Regioselective and Facile Synthesis of 7,9-Dialkyl-8-oxopurines from 7,9-Dialkyl-7,8-dihydropurines: Total Synthesis of Heteromines I and J

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Received: 21.10.2013; Accepted after revision: 09.12.2013

Abstract: A novel protocol for the synthesis of 6-halo-8-oxo-7,8-dihydro-9*H*-purines based on the oxidation of 7,9-dialkyl-7,8-dihydro-9*H*-purines has been developed. The presented methodology was used as a key step in the synthesis of heteromines I and J.

Key words: oxidation, reduction, heterocycles, nucleobases, natural product

Caissarone[1] and heteromines I and J are examples,[2] among others,[3] of naturally abundant 8-oxopurines (Figure 1). The 8-oxopurine scaffold is also found in modified nucleobases that are formed as a result of a DNA lesion.[4] These findings have led to an extensive study of the chemical and biological properties of 8-oxopurines. The incorporation of 8-oxopurines into oligonucleotides has enabled the study of the base-pairing properties of modified oligonucleotides.[5] Apart from the fact that 8-oxopurines represent one possible form of DNA damage, they also exhibit a wide range of biological properties. For instance, antitumor[6] and antiviral[7] activities have been recently reported. 8-Oxopurines have also been used as antagonists of corticotropin-releasing hormone receptor,[8] corticotropin-releasing factor$_1$ receptor,[9] adenosine A_{2A} receptor,[10] and an agonist of toll-like receptor 7.[11] 8-Oxopurines labeled with the ^{11}C isotope have been used for positron emission tomography imaging.[12] In some cases, immunostimulant[13] and interferon-inducing[14] activities, as well as the selective inhibition of dipeptidyl peptidase IV (DPPIV),[15] have been observed.

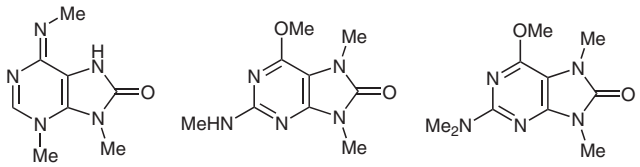
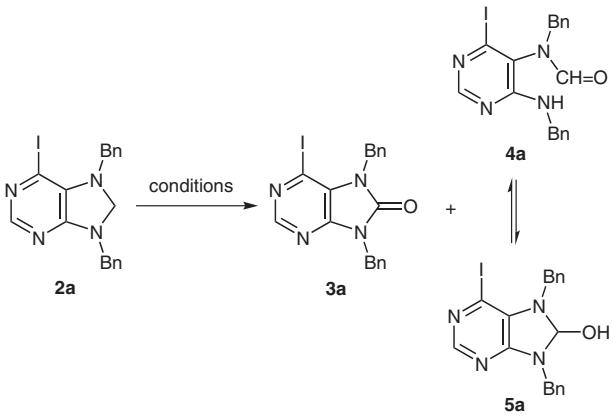


Figure 1 Structures of caissarone and heteromines I and J

Recent approaches to the synthesis of 8-oxopurines have been based on the hydrolysis of 8-bromopurines[16] or 8-sulfanylpurines.[17] The alternative route involves direct construction of the 8-oxopurine heterocycle, beginning with pyrimidine,[18,13] uracil,[19] or 2-oxoimidazole[20] derivatives. Other methodologies rely on the rearrangement of 8-(allyloxy)purines,[21] and N^7- or N^1-oxides.[22] The oxidation of adeninium salts with hydrogen peroxide also results in the formation of 8-oxopurines.[23] As a part of our ongoing research, we focused on the use of 7,8-dihydro-9*H*-purines in the synthesis of novel purine derivatives. We succeeded in developing a high-yielding and regioselective preparation of 7-substituted halopurines,[24] and 7-substituted adenines, guanines, and 6-mercaptopurines.[25] During the course of our studies, we observed that exposure of a solution of 7,8-dihydro-9*H*-purine **2a** to air afforded a small amount (≤10%) of 8-oxopurine **3a** as the product of spontaneous oxidation [26] (Scheme 1). However, to the best of our knowledge procedure for the preparation of halo-substituted 8-oxopurines, valuable intermediates in the synthesis of functionalized purines, based on oxidation of 7,8-dihydro-9*H*-purines has not been reported. Therefore, we decided to take advantage of the spontaneous formation of **3a** and explore the potential of 7,9-dialkyl-7,8-dihydro-9*H*-purines in the synthesis of 7,9-dialkyl-6-halo-8-oxopurines from a synthetic point of view.



Scheme 1 Oxidation of 7,9-dibenzyl-6-iodo-7,8-dihydro-9*H*-purine (**2a**)

For the initial study of the oxidation of 7,8-dihydro-9*H*-purines **2** to 8-oxopurines **3**, 7,9-dibenzyl-6-iodo-7,8-dihydro-9*H*-purine (**2a**) was used as the starting compound (Scheme 1). The starting **2a** was easily prepared from 9-benzyl-6-iodo-9*H*-purine (**1a**) by a previously reported procedure[24] that involves the reduction of 9-benzyl-6-iodo-9*H*-purine with diisobutylaluminum hydride, and alkylation by benzyl bromide using lithium hexamethyldi-

SYNTHESIS 2014, 46, 0660–0668
Advanced online publication: 09.01.2014
DOI: 10.1055/s-0033-1340499; Art ID: SS-2013-Z0689-OP

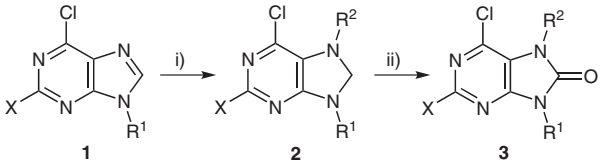
silazanide as the base. Dihydropurine **2a** was thus isolated in 85% yield. Initially we tested manganese dioxide in dichloromethane for the oxidation of **2a** to **3a**. However, the formation of a mixture of the desired oxopurine **3a** and formamidopyrimidine **4a** was observed (Table 1, entry 1). The ^{1}H NMR spectrum of isolated **4a** revealed that it is in equilibrium with its cyclic form **5a** in a ratio of 85:15. The structure of **4a** was determined by 2D NMR techniques. Oxidation in acetonitrile instead of dichloromethane led to the formation of formamidopyrimidine **4a** in 79% isolated yield (entry 2). Application of pyridinium chlorochromate led to the decomposition of **2a** (entry 3), but Jones reagent successfully oxidized **2a** to **3a** in 52% isolated yield (entry 4). The oxidation with other chromium-based oxidants like pyridinium dichromate or chromium trioxide–pyridine complex performed in dichloromethane at room temperature or at 0 °C resulted in similar yields of oxopurine **3a** (entries 5–7). When 3-chloroperoxybenzoic acid in dichloromethane at room temperature was used, the yield of **3a** increased substantially (entry 8). Further improvement was achieved when oxidation with 3-chloroperoxybenzoic acid was carried out in dichloromethane at 0 °C (entry 9).

Table 1 Optimization of the Oxidation of 7,9-Dibenzyl-6-iodo-7,8-dihydro-9*H*-purine (**2a**) to 7,9-Dibenzyl-6-iodo-8-oxo-7,8-dihydro-9*H*-purine (**3a**)

Entry	Oxidant	Conditions	Yield[a] (%)	
			3a	**4a** + **5a**
1	MnO_2	CH_2Cl_2, r.t.	49[b]	44[b]
2	MnO_2	MeCN, r.t.	12	79
3	PCC	CH_2Cl_2, r.t.	dec	–
4	Jones	acetone, 0 °C	52	–
5	CrO_3·py	CH_2Cl_2, r.t.	64	–
6	PDC	CH_2Cl_2, r.t.	50	–
7	PDC	CH_2Cl_2, 0 °C	64	–
8	MCPBA	CH_2Cl_2, r.t.	71	–
9	MCPBA	CH_2Cl_2, 0 °C	91	–

[a] Isolated yield.
[b] ^{1}H NMR yield with indene as internal standard.

To determine the scope of the presented protocol for the oxidation of 7,8-dihydro-9*H*-purines **2** to 8-oxopurines **3**, a series of 7,9-disubstituted 7,8-dihydro-9*H*-purines **2b**–**l** were prepared (Scheme 2).[24] With only one exception, the reduction of all 9-alkyl-6-chloro-9*H*-purines using diisobutylaluminum hydride proceeded smoothly. In the case of the Boc-protected 2-amino-9-benzyl-6-chloro-9*H*-purine, borane–tetrahydrofuran complex was used instead of diisobutylaluminum hydride. Subsequent alkylation with alkyl bromides and iodides produced the starting compounds **2b**–**l** with yields ranging from 59–93% (Table 2, entries 1–11).



Scheme 2 Oxidation of 7,9-dialkyl-7,8-dihydro-9*H*-purines to 8-oxopurines. *Reagents and conditions:* (i) 1. DIBAL-H, THF, r.t.; 2. LiHMDS, R^2X, DMF–THF, –78°C to r.t.; (ii) MCPBA, CH_2Cl_2, 0 °C.

The prepared 7,9-dialkyl-7,8-dihydro-9*H*-purines **2** were then used as starting compounds in the developed oxidation protocol (Scheme 2). First we focused on the 6-chloropurines **2b**–**e** that have a benzyl group at position 9. As with **2a**, 7,9-dibenzyl-6-chloro-7,8-dihydro-9*H*-purine (**2b**) was transformed to 8-oxopurine **3b** in 77% isolated yield (entry 1). Dihydropurine **2c**, which has ester functionality, was smoothly oxidized to **3c** in 90% yield (entry 2); the oxidation of **2c** was also performed on a 10-mmol scale without a significant decrease in the yield. 7,9-Dibenzyl-2,6-dichloro-9*H*-purine **2d** was also converted into 8-oxopurine **3d** in a good yield (entry 3). However, dihydropurine with an allyl group, **2e**, was oxidized with 3-chloroperoxybenzoic acid to form a mixture of the desired oxopurine **3e** and oxopurine with an epoxidized double bond. In this case, the chemoselective oxidation of **2e** to **3e** was achieved using pyridinium dichromate (entry 4). Attempts to oxidize dihydropurine **2f**, the substrate that is easily available by Michael addition to methyl vinyl ketone, failed to give pure compound **3f** (entry 5); in this case, the isolated oxopurine **3f** was 85% pure. Detailed analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed that **3f** is contaminated by 9-benzyl-6-chloro-9*H*-purine, which cannot be separated by simple column chromatography. The oxidation of **2f** with pyridinium dichromate slightly improved the purity of **3f** to 92%. We reasoned that the formation of 9-benzyl-6-chloro-9*H*-purine proceeds via acid-catalyzed retro-Michael addition. When **2f** was treated with benzoic acid in dichloromethane, 9-benzyl-6-chloropurine was detected by ^{1}H NMR after one hour, thus supporting our assumption. Moderate yields of oxopurines **3g**–**i** (entries 6–8) were obtained if the starting dihydropurines **2g**–**i** contained a methyl group. On the other hand, the starting dihydropurine containing an isopropyl group, **2j**, gave a substantially higher yield (entry 9). The oxidation of dihydropurine **2k** bearing a trityl group failed to give the expected product, however 7-benzyl-6-chloro-7*H*-purine was isolated in 52% yield as the product of deprotection and reoxidation (entry 10). The 3-chloroperoxybenzoic acid oxidation of dihydropurine **2l** with a Boc-protected amino group proceeded smoothly and the final product **3l** was isolated in 77% yield (entry 11).

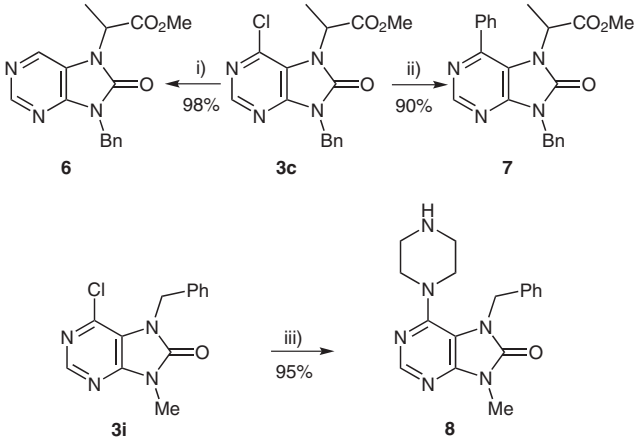
In contrast to most of the reported procedures, our protocol enables easy and efficient synthesis of 8-oxopurines

Table 2 Scope of the Developed Protocol for the Synthesis of 8-Oxopurines **3** from 9-Alkyl-9*H*-purines **1** via 7,9-Dialkyl-7,8-dihydro-9*H*-purines **2** (Scheme 2)

Entry	1	X	R^1	R^2	2	Yield[a] (%) of 2	3	Yield[a] (%) of 3
1	**1b**	H	Bn	Bn	**2b**[24b]	89	**3b**	77
2	**1b**	H	Bn	$CHMeCO_2Me$	**2c**	86	**3c**	90 (86)[b]
3	**1c**	Cl	Bn	Bn	**2d**	86	**3d**	69
4	**1b**	H	Bn	$CH_2CH{=}CH_2$	**2e**	93	**3e**	47[c]
5	**1b**	H	Bn	$(CH_2)_2Ac$	**2f**	75	**3f**	54[c,d]
6	**1d**	H	*i*-Pr	Me	**2g**	79	**3g**	47 (9)[c]
7	**1e**	H	Me	Me	**2h**	59	**3h**	56
8	**1e**	H	Me	Bn	**2i**	84	**3i**	58
9	**1d**	H	*i*-Pr	$CHMeCO_2Me$	**2j**	88	**3j**	77
10	**1f**	H	Tr	Bn	**2k**	93	–	52[e]
11	**1g**	$NBoc_2$	Bn	$CHMeCO_2Me$	**2l**	73	**3l**	76

[a] Isolated yield.
[b] The oxidation was carried out on a 10-mmol scale.
[c] PDC was used instead of MCPBA.
[d] Inseparable mixture of **3f** and 9-benzyl-6-chloro-9*H*-purine containing 92% **3f** was isolated.
[e] Isolated yield of 7-benzyl-6-chloro-7*H*-purine.

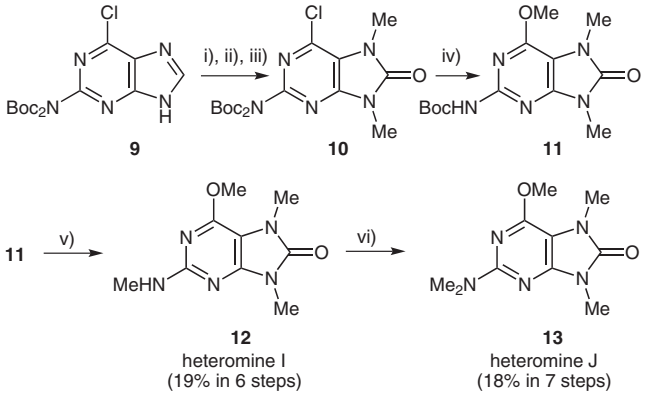
that contain halogen atoms. The chlorine atom can be subsequently substituted with various nucleophiles. The ability of the halogen atom to undergo a substitution reaction was tested on compound **3c**. It was demonstrated that **3c** readily coupled with phenylboronic acid under previously described conditions,[27] and the corresponding 6-phenyl derivative **7** was isolated in 90% yield (Scheme 3, conditions ii). Similarly, the palladium-catalyzed transfer hydrogenolysis of **3c** carried out in dry dimethylformamide at 100 °C produced dehalogenated compound **6** in quantitative yield (Scheme 3, conditions i). Chlorine substitution with amines would enable access to 8-oxoadenine derivatives. To test the feasibility of our protocol for the synthesis of 8-oxoadenines, we chose piperazinyl derivative **8**, a compound that was recently tested for DPPIV-inhibiting activity.[28] The starting oxopurine **3i**, which was prepared from **2i** in 49% yield (2 steps), was treated with piperazine in dry acetonitrile at 80 °C for 20 hours. The desired oxopurine **8** was produced in 95% yield after column chromatography (Scheme 3, conditions iii). The synthesis of compound **8** from 6-chloro-9-methyl-9*H*-purine was thus achieved in three steps with an overall yield of 46%.



Scheme 3 Reactivity of 6-chloro-8-oxopurines **3c** and **3i**. *Reagents and conditions*: (i) HCO_2Na, $PdCl_2(PPh_3)_2$, DMF, 100 °C, 98%; (ii) $PhB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene, 100 °C, 20 h, 90%; (iii) piperazine, MeCN, 80 °C, 20 h, 95%.

Recently, two new 8-oxopurine derivatives, heteromines I (**12**) and J (**13**), have been isolated from *Heterostemma altum wight*.[2] We applied the developed protocol to the synthesis of these compounds (Scheme 4). We began with readily available Boc-protected 2-amino-6-chloropurine **9**.[29] Alkylation of **9** with methyl iodide in the presence of potassium carbonate resulted in a mixture of N^7- and N^9-methylated isomers in 87% isolated yield. Reduction of this mixture with borane–tetrahydrofuran complex, methylation, and oxidation with 3-chloroperoxybenzoic acid in dry dichloromethane resulted in the production of Boc-protected 6-chloro-8-oxopurine **10** in 24% yield (3 steps). Subsequent reaction of **10** with sodium methoxide resulted in the chemoselective deprotection of one Boc group as well as chlorine displacement in one step. The corresponding monoprotected purine **11** was isolated in 91% yield. The preparation of heteromine I (**12**) was finalized

by the alkylation of **11** with methyl iodide using lithium hexamethyldisilazanide as the base, followed by the removal of the Boc group with trifluoroacetic acid. The overall isolated yield of heteromine I was 19% in six steps. The alkylation of heteromine I (**12**) with methyl iodide produced heteromine J (**13**) in quantitative yield. Thus, the overall isolated yield of heteromine J was 18% in seven steps.



Scheme 4 Straightforward synthesis of heteromines I and J. *Reagents and conditions*: (i) MeI, K_2CO_3, DMF, 87%; (ii) 1. BH_3·THF, THF, 2. LiHMDS, MeI, THF, DMF, 66%; (iii) MCPBA, CH_2Cl_2, 42%; (iv) NaOMe, MeOH, 91%; (v) 1. LiHMDS, MeI, THF, DMF, 2. TFA, CH_2Cl_2, 88%; (vi) LiHMDS, MeI, THF, DMF, 96%.

To summarize, 7,9-dialkyl-6-chloro-8-oxo-7,8-dihydro-9*H*-purines can be easily synthesized by the oxidation of the corresponding 7,8-dihydro-9*H*-purines using 3-chloroperoxybenzoic acid in dichloromethane at 0 °C. The presence of both primary and secondary alkyl groups at positions N^7 and N^9 is well tolerated, producing the 8-oxopurines in 47–90% yields. The N^9-trityl derivative(s) are deprotected and oxidized to the corresponding N^7-substituted purines under the reaction conditions. The chlorine atom at position 6 of the resulting 8-oxopurines easily undergoes Suzuki coupling and palladium-catalyzed transfer hydrogenolysis. The nucleophilic displacement of chlorine with piperazine is also smooth. Our protocol for the synthesis of 8-oxopurines was applied to the synthesis of heteromines I and J. Further applications of the use of 7,8-dihydro-9*H*-purines in the synthesis of novel purine derivatives are currently under investigation.

All reactions were performed under an argon atmosphere. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Bruker Avance III 500 MHz (^{1}H, 500.13 MHz and ^{13}C, 125.77 MHz) or a Bruker 600 Avance III (^{1}H, 600.13 MHz and ^{13}C, 150.90 MHz) spectrometer at 298 K. Unambiguous assignment of the NMR signals is based on ^{13}C{1H}, ^{13}C APT, COSY, HMQC, and ^{13}C HMBC spectra. IR spectra were recorded on Nicolet 740 FT-IR. Mass spectra were measured on ZAB-SEQ (VG Analytical). The solvents were dried and degassed by standard procedures; silica gel (Merck, Geduran Si 60, 63–200 μm) was used for column chromatography. 7,9-Dibenzyl-6-chloro-7,8-dihydro-9*H*-purine (**2b**),[24b] 2-(Boc$_2$-amino)-6-chloro-9*H*-purine (**9**),[29] 9-benzyl-6-chloro-9*H*-purine (**1b**),[30] 9-benzyl-6-iodo-9*H*-purine (**1a**),[31] 6-chloro-9-isopropyl-9*H*-purine (**1d**),[32] 6-chloro-9-methyl-9*H*-purine (**1e**),[32] 6-chloro-9-trityl-9*H*-purine (**1f**),[24b] 2,6-dichloro-9-benzyl-9*H*-purine (**1c**),[30] and 2-amino-9-benzyl-6-chloro-9*H*-purine[33] were prepared by reported procedures, other compounds were purchased.

9-Benzyl-2-[bis(*tert*-butoxycarbonyl)amino]-6-chloro-9*H*-purine (1g)

THF (10 mL) was added to a mixture of 2-amino-9-benzyl-6-chloro-9*H*-purine (0.394 g, 1.52 mmol), DMAP (19 mg, 0.152 mmol), and Boc$_2$O (0.991 g, 4.55 mmol). The resultant mixture was stirred for 24 h at r.t. The clear yellow solution was concentrated under reduce pressure and subjected to column chromatography (silica gel, EtOAc–hexane, 1:1) afforded **1g** (0.559 g, 80%) as a white solid; mp 150–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 18 H, CH_3), 5.42 (s, 2 H, CH_2), 7.26–7.35 (m, 5 H, CH^{Ph}), 8.10 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 27.7, 47.7, 83.4, 127.7, 128.6, 129.0, 129.8, 134.5, 145.9, 150.3, 150.9, 151.8, 152.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{26}ClN_5O_4Na$: 482.1566; found: 482.1570.

7,9-Dialkyl-6-chloro-7,8-dihydro-9*H*-purines 2; General Procedure

DIBAL-H (1.2 equiv) was added to a solution of 9-alkyl-6-chloropurine **1** in anhyd THF (5 mL/mmol). The resultant mixture was stirred for 2 h at r.t., it was then diluted with CH_2Cl_2 and the reaction was quenched with excess $Na_2SO_4·10H_2O$. Then the mixture was stirred for 10 min at r.t. and filtered through Celite. Evaporation to dryness gave crude 9-alkyl-6-halo-7,8-dihydro-9*H*-purine, which was dissolved in anhyd THF (1 mL/mmol) and anhyd DMF (4 mL/mmol). The prepared solution was cooled to –78 °C, and then LiHMDS (1.2 equiv) was added and the mixture was stirred for 2 min at –78 °C. The alkyl halide (2 equiv) was added, and the mixture was warmed to r.t. and stirred for 2 h at r.t. The mixture was diluted with EtOAc and the organic layer was washed with brine (3 × 30 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and subjected to column chromatography (silica gel) to give the final product.

7,9-Dibenzyl-6-iodo-7,8-dihydro-9*H*-purine (2a)

General procedure starting from **1a** (0.336 g, 1.0 mmol) using 1 M DIBAL-H in hexane (1.2 mL, 1.2 mmol), 1 M LiHMDS in THF–ethylbenzene (1.20 mL, 1.2 mmol), and BnBr (0.24 mL, 2.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **2a** (0.365 g, 85%) as a yellow solid; mp 96–98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.55 (s, 2 H, CH_2), 4.68 (s, 2 H, CH_2), 4.70 (s, 2 H, CH_2), 7.17–7.32 (m, 10 H, CH^{Ph}), 7.76 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 46.3, 51.0, 70.9, 92.5, 127.7, 127.76, 127.79, 127.9, 128.7, 128.8, 134.2, 135.0, 136.2, 149.3, 157.7.

Methyl 2-[9-Benzyl-6-chloro-7,8-dihydro-9*H*-purin-7-yl]propanoate (2c)

General procedure starting from **1b** (0.735 g, 3.0 mmol) using 1 M DIBAL-H in hexane (3.6 mL, 3.6 mmol), 1 M LiHMDS in THF–ethylbenzene (3.6 mL, 3.6 mmol), and methyl 2-bromopropanoate (0.67 mL, 6.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **2c** (0.850 g, 86%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.63 (s, 3 H, CH_3), 4.54, 4.63 (ABq, *J* = 15.3 Hz, 2 H, CH_2), 4.84 (d, *J* = 3.3 Hz, 1 H, CH_2), 4.96 (d, *J* = 3.3 Hz, 1 H, CH_2), 5.03 (q, *J* = 7.2 Hz, 1 H, CH), 7.21–7.33 (m, 5 H, CH^{Ph}), 7.81 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 15.3, 46.5, 52.2, 53.5, 67.3, 127.4, 127.6, 127.8, 128.7, 129.4, 135.0, 149.3, 160.0, 172.0.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}ClN_4O_2$: 333.1113; found: 333.1120.

7,9-Dibenzyl-2,6-dichloro-7,8-dihydro-9*H*-purine (2d)
General procedure starting from **1c** (3.20 g, 11.5 mmol) using 1 M DIBAL-H in hexane (13.8 mL, 13.8 mmol), 1 M LiHMDS in THF–hexane (13.8 mL, 13.8 mmol), and BnBr (2.74 mL, 23.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:4) afforded **2d** (3.67 g, 86%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.49 (s, 2 H, CH_2), 4.55 (s, 2 H, CH_2), 4.71 (s, 2 H, CH_2), 7.11–7.27 (m, 10 H, CH^{Ph}).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 46.6, 51.1, 70.9, 127.2, 127.5, 127.7, 127.8, 128.0, 128.7, 128.75, 128.81, 134.3, 135.8, 148.1, 161.1.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}Cl_2N_4$: 371.0825; found: 371.0832.

7-Allyl-9-benzyl-6-chloro-7,8-dihydro-9*H*-purine (2e)
General procedure starting from **1b** (0.735 g, 3.0 mmol) using 1 M DIBAL-H in hexane (3.6 mL, 3.6 mmol), 1 M LiHMDS in THF–ethylbenzene (3.6 mL, 3.6 mmol), and allyl bromide (0.52 mL, 6.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:1) afforded **2e** (0.800 g, 93%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 6.0 Hz, 2 H, CH_2), 4.56 (s, 2 H, CH_2), 4.75 (s, 2 H, CH_2), 5.14–5.24 (m, 2 H, CH_2), 5.71–5.80 (m, 1 H, CH), 7.21–7.34 (m, 5 H, CH^{Ph}), 7.80 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 46.6, 49.9, 70.3, 118.4, 127.7, 127.77, 127.81, 128.7, 128.8, 132.3, 135.1, 148.8, 159.9.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}ClN_4$: 287.1058; found: 287.1062.

4-[9-Benzyl-6-chloro-7,8-dihydro-9*H*-purin-7-yl]butan-2-one (2f)
1 M DIBAL-H in hexane (12.0 mL, 12.0 mmol) was added to a solution of **1b** (2.45 g, 10 mmol) in anhyd THF (40 mL). The resultant mixture was stirred for 2 h at r.t., diluted with CH_2Cl_2 and the reaction was quenched with excess $Na_2SO_4 \cdot 10\ H_2O$. Then the mixture was stirred for 10 min at r.t., filtered through Celite, and evaporated to dryness to give crude 6-chloro-9-benzyl-7,8-dihydro-9*H*-purine which was dissolved in anhyd DMF (30 mL) then methyl vinyl ketone (1.67 mL, 20 mmol) and DBU (1.8 mL, 12.0 mmol) were added via syringe. The mixture was stirred for 2 h at r.t., then the mixture was diluted with EtOAc. The organic layer was washed with brine (3 × 30 mL), dried ($MgSO_4$), concentrated in vacuo, and subjected to column chromatography (silica gel, EtOAc–hexane, 2:1) to give **2f** (2.39 g, 75%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, CH_3), 2.73 (t, *J* = 6.6 Hz, 2 H, CH_2), 3.58 (t, *J* = 6.6 Hz, 2 H, CH_2), 4.53 (s, 2 H, CH_2), 4.84 (s, 2 H, CH_2), 7.20–7.30 (m, 5 H, CH^{Ph}), 7.76 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 30.1, 42.3, 42.9, 46.5, 71.8, 127.8, 127.85, 127.88, 128.0, 128.7, 135.1, 148.6, 159.7, 206.7.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}ClN_4O$: 317.1164; found: 317.1173.

6-Chloro-9-isopropyl-7-methyl-7,8-dihydro-9*H*-purine (2g)
General procedure starting from **1d** (0.591 g, 3.0 mmol) using 1 M DIBAL-H in hexane (3.6 mL, 3.6 mmol), 1 M LiHMDS in THF–ethylbenzene (3.6 mL, 3.6 mmol), and MeI (0.37 mL, 6.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:1) afforded **2g** (0.500 g, 79%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.6 Hz, 6 H, CH_3), 3.05 (s, 3 H, CH_3), 4.35 (sept, *J* = 6.6 Hz, 1 H, CH), 4.90 (s, 2 H, CH_2), 7.75 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 19.4, 31.2, 39.0, 69.5, 126.9, 128.1, 148.5, 151.3.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}ClN_4$: 213.0901; found: 213.0903.

6-Chloro-7,9-dimethyl-7,8-dihydro-9*H*-purine (2h)
General procedure starting from **1e** (1.63 g, 10.0 mmol) using 1 M DIBAL-H in hexane (12.0 mL, 12.0 mmol), 1 M LiHMDS in THF–ethylbenzene (12.0 mL, 12.0 mmol), and MeI (1.25 mL, 20.0 mmol), with column chromatography (silica gel, EtOAc) afforded **2h** (1.10 g, 59%) as a white oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.96 (s, 3 H, CH_3), 3.05 (s, 3 H, CH_3), 4.83 (s, 2 H, CH_2), 7.77 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, DMSO-d_6): δ = 28.9, 34.2, 74.5, 126.8, 128.8, 148.1, 160.1.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{10}ClN_4$: 185.0589; found: 185.0589.

7-Benzyl-6-chloro-9-methyl-7,8-dihydro-9*H*-purine (2i)
General procedure starting from **1e** (0.845 g, 5.0 mmol) using 1 M DIBAL-H in hexane (6.0 mL, 6.0 mmol), 1 M LiHMDS in THF–ethylbenzene (6.0 mL, 6.0 mmol), and BnBr (1.19 mL, 10.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 2:1) afforded **2i** (1.1 g, 84%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (s, 3 H, CH_3), 4.62 (s, 2 H, CH_2), 4.74 (s, 2 H, CH_2), 7.27–7.30 (m, 5 H, CH^{Ph}), 7.75 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 29.0, 51.1, 127.7, 127.77, 127.82, 127.9, 128.6, 136.2, 148.6, 159.8.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}ClN_4$: 261.0902; found: 261.0903.

Methyl 2-(6-Chloro-9-isopropyl-7,8-dihydro-9*H*-purin-7-yl)propanoate (2j)
General procedure starting from **1d** (0.394 g, 2.0 mmol) using 1 M DIBAL-H in hexane (2.4 mL, 2.4 mmol), 1 M LiHMDS in THF–ethylbenzene (2.4 mL, 2.4 mmol), and methyl 2-bromopropanoate (0.45 mL, 4.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:1) afforded **2j** (0.504 g, 88%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.17 (m, 6 H, CH_3), 1.41 (d, *J* = 7.0 Hz, 3 H, CH_3), 3.62 (s, 3 H, CH_3), 4.30 (s, *J* = 7.0 Hz 1 H, CH), 4.93 (m, 1 H, CH_2), 4.98 (q, *J* = 7.5 Hz, 1 H, CH), 5.05 (m, 1 H, CH_2), 7.67 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 15.3, 18.8, 19.3, 44.1, 52.1, 53.5, 63.6, 127.8, 128.8, 149.3, 159.4, 172.1.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}ClN_4O_2$: 285.1113; found: 285.1117.

7-Benzyl-6-chloro-9-trityl-7,8-dihydro-9*H*-purine (2k)
General procedure starting from **1f** (0.397 g, 1.0 mmol) using 1 M DIBAL-H in hexane (1.2 mL, 1.2 mmol), 1 M LiHMDS in THF–ethylbenzene (1.20 mL, 1.2 mmol), and BnBr (0.24 mL, 2.0 mmol), with column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **2k** (0.455 g, 93%) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.62 (s, 2 H, CH_2), 4.95 (s, 2 H, CH_2), 7.22–7.35 (m, 16 H, CH^{Ph}); 7.36–7.38 (m, 4 H, CH^{Ph}), 7.63 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 51.4, 72.2, 74.6, 127.1, 127.6, 127.66, 127.71, 128.7, 129.4, 129.8, 130.3, 136.3, 141.7, 148.4, 160.1.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{26}ClN_4$: 489.1840; found: 489.1843.

Methyl 2-{9-Benzyl-2-[bis(*tert*-butoxycarbonyl)amino]-7,8-dihydro-9*H*-purin-7-yl}propanoate (2l)
Reduction: 1 M BH_3–THF complex in THF (1.1 mL, 1.1 mmol) was added to a solution of **1g** (0.460 g, 1.0 mmol) in anhyd THF (5 mL) cooled to –78 °C. Then the mixture was stirred for 1 h at 0 °C, quenched with sat. NH_4Cl and vigorously stirred for 10 min at 0 °C. The mixture was diluted with CH_2Cl_2 (30 mL), the organic layer was separate and the aqueous layer was extracted with CH_2Cl_2 (3 ×

10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo.

Alkylation: The isolated crude 9-benzyl-6-chloro-2-[bis(*tert*-butoxycarbonyl)amino]-7,8-dihydro-9*H*-purine was dissolved in anhyd THF (1 mL) and anhyd DMF (4 mL). The solution was cooled to –78 °C, subsequently 1 M LiHMDS in THF–ethylbenzene (1.2 mL, 1.2 mmol) was added and the mixture was stirred for 2 min at –78 °C. Then methyl 2-bromopropanoate (0.22 mL, 2.0 mmol) was added, the mixture was warmed to r.t. and stirred for 2 h at r.t. Then the mixture was diluted with EtOAc and washed with brine (3 × 30 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and subjected to column chromatography (silica gel, EtOAc–hexane, 1:2) to give **2l** (0.400 g, 73%) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.47 (m, 21 H, CH_3), 3.60 (s, 3 H, CH_3), 3.60 (m, 2 H, CH_2), 4.88–4.90 (m, 1 H, CH_2), 4.99–5.05 (m, 1 H, CH_2 and 1 H, CH), 7.25–7.34 (m, 5 H, CH^{Ph}).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 15.2, 27.7, 46.4, 52.1, 53.5, 67.9, 82.4, 126.0, 127.7, 127.8, 128.5, 128.7, 135.0, 149.0, 150.5, 161.6, 171.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{35}ClN_5O_6$: 548.2270; found: 548.2274.

8-Oxopurines 3; General Procedure

MCPBA (2.5 equiv) was added, in several portions, to a solution of 7,8-dihydropurine **2** (1 equiv) in CH_2Cl_2 (10 mL/mmol) cooled to 0 °C. The resultant mixture was stirred for 20 min at 0 °C. Then the mixture was diluted with CH_2Cl_2 and washed with sat. Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined layers were dried ($MgSO_4$), evaporated in vacuo and subjected to column chromatography (silica gel) to give the final product.

7,9-Dibenzyl-6-iodo-8-oxo-7,8-dihydro-9*H*-purine (3a)

General procedure starting from **2a** (0.050 g, 0.12 mmol) using MCPBA (0.074 g, 0.3 mmol) and CH_2Cl_2 (2 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **3a** (0.048 g, 91%) as a yellow solid; mp 94–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16 (s, 2 H, CH_2), 5.43 (s, 2 H CH_2), 7.25–7.31 (m, 8 H, CH^{Ph}), 7.49–7.51 (m, 2 H, CH^{Ph}), 8.35 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 43.6, 44.0, 99.9, 125.4, 126.8, 127.7, 128.2, 128.6, 128.7, 135.2, 136.1, 148.1, 150.9, 153.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}IN_4O$: 443.0363; found: 443.0369.

7,9-Dibenzyl-6-chloro-8-oxo-7,8-dihydro-9*H*-purine (3b)

General procedure starting from **2b** (0.200 g, 0.59 mmol) using MCPBA (0.367 g, 1.48 mmol) and CH_2Cl_2 (6 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:3) afforded **3b** (0.160 g, 77%) as a white solid; mp 77–79 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16 (s, 2 H, CH_2), 5.33 (s, 2 H, CH_2), 7.26–7.33 (m, 8 H, CH^{Ph}), 7.51 (d, *J* = 7.8 Hz, 2 H, CH^{Ph}), 8.46 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 44.2, 45.2, 119.1, 127.2, 127.8, 128.1, 128.5, 128.62, 128.63, 135.2, 135.8, 136.1, 150.0, 150.6, 152.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}ClN_4O$: 351.1007; found: 351.1022.

Methyl 2-(9-Benzyl-6-chloro-8-oxo-7,8-dihydro-9*H*-purin-7-yl)propanoate (3c)

General procedure starting from **2c** (0.200 g, 0.60 mmol) using MCPBA (0.371 g, 1.5 mmol) and CH_2Cl_2 (6 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **3c** (0.188 g, 90%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 5.10 (s, 2 H, CH_2), 5.49 (q, *J* = 7.2 Hz, 1 H, CH), 7.24–7.31 (m, 3 H, CH^{Ph}), 7.44–7.46 (m, 2 H, CH^{Ph}), 8.45 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 17.2, 44.2, 50.7, 52.9, 118.7, 128.1, 128.4, 128.6, 135.0, 135.8, 150.2, 150.6, 152.0, 169.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}ClN_4O_3$: 347.0905; found: 347.0906.

7,9-Dibenzyl-2,6-dichloro-8-oxo-7,8-dihydro-9*H*-purine (3d)

General procedure starting from **2d** (4.47 g, 12.05 mmol) using MCPBA (7.44 g, 30.12 mmol) and CH_2Cl_2 (120 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:4) afforded **3d** (3.20 g, 69%) as a white solid; mp 115–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (s, 2 H, CH_2), 5.29 (s, 2 H, CH_2), 7.25–7.35 (m, 8 H, CH^{Ph}), 7.51 (d, *J* = 6.9 Hz, 2 H, CH^{Ph}).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 44.5, 45.3, 118.1, 127.1, 128.0, 128.3, 128.67, 128.73, 128.8, 134.7, 135.8, 136.0, 151.0, 151.5, 152.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}Cl_2N_4O$: 385.0617; found: 385.0621.

7-Allyl-9-benzyl-6-chloro-8-oxo-7,8-dihydro-9*H*-purine (3e)

PDC (0.786 g, 2.09 mmol) was added to a solution of **2e** (0.300 g, 1.05 mmol) in anhyd CH_2Cl_2 (10 mL) cooled to 0 °C. The resultant mixture was stirred for 180 min at 0 °C and quenched with *i*-PrOH (2 mL). After 10 min the mixture was filtered through Celite, concentrated in vacuo and subjected to column chromatography (silica gel, EtOAc–hexane 1:3) to afford **3e** (0.150 g, 47%) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74–4.76 (m, 2 H, CH_2), 5.14 (s, 2 H, CH_2), 5.25 (m, 2 H, CH_2), 5.92–6.01 (m, 1 H, CH), 7.19–7.36 (m, 3 H, CH^{Ph}), 7.47–7.50 (m, 2 H, CH^{Ph}), 8.47 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 43.8, 44.1, 117.8, 119.1, 128.0, 128.5, 128.6, 132.0, 135.2, 135.7, 149.9, 150.5, 152.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}ClN_4O$: 301.0851; found: 301.0857.

4-[9-Benzyl-6-chloro-8-oxo-7,8-dihydro-9*H*-purin-7-yl]butan-2-one (3f)

PDC (0.752 g, 2.0 mmol) was added to a solution of **2f** (0.317 g, 1.0 mmol) in anhyd CH_2Cl_2 (15 mL) cooled to 0 °C. The resultant mixture was stirred for 180 min at 0 °C and quenched with *i*-PrOH (2 mL). After 10 min the mixture was filtered through Celite, concentrated in vacuo and subjected to column chromatography (silica gel, EtOAc–hexane, 1:1) to afford **3f** (0.180 g, 54%) as a white amorphous solid that was 92% pure (^{1}H NMR spectroscopy).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 2.95 (t, *J* = 7.5 Hz, 2 H, CH_2), 4.41 (t, *J* = 7.5 Hz, 2 H, CH_2), 5.05 (s, 2 H, CH_2), 7.30–7.33 (m, 3 H, CH^{Ph}), 7.46–7.49 (m, 2 H, CH^{Ph}), 8.46 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 29.9, 37.0, 42.7, 44.0, 118.9, 128.0, 128.4, 128.5, 135.0, 135.4, 149.9, 150.4, 152.2, 205.1.

6-Chloro-9-isopropyl-7-methyl-8-oxo-7,8-dihydro-9*H*-purine (3g)

General procedure starting from **2g** (0.200 g, 0.94 mmol) using MCPBA (0.580 g, 2.35 mmol) and CH_2Cl_2 (10 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:3) afforded **3g** (0.100 g, 47%) as a white solid; mp 105–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.6 Hz, 6 H, CH_3), 3.61 (s, 3 H, CH_3), 4.75 (sept, *J* = 6.6 Hz, 1 H, CH), 8.35 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 19.8, 28.8, 46.0, 119.5, 135.7, 149.8, 150.0, 152.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}ClN_4O$: 227.0694; found: 227.0697.

6-Chloro-7,9-dimethyl-8-oxo-7,8-dihydro-9*H*-purine (3h)
General procedure starting from **2h** (0.200 g, 1.08 mmol) using MCPBA (0.667 g, 2.70 mmol) and CH_2Cl_2 (10 mL) followed by column chromatography (silica gel, EtOAc–hexane, 2:1) afforded **3h** (0.120 g, 56%) as a white solid; mp 169–171 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.39 (s, 3 H, CH_3), 3.59 (s, 3 H, CH_3), 8.32 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 26.5, 28.8, 119.6, 135.6, 150.1, 150.2, 153.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_8ClN_4O$: 199.0381; found: 199.0383.

7-Benzyl-6-chloro-9-methyl-8-oxo-7,8-dihydro-9*H*-purine (3i)
General procedure starting from **2i** (0.492 g, 1.89 mmol) using MCPBA (1.16 g, 4.71 mmol) and CH_2Cl_2 (20 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **3i** (0.303 g, 58%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 3 H, CH_3), 5.25 (s, 2 H, CH_2), 7.19–7.26 (m, 5 H, CH^{Ph}), 8.36 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 26.5, 44.9, 118.9, 127.1, 127.6, 128.4, 135.4, 136.0, 150.26, 150.31, 152.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}ClN_4O$: 275.0694; found: 275.0699.

Methyl 2-[6-Chloro-9-isopropyl-8-oxo-7,8-dihydro-9*H*-purin-7-yl]propanoate (3j)
General procedure starting from **2j** (0.205 g, 0.72 mmol) using MCPBA (0.444 g, 1.8 mmol) and CH_2Cl_2 (6 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **3j** (0.165 g, 77%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.9 Hz, 6 H, CH_3), 1.71 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.68 (s, 3 H, CH_3), 4.72 (sept, *J* = 6.9 Hz, 1 H, CH), 5.42 (q, *J* = 7.2 Hz, 1 H, CH), 8.35 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 17.2, 19.6, 46.1, 50.5, 52.8, 118.5, 135.6, 150.16, 150.23, 151.5, 170.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}ClN_4O_3$: 299.0905; found: 299.0908.

Attempted Oxidation of 7-Benzyl-6-chloro-9-trityl-7,8-dihydro-9*H*-purine (2k)
MCPBA (0.309 g, 1.25 mmol) was added, in several portions, to a solution of **2k** (0.245 g, 0.5 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C. The resultant mixture was stirred for 20 min at 0 °C. Then the mixture was diluted with CH_2Cl_2 and washed with sat. Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined layers were dried ($MgSO_4$), evaporated in vacuo, and subjected to column chromatography (silica gel, EtOAc–MeOH, 20:1) to give 7-benzyl-6-chloro-7*H*-purine (0.064 g, 52%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.69 (s, 2 H, CH_2), 7.15–7.18 (m, 2 H, CH^{Ph}), 7.34–7.37 (m, 3 H, CH^{Ph}), 8.25 (s, 1 H, CH), 8.87 (s, 1 H, CH), in accordance with an authentic sample prepared by reported procedure.[30]

Methyl 2-{9-Benzyl-2-[bis(*tert*-butoxycarbonyl)amino]-8-oxo-7,8-dihydro-9*H*-purin-7-yl}propanoate (3l)
General procedure starting from **2l** (0.220 g, 0.40 mmol) using MCPBA (0.248 g, 1.0 mmol) and CH_2Cl_2 (4 mL) followed by column chromatography (silica gel, EtOAc–hexane, 1:2) afforded **3l** (0.170 g, 76%) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 18 H, CH_3), 1.78 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 5.08 (s, 2 H, CH_2), 5.47 (q, *J* = 7.2 Hz, 1 H, CH), 7.26–7.31 (m, 3 H, CH^{Ph}), 7.40–7.43 (m, 2 H, CH^{Ph}).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ =17.2, 27.7, 44.4, 50.9, 52.9, 83.5, 117.0, 128.1, 128.4, 128.7, 134.9, 135.7, 150.4, 151.5, 152.3, 169.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{33}ClN_5O_7$: 562.2063; found: 562.2065.

Equilibrium mixture of 4-(Benzylamino)-5-(*N*-benzylformamido)-6-iodopyrimidine (4a) and 7,9-Dibenzyl-8-hydroxy-6-iodo-7,8-dihydro-9*H*-purine (5a)
Anhyd MeCN (10 mL) was added to a mixture of **2a** (0.856 g, 2.0 mmol) and MnO_2 (1.74 g, 20 mmol). The resultant mixture was stirred for 3 h at r.t., concentrated under reduce pressure, and subjected to column chromatography (silica gel, EtOAc–hexane, 1:2) afforded oxopurine **3a** (0.105 g, 12%) and a mixture of **4a** and **5a** (85:15, 0.700 g, 79%) as a white solid; mp 125–127 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.02 (d, *J* = 14.1 Hz, 1 H, CH_2), 4.09 (dd, *J* = 5.7, 14.7 Hz, 1 H, CH_2), 4.32 (dd, *J* = 6.0, 14.7 Hz, 1 H, CH_2), 4.52[5a] (d, *J* = 14.4 Hz, 1 H, CH_2), 4.82–4.85 (m, 1 H, NH), 4.87[5a] (d, *J* = 14.4 Hz, 1 H, CH_2), 5.39 (d, *J* = 14.1 Hz, 1 H, CH_2), 6.91–6.95 (m, 2 H, CH^{Ph}), 7.16–7.28 (m, 8 H, CH^{Ph}), 8.03 (s, 1 H, CH), 8.16[5a] (s, 1 H, CH), 8.19 (s, 1 H, CH), 8.54[5a] (s, 1 H, CH).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 44.6[5a], 44.8, 48.7, 53.8[5a], 121.0[5a], 122.3, 127.2[5a], 127.4[5a], 127.5, 127.7, 128.37[5a], 128.43, 128.5, 128.8, 128.9[5a], 129.0[5a], 129.5, 131.6[5a], 134.0, 134.6[5a], 135.5, 137.0, 137.2[5a], 157.0[5a], 157.4, 158.1[5a], 159.1, 162.0[5a], 163.5.

Methyl 2-[9-Benzyl-8-oxo-7,8-dihydro-9*H*-purin-7-yl]propanoate (6)
Anhyd DMF (3 mL) was added to a mixture of **3c** (0.050 g, 0.15 mmol), $PdCl_2(PPh_3)_2$ (5.3 mg, 0.0075 mmol), and HCO_2Na (0.020 g, 0.30 mmol). The resultant mixture was stirred for 30 min at 100 °C, diluted with EtOAc (40 mL) and the organic layer was washed with brine (3 × 30 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and subjected to column chromatography (silica gel, EtOAc–hexane, 2:1) to give **6** (0.230 g, 98%) as a white solid; mp 88–90 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 7.5 Hz, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 5.13 (s, 2 H, CH_2), 5.31 (q, *J* = 7.5 Hz, 1 H, CH), 7.26–7.35 (m, 3 H, CH^{Ph}), 7.48–7.51 (m, 2 H, CH^{Ph}), 8.22 (s, 1 H, CH), 8.71 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 15.4, 43.4, 50.0, 52.5, 121.2, 127.7, 128.2, 128.3, 133.2, 135.2, 148.8, 151.1, 151.9, 169.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_4O_3$: 313.1295; found: 313.1299.

Methyl 2-[9-Benzyl-6-phenyl-8-oxo-7,8-dihydro-9*H*-purin-7-yl]propanoate (7)
Anhyd toluene (5 mL) was added to a mixture of **3c** (0.150 g, 0.43 mmol), phenylboronic acid (0.105 g, 0.86 mmol), K_2CO_3 (0.119 g, 0.86 mmol), and $Pd(PPh_3)_4$. The resultant mixture was stirred for 20 h at 100 °C, concentrated in vacuo, and subjected to column chromatography (silica gel, EtOAc–hexane, 1:2) to give **7** (0.150 g, 90%) as a white solid; mp 105–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.63 (s, 3 H, CH_3), 4.48 (q, *J* = 7.2 Hz, 1 H, CH), 5.17 (s, 2 H, CH_2), 7.27–7.35 (m, 3 H, CH^{Ph}), 7.50–7.53 (m, 7 H, CH^{Ph}), 8.74 (s, 1 H, CH).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 15.0, 43.6, 52.3, 52.6, 119.7, 127.9, 128.35, 128.41, 128.6, 128.7, 129.9, 135.4, 135.6, 143.9, 150.0, 150.9, 153.0, 169.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_4O_3$: 389.1608; found: 389.1606.

7-Benzyl-9-methyl-8-oxo-6-(piperazin-1-yl)-7,8-dihydro-9*H*-purine (8)
Anhyd MeCN (4 mL) was added to a mixture of piperazine (0.269 g, 3.13 mmol) and **3i** (0.215 g, 0.78 mmol). The resultant mixture was stirred for 20 h at 80 °C, concentrated in vacuo, and subjected to column chromatography (silica gel, CH_2Cl_2–MeOH, 10:1 to 3:1) to afford **8** (0.240 g, 95%) as a white foam.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 3.00 (m, 4 H, CH_2), 3.25 (m, 4 H, CH_2), 3.46 (s, 3 H, CH_3), 5.17 (s, 2 H, CH_2), 7.25–7.30 (m, 5 H, CH^{Ph}), 8.40 (s, 1 H, CH).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 26.4, 45.4, 46.2, 50.7, 111.3, 127.3, 127.7, 128.6, 136.4, 150.4, 150.8, 154.3, one signal is missing.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}N_6O$: 325.1778; found: 325.1771.

2-[Bis(*tert*-Butoxycarbonyl)amino]-6-chloro-7,9-dimethyl-8-oxo-7,8-dihydro-9*H*-purine (10)

Methylation: Anhyd DMF (4 mL) was added to a mixture of freshly dried K_2CO_3 (0.247 g, 1.79 mmol) and chloropurine **9** (0.331 g, 0.89 mmol). Then MeI (0.11 mL, 1.79 mmol) was added and the resultant mixture was stirred for 24 h at r.t. Then the mixture was diluted with EtOAc (40 mL) and the organic layer was extracted with brine (3 × 20 mL), dried ($MgSO_4$), and subjected to column chromatography (silica gel, EtOAc) to afford a mixture of N^7- and N^9-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-6-chloropurine (ratio N^9/N^7 75:25, 0.298 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 18 H, CH_3), 1.45 (s, 18 H, CH_3), 3.91 (s, 3 H, CH_3), 4.16 (s, 3 H, CH_3), 8.12 (s, 1 H, CH^{Pu}), 8.19 (s, 1 H, CH^{Pu}).

Reduction: The isolated mixture (0.290 g, 0.76 mmol) was dissolved in anhyd THF (4 mL), cooled to –78 °C and 1 M BH_3–THF in THF (0.91 mL, 0.91 mmol) was added. Then the mixture was stirred for 1 h at 0 °C, quenched with sat. NH_4Cl, and vigorously stirred for 10 min at 0 °C. The mixture was diluted with CH_2Cl_2 (30 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduce pressure.

Alkylation: The isolated crude 7,8-dihydropurine was dissolved in DMF (4.0 mL) and THF (1.5 mL), cooled to –78 °C and 1 M LiHMDS in THF–hexane (0.91 mL, 0.91 mmol) was added. Then the mixture was stirred for 2 min at –78 °C, followed by addition of MeI (0.095 mL, 1.52 mmol) and the mixture was stirred for 2 h at r.t., and diluted with EtOAc. The organic layer was washed with brine (3 × 30 mL), dried ($MgSO_4$), concentrated under reduce pressure, and subjected to column chromatography (silica gel, EtOAc–hexane, 1:1) to afford 2-[bis(*tert*-butoxycarbonyl)amino]-6-chloro-7,9-dimethyl-7,8-dihydro-9*H*-purine (0.200 g, 66%) as a yellow foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 18 H, CH_3), 2.86 (s, 3 H, CH_3), 2.97 (s, 3 H, CH_3), 4.81 (s, 3 H, CH_2).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 27.7, 29.1, 34.4, 75.5, 82.5, 126.9, 127.3, 148.0, 150.9, 161.5.

Oxidation: 2-[Bis(*tert*-butoxycarbonyl)amino]-6-chloro-7,9-dimethyl-7,8-dihydro-9*H*-purine (0.170 g, 0.43 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Then MCPBA (0.263 g, 1.06 mmol) was added and the mixture was stirred for 20 min at 0 °C. Then the mixture was diluted with CH_2Cl_2 (20 mL) and washed with sat. Na_2CO_3 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined layers were dried ($MgSO_4$), concentrated in vacuo and subjected to column chromatography (silica gel, EtOAc–hexane, 1:2) to afford **10** (0.074 g, 42%) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 18 H, CH_3), 3.38 (s, 3 H, CH_3), 3.60 (s, 3 H, CH_3).

^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 26.6, 27.7, 28.8, 83.3, 117.9, 135.4, 150.0, 150.4, 151.3, 153.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}ClN_5O_5Na$: 436.1358; found: 436.1363.

2-[(*tert*-Butoxycarbonyl)amino]-6-methoxy-7,9-dimethyl-8-oxo-7,8-dihydro-9*H*-purine (11)

Na (0.012 g, 0.5 mmol) was added to MeOH (3 mL) and the mixture was stirred until Na disappeared (approx, 2 min). **10** (0.041 g, 0.10 mmol) was added and the mixture was stirred for 30 h at r.t. The MeOH was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, EtOAc–hexane, 1:1) to afford **11** (0.028 g, 91%) as a white solid; mp 184–186 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9 H, CH_3), 3.41 (s, 3 H, CH_3), 3.51 (s, 3 H, CH_3), 4.02 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.4, 28.0, 29.1, 53.7, 80.8, 103.2, 149.9, 150.49, 150.52, 152.6, 153.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{20}N_5O_4$: 310.1510; found: 310.1506.

Heteromine I [6-Methoxy-7,9-dimethyl-2-(methylamino)-8-oxo-7,8-dihydro-9*H*-purine, 12]

Methylation: 1 M LiHMDS in THF–ethylbenzene (0.12 mL, 0.12 mmol) was added to a solution of **11** (0.031 g, 0.10 mmol) in anhyd DMF(1 mL) and THF (0.2 mL) cooled to –78 °C. Then the mixture was stirred for 5 min at –78 °C followed by addition of MeI (0.019 mL, 0.30 mmol). The resultant mixture was stirred for 1 h at r.t., diluted with EtOAc (20 mL), and the organic layer was washed with brine (3 × 10 mL), dried ($MgSO_4$), concentrated in vacuo, and subjected to column chromatography (silica gel, EtOAc–hexane, 1:1) to afford methylated **11** (0.032 g, 99%) as a white solid; mp 107–108 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, CH_3), 3.35 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 3.53 (s, 3 H, CH_3), 4.02 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.1, 28.0, 29.0, 34.8, 53.5, 80.5, 104.1, 149.5, 152.0, 153.28, 153.32, 153.9.

Deprotection: Methylated **11** (0.236 g, 0.73 mmol) was dissolved in CH_2Cl_2 (1 mL) followed by addition of TFA (0.73 mL). The mixture was stirred for 2 h at r.t., diluted with CH_2Cl_2 (20 mL), and washed with sat. Na_2CO_3 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduce pressure to afford heteromine I (**12**; 0.144 g, 88%) as a white solid; mp 171–172 °C.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 2.99 (s, 3 H, CH_3-N^2), 3.36 (s, 3 H, CH_3-N^9), 3.49 (s, 3 H, CH_3-N^7), 3.99 (s, 3 H, CH_3O), 4.75 (br s, 1 H, NH).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 26.2 (CH_3-N^9), 28.7 (CH_3-N^2), 29.2 (CH_3-N^7), 53.2 (CH_3O), 99.9 (C^5), 151.1 (C^4), 153.5 (C^8), 153.7 (C^6), 158.4 (C^2).

Heteromine J [2-(Dimethylamino)-6-methoxy-7,9-dimethyl-8-oxo-7,8-dihydro-9*H*-purine, 13]

1 M LiHMDS in THF–ethylbenzene (0.51 mL, 0.51 mmol) was added to a solution of **12** (0.094 g, 0.42 mmol) in anhyd DMF (5 mL) and THF (1.0 mL) cooled to –78 °C. Then the mixture was stirred for 5 min at –78 °C followed by addition of MeI (0.062 mL, 1.0 mmol). The resultant mixture was stirred for 1 h at r.t., and diluted with EtOAc (50 mL). The organic layer was washed with brine (3 × 20 mL), dried ($MgSO_4$), concentrated in vacuo, and subjected to column chromatography (silica gel, EtOAc–hexane, 2:1) to afford **13** (0.096 mg, 96%) as a white solid; mp 124–126 °C.

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 3.16 (s, 6 H, CH_3-N^2), 3.37 (s, 3 H, CH_3-N^9), 3.48 (s, 3 H, CH_3-N^7), 4.00 (s, 3 H, CH_3O).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 26.1 (CH_3-N^9), 29.2 (CH_3-N^7), 37.1 (CH_3-N^2), 52.9 (CH_3O), 98.8 (C^5), 151.1 (C^4), 153.3 (C^8), 153.6 (C^6), 158.0 (C^2).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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