

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

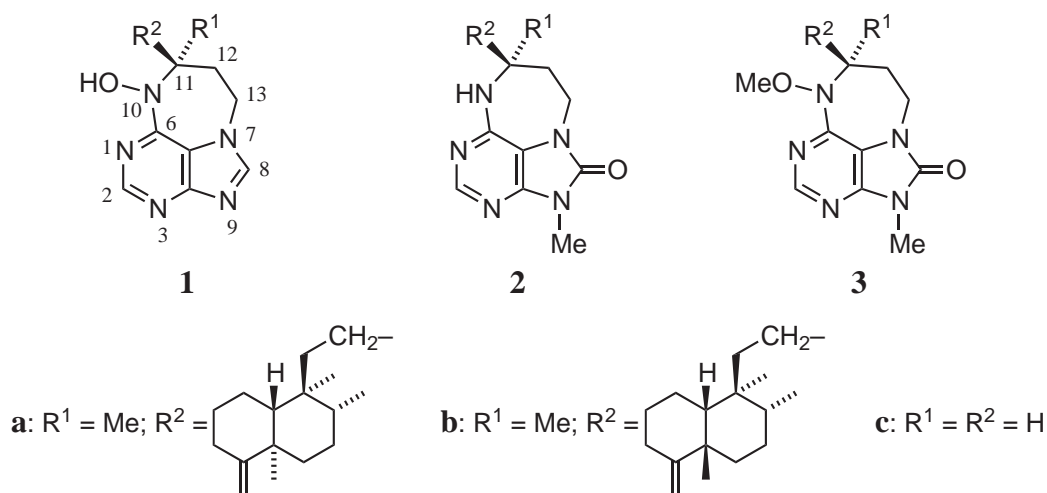
Masashi Ohba^{a,*} and Takahiro Tashiro^b

^aCenter for Instrumental Analysis, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

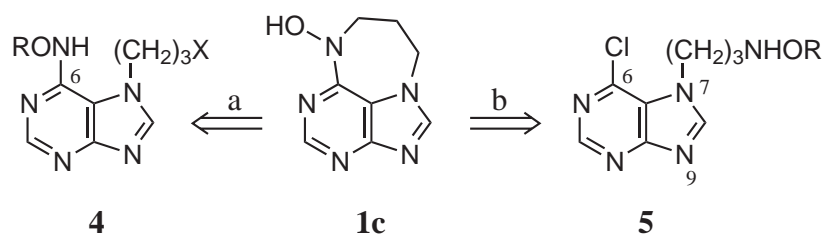
^bFaculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

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.

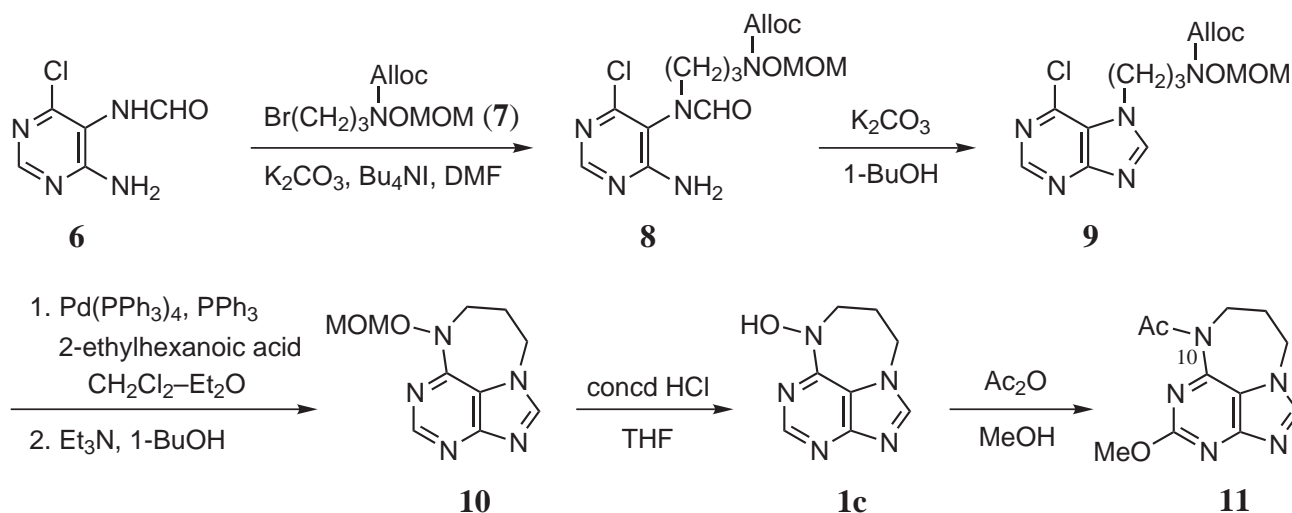
Asmarines A (**1a**) and B (**1b**), novel purine-related alkaloids¹ isolated from the Red Sea sponge *Raspailia* sp., display significant cytotoxicity against four human cancer cell lines.² The same sponge is further known to contain four closely related alkaloids, *i.e.*, asmarines C (**2b**), D (**2a**), 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.



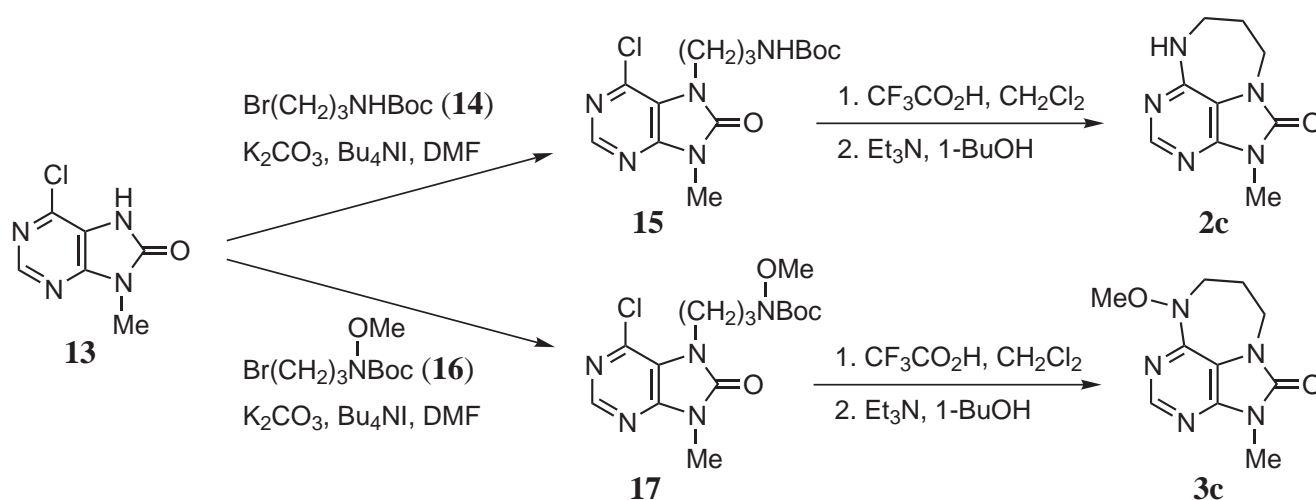
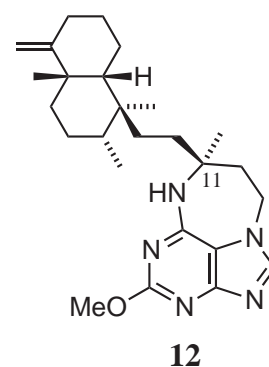
The synthesis of the tricyclic hydroxylamine (**1c**), selected as a model for a common heterocyclic portion of asmarines A and B, was first investigated. Kashman and co-workers have recently reported the construction of a [1,4]diazepino[1,2,3-*gh*]purine system *via* intramolecular alkylation at the *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



Since direct alkylation of 6-chloropurine using alkyl halide and a base⁶ or under Mitsunobu conditions⁷ 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 acid⁹ (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.



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 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.



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

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 12672051) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

REFERENCES AND NOTES

1. For a review on the purine alkaloids, see: Atta-ur-Rahman and M. I. Choudhary, 'The Alkaloids,' Vol. 38, ed. by A. Brossi, Academic Press, New York, 1990, pp. 225–323.
2. (a) T. Yosief, A. Rudi, Z. Stein, I. Goldberg, G. M. D. Gravalos, M. Schleyer, and Y. Kashman, *Tetrahedron Lett.*, 1998, **39**, 3323; (b) T. Yosief, A. Rudi, and Y. Kashman, *J. Nat. Prod.*, 2000, **63**, 299.
3. (a) M. Ohba, N. Kawase, T. Fujii, K. Aoe, K. Okamura, R. Fathi-Afshar, and T. M. Allen, *Tetrahedron Lett.*, 1995, **36**, 6101; (b) M. Ohba, N. Kawase, and T. Fujii, *Heterocycles*, 1995, **41**, 2661; (c) M. Ohba, N. Kawase, and T. Fujii, *J. Am. Chem. Soc.*, 1996, **118**, 8250; (d) M. Ohba, K. Iizuka, H. Ishibashi, and T. Fujii, *Tetrahedron*, 1997, **53**, 16977.
4. D. Pappo, A. Rudi, and Y. Kashman, *Tetrahedron Lett.*, 2001, **42**, 5941.
5. It is known that amination of 6-chloro-9-(2-tetrahydropyranyl)purine with α,α -dimethylallylamine, a sterically congested amine possessing an adjacent quarternary carbon like asmarines, provides 6-(α,α -dimethylallylamino-9-(2-tetrahydropyranyl)purine.¹³
6. (a) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, 1961, **83**, 630; (b) G. B. Elion, *J. Org. Chem.*, 1962, **27**, 2478; (c) H. J. Schaeffer and R. Vince, *J. Med. Chem.*, 1965, **8**, 33; (d) T. C. McKenzie and J. W. Epstein, *J. Org. Chem.*, 1982, **47**, 4881; (e) J. L. Kelley, M. P. Krochmal, J. A. Linn, E. W. McLean, and F. E. Soroko, *J. Med. Chem.*, 1988, **31**, 606; (f) L.-L. Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øverås, and F. Rise, *Tetrahedron*, 1994, **50**, 9743.
7. (a) W. A. Szarek, C. Depew, H. C. Jarrell, and J. K. N. Jones, *J. Chem. Soc., Chem. Commun.*, 1975, 648; (b) M. Iwakawa, B. M. Pinto, and W. A. Szarek, *Can. J. Chem.*, 1978, **56**, 326; (c) A. Toyota, N. Katagiri, and C. Kaneko, *Chem. Pharm. Bull.*, 1992, **40**, 1039; (d) S. Kozai and T. Maruyama, *Chem. Pharm. Bull.*, 1999, **47**, 574.
8. J. A. Montgomery and K. Hewson, *J. Org. Chem.*, 1961, **26**, 4469.
9. P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, 1982, **47**, 587.
10. The elemental analysis pointed to the formula $C_8H_9N_5O \cdot 1/2H_2O$.
11. N. J. Kos, H. C. van der Plas, and W. J. F. Blees, *J. Org. Chem.*, 1983, **48**, 850.
12. 6-Chloro-7,9-dihydro-9-methyl-8*H*-purin-8-one (**13**) was prepared from 5-amino-4-chloro-6-(methylamino)pyrimidine in 80% yield according to the literature procedure¹¹ but with some modification (urea, DMF, reflux, 4 h).
13. F. Skoog, H. Q. Hamzi, A. M. Szweykowska, N. J. Leonard, K. L. Carraway, T. Fujii, J. P. Helgeson, and R. N. Loepky, *Phytochemistry*, 1967, **6**, 1169.