Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5519-5522, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01063-3

Novel Stereochemical Manipulations of the Penicillin Nucleus

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Abstract The synthesis of a homochiral C2-epipenicillin *tert*-butyl amide **1** from 6-β-phthalimidopenicillanic acid is described.

Introduction

In the course of work aimed at producing β-lactams with altered biological activity we sought a means of synthesising the C2-epipenicillin *tert*-butyl amide **1** in homochiral form. Racemic **1** has previously been synthesised by Ugi, using the reaction that bears his name, from the imine carboxylic acid **2**[1], Fig. 1, but the synthesis of this precursor was lengthy and offered no means of controlling the absolute stereochemistry.

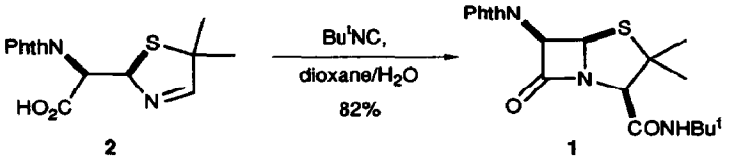

Fig. 1. Ugi Penicillin Synthesis

The actual Ugi reaction is very powerful however as the relative stereochemistry at C-2 is dictated by the mechanism of the reaction which is presumed to involve formation of a *cis*-annelated 7-membered ring, Fig. 2; accordingly our efforts focussed on preparing homochiral **2**.

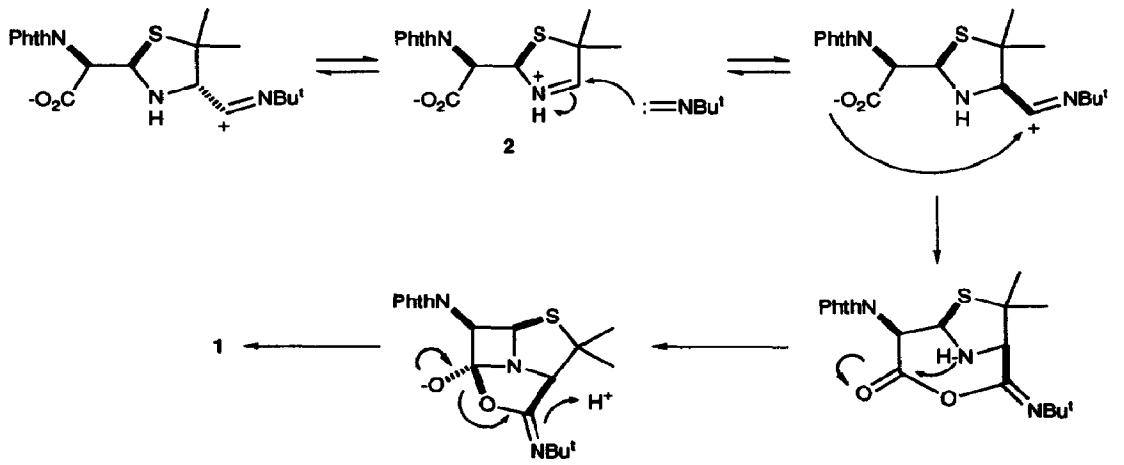

Fig. 2. Ugi Penicillin Synthesis Mechanism

Results and Discussion

The close structural resemblance between **2** and the 6-β-phthalimidopenicillanic acid derived isocyanate **3**[2] suggested that a means might exist for converting the latter to homochiral **2**. In the literature[3] it is reported that dilute acid hydrolysis of **3** infact yields the monocyclic aldehyde **4**, Fig. 3.

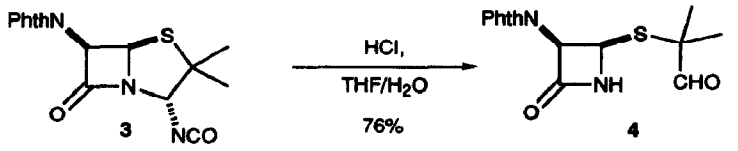

Fig. 3. Penam Hydrolysis

We reasoned however that the acid hydrolysis modes of **3** would be extremely solvent dependent and that the desired β-lactam cleavage followed by elimination to form the imine might be favoured under lower water activity conditions. In the event this expectation was realised after many exploratory reactions and **3** was quantitatively converted to **2** by reaction with tosic acid monohydrate in warm toluene[4] Fig. 4.

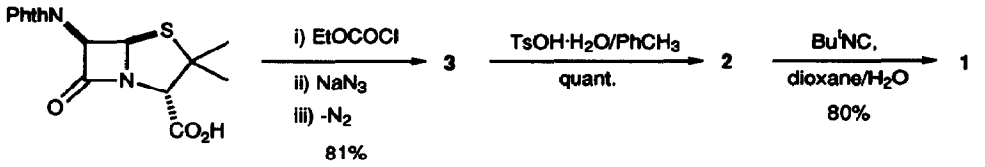

Fig. 4. β-Lactam Hydrolysis Route to 1

The difference between the two modes of acid catalysed hydrolysis of **3** constitutes an extreme solvent effect. Ugi reaction of **2** prepared in this manner with *tert*-butyl isocyanate then afforded **1** in good yield as previously reported.

Cognisant that reversible β-elimination/Michael addition in the synthesis and subsequent reaction of **2** might cause racemisation, Fig. 5, we next proceeded to investigate the stereochemical integrity of **1** produced by this route.

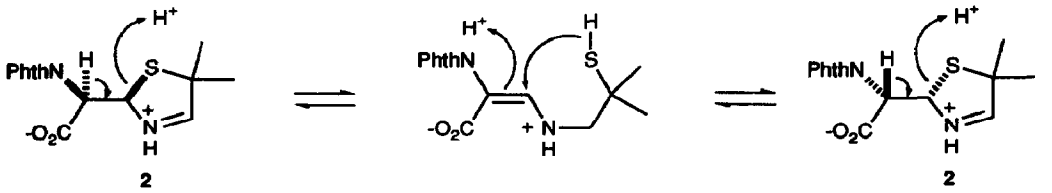

Fig. 5. Potential Racemisation of 2

Epimerisation at C-6 of **1** by treatment with catalytic potassium *tert*-butoxide gave the bis-epimeric (relative to the natural penicillin stereochemistry) derivative **5** in quantitative yield[5]. Deuteration experiments indicated that deprotonation/protonation was only occurring at the 6-position. The enantiomer **9** of derivative **5** was then prepared from 6-β-phthalimidopenicillanic acid using chemistry based on that reported by Kukolja[6]. Thus chlorinolysis of the benzhydryl derivative **6** furnished the ring opened sulfenyl chloride **7** which was closed by treatment with anhydrous stannous chloride to give the C-5 epimeric benzhydryl derivative **8**, Fig. 6.

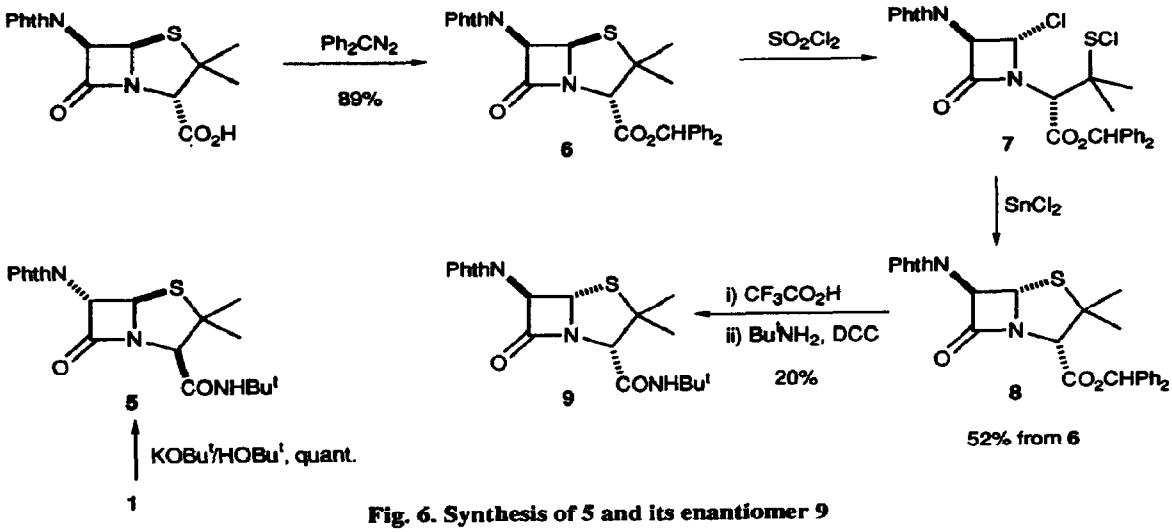

Fig. 6. Synthesis of 5 and its enantiomer 9

Deprotection of **8** followed by dicyclohexylcarbodiimide mediated coupling with *tert*-butylamine then gave **9**. Comparison of optical rotation values and CD spectra of **5** and **9**[7], Fig. 7, confirmed that our synthetic route to **1** had proceeded without significant racemisation of the intermediate **2** and that **1** had been produced in homochiral form as desired.

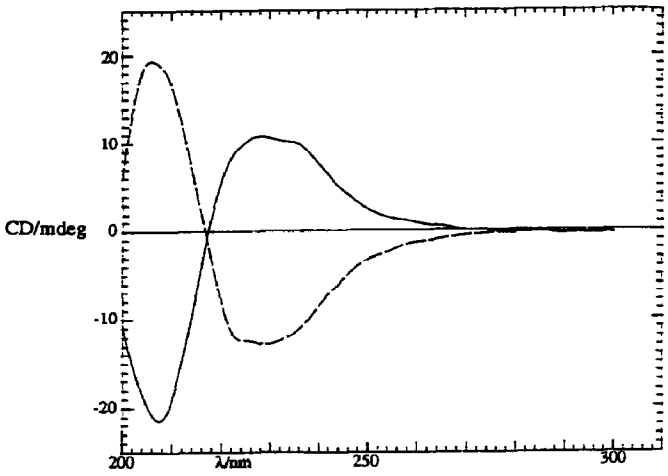

Fig. 7. CD Spectra of 5 & 9 Solid line; **5**, 0·138 mgml^{-1}; dashed line **9**, 0·119 mgml^{-1}.

In summary we have synthesised the highly functionalised C2-epipenicillin *tert*-butyl amide **1** in homochiral form in four steps with an overall yield of 65% from readily available 6-β-phthalimidopenicillanic acid.

Acknowledgements

We thank the SERC for support and Dr. A Rodger for assistance with the CD spectroscopy.

References and footnotes

1 Schutz, A.; Ugi, I. *J. Chem. Res. (S)* **1979**, *157; J. Chem. Res. (M)* **1979**, *2064*, review: Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810.

2 Perron, Y. G.; Crast, L. B.; Essery, J. M.; Fraser, R. R.; Godfrey, J. C.; Holdrege, C. T.; Minor, W. F.; Neubert, M. E.; Partyka, R. A.; Cheney, L. C. *J. Med. Chem.* **1964**, *7*, 483. Attempts to prepare the isocyanate by using the more direct diphenylphosphoryl azide method (Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203) were unsuccessful.

3 Sheehan, J. C.; Brandt, K. G. *J. Am. Chem. Soc.* **1965**, *87*, 5468.

4 Procedure: (2S,6R)-2-isocyanato-3,3-dimethyl-6-phthalimidopenam **3** (70 mg, 0.2mmol) was dissolved in toluene (6 cm^3). Tosic acid monohydrate (0.34 g, 1·8 mmol) was added and the flask was fitted to a rotary evaporator. By careful regulation of the air-bleed, the toluene was removed over a period of two hours with the bath at 60 °C. The residue was dissolved in CH_2Cl_2 (8 cm^3) and washed with water (2x 5 cm^3). The aqueous phase was back-extracted with CH_2Cl_2 (2x 5 cm^3). The combined organic extracts were extracted with $NaHCO_{3(aq.)}$ (0.5 M, 2x 8 cm^3). The combined aqueous phases were washed with ether (2x 5 cm^3), acidified to pH 3 with 6N HCl and extracted with CH_2Cl_2 (3x 8 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give **2** as a white solid (65 mg, quant.): m.p. >170 °C (dec.); (Found: C, 56·29; H, 4·30; N, 8·58. $C_{15}H_{14}N_2O_4S$ requires C, 56·59; H, 4·43; N, 8·80%); ν_{max} (KBr)/cm^{-1} 1719s, 1387s, 723s; $[\alpha]_D^{20}$ +103 ° (*c* 1·145, $CHCl_3$); ^1H NMR: The chemical shift values for this compound are very concentration dependent. The acid signal is particularly variable but the other signals are liable to vary by as much as 0·4 ppm. For a solution of about 10 $mgml^{-1}$; δ_H(200 MHz, $CDCl_3$, $(CH_3)_4Si$) 7·82 (4 H, m, $\underline{H}C_{Ar}$), 7·22 (1 H, d, N=C$\underline{H}$, *J* 2), 6·30 (1 H, dd, SC$\underline{H}$, *J* 2, 10), 4·84 (1 H, d, *J* 10) 4·16 (>1 H, br s, $CO_2\underline{H}$), 1·58 (3 H, s, C$\underline{H}_3$), 1·53 (3 H, s, C$\underline{H}_3$); δ_C(50·31 MHz, $CDCl_3$, DEPT) 174·5 (<u>C</u>=N), 169·8 (<u>C</u>=O), 167·0 (<u>C</u>=O), 134·3 ($\underline{C}H_{Ar}$), 131·6 ($\underline{C}_{Ar}$), 123·7 ($\underline{C}H_{Ar}$), 78·2 (<u>C</u>H), 63·6 ($\underline{C}(CH_3)_2$), 57·4 (<u>C</u>H), 29·6 ($\underline{C}H_3$), 29·6 ($\underline{C}H_3$); *m/z* (CI (NH_3)) 319 (MH^+).

5 For other methods of C-6 epimerisation see: Cooper, R. D. G.; DeMarco, P. V.; Spry, D. O. *J. Am. Chem. Soc.* **1968**, *91*, 1528, Wolfe, S.; Lee, W. S. *J. Chem. Soc. Chem. Commun.* **1968**, 242, Koppel, G. A. *Tet. Lett.* **1973**, 4233, Vlietinck, A.; Roets, E.; Claes, P.; Vanderhaeghe, H. *ibid.* **1972**, 285.

6 Kukolja, S. *J. Am. Chem. Soc.* **1971**, *93*, 6267, 6269.

7 **5**: m.p. 79·5-81·5 °C; (Found: C, 60·11; H, 5·57; N, 10·22. $C_{20}H_{23}N_3O_4S$ requires C, 59·83; H, 5·77; N, 10·47%); ν_{max} (KBr)/cm^{-1} 3301m, 2967m, 2929m, 1757br s, 1724s, 1573m, 1458m, 1391s, 1365s, 1293m, 1222m, 1157m, 1107m, 722s; λ_{max} (EtOH)/nm 218 (ε/dm^3 mol^{-1} cm^{-1} 35900), 290 (1450); $[\alpha]_D^{20}$ +72·4 ° (*c* 0·642, $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 8·69 (1 H, br s, N$\underline{H}$), 7·86 (4 H, m, $\underline{H}C_{Ar}$), 5·36 (1 H, d, β-lactam C$\underline{H}$, *J* 2), 5·25 (1 H, d, β-lactam C$\underline{H}$, *J* 2), 3·86 (1 H, s, C$\underline{H}(CH_3)_2$), 1·75 (3 H, s, C$\underline{H}_3$), 1·49 (3 H, s, C$\underline{H}_3$), 1.41 (9 H, s, $(C\underline{H}_3)_3C$); δ_C(50·31 MHz, $CDCl_3$, DEPT) 169·1 (<u>C</u>=O), 166·7 (<u>C</u>=O), 163·4 (<u>C</u>=O), 134·9 ($\underline{C}H_{Ar}$), 131·5 ($\underline{C}_{Ar}$), 124·1 ($\underline{C}H_{Ar}$), 76·4 (<u>C</u>H), 63·9 ($\underline{C}(CH_3)_2$), 63·7 (<u>C</u>H), 62·7 (<u>C</u>H), 52·2 ($\underline{C}(CH_3)_3$) 28·3 ($\underline{C}H_3$), 28·2 ($C(\underline{C}H_3)_2$) 27·5 ($\underline{C}H_3$); *m/z* (CI (NH_3)) 402 (MH^+).
9 displayed the same spectral and analytical properties but had $[\alpha]_D^{20}$ -78·7 ° (*c* 0·361, $CHCl_3$).

(*Received in UK* 18 *May* 1994; *accepted* 3 *June* 1994)