiral carbinol centers of the target compounds can be introduced through selective reduction of carbonyl groups and selective oxidation of double bond. Herein we report an efficient enantioselective synthesis of the title compound, 1-deoxy-8,8a-di-*epi*-castanospermine (Fig. 2).

Two earlier syntheses of the title compound have been reported.[6] The NMR data given in the older one[6a] has been reported to be erroneous.[6b,c] In this work we also found that none of the products reported by Chan correspond to the title compound.

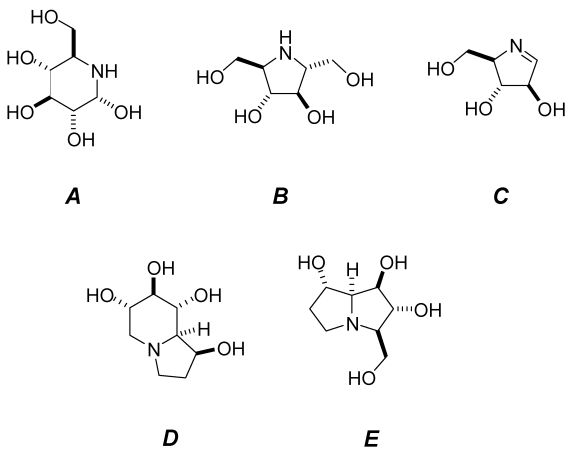

Figure 1. Alkaloidal glycosidase inhibitors. (A)) Nojirimycin; (B) (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*R*)-dihydroxypyrrolidine DMDP; (C) (3*R*,4*R*,5*R*)-3,4-dihydroxy-5-hydroxymethyl-1-pyrroline FR-900483; (D) castanospermine; (E) alexine.

Keywords: alkaloid; enantioselection; dihydroxylation; reduction.
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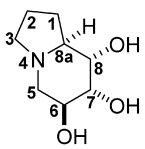


1-deoxy-8,8a-di-epi-castanospermine

(6S,7R,8S,8aS)-6,7,8-trihydroxyindolizidine

Figure 2.

2. Results and discussion

2.1. Earlier synthetic strategies for castanospermine analogues

The earlier syntheses of castanospermine analogues can be divided into three main classes according to how the indolizidine skeleton is constructed (Scheme 1). The first two classes are based on the first strategic disconnection in the indolizidine skeleton. In the pyrrolidine approach the last synthetic step in building up the carbon framework is always the formation of the bond between C-5 and nitrogen. In the piperidine approach the last transformation is the formation of the bond between C-3 and nitrogen. The third class, the miscellaneous strategies include all those strategies that do not fall into the first two classes.

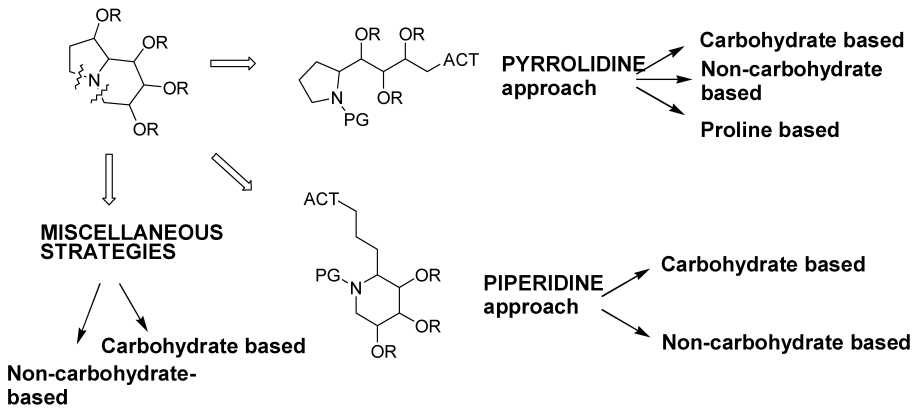
2.2. Synthetic analysis (Scheme 2)

The amino acid synthetic sequence, based on proline as starting material, belongs among the pyrrolidine syntheses. Thus, the piperidine ring would be annealed after installment of all the chiral centers in **6** (Scheme 2). The continuous chiral carbinol centers in **6** were envisioned to arise from an anti-selective dihydroxylation of the corresponding allylic alcohol **5a** (Kishi selectivity).[7] Based on our earlier experiences in the sphinogisine synthesis, we expected that the chirality in the allylic alcohol center in **5a** could be efficiently derived from the a′-chiral a,b-unsaturated enone **4**.[8] The enone would be efficiently available from L-proline through the β-keto-phosphonate **3**.[9]

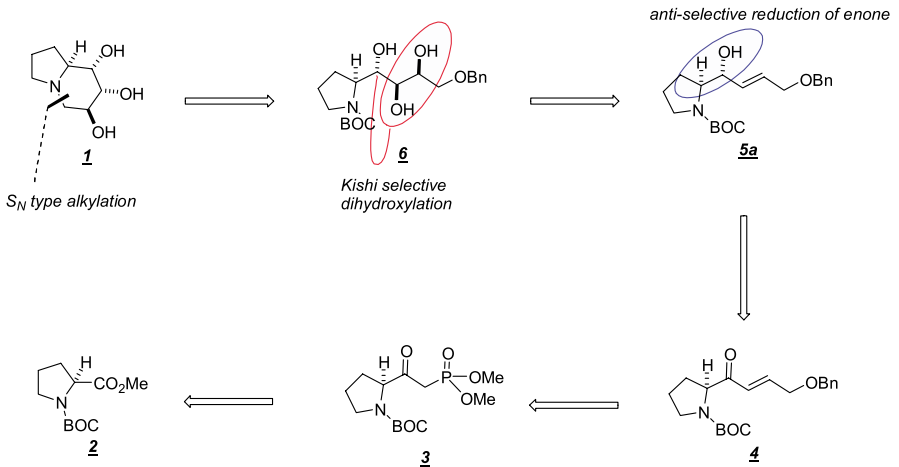
2.3. Synthesis of the allylic alcohol (Scheme 3)

Proline derived phosphonate **3** has been synthesized previously by Heathcock and von Geldern[9] from Boc-proline methyl ester and dimethyllithiomethylphoshonate (DMMP).

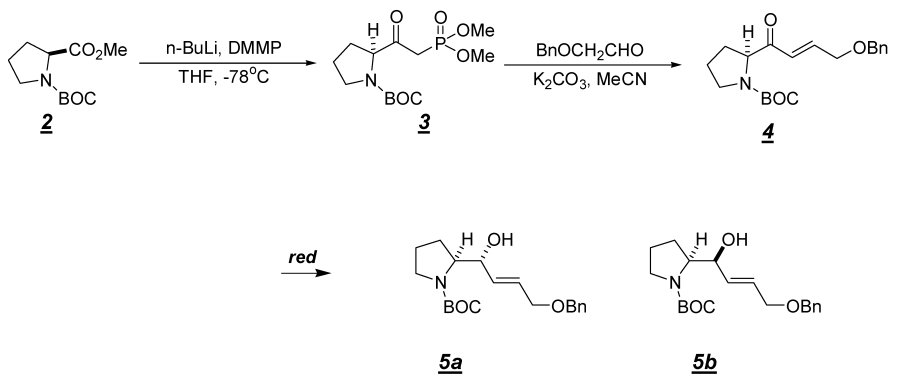
The most common application of the phosphonates is Horner–Wadsworth–Emmons olefination.[10] Preparation of non-racemic phosphonates has recently been reviewed by Wiemer.[11]



Scheme 1.



Scheme 2.



Scheme 3.

The phosphonate anion was generated at −78°C in THF by addition of *n*-BuLi, and to confirm the anion formation the mixture was allowed to warm to −40°C. The white suspension was then cooled back to −78°C and proline ester **2** was added. After the addition the mixture was allowed to warm to room temperature. Clarification of the reaction mixture indicated that the actual reaction took place already at −30°C.

The product was isolated from the reaction mixture by first adding 10 wt% citric acid with vigorous stirring until the pH was slightly acidic (5–6). Lowering the pH below 5 resulted in decomposition of the product phosphonate. Isolation was completed by extraction with EtOAc.

Purification of the phosphonate was performed by filtering through silica with two eluent systems. In larger scale reactions (>10 mmol scale), up to 25% of the starting material remained unreacted. The less polar unreacted proline ester **1** was eluted with 20% EtOAc/hexanes and then the phosphonate with 100% EtOAc. No racemization of the unreacted proline ester was detected. Optical purity of the product was determined by chiral HPLC (98%ee).

The yield reported by Heathcock and von Geldern was 96% but they did not disclose the actual reaction conditions or the scale. In our work the yield varied from 75 to 85%, depending on the scale. The lower yields were obtained in repeated 100 mmol scale. The pure β-ketophoshonate is a clear liquid and can be stored in a freezer without racemization.

Conventional methods for the HWE reaction, although milder than standard Wittig procedure, are still too vigorous for base-sensitive substrates, e.g. NaH in THF. Masamune and Roush discovered that LiCl enhances the acidity of phosphonate by complexation with phosphonate carbanion and thus allows the use of weaker bases like DBU and DIPEA.[12] However, these conditions usually require chromatographic purification of the product, which often is not stereochemically stable during purification.

An alternative mild base system method has been described by us for the preparation of base sensitive α-diazocarbonyl compounds.[13] This method was later optimized for the HWE reaction for serine derivatives.[14] In the modification, K_2CO_3/MeCN forms a base/solvent system that is strong enough to accomplish the reaction yet mild enough to avoid racemization of base labile substrates. Yields and optical purities of this modification are comparable and in some cases even better than with LiCl/DBU or LiCl/DIPEA.[15] In terms of practical advantages, K_2CO_3 is not only inexpensive but makes the purification procedure simple, consisting simply of filtration of the reaction mixture.

Thus, treatment of β-ketophosphonate **3** with powdered K_2CO_3 in MeCN, followed by addition of benzyloxyacetaldehyde[16] led to the desired reaction. As the reaction proceeded the mixture began to change color from white to yellow. The reaction mixture remains heterogeneous throughout the reaction, therefore scaling the reaction affects the reaction times: smaller scale reactions from 6 to 16 mmol were complete in 20 h, but when the reaction was scaled up to 38 mmol the reaction time doubled to 43 h. Enone **4** was much less prone to racemization on silica than the corresponding serine derived enones, and purification on silica gel chromatography could be performed (94%ee).[12] The yields varied from 55 to 68%.

Reduction of unsaturated carbonyl compounds has been a challenge for synthetic chemists because reduction of the carbonyl function often is accompanied by saturation of the olefinic functionality. The literature reports some methods to show regioselectivity, e.g. 9-BBN,[17] $NABH_4$ in the presence of lanthanoid salts,[18] diisopropylaluminumhydride (DIBAL-H),[19] and hindered alkylborohydrides.[20]

Utilization of internal asymmetric induction in the reduction step in such a way that chirality at the α position would determine the stereochemistry of the formed alcohol without the need to resort to chiral reducing agents has proved useful for serine-derived enones.[8] Similar approach was chosen in this work. The general synthetic sequence relies on anti selective reduction of the enone **4**.

Reduction experiments were performed under several different conditions to achieve selective reduction and the desired anti isomer **5a**. For purposes of comparison, both chelation controlled and non-chelation controlled reaction conditions were tested. The diastereoselectivity of each reaction was determined by HPLC (Table 1).

Selectivities can be understood by looking at the two sets of energy minimum conformations for enone **4** found by standard Monte Carlo conformation search (Fig. 3).[21] On steric grounds, conformation A can be considered more

Table 1. Reduction experiments

Entry	Conditions	Selectivity *anti*/*syn*[a]
1	DIBAL-H, toluene, −78°C	1.3:1
2	$NaBH_4$, $CeCl_3{\cdot}9H_2O$, MeOH	2.4:1
3	$NaBH_4$, $CeCl_3{\cdot}9H_2O$, *i*-PrOH	1.1:1
4	9-BBN, THF, 0°C	–
5	L-Selectride, THF, −78°C	1:5.3

[a] Ratios determined by HPLC from crude reaction mixture. The mass balance in each experiment was satisfactory (>95%).

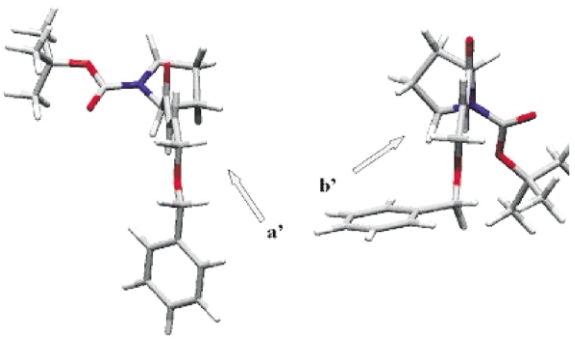


Figure 3. Minimum energy conformations for enone **4**.

favorable because steric repulsion between the 'side chain' and the N-Boc group is minimized.[22] Thus, a non-coordinating large hydride reagent would attack from the less hindered side of the molecule along the axis a′ in conformation A to give the *syn*-alcohol as the major product. The experimental results are in accordance with this, as L-selectride, bulky, non-coordinating alkylboro-hydride, in coordinating solvent cleanly gave *syn*-alcohol **5b**.

Chelation controlled conditions should favor hydride attack from the opposite face of the alkene. However, in this case steric requirements for selective reaction are not fulfilled. In condition 1, aluminum coordinates to carbonyl group prior to reduction. The bulky aluminum complex only slightly favors conformation B leading to *anti*-alcohol. Both faces are thus accessible to hydride attack and practically no selection was detected. Low selectivity was accompanied by a considerable amount of 1,4-reduction.

Another anti selective reduction protocol is hydride reduction under Luche conditions.[23] It has been suggested that cerium metal forms an adduct with the alcoholic solvent, which then coordinates to the carbonyl oxygen. Reduction with an alkoxyborohydride occurs from the less hindered side of the complex. The selectivity was not marked in this case either, but no 1,4-reduction was detected and the yield of the two alcohols was almost quantitative. In *i*-propyl alcohol the reaction rate was much slower and the selectivity was lost completely. This might be because the actual reducing species in this solvent is $NaBH_4$.

On steric grounds 9-borabicyclononane should give the anti isomer, but no reaction was detected. It has been reported that this reagent has reduced reactivity with sterically hindered ketones.[23]

The low selectivities are obviously due to relatively low barrier of rotation of the enone side chain. This is further attested by the fact that we were not able to see meaningful nOe's in the spectra of **4**.[24]

The reduction under the Luche conditions in methanol was scaled up to 19 mmol. The combined yield of the isomeric alcohols **5a** and **5b** was quantitative regardless of the scale and the selectivity remained the same. The *anti*-alcohol, **5a**, was enriched with MPLC to a 20:1 mixture which was used in further reaction steps.

2.4. Determination of the stereochemistry of the reduction

For determination of its stereochemistry, the alcohol **5a** was converted to (*S*)- and (*R*)-MTPA esters according to the procedure of Kobayashi et al.[25,26]

The NMR spectra were measured at 500 MHz and the signals were assigned with reference to two-dimensional correlation spectra (HSQC). Chemical shift differences ($\Delta\delta$) between the (*R*) and (*S*) isomers were calculated and the results were compared against the Mosher configuration model (Fig. 4). The stereochemistry of the alcohol **5a** was assigned to be *R*.

2.5. Synthesis of (2*S*,1′*S*,2*R*/*S*,3*R*/*S*)-*N*-*tert*-butoxy-carbonyl)-2-[(4′-benzyloxy-1′,2′,3′-trihydroxy)butyl]-pyrrolidine (Scheme 4)

Osmium tetroxide catalyzed *cis* hydroxylation of the alcohol **5a** produced two isomers in approximate ratio 5:1. On the basis of the mechanistic rationalization,[27] the major

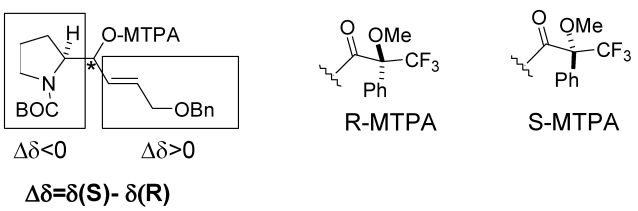
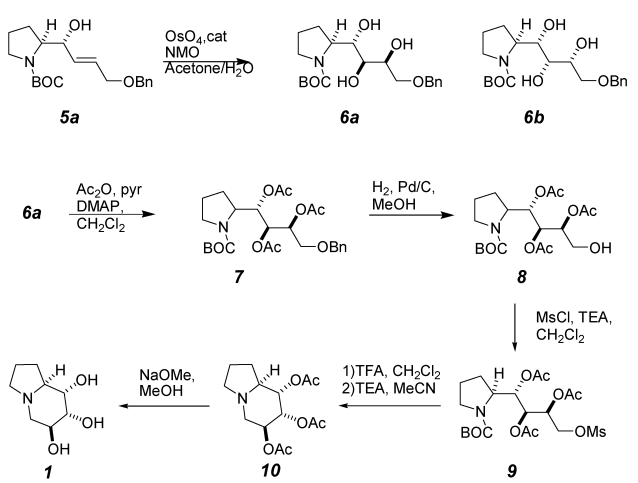


Figure 4. Determination of the configuration by Mosher method.



Scheme 4.

isomer was assumed to be the anti isomer. The assignment was also later confirmed by NMR (see below).

The reaction was performed under standard conditions (OsO_4 and *N*-methylmorpholine-*N*-oxide in acetone/water), and was complete in 16 h. The main isomer **6a** crystallized almost completely from the reaction mixture when 25% EtOAc/hexane was added. The residue was chromatographed to give pure all *syn* triol **6b**. The reaction yielded 57% of **6a** and 17% of **6b**. The major isomer was used in the synthesis of trihydroxyindolizidine **1**.

2.6. Concluding the synthesis of (6*S*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine 1 (Scheme 4)

In order to convert triol **6a** to the bicyclic indolizidine the benzyloxy group should be replaced by a good leaving group to facilitate cyclization. Literature examples show that removal of the nitrogen protective group would then lead to instant cyclization.[28] Mesylate was chosen as the leaving group.

To differentiate the hydroxyl groups in the mesylation step, triol **6a** was first converted to acetyl protected **7**. Acetylation in standard conditions (Ac_2O, pyr, CH_2Cl_2, DMAP) gave **7** almost quantitatively (96%). Debenzylation by catalytic hydrogenation gave the primary alcohol **8** (96%).

Mesylation of the primary alcohol (MsCl, Et_3N) furnished **9**, which was cyclized in two steps. The N-Boc protecting group was removed with trifluoroacetic acid in CH_2Cl_2. The reaction was over in 2 h, after which the mixture was evaporated to dryness to remove excess of TFA. The residue was dissolved in acetonitrile and 300 mol% triethylamine was added to liberate TFA salt. Cyclization took place smoothly when the mixture was stirred at room temperature to give (6*S*,7*R*,8*S*,8a*S*)-6,7,8-triacetoxyindolizidine **10** in 50% yield over two steps.

Hydrolysis of **10** gave (6*S*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine **1** in 77% yield. The title compound was thus synthesized in 9 steps and 7.3% overall yield. The stereochemistry of the product was assigned by NMR (coupling constants shown in Fig. 5). The NMR data was identical with those reported by Martin.[6b]

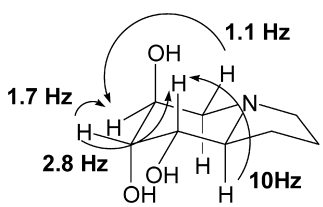


Figure 5.

3. Conclusions

A new and efficient enantioselective total synthesis of the title deoxycastanospermine derivative has been developed, based on amino acid and β-ketophosphonate chemistry, as well as employment of internal asymmetric induction for the creation of the new chiral centers proved successful. With proper choice of reaction conditions, the approach can also be applied in selective preparation of several isomers of deoxycastanospermine. The length (9 steps) and overall yield of the trihydroxyindolidine **1**, 7.3%, compares well with the literature syntheses.

4. Experimental

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. Triethylamine and pyridine were 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 followed by static evaporation with an oil pump.

Analytical TLC was performed using precoated aluminium plates (Merck Kieselgehl 60 F_{254}). The chromatograms were visualized with UV and/or polyphosphomolybdic acid in 90% EtOH (10 g/100 mL), anisaldehyde/glacial acetic acid/H_2SO_4/EtOH (5:1:5:90), 10% H_2SO_4/H_2O or ninhydrin in *i*-PrOH (1 g/100 mL, 3–5 drops of glacial acetic acid). Flash chromatography was performed using Silica gel 60 (E. Merck) as the stationary phase. HPLC was performed using the following columns: Shandon Hypersil Silica Column with Waters Guard-PakTM precolumn fitted with ResolveTM 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 ppm (δ) and referenced to internal tetramethylsilane (TMS) or solvent residual signal.

4.1.1. (2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(dimethoxy-phosphinyl)-acetyl] pyrrolidine 3. Dimethylmethyl-phosphonate (0.866 mL, 8 mmol, 200 mol%) in THF (10 mL) was cooled to −78°C. *n*-BuLi (8 mmol, 200 mol%) was added dropwise keeping internal temperature below −65°C.

After addition the mixture was allowed to warm to −20°C bath and then cooled back to −78°C. L-Boc-proline methyl ester **2** (0.916 g, 4 mmol, 100 mol%) dissolved in THF (5 mL) was added into the mixture keeping temperature below −65°C. The resulting white suspension was allowed to warm slowly to room temperature and stirred for an additional 4 h. The reaction was quenched with 10 wt% citric acid and the pH was adjusted to 3. EtOAc (20 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (2×10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the solvent was evaporated. The crude product was purified by flash chromatography (silica, 100% EtOAc) to give **3** as a clear oil (1.1 g, 3.4 mmol, 85.2%). R_f (EtOAc)=0.13. $[\alpha]_D^{20}$=+18.7 (c=4.6, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 1.34, 1.35 (2s, 9 H, rotamers), 1.74–2.13 (m, 4H), 3.14, (m, 2H, rotamers), 3.4 (m, 2H), 3.69 (d, 9H, ^3J(P, H), 11.3 Hz), 4.2 (m, 1H). δ_C (50 MHz, $CDCl_3$) 23.5, 24.3, 28.1, 29.3, 35.9, 38.5, 46.6, 52.6, 65.5, 65.9, 79.8, 80.2, 153.5, 154.5, 201.3. HRMS m/z calcd for $C_{13}H_{24}NO_6P$ (M+1) 322.1420, found 322.1459.

4.1.2. (2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(4′-benzyloxy-1′-oxo)-*E*-but-2′-en]pyrrolidine 4. To a solution of β-keto-phosponate **3** (12.14 g, 37.8 mmol, 100 mol%) in MeCN (200 mL) was added powdered K_2CO_3 (15.7 g, 113.4 mmol, 300 mol%). The resulting mixture was stirred for 15 min after which benzyloxyacetaldehyde (5.68 g, 37.8 mmol, 100 mol%) in MeCN (60 mL) was added. The mixture was stirred at room temperature for 48 h after which 10 wt% citric acid was added until pH was 5. The mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic layers were combined and successively washed with water and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation gave crude product which was purified by flash chromatography (silica, 20% EtOAc/hex) to give enone **4** as a yellowish oil (8.86 g, 25.7 mmol, 68%). R_f (25% EtOAc/hex)=0.1. $[\alpha]_D^{20}$=−28.2 (c=1.0, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 1.36, 1.45 (2s, 9H), 1.82–2.22 (m, 4H), 3.41–3.58 (m, 2H), 4.20 (dd, 2H, J=1.9, 4.1 Hz), 4.38 (dd, 1H, J=5.3, 8.3 Hz), 4.57 (s, 2H), 6.53 (dt, 1H, J=15.6, 1.9 Hz), 6.98 (dt, 1H, J=15.6, 4.1 Hz), 7.29–7.36 (m, 5H). δ_C (50 MHz, $CDCl_3$) 23.7, 28.3 (29.0), 30.2, 46.7, 64.4 (63.7), 68.9, 72.9, 79.9, 124.8, 125.5, 127.6, 127.8, 128.4, 137.7, 143.3, 153.9, 198.4. HRMS m/z calcd for $C_{20}H_{27}NO_4$ (M+1) 346.2018, found 346.2055.

4.1.3. (2*S*,1′*R*/*S*)-*N*-(*tert*-Butoxycarbonyl)-2-[(4′-benzyloxy-1′-hydroxy)-*E*-but-2′-en]pyrrolidine 5a/b. To a solution of enone **4** (6.57 g, 19.04 mmol, 100 mol%) and $CeCl_3{\cdot}7H_2O$ (8.87 g, 23.8 mmol, 125 mol%) in MeOH (150 mL) was added $NaBH_4$ (0.90 g, 23.8 mmol, 125 mol%) in portions. The reaction mixture was then allowed to stir at room temperature for 10 min. The reaction was quenched with 10% HCl until pH was 6. The mixture was diluted with diethyl ether (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Filtration and evaporation gave the crude mixture (2.4:1 *anti*/*syn*) which was purified by MPLC (silica, $CHCl_3$/Et_2O 95:5) to give *anti*-alcohol **5a** (4.21 g, 12.1 mmol, 63.6%) and *syn*-alcohol **5b** (0.6 g, 1.7 mmol, 9.1%).

5a: R_f (25% EtOAc/hex)=0.08. $[\alpha]_D^{20}$=−61.0 (c=1.0, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 1.45 (s, 9H), 1.70–2.04 (m, 4H), 3.14–3.52 (m, 2H), 4.04 (d, 2H, J=5.5 Hz), 4.15–4.26 (m, 1H), 4.5 (s, 2H), 5.68 (dd, 1H, J=15.7, 6.1 Hz), 5.84 (dt, 1H, J=15.7, 5.5 Hz), 7.22–7.38 (m, 5H). δ_C (50 MHz, $CDCl_3$) 24.0, 28.4 (4C), 48.1, 62.8, 70.2, 71.9, 75.1, 80.3, 127.6, 128.4, 129.0, 131.2, 138.4, 156.9. HRMS m/z calcd for $C_{20}H_{29}NO_4$ (M+1) 348.2175, found 348.2168.

5b: R_f (25% EtOAc/hex)=0.08. $[\alpha]_D^{20}$=−62.4 (c=1.0, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 1.47 (s, 9H), 1.75–1.91 (m, 4H), 3.28–3.43 (m, 2H), 3.83–3.87 (m, 2H), 4.05 (d, 2H, J=5.6 Hz), 4.52 (s, 2H), 5.31 (bs, 1H), 5.7 (dd, 1H, J=15.4 Hz, 6.4 Hz), 5.88 (dt, 1H, J=15.6 Hz, 5.2 Hz), 7.30–7.34 (m, 5H). δ_C (50 MHz, C_6D_6) 22.9, 27.4, 46.5, 62.3, 69.3, 71.2, 75.5, 79.0, 126.8, 127.3, 127.9, 132.3, 138.3, 156.7. HRMS m/z calcd for $C_{20}H_{29}NO_4$ (M+1) 348.2175, found 348.2167.

4.1.4. *R*-MTPA ester of 5a. Alcohol **5a** (20 mg, 0.06 mmol, 100 mol%) was dissolved in CH_2Cl_2 (1 mL), and *R*-MTPA (54 mg, 0.23 mmol, 400 mol%), dicyclohexylcarbodiimide (36.6 mL, 0.23 mmol, 400 mol%) and 4-(*N*,*N*-dimethyl)-aminopyridine (10 mg, 0.08 mmol, 120 mol%) were added. The resulting mixture was stirred at room temperature for 15 min after which it was diluted with CH_2Cl_2 and filtered. The filtrate was washed successively with 10 wt% citric acid, dilute $NaHCO_3$ solution, water and brine and dried over anhydrous Na_2SO_4. After evaporation of solvents the residue was dissolved in hexane and filtered to remove residual DCC. The product was purified by filtering through a short silica pad to give the product as a yellowish oil (20 mg, 0.035 mmol, 59%). R_f (25% EtOAc/hex)=0.46. $[\alpha]_D^{20}$=−2.8 (c=1.0, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.5 (s, 9H), 1.73, 1.63 (m, 2 H), 1.9 (m, 2H), 3.08 (m, 1H), 3.4, 3.36 (m, rotamers, tot. 1H), 3.49 (s, 3H), 3.96, 3.82 (m, rotamers, tot 1H), 4.03 (d, 2H, J=4.6 Hz), 4.50 (d, 2H, J=4.3 Hz), 5.64 (m, 1H), 5.88 (ddt, 1H), 6.12 (m, 1H), 7.35–7.29 (m, 10H). δ_C (125 MHz, $CDCl_3$) 23.2, 23.9, 25.3, 26.3, 26.9, 28.38, 28.45, 47.0, 47.2, 55.2, 59.7, 69.4, 72.0, 72.3, 76.1, 76.4, 79.6, 80.2, 84.9, 122.3, 124.6, 126.5, 126.6, 126.8, 127.4, 127.7, 128.6, 129.6, 131.6, 132.1, 138.0, 154.1, 154.6, 165.6, 166.0. HRMS m/z calcd for $C_{30}H_{36}F_3NO_5$ (M+17) 564.2572, found 564.2541.

4.1.5. *S*-MTPA ester of 5a. Prepared as above. Yield 79% of a yellowish oil. R_f (75% EtOAc/hex)=0.72. $[\alpha]_D^{20}$=−26.9 (c=1.18, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.46 (s, rotamers, 9H), 1.51, 1.55 (m, 2H), 1.87 (m, 2H), 2.6 (m, 1H), 3.26, 3.16 (m, rotamers, 1H), 3.55 (s, 3H), 3.91, 3.77 (m, rotamers, tot. 1H), 4.04 (s, 2H), 4.51 (d, 2H, J=10.1 Hz), 5.73 (m, 1H), 5.99 (ddt, 1H), 6.11 (m, 1H), 7.50–7.32 (m, 10 H). δ_C (125 MHz, $CDCl_3$) 23.2, 23.9, 25.3, 26.3, 28.4, 28.5, 46.6, 46.8, 55.5, 59.8, 59.8, 69.4, 72.1, 72.4, 76.1, 76.3, 79.4, 80.0, 84.5, 122.2, 124.5, 126.6, 126.7, 127.0, 127.1, 127.3, 127.65, 127.74, 128.3, 129.4, 132.38, 132.43, 137.9, 138.0, 153.9, 154.5, 165.5. HRMS m/z calcd for $C_{30}H_{36}F_3NO_5$ (M+17) 564.2572, found 564.2548.

4.1.6. (2*S*,1′*S*,2′*S*/*R*,3′*S*/*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(4′-benzyloxy-1′,2′,3′-trihydroxy)butyl]pyrrolidine. To a solution of alcohol **5a** (500 mg, 1.44 mmol, 100 mol%) in acetone/H_2O (8:1, 37 mL), NMO (0.399 mg, 2.88 mmol,

200 mol%) and OsO_4 (0.91 mL, 0.03 mmol, 2 mol%) were added. The resulting mixture was stirred at room temperature for 22 h after which saturated $NaHSO_4$ solution (20 mL) was added. After stirring for 30 min, the solids were filtered off and the filtrate was washed successively with water and brine and dried over Na_2SO_4. Filtration and evaporation gave crude products **6a** and **6b** as thick oil in ratio 5:1. The main product crystallized from ethyl acetate/hexanes to give pure **6a** as a white powder (309 mg, 0.82 mmol, 57%), mp 113°C. Minor isomer **6b** was isolated as a white foam (92 mg, 0.24 mmol, 17%).

6a: R_f (75% EtOAc/hex)=0.52. $[\alpha]_D^{20}=-44.7$ (c=0.3, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) 1.45 (s, 9H), 2.13–1.6 (m, 4H), 3.6–3.15 (m, 4H), 3.69 (d, 2H, J=4.9 Hz), 3.8–4.25 (m, 4H), 4.56 (s 2H), 7.32 (broad s, 5H). δ_C (50 MHz, $CDCl_3$) 24.7, 26.3, 29.0, 48.4, 60.3, 70.1, 71.3, 72.9, 73.3, 73.9, 80.4, 128.2, 128.4, 128.8, 156.2. HRMS *m/z* calcd for $C_{20}H_{31}NO_6$ (M+1) calcd 382.2230, found 382.2250.

6b: R_f (75% EtOAc/hex)=0.45. $[\alpha]_D^{20}=-31.9$ (c=1.0, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 1.40 (s, 9H), 1.6–1.9 (m, 4H), 3.16–3.30 (m, 4H), 3.60 (d, 2H, J=5.8 Hz), 3.8 (m, 1H), 4.0 (m, 1H), 4.1 (m, 1H), 5.1 (m, 1H), 7.2 (m, 5H). δ_C (50 MHz, $CDCl_3$) 24.4, 28.4, 29.1, 48.1, 70.5, 71.7, 71.9, 73.5, 76.5, 80.6, 127.7, 128.4, 138.0, 157.6. HRMS *m/z* calcd for $C_{20}H_{31}NO_6$ (M+1) calcd 382.2230, found 382.2257.

4.1.7. (2*S*,1′*S*,2′*S*,3′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(1′,2′,3′-triacetoxy-4′-benxyloxy)butyl]-pyrrolidine 7. Acetic anhydride (2.18 mL, 2500 mol%) and dimethylaminopyridine (18 mg, cat) were added to a solution of **6a** (350 mg, 0.92 mmol, 100 mol%) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at rt for 8 h after which the solvent was evaporated. The crude product was directly chromatographed (silica, 30% EtOAC/C_6) to give **7** as thick oil (450 mg, 0.89 mmol, 96%). R_f (50% EtOAc/hex)=0.67. $[\alpha]_D^{20}=-44.3$ (c=1.02, CH_2Cl_2). δ_H (200 MHz, $CDCl_3$) δ 1.43, 1.51, (2s, 9H, rotamers), 1.6–2.15 (m, tot. 6H), 1.97 (s, 3H), 2.04 (s, 6H), 3.0–3.2 (m, 1H), 3.25–3.6 (m, 3H), 3.65–3.95 (m, 1H, rotamers), 5.15–5.7 (m, 3H), 7.22–7.32 (m, 5H). δ_C (50 MHz, $CDCl_3$) 20.57, 20.72, 23.98, 25.77, 28.40, 46.68, 56.96, 67.64, 68.71, 69.75, 73.42, 79.60, 127.68, 127.82, 128.31, 137.64, 169.09, 169.70, 170.16. HRMS *m/z* calcd for $C_{26}H_{37}NO_9$ (M+1) 508.2522, found 508.2547.

4.1.8. (2*S*,1′*S*,2′*S*,3′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(1′,2′,3′-triacetoxy-4′-hydroxy)butyl]pyrrolidine 8. Compound **7** (400 mg, 0.79 mmol, 100 mol%) was dissolved in MeOH (15 mL). Air was evacuated from the reaction vessel and replaced with argon after which Pd/C 10% (40 mg, 10 wt%) was added. Argon replaced with H_2. The mixture was allowed to stir at room temperature for 18 h. Filtration through a short celite pad and evaporated to dryness gave **8** as a white waxy solid (310 mg, 0.74 mmol, 94%). Mp 158–160°C. Rf (50% EtOAc/hex)=0.31. $[\alpha]_D^{20}=-81.0$ (c=0.57, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) main rotamer 1.50 (s, 9H), 1.80–2.1 (m, 4H), 1.98 (s, 1H), 2.05 (s, 3H), 2.15 (s, 6H), 3.14 (m, 1H), 3.43–4.0 (m, 4H), 5.56 (m, 2H), 5.71, (bd, 1H, J=10.3 Hz). δ_C (50 MHz, $CDCl_3$) 20.7, 24.0, 25.7, 28.3, 46.6, 56.8, 60.1, 68.4, 69.8, 70.4, 70.8, 79.8, 153.7, 169.2, 170.5. HRMS *m/z* calcd for $C_{19}H_{31}NO_9$ (M+1) calcd 418.2077, found 418.2031.

4.1.9. (2*S*,1′*S*,2′*S*,3′(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(1′,2′,3′-triacetoxy-4′-methanesulfonyl)-butyl]pyrrolidine 9. Triethylamine (177 mL, 1.27 mmol, 200 mol%) and mesyl chloride (74 mL, 0.90 mmol, 150 mol%) were added to a solution of **8** (266 mg, 0.64 mmol, 100 mol%) in CH_2Cl_2 (10 mL) and the mixture was stirred at rt for 2 h. Water (20 mL) was added and the layers were separated. The aqueous phase was extracted with 3×15 mL CH_2Cl_2 and the organic layers were combined and dried over Na_2SO_4. Filtration and evaporation gave quantitatively **9** as clear oil which was used in the next step without further purification. R_f (75% EtOAc/hex)=0.70. δ_H (200 MHz, $CDCl_3$) (mixture of rotamers) 5.65, 5.50, 5.23 (multiplets, tot 3H), 4.34, 4.15, 3.95, 3.69, 3.40, 2.90–3.2 (multiplets, tot 8H), 2.13, 2.13, 2.09, 2.06, 1.99, 1.96 (singlets, tot 9H), 1.6–2.1 (m, 4H), 1.49, 1.41 (singlets, tot 9H). δ_C (100 MHz, $CDCl_3$) 170.1, 169.9, 169.3, 169.1, 154.6, 153.6, 79.7, 69.8, 69.7, 69.0, 68.2, 67.9, 67.4, 67.2, 65.6, 56.6, 56.4, 46.7, 46.5, 37.5, 37.2, 28.3, 25.8, 25.7, 24.3, 23.9, 20.7. HRMS *m/z* calcd for $C_{20}H_{33}NO_{11}S$ (M+1) calcd 496.1853, found 496.1854.

4.1.10. (6*S*,7*R*,8*S*,8a*S*)-6,7,8-Triacetoxyindolizidine 10. Trifluoroacetic acid (360 mL, 4.85 mmol, 800 mol%) was added to a solution of **9** (300 mg, 0.606 mmol, 100 mol%) in CH_2Cl_2 (8 mL). The resulting mixture was stirred at rt for 2 h after which TLC indicated that all starting material was consumed. The mixture was evaporated to dryness and the residue was dissolved in MeCN (5 mL). To this solution triethylamine (600 mL, 1.8 mmol, 300 mol%) was added and the mixture was stirred at room temperature for 16 h. The mixture was evaporated to dryness and chromatographed (silica, 50% EtOAc/hex) to give **10** as a clear oil (90 mg, 300 mmol, 50%). R_f (75% EtOAc/hex)=0.44. $[\alpha]_D^{20}=+16.0$ (c=1.66, $CHCl_3$). δ_H (400 MHz, C_6D_6, 60°C) 1.45–1.91 (m, 4H), 1.72 (s, 3H), 1.82 (s, 3H), 2.1 (q, 1H, J=8.3 Hz), 1.86 (s, 3H), 2.50–2.59 (m, 3H), 2.94 (dt, 1H, J=2.4, 8.3 Hz), 3.18 (dd, 1H, J=1.9, 12.6 Hz), 5.14 (dd, 1H, J=2.2, 5.4 Hz), 5.42 (dd, 1H, J=3.2, 10.1 Hz), 5.75 (t, 1H, J=3.2 Hz). δ_C (100 MHz, C_6D_6, 60°C) 20.2, 20.4, 21.4, 28.5, 51.1, 53.7, 68.7, 70.6, 73.3, 168.7, 169.3. HRMS *m/z* calcd for $C_{14}H_{21}NO_6$ 299.1369, found 299.1357.

4.1.11. (6*S*,7*R*,8*S*,8a*S*)-6,7,8-Trihydroxyindolizidine 1. To a solution of **10** (45 mg, 0.15 mmol, 100 mol%) in MeOH (5 mL) was added a catalytic amount of NaOMe. The resulting mixture was stirred at rt for 1 h after which TLC indicated that all starting material was consumed. The solvent was evaporated and the residue was chromatographed (silica, 50% EtOH/$CHCl_3$) to give **1** as a white waxy solid (20 mg, 0.12 mmol, 77%) mp 157–159°C. R_f (50% $CDCl_3$/MeOH)=0.24. $[\alpha]_D^{20}=+15.6$ (c=1.66, $CHCl_3$). δ_H (400 MHz, CD_3OD) 1.44–1.54 (m, 1H), 1.72 (m, 2H), 1.98 (m, 1H), 2.21 (q, 1H, J=9.0 Hz), 2.29 (ddd, 1H, J=6.5, 10.0, 10.0 Hz), 2.48 (dd, 1H, J=1.1, 11.0 Hz), 2.84 (dd, 1H, J=1.7, 11.0 Hz), 2.99 (dt, 1H, J=2.4, 8.8 Hz), 3.58 (dd, 1H, J=2.8, 10.0 Hz), 3.74–3.78 (m, 2H). δ_C (100 MHz, CD_3OD) 21.6, 29.0, 54.0, 54.9, 63.8, 71.5, 72.6, 72.8. HRMS *m/z* calcd for $C_8H_{15}NO_3$ 173.1052, found 173.1057.

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