Synthesis of Carbocyclic Homo-*N*-Nucleosides from Iridoids

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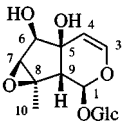
Two iridoid glucosides, antirrhinoside (**1**) and catalpol (**2**), were converted into selectively protected polysubstituted cyclopentylmethanols, which were subsequently used to prepare carbocyclic homo-*N*-nucleosides (**5**, **6** and **14**). A purine moiety was introduced either by the Mitsunobu reaction or by substitution of a primary triflate with the tetrabutylammonium salt of 6-iodopurine. The latter method was superior with regard to both ease of purification and yield. The N-9 vs. N-7 regioselectivity of the salts of different 6-substituted purine derivatives was briefly investigated.

Introduction

In the last three decades a considerable number of nucleoside analogues have been prepared, and among these, the carbocyclic nucleosides form a well-known class of biologically active analogues.[1][2][3] However, the combination of a cyclic moiety and a methylene-linked nucleobase has only been investigated occasionally, e.g. homonucleosides containing a pyrrolidine ring,[4][5] homo-*N*-nucleosides,[6][7] and carbocyclic homo-*N*-nucleosides[8][9][10][11][12][13] have been reported. Previously, the iridoid glucoside aucubin has been converted into a 3′-hydroxymethyl analogue of Carbovir®.[14] In the present work, we exploit the use of chiral building blocks derived from the iridoid glucosides, antirrhinoside (**1**) and catalpol (**2**) to obtain enantiopure carbocyclic homo-*N*-nucleoside analogues. Also a refined coupling procedure for the preparation of methylene-linked nucleosides seemed appropriate, and for this purpose the Mitsunobu reaction and displacement of primary triflates are compared.



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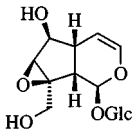

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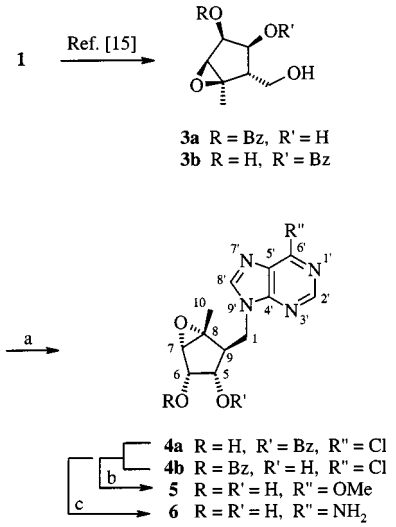
Results and Discussion

We have previously reported on the synthesis of the interconvertible monobenzoates **3a** and **3b**, which were obtained in five steps from **1**.[15] Apparently, **3a**/**3b** underwent acyl migration during reverse-phase HPLC, but now we have obtained each isomer in crystalline form after further purification by normal-phase vacuum liquid chromatography (VLC), which allowed full characterization. However, due to the observed benzoyl migration in low-scale experiments, monobenzoates **3a**/**3b** were used as a mixture in a Mitsunobu coupling with 6-chloropurine. Although two hydroxy groups were left unprotected, a facile reaction took place exclusively at the primary position giving the two monobenzoates **4a** and **4b** (Scheme 1). These were obtained in a mixture with triphenylphosphane oxide, and were therefore characterized only by ^{1}H-NMR spectroscopy. Debenzoylation of **4a**/**4b** with sodium methoxide yielded the 6-methoxypurine derivative **5** while ammonolysis afforded the adenine derivative **6** in 41% overall yield based on **3a**/**3b**. It is noteworthy that the epoxide functionality was stable under these conditions.

Scheme 1. Synthesis of nucleoside analogues **5** and **6**: (a) 6-chloropurine, Ph_3P, DEAD, THF; (b) NaOMe/MeOH; (c) liquid NH_3, 45°C, 3 d, 41% from **3a**/**3b**



Since laborious purifications are often associated with Mitsunobu reactions, a procedure employing a primary

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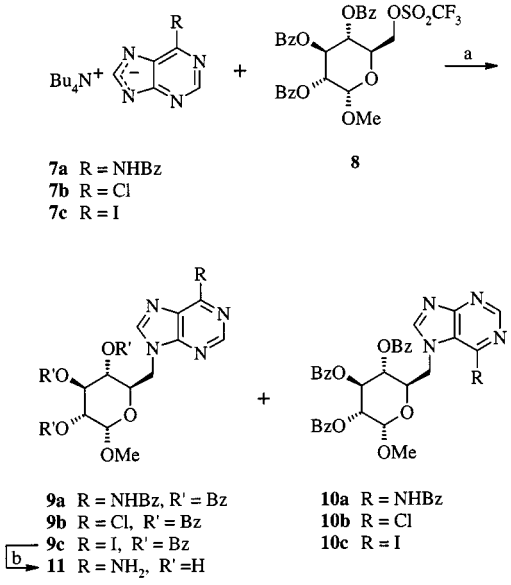
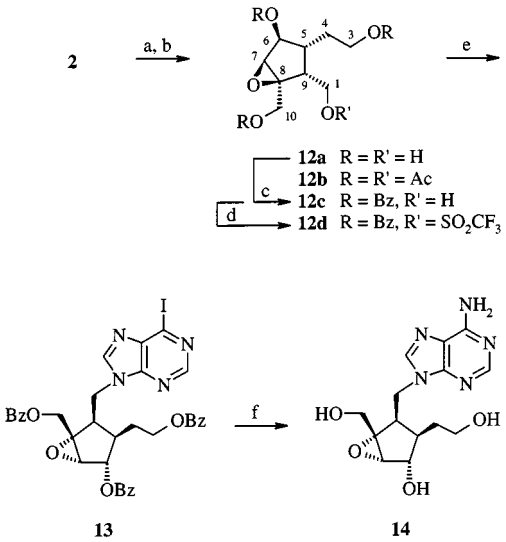
triflate was considered a suitable alternative. This would still allow coupling of the purine in the presence of an epoxide and acyl protecting groups. Recently, the tetrabutylammonium salt of 6-iodo-2-aminopurine was reported to give an especially high N-9 vs. N-7 selectivity in a substitution of a secondary triflate.[16] This prompted us to prepare the tetrabutylammonium salts of 6-benzamidopurine, 6-chloropurine, and 6-iodopurine, **7a–c**, respectively (Scheme 2). To investigate the regioselectivity of the salts **7a–c** in the coupling with a primary triflate, we tested them in a reaction with triflate **8**,[17] which was obtained from methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside.[18] It was found that the N-9 vs. N-7 regioselectivity increased significantly through the series **7a**–**7c**. For **7a**, the poor selectivity (ca. 1:1) was expected, as two sets of signals were observed in its ^{1}H-NMR spectrum (probably arising from two tight ion pairs in equilibrium). On the other hand, each of the salts **7b** and **7c** appeared as a single form in NMR, but nevertheless both N-9- and N-7-alkylated products (**9b**/**10b** and **9c**/**10c**) were produced in ratios of 4:1 (81% isolated yield) and 12:1 (87% isolated yield), respectively. Transformation of **9c** into the adenine derivative **11** was performed by treatment with liquid ammonia. For comparison, a Mitsunobu reaction with 6-chloropurine as the base was performed on methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside[18] to give the corresponding **9b** as the only isolated product, but again this was contaminated with Ph_3PO. The yield was estimated from its ^{1}H-NMR spectrum to be ca. 70%.

Scheme 2. Model experiments with purine salts **7a–7c**: (a) CH_2Cl_2, room temp., 18 h; (b) liquid NH_3, 45°C, 3 d, 89%



Next, catalpol (**2**) was investigated as starting material; it was converted into a functionalized cyclopentane **12a**[19] by performing a one-pot removal of the glucose moiety and reduction of the aglycone. Surprisingly, it proved possible to benzoylate positions 3, 6, and 10 selectively to give, in a moderate yield, tribenzoate **12c** with the sterically hindered primary hydroxy group at C-1 left unprotected. The substitution pattern of **12c** was evident from analysis of the ^{1}H-NMR spectrum. The tribenzoate, **12c**, was converted into triflate **12d**, which in turn was coupled with **7c** to yield protected nucleoside analogue **13** in 73% yield. Finally, ammonolysis afforded compound **14** in 86% yield. For comparison, a Mitsunobu coupling of **12c** and 6-chloropurine gave the 6-chloro analogue of **13** (60% estimated yield), which again was contaminated with Ph_3PO.

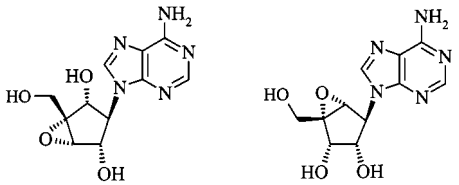
Scheme 3. Synthesis of nucleoside analogue **14**: (a) β-glucosidase, H_2O; (b) $NaBH_4$, 82% from **2**; (c) BzCl, pyridine, CH_2Cl_2, −78°C, 60%; (d) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −40°C to room temp., 4 h; (e) **7c**, CH_2Cl_2, −10°C, 18 h, 73% from **12d**; (f) liquid NH_3, 45°C, 3 d, 86%



Conclusion

Tentatively, we conclude that the use of a primary triflate in the preparation of methylene-linked nucleoside analogues is superior to the Mitsunobu procedure with regard to both ease of purification and yield.

The compounds prepared are structurally related to neplanocins B and C (**15** and **16**, respectively), which are known to be antibiotics, also exhibiting antitumor effects.[20][21] Compounds **5**, **6**, and **14** are currently being assayed for possible antiviral and antitumor activity.



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Experimental Section

General Remarks: CH_2Cl_2 and pyridine were freshly distilled from CaH_2. – Elemental analyses: Institute of Physical Chemistry,

Vienna. – Optical rotations: Perkin-Elmer 241 polarimeter. – Melting points are uncorrected. – TLC: Merck Silica Gel 60 F_{254} aluminum sheets with detection by charring with sulfuric acid and/or by UV light. – MPLC: Merck Lobar Lichroprep RP-18 (40–63 μm) Fertigsäule (size B: 25 × 310 mm) or on a column (size D: 50 × 900 mm) packed with Polygoprep C_{18} (50–60 μm; 1.5 kg, from Macherey-Nagel). – VLC (vacuum liquid chromatography): Predried (120 °C; > 24 h) Merck Silica Gel 60H, column size is given as height × diameter (cm). – NMR: Bruker AM-500 or HX-250. Solvents for ^{1}H NMR: [D_6]DMSO (δ_H = 2.50), [D_4]methanol (δ_H = 3.31), $CDCl_3$ (δ_H = 7.27), for ^{13}C NMR: [D_6]DMSO (δ_C = 39.5), [D_4]methanol (δ_C = 49.0), $CDCl_3$ (δ_C = 77.0); assignments of ^{1}H-NMR spectra were based on 1D homonuclear decoupling experiments, while ^{13}C-NMR spectra were assigned by using carbon-proton shift correlation spectra. The identity of N-7- vs. N-9-alkylated purine derivatives was established by NMR spectroscopy and by their polarity.[22] – MS: VG trio 2 (direct inlet at 150–350°C).

Separation of **3a** *and* **3b**: A mixture of **3a** and **3b** (2:1, 550 mg) was dissolved in CH_2Cl_2 (5 ml) and loaded onto a VLC column (3.5 × 3). Elution with hexane, and then hexane/Me_2CO (6:1 to 4:1) gave successive fractions of **3a** (372 mg) and **3b** (159 mg).

6-OBz Derivative **3a**: M.p. 100–102°C (from Me_2CO/hexane), $[\alpha]_D^{23}$ = −40 (*c* = 0.7, Me_2CO). – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.42 (s, 3 H, 10-H), 2.13 (br. t, *J* = 4 Hz, 1 H, 9-H), 3.55 (dt, *J* = 11, 2 × 4 Hz, 1 H, 1a-H), 3.60 (dt, *J* = 11, 2 × 4 Hz, 1 H, 1b-H), 3.64 (br. s, 1 H, 7-H), 3.69 (d, *J* = 10 Hz, 1 H, 5-OH), 4.06 (br. dd, *J* = 10, 6.5 Hz, 1 H, 5-H), 4.86 (t, *J* = 4 Hz, 1 H, 1-OH), 5.20 (dd, *J* = 6.5, 1 Hz, 1 H, 6-H), 7.54 (br. t, *J* = 8 Hz, 2 H, 2′-H and 6′-H), 7.67 (br. t, *J* = 8 Hz, 1 H, 4′-H), 8.02 (br. d, *J* = 8 Hz, 2 H, 3′-H and 5′-H); ′ denotes benzoyl signals. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.5 (C-10), 53.9 (C-9), 59.9 (C-1), 63.1 (C-7), 62.4 (C-8), 70.9 (C-5), 76.4 (C-6), 165.4 (Ph*C*O). – $C_{14}H_{16}O_5$ (264.3): calcd. C 63.63, H 6.10; found C 63.82, H 6.07.

5-OBz Derivative **3b**: M.p. 151–152°C (from Me_2CO/hexane), $[\alpha]_D^{23}$ = −78 (*c* = 0.8, Me_2CO). – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.38 (s, 3 H, 10-H), 2.22 (br. t, *J* = 4 Hz, 1 H, 9-H), 3.34 (br. s, 1 H, 7-H), 3.55 (dt, *J* = 11, 2 × 4 Hz, 1 H, 1a-H), 3.64 (ddd, *J* = 11, 4.5, 3.5 Hz, 1 H, 1b-H), 4.38 (br. t, *J* = 8.5 Hz, 1 H, 6-H), 4.88 (t, *J* = 4.5 Hz, 1 H, 1-OH), 5.01 (d, *J* = 8.5 Hz, 1 H, 6-OH), 5.14 (br. d, *J* = 8 Hz, 1 H, 5-H), 7.51 (br. t, *J* = 8 Hz, 2 H, 2′-H and 6′-H), 7.63 (br. t, *J* = 8 Hz, 1 H, 4′-H), 8.00 (br. d, *J* = 8 Hz, 2 H, 3′-H and 5′-H); ′ denotes benzoyl signals. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.4 (C-10), 51.6 (C-9), 59.9 (C-1), 61.5 (C-8), 65.3 (C-7), 71.9 (C-6), 74.8 (C-5), 165.5 (Ph*C*O). – $C_{14}H_{16}O_5$ (264.3): calcd. C 63.63, H 6.10; found C 63.81, H 6.19.

Mitsunobu Coupling of 5/6-OBz Derivatives **3a**/**3b**: To a mixture of **3a** and **3b** (2:1, 290 mg, 1.1 mmol) in dry THF (20 ml) was added Ph_3P (580 mg, 2.2 mmol) and 6-chloropurine (338 mg, 2.2 mmol). Diethyl azodicarboxylate (DEAD, 0.34 ml, 2.2 mmol) in THF (1 ml) was then added dropwise. After 1 h, TLC (hexane/Me_2CO, 2:1) showed full conversion, and the solvent was removed. The residue was purified on a VLC column (6 × 3). Elution with hexane and then hexane/Me_2CO (8:1 to 1:1) yielded fractions of impure **4a** and **4b** (566 mg, contaminated with Ph_3PO), characterized solely by ^{1}H NMR.

Compound **4a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.58 (s, 3 H, 10-H), 3.03 (br. dd, *J* = 10, 5.5 Hz, 1 H, 9-H), 3.58 (br. s, 1 H, H-7), 4.31 (dd, *J* = 14.5, 10 Hz, 1 H, 1b-H), 4.53 (br. d, *J* = 7 Hz, 1 H, 6-H), 4.53 (dd, *J* = 14.5, 5.5 Hz, 1 H, 1a-H), 5.02 (dd, *J* = 7, 1.5 Hz, 1 H, 5-H), 7.30–7.85 (*Ph*CO and Ph_3PO signals), 8.28 (s, 1 H, 2′-H), 8.76 (s, 1 H, 8′-H).

Compound **4b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.61 (s, 3 H, 10-H), 2.98 (dd, *J* = 10.5, 5.5 Hz, 1 H, 9-H), 3.80 (br. s, 1 H, 7-H), 4.01 (d, *J* = 6 Hz, 1 H, 5-H), 4.21 (dd, *J* = 14.5, 10.5 Hz, 1 H, 10b-H), 4.49 (dd, *J* = 14.5, 5.5 Hz, 1 H, 10a-H), 5.34 (br. d, *J* = 6 Hz, 1 H, 6-H), 7.40–8.10 (*Ph*CO and Ph_3P signals), 8.28 (s, 1 H, 2′-H), 8.81 (s, 1 H, 8′-H); ′ denotes purine signals.

6-Methoxypurine Nucleoside Analogue **5**: The combined impure fractions (566 mg) of **4a** and **4b** were treated with 0.1 M NaOMe in MeOH (20 ml) for 1 h at room temp. Then HOAc was added until pH = 7. The solvent was evaporated, and the residue was purified by MPLC. Elution with H_2O and then H_2O/MeOH (10:1 to 3:1) afforded **5** (201 mg, 66% overall), m.p. 165–167°C (from EtOH), $[\alpha]_D^{23}$ = −8.8 (*c* = 0.6, H_2O). – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.42 (s, 3 H, 10-H), 2.71 (dd, *J* = 10.5, 5 Hz, 1 H, 9-H), 3.38 (br. s, 1 H, 7-H), 3.43 (br. t, *J* = 7.5 Hz, 1 H, 5-H), 3.56 (d, *J* = 8.5 Hz, 1 H, 5-OH), 4.10 (dd, *J* = 14.5, 10.5 Hz, 1 H, 1a-H), 4.10 (s, 3 H, 6′-OMe), 4.14 (br. t, *J* = 6 Hz, 1 H, 6-H), 4.37 (dd, *J* = 14.5, 5 Hz, 1 H, 1b-H), 4.56 (d, *J* = 6.5 Hz, 1 H, 6-OH), 8.48 (s, 1 H, 2′-H), 8.56 (s, 1 H, 8′-H); ′ denotes purine signals. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.8 (C-10), 42.8 (C-1), 51.4 (C-9), 53.9 (OMe), 62.2 (C-8), 65.1 (C-7), 70.9 (C-6), 70.4 (C-5), 120.5 (C-5′), 143.9 (C-8′), 151.5 (C-2′), 152.2 (C-4′), 160.3 (C-6′); ′ denotes purine signals. – $C_{13}H_{16}N_4O_4$ (292.3): calcd. C 53.42, H 5.52, N 19.17; found C 53.52, H 5.41, N 19.08.

Adenine Derivative **6**: A mixture of **4a**/**4b** and Ph_3PO (1.29 g), prepared as above from **3a**/**3b** (376 mg, 1.42 mmol), was treated with liquid NH_3 (ca. 20 ml) at 45°C in a steel vessel for 3 d. The residue was dissolved in EtOH/MeOH (1:1, 6 ml) and loaded onto a VLC column (3.5 × 3). Elution with hexane, $CHCl_3$, and then $CHCl_3$/MeOH (10:1 to 7:1) yielded **6** (161 mg, 41% overall), m.p. 162–164°C (from EtOH), $[\alpha]_D^{23}$ = −15 (*c* = 0.5, H_2O). – ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.42 (s, 3 H, 10-H), 2.68 (dd, *J* = 10.5, 5.5 Hz, 1 H, 9-H), 3.38 (br. s, 1 H, 7-H), 3.45 (dd, *J* = 8.5, 6.5 Hz, 1 H, 5-H), 3.51 (d, *J* = 8.5 Hz, 1 H, 5-OH), 3.98 (dd, *J* = 14.5, 10.5 Hz, 1 H, 1a-H), 4.12 (br. dd, *J* = 8, 6.5 Hz, 1 H, 6-H), 4.27 (dd, *J* = 14.5, 5.5 Hz, 1 H, 1b-H), 4.57 (d, *J* = 8 Hz, 1 H, 6-OH), 7.24 (br. s, 2 H, 6′-NH_2), 8.16 (s, 1 H, 2′-H), 8.22 (s, 1 H, 8′-H); ′ denotes purine signals; additional signals for EtOH: δ = 1.18 (t, *J* = 7 Hz, 3 H), 3.44 (m, 2 H), 4.35 (t, *J* = 5 Hz, 1 H, EtO*H*). – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.8 (C-10), 42.2 (C-1), 51.5 (C-9), 62.3 (C-8), 65.0 (C-7), 70.3 (C-5), 71.0 (C-6), 118.6 (C-5′), 140.9 (C-8′), 149.7 (C-4′), 152.6 (C-2′), 156.0 (C-6′). – $C_{12}H_{15}N_5O_3$·EtOH (323.4): calcd. C 52.17, H 6.25, N 21.73; found C 52.40, H 6.31, N 21.90.

6-Iodopurine Tetrabutylammonium Salt **7c**: 6-Iodopurine hemihydrate (1.60 g, 6.29 mmol) was treated with tetrabutylammonium hydroxide (4.23 g of a 40% aq. solution, 6.52 mmol). Concentration gave crude **7c**, which was triturated with Et_2O to give yellow crystals (3.03 g, 98%) of m.p. 104–110°C. Recrystallization from EtOAc gave pale yellow crystals, m.p. 118°C. The salt was stable for several months when kept in a desiccator shielded from light. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7 Hz, 12 H, $CH_3[CH_2]_3$–), 1.31 (sext, *J* = 7 Hz, 8 H, $CH_3CH_2[CH_2]_2$–), 1.44 (m, 8 H, $CH_3CH_2CH_2CH_2$–), 2.98 (m, 8 H, $CH_3[CH_2]_2CH_2$–), 8.22 (s, 1 H, 8-H), 8.34 (s, 1 H, 2-H). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.6, 19.6, 23.8, 58.5 ($CH_3CH_2CH_2CH_2$–), 117.0 (C-5), 140.9 (C-6), 148.3 (C-8), 156.8 (C-2), 159.4 (C-4). – $C_{21}H_{38}IN_5$ (487.5): calcd. C 51.74, H 7.86, I 26.03, N 14.37; found C 51.97, H 7.71, I 26.13, N 14.32.

6-Chloropurine Tetrabutylammonium Salt **7b**: Prepared from 6-chloropurine as described for **7c**; colourless solid (88% crude), which was crystallized, m.p. 86−87°C (from EtOAc). − ^{1}H NMR (250 MHz, $CDCl_3$): (nBu)$_4$N$^+$ signals: δ = 0.91 (12 H), 1.29 (8 H), 1.43 (8 H), 2.99 (8 H). Purine signals: δ = 8.25 (s, 1 H, 8-H), 8.49 (s, 1 H, 2-H).

6-Benzamidopurine Tetrabutylammonium Salt **7a**: Prepared from 6-benzamidopurine as described for **7c**. Colourless non-crystalline solid (87% crude). − ^{1}H NMR (250 MHz, $CDCl_3$): (nBu)$_4$N$^+$ signals: δ = 0.91 (12 H), 1.29 (8 H), 1.43 (8 H), 2.99 (8 H). Bz signals: δ = 7.46 (m, 3 H), 8.10 (br. d, J = 8.5 Hz, 2 H). Purine signals: δ = 8.12, 8.16, 8.59, 8.63 (each s, intensity 1:1:1:1, 2 H altogether).

Methyl 6-(Adenin-9-yl)-6-deoxy-α-D-glucopyranoside (**11**): Methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (759 mg, 1.50 mmol)[18] was converted into its triflate **8** (923 mg, 1.45 mmol) by adapting a literature procedure.[17] The triflate **8** was dissolved in dry CH_2Cl_2 (20 ml) and cooled in an ice bath. Then, **7c** (715 mg, 1.47 mmol) was added and the clear solution was stirred for 18 h at room temp. The mixture was purified by VLC (4 × 3). Elution with hexane/EtOAc (1.75:1) gave **9c** (860 mg, 81%), while hexane/EtOAc (1:2) gave **10c** (70 mg; 7%). Compound **9c** (458 mg, 0.62 mmol) was treated with liquid NH_3 as described for **6**, and MPLC gave **11** (174 mg, 89%), m.p. 199°C, $[\alpha]_D^{23}$ = +86 (c = 0.4, H_2O) as earlier reported.[23][24]

6-Iodopurin-9-yl Derivative **9c**: M.p. 204−205°C (from EtOH), $[\alpha]_D^{23}$ = +36.5 (c = 0.8, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.14 (s, 3 H, 1′-OMe), 4.46−4.63 (m, 3 H, 5′-H and 2 × 6′-H), 5.20−5.25 (m, 2 H, 1′-H and 2′-H), 5.33 (t, J = 9.5 Hz, 1 H, 4′-H), 6.14 (t, J = 9.5 Hz, 1 H, 3′-H), 7.25−8.05 (m, 15 H, 3 × *Ph*CO), 8.34 (s, 1 H, 2-H), 8.51 (s, 1 H, 8-H); ′ denotes sugar signals. − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.5 (C-6′), 55.7 (MeO), 67.7 (C-5′), 69.9 (C-3′), 70.3 (C-4′), 71.7 (C-2′), 97.2 (C-1′), 122.1 (C-5), 128.2−133.7 (*Ph*CO), 138.2 (C-6), 145.4 (C-8), 148.0 (C-4), 152.0 (C-2), 165.5, 165.6, 165.7 (3 × Ph*C*O). − $C_{33}H_{27}IN_4O_8$ (734.5): calcd. C 53.96, H 3.71, I 17.28, N 7.63; found C 53.87, H 3.89, I 17.51, N 7.71.

6-Iodopurin-7-yl Derivative **10c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.90 (s, 3 H, 1′-OMe), 4.20−4.45 (m, 3 H, 5′-H and 2 × 6′-H), 5.17 (d, 1 H, J = 4 Hz, 1′-H), 5.30 (m, 1 H, 2′-H), 5.51 (t, J = 10 Hz, 1 H, 4′-H), 6.22 (t, J = 10 Hz, 1 H, 3′-H), 7.20−8.05 (m, 15 H, 3 × *Ph*CO), 8.48 (s, 1 H, 2-H), 8.72 (s, 1 H, 8-H); ′ denotes sugar signals.

6-Chloropurinyl Derivatives **9b**/**10b**: Prepared and separated as described for **9c**/**10c**. Compounds **9b**/**10b** were obtained in a 4:1 ratio (81% total yield). For **9b**, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.28 (s, 1 H, 2-H), 8.55 (s, 1 H, 8-H). Sugar signals essentially as in **9c**. − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 44.4 (C-6′), 55.7 (MeO), 67.6 (C-5′), 69.8 (C-3′), 70.1 (C-4′), 71.7 (C-2′), 97.1 (C-1′), 122.1 (C-5), 129.8−128.2 (*Ph*CO), 131.1 (C-5), 133.2−133.7 (*Ph*CO), 146.1 (C-8), 151.0 (C-4), 151.7 (C-6), 152.0 (C-2), 165.5, 165.6 (Ph*C*O); ′ denotes sugar signals. For **10b**, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, 2-H), 8.82 (s, 1 H, 8-H). Sugar signals essentially as in **10c**.

6-Benzamidopurinyl Derivatives **9a**/**10a**: Prepared as described for **9c**/**10c**. TLC of the reaction mixture showed two product spots (R_f = 0.25 and 0.33, hexane/acetone 1:1) with equal UV intensity.

Isolation of Catalpol (**2**) *from Scutellaria albida:* The ethanol extract of fresh plant material (4.18 kg) was partitioned between H_2O and Et_2O. The aq. phase was adjusted to a volume of 400 ml, and was then washed with EtOAc (5 × 500 ml) and nBuOH (500 ml). The combined organic phases were re-extracted with H_2O (2 × 250 ml). The aq. phases were concentrated to yield a residue (100 g), which was dissolved in saturated aq. $NaHCO_3$ (1.4 l) and adsorbed on act. charcoal (350 g). The suspension was filtered, and the charcoal eluted successively with H_2O (22 l) and MeOH (6 l). Concentration of the MeOH eluate yielded crude **2** (25 g), which was purified by reversed-phase MPLC (several runs) to give pure **2** (16.3 g, 0.34% of fresh weight).

One-Pot Preparation of Tetrol **12a**: Glucoside **2** (1.01 g, 2.8 mmol) was treated with β-glucosidase (35 mg; Sigma) in H_2O (10 ml) for about 18 h at 35°C. Upon cooling to room temp., $NaBH_4$ (167 mg, 4.4 mmol) was added to the mixture. After 1 h, the mixture was neutralized with HOAc, charcoal (5.8 g) was added, and upon stirring for 5 min, the charcoal was filtered off on Celite. The charcoal was eluted with H_2O (10 ml) and then with MeOH (2 × 15 ml). Concentration of the MeOH fractions yielded **12a** (0.47 g, 82%), colourless oil. − ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 1.70−1.85 (m, 3 H, 2 × 4-H and 5-H), 2.35 (br. dt, J = 7.5 Hz, 2 × 2.5 Hz, 1 H, 9-H), 3.37 (d, J = 1 Hz, 1 H, 7-H), 3.56−3.67 (m, 2 H, 3-H), 3.62 (d, J = 12.5 Hz, 1 H, 10a-H), 3.69 (dd, J = 11.5 Hz, 2.5 Hz, 1 H, 1a-H), 3.83 (dd, J = 11.5 Hz, 2.5 Hz, 1 H, 1b-H), 3.99 (dd, J = 7.5 Hz, 1 Hz, 1 H, 6-H), 4.10 (d, J = 12.5 Hz, 1 H, 10b-H). − ^{13}C NMR (125 MHz, [D$_4$]methanol): δ = 31.9 (C-4), 41.4 (C-5), 43.9 (C-9), 59.1 (C-1), 61.9 (C-10), 62.7 (C-3), 63.5 (C-7), 67.2 (C-8), 78.3 (C-6).

Tetracetate **12b**: A small sample of **12a** was acetylated in Ac_2O/pyridine (1:1). Work-up gave tetraacetate **12b** with ^{1}H-NMR data as earlier published.[19] − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6 (C-4), 36.3 (C-5), 39.3 (C-9), 59.3 (C-7), 60.8 (C-1), 62.4 (C-10), 62.7 (C-3), 62.9 (C-8), 78.4 (C-6), 171.3, 170.9, 170.4, 170.3 (4 × CH_3CO); signals for C-1, C-3, C-7 and C-8 have been reassigned.

Tribenzoate **12c**: To a solution of tetrol **12a** (315 mg, 1.54 mmol) in dry pyridine/CH_2Cl_2 (1:1, 20 ml) at −78°C was added BzCl (0.58 ml, 5.00 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at −78°C for 2.5 h, when more BzCl (89 µl, 0.77 mmol) in dry CH_2Cl_2 (3 ml) was added. After an additional 0.5 h, EtOH (0.5 ml) was added. The mixture was diluted with CH_2Cl_2 (100 ml) and washed successively with 2 M H_2SO_4 (20 ml), saturated aq. $NaHCO_3$ (30 ml) and brine (40 ml). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified on a VLC column (4 × 3). Elution with hexane and then hexane/Me_2CO (6:1) gave the desired **12c** (480 mg, 60%), colourless foam, $[\alpha]_D^{23}$ = −97 (c = 0.3, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04−2.14 (m, 2 H, 4-H), 2.52 (br. p, J = 8 Hz, 1 H, 5-H), 2.64 (br. dt, J = 8 Hz, 2 × 2.5 Hz, 1 H, 9-H), 3.90 (d, J = 1 Hz, 1 H, 7-H), 3.97 (dd, J = 11.5 Hz, 2.5 Hz, 1 H, 1a-H), 4.06 (dd, J = 11.5 Hz, 2.5 Hz, 1 H, 1b-H), 4.32−4.40 (m, 2 H, 3-H), 4.43 (d, J = 12.5 Hz, 1 H, 10a-H), 5.02 (d, J = 12.5 Hz, 1 H, 10b-H), 5.42 (dd, J = 9 Hz, 1.5 Hz, 1 H, 6-H), 7.35−7.45 (m, 6 H, 3 × 3′-H and 3 × 5′-H), 7.50−7.59 (m, 3 H, 4′-H), 7.96−8.06 (m, 6 H, 3 × 2′-H and 3 × 6′-H); ′ denotes benzoyl signals. − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.8 (C-4), 36.8 (C-5), 42.0 (C-9), 58.6 (C-1), 59.9 (C-7), 63.2 (C-10), 63.7 (C-3 and C-8), 79.6 (C-6), 166.7, 166.5, 166.3 (3 × Ph*C*O). − $C_{30}H_{28}O_8$ (516.6): calcd. C 69.76, H 5.46; found C 69.82, H 5.33.

Triflylation of Tribenzoate **12c** *and Coupling with Tetrabutylammonium Salt* **7c**. − *Compound* **13**: To a solution of dry pyridine (90 µl, 1.12 mmol) in dry CH_2Cl_2 (5 ml) at −40°C was slowly added a solution of $(CF_3SO_2)_2O$ (168 µl, 1.02 mmol) in dry CH_2Cl_2 (5 ml). After the suspension was stirred for another 5 min, **12c** (335 mg, 0.65 mmol) in CH_2Cl_2 (8 ml) was added dropwise. The mixture was allowed to heat to 0°C during 2 h, and was then stirred at room temp. for another 2 h. The clear solution was diluted with CH_2Cl_2 (35 ml) and ice (5 g) was added. The organic phase was

washed successively with cold 3% aq. HCl (10 ml), saturated aq. $NaHCO_3$ (20 ml) and brine (25 ml). Upon drying (Na_2SO_4), the volume was reduced to ca. 20 ml in vacuo and 4 Å molecular sieves (ca. 3 g) were added. After stirring for 15 min at 0°C, the tetrabutylammonium salt **7c** (350 mg, 0.72 mmol) was added to the solution. Stirring was continued for 2 h at 0°C and 18 h at −10°C. The mixture was filtered and the filtrate was concentrated to ca. 5 ml, which was loaded onto a VLC column (4.5 × 3). Elution with hexane and then hexane/Me_2CO (3:1) yielded benzoate **13** (354 mg, 73%) as an unstable solid which could only be stored below −10°C; $[\alpha]_D^{23} = -49$ (c = 0.5, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04−2.14 (m, 2 H, 4-H), 2.74 (br. p, J = 8 Hz, 1 H, 5-H), 3.77 (ddd, J = 9.5 Hz, 7.5 Hz, 4 Hz, 1 H, 9-H), 3.97 (d, J = 1 Hz, 1 H, 7-H), 4.05 (d, J = 13 Hz, 1 H, 10a-H), 4.35−4.60 (m, 3 H, 2 × 3-H and 1a-H), 4.67 (dd, J = 14.5 Hz, 4 Hz, 1 H, 1b-H), 4.77 (d, J = 13 Hz, 1 H, 10b-H), 5.34 (dd, J = 9.5 Hz, 1 Hz, 1 H, 6-H), 7.31−8.06 (15 H, 3 × *Ph*CO), 8.32 (s, 1 H, 2′-H), 8.49 (s, 1 H, 8′-H); ′ denotes purine signals. − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.7 (C-4), 36.5 (C-5), 39.0 (C-9), 42.3 (C-1), 58.4 (C-7), 62.7 (C-10), 63.5 (C-3), 63.6 (C-8), 77.6 (C-6), 122.4 (C-5′), 138.5 (C-6′), 144.3 (C-8′), 147.9 (C-4′), 151.7 (C-2′), 166.5, 166.3, 166.2 (3 × Ph*C*O); ′ denotes purine signals. − CI MS (NH_3 as reagent gas); *m/z:* 745 [M^+ + H]. − $C_{35}H_{29}IN_4O_7$ (744.5).

Ammonolysis of **13**. − *Nucleoside Analogue* **14**: Compound **13** (275 mg, 0.37 mmol) was treated with liquid NH_3 in a closed metal vessel at 45°C for 3 d. The residue was dissolved in EtOH/MeOH (2:1, 3 ml) and applied to a VLC column (3 × 3). Elution with hexane, $CHCl_3$ and then $CHCl_3$/MeOH (2:1) gave an impure fraction of **14**, purified by MPLC (size B column). Elution with H_2O/MeOH (3:1) yielded nucleoside analogue **14** (102 mg, 86%), as a hygroscopic foam, $[\alpha]_D^{23} = -57$ (c = 0.5, H_2O). − ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.50 (m, 1 H, 4a-H), 1.58 (dq-like, J = 14 Hz, 3 × 7 Hz, 1 H, 4b-H), 1.80 (dq-like, J = 9 Hz, 3 × 7 Hz, 1 H, 5-H), 3.06 (br. q, J = 7 Hz, 1 H, 9-H), 3.26 (dd, J = 13 Hz, 5.5 Hz, 1 H, 10a-H), 3.30 (m, 1 H, 3a-H), 3.33 (br. s, 1 H, 7-H), 3.36 (m, 1 H, 3b-H), 3.70 (dd, J = 13 Hz, 5.5 Hz, 1 H, 10b-H), 3.73 (dd, J = 9 Hz, 5.5 Hz, 1 H, 6-H), 4.16 (dd, J = 14.5 Hz, 7 Hz, 1 H, 1a-H), 4.20 (dd, J = 14.5 Hz, 7.5 Hz, 1 H, 1b-H), 4.47 (t, J = 5 Hz, 1 H, 3-OH), 4.66 (t, J = 5.5 Hz, 1 H, 10-OH), 5.08 (d, J = 5.5 Hz, 1 H, 6-OH), 7.18 (br. s, 2 H, 6′-NH_2), 8.14 (s, 1 H, 2′-H), 8.18 (s, 1 H, 8′-H); ′ denotes purine signals. − ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 30.2 (C-4), 39.3 (C-5), 39.7 (C-9), 40.5 (C-1), 59.5 (C-10), 60.1 (C-3), 60.8 (C-7), 65.7 (C-8), 74.6 (C-6), 118.7 (C-5′), 140.8 (C-8′), 149.6 (C-4′), 152.2 (C-2′), 155.9 (C-6′); ′ denotes purine signals. − CI MS (NH_3 as reagent gas); *m/z:* 322 [M^+ + H]. − $C_{14}H_{19}N_5O_4 \cdot 1/2\ H_2O$ (321.14): calcd. C 50.90, H 6.10, N 21.20; found C 50.77, H 6.00, N 20.86.

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