

Diastereoselective synthesis of D-xyló-isoxazolidinyl nucleosides

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Abstract

The condensation of the acetoxyisoxazolidines with silylated uracil, thymine, cytosine, *N*-acetylcytosine, and guanine proceeded in good yields and with moderate to good stereoselectivity to give isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition is dependent on the structure of the substituent at C-3 originating from the starting chiral nitron. The Vorbrüggen nucleosidation of isoxazolidine **8** at 70 °C afforded β-anomers as the exclusive nucleosides together with the isoxazoline **11**. It was found that the nucleosidation proceeded also in methylene chloride at room temperature.

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1. Introduction

Nucleosides are generally defined as DNA or RNA subunits and consist of both a base moiety such as adenine, thymine, guanine, cytosine, and uracil, and a sugar moiety such as D-ribose or D-deoxyribose.¹ Many nucleoside analogues have been synthesized with modification of the base, sugar, and phosphane region. In particular, nucleoside analogues in which the furanose ring has been replaced by different carbon or heterocyclic systems have attracted special interest by virtue of their biological action as antiviral and/or anticancer agents.² Among them, uracil, thymine, cytosine, and adenine nucleosides **1** possessing an isoxazolidinyl moiety (carbocyclic-2'-oxo-3'-azanucleosides) are emerging as an interesting class of dideoxynucleoside analogues with potential pharmacological activity.² For the synthesis of modified isoxazolidinyl nucleosides **1–3** two strategies can be used. In particular a one-step approach based on the 1,3-dipolar cycloaddition of nitrones with vinyl nucleobases and a two-step methodology based on the

Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines.^{3–12} Recently, with the aim to prepare some novel azanucleosides by the transformation of modified isoxazolidinyl nucleosides **2** we have prepared the appropriate sugar-derived nitrones **4a,b** possessing structures suitable for the building of pyrrolidine.⁹ Cycloadditions of chiral nitrones **4a** and **4b** easily prepared from D-xylose to vinylated nucleobases derived from uracil and adenine proceeded regioselectively and led to the

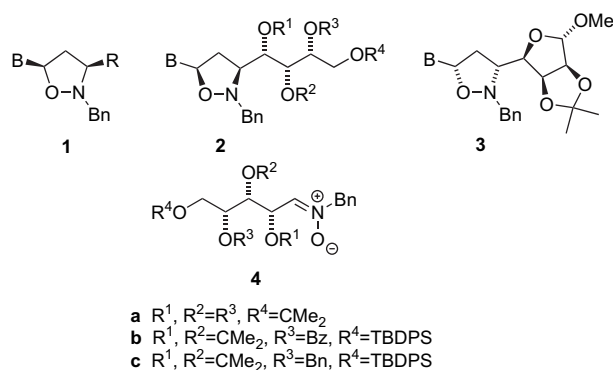


Figure 1.

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isoxazolidines **2** as a mixture of four diastereoisomers in all cases.⁹ With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions,^{9–15} we are now extending the 1,3-dipolar cycloaddition approach to synthesize novel 4'-aza-2',3'-dideoxy-furanosyl nucleosides **2** by reaction of readily available chiral sugar-derived D-xylosyl nitrones **4** to vinyl acetate with the subsequent transformation of the formed 5-acetoxyisoxazolidines (Fig. 1).

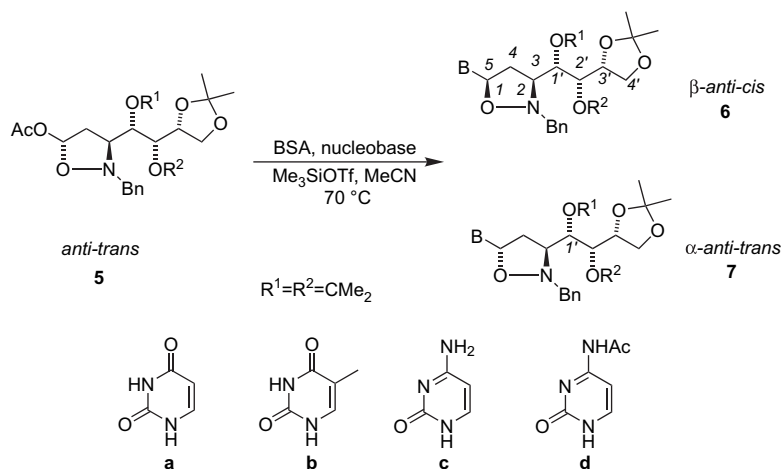
2. Results and discussion

The *anti*, *trans*-isoxazolidine **5** prepared by the 1,3-dipolar cycloaddition of nitrone **2a** with vinyl acetate¹⁹ was coupled with silylated nucleobases according to the Vorbrüggen methodology.²⁰ The condensation of **5** with silylated uracil, thymine, cytosine, and *N*-acetylcytosine at 70 °C in the presence of trimethylsilyltriflate as catalyst, proceeded with low (uracil, thymine) to good (cytosine and *N*-acetylcytosine) yields and moderate stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides (**6a/7a** ratio 63:37, **6b/7b** ratio 63:37, **6c/7c** ratio 55:45, **6d/7d** ratio 66:34, Scheme 1). The ratio of anomeric nucleosides was determined from quantitative ¹³C NMR spectra, by integration of the peaks from C-4 and C-5 of the isoxazolidines. The β-anomers **6a–d** predominate, but a significant amount of α-anomers **7a–d** were also obtained. These results are fully in accord with the data obtained for the related Vorbrüggen nucleosidations. Purification by flash chromatography allowed the isolation of pure nucleosides **6a** and **7a**; their assigned stereochemistry is supported by NMR analysis. In fact, NOE measurements performed on β-anomers **6a–d** show a positive NOE effect for protons H-3 when irradiating H-5 thus indicating a *cis* relationship between these protons. The major diastereomer **6a** has been already prepared by us by the 1,3-dipolar cycloaddition of nitrone **2a** with vinyl uracil and its structure was subsequently confirmed by X-ray crystallographic analysis.⁹ It should be noted that the chromatographic separation of **6b–d** and **7b–d** was not possible.

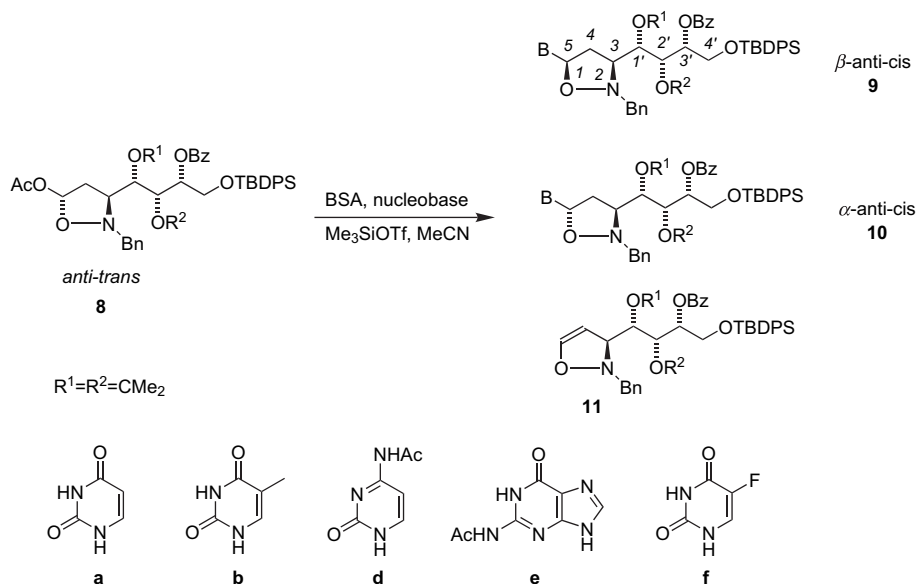
A surprising and unexpected fact is that in the case of the *anti*, *trans*-5-acetoxysubstituted isoxazolidine **8** prepared by

the 1,3-dipolar cycloaddition of nitrone **4b** with vinyl acetate,¹⁹ the Vorbrüggen nucleosidations with silylated nucleobases proceeded at 70 °C with the excellent stereoselectivity and the corresponding β-anomers **9a,b,d** are now the exclusive nucleosides for all of the used nucleobases (Scheme 2). That **9a,b,d** has the same configuration as **6a** whose structure was elucidated by X-ray analysis is inferred from the diagnostic signals and NOEDS results.

The research groups of Merino, Chiacchio, and Romeo have reported that the anomeric distribution obtained by the Vorbrüggen nucleosidation with chiral 5-acetoxyisoxazolidines depends on the attacking nucleobase.^{21–24} The attack on the intermediate oxonium from either the α- or β-side is possible, and hence the product distribution is sensitive to structural changes of the reactants. Evidently, in our case the stereoselectivity of the addition of the silylated nucleobase is more dependent on the structure of the substituent at C-3 originating from the starting chiral nitrone. Moreover, in this case the product of elimination, the corresponding isoxazoline derivative **11**, was also isolated (Scheme 2). It is noteworthy that in the case of silylated 5-fluorouracil, the isoxazoline **11** is formed as the major product (**9a/11** ratio 58:42, **9b/11** ratio 81:19, **9c/11** ratio 90:10, **9f/11** ratio 9:91). The unexpected side-product **11** was analyzed by 2D NMR spectroscopy and mass spectrometry. Using homonuclear (COSY) and one-bond (HSQC) as well as long-range (HMBC) heteronuclear correlation spectra the structure could be elucidated and the signals were assigned. The existence of a double bond within the isoxazoline ring is supported by good agreement of the chemical shifts with similar structural elements, e.g., 2-benzyl-3-isopropyl-4-isoxazoline (6.45 and 4.88 ppm for ¹H, 141.5 and 97.5 ppm for ¹³C).²⁵ The remarkably small coupling constant of 2.2 Hz between the olefinic protons is also characteristic for cyclic enol ethers. Furthermore, the shifts of the side chain are well comparable to those of similar compounds within this work. Thus the structure of the product in question is confirmed both by the correlation pattern within the 2D NMR spectra as well as the chemical shift analysis. The suggested structure of **11** was also confirmed by HRMS as well by MALDI and electrospray mass spectrometry.



Scheme 1.



Scheme 2.

To the best of our knowledge, such a formation of 2,3-dihydroisoxazoles by the Vorbrüggen nucleosidation has not been observed. 2,3-Dihydroisoxazoles represent a class of heterocycles that may be employed as useful building blocks for synthesis.²⁶ Recently, Carreira et al. have reported a conceptually simple and attractive synthesis toward 2,3,5-trisubstituted 2,3-dihydroisoxazoles via 5-*endo-dig* C–O bond formation of propargylic *N*-hydroxylamines catalyzed by Zn(II) salts.²⁷ The obtained chiral 2,3-disubstituted 2,3-dihydroisoxazole **11** represents a very rare/unusual compound of this class.

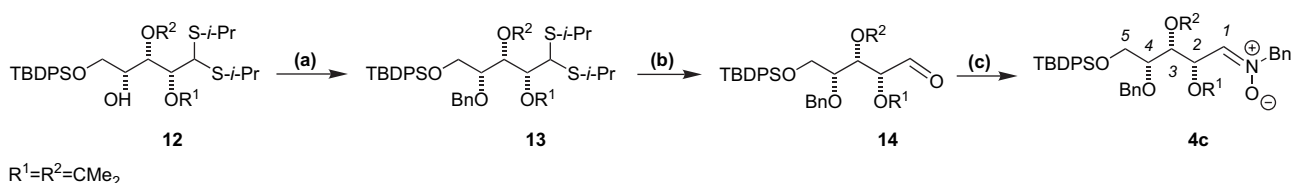
We suppose that the isoxazoline **11** is formed by the elimination of the corresponding α-anomers **10a,b** and **10d**. Therefore, we next studied the Vorbrüggen nucleosidation in methylene chloride at room temperature. Indeed, the product of elimination **11** was not detected and both β- and α-anomeric isoxazolidinyl nucleosides **9** and **10** were formed with high stereoselectivities in favor of the β-anomers **9** (**9a/10a** ratio 95:5, **9b/10b** ratio 80:20, **9d/10d** ratio 83:17, **9e/10e** ratio 70:30, Scheme 3). Also, the first successful isoxazolidinyl nucleosides **9e** and **10e** derived from *N*-acetylguanine were obtained.

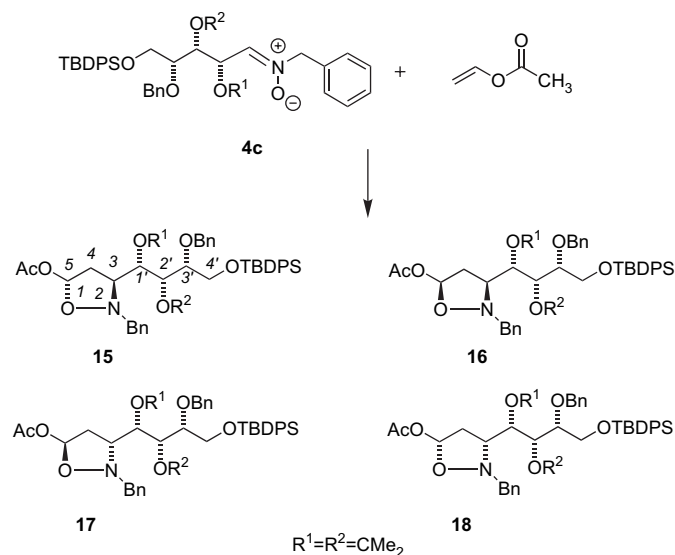
As has been already mentioned, the best stereoselectivity in the nucleosidation was achieved in the case of benzoylsubstituted isoxazolidine **8**. To exclude or to support the possibility of the participation of the neighboring benzoyl group, we have prepared the corresponding D-xylose derived benzylsubstituted

nitrone **4c** (Scheme 3). The synthesis of **4c** was performed according to the procedure previously reported by us for **4b**.¹⁹ Thus, benzoylation of silylated dithioacetal **12**⁹ with benzyl bromide afforded the protected dithioacetal **13**. Deprotection of the thiol group (HgCl₂/HgO) and condensation of aldehyde **14** with *N*-benzylhydroxylamine according to the method of Dondoni²⁸ gave nitrone **4c**.

Nitrone **4c** reacted smoothly in vinyl acetate at reflux over 24 h to give an 83:10:7 mixture of diastereoisomeric isoxazolidines **15**, **16**, and **17** in 85% yield (Scheme 4). The cycloaddition proceeded with very good diastereoselectivity for the *anti*, *trans*-isoxazolidine **15** and is completely regioselective with only the sterically favored 5-substituted isoxazolidines being detected. Purification by flash chromatography allowed the isolation of pure *endo*-adduct **15**, with the C-3/C-5 *trans* relative configuration identified by spectroscopic analysis, particularly NOE difference experiments. Based on our previous results from 1,3-dipolar cycloadditions of sugar nitrones bearing a protected hydroxy group in the α-position,^{9–19} as well as the fact that the 1,3-dipolar cycloaddition of electron-rich alkenes to chiral α-alkoxy nitrones gave preferentially *anti* adducts,⁴ we assigned to isomer **15** a C-1'/C-3 *anti* relationship as a result of dipolarophile attack from the less sterically hindered *si* diastereotopic face of nitrone **4c**.

The subsequent Vorbrüggen nucleosidation of *anti*, *trans*-benzyloxysubstituted isoxazolidine **15** with silylated uracil,

Scheme 3. (a) BnBr, NaH, THF, rt, 21 h, 61%; (b) HgCl₂/HgO, acetone, H₂O, 56 °C, 2 h; (c) BnNHOH, CH₂Cl₂, MgSO₄, rt, 12 h, 93%.



Scheme 4.

thymine, *N*-acetylcytosine, and guanine at room temperature in methylene chloride in the presence of trimethylsilyltriflate as catalyst, afforded the β -anomeric nucleosides **19** with the best diastereoselectivities in this series, i.e., uracil and acetylated cytosine reacted with 90% diastereomeric excess (**19a**/**20a** ratio 95:5, **19b**/**20b** ratio 80:20, **19d**/**20d** ratio 94:6, **19e**/**20e** ratio 63:37, Scheme 5).

3. Conclusion

In conclusion, the synthesis of isoxazolidinyl nucleosides as potential antiviral agents is reported. The condensation of the acetoxyisoxazolidines **5**, **8**, and **15** with silylated uracil, thymine, cytosine, *N*-acetylcytosine, and guanine proceeded with good yields and from moderate to good stereoselectivity in the formation of the expected isoxazolidinyl β - and α -nucleosides. The stereoselectivity of the addition of the silylated nucleobase is dependent on the structure of the substituent at C-3 originating from the starting chiral nitron. Moreover, in the

case of the *anti*, *trans*-5-acetoxysubstituted isoxazolidine **8**, the Vorbrüggen nucleosidation with silylated nucleobases is also dependent on the reaction temperature, at 70 °C the corresponding β -anomers **9a–c** are the exclusive nucleosides for all of the used nucleobases, along with the product of elimination; the corresponding isoxazoline derivative **11** was also isolated. It was found that the nucleosidation also proceeded in methylene chloride at room temperature. The cycloaddition of the chiral nitron **4c** with vinyl acetate proceeded with very good diastereoselectivity for the *anti*, *trans*-isoxazolidine **15**.

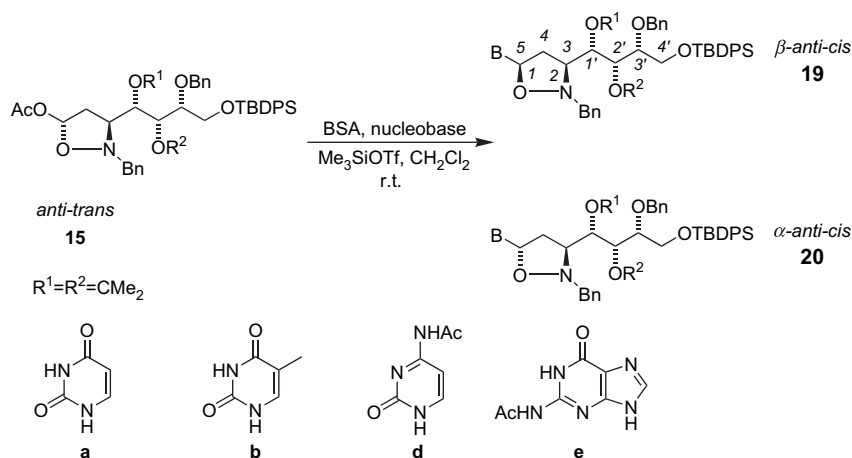
4. Experimental

4.1. General information

All commercially available starting materials and reagents (Fluka, Merck, Across or Aldrich) were used without further purification. Solvents were dried before use. Thin layer chromatography (TLC, ALUGRAM Sil G/UV₂₅₄ Macherey-Nagel) was used for the monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040–0.063 mm, Merck). The ¹H and ¹³C NMR spectra of deuteriochloroform solutions were obtained using Varian INOVA-600 (600 MHz) and VXR-300 (300 MHz) instruments, tetramethylsilane (TMS) being the internal reference. Specific rotations [α] were measured on an IBZ Messtechnik Polar-L μ P polarimeter at the sodium D line (589 nm) using a 1 dm cell. Elemental analyses were conducted using the Fisons EA 1108 Analyser. MS and HRMS analyses were performed on Varian Ionspec QFT-7 (ESI-FT ICRMS), Bruker, Esquire 3000^{plus} (ESI-IT-MS) and Shimadzu, AXIMA TOF (MALDI-TOF/RTOF-MS).

4.2. Method A: general procedure for reactions between nucleobases and isoxazolidines **5** and **8**

A suspension of the nucleobase (0.58 mmol) in dry acetonitrile (2 mL) was treated with bis(trimethylsilyl)acetamide (2.32 mmol) and heated at 70 °C for 15 min under stirring.



Scheme 5.

Isoxazolidine **5**¹⁹ or **8**¹⁹ (0.48 mmol) in dry acetonitrile (2 mL) and TMSOTf (0.72 mmol) were added to the obtained clear solution. The reaction mixture was stirred at 70 °C for 2 h. After cooling at 0 °C, the solution was neutralized by addition of aqueous 5% sodium bicarbonate and then concentrated in vacuo. After addition of methylene chloride (8 mL), the organic phase was separated, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography using ethyl acetate/hexanes (60:40).

4.2.1. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2:3,4-di-*O*-isopropylidene-*D*-xylo)isoxazolidine-5-yl]-1*H*-pyrimidine-2,4-dione **6a**⁹

Yield 34%, colorless crystals; mp 187–189 °C; R_f (hexanes/EtOAc, 60:40) 0.29; $[\alpha]_D -52.7$ (*c* 0.12, MeOH); ¹H NMR: δ 1.32, 1.34, 1.36, 1.39 (4×3H, s, CH₃), 2.57 (1H, ddd, $J=10.6, 3.2, 7.3$ Hz, H-4a), 2.89 (1H, m, H-4b), 3.24 (1H, m, H-3), 3.66 (2H, m, H-2', H-4a'), 4.02 (1H, d, $J=14.1$ Hz, NCH₂Ph), 4.10 (3H, m, H-4b', H-1', H-3'), 4.24 (1H, d, $J=14.1$ Hz, NCH₂Ph), 5.68 (1H, dd, $J=8.2, 1.8$ Hz, H-5''), 6.25 (1H, dd, $J=2.9, 7.6$ Hz, H-5), 7.35 (5H, m, H-arom), 7.95 (1H, d, $J=8.2$ Hz, H-6''), 8.65 (1H, br s, NH); ¹³C NMR: δ 23.37, 25.44, 26.02, 26.79 (C(CH₃)₂), 36.76 (C-4), 61.01 (NCH₂Ph), 64.74 (C-3), 65.50 (C-4'), 74.23, 74.52 (C-1', C-3'), 78.07 (C-2'), 82.75 (C-5), 101.68 (C-5''), 109.73 (C(CH₃)₂), 127.88–135.42 (C-arom), 141.30 (C-6''), 150.66 (CO), 163.60 (CO). Anal. Calcd for C₂₄H₃₁N₃O₇ (473.52): C, 60.88; H, 6.60; N, 8.87. Found: C, 61.22; H, 6.39; N, 8.56.

4.2.2. 1-[(3*S*,5*S*)-2-Benzyl-3-(1,2:3,4-di-*O*-isopropylidene-*D*-xylo)isoxazolidine-5-yl]-1*H*-pyrimidine-2,4-dione **7a**

Yield 8%, colorless semisolid; R_f (CH₂Cl₂/MeOH, 97:3) 0.17; ¹H NMR: δ 1.26, 1.31, 1.35, 1.38 (4×3H, s, CH₃), 2.56 (1H, ddd, $J=9.4, 2.9, 6.4$ Hz, H-4a), 2.94 (1H, m, H-4b), 3.24 (1H, m, H-3), 3.66 (2H, m, H-2', H-4a'), 4.01 (1H, d, $J=14.1$ Hz, NCH₂Ph), 4.14 (3H, m, H-4b', H-1', H-3'), 4.22 (1H, d, $J=13.5$ Hz, NCH₂Ph), 5.68 (1H, d, $J=8.2$ Hz, H-5''), 6.22 (1H, dd, $J=2.9, 7.6$ Hz, H-5), 7.35 (5H, m, H-arom), 7.85 (1H, d, $J=8.2$ Hz, H-6''), 9.27 (1H, br s, NH); ¹³C NMR: δ 26.78, 26.99 (C(CH₃)₂), 37.21 (C-4), 61.55 (NCH₂Ph), 64.34 (C-4'), 64.70 (C-3), 69.70, 74.91 (C-1', C-3'), 80.06 (C-2'), 83.37 (C-5), 101.71 (C-5''), 109.88 (C(CH₃)₂), 128.02–135.51 (C-arom), 141.01 (C-6''), 150.50 (CO), 163.36 (CO). Anal. Calcd for C₂₄H₃₁N₃O₇ (473.52): C, 60.88; H, 6.60; N, 8.87. Found: C, 61.17; H, 6.31; N, 9.23.

4.2.3. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-tert-butylidiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-1*H*-pyrimidine-2,4-dione **9a**

Yield 48%, colorless solid; mp 62–63 °C; R_f (hexanes/EtOAc, 50:50) 0.35; $[\alpha]_D -45.0$ (*c* 0.1, CH₂Cl₂); ¹H NMR: δ 1.00 (9H, s, OSiC(CH₃)₃), 1.29, 1.34 (2×3H, s, C(CH₃)₃), 2.58 (1H, ddd, $J=13.9, 2.9, 7.0$ Hz, H-4a), 2.87 (1H, m, H-4b), 3.24 (1H, m, H-3), 3.81 (1H, dd, $J=8.8, 2.6$ Hz, H-1'), 3.91 (2H, m, H-4'), 3.97 (1H, dd, $J=8.8, 2.6$ Hz, H-2'), 3.98 (1H, d, $J=13.9$ Hz, NCH₂Ph), 4.07 (1H, d, $J=14.3$ Hz, NCH₂Ph), 5.31 (1H, m, H-3'), 5.59 (1H, dd, $J=1.1, 8.1$ Hz, H-5''), 6.24 (1H, dd, $J=2.9, 7.7$ Hz, H-5), 7.20–8.06 (20H, m,

H-arom), 7.96 (1H, d, $J=8.1$ Hz, H-6''), 8.54 (1H, br s, NH); ¹³C NMR: δ 19.07 (OSiC(CH₃)₃), 26.63 (C(CH₃)₂), 26.65 (OSiC(CH₃)₃), 26.87 (C(CH₃)₂), 37.04 (C-4), 61.39 (NCH₂Ph), 62.78 (C-4'), 65.21 (C-3), 71.63 (C-3'), 73.98 (C-1'), 77.33 (C-2'), 82.78 (C-5), 101.49 (C-5''), 109.89 (C(CH₃)₂), 127.69–135.86 (C-arom), 141.48 (C-6''), 150.46 (CO), 163.17 (CO), 165.98 (CO); IR (KBr): 3194, 3069, 2932, 2858, 1711, 1688, 1270, 1112, 708 cm⁻¹. Anal. Calcd for C₄₄H₄₉N₃O₈Si (775.96): C, 68.11; H, 6.36; N, 5.42. Found: C, 68.37; H, 6.41; N, 5.65.

4.2.4. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-tert-butylidiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-5-methyl-1*H*-pyrimidine-2,4-(1*H*,3*H*)-dione **9b**

Yield 42%, colorless solid; mp 75–76 °C; R_f (hexanes/EtOAc, 50:50) 0.35; $[\alpha]_D -53.8$ (*c* 0.08, CH₂Cl₂); ¹H NMR: δ 1.00 (9H, s, OSiC(CH₃)₃), 1.31, 1.36 (2×3H, s, C(CH₃)₃), 1.84 (3H, s, CH₃), 2.57 (1H, ddd, $J=13.9, 3.1, 7.5$ Hz, H-4a), 2.87 (1H, m, H-4b), 3.23 (1H, m, H-3), 3.86 (1H, dd, $J=8.8, 2.2$ Hz, H-1'), 3.92 (2H, m, H-4'), 3.99 (1H, m, H-2'), 4.06 (1H, d, $J=13.2$ Hz, NCH₂Ph), 4.07 (1H, d, $J=14.3$ Hz, NCH₂Ph), 5.31 (1H, m, H-3'), 6.25 (1H, dd, $J=3.1, 7.4$ Hz, H-5), 7.20–8.06 (20H, m, H-arom), 7.83 (1H, d, $J=1.1$ Hz, H-6''), 8.64 (1H, br s, NH); ¹³C NMR: δ 12.38 (CH₃), 19.07 (OSiC(CH₃)₃), 26.66 (OSiC(CH₃)₃), 26.66 (C(CH₃)₂), 26.91 (C(CH₃)₂), 37.00 (C-4), 60.97 (NCH₂Ph), 62.79 (C-4'), 65.21 (C-3), 71.60 (C-3'), 74.02 (C-1'), 77.33 (C-2'), 82.24 (C-5), 109.75 (C-5''), 109.86 (C(CH₃)₂), 127.74–136.14 (C-arom), 137.53 (C-6''), 150.58 (CO), 163.84 (CO), 165.98 (CO); IR (KBr): 3411, 3192, 3070, 2931, 2857, 1690, 1270, 1112, 703 cm⁻¹. Anal. Calcd for C₄₅H₅₁N₃O₈Si (789.99): C, 68.42; H, 6.51; N, 5.32. Found: C, 68.27; H, 6.86; N, 5.30.

4.2.5. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-tert-butylidiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-4-acetylaminopyrimidine-2-one **9d**

Yield 63%, colorless solid; mp 93–94 °C; R_f (hexanes/EtOAc, 30:70) 0.17; $[\alpha]_D -4.4$ (*c* 0.16, CH₂Cl₂); ¹H NMR: δ 1.00 (9H, s, OSiC(CH₃)₃), 1.24, 1.26 (2×3H, s, C(CH₃)₃), 2.22 (3H, s, OCOCH₃), 2.60 (1H, ddd, $J=13.5, 2.3, 6.5$ Hz, H-4a), 2.99 (1H, m, H-4b), 3.27 (1H, m, H-3), 3.77 (1H, dd, $J=8.5, 2.6$ Hz, H-1'), 3.90 (2H, m, H-4'), 3.94 (1H, dd, $J=8.8, 2.3$ Hz, H-2'), 3.99 (1H, d, $J=14.1$ Hz, NCH₂Ph), 4.10 (1H, d, $J=14.1$ Hz, NCH₂Ph), 5.33 (1H, m, H-3'), 6.16 (1H, dd, $J=1.8, 7.6$ Hz, H-5), 7.20–8.05 (20H, m, H-arom), 7.28 (1H, d, $J=7.6$ Hz, H-5''), 8.14 (1H, d, $J=7.6$ Hz, H-6''), 9.85 (1H, br s, NH); ¹³C NMR: δ 19.10 (OSiC(CH₃)₃), 24.86 (OCOCH₃), 26.69 (OSiC(CH₃)₃), 26.87 (C(CH₃)₂), 37.94 (C-4), 61.84 (NCH₂Ph), 62.91 (C-4'), 65.36 (C-3), 71.75 (C-3'), 74.28 (C-1'), 77.40 (C-2'), 85.12 (C-5), 95.70 (C-5''), 109.84 (C(CH₃)₂), 127.72–136.08 (C-arom), 146.14 (C-6''), 162.49 (CO), 166.05 (CO), 170.68 (CO); IR (KBr): 3233, 3071, 2959, 2932, 2858, 1721, 1664, 1492, 1271, 1112, 703 cm⁻¹. Anal. Calcd for C₄₆H₅₂N₄O₈Si (817.01): C, 67.62; H, 6.42; N, 6.86. Found: C, 67.30; H, 6.66; N, 6.60.

4.2.6. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-*tert*-butyldiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-2-acetylguanine **9e**

Yield 22%, colorless solid; mp 102–103 °C; R_f (hexanes/EtOAc, 20:80) 0.17; ^1H NMR: δ 1.00 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.25, 1.28 (2 $\times$ 3H, s, $\text{C}(\text{CH}_3)_3$), 2.36 (3H, s, OCOCH_3), 2.81 (1H, ddd, $J=13.9$, 2.2, 7.0 Hz, H-4a), 3.02 (1H, m, H-4b), 3.27 (1H, m, H-3), 3.77 (1H, dd, $J=8.8$, 2.2 Hz, H-1'), 3.91 (2H, m, H-4'), 3.96 (1H, dd, $J=8.8$, 2.2 Hz, H-2'), 4.08 (2H, m, NCH_2Ph), 5.29 (1H, m, H-3'), 6.85 (1H, dd, $J=2.2$, 8.1 Hz, H-5), 7.11–8.06 (20H, m, H-arom), 8.57 (1H, s, H-8''), 11.31 (1H, br s, NHAc), 12.32 (1H, br s, CONH); ^{13}C NMR: δ 19.06 ($\text{OSiC}(\text{CH}_3)_3$), 24.57 (OCOCH_3), 26.53 ($\text{C}(\text{CH}_3)_2$), 26.66 ($\text{OSiC}(\text{CH}_3)_3$), 26.83 ($\text{C}(\text{CH}_3)_2$), 37.79 (C-4), 60.73 (NCH_2Ph), 62.80 (C-4'), 65.28 (C-3), 71.61 (C-3'), 73.60 (C-1'), 77.29 (C-2'), 82.84 (C-5), 109.89 ($\text{C}(\text{CH}_3)_2$), 111.29 (C-5''), 127.41–136.09 (C-arom), 143.01 (C-8''), 147.98, 153.21, 156.24 (C-2'', C-4'', C-6''), 165.98 (CO), 173.27 (CO); IR (KBr): 3133, 3070, 2932, 2857, 1718, 1686, 1269, 1252, 1112, 708 cm^{-1} . Anal. Calcd for $\text{C}_{47}\text{H}_{52}\text{N}_6\text{O}_8\text{Si}$ (857.04): C, 65.87; H, 6.12; N, 9.81. Found: C, 65.59; H, 6.31; N, 10.12.

4.2.7. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-*tert*-butyldiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-5-fluoro-1*H*-pyrimidine-2,4-(1*H*,3*H*)-dione **9f**

Yield 6%, sticky yellow oil; ^1H NMR: δ 1.00 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.29, 1.37 (2 $\times$ 3H, s, $\text{C}(\text{CH}_3)_3$), 2.57 (1H, ddd, $J=13.9$, 2.6, 7.3 Hz, H-4a), 2.87 (1H, m, H-4b), 3.23 (1H, m, H-3), 3.82 (1H, dd, $J=8.8$, 2.2 Hz, H-1'), 3.93 (3H, m, H-4', H-2'), 4.01 (1H, d, $J=13.2$ Hz, NCH_2Ph), 4.05 (1H, d, $J=13.9$ Hz, NCH_2Ph), 5.27 (1H, m, H-3'), 6.24 (1H, m, H-5), 7.19–8.06 (20H, m, H-arom), 8.24 (1H, d, $J=7.3$ Hz, H-6''), 8.91 (1H, br s, NH); ^{13}C NMR: δ 19.08 ($\text{OSiC}(\text{CH}_3)_3$), 26.54 ($\text{C}(\text{CH}_3)_2$), 26.66 ($\text{OSiC}(\text{CH}_3)_3$), 26.78 ($\text{C}(\text{CH}_3)_2$), 36.56 (C-4), 61.11 (NCH_2Ph), 62.74 (C-4'), 65.02 (C-3), 71.56 (C-3'), 73.69 (C-1'), 77.27 (C-2'), 82.62 (C-5), 110.00 ($\text{C}(\text{CH}_3)_2$), 127.70–135.75 (C-arom), 141.49 (C-6''), 149.14 (C-5''), 156.76 (CO), 157.10 (CO), 166.04 (CO). Anal. Calcd for $\text{C}_{44}\text{H}_{48}\text{FN}_3\text{O}_8\text{Si}$ (793.95): C, 66.56; H, 6.09; N, 5.29. Found: C, 66.92; H, 6.40; N, 5.42.

4.2.8. 2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-*tert*-butyldiphenylsilyl-*D*-xylo-1-yl)-2,3-dihydroisoxazole **11**

Sticky yellow oil; ^1H NMR: δ 1.00 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.43, 1.45 (2 $\times$ 3H, s, 2 $\times$ $\text{C}(\text{CH}_3)_3$), 3.87 (1H, dd, $J=8.1$, 4.4 Hz, H-1'), 3.90 (1H, m, H-4a'), 3.95 (1H, d, $J=13.9$ Hz, NCH_2Ph), 3.99 (1H, m, H-4b'), 4.18 (1H, d, $J=13.2$ Hz, NCH_2Ph), 4.23 (1H, m, H-3), 4.32 (1H, dd, $J=8.1$, 2.2 Hz, H-2'), 4.98 (1H, dd, $J=2.2$ Hz, H-4), 5.53 (1H, m, H-3'), 6.50 (1H, dd, $J=2.2$ Hz, H-5), 7.26–8.14 (20H, m, H-arom); ^{13}C NMR: δ 19.06 ($\text{OSiC}(\text{CH}_3)_3$), 26.58 ($\text{OSiC}(\text{CH}_3)_3$), 27.03 ($\text{C}(\text{CH}_3)_2$), 27.26 ($\text{C}(\text{CH}_3)_2$), 63.37 (C-4'), 63.96 (NCH_2Ph), 69.99 (C-3), 73.13 (C-3'), 76.08 (C-2'), 78.01 (C-1'), 95.57 (C-4), 109.41 ($\text{C}(\text{CH}_3)_2$), 127.44–136.56 (C-arom), 143.50 (C-5), 165.96 (CO). Exact mass calculated for $\text{C}_{40}\text{H}_{45}\text{NO}_6\text{Si}$: 663.3016. Found: 663.3012.

4.3. Preparation of nitrone **4c**

4.3.1. (2,3-*O*-Isopropylidene-4-*O*-benzyl-5-*O*-*tert*-butyldiphenylsilyl-*D*-xylo)-diisopropylthioacetal **13**

A solution of dithioacetal **12**¹⁹ (7.78 g, 15.21 mmol) in THF (32 mL) was added dropwise to a stirred solution of sodium hydride in paraffin (0.61 g, 15.21 mmol) and THF (5 mL) at 0 °C. The mixture was stirred for 1 h and benzyl bromide (2.86 g, 2 mL, 16.6 mmol) was added at 0 °C. Next the mixture was stirred for 12 h at room temperature. Then water was added, the organic layer was separated and extracted with ethyl acetate, and dried over sodium sulfate. The solvent was evaporated and the product was isolated by column chromatography (silica gel, hexanes/EtOAc, 96:4). Compound **13** was obtained in 61% yield as colorless oil; R_f (hexanes/EtOAc, 80:20) 0.53; $[\alpha]_D -34.8$ (c 2.4, CH_2Cl_2); ^1H NMR: δ 1.07 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.22–1.28 (12H, m, $\text{SCH}(\text{CH}_3)_2$), 1.37, 1.43 (2 $\times$ 3H, s, $\text{C}(\text{CH}_3)_2$), 3.09–3.24 (2H, m, $\text{SCH}(\text{CH}_3)_2$), 3.76–3.82 (1H, m, H-3), 3.89–3.95 (3H, m, H-5a, H-5b, H-1), 4.34–4.40 (2H, m, H-2, H-4), 4.51 (1H, d, $J=11.6$ Hz, OCH_2Ph), 4.75 (1H, d, $J=11.6$ Hz, OCH_2Ph), 7.24–7.73 (15H, m, H-arom); ^{13}C NMR: δ 19.2 ($\text{OSiC}(\text{CH}_3)_3$), 23.2, 23.3, 23.4 ($\text{SCH}(\text{CH}_3)_2$), 26.9, 27.0, 27.3 ($\text{OSiC}(\text{CH}_3)_3$, $\text{C}(\text{CH}_3)_2$), 35.1, 35.4 ($\text{SCH}(\text{CH}_3)_2$), 50.8 (C-1), 63.8 (C-5), 73.4 (OCH_2Ph), 78.5 (C-2), 78.6 (C-4), 79.6 (C-3), 109.6 ($\text{C}(\text{CH}_3)_2$), 127.4–138.5 (OSiPh_2 , OCH_2Ph). Anal. Calcd for $\text{C}_{37}\text{H}_{52}\text{O}_4\text{S}_2\text{Si}$ (653.02): C, 68.05; H, 8.03. Found: C, 68.42; H, 8.31.

4.3.2. 2,3-*O*-Isopropylidene-4-*O*-benzyl-5-*O*-*tert*-butyldiphenylsilyl-aldehyde-*D*-xylose **14**

To a vigorously stirred solution of dithioacetal **13** (0.340 g, 0.52 mmol) in acetone/water (10 mL, 9:1), mercury(II) oxide (0.220 g, 1.03 mmol) and mercury(II) chloride (0.280 g, 1.03 mmol) were added. The contents of the flask were stirred for 2 h under reflux. The resulting mixture was filtered through Celite®, washed with acetone and the solvent was removed on a rotary evaporator. Chloroform (10 mL) was added, the precipitate was collected by filtration and filtrate was extracted with 1 M aqueous potassium iodide (2 $\times$ 10 mL) followed by water (10 mL). The organic layer was dried with sodium sulfate and solvent was evaporated under reduced pressure to give the crude aldehyde as a pale-yellow oil (0.27 g), which was used in the next reaction without further purification.

4.3.3. (*Z*)-*N*-(1-Deoxy-2,3-*O*-isopropylidene-4-*O*-benzyl-5-*O*-*tert*-butyldiphenylsilyl-*D*-xylo-1-ylidene)-benzylamine-*N*-oxide **4c**

To a well-stirred solution of crude aldehyde **14** (4.09 g, 7.89 mmol) in methylene chloride (170 mL), anhydrous magnesium sulfate (4.37 g, 36.3 mmol) and *N*-benzylhydroxylamine (972 mg, 7.89 mmol) were added. The reaction mixture was stirred for 15 h at room temperature and the progress of the reaction was monitored by TLC (hexanes/EtOAc, 70:30). After the removal of magnesium sulfate by filtration, the solvent was evaporated under reduced pressure. The nitrone **4c** was isolated in 93% yield as a colorless oil by column chromatography (silica gel, hexanes/EtOAc, 80:20); R_f (hexanes/EtOAc, 70:30)

0.23; $[\alpha]_D +9.6$ (c 1.57, CH_2Cl_2); ^1H NMR: δ 1.03 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.35, 1.39 ($2\times 3\text{H}$, s, $\text{C}(\text{CH}_3)_2$), 3.82 (2H, d, $J=6.2$ Hz, H-5), 3.91–3.97 (1H, ddd, $J=6.3$, 2.2 Hz, H-4), 4.22 (1H, dd, $J=2.2$, 7.5 Hz, H-3), 4.73 (1H, d, $J=11.7$ Hz, OCH_2Ph), 4.79 (1H, d, $J=11.7$ Hz, OCH_2Ph), 4.88 (2H, s, NCH_2Ph), 5.35 (1H, t, $J=5.9$ Hz, H-2), 6.81 (1H, d, $J=5.7$ Hz, H-1), 7.14–7.70 (20H, m, H-arom); ^{13}C NMR: δ 19.1 ($\text{OSiC}(\text{CH}_3)_3$), 26.5, 26.6 ($\text{C}(\text{CH}_3)_2$), 26.8 ($\text{OSiC}(\text{CH}_3)_3$), 63.8 (C-5), 69.5 (NCH_2Ph), 72.1 (C-2), 73.8 (OCH_2Ph), 78.7 (C-4), 79.7 (C-3), 110.4 ($\text{C}(\text{CH}_3)_2$), 127.2–133.4, 135.5, 135.6 (OSiPh_2 , NCH_2Ph , OCH_2Ph), 137.7 (C-1). Anal. Calcd for $\text{C}_{38}\text{H}_{45}\text{NO}_5\text{Si}$ (623.85): C, 73.16; H, 7.27; N, 2.25. Found: C, 73.53; H, 7.07; N, 2.64.

4.4. 1,3-Dipolar cycloaddition of nitron 4c with vinyl acetate

A mixture of nitron **4c** (4.347 g, 6.97 mmol) and vinyl acetate (25 mL) was stirred for 24 h under reflux. When the starting nitron had been consumed (TLC), the solvent was evaporated under vacuum and the mixture of diastereoisomers in the ratio 83:10:7 in 85% yield was separated by column chromatography (silica gel, hexanes/ CH_2Cl_2 , 90:10).

4.4.1. (3*S*,5*S*)-5-Acetoxy-2-benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butyl-diphenylsilyl-*D*-xylo-1-yl)-isoxazolidine **15**

Yield 74%, colorless oil; ^1H NMR: δ 1.07 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.31, 1.38 ($2\times 3\text{H}$, s, $\text{C}(\text{CH}_3)_2$), 1.78 (3H, s, OCOCH_3), 2.51 (2H, m, H-4), 3.23 (1H, m, H-3), 3.70 (1H, dd, $J=1.5$, 7.9 Hz, H-2'), 3.79 (1H, m, H-3'), 3.88 (3H, m, H-4, NCH_2Ph), 4.00 (1H, d, $J=13.3$ Hz, NCH_2Ph), 4.30 (1H, dd, $J=7.8$ Hz, H-1'), 4.70 (1H, d, $J=11.8$ Hz, OCH_2Ph), 4.89 (1H, d, $J=11.8$ Hz, OCH_2Ph), 6.44 (1H, dd, $J=3.3$ Hz, H-5), 7.16–7.41, 7.66–7.73 (20H, m, H-arom); ^{13}C NMR: δ 19.1 ($\text{OSiC}(\text{CH}_3)_3$), 20.9 (OCOCH_3), 26.6, 27.1 ($\text{C}(\text{CH}_3)_2$), 26.7 ($\text{OSiC}(\text{CH}_3)_3$), 36.8 (C-4), 62.7 (NCH_2Ph), 64.5 (C-4'), 65.0 (C-3), 73.6 (OCH_2Ph), 74.8 (C-1'), 78.3 (C-3'), 79.8 (C-2'), 96.4 (C-5), 108.9 ($\text{C}(\text{CH}_3)_2$), 127.2–133.3 (OSiPh_2 , NCH_2Ph), 135.5–140.1 (OCH_2Ph), 170.1 (CH_3CO); IR (KBr): 2976, 2858, 2930, 1752, 1231, 1115, 701 cm^{-1} . Anal. Calcd for $\text{C}_{42}\text{H}_{51}\text{NO}_7\text{Si}$ (709.94): C, 71.05; H, 7.24; N, 1.97. Found: C, 70.68; H, 7.03; N, 2.35.

4.5. Method B: general procedure for reactions between nucleobases and isoxazolidines **8** and **15**

A suspension of the nucleobase (0.58 mmol) in dry methylene chloride (3 mL) was treated with bis(trimethylsilyl)acetamide (2.32 mmol) and stirred for 20 min at reflux. Isoxazolidine **8** or **15** (0.48 mmol) in dry methylene chloride (3 mL) and TMSOTf (0.72 mmol) were added to the obtained clear solution. The reaction mixture was stirred at room temperature for 2 h. The solution was neutralized by the addition of aqueous 5% sodium bicarbonate. The organic phase was separated, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography using ethyl acetate/hexanes (60:40).

4.5.1. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butyl-diphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-1*H*-pyrimidine-2,4-dione **19a**

Yield 61%, sticky yellow oil; R_f (hexanes/EtOAc, 50:50) 0.37; $[\alpha]_D -60.2$ (c 1.95, CH_2Cl_2); ^1H NMR: δ 1.08 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.31, 1.34 ($2\times 3\text{H}$, s, $\text{C}(\text{CH}_3)_2$), 2.47 (1H, ddd, $J=3.1$, 7.4, 13.4 Hz, H-4a), 2.79 (1H, m, H-4b), 3.04 (1H, m, H-3), 3.48 (1H, m, H-3'), 3.71 (1H, d, $J=14.0$ Hz, NCH_2Ph), 3.86 (4H, m, H-2', H-4', NCH_2Ph), 4.01 (1H, m, H-1'), 4.42 (1H, d, $J=12.0$ Hz, OCH_2Ph), 4.73 (1H, d, $J=12.0$ Hz, OCH_2Ph), 5.59 (1H, d, $J=8.1$ Hz, H-5'), 6.26 (1H, dd, $J=2.9$, 7.7 Hz, H-5), 7.21–7.45 (20H, m, H-arom), 7.91 (1H, d, $J=8.2$ Hz, H-6''), 9.96 (1H, br s, NH); ^{13}C NMR: δ 19.0 ($\text{OSiC}(\text{CH}_3)_3$), 26.6 ($\text{OSiC}(\text{CH}_3)_3$), 26.7 ($\text{C}(\text{CH}_3)_2$), 26.8 ($\text{C}(\text{CH}_3)_2$), 36.6 (C-4), 61.0 (NCH_2Ph), 63.0 (C-4'), 65.6 (C-3), 72.6 (OCH_2Ph), 73.9 (C-1'), 77.3 (C-3'), 78.1 (C-2'), 82.3 (C-5), 101.6 (C-5''), 109.4 ($\text{C}(\text{CH}_3)_2$), 127.5–137.8 (C-arom), 141.3 (C-6''), 150.7 (CO), 163.7 (CO); IR (KBr): 3193, 3067, 2931, 2857, 1687, 1270, 1112, 701 cm^{-1} . Anal. Calcd for $\text{C}_{44}\text{H}_{51}\text{N}_3\text{O}_7\text{Si}$ (761.98): C, 69.36; H, 6.75; N, 5.51. Found: C, 68.98; H, 7.09; N, 5.33.

4.5.2. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butyl-diphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-5-methyl-1*H*-pyrimidine-2,4-(1*H*,3*H*)-dione **19b**

Yield 64%, colorless solid; mp 46–48 °C; R_f (hexanes/EtOAc, 50:50) 0.37; $[\alpha]_D -66.3$ (c 0.75, CH_2Cl_2); ^1H NMR: δ 1.07 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.32, 1.34 ($2\times 3\text{H}$, s, $\text{C}(\text{CH}_3)_2$), 1.83 (3H, s, CH_3), 2.50 (1H, ddd, $J=3.5$, 7.6, 13.6 Hz, H-4a), 2.77 (1H, m, H-4b), 3.02 (1H, m, H-3), 3.47 (1H, m, H-3'), 3.70 (1H, d, $J=14.0$ Hz, NCH_2Ph), 3.85 (4H, m, H-2', H-4', NCH_2Ph), 4.04 (1H, dd, $J=2.1$, 8.7 Hz, H-1'), 4.41 (1H, d, $J=12.0$ Hz, OCH_2Ph), 4.72 (1H, d, $J=12.0$ Hz, OCH_2Ph), 6.24 (1H, dd, $J=3.4$, 7.9 Hz, H-5), 7.13–7.68 (20H, m, H-arom), 7.78 (1H, d, $J=1.8$ Hz, H-6''), 9.02 (1H, br s, NH); ^{13}C NMR: δ 12.3 (CH_3), 19.1 ($\text{OSiC}(\text{CH}_3)_3$), 26.7 ($\text{OSiC}(\text{CH}_3)_3$), 26.8 ($\text{C}(\text{CH}_3)_2$), 27.0 ($\text{C}(\text{CH}_3)_2$), 36.4 (C-4), 60.8 (NCH_2Ph), 63.2 (C-4'), 65.6 (C-3), 72.9 (OCH_2Ph), 74.1 (C-1'), 77.1 (C-3'), 78.3 (C-2'), 82.2 (C-5), 109.5 (C-5''), 109.9 ($\text{C}(\text{CH}_3)_2$), 127.6–137.4 (C-arom), 138.0 (C-6''), 150.7 (CO), 164.3 (CO); IR (KBr): 3193, 3069, 2931, 2857, 1690, 1268, 1113, 701 cm^{-1} . Anal. Calcd for $\text{C}_{45}\text{H}_{53}\text{N}_3\text{O}_7\text{Si}$ (776.00): C, 69.65; H, 6.88; N, 5.41. Found: C, 69.34; H, 7.22; N, 5.22.

4.5.3. 1-[(3*S*,5*S*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butyl-diphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-5-methyl-1*H*-pyrimidine-2,4-(1*H*,3*H*)-dione **20b**

Yield 16%, sticky yellow oil; R_f (hexanes/EtOAc, 50:50) 0.33; $[\alpha]_D -38.4$ (c 0.55, CH_2Cl_2); ^1H NMR: δ 1.06 (9H, s, $\text{OSiC}(\text{CH}_3)_3$), 1.37, 1.40 ($2\times 3\text{H}$, s, $\text{C}(\text{CH}_3)_2$), 1.77 (3H, s, CH_3), 2.35 (1H, m, H-4a), 3.01 (1H, ddd, $J=3.8$, 7.4, 13.4 Hz, H-4b), 3.41 (1H, m, H-3), 3.60 (1H, m, H-3'), 3.88 (4H, m, H-2', H-4', NCH_2Ph), 4.00 (1H, d, $J=13.8$ Hz, NCH_2Ph), 4.19 (1H, m, H-1'), 4.47 (1H, d, $J=11.8$ Hz, OCH_2Ph), 4.75 (1H, d, $J=11.9$ Hz, OCH_2Ph), 5.94 (1H, dd, $J=5.4$, 6.9 Hz, H-5), 7.05 (1H, m, C-6''), 7.23–7.69 (20H, m, H-arom), 9.01 (1H, s, NH); ^{13}C NMR: δ 12.4 (CH_3), 19.2 ($\text{OSiC}(\text{CH}_3)_3$), 26.7

(OSiC(CH₃)₃), 26.8 (C(CH₃)₂), 27.2 (C(CH₃)₂), 36.6 (C-4), 60.7 (NCH₂Ph), 63.5 (C-4'), 64.4 (C-3), 73.1 (OCH₂Ph), 74.0 (C-1'), 77.7 (C-3'), 78.5 (C-2'), 85.1 (C-5), 109.8 (C-5''), 110.1 (C(CH₃)₂), 127.7–136.1 (C-arom), 138.1 (C-6''), 150.1 (CO), 164.0 (CO); IR (KBr): 3191, 3069, 2931, 2857, 1693, 1266, 1112, 701 cm⁻¹. Anal. Calcd for C₄₅H₅₃N₃O₇Si (776.00): C, 69.65; H, 6.88; N, 5.41. Found: C, 69.42; H, 7.11; N, 5.52.

4.5.4. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butylidiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-4-acetylamino pyrimidine-2-one **19d**

Yield 69%, sticky yellow oil; ¹H NMR: δ 1.00 (9H, s, OSiC(CH₃)₃), 1.16, 1.20 (2×3H, s, C(CH₃)₂), 2.15 (3H, s, OCOCH₃), 2.44 (1H, ddd, *J*=13.4, 2.4, 6.9 Hz, H-4a), 2.84 (1H, m, H-4b), 3.00 (1H, m, H-3), 3.39 (1H, m, H-3'), 3.63 (1H, d, *J*=13.9 Hz, NCH₂Ph), 3.77 (4H, m, H-2', H-4', NCH₂Ph), 3.89 (1H, m, H-1'), 4.34 (1H, d, *J*=12.0 Hz, OCH₂Ph), 4.65 (1H, d, *J*=12.0 Hz, OCH₂Ph), 6.07 (1H, dd, *J*=2.3, 7.2 Hz, H-5), 7.16–7.62 (21H, m, H-arom, H-5''), 8.00 (1H, d, *J*=7.5 Hz, H-6''), 10.24 (1H, br s, NH); ¹³C NMR: δ 19.1 (OSiC(CH₃)₃), 24.7 (OCOCH₃), 26.6, 26.8, 26.9 (OSiC(CH₃)₃, C(CH₃)₂), 37.8 (C-4), 61.5 (NCH₂Ph), 63.0 (C-4'), 65.8 (C-3), 72.7 (OCH₂Ph), 74.1 (C-1'), 77.2 (C-3'), 78.0 (C-2'), 84.6 (C-5), 95.9 (C-5''), 109.4 (C(CH₃)₂), 127.6–138.6 (C-arom), 145.7 (C-6''), 155.4 (CO), 162.7 (C-4''), 171.1 (CO); IR (KBr): 3069, 2958, 2931, 2857, 1717, 1240, 1112, 701 cm⁻¹. Anal. Calcd for C₄₆H₅₄N₄O₇Si (803.03): C, 68.80; H, 6.78; N, 6.98. Found: C, 68.59; H, 6.99; N, 7.25.

4.5.5. 1-[(3*S*,5*R*)-2-Benzyl-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-4-*O*-tert-butylidiphenylsilyl-*D*-xylo)isoxazolidine-5-yl]-2-acetylguanine **19e**

Yield 15%, sticky yellow oil; *R*_f(EtOAc) 0.33; [α]_D –107.6 (c 0.23, CH₂Cl₂); ¹H NMR: δ 1.07 (9H, s, OSiC(CH₃)₃), 1.22 (6H, s, C(CH₃)₂), 2.34 (3H, s, OCOCH₃), 2.75 (1H, ddd, *J*=1.8, 7.0, 13.5 Hz, H-4a), 2.93 (1H, m, H-4b), 3.04 (1H, m, H-3), 3.46 (1H, m, H-3'), 3.75 (1H, d, *J*=14.2 Hz, NCH₂Ph), 3.85 (4H, m, H-2', H-4', NCH₂Ph), 3.99 (1H, dd, *J*=1.1, 8.6 Hz, H-1'), 4.42 (1H, d, *J*=12.0 Hz, OCH₂Ph), 4.72 (1H, d, *J*=12.0 Hz, OCH₂Ph), 6.81 (1H, dd, *J*=1.6, 7.8 Hz, H-5), 7.20–7.69 (20H, m, H-arom), 8.55 (1H, s, H-8''), 11.14 (1H, br s, NH), 12.28 (1H, br s, NHCO); ¹³C NMR: δ 19.1 (OSiC(CH₃)₃), 24.5 (OCOCH₃), 26.7, 26.8, 26.9 (OSiC(CH₃)₃, C(CH₃)₂), 37.7 (C-4), 60.5 (NCH₂Ph), 63.1 (C-4'), 65.7 (C-3), 72.8 (OCH₂Ph), 73.7 (C-1'), 77.2 (C-3'), 78.3 (C-2'), 82.8 (C-5), 109.7 (C(CH₃)₂), 111.3 (C-5''), 127.5–136.2 (C-arom), 143.1 (C-8''), 147.8, 153.2, 156.2 (C-2'', C-4'', C-6''), 173.1 (CO); IR (KBr): 3133, 3069, 2932, 2857, 1684, 1615, 1370, 1252, 1113, 701 cm⁻¹. Anal. Calcd for C₄₇H₅₄N₆O₇Si (843.05): C, 66.96; H, 6.46; N, 9.97. Found: C, 66.59; H, 6.73; N, 9.59.

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