Convenient Asymmetric Synthesis of 3(*S*)-3-[(*R*)-1′-*tert*-Butyldimethylsilyloxyethyl]-5-hydroxypyrrolidon-2-one, a Useful Synthon for the Thienamycin-like γ-Lactam

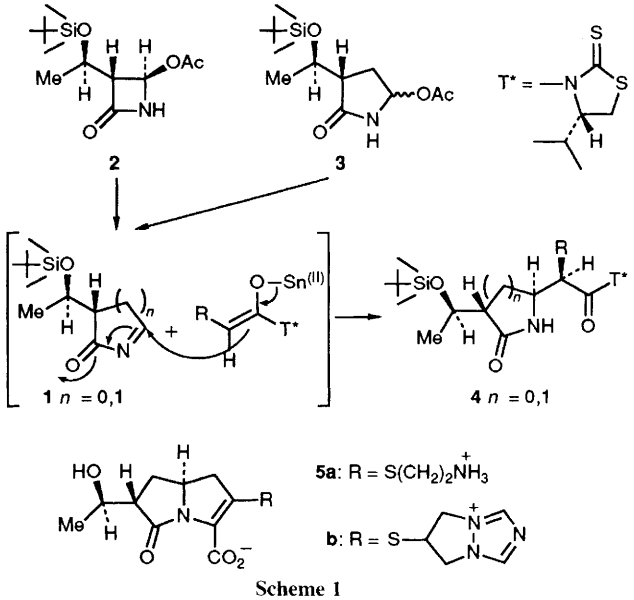
Yoshimitsu Nagao,*[a] Hiroshi Matsunaga,†[b] Toshio Kumagai[b] and Yoshinori Inoue[b]

[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*

Chiral 3-substituted 5-hydroxypyrrolidin-2-one **12**, useful for the synthesis of thienamycin-like γ-lactam, was successfully synthesised by utilising highly diastereoselective alkylation with the tin(II) enolate of **7** onto acetaldehyde, ammonolysis of the resultant amide **9**, and oxidative cyclisation of **11**.

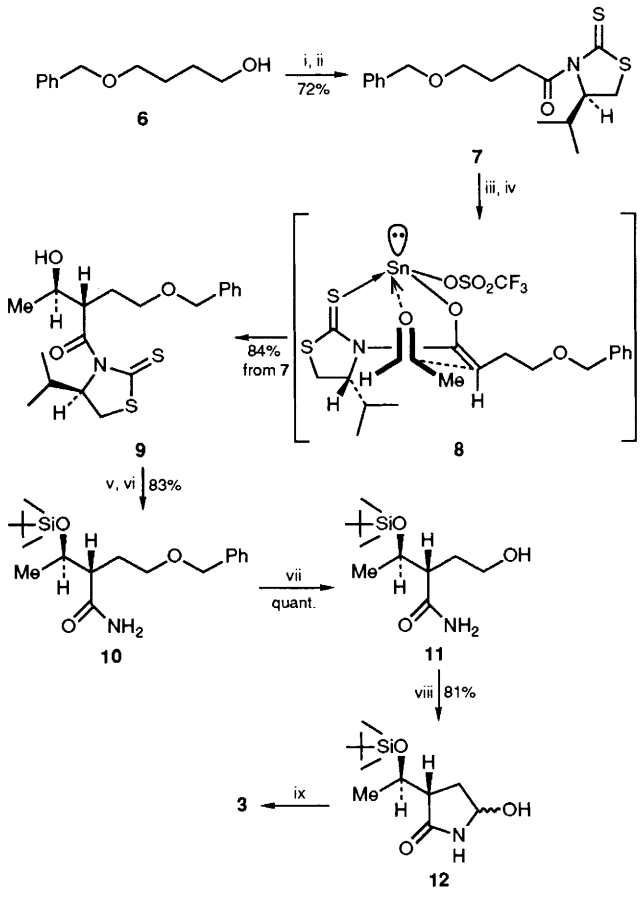
In recent years, we have reported on several new developments of non-natural lactam antibiotics and useful methods for their asymmetric synthesis.[1a–f] In 1986, we reported a highly diastereoselective alkylation of chiral tin(II) enolates [T* = 4(*S*)-isopropyl-1,3-thiazolidine-2-thione] onto cyclic acylimine (**1**: *n* = 0) obtained *in situ* from chiral 3-substituted 4-acetoxy-azetidin-2-one **2** as shown in Scheme 1.[1d] The alkylation products (**4**: *n* = 0, R = Me, OMe, SCH_2Ph, $NHCO_2CH_2Ph$) were efficiently utilised for the synthetic development of new 1β-substituted carbapenems.[1e,f] Very recently, we achieved the first asymmetric total synthesis of the thienamycin-like γ-lactam (**5a,b**).[2] In this synthesis, we planned to exploit the asymmetric alkylation between chiral tin(II) enolate and the chiral cyclic acyl imine (**1**: *n* = 1) derived from 3(*S*)-3-[(*R*)-1′-*tert*-butyldimethylsilyoxyethyl]-5-acetoxypyrrolidin-2-one **3** (Scheme 1).[3] However, synthesis of pure **3** seemed to be somewhat difficult because of its moisture sensitivity and of the delicate cyclisation of an acyclic β-formylamide derivative toward the synthetic precursor **12** under the Speckamp conditions.[4] Thus, we attempted to develop a short-step synthesis of compound **12** by a new procedure employing our chiral auxiliary, 4(*R*)-isopropyl-1,3-thiazolidine-2-thione [4(*R*)-IPTT] as shown in Scheme 2.[1b]

4-Benzyloxybutan-1-ol **6**, obtained by selective benzylation of the commercially available butane-1,4-diol, was submitted to Jones oxidation to give the carboxylic acid, which was converted to 4(*R*)-IPTT amide **7** in 72% yield by dehydrative condensation reaction. Compound **7** was treated with a suspension of tin(II) trifluoromethanesulfonate (2 mol. equiv.) and *N*-ethylpiperidine (2.2 mol. equiv.) in CH_2Cl_2 at 0 °C and the resultant tin(II) enolate was allowed to react with an excess of acetaldehyde at −78 °C.[1b] The desired aldol-type reaction proceeded smoothly *via* a plausible transition state **8**[1b] to give the chiral hydroxy compound **9** in 84% yield and in 99.1% diastereoisomeric excess (HPLC analysis). Protection of the hydroxy group of **9** with the *tert*-butyldimethylsilyl group followed by successful ammonolysis with 28% aqueous NH_3 (5 mol. equiv.) utilising the active amide structure[5] furnished amide **10** in 83% yield. Hydrogenolysis of **10** under H_2 (4 atm) on 10% Pd–C in MeOH quantitatively gave the desired



Scheme 1

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



Scheme 2 *Reagents and conditions*: i, CrO_3, H_2SO_4, acetone, water, 0 °C; ii, 4(*R*)-isopropyl-1,3-thiazolidine-2-thione, Et–N=C=N$(CH_2)_3$-NMe_2·HCl, 4-dimethylaminopyridine, CH_2Cl_2, room temp.; iii, $Sn(CF_3SO_3)_2$, *N*-ethylpiperidine, CH_2Cl_2, 0 °C; iv, MeCHO, −78 °C; v, *tert*-butyldimethylsilyl chloride, imidazole, CH_2Cl_2, 0 °C; vi, 28% aq. NH_3, CH_2Cl_2, room temp.; vii, H_2 (4 atm), 10% Pd–C, MeOH, room temp.; viii, dimethyl sulfoxide, oxalyl chloride, Et_3N, CH_2Cl_2, −78 °C to room temp.; ix, AcOH, room temp.

alcohol **11** without decomposition of the amide moiety. Surprisingly, Swern oxidation[6] of **11** in the presence of Et_3N in CH_2Cl_2 directly afforded a cyclised product **12** without the use of a particularly complicated procedure. Compound **12** {colourless solid from $CHCl_3$, m.p. 53–55 °C, $[\alpha]_D^{22}$ −28.2 (*c* 3.05, $CHCl_3$)} was shown to be a mixture of the diastereoisomers due to the different steric configuration of the C(5)–OH group in a 1 : 1 ratio (^{1}H NMR analysis). Treatment of **12** with AcOH gave its acetyl derivative **3** as a crude colourless oil. Chromatographic purification of crude **3** was fairly difficult, as expected, but could be employed without any trouble for the desired reaction.[2] Stereochemistry of the C(5)–OAc group could not be assigned by ^{1}H NMR spectroscopy. Thus, compound **3** should be available as a useful common synthon for the asymmetric synthesis of various carbapenem-like γ-lactams.[2]

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