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

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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 a smarines 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**) (K₂CO₃, Bu₄NI, 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 7alkylated 6-chloropurine (**9**) in 87% yield. Removal of the Alloc group of **9** with Pd catalyst in the presence of 2-ethylhexanoic acid⁹ (CH₂Cl₂–Et₂O, room temperature, 1.5 h) and intramolecular amination at the 6-position of the resulting amine using Et₃N (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 [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 (K₂CO₃, Bu₄NI, room temperature, 22 h) proceeded at the 7-position, giving 15 in 99% yield. Removal of the Boc group and subsequent cyclization with Et₃N (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 ¹³C-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.

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