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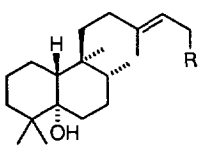
# Syntheses and Absolute Configurations of the Marine Sponge Purines (+)-Agelasimine-A and (+)-Agelasimine-B

**Masashi Ohba,* Kazuaki Iizuka, Hiroyuki Ishibashi, and Tozo Fujii**

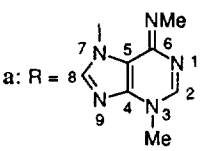
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

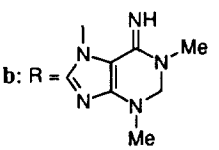
***Abstract:*** The first total syntheses of (+)-agelasimine-A and (+)-agelasimine-B, adenine-related bicyclic diterpenoids isolated from the marine sponge *Agelas mauritiana*, have been achieved *via* a highly stereoselective route. On the basis of the present results, the absolute configurations of both alkaloids have been defined as shown in stereoformulas (+)-**1a** and (+)-**1b**, respectively.


(+)-Agelasimine-A (**1a**) and (+)-agelasimine-B (**1b**) are novel adenine-related bicyclic diterpenoids isolated from the orange sponge *Agelas mauritiana*.[1] Both compounds display a wide range of interesting biological activities, such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, $Ca^{2+}$-channel antagonistic action, $\alpha_1$ adrenergic blockade, and others.[1,2] Recent reports from this laboratory have revealed that the structures and relative stereochemistries of agelasimine-A and -B are represented by formulas (±)-**1a** and (±)-**1b**, respectively.[3,4] Herein we wish to disclose the first chiral syntheses of these agelasimines [(+)-**1a** and (+)-**1b**], which have permitted assignment of their absolute configurations. The present syntheses involve a new practical method for purification of commercially available (+)-*trans*-dihydrocarvone (**5**), a convenient starting material but of unexceptionally inferior isomeric purity.




(+)-**1a**
(+)-**1b**

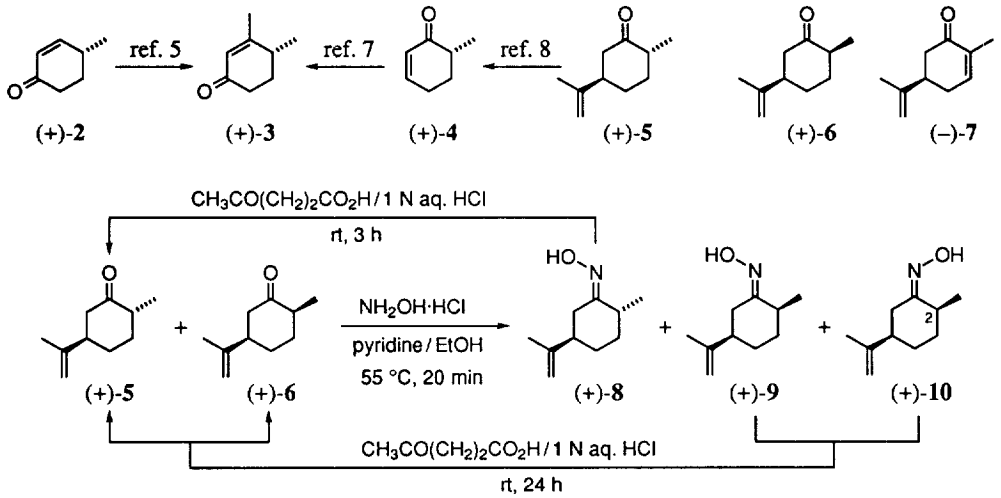



In view of our previous syntheses of (±)-**1a,b** that started from (±)-3,4-dimethyl-2-cyclohexen-1-one [(±)-**3**],[3] the chiral enone (*R*)-(+)-**3** would be a promising starting material for the chiral syntheses of both agelasimines. Among the known methods for preparing the requisite enone (+)-**3** from the alternative precursors (*R*)-(+)-**2**[5,6] and (*R*)-(+)-**4**,[7] the latter by Tokoroyama's group seemed to be the most efficient one. At the outset of the present synthesis, therefore, we needed (+)-*trans*-dihydrocarvone (**5**) in quantity, since (+)-**4** has been readily obtained from (+)-**5** by the procedure of Schreiber.[8,9] However, commercially available (+)-**5** is always contaminated by a large amount (*ca.* 20%) of its *cis*-isomer [(+)-**6**]. Although the two isomers (+)-**5**

and (+)-**6** can be separated by careful column chromatography,[10] tedious repetition of the procedure would be unfavorable for a large scale production of (+)-**5**. An alternative route to (+)-**5** *via* selective reduction of the olefinic bond conjugated with the carbonyl group in (*R*)-(–)-carvone (**7**) also gives a mixture of (+)-**5** and (+)-**6** in a ratio varying from 86 : 14 to 75 : 25.[11] Hence, we first sought an efficient procedure for separation of pure (+)-**5** from a commercially available isomeric mixture.[12]

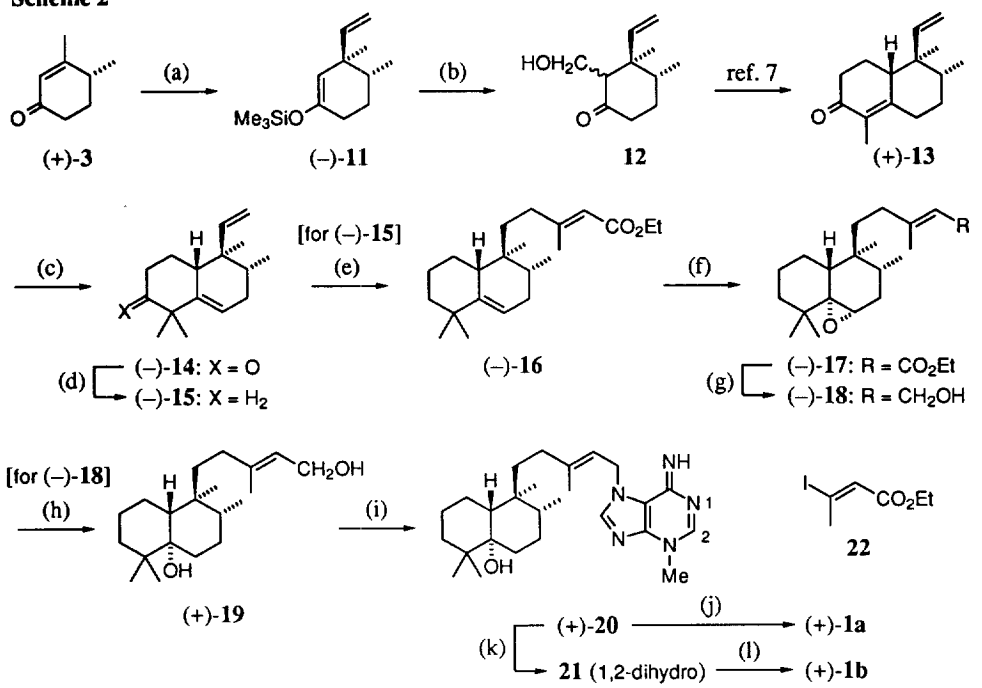
**Scheme 1**




Oximation of an 80 : 20 mixture[13] (82.3 g) of (+)-**5** and (+)-**6** with $NH_2OH$·HCl in the presence of pyridine (EtOH, 55 °C, 20 min) and subsequent crystallization of the resulting mixture of oximes from EtOH–$H_2O$ (2 : 1, v/v) provided (+)-*trans*-dihydrocarvone oxime (**8**)[14] in 60% yield. Separation of the oximes in the mother liquor was readily effected by flash chromatography[15] to afford (+)-**8** in an additional 18% yield (in 78% total yield), together with a separable 71 : 29 mixture of *cis*-dihydrocarvone oximes [(+)-**9**] and [(+)-**10**] in 19% yield. The oxime (+)-**8** thus obtained was found to be a single stereoisomer, and its configuration was determined as *anti* with respect to the adjacent methyl group according to the literature.[16] On the other hand, the oximes (+)-**9** and (+)-**10** were assigned the *anti* and *syn* configurations, respectively, on the basis of the fact that the $^1H$ NMR spectrum of (+)-**9** was analogous to that of (+)-**8**, whereas the C(2)-H (δ 3.60 in $CDCl_3$) of (+)-**10** was deshielded owing to the proximity of the hydroxy group.[17] Hydrolysis of the oxime (+)-**8** with levulinic acid containing 10% (v/v) of 1 N aqueous HCl (rt, 3 h)[18] reproduced (+)-*trans*-dihydrocarvone (**5**) [$[\alpha]_D^{18}$ +17.0° (neat); lit.[19] $[\alpha]_D^{23}$ +17.3° (neat)] in 91% yield. Under similar conditions, however, hydrolysis of the mixture of (+)-**9** and (+)-**10** proceeded only slowly to give a 13 : 87 mixture of (+)-**5** and (+)-*cis*-dihydrocarvone (**6**) in 42% yield after 3 h, together with the unaltered oximes (44%). Elongation of the reaction time to 24 h raised the yield of the deoximated ketones (+)-**5** and (+)-**6** (in a ratio of 68 : 32) to 94%. Thus, we succeeded in devising a simple and efficient procedure for a large scale preparation of (+)-*trans*-dihydrocarvone (**5**).[20]

Next, ozonolysis of (+)-**5** in MeOH and subsequent treatment with $FeSO_4$–$Cu(OAc)_2$ were carried out according to the literature procedure[8] to provide (+)-**4** (44% yield), which was then converted into (+)-**3** in 94% yield *via* treatment with MeLi followed by PCC oxidation.[7]

**Scheme 2**[a]

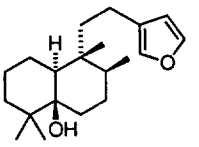



[a]Key: (a) $CH_2$=CHMgBr, CuBr·$Me_2S$, $Me_3SiCl$, HMPA, THF, –78 °C, 3 h, 90% yield; (b) aq. HCHO, $Yb(OTf)_3$, THF, rt, 20 h, 83%; (c) MeI, *t*-BuOK, *t*-BuOH, reflux, 30 min, 85%; (d) 80% aq. $NH_2NH_2$·$H_2O$, KOH, diethylene glycol, 130 °C, 1 h, 190 °C, 3 h, 84%; (e) 1) 9-BBN, THF, reflux, 2 h; 2) 22, $PdCl_2$(dppf), $Cs_2CO_3$, $Ph_3As$, THF–$H_2O$–DMF, rt, 3 h, 67%; (f) *m*-CPBA, $CH_2Cl_2$, 0 °C, 2 h, 82%; (g) DIBALH, $CH_2Cl_2$, –78 °C, 1 h, 88%; (h) $LiAlH_4$, THF, reflux, 4 h, 70%; (i) 1) $PBr_3$, $Et_2O$, 0 °C, 1 h; 2) 3-methyladenine, $AcNMe_2$, 50 °C, 2 h; 3) aq. NaOH, 60%; (j) 1) MeI, $AcNMe_2$, rt, 5 h; 2) aq. NaOH, 61%; (k) $NaBH_4$, 70% aq. MeOH, rt, 1 h; (l) 1) MeI, $AcNMe_2$, rt, 1.5 h; 2) aq. NaOH, 41% from (+)-**20**.

With the efficient synthetic route to the enone (+)-**3** in hand, we now set out to follow a sequence of reactions similar to our previous racemic syntheses,[3] as delineated in Scheme 2, for chiral syntheses of agelasimine-A and -B. Copper-catalyzed conjugate addition of vinylmagnesium bromide to (+)-**3** in the presence of $Me_3SiCl$[21] provided stereoselectively[22] the silyl enol ether (–)-**11**, which was hydroxymethylated with formaldehyde in $H_2O$ solution under the influence of a catalytic amount of $Yb(OTf)_3$[23] to give **12** as a diastereoisomeric mixture. Conversion of **12** into (+)-**13** was performed by following the literature procedure.[7] Methylation of (+)-**13** and the Huang-Minlon modification of the Wolff–Kishner reduction of the resulting deconjugated ketone (–)-**14** produced (–)-**15**. The Suzuki cross-coupling reaction[24] of the 9-BBN derivative, prepared from (–)-**15**, with (*E*)-3-iodo-2-butenoic acid ethyl ester (**22**)[3c,25] was effected by means of the procedure modified by Johnson and Braun,[26] affording the α,β-unsaturated ester (–)-**16**. Direct epoxidation of the nonconjugated endocyclic olefin in (–)-**16** with *m*-CPBA yielded (–)-**17**, which was then reduced with DIBALH at –78 °C to give the allylic alcohol (–)-**18**. Completion of the diterpene portion, a common structural unit of agelasimine-A and -B, was accomplished as the diol (+)-**19** *via* the reductive cleavage of the epoxide in (–)-**18** with $LiAlH_4$ in boiling THF.

Regioselective bromination on the primary hydroxy group of (+)-**19** and subsequent alkylation of 3-methyladenine[27] with the resulting bromide provided (+)-**20** after basification of the hydrobromide salt. Finally, methylation of (+)-**20** with MeI followed by basification furnished the desired (+)-**1a** [$[\alpha]_D^{23}$ +2.6° (*c* 1.07, MeOH)]. The IR ($CHCl_3$), $^1H$ NMR ($CDCl_3$), and mass spectra and specific rotation of synthetic (+)-**1a** proved to be identical with those recorded for natural agelasimine-A [$[\alpha]_D^{25}$ +2.3° (MeOH)].[1] Another target molecule (+)-**1b** [$[\alpha]_D^{23}$ +2.1° (*c* 1.43, MeOH)], identical with natural agelasimine-B [$[\alpha]_D^{25}$ +2.46° (MeOH)][1] by comparison of their IR ($CHCl_3$), $^1H$ NMR ($CDCl_3$), and mass spectra and specific rotations, was also obtained from (+)-**20** through reduction with $NaBH_4$, methylation of the 1,2-dihydro derivative **21** with MeI, and basification of the hydriodide salt.

In conclusion, the present results have unequivocally established the absolute configurations of agelasimine-A and agelasimine-B to be those represented by stereoformulas (+)-**1a** and (+)-**1b**, respectively. Interestingly, the absolute stereochemistry of the bicyclic portion common to these agelasimines is opposite to that of (–)-ambliol B (**23**), a major metabolite of the marine sponge *Dysidea amblia*.[28]



(–)-23

## EXPERIMENTAL

**General Methods.** All melting points were taken on a Büchi model 530 capillary melting point apparatus and are corrected. The ratios of solvent mixtures are shown in v/v. Air- and/or moisture-sensitive reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. See ref. 3c for details of chromatography. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Shimadzu FTIR-8100 IR spectrophotometer, or a JEOL JNM-GSX-500 ($^1H$ 500 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal TMS. Optical rotations were measured with a Horiba SEPA-300 polarimeter. Elemental analyses and MS measurements were performed by Dr. M. Takani and co-workers at Kanazawa University.

**(1*E*,2*R*,5*R*)-2-Methyl-5-(1-methylethenyl)cyclohexanone Oxime (*trans*-Dihydrocarvone Oxime) [(+)-8] and (1*E*,2*S*,5*R*)- and (1*Z*,2*S*,5*R*)-2-Methyl-5-(1-methylethenyl)cyclohexanone Oximes (*cis*-Dihydrocarvone Oximes) [(+)-9 and (+)-10].** To a solution of (+)-dihydrocarvone [an 80 : 20 mixture of (+)-**5** and (+)-**6**][13] (82.3 g, 0.54 mol) in EtOH (540 ml) were added $NH_2OH$·HCl (45.2 g, 0.65 mol) and pyridine (65 ml), and the mixture was heated at 55 °C for 20 min. After cooling, the reaction mixture was concentrated *in vacuo*, and the residual solid was partitioned between ether and $H_2O$. The ethereal extracts were washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a colorless semisolid. Crystallization from EtOH–$H_2O$ (2 : 1) gave a first crop (54.3 g) of (+)-**8** as colorless needles, mp 86.5–88.5 °C. The mother liquor was concentrated *in vacuo*, and the residual oil was then subjected to flash chromatography (silica gel, 10 : 1 hexane–EtOAc). Earlier fractions provided a second crop (16.0 g) of (+)-**8** as a colorless solid. The total yield of (+)-**8** was 70.3 g (78%). Recrystallization of the crude (+)-**8** from EtOH–$H_2O$ (2 : 1) produced an analytical sample as colorless needles: mp 90–91 °C (lit.[14a] mp 88–89 °C); $[\alpha]_D^{26}$ +8.6° (*c* 0.70, $CHCl_3$) [lit.[14b] $[\alpha]_D^{20}$ +9.45° (*c* 1.90, $CHCl_3$); IR (Nujol) $\nu_{max}$ 3280, 1671, 1644 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.12 (3H, d, *J* = 6.5 Hz, C2-Me), 1.27 (1H, dddd, *J* = 12.5, 12.5, 12.5, 3.5 Hz, C3-Hax), 1.44 (1H, dddd, *J* = 13, 12.5, 12.5, 3.5 Hz,

C4-Hax), 1.59 (1H, dd, $J$ = 13.5, 13 Hz, C6-Hax), 1.76 (3H, s, $CH_2$=C*Me*), 1.87 (1H, ddddd, $J$ = 13, 3.5, 3.5, 3.5, 2 Hz, C4-Heq), 1.97 (1H, dddd, $J$ = 12.5, 4, 3.5, 3.5 Hz, C3-Heq), 2.09 (1H, dddd, $J$ = 13, 12.5, 3.5, 3.5 Hz, C5-H), 2.23 (1H, ddq, $J$ = 12.5, 4, 6.5 Hz, C2-H), 3.46 (1H, ddd, $J$ = 13.5, 3.5, 2 Hz, C6-Heq), 4.76 (2H, s, C*H*$_2$=CMe), 8.53 (1H, s, OH); MS *m/z* 167 ($M^+$). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.37. Found: C, 71.57; H, 10.23; N, 8.37.

Later fractions of the above chromatography furnished *cis*-dihydrocarvone oxime (17.3 g, 19%), which was found to be a 71 : 29 mixture of (+)-**9** and (+)-**10** on the basis of $^1$H NMR spectral analysis. Separation of a portion of the mixture into the two components was effected by flash chromatography (silica gel, 6 : 1 $CHCl_3$–EtOAc) to give (+)-**10**, from earlier fractions, as a colorless oil: $[\alpha]_D^{22}$ +38.4° (*c* 1.44, $CHCl_3$); IR (neat) $\nu_{max}$ 3260, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.12 (3H, d, $J$ = 7 Hz, C2-Me), 1.52–1.70 (4H, m, C3-H$_2$ and C4-H$_2$), 1.75 (3H, s, $CH_2$=C*Me*), 2.07 (1H, dddd, $J$ = 12.5, 11.5, 3, 3 Hz, C5-H), 2.14 (1H, dd, $J$ = 13, 12.5 Hz, C6-Hax), 2.30 (1H, br d, $J$ = 13 Hz, C6-Heq), 3.60 (1H, ddq, $J$ = 3.5, 3.5, 7 Hz, C2-H), 4.73 (1H, br) and 4.75 (1H, m) (C*H*$_2$=CMe), 8.10 (1H, br, OH); MS *m/z* 167 ($M^+$). Later fractions of the second chromatography provided (+)-**9** as a colorless oil: $[\alpha]_D^{23}$ +37.4° (*c* 0.57, $CHCl_3$); IR (neat) $\nu_{max}$ 3260, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.14 (3H, d, $J$ = 7 Hz, C2-Me), 1.62–1.75 (4H, m, C3-H$_2$ and C4-H$_2$), 1.75 (3H, s, $CH_2$=C*Me*), 2.18 (1H, m, C5-H), 2.20 (1H, dd, $J$ = 10.5, 10.5 Hz, C6-Hax), 2.55 (1H, ddq, $J$ = 4.5, 4.5, 7 Hz, C2-H), 2.96 (1H, m, C6-Heq), 4.78 (1H, m) and 4.80 (1H, br) (C*H*$_2$=CMe), 8.21 (1H, br, OH); MS *m/z* 167 ($M^+$).

**(2*R*,5*R*)- and (2*S*,5*R*)-2-Methyl-5-(1-methylethenyl)cyclohexanones (*trans*- and *cis*-Dihydrocarvones) [(+)-5 and (+)-6]. (i) From *trans*-Dihydrocarvone Oxime.** A mixture of (+)-**8** (43.7 g, 0.26 mol), levulinic acid (1200 ml), and 1 N aqueous HCl (130 ml) was stirred at room temperature for 3 h. After addition of $H_2O$ (800 ml), the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Distillation of the oil under reduced pressure afforded (+)-**5** (36.3 g, 91%) as a colorless oil: bp 70–71 °C (4 mmHg); $[\alpha]_D^{18}$ +17.0° (neat) [lit.[19] $[\alpha]_D^{23}$ +17.3° (neat)]; IR (neat) $\nu_{max}$ 1713, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.04 (3H, d, $J$ = 7 Hz, C2-Me), 1.38 (1H, dddd, $J$ = 13, 13, 13, 3.5 Hz, C3-Hax), 1.65 (1H, dddd, $J$ = 13.5, 13, 11.5, 3.5 Hz, C4-Hax), 1.74 (3H, s, $CH_2$=C*Me*), 1.94 (1H, ddddd, $J$ = 13.5, 3.5, 3.5, 3, 2.5 Hz, C4-Heq), 2.13 (1H, dddd, $J$ = 13, 6.5, 3.5, 3.5 Hz, C3-Heq), 2.28 (1H, ddd, $J$ = 13, 12, 1.5 Hz, C6-Hax), 2.34 (1H, m, C5-H), 2.37 (1H, ddq, $J$ = 13, 6.5, 7 Hz, C2-H), 2.45 (1H, ddd, $J$ = 12, 2.5, 2.5 Hz, C6-Heq), 4.73 (1H, br) and 4.76 (1H, m) (C*H*$_2$=CMe).

**(ii) From the Mixture of *cis*-Dihydrocarvone Oximes.** The 71 : 29 mixture (184 mg, 1.1 mmol) of (+)-**9** and (+)-**10** described above was treated with a mixture of levulinic acid (5.4 ml) and 1 N aqueous HCl (0.6 ml) at room temperature for 24 h. Work-up of the reaction mixture in a manner similar to that described above for (+)-**5** gave a crude oil, which was then subjected to flash chromatography (silica gel, 20 : 1 hexane–EtOAc). Earlier fractions provided (+)-**5** (108 mg, 64%) as a colorless oil, identical (by comparison of the IR and $^1$H NMR spectra) with the one obtained by method (i). Later fractions of the chromatography furnished (+)-**6** (50 mg, 30%) as a colorless oil: $[\alpha]_D^{30}$ +33.6° (*c* 1.38, $CHCl_3$); IR (neat) $\nu_{max}$ 1711, 1646 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.09 (3H, d, $J$ = 7 Hz, C2-Me), 1.61 (1H, m) and 1.80–1.90 (3H, m) (C3-H$_2$ and C4-H$_2$), 1.73 (3H, s, $CH_2$=C*Me*), 2.36–2.44 (2H, m) and 2.53–2.63 (2H, m) (C2-H, C5-H, and C6-H$_2$), 4.69 and 4.83 (1H each, s, C*H*$_2$=CMe).

**(3*S*,4*R*)-[(3-Ethenyl-3,4-dimethyl-1-cyclohexen-1-yl)oxy]trimethylsilane [(–)-11].** A stirred mixture of CuBr·$Me_2S$ (2.59 g, 12.6 mmol), HMPA (66 ml, 0.38 mol), and a 1.0 M solution (315 ml, 0.315

mol) of vinylmagnesium bromide in THF was cooled to –78 °C, and a mixture of (*R*)-3,4-dimethyl-2-cyclohexen-1-one [(+)-**3**][5,7] (15.6 g, 0.126 mol) and chlorotrimethylsilane (48 ml, 0.38 mol) in THF (70 ml) was added dropwise over 1.5 h. After 3 h, triethylamine (52.5 ml, 0.38 mol) and hexane (500 ml) were added. The reaction mixture was then brought to room temperature, and the insoluble substance that resulted was removed by filtration. The filtrate was washed with $H_2O$, dried, and concentrated. Purification of the residual oil by flash chromatography (silica gel, 50 : 1 hexane–EtOAc) was carried out without delay, giving (–)-**11** (25.3 g, 90%) as a pale yellow oil: $[\alpha]_D^{32}$ –5.2° (*c* 0.88, $CHCl_3$); IR (neat) $\nu_{max}$ 1665, 1634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.19 (9H, s, $SiMe_3$), 0.84 (3H, d, *J* = 6.5 Hz, C4-Me), 0.94 (3H, s, C3-Me), 1.43–1.64 (3H, m, C4-H and C5-$H_2$), 1.93–2.08 (2H, m, C6-$H_2$), 4.58 (1H, m, C2-H), 4.940 (1H, dd, *J* = 10, 1.5 Hz) and 4.943 (1H, dd, *J* = 17.5, 1.5 Hz) (CH=C$H_2$), 5.76 (1H, dd, *J* = 17.5, 10 Hz, C*H*=$CH_2$); HRMS *m/z* calcd for $C_{13}H_{24}OSi$ 224.1956, found 224.1956.

**(3*S*,4*R*)-3-Ethenyl-2-(hydroxymethyl)-3,4-dimethylcyclohexanone (12).** To a stirred mixture of $Yb(OTf)_3$ (790 mg, 1.3 mmol), commercial 35% aqueous formaldehyde solution (32 ml), and THF (80 ml) was added dropwise a solution of (–)-**11** (2.85 g, 12.7 mmol) in THF (20 ml) over 10 min. After having been stirred at room temperature for 20 h, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and $H_2O$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (silica gel, 6 : 5 hexane–EtOAc) afforded **12** (1.91 g, 83%) as a colorless oil, which was found to be a 2 : 1 mixture of the two possible diastereoisomers on the basis of $^1H$ NMR spectral analysis. The IR and $^1H$ NMR spectra of this sample were identical with those of (±)-**12**.[3c]

**(4a*R*,5*S*,6*R*)-5-Ethenyl-4,4a,5,6,7,8-hexahydro-1,5,6-trimethyl-2(3*H*)-naphthalenone [(+)-13].** This was synthesized from **12** in 73% yield according to the literature procedure[7,29] and obtained as a pale yellow oil: $[\alpha]_D^{22}$ +15.5° (*c* 0.77, MeOH) [lit.[7] $[\alpha]_D$ +16° (*c* 1.1, MeOH)]; IR (neat) $\nu_{max}$ 1669, 1638, 1624 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.78 (3H, s, C5-Me), 0.80 (3H, d, *J* = 7 Hz, C6-Me), 1.40 (1H, dddd, *J* = 13, 13, 12.5, 5 Hz, C7-H), 1.61 (1H, ddq, *J* = 12.5, 4, 7 Hz, C6-H), 1.65–1.76 (2H, m, C4-H and C7-H), 1.81 (3H, dd, *J* = 1.5, 1.5 Hz, C1-Me), 1.90 (1H, dddd, *J* = 14, 6, 6, 6 Hz, C4-H), 2.07 (1H, dddq, *J* = 15.5, 13, 6, 1.5 Hz, C8-H), 2.17–2.27 (2H, m, C3-H and C4a-H), 2.43 (1H, ddd, *J* = 16, 6.5, 5 Hz, C3-H), 2.89 (1H, ddd, *J* = 15.5, 5, 2.5 Hz, C8-H), 4.98 (1H, dd, *J* = 17.5, 1 Hz) and 5.16 (1H, dd, *J* = 10.5, 1 Hz) (CH=C$H_2$), 5.59 (1H, dd, *J* = 17.5, 10.5 Hz, C*H*=$CH_2$).

**(4a*R*,5*S*,6*R*)-5-Ethenyl-3,4,4a,5,6,7-hexahydro-1,1,5,6-tetramethyl-2(1*H*)-naphthalenone [(–)-14].** A mixture of (+)-**13** (427 mg, 1.96 mmol), *t*-BuOK (360 mg, 3.2 mmol), and *t*-BuOH (22 ml) was heated under reflux, and a solution of MeI (0.25 ml, 4.0 mmol) in *t*-BuOH (7 ml) was added dropwise over 15 min. After having been heated for a further 30 min, the reaction mixture was concentrated *in vacuo*. The residue was neutralized by adding 1 N aqueous HCl and partitioned between $CHCl_3$ and $H_2O$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil, which was then subjected to flash chromatography (silica gel, 16 : 1 hexane–EtOAc), providing (–)-**14** (388 mg, 85%) as a colorless solid. Recrystallization of the solid from MeOH–$H_2O$ (2 : 1) afforded an analytical sample as colorless needles: mp 74.5–75.5 °C; $[\alpha]_D^{21}$ –50.6° (*c* 0.41, MeOH); MS *m/z* 232 ($M^+$). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.43; H, 10.39. The IR (Nujol) and $^1H$ NMR spectra of this sample were identical with those of (±)-**14**.[3c]

**(1*S*,2*R*,8a*R*)-1-Ethenyl-1,2,3,5,6,7,8,8a-octahydro-1,2,5,5-tetramethylnaphthalene [(–)-15].** A flask equipped with a descending condenser was charged with (–)-**14** (243 mg, 1.05 mmol), diethylene glycol (5 ml), 80% aqueous hydrazine hydrate (197 mg, 3.15 mmol), and KOH (177 mg, 3.15 mmol). The mixture was heated at 130 °C in an oil bath with stirring for 1 h. Then, the temperature of the oil bath was slowly raised to 190 °C in 1 h and kept at 190 °C for 3 h to give a small amount of distillate. After cooling, the reaction mixture was poured into $H_2O$ (6 ml), acidified with 2 N aqueous HCl, and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (silica gel, hexane) gave (–)-**15** (192 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ –60.5° (*c* 0.57, MeOH); HRMS *m/z* calcd for $C_{16}H_{26}$ 218.2035, found 218.2032. The $^1H$ NMR spectral data for this sample were in agreement with those reported for (±)-**15**.[3c]

**[1*S*(*E*),2*R*,8a*R*]-3-Methyl-5-(1,2,3,5,6,7,8,8a-octahydro-1,2,5,5-tetramethyl-1-naphthalenyl)-2-pentenoic Acid Ethyl Ester [(–)-16].** To a 0.5 M solution (5.0 ml, 2.5 mmol) of 9-BBN in THF was added a solution of (–)-**15** (178 mg, 0.82 mmol) in THF (1 ml), and the mixture was heated under reflux for 2 h. After cooling, the solution was added dropwise over 3 min to a stirred mixture of $Cs_2CO_3$ (483 mg, 1.5 mmol), $PdCl_2$(dppf) (68 mg, 10 mol %), $Ph_3As$ (25 mg, 10 mol %), the iodide **22**[3c,25] (217 mg, 0.90 mmol), DMF (3.5 ml), and $H_2O$ (0.18 ml), which had been placed in a separate flask. The resulting mixture was then stirred at room temperature for 3 h and poured into $H_2O$ (15 ml). After extraction of the aqueous mixture with ether, the ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a brown oil. Purification of the oil by flash chromatography (silica gel, 3 : 2 hexane–benzene) afforded (–)-**16** (182 mg, 67%) as a pale yellow oil: $[\alpha]_D^{22}$ –34.0° (*c* 0.38, MeOH); HRMS *m/z* calcd for $C_{22}H_{36}O_2$ 332.2715, found 332.2736. The IR and $^1H$ NMR spectra of this oil were identical with those of (±)-**16**.[3c]

**[1a*S*,3*R*,4*S*(*E*),4a*R*,8a*S*]-3-Methyl-5-(octahydro-3,4,8,8-tetramethyl-3*H*-naphth[1,8a-*b*]oxiren-4-yl)-2-pentenoic Acid Ethyl Ester [(–)-17].** To a stirred, ice-cooled solution of (–)-**16** (1.73 g, 5.2 mmol) in $CH_2Cl_2$ (36 ml) was added dropwise a solution of *m*-CPBA (ca. 80% purity, 1.35 g, 6.3 mmol) in $CH_2Cl_2$ (22 ml) over 15 min. After having been stirred at 0 °C for 2 h, the reaction mixture was washed successively with 10% aqueous $Na_2SO_3$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (silica gel, 3 : 2 $CHCl_3$–hexane) yielded (–)-**17** (1.49 g, 82%) as a slightly yellow oil: $[\alpha]_D^{17}$ –19.8° (*c* 0.24, MeOH); HRMS *m/z* calcd for $C_{22}H_{36}O_3$ 348.2665, found 348.2665. The IR and $^1H$ NMR spectra of this sample were identical with those of (±)-**17**.[3c]

**[1a*S*,3*R*,4*S*(*E*),4a*R*,8a*S*]-3-Methyl-5-(octahydro-3,4,8,8-tetramethyl-3*H*-naphth[1,8a-*b*]oxiren-4-yl)-2-penten-1-ol [(–)-18].** A solution of (–)-**17** (121 mg, 0.35 mmol) in $CH_2Cl_2$ (2 ml) was cooled to –78 °C, and a 0.95 M solution (1.2 ml, 1.1 mmol) of DIBALH in hexane was added dropwise over 3 min. After the mixture had been stirred at –78 °C for 1 h, the reaction was quenched by adding a 5 M solution (0.7 ml) of AcOH in $CH_2Cl_2$. The resulting mixture was then allowed to warm to room temperature, and aqueous tartaric acid was added. The whole was extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography (silica gel, 3 : 1 hexane–EtOAc) furnished (–)-**18** (94 mg, 88%) as a colorless oil: $[\alpha]_D^{25}$ –11.7° (*c* 0.29, MeOH); HRMS *m/z* calcd for $C_{20}H_{34}O_2$ 306.2559, found 306.2553. The IR and $^1H$ NMR spectra of this specimen were identical with those of (±)-**18**.[3c]

**[1*S*(*E*),2*R*,4a*S*,8a*R*]-Octahydro-1-(5-hydroxy-3-methyl-3-pentenyl)-1,2,5,5-tetramethyl-4a(2*H*)-naphthalenol [(+)-19].** To a stirred suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in THF (2 ml) was added a solution of (–)-**18** (81 mg, 0.26 mmol) in THF (2 ml), and the mixture was heated under reflux for 4 h. After cooling, wet ether (4 ml) and $H_2O$ (4 ml) were added in that order. The insoluble material that resulted was removed by filtration, and the filtrate was extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a pale yellow solid. Recrystallization of the solid from hexane yielded a first crop (47 mg) of (+)-**19** as colorless prisms, mp 77–81 °C. Concentration of the mother liquor and subsequent purification of the residue by preparative TLC (silica gel, 20 : 1 $CHCl_3$–MeOH) gave a second crop (10 mg) of (+)-**19** as a colorless solid. The total yield of (+)-**19** was 57 mg (70%). Further recrystallization from hexane produced an analytical sample as colorless prisms: mp 83–84 °C; $[\alpha]_D^{15}$ +5.6° (*c* 0.16, MeOH); IR (Nujol) $\nu_{max}$ 3450, 3345, 1671 $cm^{-1}$; MS *m/z* 308 ($M^+$). Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 77.63; H, 11.92. The $^1H$ NMR spectral data for this sample were in agreement with those reported for (±)-**19**.[3c]

**[1*S*(*E*),2*R*,4a*S*,8a*R*]-1-[5-(3,6-Dihydro-6-imino-3-methyl-7*H*-purin-7-yl)-3-methyl-3-pentenyl]octahydro-1,2,5,5-tetramethyl-4a(2*H*)-naphthalenol [(+)-20].** To a stirred, ice-cooled solution of (+)-**19** (400 mg, 1.3 mmol) in ether (20 ml) was added dropwise a solution of $PBr_3$ (176 mg, 0.65 mmol) in ether (3 ml) over 5 min. After the mixture had been stirred at 0 °C for 1 h, MeOH (0.6 ml) was added. The reaction mixture was then brought to room temperature, washed successively with $H_2O$, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated *in vacuo* to leave the bromide (483 mg) as a pale yellow oil. The oil was dissolved in $AcNMe_2$ (3 ml), and the solution was added to a stirred, warm (50 °C) solution of 3-methyladenine[27] (194 mg, 1.3 mmol) in $AcNMe_2$ (7 ml). After having been stirred at 50 °C for a further 2 h, the reaction mixture was concentrated *in vacuo*. A suspension of the residue in $H_2O$ (3 ml) was made strongly basic with 10% aqueous NaOH and then extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $K_2CO_3$, and concentrated to leave a yellow oil, which was purified by column chromatography (alumina, 3 : 1 $CHCl_3$–MeOH) to provide (+)-**20** (340 mg, 60%) as a yellow glass: $[\alpha]_D^{19}$ +2.5° (*c* 0.23, MeOH); HRMS *m/z* calcd for $C_{26}H_{41}N_5O$ 439.3311, found 439.3316. The IR and $^1H$ NMR spectra of this sample were identical with those of (±)-**20**.[3c]

**[1*S*(*E*),2*R*,4a*S*,8a*R*]-1-[5-[3,6-Dihydro-3-methyl-6-(methylimino)-7*H*-purin-7-yl]-3-methyl-3-pentenyl]octahydro-1,2,5,5-tetramethyl-4a(2*H*)-naphthalenol (Agelasimine-A) [(+)-1a].** A mixture of (+)-**20** (65 mg, 0.15 mmol) and MeI (105 mg, 0.74 mmol) in $AcNMe_2$ (0.9 ml) was stirred at room temperature for 5 h. The reaction mixture was then concentrated *in vacuo*, and $H_2O$ (1 ml) was added. The resulting mixture was brought to pH 11 with 10% aqueous NaOH (1 ml) and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $K_2CO_3$, and concentrated. Purification of the residual oil by preparative TLC (alumina, 8 : 1 $CHCl_3$–MeOH) furnished (+)-**1a** (41 mg, 61%) as a pale yellow glass: $[\alpha]_D^{23}$ +2.6° (*c* 1.07, MeOH); HRMS *m/z* calcd for $C_{27}H_{43}N_5O$ 453.3467, found 453.3471. The synthetic (+)-**1a** was identical [by comparison of the IR ($CHCl_3$), $^1H$ NMR ($CDCl_3$), and mass spectra and specific rotation] with natural agelasimine-A [$[\alpha]_D^{25}$ +2.3° (MeOH)].[1]

**[1*S*(*E*),2*R*,4a*S*,8a*R*]-Octahydro-1,2,5,5-tetramethyl-1-[3-methyl-5-(1,2,3,6-tetrahydro-6-imino-1,3-dimethyl-7*H*-purin-7-yl)-3-pentenyl]-4a(2*H*)-naphthalenol (Agelasimine-B) [(+)-1b].** To a stirred solution of (+)-**20** (84 mg, 0.19 mmol) in 70% aqueous MeOH (2 ml) was added $NaBH_4$ (14 mg, 0.37 mmol). After having been stirred at room temperature for 1 h, the reaction mixture was

concentrated *in vacuo*. The residue was then partitioned between saturated aqueous $K_2CO_3$ and $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with saturated aqueous $K_2CO_3$, dried over anhydrous $K_2CO_3$, and concentrated, and the total amount of the crude **21** (80 mg) thus obtained was dissolved in $AcNMe_2$ (0.4 ml). After addition of MeI (108 mg, 0.76 mmol), the mixture was stirred at room temperature for 1.5 h and then concentrated *in vacuo*. The residue, after addition of $H_2O$ (1 ml), was brought to pH 11 with 10% aqueous NaOH (1 ml) and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $K_2CO_3$, and concentrated to leave a yellow oil, which was purified successively by column chromatography (alumina, 99 : 1 $CHCl_3$–MeOH) and preparative TLC (alumina, 40 : 1 $CHCl_3$–MeOH), giving (+)-**1b** (36 mg, 41%) as a pale yellow glass: $[\alpha]_D^{23}$ +2.1° (*c* 1.43, MeOH); HRMS *m/z* calcd for $C_{27}H_{45}N_5O$ 455.3624, found 455.3604. The synthetic (+)-**1b** was identical [by comparison of the IR ($CHCl_3$), $^1H$ NMR ($CDCl_3$), and mass spectra and specific rotation] with natural agelasimine-B [$[\alpha]_D^{25}$ +2.46° (MeOH)].[1]

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