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Selective N-7 alkylation of 3-methylhypoxanthine; the first synthesis of malonganenone J

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ABSTRACT

3-Methylhypoxanthine has been reacted with various alkyl halides under basic conditions. Allylic and benzylic halides reacted mostly at N-7 to give dialkylated purines, however, ring-opened imidazole by-products, probably resulting from N-1 alkylation and hydrolysis of the formed salt, were often obtained in minor amounts. Less reactive halides required a larger excess, higher temperatures, and longer reaction times. 3,7-Dialkylpurines were again the major products and imidazoles were formed in very minor amounts, however, a considerable amount of *O*-alkylation also took place. The marine natural product malonganenone J was synthesized for the first time by selective N-7 alkylation of 3-methylhypoxanthine with geranylgeranyl bromide.

Malonganenones are marine natural products isolated from the Gorgonians (sea whips or sea fans) *Leptogorgia* sp., *Echinogorgia* sp., *Euplexaura* sp., and *Melitodes* sp.[1] Malonganenone A, D, E, I, J, L, M, and N are 7-alkylated 3-methylhypoxanthines (Fig. 1). Most of these compounds are active against various cancer cell lines.[1] Malonganenone D inhibits a receptor tyrosine kinase[1c] while malonganenone L inhibits a phosphodiesterase.[1d] Furthermore, malonganenone A was shown to inhibit plasmodial heat shock protein chaperones[2] and may thus be a lead compound for anti-malarial drugs.

No total synthesis has been described for any malonganenone to date. As a continuation of our synthetic studies directed toward marine purine–terpene hybrid natural products and analogs,[3,4] we now report the first synthesis of malonganenone J.

We envisaged that all of the malonganenones shown in Figure 1 should be available by the N-7 alkylation of 3-methylhypoxanthine with an appropriate allyl halide. However, there are surprisingly few reports regarding the alkylation reactions of 3-substituted hypoxanthines. Benzylation of compound **1a** under neutral conditions was reported to take place at N-1 giving salt **2**, which rearranged to the dibenzylated isomers **3** and **4** in almost equal amounts (Scheme 1).[5]

In the presence of a base, purines **1** have been benzylated at N-7 to give the products **5** in relatively good yields.[6] Methylation of hypoxanthine **1b**, on the other hand, resulted in ring opening to yield an unidentified product (assumed to be compound **7**, **8** or **9**) and the desired 3,7-dimethylated product **6** which was only isolated in 36% yield.[6b] Thus, we decided to study the *N*-alkylation of hypoxanthine **1b** in more detail.

3-Methylhypoxanthine (**1b**) is available by several literature procedures and we chose to prepare this starting material in two steps from adenine.[7,8] First, we examined the reactivity toward geranyl bromide (**10**);[9] a readily available allyl halide with structural resemblance to the halides required for the syntheses of the malonganenones (Scheme 2, Table 1). When the previously reported reaction conditions for benzylation of compound **1b** were employed,[5] only moderate conversion (45%) was observed (Table 1, entry 1). The starting material to product ratio was significantly improved by increasing the concentration of the reaction mixture (Table 1, entry 2), but ring opened by-products **12a**[10] and **13a** were also isolated.[11] Although the amount of compound **12a** formed could be estimated from the ^{1}H NMR spectrum of the crude products (Table 1), similar estimates for imidazole **13a** were difficult due to overlapping signals with other compounds. The reaction also took place at room temperature (Table 1, entry 3), but a somewhat longer reaction time was required and additional dialkylation leading to the imidazole **12a** occurred.

To our surprise, formation of tetraalkylammonium salt **14** (Scheme 3) was observed in the alkylations performed in DMA (Table 1, entries 1–3). This made isolation of the products more complicated and was probably the reason why the yields from reactions performed under seemingly identical conditions were not necessarily reproducible. It has been previously reported that

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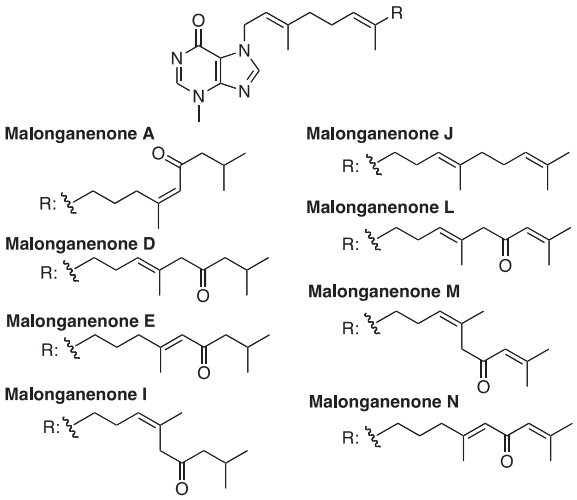
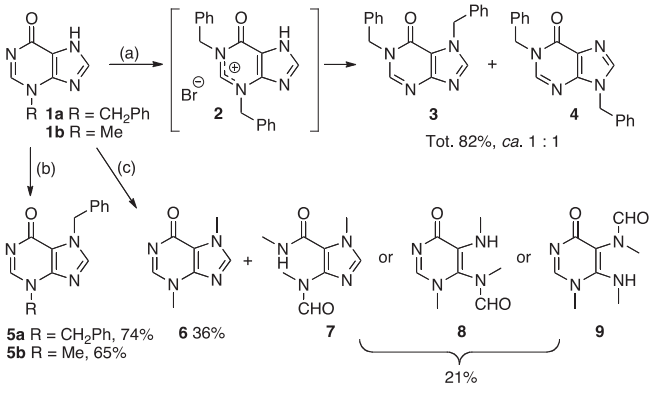
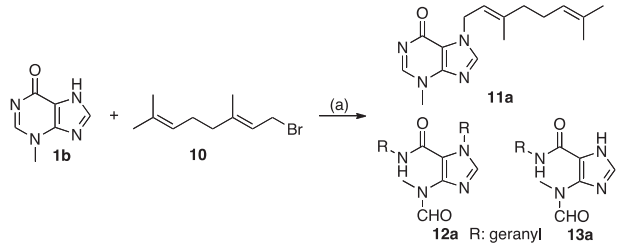


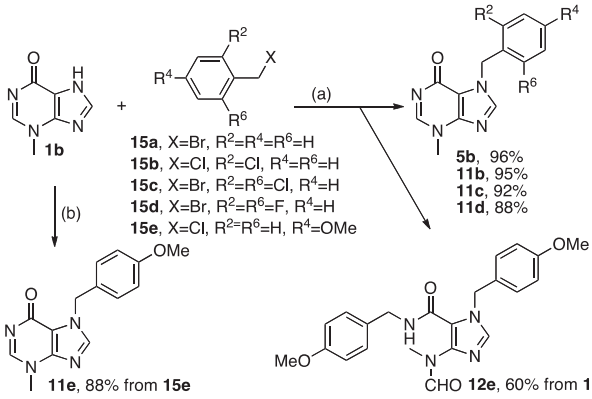
Figure 1. Structure of malonganenones A, D, E, I, J, L, M, and N.



Scheme 1. (a)[5] **1a**, $PhCH_2Br$, DMA, 110 °C; (b)[6] $PhCH_2X$, K_2CO_3, 90–110 °C, DMA; (c)[6b] (1) **1b**, K_2CO_3, DMA 110 °C, (2) MeI, rt.



Scheme 3. (a) K_2CO_3, rt, 1 h.



Scheme 4. (a) K_2CO_3 (1.0 equiv), **15** (1.2 equiv) DMSO, rt; (b) K_2CO_3 (1.0 equiv), **15e** (0.75 equiv), DMSO, 12 °C.[16]

quaternary ammonium halides can be synthesized from tertiary amides and alkyl halides in the presence of sodium or potassium carbonate at elevated temperatures.[12] According to the literature,[12a] these reactions require a temperature of at least 40 °C and are more efficient using sodium or potassium carbonates instead of cesium, lithium, and calcium carbonates. However, when hypoxanthine **1b** was alkylated with geranyl bromide at ambient temperature, the ammonium salt **14** was still formed. Compound **14** was also isolated in 22% yield when excess DMA was reacted with geranyl bromide in the presence of K_2CO_3 at ambient temperature for 1 h (Scheme 3). Changing the base to Cs_2CO_3 (data not shown) or to NaH did not improve the reaction outcome and salt **14** was also formed in DMF (Table 1, entries 4 and 5).

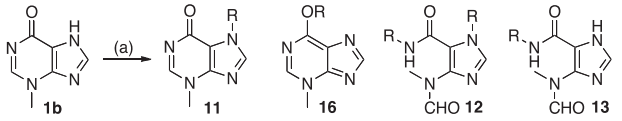
Thus, we chose to switch to a non-amide containing solvent. When hypoxanthine **1b** was alkylated in DMSO (Table 1, entries 6 and 7), full conversion and minimal ring opening took place and the desired geranylpurine **11a** was isolated in high yields. The reactions in DMSO turned out to be more reproducible and could be performed at ambient temperatures.

We then extended the alkylation study of 3-methylhypoxanthine (**1b**) to include benzyl (Scheme 4) and alkyl halides

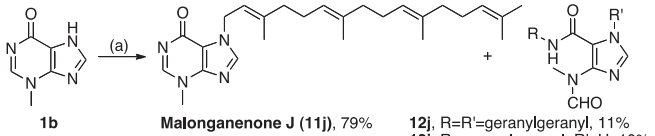
Table 1
N-Alkylation of 3-methylhypoxanthine (**1b**) with geranyl bromide (**10**)

Entry	Base (equiv)	**10** (equiv)	Solvent	Conc. **1b** (M)	Temp. (°C)	Time[a] (h)	Ratio **1b**:**11a**:**12a**[b]	Yield **11a**[c] (%)	Yield **12a**[c] (%)	Yield **13a**[c] (%)
1	K_2CO_3 (1.0)	1.2	DMA	0.032	110 (90[d])	2.5	55:45:0	—[e]	—[e]	—[e]
2	K_2CO_3 (1.0)	1.2	DMA	0.25	110 (90[d])	1.0	11:82:7	69	5	12
3	K_2CO_3 (1.0)	1.2	DMA	0.25	rt	2.0	0:61:39	36	10	—[e]
4	NaH (1.2)	1.2	DMA	0.25	rt	1.0	42:41:17	—[e]	—[e]	—[e]
5	NaH (1.2)	1.2	DMF	0.25	rt	2.0	0:41:59	—[e]	—[e]	—[e]
6	K_2CO_3 (1.2)	1.5	DMSO	0.022	110 (90[d])	1.5	0:98:2	86	—[e]	—[e]
7	K_2CO_3 (1.0)	1.2	DMSO	0.022	rt	2.5	0:90:10	87	—[e]	5

[a] Reaction time after geranyl bromide addition.
[b] From ^1H NMR spectrum of the crude product, the amount of compound **13a** could not be determined due to overlapping signals.
[c] Isolated yield.
[d] Temp. with base only (temp. after geranyl bromide addition).
[e] Not isolated.



Scheme 5. (a) RX, K_2CO_3, DMSO, see Table 2.



Scheme 6. (a) (1) K_2CO_3, DMSO, rt, 1 h, (2) geranylgeranyl bromide, 3 h.

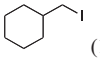
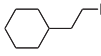
(Scheme 5, Table 2). Under the optimized conditions (Table 1, entry 7) benzyl bromide (**15a**) gave the desired product **5b** in an excellent yield and only ca. 2% of the benzyl analog of imidazole **12a** was observed in the ^{1}H NMR spectrum of the crude product. Halogenated benzyl halides **15b**–**15d** also gave the 7-benzylated hypoxanthines **11b**–**11d** in very good yields. The reaction with 1.2 equiv of the more reactive halide **15e** resulted only in the formation of dibenzylated ring opened product **12e** (60% based on **1b**, quantitative based on **15e**). However, the desired product **11e** was synthesized in high yield when the amount of benzyl halide and the reaction temperature were reduced.

Hypoxanthine **1b** reacted readily with *n*-pentyl iodide to give the 7-alkylated compound **11f** in high yield, together with minor amounts of ring-opened products **12f** and **13f** (Table 2, entry 1), and almost identical results were obtained with *n*-pentyl bromide (Table 2, entry 2). The more sterically hindered cyclohexylmethyl bromide or iodide[13] reacted slowly at ambient temperature. Only small amounts of the desired compound **11g** were formed under standard conditions and no ring-opened products **12g** or **13g** were observed. Interestingly *O*-alkylation leading to compound **16g** also took place (Table 2, entries 3–5).[14] When 2 equiv of the bromide were used and the reaction temperature raised to 50 °C, the conversion was greatly improved, but both the N-7 and *O*-alkylated isomers were formed (Table 2, entry 6). The less hindered cyclohexylethyl bromide reacted at ambient temperature and fairly good N-7 selectivity was observed (Table 2, entry 7). When cyclopentyl bromide was used as the alkylating agent, 2 equiv of the bromide, a reaction temperature of 50 °C, and a prolonged reaction time was required for full conversion. In this case *O*-alkylation was more efficient than the reaction with less reactive halides (Table 2, entries 8–9). There are few prior literature reports on the synthesis of 6-alkoxy-3-alkylpurines,[15] and such compounds have not been made by *O*-alkylation of a 3-alkylhypoxanthine.

Finally, the natural product malonganenone J (**11j**) was synthesized for the first time using the developed mild and selective alkylation conditions (Scheme 6). When 1.2 equiv of geranylgeranyl bromide[9] were used, only 75% conversion was achieved and malonganenone J (**19**) was isolated in 68% yield. When the amount of allylation agent was increased to 1.6 equiv, 79% of the target compound **11j** was isolated and also ring opened compounds **12j** and **13j** were obtained.

In conclusion, we have shown that 3-methylhypoxanthine can be alkylated predominately at N-7 upon reaction with alkyl halides in the presence of a base. Minor amounts of imidazoles, formed by N-1 alkylation and subsequent ring opening of the intermediate purinium salt, were often observed. The formation of imidazoles **12** and **13**, strongly indicate that the by-product in the literature reaction[6b] shown in Scheme 1, was compound **7**. A substantial amount of *O*-alkylation also took place when less reactive alkyl halides were used. DMSO was shown to be a superior solvent in these reactions compared to DMA and DMF. The marine natural product malonganenone J was synthesized for the first time by the reaction between 3-methylhypoxanthine and geranylgeranyl bromide.

Table 2
N-Alkylation of 3-methylhypoxanthine (**1b**) with alkyl halides

Entry	K_2CO_3 (equiv)	RX (equiv)	Temp. (°C)	Time[a] (h)	Unconverted **1b**[b]	Yield **11**[c] (%)	Yield **16**[c] (%)	Yield **12**[c] (%)	Yield **13**[c] (%)
1	1.0	$CH_3(CH_2)_4I$ (1.2)	rt	3.0	None	84, **11f**	—[e]	6, **12f**[d]	<5, **13f**
2	1.0	$CH_3(CH_2)_4Br$ (1.2)	rt	3.8	None	89, **11f**	—[e]	7, **12f** and **13f** 1:4 ratio	
3	1.0	 (1.2)	rt	4.0	ca. 85%	15, **11g** and **16g** 20:1 ratio		—[e]	—[e]
4	1.2	 (1.6)	rt	24	ca. 65%	30, **11g** and **16g** 19:1 ratio		—[e]	—[e]
5	1.2	 (1.6)	rt	24	ca. 60%	25, **11g**	—[f]	—[e]	—[f]
6	1.2	 (2.0)	rt (50[g])	24	ca. 17%	56, **11g**	14, **16g**	—[e]	—[f]
7	1.0	 (1.2)	rt	4.0	None	65, **11h**	6, **16h**	—[e]	5, **13h**
8	1.0	 (1.2)	rt	4.0	ca. 80%	11, **11i**	6, **16i**	—[e]	—[e]
9	1.2	 (2.0)	rt (50[g])	30	None	48, **11i**	23, **16i**	—[e]	5, **13i**

[a] Reaction time after RX addition.
[b] From ^{1}H NMR spectrum of the crude product.
[c] Isolated yield.
[d] Contained 10% of the isomer resulting from 1,9 dialkylation of the starting hypoxanthine followed by ring opening.
[e] Not observed.
[f] Formed in minor amounts but not isolated in pure form.
[g] Temp. with base only (temp. after RX addition).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.078.

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7. Adenine was methylated at N-3 as described in Ref. 3e, and reacted with HNO_2 to give the target compound **1b** according to: Itaya, T.; Matsumoto, H. *Chem. Pharm. Bull.* **1985**, *33*, 2213–2219.
8. Synthesis of compound **1b** according to: Wright, A. E.; Roth, G. P.; Hoffman, J. K.; Divlianska, D. B.; Pechter, D.; Sennett, S. H.; Guzman, E. A.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2009**, *72*, 1178–1183. gave, in our hands, not completely pure product and unidentified by-products(s) which interfered with the alkylation reactions.
9. *E*-Geranyl bromide and geranylgeranyl bromide were synthesized from *E*-geraniol or geranylgeraniol respectively, as previously described.[4b]
10. A similar product has been formed from 1,3,7-tribenzylated hypoxanthine;[5] see also the proposed structure **7** in Scheme 1.[6b]
11. Structure elucidation was based on NMR spectroscopy, especially HMBC and HMQC. For all compounds **11** it was determined that alkylation had taken place at N-7 based on the 3 bond correlation between the protons in the CH_2 or CH attached to N-7 and C-5 (the quartenary carbon in the purine with an HMBC correlation to H-8 but not to H-2) and C-8 (the CH in the purine not correlating with the methyl group at N-3) in the purine.
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14. The structure elucidation of the *O*-alkylated isomers **16** was based on the following: In HMBC, the OCH or OCH_2 protons correlated with only one carbon in the purine identified as C-6 (the quartenary carbon with a correlation to H-2 but not to H-8). ^{15}N HMBC revealed no correlation between the OCH or OCH_2 protons and any of the nitrogen atoms. In 1D selective NOESY a strong NOE effect was seen between the CH_3 protons and H-2 and a weak effect between H-2 and the OCH or OCH_2 protons.
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16. The same set of reaction conditions as shown in Table 1, entry 7 was used unless otherwise specified.