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The first synthesis of *ent*-agelasine F

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ABSTRACT

Agelasine F has previously been isolated from marine sponges (*Agelas* sp.) and has been associated with various bioactivities including inhibitory activity on *Mycobacterium tuberculosis*. No total synthesis of this natural product has been reported. *ent*-Agelasine F has now been synthesized for the first time, starting from (*R*)-pulegone. The synthesis is considerably more efficient than a previously reported route to *rac*-agelasine F. *ent*-Agelasine F is found to exhibit antimicrobial activity.

1. Introduction

Agelasine F (Fig. 1), sometimes also referred to as ageline A,[1] has been isolated from marine sponges (*Agelas* sp.).[1–5] Antibacterial activity,[1] including activity against *Mycobacterium tuberculosis*,[6] antifungal activity,[1,5] and inhibitory effects on Na,K-ATPase[2] are reported for this natural product. Only racemic agelasine F has been synthesized.[7] Our group has previously reported the first total syntheses of agelasine D[8] and E (Fig. 1),[9] as well as several analogs,[8–10] and explored their generally potent activities against pathogenic microorganisms and cancer cell lines, as well as the ability to act as antifouling agents.[11] We envisaged that agelasine F would be available from the monoterpene (*S*)-pulegone (Fig. 1). In order to test this hypothesis, we have performed the synthesis of *ent*-agelasine F from the less expensive (*R*)-pulegone.

2. Results and discussion

(*R*)-Pulegone **1** was converted into a diastereomeric mixture of (2*R*,3*R*)- and (2*S*,3*R*)-2,3-dimethylcyclohexanone **3** by a modified literature procedure,[12] and the cyclohexanone **3** was transformed into the thermodynamic silyl enol ether **4** (Scheme 1). Alkylation of compound **4** with chloromethyl phenyl sulfide in the presence of $TiCl_4$ gave a mixture of the diastereomeric sulfides **5** and **6** in a high total yield, and with the desired isomer **5** as the major product. The sulfides were easily oxidized to the corresponding sulfones **7** and **8**, and the stereochemistry of the sulfides and sulfones were proven by X-ray crystallography of the sulfone **8**. Compound **8** crystallized as two crystallographically independent molecules as shown in Figure 2. Methylmagnesium iodide was added to the ketone **7** and, after formic acid-mediated regioselective water elimination, the desired sulfone **9** was isolated in high yield. The use of other acids (TFA, oxalic acid, H_2SO_4, H_3PO_4) in the elimination step resulted in formation of the isomeric product with an exocyclic double bond, in various amounts. In the Grignard addition, diethyl ether was superior to THF as solvent. The best total yield of compound **9** was obtained when the Grignard addition/water elimination was performed after oxidizing the sulfide **5** to sulfone **7**. When the sulfide **5** was reacted subsequently with methylmagnesium iodide and formic acid, the yield was only ca. 40%. The sulfone **9** was at first treated with *n*-butyllithium followed by the tosylate **10a** according to the procedures previously used for coupling the two monoterpene parts in the agelasine E side chain[13] and in the side chain of an agelasine analog.[10b] However, the reaction between lithiated sulfone **9** and the tosylate **10a** was sluggish and only minor amounts of the desired compound **11** were formed. This is probably a result of increased steric hindrance in **9** compared to sulfones related to the previously used tosylate **10a** (Fig. 3). Hence, we investigated the reaction between the lithiated sulfone **9** and the potentially, more reactive geraniol derivatives **10b** and **10c**. When the bromide **10b**[14] was used, a slight improvement in conversion was observed, but the best results were obtained when the sulfone

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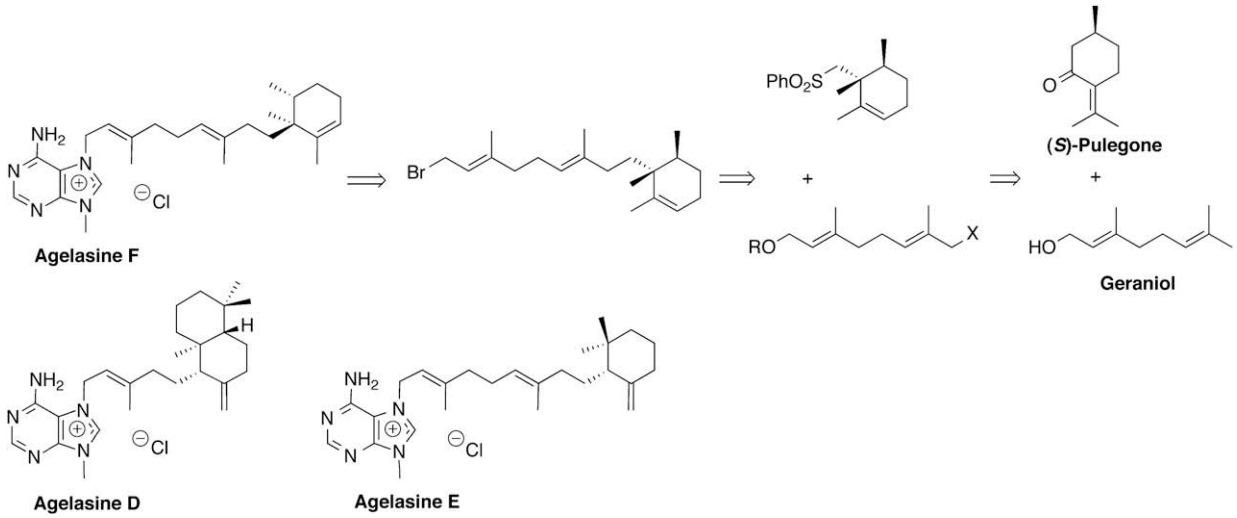
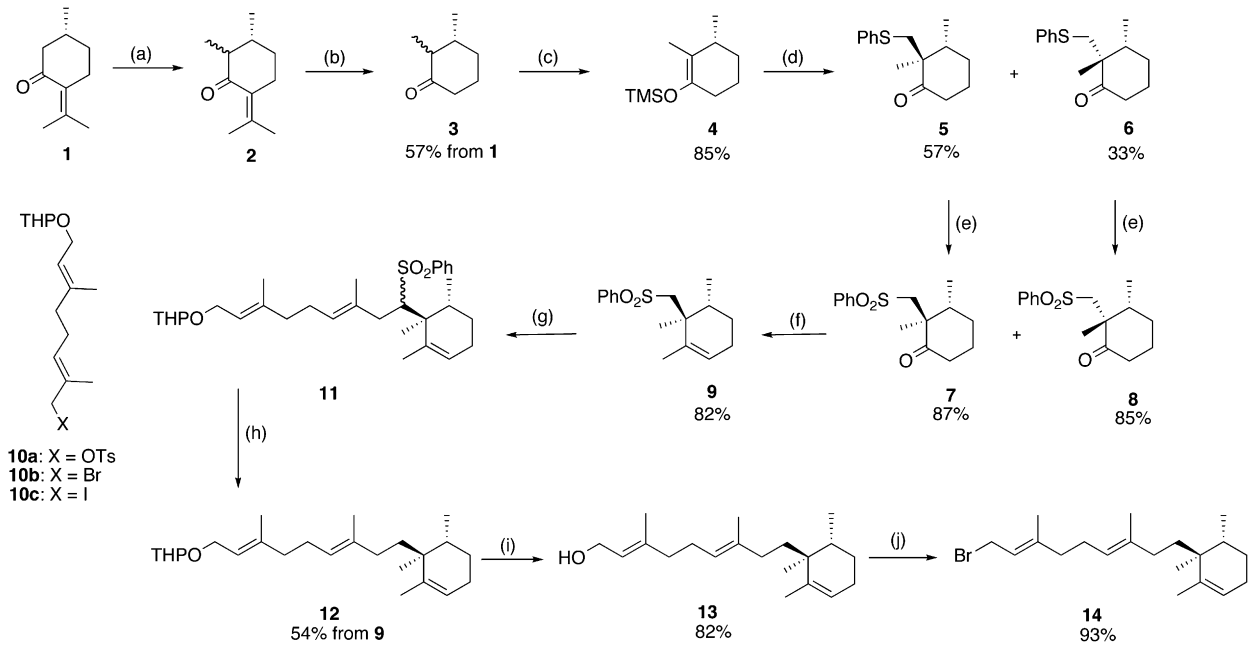


Figure 1. Structure of agelasine D, E, and F and retrosynthetic analysis of agelasine F.



Scheme 1. (a) (1) LDA, (2) MeI, THF, −78 to 0 °C; (b) KOH(aq), MeOH, Δ; (c) TMSCl, Et_3N, DMF, 130 °C; (d) $PhSCH_2Cl$, $TiCl_4$, CH_2Cl_2, −23 °C; (e) oxone, MeOH, H_2O; (f) (1) MeMgI, Et_2O, 0 °C–rt, (2) HCO_2H, 80 °C; (g) (1) *n*-BuLi, (2) compd **10c**, THF, 50 °C; (h) Na, Na_2HPO_4, EtOH, THF; (i) PPTS, EtOH, 55 °C; (j) PBr_3, Et_2O, 0 °C.

was lithiated and reacted with the iodide **10c**. The coupling product **11** was converted into the alkylating agent **14** by reductive removal of the sulfone, protecting group cleavage, and finally bromination of the alcohol **13** (Scheme 1). The optically active bromide **14** was synthesized in 10 steps from commercially available (*R*)-pulegone, whereas the previously reported method for the synthesis of *rac*-**14** is ca. 13 steps from a non-commercially available racemic cyclohexane derivative.[7] The sulfone **9** may also be a useful building block for other natural products and some examples are shown in Figure 4.

The adenine derivative **15** was reacted with the allyl bromide **14**, in analogy with our previously reported agelasine D synthesis (Scheme 2).[8b] Although the alkylation was not completely regioselective, the desired product **16a** was formed in a good yield and converted to *ent*-agelasine F (**17**) by reductive removal of the *tert*-butoxy group. Preliminary results show that *ent*-agelasine F (**17**) exhibits antimicrobial activity; MIC *Staphylococcus aureus* 2 μg/mL and MIC *Escherichia coli* 16 μg/mL. The synthesis of agelasine F, as well as an in-depth study of bioactivities for both enantiomers and analogs, will be published in due course.

3. Experimental

3.1. General

The ^1H NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. The decoupled ^{13}C NMR spectra were recorded at 75 or 50 MHz using instruments mentioned above, or at 150 MHz with AVII600 instrument equipped with TCI cryo probe. Assignments of ^1H and ^{13}C resonances are inferred from 1D ^1H NMR, 1D ^{13}C NMR, DEPT and/or from 2D NMR (gs-COSY, gs-HMQC,

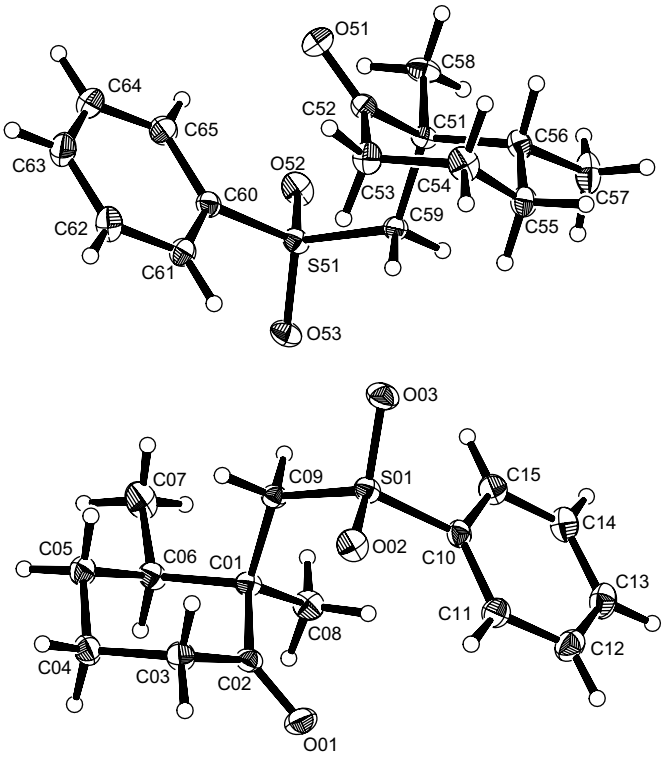


Figure 2. The two molecules in the asymmetric unit of sulfone **8**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

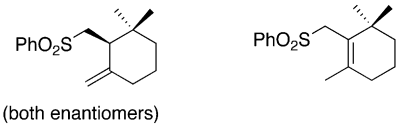


Figure 3. Sulfones previously coupled successfully with the tosylate **10a**.[9,10b]

gs-HMBC, NOESY) spectroscopical data. Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as *m*/*z* (% rel int.). Melting points were determined with a C. Reichert melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 341 polarimeter. DMA was distilled from BaO and stored over molecular sieves (3 Å). Triethylamine, DMF, and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves (3 Å). THF and diethyl ether were distilled from Na/benzophenone. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). All other reagents were commercially available and used as received. Antimicrobial activities were determined as described before.[8b]

3.2. X-ray crystallographic analysis for compound 8

Crystals of **8** suitable for X-ray crystallography were obtained from acetone–hexane (1:3) at ambient temperature. X-ray data were collected on a Siemens SMART CCD diffractometer[15] using graphite monochromated Mo Kα radiation (λ=0.71073 Å). Data collection method: ω-scan, step 0.3°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[15] Absorption corrections were applied by the use of the SADABS program.[16] The structure was determined and refined using the SHELX program package.[17] The non-hydrogen atoms were refined with isotropic thermal

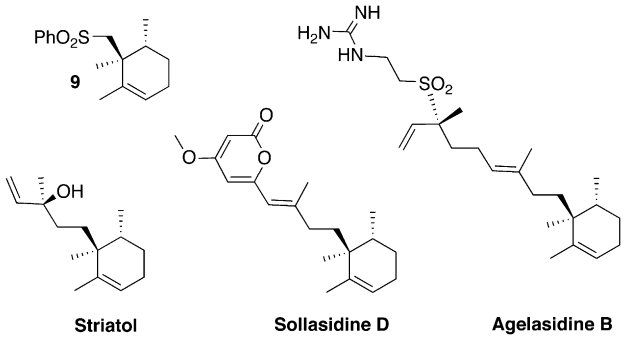


Figure 4. Selected natural products with structural resemblance to sulfone **9**.

parameters; H atoms were positioned geometrically and allowed to ride and rotate (for the CH_3 group) on their carrier atoms, with C–H bond lengths of 0.95 (aromatic C–H), 0.99 (CH_2) or 0.98 Å (CH_3) and with Uiso(H)=1.2Ueq(C) for CH_2 and aromatic C–H or 1.5Ueq(C) for CH_3. Crystallographic data (excluding structure factors) for the structure **8** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 692906. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.2.1. Crystal data for $C_{18}H_{15}ClN_4O_2$ ***8***

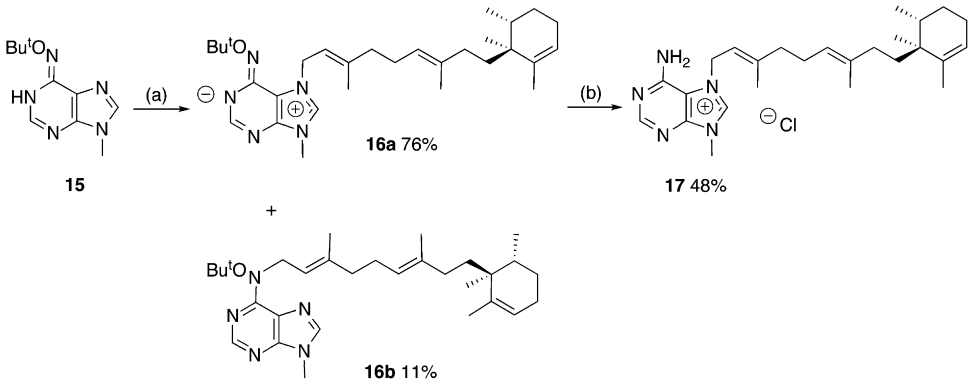
M=280.37, monoclinic, *P*2(1), *a*=9.7883 (2) Å, *b*=10.7792 (3) Å, *c*=13.8013 (3) Å, β=101.9320 (10)°, *V*=1424.71 (6) Å^3, *Z*=4, D_x=1.307 Mg m^{-3}, μ=0.23 mm^{-1}, *T*=105(2) K, measured 18,991 reflections in 2θ range 3.0–68.6°, R_{int}=0.021. Three hundred and forty-four parameters refined against 11,249 F^2, *R*=0.03 for 10,382 $I>2\sigma(I)$ and 0.0342 for all 11,249 data. Absolute structure was determined.

3.2.2. (3R)-2,3-Dimethylcyclohexanone (***3***)[12]

(*R*)-Pulegone **1** (10.0 g, 65.8 mmol) was treated with LDA [generated in situ from *n*-BuLi (1.6 M in hexane, 50 mL, 80 mmol) and diisopropylamine (5.0 mL, 71 mmol) in dry THF (80 mL)] at −78 °C for 1 h. Methyl iodide (14.4 mL, 116 mmol) was added and the mixture was stirred for 1 h at −78 °C and at 0 °C for 1 h. After satd aq NH_4Cl (40 mL) and Et_2O (200 mL) were added, the phases were separated, and the aqueous phase was extracted with Et_2O (2×200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was partly purified by flash chromatography eluting with hexane–EtOAc (30:1); yield 11.0 g mainly compound **2**. This material was treated with KOH (128 g) in water (320 mL) and MeOH (83 mL) under reflux for 38 h. The mixture was extracted with Et_2O (3×150 mL) and the combined extracts were washed with aq HCl (1 M, 30 mL) and brine (45 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was distilled under reduced pressure; yield 4.78 g (57%), mixture of isomers, colorless liquid, bp 60–62 °C/8 mmHg. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (d, *J*=6.5 Hz, 3H, CH_3), 1.04 (d, *J*=6.0 Hz, 3H, CH_3), 1.39–1.50 (m, 2H), 1.52–1.63 (m, 1H), 1.85–1.91 (m, 2H), 1.96–2.06 (m, 2H), 2.16–2.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.2, 21.2, 26.5, 34.7, 41.6, 42.0, 52.3, 213.7 (C=O).

3.2.3. (R)-(2,3-Dimethylcyclohex-1-enyloxy)trimethylsilane (***4***)

TMSCl (9.5 mL, 76 mmol) was added dropwise to a solution of (*R*)-2,3-dimethylcyclohexanone **3** (4.78 g, 38 mmol) in dry Et_3N (10.4 mL, 76.0 mmol) and dry DMF (24 mL). The mixture was heated at 130 °C and was stirred overnight. After cooling, Et_2O (70 mL) was added and the mixture washed with cold satd aq $NaHCO_3$ solution (70 mL). The aqueous phase was extracted with



Scheme 2. (a) Compd **14**, DMA, 50 °C; (b) Zn, AcOH, MeOH, H_2O, 75 °C.

cold Et_2O (3×70 mL) and the combined organic extracts were washed rapidly with cold 0.5 M aq HCl (90 mL), cold satd aq $NaHCO_3$ (2×70 mL), and cold brine (70 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography eluting with hexane–EtOAc (100:1); yield 6.40 g (85%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 9H, TMS), 1.00 (d, J=6.9 Hz, 3H, CH_3), 1.28–1.33 (m, 2H), 1.58 (q, J=0.6 Hz, 3H), 1.66–1.73 (m, 2H), 1.99–2.03 (m, 2H), 2.10–2.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.7 (TMS), 14.2, 19.9, 20.4, 30.5, 31.2, 33.6, 116.4, 143.2; MS (EI) m/z (rel %) 198 (13, M^+), 185 (5), 184 (16), 155 (10), 84 (4), 75 (17).

3.2.4. (2S,3R)-2,3-Dimethyl-(2-phenylthiomethyl)cyclohexanone (**5**) and (2R,3R)-2,3-dimethyl-(2-phenylthiomethyl) cyclohexanone (**6**)

A solution of $TiCl_4$ in CH_2Cl_2 (10.2 mL, 1.0 M, 10.2 mmol) was added to a stirring solution of (*R*)-(2,3-dimethylcyclohex-1-enyloxy)trimethylsilane **4** (1.85 g, 9.30 mmol) and chloromethyl phenyl sulfide (1.7 mL, 13 mmol) in CH_2Cl_2 (9 mL), at −23 °C under N_2 atmosphere. After 1 h, the resulting deep red solution was poured into satd aq $NaHCO_3$ (45 mL) and extracted with Et_2O (2×85 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The products were separated by flash chromatography eluting with hexane–EtOAc (15:1); yield 1.32 g (57%) of **5** and 0.774 g (33%) of **6**.

Compound **5**: colorless oil. $[\alpha]_D^{20}$ −1.1 (*c* 1.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (d, J=6.8 Hz, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.47–1.61 (m, 1H), 1.61–1.79 (m, 2H), 1.89–1.98 (m, 1H), 2.18–2.30 (m, 1H), 2.31–2.48 (m, 2H), 2.97 (d, J=12.5 Hz, 1H, H_a in CH_2S), 3.37 (d, J=12.5 Hz, 1H, H_b in CH_2S), 7.14–7.17 (m, 1H, Ph), 7.21–7.27 (m, 2H, Ph), 7.37–7.40 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5 (CH_3), 18.6 (CH_3), 24.2 (C-5), 29.1 (C-4), 37.7 (C-3), 38.0 (C-6), 41.1 (CH_2S), 53.7 (C-2), 126.1 (CH in Ph), 128.8 (2×CH in Ph), 130.1 (2×CH in Ph), 138.1 (C in Ph), 213.6 (C=O); MS (EI) m/z (rel %) 248 (86, M^+), 139 (63), 125 (21), 124 (15), 123 (100), 110 (28), 109 (19); HRMS (EI) found 248.1237, $C_{15}H_{20}OS$ requires 248.1235.

Compound **6**: colorless oil. $[\alpha]_D^{20}$ −65.8 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, J=6.9 Hz, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.53–1.61 (m, 1H), 1.61–1.73 (m, 1H), 1.73–1.87 (m, 1H), 1.88–1.97 (m, 2H), 2.28–2.42 (m, 2H, CH_2), 3.08 (d, J=12.0 Hz, 1H, H_a in CH_2S), 3.24 (d, J=12.0 Hz, 1H, H_b in CH_2S), 7.14–7.17 (m, 1H, Ph), 7.21–7.26 (m, 2H, Ph), 7.31–7.34 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7 (CH_3), 21.1 (CH_3), 24.7 (C-5), 28.9 (C-4), 38.3 (C-6), 38.8 (CH_2S), 42.2 (C-3), 52.7 (C-2), 126.1 (CH in Ph), 128.9 (2×CH in Ph), 129.7 (2×CH in Ph), 137.1 (C in Ph), 214.1 (C=O); MS (EI) m/z (rel %) 248 (81, M^+), 139 (71), 124 (12), 123 (100), 110 (20), 109 (118); HRMS (EI) found 248.1235, $C_{15}H_{20}OS$ requires 248.1235.

3.2.5. (2S,3R)-2,3-Dimethyl-2-(phenylsulfonylmethyl) cyclohexanone (**7**)

A solution of oxone (3.69 g, 4.00 mmol) in water (15 mL) was added to a stirring solution of sulfide **5** (992 mg, 6.00 mmol) in methanol (15 mL) at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 19 h at ambient temperature before Et_2O (200 mL) was added and the resulting mixture was washed with water (40 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chromatography eluting with hexane–acetone (3:1); yield 976 mg (87%), colorless crystals, mp 95–97 °C. $[\alpha]_D^{20}$ −77.3 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 3H, CH_3), 1.06 (d, J=6.8 Hz, 3H, CH_3), 1.51–1.63 (m, 1H), 1.73–1.75 (m, 1H), 1.78–1.92 (m, 2H, CH_2), 2.40–2.52 (m, 2H, CH_2), 2.68–2.72 (m, 1H), 3.23 (d, J=14.0 Hz, 1H, H_a in CH_2S), 3.93 (d, J=14.0 Hz, 1H, H_b in CH_2S), 7.51–7.60 (m, 3H, Ph), 7.93–7.96 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1 (CH_3), 18.7 (CH_3), 23.3 (C-5), 29.2 (C-4), 36.6 (C-3), 37.6 (C-6), 52.3 (C-2), 60.9 (CH_2S), 127.6 (2×CH in Ph), 129.1 (2×CH in Ph), 133.3 (CH in Ph), 142.0 (C in Ph), 211.6 (C=O); MS (EI) m/z (rel %) 280 (1, M^+), 139 (100), 121 (19), 97 (19), 95 (20), 83 (25), 77 (20); HRMS (EI) found 280.1123, $C_{15}H_{20}O_3S$ requires 280.1133.

3.2.6. (2R,3R)-2,3-Dimethyl-2-(phenylsulfonylmethyl) cyclohexanone (**8**)

Sulfide **6** (1.00 mmol) was oxidized with oxone as described for the synthesis of sulfone **7** above; yield 161 mg (85%), colorless crystals, mp 110–112 °C. $[\alpha]_D^{20}$ −9.4 (*c* 1.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, J=7.0 Hz, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.44–1.59 (m, 1H), 1.70–1.80 (m, 1H), 1.81–2.03 (m, 2H), 2.14–2.21 (m, 1H), 2.46–2.56 (m, 2H, CH_2), 3.25 (d, J=14.6 Hz, 1H, H_a in CH_2S), 3.56 (d, J=14.6 Hz, 1H, H_b in CH_2S), 7.52–7.63 (m, 3H, Ph), 7.86–7.89 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9 (CH_3), 21.4 (CH_3), 24.7 (C-5), 28.4 (C-4), 37.8 (C-6), 43.3 (C-3), 52.2 (C-2), 59.5 (CH_2S), 127.7 (2×CH in Ph), 129.3 (2×CH in Ph), 133.7 (CH in Ph), 141.3 (C in Ph), 212.1 (C=O); MS (EI) m/z (rel %) 280 (1, M^+), 139 (100), 121 (19), 97 (19), 95 (21), 83 (22), 77 (27); HRMS (EI) found 280.1132, $C_{15}H_{20}O_3S$ requires 280.1133.

3.2.7. 1-{[(1S,6R)-1,2,6-Trimethylcyclohex-2-enyl] methylsulfonyl}benzene (**9**)

To a solution of ketone **7** (958 mg, 3.40 mmol) in dry Et_2O (60 mL) was added MeMgI in Et_2O (3.8 mL, 1.0 M, 3.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 16 h. After cooling to 0 °C, satd aq NH_4Cl (10 mL) was added. The mixture was diluted with Et_2O (10 mL) and the phases separated. The aqueous phase was extracted with Et_2O (60 mL), the combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was stirred in concd formic acid (2 mL) at 80 °C for 2 h before the mixture was concentrated in

vacuo. The residue was purified by flash chromatography eluting with hexane–acetone (5:1); yield 809 mg (85%), pale yellow oil. $[\alpha]_{589}^{20}$ −47.9 (*c* 1.17, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (d, *J*=6.9 Hz, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.35–1.46 (m, 1H), 1.57–1.65 (m, 1H), 1.62 (q, *J*=1.8 Hz, 3H, CH_3), 1.95–2.02 (m, 2H, CH_2), 2.55–2.61 (m, 1H), 3.19 (d, *J*=14.6 Hz, 1H, H_a in CH_2S), 3.30 (d, *J*=14.6 Hz, 1H, H_b in CH_2S), 5.39 (m, 1H, CH=), 7.48–7.62 (m, 3H, Ph), 7.87–7.90 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7 (CH_3), 19.2 (CH_3), 21.3 (CH_3), 23.8 (C-4), 26.3 (C-5), 33.3 (C-6), 42.2 (C-1), 61.9 (CH_2S), 124.6 (C-3), 127.5 (2×CH in Ph), 129.1 (2×CH in Ph), 133.3 (CH in Ph), 136.2 (C-2), 142.0 (C in Ph); MS (EI) *m*/*z* (rel %) 278 (4, M^+), 137 (38), 136 (100), 121 (44), 107 (77), 95 (45), 94 (65), 93 (36); HRMS (EI) found 278.1350, $C_{16}H_{22}O_2S$ requires 278.1341.

3.2.8. 2-[(2E,6E)-8-Iodo-3,7-dimethylocta-2,6-dienyloxy]tetrahydro-2H-pyrane (**10c**)

To a stirred solution of (2*E*,6*E*)-2,6-dimethyl-8-(tetrahydro-2*H*-pyran-2-yloxy)octa-2,6-dien-1-ol[13] (508 mg, 2 mmol), Ph_3P (788 mg, 3.00 mmol), and imidazole (204 mg, 3.00 mmol) in a mixture of CH_3CN (3 mL) and Et_2O (5 mL) was added iodine (760 mg, 3.00 mmol) portionwise at 0 °C over 10 min. The reaction mixture was stirred for another 20 min, diluted with Et_2O (40 mL), washed with satd aq $Na_2S_2O_3$ (10 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was filtered through a plug of silica eluting with hexane–EtOAc (15:1); yield 604 mg (ca. 83%), pale yellow liquid used immediately in the next step. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43–1.65 (m, 6H), 1.65 (s, 3H), 1.75 (s, 3H), 2.02–2.15 (m, 4H), 3.45–3.54 (m, 1H), 3.89 (d, *J*=7.8 Hz, 2H), 3.99–4.08 (m, 1H), 4.11–4.27 (m, 1H), 4.60 (t, *J*=3.4 Hz, 1H), 5.37 (t, *J*=6.4 Hz, 2H), 5.57–5.69 (m, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 15.3 (CH_3), 16.2 (CH_2), 16.3 (CH_3), 19.6 (CH_2), 26.0 (CH_2), 27.0 (CH_2), 31.1 (CH_2), 38.6 (CH_2), 61.5 (CH_2), 63.6 (CH_2), 97.5 (OCHO), 122.4 (CH=), 129.2 (CH=), 133.3 (C=), 138.3 (C=).

3.2.9. 2-[(2E,6E)-3,7-Dimethyl-9-[(1S,6R)-1,2,6-trimethylcyclohex-2-enyl]nona-2,6-dienyloxy]-tetrahydro-2H-pyran (**12**)

n-BuLi (8.56 mL, 1.44 M, 8.60 mmol) was added dropwise to a stirring solution of sulfone **9** (1.19 g, 4.30 mmol) in dry THF (20 mL) at 0 °C under N_2 atmosphere and the resulting mixture was stirred at 50 °C for 40 min before a solution of crude iodide **10c** (3.18 g, 8.60 mmol) in THF (20 mL) was added. The reaction was stirred for 3 h at 50 °C. The mixture was diluted with Et_2O (120 mL), washed with satd aq NH_4Cl (40 mL), water (3×40 mL), and brine (40 mL), and evaporated in vacuo. The product **11** was partially purified by flash chromatography eluting with hexane–acetone (11:1); yield 2.20 g, pale yellow oil. A mixture of compound **11** (2.20 g), Na_2HPO_4 (19.0 g, 134 mmol), sodium (4.30 mg, 187 mmol), and ethanol (16 mL) in THF (330 mL) was stirred at ambient temperature for 16 h, before the mixture was filtered and the filtrate was diluted with Et_2O (430 mL). The resulting mixture was washed with water (300 mL), satd aq NH_4Cl (220 mL), and brine (220 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography eluting with hexane–EtOAc (23:1); yield 1.61 g (54% from compound **9**), pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3H, CH_3), 0.84 (d, *J*=6.8 Hz, 3H, CH_3), 1.23–1.62 (m, 8H, 4×CH_2), 1.58 (s, 6H, 2×CH_3), 1.64–1.78 (m, 3H, CH_2 in THP and H-6_a in cyclohexene), 1.80–2.11 (m, 8H, 4×CH_2), 3.45–3.52 (m, 1H, H-6_a in THP), 3.84–3.91 (m, 1H, H-6_b in cyclohexene), 3.97–4.03 (m, 1H, H_a in CH_2O), 4.17–4.24 (m, 1H, H_b in CH_2O), 4.60 (t, *J*=5.6 Hz, 1H, H-2 in THP), 5.07 (t, *J*=6.8 Hz, CH=), 5.35 (t, *J*=6.4 Hz, 1H, CH=), 5.37 (br s, 1H, CH=); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8 (CH_3), 16.2 (CH_3 on C-7), 16.4 (CH_3), 19.2 (CH_3 on C-2), 19.6 (CH_2), 21.0 (CH_3), 25.5 (2×CH_2), 26.3 (CH_2), 27.0 (CH_2), 30.7 (CH_2), 33.2 (C-6 in cyclohexene), 34.2 (CH_2), 35.2 (CH_2), 39.6 (CH_2), 40.4 (C-1 in cyclohexene), 62.3 (C-6 in THP), 63.6 (OCH_2), 97.7 (C-2 in THP), 120.6 (CH=), 123.2 (CH=), 124.0 (CH=), 136.3 (C=), 139.8 (C=), 140.2 (C=); MS (EI) *m*/*z* (rel %) 374 (0.4, M^+), 124 (32), 123 (100), 109 (23), 95 (22), 85 (96), 81 (36); HRMS (EI) found 374.3167, $C_{25}H_{42}O_2$ requires 374.3185.

3.2.10. (2E,6E)-3,7-Dimethyl-9-[(1S,6R)-1,2,6-trimethylcyclohex-2-enyl]nona-2,6-dien-1-ol (**13**)

A mixture of compound **12** (374 mg, 1.00 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (58 mg, 0.23 mmol) in ethanol (12 mL) was stirred at 55 °C under N_2 atmosphere for 17 h, before the mixture was evaporated in vacuo and the residue was purified by flash chromatography eluting with hexane–acetone (15:1); yield 237 mg (82%), pale yellow oil. $[\alpha]_D^{20}$ +26.4 (*c* 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3H, CH_3 on C-1 in cyclohexene), 0.83 (d, *J*=6.9 Hz, 3H, CH_3 on C-6 in cyclohexene), 1.37–1.47 (m, 4H, 2×CH_2, H-4 in cyclohexene, H-5 in cyclohexene), 1.58 (s, 6H, CH_3 on C-7, CH_3 on C-2 in cyclohexene), 1.61–1.72 (m, 1H, H-6 in cyclohexene), 1.62 (s, 3H, CH_3 on C-3), 1.87–2.09 (m, 8H, 4×CH_2, H-4, H-5, H-8, H-9), 4.12 (d, *J*=6.9 Hz, 2H, H-1), 5.07 (t, *J*=6.2 Hz, 1H, H-6), 5.36–5.40 (m, 2H, H-2, H-3 in cyclohexene); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8 (CH_3 on C-6 in cyclohexene), 16.2 (CH_3 on C-7), 16.3 (CH_3 on C-3), 19.2 (CH_3 on C-2 in cyclohexene), 21.0 (CH_3 on C-1 in cyclohexene), 25.5 (C-5), 26.3 (C-9), 27.0 (C-4 in cyclohexene), 33.1 (C-6 in cyclohexene), 34.2 (C-4), 35.2 (C-5 in cyclohexene), 39.5 (C-8), 40.3 (C-1 in cyclohexene), 59.4 (C-1), 123.1 (C-6), 123.3 (C-2), 124.0 (C-3 in cyclohexene), 136.4 (C-7), 139.7 (C-2 in cyclohexene), 139.8 (C-3); MS (EI) *m*/*z* (rel %) 290 (1, M^+), 124 (44), 123 (100), 109 (29), 95 (20), 81 (38); HRMS (EI) found 290.2600, $C_{20}H_{34}O$ requires 290.2610.

3.2.11. (5R,6R)-6-[(3E,7E)-9-Bromo-3,7-dimethylnona-3,7-dienyl]-1,5,6-trimethylcyclohex-1-ene (**14**)

The alcohol **13** (237 mg, 0.82 mmol) was dissolved in dry Et_2O (3 mL) under N_2 atmosphere at 0 °C. PBr_3 (0.065 mL, 0.82 mmol) was added and the mixture was stirred at 0 °C for 3 h. The mixture was diluted with Et_2O (18 mL) and washed with 10% aq $NaHCO_3$ (6 mL). The aqueous phase was extracted with Et_2O (6 mL) and the combined organic extracts were dried ($MgSO_4$), and evaporated in vacuo; yield 0.267 g (93%), pale yellow oil, which was used directly in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3H), 0.84 (d, *J*=6.8 Hz, 3H), 1.26–1.45 (m, 4H), 1.54–1.61 (m, 1H), 1.58 (s, 3H), 1.61–2.12 (m, 8H), 4.00 (d, *J*=9.9 Hz, 2H), 4.99–5.05 (m, 1H), 5.39 (s, 1H), 5.51 (t, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 16.0, 16.3, 19.2, 21.1, 25.5, 26.1, 27.0, 29.7, 33.2, 34.2, 35.2, 39.5, 40.4, 120.6, 122.7, 124.0, 136.7, 136.7, 139.8, 143.7; MS (EI) *m*/*z* (rel %) 352 (0.7, M^+), 124 (46), 123 (100), 109 (21), 95 (17), 81 (31); HRMS (EI) found 352.1778, $C_{20}H_{33}Br$ requires 352.1766.

3.2.12. 7-{(2′E,6′E)-3,7-Dimethyl-9-[(1R,6S)-1,2,6-trimethyl cyclohex-2-enyl]nona-2,6-dienyl}-6-tert-butoxyamino-9-methyl-7H-purinum (**16a**) and N^6-{(2′E,6′E)-3,7-dimethyl-9-[(1R,6S)-1,2,6-trimethylcyclohex-2-enyl]nona-2,6-dienyl}-N^6-tert-butoxy-9-methyl-9H-purin-6-amine (**16b**)

A mixture of purine **15**[8b] (111 mg, 0.50 mmol) and allylic bromide **14** (182 mg, 0.52 mmol) in DMA (4.5 mL) was stirred at 50 °C under N_2 atmosphere for 21 h and evaporated in vacuo. The residue was purified by flash chromatography eluting with CH_2Cl_2–MeOH satd with NH_3 (12:1 then 9:1); yield (**16a**) 188 mg (76%). The fractions containing isomer **16b** were combined, evaporated, and purified by flash chromatography eluting with hexane–EtOAc (1:1); yield (**16b**) 28 mg (11%).

Compound **16a**: mp 149–150 °C, yellow crystals. $[\alpha]_D^{20}$ +14.3 (*c* 0.52, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (s, 3H, CH_3 on C-1 in cyclohexene), 0.82 (d, *J*=6.8 Hz, 3H, CH_3 on C-6 in cyclohexene), 1.31 (s, 9H, *t*-Bu), 1.35–1.45 (m, 4H), 1.51 (s, 6H, CH_3 on C-7′ and CH_3 on C-2 in cyclohexene), 1.60–1.64 (m, 2H), 1.82 (s, 3H, CH_3 on C-3′), 1.83–1.91 (m, 3H), 2.07–2.09 (m, 4H), 3.97 (s, 3H, NCH_3), 5.02–5.08

(m, 3H, NCH_2 and H-6′), 5.37 (s, 1H, H-3 in cyclohexene), 5.53 (t, J=7.2 Hz, 1H, H-2′), 7.91 (s, 1H, H-2), 9.99 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8 (CH_3 on C-6 in cyclohexene), 16.2 (CH_3 on C-7′), 17.3 (CH_3 on C-3′), 19.2 (CH_3 on C-2 in cyclohexene), 21.0 (CH_3 on C-1 in cyclohexene), 25.5 (C-5′), 26.1 (C-9′), 27.0 (C-4 in cylohexene), 27.5 (3×CH_3 in *t*-Bu), 32.1 (NCH_3), 33.2 (C-6 in cyclohexene), 34.2 (CH_2), 35.1 (CH_2), 39.5 (CH_2), 40.3 (C-1 in cyclohexene), 48.1 (NCH_2), 79.7 (C in *t*-Bu), 111.2 (C-5), 115.5 (C-2′), 122.6 (C-6′), 124.1 (C-3 in cyclohexene), 136.0 (C-2 in cyclohexene), 136.6 (C-8), 136.8 (C-3′), 139.6 (C-6), 141.2 (C-4), 146.1 (C-7′), 149.3 (C-2); MS (EI) *m*/*z* (rel %) 493 (10, M^+), 216 (33), 166 (18), 165 (100), 135 (37), 123 (61), 81 (31); HRMS (EI) found 493.3763, $C_{30}H_{47}N_5O$ requires 493.3780.

Compound **16b**: colorless oil. $[\alpha]_D^{20}$ +17.1 (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (s, 3H, CH_3 on C-1 in cyclohexene), 0.81 (d, J=6.8 Hz, 3H, CH_3 on C-6 in cyclohexene), 1.30–1.41 (m, 4H), 1.38 (s, 9H, *t*-Bu), 1.49 (s, 3H, CH_3 on C-7′), 1.52–1.57 (m, 1H), 1.55 (q, J=1.5 Hz, 3H, CH_3 on C-2 in cyclohexene), 1.65 (s, 3H, CH_3 on C-3′), 1.76–1.94 (m, 8H), 3.81 (s, 3H, NCH_3), 4.20 (br s, 1H, H_a in NCH_2), 4.97 (t, J=6.7 Hz, 1H, H-6′), 5.30 (t, J=6.4 Hz, 1H, H-2′), 5.37 (m, 2H, H-3 in cyclohexene and H_b in NCH_2), 7.78 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.8 (CH_3 on C-6 in cyclohexene), 16.1 (CH_3 on C-7′), 16.6 (CH_3 on C-3′), 19.2 (CH_3 on C-2 in cyclohexene), 21.0 (CH_3 on C-1 in cyclohexene), 25.5 (CH_2), 26.4 (CH_2), 27.0 (CH_2), 27.2 (3×CH_3 in *t*-Bu), 29.8 (NCH_3), 33.1 (C-6 in cyclohexene), 34.1 (CH_2), 35.1 (CH_2), 39.6 (CH_2), 40.3 (C-1 in cyclohexene), 53.8 (NCH_2), 82.6 (C in *t*-Bu), 118.7 (C-2′), 119.9 (C-5), 123.3 (C-6′), 123.9 (C-3 in cyclohexene), 136.0 (C-7′), 139.5 (C-8), 139.8 (C-2 in cyclohexene), 140.8 (C-3′), 151.5 (C-2), 151.6 (C-4), 158.9 (C-6); MS (EI) *m*/*z* (rel %) 493 (0.6, M^+), 437 (50), 314 (34), 216 (17), 166 (31), 165 (100), 135 (20); HRMS (EI) found 493.3780, $C_{30}H_{47}N_5O$ requires 493.3780.

3.2.13. *ent*-Agelasine F (**17**)

A mixture of compound **16a** (174 mg, 0.35 mmol), Zn (287 mg, 4.39 mmol), and AcOH (0.35 mL) in MeOH (18 mL) and water (1.8 mL) was stirred vigorously at 75 °C for 19 h. The mixture was filtered and the solid washed with MeOH (18 mL). Satd aq NaCl (9 mL) and water (9 mL) were added to the MeOH solution, and the mixture was stirred for 1 h at ambient temperature and evaporated in vacuo. The residue was transferred to a separatory funnel using satd aq NaCl (37 mL) and $CHCl_3$ (42 mL). The phases were separated and the aqueous phase was extracted with $CHCl_3$ (3×42 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography eluting with CH_2Cl_2–MeOH (6:1); yield 161 mg (48%), colorless crystals, mp 99–100 °C. $[\alpha]_D^{20}$ +12.2 (*c* 0.64, $CHCl_3$); [lit. agelasine F $[\alpha]_D$ −8.4 (*c* 3.0, $CHCl_3$);[1] $[\alpha]_D^{25}$ −5.5 (*c* 2.45, $MeOH_3$)[2]]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (s, 3H, CH_3 on C-1 in cyclohexene), 0.81 (d, J=6.7 Hz, 3H, CH_3 on C-6 in cyclohexene), 1.21–1.44 (m, 5H), 1.53 (s, 3H, CH_3 on C-7′), 1.54 (s, 3H, CH_3 on C-2 in cyclohexene), 1.59–1.69 (m, 1H), 1.78–1.83 (m, 1H), 1.82 (s, 3H, CH_3 on C-3′), 1.87–1.97 (m, 2H), 2.01–2.08 (m, 4H), 4.06 (s, 3H, NCH_3), 4.93 (br s, 1H, H-6′), 5.37 (br s, 1H, H-3 in cyclohexene), 5.63 (br s, 2H, NCH_2), 7.15 (br s, 2H, NH_2), 8.43 (1H, H-2), 10.43 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8 (CH_3 on C-6 in cyclohexene), 16.3 (CH_3 on C-7′), 17.4 (CH_3 on C-3′), 19.2 (CH_3 on C-2 in cyclohexene), 21.0 (CH_3 on C-1 in cyclohexene), 25.5 (CH_2), 26.2 (C-4 in cyclohexene), 27.0 (CH_2), 32.2 (NCH_3), 33.2 (C-6 in cyclohexene), 34.2 (CH_2), 35.1 (CH_2), 39.5 (CH_2), 40.3 (C-1 in cyclohexene), 48.8 (NCH_2), 109.9 (C-5), 115.8 (C-2′), 122.5 (C-6′), 124.1 (C-3 in cyclohexene), 137.0 (C═), 139.6 (C═), 141.9 (C-8), 146.8 (C═), 149.5 (C-4), 152.1 (C-6), 155.4 (C-2); MS (EI) *m*/*z* (rel %) 421 (1, M^+), 149 (48), 124 (32), 123 (100), 122 (17), 109 (20), 81 (31); HRMS (EI) found 421.3190, $C_{26}H_{39}N_5$ requires 421.3205. Spectroscopical data were in good accordance with those reported for agelasine F[1–4] and *rac*-agelasine F[7] before.

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