Ph D Thesis

Synthetic Approach toward Structure Confirmation of Amphidinol 3

(合成化学的アプローチによる アンフィジノール 3 の構造確認)

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Contents

Supporting Information

NMR Data

Acknowledgment

Abbreviations

Ac	acetyl
AM	amphidinol
Am	amyl
AmB	amphotericin B
BHT	2,6-di-*t*-butylhydroxytoluene
BOM	benzyloxy methyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CDI	carboxy diimidazole
COSY	correlation spectroscopy
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBALH	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethyformamide
DMP	Dess-Martin periodinane
DQF	double-quantum filtered
EC	effective dose
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
eq	equivalent(s)
ESI	electrospray ionization

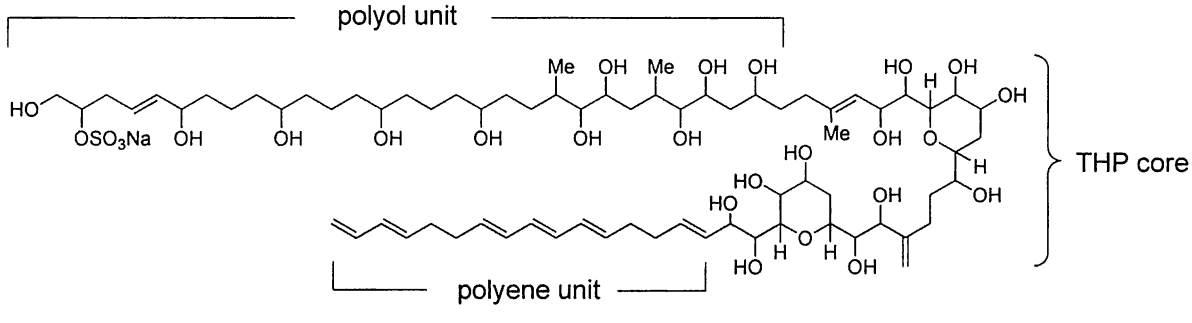
Et	ethyl
GC	gas chromatography
HETLOC	heteronuclear long range coupling
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear quantum cohearence
HPLC	high performance liquid chromatography
IC	inhibitory concentration
Ipc	isopinocampheyl
IR	infrared
JBCA	*J* based conformation analysis
KHMDS	potassium hexamethyldisilazane
LC	lethal concentration
LD	lethal dose
LDA	lithium diisopropylamide
MCPBA	*m*-chloro peroxybenzoic acid
Mes	mesityl
MOM	methoxymethyl
MS	mass spectrum
MS4A	molecular sieves 4A
MTPA	trifluoromethoxyphenyl acetyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect correlated spectroscopy
PEG	polyethylene glycol
Ph	phenyl
PMB	*p*-methoxy benzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pv	pivaloyl
Py	pyridine
quant	quantitative
rt	room temperature

SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
SDS	sodium dodecylsulphate
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butylhydroperoxide
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOCSY	totally correlated spectroscopy
Tol	tolyl
Tr	trityl
Ts	*p*-toluenesulfonyl
UV	ultoraviolet

Chapter 1. General introduction

1-1. Structures and biological activities of amphidinols

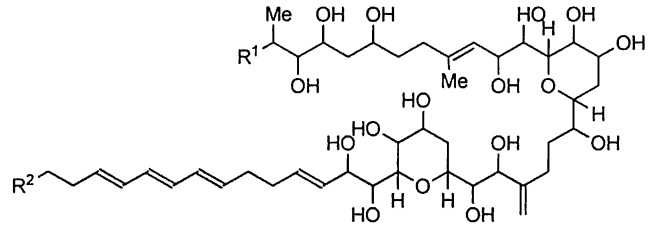
Marine diniflagellates are attracting much attention as a resource of bioactive compounds. A family of amphidinols (AMs) has been isolated as a potent antifungal agent from the dinoflagellate *Amphidinium klebsii*. AM1 was first reported by Satake *et al.* in 1991 (Figure 1-1-1).[1] AM1 is the first representative of a new class of polyketide metabolites and exhibits potent antifungal and hemolytic activities. Large segments of the structure (C1-C6 and C18-C55) were elucidated by detailed analyses of homo 2D experiments, e.g. conventional COSY, double quantum filtered (DQF) COSY and TOCSY. The stereochemistry of AM1 remains unknown because its 27 chiral centers are remote and most of them reside on acyclic parts. Since the report of AM1, other amphidinol analogues, having deferent structure on polyhydroxy and polyene chains, has been reported[2-8] (Table 1-1-1). Distinct structured features represented by amphidinols are long hydrophilic polyol chain, substituted tetrahydropyran (THP) ring system, and a hydrophobic polyene unit. The middle portion containing the two THP rings is highly conserved among the congeners and structured diversity arises from the polyol and polyene moieties.



Amphidinol 1 (AM1)

Figure 1-1-1. Planer structure of amphidinol 1

Table 1-1-1. Structures of amphidinols



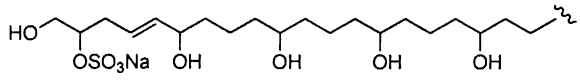
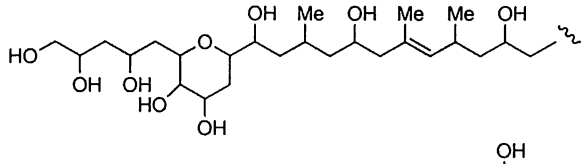
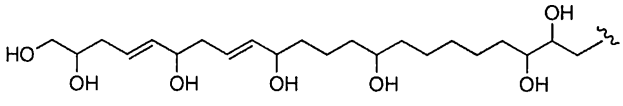
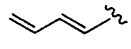
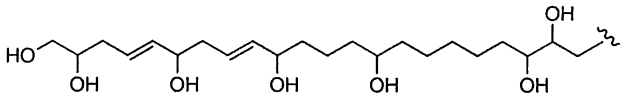
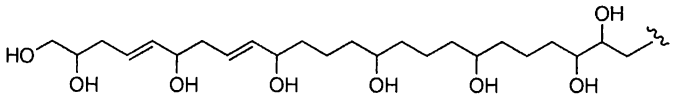
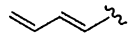
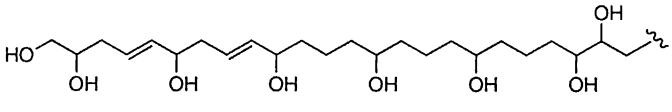
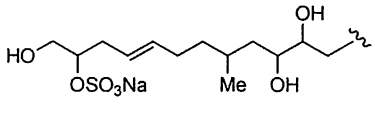
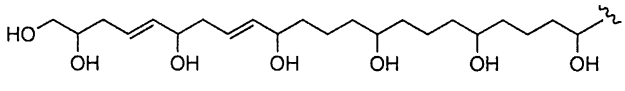
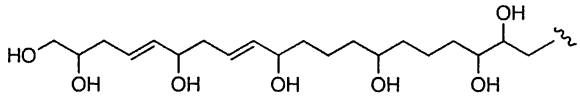
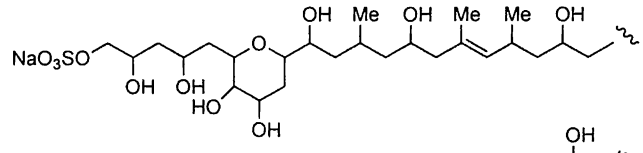
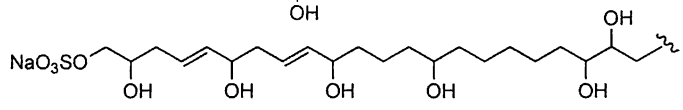
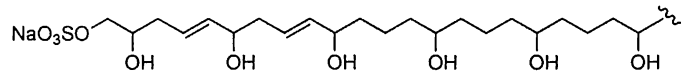
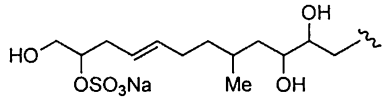
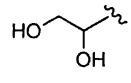
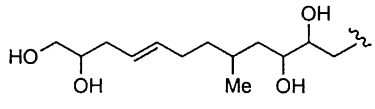
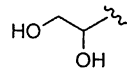
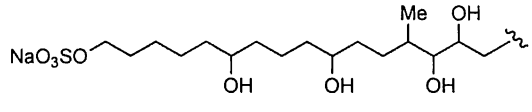
	R^1	R^2
AM1		
AM2		
AM3		
AM4		
AM5		
AM6		
AM7		
AM9		
AM10		

Table 1-1-1. Structures of amphidinols (continued)

	R^1	R^2
AM11		
AM12		
AM13		
AM14		
AM15		
AM17		

Antifungal and hemolytic activities of amphidinols are summarized in Table 1-1-2.[4-8] AM1~AM6 elicit potent antifungal activity against *Aspergillus niger* (~6.0 μg/disk), while those of other amphidinols (AM7~AM15) are lower (>10 μg/disk). On the other hand, the hemolytic activity of AM3 was the most potent among amphidinol congeners against human erythrocytes (EC_{50} = 9.4 nM), while the EC_{50} values of other amphidinols were >50 nM. It is interesting to note that structural difference of the terminal olefin (R^2) dramatically affects the hemolytic activity, i. e. substitution of the butadienyl moiety (AM3) to vinyl group (AM4) resulted in the reduction of the activity twenty times. It is also intriguing that substitution of the 1,7-heptanediol part to 1,5,9-nonanetriol part (R^1) induced reduction of the hemolytic activity around twenty times, from 9.4 nM for AM3 to 230 nM for AM5, and three times from 185 nM for AM4 to 580 nM for AM6, respectively. Among the amphidinol congeners, AM14 and AM15 elicited no hemolytic activity, which might be related to the unique structure possessing hydrophilic 1,2-diol system (R^2) on the polyene moiety.

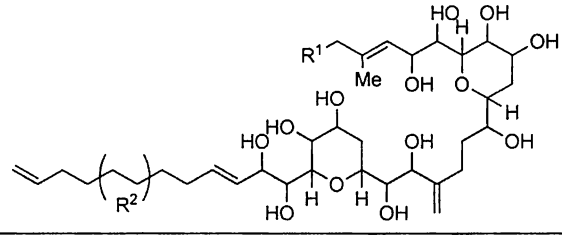
Table 1-1-2. Antifungal and hemolytic activities of amphidinols

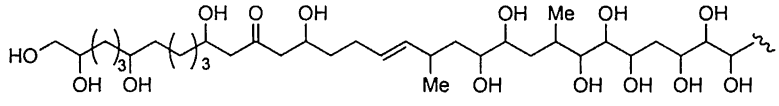
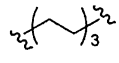
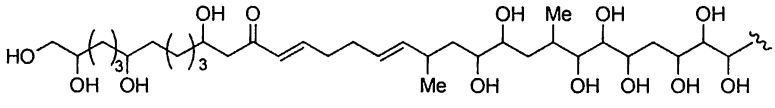
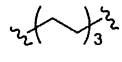
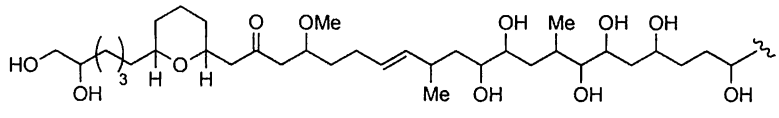
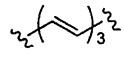
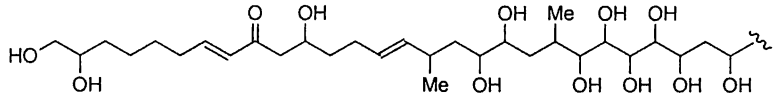
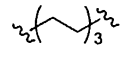
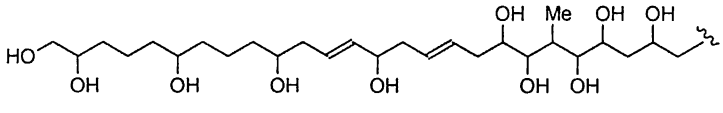
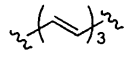
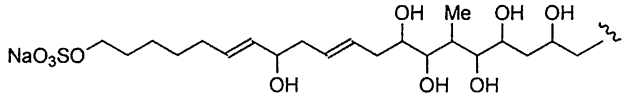
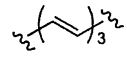
	antifungal[a] (μg/disk)	hemolysis (EC_{50} / nM)	Ref.
AM1	6	50[b]	4
AM2	6	910[b]	4
AM3	4	9.4[b]	4
AM4	6	185[b]	4
AM5	6	230[b]	4
AM6	6	580[b]	4
AM7	10	3000[b]	5
AM9	33	176[c]	6
AM10	154	6530[c]	6
AM11	256	28900[c]	6
AM12	>100	2990[c]	6
AM13	132	2020[c]	6
AM14	>60	>50000[b]	7
AM15	60	>50000[b]	7
AM17	-	4900[b]	8

[a] Against *Asperigillus niger*. [b] Against human erythrocytes. [c] Against mouse erythrocytes.

Other amphidinol congener but given different names, have been so far isolated from dinofragellate *Amphidinium* species (Table 1-1-3). The middle part of their molecules containing two tetrahydropyran ring system is structurally common to that of amphidinols. The structures of karatungiol A and B is different from AMs in which conjugate trine system is substituted with saturated aliphatic system as well as linshuiol A and B,[9] but the conjugated trine system is conserved in carteraol E and linshuiol.[10]

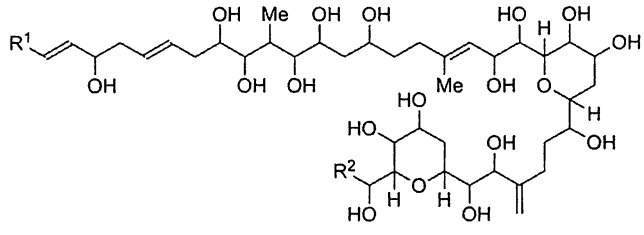
Table 1-1-3. Structures of amphidinol congeners

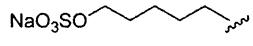
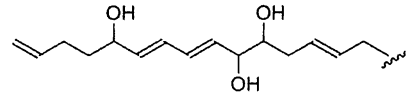
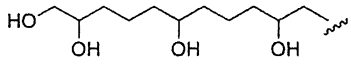
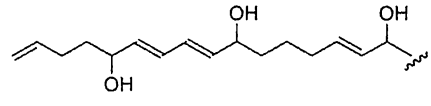
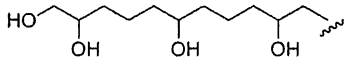
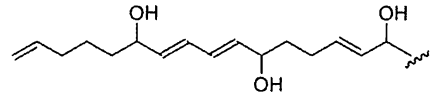


	R^1	R^2
Karatungiol A		
Karatungiol B		
Carteraol E		
Lingshuol		
Lingshuiol A		
Lingshuiol B		

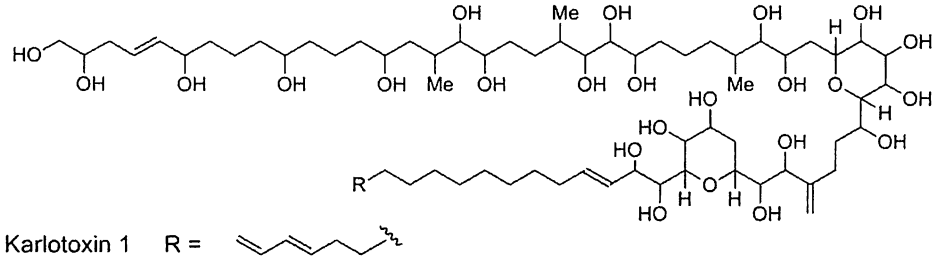
In contrast to amphidinols and other congeners equipped with hydrophobic side chains (R^2), luteophanols possess hydroxy groups in this region (Table 1-1-4).[13-15]

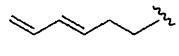
Table 1-1-4. Structures of luteophanols



	R^1	R^2
Luteophanol A		
Luteophanol B		
Luteophanol C		

Karlotoxin 1 and 2 (KmTx1 and 2) have been isolated from dinofragellate *Karlodinium veneficum* (Figure 1-1-2).[16-17] The characteristic structural feature of karlotoxin 2 is the presence of chlorine atom on the terminal butadienyl group of the aliphatic chain.



Karlotoxin 1 R = 

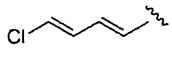
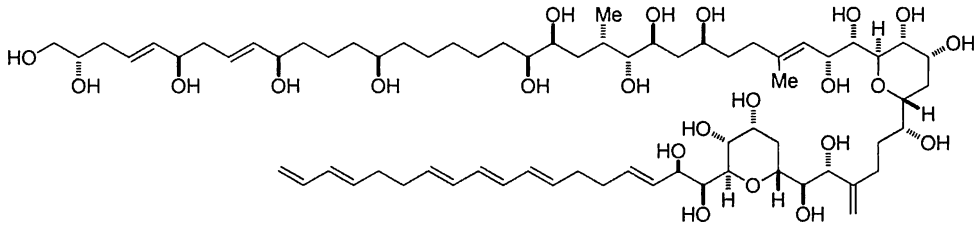
Karlotoxin 2 R = 

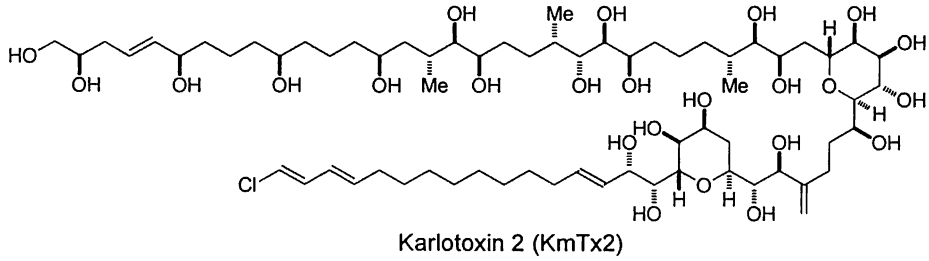
Figure 1-1-2. Structures of karlotoxins

The absolute configuration of AM3 was reported by Murata in 1999, which was the first report elucidating the stereochemistry among amphidinol family (Figure 1-1-3).[18] Recently, the absolute configuration of karlotoxin 2 (KmTx2) was determined by Hamann.[17]

The detail on the structure elucidation of AM3 is shown in Section 1-3.



Amphidinol 3 (AM3)



Karlotoxin 2 (KmTx2)

Figure 1-1-3. Absolute structures of amphidinol 3 and karlotoxin 2

Biological activities of these amphidinol congeners are summarized in Table 1-1-4. Karatungiol A possesses antifungal and antiprotozoan activity.[9] Carteraol E elicits antifungal activity and kills fish in a dose-dependent manner.[10] Linshuiol possesses a cytotoxic activity against A-549 and HL-60 cells in vitro, while linshuilol A and B elicit week cytotoxicity.[11, 12] Luteophanol A exhibits weak antimicrobial activity against Gram-positive bacteria.[13] Karlotoxin 1 elicits hemolytic activity,[16] while karlotoxin 2 kill fish in a dose-dependent manner.[17]

Table 1-1-4. Biological activities of amphidinol congeners

	biological activity		Ref.
Karatungiol A	antifungal	12 μg/disk (*Aspergillius niger*)	9
	antiprotozoan	1 μg/ml (*Trichomonas foetus*)	9
Carteraol E	antifungal	15 μg/disk	10
	fish killing	0.28 mM	10
Linshuilol	cytotoxicity	IC_{50} 0.21 μM (A-549 cell line)	11
	cytotoxicity	IC_{50} 0.23 μM (HL-60 cell line)	11
Linshuiol A and B	weak cytotoxicity	A-549 and HL-60 cell lines	12
Luteophanol A	antimicrobial	Gram-positive bacteria	13
Karlotoxin 1	Hemolysis	EC_{50} 63 nM (human erythrocyte)	16
Karlotoxin 2	fish-killing	0.1-0.8 mg/ml (*Danio reio*)	17

1-2. Studies on the mode of action of amphidinol 3

The structure of AM3 is characterized by a long carbon chain encompassing multiple hydroxyl groups and polyolefins, and the lopsided distribution of these hydrophilic and hydrophobic moieties may be reminiscent of polyene macrolides. AM3 enhances the permeability of the biological membrane by forming pores or lesions in lipid bilayers, which is thought to be responsible for their potent antifungal activity. The diameter of the pore/ lesion formed in the erythrocyte membrane has been estimated to be 2.0–2.9 nm.[20] Moreover, the complex structure of AM3 in membranes was established by NMR analysis of AM3 in the model membrane, e.g. SDS micelle and isotropic bicelles (Figure 1-2-1).[21-22] Although the conformation of C1–C20 moiety remains unelucidated due to the high flexibility, AM3 is likely to take an umbrella- like or a T-shaped structure in the membrane, with the bent polyol portion having a large cross-sectional area, the extended polyene chain having a smaller cross-section. Moreover, it was suggested that this conformation was stabilized by forming the intramolecular hydrogen bonds $O^{H}20$–$H^{O}51$, $H^{O}24$–$O^{H}50$ (Figure 1-2-2).

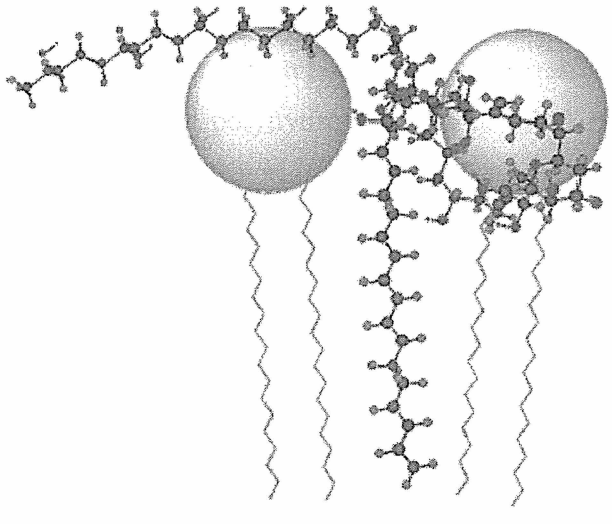


Figure 1-2-1. Hypothetical model of membrane-bound structure of AM3

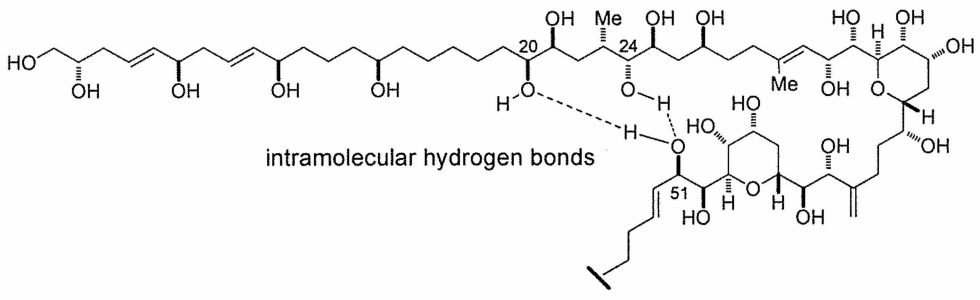


Figure 1-2-2. Intramolecular hydrogen bonds network including $O^{H}20$–$H^{O}51$, $H^{O}24$–$O^{H}50$

Morsy and co-workers observed that AM-induced membrane permeabilization is hardly influenced by membrane hydrocarbon thickness.[23] This study suggested the formation of a toroidal pore[24-25] by AM3 rather than a barrel-stave pore because the stability of the latter generally depends on the membrane thickness (Figure 1-2-3). In the toroidal pore, the lipid monolayer curves continuously from the outer leaflet to the inner in the fashion of a toroidal hole, so that the pore is lined by both the pore-formers and the lipid headgroups. In terms of toroidal pore formation, the AM3 structure shown in Figure 1-2-1 seems suitable in the following respects: (1) the disproportionately large hydrophilic portion of AM3 as compared with the hydrophobic polyene chain can induce a positive curvature strain upon the membrane surface, (2) the long and hairpin-shaped polyhydroxy chain of AM3 is likely to effectively capture the polar headgroups of lipids, and (3) the resultant association between the hydrophilic chain of AM3 and the lipid headgroups may be able to form the inner lining of the toroidal pore.

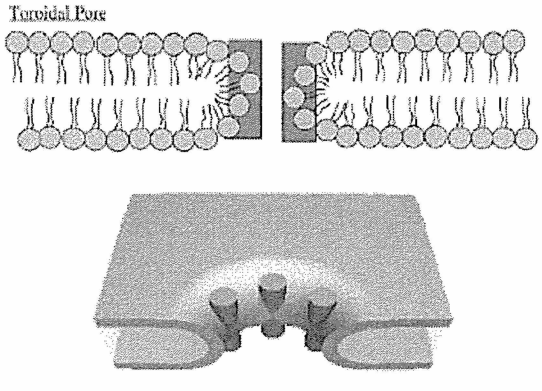


Figure 1-2-3. Troidal model

1-3. Determination of the absolute configuration of amphidinol 3

1-3-1. *J*-Based configuration analysis

Amphidinols may be one of the most challenging targets for structural elucidation since chiral centers are scattered over a flexible acyclic structure. Knowing the configuration of natural products has become crucial because it provides essential information for both total synthesis and molecular mode of actions, which are now regarded as the most challenging fields in organic and bioorganic chemistry. NMR-based methods have been devised for this purpose; e.g., NOE-based methods in combination with molecular mechanics calculations have been proposed for flexible molecules. However, even with new NOE-based techniques, it is still very difficult to assign the stereochemistry of highly flexible carbon chains, because the presence of multiple conformers, in which minor populations often make disproportionately large contributions to NOE intensity, occasionally leads to contradictory distance constraints.

Matsumori and Murata have developed a method for determination of stereochemistry of acyclic system based on the coupling constant (*J*) values, which was called *J*-Based Configuration Analysis (JBCA).[25] The *J* values depend on the specific substitution pattern of the molecular segment of interest, ranging from 0 to 16 Hz in the case of $^{3}J_{HH}$, from 0 to 9 Hz for $^{3}J_{HC}$, and from 6 to 8 Hz for the $^{2}J_{HC}$. These ranges can be dissected in small, medium, or large categories (Figure 1-3-1). Hence, considering the Newman projection of a given segment, the magnitude of each *J* can be a priori estimated for all its possible rotamers on the basis of the dihedral angle between the interested nuclei.

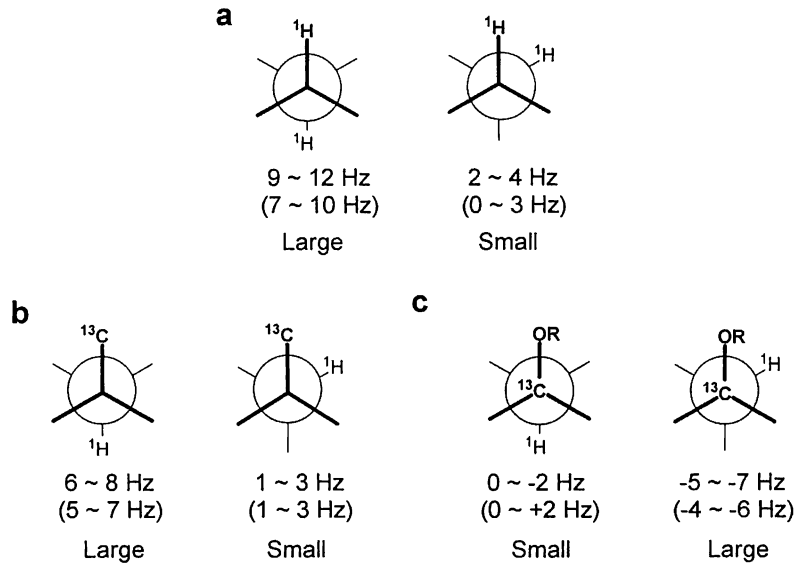
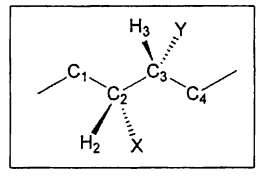
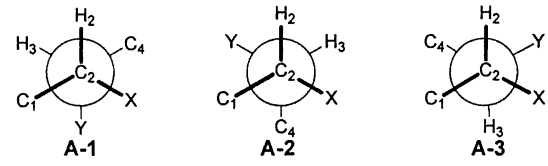


Figure 1-3-1. Dihedral angle dependence of spin-coupling constants, $^{3}J_{H,H,}$ $^{2}J_{C,H}$, and $^{3}J_{C,H}$

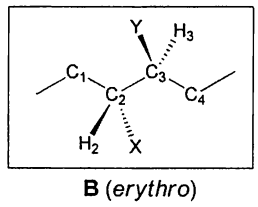
To assign the stereochemical relationship for a pair of vicinal asymmetric carbons, we have to choose a single conformer with a correct configuration from the staggered rotamers possible in *threo* and *erythro* diastereomers (Figure 1-3-2). Among those, four conformers, A-1, A-2, B-1, and B-2, can be identified using $^{3}J_{H,H}$, $^{2}J_{C,H}$, and $^{3}J_{C,H}$, while the two rotamers A-3 and B-3 with an H/H-anti orientation cannot be distinguished. For these anti conformers, NOE experiments should be a practical way to assign their configuration. In acyclic organic compounds with methyl or hydroxy substituents, these H/H-anti conformers usually assume a C/C-anti orientation (or an extended form), in which no NOE (or ROE) should be observed between H-1 and H-4 (B-3 in Figure 1-3-3). In the case of the H/H-anti and C/C-gauche conformation (A-3), if present, H-1 and H-4 should come within the range of NOE (Figure1-3-3). Using these criteria, all six conformers could be discriminated, with their relative configuration (*threo* or *erythro*) determined accordingly.



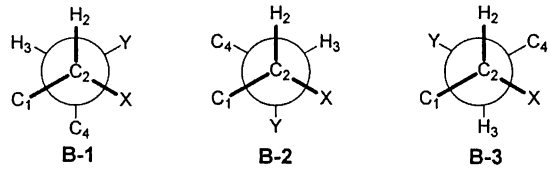
A (*threo*)



		A-1	A-2	A-3
	^3J (H-2, H-3)	Small	Small	Large
	^3J (H-2, C4)	Small	Large	Small
	^3J (C1, H-3)	Small	Large	Small
X=Me, Y=OR	^3J (Cx, H-3)	Large	Small	Small
	^2J (C3, H-2)	Small	Large	Large
X=OR, Y=OR	^3J (C2, H-3)	Small	Large	Large
	^2J (C3, H-2)	Small	Large	Large

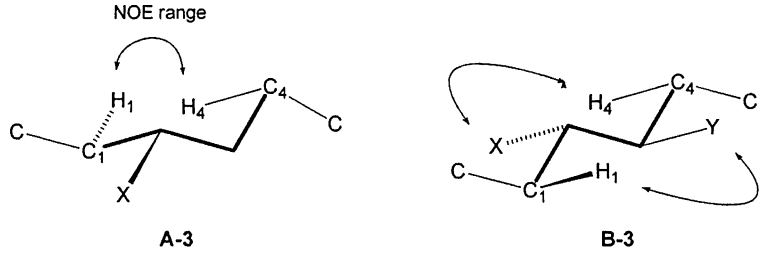


B (*erythro*)



		B-1	B-2	B-3
	^3J (H-2, H-3)	Small	Small	Large
	^3J (H-2, C4)	Large	Small	Small
	^3J (C1, H-3)	Small	Large	Small
X=Me, Y=OR	^3J (Cx, H-3)	Large	Small	Small
	^2J (C3, H-2)	Large	Small	Large
X=OR, Y=OR	^3J (C2, H-3)	Small	Large	Large
	^2J (C3, H-2)	Large	Small	Large

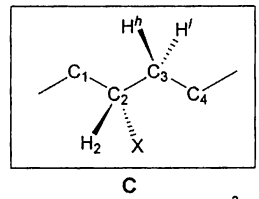
Figure 1-3-2. Dependence of $^3J_{H,H}$ and $^{2,3}J_{C,H}$ on dihedral angles between vicinal methine carbons in 2,3-disubstituted butane systems



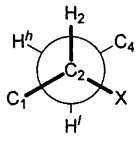
A-3 B-3

Figure 1-3-3. Distinguish between A-3 and B-3 by using NOE experiments

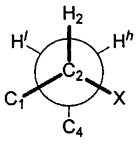
To determine the relative configuration of two methine carbons separated by a methylene group, the pair of diastereotopic methylene protons must be assigned stereospecifically (Figure 1-3-4). The method for assigning diastereotopic methylene protons with respect to the adjacent methine is similar to that for vicinal methines described above. In these structural units, six conformers are possible when a pair of protons on a methylene is stereochemically labeled according to their chemical shifts. All these conformers can be unambiguously identified using $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$, as depicted in Figure 1-3-4. With one methylene-methine relationship in hand, the same examination of another relationship leads to diastereomeric assignment of the 1,3-methine groups via the stereospecifically labeled methylene protons. If ^{1}H NMR signals of relevant protons are separated, this method can be applied to 1,4-methine systems separated by an ethylene group



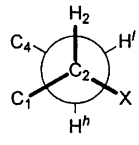
C



C-1

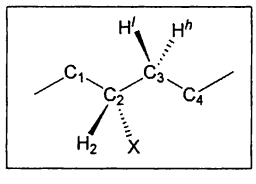


C-2

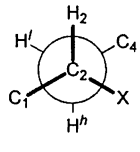


C-3

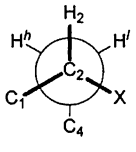
		C-1	C-2	C-3
	^3J (H-2, H-3^h)	Small	Small	Large
	^3J (H-2, H-3^l)	Large	Small	Small
	^3J (H-2, C4)	Small	Large	Small
	^3J (C1, H-3^h)	Small	Large	Small
	^3J (C1, H-3^l)	Small	Small	Large
X=Me, Y=OR	^3J (Cx, H-3^h)	Large	Small	Small
	^3J (C2, H-3^l)	Small	Large	Small
X=OR, Y=OR	^2J (C2, H-3^h)	Small	Large	Large
	^2J (C2, H-3^l)	Large	Small	Large



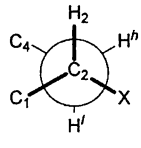
D



D-1



D-2



D-3

		D-1	D-2	D-3
	^3J (H-2, H-3^h)	Large	Small	Small
	^3J (H-2, H-3^l)	Small	Small	Large
	^3J (H-2, C4)	Small	Large	Small
	^3J (C1, H-3^h)	Small	Small	Large
	^3J (C1, H-3^l)	Small	Large	Small
X=Me, Y=OR	^3J (Cx, H-3^h)	Small	Large	Small
	^3J (C2, H-3^l)	Large	Small	Small
X=OR, Y=OR	^2J (C2, H-3^h)	Large	Small	Large
	^2J (C2, H-3^l)	Small	Large	Large

Figure 1-3-4. Dependence of $^3J_{H,H}$ and $^{2,3}J_{C,H}$ on dihedral angles between vicinal methine carbons in 2-substituted butane systems

However, two or three rotamers frequently coexist in acyclic systems. When $^3J_{H,H}$ attains an intermediate value between anti and gauche, two major rotamers with H/H-anti and gauche orientations should be considered. These conformational changes are often observed in natural products. In such a case, four out of six alternating pairs can be unambiguously identified using $^{2,3}J_{C,H}$ and $^3J_{H,H}$ as shown in Figure 1-3-5, where all four H/H-anti/gauche pairs of rotamers A-2/A-3, A-1/A-3, B-2/B-3, and B-1/B-3 give rise to different combinations of J values. When both alternating rotamers have an H/H-gauche orientation (A-1/A-2 or

B-1/B-2 in Figure 1-3-5), their configuration cannot be assigned using $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ alone. In these conformers, however, all the substituents on C2 and C3 are gathered in one side, thus making them thermodynamically disfavored. As far as we know, the occurrence of these pairs of rotamers is extremely rare in natural products.

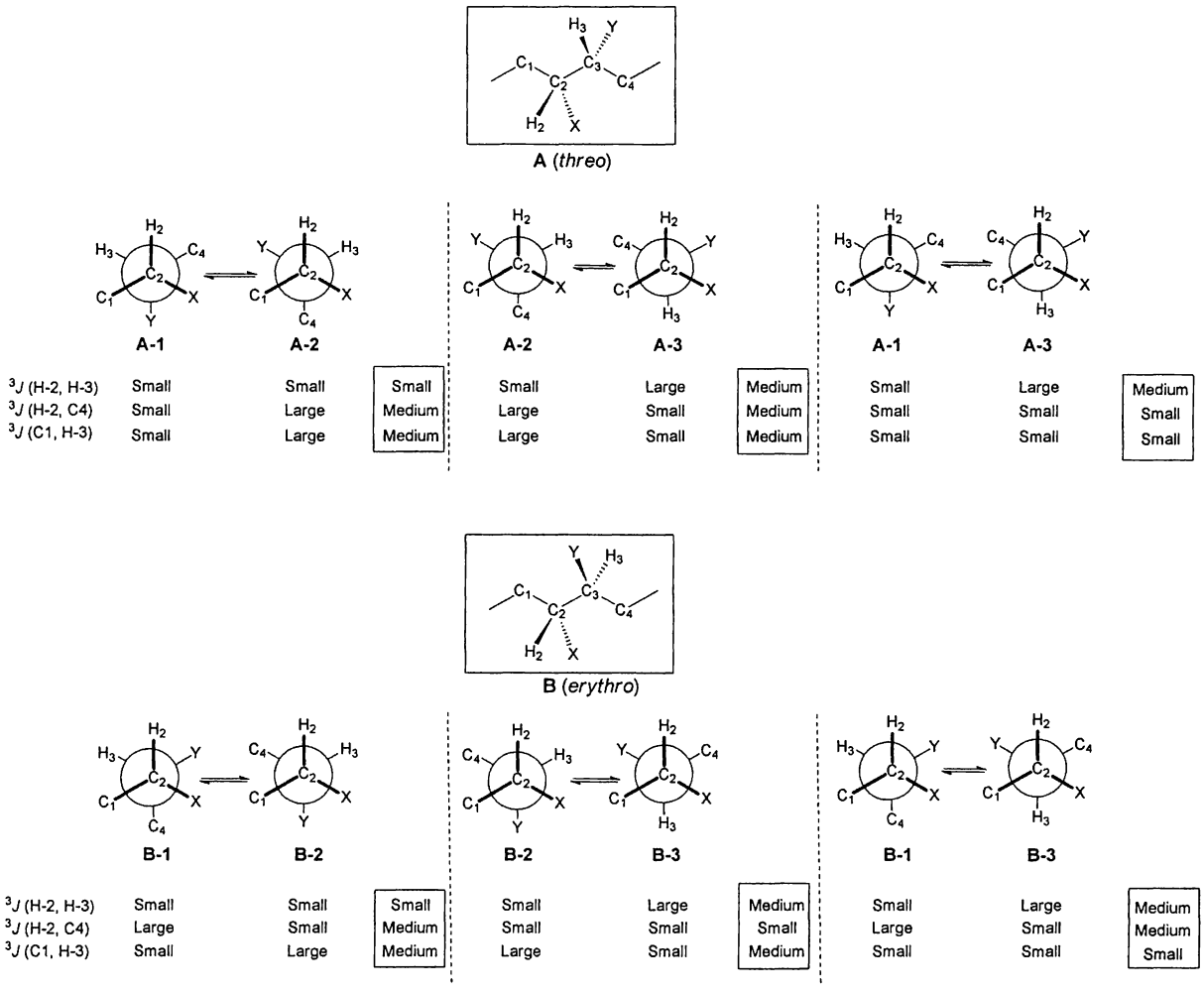


Figure 1-3-5. Dependence of $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ on dihedral angles between vicinal methine carbons in alternating butane systems

1-3-2. Determination of the relative configuration of AM3 based on JBCA Method

By applying the JBCA method, Murata and co-workers achieved to elucidate the absolute configuration of AM3. To facilitate measurements of $^{2,3}J_{C,H}$, they prepared a ^{13}C-enriched sample of AM3 (25% ^{13}C, 8 mg) by making another culture in the presence of $NaH^{13}CO_3$. The stereochemical assignment of AM3 was accomplished as follows (Figure 1-3-6); (a) the *J*-based method was used for acyclic parts with 1,2- and 1,3-chiral centers, C20-C27, C33-C35, C38-C39, C43-C45, and C49-C51, (b) NOE analysis combined with *J* analysis was used for two ether cycles and their linkage C39-C44, (c) the modified Mosher method to determine the absolute configuration at C6, C10, and C14,[26] and (d) comparison of degradation products with authentic samples by HPLC and NMR analysis to determine the absolute configuration at C2, C23, and C39.

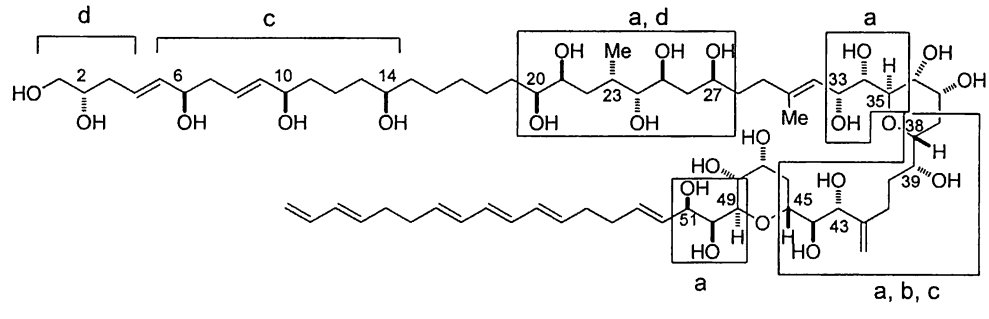


Figure 1-3-6. Methods for determination of the relative configuration of AM3. (a) JBCA method, (b) NOE analysis combined with JBCA method, (c) the modified Mosher method, and (d) HPLC and NMR analysis of the degradation products.

$^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ values of intact AM3 were measured by E.COSY and HETLOC, respectively; phasesensitive HMBC was also used for parts where the small magnetization transfer by TOCSY hampered the accurate measurement of $^{2,3}J_{C,H}$ by HETLOC. C32-C33 and C38-C39 can be used as examples to see how the *J*-based analysis works in configuration assignments. As shown in Figure 1-3-7, ^{3}J(H-32, H-33) revealed a value that is typical of gauche interaction for a 1,2-diol system. The values for ^{2}J(C32, H-33) and ^{3}J(C34, H-32) indicate that H-33 is anti to C32-OH8 and H-32 is gauche to C34, respectively. These interactions unambiguously establish the *threo* configuration for C32-C33, as depicted in Figure 1-3-7a.

For C38-C39, ^{3}J(H-38, H-39), which is intermediate between anti and gauche, suggests that this bond undergoes a conformational change. The *J*-based analysis can even be applied to such a flexible system. The two small values for ^{3}J(C37, H-39) and ^{3}J(C40, H-38) indicate gauche C37/H-39 and gauche C40/H-38 interactions in both conformers (Figure 1-3-7b). Of the six possible pairs of alternating rotamers arising from *erythro* and *threo* configurations, only one pair in Figure 1-3-7b satisfies all of these requirements. The diastereomeric relationships of C44-C45 and C50-C51 were assigned in the same manner on the basis of $^{3}J_{H,H}$ and $^{2,3}J_{C,H}$ (Figure 1-3-7c, d). The relative configurations of the consecutive stereogenic center in C20-C27 can be determined using this method, as shown in Figure 1-3-8a. The configurations of C39-C44 were elucidated using NOEs in combination with ^{3}JH,H and $^{2,3}J_{C,H}$ data (Figure 1-3-8b).

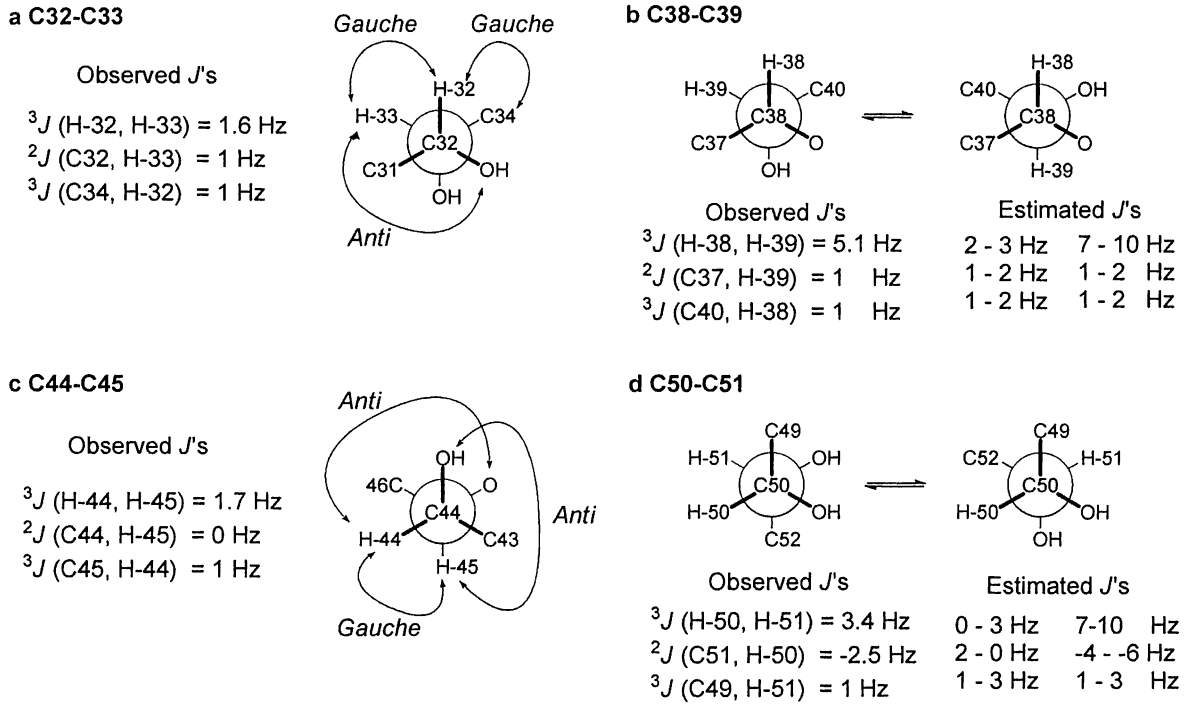


Figure 1-3-7. Relative configuration and coupling constants of C32-C33, C38-39, C44-C45 and C50-C51parts of AM3

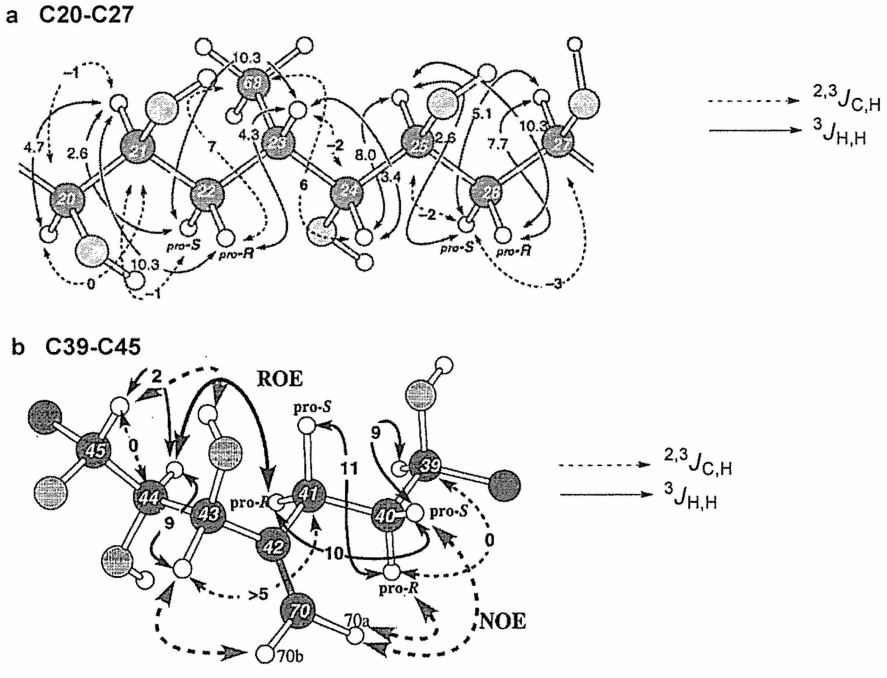


Figure 1-3-8. Relative configuration and coupling constants of C20-C27 and C39-C45 parts of AM3

1-3-3. Determination of the absolute configuration of AM3 by degradation of natural product

These NMR-based analyses using intact AM3 have revealed the relative configurations of C20-C27 and C32-C51 (Figure 1-3-9). Next, their absolute configurations and those at C2, C6, C10, and C14 were investigated using degradation products; treatment of AM3 with $HIO_4/NaBH_4$, followed by esterification with (*R*)- and (*S*)-MTPA (2-methoxy-2-trifluoromethyl-2-phenylacetic acid) and separation by HPLC, furnished MTPA esters of fragments corresponding to C2-C20 (**1b**,**c**), C21-C24 (**3b**) and C33-C50 (**4b**,**c**).

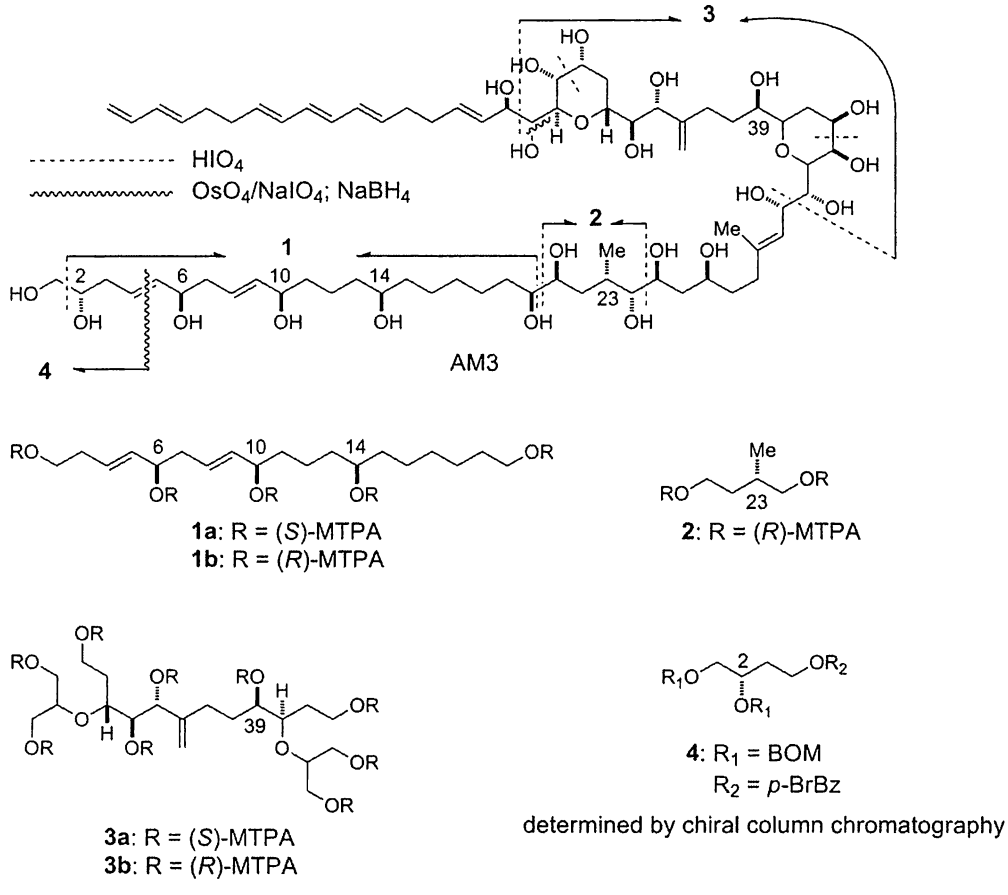


Figure 1-3-9. Determination of the absolute configuration at C2, C6, C10, C14, C23 and C39 of AM3

The absolute stereochemistries of C6, C10, C14,11 and C39 were elucidated by the modified Mosher method using **1a/2b** and **3a/3b** as shown in Figure 1-3-10 and Figure 1-3-11, respectively.

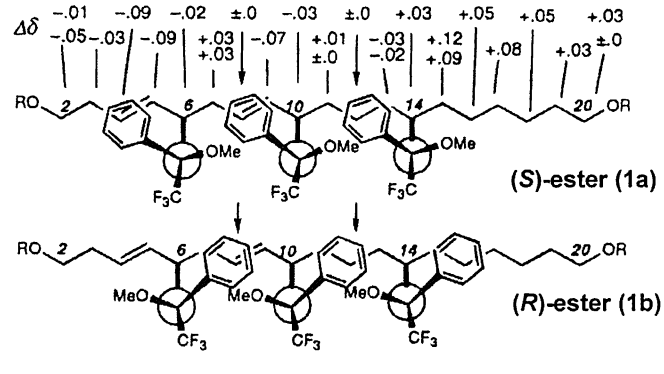
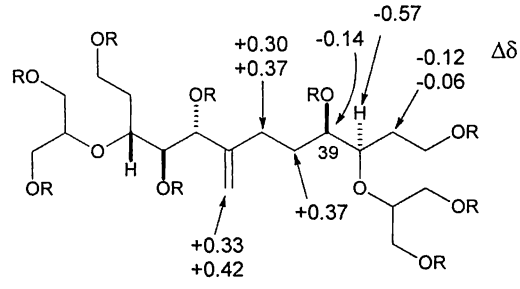


Figure 1-3-10. Result of the modified Mosher method for the Mosher esters (**1a, b**)



3a: R = (*S*)-MTPA
3b: R = (*R*)-MTPA

Figure 1-3-11. Result of the modified Mosher method for the Mosher esters (**3a, b**)

The configuration of **2** was determined to be 23*S* by comparison of the NMR data of the bis-(*R*)-MTPA esters **2** with (*S*)- and (*R*)-MTPA esters of authentic (*R*)-methyl-1,4-butanediol (Figure 1-3-12). The configuration of C2 was determined using the C1-C4 fragment obtained from the *O*-benzyloxy-methyl derivative of AM3 by treatment with $OsO_4/NaIO_4$. The resulting 1,2-dibenzyloxylmethoxy-butyl *p*-bromobenzoate **4** was chromatographed on a chiral resolution column and determined to be an (*S*)-enantiomer. Considering all of these partial configurations led to the complete structure of amphidinol 3 with the absolute configuration of 2*S*, 6*R*, 10*R*, 14*R*, 20*S*, 21*S*, 23*S*, 24*R*, 25*S*, 27*S*, 32*R*, 33*S*, 34*R*, 35*R*, 36*R*, 38*R*, 39*R*, 43*R*, 44*R*, 45*R*, 47*R*, 48*R*, 49*R*, 50*S*, and 51*R* (Figure 1-3-13).

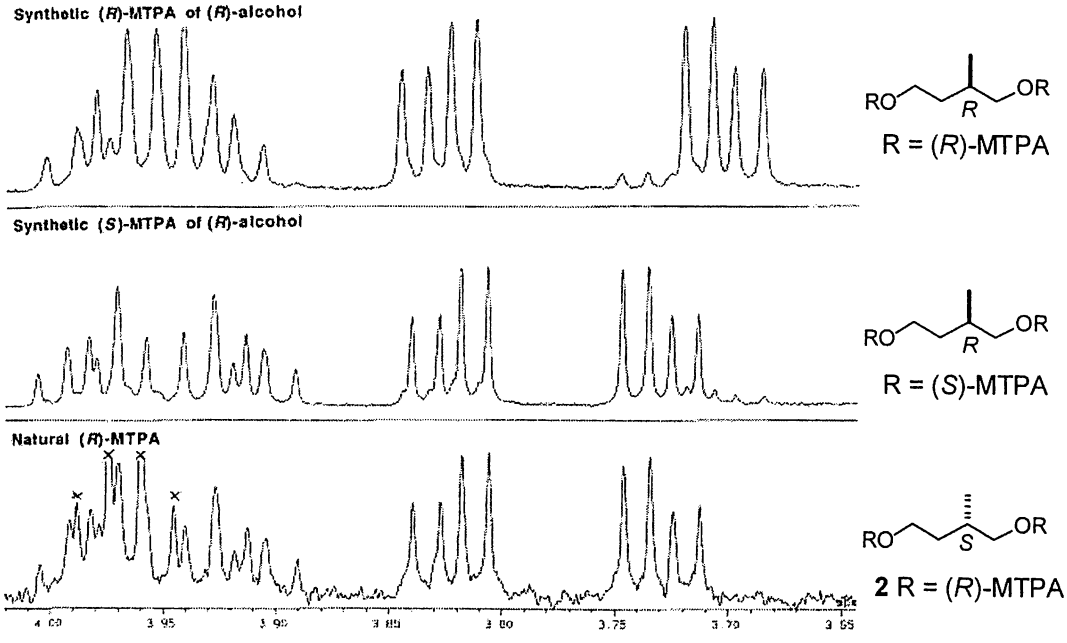
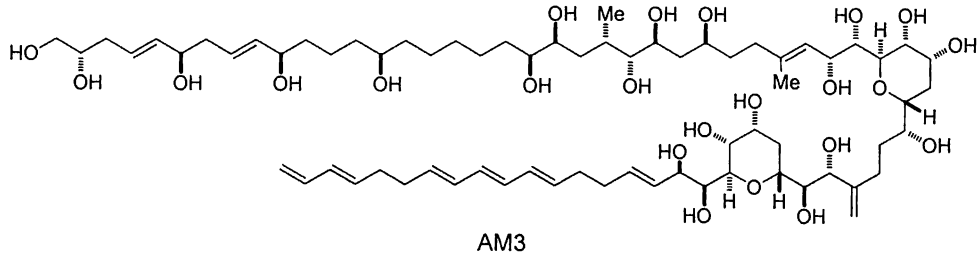


Figure 1-3-12. ^{1}H NMR comparison of C21-C24 fragment from AM3 (**2**, bottom) with (*R*)-MTPA ester (top) and (*S*)-MTPA ester (middle) of (*R*)-2-methyl-1,4-butanediol



AM3

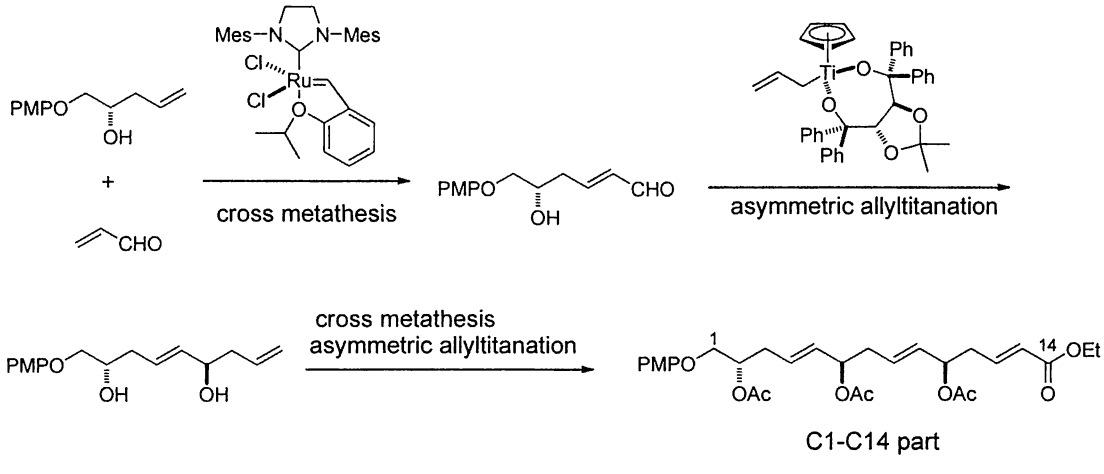
Figure 1-3-13. Absolute structure of AM3

1-4. Synthetic studies of amphidinol 3

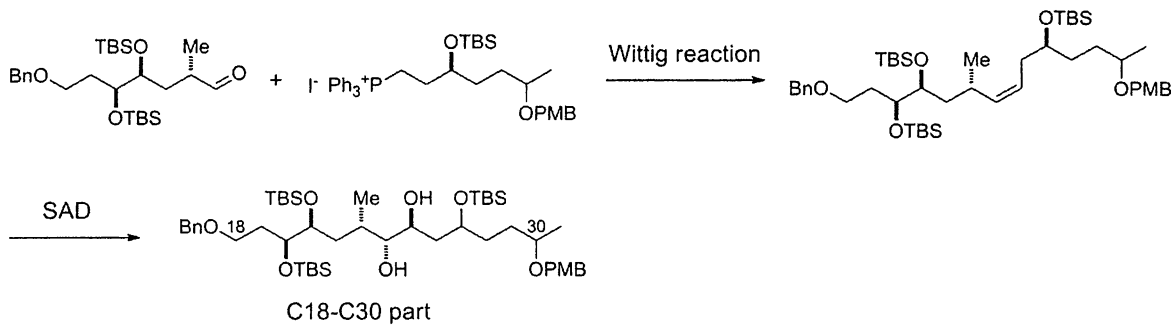
The structural features of AM3 have attracted considerable attention from the synthetic community, and a number of synthetic studies of AM3 have been reported by Cossy, Roush Paquette, and Rychnovsky groups. However, no total synthesis of AM3 has been reported. In this section, synthetic studies of AM3 are reviewed.

1-4-1. Synthetic studies by Cossy group

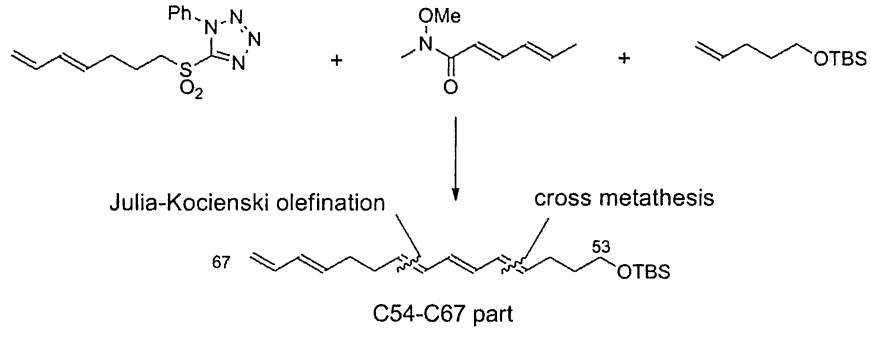
Cossy achieved syntheses of the C1-C14, C18-C30 and C53-C67 parts of AM3. The C1-C14 part was synthesized via chemoselective cross metathesis and asymmetric allyltitanation (Scheme 1-4-1).[27] The C18-C30 part of AM3 was provided by coupling of fragments via Wittig reaction giving *Z*-olefin, followed by Sharpless asymmetric dihydroxylation (SAD) (Scheme 1-4-2).[28] The C53-C67 part was synthesized via successive coupling by using olefin metathesis and Julia-Kocienski olefination (Scheme 1-4-3).[29]



Scheme 1-4-1. Synthesis of the C1-C14 part of AM3 by Cossy



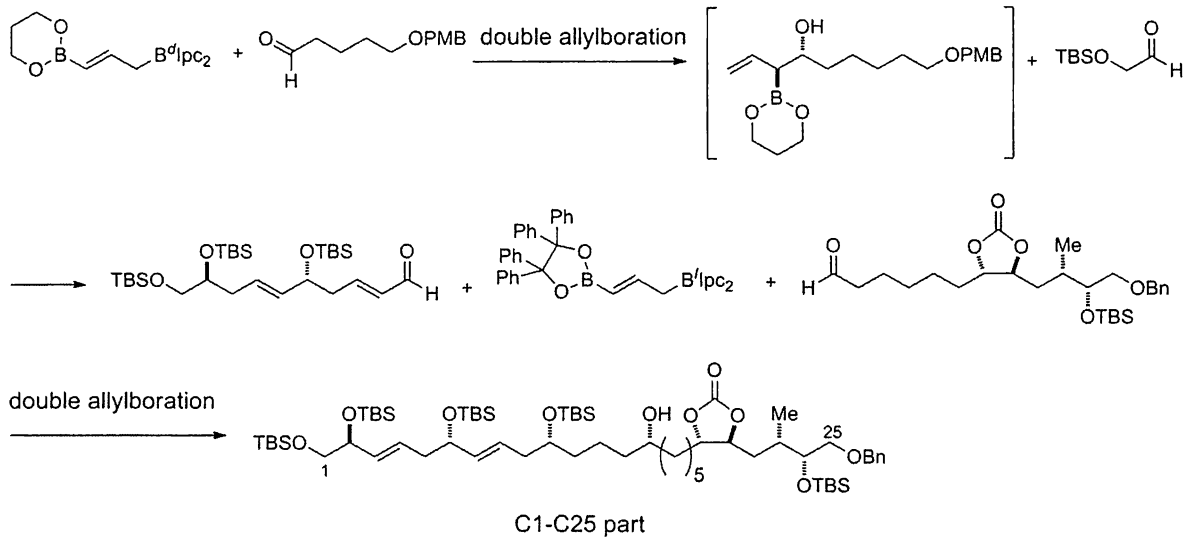
Scheme 1-4-2. Synthesis of the C18-C30 part of AM3 by Cossy



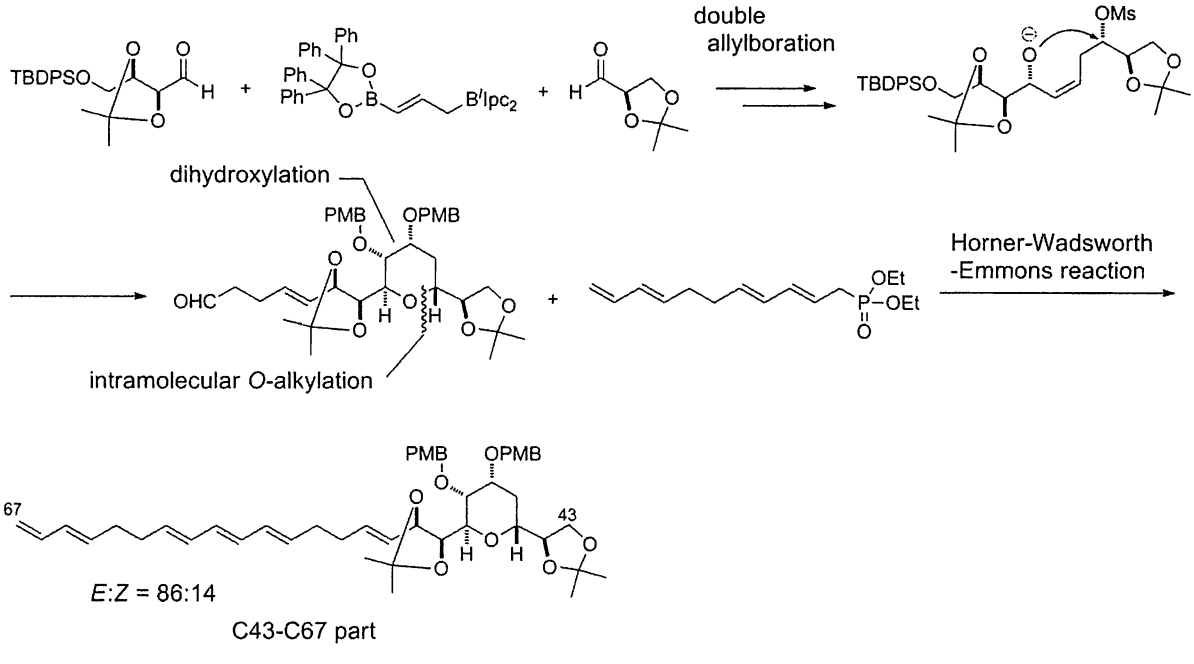
Scheme 1-4-3. Syntheses of the C53-C67 part of AM3 by Cossy

1-4-2. Synthetic studies by Roush group

Roush reported synthesis of the C1-C25 part of AM3 based on their own methodology by using double allylboration as a key step (Scheme 1-4-4).[30] They also achieved synthesis of the C43-C67 (Scheme 1-4-5).[31] The tetrahydropyran system was constructed via a sequence featuring the double-allylboration reaction, a base-mediated cyclization of hydroxy mesylate to dihydropyran, and stereoselective dihydroxylation. The polyene moiety was installed by Horner-Wadsworth-Emmons olefination between an aldehyde corresponding to the C43-C56 moiety and a phosphonate corresponding to the C57-C67 moiety to afford the C43-C67 part.



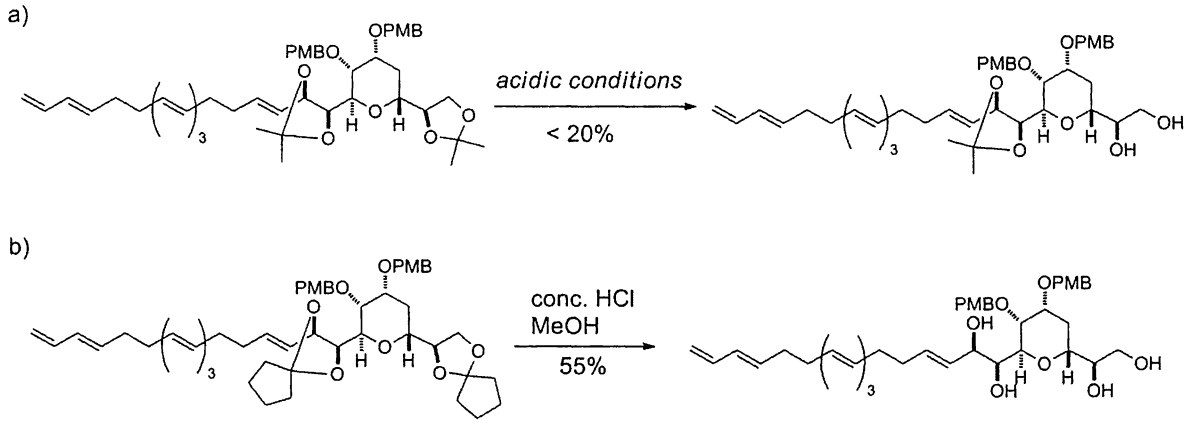
Scheme 1-4-4. Synthesis of the C1-C25 part of AM3 by Roush



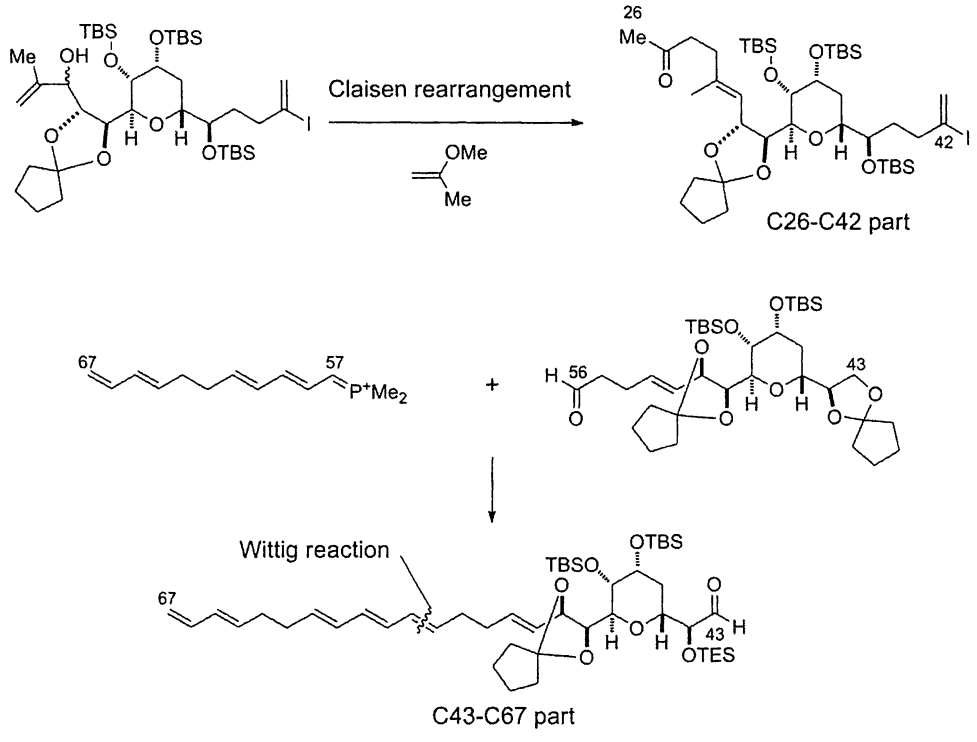
Scheme 1-4-5. Synthesis of the C43-C67 part of AM3 by Roush

However, removal of the acetonide group under the acidic conditions was unsuccessful to yield a diol in low (<20%) yield (Scheme 1-4-6), presumably due to the acid labile nature of the polyene and allylic alcohol moieties, while that of cyclohexylidene counterpart resulted in moderate yield (55%).[32] Alternatively, they reported the second generation synthesis of the

C26-C42 part via Ireland-Claisen rearrangement, and the C43-C67 part via Wittig reaction between a ylide corresponding to the C57-C67 part and an aldehyde corresponding to the C43-C56 part (Scheme 1-4-7).[32]



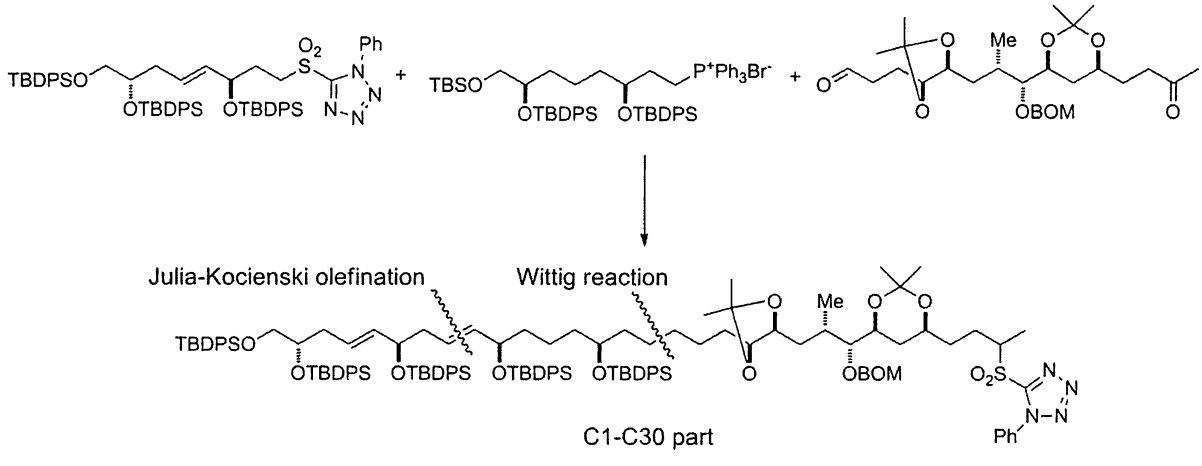
Scheme 1-4-6. Removal of protecting groups under the acidic conditions: a) acetonide, and b) cyclopentylidene acetal.



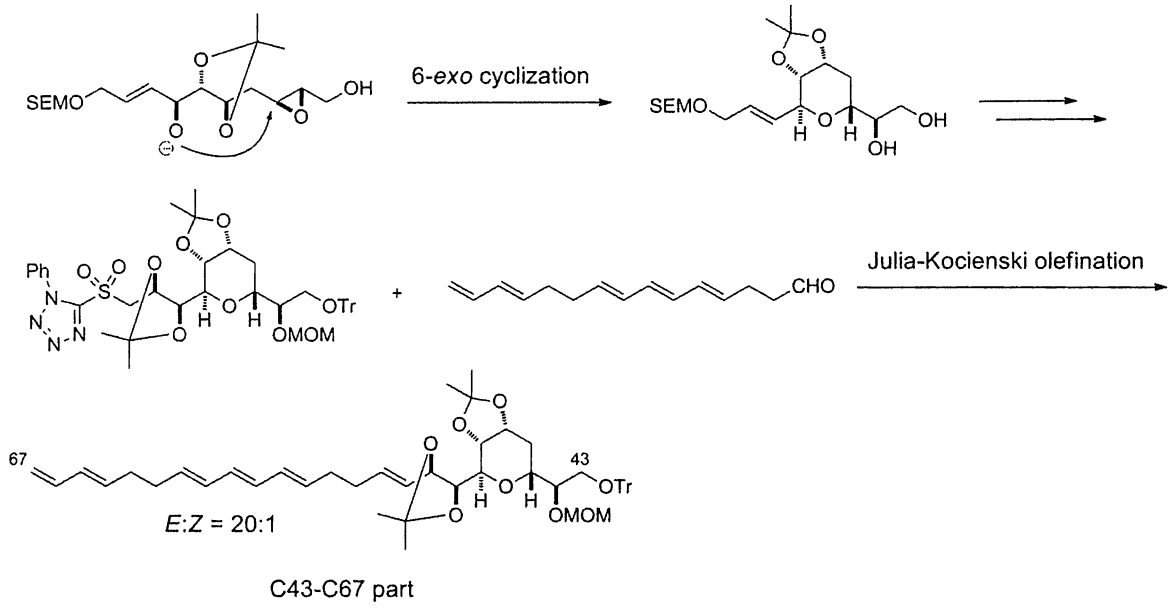
Scheme 1-4-7. Syntheses of the C26-C42 and C43-C67 parts of AM3 by Roush

1-4-3. Synthetic studies by Paquette group

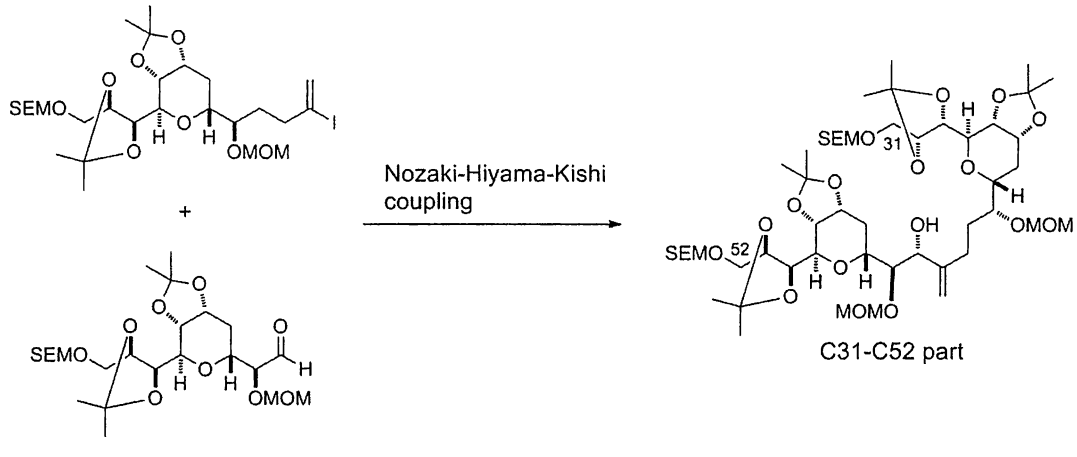
Paquette and co-workers achieved syntheses of the C1-C30, C43-C67 and C31-C52 parts of AM3. The C1-C30 part was synthesized from three building blocks via Julia-Kocienski, and Wittig olefination (Scheme 1-4-8).[33] They utilized intramolecular ring-opening of an epoxide for the construction of the tetrahydropyran ring, which was converted to a sulfone. Subsequent Julia-Kocienski olefination with an aldehyde corresponding to the olefinic side chain (C53-C67) afforded the C43-C67 part of AM3 (Scheme 1-4-9).[34] The C31-C52 part was synthesized via Nozaki-Hiyama-Kishi coupling reaction between an iodoolefin corresponding to the C31-C42 part and an aldehyde corresponding to the C43-C52 part (Scheme 1-4-10).[35]



Scheme 1-4-8. Synthesis of the C1-C30 part of AM3 by Paquette



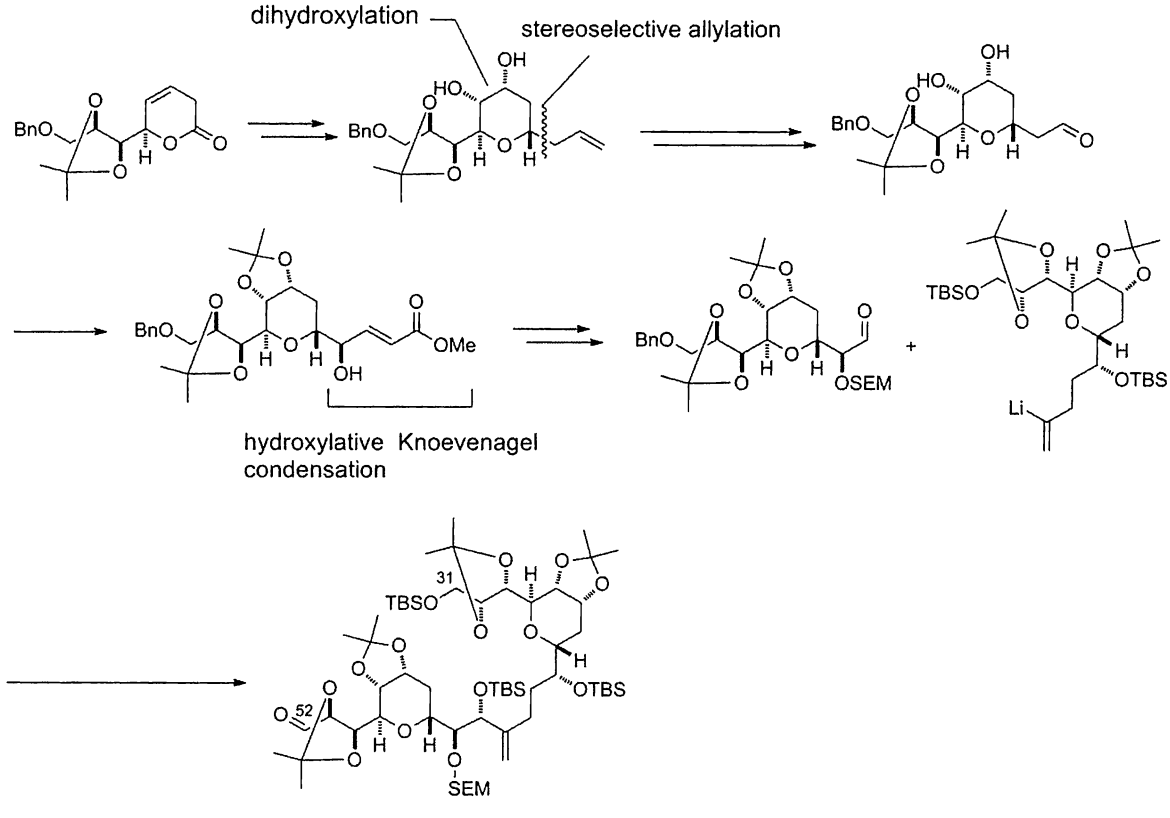
Scheme 1-4-9. Synthesis of the C43-C67 part of AM3 by Paquette



Scheme 1-4-10. Synthesis of the C31-C52 part of AM3 by Paqutte

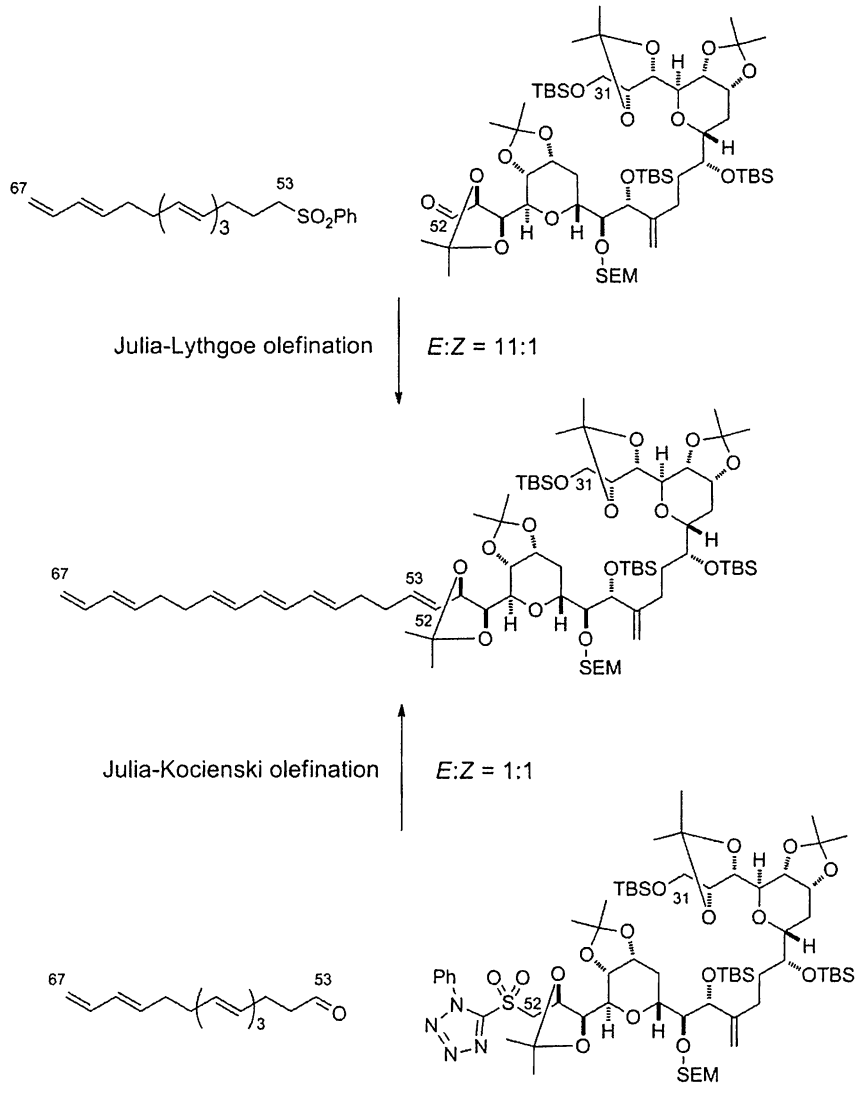
1-4-4. Synthetic Studies by Rychnovsky Group

Rychnovsky reported synthesis of the advanced intermediate of AM3 corresponding to the C31-C67 part.[36] The tetrahydropyran ring system was constructed through Lewis acid catalyzed allylation of an acetal derived from a lactone, and hydroxylative Knovenagel condensation with a chiral sulfoxide. Then, coupling with another tetrahydropyran moiety afforded the C31-C52 part (Scheme 1-4-11).



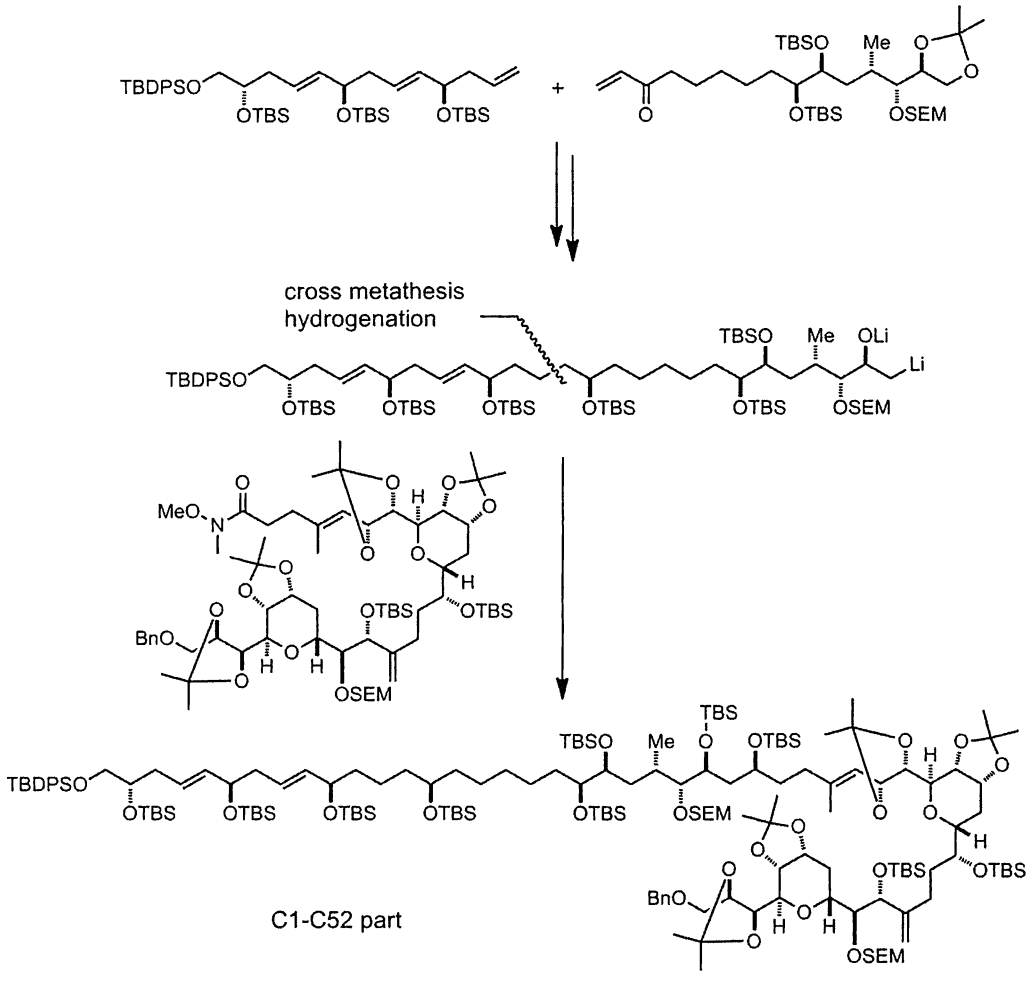
Scheme 1-4-11. Synthesis of the C31-C52 part of AM3 by Rychnovsky

Julia-Lythgoe olefination of a sulfone (C53-C67) and aldehyde (C31-C52) proceeded selectively to afford the C31-C67 part of AM3 (*E*:*Z* = 11:1), while Julia-Kocienski olefination of a sulfone (C31-C52) and an aldehyde (C53-C67) resulted in low selectivity (*E*:*Z* = 1:1) (Scheme 1-4-12).[37]



Scheme 1-4-12. Synthesis of the C31-C67 part of AM3 by Rychnovsky

The C1-C26 part was synthesized by utilizing cross metathesis reaction (Scheme 1-4-13). An unusual β-alkoxy alkyllithium reagent was generated from the C1-C26 part and added to a Weinreb amide to assemble the C1-C52 part of AM3.[38]



Scheme 1-4-13. Synthesis of the C1-C52 part of AM3 by Rychnovsky

1-5. Purpose

As mentioned in Section 1-3-3, the absolute configuration of AM3 except for C2 was elucidated by extensive NMR analysis based on JBCA method and in combination with modified Mosher method (Figure 1-5-1).

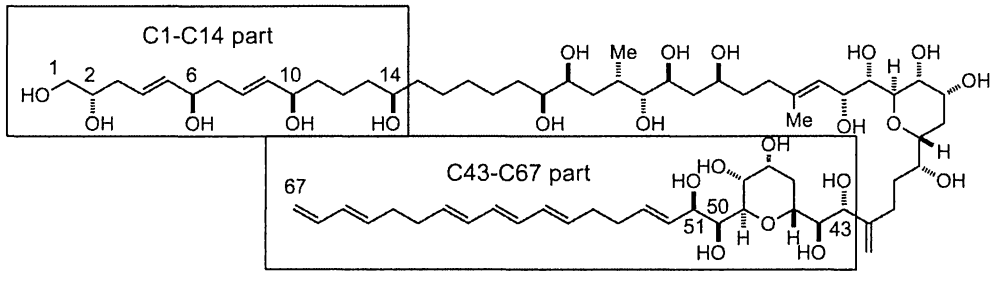


Figure 1-5-1. Structure of AM3

However, absolute configuration at C2 remained ambiguous, because it was determined by HPLC analysis of the degradation product derived from no more than 10 μg of AM3 via oxidative cleavage of the double bond in four steps. Therefore, the author planned to synthesize the C1-C14 part of AM3 and its diastereomers (Figure 1-5-2) in order to confirm the absolute configuration at C2 by comparing their spectral data with those of natural product (See Chapter 2).

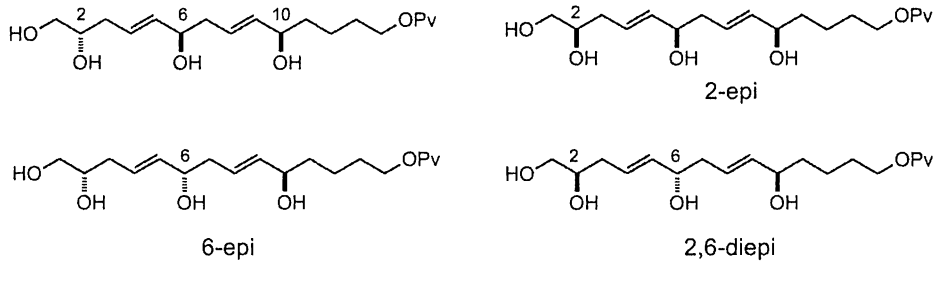
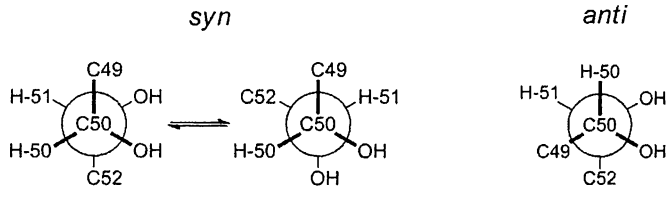


Figure 1-5-2. Structures of the C1-C14 part of AM3 and its diastereomers

As mentioned in Section 1-3-2, it was difficult to elucidate the relative configuration of C50-C51 part based on JBCA method, because this part undergoes conformational change and

^3J(H50-H51) shows an intermediate value between gauche and anti orientations (Figure 1-5-3). Therefore, the author planned to synthesize the C43-C67 part of AM3 and its diastereomers (Figure 1-5-4) in order to confirm the relative configuration at C50 and C51 by comparing their spectral data with those of natural product (See Chapter 3).



Observed J's	Estimated J's		Estimated J's
^3J (H-50, H-51) = 3.4 Hz	0 - 3 Hz	7-10 Hz	0 - 3 Hz
^2J (C51, H-50) = -2.5 Hz	2 - 0 Hz	-4 - -6 Hz	-4 - -6 Hz
^3J (C49, H-51) = 1 Hz	1 - 3 Hz	1 - 3 Hz	1 - 3 Hz

Figure 1-5-3. Relative configuration and coupling constants of the C50-C51 part of AM3

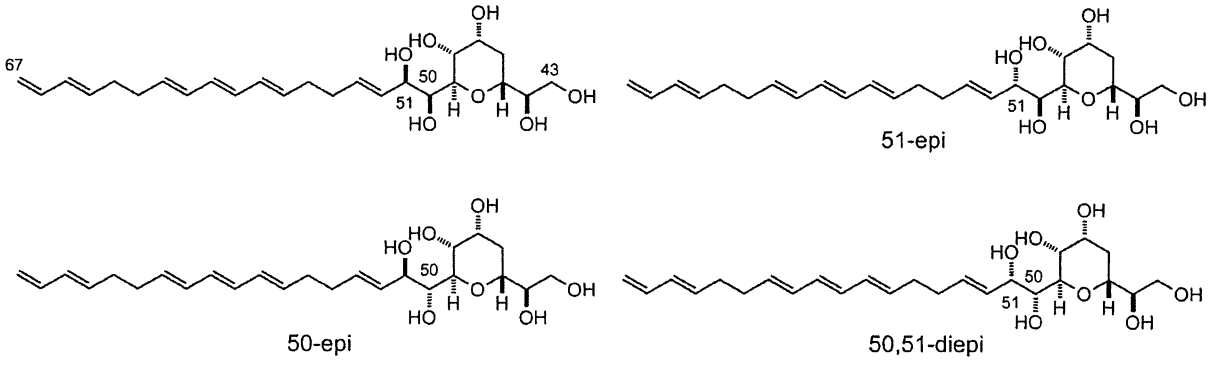


Figure 1-5-4. Structures of the C43-C67 part of AM3 and its diastereomers

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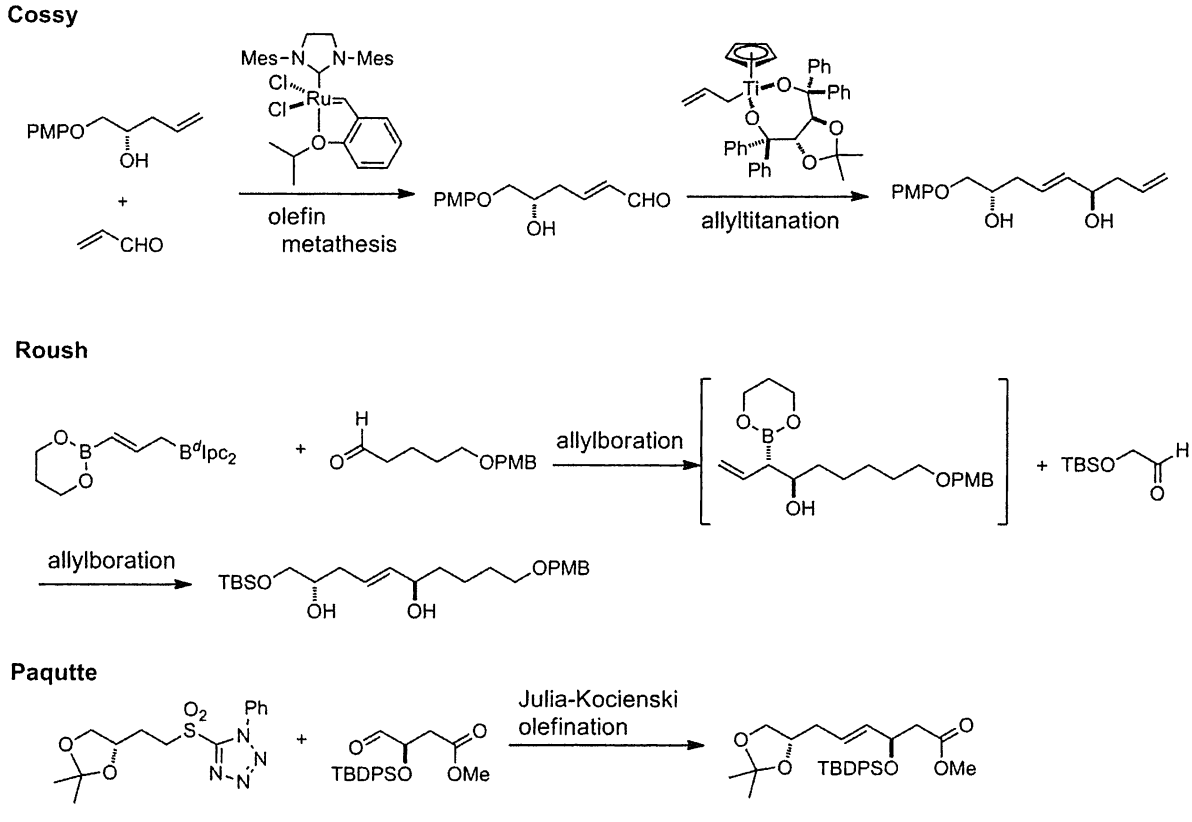
Chapter 2. Synthesis and structure confirmation of the C1-C14 part of amphidinol 3

2.0 Introduction

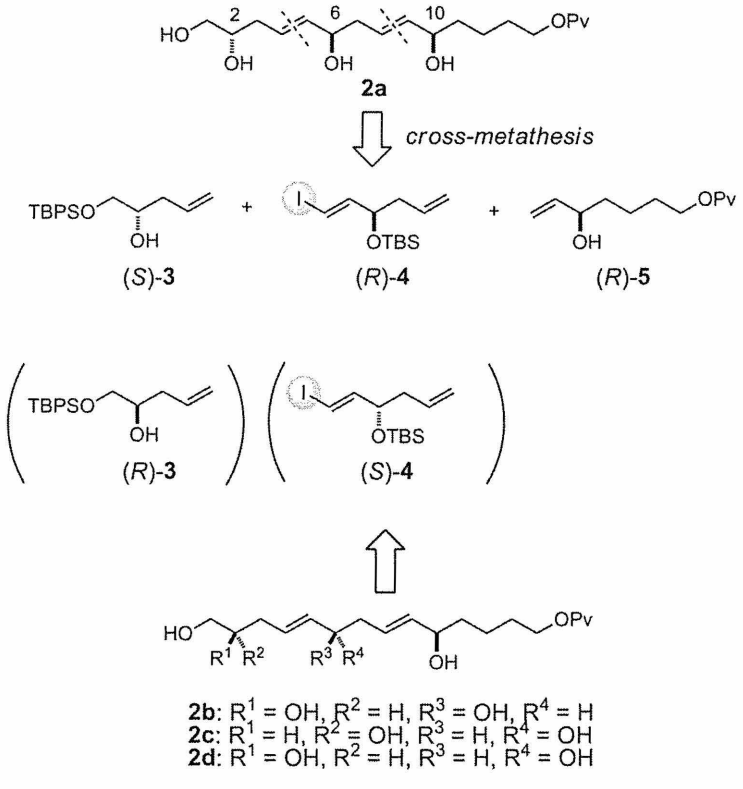
As mentioned in Chapter 1 (Section 1-4), syntheses of the 1,5-polyol part of AM3 have been reported by Cossy,[1] Roush,[2] and Paquette[3] (Scheme 2-1). Cossy used cross olefin metathesis of a chiral allylic alcohol with acrolein giving an *E*-α,β-unsaturated aldehyde, which was treated with a chiral allyltitanium reagent[4] to give a 1,5-diol. Double asymmetric allylboration[5] developed by Roush was applied for the synthesis of a 1,5-diol system directly from an aldehyde. Paquette used Julia-Kocienski olefination[6] for the coupling of a chiral aldehyde and a chiral sulfone.



Scheme 2-1. Syntheses of the1,5-polyol systems of AM3

2.1 Synthesis plan

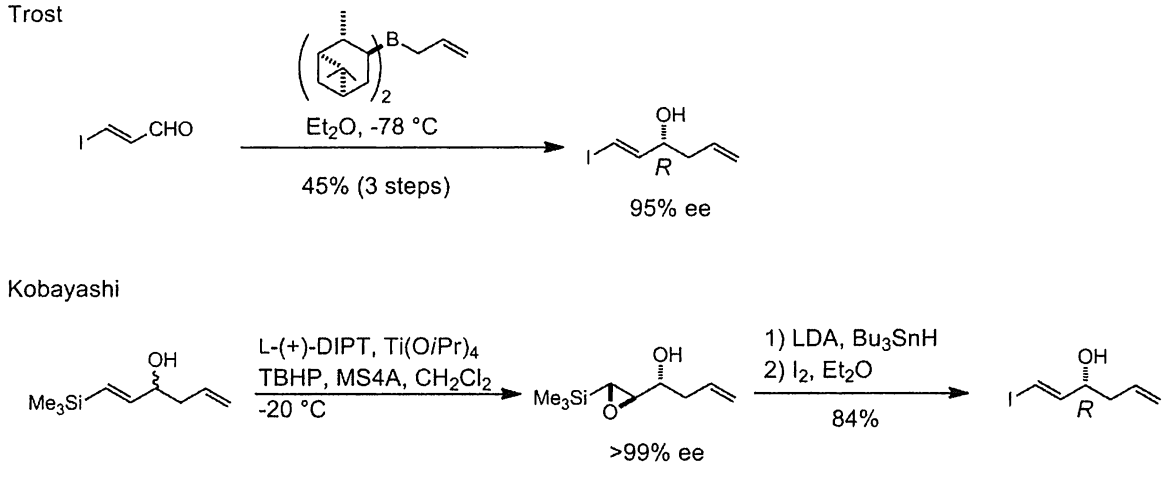
The author envisaged a versatile synthetic route to the C1-C14 segment (**2a**) of AM3 that could readily provide all diastereomers via successive coupling of the building blocks equipped with defined stereogenic centers (Scheme 2-2). In this strategy, diene (*R*)-**4** was envisioned as a key intermediate, in which the iodoolefin is regarded as a protected terminal olefin for chemoselective cross metathesis with (*R*)-**5**, and the iodoolefin moiety was to be converted to a terminal olefin afterward by reductive removal of the iodide for subsequent cross metathesis with (*S*)-**3**. Based on this strategy, all stereoisomers (**2b-2d**) could be synthesized by utilizing each enantiomer of the building blocks.



Scheme 2-2. Synthesis plan of the C1-C14 part of AM3

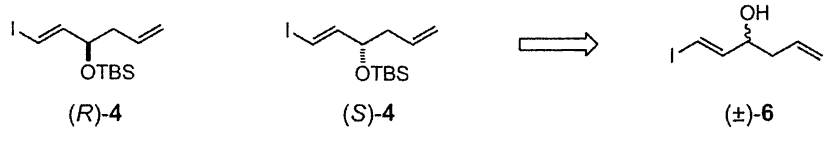
2.2 Synthesis of the building blocks

Synthesis of (*R*)-1-iodo-1,5-hexadiene-3-ol, a precursor of the building block (*R*)-**4**, has been reported by Trost[7] using Brown asymmetric allylation,[8] and by Kobayashi[9] via kinetic resolution of a racemic alcohol by using Sharpless epoxidation, respectively (Scheme 2-3).[10]



Scheme 2-3. Synthesis of (*R*)-1-iodo-1,5-hexadiene-3-ol

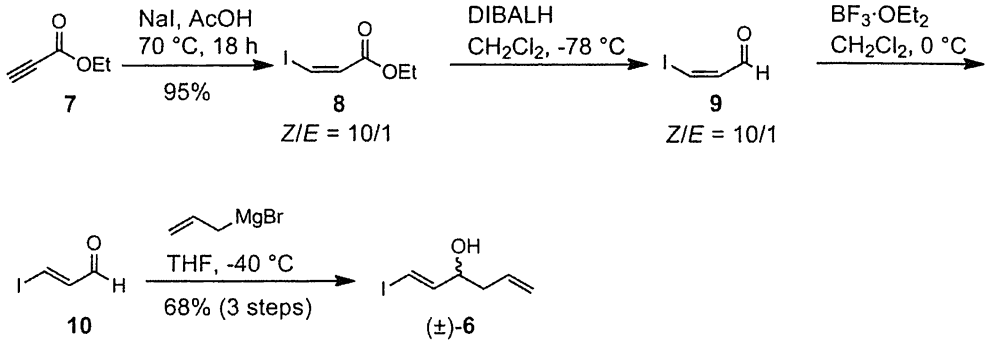
It is envisaged that lipase-catalyzed kinetic resolution of racemic 1-iodo-1,5-hexadiene-3-ol would provide both enantiomers corresponding to precursors of the building blocks (*R*)-**4** and (*S*)-**4** (Scheme 2-4).[11]



(*R*)-**4** (*S*)-**4** (±)-**6**

Scheme 2-4. Synthesis plan of (*R*)- and (*S*)-**4**

Synthesis of the racemic alcohol (±)-**6** is shown in Scheme 2-5. Refer to the report by Trost, aldehyde **10** was prepared from ethyl propionate **7**. Addition of hydrogen iodide to the alkyne **7** with NaI/AcOH resulted in the formation of *Z*-iodoolefin **7** (*Z*:*E* = 10:1) in 95% yield. Reduction of the ester **8** with DIBALH gave aldehyde **9**, which was isomerized to *E*-isomer **10** by treatment with $BF_3 \cdot OEt_2$ in dichloromethane at 0 °C. Treatment of the aldehyde with allylmagnesium bromide furnished alcohol (±)-**6** in 68% for three steps.



Scheme 2-5. Preparation of (±)-**6**

Then, lipase catalyzed kinetic resolution of (±)-**6** was examined using lipase AK (Amano, 10%w/w) in vinyl acetate at 40 °C with monitoring consumption of (±)-**6** by ^{1}H NMR analysis (Table 2-1). After 6 hours, (*R*)-**11** was obtained in 96%ee and (*S*)-**11** was recovered in 57%ee. Although ee of (*S*)-**6** increased with increasing the reaction time, that of (*R*)-**11** decreased with increasing the reaction time. In consideration of the chemical yield and ee, it is decided to terminate the reaction around 10 hours.

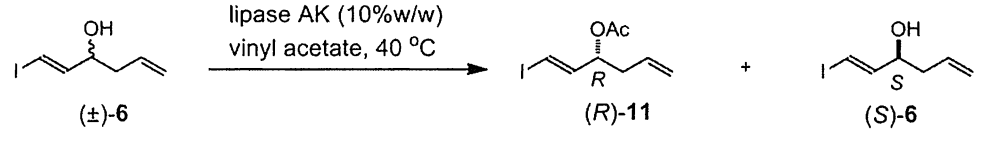


Table 2-1. Lipase catalyzed kinetic resolution of (±)-**6**.

entry	time (h)	ratio[a]	yield/%		% ee[b]	
		(*R*)-**11** : (*S*)-**6**	(*R*)-**11**	(*S*)-**6**	(*R*)-**11**[c]	(*S*)-**6**
1	6	39 : 61	-	-	96	57
2	8	44 : 56	-	-	95	70
3	10	48 : 52	39	52	94	80
4	13	50 : 50	42	52	92	90
5	24	54 : 46	45	50	88	97

[a] Determined by ^{1}H NMR. [b] Determined by HPLC analysis (Chiralpack AD, 250 x 4.6 mm, 1% 2-propanol in hexane, 1 mL/min, 254 nm). [c] ee of (*R*)-**11** was determined by HPLC analysis of corresponding alcohol (*R*)-**6**.

Optical purity of the alcohol (*S*)-**6** was determined by HPLC analysis using a chiral column (Chiralpack AD) and that of acetate (*R*)-**11** was determined by HPLC analysis of corresponding alcohol (*R*)-**6** obtained by methanolysis of the acetate (Figure 2-1). Absolute configuration of (*R*)-**6** was determined by optical rotation and modified Mosher method[12] as shown in Scheme 2-6.

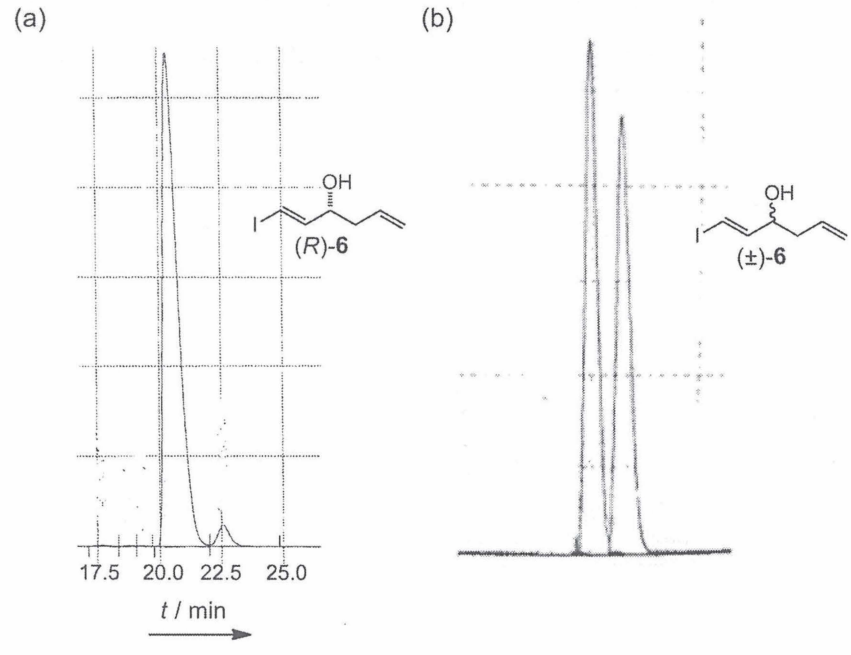
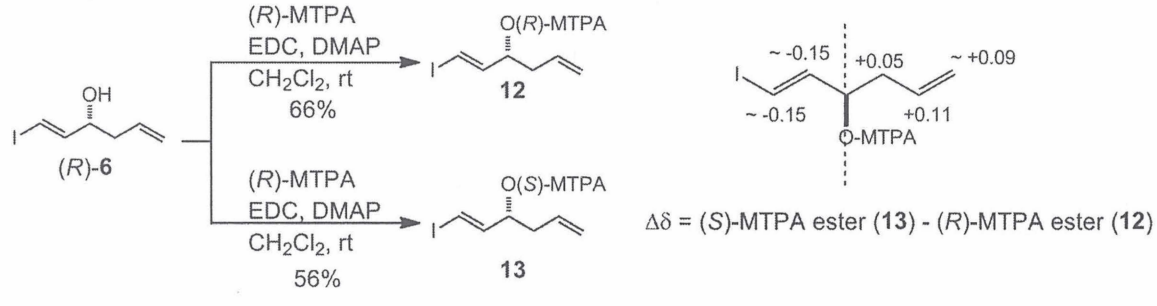
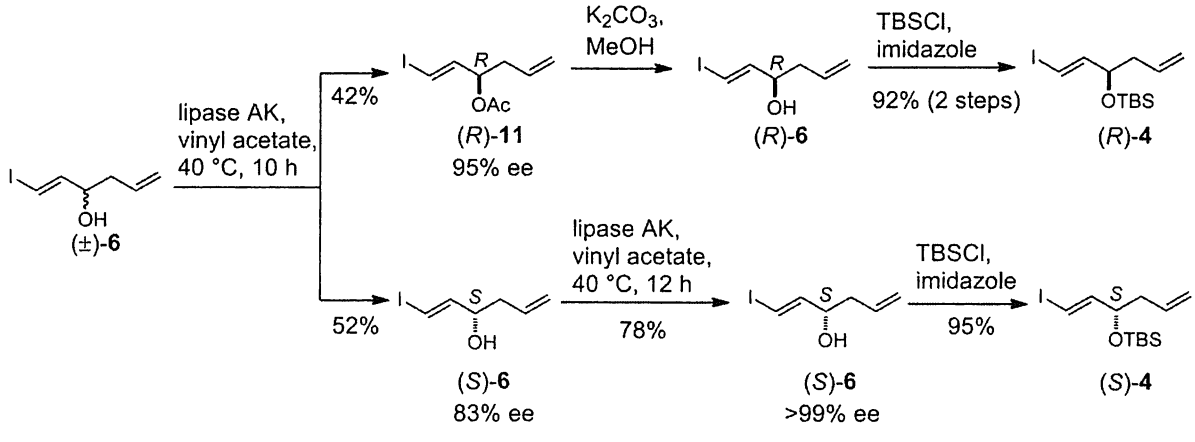


Figure 2-1. Determination of ee by HPLC analysis using a chiral column. (a) (*R*)-**6**, (b) (±)-**6** [Chiralpack AD, ϕ 4.6 x 250 mm, 1% 2-propanol in hexane, 1 mL/min, UV detection (254 nm)]



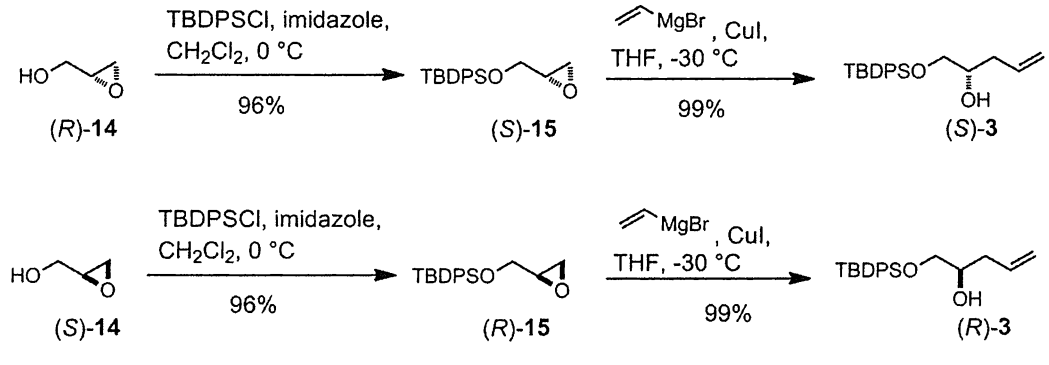
Scheme 2-6. Determination of the absolute configuration of (*R*)-**6** by modified Mosher method

Large scale synthesis of the building blocks (*R*)-**4** and (*S*)-**4** was carried out as shown in Scheme 2-7. Under the optimized conditions, racemic alcohol (±)-**6** (29.3 g) was treated with 10% w/w lipase AK (Amano) in vinyl acetate at 40 °C for 10 h to furnish acetate (*R*)-**11** (42%, 94% ee) and alcohol (*S*)-**6** (59%, 83% ee). The optical purity of (*S*)-**6** was improved to >99% ee by re-treatment with lipase AK. Methanolysis of the acetate (*R*)-**11**, followed by treatment with TBSCl in the presence of imidazole furnished the building block (*R*)-**4** in 92% for two steps. Protection of the secondary alcohols of (*S*)-**6** as TBS ether afforded the building block (*S*)-**4** (99%).



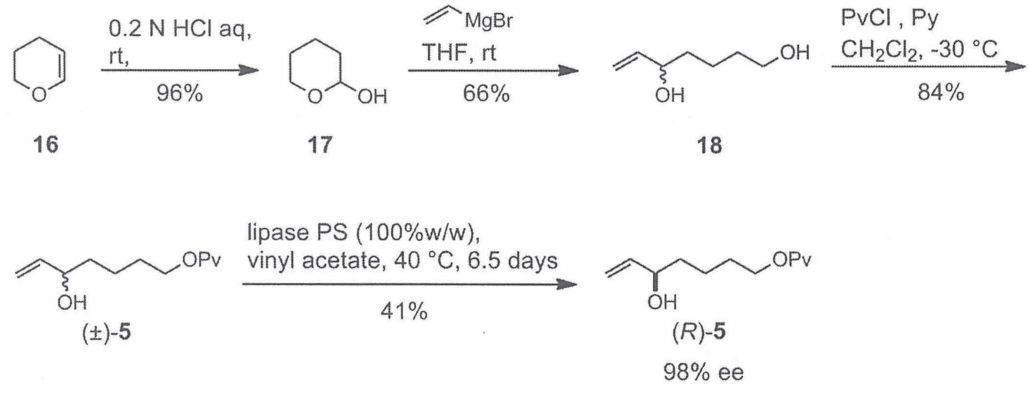
Scheme 2-7. Preparation of (*R*)- and (*S*)-**4**

Building blocks (*S*)-**3** and (*R*)-**3** were synthesized by the known procedure starting from (*R*)- and (*S*)-glycidol, respectively, via ring opening of epoxide (*R*)- and (*S*)-**15** with vinylmagnesium bromide in the presence of CuI.[13]



Scheme 2-8. Preparation of the building blocks (*R*)- and (*S*)-**3**

Building block (*R*)-**5** was synthesized via kinetic resolution catalyzed by lipase (Scheme 2-9). Racemic alcohol (±)-**5** was prepared by the known procedute,[14] i.e. hydrolysis of 3,4-dihydro-2*H*-pyran **16** with aqueous HCl, followed by treatment with the resulting hemiacetal **17** with vinylmagnesium bromide. Selective protection of the primary alcohol as a pivaloate furnished racemic compound (±)-**5**. Lipase catalyzed kinetic resolution of (±)-**5** with lipase PS (Amano) 100%w/w in vinyl acetate at 40 °C for 6.5 days afforded (*R*)-**5** in 41% yield in 98%ee. The optical purity of (*R*)-**5** was determined by HPLC analysis using a chiral column (Chiralpack AD) as shown in Figure 2-2. Absolute configuration of (*R*)-**5** was determined by modified Mosher method[12] as shown in Scheme 2-10.



Scheme 2-9. Preparation of the building block (*R*)-**5**

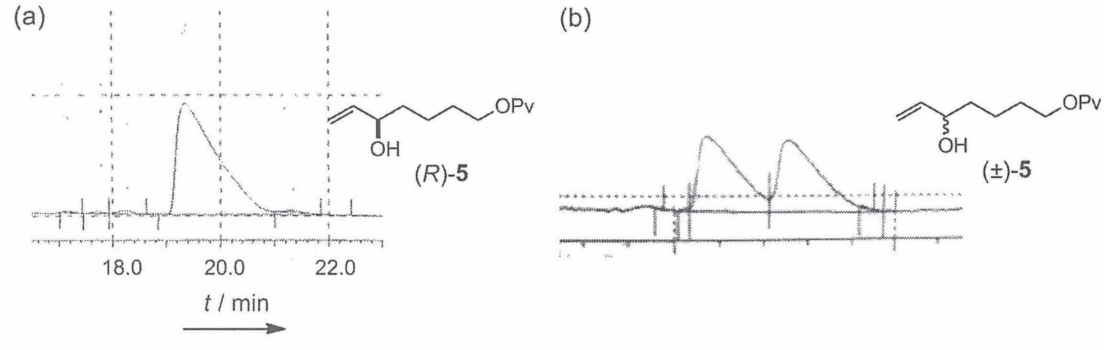
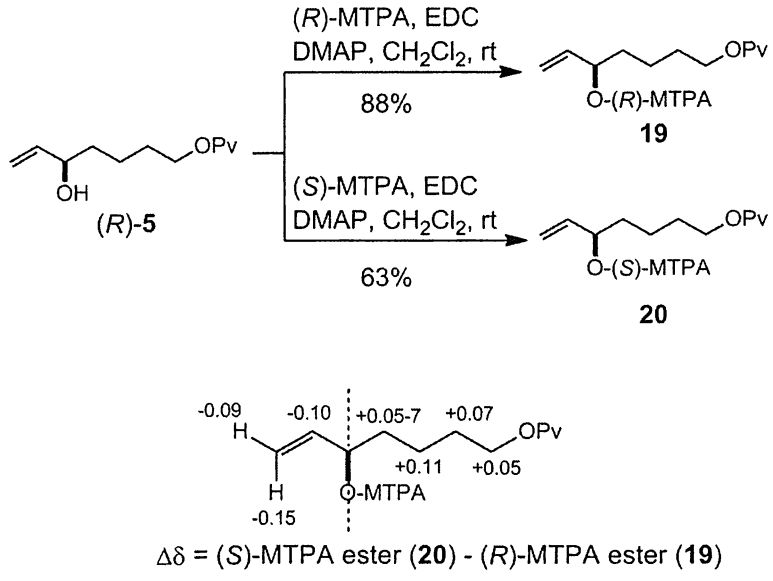


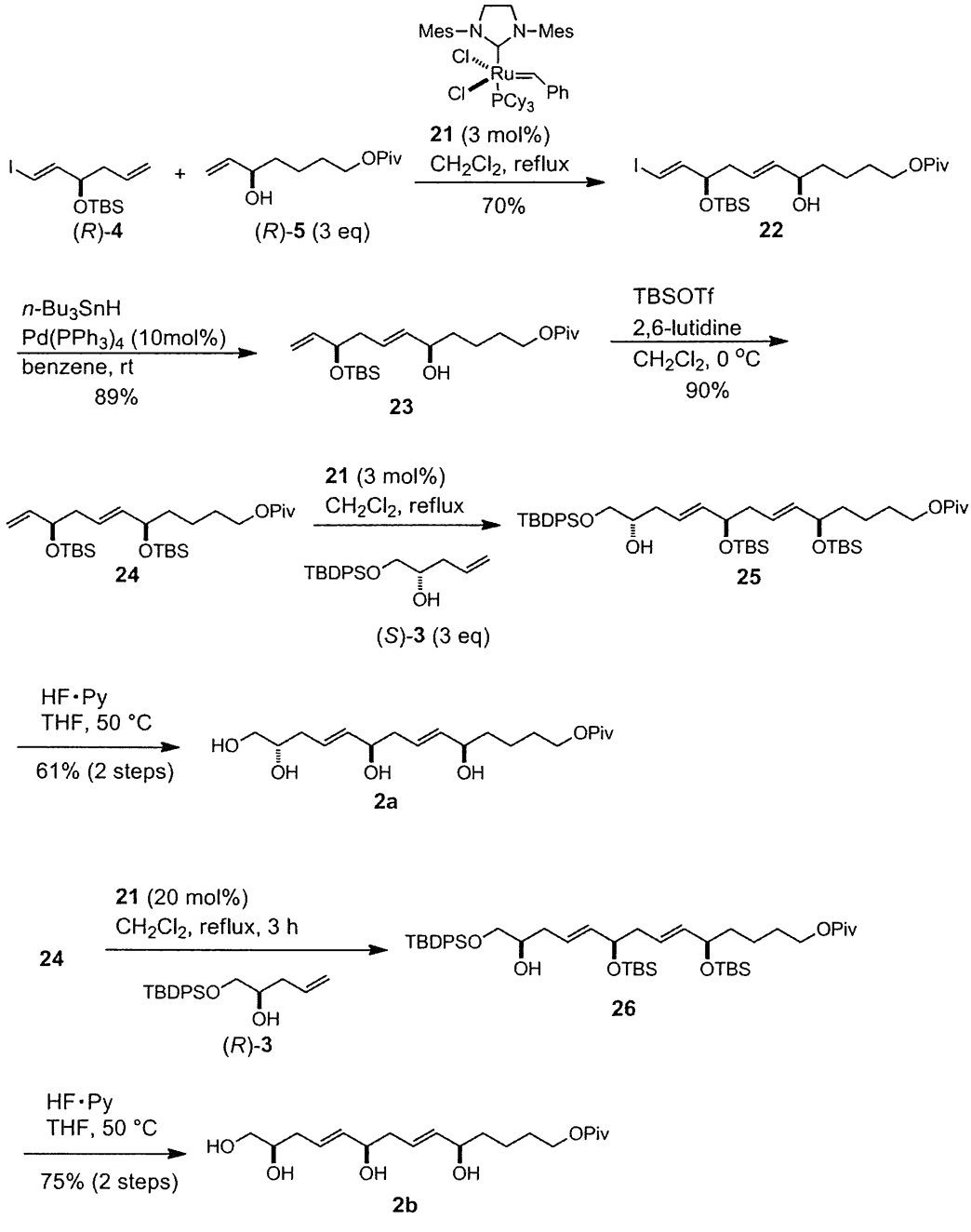
Figure 2-2. Determination of ee by HPLC analysis using chiral column. (a) (*R*)-**5**, (b) (±)-**5** [Chiralpack AD, ϕ 4.6 x 250 mm, 1% 2-propanol in hexane, 1 mL/min, UV detection (220 nm)]



Scheme 2-10. Determination of the absolute configuration of (*R*)-**5** by modified Mosher method

2.3 Synthesis of the C1-C14 part and its diastereomers

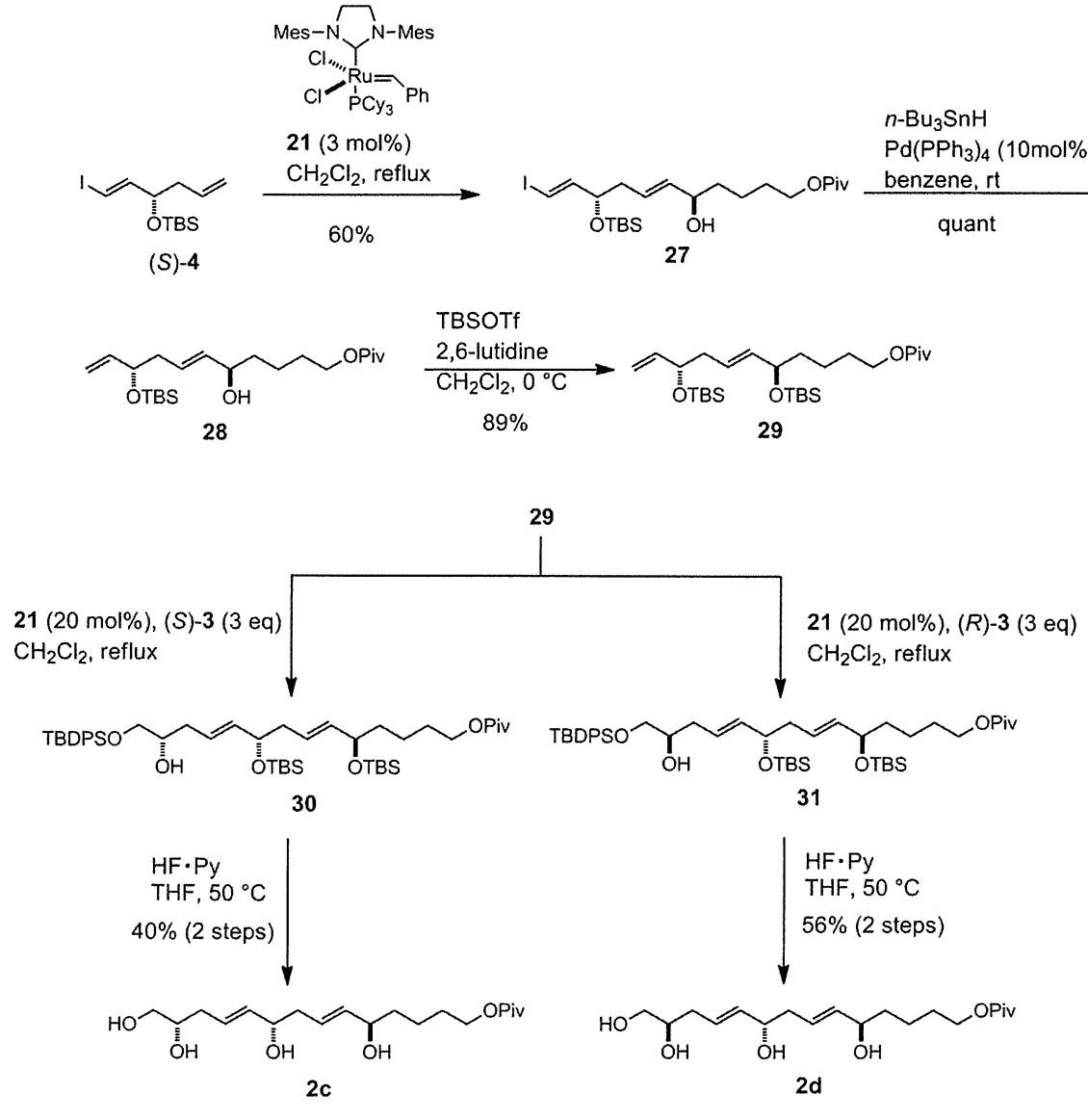
Synthesis of the C1-C14 part (2*S*, 6*R*, 10*R*)-**2a** commenced with cross metathesis of (*R*)-**4** using three equivalents of (*R*)-**5** by the action of Grubbs second generation catalyst **18** (Scheme 2-11).[15] As expected, chemoselective cross coupling between the terminal olefins was successfully achieved in the presence of iodoolefin to afford diene **22** in 70% yield (>*E*:*Z* = 10:1), presumably due to the steric hindrance of the iodoolefin moiety. Reductive removal of the iodide with Bu_3SnH in the presence of $Pd(PPh_3)_4$[16] followed by protection of the secondary alcohol with TBS ether to provide **24**. Subsequent conventional cross metathesis with three equivalents of (*S*)-**3** proceeded smoothly to provide diene **25** (>*E*:*Z* = 10:1). Removal of all silyl groups with HF·Py afforded (2*S*, 6*R*, 10*R*)-**2a**. On the other hand, cross metathesis of **24** with (*R*)-**3** followed by removal of the silyl groups furnished (2*R*, 6*R*, 10*R*)-**2b**.



Scheme 2-11. Synthesis of C1-C14 part **2a** and its C2 diastereomer **2b**

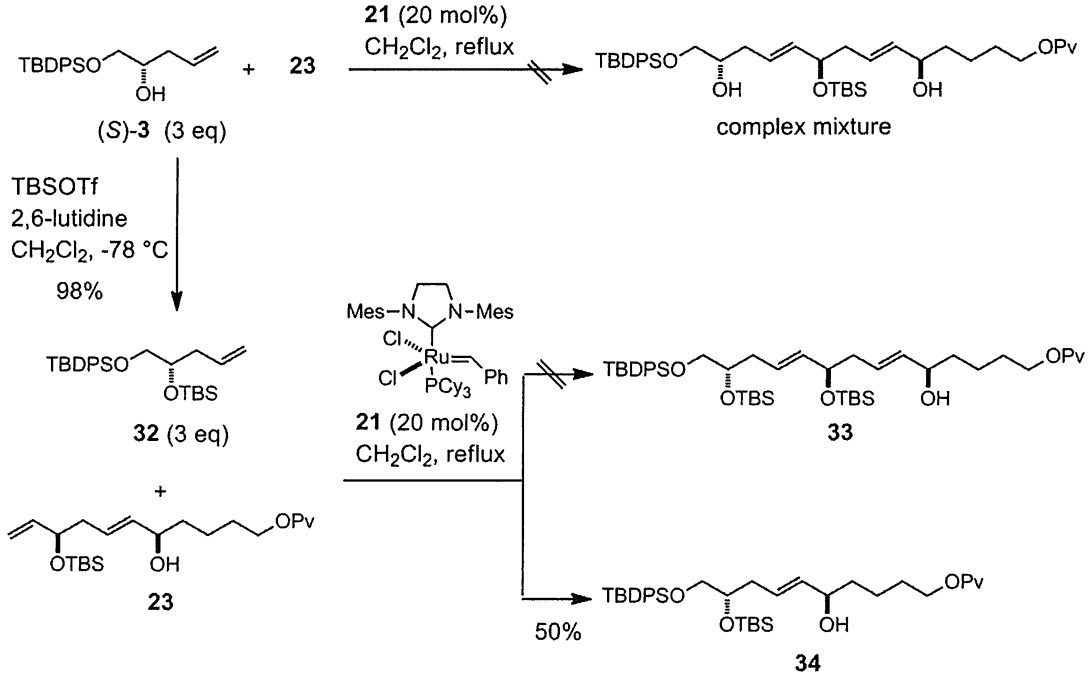
In an analogous sequence, other diastereomers (2*S*, 6*S*, 10*R*)-**2c** and (2*R*, 6*S*, 10*R*)-**2d** were also synthesized from (*S*)-**4** (Scheme 2-12). Chemoselective cross metathesis of (*S*)-**4** using three equivalents of (*R*)-**5** by the action of Grubbs second generation catalyst **21** giving diene **27** (60%, >*E*:*Z* = 10:1), was followed by reductive removal of the iodide with

$Bu_3SnH/Pd(PPh_3)_4$ and protection of the secondary alcohol as TBS ether to provide **29**. Subsequent conventional cross metathesis with three equivalents of (*S*)-**3** giving diene **30** (>*E*:*Z* = 10:1), followed by removal of all silyl groups with HF·Py afforded (2*S*, 6*S*, 10*R*)-**2c** in 40% for two steps. On the other hand, cross metathesis of **29** with (*R*)-**3** and subsequent removal of the silyl groups furnished (2*R*, 6*S*, 10*R*)-**2d**.

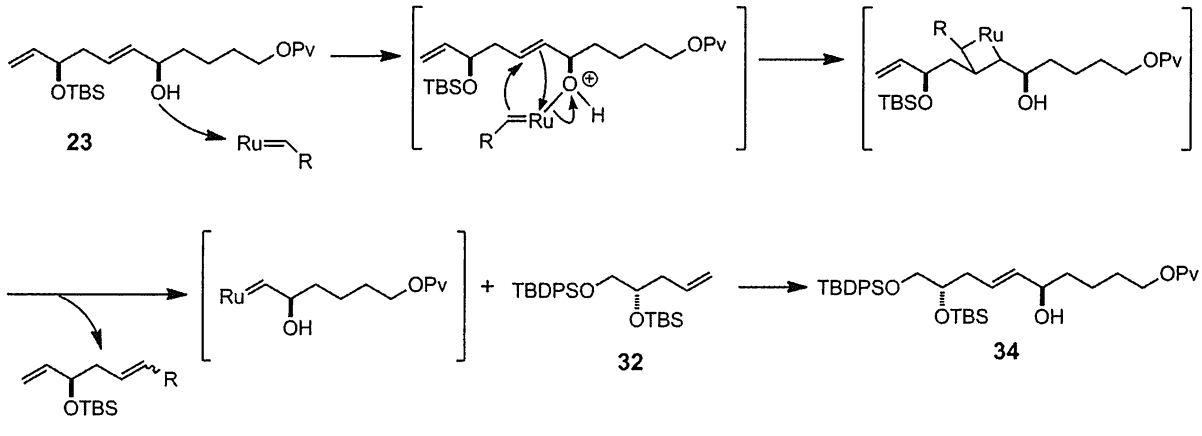


Scheme 2-12. Synthesis of diastereomers **2c** and **2d**

To achieve the successful chemoselective cross metathesis reaction, it is important to choose the building blocks with protection or without protection of the secondary alcohols (Scheme 2-13). Cross metathesis of unprotected **23** with unprotected (*S*)-**3** resulted in the formation of complex mixture, and that with protected **32** did not produce **33** but byproduct **34** in 50% yield, presumably due to cross metathesis with the internal olefin by coordination of Grubbs catalyst **18** to the alcohol (Scheme 2-14).



Scheme 2-13. Unsuccessful cross metathesis reactions



Scheme 2-14. Plausible reaction pathways giving byproduct **34**

Having obtained the diastereomers corresponding to the C1-C14 moiety, NMR spectra of **2a~2d** were compared with those of AM3. ^{1}H NMR spectra were virtually indistinguishable among the diastereomers with respect to either chemical shift or *J*-coupling patterns, due to the remote (1,5-) stereogenic centers.[17] The differences in the carbon chemical shifts of C1 to C9 between AM3 and **2a~2d** (125 MHz, 1:1 C_5D_5N/CD_3OD, 30 °C)[18] were also insignificant and within 0.2 ppm, as shown in Figure 2-3. However, the deviations at C4 of the 2,6-*syn* isomers (**2b** and **2c**) appeared to be lower than those of the 2,6-*anti* isomers (**2a** and **2d**). Since the absolute configurations at C6 and C10 in AM3 (**1**) were determined to be (6*R*, 10*R*) by the modified Mosher method, the stereochemistry at C2 became controversial.

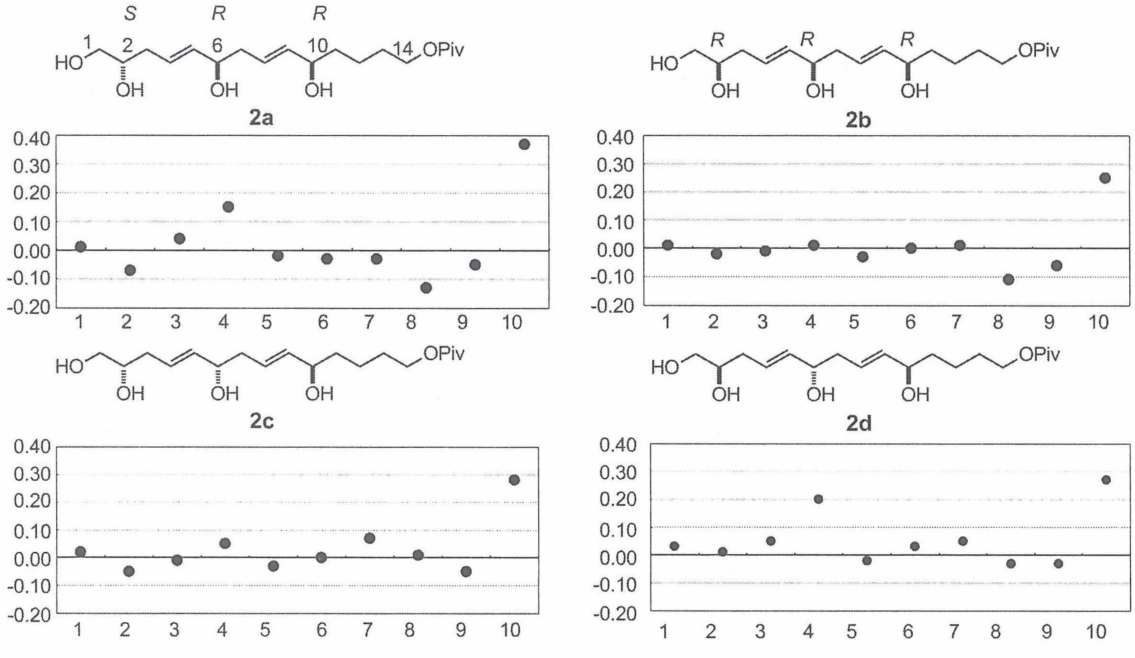
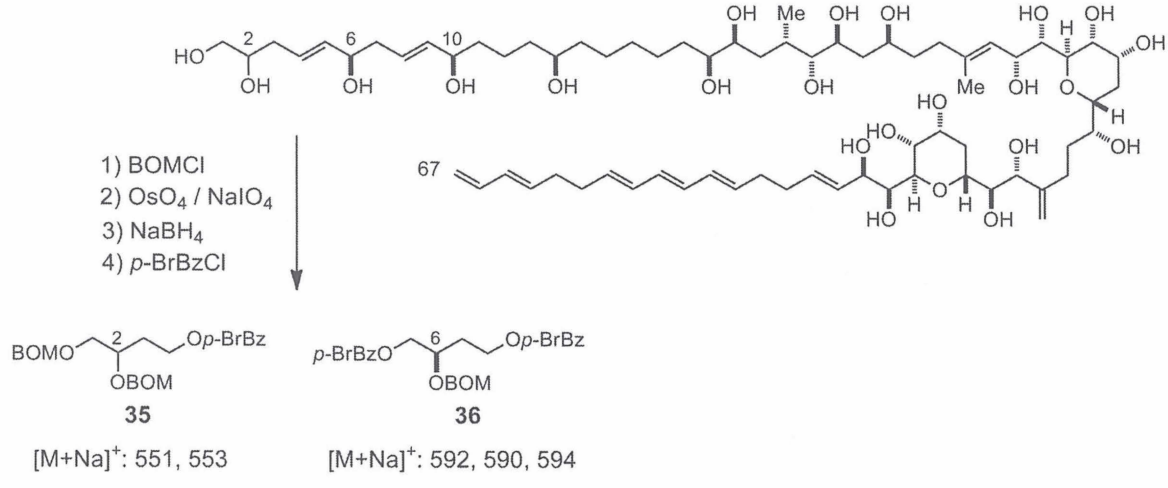


Figure 2-3. Differences in carbon NMR (125 MHz, 1:2 C_5D_5N/CD_3OD, 30 °C) chemical shifts between AM3 and the synthetic fragments (**2a~2d**). The x- and y-axes represent carbon number and Δδ (Δδ = δAM3 – δsynthetic **2** in ppm), respectively.

2.4 Degradation of the natural product and structure confirmation

Therefore, it was decided to re-confirm the absolute configuration at C2. Degradation of AM3 was previously carried out via oxidative cleavage of the double bond (C4-C5) in four steps (Scheme 2-15), i.e. protection of the hydroxy groups of AM3 as BOM ethers, 2) oxidative cleavage of the olefins with $OsO_4/NaIO_4$, 3) reduction of the resuting carbonyl

compounds with $NaBH_4$, and 4) protection of the resulting alcohols as *p*-bromobenzoate to afford compound **35**, with concomitant formation of **36** via cleavage of the C4-C5 and C8-C9 double bonds. The product **35** was analyzed by HPLC with UV detection (Figure 2-4).[18] Retention time of the degradation product **35** was identical with the authentic sample (*S*)-**37**, indicating that the absolute configuration at C2 is *S*. The fraction corresponding to the retention time around 17.0 min was collected and identified by MS analysis to give molecular ion peaks m/z = 551 and 553 $[M+Na]^+$, which correspond to the compound **35**.



Scheme 2-15. Degradation of AM3 and structures of resultant

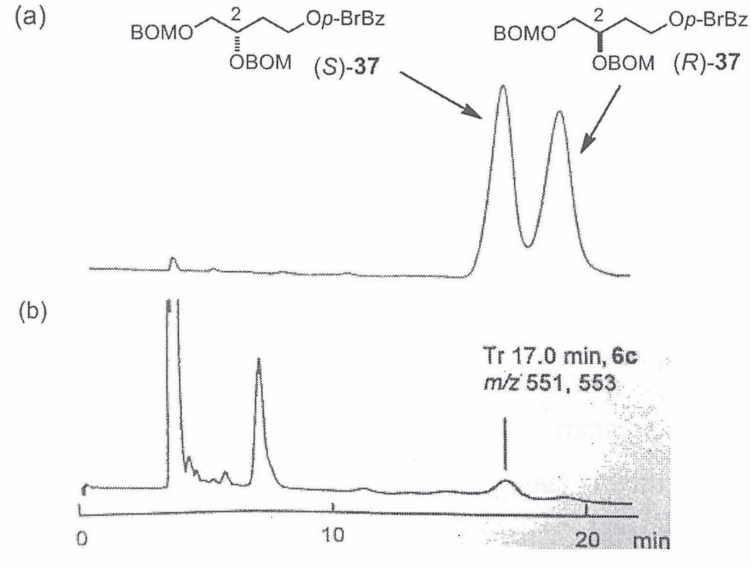
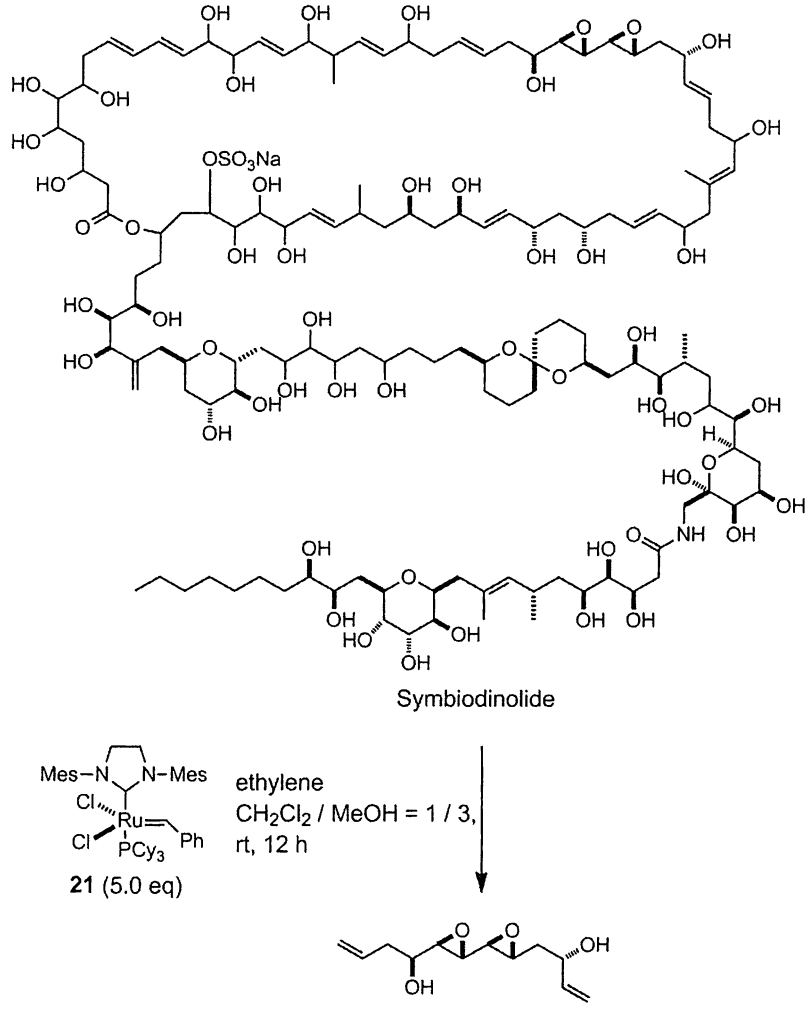


Figure 2-4. HPLC analysis using a chiral column of (a) authentic samples and (b) the degradation product derived from AM3

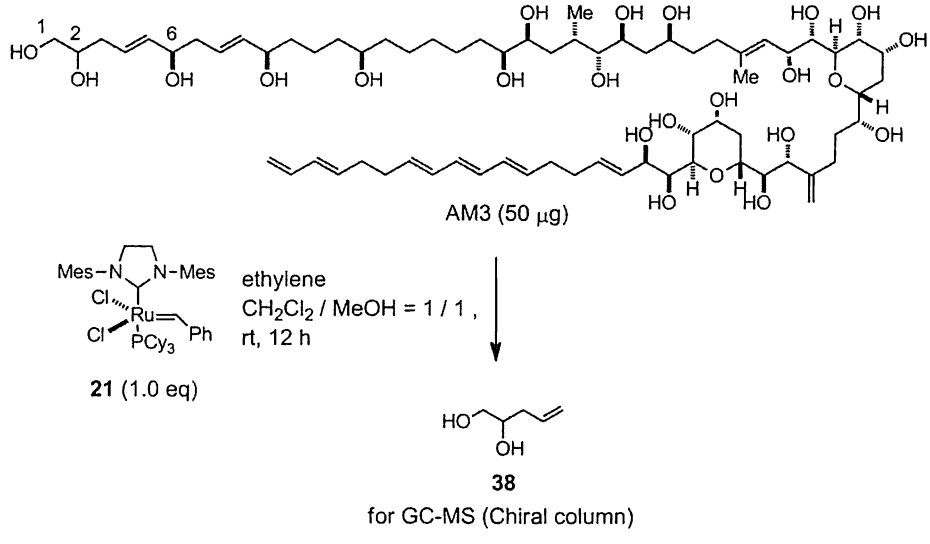
Although degradation of AM3 was carried out using a small amount of sample (~10 μmol) because of the limited availability of the natural product, it takes several synthetic operations. Uemura and co-workers reported the degradation of symbiodinolide using olefin metathesis for the structure elucidation of the natural product (Scheme 2-16).[20]



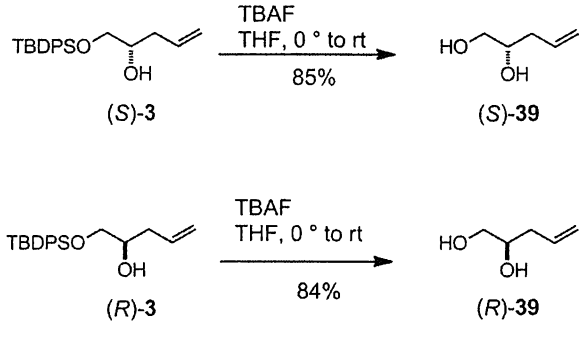
Scheme 2-16. Degradation of symbiodinolide by using olefin metathesis by Uemura

Therefore, this single step manipulation using olefin metathesis was applied to the degradation of AM3 (Scheme 2-17). For unambiguous identification of the minute degradation product, a GC-MS instrument equipped with a chiral capillary column (Varian CP-Chirasil-DEX CB) was used according to the procedure applied in the case of maitotoxin.[21] As shown in Scheme 2-16, a solution of AM3 (ca. 50 μg, estimated by the ε

value from the UV spectra) in 1:1 CH_2Cl_2/MeOH was treated with Grubbs catalyst **21** in the presence of ethylene for 15 h at room temperature, and the product **38** was analyzed by GC-MS. Authentic samples (*S*)-**39** and (*R*)-**39** were synthesized from the building blocks (*S*)-**3** and (*R*)-**3** by treatment with TBAF (Scheme 2-17). Retention times of the authentic samples (*S*)-**39** and (*R*)-**39** were 9.87 min and 9.96 min, respectively, and that of the degradation product **38** was identical with (*R*)-**39** as shown in Figure 2-5, indicating that the absolute configuration at C2 is *R* (Fugure 2-6).



Scheme 2-17. Degradation of AM3 by using olefin metathesis



Scheme 2-18. Preparation of authentic samples (*S*)- and (*R*)-**39**

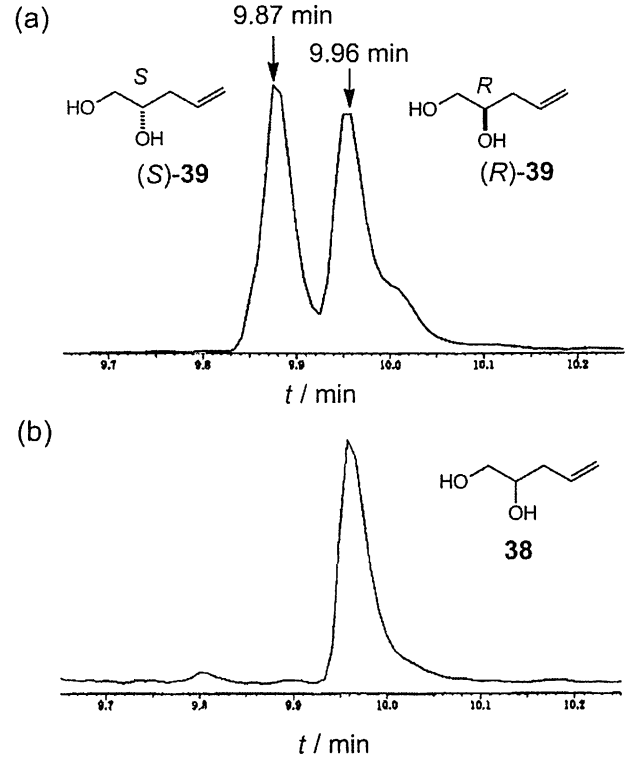


Figure 2-5. Gas chromatograms using chiral capillary column of (a) authentic samples (*S*)- and (*R*)-**39**, and (b) fragment from AM3 (**38**) [Varian Chirasil-DEX CB, Chrompack, 0.25 mm x 25 m, Helium, The column temperature was kept at 50 °C for the first 5 min. Then its temperature was raised by 20 °C/min to 130 °C and kept for 10 min]

The reason for the misassignment in the original configuration is unclear; one of the possible explanations is that the sample for HPLC analysis was contaminated with ozonolysis products derived from the other portions of AM3, and one of these fragments exhibited a peak with a similar retention time to that of the synthetic enantiomer of 1,2,4-butanetriol, while the fragment from the natural product provided no detectable peak due to the small sample size subjected to the degradation reaction sequence including three steps of derivatization.[18-19]

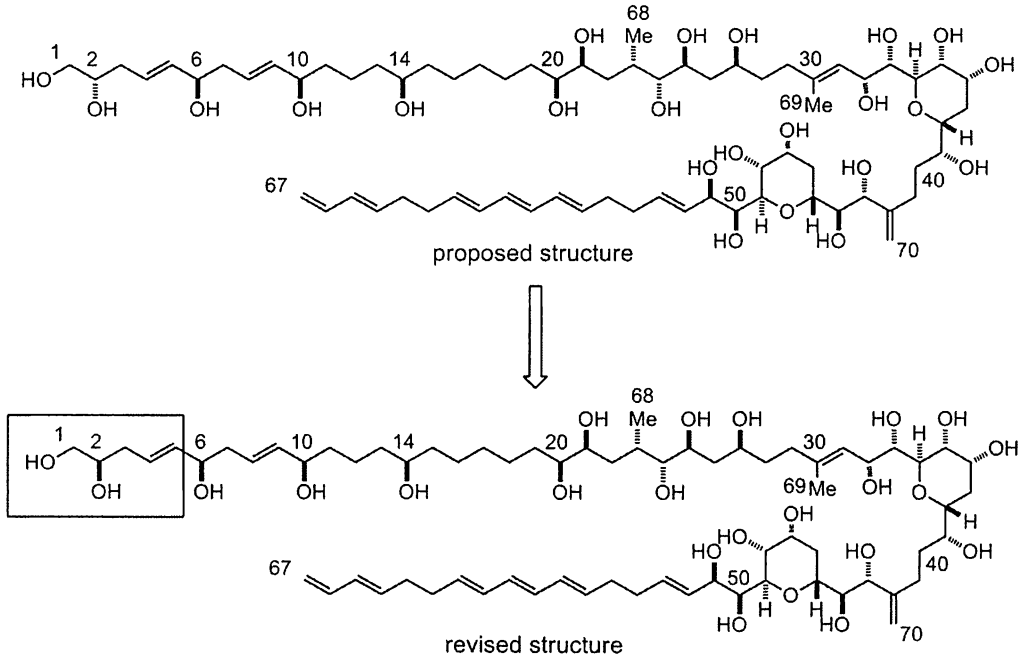


Figure 2-6. Revised structure of AM3

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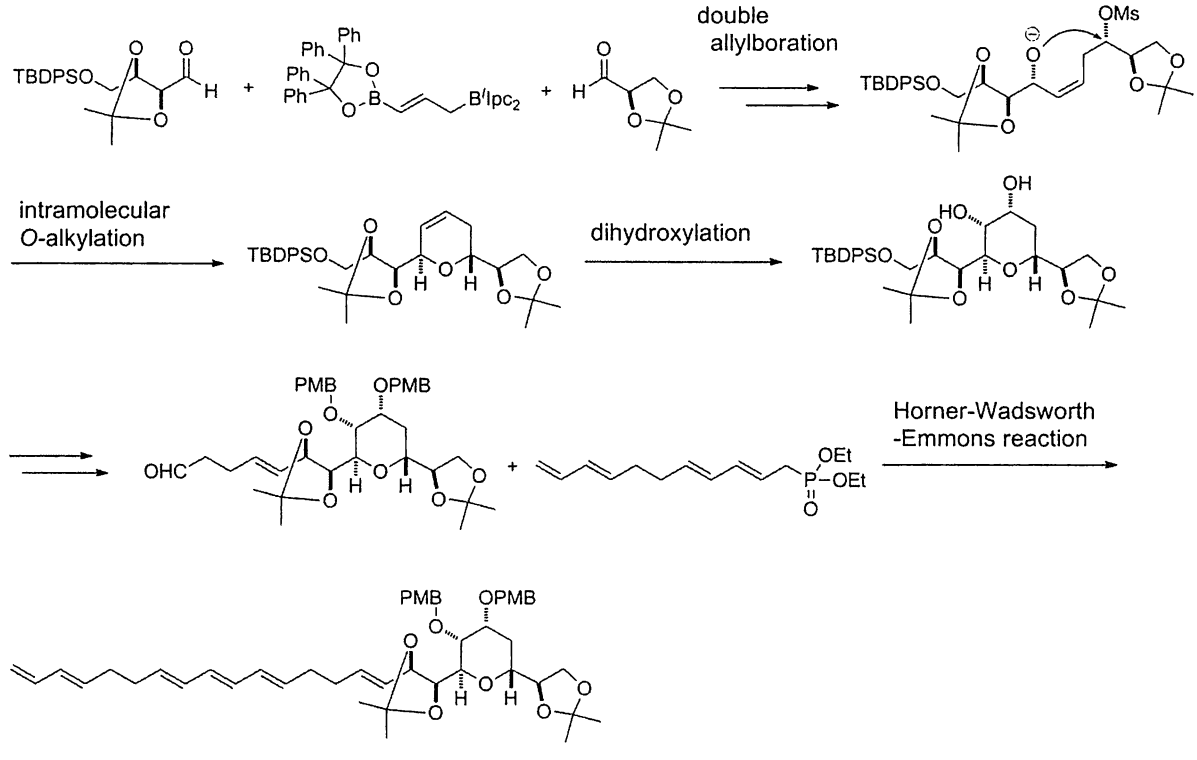
Chapter 3. Synthesis and structure confirmation of the C43-C67 part of amphidinol 3

3.0 Introduction

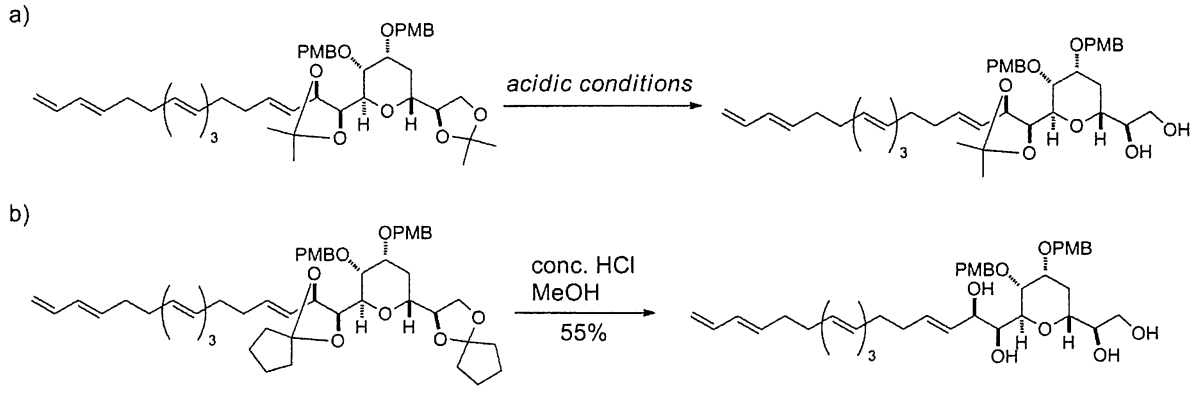
As mentioned in Chapter 1 (Section 1-4), syntheses of the partial structures containing the C43-C67 part of AM3 have been reported by Roush,[1] Rychnovsky,[2] and Paquette,[3] independently. For the construction of the tetrahyropyran ring system, Roush utilized asymmetric double allylboration giving a precursor of subsequent intramolecular *O*-alkylation (Scheme 3-1) to give a dihydropyran. Diastereoselective dihydroxylation of the *Z*-olefin with OsO_4 furnished the tetrahydropyran system. Polyolefinic side chain was introduced by using Horner-Wadsworth-Emmonns reaction to afford the C43-C67 part of AM3.



Scheme 3-1. Synthesis of the C43-C67 part of AM3 by Roush

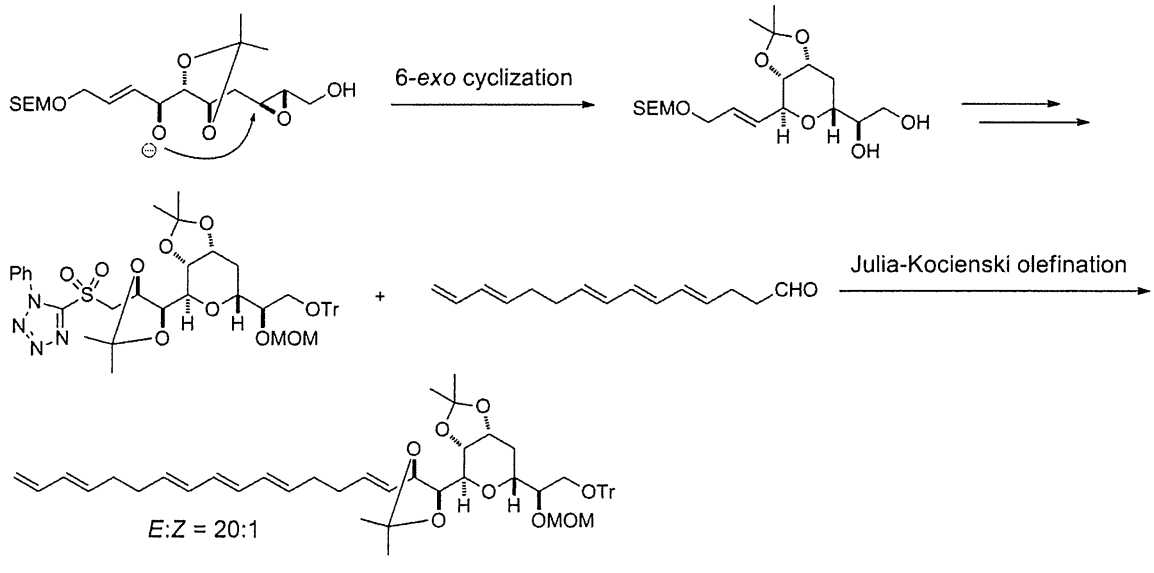
However, removal of the acetonide group under the acidic conditions was unsuccessful to yield a tetraol in low (<20%) yield (Scheme 3-2), presumably due to the acid labile nature of

the polyene and allylic alcohol moieties, while that of cyclohexylidene counterpart resulted in moderate yield (55%).



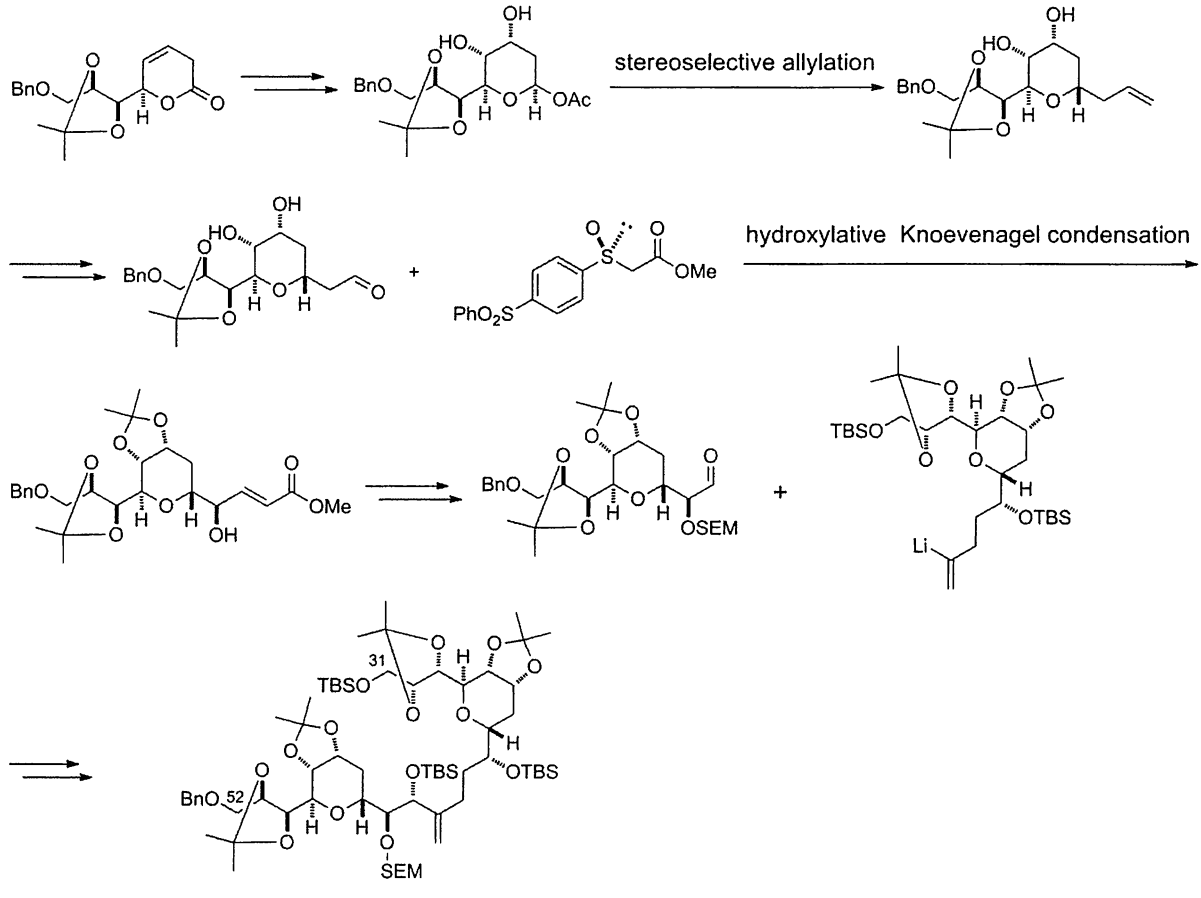
Scheme 3-2. Removal of protecting groups under the acidic conditions: a) acetonide, and b) cyclopentylidene acetal.

Paquette utilized intramolecular ring-opening of an epoxide for the construction of the tetrahydropyran ring, which was converted to a sulfone (Scheme 3-3), and subsequent Julia-Kocienski olefination with an aldehyde corresponding to the olefinic side chain (C53-C67) afforded the C43-C67 part of AM3.



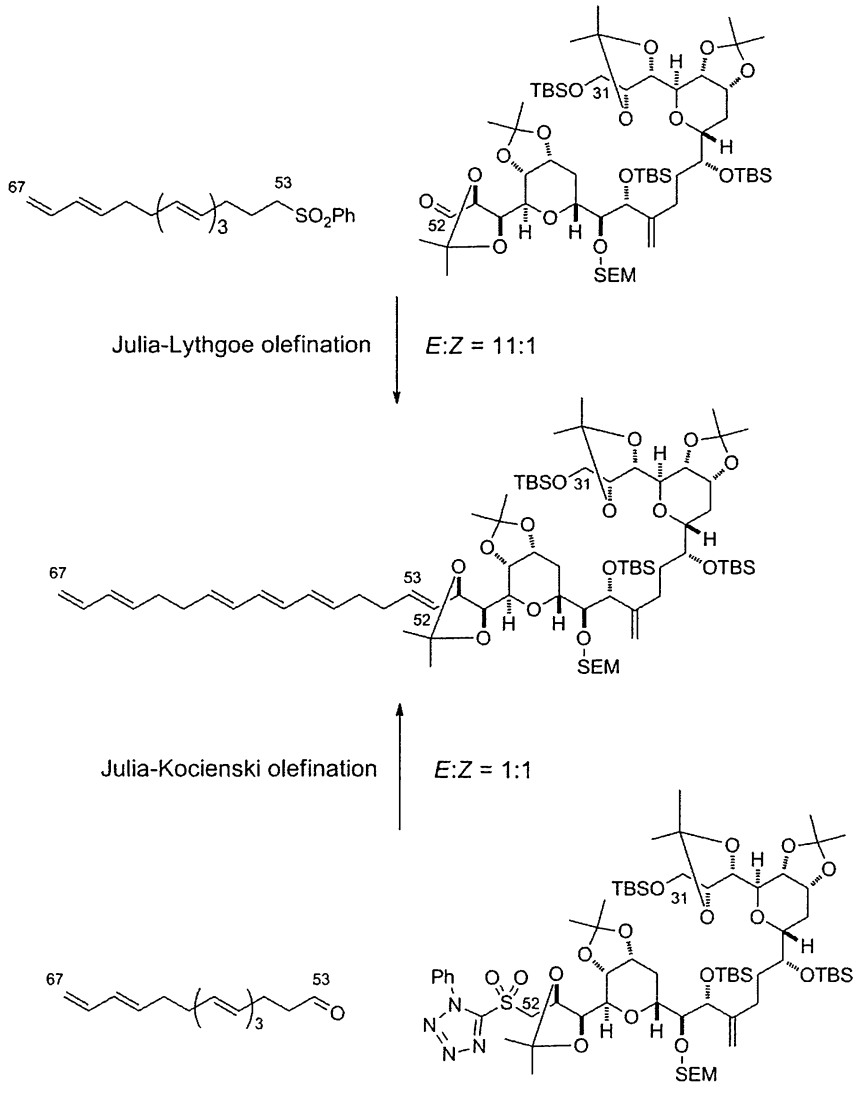
Scheme 3-3. Synthesis of the C43-C67 part of AM3 by Paqutte

Rychnovsky reported synthesis of an advanced intermediate of AM3 corresponding to the C31-C67 part (Scheme 3-4). The tetrahydropyran ring system was constructed through Lewis acid catalyzed allylation of an acetal derived from a lactone, and hydroxylative Knovenagel condensation with a chiral sulfoxide. Then, coupling with another tetrahydropyran moiety afforded the C31-C52 part.



Scheme 3-4. Synthesis of the C31-C52 part of AM3 by Rychnovsky

Introduction of the olefinic side chain was examined via different mode of Julia-type olefination sequences (Scheme 3-5). Julia-Lythgoe olefination of a sulfone (C53-C67) and aldehyde (C31-C52) proceeded selectively to afford the C31-C67 part of AM3 (*E*:*Z* = 11:1), while Julia-Kocienski olefination of a sulfone (C31-C52) and an aldehyde (C53-C67) resulted in low selectivity (*E*:*Z* = 1:1).

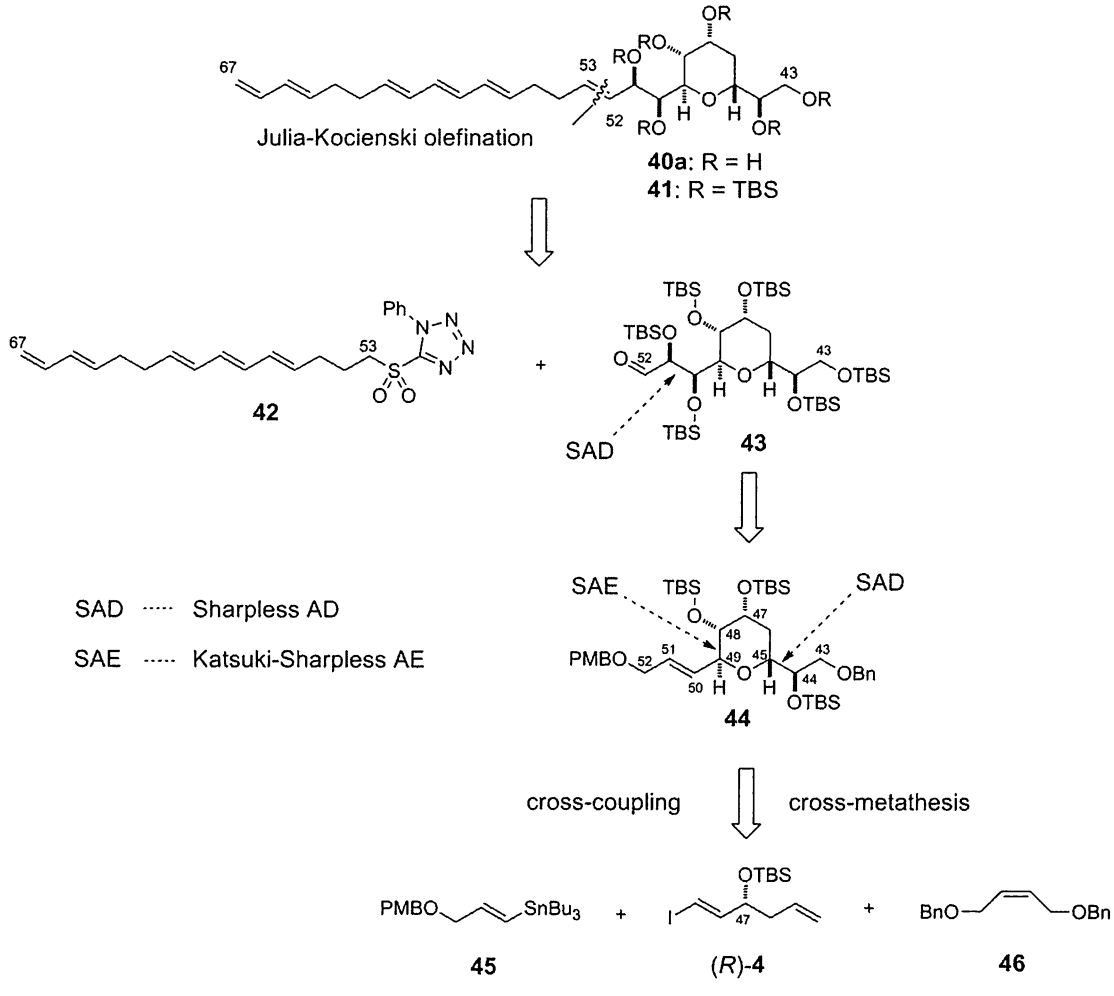


Scheme 3-5. Synthesis of the C31-C67 part of AM3 by Rychnovsky

3.1 Synthesis plan

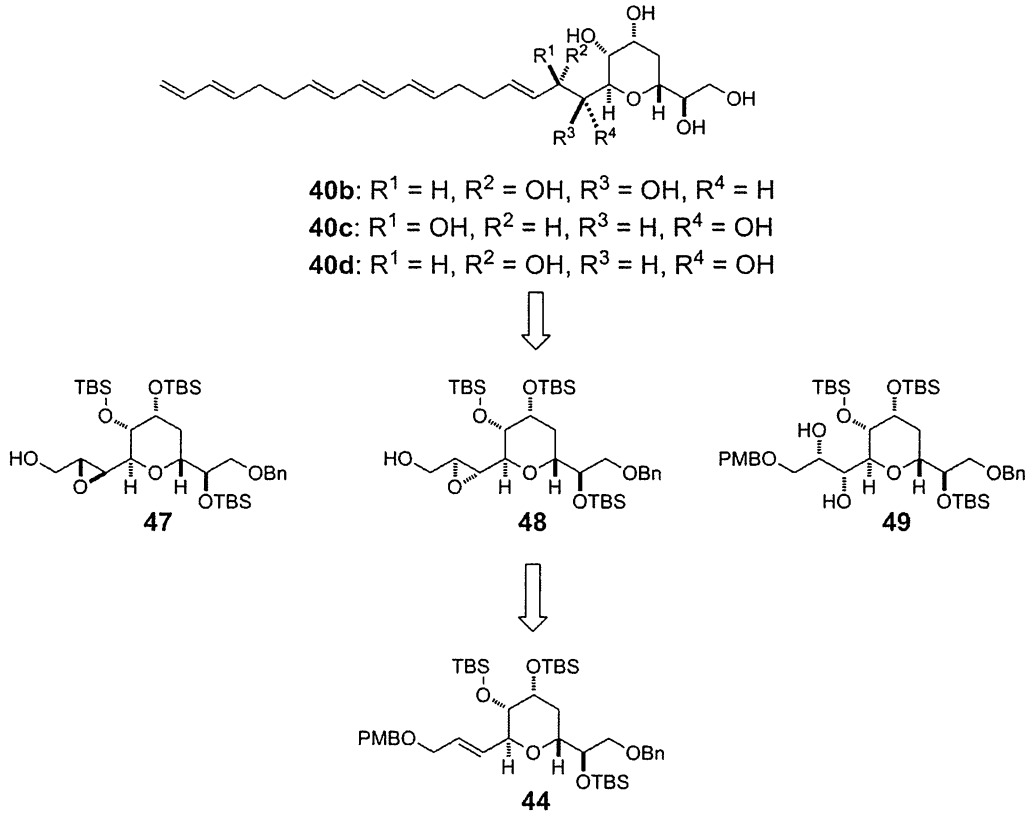
A novel strategy for synthesizing the C43-C67 part **40a** was envisaged as shown in Scheme 3-6. Considering the labile nature of the polyene and allylic alcohol moiety under the acidic conditions, TBS group was selected as protecting groups of the polyols, which can be removed under the mild conditions (HF·Py). Refer to the report by Rychnovsky (Scheme 3-5), the polyene moiety is to be introduced by Julia-Kocienski olefination[4] of aldehyde **43** corresponding to the C43-C52 part using sulfone **42** corresponding to the C52-C67 part. The

stereogenic centers of **43** would be installed by means of Sharpless asymmetric dihydroxylation (SAD)[5] with respect to C51-C50 and C45-C44, and Katsuki-Sharpless asymmetric epoxidation (SAE)[6] at C49-C48 via 6-*endo-tet* cyclization.[7] The remaining stereogenic center corresponding to C47 was to be derived from iodoolefin (*R*)-**4**, synthesized via lipase-catalyzed kinetic resolution (Chapter 2),[8] through its attachment to building blocks **46** and **45** by means of cross-metathesis and cross-coupling reactions, respectively.



Scheme 3-6. Synthesis plan of the C43-C67 fragment (**40a**) of AM3.

Based on the strategy, other diastereomers, with respect to C51 (**40b**), C50 (**40c**), and C50,C51 (**40d**), would be synthesized from the common intermediate **44** as shown in Scheme 3-7, by means of the reagent controlled asymmetric oxidations, i.e. SAE using D-(-)-DET and L-(+)-DET (**47** and **48**), and SAD using AD-mix-α (**49**).



Scheme 3-7. Synthesis plan of the diastereomers (**40b-40d**) corresponding to the C43-C67 part of AM3

3.2 Synthesis of the tetrahydropyran system corresponding to the C43-C52 part of amphidinol 3

As mentioned in Chapter 2 (Section 2-3), chemoselective cross-metathesis of the iodoolefin (*R*)-**4** was utilized for stereoselective synthesis of the C1-C14 unit of AM3[8-9] as a key step. The method was also applied for coupling with *Z*-olefin **46** as shown in Table 3-1. The cross-metathesis reaction of the terminal olefin of (*R*)-**4** with two or four equivalents of *Z*-olefin **46**[10] using 10 mol% Grubbs 2nd-generation catalyst **21**[11] in CH_2Cl_2 at 40 °C (reflux) proceeded selectively in the presence of the iodoolefin to afford diene **50** in 65 and 88% yields as a mixture of *E*- and *Z*-isomers in a 5.0 : 1 ratio (entries 1 and 2). Attempts to improve the *E*/*Z* ratio by using solvents of higher boiling points were unsuccessful, e.g., *E*/*Z* = 4.3 : 1 in 1,2-dichloroethane at 83 °C (entry 3) and 3.5 : 1 in toluene at 110 °C (entry 4). The

catalyst loading could be reduced to 2 mol% (entry 5), however the yield of **7** (71%) and the *E*/*Z* ratio (4.0 : 1) were somewhat lower than those in entry 2.

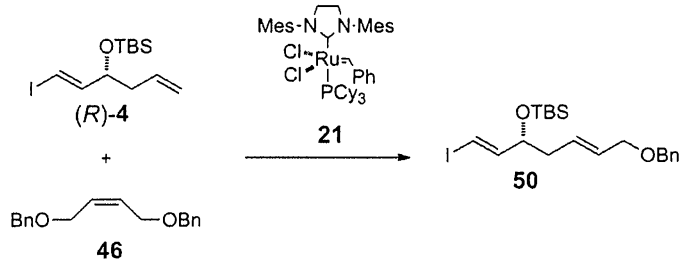


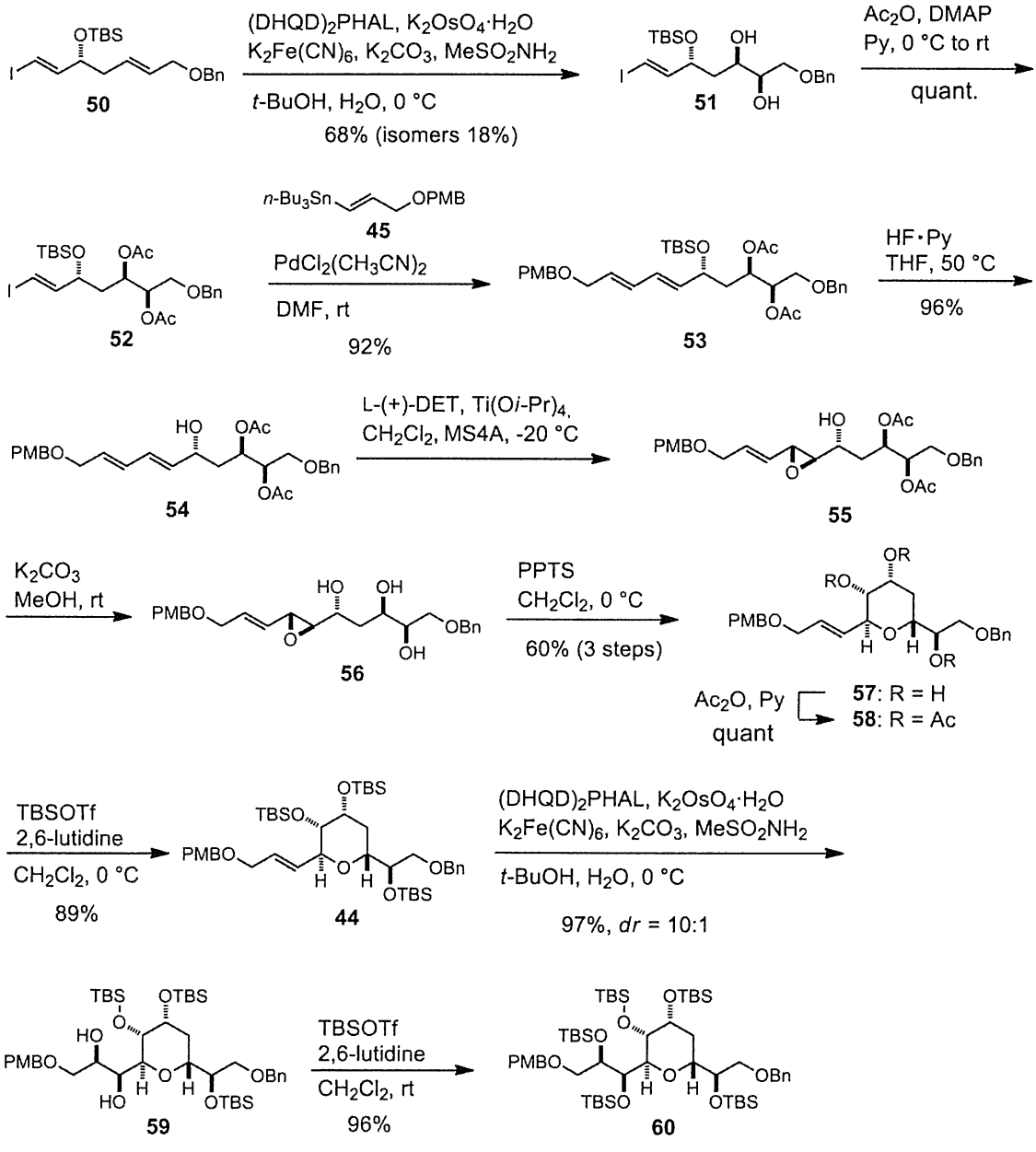
Table 3-1. Chemoselective cross-metathesis of (*R*)-**4** and **46**.

entry	**46** /eq	Solvent	temp / °C[a]	yield / %	*E*/*Z* ratio[b]
1[c]	2	CH_2Cl_2	40	65	5.0 / 1
2[c]	4	CH_2Cl_2	40	88	5.0 / 1
3[c]	4	$(CH_2Cl)_2$	83	78	4.3 / 1
4[c]	4	Toluene	110	76	3.5 / 1
5[d]	4	CH_2Cl_2	40	74	4.0 / 1

[a]The reactions were carried out under reflux. [b]Determined by ^{1}H NMR. [c]10 mol% of **21** was used. [d]2 mol% of **21** was used.

Next, the second chemoselective reaction, SAD of **50** using AD-mix-β, was carried out (Scheme 3-8). As expected, the less hindered and electron-rich olefin, in the presence of the iodoolefin, reacted stereoselectively to afford diol **51** in 68% yield, which was separated from the other stereoisomers including the diols derived from the *Z*-olefin (18%). Protection of the hydroxy groups as acetates, followed by Migita-Kosugi-Stille coupling reaction[12] with stannane **45**[13] resulted in the formation of the *E*,*E*-diene in 92% yield. Removal of the TBS group with HF·Py at 0 to 35 °C in THF provided allylic alcohol **54**, which was subjected to SAE using D-(-)-DET to furnish vinyl epoxide **55**. Solvolysis of the acetate with K_2CO_3 in MeOH, and successive treatment of the resultant epoxy alcohol **56** with PPTS resulted in 6-*endo-tet* cyclization to afford THP ring **57** in 60% yield for three steps. The structure of **57** was confirmed by NOE experiments of the corresponding triacetate **58** (Figure 3-1), i.e., NOEs between H45 and H50, and H45 and H47 were observed, in which H45 and H47 occupied 1,3-diaxial positions ($J_{H45\text{-}H46ax}$ = 12.0 Hz, $J_{H46ax\text{-}H47}$ = 12.0 Hz). Protection of the triol **57** as TBS ethers with TBSOTf/2,6-lutidine furnished **44** in 79% yield. SAD of **44** using

AD-mix-β proceeded stereoselectively to afford desired diol **59** in 97% yield (dr = 10 : 1), and protection of the resulting vicinal diol as TBS ethers provided **60**. The overall yield of **60** from the iodoolefin (*R*)-**4** was 20% over eleven steps. The fully protected **60** would be a key intermediate corresponding to not only the C43-C52 but also the C31-C40 units of AM3, in which protecting groups of the primary alcohols can be selectively removed under oxidative (for PMB ether) or reductive (for benzyl ether) conditions in the presence of TBS ethers.



Scheme 3-8. Synthesis of the C43-C52 (C31-C40) part (**60**) of AM3

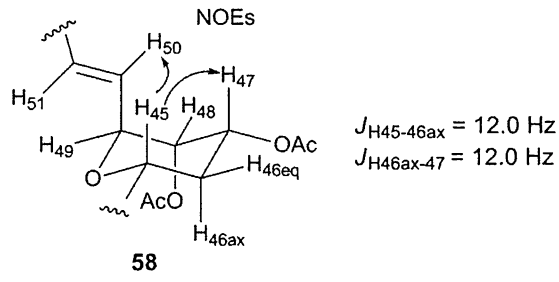
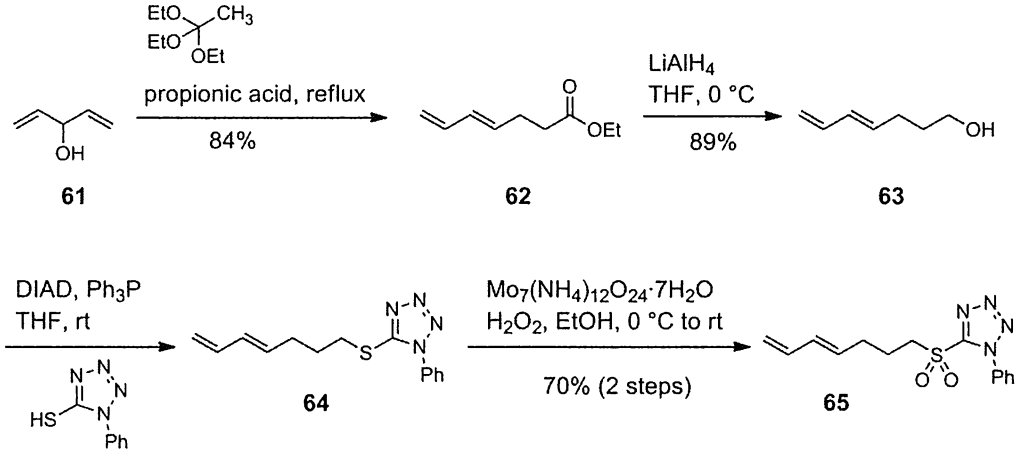


Figure 3-1. Structure determination of **58** by NMR analyses

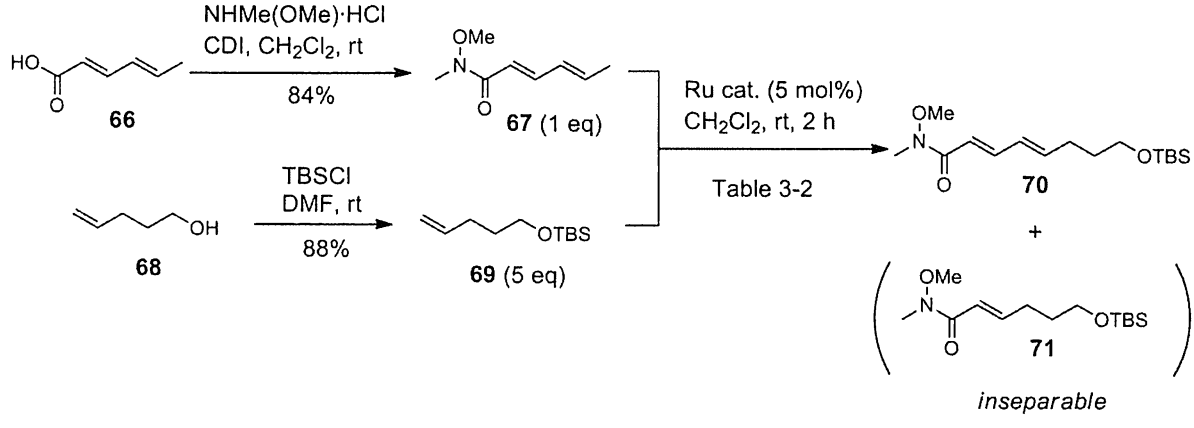
3.3 Synthesis of the C43-C67 part and its diastereomers

Next task is the introduction of the polyolefinic side chain by Julia-Kocienski olefination. Refer to the report by Cossy, the sulfone **42** was synthesized with some modification of the original procedure regarding cross-metathesis reaction.[14] 1,4-Pentadiene-3-ol **61** was subjected to the Johnson–Claisen rearrangement with ethyl orthoacetate and propionic acid to produce dienic ester **62** in 84% yield (Scheme 3-9).[15] This ester was reduced to the corresponding alcohol in 89% yield, which was then transformed to sulfide **64** by using Mitsunobu reaction with 1-phenyl-1*H*-tetra-zole-5-thiol.[16] Without purification, the sulfide **64** was subjected to a mild oxidation conditions using $Mo_7(NH_4)_{12}O_{24}\cdot 7H_2O$[17] and hydrogen peroxide to afford sulfone **65** in 70% yield for two steps.



Scheme 3-9. Synthesis of sulfone **65**

Synthesis of another building block of the polyene moiety commenced with conversion of sorbic acid **66** into Weinreb amide **67** (Scheme 3-10),[18] which was subjected to cross-metathesis reaction with the terminal olefin **69**, derived from 4-penten-1-ol **68** (Table 3-2). The cross-metathesis reaction of **67** with five equivalents of teminal olefin **69** using Hoveyda–Grubbs catalyst **72**[19] (5 mol%) provided diene **70** as an inseparable mixture with by-product **71** in a 17:1 ratio as determined by ^{1}H NMR analysis (entry 1). On the other hand, the ratio of the desired product was improved by using Grela's Hoveyda-Grubbs catalyst **73**[20] up to a 30:1 ratio (entry 2), while that with Grubbs 2nd generation catalyst **21** resulted in a lower ratio (9:1, entry 3).

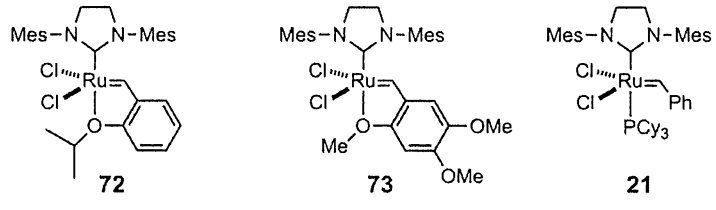


Scheme 3-10. Synthesis of diene **70**

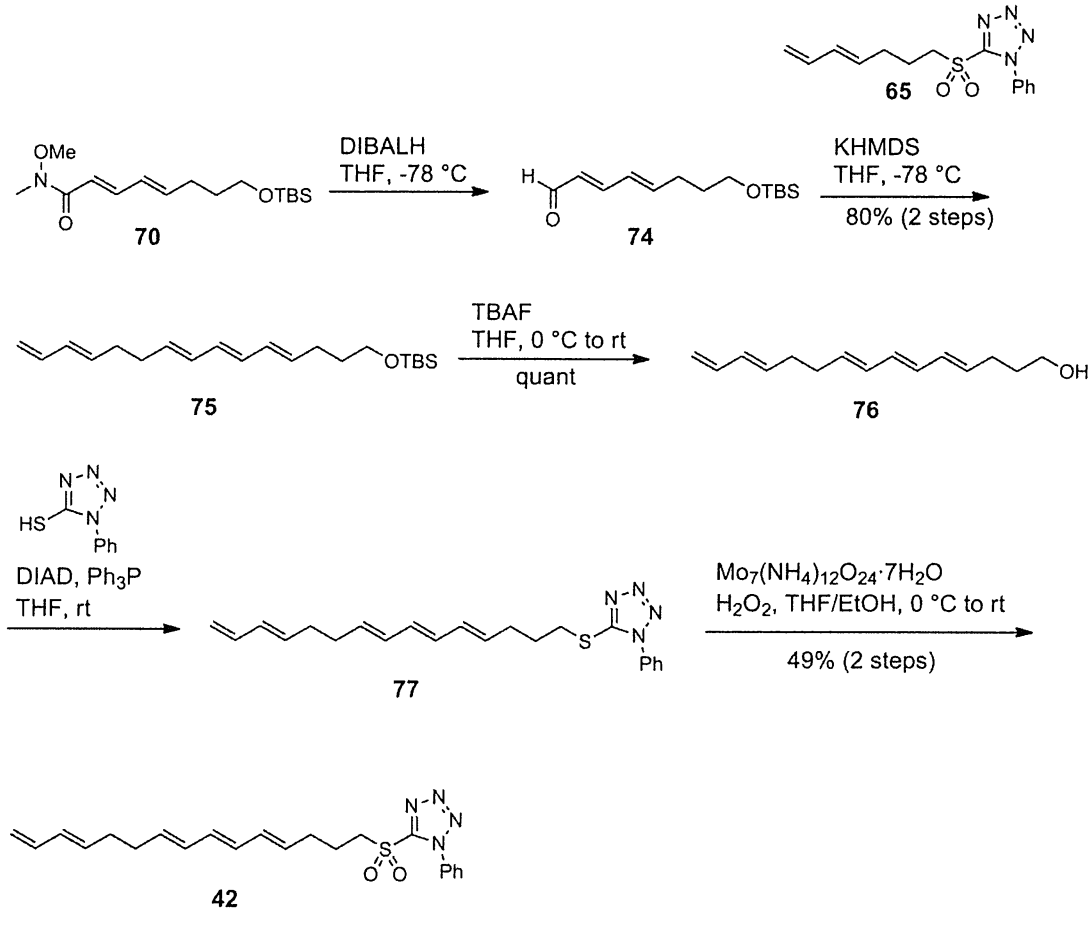
Table 3-2. Cross-metathesis reaction of **67** and **69**.

entry	Catalyst	ratio (**70**/**71**[a])	yield[b] / %
1	**72**	17/1	55
2	**73**	30/1	49
3	**21**	9/1	51

[a] Calculated by ^{1}H NMR. [b] Yields of mixtures of **70** and **71**.



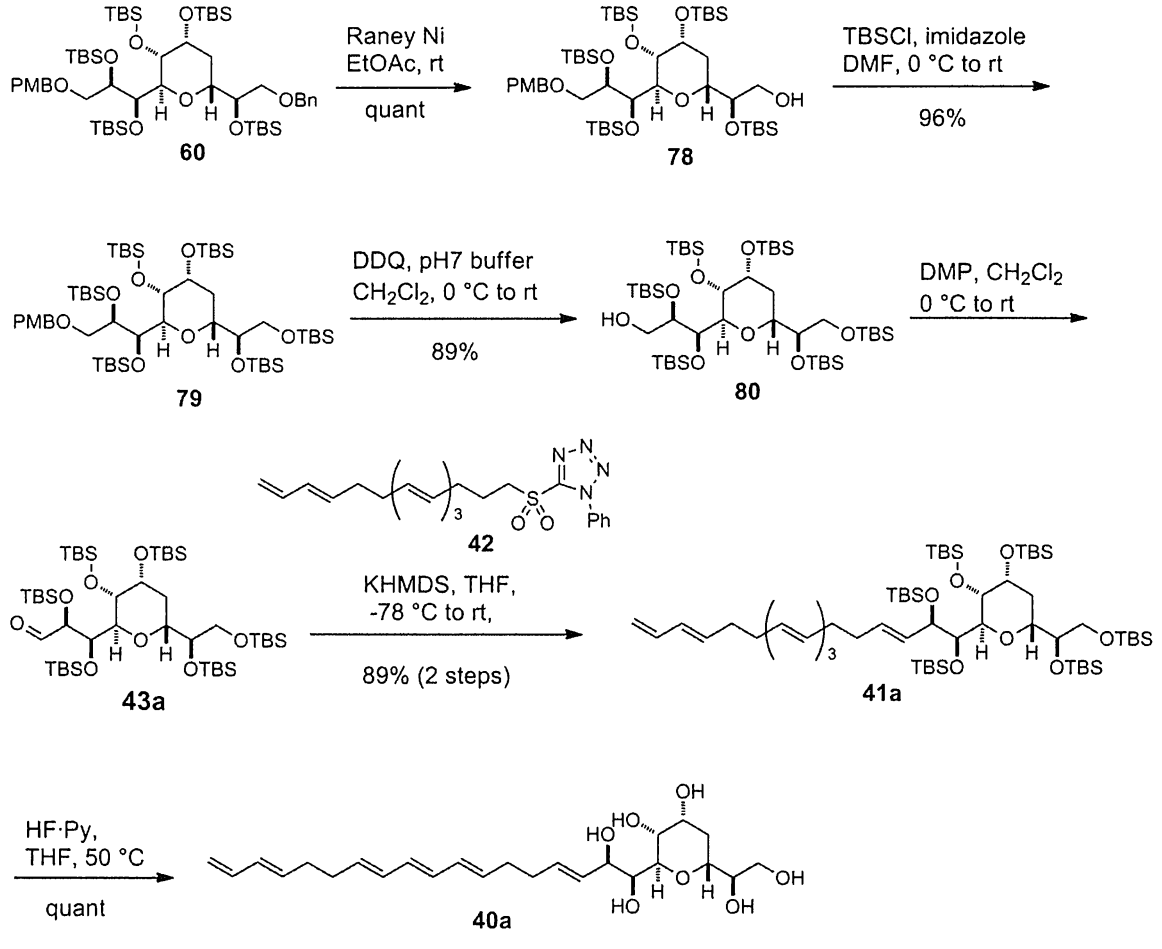
After reduction of the amide **70** with DIBALH, the unstable aldehyde **74** was immediately used without purification in the subsequent Julia–Kocienski olefination (Scheme 3-11). The sulfone **65** and the aldehyde **74** were coupled under the Barbier-type conditions with KHMDS to generate the desired polyene **75** in 80% yield for two steps.[20] The *E*/*Z* ratio for the newly created double bond was evaluated to be 9:1 by ^{1}H NMR analysis. The TBS group of **75** was removed with TBAF, and the resulting primary alcohol **76**[2b] was converted to sulfone **42** in an analogous sequence as shown in Scheme 3-6, i.e. Mitsunobu reaction giving sulfide **77**, followed by oxidation in 49% yield for two steps.



Scheme 3-11. Synthesis of sulfone **42**

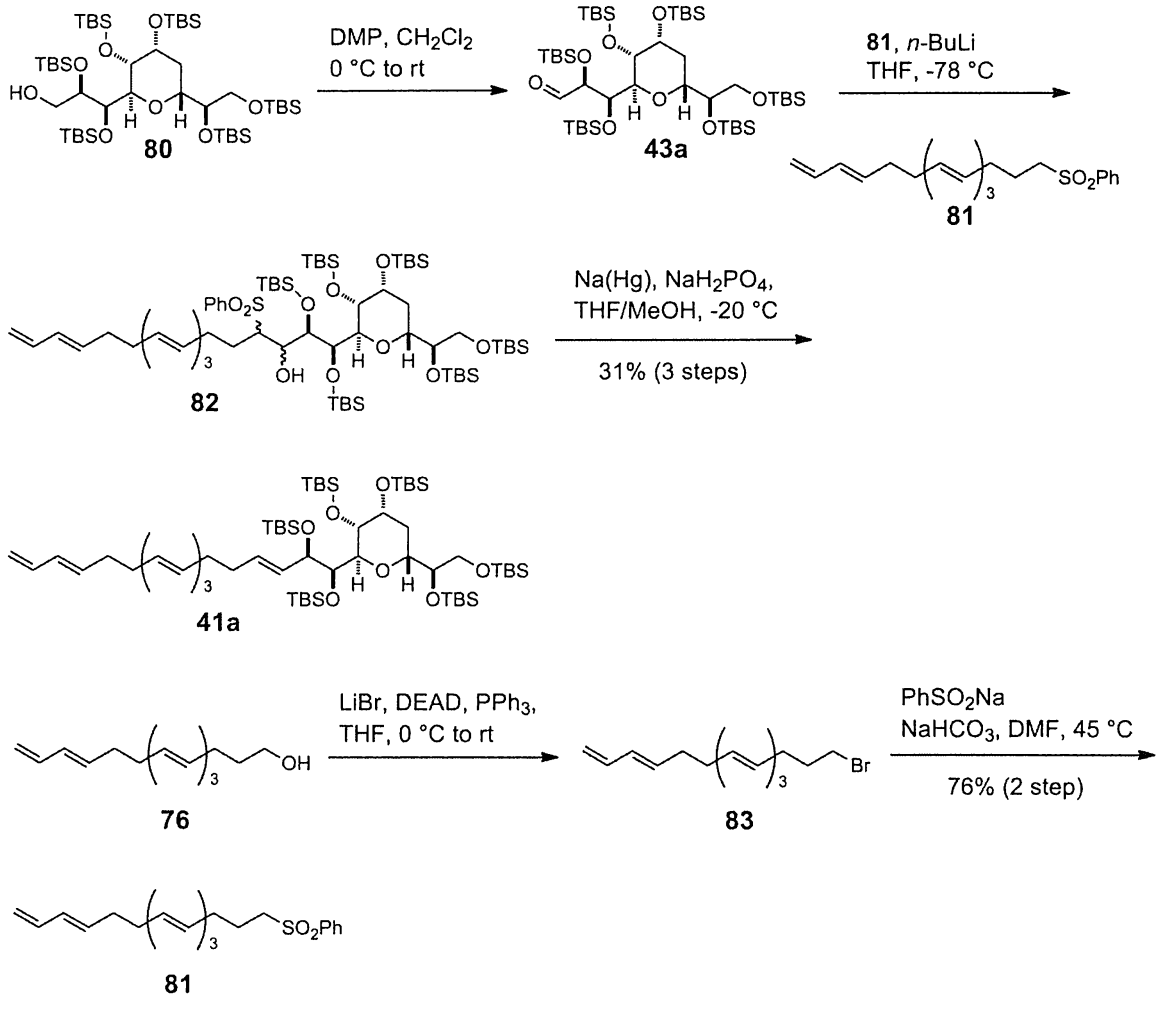
Synthesis of the C43-C67 part of AM3 (**40a**) commenced with protecting group manipulation as shown in Scheme 3-12. Hydrogenolysis of the benzyl group of **60** with Raney Ni, followed by protection of the resulting alcohol as TBS ether gave **79** in 96% yield.

Removal of the PMB group of **79** with DDQ furnished primary alcohol **80** in 89% yield, which was oxidized with Dess-Martin periodinane to yield aldehyde **43a**. Julia-Kocienski olefination of **43a** with sulfone **42** using KHMDS as a base proceeded smoothly to afford olefin **41a** in 89% yield for two steps as a single isomer. Finally, removal of the all TBS groups with HF·Py resulted in the formation of the C43-C67 part of AM3 (**40a**) quantitatively.



Scheme 3-12. Synthesis of the C43-C67 part of AM3 (**40a**)

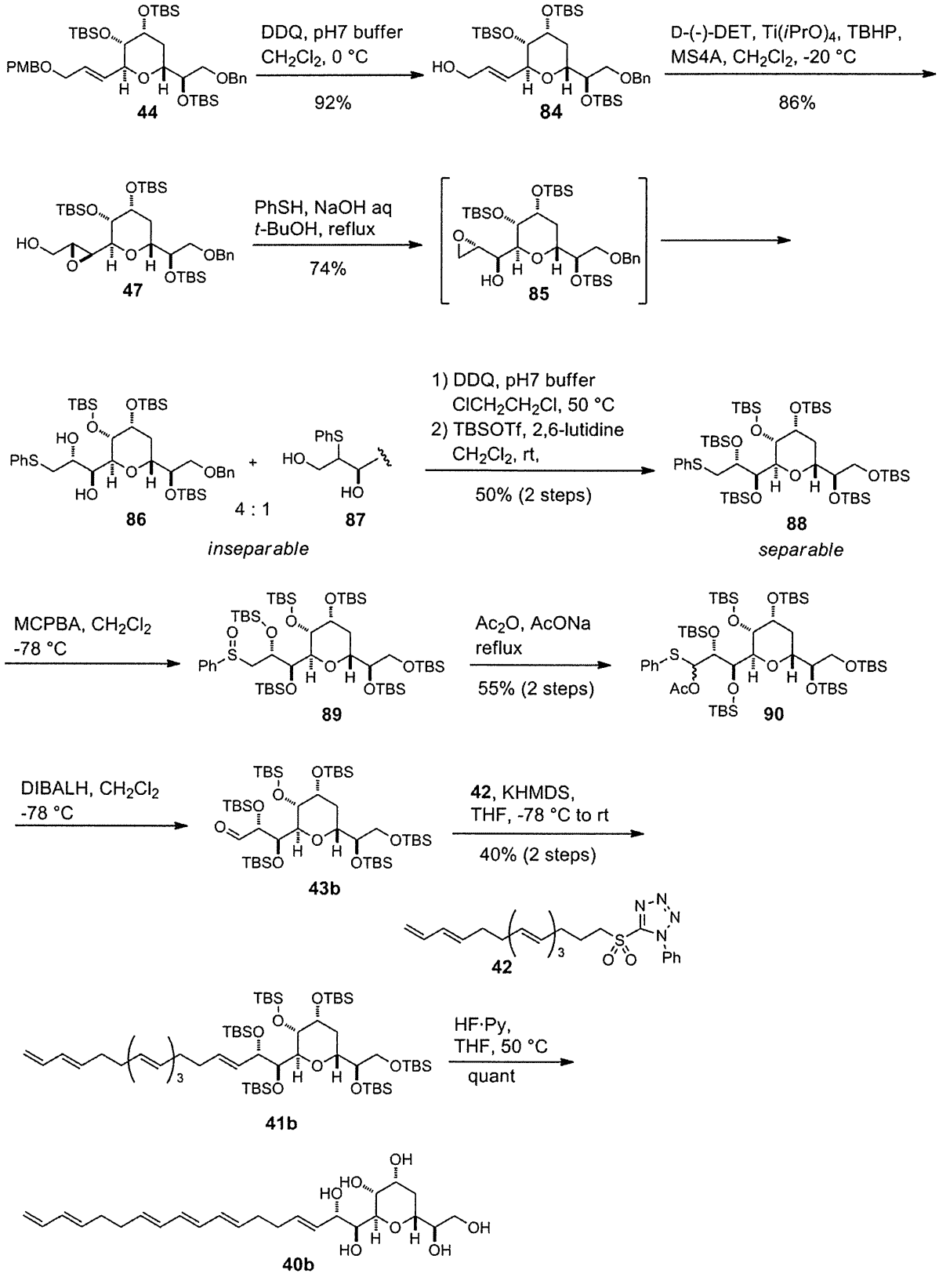
In contrast to the results by Julia-Kocienski olefination of an aldehyde **43a** with sulfone **81**,[2b] Julia-Lythgoe olefination[21] was unsuccessful (Scheme 3-13). Coupling of the aldehyde **43a** with sulfone **81** derived from **76** in two steps (78%), resulted in the formation of adduct **82**, which was treated with sodium amalgam to afford olefin **41a** in low yield (31% for three steps).



Scheme 3-13. Synthesis of **41a** via Julia-Lythgoe olefination

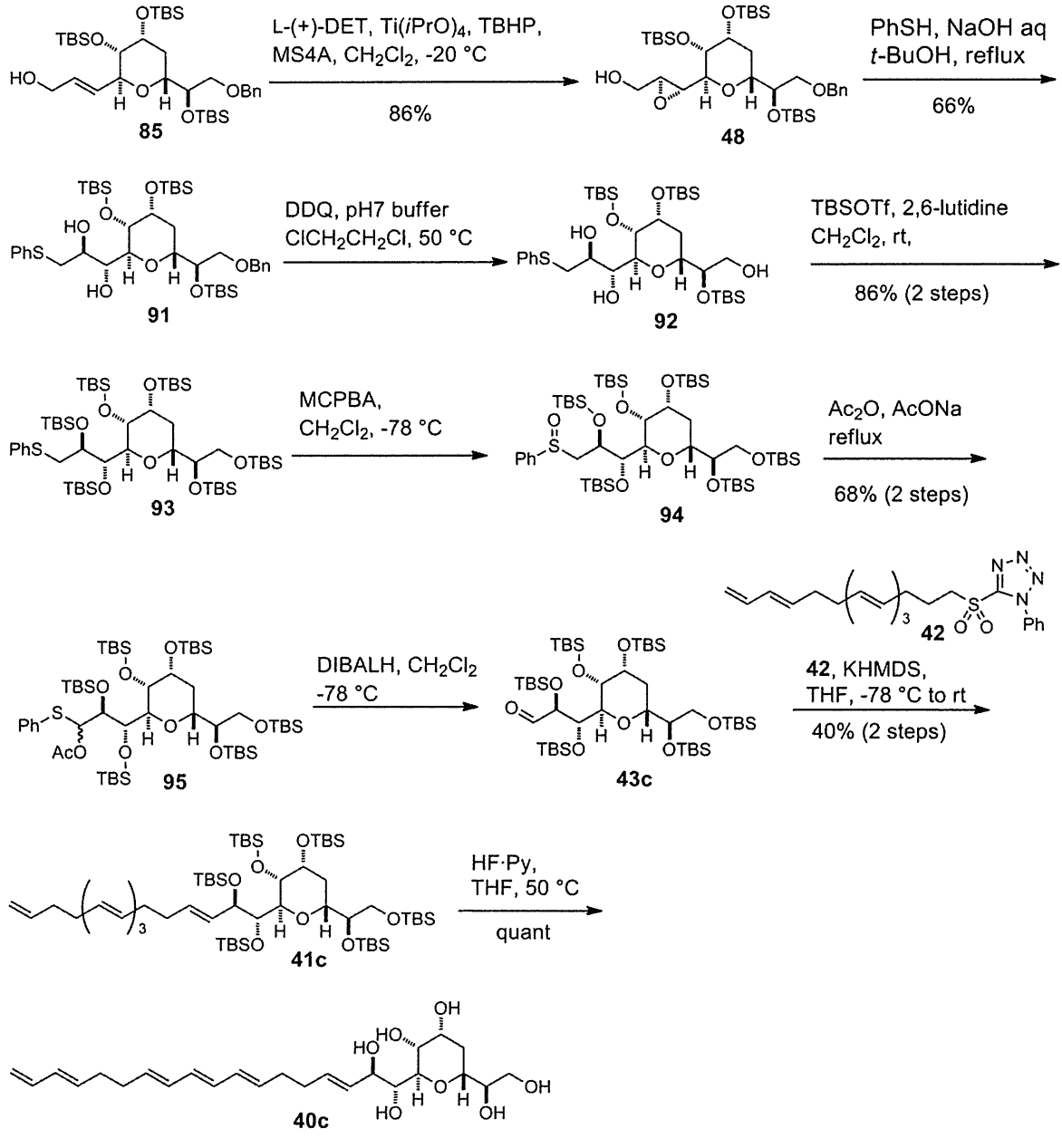
Synthesis of the diastereomer at C51 of the C43-C67 part of AM3 (**40b**) was achieved as shown in Scheme 3-14 starting from common synthetic intermediate **44**. Removal of the PMB group with DDQ gave allylic alcohol **84**, which was subjected to Katsuki-Sharpless asymmetric epoxidation (SAE) using D-(-)-DET to afford β-epoxy alcohol **47**. Ring opening of the epoxide **47** with thiophenol via Payne rearrangement (**85**) under the basic conditions proceeded regionselectively to afford sulfide **86** with concomitant regioisomer **87** in a 4 : 1 ratio as an inseparable mixture.[22] Removal of the benzyl group with DDQ in dichloroethane in the presence of pH7 buffer at 50 °C, followed by treatment of the resulting alcohol with TBSOTf/2,6-lutidine gave **88**, which was separated from a regioisomer derived from **87** by silica gel column chromatography. Then, sulfide **88** was converted to aldehyde **43b** via i)

oxidation with MCPBA giving sulfoxide **89**, ii) Pummerer rearrangement by treating with Ac_2O/AcONa,[23] and iii) reduction of the resulting mixed thioacetal **90** with DIBALH. In contrast to the synthesis of **40a**, Julia-Kociensky olefination with sulfone **42** was sluggish to furnish **41b** in 40% for two steps. Removal of the TBS groups with HF·Py afforded the diasteremer at C51 of the C43-C67 part of AM3.



Scheme 3-14. Synthesis of the diastereomer at C51 of the C43-C67 part of AM3 (**40b**)

In an analogous sequence, 50-epimer (**40c**) was synthesized as shown in Scheme 3-15. The allylic alcohol **84** was subjected to Katsuki-Sharpless asymmetric epoxidation (SAE) using L-(-)-DET to afford α-epoxy alcohol **48**. Ring opening of the epoxide **48** with thiophenol via Payne rearrangement under the basic conditions proceeded regionselectively to afford sulfide **91** in 66% yield. Removal of the benzyl group with DDQ in dichloroethane in the presence of pH7 buffer at 50 °C, followed by treatment of the resulting alcohol with TBSOTf/2,6-lutidine gave **93**. Then, sulfide **93** was converted to aldehyde **43c** via i) oxidation with MCPBA giving sulfoxide **94**, ii) Pummerer rearrangement by treating with Ac_2O/AcONa (68%, two steps), and iii) reduction of the resulting mixed thioacetal **95** with DIBALH. Julia-Kociensky olefination of the aldehyde **43c** with sulfone **42** provided **41c** in 40% yield for two steps. Removal of the TBS groups with HF·Py afforded the diastereomer **40c** at C50 of the C43-C67 part of AM3.



Scheme 3-15. Synthesis of the diastereomer at C50 of the C43-C67 part of AM3 (**40c**)

3.4 Comparison of NMR spectra of the natural product with those of synthetic specimens

Having obtained the diastereomers corresponding to the C43-C67 part, ^{13}C-NMR spectra of **40a**~**40c** were compared with those of AM3.[25] For all diastereomers, chemical shifts at C56~C67 corresponding to the acyclic polyene terminal are identical to those of AM3, but those at C43 terminal deviate because the structures are different from AM3. The differences in the chemical shifts of C43 to C55 between AM3 and **40a**~**40c** (150 MHz, 1:1 C_5D_5N/CD_3OD) were shown in Figure 3-2. The x- and y-axes represent carbon number and $\Delta\delta$ ($\Delta\delta$ = δAM3 - δsynthetic **40** in ppm), respectively. Although the deviations of **40a** at C49, C50, C52 and C53 are larger than 2.0 ppm, **40a**, the chemical shifts at C44 to C55 of 51-epimer (**40b**) are identical within 0.8 ppm. As mentioned in Chapter 1 (Section 1-3), the possibility of being 50-epimer had been ruled out based on the JBCA method, corresponding to the results that the deviation of 50-epimer (**40c**) at C49 is large (8 ppm). Comparison of ^{1}H-NMR chemical shifts furnished similar results (See Supporting Information). In addition, coupling constants of AM3 and synthetic specimens are summarized in Table 3-3. Although the ^3J(H50, H51) value of **40a** is small (1.9 Hz), that of 51-epimer (3.3 Hz) is most comparable to that of the natural product (3.2 Hz). Thus the absolute configuration of AM3 at C51 has been revised to be *S* (Figure 3-3).

Table 3-3. Coupling constants of AM3 and synthetic specimens **40a**, **40b**, and **40c**.

entry	compound	^3J(H49, H50) / Hz	^3J(H50, H51) / Hz	^2J(C51, H50) / Hz	^3J(C49, H51) / Hz
1	AM3	10.0	3.2	-2.5	1
2	**40a**	9.6	1.9		
3	**40b**	9.6	3.3		
4	**40c**	4.0	7.4		

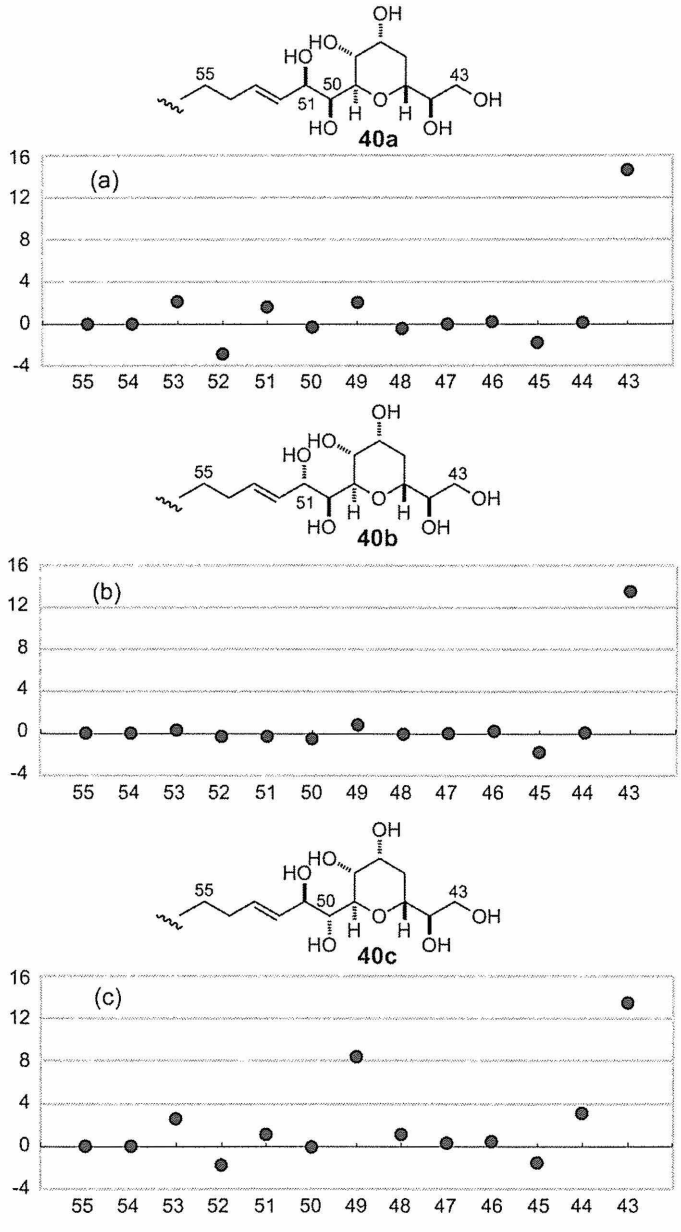


Figure 3-2. Differences in carbon NMR (150 MHz, 1:2 C_5D_5N/CD_3OD) chemical shifts between AM3 and the synthetic fragments (**40a~40c**). (a) **40a**, (b) **40b**, and (c) **40c**.

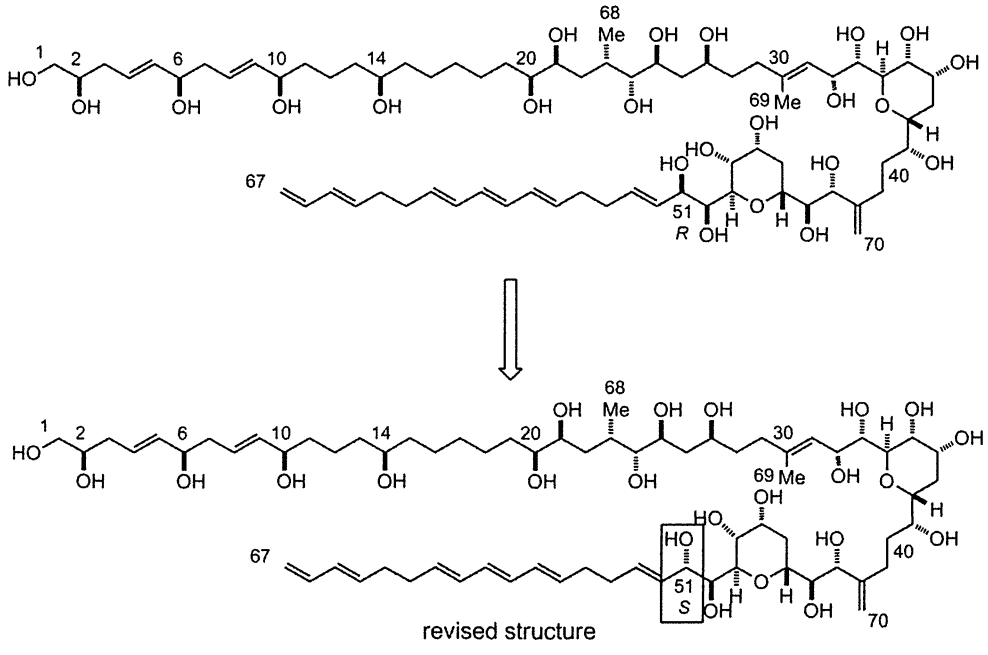


Figure 3-3. Revised structure of amphidinol 3

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Chapter 4. Conclusion

1) Stereoselective syntheses of the C1-C14 part of AM3 (**2a**) and its diastereomers (**2b-2d**) were achieved based on chemoselective cross metathesis of the building blocks, in which iodoolefin was utilized as a masked terminal olefin. Judging from the comparison of ^{13}C NMR data of the synthetic specimens with those of AM3, and by GC-MS analysis of the degradation product, the absolute configuration at C2 has been revised to be *R* (Figure 4-1).

2) Stereoselective syntheses of the C43-C67 part of AM3 (**40a**) and its diastereomers (**40b**, **40c**) were achieved. The tetrahydropyran ring system corresponding to the C43-C52 (and also to the C31-C40) part of AM3, was synthesized based on chemoselective cross metathesis, cross coupling, asymmetric oxidation, and 6-*endo-tet* cyclization. Introduction of polyene part was achieved via Julia-Kocienski olefination of the aldehyde (the C43-C52 part) with the sulfone (the C53-C67 part) to afford **40a**. On the other hand, 51- (**40b**) and 50-epimer (**40c**) were synthesized through Katsuki-Sharpless asymmetric epoxidation and epoxide opening via Payne rearrangement. Judging from the comparison of NMR data of the synthetic specimens with those of AM3, the absolute configuration at C51 has been revised to be *S* (Figure 4-1).

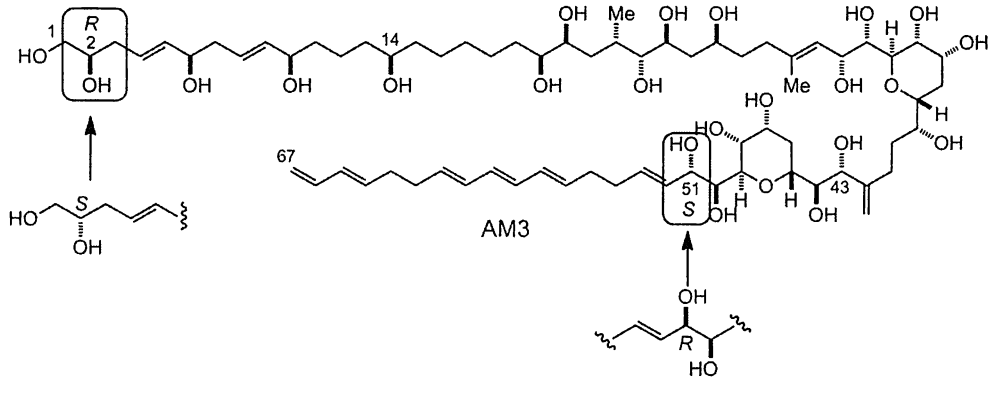
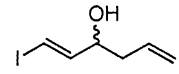


Figure 4-1. Revised structure of amphidinol 3

Supporting Information

General methods for organic synthesis. All reactions sensitive or moisture were performed under urgon atmosphere with dry glassware unless otherwise noted in particular. The dehydrated solvents, CH_2Cl_2, tetrahydrofuran (THF), toluene, *N*, *N*-dimethylformamide (DMF) werepurchased from Kanto Chemical Co. Inc. or Wako Pure Chemcal Industries Ltd., and was used without further dehydration. 2,6-lutidine and PivCl were distilled before using. CuI and molecular sieves (MS4A) were preactivated by heating in *vacuo*. All other chemicals were obtaind from local venders, and used as supplied unless otherwise stated. Thin-layer chromatography (TLC) of E. Merck silica gel 60 F254 pre-coated plates (0.25-mm thickness) was used for the reaction analyses. For column chromatography, Kanto silica gel 60N (spherical, neutral, 100-210 μm) or Merck silica gel 60 (40-63 μm, for flash chromatography) were used. Optical rotations were recorded on a JASCO P-1010 polarimeter. IR spectrometer. ^1H and ^{13}C-NMR spectra were recorded on JEOL JNM-ECA600 or JNM-ECA500 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (TMS) with reference to internal residua; solvent [^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), CHD_2OD (3.30); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), C_5D_5N (135.5), CD_3D (49.00)]. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet, br = broad, brd = broad doublet. ESI-MS spectra were recorded on a ThermoQuest LCQ-DECA mass spectrometer. High resolution mass spectra (HRMS) were recoded on AB QSTAR Elite under ESI-TOF conditions. Combustion elemental analyses were performed using Yanaco CHN CORDER MT3. Gas chromatography was recoded on a SHIMADZU GSMS-QP2010.

Chapter 2. Synthesis and structure confirmation of the C1-C14 part of amphidinol 3



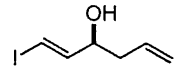
Alcohol (±)-6. To a stirred solution of 3-*Z*-iodo-acrylic acid ethyl ester **8** (30.15 g, 133.4 mmol) in CH_2Cl_2 (220 ml) at -78 °C was added 1.02 M DIBALH in hexane (137 ml, 144 mmol) over 1 h. The resultant mixture was quenched with MeOH, added sat. Na^+, K^+-tartrate aq. and warmed to rt. This solution was diluted with Et_2O and stirred for 1.5 h. The aqueous layer was extracted with Et_2O (x3), the combined organic layers were washed with brine, dried over K_2CO_3 and filtered. BHT was added a few chips to the filterate, the solution was concentrated. The crude **9** was used to next step without further purification.

To a solution of the above crude **9** in CH_2Cl_2 (220 ml) was added $BF_3 \cdot Et_2O$ (18.5 ml, 146 mmol) at 0 °C. After being stirred for 1.5 h, the resultant mixture was quenched with sat. $NaHCO_3$,aq. diluted with Et_2O. The aqueous layer was extracted with Et_2O (x3), the organic layer was washed with brine, dried over K_2CO_3, filtered and concentrated. The crude **10** was used to next step without further purification.

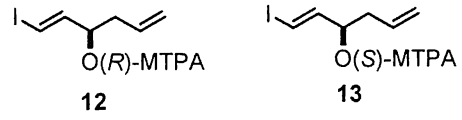
To a solution of the above crude **10** in THF (300 ml) was added 0.90 M AllylMgBr in Et_2O (163 ml, 146 mmol) at -30 °C. The resultant mixture was quenched with sat. NH_4Cl aq. and H_2O, diluted with EtOAc. The aqueous layer was extracted with EtOAc (x3), the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 10/1 to 5/1) afforded (±)-**6** (20.31 g, 68%) as a yellow oil: R_f = 0.29 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (1H, dd, *J* = 14.9, 6.0 Hz), 6.37 (1H, dd, *J* = 14.9, 1.2 Hz), 5.77 (1H, ddd, *J* = 16.6, 10.3, 7.4 Hz), 5.18-5.12 (2H, m), 4.14 (1H, ddd, *J* = 6.0, 6.0 Hz), 2.34 (1H, ddd, *J* = 13.7, 7.4, 6.0 Hz), 2.25 (1H, ddd, *J* = 13.7, 7.4, 6.0 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 143.2, 132.2, 118.6, 80.6, 74.6, 38.2, 21.0.

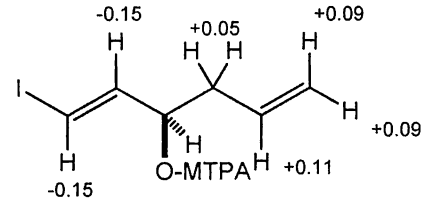
Acetate 7 and alcohol (*S*)-6. To a solution (±)-**6** (29.31 g, 0.131 mmol) in vinyl acetate (297 ml) was added Lipase AK (Amano) (2.93 g) and stirred at 40 °C for 10 h. The resultant

mixture was filtered and concentrated. Purificatin by silica gel column chromatography (hexanes/EtOAc = 20/1, 10/1 to 7/1) afforded (*R*)-**11** (14.65 g, 42%, 94.5% ee) as a pale yellow oil and (*S*)-**6** (15.73 g, 54%, 83% ee) as a pale yellow oil. Enatio excess of **7** was determined after deacetylation. Chiral HPLC (Chiralpakl AD, 1% isopropanol in hexane, 250 x 4.6 mm, 254 nm, 1 mL/min), *t*R = 20.6 min ((*R*)-**6**), *t*R = 21.7 min ((*S*)-**6**). : (*R*)-**11** $[\alpha]_D^{22}$ +63.5 (*c* 1.14, $CHCl_3$); R_f = 0.68 (hexane/EtOAc = 5/1); IR (film) 3078, 2923, 1741, 1642, 1611, 1506, 1434, 1371, 1228, 1179, 1022, 917, 749, 663, 616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (1H, dd, *J* = 15.2, 6.5 Hz), 6.42 (1H, d, *J* = 15.1 Hz), 5.69 (1H, ddt, *J* = 15.1, 11.0, 6.5 Hz), 5.23 (1H, ddd, *J* = 6.5, 6.5, 6.5 Hz), 5.09 (1H, d, *J* = 15.2 Hz), 5.08 (1H, d, *J* = 11.5 Hz), 2.35 (2H, dd, *J* = 6.5, 6.5 Hz), 2.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 143.2, 132.2, 118.6, 80.6, 74.6, 38.2, 21.0.



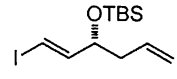
The improvement of ee of alcohol (*S*)-6. To a solution (*S*)-alcohol (*S*)-**6** (15.7 g, 0.0700 mmol, 83% ee) in vinyl acetate (159 ml) was added Lipase AK (Amano) (1.57 g) and stirred at 40 °C for 12 h. The resultant mixture was filtered and concentrated. Purificatin by silica gel column chromatography (hexanes/EtOAc = 20/1, 10/1 to 7/1) afforded (*S*)-**6** (13.5 g, 86%, >99% ee) as a pale yellow oil . Chiral HPLC (Chiralpakl AD, 1% isopropanol in hexane, 250 x 4.6 mm, 254 nm, 1 mL/min), *t*R = 20.6 min ((*R*)-**6**), *t*R = 21.7 min ((*S*)-**6**): $[\alpha]_D^{22}$ -23.7 (*c* 1.27, $CHCl_3$); R_f = 0.29 (hexane/EtOAc = 5/1); IR (film) 3356, 3068, 2978, 2986, 1652, 1339, 1171, 1033, 919, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (1H, dd, *J* = 14.9, 6.0 Hz), 6.37 (1H, dd, *J* = 14.9, 1.2 Hz), 5.77 (1H, ddd, *J* = 16.6, 10.3, 7.4 Hz), 5.18-5.12 (2H, m), 4.14 (1H, ddd, *J* = 6.0, 6.0 Hz), 2.34 (1H, ddd, *J* = 13.7, 7.4, 6.0 Hz), 2.25 (1H, ddd, *J* = 13.7, 7.4, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 133.1, 119.2, 77.4, 73.2, 41.1, 25.6.





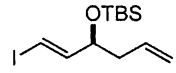
Δδ = δ (*S*)-MTPA ester - δ (*R*)-MTPA ester

(*R*)-MTPA ester 12: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.38 (5H, m), 6.54 (2H, m,), 5.58 (1H, m), 5.45 (1H, m), 5.04 (2H, m), 3.50 (3H, s), 2.39 (2H, m).; **(*S*)-MTPA ester 13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.38 (5H, m), 6.40 (2H, m,), 5.69 (1H, m), 5.44 (1H, m), 5.13 (2H, m), 3.54 (3H, s), 2.44 (2H, m).

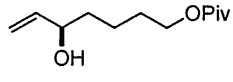


Silyl ether (*R*)-4. To a solution of (*R*)-**11** (14.47 g, 54.40 mmol) in MeOH (181 ml) was added K_2CO_3 (0.75 g, 5.46 mmol) and stirred at 0 °C for 5 h. The reaction mixture was quenched with sat. NH_4Cl aq. and reduced MeOH under reduced pressure, diluted with EtOAc. The aqueous layer was extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. This crude (*R*)-**6** was used to next step without further purification.

To a solution of the above crude (*R*)-**6** in DMF (34 ml) was added imidazole (5.34 g, 78.1 mmol) and TBSCl (9.44 g, 62.8 mmol) at 0 °C and stirred at rt for 3 h. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and H_2O, diluted with hexane. The aqueous layer was extracted with hexane (x3), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc = 1/0) afforded (*R*)-**4** (16.69 g, 2 steps 91%) as a clear oil: $[\alpha]_D^{22}$ +19.1 (*c* 1.01, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 1/0 to 30/1); IR (film) 3078, 2955, 2928, 1829, 1641, 1458, 1363, 1066, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (1H, dd, *J* = 14.3, 7.0 Hz), 6.20 (1H, dd, *J* = 14.3, 1.2 Hz), 5.74 (1H, m), 5.05-5.00 (2H, m), 4.10 (1H, dddd, *J* = 6.0, 6.0, 6.0, 1.2 Hz), 2.24 (1H, ddd, *J* = 6.0, 6.0, 1.3 Hz), 0.87 (9H, s), 0.03 (3H, s), 0.02 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 133.9, 117.7, 75.9, 74.9, 42.2, 25.8, 18.2, -4.6, -4.9.



Silyl ether (*S*)-4. To a solution of (*S*)-**6** (3.34 g, 14.9 mmol) in DMF (15 ml) was added imidazole (1.82 g, 26.8 mmol) and TBSCl (2.30 g, 17.9 mmol) at 0 °C and stirred at rt for 3 h. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and H_2O, diluted with hexanes. The aqueous layer was extracted with hexanes (x3), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc = 1/0 to 30/1) afforded (*S*)-**4** (4.19 g, 83%) as a clear oil: $[\alpha]_D^{22}$ -20.6 (*c* 1.04, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 1/0); IR (film) 3078, 2955, 2928, 2895, 2857, 1607, 1472, 1458, 1361, 1257, 1164, 1088, 1004, 946, 914, 890, 837, 776, 680 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (1H, dd, *J* = 14.3, 5.7 Hz), 6.20 (1H, dd, *J* = 14.3, 1.3 Hz), 5.77-5.69 (1H, m), 5.05-5.03 (1H, m), 5.05-5.03 (1H, m), 4.10 (1H, dddd, *J* = 6.0, 6.0, 6.0, 1.3 Hz), 2.24 (1H, ddd, *J* = 6.0, 6.0, 1.2 Hz), 2.20 (1H, ddd, *J* = Hz), 0.87 (9H, s), 0.03 (3H, s), 0.02 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 133.9, 117.7, 75.9, 74.9, 42.2, 25.8, 18.2, -4.6, -4.9.



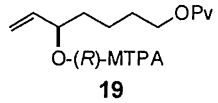
Olefin (*R*)-5. To a 2, 3-dihydro pyrane **16** (10.0 g, 119.3 mmol) was added 0.2 N HCl aq. (25 ml) at 0 ℃, stirred for 15 min, then stirred at rt for 1 h. The resultant mixture was diluted CH_2Cl_2, the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with sat. NaHCO3 aq. and brine, dried over MgSO4, filtered and concentrated in vacuo. Hemi acetal **17** (11.7 g, 96%) was afforded as a clear oil.

To a solution of **17** (8.89 g, 87.02 mmol) in THF (100 ml) was added vinylMgBr (0.75 M in THF, ml, 261 mmol) at 0 ℃ and stirred at rt for 16 h. The resultant mixture was quenched with 2N HCl aq. and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, the organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 1/1) afforded **18** (7.42 g, 66%) as a pale yellow oil.

To a solution of **18** (7.807 g, 59.97 mmol) in CH_2Cl_2 (200 ml) was added Py (14.5 ml, 180 mmol) and PivCl (8.1 ml, 66.0 mmol) at -30 ℃ and stirred for 2.5 h. The reaction mixture was quenched with sat. $NaHCO_3$ aq. and diluted with EtOAc. The aqueous layer was

extracted with EtOAc, the organic layer was washed with $KHSO_4$ aq. and brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc = 10/1, 5/1 to 2/1) afforded (±)-**5** (10.8 g, 84%) as a clear oil.

To a solution of (±)-**5** (10.8 g, 50.3 mmol) in vinyl acetate (125 ml) was added Lipase AK (Amano) (5.40 g, 50%w/w) and stirred at 40 °C for 6.5 days. The resultant mixture was filtered and concentrated under recuced pressure. Purificatin by silica gel column chromatography (hexanes/EtOAc = 10/1, 7/1, 5/1 to 3/1) afforded (*R*)-**5** (4.46 g, 41%, 98% ee) as a clear oil and (*S*)-**4** (7.42 g, 57%, 66% ee) as a clear oil. Enatio excess of (*S*)-**4** was determined after deacetylation. Chiral HPLC (Chiralpakl AD, 1% isopropanol in hexane, 250 x 4.6 mm, 1 mL/min, 220 nm UV detection), *t*R = 14.6 min (major), *t*R = 15.4 min (minor).; (*R*)-**5**: $[\alpha]_D^{28}$ -8.02 (*c* 0.91, $CHCl_3$); R_f = 0.43 (hexanes/EtOAc = 5/1); IR (film) 3440, 3078, 2973, 2958, 2871, 1729, 1713, 1644, 1542, 1481, 1460, 1425, 1398, 1366, 1287, 1162, 1034, 992, 920, 772, 737, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (1H, ddd, *J* = 16.9, 10.5, 6.0 Hz), 5.21 (1H, dd, *J* = 16.9, 1.7 Hz), 5.09 (1H, ddd, *J* = 10.5, 1.2 Hz), 4.09 (1H, ddd, *J* = 6.0, 6.0, 6.0, 1.5 Hz), 4.04 (2H, t, *J* = 6.3 Hz), 1.68-1.36 (6H, m), 1.17 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 141.0, 114.8, 73.0, 64.2, 38.7, 36.4, 28.5, 27.2, 21.7; ESI-MS *m/z* 237 $[(M+H)^+]$; Anal. calcd for $C_{14}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.12; H, 10.34.; (*S*)-**4**: $[\alpha]_D^{22}$ -5.35 (*c* 1.11, $CHCl_3$); R_f = 0.29 (hexane/EtOAc = 5/1); IR (film) 3089, 2958, 2871, 2360, 2341, 1729, 1646, 1481, 1458, 1370, 1285, 1240, 1157, 1020, 990, 933, 883, 771,668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (1H, ddd, *J* = 17.2, 10.3, 6.3 Hz), 5.21 (1H, d, *J* = 17.2 Hz), 5.21 (1H, ddd, *J* = 6.9, 6.9, 6.9 Hz), 4.03 (2H, t, *J* = 6.3 Hz), 2.04 (3H, s), 1.70-1.56 (4H, m), 1.44-1.32 (2H, m), 1.17 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 170.3, 136.3, 116.8, 74.5, 64.0, 38.7, 33.7, 28.3, 27.2, 21.5, 21.2; ESI-MS *m/z* 279 $[(M+H)^+]$; Anal. calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.44; H, 9.48.



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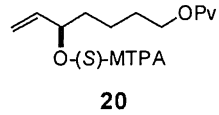

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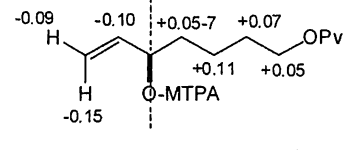
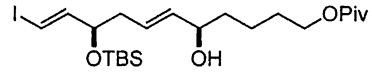


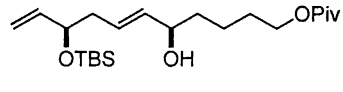
Δδ = (*S*)-MTPA ester (**20**) - (*R*)-MTPA ester (**19**)

(*R*)-MTPA ester 19: ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.38 (3H, m), 5.80 (1H, ddd, *J* = 17.3, 10.3, 7.2 Hz), 5.44 (1H, ddd, *J* = 7.2, 7.2, 7.2 Hz), 5.34 (1H, d, *J* = 17.3 Hz),

5.25 (1H, d, J = 10.3 Hz), 3.96 (2H, t, J = 6.3 Hz), 3.52 (3H, s), 1.71 (1H, m), 1.63 (1H, m), 1.56 (2H, m), 1.28 (2H, m), 1.16 (9H, s).; **(*S*)-MTPA ester 20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.38 (3H, m), 5.70 (1H, ddd, J = 17.3, 10.6 Hz), 5.42 (1H, ddd, J = 6.9, 6.9, 6.9 Hz), 5.25 (1H, dd, J = 17.3, 1.2 Hz), 5.19 (1H, dd, J = 10.6, 1.2 Hz), 4.01 (2H, t, J = 6.7 Hz), 3.53 (3H, s), 1.76 (1H, m), 1.70 (1H, m), 1.63 (2H, tt, J = 6.7, 6.7 Hz), 1.39 (2H, m), 1.16 (9H, s).

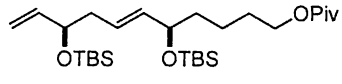


Olefin 22. To a refluxed solution of (*R*)-**4** (402.0 mg, 1.188 mmol) and (*R*)-**5** (762.0 mg, 3.56 mmol) in CH_2Cl_2 (3.0 ml) was added Grubbs cat. (2nd, 30.5 mg, 0.0359 mmol) dissolved in CH_2Cl_2 (1.0 ml) and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched with Et_3N, stirred at 0 °C to rt for 1 h and concentrated. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 10/1, 7/1, 5/1 to 1/1) afforded **22** (438.4 mg, 70%) as yellow syrup: $[\alpha]_D^{26}$ +11.9 (*c* 0.24, $CHCl_3$); R_f = 0.51 (hexane/EtOAc = 5/1); IR (film) 3458, 2955, 2930, 2857, 1727, 1605, 1471, 1462, 1397, 1361, 1285, 1257, 1160, 1082, 1006, 970, 941, 895, 836, 775, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (1H, dd, J = 14.3, 5.9 Hz), 6.20 (1H, dd, J = 14.3, 1.2 Hz), 5.57 (1H, ddd, J = 15.5, 6.9, 6.9 Hz), 5.49 (1H, dd, 15.5, 6.8 Hz), 4.10 (1H, dddd, J = 5.9, 5.9, 5.9, 1.2 Hz), 4.04 (2H, t, 6.6 Hz), 4.03 (1H, ddd, 6.8, 6.8, 6.8 Hz), 2.20 (2H, m), 1.69-1.31 (6H, m), 1.17 (9H, s), 0.87 (9H, s), 0.02 (3H, s), 0.01 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 148.4, 136.2, 126.9, 76.1, 74.8, 72.8, 64.2, 40.5, 38.7, 36.7, 28.5, 27.2, 25.8, 18.2, -4.6, -4.9; HRMS (ESI-TOF) calcd for $C_{22}H_{41}IO_4SiNa$ [(M+Na)$^+$] 547.1716 , found: .547.1718.



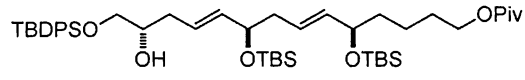
Terminal olefin 23. To a solution of **22** (417.4 mg, 0.7957 mmol) and $Pd(PPh_3)_4$ (91.9 mg, 0.0795 mmol) in benzene(8 ml) was added *n*-Bu_3SnH (0.271 ml, 1.03 mmol) at 5 °C and stirred at rt for 1 h. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and diluted with EtOAc. The organic layer was washed with birne, filtered and concentrated under

reduced pressure. Purificatin by silica gel column chromatography (hexanes/EtOAc = 20/1, 10/1 to 5/1) afforded **23** (295.9 mg, 93%) as yellow oil: $[\alpha]_D^{26}$ -6.48 (*c* 0.25, $CHCl_3$); R_f = 0.37 (hexane/EtOAc = 5/1 x2); IR (film) 3447, 2957, 2930, 2858, 1729, 1462, 1399, 1361, 1285, 1252, 1158, 1077, 1032, 1005, 970, 920, 836, 775, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, ddd, *J* = 16.5, 10.5, 6.0 Hz), 5.61 (1H, ddd, *J* = 15.5, 7.2, 7.2 Hz), 5.47 (1H, dd, *J* = 15.5, 6.8 Hz), 5.13 (1H, dd, *J* = 16.5, 1.6 Hz), 5.02 (1H, dd, *J* = 10.5, 1.6 Hz), 4.10 (1H, dddd, *J* = 7.0, 7.0, 6.0 Hz), 4.03 (1H, ddd, *J* = 6.8, 6.8, 6.8 Hz), 4.02 (2H, t, *J* = 6.6 Hz), 2.24 (1H, ddd, *J* = 14.0, 7.0, 7.0 Hz), 2.19 (1H, ddd, *J* = 14.0, 7.0 .70 Hz), 1.65-1.31 (6H, m), 1.17 (9H, s), 0.87 (9H, s), 0.03 (3H, s), 0.02 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 141.0, 135.3, 128.2, 114.0, 73.5, 72.9, 64.2, 41.1, 38.7, 36.7, 28.5, 27.2, 25.8, 21.9, 18.3, -4.4, -4.8; HRMS (ESI-TOF) calcd for $C_{22}H_{42}O_4SiNa$ $[(M+Na)^+]$ 421.2750, found: 421.2766.

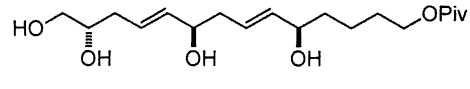


Silyl ether 24. To a solution of **23** (272.0 mg, 0.6824 mmol) in CH_2Cl_2 (7 ml) was added 2,6-lutidine (0.175 ml, 1.501 mmol) and TBSOTf (0.282 ml, 1.228 mmol) at 0 °C and stirred for 20min. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and H_2O, diluted with Et_2O. The aqueous layer was extracted with Et_2O (x3), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 50/1 to 30/1) afforded **24** (326.6 mg, 93%) as a clear oil $[\alpha]_D^{26}$ -7.60 (*c* 0.29, $CHCl_3$); R_f = 0.63 (hexane/EtOAc = 10/1); IR (film) 2956, 2930, 2897, 2858, 1731, 1481, 1472, 1462, 1398, 1389, 1361, 1284, 1252, 1156, 1077, 1033, 1005, 989, 971, 938, 921, 835, 808, 775, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, ddd, *J* = 17.2, 10.5, 5.8 Hz), 5.48 (1H, ddd, *J* = 15.5, 7.2, 7.2 Hz), 5.39 (1H, dd, *J* = 15.5, 6.5 Hz), 5.12 (1H, dd, *J* = 17.2, 1.5 Hz), 5.01 (1H, dd, *J* = 10.5, 1.5 Hz), 4.10 (1H, dddd, *J* = 6.5, 6.5, 5.8 Hz), 4.01 (3H, m), 2.24 (1H, ddd, *J* = 13.8, 6.5, 6.5 Hz), 2.18 (1H, ddd, *J* = 13.8, 6.5, 6.5 Hz), 1.62-1.28 (6H, m), 1.17 (9H, s), 0.87 (9H, s), 0.85 (9H, s), 0.03 (3H, s), 0.01 (3 H, s), 0.01 (3H, s), -0.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 141.0, 136.0, 125.9, 114.0, 73.6, 73.5, 72.9, 64.4, 41.1, 38.7, 36.7, 38.0, 28.6, 27.2, 25.9, 25.8, 21.8, 18.3, -4.2, -4.5, -4.8, -4.8; ESI-MS *m/z* 530 $[(M+NH_4)^+]$; Anal. calcd for $C_{28}H_{56}O_{34}Si_2$: C, 65.57; H, 11.00. Found: C,

65.29; H, 10.98.

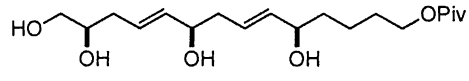


Olefin 25 . To a refluxed solution of **24** (91.2 mg, 0.178 mmol) and (*S*)-**3** (182 mg, 0.533 mmol) in CH_2Cl_2 (0.5 ml) was added Grubbs cat. (2nd, 15.1 mg, 0.0178 mmol) dissolved in CH_2Cl_2 (0.7 ml) and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched with Et_3N, stirred at 0 °C to rt for 1 h and concentrated. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 5/1) afforded **25** (114.5 mg, 78%) as syrup. $[\alpha]_D^{27}$ +0.67 (*c* 0.98, $CHCl_3$); R_f = 0.51 (hexane/EtOAc = 5/1); IR (film) 3464, 3071, 3050, 2956, 2929, 2894, 2857, 1729, 1590, 1472, 1462, 1428, 1389, 1361, 1285, 1255, 1157, 1113, 1072, 1006, 971, 938, 836, 775, 741, 702, 691, 614, 505 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.77-7.66 (4H, m), 7.25-7.17 (6H, m), 5.70 (1H, ddd, *J* = 14.8, 7.6, 7.6 Hz), 5.67 (1H, ddd, *J* = 14.8, 7.6, 7.6 Hz), 5.52 (1H, dd, *J* = 14.8, 6.5 Hz), 5.50 (1H, dd, *J* = 14.8, 6.7 Hz), 4.12 (1H, ddd, *J* = 6.5, 6.5, 6.5 Hz), 4.09-4.01 (3H, m), 3.65 (1H, dd, *J* = 10.0, 4.0 Hz), 3.57 (1H, dd, *J* = 10.0, 7.0 Hz), 2.36-2.13 (4H, m), 1.51-1.29 (6H, m), 1.19 (9H, s), 1.12 (9H, s), 1.03 (9H, s), 1.01 (9H, s), 0.13 (3H, s), 0.12 (3H, s), 0.10 (3H, s), 0.08 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 136.0, 135.8, 135.5, 134.8, 133.1, 133.1, 129.8, 127.8, 126.1, 125.7, 73.5, 73.2, 72.9, 67.4, 64.4, 41.4, 38.7, 38.0, 35.9, 28.6, 27.2, 26.8, 26.5, 25.9, 25.8, 21.8, 19.2, 18.2, -4.2, -4.3, -4.8; HRMS (ESI-TOF) calcd for $C_{47}H_{80}O_6Si_3Na$ [$(M+Na)^+$] 847.5160, found: 847.5163.



Tetraol 2a. To a solution of **25** (90.3 mg, 0.109 mmol) in THF(1 ml) was added HF·Py (250 μl, 1.96 μmol) at 0 °C and stirred at 50 °C for 5 h. Then $NaHCO_3$ solid and H_2O (few drops) were added to the resultant mixture at 0 °C. The solution was concentrated under reduced pressure. Purification by silica gel column chromatography ($CHCl_3$/MeOH = 95/5 to 85/15) afforded **2a** (30.8 mg, 79%) as a yellow syrup :R_f = 0.23 ($CHCl_3$/MeOH = 9/1); $[\alpha]_D^{27}$ -9.61 (*c* 0.33, MeOH); IR (film) 3366, 2934, 2871, 1727, 1709, 1480, 1460, 1431, 1398, 1366, 1287, 1163, 1035, 970, 878, 772, 738, 612 cm^{-1}; ^1H NMR (500 MHz, CD_3OD:C_5D_5N = 2:1) δ 5.77

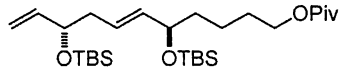
(1H, ddd, J = 15.5, 7.0, 7.0 Hz, H4), 5.71 (1H, ddd, J = 14.3, 7.4, 7.4 Hz, H8), 5.62 (1H, dd, J = 15.5, 6.5 Hz, H5), 5.55 (1H, dd, J = 14.3, 5.7 Hz, H9), 4.11 (1H, brddd, J = 6.5, 6.5, 6.5 Hz, H6), 4.06-3.97 (3H, m, H10, H14), 3.75 (1H, brs, H2), 3.60 (1H, brdd, J = 11.0, 4.6 Hz, H1), 3.55 (1H, brdd, J = 11.0, 6.3 Hz, H1), 2.31 (2H, m, H3, H7), 2.23 (2H, m, H3, H7), 1.63-1.32 (6H, m, H11, H12, H13), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, 30 °C, CD_3OD:C_5D_5N = 2:1) δ 179.50 (CO) ,137.07 (C9), 136.54 (C5), 128.31 (C4), 128.23 (C8), 73.13 (C6), 73.07 (C2), 73.01 (C10), 66.88 (C1), 65.31 (C14), 41.65 (C7), 39.56 (CMe_3), 37.94 (C11), 37.68 (C3), 29.62 (C13), 27.62 ($3CH_3$), 22.99 (C12); HRMS (ESI-TOF) calcd for $C_{19}H_{34}O_6Na$ [$(M+Na)^+$] 381.2253, found: 381.2268.



Tetraol 2b. The reaction of **24** (92.4 mg, 0.180 mmol) and olefin (*R*)-**3** (184.2 mg, 0.540 mmol) in the presence of Grubbs cat. (2nd, 15.3 mg, 0.018 mmol) in CH_2Cl_2 (1.2 ml) was carried out. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 5/1) afforded silyl ether **26** (99.2 mg, 67%) as brown syrup.

To a solution of **26** (99.2 mg, 0.120 mmol) in THF (1.2 ml) was added HF·Py (0.280 μl, 2.2 mmol) at 0 °C and stirred at 50 °C for 5 h. Then $NaHCO_3$ solid and H_2O (few drops) were added to the resultant mixture. The solution was concentrated under reduced pressure. Purification by silica gel column chromatography ($CHCl_3$/MeOH = 95/5 to 85/15) afforded **2b** (30.8 mg, 2 steps 95%) as a white solid: Mp = 76.0-78.0 °C,; R_f = 0.24 ($CHCl_3$/MeOH = 9/1); $[\alpha]_D^{27}$ -1.00 (*c* 0.22, MeOH); IR (KBr) 3390, 2927, 2866, 1728, 1712, 1480, 1459, 1398, 1364, 1287, 1165,1097, 1059, 1035, 1016, 970, 878, 735, 667 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD:C_5D_5N = 2:1) δ 5.76 (1H, ddd, J = 15.2, 7.0, 7.0 Hz, H4), 5.70 (1H, ddd, J = 14.9, 7.0, 7.0 Hz, H8), 5.62 (1H, dd, J = 15.2, 6.6, Hz, H5), 5.55 (1H, dd, J = 14.9, 6.9 Hz, H9), 4.11 (1H, brddd, J = 6.6, 6.6, 6.6 Hz, H6), 4.06-3.97 (3H, m, H10, H14), 3.73 (1H, brs, H2), 3.60 (1H, brdd, J = 11.0, 5.2 Hz, H1), 3.55 (1H, brdd, J = 11.0, 6.3 Hz, H1), 2.32 (2H, m, H3, H7), 2.22 (2H, m, H3, H7), 1.62-1.32 (6H, m, H11, H12, H13), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, CD_3OD:C_5D_5N = 2:1) δ 179.50 (CO), 137.06 (C9), 136.55 (C5), 128.47 (C4), 128.21 (C8), 73.13 (C6), 73.10 (C2), 73.02 (C10), 66.88 (C1), 65.31 (C14), 41.61 (C7), 39.56 (CMe_3), 37.94 (C11), 37.73 (C3), 29.61 (C13), 27.62 ($3CH_3$), 22.99 (C12); HRMS (ESI-TOF)

calcd for $C_{19}H_{34}O_6Na$ [$(M+Na)^+$] 381.2253, found: 381.2266.

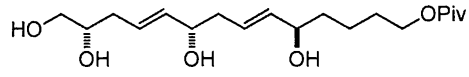


Olefin 7. The reaction of (*S*)-**4** (400 mg, 1.18 mmol) and (*R*)-**5** (760.5 mg, 3.55 mmol) in the presence of Grubbs cat. (2^{nd}, 30.0 mg, 0.0355 mmol) in CH_2Cl_2 (4.0 ml) was carried out. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 10/1, 7/1, 5/1 to 1/1) afforded **27** (373 mg, 60%) as brown syrup.

To a solution of the above **27** (353 mg, 0.672 mmol) and $Pd(PPh_3)_4$ (77.0 mg, 0.0795 mmol) in benzene (6.7 ml) was added *n*-Bu_3SnH (0.230 ml, 0.872 mmol) at 5 °C and stirred at rt for 1 h. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and diluted with EtOAc. The organic layer was washed with birne, filtered and concentrated under reduced pressure. Purificatin by silica gel column chromatography (hexanes/EtOAc = 20/1, 10/1 to 5/1) afforded terminal olefin (267 mg, quant.) as yellow oil.

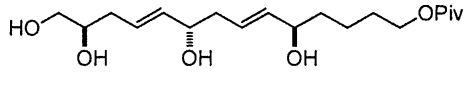
To a solution of the above terminal olefin **28** (244 mg, 0.612 mmol) in CH_2Cl_2 (7 ml) was added 2,6- lutidine (0.140 ml, 1.22 mmol) and TBSOTf (0.210 ml, 0.919 mmol) at 0 °C and stirred for 20min. To a reaction mixture was added 2,6- lutidine (0.032 ml, 0.27 mmol) and TBSOTf (0.32 ml, 0.14 mmol) at 0 °C and stirred for 10min.The resultant mixture was quenched with sat. $NaHCO_3$ aq. and H_2O, diluted with Et_2O. The aqueous layer was extracted with Et_2O (x3), the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 50/1 to 30/1) afforded **29** (279.3 mg, 89%) as a clear oil $[\alpha]_D^{26}$ +14.7 (*c* 0.28, $CHCl_3$); R_f = 0.29 (hexane/EtOAc = 30/1); IR (film) 2957, 2929, 2896, 2858, 1731, 1480, 1472, 1462, 1398, 1389, 1361, 1284, 1252, 1156, 1078, 1034, 1005, 989, 971, 939, 922, 836, 808, 775, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, ddd, *J* = 17.0, 10.5, 6.0 Hz), 5.50 (1H, ddd, *J* = 15.0, 6.4, 6.4 Hz), 5.40 (1H, dd, *J* = 15.0, 6.4 Hz), 5.12 (1H, dd, *J* = 17.0, 1.4 Hz), 5.01 (1H, dd, *J* = 10.5, 1.4 Hz), 4.09 (1H, ddd, *J* = 6.0, 6.0, 6.0 Hz), 4.01 (3H, m), 2.25-2.14 (2H, m), 1.64-1.27 (6H, m), 1.17 (9H, s), 0.87 (9H, s), 0.86 (9H, s), 0.03 (3H, s), 0.01 (3 H, s), 0.01 (3H, s), -0.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 141.1, 135.9, 125.9, 113.9, 73.7, 73.3, 72.9, 64.4, 41.2, 38.7, 38.0, 28.7, 27.2, 25.9, 25.9, 21.7, 18.2, -4.2, -4.4, -4.8, -4.8; ESI-MS *m/z* 530 [$(M+NH_4)^+$]; Anal. calcd for $C_{28}H_{56}O_4Si2$ C, 65.57; H, 11.00.

Found: C, 65.33; H, 10.86.



Tetraol 2c. The reaction of **29** (90.3 mg, 0.176 mmol) and olefin (*S*)-**3** (270 mg, 0.795 mmol) in the presence of Grubbs cat. (2nd, 15.3 mg, 0.0176 mmol) in CH_2Cl_2 (1.2 ml) was carried out. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 7/1) afforded silyl ether as a brown syrup.

To a solution of the above silyl ether **30** in THF (1.1 ml) was added HF·Py (0.130 μl, 0.10 μmol) at 0 °C and stirred at 50 °C for 5 h. Then $NaHCO_3$ solid and H_2O (a few drops) were added to the resultant mixture. The solution was concentrated under reduced pressure. Purification by silica gel column chromatography ($CHCl_3$/MeOH = 95/5 to 85/15) afforded **2c** (22.3 mg, 2 steps 40%) as a white syrup: $[\alpha]_D^{27}$ -3.25 (*c* 0.13, MeOH); R_f = 0.24 ($CHCl_3$/MeOH = 9/1); IR (film) 3350, 2933, 2871, 1727, 1481, 1399, 1367, 1286, 1162, 1034, 971, 881, 596 cm^{-1}; ^1H NMR (500 MHz, CD_3OD:C_5D_5N = 2:1) δ 5.76 (1H, ddd, *J* = 15.5, 6.9, 6.9 Hz, H4), 5.71 (1H, ddd, *J* = 15.5, 8.0, 8.0 Hz, H8), 5.61 (1H, dd, *J* = 15.5, 6.9 Hz, H5), 5.55 (1H, dd, *J* = 15.5, 6.3 Hz, H9), 4.10 (1H, ddd, *J* = 6.9, 6.9, 6.9 Hz, H6), 4.06-3.97 (3H, m, H10, H14), 3.75 (1H, m, H2), 3.59 (1H, dd, *J* = 11.2, 4.6 Hz, H1), 3.54 (1H, dd, *J* = 11.2, 6.3 Hz, H1), 2.36-2.14 (4H, m, H3, H7), 1.62-1.33 (6H, m, H11, H12, H13), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, CD_3OD:C_5D_5N = 2:1) δ 179.50 (CO), 137.05 (C9), 136.55 (C5), 128.41 (C4), 128.09 (C8), 73.10 (C6), 73.10 (C10), 73.05 (C2), 66.87 (C1), 65.32 (C14), 41.55 (C7), 39.56 (CMe_3), 37.96 (C11), 37.73 (C3), 29.62 (C13), 27.63 ($3CH_3$), 23.00 (C12); HRMS (ESI-TOF) calcd for $C_{19}H_{34}O_6Na$ [$(M+Na)^+$] 381.2253, found: 381.2267.



Tetraol 2d. The reaction of **29** (90.7 mg, 0.177 mmol) and (*R*)-**3** (270.5 mg, 0.794 mmol) in the presence of Grubbs cat. (2nd, 15.7 mg, 0.0177 mmol) in CH_2Cl_2 (1.2 ml) was carried out. Purificatin by Flash silica gel column chromatography (hexanes/EtOAc = 7/1) afforded silyl ether as a brown syrup.

To a solution of the above silyl ether **31** in THF (1.1 ml) was added HF·Py (0.186 μl, 1.46 μmol) at 0 °C and stirred at 50 °C for 5 h. Then $NaHCO_3$ solid and H_2O (a few drops) were added to the resultant mixture. The solution was concentrated under reduced pressure. Purification by silica gel column chromatography ($CHCl_3$/MeOH = 9/1 to 8/2) afforded **2d** (35.8 mg, 2 steps 56%) as a yellow syrup: $[\alpha]_D^{22}$ +3.45 (*c* 0.26, MeOH); R_f = 0.24 ($CHCl_3$/MeOH = 9/1); IR (film) 3366, 2934, 2871, 1727, 1709, 1480, 1460, 1431, 1398, 1366, 1287, 1163, 1035, 970, 878, 772, 738, 612 cm^{-1}; ^1H NMR (500 MHz, CD_3OD:C_5D_5N = 2:1) δ 5.77 (1H, ddd, *J* = 15.5, 6.9, 6.9 Hz, H4), 5.71 (1H, ddd, *J* = 15.2, 7.4, 7.4 Hz, H8), 5.61 (1H, dd, *J* = 15.5, 6.3 Hz, H5), 5.54 (1H, dd, *J* = 15.2, 6.9 Hz, H9), 4.11 (1H, ddd, *J* = 6.3, 6.3, 6.3 Hz, H6), 4.06-3.97 (3H, m, H10, H14), 3.75 (1H, m, H2), 3.60 (1H, dd, *J* = 10.9, 4.6 Hz, H1a), 3.55 (1H, dd, *J* = 10.9, 6.3 Hz, H1b), 2.31 (2H, m, H3a, H7a), 2.23 (2H, m, H3b, H7b), 1.63-1.32 (6H, m, H11, H12, H13), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, CD_3OD:C_5D_5N = 2:1) δ 179.50 (CO), 137.03 (C9), 136.54 (C5), 128.26 (C4), 128.13 (C8), 73.11 (C10), 73.07 (C6), 72.99 (C2), 66.86 C1), 65.31 (C14), 41.57 (C7), 39.56 (CMe_3), 37.95 (C11), 37.67 (C3), 29.61 (C13), 27.62 ($3CH_3$), 22.99 (C12); HRMS (ESI-TOF) calcd for $C_{19}H_{34}O_6Na$ $[(M+Na)^+]$ 381.2253, found: 381.2269.

Procedure of degradation of amphidinol 3 and GC-MS analysis.

Grubbs cat. (2nd, 32 μl from stock solution (1 mg /ml in CH_2Cl_2), 38 nmol) was added to a solution of MeOH (140 μl) and CH_2Cl_2 (160 μl). Ethylene was bubbled through the solution for ca. 1 min followed by addition of AM3 (50 μl from stock solution (1 mg/ml in MeOH), ca. 50 μg, 38 nmol). The reaction flask was flushed with ethylene, and the reaction was allowed to stir for 12 h at room temperature under an ethylene balloon. The result solution was injected to GC-MS. Chiral GCMS anlysis (Varian Chirasil-DEX CB, Chrompack, 0.25 mm x 25 m, Helium, The column temperature was kept at 50 °C for the first 5 min. Then its temperature was raised by 20 °C/min to 130 °C and kept for 10 min.; *t*R = 9.87 min ((*S*)-**39**), *t*R = 9.96 min ((*R*)-**39**).

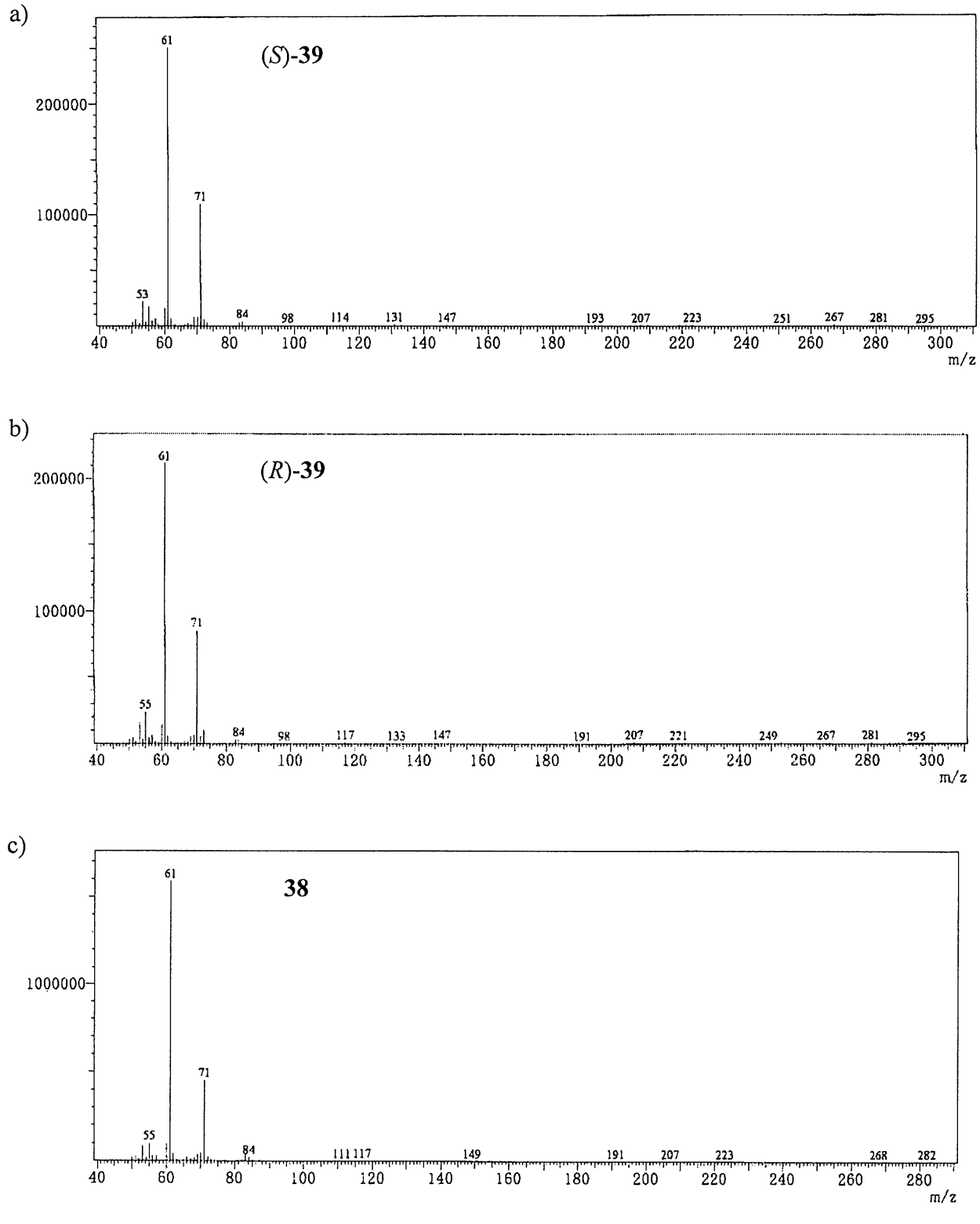
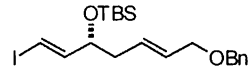
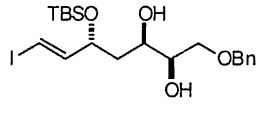


Figure S1. Mass spectra of authentic samples (a)-(b) (*S*)- and (*R*)-**39**,and (c) fragment form AM3 (**38**).

Chapter 3. Synthesis and structure confirmation of the C43-C67 part of amphidinol 3

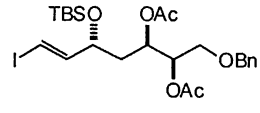


Olefin 50. To a solution of (*R*)-**4** (5.01 g, 14.8 mmol) and **46** (15.9 g, 59.2 mmol) in CH_2Cl_2 (48 mL) under reflux was added a solution of Grubbs catalyst **21** (251 mg, 0.296 mmol, 2 mol%) in CH_2Cl_2 (1.0 mL). After being stirred for 6 h, the reaction mixture was cooled to 0 °C and quenched with Et_3N, and allowed to warm to room temperature over 1 h, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/0→20/1→10/1) afforded a mixture of **50** and allyl benzyl ether. The allyl benzyl ether was removed *in vacuo* at 90 °C for 1 h to provide **50** (4.81 g, 71%) as a yellow oil: $[\alpha]_D^{26}$ +6.84 (*c* 1.05, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 10/1); IR (film) ν 2953, 2928, 2884, 2856, 1606, 1471, 1361, 1254, 1088, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 6.51 (dd, *J* = 14.3, 6.0 Hz、1H), 6.21 (dd, *J* = 14.3, 1.3 Hz, 1H), 5.74-5.54 (m, 2H), 4.41 (s, 2H), 4.11 (tdd, *J* = 6.0, 6.0, 1.3 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 6.0 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 138.4, 129.7, 129.2, 128.4, 127.7, 127.5, 76.0, 74.8, 71.9, 70.6, 65.8, 40.6, 35.9, 25.8, 18.1, -4.6, -4.9; HRMS (ESI-TOF) calcd for $C_{20}H_{31}IO_2SiNa$ [$(M+Na)^+$] 481.1036, found 481.1033.

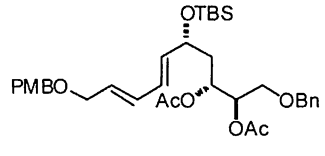


Diol 51. A mixture of $K_2OsO_4 \cdot 2H_2O$ (31.3 mg, 0.0851 mmol), $(DHQD)_2PHAL$ (331 mg, 0.425 mmol), $K_3Fe(CN)_6$ (8.40 g, 25.5 mmol), K_2CO_3 (3.52 g, 25.5 mmol) and $MeSO_2NH_2$ (2.42 g, 25.5 mmol) in *t*-BuOH (18 mL) and H_2O (28 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resultant suspension was added a solution of **50** (3.87g, 8.51mmol) in *t*-BuOH (10 ml). After being stirred for 36 h at 0 °C, the resultant mixture was quenched with solid $Na_2S_2O_3 \cdot 5H_2O$ (8.0 g), and allowed to warm to room temperature over 1 h. The aqueous layer was extracted with EtOAc, and combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered and

concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1→3/1→2/1) afforded **51** (2.27 g, 68%) as a yellow syrup: $[\alpha]_D^{27}$ +37.8 (*c* 0.89, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 2/1); IR (film) ν 3433, 2953, 2928, 2888, 2856, 1253, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 6.54 (dd, *J* = 14.4, 5.8 Hz, 1H), 6.27 (dd, *J* = 14.4, 1.2 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.42 (m, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 3.59-3.51 (m, 3H), 3.09 (brs, 1H), 2.62 (brs, 1H), 1.79 (ddd, *J* = 14.2, 10.5, 3.4 Hz, 1H), 1.53 (ddd, *J* = 14.2, 7.2, 2.2 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 137.7, 128.5, 127.9, 127.8, 76.3, 73.6, 72.9, 72.1, 68.5, 40.2, 25.8, 18.1, -4.6, -5.2; HRMS (ESI-TOF) calcd for $C_{20}H_{33}IO_4SiNa$ $[(M+Na)^+]$ 515.1091, found 515.1102.

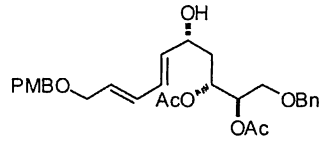


Diacetate 52. To a solution of **51** (2.17 g, 4.413 mmol) in pyridine (4.4 mL) were added DMAP (53.8 mg, 0.441 mmol) and Ac_2O (1.25 mL, 13.2 mmol) at 0 °C and stirred at room temperature for 8 h. The resultant mixture was concentrated in *vacuo*. Purification by silica gel column chromatography (hexane/EtOAc = 5/1) afforded **52** (2.52 g, 99%) as a colorless oil: $[\alpha]_D^{22}$ +27.1 (*c* 0.81, $CHCl_3$); R_f = 0.43 (hexane/EtOAc = 4/1); IR (film) ν 2954, 2929, 2889, 2857, 1744, 1371, 1222, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 6.45 (dd, *J* = 14.5, 7.4 Hz, 1H), 6.25 (d, *J* = 14.5 Hz, 1H), 5.27 (ddd, *J* = 7.7, 4.6, 4.6 Hz, 1H), 5.12 (ddd, *J* = 5.7, 4.6, 4.6 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.07 (ddd, *J* = 7.4, 7.4, 7.4 Hz, 1H), 3.51 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.49 (dd, *J* = 10.5, 5.7 Hz, 1H), 2.07 (s, 3H), 2.01 (s, 3H), 1.74-1.70 (m, 2H), 0.85 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.0, 148.6, 137.7, 128.4, 127.7, 127.7, 73.2, 72.8, 72.4, 68.9, 68.4, 38.8, 25.8, 21.0, 21.0, 18.1, -4.2, -5.1; HRMS (ESI-TOF) calcd for $C_{24}H_{37}IO_6SiNa$ $[(M+Na)^+]$ 599.1302, found 599.1287.



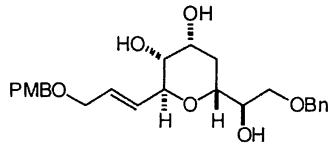
Diene 53. To a solution of **52** (3.28 g, 5.68 mmol) and **45** (2.92 g, 6.25 mmol) in DMF (18.9

mL) was added $PdCl_2(MeCN)_2$ (36.8 mg, 0.142 mmol, 2.5 mol%) at 0 °C and stirred at room temperature for 7 h. The resultant mixture was quenched with aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1→8/1→4/1) afforded **53** (3.29 g, 92%) as a colorless syrup: $[\alpha]_D^{26}$ +8.92 (*c* 0.75, $CHCl_3$); R_f = 0.48 (hexane/EtOAc = 2/1); IR (film) ν 2954, 2929, 2857, 1744, 1513, 1372, 1250, 1224, 1097, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.23 (m, 7H), 6.86 (m, 2H), 6.19 (dd, *J* = 15.0, 10.6 Hz, 1H), 6.11 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.75 (dt, *J* = 15.0, 6.0 Hz, 1H), 5.58 (dd, *J* = 15.0, 7.4 Hz, 1H), 5.29 (ddd, *J* = 8.4, 4.0, 4.0 Hz, 1H), 5.16 (m, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.43 (s, 2H), 4.13 (m, 1H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.53 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.50 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.74 (ddd, *J* = 14.2, 7.9, 4.0 Hz, 1H), 1.69 (ddd, *J* = 14.2, 8.4, 4.6 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.0, 159.1, 137.7, 136.4, 131.7, 130.2, 129.9, 129.4, 129.3, 128.2, 127.6, 113.7, 73.0, 72.7, 71.8, 70.1, 69.9, 69.1, 68.5, 55.2, 39.5, 25.8, 20.9. 20.8, 18.0, -4.0, -5.1; HRMS (ESI-TOF) calcd for $C_{35}H_{50}O_8SiNa$ $[(M+Na)^+]$ 649.3173, found 649.3193.



Alltyl alcohol 54. To a solution of **53** (2.00 g, 3.19 mmol) in THF (16.7 mL) was added HF·Py (50%, 730 μL, 10.1 mmol) at 0 °C and stirred at 35 °C for 2 d. The resultant mixture was poured into saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 2/1→3/2) afforded **54** (1.40 g, 86%) as a colorless syrup: $[\alpha]_D^{26}$ +4.10 (*c* 0.69, $CHCl_3$); R_f = 0.50 (hexane/EtOAc = 1/1); IR (film) ν 3462, 2937, 2864, 1741, 1612, 1514, 1372, 1228 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.21 (m, 7H), 6.87-6.83 (m, 2H), 6.22 (dd, *J* = 14.3, 10.5 Hz,

1H), 6.20 (dd, J = 14.2, 10.5 Hz, 1H), 5.76 (td, J = 14.3, 6.0 Hz, 1H), 5.63 (dd, J = 14.2, 6.2 Hz, 1H), 5.35 (ddd, J = 10.0, 10.0, 3.8 Hz, 1H), 5.15 (td, J = 5.6, 3.8 Hz, 1H), 4.47 (s, 2H), 4.41 (s, 2H), 4.04 (brm, 1H), 3.99 (d, J = 6.0 Hz, 2H), 3.77 (s, 3H), 3.50, (d, J = 5.6 Hz, 2H), 2.07 (s, 3H), 2.02 (s, 3H), 1.70 (ddd, J = 14.2, 10.0, 3.5 Hz, 1H), 1.64 (ddd, J = 14.2, 10.0, 3.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.2, 159.1, 137.5, 134.8, 131.7, 130.2, 129.6, 129.3, 128.3, 127.7, 113.7, 73.1, 72.7, 71.6, 69.8, 69.4, 67.8, 67.6, 55.2, 38.5, 20.8. 20.7; HRMS (ESI-TOF) calcd for $C_{29}H_{36}O_8Na$ [$(M+Na)^+$] 535.2308, found 535.2316.

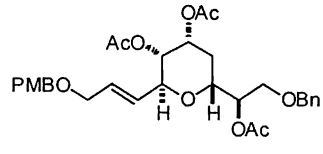


Triol 57. To a mixture of powdered MS4A (450 mg) in CH_2Cl_2 (8 mL) were added D-(-)-DET (127 μL, 0.732 mmol) and Ti(O*i*-Pr)$_4$ (174 μL, 0.585 mmol) at -25 °C. After being stirred for 30 min, a solution of **54** (1.50 g, 2.96 mmol) in CH_2Cl_2 (6 mL) was added to the mixture. After being stirred for 30 min, a solution of 2.8 M TBHP in CH_2Cl_2 (2.1 mL, 5.85 mmol) was added to the mixture. After being stirred for 18 h at -20 °C, the resultant mixture was quenched with saturated aqueous $Na_2S_2O_3$, diluted with EtOAc, and allowed to warm to room temperature. The precipitates were removed by filtration through a Celite® pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a mixture of **55** and D-(-)- DET as a yellow oil.

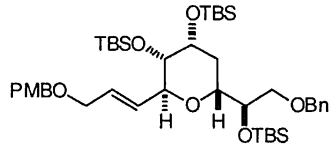
To a solution of the above mixture of **55** and D-(-)-DET in MeOH (30 mL) was added K_2CO_3 (80 mg, 0.585 mmol) at 0 °C. After being stirred for 3 h at 0 °C, the resultant mixture was quenched with pH 7.0 phosphate buffer, then MeOH was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to provide **56**. This crude **56** was used for next step without further purification.

To a solution of the above crude **56** in CH_2Cl_2 (29 mL) was added PPTS (73.2 mg, 0.292

mmol) at 0 °C and stirred for 19 h. The resultant mixture was quenched with Et_3N and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/MeOH = 1/0→30/1→20/1→10/1) afforded **57** (782 mg, 60% for 3 steps) as a colorless syrup: $[\alpha]_D^{26}$ -23.7 (*c* 0.75, $CHCl_3$); R_f = 0.30 (hexane/EtOAc = 3/1); IR (film) ν 3387, 2910, 2864, 1612, 1513, 1454, 1248, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.19 (m, 7H), 6.86-6.82 (m, 2H), 5.79 (dt, *J* = 15.9, 5.4, 1.2 Hz, 1H), 5.65 (dd, *J* = 15.9, 4.4 Hz, 1H), 4.51 (brs, 1H), 4.49 (s, 2H), 4.39 (s, 2H), 3.92 (d, *J* = 5.4 Hz, 2H), 3.81-3.74 (m, 2H), 3.76 (s, 3H), 3.71-3.68 (m, 2H), 3.54 (d, *J* = 6.0 Hz, 2H), 1.93 (ddd, *J* = 12.6, 12.6, 12.6 Hz, 1H), 1.61 (brd, *J* = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 137.9, 130.4, 130.0, 129.4, 128.4, 128.2, 127.7, 127.7, 76.9, 73.4, 72.4, 72.1, 71.0, 70.6, 69.7, 69.4, 65.9, 55.2, 30.9; HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_7Na$ [$(M+Na)^+$] 467.2046, found 467.2036.

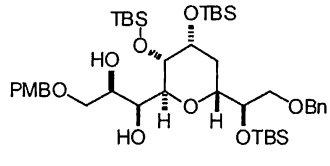


Triacetate 58. To a solution of **57** (1.4 mg, 2.9 μmol) in pyridine (60 μL) was added and Ac_2O (20 μL, 21 μmol) at 0 °C and stirred at room temperature for 6 h. The resultant mixture was concentrated in *vacuo* to provide **58** as a yellow oil. R_f = 0.50 (hexane/EtOAc = 1/1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 7H), 6.87-6.83 (m, 2H), 5.94 (dtd, *J* = 16.0, 5.5, 1.8 Hz, 1H), 5.70 (ddt, *J* = 16.0, 4.6, 1.7 Hz, 1H), 5.20 (dd, *J* = 2.3, 2.3 Hz, 1H), 5.13 (ddd, *J* = 5.8, 5.8, 4.0 Hz, 1H), 5.09 (ddd, *J* = 12.0, 4.6, 2.9 Hz, 1H), 4.59 (brs, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.41 (s, 2H), 4.07 (ddd, *J* = 12.0, 4.0, 2.9 Hz, 1H), 3.95 (dd, *J* = 5.4, 1.7 Hz, 2H), 3.77 (s, 3H), 3.67 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.58 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H), 1.89 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.64 (brd, *J* = 12.0 Hz, 1H).



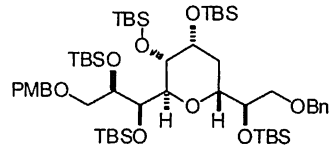
Silyl ether 44. To a solution of **57** (127 mg, 0.286 mmol) in CH_2Cl_2 (3.3 mL) were added

2,6-lutidine (172 μL , 1.5 mmol) and TBSOTf (300 μL, 1.4mmol) at 0 °C and stirred for 30 min. The resultant mixture was quenched with aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with hexane (x3). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/0) afforded **15** (178 mg, 89%) as a colorless oil: $[\alpha]_D^{26}$ -6.63 (*c* 0.15, $CHCl_3$); R_f = 0.63 (hexane/EtOAc = 5/1); IR (film) ν 2952, 2928, 2887, 2856, 1251, 1126, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.21 (m, 7H), 6.87-6.83 (m, 2H), 5.79 (dtd, *J* = 15.9, 5.4, 1.8 Hz, 1H), 5.72 (dd, *J* = 15.9, 4.3 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.42 (s, 2H), 4.38 (brs, 1H), 3.97 (d, 5.4 Hz, 2H), 3.83-3.76 (m, 3H), 3.78 (s, 3H), 3.74-3.67 (m, 2H), 3.45 (dd, *J* = 9.8, 6.3 Hz, 1H), 1.94 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.40 (brd, *J* = 12.0 Hz, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.5, 130.3, 129.4, 129.3, 129.2, 128.2, 127.6, 127.4, 113.8, 79.2, 73.7, 73.4, 73.0, 71.9, 71.7, 71.3, 69.9, 68.6, 55.3, 30.2, 26.1, 25.9, 25.8, 18.3, 18.2, -4.4, -4.5, -4.5, -4.8, -4.9; HRMS (ESI-TOF) calcd for $C_{43}H_{74}O_7Si_3Na$ $[(M+Na)^+]$ 809.4640, found 809.4598.



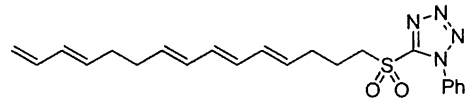
Diol 59. To a mixture of $K_2OsO_4 \cdot 2H_2O$ (9 mg, 25 μmol), $(DHQD)_2PHAL$ (39 mg, 50 μmol), $K_3Fe(CN)_6$ (487 mg, 148 μmol), K_2CO_3 (204 mg, 148 μmol) and $MeSO_2NH_2$ (140 mg, 148 μmol) in *t*-BuOH (1.5 mL) and H_2O (2.5 mL) was added a solution of **44** (390 mg, 495 μmol)) in *t*-BuOH (1.0 mL) at 0 °C. After being stirred for 18 h at 0 °C, the resultant mixture was quenched with solid $Na_2S_2O_3 \cdot 5H_2O$, and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexanes/EtOAc = 2/1→1/1→1/3) afforded **59** (375 mg, 97%) as a colorless syrup: $[\alpha]_D^{27}$ +13.3 (*c* 0.26, $CHCl_3$); R_f = 0.30 (hexane/EtOAc = 3/1); IR (film) ν 3469, 2953, 2929, 2889, 2856, 1252, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.23 (m,

5H), 7.22-7.17 (m, 2H), 6.88-6.83 (m, 2H), 4.49 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.43 (s, 2H), 4.06 (brs, 1H), 3.97 (brs, 1H), 3.91 (ddd, J = 12.0, 4.0, 2.6 Hz, 1H), 3.83-3.76 (m, 2H), 3.79 (s, 3H), 3.71 (ddd, J = 5.7, 4.6, 4.6 Hz, 1H), 3.64 (dd, J = 9.6, 4.6 Hz, 1H), 3.60 (dd, J = 9.6, 4.2 Hz, 1H), 3.54 (dd, J = 9.6, 5.6 Hz, 1H), 3.52 (m, 1H), 3.41 (dd, J = 9.6, 5.7 Hz, 1H), 2.74 (brd, J = 5.3 Hz, 1H), 2.66 (brs, 1H), 1.97 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.39 (brd, J = 12.0 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3Hx2), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3Hx2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 138.3, 129.6, 129.4, 128.2, 127.6, 127.4, 113.9, 79.4, 73.7, 73.4, 72.9, 72.3, 71.5, 68.9, 68.8, 68.3, 68.2, 55.2, 29.9, 26.2, 25.9, 18.3, 18.2, -4.3, -4.4, -4.6, -4.8, -4.8; HRMS (ESI-TOF) calcd for $C_{43}H_{76}O_9Si_3Na$ [$(M+Na)^+$] 843.4695, found: .843.4668.



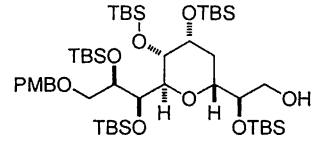
Silyl ether 60. To a solution of **59** (332 mg, 0.404 mmol) in CH_2Cl_2 (4 mL) were added 2,6-lutidine (163 μL, 1.40 mmol) and TBSOTf (276 μL, 1.20 mmol) at 0 °C and stirred at room temperature for 14 h. The resultant solution was cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 50/1→30/1→20/1) afforded **60** (406 mg, 96%) as a colorless oil: $[\alpha]_D^{27}$ +15.2 (*c* 0.40, $CHCl_3$); R_f = 0.45 (hexane/EtOAc = 20/1); IR (film) ν 2954, 2929, 2890, 2857, 1252, 1096, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.16 (m, 7H, Ph and PhOMe), 6.84-6.80 (m, 2H, PhOMe), 4.47 (s, 2H, benzyl), 4.38 (s, 2H, benzyl), 4.00-3.95 (m, 2H, H32, 34), 3.94 (brs, 1H, H35), 3.86 (brd, J = 11.4 Hz, 1H, H36), 3.80 (m, 1H, H39), 3.78 (s, 3H, MeOPh), 3.77-3.69 (m, 2H, H33, H40a), 3.48-3.39 (m, 3H, H38, H40b, H31a), 3.29 (dd, J = 8.8, 6.3 Hz, 1H, H31b), 1.87 (ddd, J = 11.4, 11.4, 11.4 Hz, 1H, H37ax), 1.48 (brd, J = 11.4 Hz, 1H, H37eq), 0.87-0.82 (m, 9Hx5, *t*-Bu-Si), 0.06 to -0.03 (m, 3Hx10, Me_2Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 138.8, 130.6, 129.0, 128.2, 127.4, 127.2, 113.6, 78.5, 73.3, 73.1, 73.1, 72.5, 72.5, 72.0, 71.9, 70.8, 69.0, 68.9, 55.2, 29.1, 25.8, 25.8, 18.4, 18.1, 18.1, 18.0, -3.2, -4.0, -4.1, -4.3, -4.3, -4.4, -4.5,

-4.8, -5.0, -5.0; HRMS (ESI-TOF) calcd for $C_{55}H_{104}O_9Si_5Na$ [$(M+Na)^+$] 1071.6424, found 1071.6405.

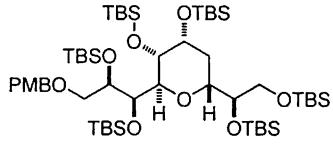


Sulfone 42 . To a solution of alcohol **76** (40 mg, 183 μmol), PTSH (49g, 275 μmol) and Ph_3P (72 mg, 275 μmol) in THF (1.8 mL) were added DIAD (1.0 M in toluene, 145 μL, 275 μmol) at 0 °C and stirred at rt for 30 min. The resultant solution was quenched with satd NH_4Cl aq and extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. This crude **77** was used for next step without further purification.

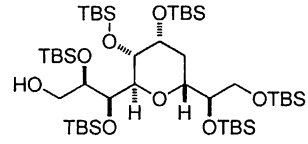
The above sulfide **77** was dissolved in THF (1.2 mL) EtOH (0.6 mL) and cooled to 0 °C. In a separate flask, $Mo_7O_{24}(NH_4)_6$ $4H_2O$ (0.045 g, 37 μmol) was dissolved in 30% aqueous H_2O_2 (200 μL, 1.83 mmol) at 0 °C. The H_2O_2 solution was added to the substrate solution dropwise, and the mixture was stirred at rt for 4 h. The reaction was quenched with water and diluted with Et_2O. The layers were separated and the organic phase was washed satd $Na_2S_2O_3$ aq and satd NaCl aq. The combined aqueous phases were extracted twice with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes/EtOAc = 7/1) afforded **42** (41 mg, 55% for 2 steps) as a colorless amorphous: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.33 (m, 2H), 6.90 (m, 3H), 6.28 (ddd, J = 17.4, 10.5, 10.5 Hz, 1H), 6.20-5.8 (m, 5H), 5.56 (m, 1H), 5.21 (m, 1H), 5.06 (d, J = 17.4 Hz, 1H), 4.92 (d, J = 10.4 Hz, 1H), 3.24 (t, J = 7.4 Hz, 1H), 2.08-1.98 (m, 4H), 1.79-1.69 (m, 4H); ^{13}C NMR (150 MHz, C_6D_6) δ 154.1, 137.6, 134.2, 134.1, 133.5, 132.9, 132.5, 132.0, 131.4, 130.9, 130.9, 130.7, 129.5, 128.3, 125.2, 115.2, 55.4, 32.8, 32.6, 30.9, 22.0; HRMS (ESI-TOF) calcd for, found: .



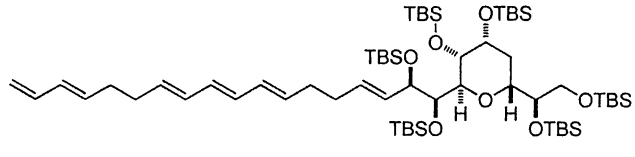
Alcohol 78. To a solution of the benzyl ether **60** (800 mg, 744 μmol) in EtOAc (2 mL) was added Raney nickel W-2 in EtOH (4 mL) at rt and stirred at 35 °C for 48 h under an atmosphere of H_2. The mixture was filtered through celite (EtOAc) and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 10/1) afforded **78** (740 mg, quant) as a colorless syrup; $[\alpha]_D^{27}$ +15.2 (*c* 0.40, $CHCl_3$); R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32-7.16 (m, 2H), 6.84-6.80 (m, 2H), 4.47 (s, 2H), 4.00-3.95 (m, 2H), 3.94 (brs, 1H), 3.86 (brd, *J* = 11.4 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.77-3.69 (m, 2H), 3.48-3.39 (m, 3H), 3.29 (dd, *J* = 8.8, 6.3 Hz, 1H), 1.87 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.48 (brd, *J* = 11.4 Hz, 1H), 0.87-0.82 (m, 9Hx5), 0.06 to -0.03 (m, 3Hx10); ^{13}C NMR (150 MHz, $CDCl_3$) δ ; HRMS (ESI-TOF) calcd for, found:.



Silyl ether 79. To a solution of the alcohol **78** (30 mg, 32 μmol) in DMF (310 μL) was added imidazole (11 g, 159 μmol) and TBSCl (19 mg, 127 μmol) at 0 °C and stirred at rt for 12 h. The resultant mixture was quenched with sat. $NaHCO_3$ aq. and H_2O, diluted with hexane. The aqueous layer was extracted with hexane (x3), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexanes/EtOAc = 20/1) afforded **79** (33 mg, 96%) as a colorless syrup: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32-7.16 (m, 2H), 6.84-6.80 (m, 2H), 4.47 (s, 2H), 4.00-3.95 (m, 2H), 3.94 (brs, 1H), 3.86 (brd, *J* = 11.4 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.77-3.69 (m, 2H), 3.48-3.39 (m, 3H), 3.29 (dd, *J* = 8.8, 6.3 Hz, 1H), 1.87 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.48 (brd, *J* = 11.4 Hz, 1H), 0.87-0.82 (m, 9Hx5), 0.06 to -0.03 (m, 3Hx10); ^{13}C NMR (150 MHz, $CDCl_3$) δ ; HRMS (ESI-TOF) calcd for, found: .



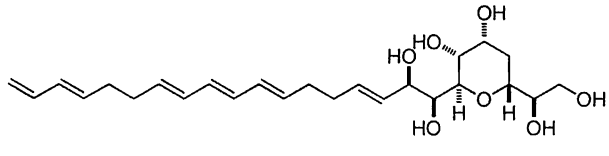
Alcohol 80. To a solution of the *p*-methoxybenzyl ether **79** (37 mg, 43.4 μmol) in CH_2Cl_2 (2 mL) at 0 °C was added pH 7 buffer (400 μL) followed by DDQ (15 mg, 65.0 μmol). The resulting suspension was stirred at 0 °C for 30 minutes before being diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), then the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. urification by silica gel column chromatography (hexanes/EtOAc = 10/1→8/1) afforded silyl ether (29 mg, 89%) as a colorless syrup: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.47 (s, 2H), 4.00-3.95 (m, 2H), 3.94 (brs, 1H), 3.86 (brd, J = 11.4 Hz, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.77-3.69 (m, 2H), 3.48-3.39 (m, 3H), 3.29 (dd, J = 8.8, 6.3 Hz, 1H), 1.87 (ddd, J = 11.4, 11.4, 11.4 Hz, 1H), 1.48 (brd, J = 11.4 Hz, 1H), 0.87-0.82 (m, 9Hx6), 0.06 to -0.03 (m, 3Hx12); ^{13}C NMR (150 MHz, $CDCl_3$) δ ; HRMS (ESI-TOF) calcd for, found: .



Olefin 41a. To a solution of alcohol **80** (5 mg, 5.2 μmol) in CH_2Cl_2 (260 μL) was aded Dess-Martin periodinane (22 mg, 52 μmol) at 0 °C and stirred at rt for 1.5 h. The mixture was diluted with hexane and the reaction was quenched with satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq. The layers were separated and the organic phase was washed with water and brine. The organic layer was dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude **43a** was used to next reaction without further purification.

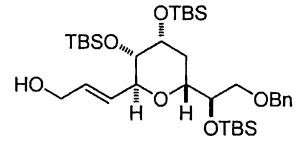
Sulfone **42** (25 mg, 61 μmol) was dissolved in THF (620 μL) and cooled to –78 °C. To the solution was added KHMDS (0.5 M in toluene, 60 μL, 30 μmol) and the mixture was maintained for 15 min. To this solution was added the solution of the above aldehyde **43a** in

THF (200 μL) via canula and stirred for 30 min. After stirring at rt for 8 h, the reaction was quenched with saturated, aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed water and brine, and dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes/EtOAc = 20/1) afforded **41a** (5.5 mg, 92% for 2 steps) as a colorless syrup: $[\alpha]^{21}_D$ +14.1 (*c* 0.28, CH_2Cl_2); R_f = 0.38 (hexane/CH_2Cl_2 = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.29 (m, 1H), 6.22-5.99 (m, 5H), 5.75 (m, 2H), 5.64 (m, 1H), 5.55 (m, 2H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.63 (brd, *J* = 6.2 Hz, 1H), 4.39 (s, 1H), 4.23 (d, *J* = 10.7 Hz, 1H), 4.18 (d, *J* = 10.5 Hz, 1H), 4.10 (brd, *J* = 12.0 Hz, 1H), 4.01 (dd, *J* = 5.7, 5.7 Hz, 1H), 3.88 (d, *J* = 10.7 Hz, 1H), 3.85 (m, 1H), 3.80 (dd, *J* = 10.7, 7.2 Hz, 1H), 2.25-2.0 (m, 9H), 1.97 (brd, *J* = 12.0 Hz, 1H), 1.10 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.02 (s, 9H), 1.01 (s, 9H), 0.40 (s, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.15, (s, 3H), 0.14 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 137.6, 133.6, 133.4, 133.2, 132.0, 131.8, 131.7, 131.6, 131.5, 130.7, 128.3, 115.2, 79.4, 76.5, 74.8, 73.4, 73.2, 69.6, 69.5, 65.2, 32.9, 32.8, 32.7, 32.6, 29.6, 26.3, 26.3, 26.2, 26.2, 26.2, 26.2, 18.7, 18.7, 18.5, 18.5, 18.4, 18.4, -3.0, -3.3, -3.7, -3.8, -3.8, -3.9, -4.1, -4.3, -4.5, -4.6, -5.1, -5.1; HRMS (ESI-TOF) calcd for, found: .

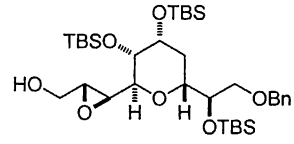


C43-C67 part 40a. To a Teflon tube containing a solution of the silyl ether **41a** (4.3 mg, 3.8 μmol) in THF (400 μL) was added 18% HF·Py (25 μL, 226 μmol) and stirred at 50°C for 36 h. The resulting solution was quenched with Et_3N and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/EtOH = 1/0 to 4/1) afforded **40a** (1.7 mg, quant) as a colorless amorphous: $[\alpha]_D$ (*c* , CH_3OH); R_f = 0.23 (EtOAc/MeOH = 4/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, CD_3OD:C_5D_5N = 2:1) δ 6.24 (m, 1H, H66), 6.04 (m, 1H, H57) 6.01 (m, 1H, H65), 5.99 (m, 1H, H60), 5.98 (m, 1H, H59), 5.97 (m, 1H, H58), 5.78 (m, 1H, H53), 5.77 (m, 1H, H52), 5.63 (m, 2H, H64 and H61), 5.60 (m, 1H, H56), 5.04 (d, *J* = 17.0 Hz, H67a), 4.89 (d, *J* = 11.7 Hz, H67b), 4.46 (brs, 1H, H51), 4.28 (dd, *J* = 3.1, 2.3 Hz,

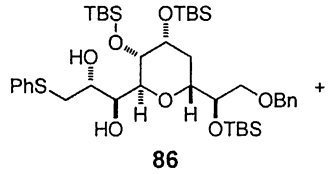
1H, H48), 4.23 (dd, J = 9.6, 2.3 Hz, 1H, H49), 4.12 (ddd, J = 10.8, 4.3, 3.3 Hz, 1H, H47), 3.92 (dd, J = 9.6, 1.9 Hz, 1H, H50), 3.88 (ddd, J = 10.8, 3.3, 3.3 Hz, 1H, H45), 3.78 (m, 1H, H43a), 3.73-3.69 (m, 1H, H44, H43b), 2.13 (ddd, J = 12.4, 10.8, 10.8 Hz, 1H, H46ax), 2.11-2.01 (m, 8H, H62, H61, H55, H54), 1.72 (ddd, J = 12.4, 3.3, 3.3 Hz, 1H, H46eq); ^{13}C NMR (150 MHz, CD_3OD:C_5D_5N = 2:1) δ 138.4 (C66), 135.2 (C64), 134.5 (C61), 134.1 (C56), 132.6 (C65), 132.6 (C53), 132.5 (C57), 132.3 (C58), 132.2 (C59), 132.1 (C60), 132.1 (C53), 115.5 (C67), 78.6 (C49), 75.2 (C44), 72.5 (C51), 72.4 (C50), 72.4 (C45), 69.2 (C48), 67.3 (C47), 64.1 (C43), 33.5 (C55), 33.5 (C54), 33.4 (C62), 33.3 (C63), 31.6 (C46); HRMS (ESI-TOF) calcd for, found: .



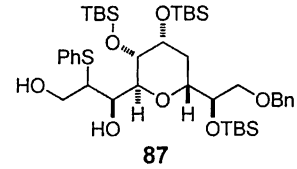
Alcohol 84. To a solution of the *p*-methoxybenzyl ether **44** (737 mg, 0.936 mmol) in CH_2Cl_2 (9.3 mL) at 0 °C was added pH 7 buffer (0.5 mL) followed by DDQ (255 mg, 1.12 mmol). The resulting suspension was stirred at 0 °C for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and satd $Na_2S_2O_3$aq. The layers were separated and the aqueous phase was extracted with CH_2Cl_2, then the combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded **84** (586 mg, 94%) as a colorless syrup: $[\alpha]^{32}_D$ -10.9 (*c* 0.72, $CHCl_3$); R_f = 0.26 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.29 (m, 3H), 7.27-7.24 (m, 2H), 5.84 (ddd, J = 15.8, 5.2, 1.7 Hz, 1H), 5.69 (ddd, J = 15.8, 4.6, 1.6 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.37 (brs, 1H), 4.14-4.09 (m, 2H), 3.81-3.75 (m, 2H), 3.72-3.65 (m, 3H), 3.45 (dd, J = 15.6, 6.0 Hz, 1H), 1.95 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.38 (brd, J = 12.0 Hz, 1H), 0.87 (s, 9H), 0.86 (s, 9Hx2), 0.05 (s, 3H), 0.04 (s, 3Hx2), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 138.6, 130.3, 129.4, 129.3, 128.2, 127.6, 127.4, 113.8, 79.2, 73.7, 73.4, 73.1, 71.9, 71.7, 71.4, 69.9, 68.6, 55.3, 30.2, 26.1, 25.9, 25.8, 18.3, 18.2, 18.2, -4.4, -4.4, -4.5, -4.5, -4.8, -4.9; HRMS (ESI-TOF) calcd for, found: .



Epoxide 47. To a mixture of powdered MS4A (350 mg) in CH_2Cl_2 (6 mL) were added D-(-)-DET (91 μL, 0.525 mmol) and Ti(O*i*-Pr)$_4$ (126 μL, 0.42 mmol) at -25 °C. After being stirred for 30 min, a solution of **84** (700 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) was added to the mixture. After being stirred for 30 min, a solution of 3.1 M TBHP in CH_2Cl_2 (0.51 mL, 1.57 mmol) was added to the mixture. After being stirred for 14 h at -20 °C, the resultant mixture was quenched with saturated aqueous $Na_2S_2O_3$, diluted with EtOAc, and allowed to warm to room temperature. The precipitates were removed by filtration through a Celite® pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with satd NaClaq, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 7/1→4/1) afforded a epoxide **47** (641 mg, 89%) as a colorless syrup: $[\alpha]^{32}_D$ +5.8 (*c* 0.60, $CHCl_3$)R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.29 (m, 3H), 7.27-7.24 (m, 2H), 5.84 (ddd, *J* = 15.8, 5.2, 1.7 Hz, 1H), 5.69 (ddd, *J* = 15.8, 4.6, 1.6 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.37 (brs, 1H), 4.14-4.09 (m, 2H), 3.81-3.75 (m, 2H), 3.72-3.65 (m, 3H), 3.45 (dd, *J* = 15.6, 6.0 Hz, 1H), 1.95 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.38 (brd, *J* = 12.0 Hz, 1H), 0.87 (s, 9H), 0.86 (s, 9Hx2), 0.05 (s, 3H), 0.04 (s, 3Hx2), 0.03 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 128.3, 127.6, 127.5, 79.6, 73.3, 73.5, 73.2, 71.7, 70.0, 69.0, 61.2, 57.0, 53.8, 30.2, 26.1, 25.9, 25.8, 18.3, 18.2, 18.2, -4.3, -4.4, -4.5, -4.6, -4.8, -5.0; HRMS (ESI-TOF) calcd for, found: .



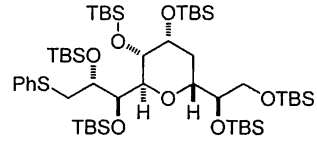
86



87

Sulfide 86 and 87. A vigorously stirred mixture of **47** (271 mg, 397 μmol) in *t*-butanol (27

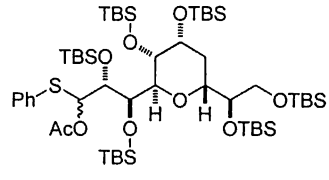
mL) and 1.5 N NaOH solution (27 mL, 40.5 mmol) was heated under reflux in a argon atmosphere. To this mixture was added thiophenol (1.0 M in *t*-butanol, 1.19 mL, 1.19 mmol) via a syringe over a period of 8 h. When all the thiophenol had been added, the reaction mixture was cooled to room temperature, diluted with satd NaCl aq, and extracted with EtOAc. The organic layer was and dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a mixture of **86** and **87** (244 mg, 78%, **86/87** = 5/1) as a pale yellow syrup: R_f = 0.45 (hexane/EtOAc = 4/1).



Silyl ether 88. To a solution of the mixture of **86** and **87** (103 mg, 0.13 mmol) in $ClCH_2CH_2Cl$ (1.3 mL) at 0 °C was added pH 7 buffer (70 μL) followed by DDQ (237 mg, 1.04 mmol). The resulting suspension was stirred at 50 °C for 4 h before being diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc, then the combined organic extracts were washed with H_2O and satd aq NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to give crude alcohol as a yellow syrup. This crude was used for next step without further purification.

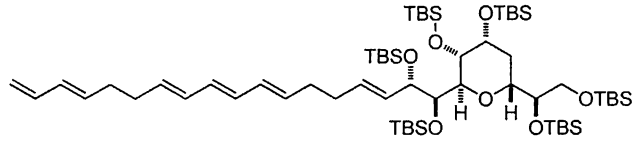
To a solution of above crude in CH_2Cl_2 (1.3 mL) were added 2,6-lutidine (120 μL, 0.520 mmol) and TBSOTf (120 μL, 1.04 mmol) at 0 °C and stirred at room temperature for 14 h. The resultant solution was cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 50/1→30/1→20/1) afforded **88** (54 mg, 40% for 2 steps) as a colorless oil: $[\alpha]^{31}_D$ +13.8 (*c* 0.32, $CHCl_3$); R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31-7.21 (m, 3H), 7.11-7.07 (m, 2H), 4.11-4.06 (m, 2H), 4.04 (brs, 1H), 3.94 (d, *J* = 9.0 Hz, 1H), 3.80 (ddd, *J* = 12.0, 4.0 2.2 Hz,

1H) 3.73 (dd, J = 5.8, 5.8 Hz, 1H), 3.55-3.50 (m, 2H), 3.22 (dd, J = 14.3, 4.5 Hz, 1H), 2.96 (dd, J = 14.3, 8.1 Hz, 1H), 1.79 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.65 (brd, J = 12.0 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9Hx2), 0.87 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05-0.03 (m, 3Hx7), 0.00 (s, 3Hx2), -0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.3, 128.9, 127.8, 125.2, 75.5, 73.1, 69.1, 68.6, 64.8, 28.3, 26.2, 26.1, 26.1, 26.0, 25.9, 25.8, -3.0. -3.7, -4.1, -4.1, -4.3, -4.4, -4.5, -4.6, -5.0, -5.2, -5.2, -5.3, -5.3; HRMS (ESI-TOF) calcd for, found: .



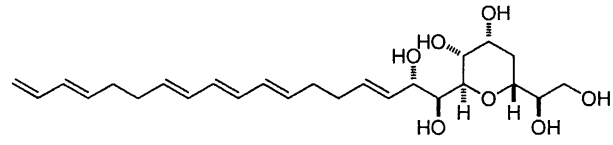
Mixed acetal 90. To a solution of phenyl sulfide **88** (28 mg, 27 μmol) in CH_2Cl_2 (530 μL) were added MCPBA (0.25 M in CH_2Cl_2, 110 μl, 275 μmol) at -78 °C and stirred for 20 min. The resultant was quenched with satd $NaHCO_3$ and satd $Na_2S_2O_3$, and stirred at 0 °C for 20 min. The layers were separated and the aqueous phase was extracted with hexane. The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. This crude **89** was used for next step without further purification.

The above crude sulfoxide **89**, dissolved in acetic anhydride (890 μL) containing sodium acetate (440 mg; 534 μmol), was refluxed under a argon atmosphere for 36 h. The mixture was concentrated under reduced pressure, diluted with hexane and washed with satd $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 30/1→20/1) afforded mixed acetal **90** (16 mg, 55% for 2 steps, dr = 1:1) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.14 (m, 10H), 6.27 (d, J = 8.6 Hz, 2H), 4.39 (d, 8.3 Hz, 1H), 4.06 (brs, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.96-3.94 (m, 2H), 3.84-3.70 (m, 2H), 3.56-3.49 (m, 2H), 1.95 (s, 3H), 1.88 (s, 3H), 1.80 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.75 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.68-164 (m, 2H), 0.94-0.84 (m, 9Hx12), 0.12-0.02 (m, 3Hx24); ^{13}C NMR (150 MHz, $CDCl_3$) δ ; HRMS (ESI-TOF) calcd for, found: .

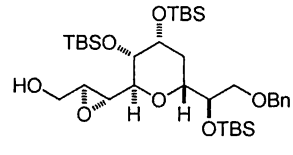


Olefin 41b. To a solution of mixed acetal **90** (10 mg, 9.0 μmol) in CH_2Cl_2 (1.1 mL) was added DIBALH (1.0 M in hexane, ml, mmol) at -78 °C and stirred for 30 min. The reaction was quenched with sat. Na^+, K^+-tartrate aq. and warmed to rt. This solution was diluted with Et_2O and stirred for 1.5 h. The aqueous layer was extracted with Et_2O. The combined **43b** organic layers were dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude was used for next step without further purification.

To the solution of sulfone **42** (15 mg, 37 μmol) in THF (370 μL) was added KHMDS (0.5 M in toluene, 30 μL, 15 μmol) and the mixture was maintained for 10 min. To the solution of sulfone are added a solution of the above aldehyde **43b** in THF (350 μl) via canula and the reaction was maintained for 30 min. After stirring at rt for 10 h, the reaction was quenched with saturated, aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed water and brine, and dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes/EtOAc = 20/1) afforded silyl ether **41b** (3.2 mg, 40% for 2 steps) as a colorless syrup: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.29 (m, 1H), 6.22-5.99 (m, 5H), 5.75 (m, 2H), 5.64 (m, 1H), 5.55 (m, 2H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.63 (brd, *J* = 6.2 Hz, 1H), 4.39 (s, 1H), 4.23 (d, *J* = 10.7 Hz, 1H), 4.18 (d, *J* = 10.5 Hz, 1H), 4.10 (brd, *J* = 12.0 Hz, 1H), 4.01 (dd, *J* = 5.7, 5.7 Hz, 1H), 3.88 (d, *J* = 10.7 Hz, 1H), 3.85 (m, 1H), 3.80 (dd, *J* = 10.7, 7.2 Hz, 1H), 2.25-2.0 (m, 9H), 1.97 (brd, *J* = 12.0 Hz, 1H), 1.10 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 1.06 (s, 9H), 1.02 (s, 9H), 1.01 (s, 9H), 0.40 (s, 3H), 0.31 (s, 3H), 0.30 (s, 3H), 0.28 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.15, (s, 3H), 0.14 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 137.6, 133.6, 133.4, 133.2, 132.0, 131.8, 131.7, 131.6, 131.5, 130.7, 128.3, 115.2, 79.4, 76.5, 74.8, 73.4, 73.2, 69.6, 69.5, 65.2, 32.9, 32.8, 32.7, 32.6, 29.6, 26.3, 26.3, 26.2, 26.2, 26.2, 26.2, 18.7, 18.7, 18.5, 18.5, 18.4, 18.4, -3.0, -3.3, -3.7, -3.8, -3.8, -3.9, -4.1, -4.3, -4.5, -4.6, -5.1, -5.1; HRMS (ESI-TOF) calcd for, found: .

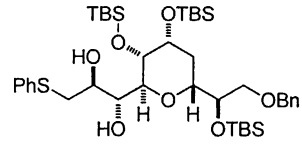


51-*epi*-C43-C67 part 40b. To a Teflon® tube containing a solution of the silyl ether **41b** (3.2 mg, 2.8 μmol) in THF (280 μL) was added 18% HF·Py (19 μL, 169 μmol) and stirred at 50°C for 48 h. The resulting solution was quenched with Et_3N and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/MeOH = 1/0→4/1) afforded **40b** (1.3 mg, quant) as a colorless amorphous: $[\alpha]_D^{28}$ -4.30 (*c* 0.06, CH_3OH); R_f = 0.26 (EtOAc/MeOH = 4/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, CD_3OD:C_5D_5N = 2:1) δ 6.24 (ddd, *J* = 16.9, 10.0, 10.0 Hz, 1H, H66), 6.04 (m, 1H, H57) 6.01 (m, 1H, H65), 5.99 (m, 1H, H60), 5.98 (m, 1H, H59), 5.97 (m, 1H, H58), 5.78 (m, 1H, H53), 5.77 (m, 1H, H52), 5.63 (m, 2H, H64 and H61), 5.60 (m, 1H, H56), 5.04 (d, *J* = 16.9 Hz, H67a), 4.89 (d, *J* = 10.0 Hz, H67b), 4.44 (brs, 1H, H51), 4.30 (brs, 1H, H48), 4.14 (m, 1H, H47), 4.14 (dd, *J* = 9.4, 3.3 Hz, 1H, H50), 4.01 (dd, *J* = 9.4, 2.2 Hz, 1H, H49), 3.91 (ddd, *J* = 11.0, 2.6, 2.6 Hz, 1H, H45), 3.78 (dd, *J* = 10.7, 5.4 Hz, 1H, H43a), 3.74 (dd, *J* = 10.7, 6.0 Hz, 1H, H43b), 3.69 (m, 1H, H44), 2.17 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 1H, H46ax), 2.11-2.00 (m, 8H, H62, H61, H55, H54), 1.71 (brd, *J* = 11.0 Hz, 1H, H46eq); ^{13}C NMR (150 MHz, CD_3OD:C_5D_5N = 2:1) δ 138.4 (C66), 135.2 (C64), 134.5 (C61), 134.1 (C56), 133.9 (C53), 132.6 (C65), 132.4 (C57), 132.3 (C58), 132.2 (C59), 132.1 (C60), 130.0 (C52), 115.5 (C67), 79.8 (C49), 75.2 (C44), 74.4 (C51), 72.6 (C50), 72.4 (C45), 68.8 (C48), 67.3 (C47), 64.3 (C43), 33.5 (C55), 33.5 (C54), 33.4 (C62), 33.3 (C63), 31.0 (C46); HRMS (ESI-TOF) calcd for, found: .



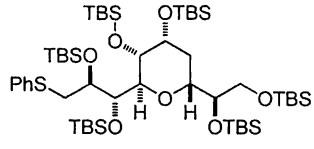
Epoxide 48. To a mixture of powdered MS4A (300 mg) in CH_2Cl_2 (2.5 mL) were added L-(-)-DET (80 μL, 468 μmol) and Ti(O*i*-Pr)$_4$ (112 μL, 375 μmol) at -25 °C. After being stirred for 30 min, a solution of **85** (250 g, 375 mmol) in CH_2Cl_2 (1.2 mL) was added to the mixture. After being stirred for 30 min, a solution of 3.1 M TBHP in CH_2Cl_2 (182 μL, 563 μmol) was added to the mixture. After being stirred for 14 h at -20 °C, the resultant mixture was

quenched with saturated aqueous $Na_2S_2O_3$, diluted with EtOAc, and allowed to warm to room temperature. The precipitates were removed by filtration through a Celite® pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a epoxide **48** (200 mg, %) as a colorless syrup: $[\alpha]^{29}_D$ -11.9 (*c* 0.33, $CHCl_3$); R_f = 0.30 (hexane/EtOAc = 4/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.02 (ddd, *J* = 11.7, 4.0, 2.6 Hz, 1H), 3.90-3.85 (m, 3H), 3.79-3.75 (m, 2H), 3.63 (dd, II =9.7, 4.5 Hz, 1H), 3.62 (m, 1H), 3.42 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.22 (m, 1H), 3.11 (dd, *J* = 2.6, 2.6 Hz, 1H), 3.45 (dd, *J* = 15.6, 6.0 Hz, 1H), 1.94 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.38 (m, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3Hx2), 0.05 (s, 3H), 0.04 (s, 3Hx2), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 128.3, 127.6, 127.4, 74.0, 73.5, 73.4, 72.1, 71.8, 69.2, 60.7, 55.8, 54.5, 29.7, 26.1, 25.9, 25.8, 18.3, 18.2, 18.2, -4.3, -4.3, -4.5, -4.5, -4.8, -5.0; HRMS (ESI-TOF) calcd for, found: .



Sulfide 91. A vigorously stirred mixture of **48** (50 mg, 73 μmol) in *t*-butanol (5.0 mL) and 1.5 N NaOH solution (5.0 mL, 7.5 mmol) was heated under reflux in a nitrogen atmosphere. To this mixture was added thiophenol (0.05 M in *t*-butanol, 4.3 ml, 219 μmol) via a syringe pump over a period of 6 h. When all the thiophenol had been added, the reaction mixture was cooled to room temperature and diluted with satd NaCl aq, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a sulfide **91** (37 mg, 64%) as a colorless syrup: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 4.53 (d, *J* =12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.01 (brs, 1H), 3.90 (brd, *J* = 11.5 Hz, 1H), 3.73-3.66 (m, 3H), 3.61 (dd, *J* = 8.6, 4.6 Hz, 1H), 3.53 (brs, 1H), 3.43-3.38 (m, 2H), 3.01 (m, 1H), 2.81 (d, *J* = 4.1 Hz, 1H), 2.02 (ddd, *J* = 11.5, 11.5,

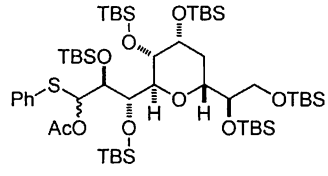
11.5 Hz, 1H), 1.36 (brd, J = 11.5 Hz, 1H), 0.86 (s, 9H), 0.85 (s, 9Hx2), 0.03-0.01 (m, 3Hx4), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 128.9, 128.7, 125.7, 84.2, 75.2, 74.5, 73.8, 72.1, 70.6, 69.7, 64.5, 36.6, 28.0, 26.1, 26.1, 26.0, 26.0, 25.8, 25.8, 18.5, 18.4, 18.2, 18.1, 18.1, 18.1, -3.8, -3.9, -4.1, -4.2, -4.3, -4.4, -4.4, -4.5, -4.8, -5.2, -5.3, -5.4; HRMS (ESI-TOF) calcd for, found: .



Silyl ether 93. To a solution of the *p*-methoxybenzyl ether **91** (38 mg, 48 μmol) in CH_2Cl_2 (1.1 mL) at 0 °C was added pH 7 buffer (70 μL) followed by DDQ (87 mg, 383 μmol). The resulting suspension was stirred at 50 °C for 2 h before being diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), then the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude alcohol as a yellow syrup. This crude **92** was subjected to the same reaction conditions, and the resulting crude was used for next step without further purification.

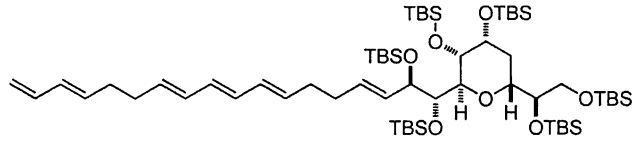
To a solution of above crude **92** in CH_2Cl_2 (2 mL) were added 2,6-lutidine (66 μL, 575 mmol) and TBSOTf (66 μL, 287 mmol) at 0 °C and stirred at room temperature for 14 h. The resultant solution was cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with hexane. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/CH_2Cl_2 = 1/0→7/1) afforded **93** (43 mg, 86% for 2 steps) as a colorless oil: $[\alpha]^{28}_D$ +24.7 (*c* 1.05, $CHCl_3$); R_f = 0.57 (hexane/CH_2Cl_2 = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.21 (m, 3H), 7.13-7.10 (m, 2H), 4.11-4.06 (m, 2H), 4.04 (brs, 1H), 3.98 (brd, J = 7.1 Hz, 1H), 3.92 (brd, J = 9.9 Hz, 1H), 3.83-3.79 (m, 2H), 3.71 (brs, 1H), 3.67-3.62 (m, 3H), 3.51 (dd, J = 9.9, 8.6 Hz, 1H), 3.17 (dd, J = 13.6, 8.2 Hz, 1H), 2.97 (dd, J = 13.6, 3.4 Hz, 1H), 1.78 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.65 (brd, J = 12.0 Hz, 1H), 0.89 (s, 9Hx2), 0.87 (s, 9H), 0.86 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.08 (m, 3Hx4), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3Hx3), -0.05 (s, 3H); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 137.5, 128.9, 128.7, 125.7, 84.2, 75.2, 74.5, 73.8, 72.1, 70.6, 69.7, 64.5, 36.6, 28.0, 26.1, 26.1, 26.0, 26.0, 25.8, 25.8, 18.5, 18.4, 18.2, 18.1, 18.1, 18.1, -3.7, -3.9, -4.1, -4.2, -4.3, -4.4, -4.4, -4.5, -4.8, -5.3, -5.3, -5.4; HRMS (ESI-TOF) calcd for, found: .



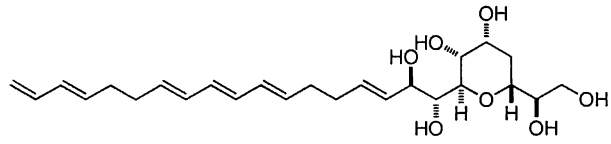
Mixed acetal 95. To a solution of phenyl sulfide **93** (21 mg, 20 μmol) in CH_2Cl_2 (1 mL) were added MCPBA (0.25 M in CH_2Cl_2, 100 μl, 25 μmol) at -78 °C and stirred for 20 min. The resultant was quenched with satd $NaHCO_3$ and satd $Na_2S_2O_3$, and stirred at 0 °C for 20 min. The layers were separated and the aqueous phase was extracted with hexane. The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. This crude **94** was used for next step without further purification.

The above crude sulphoxide **94**, dissolved in acetic anhydride (1 mL) containing sodium acetate (165 mg, 4 mmol), was refluxed under a argon atmosphere for 5 days. The mixture was concentrated under reduced pressure, diluted with hexane and washed with satd $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (hexanes/EtOAc = 30/1→20/1) afforded mixed acetal **95** (15 mg, 68% for two steps) as a colorless syrup: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49-7.14 (m, 10H), 6.27 (d, J = 8.6 Hz, 2H), 4.39 (d, 8.3 Hz, 1H), 4.06 (brs, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.96-3.94 (m, 2H), 3.84-3.70 (m, 2H), 3.56-3.49 (m, 2H), 1.95 (s, 3H), 1.88 (s, 3H), 1.80 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.75 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.68-164 (m, 2H), 0.94-0.84 (m, 9Hx12), 0.12-0.02 (m, 3Hx24); ^{13}C NMR (150 MHz, $CDCl_3$) δ ; HRMS (ESI-TOF) calcd for, found: .



Olefin 41c. To a solution of mixed acetal **95** (3 mg, 2.7 μmol) in CH_2Cl_2 (1 mL) was added DIBALH (1.0 M in hexane, 6 μl, 6 μmol) at -78 °C and stirred for 30 min. The reaction was quenched with sat. Na^+, K^+-tartrate aq. and warmed to rt. This solution was diluted with Et_2O and stirred for 1.5 h. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude **43c** was used for next step without further purification.

To the solution of sulfone **42** (15 mg, 37 mmol) in THF (400 μL) was added KHMDS (0.5 M in toluene, 38 μL, 19 μmol) and the mixture was maintained for 10 min. To the solution of sulfone are added a solution of an aldehyde **43c** in THF (400 μl) via canula and the reaction was maintained for 0.5 h, warmed to rt and stirred for 9 h. The reaction was quenched with satd NH_4Cl aq and diluted with Et_2O and water. The layers were separated and the organic phase was washed twice with water and once with brine. The combined aqueous phases were extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes/EtOAc = 1/0→30/1→20/1) afforded **41c** (1.2 mg, 40% for 2 steps) as a colorless oil: $[\alpha]^{23}_D$ +32.0 (*c* 0.07, CH_2Cl_2); R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.29 (m, 1H), 6.22-5.99 (m, 5H), 5.85 (dd, *J* = 15.7, 8.4 Hz, 1H), 5.75 (m, 1H), 5.64-5.50 (m, 3H), 5.07 (d, *J* = 17.0 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 4.31 (brd, *J* = 10.3 Hz, 1H), 4.27 (dd, *J* = 8.1, 2.9 Hz, 1H), 4.16 (dd, *J* = 7.6, 2.8 Hz, 1H), 4.06-3.99 (m, 4H), 3.87 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.23-1.98 (m, 12H), 1.10 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 1.05 (s, 9H), 1.03 (s, 9H), 1.02 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), 0.29 (s, 3H), 0.28 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.17, (s, 3H), 0.16 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 137.6, 134.3, 133.6, 133.5, 133.2, 131.9, 131.8, 131.7, 131.6, 131.5, 129.9, 128.3, 115.1, 83.2, 76.1, 75.9, 75.1, 72.7, 71.1, 70.2, 65.4, 32.8, 32.7, 32.6 32.5, 29.0, 26.5, 26.3, 26.3, 26.2, 26.1, 26.1, 18.8, 18.7, 18.6, 18.5, 18.4, 18.4, -3.5, -3.6, -3.7, -4.0, -4.1, -4.2, -4.4, -4.8, -5.1, -5.1; HRMS (ESI-TOF) calcd for, found: .



50-*epi*-C43-C67 part 40c. To a Teflon® tube containing a solution of the silyl ether **41c** (3 mg, 2.6 μmol) in THF (500 mL) was added 18% HF·Py (25 μL, mmol) and stirred at 50°C for 48 h. The resulting solution was quenched with Et_3N and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/MeOH = 1/0→4/1) afforded **40c** (1.2 mg, quant) as a colorless amorphous: R_f = 0.41 (hexane/EtOAc = 5/1); IR (film) ν 3469, 1100 cm^{-1}; ^1H NMR (600 MHz, CD_3OD:C_5D_5N = 2:1) δ 6.24 (ddd, *J* = 16.9, 10.0, 10.0 Hz, 1H, H66), 6.04 (m, 1H, H57) 6.01 (m, 1H, H65), 5.99 (m, 1H, H60), 5.98 (m, 1H, H59), 5.97 (m, 1H, H58), 5.76 (m, 1H, H53), 5.76 (m, 1H, H52), 5.63 (m, 2H, H64 and H61), 5.60 (m, 1H, H56), 5.03 (d, *J* = 16.9 Hz, H67a), 4.88 (d, *J* = 10.0 Hz, H67b), 4.29 (m, 1H, H51), 4.26 (ddd, *J* = 7.0, 4.0 Hz, 1H, H49), 4.21 (m, 1H, H44), 4.17 (m, H47), 4.00 (m, 1H, H45), 3.98 (dd, *J* = 7.0, 3.5 Hz, 1H, H48), 3.90 (dd, *J* = 7.4, 4.0 Hz, 1H, H50), 3.83 (dd, *J* = 11.4, 4.5 Hz, 1H, H43a), 3.71 (dd, *J* = 11.4, 5.5 Hz, 1H, H43b), 2.11-2.02 (m, 9H, H62, H61, H55, H54, H46eq), 1.89 (m, 1H, H46ax); ^{13}C NMR (150 MHz, CD_3OD:C_5D_5N = 2:1) δ 138.4 (C66), 135.2 (C64), 134.5 (C61), 134.1 (C56), 133.9 (C53), 132.6 (C65), 132.4 (C57), 132.3 (C58), 132.2 (C59), 132.1 (C60), 130.0 (C52), 115.5 (C67), 73.0 (C51), 72.2 (C50), 72.2 (C49), 72.2 (C45), 72.2 (C44), 67.6 (C48), 67.0 (C47), C63.2 (C43), 33.5 (C55), 33.5 (C54), 33.4 (C62), 33.3 (C63), 31.0 (C46); HRMS (ESI-TOF) calcd for, found: .

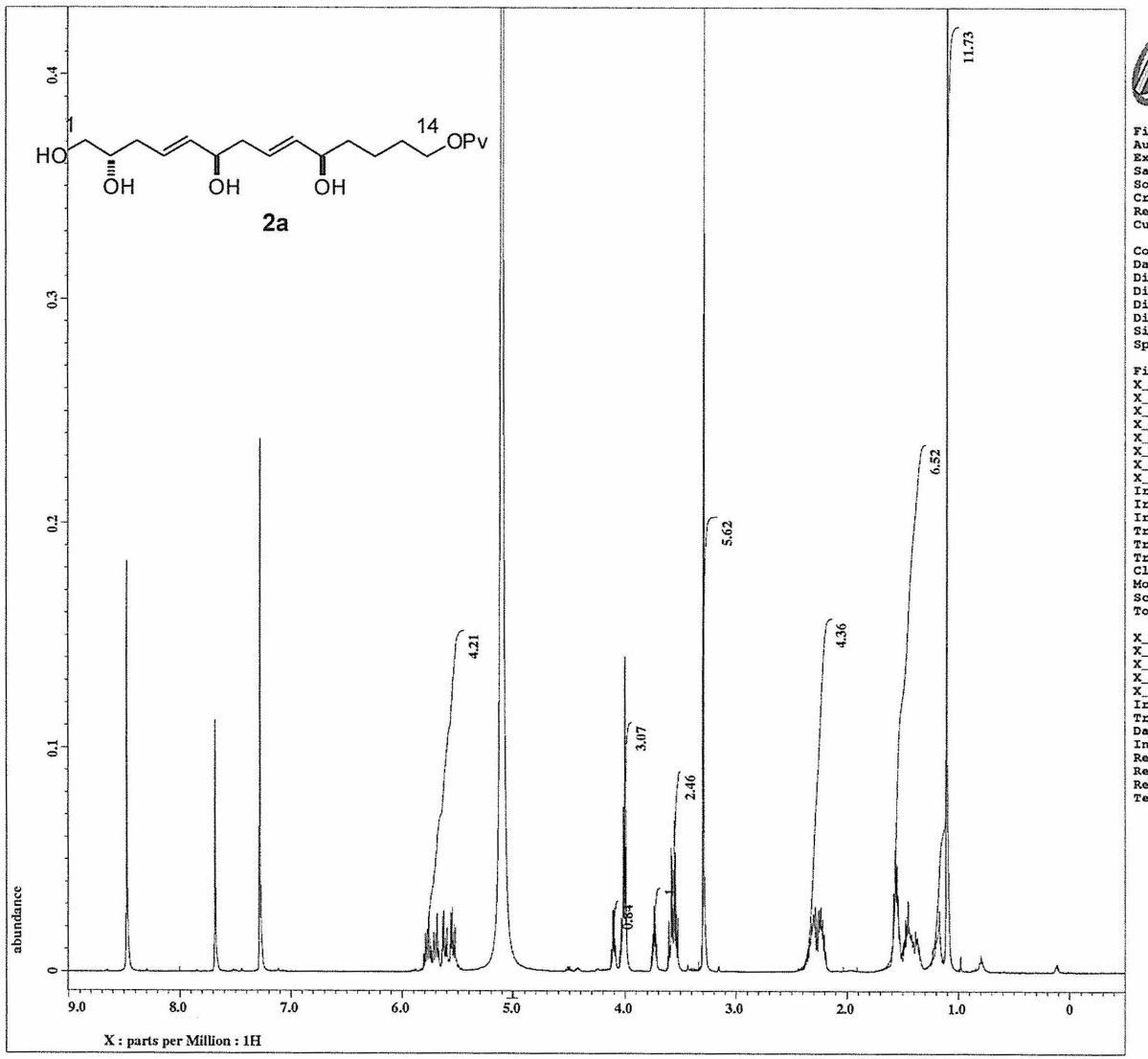
NMR Data

Chapter 2. Synthesis and structure confirmation of C1-C14 part of amphidinol 3

1. ^{1}H NMR spectra of **2a** (500 MHz, 1:2 C_5D_5N/CD_3OD)
2. ^{13}C NMR spectra of **2a** (125 MHz, 1:2 C_5D_5N/CD_3OD)
3. ^{1}H NMR spectra of **2b** (500 MHz, 1:2 C_5D_5N/CD_3OD)
4. ^{13}C NMR spectra of **2b** (125 MHz, 1:2 C_5D_5N/CD_3OD)
5. ^{1}H NMR spectra of **2c** (500 MHz, 1:2 C_5D_5N/CD_3OD)
6. ^{13}C NMR spectra of **2c** (125 MHz, 1:2 C_5D_5N/CD_3OD)
7. ^{1}H NMR spectra of **2d** (500 MHz, 1:2 C_5D_5N/CD_3OD)
8. ^{13}C NMR spectra of **2d** (125 MHz, 1:2 C_5D_5N/CD_3OD)

Chapter 3. Synthesis and structure confirmation of C43-C67 part of amphidinol 3

1. Differences in proton NMR (600 MHz, 1:2C_5D_5N/CD_3OD) chemical shifts between AM3 and the synthetic specimens (**40a~40c**)
2. ^{1}H NMR spectra of **40a** (600 MHz, 1:2 C_5D_5N/CD_3OD)
3. ^{13}C NMR spectra of **40a** (150 MHz, 1:2 C_5D_5N/CD_3OD)
4. ^{1}H NMR spectra of **40b** (600 MHz, 1:2 C_5D_5N/CD_3OD)
5. ^{13}C NMR spectra of **40b** (150 MHz, 1:2 C_5D_5N/CD_3OD)
6. ^{1}H NMR spectra of **40c** (600 MHz, 1:2 C_5D_5N/CD_3OD)
7. ^{13}C NMR spectra of **40c** (150 MHz, 1:2 C_5D_5N/CD_3OD)

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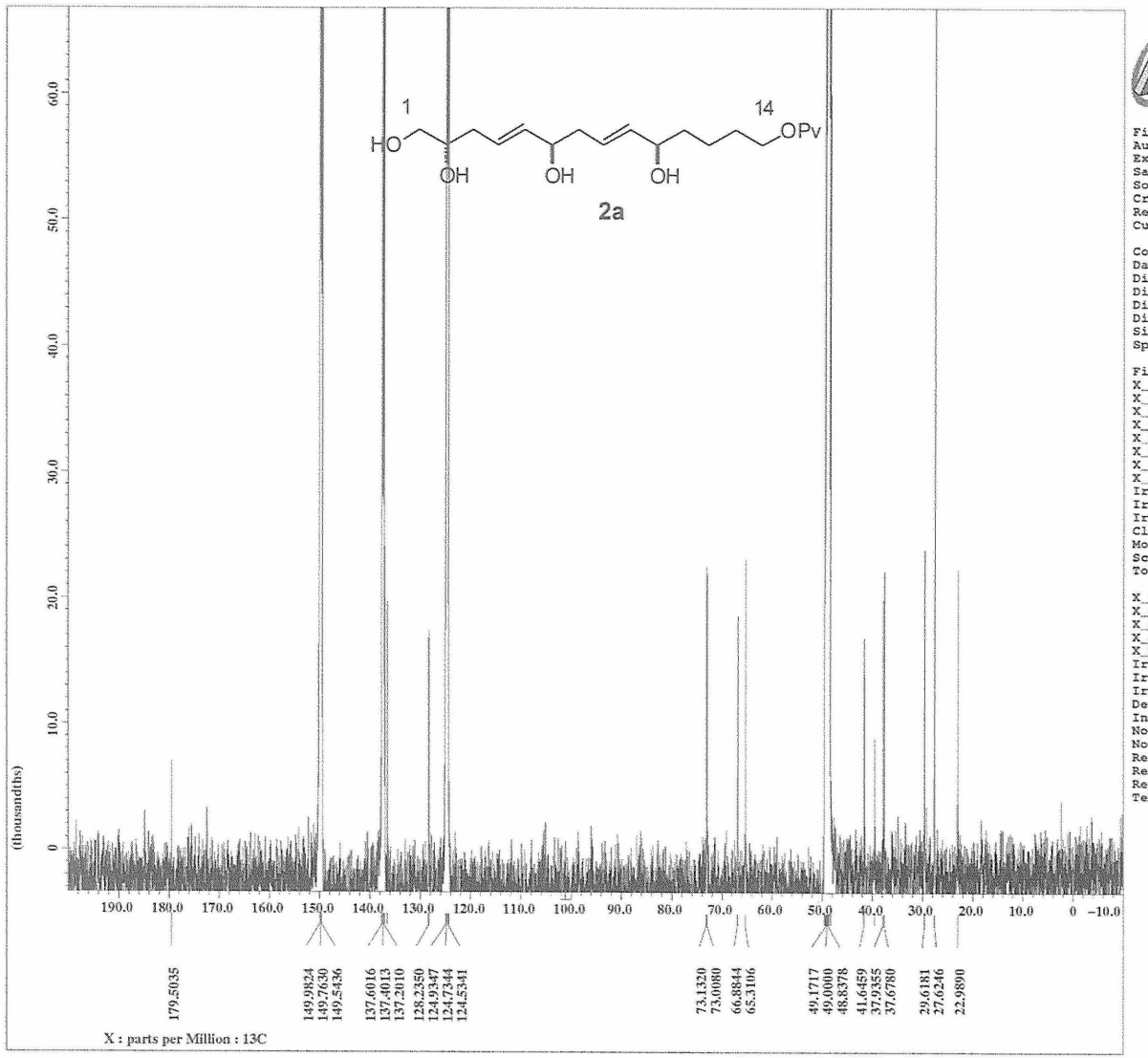


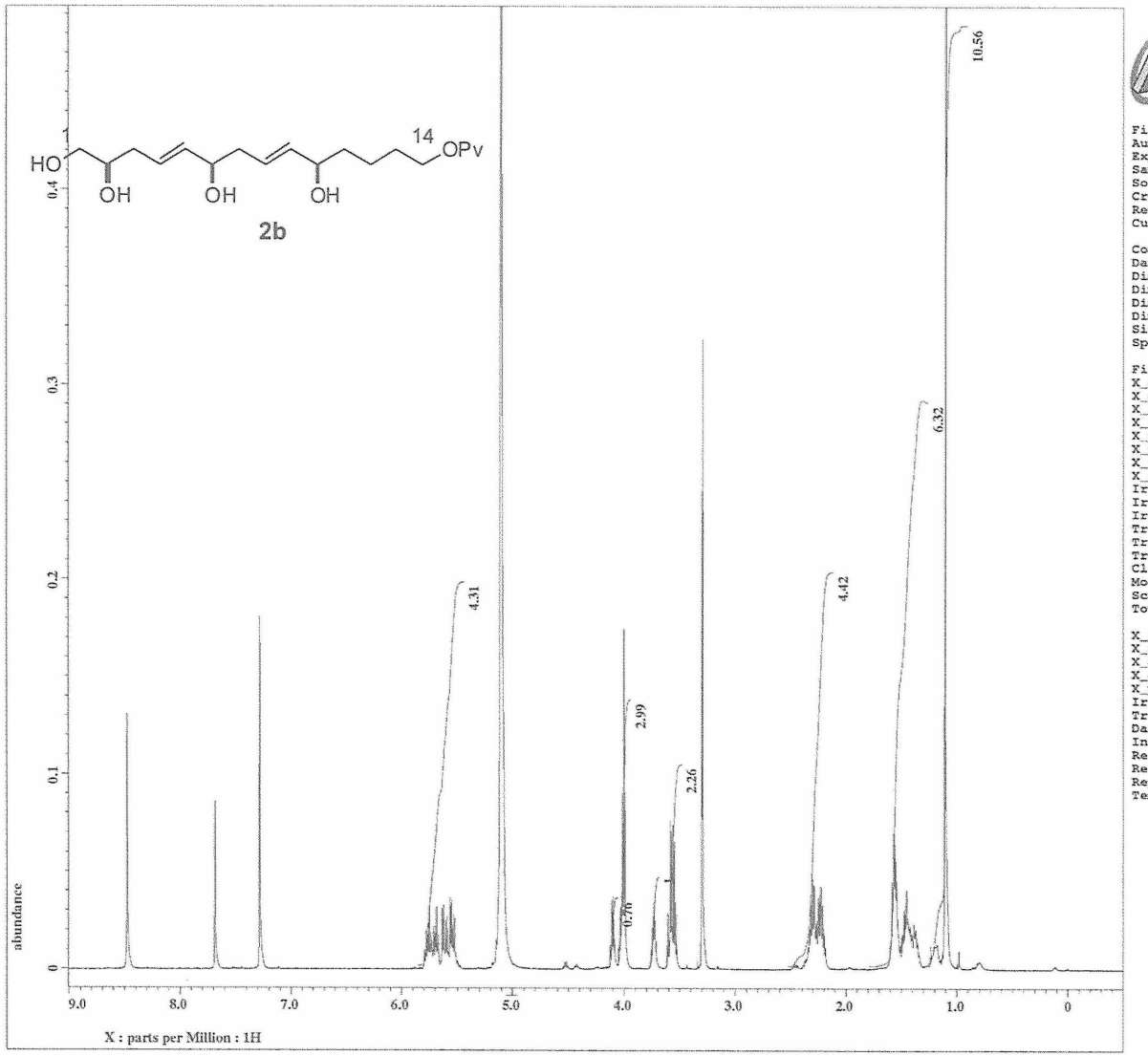
JEOL

```
Filename          = No-1-3-16-6.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 10-NOV-2007 02:51:54
Revision_time     =  7-OCT-2008 23:08:13
Current_time      =  7-OCT-2008 23:09:11

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 0.83361792[s]
X_domain          = 13C
X_freq            = 125.76529768[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 1.19959034[Hz]
X_sweep           = 39.3081761[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 2500
Total_scans       = 2500

X_90_width        = 10.4[us]
X_acq_time        = 0.83361792[s]
X_angle           = 30[deg]
X_atn             = 7.7[dB]
X_pulse           = 3.46666667[us]
Irr_atn_dec       = 20.2[dB]
Irr_atn_noe       = 20.2[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 56
Relaxation_delay  = 2[s]
Repetition_time   = 2.83361792[s]
Temp_get          = 30[dC]
```



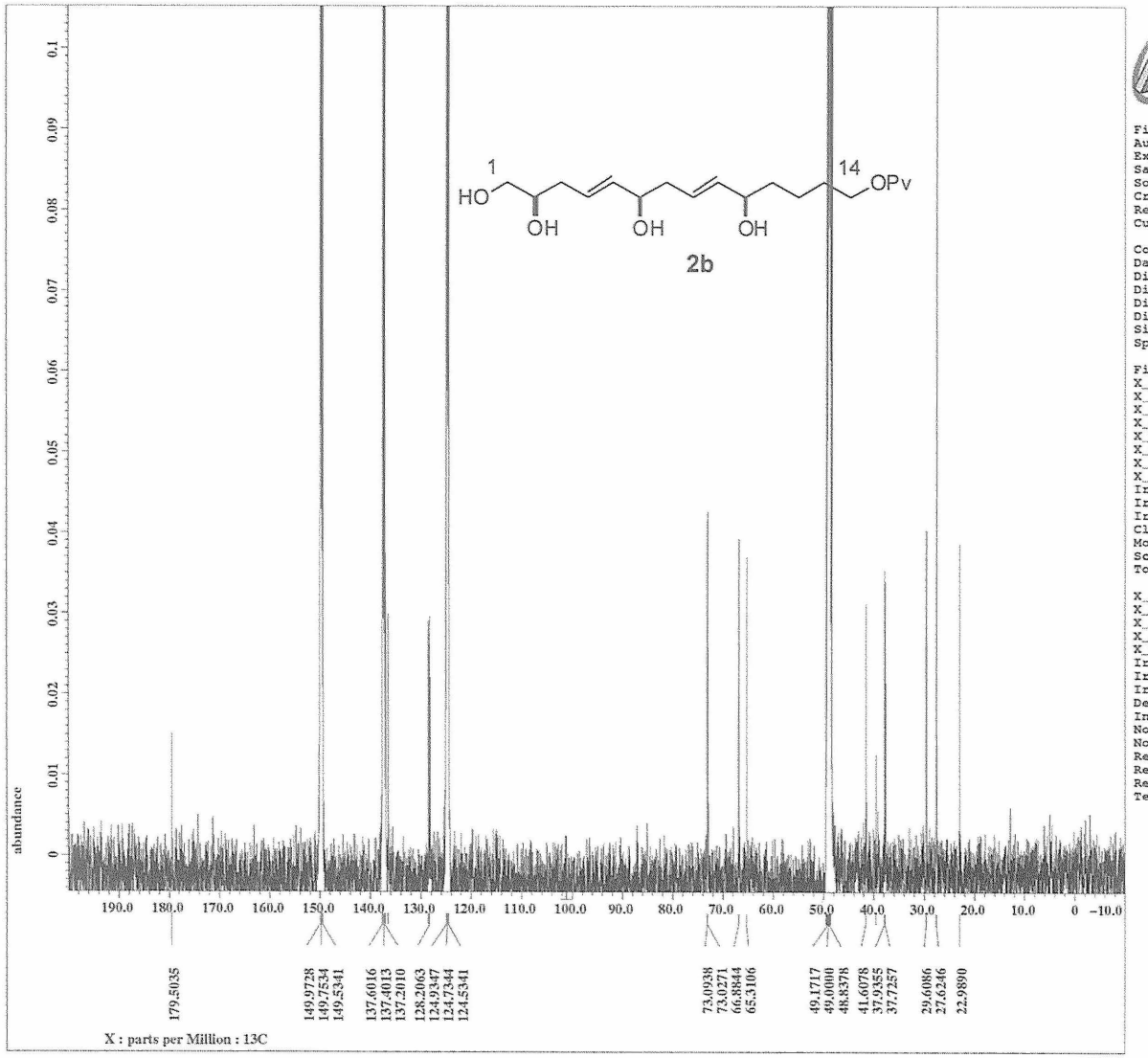
JEOL

```
Filename          = segmentB-4.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     =  1-JUL-2008 22:18:42
Revision_time     =  7-OCT-2008 22:57:01
Current_time      =  7-OCT-2008 22:57:30

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 52428
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 6.98351616[s]
X_domain          = 1H
X_freq            = 500.15991521[MHz]
X_offset          = 5.0[ppm]
X_points          = 65536
X_prescans        = 1
X_resolution      = 0.14319434[Hz]
X_sweep           = 9.38438438[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Tri_domain        = 1H
Tri_freq          = 500.15991521[MHz]
Tri_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 32
Total_scans       = 32

X_90_width        = 12.4[us]
X_acq_time        = 6.98351616[s]
X_angle           = 45[deg]
X_atn             = 2.7[dB]
X_pulse           = 6.2[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 38
Relaxation_delay  = 2.5[s]
Repetition_time   = 9.48351616[s]
Temp_get          = 30[dC]
```



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Filename          = No-2-3-22-6.jdf
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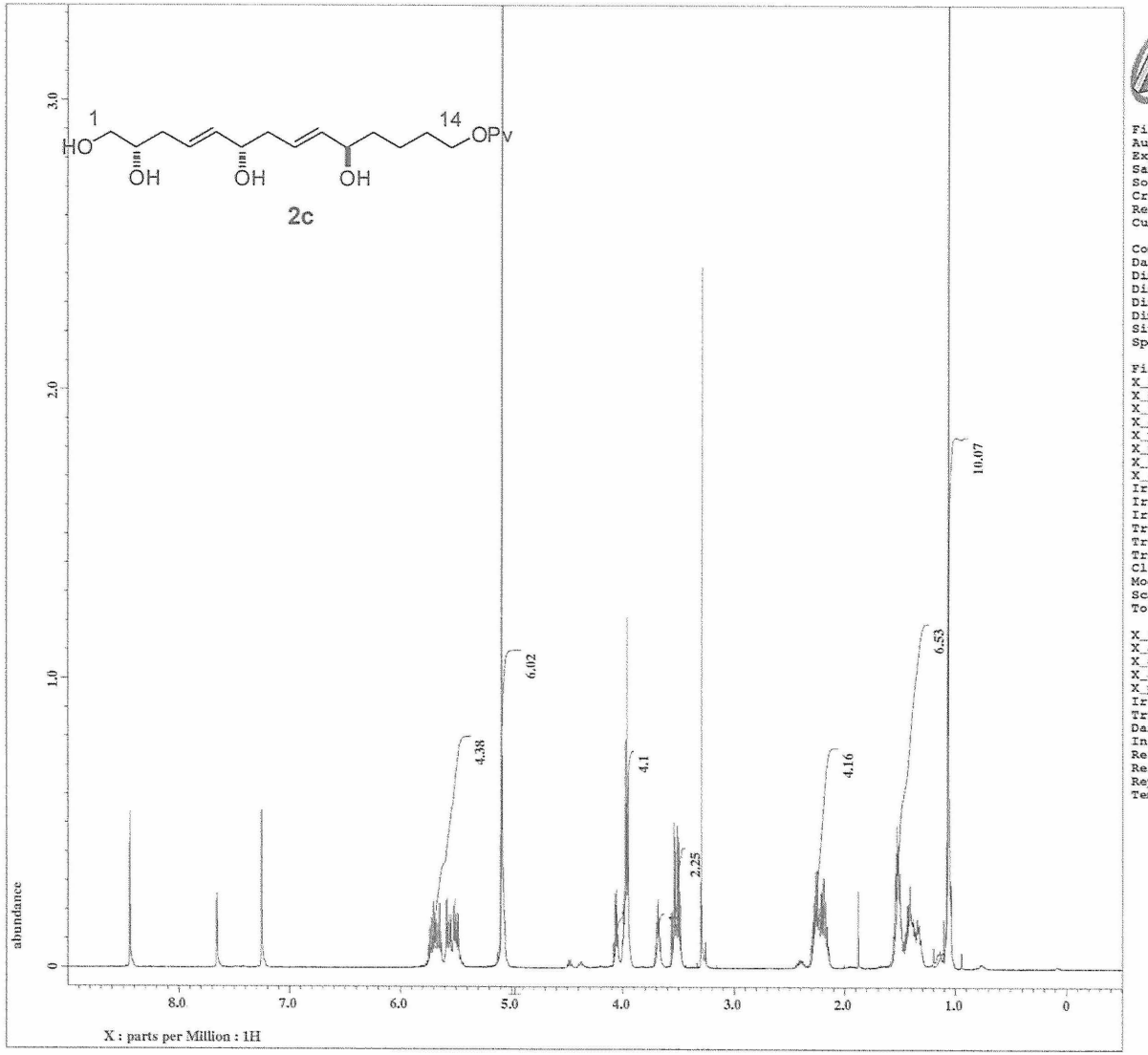
Experiment        = single_pulse_dec
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 10-NOV-2007 04:16:11
Revision_time     =  7-OCT-2008 23:10:11
Current_time      =  7-OCT-2008 23:10:51

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 0.83361792[s]
X_domain          = 13C
X_freq            = 125.76529768[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 1.19959034[Hz]
X_sweep           = 39.3081761[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 1300
Total_scans       = 1300

X_90_width        = 10.4[us]
X_acq_time        = 0.83361792[s]
X_angle           = 30[deg]
X_atn             = 7.7[dB]
X_pulse           = 3.46666667[us]
Irr_atn_dec       = 20.2[dB]
Irr_atn_noe       = 20.2[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 58
Relaxation_delay  = 2[s]
Repetition_time   = 2.83361792[s]
Temp_get          = 30[dC]
```



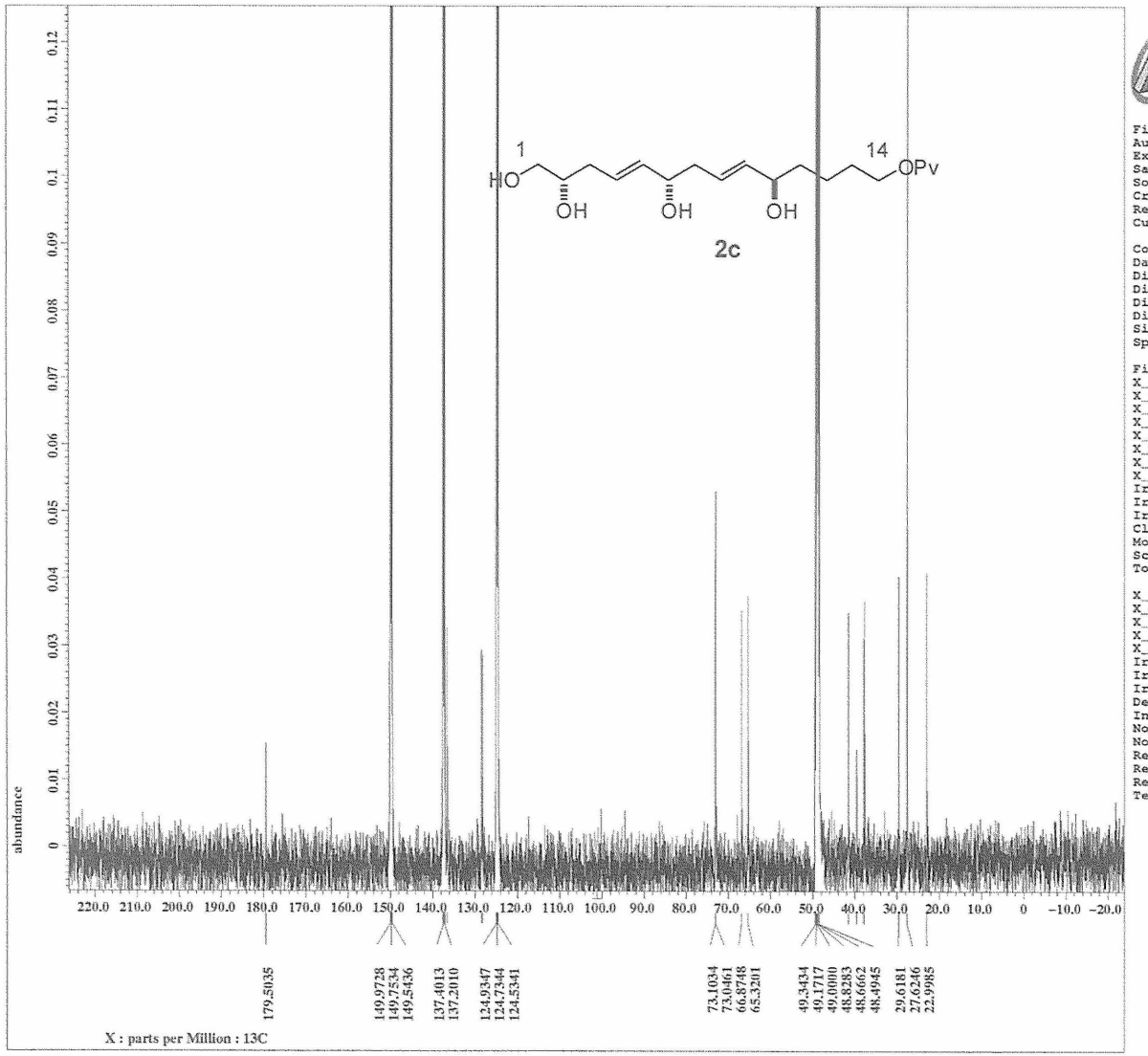
JEOL

```
Filename          = 3-36-1-12.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 16-OCT-2007 19:08:08
Revision_time     =  7-OCT-2008 23:01:15
Current_time      =  7-OCT-2008 23:02:05

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 1.74587904[s]
X_domain          = 1H
X_freq            = 500.15991521[MHz]
X_offset          = 5.0[ppm]
X_points          = 16384
X_prescans        = 1
X_resolution      = 0.57277737[Hz]
X_sweep           = 9.38438438[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Tri_domain        = 1H
Tri_freq          = 500.15991521[MHz]
Tri_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 8
Total_scans       = 8

X_90_width        = 12.4[us]
X_acq_time        = 1.74587904[s]
X_angle           = 45[deg]
X_atn             = 2.7[dB]
X_pulse           = 6.2[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 38
Relaxation_delay  = 2.5[s]
Repetition_time   = 4.24587904[s]
Temp_get          = 25.9[dC]
```



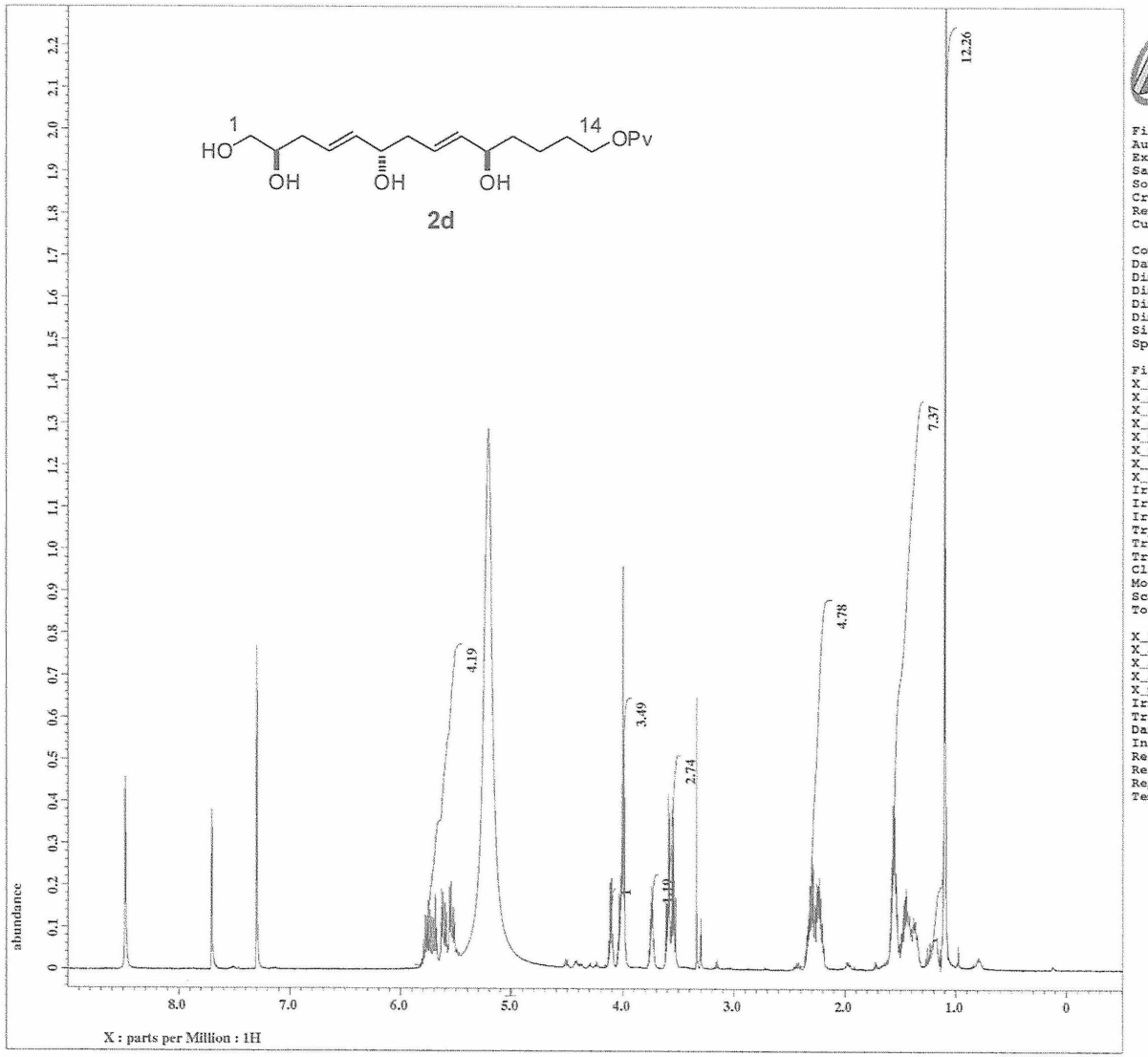
JEOL

```
Filename          = No-3-3-36-5.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 10-NOV-2007 05:33:33
Revision_time     =  7-OCT-2008 23:11:53
Current_time      =  7-OCT-2008 23:12:27

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 0.83361792[s]
X_domain          = 13C
X_freq            = 125.76529768[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 1.19959034[Hz]
X_sweep           = 39.3081761[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 1300
Total_scans       = 1300

X_90_width        = 10.4[us]
X_acq_time        = 0.83361792[s]
X_angle           = 30[deg]
X_atn             = 7.7[dB]
X_pulse           = 3.46666667[us]
Irr_atn_dec       = 20.2[dB]
Irr_atn_noe       = 20.2[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = TRUE
Noe_time          = 2[s]
Recvr_gain        = 58
Relaxation_delay  = 2[s]
Repetition_time   = 2.83361792[s]
Temp_get          = 30[dC]
```



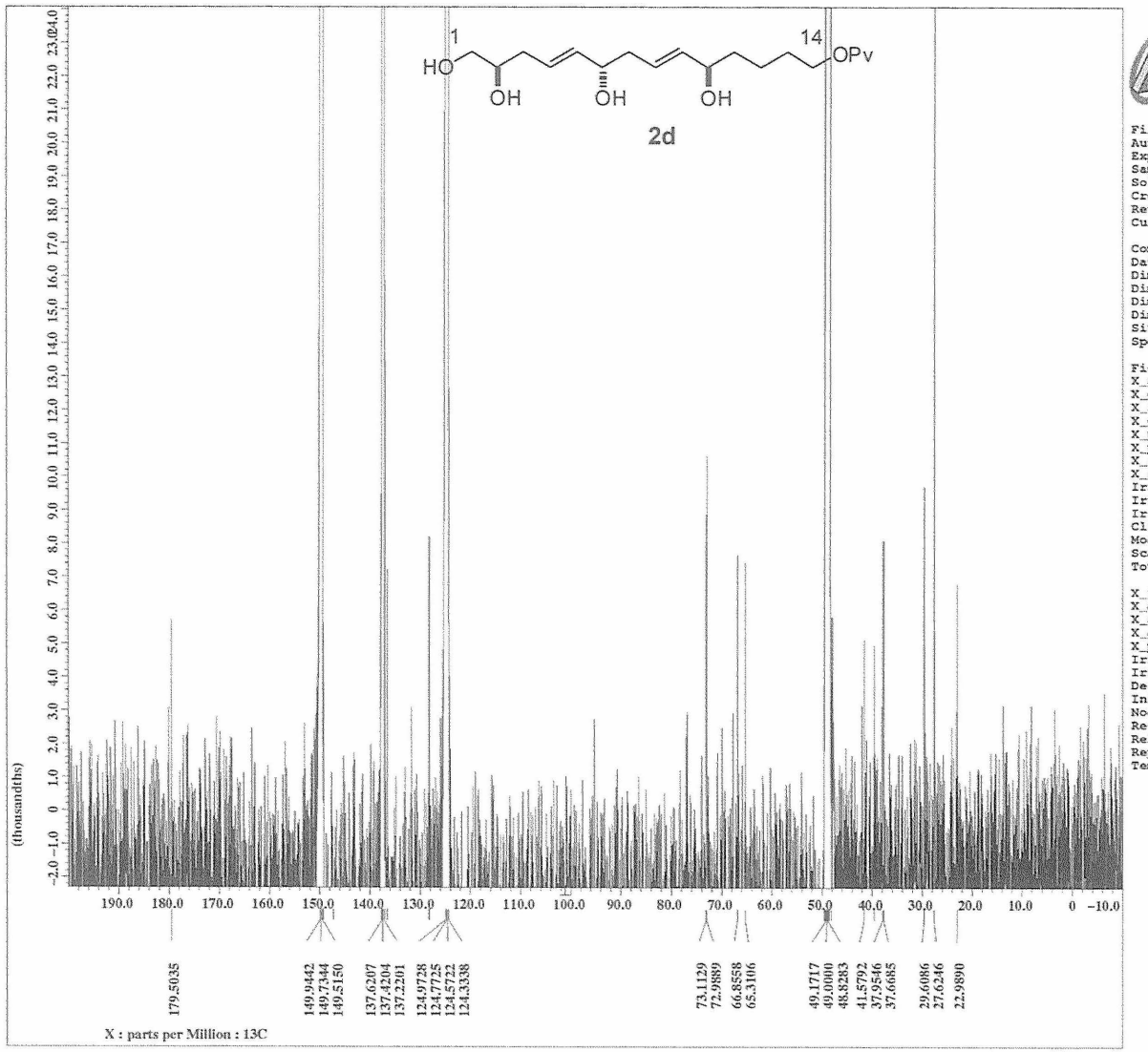
JEOL

```
Filename          = 3-40-2-9.jdf
Author            = delta
Experiment        = single_pulse.ex2
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 24-OCT-2007 02:48:08
Revision_time     =  7-OCT-2008 23:32:12
Current_time      =  7-OCT-2008 23:33:39

Comment           = single_pulse
Data_format       = 1D COMPLEX
Dim_size          = 13107
Dim_title         = 1H
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T] (500[MH
X_acq_duration    = 1.74587904[s]
X_domain          = 1H
X_freq            = 500.15991521[MHz]
X_offset          = 5.0[ppm]
X_points          = 16384
X_prescans        = 1
X_resolution      = 0.57277737[Hz]
X_sweep           = 9.38438438[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Tri_domain        = 1H
Tri_freq          = 500.15991521[MHz]
Tri_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 8
Total_scans       = 8

X_90_width        = 12.4[us]
X_acq_time        = 1.74587904[s]
X_angle           = 45[deg]
X_atn             = 2.7[dB]
X_pulse           = 6.2[us]
Irr_mode          = Off
Tri_mode          = Off
Dante_presat      = FALSE
Initial_wait      = 1[s]
Recvr_gain        = 40
Relaxation_delay  = 2.5[s]
Repetition_time   = 4.24587904[s]
Temp_get          = 26.3[dC]
```



JEOL

```
Filename          = No-4-3-40-6.jdf
Author            = delta
Experiment        = single_pulse_dec
Sample_id         = a
Solvent           = METHANOL-D3
Creation_time     = 10-NOV-2007 08:29:29
Revision_time     =  7-OCT-2008 23:13:58
Current_time      =  7-OCT-2008 23:15:07

Comment           = single pulse decouple
Data_format       = 1D COMPLEX
Dim_size          = 26214
Dim_title         = 13C
Dim_units         = [ppm]
Dimensions        = X
Site              = ECA 500
Spectrometer      = DELTA2_NMR

Field_strength    = 11.7473579[T]  (500[MH
X_acq_duration    = 0.83361792[s]
X_domain          = 13C
X_freq            = 125.76529768[MHz]
X_offset          = 100[ppm]
X_points          = 32768
X_prescans        = 4
X_resolution      = 1.19959034[Hz]
X_sweep           = 39.3081761[kHz]
Irr_domain        = 1H
Irr_freq          = 500.15991521[MHz]
Irr_offset        = 5.0[ppm]
Clipped           = FALSE
Mod_return        = 1
Scans             = 2000
Total_scans       = 2000

X_90_width        = 10.4[us]
X_acq_time        = 0.83361792[s]
X_angle           = 30[deg]
X_atn             = 7.7[dB]
X_pulse           = 3.46666667[us]
Irr_atn_dec       = 20.2[dB]
Irr_noise         = WALTZ
Decoupling        = TRUE
Initial_wait      = 1[s]
Noe               = FALSE
Recvr_gain        = 58
Relaxation_delay  = 2[s]
Repetition_time   = 2.83361792[s]
Temp_get          = 30[dC]
```

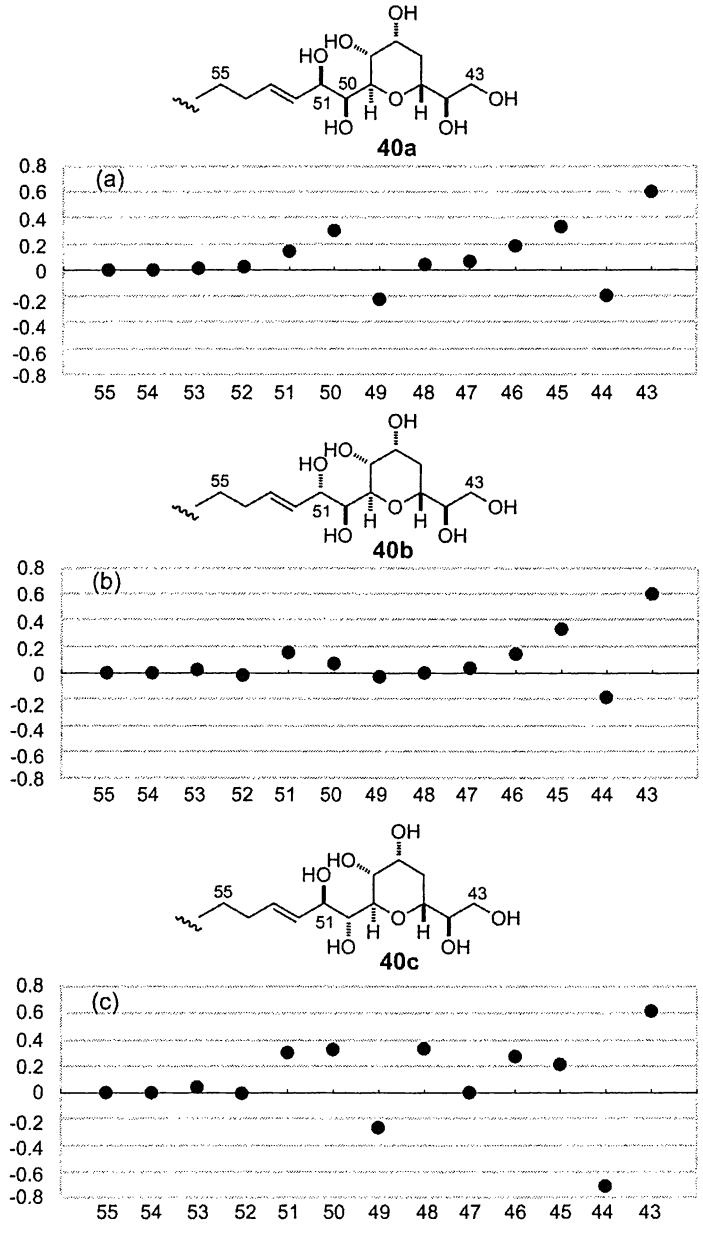
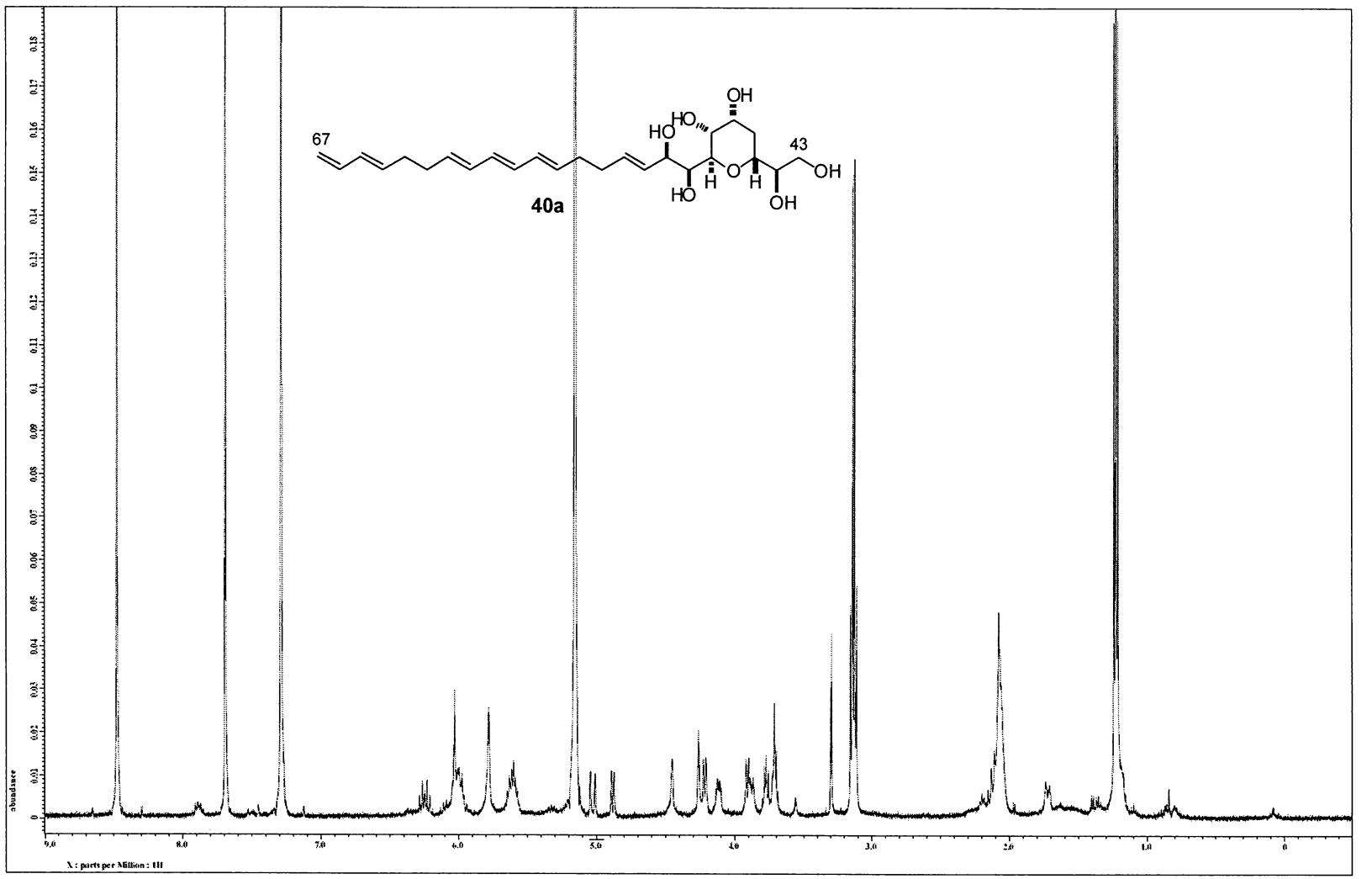
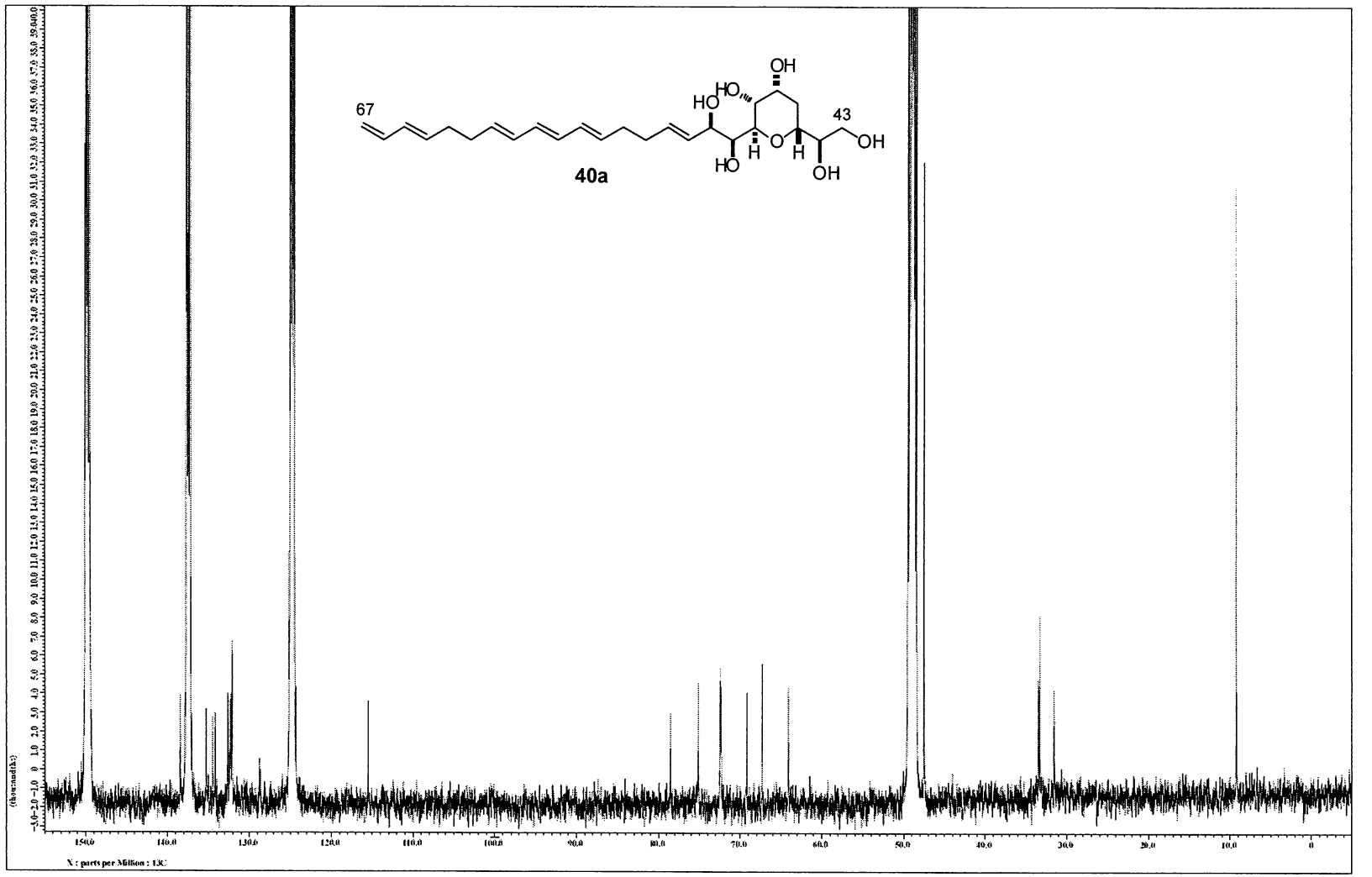
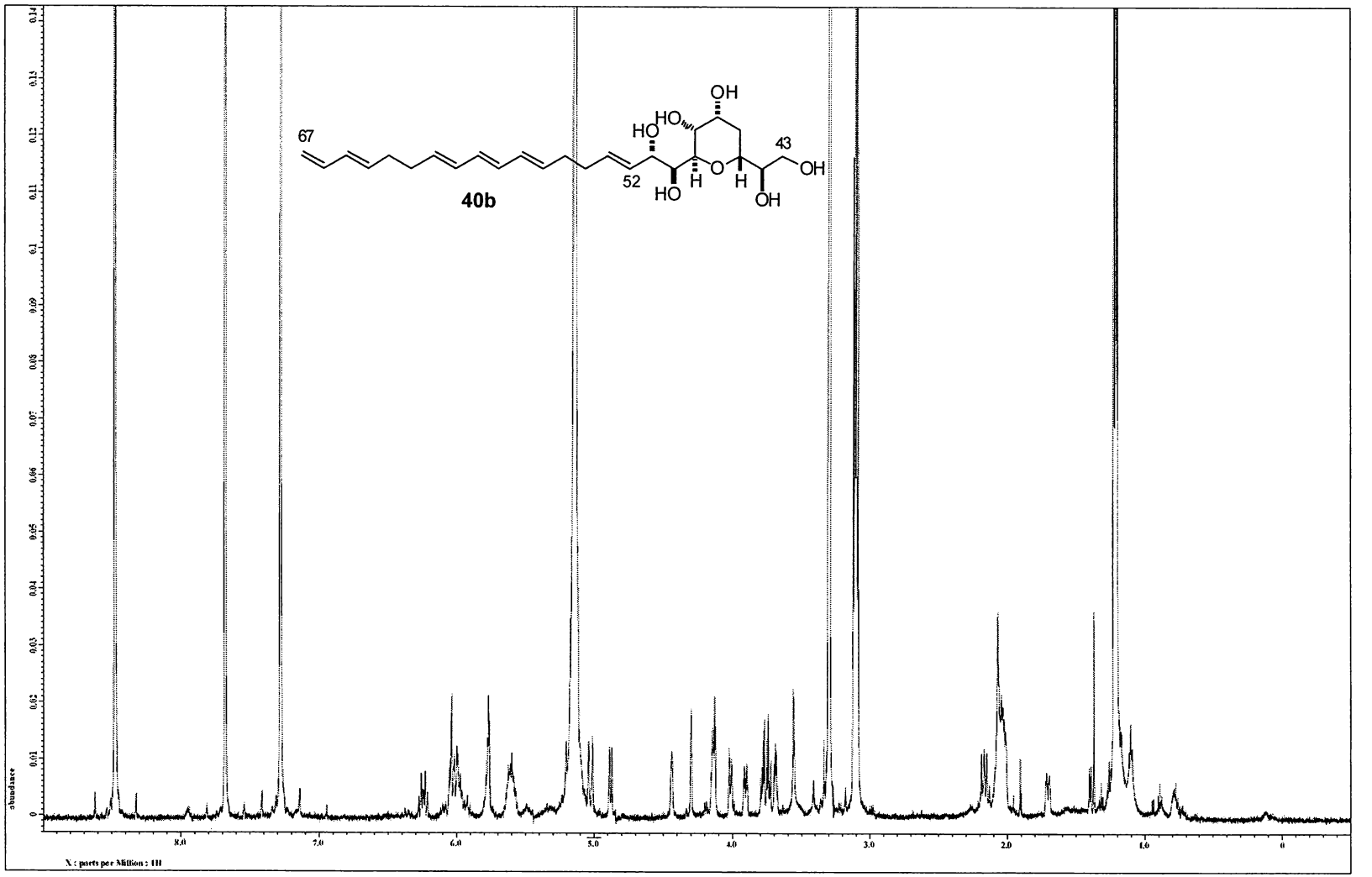
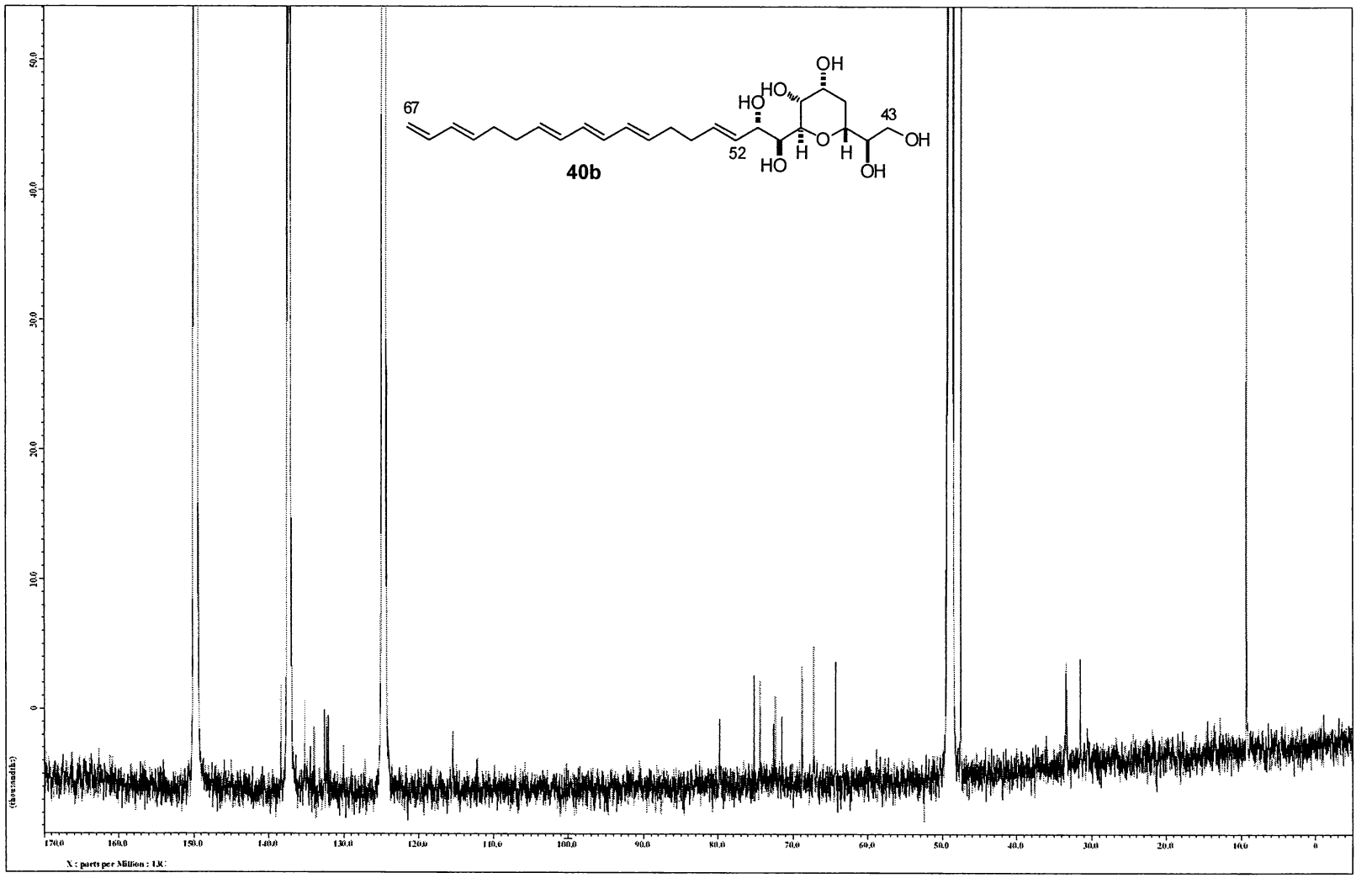


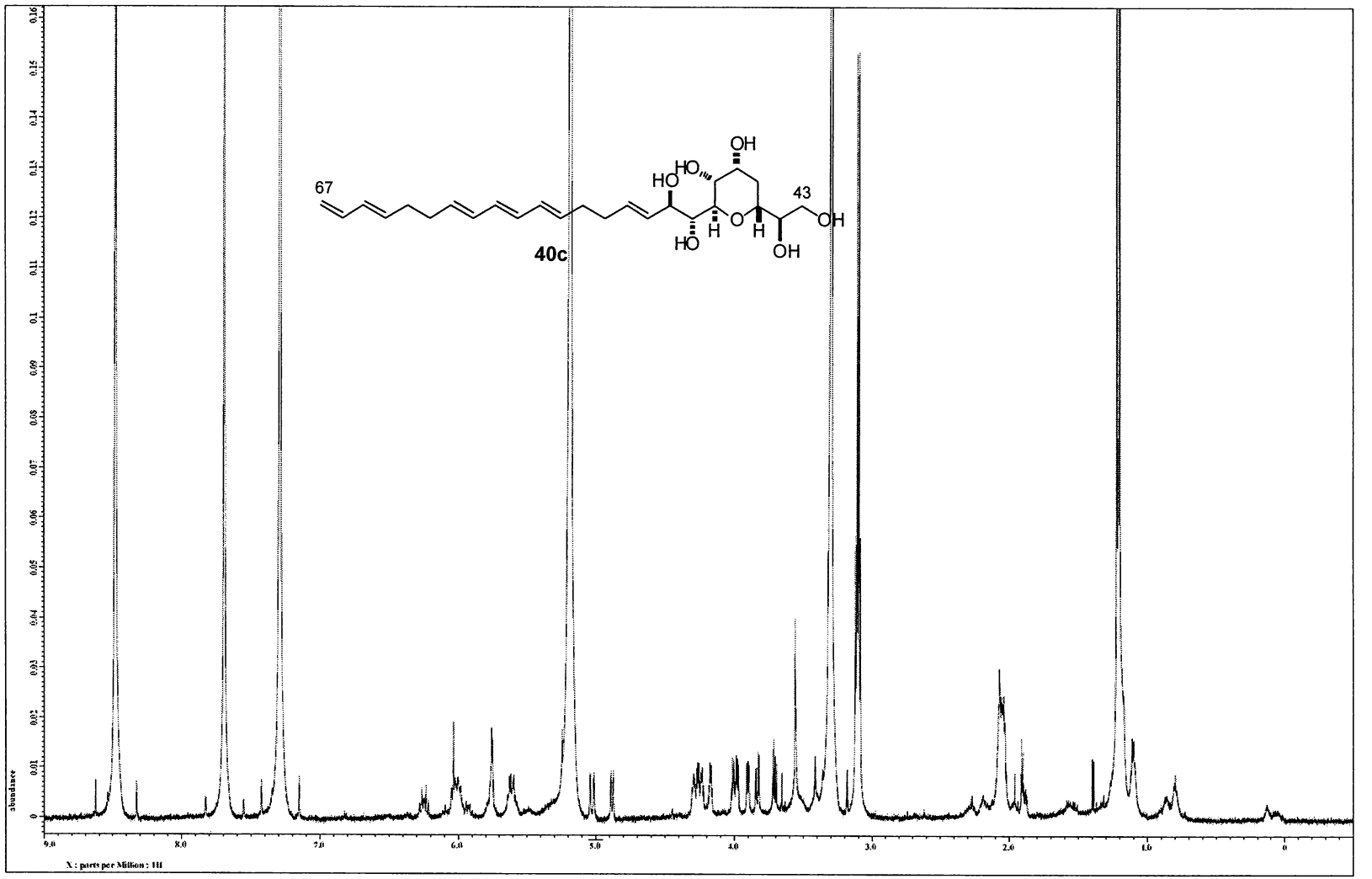
Figure S2. Differences in proton NMR (600 MHz, 1:2 C_5D_5N/CD_3OD) chemical shifts between AM3 and the synthetic fragments (**40a~40d**). The x- and y-axes represent carbon number and Δδ (Δδ = δAM3 - δsynthetic **40** in ppm), respectively. (a) **40a**, (b) **40b**, (c) **40c**, and (d) **40d**.

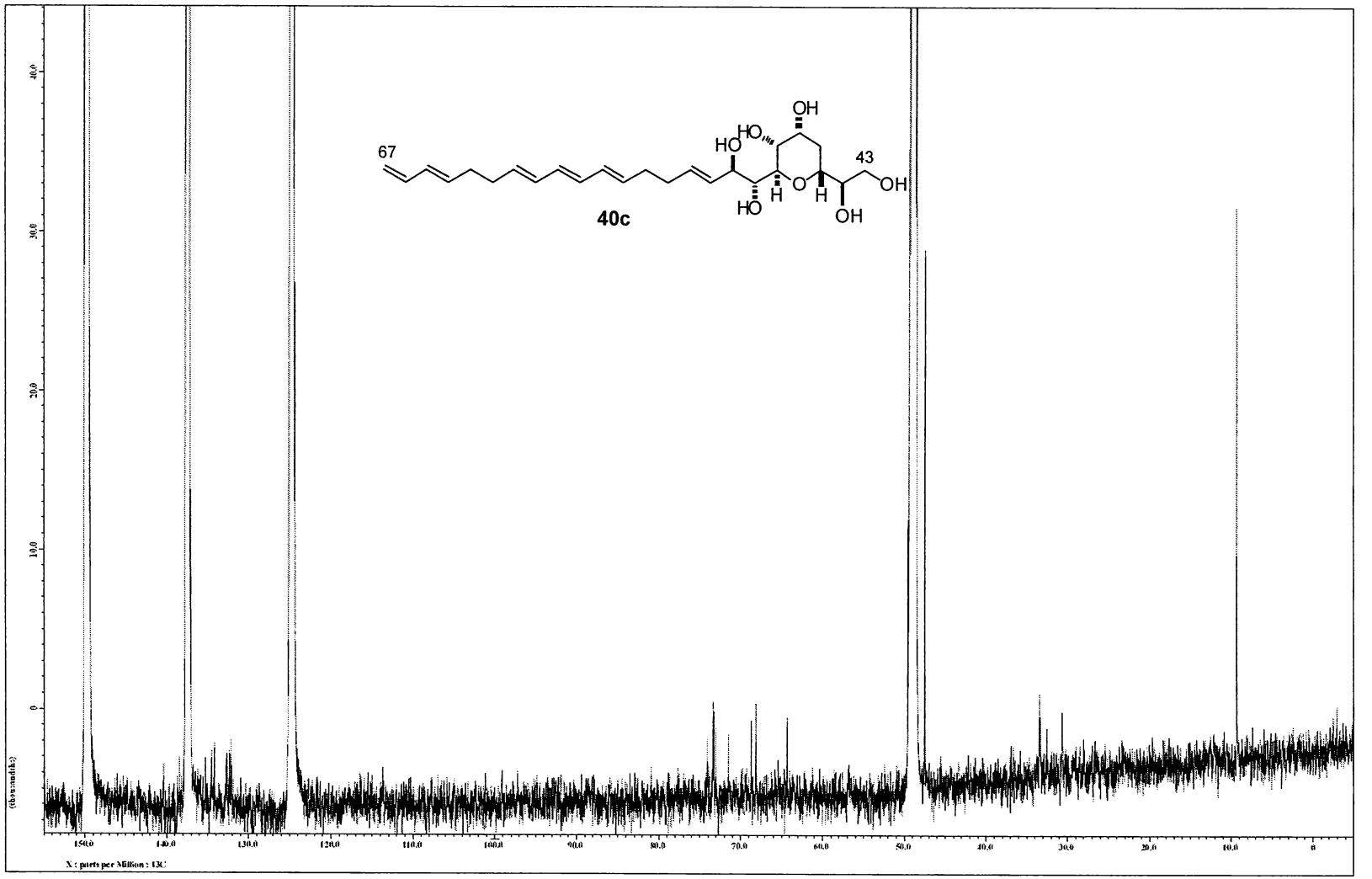

67
43
OH
HO
HO
H
O
H
OH
HO
OH
40a
Abundance
X : parts per Million : 1H


67
43
OH
HO
HO
H
O
H
OH
HO
OH
40a
X : parts per Million : 13C


67
52
43
OH
HO
HO
H
O
H
OH
HO
OH
40b
abundance
X : parts per Million : 1H


67
52
43
OH
HO
HO
H
O
H
OH
HO
OH
40b
(thousands)
50.0
40.0
30.0
20.0
10.0
0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


67
43
40c
OH
HO
HO
H
O
H
OH
HO
OH
Abundance
X : parts per Million : 1H


67
43
OH
HO
HO
H
O
H
OH
OH
40c
X : parts per Million : 13C

Acknowledgement

This research has been carried out under the direction Professor Michio Murata at the Department of Chemistry, Graduate school of Science, Osaka University.

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I would like to thank Mr. Hiroshi Adachi. He helped me to use ESI-TOF-MS machine. I would also like to thank Mr. Ken-ichi Iijima and Ms. Tomomi Hirai. They measured elementary analysis of my sample.

Additionally, I would like to thank all members in Murata's laboratory and Oishi's laboratory (Kyushu University), for their advices and discussion to the study.

Finally, I would like to express to my father, mother and sister my deepest gratitude. They have always been supportive and no matter what I have ever done they have always been there help me along the way.

To everyone else that I did not mention, thank for making my time at Osaka and Kyushu so enjoyable. I wish everyone nothing but the best in future.

Mitsunori Kanemoto

Hakata, Japan

February 2011

Publication

1. Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 5203-5206.
2. Kanemoto, M.; Murata, M.; Oishi, T. *J. Org. Chem.* **2009**, *74*, 8810-8813.

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Combinatorial Synthesis of the 1,5-Polyol System Based on Cross Metathesis: Structure Revision of Amphidinol 3

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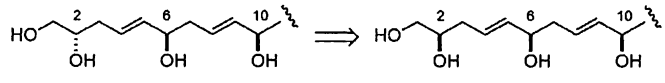
Received September 17, 2008

ABSTRACT



originally proposed structure *revised structure*

Combinatorial synthesis of a 1,5-polyol system corresponding to the C1−C14 unit of amphidinol 3 (AM3) and its diastereomers was achieved via chemoselective cross metathesis as the key step. Comparison of ^{13}C NMR data of the synthetic specimens with that of AM3 led to a controversy regarding the originally proposed structure. From GC-MS analysis of the degradation product, the absolute configuration at C2 of AM3 has been revised to be *R*.

Marine dinoflagellates are a rich source of biologically and structurally unique secondary metabolites.[1] Amphidinols (AMs) were isolated from the dinoflagellate *Amphidinium klebsii*, which elicit potent antifungal and hemolytic activity.[2] The biological activities can be accounted for by the formation of ion-permeable pores in a sterol-dependent manner.[3] AMs comprise a hydrophobic polyene unit and a hydrophilic part containing acyclic polyol and substituted tetrahydropyran rings, in which structural diversity is mainly focused on the polyol unit. Amphidinol 3 (AM3, **1**, Figure 1) is the most potent antifungal among the AMs, and the absolute configuration was elucidated by extensive NMR analysis based on the JBCA method,[4] modified Mosher method,[5] and HPLC analysis of the degradation products.[6] The striking structural feature of AM3 has attracted considerable attention from the synthetic community, and a number of synthetic studies have been reported by the Cossy,[7] Roush,[8] Rychnovsky,[9] Paquette,[10] and Markó[11] groups. During the course of our mode-of-action studies of AMs,[12] it was revealed that the structural difference of the polyol domain and the terminal olefin moiety modulate the potency

(1) (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685–1698. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.

(2) Amphidinols: (a) Satake, M.; Murata, M.; Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859–9861. (b) Paul, G. K.; Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 6279–6282. (c) Morsy, N.; Matsuoka, S.; Houdai, T.; Matsumori, N.; Adachi, S.; Murata, M.; Iwashita, T.; Fujita, T. *Tetrahedron* **2005**, *61*, 8606–8610. (d) Echigoya, R.; Rhodes, L.; Oshima, Y.; Satake, M. *Harmful Algae* **2005**, *4*, 383–389. (e) Morsy, N.; Houdai, T.; Matsuoka, S.; Matsumori, N.; Adachi, S.; Oishi, T.; Murata, M.; Iwashita, T.; Fujita, T. *Bioorg. Med. Chem.* **2006**, *14*, 6548–6554.

(3) (a) Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Mar. Biotechnol.* **1997**, *5*, 124–128. (b) Morsy, N.; Houdai, T.; Konoki, K.; Matsumori, N.; Oishi, T.; Murata, M. *Bioorg. Med. Chem.* **2008**, *16*, 3084–3090.

(4) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

(5) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

(6) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871.

(7) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454. (b) Cossy, J.; Tsuchiya, T.; Ferrie, L.; Reymond, S.; Kreuzer, T.; Colobert, F.; Jourdain, P.; Marko, I. E. *Synlett* **2007**, 2286–2288. (c) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrie, L.; Marko, I. E.; Jourdain, P. *Synlett* **2007**, 2351–2354.

(8) (a) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411–1414. (b) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509–5512. (c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681–684.

10.1021/ol802168r CCC: $40.75
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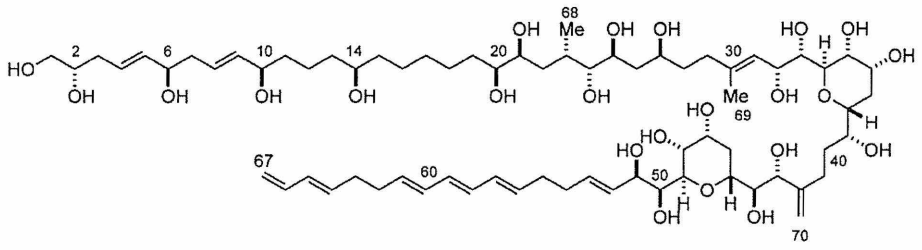
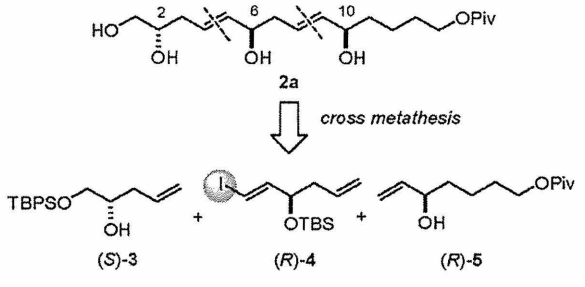


Figure 1. Originally proposed structure of amphidinol 3 (AM3, **1**).

of the biological activity, and it is of interest whether the absolute configuration of the acyclic polyol domain of AM3 has an effect on the biological activity. Herein, we report a combinatorial synthesis of the 1,5-polyol unit corresponding to the C1−C14 moiety of AM3 and its diastereomers via chemoselective cross metathesis as the key step, which has resulted in the structure revision of AM3.

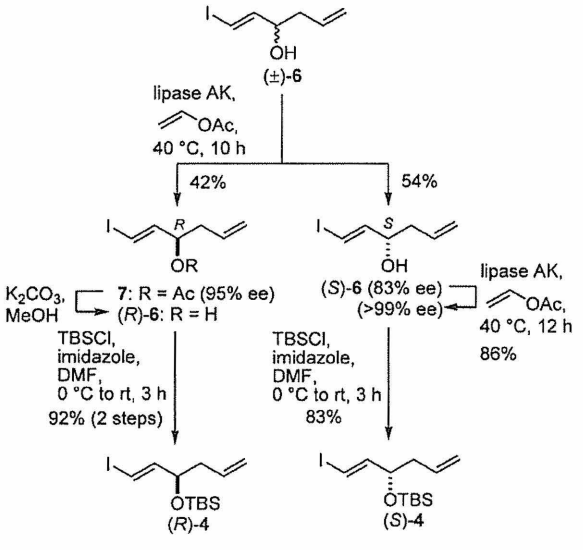
Scheme 1. Synthesis Plan



Although syntheses of the 1,5-polyol system of AM3 have been reported[7−10] using asymmetric allyltitanation,[13] double allylboration,[14] and Julia−Kocienski olefination,[15] we envisaged a versatile synthetic route to the C1−C14 segment (**2a**) of AM3 that could readily provide all diastereomers via successive coupling of the building blocks equipped with defined stereogenic centers (Scheme 1). In this strategy, diene (*R*)-**4** was envisioned as a key intermediate, in which the iodoolefin is regarded as a protected terminal olefin for chemoselective cross metathesis with (*R*)-**5**, and the iodoolefin moiety was to be converted to a terminal olefin afterward by reductive removal of the iodide for subsequent cross metathesis with (*S*)-**3**. On the basis of this strategy, all stereoisomers could be synthesized by utilizing each enantiomer of the building blocks.

Although enantioselective synthesis of the related compound of (*R*)-**4** has been reported by Trost[16] using Brown asymmetric allylation[17] and by Kobayashi[18] using Sharpless

Scheme 2. Preparation of (*R*)- and (*S*)-**4**



epoxidation,[19] we developed a versatile method, which provides both enantiomers in large quantities, using lipase-catalyzed kinetic resolution (Scheme 2).[20] Racemic alcohol (±)-**6**[21] (29.3 g) was treated with 10% w/w lipase AK (Amano) in vinyl acetate at 40 °C for 10 h to furnish acetate

(9) (a) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853–1856. (b) de Vicente, J.; Huckins, J. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258–7262. (c) Huckins, J. R.; de Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757–4760.

(10) (a) Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111–3114. (b) Chang, S.-K.; Paquette, L. A. *Synlett* **2005**, 2915–2918. (c) Bedore, M. W.; Chang, S.-K.; Paquette, L. A. *Org. Lett.* **2007**, *9*, 513–516.

(11) Dubost, C.; Markó, I. E.; Bryans, J. *Tetrahedron Lett.* **2005**, *46*, 4005–4009.

(12) (a) Houdai, T.; Matsuoka, S.; Matsumori, N.; Murata, M. *Biochim. Biophys. Acta* **2004**, *1667*, 91–100. (b) Houdai, T.; Matsuoka, S.; Morsy, N.; Matsumori, N.; Satake, M.; Murata, M. *Tetrahedron* **2005**, *61*, 2795–2802.

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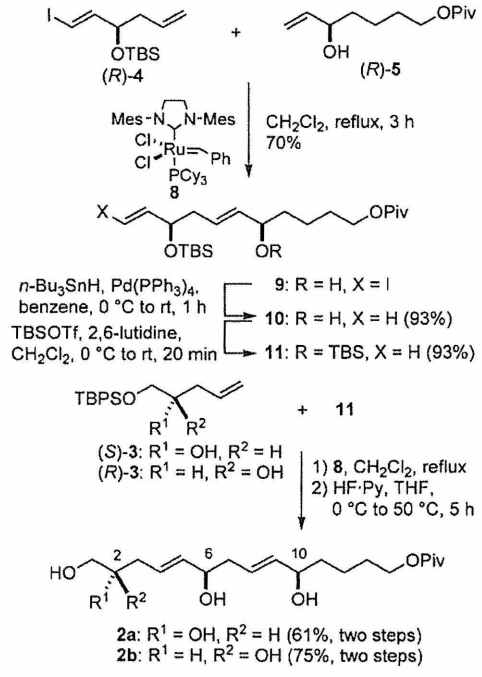
Scheme 3. Synthesis of **2a** and Its C2 Epimer **2b**



7 (42%, 95% ee) and alcohol (*S*)-**6** (59%, 83% ee). The optical purity of (*S*)-**6** was improved to >99% ee by retreatment with lipase AK. The optical purity was determined by HPLC analysis using a chiral column, and the absolute configuration was confirmed by the modified Mosher method.[22] In an analogous sequence, building block (*R*)-**5** was synthesized (98% ee) via kinetic resolution of (±)-**5**.[22]

Synthesis of the C1−C14 segment (2*S*,6*R*,10*R*)-**2a** commenced with cross metathesis of (*R*)-**4** using 3 equiv of (*R*)-**5** by the action of Grubbs second-generation catalyst **8**.[23] As expected, chemoselective cross coupling between the terminal olefins was successfully achieved in the presence of iodoolefin to afford diene **9** in 70% yield (>*E*:*Z* = 10:1), presumably due to the steric hindrance of the iodoolefin moiety. Reductive removal of the iodide with Bu_3SnH in the presence of $Pd(PPh_3)_4$[24]was followed by protection of the secondary alcohol with TBS ether to provide **11**. Subsequent conventional cross metathesis with 3 equiv of (*S*)-**3**[25] derived from (*R*)-glycidol proceeded smoothly to afford the diene (>*E*:*Z* = 10:1), while that with the counterpart **10** resulted in the formation of byproduct, due to cross metathesis with the internal olefin. Removal of all silyl groups with HF·Py afforded (2*S*,6*R*,10*R*)-**2a**. On the other hand, cross metathesis of **11** with (*S*)-**3** followed by removal of the silyl groups furnished (2*R*,6*R*,10*R*)-**2b** (Scheme 3). In an analogous sequence, other diastereomers (2*S*,6*S*,10*R*)-**2c** and (2*R*,6*S*,10*R*)-**2d** were also synthesized.[22]

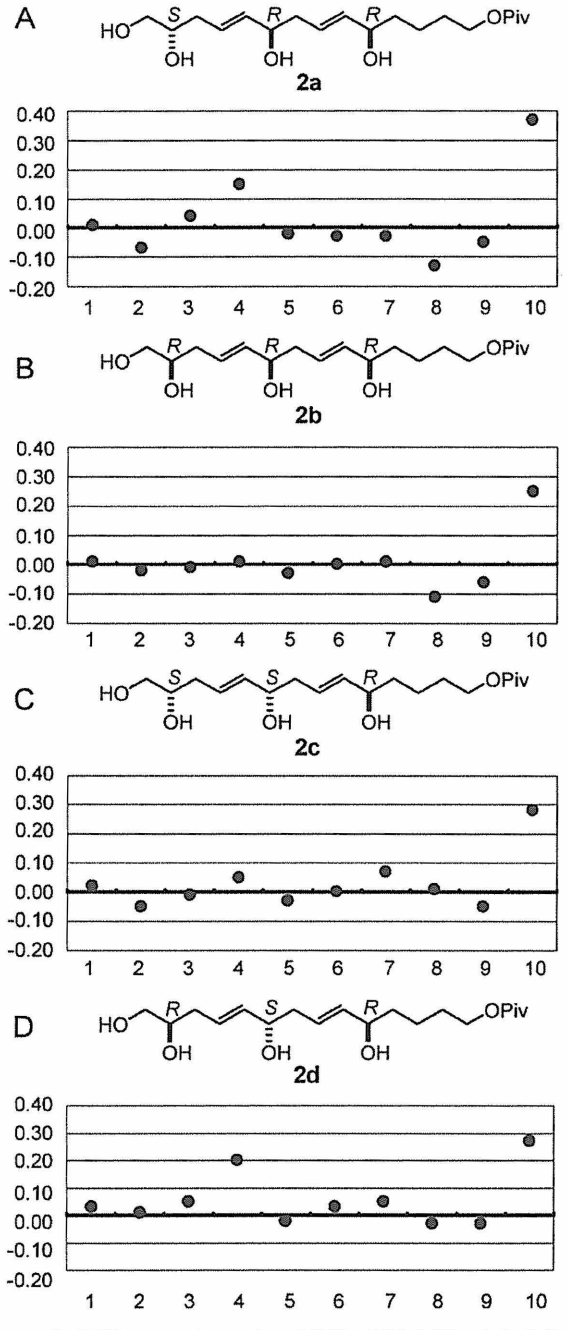


Figure 2. Differences in carbon NMR (125 MHz, 1:2 C_5D_5N/CD_3OD, 30 °C) chemical shifts between AM3 and the synthetic fragments (**2a**~**2d**). The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta$ = δAM3 − δsynthetic **2** in ppm), respectively.

Having obtained the diastereomers corresponding to the C1−C14 moiety, NMR spectra of **2a**~**2d** were compared with those of AM3. ^{1}H NMR spectra were virtually indistinguishable among the diastereomers with respect to

(21) (a) Meyer, C.; Marek, I.; Normant, J.-F. *Synlett* **1993**, 386–388. (b) Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1997**, *74*, 194–204.

(22) See Supporting Information.

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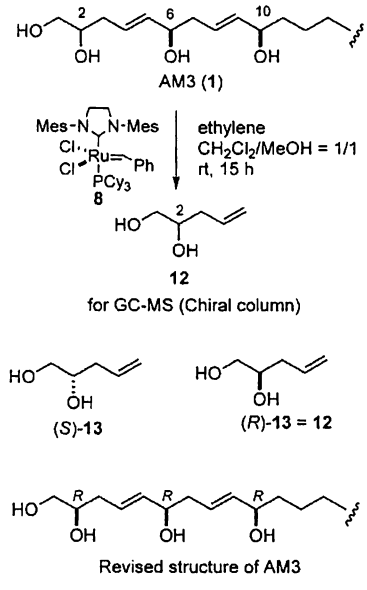
either chemical shift or *J*-coupling patterns, due to the remote (1,5-) stereogenic centers.[26] The differences in the carbon chemical shifts of C1 to C9 between AM3 and **2a**~**2d** (125 MHz, 1:2 C_5D_5N/CD_3OD, 30 °C)[4] were also insignificant and within 0.2 ppm, as shown in Figure 2. However, the deviations at C4 of the 2,6-*syn* isomers (**2b** and **2c**) appeared to be lower than those of the 2,6-*anti* isomers (**2a** and **2d**). Since the absolute configurations at C6 and C10 in AM3 (**1**) were determined to be (6*R*, 10*R*) by the modified Mosher method, the stereochemistry at C2 became controversial.

Scheme 4. Degradation of AM3



Therefore, it was decided to reconfirm the absolute configuration at C2. Although degradation of AM3 was previously carried out via oxidative cleavage of the double bond (C4–C5) in three steps and the product was analyzed by HPLC with UV detection,[6] we envisaged a single-step manipulation using olefin metathesis[27] because of the limited availability of the natural product. For unambiguous identification of the minute degradation product, a GC-MS instrument equipped with a chiral capillary column (Varian CP-Chirasil-DEX CB) was used according to the procedure applied in the case of maitotoxin.[28] As shown in Scheme 4, a solution of AM3 (ca. 50 μg, estimated by the ε value from the UV spectra) in 1:1 CH_2Cl_2/MeOH was treated with Grubbs catalyst **8** in the presence of ethylene for 15 h at room temperature, and the product **12** was analyzed by GC-MS.[22] Retention times of the authentic samples (*S*)-**13** and (*R*)-**13** were 9.84 and 9.90 min, respectively, and that of the degradation product **12** was identical with (*R*)-**13**, indicating that the absolute configuration at C2 is *R*.

The reason for the misassignment in the original configuration is unclear. One of the possible explanations is that the sample for HPLC analysis was contaminated with ozonolysis products derived from the other portions of AM3. One of these fragments exhibited a peak with a retention time similar to that of the synthetic enantiomer of 1,2,4-butanetriol, while the fragment from the natural product provided no detectable peak due to the small sample size subjected to the degradation reaction sequence including three steps of derivatization.[6]

In conclusion, a practical method for the synthesis of chiral building blocks (*R*)- and (*S*)-**4** and (*R*)- and (*S*)-**5** was developed via lipase-catalyzed kinetic resolution. Combinatorial synthesis of the 1,5-polyol system of AM3 was achieved based on cross metathesis of the building blocks, in which iodoolefin was utilized as a masked terminal olefin. From the comparison of ^{13}C NMR data of the synthetic specimens with those of AM3, and by GC-MS analysis of the degradation product, the absolute configuration at C2 has been revised to be *R*.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Kita, M.; Ohishi, N.; Konishi, K.; Kondo, M.; Koyama, T.; Kitamura, M.; Yamada, K.; Uemura, D. *Tetrahedron* **2007**, *63*, 6241–6251.
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Stereoselective Synthesis of the C31−C40/C43−C52 Unit of Amphidinol 3

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Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan

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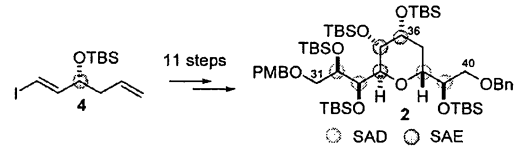

A concise synthesis of a tetrahydropyran ring system corresponding to the C31−C40 and C43−C52 units of amphidinol 3 is described. Successive chemoselective reactions, i.e., cross-metathesis to differentiate the iodoolefin from the terminal olefin and Sharpless asymmetric dihydroxylation on the resulting *E*-olefin, resulted in expeditious synthesis of an intermediate that was then cross-coupled to afford an *E,E*-diene system. Four contiguous stereogenic centers were installed via construction of the tetrahydropyran ring by means of Katsuki−Sharpless asymmetric epoxidation, 6-*endo-tet* cyclization, and Sharpless asymmetric dihydroxylation.

Marine dinoflagellates are a rich source of biologically and structurally unique secondary metabolites.[1] Amphidinol 3 (AM3, **1**), produced by the dinoflagellate *Amphidinium klebsii*, elicits potent antifungal activity (Figure 1).[2] The biological activity can be accounted for by formation of ion-permeable pores in a sterol dependent manner.[3] The *Amphidinium* sp. are known to produce a number of congeners,[4] in which AM3 is the most potent antifungal. The molecular structure of AM3 was determined in 1999 based on the JBCA method,[5] modified Mosher method,[6] and degradation of the natural product via oxidative cleavage,[2b] and the absolute configuration at C2 has recently been revised to be *R*, based on the chemical synthesis of partial structures corresponding to the C1−C14 moiety, and GC-MS analysis using a chiral capillary column of a degradation product derived from olefin cross-metathesis.[7] Distinct structural features represented by the amphidinols are a long hydrophilic polyol chain, substituted tetrahydropyran (THP) ring systems, and a hydrophobic polyene unit. The middle portion containing the two THP rings is highly conserved among the congeners, and structural diversity arises from the polyol and polyene moieties. These structural features of AM3 have attracted considerable attention from the synthetic community, and a number of synthetic studies of AM3 have been reported.[8−12] Herein we report a concise synthesis of a THP ring system corresponding to the C31−C40/C43−C52 unit of AM3.

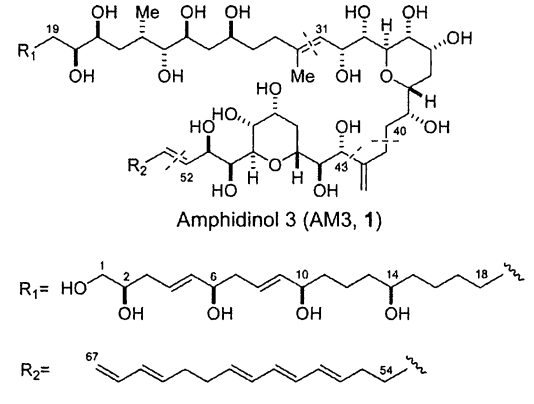

FIGURE 1. Structure of amphidinol 3 (AM3, **1**).

(1) (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(2) (a) Satake, M.; Murata, M.; Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859–9861. (b) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871.

(3) (a) Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Mar. Biotechnol.* **1997**, *5*, 124–128. (b) Houdai, T.; Matsuoka, S.; Matsumori, N.; Murata, M. *Biochim. Biophys. Acta* **2004**, *1667*, 91–100. (c) Houdai, T.; Matsuoka, S.; Morsy, N.; Matsumori, N.; Satake, M.; Murata, M. *Tetrahedron* **2005**, *61*, 2795–2802. (d) Morsy, N.; Houdai, T.; Konoki, K.; Matsumori, N.; Oishi, T.; Murata, M. *Bioorg. Med. Chem.* **2008**, *16*, 3084–3090.

(4) (a) Paul, G. K.; Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 6279–6282. (b) Morsy, N.; Matsuoka, S.; Houdai, T.; Matsumori, N.; Adachi, S.; Murata, M.; Iwashita, T.; Fujita, T. *Tetrahedron* **2005**, *61*, 8606–8610. (c) Echigoyaa, R.; Rhodesb, L.; Oshimaa, Y.; Satakea, M. *Harmful Algae* **2005**, *4*, 383–389. (d) Morsy, N.; Houdai, T.; Matsuoka, S.; Matsumori, N.; Adachi, S.; Oishi, T.; Murata, M.; Iwashita, T.; Fujita, T. *Bioorg. Med. Chem.* **2006**, *14*, 6548.

(5) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

(6) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203–10213. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (d) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147.

(7) Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 5203–5206.

(8) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454. (b) Cossy, J.; Tsuchiya, T.; Ferrie, L.; Reymond, S.; Kreuzer, T.; Colobert, F.; Jourdain, P.; Marko, I. E. *Synlett* **2007**, 2286–2288. (c) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrie, L.; Marko, I. E.; Jourdain, P. *Synlett* **2007**, 2351–2354.

(9) (a) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411–1414. (b) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509–5512. (c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681–684.

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(12) Dubost, C.; Markó, I. E.; Bryans, J. *Tetrahedron Lett.* **2005**, *46*, 4005–4009.

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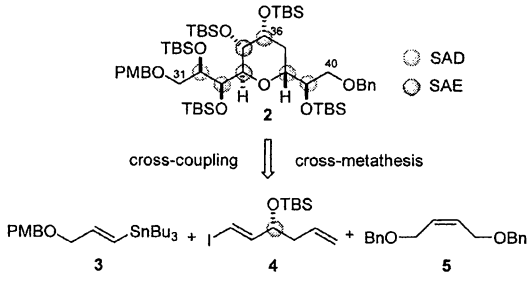
Although syntheses of the THP ring moieties of AM3 have been reported by Roush,[9b] Rychnovsky,[10a] Paquette,[11b] and Markó,[12] we envisaged a novel strategy for synthesizing **2** as shown in Scheme 1. The stereogenic centers of **2** would be installed by means of Sharpless asymmetric dihydroxylation (SAD)[13] with respect to C32−C33 (C51−C50) and C38−C39 (C45−C44), and Katsuki−Sharpless asymmetric epoxidation (SAE)[14] at C34−C35 (C49−C48) via 6-*endo-tet* cyclization.[15] The remaining stereogenic center corresponding to C36 (C47) was to be derived from iodoolefin **4** via its attachment to building blocks **5** and **3** by means of cross-metathesis and cross-coupling reactions, respectively.

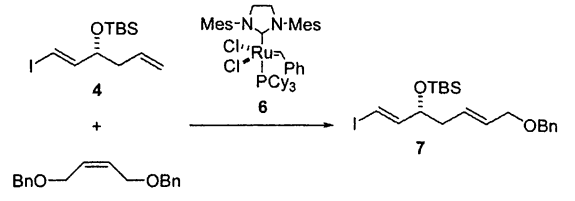
SCHEME 1. Synthesis Plan of the C31−C40/C43−C52 Unit (2) of AM3



Previously, we reported the synthesis of iodoolefin **4** via lipase-catalyzed kinetic resolution.[7] The iodoolefin **4** was utilized for stereoselective synthesis of the C1−C14 unit of AM3 through chemoselective cross-metathesis[8a,16] as a key step. The method was also applied for coupling with *Z*-olefin **5** as shown in Table 1. The cross-metathesis reaction of the terminal olefin of **4** with 2 or 4 equiv of *Z*-olefin **5**[17] using 10 mol % Grubbs second-generation catalyst **6**[18] in CH_2Cl_2 at 40 °C (reflux) proceeded selectively in the presence of the iodoolefin to afford diene **7** in 65% and 88% yields as a mixture of *E*- and *Z*-isomers in a 5.0:1 ratio (entries 1 and 2). Attempts to improve the *E*/*Z* ratio by using solvents of higher boiling points were unsuccessful, e.g., *E*/*Z* = 4.3:1 in 1,2-dichloroethane at 83 °C (entry 3) and 3.5:1 in toluene at 110 °C (entry 4). The catalyst loading could be reduced to 2 mol % (entry 5); however, the yield of **7** (71%) and the *E*/*Z* ratio (4.0: 1) were somewhat lower than those in entry 2.

Next, we moved on to the second chemoselective reaction, SAD of **7** using AD-mix-β (Scheme 2). As expected, the less hindered and electron-rich olefin, in the presence of the iodoolefin, reacted stereoselectively to afford diol **8** in 68% yield,

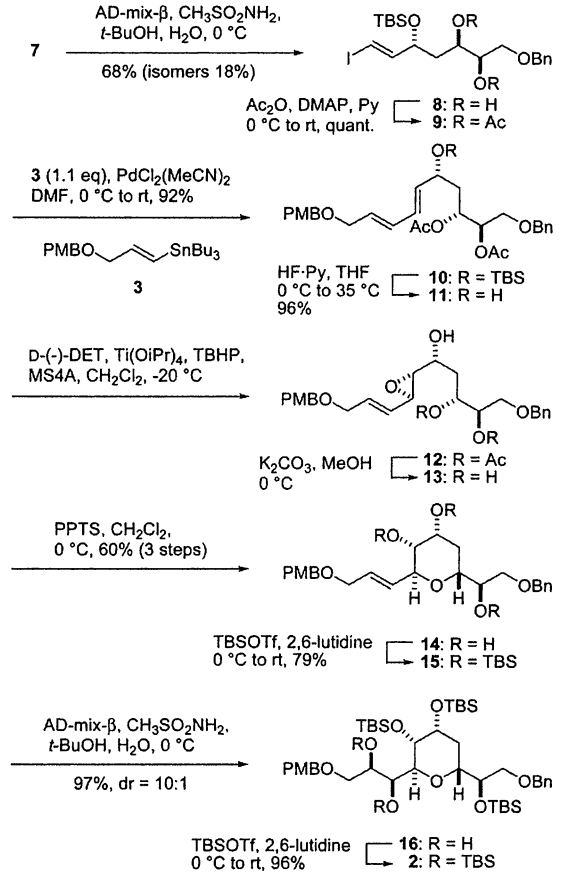
TABLE 1. Chemoselective Cross-Metathesis of 4 and 5



entry	**5** /equiv	solvent	temp/°C[a]	yield/%	*E*/*Z* ratio[b]
1[c]	2	CH_2Cl_2	40	65	5.0/1
2[c]	4	CH_2Cl_2	40	88	5.0/1
3[c]	4	$(CH_2Cl)_2$	83	78	4.3/1
4[c]	4	toluene	110	76	3.5/1
5[d]	4	CH_2Cl_2	40	71	4.0/1

[a]The reactions were carried out under reflux. [b]Determined by NMR. [c]10 mol % of **6** was used. [d]2 mol % of **6** was used.

SCHEME 2. Synthesis of the C31−C40/C43−C52 Segment (2)



which was separated from the other stereoisomers including the diols derived from the *Z*-olefin (18%). Protection of the hydroxy groups as acetates, followed by Migita−Kosugi−Stille coupling reaction[19] with stannane **3**[20] resulted in the formation of the

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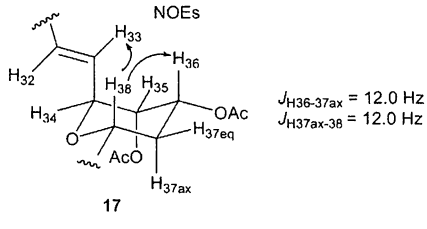
E,E-diene in 92% yield. Removal of the TBS group with HF·Py at 0 to 35 °C in THF provided allylic alcohol **11**, which was subjected to SAE, using D-(−)-DET to furnish vinyl epoxide **12**. Solvolysis of the acetate with K_2CO_3 in MeOH, and successive treatment of the resulting epoxy alcohol **13** with PPTS resulted in 6-*endo-tet* cyclization to afford the THP ring **14** in 60% yield for three steps. The structure of **14** was confirmed by NOE experiments of the corresponding triacetate **17** (Figure 2), i.e., NOEs between H38 and H33, and H38 and H36 were observed, in which H36 and H38 occupied 1,3-diaxial positions ($J_{H36-H37ax}$ = 12.0 Hz, $J_{H37ax-H38}$ = 12.0 Hz). Protection of the triol **14** as TBS ethers with TBSOTf/2,6-lutidine furnished **15** in 79% yield. SAD of **15** with AD-mix-β proceeded stereoselectively to afford the desired diol **16** in 97% yield (dr = 10: 1), and protection of the resulting vicinal diol as TBS ethers provided **2**. The overall yield of **2** from the iodoolefin **4** was 20% over 11 steps. The fully protected **2** would be a key intermediate corresponding to both the C31−C40 and C43−C52 units of AM3, in which protecting groups of the primary alcohols can be selectively removed under oxidative (for PMB ether) or reductive (for benzyl ether) conditions in the presence of TBS ethers.



17

FIGURE 2. Structure determination of **17** by NMR analysis.

In conclusion, a concise synthesis of the tetrahydropyran ring system **2**, corresponding to the C31−40/C43−C52 unit of AM3, was achieved based on chemoselective cross-metathesis, regioselective dihydroxylation, and 6-*endo-tet* cyclization. On the basis of the present method, it would be possible to synthesize an enantiomer of **2** from an enantiomer of **4** by changing the ligands used in SAD and SAE.

Experimental Section

(3*R*,1*E*,5*E*)-7-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-1-iodohepta-1,5-diene (7). To a solution of **4** (5.01 g, 14.8 mmol) and **5** (15.9 g, 59.2 mmol) in CH_2Cl_2 (48 mL) under reflux was added a solution of Grubbs catalyst **6** (251 mg, 0.296 mmol, 2 mol %) in CH_2Cl_2 (1.0 mL). After being stirred for 6 h, the reaction mixture was cooled to 0 °C, quenched with Et_3N, and allowed to warm to room temperature over 1 h, then the solvent was removed under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/0 → 20/1 → 10/1) afforded a mixture of **7** and allyl benzyl ether. The allyl benzyl ether was removed under reduced pressure at 90 °C for 1 h to provide **7** (4.81 g, 71%) as a yellow oil: $[\alpha]^{26}_D$ +6.84 (*c* 1.05, $CHCl_3$); R_f = 0.40 (hexane/EtOAc = 10/1); IR (film) ν 2953, 2928, 2884, 2856, 1606, 1471, 1361, 1254, 1088, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 6.51 (dd, *J* = 14.3, 6.0 Hz, 1H), 6.21 (dd, *J* = 14.3, 1.3 Hz, 1H), 5.74−5.54 (m, 2H), 4.41 (s, 2H), 4.11 (tdd, *J* = 6.0, 6.0, 1.3 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 6.0 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 138.4, 129.7, 129.2, 128.4, 127.7, 127.5, 76.0, 74.8, 71.9, 70.6, 65.8, 40.6, 35.9, 25.8, 18.1, −4.6, −4.9; HRMS (ESI-TOF) calcd for $C_{20}H_{31}IO_2SiNa$ [(M + Na)$^+$] 481.1036, found 481.1033.

(2*R*,3*R*,5*R*,*E*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-7-iodohept-6-ene-2,3-diol (8). A mixture of $K_2OsO_4 \cdot 2H_2O$ (31.3 mg, 0.0851 mmol), $(DHQD)_2PHAL$ (331 mg, 0.425 mmol), $K_3Fe(CN)_6$ (8.40 g, 25.5 mmol), K_2CO_3 (3.52 g, 25.5 mmol), and $MeSO_2NH_2$ (2.42 g, 25.5 mmol) in *t*-BuOH (18 mL) and H_2O (28 mL) was stirred at room temperature for 30 min, and then cooled to 0 °C. To the resulting suspension was added a solution of **7** (3.87 g, 8.51 mmol) in *t*-BuOH (10 mL). After being stirred for 36 h at 0 °C, the resulting mixture was quenched with solid $Na_2S_2O_3 \cdot 5H_2O$ (8.0 g) and allowed to warm to room temperature over 1 h. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash silica gel column chromatography (hexane/EtOAc = 5/1 → 3/1 → 2/1) afforded **8** (2.27 g, 68%) as a yellow syrup: $[\alpha]^{27}_D$ +37.8 (*c* 0.89, $CHCl_3$); R_f 0.40 (hexane/EtOAc = 2/1); IR (film) ν 3433, 2953, 2928, 2888, 2856, 1253, 1077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 6.54 (dd, *J* = 14.4, 5.8 Hz, 1H), 6.27 (dd, *J* = 14.4, 1.2 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.42 (m, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 3.59−3.51 (m, 3H), 3.09 (br s, 1H), 2.62 (br s, 1H), 1.79 (ddd, *J* = 14.2, 10.5, 3.4 Hz, 1H), 1.53 (ddd, *J* = 14.2, 7.2, 2.2 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 137.7, 128.5, 127.9, 127.8, 76.3, 73.6, 72.9, 72.1, 68.5, 40.2, 25.8, 18.1, −4.6, −5.2; HRMS (ESI-TOF) calcd for $C_{20}H_{33}IO_4SiNa$ [(M + Na)$^+$] 515.1091, found 515.1102.

(2*R*,3*R*,5*R*,6*E*,8*E*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)deca-6,8-diene-2,3-diyl Diacetate (10). To a solution of **9** (3.28 g, 5.68 mmol) and **3** (2.92 g, 6.25 mmol) in DMF (18.9 mL) was added $PdCl_2(MeCN)_2$ (36.8 mg, 0.142 mmol, 2.5 mol %) at 0 °C then the mixture was stirred at room temperature for 7 h. The resulting mixture was quenched with aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 10/1 → 8/1 → 4/1) afforded **10** (3.29 g, 92%) as a colorless syrup: $[\alpha]^{26}_D$ +8.92 (*c* 0.75, $CHCl_3$); R_f 0.48 (hexane/EtOAc = 2/1); IR (film) ν 2954, 2929, 2857, 1744, 1513, 1372, 1250, 1224, 1097, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.23 (m, 7H), 6.86 (m, 2H), 6.19 (dd, *J* = 15.0, 10.6 Hz, 1H), 6.11 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.75 (dt, *J* = 15.0, 6.0 Hz, 1H), 5.58 (dd, *J* = 15.0, 7.4 Hz, 1H), 5.29 (ddd, *J* = 8.4, 4.0, 4.0 Hz, 1H), 5.16 (m, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.43 (s, 2H), 4.13 (m, 1H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.53 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.50 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.74 (ddd, *J* = 14.2, 7.9, 4.0 Hz, 1H), 1.69 (ddd, *J* = 14.2, 8.4, 4.6 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.0, 159.1, 137.7, 136.4, 131.7, 130.2, 129.9, 129.4, 129.3, 128.2, 127.6, 113.7, 73.0, 72.7, 71.8, 70.1, 69.9, 69.1, 68.5, 55.2, 39.5, 25.8, 20.9, 20.8, 18.0, −4.0, −5.1; HRMS (ESI-TOF) calcd for $C_{35}H_{50}O_8SiNa$ [(M + Na)$^+$] 649.3173, found 649.3193.

(2*S*,3*R*,4*R*,6*R*)-6-[(1*R*)-2-Benzyloxy-1-hydroxyethyl]-2-[(*E*)-3-(4-methoxybenzyloxy)prop-1-enyl]tetrahydropyran-3,4-diol (14). To a mixture of powdered MS4A (450 mg) in CH_2Cl_2 (8 mL) were added D-(−)-DET (127 μL, 0.732 mmol) and Ti(O*i*-Pr)$_4$ (174 μL, 0.585 mmol) at −25 °C. After the mixture was stirred for 30 min, a solution of **11** (1.50 g, 2.96 mmol) in CH_2Cl_2 (6 mL) was added. After an additional 30 min of stirring, a solution of 2.8 M TBHP in CH_2Cl_2 (2.1 mL, 5.85 mmol) was added. Then after being stirred for 18 h at −20 °C, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$, diluted with EtOAc, and allowed to warm to room temperature. The

precipitates were removed by filtration through a Celite pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc = 1/1) afforded a mixture of **12** and D-(−)-DET as a yellow oil.

To a solution of the above mixture of **12** and D-(−)-DET in MeOH (30 mL) was added K_2CO_3 (80 mg, 0.585 mmol) at 0 °C. After being stirred for 3 h at 0 °C, the resulting mixture was quenched with pH 7.0 phosphate buffer, then MeOH was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide **13**. This crude **13** was used for the next step without further purification.

To a solution of the above crude **13** in CH_2Cl_2 (29 mL) was added PPTS (73.2 mg, 0.292 mmol) at 0 °C then the solution was stirred for 19 h. The resulting mixture was quenched with Et_3N and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/MeOH = 1/0 → 30/1 → 20/1 → 10/1) afforded **14** (782 mg, 60% for 3 steps) as a colorless syrup: $[\alpha]^{26}_D$ −23.7 (*c* 0.75, $CHCl_3$); R_f 0.30 (hexane/EtOAc = 3/1); IR (film) ν 3387, 2910, 2864, 1612, 1513, 1454, 1248, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.19 (m, 7H), 6.86−6.82 (m, 2H), 5.79 (dt, J = 15.9, 5.4, 1.2 Hz, 1H), 5.65 (dd, J = 15.9, 4.4 Hz, 1H), 4.51 (br s, 1H), 4.49 (s, 2H), 4.39 (s, 2H), 3.92 (d, J = 5.4 Hz, 2H), 3.81−3.74 (m, 2H), 3.76 (s, 3H), 3.71−3.68 (m, 2H), 3.54 (d, J = 6.0 Hz, 2H), 1.93 (ddd, J = 12.6, 12.6, 12.6 Hz, 1H), 1.61 (br d, J = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 137.9, 130.4, 130.0, 129.4, 128.4, 128.2, 127.7, 127.7, 76.9, 73.4, 72.4, 72.1, 71.0, 70.6, 69.7, 69.4, 65.9, 55.2, 30.9; HRMS (ESI-TOF) calcd for $C_{25}H_{32}O_7Na$ [(M + Na)$^+$] 467.2046, found 467.2036.

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Supporting Information Available: General experimental methods, additional experimental procedures, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.