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Synthesis of (3*R*,5*S*)-3-Hydroxy-7-phenyl-6-heptyn-5-olide by an Enantioselective Enzyme-catalyzed Lactonization of a Racemic 3,5-Dihydroxy Ester[1]

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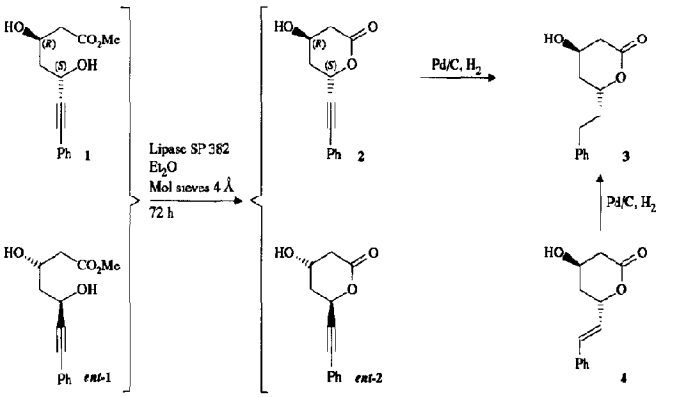
Abstract: (3*R*,5*S*)-3-Hydroxy-7-phenyl-6-heptyn-5-olide was obtained with a high enantiomeric excess by an enzyme-catalyzed enantioselective lactonization of the corresponding methyl (3*R**,5*S**)-dihydroxyalkynoate followed by spontaneous crystallization.

The 5-substituted (3*R*,5*S*)-3-hydroxy-5-pentanolide moiety is an indispensible structural element of the hydroxymethylglutaryl coenzyme A reductase inhibitors derived from compactin[2] or mevinolin.[3] Therefore, in recent years much effort has been directed to the preparation of 3-hydroxy δ-lactones with a substituent at C-5, which allows the conversion into mevinic acid analogues.[4-6] In this paper we report on the preparation of such a homochiral δ-lactone with a triple bond in the side chain at C-5.



In order to get the homochiral δ-lactone **2** the *syn*-diol ***rac*-1** was treated at 22°C in the presence of molecular sieve 4 Å with the lipase SP 382.[7] HPLC analysis revealed that within 72 h 41 % of ***rac*-1** were converted into the lactone **2**/***ent*-2**. The enantiodifferentiation of this enzyme-catalyzed intramolecular acylation was only moderate. The lactone **2** was formed with an enantiomeric excess (e.e.) of 61 % and crystallized from the reaction mixture after removal of the enzyme and cooling to 0°C with an e.e. of 98 %. Thus, 22 % of almost optically pure lactone **2** were obtained. Enantiomerically pure 3,5-dihydroxy ester ***ent*-1** could be

obtained by a simple recrystallization of the fraction of the unreacted diols ***ent*-1/1** isolated from the reaction mixture by flash chromatography with an e.e. of 70 %.

A variation of the lipase and the solvent did not improve the outcome of this biocatalytic process. For instance pancreatin, often used for enzymatic lactonizations,[4-6,8] caused a conversion of only 12 %.

The absolute configuration of the lactone **2** was determined by hydrogenation to the saturated lactone **3**,[4] which was also obtained by hydrogenation from **4**,[6] a compound of known configuration.

The δ-lactones **3** and **4** have been earlier prepared by a similar enzyme-catalyzed lactonization of the anologues of ***rac*-1** with a single[4] or a double[6] bond in place of the triple bond. A comparison reveals that the enantioselectivity of these lactonizations decreases with increasing degree of unsaturation in the C-5 substituent of the starting 3,5-dihydroxy ester.

Methyl (3*R,5*S**)-3,5-dihydroxy-7-phenyl-6-heptynoate (*rac*-1)**: This compound was prepared in diastereomerically pure crystalline form by condensation of 3-phenyl-2-propynal with the dianion of methyl acetoacetate and subsequent reduction with sodium borohydride/ethoxydimethylborane in analogy to the literature.[5,9] Yield: 72 %; M.p. 54-56°C (Et_2O/hexane); ^{13}C NMR ($CDCl_3$): δ = 41.19, 43.34, 51.88, 61.97, 67.37, 85.01, 89.20, 122.39, 128.26, 128.46, 131.69, 172.84; Anal. calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.48. Found: C, 67.75; H, 6.49.

(3*R*,5*S*)-3-Hydroxy-7-phenyl-6-heptyn-5-olide (2): Lipase SP 382[7] (0.6 g) and molecular sieve 4 Å (3 g) were added to a solution of the dihydroxy ester ***rac*-1** (1.490 g, 6 mmol) in diethyl ether (75 ml). The mixture was stirred at 22°C for 72 h and then filtered. The filtrate was kept at 0°C overnight. The precipitated colourless crystals proved to be lactone **2** (0.285 g, 22 %): M.p. 132-134°C; $[\alpha]_D^{20}$ = 14.0 (c = 2.5, CH_2Cl_2), e.e. = 98 %; HPLC: Chiralpak AD, hexane/EtOH (80:20), 1 ml/min, R_t = 3.1 min (**2**) and 8.1 min (***ent*-2**); ^{13}C NMR ($CDCl_3$): δ = 36.75, 38.87, 62.37, 66.63, 84.82, 87.26, 121.54, 128.36, 129.02, 131.76, 169.34; Anal. calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.58. Found: C, 72.31; H, 5.75.

The mother liquor was concentrated under reduced pressure and the residue separated by flash chromatography on silica gel with hexane/EtOAc (1:2) into lactone ***2*/*ent*-2** (0.245 g, 19 %, e.e. = 20 %) and diol ***ent*-1/1** (0.445 g, 30 %, e.e. = 70 %).

Methyl (3S,5R)-3,5-dihydroxy-7-phenyl-6-heptynoate (*ent*-1): Recrystallization of the diol ***ent*-1/1** from Et_2O/hexane afforded enantiomerically pure diol ***ent*-1**: M.p. 54-56°C; $[\alpha]_D^{20}$ = -0.5 (c = 2.5, CH_2Cl_2); HPLC: Chiralcel OD, hexane/*i*PrOH (50:50), 1 ml/min, R_t = 3.2 min (***ent*-1**) and 9.3 min (**1**).

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