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## Chemoenzymatic, Enantiocomplementary, Total Asymmetric Synthesis of Leukotrienes-$B_3$ and -$B_4$

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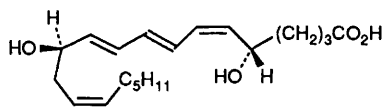
The ketone **3** has been resolved using various enzyme-catalysed reactions and the enantiomer (+)-**3** was transformed into the benzoate **8** while (−)-**3** was converted into the esters **10** and **11**; compounds **8** and **10** are complementary sections of leukotriene $B_4$ while compounds **8** and **11** are late-stage synthons for leukotriene $B_3$.

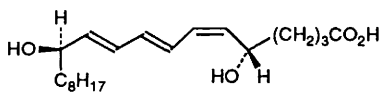
Leukotrienes are widely recognized as important compounds:[1] they occur naturally in animals and plants.[2] In particular leukotriene-$B_4$ **1** and leukotriene-$B_3$ **2** have been shown to possess interesting properties as chemokinetic and chemotactic agents.[3] Leukotriene-$B_4$ has been implicated in the onset and maintenance of irritable bowel syndrome,[4] psoriasis,[5] rheumatoid arthritis[6] and other types of inflammation[7] and it has been identified as a possible anti-bacterial agent.[8] Not surprisingly there has been considerable interest in the synthesis of the natural products[9] and analogues.[10] Some of the routes have been adapted to prepare leukotriene-B antagonists,[11] compounds with biological properties that have attracted considerable interest.[12]

We report a method of preparation of optically pure leukotrienes-B using *both* enantiomers of 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one **3**:[13] one enantiomer provides the chiral C(1)–C(6) portion of the leukotriene while the other enantiomer furnishes the C(7)–C(20) sequence in optically pure form.

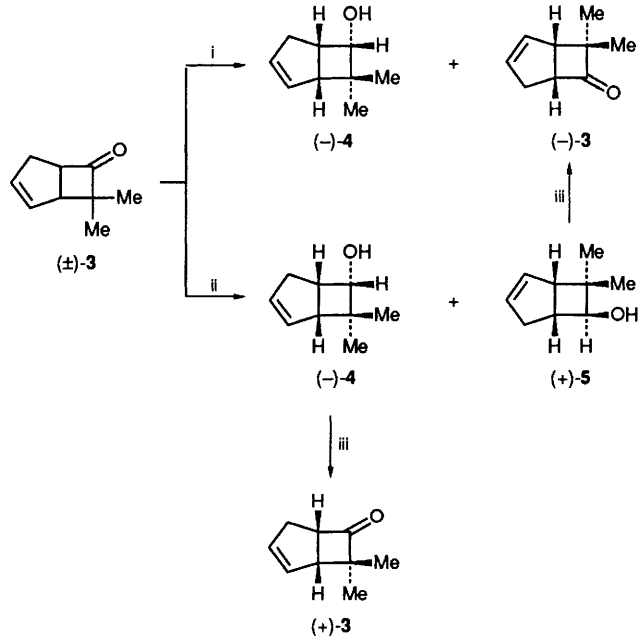
Resolution of the ketone **3** can be accomplished using enzymes. Enantioselective reduction of the ketone **3** can be effected using 3α,20β-hydroxysteroid dehydrogenase to give the alcohol (−)-**4** (>95% enantiomeric excess, e.e.) and the optically active ketone (−)-**3**. Reduced nicotinamide adenine dinucleotide (NADH) was used as the cofactor, recycling the NADH with horse liver alcohol dehydrogenase (HLAD) and ethanol (Scheme 1).[14] The fungus *Mortierella ramanniana* reduces both enantiomers of the ketone **3** to give the alcohol (−)-**4** (80% e.e.) and the diastereoisomers (+)-**5** (>97% e.e.).[15] However, we can now report that undoubtedly the best method for the production of large quantities of optically pure 7,7-dimethylbicyclo[3.2.0]hept-2-enones involves the use of the hydrolytic enzyme porcine pancreatic lipase (ppl).



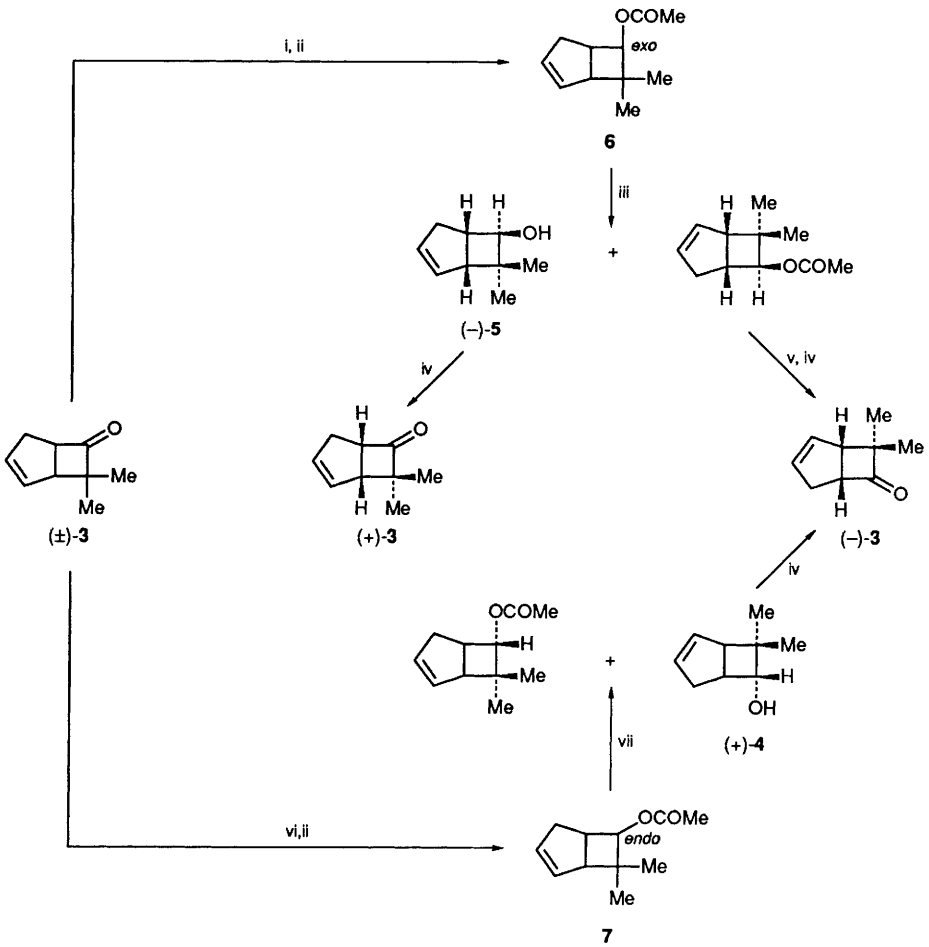

**1**



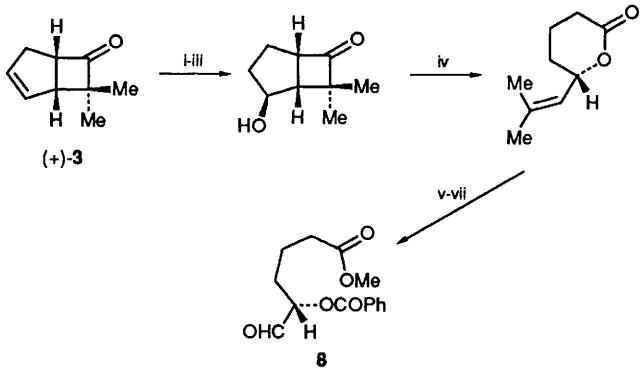

**2**




**Scheme 1** *Reagents:* i, $H_2O$, 3α, 20β-hydroxysteroid alcohol dehydrogenase, NADH, HLAD, EtOH; ii, $H_2O$, *Mortierella ramanniana*; iii, pyridinium chlorochromate




**Scheme 2** *Reagents:* i, $LiAlH_4$, $AlCl_3$, 80%; ii, $(MeCO)_2O$, pyridine 95%; iii, ppl (Sigma), $H_2O$ 40% for **5**, 35% for ester; iv, Swern oxidation, 97%; v, $LiAlH_4$ 91%; vi, $NaBH_4$, 85%; vii, *M. miehei* lipase (Novo-Nordisk), n-heptane saturated with pH 6.0 buffer

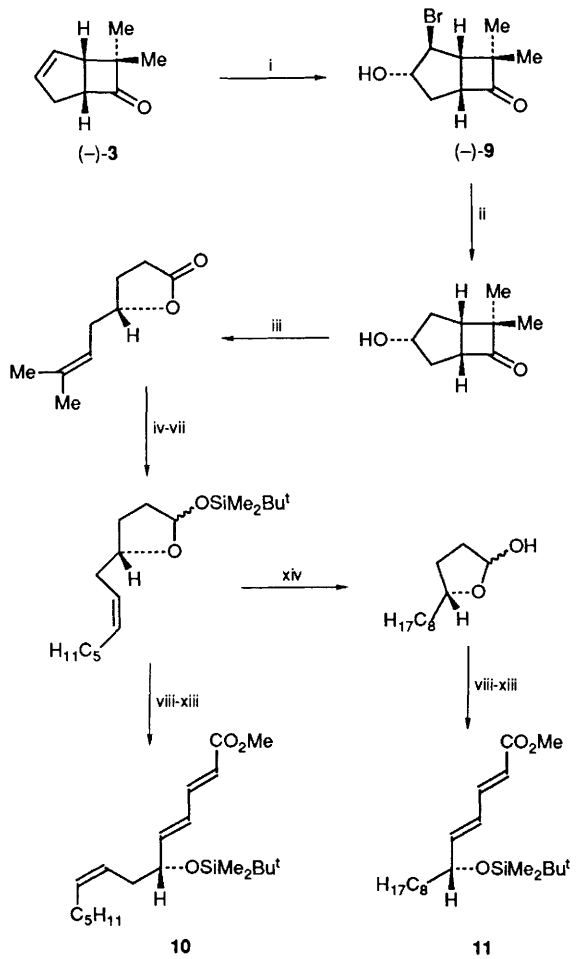



**Scheme 3** *Reagents:* i, *m*-chloroperbenzoic acid (mcpba); ii, HI, $H_2O$; iii, $Bu^n_3SnH$; iv, *hν*, pentane; v, $Et_3N$, MeOH; vi, PhCOCl, base; vii, $O_3$, then $Me_2S$

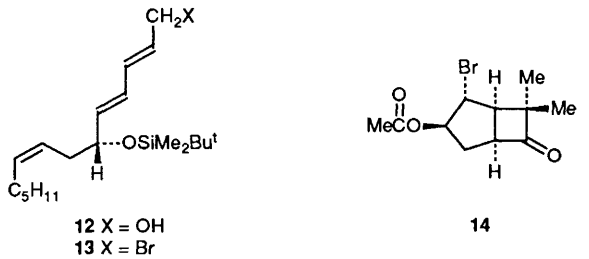
Thus, reduction of the ketone (±)-**3** with lithium aluminium hydride and aluminium chloride[16] gave the *exo*-alcohol (±)-**5** (Scheme 2), acetylation of which gave the racemic ester **6**. Crude ppl catalysed enantiospecific hydrolysis of (±)-**6** gave optically pure alcohol (−)-**5** and recovered ester **6**. The optical purity of the alcohol was established by formation of Mosher's ester and $^{19}F$ NMR spectroscopy. When the enzyme-catalysed reaction was continued until no further hydrolysis took place the ester (+)-**6** was also obtained in an optically pure state (as assessed by NMR spectroscopy using a chiral shift reagent). Chemical deesterification of the ester (+)-**6** gave the alcohol (+)-**5** and independent oxidation of the alcohols (+)-**5** and (−)-**5** gave the ketones (−)-**3** and (+)-**3** respectively. [The absolute configuration of the ketone (+)-**3** had been established previously by conversion into the pheromone (+)-eldanolide[17].]

Interestingly, a sample of purified ppl[18] did *not* catalyse hydrolysis of the ester (±)-**6**. α-Chymotrypsin (α-ct) and cholesterol esterase (ce) are sometimes found as components in crude ppl and so the effect of these enzymes on the ester (±)-**6** was investigated. α-Ct was not a catalyst for the hydrolysis of the acetate **6** while ce promoted a relatively fast deesterification reaction but gave alcohol (−)-**5** of low optical purity (82% e.e.). The latter result suggests that ce is not a major contaminant of crude ppl purchased from Sigma. On removing ppl, ct and any ce from the crude preparation, the residual protein[18] was shown to contain the active catalyst.[19] The identity of this potentially important hydrolase enzyme is under investigation. It is noteworthy that the (±)-6-*endo*-acetate **7** was not affected by crude ppl or *Pseudomonas fluorescens* lipase in pH 7 buffer at room temperature. Immobilized *Mucor miehei* lipase (Lipozyme R) catalysed very slow hydrolysis of the ester **7**, affording a 1% yield of optically pure alcohol (+)-**4** after 21 days.

The ketone (+)-**3** was converted into the benzoate **8** in stereocontrolled fashion (Scheme 3).[20] The enantiomer (−)-**3** was transformed into the bromohydrin **9** and subsequently into the esters **10** and **11** by the sequences of reactions shown in Scheme 4.[21] The two chiral synthons **8** and **10** can then be




**Scheme 4** *Reagents:* i, *N*-bromoacetamide or *N*-bromosuccinimide in $H_2O$–$Me_2CO$, 76%; ii, $Bu^n_3SnH$, 82%; iii, *hν*, benzene, 41%; iv, $Bu^i_2AlH$, 91%; v, $Me_2Bu^tSiCl$, base, 95%; vi, $O_3$, then $Me_2S$, 74%; vii, $Ph_3PCHC_5H_{11}$, 99%; viii, $HSCH_2CH_2SH$, $H^+$, 82%; ix, $CF_3SO_3SiMe_2Bu^t$, base, 92%; x, MeI, $HgCl_2$, $CdCO_3$, 80%; xi, methyl 4-chlorophenylsulphinylacetate, base, 74%; xii, PhCOCl, base, 95%; xiii, $(Ph_3P)_4Pd$, base, 76%; xiv, $H_2$, Pd on charcoal, EtOH 92%




used to prepare leukotriene-$B_4$ **1**. Thus, the ester **10** was reduced to the alcohol **12** and subsequently converted into the bromide **13**. Formation of the corresponding phosphorane followed by a Wittig reaction, chromatography and removal of the protecting groups as prescribed in the literature[9] provided a sample of leukotriene-$B_4$ identical (by HPLC and NMR) to authentic material. Similarly the units **8** and **11** can be coupled to provide leukotriene-$B_3$.

It is noteworthy that the bromohydrin **9** was obtained in enantiomerically pure form by yet another technique using an enzyme, that is, enantioselective esterification of racemic 2-*exo*-bromo-3-*endo*-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-one (±)-**9** using lipase P from *P. fluorescens*[22] in vinyl acetate.[23] When this biotransformation ceased *at* 50% conversion after 3 days the bromohydrin (−)-**9** and (1*R*,2*R*,3*R*)-3-*endo*-acetoxy-2-*exo*-bromo-7,7-dimethylbicyclo[3.2.0]heptan-6-one **14** were obtained (>99 and 96% e.e. respectively). The optical purity of **9** was determined by GC analysis of the corresponding mixed carbonate after derivatisation with (−)-menthyl chloroformate;[24] the bromoacetate was hydrolysed (MeOH, $H_2SO_4$ cat., room temp.) prior to derivatisation.

In summary a panoply of techniques involving enzyme-catalysed reactions have been used to produce the ketones (+)-**3** and (−)-**3** (or surrogates) in optically pure form. The enantiomeric ketones were then used to prepare complementary sections of leukotriene-$B_3$ and leukotriene-$B_4$.

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