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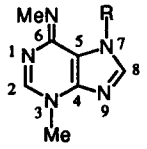
Racemic Syntheses of Agelasimine-A and Agelasimine-B, Bicyclic Diterpenoids from the Marine Sponge *Agelas mauritiana*

Masashi Ohba,*,† Nobuo Kawase,† Tozo Fujii,† Keiichi Aoe,‡ Kimio Okamura,‡ R. Fathi-Afshar,§ and Theresa M. Allen¶

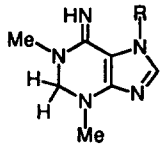
†Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan
‡Analytical Research Laboratory, Tanabe Seiyaku Co., Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan
§SynPhar Laboratories Inc., #2 Taiho Alberta Center, 4290-91A Street, Edmonton, Alberta, Canada T6E 5V2
¶Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada T6G 2H7

Abstract: The first racemic syntheses of agelasimines-A and -B, adenine-related bicyclic diterpenoids from the marine sponge *Agelas mauritiana*, have been accomplished by means of routes through the diol **10** as a key intermediate for their common diterpene portion. As a result, their structures and relative stereochemistries have been unequivocally established to be those represented by formulas (±)-**1a** and (±)-**2a**, respectively.

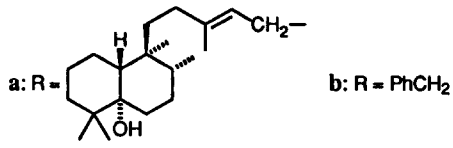
In 1988, some of us announced the isolation of two novel adenine-related bicyclic diterpenoids, agelasimine-A (**1a**) and agelasimine-B (**2a**), along with three bromine-containing alkaloids, from the orange sponge *Agelas mauritiana*.[1] Agelasimines-A and -B exhibit a wide range of interesting biological activities, such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca^{2+}-channel antagonistic action, and α_1 adrenergic blockade.[1,2] Their structures (**1a** and **2a**), featuring trisubstituted adenine nuclei and a $C_{20}H_{35}O$ portion at N(7), have been proposed on the basis of extensive spectral studies.[1] Our recent syntheses of the N(7)-benzyl analogues **1b** and **2b** as preliminaries to total syntheses of **1a** and **2a** have corroborated the substitution patterns proposed for the adenine moieties in **1a** and **2a**.[3] Herein we describe the racemic syntheses of the candidate structures **1a** and **2a**, which have confirmed the correctness of the structures proposed for agelasimines-A and -B.



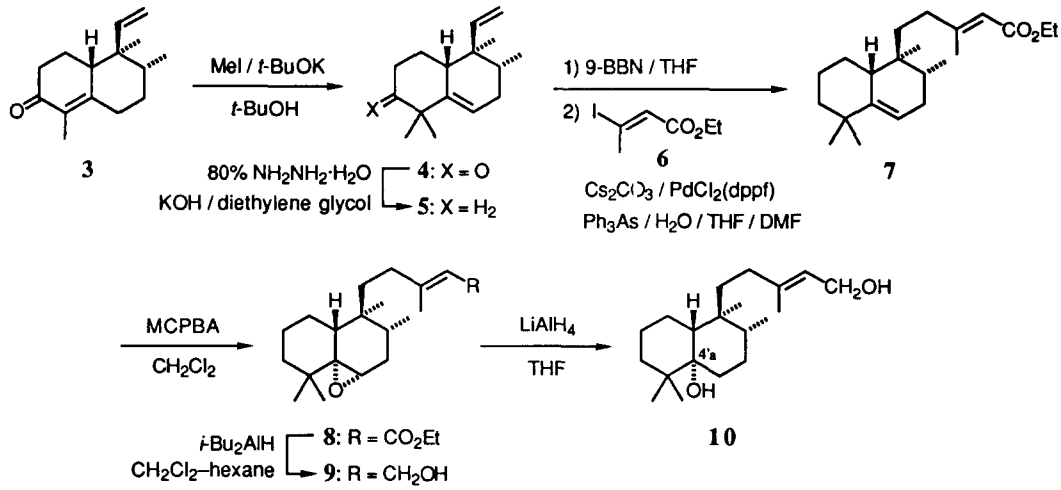
1a,b



2a,b



The synthesis of the diterpene portion, a common structural unit of agelasimines-A and -B, began with the bicyclic enone **3**, available from (±)-3,4-dimethyl-2-cyclohexanone *via* a stereoselective route by Tokoroyama's group.[4,5] Methylation of **3** with MeI under thermodynamic conditions[6] (*t*-BuOK, *t*-BuOH, reflux, 30 min) furnished the deconjugated ketone **4** (mp 53.5–54.5°C)[7] in 83% yield. Wolff–Kishner reduction of **4** was then effected by means of the Huang–Minlon modification (80% $NH_2NH_2 \cdot H_2O$; KOH; diethylene glycol; 130–150°C, 1 h; 190°C, 3 h) to provide **5** in 93% yield.



The palladium-catalyzed cross-coupling reaction of alkylboranes with 1-alkenyl halides, developed by Suzuki,[8] would be promising for elongation of the side chain by exploiting the vinyl group of **5**. In an initial experiment, the hydroboration of **5** with 9-borabicyclo[3.3.1]nonane (9-BBN) (3 eq.) in boiling THF for 2 h and the subsequent coupling reaction between the generated 9-alkyl-9-BBN and the iodide **6**[9] gave only 2% of the coupling product **7** under conventional Suzuki's conditions [K_3PO_4, $PdCl_2(dppf)$,[10] THF, DMF, 50°C, 20 h]. However, on application of the modified conditions [Cs_2CO_3, $PdCl_2(dppf)$,[10] Ph_3As, H_2O, THF, DMF, room temperature, 3 h], recently reported by Johnson and Braun,[11] the coupling reaction proceeded successfully to afford the α,β-unsaturated ester **7** in 75% yield.

Direct epoxidation of **7** with *m*-chloroperoxybenzoic acid (MCPBA) (CH_2Cl_2, 0°C, 2 h) occurred on the non-conjugated olefin, providing the epoxide **8** as the sole isomer in 85% yield. Reduction of **8** with diisobutylaluminum hydride (CH_2Cl_2–hexane, –78°C, 45 min) gave the allylic alcohol **9** (87% yield), which was then subjected to the reductive cleavage of epoxide with $LiAlH_4$ in boiling THF for 2 h. The hydride attack took place preferentially at the sterically less hindered carbon site to furnish the diol **10** (mp 134.5–135°C) in 78% yield. The structure of **10** was determined by a single crystal X-ray diffraction analysis.[12] The derived parallel view of the molecular structure of **10** (Fig. 1) not only established the relative stereochemistry of tertiary alcohol at the 4'a-position of **10**, but also confirmed those of epoxides in **8** and **9**.

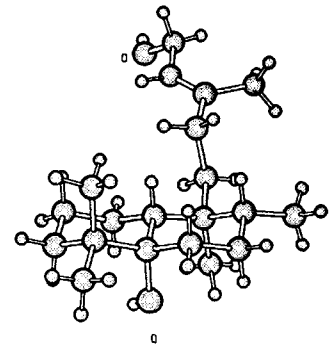
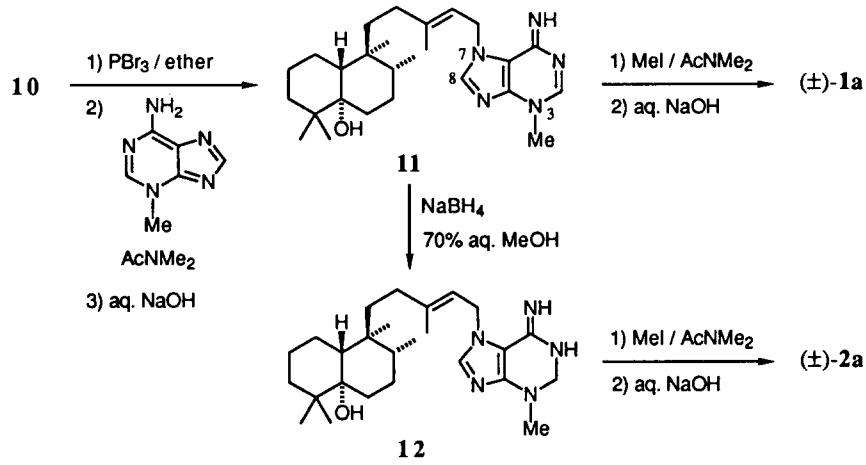


Fig. 1. A parallel view of the molecular structure of **10**

With the completion of the synthesis and characterization of the candidate for the diterpene portion of (±)-agelasimines-A and -B as the diol **10**, we next set out the construction of their adenine portions according to the synthetic routes to the N(7)-benzyl analogues **1b** and **2b**.[3a,c] Regioselective bromination on primary alcohol of **10** with PBr_3 in ether at 0°C for 1 h, subsequent alkylation of 3-methyladenine[13] with the resulting unstable bromide ($AcNMe_2$, 50°C, 2 h), and basification of the hydrobromide salt with aqueous NaOH furnished **11** in

65% yield. The structure of the alkylated product **11** was assigned on the basis of its ^{1}H NMR spectrum in $CDCl_3$. Although a 9% nuclear Overhauser effect (NOE) was observed for the C(8)-H signal (at δ 7.55) on irradiation of the N(7)-CH_2 signal (at δ 5.15), no change occurred for the N(3)-Me signal (at δ 3.66). Finally, methylation of **11** with MeI ($AcNMe_2$, room temperature, 5 h) and basification of the hydriodide salt with aqueous NaOH provided the desired (±)-agelasimine-A [(±)-**1a**] in 58% yield. The UV (MeOH), IR ($CHCl_3$), ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$), and mass spectra of (±)-**1a** were found to be virtually identical with those obtained with a natural sample.



Our effort was then focussed on the synthesis of another target (±)-agelasimine-B. Reduction of **11** with $NaBH_4$ in 70% aqueous MeOH at room temperature for 1 h afforded the 1,2-dihydro derivative **12**. On methylation (MeI, $AcNMe_2$, room temperature, 1.5 h) followed by basification with aqueous NaOH, **12** gave (±)-**2a** in 39% overall yield (from **11**). The 1,2-dihydro-1,3-dimethyladenine structure for (±)-**2a** was determined on the basis of the ^{1}H NMR spectroscopic result (in $CDCl_3$) that 3–4% NOE's were observed for the two *N*-Me signals (at δ 2.88 and 2.95) on irradiation of the C(2)-H_2 signal (at δ 4.12), revealing the proximity of these three groups. The IR ($CHCl_3$), ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$), and mass spectra of (±)-**2a** proved to be virtually identical with those recorded for natural agelasimine-B.

In conclusion, the structures and relative stereochemistries of the two adenine-related bicyclic diterpenoids, agelasimine-A and agelasimine-B, have now been defined as shown in formulas (±)-**1a** and (±)-**2a**, respectively, as a result of the above racemic syntheses.

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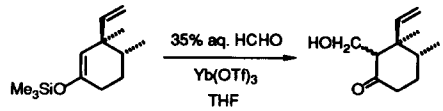
5. The hydroxy ketone **14**, an intermediate for the synthesis of the bicyclic enone **3** by Tokoroyama's group,[4] was easily prepared from the silyl enol ether **13**[14] in 77% yield *via* the hydroxymethylation reaction with 35% aqueous formaldehyde under the influence of a catalytic amount of $Yb(OTf)_3$ at room temperature for 24 h.[15]



13 **14**

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12. Crystal data for **10**: colorless prisms (0.5 × 0.4 × 0.4 mm, from ether); a = 9.992(2) Å; b = 12.091(1) Å; c = 9.046(2) Å; α = 102.40(1)°; β = 112.54(1)°; γ = 70.85(1)°; U = 948.6(3) Å^3; triclinic; space group $P\bar{1}$; Z = 2; D_x = 1.080 g/cm^3. Unit cell constants and intensity data were obtained with a Rigaku AFC-5R diffractometer using graphite-monochromated Cu $K\alpha$ radiation (λ = 1.5418 Å). Out of 3225 unique reflections ($0° \le 2\theta \le 130°$) measured by using the $\omega/2\theta$ scan technique, 2642 with $|F_o| \ge 2.67\sigma(F_o)$ were considered reliable. The structure was solved by a direct method using SHELXS-86[16] and the atomic parameters were refined by the full-matrix least-squares method. The final R value was 0.0560 [R_w = 0.0520, $\sqrt{w} = 1/\sigma(F_o)$]. Full details have been deposited at the Cambridge Crystallographic Data Center.
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