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Nucleophilic substitution at the anomeric position of 1,2-*O*-isopropylidenefuranose derivatives. A novel stereoselective synthesis of cyclic phosphates analogous to cAMP

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This work is dedicated to the memory of our friend Pilar Peregrina (Pily)

Abstract—1,2-*O*-Isopropylidenefuranose derivatives were treated with various nucleophiles in the presence of either $BF_3{\cdot}OEt_2$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf) leading to substitution products in a regio- and stereoselective manner. In particular, nucleophilic substitution of 1,2-*O*-isopropylidenefuranose derivatives when treated with allyltrimethylsilane was controlled by steric and electronic factors (similar to Woerpel's stereoelectronic model). On the other hand, when 1,2-*O*-isopropylidenefuranose derivatives were treated with trimethylsilane, in the presence of bis-*O*-trimethylsilyl-5-iodouracil or bis-*O*-trimethylsilyl-thymidine, substitution products were generated in high regio- and stereoselectivities via an unusual nucleophilic substitution with opening of the furanose ring. Based on these results, a stereoselective method for the synthesis of neutral cyclic phosphates analogous to cAMP was developed.

Keywords: Nucleosides; Analogous cAMP; Nucleophilic substitution; Oxacarbenium

1. Introduction

Nucleophilic substitution by either carbon or nitrogen nucleophiles at the anomeric position of carbohydrate derivatives is a powerful method for the synthesis of tetrahydrofurans and nucleosides.[1] A number of total synthesis of important naturally occurring compounds have been accomplished by using this reaction.[2] Generally, the nucleophilic substitution occurs via the formation of a five-membered ring oxacarbenium ion followed by the stereocontrolled addition of the respective nucleophile to the cation center. There are two stereochemical models that can explain the origin of this stereoselectivity. The first model as reported by Reissig,[3] is based on the nucleophilic attack on the oxacarbenium ion, which follows (mainly) the Felkin–Anh model.[3a] Although this model has been used to explain several nucleophilic substitution reactions,[4,2d,g] in some cases it fails to explain the nucleophilic substitution at the anomeric center of the carbohydrate acetals.[5] More recently, Woerpel has reported a more elegant stereochemical model.[6] Contrary to Reissig, the Woerpel model is based exclusively on the particular properties of the five-membered ring oxacarbenium ion, while the solvent, counterion effect and nucleophilic properties are ignored.

The Woerpel model proposes that a cyclic five-membered oxacarbenium ion generated from the ionization of an anomeric C–X bond (X = acetate or halogen) of the corresponding furanose derivative, preferentially adopts an envelope conformation, where the $C{=}O^+$ segment resides in the flattened portion. There are two

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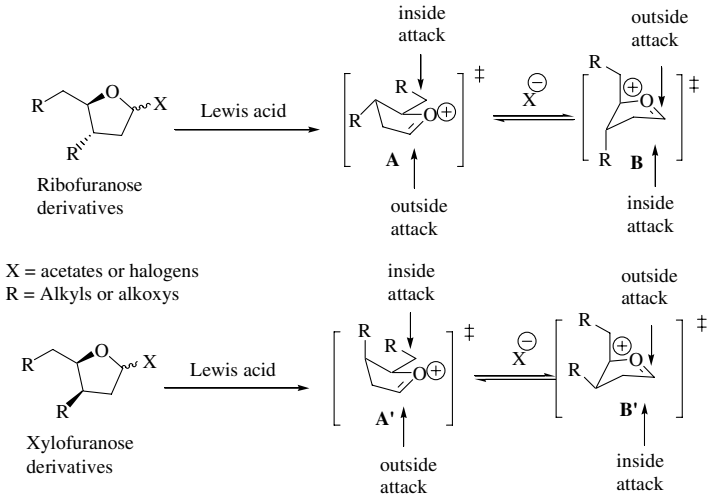


Scheme 1. Woerpel model for the stereocontrolled attack of nucleophiles on cyclic five-membered oxacarbenium ions.

well-defined diastereotopic faces that can be attacked by a suitable nucleophile, termed 'the inside face' or 'the outside face'. Nucleophilic attack on the 'inside face' is the preferred pathway due to less steric congestion, and having the lowest conformational energy of the final product (Scheme 1).

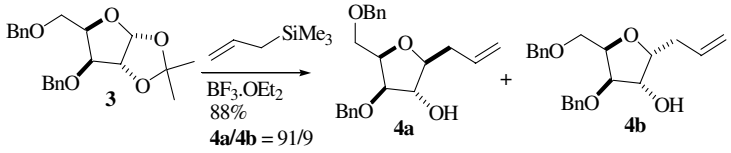
Both conformers **A** and **B** exist in a rapid equilibrium, and the approach of the nucleophile on the inside face of **A** and **B** would result in erosion of the overall stereoselectivity. Interestingly this conformational equilibrium is controlled by the R group at C-3.[7] When the R is an alkyl group, nucleophilic attack occurs preferentially on the inside face of **A**, and when R is an alkoxy group, the nucleophilic approach occurs preferentially on the inside face of **B**.[6,7] It is also important to note that a small preference for the nucleophilic approach on the outside of **A**′ or **B**′ also contributes to the overall stereoselectivity. Consequently, the counterion (X^-) and the solvent exert a minimum effect on the stereochemical outcome.[6] This suggests that the cation center and the counterion are found as free ions, however this is not common in nonpolar solvents, like toluene.[8] Furthermore, there are few reported cases describing the existence of radical cations, as contact ion pairs, in nonpolar media.[8b,c] We present here results related to the nucleophilic substitution of 1,2-*O*-isopropylidenefuranose derivatives, and their application to the synthesis of neutral cyclic phosphates analogous to cAMP.

2. Results and discussion

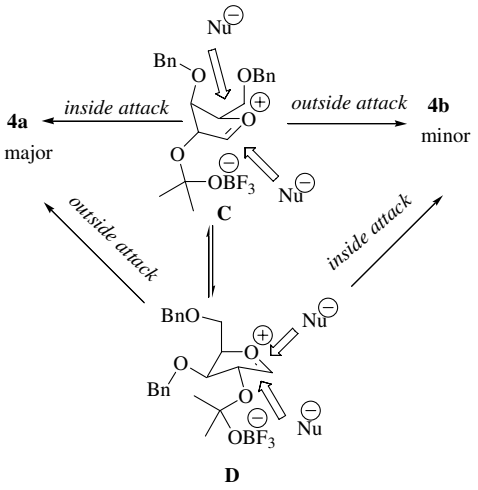
We first tested the nucleophilic substitution reaction of 1,2-*O*-isopropylidenefuranose derivative **3** using allyltrimethylsilane as the nucleophile in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid.[9] Thus, xylofuranose derivative **3** was treated under these conditions yielding a mixture of substitution products **4a** (major) and **4b** (minor) in good yield and stereoselectivity (Scheme 2).

The stereochemical assignment of the major product **4a**, was determined by 2D-NOESY spectroscopic studies, and was shown to be the cis product as predicted by the Woerpel model.[6] The stereoselective formation of major product **4a** is due not only to the stereocontrolled nucleophilic attack of allyltrimethylsilane on the inside face of **C**, but also to the nucleophilic attack on the outside face of **D** (Scheme 3). It seems that the internal counterion X^- in either **C** or **D** did not exert additional influence, either on the stereochemical outcome or reactivity. We postulate that the counterion (2-*O*-isopropyltrifluoroxyborate)[10] does not exert additional influence based on Woerpel's observation under similar conditions but different substrates (yields of 85%, and stereoselectivies of 90:10).[6a]

We then treated cyclic phosphates **5** and **6** with both Et_3SiH and allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid (Scheme 4).[11] We selected these cyclic phosphates containing the 1,2-*O*-isopropyl-



Scheme 2. Stereoselective allylation of 1,2-*O*-isopropylidenefuranose derivatives.

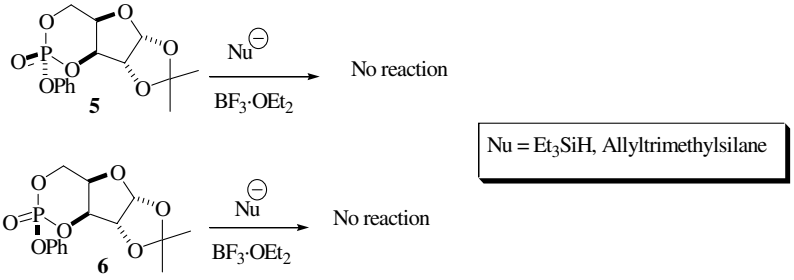


Scheme 3. Nucleophilic substitution model of 1,2-*O*-isopropylidene-furanose derivative **3**.

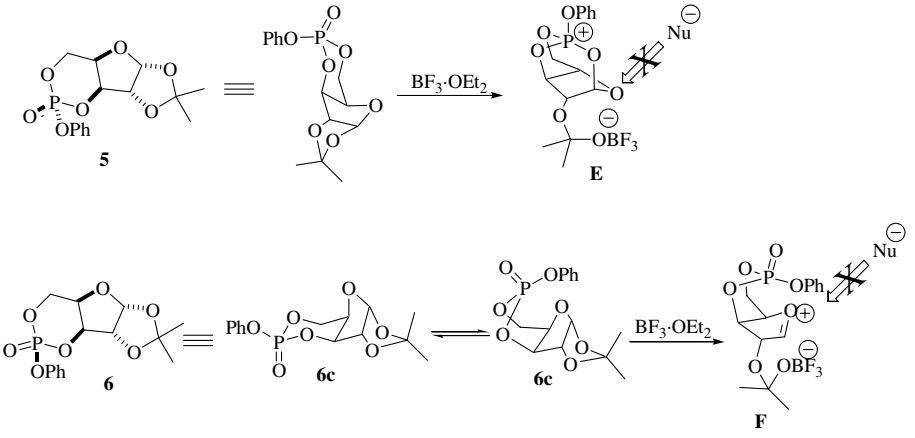
idene group to compare their reactivity toward nucleophiles with compound **3** and others as reported previously.[10,11] This preliminary study would provide valuable information for the design of a novel N-glycosylation reaction.

After many attempts (including longer reaction times, an excess of the nucleophiles, and different temperatures) cyclic phosphates **5** and **6** failed to provide the corresponding substitution products (not shown). In the case of **5**, its lack of reactivity may be attributed to the possible anchimeric assistance by the phosphoryl group toward the cation center of **E** (Robins[11] observed similar anchimeric assistance with 3-*O*-benzoyl group toward a cation center). On the other hand, the lack of reactivity of **6** may be due to the steric hindrance imposed by the phenoxy group on the favorable 'inside face' of the oxacarbenium ion **F**. This steric hindrance is increased by the chair ↔ boat equilibrium (**6c** ↔ **6b**) that which kind of six-membered ring phosphates have been shown to exist in about equimolar amount in solution and in solid state (Scheme 5).[12,13]

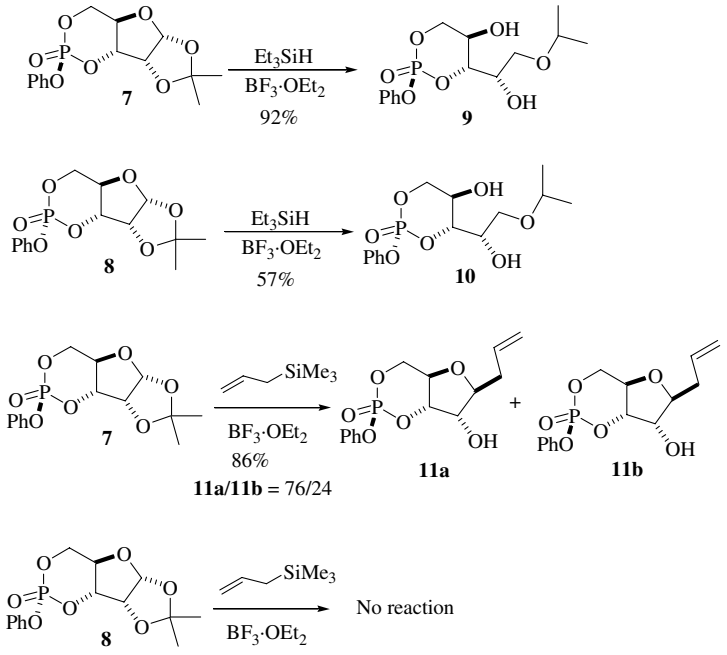
Therefore, if cyclic phosphates **5** and **6** did not react because of the reasons mentioned above, then cyclic phosphates **7** and **8** (where neither the anchimeric assistance nor the steric hindrance are present) should readily undergo nucleophilic attack (mainly on the inside face of the corresponding five-membered ring oxacarbenium ion). To test this possibility, cyclic phosphates **7** and **8** were prepared by standard methods,[14] and treated with Et_3SiH or allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$. For the reaction of **7** and **8** with Et_3SiH/$BF_3{\cdot}OEt_2$, an unusual furanose-ring opening occurred in good and moderate yields, respectively (compounds **9** and **10**). On the other hand, when **7** and **8** were allowed to react with allyltrimethylsilane/$BF_3{\cdot}OEt_2$,



Scheme 4. Nucleophilic substitution of cyclic phosphates.



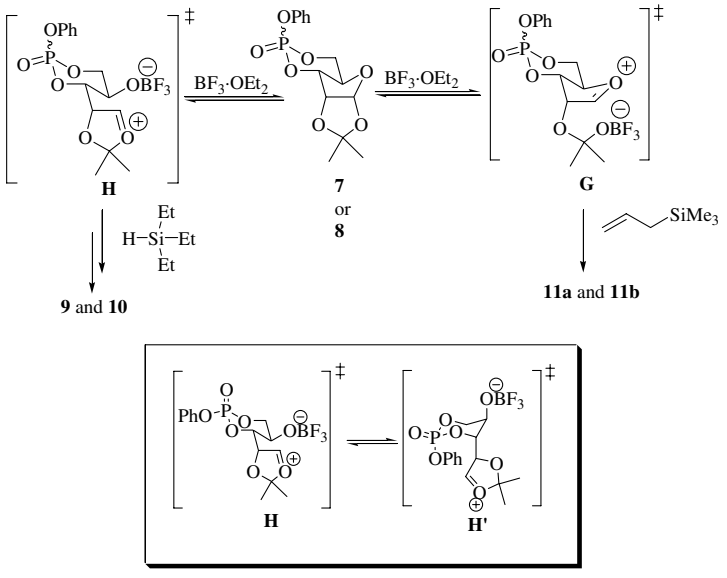
Scheme 5. Cyclic phosphates **5** and **6**, and their corresponding oxacarbenium ions **E** and **F**.



Scheme 6. Nucleophilic substitution at anomeric positions of **7** and **8**.

only **7** reacted to give **11a** and **11b** with moderate stereoselectivity (**11a** and **11b**: 76/24, respectively, see Scheme 6). This moderate stereoselectivity is very similar to that observed by Woerpel in different six–five bicyclic acetates.[6b] Based on these observations, the existence of an additional oxacarbenium ion **H** is evident (Scheme 7).[15]

This unusual bond ionization in **H** may be promoted by the energetically-favorable release of steric strain from the trans-fused bicyclic system (e.g., Gerlt found by thermochemical experiments that cAMP is 8 kcal/mol more exothermic than its acyclic analogue, and 5 kcal/mol of the 8 kcal/mol can be explained by geometric strain resulting from the trans-fusion).[16] Therefore, the difference in reactivity between **7** and **8** toward nucleophilic attack may depend not only on the intrinsic properties of the oxacarbenium ions **G** or **H**, but also on the steric properties of the nucleophiles. In this sense, it is important to note that Et_3SiH is sterically more demanding than allyltrimethylsilane, although steric and stereoelectronic factors certainly contribute to explain the difference in reactivity of cyclic



Scheme 7. Possible oxacarbenium ions generated from **7** or **8**.

phosphates **7** and **8**. Additionally, it is also important to note that **7** is considerably more stable than **8** due to the axial orientation of the phenoxy group.[12,13,17] Further work is required to confirm these assumptions. This interesting problem will be addressed in due course. Hence, the difference in reactivity between **7** and **8** may also be attributed to a very significant difference in the conformational stability of **H**. In the case of **8**, its respective oxacarbenium ion **H** is destabilized by the spontaneous interconversion to **H′** (the phenoxy group tends to reach the axial position due to the anomeric effect,[12,13,17] Scheme 7). It is important to note that to obtain **9** and **10** from **H** (or may be from **H′**), a second regioselective bond ionization followed by another hydride addition is necessary. A similar regioselective ring-opening of a terminal 1,2-*O*-isopropylidene group by a silane reagent to give 1,3-diols instead of 1,4-diols (not shown) has been recently reported by our group.[18]

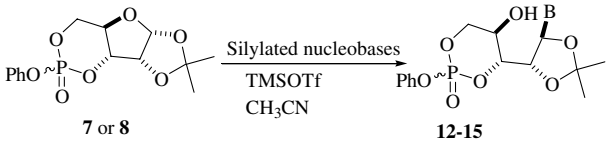
We next turned our attention to the glycosylation reaction of the cyclic phosphates with nucleobases to obtain neutral cyclic phosphates (analogues of cAMP or cGMP). To this end, cyclic phosphates **5**–**8** were allowed to react with bis-*O*-trimethylsilyl-5-iodouracil or bis-*O*-trimethylsilyl-thymidine using TMSOTf as a Lewis acid catalyst.[19] Again, **5** and **6** were recovered quantitatively, and **7** and **8** afforded neutral cyclic nucleotides with the opening at the furanose ring and the retention of the 1,2-*O*-isopropylidene group **12**–**15** (Table 1).

As shown in Table 1, exposure of phosphates **7** and **8** to the respective silylated nucleobases in the presence of TMSOTf resulted in an efficient and highly stereoselective glycosylation reaction (entries 1–3). In contrast, a dramatic decrease in yield as well as in stereoselectivity was observed for **8** with thymine (entry 4). In this case, ^{1}H NMR spectroscopy revealed the formation of a complex reaction mixture whereby one nucleoside predominated to the extent of approximately 45% as judged from the intensity of the anomeric hydrogen signals. Isolation of this product in good yield from the complex mixture reaction was not initially possible due to the apparent instability of the product. However, repeated chromatography on silica gel enabled isolation of the major product in very small amount for characterization (in the ^{1}H spectrum, the anomeric hydrogen appears at δ 6.29 ppm ($^{3}J_{H-H} = 5.4$ Hz), two singlets at δ 1.55 and 1.49 ppm are attributed to the methyl of the 1,2-*O*-isopropylidene group, and in the ^{31}P spectrum a singlet at δ −12.1 ppm is observed).

The stereochemistry of the new stereogenic center formed in **12**–**15** was determined by detailed 2D NOESY experiments, which showed a correlation between H-1′ and H-2′, each with one of the two isopropylidene methyl groups, respectively. Additionally, the methyl group that interacts with H-2′ shows a correlation with H-6 of the base. Apparently this base glycosylation reaction followed the same route as the nucleophilic attack of the Et_3SiH on oxacarbenium ion **H**. This is in agreement with the suggestion that steric factors favor the opening of the furanose ring. Thus, based on the stereochemistry of the nucleotides **12**–**15**, this novel highly stereoselective base-coupling reaction can be rationalized in terms of a stereocontrolled nucleophilic addition of silylated bases on the more favorable face of the oxacarbenium ion **I** (Scheme 8).

This novel highly stereoselective base-coupling reaction, which occurs with the opening of the furanose ring and retention of the 1,2-*O*-isopropylidene group (which might be considered as a furanose mimic) represents a very convenient way to synthesize novel cyclic phosphate analogues of cAMP or cGMP. To the best of our knowledge, this is the first reported occurrence of a 1,2-*O*-isopropylidene group that has been used in a stereoselective nucleobase glycosylation reaction.

Table 1. Stereoselective coupling reaction with silylated nucleobases[a,b]



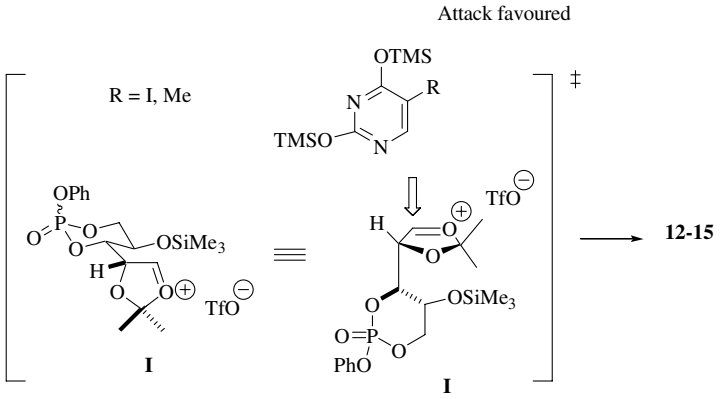
7 or **8** **12-15**

Entry	Phosphate	Base	Nucleotide (yield, %)
1	**7**	5-Iodouracil	**12** (88)
2	**7**	Thymine	**13** (85)
3	**8**	5-Iodouracil	**14** (87)
4	**8**	Thymine	**15** (45)[c]

[a] Only one diastereoisomer was observed by ^{1}H NMR and ^{31}P NMR spectroscopy.
[b] Yield of products after flash chromatography.
[c] Yield determined by NMR.

3. Conclusions

It was demonstrated herein that nucleophilic substitution at the anomeric position of 1,2-*O*-isopropylidene-furanose derivatives occurs with high regioselectivity and stereoselectivity. The product formed depends on the nature of the nucleophile and the conformational restrictions of the five-membered ring oxacarbenium ion. In addition to being of mechanistic interest, the development of this novel stereoselective *N*-glycosylation reaction offers a new access to novel cyclic phosphate analogues of cAMP and other important nucleotides (e.g., prodrugs). In this regard, novel nucleotides with biological activity are currently being synthesized in our laboratory by applying the methodology described herein. Although the experimental results indicate a similar behavior to that reported by others, a number of interesting questions related to the



Scheme 8. Stereoselective base-addition to oxacarbenium ion **I**.

mechanism of nulceophilic substitution reactions of the cyclic phosphates remain unsolved, and further studies on this matter are still needed.

4. Experimental

4.1. General methods

Reagents were obtained from commercial sources and used without purification. Solvents of technical grade were used and freshly distilled prior to use. NMR studies were carried out on 400 and 300 MHz spectrometers; tetramethylsilane was used as the reference for the ^{1}H and ^{13}C NMR spectra and chemical shifts are stated in parts per million. COSY, HSQC, and NOESY experiments were carried out to assign fully the ^{1}H and ^{13}C NMR. High resolution mass spectra were obtained by fast atom bombardment ionization.

4.2. Phosphorylation reactions

To a solution of 1,2-*O*-isopropylidene-ribofuranose (0.37 g, 1.96 mmol) and Et_3N (0.81 mL, 4.9 mmol) was added dropwise phenyldichlorophosphate (0.36 mL, 2.35 mmol) dissolved in 20 mL CH_2Cl_2 at 0 °C. The reaction mixture was allowed to react for 4 h before it was poured into water (50 mL). The aqueous layer was then extracted three times with CH_2Cl_2 (50 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (230–400 mesh) with ether–EtOAc (v/v = 2/1).

4.2.1. (R_P)-1,2-*O*-Isopropylidene-3,5-*O*-phenoxyphosphoryl-α-D-ribofuranose (7).[14] White powder (51%); decomposition temp = 172 °C; $[\alpha]_D$ +50 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.67 (s, 3H), 4.25 (m, 1H), 4.35 (m, 2H), 4.64 (ddd, 1H, $J = 22.8$, 10.2, 4.5 Hz), 4.76 (t, 1H, $J = 3.6$ Hz), 5.88 (d, 1H, $J = 3.3$ Hz), 7.18–7.39 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.1, 68.3 ($J_{CP} = 5.7$ Hz), 70.0 ($J_{CP} = 9.2$ Hz), 76.0 ($J_{CP} = 8.0$ Hz), 80.1 ($J_{CP} = 5.7$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.8 ppm.

4.2.2. (S_P)-1,2-*O*-Isopropylidene-3,5-*O*-phenoxyphosphoryl-α-D-ribofuranose (8). Syrup (41%); $[\alpha]_D$ −8.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.56 (s, 3H), 4.27–4.43 (m, 3H), 4.63 (m, 1H), 4.77 (t, 1H, $J = 3.3$ Hz), 5.90 (d, 1H, $J = 3.3$ Hz), 7.18–7.38 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.1, 68.0 ($J_{CP} = 7.95$ Hz), 69.8 ($J_{CP} = 7.95$ Hz), 76.1 ($J_{CP} = 6.8$ Hz), 79.1 ($J_{CP} = 4.6$ Hz), 106.0, 114.6, 120.3, 125.7, 129.8; ^{31}P NMR (121 MHz, $CDCl_3$): δ −9.7 ppm; FAB-HRMS *m*/*z* Calcd for $C_{14}H_{17}O_7P$ $[M+H]^+$: 329.07196. Found: 329.07198.

4.3. General procedure for the deprotection/reduction reaction of 1,2-*O*-isopropylidene xylo- and ribofuranose derivatives

A solution of 1,2-*O*-isopropylidene xylo- and ribofuranose derivatives (2.0 mmol) in 50 mL of dry CH_2Cl_2 at 0 °C was treated with Et_3SiH (12.0 mmol) and $BF_3{\cdot}OEt_2$ (12.0 mmol) before it was warmed to room temperature, and stirred for 2 h. The reaction mixture was treated with a satd aq $NaHCO_3$ (50 mL), the aq phase was extracted three times with CH_2Cl_2, dried with $MgSO_4$ and the residue purified by column chromatography on silica gel (neutral pH) with ether–EtOAc (v/v = 3/1).

For the six-membered ring phosphates **8** and **9**, the neutralization was carried out using a dilute aq $NaHCO_3$ at 0 °C; otherwise, a messy reaction occurred.

4.3.1. (R_P,4*S*,5*R*,1′*S*)-4-(1-Hydroxy-2-isopropoxy-ethyl)-5-hydroxy-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (9). Syrup (92%); $[\alpha]_D$ −17.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 3H, $J = 6.0$ Hz), 1.17 (d, 3H, $J = 6.4$ Hz), 3.57–3.65 (m, 3H), 4.01 (dt, 1H, $J = 6.4$, 3.5 Hz), 4.23 (m, 2H), 4.31 (m, 1H), 4.45 (m,

1H), 7.18–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 22.0, 64.6 ($J_{CP} = 6.1$ Hz), 66.6, 70.2 ($J_{CP} = 7.6$ Hz), 72.8, 73.0 ($J_{CP} = 10.6$), 80.5 ($J_{CP} = 7.6$ Hz), 119.3, 119.2 ($J_{CP} = 6.1$ Hz), 125.2, 129.8; ^{31}P NMR (121 MHz, $CDCl_3$): δ −12.0 ppm; MS (EI-mode) *m/z* 332, (M^+ 26%); FAB-HRMS *m/z* Calcd for $C_{14}H_{21}O_7P$ $[M+H]^+$: 333.1103. Found: 333.1101.

4.3.2. (S_P,4*S*,5*R*,1′*S*)-4-(1-Hydroxy-2-isopropoxy-ethyl)-5-hydroxy-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (10). Syrup (57%); $[\alpha]_D$ −29.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, 3H, $J = 6.0$ Hz), 1.18 (s, 3H, $J = 6.0$ Hz), 2.91 (br, 1H), 3.56 (dd, 1H, $J = 9.9$, 4.2 Hz), 3.64 (m, 2H), 3.99 (m, 1H), 4.24 (m, 1H), 4.33–4.57 (m, 3H), 7.16–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.1, 64.7 ($J_{CP} = 6.8$ Hz), 67.4, 70.5 ($J_{CP} = 5.7$ Hz), 71.4 ($J_{CP} = 5.7$ Hz), 73.0, 83.2 ($J_{CP} = 5.7$ Hz), 120.0, 125.7, 130.1; ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.3 ppm; MS (EI-mode) *m/z* 332 (M^+ 15%); HRMS (FAB-mode) *m/z* Calcd for $C_{14}H_{21}O_7P$ $[M+H]^+$: 333.1103. Found: 333.1109.

4.4. General procedure for the allylation reaction of 1,2-*O*-isopropylidene xylo- and ribofuranose derivatives

A solution of 1,2-*O*-isopropylidene xylo- and ribofuranose derivatives (2.0 mmol) in 50 mL of dry CH_2Cl_2 at 0 °C was treated with allyltrimethylsilane (3.0 mmol) and $BF_3{\cdot}OEt_2$ (3.0 mmol) (for the six-membered ring phosphates, 10.0 mmol of allyltrimethylsilane and $BF_3{\cdot}OEt_2$ were used). The reaction mixture was warmed to room temperature over 4 h. The reaction mixture was treated with satd aq $NaHCO_3$ (50 mL). The aq layer was extracted three times with CH_2Cl_2 (50 mL). The organic phase was dried with $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography on silica gel (230–400 mesh).

4.4.1. (2*S*,3*R*,4*R*,5*R*)-2-Allyl-4-(benzyloxy)-5-((benzyloxy)methyl)-tetrahydrofuran-3-ol (4a, major stereoisomer). Syrup (80%); $[\alpha]_D$ −20.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (m, 1H), 2.48 (m, 1H), 3.70 (m, 3H), 3.87 (dd, 1H, $J = 5.2$, 2.4 Hz), 3.99 (dd, 1H, $J = 4.4$, 2.2 Hz), 4.23 (m, 1H), 4.49–4.62 (m, 4H), 5.08 (2H, m), 5.84 (1H, m), 7.18–7.41 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.0, 68.7, 71.7, 73.3, 79.0, 79.1, 83.8, 85.2, 117.3, 127.3, 127.4, 127.5, 127.6, 128.1, 128.2, 134.1, 137.7. Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.51; H, 7.38.

4.4.2. (R_P)-1-Allyl-1-desoxy-2-*O*-isopropoxy-3,5-*O*-phenoxyphosphoryl-α-D-ribofuranose (11a and 11b 76/24, respectively). Data reported as a mixture of stereoisomers: Syrup (86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29–2.46 (m, 4H), 3.84 (m, 2H), 3.95 (m, 2H), 4.19–4.49 (m, 8H), 5.01 (d, 2H, $J = 17.6$ Hz), 5.15 (dd, 2H, $J = 17.6$, 2.8 Hz), 5.78 (m, 2H), 7.18–7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.4, 38.6, 61.6, 62.9 ($J_{CP} = 6.1$ Hz), 68.8, 70.3 ($J_{CP} = 10.6$ Hz), 70.5 ($J_{CP} = 9.1$ Hz), 70.9, 74.2 ($J_{CP} = 11.7$ Hz), 82.3 ($J_{CP} = 10.7$ Hz), 82.7 (10.7 Hz); 115.3, 118.4, 118.8, 119.5, 125.5, 130.0, 133.6; ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.6, −11.3; MS *m/z* 313, (M+H, 4%); FAB-HRMS *m/z* Calcd for $C_{14}H_{17}O_6P$ $[M+H]^+$: 313.0841. Found: 313.0851.

4.5. General procedure for the nucleobase-coupling reaction

The nucleobase (0.72 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (2 mL) were stirred at 100 °C for 8 h. The reaction mixture was cooled to room temperature and cyclic phosphate (0.6 mmol) and TMSOTf (0.92 mmol) in freshly distilled acetonitrile were added. The reaction mixture was then stirred until the disappearance of the respective starting material. The reaction mixture was treated with a diluted aq soln $NaHCO_3$ (30 mL). The aq layer was extracted three times with CH_2Cl_2 (50mL), the organic phase was dried with $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography on silica gel (230–400 mesh).

4.5.1. (R_P,4*R*,5*R*,1′*S*,2*R*)-4[1-(5-Iodouracil)-1,2-*O*-isopropylidene-ethyl]-5-hydroxy-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (12). Syrup (88%); $[\alpha]_D$ +10.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 1.51 (s, 3H), 1.58 (s, 3H), 4.17 (td, 1H, $J = 10.4$, 4.4 Hz), 4.22 (td, 1H, $J = 10.0$, 2.8 Hz), 4.37 (ddd, 1H, $J = 24.0$, 10.0, 4.4 Hz), 4.57 (ddd, 1H, $J = 5.6$, 3.2, 2.0 Hz), 4.78 (dt, 1H, $J = 9.6$, 2.0 Hz), 6.33 (d, 1H, $J = 5.6$ Hz), 7.24–37 (m, 5H), 7.50 (s, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$): δ 27.8, 27.1, 61.6 ($J_{CP} = 4.6$ Hz), 69.0, 70.6 ($J_{CP} = 6.8$ Hz), 80.9 ($J_{CP} = 7.9$ Hz), 81.2 ($J_{CP} = 6.8$ Hz), 83.4, 131.1, 119.5 ($J_{CP} = 4.5$ Hz), 125.4, 129.7, 143.8, 149.8, 150.4, 160.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ −11.7 ppm; FAB-HRMS *m/z* Calcd for $C_{18}H_{21}IN_2O_9P$ $[M+H]^+$: 567.0029. Found: 567.0027.

4.5.2. (R_P,4*R*,5*R*,1′*S*,2*R*)-4[1-(Thymidine)-1,2-*O*-isopropylidene-ethyl]-5-hydroxy-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (13). Syrup (85%); $[\alpha]_D$ +19.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 3H), 1.52 (s, 3H), 1.91 (s, 3H), 4.21 (td, 1H, $J = 13.0$, 1.2 Hz), 4.41 (ddd, 1H, $J = 24.2$, 10.4, 4.8 Hz), 4.49 (m, 1H), 4.59 (dt, 1H, $J = 10.4$, 1.2 Hz), 4.91 (m, 1H), 4.96 (d, 1H, $J = 4.0$ Hz), 6.13 (d, 1H, $J = 3.2$ Hz), 7.16–7.35 (m, 2H), 7.42 (d, 1H, $J = 1.2$ Hz), 10.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 27.3, 28.0, 62.1 ($J_{CP} = 4.6$ Hz), 70.9 ($J_{CP} = 6.9$ Hz), 81.8 ($J_{CP} = 9.0$ Hz), 83.3 ($J_{CP} = 7.9$ Hz), 85.2, 111.3, 114.6, 119.7, 125.4, 129.9, 135.3, 151.7, 164.3; ^{31}P NMR

(121 MHz, $CDCl_3$): δ −11.8 ppm; FAB-HRMS *m/z* Calcd for $C_{19}H_{24}N_2O_9P$ $[M+H]^+$: 455.1219. Found: 455.1211.

4.5.3. (S_P,4*R*,5*R*,1′*S*,2*R*)-4[1-(5-Iodouracil)-1,2-*O*-isopropylidene-ethyl]-5-hydroxy-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (14). Syrup (87%); $[\alpha]_D$ +11.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6): δ 1.43 (s, 3H), 1.50 (s, 3H), 3.90 (br s, 1H), 4.11 (m, 1H), 4.27 (dd, 1H, $J = 21.6$, 12.6 Hz), 4.68 (dd, 1H, $J = 17.2$, 5.2 Hz), 5.91 (d, 1H, $J = 4.4$ Hz), 6.27 (d, 1H, $J = 5.2$ Hz), 7.08–7.29 (m, 5H), 7.97 (s, 1H); ^1H NMR (100 MHz, DMSO-d_6): δ 27.9, 63.1, 68.1, 70.5, 71.9, 76.2, 85.1, 86.0, 111.9, 120.3, 125.6, 130.2, 145.4, 147.4, 150.2; ^{31}P NMR (121 MHz, $CDCl_3$): δ −13.3 ppm; FAB-HRMS *m/z* Calcd for $C_{18}H_{21}IN_2O_9P$ $[M+H]^+$: 567.0029. Found: 567.0025.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.10.015.

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