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Enzymatic Desymmetrization of meso(anti-anti)-2,4-dimethyl-1,3,5-pentanetriol

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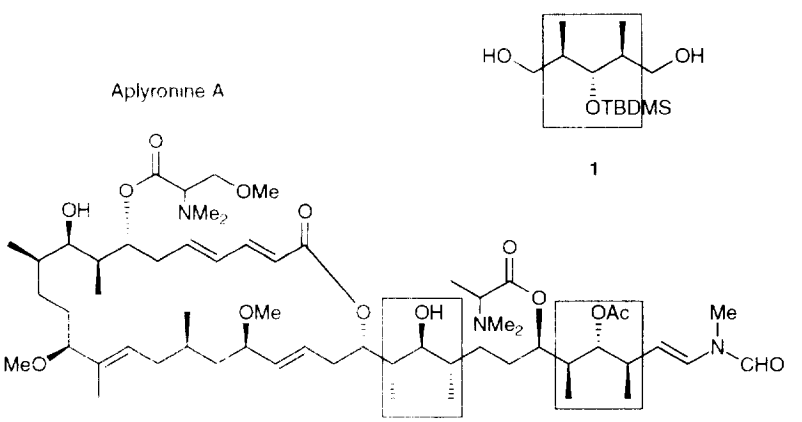
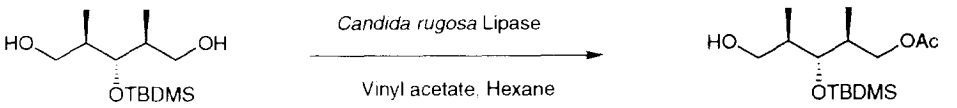
Abstract: The stereoselective acetylation of meso-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanediol by vinyl acetate in the presence of *Candida rugosa* lipase in organic medium gave the corresponding (2R, 3R, 4S) mono ester in high enantiomeric purity (ee = 97%).

A large variety of natural products contain polypropionate units (alternating hydroxyl and methyl groups on an aliphatic chain with a distinct stereochemistry). Polypropionates are a common feature of many ionophores[1] and macrolides[2] possessing remarkable biological and pharmacological activities. Several strategies have been developed to provide access to these systems containing contiguous stereogenic centers.[3] We report here the enzymatic desymmetrization of a meso-2,4-dimethyl-1,3,5-pentanetriol derivative (**1**). This fragment with anti-anti relative configuration is found in many natural products such as rifamycin,[4] calyculin A,[5] swinholide A[6], muamvatin[7] and aplyronine A.[8]



Diol **1** was prepared by diastereoselective intramolecular hydroboration of the corresponding diene according to the method of Harada *et al.*[9] Diol **1** was subjected to the enzyme catalyzed transesterification by treatment with *Candida rugosa*[10] lipase (also called *C. cylindracea*) in hexane using vinyl acetate as acyl donor to give the optically active monoacetate **2** in 94% yield[11] (Scheme 1). The enantiomeric composition of **2** was measured by ^{19}F NMR (300 MHz) analysis of the corresponding (+)-α-methoxy-α-trifluoromethyl)-α-phenyl acetates (MTPA, Mosher's esters). The enantiomeric excess was determined to be 97% ($[\alpha]_D^{22} = -8.6$ (c 2.37, $CHCl_3$)).

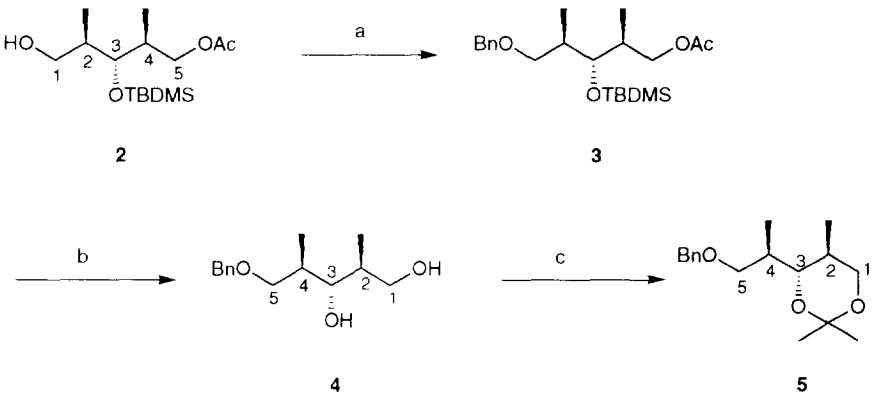
Scheme 1



1 **2**

The absolute configuration of monoester **2** was determined by correlation with compounds **4** and **5** of known absolute configuration (Scheme 2). Thus, benzylation of **2** with benzyl trichloroacetimidate in the

Scheme 2



2 **3** **4** **5**

a) Benzyl-2,2,2-trifluoroacetimidate, TMSOTf, CH_2Cl_2, Hexane, 75%; b) HCl, EtOH, 90%;
c) $Me_2C(OMe)_2$, Pyridinium *p*-toluenesulfonate, CH_2Cl_2, 92%.

presence of trimethylsilyl trifluoromethanesulfonate as an acidic catalyst gave **3**. Treatment of **3** with hydrochloric acid in methanol removed the TBDMS and acetyl protecting groups to yield **4**, $[\alpha]_D^{22} = -3.2$ (c 1.74, $CHCl_3$); lit.[12] $[\alpha]_D = +3.63$ (c 2.67, $CHCl_3$), for the 2R, 3R, 4R enantiomer (the numbering was used as indicated on the scheme). Compound **4** was treated with dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate in dichloromethane to give acetonide **5**. The optical rotation of **5** ($[\alpha]_D^{22} = +19.6$ (c 1.78, $CHCl_3$)) was compared to the values reported in the literature: $[\alpha]_D^{25} = +20.5$ (c 2.34, $CHCl_3$), for the 2S, 3R, 4R enantiomer;[13] $[\alpha]_D = -22.0$ (c 2.60, $CHCl_3$) for the 2R, 3S, 4S enantiomer. This correlation proved that compound **2** has the 2R, 3R, 4S configuration. Thus, *Candida rugosa* lipase has a S enantioselectivity.

Harada *et al.*[13,14] reported the enantiodifferentiating transformation of meso-2,4-dimethyl-1,3,5-propanetriol by kinetic acetalyzation with *d*-menthone. Also, an asymmetric Horner-Wadsworth-Emmons reaction on the corresponding dialdehyde has been reported.[15] The enzymatic desymmetrization reported here is simpler and proceeds with higher chemical (94%) and enantiomeric (ee = 97%) yields. Compound **2** and derivatives **3-5** are valuable chiral synthons for the synthesis of polypropionates. Derivatives **4** and **5** have been used in the synthesis of rifamicin S.[12] Enzymatic differentiation of enantiotopic groups of meso substrates is an efficient method for the preparation of enantiomerically pure products with multi-stereogenic centers.[16]

Acknowledgments

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11. A typical experiment:
(2R,3R,4S)-5-acetoxy-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1-pentanol. Compound **1** (172 mg, 0.665 mmol) was dissolved in hexane (23 mL) on molecular sieves (3 Å, 100 mg). Lipase from *Candida rugosa* (100 mg) and vinyl acetate (0.3 mL, 3.25 mmol) were added and the mixture was stirred at room temperature. The reaction was monitored by TLC. The reaction was quenched by filtration of the enzyme and the volatiles were evaporated. The product was purified by flash chromatography on silica gel (eluent: ethyl acetate / hexane, 1/9). Yield: 94%; $[\alpha]_D^{22} = -8.6$ (c 2.37, $CHCl_3$); IR (neat) 3450, 2950, 2920, 2850, 1745, 1250, 1030, 830, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.97 (d, J = 6.9 Hz, 3H, $CHC\underline{H}_3$), 0.99 (d, J = 6.8 Hz, 3H, $CHC\underline{H}_3$), 1.55 (s, 1H, OH), 1.88 (m, 1H, CH), 2.04 (s, 3H, $OCOCH_3$), 2.07 (m, H, CH), 3.65 (m, 3H, $C\underline{H}_2OH$ and CH-O-Si), 3.90 (dd, 1H, J_1 = 11.0 Hz, J_2 = 7.2 Hz, CHOAc), 4.16 (dd, 1H, J_1 = 11.0 Hz, J_2 = 5.5 Hz, CHOAc). ^{13}C NMR ($CDCl_3$) δ − 4.50, − 4.21, 13.89, 15.73, 18.09, 20.80, 25.88, 37.24, 37.55, 65.48, 66.23, 78.30, 170.92.

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