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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.

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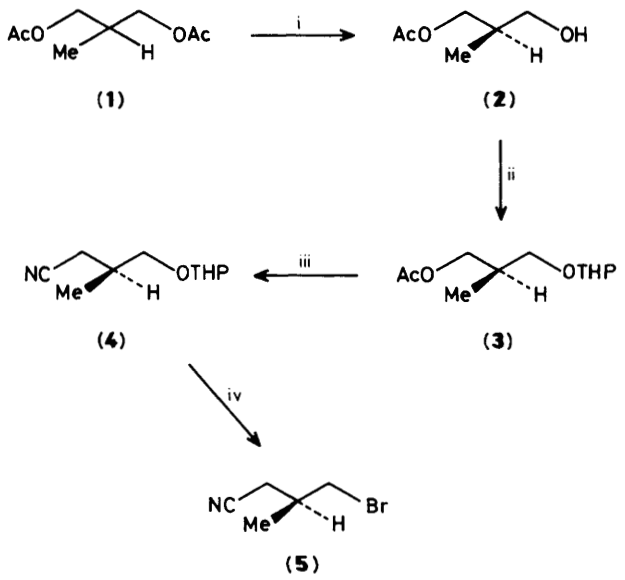
The chemo-enzymatic approach has been proved to be effective in the synthesis of chiral compounds.[1] We now describe a highly enantioselective hydrolysis of the *meso*-diacetate (**1**) catalysed by *Pseudomonas fluorescens* lipase (PFL)[2] to afford (**2**) with high optical purity, and the application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

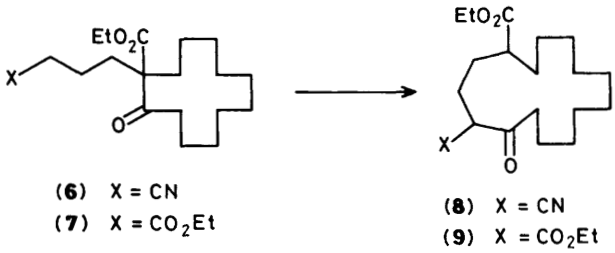
The *meso*-diacetate (**1**) (0.03 M solution in 0.5 N phosphate buffer, pH 7) was subjected to hydrolysis with *P. fluorescens* lipase (87 mg/mmol substrate). After shaking for 1.5 h at 25 °C, the monoacetate (**2**) {$[\alpha]_D^{25}$ +7.11° (*c* 0.9, $CHCl_3$), >99% enantiomeric excess (e.e.)}† was 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° (*c* 1.62, $CHCl_3$)}, required for the synthesis of (−)-muscone, *via* the reaction sequence (overall yield 41%) in Scheme 1. With (*S*)-(**5**) in

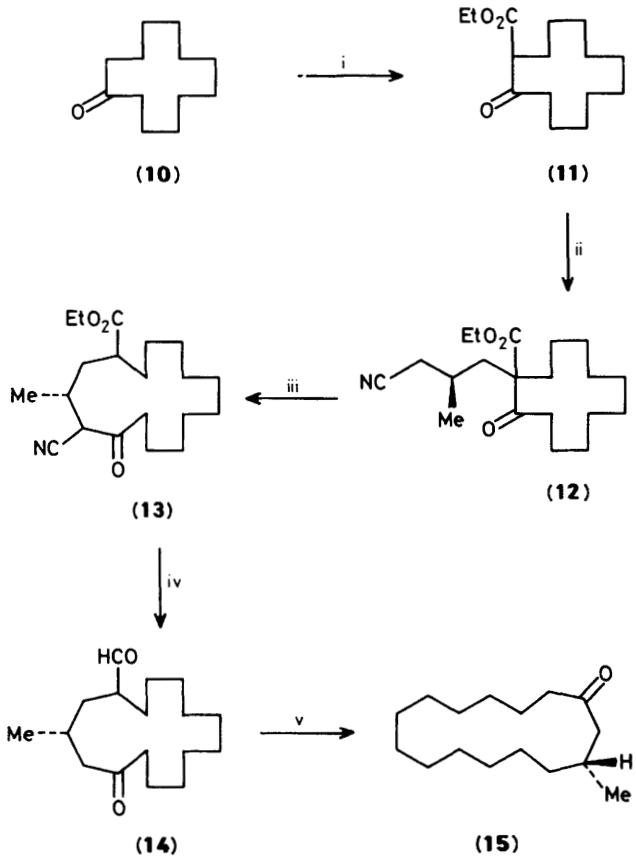


THP = tetrahydropyran-2-yl

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 di-isopropylamide (LDA); ii, (*S*)-(**5**)–Bu^{t}OK–DMSO; iii, Bu^{t}OK–DMSO; iv, (1) conc. HCl, (2) $LiAlH_4$, (3) pyridinium chlorochromate (PCC); v, Wilkinson complex, benzene.

† Optical purity was determined by means of the 270 MHz ^{1}H 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.

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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^{t}OK 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 cyanoformate gave (**11**) in 89% yield. Alkylation of (**11**) with (*S*)-(**5**) in the presence of Bu^{t}OK afforded (**12**) (85% yield), followed by treatment with Bu^{t}OK (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 $LiAlH_4$, then oxidation with PCC (overall yield 50%). Decarbonylation of (**14**) with Wilkinson complex[5] afforded (*R*)-(−)-muscone (**15**), whose spectroscopic data were identical with the reported values.[6] This synthesis represents a valuable addition to the armamentarium of ring expansion techniques.

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