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Total Synthesis of (−)-Stellettamide B and Determination of Its Absolute Stereochemistry

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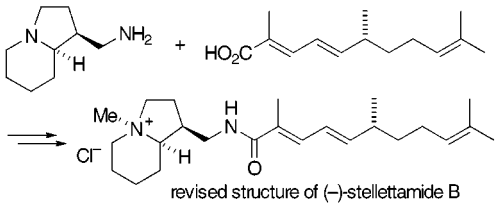
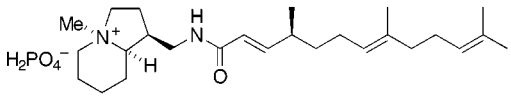
ABSTRACT



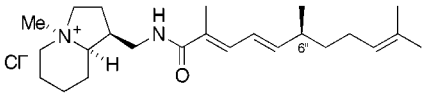
revised structure of (−)-stellettamide B

The first total synthesis of (−)-stellettamide B has been achieved by a sequence based on amide coupling of the chiral 1-(aminomethyl)-indolizidine fragment, prepared by $TiCl_4$-mediated asymmetric allylation of the tricyclic *N*-acyl-*N*,*O*-acetal, with the chiral trienoic acid fragment This synthesis led to revision of the published relative stereochemistry of the natural product and established its absolute stereochemistry to be 1*S*,4*S*,8a*R*,6′′*R*.

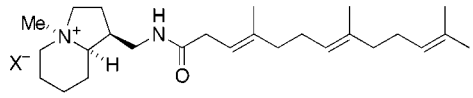
Stellettamide A (**1**), which showed antifungal and cytotoxic activity, was first isolated by Fusetani et al.[1] in 1990 from a marine sponge of the genus *Stelletta* collected in Shikine-jima Island of Japan as the first representative of an indolizidine class of marine alkaloids. Subsequently, Shin et al.[2] reported the isolation of the closely related alkaloid stellettamide B from a Korean specimen of *Stelletta* sp., which was found to have antifungal and RNA-cleaving activities. On the basis of spectroscopic data, the structure of stellettamide B was formulated as **2** having the 6′′*S* absolute configuration assigned by chemical correlation (see below).[3] Very recently, another antibacterial alkaloid, stellettamide C (**3**), was isolated from the Japanese sponge *Stelletta* sp.[4]



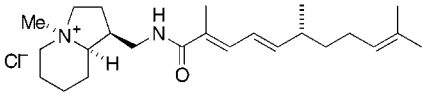
(+)-stellettamide A (**1**)



original structure of (−)-stellettamide B (**2**)



(+)-stellettamide C (**3**)



revised structure of (−)-stellettamide B (**4**)

Stellettamides A−C comprise a common indolizidine skeleton, containing a quaternary nitrogen atom and a

(1) Hirota, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1990**, *31*, 4163−4164.

(2) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod.* **1997**, *60*, 611−613.

(3) The absolute configuration of the C(6′′) chiral center in the structure of stellettamide B reported in the literature (ref 2) is erroneously depicted as *R* and should therefore be corrected to *S* (J. Shin, personal communication).

(4) Matsunaga, S.; Yamashita, T.; Tsukamoto, S.; Fusetani, N. *J. Nat. Prod.* **1999**, *62*, 1202−1204.

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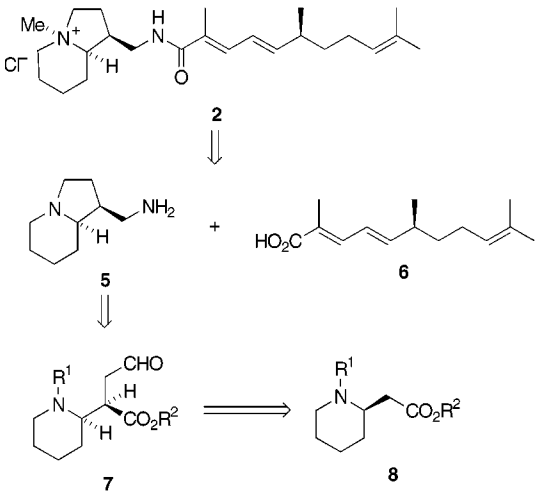
variation of the unsaturated side chain, which are connected via an amide linkage. The relative stereochemistry originally proposed for the indolizidine part of stellettamide A and its absolute stereochemistry have been established by the synthesis[5] of the antipodal stellettamide A as depicted in **1**. Moreover, the direct comparison of the degradation products obtained from stellettamides A and C confirmed that the indolizidine part of stellettamide C has the same absolute configuration, shown in **3**, as that of stellettamide A.[4] On the other hand, there is still no evidence for the absolute configuration of the indolizidine unit of stellettamide B, though the same relative stereochemistry as that for stellettamides A and C has been assigned to it on the basis of NMR study.[2] The absolute stereochemistry of the asymmetric center at C(6″) in the norsesquiterpene side chain was, however, assigned as *S* by chemical correlation of the degradation product of stellettamide B to the known (*S*)-2-methylglutaric acid.[2]

In this paper, we disclose an enantioselective synthesis of the structure **2** originally proposed for stellettamide B by a strategy involving an asymmetric allylation of a cyclic *N*-acyl-*N*,*O*-acetal as a key feature. We also report that structure **2** does not correspond to natural stellettamide B, while its epimer **4** at the C(6″) position is identical to the natural product, leading to revision of the original structure **2**. Herein, we describe the first total synthesis of stellettamide B, as its natural (−)-enantiomer, that establishes the relative and absolute stereochemistry of this alkaloid as **4**.

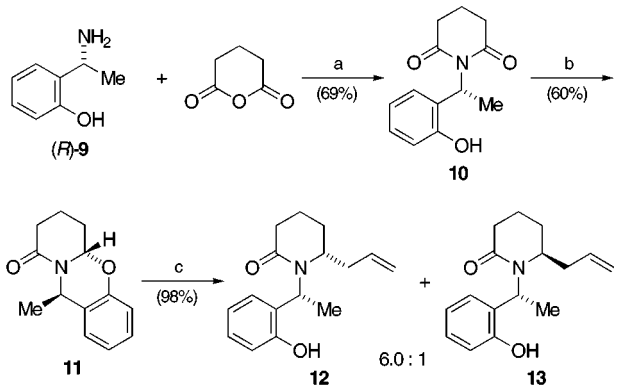
In our strategy, for the synthesis of the initial target **2**, we sought to utilize a simple and straightforward approach that involves connecting the chiral aminomethylindolizidine fragment **5** to the (*S*)-trienoic acid fragment **6** via amide coupling as outlined retrosynthetically in Scheme 1. We envisioned

Scheme 1



that **5** would be formed via the piperidine derivative **7**, which might be derived from the (*R*)-piperidinyl acetate **8**. On the basis of this analysis, at the outset, studies were directed toward the development of an effective enantioselective synthesis of **8**. Recently, our group has investigated Lewis acid-mediated asymmetric allylation of cyclic *N*-acyl-*N*,*O*-acetals, in which enantiomeric 2-(1-aminoethyl)phenol (**9**) has been proven useful as a chiral auxiliary.[6] Accordingly, our initial study was application of this methodology to the synthesis of **8**. Thus, the glutarimide **10** incorporating (*R*)-**9** as an auxiliary was converted to the tricyclic *N*,*O*-acetal **11** as a single diastereomer by partial reduction with Vitride (toluene, −78 °C) followed by acid treatment. Upon treatment of **11** with allyltrimethylsilane (3 equiv) and $TiCl_4$ (3 equiv) at 50 °C, the reaction proceeded smoothly to give allylated products in 98% yield and a ratio of 6.0:1 favoring the desired (6*R*)-isomer **12**. The stereochemical assignment of the newly generated allyl-bearing stereogenic center in **12** by NMR analysis was actually difficult, and since **12** was formed as an oil, we were unable to grow suitable crystals for X-ray crystallography. However, racemic **12**, prepared following the same reaction sequence used in Scheme 2 via

Scheme 2[a]



[a] (a) AcCl, toluene, reflux; (b) Vitride, toluene, −78 °C, then HCl; (c) allyltrimethylsilane, $TiCl_4$, toluene, 50 °C.

the $TiCl_4$-mediated allylation of racemic **11**, was obtained as a crystalline product[7] suitable for X-ray crystallography (Figure 1) which allowed assignment of the retentive stereochemistry of **12**. Preference for the formation of the (6*R*)-isomer **12** in this case can be rationalized by a retentive allylation process via an S_N1-like mechanism consistent with previous results from our laboratories.[6] Accordingly, the initially formed *N*-acyliminium ion **14** is expected to adopt conformation **A** with the hydrogen atom in the inside position and the bulky aromatic ring nearly perpendicular to the iminium C=N plane to minimize the 1,3-allylic strain. In this conformation, coordination of the titanium(IV) phenoxide with the carbonyl oxygen atom is likely. In such a stereochemical arrangement, the silane nucleophile approach can then occur from the face opposite to the aromatic ring to generate the *R* configuration at the reaction center. In this

(5) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916−7917.

(6) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739−742. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465−467.

(7) Prepared by recrystallization from benzene-hexane as colorless needles having mp 104−106 °C.

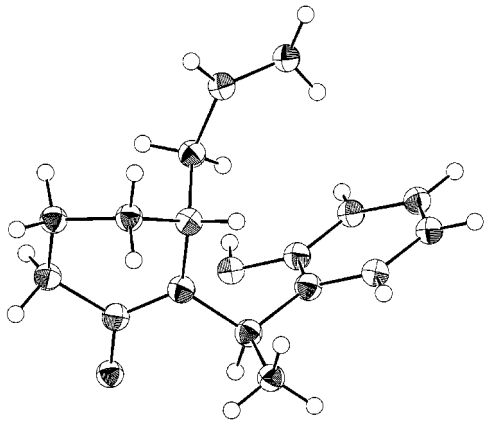
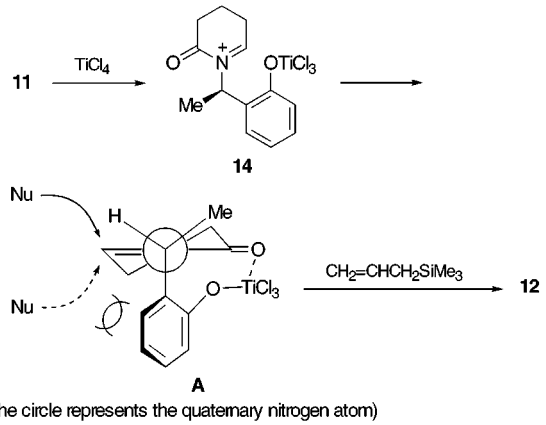


Figure 1. X-ray crystallographic structure of racemic **12** presented by one enantiomer.

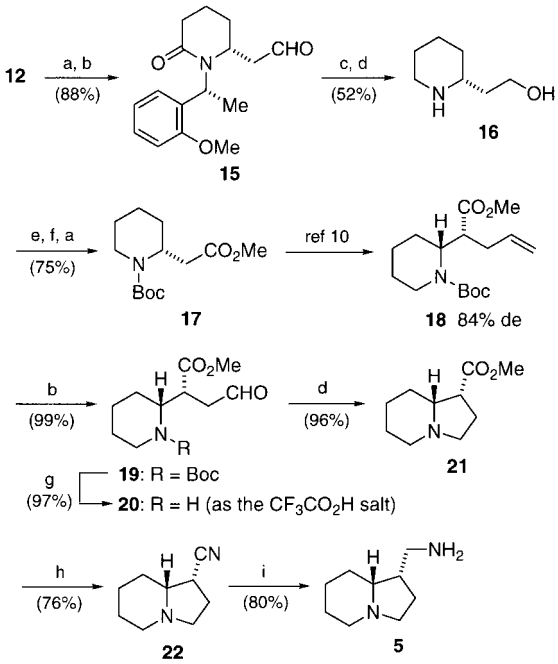
case, the preferred axial attack by the silane nucleophile is validated by Stevens' stereoelectronic principle.[8]



The (6*R*)-allyl-2-piperidinone **12** so obtained was subjected to methylation of the phenolic hydroxyl group, followed by oxidative cleavage of the olefin with OsO_4 and $NaIO_4$, to give the aldehyde **15** (Scheme 3). After $LiAlH_4$ reduction of **15**, the chiral auxiliary was cleaved by catalytic hydrogenolysis to provide the amino alcohol **16**, which was converted to the (2*R*)-piperidinyl acetate **17** via a sequence involving N-Boc protection, PDC oxidation in DMF,[9] and esterification. Diastereoselective allylation of **17** was performed according to literature procedure[10] by using allyl bromide and LHMDS to furnish the desired 1′*R* product **18** (84% de, 76% yield). Oxidative cleavage of the olefin converted **18** to the aldehyde **19**. N-Boc deprotection of **19** followed by catalytic hydrogenation resulted in the indolizidine **21** via intramolecular reductive amination as a single isomer. When the procedure for aluminum-mediated amide formation using trimethylaluminum−NH_4Cl[11] was applied

(8) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193−198.
(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399−402.
(10) Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron: Asymmetry* **1990**, *1*, 147−150.

Scheme 3[a]



[a] (a) MeI, K_2CO_3, acetone; (b) OsO_4−$NaIO_4$, dioxane−H_2O; (c) $LiAlH_4$, Et_2O, reflux; (d) H_2/Pd−C, MeOH; (e) $(Boc)_2O$, NaOH, dioxane−H_2O; (f) PDC, DMF; (g) CF_3CO_2H, CH_2Cl_2; (h) Me_3Al−NH_4Cl, benzene, 50 °C; (i) $LiAlH_4$, $(i\text{-}Pr)_2O$, reflux.

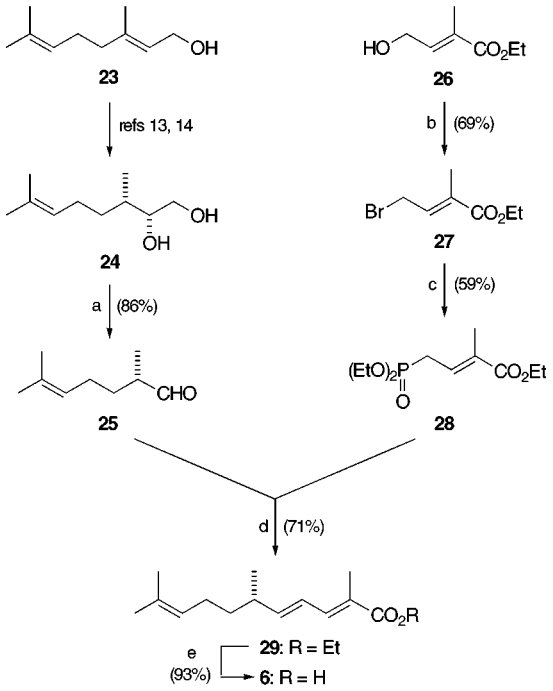
to **21**, transformation of the ester group to a cyano group to form **22** occurred instead of amide formation. The resultant nitrile **22** was converted to the aminomethylindolizidine **5** by $LiAlH_4$ reduction by using diisopropyl ether as a solvent.[12]

As the synthesis of the aminomethylindolizidine fragment **5** was thus achieved, we then undertook the preparation of the (*S*)-trienoic acid fragment **6**. Starting from geraniol (**23**), (2*R*,3*S*)-3,7-dimethyl-6-octene-1,2-diol (**24**) was prepared following known procedures involving asymmetric epoxidation[13] with L-diethyl tartrate followed by reductive ring opening (Scheme 4).[14] Compound **24** was then subjected to oxidative glycol cleavage to give the aldehyde **25**. On the other hand, ethyl (2*E*)-4-hydroxy-2-methyl-2-butenoate (**26**)[15] was converted to the phosphonate ester **28** by bromination (Ph_3P, CBr_4) followed by phosphorylation. Subsequent Horner−Emmons olefination with the aldehyde **25** (BuLi, −78 °C) resulted in the (2*E*,4*E*)-trienoate **29** as a geometrically single product (71% yield), which was then hydrolyzed to give the trienoic acid **6**.

With the trienoic acid fragment **6** now in hand, the stage was set to combine **6** with the above-described amine

(11) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) Wood, J. L.; Khatri, N. A.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 4907−4910.
(12) Considerable epimerization was observed when THF was used as a solvent.
(13) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.
(14) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004−4006.
(15) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634−644.

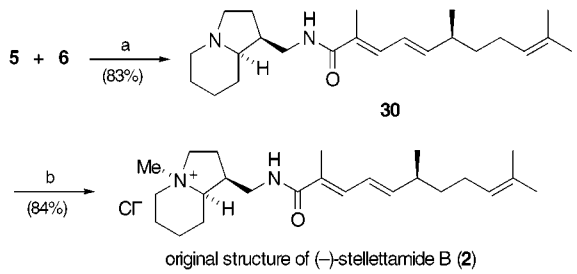
Scheme 4[a]



[a] (a) $NaIO_4$, dioxane−H_2O; (b) CBr_4, Ph_3P, MeCN; (c) $(EtO)_3P$, reflux; (d) BuLi, THF, −78 °C; (e) LiOH, THF−H_2O, reflux.

fragment **5** via amide coupling for the synthesis of the proposed structure of stellettamide B (**2**). Thus, the two fragments **5** and **6** were condensed by using DCC−DMAP to give the coupling product **30** in 83% yield (Scheme 5). Subsequent quarternization with iodomethane led to the iodomethylate which was, upon exposure to AgCl, converted to the chloromethylate, providing **2** in 84% yield. The synthetic sample of **2** exhibited a ^{13}C NMR spectrum which was quite superimposable on that of natural stellettamide B kindly supplied by Professor Shin. Otherwise, the ^1H NMR spectrum of synthetic **2** was very similar to that of the natural product, but careful inspection of these spectra revealed that there are significant differences in the signal patterns observed for the protons at C(3), C(5), and C(9) in the 1-(aminomethyl)indolizidine moiety. The most striking difference was found between the optical rotation of synthetic **2** ($[\alpha]^{24}_D$ +23.6 (*c* 0.58, $CHCl_3$)) and that reported for the

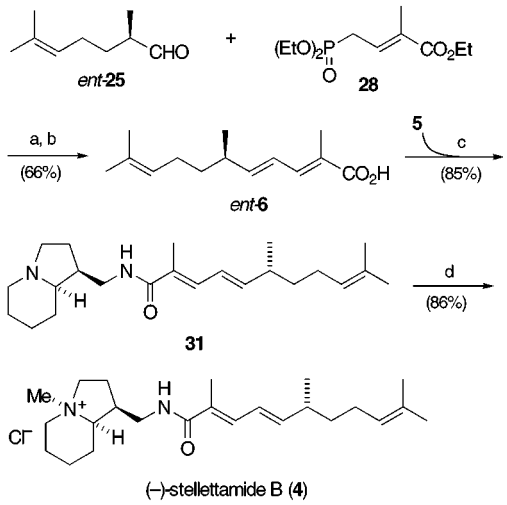
Scheme 5[a]



[a] (a) DCC, DMAP, CH_2Cl_2; (b) MeI, MeOH, then AgCl.

natural product ($[\alpha]^{25}_D$ −24.2 (*c* 0.5, $CHCl_3$)[2]). These results revealed that the structure of stellettamide B is not as originally formulated and suggested that the natural alkaloid is epimeric at C(6″) as depicted by structure **4** (or its antipode *ent*-**4**). To clarify this issue, we undertook the synthesis of **4** containing the aminomethylindolizidine structure with the same absolute stereochemistry as that found in natural stellettamides A (**1**) and C (**3**). The synthesis followed the above-described amide coupling protocol using the aminomethylindolizidine and trienoic acid fragments. The synthesis of the required (*R*)-trienoic acid *ent*-**6** was carried out by using the same sequence outlined in Scheme 4 except for the use of the (*R*)-aldehyde *ent*-**25** prepared via asymmetric epoxidation using D-diethyl tartrate. The DCC−DMAP condensation of **5** with *ent*-**6** furnished the coupling product **31** (85% yield), which was converted into the chloromethylate **4** by sequential treatment with MeI and AgCl (Scheme 6). Both ^1H and ^{13}C spectra of the obtained compound **4**

Scheme 6[a]



[a] (a) BuLi, THF, −78 °C; (b) LiOH, THF−H_2O, refl; (c) DCC, DMAP, CH_2Cl_2; (d) MeI, MeOH, then AgCl.

were found to be completely identical to those of natural stellettamide B. Additionally, the observed optical rotation value, $[\alpha]^{27}_D$ −28.0 (*c* 0.71, $CHCl_3$), agreed satisfactorily with the reported value ($[\alpha]^{25}_D$ −24.2 (*c* 0.5, $CHCl_3$)[2]).

In conclusion, the first total synthesis of (−)-stellettamide B has been achieved by a sequence based on amide coupling of the chiral 1-(aminomethyl)indolizidine fragment, prepared by $TiCl_4$-mediated asymmetric allylation of the tricyclic *N*-acyl-*N*,*O*-acetal, with the chiral trienoic acid fragment This synthesis led to revision of the published relative stereochemistry of the natural product and established its absolute stereochemistry to be 1*S*,4*S*,8a*R*,6″*R*.

Acknowledgment. We are grateful to Professor J. Shin (Korean Ocean Research and Development Institute) for providing authentic ^1H and ^{13}C NMR spectra of natural stellettamide B.

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