ORGANIC LETTERS

2010
Vol. 12, No. 19
4392−4395

An Asymmetric Hydrogenation Route To (−)-Spongidepsin

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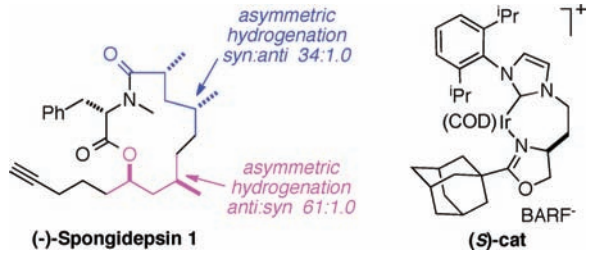
Received August 10, 2010

ABSTRACT



(−)-Spongidepsin 1, a cytotoxic marine natural product, was prepared via two iridium-catalyzed hydrogenation reactions; both were highly stereoselective, giving convenient access to pivotal intermediates. This synthesis was modified to give several spongidepsin analogues, and their cytotoxicities were compared with those of the natural product.

Typical syntheses of polyketide-derived macrolides tend to focus on asymmetric aldol[1−3] and alkylation reactions,[4,5] often involving chiral auxiliaries. These processes are frequently augmented by enzyme-mediated resolutions to generate other chirons that are not readily available from the chiral pool.[6,7] Alternative methods, however, sometimes increase synthetic efficiencies and expose opportunities for analogue syntheses.

Our group has used chiral analogues of Crabtree's catalyst in syntheses of some pivotal chirons for preparations of natural products, particularly in the polyketide series. This communication describes how those methods were applied to the preparation of (−)-spongidepsin **1** (Figure 1)[8] and some close analogues of this structure.

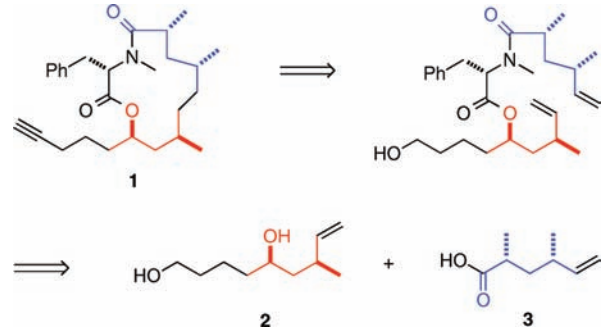


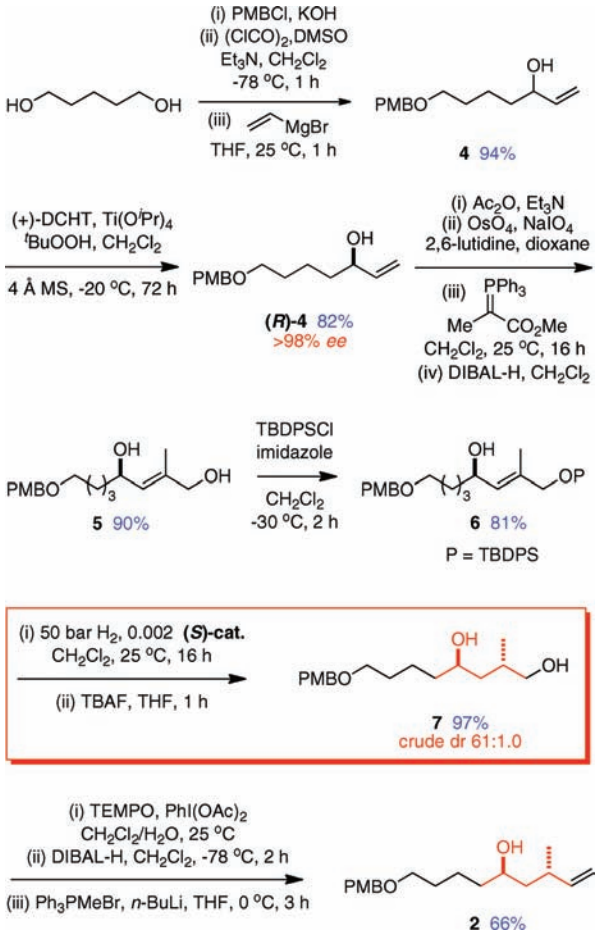
Figure 1. Retrosynthesis of **1** highlighting the chirons from stereoselective hydrogenations.

Figure 1 illustrates the target molecule containing chirons **2** and **3** that we proposed could be made via stereoselective hydrogenations. To obtain compound **2**, a Sharpless kinetic resolution[9,10] of the allylic alcohol **4** was used (Scheme 1).

(1) Brodmann, T.; Lorenz, M.; Schaeckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174.
(2) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, 7506.
(3) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, 65.
(4) Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2010**, 2535.
(5) Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, 1057.
(6) Abate, A.; Brenna, E.; Costantini, A.; Fuganti, C.; Gatti, F. G.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2006**, *71*, 5228.
(7) Ohno, M.; Otsuka, M. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley & Sons, Inc.: New York, 1989; Vol. 37, p 1.
(8) Grassia, A.; Bruno, I.; Debitus, C.; Marzocco, S.; Pinto, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2001**, 6257.

10.1021/ol1018773
Published on Web 09/07/2010

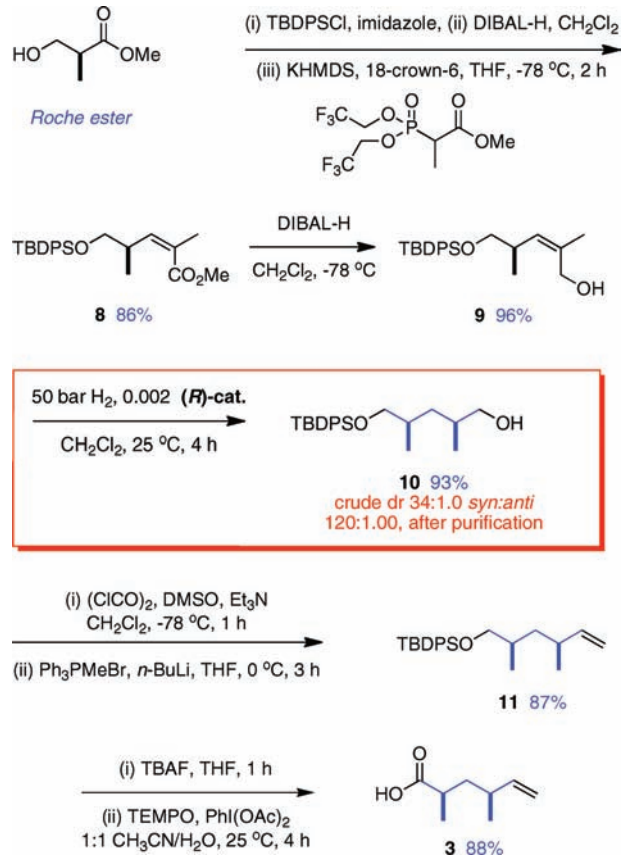
Scheme 1. Synthesis of the 1,3-Hydroxymethyl Chiron **2**



Acylation, oxidative cleavage, reaction with a stabilized Wittig reagent, and then hydride reduction gave the allylic diol **5**.

Previous studies from our group have shown that catalyst control tends to prevail in hydrogenations of acyclic chiral substrates[11−16] using catalysts like our carbene complex "**cat.**" ("**cat.**" is an abbreviation for "catalyst"; see graphical abstract for structure).[17,18] However, manipulation of the alkene component in these reactions provides a mean to optimize the "substrate-vector" such that it matches[19] the catalyst influence to maximize stereoselectivity. This can be done by interchanging ester and alcohol functionalities, altering protecting groups, or changing the alkene geometry. In the case of 1,3-hydroxymethyl chirons we have shown that an alkene with similar functionality, protection, and geometry relative to **6** was hydrogenated with high stereoselectivity.[12] The reduction of **6** to **7** occurred with similar high selectivity. Chiron **2** was then generated from **7** via routine oxidation, reduction, and Wittig homologation steps.

Scheme 2. Synthesis of the 1,3-Dimethyl Chiron **3**



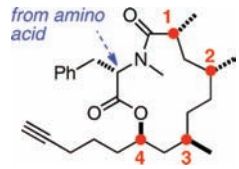
Scheme 2 oulines how the second pivotal chiron, **3**, was obtained. Previous reports from our group have shown how similar 1,3-dimethyl chirons can be made from the Roche ester.[14−16]

To complete our synthesis of (−)-spongidepsin **1**, chiron **2** was coupled with the appropriate protected *N*-methyl amino acid to give the ester **12** (after removal of a BOC group). This was then coupled with chiron **3** to form the α,ω-diene **13**. Ring-closing metathesis with the "second generation" Grubbs catalyst[20,21] gave the macrocycle **14** after simultaneous O-deprotection and alkene hydrogenation. The final steps in the synthesis were oxidation and generation of the alkyne group. Proton and ^{13}C NMR spectra of the synthetic product **1** were compared closely with those reported in previous syntheses (see below).[22−25]

Besides the amino acid-derived chirality, there are four stereogenic centers in spongidepsin. Table 1 outlines the origin of these chiral centers in the four previous total syntheses of this molecule and compares them against our

(9) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(10) Pfenninger, A. *Synthesis* **1986**, 89.
(11) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236.
(12) Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 8894.
(13) Zhao, J.; Burgess, K. *Org. Lett.* **2009**, *11*, 2053.
(14) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391.
(15) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.—Eur. J.* **2007**, 7162.
(16) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, 1129.
(17) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.
(18) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878.
(19) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, 1.

Table 1. Comparison of Syntheses of Spongidepsin

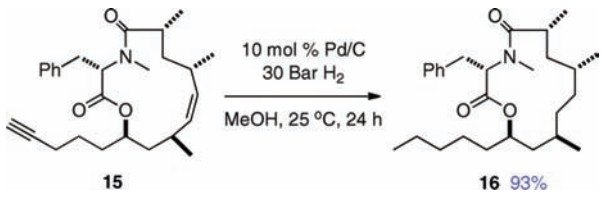


	chiral centers			
	1	**2**	**3**	**4**
Forsyth[22]		enzyme resolution[a]	hydroboration (1.0:1.0)	epoxide opening
Ghosh[23]		enzyme resolution	Evan's alkylation (98:2.0)	bromo-lactonization (19:1.0)
Cossy[24]	Roche ester	crotyl-stannylation (87:13)	asymmetric alkylation (85:15)	SmI_2-mediated (85:15)
Negishi[25]	ZACA[b] (82% ee)	ZACA (5.5:1.0)	ZACA (3.5:1.0)	allyl boration (not specified)
this work	Roche ester	hydrogenation (61:1.0)	hydrogenation (34:1.0)	Sharpless kinetic res'n

[a] Stereoselectivities are not indicated for kinetic resolution steps since they are conversion dependent. [b] ZACA is zirconium-mediated asymmetric carboalumination. There are also two "formal" syntheses of spongidepsin.[26,27]

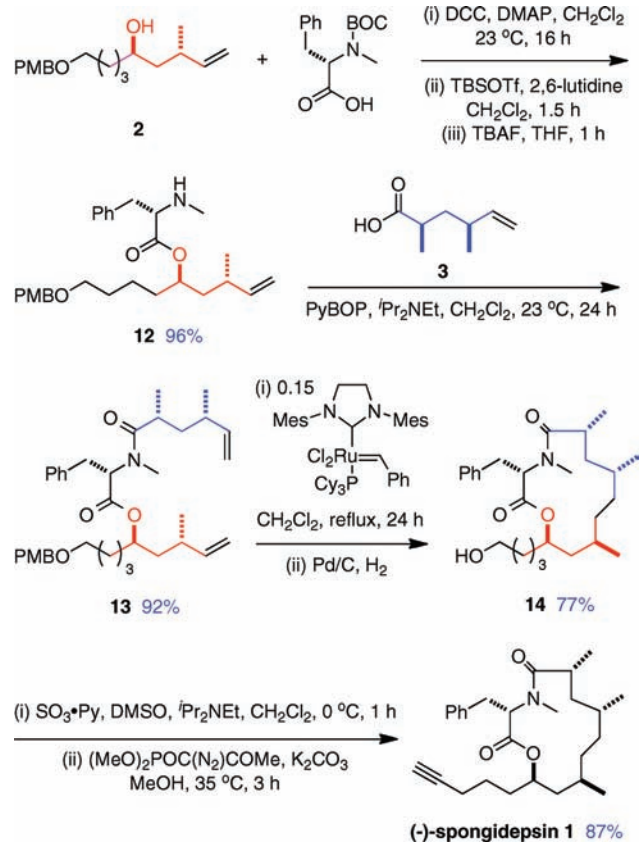
approach.[22−25] Some key steps in the other syntheses achieve more than creation of chiral centers (e.g., C−C bond formation in Negishi's zirconium-mediated asymmetric carboalumination {ZACA} reactions), so they may have advantages that are not apparent from Table 1. However, the stereoselectivities obtained in this work compare favorably with the published syntheses, and the featured hydrogenation reactions proceed with 100% conversion to product; therefore, these steps are highly efficient.

As far as we are aware, nothing has been reported on structure activity relationships for spongidepsin. Consequently, several intermediates in Scheme 3 were diverted to form analogues of the target material for testing. Thus, compounds **15** and **16** were also prepared; see Supporting Information for the preparation of **15**. Compound **16** could be conveniently obtained via reduction of **15**. Motives for making these particular compounds were to test the effects of increased conformational rigidity in the macrolide and the effects of saturating the side chain on the cytotoxicity.



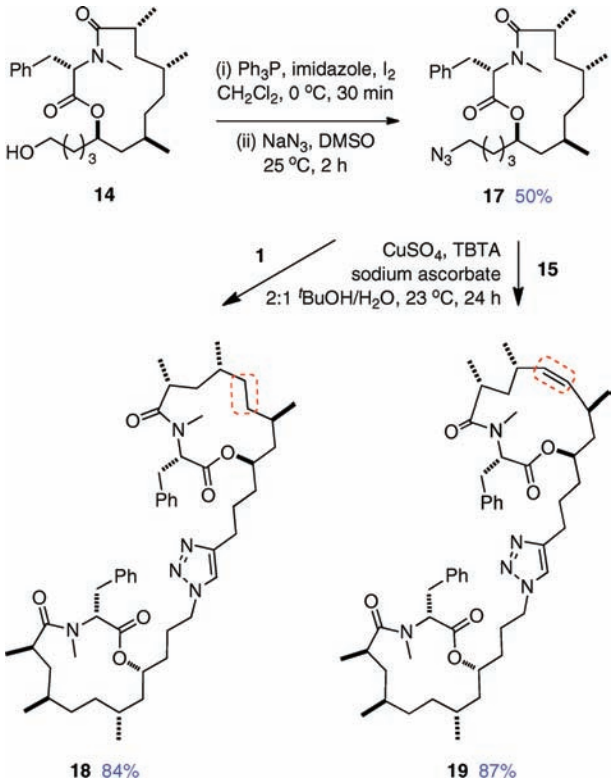
The cellular target for spongidepsin is unknown. Consequently, we also decided to prepare two bivalent molecules consisting of two macrolide fragments joined by a flexible linker via a "click reaction" (Scheme 4).[28,29] These analogues were designed to probe if this modification would have significant effects on the molecular cytotoxicities; if it did, this might implicate a homodimeric binding partner.

Scheme 3. Completion of the Synthesis of **1**



(20) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, 45.
(21) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany; Chichester, England, 2003.
(22) Chen, J.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2004**, 2148.
(23) Ghosh, A. K.; Xu, X. *Org. Lett.* **2004**, *6*, 2055.
(24) Ferrie, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441.
(25) Zhu, G.; Negishi, E.-I. *Org. Lett.* **2007**, *9*, 2771.
(26) Chandrasekhar, S.; Yaragorla, S. R.; Sreelakshmi, L.; Reddy, C. R. *Tetrahedron* **2008**, 5174.
(27) Chandrasekhar, S.; Yaragorla, S. R.; Sreelakshmi, L. *Tetrahedron Lett.* **2007**, 7339.
(28) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, 2004.
(29) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

Scheme 4. Synthesis of the Dimers of **1**[a]



[a] TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

Compounds **1**, **15**, **16**, **18**, and **19** were tested in an antiproliferative assay on human embryonic kidney (HEK-293) cells (Figure 2), and the IC_{50} values measured are

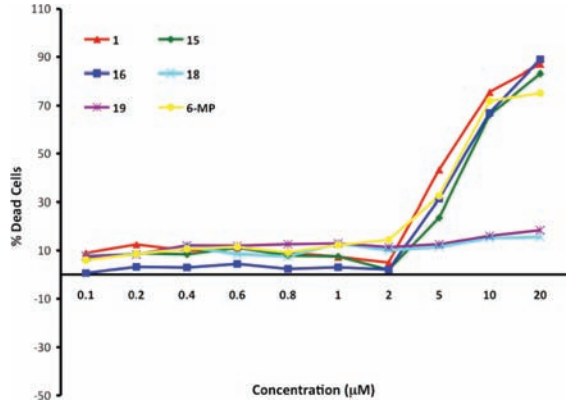


Figure 2. Antiproliferative assay for the natural product **1** and the new derivatives **1**, **15**, **16**, **18**, and **19** in MTT assays featuring human embryonic kidney cells (HEK-293).

indicated in Table 2 relative to 6-mercaptopurine (control cytotoxic compound). These assays were reproduced several times; in our hands, the cytotoxicities of compound **1** and

Table 2. In Vitro Antiproliferative Activity of **1** and Derivatives **15**, **16**, **18**, and **19**

compound	IC_{50} (μM)[a]
1	5.68 (0.66)[b]
15	8.27
16	7.32
18	noncytotoxic
19	noncytotoxic
6-mercaptopurine	7.45 (0.007)[b]

[a] Assay run for 72 h in EMEM + 2% FBS at 37 °C using human embryonic kidney cells (HEK-293). [b] Literature data.[8] IC_{50} values were measured three times and averaged.

of 6-mercaptopurine were both significantly less (1 and 3 orders of magnitude, respectively) than reported previously.[8] However, the IC_{50} of 6-mercaptopurine reported in ref 8 is about 100× less than in three other literature reports (see Supporting Information). Further, the relative cytotoxicity of the target compound **1** and 6-mercaptopurine is almost the same. We cannot account for these discrepancies; nevertheless, it is possible to confidently compare the *relative* cytotoxicities of 6-mercaptopurine,**1**, and its analogues in our assays.

Figure 2 indicates that the new monomer derivatives **15** and **16** show little effect up until 2 μM concentrations, after which they are significantly cytotoxic, just as the natural product is. Consequently, reduction of the alkyne side chain or incorporation of an alkene in the macrolide has no significant effect. Surprisingly, the bivalent molecules **18** and **19** do *not* show significant cytotoxicities in the same concentration range. Compound **1** and the new derivatives were also tested on human pancreatic carcinoma cells (Panc-1); the IC_{50} values for the monomers **1**, **15**, and **16** were in the same range, and the dimers were also noncytotoxic (Supporting Information). Together, these data indicate that incorporation of a large substituent on the alkyl chain almost completely eliminates the cytotoxic effect, and there was no positive effect from these bivalent analogues.

Asymmetric hydrogenations via chiral analogues of Crabtree's catalyst are viable for synthesis of spongidepsin. Previous studies from this group indicate all stereoisomers of chirons like **2** and **3** can be made via such methods. We infer from this that syntheses of stereoisomers of this natural product could be made via similar approaches. The results presented here indicate that practical syntheses of other analogue types are also possible.

Acknowledgment. Financial support for this work was provided by The National Science Foundation (CHE-0750193) and The Robert A. Welch Foundation (A1121).

Supporting Information Available: Experimental procedures and characterization data for the new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1018773