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A synthetic approach towards the synthesis of asmarine analogues

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Abstract—Asmarines are marine alkaloids with the unique *N*(10)-hydroxytetrahydro[1,4] diazepino[1,2,3-*g*,*h*]purine system and interesting biological activity. The heterotricyclic system was prepared from substituted purines. CH-correlations were found to be an easy way to determine the mode of cyclisation in those cases where more than one is possible, that is, obtaining the tetrahydrodiazepinopurine or tetrahydropyrimidopurine system. © 2001 Elsevier Science Ltd. All rights reserved.

The asmarines form a small group of chelodane-tetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purines with interesting biological activity.[1,2] As asmarines A and B possess selective cytotoxicity to tumour cells, a synthetic project aimed at the preparation of analogues was undertaken. This report deals with the synthesis of the 10-hydroxytetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purine system (THDAP)—the heterocyclic half of the asmarine molecule.[1]

Treatment of adenine with vinyl acrylate in dry DMSO was the first reaction that afforded a diazepinopurine system.[3] Earlier work, conducted in the 1960s, on the cyclisations of ω-adenylethanol, -propanol and -butanol, with $SOCl_2$, resulted in tricyclic compounds.[4–6] However, the cyclisation mode, of the ethanol and propanol derivatives, that was only established later,[7] was to *N*-1 and only the 4-adenylbutanol ring closed to *N*-7. The structure determinations were based mainly on the UV spectra and later on ^{13}C and ^{15}N NMR values and were not always unambiguous. Due to the low solubility of many of these compounds, we prepared, as a model compound for NMR studies, the *N*-3-benzyl derivative, **1**, by reacting 3-benzyladenine with vinylacrylate.[3,8] In the case of 3-adenylpropanol and derivatives, either the desired tetrahydro-[1,4]diazepino[1,2,3-*g*,*h*]purine (THDAP) or the tetrahydropyrimido[2,1-*i*]purine (THPP) can be obtained.[4–6] There should be a clear and easy way to distinguish between the two modes of cyclisation. CH-correlations, measured by HMQC and HMBC experiments, were found to be a good way to perform the structure elucidation, both for the assignment of the ring system as well as the substitution(s) site(s), where required. The analysis is done in two steps. In the first step, the two methines, C-2 and -8 are assigned by an HMQC experiment. Then the quaternary atoms, C-4, -5 and -6 are assigned by an HMBC experiment. In the second step, triple-bond CH-correlations from the α-methylene protons to the purine C-atoms establishes the mode of cyclisation as well as the location of the various substituents. The latter is well exhibited for compound **1** in Fig. 1. Further confirmation of the

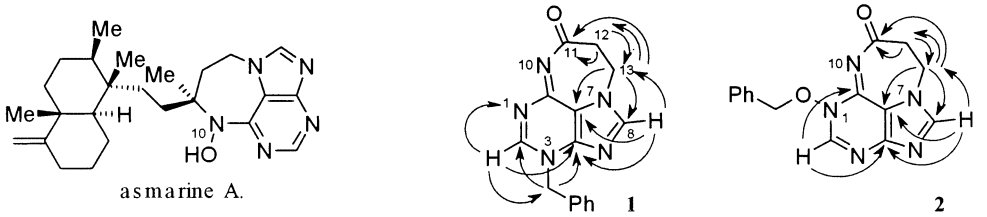

Figure 1. CH-correlation (H to C).

Keywords: marine metabolites; asmarines; diazepinopurine; pyrimidinopurine; NMR.

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suggested structures is achieved from NOEs between the α-protons and H-2 or -8, e.g. in the case of **3**, from $H_{(2)}$-13 to the H-8 purine proton. Compound **1** is an interesting intermediate of 11-substituted THDAPs due to its imineketone functionality.

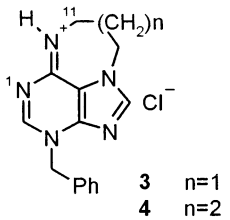
1-Benzyloxy-11-oxo-THDAP **2**[9] was synthesised in a similar way to **1** starting from 1-benzyloxyadenine.[10] Here again, the structure was fully characterised by CH-correlations in the same manner as shown for compound **1** (Fig. 1).

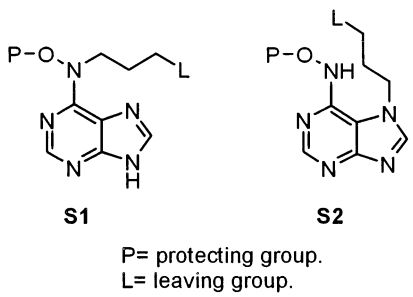
Based on Fujii's work on selective alkylations of adenine,[11] it could be expected that the *N*-3-substituted adenine will orient further alkylation to the 7-position. Indeed, reacting 3-benzyladenine[12] with 1-bromo-3-chloropropane under basic conditions gave cyclisation to the desired 3-benzyl-THDAP **3**.[13] The mode of cyclisation was clearly determined to be between N^6 and *N*-7 according to the CH-correlations from H_2-11 to C-6 and from H_2-13 to C-5 and C-8 as well as from a measured NOE between H_2-13 and H-8. Similarly, reacting 3-benzyladenine with 1-bromo-4-chlorobutane gave the higher homolog 3-benzyltetrahydro[1,4]-diazocino[1,2,3-*g*,*h*]purine **4**.[14]

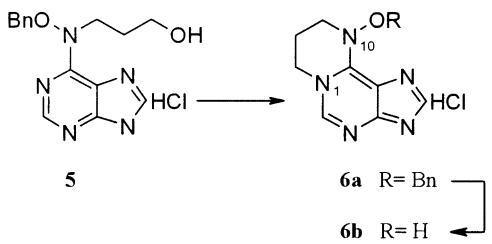
From these preliminary experiments, it became clear that, in order to synthesise the 10-hydroxy-THDAP, the heterocyclic system of asmarine, one has to start from synthon S1 or S2 which already carries a protected hydroxyamine moiety on C-6.

We began by synthesising compound **5**[15] and reacted it with $SOCl_2$ to obtain a tricyclic compound (**6a**).[16] The structure of the latter compound was determined, using the methodology described above, to be 10-benzyloxy-THPP·HCl the same cyclisation mode as found for other N^6-substituted purines[4–7] (Scheme 1). Hydrogenolysis of **6a** afforded the hydroxyamine **6b**.[17]

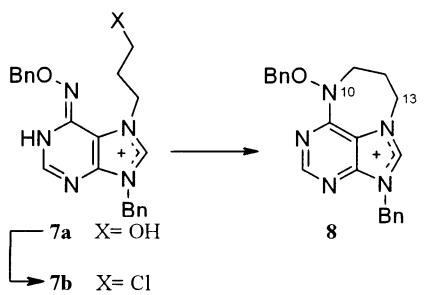
Next, a molecule of type S2 was synthesised, namely N^6-benzyloxy-7-(3-hydroxypropyl)- 9-benzylpurine **7a** (Scheme 2).[18] Contrary to the two possible modes of cyclisation of S1, vide supra, there is only a single possible closure for S2. Indeed, compound **7b**,[20] the chloro derivative of **7a**,[19] cyclised in the desired way under basic conditions to give the *N*,*O*-diprotected THDAP system **8**,[21,22]—the heterocyclic part of the asmarines. As the methodology needed to prepare the asmarine heterocycle is now established, it is possible, commencing with other starting materials, to attempt a synthesis of asmarine analogues.







Scheme 1.



Scheme 2.

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8. 3-Benzyladenine was refluxed with vinyl acrylate in dry THF for 5 h to give compound **1**; δ_H 8.71 (s, 1H), 8.35 (s, 1H), 7.30–7.43 (m, 5H), 5.46 (s, 2H), 4.41 (t, 2H), 2.85 (t, 2H); δ_C 181.3, 155.6, 147.0, 145.4, 143.0, 115.5, 54.8, 43.8; CH correlation (H to C): 2/4, 6, 14; 8/4, 5,13; 12/11, 13; 13/5, 8, 11, 12; λ (KBr) 1598, 1571, 1509 cm^{-1}; EIMS *m*/*z* (%): 224 [M^+− 55] (100), 209 [M^+−70] (5), 91 (96).

9. 1-Benzyloxy adenine was refluxed with vinylacrylate in dry THF for 5 h to afford compound **2**; δ_H 8.49 (s, 1H), 8.42 (s, 1H), 7.48–7.58 (m, 5H), 5.36 (s, 2H), 4.48 (bt, 2H), 3.01 (bt, 2H); δ_C 184.7, 158.0, 153.6, 150.0, 128.0–134.0, 123.0, 83.3, 48.8, 46.4; CH correlations (H to C): 2/4, 6; 8/4, 5, 13; 12/11, 13; 13/5, 8, 11, 12; CIMS *m/z* (%): 296 (46), 190 (92), 107 (100).
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13. 3-Benzyl adenine was heated with 1-bromo-3-chloropropane in the presence of triethylamine at 80°C for 24 h to give compound **3** HCl as a powder. δ_H 9.93 (s, 1H, NH), 9.01 (s, 1H), 8.68 (s, 1H), 7.32–7.48 (m, 5H), 5.60 (s, 2H), 4.46 (t, 2H), 3.62 (t, 2H), 2.67 (m, 2H); δ_C 153.0, 147.5, 147.3, 146.3, 134.9, 128.1, 111.4, 51.9, 48.8, 44.1, 26.6; CH correlations (H to C): 2/4, 6, 14; 8/4, 5, 13; 10/5, 12; 11/6, 12, 13; 12/11, 13; 13/5, 8, 11, 12; 14/2, 4; NOEs (H to H): 2/14; 8/13; 10/11; EIMS *m/z* (%): 265 (65), 175 (74), 91 (100).
14. 3-Benzyl adenine was heated in DMA to 70°C with 1-bromo-4-chlorobutane in the presence of triethylamine for 48 h to give compound **4** HCl as a powder; δ_H 9.7 (s, 1H, NH), 8.92 (s, 1H), 8.63 (s, 1H), 7.43–7.29 (m, 5H), 5.29 (s, 2H), 4.47 (bt, 2H), 3.67 (bt, 2H), 1.93 (bt, 2H), 1.76 (bt, 2H); δ_C 155.4, 150.7, 149.5, 146.9, 129.1–135.9, 117.4, 53.0, 47.0, 41.0, 27.3, 24.4; CH correlations (H to C): 2/4, 6, 15; 8/4, 5, 14; 10/5; 11/6, 12, 13; 12/14; 13/11, 14; 14/5, 8, 12; 15/2, 4; CIMS *m/z* (%): 280 (39), 190 (100), 91 (52).
15. 6-Chloropurine was reacted with 3-(*O*-benzyl hydroxylamino)propanol in boiling ethanol for 17 h to give compound **5** HCl as a powder; δ_H 8.61 (s, 1H), 8.53 (s, 1H), 7.32–7.55 (m, 5H), 5.19 (s, 2H), 4.19 (t, 2H), 3.44 (t, 2H), 1.82 (m, 2H); δ_C 151.3, 149.6, 146.9, 144.2, 128.1–134.0, 111.2, 75.2, 58.0, 45.7, 29.7; EIMS *m/z* (%) 299 (35), 199 (30), 91 (100).
16. Compound **5** was refluxed in a mixture of thionylchloride/$CHCl_3$ (1:1) for 4 h to give compound **6a** HCl as a powder, δ_H 8.70 (2, 1H), 8.64 (s, 1H), 7.4–7.6 (m, 5H), 5.28 (s, 2H), 4.31 (bt, 2H), 3.94 (bt, 2H), 2.30 (m, 2H); CH correlations (H to C): 2/4, 6, 13; 8/4, 5; 11/6, 12, 13; 12/11, 13; 12/11, 13; 13/2, 6, 11, 12; CIMS *m/z* (%): 281 (5), 176 (15), 107 (100).
17. Hydrogenation of compound **6a** HCl in methanol over Pd-C/5%, under 1.5 ATM, for 1 h gave **6b** HCl as a powder; δ_H 8.59 (s, 1H), 8.56 (s, 1H), 4.27 (bt, 2H), 3.76 (bt, 2H), 2.2 (m, 2H); CIMS *m/z* (%) 192 (100), 176 (19), 136 (28).
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19. N^6-Benzyloxy-9-benzyl adenine was heated with 3-bromopropanol in DMA to 70°C for 36 h to afford **7a** as a powder, δ_H 12.1 (s, 1H, NH), 9.59 (s, 1H), 7.84 (s, 1H), 7.33–7.41 (m, 10H), 5.46 (s, 2H), 5.07 (s, 2H), 4.38 (t, 2H), 3.43 (t, 2H), 1.9 (m, 2H); δ_C 149.4, 141.2, 139.0, 138.6, 137.3, 135.2, 129.0–129.8, 110.8, 76.1, 57.7, 48.5, 48.2, 32.4; CH correlations (H to C): 2/4, 6; 8/4, 5, 10, 13; 10/5, 8, 11, 12; 11/10, 12; 12/10, 11; 13/4, 8; FABMS *m/z* 390 (M^+).
20. Compound **7a** was treated with thionyl chloride at rt for 1 h. After evaporation, the residue was taken in ethanol and DBU added. After 1 h, the mixture was evaporated under vacuum to afford compound **7b** as a powder; δ_H 12.2 (bs, 1H, NH), 9.55 (s, 1H), 7.85 (s, 1H), 7.26–7.43 (m, 10H), 5.45 (s, 2H), 5.07 (s, 2H), 4.43 (t, 2H), 3.63 (t, 2h), 2.22 (m, 2H); FABMS *m/z* 408 (MH^+).
21. Compound **7b** was warmed to 60°C with 1% K_2CO_3 in DMSO for 3 days to afford compound **8**; δ_H 10.23 (s, 1H), 8.75 (s, 1H), 7.33–7.41 (m, 10H), 5.68 (s, 2H), 5.13 (s, 2H), 4.5 (bt, 2H), 4.04 (bt, 2H), 2.32 (bm, 2H); δ_C 155.3, 151.1, 147.6, 142.0, 128.3–134.9, 107.6, 75.5, 53.4, 48.9, 48.2, 24.8; CH correlations (H to C): 2/4, 6; 8/4, 5, 14; 11/6, 12, 13; 12/8, 11, 13; 13/5, 8, 11, 12; FABMS *m/z* (%) 372 (100), 266 (60), 176 (24).
22. Whereas the anion of **7a** is Br^-, in the case of **7b** and **8**, it is most likely to be Cl^-.