Preparatory Study for the Synthesis of the Marine Sponge Alkaloids Asmarines A-F: Synthesis of Their Heterocyclic Portions

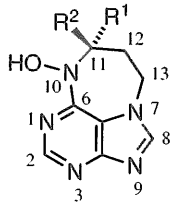
PREPARATORY STUDY FOR THE SYNTHESIS OF THE MARINE SPONGE ALKALOIDS ASMARINES A–F: SYNTHESIS OF THEIR HETEROCYCLIC PORTIONS

Masashi Ohba[a,*] and Takahiro Tashiro[b]

[a]*Center for Instrumental Analysis, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan*
[b]*Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan*

Abstract - A synthesis of three tricyclic compounds (**1c**), (**2c**), and (**3c**), selected as models for the heterocyclic portions of the marine sponge alkaloids asmarines A–F, has been accomplished through cyclization of the 7-alkyl-6-chloropurine derivatives.

Asmarines A (**1a**) and B (**1b**), novel purine-related alkaloids[1] isolated from the Red Sea sponge *Raspailia* sp., display significant cytotoxicity against four human cancer cell lines.[2] The same sponge is further known to contain four closely related alkaloids, *i.e.*, asmarines C (**2b**), D (**2a**), E (**3a**), and F (**3b**), although none of them have been isolated in pure forms.[2b] The structures of these alkaloids were elucidated through extensive spectral studies in conjunction with an X-Ray crystallographic analysis of asmarine A (**1a**).[2a] In connection with our ongoing interest in the synthetic study of purine alkaloids,[3] we sought possible synthetic routes to the heterocyclic models (**1c**), (**2c**), and (**3c**) possessing a [1,4]diazepino[1,2,3-*gh*]purine skeleton as a preliminary to the total synthesis of asmarines A–F.



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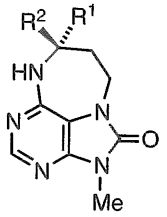

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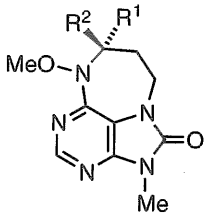

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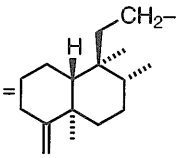
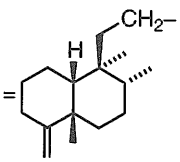
a: R^1 = Me; R^2 =

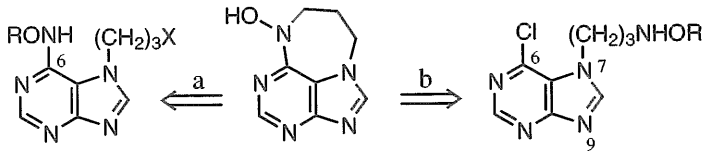


b: R^1 = Me; R^2 =



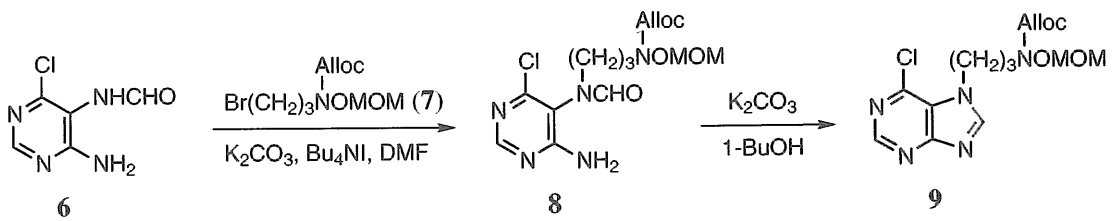
c: $R^1 = R^2$ = H

The synthesis of the tricyclic hydroxylamine (**1c**), selected as a model for a common heterocyclic portion of asmarines A and B, was first investigated. Kashman and co-workers have recently reported the construction of a [1,4]diazepino[1,2,3-*gh*]purine system *via* intramolecular alkylation at the N^6-position of 9-benzyl-N^6-benzyloxy-7-(3-chloropropyl)adeninium salt without description of the removal of two benzyl groups.[4] Toward the development of a route applicable to the synthesis of asmarines, we envisioned that intramolecular amination at the 6-position of an appropriate 7-(3-hydroxyaminopropyl)-6-chloropurine (**5**) (route b) would be preferable to cyclization at the N^6-position of the adenine derivative (**4**) (route a), because the latter route is presumed to be more difficult in constructing the stereogenic center at the 11-position of asmarines. At the outset of the present synthesis, therefore, we needed the 7-alkylated 6-chloropurine (**5**).[5]



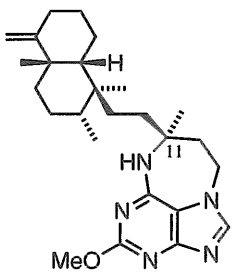
4 **1c** **5**

Since direct alkylation of 6-chloropurine using alkyl halide and a base[6] or under Mitsunobu conditions[7] has been reported to occur at the 9-position predominantly over the 7-position, we investigated an alternative route *via* cyclization of pyrimidine derivative to obtain the requisite purine (**5**). On treatment of the formamide (**6**) in DMF with the bromide (**7**) (K_2CO_3, Bu_4NI, room temperature, 24 h) according to a precedent,[8] the *N*-alkylated formamide (**8**) was obtained in 74% yield. Subsequent base-promoted cyclization of **8** was very slow in DMF, but proceeded smoothly in 1-BuOH (35–40 °C, 2 h) to afford the desired 7-alkylated 6-chloropurine (**9**) in 87% yield. Removal of the Alloc group of **9** with Pd catalyst in the presence of 2-ethylhexanoic acid[9] (CH_2Cl_2–Et_2O, room temperature, 1.5 h) and intramolecular amination at the 6-position of the resulting amine using Et_3N (1-BuOH, reflux, 2 h) provided the tricyclic compound (**10**) containing a [1,4]diazepino[1,2,3-*gh*]purine skeleton in 75% yield. Finally, deprotection of **10** with concd HCl (THF, 55 °C, 1.5 h) gave the first target (**1c**) (mp 204–205 °C)[10] in 86% yield.

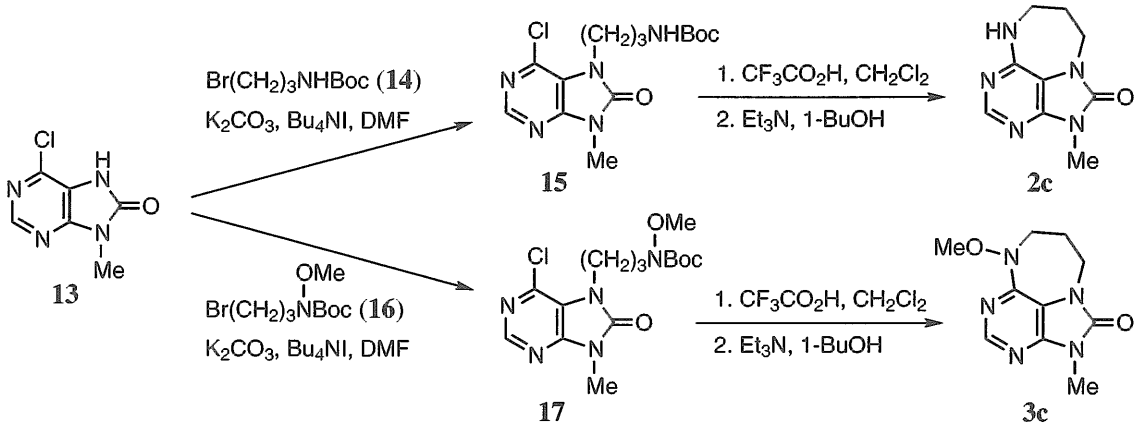


6 **8** **9** **10** **1c** **11**

In connection with the structure elucidation of asmarine B (**1b**), Kashman and co-workers further described the reaction of **1b** with excess acetic anhydride in MeOH to produce **12** *via* a four-step mechanism: acetylation of the NOH group, a [3,3] sigmatropic rearrangement, 1,6-addition of MeOH, and elimination of acetic acid.[2b] On treatment with excess acetic anhydride in MeOH at room temperature for 30 h, the hydroxylamine (**1c**) also afforded **11** in 71% yield. Concomitant acetylation at the 10-position in the latter is probably due to no sterically congested environment compared to **12**, which possesses two substituents at the 11-position.



12



Our attention was next turned to the synthesis of two heterocyclic models (**2c**) and (**3c**) for asmarines C (**2b**), D (**2a**) and asmarines E (**3a**), F (**3b**), respectively. Based on the results obtained with **1c**, we selected the 8-oxopurine (**13**)[11,12] as a starting material. Alkylation of **13** with the bromide (**14**) in DMF (K_2CO_3, Bu_4NI, room temperature, 22 h) proceeded at the 7-position, giving **15** in 99% yield. Removal of the Boc group and subsequent cyclization with Et_3N (1-BuOH, reflux, 2 h) produced the second target (**2c**) (mp 286.5–287.5 °C) in 98% yield. A parallel sequence of reactions starting from **13** and the bromide (**16**) provided the third target (**3c**) (mp 146–147 °C) through **17** in 76% overall yield. The ^1H- and ^{13}C-NMR spectral signals of the model compounds (**1c**), (**2c**), and (**3c**) thus synthesized were similar, except for those affected by two substituents at the 11-position, to the corresponding signals of **1a,b**, **2a,b**, and **3a,b**, respectively.

In conclusion, we have achieved the synthesis of three tricyclic models (**1c**), (**2c**), and (**3c**) for the heterocyclic portions of the marine sponge alkaloids asmarines A–F. The correctness of the structures proposed for the heterocyclic moieties in these alkaloids has been supported as a result of the present synthesis.

ACKNOWLEDGEMENT

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