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AN EXPEDITIOUS CHIRAL ROUTE TO ANALOGS OF MEVINOLIN AND COMPACTIN

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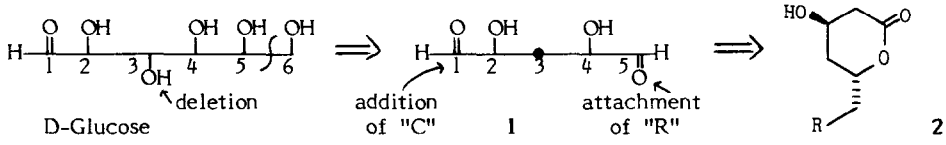
ABSTRACT: A new and novel approach to the preparation of optically active analogs of mevinolin and compactin, in which the β-hydroxy-δ-lactone moiety is derived from D-glucose, is described.

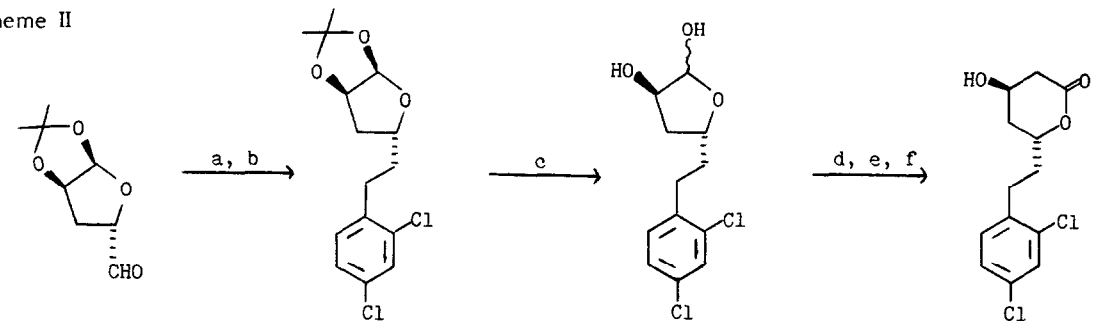
The fungal metabolites, mevinolin and compactin,[1] are potent inhibitors of HMG-CoA reductase, the enzyme which regulates the rate-limiting step of cholesterogenesis. More importantly, both compounds have now been proven to be highly effective hypocholesterolemic agents in animals as well as man. These results have thus prompted efforts in a number of laboratories directed toward the synthesis of these natural products[2] and their analogs.[3] In this report we wish to present a new and novel route to analogs of mevinolin and compactin using D-glucose as the chiral precursor for the β-hydroxy-δ-lactone moiety. Our approach, as outlined in Scheme I, requires elimination of the C-3 hydroxy and cleavage of the C-5 to C-6 bond of D-glucose to arrive at the intermediate **1**. Then, attachment of an R group at C-5 of 1 and, finally, execution of a one-carbon homologation at the C-1 terminus will provide the target compound **2**. This approach has now been validated by the successful synthesis of **6** described below (Scheme II).

Scheme I



Deoxyenation[4] of D-glucose diacetonide followed by application of Murray and Prokop's procedure[5] produced aldehyde **3** in high yield. Treatment of freshly distilled **3** with 2,4-dichlorophenylmethylenetriphenylphosphorane in THF-DMF afforded an olefinic mixture (E/Z = 1/4) which was hydrogenated to **4**[6] (87% for two steps; $[\alpha]_D$ 0.74°, c = 1.63, $CHCl_3$). Acidic hydrolysis of **4** in hot aqueous acetonitrile gave lactol **5**. All our attempts to react this lactol pair with the anion generated from diethyl (1,3-dithian-2-yl)phosphonate failed. This result was unexpected as our earlier work on the homologation of lactones[7] had demonstrated that other lactols reacted readily with this reagent to form ketene dithioacetals. Alternatively, lactol **5** was treated with phenylthiomethylenetriphenylphosphorane[8] in DMF-Me_2SO to produce a mixture of vinyl sulfides (E/Z = 1/2, 60% overall from **4**) which was hydrolyzed in the presence of mercuric ion to the corresponding lactol. Finally, oxidation of the latter lactol with N-iodosuccinimide/n-tetrabutylammonium iodide[9] gave the target compound **6**[10] ($[\alpha]_d$ 63.1°, c = 0.64, $CHCl_3$; 35% overall for two steps).

Scheme II



3 4 5 6

[a] t-BuOK, Cl-(Cl)C6H3-CH2+PPh3Cl−, THF-DMF (1:1), 0°C to r.t. [b] 10% Pd/C, EtOAc, 1 atm. [c] TsOH, CH_3CN-H_2O (10:1), 90°C, 3 h. [d] NaH, $Ph_3{}^+PCH_2SPhCl^-$, DMF-Me_2SO (2:3), 0°C to r.t. [e] $HgCl_2$, HgO, CH_3CN-H_2O (3.5:1), 65°C. [f] N-iodosuccinimide, n-Bu_4NI, CH_2Cl_2, r.t.

In summary, we have reported here a new and expeditious route to optically active analogs of mevinolin and compactin in which the lactone moiety is derived from D-glucose as exemplified in the synthesis of **6**.

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