

ASYMMETRIC SYNTHESIS OF NEW NON-NATURAL 1 β -METHYLCARBAPENEMS BEARING METHYLTHIO GROUP AT THE C6-POSITION[†]

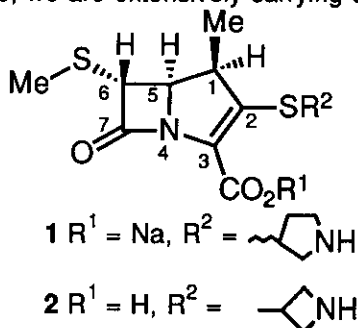
Yoshimitsu Nagao,^{a*} Takao Abe,^b Hisashi Shimizu,^b Toshio Kumagai,^b and Yoshinori Inoue^b

^aFaculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770, Japan

^bThe Chemical and Formulation Laboratories, Lederle (JAPAN) Ltd., Kashiwacho, Shiki, Saitama 353, Japan

Abstract – The asymmetric total synthesis of new non-natural 1 β -methylcarbapenems (**1** and **2**) has been accomplished starting from optically active C4-substituted azetidin-2-one (**4**).

1 β -Methylcarbapenems seem to be promising candidates for new-generation lactam-antibiotics because of their high potency, broad spectrum and fairly strong stability against renal dehydropeptidase-I.^{1,2} Therefore, we are extensively carrying out development of new non-

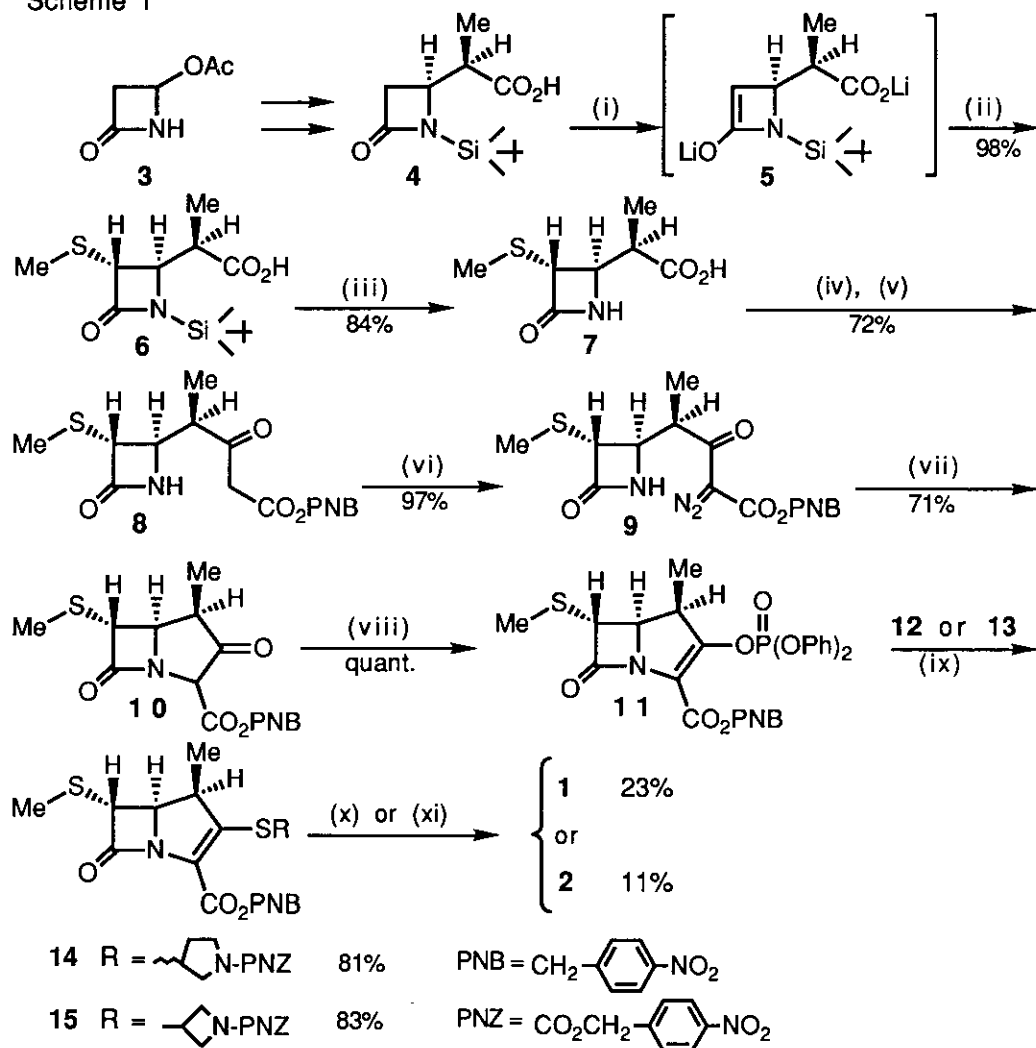


[†]Dedicated to Professor Emeritus Dr. Masatomo Hamana of Kyushu University on the occasion of his 75th birthday.

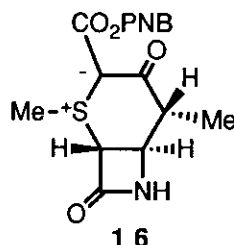
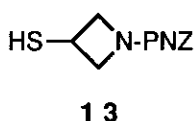
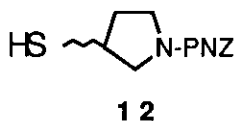
natural lactam-antibiotics involving 1 β -methylcarbapenems and useful methods for their asymmetric syntheses.^{2,3} In 1986, we reported an efficient asymmetric synthesis of (4*S*)-4[(1*R*)-1-carboxyethyl]-1-*tert*-butyldimethylsilylazetidin-2-one (**4**) by utilizing the highly diastereoselective alkylation of 4-acetoxy-2-azetidinone (**3**) with the tin(II) enolates of C4-chiral 3-propionyl-1,3-thiazolidine-2-thiones.^{3a} Thus, we attempted a total asymmetric synthesis of 6-methylthio 1 β -methylcarbapenems (**1** and **2**), exploiting optically active carboxylic acid (**4**), as shown in Scheme 1. It is a remarkable feature of this total synthesis that the commercially available and cheap compound (**3**) can be employed.

A solution of **4** in THF was added dropwise to a solution of lithium diisopropylamide (2.2 mol equiv.) in THF with stirring at -78°C under N₂ over 2 h. Then the mixture was stirred at -40°C for 1 h to obtain dianionic lithium enolate (**5**). After addition of methyl methanethiosulfonate (1.5 mol equiv.), the mixture was stirred at -40°C for 30 min and then at 0°C for 2 h to afford methylthio derivative (**6**) [mp 71-72°C, $[\alpha]_D^{25}$ -2.75° (c 0.4, CHCl₃)] in 98% yield. Stereochemistry of the C3 position of **6** was confirmed to be *R* configuration by 100 MHz ¹H nmr analysis [C3-H: δ 4.34 (*J*=2.0 Hz)] in CDCl₃.⁴ Thus, the methylthio group must be introduced exclusively from the less hindered α -side of the lithium enolate face (**5**) away from the β -C4 substituent to furnish **6**. Deprotection of the silyl group of **6** with 40% HF in MeCN gave compound (**7**) [mp 125-126°C, $[\alpha]_D^{25}$ +21.0° (c 0.22, CHCl₃)] in 84% yield. Compound (**7**) was subjected to the Masamune method,⁵ employing 1,1'-carbonyldiimidazole (CDI) (1.2 mol equiv.) and Mg(O₂CCH₂CO₂PNB)₂ (1.5 mol equiv.) in THF to give β -keto ester (**8**) as a colorless oil in 72% yield. After diazotization⁶ of **8** under the usual conditions, the resultant **9** [mp 101°C, $[\alpha]_D^{25}$ +13.25° (c 0.4, CHCl₃)] was allowed to react with Rh₂(C₇H₁₅CO₂)₄ (1 mol %) in benzene under reflux.⁶ Fortunately, the desired cyclization product (**10**) [colorless oil, $[\alpha]_D^{25}$ +155.7° (c 0.84, CHCl₃)] was obtained in 71% yield without formation of any sulfur ylide compound⁷ such as **16**. This chemoselective cyclization may be rationalized in terms of the following reason. Namely, cisoid cyclization toward the five-membered ring should be kinetically easier than transoid cyclization toward the six-membered ring fused with the azetidin-2-one moiety. Diphenylphosphoryl ester (**11**) derived from **10** was treated with *dl*-pyrrolidine thiol (**12**) (1.3 mol equiv.)⁸ and azetidine thiol (**13**) (1.3 mol equiv.) in MeCN at -35 to -10°C to give the corresponding thiol adducts **14** [mp 62-63°C, $[\alpha]_D^{25}$

Scheme 1

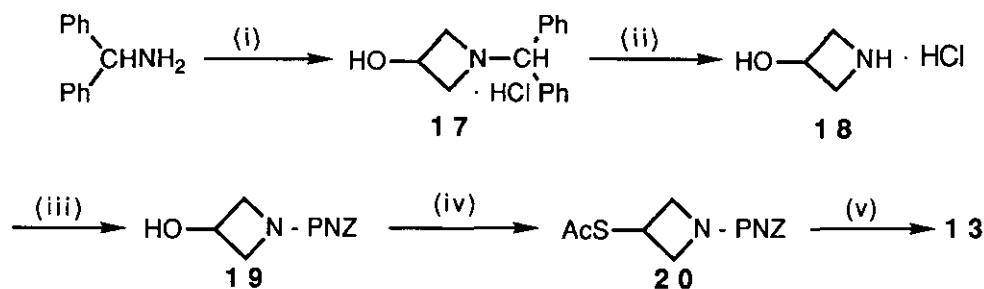


Reagents: (i) LDA; (ii) MeSSO₂Me, 10% citric acid; (iii) 40% HF; (iv) CDI;
 (v) Mg(O₂CCH₂CO₂PNB)₂; (vi) *p*-toluenesulfonyl azide; Et₃N; (vii) Rh₂(OOct)₄; (viii)
 (PhO)₂P(O)Cl, (i-Pr)₂NEt; (ix) (i-Pr)₂NEt; (x) H₂/PtO₂, NaHCO₃, Amberlite XAD-2;
 (xi) H₂/PtO₂, DIAION-HP40



+51.1° (*c* 1.32, CHCl₃) and **15** [mp 58-60°C, [α]_D²⁵+54.4° (*c* 0.5, CHCl₃)] in 81% and 84% yields, respectively. These structures were confirmed by their reasonable ¹H nmr (100 MHz) and ir spectra and elemental analyses.⁹ Deprotection of PNZ and PNB groups of **14** and **15** was also done by their catalytic hydrogenolysis on PtO₂ in THF-water (1:1) under 4 atm of H₂ pressure to furnish new 1 β -methylcarbapenems **1** [mp 240°C (decomp.), [α]_D²⁵+34.0° (*c* 0.35, water)] and **2** [mp 195°C (decomp.), [α]_D²⁵+87.5° (*c* 0.31, water)], respectively.¹⁰ Compound (**2**) exhibited significant antibacterial activities [MIC (μ g/ml)] *in vitro* screening tests.¹¹ Azetidine thiol (**13**) was transformed from known compound (**18**),¹² as shown in Scheme 2. Compound (**18**) was prepared by deprotection of the diphenylmethyl group of azetidin-3-ol (**17**) obtained from the reaction between aminodiphenylmethane and epichlorohydrin. Protection of the amino group of **18** with *p*-nitrobenzyloxycarbonyl chloride followed by the Mitsunobu reaction using thiolacetic acid as the nucleophile afforded acetylthio azetidine (**20**) (mp 91-92°C) as colorless prisms in 91% yield.¹³ Methanolysis of **20** with MeONa in THF-MeOH gave thiol (**13**) (mp 62-63°C) as colorless prisms in 99% yield.¹³

Scheme 2



Reagents: (i) epichlorohydrin, DMSO, ethanolic HCl; (ii) H₂/5%Pd-C, ethanolic HCl; (iii) PNZCl, Et₃N; (iv) AcSH, Ph₃P, EtO₂CN=NCO₂Et; (v) MeONa

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9. Compound 14: Ir (CHCl₃) 1780, 1720 1705 cm⁻¹; ¹H nmr (100 MHz, CDCl₃) δ 1.34 (3H, d, *J*=7.3 Hz), 1.80-2.20 (2H, m), 2.26 (3H, s), 3.28-3.62 (4H, m) 3.62-3.92 (2H, m), 4.17 (1H, m), 4.21 (1H, dd, *J*=2.4 and 7.3 Hz), 5.23 (2H, s), 5.31 and 5.44 (2H, AB, *J*=13.7 Hz), 7.52 (2H, d, *J*=8.8 Hz), 7.66 (2H, d, *J*=8.8 Hz), 8.23 (4H, d, *J*=8.8 Hz); Anal. Calcd for C₂₈H₂₈N₄O₉S₂: C, 53.49; H, 4.49; N, 8.91. Found: C, 53.61; H, 4.67; N, 8.63.
Compound 15: Ir (CHCl₃) 1760, 1720, 1705 cm⁻¹; ¹H nmr (100 MHz, CDCl₃) δ 1.28 (3H, d, *J*=7.3 Hz), 2.26 (3H, s), 3.04-3.36 (1H, m), 3.88-4.12 (4H, m), 4.16-4.26 (2H, m), 4.38-4.54 (1H, m), 5.19 (2H, s), 5.30 and 5.48 (2H, AB, *J*=13.7 Hz), 7.49 (2H, d, *J*=8.8 Hz), 7.66 (2H, d, *J*=8.8 Hz), 8.22 (4H, d, *J*=8.8 Hz); Anal. Calcd for C₂₇H₂₆N₄O₉S₂: C, 52.76; H, 4.27; N, 9.12. Found: C, 53.04; H, 4.48; N, 8.86.
10. Compound 1: Ir (KBr) 3800-2800, 1760, 1600 cm⁻¹; ¹H nmr (100 MHz, D₂O) δ 1.24 (3H, d, *J*=7.3Hz), 2.19 (3H, s), 2.20-2.70 (2H, m), 3.10-3.80 (4H, m), 3.80-4.10 (2H, m), 4.10-4.30 (1H, m), 4.4 (1H, d, *J*=2.0Hz); FAB MS *m/z* 336 (M⁺+1); Anal. Calcd for C₁₃H₁₇N₂O₃S₂Na·H₂O: C, 44.06; H, 5.40; N, 7.90. Found: C, 44.38; H, 5.23; N, 7.97.
Compound 2: Ir (KBr) 3700-2800, 1760, 1600 cm⁻¹; ¹H nmr (90 MHz, D₂O) δ 1.17 (3H, d, *J*=7.3 Hz), 2.14 (3H, s), 3.03-3.40 (1H, m), 3.83-4.13 (3H, m), 4.17-4.45 (4H, m); FAB MS *m/z* 323 (M⁺+Na); Anal. Calcd for C₁₂H₁₆N₂O₃S₂·3/2H₂O: C, 44.03; H, 5.81; N, 8.56. Found: C,

43.96; H, 5.53; N, 7.97.

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