Enantioselective Synthesis of *ent*-Stellettamide A via a Novel Dipolar Cycloaddition Reaction of (Trimethylsilyl)diazomethane

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Stellettamide A (**1**), the first indolizidine metabolite from a marine sponge, was isolated recently using a bioassay-guided strategy (Figure 1).[1] It possesses antifungal activity and displays cytotoxicity against K562 epithelium cell lines. The initial structural studies did not lead to assignment of the stereogenic center present in the trienoic acid side chain or of the absolute stereochemistry of the natural product. We became interested in stellettamide A as a target for synthesis since, upon retrosynthetic analysis, it presented an opportunity for the construction of the indolizidine core via a novel strategy involving an intermediate chiral pyrazoline **2** (Figure 1).[2] In this paper, we report an enantioselective synthesis of *ent*-stellettamide A that establishes its absolute stereochemistry. Moreover, the synthetic route employs an asymmetric diazoalkane dipolar cycloaddition and the use of the pyrazoline adducts of such reactions as useful starting materials for asymmetric synthesis.[3,4]

We have been interested in the development of practical [3 + 2]-cycloaddition reactions between chiral dipolarophiles and (trimethylsilyl)diazomethane.[5] This 1,3-dipole is a safe, stable diazoalkane that is commercially available as a solution in hexane and ready for use. Previous use of diazoalkane/olefin cycloadducts in synthesis has been limited to the preparation of cyclopropanes or pyrazoles obtained upon N_2 extrusion or oxidative aromatization, respectively. However, optically active pyrazolines such as **4** are potentially useful precursors to functionalized chiral acyclic synthons **7** (Scheme 1). The implementation of such a strategy would require two key points to be resolved. First, prior reports on cycloadditions of diazoalkanes with esters had highlighted the propensity of adducts **4** to undergo tautomerization to the conjugated Δ^2-pyrazoline **5**.[6] In this regard, we speculated that the electrofugal Me_3Si moiety in the Me_3SiCHN_2 cycloadduct would dictate its subsequent mode of isomerization (Scheme 1, **4** → **2** vs **4** → **5**). Second,

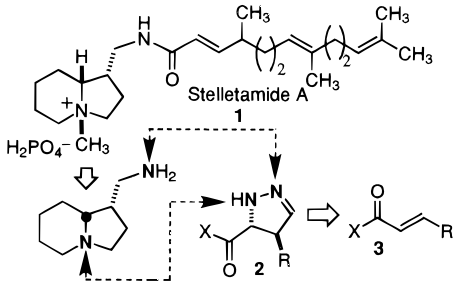
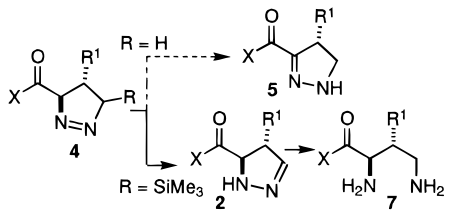


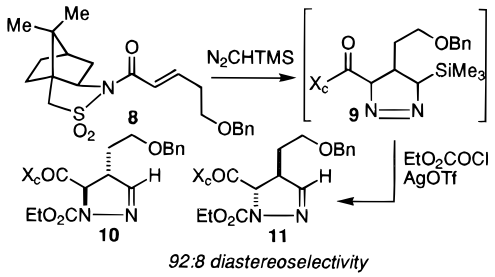
Figure 1. Retrosynthetic strategy for stellettamide A.

Scheme 1



the successful strategy would require the development of reaction methodology for N−N and C=N bond reductions of functionalized, chiral Δ^2-pyrazolines (Scheme 1, **2** → **7**).

When a solution of dipolarophile **8** in hexane/CH_2Cl_2 was treated with a commercial solution of Me_3SiCHN_2 (2.2 equiv), the pyrazoline cycloadducts were isolated in quantitative yield upon evaporation of the solvent (eq 1).



(1)

Analysis by ^1H NMR spectroscopy revealed that the adducts had been formed as a 93:7 mixture of C(2)/C(3) diastereomers. Treatment of the unpurified diastereomeric cycloadduct mixture with EtO_2CCl and AgOTf led to formation of the desired desilylated pyrazolines, which could be readily separated by chromatography on silica gel to give **10** in 71% isolated yield and **11** in 6% yield (92:8 diastereoselectivity).[7] This two-step sequence of reactions has been reproducibly carried out on a large scale to deliver substantial quantities of the protected isomerically pure pyrazoline **10**.

Having established two key stereocenters in the cycloaddition reaction, we proceeded to assemble the piperidine ring (Scheme 2). Aldehyde **12** was prepared by reduction of **10** to the corresponding primary alcohol ($LiAlH_4$, 91%) followed by Swern oxidation (93%). Treatment of **12** with the acetylide derived from Me_2-^{t}BuSiOCH$_2$C≡CH gave a secondary propargyl alcohol,

(1) (a) Hirota, H.; Matsunaga, S.; Fusetani N. *Tetrahedron Lett.* **1990**, *31*, 4163. (b) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J. R.; Sim, C. J. *J. Nat. Prod.* **1997**, *60*, 611.

(2) For a review indolizidine syntheses, see: Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535. For recent advances in methodology aimed at the preparation of indolizidines, see: (a) Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707. (b) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082. (c) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248.

(3) For general references, see: (a) Carruthers, W. *Cycloaddition Reactions in Organic Sythesis*; Pergammon: Oxford, 1990; p 269. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 4, p 1069. (c) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 4, p 1111. (d) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Wiley: New York, 1991; Vol. 5, p 239.

(4) For a comprehensive review of asymmetric dipolar cycloadditions, see: Cinquini, M., Cozzi, F. Formation of C−C Bonds by [3+2] Cycloadditions. In *Stereoselective Synthesis*; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 5, p 2953.

(5) Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379.

(6) (a) Galley, G.; Pätzel, M.; Jones, P. G. *Tetrahedron* **1995**, *51*, 1631. (b) Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Organomet. Chem.* **1972**, *44*, 279.

(7) We have obtained X-ray crystal structures of the adducts formed from the addition of crotyl and methacryloyl camphor sultam and Me_3SiCHN_2. The stereochemistry of the adducts is consistent with the models that have been previously proposed; see: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

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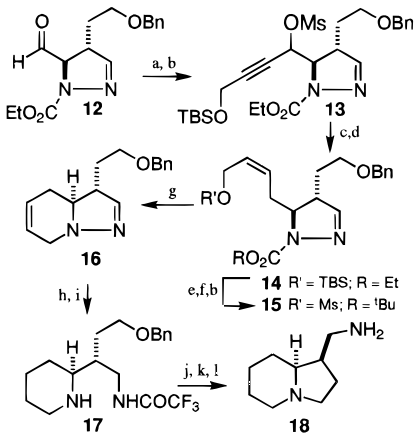
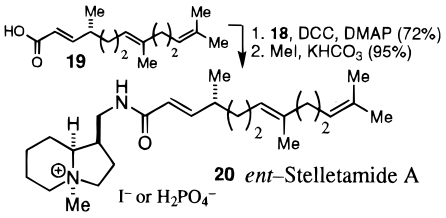
Scheme 2



[a] Key: (a) $TBSOCH_2C{\equiv}CMgBr$, THF, 0 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 68% two steps; (c) Bu_3P, Pd_2dba_3, $(NH_4)HCO_2$, PhH, 76%; (d) 5% $Pd/BaSO_4$, H_2, quinoline, MeOH, 95%; (e) $Ba(OH)_2$, aqueous dioxane, 100 °C; (f) Boc_2O, aqueous NaOH, THF, 23 °C, 80% two steps; (g) 10% H_2SO_4 dioxane; 2 N NaOH, 83%; (h) Ra−Ni, H_2, EtOH; (i) CF_3CO_2Et, THF, 0 °C, 85% two steps; (j) $Pd(OH)_2$/C, $(NH_4)HCO_2$, MeOH, reflux, 85%; (k) CBr_4, PPh_3, Et_3N, MeCN, 0 °C, 75%; (l) 5% K_2CO_3, aqueous MeOH.

which without purification underwent mesylation to afford **13** (68% two steps). Conversion of **13** to *cis*-alkene **14** was effected by hydrogenolysis of the propargyl mesylate (76%) followed by semihydrogenation of the alkyne (95%).[8] Treatment of **14** with aqueous $Ba(OH)_2$ effected hydrolysis of the ethyl carbamate and the silyl ether to afford a pyrazoline that was selectively protected as the corresponding *N*-Boc-carbamate (80%, two steps) and treated with MsCl to afford **15**. An in situ procedure was developed for cleavage of the Boc-amide with concomitant pyrazolidine ring formation: dissolution of **15** in 10% concentrated H_2SO_4/dioxane resulted in hydrolysis of the carbamate; this was followed by addition of the reaction mixture to a 2 M NaOH solution from which **16** was isolated (83%, two steps). Treatment of **16** with Ra−Ni/H_2 effected C=C and C=N reduction along with N−N bond cleavage to give a diamine, which was subsequently selectively protected as the corresponding *N*-trifluoroacetamide (**17**) (85%, two steps). Hydrogenolysis of the benzyl ether followed by treatment of the resulting primary alcohol with CBr_4 and Ph_3P resulted in ring closure.[9] Subsequent alkaline hydrolysis of the trifluoroacetamide delivered the indolizidine core of stelletta-mide **18**.

Since the relative configuration of the side chain was not determined in the isolation studies, both (*R*)- and (*S*)-trienoic acids **19** and *ent*-**19** were synthesized.[10] Each of the two carboxylic acids was coupled with **18** to produce diastereomeric indolizidines that were separately methylated (MeI, DMF) to give stellettamide A and its C(4′) epimer (eq 2). Upon spectroscopic analysis of each, diastereomer **20** was shown to be identical (^1H NMR, ^{13}C NMR and in chromatographic behavior HPLC, 72% 20mM KH_2PO_4, 28% ^{i}PrOH, Sephadex C18) with natural stellettamide A,[11] except for its optical rotation, which differed only in sign.[12]



(2)

We have described an enantioselective synthesis of the unusual marine metabolite *ent*-stellettamide A. The salient features of the route include the following: (1) unambiguous assignment of the absolute stereochemistry of stellettamide A and (2) synthesis of the indolizidine core from an optically active substituted pyrazoline that is prepared using a novel dipolar cycloaddition reaction. The development of asymmetric [3 + 2]-cycloaddition reactions utilizing Me_3SiCHN_2 as a safe, commercially available diazoalkane dipole provides rapid access to optically active pyrazolines that may be elaborated, as the synthesis described demonstrates, to give useful chiral diamine starting materials. Further applications of these dipolar cycloaddition reactions are currently being studied and will be the subject of future reports.

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Supporting Information Available: Experimental procedures including synthesis and characterization of new compounds reported herein (15 pages).

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(9) Stoilova, V.; Trifonov, L. S.; Orahovats, A. S. *Synthesis* **1979**, 105.

(10) The synthesis of **19** and *ent*-**19** commences with alkylation of *N*-propionylpseudoephedrineamide with the known homogeranyl iodide following the general procedure recently described by Myers, giving alkylated product in 92% yield as a single diastereomer by ^1H NMR spectroscopy (Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361). Reduction of the alkylation product to the corresponding aldehyde followed by condensation with (carbethoxy−methylene)triphenylphosphorane gave the ethyl esters of **19** and *ent*-**19**, which were subsequently saponified (LiOH, THF) to furnish **19** and *ent*-**19**.

(11) We are grateful to Prof. Fusetani for generously furnishing us with authentic natural stellettamide A.

(12) The iodide salt of **20** was dissolved in 25% MeOH/KH_2PO_4 and extracted with CH_2Cl_2 to give the monobasic phosphate salt, which was shown to be identical with stellettamide A by spectroscopic methods.