

Toward the Synthesis of Didemnaketal B: A Convergent Synthesis of the C9–C28 Subunit

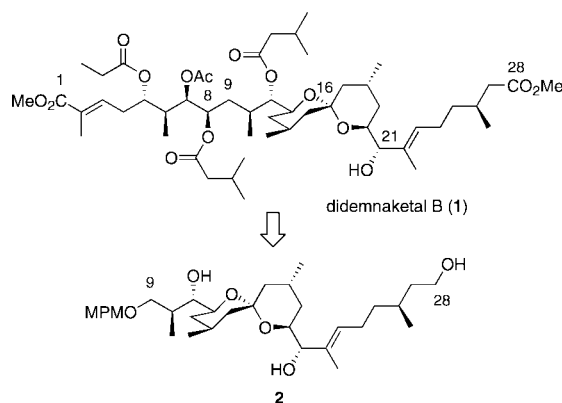
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ABSTRACT



Synthesis of the C9–C28 subunit of didemnaketal B has been developed. This subunit was convergently prepared from four chiral synthons and at the longest linear sequence required 16 steps.

Didemnaketal B (**1**), which has been recognized as a potent inhibitor of the HIV-protease, was isolated from ascidian of the genus *Didemnum* by Faulkner and co-workers.¹ The planar structure of didemnaketal B was first disclosed in 1991,¹ and the stereochemical properties, including an absolute configuration, were derived from a combination of spectroscopic and degradative studies.² Aside from biological activity, didemnaketal B contains a number of intriguing structural features such as a spiroketal moiety and two side chains with eight chiral centers. These structural and biological properties have brought interest to synthetic organic chemists. Although many of the efforts for the synthesis of didemnaketal B and related compounds have been reported,^{3,4} a total synthesis has not yet been reported.

(1) Potts, B. C. M.; Faulkner, D. J.; Chan, J. A.; Simolike, G. C.; Offen, P.; Hemling, M. E.; Francis, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 6321.

(2) Salomon, C. E.; Williams, D. H.; Lobkovsky, E.; Clardy, J. C.; Faulkner, D. J. *Org. Lett.* **2002**, *4*, 1699.

Recently, we reported on a model study for the construction of a spiroketal moiety through an enantioselective direct aldol reaction using a chiral dinuclear zinc catalyst.⁵ In this communication, we report our studies that have led to a synthesis of the C9–C28 subunit **2** containing the spiroketal moiety through a highly convergent strategy.

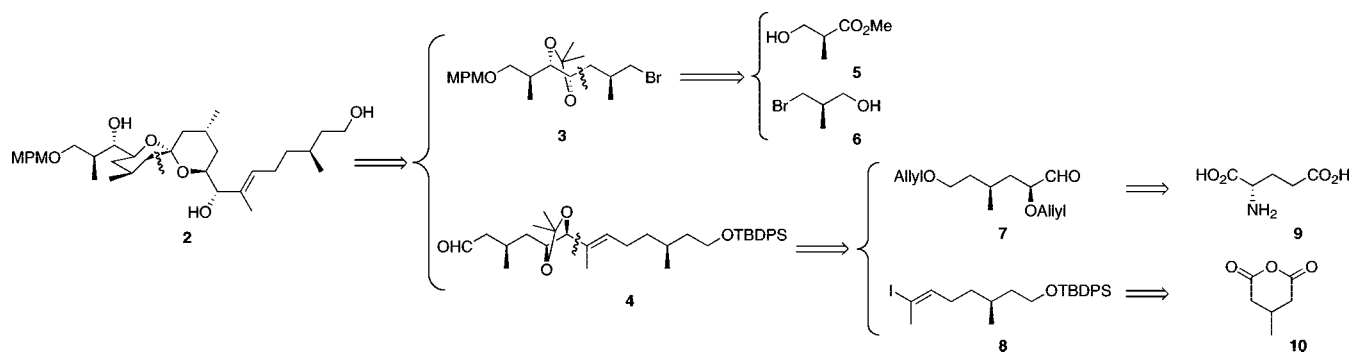
A highly convergent synthetic plan for **2** is shown in Scheme 1. Subunit **2** would be accomplished by the addition

(3) Fan, X.; Flentke, G. R.; Rich, D. H. *J. Am. Chem. Soc.* **1998**, *120*, 8893.

(4) (a) Zhao, X.-Z.; Tu, Y.-Q.; Peng, L.; Li, X.-Q.; Jia, Y.-X. *Tetrahedron Lett.* **2004**, *45*, 3713. (b) Zhao, X.-Z.; Peng, L.; Tang, M.; Tu, Y.-Q.; Gao, S.-H. *Tetrahedron Lett.* **2005**, *46*, 6941. (c) Wang, P.-Z.; Tu, Y.-Q.; Yang, L.; Dong, C.-Z.; Kitching, W. *Tetrahedron: Asymmetry* **1998**, *9*, 3789. (d) Jia, Y.-X.; Wu, B.; Li, X.; Ren, S.-K.; Tu, Y.-Q.; Chan, A. S.-C.; Kitching, W. *Org. Lett.* **2001**, *3*, 847. (e) Jia, Y.-X.; Li, X.; Wu, B.; Zhao, X.-Z.; Tu, Y.-Q. *Tetrahedron* **2002**, *58*, 1697. (f) Jia, Y.-X.; Li, X.; Wang, P.-Z.; Wu, B.; Zhao, X.; Tu, Y.-Q. *J. Chem. Soc., Perkin Trans. 1* **2002**, 565.

(5) Ito, H.; Kawabe, C.; Iguchi, K. *Heterocycles* **2006**, *67*, 695.

Scheme 1. Synthetic Plan of the C9–C28 Subunit

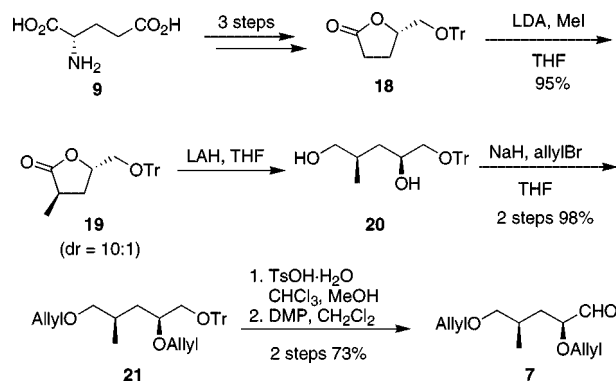


of bromide **3** to aldehyde **4** and following spiroketalization. Fragment **3** would be synthesized from commercially available chiral synthons **5** and **6** through asymmetric dihydroxylation. Fragment **4** would be prepared through the addition of fragment **8** to fragment **7**. Fragments **7** and **8** are synthesized through diastereoselective methylation from an L-glutamic acid (**9**) and an enantioselective alcoholysis of **10** using lipase, respectively.

Synthesis of the fragment **3** containing four chiral centers began with a commercially available chiral synthon **5** (Scheme 2). Protection of the hydroxyl group of **5** and half-reduction gave known aldehyde **11**.⁶ Subsequent formation of a carbon–carbon triple bond by the treatment of **11** with the Ohira–Bestmann reagent **12**⁷ gave alkyne **13** in 61% yield over the three steps. Subsequent treatment of **13** with a Schwaltz reagent (Cp_2ZrHCl) and iodine provided (*E*)-iodoalkene **14** in 89% yield. The coupling reaction of two fragments **14** and **15**, prepared from **6** by the protection of

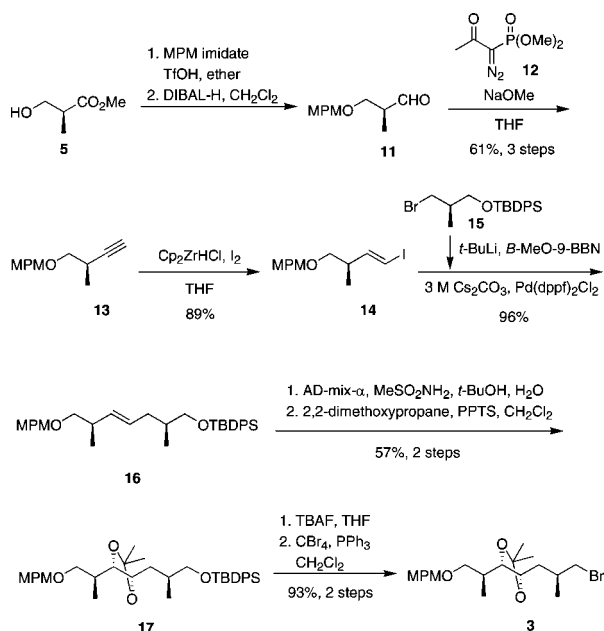
a hydroxyl group, was examined. The $\text{S}_\text{N}2$ reaction of the anion, derived from **14**, with a bromide **15** did not proceed due to steric reasons around the carbon atom bearing a

Scheme 3. Synthesis of Fragment 7

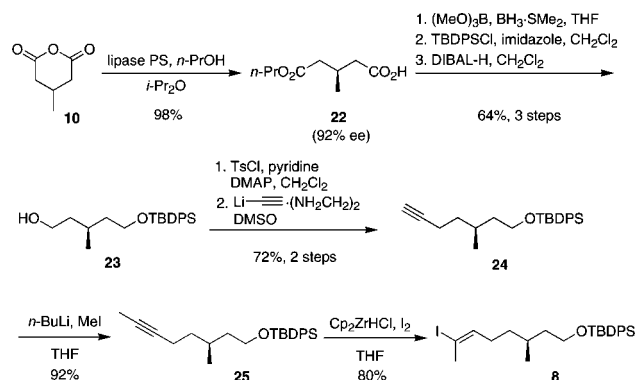


bromine atom on **15**. The coupling reaction of **14** with **15** was achieved by employing the Suzuki–Miyaura coupling reaction⁸ after converting **15** to an organoboron reagent, and **16** was obtained in excellent yield (96%). The Sharpless asymmetric dihydroxylation of **16** for the creation of two

Scheme 2. Synthesis of Fragment 3

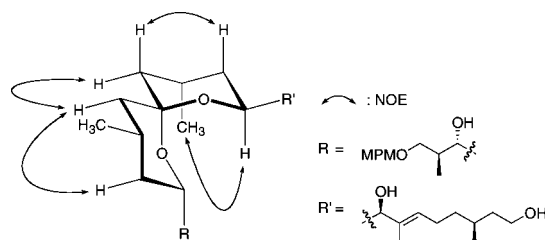


Scheme 4. Synthesis of Fragment 8



The synthesis of fragment **8** is shown in Scheme 4. Compound **22** was prepared from 3-methylglutaric anhydride (**10**) by enantioselective alcoholysis using lipase PS with *n*-PrOH according to the literature procedure (98% yield, 92% ee).¹² Reduction of the carboxylic acid moiety of **22**

Fragment **4** was synthesized through the coupling reaction of fragments **7** with **8** (Scheme 5). The addition reaction of a vinyl lithium derivative, which was prepared from **8** by treatment with an *s*-BuLi, with aldehyde **7** proceeded to give **26** in 77% yield as a diastereomeric mixture (1:1). Although the addition reaction of the analogues of fragment **7** having other protecting groups (MPM or MOM) was examined, the diastereoselectivity of the reaction did not improve. At this stage, separation of the diastereomer was not successful. Therefore, **26** was converted to **28** as a diastereomeric mixture. Deprotection of allyl groups of **26** using a reaction



3875

of a zirconocene equivalent¹³ and selective protection of a 1,2-diol moiety using 2,2-dimethoxypropane gave **28** in 86% yield for two steps. After separation of diastereomers, the desired diastereomer of **28**¹⁴ was converted to a bromide **29** in 79% yield. One carbon elongation was examined by the formylation of **29** using a *t*-BuLi with DMF, and fragment **4** was obtained in 53% yield. The coupling reaction of fragments **3** and **4** was achieved as follows (Scheme 5). Lithiation of **3** by the reaction of **3** with *t*-BuLi and an addition of the resultant anion to aldehyde **4** gave compound **30** in excellent yield (94%). The hydroxyl group of **30** was oxidized by Swern oxidation to give **31** in 76% yield. The formation of a spiroketal moiety was achieved during the

deprotection of two acetonide groups by treating **31** with TsOH in methanol, and subunit **2** was obtained in 86% yield as a single isomer. The relative stereochemistry of the spiroketal moiety of subunit **2** was determined by NOESY spectra: NOE correlations of **2** are shown in Figure 1.

In conclusion, we have described a convergent synthesis of the C9–C28 subunit of didemnaketal B. The present strategy required only 16 steps even in the longest linear sequence.

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Supporting Information Available: Detailed experimental procedure and characterization data for new compounds and ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801395Q

(12) (a) Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1988**, *52*, 3087. (b) Yamamoto, Y.; Yamamoto, K.; Nishioka, T.; Oda, J. *Tetrahedron Lett.* **1988**, *29*, 1717.

(13) Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774.

(14) Relative stereochemistry of both diastereomers was determined by NOESY spectra.