Stereospecific Synthesis of a 1β-Methylcarbapenem Intermediate

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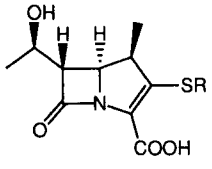
With the discovery of penicillin by A. FLEMING[1] in the 1930s, the modern brilliant history of antibiotics began. Since then, many kinds of antibiotics, both natural and even more effective synthetic ones, have been developed. Above all, the β-lactam antibiotics, namely, penicillins, cephalosporins,[2] cephamycins (7-methoxycephalosporins),[3] and thienamycin (carbapenem)[4] have liberated human beings from many infectious diseases. However, the appearance of resistant bacteria has necessitated discovery of new types of antibiotics with a broader spectrum of activity to combat the resistant strains. As a result, 1β-methylcarbapenem was synthesized and reported to be a powerful β-lactam antibiotic by a Merck group.[5] This antibiotic resisted deactivation by β-lactamases produced by bacteria, prevented the production of β-lactamase itself, and also imparted chemical stability. Therefore, many chemists became eager to develop an effective synthetic route to this type of antibiotic and to find new analogs of 1β-methylcarbapenem.

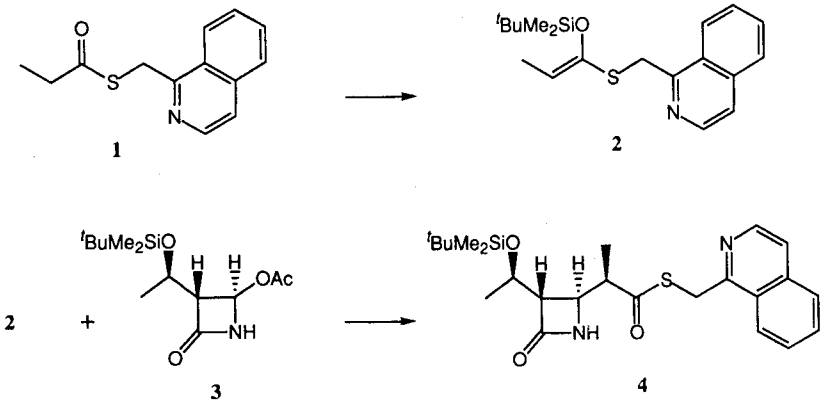


1β-Methylcarbapenem

We were also interested in finding a new effective route to 1β-methylcarbapenem, which has four contiguous chiral centers. We tried to elaborate these chiral centers stereoselectively, especially at the 1 and 5 positions in the carbapenem skeleton, by the reaction of (3*R*,4*R*)-3-[(1*R*)-*tert*-butyldimethylsilyloxy)ethyl]-4-acetoxy-2-azetidinone (**3**)[6] with (*E*)-1-(*tert*-butyldimethylsilyloxy)-1-[(1-isoquinolylmethyl)thio]-1-propene (**2**). In this paper, we describe a highly diastereoselective preparation of a thioester (**4**) which is a 1β-methylcarbapenem intermediate.

The reaction of 4-acetoxyazetidinone with the *O*-enolsilyl ether of acetate was reported by BARRETT *et al.*[7] By analogy of this reaction, the reaction of **3** with the *O*-enoltrimethylsilyl ether of phenyl thioacetate using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst to give a 4-(phenylthiocarbonyl)methyl compound, which was easily converted to various kinds of alkylthioesters, was reported.[8] BARRETT's procedure was further applied to the reaction of **3** with various kind of *O*-enolsilyl ethers of thiopropionates[9,10] to prepare 1-methylcarbapenem intermediates.

We also attempted this reaction using the *O*-*tert*-butyldimethylsilylenol ether of *S*-(1-isoquinolylmethyl) thiopropionate (**1**) to investigate the configuration of the 1-methyl chiral center. Treatment of **1** with lithium bis(trimethylsilyl)amide, and then *tert*-butyldimethylsilyl chloride in tetrahydrofuran-hexamethylphosphoramide at −78 °C yielded exclusively one product, (*E*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-[(1-isoquinolylmethyl)thio]-1-propene (**2**), in 62% yield by alumina column chromatography. The geometry of **2** was not determined in this stage. However, after the reaction of **2** with **3**, the 1(*R*)-methyl thioester (**4**) was obtained. Reaction of the (*Z*)-isomer of silylenol ether **2** with **3** gave a diastereomeric mixture of 1(*R*)- and 1(*S*)-methyl thioesters



without exception.[9,10] Therefore, judging from this result, it was concluded that the geometry of **2** is *E*. Next, as mentioned above, the reaction of **2** with 4-acetoxyazetidinone (**3**) using zinc chloride as a Lewis acid in dichloromethane at room temperature afforded a thioester (**4**) in 98% yield, stereospecifically.

Thus, we have shown that the 1-isoquinolylmethyl thioester of thiopropionic acid gives only the *E*-isomer of the silylenol ether of thiopropionate, and in subsequent reaction with **3**, the *E*-isomer yields 1(*R*)-methyl thioester almost quantitatively, which is convertible to 1β-methylcarbapenem, according to the reported methods.

Experimental

General

Melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. Optical rotation was recorded on a Perkin-Elmer 241 polarimeter. IR spectra were obtained on an A-102 spectrometer. Mass spectra were measured on a JEOL JMS-AX-505H mass spectrometer. ^{1}H NMR spectra were recorded with a JEOL EX-270 spectrometer for 270 MHz, and JEOL GX-400 spectrometer for 400 MHz using TMS as an internal reference.

S-(1-Isoquinolylmethyl) thiopropionate (**1**)

(i) A solution of 1-isoquinolic acid methyl ester (5.04 g, 26.9 mmol) in EtOH (10 ml) was poured into a suspension of $NaBH_4$ (3.06 g, 80.9 mmol) and LiCl (3.43 g, 80.9 mmol) in EtOH (60 ml) and THF (40 ml) with ice-cooling. After stirring for 4 hours, the reaction mixture was concentrated *in vacuo*, diluted with sat. NaCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was separated on a silica gel column. Elution with hexane - EtOAc (2 : 1) gave 1-isoquinolylmethanol (1.68 g, 10.6 mmol, 39%), which was dissolved in CH_2Cl_2 (50 ml) containing Et_3N (2.21 ml, 15.8 mmol). (ii) To this solution was added MsCl (0.90 ml, 11.6 mmol) dropwise at 5°C. After 1 hour, the reaction mixture was diluted with CH_2Cl_2 (100 ml), washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and separated on a silica gel column. Elution with hexane - EtOAc (3 : 1) gave a mesylate (2.18 g, 87%). (iii) To a solution of this mesylate (2.16 g, 9.10 mmol) in DMF (50 ml) was added AcSK (1.25 g, 10.9 mmol) at 5°C with stirring. After 30 minutes, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was separated on a silica gel column. Elution with hexane - EtOAc (3 : 1) gave *S*-(1-isoquinolyl)-methyl thioacetate (1.98 g, quantitatively), which was dissolved in MeOH (20 ml). (iv) To this solution was added 4.40 ml (22.8 mmol) of 28% solution of NaOMe in MeOH, and the solution was stirred for 1 hour with ice-cooling. The reaction mixture was concentrated *in vacuo*, diluted with water, adjusted to pH 7 with 1 M HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was dissolved in CH_2Cl_2 (20 ml). (v) To this solution was added Et_3N (1.40 ml, 10.0 mmol) and then EtCOCl (0.87 ml, 10.0 mmol). After stirring for 1 hour at 5°C, the reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue, which was separated on a silica gel column. Elution with hexane - EtOAc (3 : 1) gave *S*-(1-isoquinolylmethyl) thiopropionate (1.71 g, 81%). MS: *m/z* 231 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, J=7 Hz), 2.64 (2H, q, J=7 Hz), 4.84 (2H, s), 7.56~7.72 (3H, m), 7.83 (1H, d, J=7 Hz), 8.17 (1H, d, J=7 Hz), 8.45 (1H, d, J=6 Hz).

(*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-[1-(isoquinolylmethyl)thio]-1-propene (**2**)

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.81 ml, 8.58 mmol) in THF (20 ml) and HMPA (1.49 ml, 8.56 mmol) was added *n*-BuLi (4.91 ml, 7.86 mmol, 1.6 M in hexane) at −78°C. The solution was stirred for 10 minutes, and *tert*-butyldimethylsilyl chloride (2.16 g, 14.3 mmol) and Et_3N (2.99 ml, 21.4 mmol) were added. After stirring for 10 minutes at −78°C, a solution of **1** (1.65 g, 7.15 mmol) in THF (5 ml) was added dropwise. After stirring for 10 minutes, the temperature was elevated to room temperature, and the reaction mixture was diluted with pentane, washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and separated on an alumina column. Elution with hexane - EtOAc (4 : 1) gave **2** (1.52 g, 62%) as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.24 (6H, s), 1.01 (9H, s), 1.51 (3H, d, J=7 Hz), 4.51 (2H, s), 4.98 (1H, q, J=7 Hz), 7.53~7.69 (3H, m), 7.81 (1H, d, J=7 Hz), 8.18 (1H, d, J=7 Hz), 8.45 (1H, d, J=6 Hz).

(3*S*,4*S*)-3-[(1*R*)-(1-*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-((1-isoquinolylmethyl)thiocarbonyl)ethyl]-2-azetidinone (**4**)

To a solution of **2** (529 mg, 1.53 mmol) and **3** (200 mg, 0.70 mmol) in CH_2Cl_2 (5 ml) was added $ZnCl_2$ (208 mg,

1.53 mmol) with ice-cooling under nitrogen with stirring. The mixture was stirred for 12 hours at room temperature, diluted with CH_2Cl_2 (50 ml), washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*, and separated on a silica gel column. Elution with hexane-EtOAc (1:1) gave **4** (315 mg, 98%) as a white solid. mp 127~129°C (from *i*-Pr_2O); MS: *m/z* 459 ($M^+ + 1$). $[\alpha]_D^{20}$ −33.2° (*c* 0.5, MeOH). *Anal.* Calcd for $C_{24}H_{34}N_2O_3SSi$: C 62.84, H 7.47, N 6.11, S 6.99. Found: C 62.88, H 7.51, N 5.95, S 7.06. IR (KBr) cm^{-1} 1763, 1719 and 1684; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (6H, s), 0.86 (9H, s), 1.11 (3H, d, J=6 Hz), 1.29 (3H, d, J=7 Hz), 2.93 (1H, m), 3.02 (1H, dd, J=2, 4 Hz), 3.92 (1H, dd, J=2, 6 Hz), 4.17 (1H, m), 4.83 (2H, s), 5.88 (1H, bs), 7.58~7.74 (3H, m), 7.85 (1H, d, J=8 Hz), 8.13 (1H, d, J=8 Hz), 8.44 (1H, d, J=5 Hz).

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