Enzyme-catalysed Hydrolysis of 3,5-*cis*-Diacetoxy-4-*trans*-benzyloxymethylcyclopentene and the Synthesis of Aristeromycin Precursors

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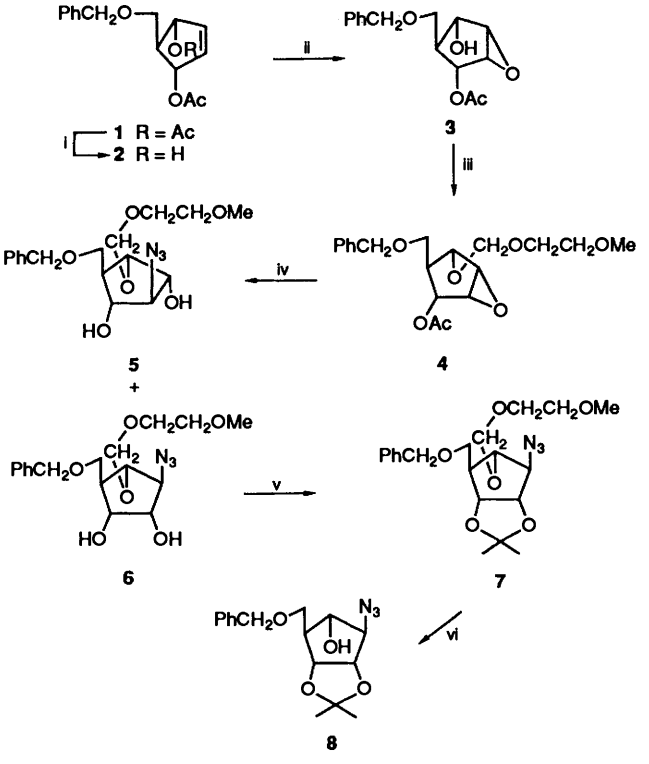
The optically active mono-ester **2** was obtained by enzyme-catalysed hydrolysis of the diester **1** and converted into the azide **8** and the amine **13**, synthetic precursors of (+)- and (−)-aristeromycin.

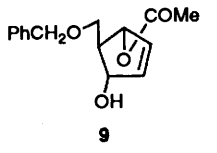
We reported that hydrolysis of the diester **1** by porcine pancreatic lipase gave the monoester **2**, $[\alpha]_D$ +63.2 (*c* 1.0, $CHCl_3$).[1] The assignment of absolute configuration was made on the basis of the following sequence of reactions. Compound **2** was converted into the epoxide **3** (Scheme 1) and protected



Scheme 1 *Reagents and conditions:* i, porcine pancreatic lipase, phosphate buffer (0.1 mol dm^{-3}), pH 7, 5 d (92%, >95% e.e.) or electric eel acetylcholinesterase (95%, >95% e.e.);[3] ii, *m*-chloroperoxybenzoic acid, CH_2Cl_2, 0 °C–room temp., 24 h (80%); iii, $CH_3O(CH_2)_2OCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, 48 h (81%); iv, 2% K_2CO_3, MeOH, 2 h (95%), then NaN_3, NH_4Cl, EtOH, H_2O (4:1), reflux, 3 d; v, 2,2-dimethoxypropane, TsOH (cat.). 2 h (92%); vi, Me_2BBr, CH_2Cl_2, Et_2O (10:1), −78 °C, 2 h (75%)

as the methoxyethoxymethyl ether **4**. Hydrolysis of the ester moiety was followed by azide opening of the oxirane ring which was non-specific giving two products **5** and **6**. The latter compound was converted into the acetonide **7** and partially deprotected to give the azide **8**, $[\alpha]_D$ −26.6 (*c* 1.1, $CHCl_3$), a compound previously made by Martin *et al.*[2], $[\alpha]_D$ −26.0 (*c* 0.3, $CHCl_3$) and utilized in a synthesis of aristeromycin.

At the same time as the appearance of our communication Danishefsky *et al.* published a paper describing the hydrolysis of the diester **1** with electric eel acetylcholinesterase to give the monoester **9**.[3] This ester was converted, using stereochemically well-defined reactions, into allosamidin **10**: allosamizoline, a



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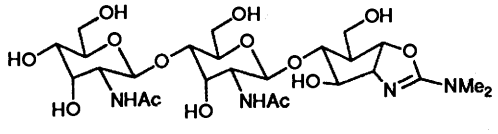

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unit with an established absolute configuration, forms part of the structure of this natural product.[4] Disconcertingly, the compound obtained from the acetylcholinesterase reaction was identical {$[\alpha]_D$ +61.8 (*c* 1.0, $CHCl_3$)}[5] to the one formed from the porcine pancreatic lipase reaction. We have undertaken further studies to try to understand this discrepancy.

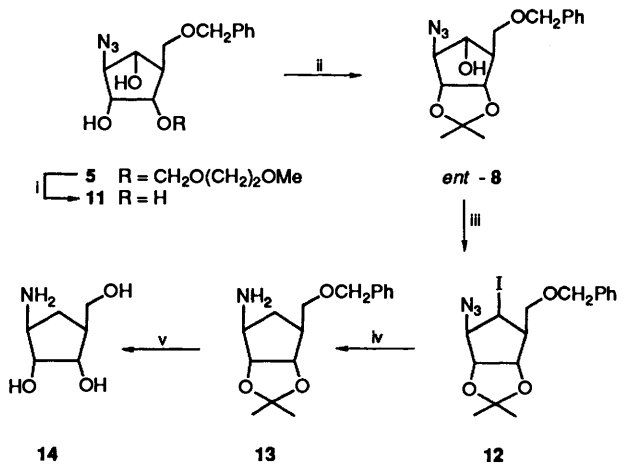
Evidence that compound **5** was undoubtedly a 1,3-diol was provided by NMR spectroscopy which showed couplings between the proton C*H*N_3 and the adjacent protons C*H*OH but not between the two protons bonded to carbon atoms in the secondary alcohol units.

Conversion of the azide **5** into the triol **11** (Scheme 2) followed by acetonide formation gave the compound (*ent*)-**8**, $[\alpha]_D$ +27.8 (*c* 1.0, $CHCl_3$). Conversion of this compound into the iodide **12**, reduction to afford the amine **13** and deprotection to give the triol **14** followed the recommended procedures of Martin *et al.*[2], except that the reduction step was performed using tributyltin hydride and azoisobutyronitrile (AIBN). The triol, **14**, $[\alpha]_D$ +10.9 (*c* 1.1, H_2O), was the enantiomer of the material, $[\alpha]_D^{20}$ −10.3 (*c* 1.52, H_2O), prepared by Ohno and co-workers[6] as part of their campaign on the synthesis of carbocyclic nucleosides.

In summary, the optically active epoxide **3** has been converted into the azide **8** and the amine **14** previously prepared by Martin and Ohno respectively. The chemical transformations appear to be straightforward and this suggests that the hydrolysis of the diester **1**, catalysed by porcine pancreatic liapse or acetylcholinesterase, gives the monoester **2**.

Experimental

(1S),(1β,2α,3α,4β)-*Benzyloxymethyl*-2,3-*dimethylmethylenedioxycyclopentamine* **13**.—A solution of compound **12** (0.074 mol dm^{-3}, 0.16 g), tributyltin hydride (0.224 mol dm^{-3}; 0.30 cm^3) and AIBN (cat.) in dry benzene (5 cm^3) was deoxygenated for 30 min and then heated at reflux for 45 min. The reaction mixture was concentrated under reduced pressure and the residue partitioned between acetonitrile (10 cm^3) and hexane (20 cm^3). The acetonitrile was washed with hexane (10 cm^3)



Scheme 2 *Reagents and conditions:* i, Me_2BBr, CH_2Cl_2, Et_2O (10:1), −78 °C, 2 h (72%); ii, 2,2-dimethoxypropane, TsOH (cat.), 2 h (95%); iii, trifluoromethylsulfonic acid anhydride, pyridine, CH_2Cl_2, O °C, 0.5 h, then LiI, DMF, 1 h (73%); iv, Bu_3SnH, AIBN, benzene, reflux (79%); v, 80% acetic acid, 2 h (78%) then Na–NH_3(l), 1 h (75%)

and concentrated under reduced pressure. The crude residue was flash chromatographed over silica gel using dichloromethane–methanol (20:1) as eluent. The title compound **13** (0.08 g, 0.29 mmol, 79%) was obtained as an oil; $[\alpha]_D^{25}$ +3.3 (*c* 1.22, $CHCl_3$); δ_H(250 MHz, $CDCl_3$) 7.34 (5 H, m, Ph), 4.92 (2 H, br s, NH_2), 4.48–4.60 (2 H, m, 2-H, benzylic), 4.32–4.42 (2 H, m, 3-H, benzylic), 3.75 (1 H, m, 1-H), 3.16 (2 H, m, 5-H), 2.30 (1 H, m, 6-H), 2.20 (1 H, m, 4-H), 1.65 (1 H, m, 6-H), 1.42 (3 H, s, Me), 1.13 (3 H, s, Me) [Found (CI) $M^+ + H$, 278.1756. $C_{16}H_{24}NO_3$ requires $M + H$, 278.1756].

Acknowledgements

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