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Synthesis of a Cyclic Tetrameric Purine by Successive Cross-Coupling Reactions and Subsequent Pd-Catalyzed Cyclization

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The tetrameric *N*-benzyl-protected purine (quaterpurine) **2** was synthesized and characterized as its palladium complex [**2**·Pd]. The synthesis commenced with the Pd-catalyzed cross-coupling of 8-zincated 9-benzyl-6-chloro-8-iodopurine (**9**) and 9-benzyl-6-iodopurine (**11**) establishing the first C-6/C-8 bond. The sequence was repeated twice after iodo-dechlorination at C-6′ (C-6′′) of the respective dimer **12** and trimer **15**. The final ring closure was achieved at the tetrameric 6′′′-chloro-8-iodoquaterpurine **3b** by a reductive intramolecular cross-coupling with hexamethylditin in the presence of $Pd_2(dba)_3$ and P(2-furyl)$_3$. The overall yield in the eight step sequence was 17 % starting from 9-benzyl-6-chloropurine (**8**), the immediate precursor of **11**. Other strategies to combine the purine fragments, i.e. by dimer/dimer bond formation or by regioselective cross-coupling, were not successful.
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Introduction

Although the area of color chemistry belongs to the most mature research fields in Organic Chemistry, the interest in new chromophores and the need to develop new colorants has never ceased.[1] There are numerous non-classical applications for colorants as dyes and pigments, e.g. in optical data storage,[2] in solar energy conversion,[3] or in photodynamic therapy.[4] In search for new chromophores, which might be tunable by appropriate substitution, a recent report by Tauer[5] attracted our attention. This article describes so-called quaterheterocycles **1** (Figure 1), which can formally be conceived as [16]annulenes. The benzimidazole derivative **1a** exhibits in DMSO a long wavelength absorption at 393 nm ($\varepsilon \approx 10000$) and shows a strong band at 349 nm ($\varepsilon \approx 60000$). The benzoxazole **1b** behaves similarly but lacks the long wavelength absorption. The straightforward synthesis of compounds **1** was based on a low-yielding cyclocondensation of 2,3-difunctionalized benzoic acids.

We envisioned tetrameric purines of the general structure **A** (PG = protecting group) as highly interesting analogues of the quaterheterocycles. If a stepwise synthesis could be devised they would not only allow for a broad substituent (R^1–R^4) variation but they would also provide an option for protecting group(s) (PG^1–PG^4) removal from the purine. The resulting heterocycle should be amenable to a reduction (hydrogenation) which would generate after tautomerization an [18]annulene. For obvious reasons the reduction of compounds **1** is not feasible.

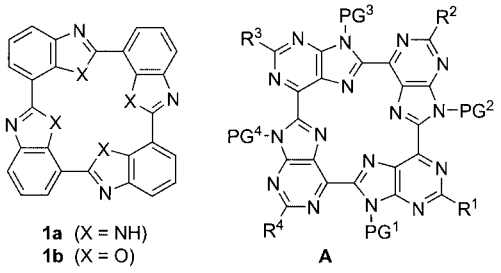

Figure 1. Quatercompounds **1** and general structure of tetrameric purines **A**.

As a first target the C_4-symmetric *N*-benzyl-protected tetrameric purine **2** was chosen (Scheme 1). The synthesis of the compound should ideally comprise a repetitive strategy, which should incorporate the four purine moieties successively. If this was successful it would be feasible in further work to exchange the purine building blocks at will and to modify the substitution pattern accordingly.

In this account we report on the synthesis of compound **2** by successive cross-coupling reactions between carbon atoms C-6 and C-8 of individual purine building blocks. We provide full details on the preliminary experiments and on the evolution of our synthetic strategy. It turned out that the goal of successive cross-coupling was in this case best achieved by addressing the electrophilic and nucleophilic positions of the purine core separately. Attempts to apply regioselective cross-coupling reactions to our synthetic target proved to be less rewarding.

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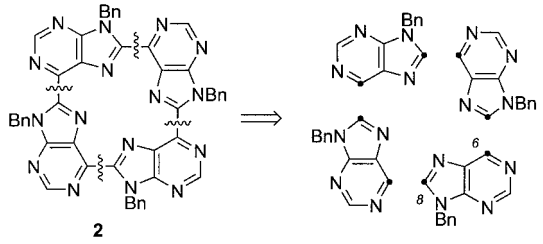
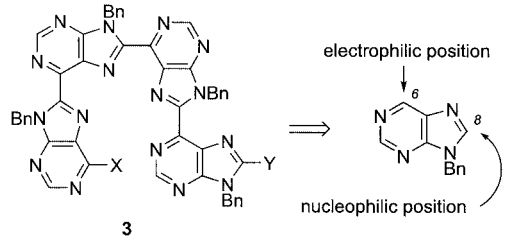


Scheme 1. Target compound **2** and disconnection into four purine units which need to be connected at the indicated (·) positions.

Reactivity of Purines

The retrosynthetic disconnection indicated in Scheme 1 requires a final C–C bond formation step at an appropriately functionalized (X,Y) non-cyclic tetrameric purine **3** (Scheme 2). Starting from monomeric building blocks three C–C bond forming reactions between C-6/C-8 are required. Alternatively, one could consider the fusion of two dimeric purines, which already bear the functional groups X and Y or appropriate precursors thereof. The general reactivity pattern of purines[6] in cross-coupling reactions[7] suggested to employ the 6-position as electrophilic site and the 8-position as nucleophilic site. Indeed, regioselective cross-coupling reactions[8] at 6,8-dichlorinated purines show a preference for a displacement at the 6-position,[9] while the 8-position could possibly be metalated by direct metalation or halogen–metal exchange.[10] Based on this consideration, it was appealing to employ a 6,8-dihalopurine as monomeric building block, which was to be subjected to a regioselective cross-coupling with an appropriately 6-functionalized (X) 8-metalated purine. After metalation of the 8-position in the dimer the next cross-coupling with a 6,8-dihalopurine could be conducted leading to a trimer. Repetition of the sequence would generate the tetrameric target **3**. In this scenario the individual purine building blocks could be introduced at will changing the substituent at C-2 and the protecting group at N-9.

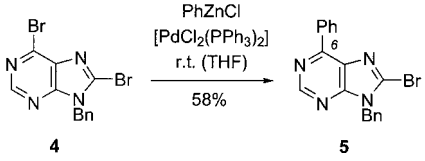


Scheme 2. Basic retrosynthetic consideration for the construction of open chain precursor **3**.

There is precedence for the generation of C-8 nucleophilic purines by deprotonation.[11] If deprotonated purines could be employed in a cross-coupling, the assembly would be even further simplified. It would be sufficient to employ a 6-halopurine as monomeric building block and to repeat a sequence of deprotonation/cross-coupling. In the following section our attempts to achieve a regioselective cross-coupling are described. They turned out not to offer a suitable route for dimer, trimer, nor tetramer formation. In the subsequent chapters our successful route is being described, which relies on a repetitive activation/cross-coupling strategy.

Regioselective Cross-Coupling Attempts

Possible 6,8-dihalopurines were first evaluated as cross-coupling substrates. In previous regioselective cross-coupling experiments, 9-protected 6,8-dichloropurines have been employed frequently.[9] The metalation of an 8-chloropurine – which was required for trimer and tetramer formation – is difficult, however. On the other side of the reactivity scale, 9-protected 6,8-diiodopurines were assumed to react with insufficient regioselectivity in the cross-coupling. In addition, synthetic access to these purines has not been reported.[12] The easily available 6,8-dibromopurine **4** was hence identified as the best starting material. Purine **4** was obtained from the known 9-benzyl-6-bromopurine[13] by deprotonation at C-8 (LDA in THF, –78 °C) and subsequent nucleophilic bromination[14] (BrCN, –78 °C). A regioselective Negishi cross coupling[15] at position C-6 was feasible under standard conditions (Scheme 3) to yield bromide **5**.



Scheme 3. Regioselective cross-coupling at position C-6 of dibromopurine **4**.

Further optimization reactions were not conducted. There was no hint for the occurrence of the other regioisomer. Although the outcome of this experiment is not extremely surprising given the precedence for similar reactions on 9-benzyl-6,8-dichloropurine[9a] it is to the best of our knowledge the first example for a regioselective cross-coupling on a 6,8-dibromopurine.

In Figure 2, starting materials are depicted, which were to be coupled as first monomeric building block with dibromide **4**. The triply protected adenine **6** was readily available from 9-benzyladenine by a twofold *tert*-butoxycarbonyl (Boc) protection (Boc_2O, DMAP in THF, room temp.).[16] The bromo analogue **7** was synthesized in a similar fashion from *N*-benzylated 8-bromoadenines.[17] The transformation of the $NBoc_2$ group into a suitable leaving group for cyclization (cf. Scheme 2, X in compound **3**) was envisioned after deprotection and diazotization. The diazotization of 9-benzyladenine and a subsequent displacement of the diazo group[18] were employed for the preparation of chloropurine **8**.[19]

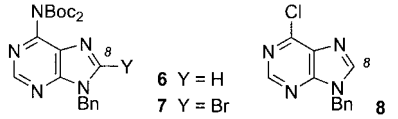


Figure 2. Potential precursors for a metalated purine at C-8.

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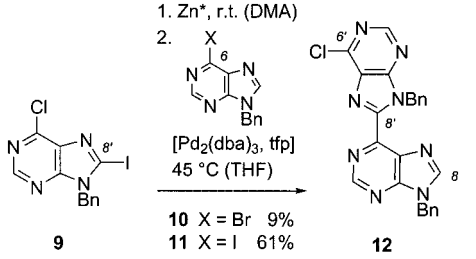
Attempts to deprotonate purine **6** failed, whereas the chloro compound **8** could be deprotonated readily with LDA in THF (–78 °C).[11] Transmetalation to zinc was conducted under standard conditions[20] employing $ZnCl_2$ in THF. Disappointingly, subsequent cross-coupling reactions with 6-bromopurines proceeded sluggishly under a variety of conditions in THF as the solvent. Standard palladium catalysts commonly employed for Neghishi reactions [e.g. $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2$(dppf), $PdCl_2$(*o*-tol)$_3$] did not deliver any cross-coupling product neither at ambient nor at elevated (45 °C) temperature. The in situ generated palladium complex formed from $Pd_2(dba)_3$ (dba: dibenzylidene acetone) and P(2-furyl)$_3$ (tfp: tri-2-furylphosphane) turned out to be slightly more effective. At 45 °C the cross coupling with 9-benzyl-6-bromopurine delivered 12% of the desired cross-coupling product and 24% of the C-8 dimer of the chloro compound **8**. Attempts to further optimize this result remained fruitless.

The bromo compound **7** offered the possibility to generate a metalated intermediate while avoiding the presence of diisopropylamine. However, neither attempted halogen–metal exchange reactions (BuLi, *t*BuLi) nor direct zincation reactions[21] delivered the desired C-8 metalation product. In the former reactions, decomposition occurred indicating the instability of the protecting groups towards strong lithium nucleophiles. A method, which had been previously used[22] for a halogen–metal exchange/in situ zincation in the presence of Boc groups, was not applicable to **7**, either. We speculated that the failure of the metalation was due to the labile $NBoc_2$ group at C-6 and decided to attempt the metalation with a more robust substituent at C-6. The iodination of compound **8** at C-8 has been reported by Gundersen et al.[9a] and made iodide **9** readily available (Scheme 4).



Scheme 4. Bond formation between C-6 and C-8′ by Negishi cross-coupling.

Successful Dimer Formation

Iodide **9** underwent a smooth direct metalation at C-8 employing activated zinc[21] in *N*,*N*-dimethylacetamide (DMA) as the solvent. Cross-coupling attempts with 6-bromopurines, such as **10**,[13] remained unsatisfactory, however. Again, the best catalyst was found to be $Pd_2(dba)_3$/tfp but yields of dimer **12** were disappointingly low. Iodide **11**, which was easily prepared from chloride **8** by treatment with aqueous HI at 0 °C (88% yield),[23] was eventually employed to increase the electrophilicity of the 6-substituted purine. This switch turned out to be an effective remedy to achieve the desired cross-coupling. Dimer **12** was obtained in 61% yield.

It was quickly shown that the conversion of dimer **12** into either one of the two compounds **13** and **14** was extremely facile. We therefore decided to give up the regioselective cross-coupling strategy and we concentrated on the repetitive activation of an appropriate position. Dimer **13** was prepared in 77% yield from cross-coupling product **12** by treatment with *N*-iodosuccinimide (NIS) in refluxing THF. Iodide **14** was obtained quantitatively from chloride **12** by the previously mentioned iodo-de-chlorination (HI in H_2O, 0 °C). To proceed further it was considered to conduct either metalation at C-8 of compound **13** with subsequent cross-coupling to **11** or repeated cross-coupling with the zinc reagent derived from **9** at C-6′ of iodide **14**. Disappointingly, the metalation of iodide **13** failed under the conditions successfully applied to iodide **9**. The failure also precluded the connection of **13** and **14** employing **13** as the nucleophile and **14** as the electrophile. We shortly investigated, whether the alternative combination, i.e. a cross-coupling with iodide **13** as the electrophilic partner was possible. While 6-metalated purines were accessible[21] and could be coupled to trivial iodides, such as iodobenzene, the reaction with iodide **13** at C-8 was not feasible (Figure 3).

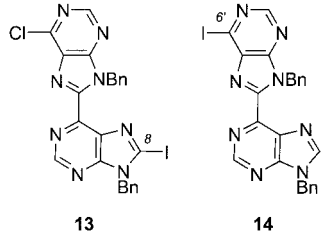


Figure 3. Dimeric purines **13** and **14** with respective reactive sites at C-8 and C-6′.

The alternative strategy, i.e. to attach the monomeric building blocks successively to the 6-position, was evaluated simultaneously. It eventually opened a route for the completion of the synthesis.

Completion of the Synthesis

In a test reaction, phenylzinc chloride (generated from phenyllithium and zinc chloride) underwent a clean cross-coupling with iodide **14** at carbon atom C-6′. The coupling conditions were identical to the conditions found for the transformation **11**→**12** [$Pd_2(dba)_3$/tfp at 45 °C in THF]. The result indicated that an oxidative addition at the substrate was possible with the given catalyst system. The obvious way to proceed was to use the same conditions for the metalation as applied to **9** in the reaction **11**→**12** and to analogously attempt the cross-coupling with **14**. Surprisingly, the reaction, which had worked with the monomeric iodide **11**, did not work with the dimeric iodide **14**. After considerable experimentation we found that an iodine–magnesium exchange[24] was in contrast to the iodine–lithium

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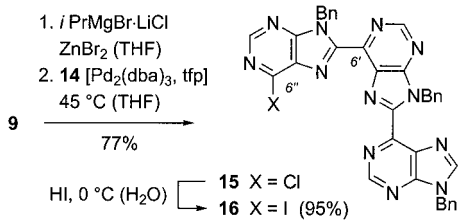
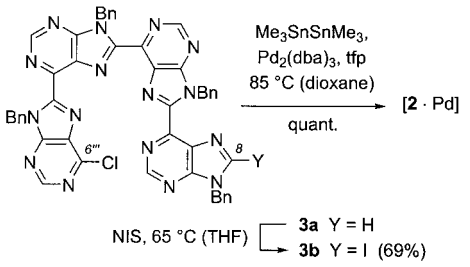
exchange reaction complete and that after transmetalation to zinc (zinc bromide in THF) a successful cross-coupling could be achieved [$Pd_2(dba)_3$/tfp at 45 °C in THF] upon addition of lithium chloride (Scheme 5). Ideally, the lithium chloride was introduced as *i*PrMgBr·LiCl reagent.[25] Although the conditions were found empirically, they can be rationalized in retrospective. The Grignard reagent is more effective in the halogen–metal exchange step than butyllithium. Lithium chloride enhances the rate of the oxidative addition step in the catalytic cross-coupling cycle,[26] while the use of the $Pd_2(dba)_3$/tfp as catalyst makes the transmetalation reasonably fast[27] and avoids hydro-de-halogenation and substrate dimerization.



Scheme 5. Synthesis of the trimeric purines **15** and **16**.

With the conditions for a successful cross-coupling at dimeric purine **14** in hand, we repeated the conversion **11**→**12** under these conditions. The cross-coupling yield could be improved to 85%. Moreover, we applied the very same conditions to the cross-coupling of the analogous trimer **16**. To this end, chloride **15** was converted into the 6′′-iodide **16** and the iodide was subjected to the conditions of the cross-coupling reaction. We were pleased to note, that the cross-coupling protocol proved its generality. The tetrameric chloride **3a** (Scheme 6) was obtained from metalated purine **9** and from iodide **16** in full analogy to **15**. The unreactive 8-position could be easily functionalized by NIS treatment (**3a**→**3b**). Attempts to convert the 6′′′-chloro-8-iodopurine **3b** into the corresponding diiodide failed. Based on the ease, with which cross-coupling reactions at 6-chloropurines occur,[6] we speculated that the 6′′′-chloride **3b** should be sufficiently reactive for an oxidative addition by palladium. Indeed, the desired tetrameric purine was generated by this means. Optimization unexpectedly revealed that quantitative amounts of palladium are required to drive the reaction to completion (Scheme 6). Dioxane was used as solvent and tfp as phosphane ligand. The product was not soluble in organic solvents but could only be dissolved in



Scheme 6. Completion of the synthesis starting from the open tetrameric purine **3a**.

trifluoroacetic acid (TFA). TFA solutions confirmed the expected highly symmetric structure in the NMR spectrum. Mass spectral analysis of the coupling product proved its elemental composition as palladium complex [**2**·Pd]. Further information about the site and coordination of palladium could not be obtained.

Conclusion

In summary, the tetrameric purine **2** was obtained from known 9-benzyl-6-chloropurine (**8**) in eight synthetic steps and in 17% overall yield as its palladium complex [**2**·Pd]. Key steps of the synthetic route are the consecutive Negishi cross-coupling of the 8-zincated purine derived from 6-chloro-8-iodopurine **9** and the ring closure by a Pd-catalyzed reductive cyclization mediated by hexamethylditin. The route is currently applied to other purines. In addition, the spectroscopic properties of the relevant heterocycles are investigated. Results of this study will be disclosed in due course.

Experimental Section

General Remarks: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Common solvents [ether, ethyl acetate (EtOAc), dichloromethane, methanol (MeOH), pentane (P) and toluene] were distilled prior to use. Anhydrous dichloromethane, *N*,*N*-diisopropylamine and pyridine were distilled from CaH_2, prior to use. Relevant literature known compounds: 9-benzyl-6-bromopurine (**10**),[13] *i*PrMgBr·LiCl,[25] and tri(2-furyl)phosphane (tfp).[28] All other reagents were used as received. IR: Perkin–Elmer 241 FT-IR. ^1H and ^{13}C NMR: Bruker AC-250, AV-360 and AMX-500. Chemical shifts are reported relative to tetramethylsilane as internal reference. The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. TLC: Merck glass sheets 0.25 mm silica gel 60-F_{254}. Detection by UV and coloration with cerium ammonium molybdate solution (CAM). Flash chromatography: Merck silica gel 60 (230–400 mesh) (ca. 50 g for 1 g of material to be separated), eluent given in brackets. MS: Finnigan MAT 8200 (EI), Finnigan MAT 95S (HRMS), Bruker Biflex III and Ultraflex 2 (MALDI), Finnigan LTQ FT (ESI). If not indicated, all bromine and chlorine containing compounds gave the expected mass pattern, i.e. Cl (^{35}Cl/^{37}Cl = 3:1), Br (^{79}Br/^{81}Br = 1:1), and Br_2 ($^{81}Br^{81}Br$/$^{79}Br^{81}Br$/$^{79}Br^{79}Br$ = 1:2:1). For simplicity, the intensity of only one signal, i.e. M^+(^{35}Cl), M^+(^{81}Br), or M^+($^{79}Br^{81}Br$) is provided in the analytical data.

9-Benzyl-6,8-dibromopurine (4): To a solution of diisopropylamine (1.17 mL, 850 mg, 8.39 mmol) in THF (30 mL) was added at 0 °C butyllithium in hexane (2.5 M, 3.35 mL, 8.39 mmol). The solution was treated dropwise at –78 °C with 9-benzyl-6-bromopurine (**10**) (2.02 g, 6.99 mmol) in THF (15 mL). After 2 h, BrCN (1.48 g, 14.0 mmol) in THF (5 mL) was added dropwise. The reaction was quenched with aqueous NH_4Cl (5 mL) after 1.5 h. The reaction mixture was diluted with EtOAc (100 mL), washed with aqueous NaCl (100 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (P/EtOAc, 3:1) to afford **4** (872 mg, 2.37 mmol, 34%) as a light brown solid. M.p. 98 °C. R_f = 0.63 (P/EtOAc, 1:1). ^1H NMR (360 MHz, $CDCl_3$): δ = 5.48 (s, 2 H), 7.30–7.40 (m, 5

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H), 8.70 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 48.3 (t), 127.9 (d), 128.7 (d), 129.0 (d), 134.0 (s), 134.1 (s), 134.4 (s), 141.4 (s), 151.7 (s), 152.1 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3062 cm^{-1} (w, C_{ar}-H), 3028 (w, C_{ar}-H), 1586 (s), 1560 (s), 1452 (s), 1428 (s), 1368 (m), 1347 (m), 1325 (vs), 1246 (m), 1133 (m), 920 (w), 898 (w), 854 (w), 726 (s). MS (EI, 70 eV): *m*/*z* (%) = 368 (15) [M^+(^{81}Br^{79}Br)], 289 (42) [M^+(^{81}Br^{79}Br) – ^{79}Br], 274 (15), 91 (100) [$C_7H_7^+$], 77 (28) [$C_6H_5^+$], 65 (40) [$C_5H_5^+$]. HRMS calcd. for $C_{12}H_8{}^{79}Br_2N_4$ 365.9116, found 365.9108.

9-Benzyl-8-bromo-6-phenylpurine (5): Phenyl bromide (58.0 μL, 86.0 mg, 550 μmol) was dissolved in THF (1 mL), cooled to –78 °C and butyllithium in hexane (2.5 M, 240 μL, 600 μmol) was slowly added. After stirring for 15 min at –78 °C $ZnCl_2$ in THF (1 M, 1.00 mL, 1.00 mmol) was added and after an additional 1 h at –78 °C the mixture was warmed to room temp. This solution was added to a solution of $PdCl_2(PPh_3)_2$ (35 mg, 10 mol-%) and 9-benzyl-6,8-dibromopurine (**4**) (156 mg, 424 μmol) in THF (0.5 mL). The reaction mixture was stirred at ambient temperature for 16 h and quenched with aqueous NH_4Cl (2 mL). The organic layer was washed with water (2 mL) and aqueous NaCl (2 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (P/EtOAc, 9:1) to afford **5** (89.0 mg, 244 μmol, 58%) as a light yellow solid. M.p. 134 °C. R_f = 0.64 (P/EtOAc, 7:3). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.52 (s, 2 H), 7.30–7.39 (m, 5 H), 7.50–7.59 (m, 3 H), 8.73–8.78 (m, 2 H), 9.01 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 48.1 (t), 128.3 (d), 128.9 (d), 129.2 (d), 129.4 (d), 130.2 (d), 131.7 (d), 131.7 (s), 133.5 (s), 135.2 (s), 135.5 (s), 153.0 (d), 154.0 (s), 154.2 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3055 cm^{-1} (w, C_{ar}-H), 2925 (w, C-H), 1582 (vs), 1555 (vs), 1496 (s), 1455 (s), 1430 (s), 1372 (m), 1320 (s), 1235 (m), 1164 (m), 764 (m), 721 (m), 689 (m), 656 (m). MS (EI, 70 eV): *m*/*z* (%) = 366 (31) [M(^{81}Br)$^+$], 364 (30) [M(^{79}Br)$^+$], 285 (52) [M^+ – Br], 91 (100) [$C_7H_7^+$], 65 (14) [$C_5H_5^+$]. HRMS calcd. for $C_{18}H_{13}{}^{79}BrN_4$ 364.0324, found 364.0323.

9-Benzyl-6-chloropurine (8): To a suspension of adenine (20.6 g, 153 mmol) in DMF (400 mL) was added at 0 °C NaH (60% in mineral oil, 6.11 g, 153 mmol). After 1 h stirring at room temp. benzyl chloride (35.1 mL, 306 mmol) was added. After additional stirring for 24 h the reaction was concentrated under reduced pressure and H_2O was added. The precipitate was filtered and washed with H_2O and Et_2O. The remaining benzyladenine was dried in vacuo. To benzyladenine (34.0 g, 151 mmol) in dry dichloromethane (500 mL) was added at 0 °C TMSCl (194 mL, 165 g, 1.51 mol). After 10 min stirring *tert*-butyl nitrite (99.3 mL, 86.4 g, 755 mmol) and benzyltriethylammonium chloride (68.9 g, 302 mmol) were added. After 27 h stirring at ambient temperature the reaction mixture was diluted with dichloromethane (300 mL), and then added slowly to aqueous $NaHCO_3$ (1 L). The aqueous layer was extracted with dichloromethane (2 × 300 mL). The combined organic layers were washed with brine (400 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/Et_2O, 8:2) to afford 9-benzyl-6-chloropurine (**8**)[19] (28.0 g, 115 mmol, 75%) as an off-white solid. M.p. 86 °C (ref.[19] m.p. 86–87 °C). R_f = 0.41 (P/EtOAc, 1:1). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.46 (s, 2 H), 7.27–7.42 (m, 5 H), 8.10 (s, 1 H), 8.79 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 48.0 (t), 128.0 (d), 128.9 (d), 129.3 (d), 131.3 (s), 134.4 (s), 144.9 (d), 151.1 (s), 151.8 (s), 152.3 (d) ppm. MS (EI, 70 eV): *m*/*z* (%) = 246 (23) [M(^{37}Cl)$^+$], 245 (32) [M(^{37}Cl)$^+$ – H], 244 (71) [M(^{35}Cl)$^+$], 243 (100) [M(^{35}Cl)$^+$ – H], 182 (15), 91 (74) [$C_7H_7^+$], 65 (15) [$C_5H_5^+$].

9,9′-Dibenzyl-6′-chloro-[6,8′]bipurine (12): Zinc dust (1.33 g, 20.3 mmol) in DMA (3 mL) and 1,2-dibromoethane (59 μL) were heated three times with a heatgun until evolution of ethylene occurred. At ambient temperature TMSCl (200 μL) was added and the reaction mixture was stirred for 5 min. A solution of 9-benzyl-6-chloro-8-iodopurine (**9**) (2.50 g, 6.76 mmol) in DMA (4.5 mL) was added dropwise and the reaction mixture was heated to reflux for 1 min. After cooling to room temperature for 2.5 h THF (4 mL) was added. Stirring was stopped and the remaining zinc dust was allowed to settle (1.5 h). The supernatant liquid was transferred via syringe to a solution of $Pd_2(dba)_3$ (216 mg, 5 mol-%), tfp (216 mg, 20 mol-%) and 9-benzyl-6-iodopurine (**11**) (1.59 g, 4.73 mmol) in THF (10 mL). The reaction mixture was stirred at 45 °C for 16 h and was quenched with aqueous NH_4Cl (100 mL), extracted with dichloromethane (3 × 100 mL), washed with brine (100 mL) and dried (Na_2SO_4). After filtration the solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography (P/EtOAc, 4:6) to give the desired product **12** (1.30 g, 2.87 mmol, 61%) as an off-white solid. M.p. 194 °C. R_f = 0.16 (P/EtOAc, 4:6). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.51 (s, 2 H), 6.24 (s, 2 H), 7.13 (s, 5 H), 7.28–7.40 (m, 5 H), 8.30 (s, 1 H), 8.84 (s, 1 H), 9.13 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.6 (t), 48.1 (t), 127.5 (d), 127.8 (d), 127.9 (d), 128.5 (d), 128.8 (d), 129.2 (d), 131.8 (s), 132.1 (s), 134.6 (s), 136.0 (s), 145.8 (s), 147.2 (d), 149.0 (s), 151.8 (d), 152.2 (s), 152.8 (d), 153.3 (s), 153.4 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3200–3600 cm^{-1} (w), 3062 (w), 1574 (vs), 1558 (s), 1504 (m), 1452 (m), 1397 (w), 1339 (m), 1322 (s), 1247 (m), 1223 (w), 1152 (m), 1020 (w), 938 (w), 727 (m), 705 (m), 644 (w). MS (EI, 70 eV): *m*/*z* (%) = 452 (69) [M^+], 361 (100) [M^+ – Bn], 91 (95) [$C_7H_7^+$]. $C_{24}H_{17}ClN_8$ (452.90): calcd. C 63.65, H 3.78, N 24.74; found C 63.55, H 3.72, N 24.73.

General Iodination Procedure with Aqueous HI: The respective 6-chloropurine (1 mmol) was added at 0 °C in small portions to vigorously stirred 57% aqueous HI (2 mL/mmol). After stirring at 0 °C for 1 h the reaction mixture was carefully added to aqueous $NaHCO_3$ (10 mL/mmol). The aqueous layer was extracted with dichloromethane (3 × 10 mL/mmol), washed with aqueous NaS_2O_3 (10 mL/mmol) and brine (10 mL/mmol). The organic layer was dried (Na_2SO_4), filtered, the solvent was removed under reduced pressure. The procedure was repeated twice to achieve complete iodination providing the desired 6-iodopurine.

9-Benzyl-6-iodopurine (11): According to the General HI Iodination Procedure, iodide **11** was obtained from 9-benzyl-6-chloropurine (**8**) (10.0 g, 44.6 mmol) as a light brown solid (13.2 g, 39.3 mmol, 88%). M.p. 142 °C (ref.[23] m.p. 152–154 °C). R_f = 0.35 (P/EtOAc, 1:1). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.42 (s, 2 H), 7.28–7.37 (m, 5 H), 8.10 (s, 1 H), 8.65 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.9 (t), 122.1 (d), 127.9 (d), 128.8 (d), 129.2 (s), 134.5 (s), 138.4 (s), 144.3 (d), 148.1 (s), 152.2 (d) ppm. MS (EI, 70 eV): *m*/*z* (%) = 336 (7) [M^+], 244 (44) [M^+ – Bn], 243 (43), 209 (9) [M^+ – I], 182 (10), 91 (100) [$C_7H_7^+$], 65 (25) [$C_5H_5^+$].

9,9′-Dibenzyl-6′-iodo-[6,8′]bipurine (14): According to the General HI Iodination Procedure, iodide **14** was obtained from 6′-chloropurine **12** (1.02 g, 2.26 mmol) as a light brown solid (1.31 g, 2.41 mmol, quant.). M.p. 144–148 °C. R_f = 0.40 (CH_2Cl_2/EtOAc, 4:6). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.50 (s, 2 H), 6.17 (s, 2 H), 7.10–7.14 (m, 5 H), 7.28–7.35 (m, 2 H), 7.35–7.39 (m, 3 H), 8.25 (s, 1 H), 8.71 (s, 1 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.6 (t), 48.0 (t), 123.7 (s), 127.5 (d), 127.8 (d), 127.9 (d), 128.5 (d), 128.8 (d), 129.2 (d), 132.3 (s), 134.6 (s), 135.9 (s), 138.6 (s), 145.9 (s), 147.0 (d), 148.3 (s), 149.6 (d), 151.8 (s), 152.7 (d), 153.3 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3600–3200 cm^{-1} (s), 3059 (w, Ar-H), 3031 (w), 1583 (s), 1552 (vs), 1496 (m), 1453 (s), 1396 (w), 1323 (s), 1233 (m), 1211 (m), 1133 (m), 1015 (w), 929 (w), 834 (w), 727

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(s), 696 (m), 642 (m). MS (EI, 70 eV): *m*/*z* (%) = 544 (20) [M^+], 453 (22), 361 (11), 336 (13), 91 (100) [$C_7H_7^+$], 65 (15) [$C_5H_5^+$]. HRMS calcd. for $C_{24}H_{17}N_8I$ 544.0621, found 544.0615.

9,9′,9′′-Tribenzyl-6′′-iodo-[6,8′,6′,8′′]terpurine (16): According to the General HI Iodination Procedure, iodide **16** was obtained from 6′′-chloropurine **15** (1.02 g, 2.26 mmol) as a light brown solid (825 mg, 1.10 mmol, 95%). M.p. 129 °C. R_f = 0.38 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (360 MHz, [D$_6$]DMSO): δ = 5.58 (s, 2 H), 6.03 (s, 2 H), 6.05 (s, 2 H), 6.98–7.18 (m, 10 H), 7.30–7.39 (m, 5 H), 8.78 (s, 1 H), 8.93 (s, 1 H), 9.14 (s, 1 H), 9.21 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ = 46.6 (d), 46.9 (d), 47.1 (d), 124.1 (d), 126.8 (d), 127.0 (d), 127.4 (d), 127.5 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.6 (d), 131.4 (s), 131.9 (s), 135.8 (s), 136.0 (s), 137.7 (s), 144.5 (s), 145.7 (s), 148.6 (s), 148.9 (d), 149.2 (s), 150.4 (s), 151.4 (d), 152.6 (d), 152.7 (d), 152.8 (s), 153.8 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3600–3200 cm^{-1} (m), 3062 (w), 3030 (m), 1574 (vs), 1557 (vs), 1496 (m), 1455 (s), 1328 (s), 1236 (m), 1141 (m), 1030 (w), 929 (w), 728 (s), 698 (m), 642 (w). MS (MALDI): *m*/*z* = 752.996 (100) [M^+ + H].

General Iodination Procedure with *N*-Iodosuccinimide (NIS): A mixture of 8-hydropurine (1 equiv.) and NIS (3 equiv.) in dry THF (10 mL/mmol) was heated at reflux for 72 h. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (20 mL/mmol), washed with aqueous NaS_2O_3 (10 mL/mmol), aqueous NaCl (10 mL/mmol) and dried (Na_2SO_4). After filtration the solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography to give the desired 8-iodopurine.

9-Benzyl-6-chloro-8-iodopurine (9): According to the General NIS Iodination Procedure, iodide **8** was obtained from 6-chloropurine **8** (1.96 g, 8.03 mmol) and NIS (9.03 g, 40.2 mmol) as a white solid (3.00 g, 8.03 mmol, quant.). M.p. 136 °C (ref.[9a] m.p. 134–136 °C). R_f = 0.68 (CH_2Cl_2/Et_2O, 9:1). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.47 (s, 2 H), 7.33 (s, 5 H), 8.71 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 49.7 (t), 108.0 (s), 127.9 (d), 128.6 (d), 129.0 (d), 133.8 (s), 134.3 (s), 149.4 (s), 152.1 (d), 153.1 (s) ppm. MS (EI, 70 eV): *m*/*z* (%) = 370 (28) [M^+], 243 (85) [M^+ – I], 127 (25) [I^+], 91 (100) [$C_7H_7^+$], 77 (35) [Ph^+], 65 (42) [$C_5H_5^+$], 51 (18) [$C_4H_3^+$].

9,9′-Dibenzyl-6′-chloro-8-iodo-[6,8′]bipurine (13): According to the General NIS Iodination Procedure, iodide **13** was obtained from 9,9′-dibenzyl-6′-chloro-[6,8′]bipurine (**12**) (1.97 g, 4.36 mmol) and NIS (2.94 g, 16.1 mmol) as a white solid (1.94 g, 5.35 mmol, 77%). M.p. 236 °C. R_f = 0.65 (CH_2Cl_2/EtOAc, 1:1). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.53 (s, 2 H), 6.22 (s, 2 H), 7.12 (s, 5 H), 7.30–7.35 (m, 5 H), 8.85 (s, 1 H), 9.05 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 48.1 (t), 49.3 (t), 111.7 (s), 127.5 (d), 127.8 (d), 127.9 (d), 128.5 (d), 128.6 (d), 128.9 (d), 131.8 (s), 134.3 (s), 134.4 (s), 135.9 (s), 144.2 (s), 148.7 (s), 151.6 (d), 152.4 (s) 152.9 (d), 153.4 (s), 154.5 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3600–3300 cm^{-1} (m), 3032 (m), 1581 (vs), 1496 (s), 1466 (s), 1452 (vs), 1413 (s), 1350 (s), 1310 (s), 1250 (s), 1153 (s), 1029 (w), 945 (m), 859 (w), 720 (s), 649 (m), 602 (w), 571 (w), 536 (w). MS (EI, 70 eV): *m*/*z* (%) = 578 (7) [M^+], 451 (41) [M^+ – I], 91 (100) [$C_7H_7^+$]. $C_{24}H_{16}ClIN_8$ (578.80): calcd. C 49.80, H 2.79, N 19.36; found C 50.08, H 2.74, N 19.16.

9,9′,9′′,9′′′-Tetrabenzyl-6′′′-chloro-8-iodo-[6,8′,6′,8′′,6′′,8′′′]quaterpurine (3b): According to the General NIS Iodination Procedure, iodide **3b** was obtained from purine **3a** (88 mg, 101 μmol) and NIS (68 mg, 303 μmol) as a light brown solid (59.4 mg, 59.3 μmol, 59%). M.p. 177 °C. R_f = 0.25 (EtOAc/EtOH, 95:5). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.51 (s, 2 H), 6.24 (s, 2 H), 6.40 (s, 2 H), 6.49 (s, 2 H), 6.92–7.02 (m, 5 H), 7.10–7.18 (m, 10 H), 7.28–7.38 (m, 5 H), 8.68 (s, 1 H), 9.04 (s, 1 H), 9.16 (s, 1 H), 9.22 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.7 (t), 48.0 (t), 49.3 (t), 111.3 (s), 127.4 (d), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.3 (d), 128.5 (d), 128.6 (d), 129.0 (d), 131.8 (s), 132.0 (s), 132.3 (s), 134.4 (s), 134.6 (s), 136.0 (s), 136.1 (s), 136.3 (s), 144.3 (s), 146.5 (s), 146.6 (s′), 150.4 (s), 150.6 (s), 151.6 (d), 152.1 (s), 152.4 (d), 152.8 (s), 153.2 (d), 153.7 (s), 154.5 (s), 154.6 (s), 154.8 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1} (br. m), 3062 (w), 3031 (m), 1576 (vs), 1496 (m), 1452 (s), 1341 (s), 1246 (m), 1151 (m), 933 (w), 726 (s), 696 (m). MS (MALDI): *m*/*z* = 995.077 [M^+ + H], 1017.064 [M^+ + Na].

General Procedure for the Negishi Cross-Coupling: To 9-benzyl-6-chloro-8-iodopurine (**9**) (1.4 equiv.) was added *i*PrMgBr·LiCl[26] (0.72 M in THF, 1.4 equiv.) at –40 °C. After 15 min stirring at –40 °C $ZnBr_2$ (1 M in THF, 1.4 equiv.) was added, the stirring was continued for 20 min at –40 °C and then the mixture was allowed to reach ambient temperature. The zinc reagent was transferred via syringe to a solution of $Pd_2(dba)_3$ (5 mol-%), tfp (20 mol-%) and the corresponding 6-iodopurine (1.0 equiv.) in THF or DMA (10 mL/mmol). The reaction mixture was stirred at 45 °C for 16 h and then quenched with aqueous NH_4Cl (20 mL/mmol), extracted with dichloromethane (3 × 20 mL/mmol), washed with aqueous NaCl (20 mL/mmol) and dried (Na_2SO_4). After filtration the solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography to afford the desired product.

9,9′,9′′-Tribenzyl-6′′-chloro-[6,8′,6′,8′′]terpurine (15): According to the General Cross-Coupling Procedure, terpurine **15** was obtained from 9-benzyl-6-chloro-8-iodopurine (**9**) (1.01 g, 2.76 mmol) and 6′-iodopurine **14** (970 mg, 1.84 mmol) in THF as an off-white solid (937 mg, 1.41 mmol, 77%). M.p. 133 °C. R_f = 0.25 (EtOAc/EtOH, 99:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (s, 2 H), 6.36 (s, 4 H), 7.05–7.12 (m, 5 H), 7.14–7.18 (m, 5 H), 7.26–7.36 (m, 5 H), 8.30 (s, 1 H), 8.84 (s, 1 H), 9.11 (s, 1 H), 9.18 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.5 (t), 47.8 (t), 48.0 (t), 127.4 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.4 (d), 128.5 (d), 128.7 (d), 129.2 (d), 131.9 (s), 132.1 (s), 132.6 (s), 134.6 (s), 136.0 (s), 136.2 (s), 145.8 (s), 146.5 (s), 147.1 (s), 149.4 (s), 150.5 (s), 151.6 (d), 152.3 (s), 152.7 (d), 152.8 (d), 153.4 (s), 153.5 (s), 154.7 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3600–3200 cm^{-1} (m), 3062 (w), 3031 (m), 2928 (w), 1654 (s), 1577 (vs), 1560 (s), 1497 (m), 1453 (s), 1327 (s), 1243 (m), 1146 (m), 1030 (w), 936 (w), 727 (s), 696 (m), 642 (w). MS (MALDI): *m*/*z* = 661.053 [M^+].

9,9′,9′′,9′′′-Tetrabenzyl-6′′′-chloro-[6,8′,6′,8′′,6′′,8′′′]quaterpurine (3a): According to the General Cross-Coupling Procedure, quaterpurine **3a** was obtained from 9-benzyl-6-chloro-8-iodopurine (**9**) (184 mg, 498 μmol) and 6′′-iodopurine **16** (250 mg, 333 μmol) in DMA as a light brown solid (132 mg, 152 μmol, 46%). M.p. 160 °C. R_f = 0.25 (CH_2Cl_2/EtOAc/MeOH, 49:50:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.53 (s, 2 H), 6.36 (s, 2 H), 6.48 (s, 2 H), 6.55 (s, 2 H), 6.81 (d, ^3J = 7.1 Hz, 2 H), 6.89 (t, ^3J = 7.1 Hz, 2 H), 6.97 (t, ^3J = 7.1 Hz, 1 H), 7.12–7.21 (m, 10 H), 7.34–7.37 (m, 2 H), 7.39–7.43 (m, 3 H), 8.39 (s, 1 H), 8.58 (s, 1 H), 9.14 (s, 1 H), 9.18 (s, 1 H), 9.21 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.6 (t), 47.9 (t), 48.0 (t), 48.6 (t), 127.1 (d), 127.4 (d), 127.6 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.9 (d), 129.3 (d), 131.9 (s), 132.5 (s) 134.5 (s), 136.1 (s), 136.2 (s), 136.4 (s), 145.8 (s), 146.2 (s), 146.5 (s), 147.4 (d), 150.0 (s), 150.8 (s), 151.1 (s), 151.5 (d), 152.2 (d), 152.5 (d), 153.6 (s), 153.7 (d), 154.5 (s), 155.0 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1} (m br.), 3062 (w), 3031 (m), 1575 (vs), 1496 (m), 1455 (s), 1328 (s), 1236 (m), 1141 (m), 1030 (w), 929 (w), 728 (s), 698 (m), 643 (w). MS (MALDI): *m*/*z* = 869.45 [M^+ + H], 891.45 [M^+ + Na].

9-Benzyl-[6,8′]cyclotetrapurine (2·Pd): Purine **3b** (50.0 mg, 50.3 μmol), $Pd_2(dba)_3$ (23.0 mg, 50.3 μmol), tfp (46.0 mg,

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200 μmol) and $Me_3SnSnMe_3$ (20.8 μL, 106 μmol) were stirred at 85 °C in 1,4-dioxane (20 mL) for 2 d. The reaction mixture was filtered and washed with Et_2O. The residue was dissolved in TFA and evaporated under reduced pressure to afford the product **2**·Pd (47.0 mg, 50.1 μmol, *quant*.) as a green-blue solid. ^{1}H NMR (360 MHz, [D]TFA): δ = 6.95 (s, 8 H), 7.43 (s, 12 H), 7.68 (s, 8 H), 9.86 (s, 4 H) ppm. ^{13}C NMR (90.6 MHz, [D]TFA): δ = 53.1 (d), 128.6 (s), 130.5 (d), 131.4 (d), 131.7 (d), 135.7 (s), 144.0 (s), 146.4 (d), 156.3 (s), 158.7 (d) ppm. MS (MALDI): *m*/*z* (%) = 845 (90), 936 (100) [M^+ + Pd]. HRMS calcd. for $C_{48}H_{32}N_{16}{}^{104}Pd$ 938.2031, found 938.2039.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **2**·Pd, **3a**, **3b**, **4**, **5**, **8**, **9**, **11**–**16**.

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