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Total Synthesis

Total Synthesis and Structure Revision of Didemnaketal B

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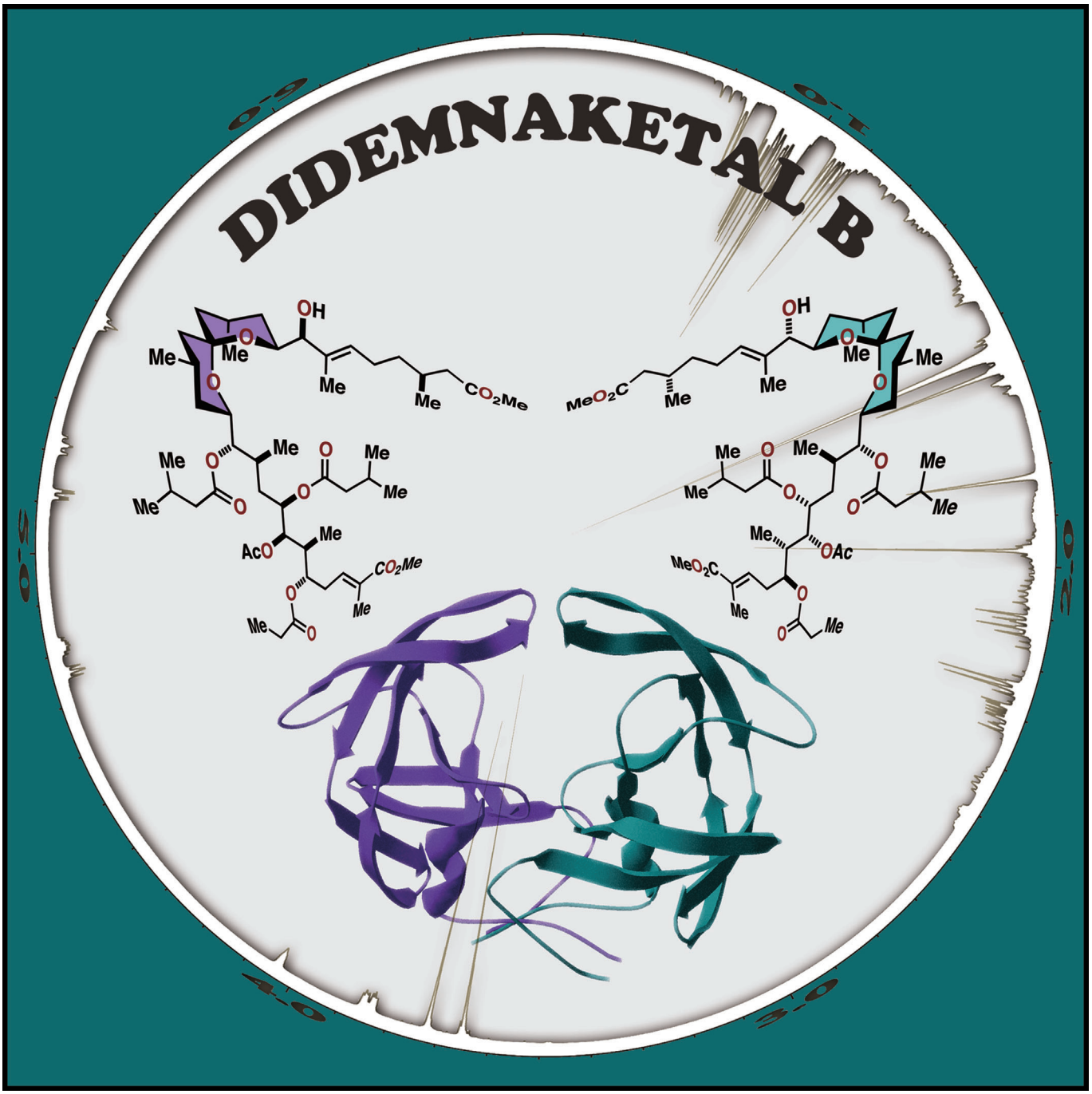

Abstract: Didemnaketal B, a structurally complex spiroacetal that exhibits potent HIV-1 protease inhibitory activity, was originally discovered by Faulkner and his colleagues from the ascidian *Didemnum* sp. collected at Palau. Its absolute configuration was proposed on the basis of degradation/derivatization experiments of the authentic sample. However, our total synthesis of the proposed structure of didemnaketal B questioned the stereochemical assignment made by Faulkner et al. Here we describe in detail our first total synthesis of the proposed structure **2** of didemnaketal B, which features 1) a convergent synthesis of the C7–C21 spiroacetal domain by means of a strategy exploiting Suzuki–Miyaura coupling, 2) an Evans *syn*-aldol reaction and a vinylogous Mukaiyama aldol reaction for the assembly of the C1–C7 acyclic domain, and 3) a Nozaki–Hiyama–Kishi reaction for the construction of the C21–C28 side chain domain. The NMR spectroscopic discrepancies observed between synthetic **2** and the authentic sample as well as careful inspection of the Faulkner's stereochemical assignment led us to postulate that the absolute configuration of the C10–C20 domain of **2** has been erroneously assigned. Accordingly, the total synthesis of the revised structure **65** was achieved to show that the NMR spectroscopic properties of synthetic **65** were in good agreement with those of the authentic sample. Furthermore, application of the phenylglycine methyl ester (PGME) method to the C7–C21 spiroacetal domain enabled us to establish the absolute configuration of didemnaketal B.

Introduction

Didemnaketals A and B were isolated from the extract of the magenta ascidian *Didemnum* sp., collected at Auluptagel Island, Palau, by Faulkner and co-workers.[1] However, it was later described by Faulkner and Pika that didemnaketal C was the only metabolite found in *Didemnum* sp. freshly collected at the same location.[2] It was thus speculated that didemnaketals A and B might be artificial degradation products of didemnaketal C upon prolonged storage of the ascidian specimens in methanol.[2]

HIV-1 protease is a homodimeric aspartic protease, with each monomer consisting of 99 amino acids. HIV-1 protease is known to be essential for maturation and replication of HIV.[3] Didemnaketals A and B exhibited potent inhibitory activity against HIV-1 protease in a peptidolysis assay,[1] whereas didemnaketal C was found to be inactive.[2] Rich and co-workers identified novel HIV-1 protease inhibitors inspired by the structures of didemnaketals.[4] Importantly, the "truncated" analogues of didemnaketals synthesized by Rich et al. have been shown to exert their activity by inhibition of the dimerization of HIV-1 protease monomers, a process that is essential for the formation of the active site of HIV-1 protease.

The gross structures of didemnaketals were determined by extensive 2D-NMR spectroscopic analyses.[1] The complete stereostructure of didemnaketal B was subsequently proposed as that shown by **2** (Figure 1) on the basis of extensive degradation/derivatization experiments.[5] The relative stereochemical relationship of the C5/C6, C6/C7, and C7/C8 stereogenic centers was correlated by NMR spectroscopic analyses on suitable acetonide derivatives, and the relative configuration of the C10–C20 spiroacetal domain was firmly established by X-ray crystallographic analysis of a degradation product. The absolute configuration of the C5, C8, C11, and C21 stereogenic centers was determined by application of the modified Mosher analysis,[6] while that of the C20 and C26 stereogenic centers was assigned on the basis of the phenyl glycine methyl ester (PGME) method.[7] Consequently, the structures of didemnaketals A and C have been believed to be those shown by **1** and **3**, respectively.

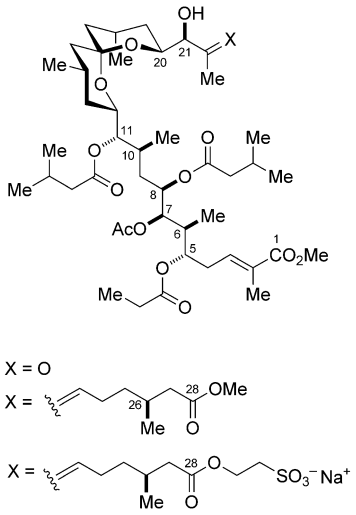

Figure 1. Proposed structures **1**–**3** of didemnaketal A–C. Ac = acetyl.

The structural complexity and biological activity of didemnaketals heightened the interest of the synthetic community.[8–10] Very recently, the Tu group has reported the total synthesis of the nominal structure **1** of didemnaketal A.[11] Independently, our group has completed the total synthesis of the proposed structure **2** of didemnaketal B.[12] However, comparison of the NMR spectroscopic data of synthetic **1** and **2** with those of the respective authentic samples revealed their non-identity and indicated possible stereochemical misassignment(s) in the proposed structures **1**–**3** of didemnaketals A–C. Thus, the correct structures of these complex spiroacetals remain to be elucidat-

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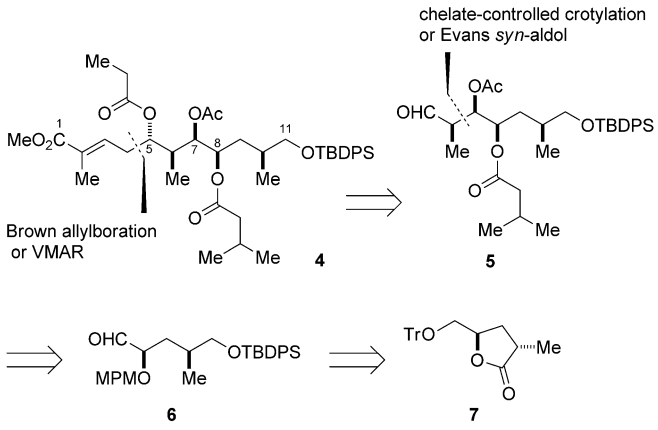
ed. Here, we report in detail our studies on the total synthesis of the proposed and revised structures of didemneketal B, which culminated in the establishment of the complete stereostructure of this complex spiroacetal.

Results and Discussion

Initial model studies on the C1–C11 domain

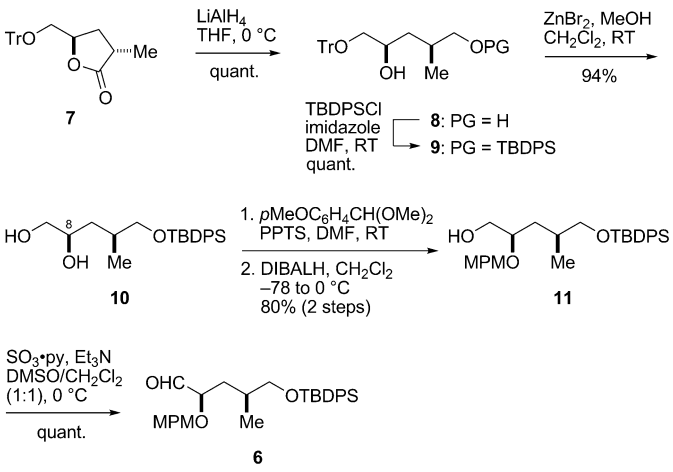
Given the complex structure of didemnaketal B, we first carried out synthetic studies on the C1–C11 and the C9–C28 model compounds, the latter of which has been disclosed previously.[10] Here, we describe the results of our initial model studies on the C1–C11 acyclic domain. Our synthesis plan toward the C1–C11 model compound **4** is summarized in Scheme 1. This



Scheme 1. Synthesis plan toward the C1–C11 model compound **4**. TBDPS = *tert*-butyldiphenylsilyl, MPM = *p*-methoxyphenylmethyl, Tr = triphenylmethyl.

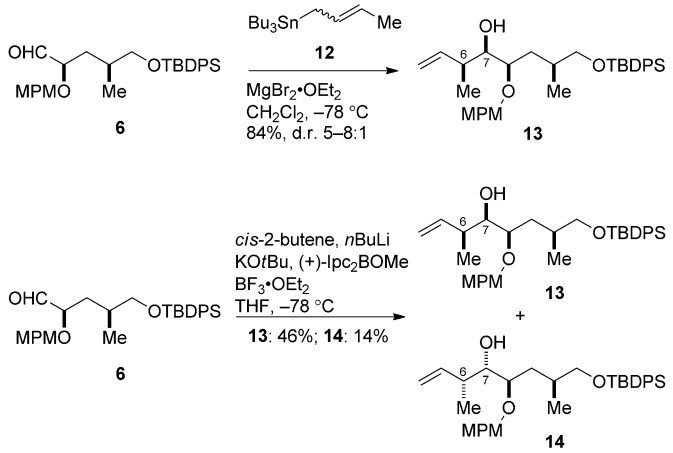
domain harbors multiple *O*-acyl groups that are prone to migration or cleavage under acidic or basic conditions. Evidently, a carefully planned protecting group strategy is mandatory for differentiating the *O*-acylated C5, C7, and C8 hydroxy groups. Thus, we planned to assess our protecting group strategy in this model synthesis. We considered that the target compound **4** could be obtained from the aldehyde **5** through a Brown asymmetric allylboration[13] or a vinylogous Mukaiyama aldol reaction (VMAR).[14,15] The aldehyde **5** in turn would be available from the aldehyde **6** by using a chelate-controlled diastereoselective crotylation[16] or an Evans *syn*-aldol reaction.[17] Finally, the aldehyde **6** was traced back to the γ-lactone **7**.[18]

As shown in Scheme 2, the synthesis of the aldehyde **6** commenced with $LiAlH_4$ reduction of the lactone **7**[18] to give the diol **8**.[19] Selective silylation of the primary alcohol within **8** gave the silyl ether **9**. Removal of the triphenylmethyl (Tr) group[20] provided the 1,2-diol **10**. We preferred to protect the C8 hydroxy group as its *p*-methoxyphenylmethyl (MPM) ether, since the MPM group can be removed by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under mild, buffered conditions compatible with *O*-acyl groups. Thus, acetalization of **10** ($pMeOC_6H_4CH(OMe)_2$, pyridinium *p*-toluenesulfonate (PPTS)) followed by regioselective reduction of the resultant acetal using diisobutylaluminum hydride (DIBALH)[21] afforded the alcohol **11** (80%, two steps), which was oxidized to the aldehyde **6** under the Parikh–Doering conditions (quant.).[22]



Scheme 2. Synthesis of aldehyde **6**. RT = room temperature, DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *p*-toluenesulfonate, DIBALH = diisobutylaluminum hydride, py = pyridine, DMSO = dimethylsulfoxide, quant. = quantitative.

To generate the C6 and C7 stereogenic centers, we initially investigated diastereoselective crotylation of the aldehyde **6**, which was brought about by exploiting the C8 alkoxy functionality (Scheme 3, top). Thus, treatment of **6** with the crotyl-

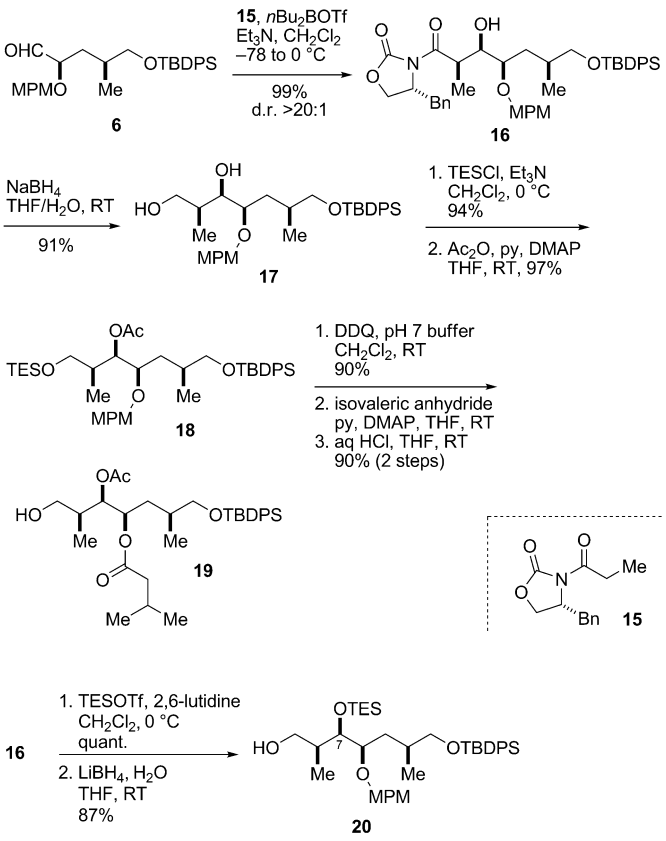


Scheme 3. Diastereoselective crotylation of aldehyde **6**. d.r. = diastereomer ratio, Ipc = isopinocampheyl.

stannane **12** in the presence of $MgBr_2{\cdot}OEt_2$ (CH_2Cl_2, −78 °C)[16] provided the alcohol **13** in 84% yield with 5–8:1 diastereoselectivity.[23] Although we were able to obtain the desired alcohol **13** with acceptable diastereoselectivity, it was unfortunate that we could not remove the minor stereoisomer (presumably C6/C7-*anti* isomer) even after several transformations. Meanwhile, Brown asymmetric crotylation[24] of **6** using (+)-*B*-(*Z*)-crotyldiisopinocampheylborane generated in situ gave the alcohol

13 (46%) with only moderate diastereoselectivity (d.r. 3.3:1) (Scheme 3, bottom). The minor diastereomer **14** isolated alongside (14%) had C6/C7-*syn* relative configuration, as confirmed by NMR analyses on an acetonide derivative (not shown).

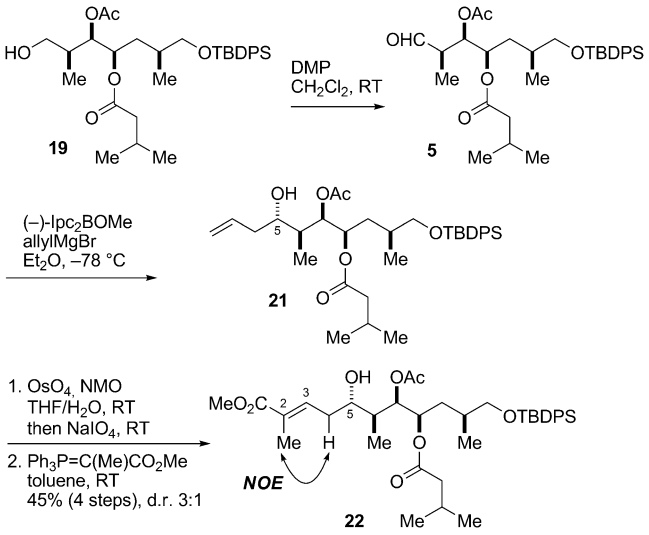
These unsatisfactory results led us to examine Evans *syn*-aldol reaction[17] of **6** (Scheme 4). Thus, exposure of the aldehyde **6** to a boron enolate, generated in situ from the oxazolidinone **15** (di-*n*-butylboron trifluoromethanesulfonate (nBu$_2$BOTf), Et$_3$N, CH$_2$Cl$_2$, −78 to 0 °C), delivered the alcohol **16** in 99% yield with greater than 20:1 diastereoselectivity. The chiral auxiliary of **16** was removed by the reduction with NaBH$_4$ in THF/H$_2$O[25] to give the 1,3-diol **17**.[23]



Scheme 4. Synthesis of alcohols **19** and **20**. OTf = trifluoromethanesulfonate, TES = triethylsilane, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DMAP = 4-dimethylaminopyridine.

We elaborated the 1,3-diol **17** to the alcohol **19** by standard chemistry (Scheme 4). Selective silylation of the primary alcohol of **17** (94%) and acylation of the remaining hydroxy group (97%) gave the acetate **18**. Removal of the MPM group (90%), acylation of the liberated hydroxy group with isovaleric anhydride, and acidic removal of the triethylsilyl (TES) group afforded the alcohol **19** (90%, two steps). We also prepared the alcohol **20** from the Evans *syn*-aldol product **16**. Silylation of **16** (quant.) and subsequent removal of the chiral auxiliary with LiBH$_4$ (87%) delivered the alcohol **20**. Here, TES group was chosen for the protection of the C7 hydroxy group because of its ready cleavability under mild acidic conditions that are compatible with *O*-acyl groups.

With suitably protected alcohols **19** and **20** available, we investigated the construction of the C1–C5 domain by means of a Brown allylboration,[13] as illustrated in Scheme 5. Oxidation of **19** with Dess–Martin periodinane (DMP)[26] gave the aldehyde **5**, which was allylated with (−)-*B*-allyldiisopinocampheylborane to afford the homoallylic alcohol **21** with an approximately 3:1 diastereoselectivity at the C5 position. Oxidative cleavage of the double bond of **21**, followed by Wittig olefination using Ph$_3$P=C(Me)CO$_2$Me, provided the α,β-unsaturated ester **22** (45% combined yield for the four steps, d.r. 3:1). The major diastereomer could be isolated in a pure form by preparative thin-layer chromatography (27% isolated yield).[23] The geometry of the C2–C3 double bond was confirmed to be *E* by an NOE experiment as shown. The low level of diastereoselectivity observed for the Brown allylboration can be reasoned by the Felkin–Anh model;[27] the aldehyde **5** intrinsically prefers the *syn*-adduct (Figure 2).



Scheme 5. Brown allylboration of aldehyde **5**. DMP = Dess–Martin periodinane, NMO = *N*-methylmorpholine *N*-oxide.

Next, we investigated the VMAR[14] of the aldehyde **23**, derived from the alcohol **20**, with the dienol silyl ether **24**[28] for

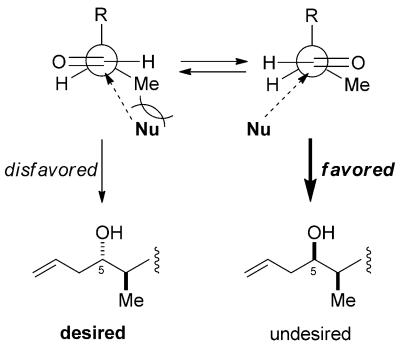
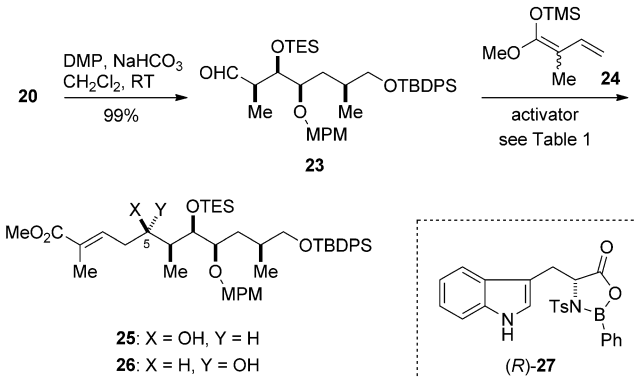


Figure 2. Felkin–Anh model for **5** and **23**.

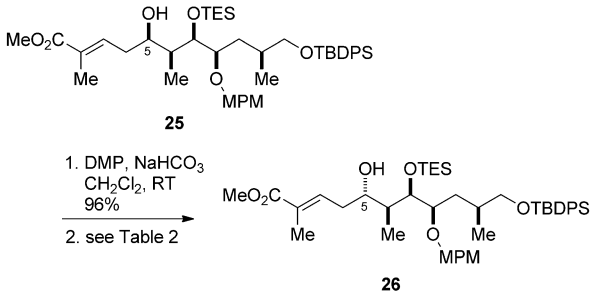


Scheme 6. VMAR of aldehyde **23** with dienol silyl ether **24**.

Table 1. VMAR of aldehyde **23** and dienol silyl ether **24.**

	Reagents and conditions	Yield[a] [%]	**25**:**26**[b]
1	**24**, $BF_3{\cdot}OEt_2$, CH_2Cl_2/Et_2O (10:1), −78 °C, 50 min	94[c]	>20:1
2	**24**, (*S*)-TolBINAP, $Cu(OTf)_2$, TBAT, THF, RT, 22 h	32 (62)	1:2.8
3	**24**, (*R*)-**27**, *i*PrOH, *n*BuCN, −78 to −40 °C, 23 h	10 (59)	>20:1

[a] Recovery of **23** is reported in parentheses. [b] Diastereomer ratio was estimated by 600 MHz ^{1}H NMR spectroscopic analysis. [c] Overall yield from **20**. TolBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, TBAT = tetra-*n*-butylammonium difluorotriphenylsilicate.



Scheme 7. Inversion of the C5 stereogenic center of alcohol **25**.

Table 2. Inversion of the C5 stereogenic center of alcohol **25**.

	Reagents and conditions	Yield [%]	**26**:**25**[a]
1	$NaBH_4$, MeOH, −40 to −20 °C	81	1.2:1
2	$NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/THF (1:1), −78 °C	69	1.9:1
3	$NaBH_4$, $CeCl_3{\cdot}7H_2O$, *i*PrOH/THF (1:1), −78 to 0 °C	79	1.2:1
4	$LiAlH(OtBu)_3$, THF, −78 °C to RT	18	5.6:1
5	L-Selectride®, THF, −78 °C to RT	0	N.A.[b]
6	(*R*)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}$THF, THF, −40 °C	97	>20:1

[a] Diastereomer ratio was estimated by 600 MHz ^{1}H NMR spectroscopic analysis. [b] N.A. = not applicable. CBS = Corey–Bakshi–Shibata.

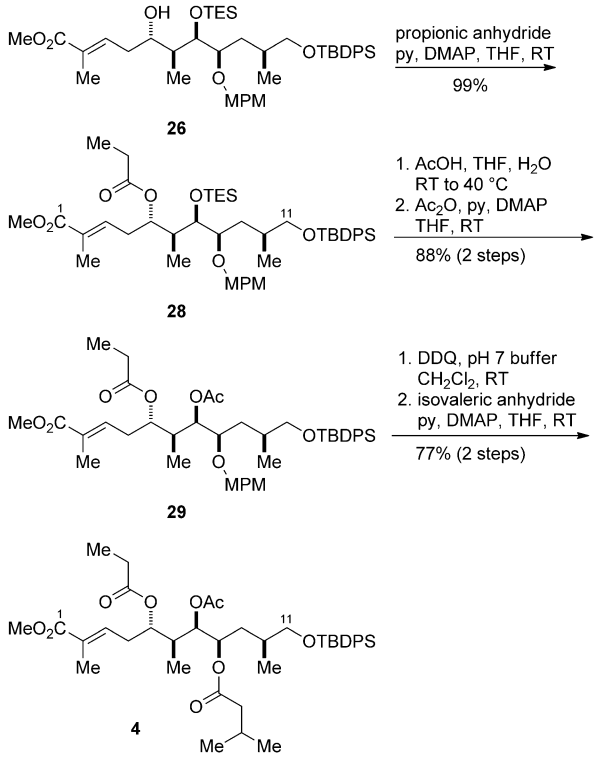
the assembly of the C1–C5 domain, as summarized in Scheme 6 and Table 1. In line with the Felkin–Anh model illustrated in Figure 2, the strong *syn*-selectivity[27] was prominent in the VMAR of **23** with **24** under the standard conditions ($BF_3{\cdot}OEt_2$, CH_2Cl_2/Et_2O (10:1), −78 °C), giving the alcohol **25** in 94% yield with greater than 20:1 diastereoselectivity (Table 1, entry 1).[23,29] We also performed the VMAR under the influence of a chiral Lewis acid. VMAR of **23** with **24** catalyzed by in situ prepared chiral copper species [CuF·(*S*)-tolBINAP][30] (TolBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) provided **26** in 32% yield with only moderate diastereoselectivity (Table 1, entry 2). The reaction had to be performed at room temperature; it did not proceed at all under low temperature conditions. Meanwhile, oxazaborolidinone-catalyzed VMAR of **23** with **24** ((*R*)-**27**, *i*PrOH, *n*BuCN, −78 °C)[31] proved to be unproductive and delivered the undesired alcohol **25** as the major stereoisomer in only 10% yield (Table 1, entry 3).

Given the high Felkin selectivity observed for the aldehydes **5** and **23**, we were interested in whether the conversion of the undesired C5 epimeric alcohol **25** to the desired alcohol **26** by an oxidation/reduction sequence might be possible (Scheme 7 and Table 2). Oxidation of **25** with DMP[26] provided the corresponding ketone in 96% yield (Scheme 7). Subsequent reduction with $NaBH_4$ in the absence or presence of $CeCl_3{\cdot}7H_2O$[32] proceeded with low diastereoselectivity to give a mixture of **25** and **26** (Table 2, entries 1–3). The use of a bulky reductant $LiAlH(OtBu)_3$ was beneficial for improving the diastereoselectivity, although the product yield was unacceptably low (Table 2, entry 4). Meanwhile, L-Selectride® caused the 1,4-reduction of the α,β-unsaturated ester moiety and reduction of the ester functionality, and it did not give **25** nor **26** at all (Table 2, entry 5). Eventually, we resorted to Corey–Bakshi–Shibata (CBS) reduction[33] using (*R*)-2-methyl-CBS-oxazaborolidine and $BH_3{\cdot}$THF, which afforded **26** in an almost quantitative yield as a single stereoisomer (d.r. > 20:1; Table 2, entry 6).

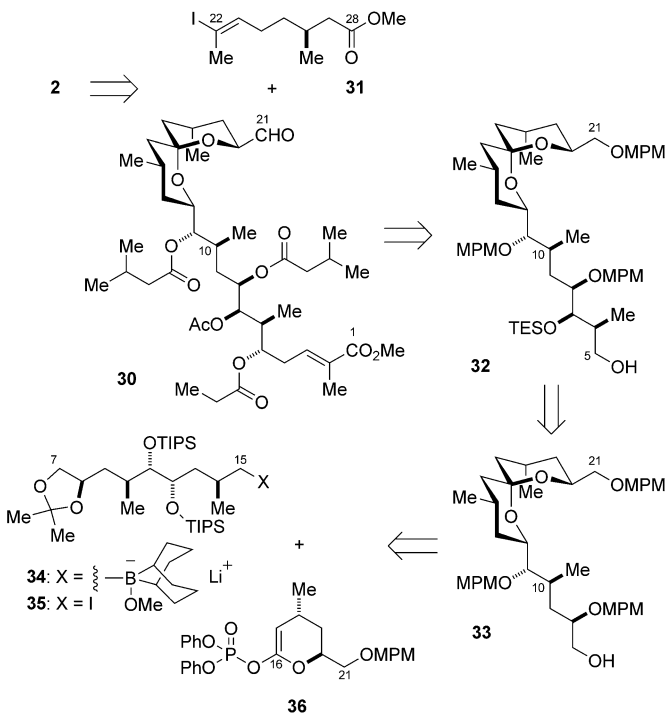
The completion of the synthesis of the C1–C11 model compound **4** is depicted in Scheme 8. Acylation of **26** with propionic anhydride gave the propionate **28** (99%). Cleavage of the TES ether under mild acidic conditions proceeded without incident and subsequent acetylation of the resultant alcohol provided the acetate **29** in 88% yield (two steps). Removal of the MPM group followed by acylation of the derived alcohol with isovaleric anhydride furnished the C1–C11 model compound **4** in 77% yield (two steps). Importantly, we did not observe any migration or cleavage of the *O*-acyl groups during this four-step sequence from **28** to **4**.

Total synthesis of the proposed structure 2 of didemnaketal B

Having completed the studies on the synthesis of the C1–C11 model compound **4**, we then focused our attention to the total synthesis of the proposed structure **2** of didemnaketal B. Our synthesis plan toward **2** is illustrated in Scheme 9. We envisioned that the C21–C28 side chain could be introduced at the final stage of the total synthesis by means of a Nozaki–Hiyama–Kishi (NHK) reaction[34] of the aldehyde **30** and the vinyl iodide **31**,[10] given the high functional group tolerance of the process. The construction of the C1–C7 domain of the aldehyde **30** could be achieved via the intermediary of the alco-

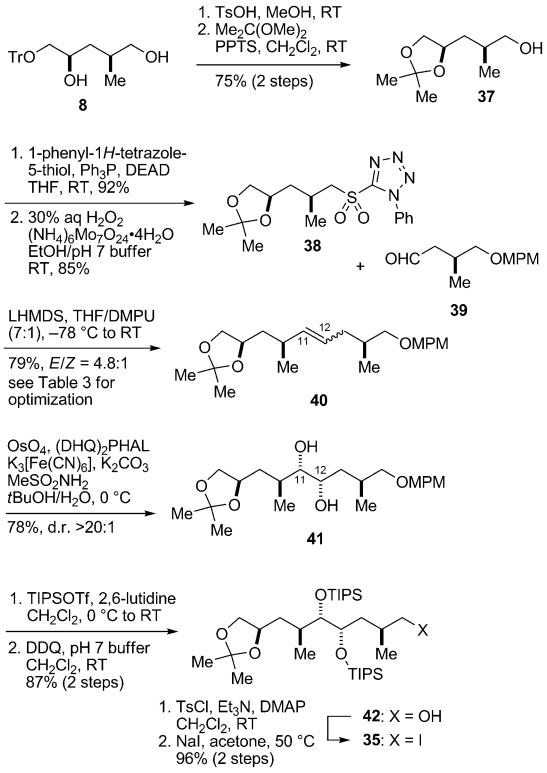


Scheme 8. Synthesis of the C1–C11 model compound **4**.



Scheme 9. Synthesis plan toward **2**. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

hols **32** and **33** by considering the results of the synthesis of **4**. On the basis of our preliminary work on the synthesis of a C9–C28 model compound,[10] we planned to synthesize the alcohol



Scheme 10. Synthesis of iodide **35**. Ts = *p*-toluenesulfonyl, DEAD = diethyl azodicarboxylate, LHMDS = lithium hexamethyldisilazide, DMPU = *N*,*N*-dimethylpropyleneurea, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether.

33 from the alkylborate **34** prepared from the iodide **35** and the lactone-derived enol phosphate **36**[10] by means of a Suzuki–Miyaura coupling.[35,36]

The synthesis of the iodide **35** commenced with the diol **8**[19] (Scheme 10). The diol **8** was exposed to acidic methanol to remove the Tr group and the 1,2-diol moiety of the resultant triol was protected as its acetonide to give the alcohol **37** (75%, two steps). Mitsunobu reaction[37] of **37** with 1-phenyl-1*H*-tetrazole-5-thiol (92%) followed by oxidation[38] of the derived sulfide under buffered conditions[39] delivered the sulfone **38** (85%).

Julia–Kocienski olefination[40] of the sulfone **38** with the aldehyde **39**[10] required optimization studies, as summarized in Table 3. At first, a series of bases were screened (Table 3, entries 1–4). The reaction was performed in THF at −78 °C to room temperature (warmed gradually over several hours). Although the reaction employing potassium hexamethyldisilazide (KHMDS) resulted in the best *E*/*Z* selectivity, the yield of **40** was unsatisfactory (Table 3, entry 1). The use of other bases was detrimental to the stereoselectivity at the expense of improving the product yield (Table 3, entries 2–4). These results led us to use lithium hexamethyldisilazide (LHMDS) as the base and examine a series of solvents (Table 3, entries 5–9). It has been reported that the polarity of solvent has a profound effect on the stereoselectivity of Julia–Kocienski olefination.[41] Indeed, DMF, THF/DMPU (7:1), and DMF/DMPU (7:1) (DMPU = *N*,*N*-dimethylpropyleneurea) were found to be beneficial for improving the stereoselectivity (Table 3, entries 6–8). Finally,

Table 3. Optimization of Julia–Kocienski olefination of sulfone **38** with aldehyde **39**.[a]

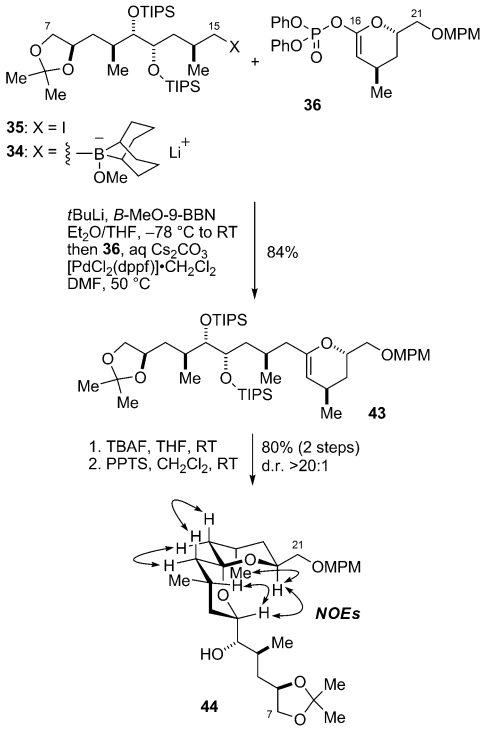
	Base	Solvent	Yield [%]	E/Z[b]
1	KHMDS	THF	42	10:1
2	NaHMDS	THF	78	1.5:1
3	LHMDS	THF	70	2.7:1
4	LDA	THF	61	2.6:1
5	LHMDS	DME	86	2.6:1
6	LHMDS	DMF	47	5.9:1
7	LHMDS	THF/DMPU (7:1)	65	5.4:1
8	LHMDS	DMF/DMPU (7:1)	42	5.3:1
9[c]	LHMDS	THF/DMPU (7:1)	79	4.8:1

[a] Unless otherwise noted, the reaction was performed using 1 equivalent of sulfone **38**, 1.2–1.5 equivalents of aldehyde **39**, 1.1–1.4 equivalents of base in the indicated solvent at −78 °C to RT (warmed gradually over several hours). [b] E/Z ratio was estimated by 600 MHz ^{1}H NMR spectroscopic analysis. [c] The reaction was carried out at −78 °C for 20 min and then quickly warmed to RT. KHMDS = potassium hexamethyldisilazide, NaHMDS = sodium hexamethyldisilazide, LHMDS = lithium hexamethyldisilazide, LDA = lithium diisopropylamide, DME = 1,2-dimethoxyethane, DMPU = *N*,*N*-dimethylpropyleneurea.

the best result was obtained when the reaction was carried out using LHMDS in THF/DMPU (7:1) at −78 °C for 20 min and then at room temperature (Table 3, entry 9). Under these conditions, the olefin **40** was isolated in 79% yield with an acceptable E/Z selectivity. The major isomer had the desired *E*-configured double bond as confirmed by a large $^3J_{H,H}$ value ($^3J_{H11,H12}$ = 15.1 Hz). At this stage, the minor *Z*-isomer could not be separated by flash column chromatography using silica gel.

To introduce the C11 and C12 stereogenic centers with correct configuration, Sharpless asymmetric dihydroxylation[42] of **40** was performed using hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) as a chiral ligand (Scheme 10). Gratifyingly, we found that the minor *Z*-isomer of **40** was significantly less reactive than the major *E*-isomer under these conditions. Thus, we were able to isolate the diol **41** in 78% yield as a single stereoisomer (d.r. > 20:1). The absolute configuration of the C11 and C12 stereogenic centers was tentatively assigned as shown on the basis of the Sharpless mnemonic[42] and later determined by a NOESY experiment on the spiroacetal **44** (Scheme 11). Silylation of the diol **41** was followed by removal of the MPM group to give the alcohol **42** (87%, two steps), which was converted to the iodide **35** via a tosylate (96%, two steps).

With the requisite iodide **35** available, the synthesis of the spiroacetal **44** was next undertaken (Scheme 11). Treatment of the iodide **35** with *t*BuLi in the presence of *B*-methoxy-9-borabicyclo[3.3.1]nonane (*B*-MeO-9-BBN) (THF/Et_2O, −78 °C to room temperature)[43] generated the alkylborate **34**, which was reacted in situ with the lactone-derived enol phosphate **36**[10] under the influence of $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and aqueous Cs_2CO_3 in DMF at 50 °C to afford the endocyclic enol ether **43** in 84% yield. The silyl ethers within **43** were cleaved with tetra-*n*-butylammonium fluoride (TBAF) and the resultant dihydroxy enol ether was exposed to PPTS in CH_2Cl_2 at room temperature under thermodynamic conditions to deliver the spiroacetal **44** in 80% yield

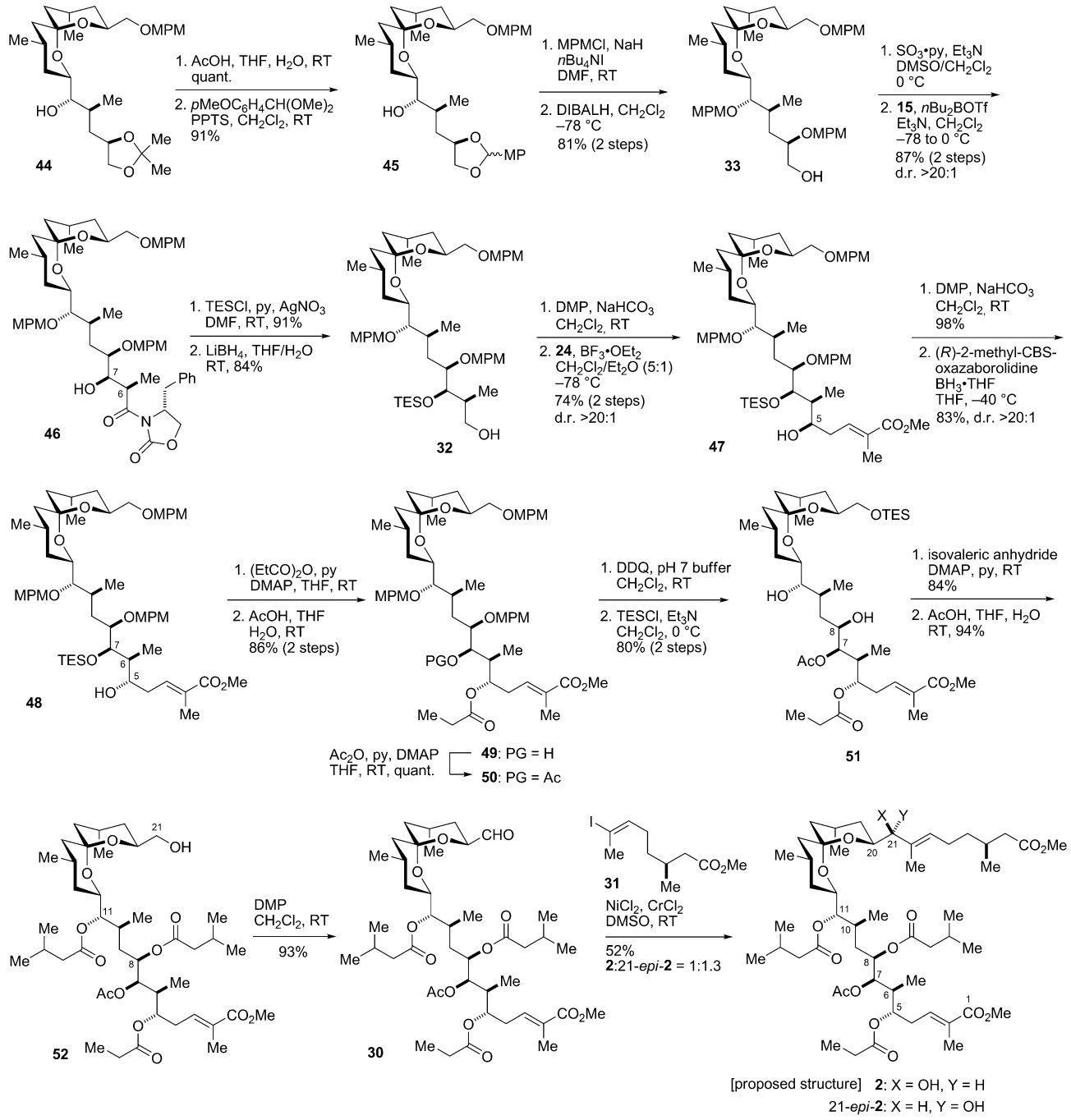


Scheme 11. Synthesis of spiroacetal **44**. *B*-MeO-9-BBN = *B*-methoxy-9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, TBAF = tetra-*n*-butylammonium fluoride.

(two steps) as a sole isolable product (d.r. > 20:1).[36] The absolute configuration of **44** was established by a NOESY experiment.[23]

Having completed the C7–C21 spiroacetal domain, we made efforts toward the assembly of the C1–C7 domain and completion of the total synthesis of **2**, as summarized in Scheme 12. With the success of our synthesis of the C1–C11 model compound **4** in mind, we thought to protect the C8 and C11 hydroxy groups as their MPM ethers and the C7 hydroxy group as its TES ether. In this way, the C5, C7, C8, and C11 hydroxy groups could be effectively differentiated. Accordingly, the acetonide group of the spiroacetal **44** was replaced with a *p*-methoxybenzylidene acetal to provide the alcohol **45**. Protection of **45** as its MPM ether followed by regioselective reductive cleavage of the *p*-methoxybenzylidene acetal (DIBALH, CH_2Cl_2, −78 °C)[21] afforded the alcohol **33**. Because of the sensitivity of the *p*-methoxybenzylidene acetal moiety, the DIBALH reduction process had to be carried out at low temperature (−78 °C). After oxidation of **33** under the Parikh–Doering conditions,[22] Evans *syn*-aldol reaction[17] of the derived aldehyde with the boron enolate generated from the oxazolidinone **15** furnished the alcohol **46** in 87% yield for the two steps (d.r. > 20:1).[23] Silylation of the alcohol **46** (TESCl, pyridine, $AgNO_3$, 91%)[44] followed by reduction with $LiBH_4$ in aqueous THF (84%) gave the appropriately protected alcohol **32**.

To complete the construction of the C1–C7 backbone, the alcohol **32** was oxidized with DMP[26] and the resultant aldehyde was reacted with the dienol silyl ether **24**[28] ($BF_3\cdot OEt_2$, CH_2Cl_2/Et_2O (5:1), −78 °C) to provide the alcohol **47** in 74% yield (two



Scheme 12. Completion of the total synthesis of the proposed structure **2** of didemnaketal B.

steps) with greater than 20:1 diastereoselectivity. The VMAR was confirmed to be highly *syn*-selective, as evidenced by NMR spectroscopic analyses on an acetonide derivative.[23] Oxidation of **47** with DMP (98%)[26] followed by the reduction with (*R*)-2-methyl-CBS-oxazaborolidine/BH_3·THF[33] furnished the alcohol **48** (83%, d.r. > 20:1). The absolute configuration of the C5, C6, and C7 stereogenic centers of **48** was unambiguously established by the application of the modified Mosher analysis as well as NMR spectroscopic analyses on an acetonide derivative.[6,23]

Acylation of the alcohol **48** using propionic anhydride followed by cleavage of the C7 TES ether under mild acidic conditions gave the alcohol **49** in 86% yield (two steps). Acetylation of **49** provided the acetate **50** quantitatively. All the MPM groups within **50** were removed by using DDQ under buffered conditions, and the resultant primary hydroxy group was selectively silylated to afford the diol **51** in 80% yield (two steps). A partial migration of the C7 acetyl group to the C8 hydroxy group occurred during the cleavage of the MPM ethers, and the diol **51** was contaminated with the minor constitutional

isomer (ca. 10%, as judged by 600 MHz ^{1}H NMR spectroscopic analysis). After acylation of the C8 and C11 hydroxy groups with isovaleric anhydride (84%), the C21 TES ether was then cleaved by aqueous acetic acid to give the alcohol **52** in 94% yield. At this stage, the minor isomer was removed by flash column chromatography using silica gel. Oxidation of **52** with DMP[26] delivered the aldehyde **30** in 93% yield. Finally, NHK reaction[34] of **30** with the vinyl iodide **31**[10] ($NiCl_2$, $CrCl_2$, DMSO, room temperature) afforded a 1:1.3 mixture of **2** and its C21-epimer, 21-*epi*-**2** in 52% combined yield. These stereoisomers could be separated by preparative reverse-phase HPLC. The absolute configuration of the newly generated C21 stereogenic center of **2** and 21-*epi*-**2** was individually established by the application of the modified Mosher analysis.[6,23]

Detailed NMR spectroscopic analyses and stereochemical studies on didemnaketal B

Surprisingly, we found that neither synthetic **2** nor 21-*epi*-**2** was spectroscopically identical with authentic didemnaketal B, although the COSY, HMQC, and HMBC correlations observed in our synthetic **2** and 21-*epi*-**2** supported the identity of the gross structure with that of didemnaketal B. We carefully assigned the ^{1}H NMR signals of the synthesized **2** and 21-*epi*-**2**, and compared with those of didemnaketal B.[1,45] Selected data are summarized in Table 4. Significant ^{1}H NMR chemical shift deviations ($|\Delta\delta| \geq 0.1$ ppm) were found between the H8 and H9a protons of didemnaketal B and those of **2**/21-*epi*-**2**. Furthermore, the ^{13}C NMR signals of the C8 and C10 positions of didemnaketal B differed largely from those of **2**/21-*epi*-**2** ($|\Delta\delta| \geq 1.0$ ppm). These observations indicated the possible stereochemical misassignment around the C8 and C10 stereogenic centers. Additional discrepancies were observed in the ^{1}H and ^{13}C NMR spectroscopic data of **2** and didemnaketal B around the C20 and C21 positions. The ^{1}H NMR chemical shift values for the H19b, H20, and H21 protons of didemnaketal B evidently differed from those of **2**. The ^{13}C NMR resonances for the C19 and C21 positions of didemnaketal B also deviated from those of **2**. In contrast, the ^{1}H and ^{13}C NMR chemical shift values for the C19–C21 domain of didemnaketal B were in close agreement with those of 21-*epi*-**2**. Thus, it is likely that the relative configuration of the C20 and C21 stereogenic centers was incorrectly assigned in the proposed structure **2**.

While Faulkner and co-workers have firmly determined the relative configuration of the C1–C8 and C10–C20 domains by degradation/derivatization experiments and X-ray crystallography, they have not confirmed the relative configuration of the C8/C10, C20/C21, and C21/C26 stereogenic centers by any reliable means (as indicated by thick waves in Figure 3).[5] Our result is indicative of possible misassignments of the relative configuration of the C8/C10 and C20/C21 stereogenic centers.

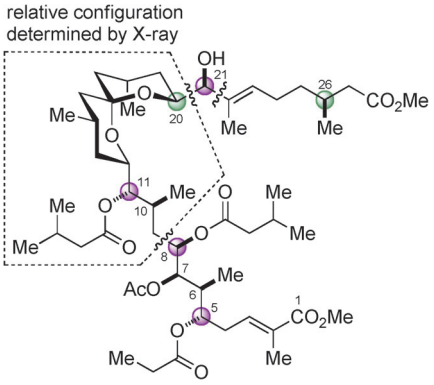


Figure 3. Summary of stereochemical assignment of didemnaketal B by Faulkner et al.[5] The relative stereochemical relationship of the C5/C6, C6/C7, and C7/C8 stereogenic centers was established by degradation/derivatization experiments. The relative configuration of the C10–C20 domain was determined by an X-ray crystallographic analysis of a degradation product. The absolute configuration of the C5, C8, C11, and C21 stereogenic centers (colored in purple) was assigned on the basis of the modified Mosher analysis, whereas that of the C20 and C26 stereogenic centers (colored in green) was established on the basis of the PGME analysis. The relative configuration of the C8/C10, C20/C21, and C21/C26 stereogenic centers was not confirmed, as indicated by thick waves.

Table 4. Deviation of the ^{1}H and ^{13}C NMR chemical shifts between didemnaketal B (DKB) and synthetic **2**/21-*epi*-**2** in $CDCl_3$.[a]

Position	^{1}H NMR		^{13}C NMR	
	$\Delta[\delta(\text{DKB})-\delta(\mathbf{2})]$	$\Delta[\delta(\text{DKB})-\delta(21\text{-}epi\text{-}\mathbf{2})]$	$\Delta[\delta(\text{DKB})-\delta(\mathbf{2})]$	$\Delta[\delta(\text{DKB})-\delta(21\text{-}epi\text{-}\mathbf{2})]$
7	0.05	0.04	0.7	0.9
8	0.13	0.13	−1.7	−1.7
9a	−0.11	−0.11	0.1	−0.1
9b	−0.05	0.01		
10	−0.06	−0.06	−1.1	−1.0
11	0.03	0.05	−0.2	−0.1
18	−0.01	0.02	0.1	0.1
19a	0.02	0.07	−2.8	0.4
19b	0.20	−0.02		
20	0.15	0.01	−0.1	0.0
21	0.29	0.01	−3.5	0.3
22	N/A[b]	N/A[b]	−0.2	0.3

[a] Chemical shifts were reported in ppm. ^{1}H and ^{13}C NMR spectra of synthetic **2** and 21-*epi*-**2** were measured at 600 and 150 MHz, respectively. According to reference [1], ^{1}H and ^{13}C NMR spectra of DKB were measured at 500 and 90 MHz, respectively. [b] N/A = not applicable.

We questioned the absolute configuration of the C10–C20 domain of the proposed structure **2**. Faulkner and co-workers have assigned the configuration of the C20 stereogenic center on the basis of the PGME analysis using (*R*)-**53**/(*S*)-**53**, derived from authentic didemnaketal B (Figure 4A). Importantly, Faulkner et al. have suggested that the PGME amides (*R*)-**53**/(*S*)-**53** forms an intramolecular hydrogen bond between the N–H hydrogen atom and the oxygen atom of the C16–C20 tetrahydropyran. The conformation proposed by Faulkner et al. is in ac-

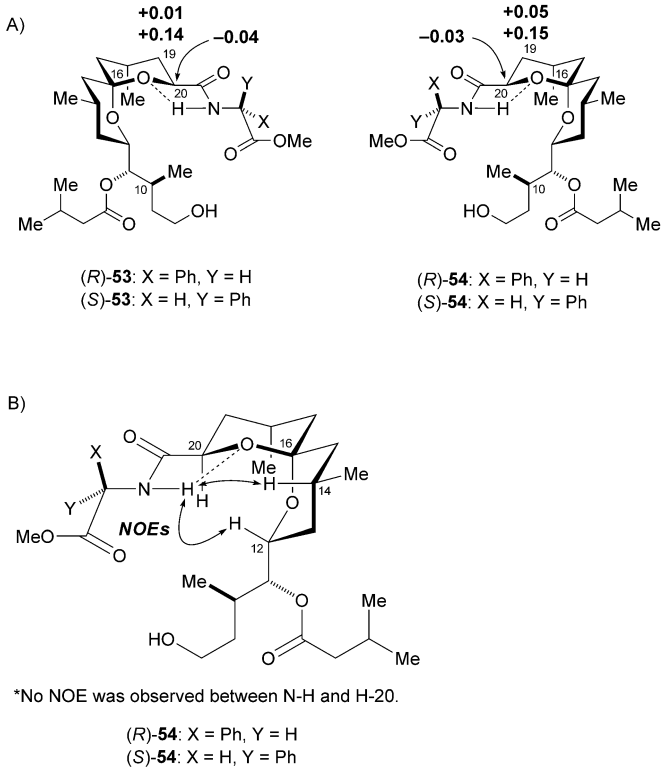


Figure 4. A) Structures and observed $\Delta\delta$ values of PGME amides (*R*)-**53**/(*S*)-**53** and (*R*)-**54**/(*S*)-**54**. For PGME amides (*R*)-**53**/(*S*)-**53**, $\Delta\delta$ values are taken from reference [5] and their stereostructures are depicted according to the proposed structure **2** of didemnaketal B. B) NOE enhancements observed for (*R*)-**54**/(*S*)-**54**.

cordance with the Kusumi model for α-oxy-α-monosubstituted acetic acid derivatives.[7b]

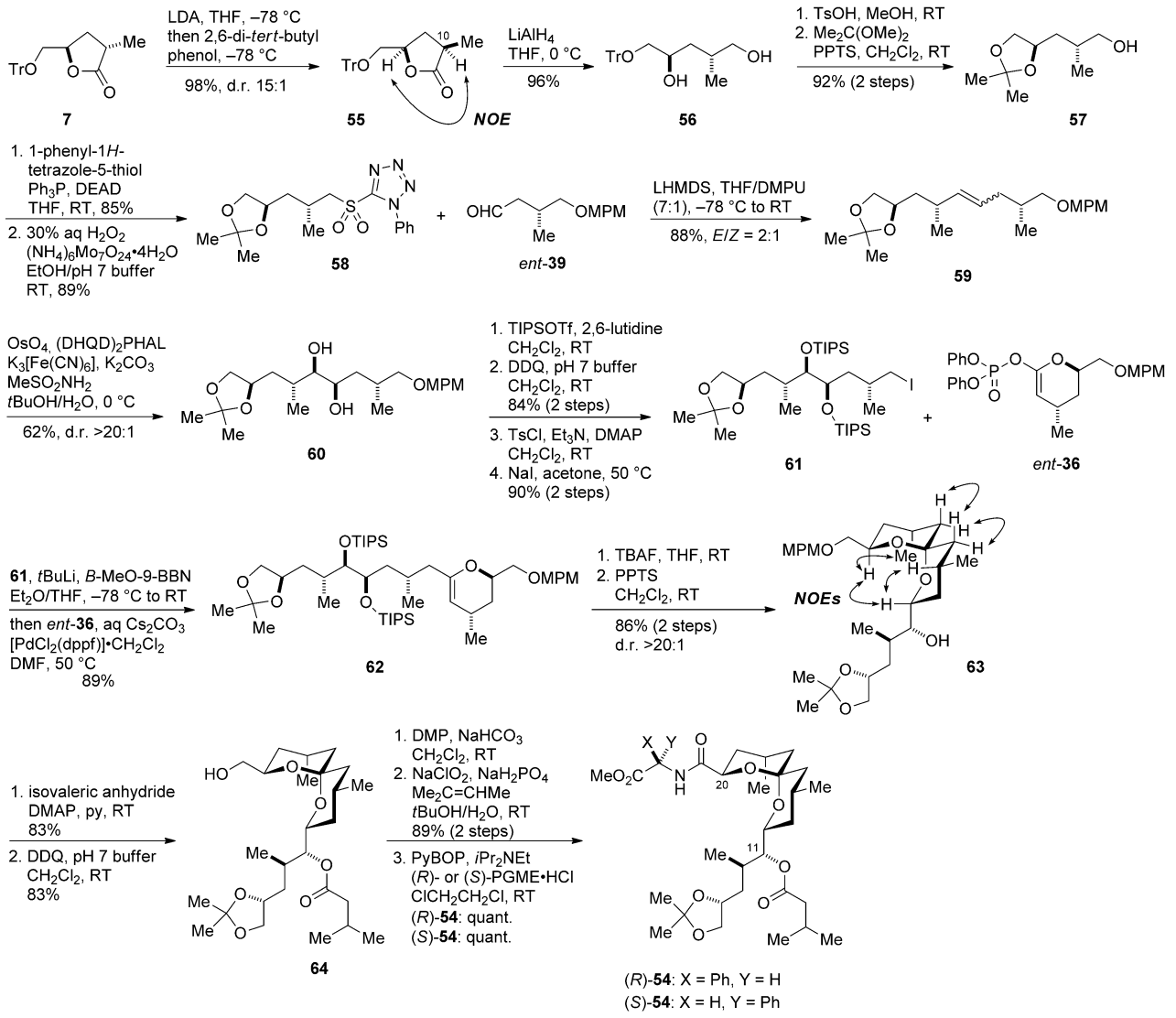
Faulkner et al. have reported that the PGME amides (*R*)-**53**/(*S*)-**53** showed a negative $\Delta\delta$ value for the H20 methine proton and positive $\Delta\delta$ values for the H19 methylene protons, and assigned the absolute configuration of the C20 stereogenic center as *S* (Figure 4A). However, the signs of the observed $\Delta\delta$ values are opposite to those expected from the principle of the PGME analysis.[7] The $\Delta\delta$ values for the H19 methylene protons should be negative, as the anisotropic effect of the phenyl group on the H19 methylene protons should be more prominent in (*S*)-**53** than in (*R*)-**53**. On the other hand, the $\Delta\delta$ value for the H20 methine proton should be positive, because it would be more shielded in (*R*)-**53** than in (*S*)-**53**. Therefore, the absolute configuration of the C20 stereogenic center should have been assigned as *R*, not *S*.

To reinforce our argument, we actually prepared the PGME amides (*R*)-**54**/(*S*)-**54** with the 20*R* configuration, as shown in Scheme 13. The synthesis started with deprotonation/kinetic protonation[46] of the γ-lactone **7**[18] to epimerize the C10 stereogenic center, giving the γ-lactone **55** in 98% yield with excellent diastereoselectivity (d.r. 15:1). The major stereoisomer **55** could be isolated in a pure form by flash column chromatography using silica gel. The absolute configuration of the C10 stereogenic center of **55** was established by an NOE experiment as shown. The γ-lactone **55** was elaborated to the spiroacetal **63** in a similar manner as described for **44**. Thus, $LiAlH_4$ reduction of **55** delivered the diol **56**, which was transformed to the sulfone **58** via the alcohol **57**. Julia–Kocienski olefination[40] of **58** with the known aldehyde *ent*-**39**[47] (LHMDS, THF/DMPU, −78 °C to room temperature) provided the olefin **59** in 88% yield, albeit with moderate stereoselectivity (*E*/*Z* = 2:1). The use of other bases such as KHMDS, NaHMDS, or LDA did not improve the stereochemical outcome. Sharpless asymmetric dihydroxylation[42] of **59** using hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2PHAL$) under the standard reaction conditions afforded the diol **60** in 62% yield (d.r. > 20:1),[48] which was converted to the iodide **61** by a four-step sequence. Lithiation of **61** with *t*BuLi in the presence of *B*-MeO-9-BBN (Et_2O/THF, −78 °C to room temperature) generated the corresponding alkylborate,[43] which without isolation was coupled with the lactone-derived enol phosphate *ent*-**36**[49] (aqueous Cs_2CO_3, $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, 50 °C) to provide the endocyclic enol ether **62** in 89% yield.[35] After desilylation of **62** with TBAF, the derived dihydroxy enol ether was treated with PPTS (CH_2Cl_2, room temperature) to furnish the spiroacetal **63** (86%, two steps) as a single stereoisomer (d.r. > 20:1).[36] The absolute configuration of **63** was established by a NOESY experiment, as shown. Acylation of **63** with isovaleric anhydride followed by removal of the MPM group gave the alcohol **64**. A two-stage oxidation[26,50] of **64** to the corresponding carboxylic acid and subsequent amidation with (*R*)- or (*S*)-PGME·HCl using 1*H*-benzotriazol-1-yloxy tri(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)[51] afforded the PGME amides (*R*)-**54**/(*S*)-**54**.

As shown in Figure 4A, we confirmed that our synthetic PGME amides (*R*)-**54**/(*S*)-**54** showed a negative $\Delta\delta$ value for the H20 methine proton and positive $\Delta\delta$ values for the H19 methylene protons, as reported for the authentic PGME amides (*R*)-**53**/(*S*)-**53**. Thus, we concluded that the absolute configuration of the C10–C20 domain of the proposed structure **2** had been assigned incorrectly. Furthermore, we confirmed the conformation of our PGME amides (*R*)-**54**/(*S*)-**54** by NMR spectroscopic analyses (Figure 4B). NOEs were observed between the N–H and the H12 protons as well as between the N–H and the H14 protons, whereas no NOE was detected between the N–H and H20 protons. In addition, the N–H protons of (*R*)-**54** and (*S*)-**54** appeared somewhat downfield (δ = 7.64 and 7.59 ppm, respectively).[52] These data indicated that the intramolecular hydrogen bond was actually formed between the N–H hydrogen atom and the oxygen atom of the C16–C20 tetrahydropyran.

Total synthesis and structure revision of didemnaketal B

Taken altogether, we envisioned that the stereoisomer **65** most likely represents the correct stereostructure of didemnaketal B (Scheme 14). Accordingly, we embarked on the total synthesis of **65** to confirm whether this revised structure is indeed correct. The spiroacetal **63** was converted to the alcohol **66** by a four-step sequence. Parikh–Doering oxidation[22] of **66** followed by Evans *syn*-aldol reaction[17] with the boron enolate derived from the oxazolidinone **15** provided the alcohol **67** in

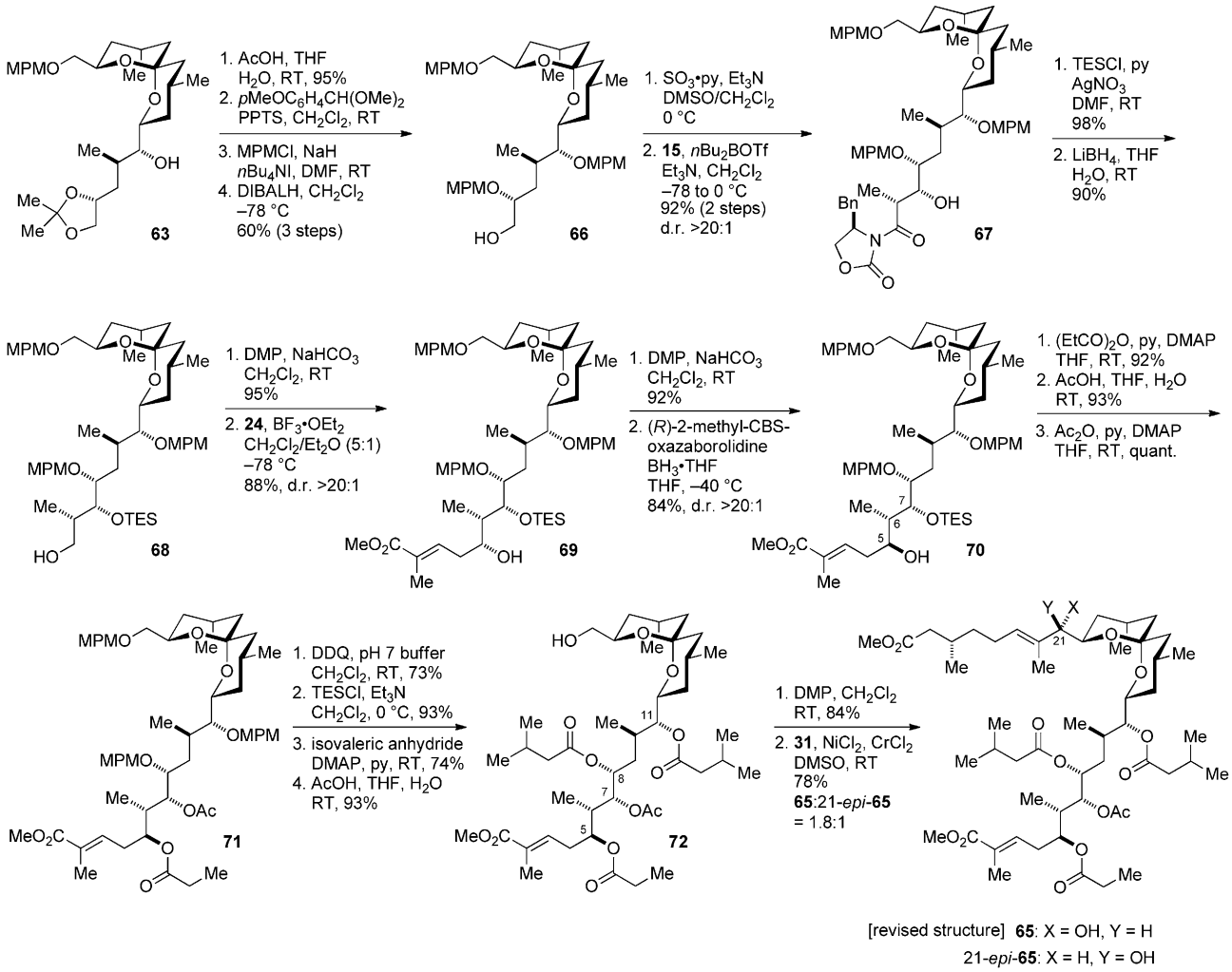


Scheme 13. Synthesis of PGME amides (*R*)-**54**/(*S*)-**54**. $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, PyBOP = 1*H*-benzotriazol-1-yloxy tri(pyrrolidino)phosphonium hexafluorophosphate.

92% yield (two steps, d.r. > 20:1). Silylation of **67** and reductive cleavage of the oxazolidinone auxiliary afforded the alcohol **68**.[53] After oxidation of **68** with DMP (95%),[26] the resultant aldehyde was subjected to the VMAR[14] with the dienol silyl ether **24** to deliver the alcohol **69** in 88% yield (d.r. > 20:1). The *syn*-selectivity of the VMAR was confirmed by NMR spectroscopic analyses on an acetonide derivative.[23] Dess–Martin oxidation[26] of **69** (92%) was followed by CBS reduction[33] to afford the alcohol **70** (84%, d.r. > 20:1) with correct configuration at the C5 position. The absolute configuration of the C5 stereogenic center was established by the modified Mosher method,[6,23] while the relative configuration of the C5/C6 and C6/C7 stereogenic centers was correlated by NMR spectroscopic analyses on an acetonide derivative.[23] The alcohol **70** was uneventfully elaborated to the alcohol **72** in seven steps by sequential acylation of the C5, C7, C8, and C11 hydroxy groups. Finally, oxidation of **72** with DMP[26] (84%) and NHK reaction[34] of the derived aldehyde with the vinyl iodide **31**[10] under the standard conditions furnished the revised structure **65** of didemnaketal B and its C21 epimer 21-*epi*-**65** in 78% combined yield (d.r. 1.8:1). The spectroscopically pure **65** and 21-*epi*-**65** were isolated after preparative reverse-phase HPLC separation. The absolute configuration of the C21 stereogenic center of **65** and 21-*epi*-**65** was established on the basis of the modified Mosher analysis.[6,23] Gratifyingly, the spectroscopic properties (^1H and ^{13}C NMR and HRMS) of **65** matched those of authentic didemnaketal B.[1] Although the specific rotation value of the authentic sample has not been reported, the PGME analysis on the authentic (*R*)-**53**/(*S*)-**53** and the synthetic (*R*)-**54**/(*S*)-**54** (Figure 4) allowed us to revise the stereostructure of didemnaketal B to be that shown as **65**.

Conclusion

In this full account, we described in detail our synthetic studies toward didemnaketal B, a potent HIV-1 protease inhibitor of



Scheme 14. Total synthesis of the revised structure **65** of didemnaketal B.

marine ascidian origin. The salient features of our total synthesis of didemnaketal B include: 1) stereocontrolled convergent synthesis of the C7–C21 spiroacetal domain by means of a Suzuki–Miyaura coupling, 2) assembly of the C1–C7 acyclic domain using an Evans *syn*-aldol and a vinylogous Mukaiyama aldol reactions, and 3) a late-stage introduction of the C21–C28 side chain by means of a Nozaki–Hiyama–Kishi reaction. Detailed comparison of the NMR chemical shifts of our synthetic **2**/21-*epi*-**2** with those of didemnaketal B suggested that the relative configuration of the C8/C10 and C20/C21 stereogenic centers have been erroneously assigned in the proposed structure **2**. Further inspection of Faulkner's stereochemical assignment coupled with the PGME analysis on the authentic and synthetic PGME amides (i.e., (*R*)-**53**/(*S*)-**53** and (*R*)-**54**/(*S*)-**54**, respectively) revealed that the absolute configuration of the C10–C20 domain might have been incorrectly assigned in the proposed structure **2**. On the basis of these structural analyses, we revised the structure of didemnaketal B as that represented by **65**, which was ultimately verified by total synthesis. We consider that the structures of didemnaketals A and C should also be revised accordingly. Now that the correct structure of didemnaketal B has been elucidated, further studies on the structure-activity relationships of this intriguing compound and the synthesis of truncated analogues will be undertaken in due course.[54]

Acknowledgements

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Keywords: natural products · spiroacetals · stereochemical assignment · structure elucidation · total synthesis

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