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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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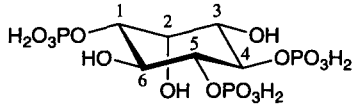
Abstract D-Glucose was converted into the propargylsilane aldehyde **3**, which underwent ring closure with retention of silicon, in the presence of camphorsulfonic acid, to give **5**, and this was elaborated, via ketone **22**, into **2**, which had previously been transformed into D-*myo*-inositol-1,4,5-tris(dihydrogenphosphate). 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



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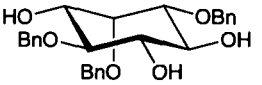

2

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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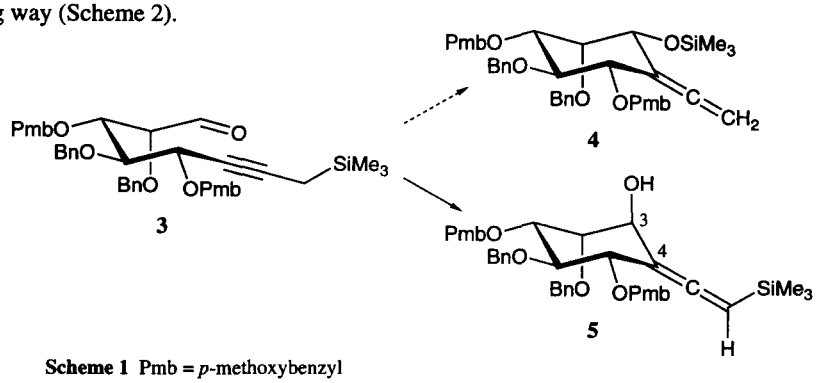
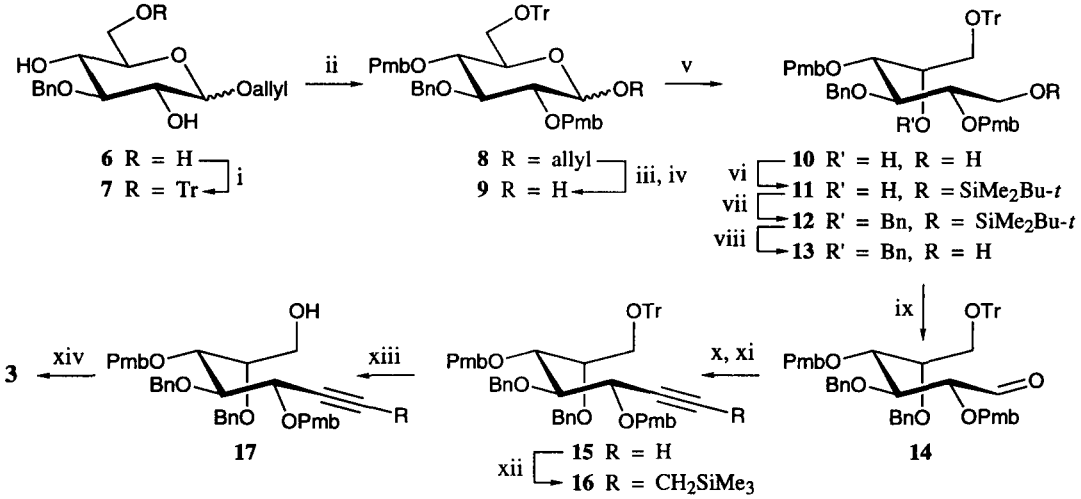
the following way (Scheme 2).



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%.

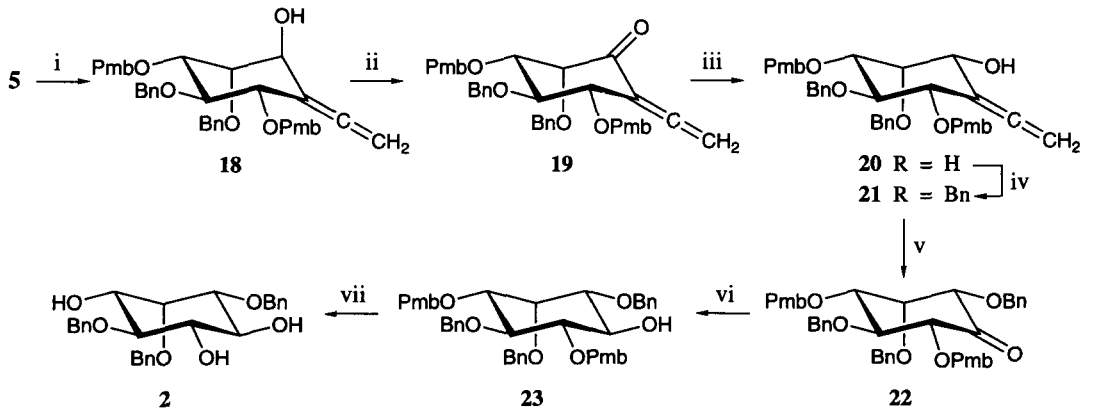
Removal of the silicon protecting group (**12** → **13**, Bu_4NF, 92%) and Swern oxidation (**13** → **14**, 89%) now set the stage for elaboration of the acetylenic unit. This was initiated (**14** → **15**) by a standard two-step sequence:[19] conversion of the aldehyde into a 1,1-dibromoalkene (Ph_3P,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

1 (a) Billington, D. C. *The Inositol Phosphates*, VCH: Weinheim, 1993. (b) Potter, V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933-1972.
2 Prestwich, G. D. *Acc. Chem. Res.* **1996**, *29*, 503-513.
3 E.g. Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 4995-5026.
4 Falk, J. R.; Yadagiri, P. *J. Org. Chem.* **1989**, *54*, 5851-5852.
5 Tegge, W.; Ballou, C. E. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 94-98.
6 Sato, K.; Bokura, M.; Taniguchi, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1633-1640.
7 Tethered versions of **1** have also been made from glucose: see reference 2.
8 Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779-2831.
9 Racemic series: Yu, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979-982. Optically active series: Dreef, C. E.; Tuinman, R. J.; Elie, C. J. J.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 395-397.
10 (a) Martin, S. F.; Josey, J. A.; Wong, Y.-L.; Dean, D. W. *J. Org. Chem.* **1994**, *59*, 4805-4820. (b) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049-4051. (c) For the composition of the reagent, see: Davies, A. G.; Osei-Kissi, D. K. *J. Organomet. Chem.* **1994**, *474*, C8-C10.
11 *Cf.* Chung, S.-K.; Chang, Y.-T.; Sohn, K.-H. *J. Chem. Soc., Chem. Commun.* **1996**, 163-164.
12 α,β-Unsaturated ketones incorporating a suitably located propargylsilane unit undergo cyclization with loss of silicon (see reference 13). For a single example of cyclization onto a carbonyl, also with loss of silicon, see reference 14.
13 (a) Schinzer, D.; Dettmer, G.; Ruppelt, M.; Sólyom, S.; Steffen, J. *J. Org. Chem.* **1988**, *53*, 3823-3828. (b) Schinzer, D.; Kabbara, J.; Ringe, K. *Tetrahedron Lett.* **1992**, *33*, 8017-8018. (c) Schinzer, D.; Ringe, K. *Synlett* **1994**, 463-464. (d) Schinzer, D.; Ruppelt, M. *Ber.* **1991**, *124*, 247-248.
14 Schinzer, D.; Panke, G. *J. Org. Chem.* **1996**, *61*, 4496-4497.
15 For cyclizations of allenylsilanes that occur with retention of silicon, and for which the presence of the silicon substituent is essential, see reference 16.
16 Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem.* **1995**, *60*, 5366-5367.
17 Three steps from D-glucose (76%): Fukase, K.; Matsumoto, T.; Ito, N.; Yoshimura, T.; Kotani, S.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2643-2654.
18 Gigg, R.; Warren, C. D. *J. Chem. Soc., (C)* **1968**, 1903-1911.
19 Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529-3530.
20 We also examined other conditions: 140 °C, *p*-xylene; Me_2AlCl, CH_2Cl_2, -78 °C; CF_3CO_2H, CH_2Cl_2 or $CHCl_3$, room temperature; camphorsulfonic acid, CH_2Cl_2 or $CHCl_3$, room temperature.
22 *Cf.* (a) Slomp, G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915-921. (b) Boddy, I. K.; Boniface, P. J.; Cambie, R. C.; Craw, P. A.; Huang, Z.-D.; Larsen, D. S.; McDonald, H.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1984**, *37*, 1511-1529.
23 Various versions of the Meerwein-Ponndorf-Verley reduction gave complex mixtures; DIBAL, DIBAL/methylaluminium bis(2,6-di-*tert*-butylphenoxide) [MAD], $NaBH_4$/MAD and Bu_4NBH_4/MAD gave the axial alcohol. For other examples of reduction to equatorial alcohols, see Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031; Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.-e.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131-7134.
24 Bu_2SnH_2, THF, room temperature: axial:equatorial alcohols = 2:1; Bu_2SnH_2/Bu_2SnCl_2, THF, reflux: axial:equatorial alcohols = 1:2 (80%); Bu_2SnH_2/Bu_2SnCl_2, PhMe, reflux: only equatorial alcohol. We did not try Ph_3SnH or Bu_3SnH (*cf.* Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 426-427, footnote 29).
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, $CHCl_3$).
26 Desai, T.; Gigg, J.; Gigg, R.; Payne, S. *Carbohydr. Res.* **1992**, *225*, 209-2228.
27 Ozaki, S.; Kondo, Y.; Shiotani, N.; Ogasawara, T.; Watanabe, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 729-737.