A General Route to 4-C-Substituted Pyrimidine Nucleosides

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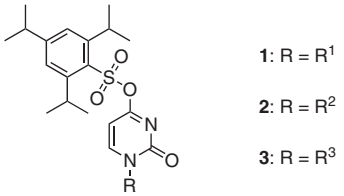
Abstract: Palladium-catalyzed cross-coupling reactions of tin and zinc nucleophiles with arylsulfonates of pyrimidine nucleosides have been achieved to give a wide range of 4-C-substituted pyrimidine nucleosides. This method also allows the construction of pyrimidine-pyrimidinone dinucleosides, containing the carbon skeleton of the (6-4) DNA photo lesion.

Key words: cross-coupling, nucleosides, palladium, pyrimidines, (6-4) lesion

Nucleosides and nucleoside analogues belong to the most important classes of antiviral and antitumor drugs. Even today, around 30 years after the discovery of the first successful antiviral drug, acyclovir, plenty of new nucleoside derivatives, many of them pyrimidine derivatives, are synthesized and tested.[1,2] Compared to other substituted pyrimidine nucleosides, C4-substituted pyrimidines, especially 2-pyrimidinones, are quite rare in the literature. In fact, a general method for their synthesis from a common precursor is missing. Most of the known compounds have been prepared by glycosylation of the preassembled heterocycle with a suitable glycosyl donor.[3,4] 2-Pyrimidinone nucleosides are not only of pharmacological interest, but they occur also in nature, for example as part of the carbon framework of the (6-4) DNA photo lesion, which is one of the major mutagenic and cytotoxic lesions known in DNA.[5]

Both 4-N- and 4-O-substituted pyrimidines can be easily prepared from uridines by conversion of the O4 into a suitable leaving group (for example a chloride or an arylsulfonate) and substitution of this leaving group by a nitrogen or oxygen nucleophile.[6,7] For carbon nucleophiles, however, this reaction is limited to extremely nucleophilic compounds such as malonic diesters.[8] Organometallic nucleophiles like organolithium or organocopper compounds react only sluggishly or, like alkyl Grignard reagents, add preferentially to the 6-position without substituting the leaving group.[9] We anticipated that these problems can be overcome by using palladium catalysis, which is of increasing importance in contemporary purine nucleoside chemistry.[10–14] Two examples for the synthesis of 4-carbon substituted pyrimidine nucleosides using palladium-catalyzed cross-coupling are known, but are not generally applicable, limited to alkyne nucleophiles (Sonogashira coupling), or low yielding.[15,16] As starting material we chose the 2,4,6-triisopropylbenzenesulfonates of various uridine derivatives such as **1**, **2**, **3** (Figure 1 and Scheme 1). These compounds are conveniently prepared in high yields from the corresponding uridine nucleosides and can be easily purified by column chromatography. The compounds are stable and can be stored at –20 °C for months.[8] In contrast, the corresponding chlorides were, at least in our hands, unstable. In addition, the methods used for their preparation (using $SOCl_2$ for example) are generally not compatible with many of the typically used protecting groups of the sugar hydroxyl groups.



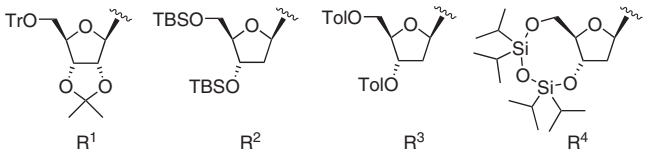
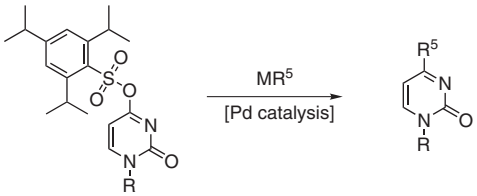


Figure 1 Structures of the starting materials used



Scheme 1 General reaction scheme; M = $SnBu_3$, ZnCl; R^5 = alkyl, alkenyl, aryl, heteroaryl

Initial attempts to use the arylsulfonates in Suzuki cross-coupling reactions or in Heck reactions were unsuccessful. Under the elevated temperatures needed for the activation of the arylsulfonates they quickly hydrolyzed back to uridine. Therefore we focused our attention on Stille and Negishi couplings as they usually proceed at lower temperatures and do not need a base. As a first attempt, the Stille coupling of phenylethynyltributyltin (**4**) with **1** was investigated (Table 1, entry 1). Gratifyingly, the reaction gave the desired product smoothly under fairly standard conditions [DMF, $Pd(PPh_3)_4$, CuI, 55 °C, 24 h]. Without CuI or with other additives (Bu_4NBr), the arylsulfonate

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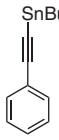
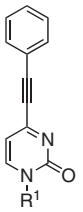
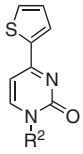
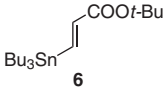
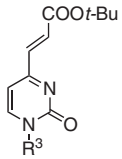
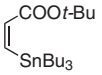
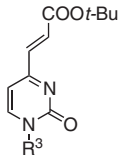
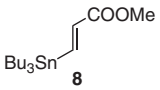
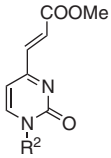
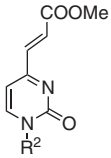
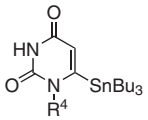
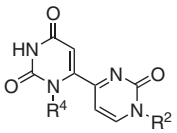
hydrolysis created problems. The reaction conditions proved to be quite generally applicable, as under these conditions other tin nucleophiles and the arylsulfonates **2** and **3** could be applied equally well (Table 1). Alkynyl, alkenyl and heteroaromatic tin nucleophiles could be used and, usually, the desired products were obtained after column chromatography in high purity and good yields.

Quite surprising was the reaction of the acrylic acid nucleophiles. The reaction of (*E*)- and (*Z*)-3-tributylstannylacrylic acid *tert*-butyl ester (entries 3 and 4) gave exclusively the same product featuring the *E*-configured double bond. Interestingly the reaction of the *E*-nucleophile was slow and only the use of 2.5 equivalents of the tin compound gave acceptable yields. To investigate the influence of the bulky *tert*-butyl ester, the reaction was carried out with (*E*)- and (*Z*)-3-tributylstannylacrylic acid methyl ester (entries 5 and 6). Again, the product with the *E*-configured double bond was usually the only product. In one or two cases, however, a *E*/*Z*-product mixture was isolated from the reaction when the *Z*-configured nucleophile **7** was used. Upon standing at room temperature, the chloroform solution of *Z*-configured product isomerized within two days to the *E*-compound. This possibly explains the outcome of our reactions: The Stille coupling proceeds, as it is generally the case, with retention of configuration at the double bond.[17] Afterwards the isomerization from the *Z*- to the *E*-double bond geometry takes place in a second step by a yet unknown mechanism.

After the successful application of the tin nucleophiles, we also investigated the reaction of the arylsulfonates with zinc organometallics (Negishi coupling, Table 2). Phenylzinc chloride (derived from phenyl-Grignard and zinc chloride) reacted with **1** under conditions fairly similar to the Stille couplings above [$Pd(PPh_3)_4$, THF] even at room temperature to give the 4-phenyl-2-pyrimidinone nucleoside **18** in good yield (Table 2, entry 1). The ease of this reaction prompted us to investigate the cross-coupling of the sterically more demanding thymidine nucleoside **16**. To our surprise the reaction proceeded also smoothly but required longer reaction times (3 d, entry 2). In this case, the application of 2.5 mol% $Pd(dppf)Cl_2$ as catalyst was superior to $Pd(PPh_3)_4$, as it allowed easier removal of the catalyst from the product. Using this protocol, even sp^3-sp^2 cross-couplings were possible. Dimethylzinc or *n*-butylzinc chloride could be coupled using $Pd(PPh_3)_4$. Here, however, the yields were slightly lower. The catalyst loading for the reaction with dimethylzinc can be as low as 0.5% without any loss of yield. The use of $Pd(dppf)Cl_2$, a catalyst known to suppress the problematic β-hydride elimination, for the reaction with *n*-butylzinc chloride did not improve the yield.[18]

As our method works under very mild conditions, we prepared the highly functionalized 6-tributylstannyluridine nucleoside **10** (Table 1, entry 7, two steps from uridine).[19] This stannylated nucleoside was anticipated to function as a precursor for the dihydropyrimidine part of the (6-4) DNA lesion on the way towards the first total synthesis of the lesion. Coupling of this compound to arylsulfonate **2**

Table 1 Stille-Type Cross Coupling of 4-(2,4,6-Triisopropylbenzenesulfonate)pyrimidine Nucleosides[a]

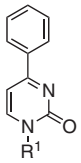
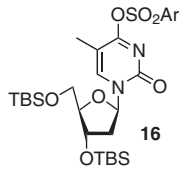
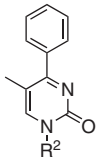
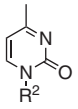
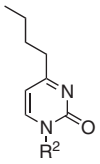
Entry	Substrate	Nucleophile	Product	Yield (%)
1	**1**	 **4**	 **11**	64
2	**2**	 **5**	 **12**	76
3	**3**	 **6**	 **13**	48[b]
4	**3**	 **7**	 **13**	71
5	**2**	 **8**	 **14**	71[b]
6	**2**	 **9**	 **14**	76
7	**2**	 **10**	 **15**	64[c]

[a] Conditions: arylsulfonate (1 equiv), tin nucleophile (1.5 equiv), CuI (20 mol%), $Pd(PPh_3)_4$ (10 mol%), DMF, 24 h, 55 °C. For R^1–R^4, see Figure 1.

[b] 2.5 equiv of tin nucleophile was used.

[c] 1 equiv of tin nucleophile was used.

Table 2 Negishi-Type Cross-Coupling of 4-(2,4,6-Triisopropylbenzenesulfonate)pyrimidine Nucleosides[a]

Entry	Substrate	Nucleophile	Product	Yield (%)
1	**1**	 **17**	 **18**	74
2	 **16**	 **17**	 **19**	68[b]
3	**2**	Me_2Zn	 **20**	61[c]
4	**2**	BuZnCl	 **21**	48

[a] Conditions: arylsulfonate (1 equiv), zinc nucleophile (2 equiv), $Pd(PPh_3)_4$ (10 mol%), THF, r.t. Ar = 2,4,6-triisopropylbenzene. For R^1 and R^2, see Figure 1.
[b] $Pd(dppf)Cl_2$ (2.5 mol%) instead of $Pd(PPh_3)_4$; reaction time: 3 d.
[c] 0.5 mol% catalyst was used.

gave the interesting pyrimidine-pyrimidinone dinucleoside **15** in fairly good 68% yield. This dinucleoside contains the complete carbon framework of the (6-4) lesion derived from a CC (or UC) dinucleotide and should therefore be a highly valuable starting material for the total synthesis of this biologically interesting lesion (Figure 2).

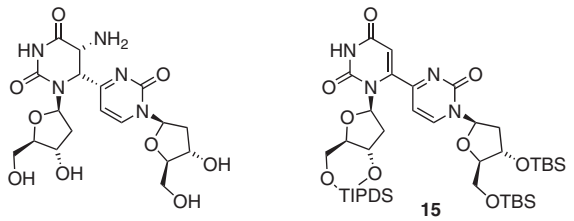


Figure 2 Comparison of the (6-4) lesion derived from UC or CC (after imine hydrolysis) and compound **15**

Initial deprotection experiments were performed with the compounds **12** (TBS-protected) **13** (toluoyl-protected). Compound **12** could be deprotected using HF/pyridine to give the unprotected nucleoside, 1-(2′-deoxyribofuranosyl)-4-thienyl-2-(1*H*)-pyrimidinone (**22**). The purification of the highly polar product, however, was as expected difficult and needs further optimization (isolated yield 41%). Deprotection of compound **13** is an especially difficult task due to the highly electrophilic double bond bearing two electron-withdrawing substituents.[20] Nevertheless deprotection was possible in our hands using sodium methoxide and short reaction times. These conditions gave the unprotected nucleoside, (*E*)-3-[1-(2′-deoxyribofuranosyl)-2-(1*H*)-pyrimidinon-4-yl]acrylic acid *tert*-butyl ester (**23**) as the major product (isolated yield 38%). Minor side products were formed due to Michael-type addition to the double bond.

In summary, we have developed a new method for the synthesis of 4-carbon substituted uridines, capable of introducing sp-, sp^2- and sp^3-carbon substituents. This method will provide an expedient route towards the assembly of the carbon framework of the (6-4) DNA lesion.

All reactions were carried out in Schlenk glassware under an inert gas atmosphere. Reactions were monitored by TLC. Yields refer to isolated yields of analytically pure compounds. Pre-coated silica gel $60F_{254}$ (Merck) was used for TLC, silica gel 60 (0.040–0.063 mm, Merck) was used for column chromatography. NMR spectra were recorded on Varian or Bruker NMR spectrometers (300, 400 or 600 MHz). Mass spectra were measured on a Finnigan MAT 95 Q (FAB) or a Finnigan LTQ-FT (ESI). IR spectroscopy was performed on a PerkinElmer FT-IR spectrum 100 or a PerkinElmer Spectrum BX. The following compounds were prepared by literature procedures: 2′,3′-*O*-isopropylidene-5′-*O*-trityluridine,[21] 2′-deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-4-*O*-[(2,4,6-triisopropylbenzene)sulfonyl]uridine (**2**),[22] 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-4-*O*-[(2,4,6-triisopropylbenzene)sulfonyl]thymidine (**16**),[8] 2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)uridine,[23] (*E*)- and (*Z*)-3-tributylstannylacrylic acid methyl ester (**8** and **9**) and (*E*)- and (*Z*)-3-tributylstannylacrylic acid *tert*-butyl ester (**6** and **7**).[24]

2′,3′-*O*-Isopropylidene-5′-*O*-trityl-4-*O*-[(2,4,6-triisopropylbenzene)sulfonyl]uridine (1)

2′,3′-*O*-Isopropylidene-5′-*O*-trityluridine (1.00 g, 1.9 mmol) was dissolved in THF (25 mL). NaH (60% suspension in mineral oil, 360 mg, 9.0 mmol) was carefully added and the resulting suspension was stirred for 45 min at r.t. 2,4,6-Triisopropylbenzenesulfonylchloride (983 mg, 3.2 mmol) was added and the suspension was stirred for 14 h at r.t. Aq sat. NH_4Cl (30 mL) was added and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 4:1) to give the product (820 mg, 54%) as a colorless oil; R_f = 0.21 (isohexanes–EtOAc, 4:1).

IR (KBr): 3059, 2962, 2932, 2872, 1693, 1631, 1599, 1543, 1450, 1384, 1279, 1196, 1187, 1157, 1113, 1074, 809, 777, 706, 558 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.29 [m, 18 H, $CH(CH_3)_3$], 1.33 [s, 3 H, $C(CH_3)_2$], 1.55 [s, 3 H, $C(CH_3)_2$], 2.85–2.96 [m, 1 H, *para* $CH(CH_3)_3$], 3.36 (dd, *J* = 10.8, 4.8 Hz, 1 H, H-5′A), 3.48 (dd, *J* = 10.8, 2.7 Hz, 1 H,, H-5′B), 4.18–4.29 [m, 2 H, *ortho* $CH(CH_3)_3$], 4.42–4.47 (m, 1 H, H-4′), 4.73–4.80 (m, 2 H, H-2′, H-3′), 5.64 (d, *J* = 7.2 Hz, 1 H, H-5), 5.89 (d, *J* = 1.2 Hz, 1 H, H-1′), 7.20 (s, 2 H_{arom}), 7.26–7.36 (m, 15 H, 3 C_6H_5), 8.07 (d, *J* = 7.2 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (2 C), 24.5 (2 C), 24.6 (2 C), 25.3, 27.2, 29.6 (2 C), 34.3, 63.3, 80.0, 85.9, 87.0, 87.6, 93.8, 94.7, 114.1, 124.0 (2 C), 127.5 (3 C), 128.0 (6 C), 128.6 (6 C), 130.6, 142.9 (3 C), 146.1, 151.2 (2 C), 153.7, 154.5, 167.1.

HRMS-ESI (+): *m/z* [M + $HNEt_3$]$^+$ calcd for $C_{52}H_{68}N_3O_8S$: 894.4722; found: 894.4717.

2′-Deoxy-3′,5′-bis-*O*-(4-toluoyl)-4-*O*-[(2,4,6-triisopropylbenzene)sulfonyl]uridine (3)

2′-Deoxy-3′,5′-bis-*O*-(4-toluoyl)uridine (300 mg, 0.65 mmol) was dissolved in THF (20 mL). NaH (60% suspension in mineral oil, 129 mg, 3.23 mmol) was carefully added and the resulting suspension was stirred for 45 min at r.t. 2,4,6-Triisopropylbenzenesulfonyl chloride (392 mg, 1.29 mmol) was added and the suspension was stirred for 14 h at r.t. Aq sat. NH_4Cl (30 mL) was added and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 4:1) to give the product (407 mg, 86%) as a white, amorphous solid.

IR (KBr): 2962, 2871, 1717, 1688, 1628, 1611, 1543, 1463, 1382, 1273, 1180, 1101, 1020, 754, 691, 556 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23–1.32 [m, 18 H, CH(CH_3)$_3$] 2.14–2.20 (m, 1 H, H-2′A), 2.42 (s, 6 H, ArCH_3), 2.86–2.94 [m, 1 H, *para* CH(CH$_3$)$_3$], 3.05 (ddd, *J* = 14.4, 5.7 Hz, 1.5 Hz, 1 H, H-2′B), 4.22–4.28 [m, 2 H, *ortho* CH(CH$_3$)$_3$], 4.59–4.62 (m, 1 H, H-4′), 4.65 (dd, *J* = 12.0, 3.6 Hz, 1 H, H-5′A), 4.75 (dd, *J* = 12.0, 3.0 Hz, 1 H, H-5′B), 5.54–5.57 (m, 1 H, H-3′), 5.94 (d, *J* = 7.2 Hz, 1 H, H-5), 6.21 (dd, *J* = 7.8, 5.4 Hz, 1 H, H-1′), 7.20 (s, 2 H$_{arom}$), 7.22–7.27 (m, 4 H, H$_{tol}$), 7.80–7.83 (m, 2 H, H$_{tol}$), 7.90–7.93 (m, 2 H, H$_{tol}$), 8.07 (d, *J* = 7.2 Hz, 1 H, H-6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.7 (2 C), 23.4 (2 C), 24.4 (2 C), 24.6 (2 C), 29.6 (2 C), 34.2, 39.3, 63.9, 74.8, 84.0, 88.0, 95.0, 124.0 (2 C), 126.2, 126.3, 129.2 (2 C), 129.4 (4 C), 129.8 (2 C), 130.5, 144.5 (2 C), 144.6, 151.2 (2 C), 153.6, 154.5, 166.0, 166.0, 167.1.

HRMS-ESI (+): *m/z* [M + Na]$^+$ calcd for $C_{40}H_{46}N_2O_9S$ + Na: 753.2816; found: 753.2829.

2′-Deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-6-(tributylstannyl)uridine (10)

Diisopropylamine (0.35 mL, 2.5 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. *n*-BuLi (1.6 M in hexanes, 1.58 mL, 2.5 mmol) was added dropwise and the solution was stirred for 1 h at 0 °C. The solution was cooled to –78 °C and 2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)uridine (295 mg, 0.6 mmol) in THF (4 mL) was added dropwise. The resulting yellow solution was stirred for 2 h at –78 °C. Bu_3SnCl (0.34 mL, 1.3 mmol) was added dropwise and the solution was stirred for 100 min at –78 °C. Aq sat. NH_4Cl solution (20 mL) and EtOAc (20 mL) were added, the layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 6:1) to give the product (357 mg, 75%) as a colorless oil; R_f = 0.69 (isohexanes–EtOAc, 4:1).

IR (ATR): δ = 3261, 2924, 2868, 1712, 1680, 1558, 1462, 1428, 1368, 1336, 1231, 1158, 1088, 1065, 1029, 962, 886, 864, 825, 784, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–1.69 [m, 55 H, Sn(C$_4$H$_9$)$_3$ + CH(CH$_3$)$_3$], 2.24–2.35 (m, 1 H, H-2′A), 2.91–3.02 (m, 1 H, H-2′B), 3.73–3.81 (m, 1 H, H-4′), 3.97–4.03 (m, 2 H, H-5′), 4.94–5.04 (m, 1 H, H-3′), 5.32 (dd, *J* = 9.0, 3.3 Hz, 1 H, H-1′), 5.58–5.70 (m, 1 H, H-5), 8.09 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6 (3 C), 12.6, 12.7, 13.3 (2 C), 13.6 (3 C), 17.0 (2 C), 17.2, 17.3, 17.4 (2C), 17.5, 17.6, 27.1 (3 C), 28.7 (3 C), 39.8, 64.1, 73.6, 85.9, 94.0, 110.7, 149.6, 161.6, 167.8.

HRMS-ESI (–): *m/z* [M – H]$^-$ calcd for $C_{33}H_{63}N_2O_6Si_2Sn$: 759.3252; found: 759.3250.

Stille-Type Cross Couplings; General Procedure

Arylsulfonate (1 equiv), tin reagent (1.5 equiv), CuI (0.2 equiv) and (Ph_3P)$_4$Pd (0.1 equiv) were dissolved in DMF (1 mL per 0.1 mmol arylsulfonate). The solution was stirred 55 °C for 24 h. After cooling to r.t., the solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 1:1).

1-(2′,3′-*O*-Isopropylidene-5′-*O*-tritylribofuranosyl)-4-(phenylethynyl)-2-(1*H*)-pyrimidinone (11)

The standard procedure was followed using arylsulfonate **1** (150 mg, 0.19 mmol), (phenylethynyl)tributyltin (98 μL, 0.28 mmol), CuI (8 mg, 0.04 mmol) and (Ph_3P)$_4$Pd (23 mg, 0.02 mmol) affording the product (74 mg, 64%) as a colorless oil; R_f = 0.30 (isohexanes–EtOAc, 1:1).

IR (film): 3086, 3060, 2988, 2931, 2871, 2217s, 1661, 1611, 1505, 1492, 1448, 1383, 1374, 1314, 1271, 1213, 1158, 1114, 1078, 910, 876, 791, 759, 732, 707, 632, 541 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 3.40 (dd, *J* = 10.8, 5.1 Hz, 1 H, H-5′A), 3.51 (dd, *J* = 10.8, 2.9 Hz, 1 H, H-5′B), 4.47–4.52 (m, 1 H, H-4′), 4.76 (dd, *J* = 6.2, 3.5 Hz, 1 H, H-3′), 4.91 (dd, *J* = 6.2, 1.5 Hz, 1 H, H-2′), 5.97 (d, *J* = 1.5 Hz, 1 H, H-1′), 6.15 (d, *J* = 6.9 Hz, 1 H, H-5), 7.25–7.45 [m, 18 H, C≡CC_6H_5 + C(C_6H_5)$_3$], 7.58–7.62 (m, 2 H, C≡CC_6H_5), 8.10 (d, *J* = 6.9 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 27.2, 63.5, 80.3, 85.9, 87.1, 87.2, 87.5, 94.5, 95.8, 106.4, 114.0, 120.8, 127.4 (3 C), 128.0 (6 C), 128.5 (8 C), 130.3, 132.7 (2 C), 143.1 (3 C), 143.7, 154.6, 159.2.

HRMS-FAB (+): *m/z* [M + H]$^+$ calcd for $C_{39}H_{35}N_2O_5$: 611.2540; found: 611.2555.

1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-4-thienyl-2-(1*H*)-pyrimidinone (12)

The standard procedure was followed using arylsulfonate **2** (144 mg, 0.2 mmol), 2-tributyltinthiophene (**5**; 100 μL, 0.3 mmol), CuI (8 mg, 0.04 mmol) and (Ph_3P)$_4$Pd (23 mg, 0.02 mmol) affording the crude product. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 2:1) to give the title compound (79 mg, 76%) as a colorless oil; R_f = 0.76 (isohexanes–EtOAc, 1:1).

IR (ATR): 3087, 2954, 2929, 2856, 1646, 1608, 1530, 1512, 1446, 1417, 1336, 1308, 1249, 1179, 1095, 1065, 1032, 947, 878, 832, 776, 706, 668 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.87 (s, 9 H, *t*-C_4H_9), 0.93 (s, 9 H, *t*-C_4H_9), 2.18 (ddd, *J* = 13.5, 6.6, 4.5 Hz, 1 H, H-2′A), 2.50–2.61 (m, 1 H, H-2′B), 3.74–3.82 (m, 1 H, H-5′A), 3.92–4.00 (m, 2 H, H-4′, H-5′B), 4.33–4.42 (m, 1 H, H-3′), 6.25 (dd, *J* = 6.6, 4.5 Hz, 1 H, H-1′), 6.61 (d, *J* = 7.1 Hz, 1 H, H-5), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1 H, H-4$_{thienyl}$), 7.57 (dd, *J* = 5.1, 1.2 Hz, 1 H, H-3$_{thienyl}$), 7.76 (dd, *J* = 3.6, 1.2 Hz, 1 H, H-5$_{thienyl}$), 8.41 (d, *J* = 7.1 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5, –5.5, –5.0, –4.6, 17.9, 18.3, 25.7 (3 C), 25.9 (3 C), 42.2, 61.6, 69.7, 87.0, 87.7, 99.6, 128.3, 129.8, 132.5, 141.8, 143.0, 155.3, 165.4.

HRMS-ESI (+): *m/z* [M + $HNEt_3$]$^+$ calcd for $C_{31}H_{58}N_3O_4SSi_2$: 624.3681; found: 624.3660.

(*E*)-3-1-[2′-Deoxy-3′,5′-bis-*O*-(4-toluoyl)ribofuranosyl]-2-(1*H*)-pyrimidinon-4-yl-acrylic Acid *tert*-Butyl Ester (13)

*Using (Z)-3-Tributyltinacrylic Acid tert-Butyl Ester (**7**)*: The standard procedure was followed using arylsulfonate **3** (730 mg, 0.19 mmol), ester **7** (670 mg, 1.6 mmol), CuI (38 mg, 0.2 mmol) and $(Ph_3P)_4Pd$ (116 mg, 0.1 mmol) affording the product (405 mg, 71%) as a white, amorphous solid; R_f = 0.46 (isohexanes–EtOAc, 1:1).

IR (KBr): 2978, 1718, 1664, 1612, 1518, 1452, 1370, 1312, 1272, 1179, 1154, 1106, 1020, 976, 843, 794, 754, 692 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, *t*-C_4H_9), 2.27–2.33 (m, 1 H, H-2′A), 2.40 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 3.19–3.24 (m, 1 H, H-2′B), 4.66 (dd, *J* = 12.0, 3.0 Hz, 1 H, H-5′A), 4.67–4.70 (m, 1 H, H-4′), 4.79 (dd, *J* = 12.0, 1.8 Hz, 1 H, H-5′B), 5.59–5.62 (m, 1 H, H-3′), 6.30 (d, *J* = 7.2 Hz, 1 H, H-5), 6.33–6.36 (m, 1 H, H-1′), 6.85 (d, *J* = 16.2 Hz, 1 H, CH=CH), 7.19–7.30 (m, 5 H, H_{arom}, CH=CH), 7.78–7.82 (m, 2 H_{arom}), 7.93–7.98 (m, 2 H_{arom}), 8.13 (d, *J* = 7.2 Hz, 1 H, H-6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.6, 21.7, 28.0 (3 C), 39.6, 64.1, 75.0, 81.7, 84.2, 88.5, 103.0, 126.2, 126.3, 129.3 (2 C), 129.4 (4 C), 129.8 (2 C), 131.2, 139.4, 142.7, 144.5 (2 C), 155.1, 164.6, 166.0, 166.1, 168.4.

HRMS-ESI (+): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{35}N_2O_8$: 575.2388; found: 575.2379.

*Using (E)-3-Tributyltinacrylic Acid tert-Butyl Ester (**6**)*: The standard procedure was followed except that 2.5 equiv of (*E*)-3-tributyltinacrylic acid *tert*-butyl ester (**6**) were used. Arylsulfonate **3** (146 mg, 0.2 mmol), ester **6** (208 mg, 0.5 mmol), CuI (8 mg, 0.04 mmol) and $(Ph_3P)_4Pd$ (23 mg, 0.02 mmol) afforded the product **13** (56 mg, 49%) as a white, amorphous solid. For analytical and spectral data, see above.

(*E*)-3-1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-2-(1*H*)-pyrimidinon-4-ylacrylic Acid Methyl Ester (14)

*Using (Z)-3-Tributyltinacrylic Acid Methyl Ester (**9**)*: The standard procedure was followed using arylsulfonate **2** (620 mg, 0.86 mmol), ester **9** (810 mg, 2.16 mmol), CuI (33 mg, 0.17 mmol) and $(Ph_3P)_4Pd$ (116 mg, 0.1 mmol) affording the product (340 mg, 76%) as a colorless oil; R_f = 0.69 (isohexanes–EtOAc, 1:1).

IR (ATR): 2953, 2929, 2857, 1728, 1664, 1608, 1520, 1461, 1390, 1362, 1300, 1252, 1110, 1077, 1029, 980, 965, 882, 833, 776, 673 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.86 (s, 9 H, *t*-C_4H_9), 0.90 (s, 9 H, *t*-C_4H_9), 2.17 (ddd, *J* = 13.5, 6.6, 4.2 Hz, 1 H, H-2′A), 2.54–2.60 (m, 1 H, H-2′B), 3.76–3.79 (m, 1 H, H-5′A), 3.80 (s, 3 H, OCH_3), 3.94–3.98 (m, 2 H, H-4′, H-5′B), 4.33–4.37 (m, 1 H, H-3′), 6.19 (dd, *J* = 6.6, 4.2 Hz, 1 H, H-1′), 6.37 (d, *J* = 6.6 Hz, 1 H, H-5), 7.02 (d, *J* = 15.9 Hz, 1 H, CH=CH), 7.39 (d, *J* = 15.9 Hz 1 H, CH=CH), 8.53 (d, *J* = 6.6 Hz, 1 H, H-6).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.5, –5.5, –5.0, –4.6, 17.9, 18.3, 25.6 (3 C), 25.9 (3 C), 42.2, 52.1, 61.5, 69.6, 87.4, 87.9, 103.1, 128.3, 140.7, 144.4, 155.2, 166.1, 167.4.

HRMS-ESI (+): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{45}N_2O_6Si_2$: 525.2811; found: 525.2827.

*Using (E)-3-Tributyltinacrylic Acid Methyl Ester (**8**)*: The standard procedure was followed except that 2.5 equiv of (*E*)-3-tributyltinacrylic acid methyl ester (**8**) were used. Arylsulfonate **2** (264 mg, 0.37 mmol), ester **8** (383 mg, 0.1 mmol), CuI (15 mg, 0.08 mmol) and $(Ph_3P)_4Pd$ (42 mg, 0.04 mmol) afforded the product (136 mg, 71%) as a colorless oil. For analytical and spectral data, see above.

1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-4-[2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-6-uridyl]-2-(1*H*)-pyrimidinone (15)

The standard procedure was followed except that only 1 equiv of tin reagent was used and that the reaction time was prolonged to 48 h. Arylsulfonate (**2**; 876 mg, 1.2 mmol), tin reagent **10** (920 mg, 1.2 mmol), CuI (46 mg, 0.2 mmol) and $(Ph_3P)_4Pd$ (140 mg, 0.1 mmol) afforded the product (706 mg, 64%) as a colorless oil; R_f = 0.72 (isohexanes–EtOAc, 1:1).

IR (ATR): 2950, 2930, 2865, 1672, 1518, 1463, 1387, 1364, 1279, 1263, 1091, 1029, 916, 884, 833, 776, 692 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.90 (s, 9 H, *t*-C_4H_9), 0.92 (s, 9 H, *t*-C_4H_9), 0.97–1.38 [m, 28 H, $CH(CH_3)_3$], 2.20–2.26 (m, 1 H, H-2′A_{2Py}) 2.36–2.42 (m, 1 H, H-2′A_{Ur}), 2.63–2.69 (m, 1 H, H-2′B_{2Py}), 2.93–2.99 (m, 1 H, H-2′B_{Ur}), 3.69–3.73 (m, 1 H, H-4′$_{Ur}$), 3.78–3.82 (m, 1 H, H-5′A_{2Py}), 3.93–3.97 (m, 2 H, H-5′$_{Ur}$), 3.98–4.02 (m, 1 H, H-5′B_{2Py}), 4.02–4.05 (m, 1 H, H-4′$_{2Py}$), 4.39–4.44 (m, 1 H, H-3′$_{2Py}$), 4.92–4.98 (m, 1 H, H-3′$_{Ur}$), 5.67 (dd, *J* = 9.0, 3.0 Hz, 1 H, H1′$_{Ur}$), 5.79 (s, 1 H, H-5_{Ur}), 6.18–6.22 (m, 1 H, H-1′$_{2Py}$), 6.54 (d, *J* = 6.9 Hz, 1 H, H-5_{2Py}), 8.15 (s, 1 H, NH), 8.69 (d, *J* = 6.9 Hz, 1 H, H-6_{2Py}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = –5.5 (2 C), –4.9, –4.5, 12.5, 12.6, 13.2, 13.6, 17.0 (2 C), 17.1, 17.3, 17.4 (2 C), 17.5, 17.6, 17.9, 18.3, 25.7 (3 C), 25.9 (3 C), 40.2, 42.4, 61.7, 64.1, 70.0, 73.6, 86.4, 87.4, 88.0, 88.4, 102.7, 104.4, 145.8, 149.1 152.1, 154.1, 161.5, 167.0.

HRMS-ESI (+): *m*/*z* $[M + H]^+$ calcd for $C_{42}H_{77}N_4O_{10}Si_4$: 909.4711; found: 909.4734.

Negishi-Type Cross-Coupling Reactions; General Procedure

$ZnCl_2$ (1 M in THF, 2.2 equiv) was dissolved in THF (0.5 mL per 0.1 mmol arylsulfonate) and the solution was cooled to 0 °C. A lithium or magnesium organometallic compound in THF (2 equiv) was added dropwise and the solution was stirred for 1 h at 0 °C. $(Ph_3P)_4Pd$ (0.1 equiv) and the arylsulfonate (1 equiv in 0.5 mL THF per 0.1 mmol arylsulfonate) were added and the resulting solution was stirred for 18 h at r.t. Aq sat. NH_4Cl (20 mL) and EtOAc (20 mL) were added, the layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by flash chromatography.

1-(2′,3′-*O*-Isopropylidene-5′-*O*-tritylribofuranosyl)-4-phenyl-2-(1*H*)-pyrimidinone (18)

The standard procedure was followed using arylsulfonate **1** (141 mg, 0.18 mmol), phenylmagnesium bromide (1 M in THF, 0.38 mL, 0.38 mmol), $ZnCl_2$ solution (0.4 mL, 0.4 mmol) and $(Ph_3P)_4Pd$ (23 mg, 0.02 mmol) affording the crude product. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 1:3) to give the title compound (77 mg, 74%) as a colorless oil; R_f = 0.71 (isohexanes–EtOAc, 1:3).

IR (Film): 3059, 2986, 2934, 2871, 1674, 1621, 1519, 1494, 1449, 1382, 1374, 1272, 1214, 1158, 1120, 1079, 874, 765, 706, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 [s, 3 H, $C(CH_3)_2$], 1.59 (s, 3 H, $C(CH_3)_2$], 3.46 (dd, *J* = 10.8, *J* = 5.1 Hz, 1 H, H-5′A), 3.52 (dd, *J* = 10.8, 3.0 Hz, 1 H, H-5′B), 4.44–4.50 (m, 1 H, H-4′), 4.83 (dd, *J* = 6.1, 4.0 Hz, 1 H, H-3′), 4.95 (dd, *J* = 6.1, 1.4 Hz, 1 H, H-2′), 6.03–6.06 (m, 1 H, H-1′), 6.45 (d, *J* = 7.1 Hz, 1 H, H-5), 7.19–7.54 (m, 18 H, 3H C_6H_5 + 15 H trityl C_6H_5), 8.00–8.05 (m, 2 H, C_6H_5), 8.16 (d, *J* = 7.1 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 27.2, 63.6, 80.2, 85.8, 87.4 (2 C), 94.2, 100.8, 114.0, 127.3 (3 C), 127.9 (8 C), 128.6 (6 C), 128.7 (2 C), 132.0, 135.8, 143.2 (3 C), 144.0, 155.5, 171.7.

HRMS-FAB (+): *m/z* [M + Na]$^+$ calcd for $C_{37}H_{34}N_2O_5$ + Na: 609.2360; found: 609.2397.

1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-4-phenyl-5-methyl-2-(1*H*)-pyrimidinone (19)

The standard general procedure was followed except that 2.5 mol% of Pd(dppf)Cl_2 was used as catalyst with an extended reaction time of 3 d. Arylsulfonate **8** (649 mg, 0.88 mmol), phenylmagnesium bromide (0.5 M in THF, 3.52 mL, 1.76 mmol), $ZnCl_2$ solution (1 M in THF, 1.94 mL, 1.94 mmol) and Pd(dppf)Cl_2 (18 mg, 0.022 mmol, 0.025 equiv) afforded the crude product. This was purified by flash chromatography (silica gel, isohexanes–EtOAc, 1:3) to give the title compound (316 mg, 68%) as a colorless oil; R_f = 0.67 (isohexanes–EtOAc, 1:1).

IR (ATR): 2953, 2929, 2857, 1659, 1489, 1471, 1462, 1390, 1326, 1252, 1190, 1076, 1029, 1003, 990, 968, 885, 831, 775, 711, 698, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.89 (s, 9 H, *t*-C_4H_9), 0.92 (s, 9 H, *t*-C_4H_9), 2.12 (s, 3 H, 5-CH_3), 2.04–2.16 (m, 1 H, H-2′A), 2.65 (ddd,, *J* = 13.5, 6.2, 3.9 Hz, 1 H, H-2′B), 3.80 (dd, *J* = 11.5, 2.6 Hz, 1 H, H-5′A), 3.95 (dd, *J* = 11.5, 2.6 Hz, 1 H, H-5′B), 4.00–4.05 (m, 1 H, H-4′), 4.43–4.37 (m, 1 H, H-3′), 6.19 (t, 1 H, *J* = 6.3 Hz, H-1′), 7.40–7.46 (m, 3 H, C_6H_5), 7.57–7.61 (m, 2 H, C_6H_5), 8.06 (s, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4 (2 C), –4.9, –4.5, 16.7, 18.0, 18.4, 25.7 (3 C), 25.9 (3 C), 42.6, 62.6, 71.6, 87.3, 88.4, 111.0, 128.1 (2 C), 128.5 (2 C), 129.8, 137.9, 142.0, 155.1, 174.5.

HRMS-ESI (+): *m/z* [M + $HNEt_3$]$^+$ calcd for $C_{34}H_{62}N_3O_4Si_2$: 632.4273; found: 632.4271.

1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-4-methyl-2-(1*H*)-pyrimidinone (20)

The standard procedure was followed except 0.5 mol% of Pd(PPh_3)$_4$ catalyst, double the volume of THF and 4 equiv of MeLi were used. Arylsulfonate **2** (318 mg, 0.44 mmol), MeLi (1.6 M in Et_2O, 4 equiv, 1.1 mL, 1.76 mmol), $ZnCl_2$ solution (1 M in THF, 2.2 equiv, 0.97 mL, 0.97 mmol) and Pd(PPh_3)$_4$ (0.005 equiv, 2.5 mg, 0.002 mmol) afforded the crude product. This was purified by flash chromatography (silica gel, isohexanes–EtOAc, 1:1, later pure EtOAc) to give the title compound (121 mg, 61%) as a slightly yellow oil; R_f = 0.30 (isohexanes–EtOAc, 1:1).

IR (ATR): 2953, 2929, 2856, 1658, 1623, 1523, 1462, 1252, 1110, 1077, 833, 775, 671 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.86 (s, 9 H, *t*-C_4H_9), 0.90 (s, 9 H, *t*-C_4H_9), 2.09–2.17 (m, 1 H, H-2′A), 2.39 (s, 3 H, 4-CH_3), 2.49–2.58 (m, 1 H, H-2′B), 3.77 (dd, *J* = 12.0, 2.4 Hz, 1 H, H-5′A), 3.93–3.97 (m, 2 H, H-4′, H-5′B), 4.32–4.38 (m, 1 H, H-3′), 6.16–6.21 (m, 2 H, H-5, H-1′), 8.31 (d, *J* = 6.6 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –5.6, –5.0, –4.6, 17.8, 18.3, 25.0, 25.6 (3 C), 25.8 (3 C), 42.2, 61.6, 69.7, 86.9, 87.7, 104.2, 142.3, 154.9, 175.8.

HRMS-ESI (+): *m/z* [M + H]$^+$ calcd for $C_{22}H_{43}N_2O_4Si_2$: 455.2756; found: 455.2759.

1-[2′-Deoxy-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)ribofuranosyl]-4-butyl-2-(1*H*)-pyrimidinone (21)

The standard procedure was followed using arylsulfonate **2** (144 mg, 0.2 mmol), *n*-BuLi (1.6 M in hexanes, 0.4 mL, 0.4 mmol), $ZnCl_2$ solution (0.44 mL, 0.44 mmol) and $(Ph_3P)_4Pd$ (23 mg, 0.02 mmol) affording the crude product. The crude product was purified by flash chromatography (silica gel, isohexanes–EtOAc, 2:1, later 1:1) to give the product (48 mg, 48%) as a colorless oil; R_f = 0.66 (isohexanes–EtOAc, 1:1).

IR (ATR): 2954, 2929, 2857, 1660, 1620, 1520, 1462, 1390, 1361, 1276, 1252, 1191, 1110, 1076, 1029, 1006, 965, 883, 833, 776, 671 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.85 (s, 9 H, *t*-C_4H_9), 0.90 (s, 9 H, *t*-C_4H_9), 0.86–0.93 (m, 3 H, CH_2CH_3), 1.29–1.42 (m, 2 H, CH_2CH_3), 1.61–1.73 (m, 2 H, $ArCH_2CH_2$), 2.13 (ddd, *J* = 13.5, 6.6, 4.5 Hz, 1 H, H-2′A), 2.48–2.61 (m, 3 H, $ArCH_2$, H-2′B), 3.75 (dd, *J* = 12.0, 2.7 Hz, 1 H, H-5′A), 3.90–3.97 (m, 2 H, H-4′, H-5′B), 4.31–4.39 (m, 1 H, H-3′), 6.14 (d, *J* = 6.8 Hz, 1 H, H-5), 6.19 (dd, *J* = 6.6, 4.5 Hz, 1 H, H-1′), 8.28 (d, *J* = 6.8 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.0, –4.6, 13.8, 17.9, 18.3, 22.4, 25.6 (3 C), 25.8 (3 C), 30.0, 38.4, 42.2, 61.6, 69.8, 86.9, 87.7, 103.7, 142.1, 155.5, 179.6.

HRMS-ESI (+): *m/z* [M + $HNEt_3$]$^+$ calcd for $C_{31}H_{64}N_3O_4Si_2$: 598.4430; found: 598.4425.

1-(2′-Deoxyribofuranosyl)-4-thienyl-2-(1*H*)-pyrimidinone (22)

Compound **12** (55 mg, 0.1 mmol) was dissolved in EtOAc (2 mL) and treated with HF/pyridine complex (70 μL). The solution was shaken for 14 h at r.t. Methoxytrimethylsilane (200 μL) was added and the solution was shaken for another 2 h at r.t. The solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1) to give the title compound (12 mg, 41%) as a white, amorphous solid; R_f = 0.43 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.03–2.11 (m, 1 H, H-2′A), 2.35 (ddd, *J* = 13.3, 6.2, 4.3 Hz, 1 H, H-2′B), 3.56–3.63 (m, 1 H, H-5′A), 3.67 (ddd, *J* = 12.0, 5.2, 4.0 Hz, 1 H, H-5′B), 3.87–3.91 (m, 1 H, H-4′), 4.21–4.27 (m, 1 H, H-3′), 5.11 (t, *J* = 5.2 Hz, 1 H, 5′-OH), 5.27 (d, *J* = 4.4 Hz, 1 H, 3′-OH), 6.11 (t, *J* = 6.2 Hz, 1 H, H-1′), 7.09 (d, *J* = 7.2 Hz, 1 H, H-5), 7.25 (dd, *J* = 5.0, 3.8 Hz, 1 H, H-$4_{thienyl}$), 7.90 (dd, *J* = 5.0, 1.0 Hz, 1 H, H-$3_{thienyl}$), 7.25 (dd, *J* = 3.8, 1.0Hz, 1 H, H-$5_{thienyl}$), 8.46 (d, *J* = 7.1 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.9, 60.6, 69.5, 86.4, 87.9, 99.5, 128.8, 131.2, 133.3, 141.6, 144.0, 154.2, 164.7.

HRMS-ESI (+): *m/z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_4S$: 295.0747; found: 295.0745.

(*E*)-3-[1-(2′-Deoxyribofuranosyl)-2-(1*H*)-pyrimidinon-4-yl]acrylic Acid *tert*-Butyl Ester (23)

Compound **13** (49 mg, 0.09 mmol) was dissolved in THF (2.5 mL) and MeOH (2.5 mL). NaOMe (10 mg, 1.85 mmol) was added and the solution was stirred for 1 h at r.t. The solution was neutralized with AcOH, the solvent removed under vacuum and the crude product was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1) to give the title compound (11 mg, 38%) as a white, amorphous solid; R_f = 0.46 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (400 MHz, CD_3CN): δ = 1.62 (s, 9 H, *t*-C_4H_9), 2.22–2.31 (m, 1 H, H-2′A), 2.57 (ddd, *J* = 13.6, 6.4, 4.8 Hz, 1 H, H-2′B), 3.30–3.35 (br m, 1 H, 5′-OH), 3.45–3.49 (br m, 1 H, 3′-OH), 3.76–3.83 (m, 1 H, H-5′A), 3.85–3.92 (m, 1 H, H-5′B), 4.05–4.09 (m, 1 H, H-4′), 4.39–4.46 (m, 1 H, H-3′), 6.19 (t, *J* = 6.0 Hz, 1 H, H-1′), 6.72 (d, *J* = 6.8 Hz, 1 H, H-5), 6.92 (d, *J* = 16.0 Hz, 1 H, CH=CH), 7.38 (d, *J* = 16.0 Hz, 1 H, CH=CH), 8.54 (d, *J* = 6.8 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, CD_3CN): δ = 28.1 (3 C), 42.0, 61.9, 70.9, 82.1, 88.6, 88.9, 103.5, 130.9, 141.1, 145.8, 156.0, 165.6, 168.8.

HRMS-ESI (+): *m/z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_6$: 339.1551; found: 339.1542.

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