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

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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(\mathfrak{n}) 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.^{17-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, SCH₂Ph, NHCO₂CH₂Ph) were efficiently utilised for the synthetic development of new 1ß-substituted carbapenems. ie.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(11) enolate and the chiral cyclic acyl imine (1: n = 1)derived from 3(S)-3-[(R)-1'-tert-butyldimethylsilyoxyethyl]-5acetoxypyrrolidin-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 -formulamide 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-1,3thiazolidine-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(11) trifluoromethanesulfonate (2 mol. equiv.) and *N*-ethylpiperidine (2.2 mol. equiv.) in CH₂Cl₂ at 0 °C and the resultant tin(11) 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 NH₃ (5 mol. equiv.) utilising the active amide structure⁵ furnished amide **10** in 83% yield. Hydrogenolysis of **10** under H₂ (4 atm) on 10% Pd–C in MeOH quantitatively gave the desired



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Scheme 2 Reagents and conditions: i, CrO₃, H₂SO₄, acetone, water, 0°C; ii, 4(*R*)-isopropyl-1,3-thiazolidine-2-thione, Et–N=C=N(CH₂)₃-NMe₂·HCl, 4-dimethylaminopyridine, CH₂Cl₂, room temp.; iii, Sn(CF₃SO₃)₂, *N*-ethylpiperidine, CH₂Cl₂, 0°C; iv, MeCHO, –78°C; v, *tert*-butyldimethylsilyl chloride, imidazole, CH₂Cl₂, 0°C; vi, 28% aq. NH₃, CH₂Cl₂, room temp.; vii, H₂ (4 atm), 10% Pd–C, MeOH, room temp.; vii, dimethyl sulfoxide, oxalyl chloride, Et₃N, CH₂Cl₂, -78°C to room temp.; ix, AcOH, room temp.

alcohol **11** without decomposition of the amide moiety. Surprisingly, Swern oxidation⁶ of **11** in the presence of Et₃N in CH₂Cl₂ directly afforded a cyclised product **12** without the use of a particularly complicated procedure. Compound **12** {colourless solid from CHCl₃, m.p. 53–55 °C, $[\alpha]_D^{22} - 28.2$ (*c* 3.05, CHCl₃)} 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 (¹H 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 ¹H 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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