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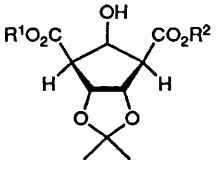
Hydrolysis of the diester **1** catalysed by pig liver esterase provided the mono-ester **3**. This ester was converted into the amine **9**, a precursor of neplanocin **10**, thereby confirming the previously proposed configuration of **3**.

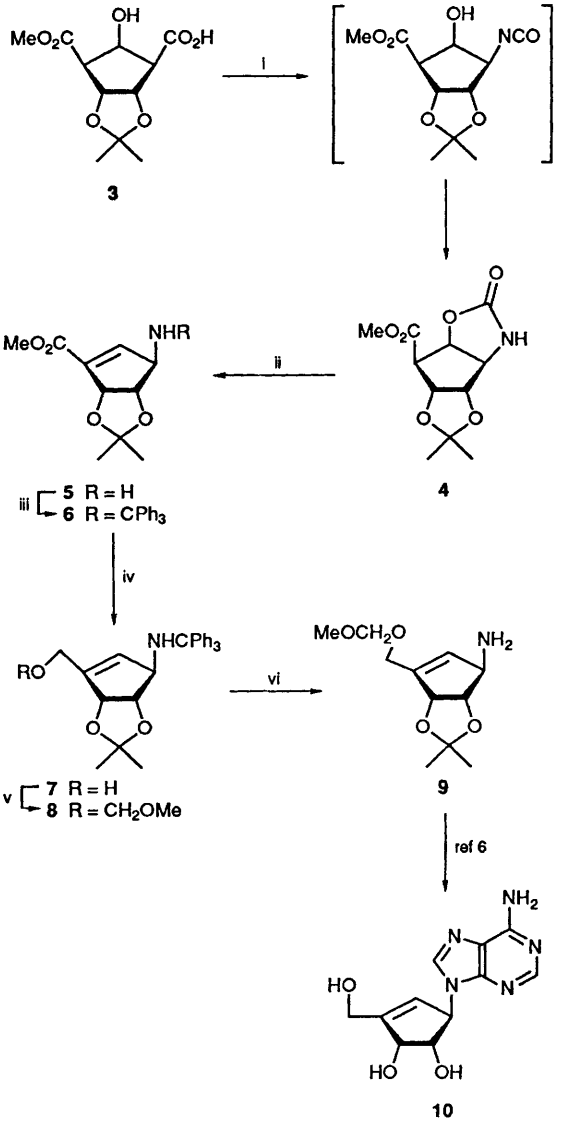
Zemlicka *et al.* reported that the *meso*-diester **1** was hydrolysed by pig liver esterase to give the mono ester **2** {$[\alpha]_D$ +5.5 (*c*, 0.51 in dioxane)*}.[1] Structural assignment was made on the basis of X-ray data. This specific hydrolysis seemed to be satisfactorily explained by the accepted active site model of the enzyme.[2] 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**.[3] 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**.



1 $R^1 = R^2 = Me$
2 $R^1 = H, R^2 = Me$
3 $R^1 = Me, R^2 = H$

The product **3** from the enzyme-catalysed hydrolysis was transformed into the oxazolidinone **4** using diphenyl phosphoryl azide,[4] 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[5] afforded the bicyclic compound **9** {$[\alpha]_D^{23}$ −34.4 (*c* 0.61 $CHCl_3$)}, a compound which had been prepared previously by Ohno {$[\alpha]_D^{20}$ −37.1 (*c* 1.0, $CHCl_3$)}.[6] The amine **9** was converted into the naturally occurring carbocyclic nucleoside neplanocin A **10** in four well-documented steps.[6]

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.



Scheme 1 *Reagents and conditions:* i, $(PhO)_2P(O)N_3$, dimethylaminopyridine, THF, 48 h (81%); ii, KF, TsF, pyridine, THF (79%); iii, Ph_3CCl, dimethylformamide, Et_3N (77%); iv, Bu^i_2AlH, toluene, −78 °C, 6 h (76%); v, $MeOCH_2Cl$, Pr^i_2NEt, dimethylformamide (97%); vi, *N*-hydroxybenzotriazole, CF_3CH_2OH, 3 h (67%)

Experimental

Methyl (3R,4S,5R)-4,5-*Isopropylidenedioxy*-3-*triphenylmethylaminocyclopent*-1-*enecarboxylate* **6**.—A solution of trityl chloride (88 mg, 3.16×10^{-4} mol) in dichloromethane (1 cm^3) was added to a stirred solution of **4** (67.7 mg, 2.6×10^{-4} mol), triethylamine (88 cm^3, 6.3×10^{-4} mol) and DMAP (4 mg, 2.63×10^{-5} mol) in dichloromethane (2 cm^3) at 0 °C. After 24 h

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

at room temperature water (1 cm^3) was added, the layers were separated and the aqueous layer was further extracted with dichloromethane (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$) 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_f 0.25 [light petroleum (b.p. 60–80 °C)–ethyl acetate (4:1)]; $[\alpha]_D^{26}$ −40.45 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} 3336 (NH str.), 3027 (CH str.), 1719 (C=O str.) and 638; δ_H(250 MHz; $CDCl_3$) 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_3), 1.6 (1 H, br s, NH) and 1.26 and 1.28 [3 H, s, $C(CH_2)_2$]; δ_C (62.9 MHz; $CDCl_3$), 146.06 (CH, C-2), 128.65–126.68 (CH, Ar), 111.58 [$C(CH_3)_2$], 86.43 (OCH), 81.98 (OCH), 63.98 (CNH), 51.75 (OCH_3) and 27.20 and 25.40 [$C(CH_3)_2$] (Found: M^+, 455.2199. $C_{29}H_{29}NO_4$ requires M^+, 455.2096).

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