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Lipase-catalysed resolution of *cis*-1-ethoxycarbonyl-2-hydroxy-cyclohexane: enantioselective total synthesis of 10-ethyl-trinem

Mauro Panunzio,[a,*] Roberto Camerini,[a] Andrea Mazzoni,[a] Daniele Donati,[b] Carla Marchioro[b] and Roberta Pachera[b]

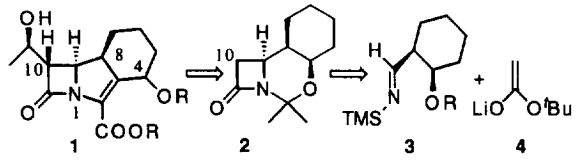
[a] Dipartimento di Chimica 'G. Ciamician', C.S.F.M.-C.N.R., Via Selmi 2, 40126 Bologna, Italy
[b] Glaxo Wellcome S.p.A., Medicines Research Centers, Via A. Fleming 4, 37100 Verona, Italy

Abstract: *Pseudomonas fluorescens* lipase (PFL) was used as catalyst for enzymatic resolution of 1-ethoxycarbonyl-2-hydroxy-cyclohexane. The resulting ester was used for the total synthesis of the novel enantiomerically pure 10-ethyl trinem. © 1997, Elsevier Science Ltd. All rights reserved.

Since the Glaxo group discovered that the trinems of general structure **1** show remarkably high biological activity associated to an enhanced chemical and metabolic stability, a number of synthetic methods on related structures has been published.[1] While most of the reported methods employ the optically active 4-acetoxy-2-azetidinone as the precursor, we have recently reported an alternative route to **1** which involves as the key step the [2+2] cycloaddition between *N*-trimethylsilylimine **3** and the lithium enolate **4** (Scheme 1).[2]

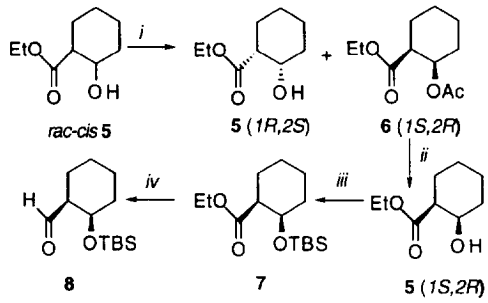
However, although the reaction is highly diastereoselective, a racemic mixture of azetidinone **2** was obtained. Thus, we became interested in the synthesis of **2** as a single enantiomer starting from enantiomerically enriched *N*-trimethylsilylimine[3] **3** obtained through the enzymatic resolution of the parent ester *rac-cis* **5**. Another important aim of this study was to ascertain the enantioselectivity of our [2+2] approach, including the subsequent functionalization of the C-10 center (trinem numbering, Scheme 1), in the synthesis of optically active trinems.

Enzymatic reactions are characterised by a number of advantageous properties for their preparative applications because of the usually mild reaction conditions and the regio- and stereoselectivity of enzymes.[4] We report here on the use of *Pseudomonas Fluorescens Lipase* (*PFL*) in the resolution of *rac-cis* 1-ethoxycarbonyl-2-hydroxy-cyclohexane **5** (Scheme 2) and the application of our methodology to the synthesis of enantiomerically enriched novel 10-ethyl-trinem **11**. *PFL* is available in large quantities as a crude product and, in the present study, it has been proved to be very efficient in the resolution of alcohol **5** through the formation of the optically active acetate **6**, which, in turn, has been hydrolysed to the enantiomerically pure alcohol **5** (*1S,2R*) using the same enzymatic system.[5] In both the processes an *ee* >98% has been obtained as checked by NMR experiment and comparison with literature data.[6,8]



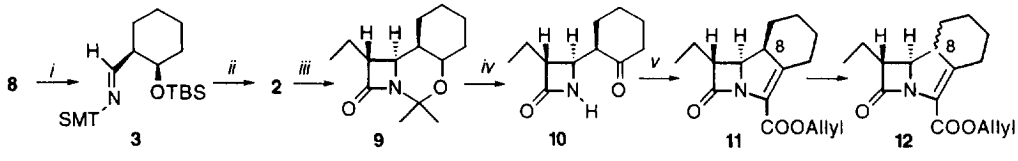
Scheme 1.

* Corresponding author. Email: panunzio@ciam.unibo.it



Reag. and cond.:*i :PFL*, TEA, Vinyl acetate, THF, 45% (ee>98);
ii: PF L, Phosphate buffer, 70%, ee>98; *iii: then iv:* Ref. 7 (82%)

Scheme 2.



Reag. and cond.: *i, ii:* Ref. 7; *iii:* LDA, EtI, THF, 80%; (de=ee>98); *iv:* Jones, acetone, 60% ; *v;* Ref. 1

Scheme 3.

Resolution of rac-cis alcohol **5**: Racemic *cis*-alcohol[7] **5** (57 g, 198 mmol) was dissolved in dry THF (800 ml). Vinyl acetate (216 ml), TEA (34 ml) and *PFL* (10 g) were added. After stirring at r.t. for 10 days, evaluating the conversion of the substrate by GC (the best results on three different experiments are obtained by stopping the reaction at 45% conversion), the mixture was filtered through celite and the *PFL* washed with ethyl acetate. The solvent was evaporated and the crude mixture distilled to remove the unreacted enantiomerically pure alcohol **5** (*1R,2S enantiomer*). The residue was purified by short flash column chromatography to give the enantiomerically pure acetate **6** (31.4 g). According the Sih's method[9] of analyses of enzymatic resolution, the enantiomeric ratio was E=92. Acetate **6** (2.62 g) was dissolved in phosphate buffer (0.1 M, pH=7.20, 100 ml) containing acetone (10 ml). *PFL* (1.2 g) was added and the mixture stirred vigorously for 42 h, keeping the pH constant at pH=7 by the dropwise addition of 2 M aqueous sodium hydroxide. The mixture was extracted with ethyl acetate, the organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (cyclohexane/ethyl acetate 3/7) to give the enantiomerically pure alcohol **5** (*1S,2R enantiomer*) (70% yield, ee >98).[6,8] Elaboration of **5** (*1S,2R*), following the already reported procedure,[6] furnished the optically active azetidinone **2**.

Next we attempted the enantioselective synthesis of 10-ethyl-trinem **11** following the synthetic sequence reported in Scheme 3. It must be pointed out that, during this sequence to the target, no loss of enantiomeric purity was noted as a probe of a *complete diastereo- and enantioselective sequence.* Alkylation of **2** by treatment with LDA followed by addition of ethyl iodide furnished the compound **9** in 80%. This compound was processed to the final trinem **11** following the well established Glaxo Wellcome procedure (Y=25% from **10**).[1] Trinem **11** showed a remarkable chemical instability since, on standing, an epimerization of the C-8 stereogenic centre takes place.[8,10] On the other hand any attempt to hydrolyse the ester functionality resulted in complete decomposition.

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8. All compounds gave spectral data consistent with the reported structure. The enantiomeric purity of compounds **5** and **6** was determined by 500 ^{1}H NMR spectroscopy using chiral lanthanide shift reagents. Significant splitting in δ of enantiomers were obtained with Eu(tcf)$_3$ at 25°C in $CDCl_3$. Selected data follow: **9:** m.p. 82–84°C; I.R. (nujol) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$): 4.00 (1H, m); 3.74 (1H, m); 2.88 (1H, dd, J=2.5, 14.5); 2.83 (1H, dd, J=5.0, 14.5); 1.85 (2H, m); 1.78 (3H, s); 1.7–1.62 (7H, m); 1.42 (3H, s); 1.30 (1H, m). **11**: I.R. (nujol) 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$): 6.01–5.91 (1H, m); 5.45–5.38 (1H, m); 5.26–5.22 (1H, m); 4.82–4.76 (1H, m); 4.69–4.63 (1H, m); 3.90–3.85 (1H, J=3.06, 10.14); 3.46–3.42 (1H, m); 3.16–3.10 (1H, m); 2.80–2.78 (1H, m); 1.06–0.96 (3H, t).
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10. The epimerization of the C-8 stereogenic center is quite unusual and the intimate mechanism is, at present, obscure. Work is in progress to clarify this aspect.

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