Asymmetric Synthesis of 4′-*epi*-Trachycladines A and B

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Dedicated to Professor Steven Ley on the occasion of his 60th birthday

Abstract: The first asymmetric synthesis of 4′-*epi*-trachycladines A and B is reported. Starting from 2,2-dimethyl-1,3-dioxan-5-one the title nucleosides were synthesised in 14 steps employing the SAMP-/RAMP-hydrazone methodology. The dioxanone-SAMP-hydrazone was first transformed into a trisubstituted derivative by a triple α-/α′-alkylation. Removal of the chiral auxiliary and subsequent reduction gave the corresponding alcohol, which could be transformed over four steps into TBS-protected 2′-*C*-methyl-5′-deoxy-L-lyxose. The trachycladines were then obtained via the corresponding triacetate using standard Vorbrüggen and silyl-Hilbert–Johnson conditions in an overall yield of 18–21%. Such 2′-*C*-branched ribonucleosides are potential agonists for adenosine receptors and play an important role in drug discovery.

Key words: nucleosides, asymmetric synthesis, hydrazones, quaternary stereocenters, Vorbrüggen coupling

Nucleoside-type natural products play an important role as models in drug development and in medicinal chemistry for the treatment of diseases like cancer, fungal, bacterial and viral infections.[1] In particular, marine organisms are the source of a great variety of these compounds.[2] In 1995 *Molinski* and *Searle* isolated the nucleosides trachycladines A (**1a**) and B (**1b**) from the sponge *Trachycladus laevispirulifer* Carter (Axinellida, Trachycladidae) collected at Exmouth Gulf, Western Australia (Figure 1).[3] Trachycladine A (or kumusine) has also been isolated from the marine sponges *Theonella Cupola* and *Theonella* sp.[4] Both nucleosides contain the previously undescribed sugar moiety 2′-*C*-methyl-5′-deoxy-D-ribose. Additionally trachycladine A is an analogue of 2-chloro-2′-deoxyadenosine which combines a remarkable activity against hairy cell leukaemia and low toxicity in clinical trials.[5] Trachycladine A shows in vitro cytotoxicity against several human cell lines including leukaemia (CCRF-CEM), colon tumour (HCT-116) and breast tumour cells (MCF-7).[3] Biological testing of trachycladine B could not be performed due to its insufficient availability. The trachycladines A and B have not been synthesised so far.

It should be mentioned that structurally related 2′-*C*-branched ribonucleosides, which were prepared synthetically, act as potent anti-viral agents[6] as well as selective agonists for adenosine receptors.[7]

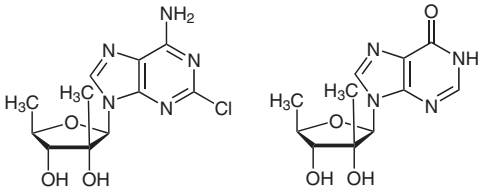

Figure 1

As is shown in the retrosynthetic analysis (Scheme 1), the title nucleosides **2a** and **2b** may be synthesised from the sugar triacetate **3** under Vorbrüggen[8] (**2a**) or silyl-Hilbert–Johnson[9] (**2b**) conditions. Compound **3** can be traced back to the parent 2′-*C*-methyl-5′-deoxy-L-lyxose (**4**), which should be obtainable from the selectively protected tetrol **5**. A retro-reduction leads to the ketone **6** and based on the SAMP-/RAMP-hydrazone methodology[10] to the commercially available dioxanone **7**.[11]

Thus, our synthetic route started with 2,2-dimethyl-1,3-dioxan-5-one employing the SAMP-/RAMP-hydrazone methodology.[10,12] As previously reported for the RAMP-hydrazone of **7** the enantiomeric SAMP-hydrazone of **7** was alkylated twice with MeI at the α- and α′-positions.[13]

Subsequent α-alkylation with benzyloxymethyl chloride (BOMCl) afforded the trisubstituted hydrazone **8** in very good overall yield (68% over 4 steps), and excellent diastereo- and enantiomeric excesses (de, ee ≥ 96%). Next the chiral auxiliary was removed by ozonolysis in 63% yield. In the following step, the racemisation-prone ketone **6** was reduced with L-Selectride® to the corresponding alcohol **5** with high diastereoselectivity and quantitative yield (Scheme 2).

In our first approach to the desired 2′-*C*-methyl-5′-deoxy-L-lyxose (**4**) we planned to establish a route via the 1,2-diol **10**. As is depicted in Scheme 3, the alcohol **5** could be transformed into the 1,3-dioxolane **9** by using camphorsulfonic acid (CSA) in dry acetone in 86% yield. In the following step, the removal of the benzyl protecting group was performed by hydrogenation using 10% Pd/C. However, every attempt to oxidise the resulting 1,2-diol **10** to the corresponding α-hydroxyaldehyde did not lead to the desired product in acceptable yields.

Therefore, our second approach involved a different protecting group strategy. The secondary hydroxyl group of the alcohol **5** was protected as TBS-ether **11** under stan-

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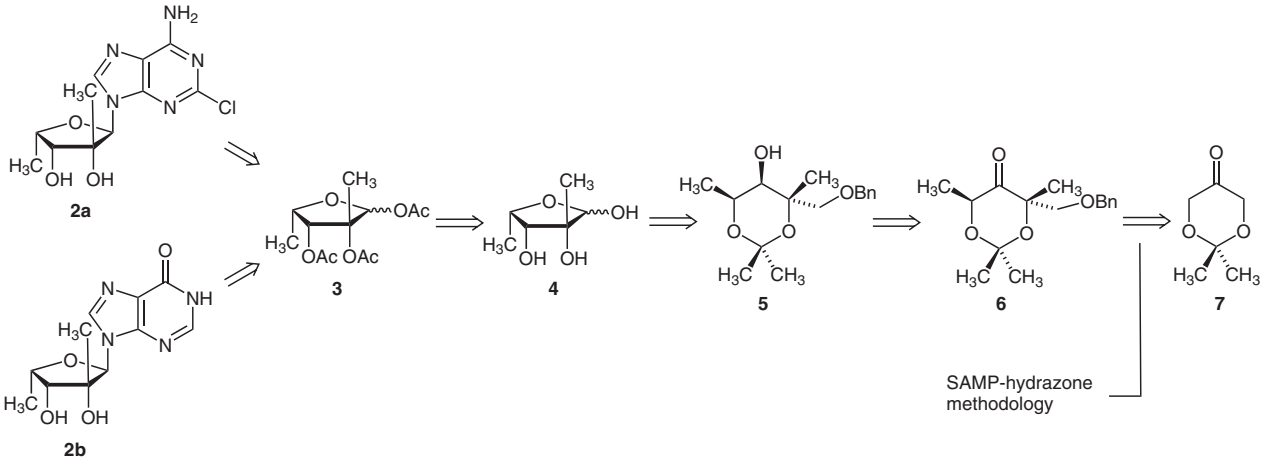
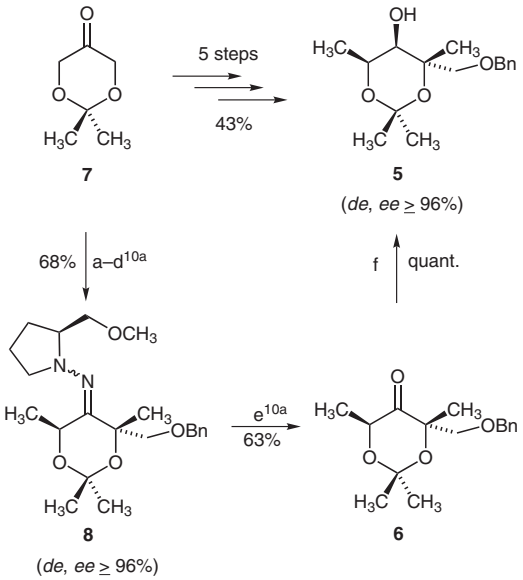
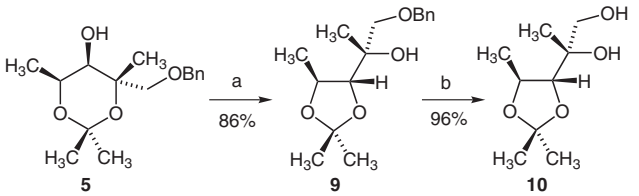


Scheme 1 Retrosynthetic analysis of 4′-*epi*-trachycladines A (**2a**) and B (**2b**).



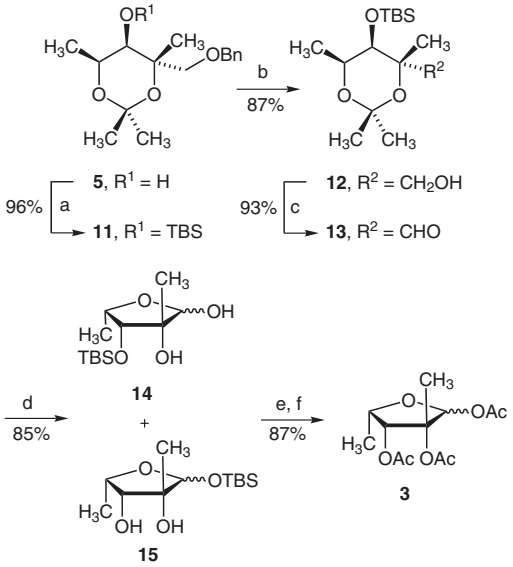
Scheme 2 Asymmetric synthesis of **5**. *Reagents and conditions*: a) SAMP, C_6H_6, 70 °C, 3.5 h; b) 1. *t*-BuLi, THF, –78 °C, 2. MeI, –100 °C to r.t.; c) 1. *t*-BuLi, THF, –78 °C, 2. MeI, –100 °C to r.t.; d) 1. *t*-BuLi, THF, –78 °C, 2. BOMCl, –100 °C to r.t.; e) O_3, CH_2Cl_2, –78 °C, 5 min; f) L-Selectride®, THF, –78 °C.

dard conditions. An attempt to cleave the benzyl protecting group of compound **11** using 10% Pd/C afforded the 1,2-diol **10**, due to some acidic traces in the catalyst. Therefore, the deprotection step was performed under Birch conditions and gave the primary alcohol **12** in 87% yield. Subsequent oxidation with Dess–Martin periodinate (DMP) generated 93% of the air-sensitive aldehyde **13** (Scheme 4).



Scheme 3 Preparation of the 1,2-diol **10**. *Reagents and conditions*: a) CSA, acetone, r.t., 2 h; b) 10% Pd/C, MeOH, r.t., 14 h.

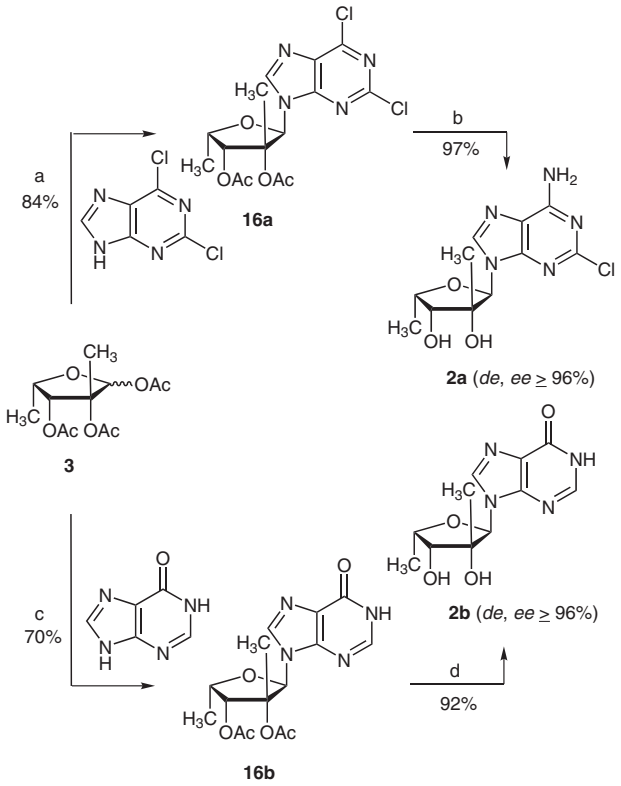
Initial attempts to convert the aldehyde **13** directly to the 2-*C*-methyl-5-deoxy-L-lyxose by cleavage under strong acidic conditions led to a mixture of products. Therefore, a stepwise deprotection of **13** was performed. The selective cleavage of the acetonide protecting group was achieved by treatment with diluted CSA in MeOH to give a mixture of TBS-protected sugars **14** and **15** in 85% yield. Unfortunately, all attempts to acylate the sugar **14** directly to the corresponding TBS-protected diacetate failed. Merely small amounts of triacetate **3** were isolated when the acylation step was performed under acidic conditions. Thus, we concluded that the acylation of the tertiary hydroxyl group of the sugar **14** is hindered by its sterically demanding TBS-group. Therefore, the crude mixture of **14** and **15** was deprotected with TBAF in THF.



Scheme 4 Preparation of the triacetate **3**. *Reagents and conditions*: a) 2,6-Lutidine, TBSOTf, CH_2Cl_2, 0 °C, 8 h; b) Ca/NH_3, –33 °C, 3 h; c) DMP, pyridine, CH_2Cl_2, r.t., 5 h; d) CSA, MeOH, r.t., 1.5 h; e) TBAF, THF, r.t., 1 h; f) Ac_2O, pyridine, 100 °C, 2.5 h.

The resulting sugar was directly transformed to the corresponding triacetate **3**. Due to very low reactivity of the tertiary *C*-2 hydroxyl group very harsh acylation conditions had to be employed.

Finally, as shown in Scheme 5, coupling of the triacetate **3** with 2,6-dichloropurine was performed under Vorbrüggen conditions[8] to afford **16a** in a good yield. A similar coupling of 2,6-dichloropurine with a 2-*C*-methyl-D-ribose derivative has been described in the literature.[7a] Next, deprotection of **16a** as well as the substitution of the 6-chloro functionality was performed in methanolic NH_3 and gave the desired 4′-*epi*-trachycladine A (**2a**) in 97% yield (de, ee ≥ 96%).



Scheme 5 Final steps of the 4′-*epi*-trachycladine synthesis. *Reagents and conditions*: a) TMSOTf, DBU, MeCN, r.t., 1.5 h; b) NH_3, MeOH, r.t., 24 h; c) 1. BSA, MeCN, 70 °C, 1 h; 2. TMSOTf, DBU, MeCN, 75 °C, 1 h; d) NH_3, MeOH, r.t., 24 h.

The α-configuration of the nucleoside **2a** was confirmed by NOESY measurements, which showed an interaction of H-8 with the H-3′, H-4′ and C-2′-CH_3 protons (Figure 2).

In a similar way, the triacetate **3** was coupled with in situ silylated hypoxanthine[14] employing standard silyl-Hilbert–Johnson conditions.[9] The configuration of the product was confirmed by NOESY and *H*C-HMBC measurements as well as by comparison of its ^{13}C NMR signals with those of inosine.[15] Finally, deprotection of the diacetate **16b** with NH_3 in MeOH afforded the title compound **2b** as a colourless solid (de, ee ≥ 96%).

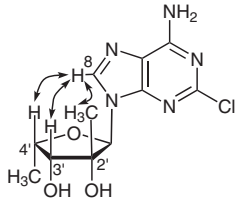


Figure 2 NOESY interactions between H-8 and C-2′-CH_3, H-3′ and H-4′ in **2a**.

In conclusion, we have carried out the first asymmetric synthesis of 4′-*epi*-trachycladines A and B by employing the SAMP-/RAMP-hydrazone methodology in key steps. The total yield over 14 steps starting from the commercially available dioxanone **7** was 18–21% and the title nucleosides were obtained as virtually pure stereoisomers.

All moisture-sensitive reactions were carried out using standard Schlenk techniques unless stated otherwise. All reagents were purchased from common commercial suppliers and used from freshly opened containers. Solvents for flash chromatography and for workup were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium/lead and benzophenone under Ar. Preparative flash column chromatography was carried out with Merck silica gel 60 (particle size 0.040–0.063 mm). Optical rotation values were measured with a Perkin-Elmer P 241 polarimeter. IR spectra were taken with a Perkin-Elmer FT/IR 1760 spectrometer. NMR spectra were recorded on Varian Mercury 300, Varian Inova 400 and Varian Unity 500 instruments; TMS was used as internal standard. Mass spectra were acquired on a Varian MAT 212 (EI, 70 eV, 1 mA) and a Finnigan MAT SSQ 7000 (CI, 100 eV) spectrometer. Microanalyses were obtained with a Vario EL element analyzer. HRMS measurements were performed on a Finnigan MAT, MAT 95 instrument. Merck silica gel TLC plates 60 F254 have been used for TLC analyses. Melting points were determined on a Tottoli melting point apparatus and are uncorrected. The compounds **5**, **6** and **8** have already been reported as enantiomers.[10a]

(*S*)-1-(Benzyloxy)-2-[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]propan-2-ol (9)

To a stirred solution of the alcohol **5** (0.49 g, 1.75 mmol) in dry acetone (40 mL) a solution of CSA (13 mg, 0.056 mmol) in dry acetone (9.0 mL) was added slowly. After stirring for 2.5 h at ambient temperature, sat. $NaHCO_3$ (1.0 mL) was added and the solvent was removed under reduced pressure. The oily residue was partitioned between water (5 mL) and Et_2O (50 mL) and the aqueous layer extracted with Et_2O (2 × 50 mL). Evaporation of the solvent and purification by flash chromatography (silica gel, Et_2O–hexane, 1:5) yielded **9** as a colourless oil (0.42 g, 86%); de, ee ≥96%; $[\alpha]_D^{25}$ –2.3 (*c* = 1.03, $CHCl_3$).

IR (film): 3492, 2983, 2932, 1455, 1374, 1247, 1217, 1174, 1081, 863, 742, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 [s, 3 H, C(OH)CH_3], 1.34 (d, *J* = 5.9 Hz, 3 H, OCHCH_3), 1.37 [s, 3 H, C(CH_3)CH_3], 1.40 [s, 3 H, C(CH_3)CH_3], 2.50 (br s, 1 H, OH), 3.36 [d, *J* = 9.1 Hz, 1 H, C(OH)CH_2], 3.50 [d, *J* = 9.1 Hz, 1 H, C(OH)CH_2], 3.67 [d, *J* = 8.2 Hz, 1 H, OC*H*C(OH)CH_3], 4.15 (dq, *J* = 5.9, 8.2 Hz, 1 H, OC*H*CH_3), 4.56 (s, 2 H, OCH_2Ph), 7.39–7.28 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 (OCH*C*H_3), 20.4 [C(OH)*C*H_3], 27.0 [C(*C*H_3)CH_3], 27,4 [C(CH_3)*C*H_3], 71.9 [*C*(OH)CH_3], 72.8 (O*C*HCH_3), 73.4 (O*C*H_2Ph), 75.2 [C(OH)*C*H_2],

84.3 [O*C*HC(OH)CH_3], 107.9 [*C*(CH_3)CH_3], 127.6 (*C*Ph), 127.7 (*p*-*C*Ph), 128.4 (*C*Ph), 137.9 (*C*Ph).

MS (EI, 70 eV): *m*/*z* (%) = 281 (1) $[M]^+$, 265 (14), 222 (4), 204 (3), 165 (21), 115 (27), 101 (11), 91 (100), 59 (24).

Anal. Calcd for $C_{16}H_{24}O_4$ (280.17): C, 68.54; H, 8.63. Found: C, 68.64; H, 8.18.

(*S*)-2-[(4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl]propane-1,2-diol (10)

To a solution of 1,3-dioxolane **9** (0.12 g, 0.43 mmol) in MeOH (12 mL) 10% Pd/C was added and stirred under H_2 at atmospheric pressure for 14 h. Removal of the catalyst, evaporation of the solvent and chromatographic purification of the product (silica gel, EtOAc–CH_2Cl_2–MeOH, 25:75:3) afforded the 1,2-diol **10** as colourless crystals; yield: 0.08 g (96%); de, ee ≥ 96% (NMR); mp 51 °C; $[\alpha]_D^{23}$ +6.0 (*c* = 1.04, $CHCl_3$).

IR (film): 3415, 2987, 2935, 2907, 1460, 1374, 1251, 1214, 1174, 1055, 984, 861, 801, 680, 599 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 [s, 3 H, C(OH)C*H*$_3$], 1.36 (d, *J* = 6.0 Hz, 3 H, OCHC*H*$_3$), 1.40 [s, 3 H, C(C*H*$_3$)CH$_3$], 1.41 [s, 3 H, C(CH$_3$)C*H*$_3$], 2.20 (m, 1 H, CH$_2$O*H*), 2.51 [s, 1 H, C(CH$_3$)O*H*], 3.46 [dd, *J* = 10.1, 6.6 Hz, 1 H, C*H*$_2$OH], 3.61 [d, *J* = 8.2 Hz, 1 H, OC*H*C(OH)CH$_3$)], 3.69 (dd, *J* = 11.1, 4.5 Hz, 1 H, C*H*$_2$OH), 4.11 (dq, *J* = 6.0, 8.0 Hz, 1 H, OC*H*CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (OCH*C*H$_3$), 20.8 [C(OH)*C*H$_3$], 26.9 [C(*C*H$_3$)CH$_3$], 27.3 [C(CH$_3$)*C*H$_3$], 67.5 [C(OH)*C*H$_2$], 71.8 [*C*(OH)CH$_3$], 72.8 (OC*H*CH$_3$), 85.8 [O*C*HC(OH)CH$_3$], 107.8 [*C*(CH$_3$)CH$_3$].

MS (CI, isobutane): *m*/*z* (%) = 192 (4), 191 (37) $[M + H]^+$, 173 (7), 133 (29), 115 (100), 97 (13).

Anal. Calcd for $C_9H_{18}O_4$ (190.12): C, 56.82; H, 9.54. Found: C, 56.64; H, 9.55.

[(4*S*,5*R*,6*S*)-4-(Benzyloxymethyl)-2,2,4,6-tetramethyl-1,3-dioxan-5-yloxy](*tert*-butyl)dimethylsilane (11)

The alcohol **5** (0.23 g, 0.79 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and 2,6-lutidine (0.17 g, 1.58 mmol) was added at 0 °C. The reaction mixture was stirred for 15 min at this temperature and treated dropwise with TBSOTf (0.72 g, 1.03 mmol). After being stirred at 0 °C for 8 h, the reaction mixture was poured into water (10 mL) and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography (silica gel, Et_2O–hexane 1:9) afforded **11** as a colourless oil (0.30 g, 96%); de, ee ≥ 96% (NMR); $[\alpha]_D^{24}$ –4.7 (*c* = 1.17, $CHCl_3$).

IR ($CHCl_3$): 2988, 2934, 2891, 2859, 1468, 1371, 1251, 1210, 1184, 1107, 1012, 989, 865, 838, 775 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.02–0.10 [m, 6 H, Si(CH$_3$)$_2$], 1.01 [s, 9 H, C(C*H*$_3$)$_3$], 1.27 (d, *J* = 6.3 Hz, 3 H, CHC*H*$_3$), 1.40 [s, 3 H, C(C*H*$_3$)CH$_2$O], 1.50 [s, 3 H, C(C*H*$_3$)CH$_3$], 1.58 [s, 3 H, C(CH$_3$)C*H*$_3$], 3.36 [s, 2 H, C(CH$_3$)C*H*$_2$O], 4.00 [m, 1 H, C*H*O-Si(CH$_3$)$_2$], 4.09 (m, 1 H, C*H*CH$_3$), 4.45 (s, 2 H, OC*H*$_2$Ph), 7.13–7.32 (m, 5 H, Ph).

^{13}C NMR (100 MHz, C_6D_6): δ = –4.4 [Si(*C*H$_3$)CH$_3$], –4.1 [Si(CH$_3$)*C*H$_3$], 17.8 (CH*C*H$_3$), 18.3 [*C*(CH$_3$)$_3$], 21.6 (C*C*H$_3$), 26.2 [C(*C*H$_3$)$_3$], 27.3 [C(*C*H$_3$)CH$_3$], 30.1 [C(CH$_3$)*C*H$_3$], 66.5 (*C*HCH$_3$), 69.5 [*C*HOSi(CH$_3$)$_2$], 73.2 (O*C*H$_2$Ph), 75.8 (C*C*H$_2$O), 77.5 (*C*CH$_3$), 98.9 [*C*(CH$_3$)CH$_3$], 127.3 (*o*-*C*Ph), 128.2 (*m*-*C*Ph, *p*-*C*Ph), 138.7 (*C*Ph).

MS (CI, methane): *m*/*z* (%) = 393 (1) $[M - 1]^+$, 379 (12), 337 (14), 279 (13), 245 (28), 235 (15), 230 (19), 229 (100), 215 (14), 213 (10).

MS (EI, 70 eV): *m*/*z* (%) = 235 (14), 215 (16), 187 (12), 173 (27), 172 (69), 131 (17), 115 (63), 92 (10), 91 (100), 75 (11), 73 (17).

Anal. Calcd for $C_{22}H_{38}O_4Si$ (394.62): C, 66.96; H, 9.71. Found: C, 67.28; H, 9.21.

[(4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,2,4,6-tetramethyl-1,3-dioxan-4-yl]methanol (12)

To a deep blue solution of calcium (0.27 g, 3.48 mmol) in liquid NH_3 (40 mL) benzylether **11** in THF (2 mL) was added. The resulting solution was refluxed for 3 h. Some solid NH_4Cl was added to the reaction mixture until the disappearance of the blue colour. The mixture was warmed to r.t. and the residue was taken up in water (10 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to a syrup, which was passed through silica gel (Et_2O–hexane, 1:10 followed by 1:5) to give **12** (0.18 g, 87%); de, ee ≥ 96% (NMR); $[\alpha]_D^{24}$ –11.5 (*c* = 1.34, $CHCl_3$).

IR ($CHCl_3$): 3508, 2987, 2936, 2860, 1467, 1375, 1253, 1184, 1099, 983, 868, 840, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, Si(C*H*$_3$)CH$_3$], 0.08 [s, 3 H, Si(CH$_3$)C*H*$_3$], 0.92 [s, 9 H, C(C*H*$_3$)$_3$], 1.22 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 1.27 [s, 3 H, C(C*H*$_3$)CH$_2$O], 1.35 [d, *J* = 0.6 Hz, 3 H, C(C*H*$_3$)CH$_3$], 1.44 [d, *J* = 9.6 Hz, 3 H, C(CH$_3$)C*H*$_3$], 2.06 (dd, *J* = 9.6, 3.6 Hz, 1 H, CH$_2$O*H*), 3.28–3.40 (m, 2 H, C*H*$_2$OH), 4.01 (d, *J* = 5.8 Hz, 1 H, CHOSi), 4.11–4.18 (m, 1 H, C*H*CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 [Si(*C*H$_3$)CH$_3$], –4.2 [Si(CH$_3$)*C*H$_3$], 17.1 (CH*C*H$_3$), 18.1 [*C*(CH$_3$)$_3$], 20.1 (C*C*H$_3$), 25.9 [C(*C*H$_3$)$_3$], 26.0 [C(*C*H$_3$)CH$_3$], 30.1 [C(CH$_3$)*C*H$_3$], 68.0 [C*C*H$_2$OH, *C*HCH$_3$, *C*HOSi(CH$_3$)$_2$], 77.4 (*C*CH$_3$), 99.4 [*C*(CH$_3$)CH$_3$].

MS (CI, methane): *m*/*z* (%) = 305 (7) $[M + 1]^+$, 289 (12), 247 (16), 231 (19), 230 (19), 229 (100), 189 (15), 187 (28), 186 (11), 185 (63), 173 (24), 172 (19), 145 (23), 115 (14), 97 (10).

MS (EI, 70 eV): *m*/*z* (%) = 173 (15), 172 (50), 145 (73), 133 (11), 131 (14), 116 (14), 115 (100), 75 (68), 73 (25).

Anal. Calcd for $C_{15}H_{32}O_4Si$ (304.5): C, 59.17; H, 10.59. Found: C, 59.45; H, 10.62.

(4*R*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,2,4,6-tetramethyl-1,3-dioxane-4-carbaldehyde (13)

To a solution of alcohol **12** (0.27 g, 0.89 mmol) in CH_2Cl_2 (26 mL) pyridine (0.76 mL, 0.74 g, 9.3 mmol) was added. The solution was treated dropwise with DMP (1.07 g, 2.52 mmol) in CH_2Cl_2 (12 mL) and stirred for 5 h at ambient temperature. Sat. $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (2 mL) were added and the mixture was stirred for 15 min. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (silica gel, Et_2O–hexane, 1:10) gave **13** as an air-sensitive colourless liquid (0.25 g, 93%); de, ee ≥ 96% (NMR); $[\alpha]_D^{24}$ –48.8 (*c* = 0.70, $CHCl_3$).

IR (film): 2937, 2896, 1730, 1467, 1371, 1258, 1202, 1160, 1117, 1059, 1006, 863, 839, 776, 685 cm^{-1}.

^1H NMR (300 MHz, C_6D_6): δ = 0.00 [s, 3 H, Si(C*H*$_3$)CH$_3$], 0.02 [s, 3 H, Si(CH$_3$)C*H*$_3$], 1.06 [s, 9 H, C(CH)$_3$], 1.17 (s, 3 H, CH$_3$), 1.54 [s, 3 H, C(CH$_3$)C*H*$_3$], 3.85–3.39 (m, 2 H, C*H*CH$_3$, CHOSi), 9.64 (s, 1 H, CHO).

^{13}C NMR (75 MHz, C_6D_6): δ = –5.0 [Si(*C*H$_3$)CH$_3$], –4.8 [Si(CH$_3$)*C*H$_3$], 17.2 (CH*C*H$_3$), 17.4 [*C*(CH$_3$)$_3$], 19.7 (C*C*H$_3$), 22.5 [C(*C*H$_3$)CH$_3$], 25.0 [C(*C*H$_3$)$_3$], 29.4 [C(CH$_3$)*C*H$_3$], 65.0, 65.9 (*C*HCH$_3$, *C*HOSi), 80.7 (*C*CH$_3$), 97.9 [*C*(CH$_3$)CH$_3$], 203.2 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 416 (39), 273 (10), 229 (20), 215 (31), 187 (17), 172 (62), 159 (24), 143 (26), 131 (33), 115 (100).

Anal. Calcd for $C_{15}H_{30}O_4Si$ (302.5): C, 59.55; H, 10.00. Found: C, 59.63; H, 10.23.

3-(*tert*-Butyldimethylsilyloxy)-2-*C*-methyl-5-deoxy-L-lyxo-furanose (14)

To a solution of the aldehyde **13** (0.23 g, 0.77 mmol) in MeOH (18 mL), a solution of CSA (3.8 mg, 0.016 mmol) in MeOH (3.8 mL) was added slowly. After 1.5 h at ambient temperature solid $NaHCO_3$ (10 mg) was added and the mixture was stirred for an additional 30 min. The solution was filtered and concentrated under reduced pressure. The syrupy residue was purified by chromatography (silica gel, EtOAc–hexane 2:1) to give a mixture of **14** and **15** (0.17 g, 85%) as a colourless oil. A small sample of **14** was purified by flash chromatography for spectroscopic data; de, ee ≥ 96%; α/β-ratio in C_6D_6: 1:4 (NMR).

IR (film): 3402, 2934, 2860, 1466, 1382, 1257, 1207, 1156, 1055, 843, 779, 675 cm^{-1}.

Major Diastereomer

^1H NMR (500 Hz, C_6D_6): δ = 0.00 [s, 3 H, Si(CH_3)CH_3], 0.10 [s, 3 H, Si(CH_3)CH_3], 0.94 [s, 9 H, C(CH_3)$_3$], 1.16 (s, 3 H, C-2-CH_3), 1.29 (d, *J* = 6.7 Hz, 3 H, H-5), 3.24 (s, 1 H, C-2-OH), 3.37 (d, *J* = 4.3 Hz, 1 H, H-3), 3.49 (d, *J* = 10.7 Hz, 1 H, C-1-OH), 3.85 (dq, *J* = 6.7, 4.4 Hz, 1 H, H-4), 4.89 (d, *J* = 10.4 Hz, 1 H, H-1).

^{13}C NMR (100 Hz, C_6D_6): δ = –4.9 [Si(*C*H_3)CH_3], –4.7 [Si(CH_3)*C*H_3], 17.1 (C-2-*C*H_3), 18.3 [Si*C*(CH_3)$_3$], 22.3 (C-5), 25.8 [SiC(*C*H_3)$_3$], 76.3 (C-4), 76.8 (C-2), 78.5 (C-3), 101.6 (C-1).

Minor Diastereomer

^1H NMR (500 Hz, C_6D_6): δ = –0.04 [s, 3 H, Si(CH_3)CH_3], 0.01 [s, 3 H, Si(CH_3)CH_3], 0.94 [s, 9 H, C(CH_3)$_3$], 1.37 (d, *J* = 6.7 Hz, 3 H, H-5), 1.50 (s, 3 H, C-2-CH_3), 2.65 (d, *J* = 3.4 Hz, 1 H, C-1-OH), 3.08 (s, 1 H, C-2-OH), 4.03 (d, *J* = 6.4 Hz, 1 H, H-3), 4.42 (dq, *J* = 6.7, 6.6 Hz, 1 H, H-4), 5.35 (d, *J* = 3.1 Hz, 1 H, H-1).

^{13}C NMR (100 Hz, C_6D_6): δ = –4.9 [Si(*C*H_3)CH_3], –4.7 [Si(CH_3)*C*H_3], 16.9 (C-2-*C*H_3), 18.3 [Si*C*(CH_3)$_3$], 21.4 (C-5), 25.8 [SiC(*C*H_3)$_3$], 75.7 (C-4), 77.8 (C-3), 79.4 (C-2), 102.4 (C-1).

MS (EI, 70 eV): *m*/*z* (%): 245 (2) $[M - OH]^+$, 229 (3), 201 (6), 187 (27), 159 (78), 143 (74), 115 (75), 103 (16), 84 (58), 75 (100).

MS (ESI–): *m*/*z* (%) = 261 (10) $[M - H]^-$, 262 (76).

Anal. Calcd for $C_{12}H_{26}O_4Si$ (262.16): C, 54.92; H, 9.99. Found: C, 54.47; H, 9.65.

1,2,3-Tri-*O*-Acetyl-2-*C*-methyl-5-deoxy-L-lyxo-furanose (3)

A mixture of the crude products **14** and **15** (0.32 g, 0.88 mmol) was dissolved in THF (17 mL) and treated dropwise with 1.0 M TBAF in THF (1.2 mL, 1.2 mmol). The reaction mixture was stirred at ambient temperature for 1 h and evaporated to dryness. The syrupy residue was thoroughly dried under vacuum and dissolved in dry pyridine (15 mL). Ac_2O (8 mL) was slowly added and the reaction mixture was stirred for 2.5 h at 100 °C. Solvent evaporation at ambient temperature under reduced pressure gave a yellow residue, which was partitioned between sat. $NaHCO_3$ (10 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash chromatography (silica gel, EtOAc–hexane, 1:2) yielded triacetate **3** as slightly yellowish crystals (0.21 g, 87% over 2 steps); de, ee ≥ 96% (NMR); α/β-ratio: 8:1; mp: 51 °C; $[\alpha]_D^{25}$ –76.2 (*c* = 0.98, $CHCl_3$).

IR (KBr): 3477, 2998, 2941, 1751, 1450, 1378, 1231, 1151, 1086, 1026, 915, 884, 837, 615, 523 cm^{-1}.

Major Diastereomer

^1H NMR (400 Hz, $CDCl_3$): δ = 1.20 (d, *J* = 6.6 Hz, 3 H, H-5), 1.63 (s, 3 H, C-2-CH_3), 2.06 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$), 2.13 (s, 3 H, $COCH_3$), 4.48 (dq, *J* = 6.4, 4.4 Hz, 1 H, H-4), 5.37 (d, *J* = 4.4 Hz, 1 H, H-3), 6.36 (s, 1 H, H-1).

^{13}C NMR (100 Hz, $CDCl_3$): δ = 14.8 (C-5), 17.5 (C-2-*C*H_3), 20.5 (CO*C*H_3), 21.1 (CO*C*H_3), 21.4 (CO*C*H_3), 75.8 (C-3), 77.8 (C-4), 86.0 (C-2), 98.8 (C-1) 169.1 (*C*OCH_3), 169.3 (*C*OCH_3), 169.5 (*C*OCH_3).

Minor Diastereomer

^1H NMR (400 Hz, $CDCl_3$): δ = 1.25 (d, *J* = 6.3 Hz, 3 H, H-5), 1.60 (s, 3 H, C-2-CH_3), 2.03 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $COCH_3$), 4.48 (dq, *J* = 6.4, 5.0 Hz, 1 H, H-4), 5.38 (d, *J* = 5.0 Hz, 1 H, H-3), 6.22 (s, 1 H, H-1).

^{13}C NMR (100 Hz, $CDCl_3$): δ = 16.0 (C-5), 17.5 (C-2-*C*H_3), 21.0 (CO*C*H_3), 21.1 (CO*C*H_3), 21.4 (CO*C*H_3), 75.0 (C-4), 76.8 (C-3), 86.0 (C-2), 97.6 (C-1), 168.7 (*C*OCH_3), 169.3 (*C*OCH_3), 169.5 (*C*OCH_3).

MS (EI, 70 eV): *m*/*z* (%) = 241 (1), 215 (100) $[M - OAc]^+$, 172 (14), 145 (36), 126 (9), 113 (48), 103 (32), 84 (89), 69 (60).

MS (CI, isobutane): *m*/*z* = 217 (2), 216 (11), 215 (100) $[M - OAc]^+$.

Anal. Calcd for $C_{12}H_{18}O_7$ (274.11): C, 52.55; H, 6.62. Found: C, 52.57; H, 6.68.

2,6-Dichloro-9-(2′,3′-di-*O*-acetyl-2′-*C*-methyl-5′-deoxy-α-L-lyxofuranosyl)purine (16a)

To a stirred solution of 2,6-dichloropurine (86 mg, 0.46 mmol), triacetate **3** (61 mg, 0.22 mmol) and DBU (154 mg, 1.00 mmol) in dry MeCN (3.0 mL) cooled to –15 °C was slowly added a solution of TMSOTf (640 mg, 2.88 mmol) in dry MeCN (3.3 mL). The reaction mixture was allowed to warm to ambient temperature, stirred for further 1.5 h and quenched with sat. $NaHCO_3$ (20 mL) at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL), washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography (silica gel, EtOAc–hexane, 1:2) afforded pure crystalline **15** (74 mg, 84%); de, ee ≥ 96% (NMR); mp 112 °C; $[\alpha]_D^{24}$ –46.1 (*c* = 1.15, $CHCl_3$).

IR ($CHCl_3$): 3125, 3002, 2939, 1753, 1593, 1556, 1491, 1362, 1248, 1168, 1141, 1090, 919, 883, 803, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.6 Hz, 3 H, H-5′), 1.44 (s, 3 H, C-2′-CH_3), 2.10 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, $COCH_3$), 4.98 (dq, *J* = 6.5, 3.7 Hz, 1 H, H-4′), 5.76 (d, *J* = 3.6 Hz, 1 H, H-3′), 6.46 (s, 1 H, H-1′), 8.30 (s, 1 H, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (C-5′), 18.0 (C-2′-*C*H_3), 20.5 (CO*C*H_3), 21.1 (CO*C*H_3), 77.0 (C-3′), 77.4 (C-4′), 84.8 (C-2′), 90.1 (C-1′), 131.0 (C-5), 144.4 (C-8), 151.8, 152.4, 153.0, 168.9 (*C*OCH_3), 169.0 (*C*OCH_3).

MS (EI, 70 eV): *m*/*z* (%) = 342 (5) $[M - HOAc]^+$, 282 (25), 215 (100), 188 (30), 153 (15), 113 (33), 101 (9), 95 (13).

MS (ESI+): *m*/*z* (%) = 529 (12), 425 (90) $[M + Na]^+$, 297 (100), 255 (5), 215 (11).

HRMS: *m*/*z* calcd for $[C_{15}H_{16}N_4O_5Cl_2 - C_2H_4O_2]$: 342.0286; found: 342.0287.

2-Chloro-9-(2′-*C*-methyl-5′-deoxy-α-L-lyxofuranosyl)adenine (2a)

A solution of **16a** (30 mg, 0.075 mmol) in MeOH (5 mL) was saturated with gaseous NH_3 at –20 °C and stirred at r.t. in a sealed tube for 24 h. The reaction mixture was evaporated in vacuo and the residue was purified by flash chromatography (silica gel, EtOAc–CH_2Cl_2–MeOH, 25:75:5) to give **2a** as a colourless solid (22 mg, 97%); de, ee ≥ 96% (NMR); mp 97 °C; $[\alpha]_D^{24}$ –32.6 (*c* = 0.92, acetone).

IR (KBr): 3372, 3201, 1653, 1597, 1461, 1349, 1311, 1249, 1093, 1041, 940, 751, 684 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.09 (s, 3 H, C-2′-CH_3), 1.33 (d, *J* = 6.6 Hz, 3 H, H-5′), 3.32 (br s, 1 H, OH), 4.16 (d, *J* = 4.7 Hz, 1 H, H-3′), 4.68 (br s, 1 H, OH), 4.77 (dq, *J* = 6.6, 6.6 Hz, 1 H, H-4′), 6.10 (s, 1 H, H-1′), 7.10 (br s, 2 H, NH_2), 8.14 (s, 1 H, H-8).

^{13}C NMR (100 MHz, acetone-d_6): δ = 16.0 (C-5′), 21.1 (C-2′-*C*H_3), 77.5 (C-3′), 78.9 (C-4′), 80.6 (C-2′), 92.0 (C-1′), 119.6 (C-5), 140.3 (C-8), 151.4 (C-4), 154.3 (C-2), 157.6 (C-6).

MS (EI, 70 eV): *m*/*z* (%) = 264 (1) [M – H_3O_2]$^+$, 236 (2), 219 (1), 153 (2), 136 (2), 107 (1), 74 (14), 59 (100).

HRMS: *m*/*z* calcd for [$C_{11}H_{14}N_5O_3Cl$ – H_3O_2]: 264.0652; found: 264.0652.

9-(2′,3′-Di-*O*-acetyl-2′-*C*-methyl-5′-deoxy-α-L-lyxofuranosyl)hypoxanthine (16b)

To a solution of hypoxanthine (66 mg, 0.48 mmol) in anhyd MeCN (2.0 mL) BSA (0.30 mL, 0.25 g, 1.21 mmol) was added. The reaction mixture was heated at 70 °C for 1 h and cooled to r.t. Triacetate **3** (40 mg, 0.15 mmol) dissolved in dry MeCN (2.0 mL) was added, followed by DBU (120 mg, 0.79 mmol) in dry MeCN (2.0 mL). The solution was cooled to –30 °C and TMSOTf (0.34 g, 1.52 mmol) dissolved in dry MeCN (3.0 mL) was added dropwise. The solution was heated under reflux for 1.5 h and poured into cold sat. $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, THF–hexane, 9:1; then EtOAc–CH_2Cl_2–MeOH, 25:75:5) to give a colourless solid, which could be further purified by preparative HPLC (Kromasil 100 Sil 7 µm, hexane–EtOH, 6:4); yield: 44 mg, 70%; de, ee ≥ 96% (NMR); mp 53 °C; $[\alpha]_D^{25}$ –71.4 (*c* = 1.01, acetone).

IR (KBr): 3451, 3212, 3113, 3054, 2995, 2940, 1754, 1698, 1589, 1549, 1378, 1245, 1140, 1088, 1042, 1020, 891, 797, 607 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.9 Hz, 3 H, H-5′), 1.40 (s, 3 H, C-2′-CH_3), 2.02 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 4.93 (dq, *J* = 6.3, 3.6 Hz, 1 H, H-4′), 5.75 (d, *J* = 3.6 Hz, 1 H, H-3′), 6.17 (br s, 1 H, NH), 6.37 (s, 1 H, H-1′), 8.05 (s, 1 H, H-8), 8.20 (s, 1 H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (C-5′), 17.7 (C-2′-*C*H_3), 20.5 (CO*C*H_3), 21.2 (CO*C*H_3), 77.0 (C-3′), 77.1 (C-4′), 85.0 (C-2′), 89.8 (C-1′), 124.6 (C-5), 139.2 (C-8), 145.1 (C-2), 148.5 (C-4), 158.7 (C-6), 169.0 (*C*OCH_3).

MS (EI, 70 eV): *m*/*z* (%) = 350 (3) [M]$^+$, 231 (3), 215 (100), 165 (3), 137 (8), 113 (28), 95 (5), 85 (8), 69 (4).

HRMS: *m*/*z* calcd for $C_{15}H_{18}N_4O_6$: 350.1226; found: 350.1224.

9-(2-*C*′-Methyl-5′-deoxy-α-L-lyxo-furanosyl)hypoxanthine (1b)

The diacetate **16b** (30 mg, 0.086 mmol) was deprotected by the procedure described for the nucleoside **16a** to give 4′-*epi*-trachycladine B (**2b**). The crude product was purified by flash chromatography (silica gel, EtOAc–CH_2Cl_2–MeOH, 25:75:10) to yield **2b** (21 mg, 92%) as a colourless solid; de, ee ≥ 96% (NMR); mp 172 °C; $[\alpha]_D^{23}$ –55.8 (*c* = 1.06, MeOH).

IR (KBr): 3426, 3134, 3053, 2937, 2899, 1691, 1591, 1548, 1462, 1220, 1080, 647, 600 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.05 (s, 3 H, C-2′-CH_3), 1.34 (d, *J* = 6.7 Hz, 3 H, H-5′), 3.98 (d, *J* = 4.5 Hz, 1 H, H-3′), 4.74 (dq, *J* = 6.4, 4.5 Hz, 1 H, H-4′), 6.16 (s, 1 H, H-1′), 8.05 (s, 1 H, H-8), 8.15 (s, 1 H, H-2).

^{13}C NMR (75 MHz, CD_3OD): δ = 15.9 (C-5′), 20.9 (C-2′-*C*H_3), 78.3 (C-3′), 79.8 (C-4′), 81.3 (C-2′), 92.9 (C-1′), 125.8 (C-5), 140.2 (C-8), 147.2 (C-2), 150.2 (C-4), 159.6 (C-6).

MS (EI, 34 eV): *m*/*z* (%) = 266 (0.7) [M]$^+$, 165 (4), 84 (92), 66 (100).

MS (ESI+): *m*/*z* (%) = 288 (2) [M – H + Na]$^+$, 160 (3), 159 (100).

MS (ESI–): *m*/*z* (%) = 265 (2) [M – H]$^-$, 136 (3), 135 (100), 97 (1).

HRMS: *m*/*z* calcd for $C_{11}H_{14}N_4O_4$: 266.1015; found: 266.1014.

Anal. Calcd for $C_{11}H_{14}N_4O_4 \cdot 1^2/_3H_2O$ (296.28): C, 44.59; H, 5.90, N, 18.91. Found: C, 44.43; H, 5.59, N, 18.50.

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