ORGANIC LETTERS

2002
Vol. 4, No. 21
3719−3722

Diastereoselective Synthesis of the C(17)–C(28) Fragment (The C–D Spiroketal Unit) of Spongistatin 1 (Altohyrtin A) via a Kinetically Controlled Iodo-Spiroketalization Reaction

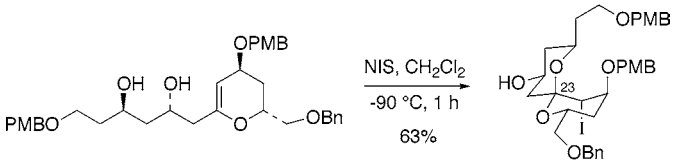
Edward B. Holson and William R. Roush*

Department of Chemistry, University of Michigan, 930 North University, Ann Arbor, Michigan 48109

roush@umich.edu

Received August 7, 2002

ABSTRACT



2 **15**, 8:1 d.r.

A convergent and stereocontrolled synthesis of spiroketal 15 corresponding to the C–D fragment of spongistatin 1 has been accomplished by a sequence utilizing a kinetically controlled intramolecular iodo-spiroketalization of glycal 2, which in turn was synthesized via a ring-closing metathesis reaction.

The spongipyran macrolides are a class of marine natural products that were independently isolated and characterized by Pettit,[1−3] Kitagawa,[4,5] and Fusetani[6] in 1993. The extraordinary cytotoxicity of this class of compounds toward neoplastic cell lines and the very small amounts available from natural sources have stimulated numerous studies on the synthesis of these compounds.[7,8] Thus far, total syntheses of two members of this class have been reported.[9−13] We have previously published a synthesis of the E−F bispyran unit,[14] and we now report a synthesis of the C−D spiroketal fragment of spongistatin 1. Our intention was to construct

(1) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1805.

(2) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166.

(3) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302.

(4) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989.

(5) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795.

(6) Fusetani, N.; Shimoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

(7) For a comprehensive list of references to synthetic approaches to the spongistatins, see ref 13 and the references therein.

(8) Paterson, I.; Coster, M. J. *Tetrahedron Lett.* **2002**, *43*, 3285.

(9) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(10) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J. S.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192.

(11) Paterson, I.; Chen, D. Y. K.; Coster, M. J.; Acena, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055.

(12) Smith, A. B.; Lin, Q. Y.; Doughty, V. A.; Zhuang, L. H.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 196.

(13) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. C. *J. Am. Chem. Soc.* **2002**, *124*, 5661.

(14) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730.

10.1021/ol0266875 CCC: $22.00
Published on Web 09/17/2002

this spiroketal fragment in a convergent and highly stereocontrolled fashion with particular attention to the stereochemistry at the C(23) spiroketal center.

On the basis of the work of several groups on the synthesis of the C−D system,[9,11−13,15−20] it was clear that highly stereocontrolled installation of the C(23) spiroketal center would require a kinetically controlled event. Other groups have successfully established the stereochemistry at this site under kinetic control;[16,19,20] however, many approaches have relied on equilibration of the C(23) stereocenter under a variety of acidic conditions ($Mg(O_2CCF_3)_2$,[9] $ZnCl_2$,[18] $Ca(ClO_4)_2/HClO_4$,[12] CF_3COOH,[17] HF/pyridine,[10] HCl[11]) taking advantage of an internal metal chelate or intramolecular hydrogen bond that favors the naturally occurring C−D spiroketal stereochemistry. These interactions compensate for the absence of double anomeric stabilization of the C−D spiroketal.

Our approach focused on the kinetic formation of the correct C(23) stereochemistry via an intramolecular iodospiroketalization reaction. A key intermediate in our synthesis is glycal **2** (Figure 1). Activation of glycal **2** with NIS

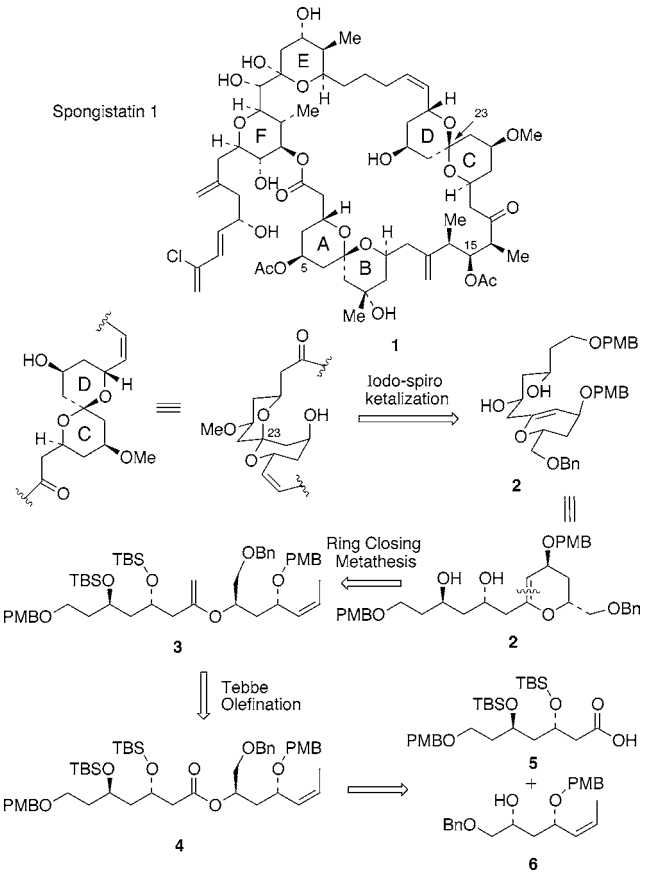


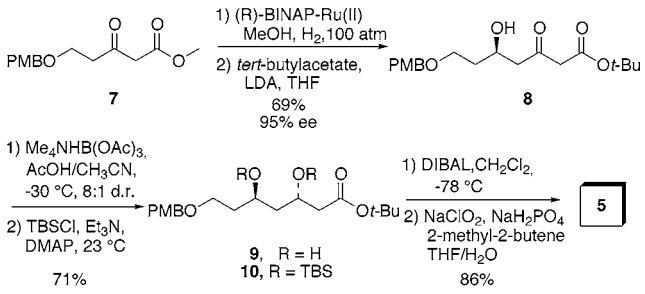
Figure 1. Retrosynthetic Analysis of the C−D Spiroketal.

followed by intramolecular trans diaxial addition of the δ-hydroxy group would provide the C(23) C−D spiroketal center with the configuration found in the natural product.

The propensity for the axial addition of electrophilic reagents and alcohols to activated glycals is well precedented in intermolecular reactions in carbohydrate chemistry.[21,22] Several groups have used this type of reaction in constructing spiroketals.[23−26] However, this strategy has not been applied to the stereoselective synthesis of the intrinsically less stable spiroketal isomer (the isomer that contains less than the maximal number of stabilizing anomeric effects). In addition to controlling the stereochemistry at the C(23) spiroketal center, we hoped that introduction of a heteroatom adjacent to the ketal linkage would provide enhanced stability of this unit toward acid-catalyzed epimerization.[27] Another feature of our strategy is the formation of glycal **2** from the ester **4** via a Tebbe olefination−ring-closing metathesis (RCM) sequence.[28] Ester **4** would in turn be derived from two components of roughly equal complexity, e.g., **5** and **6** (Figure 1).

Synthesis of carboxylic acid **5** began with Noyori hydrogenation[29] of the readily available β-ketoester **7**,[30] which provided the β-hydroxy ester in 81% yield and excellent enantioselectivity (95% ee, determined by Mosher ester analysis[31,32]) (Scheme 1). Homologation of the β-hydroxy

Scheme 1. Synthesis of Carboxylic Acid **5**



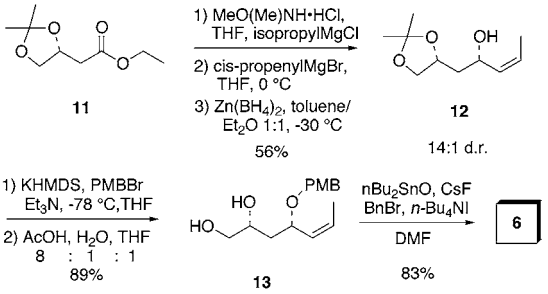
ester via Claisen condensation with the lithium enolate of *tert*-butyl acetate provided the β-keto-δ-hydroxy ester **8**

(15) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119.
(16) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267.
(17) Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895.
(18) Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649.
(19) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957.
(20) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911.
(21) Thiem, J.; Klaffke, W. In *Top. Curr. Chem.* **1990**, *154*, 285.
(22) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
(23) Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1982**, *23*, 4625.
(24) Greck, C.; Grice, P.; Ley, S. V.; Wonnacott, A. *Tetrahedron Lett.* **1986**, *27*, 5277.
(25) Diezmartin, D.; Grice, P.; Kolb, H. C.; Ley, S. V.; Madin, A. *Tetrahedron Lett.* **1990**, *31*, 3445.
(26) Uchiyama, M.; Oka, M.; Harai, S.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 1931.
(27) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837.
(28) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.
(29) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.
(30) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

in 85% yield. Reduction of **8** with tetramethylammonium triacetoxyborohydride[33] provided the anti 1,3-diol **9** in 86% yield and 8:1 diastereoselectivity; the stereochemistry of **9** was determined by conversion of the diol to the acetonide.[34,35] At this juncture, we chose to delay the differentiation of the two hydroxyl groups until the iodo-spiroketalization event. Therefore, protection of the alcohols as TBS ethers (TBSCl, Et_3N, DMAP, CH_2Cl_2) followed by separation of the diastereomers by column chromatography provided diastereomerically pure ester **10**. Finally, conversion of the *tert*-butyl ester to the carboxylic acid via a two-step reduction and oxidation sequence provided the acid **5** in excellent yield (86% over two steps).

The synthesis of fragment **6** began with ester **11** (derived from commercially available D-malic acid)[36] (Scheme 2).

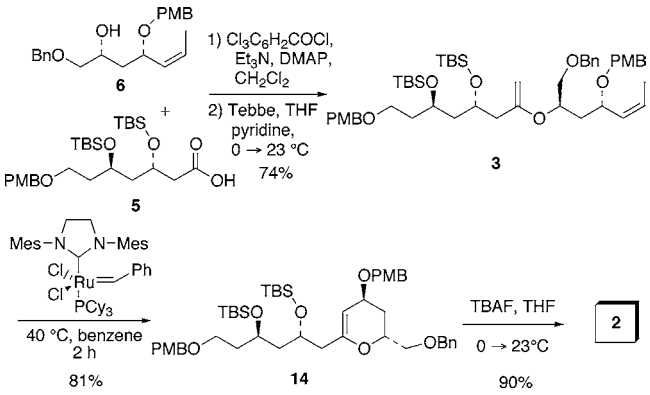
Scheme 2. Synthesis of Alcohol **6**



Formation of the Weinreb amide using the Merck protocol[37] followed by addition of the *cis*-propenyl Grignard reagent and zinc borohydride reduction[38] of the resulting enone provided alcohol **12** in good yield (56% over three steps) and selectivity (14:1 dr); the stereochemistry of the new hydroxyl center was determined by Mosher analysis.[31,32] Protection of the secondary alcohol as the *p*-methoxybenzyl (PMB) ether followed by acetonide deprotection (AcOH, H_2O, THF) provided diol **13** in 89% overall yield. Finally, protection of the primary alcohol as a benzyl ether via the stannylene acetal[39] provided the fully differentiated alcohol **6** in 83% yield.

Coupling of carboxylic acid **5** and alcohol **6** was effected by using the Yamaguchi protocol,[40] which provided ester **4** in 98% yield (Scheme 3). Initially, we attempted a one-pot

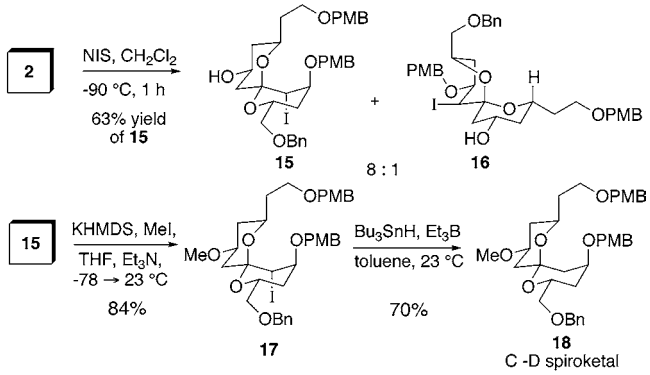
Scheme 3. Synthesis of Glycal **2**



olefination and RCM reaction sequence[28] using excess Tebbe reagent[41] ($Cp_2Ti(Cl)CH_2AlMe_2$) in refluxing THF but did not observe formation of the ring-closed product, and only small amounts of the enol ether. Consequently, we adopted a two-step sequence involving olefination followed by RCM.[42,43] Treatment of ester **4** with the Tebbe reagent provided the enol ether **3** (75%), which underwent RCM using Grubbs's second generation ruthenium catalyst[44] to provide glycal **14** in 81% yield. Deprotection of the bis-TBS ether **14** using TBAF then provided the dihydroxy glycal **2**, the substrate for the spiroketalization sequence.

After examining several electrophilic activating agents (*N*-(phenylseleno)pthalimide, NBS, I(sym-collidine)$_2$$ClO_4$, PhSeBr, PhSeCl, PhSCl, arylbis(arylthio)sulfonium salts[45]) to effect the spiroketalization, the best yields and selectivities were achieved by treating **2** with NIS in CH_2Cl_2 at −90 °C (Scheme 4). This protocol provided the spiroketal **15** in 63% yield with 8:1 diastereoselectivity.

Scheme 4. Iodo-spiroketalization Sequence



The configuration of the major spiroketal isomer **15** was confirmed via ^1H NMR NOE experiments (Figure 2). Critical

(31) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(32) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(33) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(34) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
(35) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
(36) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
(37) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(38) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.
(39) Nagashima, N.; Ohno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1972.
(40) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(41) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(42) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755.
(43) Rainer, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.

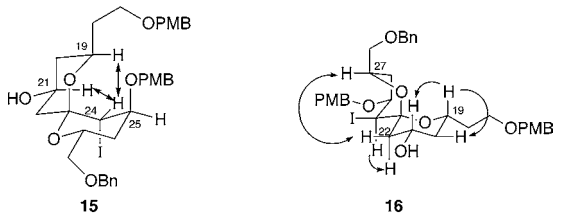


Figure 2. Diagnostic ^{1}H NMR NOEs in **15** and **16**.

among these are the H(24)−H(21)[18,19] and H(24)−H(19)[10,11] enhancements.

The configuration of the minor isomer **16** was also assigned on the basis of several key ^{1}H NMR NOE enhancements (Figure 2). The chair conformation for the C(19)−C(22) segment is defined by the NOE enhancement between H(19)−H(21). The second ring, which adopts a more boatlike conformation, is defined by H(24)−H(25) and H(24)−H(22ax) NOE enhancements. The most telling NOEs are between H(22)−H(27).

Treatment of **15** with KHMDS and MeI gave the methyl ether **17**, which was subjected to reductive dehalogenation using tributyltin hydride and triethylborane[46] to provide the fully elaborated C−D spiroketal **18** in 59% yield over two steps.

In summary, we have achieved a highly stereoselective and convergent synthesis of the C−D spiroketal fragment **18** of spongistatin 1. Formation of the monoanomeric spiroketal linkage at C(23) was accomplished under kinetically controlled iodo-spiroketalization conditions, which provided the desired configuration with good stereochemical control. A second application of this methodology to the synthesis of the A−B spiroketal is presented in the following paper.

Acknowledgment. We thank the NIH (GM 38436) for support of this research.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**6**, **8**−**10**, and **12**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0266875

(44) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(45) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084.
(46) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.