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ASYMMETRIC SYNTHESIS OF STELLETTAMIDES A AND C

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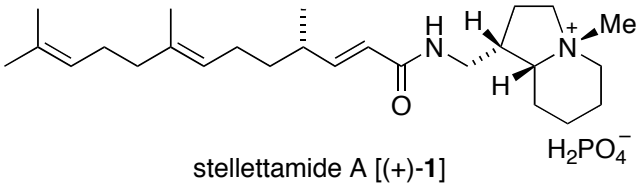
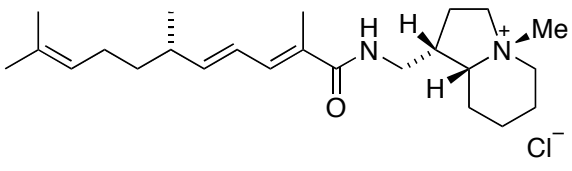
Abstract – The first synthesis of the marine indolizidine alkaloids, (+)-stellettamide A and (–)-stellettamide C, has been achieved through a coupling reaction with the aminomethylindolizidine fragment and the chiral or achiral trienecarboxylic acid fragment, both of which could be derived from farnesol as a common precursor.

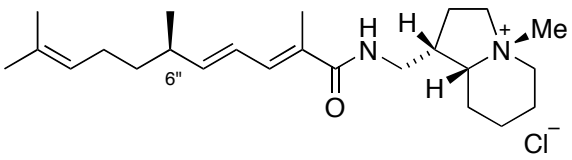
Stellettamide A (**1**) was isolated from the marine sponge genus *Stelletta*, which was collected near Shikinejima island of Japan in 1990 by Fusetani and coworkers,[1] as the first example of an indolizidine class of marine alkaloids. Stellettamide A exhibits calmodulin inhibitory activity[2] as well as antifungal and cytotoxic activities against tumor cell lines.[1] The absolute stereochemistry of stellettamide A was established on the basis of the enantioselective synthesis of the antipodal (–)-**1** by Carreira[3] in 1997. In 1997, Shin reported a closely related alkaloid stellettamide B,[4] which was obtained from the same genus *Stelletta* collected near Keomun island of Korea, and disclosed structure **2**. The configuration at the C6" position in stellettamide B was revised to be *R* by our total synthesis[5] as shown in (–)-**3**. Soon after, a new compound of this class, stellettamide C (**4**) was isolated from the Japanese *Stelletta* sponge.[6] The



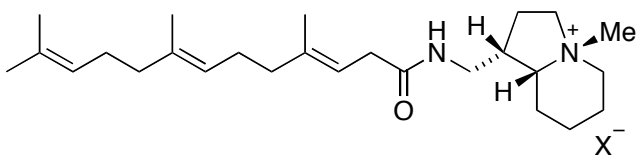
stellettamide A [(+)-**1**]



proposed structure **2** for stellettamide B



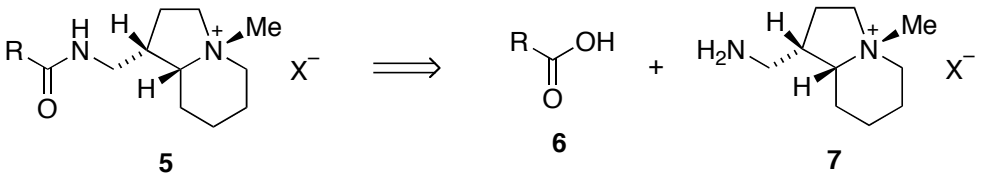
revised structure (–)-**3** for stellettamide B



proposed structure **4** for stellettamide C

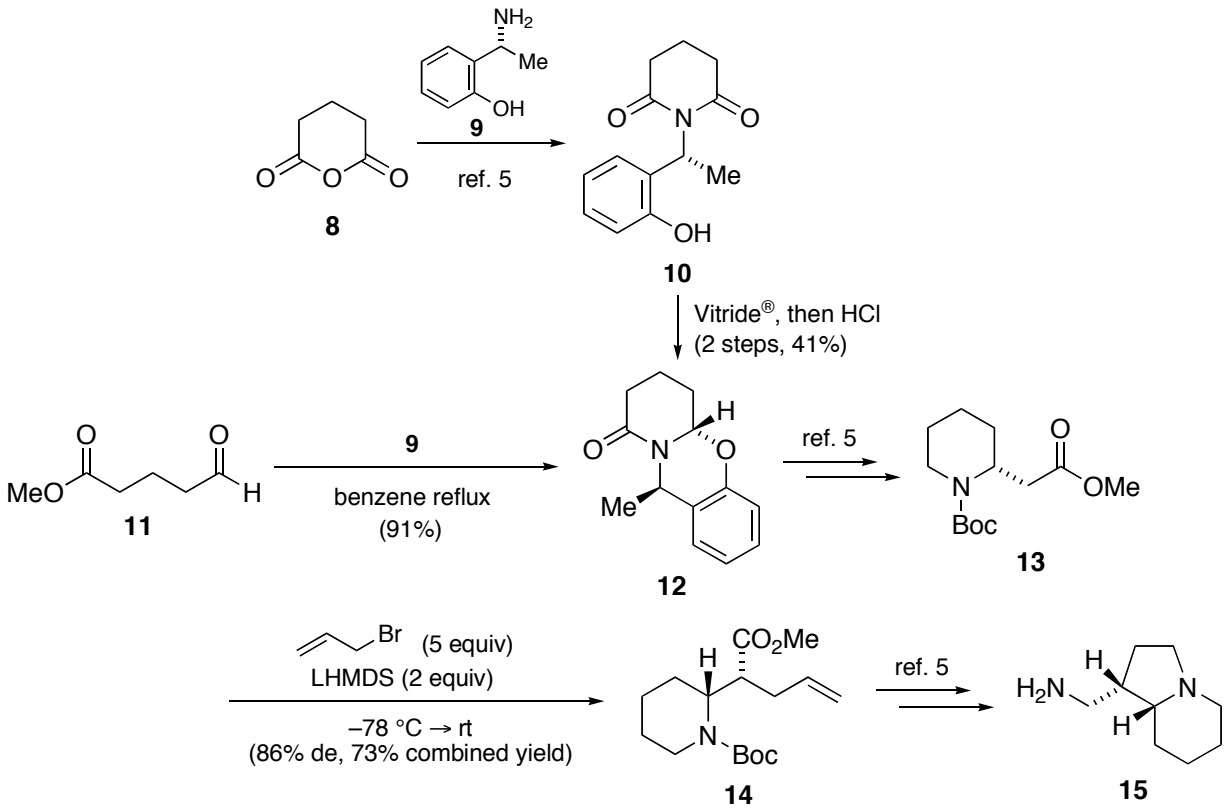
chemical features of this family are recognized to consist of trienecarboxylic acid fragments as structural variations and the aminomethylindolizidine fragment as a common component. Though there are, so far, no additional examples of the synthesis of stellettamides, two synthetic approaches focusing on the synthesis of the aminomethylindolizidine fragment in an enantiomerically pure form[7] and a racemic form[8] have been reported. In this paper we present the first synthesis of the enantiomerically correct form of natural stellettamide A and (1*S*,4*S*,8a*R*)-stellettamide C (**4**).

Our synthetic plan was based on a straightforward application employing the connection of trienecarboxylic acid fragment **6** with the formerly synthesized aminomethylindolizidine fragment **7** *via* amide linkage formation (Scheme 1). For the synthesis of aminomethylindolizidine fragment **7**, we



Scheme 1

intend to improve some points, and significant improvements (**11**→**12** and **13**→**14**) were made as illustrated in Scheme 2. Firstly, in the formation of *N*,*O*-acetal **12**, the formation required two steps from glutaric anhydride (**8**) and the combined chemical yield was somewhat poor (41%). The yield was improved by the condensation of 2-(1-aminoethyl)phenol **9** with formyl ester **11**, giving the cyclic

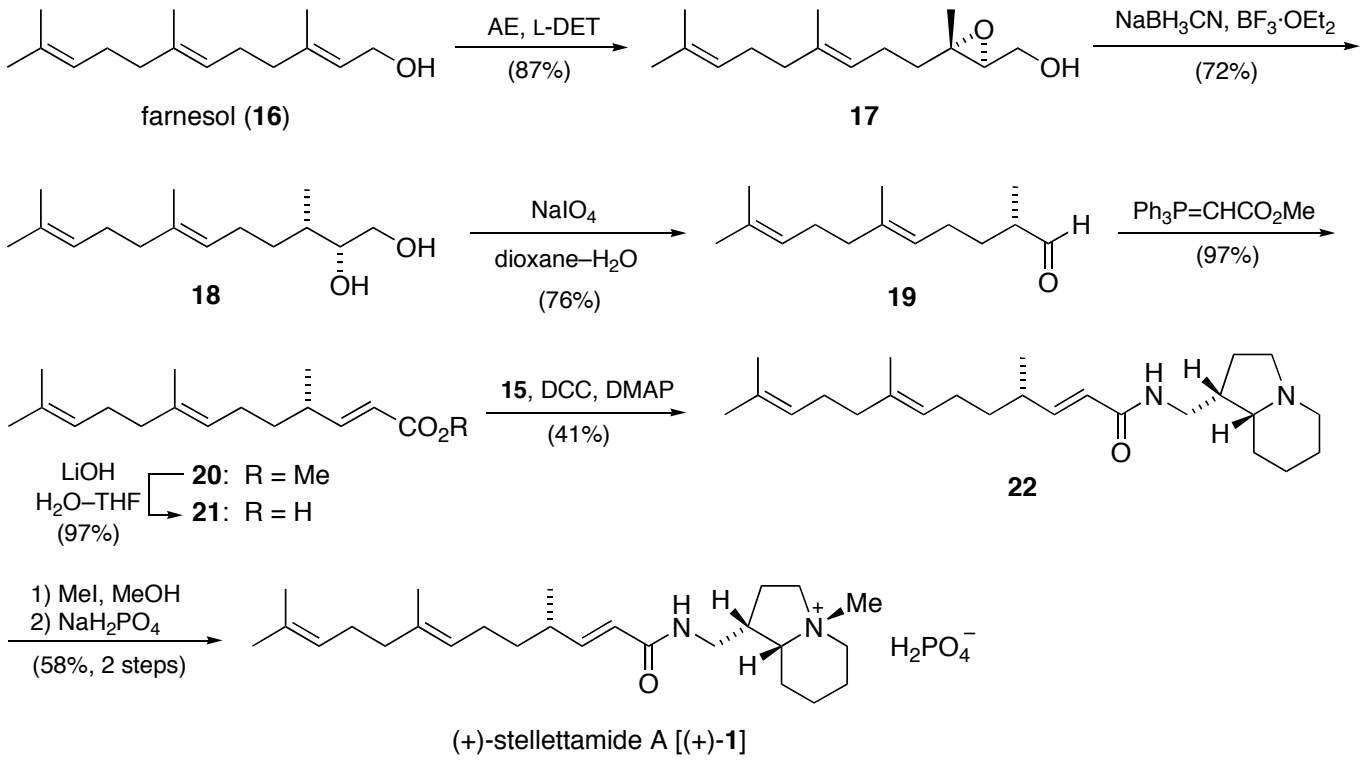


Scheme 2

N,*O*-acetal **12** in a 91% yield.[9] Secondly, in the allylation process of the piperidinylmethyl ester (**13**→**14**), we sometimes experienced substantial loss of the optical purities (~90–60% ee) of the resulting allylated products. This serious drawback was avoided by adding an excess amount of allylbromide (5 equiv) to the base (LHMDS) (2 equiv).[10] No racemization with **14** occurred in the allylation reaction (>99% ee, Chiralpak AD, hexane–IPA–Et_2NH, 1900:100:5, v/v). With the aminomethylindolizidine **15** having high enantiomeric purity in hand, we next investigated the synthesis of trienecarboxylic acid fragments for stellettamides A and C.

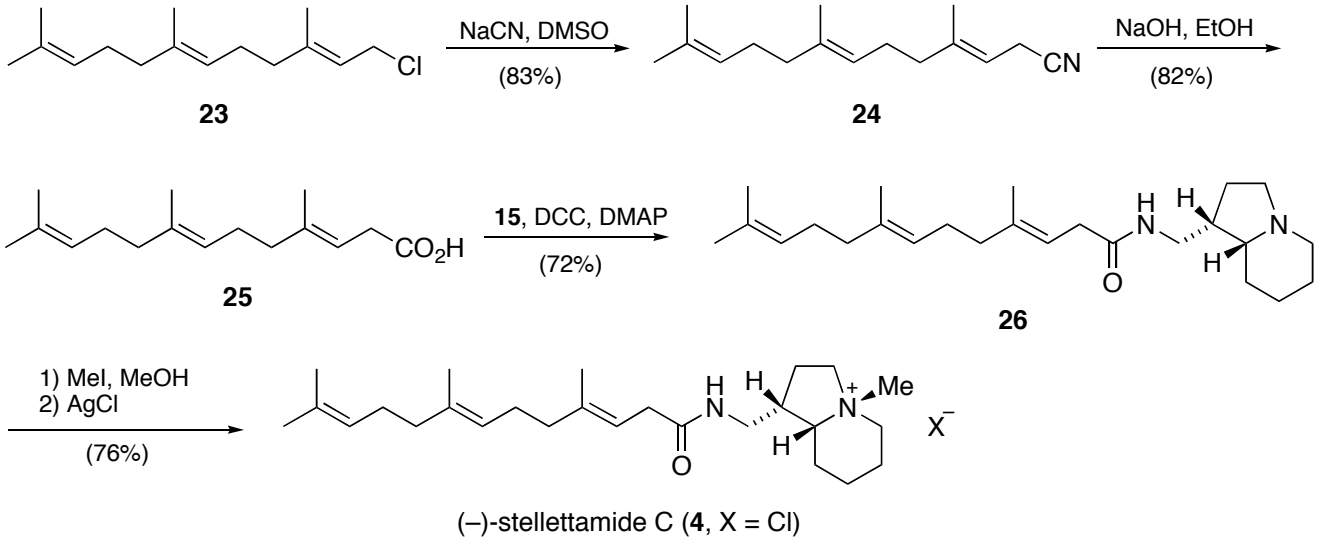
Farnesol (**16**) was treated under Sharpless asymmetric epoxidation conditions using L-DET and *t*-BuOOH to give the epoxy alcohol **17**.[11] Reductive cleavage of the epoxide in the presence of $BF_3{\cdot}OEt_2$ gave glycol **18**,[12] which was consecutively applied to oxidative cleavage using $NaIO_4$ to yield aldehyde **19**. Wittig olefination followed by basic hydrolysis afforded trienecarboxylic acid **21** for the fragment of stellettamide A.

The acid **21** and the indolizidine fragment **15** were connected by the DCC–DMAP coupling to yield amide **22**. Finally iodomethylation of **22** with iodomethane, followed by a counter-ion exchange[3] from the iodide to the phosphate with sodium biphosphate furnished (+)-stellettamide A. The synthetic material coincided in all aspects with those of the reported stellettamide A as well as in terms of optical



Scheme 3

rotation [$[\alpha]^{22}_D$ +23.8 (*c* 0.79, EtOH), lit.,[1] $[\alpha]_D$ +23.1 (*c* 0.3, EtOH)]. This sequence established the first total synthesis of (+)-stellettamide A [(+)-**1**] as the enantiomerically correct form of a natural product.



Scheme 4

Trienecarboxylic acid fragment **25**, for the synthesis of stellettamide C, was obtained by homologation of the farnesyl chloride (**23**) followed by hydrolysis under usual conditions (Scheme 4). Dehydrocondensation of the resulting carboxylic acid **25** with the indolizidine **15** gave nor-stellettamide C (**26**). By treatment of **26** with iodomethane, followed by silver chloride,[13] yielded stellettamide C (**4**, X = Cl). The complete exchange of the counter ion from the iodide ion to the chloride ion was confirmed by the measurement of an energy dispersive X-ray spectrum as shown in Figure 1. Both ^{1}H and ^{13}C NMR spectra of the synthetic material were found to be identical to those of natural stellettamide C, though the careful measurement of the optical rotation[14] [$[\alpha]^{20}_{D}$ –1.5 (*c* 0.34, MeOH)] showed the opposite sign to the natural stellettamide C (**4**, X = undefined) [lit.,[6] $[\alpha]^{23}_{D}$ +1.1 (*c* 0.32, MeOH)]. These results suggest that the absolute stereochemistry of natural stellettamide C was the antipodal structure of **4**, having (1*R*,4*R*,8a*S*)-indolizidine moiety, although the absolute stereochemistry for the indolizidine part of stellettamides A and B was already established to be 1*S*,4*S*,8a*R* by asymmetric syntheses.[3,5] This

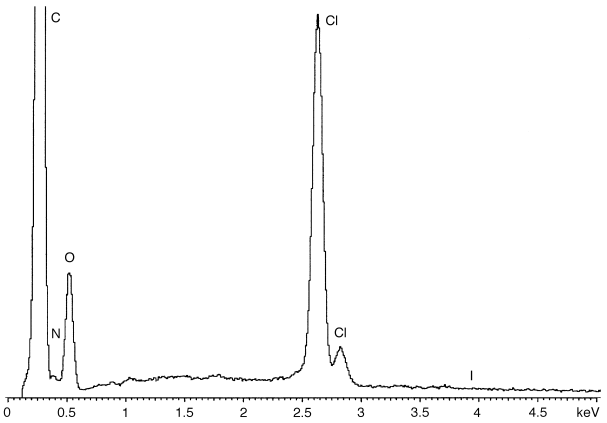


Figure 1. Energy dispersive X-ray spectrum of **4** was obtained by electron bombardments at 20 kV on a Horiba EMAX scanning electron microscope.

contradiction might be the consequence of the weak degrees of the optical rotation value of stellettamide C. In addition, the counter ion of the natural material (**4**, X = undefined) has not been established and thereby it is possible that the difference of the counter ions might influence the sign of the optical rotation.

In summary, we have synthesized the natural form of (+)-stellettamide A and the proposed structure of (1*S*,4*S*,8a*R*)-(–)-stellettamide C by applying a convergent strategy to aminomethylindolizidine fragment with chiral or achiral trienecarboxylic acid fragments.

ACKNOWLEDGEMENTS

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9. A solution of **11** (98.0 mg, 0.753 mmol) and **9** (69.0 mg, 0.503 mmol) in benzene (5 mL) was heated to reflux using a Dean-Stark apparatus for water removal. After 24 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give **12** (99.5 mg, 91%) as a colorless oil.
10. To a stirred solution of **13** (100 mg, 0.389 mmol) in THF (4 mL) was added LHMDS (1.0 M in THF, 0.78 mL, 0.780 mmol) at –78 °C. After stirring at –78 °C for 30 min, allylbromide (238 mg, 1.96 mmol) was added and stirring was continued for additional 30 min. The reaction mixture was allowed to warm to room temperature and diluted with ether (20 mL). Water (10 mL) was added, and the mixture was extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Purification of the residue by column chromatography (hexane–EtOAc, 10:1) gave **14** (77.7 mg, 67%) as a colorless oil.
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12. Data for selected new compounds: Compound **18**: $[\alpha]^{28}_{D}$ –13.2 (*c* 1.01, $CHCl_3$); IR (neat) 3376, 2966, 2924, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.8 Hz), 1.14–1.27 (1H, m), 1.41–1.75 (2H, m), 1.60 (6H, s), 1.68 (3H, d, *J* = 0.5 Hz), 1.91–2.13 (6H, m), 3.51–3.68 (3H, m), 5.03–5.15 (2H, m). Compound **19**: $[\alpha]^{23}_{D}$ +23.6 (*c* 1.37, $CHCl_3$); IR (neat) 2968, 2922, 2856, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* = 7.1 Hz), 1.35–1.43 (1H, m), 1.58 (3H, s), 1.59 (3H, s), 1.66 (3H, s), 1.72–1.80 (1H, m), 1.95–2.01 (2H, m), 2.01–2.09 (4H, m), 2.34 (1H, tdd, *J* = 13.8, 6.9, 1.8 Hz), 5.04–5.11 (2H, m), 9.61 (1H, d, *J* = 1.8 Hz). Compound **21**: $[\alpha]^{30}_{D}$ +47.7 (*c* 1.21, $CHCl_3$); IR (neat) 2965, 2918, 1696, 1651, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, *J* = 6.8 Hz), 1.35–1.53 (2H, m), 1.58 (3H, s), 1.60 (3H, s), 1.68 (3H, d, *J* = 0.5 Hz), 1.93–2.03 (4H, m), 2.03–2.11 (2H, m), 2.29–2.42 (1H, m), 5.04–5.13 (2H, m), 5.79 (1H, dd, *J* = 15.7, 0.8 Hz), 6.99 (1H, dd, *J* = 15.6, 7.9 Hz).
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14. The optical rotation was measured using a 100 mm length quartz cell with a methanolic solution, which was prepared 1 hour in advance by using a 2-mL volumetric flask.