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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of protected *threo*-β-hydroxy-L-glutamic acid using a chiral aziridine

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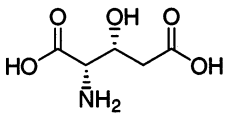
Abstract

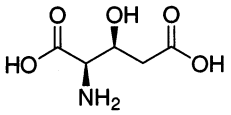
Threo-β-hydroxy-L-glutamic acid derivatives with different carboxylic acid protecting groups were stereoselectively prepared from a chiral aziridine-2-carboxylate using an aldol reaction, stereoselective ketone reduction, and aziridine ring transformation. © 2000 Published by Elsevier Science Ltd.

1. Introduction

It is well known that L-glutamic acid plays important roles in living organisms as an excitatory neurotransmitter acting on many kinds of subclasses of the glutamate receptor[1] and a precursor in a wide variety of metabolic processes.[2] Owing to such biological importance, many scientists have shown their interest in the modification of the structure of this amino acid and also studied analogues of L-glutamic acid to modulate its biological activity.[3,4] In particular, *threo*-β-hydroxyglutamic acid[5,10a] has significant biological activities as an enzyme inhibitor due to the presence of the α,β-amino-hydroxy system. As for its structure, two stereogenic centers and three different functional groups make it useful as a chiral synthon[6] (Fig. 1).



***Threo*-β-hydroxy-*L*-glutamic acid**



***Threo*-β-hydroxy-*D*-glutamic acid**

Figure 1.

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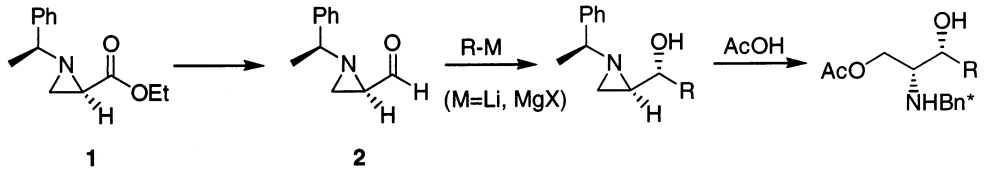
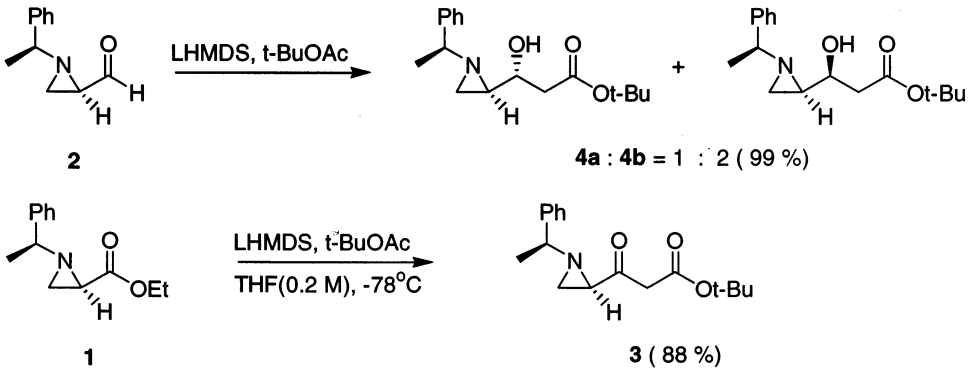
2. Results and discussion

Recently, we reported that enantiomerically pure aziridine-2-carboxylates were prepared from the reaction of enantiomerically pure α-methylbenzylamine and dibromopropionate ester[7] and a variety of 2-amino-1,3-propanediols were obtained from regiospecific ring opening of the aziridine-2-methanols from organometallic addition to the corresponding aziridine-2-carboxaldehyde **2** (Scheme 1).[8,9]



Scheme 1.

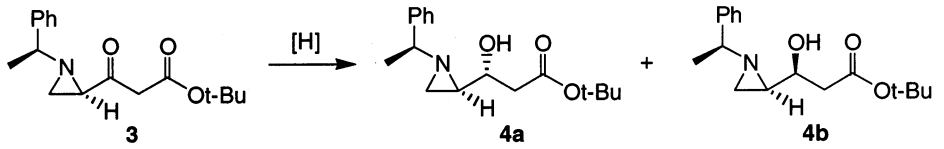
The aldol reaction to the enantiomerically pure aziridine 2-carboxaldehyde **2**, which is a configurationally stable α-amino aldehyde, provides a mixture of two diastereomers **4a** and **4b** almost quantitatively in the diastereomeric ratio of 1:2. However, the precursor of the *threo*-β-hydroxy-L-glutamic acid compound was obtained as the minor product **4a**. We found that the diastereomeric ratio of the aldol products could be controlled by stereoselective reduction[10] of the β-keto ester **3**, which was prepared from the chiral aziridine 2-carboxylate **1** using the same aldol conditions in good yield (Scheme 2).



Scheme 2.

We varied the reduction conditions to obtain high stereoselectivity with numerous hydride reducing reagents, reaction solvents, and reaction temperatures. Of the various conditions, sodium borohydride in IPA at –40°C (Entry 6)[11] provided the best result in terms of selectivity and yield (Scheme 3).

The absolute configuration at C-3 of the aldol products **4a** and **4b** was established by transformation of the aldol products to 2,3-disubstituted chiral aziridines **11a** and **11b**. Treatment of the amino alcohols **10a** and **10b**, which were obtained by an AcOH ring opening reaction, with MsCl and Et_3N in CH_2Cl_2 at −78°C provided the corresponding 2,3-disubstituted chiral aziridines **11a** and **11b** (Scheme 4).[12] It is well known that *cis*-2,3-disubstituted aziridines are thermodynamically more stable than *trans*-2,3-disubstituted aziridines.[13] The aldol product **4a** was readily transformed to *cis*-2,3-disubstituted chiral aziridine **11a** but **4b** provided the

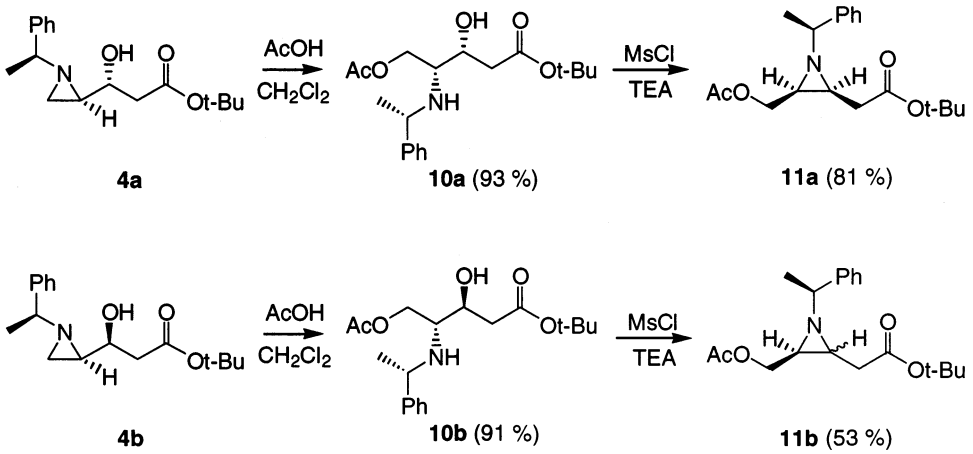


3 4a 4b

Entry	Solvent	Reducing agent	Diastereomer ratio (**4a** : **4b**)	Temp.(°C)	Yield (%)
1	THF	L-selectride	99>>:1	-78	30
2	THF	$Zn(BH_4)_2$	1:99>>	-78	41
3	MeOH	$NaBH_4$	7:1	-78	85
4	MeOH	BER	1.3:1	r.t.	90
5	MeOH	$NaBH_4$	4:1	-98	92
6	**IPA**	**$NaBH_4$**	**10:1**	**-40**	**88**
7	EtOH	$NaBH_4$	4.6:1	-78	78
8	EtOH/H_2O	$NaBH_4$(with NH_4Cl)	1.3:1	r.t.	99
9	IPA/MeOH	$NaBH_4$	3.4:1	-78	79
10	MeOH	$NaBH_4$	4:1	-78	95

Scheme 3.

diastereomeric mixture **11b** of *trans*- and *cis*-2,3-disubstituted chiral aziridines in poor yield. The mesylation of the *erythro* isomer **10b** seems to be followed by elimination due to the presence of Et_3N to provide the α,β-unsaturated ester to which amine adds conjugatively to form the mixture of *cis*- and *trans*-2,3-disubstituted aziridines.

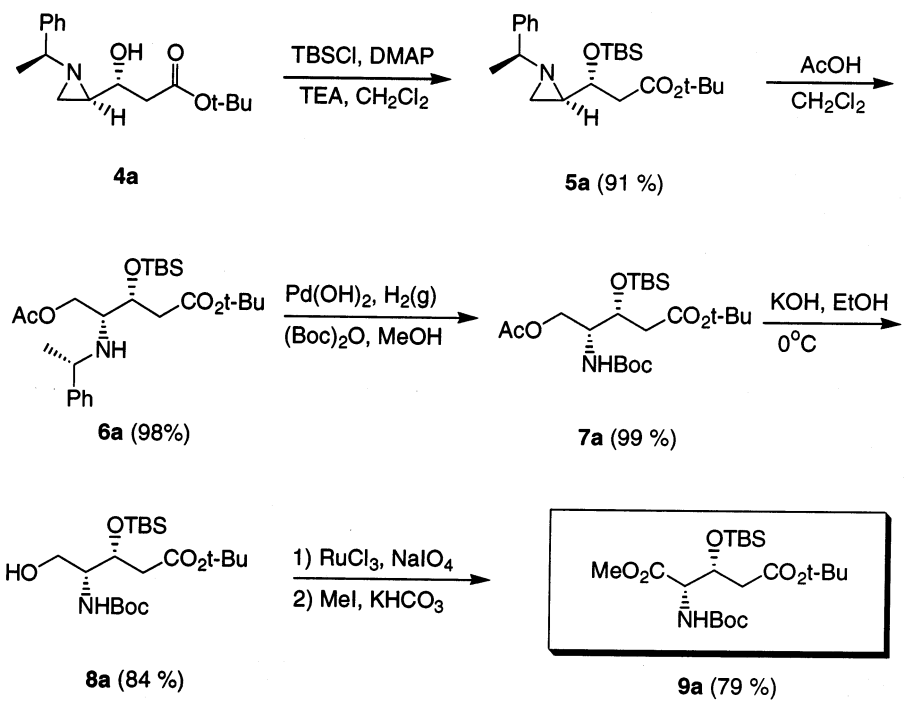


4a **10a** (93 %) **11a** (81 %)

4b **10b** (91 %) **11b** (53 %)

Scheme 4.

For the selective oxidation of the primary alcohol, the secondary alcohol of **4a** was protected with a TBDMS group. The protected aldol product **5a** was treated with AcOH in CH_2Cl_2 to provide the 1-substituted 2-amino-1,3-propandiol **6a** in high yield.[9] The α-methylbenzyl group was replaced with the Boc group by catalytic hydrogenation in the presence of $(Boc)_2O$ to provide the *N*-Boc derivative **7a** quantitatively.[8] The acetyl group in **7a** was readily hydrolyzed by KOH in ethanol to give the amino alcohol **8a**, which was oxidized to the corresponding carboxylic acid using $RuCl_3$ and $NaIO_4$[14] and the crude carboxylic acid was converted to its methyl ester **9a** using MeI in the presence of potassium hydrogen carbonate in DMF at room temperature in 79% yield[15] (Scheme 5). Sequential treatments of **9a** including ester hydrolysis with KOH in ethanol, dimethylation with MeI and $KHCO_3$, and desilylation with TBAF afforded the known 2(*S*)-*tert*-butoxycarbonylamino-3(*S*)-hydroxypentanedioic acid 1,5-dimethyl ester $\{[\alpha]_D^{30} = +32.9$ (*c* 1.0, $CHCl_3$); lit.[3k] $[\alpha]_D^{20} = +28.9$ ($CHCl_3$)$\}$ in 21% yield. We also prepared the C-3 diastereomer of **9a** using the same procedure from the aldol product **4b** in comparable yield.



Scheme 5.

3. Conclusion

In summary, we have developed a methodology to prepare the *threo*-β-hydroxy-L-glutamic acid derivative with different acid protecting groups from chiral aziridine-2-carboxylate through an aldol reaction, stereoselective ketone reduction, and aziridine ring transformation. The two different acid protecting groups allow selective functionalization of the carboxylic acid groups. We can also prepare *threo*-β-hydroxy-D-glutamic acid derivatives by the same protocol if the enantiomer of chiral aziridine-2-carboxylate **1** is used as the starting material.

4. Experimental

4.1. General

Flash chromatography was performed on a Tokyo Rikagikai EF-10 with Merck 230~400 mesh silica gel. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and all melting points were not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz) and Varian Gemini 500 (500 MHz) spectrometers. NMR spectra were recorded in ppm (δ) related to tetramethylsilane ($\delta = 0.00$) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. Elemental analysis was performed by a Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on a Rudolph Autopol III. digital polarimeter. Data are reported as follows: $[\alpha]_D^{25}$ (concentration g/100 mL, solvent). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade. All glassware was dried in an oven at 150°C prior to use. Methylene chloride and triethylamine were dried from calcium hydride prior to use. Small and medium scale purifications were performed by flash chromatography.

4.2. *3-Oxo-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionic acid* tert-*butyl ester* **3**

To a solution of LHMDS (1.46 mL, 1.46 mmol) in 2.90 mL of THF under a nitrogen atmosphere at −78°C was added *t*-BuOAc (0.20 mL, 1.459 mmol). The reaction mixture was stirred for 30 minutes at −78°C and then treated with **1** (160 mg, 0.730 mmol) in 0.80 mL of THF at −78°C. The mixture was stirred for 30 minutes at −78°C and then quenched with 2 mL of water at −78°C then warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (5×5 mL). The combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane/TEA, 10:90:0.01) gave 186 mg (88%) of **3** as yellow oil. $[\alpha]_D^{27} = +70.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 3.35 (d, $J = 15.7$ Hz, 1H), 3.22 (d, $J = 15.7$ Hz, 1H), 2.59 (q, $J = 6.6$ Hz, 1H), 2.33 (d, $J = 2.7$ Hz, 1H), 2.20 (dd, $J = 6.9$, 3.0 Hz, 1H), 1.85 (d, $J = 6.9$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.24, 166.43, 143.62, 128.54, 127.35, 126.45, 81.73, 69.63, 45.96, 44.13, 35.19, 27.91, 23.52. Anal. calcd for $C_{17}H_{23}NO_3$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.62; H, 8.54; N, 5.17.

4.3. *3(*R*)-Hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionic acid* tert-*butyl ester* ***4a*** *and 3(*S*)-hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionic acid* tert-*butyl ester* ***4b***

To a solution of $NaBH_4$ (34.2 mg, 0.905 mmol) in 2.30 mL of IPA at −40°C was added **3** (130 mg, 0.452 mmol). The reaction mixture was stirred for 1 hour at −40°C and then quenched with 2 mL of water at −40°C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×5 mL). The combined organic extracts were washed with 2 mL of brine, dried

over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 30:70) gave 106 mg (80%) of **4a** and 10 mg (8%) of **4b** as a yellow oil. **4a**: $[\alpha]_D^{27} = -46.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 3.71 (m, 1H), 2.49 (q, $J = 6.6$ Hz, 1H), 2.26 (br, OH), 2.15 (dd, $J = 15.4$, 7.7 Hz, 1H), 1.98 (dd, $J = 9.9$, 5.5 Hz, 1H), 1.95 (d, $J = 3.3$ Hz, 1H), 1.65–1.60 (m, 1H), 1.49 (d, $J = 6.6$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 144.21, 128.46, 127.36, 126.81, 80.38, 69.47, 67.31, 41.61, 41.36, 31.10, 27.90, 22.41. Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.03; H, 8.71; N, 4.86. **4b**: $[\alpha]_D^{26} = -23.4$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 3.72 (m, 1H), 3.02 (br, OH), 2.53 (q, $J = 6.6$ Hz, 1H), 2.18 (dd, $J = 16.2$, 4.9 Hz, 1H), 2.11 (dd, $J = 16.2$, 7.4 Hz, 1H), 1.96 (d, $J = 3.3$ Hz, 1H), 1.66–1.60 (m, 1H), 1.47 (d, $J = 3.8$ Hz, 1H), 1.42 (d, $J = 6.3$ Hz, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.33, 144.28, 128.47, 127.28, 126.78, 80.85, 69.55, 67.30, 41.33, 40.35, 30.84, 28.05, 22.80. Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.02; H, 8.72; N, 4.87.

*4.4. 3(*R*)-(*tert-*Butyldimethylsilanyloxy)-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionic acid* tert-*butyl ester* ***5a***

To a solution of TBDMSCl (358 mg, 2.38 mmol) in 4.00 mL of CH_2Cl_2 under a nitrogen atmosphere at room temperature was added DMAP (151 mg, 1.19 mmol) and TEA (0.58 mL, 4.16 mmol). The mixture was stirred for 5 minutes and then treated with **4a** (346 mg, 1.19 mmol) in 2.00 mL of CH_2Cl_2. The mixture was stirred for 17 hours at room temperature and was treated with 4 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×7 mL). The combined organic extracts were washed with 5 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 10:90) gave 438 mg (91%) of **5a** as a colorless oil. $[\alpha]_D^{26} = +1.85$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 3.90 (dd, $J = 11.5$, 6.0 Hz, 1H), 2.43 (q, $J = 6.6$ Hz, 1H), 2.30 (dd, $J = 15.1$, 6.0 Hz, 1H), 2.21 (dd, $J = 14.8$, 6.0 Hz, 1H), 1.83 (d, $J = 3.6$ Hz, 1H), 1.73–1.68 (m, 1H), 1.40 (s, 9H), 1.37 (d, $J = 6.6$ Hz, 3H), 1.35 (d, $J = 6.9$ Hz, 1H), 0.79 (s, 9H), –0.05 (s, 3H), –0.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 144.21, 128.29, 127.17, 127.04, 80.16, 70.14, 69.77, 43.43, 41.56, 30.58, 28.07, 25.78, 22.64, 17.95, –4.65, –4.99. Anal. calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.69; N, 3.45. Found: C, 68.11; H, 9.83; N, 3.53.

*4.5. 3(*S*)-(*tert-*Butyldimethylsilanyloxy)-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionic acid* tert-*butyl ester* ***5b***

90% yield (colorless oil), $[\alpha]_D^{27} = -32.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 3.48 (td, $J = 7.7$, 3.3 Hz, 1H), 2.39 (q, $J = 6.6$ Hz, 1H), 1.96 (dd, $J = 15.4$, 3.3 Hz, 1H), 1.86 (dd, $J = 15.4$, 8.2 Hz, 1H), 1.84 (d, $J = 3.6$ Hz, 1H), 1.64–1.58 (m, 1H), 1.49 (d, $J = 6.9$ Hz, 1H), 1.41 (d, $J = 6.6$ Hz, 3H), 1.35 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), –0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.44, 143.95, 128.34, 127.40, 127.23, 79.87, 71.88, 70.11, 42.92, 42.33, 34.33, 28.11, 25.80, 22.21, 17.98, –4.06, –4.96. Anal. calcd for $C_{23}H_{39}NO_3Si$: C, 68.10; H, 9.69; N, 3.45. Found: C, 68.15; H, 9.66; N, 3.43.

*4.6. 5-Acetoxy-3(*R*)-(*tert*-butyldimethylsilanyloxy)-4(*R*)-(1′(*S*)-α-methylbenzylamino)-pentanoic acid* tert*-butyl ester* **6a**

To a solution of **5a** (191 mg, 0.471 mmol) in 2.36 mL of CH_2Cl_2 under a nitrogen atmosphere at room temperature was added AcOH (0.14 mL, 2.354 mmol). The mixture was stirred for 10 hours and then quenched with 1 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×8 mL). The combined organic extracts were washed with 5 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 10:90) gave 215 mg (98%) of **6a** as a colorless oil. $[\alpha]_D^{27} = -26.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H), 4.22 (dd, $J = 11.2$, 5.4 Hz, 1H), 4.12 (dd, $J = 5.9$, 2.9 Hz, 1H), 4.05 (dd, $J = 11.2$, 6.8 Hz, 1H), 3.95 (q, $J = 6.8$ Hz, 1H), 2.71 (dd, $J = 16.1$, 6.3 Hz, 1H), 2.64 (m, 1H), 2.30 (dd, $J = 16.1$, 8.7 Hz, 1H), 2.07 (s, 3H), 1.38 (s, 9H), 1.30 (d, $J = 6.8$ Hz, 3H), 0.85 (s, 9H), –0.01 (s, 3H), –0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.90, 170.87, 145.54, 128.36, 126.92, 126.82, 80.21, 69.17, 63.41, 56.69, 55.69, 37.70, 28.03, 25.79, 25.28, 20.93, 17.92, –4.74, –5.17. Anal. calcd for $C_{25}H_{43}NO_5Si$: C, 64.48; H, 9.31; N, 3.01. Found: C, 64.46; H, 9.36; N, 3.08.

*4.7. 5-Acetoxy-3(*S*)-(*tert*-butyldimethylsilanyloxy)-4(*R*)-(1′(*S*)-α-methylbenzylamino)-pentanoic acid* tert*-butyl ester* **6b**

94% yield (colorless oil), $[\alpha]_D^{25} = -30.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5H), 4.35 (dd, $J = 11.4$, 4.0 Hz, 1H), 4.15 (td, $J = 7.0$, 4.5 Hz, 1H), 4.07 (dd, $J = 11.5$, 3.1 Hz, 1H), 3.94 (q, $J = 6.4$ Hz, 1H), 2.26–2.49 (m, 2H), 2.38 (dd, $J = 16.1$, 4.5 Hz, 1H), 2.11 (s, 3H), 1.47 (s, 9H), 1.28 (d, $J = 6.5$ Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.03, 171.02, 145.31, 128.35, 126.97, 126.94, 80.16, 69.41, 61.00, 58.32, 54.75, 42.00, 28.10, 25.72, 25.40, 20.93, 17.86, –4.67, –5.12. Anal. calcd for $C_{25}H_{43}NO_5Si$: C, 64.48; H, 9.31; N, 3.01. Found: C, 64.52; H, 9.29; N, 3.08.

*4.8. 5-Acetoxy-4(*R*)-*tert*-butoxycarbonylamino-3(*R*)-(*tert*-butyldimethylsilanyloxy)-pentanoic acid* tert*-butyl ester* **7a**

To a solution of **6a** (123 mg, 0.264 mmol) in 1.30 mL of MeOH was added $Pd(OH)_2$ (25 mg, 20 wt%) and $(Boc)_2O$ (115 mg, 0.528 mmol). The mixture was stirred at a balloon pressure of hydrogen for 3 hours at room temperature. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 10:90) gave 119 mg (99%) of **7a** as a colorless oil. $[\alpha]_D^{26} = +0.60$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (d, $J = 8.8$ Hz, NHBoc), 4.32 (br, 1H), 4.10 (br, 1H), 3.99–3.93 (m, 2H), 2.51 (dd, $J = 16.1$, 7.3 Hz, 1H), 2.40 (dd, $J = 16.1$, 5.4 Hz, 1H), 2.06 (s, 3H), 1.46 (s, 18H), 0.89 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.59, 169.97, 155.42, 80.92, 79.47, 67.49, 63.36, 52.45, 40.57, 28.26, 28.01, 25.78, 20.73, 17.93, –4.76, –5.19. Anal. calcd for $C_{22}H_{43}NO_7Si$: C, 57.24; H, 9.39; N, 3.03. Found: C, 57.25; H, 9.48; N, 3.07.

*4.9. 5-Acetoxy-4(*R*)-*tert*-butoxycarbonylamino-3(*S*)-(*tert*-butyldimethylsilanyloxy)-pentanoic acid* tert*-butyl ester* **7b**

97% yield (colorless oil), $[\alpha]_D^{27} = -3.95$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, $J = 8.2$ Hz, NHBoc), 4.27–4.21 (m, 3H), 3.87 (br, 1H), 2.521 (dd, $J = 16.5$, 6.3 Hz, 1H), 2.43 (dd,

$J=16.5$, 5.8 Hz, 1H), 2.07 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H), 0.88 (s, 9H), 0.087 (s, 3H), 0.074 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.85, 170.33, 55.26, 80.95, 79.55, 68.95, 63.11, 54.02, 41.25, 28.32, 28.09, 25.74, 20.83, 17.94, −4.58, −5.15. Anal. calcd for $C_{22}H_{43}NO_7Si$: C, 57.24; H, 9.39; N, 3.03. Found: C, 57.24; H, 9.61; N, 3.13.

4.10. *4(*R*)*-tert-*Butoxycarbonylamino-3(*R*)-(*tert-*butyldimethylsilanyloxy)-5-hydroxy-pentanoic acid* tert-*butyl ester* ***8a***

To a solution of **7a** (92 mg, 0.199 mmol) in 1.00 mL of EtOH at 0°C was added KOH (13.4 mg, 0.239 mmol). The mixture was stirred for 10 minutes at 0°C and then quenched with 1 mL of water. The product was extracted with CH_2Cl_2 (7×7 mL) and the combined organic extracts were washed with 4 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 20:80) gave 70 mg (84%) of **8a** as a colorless oil. $[\alpha]_D^{27}=-6.45$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (d, $J=7.8$ Hz, NHBoc), 4.34–4.32 (m, 1H), 3.73–3.62 (m, 3H), 2.53 (dd, $J=16.1$, 7.8 Hz, 1H), 2.41 (dd, $J=16.1$, 5.4 Hz, 1H), 1.46 (s, 9H), 1.45 (s, 9H), 0.89 (s, 9H), 0.115 (s, 3H), 0.096 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.35, 156.45, 80.97, 79.61, 70.61, 63.57, 55.61, 40.69, 28.34, 28.06, 25.81, 17.95, −4.57, −5.00. Anal. calcd for $C_{20}H_{41}NO_6Si$: C, 57.24; H, 9.85; N, 3.34. Found: C, 57.28; H, 9.82; N, 3.39.

4.11. *4(*R*)*-tert-*Butoxycarbonylamino-3(*S*)-(*tert-*butyldimethylsilanyloxy)-5-hydroxy-pentanoic acid* tert-*butyl ester* ***8b***

87% yield (colorless oil), $[\alpha]_D^{27}=-0.90$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (br, NHBoc), 4.39 (m, 1H), 3.92 (dd, $J=11.3$, 8.0 Hz, 1H), 3.67–3.58 (m, 2H), 2.96 (br, OH), 2.48 (d, $J=6.0$, 2H), 1.46 (s, 18H), 0.88 (s, 9H), 0.14 (s, 3H), 0.098 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.94, 155.78, 81.01, 79.50, 70.91, 62.36, 55.22, 41.04, 28.34, 28.06, 25.75, 17.90, −4.82, −5.08. Anal. calcd for $C_{20}H_{41}NO_6Si$: C, 57.24; H, 9.85; N, 3.34. Found: C, 57.24; H, 9.82; N, 3.33.

4.12. *2(*S*)*-tert-*Butoxycarbonylamino-3(*R*)-(*tert-*butyldimethylsilanyloxy)-pentanedioic acid 5*-tert-*butyl ester 1-methyl ester* ***9a***

To a vigorously stirred mixture of **8a** (70 mg, 0.167 mmol) and 0.84 mL of a 1/1/1.5 $CCl_4/H_2O/CH_3CN$ mixture at room temperature was added $RuCl_3$ (0.69 mg, 0.0033 mmol) and $NaIO_4$ (146 mg, 0.684 mmol). The reaction mixture was stirred for 7 hours and then quenched with 2 mL of water at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10×7 mL). The combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To a solution of the crude acid in 0.84 mL of DMF were added $KHCO_3$ (50 mg, 0.498 mmol) and MeI (0.021 mL, 0.334 mmol). The reaction mixture was stirred for 5 hours at room temperature and then quenched with 2 mL of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×7 mL). Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 20:80) gave 59 mg (79%) of **9a** as a colorless oil. $[\alpha]_D^{27}=+10.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300

MHz, $CDCl_3$) δ 5.11 (d, $J=9.9$ Hz, NHBoc), 4.67 (m, 1H), 4.44 (dd, $J=9.9$, 1.4 Hz, 1H), 3.72 (s, 3H), 2.54 (dd, $J=16.5$, 7.7 Hz, 1H), 2.38 (dd, $J=16.5$, 5.5 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 9H), 0.82 (s, 9H), 0.038 (s, 3H), −0.003 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.29, 169.81, 155.89, 81.04, 79.83, 69.49, 57.61, 52.13, 40.44, 28.28, 28.04, 25.64, 17.84, −4.64, −5.34. Anal. calcd for $C_{21}H_{41}NO_7Si$: C, 56.35; H, 9.23; N, 3.13. Found: C, 56.16; H, 9.26; N, 3.23.

4.13. 2(S)-tert-Butoxycarbonylamino-3(S)-(tert-butyldimethylsilanyloxy)-pentanedioic acid 5-tert-butyl ester 1-methyl ester **9b**

84% yield (colorless oil), $[\alpha]_D^{27}=+99.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (br, NHBoc), 4.42 (m, 2H), 3.75 (s, 3H), 2.56 (dd, $J=17.0$, 6.0 Hz, 1H), 2.48 (dd, $J=16.8$, 7.1 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H), 0.86 (s, 9H), 0.112 (s, 3H), 0.059 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.36, 169.97, 154.87, 80.80, 79.73, 70.10, 58.48, 52.03, 40.78, 28.25, 28.06, 25.62, 17.91, −4.80, −5.12. Anal. calcd for $C_{21}H_{41}NO_7Si$: C, 56.35; H, 9.23; N, 3.13. Found: C, 56.31; H, 9.25; N, 3.16.

4.14. [3(S)-Acetoxymethyl-1-(1′(S)-α-methylbenzyl)-aziridin-2(S)-yl]-acetic acid tert-butyl ester **11a**

To a solution of **10a** (114 mg, 0.324 mmol) in 16.00 mL of CH_2Cl_2 under a nitrogen atmosphere at −78°C was added TEA (0.45 mL, 3.244 mmol). The mixture was stirred for 15 minutes at −78°C and treated with MsCl (0.126 ml, 1.480 mmol). The reaction mixture was warmed to room temperature and quenched with 1 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×9 mL). The combined organic extracts were washed with 7 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 20:80) gave 87 mg (81%) of **11a** as a colorless oil. $[\alpha]_D^{27}=-8.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 4.23 (dd, $J=11.7$, 4.9 Hz, 1H), 4.05 (dd, $J=11.7$, 7.3 Hz, 1H), 2.63 (q, $J=6.8$ Hz, 1H), 2.47 (dd, $J=16.6$, 4.9 Hz, 1H), 2.21 (dd, $J=16.6$, 6.8 Hz, 1H), 2.09 (s, 3H), 1.93 (m, 2H), 1.39 (d, $J=6.8$ Hz, 3H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.83, 170.40, 144.22, 128.27, 126.94, 126.62, 80.62, 69.20, 63.69, 40.73, 38.81, 35.36, 27.89, 23.22, 20.83. Anal. calcd for $C_{17}H_{23}NO_3$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.42; H, 8.17; N, 4.23.

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