A Facile Synthesis of (4*S*)-4-[(1*R*)-1-Carboxyethyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one: A Key Intermediate of 1-β-Methylcarbapenems

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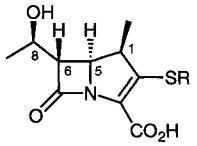
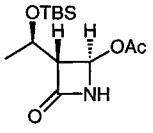
Titanium enolate-mediated aldol-type reaction of the chiral *N*-propionyl-1,3-benzoxazinone **4** with 4-acetoxyazetidin-2-one (**5**) gave the 2-(2-oxoazetidin-4-yl)propionic acid derivative **6** in high yield with high selectivity, which was transformed into (4*S*)-4-[(1*R*)-1-carboxyethyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one (**3**), a key intermediate of 1-β-methylcarbapenems **1**.

The 1-β-methylcarbapenems **1** have recently aroused considerable attention as one of the most promising candidates for the next generation of β-lactam antibiotics. This has stimulated extensive research toward development of an efficient synthetic method of **1**.[1] One of the most challenging problems encountered in their synthesis is the construction of the four contiguous stereogenic centers. The majority of exploratory approaches to this goal involve induction of the C-5 and C-1 chiralities utilizing those of the acetoxyazetidinone **2** which correspond to C-6 and C-8 of **1**.[1] We have also developed an efficient method for the process by the use of the Reformatsky reaction of **2** with a novel 3-propionyl-1,3-benzoxazinone derivative.[1d] An alternative fascinating approach toward **1** would involve the construction of C-5 and C-1 asymmetric centers followed by introduction of the chiralities at C-6 and C-8.[2] We report herein a practical synthesis of (4*S*)-4-[(1*R*)-1-carboxyethyl]-1-(*tert*-butyldimethylsilyl)azetidin-2-one (**3**), a key intermediate for the latter approach, by using a novel 1,3-benzoxazinone auxiliary.



1



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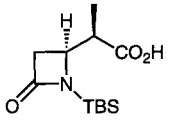


3

The compound **3** has been synthesized utilizing the aldol-type reaction of a chiral *N*-propionyl-1,3-thiazolidin-2-thione with 4-acetoxyazetidin-2-one **5** as a key step.[2] Both the stereoselectivity and yield of this method were satisfactory. However, it requires rather expensive tin(II) triflate. We recently developed a novel chiral 1,3-benzoxazinone auxiliary obtainable from menthone and salicylamide, and found that the titanium enolate of 3-propionyl derivative **4** and benzaldehyde underwent the highly *syn*-selective asymmetric aldol reaction.[3] With this information in mind, the titanium enolate-mediated aldol-type reaction of **4** with **5** was investigated.

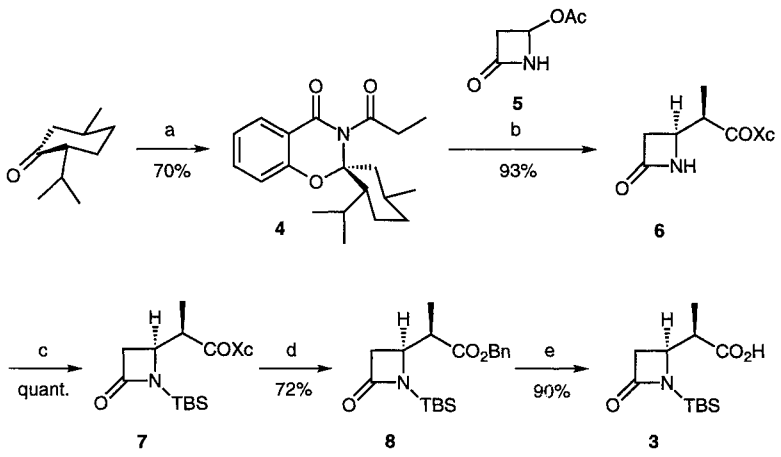
Taking the stereochemical outcome previously obtained by employing benzaldehyde as an electrophile into consideration, **4** derived from *d*-menthone was predicted to be appropriate to construct the required two adjacent stereogenic centers in **3** by the aldol reaction.[3] The *N*-propionyl-1,3-benzoxazinone **4** was prepared in 70% yield by the condensation of *d*-menthone and salicylamide followed by stereospecific isomerization and acylation according to our reported procedure (Scheme).[3] The titanium enolate was generated by treatment of **4** with sodium bis(trimethylsilyl)amide (2.0 equiv, −78 °C, 1 h) followed by transmetallation with chlorotitanium triisopropoxide (2.0 equiv, −78 °C, 1 h). Addition of **5**[4] (1.0 equiv) to the mixture cleanly effected the condensation to afford the desired 2-(2-oxoazetidin-4-yl)propionic acid derivative **6** in high yield with high selectivity (93% based on **5**, d r > 95:5). *N*-Silylation of **6** was conducted by treatment with *tert*-butyldimethylsilyl chloride (TBSCl) and triethylamine in dimethylformamide to afford **7** in quantitative yield. The structure of **7** was confirmed by X-ray crystallographic analysis as shown in the Figure.[5] The chiral auxiliary involved in **7** was removed by treating with lithium benzyloxide in tetrahydrofuran (−5 °C, 17 h), affording benzyl 2-(2-oxoazetidin-4-yl)propionate (**8**) in 72% yield. Hydrogenolysis of **8** over palladium on carbon gave the target compound **3** in 90% yield. The physicochemical properties of **3** obtained by the present synthesis were in complete agreement with those reported.[2]

In summary, a facile synthesis of the 1-β-methylcarbapenem key intermediate **3** was completed. The present synthesis has the following distinct advantages over the previously reported method:[2] (1) easy accessibility of the chiral auxiliary, (2) use of less hazardous chlorotitanium triisopropoxide, (3) high selectivity and high yield of the reaction, (4) the intermediates are easy to crystallize permitting facile isolation of the products in enantiomerically pure forms.

IR spectra were recorded on a Perkin–Elmer 1640 IR spectrophotometer and ^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer. Mass spectra were taken on a Hitachi M-2000A spectrometer at an ionizing potential of 70 eV. Microanalyses were performed by Perkin–Elmer 2400 Series II CHNS/O Analyzer. Flash chromatography was accomplished by using silica gel 60 (230–400 mesh, E. Merck).

3-Propionyl-*spiro*{2,3-dihydro-4*H*-1,3-benzoxazine-2,1′-[(2′*R*,5′*S*)-2′-isopropyl-5′-methylcyclohexane]}-4-one (4):

A mixture of salicylamide (16.5 g, 0.12 mol), *d*-menthone (15.4 g, 0.1 mol) and TsOH·H_2O (1.9 g, 0.01 mol) in toluene (200 mL) was refluxed for 20 h under continuous removal of the water separated. The mixture was washed successively with water, 10% aq NaOH (100 mL), and water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/$CHCl_3$/EtOAc, 5:5:1) to give the chiral auxiliary as a mixture of the isomers. A solution of the auxiliary and DBU (1.1 mL, 7.3 mmol) in *N*-methylpyrrolidone (73 mL) was stirred at 25 °C for 24 h, then at −20 °C for 24 h. Water (300 mL) was added and the product was extracted with EtOAc (3 × 100 mL). The combined extracts were washed successively with 10% aq citric acid (100 mL), water (100 mL), and brine (100 mL), dried ($MgSO_4$), and evaporated in vacuo. To the residue were added toluene (150 mL), Et_3N (10.2 mL, 73 mmol), CuCl (360 mg, 3.7 mmol), and propionyl chloride (6.4 mL, 73 mmol), and the resulting solution was stirred at 60 °C for 4 h. The mixture was washed successively with 10% aq citric acid (100 mL) and water (100 mL), dried ($MgSO_4$), and



Xc: Chiral auxiliary

Scheme

a: i) salicylamide, *p*-TsOH, Toluene, reflux, 20 h ii) DBU, *N*-methylpyrrolidone,25°C, 24h, -20°C, 24 h iii) EtCOCl, *i*-Pr_2EtN, CuCl (cat.), Toluene, 60°C, 4 h; b: i) $NaN(TMS)_2$, THF, -78°C, 1 h ii) $ClTi(Oi\text{-}Pr)_3$, -78°C, 1 h iii) **5** , -78°C-25°C, 3 h; c: TBS-Cl, Et_3N, DMF, 25°C, 17 h; d: BnOLi, THF, -5°C, 17 h; e: H_2 (3.5 atm), Pd-C, MeOH, 25°C, 1 h.

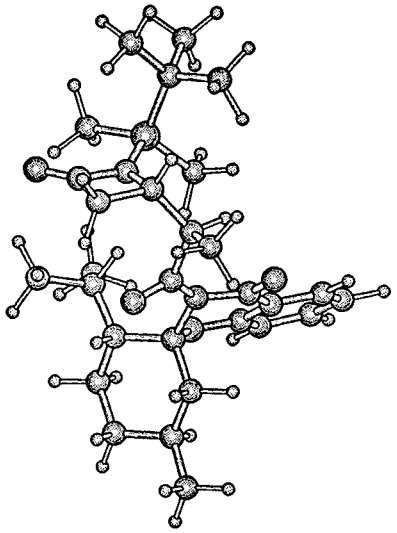


Figure. Parallel View of Compound **7**

evaporated in vacuo. The residue was chromatographed on a column of silica gel (hexane/EtOAc, 20:1) to afford 23.1 g (70%) of pure **4** as colorless crystals; mp 104–106°C; $[\alpha]_D^{23}$ + 7.9 (c = 1.1, MeOH).

IR (KBr): ν = 1723, 1693, 1468, 1323 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.76 (d, J = 6.3 Hz, 3 H), 0.88–1.27 (m, 10 H), 1.53–2.03 (m, 5 H), 2.22–2.30 (m, 1 H), 2.45–2.53 (m, 1 H), 2.66 (dq, J = 16.5, 7.3, 1 H), 3.14 (dq, J = 16.5, 7.5 Hz, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 7.03–7.11 (m, 1 H), 7.45–7.53 (m, 1 H), 7.95–8.00 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 9.6, 18.1, 21.5, (3q), 21.7 (t), 23.1 (q), 26.3, 29.1 (2d), 34.1, 34.9, 42.4 (3t), 44.3 (q), 99.7 (s), 117.0 (d), 117.1 (s), 122.1 (d), 128.3, 135.6 (2d), 154.9, 163.1, 181.1 (3s).

MS: m/z = 329 (M^+ + 1).

$C_{20}H_{26}NO_3$	calc.	C 73.14	H 7.98	N 4.27
(328.4)	found	73.23	7.95	3.92.

3-{(2*R*)-2-[(4*S*)-2-Oxoazetidin-4-yl]propionyl}-*spiro*{2,3-dihydro-4*H*-1,3-benzoxazin-2,1′-[(2′*R*,5′*S*)-2′-isopropyl-5′-methylcyclohexane]}-4-one (6):

To a solution of **4** (42.8 g, 0.13 mol) in THF (1200 mL) was added $NaN(TMS)_2$ (1M in THF) (130 mL, 0.13 mol) at −78°C. After stirring for 1 h at −78°C, Cl-Ti(OPr-*i*)$_3$ (1M in hexane) (130 mL, 0.13 mol) was added at −78°C and the resulting mixture was stirred at the same temperature for 1 h. Then, **5**[4] (8.4 g, 0.065 mol) in THF (60 mL) was added at −78°C, and the whole was gradually warmed up to 25°C and further stirred for 3 h. The mixture was evaporated in vacuo and CH_2Cl_2 (500 mL) was added to the residue. The resulting insoluble materials were removed by filtration through a pad of Celite, and the filtrate was washed with water (200 mL) and sat. aq $NaHCO_3$ (200 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by chromatography on a silica gel column (hexane: EtOAc, 9:1) to afford 24.1 g (93%) of **6** as colorless crystals; mp 89–91°C; $[\alpha]_D^{23}$ −69.2 (c = 1.08, MeOH).

IR (KBr): ν = 1754, 1693, 1611 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.75–1.12 (m, 10 H), 1.39 (d, J = 6.6 Hz, 3 H), 1.62–1.95 (m, 5 H), 2.04–2.37 (m, 2 H), 2.62–2.80 (m, 2 H), 2.97–3.08 (m, 1 H), 3.32–3.44 (m, 1 H), 3.90–3.96 (m, 1 H), 6.48 (br s, 1 H), 6.95 (d, J = 8.2 Hz, 1 H), 7.07–7.15 (m, 1 H), 7.54–7.59 (m, 1 H), 7.94–7.99 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 12.3, 17.9, 21.5 (3q), 21.7 (t), 23.3 (q), 26.3, 29.1 (2d), 34.0 (t), 41.9 (2t), 44.5, 47.8, 50.1 (3d), 100.6, 116.7 (2s), 117.1, 122.3, 128.4, 136.3 (4d), 154.9, 164.3, 167.1, 181.7 (4s).

MS: m/z = 399(M^+ + 1).

$C_{23}H_{30}N_2O_4$	calc.	C 69.32	H 7.59	N 7.03
(398.5)	found	69.44	7.37	7.22.

3-{(2*R*)-2-[4*S*)-1-*tert*-Butyldimethylsilyl-2-oxoazetidin-4-yl]propionyl}*spiro*-{2,3-dihydro-4*H*-1,3-benzoxazin-2,1′-[(2′*R*,5′*S*)-2′-isopropyl-5′-methylcyclohexane]}-4-one (7):

To a solution of **6** (12.0 g, 0.030 mol) in DMF (30 mL) were added TBSCl (4.9 g, 0.033 mol) and Et_3N (11.3 mL, 0.11 mol) at 0°C. After stirring for 17 h at 25°C, water (100 mL) was added, and the product extracted with Et_2O (3 × 100mL). The combined extracts were washed with water (3 × 200 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane:EtOAc, 20:1 to 4:1) to afford **7** (15.3 g, quant.) as colorless crystals; mp 128–130°C; $[\alpha]_D^{23}$ −72.2 (c = 1.04, MeOH).

IR (KBr): ν = 1754, 1693, 1611 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.11 (s, 3 H), 0.26 (s, 3 H), 0.76 (d, J = 5.9 Hz, 3 H), 0.91–1.00 (m, 16 H), 1.37 (d, J = 6.6 Hz, 3 H),

1.58–1.94 (m, 6H), 2.05–2.25 (m, 1H), 2.79–2.87 (m, 1H), 3.05–3.29 (m, 2H), 3.56–3.76 (m, 2H), 6.93 (d, $J = 8.3$ Hz, 1H), 7.06–7.14 (m, 1H), 7.49–7.58 (m, 1H), 7.94–7.98 (m, 1H).

^{13}C NMR ($CDCl_3$): $\delta = -4.9$, 17.2, 17.9 (3q), 18.9 (s), 21.5 (q), 21.7 (t), 23.3 (q), 26.3 (d), 26.5 (q), 29.2 (d), 34.1, 41.8, 42.6 (3t), 45.5, 47.6, 53.8 (3d), 101.0, 116.8 (2s), 116.9, 122.1, 128.4, 136.2 (4d), 154.8, 165.4, 172.9, 180.1 (4s).

MS: $m/z = 513$ ($M^+ + 1$).

$C_{29}H_{44}N_2O_4Si$	calc.	C 67.93	H 8.65	N 5.46
(512.8)	found	67.98	8.76	5.71.

(4*S*)-4-[1*R*)-1-(Benzyloxycarbonyl)ethyl]-1-(*tert*-butyldimethylsilyl)-2-oxoazetidine (8):

To a solution of benzyl alcohol (1.24 mL, 0.012 mol) in THF (20 mL) was added BuLi (1.6 M in hexane) (6.56 mL, 0.011 mol) at −60 °C, and the resulting mixture was warmed to 25 °C. The solution of BnOLi thus obtained was added dropwise to a solution of **7** (5.13 g, 10 mmol) in THF (30 mL) at −60 °C. After stirring for 17 h at −5 °C, the reaction was quenched by adding 10% aq citric acid (30 mL), and the mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by chromatography on a column of silica gel ($CHCl_3$/hexane/EtOAc, 15:15:1 to 10:10:1) to afford **8** (2.51 g, 72%) as a colorless oil; $[\alpha]_D^{23}$ −45.6 ($c = 1.24$, MeOH).

^{1}H NMR ($CDCl_3$): $\delta = 0.15$ (s, 3H), 0.19 (s, 3H), 0.94 (s, 9H), 1.18 (d, $J = 7.1$ Hz, 3H), 2.88–3.21 (m, 3H), 3.67–3.74 (m, 1H), 5.04–5.21 (m, 2H), 7.35 (s, 5H).

^{13}C NMR ($CDCl_3$): $\delta = 0.0$, 14.0 (2q), 19.0 (s), 26.4 (q), 41.3 (t), 42.2, 51.7, 66.8, 128.4 (d), 128.6 (d), 128.7 (d), 135.6 (s), 172.4 (s), 172.9 (s).

MS: $m/z = 348$ ($M^+ + 1$).

$C_{19}H_{29}NO_3Si$	calc.	C 65.67	H 8.41	N 4.03
(347.5)	found	65.89	8.72	3.77.

(4*S*)-4-[(1*R*)-1-Carboxyethyl]-1-(*tert*-butyldimethylsilyl)-2-oxoazetidine (3):

A mixture of **8** (1.8 g, 5.3 mmol) and 10% Pd/C (0.2 g) in MeOH (30 mL) was stirred at 25 °C under H_2 (3.5 atm) using a Parr apparatus for 1 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The crystals formed were collected and recrystallized from CH_2Cl_2 and hexane to afford 1.2 g (90%) of **3** as colorless crystals; mp 115–117 °C; $[\alpha]_D^{23}$ −56.3 ($c = 0.62$, $CHCl_3$) [Lit.[2] $[\alpha]_D^{23}$ −54.6 ($c = 0.6$, $CHCl_3$)].

IR (KBr): $\nu = 2938$, 1725 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 0.22$ (s, 3H), 0.29 (s, 3H), 0.96 (s, 9H), 1.19 (d, $J = 7.0$ Hz, 3H), 2.88–3.01 (m, 1H), 3.03–3.24 (m, 2H), 3.70–3.76 (m, 1H).

^{13}C NMR ($CDCl_3$): $\delta = 5.3$, 19.1 (2q) 24.2 (s), 31.7 (q), 45.8 (t), 47.0, 56.9 (2d), 178.1, 180.4 (2s).

MS: $m/z = 258$ ($M^+ + 1$).

The authors are indebted to Mr. H. Hiramatsu of this company for the X-ray analysis.

(1) For example, see:
(a) Shih, D.H.; Baker, F.; Cama, L.; Christensen, B.G. *Heterocycles* **1984**, *21*, 29.
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