Biomimetic Synthesis of Agelasidine A

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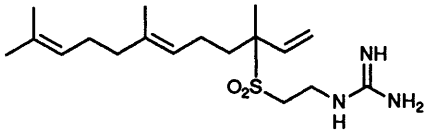
Agelasidine A **1** was synthesized using the [2,3]sigmatropic rearrangement of an allylic sulfinate to an allylic sulfone at low concentration. This biomimetic approach provided an efficient three-step synthesis of agelasidine A **1** from farnesol **16** in 54% overall yield.

A sesquiterpene derivative of taurocyamine, agelasidine A **1**, has been isolated as a bioactive metabolite from the Okinawan sea sponge *Agelas nakamurai* by Nakamura[1] and from the Pacific sea sponge *Agelas* sp. by Faulkner.[2] Agelasidine A **1** is the first marine natural product containing both guanidine and sulfone groups and its unique structure is characterized by a quaternary carbon atom attached to a sulfur atom as shown.



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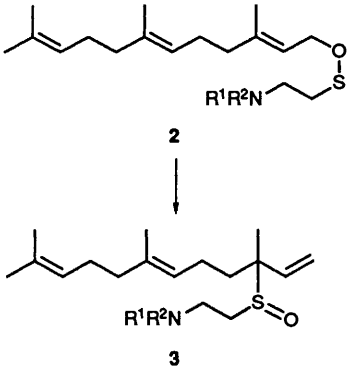
Nakamura postulated that the biosynthesis of agelasidine A **1** is derived from farnesol through a [2,3]sigmatropic rearrangement of its aminoethyl sulfenate **2** as shown in eqn. (1).[3] Sigmatropic rearrangement of allylic sulfenate **2** to allylic sulfoxide **3**, followed by oxidation to a sulfone and introduction of a guanidine group is a conceivable biosynthetic pathway for this molecule.

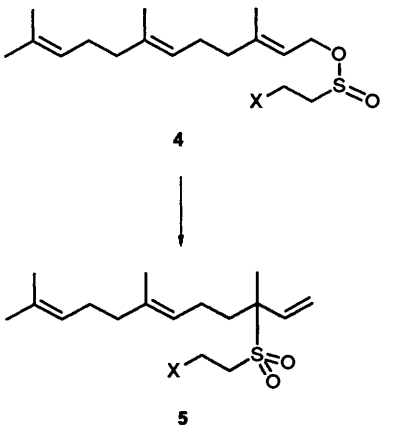


2 **3** (1)

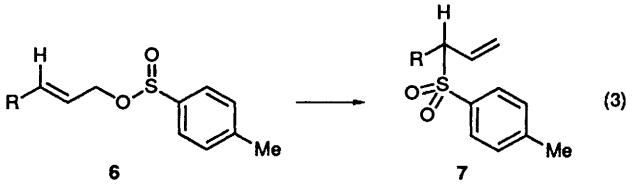
Based on this biogenetic line, a synthetic approach to this molecule was designed. The crucial step of this plan is the [2,3]sigmatropic rearrangement of an allylic sulfinate **4** to an allylic sulfone **5** [eqn. (2)] which produces the sulfone moiety and quaternary carbon atom in a single step.[4]

Results and Discussion

The optimal conditions for the rearrangement of an allylic sulfinate to an allylic sulfone were explored first. Hiroi observed solvent effects such that the [2,3]sigmatropic rearrangement of allylic toluene-*p*-sulfinates **6** proceeds smoothly in *N,N*-dimethylformamide (DMF) [eqn. (3)].[5] Based on their observations of the solvent effect in the case of allylic arene-sulfinates, we chose DMF as the solvent and explored the rearrangement of allylic alkane sulfinates.

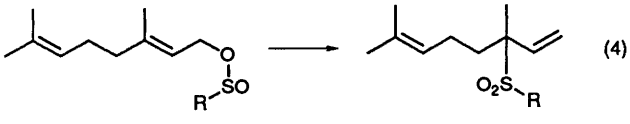


4 **5** (2)



6 **7** (3)

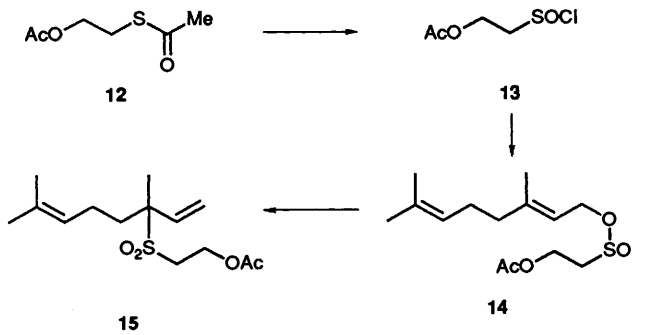
Geranyl alkanesulfinates **8** (R = Me) and **9** (R = Et) were prepared from geraniol and alkanesulfinyl chlorides in pyridine.[6] Rearrangement of these geranyl methane-, and ethane-sulfinates, **8** and **9**, in DMF at 80–100 °C provided allylic sulfones, **10** and **11**, in poor yield (~0–11%) [eqn. (4)]. This may be due to either difficulties with the rearrangement or instability of the allylic sulfones under thermal conditions. Indeed, the allylic sulfones **10** and **11** decayed upon storage at room temperature.



8 = Me, **9** = Et **10** = Me, **11** = Et (4)

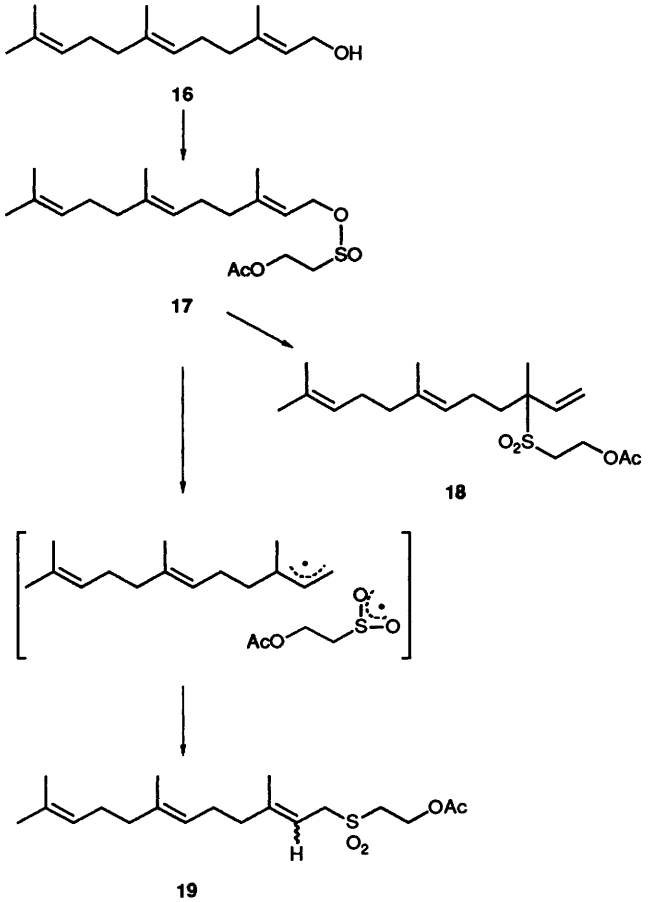
On the other hand, thioacetate **12** with sulfuryl chloride and acetic anhydride was converted into sulfinyl chloride **13**, which was treated with geraniol to provide the allylic sulfinate **14**. In contrast to the disheartening results in the case of the allylic methane- and ethane-sulfinates, an allylic sulfinate **14** with an acetoxy group at the β-position on the alkane group underwent smooth rearrangement to sulfone **15** in reasonable yield (50–79%) (Scheme 1).

Encouraged by this result, we prepared allylic sulfinate **17** from farnesol **16** and investigated the optimum set of reaction conditions. In this case, we noted the formation of a [1,3]sigmatropic rearrangement product **19** as a by-product. This process is thermally forbidden; accordingly, homolytical cleavage of the



Scheme 1

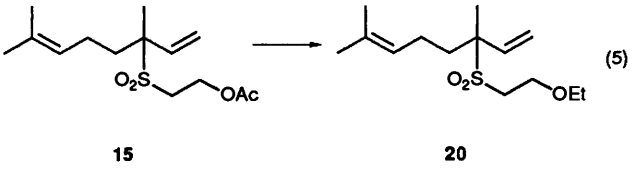
C–O bond of compound **17** followed by recombination of the resulting radical pair seemed to be a probable reaction pathway for this by-product **19** (Scheme 2).[7]



Scheme 2

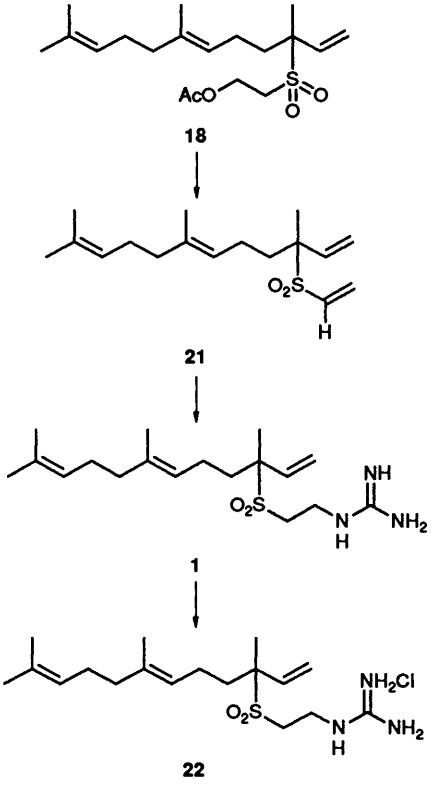
We envisaged that such radical species attack other molecules intermolecularly; therefore, this process would cause a decrease in the yield of the concerted [2,3]sigmatropic process. We reasoned that such side-reactions could be suppressed, if the reaction could be carried out at low concentration. This was, indeed, the case, and the yield of this rearrangement at a variety of concentrations was 56% (1.7×10^{-1} mol dm^{-3}), 71% (8.3×10^{-2} mol dm^{-3}) and 78% (5.5×10^{-2} mol dm^{-3}). Indeed, the important effect of concentration on yield in this rearrangement has now been realized.

The final stage of our synthesis of agelaside A was the introduction of guanidine at the β-position of the sulfone. Vinyl sulfones have been known as good Michael acceptors towards a variety of nucleophiles.[8] We presumed that treatment of sulfone **18** with a strong base, such as guanidine, would provide the vinyl sulfone **21**, which would undergo attack of guanidine to produce agelasidine A (Scheme 3). Guanidine was prepared from guanidine hydrochloride and sodium ethoxide in ethanol. The ethanol was evaporated off, and the resulting guanidine was immediately dissolved in aq. 1,4-dioxane. Substitution of ethanol with aq. 1,4-dioxane as solvent was essential, owing to the fact that exclusive formation of the ether **20** from the model compound **15** was observed when an ethanolic solution of guanidine was used [eqn. (5)].



(5)

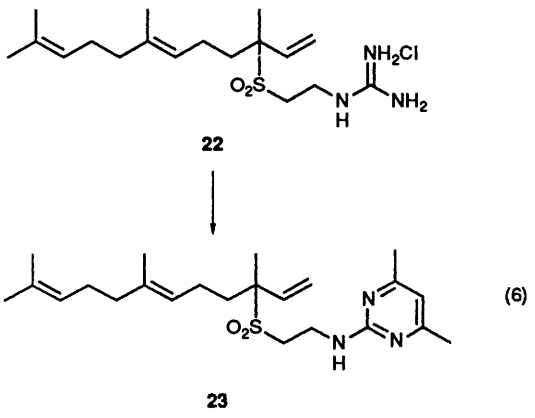
Treatment of sulfone **18** with guanidine in 1,4-dioxane resulted in rapid elimination of the acetoxy group, and the vinyl sulfone **21** was observed by TLC analysis of the reaction mixture. This vinyl sulfone **21** was identified using an authentic sample which was the intermediate of our previous synthesis.[3] The addition of guanidine to the vinyl sulfone **21** was relatively slow; therefore, the starting material **18** should be added slowly to the solution having a large excess of guanidine.* This process prevents the reaction between agelasidine A **1** and any unchanged vinyl sulfone **21**.



Scheme 3

The usual work-up of the reaction mixture gave crude agelasidine A **1**, which was purified by silica gel chromatography. It is well known that protonated guanidine behaves as an ion exchanger during various operations;[9] therefore, the resulting agelasidine A **1** was dissolved in ethyl acetate and treated with saturated aq. sodium chloride to provide the hydrogen chloride

* To the best of our knowledge, this is the first example of the addition of guanidine to a vinyl sulfone.



(6)

salt of agelasidine A, **22**, in 70% yield from sulfone **18**.* The ^{1}H NMR (200 MHz; CD_3OD) and TLC behaviour of synthetic agelasidine A hydrochloride **22** was indistinguishable from that of natural agelasidine A hydrochloride.

Nakamura reported colourless crystals of agelasidine A hydrochloride,[1] and Faulkner isolated agelasidine A as an unstable yellow oil.[2] In our case, several attempts at crystallization of agelasidine A hydrochloric acid salt **22** failed, and a considerable amount of agelasidine A was lost due to its instability. These confusing results may be due to the unfavourable properties of the guanidine moiety. Finally, this was clarified by conversion of agelasidine A hydrochloride **22** into the pyrimidine derivative **23** by treatment with acetylacetone in pyridine at 110 °C [eqn. (6)]. ^{1}H as well as ^{13}C NMR results of synthetic pyrimidine derivative **23** were in good agreement with those reported in the literature.[1]

Experimental

General Details.—M.p.s were determined on a oil-bath apparatus and are uncorrected. IR spectra were recorded using a Shimadzu IR-420 infrared spectrometer for chloroform solutions unless otherwise stated. ^{1}H NMR spectra were determined using a JEOL FX-200 spectrometer operating at 200 MHz unless otherwise stated. The other spectrometer used was a JEOL EX 270. ^{13}C NMR spectra were determined using the JEOL-90 instrument, operating at 22.50 MHz unless otherwise stated; the JEOL EX 270 instrument operating at 67.80 MHz was also used. Dilute solutions in deuteriochloroform were used throughout unless stated otherwise with tetramethylsilane as the internal standard. All *J*-values are in Hz. High-resolution mass spectra were recorded on a JMS-DX 705L instrument by S. Kitamura (Nagoya University).

DMF were dried over molecular sieves 4 Å. Pyridine was dried over potassium hydroxide.

2-Thioacetylethyl Acetate **12**.—Acetic anhydride (200 cm^3) was added *via* dropping funnel to a solution of 2-mercaptoethanol (47.9 g, 0.61 mol) in pyridine (300 cm^3) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was poured into water. The separated aqueous layer was extracted with diethyl ether. The combined organic phase was washed successively with water, saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was purified by Kugelrohr distillation (110–120 °C; 20 mmHg, water aspirator) to give title compound **12** (83.8 g, 80%), $\nu_{max}(CHCl_3)$/cm^{-1} 1720 (AcS) and 1670 (AcO); δ_H(200 MHz; $CDCl_3$) 2.06 (3 H, s, Ac), 2.36 (3 H, s, Ac), 3.13 (2 H, t, *J* 7, CH_2SAc) and 4.17 (2 H, t, *J* 7, CH_2OAc).

3-(2-Acetoxyethylsulfonyl)-3,7-dimethylocta-1,6-diene **15**.—A solution of thioacetate **12** (32.81 g, 203 mmol) in acetic anhydride (18.5 cm^3, 196 mmol) was cooled to −20 °C, and was then treated with sulfuryl chloride (31 cm^3, 390 mmol). The cooling bath was removed, and the mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure (water aspirator) for 15 min to remove acetyl chloride to give the sulfinyl chloride **13** (36.7 g, 91%). Distillation of this sulfinyl chloride **13** caused decomposition; therefore, this sulfinyl chloride was used for further reaction without purification. This sulfinyl chloride **13** could be stored in a refrigerator at −20 °C for several days and could be used for subsequent reactions.

To a solution of geraniol (1 g, 6.5 mmol) in pyridine (30 cm^3) cooled to −20 °C was added sulfinyl chloride **13** (1.93 g, 1.46 mmol). The reaction mixture was stirred at −20 °C for 1 h. TLC analysis showed the absence of geraniol. The reaction mixture was diluted with diethyl ether, and was poured into water. The aqueous layer was extracted with three portions of diethyl ether. The combined organic extracts were washed successively with 1 mol dm^{-3} hydrochloric acid, saturated aq. sodium hydrogen carbonate, and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a residual oil (2.01 g). Purification by silica gel chromatography with diethyl ether–hexane (2:1) provided allylic sulfinate **14** (1.76 g, 94%). This allylic sulfinate was immediately dissolved in DMF (35 cm^3), and the resulting solution was heated under argon at 140 °C for 25 min. The reaction mixture was poured into water, and the aqueous layer was extracted with three portions of diethyl ether. The combined extracts were washed successively with two portions of water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by silica gel chromatography with diethyl ether–hexane (1:3 followed by 1:1) provided the *title allylic sulfone* **15** (1.4 g, 79%), m.p. 28 °C (from diethyl ether–hexane) (Found: C, 58.3; H, 8.4. $C_{14}H_{24}O_4S$ requires C, 58.31; H, 8.39%); $\nu_{max}(CHCl_3)$/cm^{-1} 1730 (AcO), 1130 and 940; δ_H(200 MHz; $CDCl_3$) 1.50 (3 H, s, $MeCSO_2$), 1.58 (3 H, s, Me_2C=H), 1.68 (3 H, s, Me_2C=CH), 2.07 (3 H, s, AcO), 3.25 (2 H, t, *J* 6, SO_2CH_2), 4.50 (2 H, t, *J* 6, AcOCH_2), 5.09 (1 H, br, Me_2C=C*H*), 5.40 (1 H, d, *J* 17, C=CH_2*trans*), 5.53 (1 H, d, *J* 10, C=CH_2*cis*) and 6.00 (1 H, dd, *J* 17 and 10, CC*H*CH_2).

3-(2-Acetoxyethylsulfonyl)-3,7,11-dodeca-1,6,10-triene **18**.—To a solution of farnesol **16** (1 g, 4.5 mmol) in pyridine (30 cm^3) cooled to −20 °C was added sulfinyl chloride **13** (0.89 g, 4.5 mmol). The reaction mixture was stirred at −20 °C for 35 min, and TLC analysis showed the absence of farnesol. The reaction mixture was diluted with diethyl ether, and poured into water. The aqueous layer was extracted with three portions of diethyl ether. The combined organic extracts were washed successively with 1 mol dm^{-3} hydrochloric acid, saturated aq. sodium hydrogen carbonate, and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford a residual oil (1.70 g). Purification by silica gel chromatography with diethyl ether–hexane (2:1) provided allylic sulfinate **17** (1.60 g, 99%). This sulfinate **17** was immediately dissolved in DMF (78 cm^3), and the solution was heated under argon at 140 °C for 35 min. The reaction mixture was poured into water, and the aqueous layer was extracted with three portions of diether ether. The combined extracts were washed successively with two portions of water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel

* We thank Dr. H. Iio (Osaka City University) for detailed information on these procedures (personal communication). See the references; H. Iio, K. Asao and T. Tokoroyama, *J. Chem. Soc., Chemical Commun.*, 1985, 774; K. Asao, Ph.D. Thesis, Osaka City University, 1988.

chromatography with diethyl ether–hexane (1:3 followed by 1:1) to provide allylic sulfone **18** (1.25 g, 78%) and by-product **19** (0.064 g, 4%) as an inseparable mixture of *Z*- and *E*-isomers. M.p. 35 °C (from diethyl ether–hexane) (Found: C, 63.9; H, 9.0. $C_{19}H_{32}O_4S$ requires C, 64.02; H, 9.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (AcO), 1130 and 940; δ_H(200 MHz; $CDCl_3$) 1.51 (3 H, s, $MeCSO_2$), 1.57 (3 H, s, Me_2C=CH), 1.60 (3 H, s, Me_2C=CH), 1.68 (3 H, s, Me_2C=CH), 1.9–2.1 (8 H), 2.02 (3 H, s, AcO), 3.26 (2 H, t, *J* 6, SO_2CH_2), 4.51 (2 H, t, *J* 6, $AcOCH_2$), 5.0–5.15 (2 H, Me_2C=C*H*), 5.40 (1 H, d, *J* 18, C=CH*trans*), 5.52 (1 H, d, *J* 11, C=CH*cis*) and 6.05 (1 H, dd, *J* 18 and 11, CC*H*=CH_2).

Agelasidine A Hydrochlorid **22**.—Sodium hydride (5.6 g, 0.14 mol; 60% dispersion in mineral oil) was washed with three portions of hexane, and was then treated with ethanol (100 cm^3) at 0 °C under argon. To this solution of sodium ethoxide in ethanol was added guanidine hydrochloride (14 g, 0.146 mol) portionwise at room temperature. After the mixture had been stirred for 1 h, a white precipitate was observed. The solution was filtered on Super Cell, and was then concentrated under reduced pressure. After two azeotropic removals of traces of ethanol with benzene, the resulting guanidine was immediately dissolved in a mixture of 1,4-dioxane (50 cm^3) and water (50 cm^3). To this solution was added a solution of compound **18** in dioxane through a dropping funnel at 0 °C during 3 h. The cooling bath was removed, and the mixture was stirred overnight. Dioxane was evaporated off, and the aqueous layer was neutralized with 6 mol dm^{-3} hydrochloric acid (~60 cm^3) and then extracted with three portions of dichloromethane. The combined organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on silica gel with ethyl acetate followed by dichloromethane–methanol (9:1) as eluent provided agelasidine A (832 mg).

This agelasidine A was dissolved in ethyl acetate and treated with saturated aq. sodium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic phase was dried (Na_2SO_4), and concentrated under reduced pressure to afford agelasidine A hydrogen chloride salt **22** (770 mg, 70%).

Several attempts at crystallization of agelasidine A hydrochloric salt **22** failed, and considerable amounts of agelasidine A were lost due to its instability;[2] $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–3200, 1660, 1280 and 1130 [lit.,[2] $\nu(CHCl_3)/cm^{-1}$ 3450, 1650, 1290 and 1140].

For the assignment of NMR data of agelasidine A hydrochloric acid salt **22** and the pyrimidine derivative of agelasidine A, compound **23**, see ref. 1, δ_H(270 MHz; CD_3OD) 1.52 (3 H, s, $MeCSO_2$), 1.59 (3 H, s, Me_2C=CH), 1.59 (3 H, s, Me_2C=CH), 1.66 (3 H, s, Me_2C=CH), 3.71 (2 H, t, *J* 6.6, $NHCH_2$), 5.0–5.2 (2 H, Me_2C=C*H*), 5.49 (1 H, d, *J* 17.5, C=CH*trans*), 5.57 (1 H, d, *J* 11, C=CH*cis*), 5.57 (1 H, d, *J* 11) and 6.01 (1 H, dd, *J* 17.5 and 11, CC*H*=CH_2) [lit.,[2] δ_H(360 MHz; CD_3OD) 1.52 (3 H, s), 1.59 (3 H, s), 1.59 (3 H, s), 1.66 (3 H, s), 3.28 (2 H, t, *J* 6), 3.71 (2 H, t, *J* 6), 5.07 (1 H, br t, *J* 6.5), 5.13 (1 H, br t, *J* 6.5), 5.49 (1 H, dd, *J* 17.5), 5.59 (1 H, d, *J* 11) and 6.0 (1 H, dd, *J* 17.5 and 11)]; δ_H(270 MHz; $CDCl_3$) 1.51 (3 H, s, $MeCSO_2$), 1.58 (3 H, s, Me_2C=CH), 1.60 (3 H, s, Me_2C=CH), 1.68 (1 H, s), 2.74 (1 H, br s, NH), 3.31 (2 H, br s, SO_2CH_2), 3.79 (2 H, br s, $NHCH_2$), 5.0–5.12 (2 H, Me_2C=C*H*), 5.42 (1 H, d, *J* 17.5, C=CH*trans*), 5.54 (1 H, d, *J* 10.9, C=CH*cis*), 5.93 (1 H, dd, *J* 17.5 and 10.9, CC*H*=CH_2), 7.19 (4 H, br s, NH) and 7.87 (1 H, br s, NH); [lit.,[2] δ_H(360 MHz; $CDCl_3$) 1.50 (3 H, s), 1.57 (3 H, s), 1.59 (3 H, s), 1.68 (1 H, s), 2.56 (1 H, br s), 3.31 (2 H, br s), 3.78 (2 H, br s), 5.09 (2 H, br s), 5.44 (1 H, d, *J* 17.6), 5.56 (1 H, d, *J* 10.8), 5.94 (1 H, dd, *J* 17.6 and 10.8), 7.15 (2 H, br s) and 7.74 (1 H, br s)]; δ_C(67.80 MHz; $CDCl_3$) 16.0, 16.1, 17.7, 22.0, 25.7, 26.7, 31.5, 35.0, 39.7, 45.9, 68.3, 121.4, 121.8, 122.6, 124.2, 131.5, 134.7, 136.5 and 157.6 [lit.,[2] δ_C(50 MHz; $CDCl_3$) 15.9, 16.1, 17.7, 22.0, 25.7, 26.6, 31.4, 34.9, 39.7, 45.8, 68.2, 121.7, 122.5, 124.1, 132.2, 134.6, 136.4 and 157.4].

Pyrimidine Derivative of Agelasidine A, Compound **23**.—A solution of agelasidine A (167 mg, 0.147 mmol) in a mixture of acetylacetone (1.5 cm^3) and pyridine (3 cm^3) was heated at 100 °C for 12 h. The solvent was removed under reduced pressure, and the resulting residue was purified by preparative TLC to afford the pyrimidine **23** (56 mg, 28%), m.p. 73 °C (lit.,[3] 52 °C) (from diethyl ether–hexane) (Found: C, 65.9; H, 8.9; N, 10.1. $C_{23}H_{37}N_3O_2S$ requires C, 65.84; H, 8.89; N, 10.02%); δ_H(200 MHz; C_6D_6) 1.20 (3 H, s), 1.49 (3 H, s), 1.57 (3 H, s), 1.69 (3 H, s), 2.09 (6 H, s), 2.94 (2 H, t, *J* 6), 3.92 (2 H, q, *J* 6), 4.90 (1 H, d, *J* 18), 4.99 (1 H, d, *J* 11), 5.05 (1 H, br t, *J* 6), 5.87 (1 H, dd, *J* 18 and 11) and 5.90 (1 H, s); [lit.,[1] δ_H(270 MHz; C_6D_6) 1.19 (3 H, s), 1.50 (3 H, br s), 1.57 (3 H, br s), 1.69 (3 H, br s), 2.00 (2 H, m), 2.02 (2 H, m), 2.09 (6 H, s), 2.13 (2 H, m), 2.92 (2 H, t, *J* 7), 3.91 (2 H, q, *J* 7), 4.90 (1 H, d, *J* 17), 4.98 (1 H, d, *J* 11), 5.57 (1 H, br t, *J* 7), 5.87 (1 H, dd, *J* 17 and 11) and 5.90 (1 H, s); δ_C(25.50 MHz; C_6D_6) 15.9, 16.0, 17.7, 22.5, 23.8, 25.8, 27.1, 32.3, 35.2, 40.0, 46.9, 67.6, 109.9, 119.5, 123.7, 124.8, 131.3, 135.9, 136.6, 162.5 and 167.5 [lit.,[1] δ_C(22.50 MHz; C_6D_6) 16.0, 16.0, 17.7, 22.2, 23.9, 25.6, 26.7, 32.0, 35.0, 39.7, 46.7, 67.9, 110.1, 120.1, 123.0, 124.3, 131.3, 136.0, 136.2, 161.9 and 167.4].

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