β-Amino ester route to tussilagine, isotussilagine and (−)-petasinecine

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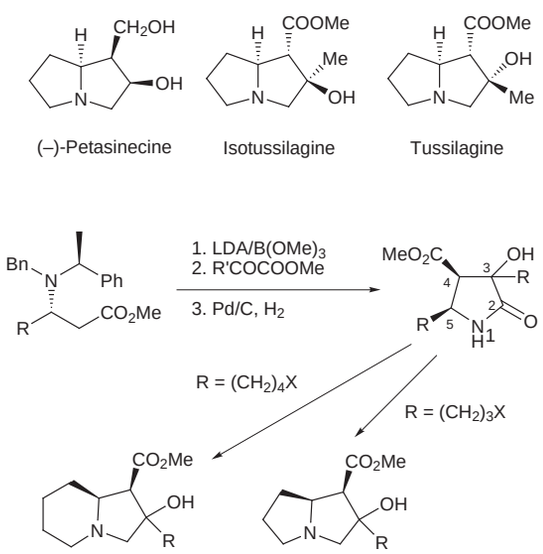
Condensation of enantiopure β-amino ester **2a** with methyl pyruvate provides two diastereoisomers **3** and **4**. Both **3** and **4** are subjected to hydrogenation followed by cyclization producing pyrrolidinones **5** and **8**. From **5** and **8** isotussilagine and tussilagine are obtained respectively, by using a Mitsunobu reaction as a key step. In a similar manner, (−)-petasinecine is synthesized from the condensation product of **2b** with ethyl glyoxalate.

Due to their diverse biological activities and their wide distribution in nature,[1] pyrrolizidine alkaloids have repeatedly served as the target compounds for a great number of annulation strategies.[2] As a continuing program on the synthesis from enantiopure β-amino acid derivatives,[3] we have developed a new methodology for synthesizing enantiopure 3,4,5-polysubstituted pyrrolidinones.[3a] This strategy was based on an aldol condensation–deprotection–cyclization approach (Scheme 1). It



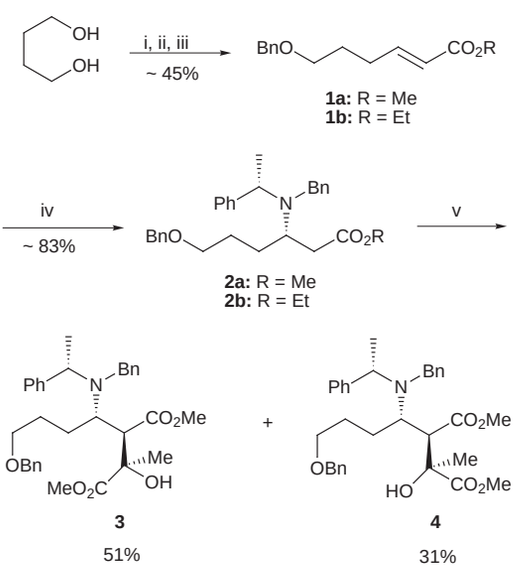
Scheme 1

is obvious that if the 5-substituent possessed a functional group (R = $(CH_2)_nX$), another ring could be introduced by simple alkylation, which would lead to the formation of pyrrolizidine or indolizidine skeletons. With this idea in mind, we investigated the synthesis of three pyrrolizidines; tussilagine, isotussilagine and (−)-petasinecine.[3b]

Tussilagine and its C-2 epimer isotussilagine are two atypical and non-toxic pyrrolizidines bearing a methyl group at the C-2 position. Both compounds have been found to exist in *Tussilago farara*, *Echinacea purpurea*, *Arnica* and *E. angustifolia* and their structures were identified by X-ray analysis.[4] Although a synthetic route for these compounds was reported,[5] neither compound has been prepared *via* an enantio- and diastereocontrolled route.

Results and discussion

Our synthesis started from butane-1,4-diol. As shown in Scheme



Scheme 2 *Reagents and conditions*: i, KOH, BnBr; ii, PCC, NaOAc, CH_2Cl_2; iii, $Ph_3P{=}CHCO_2Et$; iv, lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide; v, LDA, −78 °C, 1 h, then CH_3COCO_2Me.

2, after this diol was mono-protected with a benzyl group, the generated mono-alcohol was oxidized with PCC to afford the corresponding aldehyde, which was reacted with methyl or ethyl triphenylphosphoranylidene to provide α,β-unsaturated ester **1a** or **1b**. Addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide[6] to **1a** or **1b** gave **2a** or **2b** respectively, as a single isomer in about 83% yield. Next, treatment of **2a** with LDA followed by trapping of the generated anion with methyl pyruvate afforded two separable diastereoisomers **3** and **4**.

As we expected, the compounds **3** and **4** could be hydrogenated under Pd/C catalysis to provide pyrrolidinones **5** and **8**, respectively (Scheme 3). Their structures were assigned from their NOESY spectra (Fig. 1). Significant NOEs were observed between the 3-Me and 4-H, 3-Me and 5-H, and 4-H and 5-H in the spectrum of **5** and we therefore assigned the (3*R*,4*R*,5*S*)-stereochemistry of **5**. In the spectrum of **8** an NOE was observed only between 4-H and 5-H, which implied the (3*S*,4*R*,5*S*)-stereochemistry of **8**. With pyrrolidinone **5** in hand, the next step was to form another five-membered ring to establish the skeleton of isotussilagine. After some experimentation, we found that a Mitsunobu reaction was suitable for this step. Thus, treatment of **5** with PBu_3–ADDP [1,1′-(azodicarbonyl)-diperidine][7] produced the ring-closure product **6** in a 91% yield. The amide **6** could be reduced selectively to the amine **7** using

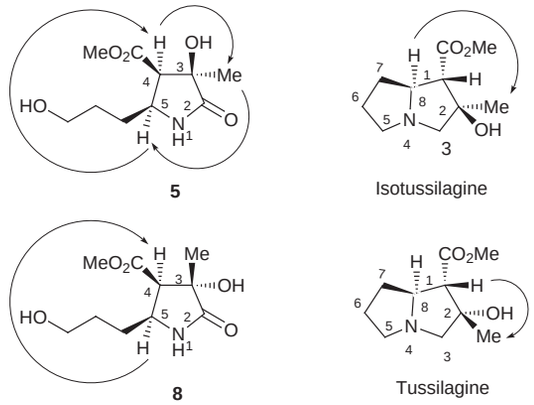
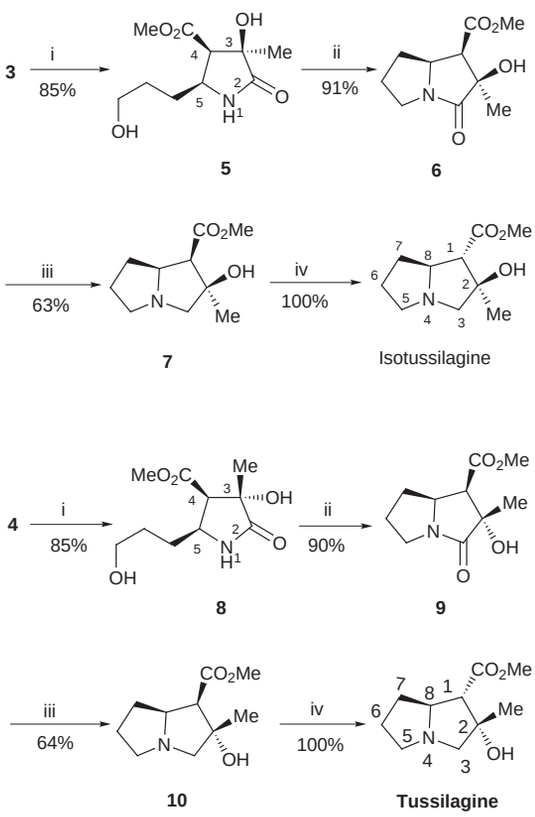


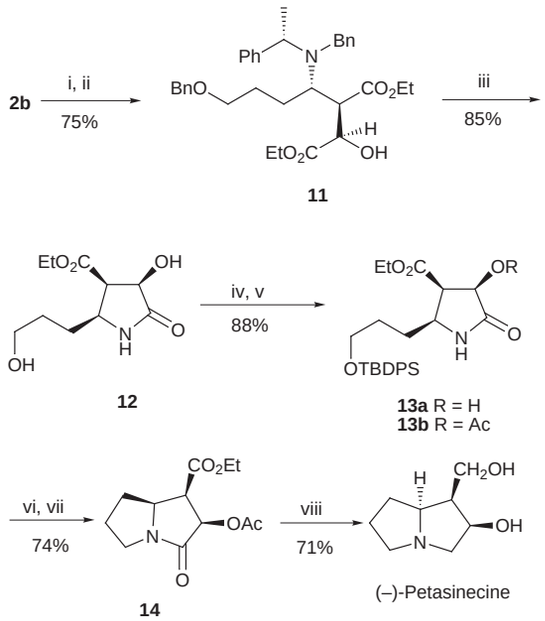
Fig. 1

the borane–tetrahydrofuran complex; **7** is the 1-epimer of isotussilagine. We considered that **7** was not as thermodynamically stable as isotussilagine and that it should be possible to convert it into the target molecule by treatment with base. Accordingly, after stirring a mixture of **7** and K_2CO_3 in methanol at room temperature for 1 day, we found that **7** was converted completely to isotussilagine. The product had spectra identical with those reported[4,5] and its structure was further confirmed by its NOESY spectrum, in which an NOE signal between the 2-Me and 8-H, but no NOE signal between the 2-Me and 1-H, was observed (Fig. 1). Therefore, we have developed a stereoselective route for synthesizing isotussilagine, with a 9.3% overall yield, from butane-1,4-diol. In a similar manner, we synthesized tussilagine from ester **4** in a 5.6% overall yield. Its spectral data were the same as those reported.[4]



Scheme 3 *Reagents and conditions*: i, Pd/C, H_2; ii, PBu_3, 1,1′-(azodicarbonyl)dipiperidine; iii, 1.0 M BH_3·THF; iv, K_2CO_3, MeOH.

The above methodology could be extended to the synthesis of (−)-petasinecine, which was isolated from *Petasites japonicus* Maxim[8] and has been synthesized from (*S*)-proline by Mulzer and Shanyoor.[9] As outlined in Scheme 4, condensation of **2b** with ethyl glyoxalate by a known procedure[3a] afforded **11** as the



Scheme 4 *Reagents and conditions*: i, LDA, −78 °C, 1 h, then $B(OMe)_3$; ii, $OHCCO_2Et$; iii, Pd/C, H_2, MeOH; iv, TBDPSCl, imidazole; v, Ac_2O, pyridine; vi, pyridine, HF; vii, PPh_3, diethyl azodicarboxylate; viii, $LiAlH_4$.

major isomer. Deprotection of **11** by Pd/C-catalyzed hydrogenation provided the cyclization product **12**. At this time it was found that the Mistunobu reaction conditions could not be used directly for further ring-closure because of the elimination of the 3-hydroxy group under these conditions. Thus, we tried to protect the 3-hydroxy group before closing the ring. Treatment of **12** with 1 equiv. of *tert*-butyldiphenylsilyl chloride protected the primary alcohol selectively, and then the secondary alcohol was masked with an acetyl group to provide **13b**. Deprotection of **13b** with HF–pyridine followed by a typical Mistunobu reaction gave **14** in 74% yield. Finally, reduction of **14** with LAH afforded the target molecule in 71% yield.

In conclusion, we have developed a general route to synthesize tussilagine, isotussilagine and (−)-petasinecine from enantiopure β-amino acid derivatives. Further application of this methodology to the synthesis of indolizidine alkaloids is in hand and will be reported in due course.

Experimental

General procedures

IR spectra were measured on a Shimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Bruker AM-300 spectrometer. *J* Values are given in Hz. MS spectra were determined on a Finnigan 4201 spectrometer or a VG Quattro MS/MS spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter. $[a]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Analytically pure DMF was used directly without further purification. CH_2Cl_2 was distilled from CaH_2, and THF was distilled from a deep blue ketyl prior to use. All other solvents were of reagent grade quality and used as received. Na_2SO_4 was used as the drying agent in all workup procedures. All reactions were run in flame-dried glassware under a nitrogen atmosphere unless stated otherwise.

Ethyl (*E*)-6-benzyloxyhex-2-enoate 1b

A mixture of butane-1,4-diol (59.1 g, 0.66 mol) and potassium hydroxide (17.8 g, 0.32 mol) was heated to 120 °C under reduced pressure to remove the water. Benzyl bromide (44.4 g, 0.26 mol) was then added dropwise to this solution at 100 °C. The resulting mixture was stirred for 2 h at this temperature, and then cooled to room temperature. Water (150 mL) was added to

dissolve the solid, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and distilled to give 38.9 g (83%) of the mono-protected alcohol.

To a suspension of pyridinium chlorochromate (72.8 g, 0.36 mol) and anhydrous sodium acetate (0.3 g, 4.5 mmol) in 500 mL of CH_2Cl_2 was added the above alcohol (38.9 g, 0.22 mol) in a dropwise manner at 0 °C. After the mixture was stirred at room temperature for 2 h, the suspension was filtered through a short silica column. The filtrate was concentrated and distilled to give 26.2 g (68%) of the corresponding aldehyde.

A mixture of (ethoxycarbonylmethylene)triphenylphosphorane (37.2, 106.7 mmol) and the above aldehyde (19.1 g, 107.3 mmol) in 250 mL of anhydrous CH_2Cl_2 was stirred overnight at room temperature. After the mixture was concentrated, it was filtered through a sintered glass funnel, and the solid (Ph_3PO) was washed with petroleum ether (300 mL). The combined filtrates were concentrated and the residual oil was chromatographed to afford compound **1b** (22.6 g, 85%), δ_H (60 MHz, CCl_4) 7.2–7.1 (m, 5H, ArH), 6.7 (m, 1H, CH), 5.79 (d, *J* 15.1, 1H, CH), 4.3 (s, 2H, PhCH_2O), 4.1 (m, 2H), 3.4 (m, 2H, OCH_2), 2.5–2.0 (m, 2H, CH_2), 2.0–1.5 (m, 2H, CH_2), 1.2 (t, *J* 7, 3H, CH_3); *m*/*z* (EI) 249 ($M + H^+$).

Methyl (*E*)-6-benzyloxyhex-2-enoate 1a

Following the same procedure for preparing **1b**, methyl ester **1a** was prepared in about 45% overall yield, δ_H (60 MHz, CCl_4) 7.2–7.1 (m, 5H, ArH), 6.7 (m, 1H, CH), 5.8 (d, *J* 15.2, 1H, CH), 4.3 (s, 2H, PhCH_2O), 3.8 (s, 3H, $COOCH_3$), 3.4 (m, 2H, OCH_2), 2.5–2.0 (m, 2H, CH_2), 2.0–1.5 (m, 2H, CH_2); *m*/*z* (EI) 235 ($M + H^+$).

Ethyl (3*S*)-3-{*N*-benzyl-*N*-[(*S*)-1-phenylethyl]amino}-6-benzyloxyhexanoate 2b

(*S*)-(−)-*N*-Benzyl-2-methylbenzylamine (23.2 g, 0.11 mol) was dissolved in THF (300 mL). After the resultant solution was cooled to −78 °C, *n*-butyllithium (2.5 M in hexane, 45 mL, 0.11 mol) was added dropwise and the mixture was then stirred for 45 min. To this stirring solution α,β-unsaturated ester **1b** (25.0 g, 0.1 mol) in THF (80 mL) was added at −78 °C. After the mixture was stirred for an additional 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to dryness. The crude product was purified by column chromatography to yield **2b** (38.4 g, 83%) as a colorless liquid, $[\alpha]_D^{20} = -4.9$ (*c* 1.6, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3060 (Ar-H), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 7.44–7.22 (m, 15H, ArH), 4.50 (s, 2H, PhCH_2O), 4.01 (q, *J* 7.2, 2H, CO_2CH_2), 3.85 (q, 1H, PhC*H*NMe), 3.82 (d, *J* 14.8, 1H, PhCH_2), 3.50 (d, *J* 14.8, 1H, PhCH_2N), 3.45 (t, *J* 6.6, 2H, OCH_2), 3.38 (m, 1H, NCH), 2.04–1.93 (m, 2H, CH_2CO), 1.72–1.53 (m, 4H, CH_2), 1.35 (d, *J* 7.1, 3H, NCHCH_3), 1.17 (t, *J* 7.1, 3H, CH_2CH_3); *m*/*z* (EI) 459 (M^+) (Found: *m*/*z* 459.2767 (M^+). $C_{30}H_{37}NO_3$ requires 459.2772).

Methyl (3*S*)-3-{*N*-benzyl-*N*-[(*S*)-1-phenylethyl]amino}-6-benzyloxyhexanoate 2a

Following the same procedure for preparing **2b**, ester **2a** was prepared from **1a** in 81% yield, $[\alpha]_D^{20} = -8.7$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3060 (Ar-H), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 7.40–7.21 (m, 15H, ArH), 4.53 (s, 2H, PhCH_2O), 3.87 (q, 1H, PhC*H*NMe), 3.84 (d, *J* 14.8, 1H, PhCH_2), 3.70 (s, 3H, $COOCH_3$), 3.53 (d, *J* 14.8, 1H, PhCH_2N), 3.49 (t, *J* 6.6, 2H, OCH_2), 3.40 (m, 1H, NCH), 2.06–1.96 (m, 2H, CH_2CO), 1.74–1.58 (m, 4H, CH_2), 1.41 (d, *J* 7.1, 3H, NCHCH_3); *m*/*z* (EI) 445 (M^+) (Found: *m*/*z* 445.2607 (M^+). $C_{29}H_{35}NO_3$ requires 445.2616).

(3*R*,4*R*,5*S*)-3-Hydroxy-3-methyl-4-methoxycarbonyl-5-(3′-hydroxypropyl)pyrrolidin-2-one 5

A solution of compound **2a** (8.8 g, 19.8 mmol) in 80 mL of anhydrous THF was added in a dropwise manner to a freshly prepared solution of LDA (30 mmol) at −78 °C. The mixture was stirred at this temperature for 1.5 h before methyl pyruvate (2.6 mL, 30 mmol) in 30 mL THF was added. After the mixture was stirred for additional 1 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation to give a colorless oil. Chromatography of the residual oil eluting with 1:8 ethyl acetate–petroleum ether afforded 4.24 g (51%) of **3** and 2.58 g (31%) of **4** as crude products.

To a solution of **3** (3.5 g, 6.2 mmol) in 60 mL of methanol was added 0.3 g of 10% Pd/C. The resultant suspension solution was stirred under hydrogen (8 MPa) at 50 °C for 24 h. After Pd/C was filtered off, the filtrate was concentrated. The residual oil was purified by column chromatography (silica gel; 1:10 methanol–ethyl acetate) to afford 1.21 g (85%) of **5** as a white solid, $[\alpha]_D^{17} = -74.6$ (*c* 0.6, MeOH); ν_{max} (KBr)/cm^{-1} 3278 (O–H), 3180 (N–H), 1742 (C=O), 1701 (C=O); δ_H (300 MHz, DMSO-d_6) 7.99 (s, 1H, NH), 3.80 (m, 1H, NCH), 3.60 (s, 3H, OCH_3), 3.37 (m, 2H, OCH_2), 3.01 (d, *J* 6.1, 1H, CHCOO), 1.55–1.30 (m, 4H, CH_2CH_2), 1.16 (s, 3H, CH_3); *m*/*z* (EI) 232 ($M^+ + H^+$) (Found: *m*/*z* 213.100 ($M^+ - H_2O$). $C_{10}H_{15}NO_4$ requires 213.100).

(3*S*,4*R*,5*S*)-3-Hydroxy-3-methyl-4-methoxycarbonyl-5-(3′-hydroxypropyl)pyrrolidin-2-one 8

Following the same procedure for preparing **5** from **3**, the pyrrolidinone **8** was obtained from the crude ester **4** in 85% yield, $[\alpha]_D^{17} = -48$ (*c* 0.85, MeOH); ν_{max} (KBr)/cm^{-1} 3241 (O–H), 3178 (N–H), 1740 (C=O), 1700 (C=O); δ_H (300 MHz, DMSO-d_6) 7.85 (s, 1H, NH), 3.56 (s, 3H, OCH_3), 3.54 (m, 2H, OCH_2), 3.37 (m, 1H, NCH), 3.03 (d, *J* 5.9, 1H, CHCOO), 1.55–1.44 (m, 4H, CH_2CH_2), 1.27 (s, 3H, CH_3); *m*/*z* (EI) 232 ($M^+ + H^+$) (Found: *m*/*z* 213.103 ($M^+ - H_2O$). $C_{10}H_{15}NO_4$ requires 213.100).

(1*R*,2*R*,8*S*)-1-Methoxycarbonyl-2-hydroxy-2-methylhexahydro-3*H*-pyrrolizin-3-one 6

To a solution of **5** (231 mg, 1 mmol) in 10 mL of THF was added in a sequence of tributylphosphine (0.3 mL, 1.2 mmol) and 1,1′-(azodicarbonyl)dipiperidine (302 mg, 1.2 mmol) at 0 °C. After the mixture was stirred for 24 h at room temperature, it was concentrated and the residue was chromatographed (silica gel; 3:1 ethyl acetate–petroleum ether as eluent) to afford 193 mg (91%) of **6**, $[\alpha]_D^{17} = -91$ (*c* 0.8, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3301 (O–H), 1743 (C=O), 1693 (C=O); δ_H (300 MHz, $CDCl_3$) 4.28 (m, 1H, C8-H), 3.71 (s, 3H, OCH_3), 3.55 (m, 1H, C5-H), 3.30 (d, *J* 6.3, 1H, C1-H), 3.18 (m, 1H, C5-H), 2.15–1.90 (m, 4H, CH_2CH_2), 1.44 (s, 3H, CH_3); *m*/*z* (EI) 214 ($M^+ + H^+$) (Found: *m*/*z* 213.099 (M^+). $C_{10}H_{15}NO_4$ requires 213.100).

Following the same procedure, compound **9** was prepared from **8** in 90% yield, $[\alpha]_D^{17} = -103$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3277 (O–H), 1741 (C=O), 1695 (C=O); δ_H (300 MHz, $CDCl_3$) 3.96 (dt, *J* 6.3, 10.7, 1H, C8-H), 3.70 (s, 3H, OCH_3), 3.58 (dt, *J* 7.4, 13.2, 1H, C5-H), 3.33 (br s, 1H, OH), 3.29 (d, *J* 6.1, 1H, C1-H), 3.11 (dt, *J* 4.4, 12.0, 1H, C5-H), 2.12–1.94 (m, 4H, CH_2CH_2), 1.51 (s, 3H, CH_3); *m*/*z* (EI) 214 ($M^+ + H^+$) (Found: *m*/*z* 213.101 (M^+). $C_{10}H_{15}NO_4$ requires 213.100).

(1*R*,2*R*,8*S*)-1-Methoxycarbonyl-2-hydroxy-2-methylhexahydro-1*H*-pyrrolizine 7

To a solution of compound **6** (200 mg, 0.94 mmol) in THF (10 mL) was added dropwise the borane–tetrahydrofuran complex

(0.8 M, 2 mL) at 0 °C. After the addition, the resultant reaction mixture was stirred at the same temperature for 1 h. The stirring was continued at room temperature overnight and then the mixture was heated to reflux for 1 h. After removal of the solvent, the residue was diluted with 10 mL of ether. To this solution TMEDA (72 μL) was added and the resultant mixture was stirred for 15 min. After the precipitate was filtered off and washed with ether (2 × 5 mL), the filtrate was concentrated and the residual oil was chromatographed (silica gel; 1:3 ethyl acetate–petroleum ether as eluent) to afford 117 mg (63%) of **7**, $[a]_D^{25} = -23$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3251 (O–H), 1738 (C=O); δ_H (300 MHz, $CDCl_3$) 4.26 (s, 1H, OH), 4.20 (m, 1H, C8-H), 3.72 (s, 3H, OCH_3), 3.46 (d, *J* 11.9, 1H, C3-H), 3.35 (d, *J* 11.9, 1H, C3-H), 3.33 (d, *J* 7.5, 1H, C1-H), 3.16 (m, 1H, C5-H), 2.35–1.96 (m, 3H, CH_2 and NCH), 1.73–1.65 (m, 2H, CH_2), 1.31 (s, 3H, CH_3); *m*/*z* (ESI) 200 ($M^+ + H^+$). *m*/*z* (EI) 200 ($M^+ + H^+$) (Found: *m*/*z* 199.1203 (M^+). $C_{10}H_{17}NO_3$ requires 199.1211).

Following the same procedure, **10** was prepared from **9** in 63% yield, $[a]_D^{25} = -4.5$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3289 (O–H), 1741 (C=O); δ_H (300 MHz, $CDCl_3$) 4.00 (m, 1H, C8-H), 3.79 (br s, 1H, OH), 3.75 (s, 3H, OCH_3), 3.39 (m, 2H, C3-H), 3.25 (m, 2H, C5-H), 3.20 (d, *J* 6.5, 1H, C1-H), 2.20–1.80 (m, 4H, CH_2CH_2), 1.38 (s, 3H, CH_3); *m*/*z* (ESI) 200 ($M^+ + H^+$) (Found: *m*/*z* 199.1208 (M^+). $C_{10}H_{17}NO_3$ requires 199.1211).

Isotussilagine [(1*S*,2*R*,8*S*)-1-Methoxycarbonyl-2-hydroxy-2-methylhexahydro-1*H*-pyrrolizine]

Compound **7** (20 mg, 0.1 mmol) was dissolved in methanol (5 mL). Whilst stirring anhydrous potassium carbonate (10 mg) was added to this solution. After the mixture was stirred overnight at room temperature, it was diluted with 5 mL of water and 10 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography eluting with 1:2 ethyl acetate–petroleum ether to afford 20 mg (100%) of isotussilagine, $[a]_D^{25} = 129$ (*c* 0.17, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3277 (O–H), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 4.44 (dt, *J* 10.1, 1.8, 1H, C8-H), 4.00 (s, 1H, OH), 3.77 (s, 3H, OCH_3), 3.58 (d, *J* 12.2, 1H, C3-H), 3.15 (dt, *J* 11.6, 5.8, 1H, C5-H), 3.03 (m, 1H, C5-H), 2.95 (d, *J* 12.2, 1H, C3-H), 2.63 (d, *J* 10.5, 1H, C1-H), 2.31–1.58 (m, 4H, CH_2CH_2), 1.48 (s, 3H, CH_3); *m*/*z* (EI) 200 ($M^+ + H^+$) (Found: *m*/*z* 199.1198 (M^+). $C_{10}H_{17}NO_3$ requires 199.1211).

Tussilagine [(1*S*,2*S*,8*S*)-1-Methoxycarbonyl-2-hydroxy-2-methylhexahydro-1*H*-pyrrolizine]

Following the same procedure for preparing isotussilagine from **7**, tussilagine was obtained from **10** quantitatively, $[a]_D^{25} = -2.7$ (*c* 0.15, EtOH) (lit.[4] $[a]_D^{25} = -2.7$ (*c* 0.15, EtOH)); ν_{max} (KBr)/cm^{-1} 3283 (O–H), 1744 (C=O); δ_H (300 MHz, DMSO-d_6) 3.84 (dt, *J* 10.3, 4.8, 1H, C8-H), 3.65 (s, 3H, OCH_3), 3.18 (s, 2H, C3-H), 3.08 (dt, *J* 10.8, 6.8, 1H, C5-H), 2.92 (d, *J* 8.6, 1H, C1-H), 2.68 (m, 1H, C5-H), 2.10 (m, 1H, CH), 1.98 (m, 2H, CH_2), 1.80 (m, 1H, CH), 1.20 (s, 3H, CH_3). *m*/*z* (EI) 200 ($M^+ + H^+$) (Found: *m*/*z* 199.1201 (M^+). $C_{10}H_{17}NO_3$ requires 199.1211).

Ethyl (2*R*,3*R*,4*S*)-2-hydroxy-3-ethoxycarbonyl-4-{*N*-benzyl-*N*-[(*S*)-1-phenylethyl]amino}-7-benzyloxyheptanoate 11

A freshly prepared solution of LDA (31 mmol, in 50 mL of THF) was added dropwise to a stirred solution of compound **2b** (4.8 g, 10.5 mmol) in 50 mL anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 1.5 h before trimethyl borate (3.5 mL, 31 mmol) was added dropwise. After the mixture was stirred for another 0.5 h at the same temperature, a solution of ethyl glyoxalate (3.2 g, 31 mmol) in 30 mL of THF was added. The reaction mixture was stirred for an additional 1 h at −78 °C before it was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a colorless oil. Purification of this oil by column chromatography (1:8 ethyl acetate–petroleum ether as eluent) gave 4.4 g (75%) of **11**, $[a]_D^{22} = -21$ (*c* 1.4, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3272 (O–H), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 7.43–7.17 (m, 15H, ArH), 4.48 (s, 2H, PhCH_2O), 4.14–3.98 (m, 4H), 3.93–3.85 (m, 2H), 3.68 (s, 2H, PhCH_2N), 3.44 (m, 2H), 3.22 (m, 1H), 2.73 (m, 1H), 1.86–1.61 (m, 4H, CH_2), 1.26 (d, *J* 6.9, 3H, NCHCH_3), 1.20–1.08 (m, 6H, CH_3); *m*/*z* (EI) 562 ($M^+ + H^+$) (Found: *m*/*z* 561.306 (M^+). $C_{34}H_{43}NO_6$ requires 561.309).

(3*R*,4*R*,5*S*)-3-Hydroxy-4-methoxycarbonyl-5-(3′-hydroxypropyl)pyrrolidin-2-one 12

A mixture of compound **11** (3.0 g, 5.3 mmol) and 0.3 g of 10% Pd/C in 60 mL of methanol was stirred under hydrogen (8 MPa) at 50 °C for 24 h. After Pd/C was filtered off, the filtrate was concentrated and the residue was purified by column chromatography (silica gel; 1:10 methanol–ethyl acetate as eluent) to afford 1.05 g (85%) of **12** as a white solid, $[a]_D^{20} = -18$ (*c* 1.0, MeOH); ν_{max} (KBr)/cm^{-1} 3255 (O–H), 3177 (N–H), 1741 (C=O), 1701 (C=O); δ_H (300 MHz, CD_3OD) 7.86 (s, 1H, NH), 4.35 (d, *J* 4.4, 1H, HOC*H*), 4.09 (q, *J* 7.1, 2H, OCH_2Me), 3.59 (m, 1H, NCH), 3.40–3.31 (m, 3H, OCH_2 and CHCOO), 1.58–1.41 (m, 4H, CH_2CH_2), 1.20 (t, *J* 7.1, 3H, CH_3); *m*/*z* (EI) 232 ($M^+ + H^+$) (Found: *m*/*z* 231.112 (M^+). $C_{10}H_{17}NO_5$ requires 231.111).

(3*R*,4*R*,5*S*)-3-Hydroxy-4-ethoxycarbonyl-5-(3′-*tert*-butyldiphenylsilyloxypropyl)pyrrolidin-2-one 13a

To a solution of compound **12** (0.50 g, 2.2 mmol) in 5 mL anhydrous DMF was added *tert*-butyldiphenylsilyl chloride (1.19 g, 4.3 mmol) and imidazole (0.59 g, 8.7 mmol) under N_2 atmosphere. The mixture was stirred overnight at room temperature before it was poured into water to quench the reaction. The mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed successively with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residual oil was chromatographed (silica gel; 2:1 ethyl acetate–petroleum ether as eluent) to afford 0.93 g (92%) of **13a** as a colorless oil, $[a]_D^{25} = -11$ (*c* 1.1, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3287 (O–H), 3189 (N–H), 1744 (C=O), 1698 (C=O); δ_H (300 MHz, $CDCl_3$) 7.62 (m, 4H, ArH), 7.39 (m, 6H, ArH), 6.67 (s, 1H, NH), 4.44 (m, 1H, HOC*H*), 4.15 (q, *J* 7.1, 2H, OCH_2), 3.65–3.30 (m, 4H, OCH_2, NCH and CHCOO), 1.64–1.60 (m, 4H, CH_2CH_2), 1.22 (t, *J* 7.1, 3H, CH_3), 1.00 (s, 9H, $C(CH_3)_3$); *m*/*z* (EI) 470 ($M^+ + H^+$) (Found; *m*/*z* 412.159 ($M^+ - t$-Bu). $C_{22}H_{26}NO_5Si$ requires 412.158).

(3*R*,4*R*,5*S*)-3-Acetoxy-4-ethoxycarbonyl-5-(3′-*tert*-butyldiphenylsilyloxypropyl)pyrrolidin-2-one 13b

Acetic anhydride (2 mL) was added dropwise to a solution of the above silyl ether (0.25 g, 0.53 mmol) in 20 mL of pyridine at 0 °C. The resulting mixture was stirred overnight at room temperature. After pyridine was removed *in vacuo*, the residue was diluted with ethyl acetate. The solution was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography eluting with 2:3 ethyl acetate–petroleum ether to give 261 mg (96%) of **13b**, $[a]_D^{25} = -32.6$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3189 (N–H), 1734 (C=O), 1695 (C=O); δ_H (300 MHz, $CDCl_3$) 7.63 (m, 4H, ArH), 7.40 (m, 6H, ArH), 6.20 (s, 1H, NH), 5.52 (d, *J* 7.5, 1H, AcOC*H*), 4.17 (m, 2H, OCH_2), 3.72 (m, 1H, NCH), 3.67 (t, *J* 5.8, 2H, OCH_2), 3.55 (m, 1H, CHCOO), 2.13 (s, 3H, $COCH_3$), 1.76–1.59 (m, 4H, CH_2CH_2),

1.24 (t, J 7.1, 3H, CH_3), 1.04 (s, 9H, $C(CH_3)_3$); m/z (EI) 512 ($M^+ + H^+$), (Found: m/z 454.170 ($M^+ - t$-Bu). $C_{24}H_{28}NO_6Si$ requires 454.169).

(−)-Petasinecine [(1*S*,2*R*,8*S*)-1-(Hydroxymethyl)-2-hydroxy-hexahydro-1*H*-pyrrolizine]

A solution of Py–HF (4 mL, pH = 4) was added dropwise into a solution of **13b** (177 mg, 0.35 mmol) in 10 mL acetonitrile at 0 °C. The mixture was stirred at room temperature for 1 h before triethylamine was added, to adjust the pH to about 8. The solvent was removed *in vacuo* and the residue was purified by column chromatography eluting with ethyl acetate to give 88 mg (93%) of the corresponding alcohol.

Triphenylphosphine (69 mg, 0.26 mmol) and diethyl azodicarboxylate (46 mg, 0.26 mmol) were added to the solution of the above alcohol (60 mg, 0.22 mmol) in THF (5 mL) at 0 °C respectively. The mixture was stirred for 24 h at room temperature and then concentrated. The residue was chromatographed (silica gel; 2 : 1 ethyl acetate–petroleum ether as eluent) to afford compound 45 mg (80%) of **14**.

To a suspension of $LiAlH_4$ (19 mg, 0.5 mmol) in 2 mL of anhydrous THF was added a solution of the lactam **14** (44 mg, 0.17 mmol) in 1 mL of THF. The reaction mixture was refluxed for 17 h before THF was removed by distillation. Ether (3 mL) and water (40 μL) were added and the mixture was then stirred for 8 h. After the resultant precipitate was filtered, the filtrate was concentrated and chromatographed (silica gel; 1 : 1 : 20 $CHCl_3$–CH_3OH–$NH_3 \cdot H_2O$ as eluent) to give 18 mg (71%) of (−)-petasinecine as a white solid, $[a]_D^{25} = -27$ (c 0.3, EtOH); ν_{max} (KBr)/cm^{-1} 3255 (O–H), 2961 (C–H); δ_H (300 MHz, $CDCl_3$) 4.53 (m, 1H, C*H*OH), 3.96 (dd, J 10.8, 8.8, 1H, CH_2OH), 3.86 (dd, J 10.8, 5.2, 1H, CH_2OH), 3.48 (m, 1H, C8-H), 3.23 (dd, J 11.6, 7.15, 1H, C3-H), 3.11 (m, 1H, C3-H), 2.75 (m, 2H, C5-H), 2.40 (m, 1H, C1-H), 2.30 (br s, 2H, OH), 1.99–1.66 (m, 4H, CH_2CH_2); m/z (EI) 158 ($M^+ + H^+$).

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Paper 9/01330J