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A Convenient Synthesis of (2*S*,4*R*)-1-Acetoxy-2,4-*O*-Isopropylidene-1,2,5-Pentanetriol by Using Lipase Catalyzed Regio- and Enantioselective Reactions

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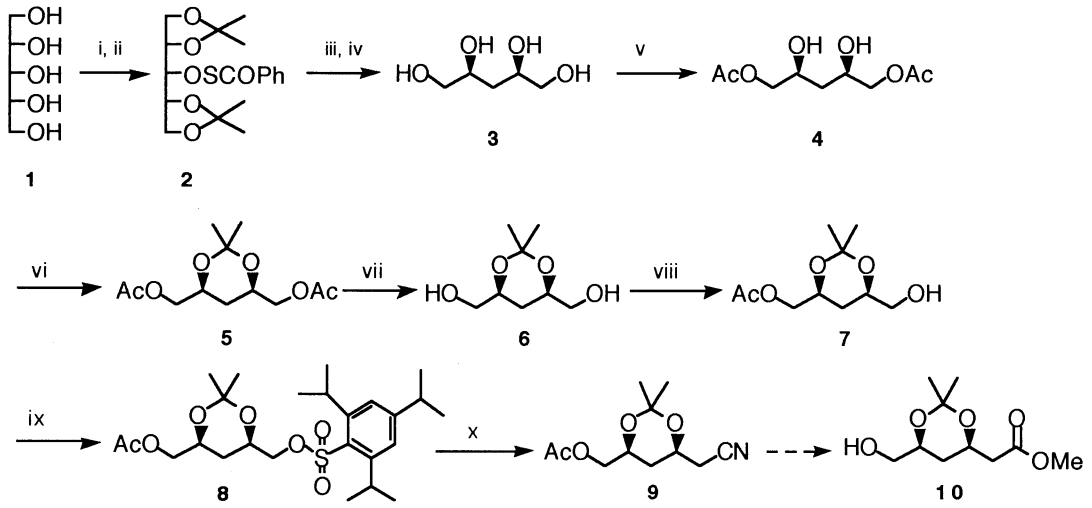
(2*S*,4*R*)-1-Acetoxy-2,4-*O*-isopropylidene-1,2,5-pentanetriol, which is expected to be an intermediate for a synthesis of an inhibitor of HMG-CoA reductase, was synthesized by lipase catalyzed regio- and enantioselective transesterifications.

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase are useful in the treatment of hypercholesterolaemia.[1] The biological activity depends largely on β,δ-dihydroxyesters or its lactone moieties,[2] and a large number of different methods have been developed for their synthesis.[3] (2*S*,4*R*)-1-Acetoxy-2,4-*O*-isopropylidene-1,2,5-pentanetriol **7** is expected to be a useful intermediate for the synthesis of (3*S*,5*R*)-3,5-*O*-isopropylidene-3,5,6-trihydroxyhexanoate **12** which is the starting material of a potent inhibitor of HMG-CoA reductase. Z.-F. Xie et al. have already reported the synthesis of the stereoisomer of **7**.[4] This method consists of one main step used a lipase catalyzed enantioselective hydrolysis. The *meso*-diacetate **4** prepared from **3** unsatisfactory yield. We report herein a convenient new synthetic method of **7** based on two key steps using a lipase from the same origin catalyzed Regio- and enantioselective transesterifications.

As shown in Scheme 1, meso-pentanetetraol **3** (0.19 mol) derived from ribitol **1** in 4 steps[4] was treated with lipase PS (9.0 g, *Pseudomonas* species, Amano Pharmaceutical Co.,Ltd.), vinylacetate (0.57 mol), and DMF (200 ml) at room temperature for 6 h to give diacetate **4** (0.143 mol) as a viscous oil in 75% yield, which was used in the next step without any purification. In the reaction, only the primary hydroxy groups were esterified regioselectively. Protection of dihydroxy groups of **4** with 2,2-dimethoxypropane (400 ml) in the presence of a catalytic amount of p-TsOH gave dioxane **5** which was recrystallized from n-hexane (63%, mp 51-54 °C). Reaction of **5** (0.09 mol) with $LiAlH_4$ in THF afforded diol **6** as a colorless oil in quantitative yield. A suspension of **6** (0.09 mol) and lipase PS (1.5 g) in vinylacetate (0.045 mol) was stirred at room temperature for 2 h. After filtration of lipase, evaporation of the solvent afforded the crude product which was purified by silica gel column chromatography to give **7** in 77% yield ($[\alpha]_D^{27}$ +5.1° (c 2.80, $CHCl_3$)). The stereochemistry of **7** was confirmed to be (2*S*,4*R*)-form by the comparison of the specific rotation with the authentic data.[5] The enantiomeric purity of **7** was determined to be more than 95%ee by a ^{1}H-NMR spectral analysis (400 MHz) of the respective (R)-MTPA ester. One carbon elongation of **7** was undertaken by conversion into the corresponding 2,4,6-triisopropylbenzenesulfonate **8** (38%) followed by introduction of the nitrile function. (3*S*,5*R*)-3,5-*O*-isopropylidene-3,5,6-trihydroxyhexanoate **10** can be obtained *via* several steps from **9**.



Scheme 1.

i) $Me_2C(OMe)_2$ / p-TsOH / DMF, r.t., 99%; ii) PhOSCl / 4-(dimethylamino)pyridine / MeCN, r.t., 4 d, quant.; iii) n-Bu_3SnH / AIBN / toluene / N_2, 70 °C, 8 h, 90% ; iv) p-TsOH / MeOH, r.t., 3d ; v) vinyl acetate / Lipase / DMF, r.t., 6 h, 75% ; vi) $Me_2C(OMe)_2$ / p-TsOH / DMF, r.t., 63%; vii)$LiAlH_4$ / THF, -10 - 0 °C, 1.5 h, r.t., 3 h ; viii) vinyl acetate / Lipase, r.t., 2 h, 77% ; ix) 2,4,6 - triisopropylbenzenesulfonyl chloride / pyridine, r.t., overnight, 38%; x) NaCN / DMSO, r.t., 7 d, 25%

It is remarkable that in the two enzymatic transesterifications catalyzed by the same lipase, **3** was esterified regioselectively on both primary hydroxy groups, but **6** was esterified stereoselectively on only one hydroxy group. This is considered that the rigid dioxane structure of **6** affects the selectivity of the enzymatic reaction.

The valuable compound **7** could be obtained effectively by the method based on two key steps using enzymatic transesterifications catalyzed by lipase. All steps of the method can be carried out under mild conditions.

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5) According to the literature, the specific rotation of (2*S*,4*R*)-**7** is $[\alpha]_D^{25}$ -4.64° (c 2.80, $CHCl_3$) ; Z. - F. Xie and K. Sakai, *Chem. Pharm. Bull.*, **37**, 1650 (1989).

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