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# Stereoselective synthesis of farnesylphosphoryl β-D-arabinofuranose

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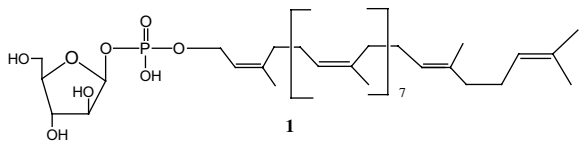
**Abstract**—Decaprenylphosphoryl β-D-arabinofuranose (DPA) is a key arabinose donor in mycobacteria. In an effort to establish a practical synthetic scheme for DPA, the synthesis of nerylphosphoryl and farnesylphosphoryl β-D-arabinofuranoses has been developed. The products were obtained by coupling of a suitably protected β-D-arabinofuranosyl phosphate intermediate with activated forms of the $C_{10}$ nerol and $C_{15}$ *trans*,*trans*-farnesol and subsequent deprotection.


The human pathogen *Mycobacterium tuberculosis* causes tuberculosis and is responsible for the most deaths of millions of people by any single infectious agent.[1] The global rise in tuberculosis and drug-resistant *M. tuberculosis*[2] require the development of new drug targets and drugs. The D-arabinan segments of the mycobacterial cell wall are excellent targets for new drug development due to the xenobiotic status of D-arabinofuranose.[3,4] A key mycobacterial arabinose donor, β-D-arabinofuranosyl-1-monophosphoryldecaprenol (DPA; **1**, Fig. 1) was found in the lipid extracts of *Mycobacterium smegmatis* and implicated in the biogenesis of the two major cell wall polysaccharides arabinogalactan (AG) and lipoarabinomanan (LAM).[5] In order to study the biosynthesis of AG and LAM in mycobacteria, it was necessary to develop a synthetic scheme which will provide sufficient amounts of this important donor. The only published procedures for DPA[4,6] (which were based on phosphorimidate intermediates[7]) gave an anomeric mixture in which the inactive α-anomer was favored by a 5:1 ratio. In an effort to reverse the anomeric preference in the synthesis of DPA we explored other synthetic schemes.

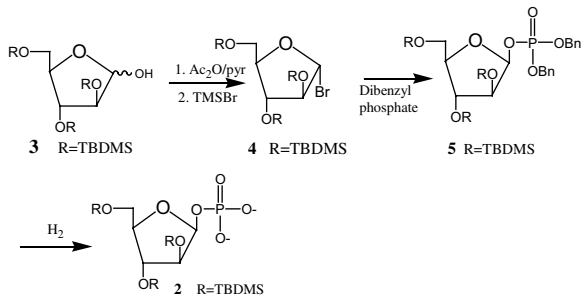



**1**

**Figure 1.** The structure of DPA.

Synthesis of polyprenylphosphoryl sugars was first described by Warren and Jeanloz,[8] who coupled a fully acetylated α-D-mannopyranosyl phosphate with ficaprenol in the presence of dicyclohexylcarbodiimide or triisopropylbenzenesulfonyl chloride as an activating agent. This approach has later been improved by coupling of the sugar phosphate with a polyprenyl trichloroacetimidate intermediate.[9] The improved method has been used successfully in the synthesis of various polyprenylphosphoryl hexoses, but has never been applied to the synthesis of the analogous pentose derivatives.

Our approach to the synthesis of DPA is based on the stereoselective synthesis of β-D-arabinofuranosyl phosphate (**2**, Scheme 1) and coupling it to an activated form of the polyprenol as described above.[9] In order to study the applicability of this approach[9] to the synthesis of DPA, we have chosen to employ the more abundant *E*,*E*-farnesol as a model compound.




**3** R=TBDMS **4** R=TBDMS **5** R=TBDMS

**2** R=TBDMS

**Scheme 1.** Synthesis of β-D-arabinofuranosyl phosphate.

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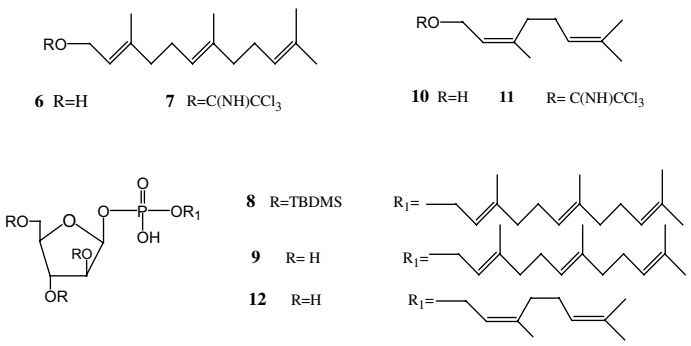


**Scheme 2.** Synthesis of *E,E*-farnesylphosphoryl and nerylphosphoryl β-D-arabinofuranoses.

Anomeric stereoselectivity in the synthesis of **2** can be achieved by selecting suitable protecting groups. Selective manipulation of protecting groups that led to the stereoselective synthesis of β- and α-D-arabinose 1,5-diphosphates has already been demonstrated by Maryanoff et al.:[10] Phosphorylation of a 2,3-di-*O*-benzyl-D-arabinofuranosyl bromide derivative with dibenzyl phosphate gave mainly (92%) the β-anomer. On the other hand, when the analogous 2,3-di-*O*-acetyl product was employed, the major product was the α-anomer. However, the employment of non-participating benzyl groups in the stereoselective synthesis of the β-phosphate as described by Maryanoff et al.[10] is not applicable to our work since the removal of the benzyl groups from the phosphate moiety (Scheme 1) will result in the loss of the other benzyl groups as well. Moreover, the de-benzylation of the final product by catalytic hydrogenation will also reduce the double bonds in the lipid moiety. Instead, we have selected a different non-participating group for our synthetic scheme, the *tert*-butyl-dimethylsilyl group (TBDMS). The TBDMS group (which has already been used before in the synthesis of DPA[4,6]) can be removed by mild treatment with ammonium fluoride.

Acetylation of 2,3,4-tri-*O*-TBDMS-D-arabinofuranose (**3**, Scheme 1)[4] with acetic anhydride and pyridine followed by treatment with trimethylsilyl bromide in methylene chloride gave the α-bromide **4** (as judged by $^1$H NMR). Treatment of the bromide **4** with dibenzyl phosphate in the presence of triethyl amine gave a mixture of the anomeric phosphates (77% yield, based on the starting material **3**) in which the desired β-anomer (**5**) was favored by a 4:1 ratio as shown by $^1$H NMR.[11] Column chromatography on silica gel (using 3:1, petroleum ether–ethyl acetate for elution) gave fractions, which contained a higher proportion of the β-anomer but complete separation of the two anomers could not be achieved at that point. Catalytic hydrogenolysis of the dibenzyl phosphate **5** with Pd–C 10% catalyst in the presence of triethyl amine gave a product, which was mostly in the β-anomeric form (**2**; 90% as shown by $^1$H NMR). Coupling of the triethylamine salt of **2** (obtained by drying the hydrogenolysis mixture) with *E,E*-farnesol (**6**, Scheme 2) proceeded by the published synthetic scheme.[9] Our first attempt to convert *E,E*-farnesol (**6**) to the corresponding trichloroacetimidate derivative **7**, using the published procedure (which employs a catalytic phase transfer system) was unsuccessful. The product was obtained as shown by TLC, but it decomposed during the work-up. The synthesis of **7** was accomplished only when the reaction was carried out under anhydrous conditions: treatment of **6** with trichloroacetonitrile in dichloro methane in the catalytic presence of DBU.[12] The product **7** was immediately treated with the triethylamine salt of **2** in toluene (65 °C, 3 h) to give the product (**8**), which was purified by column chromatography and obtained in 33% yield (based on the dibenzyl phosphate intermediate **5**; only the β-anomer was isolated). Finally, deprotection of **8** with ammonium fluoride (in 15% methanolic ammonia, 65 °C) gave *E,E*-farnesylphosphoryl β-D-arabinofuranose (**9**), which was also purified by column chromatography (the experimental procedure for the synthesis of the products **7**–**9** is described in Ref. 13). The physical data[14] of the product are in agreement with the structure and with the published results (obtained from the supplementary data of Ref. 4).

Likewise, conversion of the $C_{10}$-nerol (**10**) (which contains a *cis*-α-isoprene unit in contrast to the *trans* configuration of farnesol) into the corresponding trichloroacetimidate intermediate (**11**), followed by coupling to the triethylamine salt of **2** and subsequent deprotection, gave the final product **12**.[15]

## Acknowledgements

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11. The α-anomer appears as a doublet ($J_{1,2}$ = 0 Hz, $J_{1,P}$ = 3.6 Hz) and the β-anomer signal appears as a pair of doublets ($J_{1,2}$ = 3.3 Hz, $J_{1,P}$ = 5.1 Hz).
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13. Synthesis of **9**. To a cold (ice-bath) solution of *E*,*E*-farnesol (90 mg) in methylene chloride (1 mL) was added trichloroacetonitrile (60 μL) and DBU (7 μL). The mixture was stirred at room temperature for 90 min and dried. The residue was chromatographed on silica gel (60 Å, 70–230 mesh). Elution with petroleum ether–ethyl acetate, 10:1 gave the pure trichloroacetimidate intermediate **7** (90 mg). A solution of **7** in toluene (2.5 mL) was added to the triethyl amine salt of **2** (110 mg) and the mixture was stirred at 65 °C for 3 h. It was then dried and the residue was chromatographed on silica gel. The product (**8**) was eluted with a mixture of 50:10:3, methylene chloride–methanol–ammonium hydroxide (42 mg).The product (**8**, 60 mg) was deprotected by treatment with ammonium fluoride (200 mg) and 15% methanolic ammonium hydroxide (4 mL) in methanol (10 mL) at 65 °C for 22 h. The mixture was cooled and diluted with methylene chloride. The precipitate was filtered off and washed with methylene chloride–methanol, 5:1.The filtrate was dried and the residue was chromatographed on silica gel. The product was eluted with a mixture of 65:125:4, methylene chloride–methanol–ammonium hydroxide.
14. Physical data for **9**. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 5.47 (t, $J$ = 4.5 Hz, 1H), 5.40 (t, $J$ = 6.7, 1H), 5.10 (m, 2H), 4.43 (t, $J$ = 6.0 Hz, 2H), 4.08 (t, $J$ = 7.2 Hz, 1H), 3.97 (m, 1H), 3.76 (m, 2H), 3.61 (dd, $J$ = 4.5, 12.0 Hz, 1H), 2.02 (m, 8H), 1.69 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H). Mass spectrometry-electrospray negative ion: 433.13 (M−1); electrospray positive ion: 456.93 ($M+Na^+$). Optical rotation: $[\alpha]_D$ −12.5 (*c* 0.75, methanol).
15. The product **12** was obtained by the same procedure described for **9**. $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ = 5.45 (t, $J$ = 4.8 Hz, 1H), 5.36 (t, $J$ = 5.9 Hz, 1H), 5.05 (m, 1H), 4.08 (m, 2H), 3.78 (m, 2H), 3.60 (dd, $J$ = 4.5, 12 Hz, 1H), 3.30 (m, 2H), 2.06 (m, 4H), 1.72 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H).