A SYNTHETIC APPROACH TO THE MARINE SPONGE ALKALOIDS AGELASIMINE A AND AGELASIMINE B†

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Abstract—Syntheses of 7-benzyl-N6,3-dimethyladenine (1b) and 7-benzyl-1,2-dihydro-1,3-dimethyladenine (2b), selected as models for the marine sponge alkaloids agelasimine A (1a) and agelasimine B (2a), respectively, have been achieved via four-step routes starting from 3-methyladenine (7). The key steps involved are regioselective methylations of 7-benzyl-3-methyladenine (9) and 7-benzyl-1,2-dihydro-3-methyladenine (11).

Agelasimine A (1a) and agelasimine B (2a) are novel adenine-related bicyclic diterpenoids isolated by Fathi-Afshar and Allen from the orange sponge Agelas mauritiana.1 Both compounds exhibit a wide range of interesting biological activities such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca2+-channel antagonistic action, α1 adrenergic blockade, and others.1,2 Their chemical structures have been proposed on the basis of interpretation of their spectral data.1 In an attempt to confirm the correctness of the proposals by chemical synthesis, we sought possible synthetic routes to the N(7)-benzyl analogues (1b and 2b) in the present study as preliminaries to total syntheses of 1a and 2a.

The first target selected for synthesis was 7-benzyl-N6,3-dimethyladenine (1b). Montgomery and Thomas reported that treatment of either 3-benzyladenine (3: R = PhCH2) or 7-benzyladenine (4: R = PhCH2) with benzyl chloride in AcNMe2 in the presence of K2CO3 at 110°C overnight gave N6,3,7-tribenzyladenine (5).3 The reaction in both cases is likely to have proceeded through the intermediate 3,7-dibenzyladenine (6: R1 = R2 =

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Scheme 1

Scheme 2
PhCH₂), since alkylation of either 3-alkyladenines (3) or 7-alkyladenines (4) is known to produce 3,7-dialkyladenines (6). In view of such an assumed preference for N⁶-benzylation of 6 (R¹ = R² = PhCH₂), we planned to follow a similar sequence of reactions for synthesis of 1b (Scheme 1). Treatment of 7-benzyl-3-methyladenine hydrobromide (8), prepared from 3-methyladenine (7) by benzylation according to the previously reported procedure, in hot H₂O with 10% aqueous NaOH gave the free base (9. H₂O) [mp 163–163.5°C (decomp)] in 80% yield. On methylation with MeI in AcNMe₂ at room temperature for 5 h, 9. H₂O furnished 7-benzyl-N⁶,3-dimethyladenine hydriodide (10) [mp 229–230°C (decomp)] in 89% yield. Basification of a warm aqueous solution of 10 with 10% aqueous NaOH afforded the desired free base (lb) [mp 153–154.5°C] in 86% yield. The uv spectra of 1b in various solvents were similar to those reported for N⁶,3,7-trisubstituted adenines. In addition, the above stability of 1b under alkaline conditions may rule out the possibility that the methylated product from 9. H₂O was not 10, but the 1,3-dimethyl or the 3,9-dimethyl analogue that is expected to be very unstable under alkaline conditions.

For the synthesis of the second target (2b), 8 was reduced with NaBH₄ in H₂O at room temperature for 30 min. The resulting, unstable oily 1,2-dihydro derivative (11) was then methylated with MeI in AcNMe₂ at room temperature for 4.5 h to give the crude salt (2b-HI). On treatment with aqueous NaOH, the crude salt provided the desired free base (2b) (mp 96–97°C) in 15% overall yield (from 8). The 1,2-dihydro-1,3-dimethyladenine structure was assignable to the free base on the basis of its ¹H nmr spectrum in CDCl₃: the nuclear Overhauser effects (4% each) observed for the two N-Me signals (at δ 2.90 and 2.91) on irradiation of the C(2)-methylene signal (at δ 4.13) revealed the proximity of these three groups. On reduction with NaBH₄ in 50% aqueous EtOH at room temperature for 20 min, 1b produced the oily 1,2-dihydro-N⁶,3-dimethyl isomer (12) in 84% yield. Finally, the model compounds (1b) and (2b) thus synthesized were found to bear similarity in ¹H and ¹³C nmr spectra to agelasimine A and agelasimine B, respectively, supporting the correctness of the substitution patterns of the adenine moieties in structures 1a and 2a proposed for these marine sponge alkaloids. Oxidation of 2b with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CHCl₃ at room temperature for 10 min, followed by successive treatments with aqueous HCl and 10% aqueous NaOH, gave 1b in 30% yield. This conversion is analogous to the previously reported transformation of 1,2-dihydro-1,3-dimethyladenine (13) into N⁶,3-dimethyladenine (16) through 14 and 15 (Scheme 2), but it may be suggestive of a possible biosynthetic pathway to agelasimine A (1a) from agelasimine B (2a).
REFERENCES


5. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.

6. Selected spectral data for 1b: uv $\lambda_{\text{max}}^\text{MeOH}$ 227 nm [shoulder (sh)] (ε 11000), 287 (17400); $\lambda_{\text{max}}^\text{H2O}$ (pH 1) 225 (sh) (11000), 285 (17100); $\lambda_{\text{max}}^\text{H2O}$ (pH 7) 225 (sh) (10900), 284 (17200); $\lambda_{\text{max}}^\text{H2O}$ (pH 13) 285 (6600); $^1$H nmr (CDCl$_3$) δ: 3.25 [3H, s, N(3)-Me], 3.61 [3H, s, N6-Me], 5.74 [2H, s, CH$_2$Ph], 7.32 [5H, m, CH$_2$Ph], 7.38 and 7.58 [1H each, s, purine protons]; $^{13}$C nmr (CDCl$_3$) δ: 33.9 and 34.7 (two Me's), 49.9 [C(2)], 113.9, 128.0, 128.2, and 128.8 (Ph), 136.7 [C(5)], 137.7 [C(8)], 142.5 [C(4) or C(6)], 145.2 [C(2)], 150.1 [C(6) or C(4)].


11. Selected spectral data for 2b: uv $\lambda_{\text{max}}^\text{MeOH}$ 243 nm (sh) (ε 8000), 328 (6300); $^\text{95% eq. EtOH}$ 244 (sh) (7700), 305 (4700); $\lambda_{\text{max}}^\text{H2O}$ (pH 1) 226 (sh) (11900), 323 (5800); $\lambda_{\text{max}}^\text{H2O}$ (pH 7) 325 (6000); $\lambda_{\text{max}}^\text{H2O}$ (pH 13) 243 (7300), 290 (5800); $^1$H nmr (CDCl$_3$) δ: 2.90 and 2.91 (3H each, s, two N-Me's), 4.13 [2H, s, C(2)-H's], 5.55 (2H, s, CH$_2$Ph), 7.2-7.4 [6H, broad s, C(8)-H and CH$_2$Ph]; $^{13}$C nmr (CDCl$_3$) δ: 33.0 and 35.1 (two Me's), 49.9 [N(7)-CH$_2$], 71.1 [C(2)], 107.4 [C(5)], 127.2, 127.8, 128.7 and 136.4 (Ph), 138.1 [C(8)], 154.2 [C(4) or C(6)], 155.1 [C(6) or C(4)].

12. $^1$H nmr (CDCl$_3$) δ: 2.76 and 2.89 (3H each, s, two N-Me's), 4.34 [2H, s, C(2)-H's], 5.34 (2H, s, CH$_2$Ph), 7.2-7.4 [6H, broad s, C(8)-H and CH$_2$Ph].

13. Except for signals arising from the N(7)-substituent.

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