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Toward the total synthesis of Scleritodermin A: preparation of the C_1–N_{15} fragment

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Abstract—The synthesis of the C_1–N_{15} fragment of the marine natural product Scleritodermin A has been accomplished through a short and stereocontrolled sequence. Highlights of this route include the synthesis of the novel ACT fragment and the formation of the α-keto amide linkage by the use of a highly activated α,β-ketonitrile.

Marine sponges of the order Lithistida are excellent sources of bioactive metabolites.[1] They produce cyclic peptides with non-proteinogenic amino acids and polyketide moieties, such as Cyclotheonamides,[2] Oriamide,[3] and Keramamides.[4] Recently, another macrocyclic compound, Scleritodermin A (**1**), was isolated by Schmidt et al. from the sponge *Scleritoderma nodosum*.[5] It shows significant cytotoxic activity against a panel of human tumor cells lines (IC_{50} <2 μM). The structure of Scleritodermin A incorporates a novel conjugated thiazole moiety 2-(1-amino-2-*p*-hydroxyphenylethane)-4-(4-carboxy-2,4-dimethyl-2*Z*, 4*E*-propadiene)-thiazole (**ACT**), L-proline, L-serine, and the unusual amino acids keto-*allo*-isoleucine and *O*-methyl-*N*-sulfo-D-serine.

It has been suggested that the α-keto amide function of the Cyclotheonamides is involved in the deactivation of a protease.[6,7] The same function, is presented in immunosupressants such as rapamycin and FK-506.[8]

In spite of such an interesting biological activity, the synthetic challenge defined by the assemblage of the thiazole ring, the polyketide chain, and the α-keto amide function in the macrocycle, has not been described in the literature up to date.

Our interest on the synthetic studies of marine natural products[9] stimulated us to embark upon a total synthesis of this compound and its analogs. We describe, herein, the synthesis of the **ACT** fragment and its coupling to the α,β-ketonitrile derived from L-*allo*-Ile to obtain the key intermediate C_1–N_{15} fragment.

Our retrosynthetic analysis of Scleritodermin A is shown in Scheme 1. Disconnection at the ester group of the macrolactone and cleavage of the amide bond between keto-*allo*-Ile and L-proline give C_1–N_{15} fragment (**2**). This fragment contains a conjugated thiazole and the α-ketoamide moiety, also found in other marine natural products like Oriamide and Keramamides. The disconnection of the amide bond in fragment **2** produces the **ACT** derivative, which could be obtained from thiazole **6**. We propose to synthesize this compound (**6**) by cyclodehydration of a β-hydroxy thioamide derived from L-serine and L-tyrosine.

For synthesizing the **ACT** derivative we began by protecting the amino group of the *O*-benzyl-L-tyrosine with Boc. Then, a coupling reaction with L-serine methyl ester provided product **3** in a 96% yield,[10] Scheme 2. When the corresponding β-hydroxy thioamide **5** was obtained by using the Lawesson's reagent (after protection of the alcohol group), the reaction proceeded in a poor yield. In contrast, **5** was obtained in a high yield using Wipf's procedure by cyclodehydration of the β-hydroxy amide with DAST,[11] giving oxazoline **4** (87%) and then thiolysis using H_2S,[12] (92%). For the synthesis of the thiazole rings our group had reported the use of Deoxo-Fluor and *in situ* oxidation,[9c] but no reports were found in the literature using DAST and $BrCCl_3$/DBU. To produce the desired thiazole **6** from thioamide **5**, we

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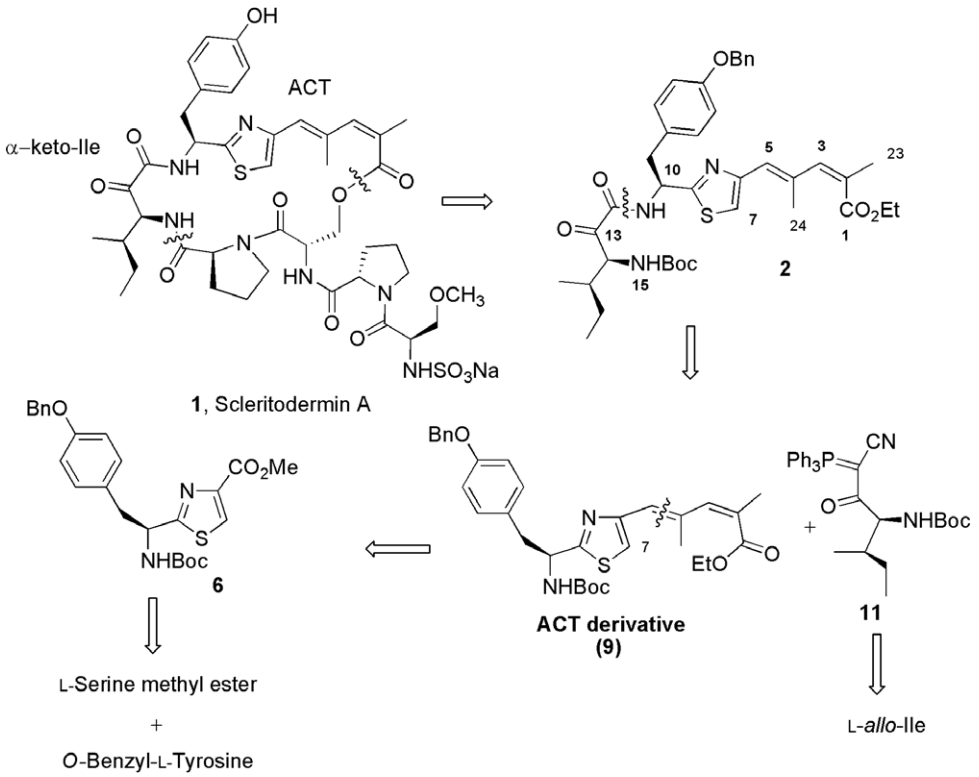
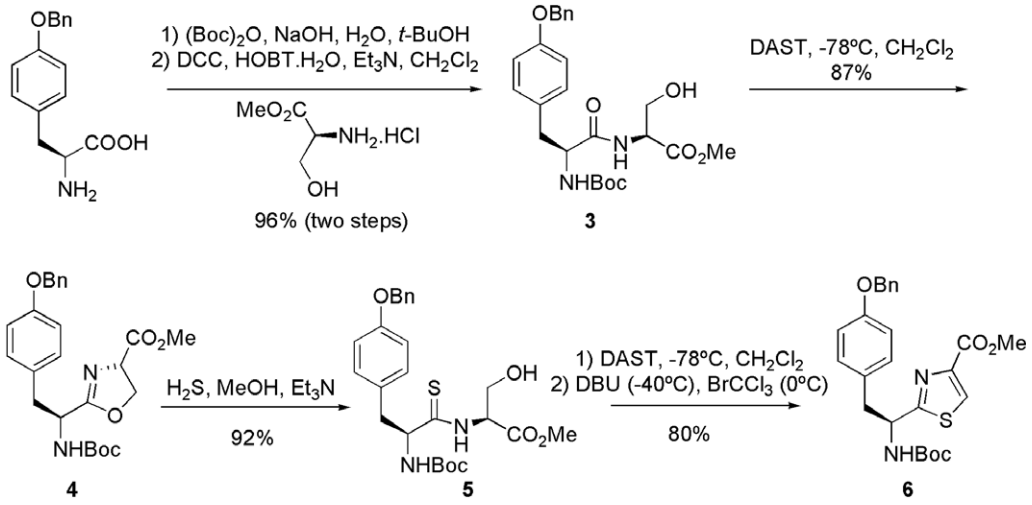


Scheme 1. Retrosynthetic analysis of Scleritodermin A (**1**).



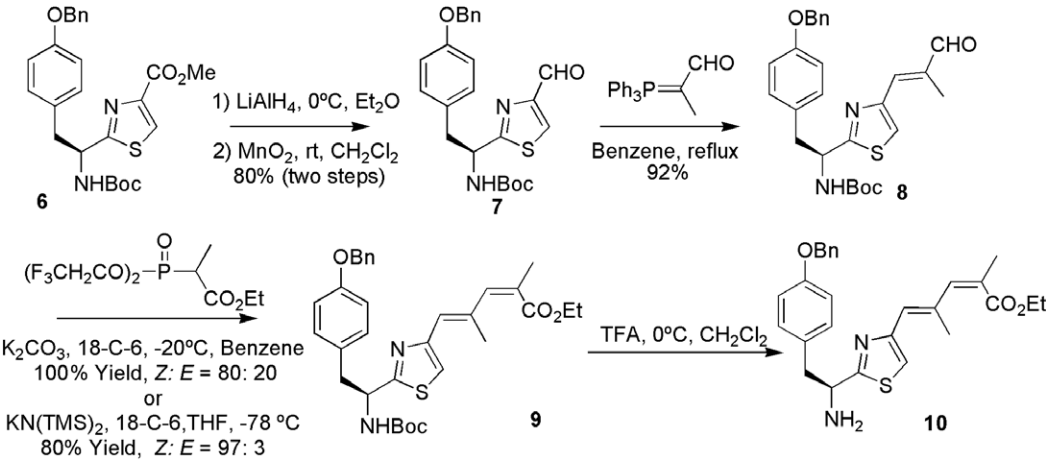
Scheme 2. Synthesis of thiazole **6**.

investigated both procedures. The better yield was obtained using DAST/$BrCCl_3$/DBU (80%). The issue of potential racemization of the tyrosine stereogenic center under the dehydration–dehydrogenation conditions was addressed by chiral HPLC analysis of the thiazole derived from dipeptide **5**.[13]

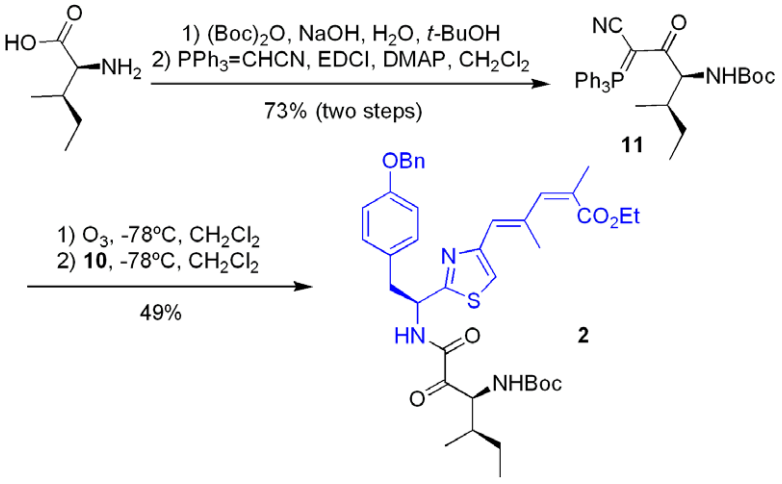
For synthesizing the **ACT** derivative, the ester group of **6** had to be converted to the corresponding aldehyde. Since the reduction of **6** using DIBALH rendered the aldehyde **7** in a poor yield, we used instead $LiAlH_4$ and then activated MnO_2 (80% yield two steps, Scheme 3).

The Wittig reaction between aldehyde **7** and 2-(triphenylphosphoranylidene)-propianaldehyde rendered exclusively *E* alkene (**8**) in a 92% yield.

For the last coupling reaction of the **ACT** derivative synthesis (**9**), we investigated different conditions. When the ylide ethyl 2-(triphenylphosphoranylidene)propionate was refluxed in benzene, the *E* isomer was obtained



Scheme 3. Synthesis of **ACT** derivative.



Scheme 4. Synthesis of the C_1–N_{15} fragment.

exclusively. Then, the reaction was done in MeOH at 0 °C,[14] but again only the *E* isomer was obtained. Finally, we used the modification of Still–Gennari for the HWE reaction,[15] and the **9** fragment was obtained in *Z*:*E*, 80:20 using K_2CO_3 or 97:3 using $KN(TMS)_2$ as the base. The configuration of the two double bonds was confirmed by NOE correlation between: (1) H_7 of the thiazole ring and the methyl group attached to C_4 and (2) H_3 and the methyl group attached to C_2 (see Scheme 1). Finally, the amine **10** was obtained by cleaving the Boc group of **9**.

Our synthesis of α-ketoamide **2** (C_1–N_{15} fragment) utilized the reaction of the nucleophile **10** and a highly electrophilic α,β-ketonitrile derived from L-*allo*-Isoleucine. This procedure was described by Wasserman and Zhang[16] for the synthesis of Cyclotheonamide E_2 and E_3. The synthesis of Cyclotheonamides A and B have been reported by Schreiber and Hagihara,[17] Wipf and Kim,[18] Shioiri and co-workers,[19] Maryanoff et al.[6] and Ottenheijm and co-workers.[20] All of them obtained the α-ketoamide function by the oxidation of α-hydroxy precursors in the final steps of the procedures.

Protection of the amine group of L-*allo*-Isoleucine with Boc and further reaction of its carboxylic acid with the (triphenylphosphoranylidene)acetonitrile ylide using the coupling reagent EDCI, allowed us to obtain cyano keto phosporane **11** (Scheme 4). Ozonolysis of **11** generated the α,β-ketonitrile, not isolable. Finally, **10** was added to obtain the desired C_1–N_{15} fragment (**2**) in 49% yield. The structure of this product was confirmed by the presence of a signal at 194.5 ppm (^{13}C NMR) assignable to the C_{13} (keto function).[21]

In conclusion, a key fragment of Scleritodermin A was prepared in a good overall yield from readily available starting materials. Further progress toward the total synthesis of this natural product will be reported in the due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.034.

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21. *Synthesis of C_1–N_{15}-fragment* (**2**): Compound **9** (128 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) was added at 0 °C. The reaction mixture was stirred until TLC indicated that all starting material had been consumed. The solvent was evaporated and the residue was dissolved with saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the nucleophile **10** as a yellow oil (103 mg). Compound **10** was used without further purification.
A solution of **11** (126 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was ozonized at −78 °C until the color of the solution remained blue (or yellow-blue). After the solution was purged with N_2 to remove the excess O_3, the nucleophile **10** (103 mg, 0.22 mmol) was introduced at −78 °C. The reaction was stirred at −78 °C for 2 h and then quenched with HCl 1 M and extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:2) gave the desired product **2** (*Z*/*E* mixture) as a yellow oil (76 mg, 49%).
Compound **2**: $R_f = 0.45$ (EtOAc/*n*-hexane, 1: 2); IR (film) 2926, 1716, 1699, 1508, 1248, 1016, 748; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.68 (d, $3H_{35}$, $J = 6.9$ Hz), 1.00 (t, $3H_{34}$, $J = 6.9$ Hz), 1.31 (m, $5H_{33,\ 27}$), 1.44 (s, $9H_{31}$), 1.96 (m, $1H_{32}$), 2.06 (s, $3H_{24}$), 2.20 (s, $3H_{21}$), 3.29 (m, $2H_{10}$), 4.23 (q, $2H_{26}$, $J = 7.2$ Hz), 5.03 (m, $3H_{28,15}$), 5.20 (m, $1H_9$), 5.50 (m, $1H_5$), 6.31 (s, $1H_{22}$), 6.50 (s, $1H_1$), 6.88 (d, $2H_{13}$, $J = 8.7$ Hz), 7.03 (m, $3H_{12,3}$), 7.42 (m, $5H_{17,18,19}$), 7.67 (m, $1H_6$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.0 (C_{34}), 14.1 (C_{35}), 14.5 (C_{27}), 17.8 (C_{21}), 22.0 (C_{24}), 28.6 (C_{31}), 30.0 (C_{33}), 36.7 (C_{32}), 41.4 (C_{10}), 52.5 (C_5), 58.8 (C_9), 61.1 (C_{26}), 70.4 (C_{15}), 79.9 (C_{30}), 115.3 (C_{13}), 117.5 (C_3), 124.2 (C_1), 127.8 (C_{18}), 128.3 (C_{19}), 128.9 (C_{17}), 129.3 (C_{11}), 129.6 (C_{23}), 130.8 (C_{12}), 136.4 (C_{20}), 137,5 (C_{16}), 137.9(C_{22}), 153.6 (C_2), 152.4 (C_{29}), 158.4 (C_{14}), 167.4 (C_4), 169.2 (C_{25}), 170.2 (C_7), 194.5 (C_8); HRMS *m*/*z* calcd for $C_{39}H_{49}N_3O_7S$ (M^+) 703.3291. Found 703.3247.