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A HIGHLY ENANTIOSELECTIVE HYDROLYSIS OF CIS-3,5-DIACETOXYCYCLOPENT-1-ENE. AN ENZYMATIC PREPARATION OF 3(R)-ACETOXY-5(S)-HYDROXYCYCLOPENT-1-ENE.

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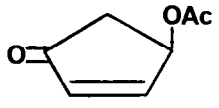
ABSTRACT: Exposure of cis-3,5-diacetoxycyclopent-1-ene (3) to the hydrolase enzyme acetylcholinesterase (from electric eel) affords in 94% yield 3(R)-acetoxy-5(S)-hydroxycyclopent-1-ene (2) with an e.e. of 96% (greater than 99% e.e. after one recrystallization).

The preparation of optically active 3-acetoxy-5-hydroxycyclopent-1-enes has been the object of several synthetic endeavors.[1] These compounds derive much of their importance from the fact that they are immediate chiral precursors[1b,2] to 4-acetoxy-2-cyclopenten-1-one (1) - a synthon of enormous utility.[3]



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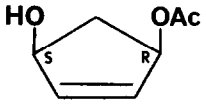

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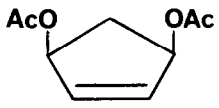

3

In conjunction with our synthetic studies on carbocyclic nucleosides, we sought an efficient procedure for the enantiospecific preparation of 3(R)-acetoxy-5(S)-hydroxycyclopent-1-ene (2). It occurred to us that access to optically pure 2 might be achieved through an enzyme catalyzed enantioselective hydrolysis of the corresponding meso-diester (3).[4] In this way, chirality would be induced via the process of enantiotopic group differentiation.[1c] This approach to the preparation of optically active synthetic intermediates is an effective alternative to dipping into the "chiral pool".

After careful evaluation of numerous enzymes, we now wish to report that 2 can be prepared in high optical (>99% e.e.) and chemical (94%) yields using the commercially-available enzyme acetyl cholinesterase. The concomitant hydrolysis of both ester functions, a problem which usually accompanies[1c] these reactions, appears to be absent here. In fact, diol is only detected after prolonged exposure to the enzyme. Thus, the reaction may be run to completion without any noticeable interference from the bis-hydrolyzed product.

Hydrolase enzymes are particularly well-suited for laboratory use as they are easily handled and do not require a cofactor for activity. The following moderately scaled experimental procedure clearly illustrates the simplicity with which this reaction may be carried out:

To a slowly stirred solution of acetyl cholinesterase[6a] (4.9 mg, 1225 units) and sodium azide (15 mg, 0.23 mmol) in 150 mL of aqueous phosphate buffer (0.58 M, pH 6.85, 23°C) was added 3[4] (3.26 g, 17.7 mmol) in one portion. The reaction was monitored via TLC analysis (1:1; hexane:ethyl acetate) and judged complete after 5.5 hours. The reaction mixture was repeatedly extracted with ether:ethyl acetate (1:1). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2.55 g of partially crystalline material. Distillation through a shortpath apparatus at 70°C/0.2 mm provided 2.35 g (93.6% yield) of a colorless crystalline solid, mpt. 40.5-48.5°C, $[\alpha]_D^{23}$ + 63.4° (c 1.53, $CHCl_3$), 96% e.e.[7] Recrystallization from pentane:ether (1:1) furnished colorless needles of enhanced optical purity, mpt. 46-48.5°C, $[\alpha]_D^{23}$ + 66.3°, >99% e.e.[7]

Our results complement the very recent findings of Laumen and Schneider[1a,b] who were able to enzymatically prepare the optical antipode of 2 in high enantiomeric purity (98% e.e. after recrystallization, 59% yield), but were considerably less successful in their attempt at 2 (50% e.e., 82% yield).

Finally, immobilized acetyl cholinesterase[6b] has been found equally effective and offers the additional advantage of reusability. We anticipate that this bound enzyme will appeal to those whose projects demand a higher throughput of material. Enantioselective hydrolysis studies on selected meso-diesters with bound acetyl cholinesterase are in progress.

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(3) For review see: Michael Harre, Peter Raddatz, Rainer Walenta and Ekkehard Winterfeldt, Angew. Chem. Int. Ed. Engl., 1982, 21, 480.

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(6) (a) Sigma, No. C-3389, from electric eel, EC 3.1.1.7. (b) Sigma, No. C-2511.

(7) The enantiomeric excess was quantified by capillary GC analysis (25 m OV-101 crosslinked methyl silicone column) of the MTPA derived esters[8] and verified by ^{19}F NMR measurement.

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