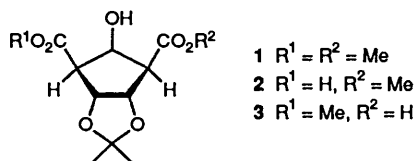


# Enzyme-catalysed Hydrolysis of Dimethyl 7-Hydroxy-3,3-dimethyl-2,4-dioxabicyclo[3.3.0]octane-6,8-dicarboxylate and a Novel Synthesis of Neplanocin A

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Hydrolysis of the diester **1** catalysed by pig liver esterase provided the mono-ester **3**. This ester was converted into the amine **9**, a precursor of neplanocin **10**, thereby confirming the previously proposed configuration of **3**.

Zemlicka *et al.* reported that the *meso*-diester **1** was hydrolysed by pig liver esterase to give the mono ester **2**  $\{[\alpha]_D + 5.5$  (*c*, 0.51 in dioxane)\* $\}$ .<sup>1</sup> Structural assignment was made on the basis of X-ray data. This specific hydrolysis seemed to be satisfactorily explained by the accepted active site model of the enzyme.<sup>2</sup> We have previously repeated the literature reaction to give the same mono ester  $\{[\alpha]_D + 6.4$  (*c*, 0.55 dioxane) $\}$  and provided circumstantial evidence that the absolute configuration of the product was that shown in formula **3**.<sup>3</sup> Herein we describe a series of stereocontrolled reactions starting from **3** to give a neplanocin intermediate of known absolute configuration and, in so doing, provide more convincing evidence that the product obtained on pig liver esterase-catalysed hydrolysis of **1** is, indeed, compound **3** and not compound **2**.

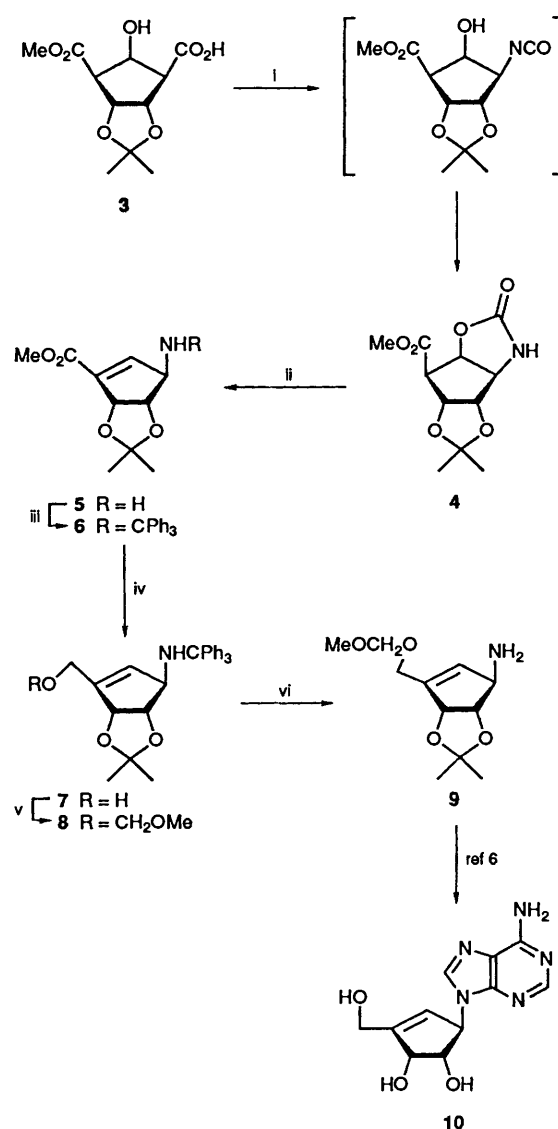


The product **3** from the enzyme-catalysed hydrolysis was transformed into the oxazolidinone **4** using diphenyl phosphoryl azide,<sup>4</sup> presumably through the intermediacy of an isocyanate (Scheme 1). Treatment of the tricyclic compound **4** with tosyl fluoride and potassium fluoride in pyridine and tetrahydrofuran (THF) furnished the amino ester **5**, which was protected as the trityl derivative **6**. Alternatively the amine **6** can be synthesised directly from the oxazolidinone **4** by treatment of **4** with trityl chloride in the presence of base (55% yield). Reduction of the ester moiety provided the alcohol **7** which was treated with methoxymethyl chloride and base to give the fully protected compound **8**. Deprotection of the amino group using hydroxybenzotriazole in trifluoroethanol<sup>5</sup> afforded the bicyclic compound **9**  $\{[\alpha]_D^{23} - 34.4$  (*c* 0.61  $\text{CHCl}_3$ ) $\}$ , a compound which had been prepared previously by Ohno  $\{[\alpha]_D^{20} - 37.1$  (*c* 1.0,  $\text{CHCl}_3$ ) $\}$ .<sup>6</sup> The amine **9** was converted into the naturally occurring carbocyclic nucleoside neplanocin A **10** in four well-documented steps.<sup>6</sup>

In summary this paper shows that the readily available diester **1** can be converted into neplanocin A **10**. It also provides a salutary warning of the dangers involved in the assignment of absolute configuration to low molecular weight chiral compounds lacking a heavy atom, using X-ray data alone.

## Experimental

*Methyl (3R,4S,5R)-4,5-Isopropylidenedioxy-3-triphenylmethylaminocyclopent-1-enecarboxylate* **6**.—A solution of



**Scheme 1** Reagents and conditions: i,  $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ , dimethylaminopyridine, THF, 48 h (81%); ii, KF, TsF, pyridine, THF (79%); iii,  $\text{Ph}_3\text{CCl}$ , dimethylformamide,  $\text{Et}_3\text{N}$  (77%); iv,  $\text{Bu}^i_2\text{AlH}$ , toluene,  $-78^\circ\text{C}$ , 6 h (76%); v,  $\text{MeOCH}_2\text{Cl}$ ,  $\text{Pr}^i_2\text{NEt}$ , dimethylformamide (97%); vi, *N*-hydroxybenzotriazole,  $\text{CF}_3\text{CH}_2\text{OH}$ , 3 h (67%).

trityl chloride (88 mg,  $3.16 \times 10^{-4}$  mol) in dichloromethane (1  $\text{cm}^3$ ) was added to a stirred solution of **4** (67.7 mg,  $2.6 \times 10^{-4}$  mol), triethylamine (88  $\text{cm}^3$ ,  $6.3 \times 10^{-4}$  mol) and DMAP (4 mg,  $2.63 \times 10^{-5}$  mol) in dichloromethane (2  $\text{cm}^3$ ) at  $0^\circ\text{C}$ . After 24 h

\*  $[\alpha]_D$  Values are recorded in units of  $10^{-1}$  deg  $\text{cm}^2 \text{g}^{-1}$ .

at room temperature water (1 cm<sup>3</sup>) was added, the layers were separated and the aqueous layer was further extracted with dichloromethane (3 × 5 cm<sup>3</sup>). The combined extracts were dried (MgSO<sub>4</sub>) and concentrated; flash chromatography [light petroleum (b.p. 60–80 °C)–ethyl acetate (4:1)] of the residue gave the tritylamine **6** as a white foam (64.1 mg, 55%); *R*<sub>f</sub> 0.25 [light petroleum (b.p. 60–80 °C)–ethyl acetate (4:1)]; [ $\alpha$ ]<sub>D</sub><sup>26</sup> –40.45 (*c* 1.1 in CHCl<sub>3</sub>);  $\nu_{\max}/\text{cm}^{-1}$  3336 (NH str.), 3027 (CH str.), 1719 (C=O str.) and 638;  $\delta_{\text{H}}$ (250 MHz; CDCl<sub>3</sub>) 7.5–7.3 (15 H, m, ArH), 5.5 (1 H, d, *J* 2.0, 2-H), 5.27 (1 H, dd, *J* 6.0 and 2.0, 3-H), 4.37 (1 H, d, *J* 6.0, 4-H), 3.86 (1 H, s, 3-H), 3.73 (3 H, s, OCH<sub>3</sub>), 1.6 (1 H, br s, NH) and 1.26 and 1.28 [3 H, s, C(CH<sub>2</sub>)<sub>2</sub>];  $\delta_{\text{C}}$  (62.9 MHz; CDCl<sub>3</sub>), 146.06 (CH, C-2), 128.65–126.68 (CH, Ar), 111.58 [C(CH<sub>3</sub>)<sub>2</sub>], 86.43 (OCH), 81.98 (OCH), 63.98 (CNH), 51.75 (OCH<sub>3</sub>) and 27.20 and 25.40 [C(CH<sub>3</sub>)<sub>2</sub>] (Found: *M*<sup>+</sup>, 455.2199. C<sub>29</sub>H<sub>29</sub>NO<sub>4</sub> requires *M*<sup>+</sup>, 455.2096).

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