ACETYLATIONS OF (±)-AGELASIMINE-A AND (±)-AGELASIMINE-B: A RACEMIC SYNTHESIS OF PURINO-DITERPENE DERIVED FROM ANTI-MICROBIAL METABOLITES OF *AGELAS MAURITIANA*

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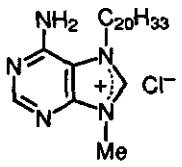
Abstract ——— The reaction of (±)-agelasimine-A [(±)-**3a**] with acetic anhydride in pyridine yielded the imidazole derivative [(±)-**5a**], which was found to correspond to "diacetylagelasimine-A". A similar acetylation of (±)-agelasimine-B [(±)-**4a**] provided (±)-**7a** and (±)-**2a**. On treatment with boiling 50% aqueous EtOH, (±)-**7a** gave (±)-**2a** and the dihydrohypoxanthine derivative [(±)-**8a**]. It is suggested that purino-diterpene (**2a**), isolated from the acetylated mixture of the crude extract of the sponge *Agelas mauritiana*, might have originated from agelasimine-B (**4a**) through N^6-acetylagelasimine-B (**7a**).

Since the isolation and partial structural elucidation of agelasine (**1**), a novel quaternary 9-methyladenine derivative of an unidentified diterpene from the sponge *Agelas dispar*, were reported by Cullen and Devlin in 1975,[1] a number of adenine-related diterpenoids have been isolated from certain genera of marine sponges.[2,3] In 1984, Faulkner and co-workers announced the structure of purino-diterpene (**2a**), an artifact separated from the acetylated mixture of the crude extract of the Enewetak sponge *Agelas mauritiana*, on the basis of an X-ray crystallographic analysis.[4] Thereafter Fathi-Afshar and Allen isolated agelasimine-A and agelasimine-B from the same sponge (*A. mauritiana*) and deduced that their structures are **3a** and **4a**, respectively, possessing the same diterpene portion as that of **2a**, as a result of extensive spectral studies.[3] The correctness of these structures and relative stereochemistries has been unequivocally confirmed by our recent success in synthesizing the racemic candidate structures [(±)-**3a** and (±)-**4a**].[5] In



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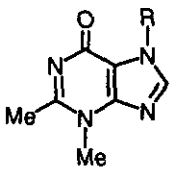

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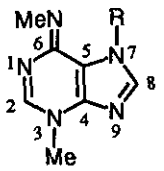

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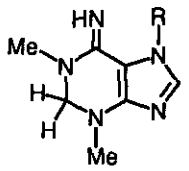

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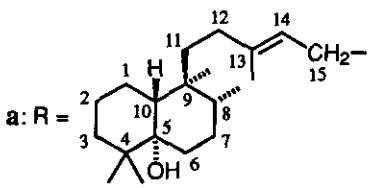
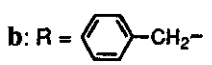
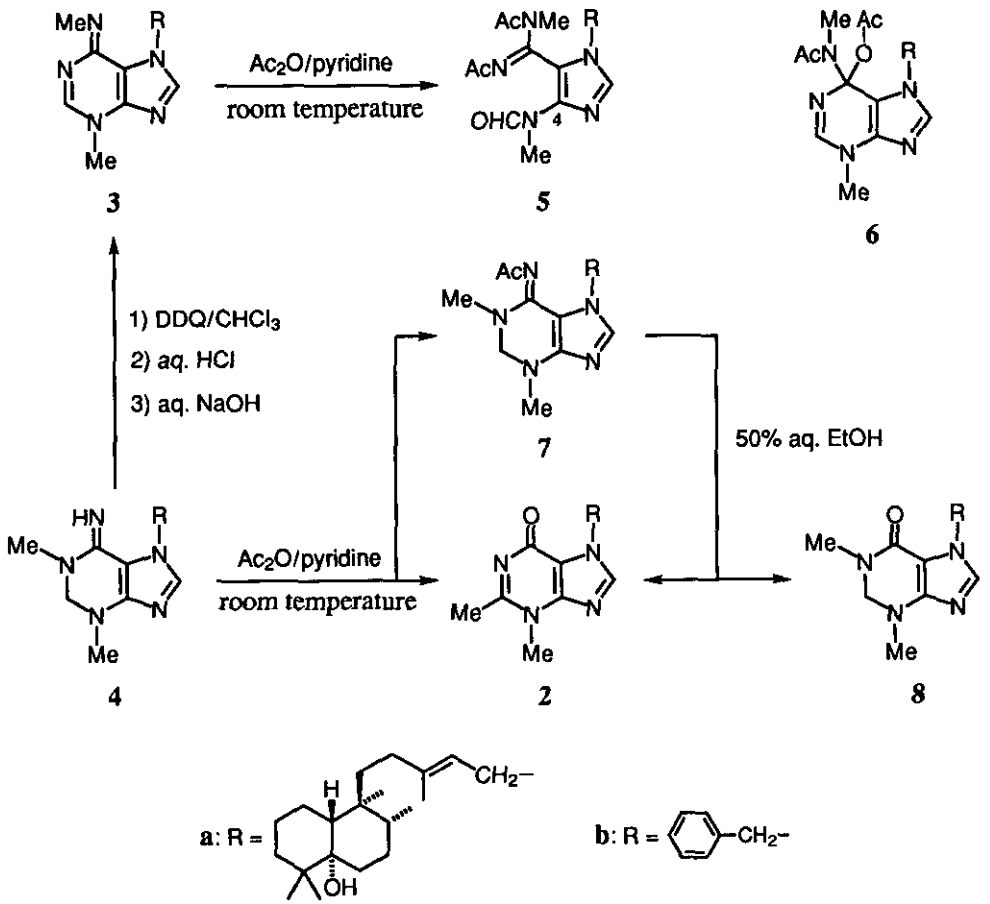




this communication, we wish to describe the acetylations of (±)-**3a** and (±)-**4a**, the latter of which have led to the formation of purino-diterpene [(±)-**2a**].

In connection with the structure determination of the above two marine sponge diterpenoids, Fathi-Afshar and Allen further described the reactions of **3a** and **4a** with acetic anhydride in pyridine to form diacetyl-agelasimine-A and N^6-acetylagelasimine-B (**7a**), respectively.[3] On the basis of ms fragmentation and ^{1}H nmr spectral data, they applied structure (**6a**) to diacetylagelasimine-A, although its exact nature has not been firmly established (mixture of isomers).[3] In order to check the structure of diacetylagelasimine-A, (±)-**3a**[5] was first treated with an excess of acetic anhydride in pyridine at room temperature for 44 h according to the reported procedure,[3] affording a 1 : 1 adduct of (±)-**3a** and acetic anhydride in 54% yield as a glassy material.[6] The ^{1}H nmr spectrum of the adduct in $CDCl_3$ at 27°C showed two sets of signals, all with a 3 : 1 ratio of relative integral intensities, for many different species of protons. Similar two sets of signals observed in Me_2SO-d_6 at 27°C coalesced into one set at 100°C. We have already reported that the acetylation of the N(7)-benzyl analogue (**3b**) produced the imidazole derivative (**5b**), whose structure was definitely determined on the basis of an X-ray crystallographic analysis, and that **5b** exhibited a similar ^{1}H nmr spectral behavior, presumed to be a result of *cis–trans* equilibration of the *N*-methylformamide group at C(4).[7] Therefore, structure [(±)-**5a**] was assignable to the adduct.[8] A set of signals arising from the major geometrical isomer in the ^{1}H nmr spectrum ($CDCl_3$) of (±)-**5a** was found to be virtually identical with the data[3] reported for diacetylagelasimine-A. Thus, the structure of "diacetylagelasimine-A" prepared by a similar acetylation of agelasimine-A (**3a**) should be represented not by the proposed[3] purine form (**6a**), but by the monocyclic imidazole form (**5a**).

We next investigated the acetylation of (±)-agelasimine-B [(±)-**4a**]. On treatment with an excess of acetic anhydride in pyridine at room temperature for 1 h, (±)-**4a**[5] provided (±)-**7a** in 48% yield. The ms and ^{1}H



nmr spectra ($CDCl_3$) of (±)-**7a** were in agreement with those of N^6-acetylagelasimine-B described in the literature.[3] Elongation of the reaction time from 1 h to 50 h led to the formation of (±)-**2a** (mp 178.5–180.5°C)[9] in 60% yield together with (±)-**7a** in 15% yield. A parallel result was also obtained from the acetylation of (±)-**4a** in the absence of pyridine. When treated with boiling 50% aqueous EtOH, (±)-**7a** was converted to (±)-**2a** and the dihydrohypoxanthine derivative [(±)-**8a**] in 22% and 39% yields, respectively.[8] The ^1H nmr spectral data for (±)-**2a** thus synthesized were virtually identical with those reported selectively for purino-diterpene[4] (isolated from the acetylated mixture of the crude extract of the sponge *Agelas mauritiana*).

Finally, oxidation of (±)-**4a**[5] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$ at room temperature for 1 h, followed by successive treatment with 10% aqueous HCl and 10% aqueous NaOH, provided (±)-**3a** in 43% yield. This transformation may imply the possibility of a biosynthetic pathway from agelasimine-B (**4a**) to agelasimine-A (**3a**).

In conclusion, the present results have emphasized the propriety of our previous suggestion[7] that purino-

diterpene (**2a**) might have been derived from agelasimine-B (**4a**) through N^6-acetylagelasimine-B (**7a**). They have also disclosed that the "diacetylagelasimine-A" has the imidazole structure (**5a**) instead of **6a**.

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6. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.
7. (a) T. Fujii, T. Saito, J. Chikazawa, M. Ohba, and T. Date, *Heterocycles*, 1994, **38**, 733; (b) T. Fujii, T. Saito, J. Chikazawa, Y. Nakamura, and M. Ohba, *Chem. Pharm. Bull.*, 1994, **42**, 2461.
8. For the reaction mechanism proposed for the benzyl analogue, see ref. 7.
9. Recrystallized from AcOEt. Selected spectral data: uv λ_{max}^{MeOH} 267 nm (ε 11700); $\lambda_{max}^{95\%\ aq.\ EtOH}$ 268 (11900); $\lambda_{max}^{solvent\ A}$ 256 (10600); $\lambda_{max}^{solvent\ N}$ 267 (12000); $\lambda_{max}^{solvent\ B}$ 266 (11800);[10] ir ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1638 (CO); ^1H nmr ($CDCl_3$) δ: 0.80 [3H, d, J = 7 Hz, C(8)-Me], 0.83, 0.86, and 0.97 [3H each, s, C(4)-Me's and C(9)-Me], 1.05–2.0 [16H, m, C(1)-H's, C(2)-H's, C(3)-H's, C(6)-H's, C(7)-H's, C(8)-H, C(10)-H, C(11)-H's, and C(12)-H's], 1.17 (1H, s, OH), 1.79 [3H, s, C(13)-Me], 2.58 [3H, s, C(2')-Me], 3.83 [3H, s, N(3')-Me], 5.08 [2H, d, J = 7.5 Hz, C(15)-H's], 5.48 [1H, t, J = 7.5 Hz, C(14)-H], 7.62 [1H, s, C(8')-H];[11] ^{13}C nmr ($CDCl_3$) δ: 16.0 (q), 16.8 (q), 17.4 (q), 21.7 (t), 21.7 (q), 22.1 (t), 24.1 (q), 24.4 (q), 26.3 (t), 32.0 (t), 32.9 (t), 33.1 (q), 36.0 (t), 36.5 (d), 36.9 (t), 38.8 (s), 38.9 (s), 40.9 (d), 44.4 (t), 76.3 (s), 114.2 (s), 117.6 (d), 139.7 (d), 144.0 (s), 148.8 (s), 155.9 (s), 162.2 (s); hrms Calcd for $C_{27}H_{42}N_4O_2$: 454.3308, Found: 454.3324.
10. Solvent A stands for 80% (v/v) aqueous EtOH containing HCl at 0.1 M concentration; solvent N, 80% (v/v) aqueous EtOH; solvent B, 80% (v/v) aqueous EtOH containing NaOH at 0.1 M concentration.
11. For convenience, each position of the purine ring is indicated by a primed number.

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