Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 6445–6454

TETRAHEDRON

Facile conversion of 2-azetidinones to 2-piperidones: application to a formal synthesis of *Prosopis* and *Cassia* alkaloids

Hyeon Kyu Lee,* Jong Soo Chun and Chwang Siek Pak*

Bio-Organic Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung, Taejon 305-606, South Korea

Received 17 May 2003; revised 4 July 2003; accepted 7 July 2003

Abstract—Nonracemic 5,6-disubstituted 2-piperidones were prepared from readily accessible 3,4-disubstituted-2-azetidinones having pre-installed substituents by reductive ring opening of 2-azetidinones followed by stereoselective installation of *Z*-α,β-unsaturated ester and lactam formation. For the synthetic application to the naturally occurring piperidine alkaloids, such as *Prosopis* and *Cassia* alkaloids, 5-hydroxy-2-piperidones (+)-**13** and (−)-**24** were prepared from 2-azetidinones (−)-**6b** and (+)-**18** via two-carbon ring homologation.

1. Introduction

A large number of functionalized piperidine alkaloids have been found in nature and many of them have shown valuable biological and pharmacological properties.[1] For example, naturally occurring 3-piperidinols with long aliphatic appendage such as *Prosopis* (**A**, **B**) and *Cassia* (**C**, **D**) alkaloids (Fig. 1) received increasing attention as medicinal agents due to a variety of phamacological properties.[2] Consequently, the development of efficient synthetic methods for these alkaloids has been an active area of research.[3–7]

A 2-azetidinone (β-lactam) skeleton is well established as the key pharmacophore of β-lactam antibiotics, the most widely employed class of antibacterial agents.[8] As a result, diverse practical methods for preparing 2-azetidinones have been developed.[9] There are also many applications of 2-azetidinones as useful chiral building blocks for other classes of molecules.[10] For example, 2-azetidinones were converted to nonproteogenic amino acids and peptides,[10e] and their ring expansion by the action of internal or external nucleophiles to 2-pyrrolidinones[10d] were reported. A recent application include a facile synthesis of sphingosine and phytosphingosine.[10c]

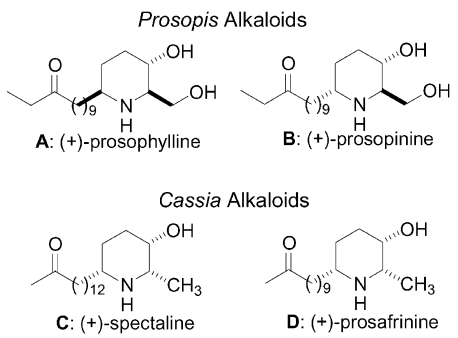
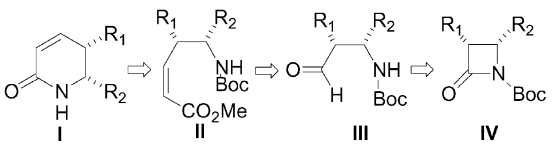


Figure 1.

We recently reported a new method for preparing 2-piperidones that may serve as versatile intermediates for asymmetric syntheses of various piperidine and indolizidine alkaloids starting with readily accessible 2-azetidinones.[11]

We herein report a full details of the asymmetric synthesis of nonracemic 2-piperidones and subsequent application to an efficient formal synthesis of *Prosopis* and *Cassia* alkaloids starting with readily available 2-azetidinones. Our construction of 2-piperidone involves reductive ring opening of a 2-azetidinone followed by stereoselective installation of *Z*-α,β-unsaturated ester and subsequent lactam formation (Scheme 1).



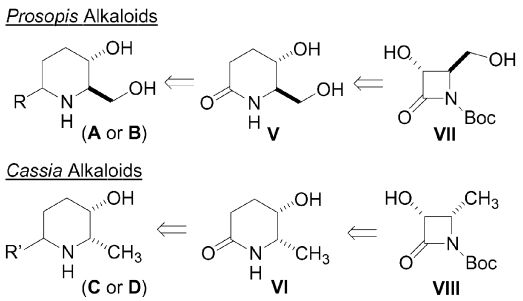
Scheme 1.

2. Results and discussion

Previous syntheses of the *Prosopis* alkaloids[4a,c,6l,m] such as, (+)-prosophylline (**A**) or (+)-prosopinine (**B**), utilized (5*S*,6*R*)-5,6-disubstituted-2-piperidinone **V** as a key

Keywords: 2-azetidinone; 2-piperidone; ring homologation; piperidine alkaloid.
* Corresponding authors. Tel.: +82-428-607-016; fax: +82-428-610-307; e-mail: leehk@krict.re.kr

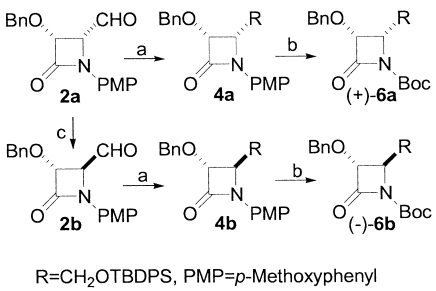
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)01063-9



Scheme 2.

intermediate, whereas (5*S*,6*S*)-5,6-disubstituted-2-piperidinone **VI** was used as a key building block for the synthesis of *Cassia* alkaloids[4a,c] such as, (+)-spectaline (**C**) and (−)-prosafrinine (**D**). We envisaged that these key intermediates 2-piperidinone **V** and **VI** could be derived from the corresponding 3,4-disubstituted 2-azetidinones **VII** and **VIII** via two-carbon ring homologation as shown in Scheme 2. The substitutents and stereochemistry of C-3 and C-4 in 2-azetidinones **VII** and **VIII** correspond to C-5 and C-6 substitutents of 2-piperidones.

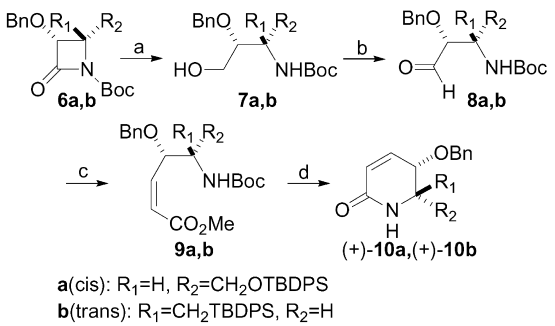
We chose enantiomerically pure 4-formyl-2-azetidinone **2a**[12,13] as starting material for the preparation of 2-piperidones **V** and **VI**. 4-Formyl-2-azetidinone **2a** was first converted to **4a** by reduction of the 4-formyl group and protection of the resulting alcohol with *t*-butyldiphenylsilyl chloride (Scheme 3). Removal of the PMP group in **4a** with CAN and subsequent treatment with $(Boc)_2O$ furnished 3,4-*cis*-*N*-Boc-2-azetidinone **6a**.



Scheme 3. (a) $NaBH_4$, THF-H_2O, 0°C, 2 h; TBDPSCl, Imidazole, DMF, room temperature, 24 h; (**4a**: 90%, **4b**: 81%); (b) CAN, CH_3CN–H_2O, 0°C, 30 min; $(Boc)_2O$, cat. DMAP, CH_3CN, 4 h (**6a**: 82%, **6b**: 66%); (c) 40% aq.$(CH_3)_2NH$, benzene, room temperature, 48 h, (96%).

3,4-*trans*-*N*-Boc-2-Azetidinone (−)-**6b** was prepared from the corresponding 3,4-*trans*-*N*-PMP-4-formyl-2-azetidinone **2b** that is prepared by the known, dimethylamine-induced epimerization[14] of 3,4-*cis*-*N*-PMP-4-formyl-2-azetidinone **2a**.

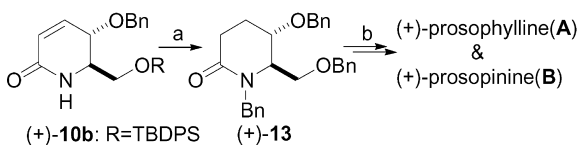
The *cis*-*N*-Boc-2-azetidinone (+)-**6a** was next converted to 2-piperidone **10a** via two-carbon homologation as shown in Scheme 4. Thus, treatment of **6a** with $LiAlH_4$ in THF at 0°C afforded 3-*N*-Boc-amino alcohol **7a** in 87% yield. Oxidation of **7a** by IBX (2-iodoxybenzoic acid)[15] in DMSO at room temperature cleanly produced pure 3-*N*-Boc-amino aldehyde **8a**, which was used for the next step without further purification. The aldehyde **8a** was dissolved in dry



Scheme 4. (a) $LiAlH_4$, THF, 0°C, 10 min, (**7a**: 87%, **7b**: 95%); (b) IBX, DMSO, room temperature, 3 h, (**8a**: 93%, **8b**: 95%); (c) $Ph_3P{=}CHCO_2Me$, MeOH, room temperature, 12 h, (**9a**: 87%, *E*:*Z*=1:7, **9b**: 81%, *E*:*Z*=1:4); (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, then cat. DMAP, toluene, reflux, 1 h, (**10a**: 95%, **10b**: 89%).

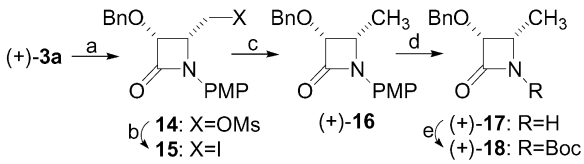
MeOH[16,17] and treated with methyl (triphenylphosphoranylidene)acetate at room temperature to give a 7:1 mixture of the *Z*-α,β-unsaturated ester **9a** and its *E*-isomer in 81% overall yield from **7a**. These two isomers were separated by flash chromatography. Finally, removal of *N*-Boc protection group of **9a** was achieved under mild conditions (TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h)[18] and subsequent cyclization in the presence of catalytic DMAP in toluene gave 5,6-*cis*-disubstituted-2-piperidone **10a** in 95% yield from **9a**. Similarly, 5,6-*trans*-disubstituted-2-piperidone **10b** was also prepared from the 3,4-*trans*-*N*-Boc-2-azetidinone **6b**.[22]

With 2-piperidone (+)-**10b** in hand, (+)-**13** was readily prepared from reduction of the double bond and simple manipulation of protecting groups: hydrogenation of the double bond, followed by subsequent desilylation of **10b** with $(n\text{-Bu})_4NF$ and benzylation provided tribenzylated 2-piperidinone (+)-**13**, a key common intermediate for the chiral synthesis of *Prosopis* alkaloids Scheme 5. The conversion of (±)-**13** to (±)-prosopinine was already elaborated by Stille[6l,m] and the conversion of (−)-**13** to (−)-prosophylline and (−)-prosopinine was reported by Momose group.[4a,c] Thus our synthesis of (+)-**13** constitutes formal synthesis of (+)-prosophylline (**A**) and (+)-prosopinine (**B**).



Scheme 5. (a) (i) H_2, Pd/C, EtOAc, (92%); (ii) $(n\text{-Bu})_4NF$, THF, 0°C, 1 h, (87%); (iii) NaH, BnBr, cat. $(n\text{-Bu})_4NI$, THF, 0°C, 2 h, (87%); (b) Refs. 4a, c,6l,m.

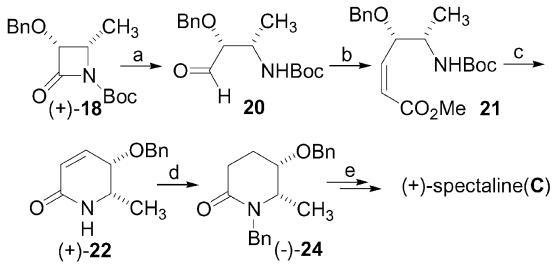
For the synthesis of *Cassia* alkaloids such as spectaline (**C**) and prosafrinine (**D**), the methyl group in the C-2 position of the piperidine-3-ol skeleton was required in place of the hydroxymethyl group as in *Prosopis* alkaloids. Thus, *N*-Boc-4-methyl-2-azetidinone **18** was easily prepared from the 4-hydroxymethyl-2-azetidinone (+)-**3a** as depicted in Scheme 6. Conversion of the hydroxy group of **3a** to iodide **15**, followed by hydrogenolysis afforded *N*-PMP-4-methyl-2-azetidinone **16**. Removal of the PMP protecting group in **16** with CAN and subsequent treatment with $(Boc)_2O$



Scheme 6. (a) MsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0°C, (quant.); (b) NaI, $NaHCO_3$, DMF, 60–70°C, 6 h, (68%); (c) H_2, Pd/C, $NaHCO_3$, EtOH, 24 h, (92%); (d) CAN, CH_3CN–H_2O, 0°C, 30 min (76%); (e) $(Boc)_2O$, cat. DMAP, CH_3CN, 4 h (93%)

furnished *N*-Boc-4-methyl-2-azetidinone (+)-**18** in good yield.

N-Boc-4-methyl-2-azetidinone (+)-**18** was then transformed to the corresponding (5*S*,6*S*)-5-benzyloxy-6-methyl-2-piperidone (+)-**22** by the essentially identical procedure for **6a** to **10a**. Thus, reduction of the (+)-**18** with $LiAlH_4$, oxidation of the resulting alcohol by IBX in DMSO and subsequent treatment of the 3-*N*-Boc-amino aldehyde **20** with $Ph_3P{=}CHCO_2Me$ in dry MeOH produced a 3.5:1 mixture of α,β-unsaturated esters *Z*- and *E*-**21**. After purification of *Z*-**21** by flash chromatography, removal of the *N*-Boc protecting group of *Z*-**21** by TMSOTf and subsequent cyclization by catalytic DMAP in toluene afforded the 5-benzyloxy-6-methyl-2-piperidone **22** in good yield Scheme 7.[22]



Scheme 7. (a) (i) $LiAlH_4$, THF, 0°C, 10 min, (87%), (ii) IBX, DMSO, room temperature, 3 h, (95%); (b) $Ph_3P{=}CHCO_2Me$, MeOH, room temperature, 12 h, (98%, *E*:*Z*=1:3.5); (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, then cat. DMAP, toluene, reflux, 1 h, (85%); (d) (i) BnBr, NaH (87%); (ii) H_2-Pd/C, EtOAc, room temperature, (99%); (e) Ref. 4a.

Finally, reduction of the double bond and *N*-benzylation at nitrogen of **22** provided (−)-**24**, a key intermediate for the chiral synthesis of *Cassia* alkaloids. The spectroscopic data of (−)-**24** were identical in every respect to the literature values.[4a] Since (−)-**24** was previously converted to (+)-spectaline and (+)-prosafrinine by Momose,[4a] the present work represents formal syntheses of (+)-spectaline (**C**) and (+)-prosafrinine (**D**).

Since the enantiomers of 2-azetidinones (−)-**6b** and (+)-**3a** are available by literature methods,[20,21] 2-piperidones (−)-**13** and (+)-**24** can be prepared from 2-azetidinones (+)-**6b** and (−)-**3a** by the same procedure of the present work for the synthesis of antipodal *Prosopis* and *Cassia* alkaloids.

In summary, we have developed a convenient method for the conversion of 2-azetidinones to 2-piperidones via two-carbon ring homologation. This methodology was successfully applied to the synthesis of naturally occurring *Prosopis* and *Cassia* alkaloids.

3. Experimental

Flash column chromatography was performed on silica gel (230–400 mesh). THF and Et_2O were refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was distilled from calcium hydride. DMF, benzene, CH_3CN, MeOH, toluene were dried, distilled, and stored under nitrogen. All other reagent grade chemicals obtained from commercial sources were used as received.

3.1. (3*R*,4*S*)-1-(4-Methoxyphenyl)-3-benzyloxy-4-formyl-2-azetidinone (2b)[14]

A mixture of **2a**[13] (4.98 g, 16 mmol) and dimethylamine (40% aq, 40 mL) in benzene (200 mL) was stirred at room temperature for 48 h. The organic layer was separated and washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), and dried with $MgSO_4$ followed by filtration and evaporation of the solvent under reduced pressure afforded crude product. The crude products were difficult to purify and directly subjected to $NaBH_4$ reduction in next step without further purification. Crude yield: 4.77 g (96%); (*cis*:*trans*=5:95 judged from the *cis*:*trans* ratio of reduced alcohols *cis*-**3a**:*trans*-**3b** ratio) in next step which were easily separated by flash chromatography).

3.2. (+)-(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-benzyloxy-4-hydroxymethyl-2-azetidinone (3a)

To a stirred solution of **2a**[13] (20.0 g, 64 mmol) in THF–H_2O (9:1, 600 mL) at 0°C was added $NaBH_4$ (7.3 g, 190 mmol) in small portions. The solution was stirred for 2 h at room temperature before the reaction was quenched by cautious addition of acetone and saturated NH_4Cl solution. THF was evaporated in vacuo and CH_2Cl_2 (200 mL) was added and washed with saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). After filtration and evaporation of solvent in vacuo, the crude product was purified by flash chromatography (from 1:1 to 1:3 hexane–EtOAc) to afford the product as a white solid. Yield 18.63 g (93%); mp 112–114°C; $[\alpha]_D^{21}$=+113.0° (*c*=0.5, CH_2Cl_2); IR (KBr) ν 3539, 1725, 1252, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 7H), 6.88 (d, 2H, *J*=9.15 Hz), 5.03 (d, 1H, *J*=11.5 Hz), 4.87 (d, 1H, *J*= 5.1 Hz), 4.78 (d, 1H, *J*=11.5 Hz), 4.25 (m, 1H), 4.02 (m, 2H), 3.79 (s, 3H), 2.38 (dd, 1H, *J*=5.3, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.06, 156.53, 136.41, 130.47, 128.69, 128.44, 128.21, 118.79, 114.48, 80.88, 73.69, 59.43, 57.67, 55.48; MS *m*/*z* 313 (M^+), 256, 149, 134, 91; HRMS (EI) calcd for $C_{18}H_{19}NO_4$ 313.1314, found 313.1309.

3.3. (−)-(3*R*,4*R*)-1-(4-Methoxyphenyl)-3-benzyloxy-4-hydroxymethyl-2-azetidinone (3b)

Crude **2b** was subjected to $NaBH_4$ reduction in THF–H_2O (9:1) via essentially the same procedure for **3a** affording a mixture of *cis*-**3a** and *trans*-**3b** alcohols which were separated by flash chromatography (4:1 hexane–EtOAc). Yield 90%, *cis*-**3a**:*trans*-**3b**=5:95); $[\alpha]_D^{22}$=−2.8° (*c*=1.56, $CHCl_3$); IR (NaCl) ν 3441, 1753, 1249, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 7.33 (d, 2H, *J*=8.94 Hz), 6.87 (d, 2H, *J*=8.95 Hz), 4.92 (d, 1H, *J*=11.8 Hz), 4.76 (d, 1H, *J*=1.6 Hz), 4.67 (d, 1H, *J*=11.8 Hz),

4.01 (dd, 1H, J=1.6, 2.8 Hz), 3.93 (d, 1H, J=3.6 Hz), 3.79 (d, 1H, J=1.6 Hz), 3.78 (s, 3H), 3.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.67, 163.99, 161.92, 156.56, 136.97, 130.06, 128.78, 128.52, 128.42, 119.40, 119.21, 118.36, 114.51, 114.47, 83.075, 82.74, 72.77, 66.00, 61.62, 59.08, 55.39; MS m/z 313 (M^+), 254, 164, 149, 134, 123; HRMS (EI) calcd for $C_{18}H_{19}NO_4$ 313.1314, found 313.1310.

3.4. (+)-(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (4a)

A mixture of **3a** (5.2 g, 16.6 mmol), imidazole (3.4 g, 49.8 mmol), TBDPS-Cl (5.18 mL, 19.92 mmol), and DMAP (0.2 g, 1.6 mmol) in dry DMF (30 mL) was stirred at room temperature for 24 h. The reaction mixture was quenched by addition of water (100 mL) and extracted with Et_2O (2×100 mL). Combined organic layer was washed with water, saturated $NaHCO_3$, and brine. After drying ($MgSO_4$), filtration, and evaporation of solvent the crude product was purified by flash column chromatography (from 10:1 to 5:1 hexane–EtOAc) to afford the product as white solid. Yield 8.9 g (97%); mp 62–63°C; $[\alpha]_D^{22}$=+22.5° (c=1.12, $CHCl_3$); IR (NaCl) ν 1770, 1382 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 5H), 7.39 (m, 10H), 7.24 (d, 2H, J=9.05 Hz), 6.74 (d, 2H, J=9.15 Hz), 4.80 (m, 3H), 4.23 (dd, 1H, J=4.9, 10.3 Hz), 4.09 (dd, 1H, J=5.5, 11.4 Hz), 3.94 (dd, 1H, J=4.9, 11.5 Hz), 3.76 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.29, 156.18, 136.94, 135.66, 135.55, 132.87, 132.69, 130.74, 129.85, 129.80, 128.40, 127.97, 127.95, 127.79, 127.77, 118.75, 114.16, 80.55, 73.23, 60.86, 59.25, 55.42, 26.72, 19.05, 14.16; MS m/z 551 (M^+), 466, 346, 177, 135, 91; HRMS (EI) calcd for $C_{34}H_{37}NO_4Si$ 551.2491, found 551.2484.

3.5. (−)-(3*R*,4*R*)-1-(4-Methoxyphenyl)-3-benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (4b)

Prepared from **3b**, TBDPS-Cl, and imidazole with catalytic DMAP in dry DMF via essentially the same procedure for **4a**. Yield 90%; $[\alpha]_D^{21}$=−5.2° (c=0.62, $CHCl_3$); IR (NaCl) ν 1753, 1392, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.36 (m, 15H), 6.83 (d, 2H, J=9.13 Hz), 4.89 (d, 1H, J=11.6 Hz), 4.84 (m, 1H), 4.67 (d, 1H, J=11.6 Hz), 3.97 (m, 2H), 3.80 (s, 3H), 3.70 (m, 1H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.71, 156.42, 137.06, 135.48, 132.69, 132.15, 130.18, 129.88, 128.52, 128.25, 128.16, 127.80, 127.63, 119.31, 114.38, 82.44, 72.81, 61.38, 59.73, 55.48, 26.60, 19.06; MS m/z 551 (M^+), 466, 346, 177, 135; HRMS (EI) calcd for $C_{34}H_{37}NO_4Si$ 551.2491, found 551.2489.

3.6. (−)-(3*R*,4*S*)-3-Benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (5a)

A solution of $(NH_4)_2Ce(NO_3)_6$ (42.9 g, 78.2 mmol) in water (250 mL) was added dropwise to a solution of **4a** (14.4 g, 26.1 mmol) in CH_3CN (240 mL) at 0°C. The mixture was stirred at this temperature for 30 min. Then, water (400 mL) was added, and this mixture was extracted with EtOAc (3×200 mL) and washed with a saturated solution of $NaHCO_3$ (350 mL). The aqueous layer of $NaHCO_3$ was extracted again with EtOAc (100 mL), and all organic layers were combined and washed with 10% $NaHSO_3$ (3×300 mL), $NaHCO_3$ (100 mL), brine (100 mL), and dried over $MgSO_4$. After filtration and evaporation of solvents in vacuo, the crude product was purified by flash chromatography (from 3:1 to 1:2 hexane–EtOAc) to afford the product as a yellow oil. Yield 10.0 g (86%); $[\alpha]_D^{22}$=−20.0° (c=0.23, $CHCl_3$); IR (NaCl) ν 3270, 1765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 5H), 7.40 (m, 10H), 5.98 (br s, 1H), 4.76 (d, 1H, J=11.8 Hz), 4.69 (d, 1H, J=2.2 Hz), 4.63 (d, 1H, J=11.8 Hz), 3.83 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.29, 136.85, 135.51, 133.12, 133.09, 129.90, 129.85, 128.42, 128.00, 127.95, 127.83, 127.79, 82.10, 73.16, 63.57, 60.39, 55.63, 26.80, 21.04, 19.16, 14.18; MS m/z 360 (M^+−85), 192, 177, 162, 135, 91; HRMS (CI, methane) calcd for $C_{27}H_{31}NO_3Si$ 446.2151 (MH^+), found 446.2149.

3.7. (+)-(3*R*,4*R*)-3-Benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (5b)

Prepared from **4b** and $(NH_4)_2Ce(NO_3)_6$ in CH_3CN–H_2O via essentially the same procedure for **5a**. Yield: 72%; mp 106–108°C; $[\alpha]_D^{21}$= +36.43° (c=1.01, $CHCl_3$); IR (KBr) ν 3270, 1765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 5H), 7.32 (m, 10H), 5.76 (br s, 1H), 4.80 (d, 1H, J=11.6 Hz), 4.59 (d, 1H, J= 11.6 Hz), 4.53 (t, 1H, J=1.63 Hz), 3.64 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.04, 136.89, 135.52, 132.83, 129.99, 128.48, 128.11, 127.85, 83.69, 72.55, 63.35, 57.87, 26.76, 19.16; MS m/z 359 (M^+−86), 289, 259, 180, 162, 135; HRMS (CI, methane) calcd for $C_{27}H_{31}NO_3Si$ 446.2151 (MH^+), found 446.2144.

3.8. (+)-(3*R*,4*S*)-1-(*t*-Butyloxycarbonyl)-3-benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (6a)

To a solution of **5a** (2.1 g, 4.71 mmol) and di-*tert*-butyl dicarbonate (1.13 g, 5.18 mmol) in dry CH_3CN (20 mL) was added DMAP (0.03 g, 0.24 mmol) and stirred at room temperature for 4 h. After completion of the reaction CH_3CN was evaporated in vacuo and CH_2Cl_2 (20 mL) was added and washed with saturated $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). After filtration and evaporation of solvent, the crude product was purified by flash chromatography (7:1 hexane–EtOAc) to afford the product as a colorless oil. Yield 2.44 g (95%); $[\alpha]_D^{22}$= +13.1° (c=0.55, $CHCl_3$); IR (NaCl) ν 1722, 1369, 1153 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 5H), 7.32 (m, 10H), 4.87 (d, 1H, J=11.6 Hz), 4.75 (d, 1H, J= 11.8 Hz), 4.73 (d, 1H, J=4.9 Hz), 4.14 (m, 2H), 3.94 (m, 1H), 1.44 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.26, 147.98, 136.62, 135.68, 135.54, 132.97, 132.83, 129.61, 128.42, 128.23, 128.07, 127.60, 127.56, 127.15, 83.24, 80.21, 73.59, 60.34, 58.55, 57.86, 27.90, 26.55, 21.00, 19.10, 14.15; MS m/z 545 (M^+), 508, 490, 462, 404, 388, 282, 236, 177, 91; HRMS (CI, methane) calcd for $C_{32}H_{39}NO_5Si$ 546.2675 (MH^+), found 546.2673.

3.9. (−)-(3*R*,4*R*)-1-(*t*-Butyloxycarbonyl)-3-benzyloxy-4-(*t*-butyldiphenylsilyloxymethyl)-2-azetidinone (6b)

Prepared from **5b** and di-*tert*-butyl dicarbonate with catalytic DMAP in dry CH_3CN via essentially the same

procedure for **6a**. Yield 92%; $[\alpha]_D^{22}=-18.5°$ (c=0.54, $CHCl_3$); IR (NaCl) ν 1723, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 5H), 7.32 (m, 10H), 4.84 (d, 1H, J=11.6 Hz), 4.76 (d, 1H, J=2.2 Hz), 4.60 (d, 1H, J=11.6 Hz), 4.04 (dd, 1H, J=3.6, 11.3 Hz), 3.86 (dd, 1H, J=1.02, 2.2 Hz), 3.69 (tt, 1H, J=1.02, 11.2 Hz), 1.46 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.14, 164.40, 148.12, 136.58, 135.49, 132.75, 129.92, 128.54, 128.22, 127.83, 83.39, 81.88, 72.91, 60.79, 59.72, 27.92, 26.70, 21.02, 19.24; MS m/z 433 (M^+-112), 404, 345, 282, 177; HRMS (CI, methane) calcd for $C_{32}H_{39}NO_5Si$ 546.2675 (MH^+), found 546.2682.

3.10. (−)-(2*R*,3*S*)-2-Benzyloxy-3-(*t*-butyloxycarbonyl)-amino-4-(*t*-butyldiphenylsilyloxymethyl)butan-1-ol (7a)

To a suspension of $LiAlH_4$ (0.15 g, 4.09 mmol) in THF (10 mL) was added dropwise a solution of **6a** (2.23 g, 4.09 mmol) in THF (10 mL) at 0°C. After stirring at that temperature for 20 min, ice-water (20 mL) and Rochelle salt (20 mL) was added and the reaction mixture was stirred for additional 1 h. The reaction mixture was extracted with CH_2Cl_2 (3×30 mL) and washed with $NaHCO_3$ and brine and dried ($MgSO_4$). After filtration and evaporation of solvent in vacuo, the crude product was purified by flash column chromatograph (from 7:1 to 2:1 hexane–EtOAc) to afford the product as colorless oil. Yield 1.96 g (87%); $[\alpha]_D^{22}=-15.8°$ (c=0.82, $CHCl_3$); IR (NaCl) ν 3444, 1366, 1112, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 5H), 7.39 (m, 10H), 4.59 (d, 1H), 4.57 (d, 1H, J=11.4 Hz), 4.46 (d, 1H, J=11.4 Hz), 4.05 (m, 1H), 3.75 (m, 4H), 3.51 (m, 1H), 3.23 (m, 1H), 1.41 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.15, 156.98, 138.02, 135.60, 135.57, 133.16, 133.00, 129.83, 129.80, 128.40, 127.82, 127.79, 127.76, 102.19, 79.95, 77.54, 73.07, 62.76, 60.61, 60.38, 52.01, 28.25, 26.83, 19.18, 14.18; MS m/z 436 (M^+-113), 314, 240, 199, 162, 135, 105; HRMS (CI, methane) calcd for $C_{32}H_{43}NO_5Si$ 550.2988 (MH^+), found 550.3017.

3.11. (+)-(2*R*,3*R*)-2-Benzyloxy-3-(*t*-butyloxycarbonyl)-amino-4-(*t*-butyldiphenylsilyloxymethyl)butan-1-ol (7b)

Prepared from **6b** and $LiAlH_4$ in dry THF via essentially the same procedure for **6a** as colorless oil. Yield 95%; $[\alpha]_D^{22}=+6.5°$ (c=1.5, $CHCl_3$); IR (NaCl) ν 3444, 1366, 1113, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 5H), 7.27 (m, 10H), 5.03 (d, 1H, J=8.95 Hz), 4.70 (d, 1H, J=11.6 Hz), 4.51 (d, 1H, J=11.4 Hz), 4.11 (m, 1H), 3.81 (m, 3H), 3.65 (m, 1H), 3.54 (m, 1H), 3.34 (m, 1H), 1.44 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.63, 138.04, 135.55, 132.83, 129.92, 128.34, 127.84, 127.61, 108.14, 80.11, 78.04, 71.53, 62.75, 59.75, 51.12, 28.31, 26.94, 19.31; MS m/z 540 (M^+-9), 476, 436, 314; HRMS (CI, methane) calcd for $C_{32}H_{43}NO_5Si$ 550.2988 (MH^+), found 550.2995.

3.12. (2*R*,3*S*)-2-Benzyloxy-3-(*t*-butyloxycarbonyl)amino-4-(*t*-butyldiphenylsilyloxymethyl)butanal (8a)

2-Iodoxybenzoic acid (IBX, 2.05 g, 7.33 mmol) was added to a solution of **7a** (2.69 g, 4.88 mmol) in DMSO (20 mL). After stirring at room temperature for 3 h, the reaction mixture was diluted with water (40 mL), filtered, and extrcacted with Et_2O (3×30 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$) and evaporated in vacuo. The crude aldehyde was pure enough to used in next step without further purification. Yield 2.49 g (93%); IR (NaCl) ν 3441, 2858, 1720, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.64 (m, 5H), 7.35 (m, 10H), 4.94 (d, 1H, J=9.16 Hz), 4.74 (d, 1H, J=11.4 Hz), 4.51 (d, 1H, J= 11.4 Hz), 4.25 (m, 2H), 3.85 (dd, 1H, J=4.17, 9.56 Hz), 3.65 (m, 1H), 1.39 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.01, 155.38, 135.52, 134.77, 129.86, 129.75, 128.49, 127.81, 81.74, 79.83, 61.87, 28.25, 26.67, 19.16; MS m/z 474 (M^+-73), 434, 342, 240, 199, 162, 135, 91, 57; HRMS (CI, methane) calcd for $C_{32}H_{41}NO_5Si$ 548.2832 (MH^+), found 548.2839.

3.13. (2*R*,3*R*)-2-Benzyloxy-3-(*t*-butyloxycarbonyl)-amino-4-(*t*-butyldiphenylsilyloxymethyl)butanal (8b)

Prepared from **7b** and 2-iodoxybenzoic acid in DMSO via essentially the same procedure for **8a**. Yield 95%; IR (NaCl) ν 3446, 2858, 1715, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.61 (m, 5H), 7.33 (m, 10H), 4.78 (m, 1H), 4.75 (d, 1H, J=11.4 Hz), 4.53 (d, 1H, J=11.4 Hz), 4.16 (br s, 1H), 3.92 (dd, 1H, J=2.2 Hz), 3.74 (m, 2H), 1.39 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.97, 155.00, 135.57, 132.58, 129.83, 128.55, 128.17, 128.02, 127.81, 127.77, 83.39, 73.28, 61.84, 52.19, 40.96, 28.24, 26.77, 19.13; MS m/z 547 (M^+), 492, 474, 434, 342, 204; HRMS (CI, methane) calcd for $C_{32}H_{41}NO_5Si$ 548.2832 (MH^+), found 548.2864.

3.14. Methyl (4*S*,5*S*)-4-benzyloxy-5-(*t*-butyloxycarbonyl)-amino-6-(*t*-butyldiphenylsilyloxy)-2-hexenoate (*E* and *Z*-9a)

To a solution of **8a** (2.37 g, 4.33 mmol) in dry methanol (40 mL) was added $Ph_3P{=}CHCO_2Me$ (1.74 g, 5.19 mmol) and stirred for 12 h at room temperature. After the reaction mixture was evaporated in vacuo, crude reaction product was separated to pure E and Z isomers by flash chromatography (from 15:1 to 7:1 hexane–EtOAc). Yield 2.27 g (87%, E:Z=1:7).

E-isomer (*E*-**9a**): $[\alpha]_D^{22}=-3.9°$ (c=0.96, $CHCl_3$); IR (NaCl) ν 3447, 1723, 1366, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 5H), 7.32 (m, 10H), 6.96 (dd, 1H, J=5.1, 15.8 Hz), 6.08 (dd, 1H, J=1.2, 15.8 Hz), 4.74 (d, 1H, J= 9.7 Hz), 4.56 (d, 1H, J=11.4 Hz), 4.44 (m, 1H), 4.34 (d, 1H, J=11.4 Hz), 3.93 (m, 1H), 3.74 (s, 3H), 3.68 (m, 2H), 1.38 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.21, 155.35, 145.55, 135.44, 133.07, 129.71, 128.31, 127.70, 122.74, 79.36, 71.75, 62.19, 54.42, 51.53, 28.16, 26.74, 19.10, 14.10; MS m/z 604 (M^++1), 530, 504, 490, 446, 368, 342, 264, 240; HRMS (CI, methane) calcd for $C_{35}H_{45}NO_6Si$ 604.3094 (MH^+), found 604.3079.

Z-isomer (*Z*-**9a**): $[\alpha]_D^{21}=+6.5°$ (c=1.23, $CHCl_3$); IR (NaCl) ν 3448, 1722, 1365, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 5H), 7.32 (m, 10H), 6.28 (dd, 1H, J=8.9, 11.8 Hz), 5.99 (dd, 1H, J=1.0, 11.8 Hz), 5.45 (dd, 1H, J= 8.7, 10.1 Hz), 4.82 (d, 1H, J=9.9 Hz), 4.52 (d, 1H, J= 11.4 Hz), 4.39 (d, 1H, J=11.4 Hz), 4.06 (m, 1H), 3.79

(m, 2H), 3.70 (s, 3H),1.39 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.78, 155.41, 147.11, 138.07, 135.55, 133.33, 133.29, 129.56, 128.20, 127.94, 127.60, 127.56, 122.44, 79.07, 72.77, 71.42, 62.92, 60.28, 55.25, 51.32, 28.28, 28.13, 26.74, 20.95, 19.18, 14.12; MS *m/z* 604 (M^++1), 504, 490, 342, 240, 194, 162; HRMS (CI, methane) calcd for $C_{35}H_{45}NO_6Si$ 604.3094 (MH^+), found 604.3095.

3.15. Methyl (4*S*,5*R*)-4-benzyloxy-5-(*t*-butyloxycarbonyl)-amino-6-(*t*-butyldiphenylsilyloxy)-2-hexenoate (*E* and *Z*-9b)

Prepared from **8b** and $Ph_3P{=}CHCO_2Me$ in dry methanol via essentially the same procedure for **9a**. Yield 81%, *E*:*Z*=1:4.

E-isomer (*E*-**9b**): $[\alpha]_D^{22}=-4.9°$ (*c*=0.9, $CHCl_3$); IR (NaCl) ν 3449, 1722, 1383, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 5H), 7.25 (m, 10H), 6.90 (dd, 1H, *J*=6.7, 15.8 Hz), 6.05 (d, 1H, *J*=15.8 Hz), 4.77 (d, 1H, *J*=9.16 Hz), 4.58 (d, 1H, *J*=11.4 Hz), 4.35 (d, 1H, *J*=11.4 Hz), 4.20 (d, 1H, *J*=6.10 Hz), 3.92 (m, 1H), 3.73 (s, 3H), 3.69 (m, 1H), 1.40 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.12, 155.23, 145.63, 137.59, 135.55, 132.96, 129.81, 128.38, 127.77, 127.63, 123.60, 79.45, 78.23, 71.60, 62.60, 60.39, 54.47, 51.59, 28.26, 26.86, 19.24; MS *m/z* 604 (M^++1), 548, 504, 490, 342; HRMS (CI, methane) calcd for $C_{35}H_{45}NO_6Si$ 604.3094 (MH^+), found 604.3092.

Z-isomer (*Z*-**9b**): $[\alpha]_D^{21}=+3.1°$ (*c*=1.34, $CHCl_3$); IR (NaCl) ν 3447, 1745, 1366, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 5H), 7.25 (m, 10H), 6.24 (dd, 1H, *J*=8.9, 11.6 Hz), 6.02 (d, 1H, *J*=11.8 Hz), 5.36 (t, 1H, *J*=8.9 Hz), 5.19 (d, 1H, *J*=9.97 Hz), 4.55 (d, 1H, *J*=11.4 Hz), 4.43 (d, 1H, *J*=11.4 Hz), 4.05 (br s, 1H), 3.80 (m, 2H), 3.75 (s, 3H),1.39 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.64, 155.58, 148.83, 138.01, 135.62, 133.31, 129.64, 128.30, 127.67, 127.59, 123.04, 108.26, 78.99, 73.88, 71.93, 62.60, 54.74, 51.45, 28.35, 26.87, 19.38; MS *m/z* 604 (M^++1), 530, 504, 490, 342, 240; HRMS (CI, methane) calcd for $C_{35}H_{45}NO_6Si$ 604.3094 (MH^+), found 604.3099.

3.16. (+)-(5*S*,6*S*)-5-Benzyloxy-6-(*t*-butyldiphenylsilyloxymethyl)-1,2,5,6-tetrahydro-2-pyridinone (10a)

To a solution of *Z*-**9a** (1.83 g, 2.95 mmol) and 2,6-lutidine (0.63 g, 5.95 mmol) in CH_2Cl_2 (30 mL) was added TMSOTf (0.82 mL, 4.43 mmol) dropwise at 0°C and stirred for 1 h. The reaction mixture was quenched by addition of saturated $NaHCO_3$ solution (30 mL) and the organic layer was separated and dried over $MgSO_4$. After filtration and evaporation of the solvent in vacuo, the resulting oil was dissolved in toluene (20 mL) and DMAP (0.01 g, 0.09 mmol) was added, and the reaction mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and washed with 1N HCl solution, saturated $NaHCO_3$ (20 mL), and brine (20 mL) successively. After drying ($MgSO_4$) and evaporation of the solvent in vacuo the crude product was purified by flash chromatography (from 3:1 to 1:1 hexane–EtOAc) to give the product as a colorless oil. Yield 1.32 g (95%); $[\alpha]_D^{22}=+109.2°$ (*c*=1.31, $CHCl_3$); IR (NaCl) ν 3220, 1684, 1618, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.16 (m, 15H), 6.61 (dd, 1H, *J*=4.49, 9.97 Hz), 6.06 (dd, 1H, *J*=2.2, 10.0 Hz), 5.91 (br s, 1H), 4.50 (d, 1H, *J*=11.7 Hz), 4.40 (d, 1H, *J*=11.7 Hz), 4.07 (t, 1H, *J*=4.56 Hz), 3.95 (t, 1H, *J*=9.61 Hz), 3.85 (dd, 1H, *J*=4.26, 10.33 Hz), 3.75 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.54, 138.73, 137.28, 135.41, 132.77, 129.83, 128.33, 127.78, 127.53, 127.06, 70.84, 68.06, 62.50, 60.26, 55.81, 26.71, 19.05, 14.09; MS *m/z* 471 (M^+), 414, 306, 246, 218, 91; HRMS (CI, methane) calcd for $C_{29}H_{33}NO_3Si$ 472.2307 (MH^+), found 472.2331.

3.17. (+)-(5*S*,6*R*)-5-Benzyloxy-6-(*t*-butyldiphenylsilyloxymethyl)-1,2,5,6-tetrahydro-2-pyridinone (10b)

Prepared from *Z*-**9b**, TMSOTf and 2,6-lutidine in CH_2Cl_2 and subsequent DMAP catalyzed cyclization in refluxing toluene via essentially the same procedure for **10a**. Yield 89%; $[\alpha]_D^{22}=+34.7°$ (*c*=1.13, $CHCl_3$); IR (NaCl) ν 3213, 1686, 1620, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 5H), 7.26 (m, 10H), 6.57 (dd, 1H, *J*=2.8, 10.2 Hz), 5.95 (dd, 1H, *J*=1.6, 9.9 Hz), 5.74 (br s, 1H), 4.58 (d, 1H, *J*=11.8 Hz), 4.43 (d, 1H, *J*=11.6 Hz), 4.09 (m, 1H), 3.76 (m, 2H), 3.72 (d, 1H, *J*=4.5 Hz), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.47, 145.72, 140.09, 137.07, 135.52, 132.62, 130.14, 128.50, 127.88, 127.78, 127.71, 124.94, 71.16, 70.79, 56.09, 26.82, 19.14; MS *m/z* 472 (M^++1), 414, 380, 368, 298, 278; HRMS (CI, methane) calcd for $C_{29}H_{33}NO_3Si$ 472.2307 (MH^+), found 472.2314.

3.18. (+)-(5*S*,6*R*)-5-(Benzyloxy)-6-(*t*-butyldiphenylsilyloxymethyl)-2-piperidinone (11)

A mixture of **10b** (472 mg, 1 mmol) and 10% palladium on carbon (10% w/w) in EtOAc (10 mL) was stirred under an atmosphere of H_2 for 1 h. After filtration over Celite and concentration in vacuo, the crude product was purified by silica gel column chromatography. Yield: 436 mg (92%); R_f 0.1 (hexane–EtOAc 1:1); $[\alpha]_D^{20}=+20.75°$ (*c*=0.54, $CHCl_3$); IR (KBr) ν 3209, 3070, 2931, 2858, 1669, 1428, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (m, 4H), 7.45 (m, 2H), 7.40 (m, 4H), 7.27 (m, 3H), 7.17 (m, 2H), 5.9 (broad-s, 1H), 4.56 (d, 1H, *J*=11.8 Hz), 4.38 (d, 1H, *J*=11.8 Hz), 3.75 (dd, 1H, *J*=4, 9.95 Hz), 3.56 (m, 1H), 3.49 (m, 2H), 2.54 (m, 1H), 2.27 (m, 1H), 2.01 (m, 1H), 1.87 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.12, 137.65, 135.55, 135.49, 132.74, 132.65, 129.98, 129.94, 128.43, 127.88, 127.86, 127.80, 127.48, 71.90, 70.67, 65.46, 58.38, 28.16, 26.80, 23.96, 19.14; MS *m/z* 418, 416, 248, 199, 135; HRMS (EI) calcd for $C_{29}H_{33}NO_3Si$ 473.2386, found 473.2383.

3.19. (+)-(5*S*,6*R*)-1-Benzyl-5-(benzyloxy)-6-(benzyloxymethyl)hexahydro-2-pyridinone (13)

To a solution of **11** (362 mg, 0.77 mmol) in THF (5 mL) was added (n-Bu)$_4$NF (1.14 mL of 1 M solution in THF, 1.15 mmol) at 0°C. The reaction mixture was stirred for 1 h at room temperature, quenched with aqueous $NaHCO_3$, and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc 1:3) to give (5*S*,6*R*)-5-(benzyloxy)-6-(hydroxymethyl)-2-piperidinone (**12**) as a colorless oil. [Yield: 158 mg (87%); R_f 0.2 (hexane–EtOAc 1:3)] To a slurry

of 60% NaH (110 mg, 2.75 mmol) in THF (5 mL) was added a solution of **12** (158 mg, 0.68 mmol) in THF (5 mL) at 0°C. After stirring for 10 min at this temperature, benzyl bromide (0.32 mL, 2.75 mmol) and $(n\text{-Bu})_4NI$ (10 mg, 0.027 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and quenched with saturated NH_4Cl (10 mL) at 0°C. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (from 1:1 to 1:2 hexane–EtOAc) to give **13** as a colorless oil. Yield 245 mg (87%); R_f 0.1 (hexane–EtOAc 1:1). $[\alpha]_D^{20}=+45.8°$ (c=0.85, $CHCl_3$) [lit.[19] $[\alpha]_D^{20}=+48.6°$ (c=1.2, $CHCl_3$), lit.[4a] $[\alpha]_D^{26}=-46.7°$ (c=3.32, $CHCl_3$) for (−)-**13**]; IR (NaCl) ν 3062, 3030, 2926, 1641, 1452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.18 (m, 15H), 5.36 (d, 1H, J=14.0 Hz), 4.44 (d, 1H, J=12.0 Hz), 4.40 (d, 1H, J=11.75 Hz), 4.37 (d, 1H, J=11.75 Hz), 4.29 (d, 1H, J=11.75 Hz), 4.01 (d, 1H, J=15.3 Hz), 3.86 (q, 1H, J=3.25 Hz), 3.66 (q, 1H, J= 3.2 Hz), 3.55 (dd, 1H, J=4.0, 9.9 Hz), 3.42 (dd, 1H, J=7.1, 9.9 Hz), 2.69 (ddd, 1H, J=9.5, 10.2, 18.05 Hz), 2.41 (ddd, 1H, J=3.95, 5.9, 17.85 Hz), 2.03–1.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.21, 138.03, 137.52, 137.22, 128.48, 128.43, 128.27, 127.88, 127.77, 127.59, 127.51, 127.29, 127.09, 73.26, 71.97, 70.00, 69.34, 58.55, 47.89, 27.41, 22.38; MS m/z 415 (M^+), 324, 294, 181, 105, 91, 65; HRMS (EI) calcd for $C_{27}H_{29}NO_3$ 415.2147, found 415.2143.

3.20. (+)-(3*R*,4*S*)-1-(*p*-Anisyl)-4-(methanesulfonyl-oxymethyl)-3-(benzyloxy)-2-azetidinone (14)

To a stirred solution of **3a** (300 mg, 0.957 mmol) and DMAP (12 mg, 0.096 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.4 mL, 2.872 mmol) and methanesulfonyl chloride (0.11 mL, 1.435 mmol) at 0°C. The reaction mixture was stirred for 6 h at room temperature, quenched with saturated $NaHCO_3$ (7 mL) at 0°C, extracted with CH_2Cl_2 (3×10 mL), and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:1 hexane–EtOAc) to give **14** as a colorless oil. Yield 375 mg (100%); R_f 0.37 (hexane–EtOAc 2:1); $[\alpha]_D^{21}=+84.8$ (c=2.43, $CHCl_3$); IR (NaCl) ν 1754, 1513, 1456, 1359, 1249, 1176, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 7H), 6.89–6.87 (m, 2H), 4.91 (d, 1H, J=11.5 Hz), 4.90 (d, 1H, J=4.6 Hz), 4.75 (d, 1H, J= 11.5 Hz), 4.57–4.48 (m, 3H), 3.79 (s, 3H), 2.88 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.77, 156.74, 136.35, 129.94, 128.62, 128.38, 128.17, 118.80, 114.48, 80.48, 73.62, 66.86, 55.92, 55.45, 37.21; MS m/z 391 (M^+), 334, 244, 176, 160, 149, 133, 117, 105, 91; HRMS (EI) calcd for $C_{19}H_{21}NO_6S$ 391.1089, found 391.1084.

3.21. (+)-(3*R*,4*R*)-1-(*p*-Anisyl)-4-iodomethyl-3-(benzyloxy)-2-azetidinone (15)

To a stirred solution of **14** (309 mg, 0.79 mmol) in DMF (9 mL) were slowly added NaI (237 mg, 1.58 mmol) and $NaHCO_3$ (200 mg, 2.37 mmol). The reaction mixture was heated to 60–70°C for 6 h and then cooled to room temperature. Et_2O (20 mL) was added. The layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (7:1 hexane–EtOAc) to give **15** as a colorless oil. Yield 228 mg (68%); R_f 0.67 (hexane–EtOAc 2:1). $[\alpha]_D^{21}=+107.8°$ (c=3.68, $CHCl_3$); IR (NaCl) ν 1754, 1511, 1384, 1247, 1124, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.29 (m, 7H), 6.88–6.86 (m, 2H), 4.91 (s, 2H), 4.80 (d, 1H, J=4.8 Hz), 4.52 (ddd, 1H, J=2.7, 4.8, 10.1 Hz), 3.77 (s, 3H), 3.49 (dd, 1H, J=2.7, 10.1 Hz), 3.40 (t, 1H, J= 10.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.91, 156.68, 136.86, 129.61, 128.46, 128.06, 127.90, 118.70, 114.60, 80.89, 74.14, 59.04, 55.48; MS m/z 423 (M^+), 366, 268, 239, 177, 149, 133, 117, 91; HRMS (EI) calcd for $C_{18}H_{18}NO_3I$ 423.0331, found 423.0329.

3.22. (+)-(3*R*,4*S*)-1-(*p*-Anisyl)-4-methyl-3-(benzyloxy)-2-azetidinone (16)

A mixture of **15** (54 mg, 0.127 mmol), 10% palladium on carbon (27 mg, 50% w/w), and $NaHCO_3$ (162 mg, 1.91 mmol) in EtOH (6 mL) was shaken for 2 h under 50 psi hydrogen pressure using Parr hydrogenator. The mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–EtOAc 7:1) to give **16** as a white solid. Yield 105 mg (92%); R_f 0.28 (hexane–EtOAc 5:1); mp 110–111°C; $[\alpha]_D^{21}=+116.8°$ (c=1.61, $CHCl_3$); IR (KBr) ν 1743, 1517, 1394, 1251, 1143, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 7H), 6.88–6.85 (m, 2H), 4.88 (d, 1H, J=11.8 Hz), 4.76–4.73 (m, 1H), 4.71 (d, 1H, J=11.8 Hz), 4.26 (quintet-like, 1H, J=6.0 Hz), 3.78 (s, 3H), 1.41 (d, 3H, J=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.16, 156.19, 137.07, 130.44, 128.43, 127.99, 127.94, 118.53, 114.40, 80.92, 73.03, 55.44, 53.85, 12.96; MS m/z 297 (M^+), 240, 178, 149, 134, 106, 91; HRMS (EI) calcd for $C_{18}H_{19}NO_3$ 297.1364, found 297.1376.

3.23. (+)-(3*R*,4*S*)-4-Methyl-3-(benzyloxy)-2-azetidinone (17)

Prepared from **16** via essentially the same procedure for **5a**. Yield 76%; white solid. R_f 0.13 (hexane–EtOAc 2:1); mp 82–83°C; $[\alpha]_D^{21}=+66.0°$ (c=1.4, $CHCl_3$); IR (KBr) ν 3189, 1710, 1446, 1340, 1211, 1159, 1062, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 6.36 (br s, 1H), 4.81 (d, 1H, J=11.8 Hz), 4.67–4.63 (m, 1H), 4.65 (d, 1H, J=11.8 Hz), 3.92–3.80 (m, 1H), 1.28 (d, 3H, J=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.68, 137.09, 128.39, 127.98, 127.85, 82.44, 72.69, 50.57, 15.60; MS m/z 192 (M^++1), 148, 119, 91, 77, 65, 44; HRMS (CI, methane) calcd for $C_{11}H_{13}NO_2$ 192.1024 (MH^+), found 192.1021.

3.24. (+)-(3*R*,4*S*)-1-(*t*-Butyloxycarbonyl)-4-methyl-3-(benzyloxy)-2-azetidin-one (18)

Prepared from **17** via essentially the same procedure for **6a**. Yield 93%; colorless oil. R_f 0.72 (hexane–EtOAc 2:1); $[\alpha]_D^{21}=+85.0°$ (c=3.12, $CHCl_3$); IR (NaCl) ν 1806, 1722, 1334, 1259, 1157, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 4.84 (d, 1H, J=11.8 Hz), 4.66 (d, 1H, J=11.8 Hz), 4.65–4.62 (m, 1H), 4.15 (quintet-like, 1H,

J=6.3 Hz), 1.51 (s, 9H), 1.38 (d, 3H, J=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.07, 147.99, 136.65, 128.46, 128.12, 127.97, 83.30, 80.63, 73.08, 53.96, 27.98, 13.09; MS m/z 292 (M^++1), 236, 208, 181, 148, 119, 91; HRMS (CI, methane) calcd for $C_{16}H_{22}NO_4$ 292.1548 (MH^+), found 292.1549.

3.25. (−)-(2*R*,3*S*)-3-(*t*-Butyloxycarbonyl)amino-2-(benzyloxy)butan-1-ol (19)

To a slurry of $LiAlH_4$ (38 mg, 1 mmol) in THF (5 mL) at 0°C was added slowly a solution of **18** (290 mg, 1 mmol) in THF (3 mL). The resulting mixture was stirred for 10 min at this temperature, and a few drops of water were added slowly until no more hydrogen gas evolved. The resulting mixture was dried ($MgSO_4$), filtered over Celite, concentrated under reduced pressure, and purified by silica gel column chromatography. Yield 257 mg (87%); colorless oil. R_f 0.25 (hexane–EtOAc 3:1); $[\alpha]_D^{21}$=−55.9° (c=2.22, $CHCl_3$); IR (NaCl) ν 3434, 1689, 1504, 1454, 1367, 1249, 1168, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 4.70 (d, 1H, J=9.0 Hz), 4.62 (d, 1H, J=11.6 Hz), 4.52 (d, 1H, J= 11.6 Hz), 4.02 (t, 1H, J=7.7 Hz), 3.70 (dd, 1H, J=5.4, 8.8 Hz), 3.61–3.39 (m, 3H), 1.44 (s, 9H), 1.20 (d, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.96, 138.05, 128.47, 128.05, 127.98, 81.38, 79.95, 73.39, 60.63, 45.84, 28.31, 17.75; MS m/z 296 (M^++1), 286, 265, 240, 221, 178, 134, 118, 91, 57, 44; HRMS (CI, methane) calcd for $C_{16}H_{25}NO_4$ 296.1861 (MH^+), found 296.1857.

3.26. (2*R*,3*S*)-3-(*t*-Butyloxycarbonyl)amino-2-(benzyloxy)butanal (20)

Prepared from **19** via essentially the same procedure for **8a**. Crude yield 95%. Yellow oil. IR (NaCl) ν 3411, 1710, 1500, 1454, 1367, 1247, 1168, 1066 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.37–7.32 (m, 5H), 4.90–4.88 (m, 1H), 4.79 (d, 1H, J=11.6 Hz), 4.54 (d, 1H, J=11.6 Hz), 4.26–4.24 (m, 1H), 3.80 (br s, 1H), 1.41 (s, 9H), 1.21 (d, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.84, 155.12, 136.92, 129.73, 128.47, 128.18, 85.16, 79.69, 73.00, 46.42, 28.24, 17.83; MS m/z 293 (M^++1), 220, 208, 144, 118, 91, 57, 44; HRMS (CI, methane) calcd for $C_{16}H_{23}NO_4$ 294.1705 (MH^+), found 294.1702.

3.27. Methyl (4*S*,5*S*)-5-(*t*-butyloxycarbonyl)amino-4-(benzyloxy)-2-hexeno-ate (*E* and *Z*-21)

Prepared from **20** via essentially the same procedure for **9a**. Yield 98% (*E*:*Z*=1:3.5); colorless oil.

E-isomer: $[\alpha]_D^{21}$=−12.7° (c=2.04, $CHCl_3$); IR (NaCl) ν 3363, 1712, 1500, 1454, 1365, 1251, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 6.88 (dd, 1H, J=5.9, 15.9 Hz), 6.07 (dd, 1H, J=1.5, 15.9 Hz), 4.65 (m, 1H), 4.62 (d, 1H, J=11.6 Hz), 4.39 (d, 1H, J=11.6 Hz), 4.00 (br s, 1H), 3.90–3.77 (m, 1H), 3.75 (s, 3H), 1.42 (s, 9H), 1.16 (d, 3H, J=6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.32, 155.30, 145.22, 137.57, 128.42, 127.87, 127.83, 123.09, 79.95, 71.60, 60.37, 51.64, 48.94, 28.32, 17.40; MS m/z 294 (M^+−55), 276, 262, 250, 232, 206, 144, 115, 91, 57, 44; HRMS (CI, methane) calcd for $C_{19}H_{27}NO_5$ 350.1967 (MH^+), found 350.1967.

Z-isomer: $[\alpha]_D^{21}$=+22.8° (c=2.54, $CHCl_3$); IR (NaCl) ν 3382, 1722, 1498, 1454, 1367, 1228, 1176, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H), 6.26 (dd, 1H, J=8.6, 11.7 Hz), 5.97 (dd, 1H, J=1.1, 11.7 Hz), 4.99 (d, 1H, J=7.3 Hz), 4.86 (d, 1H, J=7.3 Hz), 4.56 (d, 1H, J= 11.5 Hz), 4.40 (d, 1H, J=11.5 Hz), 3.91 (br s, 1H), 3.71 (s, 3H), 1.42 (s, 9H), 1.26 (d, 3H, J=6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.11, 155.47, 148.72, 138.01, 128.30, 127.81, 127.73, 122.20, 79.65, 76.96, 71.68, 51.40, 50.21, 28.35, 18.64; MS m/z 350 (M^++1), 294, 276, 262, 250, 232, 206, 144, 115, 91, 57, 44; HRMS (CI, methane) calcd for $C_{19}H_{27}NO_5$ 350.1967 (MH^+), found 350.1964.

3.28. (+)-(5*S*,6*S*)-5-(Benzyloxy)-6-methyl-1,2,5,6-tetrahydro-2-pyridinone (22)

Prepared from **21** via essentially the same procedure for **10a**. Yield 85%; white solid; R_f 0.06 (hexane–EtOAc 1:1); mp 78–79°C; $[\alpha]_D^{21}$=+116.0° (c= 2.12, $CHCl_3$); IR (KBr) ν 3185, 1693, 1606, 1425, 1334, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 6.63 (dd, 1H, J=4.0, 10.0 Hz), 6.08 (br s, 1H), 6.00 (dd, 1H, J=2.2, 10.0 Hz), 4.61 (d, 1H, J=11.8 Hz), 4.57 (d, 1H, J=11.8 Hz), 4.07 (t, 1H, J=4.5 Hz), 3.78–3.73 (m, 1H), 1.31 (d, 3H, J=6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.09, 139.97, 137.62, 128.50, 127.98, 127.71, 125.92, 71.11, 70.85, 49.94, 15.52; MS m/z 217 (M^+), 174, 145, 126, 111, 91; HRMS (EI) calcd for $C_{13}H_{15}NO_2$ 217.1102, found 217.1105.

3.29. (+)-(5*S*,6*S*)-1-Benzyl-5-(benzyloxy)-6-methyl-1,2,5,6-tetrahydro-2-pyridinone (23)

To a slurry of 60% NaH (165 mg, 4.12 mmol) in THF (8 mL) was added a solution of **22** (448 mg, 2.06 mmol) in THF (13 mL) at 0°C. After stirring for 10 min at this temperature, benzyl bromide (0.5 mL, 4.12 mmol) and tetra-*n*-butylammonium iodide (30 mg, 0.08 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and quenched with saturated NH_4Cl (20 mL) at 0°C. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (from 7:1 to 5:1 hexane–EtOAc) to give **23** as a colorless oil. Yield 550 mg (87%); R_f 0.65 (hexane–EtOAc 1:1). $[\alpha]_D^{21}$=+24.7° (c=2.12, $CHCl_3$); IR (NaCl) ν 1666, 1614, 1450, 1257, 1118, 1076 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.20 (m, 10H), 6.38 (tt, 1H, J=1.7, 10.0 Hz), 5.92 (dd, 1H, J=2.5, 10.0 Hz), 5.30 (d, 1H, J=15.0 Hz), 4.47 (d, 1H, J=11.7 Hz), 4.43 (d, 1H, J= 11.7 Hz), 4.42–4.40 (m, 1H), 3.87 (d, 1H, J=15.0 Hz), 3.62–3.57 (m, 1H), 1.18 (d, 3H, J=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.13, 140.27, 137.82, 137.06, 128.64, 128.48, 127.98, 127.83, 127.66, 127.42, 123.87, 74.03, 71.17, 52.88, 47.43, 10.93; MS m/z 307 (M^+), 216, 201, 186, 174, 134, 106, 91; HRMS (EI) calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1565.

3.30. (−)-(5*S*,6*S*)-1-Benzyl-5-(benzyloxy)-6-methylhexahydro-2-pyridinone (24)

A mixture of **23** (103 mg, 0.34 mmol) and 10% palladium

on carbon (30% w/w) in EtOAc (10 mL) was stirred under an atmosphere of H_2 for 1 h. After filtration over Celite and concentration in vacuo, the crude product was purified by silica gel column chromatography. Yield 104 mg (99%); colorless oil; R_f 0.14 (hexane–EtOAc 2:1); $[\alpha]_D^{21}=-60.7°$ (c=2.33, $CHCl_3$) [lit.[4a] $[\alpha]_D^{26}=-60.9°$ (c=2.24, $CHCl_3$)]; IR (NaCl) ν 1641, 1452, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.20 (m, 10H), 5.32 (d, 1H, J=15.0 Hz), 4.47 (d, 1H, J= 12.0 Hz), 4.43 (d, 1H, J=12.0 Hz), 3.94 (d, 1H, J=15.0 Hz), 3.66–3.63 (m, 1H), 3.56–3.54 (m, 1H), 2.64–2.60 (ddd, 1H, J=3.7, 7.5, 18.4 Hz), 2.53–2.46 (ddd, 1H, J=8.0, 9.5, 17.7 Hz), 2.03–1.94 (m, 2H), 1.22 (d, 3H, J=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.18, 137.76, 137.34, 128.59, 128.40, 127.73, 127.50, 127.30, 73.98, 70.65, 52.75, 47.77, 29.14, 22.02, 13.49; MS m/z 309 (M^+), 218, 203, 174, 134, 112, 91; HRMS (EI) calcd for $C_{20}H_{23}NO_2$ 309.1728, found 309.1724.

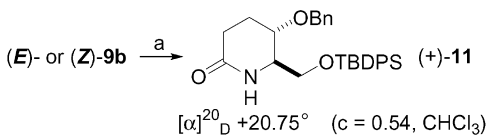
Acknowledgements

This work was supported by the Ministry of Science and Technology of Korea. We thank to Dr Jin K. Cha for his kind reading of the manuscript.

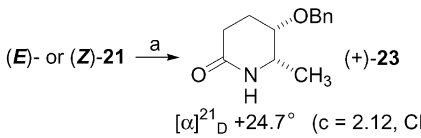
References

1. For piperidine alkaloids, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (d) O'Hagen, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (e) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155–299. (f) Elbein, A. D.; Molyneux, R. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5. (g) Fodor, G. B.; Colasanti, B. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1–90.
2. For *Prosopis* & *Cassia* alkaloids, see: (a) Astudillo, S. L.; Jurgens, S. K.; SchmedaHirschmann, G.; Griffith, G. A.; Holt, D. H.; Jenkins, P. R. *Planta Med.* **1999**, *65*, 161. (b) Bolzani, V.; da, S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 5929. (c) Aguinaldo, A. M.; Read, R. W. *Phytochemistry* **1990**, *29*, 2309. (d) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89–183. (e) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutrarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. (f) Ratle, G.; Monseur, X.; Das, B.; Yassi, J.; Khuong-Huu, Q.; Goutrarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945.
3. For some recent example of synthesis of piperidine alkaloids, see: (a) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004. (b) Nishimura, Y.; Adachi, H.; Satoh, T.; Shitara, E.; Nakamura, H.; Kojima, F.; Takeuchi, T. *J. Org. Chem.* **2000**, *65*, 4871. (c) Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (d) Sun, H.; Millar, K. M.; Yang, J.; Abboud, K.; Horenstein, B. A. *Tetrahedron Lett.* **2000**, *41*, 2801. (e) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427. (f) Williams, S. J.; Hoos, R.; Winters, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 2223. (g) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (h) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041. (i) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J.; Concolino, T. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 2651. (j) Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589. (k) Pahl, A.; Wartchow, R.; Meyer, H. H. *Tetrahedron Lett.* **1998**, *39*, 2095. (l) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc. Chem. Commun.* **1998**, 633. (m) Bayquen, A. V.; Read, R. W. *Tetrahedron* **1996**, *52*, 13467. (n) Altenbach, H.-J.; Himmeldirk, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1077. (o) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (p) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.
4. (a) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914. (b) Momose, T.; Toyooka, N.; Jin, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2005. (c) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715. (d) Momose, T.; Toyooka, N. *Tetrahedron Lett.* **1993**, *34*, 5785. (e) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett.* **1992**, *33*, 5389.
5. For synthesis of prosophylline and/or desoxoprosophylline, see: (a) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 3431. (b) Koulocheri, S. D.; Magiatis, P.; Haroutounian, S. A. *J. Org. Chem.* **2001**, *66*, 7915. (c) Datta, A.; Kumar, J. S. R.; Roy, S. *Tetrahedron* **2001**, *57*, 1169. (d) Koulocheri, S. D.; Haroutounian, S. A. *Tetrahedron Lett.* **1999**, *40*, 6869. (e) Yang, C.; Liao, L.; Xu, Y.; Zhang, H.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **1999**, *10*, 2311. (f) Koulocheri, S. D.; Haroutounian, S. A. *Synthesis* **1999**, 1889. (g) Herdeis, C.; Telser, J. *Eur. J. Org. Chem.* **1999**, 1407. (h) Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227. (i) Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999. (j) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 3887. (k) Lucker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (l) Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681. (m) Tadano, K.; Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Ogawa, S. *Synlett* **1993**, 565. (n) Natume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973. (o) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn* **1981**, *54*, 488. (p) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, 75.
6. (a) For synthesis of prosopinine and/or desoxoprosopinine: (a) Ref. 5b. (b) Enders, D.; Kirchhoff, J. H. *Synthesis* **2000**, 2099. (c) Ref. 5e. (d) Agami, C.; County, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783. (e) Agami, C.; County, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505. (f) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469. (g) Ref. 5j. (h) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776. (i) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793. (j) Yuasa, Y.; Ando, J.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1525. (k) Ref. 5l. (l) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575. (m) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669. (n) Ref. 5m. (o) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (p) Holmes,

A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (q) Ref. 5o. (r) Ref. 5p.
7. For synthesis of spectaline and/or cassine: Ref. 4a–c.
8. For some reviews on β-lactam antibiotics, see: (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vols. 1–3. (b) In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry, Burling House: London, 1984. (c) In *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992.
9. (a) Georg, G. I.; Rabikumar, V. T. The Organic Chemistry of β-Lactams; Georg, G. I., Ed.; VCH: New York, 1992; p 295. (b) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.
10. (a) Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p 197. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley: New York, 1997; p 279. (c) Lee, H. K.; Kim, E.-K.; Pak, C. S. *Tetrahedron Lett.* **2002**, *43*, 9641. (d) Ha, D.-C.; Kang, S.; Chung, C.-M.; Lim, H.-K. *Tetrahedron Lett.* **1998**, *39*, 7541. (e) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383. (f) Palomo, C.; Cossio, F. P.; Cuevas, C.; Odriozola, J. M.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4827. (g) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.
11. (a) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron Lett.* **2001**, *42*, 3483. (b) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471.
12. Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.
13. Alcaide, B.; Martin-Cantalejo, Y.; Perez-Castells, J.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 9156.
14. Alcaide, B.; Aly, M. F.; Rodriguez-Vicente, A. *Tetrahedron Lett.* **1998**, *39*, 5865.
15. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.
16. Sanchez-Sancho, F.; Valverde, S.; Herradon, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209.
17. Recently highly *Z*-selective Horner–Wadsworth–Emmons reaction of aldehyde was also reported Ando, K. *J. Org. Chem.* **1998**, *63*, 8411.
18. Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.
19. Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602.
20. Palomo, C.; Cossio, F. P.; Cuevas, C. *Tetrahedron Lett.* **1991**, *32*, 3109.
21. Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **1999**, *40*, 9063.
22. *E*-**9b** and *E*-**21** were also converted to the corresponding 2-piperidinones **11** and **23** via hydrogenation of double bond and subsequent cyclization in good overall yields



$[\alpha]^{20}_D$ +20.75° (c = 0.54, $CHCl_3$)



$[\alpha]^{21}_D$ +24.7° (c = 2.12, $CHCl_3$)

(a) (i) H_2(1 atm), Pd–C, THF; (ii) TMSOTf, 2,6-lutidine, CH_2Cl_2; (iii) cat. DMAP, tolune, reflux (**11**: 83%, **23**: 87%).