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# A synthetic route from D-glucose to D-*myo*-inositol-1,4,5-tris(dihydrogenphosphate): use of an unusual ene reaction and the $Bu_2SnCl_2/Bu_2SnH_2$ reagent

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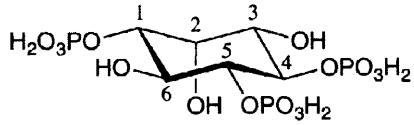
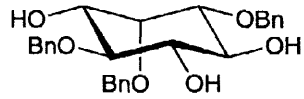
**Abstract** D-Glucose was converted into the propargylsilane aldehyde **3**, which underwent ring closure with retention of silicon, in the presence of camphorsulfonic acid, to give **5**, and this was elaborated, via ketone **22**, into **2**, which had previously been transformed into D-*myo*-inositol-1,4,5-tris(dihydrogenphosphate). A crucial step in the synthesis is the stereoselective reduction of **22** with $Bu_2SnCl_2/Bu_2SnH_2$, a reagent system that shows a strong preference for generating equatorial alcohols. 

D-*Myo*-Inositol-1,4,5-tris(dihydrogenphosphate) (**1**) has a very prominent role in the biochemistry of calcium metabolism,[1] and the compound, as well as numerous analogs — including versions tethered[2] to affinity probes — has been the object of much synthetic work.[1] Other phosphorylated inositols have, likewise, been intensively studied.[1] A resolution is usually employed in the synthesis of optically pure **1**,[1,3] although




**1**




**2**

there are a few reports where it has been obtained from compounds in the chiral pool, and (-)-quinic acid,[4] D-pinnitol,[5] and glucose[6,7] have been used for this purpose. In the case of glucose, the carbocyclic skeleton has been generated by Ferrier[8] rearrangement. We describe a synthesis from D-glucose of the tri-*O*-benzylinositol **2**, which is convertible[9] into **1** in two efficient steps. Our synthesis is based on an unusual ene reaction, and the use of $Bu_2SnCl_2/Bu_2SnH_2$[10] for converting a hindered cyclohexanone into the corresponding *equatorial* alcohol. In principle, many other[11] inositol phosphates should be available by the present method, but we have not yet tested these possibilities.

Our plan was to convert D-glucose into acetylenic aldehyde **3**, in the expectation that the presence of the silyl group would facilitate a heteroatom version of the ene reaction (e.g., **3** → **4**), with transfer of silicon from carbon to oxygen, or simply with loss of silicon.[12] In the event, neither pathway is followed; the silicon unit is retained on carbon, and is actually required[15] for efficient ring closure (which occurs in the sense **3** → **5**).

Aldehyde **3** was prepared from readily available 2-propenyl 3-*O*-benzyl-D-glucopyranosides (**6**)[17] in

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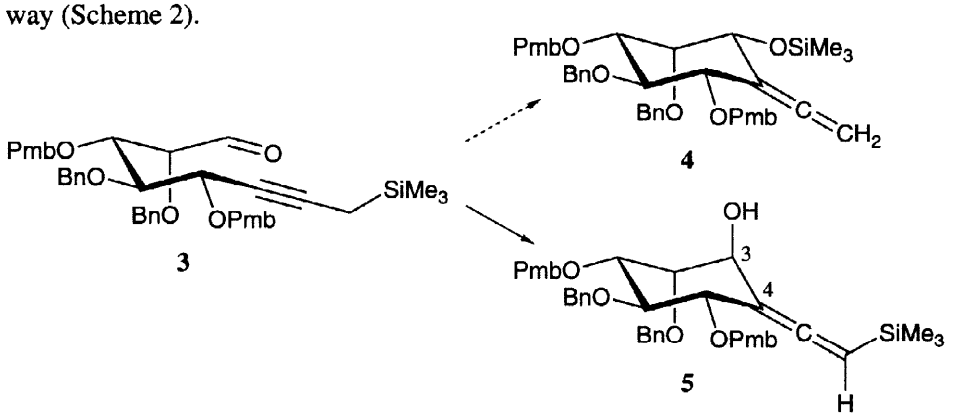
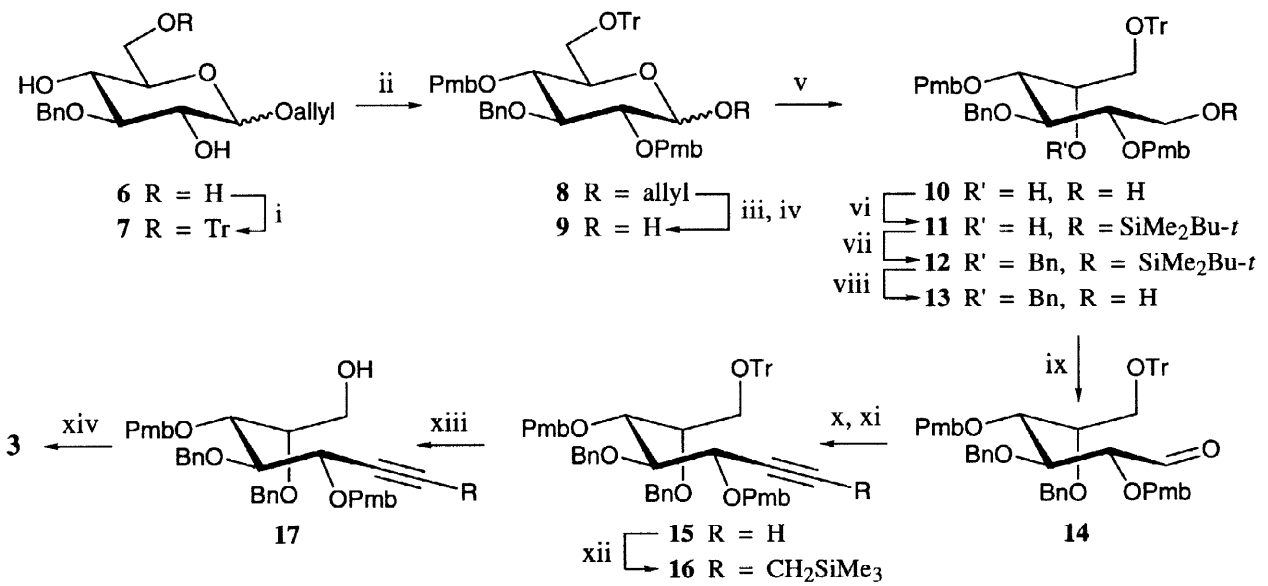
the following way (Scheme 2).




**Scheme 1** Pmb = *p*-methoxybenzyl

The C(6) primary hydroxyl was protected by tritylation (TrCl, DMAP, 110 °C, 80%; **6** → **7**), and the remaining hydroxyls were masked as *p*-methoxybenzyl ethers [*p*-$MeOC_6H_4CH_2Cl$ (PmbCl), NaH, 91%; **7** → **8**]. At that point, deallylation (**8** → **9**), best done by successive treatment with *t*-BuOK/DMSO (100 °C) and $HgCl_2$/HgO/acetone/water[18] (88% overall), yielded a mixture of epimeric lactols, and these were reduced ($LiAlH_4$, 93%) to the glucitol **10**. Next, the primary hydroxyl was protected (*t*-$BuMe_2SiCl$, $Et_3N$, DMAP, 99%) so that the remaining secondary hydroxyl could be benzylated (NaH, BnBr, 96%) (**10** → **11** → **12**).




**Scheme 2** *Reagents and conditions*: i, TrCl, Pyridine, DMAP, 110 °C, 8 h, 80%; ii, NaH, PmbCl, 0 °C to room temperature, then reflux, 24 h, 91%; iii, *t*-BuOK, DMSO, 100 °C, 1 h; iv, $HgCl_2$, HgO, acetone-water, room temperature, 4 h, 88% from **8**; v, $LiAlH_4$, THF, 0 °C to room temperature, 4 h, 93%; vi, *t*-$BuMe_2SiCl$, $Et_3N$, DMAP, $CH_2Cl_2$, room temperature, 16 h, 99%; vii, NaH, BnBr, 0 °C to room temperature, then reflux, 24 h, 96%; viii, $Bu_4NF$, THF, room temperature, 4 h, 92%; ix, Swern oxidation, 89%; x, $Ph_3P$, $CBr_4$, $CH_2Cl_2$, -20 °C, then cool to -60 °C and add $Et_3N$, then warm to room temperature, 83%; xi, *n*-BuLi, THF, -78 °C, 85%; xii, *n*-BuLi, THF, -78 °C, $Me_3SiOSO_2CF_3$, room temperature, overnight, 82%; xiii, CSA, MeOH, $CH_2Cl_2$, room temperature, 36 h, 94%; xiv, Swern oxidation, 92%.

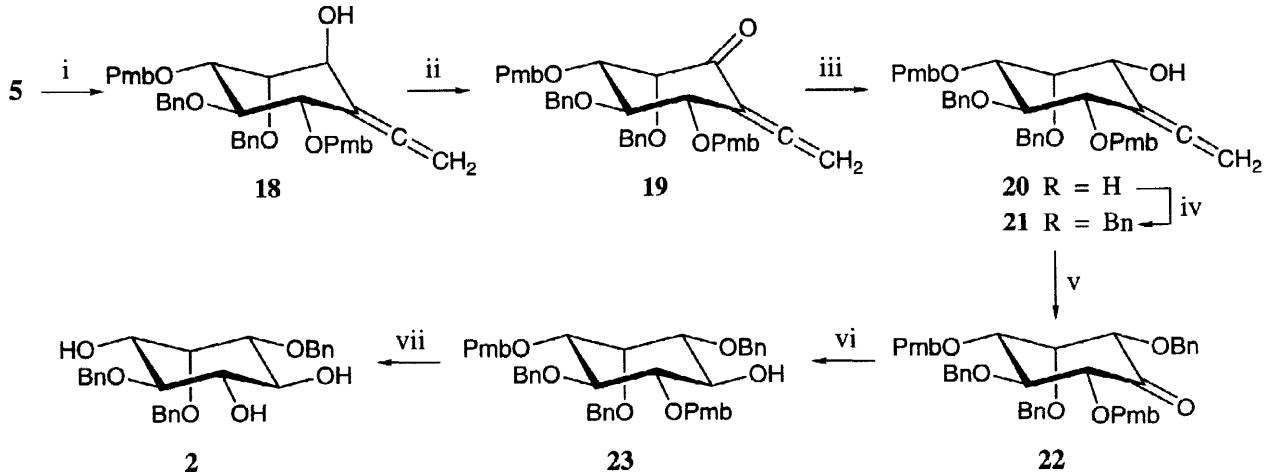
Removal of the silicon protecting group (**12** → **13**, $Bu_4NF$, 92%) and Swern oxidation (**13** → **14**, 89%) now set the stage for elaboration of the acetylenic unit. This was initiated (**14** → **15**) by a standard two-step sequence:[19] conversion of the aldehyde into a 1,1-dibromoalkene ($Ph_3P$, $CBr_4$, 83%), followed by treatment

with *n*-BuLi (85%). Finally, deprotonation of the resulting terminal acetylene with *n*-BuLi, and reaction with $Me_3SiCH_2OSO_2CF_3$, served to complete the propargyl silane unit (**15** → **16**, 82%). At that point, detritylation [**16** → **17**, camphorsulfonic acid (CSA), MeOH, 94%] was accomplished without affecting the silane, and Swern oxidation (92%) gave aldehyde **3**.

When this compound was exposed to the action of CSA in PhMe at room temperature, it was converted smoothly (91%) into **5**, whose stereochemistry was assigned by comparison of its $^1H$ NMR spectrum with that of the fully benzylated analog (Bn instead of Pmb in **5**). The latter, which was made by a similar route to that just described, is a crystalline compound whose structure was established by X-ray analysis. When the silicon group is absent (H instead of $SiMe_3$ in **3**), little, if any cyclization occurred in the presence of CSA.[20]

In order to convert **5** into **2**, our main tasks were to invert the stereochemistry at C(3), benzylate the resulting alcohol, cleave the exocyclic double bond at C(4) to a ketone, and then reduce that ketone to an equatorial alcohol. These operations proved unexpectedly troublesome, but each step was eventually achieved by a judicious choice of reagents and the order of using them.

Treatment of **5** with $K_2CO_3$ in MeOH-THF at reflux gave the desilylated allene **18** (86%), and this could be oxidized to the corresponding ketone **19**, best using the Dess-Martin reagent (84%). Reduction ($NaBH_4$, $CeCl_3$, -78 °C to room temperature, 92%) gave the inverted alcohol **20**, which was then benzylated (**20** → **21**, NaH, BnBr, 87%). Ozonolytic cleavage ($O_3$, $CH_2Cl_2$-pyridine,[22] -78 °C) of the allene, using a deficiency of ozone, afforded ketone **22** [81% after correction for recovered **21** (23%)]. Reduction in the appropriate stereochemical sense (to an *equatorial* alcohol) required extensive effort,[23] until the $Bu_2SnCl_2/Bu_2SnH_2$[10] combination was tried. Under the proper conditions[24] (PhMe, reflux) reduction occurred in the desired manner (**22** → **23**, 88%). Most reagents we tried delivered the hydride equatorially,




**Scheme 3** *Reagents and conditions*: i, $K_2CO_3$, 3:1 MeOH-THF, reflux, 4 h, 86%; ii, Dess-Martin periodinane, $CH_2Cl_2$, 30 min, 84%; iii, $NaBH_4$, $CeCl_3.7H_2O$, 1:10 THF-MeOH, -78 °C to 0 °C, 92%; iv, NaH, BnBr, 0 °C to room temperature, then reflux, 24 h, 87%; v, $O_3$ (<1 equiv.), 1:6 pyridine-$CH_2Cl_2$, -78 °C, 81% after correction for recovered **22** (23%); vi, 1:1 *n*-$Bu_2SnCl_2$/*n*-$Bu_2SnH_2$, PhMe, reflux, 24 h, 88%; vii, DDQ, 1:20 water-$CH_2Cl_2$, room temperature, 4 h, 70%.

and the use of the $Bu_2SnCl_2/Bu_2SnH_2$, as well as the sensitivity of the outcome to the reaction temperature,[24] is worthy of note. Finally, removal of the *p*-methoxybenzyl groups (DDQ, 70%) afforded the target compound (**23** → **2**).[25]

All new compounds, were satisfactorily characterized by spectroscopic methods, including high resolution mass measurements.

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25 Our material had: mp 122-123 °C, $[\alpha]_D$ = + 10.3° (c 1.73 in $CHCl_3$), [lit. (reference 26) mp 121-123 °C, $[\alpha]_D^{25}$ = +10° (c = 1, $CHCl_3$); lit.(reference 27) mp 117-119 °C, $[\alpha]_D^{16}$ = +15.5° (c 1, $CHCl_3$); lit.(reference 6) mp 117-119 °C, $[\alpha]_D^{24}$ = +12° (c = 0.79, $CHCl_3$).

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