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SYNTHESIS OF A CHIRAL SYNTHON FOR THE LACTONE PORTION OF COMPACTIN AND MEVINOLIN

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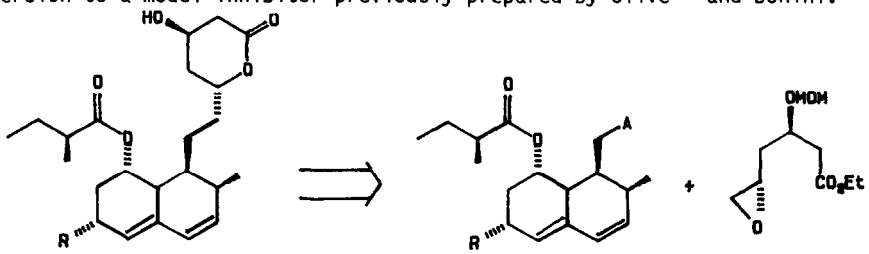
ABSTRACT: The stereoselective Michael addition of alcohols to 6-tosyloxymethyl-5,6-dihydro-2H-pyran-2-one afforded high yields of a key chiral synthon for the lactone portion of compactin and mevinolin.

Compactin (1) mevinolin (2) and related compounds have been shown to lower serum cholesterol levels in animal models and man and thus may provide important tools in the prevention and treatment of coronary artery disease.[1] In recent years, these compounds have been the targets of an increasing number of synthetic efforts, yet their synthesis remains a formidable challenge.[2] Introduction of the 4R,6R-lactone ring stereochemistry, which is required for biological activity, has proved the most problematic.[3] Despite recent improvements in synthetic methodology for controlling 1,3-asymmetry,[4,5] most syntheses suffer from low overall yields, a large number of steps, and/or are achiral. An attractive chiral synthon, epoxide 3, has been described by Guindon.[6] His synthesis, however, was lengthy and suffered from low stereoselectivity. In this connection, we wish to report an efficient, high yielding, highly stereoselective synthesis of an analogous chiral synthon which should be suitable for the large scale preparation of these biologically important molecules. Additionally, we demonstrate its utility by conversion to a model inhibitor previously prepared by Clive[7a] and Bonini.[7b]

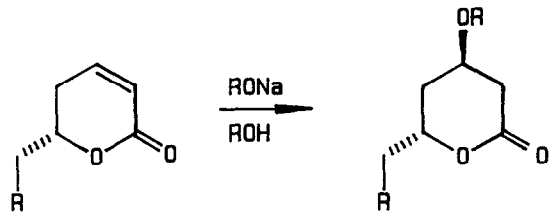


1. R=H compactin
2. R=CH_3 mevinolin

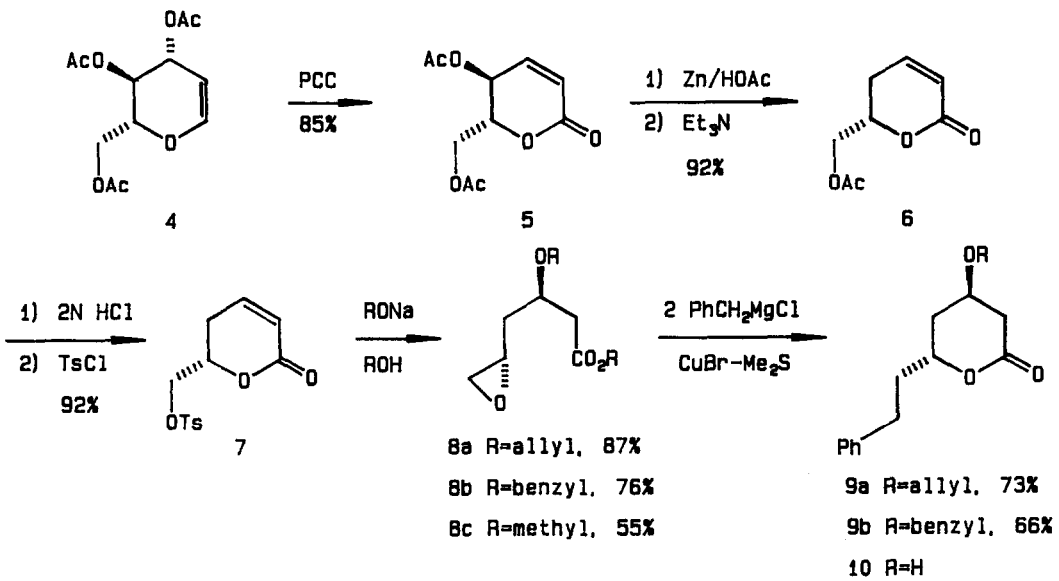
A=activating group

3

An effective, but little used, method for introducing the requisite 1,3-asymmetry is the Michael addition of an alcohol to an α,β-unsaturated lactone.[8] We felt that application of this reaction to a suitable precursor could provide an effective means for preparing mevinolin analogs.



To this end, treatment of inexpensive, commercially available tri-O-acetyl-D-glucal (4) with PCC in refluxing dichloroethane for 22 hours followed by filtration through silica gel afforded the unsaturated lactone 5 in 85% yield.[9] Reductive deconjugation (Zn/HOAc/80°/3.5 hr)[10] followed by reconjugation (excess Et_3N/EtOAc/25°C) produced the 5-deoxygenated lactone (6) in 92% overall yield. Hydrolysis (2N HCl/25°C) and tosylation afforded tosylate 7 in 92% isolated yield.[11,12]



Treatment of compound 7 with 1.5 equivalents of sodium allyl alcoholate in allyl alcohol, first at -43°C, then warming to 0°C, and finally stirring at room temperature, effected both stereoselective Michael addition and epoxide formation to produce key chiral epoxide 8a, $[\alpha]_D$ - 27.1° (c 1.10 MeOH), in 87% yield as a 32:1 mixture of RS and SS diastereomers by HPLC.[13,14] The use of other alcohols afforded comparable yields (76% benzyl, 55% methyl) and diastereomeric ratios.

The utility of 8a was demonstrated by its two step conversion to the known [7a,b] hydroxylactone 10. Thus, reaction of 8a with dibenzyl cuprate at -78°C and then warming to 0°C afforded lactone 9a, $[\alpha]_D$ + 47.63° (c 0.65 MeOH), in 73% yield after flash chromatography.[15] Deprotection[16] (10% Pd-C in 2:1 dioxane-water) produced target lactone 10 in 50% yield after flash chromatography ($[\alpha]_D$ + 68.88 (c 2.29 $CHCl_3$)).[17]

In summary, we have demonstrated that the addition of alcohols to $\Delta^{\alpha,\beta}$-unsaturated lactones is an effective method for introducing the requisite lactone stereochemistry found in the mevinic acids. Additionally, we have developed an efficient, six step synthesis of a chiral lactone synthon in 63% yield from commercial tri-O-acetyl-D-glucal and demonstrated its utility by conversion to a model HMG-CoA reductase inhibitor. Efforts to further define the utility of this synthon are in progress.

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12. Analytical and spectral data for compound 7 are in complete agreement with literature values (Ref. 11).
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14. A full experiment is as follows: To a solution of tosylate 6 (13.9 g, 49 mmol) in 125 mL of allyl alcohol cooled to -43°C was added dropwise 20 mL of a 1.25 M solution of sodium allyl alcoholate in allyl alcohol (from NaH and allyl alcohol). The solution was allowed to warm slowly to 0°C, cooled to -40°C and a further 40 mL of the 1.25 M alcoholate solution was added. The solution was allowed to warm to room temperature and stirred for 1½ hr. Glacial acetic acid (3 mL) was added. The solution was concentrated, partitioned between ethyl acetate (300 mL) and sat'd aq. $NaHCO_3$. The organic layer was washed with brine and dried ($MgSO_4$). Flash chromatography on silica gel eluting with ethyl acetate-hexane (50:50 v/v) afforded 9.43 g of 7a as a colorless oil. IR(film) 3050, 2993, 2926, 1738, 1648, 1177 cm^{-1}. 200 MHz NMR ($CDCl_3$) δ 1.75(M, 2H), 2.45-2.8(M, 4H), 3.05(M, 1H), 4.03(M, 3H), 4.60(M, 2H), 5.1-5.4(M, 4H), 5.8-6.4(M, 2H). Anal. ($C_{12}H_{18}O_4$) C,H.
15. The hydroxy acid derived by saponification of the initial adduct lactonized during silica gel chromatography. Compound 8a: IR(film) 1738, 1254, 1079, 1053, 702 cm^{-1}. 200 MHz NMR ($CDCl_3$) δ 1.5-2.1(M, 4H), 2.70(M, 2H), 2.7-3.0(M, 2H), 3.99(M, 2H), 4.65(M, 1H), 5.1-5.3(M, 2H), 5.8(M, 1H), 7.2(M, 5H).
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