A Novel Stereoselective Route to β-Lactams: Diastereoselective Synthesis of a Key Intermediate for Carbapenem Antibiotic (+)-PS-5

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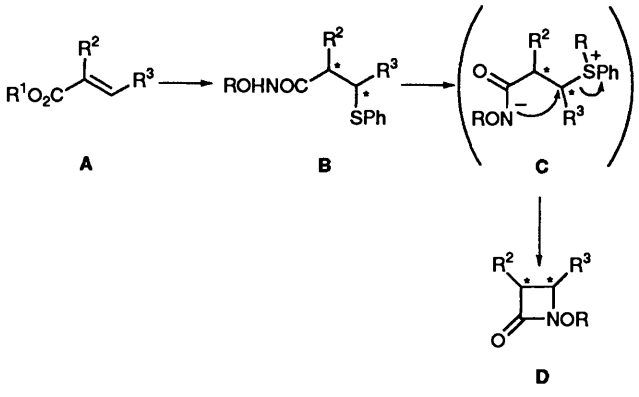
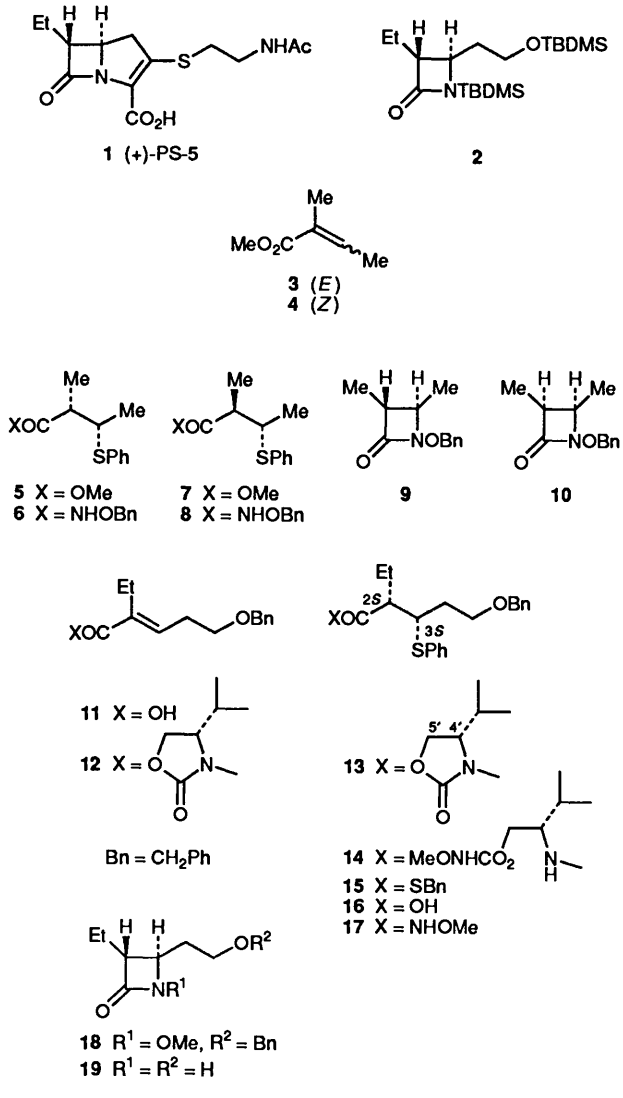
A combination of stereoselective addition of thiophenol to olefins and subsequent substitution of the corresponding sulfonium group with an *O*-alkylhydroxamate anion has provided a new practical and stereoselective method for the construction of β-lactams which has been successfully applied to the formal asymmetric synthesis of the carbapenem antibiotic (+)-PS-5 **1**.

In the synthesis of carbapenem antibiotics, the control of the relative and absolute stereochemistries of the contiguous chiral centres and the construction of the β-lactam ring[1] remain difficult synthetic tasks. In particular, a stereoselective and practical method for the construction of *cis*-β-lactams has not been exploited compared with many known[1] synthetic works on the *trans*-lactams. We now provide a potential method for stereoselective syntheses of both *cis*- and *trans*-β-lactams by the newly developed stereospecific nucleophilic addition of thiols to olefins (**A** ⟶ **B**)[2] and stereoselective displacement reaction of the corresponding sulfonium group with an *O*-alkylhydroxamate anion (**B** ⟶ **C** ⟶ **D**). The usefulness of this method is demonstrated by the asymmetric synthesis of a key intermediate **2** for the carbapenem antibiotic (+)-PS-5 **1** in 42% total yield from the acid **11**.



Methyl (*E*)-2-methylbut-2-enoate **3** was treated with 10 equiv. of thiophenol in the presence of 0.1 equiv. of lithium thiophenoxide to give the *erythro*-adduct **5**[2] in 95% yield. Treatment of the *erythro*-**5** with benzyloxyamine hydrochloride and trimethylaluminium[3] afforded the *O*-benzyl hydroxamate **6** in 81% yield. *S*-Alkylation of the sulfide **6** with methyl iodide in the presence of silver perchlorate[4] followed by treatment of the resulting sulfonium salt with potassium carbonate underwent smooth lactamization by intramolecular substitution to give the *trans*-lactam **9** with high stereoselectivity (*trans*:*cis* = 90:10) in 60% yield. In a similar manner, the *Z*-ester **4** was transformed into the *cis*-β-lactam **10** *via* the *threo*-adduct **7** and the hydroxamate **8** with high stereoselectivity (*cis*:*trans* = 92:8). The stereostructures of **9** and **10** were confirmed by their ^{1}H NMR spectral characteristics;[5] **9**: $J_{3,4}$ 2 Hz; **10**: $J_{3,4}$ 6 Hz.

The synthetic utility of this method is shown by a stereoselective synthesis of the known[6] key intermediate **2** for the synthesis of (+)-PS-5 **1**. The chiral imide **12**, prepared from the *E*-carboxylic acid **11**† and (−)-4-isopropyloxazolidin-2-one (Evans's reagent) was treated with 10 equiv. of thiophenol in the presence of 5 equiv. of lithium thiophenoxide in THF at −78 °C. The desired (2*S*,3*S*)-adduct **13** was obtained in 78% yield and the stereostructure was deduced by the chemical conversion described later into the final β-lactam **2**. Attempted transamination[3,8] of **13** by treatment with methoxyamine hydrochloride and trimethylaluminium into the hydroxamate **17** was unsuccessful and instead gave the undesired amide **14** in



† Compound **11** was prepared by the conventional method involving Wittig–Horner reaction, olefin isomerisation,[7] and hydrolysis.

84% yield, as a result of the attack of methoxyamine on the oxazolidinone carbonyl group. Recently, we have found that aluminium thiobenzyloxy 'ate' complex is an excellent reagent for the cleavage of *N*-acylcamphorsultam.[4a] Therefore, the method was successfully applied to **13** to give the thio ester **15** in 93% yield. Hydrolysis of the thio ester **15** in the presence of silver trifluoroacetate proceeded smoothly to give the corresponding acid **16** in 96% yield, which was then treated with methoxyamine hydrochloride and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride to give the desired hydroxamate **17** in 86% yield. Formation of the azetidinone **18** was accomplished in 83% yield through *S*-alkylation of **17** and subsequent treatment of potassium carbonate. Cleavage of both N–O and O–CH_2Ph bonds of **18** by the conventional method[9] (Na–liq. NH_3, −78 °C) was unsuccessful. However, when calcium[10] is used in place of sodium, the reductive cleavage reaction proceeded smoothly to give the desired product **19** in 96% yield. Finally, treatment of **19** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS–OTf) in the presence of 2,6-lutidine (2,6-dimethylpyridine) afforded the disilylated β-lactam **2**, $[\alpha]_D$ −34.2 (*c* 0.79, $CHCl_3$) {lit.,[11] $[\alpha]_D$ −37.73 (*c* 2.25, $CHCl_3$),[11a] −30.1 (*c* 2.9, $CHCl_3$)[11b]} in 42% overall yield from the carboxylic acid **11** in a nine-step sequence. Since β-lactam **2** had previously been transformed into (+)-PS-5 **1**,[6] the present method provides a new highly efficient asymmetric synthesis of (+)-PS-5 **1**.

Experimental

Addition of Thiophenol to the Chiral Imide **12**.—Thiophenol (1 cm^3, 10.8 mmol) was added at 0 °C to a stirred solution of butyllithium (10% solution in hexane; 2.3 cm^3, 3.6 mmol) in tetrahydrofuran (THF) (5 cm^3) to give a solution of a 2:1 mixture of thiophenol and lithium thiophenoxide. To this solution was added a solution of imide **12** (250 mg, 0.72 mmol) in THF (5 cm^3) at −78 °C. After being stirred at −78 °C for 5 h, the mixture was made alkaline by the addition of 5% aqueous NaOH and extracted with CH_2Cl_2. The extract was dried and concentrated to give a residue which was purified by medium-pressure column chromatography [Lobar größe B column (310–25, Lichroprep Si 60, Merck), hexane–AcOEt 3:1] to give compound **13** as a colourless oil (257 mg, 78%); $[\alpha]_D$ −2.5* (*c* 2.77, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1778 and 1692; δ(500 MHz; $CDCl_3$)† 7.39 ~ 7.21 (10 H, m, 2 × Ph), 4.49 (1 H, m, 4′-H), 4.48 and 4.45 (2 H, ABq, *J* 12, OC*H*$_2$Ph), 4.24 (1 H, t, *J* 9, 5′-H), 4.18 (2 H, m, 3- and 5′-H), 3.79 (1 H, dt, *J* 10, 5.5, 5-H), 3.70 (1 H, ddd, *J* 10, 7, 5, 5-H), 3.61 (1 H, ddd, *J* 10, 6, 4, 2-H), 2.27 (1 H, m, C*H*Me$_2$), 2.13 (1 H, m, 4-H), 1.95 ~ 1.78 (3 H, m, 4-H and C*H*$_2$Me), 0.89 (3 H, d, *J* 7, CH*Me*), 0.87 (3 H, t, *J* 7, CH_2*Me*) and 0.80 (3 H, d, *J* 7, CH*Me*) (Found: M^+, 455.2110. $C_{26}H_{33}NO_4S$ requires *M*, 455.2128).

* $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.
† *J* Values are given in Hz.

Intramolecular Cyclisation of the Hydroxamate **17**.—Methyl iodide (2 cm^3, 31 mmol) was added at room temperature to a stirred solution of hydroxamate **17** (116 mg, 0.3 mmol) and silver perchlorate (280 mg, 1.4 mmol) in MeCN (4 cm^3). After being stirred at room temperature for 15 h, the mixture was filtered to remove the resulting silver iodide. The filtrate was concentrated to give the sulfonium salt. To a stirred suspension of K_2CO_3 (360 mg, 2.6 mmol) in refluxing acetone (12 cm^3) was added a solution of the sulfonium salt in acetone (7 cm^3) and the mixture was refluxed for 2 h. After addition of water, the mixture was extracted with CH_2Cl_2. The extract was dried and concentrated to give a residue which was purified by medium-pressure column chromatography [Lobar größe B column (310–25, Lichroprep Si 60, Merck), CH_2Cl_2–AcOEt, 10:1] to give azetidinone **18** as a colourless oil (66 mg, 83%); $[\alpha]_D$ −1.3 (*c* 2.27, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1760; δ(500 MHz; $CDCl_3$) 7.40–7.26 (5 H, m, Ph), 4.50 (2 H, s, PhC*H*$_2$), 3.75 (3 H, s, OMe), 3.71 (1 H, ddd, *J* 7.5, 6, 2, 4-H), 3.60 (2 H, m, OCH_2), 2.57 (1 H, ddd, *J* 8, 6, 2, 3-H), 2.14 (1 H, dq, *J* 14, 6, OCH_2CH), 1.91 (1 H, dtd, *J* 14, 7.5, 6, OCH_2CH), 1.80–1.58 (2 H, m, C*H*$_2$Me) and 1.00 (3 H, t, *J* 7.5, CH_2*Me*) (Found: M^+, 263.1549. $C_{15}H_{21}NO_3$ requires *M*, 263.1521).

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