Chemoenzymatic Synthesis of Carbocyclic Oxetanocin-A Involving a Novel Photochemical Rearrangement

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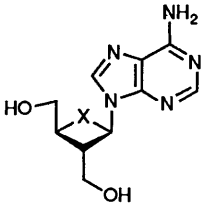
The anti-herpes agent carbocyclic oxetanocin-A (−)-**2** has been prepared from the bicyclic ketone **3** *via* resolution of the bromohydrin **4** (using an enzyme-catalysed trans-esterification reaction) and a photocatalysed rearrangement of the epoxide (+)-**6** to the lactone (+)-**7**.

There is considerable current interest in the synthesis of carbocyclic nucleosides[1] because of their interesting biological activity.[2] In some cases this activity mimics that of the corresponding oxygen heterocycle[3] but, interestingly, in other instances it does not.[4]

In the case of the four-membered ring compound oxetanocin-A **1** and the corresponding carbocyclic compound **2**, potent antiviral activity is exhibited by both compounds and, as a consequence, the cyclobutane derivative **2** has been the subject of close scrutiny.[5] We report a new synthesis of **2** in optically active form, utilising a route which could be adapted to provide a wide range of novel analogues.



1 X = O
2 X = CH_2

The bicyclic ketone **3** (Scheme 1) is readily prepared by cycloaddition of cyclopentadiene and diphenylketene.[6] Treatment of this ketone with *N*-bromoacetamide in aqueous acetone provided the bromohydrin **4** (73%) which was readily separated from the isomeric impurity **5** (12%).[7] The bromohydrin was resolved by acylation using vinyl acetate and immobilised *Mucor miehei* lipase (Lipozyme®)[8] and the optically pure bromohydrin (+)-**4** (42%) was converted into the epoxide (+)-**6** (90%) using base.

Photolysis of this epoxide in dry benzene using a 400W lamp over 4 h furnished the lactone (+)-**7**[9] which was converted into the ester (+)-**8** (85%) by acid-catalysed methanolysis. Compound (−)-**9** was also produced from (+)-**7** (8% yield): since the starting compound (+)-**7** was pure, as judged by ^1H and ^{13}C NMR spectroscopy, the mechanism of formation of this impurity is not clear.

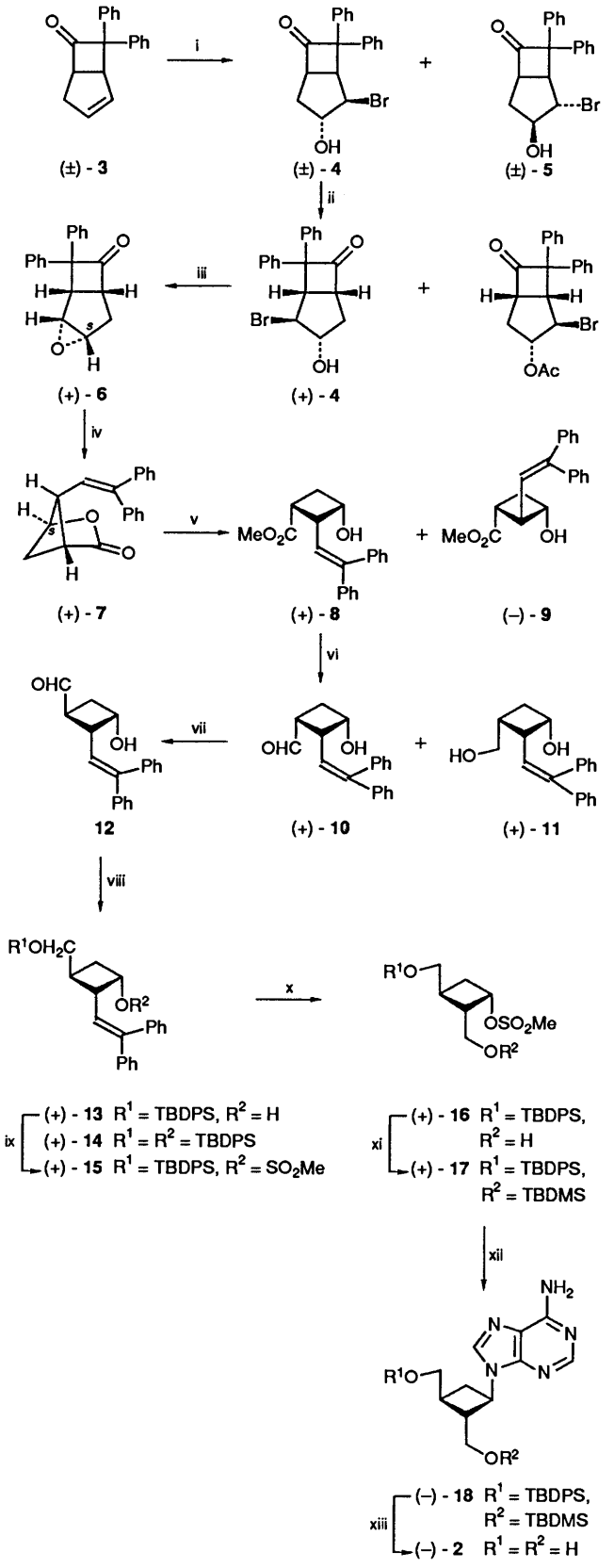
Reduction of the ester (+)-**8** using diisobutylaluminium hydride (DIBAL-H) in toluene at −100 °C gave the required aldehyde (+)-**10** (74%) and a small amount of the over-reduced compound (+)-**11** (15%). Treatment of the aldehyde (+)-**10** with triethylamine in toluene at 90 °C afforded the isomeric compound **12** (60% yield; 70% based on starting material consumed). The latter compound was reduced with DIBAL-H to give the corresponding diol (70%) which was treated with *tert*-butyldiphenylsilyl chloride and base in dichloromethane at 0 °C to give the desired material (+)-**13** (85%) and the diprotected compound **14** (7%).

Ozonolysis of the alcohol (+)-**13** was troublesome and, apart from benzophenone, no products could be identified. However, conversion of the alcohol (+)-**13** into the mesylate (+)-**15** (90%) gave a compound which was cleaved rapidly and cleanly by ozone using a mixture of dichloromethane in methanol as the solvent at −78 °C. Sodium borohydride reduction of the crude reaction mixture provided the alcohol (+)-**16** (77%) which was converted into the disilylated compound (+)-**17** (95%) in standard fashion. The optimum conditions for the reaction of the mesylate (+)-**17** with adenine consisted of heating the two compounds in dimethylformamide at 140 °C in the presence of sodium hydride and 18-crown-6 whereupon the purine derivative (−)-**18** was isolated in 41% yield. Deprotection (tetrabutylammonium fluoride in tetrahydrofuran at room temperature) furnished the desired carbocyclic compound (−)-**2** (91%) $[\alpha]_D^{27}$ −36.6 (*c* 0.95 pyridine) {lit.,[5] $[\alpha]_D$ −45.7 (*c* 1.00 pyridine)} with physical properties identical with those described previously.[5]

Thus, from the readily obtained ester **8**,[9] now available in optically active form, carbocyclic oxetanocin-A can be prepared in nine steps and 8% overall yield.

Experimental

(1S,2S,3S)1-*Methylsulfonyloxy*-2-*hydroxymethyl*-3-*tert*-*butyldiphenylsilyloxymethylcyclobutane* **16**.—Argon was passed through a stirred solution of the mesylate (+)-**15** (96 mg, 0.16 mmol) in a mixture of dry dichloromethane (4.0 cm^3) and dry methanol (8.0 cm^3) for 15 min. The solution was cooled to −78 °C and dry ozone/oxygen was passed through it for 2 h. Argon was then passed through the solution for 15 min after which time sodium borohydride (31 mg, 0.80 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and allowed to warm to room temperature. The solvent was evaporated and the reaction mixture was cooled to 0 °C when aqueous ammonium chloride (10% w/v, 3.0 cm^3) was added. The aqueous solution was extracted with dichloromethane (3 × 5.0 cm^3) and the combined organic extracts were washed with water (5.0 cm^3), dried and evaporated to give a pale yellow oil. Chromatography of the latter over silica gel [eluent: dichloromethane–acetone (25:1 v/v)] gave the *alcohol* (+)-**16** (55.2 mg, 77%) as a colourless, viscous oil; $[\alpha]_D^{24}$ +12.6 (*c* 1.0 in MeOH); ν_{max}(film)/cm^{-1} 3561 (OH), 1428 and 1175 (OSO_2); δ_H 7.72–7.35 (10 H, m, ArH), 5.27 (1 H, m, 1-H), 3.92 (1 H, dd, *J* 8, 11.5, CH_AOH), 3.74 (1 H, dd, *J* 5.5, 11.5, CH_BOH), 3.69–3.57 (2 H, m, $CH_2OTBDPS$), 3.02 (3 H, s, OSO_2CH_3),



Scheme 1 *Reagents and conditions:* i, *N*-bromoacetamide, Me_2CO, H_2O, 6 h, room temp.; ii, Lipozyme, vinyl acetate, 42 °C, 10 days; iii, K_2CO_3, MeOH, 1 h, room temp.; iv, *hv* (400W), dry C_6H_6, room temp., 4 h (44%); v, *p*-$MeC_6H_4SO_3H$, MeOH, 12 h, room temp.; vi, $HAlBu^i_2$, toluene, −100 °C, 2 h; vii, Et_3N, toluene, 90 °C, 4 h; viii, $HAlBu^i_2$, toluene, − 78 °C room temp., 3 h then Bu^tPh_2SiCl, dimethylaminopyridine, Et_3N, CH_2Cl_2, 0 °C, 4 h; ix, *p*-$MeSO_2Cl$, Et_3N, CH_2Cl_2, room temp.; x, O_3, CH_2Cl_2/MeOH, −78 °C, 2 h then $NaBH_4$; xi, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, room temp., 1 h; xii, adenine, DMF, NaH, 18-C-6, 140 °C, 16 h; xiii, Bu_4NF, THF, room temp, 2 h

2.84–2.72 (1 H, m, 2-H), 2.44–2.30 (3 H, m, 3-H and 2 × 4-H), 1.86 (1 H, br s, OH) and 1.09 (9 H, s, Bu^t); δ_C 133.25 (C, C-Ar), 135.59, 129.83 and 127.79 (3 × CH, C-Ar), 75.55 (CH, C-1), 65.38 and 61.20 (2 × CH_2, CH_2OH and $CH_2OTBDPS$), 45.61 (CH, C-2), 38.05 (CH_3, OSO_2CH_3), 35.21 (CH, C-3), 30.36 (CH_2, C-4), 26.89 (CH_3, Bu^t) and 19.26 (C, Bu^t) (Found: M + H^+, 449.182. $C_{23}H_{32}O_5SSi$ requires *M* + H, 449.182).

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