Synthesis of putative chain terminators of mycobacterial arabinan biosynthesis

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The synthesis of a variety of arabinose derivatives that have been modified at C-5 was achieved from D-arabinose. The 5-fluoro and 5-methoxy compounds were converted into the corresponding farnesyl phosphodiesters as putative chain terminators of mycobacterial arabinan biosynthesis. Biological testing of these materials revealed no effective anti-mycobacterial activity.

Introduction

Mycobacterium tuberculosis and *Mycobacterium leprae*, the bacteria responsible for tuberculosis and leprosy respectively, are probably the most well-known of the pathogenic strains of mycobacteria. Recently, tuberculosis (TB) in particular has 're-appeared' as a major threat to human health. Indeed one third of the world's population is currently estimated to be infected with tuberculosis, and the disease kills more than three million people each year. Although there are a variety of drugs available for the treatment of TB, strains of these bacteria have already developed resistance, and there is therefore clearly an urgent need to develop new therapeutic agents active against TB, and indeed major initiatives have been set up around the world to fund drug discovery and facilitate drug screening for useful bioactivity.[1]

Inhibition of the biosynthesis of the mycobacterial cell wall represents an exciting therapeutic opportunity for the development of new drugs to combat TB.[2] In particular, assembly of the carbohydrate sections of the cell wall, many of the structures of which are unique to mycobacteria, has been a field of intense interest over recent years. Several research groups have to date been attempting to inhibit mycobacterial cell wall synthesis biosynthesis by inhibition of particular enzymes involved in the proposed biosynthetic pathways. These include attempted inhibition of glycosyl transferases[3] and also of the Gal*p*–Gal*f* mutase enzyme which catalyses a crucial pyranose–furanose isomerisation during assembly of the galactan cell wall component.[4] However, the design of such inhibitors can be problematic, since in several cases little is known about the structure of the precise enzymes involved. We have therefore recently initiated a research program aimed at developing a new strategy for the inhibition of poly- and oligosaccharide biosynthesis by a different mode of action.[5] This alternative strategy is to attempt to invoke chain termination of oligosaccharide biosynthesis. A potential advantage of such an approach is that one would not have to rely on precise structural information about specific enzymes in particular biochemical pathways, one may be able to simply exploit structural analysis of the key targeted oligosaccharide structure, although in certain cases an understanding of the relevant biosynthetic pathway would also be required.

Chain-termination of oligonucleotide synthesis originally developed by Sanger *et al.*[6] as a means of DNA sequencing has subsequently found routine and widespread use as a means of interfering with oligonucleotide synthesis, and, moreover, has become the molecular basis of anti-viral therapies in clinical use.[7] However, although chain-termination processes have been implicated in the biological effects of a variety of monosaccharide derivatives on mammalian glycoconjugate[8] and glycosoaminoglycan biosynthesis,[9] a chain termination approach has not yet been widely promulgated as a strategy for the development of new classes of inhibitors of the biosynthesis of pathogenic oligosaccharides. This research paper concerns investigations into the feasibility of using a chain termination strategy as a method for developing inhibitors of the biosynthesis of key components of the mycobacterial cell wall.

Two major components of the mycobacterial cell wall are arabinogalactan and lipoarabinomannan, both of which contain large domains of D-arabinofuranose units that are predominantly linked α(1–5).[10] It has previously been demonstrated that biosynthesis of these arabinan structures is crucial for bacterial survival[11] and since arabinofuranose does not appear in mammalian oligosaccharides, it has been proposed that inhibition of arabinan biosynthesis represents a potentially selective therapeutic opportunity. Mycobacterial arabinan is assembled stepwise by arabinosyl transferases that use a decaprenol β-D-arabinofuranosyl phosphodiester as the glycosyl donor. With respect to a chain termination approach, putative chain terminators of mycobacterial arabinan biosynthesis are therefore arabinose-derived monosaccharides and phosphodiesters which are precursors to, or analogues of, this decaprenol donor in which the 5-hydroxyl that is essential for further elongation of the oligosaccharide chain has been replaced by a non-extendable isosteric group.[12] Although it has been proposed that the *arabino* decaprenol phosphodiester donor is actually biosynthesised from a *ribo* precursor,[13] at the outset of this project it was not clear precisely when epimerisation of the 2-hydroxyl occurs,[14] or if arabinose units themselves can be converted to the *arabino* decaprenolphosphate donor *in vivo.*

Results and discussion

As a first foray into the field a decision was taken to access a series of compounds where the normal 5-hydroxyl of arabinose was replaced by –H, –OMe, –F and $–N_3$. It was reasoned that monosaccharide derivatives might perhaps act as biosynthetic

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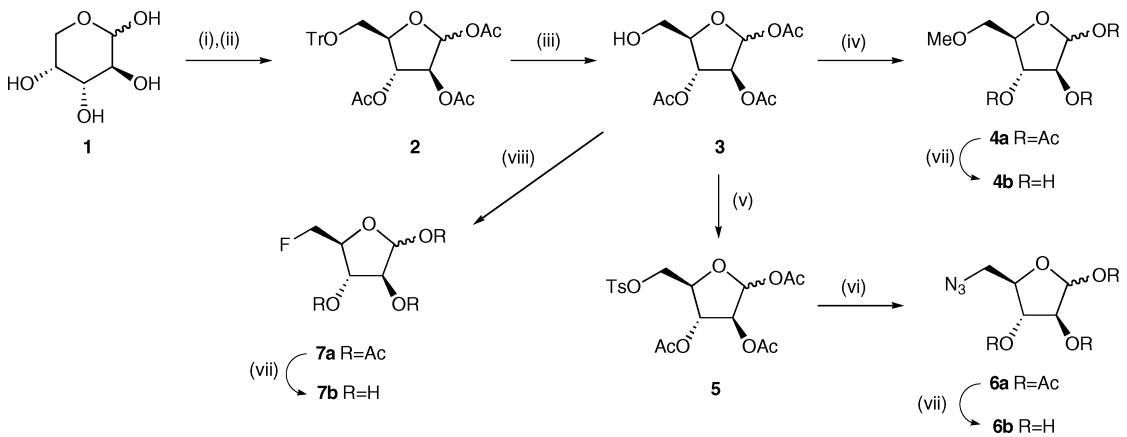
precursors of the actual glycosyl donor, whilst in line with the work of Brennan and Liav[15] and Lowary and Joe,[16] farnesyl phosphodiesters were targeted as analogues of the natural decaprenol phosphodiester donor substrate. Selective access to the 5-hydroxyl required the synthesis of selectively protected alcohol **3**, which was the key divergent intermediate. Although the synthesis of **3** has previously been reported,[17] in our hands it proved much more difficult to obtain **3** in good yield than could be directly inferred from previous procedures. The major issue was the lability of the anomeric acetate, which was prone to readily undergo hydrolysis under the conditions required for cleavage of the trityl ether. Although a selective silylation procedure[18] was initially investigated, this eventually proved to be less efficient than the trityl approach. Only after considerable optimisation was an efficient procedure arrived upon, in contrast to previous literature reports.[17] In an optimised process, careful reaction of D-arabinose with trityl chloride in pyridine at room temperature for 48 h, whilst ensuring that the reaction temperature did not exceed 30 °C, was followed by acetylation with acetic anhydride in pyridine to produce to ester **2**.[19] Removal of the trityl group without loss of the anomeric acetate was then achieved by heating in 80% aqueous acetic acid at 100 °C for 25 minutes,[20] producing the key alcohol **3** (65% yield, Scheme 1). Methylation of the free hydroxyl group was achieved by reaction with methyl triflate in the presence of excess di-*tert*butylmethyl pyridine (DTBMP) and catalytic $Hg(CN)_2$ in dichloromethane to yield methyl ether **4a**. Zemplen deacetylation then cleanly produced triol **4b**. Introduction of azide at C-5 was achieved by tosylation of alcohol **3** to give **5** (80% yield), which underwent smooth reaction upon heating with sodium azide at 80 °C in dimethyl sulfoxide (DMSO) to give azido acetate **6a** (83% yield), which then underwent smooth Zemplen de-acetylation to give azido triol **6b** (92% yield).

Introduction of fluoride at the C-5 position proved somewhat problematic. In particular, attempted reaction of the corresponding primary triflate with tetrabutylammonium fluoride (TBAF) produced only low yields of desired fluoride **7a**. Direct introduction of fluorine was next attempted by treatment of alcohol **3** with diethylamino sulfur trifluroide (DAST) in dichloromethane at low temperature following the procedure of Lloyd *et al.*,[21] but again this process only gave **7a** in poor yield (~30%). However, a change of reaction solvent to diglyme[22] produced a satisfactory increase in yield (60%). Finally de-acetylation gave fluoride triol **7b** (93% yield).

Deoxygenation of the 5-position of arabinose was attempted using a variety of procedures. Initially, a Barton–McCombie deoxygenation was investigated. Reaction of alcohol **3** with thiocarbonyldiimidazole smoothly produced thiocarbamate **8**. However, free radical mediated reduction of **8** did not prove to be high yielding. Even using a recently published modification with tetrabutylammonium peroxydisulfate as initiator,[23] deoxy material **9a** was only isolated in a poor 40% yield. As an alternative, a de-halogenation procedure was attempted. Previously synthesized tosylate **5** underwent displacement when heated with sodium iodide in butanone (90%) to yield iodide **10**. However, it was found that **10** could actually be synthesised more efficiently directly from alcohol **3** by reaction with triphenylphosphine and iodine in the presence of imidazole[24] (83% yield). Iodide **10** underwent smooth palladium mediated catalytic hydrogenation in the presence of triethylamine[25] in ethanol to give the required deoxy ester **9a** (83% yield). Ester **9a** could be smoothly de-acetylated to produce deoxy triol **9b** (95% yield, Scheme 2).

With a series of arabinose derivatives modified at the 5-position in hand, attention turned to the synthesis of the corresponding glycosyl phosphates, and farnesyl phosphodiesters. Synthesis of the protected glycosyl phosphates was envisaged by initial conversion of the relevant glycosyl acetate to the glycosyl bromide and then subsequent reaction with dibenzyl phosphate. Fluoride **7a** was cleanly converted to the corresponding α-glycosyl bromide,[26] which was then immediately reacted with dibenzylphosphate to produce an anomeric mixture of fluoro glycosylphosphates **11** (Scheme 3). It is notable that the products of this reaction, and similar ones attempted on the other arabinose derivatives, were always produced in separable anomeric mixtures, the major component of which was the desired β-anomer, indicating that simple neighbouring group participation of the 2-*O* acetate is not the dominant process.[27] Although the glycosyl phosphate **11** was relatively unstable, it was possible to remove the benzyl protection by catalytic hydrogenation. However, this reaction unexpectedly produced a mixture of products, namely mono- and di-acetates **12** and **13**. Somewhat fortuitously, 2-*O* de-acetylation was concomitant



Scheme 1 *Reagents and conditions:* (i) TrCl, pyridine, rt, 48 h, 50%; (ii) Ac_2O, pyridine, rt, 90%; (iii) 80% aqueous AcOH, 100 °C, 25 min, 65%; (iv) MeOTf, DTBMP, 1 mol% $Hg(CN)_2$, CH_2Cl_2, 78%; (v) TsCl, pyridine, 48 h, 80%; (vi) NaN_3, DMSO, 80 °C, 24 h, 83%; (vii) NaOMe, MeOH, rt, **4b**, 90%; **6b**, 92%; **7b**, 93%; (viii) DAST, diglyme, −40 °C to rt, 60%.

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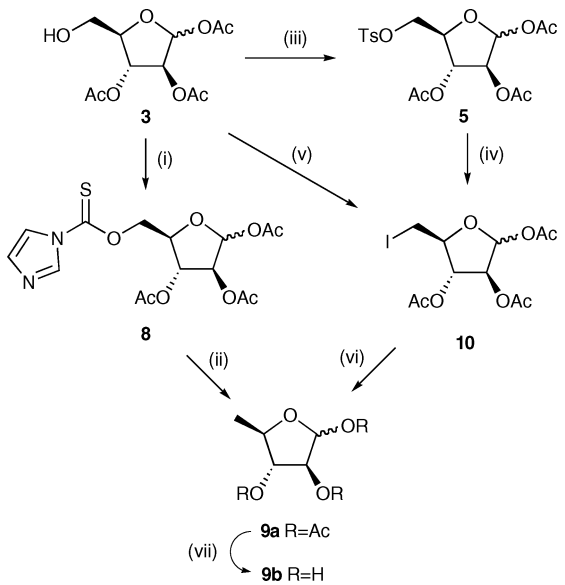


Scheme 2 *Reagents and conditions:* (i) thiocarbonyldiimidazole, CH_2Cl_2, rt, 16 h, 88%; (ii) $(Bu_4N)_2S_2O_8$, $NaHCO_2$, $NaHCO_3$, DMF, 65 °C, 0.5 h, 40%; (iii) TsCl, pyridine, rt, 48 h, 80%; (iv) NaI, butanone, 80 °C, 18 h, 90%; (v) PPh_3, I_2, imidazole, pyridine, rt, 2.5 h, 100 °C, 80%; (vi) 10% Pd/C, H_2, NEt_3, EtOH, rt 48 h, 83%; (vii) NaOMe, MeOH, rt, 16 h, 95%.

with benzyl cleavage for only the β-anomer, allowing access to monoacetate **12** as the pure β-anomer. Conversion of phosphates **12** and **13** into the corresponding farnesyl phosphodiesters **14** and **15** was then achieved using farnesyl trichloroacetimidate following the procedures developed by Brennan *et al.*,[15,28] and Lowary and Joe.[16]

Final removal of acetate protecting groups on the arabinose was investigated, but the completely de-protected products proved to be particularly unstable, in line with the observations of Lowary and Joe.[16b] In particular, the de-protected products would certainly not be stable to the conditions required for biological testing, which was to be performed in aqueous solution over a protracted period of time. For this reason, acetate protecting groups, which afforded significantly increased stability to the farnesyl phosphodiesters, were not removed.

A similar sequence of reactions then allowed access to the corresponding methoxy derivative, conversion to the α-glycosyl bromide was followed by reaction with dibenzyl phosphate to give **16a**, again as an anomeric mixture, which was then hydrogenated to give triethylamine salt **16b**, though in this case no loss of the 2-*O* acetate was observed, and so no separation of the mixture of anomers was possible. Finally reaction with farnesyl trichloroacetimidate gave phosphodiesters **17**.

Due to selectivity issues it was decided to reduce the 5-azide of compound **6a** before a similar reaction sequence was attempted. Thus reaction of azide with thioacetic acid directly produced the corresponding acetamide **18** (Scheme 3). Although **18** could be converted into the corresponding glycosyl bromide, unfortunately production of the required glycosyl phosphate **19** proved to be impossible in a satisfactory process due to the extreme lability of the reaction product (~20% maximum yield obtained, product rapidly decomposes). In fact, similar investigations into production of the corresponding 5-deoxy glycosyl phosphate derived from **9a** also proved fruitless, again due to the extreme lability of these compounds. We conclude that, at least in our hands, the glycosyl phosphate derivatives which did not have a strongly electron withdrawing group at the 5-position were too unstable to be efficiently handled or purified.

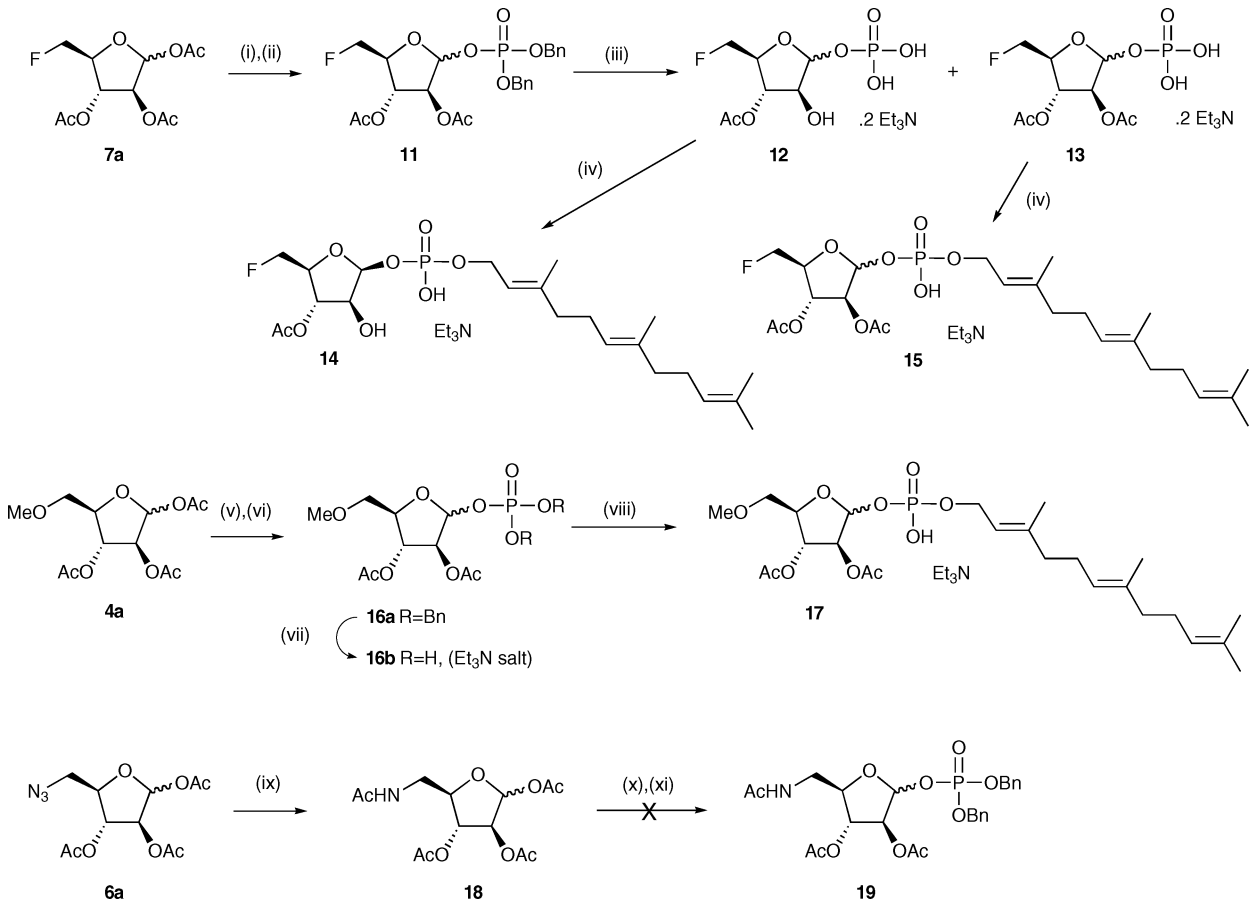
Nonetheless a significantly diverse array of arabinose derivatives modified at the 5-position and the two farnesyl phosphodiesters were available for biological investigation. Testing was performed using *Mycobacterium bovis* BCG as a model substrate by spotting *M. bovis* BCG cultures onto 6 well plates containing solid media and the test compounds at various concentrations.[29] These cultures were then grown in an incubator at 37 °C for 7–14 days[30] and any effect of the test compound on cell growth was measured. In this manner compounds **4a**, **4b**, **6a**, **6b**, **7a**, **7b**, **9a**, **9b**, **10**, **14**, **17** and **18** were all tested for biological activity, each at concentrations of 0 (control), 10, 20, 40, 80 and 100 μg mL^{-1}. Disappointingly, none of the test compounds displayed any significant anti-mycobacterial effects, even at the highest concentrations of 100 μg mL^{-1}. However, the antitubercular drug, isoniazid (INH), which was repeatedly used as a positive control, was in all cases seen to inhibit cell growth at concentrations above 0.1 μg mL^{-1}. We therefore concluded that none of the above compounds displayed significant anti-mycobacterial properties.

Since it has been proposed that the biosynthesis of the *arabino* decaprenol phosphodiester donor occurs *via* initial phosphorylation of the 5-position, it is perhaps not surprising that the simple arabinose derivatives modified at C-5 are unable to enter into the biosynthetic pathway and lead to chain termination. However, it could possibly have been expected that the farnesyl phosphodiesters may have been capable of producing a chain termination effect by directly entering the biosynthetic pathway and themselves acting as glycosyl donors.[31] The disappointing lack of biological activity of these compounds could be for a number of reasons. For example, it may result from low intracellular transport, inefficient intracellular de-acetylation, or it may be that the mycobacterial arabinosyl transferases do not process these modified donors. Nonetheless further investigations into the use of chain-terminating strategies for the rational design of small molecule inhibitors of pathogenic cell wall biosynthesis are currently in progress, and the results will be reported in due course.

Experimental

1,2,3-Tri-*O*-acetyl-5-*O*-trityl-D-arabinofuranose 2[19]

D-Arabinose **1** (10.0 g, 67 mmol, 1 eqv) was stirred in refluxing pyridine (350 mL) until it dissolved, the solution was then allowed to cool to 25 °C. Trityl chloride (18.6 g, 67 mmol, 1 eqv) was added in one portion and the reaction stirred under an argon atmosphere for 48 h whilst ensuring the temperature did not exceed 30 °C. The reaction was quenched with methanol (25 mL) and the solvent was subsequently removed *in vacuo.* The residue was dissolved in ethyl acetate (100 mL) and the resultant organic layer was washed with water (500 mL), separated, and the organic layer and washings were dried over $MgSO_4$. The crude 5-*O*-trityl-D-arabinofuranose was separated from trityl alcohol by wet-flash chromatography (the column was first eluted with 1 : 1 40–60 light petrol–ethyl acetate to wash out TrOH and the product was obtained following elution with 1 : 8 40–60 light petrol–ethyl acetate). The gummy product (12.5 g, 46%) was then dissolved in pyridine (85 mL) before



Scheme 3 *Reagents and conditions:* (i) TMSBr, CH_2Cl_2, −40 °C; (ii) $(BnO)_2P(O)OH$, Et_3N, 38% over two steps; (iii) H_2, Pd on C, EtOH, Et_3N, rt, 95%; (iv) farnesyl trichloroacetimidate, toluene–DMF, 65 °C, **14**: 24%, **15** : 14%; (v) TMSBr, CH_2Cl_2, −40 °C; (vi) $(BnO)_2P(O)OH$, Et_3N, 57% over two steps; (vii) H_2, Pd on C, EtOH, Et_3N, rt, 77%; (viii) farnesyl trichloroacetimidate, toluene–DMF, 65 °C, 39%; (ix) AcSH, rt, 70%; (x) TMSBr, CH_2Cl_2, −40 °C; (xi) $(BnO)_2P(O)OH$, Et_3N, ∼20% over two steps (product rapidly decomposes).

the solution was cooled in ice and acetic anhydride (16.5 mL) slowly added. The reaction was allowed to stir for 16 hours at room temperature under an atmosphere of argon. The solvent was removed *in vacuo* (azeotrope 3× with toluene–ethanol) and the residue dissolved in DCM (75 mL). The solution was washed with sat $NaHCO_3$ (aq) (200 mL) before purification by wet-flash chromatography (5 : 1 40–60 light petrol–ethyl acetate), to yield trityl ether **2**, as a colourless oil (14.9 g, 90%); α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$)[14] 2.09, 2.10, 2.11 (9H, 3 × s, 3 × OAc β), 2.12, 2.13, 2.17 (9H, 3 × s, 3 × OAc α), 3.34–3.43 (4H, m, H-5α, H-5β, H-5′α, H-5′β), 4.20 (1H, dd, $J_{3,4}$ 5.8 Hz, $J_{4,5}$ 10.2 Hz, H-4β), 4.37 (1H, dd, $J_{3,4}$ 4.5 Hz, $J_{4,5}$ 9.2 Hz, H-4α), 5.24 (1H, d, $J_{2,3}$ 1.7 Hz, H-2α), 5.32 (1H, dd, H-3α), 5.38 (1H, dd, $J_{1,2}$ 4.6 Hz, $J_{2,3}$ 7.3 Hz, H-2β), 5.61 (1H, dd, H-3β), 6.26 (1H, s, H-1α), 6.44 (1H, d, H-1β), 7.28–7.38 (9H, m, ArH), 7.50–7.54 (6H, m, ArH); *m/z* (ES^+) 577 (M + $MeCN/NH_4^+$, 100%).

1,2,3-Tri-*O*-acetyl-D-arabinofuranose 3[17]

Trityl ether **2** (10 g, 19.29 mmol) was stirred in 80% aqueous AcOH (100 mL) at 100 °C for 25 minutes and cooled immediately in an ice-bath. The trityl alcohol by-product that crystallised was filtered off, the filtrate treated with brine (100 mL) and extracted with DCM (3 × 40 mL). The organic layers were combined, washed with sat $NaHCO_3$ (aq), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by wet-flash chromatography (the column was initially eluted with 5 : 1 40–60 light petrol–ethyl acetate to remove residual trityl alcohol and the product was obtained on elution with 2 : 3 40–60 light petrol–ethyl acetate). Alcohol **3** was obtained as a colourless oil (3.4 g, 64%); α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$)[17] 2.13, 2.15, 2.17 (9H, 3 × s, 3 × OAc α), 2.17, 2.18, 2.18 (9H, 3 × s, 3 × OAc β), 3.97–3.80 (4H, m, H-5α, H-5β, H-5′α, H-5′β), 4.13–4.19 (1H, m, H-4β), 4.28 (1H, dd, $J_{3,4}$ 5.1 Hz, $J_{4,5}$ 8.7 Hz, H-4α), 5.16 (1H, dd, $J_{2,3}$ 1.9 Hz, H-3α), 5.30 (1H, d, H-2α), 5.44–5.45 (2H, m, H-2β, H-3β), 6.23 (1H, s, H-1α), 6.43 (1H, d, $J_{1,2}$ 3.6 Hz H-1β); *m/z* (ES^+) 310 (M + Na^+, 15%), 335 (M + $MeCN/NH_4^+$, 100%).

1,2,3-Tri-*O*-acetyl-5-*O*-methyl-D-arabinofuranose 4a

Alcohol **3** (1.90 g, 6.88 mmol, 1 eqv), 2,6-di-*tert*butyl-4-methylpyridine (3.39 g, 16.50 mmol, 2.4 eqv) and $Hg(CN)_2$ (0.017 g, 0.07 mmol, 0.01 eqv) were stirred in DCM (35 mL) at room temperature under an atmosphere of argon. On addition of methyl triflate (1.7 mL, 15.00 mmol, 2.2 eqv), the reaction turned green within 5 minutes and the reaction mixture was then heated

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to 40 °C for 24 h. The reaction mixture was washed with 1 M HCl (2 × 75 mL) and brine (75 mL) before the organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by wet-flash chromatography (the column was initially eluted with 3 : 1 40–60 light petrol–ethyl acetate to remove residual base and the product was obtained on elution with 1 : 1 40–60 light petrol–ethyl acetate) to afford methyl ether **4a** as a colourless oil (1.56 g, 78%). α–β ratio approx 9 : 4 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 1747 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.12, 2.14, 2.16 (9H, 3 × s, 3 × OAc β), 2.16, 2.17, 2.17 (9H, 3 × s, 3 × OAc α), 3.44 (3H, s, CH_3-α), 3.46 (3H, s, CH_3-β), 3.61–3.72 (4H, m, H-5α, H-5β, H-5′α, H-5′β), 4.18–4.21 (1H, m, H-4β), 4.33–4.36 (1H, m, H-4α), 5.16 (1H, d, $J_{3,4}$ 5.3 Hz, H-3α), 5.20 (1H, d, H-2α), 5.40 (1H, dd, $J_{1,2}$ 4.6 Hz, H-2β), 5.44–5.47 (1H, m, H-3β), 6.25 (1H, s, H-1α), 6.41 (1H, d, $J_{1,2}$ 4.7 Hz H-1β); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.6, 20.7, 20.8, 21.0, 21.1 (6 × CH_3, 3 × OAc β, 3 × OAc α) 59.53, 59.5 (OCH_3-α, OCH_3-β), 71.4, 73.3 (C5-α, C5-β), 74.5 (C3-β), 75.3 (C2-β), 76.7 (C3-α), 87.9 (C4-β), 80.9 (C2-α), 83.3 (C4-α), 93.7 (C1-β), 99.3 (C1 α), 169.2, 169.3, 169.6, 169.8, 170.0, 170.3 (3 × C=O α, 3 × C=O β); *m/z* (APCI$^+$) 313 (M + Na$^+$, 100%), 349 (M + MeCN/NH_4^+, 35%); HRMS (ES$^+$) calculated $C_{12}H_{18}O_8$ 313.0899. Found 313.0895. (Found: C, 49.74; H, 6.27. $C_{12}H_{18}O_8$ requires C, 49.65; H, 6.25%.)

5-*O*-Methyl-D-arabinofuranose 4b[32]

Triacetate **4a** (300 mg, 1.03 mmol) was dissolved in dry methanol (5 mL). Sodium methoxide (6 mg, 0.10 mmol) was added and the reaction mixture was stirred at room temperature under an argon atmosphere. After 30 minutes, t.l.c. (petrol–ethyl acetate, 1 : 1) indicated complete consumption of starting material. Dowex ion-exchange resin was added until pH paper indicated the reaction mixture was pH neutral. The solid material was filtered off and the filtrate concentrated *in vacuo* to afford triol **4b** as a colourless oil (152 mg, 90%) α–β ratio approx 3 : 1 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$)[32] 3.40 (3H, s, Me-α), 3.41 (3H, s, Me-β), 3.52 (1H, dd, $J_{4,5'}$ 5.9 Hz, $J_{5,5'}$ 10.6 Hz, H-5′α), 3.54–3.56 (2H, m, H-5β, H-5′β), 3.59 (1H, dd, $J_{4,5}$ 3.5 Hz, H-5α), 3.82 (1H, dd, $J_{3,4}$ 12.9 Hz, $J_{2,3}$ 4.3 Hz, H-3β), 3.83 (1H, dd, $J_{2,3}$ 4.3 Hz, $J_{3,4}$ 6.3 Hz, H-3α) 3.88 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{2,3}$ 6.5 Hz H-2β), 3.91 (1H, dd, $J_{1,2}$ 2.4 Hz, H-2α), 4.10 (1H, dd, $J_{3,4}$ 5.9 Hz, $J_{4,5}$ 3.5 Hz, H-4β), 4.12 (1H, dd, $J_{3,4}$ 6.3 Hz, H-4α), 5.12 (1H, d, H-1α), 5.19 (1H, d, H-1β); *m/z* (ES$^-$) 163 (M − H$^+$, 90%).

1,2,3-Tri-*O*-acetyl-5-*O*-tosyl-D-arabinofuranose 5

Alcohol **3** (1.83 g, 6.6 mmol, 1 eqv) was dissolved in dry DCM (40 mL) and pyridine (5 mL). Tosyl chloride (1.9 g, 9.9 mmol 1.5 eqv) was added slowly before leaving the reaction to stir at room temperature for 48 h under an atmosphere of argon. The reaction mixture was washed with water and the aqueous layer was further extracted with DCM (3 × 20 mL). The combined organic layers were washed with 1 M HCl (40 mL), sat $NaHCO_3$ (aq), and brine (40 mL) before being dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by wet-flash chromatography (1 : 1 40–60 light petrol–ethyl acetate) to afford tosylate **5**, as a colourless oil (2.25 g, 79%) α–β ratio approx 3 : 1 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$) 2.05, 2.06, 2.08 (9H, 3 × s, 3 × OAc β), 2.09, 2.10, 2.10 (9H, 3 × s, 3 × OAc α), 2.45 (6H, s, CH_3α, CH_3β), 4.15–4.32 (6H, m, H-4α, H-4β, H-5α, H-5β, H-5′α, H-5′β), 4.99 (1H, dd, $J_{3,4}$ 4.0 Hz, H-3α), 5.16 (1H, d, $J_{2,3}$ 0.5 Hz, H-2α), 5.29–5.31 (2H, m, H-2β, H-3β), 6.11 (1H, s, H-1α), 6.33 (1H, d, $J_{1,2}$ 3.8 Hz H-1β), 7.35 (2H, d, *J* 8.3 Hz, ArH), 7.79 (2H, d, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.5, 20.6, 20.6, 20.9, 21.0 (6 × CH_3 3 × OAc β, 3 × OAc α) 21.7 (2 × $ArCH_3$), 67.8 (C5-α), 69.3 (C5-β), 74.2 (C3-β), 75.0 (C2-β), 76.6 (C3-α), 79.3 (C2-α), 80.1 (C4-αβ), 82.5 (C4-α), 93.2 (C1-β), 99.2 (C1-α), 128.0, 128.1 (ArCHα, ArCHβ), 129.9, 130.0 (ArCHα, ArCHβ), 132.5, 132.7 (ArCα, ArCβ), 145.0, 145.1 (ArCHα, ArCHβ) 169.1, 169.2, 169.5, 169.7, 170.0, 170.3 (3 × C=O α, 3 × C=O β).

1,2,3-Tri-*O*-acetyl-5-azido-5-deoxy-D-arabinofuranose 6a[33]

Tosylate **5** (1.1 g, 2.6 mmol) and sodium azide (0.7 g, 10 mmol, 3 eqv) were heated to 80 °C in DMSO (15 mL) under an atmosphere of argon for 24 h. On cooling, the reaction mixture was diluted with DCM (40 mL) and washed with water (200 mL) before drying the organic layer over $MgSO_4$. The crude product was purified by wet-flash chromatography (2 : 1 40–60 light petrol–ethyl acetate) and azide **6a** was obtained as a colourless oil (663 mg, 83%) α–β ratio approx 3 : 1 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$)[33] 2.05, 2.10, 2.11 (9H, 3 × s, 3 × OAc β), 2.13, 2.14, 2.15 (9H, 3 × s, 3 × OAc α), 3.44–3.46 (1H, m, H-5′β), 3.48–3.49 (1H, m, H-5′α), 3.61 (1H, dd, $J_{4,5}$ 3.6 Hz, $J_{5,5'}$ 13.1 Hz, H-5β), 3.70 (1H, dd, $J_{4,5}$ 3.1 Hz, $J_{5,5'}$ 13.5 Hz, H-5α), 4.12–4.15 (1H, m, H-4β), 4.30 (1H, dd, $J_{3,4}$ 4.6 Hz, H-4α), 5.06 (1H, d, H-3α), 5.23 (1H, s, H-2α), 5.38–5.40 (2H, m, H-2β, H-3β), 6.23 (1H, s, H-1α), 6.41 (1H, d, $J_{1,2}$ 4.0 Hz, H-1β); *m/z* (ES$^+$) 324 (M + Na$^+$, 50%), 360 (M + MeCN/NH_4^+, 55%).

5-Azido-5-deoxy-D-arabinofuranose 6b[33]

Triacetate **6a** (480 mg, 1.60 mmol) was dissolved in dry methanol (10 mL). Sodium methoxide (9 mg, 0.16 mmol) was added and the reaction mixture was stirred at room temperature under an argon atmosphere. After 30 minutes, t.l.c. (petrol–ethyl acetate, 1 : 1) indicated complete consumption of starting material. Dowex ion-exchange resin was added until pH paper indicated the reaction mixture was pH neutral. The solid material was filtered off and the filtrate concentrated *in vacuo* to afford triol **6b** as a colourless oil (256 mg, 92%) α–β ratio approx 4 : 3 ratio (by integration of the ^{1}H NMR spectrum); δ_H (400 MHz, $CDCl_3$)[33] 3.32–3.46 (3H, m, H-5α, H-5′α, H-5β), 3.51 (1H, dd, $J_{4,5}$ 3.4 Hz, $J_{5,5'}$ 13.1 Hz, H-5β), 3.80 (1H, dt, $J_{3,4}$ 6.2 Hz, $J_{4,5,5'}$ 4.7 Hz, H-4α), 3.86 (1H, dd, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 6.3 Hz, H-3β), 3.91–3.95 (2H, m, H-2α, H-2β), 3.98–4.12 (1H, m, H-3α), 4.12 (1H, dt, $J_{3,4}$ 6.2 Hz, $J_{4,5}$ 3.4 Hz H-4β), 5.16 (1H, d, $J_{1,2}$ 2.6 Hz, H-1α), 5.22 (1H, d, $J_{1,2}$ 4.4 Hz, H-1β); *m/z* (ES$^-$) 174 (M − H$^+$, 100%).

1,2,3-Tri-*O*-acetyl-5-fluoro-5-deoxy-D-arabinofuranose 7a

Triacetate **3** (0.28 g, 1.0 mmol, 1 eqv), was stirred in dry diglyme (5 mL). The mixture was stirred at room temperature for 5 minutes under an atmosphere of argon before cooling to −40 °C. (Diethylamino)sulfur trifluoride (DAST) (0.66 mL, 5.0 mmol, 5.0 eqv) was added and the mixture stirred for 30 minutes. The reaction vessel was then warmed to room temperature and allowed to stir for 16 hours. The reaction was carefully quenched with sat $NaHCO_3$ (aq) (50 mL) and the resultant solution extracted with

diethyl ether (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by wet-flash chromatography (1 : 1 40–60 light petrol–ethyl acetate) to afford fluoride **7a** as a colourless oil (0.17 g, 61%). α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.08, 2.09, 2.11, 2.12, 2.12, 2.14 (18H, 6 × s, 3 × OAc α, 3 × OAc β), 4.13–4.22 (1H, m, H-4β), 4.27–4.37 (1H, m, H-4α), 4.48–4.73 (4H, m, H-5α, H-5′α, H-5β, H-5′β), 5.09 (1H, dd, $J_{2,3}$ 0.9 Hz, $J_{3,4}$ 4.9 Hz, H-3α), 5.22 (1H, s, H-2α), 5.35 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{3,4}$ 6.0 Hz, H-2β), 5.43 (1H, dd, $J_{2,3}$ 7.3, $J_{3,4}$ 6.0 Hz, H-3β), 6.21 (1H, s, H-1α), 6.36 (1H, d, $J_{1,2}$ 4.5 Hz H-1β); δ_F (376.6 MHz, $CDCl_3$) −228.70 (td, $J_{F,H\ geminal}$ 46.9, $J_{F,H\ vicinal}$ 22.1 Hz, F-β), −230.78 (td, $J_{F,H\ geminal}$ 46.9, $J_{F,H\ vicinal}$ 24.2 Hz, F-α); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.6, 20.7, 20.7, 20.9, 21.0 (6 × CH_3 3 × OAc β, 3 × OAc α), 73.3 (C3-β, d, $J_{C3\text{-}F}$ 7.1 Hz), 75.1 (C2-β), 76.0 (C3-α, d, $J_{C3\text{-}F}$ 6.6 Hz), 80.3 (C4-β, d, $J_{C4\text{-}F}$ 19.9 Hz), 80.5 (C2-α), 81.3 (C5-α, d, $J_{C5\text{-}F}$ 174.7 Hz), 82.4 (C5-β, d, $J_{C5\text{-}F}$ 175.6 Hz), 83.4 (C4-α, d, $J_{C4\text{-}F}$ 19.3 Hz), 93.3 (C1-β), 99.4 (C1- α), 169.2, 169.4, 169.6, 169.8, 170.1, 170.4 (3 × C=O α, 3 × C=O β); *m/z* (ES$^+$) 301 (M + Na$^+$, 100%); HRMS (ES$^+$) calculated $NaC_{11}H_{15}FO_7$ 301.0694. Found 301.0696.

5-Fluoro-5-deoxy-D-arabinofuranose 7b

Triacetate **7a** (100 mg, 0.36 mmol) was dissolved in dry methanol (1 mL). A freshly prepared solution of 1 M sodium methoxide (0.050 mL) was added and the reaction mixture was stirred at room temperature for 16 h. Dowex ion-exchange resin was added until pH paper indicated the reaction mixture was pH neutral. The solid material was filtered off and the filtrate concentrated *in vacuo.* The residue was purified by wet-flash chromatography (1 : 10 methanol–ethyl acetate) to afford triol **7b** as a colourless oil (54 mg, 93%). α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 3364 (bs, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.83–4.00 (4H, m, H-2α, H-2β, H-3α, H-3β), 4.09–4.19 (1H, m, H-4α), 4.38–4.63 (4H, m, H-5α, H-5′α, H-5β, H-5′β), 5.14 (1H, d, $J_{1,2}$ 2.5 Hz H-1α), 5.21 (1H, d, $J_{1,2}$ 4.3 Hz H-1β); δ_F (376.6 MHz, $CDCl_3$) −227.18 (td, $J_{F,H\ geminal}$ 47.8, $J_{F,H\ vicinal}$ 18.8 Hz, F-β), −230.32 (td, $J_{F,H\ geminal}$ 47.7, $J_{F,H\ vicinal}$ 22.5 Hz, F-α); δ_C (100.6 MHz, $CDCl_3$) 74.8 (C3-β, d, $J_{C3\text{-}F}$ 7.1 Hz), 76.2 (C3-α, d, $J_{C3\text{-}F}$ 6.9 Hz), 77.4 (C2-β), 80.8 (C4-β, d, $J_{C4\text{-}F}$ 19.3 Hz), 81.9 (C4-α, d, $J_{C4\text{-}F}$ 18.6 Hz), 82.6 (C5-β, d, $J_{C5\text{-}F}$ 171.0 Hz), 82.8 (C2-α), 84.2 (C4-α, d, $J_{C5\text{-}F}$ 171.0 Hz), 96.5 (C1-β), 102.5 (C1-α); *m/z* (ES$^+$) 175 (M + Na$^+$, 100%), HRMS (ES$^+$) calculated $NaC_5H_9FO_4$ 175.0377. Found 175.0377.

1,2,3-Tri-*O*-acetyl-5-iodo-5-deoxy-D-arabinofuranose 10

Alcohol **3** (0.85g, 3.1 mmol, 1 eqv), triphenylphosphine (1.18 g, 4.5 mmol, 1.45 eqv), imidazole (0.63 g, 9.3 mmol, 3 eqv) and iodine (1.18 g, 4.65 mmol, 1.5 eqv) were stirred in dry toluene (20 mL) before heating the mixture to 100 °C for 2.5 hours. On cooling, the reaction mixture was concentrated *in vacuo* and redissolved in DCM (40 mL). The DCM layer was washed with 10% thiosulfate solution (40 mL) and the organic layer dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by wet-flash chromatography (2 : 1 40–60 light petrol–ethyl acetate) to afford iodide **11** as a colourless oil (0.94 g, 80%). α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 1748 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.06, 2.07, 2.11, 2.11, 2.13, 2.13 (18H, 6 × s, 3 × OAc α, 3 × OAc β), 3.34–3.47 (4H, m, H-5α, H-5′α, H-5β, H-5′β), 4.17–4.25 (2H, s, H-4α, H-4β), 4.99 (1H, dd, $J_{2,3}$ 1.6 Hz, $J_{3,4}$ 4.7 Hz, H-3α), 5.20 (1H, d, H-2α), 5.32–5.38 (2H, m, H-2β, H-3β), 6.20 (1H, s, H-1α), 6.39 (1H, d, $J_{1,2}$ 4.1 Hz H-1β); δ_C (100.6 MHz, $CDCl_3$) 4.2 (C5-α), 5.7 (C5-β), 20.5, 20.7, 20.8, 20.9, 21.0, 21.1 (6 × CH_3 3 × OAc β, 3 × OAc α), 76.0 (C2-β), 77.3 (C3-β), 80.2 (C3-α), 81.5 (C2-α), 81.8 (C4-β), 84.4 (C4-α), 93.8 (C1-β), 99.3 (C1- α), 169.1, 169.2, 169.5, 169.7, 169.9, 170.1 (3 × C=O α, 3 × C=O β); *m/z* (ES$^+$) 409 (M + Na$^+$, 100%), 449 (M + MeCN/NH_4^+, 80%); HRMS (ES$^+$) calculated $NaC_{11}H_{15}IO_7$ 408.9755. Found 408.9755.

1,2,3-Tri-*O*-acetyl-5-deoxy-D-arabinofuranose 9a

Iodide **10** (0.19 g, 0.5 mmol), triethylamine (0.12 mL, 1.4 mmol) and 10% Pd/C (50 mg, 25% w/w) were stirred in ethanol (5 mL) and the solution purged of air and flushed 3 × with hydrogen gas. The mixture was stirred at room temperature under an atmosphere of hydrogen for 48 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo.* The residue was purified by wet-flash chromatography (1 : 1 40–60 light petrol–ethyl acetate) to afford triacetate **9a** as a colourless oil (0.13 g, 83%). α–β ratio approx 1 : 1 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 1748 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, $J_{4,5}$ 6.4 Hz, H-5α), 1.45 (3H, d, $J_{4,5}$ 6.6 Hz, H-5β), 2.70, 2.80, 2.80, 2.90, 2.11, 2.11 (18H, 6 × s, 3 × OAc α, 3 × OAc β), 4.08–4.14 (1H, m, H-4β), 4.23–4.29 (1H, m, H-4α), 4.84 (1H, dd, $J_{2,3}$ 2.2 Hz, $J_{3,4}$ 5.4 Hz, H-3α), 5.18–5.21 (2H, m, H-3β, H-2α), 5.31 (1H, dd, $J_{1,2}$ 4.6 Hz, $J_{2,3}$ 6.7 Hz, H-2β), 6.12 (1H, s, H-1α), 6.33 (1H, d, $J_{1,2}$ 4.6 Hz H-1β); δ_C (100.6 MHz, $CDCl_3$) 18.6 (C5-α), 20.5 (C5-β), 20.7, 20.8, 20.8, 20.9, 21.1, 21.1 (6 × CH_3 3 × OAc β, 3 × OAc α), 75.7 (C2-β), 78.6 (C2-α), 79.2 (C4-β), 80.3 (C4-α), 81.0 (C3-β), 81.3 (C3-α), 93.9 (C1-β), 99.2 (C1-α), 169.5, 169.5, 169.6, 169.8, 170.1, 170.5 (3×C=O α, 3×C=O β); *m/z* (ES$^+$) 283 (M + Na$^+$, 100%), HRMS (ES$^+$) calculated $NaC_{11}H_{16}O_7$ 283.0788. Found 283.0788.

5-Deoxy-D-arabinofuranose 9b[32]

Triacetate **9a** (300 mg, 1.15 mmol) was dissolved in dry methanol (5 mL). A freshly prepared solution of 1 M sodium methoxide (0.1 mL) was added and the reaction mixture was stirred at room temperature for 16 h. Dowex ion-exchange resin was added until pH paper indicated the reaction mixture was pH neutral. The solid material was filtered off and the filtrate concentrated *in vacuo.* The residue was purified by wet-flash chromatography (1 : 10 methanol–ethyl acetate) to afford triol **9b** as a colourless oil (148 mg, 95%). α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum); ν_{max} (thin film) 3357 (bs, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{4,5}$ 6.3 Hz, H-5α), 1.32 (3H, d, $J_{4,5}$ 6.1 Hz, H-5β), 3.54 (1H, dd, $J_{2,3}$ 5.0 Hz, $J_{3,4}$ 7.1 Hz, H-3α), 3.66–3.80 (2H, m, H-3β, H-4β), 3.87 (1H, dd, $J_{1,2}$ 4.6 Hz, $J_{2,3}$ 6.7 Hz, H-2β), 3.90 (1H, dd, $J_{1,2}$ 2.5 Hz, $J_{2,3}$ 5.0 Hz, H-2α), 4.00–4.06 (1H, m, H-4α), 5.08 (1H, d, $J_{1,2}$ 2.5 Hz H-1α), 5.14 (1H, d, $J_{1,2}$ 4.6 Hz H-1β); δ_C (100.6 MHz, $CDCl_3$) 18.1 (C5-α), 19.7 (C5-β), 77.6 (C2-β), 77.7 (C2-α), 78.4 (C4-α), 80.5 (C3-β), 82.7 (C3-α), 83.7 (C4-β), 95.9 (C1-α), 102.2 (C1-β); *m/z* (FI) 135 (M$^+$, 100%), HRMS (ES$^+$) calculated $C_5H_{10}O_4$ 135.1067. Found 135.0660.

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Dibenzyl 2,3-di-*O*-acetyl-5-fluoro-5-deoxy-D-arabinofuranosyl phosphate 11

Triacetate **7a** (330 mg, 1.2 mmol, 1 eqv) was dissolved in DCM (5 mL) and cooled to −40 °C under an atmosphere of argon. Trimethylsilyl bromide (1.51 mL, 11.8 mmol, 10 eqv) was added and the reaction stirred for 10 minutes before warming to room temperature. The reaction was allowed to stir overnight. The solvent was removed *in vacuo* (azeotrope 3 × with toluene). The crude product was dried under vacuum for 1–2 hours before being used immediately without purification in the next step. δ_H (400 MHz, $CDCl_3$) 2.13, 2.18 (6H, 2 × s, 2 × OAc), 4.44–4.54 (1H, m, H-4), 4.68–4.83 (2H, m, H-5, H-5′), 5.08 (1H, d, $J_{3,4}$ 5.0 Hz, H-3), 5.55 (1H, s, H-2), 6.39 (1H, s, H-1); δ_C (100.6 MHz, $CDCl_3$) 20.6, 20.7 (2 × s, 2 × OAc), 75.5 (C-3), 80.6 (C-5), 84.7 (C-4), 84.9 (C-2), 88.3 (C-1), 169.5, 170.3 (2 × Ac C=O). Crude bromide (345 mg, ∼1.1 mmol) and dibenzyl phosphate (460 mg, 1.65 mmol) were dried under vacuum before flushing the flask with argon and addition of dry toluene (5 mL). Dry triethylamine (0.34 mL, 1.82 mmol) was added to the mixture. A precipitate was observed within 1–2 minutes and the reaction mixture was allowed to stir for 16 hours at room temperature under an atmosphere of argon. The solvent was removed *in vacuo* (azeotrope 3 × with toluene) and the residue was purified by flash chromatography (1 : 1 40–60 light petrol–ethyl containing 3% triethylamine) to yield dibenzyl phosphate **11** as a waxy solid (210 mg, 38% yield); α–β ratio approx 3 : 1 ratio (by integration of the ^{1}H NMR spectrum). δ_H (400 MHz, $CDCl_3$) 1.94, 2.07, 2.08, 2.10 (12H, 4 × s, 2 × OAc α, 2 × OAc β), 4.13–4.34 (2H, m, H-4a, H-4β), 4.45–4.70 (4H, m, H-5β, H-5′β, H-5α, H-5′α), 5.00–5.11 (9H, m, 2 × $PhCH_2$α, 2 × $PhCH_2$β, H-3α), 5.18 (1H, s, H-2α), 5.23 (1H, ddd, $J_{1,2}$ 4.8 Hz, $J_{2,3}$ 7.1 Hz, $J_{2,P}$ 2.3 Hz, H-2β), 5.38 (1H, dd, $J_{3,4}$ 6.1 Hz, H-3β), 5.85 (1H, d, $J_{1,P}$ 4.8 Hz, H-1α), 6.06 (1H, dd, $J_{1,P}$ 5.1 Hz, H-1β), 7.30–7.38 (20H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.3, 20.6, 20.7, 20.7 (4 × s, 2 × OAc α, 2 × OAc β), 69.4, 66.4–69.6 (2 × $PhCH_2$α, 2 × $PhCH_2$β), 72.9 (d, $J_{C3,F}$ 7.2 Hz, C3-β), 75.6 (d, $J_{C3,F}$ 7.2 Hz, C3-α), 75.9 (dd, $J_{C2,P}$ 7.2 Hz, d, $J_{C2,F}$ 1.6 Hz, C2-β), 80.7 (d, $J_{C4,F}$ 19.9 Hz, C4-β), 81.2 (d, $J_{C2,P}$ 12.0 Hz, C2-α), 81.2 (d, $J_{C5,F}$ 173.4 Hz, C5-α), 82.7 (d, $J_{C5,F}$ 174.9 Hz, C5-β), 83.8 (d, $J_{C4,F}$ 19.2 Hz, C4-α), 97.6 (d, $J_{C\text{-}P}$ 4.8 Hz, C1-β), 103.1 (d, $J_{C\text{-}P}$ 5.6 Hz, C1-α), 127.9–128.1 (Ar-CH), 128.5–128.7 (Ar-CH), 135.4–135.6 (Ar-C), 169.4, 170.0, 170.1, 170.3 (2 × Ac C=O α, 2 × Ac C=O β); δ_F (376.6 MHz, $CDCl_3$) −226.54 (td, $J_{F,H\ geminal}$ 47.0, $J_{F,H\ vicinal}$ 20.7 Hz, F-β), −230.8 (td, $J_{F,H\ geminal}$ 47.0, $J_{F,H\ vicinal}$ 25.2 Hz, F-α); δ_P (162 MHz, $CDCl_3$) −1.81 (P-β), −2.21 (P-α); *m/z* (ES^+) 519 (M + Na^+, 10%), 555 (M + $MeCN/NH_4^+$, 100%); HRMS (ES^+) calculated $NaC_{23}H_{26}FO_9P$ 519.1191. Found 519.1191. ν_{max} (thin film) 1745 (s, C=O), 697, 739 (s, Ar CH bending) cm^{-1}.

2,3-Di-*O*-acetyl-5-fluoro-D-arabinofuranosyl phosphate 13 and 3-*O*-acetyl-5-fluoro-5-deoxy-β-D-arabinofuranose phosphate 12

Dibenzyl phosphate **11** (120 mg, 0.24 mmol) was dissolved in a mixture of ethanol (5 mL) and triethylamine (0.4 mL, 3.0 mmol) before addition of 10% Pd/C (80 mg, 30% w/w). The reaction vessel was evacuated and flushed (3×) with hydrogen gas before allowing the reaction mixture to stir for 48 hours at room temperature under a balloon of hydrogen. The catalyst was filtered and washed with ethanol. The filtrate was concentrated and the residue was dried under vacuum to afford an oil (120 mg, total yield >95%), which was composed of a 1.5 : 1 : 2.5 mixture (by integration of the ^{1}H NMR spectrum) of α-diacetate salt **13**, α,β-diacetate salt **13**β and β-monoacetate salt **12**. Diagnostic signals: **13**α δ_H (400 MHz, $CDCl_3$) 5.73 (1H, d, $J_{1,P}$ 6.5 Hz, H-1α); δ_F (376.6 MHz, $CDCl_3$) −232.27 (td, $J_{F,H\ geminal}$ 48.2, $J_{F,H\ vicinal}$ 26.4 Hz, F-α); **13**β δ_H (400 MHz, $CDCl_3$) 5.83 (1H, dd, $J_{1,2}$ 4.4 Hz, $J_{1,P}$ 7.2 Hz, H-1β); δ_F (376.6 MHz, $CDCl_3$) −226.00 (td, $J_{F,H\ geminal}$ 47.0, $J_{F,H\ vicinal}$ 17.2 Hz, F-β); *m/z* (ES^-) 327 (M^-, 100%); HRMS (ES^-) calculated $C_{10}H_{16}O_{10}P$ 327.0476. Found 327.0477; **12** δ_H (400 MHz, $CDCl_3$) 5.69 (1H, dd, $J_{1,2}$ 4.4 Hz, d, $J_{1,P}$ 6.1 Hz, H-1β); δ_F (376.6 MHz, $CDCl_3$) −225.65 (td, $J_{F,H\ geminal}$ 47.0, $J_{F,H\ vicinal}$ 17.2 Hz, F-β).

***trans*,*trans*-Farnesyl-3-*O*-acetyl-5-fluoro-5-deoxy-β-D-arabinofuranose phosphate ammonium salt 14 and *trans*,*trans*-farnesyl-2,3-di-*O*-acetyl-5-fluoro-5-deoxy-D-arabinofuranose phosphate ammonium salt 15**

The crude mixture of glycosyl phosphates **12** and **13** (115 mg, 0.22 mmol) was dried under vacuum for several hours before DMF (0.4 mL) and a solution of freshly prepared farnesyl trichloroacetimidate (0.44 mmol) in dry toluene (5 mL) was added *via* cannula. The resulting mixture was heated to 65 °C for 16 hours under an atmosphere of argon. The solvent was removed *in vacuo* to afford an oil, which was subjected to wet-flash chromatography (7 : 1 : 0.1 DCM–methanol: 35% NH_3 aq). The initial fractions contained a mixture of diacetate phosphodiesters **15**α and **15**β (15 mg, 14% yield). Diagnostic signals: **15**α δ_H (400 MHz, $CDCl_3$) 5.72 (1H, d, $J_{1,P}$ 6.1 Hz, H-1α); δ_C (100.6 MHz, $DOCD_3$) 103.1 (d, $J_{C1,P}$ 4.8 Hz, C-1α); δ_F (376.6 MHz, $CDCl_3$) −232.41 (td, $J_{F,H\ geminal}$ 47.4, $J_{F,H\ vicinal}$ 25.3 Hz, F-α); δ_P (162 MHz, decoupled, $DOCD_3$) −2.93 (P-α); **15**β δ_H (400 MHz, $CDCl_3$) 5.85 (1H, dd, $J_{1,2}$ 4.1 Hz, $J_{1,P}$ 6.5 Hz, H-1β), δ_C (100.6 MHz, $DOCD_3$) 97.5 (d, $J_{C1,P}$ 4.8 Hz, C-1β); δ_F (376.6 MHz, $CDCl_3$) −226.08 (td, $J_{F,H\ geminal}$ 47.0, $J_{F,H\ vicinal}$ 17.1 Hz, F-β); δ_P (162 MHz, decoupled, $DOCD_3$) −2.46 (P-β); *m/z* (ES^-) 519 (M^-, 100%); HRMS (ES^-) calculated $C_{24}H_{37}FO_9P$ 519.2154. Found 519.2154.

Further elution gave pure β-phosphodiester monoacetate **14** as an oil (25 mg, 24% yield); $[\alpha]_D^{22}$ −40 (*c*, 0.25 $HOCH_3$); δ_H (400 MHz, $DOCD_3$) 1.61, 1.69, 1.71 (farnesyl-CH_3), 1.98–2.12 (farnesyl CH_2), 2.13 (3H, s, OAc), 4.11 (1H, dtd, $J_{3,4}$ 6.9 Hz, $J_{4,5}$ 6.9 Hz, $J_{4,5'}$ 2.8 Hz, $J_{4,F}$ 16.8 Hz, H-4), 4.31 (1H, dd, $J_{1,2}$ 4.4 Hz, $J_{2,3}$ 5.4 Hz, H-2), 4.54–4.73 (2H, m, H-5, H-5′), 4.50 (farnesyl CH_2), 5.07–5.16 (m, farnesyl CH, H-3), 5.40–5.44 (farnesyl CH), 5.65 (1H, dd, $J_{1,P}$ 6.6 Hz, H-1); δ_C (100.6 MHz, $DOCD_3$) 16.1, 16.5 (2 × s, 2 × farnesyl CH_3), 17.8, (1 × farnesyl), 20.8 (OAc CH_3), 25.9 (1 × farnesyl CH_3), 27.4, 27.8 (2 × farnesyl CH_2), 40.7, 40.9 (2 × farnesyl CH_2), 63.6 (1 × farnesyl CH_2), 77.1 (d, $J_{C2,P}$ 7.6 Hz, C-2), 77.8 (d, $J_{C3,F}$ 7.6 Hz, C-3), 79.7 (d, $J_{C4,F}$ 20.0 Hz, C-4), 85.2 (d, $J_{C5,F}$ 171.7 Hz, C-5), 99.4 (d, $J_{C1,P}$ 5.7 Hz, C-1), 122.5, 122.5 (2 × farnesyl CH), 125.5 (1 × farnesyl CH), 132.1, 136.2 (farnesyl CH=CR_2), 140.7 (farnesyl CH=CR_2), 172.5 (2 × Ac C=O); δ_F (376.6 MHz, $CDCl_3$) −226.50 (td, $J_{F,H\ geminal}$ 47.4, $J_{F,H\ vicinal}$ 16.7 Hz); δ_P (162 MHz, decoupled, $DOCD_3$) −1.73 (P-β); *m/z* (ES^-) 477 (M^-, 100%); HRMS (ES^-) calculated $C_{22}H_{35}FO_8P$ 477.204. Found 477.2051.

Dibenzyl 2,3-di-*O*-acetyl-5-*O*-methyl-D-arabinofuranosyl phosphate 16a

Triacetate **4a** (290 mg, 1.0 mmol, 1 eqv) was dissolved in DCM (5 mL) and cooled to −40 °C under an atmosphere of argon.

Trimethylsilyl bromide (1.33 mL, 10 mmol, 10 eqv) was added and the reaction stirred for 10 minutes before warming to room temperature. The reaction was then allowed to stir overnight. The solvent was removed *in vacuo* (azeotrope 3 × with toluene, with water bath temperature <30 °C). The crude product was dried under vacuum for 1–2 hours before being used immediately without further purification) in the next step. δ_H (400 MHz, $CDCl_3$) 2.13, 2.17 (6H, 2 × s, 2 × OAc), 3.44 (3H, s, OCH_3), 3.70 (1H, dd, $J_{4,5}$ 5.1 Hz, $J_{5,5'}$ 10.9 Hz, H-5), 3.76 (1H, dd, $J_{4,5'}$ 3.1 Hz, H-5′), 4.47–4.50 (1H, m, H-4), 5.09 (1H, d, $J_{3,4}$ 5.1 Hz, H-3), 5.50 (1H, s, H-2), 6.39 (1H, s, H-1). The crude bromide (320 mg, ~1.0 mmol) and dibenzyl phosphate (420 mg, 1.5 mmol) were dried under vacuum before flushing the flask with argon and addition of dry toluene (5 mL). Dry triethylamine (0.3 mL, 1.6 mmol) was added to the mixture. A precipitate was observed within 1–2 minutes and the reaction mixture was allowed to stir for 16 hours at room temperature under an atmosphere of argon. The solvent was removed *in vacuo* (azeotrope 3 × with toluene with water bath temperature <30 °C) and the residue was purified by flash chromatography (2 : 3 40–60 light petrol–ethyl containing 3% triethylamine) to give dibenzyl phosphate **16a** as an oil (290 mg, 57%); α–β ratio approx 1 : 1 ratio (by integration of the ^{1}H NMR spectrum). δ_H (400 MHz, $CDCl_3$) 1.96, 2.07, 2.10, 2.10 (12H, 4 × s, 2 × OAc α, 2 × OAc β), 3.29 (3H, s OMeβ), 3.40 (3H, s OMeα), 3.50–3.70 (4H, m, H-5β, H-5′β, H-5α, H-5′α), 4.10–4.18 (1H, m, H-4β), 4.30 (1H, dt, $J_{3,4}$ 5.1 Hz, $J_{4,5}$ 5.1 Hz, $J_{4,5'}$ 3.3 Hz, H-4α), 5.06–5.12 (9H, m, 2 × $PhCH_2$α, 2 × $PhCH_2$β, H-3α), 5.17 (1H, d, $J_{2,3}$ 1.5 Hz H-2α), 5.23 (1H, ddd, $J_{1,2}$ 4.8 Hz, $J_{2,3}$ 7.1 Hz, $J_{2,P}$ 2.3 Hz, H-2β), 5.40 (1H, dd, $J_{3,4}$ 6.1 Hz, H-3β), 5.85 (1H, d, $J_{1,P}$ 4.6 Hz, H-1α), 6.03 (1H, t, $J_{1,P}$ 4.8 Hz, H-1β), 7.29–7.40 (20H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 20.4, 20.7, 20.8, 20.8 (4 × s, 2 × OAc α, 2 × OAc β), 59.2, 59.5 (CH_3α, CH_3β), 66.3, 66.4, 69.4, 69.5 (2 × $PhCH_2$α, 2 × $PhCH_2$β), 71.2 (C5-β), 73.6 (C5-α), 74.3 (C3-β), 76.1 (C2-β), 76.4 (C3-α), 81.0 (C4-β), 81.7 (C2-α), 83.8 (C4-α), 98.0 (d, $J_{C\text{-}P}$ 5.6 Hz, C1-β), 103.1 (d, $J_{C\text{-}P}$ 5.6 Hz, C1-α), 127.8–128.0 (Ar-CH), 128.4–128.6 (Ar-CH), 135.4–135.7 (Ar-C), 169.4, 170.0, 170.1, 170.2 (2 × Ac C=O α, 2 × Ac C=O β); δ_P (162 MHz, $CDCl_3$) −1.73 (P-β), −2.20 (P-α); *m/z* (ES^+) 531 (M + Na^+, 30%), 567 (M + MeCN/NH_4^+, 100%); HRMS (ES^+) calculated $NaC_{24}H_{29}O_{10}P$ 531.1391. Found 531.1384. ν_{max} (thin film) 1747 (s, C=O), 698, 741 (s, Ar CH bending) cm^{-1}.

2,3-Di-*O*-acetyl-5-*O*-methyl-D-arabinofuranosyl phosphate triethylammonium salt 16b

Dibenzyl phosphate **16a** (290 mg, 0.6 mmol) was dissolved in a mixture of ethanol or ethyl acetate (5 mL) and triethylamine (0.4 mL, 3.0 mmol) before addition of 10% Pd/C (80 mg, 30% w/w). The reaction vessel was evacuated and flushed (3×) with hydrogen gas before allowing the reaction mixture to stir for 48 hours at room temperature under a balloon of hydrogen. The catalyst was filtered and washed with ethanol. The filtrate was concentrated and the residue was dried under vacuum to afford the triethylammonium salt **16b** as an oil (230 mg, 77%); α–β ratio approx 3 : 2 ratio (by integration of the ^{1}H NMR spectrum). δ_H (400 MHz, $DOCD_3$) 1.33 (t, $N(CH_2CH_3)_3$), 2.08, 2.09, 2.10, 2.11 (12H, 4 × s, 2 × OAc α, 2 × OAc β), 3.19 (q, $N(CH_2CH_3)_3$), 3.40 (6H, s, OMe α,β), 3.60–3.72 (4H, m, H-5β, H-5′β, H-5α, H-5′α), 4.08 (1H, aq, $J_{3,4}$ 5.8 Hz, $J_{4,5}$ 6.1 Hz, $J_{4,5'}$ 5.8 Hz, H-4β), 4.35 (1H, dt, $J_{3,4}$ 5.1 Hz, $J_{4,5}$ 3.4 Hz, $J_{4,5'}$ 3.4 Hz, H-4α), 4.90–5.01 (1H, m, H-3α), 5.15–5.19 (2H, d H-2α, H-2β), 5.35 (1H, dd, $J_{2,3}$ 7.1 Hz, H-3β), 5.69 (1H, d, $J_{1,P}$ 6.1 Hz, H-1α), 5.80 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{1,P}$ 6.8 Hz, H-1β); δ_C (100.6 MHz, $DOCD_3$) 8.1 ($N(CH_2CH_3)_3$) 19.6, 19.7, 19.7, 19.7 (4 × s, 2 × OAc α, 2 × OAc β), 46.5 ($N(CH_2CH_3)_3$), 58.5, 58.7 (OCH_3α, OCH_3β), 71.9 (C5-β), 74.5 (C5-α), 75.7 (C3-β), 76.7 (d, $J_{C2,P}$ 5.6 Hz,C2-β), 77.6 (C3-α), 80.0 (C4-β), 82.2 (d, $J_{C2,P}$ 11.2 Hz, C2-α), 82.7 (C4-α), 96.3 (d, $J_{C\text{-}P}$ 4.0 Hz, C1-β), 103.1 (d, $J_{C\text{-}P}$ 3.2 Hz, C1-α), 170.3, 170.9, 171.0, 171.0 (2 × Ac C=O α, 2 × Ac C=O β); *m/z* (ES^-) 327 (M^-, 100%); HRMS (ES^-) calculated $C_{10}H_{16}O_{10}P$ 327.0476. Found 327.0477.

trans,*trans*-Farnesyl-2,3-di-*O*-acetyl-5-O-methyl-D-arabinofuranose phosphate 17

Triethylammonium salt **27**(200 mg, 0.4 mmol) was dried under vacuum for several hours before a dry DMF (0.4 mL) and a freshly prepared solution of farnesyl trichloroacetimidate (0.8 mmol) in dry toluene (5 mL) were added. The resulting mixture was heated to 65 °C for 16 hours under an atmosphere of argon. The solvent was removed *in vacuo* to afford an oil, which was purified by flash chromatography (7 : 1 : 0.1 DCM–methanol–35% NH_4OH). Phosphodiester **17** was obtained as an oil (79 mg, 39% yield); α–β ratio approx 1 : 1 ratio (by integration of the ^{1}H NMR spectrum). δ_H (400 MHz, $DOCD_3$) 1.62, 1.69, 1.72 (farnesyl-CH_3) 1.98, 2.00, 2.01, 2.01 (12H, 4 × s, 2 × OAc α, 2 × OAc β), 2.06–2.10 (farnesyl CH_2), 3.39 (3H, s, OMeβ), 3.41 (3H, s, OMeα), 3.59–3.71 (4H, m, H-5β, H-5′β, H-5α, H-5′α), 4.11 (1H, dt, $J_{3,4}$ 5.1 Hz, $J_{4,5}$ 3.5 Hz, $J_{4,5'}$ 5.1 Hz, H-4β), 4.36 (1H, dt, $J_{3,4}$ 5.1 Hz, $J_{4,5}$ 5.1 Hz, $J_{4,5'}$ 3.3 Hz, H-4α), 4.41–4.51 (farnesyl CH_2), 5.02 (1H, dd, $J_{2,3}$ 1.3 Hz, H-3α), 5.09–5.17 (farnesyl CH), 5.18 (1H, d H-2α), 5.20–5.24 (1H, m, H-2β), 5.36 (1H, dd, $J_{2,3}$ 5.7 Hz, H-3β), 5.40–5.46 (farnesyl CH), 5.69 (1H, d, $J_{1,P}$ 6.0 Hz, H-1α), 5.80 (1H, dd, $J_{1,2}$ 4.4 Hz, $J_{1,P}$ 6.3 Hz, H-1β); δ_C (100.6 MHz, $DOCD_3$) 16.1, 16.2, 16.6, 16.6 (4 × s, 2 × farnesyl CH_3-α, 2 × farnesyl CH_3-β), 17.8, 17.8 (1 × farnesyl CH_3-α, 1 × farnesyl CH_3-β), 20.6, 20.7, 20.7, 20.8 (4 × s, 2 × OAc α, 2 × OAc β), 26.0 (1 × farnesyl CH_3-α, 1 × farnesyl CH_3-β), 27.4, 27.4, 27.8, 27.9 (2 × farnesyl CH_2-α, 2 × farnesyl CH_2-β), 40.7, 40.9 (2 × farnesyl CH_2-α, 2 × farnesyl CH_2-β), 59.5, 59.8 (OCH_3α, OCH_3β), 63.5, 63.6 (1 × farnesyl CH_2-α, 1 × farnesyl CH_2-β), 72.9 (C5-β), 75.6 (C5-α), 76.9 (C3-β), 77.7 (d, $J_{C2,P}$ 6.7 Hz,C2-β), 78.6 (C3-α), 81.4 (C4-β), 83.5 (d, $J_{C2,P}$ 9.5 Hz, C2-α), 84.1 (C4-α), 97.7 (d, $J_{C\text{-}P}$ 3.8 Hz, C1-β), 103.1 (d, $J_{C\text{-}P}$ 4.8 Hz, C1-α), 122.3, 122.3, 122.4, 122.4 (2 × farnesyl CH-α, 2 × farnesyl CH-β), 125.1, 125.2, 125.5 (1 × farnesyl CH-α, 1 × farnesyl CH-β), 132.1, 136.3, 136.4 (farnesyl CH=CR_2), 140.8, 140.9 (farnesyl CH=CR_2), 171.2, 171.8, 171.9, 172.0 (2 × Ac C=O α, 2 × Ac C=O β); δ_P (162 MHz, $DOCD_3$) −1.81 (P-β), −2.31 (P-α); *m/z* (ES^-) 531 (M^-, 95%); HRMS (ES^-) calculated $C_{25}H_{40}O_{10}P$ 531.2354. Found 531.2369.

1,2,3-Tri-*O*-acetyl-5-*N*-acetyl-D-arabinofuranose 18

Azide **6a** (500 mg, 1.75 mmol) was dissolved in thioacetic acid (0.5 mL, 6.50 mmol). The resulting mixture was allowed to stir for 16 hours at room temperature under an atmosphere of argon. The solvent was removed *in vacuo* (azeotrope 3 × with toluene–ethanol) and the residue was purified by wet-flash chromatography (the column was first eluted with 1 : 1 40–60 light petrol–ethyl

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acetate to wash out sulfur residues and product was obtained following elution with 5% methanol in ethyl acetate) to afford acetamide **18** as an oil (360 mg, 70%); α–β ratio approx 2 : 1 ratio (by integration of the ^{1}H NMR spectrum). δ_H (400 MHz, $CDCl_3$) 2.08, 2.07, 2.07, 2.06 (12H, 4 × s, 3 × OAc α, 1 × NHAc α) 1.94, 1.95, 2.03, 2.06 (12H, 4 × s, 1 × OAc β, 1 × NHAc β), 3.31–3.38 (1H, m, H-5β), 3.42–3.49 (1H, m, H-5α), 3.56–3.62 (1H, m, H-5′α), 3.66–3.72 (1H, m, H-5′β), 4.02 (1H, dt, $J_{3,4}$ 5.3 Hz, $J_{4,5}$ 5.3 Hz, $J_{4,5'}$ 7.8 Hz, H-4β), 4.23 (1H, dt, $J_{3,4}$ 4.8 Hz, $J_{4,5}$ 4.8 Hz, $J_{4,5'}$ 6.3 Hz, H-4α), 4.89 (1H, $J_{2,3}$ 1.7 Hz, dd, H-3α), 5.14 (1H, d, H-2α), 5.21 (1H, dd, $J_{2,3}$ 5.3 Hz, H-3β), 5.28 (1H, dd, $J_{1,2}$ 4.5 Hz, H-2β), 6.08 (1H, s, H-1α), 6.19–6.21 (2H, m, NHα, NHβ), 6.31 (1H, d, H-1β); δ_C (100.6 MHz, $CDCl_3$) 20.6, 20.7, 21.0 (3 × s, 3 × OAc α), 20.4, 20.8, 21.1 (3 × s, 3 × OAc β), 23.1 (2 × s, NHAc α, NHAc β), 40.7, 42.6 (C5-α, C5-β), 75.4 (C3-β), 75.6 (C2-β), 77.5 (C3-α), 80.6 (C2-α, C4-β), 83.1 (C4-α), 93.6 (C1-α), 99.0 (C1-β), 169.2, 169.4, 169.4, 169.7, 170.1, 170.2, 170.4, 170.5 (4 × Ac C=O α, 4 × Ac C=O β); *m/z* (ES^+) 340 ($M + Na^+$, 50%), 376 ($M + MeCN/NH_4^+$, 100%); HRMS (ES^+) calculated $NaC_{13}H_{19}NO_6$ 340.1003. Found 340.1003; ν_{max} (thin film) 1748 (s, C=O ester), 1660 (s, C=O amide), 1547 (s, N-H bending) cm^{-1}.

Spot culture method for testing of anti-mycobacterial activity

Purified test compounds **4a**, **4b**, **6a**, **6b**, **7a**, **7b**, **9a**, **9b**, **10**, **14**, **17** and **18** were prepared in DMSO at a range of concentrations up to 100 mg mL^{-1}. These stock solutions were added into different wells of 6-well plates, with 5 μL DMSO alone added to control wells (0.1% v/v). Molten MB agar (5 mL) containing OADC (oleic acid-albumin-dextrose-catalase, Difco) was poured immediately into the wells of the 6-well plates containing the extracts with thorough mixing. Once solidified, the MB agar containing test reagents and controls was inoculated with 5 μL of a 10^5 dilution of a mid-log phase culture (OD 1.0) of *M. bovis* BCG Pasteur containing approximately 500 cells. The cells were allowed to soak onto MB agar before the plates were covered, sealed with parafilm, inverted and incubated at 37 °C for 7–14 days. The resulting circular spot cultures were photographed using a BioRad Gel-Doc 2000 system.

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