

A Facile Synthesis of (–)-Muscone using a Chemo-enzymatic Approach

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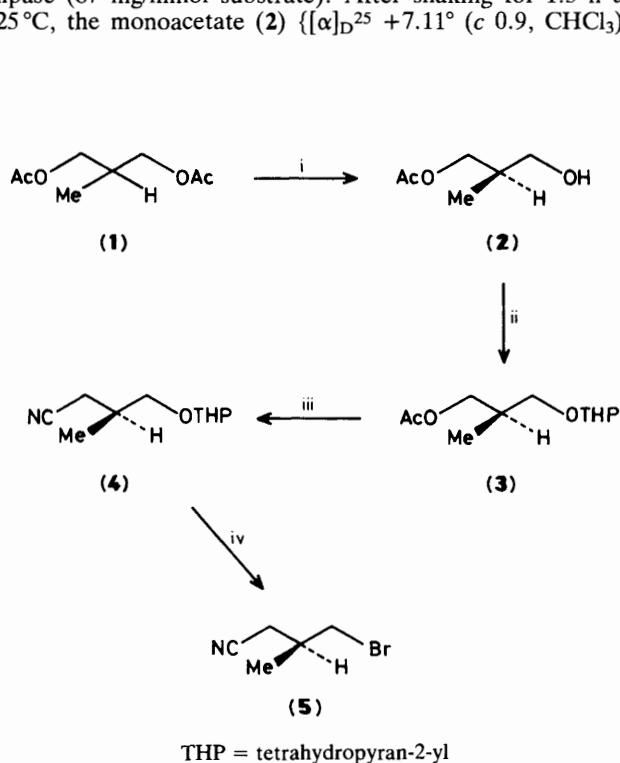
Pseudomonas fluorescens lipase catalysed hydrolysis of the *meso*-diacetate (1) to give specifically the (*R*)-enantiomer (2) with high optical purity allows the synthesis of (–)-muscone in combination with a three-carbon ring expansion.

The chemo-enzymatic approach has been proved to be effective in the synthesis of chiral compounds.¹ We now describe a highly enantioselective hydrolysis of the *meso*-diacetate (1) catalysed by *Pseudomonas fluorescens* lipase (PFL)² to afford (2) with high optical purity, and the application of this chiral synthon (2) to the synthesis of (–)-muscone by a reaction sequence based on three-carbon ring expansion.³

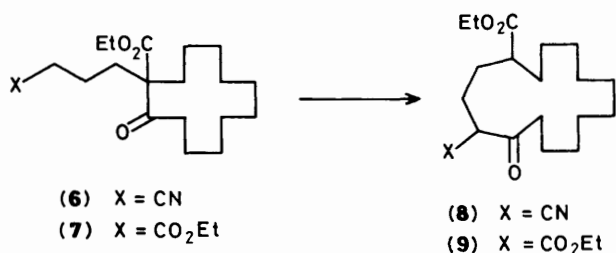
The *meso*-diacetate (1) (0.03 M solution in 0.5 N phosphate buffer, pH 7) was subjected to hydrolysis with *P. fluorescens* lipase (87 mg/mmol substrate). After shaking for 1.5 h at 25 °C, the monoacetate (2) $\{[\alpha]_D^{25} +7.11^\circ (c\ 0.9, \text{CHCl}_3)\}$,

>99% enantiomeric excess (e.e.)[†] was obtained in 33% yield, in addition to the recovery (66%) of (1). This hydrolysis is highly enantioselective, in contrast to the results (16% e.e.) obtained with porcine pancreatic lipase (PPL) by Sih.⁴

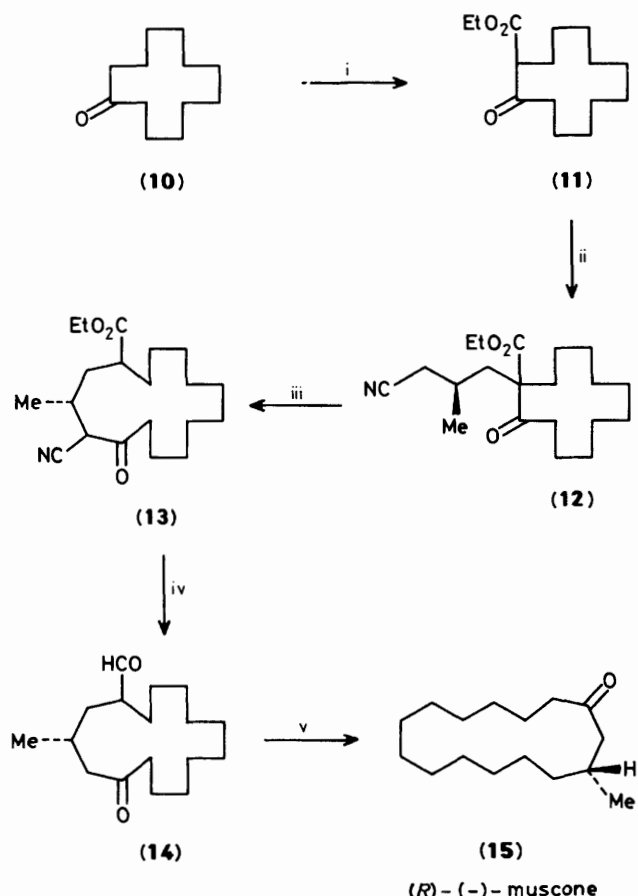
Compound (2) was readily converted to (*S*)-4-bromo-3-methylbutanenitrile (5) $\{[\alpha]_D^{25} -20.1^\circ (c\ 1.62, \text{CHCl}_3)\}$, required for the synthesis of (–)-muscone, via the reaction sequence (overall yield 41%) in Scheme 1. With (*S*)-(5) in



Scheme 1. Reagents and conditions: i, PFL; ii, dihydropyran (DHP)-*p*-TsOH; iii, (1) K_2CO_3 -MeOH, (2) mesyl chloride-pyridine, (3) NaCN-DMSO; iv, (1) aq. AcOH, (2) *N,N'*-carbonyldiimidazole-allyl bromide.



Scheme 2



Scheme 3. Reagents and conditions: i, EtOCOCN-lithium diisopropylamide (LDA); ii, (*S*)-(5)-Bu⁺OK-DMSO; iii, Bu⁺OK-DMSO; iv, (1) conc. HCl, (2) LiAlH₄, (3) pyridinium chlorochromate (PCC); v, Wilkinson complex, benzene.

[†] Optical purity was determined by means of the 270 MHz ¹H n.m.r. spectra of the (+)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) ester, and the absolute configuration was established by conversion of (2) to (+)-methyl 3-hydroxy-2-methylpropionate (*Aldrichimica Acta*, 1984, 17, 42) via Jones oxidation followed by treatment with diazomethane, and then methanolysis with K_2CO_3 -MeOH.

hand, we needed to construct the 15-membered ring skeleton for the preparation of (–)-muscone. Based on the one-pot three-carbon ring expansion method of cyclic β -keto esters from this laboratory,³ we undertook the ring enlargement of a 12-membered ring β -keto ester with a cyanopropyl (**6**) or ethoxycarbonylpropyl function (**7**) at the α -position (Scheme 2). As expected, treatment with Bu^tOK in dimethyl sulphoxide (DMSO) afforded three-carbon ring expanded products (**8**) or (**9**) in 64% and 61% yields, respectively. Using (**5**) to effect this three-carbon ring enlargement lead to a facile synthesis of (–)-muscone as outlined in Scheme 3. Ethoxycarbonylation of commercially available (**10**) with ethyl cyanofornate gave (**11**) in 89% yield. Alkylation of (**11**) with (*S*)-(**5**) in the presence of Bu^tOK afforded (**12**) (85% yield), followed by treatment with Bu^tOK (1.1 equiv.) to afford the ring expanded product (**13**) (70% yield). The keto aldehyde (**14**) was obtained *via* acid hydrolysis followed by reduction with LiAlH₄, then oxidation with PCC (overall yield 50%). Decarbonylation of (**14**) with Wilkinson complex⁵ afforded (*R*)-(–)-muscone (**15**), whose spectroscopic data were iden-

tical with the reported values.⁶ This synthesis represents a valuable addition to the armamentarium of ring expansion techniques.

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References

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