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Exploitation of microbiological methods for the synthesis of biologically active natural products and analogues

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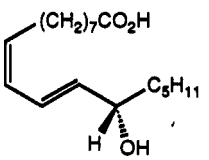
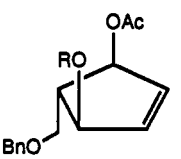
Abstract

The importance of enzyme catalysed reactions in organic synthesis is illustrated by the use of esterases, lipases, and oxidoreductases, for the preparation of important natural products (e.g. leukotrienes, prostaglandins, pheromones) and analogues (e.g. carbocyclic nucleosides) in optically active form.

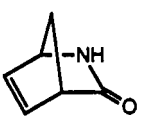
There is an increasing amount of attention being paid to the synthesis of chiral substances in optically pure form. The use of chiral catalysts to provide optically active substances from achiral or racemic compounds has been recognised as an efficient way of providing the necessary starting materials. This philosophy has led to the remarkable, exponential increase in the use of enzymes as catalysts in organic synthesis.[1] Thus the use of esterases, lipases, dehydrogenases, mono-oxygenases, dioxygenases and lipoxygenases in synthetic organic chemistry is becoming quite commonplace.



(1)



(2) R = Ac
(3) R = H



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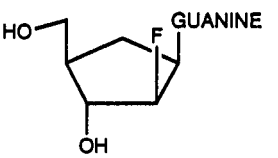
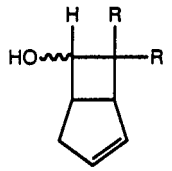
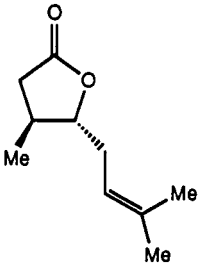


(5)

The enantioselective hydrolysis of 3-acetoxyoct-1-yne is accomplished using Mucor miehei lipase or yeast; the oct-1-yn-3(s)-ol that is obtained by this process has been used to prepare the anti-fungal agent coriolic acid (1).[2] Similarly the conversion of the diester (2) into the mono-ester (3) using porcine pancreatic lipase gives access to selected carbocyclic ribonucleosides.[3] The γ-lactam (4) is hydrolysed enantioselectively using Pseudomonas solanacearum and the (-)-lactam obtained in this way has been converted into the anti-HIV agent (-)-Carbovir.[4] The resolution of 6-azabicyclo-[3.2.0]hept-2-en-7-one can be carried out in a similar manner and this has led to an efficient synthesis of the anti-fungal agent (-)-cis-pentacin.[5] Complementary, very efficient methods for the preparation of dideoxydidehydrocarbocyclic nucleosides involves the selective acylation of cis- or trans-4-hydroxycyclopent-2-enyl methanol derivatives.[6] Compound (5) is a potent inhibitor of Herpes viruses and it has been obtained in optically pure form by enantioselective hydrolysis of the corresponding 5'-monophosphate using a 5'-nucleotidase.[7]



(6) R = H
(7) R = Me



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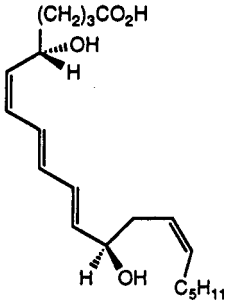
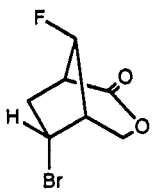


(9)

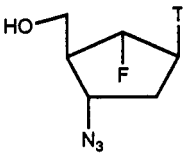
(10) R = H
(11) R = OH

The use of lipases in organic solvents to promote the enantioselective esterification of selected alcohols is well-established. The alcohol (6) can be resolved in this way giving intermediates for the preparation of prostaglandins and prostanoids.[8] In contrast, the best method of production of optically active compounds of type (7) is through reduction of the corresponding ketone (7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one) with the fungus Mortierella isabellina[9] or 3α,20β-hydroxysteroid alcohol dehydrogenase.[10] The resolved alcohols have been converted into the pheromone eldanolide (8)[11] and they can be employed in an enantioconvergent asymmetric synthesis of leukotrienes-B_3 and B_4.[12] An investigation into the preparation of a putative leukotriene-B antagonist commenced with the conversion of the hydrocarbon (10) into the diol (11) using Cunninghamella blakesleeana.[13]

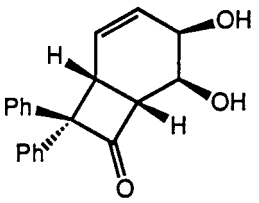
Enantioselective Baeyer-Villiger oxidation of 7anti-fluoro-5endo-bromobicyclo[2.2.1]heptan-2-one using Acinetobacter sp. 9871 furnished the lactone (12)[14] and this lactone was converted into the AZT analogue (13), a compound which demonstrated anti-HIV activity.[15] The organism Acinetobacter 9871 has been found to promote many other, often highly stereoselective, oxidation reactions.[16] The mono-oxygenase enzyme(s) responsible for these oxidation processes has (have) been isolated from the organism and coupled with a dehydrogenase enzyme to provide a "one-pot" method for the conversion of a secondary alcohol (e.g. norbornanol) into the corresponding lactone.[17] The use of soybean lipoxygenase for the synthesis of analogues of the dienol (1) has also been the subject of scrutiny.[18]



(12)



(13)



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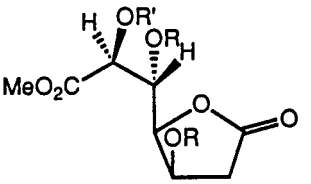

(15) R = Me,
R' = COMe

The conversion of benzene (derivatives) into (3-substituted) cyclohexa-3,5-diene-1,2-diols using Pseudomonas sp. has attracted a lot of attention. The chemistry of the dienediols is rich and varied; for example adducts derived from [4+2][19] and [2+2] reactions [e.g. the diphenylketene adduct (14)[20]] have been prepared. The latter compounds can be used to prepare unusual C_7 and C_8 sugars [the compound (15) is one example].

A wide variety of enzymes and whole cell systems have been found to be useful biocatalysts and this has led to the invention of novel routes to optically active natural products and analogues.

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