

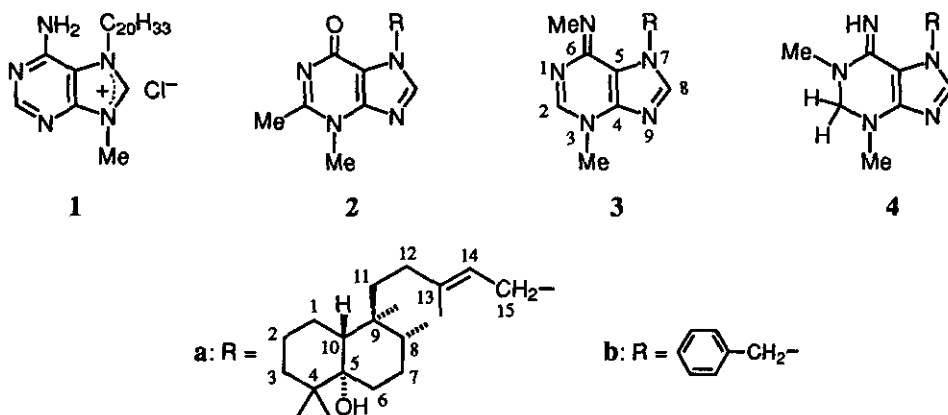
ACETYLATIONS OF (±)-AGELASIMINE-A AND (±)-AGELASIMINE-B: A RACEMIC SYNTHESIS OF PURINO-DITERPENE DERIVED FROM ANTI-MICROBIAL METABOLITES OF *AGELAS MAURITIANA*

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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 "diacetyltagelasimine-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-acetyltagelasimine-B (**7a**).

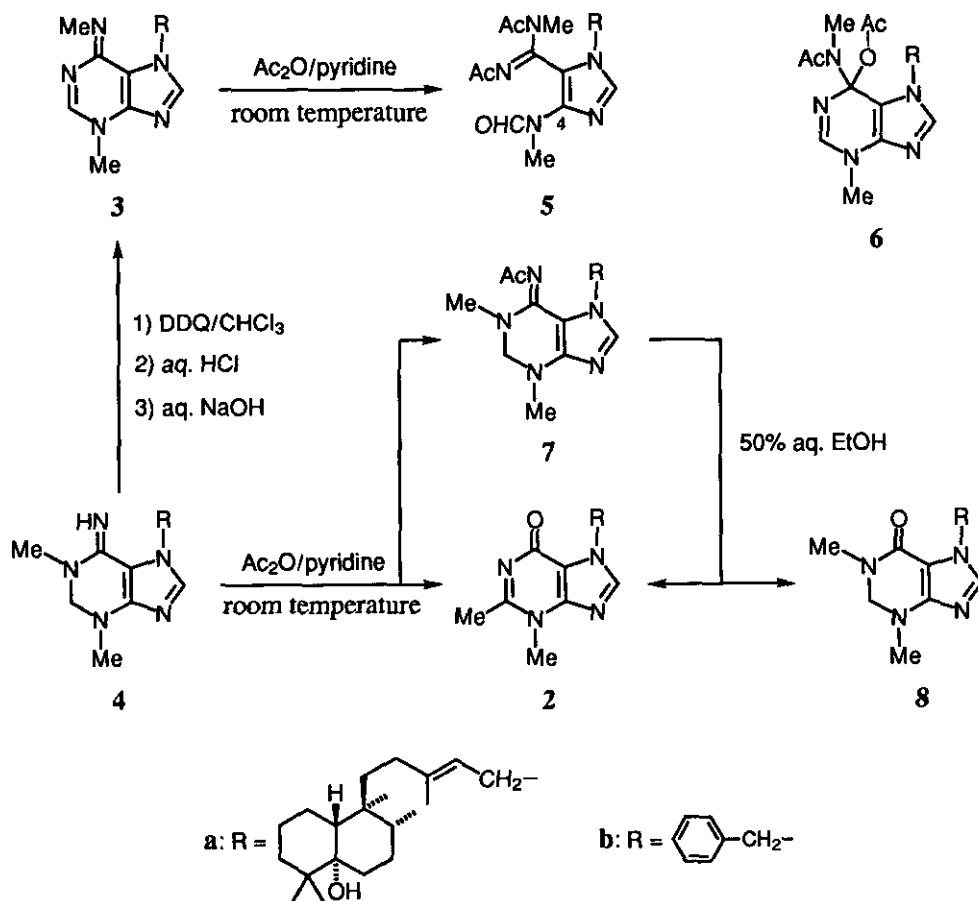
Since the isolation and partial structural elucidation of agelasine (**1**), a novel quaternary 9-methyladenine derivative of an unidentified diterpene from the sponge *Agelas dispar*, were reported by Cullen and Devlin in 1975,¹ a number of adenine-related diterpenoids have been isolated from certain 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



this communication, we wish to describe the acetylations of (\pm)-**3a** and (\pm)-**4a**, the latter of which have led to the formation of purino-diterpene [(\pm)-**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-acetyl-agelasimine-B (**7a**), respectively.³ On the basis of ms fragmentation and ¹H nmr spectral data, they applied structure (**6a**) to diacetyl-agelasimine-A, although its exact nature has not been firmly established (mixture of isomers).³ In order to check the structure of diacetyl-agelasimine-A, (\pm)-**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 (\pm)-**3a** and acetic anhydride in 54% yield as a glassy material.⁶ The ¹H nmr spectrum of the adduct in CDCl₃ 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 Me₂SO-*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 ¹H nmr spectral behavior, presumed to be a result of *cis-trans* equilibration of the *N*-methylformamide group at C(4).⁷ Therefore, structure [(\pm)-**5a**] was assignable to the adduct.⁸ A set of signals arising from the major geometrical isomer in the ¹H nmr spectrum (CDCl₃) of (\pm)-**5a** was found to be virtually identical with the data³ reported for diacetyl-agelasimine-A. Thus, the structure of "diacetyl-agelasimine-A" prepared by a similar acetylation of agelasimine-A (**3a**) should be represented not by the proposed³ purine form (**6a**), but by the monocyclic imidazole form (**5a**).

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



nmr spectra (CDCl₃) of (±)-**7a** were in agreement with those of N⁶-acetyl agelasimine-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-diterpene⁴ (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 CHCl₃ 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 suggestion⁷ that purino-

diterpene (2a) might have been derived from agelasimine-B (4a) through *N*⁶-acetyl agelasimine-B (7a). They have also disclosed that the "diacetyl agelasimine-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.
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8. For the reaction mechanism proposed for the benzyl analogue, see ref. 7.
9. Recrystallized from AcOEt. Selected spectral data: uv $\lambda_{\max}^{\text{MeOH}}$ 267 nm (ϵ 11700); $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 268 (11900); $\lambda_{\max}^{\text{solvent A}}$ 256 (10600); $\lambda_{\max}^{\text{solvent N}}$ 267 (12000); $\lambda_{\max}^{\text{solvent B}}$ 266 (11800); $^{10} \text{ ir } \nu_{\max}^{\text{Nujol}}$ 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]; $^{11} \text{ }^{13}\text{C}$ 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 $\text{C}_{27}\text{H}_{42}\text{N}_4\text{O}_2$: 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.