The First Asymmetric Total Synthesis of Thienamycin-like γ-Lactam and its Analogue

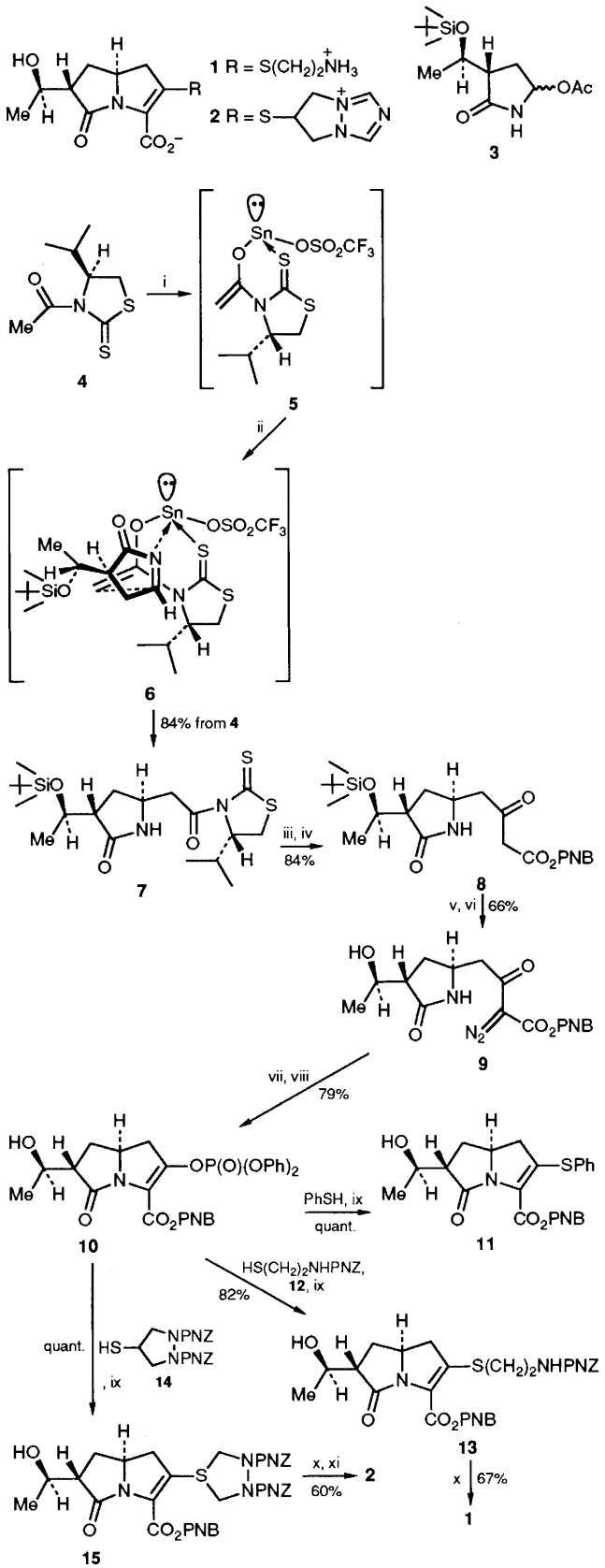
Yoshimitsu Nagao,*[a] Hiroshi Matsunaga,†[b] Toshio Kumagai,[b] Yoshinori Inoue,[b] Yoshihisa Miwa[c] and Tooru Taga[c]

[a] *Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770, Japan*
[b] *The Chemical and Formulation Research Laboratories, Lederle (Japan), Ltd, Kashiwa-cho, Shiki, Saitama 353, Japan*
[c] *Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan*

The asymmetric total synthesis of thienamycin-like γ-lactam **1** and its analogue **2** has been accomplished by utilising highly diastereoselective alkylation of tin(II) enolate **5** on acyl imine obtained *in situ* from chiral 3-substituted 5-acetoxypyrrolidin-2-one **3**.

Recently, a number of γ-lactam analogues of β-lactam antibiotics have been developed in order to examine a new class of non-natural antibacterial agents.[1] However, there has been no report on the synthesis of thienamycin-like γ-lactam **1** and its analogue **2**. Thus, synthesis of **1** and **2** intrigued us as a study in a series on the development of non-natural lactam antibiotics.[2] The successful synthetic procedure (Scheme 1) based on the highly diastereoselective imine-alkylation is described below.[3]

† Research associate of Y.N. at the Institute for Chemical Research, Kyoto University, 1987–1989.



Scheme 1 *Reagents and conditions*: i, $Sn(OSO_2CF_3)_2$, *N*-ethylpiperidine, −50 to −45 °C; ii, compound **3**, THF, 0 °C; iii, imidazole, MeCN; iv, $Mg(O_2CCH_2CO_2PNB)_2$, MeCN, 60 °C; v, conc. HCl, MeOH; vi, *p*-toluenesulfonyl azide, Et_3N, MeCN; vii, $Rh(OAc)_2$, AcOEt, 60 °C; viii, $(PhO)_2P(O)Cl$, Pr^i_2NEt, MeCN, 0 °C; ix, Pr^i_2NEt, MeCN, 0 °C; x, H_2 (4 atm), 10% Pd–C, THF–phosphate buffer solution (pH 7); xi, EtOCH=NH·HCl, $KHCO_3$, 0 °C; PNB = *p*-nitrobenzyl, PNZ = *p*-nitrobenzyloxycarbonyl

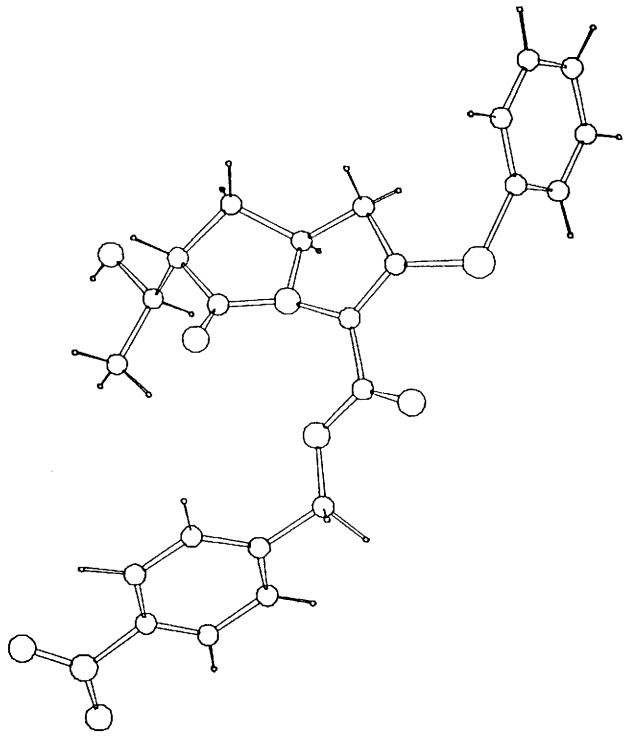


Fig. 1 Perspective view of the crystal structure of **11**

Chiral tin(II) enolate **5**, obtained *in situ* by enolisation of **4** with a solution of tin(II) trifluoromethanesulfonate (1.2 mol. equiv.) and *N*-ethylpiperidine (1.3 mol. equiv.) in tetrahydrofuran (THF) at −50 to −45 °C, was treated with 3(*S*)-3-[(*R*)-1′-*tert*-butyldimethylsilyloxyethyl]-5-acetoxypyrrolidin-2-one **3** (1.2 mol. equiv.)[3] at 0 °C to give an alkylated product **7** {yellow amorphous solid, $[\alpha]_D^{22}$ +204.09 (*c* 1.0, $CHCl_3$)} in 99% diastereoisomeric excess (d.e.) (HPLC analysis) and in 84% yield from **4**. Compound **7** might be obtained *via* a possible transition state **6**.[4] Compound **7** was converted to β-keto ester **8** in 84% yield on treatment with imidazole (1.2 mol. equiv.) followed by a decarboxylative Claisen-type reaction using $Mg(O_2CCH_2CO_2PNB)_2$ (1.5 mol. equiv.) at 60 °C. Deprotection of the *tert*-butyldimethylsilyl group of **8** under acidic conditions in MeOH and then diazotisation of the resultant alcohol gave compound **9** in 66% yield from **8**. A solution of **9** in AcOEt was heated at 60 °C in the presence of rhodium(II) acetate (0.66 w/w%) to give a cyclisation product, which was treated with diphenyl chlorophosphate (1.05 mol. equiv.) in the presence of *N*,*N*-diisopropylethylamine to produce the diphenylphospholyloxy derivative **10** in an excellent yield. Treatment of **10** with two kinds of thiols **12** (1.2 mol. equiv.) and **14** (1.2 mol. equiv.) in the presence of *N*,*N*-diisopropylethylamine resulted in the corresponding thioethers **13** {colourless prisms (AcOEt), m.p. 129–130 °C, $[\alpha]_D^{20}$ −12.2 (*c* 0.76, MeOH)} in 82% yield and **15** {pale-yellow amorphous powder, $[\alpha]_D^{20}$ −62.34 (*c* 1.03, $CHCl_3$)} quantitatively. The former was submitted to hydrogenolysis under H_2 (4 atm) on 10% Pd–C in THF–phosphate buffer solution (pH 7) to give the desired thienamycin-like γ-lactam **1** {colourless amorphous powder, $[\alpha]_D^{22}$ −6.52 (*c* 0.68, H_2O)}‡ in 67% yield. After deprotection of PNZ and PNB groups, the latter was treated with ethyl formimidate hydrochloride (5 mol. equiv.) in the presence of potassium hydrogen carbonate (2.5 mol. equiv.) at 0 °C to give triazolium carboxylate **2** {colourless

‡ Unfortunately, the γ-lactam analogues (**1** and **2**) of the carbapenems exhibited no significant microbiological activity *in vitro*.

amorphous powder, $[\alpha]_D^{22}$ −39.2 (*c* 1.11, H_2O)}‡ in 60% yield. In order to confirm the stereochemistry of all compounds mentioned in this paper, except for **4**, the benzene thioether derivative **11** {colourless prisms (AcOEt), m.p. 174.5–175 °C, $[\alpha]_D^{22}$ + 2.8 (*c* 2.26, $CHCl_3$)} was prepared from **10** and then submitted to X-ray analysis.§ The absolute configuration of three asymmetric centres in **11** was established, as depicted in Fig. 1. Thus, the corresponding asymmetric centres of all compounds derived from **3** should possess the same absolute configuration as those of **11**, respectively. Alkylation onto **3** with achiral tin(II) enolate obtained from 3-acetyl-1,3-thiazolidine-2-thione resulted in lower diastereoselectivity (56.8% d.e.) than in the case (99% d.e.) with chiral tin(II) enolate **5**. Thus, we have established a general method for the asymmetric synthesis of thienamycin-like γ-lactam and its analogues by utilising the highly diastereoselective alkylation method.

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§ *Crystal data* for **11**: $C_{23}H_{22}N_2O_6S$, M = 454.50, orthorhombic, space group $P2_12_12_1$, a = 26.893(4), b = 9.168(1), c = 8.994 Å, D_{obs} = 1.500 g cm^{-3}, D_c = 1.361 g cm^{-3}, Z = 4, $F(000)$ = 952, R = 0.043 for 1764 reflections. The absolute configuration was determined by anomalous scattering of the sulfur atom. Application of Hamilton's R-factor ratio test indicates a probability of exceeding 99% for the absolute configuration depicted in Fig. 1 ($n - m$ = 1408, and R = 0.052 for enantiomer).

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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