# Total Synthesis of the Nominal Didemnaketal A**

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Despite remarkable advances in the treatment and prophylaxis of the human immunodeficiency virus (HIV), AIDS-related infections remain a scourge for humankind. In 2010, approximately 1.8 million people died from AIDS-related causes, and there were 2.7 million new infections (including 0.39 million children) worldwide.[1] Consequently, the discovery and development of new chemotherapeutic agents against AIDS is still of great urgency. One important approach in this area would be based on structural modification of natural anti-HIV inhibitors.[2] The synthetic verification of promising structures could also lead to the discovery of efficient synthetic routes to potentially active structures.[3]

Didemnaketal A (**1**) and B (**2**; Scheme 1), isolated from the *Ascidian Didemnum Sp.* by Faulkner and co-workers, have been demonstrated to be effective HIV-1-protease inhibitors ($IC_{50} = 2$ and 10 μM, respectively).[4] Their structures and configuration were assigned on the basis of extensive NMR spectroscopic studies, Mosher chiral-shift methods, and chemical degradation of a subsequently isolated analogue, didemnaketal C (**3**; Scheme 1). It is highly likely that didemnaketals A and B are produced from didemnaketal C by oxidation and methanolysis on storage, respectively.[4c] On this basis, if the absolute configuration deduced by Faulkner and co-workers for didemnaketal B (portrayed in Scheme 1) is accepted, didemnaketal A (**1**) would be the 5*S*,6*S*,7*R*,8*R*,10*S*,11*S*,12*S*,14*S*,16*R*,18*R*,20*S*,21*R* stereoisomer. Didemnaketal A features a spiroketal moiety and a main chain containing 23 carbons and 12 stereogenic centers. Furthermore, there are three different ester groups at C5, C7, C8, and C11 and a free OH group at C21. Thus, overall, these
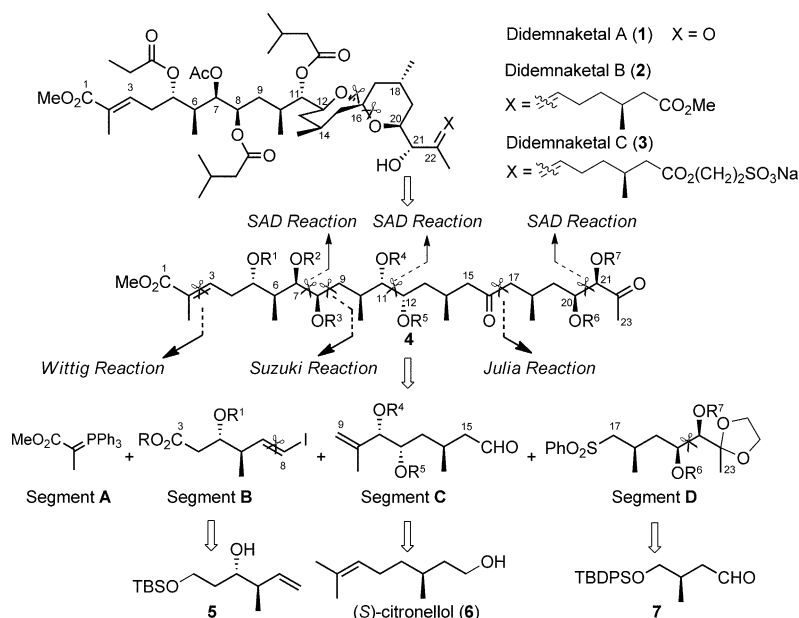
Scheme 1. Synthetic strategy toward the proposed structure of didemnaketal A. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

compounds have a rare and challenging architecture. The scarce natural supply, unusual structure, and significant HIV-1-inhibition properties of the didemnaketals have attracted the interest of synthetic chemists. Synthetic approaches toward subunits of didemnaketals were developed by Rich and co-workers,[5] Ito et al.,[6a] Fuwa et al,[6b] and our research group.[7] However, there has been no report of a total synthesis of didemnaketal A.

Such a synthesis presents at least three major challenges: 1) the polymethyl and multioxygenation patterns are arranged somewhat irregularly on the main chain (unlike more straightforward 1,3-dimethyl or 1,3-dihydroxy dispositions) and are thus difficult to generate efficiently by repetitive use of a single reliable method (e.g. aldol reaction variants); 2) acyclic stereocontrol is more difficult than that in rigid (cyclic) frameworks; and 3) chemoselective protection/deprotection and then regioselective esterification of polyhydroxy systems are tactically awkward. Herein, we report the first total synthesis of the proposed structure of didemnaketal A.

Our retrosynthetic analysis is outlined in Scheme 1. Unlocking of the spiroketal moiety furnishes precursor **4** with an elongated carbon chain and reveals two OH groups at C12 and C20 and a keto group at C16. Importantly, the six OH groups with the *syn* configuration at C7–C8, C11–C12, and C20–C21 in **4** could be stereoselectively installed by the

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Sharpless asymmetric dihydroxylation (SAD reaction). The three methyl-bearing stereogenic centers at C6, C14, and C18 could originate from "chiral pool" components. Furthermore, the bonds C2–C3, C8–C9, and C16–C17 in **4** could be formed by Wittig olefination, a Suzuki–Miyaura reaction, and Julia coupling, respectively. Following these disconnections, the four simpler segments **A**, **B**, **C**, and **D** were proposed for the construction of **4**, whereby the segments **B**, **C**, and **D** could be derived from the alcohol **5**, (S)-citronellol (**6**), and the aldehyde **7**, respectively.

Guided by this strategy, we began our synthesis of the proposed didemnaketal A structure **1** with the preparation of segment **B** (R = Me, R^1 = PMB). Starting from compound **5** (Scheme 2),[8] removal of the TBS group permitted diol
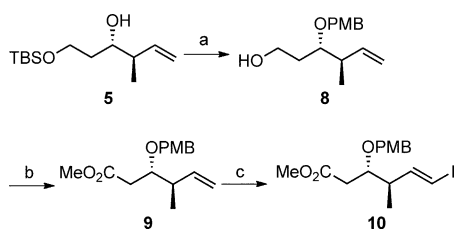
Scheme 2. Reagents and conditions: a) 1) TBAF, THF, 0 °C, 90%; 2) 4-methoxybenzaldehyde, CH$_2$Cl$_2$, CSA, room temperature, 99%; 3) DIBAL, CH$_2$Cl$_2$, −78 °C, 95%; b) Jones oxidation, acetone, then CH$_2$N$_2$/Et$_2$O, 68% (2 steps); c) 1) O$_3$, CH$_2$Cl$_2$, −78 °C, 93%; 2) CrCl$_2$, CHI$_3$, THF, 0 °C→RT, 71%. CSA = camphorsulfonic acid, DIBAL = diisobutylaluminum hydride, PMB = p-methoxybenzyl, TBAF = tetra-n-butylammonium fluoride.

protection with 4-methoxybenzaldehyde. Subsequent reductive opening of the *p*-methoxyphenyl acetal generated the alcohol **8**, which was oxidized with the Jones reagent and then esterified with CH$_2$N$_2$ to give the ester **9**. Finally, vinyl iodide **10** (segment **B**) was readily obtained by the ozonolytic cleavage of the C=C bond in **9** and a subsequent Takai reaction.[9]

The aldehyde segment **C** (R^4 = R^5 = TBS) was synthesized from (S)-citronellol (**6**; Scheme 3). Treatment of **6** with active O$_2$[10] was followed by selective protection of the primary alcohol to afford the ether **11** in 48% yield over two steps. The
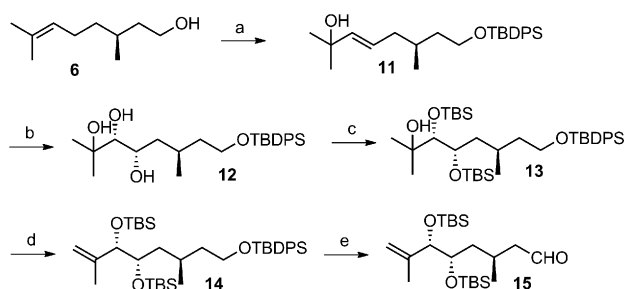
Scheme 3. Reagents and conditions: a) 1) Rose Bengal, O$_2$, *hν*, CH$_3$OH; 2) TBDPSCl, imidazole, CH$_2$Cl$_2$, 0 °C, 48% (2 steps); b) AD-mix-α, CH$_3$SO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), 0 °C, 85%; c) TBSCl, imidazole, DMF, 90 °C, 78%; d) SOCl$_2$, pyridine, 0 °C, 91%; e) 1) NH$_4$F, MeOH, reflux, 88%; 2) Dess–Martin periodinane, CH$_2$Cl$_2$, room temperature, 88%. DMF = N,N-dimethylformamide.

Sharpless asymmetric dihydroxylation (SAD)[11] of ether **11** generated the triol **12**, and selective TBS protection of the two secondary hydroxy groups, followed by the elimination of the tertiary alcohol, gave the terminal olefin **14**. Selective removal of the TBDPS protecting group and the oxidation of the resulting primary alcohol with Dess–Martin periodinane[12] furnished the aldehyde segment **C** (**15**) in 77% yield (2 steps). Significantly, only seven linear steps were required for the preparation of segment **C** from (S)-citronellol.

The sulfone segment **D** (R^6 = TBS, R^7 = MOM) was prepared from the aldehyde **7**[13] (Scheme 4), which underwent Wittig olefination[14] and protection of the resulting
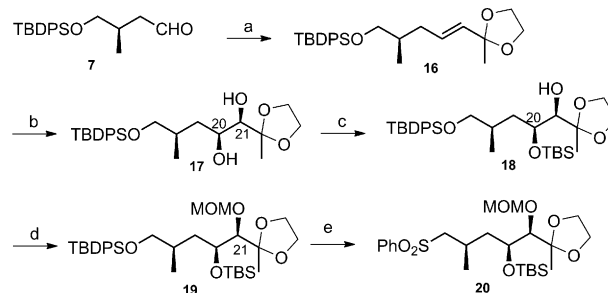
Scheme 4. Reagents and conditions: a) 1) PPh$_3$=CHCOCH$_3$, CH$_2$Cl$_2$, 55 °C, 95%; 2) glycol, PPTS, benzene, reflux, 92%; b) AD-mix-α, CH$_3$SO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), 0 °C, 91%; c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −90 °C, 72% (based on recovered starting material); d) MOMCl, NaI, DIPEA, DME, 100 °C, 95%; e) 1) NH$_4$F, CH$_3$OH, reflux, 70%; 2) I$_2$, PPh$_3$, imidazole, toluene, room temperature, 95%; 3) PhSO$_2$Na, DMF, room temperature, 84%. DIPEA = N,N-diisopropyl-N-ethylamine, DME = 1,2-dimethoxyethane, MOM = methoxymethyl, PPTS = pyridinium p-toluenesulfonate, Tf = trifluoromethanesulfonyl.

conjugated enone to afford the ketal **16** in 87% yield over two steps. The stereoselective installation of hydroxy groups at C20 and C21 by the SAD protocol yielded the diol **17**. Subsequently, selective protection of the hydroxy groups at C20 and C21 in **17** was studied. The mono-TBS ether at C20 was acquired in 72% yield by the use of TBSOTf and 2,6-lutidine in CH$_2$Cl$_2$ at −90 °C. Further protection of the hydroxy group at C21 of **18** with MOMI prepared in situ at 100 °C afforded the MOM ether **19** in excellent yield.[15] Selective desilylation of the *O*-TBDPS ether in **19**, followed by iodination of the resulting alcohol, gave the primary iodide intermediate, which reacted with sodium benzene sulfinate to provide the desired sulfone **20** in 56% yield over three steps.

With the three key building blocks **B**, **C**, and **D** available, our focus shifted to the crucial segment-coupling reactions (Scheme 5). Formation of the spiroketal moiety would result in the "internal" protection of the ketodiol unit; therefore, the Julia coupling[16] of segments **C** and **D** was attempted initially for the formation of the C9–C23 fragment. Under standard conditions, the reaction provided the anticipated coupling products, which were oxidized with the Collins reagent to form the C16 keto group. Subsequent reductive removal of the sulfone group furnished the C9–C23 fragment **21** in 82% yield over three steps. Spirocyclization with NH$_4$F·HF as a promoter afforded the desired spiroketal **22** in 86% yield.
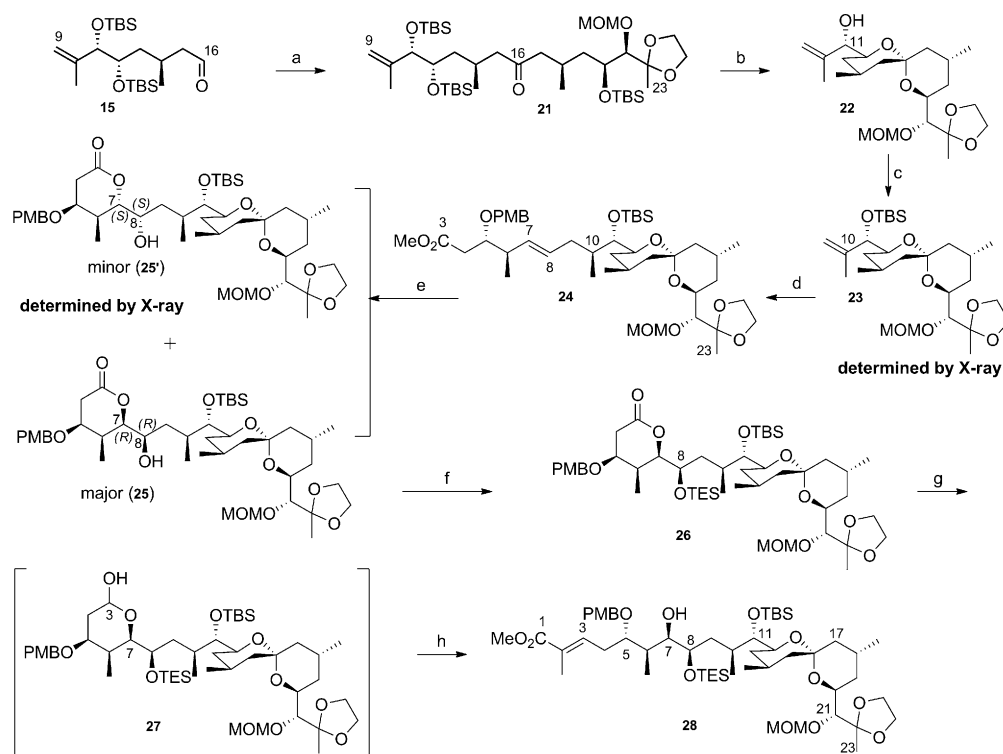
**Scheme 5.** Reagents and conditions: a) 1) *n*BuLi, THF, −78→0°C, 30 min, then **20**; 2) Collins reagent (10 equiv), CH$_2$Cl$_2$, room temperature; 3) SmI$_2$, THF, −78°C, 82% (3 steps); b) NH$_4$F·HF, CH$_3$OH, reflux, 86%; c) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, −78°C, 89%; d) 9-BBN, −78°C→RT, 4 h, then **10**, DMF, Cs$_2$CO$_3$, [Pd(dppf)$_2$Cl$_2$], AsPh$_3$, room temperature, 5 h, 77%; e) AD-mix-β, CH$_3$SO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), 0°C, then CHCl$_3$, room temperature, 3 days, 45% for **25** and 15% for **25′**; f) TESCl, imidazole, DMF, 60°C, 89%; g) DIBAL, CH$_2$Cl$_2$, −78°C; h) segment **A**, CH$_2$Cl$_2$, 55°C, 3 days, 95% (2 steps). 9-BBN = 9-borabicyclo[3,3,1]nonane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, TES = triethylsilyl.

Next, our attention was directed to the connection of segment **B** with the C9–C23 fragment (Scheme 5). Thus, reprotection of the free OH group in **22** as the TBS ether gave the Suzuki–Miyaura precursor **23**.[17] Pleasingly, the Suzuki–Miyaura coupling[18] between vinyl iodide **10** (segment **B**) and the hydroboration product derived from **23** proceeded well to produce fragment **24** (C3–C23) in 77% yield. The desired C10 methyl group was also installed stereoselectively during this process. The *E* configuration of the C=C bond in **24** was deduced from the coupling constant ($J = 16.8$ Hz) in the ^{1}H NMR spectrum. Subsequent SAD of the C=C bond in **24**, followed by in situ intramolecular trapping of the resulting C7 hydroxy group with the C3 methyl ester, generated the desired 7*R*,8*R* δ-lactone **25** in 45% yield, along with the minor undesired 7*S*,8*S* δ-lactone **25′**.[17] The structure of **25** was assigned by NMR spectroscopic studies, Mosher methods, and the X-ray crystallographic analysis of its isomer **25′**.[19] All 12 stereocenters in **25** had been correctly installed, exactly as assigned in the proposed stereostructure of didemnaketal A by Faulkner and co-workers.[4] The formation of the δ-lactone in **25** provided the possibility for tactical discrimination between the OH groups at C7 and C8. As a result, the C8 hydroxy group could be protected efficiently as the TES ether to give compound **26**. The lactone **26** was reduced to afford the lactol **27**, which was subsequently used without purification for a direct Wittig reaction with segment **A**[20] to furnish **28**. This advanced intermediate **28**, which was available in 18 steps from the known compound **7**, contained all stereocen-

ters as well as the entire chain (C1–C23) with crucially differentiated protection of the secondary hydroxy groups at C5, C8, C11, and C21 to enable later sequence-selective esterification of the corresponding alcohols.

We then considered possible conditions for the selective installation of three different ester groups at C5, C7, C8, and C11 (Scheme 6). First, acetylation of the C7 hydroxy group gave **29**. However, the dual removal of the silyl groups at C8 and C11 of **29** to yield the diol **30** proved problematic, because acetyl migration from C7 to C8 occurred prior to cleavage of the TBS ether at C11. We therefore carried out the sequence of reactions in a different order. Under mildly acidic conditions, selective cleavage of the C8 TES ether of **29** provided the desired product **31**; both acetyl migration and the deprotection of other acid-sensitive groups were avoided. The free hydroxy group at C8 in **31** was then acylated with isovaleric anhydride to introduce the C8 isovalerate ester moiety. We installed the second isovalerate ester at C11 in two steps: selective removal of the TBS group in **32**,[21] followed by acylation. Next, the PMB group at C5 of **33** was removed,[22] and acylation with propionic anhydride provided compound **34**. At this stage, detailed analysis of ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectra demonstrated that the ester groups were located in positions consistent with the conclusions reported for didemnaketal A.[4] Finally, deprotection at C21 and C22 with 40% HF afforded the target compound **1**.
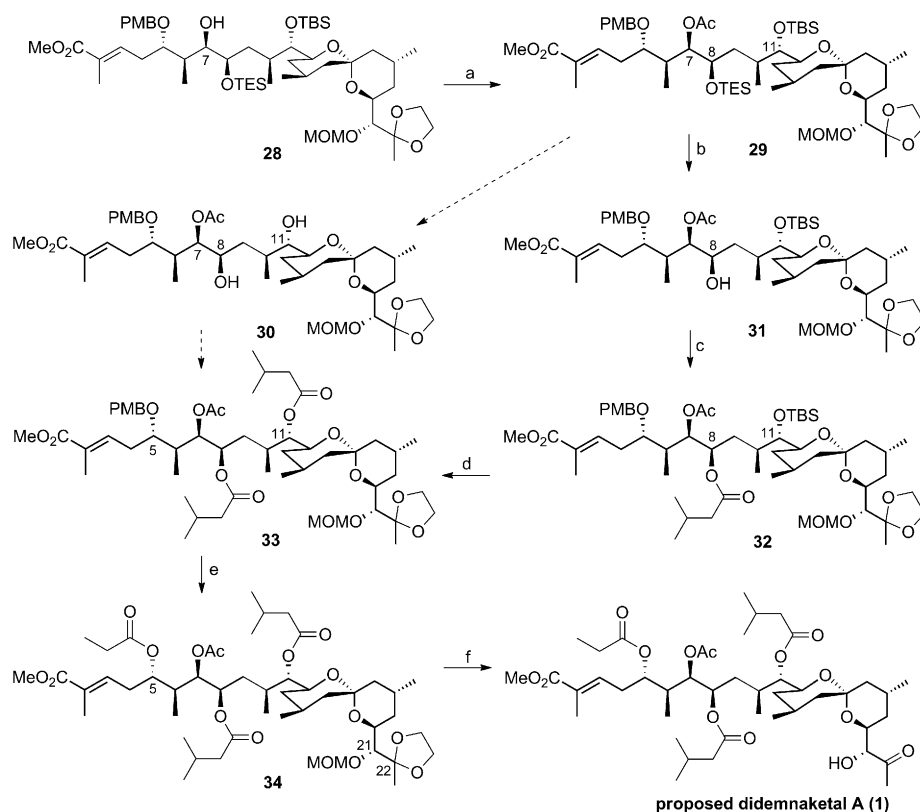
Scheme 6. Reagents and conditions: a) Ac$_2$O, CH$_2$Cl$_2$, DMAP (cat.), room temperature, 96%; b) PPTS, C$_2$H$_5$OH, 0°C, 97% (based on recovered starting material); c) isovaleric anhydride, CH$_2$Cl$_2$, DMAP (cat.), room temperature, 99%; d) HF·pyridine, THF–pyridine, room temperature, 3 days, 96%; then isovaleric anhydride, CH$_2$Cl$_2$, DMAP (cat.), room temperature, 97%; e) DDQ, CH$_2$Cl$_2$/ buffer (pH 7; 1:1), room temperature, 96%; then propionic anhydride, CH$_2$Cl$_2$, DMAP (cat.), room temperature, 89%; f) 40% HF, THF, room temperature, 89%. DMAP=4-dimethylaminopyridine, DDQ=2,3-dichloro-5,6-dicyanobenzoquinone.

To our disappointment, however, the ^{1}H and ^{13}C NMR spectra of our synthetic sample **1** were not coincident in all respects with the data reported by Faulkner and co-workers for the "natural" didemnaketal A.[4] Significant differences ($\Delta\delta > 0.08$ ppm) in the ^{1}H NMR chemical shifts were observed between the synthesized didemnaketal A (**1**) and the "natural" compound for the hydrogen atoms at C8, C10, C14, C19, C20, C21, and C36, and some clear discrepancies ($\Delta\delta > 1.0$ ppm) were also observed in the ^{13}C NMR chemical shifts for C7, C8, C10, C20, C23, and C26.[19] The absolute configuration of the C9–C20 segment in didemnaketal A was deduced by Faulkner and co-workers on the basis of the following methods: 1) determination of the relative configuration of the C9–C20 unit by X-ray crystallographic analysis of a chemical-degradation fragment;[4c] 2) assignment of the absolute configuration at C20 by the use of a chiral anisotropic reagent;[4c] and 3) confirmation of the absolute configuration at C11 by the use of an alternative Mosher method.[4c] Therefore, the assignment of the stereogenic centers between C9 and C20 could be reliable; however, the absolute configuration at C5, C6, C7, C8, and C21 was based only on the analysis of coupling constants, ROSEY correlations, and Mosher methods involving the use of bis-(methoxy(trifluoromethyl)phenylacetic acid) (bis-MTPA)

esters.[4c,23] If the details of the structural assignment of natural didemnaketal A by Faulkner et al. are considered,[24] the current spectral differences might plausibly arise from some stereochemical misassignments, in particular for C5, C6, C7, C8, and C21. On this basis, a series of stereodefined building blocks could be conceived for further stereochemical modifications to our constituent fragments in the present synthetic routes; these studies will be reported in due course.

In conclusion, we have described the first total synthesis of the proposed structure of didemnaketal A in 31 steps for the longest linear sequence. The key steps include Julia coupling, a Suzuki–Miyaura reaction, Sharpless asymmetric dihydroxylation, and Wittig olefination. The synthesis gives a vivid example of selective protection/deprotection in this polyol system. This route could provide convenient access to structurally diverse analogues for further activity evaluation.

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