ORGANIC LETTERS

2004
Vol. 6, No. 12
2055−2058

Assignment of Absolute Stereochemistry and Total Synthesis of (−)-Spongidepsin

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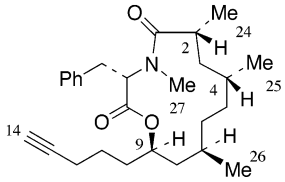
Received April 17, 2004

ABSTRACT



Spongidepsin (2, Assigned structure)

An enantioselective total synthesis of (−)-spongidepsin (2) and elucidation of the absolute stereochemistry of its four stereocenters are described. Spongidepsin (2), a 13-membered depsipeptide isolated from the Vanuatu marine sponge *Spongia* sp., has shown potent antitumor properties against a variety of NCI tumor cell lines. Our synthesis is convergent, and the absolute stereochemistry of four of the five chiral centers was assigned through synthesis.

Recently, the novel cyclodepsipeptide, spongidepsin, was isolated from the Vanuatu marine sponge *Spongia* sp. by Riccio and co-workers.[1] Spongidepsin displayed potent cytotoxicity against a variety of cancer cell lines that included the HEK-293 cell line.[2]

The gross structure of spongidepsin was initially established by extensive spectroscopic analysis. However, the relative stereochemistry of the C7 and C9 stereocenters and the absolute configuration of four of its five chiral centers were not assigned until recently when Forsyth and Chen reported their synthesis and structural elucidation of spongidepsin.[3]

Unfortunately, the extremely low natural abundance of spongidepsin has made it difficult to evaluate its biological profile in detail.[1] In view of its potent cytotoxic properties and its interesting structural features, we became interested in the chemistry and biology of spongidepsin and related novel depsipeptides and now report a total synthesis of spongidepsin **2** that is amenable to analogue construction.[4]

Spongidepsin contains a highly functionalized 13-membered ring with five chiral centers. Only the *N*-methylphenylalanine residue with L-configuration had previously been identified at isolation.[1] For determination of the relative and absolute stereochemistry, our approach was to devise a convergent, efficient synthesis that relied upon chiral starting materials derived from biocatalysis and asymmetric synthesis. Our strategy was designed to provide rapid access to all possible diastereomers for spectroscopic studies.

As outlined in Figure 1, our synthetic strategy involved a ring-closing olefin metathesis to construct the 13-membered macrocycle from diene **3**. The synthesis of **3** was planned from the enantiomerically pure C1−C5 segment **5**, the C6−C12 segment **6**, and *N*-methylphenylalanine by Mitsunobu esterification and amide coupling reactions. Since the relative stereochemistry of the C2- and C4-centers was initially assigned as *syn*, our plan was to synthesize both enantiomers

(1) Grassia, A.; Bruno, I.; Debitus, C.; Marzocco, S.; Pino, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2001**, *57*, 6257.

(2) Against HEK-293 and WEHI-164 cells, spongidepsin has shown IC_{50} values of 0.66 and 0.42 μM, respectively.

(3) Forsyth, C. J.; Chen, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2148.

(4) (a) Bai, R.; Covell, D. G.; Ghosh, A. K.; Liu, C.; Hamel, E. *J. Biol. Chem.* **2002**, *277*, 32165. (b) Ghosh, A. K.; Liu, C. *Org. Lett.* **2001**, *3*, 635.

10.1021/ol049292p CCC: $27.50
Published on Web 05/18/2004

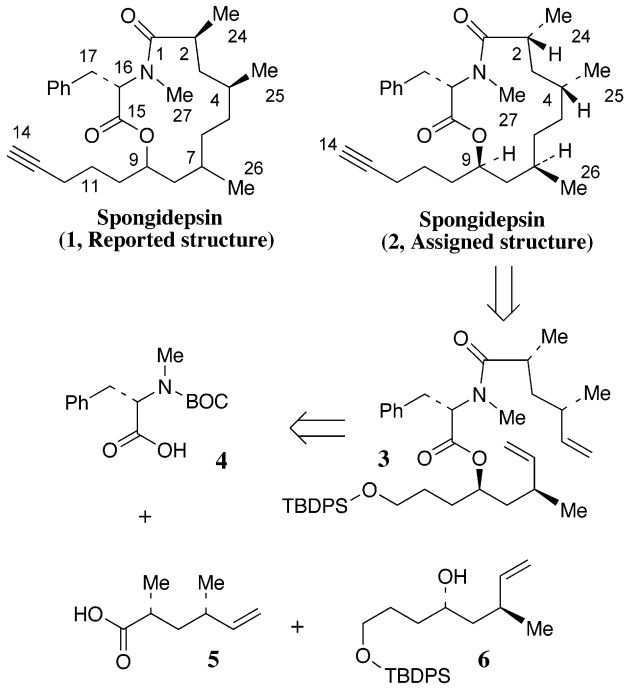


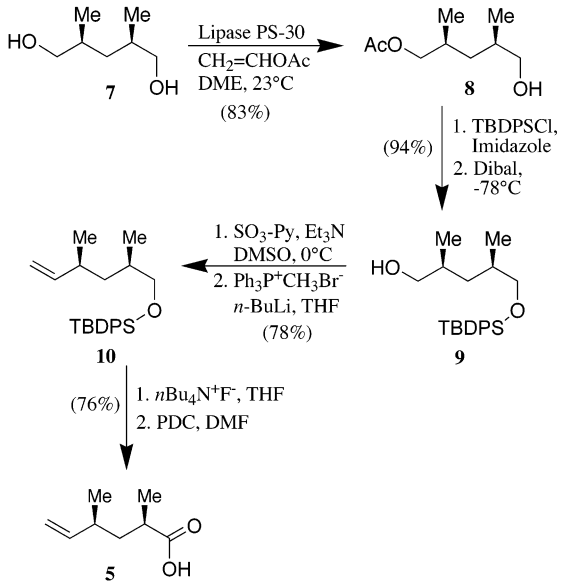
Figure 1. Retrosynthetic analysis of spongidepsin.

of the C1−C5 segment **5** using enzymatic desymmetrization of *meso-syn*-2,4-dimethylpentane-1,5-diol as the key step. An enantioselective synthesis of alcohol **6** was envisioned using an asymmetric alkylation and halolactonization reaction sequence.

Our initial strategy for elucidating the structure of spongidepsin was to construct the 13-membered ring as a diastereomeric mixture and compare the characteristic ^{1}H NMR chemical shifts (particularly the C-16 methine proton) with the reported spectral data for natural spongidepsin.[1] Such a mixture of diastereomers was generated by coupling the enantiomerically defined C1−C5 segment **5**, *ent*-**5**, and the racemic C6−C12 segment **6**, using DCC and DMAP. Mitsunobu esterification with inversion of stereochemistry at the C9-stereocenter was also investigated. This strategy ultimately led to successful identification and elucidation of the absolute stereochemistry of spongidepsin (See Figure 1).[5] Forsyth and Chen recently identified the same configuration of natural spongidepsin.[3]

Our enantioselective synthesis of C1−C5 segment **5** is outlined in Scheme 1. Multigram quantitites of *meso*-diol **7** were prepared as described previously.[6] Enzymatic desymmetrization of **7** with lipase PS-30 provided the monoacetate **8** in 83% yield and 99% ee.[7] Protection of **8** as a TBDPS ether followed by DIBAL reduction afforded alcohol **9** in 94% yield. Oxidation and subsequent Wittig methylation

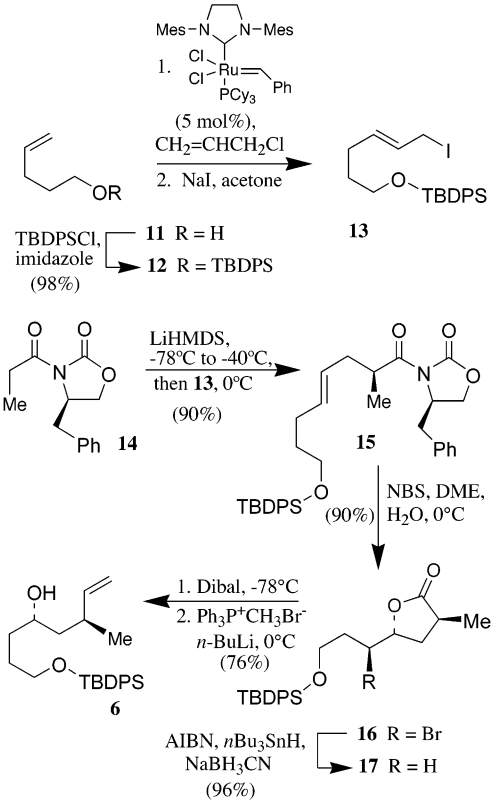
Scheme 1. Synthesis of C1−C5 Segment **5**



furnished olefin **10** in 78% yield. Removal of the silyl group and PDC-oxidation of the resulting alcohol afforded **5** in 76% yield.

Our enantioselective synthesis of the C6−C12 fragment **6** is shown in Scheme 2. Commercially available 4-pentene-1-ol was protected as its TBDPS ether to provide **12**. Cross-

Scheme 2. Synthesis of C6−C12 Segment **6**



(5) Full investigation, including biological studies, will be reported in due course.

(6) Fugita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, *3*, 493.

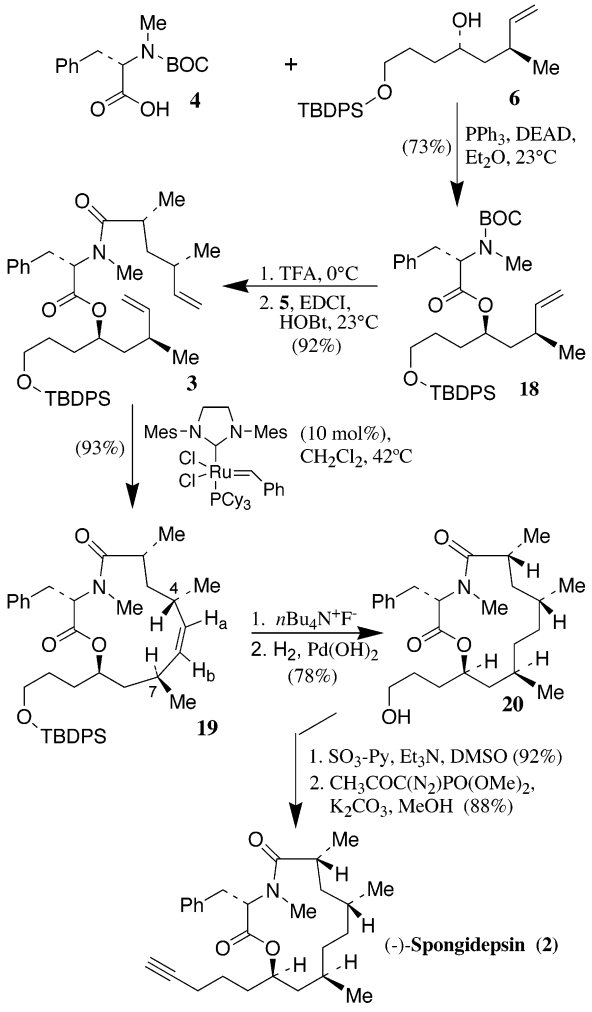
(7) (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Lin, G.-Q.: Xu, W.-C. *Tetrahedron* **1996**, *52*, 5907.

metathesis[8] of **12** with allyl chloride in CH_2Cl_2 at 42 °C in the presence of 5 mol % second-generation Grubbs's catalyst[9] afforded a 15:1 mixture (*E*:*Z*) of cross-metathesis products in 68% yield. Displacement of the chloride with sodium iodide furnished allylic iodide **13** in 92% yield. Evans' asymmetric alkylation[10] of acyloxazolidinone **14** with iodide **13** in THF afforded alkylation product **15** diastereoselectively in 90% yield and 96% de (by ^{1}H NMR analysis). Exposure of **15** to NBS using Bradbury's protocol,[11] furnished bromolactone **16** diastereoselectively. Removal of the bromide using a catalytic tributyltin hydride in a mixture (1:1) of benzene and *t*-BuOH at 84 °C provided **17** in 96% yield.[12] Dibal reduction of **17** in CH_2Cl_2 at −78 °C provided the lactol, which underwent Wittig olefination to afford **6** in 76% yield in two steps.

Our assembly of the key olefin-metathesis substrate **3** is shown in Scheme 3. Alkylation of *N*-Boc-phenylalanine with methyl iodide provided the acid. Mitsunobu esterification[13] of acid **4** with alcohol **6** furnished ester **18** in 73% yield. Trifluoroacetic acid-promoted removal of the BOC group followed by coupling of the resulting amine with acid **5** afforded **3** in 92% yield. Ring−closing metathesis of **3** in CH_2Cl_2 at 42 °C using 10 mol % second-generation Grubbs's catalyst[14] gave excellent results, affording the macrocycle **19** as a single isomer in 93% yield. The coupling constants of the olefinic protons (J_{ab} = 10.1 Hz) indicated that the *cis*-lactone had been formed.[15] Deprotection of the silyl group followed by hydrogenation in methanol afforded the saturated lactone **20**. Oxidation of **20**, followed by exposure of the resulting aldehyde to the Ohira−Bestmann reagent,[16] provided synthetic spongidepsin (**2**) with defined absolute stereochemistry of all five chiral centers. The spectral data (^{1}H and ^{13}C NMR) of synthetic spongidepsin ($[\alpha]_D^{23}$ −198, *c* 0.29, MeOH) was identical to that of natural spongidepsin (lit.[1] $[\alpha]_D^{23}$ −61.8, *c* 0.014, MeOH).[17,18]

During the course of our synthesis and structural elucidation of spondidepsin, four other possible diastereomers were synthesized with the stereochemistry depicted in Figure 2.

Scheme 3. Synthesis of (−)-Spongidepsin (**2**)



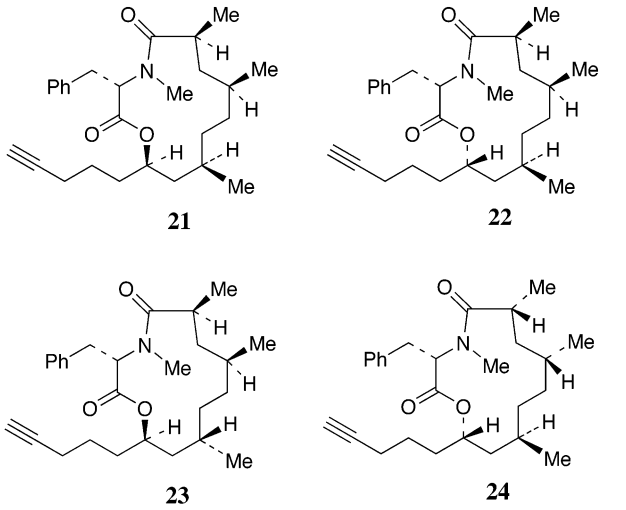


Figure 2. Diastereomers of spongidepsin.

The C1−C5 segment of diastereomers **21**−**23** was derived from *ent*-**5**, which was prepared from optically active alcohol

(8) Liu, B.; Das, S. K.; Roy, R. *Org. Lett.* **2002**, *4*, 2723.
(9) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783 and references therein.
(10) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.
(11) Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* **1989**, *30*, 3845.
(12) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200.
(13) Mitsunobu, O. *Synthesis* **1981**, 1.
(14) Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(15) Extensive NOESY experiment also suggested the formation of (*Z*)-olefin. A strong NOE was observed between the C4 and C7 methine protons. Interestingly, Forsyth and Chen have observed the formation of the (*E*)-isomer as the major product under different reaction conditions; please see ref 3.
(16) Ohira, W. *Synth. Commun.* **1989**, *19*, 561.
(17) Synthetic (−)-spongidepsin (**2**) has shown similar optical rotation in chloroform as well ($[\alpha]_D^{23}$ −209, *c* 0.75, $CHCl_3$).
(18) Our synthetic (−)-spongidepsin has shown different optical rotations than those reported previously. Reported optical rotation of natural spongidepsin is significantly lower, possibly due to measurement of rotation under very dilute conditions. Our observed rotation is also higher than the value recently reported by Forsyth and Chen[3] ($[\alpha]_D^{23}$ −67.3, *c* 1.0, MeOH).

7 using procedures similar to those in Scheme 1. The C9 stereochemistry of diastereomers **22** and **24** was derived from esterification of C6−C12 segment **6** and phenylalanine derivative **4** in the presence of DCC and DMAP. Subsequent reaction steps as described in Scheme 3 provided **22** and **24**.[5] The spectroscopic data and optical rotation of these diastereomers are quite different from that of **2**.

Thus, we have determined the absolute configuration and achieved the total synthesis of (−)-spongidepsin. The synthesis features enzymatic desymmetrization of *meso*-diol in excellent enantiomeric purity, diastereoselective alkylation and halolactonization to set the C7 and C9 stereochemistry, and efficient cross-metathesis of functionalized substrates. The synthesis now paves the way for important structure−activity studies.

Acknowledgment. The authors thank Professor Riccio for providing a copy of the ^{1}H NMR spectrum of natural spongidepsin. Partial financial support by the National Institutes of Health is gratefully acknowledged. We also thank Dr. Park for preliminary experimental assistance and Mr. Gongli Gong and Mr. Gary Schiltz for helpful discussions.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **6**, and **15**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049292P