Supplementary Information

Efficient method for the deprotection of *tert*-butyldimethylsilyl

ethers using TiCl₄ – Lewis base complex:

Application to the synthesis of 1 β -methylcarbapenems

Akira Iida,^a Hiroki Okazaki,^a Tomonori Misaki,^a Makoto Sunagawa,^b Akira Sasaki^b and Yoo Tanabe^{*a}

^a *Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan.*

Fax: (+81)79-565-9077; Tel: (+81)79-565-8369; E-mail: tanabe@kwansei.ac.jp.

^b *Research Division, Sumitomo Pharmaceuticals Co., Ltd. 1-98, Kasugade Naka 3-Chome, Konohana-ku, Osaka 554-0022, Japan*

Table of Contents

General	S2
Experimental detail of comparable experiments	
(Fig. 1, 2, 3, and scheme 5)	S3
Experimental detail of chemoselective desilylation	
(Scheme 3 and 4)	S5
Spectra data of new compounds	S6
Desilylation of 1β-methylcarbapenems	S7
¹H and ¹³C NMR spectra of 1β-methylcarbapenems	S12

General

All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM) according to the method of Still.¹ TLC analysis was performed on 0.25 mm Silicagel Merck 60 F₂₅₄ plates. Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR. Chemical shifts (δ ppm) in CDCl₃ were reported downfield from TMS (= 0) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to CDCl₃ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. GC data were obtained on a SIMAZU GC-17A. Column: Widebore DB-1701; Ø 0.53 mm X 30 m. Oven temp.; 50 °C to 250 °C (20°C / min.). Injection / Detection (FID) temp.; 250 °C. Carrier gas, N₂. Mass spectra were obtained by electrospray ionization (ESI).

Reference

1. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Experimental detail of comparable experiments (Fig. 1, 2, 3, and scheme 5)

Comparable experiments of desilylation of 2-(*t*-butyldimethylsiloxy)nonane (**1**) (Fig. 1)

A solution of TiCl_4 (114 mg, 0.60 mmol) alone ■, or with AcOEt (53 mg, 0.60 mmol) ●, or with CH_3NO_2 (37 mg, 0.60 mmol) ▲, in chlorobenzene (1.30 mL) was added to a stirred solution of 2-(*t*-butyldimethylsiloxy)nonane (**1**, 129 mg, 0.50 mmol) in chlorobenzene (0.20 mL) at 0-5 °C under an Ar atmosphere to give 2-nonanol (**1'**).

GC conversion

■ : (4 min) 9%, (6 min) 19%, (8 min) 25%, (10 min) 35%, (15 min) 81%.
● : (2 min) 66%, (4 min) 81%, (6 min) 88%, (8 min) 92%, (10 min) 95%, (15 min) 100%. ▲ : (2 min) 8%, (4 min) 20%, (6 min) 36%, (8 min) 63%, (10 min) 94%, (15 min) 100%.

Comparable experiments of desilylation of 1-(*t*-butyldimethylsiloxy)-4-methylphenol (**5**) (Fig. 2)

A solution of TiCl_4 (237 mg, 1.25 mmol) alone ■, or with AcOEt (110mg, 1.25 mmol) ●, or with CH_3NO_2 (76 mg, 1.25 mmol) in CH_2Cl_2 (1.30 mL) ▲, in CH_2Cl_2 (1.30 mL) was added to a stirred solution of 1-(*t*-butyldimethylsiloxy)-4-methylphenol (**5**, 111 mg, 0.50 mmol) in CH_2Cl_2 (0.20 mL) at 20-25 °C under an Ar atmosphere to give *p*-cresol (**5'**).

GC conversion;

■ : (15 min) 0%, (30 min) 1%, (1 h) 3%, (2 h) 9%, (3 h) 18%, (4 h) 29%.
● : (15 min) 9%, (30 min) 28%, (1 h) 60%, (2 h) 88%, (3 h) 92%, (4 h) 100%.
▲ : (15 min) 100%.

Comparable experiments of desilylation of α - and β - carbonyl substituted TBDMS ethers **1**, **9**, **10**, and **11** (Fig. 3)

A solution of TiCl_4 (137 mg, 0.72 mmol) and CH_3NO_2 (44 mg, 0.72 mmol) in CH_2Cl_2 (0.70

mL) was added to a stirred solution of 2-(*t*-butyldimethylsiloxy)nonane (**1**, 78 mg, 0.30 mmol) **▲**, or to 2-(*t*-butyldimethylsiloxy)octan-4-one (**8**, 86 mg, 0.30 mmol) **■**, or octyl 2-(*t*-butyldimethylsiloxy)butylate (**9**, 99 mg, 0.30 mmol) **◆**, or 6-(*t*-butyldimethylsiloxy)decan-5-one (**10**, 86 mg, 0.30 mmol) **●**, in CH₂Cl₂ (0.80 mL) at -20 °C under an Ar atmosphere.

GC conversion;

▲: (5 min) 7%, (10 min) 20%, (15 min) 53%, (30 min) 75%, (45 min) 88%, (60 min) 98%.

■: (5 min) 10%, (10 min) 27%, (15 min) 55%, (30 min), 93%, (45 min) 100%.

◆: (5 min) 71%, (10 min) 96%, (15 min) 100%.

●: (5 min) 100%.

Experimental detail of scheme 5

A solution of TiCl₄ (137 mg, 0.72 mmol) and CH₃NO₂ (44 mg, 0.72 mmol) in CH₂Cl₂ (0.70 mL) was added to a stirred solution of 2-(*t*-butyldimethylsiloxy)nonane (**1**, 78 mg, 0.30 mmol) in CH₂Cl₂ (0.80 mL) at -25 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 15 min. Water was added to the reaction mixture, which was extracted with Et₂O. The organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : ether = 50 : 1) to give the starting material (68mg, 87%) and desired alcohol (3mg, 7%).

A similar reaction using octyl-2-(*t*-butyldimethylsiloxy)butylate (**10**, 99 mg, 0.30 mmol) instead of **1** produced desired alcohol (62mg, 95%) (starting material : 0%).

A similar reaction using 6-(*t*-butyldimethylsiloxy)decan-5-one (**11**, 86 mg, 0.30 mmol) instead of **1** produced desired alcohol (49mg, 95%) (starting material : 0%).

Experimental detail of chemoselective desilylation (Scheme 3 and 4)

Typical procedure of scheme 3

A mixture of TiCl_4 (68 mg, 0.36 mmol) and AcOEt (32 mg, 0.36 mmol) in chlorobenzene (0.60 mL) was added to a stirred solution of 1-(*t*-butyldimethylsiloxy)decane (**2**, 82 mg, 0.30 mmol) and 1-(benzyloxy)octane (**13**, 66 mg, 0.30 mmol) in chlorobenzene (0.40 mL) at 0-5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 30 min. GC conversion; **2** (100%) and **13** (0%).

Experimental detail of scheme 4

A mixture of TiCl_4 (68 mg, 0.36 mmol) and AcOEt (32 mg, 0.36 mmol) in chlorobenzene (0.60 mL) was added to a stirred solution of 2-(*t*-butyldimethylsiloxy)nonane (**1**, 78 mg, 0.30 mmol) and 1-(*t*-butyldimethylsiloxy)-4-methylphenol (**5**, 68 mg, 0.30 mmol) in chlorobenzene (0.40 mL) at 0-5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h.

GC conversion; **1** (100%) and **5** (0%).

A mixture of TiCl_4 (61 mg, 0.32 mmol) and AcOEt (28 mg, 0.32 mmol) in chlorobenzene (0.60 mL) was added to a stirred solution of 3-(*t*-butyldimethylsiloxy)octane (**18**, 73 mg, 0.30 mmol) and 2-(*t*-butyldiphenylsiloxy)nonane (**19**, 115 mg 0.30 mmol,) in chlorobenzene (0.40 mL) at -18 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 30 min.

GC conversion; **18** (100%) and **19** (0%).

Spectra data of new compounds

2-(*t*-butyldimethylsiloxy)decan-4-one (9)

colorless oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.02 (3H, s), 0.06 (3H s), 0.83-0.93 (3H, m), 0.86 (9H, s), 1.16 (3H, d, J = 5.8), 1.21-1.37 (6H, m), 1.50-1.60 (2H, m), 2.37 (1H, dd, J = 5.2, 15.1), 2.41 (2H, t, J = 7.6), 2.62 (1H, dd, J = 7.6, 15.1), 4.24-4.34 (1H, m); ^{13}C NMR (75 MHz, CDCl_3): δ = -5.1, -4.7, 13.9, 17.8, 22.4, 23.3, 24.0, 25.7, 28.8, 31.5, 44.5, 52.1, 65.5, 209.7; IR (neat) 2957, 2930, 2859, 1716, 1253, 1136, 1007, 777 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{34}\text{O}_2\text{Si}$ ($\text{M}+\text{Na}^+$) 309.2226, found 309.2219.

Octyl-2-(*t*-butyldimethylsiloxy)butylate (10)

colorless oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.04 (3H, s), 0.06 (3H s), 0.82-0.92 (3H, s), 0.86 (9H, s), 1.19 (3H, d, J = 6.2 Hz), 1.23-1.42 (10H, m), 1.57-1.66 (2H, m), 2.39 (1H, dd, J = 5.5, 14.4 Hz), 2.48 (1H, dd, J = 7.6 14.4 Hz), 4.03 (1H, dt, J = 6.5, 14.1 Hz), 4.06 (1H, dt, J = 6.5, 14.1 Hz), 4.22-4.33 (1H, m); ^{13}C NMR (75 MHz, CDCl_3): δ -5.03, -4.53, 14.07, 17.93, 22.62, 23.89, 25.71, 25.94, 28.58, 29.15, 29.19, 31.76, 44.95, 64.51, 65.87, 171.74; IR (neat) 2957, 2930, 2858, 1740, 1253, 1180, 1140, 1084 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{38}\text{O}_3\text{Si}$ ($\text{M}+\text{Na}^+$) 353.2488, found 353.2488.

Desilylation of 1 β -methylcarbapenems

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-cyclohexylthio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (20a')

A solution of TiCl_4 (138 mg, 0.727 mmol) and CH_3NO_2 (44.3 mg, 0.727 mmol) in CH_2Cl_2 (0.600 mL) was added to a stirred solution of the TBS ether (**20a**, 87.0 mg, 0.152 mmol) in CH_2Cl_2 (0.600 mL) at -78°C under an Ar atmosphere, and the mixture was stirred at the same temperature for 14 h. Water was added to the reaction mixture, which was extracted with AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane : AcOEt = 3 : 2) to give the desired product (**20a'**, 63 mg, 91%).

Colorless crystal; mp $165 - 167^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +115.5$ (c 0.92, DMF); ^1H NMR (300 MHz, CDCl_3) δ = 1.19-2.04 (11H, m), 1.28 (3H, d, J = 7.6 Hz), 1.38 (3H, d, J = 6.5 Hz), 3.03-3.12 (1H, m), 3.26 (1H, dd, J = 2.4, 6.5 Hz), 3.41 (1H, dq, J = 7.6, 8.9 Hz), 4.22 (1H, dd, J = 2.4, 8.9 Hz), 4.27 (1H, dq, J = 6.5, 6.5 Hz), 5.22 (1H, d, J = 13.8 Hz), 5.52 (1H, d, J = 13.8 Hz), 7.65-7.68 (2H, m), 8.20-8.23 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ = 17.3, 22.0, 25.3, 25.7, 26.1, 32.1, 36.1, 43.4, 44.2, 56.1, 59.5, 65.2, 66.1, 123.7, 124.0, 128.2, 143.2, 147.6, 152.4, 160.3, 172.5; IR (KBr) 3405, 2938, 1749, 1711, 1514, 1342, 1144 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{Na}^+$) 483.1566, found 483.1566.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-3-octylthio-7-oxo-1-

azabicyclo[3.2.0]hept-2-ene-2-carboxylate (20b'**)**

Following the procedure for the preparation of **20a'**, the desilylation of the TBS ether (88.7 mg, 0.147 mmol) in CH₂Cl₂ (0.58 mL) using a solution of TiCl₄ (134 mg, 0.706 mmol) and CH₃NO₂ (43.0 mg, 0.706 mmol) in CH₂Cl₂ (0.60 mL) gave the desired product (**20b'**; 57.7 mg, 80%).

Colorless crystal; mp 96 - 99 °C; [α]_D³⁰ +93.79 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ = 0.87 (3H, t, *J* = 6.9 Hz), 1.23–1.44 (10H, m), 1.27 (3H, d, 7.2 Hz), 1.38 (3H, d, 6.5 Hz), 1.60–1.70 (3H, m), 2.80 (1H, dt, 7.6, 12.0 Hz), 2.87 (1H, dt, 7.6, 12.0 Hz), 3.26 (1H, dd, *J* = 2.4, 6.9 Hz), 3.41 (1H, dq, *J* = 7.2, 8.9 Hz), 4.21 (1H, dd, *J* = 2.4, 8.9 Hz), 4.26 (1H, dq, *J* = 6.5, 6.5 Hz), 5.23 (1H, d, *J* = 13.8 Hz), 5.51 (1H, d, *J* = 13.8 Hz), 7.64–7.67 (2H, m), 8.20–8.23 (2H, m); ¹³C NMR (75 MHz, CDCl₃) δ = 14.0, 16.9, 21.9, 22.6, 28.7, 29.0, 29.7, 31.5, 31.7, 43.2, 56.1, 59.4, 65.1, 66.0, 123.0, 123.8, 128.1, 143.1, 147.5, 153.8, 160.5, 172.5; IR (KBr) 3400, 2930, 1774, 1726, 1522, 1342, 1148 cm⁻¹; HRMS (ESI) calcd for C₂₅H₃₄N₂O₆S (M+Na⁺) 513.2035, found 513.2032.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-benzylthio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (20c'**)**

Following the procedure for the preparation of **20a'**, the desilylation of the TBS ether (86.2 mg, 0.148 mmol) in CH₂Cl₂ (0.58 mL) using a solution of TiCl₄ (135 mg, 0.710 mmol) and CH₃NO₂

(43.3 mg, 0.710 mmol) in CH₂Cl₂ (0.60 mL) stirring for 11 h gave the desired product (**20c'**; 55 mg, 79%).

Colorless crystal; mp 156 – 157 °C; [α]_D²³ +30.62 (c 0.85, DMF); ¹H NMR (300 MHz, CDCl₃) δ = 1.28 (3H, d, *J* = 7.2 Hz), 1.36 (3H, d, *J* = 6.5 Hz), 1.73-1.81 (1H, brs), 3.25 (1H, dd, *J* = 2.4, 6.5 Hz), 3.40 (1H, dq, *J* = 7.2, 9.3 Hz), 4.09 (2H, s), 4.14 (1H, dd, *J* = 2.4, 9.3 Hz), 4.25 (1H, dq, *J* = 6.5, 6.5 Hz), 5.23 (1H, d, *J* = 13.8 Hz), 5.51 (1H, d, *J* = 13.8 Hz), 7.28-7.37 (5H, m), 7.63-7.67 (2H, m), 8.19-8.23 (2H, m); ¹³C NMR (75 MHz, CDCl₃) δ = 16.8, 21.9, 36.3, 43.4, 56.1, 59.5, 65.2, 66.1, 123.7, 123.8, 127.8, 128.2, 128.7, 128.9, 136.0, 143.0, 147.6, 152.3, 160.3, 172.6; IR (KBr) 3486, 1759, 1703, 1520, 1345, 1215, 1142 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₄N₂O₆S (M+Na⁺) 491.1253, found 491.1249.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (20d'**)**

Following the procedure for the preparation of (**20a'**), the desilylation of the TBS ether (89.1 mg, 0.157 mmol) in CH₂Cl₂ in CH₂Cl₂ (0.66 mL) using a solution of TiCl₄ (142 mg, 0.751 mmol) and CH₃NO₂ (46 mg, 0.751 mmol) in CH₂Cl₂ (0.60 mL) gave the desired product (**20d'**; 63.8 mg, 89%).

Colorless crystal; mp 149 – 153 °C; [α]_D²³ +233.68 (c 1.24, DMF); ¹H NMR (300 MHz, CDCl₃) δ = 0.97 (3H, d, *J* = 7.2 Hz), 1.31 (3H, d, *J* = 6.5 Hz), 1.77-1.84 (1H, brs), 3.10 (1H, dq, *J* = 7.2, 9.3 Hz), 3.21 (1H, dd, *J* = 2.8, 6.5 Hz), 4.18 (1H, dd, *J* = 2.8, 9.3 Hz), 4.23 (1H, dq, *J* = 6.5, 6.5

Hz), 5.29 (1H, d, $J = 13.8$ Hz), 5.56 (1H, d, $J = 13.8$ Hz), 7.37-7.42 (3H, m), 7.50-7.56 (2H, m), 7.68-7.71 (2H, m), 8.21-8.27 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) $\delta = 16.2, 21.8, 43.5, 56.0, 59.7, 65.4, 65.8, 123.5, 123.8, 128.2, 128.2, 129.3, 129.4, 134.1, 142.9, 147.6, 152.1, 160.5, 173.1$; IR (KBr) 3407, 1748, 1717, 1518, 1343, 1182, 1144 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$ ($\text{M}+\text{Na}^+$) 477.1096, found 477.1091.

Allyl (4R,5S,6S) -3-(cyclohexylthio)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (20e')

Following the procedure for the preparation of (**20a'**), the desilylation of the TBS ether (74.3 mg, 0.155 mmol) in CH_2Cl_2 (0.64 mL) using a mixture of TiCl_4 (141 mg, 0.743 mmol) and CH_3NO_2 (45.3 mg, 0.743 mmol) in CH_2Cl_2 (0.60 mL) gave the desired product (**20e'**; 46.6 mg, 82%).

Colorless oil; $[\alpha]_{\text{D}}^{23} +133.67$ (c 1.02, CHCl_3); ^1H NMR (300 MHz, CDCl_3) $\delta = 1.18\text{-}2.03$ (11H, m), 1.26 (3H, d, $J = 7.2$ Hz), 1.37 (3H, d, $J = 6.2$ Hz), 2.99-3.10 (1H, m), 3.23 (1H, dd, $J = 2.4, 6.5$ Hz), 3.37 (1H, dq, $J = 7.2, 8.9$ Hz), 4.19 (1H, dd, $J = 2.4, 8.9$ Hz), 4.25 (1H, dq, $J = 6.5, 6.5$ Hz), 4.64-4.71 (1H, m), 4.80-4.87 (1H, m), 5.23-5.28 (1H, m), 5.42-5.49 (1H, m), 5.91-6.04 (1H, m); ^{13}C NMR (75 MHz, CDCl_3) $\delta = 17.1, 21.7, 25.3, 25.7, 26.1, 32.0, 36.0, 43.3, 43.9, 56.1, 59.3, 65.5, 66.0, 118.2, 124.6, 131.7, 150.9, 160.6, 172.5$; IR (KBr) 3509, 2926, 1780, 1709, 1545, 995 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_4\text{S}$ ($\text{M}+\text{Na}^+$) 388.1558, found 388.1557.

Allyl (4*R*,5*R*,6*S*)-3-[(3*S*,5*S*)-5-dimethylaminocarbonyl-1-allyloxycarbonylpyrrolidin-3-ylthio]-6-[(1*R*)-1-(hydroxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate [□] (**20f'**)

Following the procedure for the preparation of (**20a'**), the desilylation of the TBS ether (140 mg, 0.225 mmol) in CH₂Cl₂ (1.00 mL) using a mixture of TiCl₄ (205 mg, 1.08 mmol) and CH₃NO₂ (65.9 mg, 1.08 mmol) in CH₂Cl₂ (1.20 mL) gave the desired product (**20f'**; 68.0 mg, 60%).

Colorless oil; ¹H NMR (300 MHz, CDCl₃) δ = 1.26 (3H, m), 1.36 (3H, m), 1.94 (1H, m), 2.67 (1H, m), 2.97, 2.99, 3.06, 3.11 (total 6H, each singlet), 3.2-3.7 (4H, m), 3.98-4.29 (3H, m), 4.47-4.87 (5H, m), 5.15-5.5 (4H, m), 5.94 (2H, m); IR (neat) 3420, 1770, 1705, 1645, 1550, 1405, 1320, 1278, 1205, 1175, 1135, 975, 750.

Reference

1. Sunagawa, M.; Isobe, Y.; Takeuchi, Y.; Matsumura, H.; Noguchi, T.; Ozaki, Y. *Eur. Pat. Appl.* EP 256377 (1988); *Chem. Abstr.* **1988**, 109, 54576e.