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

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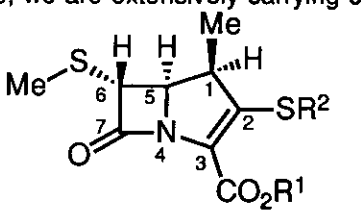
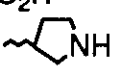
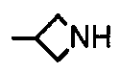
Abstract – The asymmetric total synthesis of new non-natural 1β-methylcarbapenems (**1** and **2**) has been accomplished starting from optically active C4-substituted azetidin-2-one (**4**).

1β-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-



1 R^1 = Na, R^2 = 

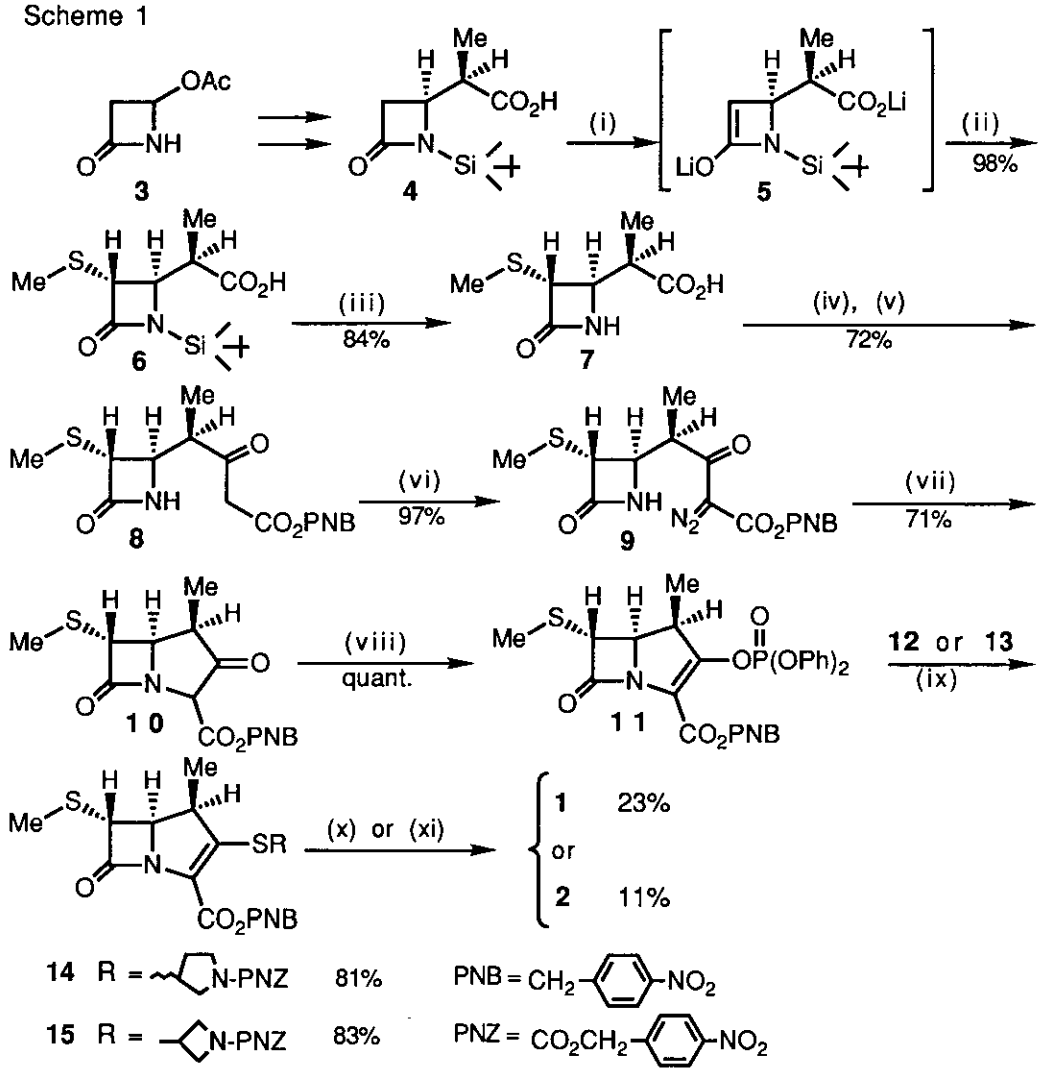
2 R^1 = H, R^2 = 

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

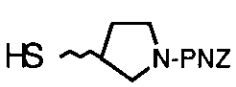
natural lactam-antibiotics involving 1β-methylcarbapenems and useful methods for their asymmetric syntheses.[2,3] In 1986, we reported an efficient asymmetric synthesis of (4*S*)-4[(1*R*)-1-carboxyethyl]-1-*tert*-butyldimethylsilylazetidin-2-one (**4**) by utilizing the highly diastereoselective alkylation 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 1β-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 N_2 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, $CHCl_3$)] in 98% yield. Stereochemistry of the C3 position of **6** was confirmed to be *R* configuration by 100 MHz ^{1}H nmr analysis [C3-H: δ 4.34 (*J*=2.0 Hz)] in $CDCl_3$.[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, $CHCl_3$)] in 84% yield. Compound (**7**) was subjected to the Masamune method,[5] employing 1,1'-carbonyldiimidazole (CDI) (1.2 mol equiv.) and $Mg(O_2CCH_2CO_2PNB)_2$ (1.5 mol equiv.) in THF to give β-keto ester (**8**) as a colorless oil in 72% yield. After diazotization[6] of **8** under the usual conditions, the resultant **9** [mp 101°C, $[\alpha]_D^{25}$+13.25° (*c* 0.4, $CHCl_3$)] was allowed to react with $Rh_2(C_7H_{15}CO_2)_4$(1 mol %) in benzene under reflux.[6] Fortunately, the desired cyclization product (**10**) [colorless oil, $[\alpha]_D^{25}$+155.7° (*c* 0.84, $CHCl_3$)] was obtained in 71% yield without formation of any sulfur ylide compound[7] 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)$MeSSO_2Me$, 10% citric acid; (iii) 40%HF; (iv) CDI; (v) $Mg(O_2CCH_2CO_2PNB)_2$; (vi) *p*-toluenesulfonyl azide; Et_3N; (vii) $Rh_2(OOct)_4$; (viii) $(PhO)_2P(O)Cl$, $(i\text{-}Pr)_2NEt$; (ix) $(i\text{-}Pr)_2NEt$; (x) H_2/PtO_2, $NaHCO_3$, Amberlite XAD-2; (xi) H_2/PtO_2, DIAION-HP40



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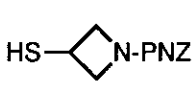

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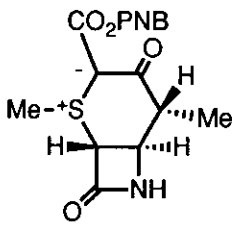

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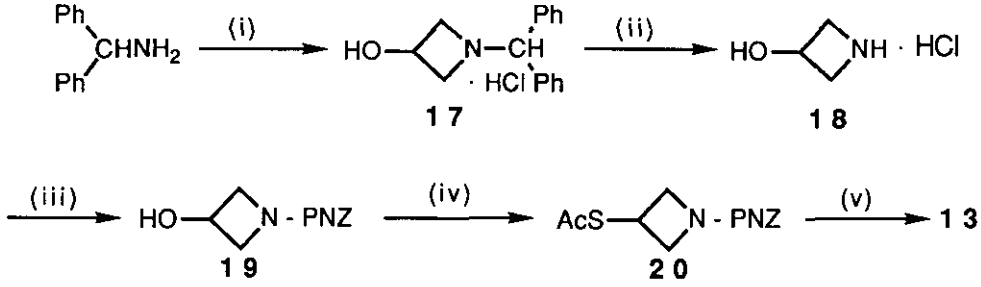
+51.1° (*c* 1.32, $CHCl_3$)] and **15** [mp 58-60°C, $[\alpha]_D^{25}$+54.4° (*c* 0.5, $CHCl_3$)] in 81% and 84% yields, respectively. These structures were confirmed by their reasonable ^1H nmr (100 MHz) and ir spectra and elemental analyses.[9] Deprotection of PNZ and PNB groups of **14** and **15** was also done by their catalytic hydrogenolysis on PtO_2 in THF-water (1:1) under 4 atm of H_2 pressure to furnish new 1β-methylcarbapenems **1** [mp 240°C (decomp.), $[\alpha]_D^{25}$+34.0° (*c* 0.35, water)] and **2** [mp 195°C (decomp.), $[\alpha]_D^{25}$+87.5° (*c* 0.31, water)], respectively.[10] Compound (**2**) exhibited significant antibacterial activities [MIC (μg/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) H_2/5%Pd-C, ethanolic HCl; (iii) PNZCl, Et_3N; (iv) AcSH, Ph_3P, $EtO_2CN{=}NCO_2Et$; (v) MeONa

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9. Compound **14**: Ir ($CHCl_3$) 1780, 1720 1705 cm^{-1}; ^1H nmr (100 MHz, $CDCl_3$) 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 $C_{28}H_{28}N_4O_9S_2$: C, 53.49; H, 4.49; N, 8.91. Found: C, 53.61; H, 4.67; N, 8.63.

   Compound **15**: Ir ($CHCl_3$) 1760, 1720, 1705 cm^{-1}; ^1H nmr (100 MHz, $CDCl_3$) 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 $C_{27}H_{26}N_4O_9S_2$: 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, D_2O) 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 $C_{13}H_{17}N_2O_3S_2Na{\cdot}H_2O$: 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, D_2O) 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 $C_{12}H_{16}N_2O_3S_2{\cdot}3/2H_2O$: C, 44.03; H, 5.81; N, 8.56. Found: C,

43.96; H, 5.53; N, 7.97.

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