Abstract: The synthesis of isoxazolidinyl nucleosides based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines 5 and 9 is reported. The 1,3-dipolar cycloaddition of D-erythro-nitrone 4 with vinyl acetate proceeded with respectable anti-facial (84:16) and endo-facial (72:28) diastereoselectivity to give the diastereomeric isoxazolidines 5–7. The reaction of D-threo-nitrone 8 with vinyl acetate is more selective and proceeds with excellent anti-facial preference producing only two diastereomers 9 and 10, although four diastereomers are possible. The condensation of the acetoxyisoxazolidines 5 and 9 with silylated uracil, thymine, N-acetylcysteine, N’-acetylguanine, and purines proceeded with moderate to excellent stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition of silylated nucleobase is dependent on the structure of the substituent at C3 originating from the starting chiral nitronate and on the attacking nucleobase.

Key words: nucleosides, isoxazolidines, cycloadditions, C-glycosyl nitrones, stereoselective synthesis

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. Many nucleoside analogues have been synthesized with modifications of the base, sugar, and phosphate 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 In particular, nucleoside analogues in which the furanose ring has been replaced by different carbon or heterocyclic systems have attracted special interest by virtue of their biological action as antiviral and/or anticancer agents. Among them, nucleosides 1 (B = uracil, thymine, cytosine, adenine) possessing an isoxazolidinyl moiety (carbocyclic-2’-oxo-3’-azanucleosides) are emerging as an interesting class of dideoxynucleoside analogues with potential pharmacological activity. For the synthesis of modified isoxazolidinyl nucleosides 1, two strategies can be used. In particular a one-step approach based on the 1,3-dipolar cycloaddition of nitrones to vinyl nucleobases and a two-step methodology based on the Vorbrüggen nucleosidation of 5-acetoxyisoxazolidines. Recently, with the aim of preparing some novel azanucleosides by the transformation of modified isoxazolidinyl nucleosides 2 and 3, we have prepared the appropriate sugar-derived nitronate possessing structures suitable for building the pyrrolidine. The condensation of the acetoxyisoxazolidines prepared from D-xylene and D-lyxose with silylated uracil, thymine, cytosine, N-acetylcysteine, and acetylguanine proceeded with good yields and moderate to good stereoselectivity with formation of the isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition was dependent on the structure of the substituent at C3 in the starting chiral nitronate. We have also found that the cycloaddition of methyl acrylate with D-erythro-nitrones 4 and D-threo-nitrones 8 possessing the sterically demanding O-tert-butyldimethylsilyl group prepared from D-glucose and D-galactose, respectively, proceeds with excellent anti- and endo-facial selectivity. Continuing in our efforts to utilize chiral 1,3-dipolar cycloadditions, we have now extended the 1,3-dipolar cycloaddition approach to the synthesis of novel 4’-aza-2’,3’-dideoxfuranosyl nucleosides 11–14 by reaction of readily available chiral sugar D-erythrose and D-threose derived nitrones 4 and 8 to vinyl acetate with subsequent transformation of the thus formed 5-acetoxyisoxazolidines (Figure 1).

Figure 1  Isoxazolidinyl nucleosides

D-erythro-Nitronate 4 reacted smoothly in refluxing vinyl acetate over 20 hours to give a 56:28:16 mixture of diastereomeric isoxazolidines 5–7 in 78% yield (Scheme 1). The cycloaddition proceeded with very good anti-facial (84:16) and endo-facial (72:28) diastereoselectivity and is completely regioselective with only the sterically favored 5-substituted isoxazolidines being detected. It is worthy of note that in case the reaction, probably for steric rea-
sons, proceeded with reversed diastereoselectivity as expected for an inverse demand cycloaddition reaction where the corresponding 3,5-cis-adducts are the major products. Purification by HPLC provided a first fraction containing pure 6 and a second fraction containing a 93:7 mixture of isoxazolidines 5 and 6. The major compound 5 could be isolated by crystallization from hexane. The trans-anti structure of 5 was established unambiguously by X-ray diffraction studies (Figure 2). This allowed us to propose the structures shown in Scheme 1 for diastereomeric isoxazolidines 6 and 7. The 3,5-cis relative configuration of 6 was confirmed by the observation of the NOEs in the 2D-NOESY 1H NMR spectra of this compound. Such NOEs were not observed for 7, therefore, the isolated isoxazolidine 7 possessed the trans-syn configuration.

On the other hand, the reaction of D-threo-nitrone 8 with vinyl acetate proceeded diastereoselectively and gave only two diastereomers 9 and 10 in a 84:16 ratio with 9, which has the anti-cis structure, predominating although four diastereomers are possible, showing now a preference for exo-attack as expected for an inverse demand cycloaddition reaction (Scheme 2). Moreover, in this case excellent anti-diastereofacial induction was observed; the corresponding syn-adducts were not detected in the reaction mixture. Thus, the corresponding adducts 9 and 10 were separated by preparative HPLC and completely characterized. The relative configuration of the cycloadducts obtained was ascertained by conventional NMR techniques including 2D NOESY, COSY, and HMBC experiments. The structure of the minor trans-anti-isoxazolidine 10 was established unambiguously by X-ray diffraction studies (Figure 3). Based on our previous results from the 1,3-dipolar cycloaddition of sugar nitrones bearing a protected hydroxy group in the α-position as well as the fact that 1,3-dipolar cycloaddition of electron-rich alkenes to chiral α-alkoxy nitrones gave preferentially anti-adducts and by comparison with the aforementioned results of the cycloaddition of nitrone 4 with vinyl acetate, we assigned a C1′/C3′ anti-relationship to major isomer 9, resulting from dipolarophile attack from the less sterically hindered si diastereotopic face of nitrone 8. Thus, the observed excellent facial diastereoselectivity for the D-galactose-derived nitrone 8 is in contrast to the previously results obtained for nitrene cycloaddition to vinyl acetate.

Next the major isoxazolidines 5 and 9 were coupled with silylated nucleobases according to the Vorbrüggen method. Following extensive screening, the best reaction conditions for the Vorbrüggen nucleosidation of acetoxy-
substituted isoxazolidines prepared from sugar-derived nitrones were found by us to be at room temperature in dichloromethane. The nucleosidation of anti-trans-isoxazolidine 5 with silylated uracil, thymine, and N-acetylcytosine at room temperature in dichloromethane in the presence of trimethylsilyl triflate as catalyst, afforded the β-anomeric nucleosides 11a–c in moderate yields (65–66%), but with excellent diastereoselectivities (ratio 11a/12a = 92:8, 11b/12b = 90:10, 11c/12c = 94:6; Scheme 3), whereas the reaction with N2-acetylguaanine gave a lower yield (36%) and the diastereoselectivity was only moderate (11d/12d = 69:31). The ratio of anomeric nucleosides was determined from quantitative 13C NMR spectra, by integration of the peaks from C4 and C5 of the isoxazolidines. Purification by flash chromatography allowed the isolation of pure nucleosides 11a–d; their assigned stereochemistry is supported by NMR analysis. In fact, NOE measurements performed on β-anomers 11a–d show a positive NOE effect for protons H3 when irradiating H5 thus indicating a cis relationship between these protons.

The Vorbrüggen nucleosidation of anti-cis-isoxazolidine 9 with silylated uracil, thymine, N-acetylcysotone, N2-acetylguaanine, and 6-chloro- and 6-bromopurine at room temperature in dichloromethane in the presence of trimethylsilyl triflate as catalyst, proceeded with low purines to good (uracil, thymine, and N-acetylcytosine) yields and from moderate to good stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides 13 and 14 (ratio 13a/14a = 91:9, 13b/14b = 73:27, 13c/14c = 87:13, 13d/14d = 52:48, 13e/14e = 70:30, 13f/14f = 66:34, Scheme 4). For uracil and N-acetyl-cytosine, the β-anomers 13 clearly predominate, while in the case of N2-acetylguaanine and purines a significant amount of α-anomer 14 was obtained. This lower diastereoselectivity is in contrast with the excellent diastereoselectivity observed for 5, but these results are fully in accord with the data obtained for the related Vorbrüggen nucleosidations.3,4,9 Purification by flash chromatography allowed the isolation not only of all β-nucleosides 13a–f, but also the three α-nucleosides 14b,14e,f were obtained. The assigned configuration is supported by NMR analysis.

In conclusion, the synthesis of isoxazolidinyl nucleosides, as potential antiviral agents, based on the Vorbrüggen nucleosidation of the 5-acetoxyisoxazolidines 5 and 9 is reported. The 1,3-dipolar cycloaddition of d-erythro-nitrore 4 with vinyl acetate proceeded with respectable anti-facial (84:16) and endo-facial (72:28) diastereoselectivity to give the diastereomeric isoxazolidines 5–7. The reaction of d-threo-nitrore 8 to vinyl acetate is more selective and proceeds with an excellent anti-facial preference producing only two diastereomers 9 and 10, although four diastereomers are possible. The condensation of the acetoxyisoxazolidines 5 and 9 with silylated uracil, thymine, N-acetylcysteine, N2-acetylguaanine, and purines proceeded with moderate to excellent stereoselectivity with formation of the expected isoxazolidinyl β- and α-nucleosides. The stereoselectivity of the addition of silylated nucleobase, is dependent on the structure of the substituent at C3 originated from the starting chiral nitrore and on the attacking nucleobase.

Scheme 3 Nucleosidation of anti-trans-isoxazolidine 5

Scheme 4 Nucleosidation of anti-cis-isoxazolidine 9
All commercially available starting materials and reagents (Fluka, Merck, Across or Aldrich) were used without further purification. Solvents were dried before use. TLC (Alugram Sil G/UV_254 Macherey-Nagel) was used for 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 CDCl3 solns were obtained using Varian Inova-600 (600 MHz), VXR-300 (300 MHz) and Bruker AC 500 (500 MHz) instruments; TMS was the internal reference. Specific rotations [α] were measured on an IBZ Messstechnik Polar-Lüp polarimeter at the Na D line (589 nm) using a 1 dm cell. HPLC analyses were performed on preparative column (diameter 32, length 237 mm) with nucleosil 50-5. Elemental analyses were conducted using the Fisons EA 1108 Analyzer. Nitrone 4 and 8 were prepared from the corresponding aldehydes by the reaction with N-benzyldihydroxylamine according to the procedure already described. 1,3-Dipolar Cycloaddition of 2-ethylthio-Nitron 4 with Vinyl Acetate; General Procedure

A mixture of the nitron 4 (1.040 g, 2.85 mmol) and vinyl acetate (25 mL) was stirred for 24 h under reflux. When starting nitron had been consumed (TLC), solvent was evaporated under vacuum to give a 56:28:16 mixture of diastereomeric isoxazolidines –7 in 78% yield. The mixture of diastereomers was separated by preparative HPLC (hexane–EtOAc, 85:15).

(3S,5S)-5-Acetoxy-2-ethyl-3-[(2R,4S,5R)-5-(tert-butyldimethylsilyloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (7)

Colorless solid; yield: 272 mg (18%); mp 77–79 °C.

H NMR (600 MHz, CDCl3): δ = 7.40–7.25 (m, 5 H, C6H5), 6.28 (dd, J = 2.5, 6.6 Hz, 1 H, H3), 4.62 (q, J = 4.9 Hz, 1 H, H2), 4.23 (d, J = 14.3 Hz, 1 H, NCH2CH3), 4.00 (m, 1 H, H4b), 3.98 (d, J = 14.3 Hz, 1 H, NCH2CH3, 3.41 (m, 2 H, H6, H5′), 3.29 (m, 1 H, H4a), 3.24 (m, 1 H, H3), 2.72 (dd, J = 2.6, 8.8, 13.2 Hz, 1 H, H4b), 2.52 (dd, J = 6.8, 9.1, 13.5 Hz, 1 H, H4a), 2.07 (s, 3 H, COCH3), 1.36 (d, J = 4.9 Hz, 3 H, CH3), 0.87 [s, 9 H, OSI(CHOH)3], 0.05, 0.03 [2 x s, 2 x 3 H, OSI(CHOH)3].

13C NMR (125.5 MHz, CDCl3): δ = 170.8 (CO), 135.7, 129.8, 128.1, 127.4 (C6H5), 98.8 (C2′), 95.3 (C5′), 77.9 (C6′), 71.3 (C4′), 64.5 (C5′), 63.9 (C3), 60.7 (NCH2CH3), 36.1 (C4), 25.6 [OSi(C(CH3)3)], 21.3 (COCH3), 20.4 (CH3CHOH), 17.8 [OSi(CH3)3], –4.2, –4.8 [OSi(CH3)3].


1,3-Dipolar Cycloaddition of 2-ethylthio-Nitron 8 with Vinyl Acetate

A mixture of the nitron 8 (1.706 g, 4.67 mmol) and vinyl acetate (25 mL) was stirred for 24 h under reflux. When starting nitron had been consumed (TLC), solvent was evaporated under vacuum to give 84:16 mixture of diastereomeric isoxazolidines 9 and 10 in 68% yield. The mixture of diastereomers was separated by preparative HPLC (hexane–EtOAc, 88:12).

(3R,5S)-5-Acetoxy-2-ethyl-3-[(2S,4R,5R)-5-(tert-butyldimethylsilyloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (9)

Colorless oil; yield: 1.254 g (59%).

[α]D = +81.3 (c 0.16, CH2Cl2).

H NMR (600 MHz, CDCl3): δ = 7.36–7.26 (m, 5 H, C6H5), 6.41 (d, J = 5.8 Hz, 1 H, H5), 4.72 (q, J = 5.1 Hz, 1 H, H2), 4.11 (m, 1 H, H4b), 4.08 (d, J = 14.1 Hz, 1 H, NCH2CH3), 3.94 (m, 1 H, H5′), 3.90 (d, J = 14.1 Hz, 1 H, NCH2CH3), 3.76 (m, 1 H, H4a), 3.71 (m, 1 H, H6′), 3.63 (m, 1 H, H3), 2.54 (dd, J = 1.3, 14.1 Hz, 1 H, H4b), 2.25 (dd, J = 6.1, 8.1, 14.1 Hz, 1 H, H4a), 2.01 (s, 3 H, COCH3), 1.36 (d, J = 4.5 Hz, 3 H, CH3), 0.96 [s, 9 H, OSI(CHOH)3], 0.17, 0.11 [2 x s, 2 x 3 H, OSI(CHOH)3].

13C NMR (125.5 MHz, CDCl3): δ = 169.8 (CO), 136.5, 129.3, 128.4, 127.6 (C6H5), 99.1 (C2′), 97.2 (C5′), 78.7 (C6′), 71.3 (C4′), 64.6 (C5′), 63.1 (NCH2CH3), 62.2 (C3), 35.8 (C4), 26.0 [OSi(C(CH3)3)], 21.3 (COCH3), 21.0 (CH3CHOH), 18.4 [OSi(CH3)3], –3.8, –3.9 [OSi(CH3)3].


(3R,5R)-5-Acetoxy-2-ethyl-3-[(2S,4R,5R)-5-(tert-butyldimethylsilyloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidine (10)

Colorless solid; yield: 189 mg (9%); mp 59–60 °C.

[α]D = –23 (c 0.10, CH2Cl2).

H NMR (600 MHz, CDCl3): δ = 7.38–7.26 (m, 5 H, C6H5), 6.40 (dd, J = 2.6, 6.4 Hz, 1 H, H5), 4.70 (q, J = 5.1 Hz, 1 H, H2), 4.30 (d, J = 13.5 Hz, 1 H, NCH2CH3), 4.06 (dd, J = 1.8, 12.3 Hz, 1 H, H4b), 3.99 (d, J = 13.5 Hz, 1 H, NCH2CH3), 3.87 (m, 1 H, H5′), 3.75 (m, 1 H, H3), 3.72 (dd, J = 1.2, 12.3 Hz, 1 H, H4a), 3.41 (dd, J = 1.3, 9.0 Hz, 1 H, H6′), 2.87 (dd, J = 3.9, 6.4, 10.3 Hz, 1 H, H4b), 2.62 (dd, J = 2.6, 7.7, 10.3 Hz, 1 H, H4a), 2.08 (s, 3 H, COCH3), 1.35 (d, J = 5.1 Hz, 3 H, CH3), 0.93 [s, 9 H, OSI(CHOH)3], 0.15, 0.08 [2 x s, 2 x 3 H, OSI(CHOH)3].

13C NMR (125.5 MHz, CDCl3): δ = 169.7 (CO), 137.3, 128.6, 128.2, 127.2 (C6H5), 99.1 (C2′), 98.9 (C5′), 79.5 (C6′), 71.1 (C4′),
Nucleosidation of Acetoxylisoxazolines; General Procedure
A suspension of the corresponding nucleoside (0.58 mmol) in anhyd CH2Cl2 (3 mL) was treated with NaO-bis(trimethylsilyl)acetamide (2.32 mmol) and stirred for 20 min at reflux. Isoxazolidine 5 or 9 (0.48 mmol) in anhyd CH2Cl2 (3 mL) and TMSOTf (0.72 mmol) were added to the obtained clear solution. The mixture was stirred for 2 h. The solution was neutralized by addition of 5% NaHCO3. The organic phase was separated, washed with H2O, dried (Na2SO4), filtered, and evaporated to dryness. The residue was purified by column chromatography (silica gel).

1-[(3S,5R)-2-Benzyl-3-[(2R,4S,5R)-5-(tert-butylidimethylsilyloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl]pyrimidine-2,4(1H,3H)-dione (11a)
According to the general procedure, the mixture from isoxazolidine 5 (0.34 mmol) and uracil (0.41 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give 11a (0.112 g, 65%) as a colorless solid; mp 71–73 ºC.

1H NMR (600 MHz, CDCl3): δ = 9.05 (br s, 1 H, NH), 8.10 (d, J = 8.2 Hz, 1 H, H6b), 7.34–7.28 (m, 5 H, C6H5), 6.27 (dd, J = 2.6, 7.9 Hz, 1 H, H5), 5.60 (dd, J = 1.8, 8.2 Hz, 1 H, H5a), 4.62 (q, J = 5.0 Hz, 1 H, H2a), 4.16 (d, J = 13.5 Hz, 1 H, NCH2CH2Cl), 3.99 (m, 1 H, H4a), 3.98 (d, J = 14.1 Hz, 1 H, NCH2CH2Cl), 3.37 (m, 3 H, H5′, H6′, H5), 3.28 (m, 1 H, H4b), 2.80 (dd, J = 7.6, 10.3, 13.5 Hz, 1 H, H4a), 2.70 (dd, J = 2.9, 7.2, 13.5 Hz, 1 H, H4b), 2.24 (s, 3 H, CO2), 2.08 (dd, J = 4.7 Hz, 3 H, CH3), 1.87 [s, 9 H, OSi(CH3)2], 0.06, 0.05 [2 × s, 2 × 3 H, OSi(CH3)2].

13C NMR (125.5 MHz, CDCl3): δ = 163.6 (CO), 150.7 (C0), 142.3 (C6′), 136.1–127.7 (C4′), 101.0 (C5), 98.5 (C2′), 82.8 (C5), 78.7 (C6′), 71.1 (C4′), 64.2 (C5′), 64.1 (C′1), 61.2 (NCH2CH2Cl), 36.0 (C5′), 24.5 (OSi(CH3)2), 20.2 (CH2Cl), 17.7 [OSi(CH3)2], –4.2, –5.0 [OSi(CH3)2].


2-(Acetylamino)-1-{[(3S,5R)-2-Benzyl-3-[(2R,4S,5R)-5-(tert-butylidimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl]pyrimidine-2,4(1H,3H)-dione (11b)
According to the general procedure, the mixture from isoxazolidine 5 (0.22 mmol) and N-acetylcysteine (0.27 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 15:85) to give 11b (0.080 g, 66%) as a colorless solid; mp 49–50 ºC.

4-(Acetamido)-1-[(3S,5R)-2-benzyl-3-[(2R,4S,5R)-5-(tert-butylidimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl]pyrimidine-2,4(1H,3H)-dione (11c)
According to the general procedure, the mixture from isoxazolidine 5 (0.22 mmol) and N-acetylcysteine (0.27 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 15:85) to give 11c (0.080 g, 66%) as a colorless solid; mp 49–50 ºC.

N-(Acetamino)-1-[(3S,5R)-2-Benzyl-3-[(2R,4S,5R)-5-(tert-butylidimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl]guanine (11d)
According to the general procedure, the mixture from isoxazolidine 5 (0.18 mmol) and N-acetylglycine (0.22 mmol) was purified by column chromatography (silica gel, CH2Cl2–MeOH, 7:3) to give 11d (0.032 g, 30%) as a colorless solid; mp 173–175 ºC.

1H NMR (600 MHz, CDCl3): δ = 12.31 (br s, 1 H, NH), 11.22 (br s, 1 H, NHC, 8.5 (s, 1 H, H8′), 7.40–7.26 (m, 5 H, C6H5), 6.78 (d, J = 2.9, 6.6 Hz, 1 H, H5), 4.97 (d, J = 14.7 Hz, 1 H, NCH2CH2Cl), 4.02 (d, J = 13.9 Hz, 1 H, NCH2CH2Cl), 3.98 (m, 1 H, H4a), 3.33 (m, 4 H, H5′, H6′, H4b), 2.94 (m, 2 H, H4a,b), 2.37 (s, 3 H, COCH3), 1.23 (d, J = 5.1 Hz, 3 H, CH3), 0.89 [s, 9 H, OSi(CH3)2], 0.08, 0.05 [2 × s, 2 × 3 H, OSi(CH3)2].

13C NMR (125.5 MHz, CDCl3): δ = 171.0 (CO), 162.5 (CO), 154.4 (CO), 146.6 (C6′), 136.2–127.8 (C4′), 98.5 (C2′), 95.5 (C5′), 85.1 (C5), 78.7 (C6′), 71.1 (C4′), 64.2 (C5′), 64.1 (C′1), 61.6 (NCH2CH2Cl), 36.8 (C4′), 25.6 [OSi(CH3)2], 24.8 (COCH3), 20.1 (CH2Cl), 17.8 [OSi(CH3)2], –4.1, –4.9 [OSi(CH3)2].


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13b

\[ [\text{u}_{\text{H}}]_{b}^{+} 85 \text{ (c. 0.1, CHCl}_{3}). \]

1H NMR (600 MHz, CDCl\(_3\)): \( \delta = 9.75 \) (br s, 1 H, NH), 7.76 (d, \( J = 1.2 \text{ Hz}, 1 \text{ H, H}^6\)), 7.34–7.28 (m, 5 H, C\(_6\)H\(_5\)), 6.32 (dd, \( J = 3.5, 7.6 \text{ Hz}, 1 \text{ H, H}^5\)), 4.70 (q, \( J = 5.0 \text{ Hz}, 1 \text{ H, H}^2\)), 4.13 (d, \( J = 14.1 \text{ Hz}, 1 \text{ H, NCH}_{2}C\(_6\)H\(_5\)\)), 4.00 (d, \( J = 14.1 \text{ Hz}, 1 \text{ H, NCH}_{2}C\(_6\)H\(_5\)\)), 3.98 (m, 1 H, H\(_4a\)), 3.75 (m, 1 H, H\(_4b\)), 3.63 (m, 1 H, H\(_5\)), 3.56 (m, 1 H, H\(_6\)), 3.14 (dd, \( J = 3.5, 6.7, 9.4 \text{ Hz}, 1 \text{ H, H}^3\)), 2.94–2.75 (m, 2 H, H\(_4a,b\)), 1.89 (d, \( J = 1.2 \text{ Hz}, 3 \text{ H, CH}_3\)), 1.34 (d, \( J = 5.3 \text{ Hz}, 3 \text{ H, CH}_3\)), 0.93 [s, 9 H, OSi(CH\(_3\))\(_3\)], 0.11, 0.08 [2 \times 2, 2 \times 3 \text{ H, OSi(CH\(_3\))}_2].

13C NMR (125.5 MHz, CDCl\(_3\)): \( \delta = 164.2 \) (CO), 150.9 (CO), 137.3 (C\(_6\))\(_6\)), 136.5, 138.5, 128.3 (C\(_6\)), 109.6 (C\(_5\)), 98.8 (C\(_2\)), 82.5 (C\(_5\)), 77.9 (C\(_4\)), 71.4 (C\(_4\)), 66.5 (C\(_3\)), 65.8 (C\(_5\)), 61.3 (NCH\(_2C\(_6\)H\(_5\))\(_3\)), 37.0 (C\(_4\)), 25.8 [OSi(CH\(_3\))]\(_2\), 20.8 (CH\(_2\)), 18.0 [OSi(CH\(_3\))]\(_2\), 12.4 (CH\(_3\)), –4.3, –4.4 [OSi(CH\(_3\))]\(_2\).

Anal. Caled for C\(_{26}H\(_{39}\)N\(_3\)O\(_6\)Si (517.7): C, 60.32; H, 7.59; N, 8.12. Found: C, 59.67; H, 7.71; N, 8.22.

14b

\[ [\text{u}_{\text{H}}]_{b}^{+} 34.5 \text{ (c. 0.1, CHCl}_{3}). \]

1H NMR (600 MHz, CDCl\(_3\)): \( \delta = 9.37 \) (br s, 1 H, NH), 7.40–7.30 (m, 5 H, C\(_6\)H\(_5\)), 7.06 (d, \( J = 1.2 \text{ Hz}, 1 \text{ H, H}^6\)), 5.96 (dd, \( J = 6.8, 6.7 \text{ Hz}, 1 \text{ H, H}^1\)), 4.77 (q, \( J = 5.0 \text{ Hz}, 1 \text{ H, H}^2\)), 4.16 (d, \( J = 14.6 \text{ Hz}, 1 \text{ H, NCH}_{2}C\(_6\)H\(_5\)\)), 4.08 (d, \( J = 1.6, 12.1 \text{ Hz}, 1 \text{ H, H}^4\)), 4.07 (d, \( J = 14.6 \text{ Hz}, 1 \text{ H, NCH}_{2}C\(_6\)H\(_5\)\)), 3.85 (m, 1 H, H\(_5\)), 3.80 (dd, \( J = 12.4, 12.4 \text{ Hz}, 1 \text{ H, H}^4\)), 3.70 (m, 2 H, H\(_6\)), 3.28 (dd, \( J = 2.4, 7.1, 14.0 \text{ Hz}, 1 \text{ H, H}^4\)), 2.47 (m, 2 H, H\(_4b\)), 1.76 (d, \( J = 1 \text{ Hz}, 3 \text{ H, CH}_3\)), 1.38 (d, \( J = 5.0 \text{ Hz}, 3 \text{ H, CH}_3\)), 0.92 [s, 9 H, OSi(CH\(_3\))\(_3\)], 0.14, 0.05 [2 \times 2, 2 \times 3 \text{ H, OSi(CH\(_3\))}_2].

13C NMR (125.5 MHz, CDCl\(_3\)): \( \delta = 164.0 \) (CO), 150.3 (CO), 136.4 (C\(_6\)), 135.6, 128.6, 128.3, 127.7 (C\(_6\)), 110.1 (C\(_5\)), 99.1 (C\(_2\)), 86.5 (C\(_5\)), 77.5 (C\(_4\)), 71.3 (C\(_4\)), 64.9 (C\(_3\)), 64.8 (C\(_5\)), 61.4 (NCH\(_2C\(_6\)H\(_5\))\(_3\)), 36.6 (C\(_4\)), 25.8 [OSi(CH\(_3\))]\(_2\), 20.8 (CH\(_2\)), 18.2 [OSi(CH\(_3\))]\(_2\), 12.3 (CH\(_3\)), –4.1, –4.3 [OSi(CH\(_3\))]\(_2\).

13C NMR (125.5 MHz, CDCl3): δ = 173.2 (CO), 156.4, 153.2, 147.9, 142.8 (C$_{amine}$), 136.4–127.6 (C$_{H}$), 111.4 (C$_{amine}$), 98.8 (C$^\beta$), 83.5 (C$_5$), 77.7 (C$^6$), 71.5 (C$^4$), 66.8 (C$_3$), 65.9 (C$^5$), 61.3 (NCH$_2$C$_6$H$_5$), 38.3 (C$_3$), 25.8 [OSi(CH$_3$)$_2$], 20.7 (CH$_3$CH$_2$), 18.1 [OSi(CH$_3$)$_2$] -4.3, -4.4 [OSi(CH$_3$)$_2$].

Calcd: for C$_9$H$_6$NO$_3$Si (584.7): C, 57.51; H, 6.89; N, 14.37. Found: C, 57.61; H, 7.12; N, 14.04.

1-({(3R,5S)-2-Benzyl-3-[(2S,4R,5R)-5-(retch-butylidimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-chloropurine (13e) and 1-({(3S,5R)-2-Benzyl-3-[(2S,4R,5R)-5-(retch-butylidimethylsiloxy)-2-methyl-1,3-dioxan-4-yl]isoxazolidin-5-yl}-4-chloropurine (14e)

According to the general procedure, the mixture from isoxazolidine 9 (0.66 mmol) and 6-bromopurine (0.18 mmol) was purified by column chromatography (silica gel, hexanes–EtOAc, 50:50) to give 13e (0.100 g, 28%) as a colorless oil and 14e (0.046 g, 13%) as a colorless oil.

13e

[α]$_D$ +103 (c 0.1 CH$_2$Cl$_2$).

1H NMR (600 MHz, CDCl$_3$): δ = 8.97 (s, 1 H, H$^2a$), 8.71 (s, 1 H, H$^8$), 7.30–7.25 (m, 5 H, C$_6$H$_5$), 6.57 (dd, J = 1.8, 7.6 Hz, 1 H, H$_5$), 4.68 (q, J = 5.1 Hz, 1 H, H$^2$), 4.19 (d, J = 14.1 Hz, 1 H, NCH$_2$C$_6$H$_5$), 4.09 (d, J = 14.1 Hz, 1 H, NCH$_2$C$_6$H$_5$), 3.98 (dd, J = 1.8, 12.3 Hz, 1 H, H$_4b$), 3.72 (dd, J = 1.2, 12.3 Hz, 1 H, H$_4b$), 3.69 (m, 1 H, H$_5$), 3.53 (m, 1 H, H$^6$), 3.24 (dd, J = 2.1, 5.6, 7.6 Hz, 1 H, H$_3$), 3.11 (dd, J = 1.8, 9.7, 14.1 Hz, 1 H, H$_4a$), 3.00 (m, 1 H, H$_4b$), 1.33 (d, J = 5.3 Hz, 3 H, CH$_3$), 0.92 [s, 9 H, OSi(CH$_3$)$_2$], 0.11, 0.10 [2 × s, 2 × 3 H, OSi(CH$_3$)$_2$].

1C NMR (125.5 MHz, CDCl$_3$): δ = 151.8, 151.7 (C$^4$, C$^6$), 150.6 (C$^2$), 145.7 (C$^8$), 136.4, 128.6, 128.5, 127.8 (C$_{H}$, C$^5$), 99.0 (C$^2$), 80.9 (C$_5$), 77.6 (C$^7$), 71.8 (C$^4$), 67.7 (C$_3$), 66.4 (C$^5$), 61.2 (NCH$_2$C$_6$H$_5$), 37.7 (C$_3$), 26.0 [OSi(CH$_3$)$_2$], 20.9 (CH$_3$CH$_2$), 18.3 [OSi(CH$_3$)$_2$] -4.1, -4.3 [OSi(CH$_3$)$_2$].

Calcd. for C$_{25}$H$_{23}$SIN$_2$O$_5$Si (546.1): C, 57.18; H, 6.64; N, 12.82; Found: C, 57.44; H, 7.06; N, 12.61.

14e

[α]$_D$ +24 (c 0.1, CH$_2$Cl$_2$).

1H NMR (600 MHz, CDCl$_3$): δ = 8.78 (s, 1 H, H$^2a$), 8.16 (s, 1 H, H$^8$), 7.30–7.21 (m, 5 H, C$_6$H$_5$), 6.32 (dd, J = 6.6, 6.7 Hz, 1 H, H$_5$), 4.80 (q, J = 5.1 Hz, 1 H, H$^2$), 4.23 (d, J = 14.1 Hz, 1 H, NCH$_2$C$_6$H$_5$), 4.11 (d, J = 14.1 Hz, 1 H, NCH$_2$C$_6$H$_5$), 4.10 (dd, J = 1.2, 12.3 Hz, 1 H, H$_4a$), 3.93 (m, 1 H, H$_3$), 3.84 (m, 1 H, H$_5$), 3.80 (m, 1 H, H$^4b$), 3.70 (m, 1 H, H$^6$), 3.38 (m, 2 H, H$_4a$b), 1.41 (d, J = 4.7 Hz, 3 H, CH$_3$), 0.92 [s, 9 H, OSi(CH$_3$)$_2$], 0.15, 0.06 [2 × s, 2 × 3 H, OSi(CH$_3$)$_2$].

1C NMR (125.5 MHz, CDCl$_3$): δ = 151.9, 151.3 (C$^4$, C$^6$), 151.0 (C$^2$), 146.4 (C$^8$), 132.4, 128.5, 124.7, 127.7 (C$_{H}$, C$^5$), 99.2 (C$^2$), 86.2 (C$_5$), 78.5 (C$^7$), 71.3 (C$^4$), 65.3 (C$_3$), 64.9 (C$^5$), 62.4 (NCH$_2$C$_6$H$_5$), 35.1 (C$_3$), 25.8 [OSi(CH$_3$)$_2$], 20.9 (CH$_3$CH$_2$), 18.2 [OSi(CH$_3$)$_2$] -4.1, -4.3 [OSi(CH$_3$)$_2$].

Calcd. for C$_{29}$H$_{29}$SIN$_2$O$_5$Si (561.6): C, 57.18; H, 6.64; N, 12.82; Found: C, 57.29; H, 6.87; N, 12.72.

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