A New Synthesis of a Key Intermediate of β-Lactam Antibiotics via Diastereoselective Alkylation of β-Hydroxy Ester

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The carbapenems, penems, monobactams, and tribactams have attracted considerable attention because of their potent activity and broad antimicrobial spectra. Since acetoxyazetidinone **1** is a common intermediate for the synthesis of many antibiotics, it has been the subject of considerable synthetic activities.[1] This important intermediate can be obtained through C-4 oxidation by means of a Ru-catalyzed reaction[2] such that the azetidinone **2** can be considered the true target. In a previous communication, we have reported an entirely new approach to the synthesis of a chiral 1β-methylcarbapenem key intermediate via diastereoselective alkylation of methyl (*R*)-3-hydroxybutyrate **4** and regioselective cuprate ring opening of a chiral epoxide.[3] On the basis of this study, it occurred to us that diastereoselective alkylation with benzyl chloromethyl ether (BOMCl) of the dianion of **4**, which is a common starting material in β-lactam chemistry[1,4] and subsequent simple transformation of the resulting discriminative alcohol functionality might enable us to stereoselectively produce an azetidinone **2**. In this paper, we present full details about diastereoselective alkylation of **4** and describe convenient synthesis of an azetidinone **2**.

Generally, alkylation of the dianion of β-hydroxy esters has been shown to yield products of high diastereomeric excess with predictable stereochemistry, but in the case of the alkylation of the dianion with BOMCl the benzyl ether was afforded with moderate diastereoselectivity (ca. 10:1) and low conversion yield (ca. 50%).[5] Previously, Sakai and co-workers reported the alkylation of cyclic β-hydroxy ester with BOMCl; the use of 1.7 equiv of LDA as a base and HMPA as an additive produced the benzyl ether in 84% isolated yield, but the diastereoselectivity was not reported.[6] This result was sharply contrasted with Ireland's study. In this case, alkylation of the **4** with BOMCl using 2.5 equiv of LDA afforded the benzyl ether and the alternate diastereomer in a ratio of 14:1 and 42.2% isolated yield (76.2% based on unrecovered starting material). Therefore, we tried to improve the yield and the diastereoselectivity of this reaction by using HMPA or DMPU as an additive and varying amount of a base. The results are summarized in Table 1. The reaction of dianion of **4** generated from LDA with freshly distilled BOMCl (1.4 equiv) in THF at −78 °C was monitored by analytical TLC for 2.5 h. Following usual workup, purification with silica gel column chromatography using *n*-hexanes/EtOAc (2:1) as eluent gave a 12:1 mixture of **5a** and **5b** in 40% isolated yield (entry 1). The ratio of **5a** and **5b** was monitored by GC on a capillary column. Addition of HMPA was effective in both yield and diastereoselectivity. The yield and the diasteroselectivity was improved to 61% and >25:1 when 1.7 equiv of LDA was used (entry 2). When excess amounts of base (2.2 and 2.4 equiv) were employed, there were dramatic improvements in yield (75% and 78%) while diastereomeric ratios were decreased (entries 6 and 8). Use of cyclic urea DMPU, which was recommended as a substitute for HMPA for safety reasons, gave no significant improvement in diasteroselectivity compared to HMPA with decreased yield (entries 3, 5, 7, and 9). As a result

Scheme 1

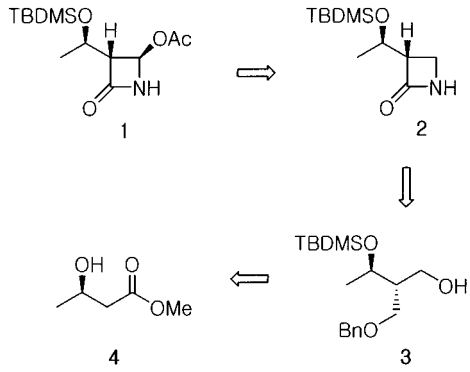
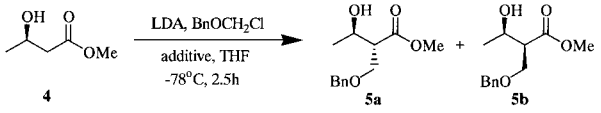


Table 1. Diastereoselective Alkylation of Methyl 3-(*R*)-Hydroxy butanoate



entry	equiv of LDA	additive[a]	yield (%)	dr (**5a**:**5b**)[b]
1	2.0	no	40	12:1
2	1.7	HMPA	61	>25:1
3	1.7	DMPU	33	23:1
4	2.0	HMPA	70	25:1
5	2.0	DMPU	35	20:1
6	2.2	HMPA	75	12:1
7	2.2	DMPU	42	10:1
8	2.4	HMPA	78	4:1
9	2.4	DMPU	39	4:1

[a] Amount of additives: HMPA (5%), DMPU (10%). [b] Determined by GC.

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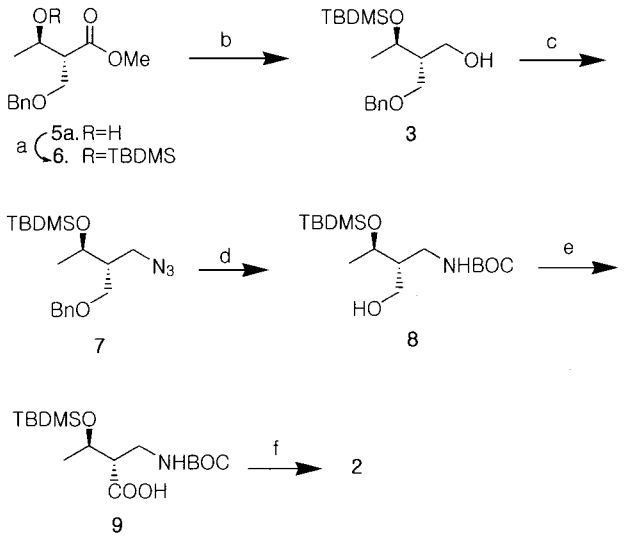
Scheme 2[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, (90%); (b) DIBALH, Et_2O, −78 °C (86%); (c) $(C_6H_5O)_2P(O)N_3$, DEAD, Ph_3P, THF, rt (95%); (d) $Pd(OH)_2$, $(BOC)_2O$, H_2 (50 psi), EtOAc, rt (81%); (e) $RuCl_3$, $NaIO_4$, $CHCl_3$−CCl_4−H_2O (2:2:3), rt (85%) (f) 30% TFA in CH_2Cl_2, 0 °C then Et_3N, $(2\text{-PyS})_2$, Ph_3P, CH_3CN, 65 °C (71% for two steps).

of extensive examination of various conditions, we found that reaction of **4** with BOMCl (1.4 equiv) using 2.0 equiv of LDA as a base and HMPA as an additive gave the desired diastereomer **5a** as the major compound with high diastereoselectivity and good yield (entry 4).

The synthetic approach to azetidinone **2** is outlined in Scheme 2. α-Benzyloxymethylated β-hydroxy butanoate **5a**, which was obtained under the optimal condition was silylated with TBDMSCl in 90% yield and followed by a DIBALH reduction in diethyl ether at −78 °C to afford alcohol **3** in 86% yield. To convert this alcohol to β-amino acid, which is the precursor of azetidinone **2**, azide was introduced by modified Bose conditions[7] using Ph_3P, DEAD, and diphenylphosphoryl azide (DPPA) in 94% yield. Fortunately, the resulting azide **7** could be directly converted to N-BOC protected alcohol **8** by means of a multireaction one-pot procedure. Thus, the simultaneous reduction of the azide and benzyl ether moieties and subsequent protection of the resulting amino group as *tert*-butoxycarbamoyl occurred by simple treatment of $Pd(OH)_2$ in the presence of $(Boc)_2O$ in EtOAc under H_2 atmosphere (50 psi) for 24 h in 82% yield. The alcohol **8** was oxidized to its corresponding acid by $RuCl_3/NaIO_4$ system in 85% yield, deprotection of the Boc group with diluted TFA in CH_2Cl_2 generated the β-amino acid **9**, and the treatment of **9** with 2,2′-dipyridyl disulfide and Ph_3P according to Ohno's procedure[8] afforded azetidinone **2** in 71% yield for the two steps. The physicochemical properties of **2** obtained by the present synthesis were in complete agreement with those reported in the literature.[9]

In summary, we report on the convenient synthesis of an important carbapenem intermediate **2** via diastereoselective benzyloxymethylation of methyl (*R*)-3-hydroxybutyrate **4** followed by one-pot reduction and protection as the key steps.

Experimental Section

General Methods. Melting points (mp) were determined on a micro melting point apparatus and are uncorrected. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). Unless otherwise noted, ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta = 0$ ppm) and the center line of the $CDCl_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Methyl (*R*)-3-hydroxybutyrate and benzyl chloromethyl ether were purchased from Tokyo Kasei Kogyo Co., Ltd. All other chemicals were of commercial grade and used without further purification or, if necessary, purified by distillation or crystallization prior to use.

(2*R*,3*R*)-Methyl 2-[(Benzyloxy)methyl]-3-hydroxybutyrate (5a). To a solution of diisopropylamine (28 mL, 0.20 mmol) and *n*-BuLi (1.6 M in hexane, 131.3 mL) in THF (455 mL) at −78 °C was added a solution of methyl (*R*)-3-hydroxybutyrate (11.812 g, 0.1mol) in THF (228 mL) over 15 min. After 60 min, a solution of benzyl chloromethyl ether (18.6 mL, 0.14mol) in HMPA (32 mL) was added over 5 min, and the reaction mixture was stirred for 3 h. The mixture was quenched by saturated aqueous NH_4Cl solution (200 mL) and extracted with Et_2O. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2:1, hexanes/EtOAc) to afford the benzyl ether **5a** (16.7 g, 70%) as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (d, 3H, J = 6.5 Hz), 2.75 (q, 1H, J = 6 Hz), 2.81 (br d, 1H), 3.73 (s, 3H), 3.76 (abx, 1H, J = 9.4, 6.0 Hz), 3.77 (abx, 1H, J = 9.4, 6.0 Hz), 4.13 (dq, 1H, J = 6.0, 6.5 Hz), 4.52 (q, 2H), 7.25−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.76, 52.55, 53.19, 67.18, 69.29, 74.07, 128.34, 128.46, 129.10, 138.46, 174.29, IR ($CHCl_3$) 3530, 3010, 2950, 2920, 2870, 1730, 1455 cm^{-1}; $[\alpha]^{25}_D$ −7.935° (*c* 1.01, $CHCl_3$); MS (CI) *m*/*z* 239 (M + H); HRMS (CI) calcd for $C_{13}H_{19}O_4$ (M + H) 239. 1285, found 239.1278 (−2.3 ppm error).

Methyl (2*R*,3*R*)-2-[(Benzyloxy)methyl]-3-(*tert*-butyldimethylsiloxy)butyrate (6). To a stirred solution of the alcohol **5a** (15 g, 62.95 mmol) in DMF (100 mL) were added imidazole (5.14 g, 75.5 mmol) and TBDMSCl (11.4 g, 75.54 mmol). The reaction mixture was stirred for 5 h, diluted with Et_2O (400 mL), and washed with H_2O and brine. The combined organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, 15:1, hexanes/EtOAc) to afford the desired silyl ether **6** (19.9 g, 90%) as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (d, 6H), 0.85 (s, 9H), 1.16 (d, 3H), 2.78 (m, 1H), 3.58 (q, 1H, J = 6.5, 9 Hz), 3.70 (q, 1H, J = 6.5, 9.5 Hz), 3.70 (s, 3H), 4.09 (dq, 1H, J = 6.5 Hz, 3.5 Hz), 4.51 (q, 2H), 7.27∼7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.48, −3.61, 18.56, 22.61, 26.36, 52.22, 55.14, 68.14, 68.73, 73.87, 128.30, 129.05, 138.79, 173.73; IR ($CHCl_3$) 2950, 2930, 2850, 1730, 1455, 1440 cm^{-1}; $[\alpha]^{22}_D$ −8.941° (*c* 1.01, $CHCl_3$); MS (CI) *m*/*z* 353 (M + H); HRMS (CI) calcd for $C_{19}H_{33}O_4Si$ (M + H) 353.2149, found 353.2148 (−0.2 ppm error).

(2*R*,3*R*)-2-[(Benzyloxy)methyl]-3-(*tert*-butyldimethylsiloxy)butan-1-ol (3). To a stirred solution of the silyl ether **6** (12.68 g, 36 mmol) in Et_2O (120 mL) at −78 °C was added DIBALH (1.5M in toluene, 52.5 mL) followed by stirring for 1 h. After addition of EtOAc (5 mL) and a saturated sodium potassium tartrate solution (150 mL) at −78 °C, the reaction mixture was stirred at 25 °C for 1 h. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The oily residue was purified by flash column chromatography (silica gel, 6:1, hexanes/EtOAc) to afford **3** (10 g, 86%) as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (d, 6H), 0.88 (s, 9H), 1.23 (d, 3H, J = 6.5 Hz), 1.71∼1.74 (m, 1H), 3.63 (q, 1H, J = 6.5, 9 Hz), 3.69 (q, 1H, J = 6.5, 9.5 Hz), 3.74 (q, 1H, J = 4, 11.5 Hz), 4.0 (q, 1H, J = 4, 11 Hz), 4.15∼4.20 (dq, 1H, J = 6.5 Hz, 3.5 Hz), 4.49∼4.55 (q, 2H), 7.27∼7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.45, −3.66, 18.55, 22.68, 26.47, 47.50,

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62.93, 69.76, 71.29, 74.15, 128.38, 128.45, 129.12, 138.86; IR (neat) 3453, 2955, 2930, 2891, 2857, 1468, 1366, 1254 cm^{-1}; $[\alpha]^{28}_D$ −8.271° (*c* 0.71, $CHCl_3$); MS (CI) *m*/*z* 325 (M + H); HRMS (CI) calcd for $C_{18}H_{33}O_3Si$ (M + H) 325.2200, found 239.2194 (−1.5 ppm error).

(1*R*,2*R*)-3-Azido-2-[(benzyloxy)methyl]-(1-methylpropoxy)-*tert*-butyldimethylsilane (7). To a stirred solution of alcohol **3** (4.8 g, 14.8 mmol), Ph_3P (7.75 g, 29.6 mmol), and DEAD (4.7 mL, 29.6 mmol) in THF (50 mL) was added a solution of DPPA (6.4 mL, 29.6 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 2 h, and the reaction mixture was evaporated and purified by flash chromatography (10:1 hexnanes/EtOAc) to afford azide **7** (4.9 g, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.04 (d, 6H), 0.88 (s, 9H), 1.23 (d, 3H, J = 6.5 Hz), 1.18 (m, 1H), 3.38 (q, 1H, J = 7.1, 12.2 Hz), 3.45 (q, 1H, J = 6.0, 9.1 Hz), 3.51 (q, 1H, J = 7.1, 4.8 Hz), 3.53 (q, 1H, J = 5.1, 9.1 Hz), 3.98 (m, 1H), 4.46∼4.53 (q, 2H), 7.26∼7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.32, −3.53, 18.69, 22.23, 26.52, 47.27, 50.27, 67.25, 69.07, 73.97, 128.35, 128.40, 129.09, 138.91; IR (neat) 2956, 2931, 2893, 2858, 2099, 1458 cm^{-1}; MS (CI) *m*/*z* 350 (M + H); HRMS (CI) calcd for $C_{18}H_{32}N_3O_2Si$ (M + H) 350.2265, found 350.2264 (+0.2 ppm error).

(2*R*,3*R*)-[3-(*tert*-Butyldimethylsiloxy)-2-(hydroxymethyl)butyl]carbamic Acid *tert*-Butyl Ester (8). A suspension of azide **7** (1.7 g, 4.9 mmol), $Pd(OH)_2$ (100 mg), and Boc_2O in EtOAc (15 mL) was hydrogenated under H_2 (50 psi) for 1day. The reaction mixture was filtered through Celite and evaporated. The oily residue was purified by flash chromatography (3:1 hexnanes/EtOAc) to afford alcohol **8** (1.32 g, 81.4%) as a white solid. mp 43−45 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07 (d, 6H), 0.88 (s, 9H), 1.2 (d, 3H, J = 6 Hz), 1.44 (s, 9H), 1.63 (m, 1H), 3.22 (dt, 1H), 3.47 (m, 1H), 3.62 (m, 2H), 3.96 (m, 1H), 5.01 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.38, −3.54, 18.59, 22.40, 26.53, 29.05, 37.95, 48.45, 62.26, 69.86, 80.21, 158.10; IR (neat) 3410, 2956, 2931, 2891, 2859, 1695, 1511, 1470, 1391, 1367 cm^{-1}; MS (CI) *m*/*z* 334 (M + H); HRMS (CI) calcd for $C_{16}H_{36}NO_4Si$ (M + H) 334.2415, found 334.2420 (+1.8 ppm error).

(2*R*,3*R*)-2-(*tert*-Butoxycarbonylaminomethyl)-3-(*tert*-butyldimethylsiloxy)butyric Acid (9). To a vigorously stirred solution of alcohol **8** (0.96 g, 2.9 mmol) in $CH_3CN/CCl_4/H_2O$ (1/1/1.5, 24.6 mL) were added $NaIO_4$ (2.5 g, 11.72 mmol) and $RuCl_3$ (2.2.mol %, 13.1 mg). After 4 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), and the layers were separated. The upper aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was diluted with ether, filtered through a Celite pad, and concentrated. The crude product was purified by flash column chromatography (1:1 hexnanes/EtOAc) to afford acid **9** (0.85 g, 85%) as a white solid. mp 120−121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) rotamer δ 0.06, 0.12 (2br, 6H), 0.90 (s, 9H), 1.22 (d, 3H, J = 6.5 Hz), 1.43, 1.47 (2br, 9H), 2.59, 2.69 (2br, 1H), 3.18, 3.25 (2br, 1H), 3.48, 3.56 (2br, 1H), 4.07, 4.26 (2br, 1H), 5.22, 6.46 (2br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) rotamer δ −4.51, −3.87, 18.54, 21.12, 22.71, 26.34, 29.07, 38.81, 40.62, 52.81, 54.76, 68.89, 69.28, 80.16, 156.68, 175.80, 176.78; IR (KBr) 3319, 3273, 2979, 2956, 2932, 2859, 1725, 1699, 1653, 1475, 1409, 1366 cm^{-1}; MS (CI) *m*/*z* 348 (M + H); HRMS(CI) calcd for $C_{18}H_{34}NO_5Si$ (M + H) 348.2207, found 348.2207 (+0.2 ppm error).

(3*S*)-3-[(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]azetidin-2-one (2). To a stirred solution of acid **9** (300 mg, 0.863 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 0.5 mL of 30% TFA in CH_2Cl_2. When no starting material could be detected by TLC, the reaction mixture was concentrated in vacuo and dissolved in CH_3CN (17.3 mL). To this solution was added Et_3N (0.12 mL). After 5 min, Ph_3P (272 mg, 1.036 mmol) and 2-Aldrithiol (22.82 mg, 1.036 mmol) were added and stirred for 12 h at 60 °C. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layer was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography to afford azetidinone (140 mg, 71%) as a white solid. mp 67−68 °C (lit.[8] mp 67−68 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (d, 6H), 0.88 (s, 9H), 1.19 (d, 3H, J = 6.24 Hz), 3.23 (qt, 1H), 3.29 (t, 1H, J = 5.1 Hz), 3.35 (q, 1H, J = 5.1, 2.55 Hz), 4.21 (m, 1H, J = 6.24, 4.54 Hz), 5.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.31, −3.56, 18.66, 22.25, 26.42, 38.34, 60.03, 65.96, 170.20; IR (neat) 3189, 2959, 2929, 2894, 2857, 1746, 1469, 1370 cm^{-1}; $[\alpha]^{27}_D$ −74.2° (*c* 0.7, $CHCl_3$) (lit.[8] $[\alpha]^{22}_D$ −74.1° (*c* 1.73, $CHCl_3$)); MS (CI) *m*/*z* 230 (M + H); HRMS (CI) calcd for $C_{11}H_{24}NO_2Si$ (M + H) 230.1578, found 230.1573 (−1.5 ppm error).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **3**, and **5**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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