On the Way to Glycoprocessing Inhibitors − Synthesis of an Imidazolo-Nectrisine-Phosphono Acid Derivative: A Potential Glycosyltranferase Inhibitor

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Assuming the transition state of glycosyltransferase inhibitors to be similar to those encountered with potent glycosidase inhibitors – i.e. a flattened conformation with a positively charged anomeric centre – we worked out a synthesis of the D-*arabino*-configured phosphonic acid target molecule **2** derived from an imidazolo-sugar. The key synthetic intermediate is the linear imidazolo L-*xylo* compound **10** which could be obtained, either from L-*threo* precursor **6** by a coupling reaction with imidazole derivative **5**, or from L-sorbose. A multi-step and site specific iodination of **10** gave the monoiodo-L-*xylo* derivative **14** which was cyclised to the D-*arabino*-configured bicyclic azasugar **15**. Phosphorylation of the Grignard derivative of the latter, followed by mono-esterification with citronellol along with some protection-deprotection steps led to target molecule **2**. The potential inhibitor **2** is supposed to be protonated at its most basic N atom by a carboxylic acid residue in the arabinosyl-transferase active site.

Introduction

Mycobacteria are widespread pathogens which are responsible for diseases, such as tuberculosis and leprosy. Arabinogalactan (AG) and lipoarabinomannan (LAM) are essential components of the mycobacterial cell wall. In view of their xenobiotic character in the human host, these arabinose-polysaccharides provide attractive targets for drug research. In 1994 β-D-arabinofuranosyl-1-monophosphoryl-decaprenol (**1**), a key mycobacterial arabinose, had been identified in the lipid extracts of *Mycobacterium smegmatis*, and considered to be an arabinosyl-donor in biogenetic pathways catalysed by glycosyltranferases.[1] To the best of our knowledge, compound **1** is the only intermediate isolated so far which is most probably involved in arabinan biosynthesis.

Selective inhibition of arabinosyltransferases is of obvious interest, since it should impair the molecular recognition processes which occur in diseases such as tuberculosis and leprosy, in which these enzymes play a key catalytic role.[2] Notwithstanding such ambitious a task, the development of glycosyltransferase inhibitors has led to little progress so far and is of recent vintage, if only because the lack of structural data for glycosyltransferases makes it difficult to design structure-based inhibitors. Nevertheless, the mechanisms of the reactions which are catalysed by glycosyltransferases have been investigated to some extent, in particular for human α-1,3-fucosyltransferase-V by C.-H. Wong and his collaborators.[3,4] It is generally postulated that these enzymatic reactions proceed through a flattened (in the pyranose series it would be through a half-chair conformed) transition state with substantial sp^2 character at the anomeric carbon.[5] Such a reaction mechanism is reminiscent of the one which operates with glycosidases and is believed to involve a positively charged transition state. With that mechanistic analogy in mind, we surmised that properly phosphorylated derivatives of potent glycosidase azasugar-inhibitors would be good candidates as potential, and hopefully potent, glycosyltransferase inhibitors. Previous work along these lines from the Eustache group[6,7] leads us to describe herein our own preliminary investigations.

As reported by us in two previous publications, the eight stereomers of type **4** imidazolo-pyrrolidinopentoses − which are imidazolo analogues of nectrisine **3** − had been synthesised and their inhibitory properties determined with half a dozen glycosidases.[8,12] In these latter series the D-*arabino* stereomer **4** proved to be the most potent inhibitor (K_i = 5 μM with α-D-mannosidase of Jack beans).[8] In view of the assumed analogy between the transition states of glycosidase and glycosyltransferase mechanisms (as alluded to

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above), in view also of the D-*arabino* configuration of the D-arabinosyl donor **1**, we set out to synthesise the sugar-derived phosphonic acid **2** as a likely candidate to inhibit D-arabinosyltranferases. The basic N(2) atom of **2** was supposed to favour binding to the enzyme's active site, while the stable phosphonate ***C*−PO**(OH)(OR) moiety had to replace the labile phosphate C***O-P***O(OH)(OR) (leaving group). In other words, the task of the phosphonate moiety is twofold: i) it permits optimal docking into the enzyme's active site; ii) it prevents the cleavage to take place inside that active site. In the herein described first approach to a potential glycosyltransferase inhibitor, we consider the citronellyl phosphonate moiety of **2** as a rough analogue of the decaprenyl phosphate part of the natural arabinosyl-donor compound **1** (Figure 1).

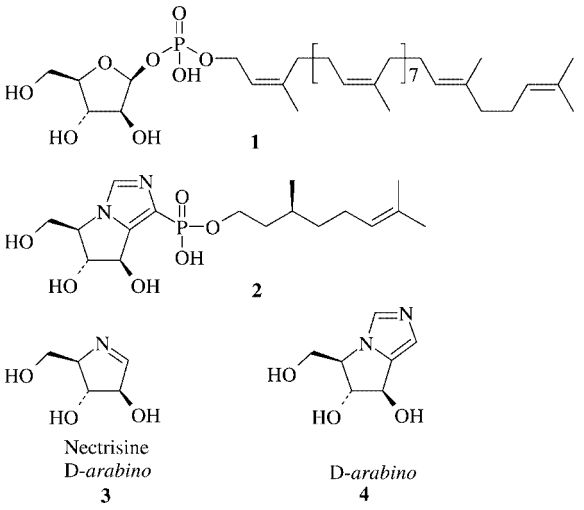
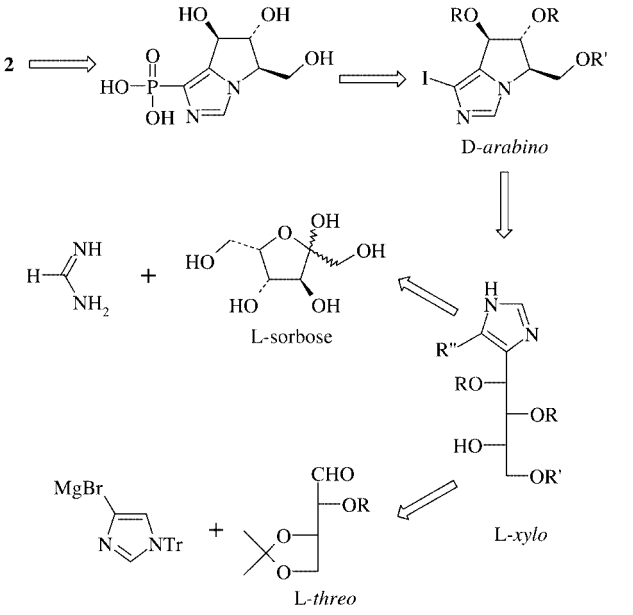


Figure 1. β-D-Arabinofuranosyl-1-monophosphoryldecaprenol (**1**), *S*-(−)-β-citronellylphosphonate imidazolo-D-arabinose (**2**), nectrisine **3** and imidazolo-D-*arabino* derivative **4**

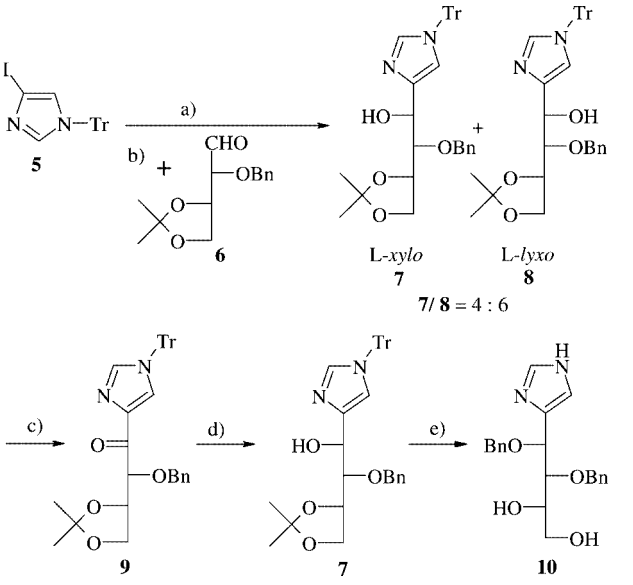
Results and Discussion

Retrosynthetic Analysis (Scheme 1): Retrosynthetic analysis of the target molecule **2** is reproduced in an abridged form in Scheme 1. The key intermediate is a linear 4′(5′)-iodo-L-*xylo* imidazole derivative which can be obtained, either from L-threose by a nucleophilic addition of a *C*-metallated imidazole to the aldehyde function, or from L-sorbose via a double condensation with formamidine, almost all reacting species having to be used with the appropriate protecting groups. Site specific iodination of the said L-*xylo* derivative, followed by intramolecular cyclisation, was expected to lead to a bicyclic D-*arabino* iodoimidazole intermediate. The Grignard derivative of the latter product had to be phosphorylated, followed by mono-esterification to the target molecule **2**. The experimental results (see below) did confirm the above retrosynthetic expectations indeed.[9]



Scheme 1. Retrosynthetic pathway for the synthesis of the citronellylphosphonate imidazolo-D-arabinose **2**

Synthesis of the L-Xylo Intermediate 10 (Scheme 2): In a first approach, we made use of the 4-iodo-1-trityl derivative **5** which had already been described by Kirk.[10] The reaction of the Grignard derivative of **5** with the known L-*threo* compound **6**[11] gave a mixture of the two diastereomers **7** and **8** (in a 4:6 ratio) which were not separated. Since only the minor L-*xylo* diastereomer **7** was of interest, the preceding mixture was oxidised (MnO_2) to the crystalline ketone **9** in 69% overall yield (from **6**); its enantiomer *ent*-**9** had already been described in a recent publication.[8]

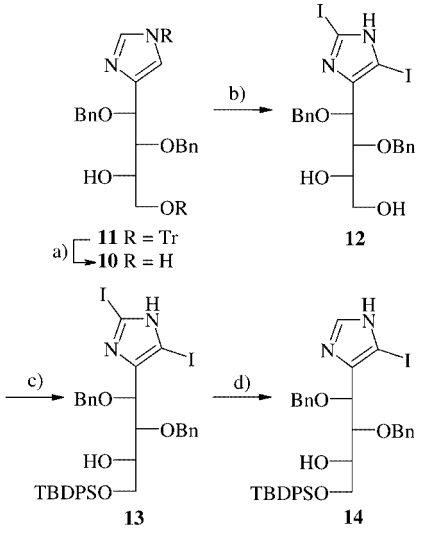


Scheme 2. Reagents and conditions: a) CH_2Cl_2, EtMgBr/Et_2O, room temp., 30 min; b) room temp., 2 h; c) CH_2Cl_2, MnO_2, room temp., 1.5 h (69% from **6**); d) THF, L-selectride, −78 °C, 30 min (84%); e) 1) THF, NaH, nBu_4N cat., 30 min, 2) BnBr, room temp., 2 h, 3) THF, 4 M HCl, reflux (77%)

L-Selectride reduction of **9** at low temperature led in 84% yield to the desired L-*xylo* derivative **7** as the major compound (95%), the minor diastereomer **8** being formed in trace amounts only (5%). *O*-Benzylation of **7** followed by removal of the acid labile protecting groups gave the target L-*xylo* molecule **10** in 77% overall yield (from **7**). The synthesis of *ent*-**10** has already been described;[8] not surprisingly, ^1H and ^{13}C NMR spectroscopic data of **10** and *ent*-**10** turned out to be identical (see Exp. Sect.).

The second approach was quite simple: the imidazolo-L-*xylo* derivative **11**, which we had obtained previously from L-sorbose,[12] was partly deprotected in acidic medium to give the target L-*xylo* key intermediate **10**.

Selective Iodination of the Imidazole Ring at C-4′,5′) (Scheme 3): By applying a procedure which had been developed with histidine derivatives by Jain and his collaborators,[13] reaction of **10** with NIS in excess led to the bis-iodo derivative **12** in close to quantitative yield. Selective



Scheme 3. Reagents and conditions: a) EtOH/6 M HCl, 65 °C, 1.5 h (71%); b) acetonitrile, NIS, room temp., 12 h (93%); b) CH_2Cl_2, NEt_3, TBDPSCl, imidazole, room temp., 12 h; d) EtOH, H_2O, Na_2SO_3, reflux, 2 h [84% for step c) and d)]

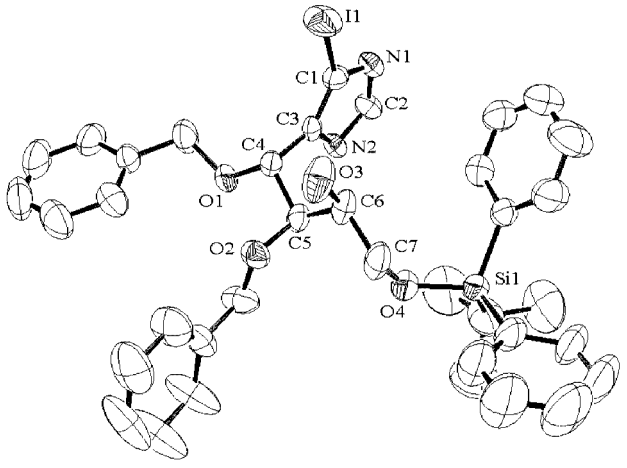
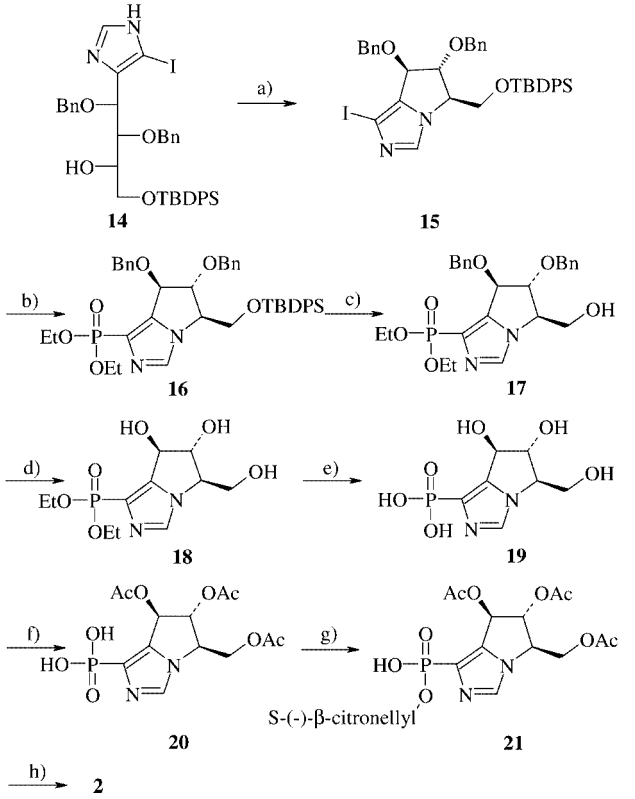


Figure 2. ORTEP plot of the structure of **14** (50% probability ellipsoids; H atoms were removed for clarity)

silylation of the primary alcohol of **12** was achieved in high yield (93%) with TBDPSCl in the presence of imidazole and Et_3N and led to **13**. That latter compound **13** was reduced with Na_2SO_3 [14] in high yield to give selectively the mono-iodo derivative **14**. The position of the iodine of **14** was demonstrated unambiguously by a single crystal X-ray diffraction analysis (Figure 2). Overall, the three-step conversion of **10** into the desired mono-iodo intermediate **14** was achieved in 78% overall yield.

Synthesis of the D-arabino Citronellyl-Phosphono Ester Target Molecule 2 (Scheme 4): *O*-Mesylation of the key L-*xylo* intermediate **14** in pyridine was at once followed by intramolecular cyclisation (via a Walden inversion) to the bicyclic D-*arabino* compound **15** in 96% overall yield. Reaction of the Grignard reagent of **15** with diethyl chlorophosphite at low temperature gave the diethyl phosphinite which, without isolation, was at once oxidised with *tert*-butyl hydroperoxide to the corresponding diethylphosphonate **16** (88% overall yield from **15**). Cleavage of the Si−O bond of **16** with TBAF led to **17** (72%), and hydrogenolysis of the two O−Bn bonds (H_2/$Pd(OH)_2$/C) of the latter gave **18** (92%). The diethylphosphonate ester moiety of compound **18** was cleaved quantitatively (Me_3SiBr) to the corresponding phosphonic acid **19**, whose triethylammonium



Scheme 4. a) 1) pyridine, MsCl, room temp., 1 h, 2) + Ac_2O, 80 °C, 18 h (96%); b) 1) CH_2Cl_2, EtMgBr/Et_2O, room temp., 30 min, 2), + $(EtO)_2PCl$, −78 °C to room temp., 3) + *tert*-butyl hydroperoxide, −15 °C to room temp. (88%); c) THF, nBu_4NF, room temp. (72%); d) EtOH, AcOH, H_2, $Pd(OH)_2$/C, room temp., 12 h; e) CH_2Cl_2, Me_3SiBr, room temp., 60 h (quant.); f) 1) NEt_3, H_2O, room temp. 15 min, 2) pyridine, Ac_2O, room temp., 16 h; g) acetonitrile, pyridine, citronellol, 70 °C, 16 h; h) MeOH, Amberlyst A-26 (OH^-), room temp., 1.5 h

salt was treated with acetic anhydride to give the triacetate phosphono acid salt **20**. Compound **20** was not purified and reacted at once with citronellol and CCl_3CN in pyridine to give a mixture containing **21**. That mixture was treated with a basic Amberlyst A-26 (OH^-) resin to give the fully characterised target molecule **2**, in poor yield though (20% overall from **20**).

Arabinosyltransferase Assay: Based on the previous use of specific neoglycolipid acceptors,[15] assays performed in the presence of membranes and the potential inhibitor **2** were examined for [^{14}C]Araf incorporation from DP-[^{14}C]A onto the synthetic acceptors. Scintillation counting followed by TLC/autoradiography of the reaction products demonstrated that **2** possessed no inhibitory activity, i.e. control acceptor activity corresponded to a duplicate set of assays determined to be 3,280 and 3,450 cpm; with the inhibitor they were within experimental error and corresponded to values between 3,190 and 3,650 cpm.

Experimental Section

General: Flash chromatography (FC): silica gel (Merck 60; 230−400 mesh). TLC: silica gel on aluminium sheets (Merck 60 HF_{254}); the spots were viewed under UV or by heating with a thermogun after spraying with a solution of $KMnO_4$ (20 g) and Na_2CO_3 (40 g) in H_2O (1 L) or a solution of phosphomolybdic acid (5% in 96% EtOH). M.p. Kofler hot-bench or Büchi SMP apparatus; corrected values. Optical rotations were all measured at +20 °C: Schmidt−Haensch Polartronic Universal polarimeter. ^{1}H and ^{13}C NMR spectra: 250 or 400 MHz and 62.9 or 100.6 MHz, respectively; Bruker ACF-250 and Bruker DSX-400 spectrometers at 300 K. ^{31}P NMR spectra: Bruker DSX-400 at 161.9 MHz. Internal references for ^{1}H NMR: $SiMe_4$ (δ = 0.00 ppm), $CDCl_3$ (δ = 7.26 ppm), CD_3OD (δ = 3.30 ppm), dioxane for spectra in D_2O (δ = 3.7 ppm); for ^{13}C NMR: $CDCl_3$ (δ = 77.03 ppm), CD_3OD (δ = 49.02 ppm), dioxane for spectra in D_2O (δ = 67.34 ppm); external reference for ^{31}P: 85% H_3PO_4 (δ = 0.0 ppm); δ in ppm and *J* in Hz. HR-MS were measured with ESI mode in the departments of spectroscopy of Hoffmann-La Roche and Novartis in Basle. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS, 69390 Vernaison, France, and by the Service de Microanalyses of the ICSN/CNRS, 91198 Gif-sur-Yvette, France. "MeOH + NH_3" stands for a solution of pure MeOH saturated at room temp. with NH_3 (ex gas form). CH_2Cl_2 was dried by distilling over P_2O_5.

Synthesis of Ketone 9: A solution of EtMgBr in Et_2O (3 M, 1.9 mL, 5.70 mmol) was added dropwise under argon at room temp. to a stirred solution of 4-iodo-1-tritylimidazole (**5**, 2.30 g, 5.27 mmol)[16] in anhydrous CH_2Cl_2. After 30 min, a solution of aldehyde **6** (1.10 g, 4.39 mmol)[11] in anhydrous CH_2Cl_2 (6 mL) was added to the stirred mixture and left to react at room temp., the reaction being monitored by TLC (EtOAc/cyclohexane, 7:3). After 2 h, the reaction was quenched with a saturated aq. solution of NH_4Cl (40 mL) and the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated to dryness in vacuo. The crude residue was purified by chromatography (EtOAc/cyclohexane, 1:1, then 8:2), the two diastereomers **7** and **8** (in a 4:6 ratio) as well as trace amounts of imidazole not being separated (all together: 2.33 g).

Precipitated activated MnO_2 (9.0 g) was added under argon at room temp. to a stirred solution of the above mixture of **7** +**8** (2.33 g in CH_2Cl_2, 40 mL). After 90 min, the reaction mixture was filtered, evaporated to dryness and the residue purified by chromatography (EtOAc/cyclohexane 1:1), to provide ketone **9** as a colourless foam (1.69 g, 69%) which was recrystallised (EtOAc/cyclohexane). M.p. 125 °C (*ent*-**9**: m.p. 126 °C[8]). $[\alpha]_D^{20}$ = +43 (*c* = 2, $CHCl_3$) (*ent*-**9**: $[\alpha]_D^{20}$ = −41[8]). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.27 (s, 3 H, C*H*$_3$ acetonide], 1.30 (s, 3 H, C*H*$_3$ acetonide], 3.96 (dd, 1 H, 4-H$_b$], 4.01 (dd, 1 H, 4-H$_a$), 4.48 and 4.70 (*AB*, *J* = 11.7, 2 H, OC*H*$_2$Ph), 4.56 (td, 1 H, 3-H), 4.70 (d, 1 H, 2-H), 7.06−7.38 (m, 20 H, H arom.), 7.47 (d, 1 H, 5′-H), 7.85 (d, 1 H, 2′-H) ppm, $J_{2',5'}$ = 1.2, $J_{2,3}$ = 4.7, $J_{3,4a}$ = 6.6, $J_{3,4b}$ = 6.8, $J_{4a,4b}$ = 8.3 Hz. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 25.4 and 26.1 ppm (2 × *C*H$_3$ acetonide), 65.7 (C-4), 72.7 (*C*H$_2$Ph), 76.2 [*C*(Ph)$_3$), 76.4 (C-3), 82.1 (C-2), 109.8 [*C*(CH$_3$)$_2$ acetonide), 127.7−129.6 (C arom. and C-5′), 137.5 (C$_s$ of Ph), 138.7 (C-4′), 139.6 (C-2′), 141.6 (C$_s$ of C*Ph*$_3$), 193.3 (C-1) ppm. $C_{36}H_{34}N_2O_4$ (558.65): calcd. C 77.39, H 6.13, N 5.01; found C 77.0, H 6.2, N 5.1. Both NMR spectra were identical with those of *ent*-**9**.[8]

Imidazolo-L-*xylo* Derivative 7: A solution of L-Selectride (1 M, 1.2 mL, 1.2 mmol) in THF was added dropwise at −78 °C to a stirred solution of **9** (455 mg, 0.81 mmol) in anhydrous THF (8 mL). The reaction was monitored by TLC (EtOAc/cyclohexane, 1:1). After 1 h at −78 °C, the solution was quenched with MeOH (2 mL), warmed up to room temp., diluted with a saturated solution of NH_4Cl (10 mL) and the aq. phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated to dryness, and purified by chromatography (EtOAc/cyclohexane, 1:1) to give a mixture of **7** + **8** (381 mg, 84%) in a 95:5 ratio, as determined by reverse phase HPLC (Chiracel OD-R column, eluent: MeOH/H_2O, 95:5). The two diastereomers were not separated. ^{1}H NMR ($CDCl_3$, 250 MHz) of **7**: delta = 1.34 and 1.41 (2s, 6 H, 2 × C*H*$_3$ acetonide), 3.14 (d large, OH), 3.73 (t, 1 H, 2-H), 3.94 (m, 2 H, 4-H$_b$), 4.26 (q, 1 H, 4-H$_a$), 4.50 and 4.68 (*AB*, *J* = 11.3, 2 H, OC*H*$_2$Ph), 4.72 (m, 1 H, 1-H), 6.90 (s, 1 H, 5′-H), 7.10−7.35 (m, 20 H, H arom.), 7.43 (d, 1 H, 2′-H) ppm.

Imidazolo-L-*xylo* Derivative 10 (*First Approach*): A suspension of NaH in oil (50%, 50 mg, ca. 1.0 mmol) was added at 0 °C to a stirred solution of almost pure **7** (as obtained above: 381 mg, 0.68 mmol) in anhydrous THF (10 mL) under argon. When the evolution of H_2 had ceased, Bu_4NI (ca. 5 mg) and BnBr (100 μL, 0.82 mmol) were added, the vigorously stirred solution was heated at 40 °C for 12 h, cooled to room temp., and MeOH (1 mL) was added slowly. The solution was concentrated to dryness, the residue taken up in CH_2Cl_2 (15 mL), and the resulting solution was washed with H_2O, then with brine and concentrated to dryness, to afford the dibenzyl intermediate which was neither purified nor characterised. The latter crude product was dissolved in a mixture of THF (10 mL) and 4 M HCl (6 mL) and heated at reflux for 4 h. THF was evaporated in vacuo, the aqueous phase was diluted with H_2O (30 mL) and extracted with Et_2O (2 × 50 mL), basified with some solid Na_2CO_3, and the heterogeneous mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated to dryness, and the crude residue was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 9:1) to afford **10** as a crystalline compound (193 mg, 77%). M.p. 114−115 °C (EtOAc/MeOH). $[\alpha]_D^{20}$ = −42 (*c* = 1, MeOH) (*ent*-**10**: m.p. 114 °C, $[\alpha]_D^{20}$ = +47 [8]). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.33 (td, 1 H, 3-H), 3.49 (dd, 1 H, 4-H$_b$), 3.51 (dd, 1 H, 4-H$_a$), 3.96 (dd, 1 H, 2-H), 4.36 and 4.47 (*AB*, *J* = 11.6, 2 H, OC*H*$_2$Ph), 4.67 and 4.94 (*AB*, *J* = 11.0, 2 H, OC*H*$_2$Ph), 4.83 (d, 1 H, 1-H), 7.10 (s, 1 H, 5′-H), 7.22−7.36 (m, 10 H, H arom.), 7.71 (s, 1 H, 2′-H)

ppm, $J_{1,2}$ = 8.3, $J_{2,3}$ = 1.6, $J_{3,4a}$ = $J_{3,4b}$ = 6.3, $J_{4a,4b}$ = 10.2 Hz. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 64.5 (C-4), 71.9 (O*C*H$_2$Ph), 72.8 (C-3), 76.6 (O*C*H$_2$Ph), 78.0 (C-1), 82.5 (C-2), 128.5−129.4 (C arom. and C-5′), 137.1 (C-2′), 139.9 (C-4′), 140.3 (2 C_s phenyl) ppm. $C_{21}H_{24}N_2O_4$·1/2H_2O (377.44): calcd. C 66.83, H 6.68, N 7.42; found C 66.8, H 6.6, N 7.5.

Imidazolo-L-*xylo* Derivative 10 (*Second Approach*): A stirred solution of the known imidazole derivative **11** (4.24 g, 4.97 mmol)[12] in EtOH/6 M HCl (70:30, 70 mL) was heated to 65 °C for 90 min. After cooling to room temp. the solution was evaporated to near dryness, then diluted with H_2O (10 mL) and extracted with Et_2O (10 mL). The aq. phase was basified with some NaOH pellets and the resulting heterogeneous mixture was extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, evaporated to dryness and the crude residue was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 9:1) to give **10** (1.30 g, 71%) as a crystalline compound (EtOAc/MeOH). The ^{1}H and ^{13}C NMR spectroscopic data of the latter compound were identical and superimposable with those of **10** as obtained according to the first approach (see above).

Formation of the 2,5-Diiodoimidazole L-*xylo* Derivative 12: A solution of **10** (2.46 g, 6.68 mmol) and NIS (3.6 g, 16.0 mmol) in CH_3CN (50 mL) was stirred at room temp. in the dark. After 12 h the solution was evaporated to near dryness, and the residue dissolved in EtOAc (60 mL). To the resulting solution a saturated aq. solution of Na_2S (15 mL) was added and the biphasic mixture was vigorously stirred at room temp. for 15 min. The organic phase was separated, washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered and the solvents evaporated to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH + NH_3, 9:1) to give **12** (3.87 g, 93%) as a pale yellow foam. $[\alpha]_D^{20}$ = −2 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.56 (dd, 1 H, 4-H$_b$), 3.62 (dd, 1 H, 4-H$_a$), 3.77 (dd, 1 H, 2-H), 3.94 (m, 1 H, 3-H), 4.32 and 4.46 (*AB*, *J* = 11.8, 2 H, OC*H*$_2$Ph), 4.50 and 4.56 (*AB*, *J* = 10.8, OC*H*$_2$Ph, 2 H), 4.74 (d, 1 H, 1-H), 7.20−7.34 (m, 10 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 64.1 (C-4), 70.9 (C-3), 71.2 (O*C*H$_2$Ph), 73.1 (C-1), 74.5 (O*C*H$_2$Ph), 79.4 (C-2), 85.2 (C-2′), 128.1−128.7 (C arom. phenyl), 136.9 (C_s arom. phenyl); the (C-4′) and (C-5′) bands could not be detected on the recorded spectrum.

Formation of 4-*O*-TBDPS Derivative 13 and of 4′-Imidazolyl-5′-iodo-1,2-di-*O*-TBDPS-L-*xylo* Derivative 14: A solution of imidazole (637 mg, 9.36 mmol), which had been dried by azeotropic distillation with toluene, anhydrous Et_3N (1.1 mL, 8.1 mmol), TBDPSCl (1.8 mL, 6.9 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (30 mL) was stirred at room temp. for 30 min. To that solution was added a solution of di-iodo derivative **12** (3.87 g, 6.24 mmol) in CH_2Cl_2 (20 mL) and the resulting mixture was stirred in the dark at room temp. for 12 h. The reaction medium was washed with a saturated aq. solution of NH_4Cl (30 mL), and the organic phase was evaporated to dryness to give crude compound **13** which was not purified any further and used as such in the next reaction step. To a solution of that crude compound **13** in EtOH (50 mL), Na_2SO_3 (1.57 g, 12.48 mmol) and H_2O (50 mL) were added. The resulting heterogeneous mixture was vigorously stirred at 80 °C for 2 h, cooled to room temp. and EtOH was evaporated in vacuo. The resulting aqueous mixture was extracted with EtOAc (2 × 50 mL), the combined organic phases were dried ($MgSO_4$), filtered and the solvents evaporated. The residue was purified by chromatography (EtOAc/cyclohexane, 1:1) to give **14** (3.85 g, 84%) as colourless crystals. M.p. 162 °C (EtOH/H_2O); one of the monocrystals was used for X-ray diffraction analysis (Figure 1).

Characterisation of 13 by NMR Spectroscopy: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.06 [s, 9 H, SiC(C*H*$_3$)$_3$], 2.82 (s_{large}, OH), 3.62 (dd, 1 H, 4-Hb), 3.74 (dd, 1 H, 4-Ha), 3.85 (dd, 1 H, 2-H), 4.16 (m, 1 H, 3-H), 4.30 and 4.44 (*AB*, *J* = 11.8, 2 H, OC*H*$_2$Ph), 4.41 and 4.47 (*AB*, *J* = 11.0, 2 H, OC*H*$_2$Ph), 4.73 (d, 1 H, 1-H), 7.10−7.65 (m, 20 H, H arom. phenyl), 10.56 (s_{large}, 1 H, NH) ppm, $J_{1,2}$ = 5.5, $J_{2,3}$ = 2.6, $J_{3,4a}$ = 6.4, $J_{3,4b}$ = 6.2, $J_{4a,4b}$ = 10.2. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 19.0 [Si*C*(CH$_3$)$_3$], 26.7 [SiC(*C*H$_3$)$_3$], 64.3 (C-4), 70.6 (C-3), 70.8 (O*C*H$_2$Ph), 72.1 (C-1), 73.9 (O*C*H$_2$Ph), 77.0 (C-2), 84.3 (C-5′), 86.4 (C-2′), 127.6−128.4 (*C*H phenyl), 129.7 (*C*H phenyl), 132.6 and 132.7 (C_s phenyl), 134.9 (C(4′)), 135.3 (*C*H phenyl), 136.7 and 136.8 (C_s phenyl) ppm.

Characterisation of Compound 14: $[\alpha]_D^{20}$ = −9.5 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.05 [s, 9 H, SiC(CH$_3$)$_3$], 2.85 (d, 1 H, OH), 3.63 (dd, 1 H, 4-H$_b$), 3.72 (dd, 1 H, 4-H$_a$), 3.91 (dd, 1 H, 2-H), 4.12 (m, 1 H, 3-H), 4.30 and 4.43 (*AB*, *J* = 11.8, 2 H, OC*H*$_2$Ph), 4.45 (s, 2 H, OC*H*$_2$Ph), 4.82 (d, 1 H, 1-H), 7.10−7.65 (m, 20 H, H arom. phenyl), 7.56 (s, 1 H, C-2′-H), 10.55 (s_{large}, NH) ppm, $J_{1,2}$ = 5.7, $J_{2,3}$ = 2.5, $J_{3,4a}$ = 6.3, $J_{3,OH}$ = 5.6, $J_{3,4b}$ = 6.6, $J_{4a,4b}$ = 10.2 Hz. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.2 [Si*C*(CH3)3], 26.9 [SiC(*C*H$_3$)$_3$], 64.6 (C-4), 70.9 (C-3), 71.0 (O*C*H$_2$Ph), 72.8 (C-1), 74.1 (O*C*H$_2$Ph), 77.6 (C-2), 86.2 (C-5′), 127.8−128.5 (*C*H phenyl), 129.3 (C-4′), 129.9 (*C*H phenyl), 133.0 and 133.1 (C_s phenyl), 135.6 (*C*H phenyl), 137.3 (C_s phenyl), 137.8 (C-2′) ppm. $C_{37}H_{41}IN_2O_4Si$ (732.73): calcd. C 60.65, H 5.64, N 3.82, I 17.32; found C 60.7, H 5.7, N 3.8, I 17.2.

Synthesis of 1-Iodo-imidazolo-D-*arabino*-pyrrolidinose Derivative 15: To a stirred solution of **14** (500 mg, 0.682 mmol) in anhydrous pyridine (8 mL) at 0 °C, MsCl (160 μL, 2.05 mmol, 3.0 equiv.uiv.) was added. After 1 h at room temp., Ac_2O (500 μL; excess) was added, the reaction mixture was heated at 80 °C for 18 h, then cooled to room temp., treated with EtOH (500 μL) and the solvents evaporated to dryness. The oily residue was taken up in a stirred mixture of EtOAc (40 mL) and H_2O (40 mL). The resulting organic phase was separated, washed with a saturated solution of $NaHCO_3$ (20 mL) and with brine (20 mL), dried ($MgSO_4$), filtered and the solvents evaporated to dryness. The residue was purified by chromatography (EtOAc/cyclohexane, 3:7) to give **15** (467 mg, 96%) as a pale yellow oil. $[\alpha]_D^{20}$ = +9 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.05 [s, 9 H, SiC(C*H*$_3$)$_3$], 3.79 (dd, 1 H, 8-H$_b$), 3.82 (dd, 1 H, 8-H$_a$), 4.27 (s_{large}, 1 H, 6-H), 4.35 (ddd, 1 H, 5-H), 4.46 and 4.51 (*AB*, *J* = 11.9, 2 H, OC*H*$_2$Ph), 4.56 and 4.67 (*AB*, *J* = 11.5, 2 H, OC*H*$_2$Ph), 4.71 (d, 1 H, 7-H), 7.19−7.60 (m, 20 H, H arom. phenyl), 7.51 (s, 1 H, 3-H) ppm, $J_{7,6}$ = 0.6, $J_{6.5}$ = 1.1, $J_{5,Ha}$ = 5.5, $J_{,Hb}$ = 8.4, $J_{Ha,Hb}$ = 10.5 Hz. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.1 [Si*C*(CH$_3$)$_3$], 26.8 [SiC(*C*H$_3$)$_3$], 64.3 (*C*H$_2$OSi), 65.0 (C-5), 71.7 (O*C*H$_2$Ph), 71.8 (O*C*H$_2$Ph), 75.6 (C-7), 76.8 (C-1), 89.3 (C-6), 127.6−128.5 (*C*H arom. phenyl), 129.9 and 130.0 (*C*H arom. phenyl), 132.3 and 132.5 (C_s phenyl), 134.5 (C-3), 135.4 and 135.5 (*C*H arom. phenyl), 136.8 and 137.4 (C_s phenyl), 138.6 (C-7a) ppm. HR-MS: [M + H]$^+$ ion 715.1852 ($C_{37}H_{40}IN_2O_3Si$, calcd. 715.1853).

Synthesis of 1-Diethylphosphonate-imidazolo-D-*arabino* -Pyrrolidinose Derivative 16: To a stirred solution of **15** (1.14 g, 1.59 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise a 3.0 M solution of EtMgBr in Et_2O (640 μL, 1.92 mmol) at room temp. After 30 min the solution was cooled to −78 °C, diethylphosphite chloride (345 μL, 2.38 mmol) was added and the reaction mixture was slowly heated to room temp. After 1 h at room temp. it was cooled to −15 °C, a solution of ca. 5 M *t*BuOOH in n-decane (480 μL, ca. 2.4 mmol) was added, the reaction mixture was stirred at −15 °C for 15 min, then at room temp. for 60 min, and finally hydrolysed with a saturated aqueous solution of $NaHCO_3$ (40 mL). The or-

ganic phase was dried ($MgSO_4$), filtered and the solvents evaporated to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH, 98:2) to give **16** (1.02 g, 88%) as a pale yellow oil. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.05 [s, 9 H, SiC(CH_3)$_3$], 1.25−1.41 (m, 6 H, 2 × OCH$_2$CH_3), 3.81 (dd, 1 H, 8-H$_b$), 3.86 (dd, 1 H, 8-H$_a$), 4.07−4.34 (m, 6 H, 5-H, 6-H and 2 × OCH_2CH$_3$), 4.39 and 4.50 (*AB*, *J* = 11.8, 2 H, OCH_2Ph), 4.72 and 4.78 (*AB*, *J* = 11.6, 2 H, OCH_2Ph), 5.04 (s, 1 H, 7-H), 7.19−7.63 (m, 20 H, H arom. phenyl), 7.72 (d, 1 H, 3-H) ppm, $J_{3,P}$ = 1.6, $J_{5,Ha}$ = 5.9, $J_{5,Hb}$ = 8.6, $J_{Ha,Hb}$ = 10.5 Hz. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.0−16.4 (CH$_2$*C*H$_3$), 19.1 [Si*C*(CH$_3$)$_3$], 26.8 [SiC(*C*H$_3$)$_3$], 62.3−62.4 (*C*H$_2$CH$_3$), 64.3 (*C*H$_2$OSi), 65.3 (C-5), 71.7 (O*C*H$_2$Ph), 71.8 (O*C*H$_2$Ph), 75.3 (C-7), 90.0 (C-6), 123.9 (d, $J^1_{C,P}$ = 248, C-1), 127.6−128.5 (*C*H phenyl), 130.0 and 130.1 (*C*H phenyl), 132.4 and 132.6 (C$_s$ phenyl), 134.2 (d, $J^3_{C,P}$ = 21, C-3), 135.4 and 135.5 (*C*H phenyl), 136.8 and 137.9 (C$_s$ phenyl), 144.4 (d, $J^2_{C,P}$ = 38, C-7a) ppm. ^{31}P NMR ($CDCl_3$, 101.2 MHz): δ = 12.1 ppm.

Synthesis of the 1-Diethylphosphonate-Imidazole-D-*arabino*-Pyrrolidinose Derivative 17: To a stirred solution of **16** (1.00 g, 1.38 mmol) in THF (30 mL) at room temp. was added dropwise a solution of 1.0 M TBAF in THF (2.0 mL, 2.0 mmol). After 1 h the reaction medium was evaporated to near dryness, taken up in EtOAc (50 mL) and the resulting solution washed with a saturated aq. solution of NH_4Cl (30 mL) and with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and the solvents evaporated to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH, 95:5) to give **17** (481 mg, 72%) as a pale yellow oil. $[\alpha]_D^{20}$ = +1 (*c* = 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.33 and 1.29 (2t, *J* = 7.1, 6 H, 2 × CH$_2$−CH_3), 3.80 (dd, 1 H, 8-H$_b$), 3.91 (dd, 1 H, 8-H$_a$), 4.06−4.24 (m, 4 H, 2 × CH_2CH$_3$), 4.33 (s, 1 H, 6-H), 4.38 (dd, 1 H, 5-H), 4.48 and 4.58 (*AB*, *J* = 11.8, 2 H, OCH_2Ph), 4.77 and 4.83 (*AB*, *J* = 11.5, 2 H, OCH_2Ph), 5.06 (s, 1 H, 7-H), 7.23−7.35 (m, 10 H, H arom. phenyl), 7.65 (d, 1 H, 3-H) ppm, $J_{3,P}$ = 1.6, $J_{5,Ha}$ = 4.8, $J_{5,Hb}$ = 7.9, $J_{Ha,Hb}$ = 11.3) Hz. ^{13}C NMR ($CDCl_3$, 62.9 MHz]: δ = 16.2 (d, $^3J_{C,P}$ = 1, CH$_2$*C*H$_3$), 16.3 (d, $^3J_{C,P}$ = 1, CH$_2$*C*H$_3$), 62.4 (d, $^2J_{C,P}$ = 6, *C*H$_2$CH$_3$), 62.5 (d, $^2J_{C,P}$ = 6, *C*H$_2$CH$_3$), 62.6 (*C*H$_2$OH), 65.5 (C-5), 71.8 (O*C*H$_2$Ph), 71.9 (O*C*H$_2$Ph), 75.5 (C-7), 90.0 (C-6), 123.3 (d, $J^1_{C,P}$ = 249, C-1), 127.7−128.5 (*C*H arom phenyl), 134.3 (d, $J^3_{C,P}$ = 21, C-3), 136.7 and 137.6 (2C$_s$, phenyl), 144.1 (d, $J^2_{C,P}$ = 37, C-7a) ppm. ^{31}P NMR ($CDCl_3$, 101.2 MHz): δ = 12.3 ppm. HR-MS: [M +]$^+$ ion 487.1996 ($C_{25}H_{32}N_2O_6P$, calcd. 487.1998).

Synthesis of 1-Diethylphosphonate-Imidazole-D-*arabino*-Pyrrolidinose Derivative 18: A solution of **17** (480 mg, 0.98 mmol) in EtOH (7 mL) and AcOH (7 mL) which contained 20% Pd(OH)$_2$/C (Pearlman catalyst) was placed under H_2 (2 at). The heterogeneous reaction mixture was vigorously stirred for 12 h at room temp., then submitted to centrifugation. The catalyst was washed several times with hot MeOH, the combined organic portions were evaporated in vacuo to dryness, the residue was dissolved in MeOH **(3** mL) and percolated over some IRA 400 (OH^- form) resin beads with MeOH. The fractions which contained the product were combined, then evaporated to dryness and the resulting residue was purified by chromatography ($CHCl_3$/MeOH 8:2) to give **18** (280 mg, 92%) as a crystalline material. M.p. 122 °C. $[\alpha]_D^{20}$ = +42 (*c* = 1, MeOH). ^1H NMR (CD_3OD, 400 MHz): δ = 1.31 and 1.32 (2t, *J* = 7.1, 6 H, 2 × CH$_2$CH_3), 3.77 (dd, 1 H, 8-H$_b$), 4.02 (dd, 1 H, 8-H$_a$), 4.09−4.16 (m, 4 H, 2 × CH_2CH$_3$), 4.19 (td, 1 H, 5-H), 4.42 (t, 1 H, 6-H), 4.92 (dd, 1 H, 7-H), 7.83 (d, 1 H, 3-H) ppm, $J_{7,P}$ = 1.2, $J_{7,6}$ = $J_{6,5}$ = 3.0, $J_{5,Ha}$ = 3.9, $J_{5,Hb}$ = 7.2, $J_{Ha,Hb}$ = 11.6, $J_{3,P}$ = 2.0 Hz. ^{13}C NMR (CD_3OD, 100.6 MHz): δ = 16.5 and 16.6 (2s, CH$_2$*C*H$_3$), 62.6 (*C*H$_2$OH), 63.9 (d, $^2J_{C,P}$ = 4, *C*H$_2$CH$_3$), 64.0 (d, $^2J_{C,P}$ = 4, *C*H$_2$CH$_3$), 68.2 (C-5), 73.4 (C-7), 85.1 (C-6), 121.7 (d, $J^1_{C,P}$ = 251, C-1), 135.6 (d, $J^3_{C,P}$ = 21, C-3), 148.7 (d, $J^2_{C,P}$ = 37, C-7a) ppm. ^{31}P NMR ($CDCl_3$, 101.2 MHz): δ = 21.4 ppm. HR-MS: [M + H]$^+$ ion 307.1061 ($C_{11}H_{20}N_2O_6P$ calcd. 307.1059). $C_{11}H_{19}N_2O_6P$ (306.26): calcd. C 43.14, H 6.25, N 9.15, P 10.11; found C 43.0, H 6.2, N 9.1, P 9.8.

Synthesis of the 1-Phosphonic Imidazole-D-*arabino*-Pyrrolidinose Acid Derivative 19: To a stirred suspension of **18** (200 mg, 0.65 mmol) in CH_2Cl_2 at 0 °C was added dropwise Me_3SiBr (2.1 mL, 16 mmol, 25 equiv.). After 15 min the reaction mixture was heated to room temp. for 60 h, then evaporated to dryness. The residue was co-distilled with toluene (2 × 10 mL) and dissolved in MeOH (18 mL) and H_2O (2 mL). The resulting solution was stirred vigorously for 10 min and the solvents evaporated to dryness. The residue was again co-distilled with toluene leading thereby to an orange coloured foam which was dissolved in H_2O (10 mL), the resulting solution was filtered and submitted to lyophilisation to give **19** (165 mg, quantitative) as a hygroscopic orange resin, whose purity was sufficient for the next step. ^1H NMR (D_2O, 250 MHz): δ = 3.86 (dd, 1 H, 8-H$_b$), 4.14 (dd, 1 H, 8-H$_a$), 4.48−4.57 (m, 2 H, 5-H and 6-H), 5.14 (d, 1 H, 7-H), 8.85 (d, 1 H, 3-H) ppm, $J_{7,6}$ = 3.1, $J_{5,Ha}$ = 3.4, $J_{5,Hb}$ = 7.0, $J_{Ha,Hb}$ = 12.2, $J^4_{3,P}$ = 1.8 Hz. ^{13}C NMR (D_2O, 62.9 MHz): δ = 60.6 (C-8), 68.2 (C-5), 72.5 (C-7), 82.4 (C-6), 124.4 (d, $J^1_{C,P}$ = 203, C-1), 132.3 (d, $J^3_{C,P}$ = 8, C-3), 141.1 (d, $J^2_{C,P}$ = 21, C-7a) ppm. ^{31}P NMR (D_2O, 101.2 MHz): δ = −0.6 ppm.

Triethylamino Salt of the D-*arabino* Phosphonic Acid 19: To a stirred solution of **19** (165 mg, 0.65 mmol) in H_2O (10 mL) at room temp. Et_3N (270 μL, 1.95 mmol) was added. After 15 min the solution was evaporated in vacuo to give a colourless solid which was dissolved again in H_2O. The resulting solution was filtered and submitted 3 times to lyophilisation to give the triethylammonium salt of acid **19** as a colourless powder, which was neither purified nor characterised. It was used as such in the next reaction step.

Synthesis of the D-*arabino*-Triacetate Derivative 20: A solution of **19** (103 mg, 0.20 mmol) in Ac_2O (1.5 mL) and pyridine (3 mL) was stirred overnight (ca. 16 h) and thence distilled in vacuo to near dryness. The residue was co-distilled 3 times with toluene, dissolved in MeOH and filtered. The filtrate was evaporated to dryness to give **20** (137 mg) as a pale yellow solid which, without any purification, was used as such for the next reaction step. ^1H NMR (CD_3OD, 250 MHz): δ = 1.31 [t, 9 H, *J* = 6.9, (CH_3CH$_2$)$_3$N], 2.08, 2.10, 2.12 (3s, 3 × 3 H, 3 COCH_3), 3.20 [q, *J* = 7.0, 6 H, (CH$_3$CH_2)$_3$N], 4.33 (dd, 1 H, 8-H$_a$), 4.70 (m, 2 H, 8-H$_b$ and 5-H), 5.50 (s, 1 H, 6-H), 6.18 (s, 1 H, 7-H), 8.16 (s, 1 H, 3-H) ppm, $J_{5,Hb}$ = 6.3, $J_{Ha,Hb}$ = 11.4 Hz.

Synthesis of the D-*arabino*-Citronellyl-Phosphonate Triacetate Derivative 21: To a stirred solution of crude **20** (137 mg), as obtained above, in pyridine (3 mL) were added Cl_3CCN (300 μL) and (*S*)-(−)-β-citronellol (40 μL, 0.22 mmol). That reaction mixture was heated at 70 °C for 16 h, thence evaporated to near dryness, co-distilled 3 times with toluene and dissolved in EtOAc (10 mL). The organic solution was washed with H_2O, and the aq. phase extracted with EtOAc (4 × 10 mL). The combined organic portions were dried ($MgSO_4$), filtered and the solvents evaporated to dryness. The residue was purified by chromatography ($CHCl_3$/MeOH/H_2O, 7:2.6:0.4) to give **21** (237 mg) as a beige solid which was not crystallised. ^1H NMR (CD_3OD, 250 MHz): δ = 0.80 (d, 3 H, *J* = 6.2, CHCH_3), 1.06 (m, 1 H, C*H*CH$_3$), 1.24−1.57 (m, 4 H, 2 × CH$_3$), 1.57 and 1.65 (2s, 2 × 3 H, C(CH_3)$_2$], 1.93 (m, 2 H, CH_2), 2.07, 2.09 and 2.11 (3s, 3 × 3 H, 3COCH_3), 3.83 (m, 2 H, CH_2OP), 4.30

(dd, 1 H, 8-H_b), 4.63 (m, 2 H, 8-H_a and 5-H), 5.05 [m, 1 H, C*H*=C(CH_3)$_2$], 5.49 (s, 1 H, 6-H), 6.12 (s, 1 H, 7-H), 7.92 (s, 1 H, 3-H) ppm, $J_{5,Hb}$ = 7.8, $J_{Ha,Hb}$ = 12.8 Hz. ^{31}P NMR (CD_3OD, 101.2 MHz): δ = 11.5 ppm.

Synthesis of the D-*arabino*-Citronellyl-Phosphonate Derivative 2: A solution of the above compound **21** (237 mg) in MeOH (10 mL) was vigorously stirred for 90 min at room temp. in the presence of Amberlyst A-26 (OH^- form) beads. After filtration, the beads were rinsed several times with MeOH, and the combined organic portions were evaporated to dryness. The residue was purified by chromatography ($CHCl_3$/MeOH/H_2O, 6:3.5:0.5) to give compound **2** (15 mg, 20%) as a faintly beige solid. ^{1}H NMR (CD_3OD, 250 MHz): δ = 0.81 (d, *J* = 6.2, 3 H, CHC*H*$_3$), 1.09 (m, 1 H, C*H*CH$_3$), 1.19−1.59 (m, 4 H, 2 × CH_2), 1.57 and 1.65 [2s, 2 × 3 H, C(C*H*$_3$)$_2$), 1.92 (m, 2 H, CH_2), 3.75 (dd, 1 H, 8-H_b), 3.83 (m, 2 H, C*H*$_2$OP), 4.05 (m, 2 H, 8-H_a), 4.11 (td, 1 H, 5-H), 4.37 (t, 1 H, 6-H), 4.94 (dd, 1 H, 7-H), 5.05 [m, 1 H, C*H*=C(CH_3)$_2$], 7.75 (s, 1 H, 3-H) ppm, $J^4_{7,P}$ = 1.0, $J_{7,6}$ = $J_{6,5}$ = $J_{5,Ha}$ = 4.0, $J_{5,Hb}$ = 7.1, $J_{Ha,Hb}$ = 11.4 Hz. ^{13}C NMR (CD_3OD, 62.9 MHz): δ = 17.8 (*C*H$_3$C=CH), 19.7 (*C*H$_3$CH), 25.9 (*C*H$_3$C=CH), 26.5 (CH_2), 30.3 (*C*HCH$_3$), 38.3 (CH_2), 38.9 (d, $J^3_{C,P}$ = 7.5, *C*H$_2$CH$_2$OP), 62.8 (*C*H$_2$OH), 64.1 (d, $J^2_{C,P}$ = 5.2, *C*H$_2$OP), 67.2 (C-5), 73.5 (C-7), 84.8 (C-6), 125.9 [*C*H=C(CH_3)$_2$], 131.9 [CH=*C*(CH_3)$_2$] ppm. HR-MS: $[M - H]^-$ ion 387.1687 ($C_{17}H_{28}N_2O_6P$, calcd. 387.1685).

X-ray Diffraction Analysis of 14: Single crystals of **14**, suitable for X-ray crystallography, were grown by crystallisation from methanol. Data were collected at 293 K. The usual corrections were applied. The computing calculations were made with the programs CRYSTALS[17,18]. Scattering factors were taken from the International Tables Vol. IV Table 2.2B.The compound has a chemical formula of $C_{37}H_{40}IN_2O_4Si$. The dimensions of the unit-cell are: *a* = 9.5364(2), *b* = 18.1656(8), *c* = 20.954(1) Å, α = β = γ = 90°. The crystal system is orthorhombic and the space group $P2_12_12_1$. The radiation used was Mo-K_α (λ = 0.71073).

CCDC-186927 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.htlm [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Arabinosyltransferase Assay:[15] DP[^{14}C]A (20,000 cpm, 9 μ M, 10 μL (stored in chloroform/methanol, 2:1) including inhibitor **2** (100 μM) were dried under a stream of argon in a microcentrifuge tube (1.5 mL) and placed in a vacuum dessicator for 15 min to remove any residual solvent. The dried constituents of the assay were then suspended in 8 μL of a 1% aqueous solution of Igepal. The remaining constituents of the arabinosyltransferase assay containing 50 mM MOPS (adjusted to pH 8.0 with KOH), 5 mM β-mercaptoethanol, 10 mM $MgCl_2$, 1 mM ATP, membranes (250 μL) were added to a final reaction volume of 80 μL. The reaction mixtures were then incubated at 37 °C for 1 h. A $CHCl_3$:CH_3OH (1:1, 533 μL) solution was then added to the incubation tubes and the entire contents centrifuged at 18,000 × g. The supernatant was recovered and dried under a stream of argon and re-suspended in C_2H_5OH/H_2O (1:1, 1 mL) and loaded onto a pre-equilibrated (C_2H_5OH/H_2O [1:1] 1 mL Whatmann strong anion exchange (SAX) cartridge which was washed with 3 mL of ethanol. The eluate was dried and the resulting products partitioned between the two phases arising from a mixture of 1-butanol (3 mL) and H_2O (3 mL). The resulting organic phase was recovered following centrifugation at 3,500 × g and the aqueous phase was again extracted twice with 3 mL of 1-butanol saturated water, the pooled extracts were back-washed twice with water saturated with 1-butanol (3 mL). The 1-butanol-saturated water fraction was dried and re-suspended in 200 μL of 1-butanol. The total cpm of radiolabeled material extractable into the 1-butanol phase was measured by scintillation counting using 10% of the labeled material and 10 mL of EcoScintA (National Diagnostics, Atlanta). The incorporation of [^{14}C]Araf was determined by substracting counts present in control assays (incubation of the reaction components in the absence of the compounds). Another 10% of the labeled material was subjected to thin-layer chromatography (TLC) in $CHCl_3$/CH_3OH/NH_4OH/H_2O (65:25:0.5:3.6) on aluminium backed Silica Gel 60 F_{254} plates (E. Merck, Darmstadt, Germany). Autoradiograms were obtained by exposing TLCs to X-ray films (Kodak X-Omat) for 3 d. Competition based experiments were performed by mixing compounds together, followed by thin-layer chromatography/autoradiography as described earlier to determine the extent of product formation.

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