hydroperoxymethyl peroxide (8f); a discussion of the ozonolysis of 1,4-dichloro-2-butene (9) in the presence of HCl to yield 1,2-dichloroethyl 1'-hydroxy-2'-chloroethyl peroxide (10); ^{1}H NMR spectra of **2a** + **8a**, **2b–e**, **2f**, **3a–d,f,g**, **4a,b,d**, and **6**; ^{13}C NMR spectra of **2a** + **8a**, **2b–f**, **3a–d,g**, **4a,b,d,f**, and **6**; and IR spectra of **2b**, **3b**, and **4b** (42 pages). Ordering information is given on any current masthead page.

Practical Synthesis of an Enantiomerically Pure Intermediate of the Lactone Moiety of Mevinic Acids

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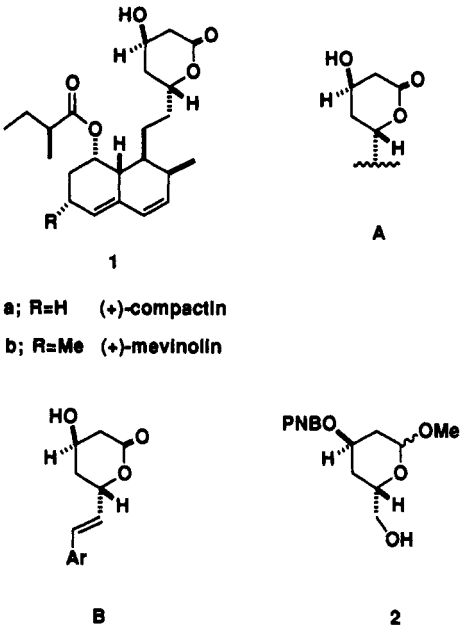
Since the recognition of hypercholesterolemia as a risk factor of atherosclerosis and coronary heart disease,[1] there have been multiple efforts to identify chemical entities capable of regulating the plasma level of this sterol.[2] Mevinic acids[3] are part of a family of fungal metabolites that have attracted considerable attention due to their biological activities as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterogenesis in man.[4,5] Compactin[6] (**1a**) and mevinolin[4b,7] (**1b**) (Chart I) are two prominent members of this family of clinically useful hypocholesterolemic agents. The key structural feature common to all mevinic acids[3] is the β-hydroxyvalerolactone function A which, in its open form, closely mimics mevalonic acid, a crucial intermediate in the terpenoid biosynthetic pathway leading to cholesterol.

Structure–activity relationships in previous series revealed[8] that the chiral lactone moiety, A, is essential for strong biological activity, whereas the hexahydronaphthalene half allows more structural variations. Recent reports[9] on the discovery of active analogues, B, which retain the lactone portion of mevinic acids have increased the potential interest of enantiospecific routes to suitable chirons.[10]

Chart I



In view of the nature of the lactone portion, a number of syntheses involved starting materials derived from carbohydrates.[11] Shorter chains derived from chiral, nonracemic hydroxy acids and similar sources have also been used.[12] The lactone moiety has also been constructed by employing a hetero-Diels–Alder approach, a protocol extensively investigated by Danishefsky and co-workers.[13]

A practical approach to incorporate the key chiral hydroxy lactone portion A in the synthesis of the natural compounds **1a,1b** or the analogues B is to employ the masked lactols as precursors of electrophilic species. Consequently, the synthesis of multigram amounts of methyl 2,4-dideoxy-3,6-bis(*O*-*p*-nitrobenzoyl)-D-*erythro*-hexopyranosides **2** from D-glucose using a few simple and high yielding steps is of considerable interest.

2,3:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (**3**) is readily available from D-glucose using standard methods.[14,15] Compound **3** (Scheme I) was transformed

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(14) Compound **3** has been previously prepared (75% yield) by reaction of D-glucose diethyldithioacetal and 4 equiv of 2-methoxypropene (Grindley, T. B.; Wickramage, Ch. *Carbohydr. Res.* **1987**, *167*, 105). In our hands, the simplest manner to carry out this operation was to dissolve the crude dithioacetal[15] in acetone. Allowing the solution to stand for 5–6 h at rt affords the required diacetonide **3**, certainly due to the presence of residual acid from the previous step acting as a catalyst.

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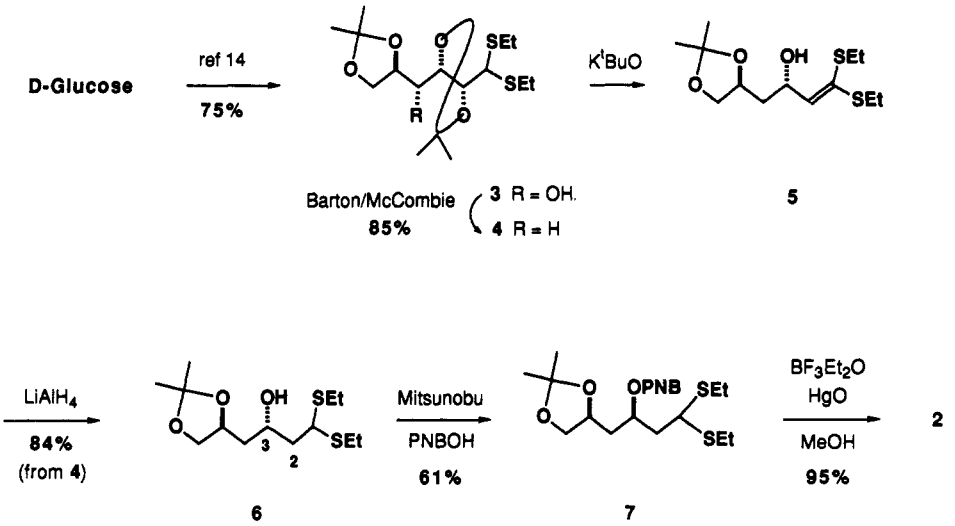
Scheme I



into its xanthate and readily deoxygenated by the Barton–McCombie method[16] to afford 4 (85% yield, two steps).

Regiospecific deoxygenation at C-2 takes advantage of the fact that aldose thioacetals are weakly acidic. In fact, treatment of compound 4 with K'BuO in DMSO–THF (1:3), according to the protocol developed by Gray and Wong,[17] resulted in elimination of acetone and formation of the ketene dithioacetal 5. $LiAlH_4$ reduction of 5 gave compound 6 in 84% overall yield from 4.

Inversion of the configuration at C-3, in compound 6, was effected by a Mitsunobu process[18] using *p*-nitrobenzoic acid[19,20] (PNBOH), in 61% yield. The remaining tasks, (a) opening of the ketal, (b) unveiling of the anomeric aldehyde function, and (c) formation of the pyranosidic methyl glycosides, were carried out in just one synthetic operation (95% yield) by treating 7 with a methanolic solution of HgO and borontrifluoride etherate ($BF_3{\cdot}Et_2O$).[21] Compound 2 has been prepared in multigram quantities.[22]

In summary, masked lactol 2, an enantiomerically pure precursor for the lactone moiety of the mevinic acids 1 and analogues B, has been prepared in eight steps and 31% yield from D-glucose. A new sequence that allows efficient dideoxygenation at C-2 and C-4 in D-glucose has been developed and should provide a useful alternative to the common method based on reductive opening of epoxides derived from 1,6-anhydro-D-glucose.[23,24]

Experimental Section

Proton and carbon NMR were obtained at 300 and 75.5 MHz, respectively, and are referenced to residual protonated solvent or internal TMS. Flash chromatography was performed on Kieselgel 60, Merck, 230–400 mesh.

2,3:5,6-Di-*O*-isopropylidene-D-glucose Diethyl Dithioacetal (3). To a solution of D-glucose (80 g, 0.44 mol) in EtSH (100 mL) at 0 °C was added concentrated HCl and the reaction mixture vigorously stirred for 1 h, after which time water was evaporated. The residue was precipitated by addition of EtOH and the resulting solid filtered to afford crude D-glucose diethyl dithioacetal, which without further purification was dissolved in acetone (2500 mL) and stirred for 6 h. Evaporation of the solvent and chromatography (hexane-ethyl acetate (9:1)) of the residue afforded 3,4:5,6-di-*O*-isopropylidene-D-glucose diethyl dithioacetal (30 g) and the expected 3 (120 g, 74%).

4-Deoxy-2,3:5,6-*O*-diisopropylidene-D-glucose Diethyl Dithioacetal (4). A mixture of 3 (25 g, 68 mmol) and sodium hydride (NaH) dispersion (60%; 5.5 g, 102 mmol) in dry tetrahydrofuran (THF) (600 mL) was stirred at room temperature for 0.5 h, at which time carbon disulfide (CS_2) (31 mL, 102 mmol) was added. The reaction mixture was stirred for 1 h, followed by addition of excess of MeI (14 mL). The resulting solution was kept with stirring for 0.5 h, diluted with diethyl ether (Et_2O), and quenched by careful addition of ice. Et_2O and water were added, and the organic layer was washed with water and dried ($MgSO_4$) and the solvent evaporated.

A solution of tributyltin hydride (TBTH) (31 mL, 115 mmol) in toluene (150 mL) was added over 1 h to a solution of the foregoing thioester in refluxing toluene (750 mL) and the reflux maintained overnight. The mixture was evaporated and the residue chromatographed (hexane–ethyl acetate (95:5)) to afford compound 4 as a colorless oil (20.2 g, 85% from 3): $[\alpha]^{22}_D = -42.5$ (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (t, 6 H, 2 Me, J = 7.5 Hz), 1.34 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.39 (s, 3 H, Me), 1.42 (s, 3 H, Me), 2.71 (ddd, 1 H, H-4a, J = 5.5, 9.3 Hz, $J_{4a,4b}$ = 10.5 Hz), 2.12 (ddd, 1 H, H-4b, J = 3.2, 7.3 Hz, $J_{4a,4b}$ = 10.5 Hz), 2.60–2.80 (m, 4 H, 2 SCH_2), 3.58 (dd, 1 H, H-6a, J_{6a6b} = 8.1 Hz, $J_{5,6a}$ = 6.6 Hz), 3.89–3.95 (m, 2 H, H-1, H-2), 4.09 (dd, 1 H, H-6a, J_{6a6b} = 8.1 Hz, $J_{5,6b}$ = 6.0 Hz), 4.15–4.27 (m, 2 H, H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 25.0, 25.2, 25.6, 26.8, 27.3, 38.8, 52.6, 69.7, 73.7, 76.8, 84.4, 108.4, 109.1. Anal. Calcd for $C_{16}H_{30}O_4S_2$: C,54.82; H, 8.63; S, 18.29. Found: C, 54.91; H, 8.82; S, 18.02.

2,4-Dideoxy-5,6-*O*-isopropylidene-D-glucose Diethyl Dithioacetal (6). A solution of 4 (20 g, 57.1 mmol) in 300 mL of dry THF was added dropwise to a mixture of 'BuOK (9.6 g, 85.6 mmol) in 450 mL of THF and 110 mL of DMSO at rt. The reaction mixture was stirred for 0.5 h and poured into ice. The aqueous layer was extracted three times with Et_2O, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated to give ketene dithioacetal 5 as a colorless oil that was used without further purification in the next step.

A solution of crude 5 in THF (250 mL) was added dropwise over 0.5 h to a suspension of $LiAlH_4$ (4.3 g, 114 mmol) in THF (200 mL) at 0 °C under argon. The reaction mixture was stirred for 5 h at rt, diluted with Et_2O, and then quenched by slow dropwise addition of a saturated solution of $NaHSO_4$ at 0 °C until

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hydrogen evolution ceased. The resulting solution was kept with stirring for 1 h, filtered trough a pad of Celite, and evaporated to afford a residue that was chromatographed (hexane–ethyl acetate (19:1) to give **6** as a colorless oil (14.1 g, 84% from **4**): $[\alpha]^{22}_D$ = +17.1 (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (t, 6 H, 2 Me, J = 7.4 Hz), 1.29 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.69–1.79 (m, 2 H, 2 H-4), 1.81 (ddd, 1 H, H-2a, $J_{1,2a}$ = 8.5 Hz, $J_{2a,3}$ = 2.9 Hz, $J_{2a,2b}$ = 11.8 Hz), 1.94 (ddd, 1 H, H-2b, $J_{1,2b}$ = 5.9 Hz, $J_{2b,3}$ = 9.0 Hz, $J_{2a,2b}$ = 11.8 Hz), 2.54–2.73 (m, 4 H, 2 SCH_2), 2.99 (b d, 1 H, OH, J = 4.4 Hz), 3.55 (t, 1 H, H-6a, $J_{6a,6b}$ = $J_{5,6a}$ = 7.45 Hz), 3.99 (dd, 1 H, H-1, $J_{1,2a}$ = 8.5 Hz, $J_{1,2b}$ = 5.9 Hz), 4.04 (dd, 1 H, H-6b, $J_{6a,6b}$ = 7.45 Hz, $J_{5,6b}$ = 6.1 Hz), 4.06–4.09 (m, 1 H, H-3), 4.11–4.32 (m, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 24.0, 24.2, 25.6, 26.8, 40.4, 43.6, 48.5, 53.2, 67.2, 69.5, 73.5, 108.7. Anal. Calcd for $C_{13}H_{26}O_3S_2$: C, 53.03; H, 8.90; S, 21.77. Found: C, 53.92; H, 8.82; S. 21.54.

2,4-Dideoxy-5,6-*O*-isopropylidene-3-(*p*-nitrobenzoyl)-D-allose Diethyl Dithioacetal (7). To a stirred solution of **6** (5.2 g, 17.69 mmol), PPh_3 (32.4 g, 123.8 mmol), and PNBOH (20.7 g, 123.8 mmol) in dry toluene (350 mL) was added a solution of DEAD (19.5 mL, 123.8 mmol) in toluene (60 mL). The reaction mixture was stirred for 1 h at rt, the suspension filtered, the solution concentrated in vacuo, and the residue chromatographed (hexane–ethyl acetate (95:5) to yield **7** (4.91 g, 61%) as a colorless oil: $[\alpha]^{22}_D$ = −14.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, Me, J = 7.4 Hz), 1.17 (t, 3 H, Me, J = 7.4 Hz), 1.20 (s, 3 H, Me), 1.29 (s, 3 H, Me), 1.87 (dt, 1 H, H-4a, $J_{4a,5}$ = $J_{3,4a}$ = 4.7 Hz, $J_{4a,4b}$ = 14.5 Hz), 2.15–2.96 (m, 2 H, H-2a), 2.29 (ddd, 1 H, H-2b, $J_{1,2b}$ = 6.2 Hz, $J_{2b,3}$ = 8.4 Hz, $J_{2a,2b}$ = 14.7 Hz), 2.47–2.66 (m, 4 H, 2 SCH_2), 3.51 (t, 1 H, H-6a, $J_{6a,6b}$ = $J_{5,6a}$ = 5.9 Hz), 3.81 (dd, 1 H, H-1, $J_{1,2a}$ = 8.6 Hz, $J_{1,2b}$ = 6.2 Hz), 4.02 (dd, 1 H, H-6b, $J_{6a,6b}$ = 12.1 Hz, $J_{5,6b}$ = 5.9 Hz), 4.10–4.17 (m, 1 H, H-5), 5.50–5.58 (m, 1 H, H-3), 8.14– 8.28 (m, 4 H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 23.9, 24.0, 25.6, 26.9, 37.8, 40.5, 47.5, 69.4, 71.9, 72.7, 109.1, 123.5, 130.7, 130.8, 135.7, 164.1. Anal. Calcd for $C_{20}H_{29}O_6S_2N$: C, 54.16; H, 6.59; S, 14.46; N, 31.6. Found: C, 52.92; H, 6.47; S, 14.28; N, 3.02.

Methyl 2,4-Dideoxy-3-(*p*-nitrobenzoyl)-D-allopyranosides (2). A solution of **7** (4.0 g, 9 mmol) in MeOH (200 mL) was added to a suspension of red mercury oxide (3.9 g, 18 mmol) and BF_3·Et_2O (4.5 mL, 36 mmol) in MeOH (80 mL) and stirred for 5 h, after which time Et_2O was added and the precipitated salts were filtered. The resulting solution was washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and evaporated in vacuo and the residue chromatographed (hexane–ethyl acetate (6:4)) to afford **2** (α/β mixture (1:1)) as a colorless oil (2.6 g, 95%): ^1H NMR ($CDCl_3$) δ (selected data) 4.78 (dd, 0.5 H, $J_{1,2ax}$ = 9.6 Hz, $J_{1,2eq}$ = 2.2 Hz, H-1β) 4.85 (d, 0.5 H, $J_{1,2}$ = 4.0 Hz, H-1α), 5.39 (quint, 0.5 H, J = 3.16 Hz, H-3β), 5.57 (quint, 0.5 H, J = 3.16 Hz, H-3α); ^{13}C NMR ($CDCl_3$) δ 31.5, 31.8, 33.6, 36.5, 56.3, 57.6, 65.1, 66.4, 66.6, 68.5, 71.2, 72.7, 98.7 (C-1, β-anomer), 100.5 (C-1, α-anomer), 124.5, 124.7, 131.7, 131.8, 137.2, 137.5, 151.5, 151.7, 164.6, 165.1. Anal. Calcd for $C_{14}H_{17}O_7N$: C, 54.02; H, 5.50; N, 4.50. Found: C, 53.89; H, 5.37; N, 4.32.

Registry No. α-**2**, 138386-35-3; β-**2**, 138386-40-0; **3**, 4258-02-0; **4**, 138386-36-4; **5**, 138386-37-5; **6**, 138386-38-6; **7**, 138386-39-7; PNBOH, 62-23-7; D-glucose, 50-99-7.

Selective Reduction of Alkynes to (*Z*)-Alkenes via Niobium- or Tantalum–Alkyne Complexes

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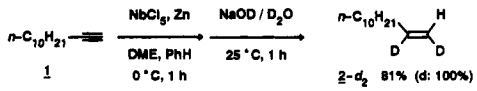
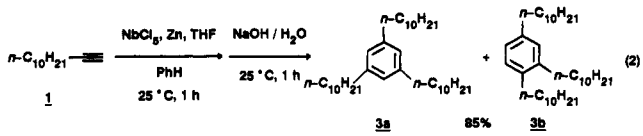
Because the rates of hydrogenation of double and triple bonds do not differ appreciably, several catalysts for partial hydogenation of alkynes leading to (*Z*)-alkenes have been developed.[1] In contrast to hydrogenation, partial reduction of alkynes with sodium in liquid ammonia gives (*E*)-alkenes predominantly.[1] In 1982, we introduced low-valent niobium prepared by the reduction of $NbCl_5$ with $NaAlH_4$ and used it for some reductions, i.e. the pinacol-type reductive coupling of aldehydes or ketones and reduction of alkynes.[2] In the latter reaction with internal alkynes, high (*Z*)-alkene preference was recognized compared to $TiCl_4$–$LiAlH_4$ reagent.[3] This observation suggests the possibility of two reaction pathways. One possibility is the formation of a niobium–alkyne complex[4,5] as an intermediate. Pedersen isolated a one-to-one complex of niobium and an alkyne which is produced by treatment of the alkyne with $NbCl_3$(DME).[5] Another possibility is a hydrometalation pathway by Nb–H species.[6] However, quenching of the reaction mixture of an internal alkyne with D_2O did not give a deuterated olefin. Thus, we reexamined our previous niobium chemistry under the conditions using a reducing agent having no hydride source.[4,7]

In contrast to the previous $NbCl_5$–$NaAlH_4$ system,[2] a combination of $NbCl_5$ and zinc was found to give a vicinal dideuterated olefin after quenching the reaction mixture with NaOD–D_2O.[8,9] Treatment of 1-dodecyne with the combination of 4 equiv of $NbCl_5$ and 6 equiv of zinc in a solvent of DME–benzene (1:1) at 0 °C for 1 h followed by addition of alkaline D_2O afforded (*E*)-1,2-dideuterio-1-dodecene (**2-d_2**) in 81% yield (eq 1). The reaction course changed dramatically when a mixed solvent of benzene and THF (8 molar quantity of $NbCl_5$) was employed. Cyclotrimerization products of 1-dodecyne, a mixture of regioisomers **3a** and **3b**, was produced in 85% combined yields (eq 2).[4a,10]





Aluminum powder was also effective for the reduction of $NbCl_5$. Ultrasonic irradiation to a mixture of $NbCl_5$ and

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