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## Chiral polypropionate subunit by a chemoenzymatic approach

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### Abstract

Enzymatic desymmetrization of *meso*-4-methyl-3,5-*syn*-dioxolan-1,3,5,7-tetrol was found to be highly enantioselective leading to both acetylated enantiomers with high enantiomeric excess. © 1998 Elsevier Science Ltd. All rights reserved.

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Optically active polypropionate units with alternating hydroxyl and methyl groups with a distinct stereochemistry, are important fragments of the carbon framework of many natural products, especially macrolide antibiotics<sup>1</sup> and ionophores,<sup>2</sup> possessing high biological and pharmacological activity. Many strategies have been developed towards the synthesis of such compounds, mainly starting with a chiral synthon followed by successive homologation in a stereoselective fashion. Among them, sequences involving asymmetric aldol reactions<sup>3</sup> followed by stereoselective reduction have been successfully developed.<sup>4</sup>

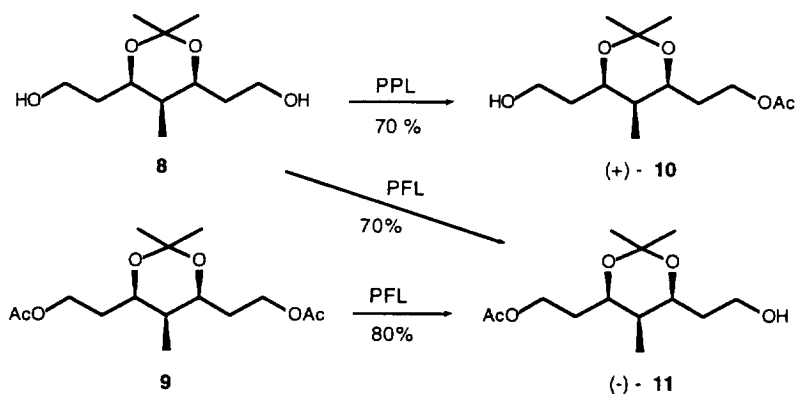
A possible alternative strategy could be employed starting from the so-called 'stereotriad' of type **1** or **2** with defined relative configurations (Fig. 1). If these synthons possess appropriate different functions at the ends, then this could allow an extended side chain homologation to various polypropionate derivatives. Stereotriads with *syn-syn* or *anti-anti* stereochemistry possess a *meso*-structure which could, in principle, be desymmetrized by chemical or by biocatalytic methodologies. So far the biocatalytic approach has been successfully used for the preparation of *syn-syn*<sup>5</sup> and *anti-anti*<sup>5,6</sup> stereotriads of type **1**, while no report has appeared on the preparation of stereotriads of type **2**, by desymmetrization of the appropriate *meso*-compound.

Previous reports from this laboratory have described the preparation (by enzymatic reactions)<sup>7,8</sup> and the utilization of the new chiral building block (+)-**3** and its enantiomer (–)-**3** as a skipped 1,3-*syn*-polyol. Optically active compound **3** has been prepared in a seven-step sequence from 3-benzyloxypropanol on a multi-gram scale.

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Scheme 2.

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- The relative stereochemistry of compounds **6a** and **b** was later confirmed by  $^1\text{H}$ -NMR analysis of compound **7** which possesses a relative *syn-syn* configuration: in fact the coupling constant of the protons on C-3 and C-5 with the proton on C-4 (on the methyl group) shows the typical value of 2 Hz, which is the usual for the axial-equatorial coupling (the corresponding axial-axial coupling for the other *anti-anti* stereoisomer would resonate at the value of 8–10 Hz). The relative configuration of the two hydroxyl groups has been easily assigned by the Rychnovsky method (Rychnovsky, S. D.; Skalitzy, D. J. *Tetrahedron Lett.* **1990**, *31*, 7) with  $^{13}\text{C}$ -NMR analysis of the corresponding acetonide derivatives.
- PPL (Porcine Pancreatic Lipase) and PFL (*Pseudomonas fluorescens* Lipase) are commercially available from FLUKA.
- Both the reactions were carried out, on a gram scale, in diethyl ether with a 0.06 M concentration of substrate, 0.6 M of vinylacetate and 30 U/mg of enzyme.
- The reaction was carried out in phosphate buffer 0.2 M at pH=7 in 2 h.
- The ee for compounds **10** and **11** were determined by  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) analysis with  $(-)\text{-Eu(hfc)}_3$  at different concentrations, which shows clear differentiation of the  $\text{CH}_3$  signals of the isopropylidene ring.
- Compounds **10** and **11**:  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 0.91 (3H, d,  $J=7.03$  Hz), 1.38 (3H, s), 1.3–1.4 (1H, m), 1.45 (3H, s), 1.62 (1H, s), 1.8–2.0 (4H, m), 2.06 (3H, s), 2.3 (1H, bs), 3.77 (2H, m), 4.04 (1H, m), 4.1–4.2 (2H, m) ppm;  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 5.14, 19.70, 20.82, 29.96, 32.27, 35.38, 35.62, 61.36, 70.09, 73.07, 99.14, 170.89 ppm. Compound **10** (from PPL):  $[\alpha]_D^{25}=+14.4$  (c 0.9,  $\text{CHCl}_3$ ). Compound **11** (from PFL):  $[\alpha]_D^{25}=-15.5$  (c 0.9,  $\text{CHCl}_3$ ).
- All new compounds exhibited satisfactory spectroscopic exact mass data.
- The *syn-syn* prepared subunits can be found, i.e. in calyculin, a potent inhibitor of protein phosphonate (for structure and synthesis see Hamada, Y.; Yokokawa, F.; Kabeya, M.; Hatano, K.; Kurono, Y.; Shioiri, T. *Tetrahedron* **1996**, *52*, 8297, and references cited therein); in the immunosuppressant  $(-)\text{-FK-506}$  (see for structure Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *111*, 1157); and in conagenin, a new immunomodulator (Hatakeyama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047).