New Chiral Nitrones in the Synthesis of Modified Nucleosides

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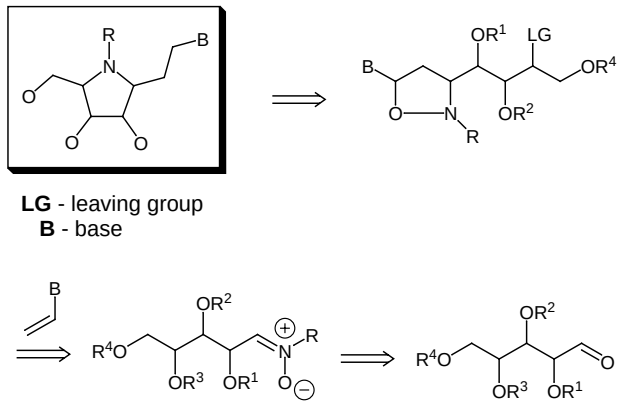
Abstract: New chiral nitrones **7** and **12,** easily prepared from D-xylose by multistep synthetic routes, undergo regioselective 1,3-dipolar cycloadditions with *N*-vinylated bases (uracil, adenine) giving isoxazolidinyl nucleosides in good yields. Attack of the dipolarophile on the *Z*-configuration of the nitrone through *exo* and *endo* transition states from the *si* face of nitrone (C-1′/C-3 *erythro*) affords C-3/C-5 *cis* (*exo*) and C-3/C-5 *trans* (*endo*) isoxazolidines as two major isomers.

Key words: chiral, dipolar cycloadditions, nitrones, isoxazolidines, modified nucleosides

The discovery of AZT (azidothymidine) promoted rapid and productive investigations in the field of modified nucleosides.[1] The potential activity of a variety of the structures against viral infections or tumor diseases stimulated great interest for the preparation of different types of modifications of glycone and aglycone moieties.[2] In this context, exciting biological results have been achieved from the generation of nucleoside analogues in which a second heteroatom has been inserted into the furanosyl ring.[3] Uracil, thymine, cytosine and adenine nucleosides possessing an isoxazolidinyl moiety **1**[4,5] as well as azanucleosides and their homoanalogues **2** are very valuable for their biological activity against HIV, HBV and HSV infections and also in anticancer therapy.[4c,6]

The first example of an isoxazolidinyl nucleoside was synthesized in 1992 by Tronchet.[7] Since this time many modified nucleosides possessing an isoxazolidinyl moiety have been created by a wide range of synthetic pathways, including Michael additions of hydroxylamines to α,β-unsaturated esters,[5,8] additions of ketene acetals to nitrones,[5,9] and 1,3-dipolar cycloadditions of nitrones to vinyl acetate[5,7,10] with the subsequent transformation of the isoxazolidines thus formed. On the other hand, 1,3-dipolar cycloaddition reactions of nitrones with *N*-vinylated bases afford modified isoxazolidinyl nucleosides directly.[4,10b,11]

With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions[12] and the goal of developing a simple route to the synthesis of isoxazolidinyl nucleosides with the possibility of subsequent transformation toward novel azanucleosides possessing an ethylene bridge between the anomeric carbon and nitrogen (Scheme 1), we focused our attention on the preparation of new sugar-derived nitrones possessing structures suitable for building pyrrolidine rings and their 1,3-dipolar cycloadditions with *N*-vinylated bases **3**, **4a** and **4b** (Figure).



Scheme 1

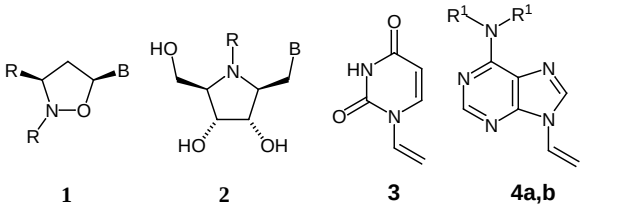


Figure **4a**) R^1 = H, **4b**) R^1 = Ms

The chiral nitrone **7** was prepared from D-xylose in four steps (Scheme 2).[13] Thus, D-xylose was converted into D-xylose diisopropyldithioacetal by treatment with 2-mercaptopropane in 92% yield. Reaction of the corresponding dithioacetal with acetone in the presence of a catalytic quantity of sulfuric acid gave protected dithioacetal **5** in 52% yield. Deprotection of the thiol group with $HgCl_2$/HgO afforded aldehyde **6**,[14] which in turn reacted with *N*-benzylhydroxylamine according to the method of Dondoni[15] to give nitrone **7** in 42% yield over two steps.

Chiral nitrone **12** (Scheme 1), an alternative suitable for building the pyrrolidine moiety in azanucleosides, was

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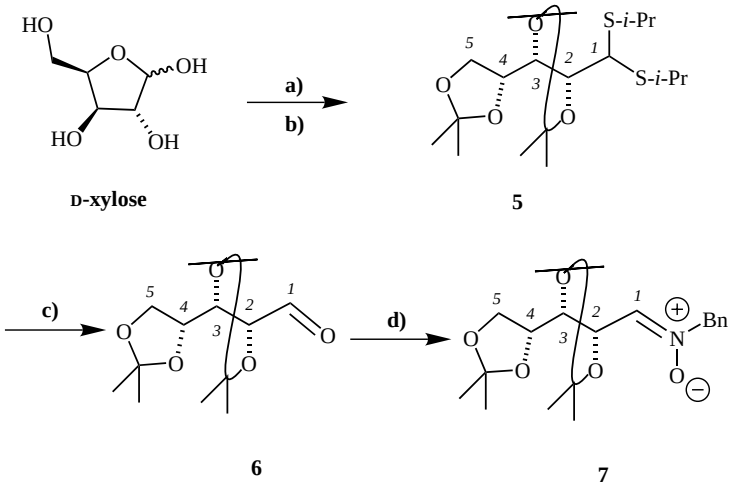
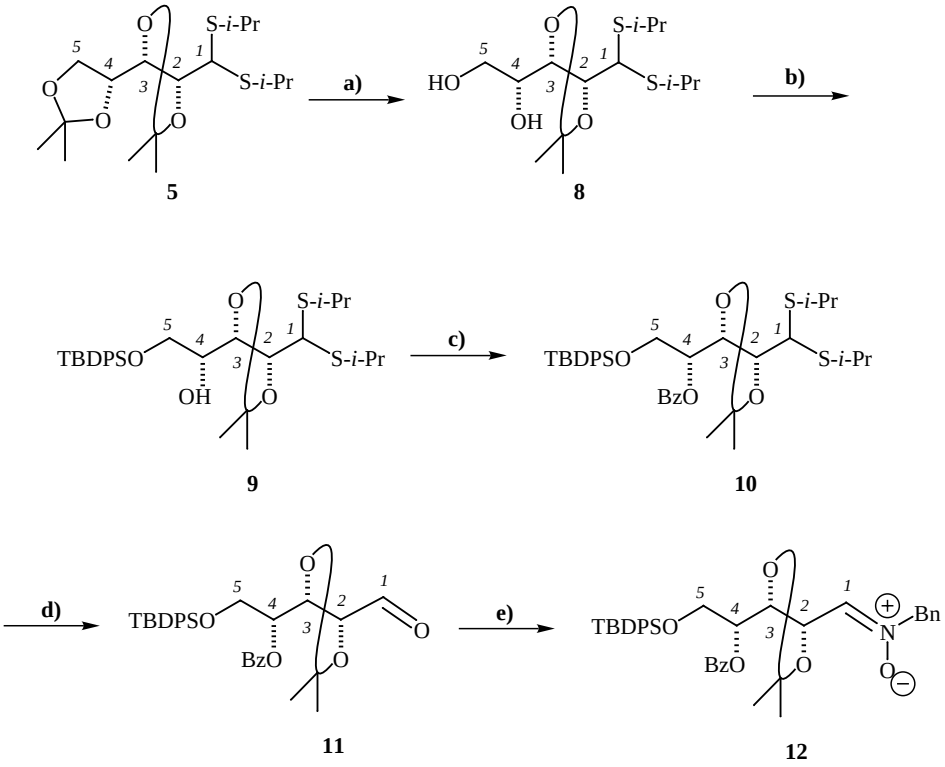


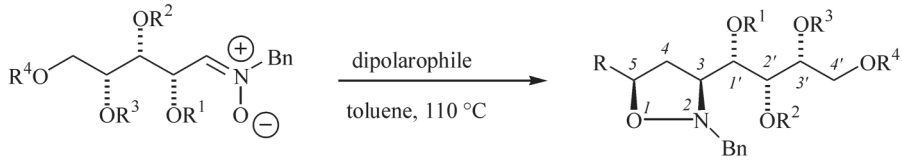
Scheme 2 (a) *i*-PrSH, HCl, r.t., 2 h, 92%; (b) acetone, H_2SO_4, r.t., 8 h, 52%; (c) acetone, H_2O, $HgCl_2$/HgO, 56 °C, 2 h; (d) BnNHOH, CH_2Cl_2, $MgSO_4$, r.t., 4 h, 42% in two steps.

prepared in five steps (Scheme 3).[13] Selective removal of the primary acetonide of **5** with ethanol/water/HCl gave diol **8** in 62% yield. Silylation of the primary alcohol group with TBDPSCl/imidazole in CH_2Cl_2 (92%) followed by benzoylation with benzoyl chloride/pyridine in CH_2Cl_2 afforded the protected dithioacetal **10** in 90% yield. Subsequent deprotection of the thiol group ($HgCl_2$/HgO) and condensation of aldehyde **11** with *N*-benzylhydroxylamine gave chiral nitrone **12** in 63% yield over two steps.[13]

Cycloadditions of nitrones **7** and **12** to *N*-vinylated bases **3**, **4a** and **4b**[16] proceeded regioselectively and led to the isoxazolidines as a mixture of four diastereoisomers in all cases (Table).[17,18] Purification by flash chromatography allowed the isolation of pure *exo*-adducts **13a**, **14a**, **15a** and *endo*-adduct **15b**,[19] identified by spectroscopic analysis, particularly NOE difference experiments, and subsequently confirmed by X-ray-crystallographic analysis in the case of **13a** (Scheme 4).[20]

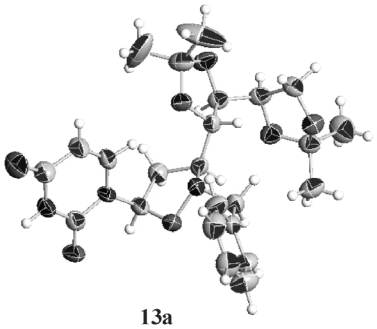


Scheme 3 (a) EtOH/H_2O (80%), HCl, 40 °C, 4 h, 62%; (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 30 min, 92%; (c) BzCl, pyridine, CH_2Cl_2, reflux, 24 h, 90%; (d) $HgCl_2$/HgO, acetone, H_2O, 56 °C, 2 h; (e) BnNHOH, CH_2Cl_2, $MgSO_4$, r.t., 4 h, 63% in two steps.



7, 12 **13a, 14a, 15a**

13b, 14b, 15b



13a

13c, 14c, 15c **13d, 14d, 15d**

13 R=uracil-1-yl, R^1, R^2=R^3, R^4=CMe_2
14 R=uracil-1-yl, R^1, R^2=CMe_2, R^3=Bz, R^4=TBDPS
15 R= *N*,*N*-dimesyladenin-9-yl, R^1, R^2=R^3, R^4=CMe_2

Scheme 4

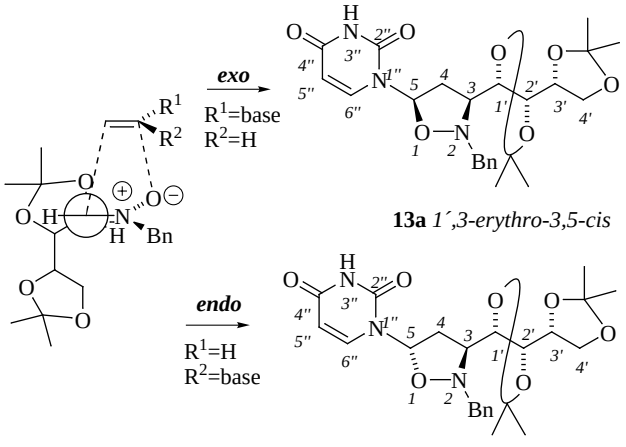
Table 1,3-Dipolar Cycloadditions of Nitrones **7** and **12** to *N*-Vinylated Bases

Entry	Nitrone	Dipolarophile	Total yield (%)	Adduct	**a**:**b**:**c**:**d**[a]
1	**7**	**3**	75	**13**	63:17:15:5
2	**7**	**4a**	86		39:34:20:7
3	**7**	**4b**	83	**15**	73:13:9:5
4	**12**	**3**	77	**14**	59:24:11:6
5	**12**	**4a**	95		45:30:19:6

[a] Ratios were determined by ^{1}H NMR and ^{13}C NMR (400 MHz) from crude reaction mixture.

In the case of cycloadditions of nitrones **7** and **12** with 9-vinyladenine (**4a**, Table, entry 2 and 5) we were not able to obtain the adenosine diastereoisomers in the pure form. To improve separation we decided to protect the free amino group of the adenine moiety. Cycloaddition of nitrone **7** with *N*,*N*-dimesylated 9-vinyladenine (**4b**, Table, entry 3) afforded a mixture of four diastereoisomers and proceeded with better selectivity in favour of major isomer **15a**. Fortunately, in this case we obtained two adenosines **15a** and **15b** in pure form.[19]

X-ray analysis of **13a** reveals a C-1′/C-3 *erythro* and C-3/C-5 *cis* stereochemistry and therefore indicates that cycloaddition arises from the more sterically accessible *si* face of the *Z*-nitrone **7**, via an *exo*-transition state for **13a** and via an *endo* transition state for **13b** (Scheme 5).



13a *1′,3-erythro-3,5-cis*

13b *1′,3-erythro-3,5-trans*

Scheme 5

Acknowledgement

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(13) **Selected Data: (*Z*)-*N*-(1-Deoxy-2,3:4,5-di-*O*-*iso*propylidene-D-*xylo*-1-ylidene)-benzylamine-*N*-oxide(7)**: Colorless solid, mp 95–97 °C (crystalized from hexanes); total yield 20%; $[\alpha]_D$ = +41.3 ($CHCl_3$, *c* 0.22); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.38, 1.43, 1.48 [4 × s, 4 × 3 H, $C(CH_3)_2$], 3.73 (dd, 1 H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 8.6 Hz, H-5a), 3.95 (dd, 1 H, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 6.7 Hz, H-3), 4.09 (dd, 1 H, $J_{4,5b}$ = 6.7 Hz, $J_{5a,5b}$ = 8.8 Hz, H-5b), 4.40 (q, 1 H, $J_{3,4}$ = 6.7 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.7 Hz, H-4), 4.89 (s, 2 H, NCH_2Ph), 5.07 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ = 6.2 Hz, H-2), 6.81 (d, 1 H, $J_{1,2}$ = 6.0 Hz, H-1), 7.41–4.42 (br s, 5 H, NCH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.8, 26.8, 27.0, 27.4 [$C(CH_3)_2$], 66.1 (C-5), 70.1 (NCH_2Ph), 73.6 (C-2), 76.8 (C-4), 81.1 (C-3), 110.1, 111.3 [$C(CH_3)_2$], 129.4, 129.5, 129.7, 129.8, 130.0, 132.5 (NCH_2Ph), 137.4 (C-1). **(*Z*)-*N*-(1-Deoxy-2,3-*O*-*iso*propylidene-4-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-D-*xylo*-1-ylidene)-benzylamine-*N*-oxide(12)**: Colorless oil, total yield 15%; $[\alpha]_D$ = +9.5 ($CHCl_3$, *c* 0.22); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 [s, 9 H, $OSiC(CH_3)_3$], 1.39, 1.50 [2 × s, 2 × 3 H, $C(CH_3)_2$], 3.99 (dd, 1 H, $J_{4,5a}$ = 5.7 Hz, $J_{5a,5b}$ = 10.4 Hz, H-5a), 4.10 (dd, 1 H, H-5b, $J_{4,5b}$ = 6.1 Hz, $J_{5a,5b}$ = 10.2 Hz, H-5b), 4.50 (dd, 1 H, $J_{2,3}$ = 6.7 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 4.86 (s, 2 H, NCH_2Ph), 5.23 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ = 6.3 Hz, H-2), 5.68 (dt, 1 H, $J_{3,4}$ = 3.8 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 5.8 Hz, H-4), 6.79 (d, 1 H, $J_{1,2}$ = 5.6 Hz, H-1), 7.28–8.11 (m, 20 H, NCH_2Ph, $OSiPh_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6 [$OSiC(CH_3)_3$], 27.0 [$C(CH_3)_2$], 27.2 [$OSiC(CH_3)_3$], 27.3 [$C(CH_3)_2$], 62.9 (C-5), 69.9 (NCH_2Ph), 72.9 (C-2), 74.0 (C-4), 78.6 (C-3), 111.0 [$C(CH_3)_2$], 128.0–136.1 (NCH_2Ph, $OSiPh_2$), 136.9 (C-1), 166.0 (COPh).
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(17) **Typical Experimental Procedure**: A mixture of nitrone and *N*-vinylated base was stirred in toluene for 12–24 h under reflux. When starting nitrone had been consumed (TLC), the toluene was evaporated under vacuum and the mixture of isomers was separated by flash column chromatography (silica gel, $CHCl_3$:MeOH = 95: 5).
(18) Yields of cycloadditions depended on the numbers of equivalents of the dipolarophiles employed, presumably due to the nitrone's instability. Nitrone **7** in the absence of dipolarophile was completely decomposed after 24 h in toluene at 110 °C.
(19) **Selected Data: 1-{(3*S*,5*R*)-2-Benzyl-3-[1,2:3,4-di-*O*-*iso*propylidene-D-*xylo*]isoxazolidine-5-yl}uracil(13a)**: Colorless solid, mp 187–189 °C (from toluene); yield 33%; $[\alpha]_D$ = –52.7 (MeOH, *c* 0.12); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38, 1.40, 1.41, 1.44 [4 × s, 4 × 3 H, $C(CH_3)_2$], 2.60 (ddd, 1 H, $J_{3,4b}$ = 7.3 Hz, $J_{4a,4b}$ = 13.7 Hz, $J_{4b,5}$ = 3.2 Hz, H-4b), 2.91 (dt, 1 H, $J_{3,4a}$ = 8.5 Hz, $J_{4a,4b}$ = 14.3 Hz, $J_{4a,5}$ = 8.5 Hz, H-4a), 3.19 (ddd, 1 H, $J_{1',3}$ = 2.9 Hz, $J_{3,4a}$ = 6.9 Hz, $J_{3,4b}$ = 8.9 Hz, H-3), 3.64 (dd, 1 H, $J_{1',2'}$ and $J_{2',3'}$ = 3.4 Hz and 8.6 Hz, H-2′), 3.87 (t, 1 H, $J_{3',4'a}$ = $J_{4'a,4'b}$ = 7.9 Hz, H-4′a), 4.00 (dd; 1 H, $J_{3',4'b}$ = 6.7 Hz, $J_{4'a,4'b}$ = 8.2 Hz, H-4′b), 4.04 (d, 1 H, NCH_2Ph, *J* = 14.3 Hz), 4.08–4.13 (m, 2 H, H-1′, H-3′), 4.24 (d, 1 H; NCH_2Ph, *J* = 14.0 Hz), 5.70 (dd, 1 H, $J_{5'',6''}$ = 8.2 Hz, $J_{5'',NH}$ = 2.1 Hz, H-5′′), 6.28 (dd, 1 H, $J_{4a,5}$ = 7.9 Hz, $J_{4b,5}$ = 2.9 Hz, H-5), 7.30–7.40 (m, 5 H, NCH_2Ph), 7.96 (d, 1 H, $J_{5'',6''}$ = 8.2 Hz, H-6′′), 8.81 (s, 1 H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 26.5, 27.3,

27.4 [$C(CH_3)_2$], 37.3 (C-4), 61.6 (NCH_2Ph), 65.3 (C-3), 66.0 (C-4′), 74.7, 75.1 (C-1′, C-3′), 78.6 (C-2′), 83.3 (C-5), 102.1 (C-5″), 110.2, 110.5 [$C(CH_3)_2$], 128.4, 128.9, 129.1, 129.6, 135.9 (NCH_2Ph), 141.7 (C-6″), 151.0, 163.8 (CO). **1-{(3*S*,5*R*)-2-Benzyl-3-[1,2-*O*-*iso*propylidene-3-*O*-benzoyl-4-*O*-*tert*-butyldiphenylsilyl-D-*xylo*]isoxazolidine-5-yl}uracil(14a)**: Colorless solid, mp 57–60 °C (purified by column chromatography); yield 40%; $[\alpha]_D$ = –30.9 ($CHCl_3$, *c* 0.13); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 [s, 9 H, $OSiC(CH_3)_3$], 1.32, 1.37 [2 × s, 2 × 3 H, $C(CH_3)_2$], 2.61 (ddd, 1 H, $J_{3,4b}$ = 7.0 Hz, $J_{4a,4b}$ = 14.0 Hz, $J_{4b,5}$ = 3.0 Hz, H-4b), 2.91 (ddd, 1 H, $J_{3,4a}$ = 9.2 Hz, $J_{4a,4b}$ = 14.0 Hz, $J_{4a,5}$ = 8.0 Hz, H-4a), 3.27 (ddd, 1 H, $J_{1',3}$ = 2.4 Hz, $J_{3,4a}$ = 9.4 Hz, $J_{3,4b}$ = 7.0 Hz, H-3), 3.84 (dd, 1 H, $J_{1',2'}$ = 8.6 Hz, $J_{1',3}$ = 2.6 Hz, H-1′), 3.94 (dd, 1 H, $J_{3',4'a}$ = 6.0 Hz, $J_{4'a,4'b}$ = 2.4 Hz, H-4′a), 3.99–4.02 (m; 2 H, H-2′, H-4′b), 4.01 (d, 1 H, NCH_2Ph, *J* = 14.8 Hz), 4.10 (d, 1 H, NCH_2Ph, *J* = 14.0 Hz), 5.35 (dt, 1 H, $J_{3',4'a}$ = 6.0 Hz, $J_{3',4'b}$ = 2.7 Hz, H-3′)5.62 (dd, 1 H, $J_{5'',6''}$ = 8.4 Hz, $J_{5'',NH}$ = 2.4 Hz, H-5″), 6.28 (dd, 1 H, $J_{4a,5}$ = 7.8 Hz, $J_{4b,5}$ = 3.0 Hz, H-5), 7.20–7.70 and 8.07–8.09 (m, 20 H, NCH_2Ph, COPh, $OSiPh_2$), 7.99 (d, 1 H, $J_{5'',6''}$ = 8.4 Hz, H-6″), 9.03 (d, 1 H, $J_{5'',NH}$ = 1.6 Hz, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5 [$OSiC(CH_3)_3$], 27.1, 27.3 [$C(CH_3)_2$, $OSiC(CH_3)_3$], 37.5 (C-4), 61.7 (NCH_2Ph), 63.3 (C-4′), 65.7 (C-3), 72.1 (C-3′), 74.5 (C-1′), 77.8 (C-2′), 83.3 (C-5), 102.0 (C-5″), 110.3 [$C(CH_3)_2$], 128.2-141.9 (NCH_2Ph, COPh, $OSiPh_2$), 151.0 (C-6″), 163.8, 166.5 (CO). **9-{(3*S*,5*R*)-2-Benzyl-3-[1,2:3,4-di-*O*-*iso*propylidene-D-*xylo*]isoxazolidine-5-yl}adenine(15a)**: Colorless solid, mp 59–62 °C (purified by column chromatography); yield 59%; $[\alpha]_D$ = –69.4 ($CHCl_3$, *c* 0.16); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31, 1.39, 1.42, 1.46 [4 × s, 4 × 3 H, $C(CH_3)_2$], 2.95 (ddd, 1 H, $J_{3,4b}$ = 6.8 Hz, $J_{4a,4b}$ = 13.6 Hz, $J_{4b,5}$ = 2.4 Hz, H-4b), 3.04 (ddd, 1 H, $J_{3,4a}$ = 9.2 Hz, $J_{4a,4b}$ = 13.6 Hz, $J_{4a,5}$ = 8.0 Hz, H-4a), 3.25 (ddd, 1 H, $J_{1',3}$ = 2.4 Hz, $J_{3,4a}$ = 9.2 Hz, $J_{3,4b}$ = 6.8 Hz, H-3), 3.64 (dd, 1 H, $J_{1',2'}$ = 8.8 Hz and $J_{2',3'}$ = 3.2 Hz, H-2′), 3.87 (dd, 1 H, $J_{3',4'a}$ = 7.2 Hz, $J_{4'a,4'b}$ = 8.0 Hz, H-4′a), 3.89 [s, 6 H, $N(SO_2CH_3)_2$], 4.01 (dd; 1 H, $J_{3',4'b}$ = 6.8 Hz, $J_{4'a,4'b}$ = 8.0 Hz, H-4′b), 4.08 (dt, 1 H, $J_{2',3'}$ = 3.6 Hz, $J_{3',4'a}$ and $J_{3',4'b}$ = 6.8 Hz, H-3′) 4.16 (d, 1 H, NCH_2Ph, *J* = 14.0 Hz), 4.17 (dd, 1 H, $J_{1',3}$ = 2.4 Hz, $J_{1',2'}$ = 8.4 Hz, H-1′), 4.30 (d, 1 H, NCH_2Ph, *J* = 14.0 Hz), 6.61 (dd, 1 H, $J_{4a,5}$ = 8.0 Hz, $J_{4b,5}$ = 2.4 Hz, H-5), 7.35–7.36 (m, 5 H, NCH_2Ph), 8.88, 8.91 (2 × s, 2 × 1 H, H-adenine); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 26.5, 27.2, 27.4 [$C(CH_3)_2$], 36.9 (C-4), 45.4 [$N(SO_2CH_3)_2$], 60.7 (NCH_2Ph), 64.9 (C-3), 66.0 (C-4′), 74.5 (C-1′, C-3′), 78.6 (C-2′), 81.0 (C-5), 110.2, 110.6 [$C(CH_3)_2$], 128.4, 128.9, 130.0, 130.9, 135.6, 146.5, 154.2 (NCH_2Ph, C-adenine), 146.3, 152.3 (CH-adenine). **9-{(3*S*,5*S*)-2-Benzyl-3-[1,2:3,4-di-*O*-*iso*propylidene-D-*xylo*]isoxazolidine-5-yl}adenine(15b)**: Colorless solid, mp 67–70 °C (purified by column chromatography); yield 10%; $[\alpha]_D$ = +13.8 ($CHCl_3$, *c* 0.05); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42, 1.43, 1.45, 1.47 [4 × s, 4 × 3 H, $C(CH_3)_2$], 3.23 (ddd, 1 H, $J_{3,4a}$ = 4.0 Hz, $J_{4a,4b}$ = 13.6 Hz, $J_{4a,5}$ = 7.6 Hz, H-4a), 3.48 (m, 1 H, H-4b), 3.60 (dd, 1 H, *J* = 4.2 Hz, *J* = 7.4 Hz, H-2′), 3.68 (m, 1 H, H-3), 3.90 [s, 6 H, $N(SO_2CH_3)_2$], 3.86–3.93 (m, 1 H, H-4a′), 4.00 (dd, 1 H, $J_{3',4'b}$ = 6.6 Hz, $J_{4'a,4'b}$ = 8.2 Hz, H-4′b) 4.18–4.23 (m, 2 H, H-1′, H-3′), 4.19 (d, 1 H, NCH_2Ph, *J* = 12.4 Hz), 4.26 (d, 1 H; NCH_2Ph, *J* = 12.8 Hz), 6.40 (dd, 1 H, $J_{4a,5}$ = 7.6 Hz, $J_{4b,5}$ = 5.2 Hz, H-5), 7.27–7.31 (m, 5 H, NCH_2Ph), 8.27, 8.92 (2 × s, 2 × 1 H, H-adenine); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 26.3, 27.0, 27.4 [$C(CH_3)_2$], 35.1 (C-4), 45.0 [$N(SO_2CH_3)_2$], 61.9 (NCH_2Ph), 65.4 (C-3), 65.7 (C-4′), 75.6 (C-1′, C-3′), 79.6 (C-2′), 86.0 (C-5), 109.8, 110.3 [$C(CH_3)_2$], 128.2–131.5 (NCH_2Ph, C-adenine), 146.8, 153.1 (CH-adenine).

(20) Crystallographic data for the structure **13a** have been deposited with the Cambridge Crystallographic Data Centre; reference number CCDC 178867(**13a**). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).