

Synthesis of (–)-Tabtoxinine-β-lactam, the Phytotoxin of Tobacco Wildfire Disease

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Received 5 March 2007; revised 8 May 2007

This paper is dedicated to the memory of Dr. Takeyoshi Sugiyama who passed away in 1999 at 53 years of age.

Abstract: Synthesis of (–)-tabtoxinine-β-lactam and its (3*R*)-isomer, the cause of tobacco wildfire disease, was achieved from L-serine using a zinc-mediated coupling reaction, Sharpless asymmetric dihydroxylation and lactamization of β-mesyloxy benzylhydroxamate amide as the key steps.

Key words: tabtoxinine-β-lactam, β-lactam, amino acids, total synthesis, natural products

Wildfire disease, caused by infection of *Pseudomonas syringae* pv. *tabaci*, has been the most serious pest for tobacco since the early twentieth century.¹ A phytotoxic compound, tabtoxin, was isolated from the phytopathogen² and its structure was finally established by Stewart as **2** (Figure 1).³ Tabtoxin (**2**) and its serine homologue **3**⁴ were later found to be inactive precursors of the true toxin, tabtoxinine-β-lactam (TβL, **1**)⁵ which is produced by host plant peptidases⁶ and causes chlorosis by irreversible inactivation of the host plant glutamine synthetase (GS).⁷ Although **2** is available by fermentation (13 mg/L),³ hydrolysis of the amide bond is complicated by isomerization to stable isotabtoxins (**4** and **5**) or tabtoxinine-δ-lactam (**6**) ($t_{1/2}$ = 24 h at pH 7.0 and 15 min at pH 4.5). TβL is expected to be a selective pesticide because the tabtoxin resistance gene (*ttr*) has been cloned⁸ and a tabtoxin-resistant protein (TTR) was characterized.⁹ Thus, an effective synthetic procedure for the synthesis of TβL has been desired. In addition to synthetic studies¹⁰ of (±)-**1**,^{11a} (–)-**1**,^{11b} its analogues,¹² **2**¹³ and tabtoxinine-δ-lactam **4**,¹⁴ we have reported a short and efficient synthesis of (–)-**1** and (3*R*)-**1** as a preliminary communication.¹⁵ Herein we describe details for the synthesis of the latter two compounds.

Our synthetic plan is depicted in Scheme 1. We selected an intramolecular S_N2 reaction of the amide anion **A** for the key β-lactam ring closure. The chirality of the tertiary oxygen function could be constructed by Sharpless dihydroxylation¹⁶ of the double bond of **B**. Such a carbon framework would be easily accessible using a metal-mediated coupling reaction between the L-serine derivative

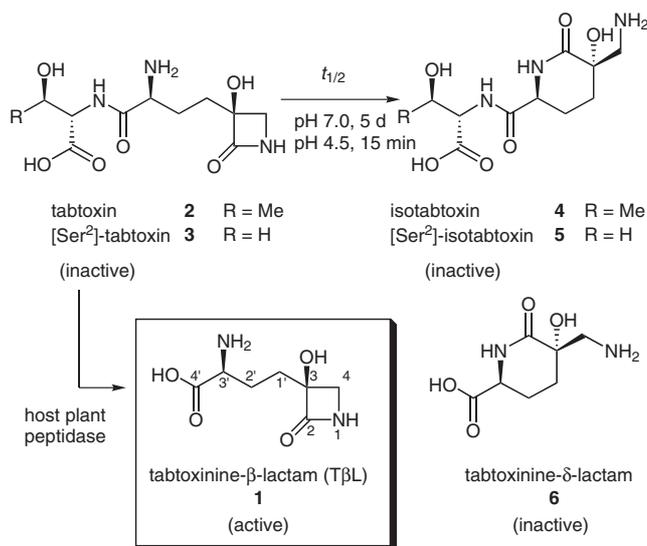
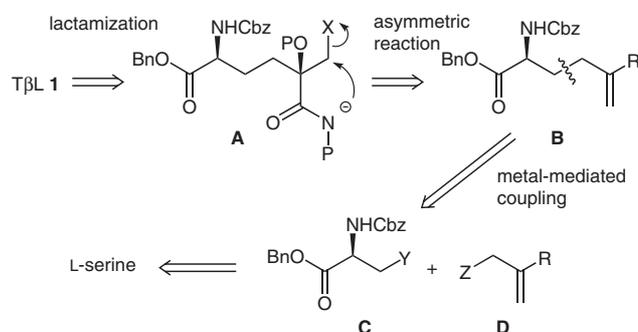


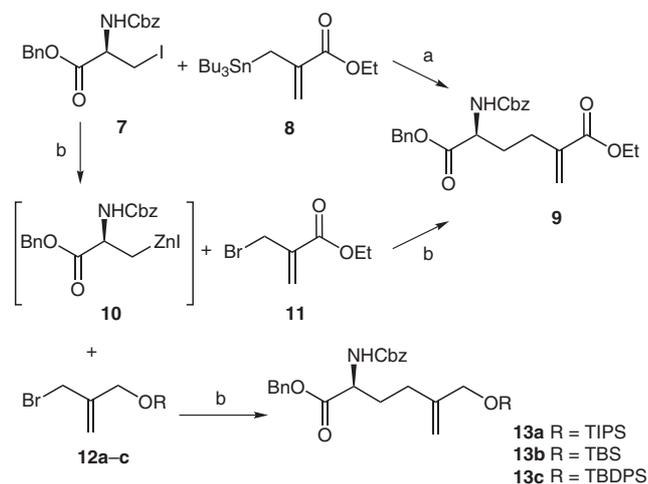
Figure 1 Tabtoxinine-β-lactam and related compounds

C and the C₄-fragment **D** (Y = metal and Z = halogen, or vice versa).

Scheme 2 shows the coupling reaction. L-Serine was converted into the known iodide **7** (= **C**,^{17b} four steps, 79% yield), which was coupled with allylic stannane **8**^{17a} using Baldwin's radical methodology¹⁷ to give **9** (= **B**) in 61% yield. Barton et al. also reported a synthesis of **9** by a decarboxylative coupling reaction.¹⁸ We then tried an alternative method using a zinc-mediated coupling reaction.¹⁹ Thus, the iodide **7** was treated with active zinc in order to generate alkyl zinc iodide **10**, which reacted with the al-



Scheme 1 Retrosynthetic analysis of **1**



Scheme 2 Synthesis of the carbon skeleton **B**: a) AIBN, toluene, 70 °C (61%); b) i. Zn, DMF, r.t., 20 min; ii. bromide, CuCN·2LiCl, DMF [**9** (98%), **13a** (87%), **13b** (85%), **13c** (80%)].

lylic bromides **11**^{19b,20} to afford **9** in 98% yield. In a similar procedure, coupling with silyl ethers **12a**,²¹ **12b**²² and **12c**²³ gave **13a**, **13b** and **13c**, respectively.

Construction of the tertiary hydroxy group was achieved by Sharpless asymmetric dihydroxylation (Table 1).¹⁶ Although diastereoselectivities were low for the α,β -unsaturated ester **9** (entries 1–3), results for silyl ethers **13a-c** (entries 4–7) were satisfactory (90–95% de).^{16b} This may be due to the steric bulk of the silicon group. The yield of **15c β** was only 35% because of the low solubility of **13c** (entry 8), however, higher temperature resulted in loss of diastereomeric purities (entry 9 and 10).

The key β -lactam ring formation step was studied using Haaf and Ruchardt's conditions.²⁴ In preliminary studies (Scheme 3), the *exo*-olefin of **16**²⁵ was dihydroxylated to **17** and the ethoxy group was substituted with amine to give amide **18**. The primary hydroxy group was tosylated to **19** and the tertiary hydroxy was protected with a trimethylsilyl (TMS) group, giving **20**; protection of the tertiary hydroxy group was necessary in order to avoid epoxy ring formation. Ring closure proceeded to give the β -lactam **21** in 80% yield when sodium hydride was used as base.

Scheme 4 shows the total synthesis of **1**. 2,2,6,6-Tetramethylpiperidine *N*-oxyl (TEMPO) oxidation²⁶ of the primary hydroxy group of **15a β** afforded carboxylic acid **24 β** , which was condensed with (benzyloxy)amine to give benzyl hydroxamate **25 β** . The triisopropylsilyl (TIPS) group was then removed to give diol **26 β** . Selective tosylation proved troublesome since preferential *N*-tosylation at the hydroxamate occurred using tosyl chloride with either pyridine or triethylamine. Instead, mesylation was successful and the resulting monomesylate **27 β** fortunately crystallized. The minor α -diastereomer was removed by a single recrystallization to give a stereochemically pure sample. The tertiary hydroxy group was protected as a *tert*-butyldimethylsilyl (TBS) ether to afford **28 β** ; a tri-

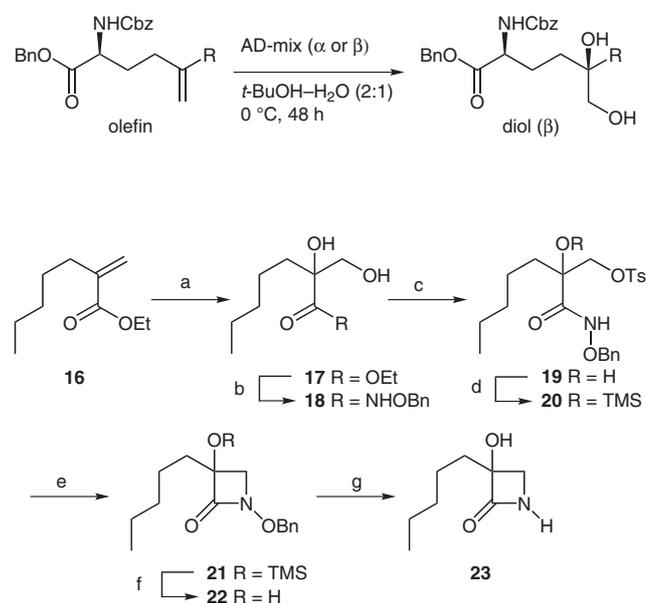
Table 1 Asymmetric Dihydroxylation

Entry	Olefin (R)	AD-mix	Diol ^a	Yield (%)	de ^b (%)
1		– ^c	14a	99	6
2	9 (CO ₂ Et)	β	14β	88	38
3		α	14a	78	23
4	13a (CH ₂ OTIPS)	β	15aβ	85	95
5		α	15aα	94	94
6	13b (CH ₂ OTBS)	β	15bβ	94	90
7		α	15bα	72	90
8	13c (CH ₂ OTBDPS)	β	15cβ	35	87
9		β	15cβ	75	82
10		α	15cα	58	68

^a Orientation of the hydroxy group was attributed from the final product (–)-**1**.

^b Diastereomeric excess (de) was determined by HPLC analysis using a Daicel CHIRALCEL[®] OD column.

^c Reaction conditions: OsO₄ (cat.), NMO (2 equiv), MeCN–H₂O (2:1).



Scheme 3 Model studies of β -lactam formation: a) K₂OsO₂(OH)₄, K₃Fe(CN)₆, K₂CO₃, *t*-BuOH–H₂O (91%); b) NH₂OBn·HCl, AlMe₃, PhMe (58%); c) TsCl, pyridine (quant.); d) TMSOTf, 2,6-lutidine, CH₂Cl₂ (88%); e) NaH, THF (80%); f) AcOH–THF–H₂O (1:2:2), r.t. (quant.); g) H₂, Raney-Ni, MeOH (54%).

methylsilyl (TMS) group at this position was unable to withstand the conditions of the next step. The diastereomeric purity (~100% de) was determined by HPLC analysis of **28β**. β-Lactam formation was achieved using potassium hexamethyldisilazide (KHMDS) to afford **29β**, with debenzylated acid **30β** as a by-product. Use of sodium hydride increased the yield of **29β**. Deprotection of the TBS group of **29β** and **30β** followed by hydrogenolysis on Raney-Ni gave (–)-**1**. The specific optical rotation was found to be in good agreement with the literature value {[α]_D²⁶ –24 (c 0.14, H₂O); lit.^{11c} [α]_D²⁵ –23.7 (c 0.30, H₂O)}. The overall yield was 28% in 12 steps from **7** and 24% in 15 steps from L-serine.

In a similar manner as described for (–)-**1**, the (3*R*)-isomer, (+)-(3*R*)-**1**, was synthesized from **15α** {[α]_D²⁵ +38 (c 0.09, H₂O); lit.^{11c} [α]_D²⁵ +35.0 (c 0.22, H₂O)}.²⁷ The overall yield was 11% from **7**.

In conclusion, the stereoselective synthesis of a phytopathogenic compound of tobacco wildfire disease (–)-tab-

toxinine-β-lactam [(–)-**1**], was achieved in 15 steps, 24% overall yield from L-serine, using zinc-mediated coupling, Sharpless asymmetric dihydroxylation and β-lactam formation from the protected hydroxamate as key steps.

Melting points are uncorrected. Elemental analysis was carried out with a Perkin–Elmer 2400II CHN analyzer. Optical rotation values were recorded on a Horiba SEPA 300 polarimeter. HPLC was performed with a Hitachi L-6000 pump and a Hitachi L-4200 UV-Vis detector. IR spectra were recorded by a Jasco Report-100 infrared spectrometer. FT-IR spectra were recorded on a Jasco 4100 infrared spectrometer. ¹H- and ¹³C NMR spectra were recorded on Varian Gemini 2000 (300 MHz for ¹H and 75 MHz for ¹³C), Varian Unity Inova 500 (500 MHz for ¹H and 125 MHz for ¹³C) and Varian Unity Inova 600 (150 MHz for ¹³C) spectrometers using TMS as an internal standard. EI and FAB mass spectra were recorded with a Jeol JMS-700 spectrometer using *m*-nitrobenzyl alcohol (NOBA) as matrix (FAB). Merck silica gel 60 (70–230 mesh) was used for column chromatography.

1-Benzyl 6-Ethyl (S)-2-Benzoyloxycarbonylamino-5-methylene-hexanedioate (**9**): Tin Coupling

A solution of iodide **7** (8.05 g, 18.5 mmol), **8** (14.9 g, 37.0 mmol, 2.0 equiv) and AIBN (0.60 g) in anhyd toluene (220 mL) was stirred at 70 °C for 3 h. After the reaction mixture was cooled to r.t., KF (6.4 g) was added and the resulting suspension was stirred for 1 d. The mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc, 10:1→5:1) to give **9** (4.82 g, 11.3 mmol, 61%) as a colorless oil.

Zinc Coupling

A suspension of Zn powder (7.18 g, 110 mgatom, 6.0 equiv) and 1,2-dibromoethane (1.0 g, 5.5 mmol, 0.3 equiv) in DMF (20 mL) was stirred at 60 °C for 30 min under nitrogen. TMSCl (0.060 g, 0.55 mmol, 0.03 equiv) was added and the mixture was stirred at 60 °C for a further 30 min. Iodide **7** (8.05 g, 18.3 mmol) in DMF (16 mL) was added dropwise and the mixture was stirred at 60 °C for 10 min. The mixture was cooled to –55 °C and a solution of CuCN·2LiCl (3.19 g, 18.3 mmol 1.0 equiv) in DMF (16 mL) was added at –55 °C. The mixture was warmed to 0 °C and stirred for 10 min then again cooled to –55 °C and bromide **11** (4.11 g, 21.4 mmol, 1.2 equiv) was added. After stirring for 6 h, unreacted Zn was filtered through a Celite pad, sat. aq. NH₄Cl (20 mL) was added to the filtrate and the mixture was extracted into EtOAc (3 × 100 mL). The combined organic layer was washed with brine (10 mL), dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give **9**.

The spectroscopic data were in good agreement with those reported.¹⁸

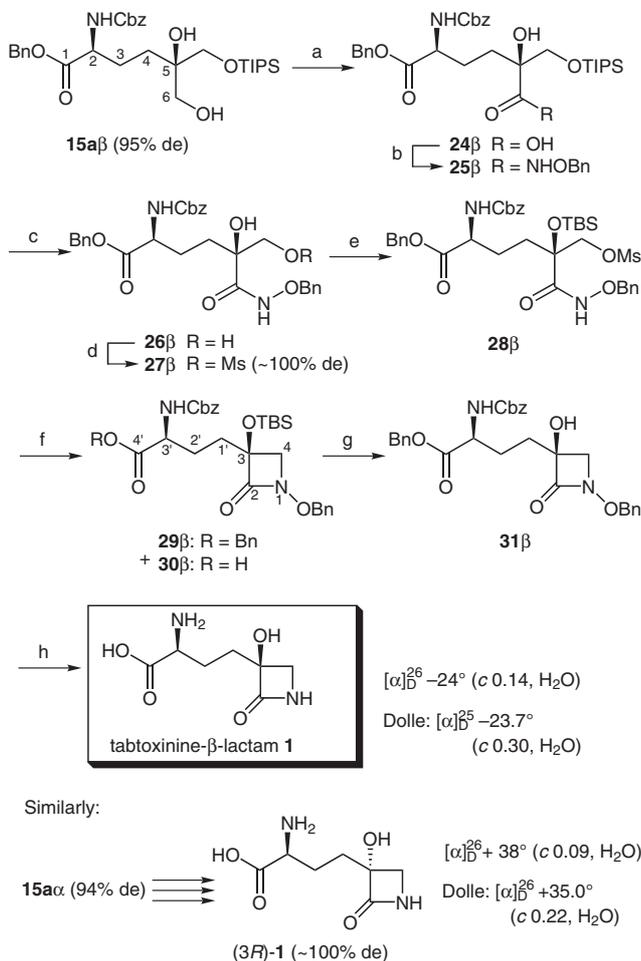
Yield: 7.66 g, 18.0 mmol (98%); colorless oil; [α]_D²⁵ +4.9 (c 1.4, CHCl₃), [α]_D²⁵ –16 (c 0.82, MeOH) [Lit.¹⁸ –17.9 (c 1.6, MeOH)].

IR (film): 3340 (s, OH), 1710 (s, C=O), 1630 (m), 1520 (s), 1190 (s), 1050 (s), 700 (s) cm^{–1}.

¹H NMR (CDCl₃, 500 MHz): δ = 1.26 (3 H, t, *J* = 7.0 Hz, CH₂CH₃), 1.85 (1 H, m, H-3), 2.05 (1 H, m, H-3), 2.28–2.38 (2 H, m, H-4), 4.17 (2 H, q, *J* = 7.0 Hz, CH₂CH₃), 4.44 (1 H, m, H-2), 5.11 (2 H, s, CH₂Ph), 5.17 (2 H, m, CH₂Ph), 5.37 (1 H, d, *J* = 8.3 Hz, NH), 5.51 (1 H, s, H-6), 6.15 (1 H, s, H-6), 7.23–7.37 (10 H, m, ArH).

1-Benzyl 6-Ethyl (2*S*,5*R*)-2-Benzoyloxycarbonylamino-5-hydroxy-6-hydroxymethylhexanedioate (**14a**)

A solution of **9** (2.50 g, 5.88 mmol), K₂OsO₂(OH)₄ (22 mg, 0.060 mmol) and NMO (2.1 g, 18 mmol) in *t*-BuOH–H₂O (1:1, 66 mL)



Scheme 4 Synthesis of (–)-**1** and (+)-(3*R*)-**1**: a) TEMPO, NaClO, NaClO₂, MeCN–H₂O, r.t., 12 h (89%); b) NH₂OBn·HCl, NaHCO₃, HOBT, EDCI, 0 °C→r.t., 12 h (95%); c) TBAF, THF; 0 °C, 1 h (86%); d) i. MsCl, Et₃N, CHCl₃, r.t., 12 h; ii. recrystallization (91%); e) TBSOTf, 2,6-lutidine, CH₂Cl₂, r.t., 2 h (88%); f) KHMDS, THF, –78→0 °C, 24 h [(**29β**) (59%) and (**30β**) (11%)]; g) TBAF, THF; 0 °C; h) H₂, Raney-Ni, H₂O–MeOH (1:2) (89% from **29β** and 68% from **30β**).

was stirred at 20 °C for 20 h. Sodium bisulfate (3.0 g) was added and the reaction mixture was stirred for a further 30 min then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with aq HCl (1 M, 1 × 20 mL) and brine (1 × 10 mL), dried with MgSO₄ and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc, 5:1) to give **14a**.

Yield: 2.67 g, 5.82 mmol (99.0%); colorless oil; 6% de.

IR (film): 3350 (s, OH), 1720 (s, C=O), 1520 (s), 1210 (s), 1050 (s) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 1.22–1.26 (6 H, 2 × t, *J* = 7.1 Hz, 2 × CH₂CH₃), 1.4–1.9 (3 H, m, H-3, H-4), 1.9–2.2 (2 H, m, H-3, OH), 3.50–3.57 (2 H, m, H-6, OH), 3.70 (1 H, m, H-6), 4.22 (2 H, q, *J* = 7.1 Hz, CH₂CH₃), 4.40 (1 H, br m, H-2), 5.10 (2 H, s, PhCH₂), 5.16 (2 H, s, PhCH₂), 5.37 (1 H, br m, NH), 7.3–7.4 (1 H, m, ArH).

MS (FAB): *m/z* = 91, 181, 263, 326, 416 [M + H – OEt]⁺, 460 [M + H]⁺.

HRMS–FAB: *m/z* [M + H]⁺ calcd for C₂₄H₃₀NO₈: 460.1971; found: 460.1974.

1-Bromo-2-tert-butylidiphenylsilyloxymethyl-2-propene (12c)

To a solution of 2-tert-butylidiphenylsilyloxymethyl-2-propen-1-ol (2.9 g, 8.9 mmol) in CH₂Cl₂ (30 mL) were added CBr₄ (4.45 g, 13.4 mmol) and PPh₃ (2.81 g, 10.7 mmol) at 0 °C. The mixture was stirred for 10 min then quenched with sat. aq NaHCO₃ (10 mL) and extracted with EtOAc (1 × 40 mL). The combined extract was washed with brine (1 × 10 mL), dried with MgSO₄, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane) to give **12c**.

Yield: 3.5 g, 9.0 mmol (quant.); colorless oil.

¹H NMR (CDCl₃, 300 MHz): δ = 1.07 (9 H, s, *t*-Bu), 4.03 (2 H, s), 4.31 (2 H, pseudo t, *J* = 1.7 Hz), 5.29 (1 H, m), 5.31 (1 H, q, *J* = 1.7 Hz), 5.30 (1 H, pseudo d, *J* = 7.6 Hz, NH), 7.3–7.5 (6 H, m, ArH), 7.65–7.72 (4 H, m, ArH).

MS (EI): *m/z* = 91, 251, 261, 263, 331, 333, 389 [M + H]⁺.

HRMS (EI): *m/z* [M + H]⁺ calcd for C₂₀H₂₆BrOSi: 389.0936; found: 389.0933.

Benzyl (S)-2-Benzyloxycarbonylamino-5-triisopropylsilyloxymethyl-5-hexenoate (13a)

A suspension of Zn powder (4.8 g, 73.4 mgatom) and 1,2-dibromoethane (0.315 mL, 3.66 mmol) in DMF (13 mL) was stirred at 60 °C for 30 min under nitrogen. TMSCl (0.093 mL, 0.073 mmol) was added and the mixture was stirred at 60 °C for further 30 min. A solution of iodide **7** (5.35 g, 12.2 mmol) in DMF (11.5 mL) was added dropwise and, after stirring at 60 °C for 10 min, the mixture was cooled to –55 °C and a solution of CuCN (1.09 g, 12.2 mmol) and LiCl (1.03 g, 24.3 mmol) in DMF (11.5 mL) was added. The mixture was warmed to 0 °C and stirred for 10 min then the mixture was again cooled to –55 °C and bromide **12a** (5.60 g, 18.2 mmol) was added. The mixture was stirred for 12 h then unreacted Zn was filtered through a Celite pad and the filtrate was quenched with sat. aq NH₄Cl (15 mL). The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layer was washed with brine (1 × 10 mL), dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–EtOAc, 5:1) to give **13a**.

Yield: 5.70 g, 10.6 mmol (87%); colorless oil; [α]_D²⁸ –8.9 (*c* 5.3, EtOH).

IR (film): 3330 (br s), 1730 (br s, C=O), 1670 (w), 1450 (s), 880 (m), 695 (s) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 0.96–1.13 [21 H, m, Si(*i*-Pr)₃], 1.82 (1 H, m), 1.87–2.5 (3 H, m), 4.08 (2 H, s, SiOCH₃), 4.44 (1 H, m, H-2), 4.79 (1 H, s, H-6), 5.09 (1 H, m, H-6), 5.11 (2 H, s,

CH₂Ph), 5.15 (1 H, d, *J* = 12.3 Hz, CHHPh), 5.20 (1 H, d, *J* = 12.3 Hz, CHHPh), 5.30 (1 H, pseudo d, *J* = 7.6 Hz, NH), 7.3–7.4 (10 H, m, ArH).

¹³C NMR (CDCl₃, 75 MHz): δ = 11.84, 17.57, 17.88, 28.07, 30.82, 53.73 (C-2), 65.86, 66.98, 67.13, 109.29 (H₂C=), 128.18, 128.24, 128.38, 128.56, 128.59, 128.69, 135.37, 136.32, 147.09 (C₂C=), 155.97 (NHC=O), 172.37 (C-1).

MS (FAB): *m/z* = 91, 181, 322, 496, 540 [M + H]⁺.

HRMS–FAB: *m/z* [M + H]⁺ calcd for C₂₈H₄₁O₅Si: 540.3145; found: 540.3149.

Benzyl (S)-2-Benzyloxycarbonylamino-5-tert-butylidimethylsilyloxymethyl-5-hexenoate (13b)

Yield: 85%; colorless oil; [α]_D²⁸ +2.6 (*c* 0.63, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 0.038 (6 H, s, Me₂Si), 89 (9 H, m, *t*-Bu), 1.82 (1 H, m), 1.95–2.10 (3 H, m), 4.00 (2 H, s, CH₂OSi), 4.44 (1 H, m, H-2), 4.78 (2 H, s, H-6), 4.78 (1 H, m), 5.03 (1 H, d, *J* = 1.4 Hz, H-6), 5.10 (2 H, s, CH₂Ph), 5.14 (1 H, d, *J* = 12.4 Hz, CHHPh), 5.20 (1 H, d, *J* = 12.4 Hz, CHHPh), 5.32 (1 H, pseudo d, *J* = 7.7 Hz, NH), 7.28–7.38 (10 H, m, ArH).

¹³C NMR (CDCl₃, 125 MHz): δ = –5.43 (MeSi), 18.32, 25.86 [(CH₃)₃C], 28.14 and 30.84 (C-3 and C-4), 53.72 (C-2), 65.72, 66.99, 67.16, 109.60 (C=CH₂), 128.10, 128.17, 128.31, 128.48, 128.51, 128.61, 135.22, 136.19, 146.91 (C=CH₂), 155.82 (NHC=O), 172.18 (C-1).

MS (FAB): *m/z* = 73, 91, 181, 322, 440, 498 [M + H]⁺.

HRMS–FAB: *m/z* [M + H]⁺ calcd for C₂₈H₄₁O₅Si: 498.2676; found: 498.2679.

Benzyl (S)-2-Benzyloxycarbonylamino-5-tert-butylidiphenylsilyloxymethyl-5-hexenoate (13c)

Yield: 80%; colorless oil; [α]_D²⁴ +4.8 (*c* 0.65, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 1.0–1.4 (9 H, m, *t*-Bu), 1.76 (1 H, m), 1.90–2.08 (3 H, m), 4.03 (2 H, s, CH₂OSi), 4.41 (1 H, m, H-2), 4.82 (1 H, s), 5.09 (1 H, s), 5.12–5.18 (3 H, m), 5.24 (1 H, pseudo d, *J* = 7.7 Hz, NH), 7.2–7.5 (16 H, m, ArH), 7.6–7.7 (4 H, m, ArH).

¹³C NMR (CDCl₃, 125 MHz): δ = 19.21, 26.73, 26.78, 28.14, 30.83, 53.68, 66.20, 67.05, 109.60, 127.61, 127.66, 127.70, 128.13, 128.50, 129.64, 129.69, 133.43, 133.45, 135.19, 135.41, 135.51, 136.16, 146.48, 155.79, 172.13, 65.72, 66.99, 67.16, 109.60 (C=CH₂), 128.10, 128.17, 128.31, 128.48, 128.51, 128.61, 135.22, 136.19, 146.91 (C=CH₂), 155.82 (NHC=O), 172.18 (C-1).

MS (FAB): *m/z* = 91, 135, 199, 322, 564, 622 [M + H]⁺.

HRMS–FAB: *m/z* [M + H]⁺ calcd for C₃₈H₄₄O₅NSi: 622.2989; found: 622.2991.

Benzyl (2S,5R)-2-Benzyloxycarbonylamino-5-triisopropylsilyloxymethyl-5,6-dihydroxyhexanoate (15aβ)

AD-mix β (5.19 g) in H₂O (15 mL) and *t*-BuOH (15 mL) was stirred at r.t. for 10 min and then cooled to 0 °C. A solution of **13a** (2.00 g, 3.71 mmol) in H₂O (3.5 mL) and *t*-BuOH (3.5 mL) was added at 0 °C and the mixture was stirred at 0 °C for 3 d. After quenching with Na₂SO₃ (5.6 g) the reaction was allowed to come to r.t. and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **15aβ**. The de was determined by HPLC using a Daicel Chiralcel[®] column [OD (4.6 × 250 mm), *i*-PrOH–hexane (1:15), 0.3 mL/min; 25 °C; detection, 254 nm; *t*_R 80.8 min (**15aβ**, 95%) and 87.4 min (**15aα**, 2.5%)].

Yield: 0.301 g, 0.566 mmol (94%); colorless oil; [α]_D²⁶ –8.7 (*c* 3.2, EtOH); 95% de.

IR (film): 3400 (br s), 1720 (br s, C=O), 1450 (s), 880 (m), 695 (s) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.95–1.2 [21 H, m, Si(*i*-Pr) $_3$], 1.45 (2 H, m), 1.78 (1 H, m), 1.98 (1 H, m), 2.28 (1 H, m, 6-OH), 2.87 (1 H, s, 5-OH), 3.41 (1 H, dd, J = 11.0, 6.9 Hz, H-6), 3.52 (1 H, dd, J = 11.3, 4.7 Hz, H-6), 3.54 (1 H, d, J = 9.6 Hz, SiOCH $_2$), 3.64 (1 H, d, J = 9.6 Hz, SiOCH $_2$), 4.43 (1 H, m, H-2), 5.10 (2 H, s, CH $_2$ Ph), 5.17 (2 H, s, CH $_2$ Ph), 5.45 (1 H, pseudo d, J = 8.8 Hz, NH), 7.28–7.4 (10 H, m, ArH).

^{13}C NMR (CDCl_3 , 150 MHz): δ = 11.72, 17.89, 17.90, 26.32, 29.21, 53.98, 66.34, 67.02, 67.20, 67.57, 73.14, 128.11, 128.18, 128.36, 128.48, 128.51, 128.60, 135.22, 136.16, 156.02 (NHC=O), 172.12 (C-1).

MS (FAB): m/z = 91, 230, 320, 530, 574 [M + H] $^+$.

HRMS–FAB: m/z [M + H] $^+$ calcd for C $_{31}$ H $_{48}$ O $_7$ NSi: 574.3200; found: 574.3205.

(2S,5S)-Isomer (15aa)

In the same manner as described above, using AD-mix α (7.26 g), **13a** (2.80 g, 5.19 mmol) was converted into **15aa**. The de was determined by HPLC using a Daicel Chiralcel $^{\text{®}}$ column [OD (4.6 \times 250 mm), *i*-PrOH–hexane (1:15), 0.3 mL/min; 25 $^{\circ}\text{C}$; detection, 254 nm; t_{R} 73.7 min (**15ab**, 3%) and 79.9 min (**15aa**, 97%)].

Yield: 2.80 g, 4.88 mmol (94%); colorless oil; $[\alpha]_{\text{D}}^{23}$ –8.5 (c 0.83, EtOH); 94% de.

^1H NMR (CDCl_3 , 300 MHz): δ = 0.95–1.2 [21 H, m, Si(*i*-Pr) $_3$], 1.35–1.55 (2 H, m), 1.79 (1 H, m), 1.98 (1 H, m), 2.25 (1 H, m, 6-OH), 2.79 (1 H, s, 5-OH), 3.42 (1 H, dd, J = 11.0, 7.1 Hz, H-6), 3.51 (1 H, m, H-6), 3.54 (1 H, d, J = 9.6 Hz, SiOCH $_2$), 3.63 (1 H, d, J = 9.6 Hz, SiOCH $_2$), 4.42 (1 H, m, H-2), 5.10 (2 H, s, CH $_2$ Ph), 5.14 (1 H, d, J = 10.4 Hz, CH $_2$ Ph), 5.20 (1 H, d, J = 10.4 Hz, CH $_2$ Ph), 5.45 (1 H, pseudo d, J = 7.5 Hz, NH), 7.28–7.4 (10 H, m, ArH).

HRMS (FAB): m/z [M + H] $^+$ calcd for C $_{31}$ H $_{48}$ O $_7$ NSi: 574.3200; found: 574.3207.

Benzyl (2S,5R)-2-Benzylloxycarbonylamino-5-tert-butylidimethylsilyloxymethyl-5,6-dihydroxyhexanoate (15bβ)

The de was determined by HPLC using a Daicel Chiralcel $^{\text{®}}$ column [OD (4.6 \times 250 mm), *i*-PrOH–hexane (1:15), 0.5 mL/min; 25 $^{\circ}\text{C}$; detection, 254 nm; t_{R} 52.7 min (**15bβ**, 95%) and 58.1 min (**15ba**, 5%)].

Yield: 94%; colorless oil; $[\alpha]_{\text{D}}^{26}$ +3.9 (c 0.76, CHCl $_3$); 90% de.

^1H NMR (CDCl_3 , 300 MHz): δ = 0.058 (6 H, s, SiMe $_2$), 0.88 (9 H, s, *t*-Bu), 1.43 (1 H, m), 1.78 (1 H, m), 1.96 (1 H, m), 2.21 (1 H, m), 2.77 (1 H, s, OH), 3.3–3.6 (4 H, m, H-6, SiOCH $_2$), 4.43 (1 H, m, H-2), 5.10 (2 H, s, CH $_2$ Ph), 5.15 (1 H, d, J = 12.4 Hz, CHHPh), 5.20 (1 H, d, J = 12.4 Hz, CHHPh), 5.32 (1 H, pseudo d, J = 8.2 Hz, NH), 7.3–7.38 (10 H, m, ArH).

MS–FAB: m/z = 73, 91, 230, 446, 532 [M + H] $^+$, 554 [M + Na] $^+$.

HRMS (FAB): m/z [M + Na] $^+$ calcd for C $_{28}$ H $_{41}$ O $_7$ NSiNa: 554.2550; found: 554.2555.

(2S,5S)-Isomer (15ba)

Yield: 72%; colorless oil; $[\alpha]_{\text{D}}^{26}$ +2.0 (c 0.56, CHCl $_3$); 90% de.

^1H NMR (CDCl_3 , 300 MHz): δ = 0.058 (6 H, s, SiMe $_2$), 0.88 (9 H, s, *t*-Bu), 1.45 (2 H, m), 1.78 (1 H, m), 1.96 (1 H, m), 2.29 (1 H, s, OH), 2.72 (1 H, s, OH), 3.36–3.55 (4 H, m, H-6, SiOCH $_2$), 4.42 (1 H, m, H-2), 5.10 (2 H, s, CH $_2$ Ph), 5.10–5.25 (2 H, m, CH $_2$ Ph), 5.48 (1 H, pseudo d, J = 7.1 Hz, NH), 7.3–7.4 (10 H, m, ArH).

HRMS (FAB): m/z [M + Na] $^+$ calcd for C $_{28}$ H $_{41}$ O $_7$ NSiNa: 554.2550; found: 554.2550.

Benzyl (2S,5R)-2-Benzylloxycarbonylamino-5-tert-butylidiphenylsilyloxymethyl-5,6-dihydroxyhexanoate (15cβ)

The de was determined by HPLC using a Daicel Chiralcel $^{\text{®}}$ column [OD (4.6 \times 250 mm), *i*-PrOH–hexane (1:10), 0.5 mL/min; 15 $^{\circ}\text{C}$; detection, 254 nm; t_{R} 40.0 min (**15ca**, 9%) and 46.0 min (**15cβ**, 91%)].

Yield: 75%; colorless oil; $[\alpha]_{\text{D}}^{25}$ +17 (c 0.065, CHCl $_3$); 82% de.

^1H NMR (CDCl_3 , 300 MHz): δ = 1.05 (9 H, s, *t*-Bu), 1.70 (1 H, m), 1.82–2.10 (3 H, m), 2.73 (1 H, s, OH), 3.39 (1 H, dd, J = 7.1, 11.3 Hz), 3.46–3.58 (3 H, m), 4.39 (1 H, m, H-2), 5.0–5.16 (4 H, m, CH $_2$ Ph), 5.38 (1 H, pseudo d, J = 8.0 Hz, NH), 7.22–7.48 (16 H, m, ArH), 7.60–7.66 (4 H, m, ArH).

MS–FAB: m/z = 91, 135, 199, 230, 320, 656 [M + H] $^+$.

HRMS (FAB): m/z [M + H] $^+$ calcd for C $_{38}$ H $_{46}$ O $_7$ NSi: 656.3044; found: 656.3040.

(2S,5S)-Isomer (15ca)

Yield: 58%; colorless oil; $[\alpha]_{\text{D}}^{25}$ +1.9 (c 0.26, CHCl $_3$); 68% de.

^1H NMR (CDCl_3 , 300 MHz): δ = 1.09 (9 H, s, *t*-Bu), 1.72 (1 H, m), 1.82–1.89 (3 H, m), 2.68 (1 H, s, OH), 3.40 (1 H, m), 3.45–3.58 (3 H, m), 4.39 (1 H, m, H-2), 5.0–5.17 (4 H, m, CH $_2$ Ph), 5.38 (1 H, m), 7.22–7.48 (16 H, m, ArH), 7.60–7.66 (4 H, m, ArH).

HRMS (FAB): m/z [M + H] $^+$ calcd for C $_{38}$ H $_{46}$ O $_7$ NSi: 656.3044; found: 656.3052.

(±)-Ethyl 2-Hydroxy-2-hydroxymethylheptanoate (17)

A mixture of **16** (2.00 g, 11.7 mmol), K $_2$ CO $_3$ (4.86 g, 35.2 mmol), K $_3$ Fe(CN) $_6$ (11.6 g, 35.2 mmol) and K $_2$ OsO $_2$ (OH) $_4$ (17.2 mg, 0.0468 mmol) in H $_2$ O (40 mL) and *t*-BuOH (40 mL) was stirred at r.t. for 12 h. To this mixture was then added Na $_2$ SO $_3$ (1.8 g) and the mixture was warmed to r.t. and extracted into EtOAc (3 \times 80 mL). The combined organic layer was washed with aq sat. NH $_4$ Cl (1 \times 15 mL) and brine (1 \times 10 mL), dried with MgSO $_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **17**.

Yield: 2.18 g, 10.6 mmol (91%); colorless oil.

IR (film): 3450 (m, OH), 1725 (s, C=O), 1255 (s), 1210 (s), 1150 (s), 1080 (s), 1050 (s), 1020 (s), 915 (m), 755 (m) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.87 (3 H, t, J = 6.9 Hz, H-7), 1.10 (1 H, m), 1.20–1.34 (4 H, m), 1.32 (3 H, t, J = 7.1 Hz, CO $_2$ CH $_2$ CH $_3$), 1.46 (1 H, m, H-3), 1.59 (2 H, m), 2.12 (1 H, pseudo dd, J = 3.2, 9.3 Hz, CH $_2$ OH), 3.53 (1 H, s, 2C-OH), 3.60 (1 H, dd, J = 3.8, 11.3 Hz, CHHOH), 3.79 (1 H, ddd, J = 11.3, 9.9, 1.1 Hz, CHHOH), 4.28 (2 H, m, CO $_2$ CH $_2$ CH $_3$).

HRMS (ED): m/z [M + H] $^+$ calcd for C $_{10}$ H $_{21}$ O $_4$: 205.1539; found: 205.1441.

(±)-N-Benzylloxy-2-hydroxy-2-hydroxymethylheptanamide (18)

To a solution of NH $_2$ OBn·HCl (5.48 g, 36.6 mmol) in toluene (80 mL) was added AlMe $_3$ in toluene (1.02 M, 48.8 mL, 49.8 mmol) at 0 $^{\circ}\text{C}$ under N $_2$. The solution was warmed to 20 $^{\circ}\text{C}$ and stirred for 1 h, then, after warming to 50 $^{\circ}\text{C}$, **17** (2.23 g, 10.9 mmol) was added and the mixture was stirred at 50 $^{\circ}\text{C}$ for 12 h. The mixture was quenched with aq HCl (5%, 20 mL), extracted into EtOAc (6 \times 100 mL) and the combined organic layer was dried with MgSO $_4$ and concentrated in vacuo. The residue was recrystallized (EtOAc–hexane) and further purified by column chromatography on silica gel (hexane–EtOAc, 1:1) to give **18**.

Yield: 1.78 g, 6.33 mmol (58%); colorless solid; mp 98.0–98.6 $^{\circ}\text{C}$.

IR (film): 3370 (s, NH), 3300 (s, OH), 1655 (s, C=O), 1060 (s), 740 (s), 700 (s) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.87 (3 H, t, J = 6.9 Hz, H-7), 1.14–1.34 (4 H, m), 1.43 (2 H, m), 1.67 (2 H, m), 2.81 (1 H, s, OH), 3.26 (1 H, s, OH), 3.39 (1 H, dd, J = 11.0, 6.0 Hz, CHHOH), 3.97 (1 H, dd, J = 11.0, 5.2 Hz, CHHOH), 4.88 (1 H, d, J = 11.1 Hz, CHHPh), 4.94 (1 H, d, J = 11.1 Hz, CHHPh), 7.30–7.45 (5 H, m, ArH), 9.18 (1 H, s, NHOBn).

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{O}_4\text{N}$: 282.1705; found: 282.1705.

(\pm)-*N*-Benzyloxy-2-hydroxy-2-(*p*-toluenesulfonyloxymethyl)heptanamide (19)

To a solution of **18** (1.00 g, 3.55 mmol) in pyridine (10 mL) was added TsCl (1.01 g, 5.30 mmol) and the mixture was stirred at r.t. for 10 h. Aq HCl (1 M, 40 mL, 40 mmol) was added at 0 °C and the mixture was extracted into EtOAc (3 \times 5 mL). The combined organic layer was washed with aq sat. NaHCO_3 (2 \times 15 mL) and H_2O (1 \times 5 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **19**.

Yield: 1.54 g, 3.54 mmol (quant.); colorless oil.

IR (film): 3300 (m), 1730 (m), 1660 (s, C=O), 1590 (w), 1170 (s), 810 (m) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.85 (3 H, t, J = 6.9 Hz, H-7), 1.16–1.37 (6 H, m, H-4, H-5, H-6), 1.48 (1 H, m, H-3), 1.70 (1 H, m, H-3), 2.45 (3 H, s, PhCH_3), 3.15 (1 H, d, J = 4.4 Hz, 2C-OH), 4.05 (1 H, d, J = 10.2 Hz, CHHOTs), 4.23 (1 H, d, J = 10.2 Hz, CHHOTs), 4.870 (1 H, d, J = 11.3 Hz, CHHPh), 4.874 (1 H, d, J = 11.3 Hz, CHHPh), 7.30–7.43 (7 H, ArH), 7.77 (2 H, d, J = 8.2 Hz, ArH), 9.11 (1 H, s, NHOBn).

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_6\text{NS}$: 436.1794; found: 436.1797.

(\pm)-*N*-Benzyloxy-2-*p*-toluenesulfonyloxymethyl-2-trimethylsilyloxyheptanamide (20)

To a mixture of **19** (1.37 g, 3.15 mmol) and 2,6-lutidine (1.47 mL, 12.6 mmol) in CH_2Cl_2 (20 mL) was added TMSOTf (1.71 mL, 9.45 mmol) at 0 °C under N_2 . The solution was warmed to r.t. and stirred for 12 h. After H_2O (2 mL) was added at 0 °C, the mixture was extracted into EtOAc (3 \times 30 mL) and the combined organic layer was washed with brine (1 \times 3 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on neutral silica gel (hexane–EtOAc, 5:1) to give **20**.

Yield: 1.40 g, 2.76 mmol (88%); colorless oil.

IR (film): 3390 (m), 1690 (s, C=O), 1600 (m), 1255 (s), 1180 (s), 1170 (s), 980 (m), 850 (s) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.12 (9 H, s, SiMe_3), 0.84 (3 H, t, J = 6.9 Hz, H-7), 1.10–1.33 (6 H, m), 1.40 (1 H, m, H-3), 1.68 (1 H, m, H-3), 2.43 (3 H, s, PhCH_3), 4.13 (1 H, d, J = 9.9 Hz, CHHOTs), 4.13 (1 H, d, J = 9.9 Hz, CHHOTs), 4.80 (1 H, d, J = 11.3 Hz, CHHPh), 4.86 (1 H, d, J = 11.3 Hz, CHHPh), 7.33–7.42 (7 H, ArH), 7.77 (2 H, d, J = 8.5 Hz, ArH), 8.91 (1 H, s, NHOBn).

MS–FAB: m/z = 73, 91, 508 $[\text{M} + \text{H}]^+$, 530 $[\text{M} + \text{Na}]^+$.

HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{38}\text{O}_6\text{NSiS}$: 508.2189; found: 508.2193.

(\pm)-1-Benzyloxy-3-pentyl-3-trimethylsilyloxy-2-azetidinone (21)

To a suspension of NaH (60%, 31 mg, 0.775 mmol, washed with hexane) in THF (5.0 mL), was added a solution of **20** (330 mg, 0.650 mmol) in THF (5.0 mL) at 0 °C under N_2 . After stirring for 12 h, the mixture was diluted with Et_2O (15 mL), filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue

was purified by column chromatography on silica gel (hexane–EtOAc, 6:1) to give **21**.

Yield: 175 mg, 0.552 mmol (80%); colorless oil.

IR (film): 1770 (s, C=O), 1450 (m), 1250 (s), 1200 (s), 990 (s), 840 (s), 750 (m), 690 (m) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.14 (9 H, s, SiMe_3), 0.88 (3 H, t, J = 6.9 Hz, H-5'), 1.19–1.73 (8 H, m), 3.23 (1 H, d, J = 4.4 Hz, H-4), 3.26 (1 H, d, J = 4.4 Hz, H-4), 4.94 (1 H, d, J = 11.3 Hz, CHH-Ph), 4.99 (1 H, d, J = 11.3 Hz, CHHPh), 7.36–7.44 (5 H, ArH).

MS–FAB: m/z = 73, 91, 147, 228, 281, 336 $[\text{M} + \text{H}]^+$.

HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{30}\text{O}_3\text{NSi}$: 336.1995; found: 336.1998.

(\pm)-1-Benzyloxy-3-hydroxy-3-pentyl-2-azetidinone (22)

A solution of **21** (75.0 mg, 0.224 mmol) in H_2O (0.50 mL), THF (0.50 mL) and AcOH (0.25 mL) was stirred at r.t. for 3 h. The mixture was extracted into EtOAc (3 \times 15 mL) and the combined organic layer was dried with Na_2SO_4 and concentrated in vacuo to give **22**.

Yield: 59.0 mg, 0.224 mmol (quant.); colorless oil.

FT-IR (ATR, Zn–Se): 3350 (m, OH), 1753 (s, C=O), 956 (m), 747 (s), 697 (s) cm^{-1} .

^1H NMR (CDCl_3 , 300 MHz): δ = 0.88 (3 H, t, J = 6.9 Hz, H-5'), 1.20–1.48 (6 H, m), 1.58–1.80 (2 H, m), 2.94 (1 H, br, OH), 3.26 (1 H, d, J = 4.7 Hz, H-4), 3.32 (1 H, d, J = 4.7 Hz, H-4), 4.97 (2 H, s, CH_2Ph), 7.37–7.43 (5 H, ArH).

MS–FAB: m/z = 91, 236, 264 $[\text{M} + \text{H}]^+$.

HRMS (FAB): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{N}$, 264.1600; found: 264.1599.

(\pm)-3-Hydroxy-3-pentyl-2-azetidinone (23)

To a suspension of Raney-Ni (10 mg) in MeOH (3.0 mL) was added a solution of **22** (59.0 mg, 0.224 mmol) in MeOH (2.0 mL). The mixture was stirred at r.t. under H_2 for 12 h then the mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **23**.

Yield: 19.0 mg, 0.121 mmol (54%); colorless needles; mp 81–81.5 °C.

IR (film): 3380 (s), 3220 (m), 3160 (m), 1710 (s, C=O), 1685 (s, C=O), 1470 (m), 1185 (m), 1150 (m), 1140 (m), 800 (m), 700 (m) cm^{-1} .

^1H NMR (CD_3OD , 300 MHz): δ = 0.92 (3 H, t, J = 6.7 Hz, H-5'), 1.29–1.58 (6 H, m), 1.65–1.80 (2 H, m), 3.17 (1 H, d, J = 5.8 Hz, H-4), 3.32 (1 H, d, J = 5.8 Hz, H-4).

Anal. Calcd for $\text{C}_8\text{H}_{15}\text{NO}_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.11; H, 10.03; N, 9.04.

1-Benzyl Hydrogen (2*S*,5*S*)-2-Benzyloxycarbonylamino-5-hydroxy-5-[(triisopropylsilyloxy)methyl]hexanedioate (24 β)

To a mixture of **15a β** (0.410 g, 0.715 mmol), TEMPO (15.4 mg, 0.0986 mmol, 0.14 equiv) and sodium phosphate buffer (4.7 mL, 0.67 M, pH 6.7) in MeCN (10 mL) were added, simultaneously, aq NaClO_2 (0.422 g, 80% in 3.0 mL H_2O) and bleach (5%, 0.20 mL) at r.t. After stirring overnight, H_2O (0.5 mL) was added at 0 °C and the pH was adjusted to 8.0 with 0.5 N NaOH. The reaction was quenched with aq Na_2SO_3 (0.43 g in 8.8 mL H_2O) and the mixture was extracted into Et_2O (3 \times 30 mL). The combined organic layer was dried with MgSO_4 , concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 1:1) to give **24 β** .

Yield: 0.374 g, 0.636 mmol (89%); colorless oil; $[\alpha]_{\text{D}}^{24} -11$ (c 1.7, EtOH).

IR (film): 3600–2400 (br s, COOH), 3520 (m), 3340 (br s, OH), 1730 (br s, C=O), 1460 (s), 880 (s), 695 (s) cm^{-1} .

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 0.90$ – 1.20 [21 H, m, Si(*i*-Pr) $_3$], 1.60 (2 H, m), 1.74–1.99 (3 H, m), 3.60 (1 H, d, $J = 9.1$ Hz, SiOCH), 3.92 (1 H, d, $J = 9.1$ Hz, SiOCH), 4.41 (1 H, m, H-2), 5.08 (2 H, s, CH_2Ph), 5.15 (2 H, s, CH_2Ph), 5.46 (1 H, br, NH), 7.20–7.4 (10 H, m, ArH).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): $\delta = 11.65$, 17.66, 26.32, 29.87, 53.70, 66.97, 67.14, 68.86, 77.96, 128.08, 128.15, 128.28, 128.43, 128.51, 128.60, 135.29, 136.24, 156.14 (NHC=O), 172.14, 177.92.

MS–FAB: $m/z = 152$, 173, 478, 586 [M – H] $^-$.

HRMS (FAB): m/z [M – H] $^-$ calcd for $\text{C}_{31}\text{H}_{44}\text{O}_8\text{NSi}$: 586.2836; found: 586.2838.

(2*S*,5*R*)-Isomer (24*a*)

Synthesized from **15a** (2.42 g, 4.22 mmol) in the same manner as described above.

Yield: 2.19 g, 3.73 mmol (88%); amorphous solid; $[\alpha]_{\text{D}}^{23} +8.6$ (c 0.50, CHCl_3).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 0.90$ – 1.20 [21 H, m, Si(*i*-Pr) $_3$], 1.71 (1 H, m), 1.80–2.00 (2 H, m), 2.11 (1 H, m), 3.72 (1 H, d, $J = 9.3$ Hz, SiOCH), 3.95 (1 H, d, $J = 9.3$ Hz, SiOCH), 4.30 (1 H, m, H-2), 5.08 (2 H, s, CH_2Ph), 5.17 (2 H, s, CH_2Ph), 5.0–5.2 (1 H, overlapped, NH), 7.20–7.45 (10 H, m, ArH).

HRMS (FAB): m/z [M + H] $^+$ calcd for $\text{C}_{31}\text{H}_{46}\text{O}_8\text{NSi}$: 588.2992; found: 588.2986.

Benzyl (2*S*,5*S*)-5-Benzylloxycarbamoyl-2-benzylloxycarbonyl-amino-5-hydroxy-6-triisopropylsilyloxyhexanoate (25β)

A mixture of **24β** (0.534 g, 0.909 mmol), $\text{NH}_2\text{OBn}\cdot\text{HCl}$ (0.290 g, 1.82 mmol, 2.0 equiv), NaHCO_3 (0.153 g, 1.82 mmol), HOBT (0.246 g, 1.82 mmol, 2.0 equiv) and EDCI (0.349 g, 1.82 mmol, 2.0 equiv) in DMF (3.5 mL) and CH_2Cl_2 (10 mL) was stirred at r.t. under N_2 for 12 h. The mixture was cooled to 0 °C, H_2O (5 mL) was added and the resulting mixture was extracted into EtOAc (3 × 20 mL). The combined organic layer was washed with sat. aq NH_4Cl (1 × 5 mL) and brine (1 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 4:1) to give **25β**.

Yield: 0.597 g, 0.862 mmol (95%); colorless oil; $[\alpha]_{\text{D}}^{26} -18$ (c 3.0, EtOH).

IR (film): 3500 (m), 3320 (br s), 1700 (br s, C=O), 1460 (s), 880 (m), 695 (s) cm^{-1} .

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 0.96$ – 1.1 [21 H, m, Si(*i*-Pr) $_3$], 1.53 (1 H, m), 1.74–1.84 (2 H, m), 3.41 (1 H, s, OH), 3.49 (1 H, d, $J = 9.3$ Hz, H-6), 3.91 (1 H, d, $J = 9.3$ Hz, H-6), 4.40 (1 H, br m, H-2), 4.82 (1 H, d, $J = 11.3$ Hz, NOCHH), 4.90 (1 H, d, $J = 11.3$ Hz, NOCHH), 5.092 (1 H, m, PhCH_2), 5.096 (2 H, m, PhCH_2), 5.28 (1 H, br d, $J = 8.0$ Hz, BnONH), 7.24–7.40 (15 H, s, ArH), 9.09 (1 H, s, NHOBn).

$^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): $\delta = 11.56$, 17.68, 26.28, 31.34, 53.64, 66.97, 67.16, 67.37, 78.38, 128.14–129.20, 135.15, 136.28, 155.96 (NHC=O), 170.98, 172.02.

MS–FAB: $m/z = 91$, 181, 214, 390, 480, 559, 649, 693 [M + H] $^+$.

HRMS (FAB): m/z [M + H] $^+$ calcd for $\text{C}_{38}\text{H}_{53}\text{O}_8\text{N}_2\text{Si}$: 693.3571; found: 693.3572.

(2*S*,5*R*)-Isomer (25*a*)

In the same manner as described above, **24a** (1.89 g, 3.22 mmol) was converted into **25a**.

Yield: 1.69 g, 2.44 mmol (76%); colorless oil; $[\alpha]_{\text{D}}^{23} +6.8$ (c 0.50, EtOH).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 0.96$ – 1.13 [21 H, m, Si(*i*-Pr) $_3$], 1.46–1.60 (2 H, m), 1.76 (1 H, m), 1.99 (1 H, m), 3.49 (1 H, s, OH), 3.50 (1 H, d, $J = 8.8$ Hz, H-6), 3.91 (1 H, d, $J = 8.8$ Hz, H-6), 4.39 (1 H, br m, H-2), 4.83 (1 H, d, $J = 11.5$ Hz, NOCHH), 4.90 (1 H, d, $J = 11.5$ Hz, NOCHH), 5.08 (1 H, m, PhCH_2), 5.10 (1 H, m, PhCH_2), 5.24 (1 H, br d, $J = 8.3$ Hz, BnONH), 7.24–7.40 (15 H, s, ArH), 9.10 (1 H, s, NHOBn).

HRMS (FAB): m/z [M + H] $^+$ calcd for $\text{C}_{38}\text{H}_{53}\text{O}_8\text{N}_2\text{Si}$: 693.3571; found: 693.3572.

Benzyl (2*S*,5*S*)-5-Benzylloxycarbamoyl-2-benzylloxycarbonyl-amino-5,6-dihydroxyhexanoate (26β)

A solution of **25β** (1.56 mg, 2.25 mmol) and aq HF (48%, 8.5 mL) in MeCN (30 mL) was stirred at r.t. for 12 h. After dilution with aq sat. NaHCO_3 (10 mL) at 0 °C, the mixture was extracted into EtOAc (3 × 20 mL). The combined organic layer was dried with Na_2SO_4 , concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 1:2) to give **26β**.

Yield: 1.04 g, 1.94 mmol (86%); colorless solid; mp 127.5–128.0 °C; $[\alpha]_{\text{D}}^{24} -20$ (c 1.0, MeOH).

IR (KBr): 3450 (s), 3370 (s), 3270 (s), 3050 (w), 3025 (w), 1730 (s, C=O), 1670 (s), 1650 (s), 1535 (s), 740 (m), 695 (s) cm^{-1} .

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.4$ – 1.9 (4 H, m, H-3, H-4), 2.44 (1 H, br s, 6-OH), 3.37 (1 H, dd, $J = 10.5$, 7.3 Hz, H-6), 3.51 (1 H, br s, OH), 3.78 (1 H, br dd, $J = 10.5$, 5.5 Hz, H-6), 4.39 (1 H, br m, H-2), 4.84 (2 H, m, CH_2Ph), 5.05 (2 H, m, PhCH_2), 5.15 (2 H, m, PhCH_2), 5.41 (1 H, br d, $J = 7.7$ Hz, BnONH), 7.3–7.44 (15 H, s, ArH), 9.14 (1 H, br s, NHOBn).

$^{13}\text{C NMR}$ (CD_3OD , 75 MHz): $\delta = 26.44$, 32.65, 55.70, 67.72, 67.95, 68.45, 79.21, 79.46, 128.97, 129.16, 129.37, 129.41, 129.56, 129.63, 129.72, 129.78, 130.64, 136.88, 137.36, 138.30, 158.80, 173.25, 173.85.

MS–FAB: $m/z = 91$, 136, 154, 537 [M + H] $^+$.

HRMS (FAB): m/z [M + H] $^+$ calcd for $\text{C}_{29}\text{H}_{33}\text{O}_8\text{N}_2$: 537.2237; found: 537.2242.

(2*S*,5*R*)-Isomer (26*a*)

In the same manner as described above, **25a** (1.44 g, 2.08 mmol) was converted into **26a**.

Yield: 1.09 g, 2.03 mmol (98%); colorless solid; $[\alpha]_{\text{D}}^{23} -1.3$ (c 0.91, MeOH).

$^1\text{H NMR}$ (CDCl_3 , 300 MHz): 1.4–1.6 (2 H, m), 1.6–2.05 (2 H, m), 3.20 (1 H, br s, OH), 3.34 (1 H, d, $J = 11.3$ Hz, H-6), 3.74 (1 H, br d, $J = 11.3$ Hz, H-6), 4.15 (1 H, br s, OH), 4.40 (1 H, m, H-2), 4.76 (1 H, d, $J = 11.0$ Hz, CH_2Ph), 4.80 (1 H, d, $J = 11.0$ Hz, CH_2Ph), 5.07 (2 H, m, PhCH_2), 5.14 (2 H, m, PhCH_2), 5.57 (1 H, br d, $J = 8.0$ Hz, BnONH), 7.2–7.4 (15 H, s, ArH), 9.35 (1 H, br s, NHOBn).

HRMS (FAB): m/z [M + H] $^+$ calcd for $\text{C}_{29}\text{H}_{33}\text{O}_8\text{N}_2$: 537.2237; found: 537.2241.

Benzyl (2*S*,5*S*)-5-Benzylloxycarbamoyl-2-benzylloxycarbonyl-amino-5-hydroxy-6-methylsulfonyloxyhexanoate (27β)

A solution of **26β** (0.165 g, 0.308 mmol) and MsCl (36 μL , 1.5 equiv) in pyridine (5 mL) was stirred at r.t. under N_2 for 6 h. H_2O (3 mL) was added at 0 °C and the mixture was extracted into EtOAc (3 × 15 mL). The combined organic layer was washed with aq sat. NH_4Cl (1 × 5 mL) and H_2O (1 × 5 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was recrystallized (hexane–EtOAc), purified further by column chromatography on silica gel (hexane–EtOAc, 1:1) and again recrystallized (hexane–EtOAc) to give **27β**.

Yield: 0.169 g, 0.275 mmol (89%); colorless powder; mp 117.5–118.0 °C; $[\alpha]_{\text{D}}^{24} +3.8$ (*c* 1.2, CHCl₃).

IR (KBr): 3350 (s), 3150 (m), 3050 (w), 3025 (w), 1730 (s, C=O), 1705 (s), 1665 (s), 1355 (s), 1175 (s), 950 (m), 740 (m), 695 (s) cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ = 1.56 (1 H, m), 1.74–1.90 (3 H, m), 2.97 (3 H, s, SCH₃), 3.65 (1 H, s, OH), 4.13 (1 H, d, *J* = 11.0 Hz, CHHOMs), 4.37 (1 H, d, *J* = 10.7 Hz, CHHOMs), 4.42 (1 H, m, H-2), 4.87 (2 H, s, NOCH₂Ph), 5.08 (2 H, s, CH₂Ph), 5.13 (1 H, d, *J* = 12.1 Hz, CHHPh), 5.20 (1 H, d, *J* = 12.9 Hz, CHHPh), 5.42 (1 H, d, *J* = 7.4 Hz, NH), 7.26–7.42 (15 H, m, ArH), 9.16 (1 H, s, NHOBn).

¹³C NMR (CDCl₃, 150 MHz): δ = 14.08, 14.11, 22.59, 25.86, 30.78, 31.52, 37.21, 53.50, 60.40, 67.12, 67.34, 73.64, 76.62, 78.39, 128.08, 128.21, 128.32, 128.49, 128.51, 128.54, 128.60, 128.85, 129.32, 134.59, 135.00, 135.93, 156.12, 168.40, 171.76.

MS–FAB: *m/z* = 91, 181, 571, 615 [M + H]⁺.

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₃₀H₃₅O₁₀N₂S: 615.2012; found: 615.2012.

(2*S*,5*R*)-Isomer (27*a*)

In the same manner as described above, **26a** (1.09 g, 2.03 mmol) was converted into **27a**.

Yield: 756 mg, 1.23 mmol (59%); colorless powder; mp 136–137.5 °C; $[\alpha]_{\text{D}}^{24} -3.0$ (*c* 0.30, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 1.48–1.70 (2 H, m), 1.92 (1 H, m), 2.03 (1 H, m), 2.98 (3 H, s, SCH₃), 4.11 (1 H, d, *J* = 10.7 Hz, CHHOMs), 4.32 (1 H, d, *J* = 10.7 Hz, CHHOMs), 4.53 (1 H, m, H-2), 4.75 (1 H, s, OH), 4.83 (1 H, d, *J* = 11.0 Hz, NOCHHPh), 4.88 (1 H, d, *J* = 11.0 Hz, NOCHHPh), 5.11 (2 H, s, CH₂Ph), 5.17 (2 H, s, CH₂Ph), 5.52 (1 H, d, *J* = 8.0 Hz, NH), 7.26–7.42 (15 H, m, ArH), 9.21 (1 H, s, NHOBn).

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₃₀H₃₅O₁₀N₂S: 615.2012; found: 615.2014.

Benzyl (2*S*,5*S*)-5-Benzyloxycarbonyl-2-benzyloxycarbonyl-amino-5-*tert*-butyldimethylsilyloxy-6-methylsulfonyloxyhexanoate (28*β*)

To a mixture of **27β** (61.0 mg, 99.2 μmol) and 2,6-lutidine (46 μL, 4.0 equiv) in CH₂Cl₂ (1.2 mL) was added TBSOTf (45 μL, 2.0 equiv) at 0 °C. The solution was warmed to r.t. and stirred overnight. H₂O (1 mL) was added at 0 °C and the mixture was extracted into EtOAc (3 × 10 mL). The combined organic layer was washed with aq sat. NaHCO₃ (1 × 3 mL) and H₂O (1 × 2 mL), dried over anhyd Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **28β**. The de was determined by HPLC using a Daicel Chiralcel[®] column [OD (4.6 × 250 mm), *i*-PrOH–hexane (1:4), 0.5 mL/min; 25 °C; detection, 254 nm; *t*_R 27.7 min].

Yield: 52.4 mg, 71.9 μmol (72%); colorless oil; $[\alpha]_{\text{D}}^{22} -6.8$ (*c* 2.2, CHCl₃); ~100% de.

IR (film): 3400 (s), 3350 (br s), 3150 (w), 3050 (m), 3025 (m), 1740–1680 (br s), 740 (m), 695 (s).

¹H NMR (CDCl₃, 300 MHz): δ = 0.029 (3 H, s, SiMe), 0.099 (3 H, s, SiMe), 0.67 (9 H, s, *t*-Bu), 1.48 (1 H, m), 1.68–1.91 (3 H, m), 2.98 (3 H, s, SMe), 4.03 (1 H, d, *J* = 10.2 Hz, H-6), 4.33 (1 H, d, *J* = 10.7 Hz, H-6), 4.36 (1 H, m, H-2), 4.82 (1 H, d, *J* = 11.8 Hz, NOCHHPh), 4.88 (1 H, d, *J* = 11.8 Hz, NOCHHPh), 5.10 (2 H, s, CH₂Ph), 5.18 (2 H, s, CH₂Ph), 5.32 (1 H, d, *J* = 8.8 Hz, NH), 7.30–7.42 (15 H, m, ArH), 8.80 (1 H, s, NHOBn).

¹³C NMR (CDCl₃, 125 MHz): δ = -3.04, -2.90, 14.07, 14.14, 18.05, 20.99, 22.59, 25.60, 26.61, 31.29, 31.54, 36.84, 53.24, 60.32, 67.02, 67.40, 72.81, 78.30, 80.43, 128.09, 128.18, 128.48, 128.61, 128.63,

128.78, 128.97, 129.07, 134.54, 134.86, 136.05, 155.64, 167.92, 171.27.

MS–FAB: *m/z* = 73, 91, 181, 671, 729 [M + H]⁺.

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₃₆H₄₉O₁₀N₂SiS: 729.2877; found: 729.2877.

(2*S*,5*R*)-Isomer (28*α*)

In the same manner as described above, **27a** (744 mg, 1.21 mmol) was converted into **28a**. The de was determined by HPLC using a Daicel Chiralcel[®] column [OD (4.6 × 250 mm), *i*-PrOH–hexane (1:4), 0.5 mL/min; 25 °C; detection, 254 nm; *t*_R 25.5 min].

Yield: 871 mg, 1.19 mmol (98%); colorless oil; $[\alpha]_{\text{D}}^{24} +5.0$ (*c* 0.22, CHCl₃); ~100% de.

¹H NMR (CDCl₃, 300 MHz): δ = 0.034 (3 H, s, SiMe), 0.10 (3 H, s, SiMe), 0.67 (9 H, s, *t*-Bu), 1.48 (1 H, m), 1.7–2.05 (3 H, m), 2.96 (3 H, s, SMe), 3.98 (1 H, d, *J* = 10.2 Hz, H-6), 4.33 (1 H, d, *J* = 10.2 Hz, H-6), 4.3–4.4 (1 H, m, H-2), 4.84 (2 H, s, NOCH₂Ph), 5.09 (2 H, s, CH₂Ph), 5.16 (2 H, s, CH₂Ph), 5.47 (1 H, d, *J* = 8.2 Hz, NH), 7.30–7.42 (15 H, m, ArH), 8.80 (1 H, s, NHOBn).

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₃₆H₄₉O₁₀N₂SiS: 729.2877; found: 729.2880.

(3*S*,3'*S*)-1-Benzyloxy-3-(3'-benzyloxycarbonyl-3'-benzyloxycarbonylaminopropyl)-3-*tert*-butyldimethylsilyloxy-2-azetidinone (29*β*) and (3*S*,3'*S*)-1-Benzyloxy-3-(3'-benzyloxycarbonyl-amino-3'-carboxypropyl)-3-*tert*-butyldimethylsilyloxy-2-azetidinone (30*β*)

To a solution of **28β** (64.1 mg, 0.0879 mmol) in anhyd THF (1.3 mL) was added a solution of KHMDS (0.5 M, 0.21 mL, 0.105 mmol) in toluene at -78 °C and the resulting mixture was stirred for 12 h while the temperature of the solution gradually raised to 0 °C. The mixture was quenched with sat. aq NH₄Cl (2 mL) and extracted into EtOAc (3 × 5 mL). The extract was dried with MgSO₄, concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane–EtOAc–AcOH, 2:1:0→0:20:1) to give **29β** and **30β**.

29*β*

Yield: 33.0 mg, 0.0521 mmol (59%); colorless oil; $[\alpha]_{\text{D}}^{26} +14$ (*c* 0.64, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 0.040 (3 H, s, SiMe), 0.092 (3 H, s, SiMe), 0.81 (9 H, s, *t*-Bu), 1.48–1.8 (3 H, m), 2.06 (1 H, m), 3.11 (1 H, d, *J* = 4.6 Hz, H-4), 3.15 (1 H, d, *J* = 4.6 Hz, H-4), 4.37 (1 H, m, H-3'), 4.89 (1 H, d, *J* = 11.3 Hz, NOCHHPh), 4.95 (1 H, d, *J* = 11.3 Hz, NOCHHPh), 5.10 (2 H, s, CH₂Ph), 5.14 (1 H, d, *J* = 12.3 Hz, CH₂Ph), 5.16 (1 H, d, *J* = 12.3 Hz, CH₂Ph), 5.26 (1 H, d, *J* = 8.3 Hz, NH), 7.26–7.41 (15 H, m, ArH).

¹³C NMR (CDCl₃, 75 MHz): -3.91, -3.82, 17.78, 25.40, 27.04, 31.82, 53.60, 60.55, 67.02, 67.24, 81.67, 128.20, 128.28, 128.41, 128.62, 128.73, 129.15, 135.01, 135.20, 136.23, 155.86, 165.27, 171.91.

MS–FAB: *m/z* = 73, 91, 429, 473, 633 [M + H]⁺.

HRMS (FAB): *m/z* [M + H]⁺ calcd for C₃₅H₄₅O₇N₂Si: 633.2996; found: 633.2999.

30*β*

Yield: 5.5 mg, 0.0101 mmol (11%); colorless oil.

¹H NMR (CDCl₃, 300 MHz): δ = 0.050 (3 H, s, SiMe), 0.103 (3 H, s, SiMe), 0.83 (9 H, s, *t*-Bu), 1.56–1.87 (3 H, m), 2.10 (1 H, m), 3.19 (1 H, d, *J* = 4.4 Hz, H-4), 3.23 (1 H, d, *J* = 4.4 Hz, H-4), 4.31 (1 H, m, H-3'), 4.91 (1 H, d, *J* = 11.5 Hz, NOCHHPh), 4.96 (1 H, d, *J* = 11.5 Hz, NOCHHPh), 5.02–5.18 (2 H, m, CH₂Ph), 5.41 (1 H, d, *J* = 7.7 Hz, NH), 7.26–7.41 (10 H, m, ArH).

MS–FAB: m/z = 73, 91, 339, 383, 543 [M + H]⁺, 565 [M + Na]⁺.

HRMS (FAB): m/z [M + H]⁺ calcd for C₂₈H₃₉O₇N₂Si: 543.2527; found: 543.2533.

(3R,3'S)-Isomer (29a)

In the same manner as described above, **28a** (844 mg, 1.16 mmol) was converted into **29a**.

Yield: 528 mg, 0.834 mmol (72%); colorless oil; $[\alpha]_D^{26}$ –12 (*c* 0.50, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 0.04 (3 H, s, SiMe), 0.08 (3 H, s, SiMe), 0.81 (9 H, s, *t*-Bu), 1.62 (1 H, m), 1.75–1.95 (2 H, m), 2.1 (1 H, m), 3.14 (1 H, d, *J* = 5 Hz, H-4), 3.18 (1 H, d, *J* = 5 Hz, H-4), 4.37 (1 H, m, H-2), 4.90 (1 H, d, *J* = 12 Hz, NOCHHPH), 4.96 (1 H, d, *J* = 12 Hz, NOCHHPH), 5.12 (2 H, s, CH₂Ph), 5.16 (2 H, s, CH₂Ph), 5.26 (1 H, d, *J* = 8.8 Hz, NH), 7.26–7.41 (15 H, m, ArH).

HRMS (FAB): m/z [M + H]⁺ calcd for C₃₅H₄₅O₇N₂Si: 633.2996; found: 633.3000.

(3S,3'S)-1-Benzylxy-3-(3'-benzylxycarbonyl-3'-benzylxy-carbonylamino-propyl)-3-hydroxy-2-azetidinone (31β)

To a solution of **29β** (50.0 mg, 92.1 μmol) in THF (1 mL) was added TBAP in THF (1 M, 111 μL, 1.2 equiv) at 0 °C under argon and the mixture was stirred for 1 h at 0 °C. After dilution with Et₂O (5 mL), the reaction was quenched with aq sat. NH₄Cl (1 mL) and extracted into EtOAc (3 × 10 mL). The combined organic layer was dried with MgSO₄, concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane–EtOAc–AcOH, 5:15:1) to give **31β**.

Yield: 38.6 mg, 90.1 μmol (98%); colorless oil; $[\alpha]_D^{26}$ –7.4 (*c* 0.26, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 1.55–1.90 (3 H, m), 2.02 (1 H, m), 3.12 (1 H, d, *J* = 4.4 Hz, H-4), 3.29 (1 H, d, *J* = 4.7 Hz, H-4), 4.27 (1 H, m, OH), 4.40 (1 H, m, H-3'), 4.89 (1 H, d, *J* = 11.3 Hz, NOCHHPH), 4.93 (1 H, d, *J* = 11.8 Hz, NOCHHPH), 5.08 (2 H, s, CH₂Ph), 5.14 (2 H, s, CH₂Ph), 5.61 (1 H, d, *J* = 8.0 Hz, NH), 7.25–7.40 (15 H, m, ArH).

¹³C NMR (CDCl₃, 75 MHz): δ = 27.4, 29.6, 30.0, 53.6, 59.8, 67.2, 67.3, 77.8, 80.3, 128.27, 128.32, 128.47, 128.62, 128.65, 128.75, 128.78, 129.25, 129.35, 134.8, 135.2, 136.1, 156.3, 165.8, 171.9.

MS–FAB: m/z = 91, 136, 154, 307, 519 [M + H]⁺.

HRMS (FAB): m/z [M + H]⁺ calcd for C₂₉H₃₁O₇N₂: 519.2131; found: 519.2140.

(3R,3'S)-Isomer (31α)

In the same manner as described above, **29a** (160 mg, 0.252 mmol) was converted into **31α**.

Yield: 125 mg, 0.241 mmol (96%); colorless oil; $[\alpha]_D^{24}$ –7.5 (*c* 0.10, CHCl₃).

¹H NMR (CDCl₃, 300 MHz): δ = 1.71 (2 H, t, *J* = 7.3 Hz), 1.85 (1 H, m), 1.97 (1 H, m), 2.02 (1 H, m), 3.11 (1 H, d, *J* = 4.7 Hz, H-4), 3.27 (1 H, d, *J* = 4.7 Hz, H-4), 3.76 (1 H, m, OH), 4.46 (1 H, m, H-3'), 4.90 (1 H, d, *J* = 11.3 Hz, NOCHHPH), 4.95 (1 H, d, *J* = 11.8 Hz, NOCHHPH), 5.10 (2 H, s, CH₂Ph), 5.15 (2 H, s, CH₂Ph), 5.55 (1 H, d, *J* = 7.7 Hz, NH), 7.25–7.40 (15 H, m, ArH).

HRMS (FAB): m/z [M + H]⁺ calcd for C₂₉H₃₁O₇N₂: 519.2131; found: 519.2136.

Tabtoxinine-β-lactam [(3S,3'S)-3-(3'-Amino-3'-carboxypropyl)-3-hydroxy-2-azetidinone] (1)

To a solution of **31β** (38.6 mg, 90.1 μmol) in H₂O (0.2 mL) and MeOH (0.2 mL) was added Raney-Ni (washed with aq 1 M HCl just before use). The suspension was stirred at r.t. under hydrogen for 2

h then the mixture was filtered, concentrated in vacuo and lyophilized to give **1**.

Yield: 17.0 mg (quant.); colorless amorphous solid; $[\alpha]_D^{26}$ –24 (*c* 0.14, H₂O) {Lit.^{11c} $[\alpha]_D^{25}$ –23.7 (*c* 0.30, H₂O)}.

IR (KBr): 3230 (s, OH, NH), 1740 (s, C=O), 1620 (m), 1400 (m), 1200 (m), 940 (w), 790 (w) cm^{–1}.

¹H NMR (D₂O, 300 MHz): δ = 1.65–2.08 (4 H, m, H-1', H-2'), 3.20 (1 H, d, *J* = 6.6 Hz, H-4), 3.32 (1 H, d, *J* = 6.6 Hz, H-4), 3.68 (1 H, t, H-3').

¹³C NMR (D₂O, 75 MHz): δ = 25.33, 30.75, 51.43, 54.93, 84.57, 174.29, 174.79.

HRMS (FAB): m/z calcd for C₇H₁₃N₂O₄: 189.0875; found: 189.0879.

3-epi-Tabtoxinine-β-lactam [(3R)-1]

In the same manner as described above, **31α** (220 mg, 0.348 mmol) was converted into (3R)-**1**.

Yield: 95.0 mg, 0.183 mmol (53%); colorless oil; $[\alpha]_D^{26}$ +38 (*c* 0.09, H₂O) {Lit.^{11c} $[\alpha]_D^{26}$ +35.0 (*c* 0.22, H₂O)}.

¹H NMR (D₂O, 500 MHz): δ = 1.6–2.1 (4 H, m, H-1', H-2'), 3.41 (1 H, d, *J* = 5.9 Hz, H-4), 3.53 (1 H, d, *J* = 5.9 Hz, H-4), 3.80 (1 H, m, H-3').

HRMS (FAB): m/z [M + H]⁺ calcd for C₇H₁₃N₂O₄: 189.0875; found: 189.0878.

Acknowledgment

We thank Dr. Yoshifumi Ito [Tohoku University, Japan] for academic assistance. This work was partially supported by a Grant-in-aid for Scientific Research from Japan Society for the Promotion of Science (No. 14760069 & 17580092), The Agricultural Chemical Research Foundation, Intelligent Cosmos Foundation and The Naito Foundation.

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