Pd-CATALYZED ALLYLIC SUBSTITUTION OF PURIN-8-YL(ALLYL) ACETATE: ROUTE TO (*E*)-ALKENYLPURINES

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Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

C^8-Alkenylpurines were synthesized starting from purin-8-yl(allyl) acetates using Pd-catalyzed allylic substitution. The described protocol allows, by reaction of purin-8-yl(allyl) acetates with stabilized nucleophiles, an access to novel (*E*)-8-alkenylpurine derivatives under $Pd_2dba_3{\cdot}CHCl_3$ catalysis in dry THF in yields ranging from 31 to 76%. A wide range of nucleophiles showed exclusive *E*-alkene formation, however, ethyl nitroacetate gave mixture of *E*/*Z*-alkenes. On contrary, purin-2-yl(allyl) acetates reacted smoothly only with dimethyl malonate.
Keywords: Heterocycles; Palladium; Nucleophilic substitution.

A significance of C^8-substituted purine derivatives has grown up within the last decade. Especially, various guanine/guanosine and adenine/adenosine derivatives bearing C^8-sp^2-carbon substituents have been prepared and studied as fluorescent/photosensitive[1–5] and electrochemical[6,7] marks in order to found a tool for the analysis of DNA or RNAs sequences. In addition, self-assebly of 8-aryl-2′-deoxyguanosine induced by the complexation of metal cations such as K^+ or Na^+ to dendrimers and oligomers was described[8]. Besides of photo- and electrochemical applications, C^8-alkenyl/arylpurines have been found as adducts that are formed by phenolic toxins[9], antagonist of the A_3-adenosine receptor[10], inhibitors of glycogen synthase kinase[11], ATP-competitive kinase[12], fructose-1,6-bisphosphatase[13,14], adenosine kinase[15] and others[16].

The importance of C^8-substituted purine derivatives requires reliable methods for the introduction of various functionalities at purine scaffold. Up to now, several ways to the purines functionalized at the position 8

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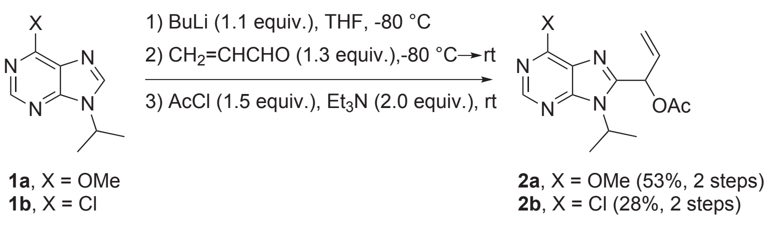
have been reported. Besides cyclization of the aminopyrimidine derivatives[11,12,14,16a,16b,17,18] cross-coupling reactions of 8-halopurines and alkenyl or aryl organometallics have often been used. Thus, numerous examples of the Sonogashira[1,6,7,10,19], Stille[2,13,20–23], Suzuki–Miyaura[4,5,24] and Heck[25] reactions have been utilized. Moreover, recently direct C–H arylation[26] and alkenylation[27] have become methods of choice.

To the best of our knowledge, there has not been any report about Pd-catalyzed allylic substitution of purinylallyl acetates in the literature. This is somewhat surprising, since the allylic substitution is, in principle, very general and may lead to the number of new structurally diverse purine derivatives of a biological interest. The lack of synthetic applications of palladium-catalyzed allylic substitution of purinyl(allyl) acetates led us to an attempt to extend this synthetic methodology also to the purine derivatives. We have started our study with purin-8-yl(allyl) acetate. The starting compounds, the acetates **2a** and **2b**, are easily available via selective C^8-lithiation of 9-isopropyl-6-substituted purines **1a** and **1b** using n-butyllithium at –80 °C (Scheme 1). Thus, the formed C^8-lithiated derivatives smoothly react with acroleine affording the allyl alcohols **2a** and **2b** in 69 and 61% yields, respectively. Subsequent acylation gave the desired acetates **2a** and **2b** in 53 and 28% overall isolated yields. The lower yield of **2b** was caused by tedious chromatographic separation from complex reaction mixture in the acylation step.

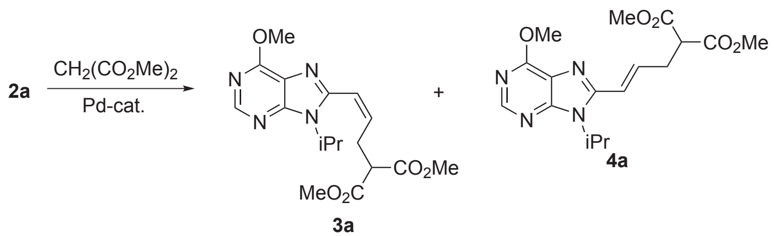


SCHEME 1

In order to develope a representative procedure, the acetate **2a** was treated with the dimethyl malonate enolate, which was generated from the dimethyl malonate and sodium hydride in dry THF. The first experiments with 5 mole % $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_4$ catalysts at ambient temperature, turned out to be a successful choice furnishing the desired substitution products **3a** and **4a** as a mixture of *Z*- and *E*-stereoisomers in high isolated yields (Table I, Entries 1, 2). When $Pd_2dba_3{\cdot}CHCl_3$ was used, single (*E*)-alkenylpurine **4a** has been obtained (Table I, Entry 3). With the same catalyst, but in 2 mole % loading, the reaction time prolonged to 16 h

(Table I, Entry 4). A similar result was obtained, when $Pd_2dba_3·CHCl_3$ was used in combination with $AsPh_3$ (Table I, Entry 5). The other tested precatalysts and ligands lead to a mixture of *E*- and *Z*-stereoisomers with isolated yields around 70% (Table I, Entries 6, 7, 8). Interestingly, the opposite stereochemical outcome, exclusive formation of (*Z*)-alkenylpurine **3a**, was observed in the presence of $Pd(OAc)_2$ and PCy_3 (Table I, Entry 9). In this case, the **3a** was accompanied by the diallylated product **5a** (Fig. 1) in 14% isolated yield. It is worth mentioning, that the **5a** was formed in other cases as the by-product usually in less than 5% yield. The ability of various alkenylpurines to readily undergo *E*/*Z*-isomerization has been re-

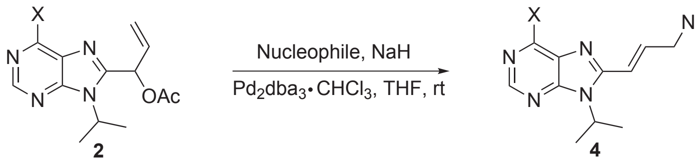
TABLE I
Optimization of Pd-catalyzed reaction of the allyl acetate **2a** with diethyl malonate

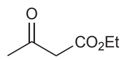
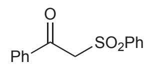
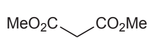
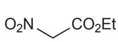
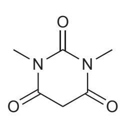


Entry	Catalyst[a]	Time, h	**3a**:**4a** Ratio[b]	**3a** + **4a** Yield[c], %
1	$Pd(PPh_3)_4$	3	58:42	73
2	$PdCl_2(PPh_3)_2$	3	55:45	81
3	$Pd_2dba_3·CHCl_3$	5	0:100	70
4	$Pd_2dba_3·CHCl_3$	16[d]	0:100	71
5	$Pd_2dba_3·CHCl_3$, $AsPh_3$	3	0:100	61
6	$Pd(OAc)_2$, dppp	3	57:43	81
7	$Pd_2dba_3·CHCl_3$, TFP	1.5	56:44	75
8	$Pd_2dba_3·CHCl_3$, 2-Cy_2Pbiphenyl	1.5	32:68	87
9	$Pd(OAc)_2$, PCy_3	15	100:0	65[e]

[a] Reaction conditions: dimethyl malonate (1.5 equiv.) was added to a suspension of NaH (1.5 equiv.) in THF. The mixture was stirred 15 min at ambient temperature, then a solution of Pd-cat. (5 mole %), phosphine ligands (10 mole %) and **2a** (1.0 equiv.) in dry THF was added. The resultant mixture was stirred at the room temperature. Isomeric purity was determined by ^1H NMR. [b] Obtained by ^1H NMR. [c] Overall isolated yield. [d] 2 mole % of the catalyst was used. [e] Accompanied by 14% of the diallylated product **5a**.

TABLE II
Pd-catalyzed reaction of the allyl acetates **2a** and **2b** with nucleophiles

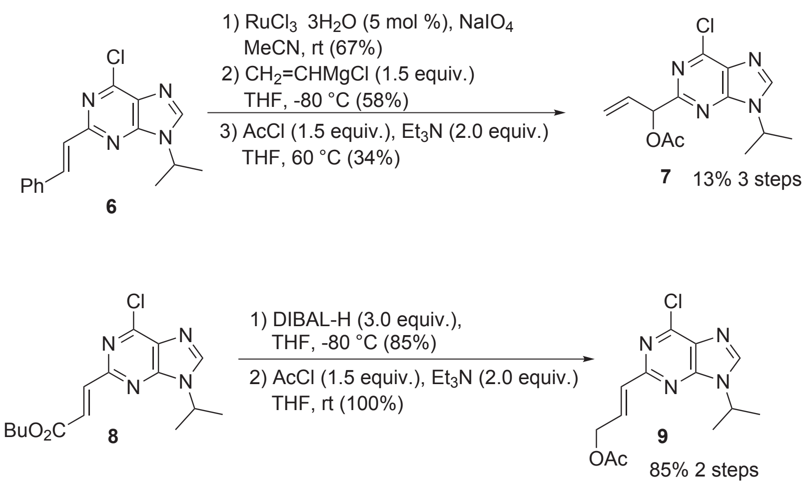


Entry	Acetate	X	Nucleophile[a]	Time, h	Product (Yield[b], %)
1	**2a**	OMe		5	**4b**, 44
2	**2a**	OMe		20	**4c**, 21
3	**2b**	Cl		3	**4d**, 54
4	**2a**	OMe	**4a**	6	**5a**, 62
5	**2a**	OMe	**4b**	6	**5b**, 49
6	**2a**	OMe		20	**3e** + **4e**, 25:75[c], 76
7	**2a**	OMe		24	**5c**[d], 34
8	**2a**	OMe	HCO_2Na[e]	27	**4f**, 66
9	**2a**	OMe	$PhSO_2Na$[e,f]	8	**4g**, 53
10	**2b**	Cl	$PhSO_2Na$[e,f]	15	**4h**, 41
11	**2a**	OMe	AcONa[e]	16	**4i**[g], 35

[a] Reaction conditions: nucleophile (1.5 equiv.) was added to a suspension of NaH (1.5 equiv.) in THF. The mixture was stirred 15 min at ambient temperature, then a solution of Pd-cat. (5 mole %) and **2a** or **2b** (1.0 equiv.) in dry THF was added. The resultant mixture was stirred at room temperature. Isomeric purity was determined by ^{1}H NMR. [b] Isolated yield. [c] A mixture of *E*- and *Z*-alkenes inseparable by column chromatography was obtained. [d] Diallylated product **5c** was isolated as the only product. [e] Reaction was performed without NaH. [f] Reaction was performed in dry DMF. [g] Unreacted **2a** (60%) was recovered.

cently reported[25,28]. However, in our case, compounds **3a** and **4a** have not isomerized neither in the presence of $Pd(OAc)_2$, PCy_3 nor with TsOH [28].

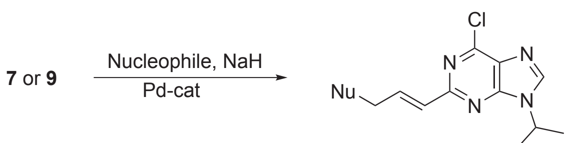
The ligandless condition developed for stereoselective formation of the *E*-alkenylpurines has been used for the testing of the reactivity of **2a** and **2b** with other nucleophiles. Ethyl acetoacetate and 2-(phenylsulfonyl)acetophenone as examples of the C-stabilized nucleophiles furnished the expected *E*-alkenes **4b** and **4c** in moderates yields (Table II, Entries 1, 2). Remarkably, acetate **2b**, which possesses two reaction centers (allylacetate and the halogen in the position 6), furnished exclusively the product of allylic substitution **4d** in 54% isolated yield (Table II, Entry 3). Nitroacetate, as the only C-nucleophile, gave the mixture of *Z*- and *E*-isomers **3e** and **4e** in 1:3 ratio (Table II, Entry 6). The ability of **4** to undergo further alkylation was verified in case of **4a** and **4b**, which have been successfully alkylated to afford diallylated products **5a** and **5b** (Fig. 1) in moderate yields (Table II, Entries 4, 5). Surprisingly, 1,3-dimethylbarbituric acid formed the diallylated product **5c** (Fig. 1) as the only product (Table II, Entry 7). Additionally, sodium formate and sodium benzenesulfinate were sufficiently reactive, and the expected allylpurines **4f**, **4g** and **4h** were obtained (Table II, Entries 8, 9, 10). Tosylamide and 9-benzylhypoxanthine as examples of N-nucleophiles, did not react with **2a** under the tested conditions at ambient temperature. Heating to 60 °C gave 6-methoxy-9-isopropyl-9-propenyl-9*H*-purine (**4f**) in 55% yield in this case, instead of the expected product of allylic substitution. When sodium acetate was used as nucleophile, partial rearrangement to the isomeric acetate **4i** was observed (Table II, Entry 11).



SCHEME 2

The ability of acetate **2b** to undergo Pd-catalyzed allylic substitution encouraged us to extend the scope of the above methodology to (purin-2-yl)-propenyl acetate. Attemps to prepare acetate **7** by reaction of purinylmagnesium chloride[29] with acroleine failed to give any isolable product. Thus, the acetate **7** was prepared via sequence of the Heck reaction of 6-chloro-2-iodo-9-isopropyl-9*H*-purine with styrene[30] giving styryl derivative **6** followed by $RuCl_3 \cdot 3H_2O$ catalyzed cleavage of double bond[31] (Scheme 2). The isolated carbaldehyde was then treated with vinylmagnesium chloride and the subsequent acylation afforded the acetate **7**. The Heck reaction of 6-chloro-2-iodo-9-isopropyl-9*H*-purine with butyl acrylate followed by the DIBAL-H reduction of the obtained ester **8** fol-

TABLE III
Pd-catalyzed reaction of the allyl acetates **2a** and **2b** with nucleophiles



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Entry	Acetate	Nucleophile[a]	Pd-cat.	Time, h	Product (Yield[b], %)
1	**9**	$CH_2(CO_2Me)_2$	$Pd_2dba_3 \cdot CHCl_3$	48	**10a** (13), **11** (12)
2	**9**	$CH_2(CO_2Me)_2$	$Pd(OAc)_2$, PCy_3	120	**10a** (26), **11** (40)
3	**9**	$CH_2(CO_2Me)_2$	$PdCl_2(PPh_3)_2$	96	**10a** (39), **11** (6)
4	**9**	$CH_2(CO_2Me)_2$	$Pd(PPh_3)_4$	72	**10a** (16), **11** (10)
5	**9**	$CH_2(CO_2Me)_2$	$Pd_2dba_3 \cdot CHCl_3$, 2-Cy_2Pbiphenyl	120	**10a** (26), **11** (20)
6	**9**	$CH_2(CO_2Me)_2$	$Pd_2dba_3 \cdot CHCl_3$[c]	24	**10a** (92), **11** (<5)
7	**9**	$CH_2(CO_2Me)_2$	$Pd(OAc)_2$, PCy_3[c]	168	**10a** (48), **11** (13)
8	**7**	$CH_2(CO_2Me)_2$	$Pd_2dba_3 \cdot CHCl_3$[c]	3	**10a** (73), **11** (5)
9	**9**	$PhSO_2Na$	$Pd_2dba_3 \cdot CHCl_3$[c]	24	**10b** (42), **11** (<5)
10	**9**	$PhCOCH_2SO_2Ph$	$Pd_2dba_3 \cdot CHCl_3$[c]	24	**10c** (40), **11** (<5)

[a] Reaction conditions: dimethyl malonate (1.5 equiv.) was added to a suspension of NaH (1.5 equiv.) in THF. The mixture was stirred 15 min at ambient temperature, then a solution of Pd-cat. (5 mole %), phosphine ligand (10 mole %) and **7** or **9** (1.0 equiv.) in dry THF was added. The resultant mixture was stirred at 60 °C. Isomeric purity was determined by ^{1}H NMR. [b] Isolated yield. [c] 3.0 Equivalents of dimethyl malonate and NaH were used.

lowed by acetylation gave the isomeric linear acetate **9** in 85% in two steps (Scheme 2).

Due to easier access, the linear acetate **9** was used for the reaction with dimethyl malonate under the same condition as **2**. The optimized reaction conditions for the formation of the *E*-alkene gave the target product **10a** in only 13% isolated yield along with 12% of the diallylated compound **11** (Fig. 1) accompanied with a chromatographically inseparable mixture of degradation products (Table III, Entry 1). The reaction under palladium acetate and tricyclohexylphospine catalysis furnished the primarily diallylderivative **11** in 40% isolated yield (Table III, Entry 2). Further variation of the catalytic system did not affect the yield of **10a** significantly (Table III, Entries 3, 4, 5). However, the high yield of **10a** was obtained when 3.0 equivalents of dimethyl malonate were used (Table III, Entry 6). Acetate **7**, gave similar results as **9** but in shorter reaction time, which corresponds with the expected higher reactivity of the acetate of the benzylic type (Table III, Entry 8). On contrary, the yields of allylic substitution of acetate **9** with 2-(phenylsulfonyl)acetophenone and sodium benzenesulfinate, as examples of other nucleophiles, were low (40 and 42%), even when an excess of nucleophiles was used (Table III, Entries 9, 10). The products were accompanied by chromatographically inseparable mixture of products of the decomposition of the purine scaffold in this case.

In conclusion we have developed a method for Pd-catalyzed allylic substitution of (6,9-disubstitutedpurin-8-yl)allyl acetates. The starting acetate **2a**

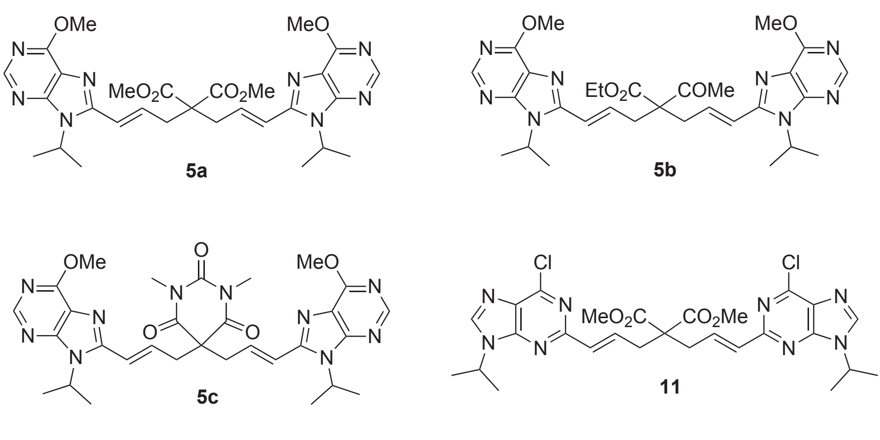

FIG. 1
Structures of the diallylated derivatives isolated in the course of the Pd-catalyzed allylic substitution of allyl acetates **2a**, **2b**, **7** and **9**

and **2b** react with various O- and C-stabilized nucleophiles in the presence of $Pd_2dba_3 \cdot CHCl_3$ in dry THF at room temperature to give novel (*E*)-8-alkenylpurines. On contrary to preferential formation of *E*-alkenes of most nucleophiles, ethyl nitroacetate gave mixture of *E*- and *Z*-alkenes inseparable by column chromatography. The application of the reaction conditions to (purin-2-yl)allyl acetate was successful only in case of dimethyl malonate. The other tested nucleophiles afforded the final products in low yields accompanied by unidentified complex mixtures. Further studies including the improvement of the reaction conditions at the position 2 of purine moiety and the extension to the position 6 are ongoing in our laboratory.

EXPERIMENTAL

All reactions were performed under an argon atmosphere. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Bruker AMX3 400 (^{1}H, 400.13 MHz; ^{13}C, 100.62 MHz) or a Bruker DRX 500 Avance (^{1}H, 500.13 MHz; ^{13}C, 125.77 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 (ν, cm^{-1}) 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, Silica Gel 60, 40–63 μm) was used for column chromatography. 9-Isopropyl-6-methoxy-9*H*-purine[32] (**1a**), 9-isopropyl-6-chloro-9*H*-purine[33] (**1b**), 6-chloro-9-isopropyl-2-(2-phenylethenyl)-9*H*-purine[30] (**6**) and butyl 3-(6-chloro-9-isopropylpurine-2-yl)acrylate[30] (**8**) were prepared by the reported procedures, other compounds were purchased.

8-(1-Acetoxyprop-2-enyl)-9-isopropyl-6-methoxy-9*H*-purine (**2a**)

A solution of BuLi (0.75 ml, 1.2 mmol, 1.6 M in hexane) was added to a solution of **1** (0.192 g, 1.0 mmol) in dry THF (10 ml) at –78 °C. Then the mixture was stirred 5 min at –78 °C followed by addition of acroleine (0.09 ml, 1.3 mmol). The resultant mixture was stirred 1 h at –80 °C and 1 h at 0 °C. Then the mixture was quenched by addition of saturated solution of NH_4Cl, extracted with dichloromethane (3 × 15 ml), dried over $MgSO_4$, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) afforded the corresponding 1-(9-isopropyl-6-methoxy-9*H*-purin-8-yl)prop-2-en-1-ol. ^{1}H NMR (300 MHz, $CDCl_3$): 1.69 m, 6 H (CH_3); 4.14 br s, 1 H (OH); 4.16 s, 3 H (CH_3); 4.86 m, 1 H (CH); 5.36 d, 1 H, ^3J = 13.4 (=CH); 5.43 d, 1 H, ^3J = 17.16 (=CH); 5.52 d, 1 H, ^3J = 4.32 (CH); 6.16 m, 1 H (=CH); 8.49 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 20.8, 49.1, 54.0, 69.1, 117.6, 120.6, 136.5, 151.1, 153.2, 153.4, 160.5. IR: 3342, 2996, 2946, 1608, 1574, 1484, 1446, 1421, 1355, 1326, 1290, 1069, 1049. HRMS (EI): calculated for $C_{12}H_{16}N_4O_2$ 248.1273, found 248.1273. Isolated alcohol (0.323 g, 1.3 mmol) was dissolved in dry THF (10 ml) followed by addition of triethylamine (0.36 ml, 2.6 mmol) and acetyl chloride (0.14 ml, 1.95 mmol). The resultant mixture was stirred 2 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.33 g, 87%) as yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.70 d, 6 H, ^3J = 6.88 (CH_3); 2.14 s, 3 H (CH_3); 4.15 s, 3 H (CH_3); 4.78 m, 1 H (CH); 5.36–5.44 m, 2 H (=CH_2); 6.27 m, 1 H

(=CH); 6.58 m, 1 H (CH-O); 8.50 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 20.50, 20.54, 20.75, 49.1, 53.6, 69.4, 119.3, 121.0, 132.2, 151.1, 149.1, 152.7, 160.6, 169.1. IR: 2996, 2947, 1743, 1608, 1574, 1485, 1447, 1409, 1372, 1357, 1326, 1292, 1265, 1070. HRMS (EI): calculated for $C_{14}H_{18}N_4O_3$ 290.1379, found 290.1369.

8-(1-Acetoxyprop-2-enyl)-6-chloro-9-isopropyl-9*H*-purine (**2b**)

A solution of LDA (2.2 mmol, prepared from diisopropylamine (0.31 ml, 2.2 mmol) and BuLi (1.38 ml, 2.2 mmol, 1.6 M solution in hexane) at –80 °C) in dry THF (5 ml) was added to a solution of **1** (0.393 g, 2.0 mmol) at –78 °C. Then the mixture was stirred 5 min at –78 °C followed by addition of acroleine (0.18 ml, 2.5 mmol). The resultant mixture was stirred 1 h at –78 °C and 1 h at 0 °C. Then the mixture was quenched by addtion of saturated solution of NH_4Cl, extracted with dichloromethane (3 × 15 ml), dried over $MgSO_4$, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) afforded corresponding 1-(6-chloro-9-isopropyl-9*H*-purin-8-yl)prop-2-en-1-ol (0.466 g, 69%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.69 d, 6 H, ^3J = 6.9 (CH_3); 3.94 d, 1 H, ^3J = 6.3 (OH); 4.93 m, 1 H (CH); 5.41 d, 1 H, ^3J = 10.5 (=CH_2); 5.48 d, 1 H, ^3J = 17.3 (=CH_2); 5.60 m, 1 H (CH-O); 6.13 m, 1 H (=CH); 8.68 s, 1 H (H-2). HRMS (EI): calculated for $C_{11}H_{13}ClN_4O$ 252.0778, found 252.0779. Isolated alcohol (0.466 g, 1.84 mmol) was dissolved in dry THF (10 ml) followed by addition of triethylamine (0.51 ml, 3.68 mmol) and acetyl chloride (0.20 ml, 2.77 mmol). The resultant mixture was stirred 2 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 1:2) gave the title compound (0.22 g, 41%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.75 d, 6 H, ^3J = 6.74 (CH_3); 2.19 s, 3 H (CH_3); 4.88 m, 1 H (CH); 5.44 d, 1 H, ^3J = 17.3 (=CH_2); 5.49 d, 1 H, ^3J = 10.5 (=CH_2); 6.26 m, 1 H (=CH); 6.64 d, 1 H, ^3J = 6.0 (CH); 8.71 s, 1 H (H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 20.6, 20.8, 20.9, 50.1, 69.9, 120.2, 131.3, 132.1, 151.2, 150.9, 152.8, 152.9, 169.3. IR: 2942, 1747, 1595, 1561, 1444, 1400, 1372, 1351, 1224, 1183, 1155, 1106, 1023, 988. HRMS (EI): calculated for $C_{13}H_{15}ClN_4O_2$ 294.0884, found 294.0881.

1-(6-Chloro-9-isopropyl-9*H*-purin-2-yl)prop-2-enyl acetate (**7**)

Water (20 ml) and acetonitrile (30 ml) was added to a mixture of **6** (1.0 g, 3.35 mmol), $RuCl_3 \cdot 3H_2O$ (0.044 g, 0.17 mmol) and sodium periodate (2.145 g, 10.04 mmol). The mixture was stirred 10 min at ambient temperature, diluted with saturated solution of $Na_2S_2O_3$ and extracted with EtOAc (3 × 20 ml). Collected organic phases were dried over $MgSO_4$, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexan 2:1) gave 6-chloro-9-isopropyl-9*H*-purin-2-carbaldehyde (0.506 g, 67%) as white solid; m.p. 151–155 °C (CH_2Cl_2–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 1.63 d, 6 H, ^3J = 6.9 (CH_3); 5.02 m, 1 H (CH); 8.40 s, 1 H (H-8); 10.00 s, 1 H (CHO). ^{13}C NMR (75 MHz, $CDCl_3$): 22.7, 48.5, 128.8, 133.3, 152.7, 151.8, 153.0, 189.4. IR ($CHCl_3$): 2928, 2854, 1723, 1583, 1554, 1481, 1393, 1350, 1320, 1292, 1172, 1147, 982, 967, 909, 883, 847. HRMS (EI): calculated for $C_9H_9ClN_4O$ 224.0454, found 224.0465. The isolated carbaldehyde (0.660 g, 3.0 mmol) was dissolved in dry THF (50 ml), cooled to –78 °C, followed by addition of vinylmagnesium chloride (2.75 ml, 4.4 mmol, 1.6 M solution in THF). The mixture was stirred 2 h at –78 °C, quenched by addition of AcOH (2 ml, 4 mmol, 2 M solution in methanol), concentrated in vacuo and column chromatography (silica gel, EtOAc) gave 1-(6-chloro-9-isopropyl-9*H*-purin-2-yl)prop-2-enol (0.480 g, 58%) as white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.63 d, 6 H,

^3J = 6.9 (CH_3); 4.92 m, 1 H (CH); 5.22 td, 1 H, ^3J = 1.7, 10.2 (=CH_2); 5.36 td,1 H, ^3J = 1.7, 4.9 (CH-O); 5.52 td, 1 H, ^3J = 1.7, 17.0 (=CH_2); 6.60 m, 1 H (=CH); 8.39 s, 1 H (H-8). ^{13}C NMR (75 Mz, $CDCl_3$): 22.5, 48.1, 74.2, 115.8, 130.6, 138.2, 143.1, 151.1, 151.6, 163.5. IR ($CHCl_3$): 3487, 1593, 1561, 1493, 1459, 1393, 1374, 1329, 1084, 1059, 976, 932, 880. HRMS (EI): calculated for $C_{11}H_{13}ClN_4O$ 252.0778, found 252.0786. Finally, obtained alcohol (0.226 g, 0.89 mmol) and DMAP (0.022 g, 0.18 mmol) was dissolved in dry THF (20 ml). Then triethylamine (0.25 ml, 1.79 mmol) and acetyl chloride (0.10 ml, 1.34 mmol), the mixture was stirred 24 h at 60 °C, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.090 g, 34%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.64 m, 6 H (CH_3); 2.20 s, 3 H (CH_3); 4.91 m, 1 H (CH); 5.35 td, 1 H, ^3J = 1.4, 10.2 (=CH_2); 5.51 td, 1 H, ^3J = 1.4, 17.0 (=CH_2); 6.20 m, 1 H (=CH); 6.31 m, 1 H (CH-O); 8.14 s, 1 H (H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 21.0, 22.3, 22.4, 48.0, 76.8, 118.7, 130.7, 133.7, 143.1, 150.9, 151.7, 160.4, 170.0. IR ($CHCl_3$): 1741, 1593, 1560, 1492, 1459, 1392, 1373, 1147, 1139, 1114, 1025, 985, 941, 881. HRMS (EI): calculated for $C_{13}H_{15}ClN_4O_2$ 294.0884, found 294.0891.

6-Chloro-9-isopropyl-2-(3-acetoxypropenyl)-9*H*-purine (**9**)

DIBAL-H (15.3 ml, 15.3 mmol, 1.0 M solution in toluene) was added to a solution of **8** (1.65 g, 5.11 mmol) in dry THF (60 ml) at –80 °C. The resultant mixture was stirred 40 min at –80 °C, quenched by addition of $Na_2SO_4 \cdot 10H_2O$ (6.6 g, 20.45 mmol), warmed to r.t., concentrated in vacuo and flash chromatography (silica gel, EtOAc) gave the alcohol (1.04 g, 81%) as yellow solid; m.p. 111–116 °C (CH_2Cl_2–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 1.65 d, 6 H, ^3J = 6.9 (CH_3); 4.46 m, 2 H (CH_2); 4.91 m, 1 H (CH); 6.83 td, 1 H, ^3J = 1.7, 15.7 (=CH); 7.32 td, 1 H, ^3J = 4.8, 11.0 (=CH); 8.10 s, 1 H (H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 22.4, 47.8, 62.5, 127.9, 129.9, 140.0, 142.8, 150.3, 151.8, 158.4. IR ($CHCl_3$): 3612, 3392, 1661, 1592, 1553, 1490, 1459, 1427, 1391, 1319, 1090, 981, 926, 904, 882. HRMS (EI): calculated for $C_{11}H_{13}ClN_4O$ 252.0778, found 252.0789. Isolated alcohol (1.04 g, 4.12 mmol) was dissolved in dry THF (60 ml) followed by addition of triethylamine (1.45 ml, 8.23 mmol) and acetyl chloride (0.43 ml, 6.17 mmol). The resultant mixture was stirred 0.5 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (1.21 g, 99%) as white solid; m.p. 115–118 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 1.66 d, 6 H, ^3J = 6.9 (CH_3); 2.15 s, 3 H (CH_3); 4.85 dd, 2 H, ^3J = 1.7, 5.5 (CH_2); 4.92 m, 1 H (CH); 6.72 td, 1 H, ^3J = 1.6, 15.7 (=CH); 7.25 m, 1 H (=CH); 8.13 s, 1 H (H-8). ^{13}C NMR ($CDCl_3$): 20.8, 22.5, 47.8, 63.6, 130.3, 130.4, 133.8, 142.9, 150.5, 151.8, 157.8, 170.5. IR ($CHCl_3$): 3683, 3616, 2400, 2361, 2334, 1736, 1592, 1553, 1425, 1390, 1321, 1084, 1029, 979, 928. HRMS (EI): calculated for $C_{13}H_{15}ClN_4O_2$ 294.0884, found 294.0886.

Pd-Catalyzed Allylic Substitution of Acetates **2a**, **2b**, **7** and **9**. General Procedure

Dimethyl malonate (1.5 equiv.) was added to a suspension of NaH (1.5 equiv.) in dry THF (10 ml per mmol of dimethyl malonate). The mixture was stirred 15 min at ambient temperature, then a solution of acetates **2a**, **2b**, **7**, **9** and Pd-cat. (5 mole %) in dry THF (5 ml per mmol of acetates) was added. The resultant mixture was stirred at room temperature. The finished reaction mixture was concentrated in vacuo and final products were isolated by column chromatography.

Dimethyl (Z)-2-[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]malonate (**3a**): A reaction mixture, prepared according the general procedure, starting from dimethyl malonate (0.06 ml, 0.53 mmol), NaH (0.021 g, 0.53 mmol, 60% suspension in mineral oil), **2a** (0.101 g, 0.35 mmol), $Pd(OAc)_2$ (0.004 g, 0.018 mmol) and PCy_3 (0.01 g, 0.036 mmol) was stirred 15 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.082 g, 65%) as white amorphous solid, that was ≥98% *Z* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.67 d, 6 H, ^3J = 6.80 (CH_3); 3.34 t, 2 H, ^3J = 6.9 (CH_2); 3.71 m, 7 H, 6 H (CH_3) + 1 H (CH); 4.18 s, 3 H (O-CH_3); 4.84 m, 1 H (CH); 6.20 m, 1 H (=CH); 6.50 d, 1 H, ^3J = 11.8 (=CH); 8.47 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.4, 28.6, 48.2, 51.0, 52.5, 54.0, 117.7, 121.6, 138.0, 148.3, 150.9, 152.4, 160.6, 169.3. IR ($CDCl_3$): 2994, 2956, 1734, 1603, 1571, 1482, 1438, 1338, 1327, 1297, 1160, 1068, 1047. HRMS (EI): calculated for $C_{17}H_{22}N_4O_5$ 362.1590, found 362.1590.

Dimethyl (E)-2-[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]malonate (**4a**): A reaction mixture, prepared according the general procedure, starting from dimethyl malonate (0.07 ml, 0.65 mmol), NaH (0.026 g, 0.65 mmol), **2a** (0.125 g, 0.43 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.022 g, 0.022 mmol) was stirred 5 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.109 g, 70%) as white amorphous solid, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.67 d, 6 H, ^3J = 6.9 (CH_3); 2.92 t, 2 H, ^3J = 7.1 (CH_2); 3.58 t, 1 H, ^3J = 7.4 (CH); 3.74 s, 6 H (CH_3); 4.15 s, 3 H (CH_3); 4.88 m, 1 H (CH); 6.60 d, 1 H, ^3J = 15.3 (=CH); 7.08 m, 1 H (=CH); 8.44 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 32.3, 47.9, 50.8, 52.5, 53.9, 119.0, 121.5, 136.9, 149.1, 150.7, 152.8, 160.3, 168.8. IR ($CDCl_3$): 3022, 2995, 2957, 1752, 1735, 1604, 1571, 1483, 1438, 1359, 1328, 1289, 1159, 1071, 1049. HRMS (EI): calculated for $C_{17}H_{22}N_4O_5$ 362.1590, found 362.1586.

Ethyl (E)-2-[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]acetoacetate (**4b**): A reaction mixture, prepared according the general procedure, starting from ethyl acetoacetate (0.10 ml, 0.75 mmol), NaH (0.030 g, 0.75 mmol), **2a** (0.145 g, 0.50 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.026 g, 0.025 mmol) was stirred 5 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.080 g, 44%) as yellow amorphous solid, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.28 t, 3 H, ^3J = 7.0 (CH_3); 1.68 d, 6 H, ^3J = 7.0 (CH_3); 2.29 s, 3 H (CH_3); 2.86 t, 2 H, ^3J = 7.0 (CH_2); 3.67 t, 1 H, ^3J = 7.3 (CH); 4.17 s, 3 H (CH_3); 4.21 m, 2 H (CH_2); 4.89 m, 1 H (CH); 6.59 d, 1 H, ^3J = 15.4 (=CH); 7.07 m, 1 H (=CH); 8.46 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 21.5, 29.4, 31.4, 47.8, 53.9, 58.5, 61.7, 118.8, 121.5, 137.4, 149.2, 150.7, 152.8, 160.3, 168.7, 201.5. IR ($CDCl_3$): 2991, 2944, 1740, 1716, 1653, 1604, 1571, 1483, 1458, 1442, 1358, 1327, 1270, 1170, 1158, 1070, 1049, 1017, 964. HRMS (EI): calculated for $C_{18}H_{24}N_4O_4$ 360.1798, found 360.1794.

(E)-2-[3-(9-Isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]-2-(phenylsulfonyl)acetophenone (**4c**): A reaction mixture, prepared according the general procedure, starting from 2-(phenylsulfonyl)acetophenone (0.159 g, 0.61 mmol), NaH (0.024 g, 0.61 mmol), **2a** (0.118 g, 0.41 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.021 g, 0.020 mmol) was stirred 20 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.094 g, 31%) as white foam, that was 98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.55 dd, 6 H, ^3J = 6.3 (CH_3); 3.13 m, 2 H (CH); 4.11 s, 3 H (CH_3); 4.69 m, 1 H (CH); 5.27 dd, 1 H, ^3J = 1.7, 4.7 (CH); 6.47 d, 1 H, ^3J = 15.3 (=CH); 6.89 m, 1 H (=CH); 7.44 m, 2 H (ArH); 7.57 m, 3 H (ArH); 7.67 m, 1 H (ArH); 7.78 m, 2 H (ArH); 7.94 m, 2 H (ArH); 8.41 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 31.5, 47.9, 53.9, 68.5, 120.1, 121.4, 128.8, 129.1, 129.2, 129.8, 134.3, 134.4, 134.5, 136.1, 136.6, 150.8, 148.6, 152.7, 160.3,

191.1. IR ($CDCl_3$): 1681, 1604, 1571, 1523, 1484, 1449, 1441, 1421, 1358, 1328, 1311, 1135, 1084, 1071, 973, 931. M+ (EI): 490.

Dimethyl (E)-2-[3-(6-chloro-9-isopropyl-9H-purin-8-yl)prop-2-enyl]malonate (**4d**): A reaction mixture, prepared according the general procedure, starting from dimethyl malonate (0.17 ml, 1.45 mmol), NaH (0.058 g, 1.45 mmol), **2b** (0.248 g, 0.96 mmol), and $Pd_2dba_3{\cdot}CHCl_3$ (0.050 g, 0.048 mmol) was stirred 3 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.191 g, 54%) as yellow oil, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.71 d, 6 H, ^3J = 6.9 (CH_3); 2.97 t, 2 H, ^3J = 7.3 (CH_2); 3.63 m, 1 H (CH); 3.77 s, 6 H (CH_3); 4.92 m, 1 H (CH); 6.66 d, 1 H, ^3J = 15.3 (=CH); 7.22 m, 1 H (=CH); 8.64 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.4, 32.3, 48.5, 50.5, 52.8, 118.5, 131.6, 139.8, 150.5, 149.3, 152.3, 152.7, 168.7.

Ethyl (Z)-2-[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]-2-nitroacetate (**3e**) *and ethyl (E)-2-[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]-2-nitroacetate* (**4e**): A reaction mixture, prepared according the general procedure, starting from ethyl nitroacetate (0.07 ml, 1.45 mmol), NaH (0.058 g, 0.64 mmol), **2a** (0.124 g, 0.43 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.022 g, 0.022 mmol) was stirred 20 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave inseparable mixture of *Z*- and *E*-stereoisomers (*Z*–*E*, 25:75, 0.125 g, 76%) characterized as the mixture. ^{1}H NMR ($CDCl_3$): 1.31 t, 3 H, ^3J = 7.2 (CH_3); 1.33 t, 3 H, ^3J = 7.1 (CH_3); 1.67 d, 6 H, ^3J = 7.2 (CH_3); 1.69 d, 6 H, ^3J = 6.9 (CH_3); 3.15–3.30 m, 2 H (CH_2); 3.68 m, 2 H (CH_2); 4.17 s, 3 H (CH_3); 4.18 s, 3 H (CH_3); 4.32 m, 2 H (CH_2); 4.33 m, 2 H (CH_2); 4.87 m, 1 H (CH); 4.89 m, 1 H (CH); 5.29 dd, 1 H, ^3J = 1.7, 5.4 (CH); 5.58 t, 1 H, ^3J = 7.2 (CH); 6.16 m, 1 H (=CH); 6.65 d, 1 H, ^3J = 11.6 (=CH); 6.68 d, 1 H, ^3J = 15.3 (=CH); 7.08 m, 1 H (=CH); 8.48 s, 1 H (H-2); 8.50 s, 1 H (H-2). ^{13}C NMR ($CDCl_3$): 13.9, 21.5, 21.6, 30.1, 33.7, 48.0, 48.3, 54.0, 54.1, 63.0, 63.4, 86.7, 87.1, 116.3, 121.2, 121.5, 121.6, 132.5, 133.6, 151.0, 151.3, 147.6, 148.4, 152.4, 152.8, 160.5, 160.8, 163.6, 164.2. IR ($CDCl_3$): 2988, 1752, 1604, 1567, 1483, 1459, 1442, 1358, 1327, 1260, 1071, 1049, 1022. HRMS (EI): calculated for $C_{16}H_{21}N_5O_5$ 363.1543, found 363.1550.

9-Isopropyl-6-methoxy-8-propenyl-9H-purine (**4f**): A reaction mixture, prepared according the general procedure, starting from sodium formate (0.159 g, 1.04 mmol), **2a** (0.151 g, 0.52 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.027 g, 0.026 mmol) was stirred 27 h at ambient temperature. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.080 g, 66%) as colorless oil, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.65 d, 6 H, ^3J = 6.9 (CH_3); 1.97 dd, 3 H, ^3J = 1.7, 6.9 (CH_3); 4.13 s, 3 H (CH_3); 4.86 m, 1 H (CH); 6.47 d, 1 H, ^3J = 15.5 (=CH); 7.19 m, 1 H (=CH); 8.42 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 21.4, 47.7, 53.8, 117.1, 121.4, 138.0, 150.0, 150.3, 152.7, 160.0. IR: 2979, 2941, 1656, 1601, 1570, 1481, 1448, 1419, 1397, 1351, 1324, 1290, 1171, 1159, 1136, 1092, 1069, 1048, 983, 959, 943, 897, 801. HRMS (ESI): calculated for $C_{12}H_{16}N_4O$ $[M + H]^+$ 233.13967, found 233.13919.

9-Isopropyl-6-methoxy-8-[3-(phenylsulfonyl)propenyl]-9H-purine (**4g**): Dry DMF (4 ml) was added to a mixture of **2a** (0.093 g, 0.32 mmol), sodium benzenesulfinate (0.079 g, 0.48 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.017 g, 0.016 mmol). The resultant mixture was stirred 8 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–MeOH, 9:1) gave the title compound (0.063 g, 53%) as yellow amorphous solid, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.63 d, 6 H, ^3J = 6.9 (CH_3); 4.07 d, 2 H, ^3J = 7.8 (CH_2); 4.18 s, 3 H (CH_3); 4.79 m, 1 H (CH); 6.63 d, 1 H, ^3J = 15.4 (=CH); 6.98 m, 1 H (=CH); 7.56 m, 2 H (ArH); 7.66 m, 1 H (ArH); 7.91 m, 2 H (ArH); 8.48 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 48.0, 54.1, 59.9, 121.7, 124.8, 125.7, 128.4, 129.3, 134.0, 138.4, 151.2, 147.7, 152.7, 160.6. IR ($CDCl_3$): 2996, 2944, 2872, 1603, 1572, 1483, 1448, 1356, 1326, 1310, 1155, 1087, 1071, 1049. HRMS (EI): calculated for $C_{18}H_{20}N_4O_3S$ 372.1256, found 372.1259.

6-Chloro-9-Isopropyl-8-[3-(phenylsulfonyl)propenyl]-9H-purine (**4h**): Dry DMF (4 ml) was added to a mixture of **2b** (0.104 g, 0.35 mmol), sodium benzenesulfinate (0.087 g, 0.53 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.019 g, 0.018 mmol). The resultant mixture was stirred 15 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.055 g, 41%) as yellow foam, that was 98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.66 d, 6 H, ^3J = 6.9 (CH_3); 4.09 d, 2 H, ^3J = 7.8 (CH_2); 4.81 m, 1 H (CH); 6.69 d, 1 H, ^3J = 15.3 (=CH); 7.08 m, 1 H (=CH); 7.57–7.71 m, 3 H (ArH); 7.92 d, 2 H, ^3J = 8.2 (ArH); 8.66 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 48.8, 59.8, 124.2, 128.1, 128.4, 129.4, 131.7, 134.1, 138.5, 151.0, 150.1, 150.9, 152.7. IR ($CDCl_3$): 3069, 2930, 2857, 1590, 1560, 1447, 1397, 1352, 1325, 1252, 1153, 1086, 997. HRMS (EI): calculated for $C_{17}H_{17}ClN_4O_2S$ 376.0761, found 376.0767.

2-(3-Acetoxypropenyl)-9-isopropyl-6-methoxy-9H-purine (**4i**): Dry THF (5 ml) was added to a mixture of **2a** (0.152 g, 0.52 mmol), sodium acetate (0.064 g, 0.78 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.027 g, 0.026 mmol). The resultant mixture was stirred 16 h at 50 °C, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.053 g, 35%) as yellow foam, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.71 d, 6 H, ^3J = 6.9 (CH_3); 2.15 s, 3 H (CH_3); 4.18 s, 3 H (CH_3); 4.85 d, 2 H, ^3J = 4.6 (CH_2); 4.90 m, 1 H (CH); 6.74 d, 1 H, ^3J = 15.4 (=CH); 7.22 m, 1 H (=CH); 8.48 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 20.8, 21.6, 48.0, 54.0, 63.6, 118.0, 121.6, 134.4, 150.9, 148.7, 152.8, 160.5, 170.4. IR: 2993, 2945, 1743, 1604, 1572, 1484, 1458, 1441, 1363, 1351, 1327, 1231, 1070. HRMS (EI): calculated for $C_{14}H_{18}N_4O_3$ 290.1379, found 290.1366.

Dimethyl (E)-2,2-bis[3-(9-isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]malonate (**5a**): A reaction mixture, prepared according the general procedure, starting from **4a** (0.144 g, 0.40 mmol), NaH (0.016 g, 0.40 mmol), **2a** (0.183 g, 0.63 mmol), and $Pd_2dba_3{\cdot}CHCl_3$ (0.021 g, 0.020 mmol) was stirred 5 h at ambient temperature. Column chromatography (silica gel, EtOAc–MeOH, 9:1) gave the title compound (0.145 g, 62%) as yellow foam, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.66 d, 12 H, ^3J = 6.9 (CH_3); 3.00 t, 2 H, ^3J = 7.4 (CH_2); 3.76 s, 6 H (CH_3); 4.17 s, 6 H (CH_3); 4.89 m, 2 H (CH); 6.62 d, 2 H, ^3J = 15.1 (=CH); 7.06 m, 2 H (=CH); 8.46 s, 2 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 37.1, 47.9, 52.8, 54.0, 57.7, 120.4, 121.5, 135.2, 149.0, 150.8, 152.8, 160.3, 170.4. IR: 2994, 2939, 1735, 1603, 1571, 1483, 1440, 1359, 1327, 1292, 1174, 1137, 1070, 1049. HRMS (EI): calculated for $C_{29}H_{36}N_8O_6$ 592.2787, found 592.2758.

(E)-5,5-bis[3-(9-Isopropyl-6-methoxy-9H-purin-8-yl)prop-2-enyl]-1,3-dimethylbarbituric acid (**5c**): A reaction mixture, prepared according the general procedure, starting from 1,3-dimethylbarbituric acid (0.091 g, 0.58 mmol), NaH (0.023 g, 0.58 mmol), **2a** (0.113 g, 0.39 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.020 g, 0.020 mmol) was stirred 24 h at ambient temperature. Column chromatography (silica gel, EtOAc–MeOH, 9:1) gave the title compound (0.080 g, 34%) as yellow oil, that was ≥98% *E* determined by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 1.68 d, 12 H, ^3J = 6.8 (CH_3); 3.05 d, 4 H, ^3J = 7.8 (CH_2); 3.26 s, 6 H (CH_3); 4.17 s, 6 H (CH_3); 4.88 m, 2 H (CH); 6.60 d, 2 H, ^3J = 15.4 (=CH); 6.90 m, 2 H (=CH); 8.46 s, 2 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 28.7, 42.6, 47.8, 54.0, 56.6, 121.8, 132.5, 151.0, 148.2, 152.7, 160.4, 169.9, 170.5. IR ($CDCl_3$): 2994, 2942, 1684, 1604, 1572, 1483, 1443, 1422,

1382, 1358, 1328, 1290, 1251, 1070. HRMS (EI): calculated for $C_{30}H_{36}N_{10}O_5$ 616.2870, found 616.2851.

Dimethyl (E)-2-[3-(6-chloro-9-isopropyl-9H-purin-2-yl)prop-2-enyl]malonate (**10a**): A reaction mixture, prepared according the general procedure, starting from dimethyl malonate (0.054 ml, 0.51 mmol), NaH (0.020 g, 0.51 mmol, 60% suspension in mineral oil), **9** (0.050 g, 0.17 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.009 g, 0.0085 mmol) was stirred 24 h at 60 °C. Column chromatography (silica gel, EtOAc) gave the title compound (0.057 g, 92%) as yellow oil, that was ≥98% *E* determined by ^1H NMR. ^1H NMR ($CDCl_3$): 1.62 d, 6 H, ^3J = 6.5 (CH_3); 2.90 dt, 2 H, ^3J = 1.4, 7.3 (CH_2); 3.61 t, 1 H, ^3J = 7.4 (CH); 3.75 s, 6 H (CH_3); 4.89 m, 1 H (CH); 6.64 td, 1 H, ^3J = 1.4, 15.4 (=CH); 7.11 m, 1 H (=CH); 8.09 s, 1 H (H-8). ^{13}C NMR ($CDCl_3$): 22.5, 31.6, 47.7, 51.0, 52.7, 130.1, 131.4, 136.3, 142.6, 150.4, 151.8, 158.2, 169.0. IR ($CHCl_3$): 1734, 1591, 1552, 1490, 1458, 1436, 1391, 1319, 987, 908. HRMS (EI): calculated for $C_{16}H_{19}ClN_4O_4$ 366.1111, found 366.1095.

(E)-6-Chloro-9-Isopropyl-2-[3-(phenylsulfonyl)propenyl]-9H-purine (**10b**): Dry DMF (4 ml) was added to a mixture of **9** (0.150 g, 0.508 mmol), sodium benzenesulfinate (0.251 g, 1.53 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.026 g, 0.025 mmol). The resultant mixture was stirred 24 h at ambient temperature, concentrated in vacuo and column chromatography (silica gel, EtOAc–hexane, 4:1) gave the title compound (0.080 g, 42%) as yellow foam, that was ≥98% *E* determined by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$): 1.63 d, 6 H, ^3J = 6.6 (CH_3); 4.04 d, 2 H, ^3J = 7.5 (CH_2); 4.89 m, 1 H (CH); 6.59 d, 1 H, ^3J = 15.6 (=CH); 7.10 m, 1 H (=CH); 7.51–7.67 m, 3 H (ArH); 7.90 d, 2 H, ^3J = 8.40 (ArH); 8.13 s, 1 H (H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 22.4, 47.9, 59.9, 125.3, 128.3, 129.1, 130.5, 133.9, 137.0, 138.3, 143.3, 150.4, 151.7, 156.7. IR: 3063, 3020, 2982, 2921, 2849, 1687, 1589, 1551, 1490, 1459, 1447, 1425, 1391, 1319, 1309, 1217, 1172, 1151, 1085, 1025, 999, 976, 922, 881, 752, 705, 688, 667. HRMS (ESI): calculated for $C_{17}H_{18}O_2N_4ClS$ $[M + H]^+$ 377.08334, found 377.08289.

(E)-2-[3-(6-Chloro-9-isopropyl-9H-purin-2-yl)prop-2-enyl]-2-(phenylsulfonyl)acetophenone (**10c**): A reaction mixture, prepared according the general procedure, starting from 2-(phenylsulfonyl)acetophenone (0.398 g, 1.53 mmol), NaH (0.024 g, 1.53 mmol), **9** (0.150 g, 0.51 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (0.026 g, 0.0254 mmol) was stirred 24 h at 60 °C. Column chromatography (silica gel, EtOAc–hexane, 2:1) gave the title compound (0.100 g, 40%) as yellow foam, that was ≥98% *E* determined by ^1H NMR. ^1H NMR (300 MHz, $CDCl_3$): 1.54 d, 6 H, ^3J = 6.9 (CH_3); 3.08 t, 2 H, ^3J = 7.5 (CH_2); 4.80 m, 1 H (CH); 5.25 m, 1 H (CH); 6.55 d, 1 H, ^3J = 15.6 (=CH); 6.91 dt, 1 H, ^3J = 7.5, 15.0 (=CH); 7.40 m, 2 H (ArH); 7.50 m, 3 H (ArH); 7.60 m, 1 H (ArH); 7.55 m, 2 H (ArH); 7.90 m, 2 H (ArH); 8.05 s, 1 H (H-8). ^{13}C NMR (75 MHz, $CDCl_3$): 22.3, 47.7, 63.5, 68.8, 128.6, 128.9, 129.0, 129.5, 132.5, 134.0, 134.3, 136.2, 136.6, 142.8, 150.1, 151.6, 157.5, 191.2. IR: 3117, 3065, 2982, 2935, 1738, 1681, 1591, 1550, 1490, 1448, 1426, 1391, 1321, 1310, 1277, 1220, 1150, 1111, 1084, 1027, 999, 977, 938, 904, 882, 837, 753, 687, 666. HRMS (ESI): calculated for $C_{25}H_{23}O_3N_4ClS$ $[M + H]^+$ 495.1252, found 495.12414.

Dimethyl (E)-2,2-bis[3-(6-chloro-9-isopropyl-9H-purin-2-yl)prop-2-enyl]malonate (**11**): A reaction mixture, prepared according the general procedure, starting from dimethyl malonate (0.054 ml, 0.51 mmol), NaH (0.020 g, 0.51 mmol, 60% suspension in mineral oil), **9** (0.050 g, 0.17 mmol), $Pd(OAc)_2$ (0.0019 g, 0.0085 mmol) and PCy_3 (0.0048 g, 0.017 mmol) was stirred 120 h at 60 °C. Column chromatography (silica gel, EtOAc) gave the title compound (0.057 g, 92%) as brown foam, that was ≥98% *E* determined by ^1H NMR. ^1H NMR ($CDCl_3$): 1.65 d, 12 H, ^3J = 6.9 (CH_3); 3.00 d, 4 H, ^3J = 7.7 (CH_2); 3.80 s, 6 H (CH_3); 4.94 m, 2 H (CH); 6.71 d, 1 H, ^3J = 15.4 (=CH); 7.08 m, 1 H (=CH); 8.12 s, 1 H (H-8). ^{13}C NMR ($CDCl_3$): 22.6, 36.0, 47.6, 52.8, 58.0, 130.2, 133.1, 134.4, 142.7, 150.4, 151.8, 158.0, 170.7. IR ($CHCl_3$): 1733, 1591, 1552, 1490, 1458, 1436, 1390, 1319, 978, 911, 880. HRMS (EI): calculated for $C_{27}H_{30}Cl_2N_8O_4$ 600.1767, found 600.1788.

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