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Total Synthesis of the Originally Proposed and Revised Structures of Scleritodermin A

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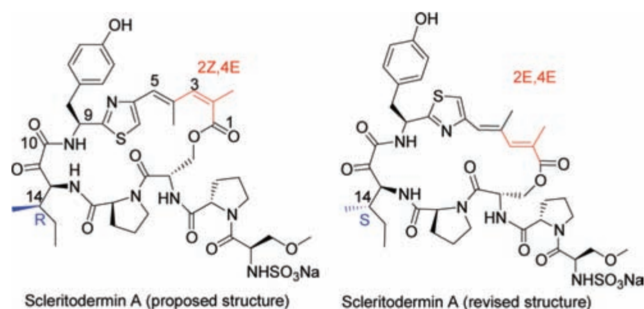
ABSTRACT



The first total synthesis of the originally proposed and revised structure of scleritodermin A, along with an isomer, were achieved by the use of an α-azido carboxyl group serving as the key α-ketoamide precursor, thus leading to a revision of the structure originally proposed for natural scleritodermin A.

Scleritodermin A is a cyclic depsipeptide isolated from the lithistid sponge *Scleritoderma nodosum*.[1] Significant in vitro cytotoxicity of this peptide was demonstrated in human tumor cell lines. Scleritodermin A (Figure 1), a highly modified peptide, has an unusual N-sulfated side chain and a novel conjugated thiazole moiety, as well as an α-ketoamide group. Intrigued by the architecture of this molecule, we initiated a research program aimed at the total synthesis of scleritodermin A, as well as the modification of its structure for fine-tuning of the biological activity of this peptide. The synthesis of naturally occurring marine metabolites bearing α-ketoamide units such as cyclotheonamides and keramamides has been extensively studied since the early 1990s.[2] Here, we

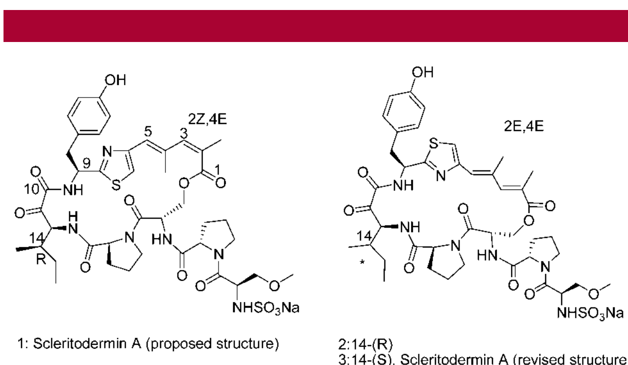


Figure 1. Originally proposed and revised structures of scleritodermin A and its isomers.

(1) Schmidt, E. W.; Raventos-Suarez, C.; Bifano, M.; Menendez, A. T.; Fairchild, C. R.; Faulkner, D. J. *J. Nat. Prod.* **2004**, *67*, 475.

(2) (a) Hagihara, M; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570. (b) Wipf, P.; Kim, H. *J. Org. Chem.* **1993**, *58*, 5592. (c) Deng, J.; Hamada, Y.; Shioiri, T.; Matsunaga, S.; Fusetani, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1729. (d) Maryanoff, B. E.; Greco, M. N.; Zhang, H. C.; Andrade-Gordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225. (e) Bastiaans, H. M. M.; Van der Baan, J.; Ottenheijm, H. C. J. *J. Org. Chem.* **1997**, *62*, 3880. (f) Sowinski, J. A.; Toogood, P. L. *Chem. Commun.* **1999**, 981. (g) Wasserman, H. H.; Zhang, R. *Tetrahedron* **2002**, *58*, 6277.

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report a new strategy for assembling these macrocyclic α-keto lactams by the use of an α-azido carboxyl group as the key intermediate and the first total synthesis of the originally proposed and revised structures of scleritodermin A.

Figure 2 depicts our retrosynthetic analysis. The unique features of our synthesis plan involved the addition of an

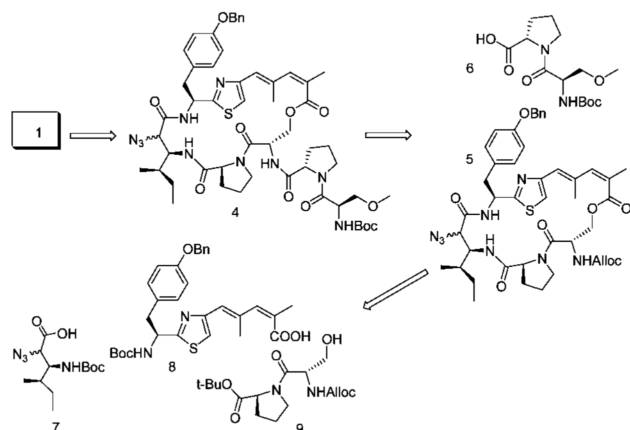
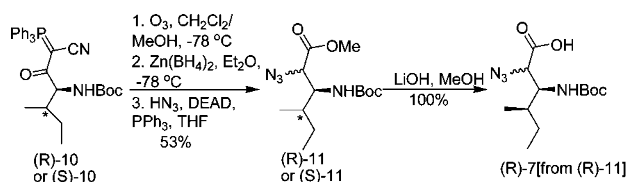


Figure 2. Retrosynthetic analysis of target molecule **1**.

azide group to the cyclic backbone of the target molecule and the application of a biomimic transamination reaction for the formation of the key α-keto lactam unit. Therefore, molecule **1** was divided into two parts: the macrocyclic core **5** and the dipeptide side chain **6**. Further disconnections provided three synthetic precursors: α-azido *β*-amino acid **7**, (2*Z*,4*E*)-conjugated thiazole moiety **8**, and dipeptide **9**.

Our synthesis process started with the preparation of fragments **7** and **8**. Ozonolysis of (*R*)-**10** in MeOH using Wasserman's procedure[3] yielded an α-keto ester, which was subsequently converted into the desired alcohol (two isomers, 6:1) after reduction with $Zn(BH_4)_2$. The subsequent application of the standard Mitsunobu reaction,[4] followed by a saponification step, resulted in the production of an amino acid (fragment **7**) (Scheme 1). In a parallel procedure

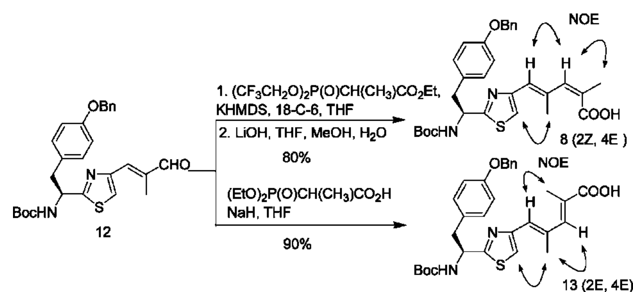
Scheme 1. Synthesis of Azido-Bearing Fragments



(Scheme 2), the aldehyde **12**, which was previously reported by Serra et al. in their attempt at synthesizing scleritodermin

(3) Wasserman, H. H.; Ho, W. B. *J. Org. Chem.* **1994**, *59*, 4364.
(4) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

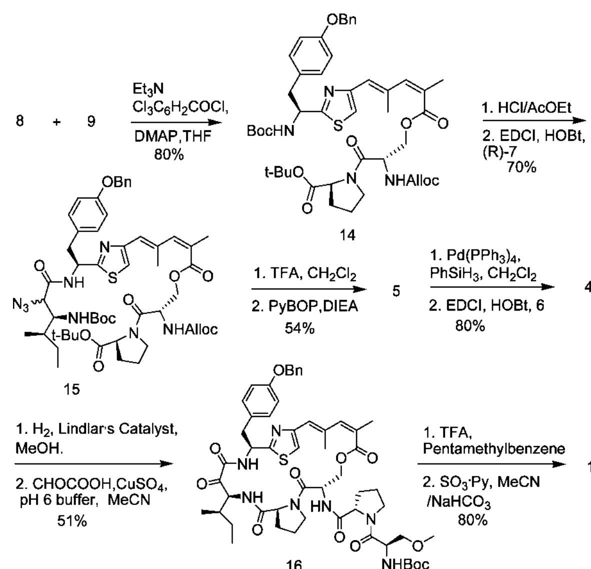
Scheme 2. Synthesis of Geometric Conjugated Thiazole Acids



A,[5] was subjected to Horner–Wadsworth–Emmons olefination according to the Still–Gennari procedure,[6] followed by saponification to yield the (2*Z*,4*E*)-conjugated thiazole acid **8**.

The coupling of fragments **8** and **9** was accomplished using Yamaguchi's protocol[7] (Scheme 3). The selective removal

Scheme 3. Fragment Coupling and Initial Synthesis



of the Boc group with HCl proceeded smoothly in the presence of the acid-labile *tert*-butyl ester.[8] The resulting amide was coupled with fragment **7** to produce the cyclization precursor, fragment **15** (two isomers, 2.6:1). Subsequently, the simultaneous unmasking of the amine and acid groups by treatment with TFA allowed the cyclization to be effected via activation with PyBop and $(i\mathrm{Pr})_2\mathrm{NEt}$ at high dilution in CH_2Cl_2 (54% yield). The Alloc protecting group

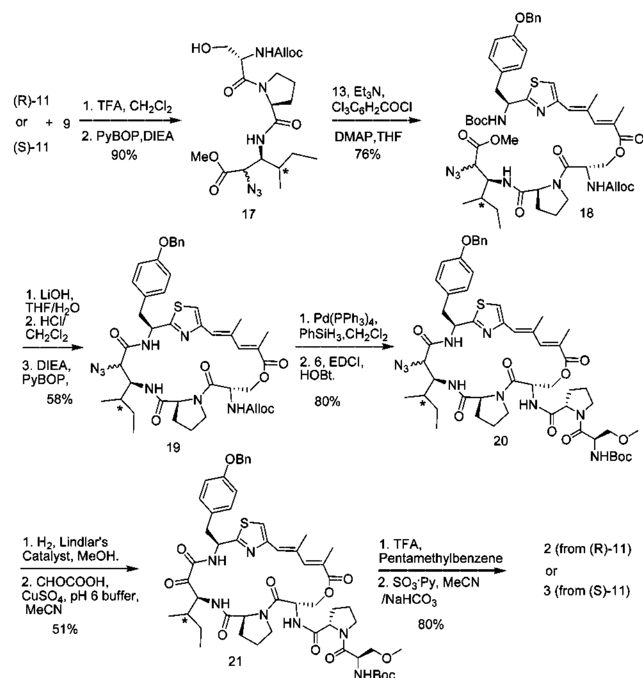
(5) Sellanes, D.; Manta, E.; Serra, G. *Tetrahedron Lett.* **2007**, *48*, 1827.
(6) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(7) Inanaga, J; Hirata, K; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(8) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216.

was removed with $Pd(PPh_3)_4$,[9] permitting the incorporation of the side chain **6** and forming fragment **4**. Several attempts to chemoselectively reduce the azide compound **4** to the corresponding amine via a Staudinger reaction using triphenylphosphine or trimethylphosphine were problematic, due to difficulties in hydrolyzing these stable phosphazine ylides. However, we were able to circumvent this problem by hydrogenating the azide group using Lindlar's catalyst; the conjugated moiety was better tolerated under this condition. With this α-amine amide in hand, the stage was now set for the critical transamination reaction. In Corey's work toward the synthesis of Et-743,[10] a pyridoxal mimic-mediated oxidative deamination was used; however a strong base such as DBU was needed. In our study we found that mild conditions[11] using glyoxylate as an electrophile and copper(II) ions as catalysts in an aqueous acetate buffer at pH 6.0 were more suitable and led to the production of compound **16** as a single diastereomer (51% yield for both steps).

With a successful route to the production of racemization-free compound **16** established, the subsequent removal of both Bn and Boc protective groups with TFA in the presence of pentamethylbenzene[12] and the selective monosulfation with sulfur trioxide pyridine complex in aqueous MeCN led to molecule **1** with a good yield. However, ^{1}H and ^{13}C NMR spectra of molecule **1** did not match those reported for natural scleritodermin A: there were significant discrepancies in chemical shifts in the region for conjugated vinylic protons. It was apparent that both CH-3 and CH-5 signals of the synthetic sample were located more than 1.0 ppm upfield from the reported value. Since the NOESY correlation between CH-3 and CH-5 signals of the natural product in the original assignment seemed much weaker than the NOESY correlation of synthetic molecule **1**, we postulated that the correct configuration of the conjugated thiazole residue might be 2*E*,4*E*. Furthermore, the observation of a difference in chemical shifts between synthetic molecule **1** and the natural sample represented the two $-CH_3$ groups at the keto-Ile moiety (0.81 and 0.79 ppm for structure **1**, versus 0.91 and 0.79 ppm for the natural sample), when taken together with the fact that the keto-Ile moiety with an (*S*)-isobutyl side chain is present in both keramamide F[13] and oriamide,[14] led us to propose that the corresponding stereocenter of scleritodermin A may be in the (*S*)-configuration, despite the 14-(*R*) assignment suggested in the original isolation paper.

To test the hypotheses proposed above, compounds **2** and **3**, which have an (*R*)- or (*S*)-isobutyl at the keto-Ile moiety and a 2*E*,4*E*-conjugated thiazole residue, respectively, were selected as our new target molecules. Fragment **13** with the required *trans* double bond was generated from aldehyde **12** (Scheme 2). It seemed reasonable to us that continuing the synthesis following the established procedure for compound **1** with (*R*)- or (*S*)-**11** derived from L-allo-Ile or L-Ile would deliver both **2** and **3**. However, our attempts to implement macrocyclization at the previous position (between Ile and Pro) gave only dimers because the favorable conformation for cyclization was changed when the *cis* double bond was replaced with a *trans* one in the precursor peptide. Using the fragments and synthetic intermediates at hand, we designed a new route for synthesis of the macrocyclic core (Scheme 4; all yields shown were based on (*S*)-**11**). Fragments (*R*)- or (*S*)-**11** and fragment **9** were deprotected and coupled to produce the required alcohol **17** in a high yield. The coupling of molecules **17** and **13** was subsequently carried out via Yamaguchi esterification,[7] giving rise to compound **18**. In addition, adoption of the LiOH condition to chemoselectively hydrolyze methyl ester groups was successful in recovering small amounts of fragment **13** (12%) from the reaction. Ultimate closure of the depsipeptide was readily achieved between the tyrosine and α-azido-β-amino acid residues, after deprotecting the Boc group. The synthesis then proceeded uneventfully following the previously described conditions and yielded molecules **2** and **3**. The ^{1}H NMR spectra of compound **2** was found to be quite similar to the spectra recorded for the natural product: the signals for CH-3 and CH-5 found at 7.54 and 7.41 ppm, respectively, were identical to the correct values, as expected, but persisting discrepancies in chemical shift at the keto-Ile moiety suggested that molecule **2** represented an epimer of the natural product. Much to our delight, the ^{1}H and ^{13}C NMR of compound **3** were identical

Scheme 4. Completion of the Synthesis



(9) Dessolin, M; Guillerez, M. G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741.
(10) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.
(11) Papanikos, A.; Rademann, J; Meldal, M. *J. Am. Chem. Soc.* **2001**, *123*, 2176.
(12) Yoshino, H.; Tsuji, M. *Chem. Pharm. Bull.* **1990**, *38*, 1735.
(13) Itagaki, F.; Shigemori, H.; Ishibashi, M.; Nakamura, T.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 5540.
(14) Chill, L.; Kashman, Y.; Schleyer, M. *Tetrahedron.* **1997**, *53*, 16147.

with those of natural scleritodermin A.[15] Curiously, the specific rotation value of our synthetic compound **3** ($[\alpha]^{25}_{D}$ −108, *c* 0.1, MeOH) was different from that reported for natural scleritodermin A ($[\alpha]_{D}$ −41, *c* 0.1, MeOH); however, we believe this discrepancy was caused by the impurity of the natural product in ^{1}H NMR and HPLC analysis.[16] Thus, we revised the two incorrect assignments reported in the original paper describing the isolation of natural product scleritodermin A, and we assigned molecule **3** described here as the correct structure of scleritodermin A.

In summary, we achieved the first total synthesis of scleritodermin A (product **3**) along with two isomers (products **1** and **2**), thus leading to a revision of the structure originally proposed for natural scleritodermin A. Although several methods to construct α-keto lactam containing macrocycles are established, such as using a protected α-hydroxy carboxyl group as the key α-ketoamide precursor[2a−f] or forming the α-ketoamide at the early stage,[2g] the application of a mild transamination reaction in this chemical environment toward the formation of the α-ketoamide unit was effective. This, combined with the fact that the azide group is inert in peptide synthesis made our strategy flexible and versatile. Since α-ketoamides are substructures found in a variety of natural products, the methodology described herein can be applied to other natural targets.

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Supporting Information Available: Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Simultaneous injection of natural and synthetic compounds gave only one major peak at t_r = 30.88 min (A = 0.05 M KH_2PO_4 in H_2O, B = CH_3OH, gradient = 0−100% B in 45 min). A sample of Scleritodermin A was kindly supplied by Professor Eric Schmidt of Utah University.

(16) See Supporting Information for details.