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Total Synthesis of the Proposed Structure of Didemnaketal B

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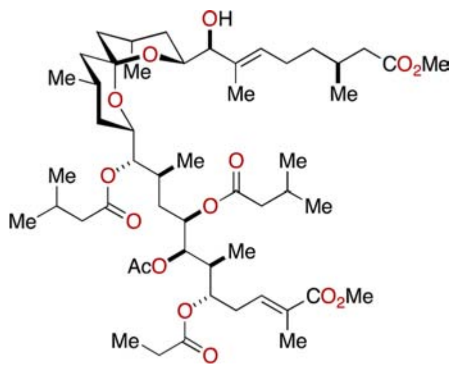
ABSTRACT



Total synthesis of the proposed structure of didemnaketal B has been accomplished. The C7−C21 spiroacetal domain was synthesized by exploiting our Suzuki−Miyaura coupling/spiroacetalization strategy. The C1−C7 acyclic domain was constructed via an Evans *syn*-aldol reaction and a vinylogous Mukaiyama aldol reaction. Finally, the C22−C28 side chain was introduced by means of a Nozaki−Hiyama−Kishi reaction. Comparison of the NMR spectroscopic data of our synthetic material with those of the authentic sample revealed that the proposed structure requires stereochemical reassignment.

In 1991, Faulkner and co-workers reported the isolation and characterization of the gross structure, including the relative stereochemistry of the spiroacetal domain, of didemnaketals A and B (**1** and **2**, respectively, Figure 1).[1] Although these compounds were isolated from the magenta ascidian *Didemnum* sp., collected from the Auluptagel Island in Palau, Faulkner and Pika later reported that **1** and **2** were produced from didemnaketal C (**3**) during the prolonged storage of the ascidian in methanol.[2] The complete stereostructure of **2** was proposed on the basis of the combination of degradation/derivatization experiments, X-ray crystallographic analysis, and application of chiral anisotropic reagents.[3] Specifically, the absolute configuration of the C5, C8, C11, and C21 stereogenic centers was assigned on the basis of the modified Mosher analysis,[4] and the relative stereochemistry of the C5/C6, C6/C7, and C7/C8 stereogenic centers was correlated by degradation/derivatization experiments, while the relative configuration of the C10−C20 domain was established by X-ray crystallographic analysis of a degradation product. The absolute configuration of the C20 and C26 stereogenic centers was determined by applying the phenylglycine methyl ester (PGME) method.[5]

Significantly, **1** and **2** exhibited potent inhibitory activity against HIV-1 protease (IC_{50} 2 and 10 μM, respectively),[1] while **3** turned out to be inactive.[2] Rich and co-workers have successfully discovered novel HIV-1 protease dimerization inhibitors based on the acyclic domain of didemnaketals, suggesting the possible biochemical mode-of-action of the parent compounds.[6] Because of their complex molecular structure and intriguing biological activity, didemnaketals represent attractive synthetic targets

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for organic chemists.[7-9] Very recently, Tu et al. have reported the total synthesis of the proposed structure **1** of didemnaketal A to show that the stereochemical assignment of the structure postulated by the Faulkner group needs to be re-examined.[10] Here, we disclose the first total synthesis of the proposed structure **2** of didemnaketal B.

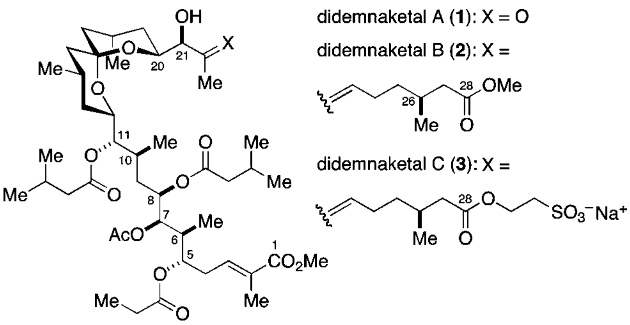

Figure 1. Proposed structures of didemnaketals A–C.

Our synthesis plan toward **2** is summarized in Scheme 1. We envisioned the C22–C28 side chain to be introduced at the final stage of the total synthesis by means of the Nozaki–Hiyama–Kishi (NHK) reaction[11] of the aldehyde **4** with the vinyl iodide **5**.[9] This obviates the need to differentiate the C21 secondary hydroxy group from the others and mitigates tedious protective group manipulations. The aldehyde **4** would be obtained from the alcohol **6** through a series of reactions that included a vinylogous Mukaiyama aldol reaction.[12] The C6 and C7 stereogenic centers within **6** would be generated from the precursor **7** in a stereoselective manner by relying on the Evans *syn*-aldol methodology.[13] We planned to construct the spiroacetal domain of **7** by means of the Suzuki–Miyaura reaction[14] of the alkylborate **8** derived from the iodide **9** and the enol phosphate **10**,[9] followed by an acid-catalyzed spiroacetalization.[15]

(7) (a) Wang, P. Z.; Tu, Y. Q.; Yang, L.; Dong, C. Z.; Kitching, W. *Tetrahedron: Asymmetry* **1998**, *9*, 3789–3795. (b) Jia, Y. X.; Wu, B.; Li, X.; Ren, S. K.; Tu, Y. Q.; Chan, A. S. C.; Kitching, W. *Org. Lett.* **2001**, *3*, 847–849. (c) Jia, Y. X.; Li, X.; Wang, P. Z.; Wu, B.; Zhao, X. Z.; Tu, Y. Q. *J. Chem. Soc., Perkin Trans. 1* **2002**, 565–570. (d) Jia, Y. X.; Li, X.; Wu, B.; Zhao, X. Z.; Tu, Y. Q. *Tetrahedron* **2002**, *58*, 1697–1708. (e) Li, X. Q.; Zhao, X. Z.; Liu, P. N.; Tu, Y. Q. *Chin. Chem. Lett.* **2004**, *15*, 757–758. (f) Zhao, X. Z.; Tu, Y. Q.; Peng, L.; Li, X. Q.; Jia, Y. X. *Tetrahedron Lett.* **2004**, *45*, 3713–3716. (g) Zhao, X. Z.; Peng, L.; Tang, M.; Tu, Y. Q.; Gao, S. H. *Tetrahedron Lett.* **2005**, *46*, 6941–6944.

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(11) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646.

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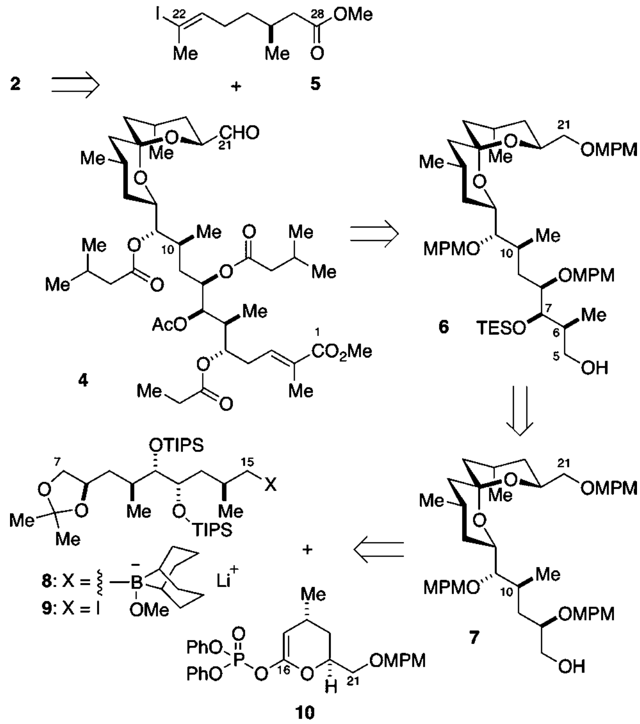
(14) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722–6737. (c) Fuwa, H. *Synlett* **2011**, 6–29.

(15) Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2549–2552.

(16) Deng, L.-S.; Huang, X.-P.; Zhao, G. *J. Org. Chem.* **2006**, *71*, 4625–4635.

Scheme 1. Synthesis Plan toward **2**



The synthesis of the iodide **9** started from the diol **11**,[16] as depicted in Scheme 2. The cleavage of the trityl ether under acidic conditions, followed by a selective protection of the resultant 1,2-diol moiety as its acetonide, led to the alcohol **12**. The Mitsunobu reaction[17] with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation under buffered conditions delivered the sulfone **13**. The Julia–Kocienski olefination[18] of **13** with the aldehyde **14**[9] was optimally performed by using LHMDS in THF/DMPU (7:1) at −78 °C to room temperature, giving the olefin **15** in 79% yield with acceptable stereoselectivity (*E*/*Z* = 5:1). Although the minor *Z*-isomer could not be removed at this stage, it was of no consequence since the ensuing Sharpless asymmetric dihydroxylation[19] of **15** preferentially proceeded on the major *E*-isomer and delivered the 1,2-diol **16** in 78% yield (dr >20:1),[20] with the less reactive *Z*-isomer remaining unreacted. The silylation of **16** followed by the cleavage of the *p*-methoxyphenylmethyl (MPM) ether gave an alcohol that was converted to the iodide **9**.

Next, we focused our attention on the construction of the spiroacetal domain of **2** (Scheme 3). Treatment of the iodide **9** with *t*-BuLi in the presence of *B*-MeO-9-BBN (Et_2O/THF, −78 °C to room temperature)[21] generated an alkylborate, which, without isolation, was coupled with the

(17) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(18) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

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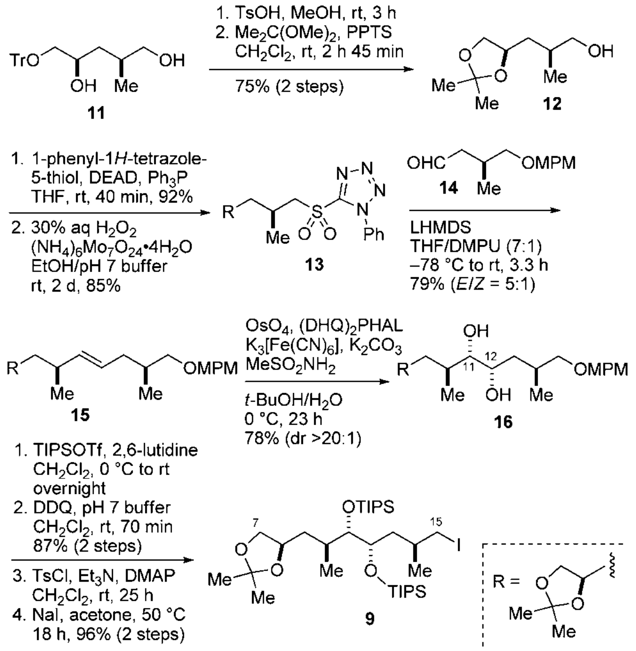
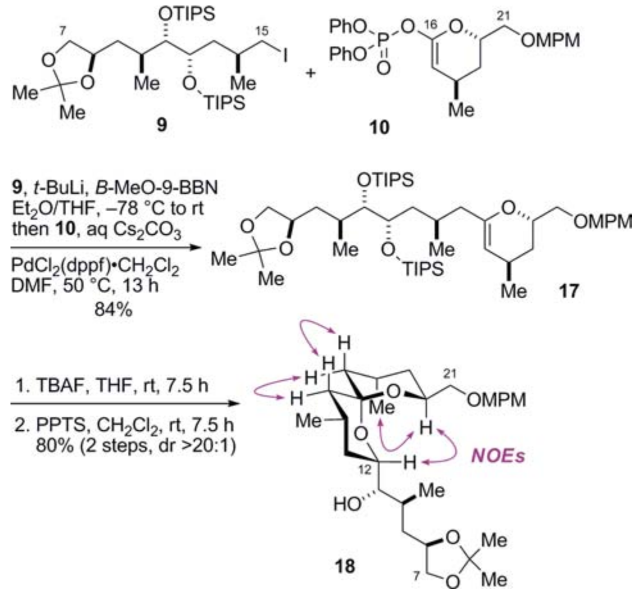
(20) The stereochemistry of the C12 stereogenic center was subsequently confirmed by a NOESY experiment on the spiroacetal **18** (Scheme 3).

Scheme 2. Synthesis of Iodide **9**



Scheme 3. Synthesis of Spiroacetal **18**



enol phosphate **10**[9] in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ and aqueous Cs_2CO_3 in DMF at 50 °C to provide the endocyclic enol ether **17** in 84% yield. After desilylation with TBAF, the resultant dihydroxy enol ether was exposed to a catalytic amount of PPTS in CH_2Cl_2 at room temperature to afford the spiroacetal **18** in 80% yield (two steps, dr > 20:1). The stereostructure of **18** was unambiguously established by a NOESY experiment as shown.[22]

Having secured access to the spiroacetal domain, we proceeded to elaborate the C1–C7 acyclic domain as summarized in Scheme 4. The alcohol **7** was obtained from **18** by standard protective group manipulations. The oxidation of **7** followed by the Evans *syn*-aldol reaction[13] of the resultant aldehyde with **19** (n-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C) afforded the alcohol **20** in 87% yield (two steps, dr > 20:1).[22] After the silylation of **20** (TESCl, pyridine, $AgNO_3$, 91%),[23] the reductive removal of the chiral auxiliary provided the alcohol **6** ($LiBH_4$, H_2O, THF, 84%). The oxidation of **6** with Dess–Martin periodinane (DMP),[24] followed by the vinylogous Mukaiyama aldol reaction[12] of the derived aldehyde with the dienol silyl ether **21**[25] ($BF_3\cdot OEt_2$, CH_2Cl_2/Et_2O (5:1), −78 °C), gave the homoallylic alcohol **22** in 74% yield (two steps, dr > 20:1).[22] However, the configuration of the C5 stereogenic center was opposite to that of the natural product, as expected from the Felkin–Anh model. The correction of the C5 stereochemistry was effectively achieved by an oxidation/reduction sequence. Thus, we found that the oxidation of **22** (DMP, 98%),[24] followed by reduction with (R)-2-methyl-CBS-oxazaborolidine/$BH_3\cdot THF$,[26] delivered the desired alcohol **23** in 83% yield (dr > 20:1).[22]

Completion of the total synthesis of **2** is depicted in Scheme 5. The acylation of the C5 hydroxy group of **23** with propionic anhydride, acidic cleavage of the silyl group, and acetylation of the resultant alcohol provided the acetate **24**. The removal of all the MPM groups within **24** by using DDQ, selective silylation of the C21 hydroxy group, acylation of the remaining C8 and C11 hydroxy groups with isovaleric anhydride, and removal of the silyl group afforded the alcohol **25** in good overall yield. This alcohol was oxidized with DMP,[24] and the NHK coupling[11] of the resultant aldehyde with the vinyl iodide **5**[9] under the standard conditions furnished **2** and its C21 epimer, 21-*epi*-**2**, as an approximately 1:1.3 mixture in 52% combined yield. These diastereomers could be separated by reversed-phase HPLC. The C21 stereogenic center of **2** and 21-*epi*-**2** was established by the modified Mosher method.[4,22]

Unfortunately, we found that neither **2** nor 21-*epi*-**2** was spectroscopically identical to the authentic sample, although the COSY, HMQC, and HMBC correlations observed in our synthetic **2**/21-*epi*-**2** supported the identity of the gross structure with that of didemnaketal B. The ^{1}H NMR data of 21-*epi*-**2** and the authentic sample were in close agreement, whereas significant chemical shift deviations around the C21 stereogenic center were observed between **2** [H19 (δ 1.38, 1.10), H20 (δ 3.72), H21 (δ 3.76)] and didemnaketal B [H19 (δ 1.56, 1.07), H20 (δ 3.84), H21 (δ 4.03)].[27] Thus, it is likely that the relative

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(22) For details on stereochemical assignment, see the Supporting Information.

(23) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; McGee, D. P. C. *Tetrahedron Lett.* **1982**, *23*, 1997–2000.

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

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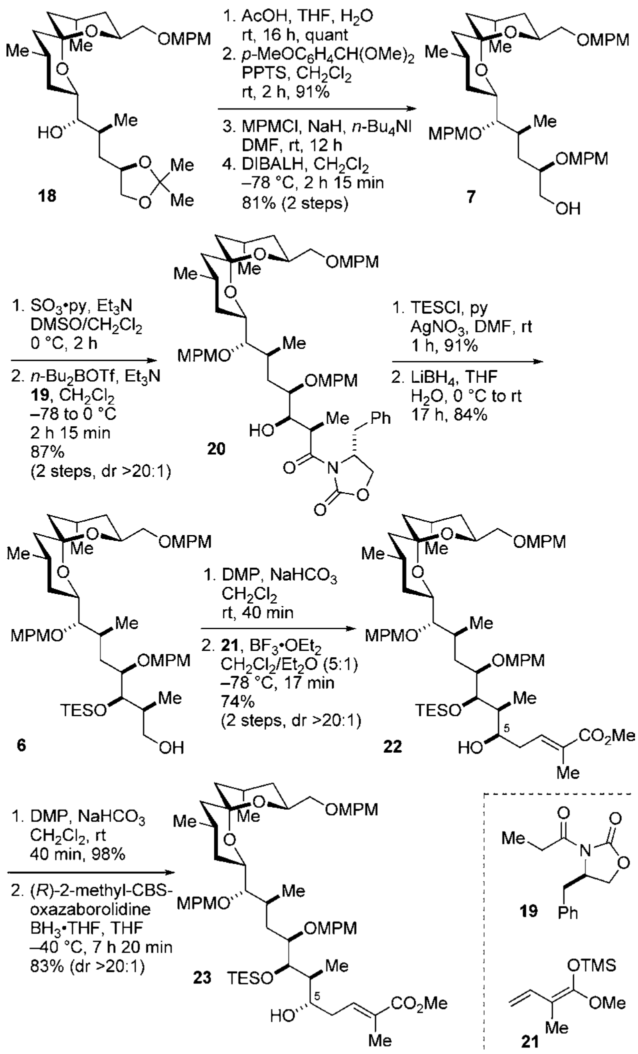
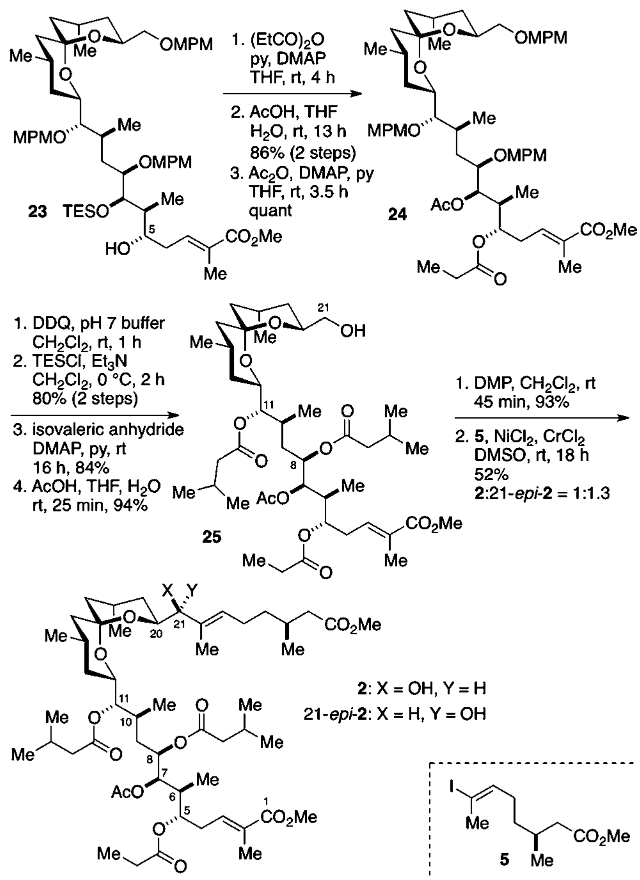
(26) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

Scheme 4. Synthesis of Alcohol **23**



Scheme 5. Completion of the Total Synthesis of **2**



its nonidentity with the authentic sample. Further studies toward the elucidation of the correct structure of didemnaketal B are currently ongoing and will be reported in due course.

stereochemistry of the C20 and C21 stereogenic centers was incorrectly assigned in the proposed structure. The nonidentity of 21-*epi*-**2** with authentic didemnaketal B was indicated by discrepancies in their ^{13}C NMR signals.[28] Thus, it appears that more than one erroneous stereochemical assignments are present in the proposed structure **2**; we speculate that the relative stereochemistry of the C8/C10 and C20/C21 stereogenic centers might be misassigned.

In conclusion, we have completed the first total synthesis of the proposed structure **2** of didemnaketal B and revealed its nonidentity with the authentic sample. Further studies toward the elucidation of the correct structure of didemnaketal B are currently ongoing and will be reported in due course.

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Note Added after ASAP Publication. Scheme 3 was incorrect in the version published ASAP on July 22, 2013; the correct version reposted July 23, 2013.

Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) Comparison tables for the ^{1}H and ^{13}C NMR chemical shifts for **2**, 21-*epi*-**2**, and didemnaketal B are provided in the Supporting Information.

(28) Faulkner et al. reported that the ^{13}C NMR data of authentic didemnaketal B showed signals at 70.6 and 16.2 ppm,[1] but such signals were not observed for 21-*epi*-**2** (or **2**) within $\Delta\delta = \pm 1.0$ ppm.

The authors declare no competing financial interest.