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

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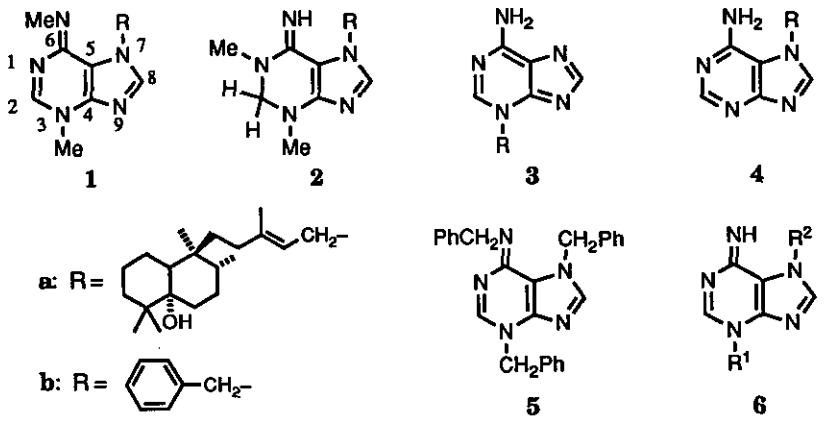
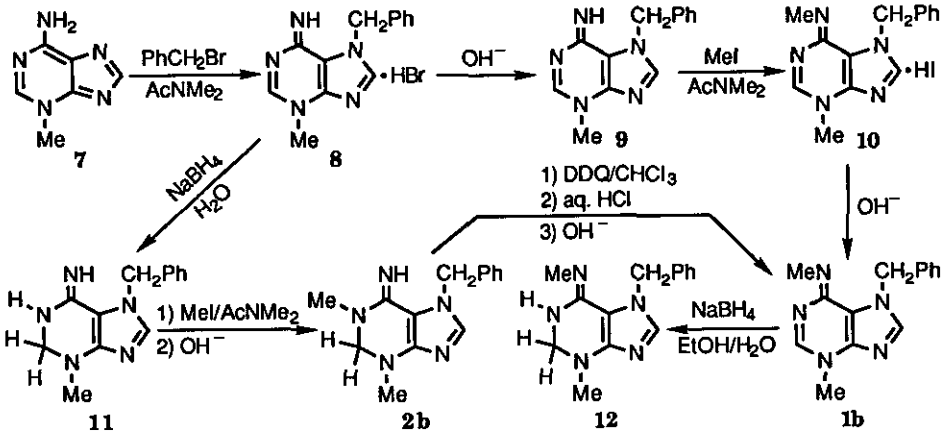
Abstract——Syntheses of 7-benzyl-N^6,3-dimethyladenine (**1b**) and 7-benzyl-1,2-dihydro-1,3-dimethyladenine (**2b**), selected as models for the marine sponge alkaloids agelasimine A (**1a**) and agelasimine B (**2a**), respectively, have been achieved via four-step routes starting from 3-methyladenine (**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, Ca^{2+}-channel antagonistic action, α_1 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**.

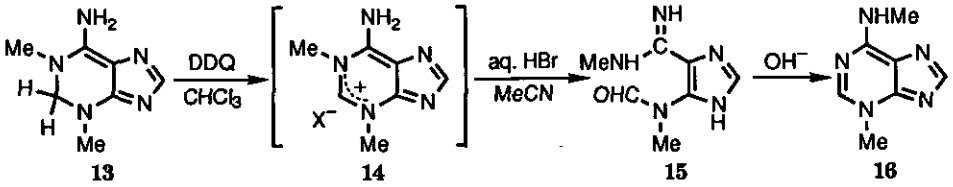
The first target selected for synthesis was 7-benzyl-N^6,3-dimethyladenine (**1b**). Montgomery and Thomas reported that treatment of either 3-benzyladenine (**3**: R = $PhCH_2$) or 7-benzyladenine (**4**: R = $PhCH_2$) with benzyl chloride in $AcNMe_2$ in the presence of K_2CO_3 at 110°C overnight gave N^6,3,7-tribenzyladenine (**5**).[3] The reaction in both cases is likely to have proceeded through the intermediate 3,7-dibenzyladenine (**6**: $R^1 = R^2 =$

† Dedicated to Professor Edward C. Taylor (Princeton University) on the occasion of his 70th birthday.





Scheme 1



Scheme 2

$PhCH_2$), since alkylation of either 3-alkyladenines (**3**) or 7-alkyladenines (**4**) is known to produce 3,7-dialkyladenines (**6**).[3,4] In view of such an assumed preference for N^6-benzylation of **6** ($R^1 = R^2 = PhCH_2$), 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,[4c] in hot H_2O with 10% aqueous NaOH gave the free base ($\mathbf{9}\cdot H_2O$) [mp 163–163.5°C (decomp)][5] in 80% yield. On methylation with MeI in $AcNMe_2$ at room temperature for 5 h, $\mathbf{9}\cdot H_2O$ furnished 7-benzyl-N^6,3-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 (**1b**) (mp 153–154.5°C)[6] in 86% yield. The uv spectra[6] of **1b** in various solvents were similar to those[3,7] reported for N^6,3,7-trisubstituted adenines. In addition, the above stability of **1b** under alkaline conditions may rule out the possibility that the methylated product from $\mathbf{9}\cdot H_2O$ was not **10**, but the 1,3-dimethyl or the 3,9-dimethyl analogue that is expected to be very unstable under alkaline conditions.[8,9]

For the synthesis of the second target (**2b**), **8** was reduced with $NaBH_4$ in H_2O at room temperature for 30 min. The resulting, unstable oily 1,2-dihydro derivative (**11**)[10] was then methylated with MeI in $AcNMe_2$ at room temperature for 4.5 h to give the crude salt ($\mathbf{2b}\cdot HI$). On treatment with aqueous NaOH, the crude salt provided the desired free base (**2b**) (mp 96–97°C)[11] 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[11] in $CDCl_3$: 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 $NaBH_4$ in 50% aqueous EtOH at room temperature for 20 min, **1b** produced the oily 1,2-dihydro-N^6,3-dimethyl isomer (**12**)[12] in 84% yield. Finally, the model compounds (**1b**) and (**2b**) thus synthesized were found to bear similarity in ^1H and ^{13}C nmr[13] 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 $CHCl_3$ 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[8] of 1,2-dihydro-1,3-dimethyladenine (**13**) into N^6,3-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**).

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5. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.
6. Selected spectral data for **1b**: uv λ_{max}^{MeOH} 227 nm [shoulder (sh)] (ε 11000), 287 (17400); $\lambda_{max}^{H_2O}$ (pH 1) 225 (sh) (11000), 285 (17100); $\lambda_{max}^{H_2O}$ (pH 7) 225 (sh) (10900), 284 (17200); $\lambda_{max}^{H_2O}$ (pH 13) 285 (6600); ^{1}H nmr ($CDCl_3$) δ: 3.25 [3H, s, N(3)-Me], 3.61 [3H, s, N^6-Me], 5.74 (2H, s, CH_2Ph), 7.32 (5H, m, CH_2Ph), 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 (CH_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)].
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10. A similar reduction of 3-benzyladenine (**3**: R = $PhCH_2$) has been reported: Y. Maki, M. Suzuki, and K. Ozeki, *Tetrahedron Lett*, 1976, 1199.
11. Selected spectral data for **2b**: uv λ_{max}^{MeOH} 243 nm (sh) (ε 8000), 328 (6300); $\lambda_{max}^{95\%\ aq.\ EtOH}$ 244 (sh) (7700), 305 (4700); $\lambda_{max}^{H_2O}$ (pH 1) 226 (sh) (11900), 323 (5800); $\lambda_{max}^{H_2O}$ (pH 7) 325 (6000); $\lambda_{max}^{H_2O}$ (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_2Ph), 7.2–7.4 [6H, broad s, C(8)-H and CH_2Ph]; ^{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_2Ph), 7.2–7.4 [6H, broad s, C(8)-H and CH_2Ph].
13. Except for signals arising from the N(7)-substituent.

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