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Tetrahedron: *Asymmetry* 16 (2005) 1989–1995
Tetrahedron: *Asymmetry*

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

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Received 10 March 2005; accepted 22 April 2005

Abstract—An efficient and stereospecific synthesis of chiral 3,5-diaminoazepan-2-one as a novel conformationally restricted surrogate of 2,4-diaminobutanoyl (Dab)-Gly dipeptide has been achieved by an intramolecular transamidation with a catalytic hydrogenation as the key steps, starting from commercially available *trans*-4-hydroxy-L-proline. This methodology represents a powerful tool for the synthesis of the Dab-Gly dipeptide surrogate as one type of Freidinger ε-lactam.

1. Introduction

Conformationally restricted peptidomimetics are a valuable tool for the search for bioactive conformations, biological potency and metabolic stability relative to the 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,b] and the resulting lactam-bridged dipeptides are often referred to as 'Freidinger lactams'. Consequently, the design and synthesis of novel Freidinger lactams are currently an area of intensive research in the field of peptide and medicinal chemistry.[2,3] In this field, we have recently reported the synthesis of novel (3*S*,5*S*)-3,5-diaminopiperidin-2-one as one example of Freidinger δ-lactams, in which the crucial step was an intramolecular transamidation of 5-azidomethylpyrrolidin-2-one with a catalytic hydrogenation.[4] Intramolecular transamidation is one of the versatile reactions for the ring-transformation of lactam compounds.[5] As an extension of our ongoing program utilizing this reaction in the synthesis of novel Freidinger lactams, we next became interested in developing an effective and stereospecific synthesis of Freidinger ε-lactam. For the Freidinger ε-lactams, syntheses of three types by the substitution pattern on the ε-lactam ring (i.e., unsubstituted, C_7-substituted and dehydro types) have already been reported (Fig. 1).[3] However, synthesis of a Freidinger ε-lactam such as compound **1** possessing an amino function at the C_3 and C_5 positions on the ε-lactam ring is still unknown.

Herein, we report the synthesis of enantiomerically pure 3,5-diaminoazepan-2-one derivative **1** by an intramolecular transamidation with catalytic hydrogenation. Compound **1** can be envisaged as a novel conformationally restricted surrogate of 2,4-diaminobutanoyl (Dab)-Gly dipeptide, in which the conformational restriction is

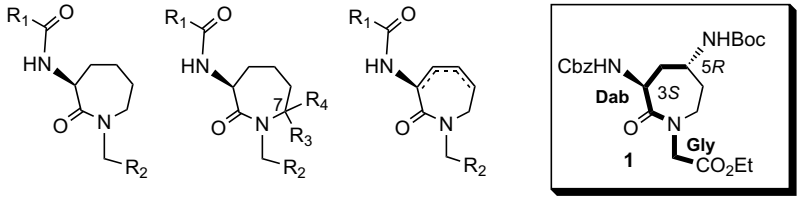

Figure 1. Freidinger ε-lactams.

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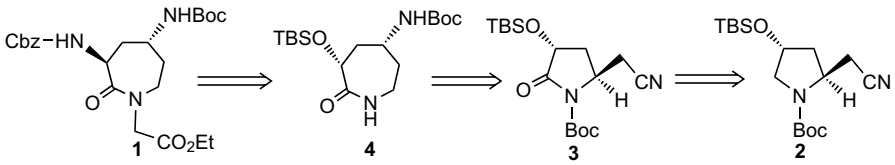
doi:10.1016/j.tetasy.2005.04.017



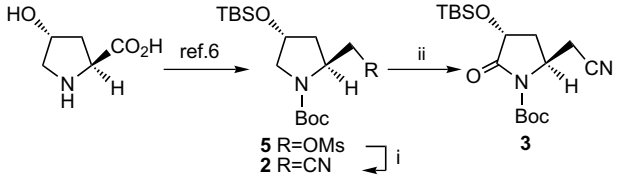
Scheme 1. Retrosynthetic analysis.

caused by the introduction of $-(CH_2)_2-$ linker between the γ-carbon of the 2,4-diaminobutanoic acid and the nitrogen of the glycine.

The retrosynthetic plan for **1** is outlined in Scheme 1. The key step in our strategy was the preparation of ε-lactam **4** from 5-cyanomethylpyrrolidin-2-one **3** via an intramolecular transamidation. Precursor **3** can be obtained through a ruthenium tetroxide (RuO_4) oxidation of 2-cyanomethylpyrrolidine **2**.

2. Results and discussion

The synthesis of target compound **1** began with *N*-Boc-5-cyanomethylpyrrolidin-2-one **3**, which in turn could be easily derived from commercially available *trans*-4-hydroxy-L-proline (Scheme 2).

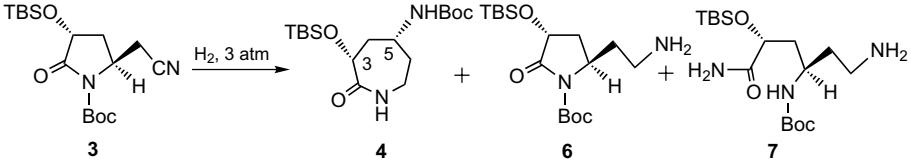


Scheme 2. Reagents and conditions: (i) KCN, 18-crown-6, DMF, 70 °C, 24 h, 90%; (ii) $RuO_2{\cdot}xH_2O$, aq $NaIO_4$, AcOEt, rt, 10 h, 75%.

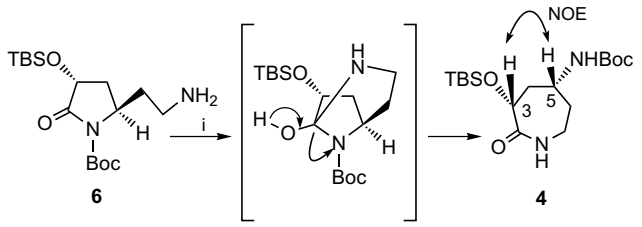
Thus, *N*-Boc-2-(methanesulfonyloxymethyl)pyrrolidine **5** was prepared from *trans*-4-hydroxy-L-proline.[6] Treatment of **5** with potassium cyanide in the presence of 18-crown-6 in dimethylformamide at 70 °C for 24 h afforded *N*-Boc-2-cyanomethylpyrrolidine **2** in 90% yield. The RuO_4 oxidation of **2** using our previously reported reaction conditions ($RuO_2{\cdot}xH_2O$/aq $NaIO_4$, AcOEt, rt)[4,7] gave the requisite *N*-Boc-5-cyanomethylpyrrolidin-2-one **3** in 75% yield as a single product, after column chromatography. With cyano γ-lactam **3** in hand, we examined an intramolecular transamidation by a catalytic hydrogenation under various conditions of catalysts, solvents and temperature (Table 1).

The catalytic hydrogenation of the cyano group in **3** with PtO_2 or 5% Rh–Al at room temperature under hydrogen (3 atm) in MeOH for 48 h afforded the desired NH ε-lactam **4** in 40% or 45% yields, respectively, together with a small amount of aminoethyl γ-lactam **6** (entries 1 and 3), while the reaction between 40 and 45 °C afforded **4** in 45% or 50 % yields, respectively (entries 2 and 4). In the catalytic hydrogenation of most nitriles to primary amines, the formation of secondary and/or tertiary amines as side reaction products is common. To minimize the side reaction, hydrogenation of **3** was next performed in the presence of aqueous ammonia or acetic acid in MeOH (entries 5 and 6). The best result of the intramolecular transamidation of **3** was obtained when the reaction was carried out with 5% Rh–Al in the presence of 5 mol equiv of aqueous ammonia in MeOH at room temperature for 48 h (entry 6). Under these conditions, **4** was obtained in 65% yield, together with carbamoyl compound **7** as a by-product, while compound **6** bearing an amine moiety at the side chain was converted to **4** in 65% yield by refluxing in MeOH for 24 h (Scheme 3).

Table 1. Intramolecular transamidation of **3** with a catalytic hydrogenation



Entry	Conditions				Products (%)		
	Catalyst	Solvent	Temperature (°C)	Time (h)	**4**	**6**	**7**
1	PtO_2	MeOH	rt	48	40	10	0
2	PtO_2	MeOH	40–45	48	45	5	0
3	5% Rh–Al	MeOH	rt	48	45	5	0
4	5% Rh–Al	MeOH	40–45	48	50	5	0
5	5% Rh–Al	MeOH, 1% aq AcOH	rt	48	58	8	0
6	5% Rh–Al	MeOH, 5% aq NH_3	rt	48	65	0	8



Scheme 3. Reagents and conditions: (i) MeOH, reflux, 24 h, 65%.

The stereochemistry at the C_5-position in **4** was determined by NOE experiments. A positive NOE effect between C_3–H (δ 4.50) and C_5–H (δ 4.10) was observed. Accordingly, the C_3–H and C_5–H in **4** was assigned to have a *cis*-configuration. The absolute configuration of **4** was unambiguously determined as (3*R*,5*R*)-**4**. Based on the results of these experiments, the intramolecular transamidation pathway as depicted in Scheme 3 was confirmed.

Next, alkylation of the ε-lactam ring nitrogen of **4** with ethyl bromoacetate using $LiN(TMS)_2$ as a base afforded **8** in 75% yield without epimerization at the C_3 center (Scheme 4). Sequential deprotection of the silyl group with tetra-*n*-butylammonium fluoride (TBAF) and mesylation of the resulting alcohol provided mesylate **11** in 75% 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 ^{1}H NMR spectra of **10** showed the presence of a single stereoisomer, indicating enantiomeric purity >95%. Thus, we are confident that no racemization had occurred during the whole sequence. Displacement of **11** with sodium azide gave azido ε-lactam **12** in 85% yield. Finally, catalytic hydrogenation of **12** using 10% Pd–C followed by protection of the amine moiety with carbobenzyloxy chloride (CbzCl) gave the target Dab-Gly dipeptide surrogate (3*S*,5*R*)-**1** in 82% yield (two steps), in which α- and γ-diamino functions and terminus carboxyl function were differentially protected.

3. Conclusion

We have developed a stereospecific synthesis of novel Freidinger ε-lactam, 3,5-diaminoazepan-2-one derivative **1** as a conformationally restricted surrogate of Dab-Gly dipeptide, by intramolecular transamidation with catalytic hydrogenation as a key step, starting from *trans*-4-hydroxy-L-proline. In addition, compound **1** can be incorporated into biologically important peptides.

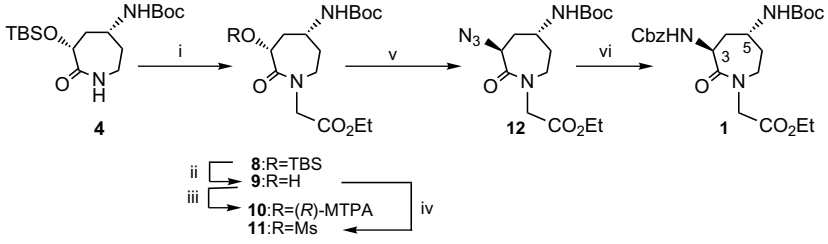
4. Experimental

4.1. General

Melting points were measured on a Yanako MP-S3 micromelting 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. ^{1}H and ^{13}C NMR spectra were measured with a JNM-ECP-500 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as internal standard in $CDCl_3$ solutions. 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}. Flash column chromatography was performed with indicated solvents on Merck silica gel, 230–400 mesh. All solvents were dried and purified before use. The *trans*-4-hydroxy-L-proline used as the chiral starting material was purchased from Sigma Chemical Co. The (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(methanesulfonyloxy)pyrrolidine **5** was prepared from *trans*-4-hydroxy-L-proline according to a literature procedure.[6]

4.2. (2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-cyanomethylpyrrolidine 2

To a solution of **5** (13.7 g, 33.4 mmol) in DMF (120 mL) was added KCN (4.40 g, 67.5 mmol) and 18-crown-6 (0.87 g, 3.30 mmol) at room temperature. The resulting mixture was heated at 70 °C for 24 h, and then diluted with AcOEt (100 mL), washed sequentially with H_2O and 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 **2** (10.2 g, 90%) as a colorless oil. $[\alpha]_D^{23} = -65.7$ (*c* 1.00, MeOH). IR (neat): 2248, 1697. ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 1.92–2.22 (m, 2H, C_3–H_2), 2.67 (dd,



Scheme 4. Reagents and conditions: (i) $BrCH_2CO_2Et$, $LiN(TMS)_2$, THF, 0 °C to rt, 1 h, 75%; (ii) TBAF, THF, rt, 1 h, 82%; (iii) (*S*)-MTPACl, 4-DMAP, CH_2Cl_2, 2 h, 95%; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 8 h, 92%; (v) NaN_3, DMF, 70 °C, 8 h, 85%; (vi) (a) 10% Pd–C/H_2, MeOH, rt, 3 h; (b) CbzCl, Et_3N, CH_2Cl_2, 0 °C, 6 h, 82% (two steps).

1H, J = 2.92, 16.9 Hz, CH_2CN), 3.06 (dd, 1H, J = 5.86, 16.9 Hz, CH_2CN), 3.40–3.45 (m, 2H, C_5–H_2), 4.05–4.20 (m, 1H, C_2–H), 4.38–4.45 (m, 1H, C_4–H). ^{13}C NMR ($CDCl_3$): δ −4.88, −4.79 (q, $Si(CH_3)_2$), 17.78 (s, $SiC(CH_3)_3$), 22.51, 23.51 (t, CH_2CN), 25.66 (q, $SiC(CH_3)_3$), 28.40 (q, $OC(CH_3)_3$), 39.99, 41.03 (t, C_3), 52.65 (d, C_2), 55.65, 55.86 (t, C_5), 69.33, 69.82 (d, C_4), 80.11, 80.50 (s, $OC(CH_3)_3$), 117.84 (s, CN), 155.18 (s, urethane C=O). FABMS m/z: 341 ($M+1^+$). HRFABMS: calcd for $C_{17}H_{33}N_2O_2Si$ ($M+1^+$): 341.2260. Found: 341.2256.

4.3. (3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-5-cyanomethylpyrrolidin-2-one 3

A solution of **2** (12.1 g, 35.5 mmol) in AcOEt (200 mL) was added to a mixture of $RuO_2{\cdot}xH_2O$ (0.2 g) and 10% aqueous $NaIO_4$ (250 mL). The solution was stirred vigorously at room temperature for 10 h. 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 through a Celite pad 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 = 10:1) to give **3** (9.45 g, 75%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **3** as colorless needles, mp 94–95 °C. $[\alpha]_D^{25} = -11.4$ (c 1.00, MeOH). IR (KBr): 2250, 1785, 1762. ^{1}H NMR ($CDCl_3$): δ 0.15, 0.18 (each s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.55 (s, 9H, $OC(CH_3)_3$), 2.20–2.30 (m, 1H, C_4–H), 2.36–2.46 (m, 1H, C_4–H), 2.80–2.92 (m, 2H, CH_2CN), 4.20–4.40 (m, 1H, C_5–H), 4.64 (dd, 1H, J = 8.70, 10.0 Hz, C_3–H). ^{13}C NMR ($CDCl_3$): δ −5.31, −4.66 (q, $Si(CH_3)_2$), 18.11 (s, $SiC(CH_3)_3$), 22.87, 23.66 (t, CH_2CN), 25.76 (q, $SiC(CH_3)_3$), 28.02 (q, $OC(CH_3)_3$), 33.09, 33.39 (t, C_4), 50.30, 52.44 (d, C_5), 69.40, 71.10 (d, C_3), 84.45, 84.49 (s, $OC(CH_3)_3$), 116.85 (s, CN), 150.02 (s, urethane C=O), 171.68 (s, lactam C=O). FABMS m/z: 355 ($M+1^+$). Anal. Calcd for $C_{17}H_{30}N_2O_4Si$: C, 57.60; H, 8.53; N, 7.90. Found: C, 57.46; H, 8.38; N, 7.82.

4.4. General procedure for the intramolecular transamidation of 3 by a catalytic hydrogenation

A mixture of cyano γ-lactam **3** (1.2 g, 3.3 mmol) and catalyst (0.2 g) in MeOH (60 mL) was stirred at room temperature or at 40–45 °C for 48 h under an H_2 atmosphere (3 atm). The catalyst was filtered through a Celite pad and the filtrate concentrated in vacuo to give a residue, which was purified by flash column chromatography ($CHCl_3$–MeOH = 50:1). The results are summarized in Table 1.

4.4.1. (3*R*,5*R*)-5-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)azepan-2-one 4 and (3*R*,5*R*)-5-(2-aminoethyl)-1-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-one 6. Entry 1: Following the general procedure, transamidation of **3** with PtO_2 at room temperature gave **4** (0.48 g, 40%) as a less polar product and **6** (0.12 g, 10%) as a more polar product.

Entry 2: Following the general procedure, transamidation of **3** with PtO_2 at 40–45 °C gave **4** (0.54 g, 45%) and **6** (0.06 g, 5%).

Entry 3: Following the general procedure, transamidation of **3** with 5% Rh–Al at room temperature gave **4** (0.54 g, 45%) and **6** (0.06 g, 5%).

Entry 4: Following the general procedure, transamidation of **3** with 5% Rh–Al at 40–45 °C gave **4** (0.58 g, 48%) and **6** (0.06 g, 5%).

Entry 5: Following the general procedure, transamidation of **3** with 5% Rh–Al at room temperature in a presence of 1% aqueous AcOH (1.2 equiv) was carried out and then saturated aqueous sodium carbonate was added to the mixture. Concentration of the solvent in vacuo gave a residue, which was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified to give **4** (0.70 g, 58%) and **6** (0.09 g, 8%).

4.4.1.1. Less polar 4. Colorless prisms, mp 94–95 °C (isopropyl ether). $[\alpha]_D^{24} = +32.1$ (c 1.30, MeOH). IR (KBr): 3434, 3315, 1700, 1682. ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.43 (s, 9H, $OC(CH_3)_3$), 1.45–1.60 and 1.67–1.78 (m, 2H, C_6–H_2), 1.96–2.05 and 2.15–2.24 (m, 2H, C_4–H_2), 2.90–3.12 and 3.55–3.85 (m, 2H, C_7–H_2), 4.00–4.15 (m, 1H, C_5–H), 4.45–4.60 (m, 1H, C_3–H), 4.93 (br s, 1H, lactam NH), 7.42 (br d, J = 8.06 Hz, BocNH). ^{13}C NMR ($CDCl_3$): δ −5.07, −4.45 (q, $Si(CH_3)_2$), 18.32 (s, $SiC(CH_3)_3$), 25.80 (q, $SiC(CH_3)_3$), 28.40 (q, $OC(CH_3)_3$), 37.25 (t, C_7), 37.47 (t, C_4), 37.66 (t, C_6), 48.66 (d, C_5), 69.97 (d, C_3), 79.48 (s, $OC(CH_3)_3$), 156.40 (s, urethane C=O), 176.38 (s, lactam C=O). FABMS m/z: 359 ($M+1^+$). Anal. Calcd for $C_{17}H_{34}N_2O_4Si$: C, 56.94; H, 9.55; N, 7.81. Found: C, 57.14; H, 9.38; N, 7.75.

4.4.1.2. More polar 6. Colorless viscous oil. $[\alpha]_D^{22} = +8.8$ (c 0.60, MeOH). IR (neat): 3550, 1785, 1765. ^{1}H NMR ($CDCl_3$): δ 0.12, 0.16 (s, 6H, $SiC(CH_3)_2$), 0.94, 0.96 (s, 9H, $SiC(CH_3)_3$), 1.40 (s, 2H, NH_2), 1.49, 1.52 (s, 9H, $OC(CH_3)_3$), 1.75–2.30 (m, 4H, C_4–H_2, $CH_2CH_2NH_2$), 2.65–2.88 (m, 2H, CH_2NH_2), 4.05–4.20 (m, 1H, C_5–H), 4.40–4.52 (m, 1H, C_3–H). ^{13}C NMR ($CDCl_3$): δ −5.03, −4.40 (q, $Si(CH_3)_2$), 18.17 (s, $SiC(CH_3)_3$), 25.76 (q, $SiC(CH_3)_3$), 28.04 (q, $OC(CH_3)_3$), 32.53 (t, C_4), 34.15 (t, $CH_2CH_2NH_2$), 37.08 (t, $CH_2CH_2NH_2$), 51.39 (d, C_5), 70.13 (d, C_3), 84.15 (s, $OC(CH_3)_3$), 150.73 (s, urethane C=O), 173.48 (s, lactam C=O). FABMS m/z: 359 ($M+1^+$). HRFABMS: calcd for $C_{17}H_{35}N_2O_4Si$ ($M+1^+$): 359.2366. Found: 359.2360.

4.4.2. (2*R*,4*R*)-6-Amino-4-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)hexane carboxamide 7. Entry 6: Following the general procedure, transamidation of **3** with 5% Rh–Al in the presence of 5% aqueous NH_3 (5 equiv) at room temperature gave **4** (0.79 g, 65%) as a less polar product and **7** (0.10 g, 8%) as a more polar product.

4.4.2.1. More polar 7. Colorless needles, mp 120–121 °C (AcOEt). $[\alpha]_D^{25} = +8.0$ (*c* 1.03, MeOH). IR (KBr): 3436, 3210, 1693, 1660. ^{1}H NMR ($CDCl_3$): δ 0.11, 0.13 (s, 6H, $Si(CH_3)_2$), 0.93, 0.95 (s, 9H, $SiC(CH_3)_3$), 1.42, 1.47 (s, 9H, $OC(CH_3)_3$), 1.66 (br s, 2H, CH_2NH_2), 1.50–2.20 (m, 4H, C_3–H_2, C_5–H_2), 2.74 (m, 2H, C_6–H_2), 3.95–4.10 (m, 1H, C_4–H), 4.15–4.25 (m, 1H, C_2–H), 5.00–5.10 (m, 1H, NHBoc), 6.20–6.70 (m, 2H, $CONH_2$). ^{13}C NMR ($CDCl_3$): δ −5.33, −4.85 (q, $Si(CH_3)_2$), 18.00 (s, $SiC(CH_3)_3$), 25.75 (q, $SiC(CH_3)_3$), 28.43 (q, $OC(CH_3)_3$), 38.58 (t, C_3, C_5), 39.92 (t, C_6), 43.86 (d, C_4), 70.71 (d, C_2), 78.79 (s, $OC(CH_3)_3$), 155.70 (s, urethane C=O), 177.26 (s, amide C=O). FABMS *m/z*: 376 ($M+1^+$). Anal. Calcd for $C_{17}H_{37}N_3O_4Si$: C, 54.37; H, 9.93; N, 11.19. Found: C, 54.22; H, 9.78; N, 10.94.

4.4.2.2. Preparation of 4 from 6. A solution of **6** (0.45 g, 1.2 mmol) in MeOH (30 mL) was refluxed for 24 h. After cooling, concentration of the solvent in vacuo gave a residue, which was purified by flash column chromatography ($CHCl_3$–MeOH = 50:1) to give **4** (0.29 g, 65%) as a solid. Recrystallization from isopropyl ether gave an analytical sample of **4** as colorless prisms, mp 94–95 °C. $[\alpha]_D^{24} = +7.7$ (*c* 0.95, MeOH). This product was identical by IR and ^{1}H NMR spectra with authentic **4** obtained above.

4.5. (3*R*,5*R*)-5-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-1-(ethoxycarbonylmethyl)azepan-2-one 8

Lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) in THF (1.0 M solution, 10.5 mL) was added to a solution of **4** (1.50 g, 4.18 mmol) in THF (40 mL) at −15 °C under a nitrogen atmosphere, and the reaction mixture stirred for 30 min. Then ethyl bromoacetate (1.40 g, 8.38 mmol) was added to the mixture. After stirring at −15 °C for 1 h, the 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, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane–AcOEt = 2:1) to give **8** (1.40 g, 75%) as a colorless oil. $[\alpha]_D^{25} = -5.4$ (*c* 0.70, MeOH). IR (neat): 3438, 1749, 1712, 1675. ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.27, 1.29 (t, 3H, J = 6.96 Hz, OCH_2CH_3), 1.43 (s, 9H, $OC(CH_3)_3$), 1.85–2.05 (m, 4H, C_4–H_2, C_6–H_2), 3.02–3.12 (m, 1H, C_7–H), 4.00–4.15 (m, 4H, C_5–H, C_7–H, CH_2CO_2Et), 4.17, 4.19 (q, 2H, J = 7.32 Hz, OCH_2CH_3), 4.55–4.63 (m, 1H, C_3–H), 6.10 (br d, 1H, J = 6.60 Hz, NHBoc). ^{13}C NMR ($CDCl_3$): δ −5.05, −5.77 (q, $Si(CH_3)_2$), 14.19 (q, OCH_2CH_3), 18.08 (s, $SiC(CH_3)_3$), 25.78 (q, $SiC(CH_3)_3$), 28.42 (q, $OC(CH_3)_3$), 33.15 (t, C_6), 44.62 (t, C_4, C_7), 48.14 (d, C_5), 51.13 (t, CH_2CO_2Et), 61.21 (t, OCH_2CH_3), 67.20 (d, C_3), 79.00 (s, $OC(CH_3)_3$), 154.91 (s, urethane C=O), 169.23, 173.49 (s, lactam and ester C=O). FABMS *m/z*: 445 ($M+1^+$). HRFABMS: calcd for $C_{21}H_{41}N_2O_6Si$ ($M+1^+$): 445.2009. Found: 445.2002.

4.6. (3*R*,5*R*)-5-(*tert*-Butoxycarbonylamino)-1-(ethoxycarbonylmethyl)-3-hydroxyazepan-2-one 9

TBAF in THF (1.0 M solution, 6.70 mL) was added dropwise to a stirred solution of **8** (0.85 g, 1.91 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 purified by column chromatography (hexane–AcOEt = 1:2) to give **9** (0.52 g, 82%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **9** as colorless needles, mp 95–96 °C. $[\alpha]_D^{23} = -9.2$ (*c* 0.90, MeOH). IR (KBr): 3353, 1745, 1698, 1652. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, J = 7.33 Hz, OCH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 1.48–1.65 (m, 2H, C_6–H_2), 2.04–2.32 (m, 2H, C_4–H), 3.19 (dd, 1H, J = 5.87, 15.80 Hz, C_7–H), 3.55 (dd, 1H, J = 11.36, 15.80 Hz, C_7–H), 3.82 (br s, 1H, OH), 4.06–4.12 (m, 2H, CH_2CO_2Et), 4.20 (q, 2H, J = 7.33 Hz, OCH_2CH_3), 4.26–4.40 (m, 2H, C_3–H, C_5–H), 4.75 (br d, 1H, J = 6.60 Hz, BocNH). ^{13}C NMR ($CDCl_3$): δ 14.16 (q, OCH_2CH_3), 28.39 (q, $OC(CH_3)_3$), 34.20 (t, C_6), 39.95 (t, C_4), 46.91 (t, C_7), 49.87 (d, C_5), 51.16 (t, CH_2CO_2Et), 61.53 (t, OCH_2CH_3), 67.02 (d, C_3), 79.64 (s, $OC(CH_3)_3$), 154.84 (s, urethane C=O), 169.92, 175.55 (s, lactam and ester C=O). FABMS *m/z*: 331 ($M+1^+$). Anal. Calcd for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.48; H, 7.84; N, 8.58.

4.7. (3*R*,5*R*)-5-(*tert*-Butoxycarbonylamino)-1-(ethoxycarbonylmethyl)-3-[(*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyloxy]azepan-2-one 10

(*S*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] (0.16 g, 0.50 mmol) was added to a stirred solution of **9** (0.15 g, 0.45 mmol) and 4-DMAP (0.28 g, 2.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated in vacuo and the residue was 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. Colorless needles, mp 65–66 °C (isopropyl ether). $[\alpha]_D^{25} = -9.3$ (*c* 1.04, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.33, OCH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 1.72–2.42 (m, 4H, C_4–H_2, C_6–H_2), 3.18 (dd, 1H, J = 5.50, 15.80 Hz, C_7–H), 3.58 (s, 3H, OCH_3), 3.55–3.70 (m, 1H, C_7–H), 3.75–3.84 (m, 2H, CH_2CO_2Et), 3.82–4.00 (m, 1H, C_5–H), 4.17 (q, 2H, J = 7.33 Hz, OCH_2CH_3), 4.65–4.82 (m, 1H, C_3–H), 5.43 (br d, 1H, J = 6.60 Hz, BocNH), 7.38–7.70 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.13 (q, OCH_2CH_3), 28.37 (q, $OC(CH_3)_3$), 34.08 (t, C_6), 35.57 (t, C_4), 46.94 (t, C_7), 49.54 (d, C_5), 51.02 (t, CH_2CO_2Et), 55.56 (q, OCH_3), 61.45 (t, OCH_2CH_3), 71.56 (d, C_3), 79.84 (s, $OC(CH_3)_3$), 121.77 (s, CCF_3), 124.63 (s, CF_3), 128.09, 128.31, 129.62, 131.74 (Ph), 154.81 (s, urethane C=O), 165.79, 169.14 (s, lactam and ester C=O). FABMS *m/z*: 547 ($M+1^+$). Anal. Calcd for $C_{25}H_{33}N_2O_8F_3$: C, 54.94; H, 6.08; N, 5.12. Found: C, 54.86; H, 6.00; N, 4.86.

4.8. (3*R*,5*R*)-5-(*tert*-Butoxycarbonylamino)-1-(ethoxycarbonylmethyl)-3-(methanesulfonyloxy)azepan-2-one 11

Methanesulfonyl chloride (0.10 g, 0.87 mmol) was added dropwise to a solution of **9** (0.24 g, 0.72 mmol) and Et_3N (0.17 g, 1.64 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the mixture stirred at 0 °C for 8 h. The mixture was concentrated in vacuo and the residue diluted with saturated aqueous Na_2CO_3 (10 mL) and extracted with AcOEt (40 mL). The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane–AcOEt = 1:2) to give **11** (0.27 g, 92%), as a colorless oil. $[\alpha]_D^{26} = -8.5$ (*c* 0.80, MeOH). IR (neat): 3370, 1743, 1673. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.33 Hz, OCH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 1.68–1.78 (m, 1H, C_6–H), 1.85–1.96 (m, 1H, C_6–H), 2.04–2.13 (m, 1H, C_4–H), 2.35–2.45 (m, 1H, C_4–H), 3.16 (s, 3H, SO_2CH_3), 3.26 (dd, 1H, J = 5.13, 16.12 Hz, C_7–H), 3.62 (dd, 1H, J = 11.40, 16.10 Hz, C_7–H), 3.85–4.00 (m, 2H, CH_2CO_2Et), 4.18, 4.20 (q, 2H, J = 7.33 Hz, OCH_2CH_3), 4.40–4.45 (m, 1H, C_5–H), 4.78–4.82 (m, 1H, C_3–H), 5.30 (br d, 1H, J = 6.80 Hz, BocNH). ^{13}C NMR ($CDCl_3$): δ 14.14 (q, OCH_2CH_3), 28.36 (q, $OC(CH_3)_3$), 33.64 (t, C_6), 37.04 (t, C_4), 39.60 (q, SO_2CH_3), 47.08 (t, C_7), 49.35 (t, C_5), 51.36 (t, CH_2CO_2Et), 61.53 (t, OCH_2CH_3), 75.78 (d, C_3), 79.84 (s, $OC(CH_3)_3$), 154.70 (s, urethane C=O), 168.88, 169.70 (s, lactam and ester C=O). FABMS *m*/*z*: 409 ($M+1^+$). HRFABMS *m*/*z*: calcd for $C_{16}H_{29}N_2O_8S$ ($M+1^+$): 409.1644. Found: 409.1640.

4.9. (3*S*,5*R*)-3-Azido-5-(*tert*-butoxycarbonylamino)-1-(ethoxycarbonylmethyl)azepan-2-one 12

Sodium azide (0.12 g, 1.85 mmol) was added to a solution of **11** (0.25 g, 0.61 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 extracted with AcOEt (30 mL). The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane–AcOEt = 1:1) to give **12** (0.18 g, 85%) as a colorless solid. Recrystallization from AcOEt–isopropyl ether gave an analytical sample of **12** as colorless needles, mp 143–144 °C. $[\alpha]_D^{25} = -26.4$ (*c* 1.05, MeOH). IR (KBr): 3332, 2105, 1758, 1743, 1697. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.33 Hz, OCH_2CH_3), 1.45 (s, 9H, $OC(CH_3)_3$), 1.78–2.25 (m, 4H, C_4–H_2, C_6–H_2), 3.42–3.62 (m, 2H, C_7–H_2), 3.70–3.82 (m, 2H, CH_2CO_2Et), 3.98–4.10 (m, 1H, C_5–H), 4.20 (q, 2H, J = 7.33 Hz, OCH_2CH_3), 4.10–4.45 (m, 1H, C_3–H), 5.05 (br s, 1H, BocNH). ^{13}C NMR ($CDCl_3$): δ 14.16 (q, OCH_2CH_3), 28.40 (q, $OC(CH_3)_3$), 33.28 (t, C_4), 34.58 (t, C_6), 45.81 (t, C_7), 46.73 (d, C_5), 51.26 (t, CH_2CO_2Et), 61.48 (t, OCH_2CH_3), 77.34 (d, C_3), 79.94 (s, $OC(CH_3)_3$), 155.15 (s, urethane C=O), 169.09, 171.26 (s, lactam and ester C=O). FABMS *m*/*z*: 356 ($M+1^+$). Anal. Calcd for $C_{15}H_{25}N_5O_5$: C, 50.69; H, 7.09; N, 19.70. Found: C, 50.54; H, 7.00; N, 19.48.

4.10. (3*S*,5*R*)-3-(Benzyloxycarbonylamino)-5-(*tert*-butoxycarbonylamino)-1-(ethoxycarbonylmethyl)azepan-2-one 1

A mixture of **12** (0.15 g, 0.42 mmol) and 10% Pd–C (0.03 g) in MeOH (30 mL) was vigorously stirred at room temperature for 3 h under an H_2 atmosphere (3 atm). The catalyst was filtered through a Celite pad and the filtrate concentrated in vacuo to give a residue, which was directly used for the next acylation without purification. Triethylamine (0.06 g, 0.60 mmol) and benzyl chloroformate (0.09 g, 0.53 mmol) were added to the solution of the resulting residue in CH_2Cl_2 (10 mL) at 0 °C and the mixture stirred 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, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane–AcOEt = 1:1) to give **1** (0.16 g, 82%) as a colorless oil. $[\alpha]_D^{24} = -15.8$ (*c* 0.88, MeOH). IR (neat): 3354, 1748, 1712, 1660. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.33 Hz, OCH_2CH_3), 1.46 (s, 9H, $OC(CH_3)_3$), 1.75–2.32 (m, 4H, C_4–H, C_6–H), 2.99 (dd, 1H, J = 4.03, 16.12 Hz, C_7–H), 3.95 (dd, 1H, J = 12.82, 16.12 Hz, C_7–H), 4.08–4.26 (m, 3H, C_5–H, CH_2CO_2Et), 4.18 (q, 2H, J = 7.33 Hz, OCH_2CH_3), 5.08, 5.14 (d, 2H, J = 12.45 Hz, CH_2Ph), 5.50 (br d, 1H, J = 7.80 Hz, BocNH), 6.20 (br d, 1H, J = 5.50 Hz, CbzNH), 7.25–7.42 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 14.14 (q, OCH_2CH_3), 28.43 (q, $OC(CH_3)_3$), 30.64 (t, C_6), 36.61 (t, C_4), 45.14 (d, C_7), 47.36 (d, C_5), 48.03 (t, C_3), 50.60 (t, CH_2CO_2Et), 61.45 (t, OCH_2CH_3), 66.76 (t, CO_2CH_2Ph), 79.59 (s, $OC(CH_3)_3$), 127.80, 128.12, 128.54, 136.35 (Ph), 155.70 (s, urethane C=O), 168.94, 172.44 (s, lactam and ester C=O). FABMS *m*/*z*: 464 ($M+1^+$). HRFABMS: calcd for $C_{23}H_{34}N_3O_7$ ($M+1^+$): 464.2397. Found: 464.2390.

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