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MEVINIC ACIDS AND ANALOGUES: PREPARATION OF A KEY CHIRAL INTERMEDIATE

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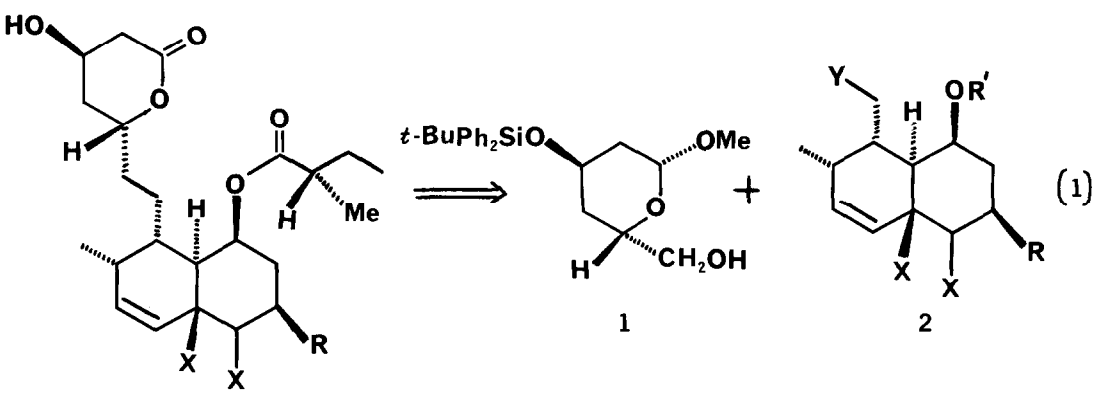
Summary: The preparation of methyl 3-O-tert-butyldiphenylsilyl-2,4-dideoxy-β-D-erythro-hexopyranoside, a key chiral intermediate for mevinic acids, and its elaboration into four mevinate analogues are described.

Mevinic acids[1-4] are extremely potent competitive inhibitors[5] of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. They are distinguished by a hexa or octahydronaphthalene bearing an ethylene linked β-hydroxy-δ-lactone appendage which closely resembles the HMG moiety of HMG-CoA and consequently are thought[6] to be competitive with respect to this substrate. The current synthetic interest[7] in this group of fungal metabolites is due largely to their potential in the treatment of hypercholesterolemia and established usefulness as adjuncts in biochemical research. In our antithetic analysis, we envisioned a general approach joining suitably protected lactone 1 and hydronaphthalene 2 fragments via the ethylene bridge (eq. 1). Reported herein are a brisk, high-yield synthesis of 1 with the requisite absolute stereochemistry and its elaboration into four mevinate analogues, 10a-c and 13.

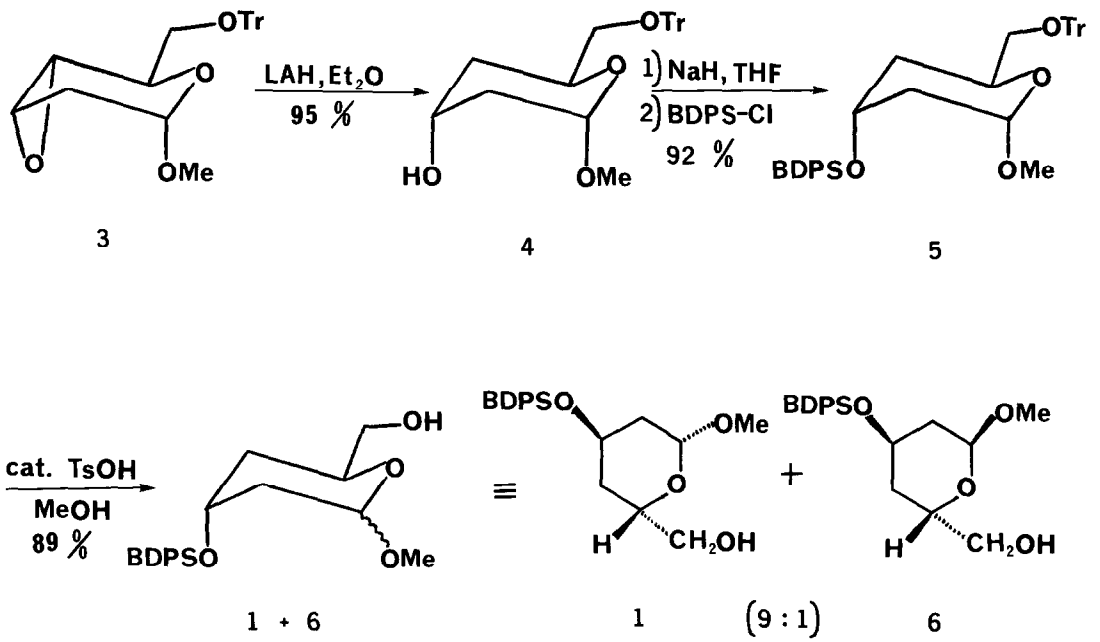


Mevinolin: R=Me,X=$\Delta^{4a,5}$
Compactin: R=H,X=$\Delta^{4a,5}$

Dihydromevinolin: R=Me,X=H
Dihydrocompactin: R=X=H

The known[8] epoxy-trityl ether 3, available in 62% yield from commercially available tri-O-acetyl-D-glucal, was reduced to 3-α-hydroxypyranoside 4[9,10] by lithium aluminum hydride (LAH) in ether at room temperature for 1 h (Scheme I). Treatment of 4 with sodium hydride and t-butyldiphenylsilyl chloride (BDPS-Cl) in tetrahydrofuran (THF) at room temperature for 12 h afforded silyl ether 5. Detritylation using a catalytic amount of p-toluenesulfonic acid (TsOH) in methanol for 12 h resulted in an equilibrium mixture of anomers 1 and 6 (9:1) which could be separated chromatographically (SiO_2, ether/hexanes 1:1, $R_f \sim 0.15$ and 0.20 for 1 and 6, respectively). Although both anomers are suitable for conversion to mevinic acids, only 1 was used in subsequent work.

Scheme I



3 4 5

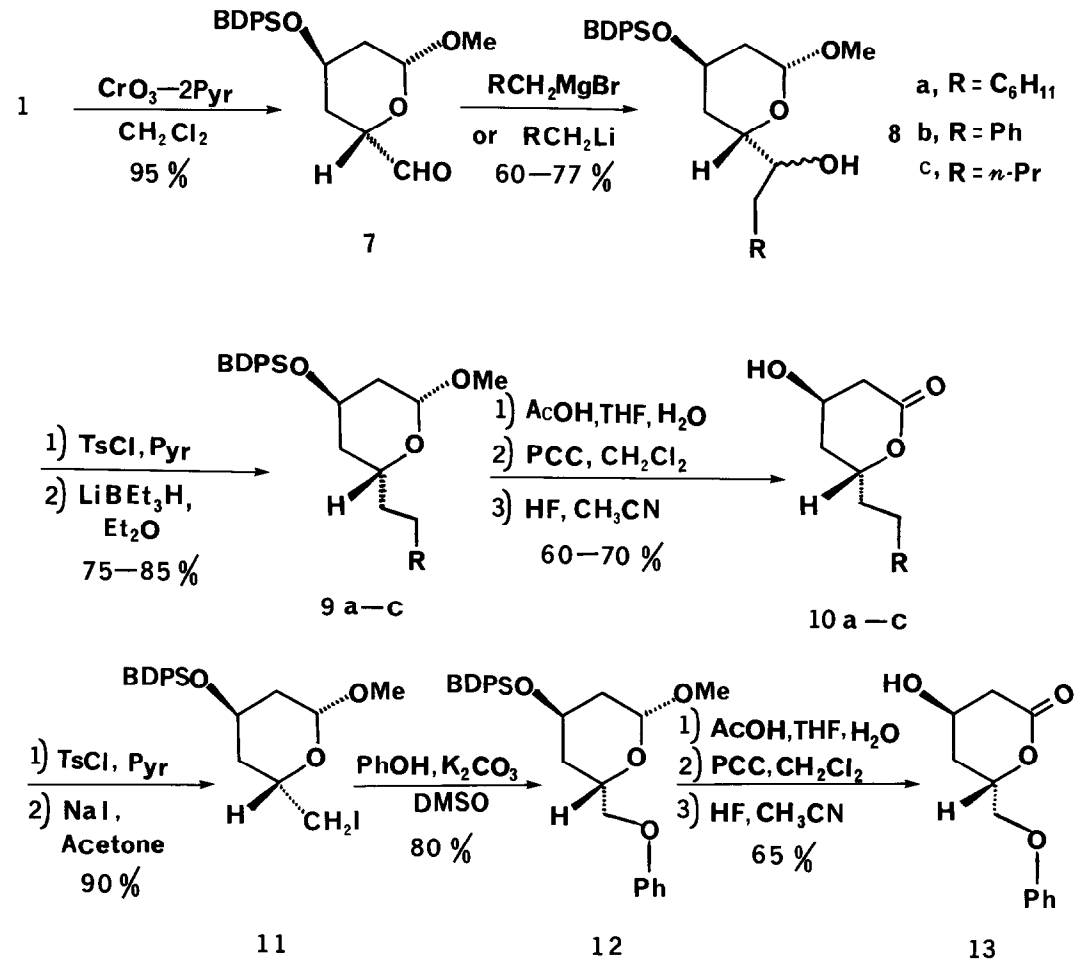
1 + 6 1 6

Tr = trityl; BDPS = t-butyldiphenylsilyl

Oxidation of 1 to aldehyde 7 by chromium trioxide-pyridine complex[11] proceeded smoothly in dry methylene chloride over 1 h (Scheme II). Addition of cyclohexylmethylmagnesium bromide, benzylmagnesium bromide, and n-butyllithium to 7 in ether at -20°C gave the corresponding alcohols 8a-c, respectively. Tosylation with tosyl chloride in pyridine followed by lithium triethylborohydride reduction generated 6-alkylpyranosides 9a-c. Alternatively, tosylation of 1 and displacement with sodium iodide in refluxing acetone for 24 h gave iodide 11. Treatment of 11

with excess phenol in dimethylsulfoxide (DMSO) in the presence of potassium carbonate at 52°C for 12 h yielded phenyl ether 12 as the sole product. The desired δ-lactone analogues 10a-c and 13[12] were prepared readily by sequential hydrolysis in AcOH/THF/H_2O (3:2:2) at 70°C for 5 h, pyridinium chlorochromate (PCC) oxidation in methylene chloride, and desilylation with excess 48% hydrofluoric acid in acetonitrile at 46°C for 15 h. The total synthesis of several mevinic acids using 1 and the elaboration procedures described above will be reported in due course.

Scheme II



BDPS = t-butyldiphenylsilyl

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References and Notes

1. The name mevinic acid as proposed for the parent system (see ref. 2a) refers to the free acid form but is used here to include the δ -lactone form.

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9. For all new compounds, satisfactory ir, nmr, and mass spectral data were obtained on chromatographically homogeneous samples.

10. Physical data for 1: mp 97-98°C; $[\alpha]_D^{24}$ -11.2° (C=4.03, $CHCl_3$); nmr ($CDCl_3$) δ 1.08 (9H,s), 1.30-2.20 (4H,m), 3.50 (3H,s), 3.40-3.70 (2H,m), 4.10 (1H,m), 4.28 (1H,m), 4.86 (1H,dd,J=2.5, 10.5 Hz), 7.36 (6H, m), 7.60 (4H, m); 4: mp 100-102°C; $[\alpha]_D^{24}$ 45.3° (C=4.30, $CHCl_3$); nmr ($CDCl_3$) δ 1.40-2.00 (4H,m), 3.12 (2H,m), 3.40 (3H,s), 3.56 (1H,d,J=10Hz), 3.90-4.40 (2H,m), 4.84 (1H,brs), 7.00-7.60 (15H,m); 5: mp 53-55°C; $[\alpha]_D^{24}$ 27.5° (C=4.18, $CHCl_3$); nmr ($CDCl_3$) δ 1.08 (9H,s), 1.20-1.80 (4H,m), 3.04 (2H,m), 3.40 (3H,s), 4.08 (1H,m), 4.44 (1H,m), 4.68 (1H,m), 7.10-7.80 (25H,m).

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12. Physical data for 10a: mp 65-67°C; nmr ($CDCl_3$) δ 0.80-2.00 (17H,m), 2.68 (2H,m), 4.39 (1H,m), 4.63 (1H,m); 10b: nmr ($CDCl_3$) δ 1.60-2.20 (4H,m), 2.72 (2H,m), 2.87 (2H,m), 4.40 (1H,m), 4.70 (1H,m), 7.22 (5H,brs); 10c: nmr ($CDCl_3$) δ 0.92 (3H,t,J=7 Hz), 1.00-2.20 (10H,m), 2.68 (2H,m), 4.39 (1H,m), 4.68 (1H,m); 13: mp 91-93°C; nmr ($CDCl_3$) δ 2.13 (2H,dd,J=3.6, 7.5 Hz), 2.76 (2H,m), 4.16 (2H,d=5 Hz), 4.52 (1H,m), 5.06 (1H,m), 6.92 (3H,m), 7.25 (2H,m).

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