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Efficient, Diastereoselective Chemical Synthesis of a β-Mannopyranosyl Phosphoisoprenoid

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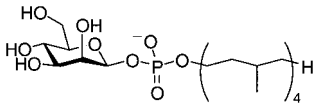
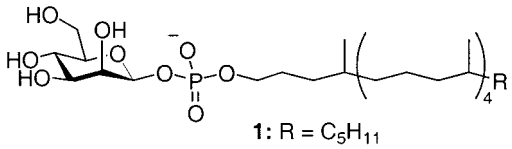
ABSTRACT



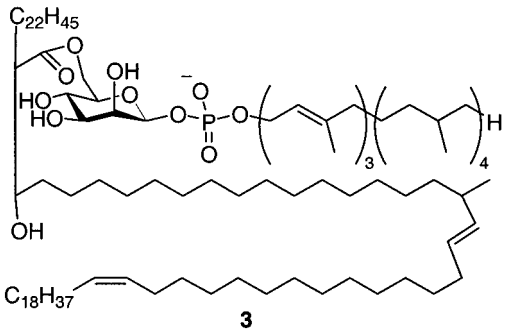
Tetrabutylammonium benzyl dihydrophytylphosphate was coupled to *S*-phenyl 2,3-di-*O*-benyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside *S*-oxide on activation with triflic anhydride in toluene at −78 °C to give the corresponding β-mannosyl phosphate in 56% yield with no detectable formation of the α-anomer. Treatment with sodium in liquid ammonia then afforded the unprotected β-mannosyl phosphoisoprenoid.

Two mycobacterial antigens, **1** and **2**, were recently isolated from the cell walls of *Mycobacterium avium* and *M. tuberculosis*, respectively, and their structures determined by a combination of hydrolysis, GC/MS, and MS/MS experiments.



1: R = C_5H_{11}
2: R = C_7H_{15}

These substances are unusual among mycobacterial isoprenoids insofar as their alkyl chains are completely saturated and the isoprene rule is violated at both ends of the chain.[1] They are, nevertheless, related to a partially saturated β-mannosyl heptaprenyl phosphate from *M. smegmatis* (**3**) that serves as a carrier of mycolic acid[2] and to a related β-mannosyl decaprenyl phosphate, from the same organism, thought to be an intermediate in α-1→6 linked mannooligosaccharide biosynthesis.[3] Human Cd1c-restricted T-cells were shown to be responsive to **1**−**3** and to a range of β-linked mannosyl phosphoisoprenoids, synthesized enzymically from phosphopolyprenols and GDP mannose, but not to a comparable series of β-glucosyl phosphoisoprenoids. Additionally, the T-cell response was shown to be inversely proportional to the length of the phosphoisoprenoid chain, preferring a C_{35} derived system over a C_{55} one and not recognizing a C_{95} dolicol based β-mannosyl phosphoisoprenoid, and to require full saturation of the aliphatic chain.[1]



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The unusual structural features of **1** and **2**, together with their apparent roles in cell−cell recognition and human mycobacterial infection, more than justify any synthetic effort, but interest in this exercise is especially heightened

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(3) Yokoyama, K.; Ballou, C. E. *J. Biol. Chem.* **1989**, *264*, 21621−21628.

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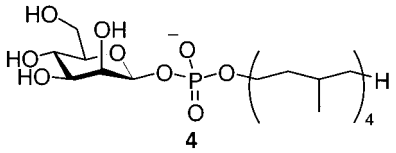
by the presence of the difficult and sensitive β-mannosyl phosphate linkage. Here, through the efficient and highly diastereoselective synthesis of the model phosphoisoprenoid **4**, we demonstrate for the first time that such β-mannosyl phosphates may be readily accessed by adaptation of our general β-mannoside synthesis.[4−6]



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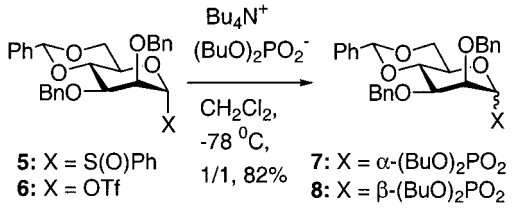
As β-mannosyl phosphates had frustrated the efforts of several other groups, giving, for example, single digit yields by the Schmidt trichloroacetimidate method,[7] and escaping others altogether,[8,9] we saw fit to begin our investigation with a model study. To this end dibutylphosphoric acid was converted to its tetrabutylammonium salt and allowed to react, at −78 °C, with the mannosyl sulfoxide **5**,[5] which had been previously activated with triflic anhydride and, so,[10] converted to the α-triflate **6**. After workup, a 1/1 mixture of the anomeric phosphates **7** and **8** was obtained from which the desired β-isomer was isolated in 41% yield (Scheme 1).

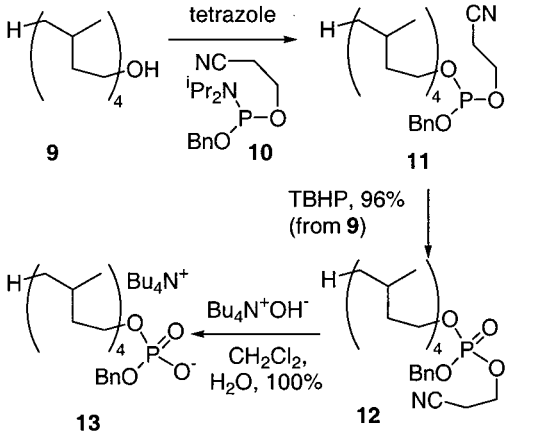
Scheme 1. Synthesis of the Dibutyl Phosphates **7** and **8**



The anomeric configuration of **7** and **8** was readily established by comparison of the $^1J_{CH}$ coupling at the anomeric carbons[11] (176.7 and 161.4 Hz, respectively), as well as by the NOE correlation between H's 1, 3, and 5 in **8**. Moreover, H5 in the 4,6-*O*-benzylidene-protected β-mannoside **8** was found to resonate at δ 3.47 in $CDCl_3$, which is a characteristic feature of β-mannosides with this protecting system.[5] Given the difficulties previously recorded in the literature for the synthesis of β-mannosyl phosphates, as well as their reported propensity for anomerization to the α-anomer, the 41% yield of **8** as an isolable, stable substance was considered very encouraging.

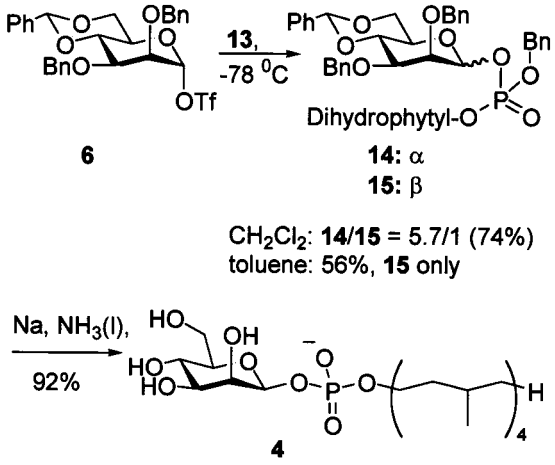
Commercial phytol, a mixture of isomers, was reduced to dihydrophytol (**9**) with hydrogen over Adams' catalyst quantitatively. This isomeric mixture was then coupled to **10**, itself obtained in 94% yield from commercial 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite and benzyl alcohol in the presence of Hunig's base, and tetrazole to give **11**, followed by oxidation to **12** with *tert*-butyl hydroperoxide in 96% yield for the two-step sequence (Scheme 2). Treatment of **12** with tetrabutylammonium hydroxide in a dichloromethane/water biphasic system then afforded salt **13** quantitatively.

Scheme 2. Synthesis of the Ammonium Phosphate **13**



Coupling of **13** with preformed **6** in dichloromethane at −78 °C was slower than the analogous coupling with dibutyl phosphate and resulted in the isolation of 63% of the α-anomer **14** and a disappointing 11% of the desired **15**. Nevertheless, **15** was isolable and did not undergo ready epimerization to **14** unless exposed to acid (Scheme 3). Both anomers, **14** and **15**, were approximately 1/1 mixtures of

Scheme 3. Synthesis of the β-Mannosyl Phosphoisoprenoid **4**



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(5) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(6) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436.
(7) Schmidt, R. R.; Stumpp, M. *Liebigs* **1984**, 680−691.
(8) Garcia, B. A.; Gin, D. Y. *Org. Lett.* **2000**, *2*, 2135−2138.
(9) The β-selective (4/1) phosphorylation of 2,3,4,6-tetra-*O*-acetylmannopyranose with limiting diphenyl chlorophosphidate has been reported: Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169−185. It is highly unlikely that this method can be extended to the significantly less reactive dialkyl chlorophosphidates required for the synthesis of the present targets. Other groups typically report α-selective phosphorylation of mannose in this type of process even with diphenyl chlorophosphidate, e.g., Boger, D. L.; Teramoto, S.; Zhou, J. *J. Am. Chem. Soc.* **1995**, *117*, 7344−7356.
(10) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.
(11) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

diastereomers at phosphorus, and in the case of **15**, these could be separated even if the configuration was not assigned. Anomeric configurations were assigned similarly to **7** and **8** (vide supra). We reasoned that the poor diastereoselectivity observed was a function of the low nucleophilicity of **13** and that this might be countermanded by moving to a less polar solvent. This would enhance the stability of the mannosyl triflate **6** and so suppress α-selective, dissociative mechanisms in favor of β-selective, associative processes. In the event, in toluene at −78 °C, the reaction was completely selective and afforded only **15** in 56% yield (Scheme 3), with the mass balance being made up mainly of the hydrolysis product of **6**. Finally, deprotection was best achieved by exposure of **15** to sodium in liquid ammonia and quenching with ammonium chloride. The target molecule (**4**) was isolated, as a single anomer, in the form of its sodium salt following partitioning of the residue left on evaporation of the ammonia between butanol and water and filtration of the butanol phase over Celite (Scheme 3). The anomeric configuration of **4** was confirmed by the NOE correlation of its anomeric hydrogen to both H3 and H5 as well as by its anomeric $^1J_{CH}$ coupling of 157.6 Hz.

The question obviously arises as to why the β-mannosyl triphosphates **8** and **15** described here are configurationally stable and may be subject to silica gel chromatography whereas Schmidt found very closely related β-mannosyl triphosphates to be very rapidly equilibrated to the α-anomer simply on standing in deuteriochloroform.[7] The answer, we believe, lies in our use of the 4,6-*O*-benzylidene protecting group as opposed to the perbenzylated donors employed by Schmidt. We have commented numerous times on the importance of this protecting group in our general β-mannosylation.[4,5,10] We believe that it is the same torsionally disarming[12] features of this group that are responsible for the stabilization of triphosphates **8** and **15**; the beneficial features of this protecting group in controlling glycosylation and anomeric configuration cannot be overstated.

In summary, we have demonstrated that β-mannosides of saturated phosphoisoprenoids may be readily obtained by our adaptation of our β-mannose selective variant[4−6] of the Kahne sulfoxide glycosylation.[13−15] We anticipate that this work will open the way for the synthesis of further analogues of **1**−**3** in significant quantities.

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Supporting Information Available: Synthesis and characterization of all new molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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