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Synthesis and Absolute Configuration of Stellettadine A: A Marine Alkaloid That Induces Larval Metamorphosis in Ascidians

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Abstract—Stellettadine A, a bisguanidinium alkaloid isolated from a marine sponge *Stelletta* sp. as an inducer of larval metamorphosis in ascidians, and its unnatural enantiomer were synthesized from the enantiomers of citronellal. The absolute configuration of stellettadine A was established as *R*.

In 1996, Tsukamoto et al.[1] isolated stellettadine A from a marine sponge, *Stelletta* sp., collected in Japan. The sponge metabolite induces at a concentration of 50 μM larval metamorphosis in ascidians, *Halocynthia roretzi*, and possesses a unique structure as bisguanidinium alkaloid acylated with a chiral norsesquiterpene acid (**1**, Fig. 1).[1] Its *S* absolute configuration as depicted in **1** was proposed on the basis of oxidative degradation of **1** to give (*S*)-(+)-2-methylglutaric acid (**2**).[1] Shortly afterwards in 1997, Shin et al.[2] isolated and identified stellettamide B (**3**) as a new metabolite of a Korean sponge of the same genus *Stelletta*. They executed oxidative degradation of **3**, and also obtained (*S*)-(+)-**2**. Accordingly, *S* configuration was assigned to **3**, although in Shin's paper *R* configuration was shown in the structure depicted.[2]

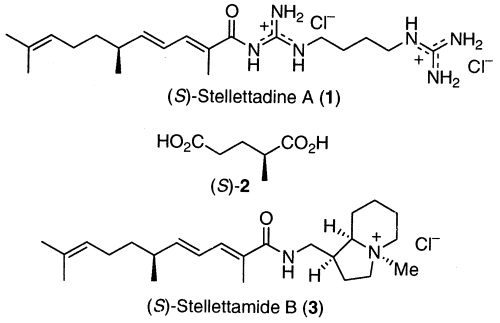

Figure 1. Structures of stellettadine A (**1**) and stellettamide B (**3**).

In view of the interesting bioactivity in connection with marine chemical ecology, we were prompted to verify the proposed structure and absolute configuration of stellettadine A by synthesizing both the enantiomers of **1** from the enantiomers of citronellal (**4**, Schemes 1 and 2). It should be emphasized that the enantiomers of citronellal, citronellol and citronellic acid are versatile building blocks for the synthesis of various different chiral compounds, and their absolute configuration is established beyond doubt.[3,4]

Scheme 1 summarizes the synthesis of (*S*)-stellettadine A (**1**). Preparation of the norsesquiterpene acid (*S*)-**7b** started from (*S*)-citronellal (**4**, Takasago, $[\alpha]_D^{23}$ −16.3 (neat), ca. 97% ee[5]). According to the protocol of Takayama et al.,[6] (*S*)-**4** was treated with methoxymethylenetriphenylphosphorane to give an *E*/*Z* mixture of methyl enol ether (*S*)-**5**, which furnished α,β-unsaturated aldehyde (*S*,*E*)-**6**,[7] $[\alpha]_D^{24}$ +56.7 ($CHCl_3$), by palladium-catalyzed oxidation with palladium(II) acetate and copper(II) acetate in the presence of aqueous sodium hydrogen carbonate. The aldehyde (*S*)-**6** was subjected to Wittig reaction with a stable ylide to afford unsaturated ester (*S*)-**7a**, $[\alpha]_D^{19}$ +63.2 ($CHCl_3$). HPLC analysis[8] of (*S*)-**7a** revealed it to be of 97.6% ee. Basic hydrolysis of (*S*)-**7a** with sodium hydroxide gave (*S*)-**7b**, $[\alpha]_D^{20}$ +78.3 ($CHCl_3$), which yielded the corresponding acyl chloride (*S*)-**7c** by treatment with oxalyl chloride in the presence of 2-methyl-2-butene as a scavenger of hydrogen chloride.

After some experimentation, we chose commercially available agmatine sulfate (**8**) as the guanidine compound to be acylated with (*S*)-**7c**. Prior to the acylation,

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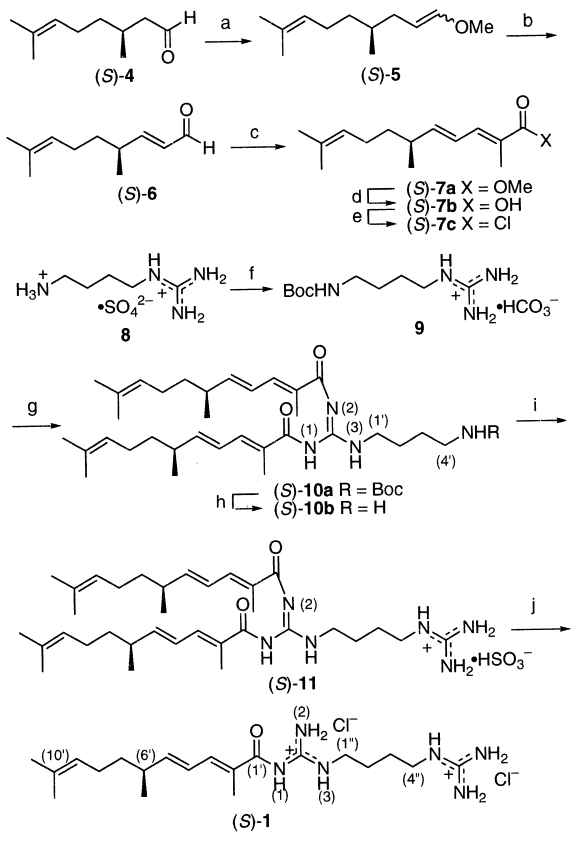
it was of course necessary to protect the non-guanidine primary amino group of **8** as *t*-butoxycarbonyl (Boc) amide[9] to avoid complication. Initial attempts to acylate the resulting Boc-protected agmatine **9** with (*S*)-**7b** or (*S*)-**7c** met with failure under several different conditions. However, the method developed by Ottenheijm and co-workers[10] in arginine chemistry could be applied successfully to overcome the difficulty. Accordingly, **9** was treated with trimethylsilyl chloride in the presence of diisopropylethylamine to give *N*-silylated intermediate, whose in situ acylation with (*S*)-**7c** in the presence of diisopropylethylamine afforded diacylated product (*S*)-**10a**, $[\alpha]_D^{23}$ +87 ($CHCl_3$), in 62% yield. In the case of acylation of arginine, its nitrogen atoms corresponding to N-1 (guanidine numbering) and N-3 of (*S*)-**10a** were reported to be acylated.[10,11] In the present case, the acylation took place at N-1 and N-2 as evidenced by the fact that the ^1H–^1H COSY cross-peak between 1′-H (δ = 3.54) and 3-H (δ = 9.37) of (*S*)-**10a** was observed as clearly as the one between 4′-H_2 (δ = 3.16) and N*H*Boc (δ = 4.56).



Scheme 1. Synthesis of (*S*)-stellettadine A (**1**). Reagents and conditions: (a) $Ph_3P(Cl)CH_2OMe$, PhLi, Et_2O; (b) $Pd(OAc)_2$, $Cu(OAc)_2$, aq $NaHCO_3$, MeCN (48%, 2 steps); (c) $Ph_3P{=}CMeCO_2Me$, C_6H_6 (86%), (d) aq NaOH, MeOH, THF (87%); (e) $(COCl)_2$, 2-methyl-2-butene, CH_2Cl_2 (quant.); (f) Boc_2O, aq $NaHCO_3$, dioxane (68%); (g) TMSCl, *i*-Pr_2NEt, CH_2Cl_2 then (*S*)-**7c**, *i*-Pr_2NEt (62%); (h) *p*-TsOH, 2-methyl-2-butene, MeOH (84%) ; (i) $NH_2C(=NH)SO_3H$, MeOH; (i) KOH, MeOH then HCl (67%, 2 steps).

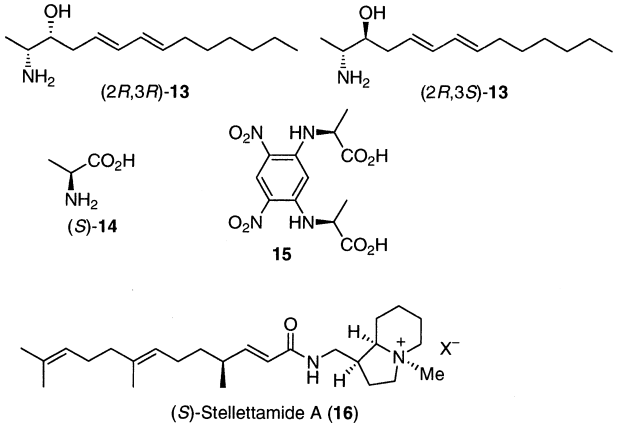
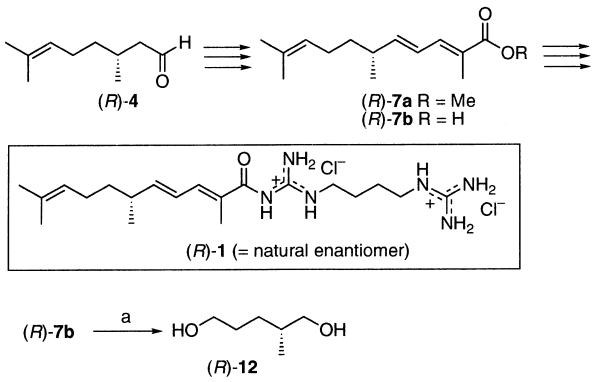


Figure 2. Structures of marine amino alcohol (2*R*,3*R*)- and (2*R*,3*S*)-**13**, and stellettamide A (**16**).

The remaining tasks were the construction of the second guanidine group at the N-terminal, and the removal of the extra acyl group at N-2. For that purpose, the Boc protective group was removed under acidic conditions, and the resulting amine (*S*)-**10b** was treated with aminoiminomethanesulfonic acid according to Miller[12] and Mosher[13] to give N-2 acylated (*S*)-stellettadine A (**11**) as an oil $[\alpha]_D^{23}$ +81 ($CHCl_3$). Finally, 1 equiv of methanolic potassium hydroxide effected removal of the extra acyl group of (*S*)-**11** by methanolysis to give (*S*)-stellettadine A (**1**) as its oily dihydrochloride[14,15] after chromatographic purification over ODS-SiO_2, along with the recovered (*S*)-**7a**. The overall yield of (*S*)-**1** was 12.5% based on (*S*)-**4** (8 steps). In the same manner, as shown in Scheme 2, (*R*)-citronellal (**4**, Takasago, $[\alpha]_D^{23}$ +15.2 (neat), ca. 97% ee[5]) was converted to (*R*)-stellettadine A (**1**) via (*R*)-**7a**, $[\alpha]_D^{25}$ −63.4 ($CHCl_3$), whose enantiomeric purity was 97.0% ee.[8] Our synthetic enantiomers of **1** showed spectral properties identical with those of natural **1**.[15]

Results obtained by the measurement of the specific rotations of the synthetic enantiomers of stellettadine A (**1**) annoyed us: (*R*)-**1** showed $[\alpha]_D^{27}$ −45.6 (*c* 1.37, MeOH), while (*S*)-**1** was dextrorotatory, $[\alpha]_D^{25}$ +39.4 (*c* 1.01, MeOH). The naturally occurring **1** was reported to exhibit $[\alpha]_D^{24}$ −32.8 (*c* 1.00, MeOH), while *S* configuration was assigned to it.[1] In order to confirm the absolute configuration of our synthetic (*R*)-**1**, a chiral intermediate (*R*)-**7b** (90 mg) was degraded by ozonolysis. After reductive work up with sodium borohydride, (+)-2-methyl-1,5-pentanediol (**12**, 35 mg, 73%), $[\alpha]_D^{26}$ +10.7 (Et_2O), was obtained. The specific rotation of (*S*)-**12** was recorded as $[\alpha]_D$ −8.5 (Et_2O).[16] Our degradation product was therefore (*R*)-**12**, and the acid **7b** was indeed the *R*-isomer. It should be noted that the erroneous assignment of absolute configuration to marine natural products is not at all uncommon. For example, two epimeric amino alcohols (2*R*,3*R*)- and (2*R*,3*S*)-**13** (Fig. 2), isolated from a Papua New Guinea sponge *Xestospongia* sp., were originally reported to possess the opposite absolute configuration on the basis of the claim that both of them afforded, after oxidative degradation, (*S*)-alanine (**14**), which was identified by HPLC comparison with authentic **15** derived from (*S*)-**14**.[17] Unambiguous synthesis of all of (2*R*,3*R*)-, (2*R*,3*S*)-, (2*S*,3*S*)-, and (2*S*,3*R*)-**13** by Mori and Matsuda[18] established the correct absolute configuration of the amino alcohols as shown in Figure 2.



Scheme 2. Synthesis of (*R*)-stellettadine A (**1**) and degradation of (*R*)-**7b**. Reagents: (a) (i) O_3, MeOH, CH_2Cl_2; (ii) $NaBH_4$ (73%).

Fortunately, the natural stellettadine A (**1**), $[\alpha]_D^{24}$ −42.7 (*c* 0.092, MeOH), was still available, and given to us by Professor Fusetani. It showed a negative Cotton effect at 283 nm (MeOH) in its CD spectrum, while synthetic (*S*)-**1** showed a positive one at 282 nm (MeOH). We thus conclude that the proposed gross structure of (−)-stellettadine A as **1**[1] is correct, but contrary to the initial proposal,[1] its absolute configuration is *R*. Finally, it should be added that the absolute configuration of a related metabolite stellettamide A (**16**) was reported to be *S* by an enantioselective synthesis.[19]

Acknowledgements

The authors are grateful to Professor N. Fusetani (the University of Tokyo) for his kind gift of natural **1**. We thank Professors N. Fusetani and S. Tsukamoto (Kanazawa University) for kindly sending to us copies of the UV, IR, ^{1}H NMR, ^{13}C NMR and MS spectra of natural stellettadine A and also for informing us of the fact that the natural product was obtained as the dihydrochloride. Our thanks are due to Takasago International Corporation for the gift of citronellal enantiomers, and also for the financial support.

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15. Properties of **1**: ν_{max} (KBr)/cm^{-1} 3330 brs (N–H), 3160 brs (N–H), 2970 m, 1690 s (C=O), 1665 s (N–H), 1620 s (N–H), 1590s (N–H), 1460 m, 1385 m, 1230 m, 1095 m, 970 m; 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: (HR FABMS) $[M-(2Cl+H)]^+$ 377.3058 $C_{20}H_{37}ON_6$ requires m/z 377.3029).
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