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Synthesis of (3*S*,5*S*)-3,5-diaminopiperidin-2-one as a conformationally restricted surrogate of Dab-Gly dipeptide

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Abstract—An efficient and stereospecific synthesis of chiral 3,5-diaminopiperidin-2-one as a novel conformationally restricted surrogate of 2,4-diaminobutanoyl (Dab)-Gly dipeptide has been achieved. The key steps include (i) ruthenium tetroxide (RuO_4) oxidation of *N*-Boc-2-azidomethylpyrrolidines with a catalytic amount of $RuO_2{\cdot}xH_2O$ in a two-phase system of aq $NaIO_4$/AcOEt and (ii) intramolecular transamidation of the resulting 2-azidomethylpyrrolidin-2-ones with 10% Pd–C in MeOH/H_2O (12/1, v/v) under an H_2 atmosphere (3 atm). This methodology represents a powerful tool for the synthesis of Dab-Gly dipeptide surrogate.

1. Introduction

Conformationally restricted peptidomimetics are valuable tools for the search for bioactive conformations, biological potency, and also metabolic stability relative to unmodified original peptides. One of the common approaches to such peptidomimetics is the incorporation of 3-amino-lactams into peptide chains.[1] This approach was pioneered by Freidinger et al.[1a,1b] and the resulting lactam-bridged dipeptides often referred to as 'Freidinger lactams'. Consequently, the design and synthesis of novel Freidinger lactams is currently an area of intensive research in the field of peptide and medicinal chemistry.[2,3] To the best of our knowledge, syntheses of several types of Freidinger δ-lactams have been reported,[2] however, the synthesis of compound **1** possessing an amino function at the C_3 and C_5 positions on the lactam ring is still not known.

Herein we report the preparation of enantiomerically pure (3*S*,5*S*)-3,5-diaminopiperidin-2-one derivative **1** as a novel conformationally restricted surrogate of 2,4-diaminobutanoyl (Dab)-Gly dipeptide, in which the conformational restriction is caused by the introduction of a methylene linker between the γ-carbon of the 2,4-diaminobutanoic acid and the nitrogen of the glycine.

Our synthetic strategy for target compound **1** is outlined retrosynthetically in Scheme 1. Key steps for the synthesis of **1** are a ruthenium tetroxide (RuO_4) oxidation of *N*-protected 2-azidomethylpyrrolidines **4** and subsequent intramolecular transamidation of 5-aminomethylpyrrolidin-2-one **6a** produced by a catalytic hydrogenation of the resulting 5-azidomethylpyrrolidin-2-one **3**. More recently, ring expansion of azido γ-lactams to δ-lactams by employing an intramolecular transamidation with a catalytic hydrogenation was reported by Langlois.[5]

2. Results and discussion

Our first synthetic targets were azido γ-lactams **3a–c** having a variety of electron-withdrawing groups at the pyrrolidine nitrogen to examine the effect of substituents on the next intramolecular transamidation. Thus, *N*-Boc-2-azidomethylpyrrolidine **4a** was first prepared from *trans*-4-hydroxy-L-proline according to Ref. 6. The RuO_4 oxidation of **4a** using our previously reported reaction conditions ($RuO_2{\cdot}xH_2O$/aq $NaIO_4$, AcOEt, rt)[4] gave the requisite γ-lactams **3a** in 85% yield as a single product, after column chromatography (Scheme 2). This oxidation can be carried out on a 20 g scale of **4a** without loss of yield. Removal of the Boc group in **3a** and subsequent reprotection of the nitrogen atom with AcCl and TsCl gave rise to **3b** (78%, two steps) and **3c** (72%, two steps), respectively.

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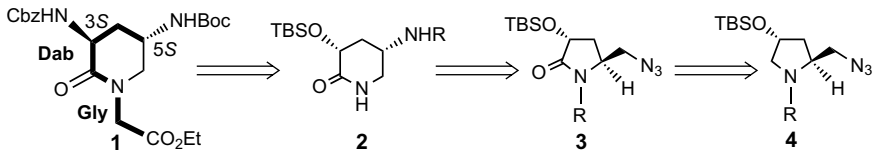
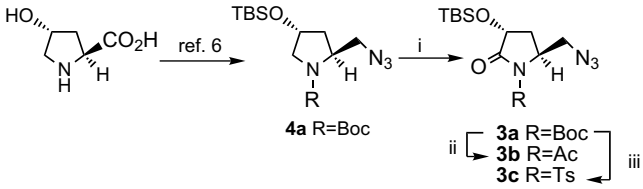


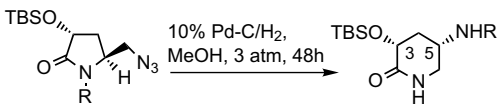
Scheme 1.



Scheme 2. Reagents and conditions: (i) $RuO_2{\cdot}xH_2O$, aq $NaIO_4$, AcOEt, rt, 85%; (ii) (a) CF_3CO_2H, CH_2Cl_2, rt; (b) AcCl, 4-DMAP, CH_2Cl_2, 0 °C to rt, 78% (two steps); (iii) (a) CF_3CO_2H, CH_2Cl_2, rt; (b) TsCl, 4-DMAP, CH_2Cl_2, 0 °C to rt, 72% (two steps).

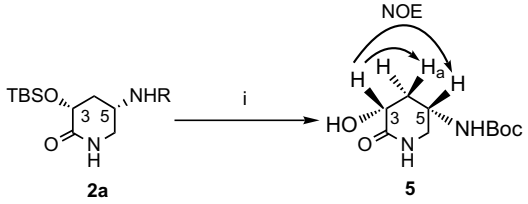
With the azido γ-lactams **3a–c** in hand, we examined an intramolecular transamidation[5,7] using a catalytic hydrogenation as a next key step. These results are summarized in Table 1. First, a catalytic hydrogenation of the azido group in **3a** with 10% Pd–C was carried out at 3 atm hydrogen atmosphere under different conditions of temperature and solvents to examine the optimum conditions on the intramolecular transamidation (entries 1–3). In the presence of H_2O as a co-solvent ($MeOH/H_2O$ = 12/1, v/v), the intramolecular transamidation of **3a** could be effected to afford the expected NH δ-lactam **2a** in 90% yield after column chromatography on silica gel (entry 3). In order to confirm the stereochemistries of the stereogenic centers at the C_3 and C_5 positions in **2a**, it was converted to the 3-hydroxypiperidin-2-one derivative **5** by treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature as shown in Scheme 3. The stereochemical assignment of **5** was determined by ^1H NMR experiments including difference NOE. Irradiation of the C_3–H (δ 4.15) resulted in enhancements of both the signals due to the C_4–H_a (δ 2.12) and C_5–H (δ 4.05). Accordingly, the C_3–H and C_5–H in **5** was assigned to have a *cis*-configuration. The absolute configuration of **5** was unambiguously determined as (3*R*,5*S*)-**5**. Based on these spectral features, the stereostructure of **2a** could be rigorously assigned as shown. This reaction's efficiency, by employing additive H_2O as more polar solvents can be explained due to the increase in electrophilicity of lactam carbonyl carbon by favorable hydrogen bonding between the H_2O and the oxygen atom of the carbonyl group, consequently nucleophilic attack on the carbonyl carbon of the amino group of the *N*-Boc aminomethyl intermediate **6a** may be enhanced (Fig. 1). Next, the application of the optimum conditions for the ring transformation of **3b** and **3c** afforded **2b** and **2c** with good success (entries 4 and 5, respectively).

Table 1. Intramolecular transamidation of **3a–c**



Entry	Substrate	R	Conditions	Product	Yield (%)
1	**3a**	Boc	rt	**2a**	65
2	**3a**	Boc	40–45 °C	**2a**	80
3	**3a**	Boc	rt, H_2O[a]	**2a**	90
4	**3b**	Ac	rt, H_2O[a]	**2b**	75
5	**3c**	Ts	rt, H_2O[a]	**2c**	80

[a] $MeOH/H_2O$ (12/1, v/v).



Scheme 3. Reagents and conditions: (i) TBAF, THF, rt, 92%.

Next, alkylation of the δ-lactam ring nitrogen of **2a** with ethyl bromoacetate using $LiN(TMS)_2$ as a base afforded **8** in 80% yield without epimerization at the C_3 center (Scheme 3). Sequential deprotection of the silyl group with TBAF and mesylation of the resulting alcohol provided mesylate **11** in 81% yield (two steps), after purification by column chromatography. The stereochemical integrity of the process was determined by the preparation of Moscher's ester **10** with (*S*)-MTPA chloride in the presence of 4-dimethylaminopyridine.[8] Analysis of the ^1H NMR spectra of **10** showed the presence of a single stereoisomer, indicating an enantiomeric purity >95%. Thus, we were confident that no racemization had occurred during the whole sequence. Displacement of **11** with sodium azide gave δ-lactam **12** in 95% yield. Finally, catalytic hydrogenation of **12** using 10% Pd–C followed by protection of the amine moiety with carbobenzyloxy chloride gave the target Dab-Gly dipeptide surrogate (3*S*,5*S*)-**1** in 82% yield (two steps), in which

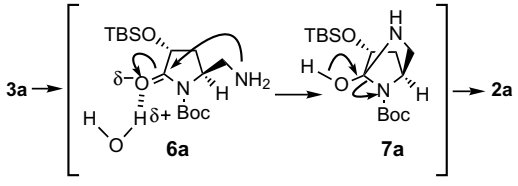
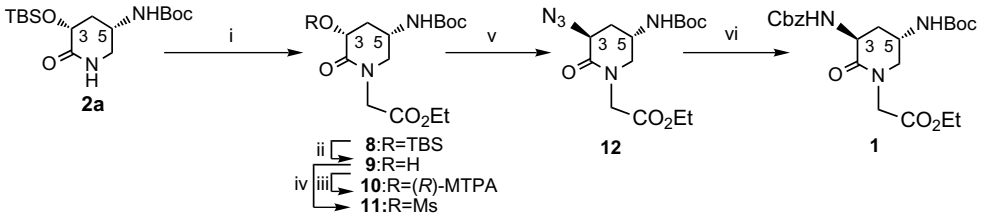


Figure 1.



Scheme 4. Reagents and conditions: (i) $BrCH_2CO_2Et$, $LiN(TMS)_2$, THF, 0 °C to rt, 80%; (ii) TBAF, THF, 92%; (iii) (*S*)-MTPACl, 4-DMAP, CH_2Cl_2, 95%; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 88%; (v) NaN_3, DMF, 70 °C, 95%; (vi) (a) 10% Pd–C/H_2, MeOH; (b) CbzCl, Et_3N, CH_2Cl_2, 82% (two steps).

α-, γ-diamino functions and terminus carboxyl function were differentially protected (Scheme 4).

3. Conclusion

In summary, we have developed an efficient and stereospecific synthesis of novel 3,5-diaminopiperidin-2-one derivative **1** as a conformationally restricted surrogate of Dab-Gly dipeptide by a sequence of RuO_4 oxidation and intramolecular transamidation starting from *trans*-4-hydroxy-L-proline. In addition, compound **1** can be incorporated into biologically important peptides.

4. Experimental

4.1. General

Melting points were measured on a Yanako MP-S3 micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. Infrared (IR) spectra were recorded with a HORIBA FT-720 spectrometer. ^1H and ^{13}C NMR spectra were measured with a JNM-ECP-500 spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as internal standard in $CDCl_3$ solutions. Coupling constants were expressed in Hz. Electron impact mass spectra (EIMS), fast atom bombardment mass spectra (FABMS), and high resolution fast atom bombardment mass spectra (HRFABMS) were obtained with JMS-SX-102A spectrometer. Routine monitoring of reaction was carried out using Merck TLC aluminum sheet silica gel 60 F_{254}. All solvents were dried and purified before use. The *trans*-4-hydroxy-L-proline used as homochiral starting material was purchased from Sigma Chemical Co.

(2*S*,4*R*)-2-Azidomethyl-1-*tert*-butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine **4a** was prepared according to a literature procedure.[6]

4.2. (3*R*,5*S*)-5-Azidomethyl-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one 3a

A solution of **4a** (20.0 g, 56.0 mmol) in AcOEt (250 mL) was added to a mixture of $RuO_2{\cdot}xH_2O$ (0.3 g) and 10% aq $NaIO_4$ (250 mL). The solution was stirred vigorously for 10 h at room temperature. The layer was separated and the aqueous layer extracted with AcOEt (120 mL). The extract was treated with 2-propanol (0.2 mL). Black-colored RuO_2, which precipitated from the solution, was filtered off and the filtrate washed with brine and dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 8:1) to give **3a** (17.6 g, 85%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **3a** as colorless needles, mp 59–60 °C. $[\alpha]_D^{24} = +17.8$ (*c* 1.34, MeOH). IR (KBr): 2094, 1756, 1718. ^1H NMR ($CDCl_3$): δ 0.14, 0.18 (each s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.55 (s, 9H, $OC(CH_3)_3$), 2.08 (ddd, 1H, J = 2.93, 9.89, 12.8 Hz, C_4–H), 2.26 (ddd, 1H, J = 1.10, 8.42, 12.8 Hz, C_4–H), 3.56 (dd, 1H, J = 2.93, 12.5 Hz, CH_2N_3), 3.71 (dd, 1H, J = 4.76, 12.5 Hz, CH_2N_3), 4.18–4.28 (m, 1H, C_5–H), 4.57 (dd, 1H, J = 8.42, 9.89 Hz, C_3–H). ^{13}C NMR ($CDCl_3$): δ −5.25, −4.48 (q, $Si(CH_3)_2$), 18.29 (s, $SiC(CH_3)_3$), 25.76 (q, $SiC(CH_3)_3$), 28.04 (q, $OC(CH_3)_3$), 32.66 (t, C_4), 52.95 (d, C_5), 53.64 (t, CH_2N_3), 70.01 (d, C_3), 83.82 (s, $OC(CH_3)_3$), 150.01 (s, urethane C=O), 172.65 (s, lactam C=O). EIMS *m*/*z*: 371 ($M+1^+$). Anal. Calcd for $C_{16}H_{30}N_4O_4Si$: C, 51.86; H, 8.16, N, 15.12. Found: C, 51.78, H, 8.08, N, 15.22.

4.3. (3*R*,5*S*)-1-Acetyl-5-azidomethyl-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one 3b

To a solution of **3a** (2.00 g, 5.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added dropwise TFA (5.0 mL). The solution was stirred for 3 h and then the solvent evaporated in vacuo. The residue was dissolved in AcOEt (30 mL) and washed with saturated aqueous $NaHCO_3$, brine, and dried with Na_2SO_4. Concentration of the solvent in vacuo gave a crude NH lactam (1.4 g), which was directly used for the next acetylation without purification. 4-Dimethylaminopyridine (1.9 g, 1.5 mmol) and acetyl chloride (0.8 g, 7.7 mmol) was added to a solution of crude NH lactam (1.4 g) in CH_2Cl_2 (20 mL) and the mixture stirred at 0 °C for 3 h. The mixture was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 5:1) to give **3b** (1.3 g, 78%) as a colorless oil. $[\alpha]_D^{25} = +22.7$ (*c* 1.1, MeOH). IR (neat): 2111, 1756, 1702. ^1H NMR

($CDCl_3$): δ 0.16, 0.19 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 2.10 (ddd, 1H, J = 8.80, 9.89, 12.82 Hz, C_4–H), 2.30 (ddd, 1H, J = 0.73, 8.80, 12.82 Hz, C_4–H), 2.54 (s, 3H, $COCH_3$), 3.48 (dd, 1H, J = 2.56, 12.45 Hz, CH_2N_3), 3.82 (dd, 1H, J = 4.03, 12.45 Hz, CH_2N_3), 4.38–4.44 (m, 1H, C_5–H), 4.71 (dd, 1H, J = 8.80, 9.89 Hz, C_3–H). ^{13}C NMR ($CDCl_3$): δ −5.15, −4.55 (q, $Si(CH_3)_2$), 18.30 (s, SiC), 25.22 (q, $COCH_3$), 25.72 (q, $C(CH_3)_3$), 32.81 (t, C_4), 51.88 (d, C_5), 53.05 (t, CH_2N_3), 70.46 (d, C_3), 171.32 (s, $COCH_3$), 174.76 (s, lactam C=O). FABMS *m*/*z*: 313 ($M+1^+$). HRFABMS: calcd for $C_{13}H_{25}N_4O_3Si$ ($M+1^+$): 313.1696. Found: 313.1690.

4.4. (3*R*,5*S*)-5-Azidomethyl-3-(*tert*-butyldimethylsilyloxy)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one 3c

The same treatment of **3a** (3.5 g, 9.4 mmol) as described for the preparation of **3b** from **3a**, except for the use of *p*-toluenesulfonyl chloride (2.2 g, 11.3 mmol) instead of acetyl chloride, gave, after column chromatography (benzene–AcOEt = 30:1), **3c** (2.9 g, 72%, two steps) as a colorless oil. $[\alpha]_D^{26} = +18.8$ (*c* 0.98, MeOH). IR (neat): 2111, 1751, 1596. ^1H NMR ($CDCl_3$): δ 0.09, 0.11 (s, 6H, $Si(CH_3)_2$, 0.86 (s, 9H, $SiC(CH_3)_3$, 2.12 (ddd, 1H, J = 8.06, 9.90, 12.82 Hz, C_4–H), 2.27 (ddd, 1H, J = 1.10, 8.06, 12.82 Hz, C_4–H), 2.44 (s, 3H, Ph–CH_3), 3.64 (dd, 1H, J = 2.56, 12.82 Hz, CH_2N_3), 3.94 (dd, 1H, J = 4.40, 12.82 Hz, CH_2N_3), 4.36–4.42 (m, 1H, C_5–H), 4.57 (dd, J = 8.06, 9.90 Hz, C_3–H), 7.35, 7.94 (d, 4H, J = 8.43 Hz, Ph–H). ^{13}C NMR ($CDCl_3$): δ −5.24, −4.60 (q, $Si(CH_3)_2$), 18.23 (s, SiC), 21.70 (q, Ph–CH_3), 25.67 (q, $SiC(CH_3)_3$), 34.08 (t, C4), 54.67 (d, C_3), 128.34, 129.77, 135.22, 145.51 (Ph), 172.31 (lactam C=O). FABMS *m*/*z*: 425 ($M+1^+$). HRFABMS: calcd for $C_{18}H_{29}N_4O_4SSi$ ($M+1^+$): 425.1679. Found: 425.1680.

4.5. General procedure for the intramolecular transamidation of 3a–c

A mixture of 5-azidomethyl derivative **3** (1.5 g, 4.0 mmol) and 10% Pd–C in MeOH/H_2O (65 mL, 12:1 v/v) was stirred for 48 h at room temperature under an H_2 atmosphere (3 atm). The catalyst was filtered off and the filtrate concentrated in vacuo to give a residue, which was partitioned between $CHCl_3$ and H_2O. The aqueous layer was backwashed with $CHCl_3$. The combined organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography. The results are summarized in Table 1.

4.5.1. (3*R*,5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]piperidin-2-one 2a.

Following the general procedure, transamidation of **3a**, after column chromatography ($CHCl_3$–MeOH = 30:1), gave **2a** (1.25 g, 90%) as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **2a** as colorless needles, mp 125–126 °C. $[\alpha]_D^{26} = -13.5$ (*c* 1.11, MeOH). IR (KBr): 3436, 3230, 1724, 1682. ^1H NMR ($CDCl_3$): δ 0.16, 0.17, 0.18, 0.19 (s, 6H, $Si(CH_3)_2$), 0.91, 0.92 (s, 9H, $SiC(CH_3)_3$), 1.42, 1.43 (s, $OC(CH_3)_3$), 2.02–2.08 (m, 2H, C_4–H_2), 3.37–3.45 (m, 2H, C_6–H_2), 4.02–4.01 (m, 1H, C_5–H), 4.16–4.21 (m, 1H, C_3–H), 6.02–6.25 (m, 2H, NH × 2). ^{13}C NMR ($CDCl_3$): δ −5.60, −4.57 (q, $Si(CH_3)_2$), 18.07 (s, $SiC(CH_3)_3$), 25.72 (q, $SiC(CH_3)_3$), 28.37 (q, $OC(CH_3)_3$), 34.39 (t, C_4), 42.59 (d, C_5), 47.67 (t, C_6), 68.03 (d, C_3), 79.33 (s, $OC(CH_3)_3$), 155.28 (s, urethane C=O), 170.33 (s, lactam C=O). FABMS *m*/*z*: 345 ($M+1^+$). Anal. Calcd for $C_{16}H_{32}N_2O_4$: C, 55.78; H, 9.36; N, 8.13. Found: C, 55.80; H, 9.05; N, 8.12.

4.5.2. (3*R*,5*S*)-5-Acetylamino-3-[(*tert*-butyldimethylsilyl)oxy]piperidin-2-one 2b.

Following the general procedure, transamidation of **3b**, after column chromatography ($CHCl_3$–MeOH = 10:1), gave **2b** (1.03 g, 75%) as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **2b** as colorless needles, mp 197–198 °C. $[\alpha]_D^{24} = -12.2$ (*c* 1.0, MeOH). IR (KBr): 3288, 3092, 1675, 1648. ^1H NMR ($CDCl_3$): δ 0.19, 0.21 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.95 (s, 3H, $COCH_3$), 2.05–2.14 (m, 2H, C_4–H_2), 3.39–3.52 (m, 2H, C_6–H), 4.18–4.24 (m, 1H, C_5–H), 4.30–4.38 (m, 1H, C_3–H), 6.14 (br s, 1H, lactam NH), 7.28 (br d, J = 5.45 Hz, $NHCOCH_3$). ^{13}C NMR ($CDCl_3$): δ −5.53, −4.57 (q, $Si(CH_3)_2$), 18.11 (s, $SiC(CH_3)_3$), 23.37 (q, $COCH_3$), 25.75 (q, $SiC(CH_3)_3$), 33.75 (t, C_4), 41.60 (d, C_5), 47.19 (t, C_6), 68.03 (d, C_3), 169.71, 169.90 (s, C=O). FABMS *m*/*z*: 287 ($M+1^+$). Anal. Calcd for $C_{13}H_{26}N_2O_3Si$: C, 54.51; H, 9.15; N, 9.78. Found: C, 54.48; H, 9.08, N, 9.80.

4.5.3. (3*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(*p*-toluenesulfonylamino)-piperidin-2-one 2c.

Following the general procedure, transamidation of **3c**, after column chromatography ($CHCl_3$–MeOH = 10:1), gave **2c** (1.12 g, 80%) as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **2c** as colorless prisms, mp 155–156 °C. $[\alpha]_D^{24} = +22.0$ (*c* 0.93, MeOH). IR (KBr): 3348, 1666, 1598. ^1H NMR ($CDCl_3$): δ 0.13, 0.15 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.83–2.03 (m, 2H, C_4–H_2), 2.43 (s, 3H, Ph–CH_3), 3.28–3.38 (m, 2H, C_6–H_2), 3.67–3.76 (m, 1H, C_5–H), 4.07–4.12 (m, 1H, C_3–H), 6.13–6.22 (m, 1H, lactam NH), 6.53–6.58 (m, 1H, NHTs), 7.30, 7.74 (d, 2H, J = 8.06, Ph–H). ^{13}C NMR ($CDCl_3$): δ −5.50, −4.57 (q, $Si(CH_3)_2$), 18.13 (s, $SiC(CH_3)_3$), 21.53 (q, Ph–CH_3), 25.73 (q, $SiC(CH_3)_3$), 35.20 (t, C_4), 45.80 (d, C_5), 47.95 (t, C_6), 67.93 (d, C_3), 126.83, 129.84, 138.08, 143.56 (Ph), 170.33 (s, lactam C=O). FABMS *m*/*z*: 399 ($M+1^+$). Anal. Calcd for $C_{18}H_{30}N_2O_4SSi$: C, 54.24; H, 7.59; N, 7.03. Found: C, 54.20; H, 7.38; N, 7.12.

4.6. (3*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-3-hydroxypiperidin-2-one 5

Tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M solution, 4.8 mL) was added dropwise to a stirred solution of **2a** (0.84 g, 2.4 mmol) in THF (20 mL) at room temperature for 3 h. The reaction mixture was concentrated, and the residue purified by column chromatography (AcOEt–MeOH = 10:1) to give **5** (0.52 g, 92%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **5**

as colorless needles, mp 199–200 °C. $[\alpha]_D^{25} = -14.9$ (*c* 0.85, MeOH). IR (KBr): 3400, 3370, 1693, 1638. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H, $OC(CH_3)_3$), 1.76–1.86 (m, 1H, C_4–H), 2.40–2.50 (m, 1H, C_4–H), 3.18–3.28 (m, 1H, C_6–H), 3.48–3.56 (m, 1H, C_6–H), 3.80 (br s, 1H, OH), 4.02–4.14 (m, 1H, C_5–H), 4.10–4.18 (m, 1H, C_3–H), 5.05, 6.17 (br s, 2H, NH × 2). ^{13}C NMR ($CDCl_3$): δ 28.36 (q, $OC(CH_3)_3$), 34.46 (t, C_4), 43.54 (d, C_5), 47.13 (t, C_6), 65.67 (d, C_3), 79.52 (s, $OC(CH_3)_3$), 155.07 (s, urethane C=O), 173.28 (s, lactam C=O). FABMS *m*/*z*: 231 ($M+1^+$). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.07; H, 7.68; N, 12.04.

4.7. (3*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-1-(ethoxycarbonylmethyl)piperidin-2-one 8

Lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) in THF (1.0 M solution, 3.6 mL) was added to a solution of **2a** (1.00 g, 2.90 mmol) in THF (30 mL) under nitrogen at −15 °C, and the reaction mixture stirred for 30 min. Then ethyl bromoacetate (0.97 g, 5.81 mmol) was added to the reaction mixture. After stirring for 1 h at −15 °C, the reaction mixture was allowed to warm up to room temperature. The reaction was quenched with saturated NH_4Cl solution (10 mL) and the mixture extracted with AcOEt (40 mL). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 1:1) to give **8** (1.15 g, 80%) as a colorless oil. $[\alpha]_D^{23} = -14.0$ (*c* 1.30, MeOH). IR (neat): 3409, 1747, 1714, 1668. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 1H, $SiC(CH_3)_3$), 1.26, 1.27 (t, 3H, J = 6.96 Hz, OCH_2CH_3), 1.43 (s, 9H, $OC(CH_3)_3$), 2.04–2.22 (m, 2H, C_4–H_2), 3.41 (br d, 1H, J = 12.10 Hz, C_6–H), 3.61 (dd, J = 4.03, 12.10 Hz, C_6–H), 3.82 (d, 1H, J = 17.20 Hz, CH_2CO_2Et), 4.08–4.16 (m, 1H, C_5–H), 4.18, 4.19 (q, 2H, J = 6.96 Hz, OCH_2CH_3), 4.27 (t, 1H, J = 4.40 Hz, C_3–H), 4.31 (d, 1H, J = 17.20 Hz, CH_2CO_2Et), 6.30 (br d, 1H, J = 8.06 Hz, NH). ^{13}C NMR ($CDCl_3$): δ −5.62, −5.60 (q, $Si(CH_3)_2$), 14.14 (q, OCH_2CH_3), 18.07 (s, $SiC(CH_3)_3$), 25.72 (q, $SiC(CH_3)_3$), 28.37 (q, $OC(CH_3)_3$), 34.50 (t, C_4), 43.17 (d, C_5), 49.04 (t, C_6), 54.60 (t, CH_2CO_2Et), 61.28 (t, OCH_2CH_3), 68.28 (d, C_3), 79.33 (s, $OC(CH_3)_3$), 155.34 (s, urethane C=O), 168.65, 168.97 (s, ester and lactam C=O). FABMS *m*/*z*: 431 ($M+1^+$). HRFABMS: calcd for $C_{20}H_{39}N_2O_6Si$ ($M+1^+$): 431.2577. Found: 431.2575.

4.8. (3*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-1-(ethoxycarbonylmethyl)-3-hydroxypiperidin-2-one 9

TBAF in THF (1.0 M solution, 6.75 mL) was added dropwise to a stirred solution of **8** (0.97 g, 2.25 mmol) in THF (20 mL) at room temperature and the mixture stirred at ambient temperature for 2 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (hexane–AcOEt = 1:3) to give **9** (0.65 g, 92%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **9** as colorless needles, mp 122–123 °C. $[\alpha]_D^{24} = -13.4$ (*c* 1.12, MeOH). IR (KBr): 3355, 1733, 1683, 1664. ^{1}H NMR ($CDCl_3$): δ 1.28, 1.29 (t, 3H, J = 6.96 Hz, OCH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.80–1.91 (m, 1H, C_4–H), 3.30 (dd, 1H, J = 6.23, 12.09 Hz, C_6–H), 3.62 (dd, 1H, J = 4.40, 12.09 Hz, C_6–H), 3.94 (d, 1H, J = 17.22 Hz, NCH_2CO_2Et), 4.05–4.18 (m, 3H, C_3–H, C_5–H, OH), 4.20, 4.21 (q, 2H, J = 6.96 Hz, OCH_2CH_3), 4.25 (d, 1H, J = 17.22 Hz, NCH_2CO_2Et), 5.40 (br d, 1H, J = 8.06 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 14.14 (q, $CO_2CH_2CH_3$), 28.37 (q, $OC(CH_3)_3$), 34.81 (t, C_4), 43.25 (d, C_5), 48.72 (t, C_6), 53.62 (t, NCH_2CO_2Et), 61.61 (t, OCH_2CH_3), 66.17 (d, C_3), 79.94 (s, $OC(CH_3)^3$), 155.22 (s, urethane C=O), 168.59, 172.55 (s, ester and lactam C=O). FABMS *m*/*z*: 317 ($M+1^+$). Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.08; H, 7.48; N, 8.72.

4.9. (3*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-1-(ethoxycarbonylmethyl)-3[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetyloxy]piperidin-2-one 10

(*S*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] (0.17 g, 0.52 mmol) was added to a stirred solution of **9** (0.15 g, 0.47 mmol) and 4-DMAP (0.29 g, 2.35 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the mixture stirred at 0 °C for 1 h. The reaction mixture was concentrated in vacuo and the residue purified by short column chromatography (hexane–AcOEt = 2:1) to give **10** (0.24 g, 95%) of MTPA ester as a single compound. The enantiomeric excess of **10** was more than 95% based on ^{1}H NMR analysis of this MTPA ester. $[\alpha]_D^{22} = -31.0$ (*c* 0.98, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 6.96 Hz, OCH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 2.15–2.25 (m, 1H, C_4–H), 2.52–2.60 (m, 1H, C_4–H), 3.30–3.38 (m, 1H, C_6–H), 3.56 (s, 3H, OCH_3), 3.60–3.68 (m, 1H, C_6–H), 3.90, 4.31 (d, 2H, J = 17.6 Hz, CH_2CO_2Et), 4.15–4.25 (m, 1H, C_5–H), 4.19 (q, 2H, J = 6.96 Hz, OCH_2CH_3), 5.37 (br d, 1H, NH), 5.50–5.56 (m, 1H, C_3–H), 7.40–7.65 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.08 (q, OCH_2CH_3), 28.33 (q, $OC(CH_3)_3$), 33.29 (t, C_4), 43.07 (d, C_5), 48.60 (t, C_6), 53.05 (t, CH_2CO_2Et), 55.51 (q, OCH_3), 61.65 (t, OCH_2CH_3), 68.70 (d, C_3), 80.11 (s, $OC(CH_3)_3$), 121.74 (s, CCF_3), 124.61 (s, CF_3), 127.87, 128.41, 129.71, 131.65 (Ph), 155.09 (s, urethane C=O), 165.60 (s, lactam C=O), 165.76, 168.63 (s, ester C=O). FABMS *m*/*z*: 533 ($M+1^+$).

4.10. (3*R*,5*S*)-5-[(*tert*-Butoxycarbonyl)amino]-1-[(ethoxycarbonyl)methyl]-3-[(methanesulfonyl)oxy]piperidin-2-one 11

Methanesulfonyl chloride (0.16 g, 1.39 mmol) was added dropwise to a solution of **9** (9.40 g, 1.26 mmol) and Et_3N (0.17 g, 1.64 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture stirred at 0 °C for 6 h. The solvent was evaporated in vacuo and the residue diluted with saturated aqueous Na_2CO_3 (10 mL), and the mixture was extracted with AcOEt (40 mL). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 1:3) to give **11** (0.43 g, 88%), as a colorless

oil. $[\alpha]_D^{23} = -5.1$ (*c* 1.17, MeOH). IR (neat): 3369, 1739, 1683. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, $J = 6.96$ Hz, OCH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 2.20–2.32 (m, 1H, C_4–H), 2.55–2.62 (m, 1H, C_4–H), 3.27 (s, 3H, SO_2CH_3), 3.37 (dd, 1H, $J = 6.96$, 12.10 Hz, C_6–H), 3.60 (dd, 1H, $J = 4.40$, 12.10 Hz, C_6–H), 3.88 (d, 1H, $J = 17.20$ Hz, CH_2CO_2Et), 4.08–4.20 (m, 1H, C_5–H), 4.22 (q, 2H, $J = 6.96$ Hz, OCH_2CH_3), 4.28 (d, 1H, $J = 17.20$ Hz, CH_2CO_2Et), 5.13 (dd, 1H, $J = 6.96$, 8.80 Hz, C_3–H), 5.22 (d, 1H, $J = 7.70$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 14.13 (q, OCH_2CH_3), 28.34 (q, $OC(CH_3)_3$), 34.91 (t, C_4), 39.29 (q, SO_2CH_3), 43.04 (t, C_6), 48.92 (t, C_6), 53.36 (t, CH_2CO_2Et), 61.77 (t, OCH_2CH_3), 74.14 (d, C_3), 80.32 (s, $OC(CH_3)_3$), 155.10 (s, urethane C=O), 165.87, 168.36 (s, ester and lactam C=O). FABMS *m*/*z*: 395 ($M+1^+$). HRFABMS *m*/*z*: calcd for $C_{15}H_{27}N_2O_8S$ ($M+1^+$): 395.1486. Found: 395.1480.

4.11. (3*S*,5*S*)-3-Azido-5-[(*tert*-butoxycarbonyl)amino]-1-ethoxycarbonylpiperidin-2-one 12

Sodium azide (0.30 g, 4.60 mmol) was added to a solution of **11** (0.60 g, 1.52 mmol) in DMF (15 mL). The mixture was heated at 70 °C for 8 h. The reaction mixture was diluted with water (10 mL) and the mixture extracted with AcOEt (30 mL). The extract was washed with brine, and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 1:1) to give **12** (0.50 g, 95%) as a colorless oil. $[\alpha]_D^{24} = -123.3$ (*c* 0.63, MeOH). IR (neat): 3332, 2109, 1747, 1712, 1695. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, $J = 6.96$ Hz, OCH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.85–1.96 (m, 1H, C_4–H), 2.29–2.39 (m, 1H, C_4–H), 3.26 (dd, 1H, $J = 5.50$, 12 10 Hz, C_6–H), 3.65 (dd, 1H, $J = 3.67$, 12.10 Hz, C_6–H), 3.74 (d, 1H, $J = 17.20$ Hz, CH_2CO_2Et), 4.05–4.14 (m, 1H, C_5–H), 4.18–4.28 (m, 3H, C_3–H and OCH_2CH_3), 4.48 (d, 1H, $J = 17.20$ Hz, CH_2CO_2Et), 5.46 (br d, 1H, $J = 7.70$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 14.11 (q, OCH_2CH_3), 28.37 (q, $OC(CH_3)_3$), 32.66 (t, C_4), 43.19 (d, C_5), 48.47 (t, C_6), 53.19 (t, CH_2CO_2Et), 56.70 (d, C_3), 61.74 (t, OCH_2CH_3), 80.06 (s, $OC(CH_3)_3$), 155.23 (s, urethane C=O), 167.66, 168.84 (s, ester and lactam C=O). FABMS *m*/*z*: 342 ($M+1^+$). HRFABMS: calcd for $C_{14}H_{24}N_5O_5$ ($M+1^+$): 342.1777. Found: 342.1774.

4.12. (3*S*,5*S*)-3-[(Benzyloxycarbonyl)amino]-5-[(*tert*-butoxycarbonyl)amino]-1-[(ethoxy-carbonyl)methyl]piperidin-2-one 1

A mixture of **12** (0.24 g, 0.70 mmol) and 10% Pd–C (0.05 g) in MeOH (30 mL) was stirred for 3 h at room temperature under an H_2 atmosphere (3 atm). The catalyst was filtered off and the filtrate concentrated in vacuo to give a residue, which was directly used for the next acylation without purification. Triethylamine (0.10 g, 0.98 mmol) and benzyl chloroformate (0.14 g, 0.80 mmol) were added to the solution of the resulting residue in CH_2Cl_2 (20 mL) and the mixture stirred at 0 °C for 6 h. The mixture was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane–AcOEt = 1:1) to give **1** (0.26 g, 82%) as a colorless oil. $[\alpha]_D^{23} = -20.5$ (*c* 1.60, MeOH). IR (neat): 3320, 1712, 1666. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, $J = 6.96$ Hz, OCH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 1.98–2.08 (m, 1H, C_4–H), 2.39–2.48 (m, 1H, C_4–H), 3.26–3.35 (m, 1H, C_6–H), 3.59–3.69 (m, 1H, C_6–H), 3.99 (br d, 1H, $J = 17.20$ Hz, CH_2CO_2Et), 4.04–4.38 (m, 3H, C_3–H, C_5–H, and CH_2CO_2Et), 4.18 (q, 2H, $J = 6.96$ Hz, OCH_2CH_3), 5.10 (s, 2H, CO_2CH_2 Ph), 5.54 (br d, 1H, $J = 7.70$ Hz, NHBoc), 5.88 (d, 1H, $J = 5.13$ Hz, NHCbz), 7.26–7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.11 (q, OCH_2CH_3), 28.37 (q, $OC(CH_3)_3$), 33.23 (t, C_4), 43.71 (d, C_5), 48.59 (t, C_6), 48.66 (d, C_3), 52.59 (t, CH_2CO_2Et), 61.56 (t, OCH_2CH_3), 66.89 (t, CO_2CH_2Ph), 79.86 (s, $OC(CH_3)_3$), 127.99, 128.09, 128.51, 136.36 (Ph), 155.38, 156.29 (s, urethane C=O), 168.92, 169.93 (s, ester and lactam C=O). HRMS *m*/*z*: 450 ($M+1^+$). HRFABMS: calcd for $C_{22}H_{32}N_3O_7$ ($M+1^+$): 450.2240. Found: 450.2238.

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