

## Synthesis and Absolute Configuration of the *p*-Nitrobenzyl Ester of SQ 27860

Masaaki Miyashita, Noritaka Chida, and Akira Yoshikoshi\*

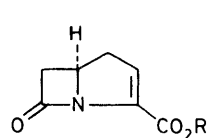
Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

Transformation of *D*-glucosamine into the *p*-nitrobenzyl ester (2) of SQ 27860 is described, revealing the absolute configuration of this carbapenem antibiotic as (1).

SQ 27860 (1) was recently reported to be the first carbapenem antibiotic produced by bacteria and it shows a wide antibacterial spectrum.<sup>1</sup> While this unstable carbapenem has been characterised as its *p*-nitrobenzyl ester, its absolute configuration has not yet been elucidated.

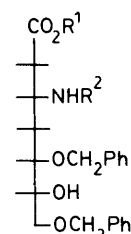
We describe herein the synthesis of (2) from the  $\beta$ -amino acid (3),<sup>2</sup> derived previously from *D*-glucosamine, and the assignment of the absolute configuration of (1) as depicted.<sup>3</sup>

The amino group in (3) was protected by conversion into a *t*-butylcarbamate [(Bu<sup>t</sup>OCO)<sub>2</sub>O, 2 M NaOH] and this was followed by esterification with diazomethane. The resulting hydroxy ester (4), [ $\alpha$ ]<sub>D</sub><sup>21</sup> +10.0° (CHCl<sub>3</sub>), obtained in 90% yield, was converted into a methanesulphonate (MeSO<sub>2</sub>Cl, pyridine), which was then treated with *N,N*-diisopropylethylamine [dimethylformamide (DMF), 90–100 °C] to give the pyrrolidine derivative (5)<sup>†</sup> in 88% yield. After quantitative removal of the benzyl groups in (5) by hydrogenolysis [H<sub>2</sub>, Pd(OH)<sub>2</sub>-C, EtOH], the primary hydroxy group in the product (6),<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> +49.9° (CHCl<sub>3</sub>), was benzooylated (PhCOCl, pyridine) to yield the benzoate (7),<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>15</sup> +63.1° (CHCl<sub>3</sub>), with high regioselectivity (84% yield). The secondary hydroxy group remaining in (7) was quantitatively protected as a (2-methoxyethoxy)methyl ether [MeO-[CH<sub>2</sub>]<sub>2</sub>OCH<sub>2</sub>Cl, Pr<sub>3</sub>N<sup>+</sup>Et] and the benzoyl group in the product was then deprotected with sodium methoxide. This was followed by Jones oxidation and esterification with *p*-nitrobenzyl bromide (NaHCO<sub>3</sub>, DMF<sup>4</sup>), to afford the nitrobenzyl ester (8),<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> -14.8° (CHCl<sub>3</sub>), in good yield (81%). Since alkaline hydrolysis of the *p*-nitrobenzyl ester group in (8) was expected to be slow owing to steric congestion, (8) was treated with lithium hydroxide in aqueous methanol at room temperature, and the crude product was then hydrolysed with 2 M hydrochloric acid to regenerate the



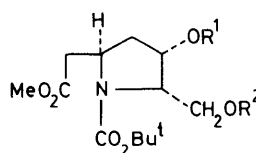
(1) R = H

(2) R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-*p*



(3) R<sup>1</sup> = R<sup>2</sup> = H

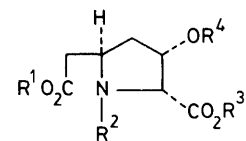
(4) R<sup>1</sup> = Me, R<sup>2</sup> = CO<sub>2</sub>Bu<sup>t</sup>



(5) R<sup>1</sup> = R<sup>2</sup> = CH<sub>2</sub>Ph

(6) R<sup>1</sup> = R<sup>2</sup> = H

(7) R<sup>1</sup> = H, R<sup>2</sup> = C(=O)Ph



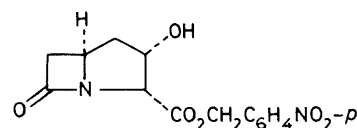
(8) R<sup>1</sup> = Me, R<sup>2</sup> = CO<sub>2</sub>Bu<sup>t</sup>

R<sup>3</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-*p*

R<sup>4</sup> = CH<sub>2</sub>O[CH<sub>2</sub>]<sub>2</sub>OMe

(9) R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = H

R<sup>3</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>-*p*



(10)

<sup>†</sup> Syrupy product.

<sup>‡</sup> Some signals in the <sup>1</sup>H n.m.r. spectrum of this compound were observed as pairs (*ca.* 1:1) at room temperature. Since the pairs unified at *ca.* 80 °C, the splitting of the signals is probably due to conformers based on restricted free rotation of the *t*-butoxycarbonyl group. A similar observation has been reported (ref. 6).

amino and hydroxy groups. The resulting hydrochloride of the  $\beta$ -amino acid (9) was suspended in dichloromethane and treated with excess of triethylamine to give a mixture of the free amino acid (9) and triethylamine hydrochloride. Removal of the triethylamine salt from the mixture by silica gel column chromatography (eluted with 70% ethanol) afforded crude (9)

as a crystalline mass. Without further purification, (9) suspended in acetonitrile–water (95:5)§ was treated with 2,2'-dipyridyl disulphide and triphenylphosphine<sup>5</sup> to give the  $\beta$ -lactam (10),  $[\alpha]_D^{17} +163^\circ$  ( $\text{CHCl}_3$ ) as an amorphous solid in 58% overall yield from (8). The  $\beta$ -lactam (10) was mesylated ( $\text{MeSO}_2\text{Cl}$ , pyridine) and then treated with triethylamine in dichloromethane. Purification of the product by Florisil column chromatography provided (2), m.p. 119–121.5°C,  $[\alpha]_D^{16} +99.0^\circ$  (toluene) in 80% yield, which was identified as SQ 27860 *p*-nitrobenzyl ester by spectral comparison (i.r. and  $^1\text{H}$  n.m.r.) and optical rotation.¶

The authors are grateful to Dr. W. L. Parker (The Squibb Institute for Medical Research) for providing the spectra of (2).

Received, 14th November 1983; Com. 1487

---

§ This reaction was sluggish in dry acetonitrile.

¶ Lit.<sup>1</sup> m.p. 119–121°C,  $[\alpha]_D^{22} +104^\circ$  (toluene).

---

## References

- 1 W. L. Parker, M. L. Rathnum, J. S. Wells, Jr., W. H. Trejo, P. A. Principe, and R. B. Sykes, *J. Antibiot.*, 1982, **35**, 653.
- 2 M. Miyashita, N. Chida, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 1982, 1354.
- 3 For the synthesis of metal salts and esters of ( $\pm$ )-(1), see L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006; H. R. Pfaendler, J. Gosteli, R. B. Woodward, and G. Rihs, *ibid.*, 1981, **103**, 4526; J. H. Bateson, A. J. G. Baxter, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3242; A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236; H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, 1979, 3867; G. A. Kraus and K. Neuenschwander, *J. Chem. Soc., Chem. Commun.*, 1982, 134.
- 4 V. Bocchi, G. Casnati, A. Dossena, and R. Marchelli, *Synthesis*, 1979, 961.
- 5 M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, *J. Am. Chem. Soc.*, 1981, **103**, 2405; S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *ibid.*, 2406.
- 6 M. D. Bachi, R. Breiman, and H. Meshulam, *J. Org. Chem.*, 1983, **48**, 1439.