Synthesis and absolute configuration of stellettadine A, a bisguanidinium alkaloid isolated from a marine sponge *Stelletta* sp.

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Received (in Cambridge, UK) 2nd January 2001, Accepted 16th February 2001
First published as an Advance Article on the web 19th March 2001

Both the enantiomers of stellettadine A (**1**), a bisguanidinium alkaloid isolated from a marine sponge *Stelletta* sp., are synthesized by starting from (*S*)- and (*R*)-citronellal (**2**). The absolute configuration of naturally occurring **1** is established as *R*.

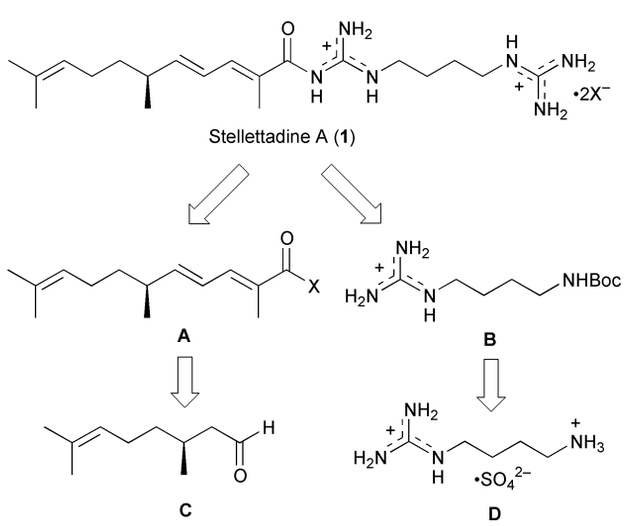
Introduction

In 1996, stellettadine A (**1**) was isolated from a marine sponge *Stelletta* sp. as a metamorphosis-inducing compound for ascidian *Halocynthia roretzi* larvae by Fusetani and his co-workers.[1] This structurally unique alkaloid consists of norsesquiterpene and arcaine (1,4-diguanidinobutane) units. Fusetani and his co-workers have also reported the isolation of four structurally related marine natural products, *viz*. stellettamide A (**12**, Scheme 3),[2] stellettazole A,[3] and bistellettadines A[4] and B,[4] which were also isolated from marine sponges (*Stelletta* sp.) We were interested in the unique structure and bioactivity of **1** and undertook its synthesis as part of our work to prepare terpenoidal marine natural products.[5] Herein we describe the first synthesis of **1** and the confirmation of its absolute configuration in full detail.[6]

Results and discussion

Synthetic plan

Our synthetic plan for **1** is very simple as shown in Scheme 1. A



Scheme 1 Structure and retrosynthetic analysis of stellettadine A (**1**).

problematic step in our synthesis is the coupling of **A** (≡**5**) and **B** (≡**7**). This is expected to be difficult, because, to the best of our knowledge, acylation of a guanidino group with a higher fatty acid has never been reported. We, however, dare adopt this strategy in view of its overall efficiency. The intermediate **A** may be synthesized by starting from citronellal (**C**) [≡(*S*)-**2**]. For the preparation of **B**, we plan to use agmatine sulfate (**D**) (≡**6**). This synthetic plan was realized as follows.

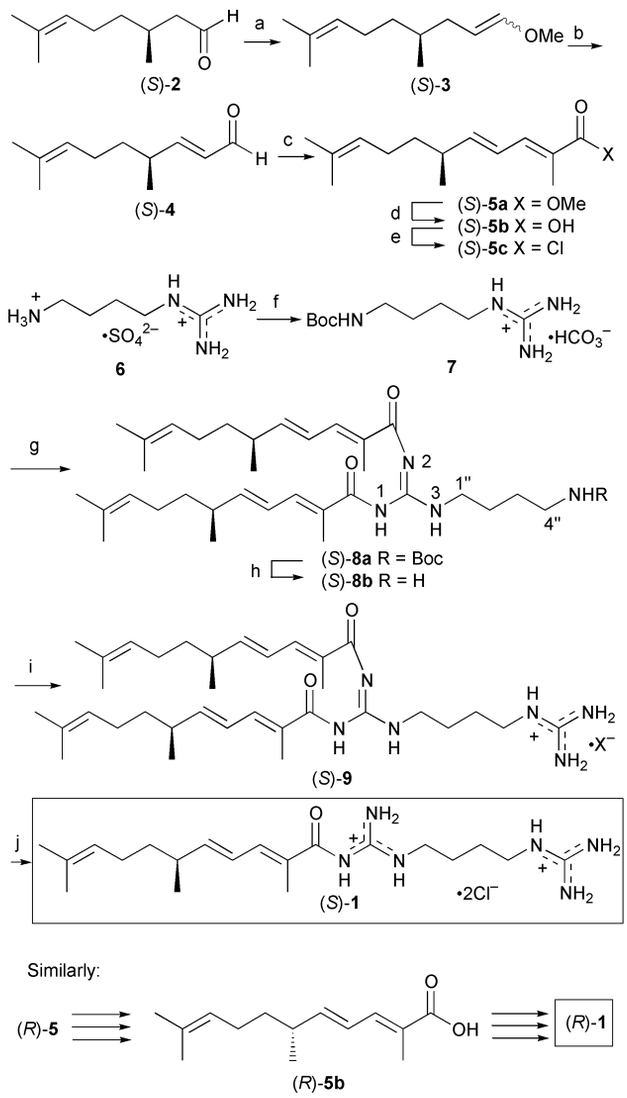
Synthesis of stellettadine A

The starting (*S*)-citronellal (**2**, >97% ee) was converted to (*S*)-**4** according to Takayama's methodology,[7] which employed the Wittig reaction with Ph_3P=CHOMe followed by $Pd(OAc)_2$-mediated oxidation (Scheme 2). The resulting enal (*S*)-**4** was directly subjected to the next Wittig reaction with Ph_3P=C(Me)CO_2Me to afford (*S*)-**5a** in good yield with high *E*/*Z* selectivity. Although the geometrical purities of the resulting (*S*)-**5a** were as high as 96% (at C-2) and >99% (at C-4), highly pure (2*E*,4*E*)-**5a** was obtained in 86% yield after careful chromatographic purification. We also estimated the enantiomeric purity of (*S*)-**5a** to be >97% ee based on HPLC analysis (*vide infra*). The ester (*S*)-**5a** was then converted to the corresponding carboxylic acid (*S*)-**5b** and thence to the acyl chloride (*S*)-**5c**.

The mono-Boc protection of agmatine sulfate **6** was achieved by treatment with Boc_2O to give acyl acceptor **7**.[8] The next step, coupling of **5b** or **5c** with **7**, was as problematic as we had feared. In spite of all our efforts, no acylated product could be obtained by the conventional procedures as follows, 1) acylation employing mixed anhydride or other activated esters; 2) conventional acylation with acyl chloride; 3) dehydrative condensation promoted by DCC, *etc*. However, we finally found that the conditions reported by Ottenheijm[9] and Moynihan[10] [*i.e.*, **6**, trimethylsilyl chloride (TMSCl), diisopropylethylamine (DIPEA) in CH_2Cl_2, then **5c**, DIPEA] gave the desired acylated product (*S*)-**8a** in 62% yield. (All our efforts to obtain the monoacylated adduct as the major product were unsuccessful.) The remaining problem to be solved was clarification of the acylated positions. Careful analysis of various NMR spectra revealed the acylated positions to be N^1 and N^2, while those of the reported acylated guanidines[9,10] were N^1 and N^3. It was for this reason that the ^{1}H–^{1}H COSY cross-peak between 1″-H_2 (at δ 3.54) and 3-H (at δ 9.37) was observed as clearly as one between 4″-H_2 (at δ 3.16) and 4″-NH (at δ 4.56).

Removal of the Boc protecting group of (*S*)-**8a** to give (*S*)-**8b** was followed by guanylation by Mosher's procedure,[11] NH_2C(=NH)SO_3H, Et_3N in MeOH, to give (*S*)-**9** in good yield. Treatment of (*S*)-**9** with methanolic KOH effected selective removal of one of the acyl groups to give the target compound (*S*)-stellettadine A **1** in 67% yield together with recovered (*S*)-**5a**. In this final step, we prepared (*S*)-**1** as its dihydrochloride because Professors Fusetani and Tsukamoto informed us that naturally occurring **1** is actually the dihydrochloride, and that stellet-

DOI: 10.1039/b100206f

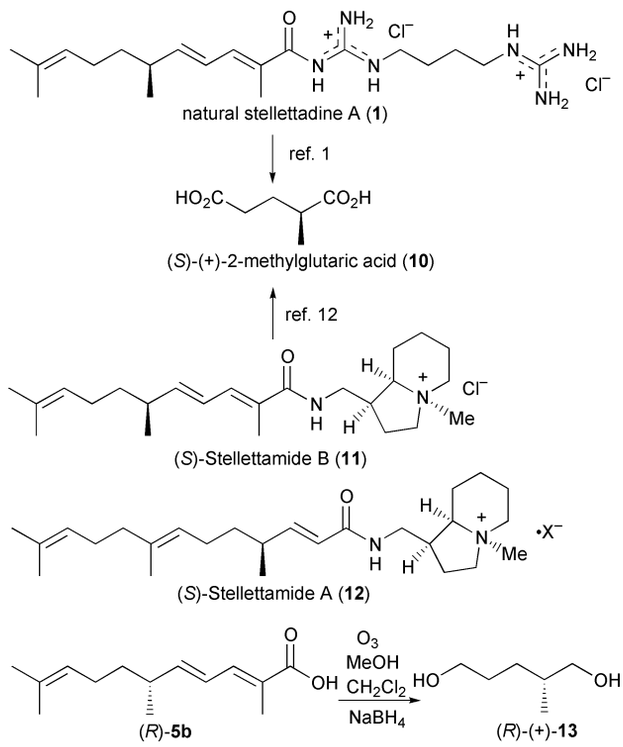


Scheme 2 Synthesis of stellettadine A (**1**). *Reagents (and yields)*: (a) $Ph_3P(Cl)CH_2OMe$, PhLi, Et_2O; (b) $Pd(OAc)_2$, $Cu(OAc)_2$, aq. $NaHCO_3$, MeCN (48%, 2 steps); (c) $Ph_3P{=}C(Me)CO_2Me$, benzene (86%); (d) aq. NaOH, MeOH, THF (87%); (e) $(COCl)_2$, 2-methylbut-2-ene, CH_2Cl_2 (quant.); (f) Boc_2O, aq. $NaHCO_3$, 1,4-dioxane (68%); (g) TMSCl, DIPEA, CH_2Cl_2; then **5c**, DIPEA (62%); (h) TsOH, 2-methylbut-2-ene, MeOH (84%); (i) $NH_2C(=NH)SO_3H$, MeOH; (j) KOH, MeOH; then aq. HCl (67%, 2 steps).

tamide B (**11**, Scheme 3), one of the structurally related metabolites of the *Stelletta* sponge, was shown to be the hydrochloride.[12] The overall yield was 13% based on (*S*)-**2** in 9 steps. In the same manner, (*R*)-citronellal (*R*)-**2** was converted to (*R*)-**1**. The various spectra of synthetic (*S*)- and (*R*)-**1** were in good accord with those of the naturally occurring **1**. However, there was a disagreement with regard to the sign of its specific rotation as follows. The rotation values of synthetic (*S*)- and (*R*)-**1** were $[a]_D^{25}$ +39.4 (*c* 1.01 in MeOH) and $[a]_D^{27}$ −45.6 (*c* 1.37 in MeOH),† respectively, although that of natural **1**, which was reported to be *S*, was $[a]_D^{24}$ −32.8 (*c* 1.00 in MeOH).[1] These results indicated that the absolute configuration of natural **1** might be *R*.

Confirmation of the absolute configuration of natural stellettadine A

Originally, the absolute configuration of natural **1** was reported as *S* on the basis of oxidative degradation of **1** to give (*S*)-(+)-2-methylglutaric acid[1] **10** (Scheme 3). In 1997, Shin and his co-workers isolated and identified stellettamide B **11** as a new metabolite of a Korean sponge of the same genus *Stelletta*.[12] They executed oxidative degradation of **11** and also obtained (*S*)-(+)-**10**. Moreover, it should be added that the absolute configuration of a related metabolite, stellettamide A **12** was reported as *S* by an enantioselective synthesis.[13] The point was that all of the absolute configurations reported for **1** and structurally related metabolites (**11** and **12**) were *S*, even though the signs of specific rotation of our synthetic (*S*)- and (*R*)-**1** suggested that natural **1** should possess the *R* configuration. In order to solve this problem, we first confirmed the absolute configurations of our synthetic samples unambiguously. Thus, a chiral intermediate (*R*)-**5b** was degraded by ozonolysis followed by reductive work-up with $NaBH_4$ to give (+)-2-methylpentane-1,5-diol **13** (73%), $[a]_D^{26}$ +10.7 (*c* 1.68 in Et_2O). The specific rotation of (*S*)-**13** was recorded as $[a]_D^{25}$ −10.0 (*c* 0.025 in Et_2O)[14] or $[a]_D$ −8.5 (*c* 2 in Et_2O).[15] Our degradation product was therefore (*R*)-**13**, and the acid **5b** was indeed the *R*-isomer. For further decisive discussion, we then measured CD spectra of our synthetic enantiomers of **1** and naturally occurring **1** which was kindly supplied by Professor Fusetani. Although a negative Cotton effect at 283 nm (MeOH) was observed in the CD spectrum of natural (−)-**1**, a positive and a negative one were observed in those of synthetic (*S*)-(+)- and (*R*)-(−)-**1**, respectively (*vide infra*). These results made it possible to revise the absolute configuration of natural stellettadine A (**1**) to be *R*, not *S* as originally reported.[1]



Scheme 3 Determination of the absolute configuration of **1** and related compounds.

Conclusions

The first and stereoselective synthesis of (*S*)- and (*R*)-stellettadine A **1**, a new acylated bisguanidinium alkaloid isolated from a marine sponge *Stelletta* sp., was achieved by starting from citronellal **2** and agmatine sulfate **6**. The absolute configuration of naturally occurring stellettadine A **1** was established as *R* unambiguously.

Experimental

The mp of **7** was uncorrected. IR spectra were measured on a JASCO A-102 spectrometer or a JASCO FT/IR-410 spec-

† Throughout this paper, $[a]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

trometer. ^{1}H NMR spectra were recorded at 90 MHz on a JEOL JNM-EX 90A spectrometer, at 300 MHz on a JEOL JNM-AL 300 spectrometer, at 400 MHz on a JEOL JNM-LA 400 spectrometer and at 500 MHz on a JEOL JNM-LA 500 spectrometer. The peak for $SiMe_4$, $CDCl_3$ (at δ 7.26) or DMSO-d_6 (at δ 2.49) was used for the internal standard. Chemical shifts are reported in ppm on the δ-scale and J-values are given in Hz. ^{13}C NMR spectra were recorded at 126 MHz on a JEOL JNM-LA 500 spectrometer. The peak for $CDCl_3$ (at δ_C 77.0) or DMSO-d_6 (at δ_C 39.5) was used for the internal standard. Optical rotations were taken with a JASCO DIP-1000 polarimeter. Optical refractivities were measured on a ATAGO Abe refractometer 1T. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734 unless otherwise stated. TLC analyses were performed on Merck silica gel plates 60F–254.

(2*E*,4*S*)-4,8-Dimethylnona-2,7-dienal (*S*)-4

To a stirred solution of $Ph_3P(Cl)CH_2OMe$ (2.44 g, 7.12 mmol) in dry Et_2O (20 cm^3) was added PhLi (1.04 mol dm^{-3} in cyclohexane; 6.5 cm^3, 6.8 mmol) dropwise at −15 °C under Ar. After having been stirred at 0 °C for 15 min, a solution of (*S*)-**2** ($[a]_D^{23}$ −16.3; >97% ee; Takasago; 0.90 g, 5.83 mmol) in dry Et_2O (5 cm^3) was added at −15 °C. The resulting mixture was stirred at room temperature for 15 min, quenched with saturated aq. NH_4Cl, and extracted with pentane. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, and dried ($MgSO_4$). After careful removal of Et_2O and pentane under reduced pressure, the resulting solution was filtered through neutral Al_2O_3. The combined filtrate and washings (with pentane) were carefully concentrated under reduced pressure to give a solution of the *crude* vinyl ether (*S*)-**3** in cyclohexane (≈7 cm^3). Because of the volatility of **3**, this solution was directly used for the next step without concentration and purification.

To a stirred suspension of $Pd(OAc)_2$ (0.73 g, 3.25 mmol) and $Cu(OAc)_2$ (1.18 g, 6.50 mmol) in MeCN (40 cm^3) and 5% aq. $NaHCO_3$ (3 cm^3) was added a solution of (*S*)-**3** in cyclohexane (≈7 cm^3) at 0 °C. After having been stirred at room temperature overnight, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with Et_2O. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the aldehyde (*S*)-**4** (463 mg, 48% in 2 steps) as a colorless oil, n_D^{23} 1.4758; $[a]_D^{24}$ +56.7 (*c* 1.04 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2740w (CHO), 1695s (C=O), 1635m (C=C); δ_H(90 MHz; $CDCl_3$) 1.10 (3H, d, *J* 6.8, 4-Me), 1.20–1.60 (2H, m, 5-H_2), 1.58 and 1.68 (total 6H, each s, Me_2C=C), 1.98 (2H, br q, *J* 7.3, 6-H_2), 2.43 (1H, m, 4-H), 5.06 (1H, br t, *J* 7.1, 7-H), 6.07 (1H, ddd, *J* 15.8, 7.7 and 0.9, 2-H), 6.75 (1H, dd, *J* 15.8 and 7.5, 3-H), 9.51 (1H, d, *J* 7.7, CHO). This was employed in the next step without further purification.

(2*E*,4*R*)-4,8-Dimethylnona-2,7-dienal (*R*)-4

In the same manner as described above, (*R*)-**2** ($[a]_D^{23}$ +15.2; >97% ee; Takasago; 879 mg, 5.70 mmol) was converted to the aldehyde (*R*)-**4** (575 mg, 61% in 2 steps) as a colorless oil, n_D^{23} 1.4745; $[a]_D^{23}$ −57.4 (*c* 1.11 in $CHCl_3$). The IR and ^{1}H NMR spectra were identical with those of (*S*)-**4**. This was employed in the next step without further purification.

Methyl (2*E*,4*E*,6*S*)-2,6,10-trimethylundeca-2,4,9-trienoate (*S*)-5a

A solution of (*S*)-**4** (2.86 g, 17.2 mmol) and Ph_3P=$CMeCO_2Me$ (13.3 g, 38.2 mmol) in benzene (100 cm^3) was stirred under reflux for 1 h. The reaction mixture was diluted with hexane, washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude ester (*S*)-**5a**. The geometrical purities of the crude product (*S*)-**5a** were estimated to be 96% (at C-2) and >99% (at C-4), respectively, based on the ^{1}H NMR analysis. This crude ester (*S*)-**5a** was carefully chromatographed on SiO_2 to give the *pure ester* (*S*)-**5a** (3.51 g, 86%) as a colorless oil, n_D^{23} 1.5057 (Found: C, 76.30; H, 10.19. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.24%); $[a]_D^{19}$ +63.2 (*c* 0.97 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1715s (C=O), 1645m (C=C), 1610w (C=C); δ_H(300 MHz; $CDCl_3$) 1.03 (3H, d, *J* 6.6, 6-Me), 1.37 (2H, q, *J* 7.4, 7-H_2), 1.58 and 1.68 (total 6H, each s, Me_2C=C), 1.93 (3H, s, 2-Me), 1.94 (2H, m, 8-H_2), 2.29 (1H, septet, *J* 7.0, 6-H), 3.75 (3H, s, OMe), 5.08 (1H, br t, *J* 7.1, 9-H), 5.95 (1H, dd, *J* 15.0 and 8.1, 5-H), 6.29 (1H, dd, *J* 15.0 and 11.2 , 4-H), 7.16 (1H, d, *J* 11.2, 3-H).

Methyl (2*E*,4*E*,6*R*)-2,6,10-trimethylundeca-2,4,9-trienoate (*R*)-5a

In the same manner as described above, (*R*)-**4** (1.33 g, 8.00 mmol) was converted to the *ester* (*R*)-**5a** (1.76 g, 93%) as a colorless oil, n_D^{23} 1.5073 (Found: C, 76.04; H, 10.54. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.24%); $[a]_D^{26}$ −63.4 (*c* 1.09 in $CHCl_3$). The IR and ^{1}H NMR spectra were identical with those of (*S*)-**5a**.

Determination of the enantiomeric purities of (*S*)- and (*R*)-5a

The enantiomeric purities of the synthesized esters (*S*)- and (*R*)-**5a** were estimated by HPLC analysis [column, Chiralcel® OD + Chiralcel® OD-H (4.6 mm × 250 mm, respectively); solvent, hexane; flow rate, 0.5 cm^3 min^{-1}; detection at 254 nm]: (*S*)-**5a** t_R/min 77.9 [98.8%, (*S*)-**5a**], 82.3 [1.2%, (*R*)-**5a**]. The enantiomeric purity of (*S*)-**5a** was estimated to be 97.6% ee. (*R*)-**5a** t_R/min 76.6 [1.5%, (*S*)-**5a**], 80.8 [98.5%, (*R*)-**5a**]. The enantiomeric purity of (*R*)-**5a** was estimated to be 97.0% ee.

(2*E*,4*E*,6*S*)-2,6,10-Trimethylundeca-2,4,9-trienoic acid (*S*)-5b

To a stirred solution of (*S*)-**5a** (3.45 g, 14.6 mmol) in THF (30 cm^3) and MeOH (30 cm^3) was added aq. NaOH (1.0 mol dm^{-3}; 30 cm^3, 30 mmol) at room temperature. After having been stirred overnight, the resulting mixture was acidified with dil. aq. HCl to pH 3 and extracted with ethyl acetate. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *acid* (*S*)-**5b** (2.80 g, 87%) as a colorless oil, n_D^{23} 1.5170 (Found: C, 75.72; H, 9.96. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%); $[a]_D^{20}$ +78.3 (*c* 1.08 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2900m (CO_2H), 1680s (C=O), 1640m (C=C), 1605m (C=C); δ_H(300 MHz; $CDCl_3$) 1.03 (3H, d, *J* 7.2, 6-Me), 1.38 (2H, q, *J* 7.2, 7-H_2), 1.59 and 1.69 (total 6H, each s, Me_2C=C), 1.94 (3H, s, 2-Me), 1.95 (2H, m, 8-H_2), 2.30 (1H, septet-like, *J* 7.1, 6-H), 5.08 (1H, t, *J* 7.1, 9-H), 6.01 (1H, dd, *J* 15.0 and 8.1, 5-H), 6.32 (1H, dd, *J* 15.0 and 11.1, 4-H), 7.28 (1H, d, *J* 11.1, 3-H).

(2*E*,4*E*,6*R*)-2,6,10-Trimethylundeca-2,4,9-trienoic acid (*R*)-5b

In the same manner as described above, (*R*)-**5a** (1.55 g, 6.56 mmol) was converted to the *acid* (*R*)-**5b** (1.28 g, 88%) as a colorless oil, n_D^{23} 1.5173 (Found: C, 75.86; H, 9.88. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%); $[a]_D^{24}$ −84.9 (*c* 1.12 in $CHCl_3$). The IR and ^{1}H NMR spectra were identical with those of (*S*)-**5b**.

(2*E*,4*E*,6*S*)-2,6,10-Trimethylundeca-2,4,9-trienoyl chloride (*S*)-5c

To a solution of (*S*)-**5b** (218 mg, 0.990 mmol) in dry CH_2Cl_2 (5 cm^3) were added 2-methylbut-2-ene (1 cm^3) and $(COCl)_2$ (0.119 cm^3, 1.39 mmol) under Ar. After having been stirred at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure to give the *crude acyl chloride*

(*S*)-**5c** (260 mg, quant.) as a pale yellow oil, ν_{max}(film)/cm^{-1} 1740s (C=O), 1630s (C=C), 1605m (C=C). This was employed in the next step without further purification.

(2*E*,4*E*,6*R*)-2,6,10-Trimethylundeca-2,4,9-trienoyl chloride (*R*)-5c

In the same manner as described above, (*R*)-**5b** (300 mg, 1.35 mmol) was converted to the crude acyl chloride (*R*)-**5c** (360 mg, quant.) as a pale yellow oil. The IR spectrum was identical with that of (*S*)-**5c**. This was employed in the next step without further purification.

4-(*tert*-Butoxycarbonylamino)butylguanidinium hydrogen carbonate 7

To a stirred solution of **6** (1.00 g, 4.38 mmol) in 10% aq. $NaHCO_3$ (8.5 cm^3) was added a solution of Boc_2O (0.95 cm^3, 4.8 mmol) in 1,4-dioxane (9 cm^3) at −10 °C. After having been stirred at room temperature overnight, the reaction mixture was extracted with Bu″OH. The extract was washed successively with water and brine, and concentrated under reduced pressure. The residue was chromatographed on Al_2O_3 to give the guanidine **7** (870 mg, 68%) as a colorless solid, mp 126–129 °C (lit.,[8] 128–130 °C) (Found: C, 45.32; H, 8.89; N, 20.67. $C_{11}H_{24}N_4O_5$ requires C, 45.19; H, 8.28; N, 19.17%); ν_{max}(Nujol)/cm^{-1} 3400m (N–H), 3270s (N–H), 3200s (N–H), 1695s (C=O), 1660s (HNC=O), 1615s (HNC=O), 1540s (HNC=O); δ_H(400 MHz; DMSO) 1.34 (9H, s, Bu^t), 1.38 (4H, br s, 2- and 3-H_2), 2.88 (2H, q-like, *J* 5.6, 4-H_2), 3.07 (2H, q-like, *J* 5.6, 1-H_2), 6.83 (1H, t, *J* 5.6, NHCO), 7.87 (1H, t, *J* 5.6, 1-NH), 6.90–7.65 (4H, m, 2 × NH_2) [Found: (positive HRFAB-MS) $(M - HCO_3)^+$ 231.1804. $C_{10}H_{23}N_4O_2$ requires *m*/*z* 231.1821].

(2′*E*,4′*E*,6′*S*)-3-[4″-(*tert*-Butoxycarbonylamino)butyl]-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*S*)-8a

To a stirred suspension of **7** (115 mg, 0.393 mmol) in dry CH_2Cl_2 (5 cm^3) were added DIPEA (0.180 cm^3, 1.06 mmol) and TMSCl (0.130 cm^3, 1.03 mmol) at room temperature under Ar, and the reaction mixture was stirred at 40 °C for 1 h. After cooling of the mixture to 0 °C, DIPEA (0.180 cm^3, 1.06 mmol) was added followed by a solution of (*S*)-**5c** (260 mg, ≈0.99 mmol) in dry CH_2Cl_2 (5 cm^3). After having been stirred at 40 °C for 4 h, the reaction mixture was quenched with water and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give *compound* (*S*)-**8a** [197 mg, 62% in 2 steps based on (*S*)-**5b**] as a colorless oil, n_D^{24} 1.5167 (Found: C, 71.44; H, 9.57; N, 8.52. $C_{38}H_{62}N_4O_4$ requires C, 71.43; H, 9.78; N, 8.77%); $[\alpha]_D^{23}$ +87 (*c* 0.76 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3290m (N–H), 1710s (C=O), 1660s (C=O), 1625s (HNC=O), 1600s (HNC=O), 1570s (HNC=O); δ_H(400 MHz; $CDCl_3$) 1.03 and 1.05 (total 6H, each d, *J* 6.8 and 6.6, 6′-Me), 1.38 (4H, m, 7′-H_2), 1.42 (9H, s, Bu^t), 1.50–1.70 (4H, m, 2″- and 3″-H_2), 1.57 and 1.67 (total 12H, each s, Me_2C=C), 1.96 (4H, m, 8′-H_2), 1.98 and 2.02 (total 6H, each d, each *J* 1.0 , 2′-Me), 2.28 (2H, m, 6′-H), 3.16 (2H, q like, *J* 6.4, 4″-H_2), 3.54 (2H, q, *J* 6.4, 1″-H_2), 4.56 (1H, br s, $NHCO_2$), 5.07 (2H, m, 9′-H), 5.92 and 6.08 (total 2H, each dd, *J* 14.9 and 8.0, 5′-H), 6.33 (2H, m, 4′-H), 7.13 and 7.43 (total 2H, each d, *J* 11.0 and 11.5 respectively, 3′-H), 9.37 (1H, br s, NCN*H*CH_2), 13.82 (1H, br s, CONHCN) [Found: *m*/*z*, 639.4857 (HRFAB-MS) $(M + H)^+$. $C_{38}H_{63}N_4O_4$ requires *m*/*z* 639.4850].

(2′*E*,4′*E*,6′*R*)-3-[4″-(*tert*-Butoxycarbonylamino)butyl]-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*R*)-8a

In the same manner as described above, (*R*)-**5c** (0.36 g, ≈0.99 mmol) was converted to *compound* (*R*)-**8a** [202 mg, 64% in 2 steps based on (*R*)-**5b**] as a colorless oil, n_D^{23} 1.5163 (Found: C, 71.15; H, 9.50; N, 8.63. $C_{38}H_{62}N_4O_4$ requires C, 71.43; H, 9.78; N, 8.77%); $[\alpha]_D^{27}$ −88 (*c* 0.89 in $CHCl_3$). Its IR and ^{1}H NMR spectra were identical with those of (*S*)-**8a**.

(2′*E*,4′*E*,6′*S*)-3-(4″-Aminobutyl)-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*S*)-8b

To a solution of (*S*)-**8a** (35 mg, 55 μmol) in MeOH (2 cm^3) were added 2-methylbut-2-ene (1 cm^3) and *p*-TsOH (≈100 mg) at room temperature. After having been stirred at room temperature overnight, the reaction mixture was added to dil. aq. NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *amine* (*S*)-**8b** (25 mg, 84%) as a colorless oil, n_D^{24} 1.5175 (Found: C, 73.91; H, 10.42; N, 10.24. $C_{33}H_{54}N_4O_2$ requires C, 73.56; H, 10.10; N, 10.40%); $[\alpha]_D^{23}$ +96 (*c* 0.91 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3280m (N–H), 1660s (C=O), 1625s (HNC=O), 1605s (HNC=O), 1575s (HNC=O); δ_H(400 MHz; $CDCl_3$) 1.047 and 1.054 (total 6H, each d, *J* 6.6, 6′-Me), 1.38 (4H, m, 7′-H_2), 1.50–1.80 (6H, m, 2″- and 3″-H_2, and NH_2), 1.58 and 1.68 (total 12H, each s, Me_2C=C), 1.97 (4H, m, 8′-H_2), 1.98 and 2.03 (total 6H, each s, 2′-Me), 2.28 (2H, m, 6′-H), 2.76 (2H, t, *J* 7.1, 4″-H_2), 3.55 (2H, q-like, *J* 6.4, 1″-H_2), 5.09 (2H, m, 9′-H), 5.93 and 6.10 (total 2H, each dd, *J* 15.0 and 8.2, 5′-H), 6.34 (2H, m, 4′-H), 7.14 and 7.45 (total 2H, each d, *J* 11.0 and 11.4 respectively, 3′-H), 9.39 (1H, br s, NCN*H*CH_2), 13.84 (1H, br s, CONHC).

(2′*E*,4′*E*,6′*R*)-3-(4″-Aminobutyl)-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*R*)-8b

In the same manner as described above, (*R*)-**8a** (290 mg, 452 μmol) was converted to the *amine* (*R*)-**8b** (199 mg, 81%) as a colorless oil, n_D^{26} 1.5172; $[\alpha]_D^{27}$ −98 (*c* 0.83 in $CHCl_3$). Its IR and ^{1}H NMR spectra were identical with those of (*S*)-**8b** [Found: *m*/*z* 539.4329 (positive HRFAB-MS) $(M + H)^+$. $C_{33}H_{55}N_4O_2$ requires *m*/*z* 539.4325].

(2′*E*,4′*E*,6′*S*)-3-(4″-Guanidinobutyl)-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*S*)-9

To a stirred solution of (*S*)-**8b** (90 mg, 0.17 mmol) and $NH_2C(=NH)SO_3H$ (50 mg, 0.40 mmol) in MeOH (3 cm^3) were added three drops of NEt_3 at room temperature. After having been stirred at room temperature for 1 h, the reaction mixture was added to dil. aq. NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *guanidine* (*S*)-**9** [73 mg, 75% (calculated as free guanidine)] as a colorless oil, n_D^{24} 1.5189; $[\alpha]_D^{23}$ +81 (*c* 0.77 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3300 br s (N–H), 1680–1550 br s (C=O and N–H); δ_H(500 MHz; $CDCl_3$) 1.05 (6H, d, *J* 6.7, 6′-Me), 1.38 (4H, m, 7′-H_2), 1.62 and 1.68 (total 12H, each s, Me_2C=C), 1.76 (4H, m, 2″- and 3″-H_2), 1.96 (4H, m, 8′-H_2), 1.98 and 2.02 (total 6H, each s, 2′-Me), 2.29 (2H, m, 6′-H), 3.20 (2H, m, 4″-H_2), 3.57 (2H, m, 1″-H_2), 5.08 (2H, m, 9′-H), 5.92 and 6.07 (total 2H, each dd, *J* 15.0 and 8.0, 5′-H), 6.29 (2H, m, 4′-H), 6.80–7.30 (4H, br s, 2 × NH_2), 7.11 and 7.41 (total 2H, each d, *J* 11.0 and 11.3 respectively, 3′-H), 7.93 {1H, s, N*H*[$C(NH_2)_2$)]$^+$}, 9.29 (1H, br s, CONHCN*H*), 13.85 (1H, br s, CONHCN); δ_C(126 MHz; $CDCl_3$) 12.2, 12.8, 17.7, 19.9, 20.3, 24.9, 25.62, 25.64, 25.7, 25.8, 26.1, 26.2, 36.5, 36.7, 37.0, 37.1, 40.4, 41.3, 123.9, 124.1, 124.4, 125.1, 126.3, 131.3, 131.6, 133.0, 137.5, 138.7, 147.5, 151.0, 155.9, 157.6, 170.1, 180.6 [Found: (HRFAB-MS) $(M + H)^+$ 581.4537. $C_{34}H_{57}N_6O_2$ requires *m*/*z* 581.4543]. It was obvious that (*S*)-**9** existed as its guanidinium salt, and the most probable structure should be the corresponding sulfite. However, the nature of the counter-anion could not be clarified.

(2′*E*,4′*E*,6′*R*)-3-(4″-Guanidinobutyl)-1,2-bis(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine (*R*)-9

In the same manner as described above, (*R*)-**8b** (183 mg, 340 μmol) was converted to the *guanidine* (*R*)-**9** [163 mg, 83% (calculated as free guanidine)] as a colorless oil, n_D^{26} 1.5190; $[\alpha]_D^{27}$ −81 (*c* 0.55 in $CHCl_3$). Its IR and ^1H NMR spectra were identical with those of (*S*)-**9** [Found: (positive HRFAB-MS) $(M + H)^+$ 581.4551. $C_{34}H_{57}N_6O_2$ requires *m*/*z* 581.4543]. It was obvious that (*R*)-**9** existed as its guanidinium salt, and the most probable structure should be the corresponding sulfite. However, the nature of the counter-anion could not be clarified.

(2′*E*,4′*E*,6′*S*)-3-(4″-Guanidinobutyl)-1-(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine·2HCl (stellettadine A) (*S*)-1

To a stirred solution of (*S*)-**9** (29 mg, ≈50 μmol) in MeOH (1 cm^3) was added KOH (0.20 mol dm^{-3} in MeOH; 0.25 cm^3, 50 μmol) at 0 °C. After having been stirred at 10 °C for 4 h, the reaction mixture was acidified with dil. HCl (1.0 mol dm^{-3}; 0.15 cm^3, 0.15 mmol). The resulting mixture was directly subjected to column chromatography on ODS-SiO_2 (Chromatorex® ODS, 100–200 mesh, Fuji Silysia Chemical Ltd.) to give the *target compound* (*S*)-**1** [20 mg, 67% in 2 steps based on (*S*)-**8b**] as a colorless, highly viscous oil and the *ester* (*S*)-**5a** [11 mg, 70% recovery in 2 steps based on (*S*)-**8b**] as a colorless oil. (*S*)-**1**: $[\alpha]_D^{25}$ +39.4 (*c* 1.01 in CH_3OH); ν_{max}(KBr)/cm^{-1} 3330 br s (N–H), 3160 br s (N–H), 2970m, 1690s (C=O), 1665s (HNC=O), 1620s (HNC=O), 1590s (HNC=O), 1460m, 1385m, 1230m, 1095m, 970m; δ_H(500 MHz; DMSO) 1.00 (3H, d, *J* 6.8, 6′-Me), 1.35 (2H, q, *J* 7.0, 7′-H_2), 1.53 and 1.63 (total 6H, s, Me_2C=C), 1.53 (4H, m, 2″- and 3″-H_2), 1.92 (3H, s, 2′-Me), 1.92 (2H, m, 8′-H_2), 2.31 (1H, m, 6′-H), 3.13 (2H, m, 4″-H_2), 3.31 (2H, m, 1″-H_2), 5.07 (1H, t, *J* 7.0, 9′-H), 6.13 (1H, dd, *J* 15.0 and 8.0, 5′-H), 6.41 (1H, dd, *J* 15.0 and 11.0, 4′-H), 7.52 (1H, d, *J* 11.0, 3′-H), 6.80–7.60 (4H, m, 2 × NH_2), 7.95 (1H, t, *J* 5.4, CONHCN*H*), 8.97 (1H, br s, one of CONHCNH_2), 9.20 (1H, br s, one of CONHCNH_2), 9.68 [1H, br s, $CH_2NHC(NH_2)_2$], 11.62 (1H, br s, CONHCN); δ_C(126 MHz; DMSO) 12.2, 17.6, 19.8, 25.0, 25.3, 25.5, 25.7, 36.2, 36.4, 40.2, 40.5, 124.2, 124.3, 126.1, 130.9, 139.1, 150.8, 153.9, 157.0, 169.4 [Found: (HRFAB-MS) $[M - (2Cl + H)]^+$ 377.3058. $C_{20}H_{37}N_6O$ requires *m*/*z* 377.3029]. (*S*)-**5a**: $[\alpha]_D^{23}$ −63 (*c* 0.10 in $CHCl_3$). Spectral data of recovered (*S*)-**5a** were identical with those mentioned before.

(2′*E*,4′*E*,6′*R*)-3-(4″-Guanidinobutyl)-1-(2′,6′,10′-trimethylundeca-2′,4′,9′-trienoyl)guanidine dihydrochloride (stellettadine A) (*R*)-1

In the same manner as described above, (*R*)-**9** (60.0 mg, ≈103 μmol) was converted to the *target compound* (*R*)-**1** [43.7 mg, 78% in 2 steps based on (*R*)-**8b**] as a colorless, highly viscous oil and the *ester* (*R*)-**5a** [21 mg, 71% recovery in 2 steps based on (*R*)-**8b**] as a colorless oil. (*R*)-**1**: $[\alpha]_D^{27}$ −45.6 (*c* 1.37 in CH_3OH). IR, ^1H and ^{13}C NMR spectra were identical with those of (*S*)-**1** [Found: (HRFAB-MS) $[M - (2Cl + H)]^+$ 377.3058. $C_{20}H_{37}N_6O$ requires *m*/*z* 377.3029]. (*R*)-**5a**: $[\alpha]_D^{23}$ −63.5 (*c* 1.00 in $CHCl_3$). Spectral data of recovered (*R*)-**5a** were identical with those mentioned before.

Degradation of (*R*)-5b to (*R*)-2-methylpentane-1,5-diol 13

Into a solution of (*R*)-**5b** (90 mg, 405 μmol) in MeOH (3 cm^3) and CH_2Cl_2 (2 cm^3), was bubbled O_3 at −70 °C until saturation. After excess of O_3 had been purged by N_2 stream, $NaBH_4$ (≈100 mg, excess) was added portionwise. This stirred mixture was allowed to warm to room temperature and was concentrated under reduced pressure. The residue was suspended in EtOAc, and the resulting suspension was filtered through SiO_2. The filtrate was concentrated under reduced pressure, and the residue was purified by preparative TLC to give (*R*)-**13** (35 mg, 73%), $[\alpha]_D^{26}$ +10.7 (*c* 1.68 in Et_2O); δ_H(90 MHz; $CDCl_3$) 0.93 (3H, d, *J* 6.6, 2-Me), 1.10–1.85 (5H, m, 2-H, 3-, 4-H_2), 1.83 (2H, br s, OH), 3.47 (2H, d, *J* 6.0, 1-H_2), 3.65 (2H, t, *J* 6.3, 5-H_2). The specific optical rotation of (*S*)-**13** was recorded as $[\alpha]_D^{25}$ − 10.0 (*c* 0.025 in Et_2O)[14] or as $[\alpha]_D$ −8.5 (*c* 2 in Et_2O).[15] Our degradation product was therefore (*R*)-**13** beyond doubt.

Measurement of CD spectra of synthetic and natural stellettadine A 1

To confirm the absolute configuration of natural **1**, we measured CD spectra of our synthetic (*S*)-(+)- and (*R*)-(−)-**1**, and naturally occurring (−)-**1** on a JASCO J-720 spectrometer. Synthetic (*S*)-(+)-**1**: Δε +0.50 (282 nm, *c* 0.0013 M in MeOH); Synthetic (*R*)-(−)-**1**: Δε −2.02 (283 nm, *c* 0.0024 M in MeOH); natural (−)-**1**: Δε −2.62 (283 nm, *c* 0.00205 M in MeOH). The reason for the small Δε of synthetic (*S*)-(+)-**1** was due to its deterioration after storage for 8 months. (The other two samples were freshly prepared or repurified.)

Acknowledgements

We thank Professors N. Fusetani (the University of Tokyo) and S. Tsukamoto (Kanazawa University) for their kind supply of natural stellettadine A and copies of the various spectra of stellettadine, and also their suggestion concerning the counter-anion (Cl^-) of stellettadine A salt. Our thanks are due to Takasago International Corporation for their gift of citronellal enantiomers, and also for their financial support.

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