A Convenient Synthesis of 1-Deoxy-8a-*epi*-Castanospermine Diastereoisomers (6*R*,7*R*,8*S*,8a*S*)-6,7,8-Trihydroxyindolizidine and (6*R*,7*R*,8*R*,8a*S*)-6,7,8-Trihydroxyindolizidine

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Keywords: Alkaloids / Natural products / Asymmetric synthesis / Cyclization / Hydroxylation

An efficient synthesis of (6*R*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine and (6*R*,7*R*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine is described from readily available *N*-BOC-L-proline, (BOC = *tert*-butoxycarbonyl) which involves the addition of ethyl lithiopropiolate to the aldehyde derived from *N*-BOC-L-proline as a key step, then cyclization to construct indolizidine skeletons and asymmetric dihydroxylation.

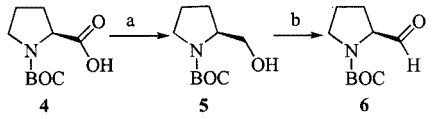
Introduction

The naturally occurring polyhydroxylated indolizidine alkaloids, represented by (+)-castanospermine (**1**) and (+)-6-*epi*-castanospermine (**2**), have been isolated from *Castanospermum australe*[1] and *Alexa leiopetala*.[2] Such indolizidine alkaloids and their derivatives have been reported to display glycosidase inhibition activity,[3] and are regarded as potential antiviral, antitumor, and immunomodulating agents.[4] Because of their unique structural features and significant bioactivity, (+)-castanospermine (**1**), (+)-6-*epi*-castanospermine (**2**) and their analogues have been synthesized by many groups from different starting materials in the past decades[5] in order to elucidate structure−activity relationships. In our previous preparation of *pumiliotoxin 251D* we developed a diastereoselective addition of ethyl lithiopropiolate to *N*-BOC-L-proline derivatives to elongate a three-carbon chain.[6] As part of our continuing program, which is directed towards a general synthesis route to hydroxylated indolizidine alkaloids, we now report a short and practical synthesis of 1-deoxy-*epi*-castanospermine **3a** and **3b**[7,8] from the readily available starting material *N*-BOC-L-proline. The attractive feature of this approach lies in its inherent flexibility, since the key intermediates **10a** and **10b** can be easily converted into a series of analogues and derivatives.

1: (+)-Castanospermine, X = H, Y = OH
2: (+)-6-*epi*-Castanospermine, X = OH, Y = H

3a: R^1 = OH, R^2 = H
3b: R^1 = H, R^2 = OH

Scheme 1



Scheme 2. (a) BH_3·Me_2S, THF, room temp., 99%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 95%

Results and Discussion

(2*S*)-*N*-BOC-pyrrolidine-2-carboxaldehyde (**6**) was prepared in two steps from commercially available *N*-BOC-proline (**4**) (Scheme 2). Compound **4** was reduced by treatment with BH_3·Me_2S to afford the alcohol **5** in 99% yield, which was followed by Swern oxidation according to a literature procedure[9] to give aldehyde **6** in 95% yield.

The addition of ethyl propiolate to aldehyde **6** using *n*BuLi as base in THF at −78 °C[10] afforded a separable mixture of **7a** and **7b** in a combined yield of 80% (Scheme 3). The ratio of diastereomeric addition products was determined by the yields of **7a** and **7b** isolated after purification by column chromatography on silica gel (*n*-hexanes/ethyl acetate, 3:1). The absolute configurations of the newly formed stereogenic centers were assigned by subsequent transformation to target compounds **3a** and **3b**, respectively. The effect of additives on the ratio of diastereoisomers was studied. When the reaction was conducted in the presence of 2 equiv. of HMPA, a 2.6:1 mixture of **7a**/**7b** was obtained. On the contrary, in the presence of 2 equiv. of Ti(O*i*Pr)$_4$ a 1:2.5 mixture of **7a**/**7b** was produced. Unfortunately, attempts to improve the stereoselectivity in the

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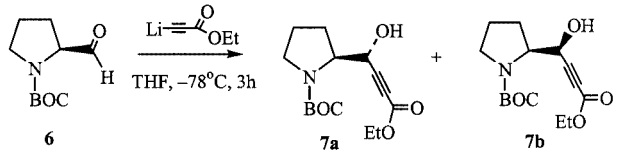
  DOI: 10.1002/ejoc.200200412

presence of various Lewis acids such as $[Cp_2TiCl_2]$, $TiCl_4$, $Ti(OiPr)_2Cl_2$ $ZnBr_2$, $Sm(OTf)_3$, $Yb(OTf)_3$ or $SnCl_4$ resulted in either little diastereoselectivity or very low yield.

Table 1. Effect of additives on the reaction

Entry	Additive	Equiv.	**7a**/**7b**[a]	Total yield (**7a** + **7b**)[b]
1	none		1.2:1.0	80%
2	HMPA	2	2.6:1.0	78%
3	$Ti(OiPr)_4$	2	1.0:2.5	74%

[a] Determined by weight after column flash chromatography. [b] Isolated yield.



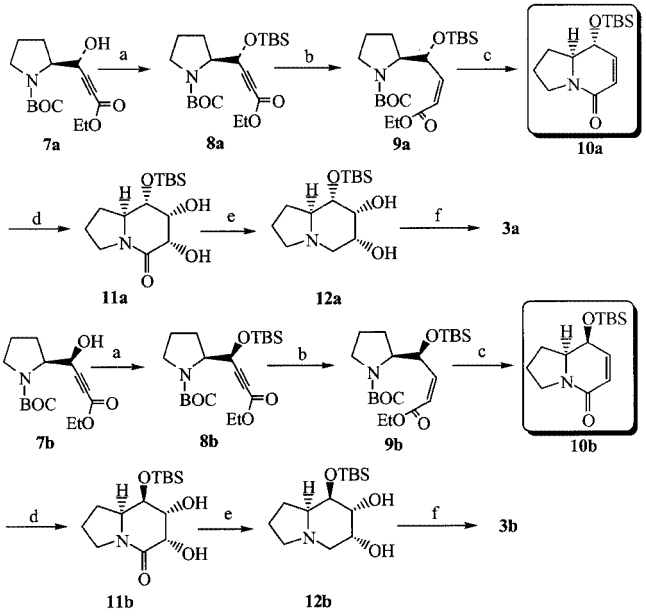
Scheme 3

Silylation of the alcohols **7a** and **7b** with TBSCl/imidazole[11] led to silyl ethers **8a** and **8b** in 98 and 99% yields, respectively (Scheme 4).[12] Then partial *cis*-hydrogenation of the carbon−carbon triple bonds to **9a** and **9b** with (*Z*)-double bonds was easily accomplished in the presence of Lindlar's catalyst. Acidic deprotection by trifluoroacetic acid and subsequent intramolecular cyclization initiated by Et_3N in CH_2Cl_2 resulted in **10a** (or **10b**).[11] Thus, dihydroxylation of key intermediates **10a** or **10b** with OsO_4/NMO[13] (NMO = *N*-methylmorpholine *N*-oxide) at room temperature provided diols **11a** or **11b** in 88 and 97% yield, respectively. Interestingly, the *syn*-dihydroxylations of **10a** and **10b** occurred from the face of the double bond in *syn* relationship to 8a-H with an *exo* approach as shown in Figure 1. Finally, reduction of the resulting intermediates **11a** and **11b** with $BH_3{\cdot}Me_2S$ in THF[14] and then exposure to TBAF yielded the two desired trihydroxyindolizidines **3a** and **3b**.

The structural assignments of **3a** and **3b** were accomplished by ^1H NMR and ^{13}C NMR spectroscopy, and from 2D ^1H-^1H COSY and NOESY homonuclear shift correlation spectra (Figure 2 and Table 2).

The NOESY spectrum shows that 8-H and 7-H are close to one another in **3a**, and 8-H and 8a-H are close to one another in **3b** based on related cross signals. This is consistent with the configurations of target compounds **3a** and **3b**, which are shown in Figure 2.

Comparison with spectroscopic data (^1H NMR) in the literature confirmed the structural assignments. In addition, comparison of the rotation of **3a** and **3b** with the literature value confirmed the absolute stereochemistry {**3a**: $[\alpha]_D^{20}$ = −35.8 (*c* = 0.92, H_2O); ref.[7] $[\alpha]_D^{25}$ = −36.3 (*c* = 0.49, H_2O); **3b**: $[\alpha]_D^{20}$ = +23.8 (*c* = 0.90, MeOH); ref.[8] $[\alpha]_D^{25}$ = +23 (MeOH)}.



Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, room temp. 12 h, 98% of **8a**, 99% of **8b**; (b) H_2, Lindlar's catalyst, 1 atm, quinoline, MeOH, room temp. 3 d, 96% of **9a**, 98% of **9b**; (c) i: TFA, CH_2Cl_2, 0 °C to room temp., then 1.5 h, ii: Et_3N,CH_2Cl_2, room temp. 2 d, 45% of **10a**, 61% of **10b**; (d) OsO_4, NMO, acetone/H_2O (10:1), 25 °C, 8 h, 88% of **11a**, 97% of **11b**; (e) i: $BH_3{\cdot}Me_2S$/THF, room temp., 4 h, reflux, 1 h, ii: EtOH, reflux, 95% of **12a**, 97% of **12b**; (f) TBAF, THF, 25 °C 1 h, 90% of **3a**, 83% of **3b**

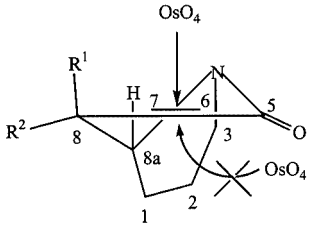


Figure 1. The *syn*-dihydroxylation of **10a** with an *exo* approach

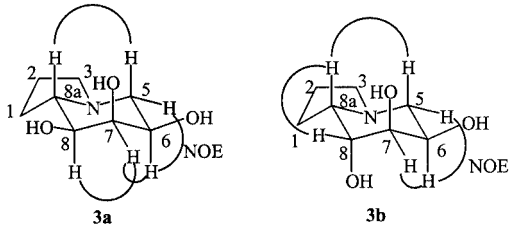


Figure 2. Graphical summary of the NOESY spectrum observed for **3a** and **3b**

Table 2. Selective coupling constants *J* [Hz] for **3a** and **3b**

Isomer	$J_{5\alpha\text{-}5\beta}$	$J_{5\alpha\text{-}6}$	$J_{5\beta\text{-}6}$	J_{6-7}	J_{7-8}	J_{8-8a}
3a	10.9	5.1	11.1	2.9	2.8	10.2
3b	10.1	5.0	10.9	3.2	3.4	1.8

In conclusion, we have completed a new efficient synthesis of two stereoisomers **3a** and **3b** of 1-deoxycastanospermine in 16 and 23% overall yields, respectively. The mild reaction conditions and high yield make the route attractive.

Experimental Section

General: All reactions were conducted under Ar unless stated otherwise and monitored by TLC on precoated silica gel HSGF254 plates (Yantai Chemical Co. Ltd.). Column chromatography was performed on silica gel 300−400 mesh (Yantai Chemical Co. Ltd.) and eluted with hexane and ethyl acetate mixtures. All solvents were refluxed and distilled from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2). The NMR spectra (^1H: 300 MHz; ^{13}C: 75.4 MHz) were recorded with a Bruker AMX-300 spectrometer and are reported in δ units in ppm and *J* values in Hz with Me_4Si as the internal standard. MS spectra (EI) were recorded with an HP-5985-A mass spectrometer. Infrared (IR) spectra were recorded with a Shimadzu IR-440 or Digital FTIR and are reported in cm^{-1}. Optical rotations were measured with a Perkin−Elmer 241Autopol Polarimeter. $[\alpha]_D$ values are reported in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed with a Carlo Erba 1106 analyzer. (*S*)-*N*-(*tert*-butoxycarbonyl)prolinol (**5**) and (*S*)-*N*-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxaldehyde (**6**) were prepared according to a previously described procedure.[9]

Compounds 7a and 7b: *n*BuLi (9.2 mL of a 2.0 M solution in hexane, 18.5 mmol) was added slowly to a stirred solution of ethyl propiolate (1.88 mL, 1.814 g, 18.5 mmol) in dry THF (150 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then a solution of aldehyde **6** (1.844 g, 9.25 mmol) in dry THF (10 mL) was added through a cannula under positive Ar pressure. The resulting solution was stirred at −78 °C for 3 h, and the reaction was monitored with TLC. Saturated aqueous NH_4Cl was added at −78 °C to quench the reaction, and then the reaction mixture was warmed to room temperature and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine and dried with Na_2SO_4, filtered and concentrated. Flash chromatography on silica gel (hexane/EtOAc, 3:1) gave **7a** (1.21 g) and **7b** (1.02 g) in a combined yield of 80%.

7a: $[\alpha]_D^{23} = -123.05$ (*c* = 1.07, $CHCl_3$). $R_f = 0.51$ (hexane/EtOAc, 3:1). IR (KBr): $\tilde{\nu}$ = 3319, 2234, 1712, 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.40 (d, *J* = 9.1 Hz, 1 H, O*H*), 4.52 (d, *J* = 8.8 Hz, 1 H, C*H*OH), 4.25 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.15−4.05 (m, 1 H, NC*H*), 3.56−3.53 (m, 1 H, NC*H*H), 3.38 (m, 1 H, NCH*H*), 2.15−1.75 (m, 4 H, CH_2CH_2), 1.50 [s, 9 H, $C(CH_3)_3$], 1.27 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 [*C*OC$(CH_3)_3$], 153.1 (*C*$O_2CH_2CH_3$), 85.6 and 80.8 (*C*≡*C*), 76.8 [O*C*$(CH_3)_3$], 66.8 (*C*HOH), 62.7 (OCH_2CH_3), 61.8 (N*C*H), 48.1 (N*C*H_2), 28.9 (CH_2CH_2), 28.2 [C(*C*$H_3)_3$], 23.7 (CH_2CH_2), 13.8 ($CO_2CH_2CH_3$) ppm. MS (EI): *m*/*z* (%) = 196 (9) [M − BOC]$^+$, 70 (100), 57 (68) [$C_4H_9^+$]. $C_{15}H_{23}NO_5$ (297.35): calcd. C 60.59, H 7.80, N 4.71; found C 60.88, H 8.02, N 4.65.

7b: $[\alpha]_D^{26} = -82.2$ (*c* = 1.14, $CHCl_3$). $R_f = 0.43$ (hexane/EtOAc, 3:1). IR (film): $\tilde{\nu}$ = 3405, 2239, 1716, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.45 (br., 1 H, O*H*), 4.50 (br., 1 H, C*H*OH), 4.25 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.05 (br., 1 H, NC*H*), 3.34−3.46 (m, 2 H, NCH_2), 2.15−1.82 (m, 4 H, CH_2CH_2), 1.45 [s, 9 H, C $(CH_3)_3$], 1.30 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0 [*C*OC$(CH_3)_3$], 153.1 (*C*$O_2CH_2CH_3$), 86.2 and 80.7 (*C*≡*C*), 65.9 [O*C*$(CH_3)_3$], 61.9 (*C*HOH), 61.7 (OCH_2CH_3), 61.4 (N*C*H), 47.4 (N*C*H_2), 28.2 [C(*C*$H_3)_3$], 27.9 and 23.7 (CH_2CH_2), 13.8 ($CO_2CH_2CH_3$) ppm. MS (EI): *m*/*z* (%) = 196 (8) [M − BOC]$^+$, 70 (100), 57 (57) [$C_4H_9^+$]. $C_{15}H_{23}NO_5$ (297.35): calcd. C, 60.59, H 7.80, N 4.71; found C 60.45, H 7.56, N 4.49.

Compounds 8a and 8b: TBSCl (2.42 g, 16.08 mmol) was added to a solution of alcohol **7a** (3.188 g, 10.72 mmol) and imidazole (1.83 g, 26.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C and the resulting mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc, 10:1) to afford TBS ether **8a** (4.32 g, 98%).

8a: $[\alpha]_D^{23} = -99$ (*c* = 1.06, $CHCl_3$). $R_f = 0.47$ (hexane/EtOAc, 3:1). IR (film): $\tilde{\nu}$ = 2234, 1717, 1693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.15 (d, *J* = 2.4 Hz, 0.6 H, C*H*OTBS), 4.90 (d, *J* = 2.7 Hz, 0.4 H, C*H*OTBS), 4.29−4.19 (m, 2 H, OCH_2CH_3), 3.95−3.85 (m, 1 H, NC*H*), 3.50−3.28 (m, 2 H, NCH_2), 2.27−1.73 (m, 4 H, CH_2CH_2), 1.48, 1.46 (2×s, 9 H, C$(CH_3)_3$], 1.35−1.29 (m, 3 H, OCH_2CH_3), 0.90 [s, 9 H, SiC$(CH_3)_3$], 0.15, 0.13, 0.08, 0.06 [4 × s, 6 H, Si$(CH_3)_2$] ppm. MS (EI): *m*/*z* (%) = 114 (100), 70 (87), 57 (57) [$C_4H_9^+$]. $C_{21}H_{37}NO_5Si$ (411.61): calcd. C 61.28, H 9.06, N 3.40; found C 61.12, H 9.14, N 3.40.

8b: $[\alpha]_D^{26} = -98$ (*c* = 1.00, $CHCl_3$). $R_f = 0.41$ (hexane/EtOAc, 8:1). IR (film): $\tilde{\nu}$ = 2241, 1717, 1696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.08 (d, *J* = 5.0 Hz, 0.45 H, C*H*OTBS), 4.90 (d, *J* = 4.9 Hz, 0.55 H, C*H*OTBS), 4.25 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.90−3.79 (m, 1 H, NC*H*), 3.55−3.33 (m, 2 H, NCH_2), 2.27−1.72 (m, 4 H, CH_2CH_2), 1.46, 1.44 [2 × s, 9 H, C$(CH_3)_3$], 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 0.87 [s, 9 H, SiC$(CH_3)_3$], 0.15, 0.13, 0.11 (3 × s, 3 H, $SiCH_3$) ppm. MS (EI): *m*/*z* (%) = 298 (35), 114 (100), 70 (92). $C_{21}H_{37}NO_5Si$ (411.61): calcd. C 61.28, H 9.06, N 3.40; found C 61.20, H 9.01, N 3.47.

Compounds 9a and 9b: Quinoline (50 μL) and reducing Lindlar's catalyst (99 mg) were added to a solution of **8a** (990 mg, 2.41 mmol) in MeOH (20 mL). The black suspension was stirred under H_2 for a period of 3 d at room temperature. The catalyst was filtered off through Celite, washed with MeOH, and the filtrate was concentrated in vacuo. Flash chromatography (silica gel, hexane/EtOAc, 12:1) gave **9a** (950 mg, 96%).

9a: $[\alpha]_D^{26} = -57.10$ (*c* = 1.35, $CHCl_3$). $R_f = 0.44$ (hexane/EtOAc, 8:1). IR (film): $\tilde{\nu}$ = 2959, 2932, 1722, 1697, 1652, 1473, 1392 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.17−6.03 (m, 1 H, C*H*=CH), 5.77−5.70 (m, 1 H, CH=C*H*), 5.59−5.44 (m, 1 H, C*H*OTBS), 4.23−4.10 (m, 2 H, OCH_2CH_3), 3.86−3.79 (m, 1 H, NC*H*), 3.35−3.23 (m, 2 H, NCH_2), 2.04−1.76 (m, 4 H, CH_2CH_2), 1.48, 1.43 [2 × s, 9 H, OC$(CH_3)_3$], 1.32−1.24 (m, 3 H, OCH_2CH_3), 0.86 [s, 9 H, SiC$(CH_3)_3$], 0.06−0.03 [m, 6 H, Si$(CH_3)_2$] ppm. MS (EI): *m*/*z* (%) = 413 (3) [M$^+$], 314 (58), 114 (100), 70 (93), 57 (63). $C_{21}H_{39}NO_5Si$ (413.62): calcd. C 60.98, H 9.50, N 3.39; found C 61.20, H 9.51, N 3.84.

9b: $[\alpha]_D^{26} = -25.2$ (*c* = 1.14, $CHCl_3$). $R_f = 0.37$ (hexane/EtOAc, 3:1). IR (film): $\tilde{\nu}$ = 2977, 2932, 1726, 1698, 1652, 1391, 1366, 1255, 1188 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.17−6.06 (m, 1 H, C*H*=CH), 5.75 (dd, *J* = 0.7, 11.7 Hz, 1 H, CH=C*H*), 5.58−5.46 (m, 1 H, C*H*OTBS), 4.15 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.00 (br., 1 H, NC*H*), 3.50−3.21 (m, 2 H, NCH_2), 2.00−1.74 (m, 4 H, CH_2CH_2), 1.45 [s, 9 H, OC$(CH_3)_3$], 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 0.85 [s, 9 H, Si$(CH_3)_3$], 0.06 (s, 3 H, $SiCH_3$), 0.00 (s, 3 H, $SiCH_3$) ppm. MS (EI): *m*/*z* (%) = 413 (0.01) [M$^+$], 313 (100), 57 (6). $C_{21}H_{39}NO_5Si$ (413.62): calcd. C 60.98, H 9.50, N 3.39; found C 61.11, H 9.44, N 3.66.

(8*S*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,3,8,8a-tetrahydro-5(1*H*)-indolizinone (10a) and (8*R*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,3,8,8a-tetrahydro-5(1*H*)-indolizinone (10b): TFA (TFA = trifluoroacetic acid) (8 mL) was added at 0 °C to a solution of **9b** (798 mg, 1.931 mmol) in CH_2Cl_2 (50 mL). The mixture was warmed to 25 °C and stirred for 1.5 h. The solvent was removed under reduced pressure. A solution of Et_3N (7 mL) in CH_2Cl_2 (30 mL) was added, and the reaction mixture was stirred at room temperature for 2 d. After evaporation of solvent under reduced pressure, the residue was purified by flash chromatography (silica gel, EtOAc/MeOH, 10:1) to afford α,β-unsaturated lactam **10b** (318 mg, 61%).

10a: $[\alpha]_D^{20} = -25.2$ (c = 1.01, $CHCl_3$). R_f = 0.82 (EtOAc/MeOH, 10:1). IR (film): $\tilde{\nu}$ = 1670, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.35 (dd, J = 10.0, 1.4 Hz, 1 H, 7-H), 5.85 (dd, J = 10.0, 2.3 Hz, 1 H, 6-H), 4.35 (dd, J = 11.2, 1.4 Hz, 1 H, 8-H), 3.61−3.50 (m, 2 H, 3-H), 3.39−3.30 (m, 1 H, 8a-H), 2.24−1.34 (m, 4 H, 1-H and 2-H), 0.83 [s, 9 H, SiC(CH_3)$_3$], 0.03 [s, 3 H, Si(CH_3)], 0.02 [s, 3 H, Si (CH_3)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6 (C-5), 144.8 (C-7), 124.3 (C-6), 72.4 (C-8), 62.6 (C-8a), 44.3 (C-3), 32.2 (C-1), 25.5 [SiC(CH_3)$_3$], 22.5 (C-2), 17.8 [SiC(CH_3)$_3$], −4.6 (SiCH_3), −4.9(SiCH_3) ppm. MS (EI): m/z (%) = 267 (11) [M^+], 252 (4) [M − Me]$^+$, 210 (24) [M − C_4H_9]$^+$. $C_{14}H_{25}NO_2Si$ (267.44): calcd. C 62.87, H 9.42, N 5.24; found C 62.92, H 9.57, N 5.13.

10b: $[\alpha]_D^{20} = +278.4$ (c = 0.87, $CHCl_3$). R_f = 0.77 (EtOAc/MeOH, 10:1). IR (film): $\tilde{\nu}$ = 1656, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.65 (dd, J = 9.7, 5.6 Hz, 1 H, 7-H), 6.02 (d, J = 9.7 Hz, 1 H, 6-H), 4.08 (dd, J = 5.6, 3.6 Hz, 1 H, 8-H), 3.61−3.50 (m, 2 H, 3-H), 3.42−3.38 (m, 1 H, 8a-H), 2.10−1.75 (m, 4 H, 1-H and 2-H), 0.83 [s, 9 H, SiC(CH_3)$_3$], 0.03 [s, 3 H, Si(CH_3)], 0.02 [s, 3 H, Si(CH_3)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (C-5), 137.9 (C-7), 127.4 (C-6), 62.6 (C-8), 60.8 (C-8a), 44.6 (C-3), 26.8 (C-1), 25.7 [SiC(CH_3)$_3$], 22.9 (C-2), 18.1 [SiC(CH_3)$_3$], −4.1 (SiCH_3), −4.8 (SiCH_3) ppm. MS (EI): m/z (%) = 267 (0.3) [M^+], 252 (5) [M − Me]$^+$, 210 (100) [M − C_4H_9]$^+$. $C_{14}H_{25}NO_2Si$ (267.44): calcd. C 62.87, H 9.42, N 5.24; found C 62.80, H 9.42, N 5.11.

(6*R*,7*R*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxyindolizidin-5-one (11a) and (6*R*,7*R*,8*R*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxyindolizidin-5-one (11b): OsO_4 (27 μL of a 2.5% solution in *t*BuOH) was added to a solution of α,β-unsaturated lactam **10b** (20 mg, 0.075 mmol) and NMO (22 mg, 0.188 mmol) in acetone/H_2O (10:1, 1 mL) and the reaction mixture was stirred at 25 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/MeOH, 10:1) to afford diol **11b** (22 mg, 97%).

11a: $[\alpha]_D^{20} = -102.3$ (c = 0.84, $CHCl_3$). R_f = 0.67 (EtOAc/MeOH, 10:1). IR (film): $\tilde{\nu}$ = 3386, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (s, 1 H, 8-H), 4.08 (s, 1 H, OH), 4.00 (s, 1 H, OH), 3.74−3.71 (m, 1 H, 7-H), 3.65 (d, J = 7.8 Hz, 1 H, 6-H), 3.50−3.45 (m, 2 H, 3-H), 2.95 (br., 1 H, 8a-H), 2.25−1.45 (m, 4 H, 1-H and 2-H), 0.90 [s, 9 H, SiC(CH_3)$_3$], 0.11 [s, 3 H, Si(CH_3)], 0.09 [s, 3 H, Si(CH_3)] ppm. ^{13}C NMR (75Mz, $CDCl_3$): δ = 168.5 (C-5), 72.9 (C-6), 71.4 (C-7), 69.8 (C-8), 59.5 (C-8a), 44.7 (C-3), 31.3 (C-1), 25.6 [SiC(CH_3)$_3$], 22.3 (C-2), 18.0 [SiC(CH_3)$_3$], −4.4 (SiCH_3), −4.7 (SiCH_3) ppm. MS (EI): m/z (%) = 302 (0.1) [M + H]$^+$, 286 (4) [M − Me]$^+$, 244 (100). $C_{14}H_{27}NO_4Si$ (301.45): calcd. C, 55.78, H 9.03, N 4.65; found C 55.74, H 8.58, N 4.65.

11b: $[\alpha]_D^{20} = -104.4$ (c = 0.84, $CHCl_3$). R_f = 0.63 (EtOAc/MeOH, 3:1). IR (film): $\tilde{\nu}$ = 3379 (br), 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.25−4.12 (m, 3 H, 6-H, 7-H and 8-H), 3.88 (br., 1 H, 8a-H), 3.48−3.43 (m, J = 5.0 Hz, 2 H, 3-H), 2.00−1.75 (m, 4 H, 1-H and 2-H), 0.85 [s, 9 H, SiC(CH_3)$_3$], 0.08 [s, 3 H, Si(CH_3)], 0.06 [s, 3 H, Si(CH_3)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2 (C-5), 70.2 (C-6), 68.2 (C-7), 67.7 (C-8), 58.7 (C-8a), 44.3 (C-3), 26.6 (C-1), 25.6 [SiC(CH_3)$_3$], 22.5 (C-2), 17.9 [SiC(CH_3)$_3$], −4.8 (SiCH_3), −5.2 (SiCH_3) ppm. MS (EI): m/z (%) = 302 (5) [M + H]$^+$, 286 (2) [M − Me]$^+$, 70 (100). $C_{14}H_{27}NO_4Si$ (301.45): calcd. C 55.78, H 9.03, N 4.65; found C 55.84, H 8.62, N 4.61.

(6*R*,7*R*,8*S*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxyindolizidine (12a) and (6*R*,7*R*,8*R*,8a*S*)-8-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxyindolizidine (12b): To a solution of lactam **11a** (112 mg, 0.365 mmol) in dry THF (10 mL), a solution of BH_3·Me_2S (0.2 mL of a 10 M solution in Me_2S, 2 mmol) was added under Ar, and the reaction mixture was kept at room temperature for 4 h and refluxed for 1 h. The excess of reducing agent was quenched by careful addition of EtOH (2 mL) at −5 °C. The solvent was evaporated and the residue was dissolved in EtOH (8 mL), heated under reflux for 2 h, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/MeOH/NH_3, 10:3:0.2) to afford **12a** (102 mg, 95%).

12a: $[\alpha]_D^{20} = -27$ (c = 0.99, MeOH). R_f = 0.57 [EtOAc/MeOH/aqueous NH_3 (25−28%), 10:1.5:0.2]. IR (film): $\tilde{\nu}$ = 3420, 1255, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95−3.93 (m, 1 H, 7-H), 3.89−3.83 (m, 1 H,6-H), 3.52 (dd, J = 9.2, 2.6 Hz, 1 H, 8-H), 3.06 (dt, J = 2.4, 8.6 Hz, 1 H, 3-H), 2.99 (dd, J = 5.0, 10.1 Hz, 1 H, 5-αH), 2.64 (br., 2 H, 2OH), 2.31−2.21 (m, 3 H, 3-H, 5-βH and 8a-H), 2.03−1.39 (m, 4 H, 1-H and 2-H), 0.90 [s, 9 H, SiC(CH_3)$_3$], 0.09 [s, 3 H, Si(CH_3)], 0.08 [s, 3 H, Si(CH_3)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.1, 72.4, 69.5 (3C-OH), 62.5 (C-8a), 53.6 (C-3), 53.1 (C-5), 28.5 (C-1), 26.0 [SiC(CH_3)$_3$], 21.5 (C-2), 18.3 [SiC(CH_3)$_3$], −4.1 (SiCH_3), −4.2 (SiCH_3) ppm. MS (EI): m/z (%) = 287 (1) [M^+], 270 (10) [M − OH]$^+$, 70 (100). HRMS (EI+): calcd. for $C_{14}H_{29}NO_3Si$ 287.19167; found 287.18758.

12b: $[\alpha]_D^{20} = +13.1$ (c = 0.96, MeOH). R_f = 0.60 [EtOAc/MeOH/aqueous NH_3 (25−28%), 10:1.5:0.2]. IR (film): $\tilde{\nu}$ = 3267−3117, 2982, 2954, 1469, 392 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.19−4.13 (m, 1 H, 6-H), 3.91 (s, 2 H, 2OH), 3.13−3.02 (m, 2 H, 7-H, 8-H), 2.50−2.18 (m, 6 H), 1.88−1.60 (m, 3 H), 0.92 [s, 9 H, SiC(CH_3)$_3$], 0.011 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.0 and 70.3 and 66.5 (3C-OH), 61.5 (C-8a), 53.6 (C-3), 52.7 (C-5), 25.9 [SiC(CH_3)$_3$], 23.8 (C-1), 21.4 (C-2), 18.2 [SiC(CH_3)$_3$], −4.7 (SiCH_3), −4.8 (SiCH_3) ppm. MS (EI): m/z (%) = 287 (1) [M^+], 270 (4) [M − OH]$^+$, 230 (10) [M − C_4H_9]$^+$, 113 (19), 84 (31), 70 (100). HRMS (EI+): calcd. for $C_{14}H_{29}NO_3Si$ 287.19167; found 287.19336.

(6*R*, 7*R*, 8*S*, 8a*S*)-6,7,8-Trihydroxyindolizidine (3a) and (6*R*, 7*R*, 8*R*, 8a*S*)-6,7,8-Trihydroxyindolizidine (3b): $n$$Bu_4NF$ (0.21 mL of a 1 M solution in THF) was added to a solution of diols **12a** (50 mg, 0.174 mmol) in THF (5 mL) and the resulting mixture was stirred at 25 °C for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography [silica gel, EtOAc/MeOH/aqueous NH_3 (25−28%) 8:3:0.5] to afford triol **3a** (27 mg, 90%).

3a: White solid, m.p.165 ±0.5 °C (ref.[7] m.p. 166−168 °C). $[\alpha]_D^{20} = -35.8$ (c = 0.92, H_2O) {ref.[7] $[\alpha]_D^{25} = -36.3$ (c = 0.49, H_2O)}. R_f = 0.48 [CH_2Cl_2/MeOH/aqueous NH_3 (25−28%), 8:3:0.2]. ^1H NMR (300 MHz, D_2O): δ = 4.02 (dd, J = 2.8, 2.9 Hz, 1 H, 7-H), 3.85 (ddd, J = 11.1, 5.1, 2.9 Hz, 1 H, 6-H), 3.50 (dd, J = 10.2, 2.8 Hz, 1 H, 8-H), 3.10−3.04 (m, 1 H, 3-H), 3.00 (dd, J = 10.9, 5.1 Hz, 1 H, 5-αH), 2.57−2.38 (m, 3 H, 8a-H, 3-H, 5-βH), 2.10−2.00 (m, 1

H, 1-H), 1.83−1.72 (m, 2 H, 2-H), 1.48−1.35 (m, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 74.3 and 73.5 and 70.0(3C-OH), 63.8 (C-8a), 55 (C-3), 52.6 (C-5), 29.2 (C-1), 22.9 (C-2).
3b: $[\alpha]_D^{20}$ = +23.5 (*c* = 0.90, MeOH) {ref.[8] $[\alpha]_D^{25}$ = +23 (MeOH)}. R_f = 0.70 [CH_2Cl_2/MeOH/aqueous NH_3 (25−28%), 8:3:0.2]. ^{1}H NMR (400 MHz, CD_3OD): δ = 4.20 (ddd, *J* = 10.9, 5.0, 3.2 Hz, 1 H, 6-H), 4.11 (dd, *J* = 3.3, 3.4 Hz, 1 H, 7-H), 3.90 (dd, *J* = 3.4, 1.8 Hz, 1 H, 8-H), 3.22−3.17 (m, 1 H, 3-H), 3.10 (dd, *J* = 10.1, 5.0 Hz, 1 H, 5-α*H*), 2.73−2.69 (m, 1 H, 8a-H), 2.52 (dd, *J* = 10.1, 10.9 Hz, 1 H, 5-β*H*), 2.45−2.38 (m, 1 H, 3-H), 2.08−1.95 (m, 3 H, 1-H and 2-H), 1.87−1.84 (m, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 72.8 and 70.3 and 67.5 (3C-OH), 62.9 (C-8a), 54.9 (C-3), 54.2 (C-5), 24.5 (C-1), 22.7 (C-2) ppm.

Acknowledgments

We thank the National Natural Sciences Foundation for funding this work.

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Received July 22, 2002

