A versatile approach to novel homo-C-nucleosides based on aldehydes and acetylenic ketones derived from ribo- and 2-deoxy-ribofuranose C-glycosides

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Dedicated to Prof. Dr. Rainer Beckert on the Occasion of his 60th Birthday

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Abstract

A series of ribofuranosyl- and 2-deoxyribofuranosyl homo- and spaced-C-nucleosides have been synthesized by reaction of fully protected 3-(1-deoxy-β-D-ribofuranosyl-1-yl)propanal (1), 3-(1,2-dideoxy-β-D-ribofuranosyl-1-yl)propanal (14), 1-(1-deoxy-β-D-ribofuranosyl-1-yl)pent-4-yn-3-on (19), 1-(1-deoxy-β-D-ribofuranosyl-1-yl)-5-phenyl-pent-4-yn-3-on (20), 1-(1,2-dideoxy-β-D-ribofuranosyl-1-yl)pent-4-yn-3-on (29), and 1-(1,2-dideoxy-β-D-ribofuranosyl-1-yl)-5-phenyl-pent-4-yn-3-on (30) with different nucleophiles. The preparation of 1 and 14 proceeds by Knoevenagel reaction with malononitrile, cyanoacetamide and 2-cyano-N-(4-methoxyphenyl)acetamide and subsequent cyclization with sulphur to thiophenes 5, 7, 8, 16 and then by cyclization with triethyl orthoformate to give thienopyrimidine 6 and thienopyrimidinone 9, 10, and 17. Treatment of acetylenic ketones 19, 20, 29, and 30 with acetamidinium chloride, benzamidinium chloride, and S-methylisothiourea sulphone provided the corresponding pyrimidines 21–26, 31, 32. Finally, the use of 4H-1,2,4-triazol-3-amine and 2-aminobenzimidazole as 1,3-N,N′-dinucleophiles afforded the triazolopyrimidines 35, 39 and the pyrimido benzimidazoles 36, 37, and 40, respectively. Deprotection of a selected number of C-nucleosides was achieved by one or two steps procedure without serious problems. That makes these C-nucleosides promising candidates for the synthesis of monomers suitable for solid phase nucleic acid oligomerization.

Keywords: Ribose, 2-deoxy-ribose, C-nucleosides, thiophenes, pyrimidines, thienopyrimidines
Introduction

The interest in nucleoside analogues is unbroken and their design and synthesis have been done with quite different intentions e.g. synthesis of homo-C-nucleosides with potential biological activity, tools for elucidating the structural and functional properties of damaged DNA, illustration of hybridizations and conformational changes of DNA and RNAs, and to give an answer to the question why DNA evolved on Earth to have the structure that it does.

Pursuing a program directed at the synthesis of homo-C-nucleosides, we have described previously an efficient route for the preparation of β-allyl C-glycosides of D-ribofuranose and 2-deoxy-D-ribofuranose. Recently we have reported the synthesis of consecutive compounds e.g. alcohols, amines, aldehydes, and acetylenic ketones. In this contribution we present our results on transformation of the furnished aldehydes (1,14) and acetylenic ketones (19, 20, 29, 30) as versatile intermediates into a selected number of different heterocycles to make the synthetic potential of these precursors visible.

Results and Discussion

Synthesis of thienopyrimidine homo-C-nucleosides
The synthesis started from the aldehyde 1 which was readily obtainable from β-allyl C-glycoside of D-ribose via hydroboration/oxidation and selective oxidation of the corresponding alcohol. Treatment of 1 with malononitrile, cyanoacetamide and 2-cyano-N-(4-methoxyphenyl)acetamide provided the corresponding Knoevenagel products 2-4 in 60%, 51%, and 77%, respectively (Scheme 1). The reaction was carried out by using an excess of the CH-acidic compounds and basic aluminium oxide in boiling toluene. The reaction time varied between 2 and 16 h as monitored by TLC. All analytical data were in accordance with the proposed structures. Additionally, the values for the coupling constants JH2-CN and JH2-C=O (13-14 Hz and 5-6 Hz, respectively) determined from coupled 13C NMR spectra confirmed the E-configuration of structures 3 and 4. When the compounds 2-4 were treated with elemental sulphur and triethylamine in N,N-dimethylformamide (DMF) for 2 h at r.t. the light yellow aminothiophenes 5, 7, and 8 were obtained in about 80% yield. The 1H NMR spectra showed signals at δ 2.81–3.02 and the 13C NMR spectra provided signals at δ 33.7–33.9 characteristic of the methylene unit of homo-C-nucleosides. For the synthesis of 4-aminothienopyrimidine 6 compound 5 was reacted with triethyl orthoformate under reflux for 2 h. Without purification the resulting formimidate was treated with a saturated ethanolic ammonia solution to afford the desired compound 6 in 74% overall yield. Cyclization to the thienopyrimidinones 9 and 10 were achieved when a mixture of compounds 7 or 8 and triethyl orthoformate were heated at reflux in DMF for 7–10 h. In spite of the drastic reaction conditions the desired derivatives 9 and 10 were obtained in about 70% yield. In the 1H NMR spectra singlets were observed at δ 8.05 and 8.02 characteristic of H-2 of 9 and 10, respectively.
Scheme 1. Syntheses of thiophenes 5, 7, 8, pyrimidine 6, and pyrimidinone 17 via Knoevenagel products 2–4. Reagents and conditions: (i) CH-acid compounds, Al₂O₃, dry toluene, reflux, 2–16 h; (ii) sulfur, NEt₃, DMF, r.t. 2 h; (iii) HC(OEt)₃, reflux 2h, then ethanol-ammonia, reflux 2 h; (iv) HC(OEt)₃, dry DMF, reflux, 7–10 h; (v) 90% aq CF₃CO₂H, CH₂Cl₂, r.t.; (vi) Bu₄NF, 1,4-dioxane, r.t. 5 h, then 90% aq CF₃CO₂H, CH₂Cl₂, r.t.
Finally, treatment of 9 and 6 with 90% trifluoroacetic acid in CH$_2$Cl$_2$ removed both the silyl and isopropylidene protecting groups, providing the unprotected derivatives 11 and 13 in 90% yield. In contrast, deprotection of thiophene 5 required a two step procedure. Firstly, the tert-butyldiphenylsilyl group (TBDPS) was cleaved off by treatment of 5 with a solution of tetrabutylammonium fluoride (TBAF) in 1,4-dioxane. After 5 h, the isopropylidene group was then removed with 90% trifluoroacetic acid in CH$_2$Cl$_2$ to give 12 in 87% overall yield.

**Scheme 2.** Synthesis of thiophenecarboxamide 16 and pyrimidinone 17. *Reagents and conditions*: (i) 2-cyanoacetamide, Al$_2$O$_3$, dry toluene, reflux, 24 h; (ii) sulfur, NEt$_3$, DMF, r.t. 2 h; (iii) HC(OEt)$_3$, dry DMF, reflux, 10 h; (iv) Bu$_4$NF, 1,4-dioxane, r.t. 2 h.

In a previous paper,$^{11}$ we described an efficient route to transfer β-allyl C-glycoside of D-ribose into the corresponding 2-deoxy ribofuranose. Employment of exactly the same conditions of hydroboration-oxidation and consecutive selective oxidation of the corresponding alcohol furnished aldehyde 14.$^{12}$ The versatility of 14 was demonstrated by the preparation of thieonopyrimidinone 18 by the same sequence of reaction steps as described for compound 13 (Scheme 2). Even the reaction conditions were identical only slightly differences of reaction time and yield occur. Thus, Knoevenagel product 15 was obtained in 52% yield. Transformation of 15 into thiophene 16 (73%) was followed by ring closure reaction to provide 17 in 69% yield. Deprotection was simply achieved by treatment of 17 with TBAF in a solution of 1,4-dioxane. After 2 h at r.t. derivative 18 was obtained in 78% yield.

As described previously,$^{12}$ aldehydes 1 and 14 can be converted to acetylenic ketones 19, 20 and 29, 30 by reaction with ethynylmagnesium bromide or phenylethynyllithium, respectively,
and followed by oxidation of the diastereomeric alcohols. Analytical sample of 20 was obtained by crystallization from ethyl acetate–n-hexane. Its constitution was confirmed by X-ray diffraction studies (Figure 1).

Figure 1

Molecular structure of alkynyl ketone 20 with atom labeling scheme. Thermal ellipsoids are drawn at the 30% probability level. Puckering parameters are \( q_2 = 0.3233(1) \) and \( \Phi_2 = -35.96(1) \) for the tetrahydrofuran ring.

Synthesis of pyrimidine-spacered C-nucleosides

Acetylenic ketones are a versatile class of compounds which can be used as starting materials for the synthesis of a broad variety of heterocycles.\(^{16-20}\) Herein we report efficient short synthesis of substituted pyrimidines and triazolopyrimidines. Following the strategy of Addlington et al,\(^ {17}\) who reported the reaction of acetylenic ketones with amidinium salts using ethyl acetate/water as solvent and sodium carbonate as base, 19 and 20 were treated with acetamidinium chloride, benzamidinium chloride, and S-methylisothiouronium sulphate to give the corresponding pyrimidines 21–26 separated from the tetrahydrofuran ring by an ethylene group (Scheme 3).

All reactions proceeded in good (60%) to excellent yield (quantitative). As expected, all analytical data were in agreement with the proposed structures. We examined the stepwise and complete deprotection of the obtained pyrimidines using the example of compound 25. Treatment of 25 with aq HCl in EtOH resulted in simultaneous removal of both silyl and isopropylidene protecting groups to give 28 in 74% yield. On the other hand, in the presence of
TBAF in 1,4-dioxane only the TBDPS group was removed and the partial protected derivative 27 was obtained in 85% yield. Again, the 2-deoxy acetylenic ketones 29 and 30 were allowed to react with selected amidinium salts e.g. S-methylisothiouronium sulphate and acetamidinium chloride to provide the pyrimidines 31 and 32, respectively (Scheme 4). Deprotection of 31 with TBAF in 1,4-dioxane afforded 33 in 78% yield.

Scheme 3. Synthesis of pyrimidines 21–26 via acetylenic ketones 19 and 20. Reagents and conditions: (i) ethynylmagnesium bromide or phenylethylnyllithium, dry THF, r.t. 4 h, then Dess-Martin oxidation; (ii) acetamidinium, benzamidinium or S-methylisothiouronium salts, cat. H2O, Na2CO3, AcOEt, reflux, 2–24 h; (iii) Bu4NF, 1,4-dioxane, r.t. 4 h; (iv) aq HCl (1M), EtOH, r.t. 12 h.
Scheme 4. Synthesis of pyrimidines 31 and 32 via acetylenic ketones 29 and 30. Reagents and conditions: (i) ethynylmagnesium bromide or phenylethynyllithium, dry THF, r.t. 4 h, then Dess-Martin oxidation; (ii) S-methylisothiouronium sulphate (for 31) and acetamidinium chloride (for 32), cat. H₂O, Na₂CO₃, AcOEt, reflux, 3–24 h; (iii) Bu₄NF, 1,4-dioxane, r.t. 24 h.

Synthesis of triazolo- and pyrimidinobenzimidazole-spacered C-nucleosides

Nucleophilic attack of 4H-1,2,4-triazol-3-amine on the triple bond of ynone 19 in boiling EtOH resulted in compound 34 in 89% yield (Scheme 5). The ¹H and ¹³C NMR spectra of 34 were fully consistent with the assigned structure. As expected, no signals of acetylenic carbon atoms were observed in the ¹³C-NMR spectra, but a resonance was visible at δ 151.7 for C-3” of the triazole ring. The E-configuration of the addition product was evident from the large coupling constant ³J₄,₅ 13.3 Hz in the ¹H NMR spectra. In order to prepare a fused heterocycle enone 34 was treated with sodium ethanolate at r.t. for 1 h to afford triazolopyrimidine 35 in 62% yield. Analogous to that addition reaction 2-aminobenzimidazole was used as 1,3-Ν,Ν’-dinucleophile and allowed to react with ynone 19 and 20. Suprisingly, the TLC of the reaction solution showed in each case the formation of a mixture two products after reflux (EtOH) for 2 h. The stepwise formation of compound 35 strongly suggested that here a mixture of an addition products (in parenthesis Scheme 5) and the fused heterocycles 36 and 37 were observed.
Scheme 5. Synthesis of triazolopyrimidine 35 and pyrimidobenzimidazoles 36 and 37. Reagents and conditions: (i) 4H-1,2,4-triazol-3-amine, dry EtOH, reflux, 4 h; (ii) ethanolic NaOMe (1M), r.t., 1 h; (iii) 1H-benzo[d]imidazole-2-amine, dry EtOH, reflux, 2 h, then ethanolic NaOMe 1 M), r.t. 1 h.

Indeed, treatment of the unseparated reaction mixture with sodium ethanolate at r.t. for 1 h caused disappearance of the side-products and provided 36 and 37 in 76% and 80% yield, respectively. The protocol of the formation of triazolopyrimidine and pyrimidobenzimidazole by reaction of 4H-1,2,4-triazole-3-amine and 2-aminobenzimidazole, respectively, was now transferred to the ynone 29 (Scheme 6). Fortunately, the course of all reactions was comparable to ynone 19. Consequently, triazolopyrimidine 39 and pyrimidobenzimidazole 40 were obtained in 69% and 63%, respectively. The regioselectivity of the ring closure reactions was evident from NOESY and HMBC experiments.
Scheme 6. Synthesis of triazolopyrimidine 39 and pyrimidobenzimidazole 40. Reagents and conditions: (i) 4H-1,2,4-triazol-3-amine, dry EtOH, reflux, 4 h; (ii) ethanolic NaOMe (1 M), r.t., 1 h; (iii) 1H-benzo[d]imidazole-2-amine, dry EtOH, reflux, 2 h, then ethanolic NaOMe 1 M, r.t. 1 h.

In summary, we have shown that fully protected ribofuranosylpropanal (1), 2-deoxy-ribofuranosylpropanal (14) and the corresponding alkynyl ketones 19, 20, 29, and 30 are suitable intermediates for the preparation of homo- and spacered C-nucleosides. The tetrahydrofuran ring and the protecting group pattern is stable enough even under drastic reaction conditions to allow the synthesis of a broad variety of heterocyclic systems. In one of our next papers, we will describe the conversion of some of our C-nucleosides into building blocks suitable for solid phase synthesis of nucleic acid oligomers.
Experimental Section

General. Melting points were determined with a Boetius micro-heating plate BHMK 05 (Rapido, Dresden) and were not corrected. Optical rotation was measured for solutions in a 2-cm cell with an automatic polarimeter GYROMAT (Dr. Kernchen Co.). \(^1\)H NMR spectra (250.13 and 300.13 MHz) and \(^{13}\)C NMR spectra (62.9 and 75.5 MHz) were recorded on Bruker spectrometers AVANCE 250 and AVANCE 300, respectively, at 298 K. The chemical shifts are referenced to solvent signals (CDCl\(_3\): \(\delta \) \(^1\)H = 7.26, \(\delta \) \(^{13}\)C = 77.0; DMSO-\(d_6\): \(\delta \) \(^1\)H = 2.49, \(\delta \) \(^{13}\)C = 39.7; CD\(_3\)OD: \(\delta \) \(^1\)H = 3.30, \(\delta \) \(^{13}\)C = 49.3). Signal assignment was performed by recording the DEPT spectra, in some cases also by recording of two-dimensional \(^1\)H,\(^1\)H COSY, \(^{13}\)C,\(^1\)H HETCOR and \(^1\)H,\(^{13}\)C HMBC spectra. For NMR numbering of atoms see Scheme 1, 3 and 5.

Mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analysis was performed on a CHNS-Flash-EA-1112 instrument (Thermoquest). For the X-ray structure determination of compound 20 an X8Apex system with CCD area detector was used (\(\lambda \) = 0.71073 Å, graphite monochromator). The refinement calculations were done by the full-matrix least-squares method of Bruker SHELXTL. The structures were solved by direct methods (Bruker-SHELXTL). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were put into idealised positions and refined using the riding models. Crystallographic data for the structure analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No 827042 for compound 20. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road Cambridge, CB2 1EZ UK, Fax. (int code) +44(1223)336-033 or via Email: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk. All washing solutions were cooled to ~5 °C. The NaHCO\(_3\) solution was saturated. Reactions were monitored by thin-layer chromatography (TLC, Silica Gel 60, F\(_{254}\), Merck KGaA). The followings solvent systems (v/v) were used: (A) ethyl acetate, (B\(_1\)) 2:1, (B\(_2\)) 1:1, (B\(_3\)) 2:3, (B\(_4\)) 1:2, (B\(_5\)) 1:3, (B\(_6\)) 1:4, (B\(_7\)) 1:5 ethyl acetate – n-hexane; (C\(_1\)) 1:1, (C\(_2\)) 4:1, (C\(_3\)) 5:1, (C\(_4\)) 6:1 ethyl acetate – methanol; (D) 12:1:0.1 ethyl acetate – methanol – acetic acid. The spots were made visible by dipping the TLC plates into a methanolic 10% H\(_2\)SO\(_4\) solution and charring with a heat gun for 3–5 min. Preparative flash chromatography was performed by elution from columns of slurry-packed Silica Gel 60 (Merck, 63–200 µm). All solvents and reagents were purified and dried according to standard procedures. KNOEVENAGEL reaction with aldehyde (1). General procedure

Malononitrile (377 mg, 5.7 mmol), 2-cyanoacetamide (479 mg, 5.7 mmol) or 2-cyano-N-(4-methoxyphenyl)acetamide (1.08 g, 5.7 mmol) was added to a stirred solution of 3-[5-O-tert-butyl]diphenylsilyl]-2,3-O-isopropylidene-1-deoxy-\(\beta\)-D-ribofuranosyl-1-yl)propanal (1, 1.17 g, 2.5 mmol) and aluminium oxide (653 mg, 6.4 mmol, basic activated 90, 101076 MERCK) in dry toluene (75 mL). After heating under reflux for 2–16 h (monitored by TLC), the reaction mixture
was cooled to r.t., the insoluble solids were filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography.

2-[3-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)propylidene]malononitrile (2). Reaction time 2.5 h; flash chromatography solvent B6; (775 mg, 60%) colorless syrup; [α]$_{D}^{21}$ = -12.5 (c 1.0, CH$_2$Cl$_2$); $R_f = 0.16$ (solvent B$_7$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.07 [s, 9H, C(CH$_3$)$_3$]; 1.35, 1.54 [2 x s, 6H, C(CH$_3$)$_2$]; 1.71–1.94 (m, 2H, H-4); 2.66–2.75 (m, 2H, H-3); 3.80 (m, 2H, H-5'); 3.82–3.86 (m, 1H, H-1'); 4.07 (q, 1H, $^3$J$_{3,4}$ 3.5, $^3$J$_{4,5}$ 3.5 Hz, H-4'); 4.28 (dd, 1H, $^3$J$_{1',2'}$ 5.4 Hz, $^3$J$_{2,3}$ 6.7 Hz, H-2'); 4.74 (dd, 1H, H-3'); 7.28 (t, 1H, $^3$J$_{2,3}$ 7.8 Hz, H-2'); 7.35–7.69 (m, 10H, 2 x Ph). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 19.3 [C(CH$_3$)$_3$]; 25.5, 27.5 [C(CH$_3$)$_2$]; 26.9 [C(CH$_3$)$_3$]; 29.7, 31.4 (C-3, C-4); 64.0 (C-5'); 81.9 (C-3'); 83.5 (C-1'); 84.4 (C-4'); 84.5 (C-2'); 110.4, 112.0 (2 CN); 114.4 [C(CH$_3$)$_2$]; 127.8, 127.8, 129.8, 129.9, 135.6 (2 (2 o-, m-, p-Ph); 133.1, 133.2 (2 i-Ph); 169.0 (C-2). CI-MS: $m/z$ (%) = 517 (3, [M+H$^+$]).

Anal. Calcd for C$_{30}$H$_{36}$N$_2$O$_4$Si (516.70): C, 69.73; H, 7.02; N, 5.42. Found: C, 69.41; H, 7.03; N, 5.41.

(E)-2-Cyano-5-(5-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)pent-2-enamide (3). Reaction time 16 h; flash chromatography solvent B$_3$; (682 mg, 51%) colorless syrup; [α]$_{D}^{21}$ = -12.7 (c 1.0, CHCl$_3$); $R_f = 0.17$ (solvent B$_4$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.06 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.53 [2 s, 6H, C(CH$_3$)$_2$]; 1.78–1.88 (m, 2H, H-4); 2.63–2.72 (m, 2H, H-3); 3.78 (m, 2H, H-5'); 3.82–3.89 (m, 1H, H-1'); 4.05 (q, 1H, $^3$J$_{3,4}$ 3.6, $^3$J$_{4,5}$ 3.6 Hz, H-4'); 4.30 (dd, 1H, $^3$J$_{1',2'}$ 5.2 Hz, $^3$J$_{2,3}$ 6.7 Hz, H-2'); 4.72 (dd, 1H, H-3'); 5.71, 6.09 (2 br s, 2H, NH$_2$); 7.34–7.47, 7.61–7.73 (2m, 11H, 2 Ph, H-2). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 19.3 [C(CH$_3$)$_3$]; 25.5, 27.5 [C(CH$_3$)$_2$]; 26.8 [C(CH$_3$)$_3$]; 28.5 (C-3); 31.8 (C-4); 64.0 (C-5'); 81.9 (C-3'); 83.4 (C-1'); 84.2 (C-4'); 84.7 (C-2'); 110.1 (C-1); 114.3 [C(CH$_3$)$_2$]; 114.9 (CN); 127.7, 129.8, 135.6 (2 o-, m-, p-Ph); 133.1, 133.2 (2 i-Ph); 160.8 (CONH$_2$); 161.3 (C-2). CI-MS: $m/z$ (%) = 535 (3, [M+H$^+$]).

Anal. Calcd for C$_{30}$H$_{38}$N$_2$O$_5$Si (534.72): C, 67.39; H, 7.16; N, 5.24. Found: C, 67.64; H, 7.22; N, 5.27.

(E)-2-Cyano-5-(5-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)-N-(4-methoxyphenyl)pent-2-enamide (4). Reaction time 12 h; flash chromatography solvent B$_3$; (1.23 g, 77%) colorless syrup; [α]$_{D}^{21}$ = -16.1 (c 1.0, CHCl$_3$); $R_f = 0.45$ (solvent B$_4$).

$^1$H NMR (250 MHz, CDCl$_3$) δ 1.06 [s, 9H, C(CH$_3$)$_3$]; 1.35, 1.54 [2 s, 6H, C(CH$_3$)$_2$]; 1.81–1.91 (m, 2H, H-4); 2.67–2.76 (m, 2H, H-3); 3.79 (m, 2H, H-5'); 3.81 (s, 3H, OCH$_3$); 3.84–3.91 (m, 1H, H-1'); 4.06 (q, 1H, $^3$J$_{3,4}$ 3.5 Hz, $^3$J$_{4,5}$ 3.5 Hz, H-4'); 4.32 (dd, 1H, $^3$J$_{1',2'}$ 5.3 Hz, $^3$J$_{2,3}$ 6.7 Hz, H-2'); 4.74 (dd, 1H, H-3'); 6.87–6.93 (m, 2H, m-NHC$_6$H$_4$); 7.35–7.70 (m, 10H, 2 Ph); 7.44–7.49 (m, 2H, o-NHC$_6$H$_4$); 7.77 (t, 1H, $^3$J$_{2,3}$ 7.9 Hz, H-2). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 19.3 [C(CH$_3$)$_3$]; 25.5, 27.5 [C(CH$_3$)$_2$]; 26.8 [C(CH$_3$)$_3$]; 28.6 (C-3); 31.9 (C-4); 55.5 (OCH$_3$); 64.1 (C-5'); 81.9 (C-3'); 83.4 (C-1'); 84.3 (C-4'); 84.7 (C-2'); 111.1 (C-1); 114.3 (m-NHC$_6$H$_4$); 114.3
[C(CH₃)₂]; 114.9 (CN); 122.4 (o-NHC₆H₄); 129.7 (i-NHC₆H₄); 127.7, 129.8, 135.5 (2 o-, m-, p-Ph); 133.2, 133.3 (2 i-Ph); 157.2 (CONH); 160.7 (C-2). CI-MS: m/z (%) = 641 (8, [M+H]+).


*(E)-2-Cyano-5-[3,5-O-(tetraisopropylidisiloxan-1,3-diyl)-1,2-dideoxy-β-D-ribofuranos-1-yl]pent-2-enamide (15).* Starting from aldehyde 14 (1.04 g, 2.5 mmol) and 2-cyanoacetamide (479 mg, 5.7 mmol) Knoevenagel product 15 (628 mg, 52%) was obtained as colorless syrup according to the procedure described for compound 3; reaction time 24 h; flash chromatography solvent B₂; [α]D² ≠ 25.9 (c 1.0, CH₂Cl₂); Rf = 0.35 (solvent B₂). ¹H NMR (250 MHz, CDCl₃) δ 1.00–1.06 [m, 28H, 4 CH(CH₃)₂]; 1.65–1.77 (m, 2H, H-4); 1.80 (dt, 1H, J₁₂₂₆ 7.8 Hz, J₃₂₄₆ 7.8 Hz, J₂₃₂₄ 12.5 Hz, H-2'a); 2.05 (dd, 1H, J₂₂₃ 4.5 Hz, J₁₂₂₂ 6.6 Hz, H-2'b); 2.63 (m, 2H, H-3); 3.70 (m, 2H, H-5'a, H-4'); 4.00 (m, 1H, H-5'b); 4.07 (m, 1H, H-1'); 4.37 (dt, 1H, J₃₄₅ 7.8 Hz, H-3'); 5.80, 6.18 (2 x br s, 2H, NH₂); 7.69 (t, 1H, J₃₂₃ 7.9 Hz, H-2). ¹³C NMR (62.9 MHz, CDCl₃) δ 12.5, 12.9, 13.3, 13.5 [4 CH(CH₃)₂]; 16.9, 17.0, 17.1, 17.3 (2), 17.4, 17.5 (2) [4 CH(CH₃)₂]; 28.6 (C-3); 33.5 (C-4); 40.2 (C-2'); 63.7 (C-5'); 73.4 (C-3'); 77.2 (C-1'); 86.0 (C-4'); 109.9 (C-1); 114.9 (CN); 161.0 (CONH₂); 161.8 (C-2). ESI-MS (−): m/z = 481 (100, [M−H]).

Anal. Calcd. For C₃₂H₄₂N₂O₅Si₂ (482.76): C, 57.22; H, 8.77; N, 5.80. Found: C, 57.23; H, 8.74; N, 5.72.

**Preparation of thiophenes 5, 7, 8, and 16 – General procedure**

Sulfur (50 mg, 1.6 mmol) and triethylamine (0.22 mL, 1.6 µmol) were added to a stirred solution of compounds 2, 3, 4 or 15 (1.0 mmol) in dry N,N-dimethylformamide (5.0 mL). After stirring for 2 h at r.t. aq sat NaCl (75 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic phases were washed with water (2 x 75 mL), dried and concentrated. The residue was purified by flash chromatography.

**2-Amino-5-[(5-O-tert-butylidiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)methyl]thiophene-3-carbonitrile (5).** Flash chromatography solvent B₄; (439 mg, 80%) yellow syrup; [α]D² = –20.1 (c 1.0, CH₂Cl₂); Rf = 0.42 (solvent B₄). ¹H NMR (250 MHz, CDCl₃) δ 1.07 [s, 9H, C(CH₃)₃]; 1.34, 1.53 [2 s, 6H, C(CH₃)₂]; 2.85 (dd, 1H, J₁₂₂₆ 7.3 Hz, J₁₉₁₂₆ 15.3 Hz, H-1''a); 2.97 (dd, 1H, J₁₂₂₅ 4.6 Hz, H-1''b); 3.81 (m, 2H, H-5'); 4.02 (dt, 1H, H-1'); 4.08 ('q', 1H, J₃₄₅ 3.6 Hz, J₃₄₅ 3.6 Hz, H-4'); 4.36 (dd, 1H, J₂₂₃ 6.7 Hz, J₁₂₂₂ 5.0 Hz, H-2'); 4.70 (dd, 1H, H-3'); 6.45 (s, 1H, H-4); 7.34–7.71 (m, 10H, 2 Ph). ¹³C NMR (75.5 MHz, CDCl₃) δ 19.3 [C(CH₃)₃]; 25.5, 27.5 [C(CH₂)₂]; 26.8 [C(CH₃)₂]; 33.7 (C-1'''); 64.1 (C-5'); 81.8 (C-3'); 83.7 (C-1'); 84.1 (C-4'); 84.6 (C-2'); 87.3 (C-3); 114.3 [C(CH₃)₂]; 115.6 (CN); 123.3 (C-4); 124.9 (C-5); 127.8, 129.8, 135.6 (2 o-, m-, p-Ph); 133.1, 133.2 (2 i-Ph); 161.7 (C-2). EI-MS: m/z (%) = 548 (3, [M]+). Anal. Calcd for C₃₀H₃₆N₂O₄SSi (548.77): C, 65.66; H, 6.61; N, 5.10; S, 5.84. Found: C, 65.45; H, 6.92; N, 4.94; S, 5.68.

**2-Amino-5-[(5-O-tert-butylidiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)methyl]thiophene-3-carboxamide (7).** Flash chromatography solvent B₁; (453 mg, 80%)
yellow crystals; m.p. 88–90 °C (ethyl acetate – n-heptane); [α]$_D^{21}$ =−13.6 (c 1.0, CHCl$_3$); $R_f = 0.14$ (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.06 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.53 [2 s, 6H, C(CH$_3$)$_2$]; 2.81–3.02 (m, 2H, H-1''); 3.81 (m, 2H, H-5''); 4.04–4.10 (m, 2H, H-1', H-4'); 4.38 (dd, 1H, $^3$J$_{1,2'}$ 5.0 Hz, $^3$J$_{2,3'}$ 6.7 Hz, H-2'); 4.68 (dd, 1H, $^3$J$_{3,4'}$ 3.7 Hz, H-3'); 5.55 (br, NH$_2$); 6.41 (s, 1H, H-4); 7.33–7.72 (m, 10H, 2 Ph); one NH$_2$ signal not detected. $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 19.3 [C(CH$_3$)$_3$]; 25.6, 27.4 [C(CH$_3$)$_2$]; 26.9 [C(CH$_3$)$_3$]; 33.8 [C-1'']; 64.2 (C-5'); 81.8 (C-3'); 83.7 (C-1'); 84.3 (C-4'); 84.6 (C-2'); 106.6 (C-3); 114.2 [C(CH$_3$)$_2$]; 121.3 (C-4); 121.7 (C-5); 127.8, 129.7, 129.7, 135.7 (2 o-, m-, p-Ph); 133.1, 133.3 (2 i-Ph); 161.7, 167.7 (C-2, C=O). C$_{30}$H$_{38}$N$_2$O$_5$SSi (566.78); HRMS (EI): m/z calculated for [M$^+$] = 566.22679, found 566.22652.

**2-Amino-5-[(5-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)methyl]-N-(4-methoxyphenyl)thiophene-3-carboxamide (8).** Flash chromatography solvent B$_2$; (511 mg, 76%) yellow foam; [α]$_D^{22}$ =−8.9 (c 1.0, CH$_2$CL$_2$); $R_f = 0.38$ (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.08 [s, 9H, C(CH$_3$)$_3$]; 1.36, 1.55 [2 s, 6H, C(CH$_3$)$_2$]; 2.89 (dd, 1H, $^3$J$_{1,2'}$ 7.2 Hz, $^3$J$_{1,1''}$ 15.5 Hz, H-1'a); 2.99 (dd, 1H, $^3$J$_{1,1''}$ 5.0 Hz, H-1'b); 3.80 (s, 3H, OCH$_3$); 3.83 (m, 2H, H-5''); 4.07–4.16 (m, 2H, H-1', H-4'); 4.42 (dd, 1H, $^3$J$_{1,2'}$ 4.8 Hz, $^3$J$_{2,3'}$ 6.7 Hz, H-2'); 4.72 (dd, 1H, $^3$J$_{3,4'}$ 3.7 Hz, H-3'); 6.53 (s, 1H, H-4'); 6.86 (m, 2H, m-NHC$_6$H$_4$); 7.18 (br s, NH$_2$); 7.35 (m, 2H, o-NHC$_6$H$_4$); 7.35–7.70 (m, 10H, 2 Ph). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 19.3 [C(CH$_3$)$_3$]; 25.6, 27.5 [C(CH$_3$)$_2$]; 26.9 [C(CH$_3$)$_3$]; 33.9 (C-1''); 55.5 (OCH$_3$); 64.2 (C-5'); 81.8 (C-3'); 83.8 (C-1'); 84.3 (C-4'); 84.6 (C-2'); 108.1 (C-3); 114.1 (m-NHC$_6$H$_4$); 114.2 [C(CH$_3$)$_2$]; 122.4 (o-NHC$_6$H$_4$); 127.7, 127.8, 129.7, 129.8, 135.6 (2) (2 o-, m-, p-Ph); 130.8 (i-NHC$_6$H$_4$); 133.2, 133.3 (2 i-Ph); 156.3 (C=O); 160.9, 163.9 (C-2, p-NHC$_6$H$_4$). C$_{37}$H$_{44}$N$_2$O$_6$SSi (672.91); HRMS (EI): m/z calculated for [M$^+$] = 672.26814, found 672.26830.

**2-Amino-5-[[3,5-O-(tetraisopropylidisoloxan-1,3-diyl)-1,2-dideoxy-β-D-ribofuranosyl-1-yl)methyl]thieno[2,3-d]pyrimidin (16).** Flash chromatography solvent B$_2$; (398 mg, 73%) yellow syrup; [α]$_D^{24}$ =−25.8 (c 1.0, CH$_2$CL$_2$); $R_f = 0.20$ (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.00–1.08 [m, 28H, 4 CH(CH$_3$)$_2$]; 1.87 (dt, 1H, $^3$J$_{1,2'a}$ 7.9 Hz, $^3$J$_{2'a,3'}$ 7.9 Hz, $^3$J$_{2'a,2'b}$ 12.9 Hz, H-2'a); 2.02 (ddd, 1H, $^3$J$_{2'b,3'}$ 4.4 Hz, $^3$J$_{1,2'b}$ 6.6 Hz, H-2'b); 2.80 (m, 2H, H-1''); 3.70–3.79 (m, 2H, H-5'a, H-4'); 4.04 (m, 1H, H-5'b); 4.23 (m, 1H, H-1''); 4.33 (dt, 1H, $^3$J$_{3,4'}$ 7.9 Hz, H-3'); 5.37 (br s, 2H, NH$_2$); 6.06 (br s, 2H, NH$_2$); 6.42 (s, 1H, H-4'). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 12.5, 13.0, 13.3, 13.4 [4 CH(CH$_3$)$_2$]; 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6 [4 CH(CH$_3$)$_2$]; 35.4 (C-1''); 39.5 (C-2'); 64.0 (C-5'); 73.8 (C-3'); 77.3 (C-1'); 86.2 (C-4'); 107.1 (C-3); 121.4 (C-4); 121.5 (C-5); 161.4, 167.6 (C-2, C=O). ESI-MS (−) m/z = 513 (100, [M−H$^-$]). Anal. Calcd for C$_{23}$H$_{22}$N$_2$O$_5$SSi$_2$ (514.83): C, 53.66; H, 8.22; N, 5.44; S, 6.23. Found: C, 53.38; H, 8.41; N 5.21; S; 5.94.

**4-Amino-6-[(5-O-tetrt-butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)methyl]thieno[2,3-d]pyrimidin (6).** A mixture of compound 5 (165 mg, 0.3 mmol) and triethylorthoformiate (3.0 mL, 18 mmol) was heated under reflux for 2 h. The reaction mixture was concentrated and the obtained syrup was dissolved in a solution of ethanol–ammonia (1:1, 6.0 mL). After heating under reflux for 2 h the
mixture was allowed to attain r.t. and then concentrated. Purification by flash chromatography solvent B2 afforded compound 6 (128 mg, 74%) as a colorless foam, [α]$_D^{21}$ = −15.5 (c 1.0, CHCl$_3$); $R_f$ = 0.18 (solvent B2).

$^1$H NMR (250 MHz, CDCl$_3$) δ 1.07 [s, 9H, C(CH$_3$)$_3$]; 1.35, 1.54 [2 s, 6H, C(CH$_3$)$_2$]; 3.12 (dd, 1H, $^3$J$_{1':1''}$a 7.9 Hz, $^2$J$_{1'a,1'b}$ 15.3 Hz, H-1''a); 3.23 (dd, 1H, $^3$J$_{1':1''}$b 4.8 Hz, H-1''b); 3.82 (m, 2H, H-5'); 4.13 (q, 1H, $^3$J$_{3':4}$ 3.6 Hz, $^2$J$_{3',5'}$ 3.6 Hz, H-4'); 4.22 (dt, 1H, $^3$J$_{1',2'}$ 4.8 Hz, H-1'); 4.44 (dd, 1H, $^3$J$_{2',3'}$ 6.7 Hz, H-2'); 4.74 (dd, 1H, H-3'); 5.50 (br s, NH$_2$); 6.88 (s, 1H, H-5); 7.33–7.72 (m, 10H, 2 Ph); 8.40 (br s, 1H, H-2). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 19.2 [C(CH$_3$)$_3$]; 25.5, 27.5 [C(CH$_3$)$_2$]; 26.8 [C(CH$_3$)$_3$]; 34.9 (C-1''); 64.2 (C-5''); 81.9 (C-3''); 84.1 (C-1'''); 84.2 (C-4''); 84.7 (C-2''); 114.3 [C(CH$_3$)$_2$]; 115.7 (C-5''); 115.7 (C-4a); 127.7, 127.8, 129.8, 129.9, 135.6 (2) (2 o-, m-, p-Ph); 133.1, 133.2 (2 i-Ph); 138.8 (C-6); 152.7 (C-2); 156.7 (C-7a); 167.4 (C-4).

EI-MS: $m/z$ (%) = 576 (3, [M+H]$^+$). Anal. Calcd for C$_{31}$H$_{37}$N$_5$O$_4$Si (575.79): C, 64.66; H, 6.48; N, 7.30; S, 5.57. Found: C, 64.66; H, 6.91; N, 7.12; S, 5.71.

**Preparation of thienopyrimidinones (9, 10, and 17). General procedure**

Triethylthlofoformiate (0.25 mL, 1.5 mmol) was added to a solution of compound 7 (283 mg, 0.5 mmol), 8 (337 mg, 0.5 mmol), or 16 (257 mg, 0.5 mmol) in dry DMF (5.25 mL) and the reaction mixture was heated under reflux for 7–10 h (monitored by TLC). After cooling to r.t. the mixture was concentrated and the residue was purified by flash chromatography.

6-[(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one (9). Reaction time 7 h; flash chromatography solvent B$_1$; (205 mg, 72%) light yellow solid; m.p. 71–73 °C; [α]$_D^{21}$ = −22.5 (c 0.9, CHCl$_3$); $R_f$ = 0.13 (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.07 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.53 [2 s, 6H, C(CH$_3$)$_2$]; 3.09–3.29 (m, 2H, H-1''); 3.82 (m, 2H, H-5''); 4.11–4.21 (m, 2H, H-4', H-1''); 4.44 (dd, 1H, $^3$J$_{1',2'}$ 5.0 Hz, $^3$J$_{2',3'}$ 6.6 Hz, H-2''); 4.74 (dd, 1H, $^3$J$_{3',4'}$ 3.5 Hz, H-3''); 7.29 (s, 1H, H-5); 7.33–7.72 (m, 10H, 2 Ph); 8.05 (br s, 1H, H-2); 12.49 (br s, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 19.2 [C(CH$_3$)$_3$]; 25.6, 27.5 [C(CH$_3$)$_2$]; 26.9 [C(CH$_3$)$_3$]; 34.8 (C-1''); 64.1 (C-5''); 82.0 (C-3''); 84.0 (C-1'''); 84.2 (C-4''); 84.7 (C-2''); 114.3 [C(CH$_3$)$_2$]; 119.6 (C-5''); 124.7 (C-4a); 127.7, 127.8, 129.7, 129.8, 135.6 (2) (2 o-, m-, p-Ph); 133.0, 133.1 (2 i-Ph); 139.4 (C-6); 143.1 (C-2); 159.5 (C-7a); 165.0 (C-4).

CI-MS: $m/z$ (%) = 577 (6, [M+H]$^+$). Anal. Calcd for C$_{31}$H$_{36}$N$_5$O$_4$Si (576.21): C, 64.55; H, 6.29; N, 4.86; S, 5.56. Found: C, 64.28; H, 6.49; N, 4.64; S, 5.35.

6-(5-O-tet-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)methyl)-3-(4-methoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (10). Reaction time 7 h; flash chromatography solvent B$_4$; (236 mg, 69%) yellow syrup; [α]$_D^{21}$ = −14.4 (c 1.0, CH$_2$Cl$_2$); $R_f$ = 0.42 (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.08 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.54 [2 s, 6H, C(CH$_3$)$_2$]; 3.12 (dd, 1H, $^3$J$_{1',1''}$a 7.5 Hz, $^2$J$_{1'a,1'b}$ 15.3 Hz, H-1''a); 3.22 (dd, 1H, $^3$J$_{1',1''}$b 5.0 Hz, H-1''b); 3.82 (m, 2H, H-5'); 3.87 (s, 3H, OCH$_3$); 4.12 (q, 1H, $^3$J$_{3',4'}$ 3.5 Hz, $^3$J$_{4',5'}$ 3.5 Hz, H-4'); 4.17 (dt, 1H, $^3$J$_{1',2'}$ 5.0 Hz, H-1''); 4.44 (dd, 1H, $^3$J$_{2',3'}$ 6.6 Hz, H-2''); 4.74 (dd, 1H, H-3''); 7.03 (m, 2H, m-NHC$_6$H$_4$); 7.30 (m, 2H, o-NHC$_6$H$_4$); 7.31 (s, 1H, H-5); 7.37–7.72 (m, 10H, 2 Ph); 8.02 (s, 1H, H-2).
Deprotection of compounds (6) and (9)

90% Trifluoroacetic acid (25 mL) was added to a solution of compound 6 (576 mg, 1.0 mmol) or compound 9 (576 mg, 1.0 mmol) in CH$_2$Cl$_2$ (10 mL). After stirring at r.t. (monitored by TLC), the reaction mixture was concentrated. Traces of acid were removed by evaporation with repeated addition of toluene. The residue was then subjected to flash chromatography.

4-Amino-6-[(1-deoxy-β-D-ribofuranos-1-yl)methyl]thieno[2,3-d]pyrimidine (11)

Flash chromatography solvent C$_2$; (268 mg, 90%) colorless foam; $[\alpha]_{D}^{21}$ = 7.8 (c 1.0, MeOH); $R_f$ = 0.14 (solvent C$_2$). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 2.92 (dd, 1H, $^3$J$_{1\alpha',1'}$ 7.8 Hz, $^3$J$_{1\alpha',1\beta}$ 15.2 Hz, H-1″a); 3.13 (dd, 1H, $^3$J$_{1\beta',1\beta'}$ 3.5 Hz, H-1″b); 3.39 (m, 2H, H-5′); 3.60 (q, 1H, $^3$J$_{1\beta,2}$ 6.2 Hz, $^3$J$_{2,3'}$ 6.2 Hz, $^3$J$_{2,OH}$ 6.2 Hz, H-2′); 3.73 (m, 1H, H-3′); 3.83 (m, 1H, H-1′); 4.65 (t, 1H, $^3$J$_{3,OH}$ 5.6 Hz, OH-5′); 4.81 (d, 1H, $^3$J$_{3,OH}$ 5.1 Hz, OH-3′); 4.88 (d, 1H, OH-2′); 7.29 (s, 1H, H-5′); 7.34 (br s, NH$_2$); 8.18 (s, 1H, H-2′). $^{13}$C NMR (75.5 MHz, DMSO-D$_6$) δ 34.3 (C-1″); 62.0 (C-5′); 71.1 (C-3′); 73.8 (C-2′); 81.6 (C-1′); 85.0 (C-4′); 115.7 (C-4a); 117.6 (C-5); 136.9 (C-6); 153.3 (C-2); 157.7 (C-7a); 165.9 (C-4′). EI-MS: m/z (%) = 297 (15, $[^{15}$N$+^1$H$^+$/[^{14}$N$+^1$H$^+]$). Anal. Calcd for C$_{12}$H$_{15}$N$_3$O$_4$S (297.33): C, 48.47; H, 5.08; N, 14.13; S, 10.78. Found: C, 48.30; H, 4.94; N, 14.23; S, 10.49.

6-[(1-Deoxy-β-D-ribofuranos-1-yl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one (13).

Flash chromatography solvent C$_2$; (268 mg, 90%) colorless foam; $[\alpha]_{D}^{21}$ = 7.5 (c 1.1, MeOH); $R_f$ = 0.20 (solvent C$_2$). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 2.94 (dd, 1H, $^3$J$_{1\alpha',1'}$ 7.6 Hz, $^3$J$_{1\alpha',1\beta}$ 15.3 Hz, H-
2-Amino-5-[(1-deoxy-β-D-ribofuranosyl-1-yl)methyl]thiophene-3-carbonitrile (12)

A solution of tetrabutylammonium fluoride (TBAF) in 1,4-dioxane (1.0 M, 0.8 mL) was added dropwise to a solution of compound 5 (283 mg, 0.5 mmol) in 1,4-dioxane (7 mL). The reaction mixture was stirred at r.t. for 5 h, and then concentrated. The residue was dissolved in CH2Cl2 (4 mL) and a solution 90% trifluoroacetic acid (6 mL) was added. After stirring at r.t. (monitored by TLC), the reaction mixture was concentrated. Traces of acid were removed by evaporation with repeated addition of toluene. Purification by flash chromatography (solvent C4) afforded compound 12 (118 mg; 87%) as yellow foam; [a]26D = −32.9 (c 0.5, MeOH); Rf = 0.31 (solvent D). 1H NMR (300 MHz, CD3OD) δ 2.91–3.16 (m, 2H, H-1''b); 3.35–3.68 (m, 2H, H-5''); 3.72–3.75, 3.81–3.87, 3.92–3.97 (3 m, 4H) (H-1',2',3',4'); 7.19 (s, 1H, H-4'). 13C NMR (75.5 MHz, CD3OD) δ 34.2 (C-1''); 63.7 (C-5''); 72.8 (C-3'); 75.3 (C-2''); 83.8 (C-1'); 86.2 (C-4'); 106.2 (C-3'); 118.0 (CN); 122.6 (C-4'); 122.7 (C-5'); 169.3 (C-2). C11H14N2O4S (270.30); HRMS (CI): m/z calculated for [M+H]+ = 271.07470, found 271.07486.

6-[(1,2-Dideoxy-β-D-ribofuranosyl-1-yl)methyl]thieno[2,3-d]pyrimidin-4(3H)-one (18).

A solution of TBAF in 1,4-dioxane (1.0 M, 1.5 mL) was added dropwise to a solution of compound 17 (525 mg, 1.0 mmol) in 1,4-dioxane (15 mL). The reaction mixture was stirred at r.t. for 2 h, and then concentrated. Flash chromatography (solvent C1) of the residue provided compound 18 (220 mg, 78%) as colorless solid; m.p. 204 °C; [a]25D +5.6 (c 1.0, DMSO); Rf = 0.22 (solvent C3). 1H NMR (250 MHz, DMSO-d6) δ 1.62 (ddd, 1H, 3J1,2a 9.7 Hz, 3J2a,3 5.9 Hz, 3J2a,2b 12.7 Hz, H-2'a); 1.77 (ddd, 1H, 3J2b,3 2.1 Hz, 3J1,2b 5.6 Hz, H-2'b); 3.02 (m, 2H, H-1''); 3.26 (dd, 1H, 3J4,5a 6.0 Hz, 3J5a,5b 11.4 Hz, H-5'a); 3.36 (dd, 1H, 3J4,5b 4.6 Hz, H-5'b); 3.64 (ddd, 1H, 3J3,4' 2.6 Hz, H-4''); 4.02 (m, 1H, H-3''); 4.22 (m, 1H, H-1''); 4.63 (br s, 1H, OH-5''); 4.90 (br s, 1H, OH-3''); 7.15 (s, 1H, H-5); 8.04 (s, 1H, H-2); 12.38 (br s, 1H, NH). 13C NMR (62.9 MHz, DMSO-d6) δ 35.7 (C-1''); 39.6 (C-2''); 62.4 (C-5''); 72.0 (C-3''); 77.4 (C-4''); 87.6 (C-4''); 119.7 (C-5); 124.5 (C-4'a); 138.5 (C-6); 145.1 (C-2); 157.1 (C-7a); 163.4 (C-4). ESI-MS(+) m/z = 283 [M+H]+. Anal. Calcd for C12H13N2O4S (282.32): C, 51.05; H 5.00; N, 9.92; S, 11.36. Found: C, 50.94; H, 4.95; N, 9.65; S, 11.16.

Preparation of pyrimidines (21–26, 31 and 32). General procedure

H2O (75 μL) was added to a solution of compound 19 (493 mg, 1.0 mmol); 20 (569 mg, 1.0 mmol), 29 (455 mg, 1.0 mmol), or 30 (517 mg, 1.0 mmol) in ethyl acetate (7.5 mL). Sodium
carbonate (254 mg, 2.4 mmol) and acetamidinium hydrochloride (132 mg, 1.4 mmol), benzamidinium hydrochloride (219 mg, 1.4 mmol) or S-methylisothiouronium sulphate (264 mg, 1.4 mmol) was added to the solution above and the reaction mixture was heated under reflux (monitored by TLC). The reaction mixture was cooled, diluted with ethyl acetate (50 mL) and washed with water (2 x 50 mL), dried, and concentrated. The residue was then purified by flash chromatography.

4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]-2-methylpyrimidine (21). Reaction time 4 h; flash chromatography solvent B2; (426 mg, 80%) colorless solid; m.p. 90–92 ºC (ethyl acetate – n-heptane); [α]D23 −10.7 (c 1.0, CHCl3); Rf = 0.21 (solvent B2). 1H NMR (250 MHz, CDCl3) δ 1.04 [s, 9H, C(CH3)3]; 1.34, 1.51 [2 s, 6H, C(CH3)2]; 1.90–2.13 (m, 2H, H-2”); 2.69 (s, 3H, 2-CH3); 2.81–2.92 (m, 2H, H-1”); 3.78 (m, 2H, H-5’); 3.88 (dt, 1H, 3J1,2 = 5.4 Hz, 3J1,2 = 7.8 Hz, H-1’); 4.04 (q, 1H, 3J3,4 = 3.7 Hz, 3J4,5 = 3.7 Hz, H-4’); 4.36 (dd, 1H, 3J2,3 = 6.7 Hz, H-2’); 4.73 (dd, 1H, H-3’); 4.64 (dd, 1H, J5,6 = 5.0 Hz, H-5’); 7.35–7.47, 7.63–7.71 (2 m, 10H, 2 Ph); 8.46 (d, 1H, H-6’). 13C NMR (62.9 MHz, CDCl3) δ 19.3 [C(CH3)3]; 25.5, 27.5 [C(CH3)2]; 25.8 (2-CH3); 26.8 [C(CH3)3]; 32.7, 33.9 (C-1”, C-2”); 64.2 (C-5’); 81.9 (C-3’), 83.5 (C-1’); 84.3 (C-4’); 84.4 (C-2’); 114.1 [C(CH3)2]; 117.4 (C-5); 127.6, 127.7, 129.7, 129.8, 135.6, 135.7 (2 o-, m-, p-Ph); 133.2, 133.3 (2 i-Ph); 156.3 (C-6); 167.7 (C-2); 170.2 (C-4). C31H40N2O4Si (532.74); HRMS (EI): m/z calculated for [M]+ = 532.27519; found 532.27465.

4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]-2-methyl-6-phenylpyrimidine (22). Reaction time 24 h; flash chromatography solvent B5; (365 mg, 60%) colorless solid; m.p. 96–98 ºC (ethyl acetate – n-heptane); [α]D23 −5.4 (c 1.0, CHCl3); Rf = 0.39 (solvent B5). 1H NMR (250 MHz, CDCl3) δ 1.05 [s, 9H, C(CH3)3]; 1.34, 1.50 [2 s, 6H, C(CH3)2]; 1.99–2.13 (m, 2H, H-2”); 2.76 (s, 3H, 2-CH3); 2.88–2.96 (m, 2H, H-1”); 3.80 (m, 2H, H-5’); 3.93 (dt, 1H, 3J1,2 = 5.4 Hz, 3J1,2 = 7.5 Hz, H-1’); 4.05 (q, 1H, 3J3,4 = 3.7 Hz, 3J4,5 = 3.7 Hz, H-4’); 4.39 (dd, 1H, 3J2,3 = 6.7 Hz, H-2’); 4.74 (dd, 1H, H-3’); 7.33 (s, 1H, H-5’); 7.36–7.48, 7.67–7.72, 7.96–8.01 (3 m, 15H, 3 Ph). 13C NMR (62.9 MHz, CDCl3) δ 19.3 [C(CH3)3]; 25.5, 27.5 [C(CH3)2]; 26.2 (2-CH3); 26.8 [C(CH3)3]; 33.0, 34.2 (C-1”, C-2”); 64.2 (C-5’); 81.9 (C-3’), 83.6 (C-1’); 84.3 (C-4’); 84.9 (C-2’); 113.0 (C-5); 114.0 [C(CH3)2]; 127.3, 127.7, 127.8, 128.8, 129.7, 129.8, 130.5, 135.6 (3 o-, m-, p-Ph); 133.2, 133.3, 137.3 (3 i-Ph); 164.0 (C-6); 168.1 (C-2); 170.2 (C-4). CI-MS: m/z (%) 609 (100, [M+H]+). Anal. Calcd for C37H44N2O4Si (608.84): C, 72.99; H, 7.28; N, 4.60. Found: C, 72.63; H, 7.26; N, 4.33.

4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]2-phenylpyrimidine (23). Reaction time 2.5 h; flash chromatography solvent B5; (559 mg, 94%) colorless foam; [α]D25 +12.5 (c 1.0, CHCl3); Rf = 0.30 (solvent B5). 1H NMR (250 MHz, CDCl3) δ 1.06 [s, 9H, C(CH3)3]; 1.36, 1.53 [2 s, 6H, C(CH3)2]; 2.08–2.28 (m, 2H, H-2”); 2.96 (m, 2H, H-1”); 3.81 (m, 2H, H-5’); 3.97 (dt, 1H, 3J1,2 = 5.3 Hz, 3J1,2 = 8.0 Hz, H-1’); 4.08 (q, 1H, 3J3,4 = 3.6 Hz, 3J4,5 = 3.6 Hz, H-4’); 4.40 (dd, 1H, 3J2,3 = 6.7 Hz, H-2’); 4.76 (dd, 1H, H-3’); 7.01 (d, 1H, 3J5,6 = 5.2 Hz, H-5’); 7.34–7.41, 7.44–7.48, 7.67–7.72, 8.43–8.47 (4 m, 15H, 3 Ph); 8.64 (d, 1H, H-6’).

13C NMR (75.5 MHz, CDCl3) δ 19.3 [C(CH3)3]; 25.6, 27.5 [C(CH3)2]; 26.8 [C(CH3)3]; 32.3, 34.0 (C-1”, C-2”); 64.2 (C-5’); 81.9 (C-3’); 83.7 (C-1’); 84.3 (C-4’); 84.9 (C-2’); 114.1 [C(CH3)2]; 132.0, 133.7, 137.3 (3 i-Ph); 164.0 (C-6); 168.1 (C-2); 170.2 (C-4).
4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)ethyl]-2,6-diphenylpyrimidine (24). Reaction time 10 h; flash chromatography solvent B6; (537 mg, 80%) colorless foam; [α]D25 13.7 (c 0.5, CHCl3); RF = 0.44 (solvent B). 1H NMR (250 MHz, CDCl3) δ 1.07 [s, 9H, C(CH3)3]; 1.37, 1.53 [2 s, 6H, C(CH3)2]; 2.11–2.32 (m, 2H, H-2’); 3.03 (m, 2H, H-1’); 3.83 (m, 2H, H-5’); 4.02 (dt, 1H, J1,2: 5.4 Hz, J1,2: 7.8 Hz, H-1’); 4.09 (q, 1H, J3,4: 3.7 Hz, J4,5: 3.7 Hz, H-4’); 4.44 (dd, 1H, J2,3: 6.7 Hz, H-2’); 4.78 (dd, 1H, H-3’); 7.36–7.41, 7.47–7.52, 7.69–7.75, 8.15–8.19, 8.59–8.63 (5 m, 20H, 4 Ph); 7.44 (s, 1H, H-5). 13C NMR (62.9 MHz, CDCl3) δ 19.3 [C(CH3)3]; 25.6, 27.5 [C(CH3)2]; 26.8 [C(CH3)3]; 32.7, 34.2 (C-1”, C-2”); 64.2 (C-5’); 81.9 (C-3’); 83.8 (C-1’); 84.3 (C-4’); 85.0 (C-2’); 113.6 (C-5); 114.1 [C(CH3)2]; 127.2, 127.7, 127.8, 128.3, 128.4, 128.9, 129.7, 129.8, 130.5, 130.6, 135.6, 135.7 (4 o-’, m-’, p-Ph); 133.2, 133.3, 137.3, 138.1 (4 i-Ph); 163.8, 164.2 (C-2, C-6); 170.4 (C-4). CI-MS: m/z (% = 671 (100, [M]+). Anal. Calcd for C42H60N2O4Si (670.91): C, 75.19; H, 6.91; N, 4.18. Found: C, 75.25; H, 7.11; N, 3.97.

4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)ethyl]-2-methylthio-6-phenylpyrimidine (25). Reaction time 3 h; flash chromatography solvent B6; (554 mg, 98%) colorless syrup; [α]D22 −10.5 (c 1.0, CH2Cl2); RF = 0.45 (Bu4). 1H NMR (250 MHz, CDCl3) δ 1.05 [s, 9H, C(CH3)3]; 1.34, 1.51 [2 s, 6H, C(CH3)2]; 1.93–2.14 (m, 2H, H-1’); 2.53 (s, 3H, SCH3); 2.78–2.86 (m, 2H, H-2’); 3.78 (m, 2H, H-5’); 3.88 (dt’, 1H, J1,2: 5.4 Hz, J1,2: 8.0 Hz, H-1’); 4.04 (q, 1H, J3,4: 3.7 Hz, J4,5: 3.7 Hz, H-4’); 4.36 (dd, 1H, J2,3: 6.7 Hz, H-2’); 4.72 (dd, 1H, H-3’); 6.76 (d, 1H, J5,6: 5.0 Hz, H-5); 7.33–7.42, 7.66–7.71 (2 m, 10H, 2 Ph); 8.34 (d, 1H, H-6). 13C NMR (75.5 MHz, CDCl3) δ 14.0 (SCH3); 19.3 [C(CH3)3]; 25.4, 27.5 [C(CH3)2]; 26.8 [C(CH3)3]; 32.2, 33.7 (C-1”, C-2”); 64.2 (C-5’); 81.9 (C-3’); 83.5 (C-1’); 84.2 (C-4’); 84.9 (C-2’); 114.1 [C(CH3)2]; 115.4 (C-5); 127.6, 127.7, 129.7, 129.8, 135.6, 135.7 (2 o-’, m-’, p-Ph); 133.2, 133.3 (2 i-Ph); 156.6 (C-6); 170.2 (C-4); 172.3 (C-2). C31H30N2O4SSi (564.81); HRMS (Cl-MS): m/z calculated for [M+H]+ = 565.25344; found 565.25508.

4-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)ethyl]-2-methylthio-6-phenylpyrimidine (26). Reaction time 24 h; flash chromatography solvent B5; (513 mg, 80%) colorless syrup; [α]D22 −8.1 (c 1.0, CH2Cl2); RF = 0.51 (solvent B). 1H NMR (250 MHz, CDCl3) δ 1.05 [s, 9H, C(CH3)3]; 1.34, 1.51 [2 s, 6H, C(CH3)2]; 1.98–2.18 (m, 2H, H-2’); 2.62 (s, 3H, SMe); 2.82–2.97 (m, 2H, H-3’); 3.80 (m, 2H, H-5’); 3.94 (dt, 1H, J1,2: 5.2 Hz, J1,2: 7.6 Hz, H-1’); 4.05 (q, 1H, J3,4: 3.8 Hz, J4,5: 3.8 Hz, H-4’); 4.38 (dd, 1H, J2,3: 6.7 Hz, H-2’); 4.74 (dd, 1H, H-3’); 7.20 (s, 1H, H-5); 7.33–7.49, 7.67–7.72, 7.99–8.04 (3 m, 15H, 3 Ph). 13C NMR (75.5 MHz, CDCl3) δ 14.1 (SCH3); 19.3 [C(CH3)3]; 25.5, 27.5 [C(CH3)2]; 26.8 [C(CH3)3]; 32.6, 33.7 (C-1”, C-2”); 64.2 (C-5’); 81.8 (C-3’); 83.6 (C-1’); 84.3 (C-4’); 84.9 (C-2’); 111.1 (C-5’); 114.1 [C(CH3)2]; 127.2, 127.6, 127.7, 128.8, 129.7, 129.8, 131.0, 135.6 (3 o-’, m-’, p-Ph); 133.2, 133.3, 136.5 (3 i-Ph); 164.0 (C-6); 170.3 (C-4); 172.0 (C-2). CI-MS: m/z (%) = 641 (100, [M]+).
Anal. Calcd for C$_{27}$H$_{44}$N$_2$O$_4$SSi (640.91): C, 69.34; H, 6.92; N, 4.37; S, 5.00. Found: C, 69.63; H, 7.16; N, 4.12; S, 4.89.

4-[2-[3,5-O-[(Tetraisopropylidisiloxan-1,3-diyl)-1,2-dideoxy-β-d-ribofuranos-1-yl]ethyl]-2-methylthiopyrimidine (31). Reaction time 3 h; flash chromatography solvent B$_5$; (503 mg, 98%) colorless syrup; [α]$_D^{22}$ = −25.7 (c 1.0, CH$_2$Cl$_2$); $R_f$ = 0.50 (solvent B$_7$). $^1$H NMR (250 MHz, CDCl$_3$) δ 0.99–1.05 [m, 28H, 4 CH(CH$_3$)$_2$]; 1.75–2.14 (m, 4H, H-2", H-2‘); 2.53 (s, 3H, SCD$_3$); 2.75 (m, 2H, H-1‘); 3.66–3.76 (m, 2H, H-5’a, H-4’); 3.92–4.02 (m, 1H, H-5’b); 4.03–4.12 (m, 1H, H-1’); 4.36 (dt, 1H, $^3$J$_{2b,3}$ 4.5 Hz, $^3$J$_{2a,3}$ 7.9 Hz, $^3$J$_{3,4}$ 7.9 Hz, H-3’); 6.80 (d, 1H, $^3$J$_{5,6}$ 5.1 Hz, H-5); 8.35 (d, 1H, H-6). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 12.5, 12.9, 13.3, 13.4 [4 CH(CH$_3$)$_2$]; 14.0 (SCH$_3$); 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5 (2) [4 CH(CH$_3$)$_2$]; 33.8, 33.9 (C-1",C-2’); 40.3 (C-2’); 63.8 (C-5’); 73.6 (C-3’); 76.8 (C-1’); 85.9 (C-4’); 115.4 (C-5’); 156.8 (C-6’); 170.4 (C-4’); 172.3 (C-2). Anal. Calcd for C$_{24}$H$_{44}$N$_2$O$_4$SSi$_2$ (512.85): C, 56.21; H, 8.65; N, 5.46; S, 6.25. Found: C, 56.31; H, 8.82; N, 5.22; S, 6.01.

4-[2-[3,5-O-[(Tetraisopropylidisiloxan-1,3-diyl)-1,2-dideoxy-β-d-ribofuranos-1-yl]ethyl]-2-methyl-6-phenylpyrimidine (32). Reaction time 24 h; flash chromatography solvent B$_7$; (496 mg, 89%) colorless syrup; [α]$_D^{25}$ = −25.1 (c 1.0, CH$_2$Cl$_2$); $R_f$ = 0.31 (solvent B$_7$). $^1$H NMR (250 MHz, CDCl$_3$) δ 0.99–1.10 [m, 28H, 4 CH(CH$_3$)$_2$]; 1.86 (dt, 1H $^3$J$_{1',2'a}$ 8.0 Hz, $^3$J$_{2a,3'}$ 8.0 Hz, $^2$J$_{2a,2b}$ 12.9 Hz, H-2’a); 1.92–2.03 (m, 2H, H-2’); 2.06 (d, 1H, $^3$J$_{1',2'b}$ 4.6 Hz, $^3$J$_{1',2'b}$ 4.6 Hz, H-2’b); 2.75 (s, 3H, 2-CH$_3$); 2.86 (m, 2H, H-1‘); 3.74 (m, 2H, H-5’a, H-4’); 4.03 (m, 1H, H-5’b); 4.11 (m, 1H, H-1’); 4.39 (dt, 1H, $^3$J$_{3,4'}$ 8.0 Hz, H-3’); 7.37 (s, 1H, H-5’); 7.46–7.50, 8.02–8.06 (2 m, 5H, Ph). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 12.5, 12.9, 13.4, 13.5 [4 CH(CH$_3$)$_2$]; 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.6 (2) [4 CH(CH$_3$)$_2$]; 26.3 (2-CH$_3$); 34.3, 34.8 (C-1",C-2’); 40.3 (C-2’); 63.8 (C-5’); 73.6 (C-3’); 76.9 (C-1’); 85.9 (C-4’); 113.0 (C-5’); 127.2, 128.9, 130.5 (o-, m-, p-Ph); 137.3 (i-Ph); 164.1 (C-6’); 168.0 (C-2’); 170.5 (C-4’).

ESI-MS (+): $m/z$ = 557 [M+H]$^+$. Anal. Calcd for C$_{30}$H$_{48}$N$_2$O$_4$Si$_2$ (568.88): C, 64.70; H, 8.69; N, 5.03. Found: C, 64.51; H, 8.76; N, 4.88.

4-[2-(2,3-O-Isopropylidene-1-deoxy-β-d-ribofuranos-1-yl)ethyl]-2-methylthiopyrimidine (27). A solution of TBAF in 1,4-dioxiane (1.0 M, 1.5 mL) was added dropwise to a solution of compound 25 (565 mg, 1.0 mmol) in 1,4-dioxiane (15 mL). The reaction mixture was stirred at r.t. for 4 h (monitored by TLC), and then concentrated. Flash chromatography (B$_1$) of the residue provided compound 27 (277 mg, 85%) as a colorless syrup; [α]$_D^{22}$ = −14.6 (c 1.0, CH$_2$Cl$_2$); $R_f$ = 0.28 (solvent B$_1$). $^1$H NMR (300 MHz, CDCl$_3$) δ 1.33, 1.51 [2 s, 6H, C(CH$_3$)$_2$]; 1.98–2.12 (m, 2H, H-2’); 2.54 (s, 3H, SCD$_3$); 2.72–2.89 (m, 2H, H-1‘); 3.66 (ddd, 1H, $^3$J$_{3,5'a}$ 4.0 Hz, $^3$J$_{5'a,OH}$ 7.8 Hz, $^2$J$_{5'a,b}$ 11.9 Hz, H-5’a); 3.78 (ddd, 1H, $^3$J$_{5'b,OH}$ 3.2 Hz, $^3$J$_{4',5'b}$ 4.0 Hz, H-5’b); 3.90 (dt, 1H, $^3$J$_{1',2'}$ 5.8 Hz, $^3$J$_{1',2'}$ 7.0 Hz, H-1’); 3.98 (q, 1H, $^3$J$_{3,4'}$ 4.0 Hz, H-4’); 4.34 (dd, 1H, $^3$J$_{2',3'}$ 6.7 Hz, H-2’); 4.64 (dd, 1H, H-3’); 6.82 (d, 1H, $^3$J$_{5,6}$ 5.0 Hz, H-5’); 8.37 (d, 1H, H-6’); OH signal not detected. $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 14.1 (SCH$_3$); 25.4, 27.5 [C(CH$_3$)$_2$]; 31.8, 33.5 (C-1",C-2’); 62.7 (C-5’); 81.5 (C-3’); 83.8 (C-1’); 84.3 (C-4’); 84.8 (C-2’); 114.6 [C(CH$_3$)$_2$]; 115.5 (C-5’); 156.9 (C-6’); 170.1 (C-4’); 172.4 (C-2). CI-MS: $m/z$ (%) = 327 (100, [M+H]$^+$). C$_{15}$H$_{22}$N$_2$O$_4$S (326.41): C, 55.19; H, 6.79; N, 8.58; S, 9.82. Found: C, 55.09, H, 7.07; N, 8.36; S, 9.58.
4-[2-(2,3-O-Isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]-2-methylthiopyrimidine (28). Aq HCl (0.1 M, 2.5 mL) was added to a solution of compound 25 (565 mg, 1.0 mmol) in EtOH (8 mL), and the mixture was stirred overnight at r.t (monitored by TLC). The mixture was then neutralized by addition of solid NaHCO₃, and concentrated after addition of a small amount of silica gel. The residue was purified by flash chromatography (solvent C₄) to afford compound 28 (74%) as a colorless syrup; [α]²³_D −24.3 (c 0.5, MeOH); Rf = 0.32 (solvent C₄). ¹H NMR (250 MHz, DMSO-d₆) δ 1.68–2.01 (m, 2H, H-2″); 2.49 (s, 3H, SCH₃); 2.65–2.85 (m, 2H, H-1″); 3.36–3.46 (m, 2H, H-5′); 3.56 (m, 2H, H-1′, H-2′); 3.62 (m, 1H, H-4′); 3.76 (m, 1H, H-3′); 4.63 (t, 1H, ³J₅,OH 5.6 Hz, OH-5′); 4.72 (m, 2H, OH-2′, OH-3′); 7.08 (d, 1H, ³J₅,5, 5.1 Hz, H-5); 8.48 (d, 1H, H-6). ¹³C NMR (75.5 MHz, DMSO-d₆) δ 13.4 (SCH₃); 31.7 (C-2″); 33.2 (C-1″); 62.0 (C-5″); 71.3 (C-3″); 74.4 (C-2″); 80.9 (C-1′); 84.6 (C-4′); 116.0 (C-5′); 157.2 (C-6); 170.6, 170.9 (C-2,4). C₁₂H₁₉N₂O₄S (286.35); HRMS (CI-MS): m/z calculated for [M+H]^+ = 287.10600; found 287.10513

4-[2-(1,2-Dideoxy-β-D-ribofuranos-1-yl)ethyl]-2-methylthiopyrimidine (33). Starting from compound 31 (513 mg, 1.0 mmol), compound 33 (211 mg, 78%) was obtained after a reaction time of 24 h and purification by flash chromatography (solvent C₄) as colorless a solid according to the procedure described for compound 18; m.p. 112–114 °C; [α]²³_D = −2.0 (c 1.0, MeOH); Rf = 0.36 (solvent C₃). ¹H NMR (250 MHz, DMSO-d₆) δ 1.56 (ddd, 1H, ³J₁₂a,₃ 6.0 Hz, ³J₁₂a,₂a 9.8 Hz, ³J₂a₂b 12.7 Hz, H-2′a); 1.84 (m, 2H, H-2″); 2.02 (ddd, 1H, ³J₂b₂,₃ 1.6 Hz, ³J₁₂b₂,₅ 5.4 Hz, H-2′b); 2.48 (s, 3H, SCH₃); 2.72 (m, 2H, H-1″); 3.27–3.35 (m, 2H, H-5′a, H-4′); 3.59 (ddd, 1H, ³J₅,2₅ 2.6 Hz, ³J₅,OH 5.3 Hz, ³J₂a₂b 7.8 Hz, H-5′b); 3.97 (m, 1H, H-1′); 4.03 (m, 1H, H-3′); 7.09 (d, 1H, ³J₅,6 5.1 Hz, H-5); 8.49 (d, 1H, H-6). ¹³C NMR (62.9 MHz, DMSO-d₆) δ 13.4 (SCH₃); 33.4, 33.6, (C-1″,2″); 40.2 (C-2); 62.5 (C-5′); 72.1 (C-3′); 76.8 (C-1′); 87.3 (C-4′); 115.9 (C-5′); 157.2 (C-6); 170.6, 170.9 (C-2,4). ESI-MS (+): m/z: 271 [M+H]^+. Anal. Calcd for C₁₂H₁₈N₂O₃S (270.35): C, 53.31; H, 6.71; N, 10.36; S, 11.86. Found: C, 53.08; H, 6.50; N, 10.32; S, 11.69.

Preparation of aminotriazoles (34 and 38). General procedure
A mixture of compound 19 (246 mg, 0.5 mmol) or 29 (227 mg, 0.5 mmol) and 4H-1,2,4-triazol-3-amine (50 mg, 0.6 mmol) in dry EtOH (5 mL) was heated under reflux for 4 h (monitored by TLC), and concentrated. The residue was purified by flash chromatography.

(E)-1-(5-Amino-1H-1,2,4-triazol-1-yl)-5-(5-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)pent-1-ene-3-one (34). Flash chromatography solvent A; (257 mg, 89%); yellow solid; m.p. 118–119 °C; [α]²³_D = −2.6 (c 1.0, CH₂Cl₂); Rf = 0.25 (solvent A)
α-, m-, p-Ph); 132.1 (C-5); 133.2, 133.3 (2 i-Ph); 151.7 (C-3’); 199.6 (C-3); C-5” signal not detected. C_{31}H_{40}NaO_{3}Si (576.76); HRMS (CI-MS): m/z calculated for [M+H]⁺ = 577.28462; found 577.28429.

(E)-1-(5-Amino-1H-1,2,4-triazol-1-yl)-5-[(3,5-O-(tetraisopropylsilsiloxan-1,3-diyl)-1,2-dideoxy-β-D-ribofuranosyl-1-yl)pent-1-en-3-one (38). Flash chromatography solvent B1; (152 mg, 58%) yellow solid; m.p. 170 °C; [α]_{D}^{25} = −34.2 (c 0.8, CH_{2}Cl_{2}); R_{f} = 0.19 (solvent B1).

1H NMR (250 MHz, CDCl_{3}) δ 0.99–1.05 [m, 28H, 4 CH(CH_{3})_{2}]; 1.72–1.87 (m, 3H, H-1, H-2’a); 2.02 (dd, 1H, J_{2b,3} 4.8 Hz, J_{2a,2b} 6.8 Hz, J_{2a,2b} 12.5 Hz, H-2’b); 2.68 (m, 2H, H-2); 3.66–3.76 (m, 2H, H-5’a, H-4’); 3.99 (m, 1H, H-5’b); 4.04 (m, 1H, H-1’); 4.35 (dt, 1H, J_{2a,3} 8.0 Hz, J_{3,4} 8.0 Hz, H-3’); 6.11 (br s, 2H, NH_{2}); 6.72 (d, 1H, J_{4,5} 13.3 Hz, H-4); 7.56 (s, 1H, H-3’); 8.05 (d, 1H, H-5). 13C NMR (62.9 MHz, CDCl_{3}) δ 12.5, 12.9, 13.3, 13.4 [4 CH(CH_{3})_{2}]; 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5 (2) [4 CH(CH_{3})_{2}]; 29.8 (C-1); 39.3 (C-2); 40.0 (C-2’); 63.5 (C-5’); 73.2 (C-3’); 76.5 (C-1’); 85.8 (C-4’); 113.0 (C-4); 132.4 (C-5); 151.6 (C-3’); 200.1 (C-3); C-5” signal not detected. ESI-MS (−): m/z = 523 [M−H]−. Anal. Calcd for C_{32}H_{44}NaO_{3}Si_{2} (524.80): C, 54.93; H, 8.45; N, 10.68. Found: C, 54.79; H, 8.15; N, 10.72.

Preparation of triazolopyrimidines (35 and 39). General procedure

Ethanolic NaOMe (1 M, 1.4 mL) was added to a solution of compound 34 (288 mg, 0.5 mmol) or 38 (262 mg, 0.5 mmol) in dry EtOH (10 mL). After stirring at r.t. for 1 h, the reaction mixture was neutralized with IR 120 (H⁺) Amberlite resin, filtered, dried, and concentrated. The residue was purified by flash chromatography (solvent B2).

5-[2-(5-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranosyl-1-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyrimidine (35). Yield (173 mg, 62%); colorless syrup; [α]_{D}^{22} = −15.4 (c 1.0, CH_{2}Cl_{2}); R_{f} = 0.18 (solvent B2). 1H NMR (250 MHz, CDCl_{3}) δ 1.04 [s, 9H, C(CH_{3})_{3}]; 1.33, 1.50 [2 s, 6H, C(CH_{3})_{2}]; 2.04–2.29 (m, 2H, H-2’’); 3.07 (m, 2H, H-1”); 3.79 (m, 2H, H-5’’); 3.93 (dt, 1H, J_{1’’,2’’} 5.1 Hz, J_{1’’,2’’} 8.3 Hz, H-1’’); 4.04 (q, 1H, J_{4’’,a} 3.8 Hz, J_{4’’,a} 3.8 Hz, H-4’’); 4.38 (dd, 1H, J_{2’’,3} 6.6 Hz, H-2’’); 3.99 (m, 1H, H-5’’); 4.04 (m, 1H, H-1’’); 4.72 (dd, 1H, H-3’’); 6.89 (d, 1H, J_{6,7} 7.0 Hz, H-6’’); 7.32–7.42, 7.65–7.70 (2 m, 10H, 2 Ph); 8.43 (s, 1H, H-2’); 8.63 (d, 1H, H-7’). 13C NMR (75.5 MHz, CDCl_{3}) δ 19.3 [C(CH_{3})_{3}]; 25.5, 27.4 [C(CH_{3})_{2}]; 26.8 [C(CH_{3})_{3}]; 32.1, 34.6 (C-1”, C-2”); 64.1 (C-5’’); 81.8 (C-3’); 83.4 (C-1’’); 84.3 (C-4’’); 110.9 (C-6’); 114.1 [C(CH_{3})_{2}]; 127.6, 127.7, 129.7, 129.8, 135.5, 135.6 (2 α- m-, p-Ph); 133.2, 133.3 (2 i-Ph); 134.9 (C-7); 155.1 (C-3a); 156.1 (C-2’’); 168.4 (C-5’’). Anal. Calcd for C_{31}H_{38}NaO_{3}Si (558.74): C, 66.64; H, 6.85; N, 10.03. Found: C, 66.56; H, 6.72; N, 10.26.

5-[2-(5-O-(Tetraisopropylsilsiloxan-1,3-diyl)-1,2-dideoxy-β-D-ribofuranosyl-1-yl)ethyl]-[1,2,4]triazolo[1,5-a]pyrimidine (39). Yield (175 mg, 69%); colorless solid; m.p. 80–82 °C; [α]_{D}^{25} = −31.6 (c 1.0, CH_{2}Cl_{2}); R_{f} = 0.13 (solvent B2). 1H NMR (250 MHz, CDCl_{3}) δ 1.00–1.06 [m, 28H, 4 CH(CH_{3})_{2}]; 1.86 (dt, 1H, J_{2a,1’} 7.7 Hz, J_{2a,1’} 7.7 Hz, J_{2a,2b} 12.5 Hz, H-2’a); 2.07 (dd, 1H, J_{2a,3} 4.6 Hz, J_{2a,3} 6.7 Hz, J_{2a,2b} 12.5 Hz, H-2’b); 1.94–2.21 (m, 2H, H-1”); 3.05 (m, 2H, H-2”); 3.66–3.77 (m, 2H, H-5’a, H-4’’); 4.00 (m, 1H, H-5’’b); 4.07–4.18 (m, 1H, H-1”); 4.38 (dt’’, 1H, J_{2a,3} 8.0 Hz, J_{3,4} 8.0 Hz, H-3’’); 6.99 (d, 1H, J_{6,7} 7.0 Hz, H-6’’); 8.43 (s, 1H, H-2’); 8.68 (d,
1H, H-7). $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 12.5, 12.9, 13.3, 13.5 [4 CH(CH$_3$)$_2$]; 16.9, 17.0, 17.1, 17.3, 17.4, 17.4, 17.5 [4 CH(CH$_3$)$_2$]; 34.0, 34.7 (C-1", C-2"); 40.3 (C-2'); 63.7 (C-5'); 73.4 (C-3'); 76.5 (C-1'); 86.0 (C-4'); 111.0 (C-6); 134.9 (C-7); 156.1 (C-2'); 156.1 (C-3a); 168.8 (C-5).

ESI-MS (−): $m/z = 505$ [M−H]$.^-$ Anal. Calcd for C$_{24}$H$_{32}$N$_4$O$_4$Si$_2$ (506.79): C, 56.88; H, 8.35; N, 11.06. Found: C, 56.77; H, 8.15; N, 10.82.

**Preparation of pyrimidobenzimidazoles (36, 37 and 40). General procedure**

A mixture of compound 19 (493 mg, 1.0 mmol), 20 (569 mg, 1.0 mmol) or 29 (455 mg, 1.0 mmol) and 1H-benzimidazole-2-amine (266 mg, 2.0 mmol) in dry EtOH (10 mL) was heated under reflux for 2 h (monitored by TLC). The reaction mixture was cooled to r.t. and ethanolic NaOMe (1.0 M, 3.0 mL) was added. After stirring at r.t. for 1 h, the reaction mixture was neutralized with IR 120 (H$^+$) Amberlite resin, filtered, dried, and concentrated. The residue was purified by flash chromatography.

2-[2-(5-O-tert-Butyldiaryl)aryl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]-pyrimido[1,2-α][benzimidazole (36). Flash chromatography solvent B$_2$; (462 mg, 76%) yellow foam; [α]$_D^{24}$ = −21.3 (c 1.0, CH$_2$Cl$_2$); $R_f = 0.14$ (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.05 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.51 [2 s, 6H, C(CH$_3$)$_2$]; 2.07–2.30 (m, 2H, H-2’); 3.06 (m, 2H, H-1’); 3.80 (m, 2H, H-5’); 3.96 (dt, 1H, $^3$J$_{1,2}$ 5.0 Hz, $^3$J$_{1,2}$ 8.0 Hz, H-1’); 4.04 (q, 1H, $^3$J$_{3,4}$ 3.8 Hz, $^3$J$_{4,5}$ 3.8 Hz, H-4’); 4.41 (dd, 1H, $^3$J$_{2,3}$ 6.6 Hz, H-2’); 4.74 (dd, 1H, H-3’); 6.77 (d, 1H, $^3$J$_{3,4}$ 7.0, H-3); 7.33–7.42, 7.66–7.71 (2 m, 11H, 2 Ph, H-7); 7.54 (m, 1H, H-8); 7.83 (d, 1H, $^3$J$_{6,7}$ 8.0 Hz, H-6); 8.01 (d, 1H, $^3$J$_{8,9}$ 8.2 Hz, H-9); 8.59 (d, 1H, H-4'). $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 19.3 [C(CH$_3$)$_3$]; 25.5, 27.5 [2 C(CH$_3$)$_2$]; 26.8 [C(CH$_3$)$_3$]; 31.8 [C-1”]; 35.1 [C-2’’]; 64.2 [C-5’’]; 81.8 [C-3’’]; 83.5 (C-1’); 84.3 (C-4’); 84.9 (C-2’); 107.8 (C-3); 110.4 (C-6); 111.4 [C(CH$_3$)$_2$]; 120.1 (C-9); 121.9 (C-7); 126.4 (C-8); 126.6 (C-5a); 127.6, 127.7, 129.7, 129.8, 135.5, 135.6 (2 o-, m-, p-Ph); 132.5 (C-4); 133.3, 133.4 (2 i-Ph); 143.3 (C-9a); 150.4 (C-10a); 169.3 (C-2). C$_{36}$H$_{41}$N$_3$O$_3$Si (607.81); HRMS (EI-MS): m/z calculated for [M]$^+$ = 607.28663; found 607.28608.

2-[2-(5-O-tert-Butyldiaryl)aryl-2,3-O-isopropylidene-1-deoxy-β-D-ribofuranos-1-yl)ethyl]-4-phenyl- pyrimido[1,2-α][benzimidazole (37). Flash chromatography solvent B$_2$; (547 mg, 80%) yellow foam; [α]$_D^{24}$ = −20.2 (c 1.0, CH$_2$Cl$_2$); $R_f = 0.21$ (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.03 [s, 9H, C(CH$_3$)$_3$]; 1.34, 1.51 [2 s, 6H, C(CH$_3$)$_2$]; 2.10–2.36 (m, 2H, H-2’); 3.07 (m, 2H, H-1’); 3.80 (m, 2H, H-5’); 4.01 (dt, 1H, $^3$J$_{1,2}$ 5.0 Hz, $^3$J$_{1,2}$ 8.1 Hz, H-1’); 4.05 (q, 1H, $^3$J$_{3,4}$ 3.8 Hz, $^3$J$_{4,5}$ 3.8 Hz, H-4’); 4.42 (dd, 1H, $^3$J$_{2,3}$ 6.7 Hz, H-2’); 4.74 (dd, 1H, H-3’); 6.58 (s, 1H, H-3); 6.64 (d, 1H, $^3$J$_{6,7}$ 8.4 Hz, H-6); 6.99 (m, 1H, H-7); 7.30–7.38, 7.49–7.70 (2 m, 15H, 3 Ph); 7.44 (m, 1H, H-8); 7.94 (d, 1H, $^3$J$_{8,9}$ 8.2 Hz, H-9). $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 19.2 [C(CH$_3$)$_3$]; 25.5, 27.5 [C(CH$_3$)$_2$]; 26.8 [C(CH$_3$)$_3$]; 31.9 [C-1’’]; 34.8 (C-2’’); 64.2 (C-5’’); 81.8 (C-3’); 83.6 (C-1’); 84.3 (C-4’); 84.9 (C-2’); 108.7 (C-3); 114.1 [C(CH$_3$)$_2$]; 114.4 (C-4); 120.1 (C-9); 120.9 (C-7); 125.7 (C-8); 127.3 (C-5a); 127.6, 127.7, 128.2, 129.6, 129.7, 130.9, 135.6 (3 o-, m-, p-Ph); 132.2, 133.2, 133.3 (3 i-Ph); 144.6 (C-9a); 148.5 (C-4’); 151.9 (C-10a); 168.1 (C-2). C$_{42}$H$_{55}$N$_3$O$_4$Si (683.91); HRMS (EI-MS): m/z calculated for [M]$^+$ = 683.31793; found 683.31738.
2-[2-[3,5-O-(Tetraisopropyldisiloxan-1,3-diyl)-1,2-didesoxy-β-D-ribofuranos-1-yl]ethyl]-pyrimido[1,2-a]benzimidazole (40). Flash chromatography solvent B$_1$; (350 mg, 63%) colorless syrup; [α]$_D^{22}$ $-$25.7 (c 1.0, CH$_2$Cl$_2$); $R_f$ = 0.14 (solvent B$_2$). $^1$H NMR (250 MHz, CDCl$_3$) δ 1.00–1.07 [m, 28H, 4CH(CH$_3$)$_2$]; 1.83–2.24 (m, 4H, H-1", H-2’); 3.01 (m, 2H, H-5'a, H-4’); 4.01 (m, 1H, H-5'b); 4.16 (m, 1H, H-1’); 4.39 (dt, 1H, $^3$J$_{3',2'b}$ 5.0 Hz, $^3$J$_{3',2'a}$ 8.0 Hz, $^3$J$_{3',4'}$ 8.0 Hz, H-3’); 6.81 (d, 1H, $^3$J$_{3,4}$ 7.0 Hz, H-3); 7.38 (m, 1H, H-7); 7.53 (m, 1H, H-8); 7.83 (d, 1H, $^3$J$_{6,7}$ 8.2 Hz, H-6); 7.97 (d, 1H, $^3$J$_{8,9}$ 8.2 Hz, H-9); 8.60 (d, 1H, H-4’). $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 12.5, 12.9, 13.3, 13.5 [4CH(CH$_3$)$_2$]; 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5 (2) [4CH(CH$_3$)$_2$]; 33.5 (C-1’); 35.1 (C-2’); 40.3 (C-2’); 63.8 (C-5’); 73.5 (C-3’); 76.8 (C-1’); 85.9 (C-4’); 107.6 (C-3’); 110.3 (C-6); 120.3 (C-9); 121.7 (C-7); 126.2 (C-8); 126.9 (C-5a); 132.3 (C-4’); 144.0 (C-9a); 150.7 (C-10a); 169.1 (C-2’). ESI-MS (–): $m/z$ = 554 [M–H]$. Anal. Calcd for C$_{29}$H$_{45}$N$_3$O$_4$Si$_2$ (555.86): C, 62.66; H, 8.16; N, 7.56. Found: C, 62.89; H, 8.29; N, 7.37.

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References