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ENANTIOSELECTIVE SYNTHESIS OF THE HYDROXY-LACTONE MOIETY OF MEVINIC ACIDS

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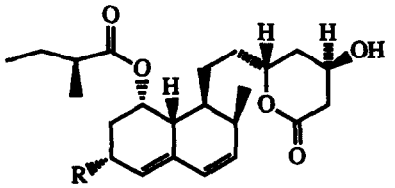
Abstract: 2-Oxa-4*endo*-hydroxybicyclo[3.3.0]-oct-7-en-3-one was resolved with *Pseudomonas fluorescens lipase* and one of the enantiomers was converted into a key intermediate in the synthesis of mevinic acids.

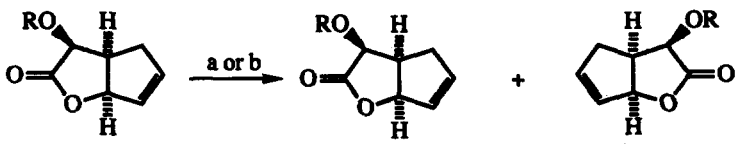
Mevinic acids such as compactin and mevinolin have been shown to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in the cholesterol biosynthesis.[1] Structure activity relationships revealed that the hydroxy-lactone moiety of such compounds is essential for biological activity,[2] consequently a great amount of effort has been directed toward the synthesis of this enantiomerically pure moiety[3] and simple derivatives.[4]



R= H (+)-compactin
R= Me (+)-mevinolin

Water promoted hetero Diels-Alder cycloaddition of glyoxylic acid with cyclopentadiene and rearrangement of the bicyclic olefinic adduct yields endo- (±)-1 and exo-hydroxylactones in a 4:1 ratio.[5] The major compound is purified by either column chromatography, or recrystallization from extraction liquors. This hydroxylactone has been shown to be a new synthon, used by Grieco in the synthesis of Sesbanimides[6] and by our group in the synthesis of (-)-Carbovir.[7] endo-Hydroxylactone (±)-1 has been resolved using *Pseudomonas fluorescens lipase* (PFL) either by esterification in an organic solvent, or hydrolysis of the acetyl ester in a buffer solution. Thus when hydroxylactone 1 is esterified with PFL in vinyl acetate, the ester (-)-2 and alcohol (+)-1 are obtained; contrarywise when acetyl ester 2 is hydrolyzed with PFL in an aqueous solution the ester (+)-2 and alcohol (-) -1 are obtained (Scheme I).

In our previous communication the absolute stereochemistry of the resolved lactones was determined by the synthesis of (-)-Carbovir starting from the (-)-lactone 2.[7] In this communication, we show how the (+)-lactone 2 can be converted into a chiral intermediate for the synthesis of hypocholestaemic agents.

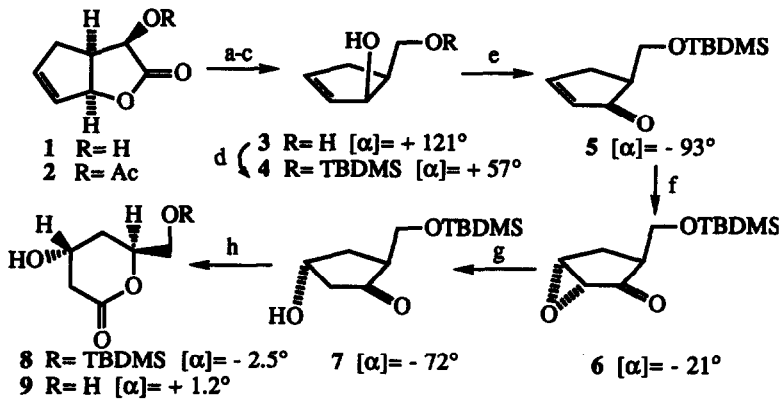


(±) 1 R= H
(±) 2 R= Ac

(-) 2 R= Ac
(-) 1 R= H

(+) 1 R= H
(+) 2 R= Ac

Reagents: a. PFL, vinyl acetate; b. PFL, buffer solution, pH=7.
Scheme I. Resolution of the *endo*-Hydroxylactone.



Reagents: a. $LiAlH_4$, THF, reflux; b. $NaIO_4$, H_2O; c. $NaBH_4$; d. TBDMSCl, Et_3N, DMAP, CH_2Cl_2; e. PCC, CH_2Cl_2; f. H_2O_2, NaOH, MeOH, 0°C; g. Al (Hg), THF-H_2O; h. m-CPBA, Na_2CO_3, CH_2Cl_2.

Scheme II. Synthesis of the Hydroxy Lactone Moiety.

Hydroxylactone (+)-**1** or ester (+)-**2** can be reduced to the diol **3** in a three step sequence which embodies $LiAlH_4$ reduction, sodium periodate diol cleavage, and $NaBH_4$ reduction (39%).[7] Diol **3** is selectively monoprotected with TBDMSCl using DMAP and triethylamine (70%).[8] Allylic alcohol **4** is oxidized (PCC in CH_2Cl_2) to afford the cyclopentenone **5**, which was stereoselectively oxidized to the epoxide **6** (66%). The α,β-epoxycyclopentanone was reduced using Keck's aluminium amalgam conditions[9,10] to the β-hydroxy cyclopentanone **7** (100%). Baeyer-Villiger oxidation of cyclopentanone **7** provided the desired lactone **8** (93%) which posseses the correct stereogenic centres of the mevinic acids. In order to correlate this compound with a known intermediate, the protecting group was removed; the diol **9** was identical to that reported by Takano.[11]

Other synthetic uses of the hydroxylactone enantiomers (+)-**1** and (-)-**1** are under investigation.

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