Preparation of Optically Active 6'-Fluorocarbocyclic Nucleosides utilising an Enantiospecific Enzyme-catalysed Baeyer–Villiger Type Oxidation

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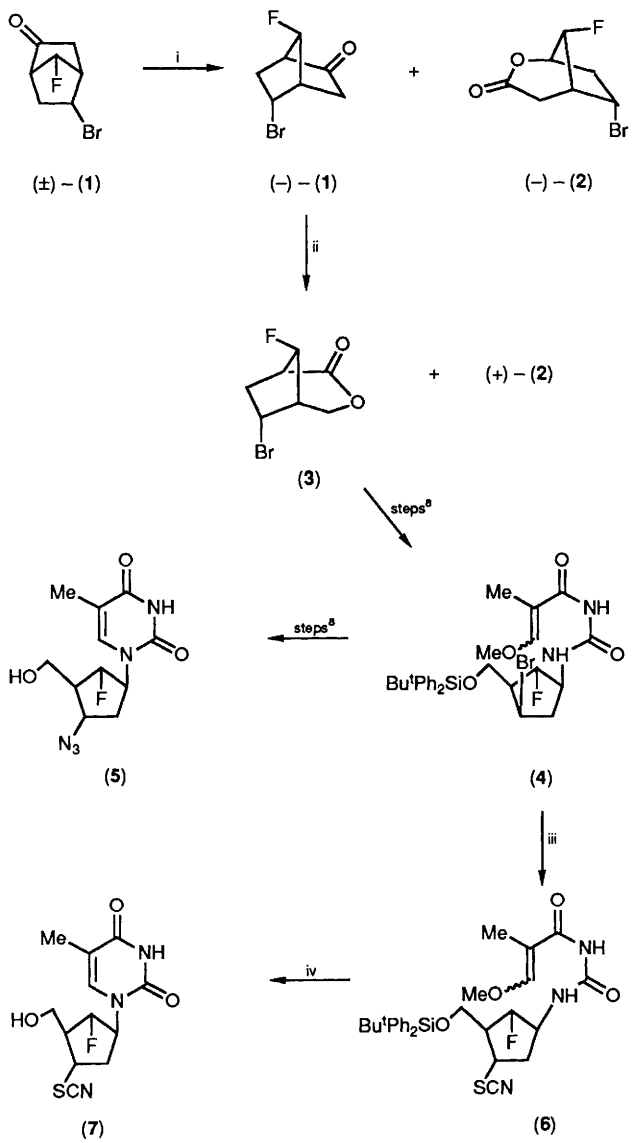
Kinetic resolution of the racemic ketone (±)-(**1**) was achieved using *Acinetobacter* NCIB 9871: the optically active norbornanone was converted into the carbocyclic nucleosides (**5**) and (**7**).

It has been established that certain micro-organisms can convert cyclic ketones (including norbornanones) into the corresponding lactones.[1] In certain cases the mono-oxygenase enzyme has been isolated, partially purified and shown to provide a mild method for performing the Baeyer–Villiger oxidation.[2] In most cases, however, a whole-cell biotransformation using a fungus or *streptomycete* has been the experimental method of choice and this has been shown to provide a perfectly satisfactory strategy for use by the synthetic organic chemist.[3]

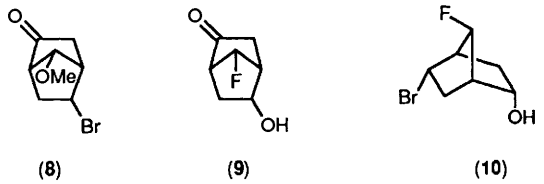
Interestingly the regioselectivity of the enzyme-catalysed reaction differs, in some instances, from the chemical process involving a peracid.[4] More importantly the enzymic reaction can convert racemic[5] and mesomeric substrates into optically active products.[6] A reaction of the latter type has been used to prepare synthons of *cis*-chrysanthemic acid.[7]

We report an enantioselective transformation of a 5,7-disubstituted norbornanone promoted by a readily available and easy-to-handle micro-organism which affords, in an optically pure form, a key intermediate for the synthesis of anti-viral 6'-fluorocarbocyclic nucleosides.

The racemic ketone (**1**)[8] was incubated with *Acinetobacter* NCIB 9871 (grown on cyclohexanol)[9] until half the starting material had been consumed as judged by GC analysis. Centrifugation, removal of the spent cells, and extraction of the aqueous medium afforded a mixture of ketone (−)-(**1**) and



Scheme 1. *Reagents and conditions*: i, *Acinetobacter* NCIB 9871, *ca.* 200 mg (±)-(**1**)/l culture; ii, *m*-chloroperoxybenzoic acid; iii, NaSCN; iv, HCl.



lactone (−)-(**2**). After chromatography the ketone (−)-(**1**) ($[\alpha]_D^{23}$ = −27°, 30% yield) was shown to be >95% optically pure by NMR spectroscopy employing a chiral shift reagent: the absolute configuration of the ketone was assigned by preparing a small sample of 5-bromo-7-fluoro norbornanone (−)-(**1**) from (+)-bicyclo[3.2.0]hept-2-en-6-one.[10] The lactone (−)-(**2**) was also obtained in 36% yield in a state of high optical purity [>95% enantiomeric excess (e.e.) by chiral shift NMR]. The exquisite enantioselectivity of the microbiological oxidation process is due to the presence of the halogen atoms since both enantiomers of bicyclo[2.2.1]heptan-2-one are oxidized by the bacterium.

As expected chemical oxidation of the ketone (−)-(**1**) gave the lactones (**3**) and (+)-(**2**) in the ratio 3.5 : 1.[8] The fluorine atom at C-7 militates against migration of the methine centre to the incoming oxygen atom during the peracid oxidation but, obviously, the same atom does not have the same influence on the regioselectivity of the enzyme-catalysed reaction. The lactone (**3**) furnished the dihalide (**4**) in four steps (35% yield) and this compound afforded the optically pure antiviral carbocyclic nucleoside (**5**) {$[\alpha]_D^{23}$ = +23° (methanol)} (32%) on displacement of the bromine atom using azide followed by acid treatment.[8] The dihalide (**4**) was also reacted with thiocyanate to give the cyclopentane derivative (**6**) (83%) and this compound produced the nucleoside analogue (**7**) (57%) ($[\alpha]_D^{23}$ = +10° methanol) on treatment with acid. This demonstrates still further the wide range of carbocyclic nucleosides that can be made available from the ketone (−)-(**1**).

The biological oxidation of some other 5,7-disubstituted norbornanones using *Acinetobacter* NCIB 9871 was unsuccessful. Replacement of the fluorine atom by a methoxy group [compound (**8**)] or replacement of the bromine atom by an hydroxy group [compound (**9**)] gave rise to substrates which were not oxidized by the micro-organism.

Another cycloalkanol-grown bacterium *Pseudomonas* NCIB 9872[11] did not convert the ketone (±)-(**1**) into the corresponding lactone but instead produced the alcohol (**10**) (>95% e.e.) (27% yield after conversion of *ca.* one-third of the substrate).

Currently we are exploring the capability of other organisms to provide access to useful optically active norbornanones and 2-oxanorbornanones having different substitution patterns.

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