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Convergent Assembly of the Spiroacetal Subunit of Didemnaketal B

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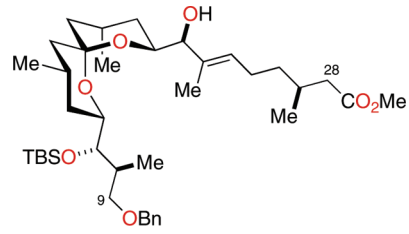
ABSTRACT



A highly convergent synthesis of the C9−C28 spiroacetal subunit of didemnaketal B has been accomplished. Assembly of the C9−C15 alkylborate and C16−C21 enol phosphate by means of Suzuki−Miyaura coupling and acid-catalyzed cyclization of the derived dihydroxy enol ether enabled a rapid and efficient construction of the spiroacetal subunit. The C22−C28 side chain was incorporated via Nozaki−Hiyama−Kishi coupling to complete the synthesis.

Didemnaketals A and B (**1** and **2**, respectively, Figure 1) were isolated from the magenta ascidian *Didemnum* sp. collected at Auluptagel island, Palau, by Faulkner and coworkers.[1] The gross structure of **1** and **2** including relative stereochemistry of the spiroacetal subunit was established on the basis of extensive 2D NMR analysis. These terpenoids have been shown to exhibit potent HIV-1 protease inhibitory activity (IC_{50} 2−10 μM) presumably via a dissociative mechanism. Faulkner et al. later found that the actual metabolite of the ascidian was didemnaketal C (**3**).[2] It was hence assumed that **1** and **2** were produced from **3** during prolonged storage of the ascidian sample in methanol. The complete stereostructure of **2** and **3** was finally determined by a combination of degradation and derivatization of the natural sample, application of the modified Mosher method,[3] and spectroscopic comparison with reference compounds.[4,5] The densely functionalized complex molecular structure and interesting biological property of didemnaketals stimulated considerable interest within the synthetic community.[6−8] As a part of our efforts toward the total synthesis of didemnaketals, we describe herein a highly convergent synthesis of the C9−C28 subunit of didemnaketal B, which features Suzuki−Miyaura coupling[9] and Nozaki−Hiyama−Kishi (NHK) coupling[10] as key fragment assembly processes.

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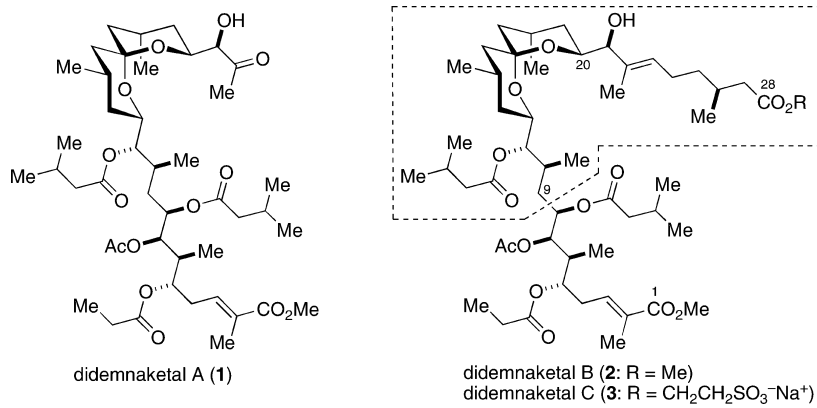
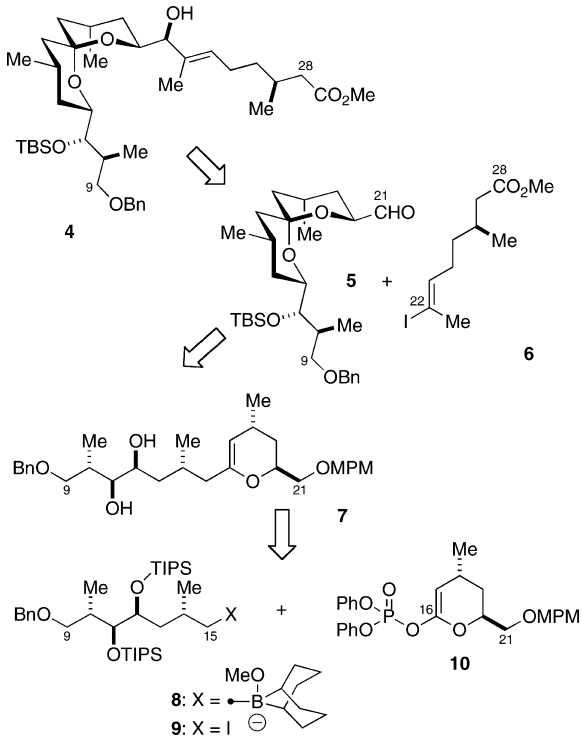


Figure 1. Structures of didemnaketals A−C.

Our synthesis plan toward the C9−C28 subunit **4** of didemnaketal B is summarized in Scheme 1. We envisioned

Scheme 1. Synthesis Plan for the C9−C28 Subunit **4**



that the C22−C28 side chain could be incorporated via NHK coupling of aldehyde **5** and vinyl iodide **6**. The spiroacetal moiety of **5** was planned to be constructed by means of acid-catalyzed cyclization of dihydroxy enol ether **7** under thermodynamic conditions. In turn, **7** could be synthesized via Suzuki−Miyaura coupling of alkylborate **8** generated from iodide **9** and enol phosphate **10**.[11,12]

The synthesis of the C9−C15 iodide **9** commenced with Mitsunobu coupling[13] of the known alcohol **11**[14] with 1-phenyl-1*H*-tetrazole-5-thiol (95%) followed by *m*CPBA oxidation (100%) to give sulfone **12** (Scheme 2). Julia−Kocienski olefination[15] of **12** with the known aldehyde **13**[16] required optimization, but we eventually found that deprotonation of **12** with KHMDS in THF/DMPU (7:1) at −78 °C followed by addition of **13** and warming the reaction mixture to room temperature afforded olefin **14** in 82% yield as an inseparable mixture of *E*/*Z* isomers (*E*/*Z* = ca. 16:1). Sharpless asymmetric dihydroxylation[17] of **14** under standard conditions using $(DHQ)_2PHAL$ as a chiral ligand provided 1,2-diol **15** in 81% yield after removal of the minor diastereomer by recrystallization (see the Supporting Information for details on stereochemical assignment of the major diastereomer). Bis-silylation of **15** (TIPSOTf, 2,6-lutidine, 100%) and oxidative removal of the MPM group (DDQ, 89%) gave alcohol **16**, which was converted to iodide **9** via tosylation and displacement with NaI (98% for the two steps).

The C16−C21 enol phosphate **10** was prepared from the known epoxide **17**[18] (Scheme 3). Regioselective epoxide opening with vinylMgBr/CuI gave a homoallylic alcohol, which was acylated with acryloyl chloride to deliver diene **18** in 95% yield (two steps). Ring-closing metathesis[19] of **18** under the influence of the Grubbs second-generation

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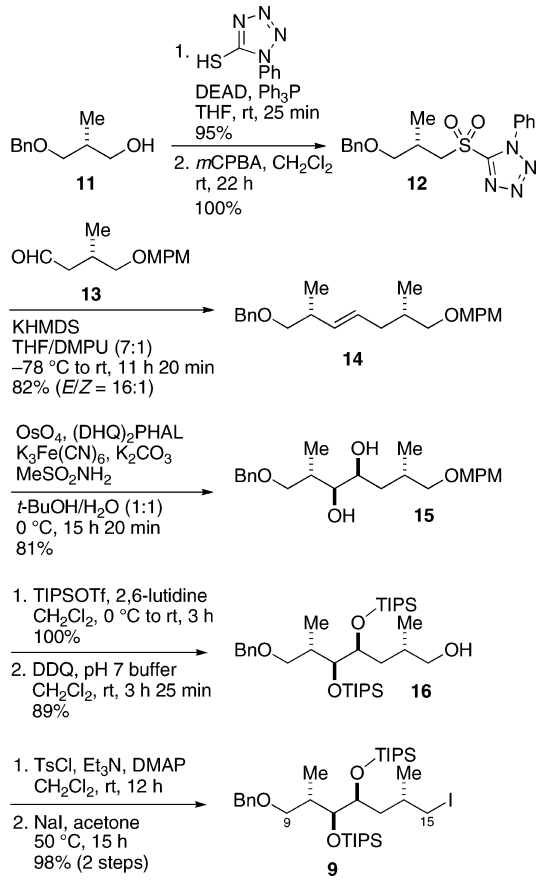
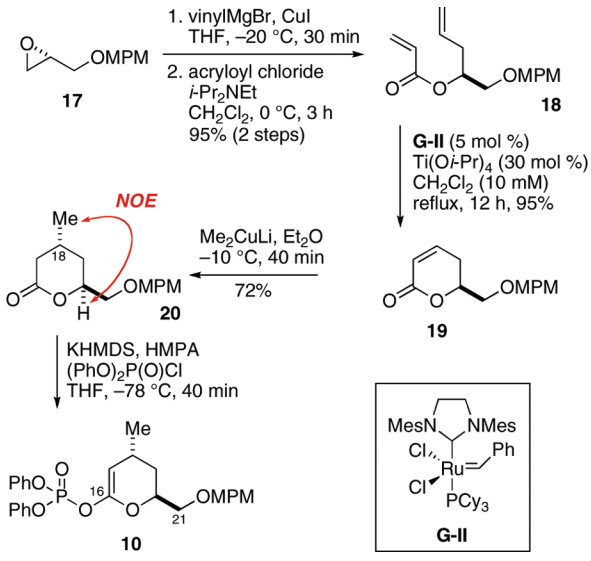
Scheme 2. Synthesis of the C9−C15 Iodide **9**



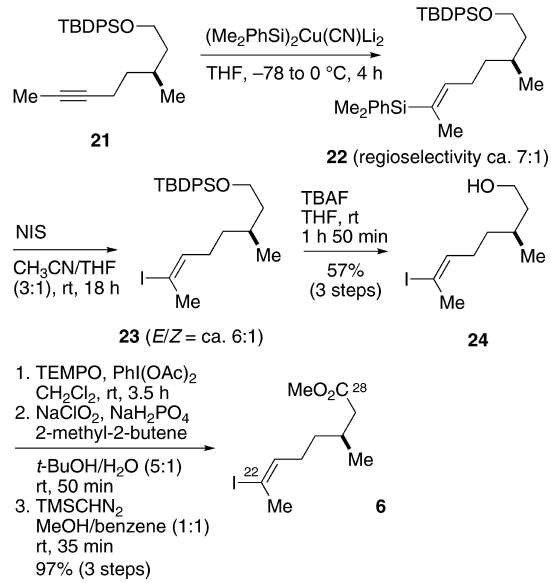
Scheme 3. Synthesis of the C16−C21 Enol Phosphate **10**



catalyst (**G-II**)[20] (Ti(O*i*-Pr)$_4$[21] (30 mol %), CH_2Cl_2 (10 mM), reflux) afforded α,β-unsaturated lactone **19** in 95% yield. Stereoselective 1,4-addition of Me_2CuLi gave lactone **20** in 72% yield as a single stereoisomer.[22] The stereochemistry of the newly generated stereogenic center at C18 was confirmed by an NOE experiment as shown. Finally, treatment of **20** with KHMDS in the presence of $(PhO)_2P(O)Cl$ furnished the C16−C21 enol phosphate **10**.

The C22−C28 vinyl iodide **6** was synthesized from the known alkyne **21**[8] (Scheme 4). Regioselective silylcupration

Scheme 4. Synthesis of the C22−C28 Vinyl Iodide **6**



of **21** with $(Me_2PhSi)_2Cu(CN)Li_2$ (THF, −78 to 0 °C)[23] gave vinylsilane **22** with approximately 7:1 regioselectivity. Iododesilylation of vinylsilane **22** (NIS, CH_3CN/THF)[24] was accompanied with a partial erosion of the double bond geometry to deliver vinyl iodide **23** (*E*/*Z* = ca. 6:1 for the major regioisomer). Subsequent cleavage of the TBDPS ether with TBAF delivered alcohol **24** in 57% overall yield from **21**, after removal of the minor products. A two-stage oxidation of **24** to the corresponding carboxylic acid followed by esterification with $TMSCHN_2$ afforded the C22−C28 vinyl iodide **6** in 97% overall yield.

Completion of the synthesis of the C9−C28 subunit **4** is illustrated in Scheme 5. Treatment of iodide **9** with *t*-BuLi in the presence of *B*-MeO-9-BBN (Et_2O, −78 °C; then add THF, room temperature)[25] generated alkylborate **8**. Without

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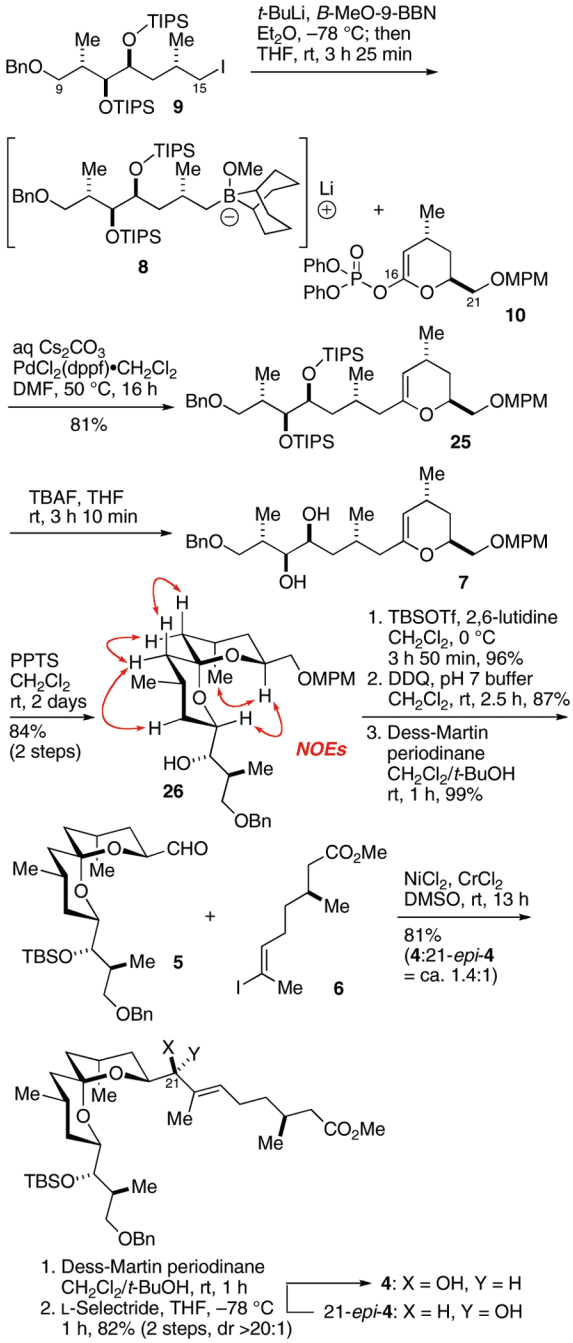
Scheme 5. Completion of the Synthesis of **4** and 21-*epi*-**4**



isolation, this was coupled with enol phosphate **10** by the action of $PdCl_2(dppf)•CH_2Cl_2$ catalyst (10 mol %) and aqueous Cs_2CO_3 in DMF at 50 °C to afford endocyclic enol ether **25** in 81% yield. Desilylation of the TIPS groups with TBAF led to dihydroxy enol ether **7**, which was exposed to PPTS in CH_2Cl_2 at room temperature to furnish spiroacetal **26** as a sole isolable product in 84% yield (two steps). The stereochemistry of the newly created stereogenic centers was established by NOE experiments on **26** as shown.

Protection of the hydroxy group within **26** as its TBS ether (TBSOTf, 2,6-lutidine, 96%), removal of the MPM group (DDQ, 87%), and subsequent Dess−Martin oxidation[26] of the derived alcohol (99%) led to aldehyde **5**. Finally, NHK coupling of **5** with vinyl iodide **6** under standard conditions ($NiCl_2$, $CrCl_2$, DMSO, room temperature) afforded an approximately 1.4:1 separable mixture of the C9−C28 subunit **4** and its C21 epimer 21-*epi*-**4** in 81% combined yield. The stereochemistry of the C21 stereogenic center of the major isomer was determined by application of the modified Mosher method (see the Supporting Information for details).[3] Although the NHK coupling proceeded with only moderate diastereoselectivity, we found, after extensive investigation, that 21-*epi*-**4** could be efficiently transformed into the desired **4** via an oxidation/reduction sequence; oxidation of 21-*epi*-**4** with Dess−Martin periodinane gave an enone quantitatively, which was reduced with L-selectride to provide the desired **4** in 82% yield as a single stereoisomer.

In conclusion, a highly convergent assembly of the fully functionalized C9−C28 spiroacetal subunit **4** of didemnaketal B (**2**) has been accomplished by exploiting Suzuki−Miyaura coupling and NHK coupling. The present synthesis proceeded with only 15 linear steps from the known alcohol **11**. Further studies toward the total synthesis of didemnaketals are currently ongoing and will be reported in due course.

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

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