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Total Synthesis of (−)-Spongidepsin

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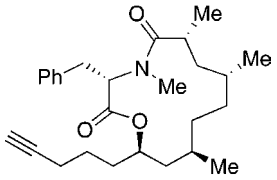
ABSTRACT



(-)-Spongidepsin

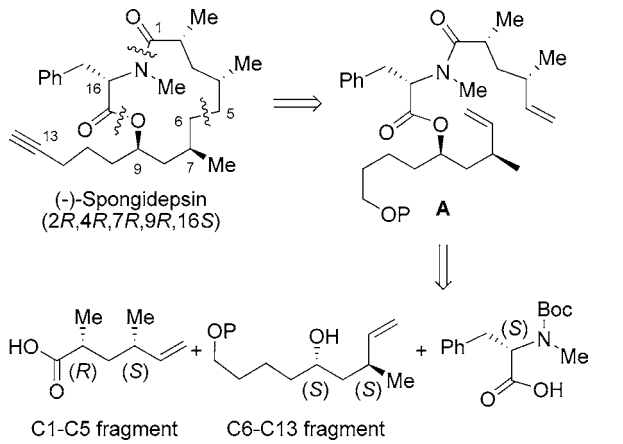
A convergent and rapid stereoselective synthesis of (−)-spongidepsin has been achieved from the Roche ester in 14 steps with an overall yield of 13%.

(−)-Spongidepsin is a cyclodepsipeptide isolated from the Vanuatu marine sponge *Spongia* sp. This compound exhibits cytotoxic and antiproliferative activities against J774.A1, WEHI-164, and HEK-293 cancer cell lines.[1] (−)-Spongidepsin is a 13-membered macrolactam with five stereogenic centers. The structure of spongidepsin was established by spectroscopic analysis, and the *N*-methylphenylalanine residue with the (L) configuration has been identified at isolation. The absolute configurations of the other four stereogenic centers were determined by total synthesis. Up to now, only two syntheses of spongidepsin have been achieved.[2,3]

We would like to report here a highly convergent synthesis of (−)-spongidepsin using a ring-closing metathesis (RCM) to build up the 13-membered macrocycle, a diastereoselective crotylstannylation to control the C2 and C4 stereogenic centers, an enantioselective 1,4-addition of a ketyl radical to an optically active α,β-unsaturated ester, and a diastereoselective alkylation of a five-membered lactone to control the C7 and C9 stereogenic centers.

As outlined in our retrosynthetic analysis, the 13-membered macrolactam might be prepared by ruthenium-catalyzed RCM of diene **A** and subsequent palladium-catalyzed alkene hydrogenation. Diene **A** was planned to be synthesized by coupling of (*S*)-*N*-methylphenylalanine with the C6−C13 fragment under Mitsunobu conditions, followed by the coupling with the C1−C5 fragment (Scheme 1).

Scheme 1



(-)-Spongidepsin
(2*R*,4*R*,7*R*,9*R*,16*S*)

The synthesis of the C1−C5 fragment was achieved in seven steps from the commercially available Roche ester (*S*)-**1** (Scheme 2). After protection of the primary alcohol using *tert*-butyldiphenylsilyl chloride (TBDPSCl, imidazole, DMF, 0 °C to room temperature), the protected methyl ester was reduced with DIBAL-H (hexanes, −78 °C) to furnish

(1) Grassia, A.; Bruno, I.; Debitus, C.; Marzocco, S.; Pinto, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2001**, *57*, 6257.
(2) Chen, J.; Forsyth, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2148.
(3) Ghosh, A. K.; Xu, X. *Org. Lett.* **2004**, *6*, 2055.

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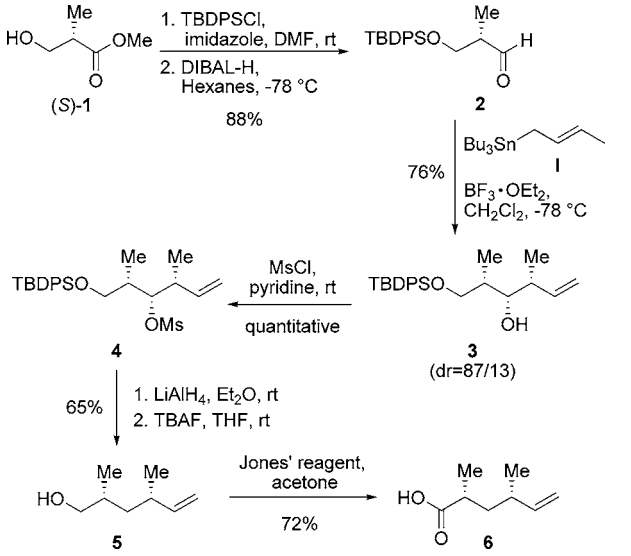
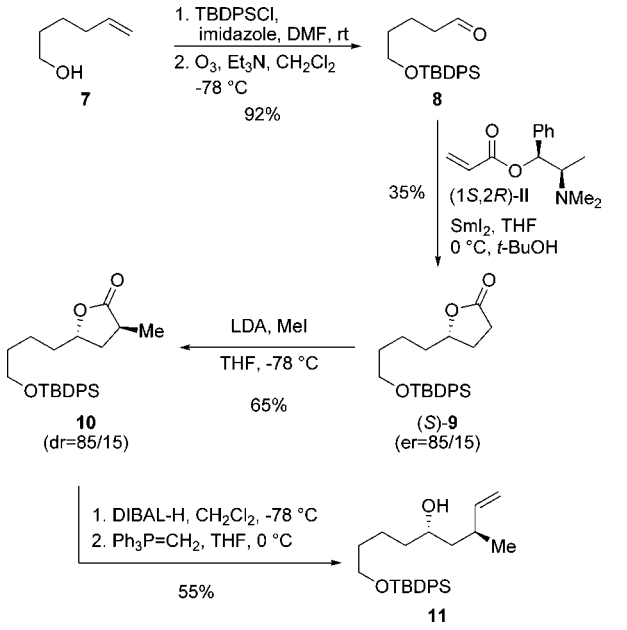
Scheme 2



Scheme 3



the protected hydroxy aldehyde **2** in 88% yield (overall yield for the two steps).[4]

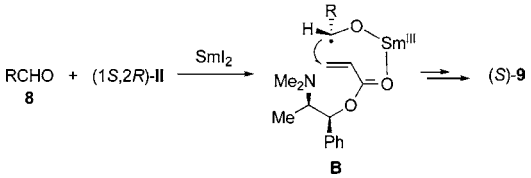
By treatment of **2** with but-2-enyl-(tri-*n*-butyl)-stannane **I** in the presence of $BF_3{\cdot}OEt_2$ (CH_2Cl_2, −78 °C), the diastereoselective crotylstannylation produced the *syn*−*syn* stereotriad **3** with a good level of diastereoselectivity (dr = 87:13) in 76% isolated yield.[5,6]

To transform **3** into the unsaturated primary alcohol **5**, compound **3** was mesylated (MsCl, pyridine, CH_2Cl_2, room temperature) to produce **4** quantitatively, which was reduced with $LiAlH_4$ (Et_2O, room temperature) and then transformed into the unsaturated alcohol **5** in 65% yield after treatment with TBAF (THF, room temperature) (overall yield for the two steps). After oxidation of **5** using Jones' reagent (CrO_3, H_2O, H_2SO_4, acetone, 0 °C to room temperature), the desired unsaturated carboxylic acid **6** was obtained in 72% yield. Compound **6** was thus obtained from the commercially available Roche ester (*S*)-**1**, with an overall yield of 31% (Scheme 2).

The stereoselective synthesis of the C6−C13 fragment **11** started with 5-hexen-1-ol **7**. After protection of **7** as a TBDPS ether (TBDPSCl, imidazole, DMF, room temperature), an ozonolysis of the terminal double bond was achieved (O_3, −78 °C, CH_2Cl_2 then Et_3N)[7] to produce the protected hydroxyaldehyde **8** in 92% yield. The crucial step was the transformation of **8** to **9** by using an intermolecular stereoselective condensation of a ketyl radical to an optically active α,β-unsaturated ester mediated by SmI_2, which should undergo direct cyclization to produce lactone **9**. Thus, the treatment of **8** with SmI_2 (THF, *tert*-BuOH, 0 °C) in the presence of the easily available α,β-unsaturated aminoester (1*S*,2*R*)-**II** produced lactone (*S*)-**9** in 35% isolated yield (er = 85:15).[8,9] This lactone was then transformed to the desired C6−C13 fragment in a three-step sequence. The first step involved a diastereoselective alkylation of **9** by using MeI (LDA, THF, −78 °C), providing the methylated lactone **10** in 65% yield as an inseparable mixture of diastereomers (dr = 85:15).[10] After reduction of **10** to the corresponding lactol (DIBAL-H, CH_2Cl_2, −78 °C), followed by a Wittig methylenation ($Ph_3P{=}CH_2$, THF, 0 °C), the C6−C13 fragment **11** was isolated in 55% yield (Scheme 3).

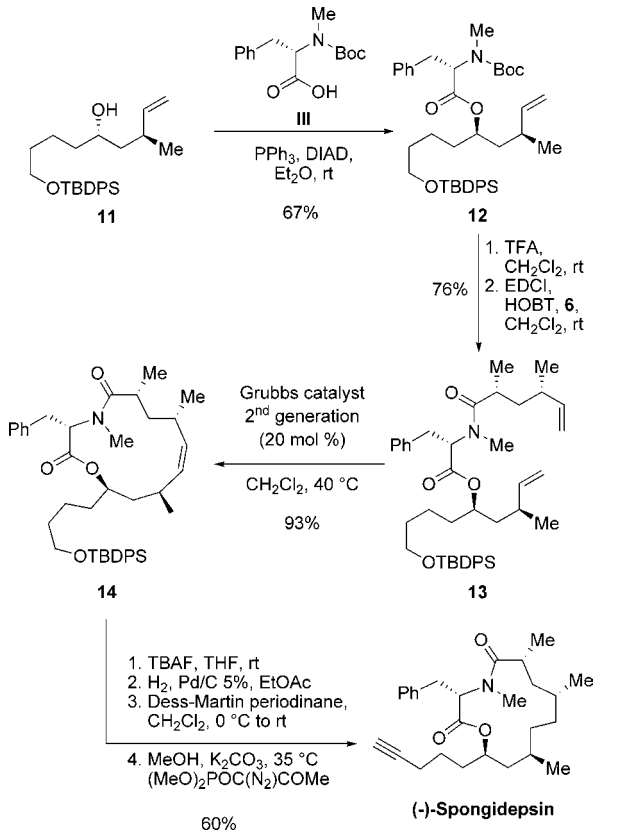
The assembly of (*S*)-*N*-methylphenylalanine with compounds **11** and **6**, to produce the key dienic substrate **13** required for the ring-closing metathesis, is shown in Scheme 4. At first, a Mitsunobu esterification (PPh_3, DIAD, Et_2O, room temperature)[11] of the *N*-Boc protected (*S*)-*N*-methylphenylalanine **III** with the secondary alcohol **11** led to the ester **12** accompanied by minor isomers. After separation by flash chromatography on silica gel, ester **12** was obtained

(4) Johns, A. B.; Grant, C. M.; Marshall, J. A. *Org. Synth.* **2002**, *79*, 59.
(5) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.
(6) The dr was determined on the crude reaction mixture by ^{1}H NMR spectroscopy.
(7) Hon, Y. S.; Lin, S. W.; Lu, L.; Chen, Y. J. *Tetrahedron* **1995**, *51*, 5019.
(8) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.
(9) After reduction of aldehyde **8** by SmI_2, a ketyl radical is formed. An intermolecular complexation of the Sm^{III} attached to the ketyl intermediate can take place with the ester carbonyl group of (1*S*,2*R*)-**II** to produce **B** to minimize the steric interactions.



The (*S*) configuration of lactone **9** was obtained using (1*S*,2*R*)-**II**, derived from (+)-(1*S*,2*R*)-*N*-methylephedrine (ref 8). The er of this lactone was determined by HPLC analysis using a Daicel Chiralpak AS-H column: hexane/EtOH 97:3, 1 mL/min, 215 nm, t_R(*S*) 13.3 min, t_R(*R*) 14.7 min.
(10) Based on the ^{1}H NMR spectra.
(11) Mitsunobu, O. *Synthesis* **1991**, 1.

Scheme 4



in 67% isolated yield. Removal of the *N*-Boc protecting group with TFA (CH_2Cl_2, room temperature) produced the free amine which was coupled with the unsaturated acid **6** to afford diene **13** in 76% yield (overall yield for the two steps). Ring-closing metathesis of this diene **13** using Grubbs catalyst second generation (20 mol %, CH_2Cl_2, 40 °C) furnished the (*Z*)-macrolactam **14** in 93% yield. As described previously,[3] the TBDPS ether was cleaved by TBAF (THF, room temperature) and the (*Z*)-macrocyclic double bond was reduced using a hydrogenation (Pd/C 5%, AcOEt, room temperature).[12] The terminal alcohol was then oxidized to an aldehyde using Dess−Martin periodinane[13] and then transformed to a terminal acetylenic group using Bestmann's reagent (K_2CO_3, MeOH, 35 °C).[14] (−)-Spongidepsin was obtained in 60% yield for the last four steps. All the spectral data (^{1}H, ^{13}C NMR),[15] HMRS, and the optical rotation ($[\alpha]_D^{20}$ −210.5, *c* 0.49, MeOH)[16] matched with those of the synthetic (−)-spongidepsin reported by Ghosh.[17]

In summary, by using a convergent synthesis and diastereoselective reactions such as a crotylstannylation, 1,4-addition of a ketyl radical to an optically active α,*β*-unsaturated ester, and a diastereoselective alkylation, we synthesized (−)-spongidepsin in 14 steps from the commercially available Roche ester (*S*)-**1** with an overall yield of 13%.

Acknowledgment. L.F. thanks the MRES for a grant. We thank Dr. Fisher and Dr. Trimmer from Materia for a generous gift of Grubbs catalyst second generation.

Supporting Information Available: Experimental procedures for all compounds and ^{1}H and ^{13}C NMR spectra for compounds **1**−**14** and (−)-spongidepsin. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061029W

(12) In our efforts to shorten the synthesis, when Pd/C hydrogenation and TBAF deprotection were carried out in one pot, epimerization of the macrocycle was observed.

(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(14) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

(15) See Supporting Information for ^{1}H and ^{13}C NMR spectra of our synthetic (−)-spongidepsin.

(16) At higher dilution, our (−)-spongidepsin has shown a similar optical rotation: $[\alpha]_D^{20}$ −209.4 (*c* 0.18, MeOH).

(17) Spongidepsin synthesized by Ghosh shows optical rotation similar to ours ($[\alpha]_D^{23}$ −198 (*c* 0.29, MeOH)) (see ref 3). However, spongidepsin synthesized by Forsyth (ref 2) and the natural spongidepsin isolated by Riccio (ref 1) show different optical rotations: $[\alpha]_D^{23}$ −67.3 (*c* 1, MeOH) and $[\alpha]_D^{23}$ −61.8 (*c* 0.14, MeOH), respectively.