Enzymatic Hydrolysis of 3,7-Diacetoxycycloheptene Derivatives

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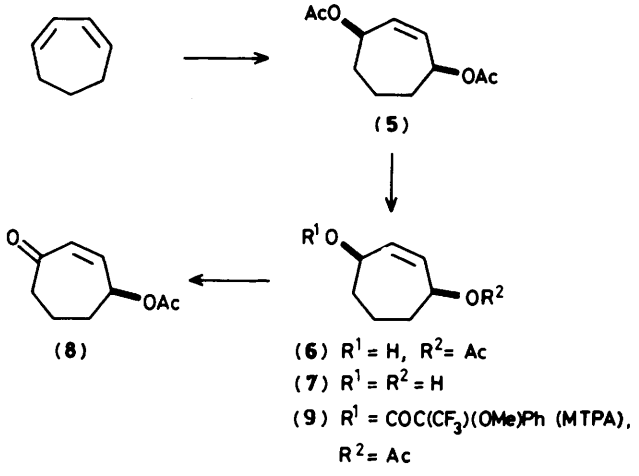
Hydrolysis of 3,7-diacetoxycycloheptene using electric eel acetylcholinesterase gives optically pure (3*R*,7*S*)-3-hydroxy-7-acetoxycycloheptene, and hydrolysis using lipase enzyme from *Candida cyclindracea* gives the same hydroxy acetate, but in only 44% enantiomeric excess, in contrast to the normal behaviour of lipase which gives (*S*) alcohols for related hydrolyses; 3,7-diacetoxy-4,6-dimethylcycloheptene (**10**) is not hydrolysed by acetylcholinesterase, but is readily hydrolysed by lipase to give (3*S*,4*R*,6*S*,7*R*)-3-hydroxy-7-acetoxy-4,6-dimethylcycloheptene.

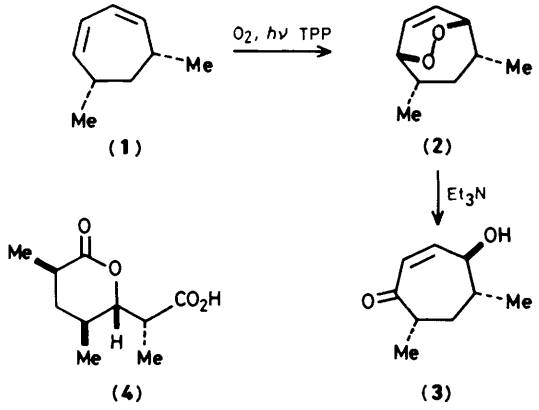
Recent work in our laboratory[1] has demonstrated that cyclohepta-1,3-diene can be converted, *via* its $Fe(CO)_2L$ complexes [L = PPh_3 or $P(OPh)_3$] into disubstituted cyclohepta-1,3-dienes with complete control over *relative* stereochemistry, and in this manner *cis*-5,7-dimethylcyclohepta-1,3-diene (**1**) can be prepared. More recently, we described[2] the stereoselective conversion of (**1**) into the endoperoxide (**2**), which can be converted to (**3**), and this is currently being evaluated as an intermediate for synthesis of the important Prelog–Djerassi lactone[3] (**4**). Since (**1**) is symmetrical, the sequence described unavoidably leads to racemic material, and so we have examined the use of enzymes[4] for the preparation of (**3**) in optically pure form.

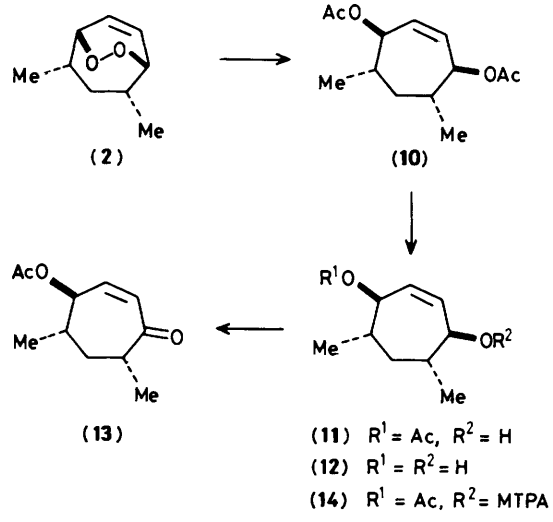
Preliminary studies were focussed on enzymatic hydrolysis of 3,7-diacetoxycycloheptene (**5**) prepared (Scheme 1) from cyclohepta-1,3-diene by the three-step sequence: (i) O_2, *hν*, tetraphenylporphyrin (TPP); (ii), thiourea, MeOH, room temp., 12 h; (iii) Ac_2O, pyridine, CH_2Cl_2, room temp., 12 h. Treatment of (**5**) with electric eel acetylcholinesterase,[5] following the method of Deardorff *et al.*,[4] allowed isolation of hydroxy acetate (**6**) (39% yield) together with recovered diacetate (50—55% yield) and diol (**7**) (*ca.* 5% yield), after 8 h reaction time. Attempts to increase the yield of (**6**) led to greater amounts of (**7**), and inconvenient chromatographic separation of products. Since (**6**) showed only a small optical rotation, it was converted into the enone (**8**), which gave $[\alpha]_D^{23}$ −98.3° (*c* 5.00, $CHCl_3$). The n.m.r. spectra of (**8**), and its racemic analogue, recorded in the presence of the chiral lanthanide shift reagent Eu(hfbc)$_3$ (hfbc = heptafluorobutyrylcamphorato), indicated high optical purity for (**6**), but the small splitting observed for the acetate CH_3 group did not allow an accurate measurement. Consequently, both racemic and optically active (**6**) were converted into their (*R*)-α-methoxy-α-trifluoromethylphenylacetate (MPTA) esters (**9**), the ^{19}F n.m.r. spectra of which demonstrated 100% enantiomeric excess for the optically active compound. Analysis of the ^1H n.m.r. spectra of racemic (**9**) and optically pure (**9**), according to Mosher's method,[6] showed that the enzymatic hydrolysis gave (*R*)-alcohol, as shown in the structure (**6**).

Treatment of (**5**) with lipase from *Candida cylindracea*,[7] using the method of Eichberger *et al.*,[4] resulted in monohydrolysis [40% yield of (**6**) together with *ca.* 50% recovery of (**5**) and *ca.* 10% yield of (**7**) after 30 h reaction time; reaction quenched immediately after detection of (**7**) by t.l.c.]. However, analysis of the ^{19}F n.m.r. spectrum of the (*R*)-MTPA ester of (**6**) from this reaction indicated only 44%



Scheme 1





Scheme 2

enantiomeric excess (e.e.), again in favour of the (*R*) alcohol ($[\alpha]_D^{21}$ −42.5° after conversion into (**8**); *c* 1.34, $CHCl_3$). This was unexpected, since hydrolysis of diacetoxycyclopentene is known to give predominantly (*R*) alcohol with esterases, but predominantly (*S*) alcohol from lipase hydrolysis.[4]

Attention was next turned to the dimethyl-substituted cycloheptene diacetate (**10**) (Scheme 2), readily obtained *via* endoperoxide (**2**). All attempts to effect the hydrolysis of this compound using acetylcholinesterase failed, diacetate (**10**) being recovered quantitatively. However, lipase-catalysed hydrolysis of (**10**), as above, gave a monoacetate (**11**) [61%, together with 35% recovered (**10**) and *ca.* 2—3% of diol (**12**)]. Oxidation of (**11**) [pyridinium chlorochromate (PCC), CH_2Cl_2, room temp., 1 h] gave the enone (**13**), which showed $[\alpha]_D^{23}$ +95.4° (*c* 2.00, $CHCl_3$). Conversion of (**11**) into its (*R*)-MTPA ester (**14**) and comparison of the ^{19}F n.m.r. spectrum of this with that of (**14**) derived from racemic material showed 100% e.e. Analysis of the ^1H n.m.r. spectra of (**14**) (optically pure *vs.* racemic) using Mosher's method,[6] showed (**11**) to be the (*S*)-hydroxy-(*R*)-acetoxy compound. This is exactly the result expected on the basis of earlier work with cyclopentene diacetates,[4] but the influence of the methyl substituents is noteworthy: there is considerable improvement in enantioselectivity as well as a *reversal* of induced chirality caused by substitution adjacent to the site of hydrolysis. Thus, care is required when using this methodology to produce optically active compounds in series which are not identical to those already investigated.

In summary, excellent enantioselectivity can be obtained during enzymatic hydrolysis of cycloheptene diacetates. Since enones related to (**8**) have already been converted into synthetic precursors of the Prelog–Djerassi lactone[2,3] this clearly gives useful asymmetric synthesis methodology. Coupled with the use of organoiron chemistry, this allows asymmetric synthesis of highly substituted cycloheptenones, whose synthetic utility is currently being evaluated in our laboratory.

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3 J. D. White and Y. Fukuyama, *J. Am. Chem. Soc.*, 1979, **101**, 226; G. Stork and V. Nair, *J. Am. Chem. Soc.*, 1977, **101**, 1315. These publications describe approaches to (**4**) using intermediates related to (**3**).
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