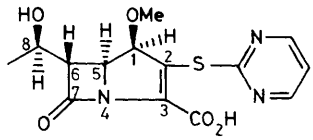
Asymmetric Total Synthesis of a New Non-natural 1β-Methoxycarbapenem

Yoshimitsu Nagao,*[a] Takao Abe,[a] Hisashi Shimizu,[b] Toshio Kumagai,[b] and Yoshinori Inoue[b]

[a] *Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan*
[b] *The Chemical and Formulation Laboratory, Lederle (Japan) Ltd., Kashiwacho, Shiki, Saitama 353, Japan*

The asymmetric total synthesis of the new non-natural 1β-methoxycarbapenem (**1**) has been achieved *via* highly diastereoselective alkylation at the C-4 position of 4-acetoxyazetidin-2-one (**4**) with the tin enolate of thiazolidinethione (**3**); the stereochemistry has been confirmed by an *X*-ray crystal structure determination of the derivative (**13**).

The synthetic development of new artificial 1β-substituted carbapenems is of current interest in the study of β-lactam antibiotics.[1] Recently, we have reported a highly diastereoselective alkylation method which should be generally applicable to the syntheses of various 1β-substituted carbapenems.[1c,2] Thus, we attempted the asymmetric total



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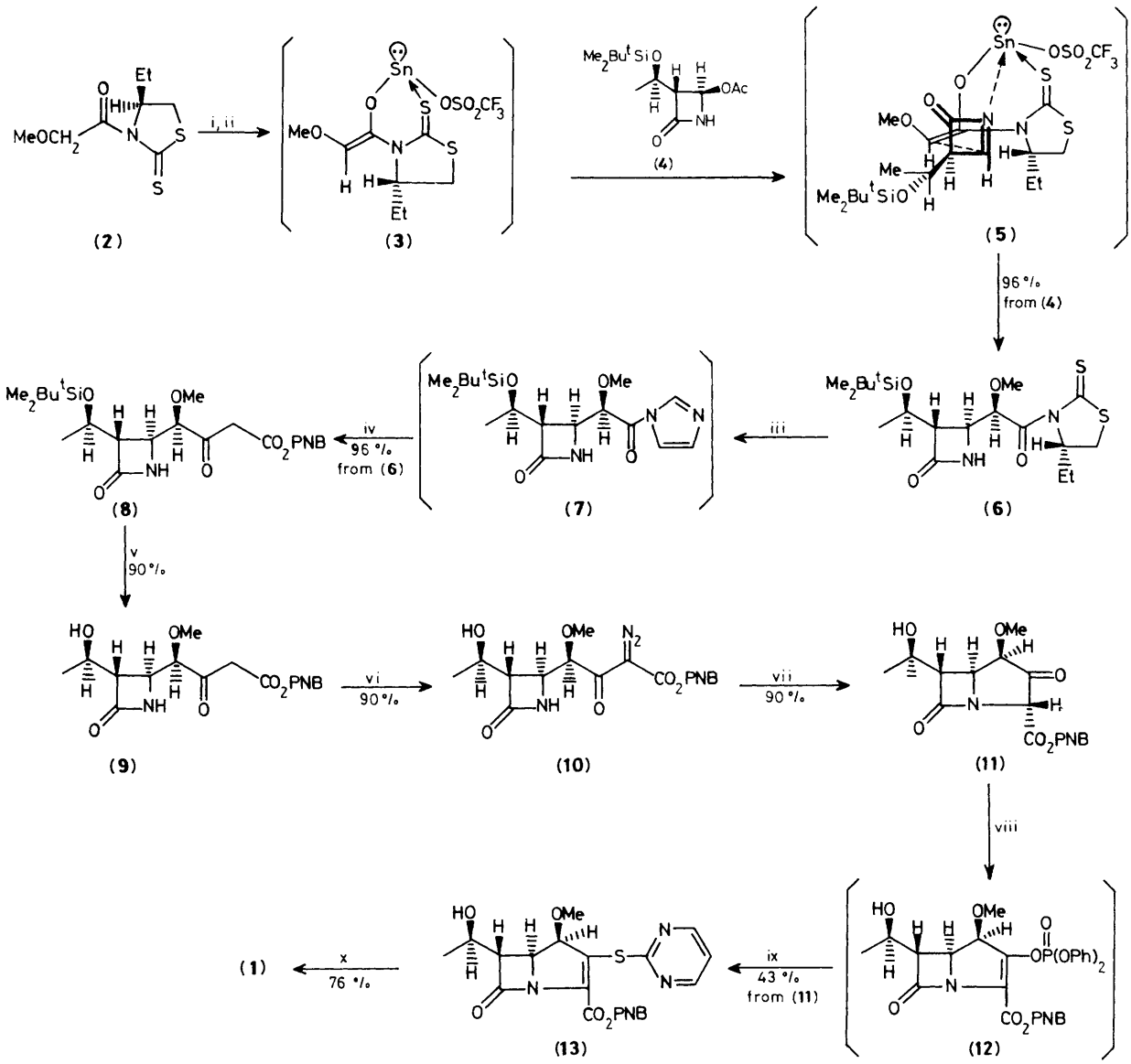

Scheme 1. *Reagents and conditions:* i, $Sn(OSO_2CF_3)_2$, THF, −78 °C; ii, *N*-ethylpiperidine, THF, −60 to 78 °C; iii, imidazole, MeCN; iv, $Mg(O_2CH_2CO_2PNB)_2$, MeCN; v, conc. HCl, MeOH; vi, *p*-dodecylbenzenesulphonyl azide, Et_3N, MeCN; vii, $Rh_2(OAc)_4$, toluene–AcOEt (1:1), 80 °C; viii, $(PhO)_2P(O)Cl$, Pr^i_2NEt, MeCN, 0 °C; ix, 2-mercaptopyrimidine, Pr^i_2NEt, dimethylformamide, 0 °C to room temp.; x, H_2 (3 atm), PtO_2, THF–H_2O (1:1). PNB = *p*-nitrobenzyl.

synthesis of the new 1β-substituted carbapenem (**1**), and now report our results (Scheme 1).

The chiral tin(II) enolate (**3**), prepared *in situ* by treatment of the (4*S*)-thiazolidinethione (**2**) (23.7 mmol) with tin(II) trifluoromethanesulphonate[3] (30.5 mmol) in tetrahydrofuran (THF) at −78 °C and then with *N*-ethylpiperidine[3] (32.2 mmol) at −60 to −78 °C for 2 h, was allowed to react with the (3*R*,4*R*) azetidinone (**4**) (16.9 mmol) in THF at 0 °C for 30 min. This reaction afforded the desired 4-alkylated azetidin-2-one (**6**) {yellow oil, $[\alpha]_D^{26}$ +178.6° (*c* 1.85, $CHCl_3$)} with high diastereoselectivity [96% diastereoisomeric excess, h.p.l.c. analysis] and in 96% yield. The highly diastereoselective formation of β-methoxy derivative (**6**) can be rationalised in terms of a possible 6-membered transition state (**5**),[2] where the cyclic acyl imine obtained by elimination of acetic acid from (**4**) can predominantly be placed on the upper side of the *Z*-enolate (**3**) avoiding steric repulsion between the ethyl group of the thiazolidine moiety and the bulky 3-substituent of the cyclic acyl imine moiety. Pure compound (**6**) having an active amide structure[4] was subjected to aminolysis with imidazole (1.2 mol. equiv.) in MeCN at room temperature for 3.5 h to give the imidazole derivative (**7**), which was immediately treated with magnesium *p*-nitrobenzylmalonate[5] (1 mol. equiv.) at room temperature for 18 h to afford β-keto ester (**8**) [96% yield from (**6**)]. Deprotection [96% yield of (**9**)] of the t-butyldimethylsilyl group of (**8**) followed by diazotization with *p*-dodecylbenzenesulphonyl azide[5] (1.2 mol. equiv.) in the presence of Et_3N (1.2 mol. equiv.) furnished diazo

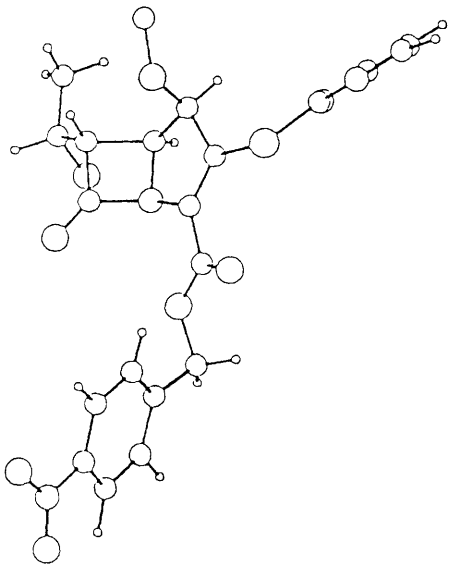

Figure 1. Perspective view of the crystal structure of (**13**).

compound (**10**) {pale yellow prisms (AcOEt–Pr^i_2O), m.p. 63—64 °C, $[\alpha]_D^{26}$ −10.6° (*c* 0.75, $CHCl_3$)} in 90% yield. Annulation of (**10**) in the presence of $Rh_2(OAc)_4$[5] (1 mol%) at 80 °C for 30 min in toluene–AcOEt (1 : 1) gave compound (**11**) {90% yield, colourless prisms (toluene), m.p. 140—143 °C, $[\alpha]_D^{25}$ +37.6° (*c* 0.82, $CHCl_3$)} which was successfully converted to 2-mercaptopyrimidine adduct (**13**) {colourless prisms (hexane–AcOEt), m.p. 154—156 °C (decomp.), $[\alpha]_D^{25}$ +156.9° (*c* 1.11, $CHCl_3$)} in 43% overall yield from (**11**) *via* the diphenylphosphoryl ester (**12**) as shown in Scheme 1. The absolute stereochemistry of (**13**) derived from known compound (**4**)[1] was readily confirmed by its relative stereochemistry obtained from the *X*-ray analysis. (Figure 1).† Finally, hydrogenolytic deprotection of the *p*-nitrobenzyl group of (**13**) afforded the desired new 1β-methoxycarbapenem carboxylic acid (**1**) {colourless amorphous solid (water), m.p. 157—158 °C (decomp.), $[\alpha]_D^{25}$ +36.6° (*c* 0.5, H_2O)} in 76% yield. Thus, we have established an efficient synthetic procedure for the new non-natural 1β-methoxycarbapenem (**1**) in a completely stereocontrolled manner.

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† *Crystal data* for (**13**): $C_{21}H_{20}N_4O_7S$, M = 472.5, orthorhombic, space group $P2_12_12_1$, a = 16.354(1), b = 21.784(2), c = 6.177(1) Å, U = 2200.7(3) Å^3, D_c = 1.426 g cm^{-3}, Z = 4, $F(000)$ = 984, Cu-K_α radiation (λ = 1.54178 Å), R = 0.044 for 1399 reflections. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.