Synthetic Study of the WXYZA'B'C'D'E'F' Ring Segment of Maitotoxin

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Doctor Thesis

Synthetic Study of the WXYZA'B'C'D'E'F' Ring Segment of Maitotoxin

マイトトキシンの WXYZA'B'C'D'E'F'環部の合成研究

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Abstract

Maitotoxin (MTX) is a ladder-shaped polyether produced by the dinoflagellate *Gambierdiscus toxicus*. MTX is comprised of 32 cyclic ethers and 98 stereogenic centers, and its molecular weight is 3422. It was difficult to determine the molecular structure of MTX because of the limited availability of MTX from natural sources and the complex and large molecular structure. MTX is known to elicit potent acute toxicity against mice and potent Ca^{2+} influx activity against all the cell types examined to date. However, the mode-of-action of MTX remains unknown. Although synthetic studies of the partial structures of MTX were reported, total synthesis of MTX has not been achieved yet. The structure of MTX is divided into two parts, hydrophobic (northern hemisphere) and hydrophilic (southern hemisphere) moieties depending on the distribution of polar functional groups. It was reported that the partial structure of MTX corresponding to the hydrophobic region elicited inhibitory activity against MTX-induced Ca^{2+} influx. In this study, the objective is synthesis of the WXYZA'B'C'D'E'F' ring segment including the side chain of MTX as a part of the structure-activity relationship studies of MTX based on the chemical synthesis of the partial structures of MTX to develop more potent inhibitor against MTX-induced Ca^{2+} influx activity.

As a convergent strategy via two-rings construction, α-cyano ether method was developed in our laboratory. Therefore, it was envisaged that the WXYZA'B'C'D'E'F' ring could be synthesized based on the α-cyano ether via coupling of the WXYZ and C'D'E'F' ring fragments through the construction of the A'B' ring. Although synthesis of the WXYZ ring and the C'D'E'F' ring including a tetrahydropyran derivative as a precursor of these fragments were reported by our group, it is necessary to carry out large scale synthesis of these fragments to complete the synthesis of the WXYZA'B'C'D'E'F' ring segment, and problems encountered through scale up of the reactions are to be overcome.

A tetrahydropyran derivative, a common intermediate for synthesizing the WXYZ ring and the C'D'E'F' ring was prepared in large scale. A ketoester derived from 2-deoxy-D-ribose was subjected to methylation of the ketone moiety with trimethylaluminum followed by reduction of the ester moiety with diisobutylaluminum hydride (DIBALH) in one-pot under the batch conditions. However, there were drawbacks in the large scale synthesis as follows: 1) limitation of the volume of glassware, 2) temperature control at −78 °C for a long time, 3) safety issue in quenching the reaction mixture. Therefore, a microflow reactor was utilized to overcome the problems. A solution of the ketoester (85 g) in tetrahydrofuran (THF) and a solution of methylmagnesium bromide in THF were transmitted to the microflow reactor (Comet-X01) by using syringe pumps at room temperature, followed by mixed with a solution of DIBALH in toluene in the next microflow reactor at room temperature. For quenching, the eluent was poured dropwise into a mixture of aqueous Rochelle salt and ether at 0 °C. As a result, desired diol (64 g) was obtained in comparable yield (83%) in the case of the batch reactions. The diol was converted to the common intermediate (19 g) via Shi epoxidation, Wittig reaction, and acid catalyzed 6-*endo* cyclization.

The E’ ring was prepared from the common intermediate. After converting to a substrate comprising a ketone and an α,β-alkoxyacrylate, SmI_2-induced reductive cyclization was applied to construct the D’ ring. Furthermore, after converting to a substrate comprising an aldehyde and an α,β-alkoxyacrylate, construction of the C’ ring was carried out in an analogous sequence to afford the C’D’E’ ring. On the other hand, the side chain of the F’ ring was synthesized from 1,3-propanediol via Katsuki–Sharpless asymmetric epoxidation, diastereoselective Michael addition, and Noyori asymmetric hydrogen transfer reaction. Hydroboration of a terminal olefin corresponding to the C’D’E’ ring, followed by Suzuki–Miyaura coupling of the resulting alkylborane with the iodoolefin corresponding to the side chain resulted in the formation of a coupling product. Then, construction of the F’ ring was carried out by Pd(II) catalyzed cyclization to afford the C’D’E’F’ ring fragment.

The Z ring and the W ring were prepared from the common intermediate. After conversion of a terminal alkyne corresponding to the Z ring lithium acetylide, addition of an aldehyde corresponding to the W ring resulted in the formation of a coupling product. Hydrogenation of the alkyne and oxidation of the alcohol furnished a ketone. The next transformation, cyclodehydration of the hydroxy ketone using the acidic resin Nafion NR-50 was problematic. It was necessary to use excess amount of expensive Nafion NR-50. After considerable experimentation to optimize the reaction conditions, phosphorous (V) oxide was found to be suitable for this transformation to afford the desired compound. Then, the Y ring was constructed through ring expansion on of a six-membered ring ketone to a seven-membered one, and the X ring was constructed through the formation of *O*,*S*-acetal followed by oxidation/methylation sequence to afford the WXYZ ring fragment.

A convergent method via two-rings construction, α-cyano ether method developed in our laboratory, was applied to synthesize the WXYZA’B’C’D’E’F’ ring segment. Coupling of the C’D’E’F’ ring diol and the WXYZ ring aldehyde by acetal formation followed by regioselective cleavage of the acetal furnished an α-cyano ether. Conversion of the resulting primary alcohol to a terminal olefin by Nishizawa–Grieco method, followed by ring closing metathesis reaction of the diene resulted in the formation of the B’ring. After conversion to an *O*,*S*-acetal, radical reduction was subjected to construct the A’ ring system. However, the reaction was turned out to be irreproducible. After considerable experimentation to optimize the reaction conditions, the reaction with triphenyltin hydride in the presence of triethylboran was found to be reproducible. Finally, introduction of the terminal olefin in the side chain culminated in the completion of the synthesis of the WXYZA’B’C’D’E’F’ ring segment of MTX. The longest linear sequence was 53 steps, and the total number of steps was 104 steps. The chemical shifts of ^{1}H and ^{13}C NMR data of the synthetic specimen were in good accordance with those of the natural product, confirming the proposed structure of MTX. The WXYZA’B’C’D’E’F’ ring segment of MTX synthesized in this study is the largest partial structure reported to date, whose molecular weight is 1140.

Contents

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
AIBN	2,2'-azobisisobutyronitrile
AZADOL	2-hydroxy-2-azaadamantane
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
calcd	calculated
cat	catalytic or catalyst
COSY	correlation spectroscopy
CSA	(±)-10-camphorsulfonic acid
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DET	diethyltartrate
DFT	density functional theory
$(DHQ)_2AQN$	hydroquinine (anthraquinone-1,4-diyl) diether
DIBALH	diisobutyulalminium hydride
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dqf-COSY	double quantum filtered correlation spectroscopy
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomer ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDTA	ethylenediaminetetraacetic acid
eq	equivalent(s)
ESI	electrospray ionization
Et	ethyl

GC	gas chromatography
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
i	iso
IC_{50}	50% inhibitory concentration
IR	infrared
JBCA	*J*-based conformation analysis
LD_{50}	50% lethal dose
M	molar
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MS	mass spectrometry
MS3A	molecular sieves 3A
MS4A	molecular sieves 4A
MTX	maitotoxin
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NAP	2-naphtylmethyl
NHK	Nazaki–Hiyama–Kishi
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p	para
Ph	phenyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
Pv	pivaloyl
Py	pyridine
quant	quantitative
ROESY	rotating frame Overhauser effect spectroscopy

rt	room temperature
t	tertiary
FAB	fast atom bombardment
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCCA	trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
TOF	time-of-flight
Tr	triphenylmethyl (trityl)
t_R	retention time
TS	transition state
Ts	*para*-toluenesulfonyl (tosyl)

Chapter 1. Introduction

1-1. Maitotoxin

Marine dinoflagellates are a rich source of biologically and structurally interesting secondary metabolites.[1] Maitotoxin (MTX) is a ladder-shaped polyether produced by the dinoflagellate *Gambierdiscus toxicus* (Figure 1-1-1), and one of the causative toxins of ciguatera, sea food poisoning prevalent in the tropical and subtropical regions.[2] The molecular structure was determined by Yasumoto and Murata group using extensive NMR analysis.[3] The relative and absolute configuration was determined by Tachibana group based on chemical synthesis and degradation of the natural product.[4,5,7] The relative configuration was also determined by Kishi group based on chemical synthesis of partial structures.[4,6] MTX is comprised of thirty-two cyclic ethers containing ninety-eight chiral centers. Furthermore, the molecular weight of MTX (3422) is the largest among nonpeptide secondary metabolites. MTX can be divided into two parts depending on the distribution of the polar functional groups, the hydrophilic (southern hemisphere, the A–O ring) and hydrophobic (northern hemisphere, the P–F' ring) regions.

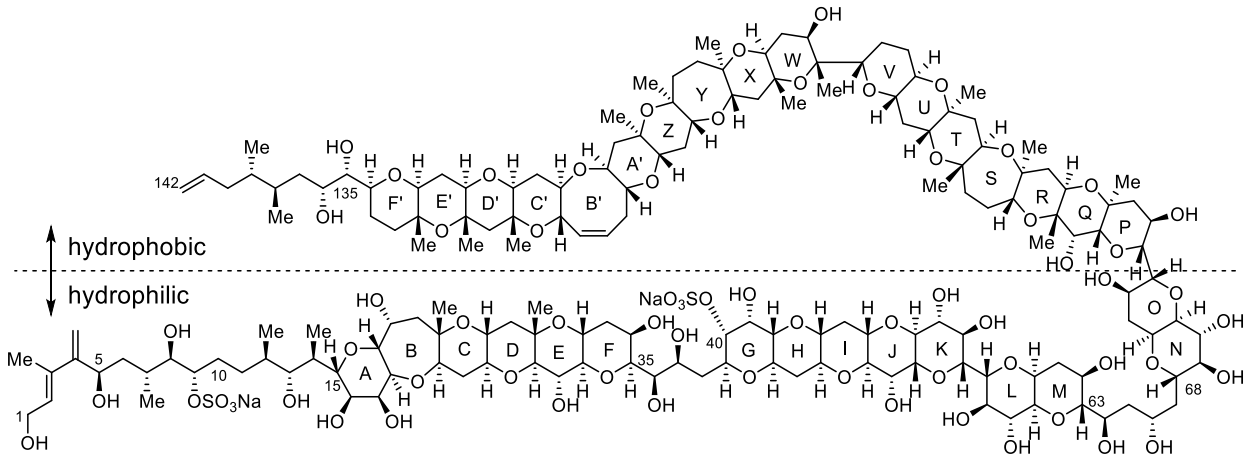


Figure 1-1-1. Structure of MTX.

It is known that MTX shows high toxicity toward mammals (LD_{50} = 50 ng/kg, mice i.p.), it induces Ca^{2+} influx at extremely low concentration (0.3 nM, rat C6 glioma cell), and it causes hemolysis of red blood cells (15 nM).[3c,8]

1-2. Structure determination of maitotoxin

As mentioned in Section 1-1, planar structure of MTX was determined by Yasumoto and Murata group. In this section, determination of the stereochemistry of MTX is mentioned focusing on the WXYZA'BC'D'E'F' ring section.

1-2-1. Determination of the planar structure

Although the structure of MTX was determined by extensive NMR spectra including 2D-NMR techniques, overlapping as well as poor resolution of both ^{1}H and ^{13}C NMR signals were problems due to the large molecular size. Therefore, MTX was divided into three parts by periodate degradation (Figure 1-2-1). Structures of these fragments were determined by extensive NMR analysis and negative FAB MS/MS analysis.[3a,3b]

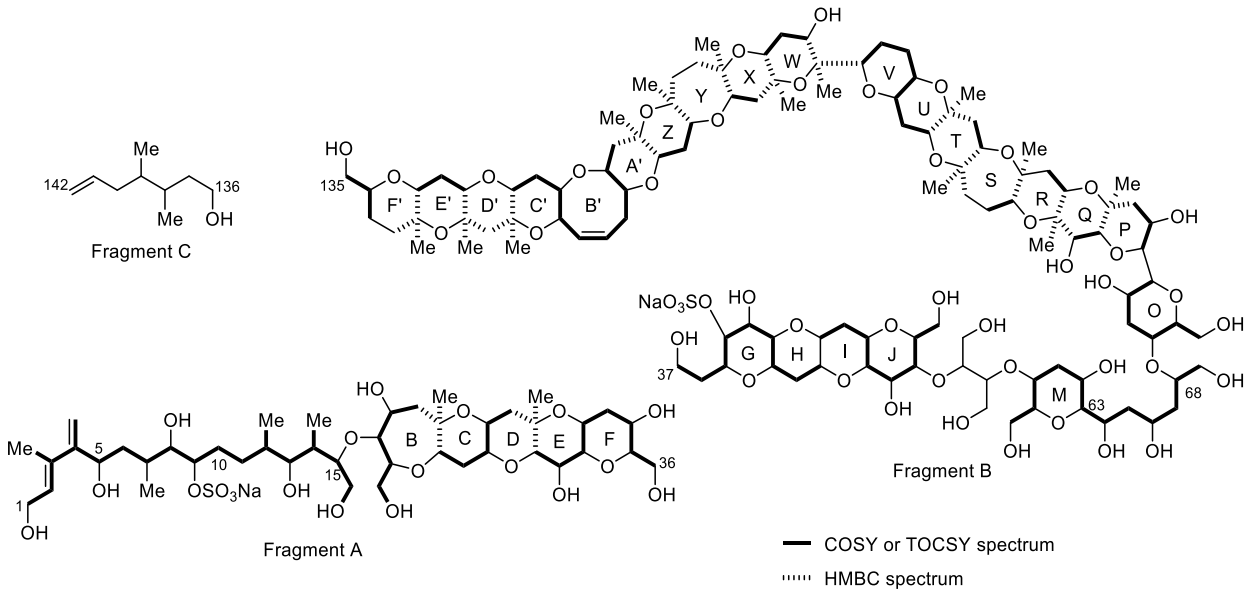


Figure 1-2-1. 2D NMR analysis of the degradation products derived from MTX.

1-2-2. The relative and absolute configuration of the WXYZA'B'C'D'E'F' ring segment

Murata and Yasumoto group determined the relative configuration of fused polycyclic ether domains by NOE correlations and $^{3}J_{H,H}$ values, and those of the VWXYZA'B'C'D'E'F' ring moiety is shown in Figure 1-2-2.[3c]

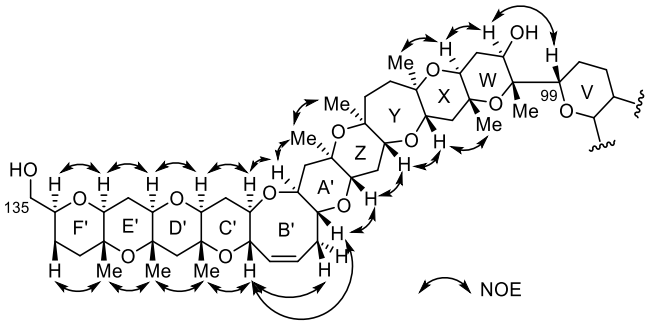


Figure 1-2-2. NOE correlations corresponding to the WXYZA'B'C'D'E'F' ring section of the degradation product.

The relative configuration between the V and W rings was deduced by NOE and $^{3}J_{H,H}$ data with the aid of MM2 calculations (Figure 1-2-3).[3c] The NOE was detected between Me155 and H102ax and the chemical shifts of Me155 and Me156 (δ 19.0 and 19.8) were typical for 2,6-diaxal dimethyl on tetrahydropyran, demonstrating equatorial substitution of C99 on the W ring. NOEs of H99/H101 and Me155/H98 indicated antiperiplanar orientation of H99/Me155. MM2 calculations supported the deduced stereochemistry.

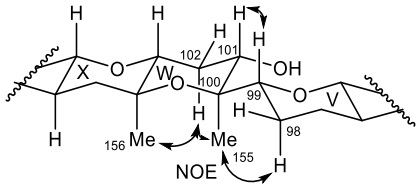


Figure 1-2-3. NOE correlations corresponding to the VWX ring of the degradation product.

The relative configuration between C136 and C138 was determined by JBCA method (Figure 1-2-4).[5] The relative configuration of the C134, C135, and C136 was also determined by JBCA method. However, NOEs and coupling constants suggested the presence of conformational isomers. Therefore, to confirm the proposed structure, the model compound corresponding to the C134–C136 section was synthesized (Scheme 1-2-1).[5] The model compound was synthesized from tri-*O*-acetyl-D-glucal via allylic reduction, Wittig reaction, and Sharpless asymmetric dihydroxylation. The *J* values of the C134–C136 portion of the model compound were in

accordance with those of MTX, thereby confirming the assignment by the JBCA method.

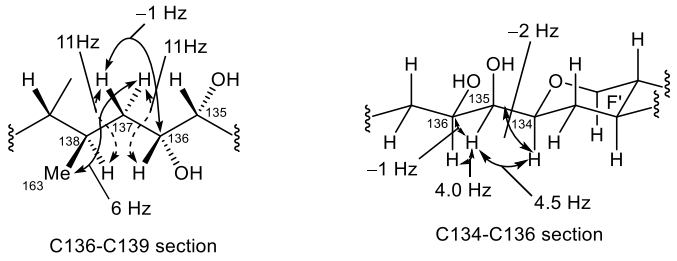
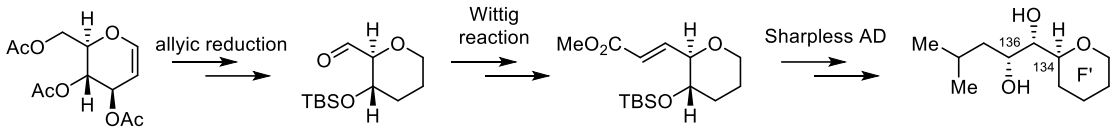
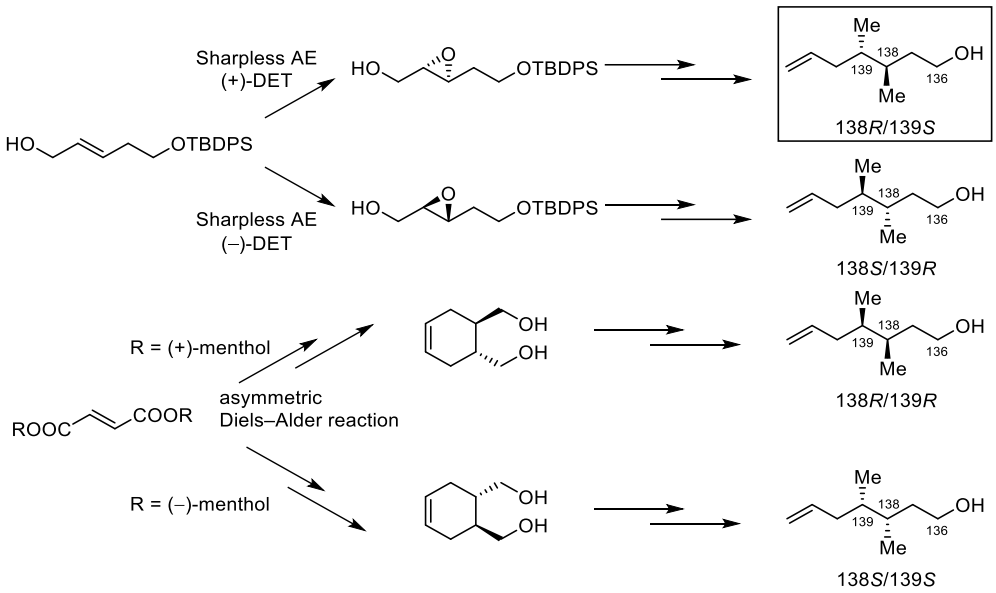


Figure 1-2-4. Determination of the relative configuration of the C134–C136 section by JBCA method.



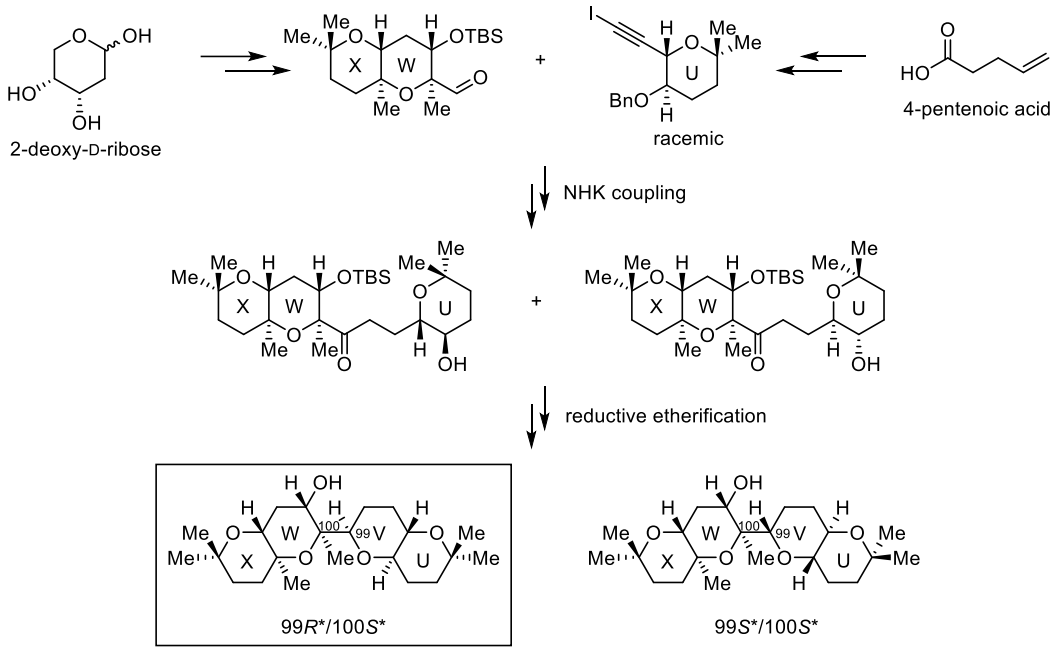
Scheme 1-2-1. Determination of the relative configuration of the C134–C136 section by chemical correlation.

Since it was difficult to assign the relative configuration of C138/C139 by the JBCA method, four model compounds corresponding to the C136–C142 section were synthesized to determine the relative configuration by Tachibana group (Scheme 1-2-2).[5] The C138/C139 *anti* isomers were synthesized via Katsuki–Sharpless asymmetric epoxidation. On the other hand, the C138/C139 *syn* isomers were synthesized via asymmetric Diels–Alder reaction. By using a chiral column, GC/MS analysis of the model compounds with the authentic sample prepared by degradation of MTX clearly demonstrated that the retention time and MS data of the model compound of 138*R*/139*S* isomer were matched with those of the authentic sample. As a result, not only the relative configuration but also the complete absolute configuration of MTX were assigned.



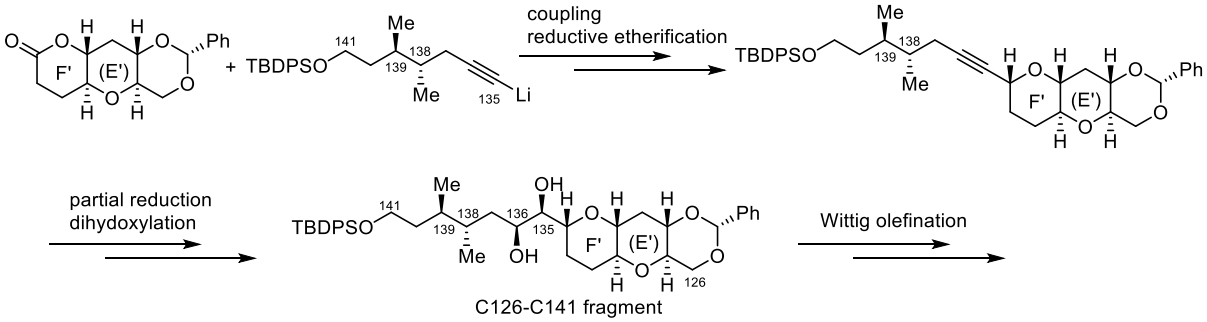
Scheme 1-2-2. Determination of the relative and absolute configuration of the C138/C139 by chemical correlation.

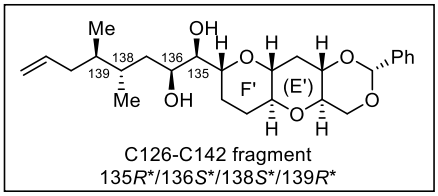
Kishi group independently reported determination of the relative configuration of MTX based on the chemical synthesis of partial structures.[6] The relative configuration of V/W ring was determined by chemical correlation of the synthetic model compounds (Scheme 1-2-3).[6a] The WX ring aldehyde was prepared from 2-deoxy-D-ribose and the U ring iodoacetylene (racemic) was prepared from 4-pentenoic acid. Coupling of these fragments by NHK reaction furnished the UWX ring ketone as two diastereomers with respect to the U ring. The resulting hydroxyketones were converted to the UVWX ring through the construction of the V ring by reductive etherification, respectively. Comparison of the ^{1}H and ^{13}C NMR data of the model compounds with those of MTX revealed that the relative configuration was to be 99*R**/100*S**.

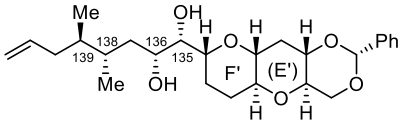


Scheme 1-2-3. Determination of the relative configuration of the V/W ring by chemical correlation.

The relative configuration of the F' ring and the side chain was determined by synthesizing the model compounds corresponding to the E'F' ring (Scheme 1-2-4).[6b] Coupling of the F' ring lactone with the lithium acetylide derived from the C135–C141 section followed by reductive etherification gave the alkyne, which was converted to the C126–C142 section via partial reduction, dihydroxylation, and Wittig olefination. In an analogues sequence, other fifteen diastereomers at C135, C136, C138, and C139 were synthesized. Comparison of the ^{1}H and ^{13}C NMR data of the model compounds with those of MTX revealed that the relative configuration was to be 135*R**/136*S**/138*S**/139*R**. Later, the absolute configuration of MTX was determined by Tachibana group to be 135*S*/136*R*/138*R*/139*S*.



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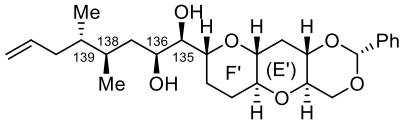
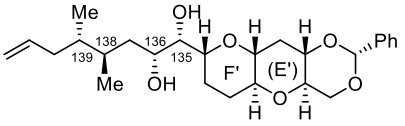

135*R**/136*S**/138*R**/139*S**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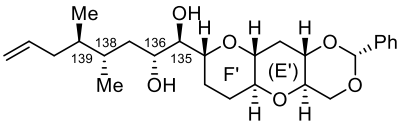
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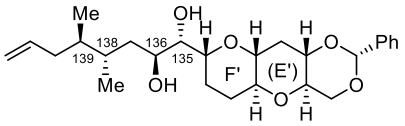
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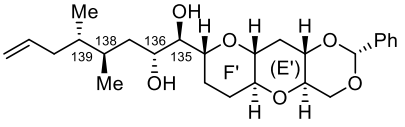
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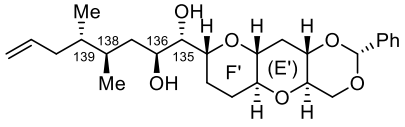
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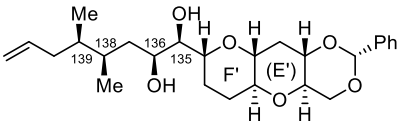
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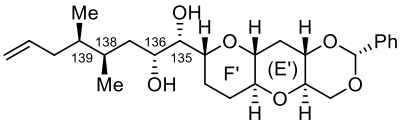
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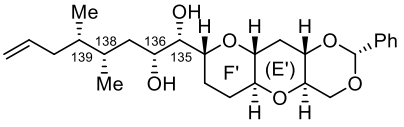
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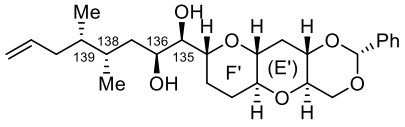
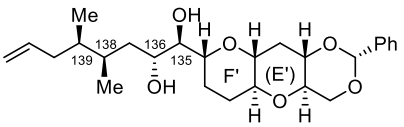

135*R**/136*S**/138*S**/139*S**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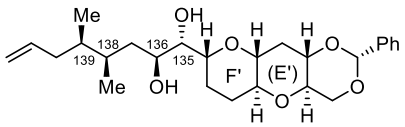
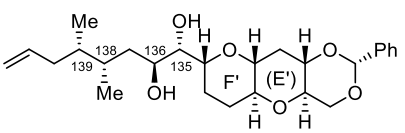
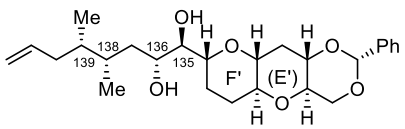

135*S**/136*R**/138*R**/139*R**


135*S**/136*S**/138*S**/139*S**


135*R**/136*S**/138*S**/139*S**

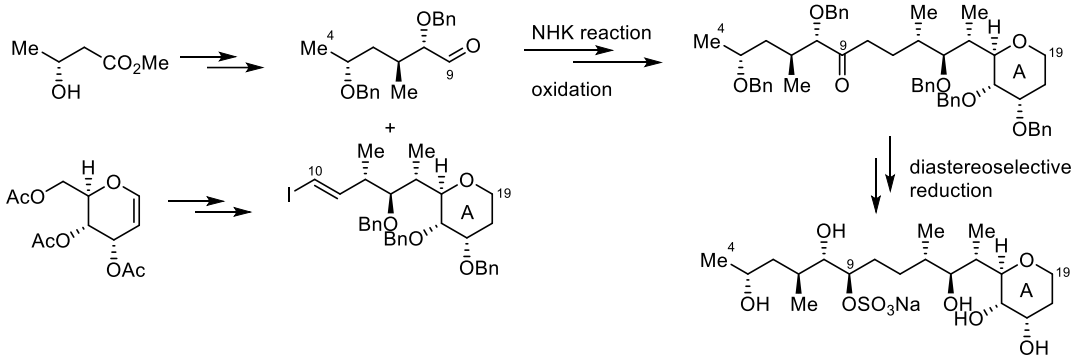
Scheme 1-2-4. Determination of the relative configuration of the C135, C136, C138, and C139 by chemical correlation.

1-3. Synthetic studies of maitotoxin

Although synthetic studies of MTX was reported by Tachibana group and Kishi group, independently, for structure determination of MTX, synthetic studies of MTX were also reported by Nicolaou group, Nakata group, Jamison group, and Oishi group.

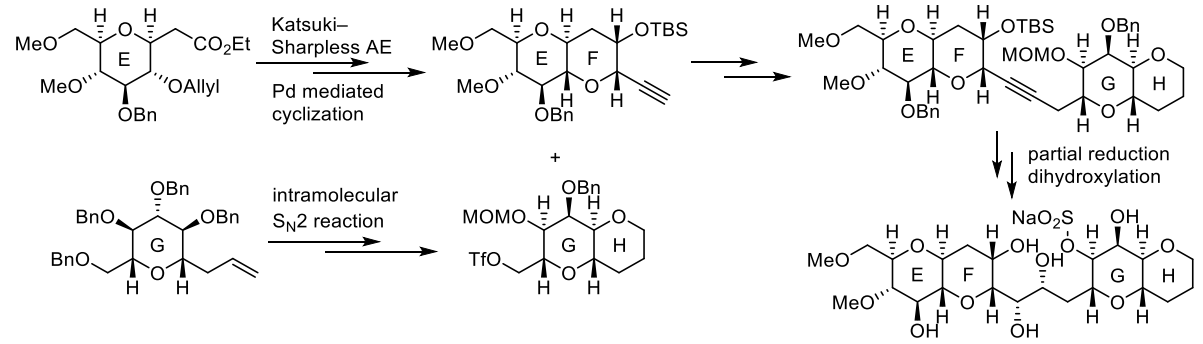
1-3-1. Tachibana group

The C4–C19 section was synthesized as shown in Scheme 1-3-1.[7a] NHK coupling of the C4–C9 aldehyde prepared from (*S*)-3-hydroxybutyrate and the C10–C19 iodoolefin prepared from tri-*O*-acetyl-D-glucal, followed by oxidation of the resulting alcohol gave the ketone. Diastereoselective reduction of the ketone at C9 with $Zn(BH_4)_2$ provide the secondary alcohol as a single diastereomer, which was converted to the sulfate.



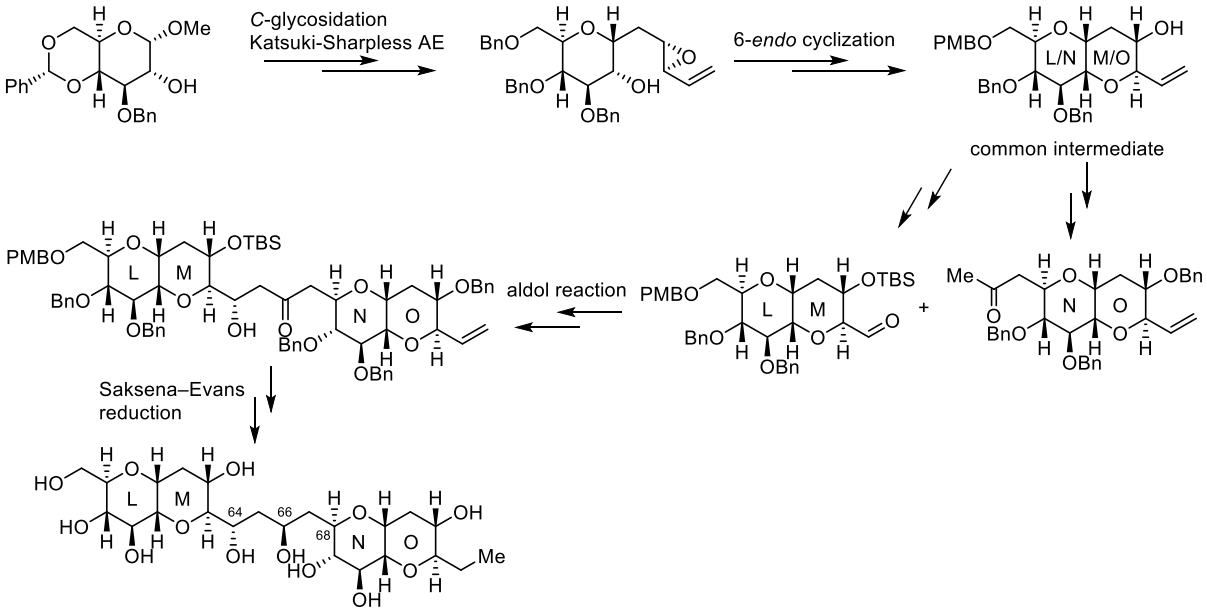
Scheme 1-3-1. Synthesis of the C4–C19 section.

The EFGH ring was synthesized as shown in Scheme 1-3-2.[7b] The EF ring alkyne was prepared via Katsuki–Sharpless asymmetric epoxidation and palladium mediated cyclization. The GH ring triflate was prepared from the D-glucose derivative through the construction of the H ring via intramolecular S_N2 reaction. Lithium acetylide generated from the EF ring alkyne was reacted with the GH ring triflate to furnish the alkyne. Partial reduction of the alkyne to *E*-alkene followed by dihydroxylation afforded the EFGH ring.



Scheme 1-3-2. Synthesis of the EFGH ring.

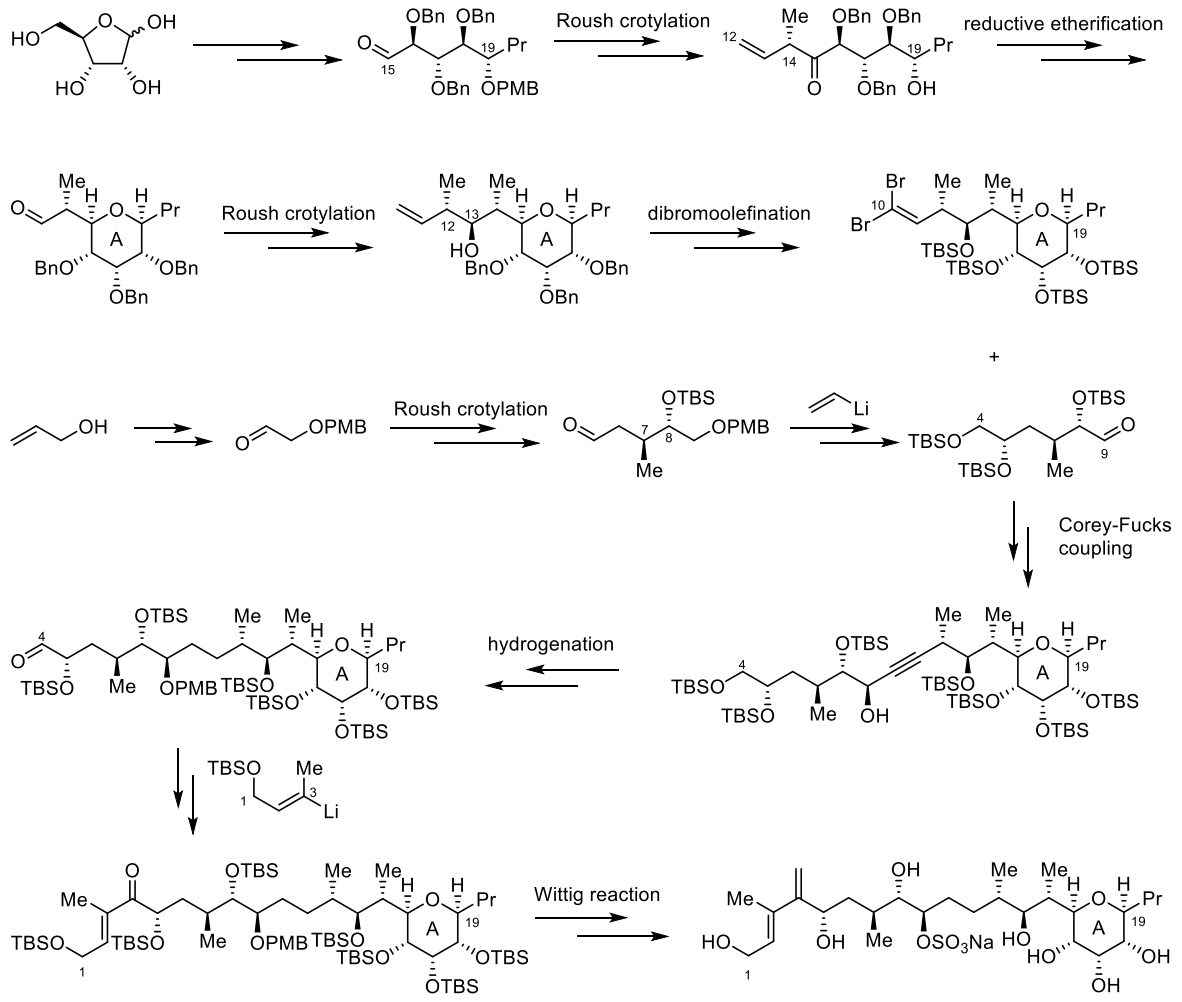
The LMNO ring was synthesized as shown in Scheme 1-3-3.[7c,7d] The common intermediate of the LM and the NO rings were synthesized from the D-glucose derivative via *C*-glycosylation, Katsuki–Sharpless asymmetric epoxidation, and acid catalyzed 6-*endo* cyclization of vinyl epoxide. The common intermediate was converted to the LM ring aldehyde and the NO ring methyl ketone, respectively, which were subjected to aldol reaction to furnish the β-hydroxyketone. The resulting β-hydroxyketone was converted to the 1,3-*anti* diol by Saksena–Evans reduction to afford the LMNO ring.



Scheme 1-3-3. Synthesis of the LMNO ring.

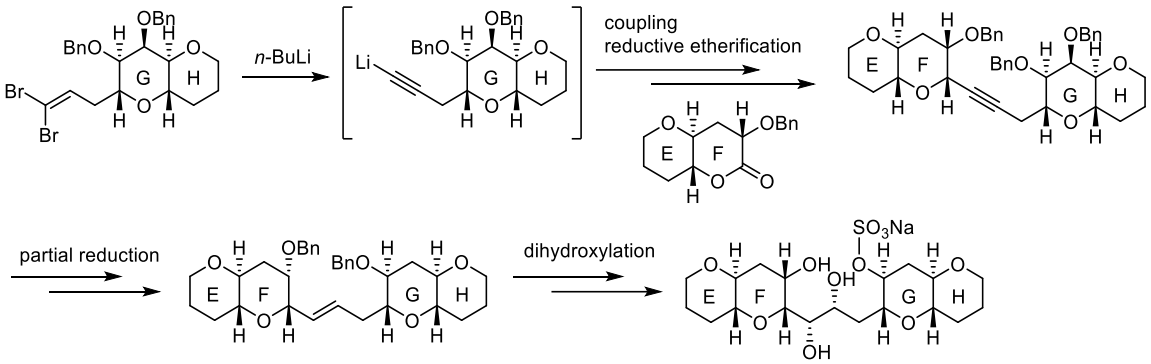
1-3-2. Kishi group

The C1–C19 section of MTX was synthesized based on Roush crotylation chemistry as shown in Scheme 1-3-4.[6b] The C10–C19 section was synthesized via Roush crotylation of the aldehyde prepared from D-ribose with controlling the stereochemistry at C14. The A ring aldehyde was prepared via reductive etherification of the hydroxyketone. Stereochemistry at C12 and C13 was also controlled by using Roush crotylation of the aldehyde, and the resulting terminal olefin was converted to the dibromoolefin. On the other hand, the C4–C9 section was synthesized via Roush crotylation of the aldehyde prepared from 2-propen-1-ol to construct of the stereochemistry at C7 and C8. The C4–C9 aldehyde was prepared via addition of vinyllithium to the aldehyde. The C10–C19 dibromoolefin was treated with *n*-BuLi to furnish the lithium acetylide, which was coupled with the C4–C9 aldehyde to afford the alkyne. The alkyne was converted to the α,β-unsaturated ketone via hydrogenation, addition of alkenyllithium corresponding to the C1–C3 section followed by oxidation. The ketone was converted to the *exo*-olefin by Wittig olefination to furnish the C1–C19 section.



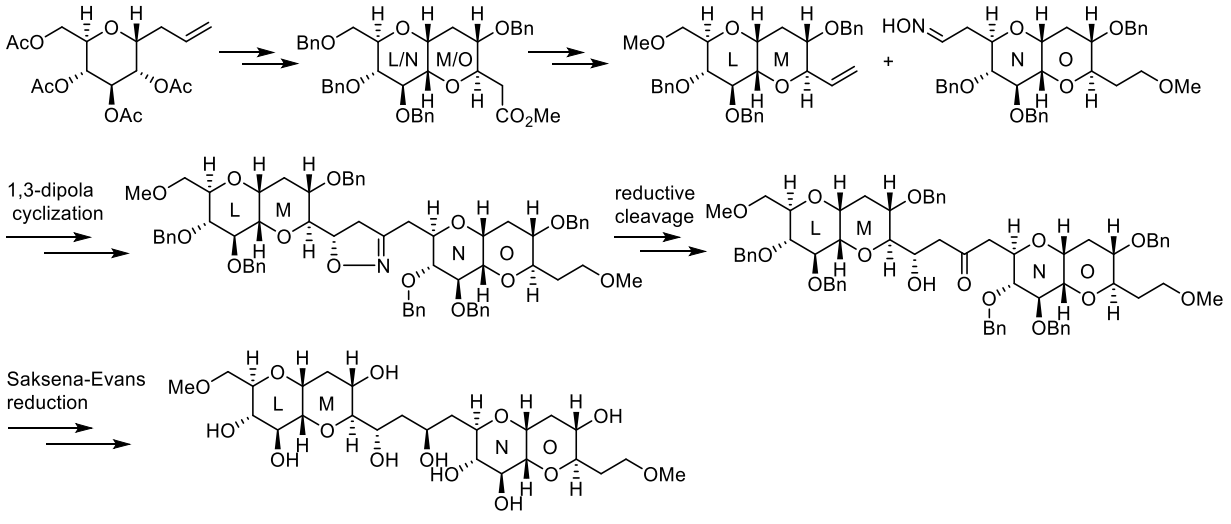
Scheme 1-3-4. Synthesis of the C11–C19 section.

The EFGH ring was synthesized as shown in Scheme 1-3-5.[6b] The GH ring dibromoolefin was treated with *n*-BuLi to generate the lithium acetylide, which was coupled with the EF ring lactone followed by reductive etherification furnished the alkyne. Partial reduction of the alkyne giving the *E*-olefin followed by dihydroxylation afforded the EFGH ring.



Scheme 1-3-5. Synthesis of the EFGH ring.

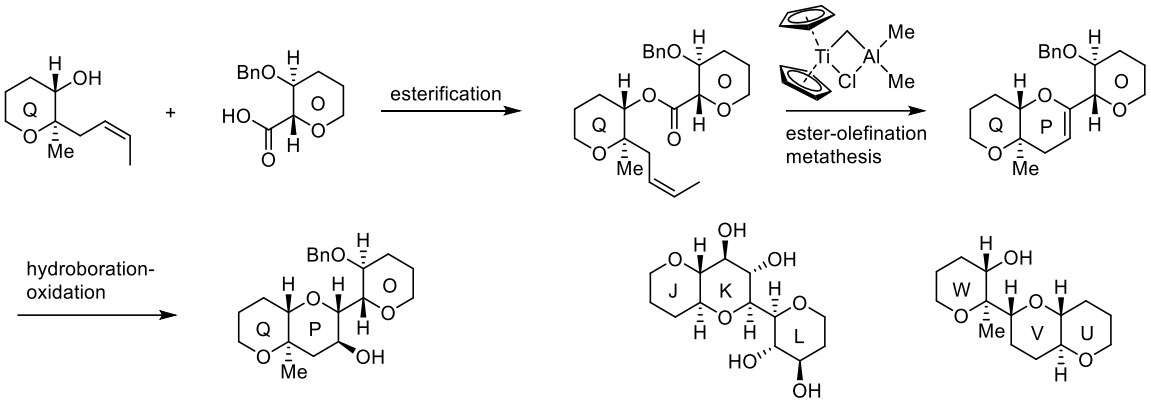
The LMNO ring was synthesized as shown in Scheme 1-3-6.[6b] The LM and NO rings were synthesized from the common intermediate prepared from the D-glucose derivative.[5b] The LMNO ring was obtained via 1,3-dipolar cycloaddition of the LM ring olefin and the NO ring nitrile oxide. Reductive cleavage of the N-O bond gave the β-hydroxyketone, which was converted to the 1,3-*anti* diol by Saksena–Evans reduction to furnish the LMNO ring.



Scheme 1-3-6. Synthesis of the LMNO ring.

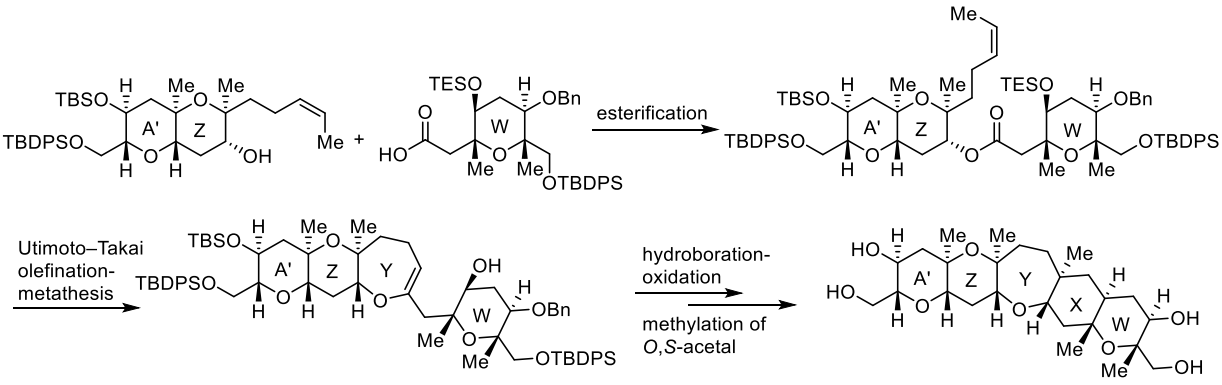
1-3-3. Nicolaou group

Nicolaou group developed a convergent strategy for synthesizing polycyclic ether systems based on Tebbe reagent mediated ring closing reaction.[9a] This method was applied to synthesize the OPQ ring of MTX (Scheme 1-3-7).[9a] Esterification of the Q ring alcohol and the O ring carboxylic acid followed by ester carbonyl olefination-ring closing metathesis sequence mediated by Tebbe reagent furnished the cyclic enol ether. Hydroboration-oxidation of the enol ether afforded the OPQ ring. In an analogous sequence, the JKL and UVW rings were also synthesized.



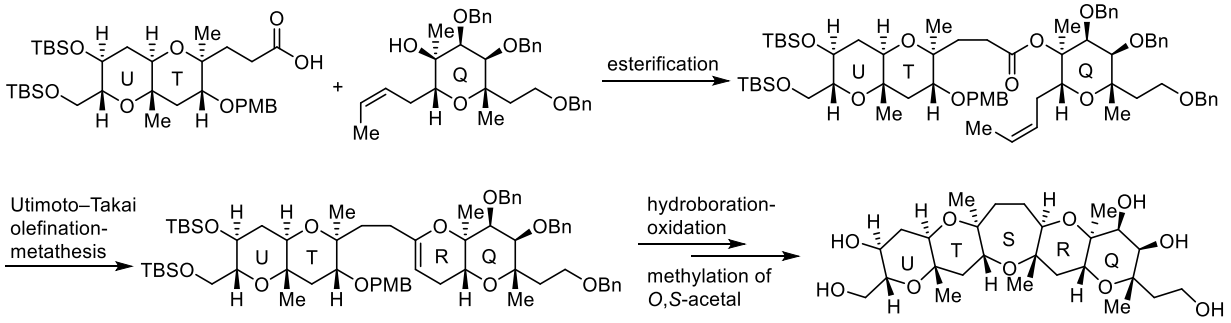
Scheme 1-3-7. Synthesis of the OPQ, JKL, and UVW rings.

The similar strategy was applied to the synthesis of the WXYZA' ring (Scheme 1-3-8).[9b] Esterification of the W ring carboxylic acid and the ZA' ring alcohol gave the ester, which was subjected to Utimoto–Takai olefination-metathesis sequence to construct of the Y ring. The X ring was constructed via hydroboration-oxidation and methylation of *O*,*S*-acetal to afford the WXYZA' ring.



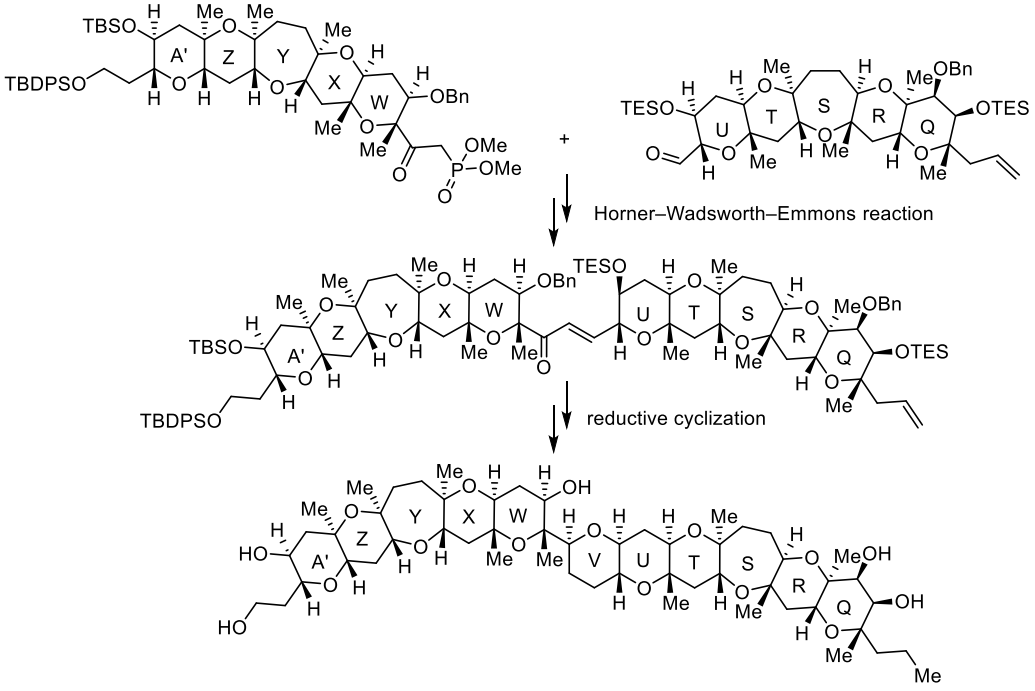
Scheme 1-3-8. Synthesis of the WXYZA' ring.

The strategy was also applied to the synthesis of the QRSTU ring (Scheme 1-3-9).[9c] Condensation of the UT ring carboxylic acid and the Q ring alcohol gave the ester, which was subjected to Utimoto–Takai olefination-metathesis sequence to construct the R ring to furnish the enol ether. The S ring was construct via hydroboration-oxidation and methylation of *O*,*S*-acetal to afford the QRSTU ring.



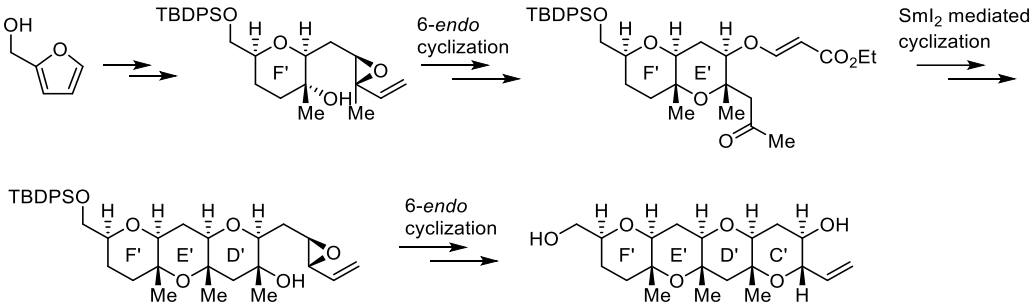
Scheme 1-3-9. Synthesis of the QRSTU ring.

The QRSTUVWXYZA' ring was synthesized as shown in Scheme 1-3-10.[9d] Horner–Wadsworth–Emmons reaction of the WXYZA' ring phosphonate and the QRSTU ring aldehyde giving the enone, followed by construction of the V ring by reductive etherification afforded the QRSTUVWXYZA' ring.



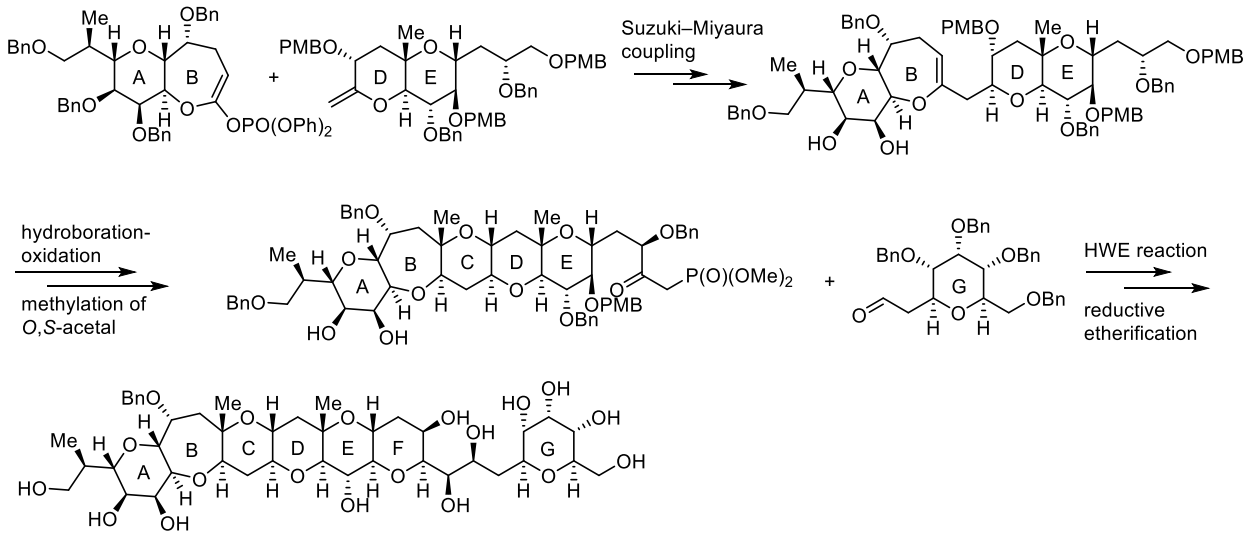
Scheme 1-3-10. Synthesis of the QRSTUVWXYZA' ring.

The C'D'E'F' ring was synthesized based on the linear strategy as shown in Scheme 1-3-11.[9e] The F' ring prepared from furfuryl alcohol was subjected to acid catalyzed 6-*endo* cyclization of the vinyl epoxide to construct the E' ring. Then, SmI_2 mediated reductive cyclization was utilized to construct the D' ring. The 6-*endo* cyclization of the vinyl epoxide was applied again to construct the C' ring to afford the C'D'E'F' ring.



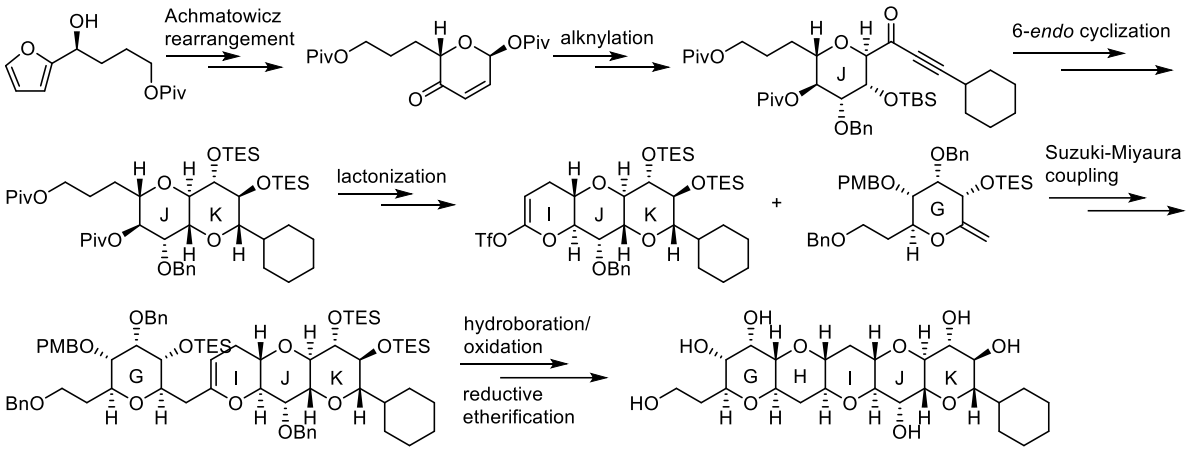
Scheme 1-3-11. Synthesis of the C'D'E'F' ring.

The ABCDEFG ring was synthesized as shown in Scheme 1-3-12.[9f] Suzuki–Miyaura coupling of the AB ring enol phosphate and the DE ring *exo*-olefin followed by hydroboration-oxidation and methylation of *O*,*S*-acetal resulted in the formation of the ABCDE ring. Then, Horner–Wadsworth–Emmons olefination of the ABCDE ring phosphonate with the G ring aldehyde followed by construction of the F ring via reductive etherification afforded the ABCDEFG ring.



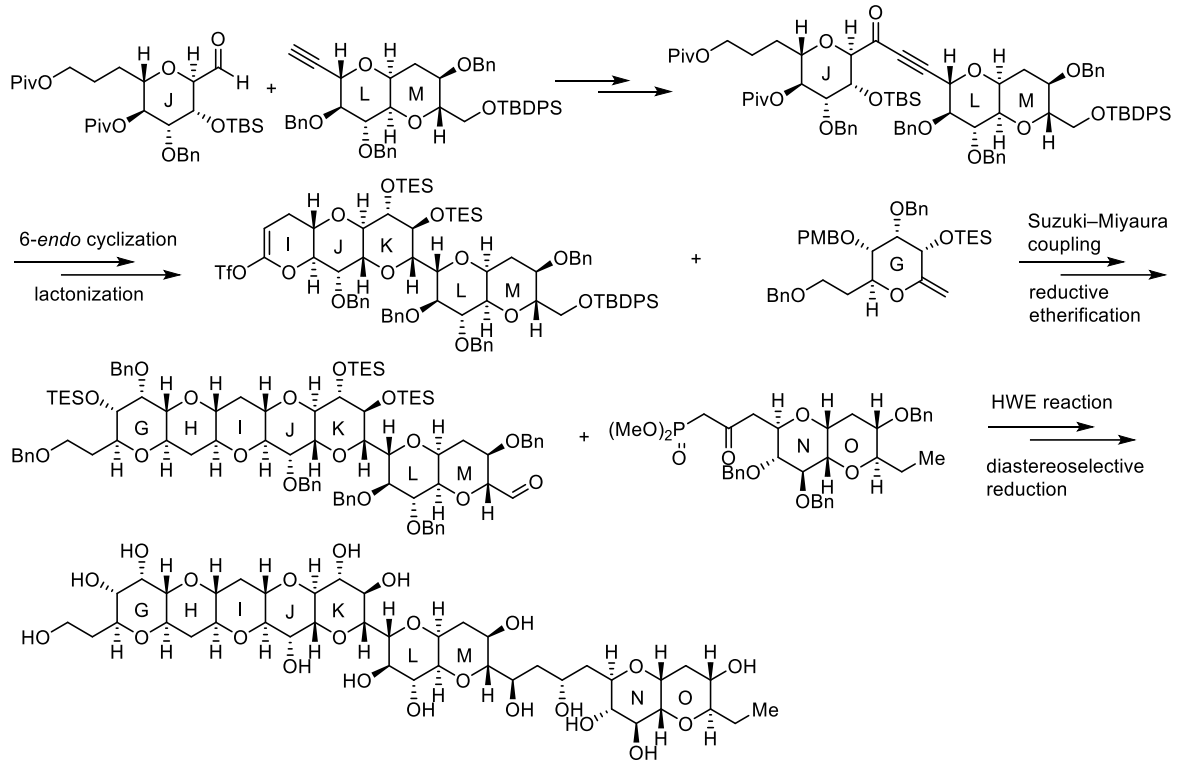
Scheme 1-3-12. Synthesis of the ABCDEFG ring.

The GHIJK ring was synthesized as shown in Scheme 1-3-13.[9g] The J ring was synthesized from furfuryl alcohol derivative via Achmatowicz rearrangement and alkynylation. The K ring was constructed via AgOTf induced 6-*endo* cyclization of the ynone. After construction of the I ring via lactonization, the enol triflate was coupled with the G ring *exo*-olefin by Suzuki–Miyaura coupling. The H ring was constructed via hydroboration/oxidation and reductive etherification to afford the GHIJK ring.



Scheme 1-3-13. Synthesis of the GHIJK ring.

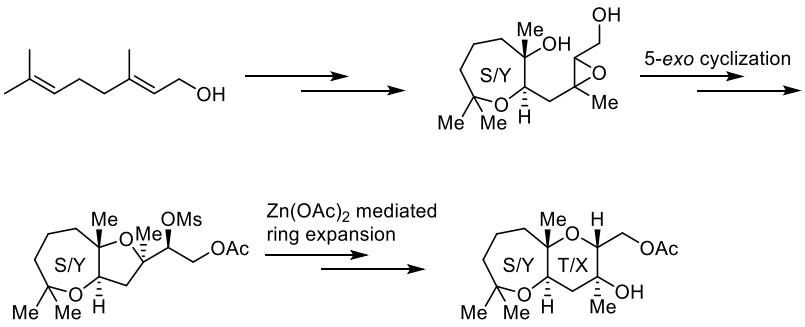
The GHIJKLMNO ring was synthesized as shown in Scheme 1-3-14.[9h] Coupling of the J ring aldehyde with the LM ring alkyne giving the ynone followed by successive construction of the K and I rings via AgOTf mediated 6-*endo* cyclization and lactonization, respectively, furnished the enol triflate. Suzuki–Miyaura coupling of the IJKLM ring enol triflate with the G ring *exo*-olefin followed by reductive etherification resulted in the formation of the GHIJKLM ring. After converting to the aldehyde, Horner–Wadsworth–Emmons reaction with the NO ring phosphonate followed by diastereoselective reduction afforded the GHIJKLMNO ring.



Scheme 1-3-14. Synthesis of the GHIJKLMNO ring.

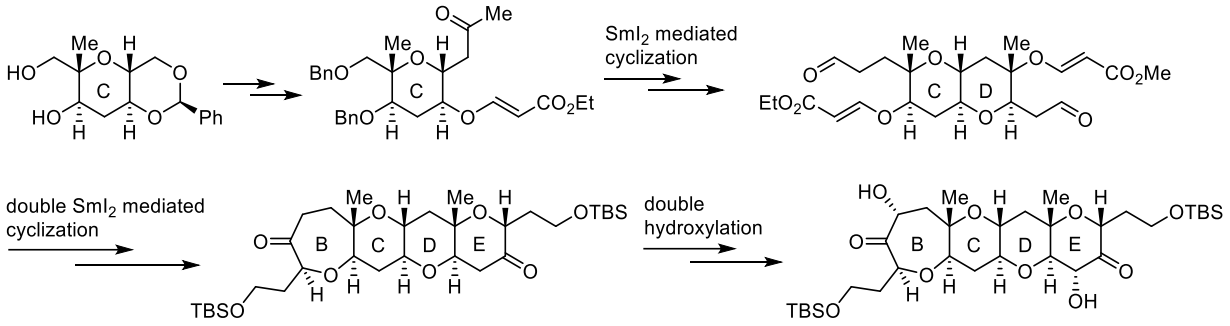
1-3-4. Nakata group

The common bicyclic ether system corresponding to the ST and XY rings was synthesized as shown in Scheme 1-3-15.[10a] The S/Y ring epoxy alcohol prepared from geraniol was subjected to TBAF mediated 5-*exo* cyclization. Ring expansion of the five membered ring to the six membered one was achieved by treating the mesylate with $Zn(OAc)_2$ to afford the common bicyclic ether.



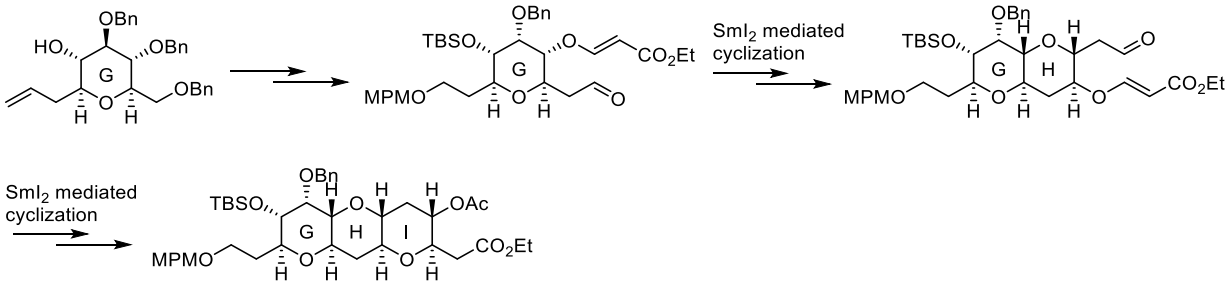
Scheme 1-3-15. Synthesis of the common bicyclic ether system corresponding to the ST and XY rings.

Nakata group developed the SmI_2 mediated reductive cyclization to construct polycyclic ether system.[9] This method was applied to the synthesis of the BCDE ring (Scheme 1-3-16).[10b] The C ring possessing the ketone and β-alkoxyacrylate moieties was prepared from the tetrahydropyran derivative. The D ring was constructed via SmI_2 mediated reductive cyclization. The method was also applied to the two-directional strategy. The CD ring possessing bis-aldehyde and bis-β-alkoxyacrylate moieties was subjected to SmI_2 mediated double cyclization to construct the B and E rings simultaneously, and double hydroxylation of the diketone furnished the BCDE ring.



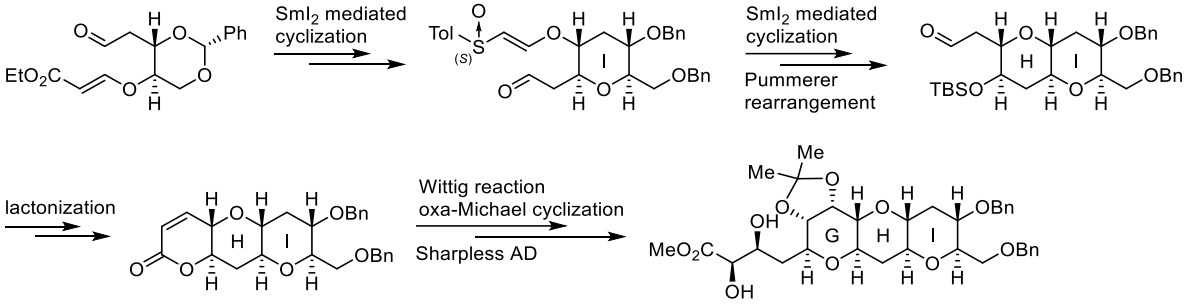
Scheme 1-3-16. Synthesis of the BCDE ring.

The GHI ring was synthesized by iterative utilization of the SmI_2 mediated reductive cyclization (Scheme 1-3-17).[10c] The G ring was converted to the β-alkoxyacrylate possessing the aldehyde moiety, and the H ring was constructed by SmI_2 mediated reductive cyclization. In an analogous sequence, the I ring was also constructed to afford the GHI ring.



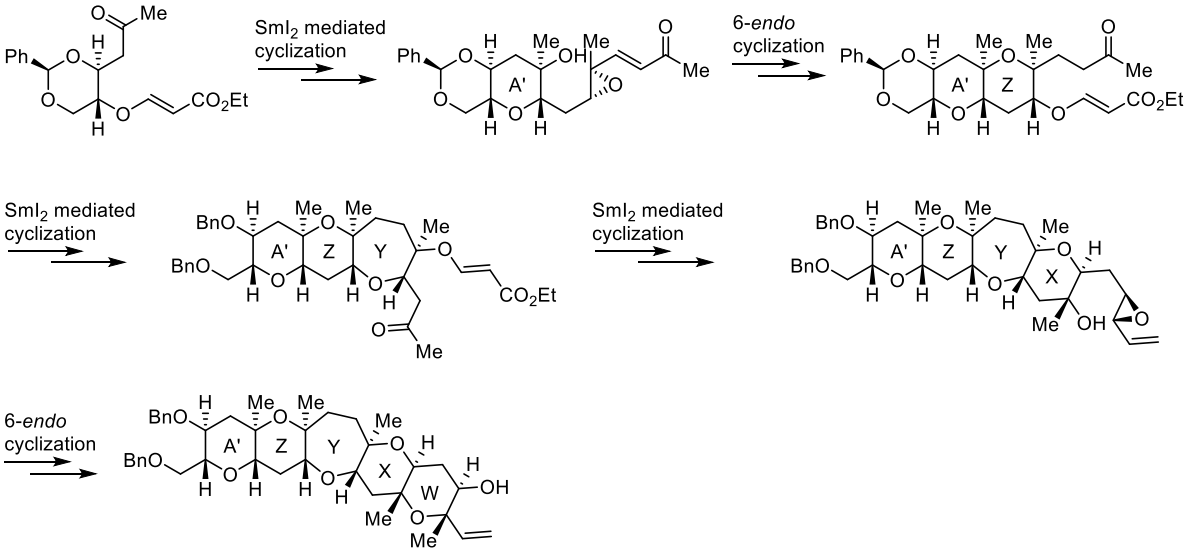
Scheme 1-3-17. Synthesis of the GHI ring (1).

The GHI ring having the side chain with the 1,2-diol moiety was synthesized as shown in Scheme 1-3-18.[10d] The I ring was constructed via SmI_2 mediated reductive cyclization of the β-alkoxyacrylate with the aldehyde moiety. Then, construction of the H ring via SmI_2 mediated reductive cyclization was carried out for the β-alkoxy-α,β-unsaturated sulfoxide in this case, which was followed by Pummerer rearrangement to furnish the aldehyde. The G ring was constructed via lactonization, Wittig reaction, and oxa-Michael reaction. The 1,2-diol moieties in the side chain and the G ring were introduced by Sharpless asymmetric dihydroxylation to afford the GHI ring.



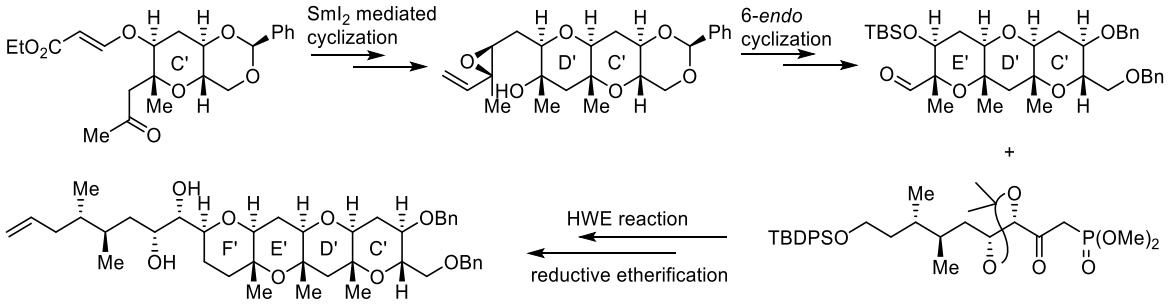
Scheme 1-3-18. Synthesis of the GHI ring (2).

The WXYZA' ring was synthesized via linear and iterative strategy (Scheme 1-3-19).[10e] The A' ring was synthesized via SmI_2 mediated reductive cyclization and the Z ring was constructed by acid catalyzed 6-*endo* cyclization of the alkenyl epoxide. The Y and X rings were successively formed by SmI_2 mediated reductive cyclization. The W ring was constructed by 6-*endo* cyclization of the hydroxy vinyl epoxide to afford the WXYZA' ring.



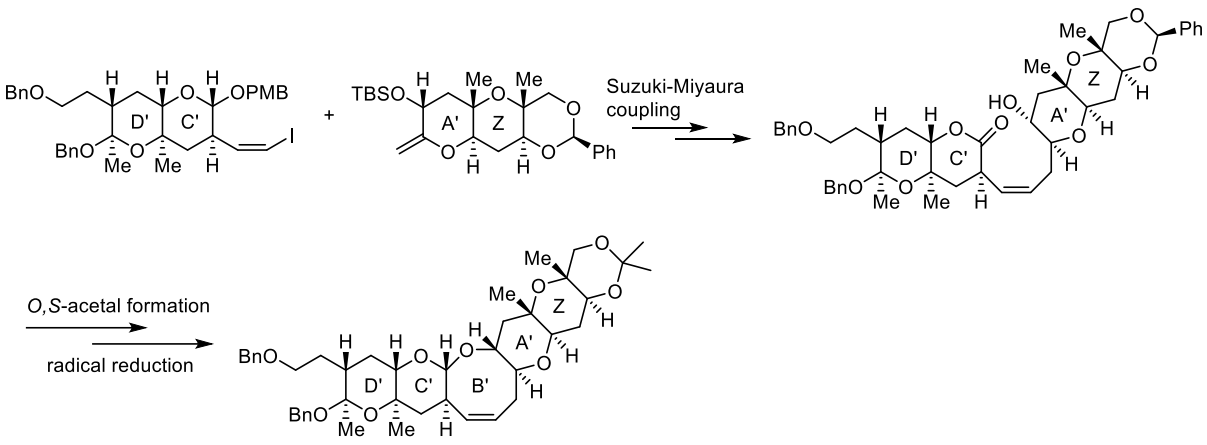
Scheme 1-3-19. Synthesis of the WXYZA' ring.

The C'D'E' ring was synthesized based on the linear strategy as shown in Scheme 1-3-20.[10f,10g] The D' ring was constructed by SmI_2 mediated reductive cyclization, and the E' ring was constructed by acid catalyzed 6-*endo* cyclization. Introduction of the side chain was achieved by Horner–Wadsworth–Emmons reaction of the C'D'E' ring aldehyde and the phosphonate corresponding to the side chain. Construction of the F' ring was carried out by reductive etherification to afford the C'D'E'F' ring.



Scheme 1-3-20. Synthesis of the C'D'E'F' ring.

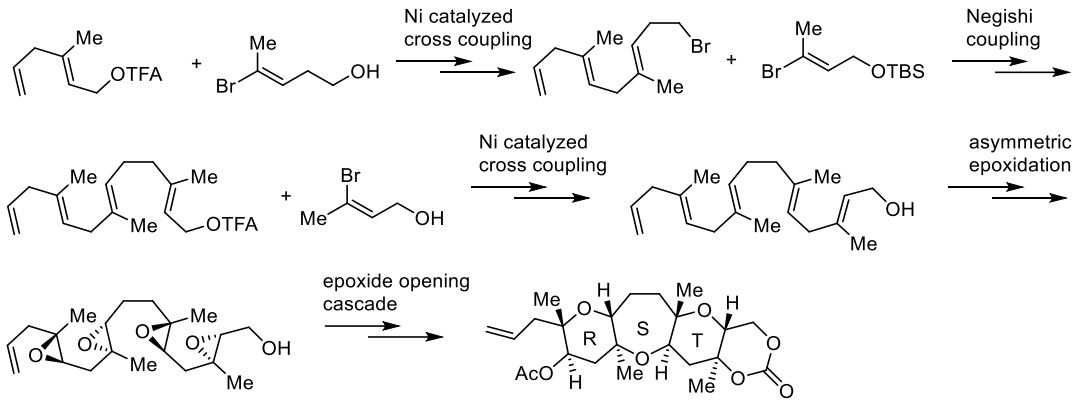
The *ent*-ZA'B'C'D' ring was synthesized by Saito and Nakata group as shown in Scheme 1-3-21.[10h] Hydroboration of the the ZA' ring *exo*-olefin followed by Suzuki−Miyaura coupling with the C'D' ring iodoolefin resulted in the formation of the coupling product. Then, construction of the B' ring was achieved via *O*,*S*-acetal formation followed by radical reduction to afford the *ent*-ZA'B'C'D' ring.



Scheme 1-3-21. Synthesis of the *ent*-ZA'B'C'D' ring.

1-3-5. Jamison group

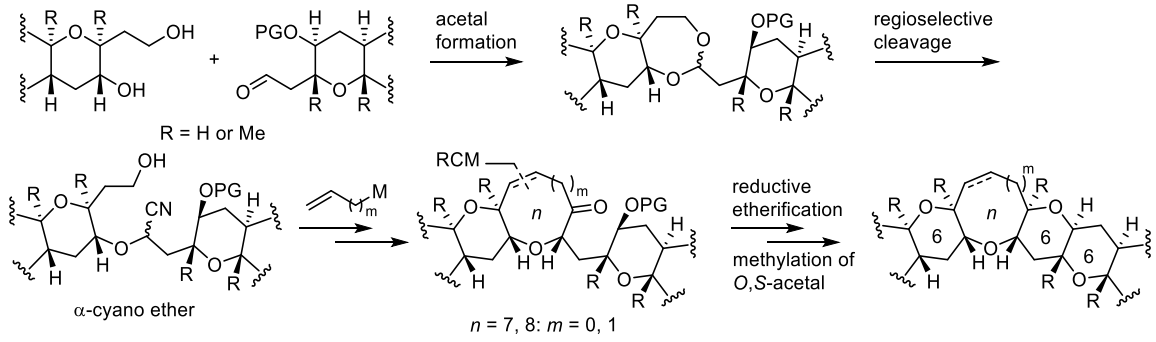
Jamison group reported the biomimetic synthesis of polycyclic ether systems via epoxide opening cascade reaction,[11a] which was applied to synthesize the RST ring of MTX (Scheme 1-3-22).[11b] The pentane was prepared via Ni catalyzed cross coupling and Negishi coupling reactions. Asymmetric epoxidation of the tetraene giving the tetraepoxide followed by ring opening cascade reaction resulted in the formation of the RST ring.



Scheme 1-3-22. Biomimetic synthesis of the RST ring.

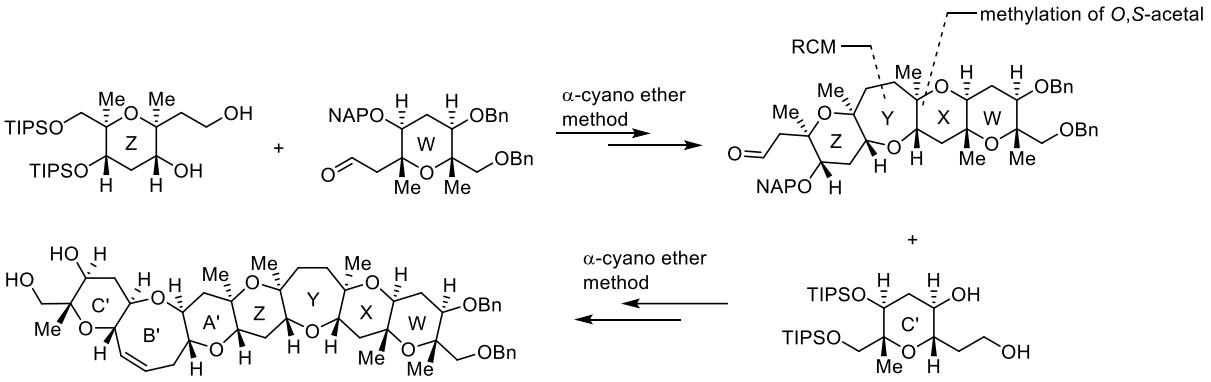
1-3-6. Oishi group

Oishi group have developed two types of convergent methods for synthesizing ladder-shaped polyethers. The 6/*n*/6/6-tetracyclic ether systems (*n* = 7, 8) were constructed based on the α-cyano ether method (Method A) as shown in Scheme 1-3-23.[12a] Coupling of the diol and the aldehyde giving seven-membered ring acetal followed by regioselective cleavage gave the α-cyano ether. The seven- and eight-membered rings were constructed by ring closing metathesis, and subsequent formation of the six-membered ring ether was achieved by reductive etherification or methylation of *O*,*S*-acetal.



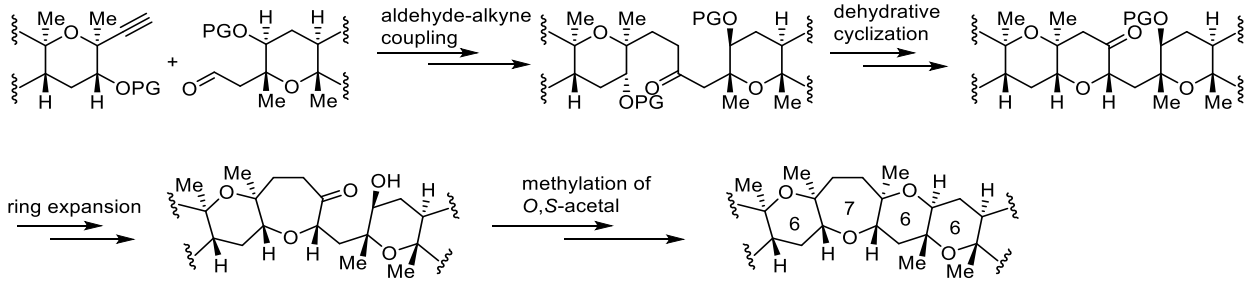
Scheme 1-3-23. Convergent methods for synthesizing ladder-shaped polyethers (Method A).

The α-cyano ether method was applied to synthesize the WXYZA'B'C' ring system in a highly convergent manner (Scheme 1-3-24).[12b] Union of the W and Z rings by the α-cyano ether method gave the WXYZ ring aldehyde, which was unified with the C' ring diol by the α-cyano ether method to afford the WXYZA'B'C' ring.

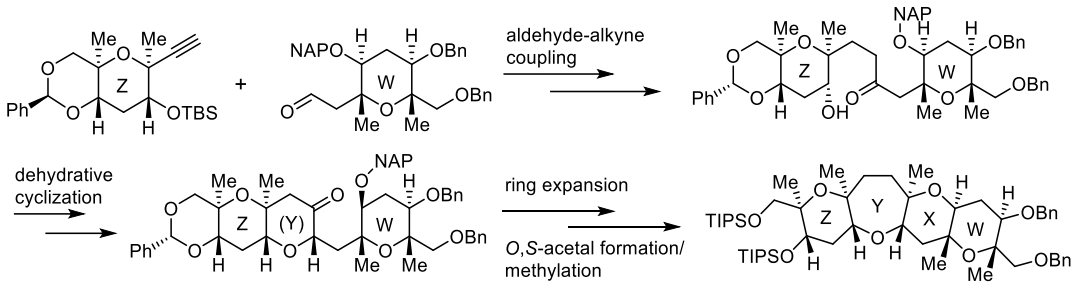


Scheme 1-3-24. Synthesis of the WXYZA'B'C' ring.

On the other hand, Oishi group developed an alternative strategy for synthesizing the 6/7/6/6-tetracyclic ether system (Scheme 1-3-25).[12c] Coupling of the alkyne and the aldehyde giving the ketone followed by dehydrative cyclization furnished the six-membered ring ketone. Ring expansion to the seven-membered ring ketone, followed by methylation of *O*,*S*-acetal and resulted in the formation of the 6/7/6/6-tetracyclic ether (Method B). Based on this strategy, the WXYZ ring was synthesized from the W ring aldehyde and the Z ring alkyne through the construction of the XY ring (Scheme 1-3-26).[12c]

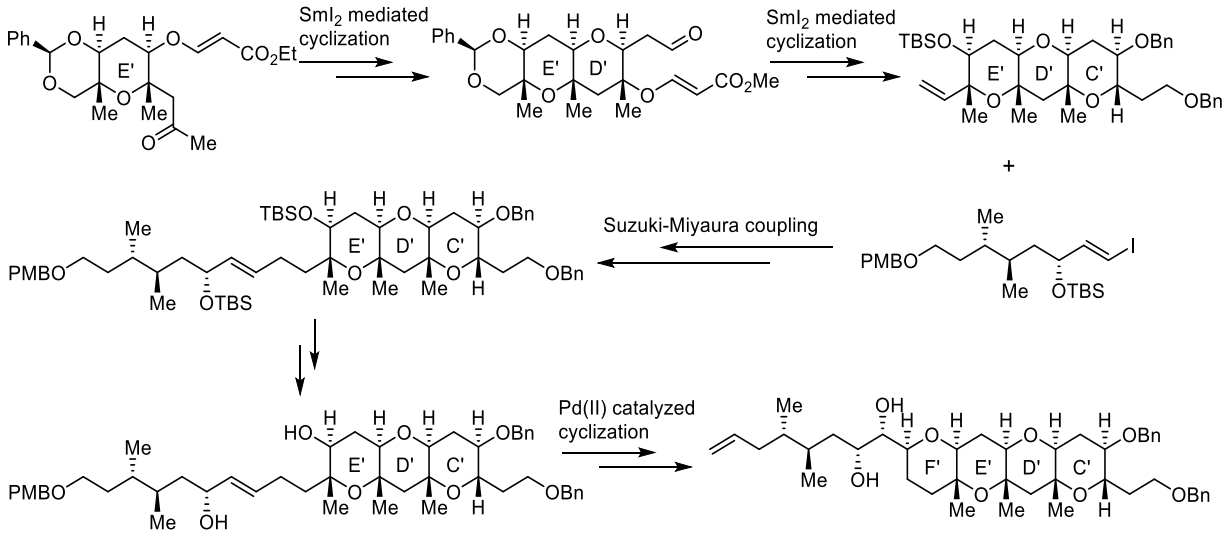


Scheme 1-3-25. Convergent method for synthesizing ladder-shaped polyethers (Method B).



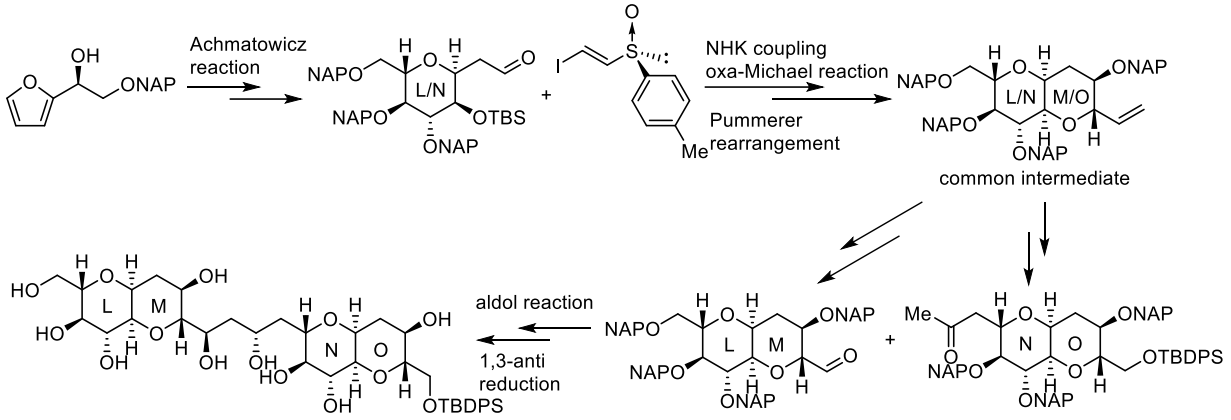
Scheme 1-3-26. Synthesis of the WXYZ ring.

The C'D'E'F' ring with the side chain was synthesized based on the linear strategy as shown in Scheme 1-3-27.[12d] Starting from the E' ring, the D' and C' rings were constructed in an iterative manner based on SmI_2 mediated reductive cyclization. Construction of the F' ring was accomplished via Suzuki−Miyaura coupling with the iodoolefin corresponding to the side chain fragment and Pd(II) catalyzed cyclization of the allylic alcohol to afford the C'D'E'F' ring.



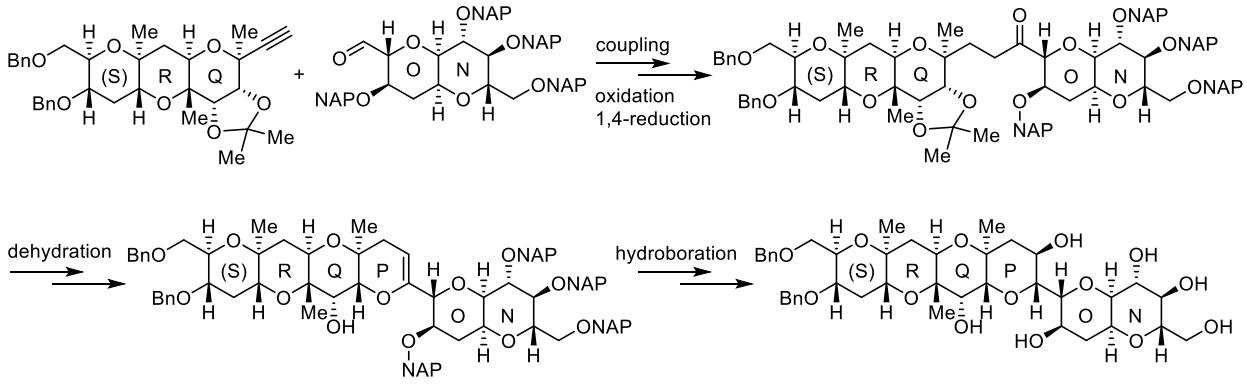
Scheme 1-3-27. Synthesis of the C'D'E'F' ring.

The LMNO ring was synthesized as shown in Scheme 1-3-28.[12f] The common *cis*-fused pyranopyran intermediate for synthesizing the LM and NO rings was prepared from the furfuryl alcohol derivative via Achmatowicz reaction, Nozaki−Hiyama−Kishi reaction with iodoolefin possessing the sulfoxide moiety, intramolecular oxa-Michael addition, and Pummerer rearrangement. The common intermediate was converted to the LM ring aldehyde and the NO ring methyl ketone, respectively, which were subjected to the aldol reaction followed by 1,3-*anti* reduction to afford the LMNO ring.



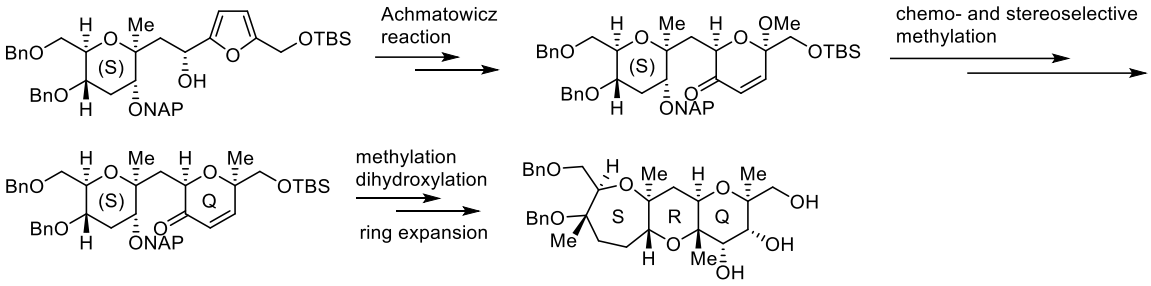
Scheme 1-3-28. Synthesis of the LMNO ring.

The NOPQR(S) ring in which the seven-membered S ring was substituted with the six-membered one, was synthesized as shown in Scheme 1-3-29.[12f] Coupling of the QR(S) ring alkyne and NO ring aldehyde, followed by oxidation of the resulting secondary alcohol giving the ynone and 1,4-reduction furnished saturated ketone. Construction of the P ring via dehydrative cyclization and hydroboration resulted in the formation of the NOPQR(S) ring.



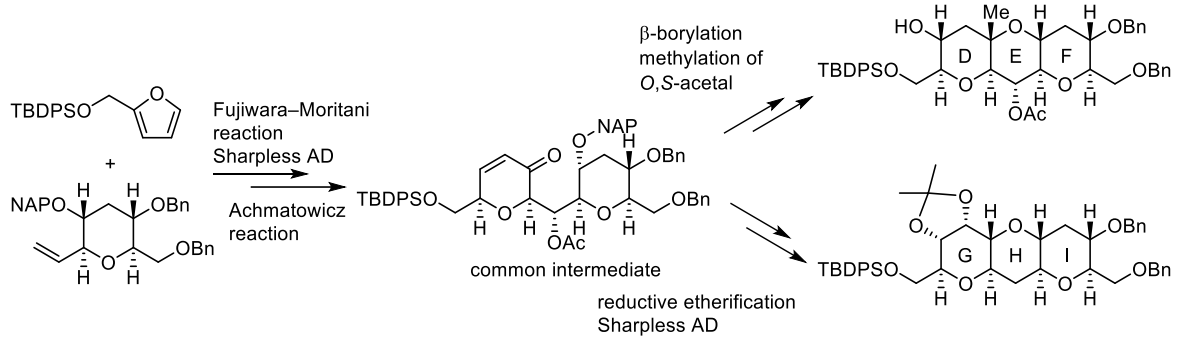
Scheme 1-3-29. Synthesis of the NOPQR(S) ring.

Oishi group developed convergent method for synthesizing tricyclic ether systems by furan based strategy. The QRS ring system was synthesized as shown in Scheme 1-3-30.[12e] The furfuryl alcohol derivative was converted to the methyl acetal via Achmatowicz reaction, which was subjected to the chemo- and stereoselective methylation of the methyl acetal in the presence of the carbonyl group by treating with $Me_2Zn/BF_3{\cdot}OEt_2$. After construction of the R ring via methylation and dihydroxylation, ring expansion of the six-membered ring to the seven-membered one resulted in the formation of the QRS ring.



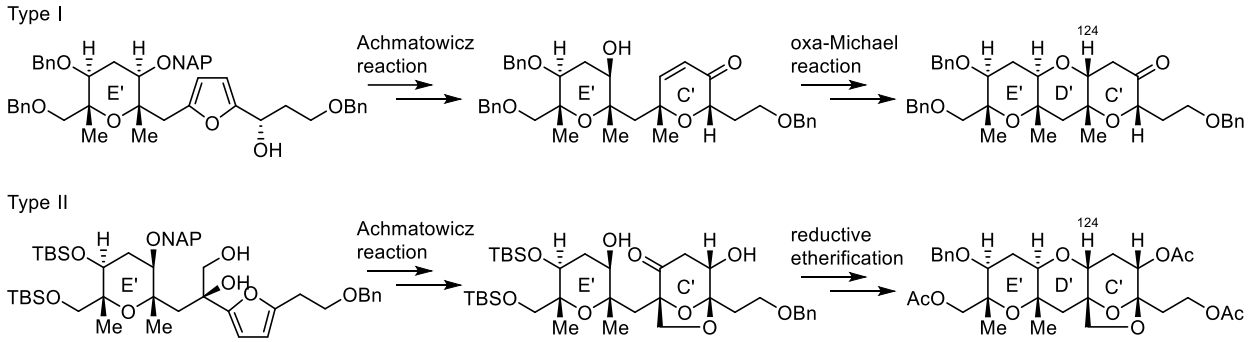
Scheme 1-3-30. Synthesis of the QRS ring.

The furan based strategy was also applied to the unified synthesis of the DEF and GHI rings (Scheme 1-3-31).[12g] Fujiwara–Moritani reaction of the furan derivative and the terminal olefin followed by Sharpless asymmetric dihydroxylation and Achmatowicz reaction furnished the common intermediate. The common intermediate was converted to the DEF ring via β-borylation of the enone followed by methylation of the *O*,*S*-acetal. On the other hand, the common intermediate was converted to the GHI ring via reductive etherification followed by Sharpless asymmetric dihydroxylation.



Scheme 1-3-31. Unified synthesis of the DEF and GHI rings.

Attempts to synthesize the C'D'E' ring by two types (Type I and II) of furan based strategy are shown in Scheme 1-3-32.[12h,12i] Although the furfuryl alcohol derivative corresponding to the E' ring was converted to the enone via Achmatowicz reaction, intramolecular oxa-Michael reaction was unsuccessful and gave 124-*epi* diastereomer as a single isomer due to the steric hindrance of angular methyl group (Type I). On the other hand, Achmatowicz reaction of the diol with the E' ring furnished the bicyclic acetal (Type II). However, reductive etherification was also unsuccessful and furnished 124-*epi* diastereomer.



Scheme 1-3-32. Attempts to synthesize of the C'D'E' ring by furan based strategy.

1-4. Structure-activity relationship studies of partial structures of maitotoxin

1-4-1. Identification of target protein

Although a number of biochemical studies of MTX have been reported, not only the target proteins but also its precise mode of action at the molecular level has not been elucidated. On the other hand, Schilling group proposed that MTX bind to the plasmalemmal Ca^{2+}-ATPase (PMCA) pump and convert the pump into a nonselective cation channel.[13] An attempt to identify the target molecule of MTX using the photoactive and biotinylating probe was reported by Konoki et al. (Figure 1-4-1).[14] However, it was difficult to identify the target protein due to the nonspecific binding with the proteins and short supply of the labeling probe.

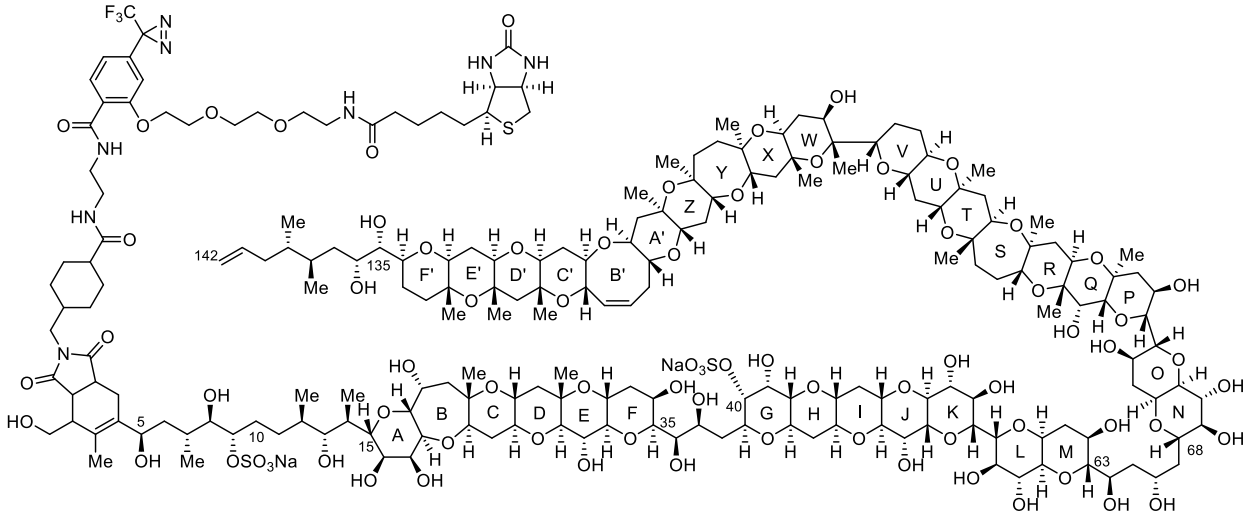


Figure 1-4-1. Photoaffinity probe derived from MTX.

1-4-2. Structure-activity relationship studies of partial structures of maitotoxin

Konoki et al. reported that MTX-induced Ca^{2+} influx was inhibited by the presence of brevetoxin A and B with the IC_{50} values of 16 μM and 13 μM, respectively (Figure 1-4-2).[15] On the other hand, synthesized partial structures corresponding to the *ent*-EFGH ring and *ent*-LMNO ring also inhibited MTX-induced Ca^{2+} influx at IC_{50} values of 200 μM and 500 μM, respectively (Figure 1-4-3).[6b] Inspired by the results reported by Konoki, inhibitory activity of the synthesized partial structures of MTX was evaluated by Oishi group (Figure 1-4-4).[12b,12d,12e] The WXYZA'B'C', C'D'E'F', and QRS rings corresponding to the hydrophobic region, blocked MTX-induced Ca^{2+} influx at IC_{50} values of 30 μM, 59 μM, and 44 μM, respectively. However, the LMNO and NOPQR(S) rings containing the hydrophilic region elicited weak or no inhibition against the MTX induced Ca^{2+} influx.[12d] On the other hand, hydrophobic artificial ladder-shaped

polyethers, the 6/7/6/6/7/6/6 heptacyclic (ALP7B) and 6/7/6/6/7/6/6/7/6/6 decacyclic (ALP 10B) ethers showed inhibitory activity at IC_{50} values of 2 μM and 15 μM, respectively (Figure 1-4-5).[16]

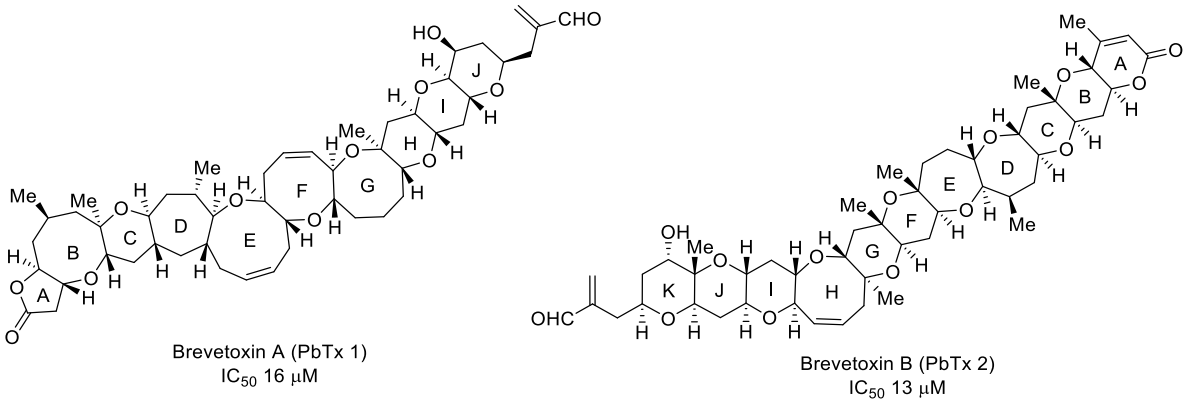


Figure 1-4-2. Inhibitory activity against the MTX-induced Ca^{2+} influx by brevetoxin A and B.

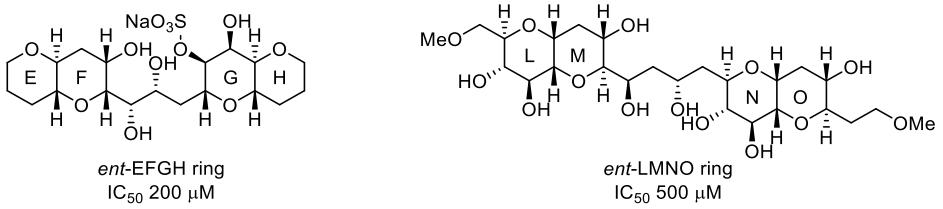


Figure 1-4-3. Inhibitory activity against the MTX-induced Ca^{2+} influx by synthesized partial structures corresponding to the *ent*-EFGH ring and *ent*-LMNO ring.

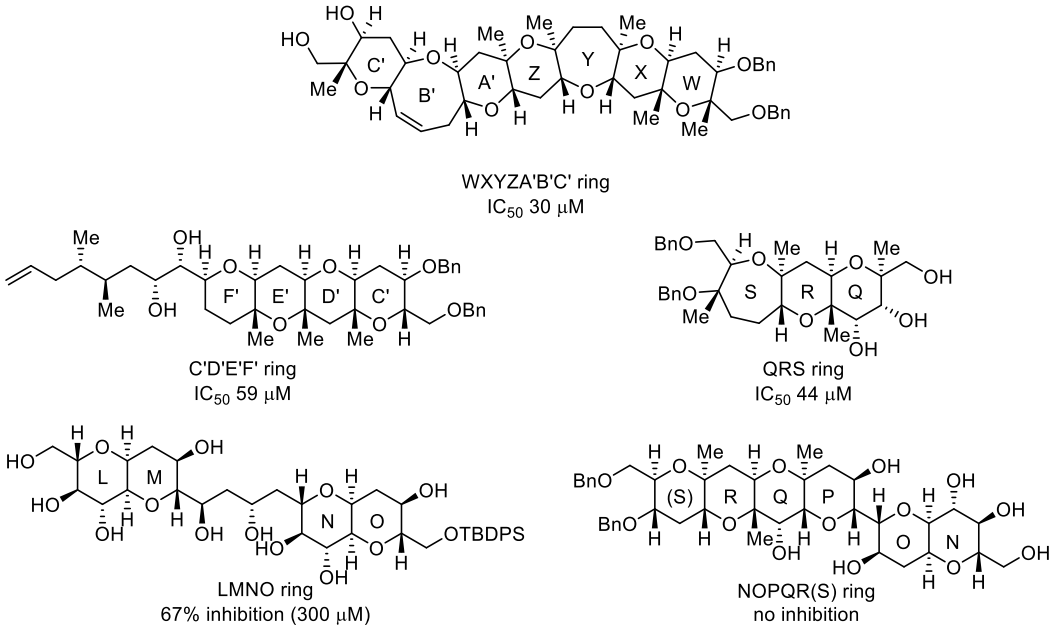


Figure 1-4-4. Inhibitory activity against the MTX-induced Ca^{2+} influx by synthesized partial structures reported by Oishi group.

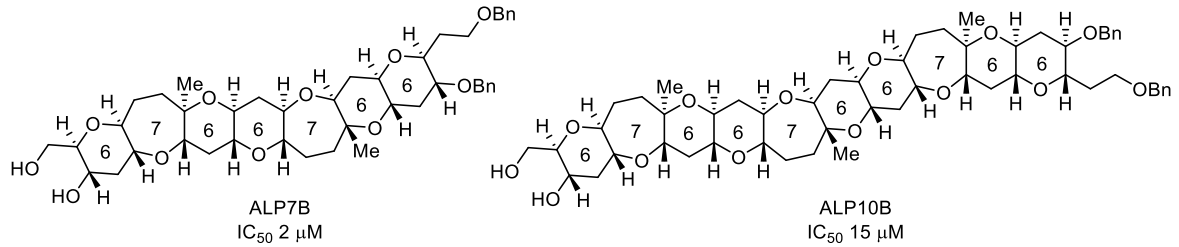


Figure 1-4-5. Inhibitory activity against the MTX-induced Ca^{2+} influx by ALP7B and ALP10B.

Refer to the results reported by Oishi group, the similar experiments were carried out by Nicolaou group (Figure 1-4-6).[9d] The synthetic fragments corresponding to the hydrophobic region, the C'D'E'F' and QRSTUVWXYZA' rings blocked MTX-induced Ca^{2+} influx at IC_{50} values of 2.3 μM and 3.2 μM, respectively. On the other hand, the partial structures corresponding to the WXYZA', QRSTU, and ABCDEFG rings did not show inhibitory activity.

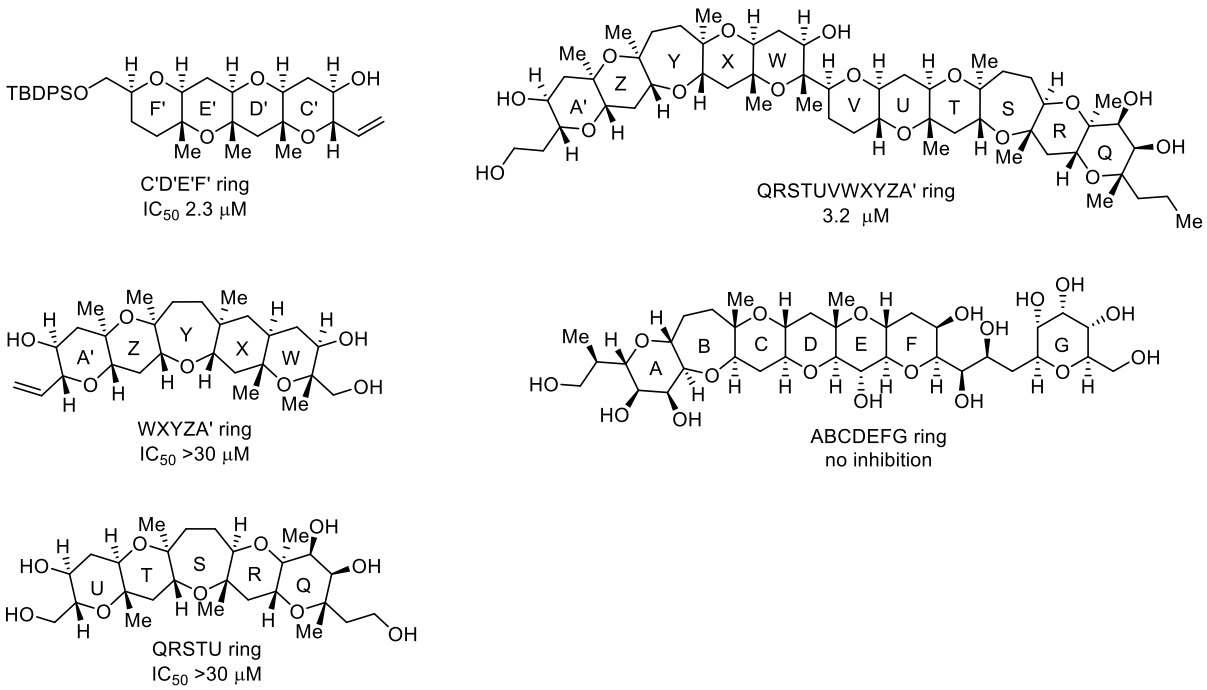


Figure 1-4-6. Inhibitory activity against the MTX-induced Ca^{2+} influx by synthesized partial structures reported by Nicolaou group.

The hypothetical mechanism of the inhibition of the MTX-induced Ca^{2+} influx caused by synthesized partial structure of MTX and other LSP molecules was shown Figure 1-4-7.[14] Because of the Ca^{2+} influx activity of MTX, the target proteins of MTX might be transmembrane proteins such as Ca^{2+}-pump or Ca^{2+}-channel. When, MTX induce the Ca^{2+} influx, the hydrophobic region of MTX would be inserted into the lipid membrane and bind to the target protein. As a result, MTX would induce conformational change of the target protein to convert into the non-selective cation channel. On the other hand, judging from the results of structure-activity relationship studies, the hydrophobic LSPs and the partial structures of MTX corresponding to the hydrophobic region might competitively bind to the target protein resulting in inhibition of the MTX-induced Ca^{2+} influx.

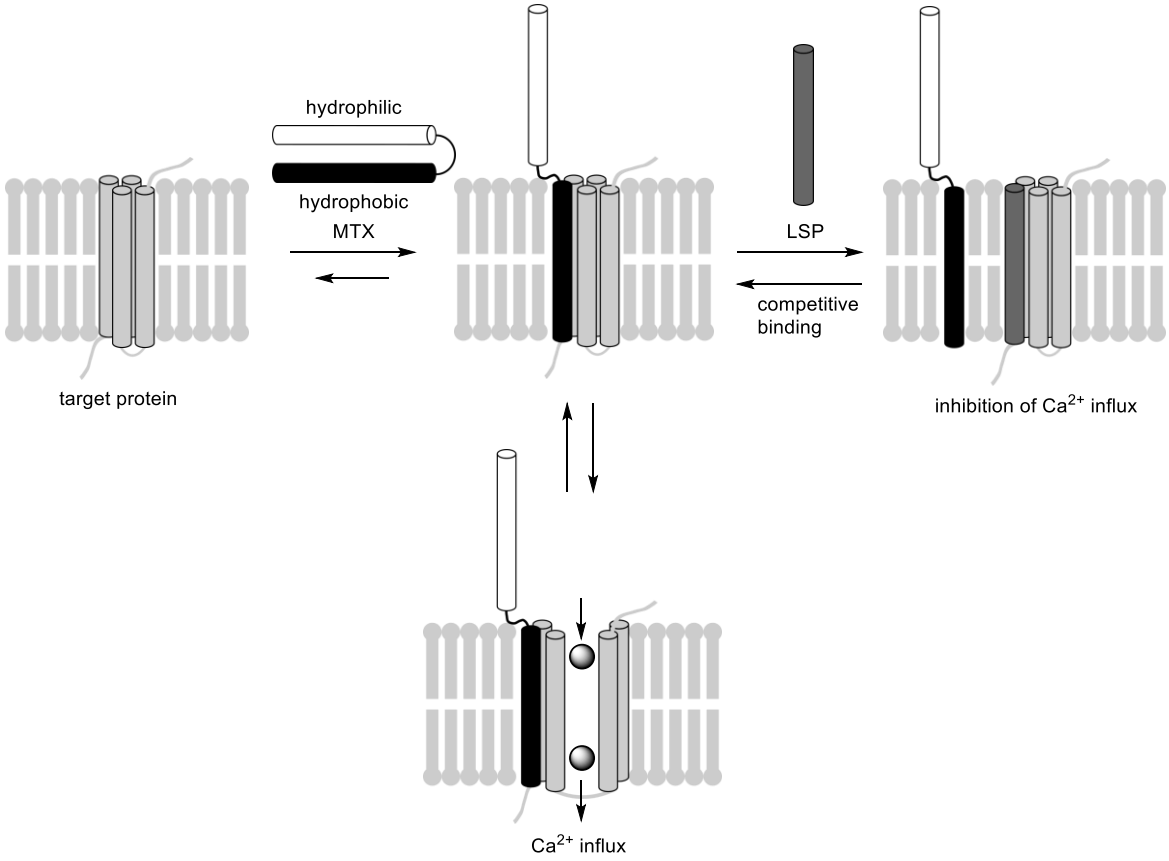


Figure 1-4-7. Hypothetical scheme for the inhibition of MTX-induced Ca^{2+} influx by LSPs.

1-5. Objective

Based on the results of structure-activity relationship studies reported by Oishi group and Nicolaou group, it is suggested that the C'D'E'F' ring section, and larger molecule containing the WXYZ ring system seem to elicit more potent inhibitory activity compared with other sections. Therefore, the more extended partial structure corresponding to the WXYZA'BC'D'E'F' ring is expected to inhibit MTX-induced Ca^{2+} influx in a more potent manner. In additions, the structure is similar to that of brevetoxin B, which inhibits the MTX-induced Ca^{2+} influx.

In this study, the objective is synthesis of the WXYZA'B'C'D'E'F' ring segment of MTX and evaluation of the inhibitory activity against MTX-induced Ca^{2+} influx (Figure 1-5-1).

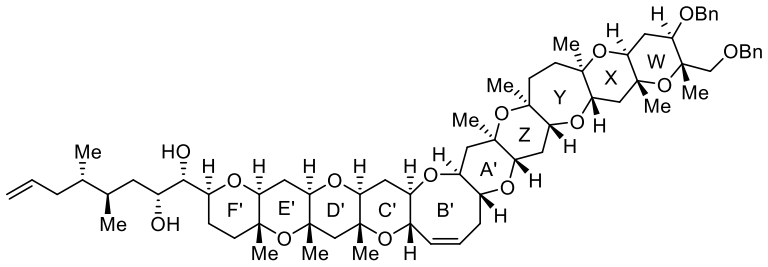
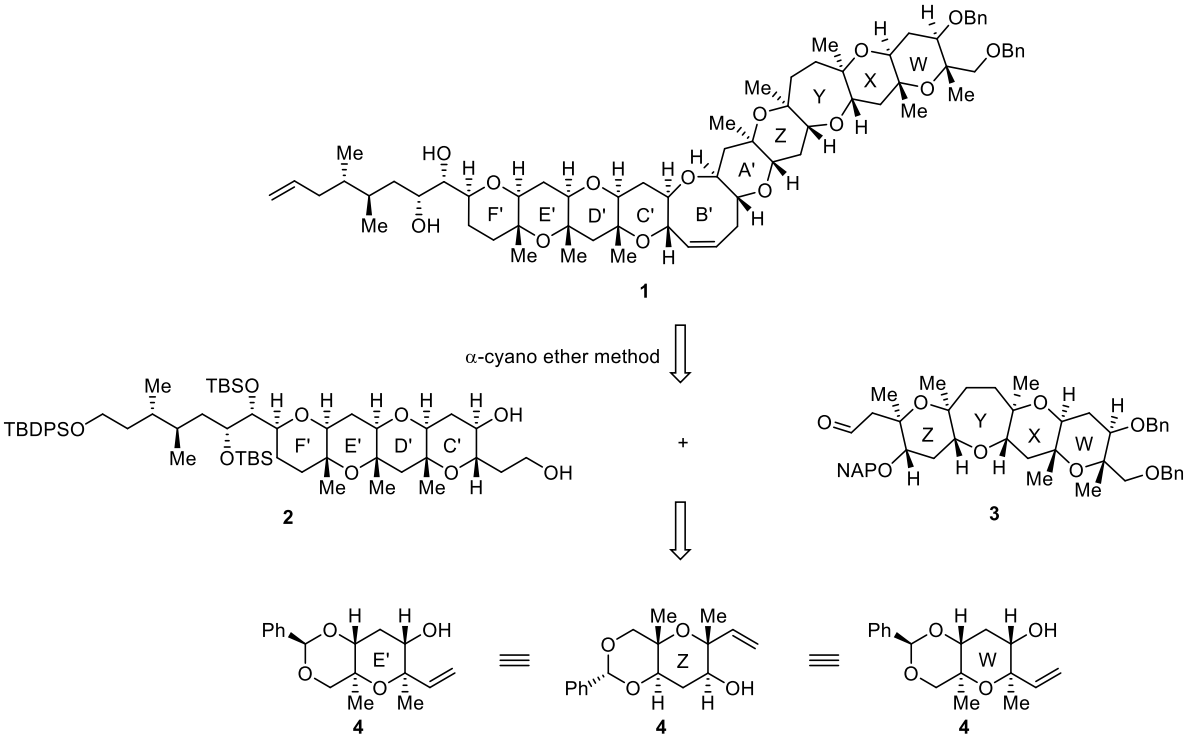


Figure 1-5-1. Structure of the WXYZA'B'C'D'E'F' ring segment of MTX.

1-6. Synthesis plan

Synthesis plan of the WXYZA'B'C'D'E'F' ring segment **1** is shown in Scheme 1-6-1. The target compound **1** would be synthesized from the C'D'E'F' ring **2** and the WXYZ ring **3** through the construction of the A'B' ring by the α-cyano ether method.[10a] The C'D'E'F' ring **2** and the WXYZ ring **3** are to be synthesized form the common tetrahydropyran derivative **4** corresponding to the W, Z, and E' rings. In this strategy, it would be a daunting task to synthesize the large molecule whose molecular weight is 1140 and to construct the seven- and eight-membered ring systems with the consecutive angular methyl groups, eight angular methyl groups in total.



Scheme 1-6-1. Synthesis plan of the WXYZA'B'C'D'E'F' ring segment **1**.

References

1. T. Ysumoto, *Igaku no Ayumi* **1980**, *112*, 886.
2. a) T. Yasumoto, R. Bagins, J. P. Vernoux, *Bull. Jpn. Soc. Sci. Fish.* **1976**, *42*, 359. b) T. Yasumoto, I. Nakajima, R. Bagnis, *Bull. Jpn. Soc. Sci. Fish.* **1977**, *43*, 1021.
3. a) M. Murata, T. Iwashita, A. Yokoyama, M. Sasaki, T. Yasumoto, *J. Am. Chem. Soc.* **1992**, *114*, 6594. b) M. Murata, H. Naoki, T. Iwashita, M. Sasaki, A. Yokoyama, T. Yasumoto, *J. Am. Chem. Soc.* **1993**, *115*, 2060. c) M. Murata, H. Naoki, S. Matsunaga, M. Satake, T. Yasumoto, *J. Am. Chem. Soc.* **1994**, *116*, 7098.
4. H. Fuwa, *Mar. Drugs.* **2021**, *19*, 257.
5. T. Nonomura, M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem. Int. Ed.* **1996**, *35*, 1675.
6. a) L. R. Cook. H. Oinuma, M. A. Semones, Y. Kishi, *J. Am. Chem. Soc.* **1997**, *119*, 7928. b) W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946.
7. a) M. Sasaki, N. Matsumori, T. Maruyama, M. Murata, K. Tachibana, T. Yasumoto. *Angew. Chem. Int. Ed.* **1996**, *35*, 1672. b) M. Sasaki, N. Matsumori, M. Murata, K. Tashibana, *Tetrahedron Lett.* **1995**, *36*, 9011. c) M. Sasaki, T. Nonomura, M. Murata, K. Tachibana, *Tetrahedron Lett.* **1994**, *35*, 5023. d) M. Sasaki, T. Nonomura, M. Murata, K. Tachibana, *Tetrahedron Lett.* **1995**, *36*, 9007.
8. a) T. Igarashi, S. Aritake, T. Yasumoto, *Nat. Toxins* **1999**, *7*, 71.
9. a) K. C. Nicolaou, M. H. D. Postema, E. W. Yue, A. Nadin, *J. Am. Chem. Soc.* **1996**, *118*, 10335. b) K. C. Nicolaou, T. M. Baker, T. Nakamura, *J. Am. Chem. Soc*. **2011**, *133*, 220. c) K. C. Nicolaou, R. J. Aversa, J. Jin, F. Rivas, *J. Am. Chem. Soc*. **2010**, *132*, 6855. d) K. C. Nicolaou, P. Heretsch, T. Nakamura, A. Rudo, M. Murata, K. Konoki, *J. Am. Chem. Soc.* **2014**, *136*, 16444. e) K. C. Nicolaou, J. H. Seo. T. Nakamura, R. J. Aversa, *J. Am. Chem. Soc.* **2011**, *133*, 214. f) K. C. Nicolaou, R. J. Aversa, J. Jin, F. Rivas, *J. Am. Chem. Soc*. **2010**, *132*, 6855. g) K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. Int. Ed.* **2007**, *46*, 8875. h) K. C. Nicolaou, M. O. Frederick, A. C. B. Burtoloso, R. M. Denton, F. Rivas, K. P. Cole, R. J. Aversa, R. Gibe, T. Umezawa, T. Suzuki, *J. Am. Chem. Soc.* **2008**, *130*, 7466.
10. a) K. Nagasawa, N. Hori, R. Shiba, T. Nakata, *Heterocycles* **1997**, *44*, 105. b) M. Satoh, M. H. Koshino, T. Nakata, *Org. Lett.* **2008**, *10*, 1683. c) M. Satoh, M. Mori, T. Nakata, *Heterocycles* **2007**, *74*, 259. d) M. Nagatomo, T. Nakata, *Heterocycles* **2008**, *76*, 1069. e) M. Morita, T. Haketa, H. Koshino, T. Nakata, *Org. Lett.* **2008**, *10*, 1679. f) Y. Sakamoto, G.

Matsuo, H. Maatsukura, T. Nakata, *Org. Lett*. **2001**, *3*, 2749. g) M. Morita, S. Ishiyama, H. Koshino, T. Nakata, *Org. Lett.* **2008**, *10*, 1675. h) T. Saito, M. Morita, H. Koshino, M. Sodeoka, T. Nakata, *Org. Lett*. **2017**, *19*, 3203.

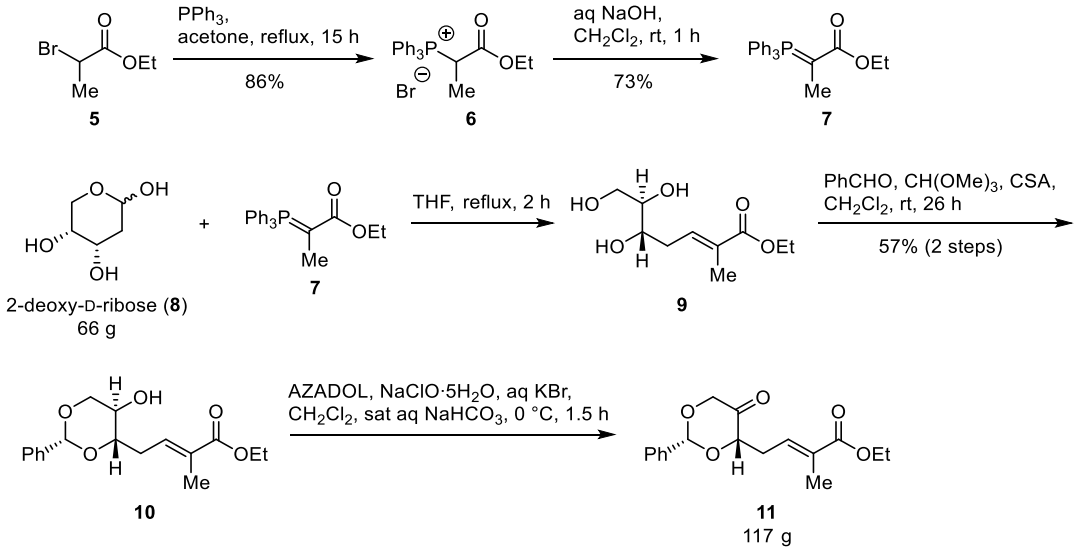
11. a) I. Vilotijevic, T. F. Jamison, Science **2007**, *317*, 1189. b) C. P. McGeough, A. E. Strom, T. F. Jamison, *Org. Lett.* **2019**, *21*, 3606.
12. a) T. Oishi, K. Watanabe, M. Murata, *Tetrahedron Lett*. **2003**, *44*, 7315. b) T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 3599. c) N. Osato, H. Onoue, Y. Toma, K. Torikai, M. Ebine, M. Satake, T. Oishi, *Chem. Lett.* **2018**, *47*, 265. d) M. Kunitake, T. Oshima, K. Konoki, M. Ebine, K. Torikai, M. Murata, T. Oishi, *J. Org. Chem.* **2014**, *79*, 4948. e) H. Onoue, T. Baba, K. Konoki, K. Torikai, M. Ebine, T. Oishi, *Chem. Lett*. **2014**, *43*, 1904. f) H. Onoue, R. Marubayashi, E. Ishikawa, K. Konoki, K. Torikai, M. Ebine, M. Murata, T. Oishi, *J. Org. Chem*. **2017**, *82*, 9595. g) T. Yasudomi, H. Yakushiji, K. Torikai, M. Ebine, T. Oishi, *Chem. Lett* **2019**, *48*, 1156. h) H. Yamamoto, K. Torikai, M. Ebine, T. Oishi, *Heterocycles* **2018**, *97*, 158. i) Y. Watanabe, K. Torikai, Y. Yasuno, T. Oishi, *Heterocycles* **2021**, *102*, 2313.
13. W. G. Sinkins, M. Estacion, V. Prasad, M. Goel, G. E. Shull, D. L. Kuze, W. P. Schilling, *Am. J. Physiol. Cell Physiol.* **2009**, *297*, C1533.
14. K. Konoki, M. Hashimoto, K. Honda, K. Tachibana, R. Tamate, F. Hasegawa, T. Oishi, M. Murata, *Heterocycles* **2009**, *79*, 1007.
15. K. Konoki, M. Hashimoto, T. Nonomura, M. Sasaki, M. Murata, K. Tachibana, *J. Neurochem.* **1998**, *70*, 409.
16. T. Oishi, K. Konoki, R. Tamate, K. Torikai, F. Hasegawa, N. Matsumori, M. Murata, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3619.

Chapter 2. Large scale synthesis of building blocks

In general, multi-step synthesis requires the supply of starting materials in large quantity. Theoretically, if the yield of each step is 90%, the overall yield from the starting material is calculated to be 35% yield after linear sequence of 10 steps. Therefore, supply of a large amount of synthetic intermediates is essential in this study, because the longest linear sequence and the total number of steps are estimated to exceed around 50 steps and 100 steps, respectively.

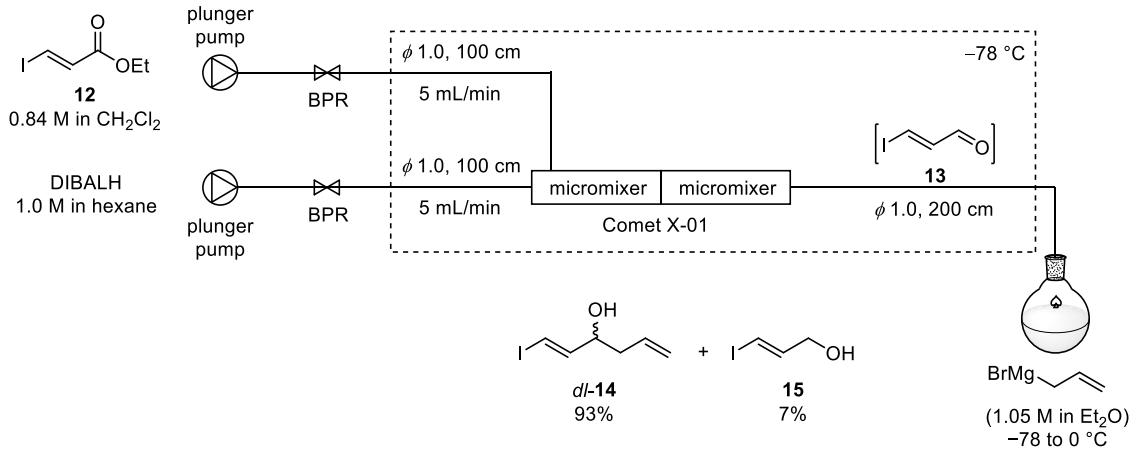
2-1. Synthesis of the common tetrahydropyran derivative

Large scale synthesis of common tetrahydropyran derivative **4** was examined according to the literature reported by Nicolaou group[1a] and the modified synthetic method.[1b] The stabilized ylide **7** was prepared from ethyl 2-bromopropionate **5** via formation of phosphonium salt **6** followed by deprotonation with sodium hydroxide (Scheme 2-2-1). Wittig reaction of 2-deoxy-D-ribose **8** with phosphorus ylide **7** gave triol **9**, and the crude material was directly treated with benzaldehyde in the presence of CSA and methyl orthoformate to furnish alcohol **10** in 57% yield for 2 steps. Oxidation of secondary alcohol **10** using AZADOL[2] as a catalyst in the presence of NaClO as a cooxidant afforded crude ketone **11**. Starting from 66 g of 2-deoxy-D-ribose **8**, 117 g of ketone **11** was prepared.



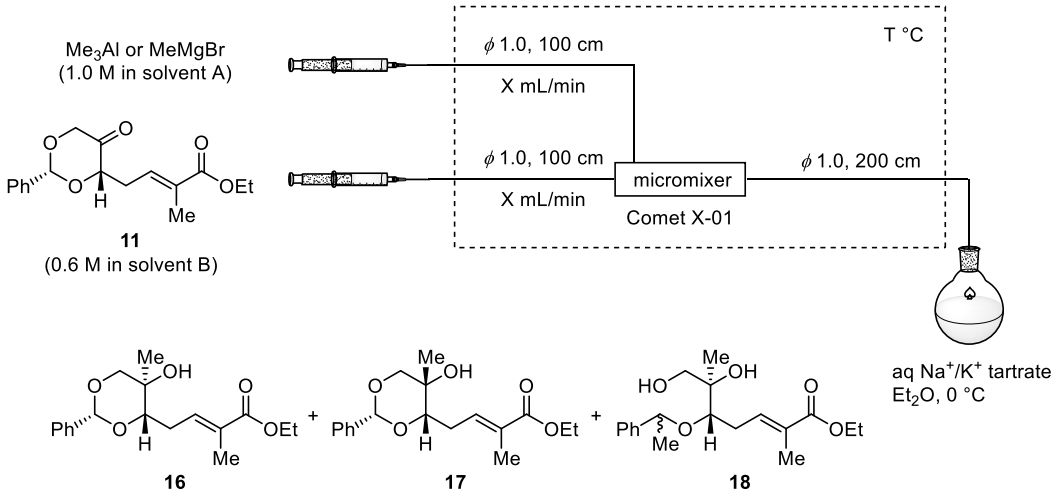
Scheme 2-2-1. Synthesis of the ketone **11**.

The next task was diastereoselective methylation and subsequent 1,2-reduction of ketoester **11**. If the 117 g of ketone **11** were to be reacted by the original procedure under the batch conditions, 560 mL of trimethylaluminum solution and 870 mL of DIBALH solution would be added at low temperature. Therefore, it was difficult to carry out the reaction under the batch conditions in the laboratory due to the limitations of the equipment. In recent years, the problems have overcome by using microflow reactors.[3] The microflow chemistry is safer than conventional batch reactions due to small reaction volumes in the reactor and precise temperature control. The greatest advantage is that it is easy to scale up under the identical reaction conditions, and it is possible to carried out reactions on a large scale of several hundred grams even in the laboratory. In Oishi group, the large scale synthesis of (*E*)-1-iodohexa-1,5-dien-3-ol (*dl*-**14**) under the microfluidic conditions was reported (Scheme 2-1-2).[4] A solution of ester **12** (70.2 g) in CH_2Cl_2 and a solution of DIBALH in hexane were transmitted to micromixer (Comet-X01,[5] two reactors in series) for half reduction giving aldehyde **13**. The resulting eluent was poured into a solution of allylmagnesium bromide in Et_2O (1.05 M) at −78 °C. After completing the elution, the resulting reaction mixture was allowed to warm up to 0 °C to afford *dl*-**14** in 93% yield (64.9 g) with concomitant formation of a small amount of **15** (7%). Therefore, the reactor was applied to the reaction of ketoester **11**.



Scheme 2-1-2. Flow and batch synthesis: DIBALH reduction of ester **12** under the flow conditions followed by Grignard reaction under the batch conditions.

Methylation of ketone **11** under the flow conditions was carried out as shown in Scheme 2-1-3. A solution of reagent (Me_3Al or MeMgBr) in solvent A (1.0 M) and a solution of **11** in solvent B (0.6 M) were transferred to the Comet X-01 for mixing at a rate of X mL/min at T °C. After passing through the tube, the reaction mixture was poured into a mixture of Et_2O and aqueous solution of Rochelle salt at 0 °C.



Scheme 2-1-3. Methylation of ketone **11** under the flow conditions.

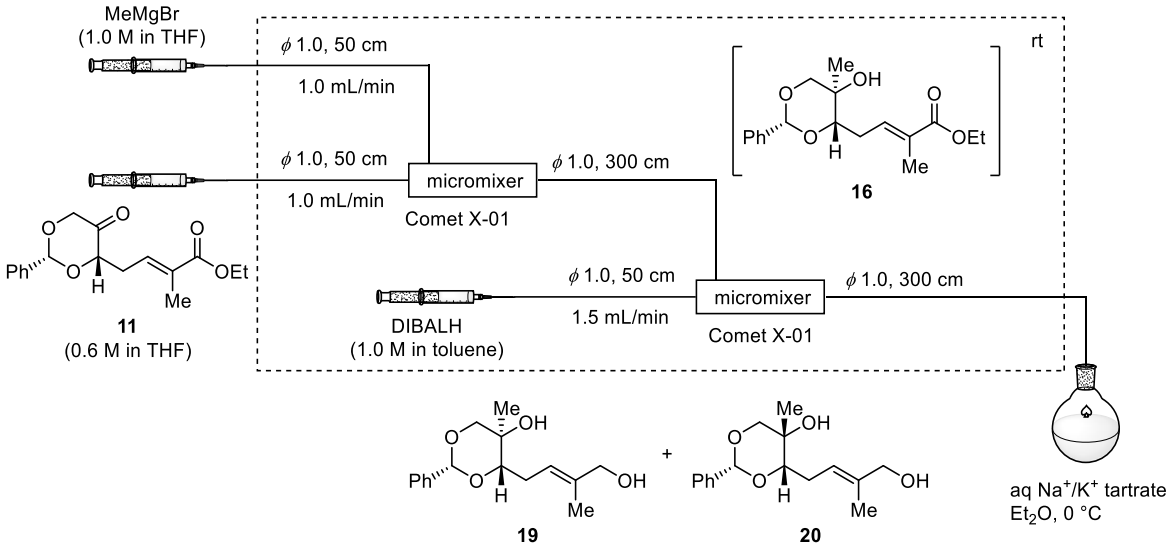
As shown in Table 2-1-1, mixing a solution of **11** in CH_2Cl_2 with a solution of Me_3Al in hexane at a rate of 5.0 mL/min at 0 °C resulted in the formation of **16** with recovery **11** in a 55% and 45% ratio as determined by 600 MHz ^{1}H NMR analysis (entry 1). Decreasing the flow rate to 2.5 mL/min (entry 2) did not increase the ratio of **16** to give the same results as entry 1. In order to increase the reaction rate, the temperature was raised from 0 °C to room temperature (entry 3). Although the ratio of **16** was improved, its diastereomer **17** was obtained in 3% with concomitant formation of byproduct **18** in 6% and recovery of **11** (15%). Decreasing the flow rate to 1.0 mL/min (entry 4) increased the ratio of **17** to 82%, while the starting material **11** remained in 10% with **17** (3%) and **18** (6%). Then, methylation reagent was changed from Me_3Al to MeMgBr (entry 5). As a result, the ratio of **16** was improved to 85% but the diastereomer **17** was obtained in 12% with recovery of **11** (3%), but no byproduct **18** was obtained. Therefore, conditions in entry 5 were to be the most suitable for this transformation.

Table 2-1-1. Methylation of ketone **11** under the flow conditions.

entry	reagent/solvent A	solvent B	T (°C)	flow rate (mL/min)	ratio (%)[a]			
					16	**17**	**18**	**11**
1	Me_3Al/hexane	CH_2Cl_2	0	5.0	55	0	0	45
2	Me_3Al/hexane	CH_2Cl_2	0	2.5	55	0	0	45
3	Me_3Al/hexane	CH_2Cl_2	rt	2.5	77	3	6	15
4	Me_3Al/hexane	CH_2Cl_2	rt	1.0	82	3	6	10
5	MeMgBr/THF	THF	rt	1.0	85	12	0	3

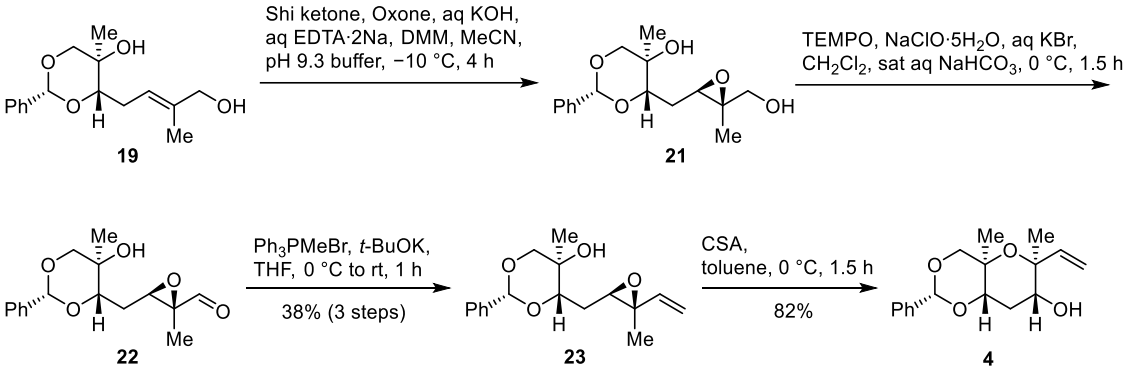
[a]The ratio was determined by 600 MHz ^{1}H NMR analysis.

Having succeeded in methylation of ketone **11**, successive methylation of the ketone and 1,2-reduction of the α,β-unsaturated ester giving alcohol **19** was examined as shown in Scheme 2-1-4. Under the optimized reaction conditions (Table 2-1-1, entry 5), a solution of 0.6 M **11** (84.7 g) in THF (400 mL) and a solution of 1.0 M MeMgBr in THF were transmitted to the first Comet X-01 by using syringe pumps at a rate of 1.0 mL/min, respectively, at room temperature. Then, the eluent was transmitted to the second Comet X-01, which was mixed with a solution of 1.0 M DIBALH in toluene at a rate of 1.5 mL/min at room temperature. After passing through the tube, the eluent was poured into a mixture of aqueous solution of Rochelle salt and Et_2O at 0 °C to afford **19** in 83% yield (63.7 g) and diastereomer **20** in 6% yield (4.3 g).



Scheme 2-1-4. Methylation and DIBALH reduction of ketoester **11** under the flow conditions.

The common tetrahydropyran derivative **4** was synthesized from **19** as shown in Scheme 2-1-5. Shi asymmetric epoxidation[6] of **19** gave epoxyalcohol **21**, which was subjected to TEMPO oxidation[7] giving aldehyde **22**, followed by Wittig olefination to afford terminal olefin **23** in 38% yield for 3 steps. The 6-*endo* cyclization of vinyl epoxide **23** was carried out by using catalytic amount of CSA in toluene to afford the common tetrahydropyran derivative **4** in 82% yield.[8]

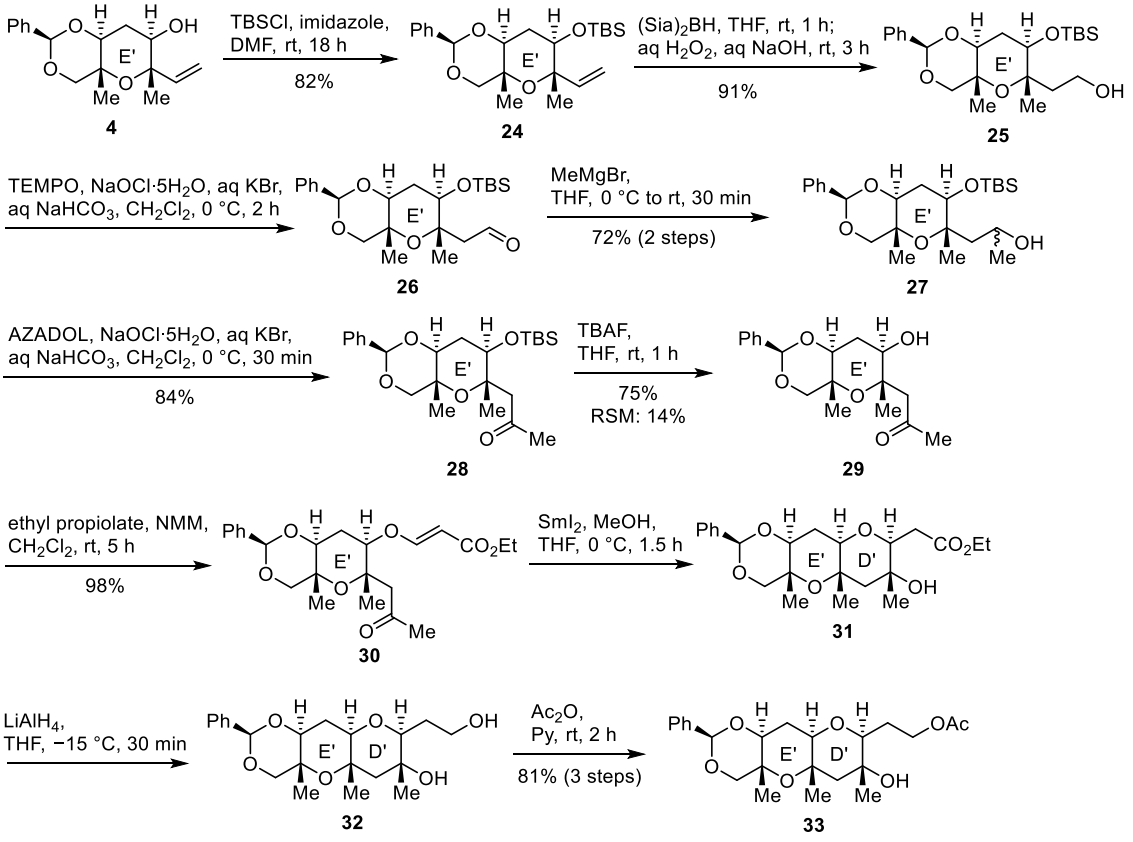


Scheme 2-1-5. Synthesis of the common tetrahydropyran derivative **4**.

2-2. Synthesis of the C'D'E'F' ring fragment

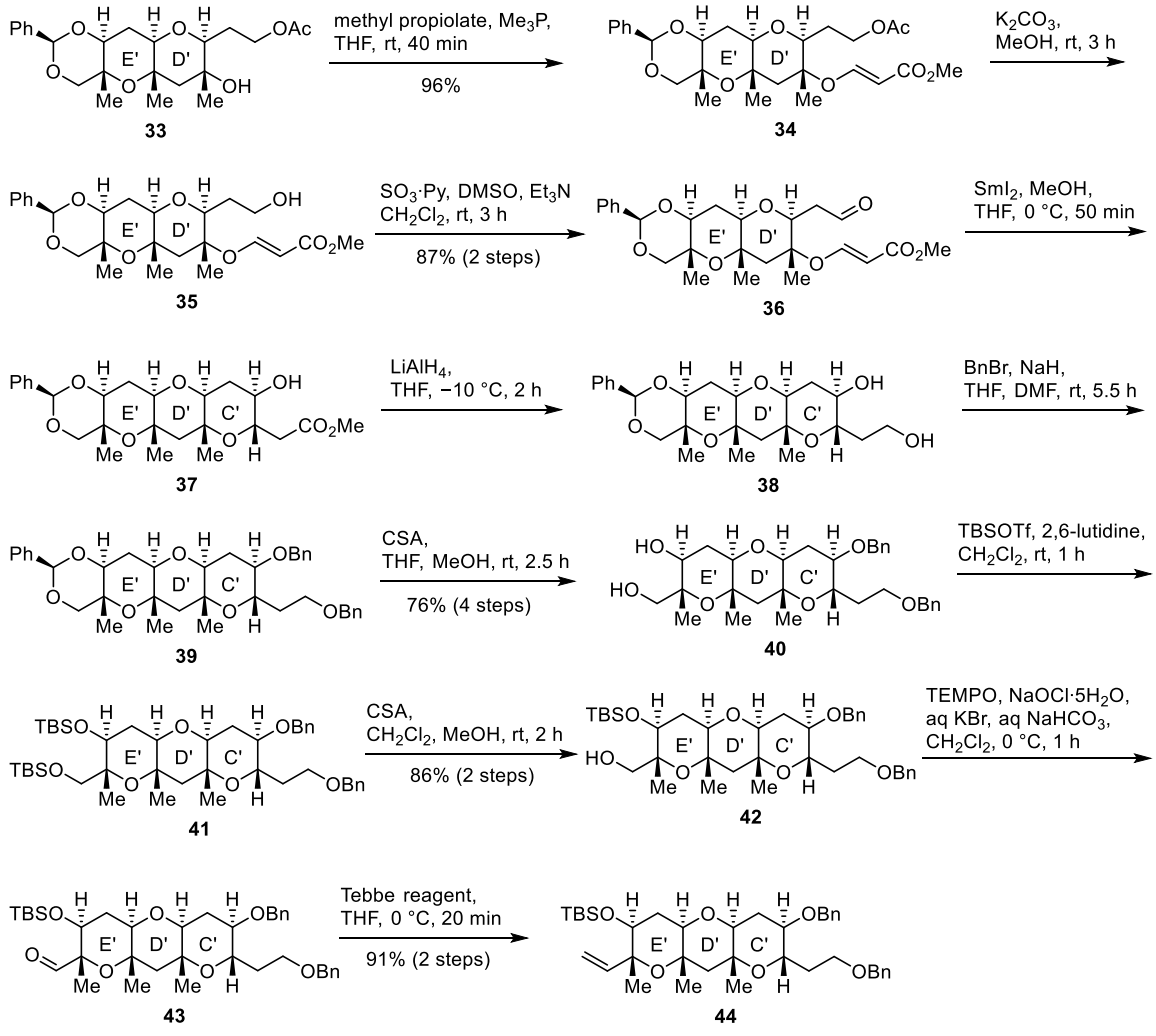
2-2-1. Synthesis of the C'D'E' ring

According to the literature, the large scale synthesis of the C'D'E'F' ring fragment was examined.[9] The D'E' ring **33** was synthesized as shown in Scheme 2-2-1. The common tetrahydropyran derivative **4** corresponding to the E' ring was converted to the TBS ether **24** in 82% yield by protection of the secondary alcohol. Hydroboration of terminal olefin **24** with disiamylborane gave primary alcohol **25** in 91% yield after oxidative workup. TEMPO oxidation[7] of **25** furnished aldehyde **26**, and treatment of **26** with methylmagnesium bromide afforded alcohol **27** in 72% yield for 2 steps as a mixture of diastereomers. AZADOL oxidation[2] of the resulting secondary alcohol **27** furnished ketone **28** in 84% yield. Removal of the TBS group of **28** with TBAF gave secondary alcohol **29** in 75% yield with recovery of **28** in 14% yield. Oxa-Michael reaction of the secondary alcohol **29** with ethyl propiolate in the presence of NMM resulted in the formation of the *trans*-β-alkoxyacrylate **30** in 98% yield. Construction of the D' ring was achieved by treating with SmI_2 in the presence of MeOH to furnish the C'D' ring **31** as a single isomer.[10] Reduction of ester **31** with $LiAlH_4$ and primary selective acetylation of the resulting diol **32** afforded **33** in 81% yield for 3 steps.



Scheme 2-2-1. Synthesis of the D'E' ring **33**.

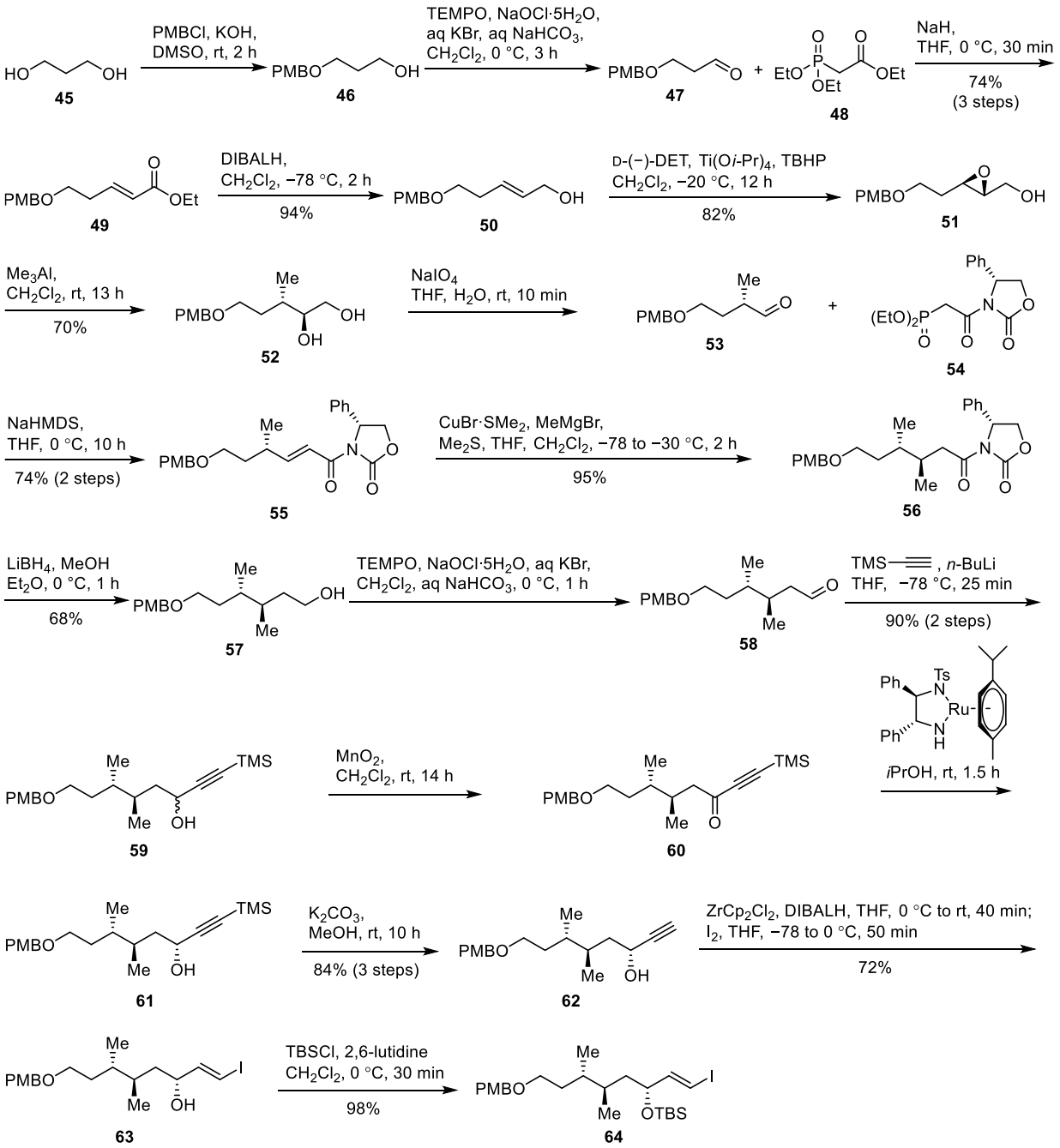
The C'D'E' ring **44** was synthesized as shown in Scheme 2-2-2. Oxa-Michael addition of tertiary alcohol **33** was carried out with methyl propiolate in the presence of trimethylphosphine to furnish *trans*-β-alkoxyacrylate **34** in 96% yield.[11] Methanolysis of acetate **34** with K_2CO_3 gave primary alcohol **35**, which was subjected to Parikh–Doering oxidation to afford aldehyde **36** in 87% yield for 2 steps.[12] In an analogous sequence, construction of the C' ring was carried out by the SmI_2 induced reductive cyclization to afford **37** as a single isomer. After reduction of ester **37** with $LiAlH_4$, protection of the resulting diol **38** as benzyl ethers, and removal of benzylidene acetal with CSA gave diol **40** in 76% yield for 4 steps. The diol **40** was protected as TBS ethers, and selective deprotection of the primary TBS group of **41** with CSA in methanol furnished primary alcohol **42** in 86% yield for 2 steps. The resulting alcohol **42** was subjected to TEMPO oxidation[7] giving aldehyde **43**, which was converted to terminal olefin **44** with Tebbe reagent in 91% yield for 2 steps.[13] As a result, 4.12 g of the C'D'E' ring was synthesized from 16.6 g of the common tetrahydropyran derivative **4**.



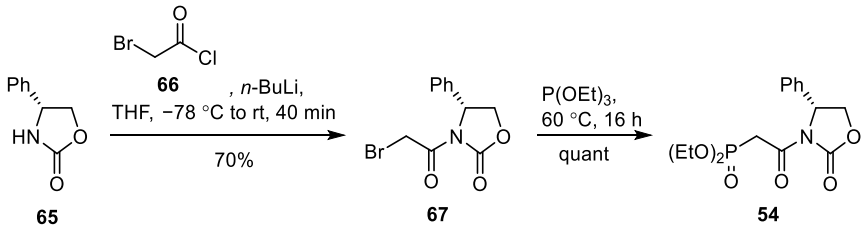
Scheme 2-2-2. Synthesis of the C'D'E' ring **44**.

2-2-2. Synthesis of the side chain

Synthesis of the side chain **64** is shown Scheme 2-2-3. Selective protection of 1,3-propanediol **45** as PMB ether gave alcohol **46**. TEMPO oxidation of alcohol **46** gave aldehyde **47**, which was reacted with ethyl diethylphosphonoacetate **48** to afford α,β-unsaturated ester **49** in 74% yield for 3 steps. Reduction of ester **49** with DIBALH gave allylic alcohol **50** in 94% yield. Katsuki–Sharpless asymmetric epoxidation[14] of the resulting allylic alcohol **50** furnished the epoxy alcohol **51** in 82% yield. Regio- and stereoselective epoxide opening of epoxy alcohol **51** with Me_3Al afforded the diol **52** in 70% yield, which was subjected to oxidative cleavage with $NaIO_4$ to furnish aldehyde **53**.[15] The known phosphonate **54**[16] was prepared from (*R*)-4-phenyl-2-oxazolidinoe **65** via alkylation with bromoacetyl chloride **66** followed by Arbuzov reaction by treating with $P(OEt)_3$ as shown in Scheme 2-2-4. Treatment of **54** with NaHMDS, followed by addition of aldehyde **53** resulted in the formation of olefin **55** in 74% for 2 steps. Diastereoselective 1,4-addition of α,β-unsaturated carbonyl compound **55** with organocuprate proceeded in a highly stereoselective manner to afford **56** in 95% yield as a single diastereomer.[17] Removal of the chiral auxiliary with $LiBH_4$ in the presence of MeOH gave primary alcohol **57** in 68% yield. TEMPO oxidation of **57** followed by nucleophilic addition of the resulting aldehyde **58** with lithium trimethylsilylacetylide afforded the propargylic alcohol **59** in 90% yield for 2 steps as a mixture of diastereomers. Oxidation of the propargylic alcohol **59** with MnO_2, followed by diastereo-selective reduction of the resulting ynone **60** with Noyori asymmetric hydrogen transfer catalyst,[18] and removal of TMS group of **61** with K_2CO_3 in methanol furnished alcohol **62** in 84% yield for 3 steps. The terminal alkyne **62** was subjected to hydrozirconation-iodination reaction by treating with Schwarz reagent prepared in situ from Cp_2ZrCl_2 and DIBALH followed by iodine to give iodoolefin **63** in 72% yield. Protection of the alcohol **63** as a TBS ether afforded **64** in 96% yield. As a result, 7.65 g of the side chain **64** was synthesized.



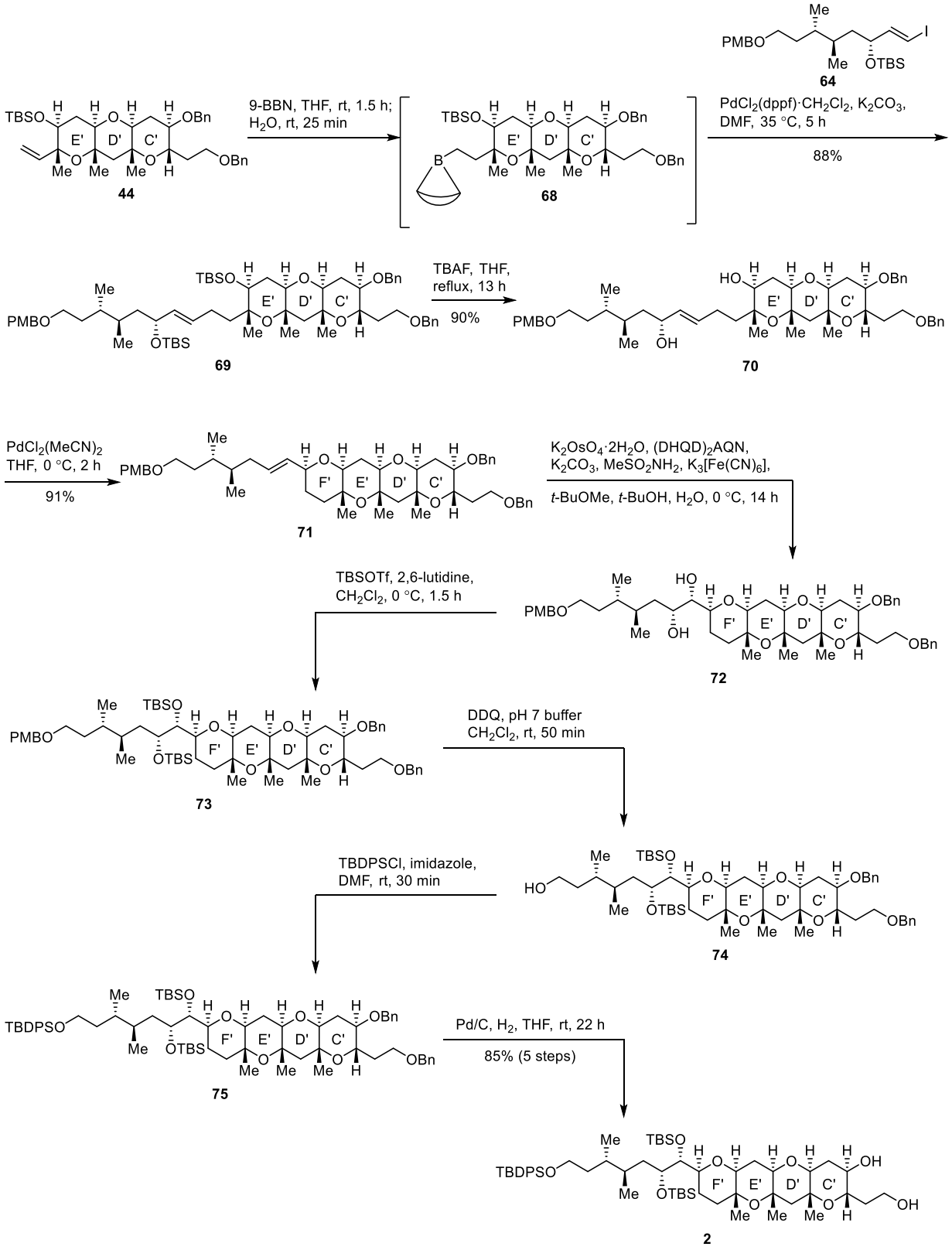
Scheme 2-2-3. Synthesis of the side chain **64**.



Scheme 2-2-4. Synthesis of phosphonate **54**.

2-2-3. Synthesis of C'D'E'F' ring fragment

Synthesis of the C'D'E'F' ring fragment is shown in Scheme 2-2-5. Hydroboration of terminal olefin **44** giving alkylborane **68** followed by Suzuki–Miyaura coupling[19] with iodoolefin **64** resulted in the formation of coupling product **69** in 88% yield. After removal of the TBS groups with TBAF giving diol **70** in 90% yield, construction of the F' ring was carried out by Uenishi method by treating with $PdCl_2(MeCN)_2$ to afford **71** in 91% yield as a single diastereomer.[20] Stereoselective dihydroxylation of olefin **71** was achieved by Sharpless asymmetric dihydroxylation using $(DHQD)_2AQN$ as a ligand to obtain diol **72** as a single diastereomer.[21] After protection of the diol **72** as TBS ether **73**, removal of PMB group of **73** with DDQ giving **74** followed by protection of the resulting primary alcohol as TBDPS ether gave **75**. Removal of the benzyl group of **75** by hydrogenolysis with $Pd(OH)_2/C$ under a hydrogen atmosphere afforded the C'D'E'F' ring fragment **2** in 85% yield for 5 steps. As a result, 4.16 g of the C'D'E'F' ring fragment **2** was synthesized.



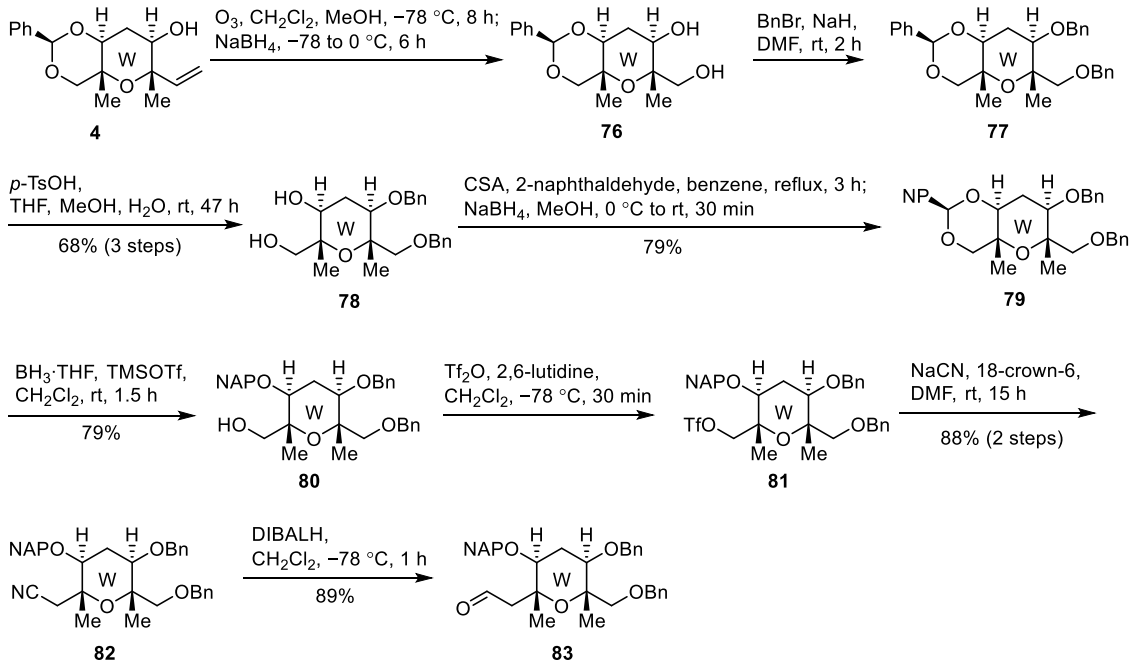
Scheme 2-2-5. Synthesis of the C'D'E'F' ring fragment **2**.

2-3. Synthesis of the WXYZ ring fragment

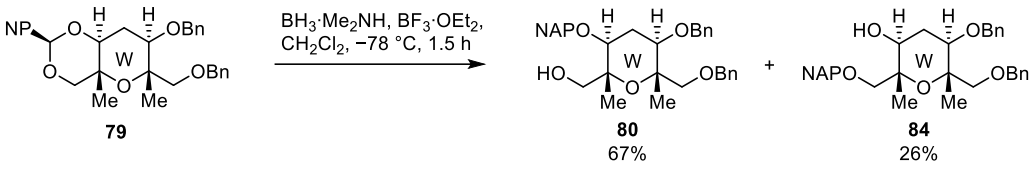
In the previous study by our group, the WXYZ ring was synthesized by α-cyano ether method (Method A).[22] Alternatively, the WXYZ ring fragment was synthesized via alkyne-aldehyde coupling and ring expansion (Method B).[23] In this study, large scale synthesis of the WXYZ fragment was caried out by method B.

2-3-1. Synthesis of the W and Z rings

The W ring aldehyde **83** was synthesized from the common tetrahydropyran derivative **4** corresponding to the W ring as shown in Scheme 2-3-1. Ozonolysis of terminal olefin **4** gave diol **76** after reductive workup with $NaBH_4$. Protection of the resulting diol **77** as benzyl ether **77** followed by removal of benzylidene acetal with CSA furnished diol **78** in 68% yield for 3 steps. Conversion of the diol as 2-naphthylidene acetal **79** in 79% yield, followed by regioselective reductive cleavage of the acetal with BH_3·THF in the presence of TMSOTf[24] provided primary alcohol **80** in 79% yield. Previously, this transformation was carried out by using BH_3·Me_2NH in the presence of BF_3·OEt_2 to give primary alcohol **80** in 67% yield with concomitant formation of secondary alcohol **84** in 26% yield (Scheme 2-3-2).[22] The primary alcohol **80** was converted to triflate **81**, which was treated with NaCN in the presence of 18-crown-6 to furnish nitrile **82** in 88% yield for 2 steps. Reduction of nitrile **82** with DIBALH afforded the W ring aldehyde **83** in 89% yield.

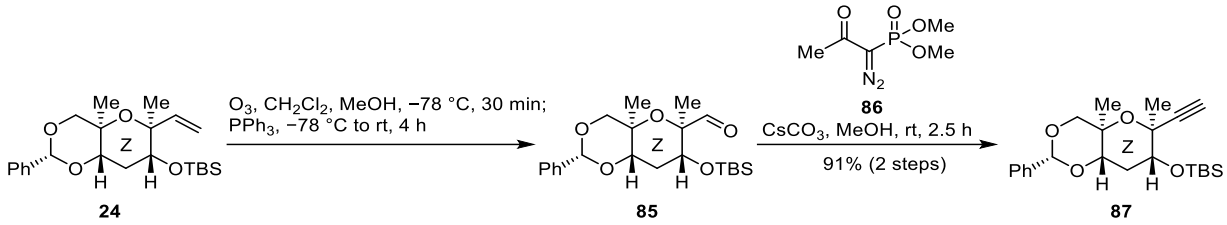


Scheme 2-3-1. Synthesis of the W ring **83**.



Scheme 2-3-2. Previous results of reductive cleavage of acetal **76**.

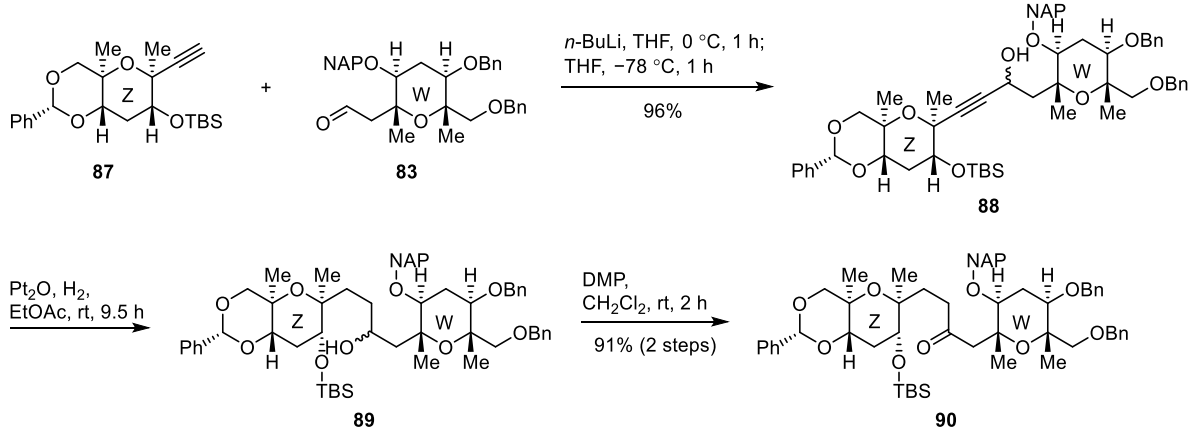
The X ring **87** was synthesized as shown in Scheme 2-3-2. Ozonolysis of terminal olefin **24** gave aldehyde **85** after reductive workup with PPh_3. The resulting aldehyde **85** was converted to terminal alkyne **87** with Ohira–Bestmann reagent **86**[25] in the presence of Cs_2CO_3 in 91% yield for 2 steps.



Scheme 2-3-3. Synthesis of the Z ring **87**.

2-3-2. Synthesis of the WXYZ ring fragment

Having synthesized the W and Z rings, coupling of the building blocks was examined (Scheme 2-3-4). Alkyne **87** was treated with *n*-BuLi and the resulting lithium acetylide was reacted with aldehyde **83** to obtain propargylic alcohol **88** in 96% yield as a mixture of diastereomers. Hydrogenation of alkyne **88** with PtO_2 under a hydrogen atmosphere, followed by Dess–Martin oxidation[26] of the resulting saturated alcohol **89** gave ketone **90** in 87% yield for 2 steps.



Scheme 2-3-4. Synthesis of ketone **90**.

Since the next step, removal of the TBS group of **90** was problematic, optimization of the reaction conditions was examined (Table 2-3-1). As reported by our group,[23] removal of the TBS group of **90** with TBAF resulted in the formation of a mixture of hydroxy ketone **91** and corresponding hemiacetal **92** in 54% yield in a 1:1 ratio with 40% recovery of **90** (entry 1). The stereochemistry of **92** was determined by ROE experiments. Increasing the reaction time caused decreasing the yield of **91** and **92** (39%), accompanied with unidentified byproducts (entry 2). Addition of acetic acid to suppress the basicity of TBAF gave **91** and **92** in 65% yield with recovery of **90** in 20% yield (entry 3). On the other hand, treatment of **90** with HF·Py in pyridine resulted in the formation of **91** and **92** in 81% yield without recovery of **90** (entry 4).

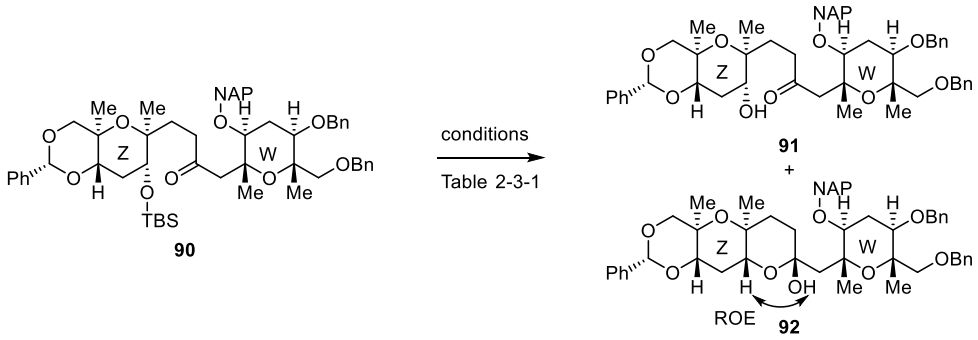


Table 2-3-1. Removal of TBS group of **90**.

entry	conditions	yield (%)[a]	
		91 + **92**	**90**
1[b]	TBAF, THF, rt, 1 h	54	40
2	TBAF, THF, rt, 4 h	39	-[c]
3	TBAF, AcOH, THF, reflux, 15 h	64	20
4	HF·Py, pyridine, 50 °C, 38 h	81	-

[a] Isolated yield. [b] Ref. 23. [c] Unidentified byproducts.

Then, dehydrative cyclization of **91** and **92** was examined as shown in Table 2-3-2. As reported by our group,[23] treatment of a mixture of **91** and **92** with an acidic resin Nafion NR-50[27] in toluene under reflux resulted in the formation of dihydropyran derivative **93** in 76% yield (entry 1). However, this condition was not suitable for large scale synthesis because expensive Nafion NR-50 (880 JPY/g) was used in excess amount (600 wt%). After considerable experimentation, the inexpensive reagent P_2O_5 (5.6 JPY/g) was found to be suitable for this reaction. Thus, a mixture of **91** and **92** was treated with P_2O_5 (5.0 eq) in toluene at room temperature (entry 2).[28] The dehydrative cyclization proceeded smoothly to afford the desired product **93** in 79% yield.

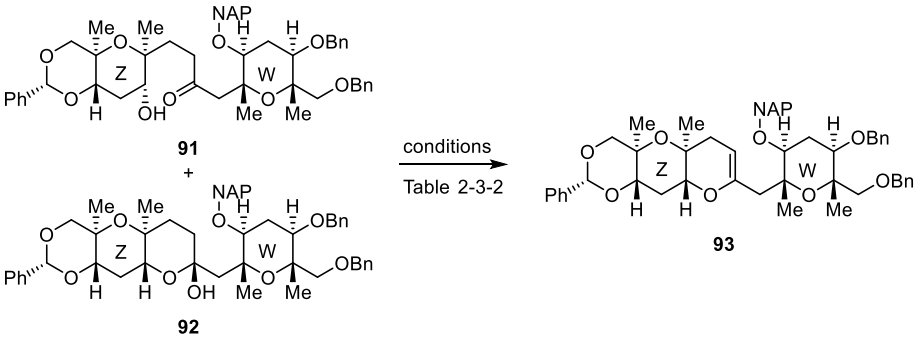
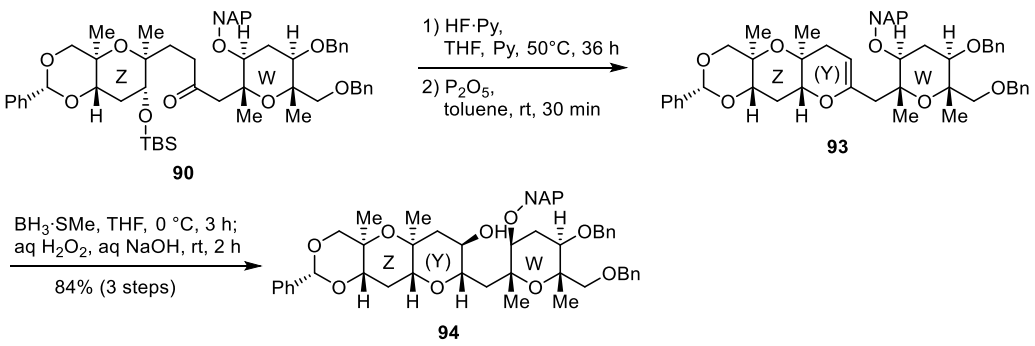


Table 2-3-2. Dehydrative cyclization of a mixture of **91** and **92**.

entry	conditions	yield (%)[a]
1[b]	Nafion NR-50 (600 wt%), MS4A, toluene, reflux, 30 min	76
2	P_2O_5 (0.85 wt%, 5.0 eq), toluene, rt, 40 min	79

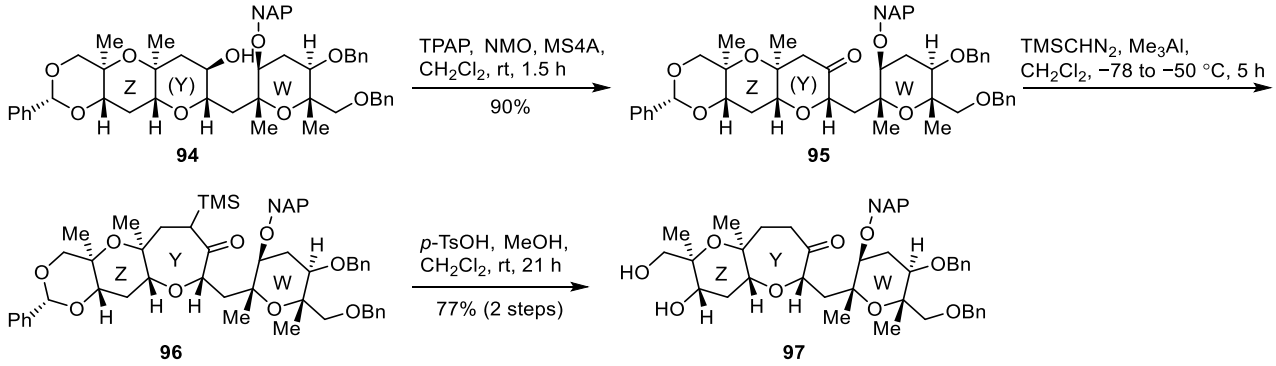
[a] Isolated yield. [b] Ref. 23.

Having optimized the reaction conditions, sequential removal of the TBS group of **90** followed by dehydrative cyclization giving **93** was carried out by treating with HF·Py and P_2O_5 (Scheme 2-3-5). Hydroboration of **93** followed by oxidative workup afforded alcohol **94** in 84% yield for 3 steps.

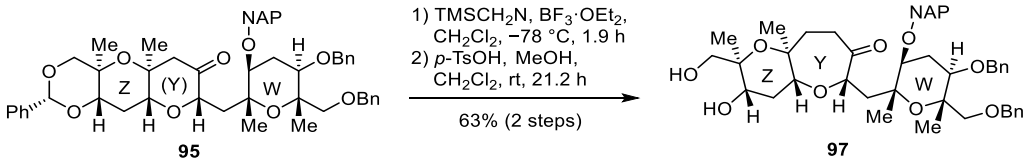


Scheme 2-3-5. Synthesis of alcohol **94**.

The seven-membered ring ketone **97** was synthesized as shown in Scheme 2-3-6. Ley oxidation[29] of **94** with TPAP in the presence of NMO as a cooxidant furnished ketone **95** in 90% yield. As a result, 10.9 g of the six-membered ring ketone **95** was synthesized. The ring-expansion of the six-membered ring ketone **95** into the seven-membered one was carried out by treating with $TMSCHN_2$ in the presence of Me_3Al as a Lewis acid[30] to furnish seven-membered ring ketone **96** as a mixture of diastereomers with respect to the TMS group. The mixture was subjected to the methanolysis conditions with *p*-TsOH in CH_2Cl_2/MeOH to remove the TMS group and benzylidene acetal to afford the diol **97** in 77% yield for 2 steps. Previously, ring-expansion of ketone **95** was carried out by using $TMSCHN_2$ in the presence of $BF_3{\cdot}OEt_2$ as a Lewis acid to furnish **97** in 63% yield for 2 steps after methanolysis (Scheme 2-3-7).[23]



Scheme 2-3-6. Synthesis of seven-membered ring ketone **97**.



Scheme 2-3-7. Previous reaction conditions of ring-expansion of **95**.

The next step, protection of diol **97** as TIPS ether was problematic due to the concomitant formation of silyl enol ether **99** or incomplete protection giving mono TIPS ether **110** as reported by our group (Table 2-3-3, entries 1–3). Treatment of diol **97** with TIPSOTf in the presence of 2,6-lutidine afforded bis TIPS ether **98** and silyl enol ether **99** in 64% and 34% yield, respectively (entry 1).[23] By replacing 2,6-lutidine with *N*-Me-imidazole, not desired **98**, but mono TIPS ether **100** was obtained in 76% yield without formation of **99** (entry 2). Changing the reagent to TIPSCl and I_2 also gave mono TIPS ether **100** in 90% yield (entry 3).[32] When the reagent was changed from TIPSOTf to TIPSCl and $AgNO_3$, the desired bis TIPS ether **98** was obtained in 54% yield with mono TIPS ether **100** in 29% yield (entry 4).[33] On the other hand, treatment of diol **97** with

TIPSOTf in the presence of Et_3N, followed by in situ protonolysis of silyl enol ether by using with TFA gave **98** in 80% yield (entry 5).[34] Therefore, conditions in entry 5 were to be the most suitable for this transformation. Then, the diol **97** was converted to *O*,*S*-acetal **102** as shown in Scheme 2-3-8. Conversion of diol **97** was carried out under conditions of entry 5 to furnish bis TIPS ether **98**, which was used for the next reaction without purification. Removal of NAP group of **98** with DDQ afforded hydroxy ketone **101** in 80% for 2 steps. Treatment of the hydroxy ketone **101** with EtSH in the presence of TfOH followed by protection of the partially desilylated products furnished *O*,*S*-acetal **102** in 93% yield as an inseparable diastereomers.

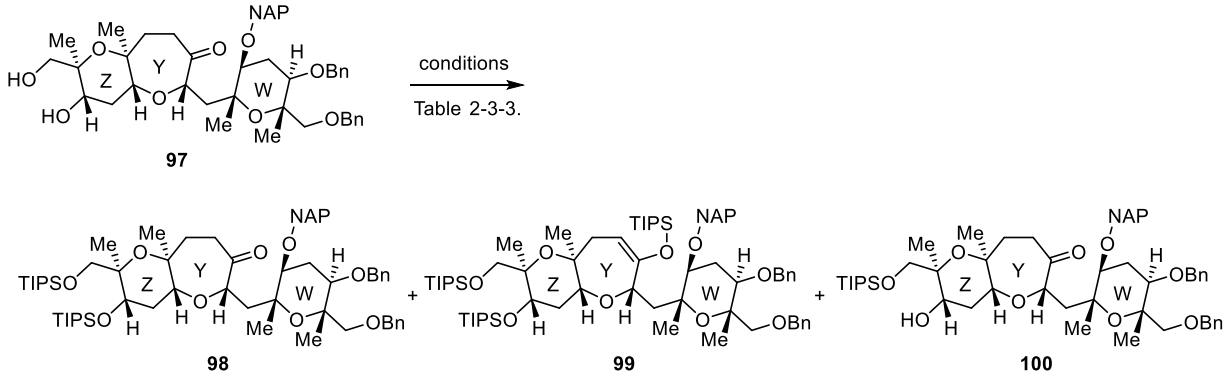
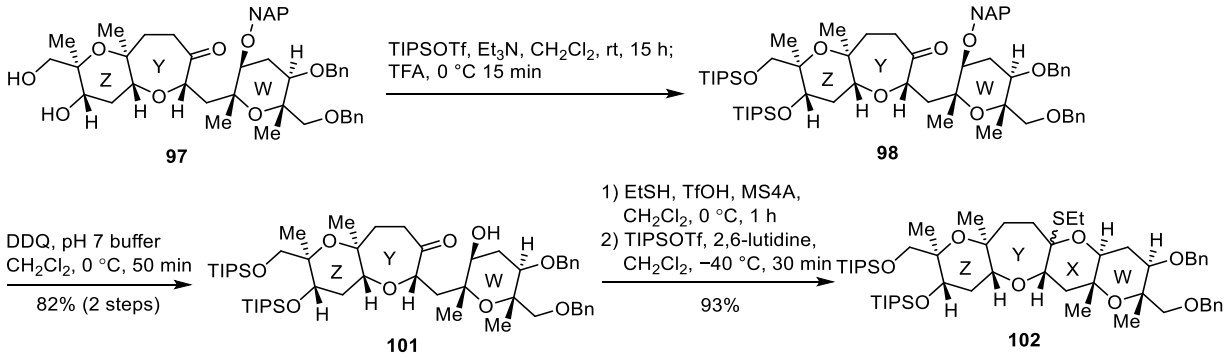


Table 2-3-3. Protection of diol **94** as bis TIPS ether **98**.

entry	conditions	yield (%)[a]		
		98	**99**	**100**
1[b]	TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 14 h	64	34	-
2[c]	TIPSOTf, *N*-Me-imidazole, CH_2Cl_2, rt, 26 h	-	-	76
3[c]	TIPSCl, I_2, *N*-Me-imidazole, CH_2Cl_2, rt, 14 h	-	-	90
4	TIPSCl, $AgNO_3$, Py, DMF, 40 °C, 23 h	54	-	29
5	TIPSOTf, Et_3N, CH_2Cl_2, rt, 15 h; TFA, 0 °C, 10 min	80	-	-

[a] Isolated yield. [b] Ref. 23. [c] Ref. 31.



Scheme 2-3-8. Synthesis of *O*,*S*-acetal **102**.

As reported by our group, introduction of the angular methyl group was examined as shown in Table 2-3-4 (entries 1–3).[22,35] Oxidation of sulfide **102** with MCPBA at 0 °C giving sulfoxide **103** and/or sulfone **104** as intermediates followed by addition of Me_3Al gave hydroxyketone **101** in 82% yield as a byproduct due to hydrolysis of **103** and/or **104** (entry 1). To prevent hydrolysis of the intermediates, the reaction temperature was decreased at −40 °C, and desired product **105** was obtained in 73% yield with recovery of unreacted sulfoxide **103** in 23% yield (entry 2). Scaling up the reaction to 1.5 g scale decreased the yield of **105** (52%) with concomitant formation of **103** (32%) and unidentified byproducts (entry 3). Nicolaou group reported that the similar reaction was carried out in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to give the desired product in good yield.[36] Therefore, this procedure was applied to this reaction. Namely, MCPBA oxidation was carried out in the presence of DTBMP at −10 °C, then treated with Me_3Al (entry 4). As a result, desired product **105** was obtained in 73% yield without byproducts. Scaling up the reaction by using 1.78 g of **102** gave **105** in 85% yield (entry 5). As a result, 1.37 g of **105** was synthesized.

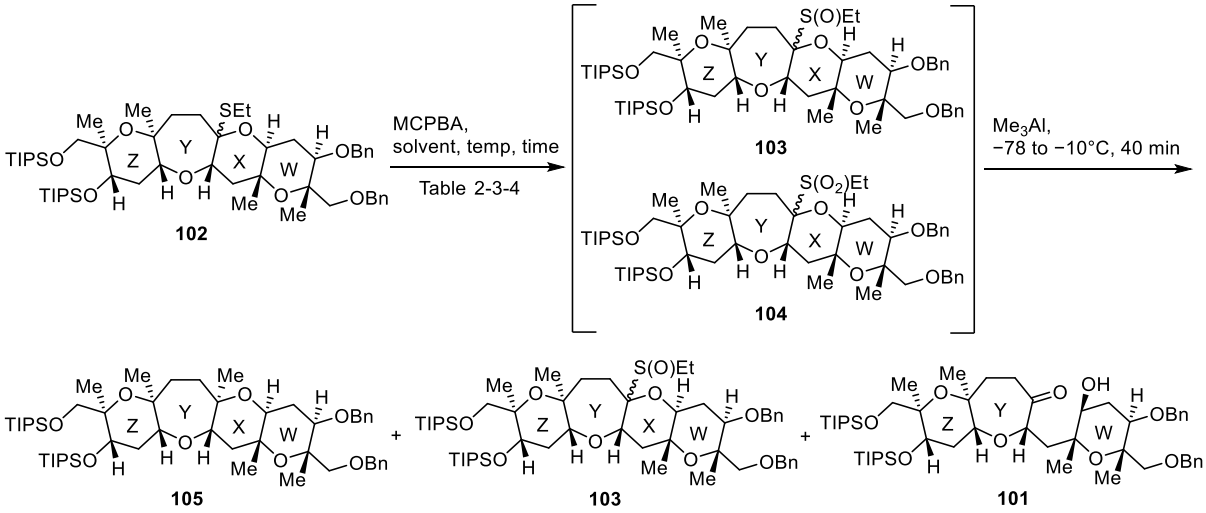
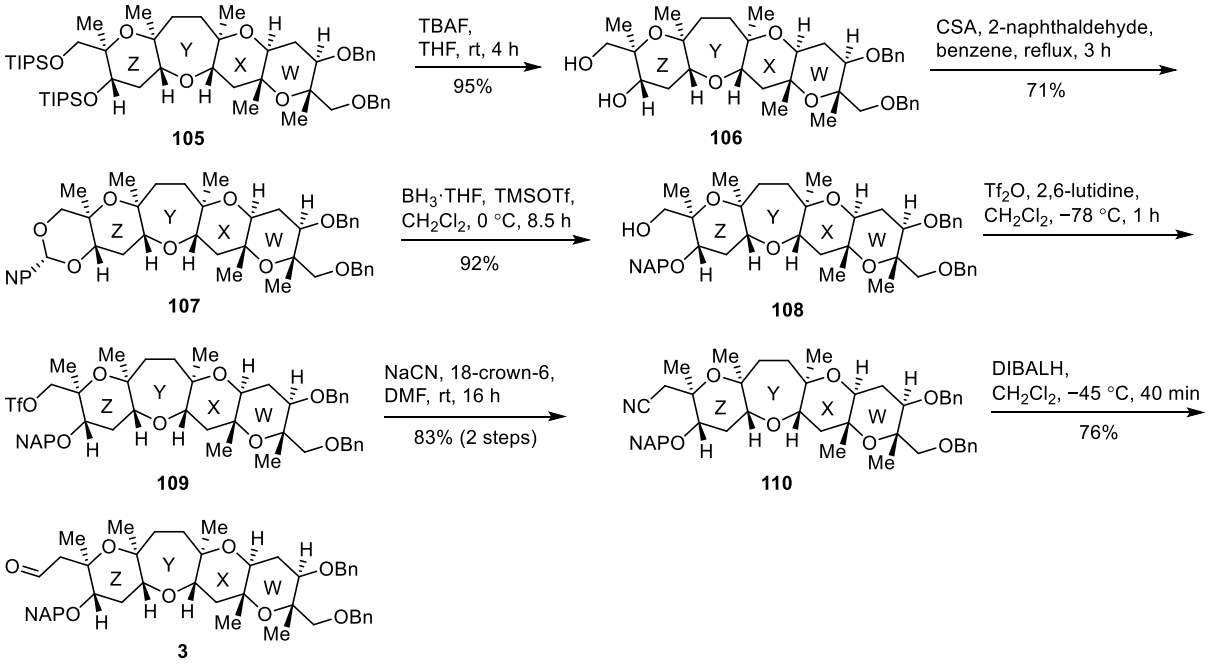


Table 2-3-4. Methylation of *O*,*S*-acetal **102** giving **105**.

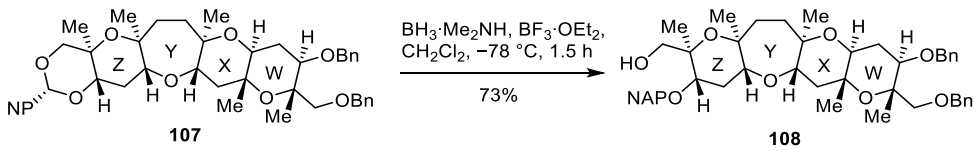
entry	**102**/mg	solvent	additive	temp (°C)	time (h)	yield (%)[a]		
						105	**103**	**101**
1[b]	439	CH_2Cl_2	-	−78 to 0	2.0	-	-	82
2[c]	674	CH_2Cl_2	-	−78 to −40	1.0	73	23	-
3[b]	1530	CH_2Cl_2	-	−78 to −40	1.0	52	32	-[d]
4	378	toluene	DTBMP	−78 to −10	15	87	-	-
5	1780	toluene	DTBMP	−78 to −10	15	85	-	-

[a] Isolated yield. [b] Ref 35. [c] Ref 22. [d] Unidentified byproducts.

The WXYZ ring fragment **3** was synthesized as shown in Scheme 2-3-9. Removal of the TIPS groups of **105** with TBAF gave diol **106** in 98% yield. Conversion of diol **106** by treating with 2-naphthaldehyde in the presence of CSA in benzene gave 2-naphthylidene acetal **107** in 71% yield, and regioselective reductive cleavage of the acetal **107** with BH_3·THF in the presence of TMSOTf provided primary alcohol **108** in 92% yield. Previously, this transformation was carried out by using BH_3·Me_2NH in the presence of BF_3·OEt_2 to give primary alcohol **108** in 73% yield (Scheme 2-3-10).[22] The primary alcohols **108** was converted to triflate **109** with Tf_2O in the presence of 2,6-lutidine, which was treated with NaCN in the presence of 18-crown-6 to afford nitrile **110** in 83% yield for 2 steps. Reduction of nitrile **110** with DIBALH afforded the WXYZ ring fragment **3** in 76% yield. As a result, 148 mg of the WXYZ ring fragment **3** was synthesized.



Scheme 2-3-9. Synthesis of the WXYZ fragment **3**.



Scheme 2-3-10. Previous results of reductive cleavage of acetal **108**.

References

1. a) K. C. Nicolaou, D. A. Nugiel, E. Couladourus, C.-K. Hwang, *Tetrahedron* **1990**, *46*, 4517. b) T. Nakashima, T. Baba, H. Onoue, W. Yamashita, K. Torikai, *Synthesis* **2013**, *45*, 2417.
2. M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412.
3. For recent reviews on microreactors, see: a) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802. b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2. c) B. Gutmann, D.Cantillo, C. O. Kappe, *Angew. Chem., Int. Ed.* **2015**, *54*, 6688.
4. S. Katayama, T. Koge, S. Katsuragi, S. Akai, T. Oishi, *Chem. Lett.* **2018**, *47*, 1116.
5. For examples to use Comet X-01, see: a) I. V. Myachin, Z. Z. Mamirgova, E. V. Stepanova, A. I. Zinin, A. O. Chizhov, L. O. Kononov, *Eur. J. Org. Chem.* **2022**, e202101377. b) T. Ikawa, S. Masuda, S. Akai, *Chem. Pharm. Bull.* **2018**, *66*, 1153. c) N. Konishi, T. Shirahata, M. Yokoyama, T. Katsumi, Y. Ito, N. Hirata, T. Nishino, K. Makino, N. Sato, T. Nagai, H. Kiyohara, H. Yamada, E. Kaji, Y. Kobayashi, *J. Org. Chem.* **2017**, *82*, 6703. d) T. Doi, H. Otaka, K. Umeda, M. Yoshida, *Tetrahedron* **2015**, *71*, 6463 e) Y. Uchinashi, K. Tanaka, Y. Manabe, Y. Fujimoto, K. Fukase, *J. Carbohydr. Chem.* **2014**, *33*, 55.
6. a) Y. Tu, Z. -X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806. b) Z. -X. Wang, Y. Tu, M. Frohn, J. -R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224.
7. a) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559. b) P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970.
8. Y. Sakamoto, G. Matsuo, H. Matsukura, T. Nakata, *Org. Lett.* **2001**, *3*, 2479.
9. M. Kunitake, T. Oshima, K. Konoki, M. Ebine, K. Torikai, M. Murata, T. Oishi, *J. Org. Chem.* **2014**, *79*, 4948.
10. a) N. Hori, H. Matsukura, G. Matsuo, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 2811. b) N. Hori, H. Matsukura, T. Nakata, *Org. Lett.* **1999**, *1*, 1099. c) G. Matsuo, N. Hori, T. Nakata, *Tetrahedron Lett*. **1999**, *40*, 8859. d) K. Suzuki, H. Matsukura, G. Matsuo, H. Koshino, T. Nakata, *Tetrahedron Lett.* **2002**, *43*, 8653. e) N. Hori, H. Matsukura, G. Matsuo, T. Nakata, *Tetrahedron* **2002**, *58*, 1853.
11. a) J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett.* **1993**, 241. b) K. Sato, M. Sasaki, *Org. Lett.* **2005**, *7*, 2441.
12. J. R. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.
13. F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611.
14. T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5974.

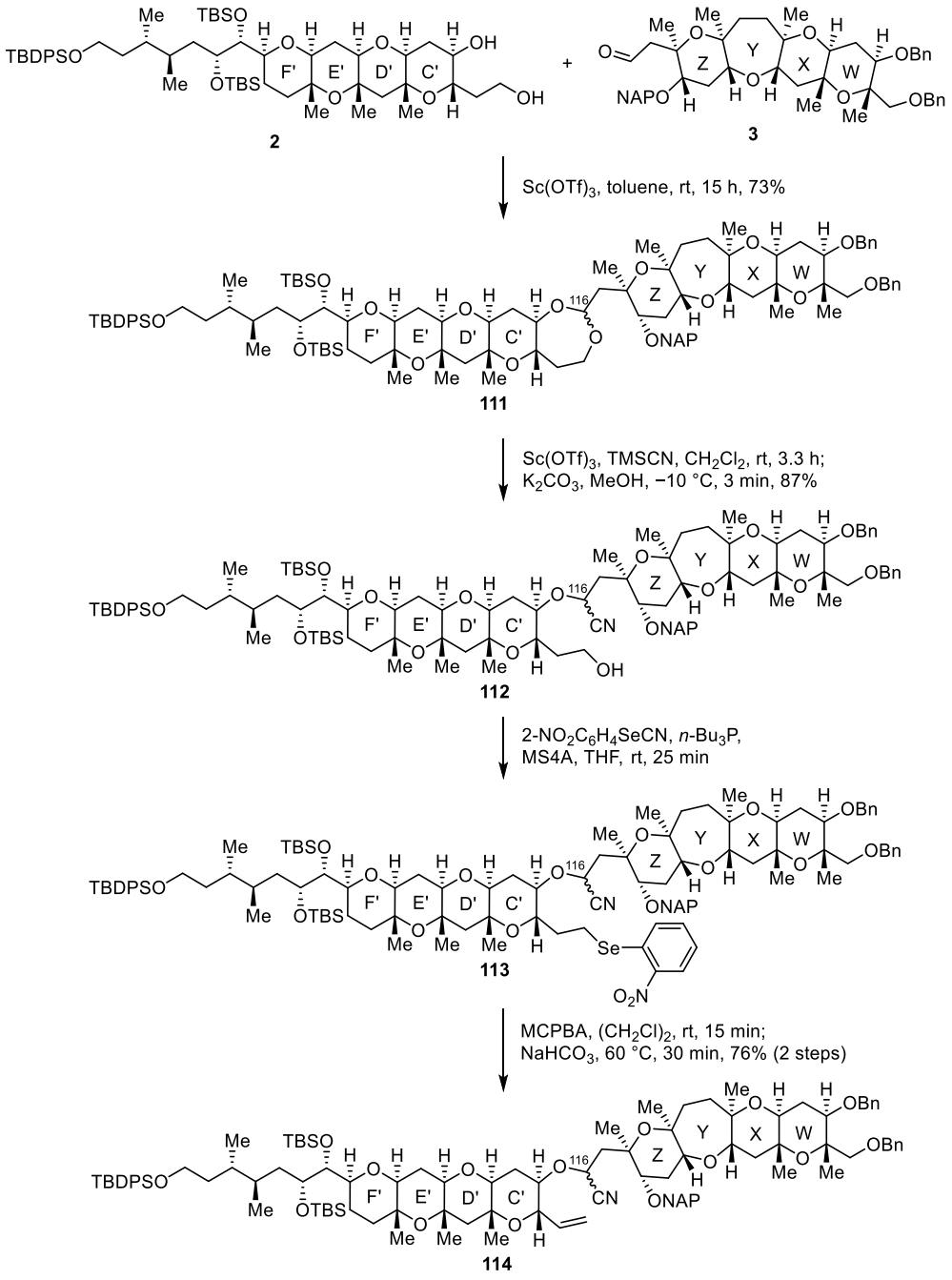
15. a) T. Oka, A. Murai, *Tetrahedron* **1998**, *54*, 1. b) A. Hara, R. Morimoto, Y. Ishikawa, S. Nishiyama, *Org. Lett.* **2011**, *13*, 4036.
16. E. Nicolas, K. C. Russell, V. J. Hruby, *J. Org. Chem.* **1993**, *58*, 766.
17. a) M. Morita, S. Ishiyama, H. Koshino, T. Nakata, *Org. Lett.* **2008**, *10*, 1675. b) D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, J. O. Liu, *J. Am. Chem. Soc.* **1998**, *120*, 12237.
18. K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738.
19. N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
20. a) J. Uenishi, Y. S. Vikhe, N. Kawai, *Chem.-Asian J.* **2008**, *3*, 473. b) N. Kawai, J.-M. Lagrange, J. Uenishi, Eur. *J. Org. Chem.* **2007**, 2808. c) N. Kawai, J.-M. Lagrange, M. Ohmi, J. Uenishi, *J. Org. Chem.* **2006**, *71*, 4530. d) S. S. Palimkar, J. Uenishi, H. Ii, *J. Org. Chem.* **2012**, *77*, 388. e) H. Yokoyama, S. Nakayama, M. Murase, M. Miyazawa, S. Yamaguchi, Y. Hirai, *Heterocycles* **2009**, *77*, 211.
21. W. Zheng, J. A. DeMattei, J.-P.Wu, JJ.-W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946.
22. a) T. Oishi, K. Watanabe, M. Murata, *Tetrahedron Lett*. **2003**, *44*, 7315. b) T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 3599.
23. N. Osato, H. Onoue, Y. Toma, K. Torikai, M. Ebine, M. Satake, T. Oishi, *Chem. Lett.* **2018**, *47*, 265.
24. K. Daragics, P. Fügedi, *Tetrahedron Lett.* **2009**, *50*, 2914.
25. S. Ohira, *Synth. Commun.* **1989**, *19*, 561.
26. D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
27. a) G. A. Olah, P. S. Iyer, G. K. S. Prakash, *Synthesis (Mass.)* **1986**, 513. b) M. Morita, S. Ishiyama, H. Koshino, T. Nakata, *Org. Lett.* **2008**, *10*, 1675.
28. a) A. Boschi, C. Chiappe, A. D. Rubertis, M. F. Ruasse, *J. Org. Chem* **2000**, *65*, 8470. b) S. Jakkampudi, R. Parella, H. D. Arman, J. C.-G. Zhao, *Chem. Eur. J.* **2019**, *25*, 7515.
29. S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
30. a) T. Sakai, A. Sugimoto, Y. Mori, *Org. Lett.* **2011**, *13*, 5850. b) T. Sakai, S. Ito, H. Furuta, Y. Kawahara, Y. Mori, *Org. Lett.* **2012**, *14*, 4564. c) S. Yamashita, K. Takeuchi, T. Koyama, M. Inoue, Y. Hayashi, M. Hirama, *Chem. Eur. J.* **2015**, *21*, 2621.
31. a) H. Onoue, unpublished results. b) H. Onoue, *Doctor Thesis*, Kyushu university (2018).
32. A. Bartoszewicz, M. Kalek, J. Stawinski, *Tetrahedron* **2008**, *64*, 8843.
33. Y. Kaburagi, Y. Kishi, *Org. Lett.* **2007**, *9*, 723.
34. H. Nakamura, M. Kawakami, C. Tsukano, Y. Takemoto, *Chem. Eur. J.* **2019**, *25*, 8701.
35. F. Hasegawa, unpublished results.

36. K. C. Nicolaou, P. Heretsch, T. Nakamura, A. Rudo, M. Murata, K. Konoki, *J. Am. Chem. Soc.* **2014**, *136*, 16444.

Chapter 3. Synthesis of the WXYZA'B'C'D'E'F' ring segment of maitotoxin

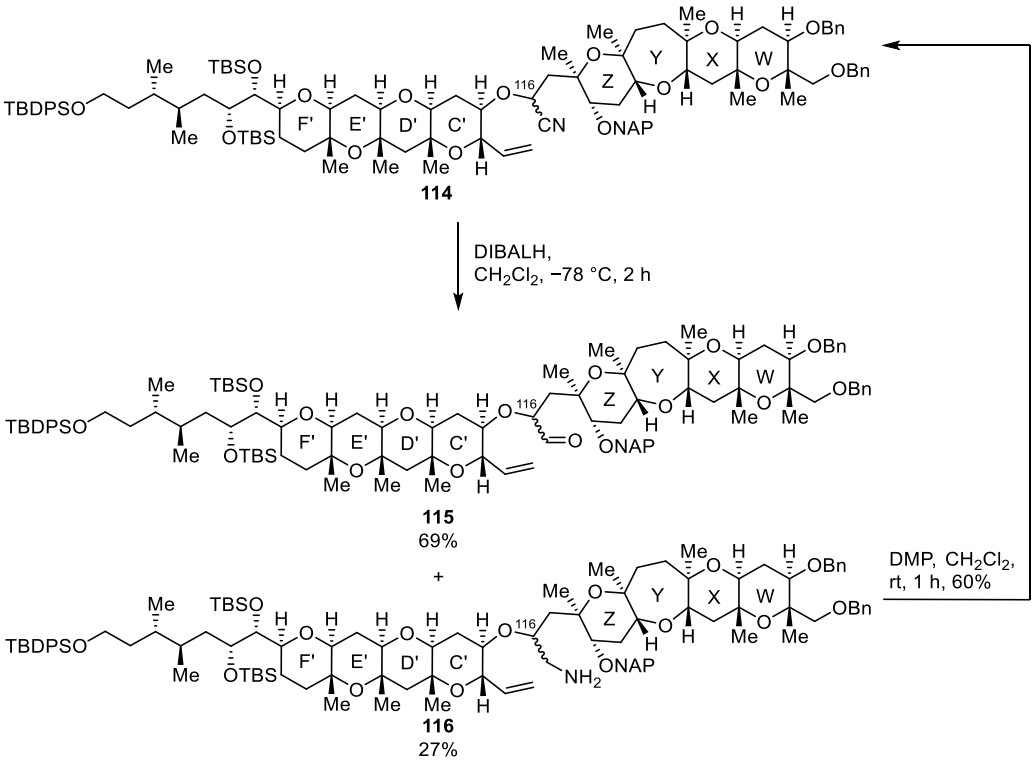
3-1. Synthesis of the WXYZA'B'C'D'E'F' ring segment of maitotoxin

Having synthesized the WXYZ and C'D'E'F' ring fragments, coupling of these fragments to obtain the WXYZA'B'C'D'E'F' ring segment was examined. Coupling of the C'D'E'F' ring diol **2** and the WXYZ ring aldehyde **3** commenced with acetal formation with $Sc(OTf)_3$[1] in toluene to afford seven-memberd ring acetal **111** as a mixture of diastereomers at C116 (Scheme 3-1-1). Regioselective cleavage of acetal **111** with TMSCN in the presence of $Sc(OTf)_3$ in dichloromethane followed by treatment with K_2CO_3 in methanol resulted in the formation of α-cyano ether **112** in 87% yield as a mixture of diastereomers at C116. The resulting primally alcohol **112** was converted to terminal olefin **114** by Grieco–Nishizawa protocol[2] in 76% yield for 2 steps. Namely, primary alcohol was treated with $2\text{-}NO_2C_6H_4SeCN$ in the presence of *n*-Bu_3P and MS4A in THF at room temperature for 25 min to furnish selenide **113**, which was subjected to oxidation with MCPBA in dichloroethane at room temperature for 15 min followed by *syn*-elimination of the resulting selenoxide in the presence of $NaHCO_3$ to give **114**.



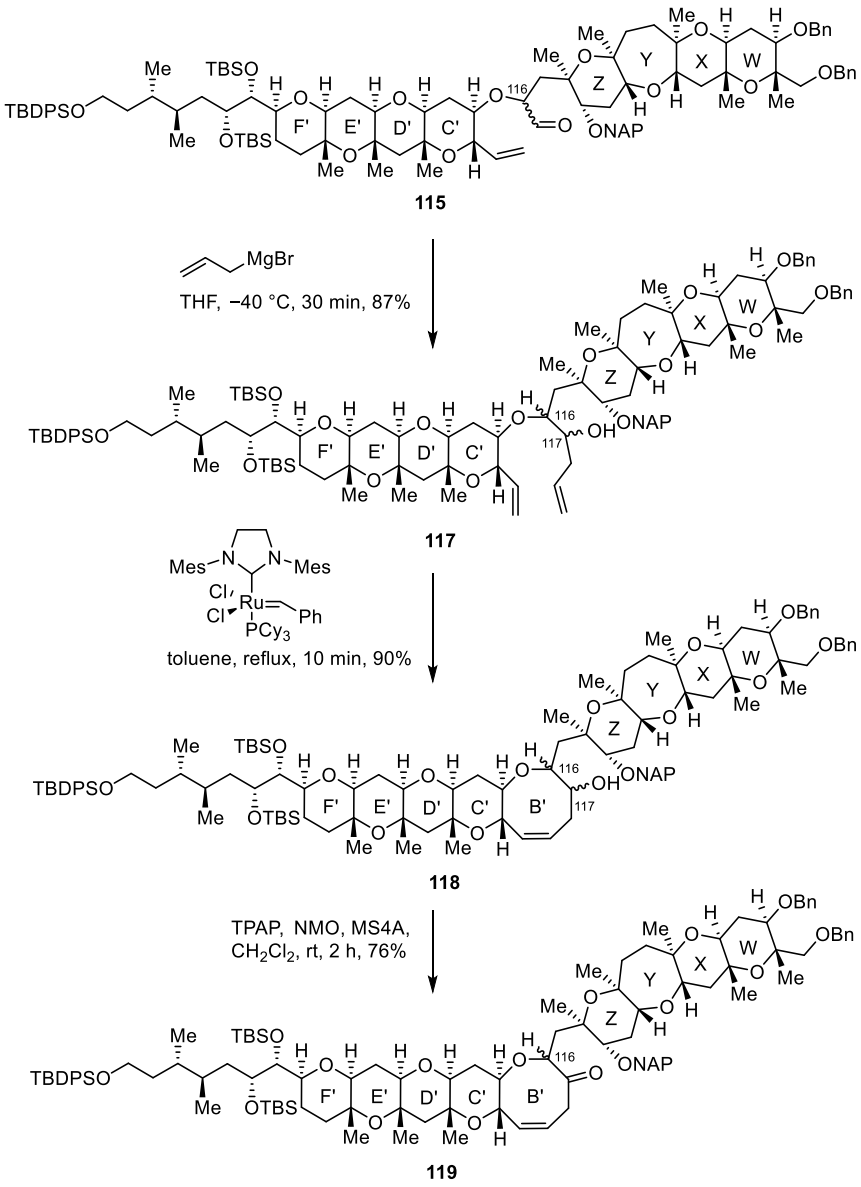
Scheme 3-1-1. Synthesis of α-cyano ether **114**.

Reduction of nitrile **114** with DIBALH gave aldehyde **115** in 69% yield with concomitant formation of primary amine **116** in 27% yield as a byproduct (Scheme 3-1-2). The primary amine **116** was recovered by treating with DMP to give nitrile **114** in 60% yield.[3]



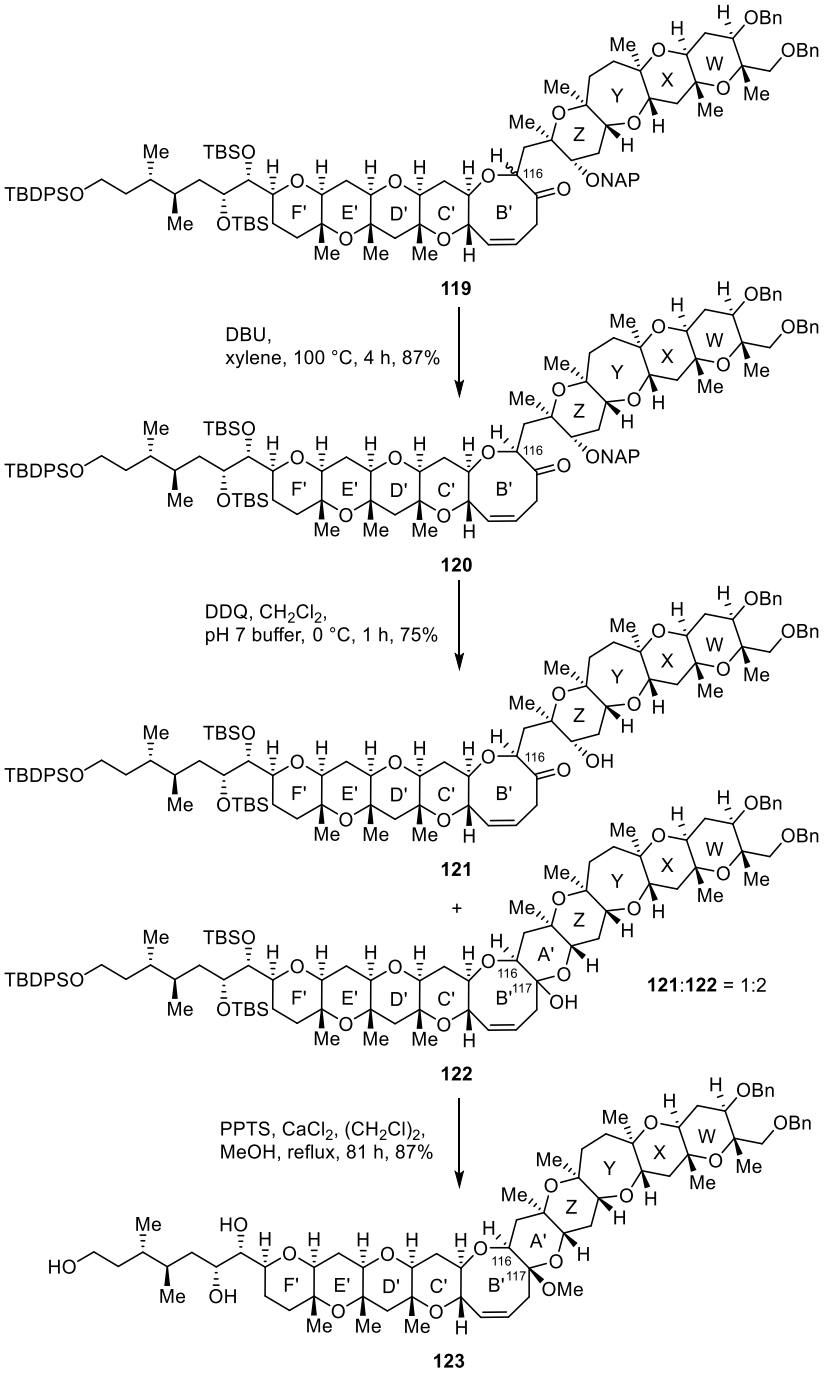
Scheme 3-1-2. Synthesis of aldehyde **115**.

The aldehyde **115** was reacted with allylmagnesium bromide to furnish alcohol **117** in 87% yield as a mixture of diastereomers with respect to C116 and C117 (Scheme 3-1-3). Ring-closing metathesis of the diene **117** with Grubbs second generation catalyst[4] afforded eight-membered cyclic ether **118** in 90% yield. TPAP oxidation[5] of the secondary alcohol **118** gave corresponding ketone **119** in 76% yield as a mixture of diastereomers at C116.



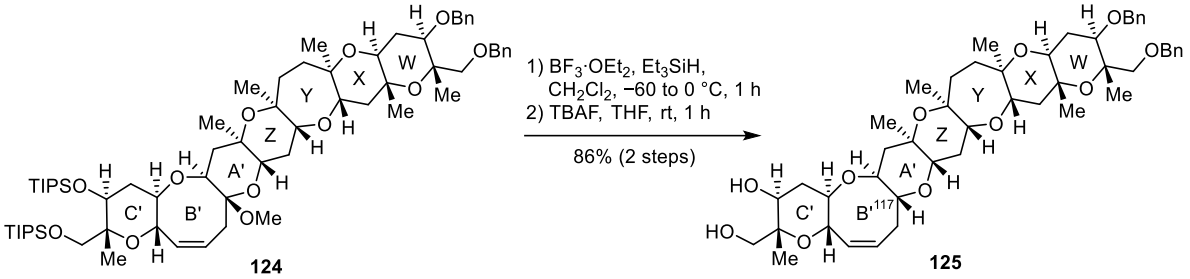
Scheme 3-1-3. Synthesis of eight-membered ring ketone **119**.

Epimerization of the ketone **119** by treating with DBU as a base in a sealed tube afforded eight-membered ring ketone **120** in 87% yield as a single isomer (Scheme 3-1-4).[6] Removal of the NAP group of **120** with DDQ gave a mixture of hydroxyketone **121** and corresponding hemiacetal **122** in 75% yield in a 1:2 ratio. This mixture was treated with PPTS in the presence of $CaCl_2$ in MeOH and 1,2-dichloroethane to furnish methyl acetal **123** in 87% yield, accompanied by unexpected concomitant removal of all silyl groups.

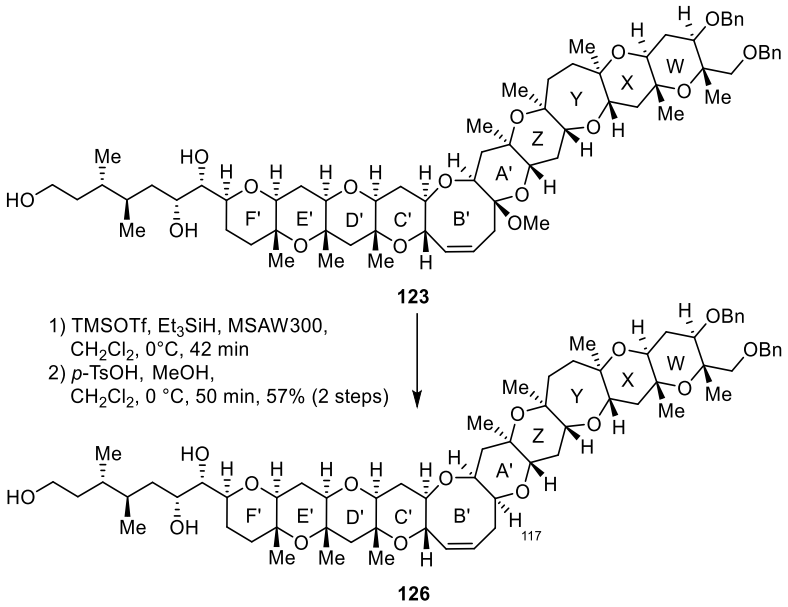


Scheme 3-1-4. Synthesis of methyl acetal **123**.

In the study reported by Oishi group,[7] synthesis of the WXYZA'B'C' ring system was successfully achieved by reductive etherification of methyl acetal **124** (Scheme 3-1-5). Treatment of **124** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ followed by removal of TIPS groups with TBAF furnished desired product **125** in 86% yield for 2 steps. Therefore, this method was applied to the synthesis of the WXYZA'B'C'D'E'F' ring system (Scheme 3-1-6).[8] However, reductive etherification of the methyl acetal **123** with Et_3SiH in the presence of TMSOTf followed by removal of TMS group with $TsOH{\cdot}H_2O$ resulted in the formation of undesired diastereomer **126** at C117 in 57% yield as a single isomer.

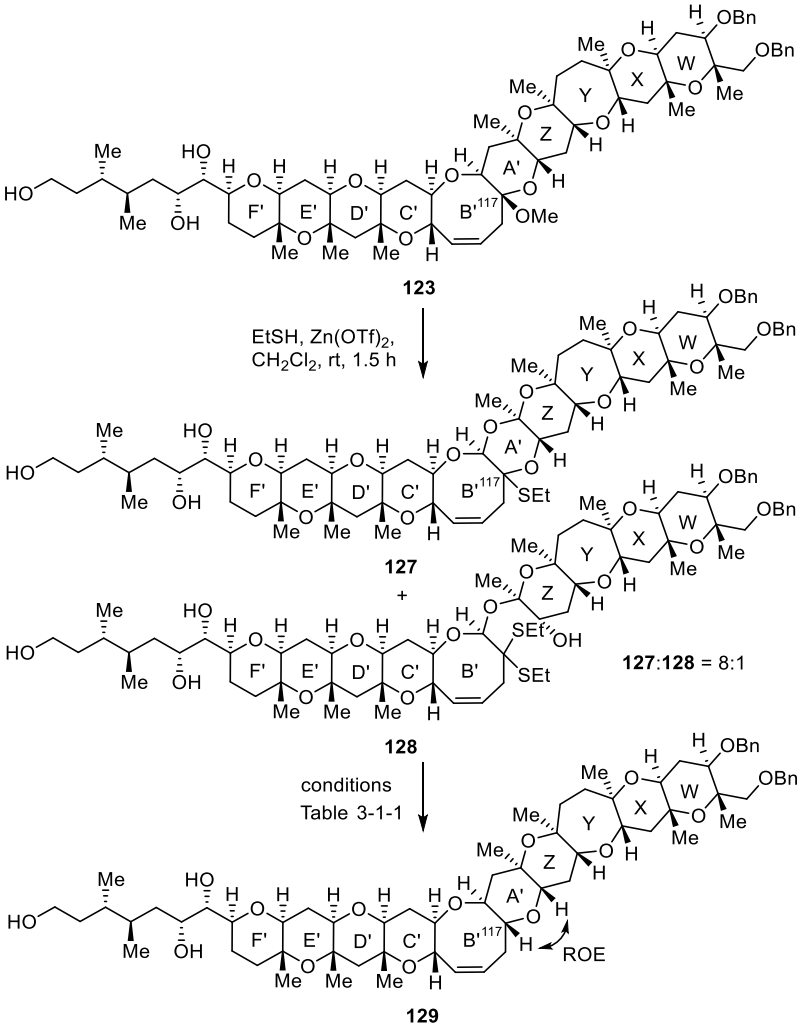


Scheme 3-1-5. Reductive etherification of methyl acetal **122** corresponding to the WXYZA'B'C' ring.



Scheme 3-1-6. Reductive etherification of methyl acetal **123** corresponding to the WXYZA'B'C' D'E'F' ring.

Therefore, reductive etherification under the radical conditions was examined. Treatment of the methyl acetal **123** with EtSH in the presence of $Zn(OTf)_2$ resulted in the formation of *O*,*S*-acetal **127** with concomitant formation of dithioacetal **128** as an inseparable mixture of **127** and **128** in a 8:1 ratio (Scheme 3-1-7). Although *O*,*S*-acetal **127** was treated with Ph_3SnH in the presence of AIBN as a radical initiator, no desired product was obtained but with unidentified byproducts in the previous study by Oishi group (Table 3-1-1, entry 1).[8] When, radical initiator and hydride were changed to VA-044 and $(TMS)_3SiH$,[9] respectively, the desired compound **129** was obtained in 41% yield for 2 steps in the previous study (entry 2). However, this procedure was turned out to be not reproducible in this study. Then, the reaction was caried out by using Et_3B and Ph_3SnH at room temperature (entry 3).[10] The desired product **129** was obtained in 48% yield for 2 steps. This reaction was repeated again 4 times to afford **129** with high reproducibility (41%, 38%, 52%, and 47% yield for 2 steps). Stereochemistry of **129** was determined by ROE experiments.



Scheme 3-1-7. Radical reduction of *O*,*S*-acetal **127** corresponding to the WXYZA'B'C'D'E'F' ring.

Table 3-1-1. Radical reduction of *O*,*S*-acetal **127**.

entry	radical initiator	hydride	temperature (°C)	time (h)	yield **129** (%)[a]
1[b]	AIBN	Ph_3SnH	110	2.3	-[c]
2[b]	VA-044	$(TMS)_3SiH$	70	0.6	41[d]
3	Et_3B	Ph_3SnH	rt	16	48

[a] Isolated yield for two steps. [b] Ref. 8. [c] Unidentified byproducts. [d] Not reproducible.

The difference of the diastereoselectivity in the construction of the A' ring is discussed as follows (Figure 3-1-1). In general, Lewis acid catalyzed reductive etherification proceeds through S_N1 mechanism via an oxocarbenium ion, and stereoelectronically favored axial attack of a hydride occurs. Therefore, in that case of the WXYZA'B'C' ring, the desired isomer was obtained (path B). On the other hand, in the case of the WXYZA'B'C'D'E'F' ring, formation of the oxocarbenium ion might be disfavored due to the ring strain enhanced by the existence of the triad angular methyl groups on the C'D'E' ring moiety. Therefore, it was envisaged that the reaction might proceed via not the oxocarbenium ion but a transition state in which methoxy group is activated by coordination of trimethylsilyl cation, and hydride attack might occur from the backside against the leaving group (path A).

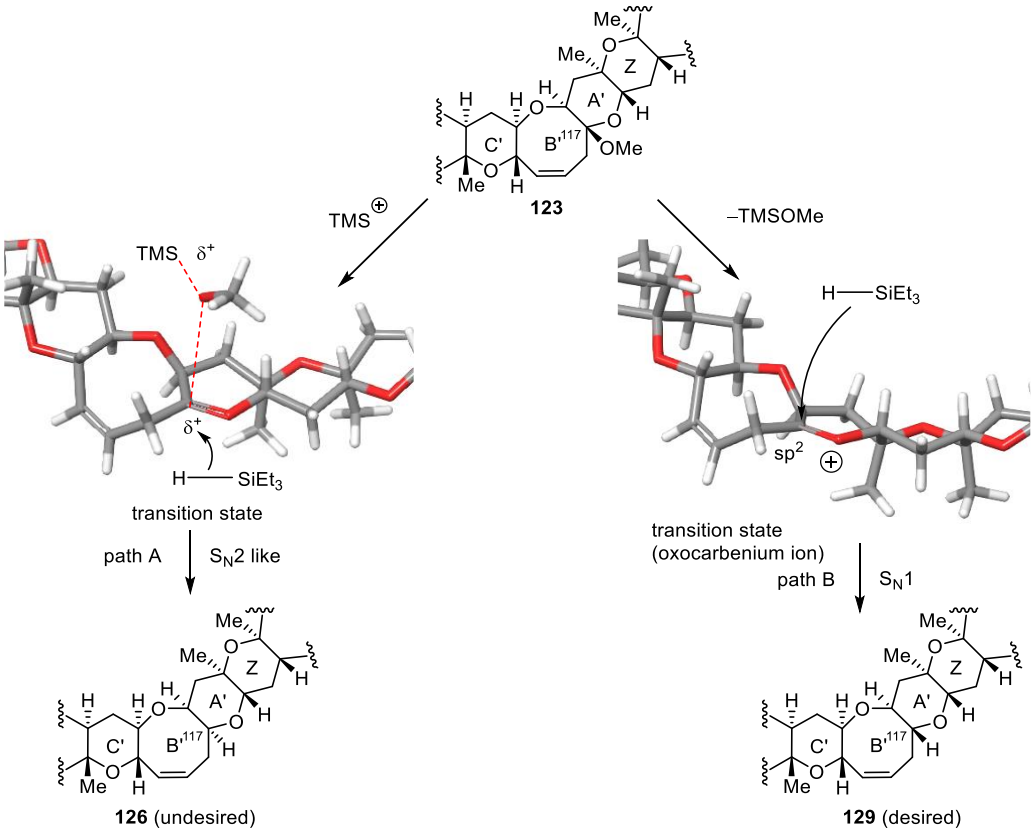


Figure 3-1-1. Plausible reaction mechanism of reductive etherification.

On the other hand, in the case of radical reduction of the *O*,*S*-acetal, abstraction of ethylthio radical resulted in the formation of an α-oxy radial, which might exist as sp^3 radical rather than sp^2 one due to the ring strain, and the hydride approached from the axial orientation in the chair conformation of the A' ring to afford the desired diastereomer (Figure 3-1-2).

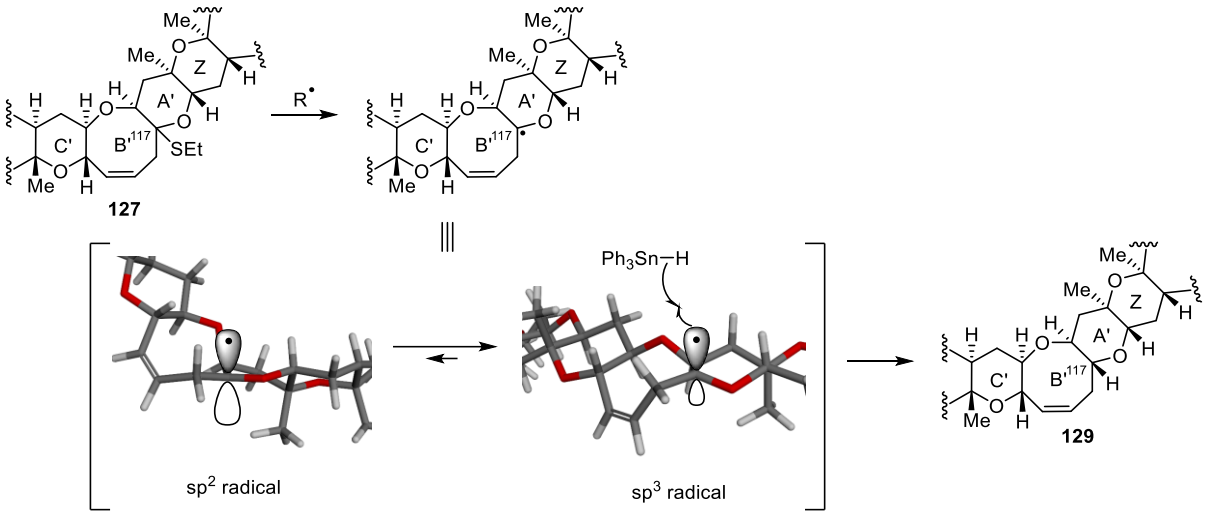
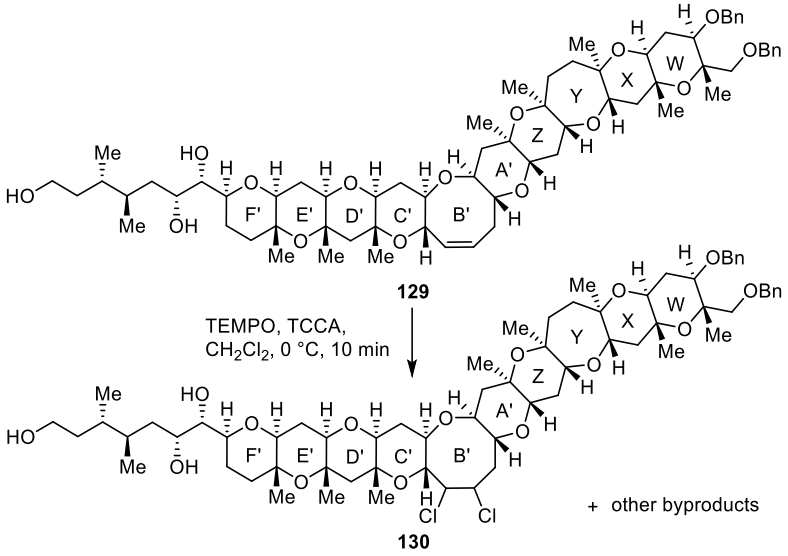


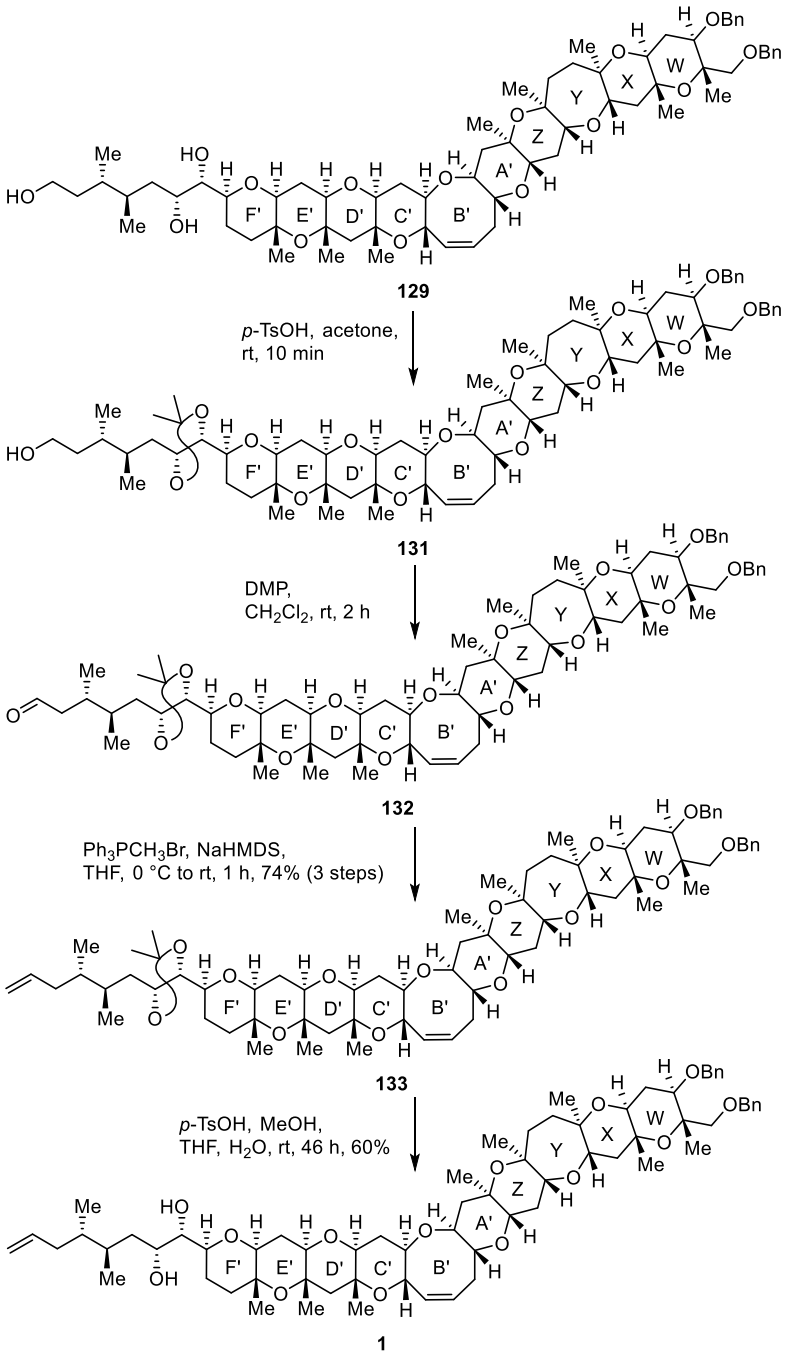
Figure 3-1-2. Plausible reaction mechanism of radical reduction.

The remaining task was the introduction of the terminal olefin in the F' ring side chain. An attempt to oxidize the primary alcohol of **129** selectively in the presence of the secondary alcohols with TEMPO and TCCA was unsuccessful to furnish complex mixture (Scheme 3-1-8).[11] Judging from MS analysis of the crude product, one of the byproduct was deduced to be dichloride **130** which would be formed via chlorination of the B' ring olefin.



Scheme 3-1-8. An attempt of selective oxidation of primary alcohol **129**.

Therefore, stepwise transformation via protection of the secondary alcohols was examined (Scheme 3-1-9). Protection of the 1,2-diol of **129** at C135 and C136 as acetonide **131** with *p*-TsOH in acetone, followed by Dess–Martin oxidation of the remaining primary alcohol **131** gave aldehyde **132**, which was subjected to Wittig olefination to furnish **133** in 74% yield for 3 steps. Finally, removal of the acetonide with *p*-TsOH in THF/MeOH/H_2O resulted in the formation of the WXYZA'B'C'D'E'F' ring segment **1** in 60% yield.



Scheme 3-1-9. Synthesis of the WXYZA'B'C'D'E'F' ring segment **1**.

The outline of this synthetic study is shown in Scheme 3-1-10. The synthesis of the WXYZA' B'C'D'E'F' ring segment **1** was successfully achieved in a highly convergent manner from the C'D'E'F' ring diol **2** and the WXYZ ring aldehyde **3** in 16 steps. The C'D'E'F' ring was synthesized from the C'D'E' ring olefin **44** and side chain iodoolefin **64** in 8 steps through the construction of the F' ring. The WXYZ ring was prepared from the W ring aldehyde **83** and the Z ring terminal alkyne **87** through the construction of the XY ring. The W, Z, and C'D'E' rings were obtained from the common tetrahydropyran derivative **4** in 8, 2, and 21 steps, respectively. The common tetrahydropyran derivative **4** was synthesized in 8 steps from 2-deoxy-D-ribose **8** and stabilized ylide **7**, prepared from ethyl 2-bromopropionate **5**. The side chain **64** was prepared from aldehyde **53** and phosphate **54** in 10 steps, which were synthesized from commercially available diol **45** in 7 steps and oxazolidinone **56** in 2 steps, respectively. The longest linier sequence (LLS) from commercially available starting materials is 53 steps, with 104 total steps (TS).

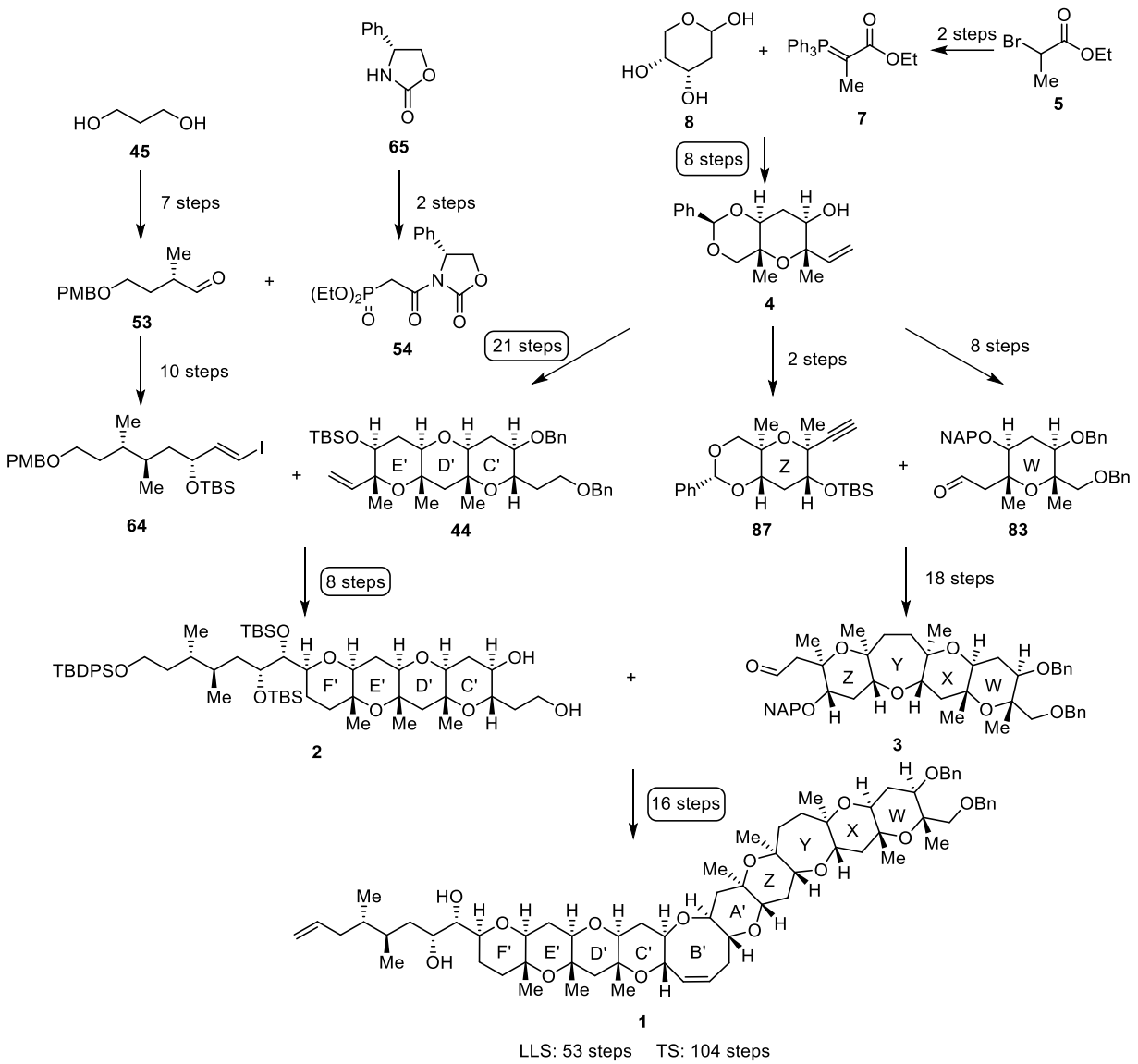


Figure 3-1-10. Longest liner sequence and total steps in the synthesis of the WXYZA'B'C'D'E'F' ring **1**.

3-2. Comparison of NMR data

^{1}H and ^{13}C NMR data of the WXYZA'B'C'D'E'F' ring segment **1** was compared with those of MTX as shown in Table 3-2-1 and Table 3-2-2, respectively. From the left column, position, chemical shifts δ of MTX, δ of **1**, and $\Delta\delta$ = δ (MTX) − δ (**1**) are indicated. The deference of ^{1}H and ^{13}C NMR chemical shifts were graphically depicted in Figure 3-2-1 and Figure 3-2-2, respectirely. The x- and y- axes represent proton or carbon number and $\Delta\delta$ values, respectively. The ^{1}H and ^{13}C NMR chemical shifts for **1** were in good accordance with those for MTX, supporting the proposed structure, but those at the W ring terminus deviated due to the structural difference from MTX.

Table 3-2-1. Differences in ^{1}H NMR (600 MHz, C_5D_5N/CD_3OD) chemical shifts between MTX and the synthetic WXYZA'B'C'D'E'F' ring segment.

position	MTX/ppm[b]	**1**/ppm[a]	$\Delta\delta_H$/ppm	position	MTX/ppm[b]	**1**/ppm[a]	$\Delta\delta_H$/ppm
99	3.31	3.38	−0.07	122	3.33	3.31	0.02
99	3.31	3.30	0.01	123ax	1.65	1.66	−0.01
155	1.33	1.19	0.14	123eq	2.09	2.10	−0.01
101	3.85	3.91	−0.06	124	3.22	3.22	0.00
102ax	1.78	1.67	0.11	160	1.22	1.23	−0.01
102eq	1.90	2.11	−0.21	126ax	1.62	1.62	0.00
103	3.40	3.42	−0.02	126eq	1.97	1.98	−0.01
156	1.32	1.37	−0.05	161	1.33	1.34	−0.01
105ax	1.62	1.71	−0.09	128	3.33	3.33	0.00
105eq	1.93	1.98	−0.05	129ax	1.83	1.84	−0.01
106	3.58	3.60	−0.02	129eq	1.95	1.95	0.00
157	1.28	1.24	0.04	130	3.23	3.24	−0.01
108a	1.77	1.77	0.00	162	1.29	1.30	−0.01
108b	1.94	1.96	−0.02	132ax	1.50[c]	1.48	0.02
109a	1.77	1.77	0.00	132eq	1.74[c]	1.72	0.02
109b	1.89	1.94	−0.05	133ax	1.64	1.65	−0.01
158	1.27	1.27	0.00	133eq	1.92	1.93	−0.01
111	3.43	3.44	−0.01	134	3.77	3.77	0.00
112ax	1.76	1.78	−0.02	135	3.36	3.35	0.01
112eq	1.88	1.90	−0.02	136	3.85	3.84	0.01
113	3.09	3.10	−0.01	137	1.25	1.25	0.00
159	1.15	1.16	−0.01	137	1.76	1.76	0.00
115ax	1.43	1.44	−0.01	138	1.85	1.85	0.00
115eq	2.09	2.09	0.00	163	0.85	0.86	−0.01
116	3.66	3.67	−0.01	139	1.39	1.40	−0.01
117	3.40	3.40	0.00	164	0.76	0.75	0.01
118a	2.30	2.31	−0.01	140	1.73	1.76	−0.03
118b	2.77	2.78	−0.01	140	2.07	2.08	−0.01
119	5.64	5.64	0.00	141	5.70	5.70	0.00
120	5.75	5.75	0.00	142a	4.88	4.88	0.00
121	4.35	4.35	0.00	142b	4.91	4.91	0.00

[a] These data were measured in CD_3OD/C_5D_5N (1:1) at room temperature (25 °C) using Shigemi MMS-005J microcell. CD_2HOD and CD_3OD were taken as a standard peak at δ 3.31.

[b] These chemical shifts of ^1H NMR of MTX was described in previous report.[12]

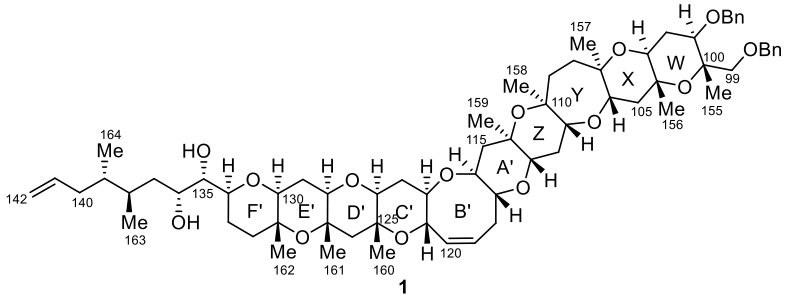
[c] These chemical shifts of H-132ax and H-132eq were revied.[13]

Table 3-2-2. Differences in ^{13}C NMR (150 MHz, C_5D_5N/CD_3OD) chemical shifts between MTX and the synthetic WXYZA'B'C'D'E'F' ring segment.

position	MTX/ppm[b]	**1**/ppm[a]	$\Delta\delta_C$/ppm	position	MTX/ppm[b]	**1**/ppm[a]	$\Delta\delta_C$/ppm
99	87.8	77.1	10.7	121	72.1	72.3	−0.2
100	78.8	78.8	0.0	122	80.3	80.3	0.0
155	19.5	21.7	−2.2	123	33.4	33.4	0.0
101	74.7	77.7	−3.0	124	84.1	84.1	0.0
102	31.0	28.0	3.0	125	73.5	73.5	0.0
103	72.6	72.5	0.1	160	18.3	18.2	0.1
104	74.6	74.7	−0.1	126	54.0	54.0	0.0
156	20.2	20.3	−0.1	127	75.6	75.5	0.1
105	42.8	42.9	−0.1	161	22.2	22.2	0.0
106	84.6	84.6	0.0	128	86.9	86.9	0.0
107	79.6	79.7	−0.1	129	28.9	28.8	0.1
157	18.3	18.3	0.0	130	84.2	84.3	0.0
108	39.1	39.2	0.0	131	74.8	74.8	0.0
109	40.4	40.4	0.0	162	22.0	21.9	0.1
110	79.6	79.1	0.5	132	39.4	39.4	0.0
158	23.5	23.5	0.0	133	26.5	26.5	0.0
111	87.7	87.7	0.0	134	81.6	81.6	0.0
112	30.3	30.4	−0.1	135	77.7	77.7	0.0
113	83.8	83.8	0.0	136	70.2	70.3	−0.1
114	74.1	74.1	0.0	137	37.8	37.7	0.1
159	21.7	21.6	0.1	138	34.1	34.0	−0.1
115	46.7	46.8	−0.1	163	16.7	16.7	0.0
116	76.6	76.9	−0.3	139	39.4	39.4	0.0
117	84.7	84.7	0.0	164	16.5	16.4	0.1
118	31.5	31.5	0.0	140	38.8	38.8	0.0
119	126.8	126.8	0.0	141	139.3	139.3	0.0
120	135.9	136.5	−0.6	142	115.8	115.8	0.0

[a] These data were measured in CD_3OD/C_5D_5N (1:1) at room temperature (25 °C) using Shigemi MMS-005J microcell. CD_2HOD and CD_3OD were taken as a standard peak at δ 48.94.

[b] These chemical shifts of ^{13}C NMR of MTX was described in previous report.[13]



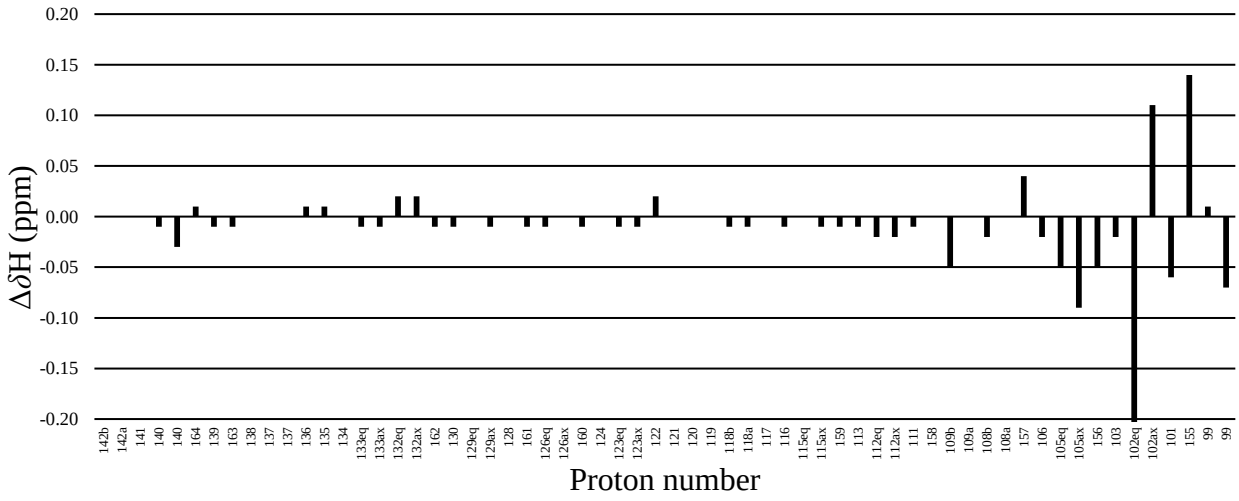


Figure 3-2-1. Comparison of the ^{1}H NMR (600 MHz, C_5D_5N/CD_3OD) data.

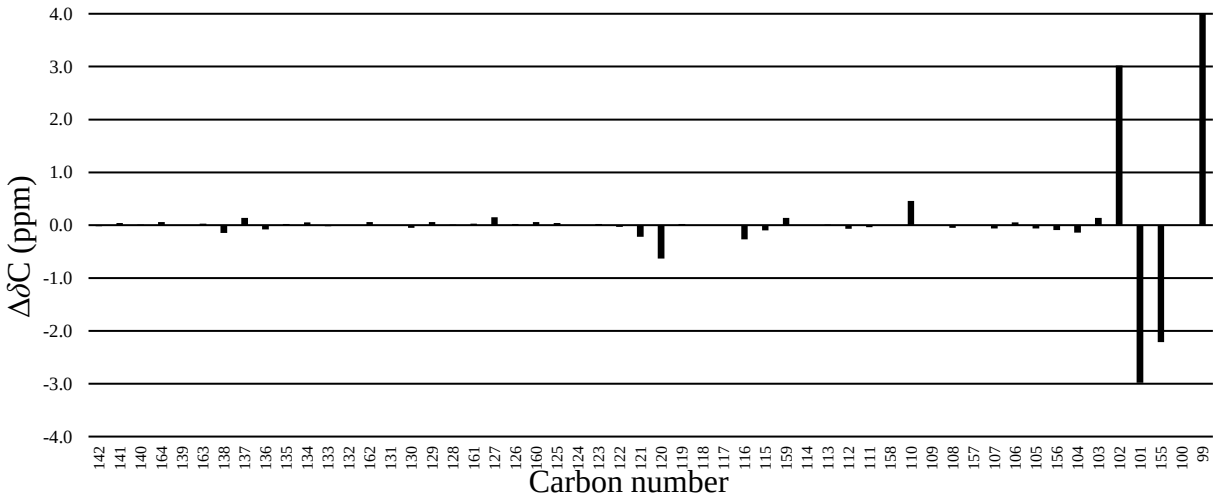


Figure 3-2-2. Comparison of the ^{13}C NMR (150 MHz, C_5D_5N/CD_3OD) data.

3-3. Evaluation of biological activity

Having synthesized the WXYZA'B'C'D'E'F' ring segment **1**, the biological activity was evaluated. As already reported by Oishi group in collaboration with Konoki group, the WXYZA'B'C' ring and the C'D'E'F' ring elicited inhibitory activity against the MTX-induced Ca^{2+} influx with IC_{50} values of 30 μM and 59 μM, respectively (Figure 3-3-1). Therefore, it was expected that the WXYZA'B'C'D'E'F' ring possessing both the WXYZA'B'C' ring and the C'D'E'F' ring moieties and larger molecular size would elicit more potent inhibitory activity. Contrary to the expectation, the WXYZA' B'C'D'E'F' ring fragment **1** did not inhibit the Ca^{2+} influx activity induced by MTX at 50 μM. Although the reason was not clarified yet, one on the reasons would be its poor solubility in aqueous media.

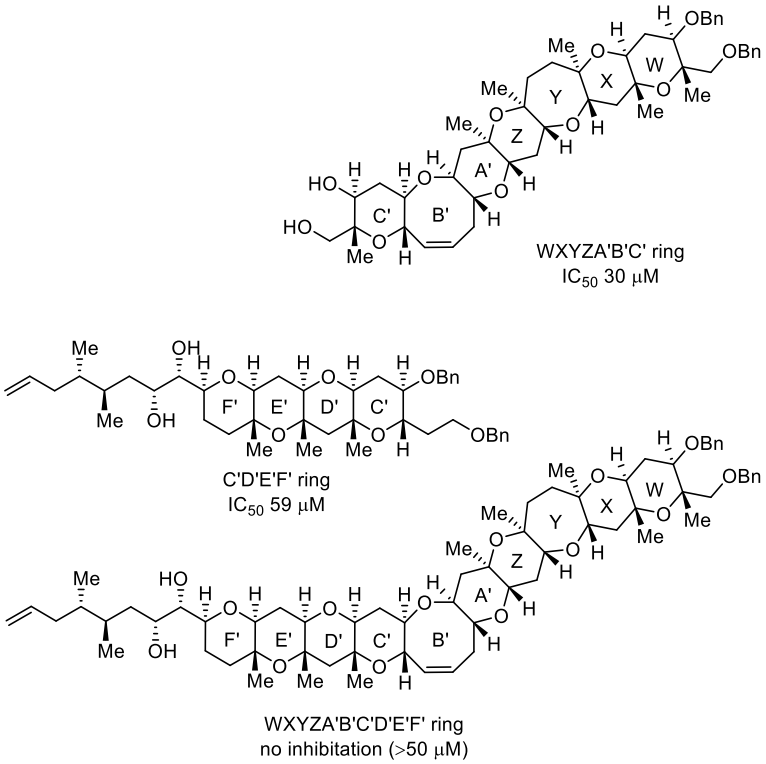


Figure 3-3-1. Evaluation of inhibitory activity against MTX-induced Ca^{2+} influx by synthetic fragment of MTX.

References

1. a) S. Fukuzawa, T. Tsuchimoto, T. Hotaka, T. Hiyama, *Synlett* **1995**, 1077. b) K. Ishihara, Y. Karumi, M. Kubota, H. Yamamoto, *Synlett* **1996**, 839. c) M. Inoue, M. Sasaki, K. Tachibana, *Angew. Chem. Int. Ed.* **1998**, *37*, 965.
2. P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485.
3. K. C. Nicolaou, C. J. N. Mathison, *Angew. Chem. Int. Ed.* **2005**, *44*, 5992.
4. M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
5. S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
6. K. Watanabe, M. Suzuki, M. Murata, T. Oishi, *Tetrahedron Lett.* **2005**, *46*, 3991.
7. T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 3599.
8. H. Onoue, *Doctor Thesis*, Kyushu university (2018).
9. H. Fujioka, Y. Ohba, K. Nakahara, M. Takatsuji, K. Murai, M. Ito, Y. Kita, *Org. Lett.* **2007**, *9*, 5605.
10. K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547.
11. a) L. D. Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041. b) W. Li, A. Silipo, A. Molinaro, B. Yu, *Chem. Commun.* **2015**, *51*, 6964.
12. M. Murata, H. Naoki, S. Matsunaga, M. Satake, T. Yasumoto, *J. Am. Chem. Soc.* **1994**, *116*, 7098.
13. M. Satake, S. Ishida, T. Yasumoto, M. Murata, H. Utsumi, T. Hinomoto, *J. Am. Chem. Soc.* **1995**, *117*, 7019.

Chapter 4. Conclusion

In conclusion, convergent synthesis of the WXYZA'B'C'D'E'F' ring segment of MTX was achieved. The common tetrahydropyran derivative was synthesized from 2-deoxy-D-ribose in large scale, in which microflow reactor was effectively utilized for synthesizing the intermediate. A solution of the keto ester (85 g) in THF and a solution of methylmagnesium bromide in THF were transmitted to the microflow reactor (Comet X-01) by using syringe pumps at room temperature, followed by mixed with a solution of DIBALH in toluene in the next microflow reactor at room temperature to obtain the diol in comparable yield in the case of batch reaction. The intermediate was converted to the tetrahydropyran derivative in large scale which was the common intermediate for the E', W, and Z rings. The C'D'E' ring was prepared from the common tetrahydropyran derivative corresponding to the E' ring. The C' and D' rings were constructed by SmI_2 mediated reductive cyclization. On the other hand, the side chain of the F' ring was synthesized from 1,3-propanediol via Katsuki–Sharpless asymmetric epoxidation, diastereoselective Michael addition, and Noyori asymmetric hydrogen transfer reaction. Suzuki–Miyaura cross coupling of the C'D'E' ring and the side chain, followed by Pd catalyzed cyclization for the construction of the F' ring gave the C'D'E'F' ring fragment. The WXYZ ring fragment was synthesized from the W ring aldehyde and the Z ring alkyne via acetylide–aldehyde coupling. Dehydrative cyclization and ring expansion was utilized to construct the Y ring. Methylation of *O*,*S*-acetal to construct the X ring afforded the WXYZ ring fragment. Having the C'D'E'F' and WXYZ ring fragments in hand, the convergent method via two-rings construction, α-cyano ether method developed in our laboratory, was applied to synthesize the WXYZA'B'C'D'E'F' ring. The WXYZ ring aldehyde and the C'D'E'F' ring diol were combined via the α-cyano ether method through the construction of the B' ring via ring-closing metathesis and that of the A' ring via *O*,*S*-acetal formation followed by radical reduction. Introduction of the terminal olefin in the side chain culminated in the convergent synthesis of the WXYZA'B'C'D'E'F' ring segment. The longest linear sequence was 53 steps, and the total number of steps was 104 steps. Comparison of the NMR data of the synthetic specimen with those of MTX resulted in confirmation of the proposed structure corresponding moiety. The WXYZA'B'C'D'E'F' ring segment did not inhibit the Ca^{2+} influx activity induced by MTX at 50 μM.

Experimental Section

General methods for organic syntheses

All reactions sensitive to air or moisture were performed under argon atmosphere with dry glassware unless otherwise noted. The dehydrated solvents, CH_2Cl_2, tetrahydrofuran (THF), toluene, *N*,*N*-dimethylformamide (DMF) were used without further dehydration. Ti(O*i*-Pr)$_4$, D-(−)-DET, TBSOTf, TESCl, Et_3N, benzaldehyde and 2,6-lutidine were distilled before use. $Sc(OTf)_3$, $Zn(OTf)_2$, $CaCl_2$, and molecular sieves 4A (MS4A) were preactivated by heating in vacuo. All other chemicals were obtained from local venders and used as supplied unless otherwise stated. Dess–Martin periodinane[1] and Ohira–Bestmann reagent were prepared according to the literature. Thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F_{254}, 0.25 mm thickness) for the reaction analyses. For normal phase column chromatography, silica gel 60N (Kanto Chemical Co., Ltd., spherical, neutral, 100–210 μm) was used. For normal phase flash column chromatography, silica gel 60N (Kanto Chemical Co., Ltd., spherical, neutral, 40–50 μm) was used.

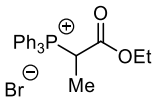
Instruments

Optical rotations were recorded on a JASCO P-1010 polarimeter. IR spectra were recorded on FT/IR equipment. ^{1}H NMR spectra were recorded at JNM ECA-600 or JNM ECS-400 facilities (JEOL) in 600 or 400 MHz, and ^{13}C NMR spectra were recorded at 150 or 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane (TMS) with reference to internal residual solvent [^{1}H NMR: $CHCl_3$ (7.26), C_6D_5H (7.16); ^{13}C NMR: $CDCl_3$ (77.16), C_6D_6 (128.06)]. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet. High resolution mass spectra were recorded on ESI-TOF equipment.

Chapter 2. Large scale synthesis of building blocks

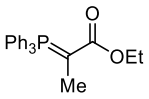
2-1. Synthesis of the common tetrahydropyran derivative

The spectroscopic date of **4**, **9**–**11**, and **19**–**23** were identical to those in the literature.[2]



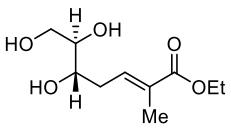
6

Phosphonium salt 6. Ethyl-2-bromopropionate **5** (120 mL, 1.00 mol) was added to a solution of PPh_3 (250 g, 0.953 mol) in acetone (477 mL) at room temperature. After stirring at reflux for 15 h, the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (160 mL) and poured into Et_2O (1.0 L) with rapidly stirring (330 rpm). The resulting precipitate was filtered, washed with cold Et_2O and dried under reduced pressure to give phosphonium salt **6** as a white solid (363 g, 86%).



7

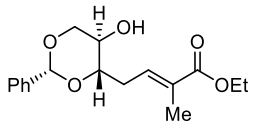
Phosphorus ylide 7. The solution of phosphonium salt **6** (363 g, 0.819 mol) in CH_2Cl_2 (327 mL) was added dropwise to the solution of NaOH (36.0 g, 0.819 mol) in H_2O (655 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated to 1/3 of original volume under reduced pressure. The suspension was poured into Et_2O. The resulting precipitate was filtered, washed with cold Et_2O and dried under reduced pressure to give phosphonium ylide **7** as a pale yellow solid (216 g, 73%).



9

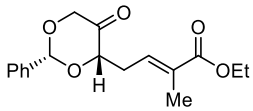
Triol 9. The phosphonium ylide **7** (216.2 g, 0.596 mol) was added to a solution of 2-deoxy-D-ribose (66.6 g, 0.496 mol) in dry THF (400 mL). After stirring at reflux for 2 h, the

reaction mixture was concentrated under reduced pressure. The crude material was used for the next reaction without further purification.



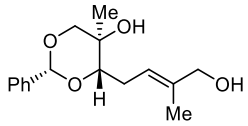
10

Benzylidene acetal 10. PhCHO (61.2 mL, 0.600 mol), $CH(OMe)_3$ (71.5 mL, 0.600 mol), and CSA (40.3 g, 0.173 mol) were added to a solution of crude **9** in dry CH_2Cl_2 (450 mL). After stirring at room temperature for 26 h, the reaction mixture was quenched with Et_3N at 0 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1→1/5) to give **10** (87.2 g, 0.284 mol, 57% for 2 steps) as a colorless solid.



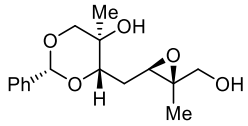
11

Ketone 11. AZADOL (59.4 mg, 0.388 mmol) and aqueous KBr (0.5 M, 38.8 mL, 19.4 mmol) were added to a solution of alcohol **10** (119.1 g, 0.388 mol) in CH_2Cl_2 (880 mL) at 0 °C, and then a mixture of $NaClO{\cdot}5H_2O$ (95.7 g, 0.582 mol) and saturated aqueous solution of $NaHCO_3$ (970 mL) was added dropwise to the reaction mixture 0 °C. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ at 0 °C, and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used for the next reaction without further purification.



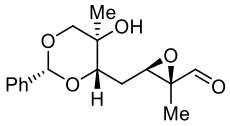
19

Diol 19. A solution of ketone **11** in THF (0.6 M) and a solution of MeMgBr in THF (1.0 M) were introduced to micromixer (Comet X-01) directly connected in series by using a syringe pump at a flow rate of 1.0 mL/min at room temperature through a Teflon tube (ϕ1.0 mm × 0.5 m), respectively. After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture and DIBALH in toluene (1.0 M) were introduced to micromixer at room temperature through a Teflon tube (ϕ1.0 mm × 0.5 m). The flow rate of DIBALH in toluene was 1.5 mL/min. After passing through a Teflon tube (ϕ1.0 mm × 3.0 m), the reaction mixture was poured into a mixture of Et_2O and saturated aqueous Na^+,K^+ tartrate at 0 °C with stirring. After stirring for 16 h, the reaction mixture was extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to give alcohol **19** (63.7 g, 0.288 mol, 83%) as a colorless sticky oil.



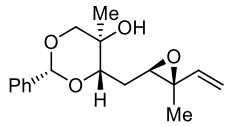
21

Epoxide 21. The solution of Oxone (82.0 g, 0.133 mol, in 288 mL of 0.4 mM aq EDTA·2Na) and 1.47 M aq KOH (305 mL, 0.448 mol) were slowly added to a solution of diol **19** (32.1 g, 0.115 mol) and Shi's ketone (7.15 g, 27.7 mmol) in DMM (575 mL), MeCN (288 mL), and pH 9.3 aq K_2CO_3–AcOH buffer (575 mL) at −10 °C from separate dropping funnels over a period of 3 h. After stirring at −10 °C for 4 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ at −10 °C, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used for the next reaction without further purification. Two time operation of the above procedure furnished 60.0 g of crude epoxide.



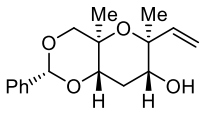
22

Aldehyde 22. TEMPO (900 mg, 5.75 mmol) and aqueous KBr (0.5 M, 23.0 mL, 11.5 mmol) were added to a solution of crude alcohol **21** (33.6 g) in CH_2Cl_2 (383 mL) at 0 °C, and then a mixture of $NaClO{\cdot}5H_2O$ (20.8 g, 0.126 mol) and saturated aqueous solution of $NaHCO_3$ (61.3 mL) was added dropwise to the reaction mixture at 0 °C. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ at 0 °C, and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used for the next reaction without further purification. The crude material was used for the next reaction without further purification. Two time operation of the above procedure furnished 55.5 g of crude aldehyde.



23

Olefin 23. *t*-BuOK (85% purity, 60.4 g, 0.457 mol) was added to a suspension of methyltriphenyl-phosphonium bromide (171 g, 0.479 mol) in dry THF (872 mL) at 0 °C. After stirring at 0 °C for 30 min, the solution of the crude aldehyde (55.5 g) in dry THF (335 mL) was added to the reaction mixture via cannula. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 5/1 to 3/1) to give olefin **23** (24.3 g, 83.5 mmol, 38% for 3 steps) as a colorless solid.

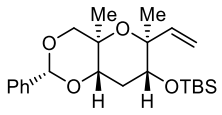


4

THP ring 4. CSA (923 mg, 8.97 mmol) was added to a solution of olefin **23** (23.1 g, 79.5 mmol) in toluene (795 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with Et_3N at 0 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 to 3/1) to give **4** (19.0 g, 65.2 mmol, 82%) as a colorless solid.

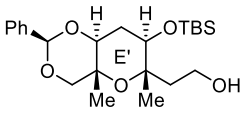
2-2. Synthesis of the C'D'E'F' ring fragment

The spectroscopic date of **24**–**75** were identical to those in the literature.[3]



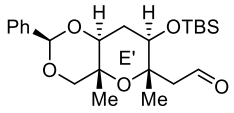
24

TBS ether 24. TBSCl (28.3 g, 188 mmol) and imidazole (25.5 g, 376 mmol) were added to the solution of alcohol **4** (18.2 g, 62.6 mmol) in DMF (63 mL). After stirring at room temperature for 18 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with hexane. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 1/0 to 20/1) to give TBS ether **24** (20.8 g, 51.2 mmol, 82%) as a colorless solid.



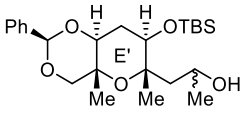
25

Alcohol 25. 2-Methyl-2-butene (11.8 mL, 110 mmol) was added to a solution of $BH_3 \cdot SMe_2$ (5.2 mL, 54.5 mmol) in dry THF (106 mL) at 0 °C. After stirring at room temperature for 1 h, a solution of olefin **24** (16.6 g, 41.0 mmol) in dry THF (15 mL+5.0 mL × three rinses) was added via cannula to the reaction mixture at 0 °C. After stirring at room temperature for 1 h, a solution of NaOH (3 M in H_2O, 82.0 mL, 246 mmol) and H_2O_2 (35% in H_2O, 40.0 mL, 410 mmol) was added to the reaction mixture. After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 2/1) to give alcohol **25** (15.7 g, 37.2 mmol, 91%) as a colorless solid.



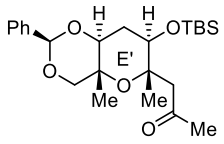
26

Aldehyde 26. TEMPO (58.1 mg, 0.732 mmol) and KBr (0.5 M in H_2O, 7.4 mL, 3.72 mmol) were added to a solution of alcohol **25** (15.7 g, 37.2 mmol) in CH_2Cl_2 (74 mL) at 0 °C, and then a mixture of a solution of $NaOCl{\cdot}5H_2O$ (6.70 g, 40.9 mmol) and saturated aqueous solution of $NaHCO_3$ (53 mL) was added dropwise to the reaction mixture over 20 min. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde (15.3 g) as a pale brown amorphous sold. The crude material was used directly in the next reaction without further purification.



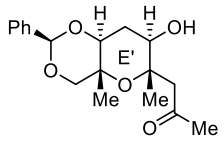
27

Alcohol 27. A solution of MeMgBr (1 M in THF, 45.0 mL, 45.0 mmol) was added dropwise to a solution of crude aldehyde **26** in dry THF (93 mL) at 0 °C over 10 min. After stirring at room temperature for 20 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) to give alcohol **27** (11.8 g, 27.0 mmol, 72% yield for 2 steps, diastereomeric mixture) as a colorless amorphous sold.



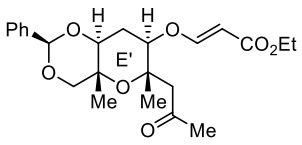
28

Ketone 28. AZADO (41.2 mg, 0.269 mmol) and KBr (0.5 M in H_2O, 5.3 mL, 2.7 mmol) were added to a solution of the alcohol **27** (11.8 g, 26.9 mmol) in CH_2Cl_2 (54 mL) at 0 °C, and then a mixture of a solution of $NaOCl{\cdot}5H_2O$ (7.96 g, 43.4 mmol) and saturated aqueous solution of $NaHCO_3$ (38 mL) was added dropwise to the reaction mixture over 5 min. After stirring at 0 °C for 25 min, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 20/1) to give ketone **28** (9.79 g, 22.5 mmol, 84%) as a colorless solid.



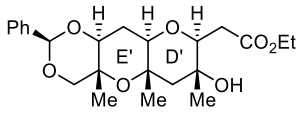
29

Alcohol 29. A solution of TBAF (1.0 M in THF, 34.0 mL, 34.0 mmol) was added to a solution of TBS ether **28** (9.79 g, 22.5 mmol) in dry THF (113 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 1/1) to give alcohol **29** (5.43 g, 16.9 mmol, 75%) as colorless amorphous sold and recovery of TBS ether **28** (1.33 g, 3.05 mmol, 14%).



30

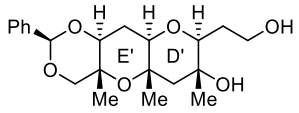
β-Alkoxyacrylate 30. NMM (6.03 mL, 54.9 mmol) and ethyl propiolate (2.79 mL, 27.4 mmol) were added to a solution of alcohol **29** (5.86 g, 18.3 mmol) in dry CH_2Cl_2 (92 mL) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1 to 2/1) to give β-alkoxyacrylate **30** (7.48 g, 17.9 mmol, 98%) as yellow amorphous sold.



31

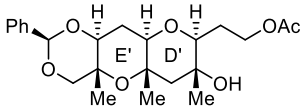
Preparation of SmI_2 in THF solution. CH_2I_2 (2.81 mL, 35.0 mmol) was added to a suspension of Sm (6.84 g, 45.5 mmol) in dry THF (350 mL) at 0 °C. After stirring at room temperature for 3 h, the suspension was turned to deep blue solution. This solution was used directly the next reaction.

D'E' Ring 31. A solution of freshly prepared SmI_2 (302 mL) was added to a solution of β-alkoxyacrylate **30** (5.33 g, 12.7 mmol) in dry THF (127 mL) and dry MeOH (1.90 mL, 47.0 mmol) at 0 °C via cannula. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous solution of $Na_2S_2O_3$ and saturated aqueous solution of $NaHCO_3$, and the resulting cake was removed by filtration through a pad of Hyflo Super-Cel. The filtrate was concentrated to a half volume under reduced pressure and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude D'E' ring **31** (5.42 g) as colorless solid. The crude material was used directly in the next reaction without further purification.



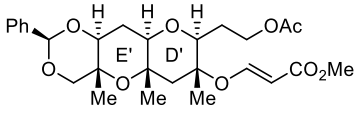
32

Diol 32. The solution of crude material of **31** (5.42 g) in dry THF (18 mL) was added to the solution of $LiAlH_4$ (626.5 mg, 16.5 mmol) in dry THF (80 mL) at −15 °C via cannula. After stirring at −15 °C for 30 min, the reaction mixture was quenched with H_2O (0.6 mL) and solution of NaOH (3 M in H_2O, 0.6 mL). The reaction mixture was allowed to warm to room temperature, and H_2O (1.8 mL) was added to the mixture. The resulting cake was removed by filtration through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure to give crude diol **32** (5.16 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



33

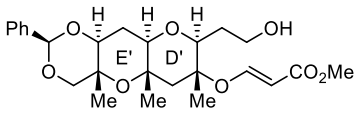
Acetate 33. Ac_2O (16.4 mL, 174 mmol) was added to a solution of the crude of diol **32** (6.84 g, ca. 17.4 mmol) in pyridine (79.2 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1 M aqueous solution of HCl, saturated aqueous solution of $NaHCO_3$, and saturated aqueous solution of NaCl sequentially, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization (hexane/ethyl acetate = 5/1). The mother liquid was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/2) to give acetate **33** (5.92 g, 14.0 mmol, 81% yield for 3 steps) as colorless solid.



34

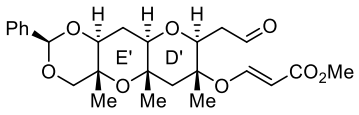
β-alkoxyacrylate 34. Methyl propiolate (0.62 mL, 7.6 mmol) was added dropwise to a mixture of tertiary alcohol **33** (1.07 g, 2.54 mmol) and a solution of Me_3P (1.0 M, 12.2 mL, 12.2 mmol)

in THF at room temperature by using a syringe pump at a flow rate of 0.1 mL/min. After stirring at room temperature for 10 min, Methyl propiolate (0.62 mL, 7.6 mmol) was added dropwise to a mixture of the reaction mixture by using a syringe pump at a flow rate of 0.1 mL/min. After stirring at room temperature for 10 min, Methyl propiolate (0.62 mL, 7.6 mmol) was added dropwise to a mixture of the reaction mixture by using a syringe pump at a flow rate of 0.1 mL/min. After stirring at room temperature for 40 min, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 1/1) to give β-alkoxyacrylate **34** (1.23 g, 2.43 mmol, 96%) as colorless solid.



35

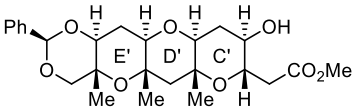
Alcohol 35. K_2CO_3 (769 mg, 5.56 mmol) was added to a solution of acetate **34** (7.02 g, 13.9 mmol) in MeOH (139 mL) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude alcohol **35** (6.81 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



36

Aldehyde 36. Dry DMSO (7.9 mL, 111 mmol), Et_3N (12 mL, 83.4 mmol), and SO_3·py (6.63 g, 41.7 mmol) were added sequentially to a solution of crude alcohol **35** (6.81 g) in dry CH_2Cl_2 (116 mL) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and

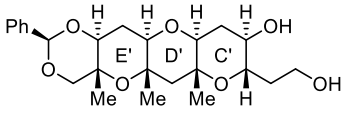
concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1) to give aldehyde **36** (5.55 g, 12.1 mmol, 87% for 2 steps) as colorless solid.



37

Preparation of SmI_2 in THF solution. CH_2I_2 (3.20 mL, 40.0 mmol) was added to a suspension of Sm (7.82 g, 52.0 mmol) in dry THF (400 mL) at 0 °C. After stirring at room temperature for 3 h, the suspension was turned to deep blue solution. This solution was used directly the next reaction.

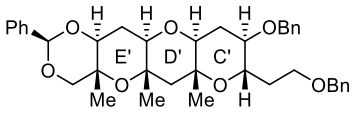
C'D'E' Ring 37. A solution of freshly prepared SmI_2 (264 mL) was added to a solution of β-alkoxyacrylate **36** (5.55 g, 12.1 mmol) in dry THF (120 mL) and dry MeOH (1.8 mL, 44.6 mmol) at 0 °C via cannula. After stirring at 0 °C for 50 min, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous solution of $Na_2S_2O_3$ and saturated aqueous solution of $NaHCO_3$, and the resulting cake was removed by filtration through a pad of Hyflo Super-Cel. The filtrate was concentrated to a half volume under reduced pressure and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude C'D'E' ring **37** (5.99 g) as colorless solid. The crude material was used directly in the next reaction without further purification.



38

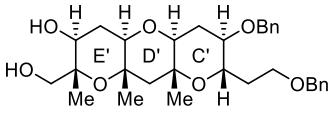
Diol 38. The solution of crude material of **37** (5.99 g) in dry THF (13 mL) was added to the solution of $LiAlH_4$ (594.4 mg, 15.6 mmol) in dry THF (80 mL) at −10 °C via cannula. After being stirred at −10 °C for 2 h, the reaction mixture was quenched with H_2O (0.6 mL) and solution of NaOH (3 M in H_2O, 0.6 mL). The reaction mixture was allowed to warm to room temperature, and H_2O (1.8 mL) was added to the reaction mixture. The resulting cake was removed by filtration through a pad of Hyflo Super-Cel. The filtrate was concentrated under

reduced pressure to give crude diol **38** (4.91 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



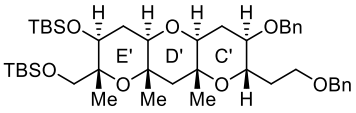
39

Benzyl ether 39. NaH (60% in mineral oil, 1.45 g, 36.2 mmol) and BnBr (3.6 mL, 30.1 mmol) were added to a solution of crude diol **38** (4.91 g) in DMF (24 mL) at 0 °C. After stirring at room temperature for 5.5 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated under reduced pressure to give crude benzyl ether **39** (8.03 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



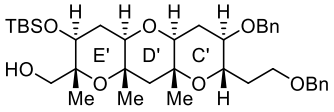
40

Diol 40. CSA (776 mg, 2.41 mmol) was added to a solution of crude benzyl ether **39** (8.03 g) in THF (80 mL) and MeOH (40 mL) at 0 °C. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/2) to give diol **40** (4.81 g, 9.13 mmol, 76% for 4 steps) as colorless amorphous sold.



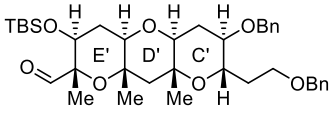
41

TBS ether 41. TBSOTf (5.5 mL, 23.7 mmol) and 2,6-lutidine (5.5 mL, 47.5 mmol) were added to a solution of the diol **40** (4.18 g, 9.13 mmol) in dry CH_2Cl_2 (46 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of $KHSO_4$ and saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude TBS ether **41** (7.24 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



42

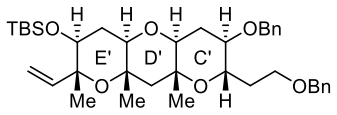
Alcohol 42. CSA (2.54 g, 11.0 mmol) was added to a solution of crude TBS ether **40** in CH_2Cl_2 (60 mL) and MeOH (30 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 14/1 to 2/1) to give alcohol **42** (5.02 g, 7.83 mmol, 86% yield for 2 steps) as colorless amorphous sold.



43

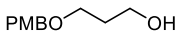
Aldehyde 43. TEMPO (218 mg, 1.38 mmol) and KBr (0.5 M in H_2O, 1.38 mL, 0.694 mmol) were added to a solution of alcohol **42** (4.45 g, 6.94 mmol) in CH_2Cl_2 (13.8 mL) at 0 °C, and then a mixture of a solution of $NaOCl{\cdot}5H_2O$ (1.26 g, 7.63 mmol) and saturated aqueous solution of $NaHCO_3$ (10.0 mL) was added dropwise to the reaction mixture over 10 min. After

stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde (4.66 g) as a pale brown amorphous sold. The crude material was used directly in the next reaction without further purification.



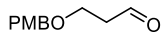
44

Olefin 44. A solution of Tebbe reagent (0.5 M in toluene, 20.8 mL, 10.4 mmol) was added dropwise to a solution of the crude aldehyde **43** in dry THF (116 mL) at 0 °C. After stirring at 0 °C for 20 min, the reaction mixture was diluted with Et_2O and quenched with a solution of NaOH (1.5 M in H_2O, 7.3 mL). After stirring for 1 h, and the resulting cake was removed by filtration through a pad of Hyflo Super-Cel. The filtrate was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to (hexane/ethyl acetate = 1/0 to 7/1) give olefin **44** (4.02 g, 6.32 mmol, 91% for 2 steps) as pale brown amorphous sold.



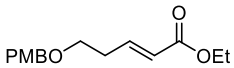
46

Alcohol 46. KOH (7.37 g, 131 mmol) and PMBCl (8.90 mL, 65.7 mmol) were added to a solution of 1,3-propanediol **45** (10.0 g, 131 mmol) in DMSO (44.0 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with 6 M aqueous solution of HCl and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude PMB ether **46** (10.62 g) as colorless sticky oil. The crude material was used directly in the next reaction without further purification.



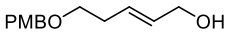
47

Aldehyde 47. TEMPO (1.04 g, 6.69 mmol) and KBr (0.5 M in H_2O, 26.7 mL, 13.4 mmol) were added to a solution of crude alcohol **46** (27.3 g) in CH_2Cl_2 (267 mL) at 0 °C, and then a mixture of a solution of $NaOCl{\cdot}5H_2O$ (24.2 g, 147 mmol) and saturated aqueous solution of $NaHCO_3$ (191 mL) was added dropwise to the reaction mixture over 20 min. After stirring at 0 °C for 3 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde **47** (25.4 g) as a pale brown sticky oil. The crude material was used directly in the next reaction without further purification.



49

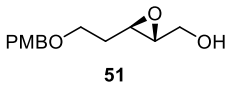
α,β-Unsaturated ester 49. Ethyl diethylphosphonoacetate **48** (31.3 mL, 156.7 mmol) was added to the suspension of NaH (60% in mineral oil, 5.74 g, 143 mmol) in dry THF (200 mL) at 0 °C. After stirring at 0 °C for 30 min, the solution of crude aldehyde **47** (25.4 g) and dry THF (60 mL) was added to a suspension. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give α,β-unsaturated ester **49** (27.4 g, 96.3 mmol, 74% yield for 3 steps) as colorless liquid.



50

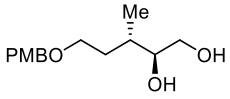
Alcohol 50. DIBALH (1.0 M in toluene, 212 mL, 212 mmol) was added to a solution of α,β-unsaturated ester **49** (27.4 g, 96.3 mol) in dry CH_2Cl_2 (240 mL) at −78 °C. After stirring at −78 °C for 2 h, the resulting solution was quenched with MeOH and saturated aqueous solution

of Rochelle's salt. After stirring at room temperature for 16 h, the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 1/1to 1/5) to give alcohol **50** (19.7 g, 88.5 mmol, 94%) as a as colorless oil.



51

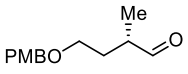
Epoxide 51. D-(−)-DET (5.66 mL, 33.2 mmol) and Ti(O*i*Pr)$_4$ (7.56 mL, 25.6 mmol) were added to a mixture of powdered MS4A (10.0 g) in dry CH_2Cl_2 (100 mL) at −25 °C. After stirring for 30 min, a solution of allylic alcohol **50** (28.4 g, 128 mmol) in dry CH_2Cl_2 (60 mL) was added to the mixture. After stirring for 30 min, TBHP (4.5 M in CH_2Cl_2, 56.7 mL, 256 mmol) was added to the mixture. After stirring at −20 °C for 12 h, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ and stirred at room temperature for 1 h. The precipitates were removed by filtration through a Hyflo pad. The organic layer was separated, and the aqueous solution was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 1/1 to 1/5) to give epoxide **51** (24.8 g, 104 mmol, 82%) as a colorless oil.



52

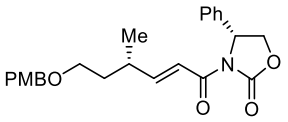
Diol 52. Me_3Al (1.0 M in hexane, 240 mL, 240 mmol) was added to a solution of epoxide **51** (13.0 g, 54.6 mol) in dry CH_2Cl_2 (273 mL) at 0 °C. After stirring at room temperature for 13 h, the reaction mixture was diluted with Et_2O (240 mL) and quenched with water (9.6 mL). After stirring at room temperature for 30 min, 4 M aqueous solution of NaOH (9.6 mL) and water (9.6 mL) were added to the mixture. After stirring at room temperature for 1 h, the resulting solution was dried over anhydrous $MgSO_4$. After stirring at room temperature for 1 h, the resulting mixture was filtrated by through a pad of Hyflo Super-Cel. The filtrate was

concentrated under reduced pressure to give crude diol **52** (11.9 g) as colorless oil. Two times operation of the above procedure furnished 20.33 g of crude diol. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 1/1 to 1/5) to give diol **52** (17.7 g, 69.4 mmol, 70%) as a colorless oil.



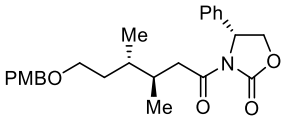
53

Aldehyde 53. A solution of diol **52** (13.4 g, 52.7 mmol) in THF (30 mL + 5.0 mL × three rinses) was added to a solution of $NaIO_4$ (13.5 g, 63.2 mmol) in THF (20 mL) and H_2O (30 mL) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was diluted with EtOAc and quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde **53** (12.0 g) as pale yellow oil. The crude material was used directly in the next reaction without further purification.



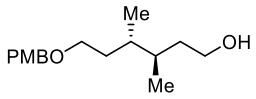
55

Olefin 55. A solution of NaHMDS (1.0 M in THF, 90 mL, 90.0 mmol) was added dropwise to a solution of phosphonate **54** (36.0 g, 105 mmol) in dry THF (500 mL) over 10 min at 0 °C. After stirring for 30 min, the mixture was cooled to 0 °C, and a solution of crude aldehyde **53** (12.0 g) in dry THF (20 mL + 3.0 mL × three rinses) was added via cannula. After stirring at room temperature for 10 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ ethyl acetate = 5/1 to 3/1) to give olefin **55** (16.1 g, 39.2 mmol, 74% yield for 2 steps) as yellow oil.



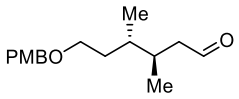
56

Amide 56. A solution of MeMgBr (1.0 M in THF, 141 mL, 141 mmol) was added dropwise to a solution of $CuBr{\cdot}SMe_2$ (20.1 g, 98.0 mmol) in dry THF (200 mL) and dry Me_2S (120 mL) over 10 min at −78 °C. After stirring at −78 °C for 20 min, the mixture was allowed to warm to 0 °C. After stirring for 20 min, the mixture was cooled to −78 °C. The mixture was added to a solution of olefin **55** (16.1 g, 39.2 mmol) in dry THF (200 mL) and dry CH_2Cl_2 (140 mL) at −78 °C via cannula over 5 min, and then the reaction mixture was allowed to warm to −30 °C over 2 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/1 to 1/1) to give amide **56** (15.9 g, 37.3 mmol, 95%) as colorless solid.



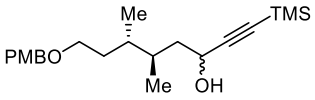
57

Alcohol 57. $LiBH_4$ (1.34 g, 61.4 mmol) and dry MeOH (2.5 mL, 61.4 mmol) were added to a solution of amide **56** (21.8 g, 51.2 mmol) in dry Et_2O (510 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with a solution of NaOH (3.0 M in H_2O). After stirring at room temperature for 30 min, the reaction mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) to give alcohol **57** (9.22 g, 34.6 mmol, 68%) as pale yellow oil.



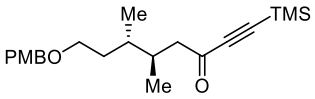
58

Aldehyde 58. TEMPO (108 mg, 0.690 mmol) and KBr (0.5 M in H_2O, 6.9 mL, 3.47 mmol) were added to a solution of alcohol **57** (9.22 g, 34.6 mmol) in CH_2Cl_2 (70 mL) at 0 °C, and then a mixture of a solution of $NaOCl{\cdot}5H_2O$ (6.30 g, 38.1 mmol) and saturated aqueous solution of $NaHCO_3$ (50 mL) was added dropwise to the reaction mixture over 20 min. After stirring at 0 °C for 40 min, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde **57** (9.28 g) as a pale yellow oil. The crude material was used directly in the next reaction without further purification.



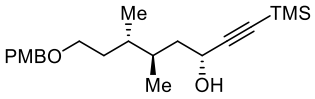
59

Alcohol 59. A solution of *n*-BuLi (1.6 M in hexane, 32.4 mL, 51.9 mmol) was added to a solution of trimethylsilylacetylene (9.1 mL, 6.36 mmol) in dry THF (150 mL) at 0 °C. After stirring for 40 min at 0 °C, the mixture was cooled to −70 °C, and a solution of the crude aldehyde **58** (9.28 g) in dry THF (20 mL + 3.0 mL x 3 rinse) was added via cannula over 5 min. After stirring at −78 °C for 25 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1 to 3/1) to give alcohol **59** (11.3 g, 31.2 mmol, 90% yield for 2 steps) as pale yellow oil.



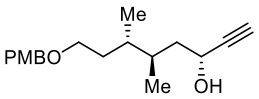
60

Ketone 60. MnO_2 (113 g, 1000 wt%) was added to a solution of the alcohol **59** (11.3 g, 31.2 mmol) in dry CH_2Cl_2 (210 mL) at room temperature. After stirring at room temperature for 14 h, the reaction mixture was filtered through a pad of Hyflo Super-Cel, and the filtrate was concentrated under reduced pressure to give crude ketone **60** (10.9 g) as a pale yellow oil. The crude material was used directly in the next reaction without further purification.



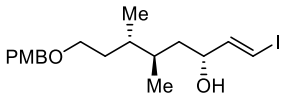
61

Alcohol 61. Ru[(*R*,*R*)-Tsdpen](*p*-cymene) (723 mg, 1.20 mmol) was added to a solution of crude ketone **60** (10.9 g) in *i*-PrOH (200 mL) at 0 °C. After stirring at room temperature for 1.5 h, the reaction mixture was concentrated under reduced pressure to give crude alcohol **61** (13.1 g) as a pale yellow oil. The crude material was used directly in the next reaction without further purification.



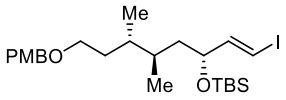
62

Terminal alkyne 62. K_2CO_3 (833 mg, 6.03 mmol) was added to a solution of crude alcohol **61** (13.1 g) in MeOH (100 mL) at 0 °C. After stirring at room temperature for 10 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1 to 5/1) to give terminal alkyne **62** (7.65 g, 26.3 mmol, 84% for 3 steps) as pale yellow oil.



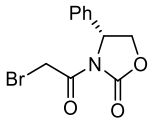
63

Iodoolefin 63. A solution of DIBALH (1.0 M in toluene, 9.2 mL, 9.2 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (2.79 g, 9.57 mmol) in dry THF (30 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of terminal alkyne **62** (1.16 g, 3.99 mmol) in dry THF (10 mL + 1.0 mL × 2 rinse) was added via cannula to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 40 min, the reaction mixture was cooled to −78 °C, and then a solution I_2 in THF (11 mL, 11 mmol) was added to the reaction mixture at −78 °C over 5 min; the reaction mixture was allowed to warm to 0 °C. After stirring at 0 °C for 50 min, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and sodium potassium tartrate, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 18 h, the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10/1 to 2/1) to give iodoolefin **63** (1.20 g, 2.87 mmol, 72%) as a brown oil.



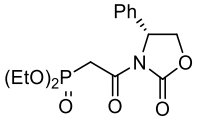
64

TBS ether 64. 2,6-Lutidine (1.5 mL, 13.2 mmol) and TBSOTf (1.5 mL, 6.59 mmol) were added sequentially to a solution of alcohol **63** (2.30 g, 5.49 mmol) in dry CH_2Cl_2 (55 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed sequentially with saturated aqueous solution of $KHSO_4$ and saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 50/1 to 14/1) to give TBS ether **64** (2.86 g, 5.37 mmol, 98%) as a pale yellow oil.



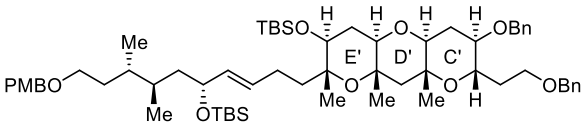
67

Oxazolidinone 67. The solution of *n*-BuLi (1.6 M in hexane, 84 mL, 0.135 mol) was added to a solution of (*R*)-(−)-4-phenyl-2-oxazolidinone **65** (20.0 g, 0.123 mol) in dry THF (200 mL) at −78 °C for 20 min. After stirring at room temperature for 40 min, the reaction mixture was cooled to −78 °C and the solution of bromoacetyl chloride (15.3 mL, 0.183 mol) in dry THF (50 mL) was added to the mixture. After stirring at room temperature for 40 min, the reaction mixture was quenched with pH 7 buffer and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) and recrystallized from EtOAc-hexane to give oxazolidinone **67** (24.3 g, 85.6 mmol, 70%) as color less solid.



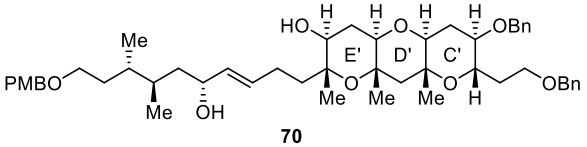
54

Phosphonate 54. $P(OEt)_3$ (87 mL, 0.504 mol) was added to oxazolidinone **67** (44.7 g, 0.157 mol) at room temperature. After stirring at 60 °C for 16 h, the reaction mixture cooled to room temperature. The mixture was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/3) to give phosphonate **54** (53.8 g, 0.158 mol, quant) as pale yellow oil.



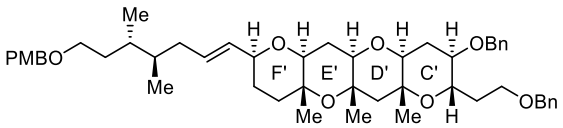
69

Olefin 69. The solution of olefin **44** (1.20 g, 1.88 mmol) in degassed THF (6.0 mL) was added to a suspension of 9-BBN dimer (1.14 g, 4.67 mmol) in degassed THF (6.0 mL) at 0 °C via cannula. After stirring at room temperature for 1.5 h, degassed H_2O (0.50 mL, 28.0 mmol) was added to the reaction mixture at 0 °C. After stirring at room temperature for 25 min, the reaction mixture was added to a suspension of $PdCl_2(dppf)\cdot CH_2Cl_2$ (246 mg, 0.300 mmol) and K_3PO_4 (1.33 g, 6.26 mmol) in degassed DMF (12.0 mL) via cannula at 35 °C, and rinse with degassed THF (6.0 mL). The solution of iodoolefin **64** (1.23 g, 2.31 mmol) in degassed DMF (4.0 mL + 2.0 mL rinse) was added to the reaction mixture via cannula at 35 °C. After stirring at 35 °C for 5 h, the reaction mixture was quenched with $NaBO_3\cdot 4H_2O$ (4.80 g, 31.0 mmol) and H_2O (5 mL) at room temperature. After stirring at room temperature for 10 h, saturated aqueous solution of $Na_2S_2O_3$ was added to the reaction mixture. After stirring at room temperature for 3 h, the mixture was extracted with a 4:1 mixture of hexane and EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1 to 5/1) to give olefin **69** (1.72 g, 1.64 mmol, 88%) as yellow amorphous sold.



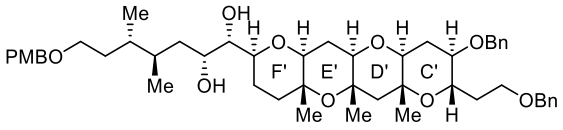
70

Diol 70. A solution of TBAF (1.0 M in THF, 12.5 mL, 12.5 mmol) was added dropwise to a solution TBS ether **69** (6.01 g, 5.20 mmol) in dry THF (52 mL) at room temperature. After stirring under reflux for 13 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl at room temperature and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/2) to give diol **70** (3.83 g, 4.69 mmol, 90%) as pale brown amorphous sold.



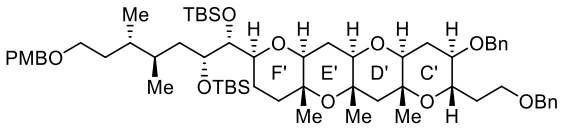
71

Olefin 71. $PdCl_2(MeCN)_2$ (365 mg, 1.40 mmol) was added to a solution of diol **70** (3.83 g, 4.69 mmol) in dry THF (47 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) to give olefin **71** (3.39 g, 4.25 mmol, 91%) as colorless amorphous sold.



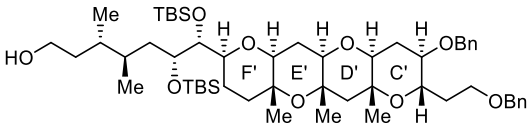
72

Diol 72. A mixture of $K_2OsO_4 \cdot 2H_2O$ (156.7 mg, 0.425 mmol), $(DHQD)_2AQN$ (802 mg, 0.940 mmol), $K_3[Fe(CN)_6]$ (4.20 g, 12.8 mmol), K_2CO_3 (1.76 g, 12.8 mmol), and $MeSO_2NH_2$ (1.21 g, 12.8 mmol) in *t*-BuOH (21 mL) and H_2O (21 mL) was stirred at room temperature for 30 min and then *t*-BuOMe (12 mL) was added to this suspension. A solution of olefin **71** (3.39 g, 4.25 mmol) in *t*-BuOMe (17 mL + 2.0 mL × three rinses) was added to this suspension at 0 °C. After stirring at 0 °C for 14 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and allowed to warm to room temperature. After stirring at room temperature for 5 h, the mixture was extracted with EtOAc. The organic layer was washed with 1 M aqueous solution of HCl and saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude diol **72** (3.53 g) as a pale yellow amorphous sold. The crude material was used directly in the next reaction without further purification.



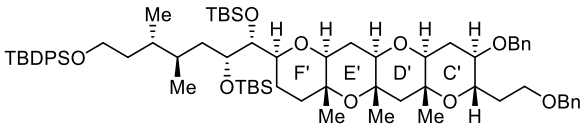
73

TBS ether 73. 2,6-Lutidine (2.5 mL, 21.7 mmol) and TBSOTf (2.5 mL, 10.8 mmol) were added sequentially to a solution of crude diol **72** (4.00 g, ca. 4.93 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed sequentially with 1 M aqueous solution of HCl and saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude TBS ether **73** (5.23 g) as a pale yellow amorphous sold. The crude material was used directly in the next reaction without further purification.



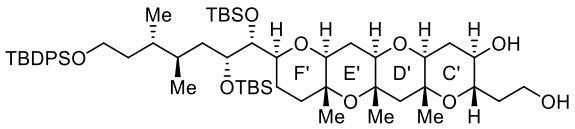
74

Alcohol 74. DDQ (2.23 g, 9.86 mmol) was added to a solution of crude PMB ether **73** (5.23 g) in CH_2Cl_2 (99 mL) and pH 7.0 buffer (33 mL) at 0 °C. After stirring at room temperature for 50 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and saturated aqueous solution of $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude alcohol **74** (5.19 g) as a pale yellow amorphous sold. The crude material was used directly in the next reaction without further purification.



75

TBDPS ether 75. Imidazole (1.00 g, 14.8 mmol) and TBDPSCl (1.53 mL, 5.92 mmol) were added to a solution of crude alcohol **74** (5.19 g) in DMF (16 mL) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude TBDPS ether **75** (6.63 g) as a pale yellow amorphous sold. The crude material was used directly in the next reaction without further purification.



2

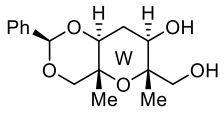
Diol 2. $Pd(OH)_2/C$ (580 mg, 10 wt%) was added to a solution of the crude benzyl ether **71** (6.63 g) in THF (99 mL) at room temperature. After stirring at room temperature for 22 h under H_2 atmosphere, the reaction mixture was filtered through a pad of Hyflo Super-Cel and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give diol **2** (4.16 g, 4.17 mmol, 85% for 5 steps) as a colorless amorphous sold.

2: R_f = 0.20 (hexane/EtOAc = 1/1); $[\alpha]_D^{17}$ −5.7 (*c* 1.21, $CHCl_3$); IR (neat) 2954, 2927, 2857, 1470, 1428, 1387, 1358, 1252, 1107, 1022, 836, 733, 705, 681 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.2, 1.2 Hz, 4H), 7.44–7.36 (m, 6H), 3.82–3.75 (m, 2H), 3.74–3.69 (m, 1H), 3.69–3.62 (m, 3H), 3.51–3.46 (m, 2H), 3.42 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.29 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.21 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.11 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.78 (brs, 2H), 2.19 (ddd, *J* = 11.4, 5.4, 3.6 Hz, 1H), 2.01 (d, *J* = 12.6 Hz, 1H), 2.03–1.94 (m, 2H), 1.83 (q, *J* = 12.0 Hz, 1H), 1.80–1.73 (m, 2H), 1.72–1.54 (m, 6H), 1.52–1.46 (m, 1H), 1.43 (s, 3H), 1.43–1.37 (m, 2H), 1.36 (s, 3H), 1.36–1.32 (m, 1H), 1.30 (s, 3H), 1.30–1.25 (m, 1H), 1.02 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.78 (d, *J* = 12.6 Hz, 3H), 0.76 (d, *J* = 12.6 Hz, 3H), 0.06 (s,

3H), 0.05 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 134.33, 134.30, 129.6, 127.7, 86.2, 83.12, 83.09, 80.0, 77.3, 74.9, 74.5, 74.0, 73.3, 71.4, 62.8, 61.4, 53.1, 38.8, 36.2, 35.8, 34.8, 33.7, 33.3, 27.9, 27.1, 26.08, 26.05, 21.7, 21.5, 19.4, 18.5, 18.3, 18.2, 16.4, 16.0, −3.5, −3.8, −4.5; HRMS (ESI-TOF) *m*/*z* 1019.6265 $[M + Na]^+$ (calcd for $C_{56}H_{96}O_9Si_3Na$, 1019.6254).

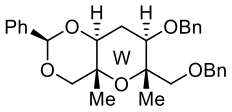
2-3. Synthesis of the WXYZ ring fragment

The spectroscopic date of **3** and **76**–**110** were identical to those in the literature.[4,5]



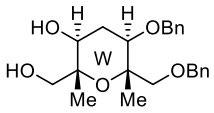
76

Diol 76. To a solution of **4** (18.36 g, 63.2 mmol) in CH_2Cl_2 (180 mL) and MeOH (180 mL) was bubbled O_3 gas at −78 °C for 8 h, then O_2 gas was bubbled in the resultant solution at the same temperature for 10 min. $NaBH_4$ (7.18 g, 190 mmol) was added to the reaction mixture at −78 °C. After the solution was warmed to 0 °C over 6 h, quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude diol **76** (17.6 g) as a pale yellow amorphous sold. The crude material was used directly in the next reaction without further purification.



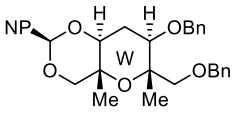
77

Benzyl ether 77. NaH (60% in mineral oil, 7.59 g, 190 mmol) and BnBr (20 mL, 164 mmol) were added to a solution of crude diol **76** (17.6 g) in DMF (130 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude benzyl ether **77** (36.8 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



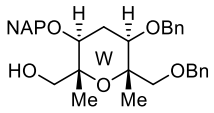
78

Diol 78. *p*-TsOH·H_2O (8.41 g, 44.3 mmol) was added to a solution of crude benzyl ether **77** (36.8 g) in THF (100 mL), MeOH (100 mL), and H_2O (10 mL) at 0 °C. After stirring at room temperature for 47 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) to give diol **78** (16.7 g, 43.2 mmol, 68% for 3 steps) as colorless oil.



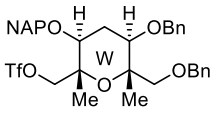
79

2-Naphthylidene acetal 79. 2-Naphthaldehyde (13.7 g, 88.1 mmol) and CSA (1.02 g, 4.40 mmol) were added to a solution of diol **78** (12.6 g, 44.0 mmol) in dry benzene (160 mL) at room temperature. After stirring at reflux with Dean–Stark trap for 3 h, the reaction mixture was quenched with Et_3N (6.1 mL) at 0 °C. MeOH (27 mL) and $NaBH_4$ (1.66 g, 44.0 mmol) were added to a rection mixture at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 10/1) to give 2-naphthylidene acetal **79** (16.8 g, 32.0 mmol, 79%) as colorless oil.



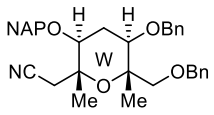
80

Primary alcohol 80. A solution of BH_3·THF (1.0 M in THF, 64.0 mL, 64.0 mmol) and TMSOTf (0.86 mL, 4.79 mmol) were added to a solution of 2-naphthylidene acetal **79** (16.8 g, 32.0 mmol) in CH_2Cl_2 (99 mL) at room temperature. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with Et_3N and MeOH, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 10/1 to 5/1) to give primary alcohol **80** (13.4 g, 25.4 mmol, 79%) as a colorless oil.



81

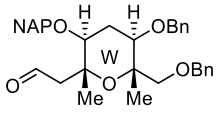
Triflate 81. 2,6-Lutidine (3.5 mL, 30.5 mmol) and Tf_2O (4.7 mL, 27.9 mmol) were added to a solution of primary alcohol **80** (13.4 g, 25.4 mmol) in dry CH_2Cl_2 (140 mL) at −78 °C. After stirring at −78 °C for 20 min, the reaction mixture was quenched with MeOH and saturated aqueous solution of NaCl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude triflate **81** (17.6 g) as colorless oil. The crude material was used directly in the next reaction without further purification.



82

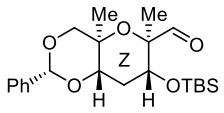
Nitrile 82. 18-Crown-6 (8.72 g, 33.0 mmol) and NaCN (3.73 g, 76.2 mmol) were added to a solution of crude triflate **81** (17.6 g) in dry DMF (51 mL) at room temperature. After stirring at room temperature for 15 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (hexane/ethyl acetate = 3/1) to give nitrile **82** (12.0 g, 22.4 mmol, 88% for 2 steps) as colorless oil.



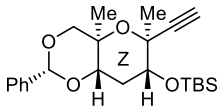
83

Aldehyde 83. DIBALH (1.0 M in toluene, 45 mL, 45.0 mmol) was added to a solution of nitril **82** (12.0 g, 22.4 mmol) in dry CH_2Cl_2 (220 mL) at −78 °C. After stirring at −78 °C for 1 h, the resulting solution was quenched with MeOH and diluted with saturated aqueous solution of Rochelle's salt. After stirring at room temperature for 16 h, the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 8/1) to give aldehyde **83** (10.7 g, 19.9 mmol, 89%) as a as colorless oil.



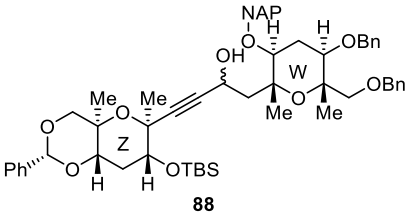
85

Aldehyde 85. A stirred solution of the olefin **24** (20.8 g, 51.3 mmol) in CH_2Cl_2/MeOH (342 mL, 5:1) was cooled to −78 °C. O_3 gas was bubbled through the solution for 30 min and residual O_3 was removed by bubbling O_2 gas. After PPh_3 (40.3 g, 154 mmol) was added, the solution warmed to room temperature over 4 h and concentrated under the reduced pressure to give crude aldehyde **85** (73.5 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



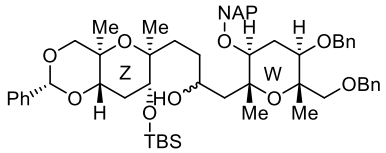
87

Terminal alkyne 87. $CsCO_3$ (50.1 g, 154 mmol) was added to a solution of crude aldehyde **85** (73.5 g) and Ohira–Bestmann reagent **86** (39.4 g, 205 mmol) in dry MeOH (830 mL) at 0 °C. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 100/1 to 30/1) to give terminal alkyne **87** (18.8 g, 46.7 mmol, 91% for 2 steps) as colorless oil.



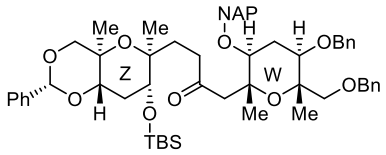
88

Alcohol 88. *n*-BuLi (2.7 M in hexane, 15 mL, 41.5 mmol) was added to a solution of alkyne **87** (17.5 g, 43.5 mmol) in THF (290 mL) at 0 °C. After stirring at 0 °C for 1 h, a solution of aldehyde **83** (6.21 g, 11.5 mmol) in THF (120 mL) was added to a reaction mixture via cannula at −78 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 100/1 to 7/1) to give an alcohol **88** (10.4 g, 11.0 mmol, 96%) as a colorless amorphous sold.



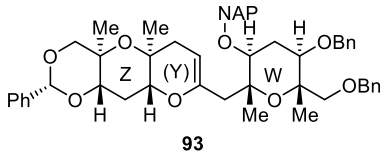
89

Saturated alcohol 89. PtO_2 (827 mg, 3.64 mmol) was added to a solution of alkyne **88** (17.2 g, 18.2 mmol) in EtOAc (240 mL) at room temperature. After stirring at room temperature for 9.5 h under H_2 atmosphere, the reaction mixture was filtered through a pad of Hyflo Super-Cel and concentrated under reduced pressure to give crude alcohol **89** (17.2 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



90

Ketone 90. DMP (11.5 g, 27.3 mmol) was added to a solution of crude alcohol **89** (17.2 g) in CH_2Cl_2 (830 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 20/1 to 10/1) to give ketone **90** (15.6 g, 16.6 mmol, 91% for 2 steps) as colorless amorphous sold.

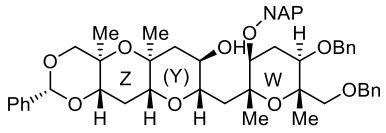


93

Dihydropyran 93. HF·Py (70%, 9.5 mL, 74.3 mmol) was added to a solution of TBS ether **90** (9.05 g, 9.59 mmol) in THF (38 mL) and Py (9.5 mL) at room temperature. After stirring at 50 °C for 36 h, The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ at 0 °C and extracted with EtOAc. The organic layer was washed with saturated aqueous solution

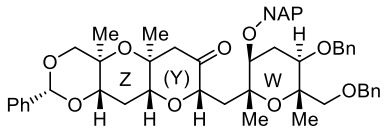
of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1 to 2/1) to give a mixture of alcohol **91**, corresponding hemiacetal **92**, and dihydropyran **93** (7.47 g, **91**:**92**:**93** = 1:1.4:1.8).

P_2O_5 (6.45 g, 45.5 mmol) was added to a solution of the above mixture (7.47 g) in toluene (180 mL) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was filtered through a pad of Hyflo Super-Cel. The organic layer was washed with saturated aqueous solution of $NaHCO_3$ and saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude dihydropyran **93** (8.05 g) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



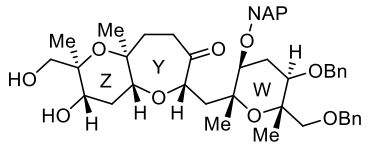
94

Alcohol 94. $BH_3 \cdot SMe_2$ (6.0 mL, 63.6 mmol) was slowly added to a solution of crude dihydropyran **93** (8.05 g) in THF (460 mL) at 0 °C. After stirring at room temperature for 3 h, 2 M aqueous NaOH (180 mL, 360 mmol) and 35% H_2O_2 (48 mL, 545 mmol) were added to the reaction solution at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1 to 2/1) to give alcohol **94** (6.32 g, 7.62 mmol, 84% for 3 steps) as colorless amorphous sold.



95

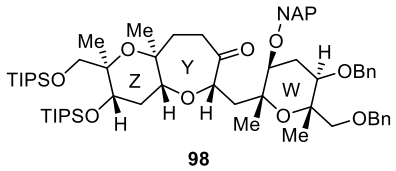
Ketone 95. MS4A (powdered, 12.0 g), NMO (3.37 g, 28.8 mmol) and TPAP (1.52 g, 4.32 mmol) were added to a solution of the alcohol **94** (12.0 g, 14.4 mmol) in CH_2Cl_2 (290 mL). The mixture was stirred at room temperature for 1.5 h, and directly subjected to column chromatography on flash silica gel (hexane/EtOAc = 10/1 to 6/1) to give ketone **95** (10.8 g, 13.0 mmol, 90%) as a colorless amorphous sold.



97

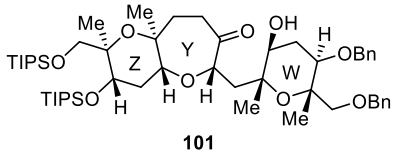
Ketone 97. MS4A (powdered, 6.0 g), $TMSCHN_2$ (0.6 M in hexane, 25.0 mL, 14.8 mmol) and $AlMe_3$ (1.0 M in hexane, 4.2 mL, 4.20 mmol) were added to a solution of the ketone **95** (2.46 g, 2.97 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After stirring at −78 to −30 °C for 5 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous solution of $NaHCO_3$ solution and saturated aqueous solution of Rochelle's salt. After stirring at room temperature for 16 h, the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

p-TsOH·H_2O (565 mg, 2.97 mmol) were added to a solution of the above crude in CH_2Cl_2/MeOH (150 mL, 1:1) at 0 °C and the resultant solution was stirred at room temperature for 21 h. The reaction was quenched with Et_3N and evaporated. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 5/1 to 3/2) to give diol **97** (1.73 g, 2.29 mmol, 77% for 2 steps) as colorless amorphous sold.



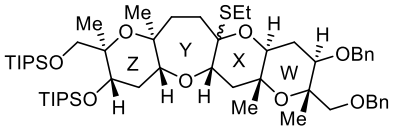
98

TIPS ether 98. Et_3N (1.9 mL, 13.7 mmol) and TIPSOTf (3.1 mL, 11.5 mmol) were added to a solution of diol **97** (1.74 g, 2.29 mmol) in CH_2Cl_2 (23 mL) at 0 °C. After stirring at room temperature for 15 h, TFA (1.2 mL) was added to a reaction mixture at 0 °C. After stirring at 0 °C for 15 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude TIPS ether **98** (4.06 g) as a colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



101

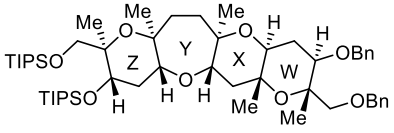
Hydroxy ketone 101. DDQ (778 mg, 3.43 mmol) was added to a solution of crude NAP ether **98** (4.06 g) in CH_2Cl_2 (73 mL) and pH 7.0 buffer (3.6 mL) at 0 °C. After stirring at 0 °C for 50 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and saturated aqueous solution of $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1 to 5/1) to give the hydroxy ketone **101** (1.75 g, 1.89 mmol, 82% for 2 steps) as colorless amorphous sold.



102

***O,S*-Acetal 102.** TfOH (45 mM in CH_2Cl_2 4.2 mL, 0.188 mmol) was added to a solution of hydroxy ketoe **101** (1.74 g, 1.88 mmol) and EtSH (2.8 mL, 37.6 mmol) in CH_2Cl_2 (94 mL) at 0 °C twice, every 30 min. After stirring at 0 °C for 1 h in total, the mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

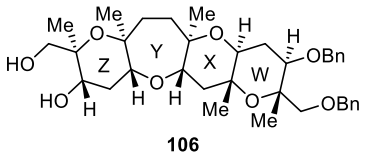
TIPSOTf (0.50 mL, 1.88 mmol) and 2,6-lutidine (0.43 mL, 3.76 mmol) were added to a solution of the above crude in CH_2Cl_2 (20.6 mL) at −78 °C. The reaction solution was warmed to −40 °C over 30 min and the mixture was quenched with MeOH and saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with saturated aqueous solution of $KHSO_4$, H_2O, saturated aqueous solution of $NaHCO_3$ and saturated aqueous solution of NaCl in that order, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 50/1 to 5/1) to give *O,S*-acetal **102** (1.69 g, 1.74 mmol, 93% for 2 steps) as colorless amorphous sold.



105

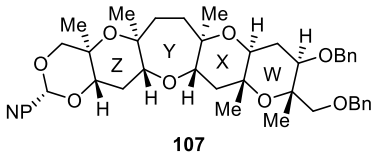
WXYZ ring 105. A solution of *O,S*-acetal **102** (1.69 g, 1.74 mmol) in toluene (120 mL) was added to a solution of MCPBA (72% purity, 1.66 g, 6.96 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.78 g, 8.70 mmol) in dry toluene (58 mL) at −78 °C. After stirring at −10 °C for 15 h, Me_3Al (1.06 M in hexane, 49 mL, 52.2 mmol) was added to the reaction mixture at −78 °C. After stirring at −10 °C for 15 h, the reaction mixture was diluted with Et_2O, quenched with saturated aqueous solution of Rochelle's salt. After stirring at room temperature for 4 h,

the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 50/1 to 3/1) to give WXYZ ring **105** (1.37 g, 1.49 mmol, 85%) as colorless amorphous sold.



106

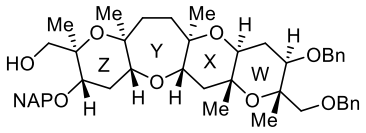
Diol 106. A solution of TBAF (1.0 M in THF, 2.80 mL, 2.80 mmol) was added dropwise to a solution TIPS ether **105** (548 mg, 0.565 mmol) in dry THF (5.6 mL) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl at room temperature and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 0/1) to give diol **106** (327 mg, 0.536 mmol, 95%) as colorless solid.



107

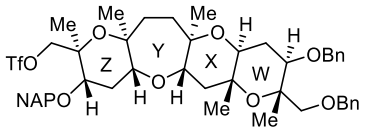
2-Naphthylidene acetal 107. 2-Naphthaldehyde (109 mg, 0.697 mmol) and CSA (23.1 mg, 99.6 μmol) were added to a solution of diol **106** (304 mg, 0.352 mmol) in dry benzene (10 mL) at room temperature. After stirring under reflux with Dean–Stark trap for 3 h, the reaction mixture was quenched with Et_3N (70 μL) at 0 °C. MeOH (1.6 mL) and $NaBH_4$ (9.4 mg, 0.249 mmol) were added to a rection mixture at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over

anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 10/1) to give naphthylidene acetal **107** (16.8 g, 32.0 mmol, 71%) as colorless amorphous sold.



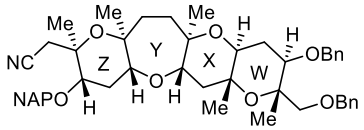
108

Primary alcohol 108. A solution of BH_3·THF (0.9 M in THF, 1.6 mL, 1.47 mmol) and TMSOTf (8.0 μL, 44.2 μmol) were added to a solution of naphthylidene acetal **107** (221.0 mg, 0.295 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C. After stirring at 0 °C for 8.5 h, the reaction mixture was quenched with Et_3N and MeOH, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 3/1) to give primary alcohol **108** (203 mg, 0.271 mmol, 92%) as a colorless amorphous sold.



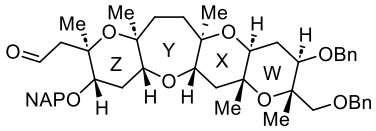
109

Triflate 109. 2,6-Lutidine (0.07 mL, 0.62 mmol) and Tf_2O (0.07 mL, 0.46 mmol) were added to a solution of primary alcohol **108** (232 mg, 0.309 mmol) in dry CH_2Cl_2 (3.0 mL) at −78 °C. After stirring at −78 °C for 1 h, the reaction mixture was quenched with MeOH and saturated aqueous solution of NaCl, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give crude triflate **109** (238 mg) as colorless amorphous sold. The crude material was used directly in the next reaction without further purification.



110

Nitrile 110. 18-Crown-6 (123 mg, 0.463 mmol) and NaCN (45.4 mg, 0.927 mmol) were added to a solution of crude triflate **109** (238 mg) in dry DMF (1.1 mL) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 1/1) to give nitrile **110** (195 mg, 0.256 mmol, 83% for 2 steps) as colorless amorphous sold.

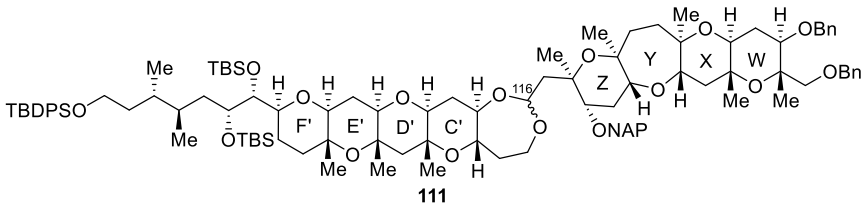


3

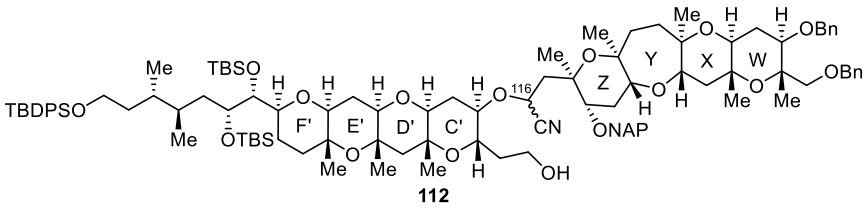
Aldehyde 3. DIBALH (1.0 M in toluene, 0.51 mL, 0.51 mmol) was added to a solution of nitril **110** (195 mg, 0.256 mmol) in dry CH_2Cl_2 (20 mL) at −45 °C. After stirring at −45 °C for 40 min, the resulting solution was quenched with MeOH and saturated aqueous solution of Rochelle's salt. After stirring at room temperature for 16 h, the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel, hexane/EtOAc = 8/1) to give aldehyde **3** (148 mg, 0.194 mmol, 76%) as a as colorless amorphous sold.

Chapter 3. Synthesis of the WXYZA'B'C'D'E'F' ring segment of maitotoxin

3-1. Synthesis of the WXYZA'B'C'D'E'F' ring segment of maitotoxin



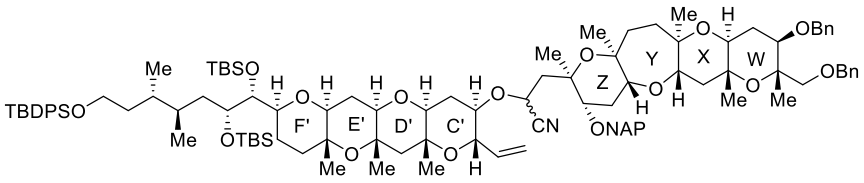
Seven-memberd ring acetal 111. A solution of C'D'E'F' ring fragment **2** (583 mg, 0.582 mmol) and WXYZ ring fragment **3** (148 mg, 0.194 mmol) in toluene (5.7 mL) was added to a suspension of $Sc(OTf)_3$ (57.1 mg, 0.116 mmol) in toluene (2.0 mL) at room temperature. After stirring at room temperature for 15 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 to 1/1) to give acetal **111** (247 mg, 0.142 mmol, 73%) as a colorless amorphous sold solid and recovered C'D'E'F' ring fragment **2** (154 mg, 0.154 mmol, 26%) as a colorless amorphous solid.



α-Cyano ether 112. A solution of acetal **111** (247 mg, 0.142 mmol) and TMSCN (0.36 mL, 2.84 mmol) in CH_2Cl_2 (7.4 mL) was added to a suspension of $Sc(OTf)_3$ (41.9 mg, 85.1 μmol) in CH_2Cl_2 (2.1 mL) at 0 °C. After stirring at room temperature for 3.3 h, K_2CO_3 (88.2 mg, 0.638 mmol) and MeOH (4.7 mL) were added to the reaction mixture at −10 °C. After stirring at −10 °C for 3 min, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel,

hexane/EtOAc = 5/1 to 0/1) to give α-cyano ether **112** (219 mg, 0.124 mmol, 87% 1.2 : 1 diastereomeric mixture) as a colorless amorphous solid.

112: R_f = 0.40, 0.28 (hexane/EtOAc = 3/1); HRMS (ESI-TOF) *m*/*z* 1791.0387 $[M + Na]^+$ (calcd for $C_{105}H_{153}NO_{16}Si_3Na$, 1791.0389)

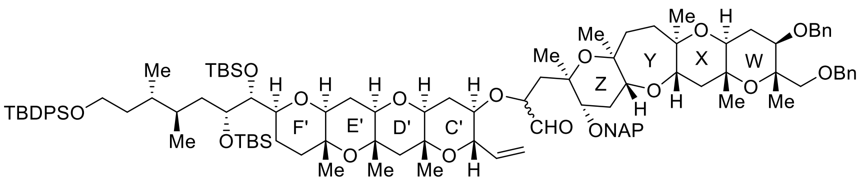


114

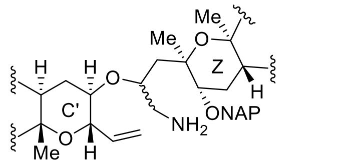
Terminal olefin 114. α-Cyano ether **112** (259 mg, 146 μmol), *o*-$NO_2C_6H_4SeCN$ (665 mg, 2.93 mmol), and powdered MS4A (260 mg) were suspended in THF (9.7 mL). After stirring at room temperature for 25 min, *n*-Bu_3P (0.90 mL, 3.66 mmol) was rapidly added to the suspension at room temperature. After stirring at room temperature for 25 min, the reaction mixture was diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 = 1/1 to hexane/EtOAc = 4/1), and slightly impure mixture was used for the next reaction.

MCPBA (72.8 mg, 0.300 mmol) was added to a solution of the above mixture in dichloroethane (7.8 mL) at 0 °C. After stirring at room temperature for 15 min, $NaHCO_3$ (35.7 mg, 0.426 mmol) was added to the reaction mixture. After stirring at 60 °C for 30 min, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of Na_2CO_3 and NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 = 1/1 to hexane/EtOAc = 5/1) to give terminal olefin **114** (195 mg, 0.111 mmol, 76% for 2 steps, diastereomeric mixture) as a pale yellow amorphous solid.

114: R_f = 0.36 (hexane/EtOAc = 3/1); HRMS (ESI-TOF) *m*/*z* 1174.0384 $[M + Na]^+$ (calcd for $C_{105}H_{151}NO_{15}Si_3Na$, 1773.0284).



115

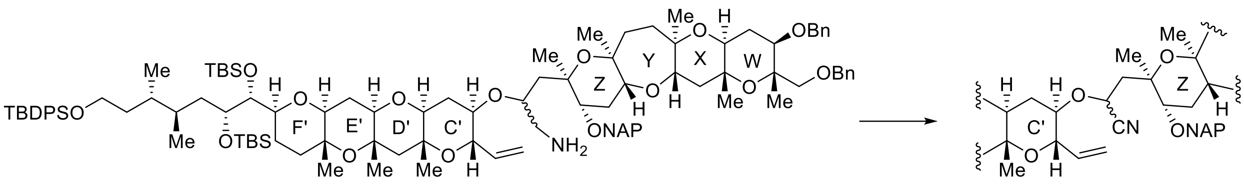


116

Aldehyde 115 and amine 116. DIBALH (1.0 M in hexane, 0.105 mL, 0.105 mmol) was added to a solution of olefin **114** (123 mg, 70.3 μmol) in dry CH_2Cl_2 (3.5 mL) at −78 °C via syringe pump (flow rate: 3.5 μL/min). After stirring at −78 °C for 2 h, the resulting solution was diluted with EtOAc and saturated aqueous solution of Rochelle’s salt. After stirring at room temperature for 1.3 h, the resulting solution was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 to MeOH/EtOAc = 1/9) to give aldehyde **115** (84.4 mg, 48.1 μmol, 69%, diastereomeric mixture) as a pale yellow amorphous solid and amine **116** (32.7 mg, 18.6 μmol, 27%, diastereomeric mixture) as a colorless amorphous solid.

115: R_f = 0.43 (hexane/EtOAc = 2/1); HRMS (ESI-TOF) *m*/*z* 1776.0304 $[M + Na]^+$ (calcd for $C_{105}H_{152}O_{16}Si_3Na$ 1776.0280).

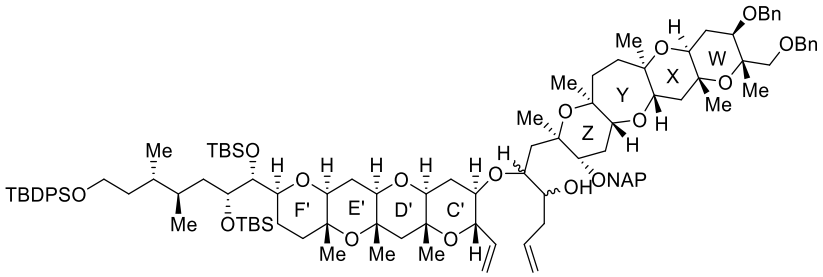
116: R_f = 0.01 (hexane/EtOAc = 2/1); HRMS (ESI-TOF) *m*/*z* 1777.0552 $[M + Na]^+$ (calcd for $C_{105}H_{155}NO_{15}Si_3Na$ 1777.0597).



116 114

Oxidation from 116 to 114. Dess–Martin periodinane (44.2 mg, 104 μmol) was added to a solution of amine **116** (16.7 mg, 9.51 μmol) in CH_2Cl_2 (500 μL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and Na_2CO_3 and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel,

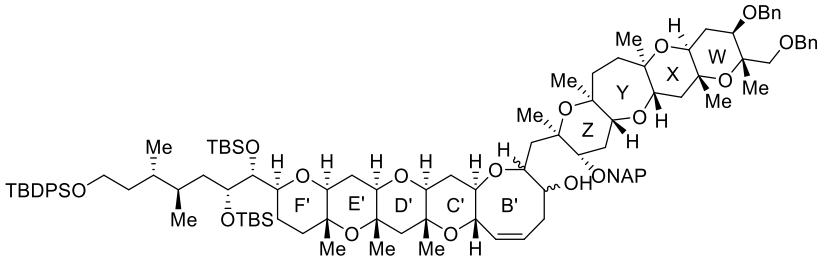
hexane/EtOAc = 15/1 to 5/1) to give nitrile **114** (10.0 mg, 5.71 μmol, 60%) as a colorless amorphous solid.



117

Olefin 117. Allylmagnesium bromide (1.0 M in Et_2O, 0.54 mL, 0.54 mmol) was added to a solution of aldehyde **115** (118 mg, 66.9 μmol) in dry THF (4.5 mL) at −40 °C. After stirring at −40 °C for 30 min, the reaction mixture was quenched with H_2O and saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 to 4/1) to give olefin **117** (104 mg, 57.9 μmol, 87%, diastereomeric mixture) as a pale yellow amorphous solid.

117: R_f = 0.43, 0.33, and 0.26 (hexane/EtOAc = 2/1); HRMS (ESI-TOF) *m*/*z* 1818.0746 $[M + Na]^+$ (calcd for $C_{108}H_{158}O_{16}Si_3Na$ 1818.0750).

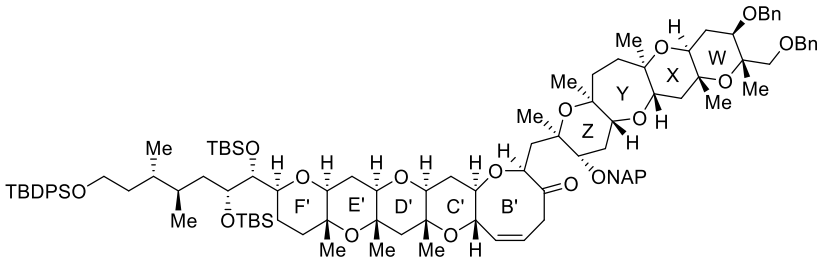


118

Alcohol 118. A solution of Grubbs' catalyst 2nd generation (4.9 mg, 5.79 μmol) in degassed toluene (1.0 mL) was added to a solution of olefin **117** (104 mg, 57.9 μmol) in degassed toluene (4.7 mL) at 110 °C. After stirring at 110 °C for 10 min, Et_3N was added to the reaction mixture

at room temperature. After stirring at room temperature under air for 1.1 h, the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane = 10/1 → 2/1) to give alcohol **118** (92.1 mg, 52.0 μmol, 90%, diastereomeric mixture) as a pale brown amorphous solid.

118: R_f = 0.23, 0.16, and 0.1 (hexane/EtOAc = 2/1); HRMS (ESI-TOF) *m*/*z* 1790.0454 [M + Na]$^+$ (calcd for $C_{106}H_{154}O_{16}Si_3Na$ 1790.0437).



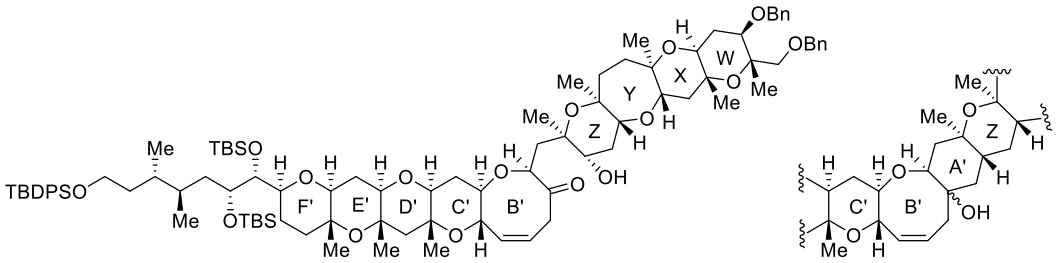
120

Ketone 120. NMO (30.4 mg, 0.260 mmol) and TPAP (3.6 mg, 10.4 μmol) were added to a suspension of alcohol **118** (92.1 mg, 52.0 μmol) and MS4A (92.0 mg) in CH_2Cl_2 (2.6 mL) at 0 °C. After stirring at room temperature for 2 h, the resulting mixture was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 4/1) to give ketone **119** (70.0 mg, 39.6 μmol, 76%, diastereomeric mixture) as a colorless amorphous solid.

In an Ace pressure tube, DBU (47 μL, 0.316 mmol) was added to a solution of above ketone (16.4 mg, 9.28 μmol) in xylene (2.3 mL) at room temperature. After warmed at 100 °C for 4 h without stirring, the reaction mixture was cooled to room temperature. The resulting solution was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1 → 4/1) to give ketone **120** (14.3 mg, 8.09 μmol, 87%) as a single isomer as a colorless amorphous solid. Four times operation of these processes furnished 52.8 mg of ketone **120** from 92.1 mg of alcohol **118**.

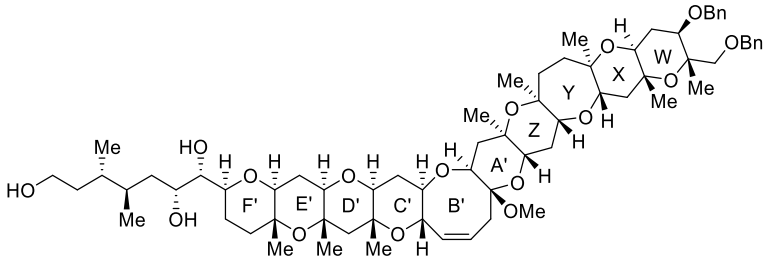
120 : $[\alpha]_D^{25}$ −68.6 (*c* 0.72, $CHCl_3$); R_f = 0.57 (hexane/EtOAc = 2/1); IR (neat) 2953, 2930, 2857, 1716, 1461, 1428, 1380, 1254, 1103, 1055, 1027, 916, 835, 780, 737, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79–7.73 (m, 3H), 7.68 (s, 1H), 7.63–7.59 (m, 5H), 7.46–7.40 (m, 2H), 7.39–7.34 (m, 3H), 7.34–7.29 (m, 5H), 7.27–7.22 (m, 3H), 7.22–7.16 (m, 5H), 5.56 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.38 (dd, *J* = 10.8, 10.2 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0

Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.34–4.27 (m, 1H), 4.13 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.86 (dd, *J* = 10.2, 10.2 Hz, 1H), 3.78 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.69–3.55 (m, 3H), 3.51–3.42 (m, 3H), 3.40 (dd, *J* = 6.0, 2.4 Hz, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.28 (d, *J* = 10.8 Hz, 1H), 3.26 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.16 (dd, *J* = 12.6, 3.0 Hz, 1H), 3.07–3.01 (m, 2H), 2.97 (dd, *J* = 12.6, 2.4 Hz, 1H), 2.73 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.69 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.24–2.17 (m, 1H), 2.13–2.05 (m, 2H), 2.05–2.00 (m, 1H), 1.95–1.85 (m, 4H), 1.85–1.48 (m, 14H), 1.48–1.42 (m, 1H), 1.42–1.20 (m, 5H), 1.34 (s, 3H), 1.31 (s, 3H), 1.27 (s, 6H), 1.24 (s, 3H), 1.23 (s, 3H), 1.20 (s, 6H), 0.992 (s, 9H), 0.843 (s, 9H), 0.817 (s, 9H), 0.74 (d, *J* = 6.0 Hz, 3H), 0.71 (d, *J* = 7.2 Hz, 3H), 0.040 (s, 3H), 0.013 (s, 3H), 0.010 (s, 3H), −0.016 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.1, 139.0, 138.6, 136.2, 135.7, 134.18, 134.16, 133.3, 133.0, 129.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 126.6, 126.4, 126.2, 126.1, 121.8, 85.7, 85.1, 83.4, 83.3, 82.9, 82.8, 82.3, 82.2, 80.1, 78.8, 78.1, 77.6, 77.3, 76.7, 75.9, 74.3, 73.8, 73.7, 73.6, 73.2, 72.4, 71.6, 71.2, 71.1, 71.0, 62.6, 52.7, 46.7, 41.9, 40.9, 39.1, 38.7, 38.2, 36.1, 34.7, 33.6, 32.7, 29.8, 28.8, 27.8, 27.0, 26.1, 26.0, 23.1, 21.6. 21.5, 21.03, 20.95, 19.8, 19.3, 18.5, 18.1, 17.9, 16.3, 16.0, −3.48, −3.74, −4.63; HRMS (ESI-TOF) *m*/*z* 1788.0276 $[M + Na]^+$ (calcd for $C_{106}H_{152}O_{16}Si_3Na$, 1788.0280).



Hydroxy ketone 121 and hemiacetal 122. DDQ (34.0 mg, 0.150 mmol) was added to a solution of NAP ether **121** (53.0 mg, 30.0 μmol) in CH_2Cl_2 (3.0 mL) and pH 7 buffer (500 μL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1 to 2/1) to give a mixture of hydroxy ketone **121** and hemiacetal **122** (36.6 mg, 22.5 μmol, 75%, **121**:**122** = 1:2) as a colorless amorphous solid.

121 + **122**: R_f = 0.06 (hexane/EtOAc = 2/1); HRMS (ESI-TOF) *m*/*z* 1647.9676 $[M + Na]^+$ (calcd for $C_{95}H_{144}NO_{16}Si_3Na$, 1647.9654).

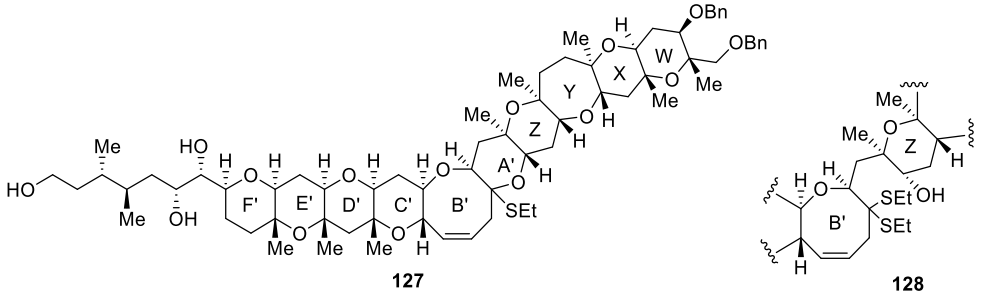


123

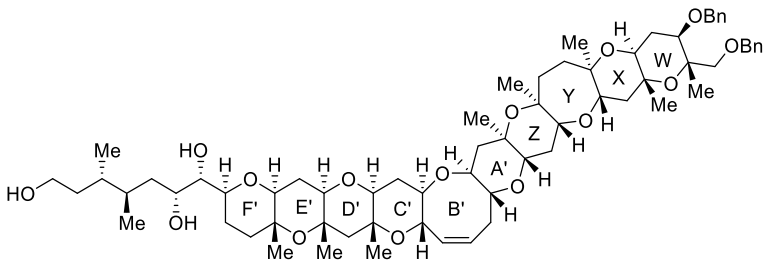
Methylacetal 123. $CaCl_2$ (grinded and preactivated using heat-gun, 175 mg, 1.58 mmol) and PPTS (170 mg, 0.675 mmol) were added to a solution of hydroxy ketone **121** and hemiacetal **122** (36.6 mg, 22.5 μmol) in 1,2-dichloroethane (2.3 mL) and MeOH (2.3 mL) at 0 °C. After stirring at reflux for 81 h, the reaction mixture was quenched with Et_3N and saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 to 0/1) to give methylacetal **123** (23.4 mg, 19.9 μmol, 87%) as a single isomer as a colorless amorphous solid.

123: $[\alpha]_D^{25}$ −30.5 (*c* 0.52, $CHCl_3$); R_f = 0.15 (EtOAc); IR (neat) 3501, 2950, 2872, 1455, 1381, 1278, 1095, 1071, 1020, 869, 734, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27–7.23 (m, 6H), 7.23–7.17 (m, 4H), 5.73–5.66 (m, 2H), 4.61 (d, *J* = 12.6 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.6 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.35–4.32 (m, 1H), 3.87 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.79 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.72–3.64 (m, 2H), 3.62–3.55 (m, 2H), 3.46 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.43 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.31 (s, 3H), 3.35–3.25 (m, 3H), 3.22 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.20–3.11 (m, 4H), 2.65–2.59 (m, 1H), 2.54–2.48 (m, 1H), 2.11–2.05 (m, 1H), 2.04–2.00 (m, 1H), 1.98 (d, *J* = 12.0 Hz, 1H), 1.96–1.88 (m, 4H), 1.88–1.83 (m, 1H), 1.83–1.73 (m, 7H), 1.73–1.68 (m, 1H), 1.68–1.60 (m, 6H), 1.60–1.50 (m, 4H), 1.44 (ddd, *J* = 13.2, 13.2, 5.4 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.32–1.31 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.08 (ddd, *J* = 13.2, 9.6, 3.0 Hz, 1H), 0.841 (d, *J* = 7.2 Hz, 3H), 0.820 (d, *J* = 6.6 Hz, 3H); ^1H NMR (600 MHz, C_6D_6) δ 7.36–7.30 (m, 2H), 7.21–7.10 (m, 6H), 7.10–7.05 (m, 2H), 5.95 (dd, *J* = 10.8, 5.4 Hz, 1H), 5.74 (ddd, *J* = 10.8, 7.8, 7.8 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* =

7.2, 5.4 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.6 Hz, 1H), 4.18 (d, *J* = 12.6 Hz, 1H), 4.11 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.01 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.86 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.61–3.53 (m, 3H), 3.53–3.46 (m, 2H), 3.46–3.43 (m, 2H), 3.33 (d, *J* = 10.8 Hz, 1H), 3.27–3.19 (m, 2H), 3.15 (dd, *J* = 13.2, 1.8 Hz, 1H), 3.12–3.06 (m, 2H), 3.03 (s, 3H), 2.69 (dd, *J* = 12.0, 10.8 Hz, 1H), 2.45 (dd, *J* = 12.0, 7.8 Hz, 1H), 2.31–2.25 (m, 2H), 2.22–2.12 (m, 4H), 2.10–1.95 (m, 6H), 1.95–1.72 (m, 10H), 1.72–1.61 (m, 2H), 1.49–1.43 (m, 1H), 1.41 (s, 3H), 1.38–1.20 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.15–1.12 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 138.7, 136.4, 128.40, 128.39, 127.6, 127.5, 127.4, 126.7, 103.2, 87.3, 86.0, 84.1, 83.5, 83.4, 81.4, 79.6, 78.9, 78.4, 78.2, 77.1, 76.8, 76.1, 75.9, 74.7, 73.8, 73.4, 73.2, 72.7, 72.5, 71.6, 71.4, 71.2, 70.7, 61.8, 52.9, 47.8, 42.0, 41.2, 39.6, 38.4, 38.1, 37.2, 36.0, 34.6, 34.1, 33.4, 32.2, 29.8, 29.0, 27.9, 27.2, 25.6, 23.5, 21.6, 21.2, 21.1, 20.2, 19.9, 18.2, 18.0, 16.4, 16.3; HRMS (ESI-TOF) *m*/*z* 1195.6943 $[M + Na]^+$ (calcd for $C_{68}H_{100}O_{16}Na$, 1195.6904).



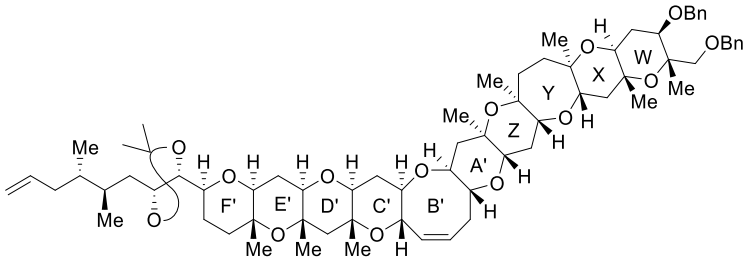
***O,S*-Acetal 127 and dithioacetal 128.** A solution of methylacetal **123** (5.6 mg, 4.77 μmol) and EtSH (0.70 mL, 9.54 mmol) in CH_2Cl_2 (1.5 mL) predried over MS3A (2.3 mg) was added to a suspension of $Zn(OTf)_2$ (17.3 mg, 47.7 μmol, preactivated using heat-gun) in CH_2Cl_2 (50 μL) at 0 °C. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with saturated aqueous solution of Et_3N and saturated aqueous of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 to 0/1) to give a 8:1 mixture of *O,S*-acetal **127** and dithioacetal **128** (4.8 mg), and it was used for the next reaction without further purification.



129

Triol 129. Et_3B (1.0 M in THF, 50 μL, 50.0 μmol) and Ph_3SnH (144 mg, 0.410 mmol) were added to a mixture of **127** and **128** in dry toluene (0.12 mL) at room temperature. After stirring at room temperature for 16 h, the reaction mixture was diluted with Et_2O at 0 °C. The mixture of saturated aqueous $NaHCO_3$ and 30% H_2O_2 (v/v = 5/1, 500 μL) was added to the reaction mixture. After stirring for 30 min, the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 to 0/1) to give triol **129** (2.6 mg, 2.27 μmol, 48% for 2 steps) as a colorless amorphous solid.

129: $[\alpha]_D^{16}$ −25.6 (*c* 0.19, $CHCl_3$); R_f = 0.23 (hexane/EtOAc = 1/10); IR (neat) 2950, 2867, 1460, 1383, 1254, 1102, 1066, 1026, 695 cm^{-1}; ^1H NMR (600 MHz, CD_3OD:C_5D_5N = 1:1) δ 7.32–7.29 (m, 2H), 7.26–7.22 (m, 6H), 7.19–7.16 (m, 2H), 5.75 (dd, *J* = 11.4, 5.4 Hz, 1H), 5.65 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.35–4.32 (m, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 3.92 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.85 (ddd, *J* = 9.6, 3.6, 3.0 Hz, 1H), 3.76 (ddd, *J* = 10.8, 4.2, 3.6 Hz, 1H), 3.70–3.64 (m, 2H), 3.63–3.57 (m, 2H), 3.46–3.36 (m, 4H), 3.36–3.28 (m, 4H), 3.25–3.19 (m, 2H), 3.11 (dd, *J* = 11.4, 2.4 Hz, 1H), 2.82–2.74 (m, 1H), 2.32 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.13–2.07 (m, 3H), 2.03–1.56 (m, 24H), 1.53–1.47 (m, 1H), 1.44 (dd, *J* = 10.8, 10.8 Hz, 1H), 1.40–1.08 (m, 2H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD:C_5D_5N = 1:1) δ 140.0, 139.9, 136.5, 129.20, 129.17, 128.5, 128.4, 128.3, 126.8, 87.7, 86.9, 84.7, 84.6, 84.3, 84.1, 83.8, 81.6, 80.3, 79.7, 79.2, 78.8, 77.7, 77.1, 76.9, 75.5, 74.8, 74.7, 74.2, 74.1, 73.5, 72.5, 72.3, 71.8, 70.3, 61.3, 54.0, 46.8, 42.9, 40.4, 39.4, 39.2, 37.7, 37.1, 35.7, 34.3, 33.4, 31.5, 30.4, 28.8, 28.0, 26.5, 23.5, 22.2, 21.9, 21.7, 21.6, 20.3, 18.3, 18.2, 16.7, 16.6; HRMS (ESI-TOF) *m*/*z* 1165.6814 $[M + Na]^+$ (calcd for $C_{67}H_{98}O_{15}Na$, 1165.6798).



133

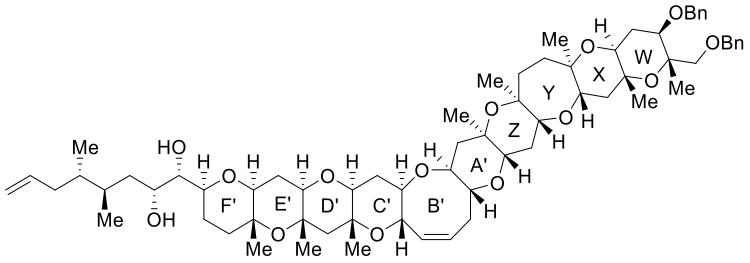
Olefin 133. TsOH·H_2O (2.0 mg, 10.0 μmol) was added to a solution of triol **129** (2.0 mg, 1.75 μmol) in acetone (30 μL) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was quenched with Et_3N, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The corresponding acetonide was used for the next reaction without further purification.

Dess–Martin periodinane (29.4 mg, 69.3 μmol) was added to a solution of the crude acetonide (2.8 mg) in CH_2Cl_2 (0.30 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and Na_2CO_3 and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The corresponding aldehyde was used for the next reaction without further purification.

NaHMDS (1.0 M in THF, 40 μL, 40.0 μmol) was added to a suspension of methyltriphenyl-phosphonium bromide (18.7 mg, 52.5 μmol) in dry THF (0.10 mL) at 0 °C. After stirring at 0 °C for 30 min, the solution of the crude aldehyde (3.8 mg) in dry THF (0.20 mL) was added to the reaction mixture via cannula. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1 to 3/1) to give olefin **133** (1.4 mg, 1.19 μmol, 74% for 3 steps) as a colorless amorphous solid.

133: $[\alpha]_D^{24}$ −13.2 (*c* 0.26, $CHCl_3$); R_f = 0.60 (hexane/EtOAc = 1/1); IR (neat) 2929, 2855, 1738, 1456, 1379, 1258, 1213, 1104, 1070, 1023, 735, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32–7.27 (m, 6H), 7.26–7.22 (m, 4H), 5.82–5.68 (m, 3H), 5.03–4.95 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.30

(dd, *J* = 9.0, 4.2 Hz, 1H), 4.00 (ddd, *J* = 7.2, 7.2, 2.4 Hz, 1H), 3.84 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.64–3.58 (m, 2H), 3.53 (ddd, *J* = 12.0, 4.8, 3.0 Hz, 1H), 3.46 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.43–3.37 (m, 2H), 3.34–3.29 (m, 3H), 3.28 (dd, *J* = 12.6, 3.0 Hz, 1H), 3.26–3.21 (m, 1H), 3.19 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.16 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.07 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.80–2.74 (m, 1H), 2.40–2.30 (m, 1H), 2.13–2.08 (m, 2H), 2.08–1.43 (m, 22H), 1.43–1.20 (m, 4H), 1.43 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.34 (s, 6H), 1.33 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 138.7, 138.3 135.3, 128.42, 128.40, 127.6, 127.5, 127.4, 126.4, 115.6, 109.0, 87.3, 86.3, 84.0, 83.7, 83.5, 83.4, 83.14, 83.07, 79.6, 79.2, 78.9, 78.3, 78.2, 76.8, 76.1, 76.0, 75.3, 74.5, 73.84, 73.75, 73.3, 72.8, 71.6, 71.4, 71.3, 53.0, 46.0, 42.0, 39.7, 38.4, 38.2, 37.9, 37.8, 34.0, 32.4, 32.1, 30.8, 29.5, 28.0, 27.6, 27.2, 27.0, 25.8, 23.0, 21.7, 21.35, 21.30, 21.0, 19.8, 18.0, 16.2, 16.0; HRMS (ESI-TOF) *m*/*z* 1201.7164 $[M + Na]^+$ (calcd for $C_{71}H_{102}O_{14}Na$, 1201.7162).



1

WXYZA'B'C'D'E'F' ring segment 1. TsOH·H_2O (3.0 mg, 15.8 μmol) was added to a solution of olefin **133** (2.6 mg, 2.20 μmol) in MeOH (400 μL), THF (80 μL), and H_2O (40 μL) at 0 °C. After stirring at room temperature for 46 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1) to give WXYZA'B'C'D'E'F' ring segment **1** (1.5 mg, 1.31 μmol, 60%) as a colorless amorphous solid.

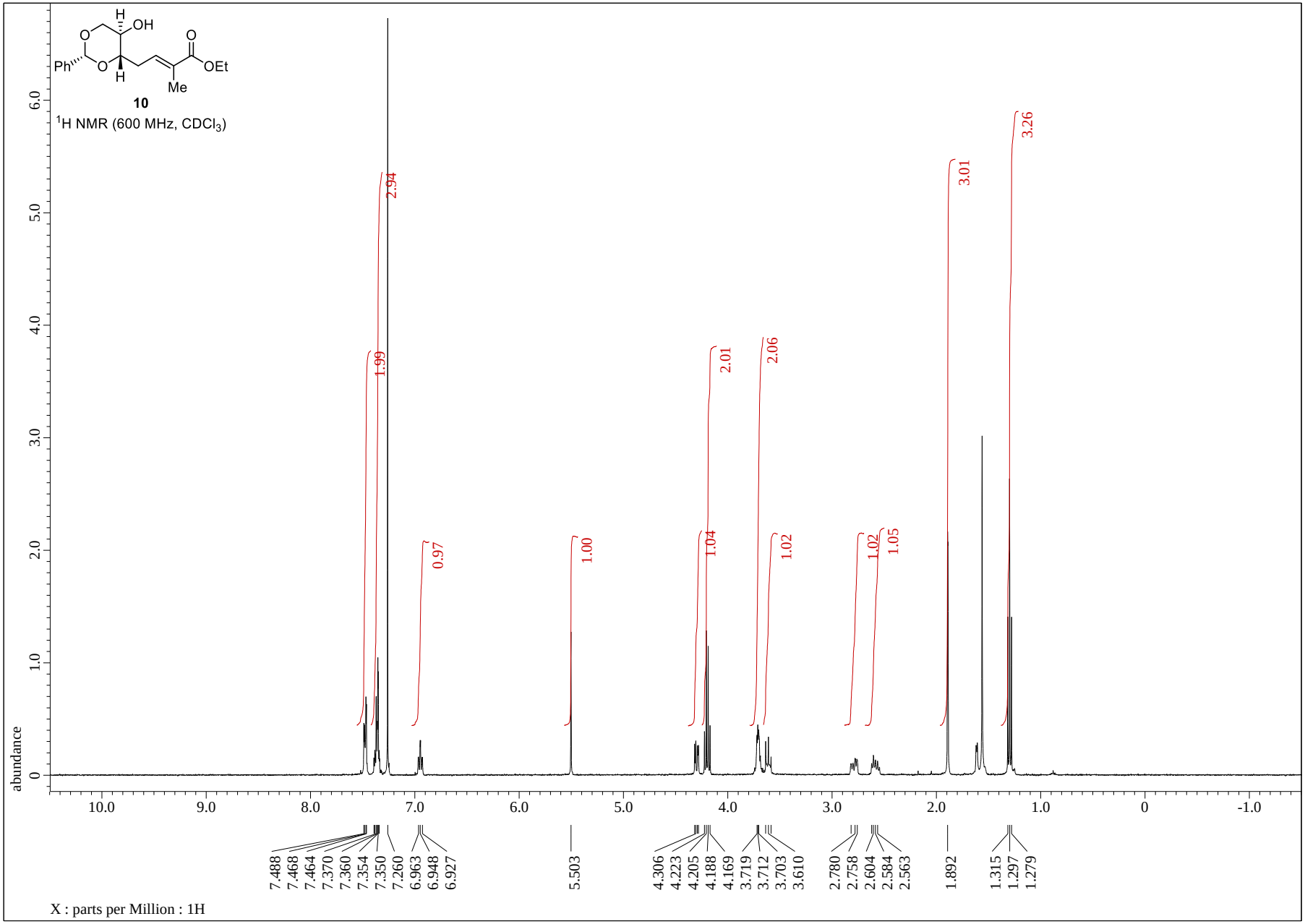
1: $[\alpha]_D^{26}$ −30.6 (*c* 0.15, $CHCl_3$); R_f = 0.22 (hexane/EtOAc = 1/1); IR (neat) 3502, 2929, 2871, 2366, 2348, 2326, 2309, 1488, 1473, 1456, 1396, 1379, 1339, 1102, 1069, 1017, 696 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD:C_5D_5N = 1:1) δ 7.32–7.29 (m, 2H), 7.26–7.22 (m, 6H), 7.19–7.16 (m, 2H), 5.75 (dd, *J* = 10.8, 5.4 Hz, 1H), 5.73–5.67 (m, 1H), 5.67–5.61 (m, 1H), 4.95–4.85 (m, 2H),

4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.37–4.29 (m, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.91 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.84 (ddd, *J* = 10.2, 3.0, 3.0 Hz, 1H), 3.77 (ddd, *J* = 11.4, 4.2, 4.2 Hz, 1H), 3.67 (ddd, *J* = 11.4, 11.4, 5.4 Hz, 1H), 3.60 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.48–3.37 (m, 4H), 3.35 (dd, *J* = 4.8, 4.2 Hz, 1H), 3.34–3.29 (m, 3H), 3.24 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.22 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.10 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.81–2.74 (m, 1H), 2.31 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.15–2.04 (m, 4H), 2.04–1.58 (m, 20H), 1.55–1.46 (m, 1H), 1.46–1.10 (m, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD:C_5D_5N = 1:1) δ 140.0, 139.9, 139.3, 136.5, 129.20, 129.16, 128.5, 128.4, 128.3, 126.8, 115.8, 87.7, 86.9, 84.7, 84.6, 84.3, 84.1, 83.8, 81.6, 80.3, 79.7, 79.1, 78.8, 77.73, 77.76, 77.1, 76.9, 75.5, 74.8, 74.7, 74.2, 74.1, 73.5, 72.5, 72.3, 71.8, 70.3, 54.0, 46.8, 42.9, 40.4, 39.4, 39.2, 38.8, 37.7, 34.2, 33.4, 31.5, 30.4, 28.8, 28.0, 26.5, 23.5, 22.2, 21.9, 21.7, 21.6, 20.3, 18.3, 18.2, 16.7, 16.4; HRMS (ESI-TOF) *m*/*z* 1161.6851 $[M + Na]^+$ (calcd for $C_{68}H_{98}O_{14}Na$, 1161.6849).

References

1. R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899. For the preparation of IBX, see M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.
2. T. Nakashima, T. Baba, H. Onoue, W. Yamashita, K. Torikai, *Synthesis* **2013**, *45*, 2417.
3. M. Kunitake, T. Oshima, K. Konoki, M. Ebine, K. Torikai, M. Murata, T. Oishi, *J. Org. Chem.* **2014**, *79*, 4948.
4. T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 3599.
5. N. Osato, H. Onoue, Y. Toma, K. Torikai, M. Ebine, M. Satake, T. Oishi, *Chem. Lett.* **2018**, *47*, 265.

Spectral Data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1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
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1.99
0.97
1.00
2.01
1.04
2.06
1.02
1.02
1.05
3.01
3.26
7.488
7.468
7.464
7.370
7.360
7.354
7.350
7.260
6.963
6.948
6.927
5.503
4.306
4.223
4.205
4.188
4.169
3.719
3.712
3.703
3.610
2.780
2.758
2.604
2.584
2.563
1.892
1.315
1.297
1.279

11
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
2.06
3.05
0.94
1.00
1.85
2.12
2.05
1.06
1.07
3.09
3.33
7.527
7.523
7.514
7.512
7.412
7.405
7.402
7.400
7.260
6.852
6.850
6.840
6.837
5.984
4.589
4.582
4.576
4.570
4.462
4.453
4.217
4.210
4.199
4.187
4.175
2.884
2.877
2.873
2.870
2.736
2.723
2.709
2.696
1.885
1.306
1.295
1.282

Me
OH
O
Ph
O
H
OH
Me
19
1H NMR (600 MHz, CDCl3)
4.04
2.67
2.49
2.07
1.15
1.02
1.00
1.03
1.06
3.78
3.29
abundance
X : parts per Million : 1H
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7.474
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7.379
7.369
7.356
7.352
7.348
7.345
7.340
7.328
7.260
5.610
5.596
5.586
5.491
4.025
3.910
3.907
3.893
3.888
3.655
3.647
3.639
3.632
2.549
2.529
2.515
2.286
2.275
2.262
2.250
1.715
1.442
1.439

Me
OH
O
Ph
O
H
O
Me
23
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

Me
Me
O
O
Ph
O
H
H
OH
4
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
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3.38
1.04
1.00
0.96
1.03
1.20
0.94
1.03
1.08
1.10
1.21
3.46
3.07
7.497
7.494
7.483
7.481
7.388
7.378
7.365
7.363
7.353
7.260
5.942
5.924
5.913
5.895
5.580
5.319
5.290
5.168
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5.149
3.925
3.908
3.741
3.721
3.671
3.664
3.649
3.643
3.609
3.591
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2.156
2.150
2.142
2.023
2.003
1.983
1.589
1.425

Me
Me
O
O
Ph
O
H
H
OTBS
24
1H NMR (600 MHz, CDCl3)
abundance
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1.08
1.05
1.09
2.14
3.07
3.15
2.86
3.25
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7.494
7.483
7.388
7.385
7.375
7.362
7.358
7.353
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7.336
7.260
5.906
5.888
5.877
5.859
5.570
5.273
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5.242
5.070
5.068
5.050
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3.914
3.711
3.703
3.694
3.632
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3.611
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3.588
2.046
2.023
2.016
2.006
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1.968
1.583
1.368
0.875
0.069
0.039
X : parts per Million : 1H

Ph
O
H
H
OTBS
E'
O
O
Me
Me
OH
25
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abundance
X : parts per Million : 1H
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3.33
3.19
3.05
2.26
1.61
1.00
0.95
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7.470
7.467
7.384
7.375
7.369
7.364
7.362
7.358
7.352
7.349
7.260
5.563
3.853
3.837
3.811
3.803
3.793
3.784
3.535
3.532
2.976
2.967
2.959
2.017
2.000
1.982
1.979
1.961
1.587
1.353
0.864
0.092
0.062

Ph
O
H
H
OTBS
E'
O
O
Me
Me
Me
OH
27
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

Ph
O
H
H
OTBS
E'
O
O
Me
Me
O
Me
28
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
7.480
7.478
7.467
7.464
7.384
7.379
7.369
7.356
7.352
7.345
7.334
7.331
7.260
5.542
4.150
4.140
4.131
4.122
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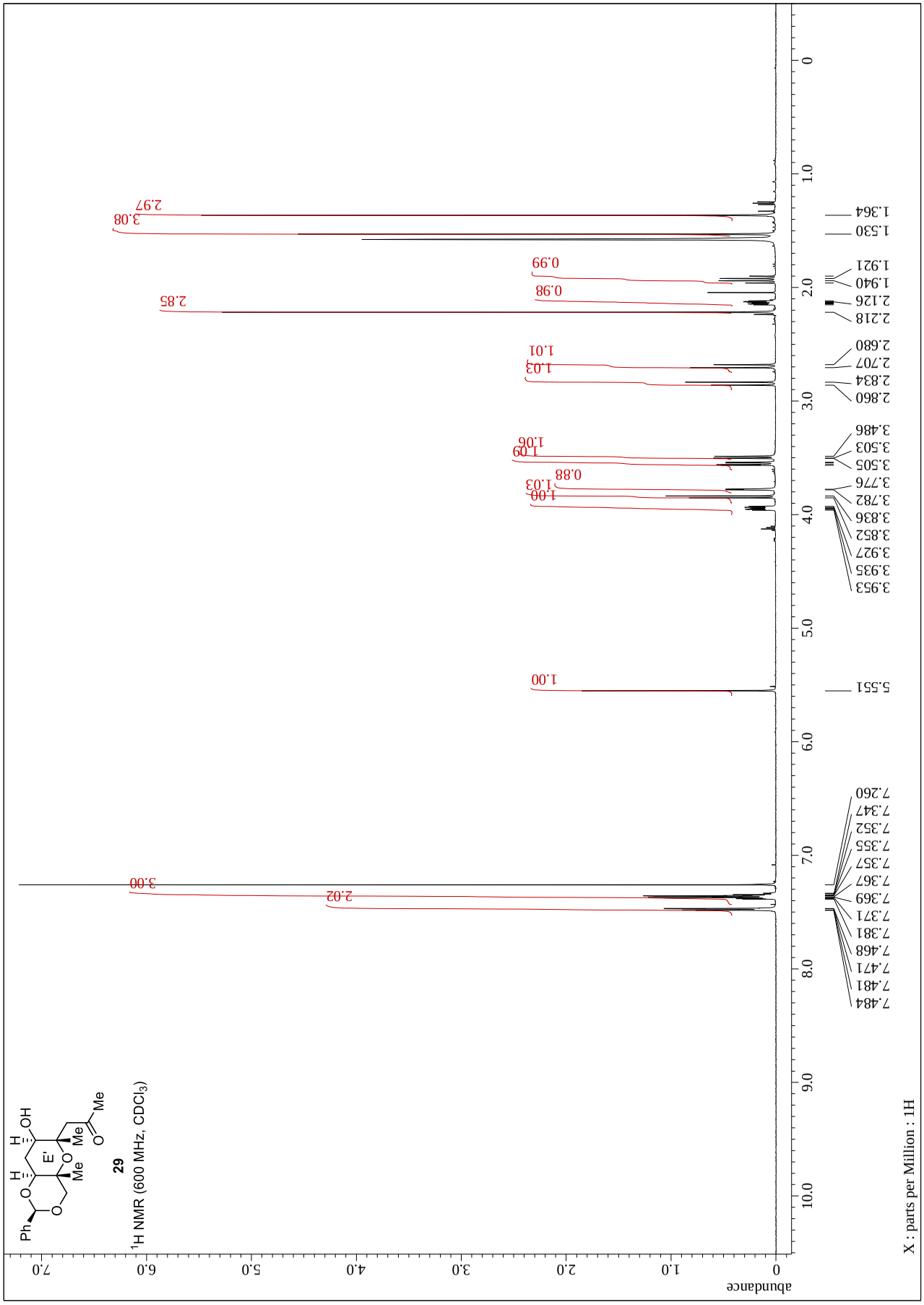
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7.260
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3.782
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2.680
2.218
2.126
1.940
1.921
1.530
1.364
3.00
2.02
1.00
1.00
1.03
0.88
1.09
1.06
1.03
1.01
2.85
0.98
0.99
3.08
2.97

Ph
O
H
H
O
CO2Et
E'
O
Me
Me
O
Me
30
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
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7.466
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7.454
7.389
7.384
7.375
7.365
7.362
7.353
7.260
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5.375
5.354
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4.625
4.170
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3.853
3.582
3.500
3.482
2.755
2.732
2.365
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2.182
2.016
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1.02
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3.08
1.05
4.32
3.04
3.07
3.74

Ph
O
H
H
H
O
OAc
E'
D'
O
O
Me
Me
Me
OH
33
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

34
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

Ph
O
H
H
H
O
O
E'
D'
O
O
Me
Me
Me
CO2Me
36
1H NMR (600 MHz, CDCl3)
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2.90
1.00
0.86
1.33
1.00
1.09
0.96
4.21
1.92
0.87
1.06
0.97
0.92
3.03
2.95
3.02
9.801
9.798
9.794
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7.539
7.479
7.476
7.466
7.464
7.386
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5.345
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3.836
3.819
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3.682
3.535
3.520
2.600
2.592
2.589
2.311
2.291
1.975
1.955
1.608
1.485
1.411
X : parts per Million : 1H

HO
H
H
H
H
OBn
E'
D'
C'
HO
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OBn
Me
Me
Me
H
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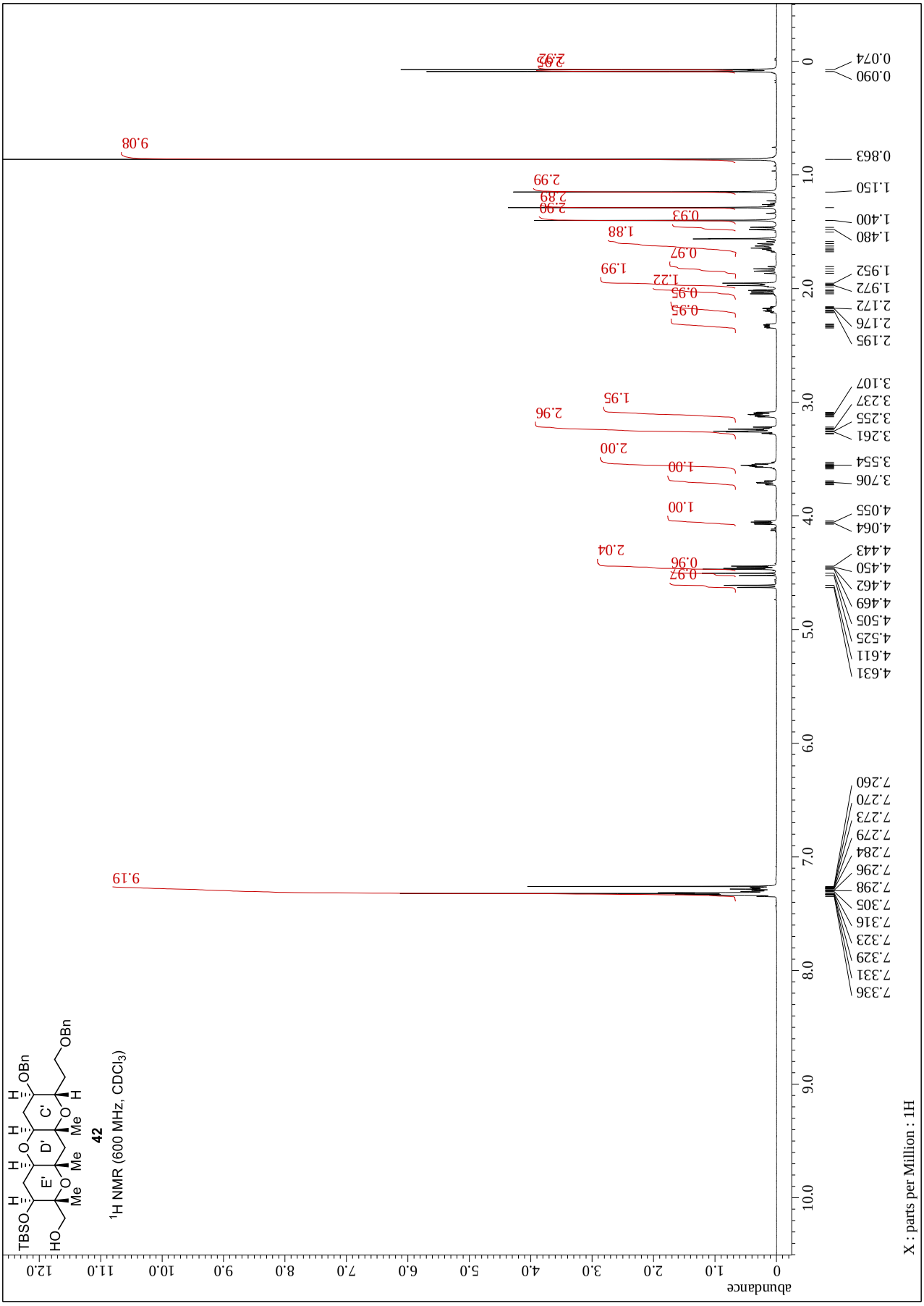
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H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HO
E'
D'
C'
OBn
Me
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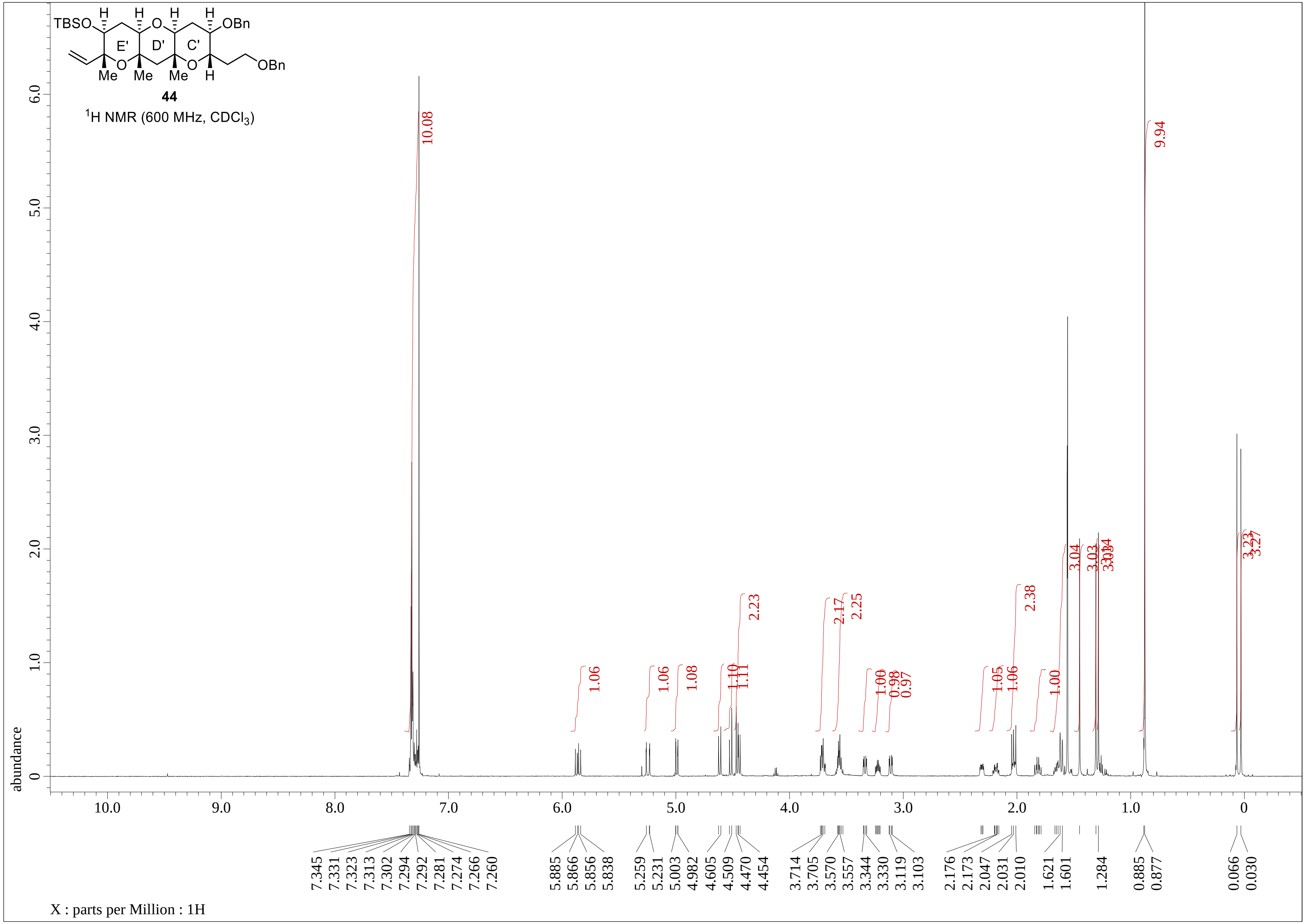
abundance
X : parts per Million : 1H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OBn
OBn
E'
D'
C'
Me
Me
Me
H
44
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
10.08
9.94
1.06
1.06
1.08
1.10
1.11
2.23
2.17
2.25
1.00
0.98
0.97
1.05
1.06
2.38
1.00
3.04
3.03
3.01
3.04
3.23
3.27
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
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7.331
7.323
7.313
7.302
7.294
7.292
7.281
7.274
7.266
7.260
5.885
5.866
5.856
5.838
5.259
5.231
5.003
4.982
4.605
4.509
4.470
4.454
3.714
3.705
3.570
3.557
3.344
3.330
3.119
3.103
2.176
2.173
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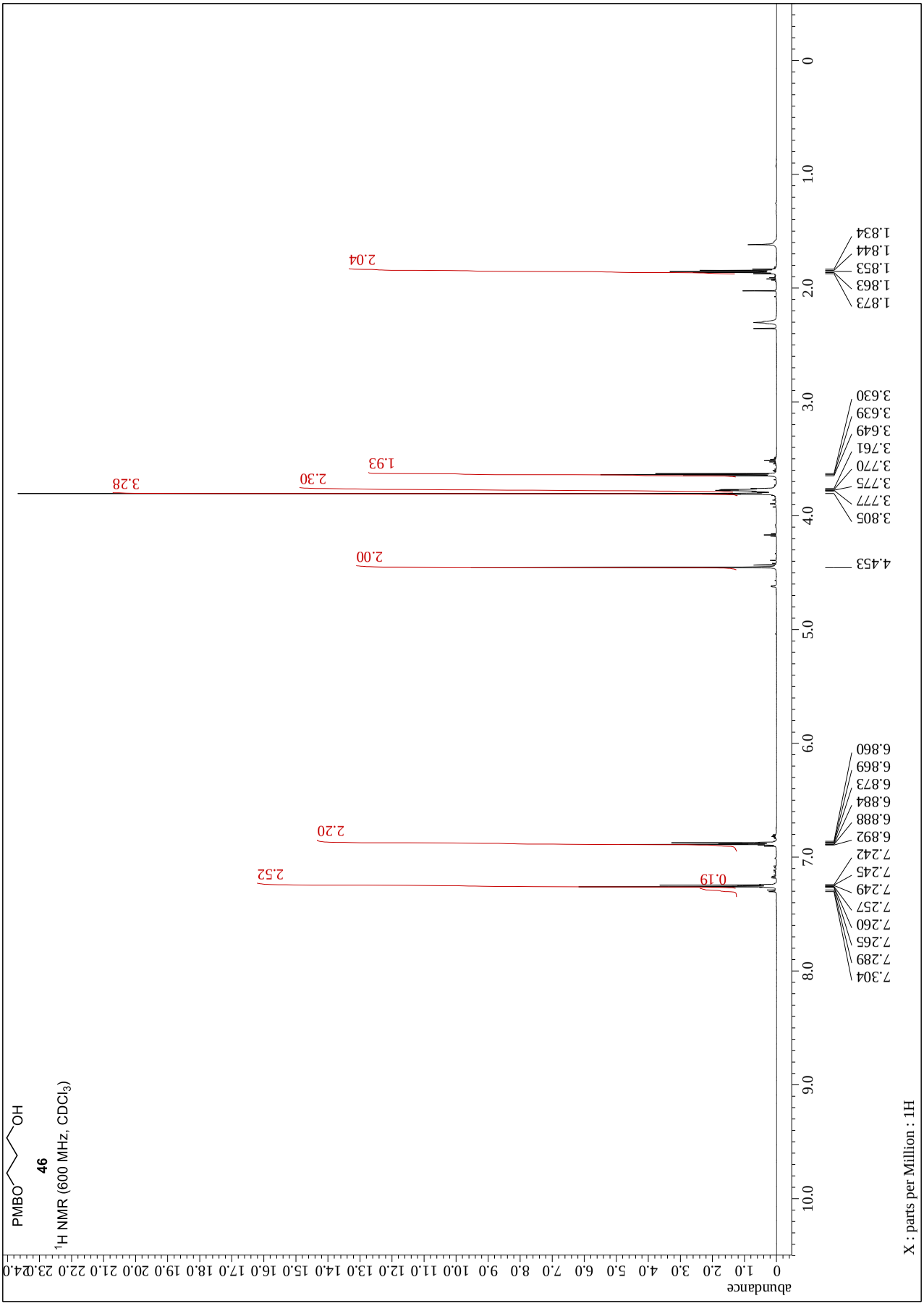
0.885
0.877
0.066
0.030
X : parts per Million : 1H


PMBO
OH
46
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
X : parts per Million : 1H
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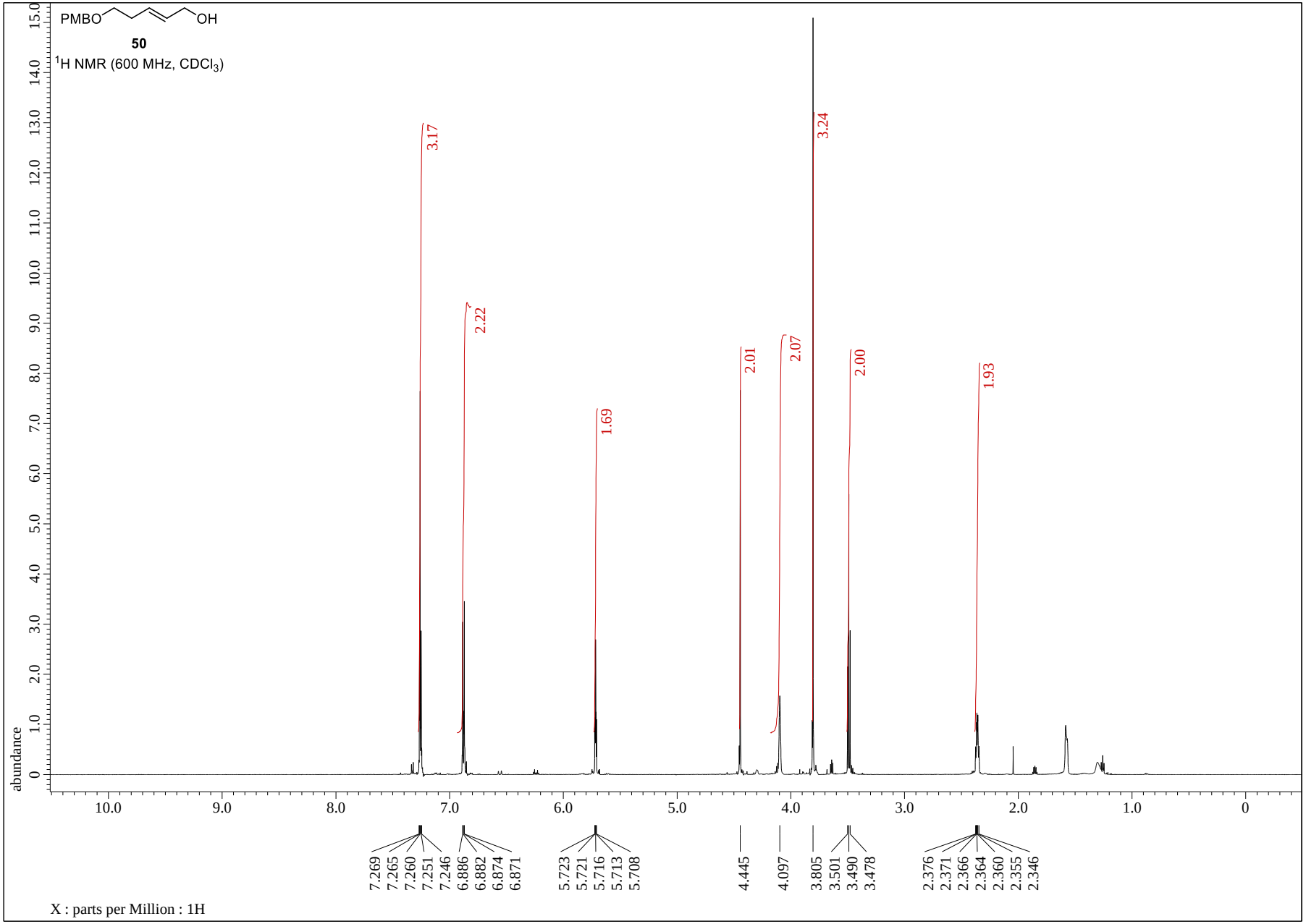
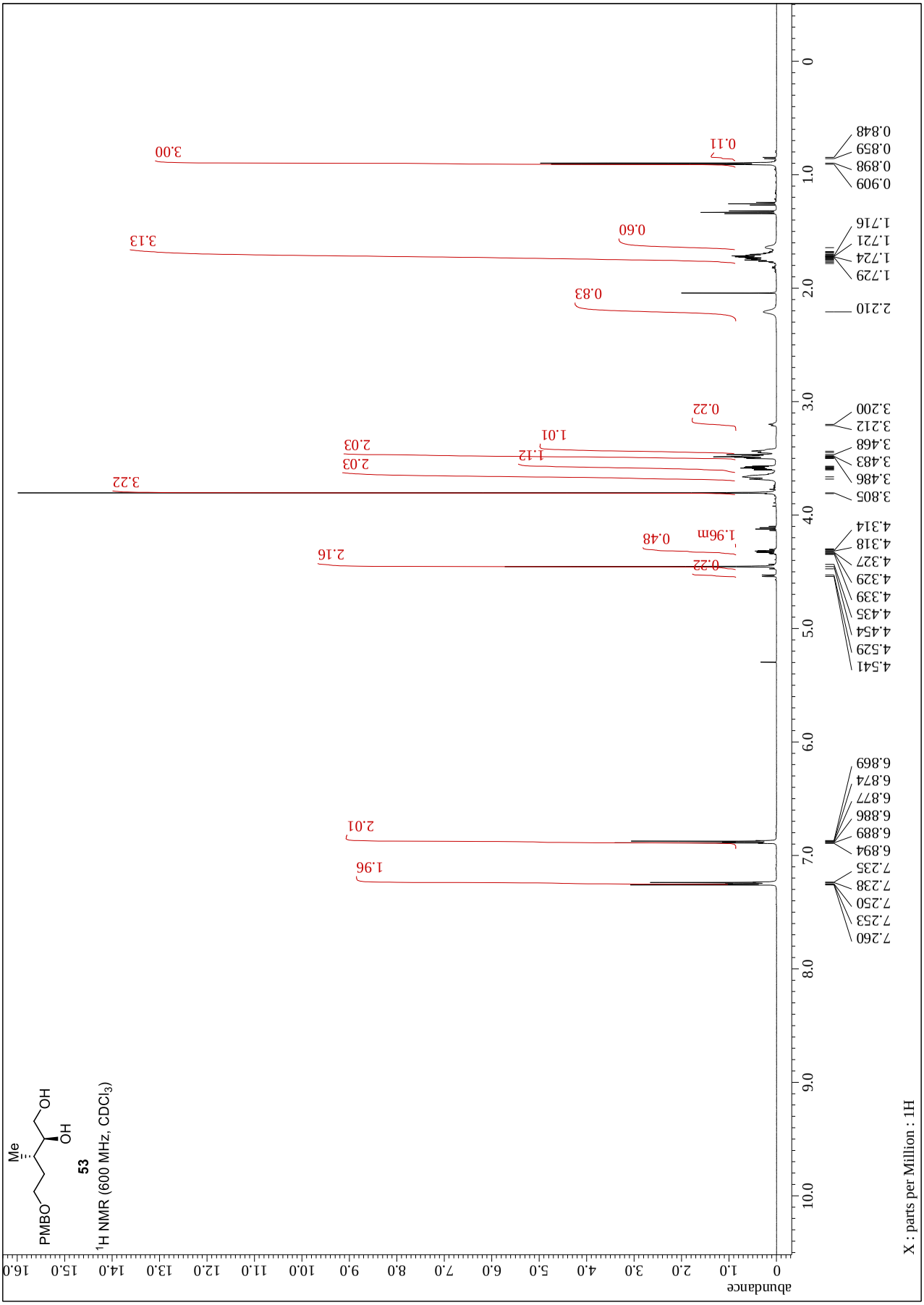
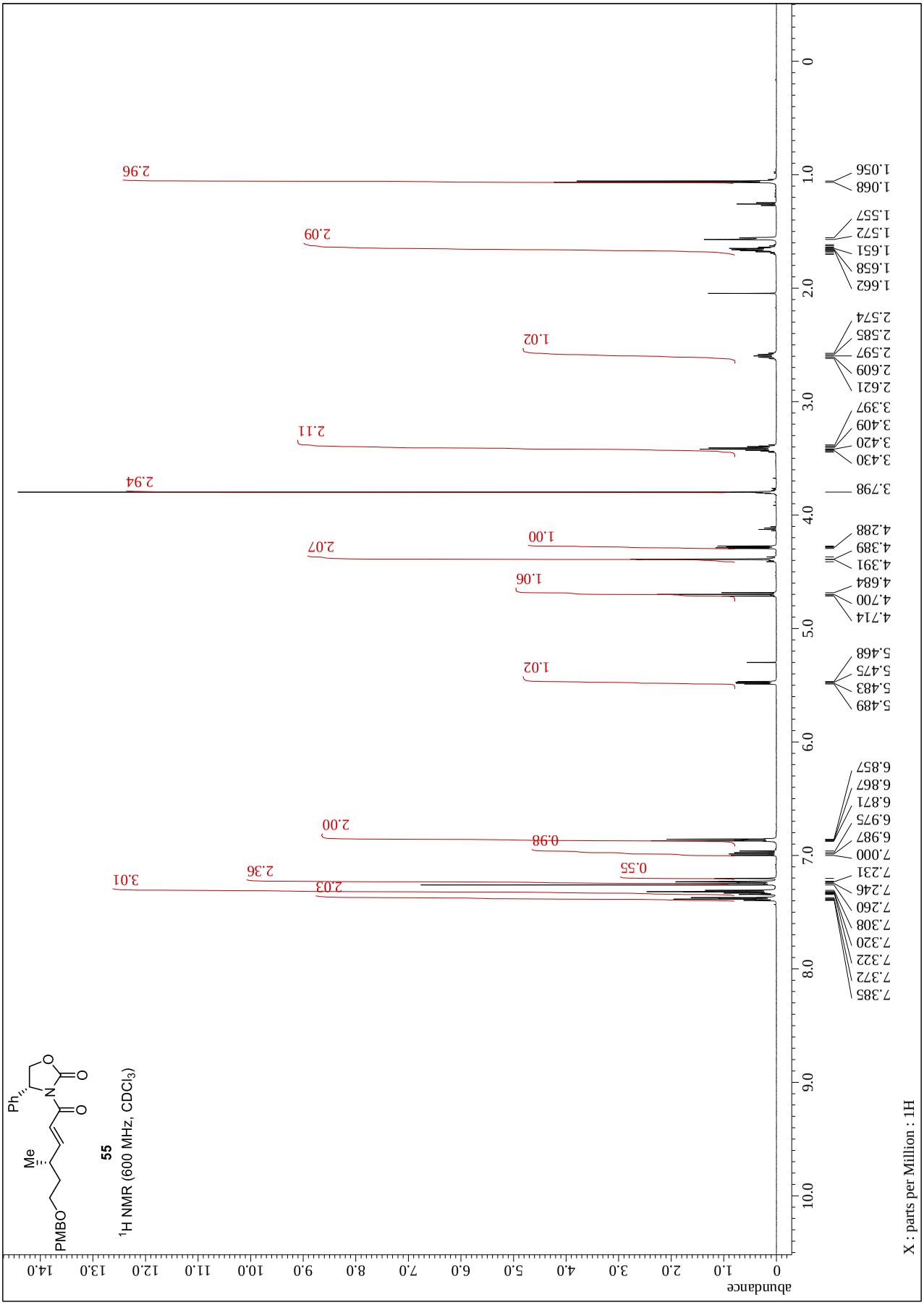
2.04
2.20
2.30
2.52
2.00
1.93
3.28
1.873
1.863
1.853
1.844
1.834
3.805
3.777
3.775
3.770
3.761
3.649
3.639
3.630
4.453
7.304
7.289
7.265
7.260
7.257
7.249
7.245
7.242
6.892
6.888
6.884
6.873
6.869
6.860

PMBO
OEt
O
49
1H NMR (600 MHz, CDCl3)
abundance
2.72
2.16
0.95
0.89
2.00
2.05
3.10
2.01
1.98
2.98
7.266
7.260
7.249
7.244
6.986
6.969
6.964
6.947
6.891
6.887
6.875
6.869
5.906
5.901
5.898
5.867
5.863
5.859
4.212
4.195
4.176
4.158
3.806
3.569
3.553
3.536
2.522
2.519
2.506
2.502
2.489
2.486
2.468
1.303
1.285
1.268
X : parts per Million : 1H


PMBO
OH
50
1H NMR (600 MHz, CDCl3)
abundance
3.17
2.22
1.69
2.01
2.07
3.24
2.00
1.93
7.269
7.265
7.260
7.251
7.246
6.886
6.882
6.874
6.871
5.723
5.721
5.716
5.713
5.708
4.445
4.097
3.805
3.501
3.490
3.478
2.376
2.371
2.366
2.364
2.360
2.355
2.346
X : parts per Million : 1H

PMBO
O
OH
51
1H NMR (600 MHz, CDCl3)
abundance
2.57
1.94
3.09
1.99
0.98
1.13
1.00
1.03
0.93
0.93
1.00
1.00
0.88
1.09
7.269
7.265
7.260
7.253
7.250
7.245
6.894
6.889
6.886
6.877
6.874
6.869
4.473
4.453
4.451
4.431
3.887
3.806
3.580
3.570
3.098
3.095
2.976
2.972
2.968
1.921
1.919
1.911
1.833
1.822
1.809
1.798
1.671
1.662
1.660
1.650
1.604
X : parts per Million : 1H


PMBO
Me
OH
OH
53
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
3.00
0.11
3.13
0.60
0.83
2.10
1.729
1.724
1.721
1.716
0.909
0.898
0.859
0.848
3.22
2.03
2.03
1.12
1.01
0.22
3.805
3.486
3.483
3.468
3.212
3.200
2.16
0.22
1.96m
0.48
4.541
4.529
4.454
4.435
4.339
4.329
4.327
4.318
4.314
2.01
1.96
7.260
7.253
7.250
7.238
7.235
6.894
6.889
6.886
6.877
6.874
6.869


55
^{1}H NMR (600 MHz, $CDCl_3$)
PMBO
Me
Ph
abundance
X : parts per Million : 1H
3.01
2.36
2.03
0.55
2.00
0.98
1.02
1.06
2.07
1.00
2.94
2.11
1.02
2.09
2.96
7.385
7.372
7.322
7.320
7.308
7.260
7.246
7.231
7.000
6.987
6.975
6.871
6.867
6.857
5.489
5.483
5.475
5.468
4.714
4.700
4.684
4.391
4.389
4.288
3.798
3.430
3.420
3.409
3.397
2.621
2.609
2.597
2.585
2.574
1.662
1.658
1.651
1.572
1.557
1.068
1.056

Ph
Me
PMBO
N
O
Me
O
O
56
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

Me
PMBO
OH
Me
57
1H NMR (600 MHz, CDCl3)
abundance
2.15
1.93
0.94
1.12
1.10
1.03
1.04
1.07
3.00
22.42m
22.88m
4.52
2.28
2.54
3.24
7.263
7.260
7.253
7.250
7.245
6.888
6.883
6.880
6.872
6.868
6.864
4.448
4.429
4.422
4.403
4.393
3.801
3.616
3.490
3.485
3.436
3.420
2.899
2.891
2.798
2.784
2.757
1.587
1.576
1.569
1.565
1.558
1.346
1.331
0.860
0.849
0.846
0.835
X : parts per Million : 1H

Me
PMBO
Me
OH
62
1H NMR (600 MHz, CDCl3)
abundance
2.49
1.94
2.96
2.95
0.90
1.00
0.82
0.77
1.98
1.04
1.37
1.00
1.00
2.85
2.98
7.266
7.260
7.251
6.889
6.884
6.881
6.869
6.865
4.450
4.430
4.420
4.400
4.392
4.389
4.377
4.374
3.805
3.488
3.436
3.425
3.421
2.457
2.453
1.881
1.871
1.774
1.757
1.585
1.462
0.898
0.887
0.846
0.834
X : parts per Million : 1H

Me
PMBO
Me
OH
I
63
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
2.98
1.88
0.87
0.86
2.93
1.16
1.01
1.01
0.99
1.00
3.09
2.92
1.76
1.32
1.08
0.99
0.98
0.93
0.61
7.262
7.260
7.249
6.888
6.873
6.544
6.315
6.291
4.445
4.426
4.416
4.397
4.124
4.113
3.809
3.491
3.489
3.480
3.437
3.435
3.423
1.585
1.580
1.494
1.362
1.352
1.270
1.259
1.250
1.246
1.227
0.881
0.870
0.823
0.811

Me
PMBO
Me
OTBS
I
64
1H NMR (600 MHz, CDCl3)
abundance
4.06
1.93
0.89
0.87
1.99
1.06
3.02
46.74m
1.91
2.79
0.95
1.00
0.91
8.61
2.70
3.12
2.75
2.73
7.260
7.247
6.883
6.868
6.521
6.497
6.197
6.175
6.173
4.442
4.422
4.419
4.399
4.101
4.091
3.805
3.469
3.466
3.432
3.415
2.373
2.370
1.647
1.636
1.630
1.624
1.554
1.118
0.874
0.843
0.804
0.026
0.008
X : parts per Million : 1H

69
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

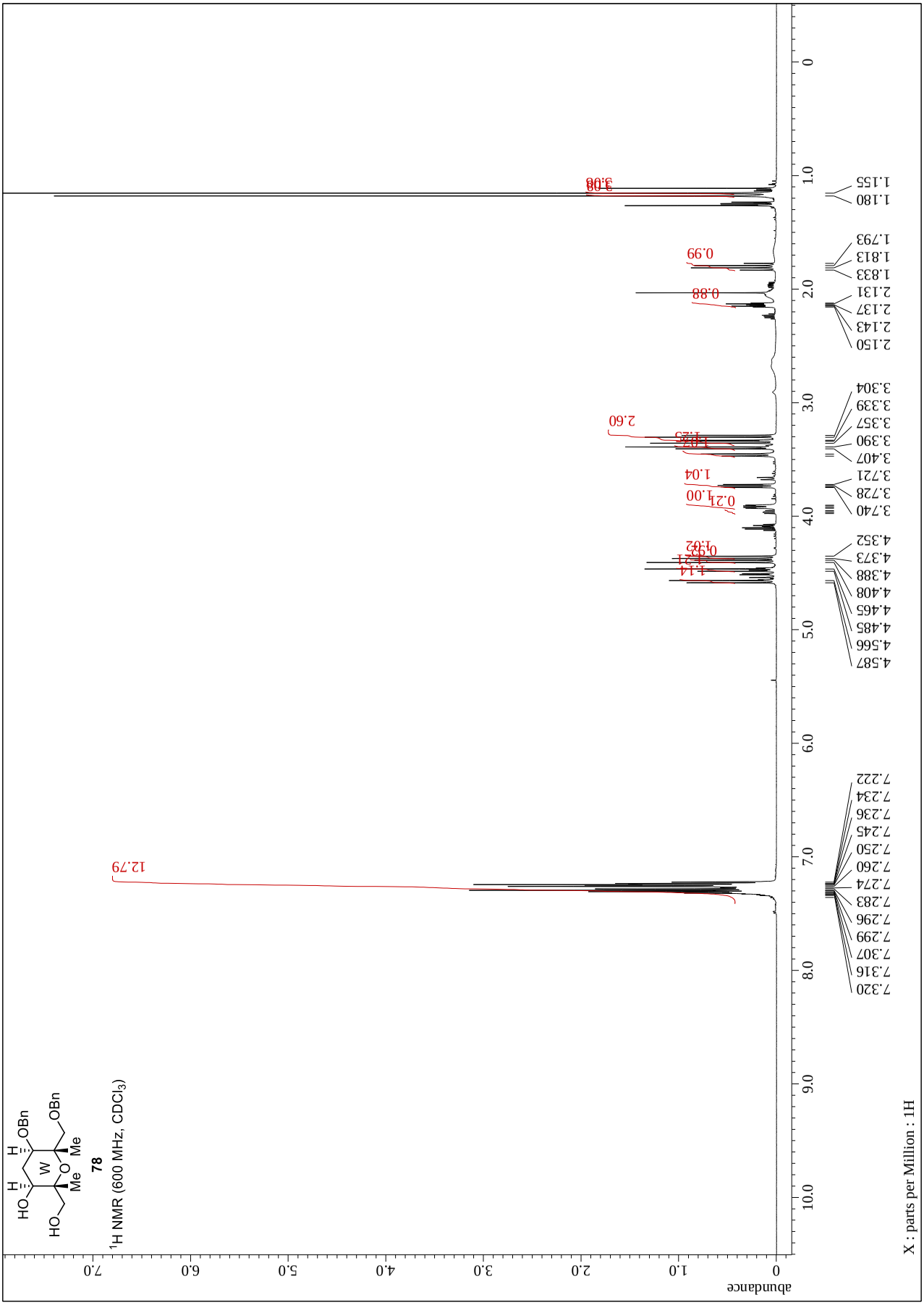
70
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

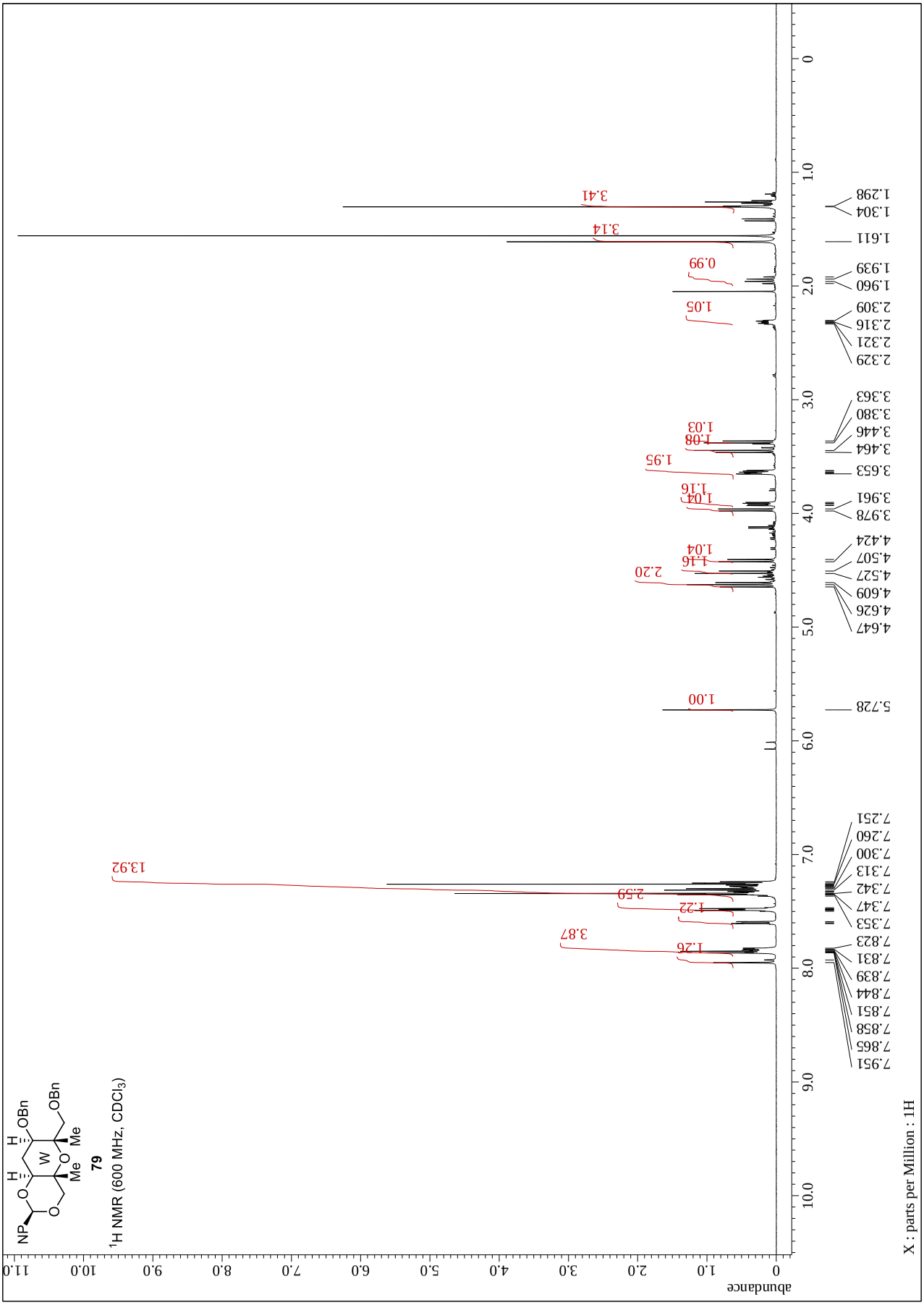
Me
PMBO
Me
H
O
F'
E'
D'
C'
OBn
OBn
Me
Me
Me
O
O
H
70
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

72
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBDPSO
Me
TBSO
Me
OTBS
F'
E'
D'
C'
OH
OH
Me
Me
Me
2
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H
4.25
5.93
2.08
3.20
1.98
1.09
1.03
1.86
1.04
3.15
3.21
8.11
1.20
5.34
5.07
4.09
8.96
6.12
3.46
2.72
7.675
7.663
7.661
7.377
7.260
3.785
3.780
3.669
3.658
3.646
3.642
3.634
3.631
3.481
3.205
3.103
2.778
2.188
2.182
2.179
2.002
1.671
1.595
1.574
1.434
1.355
1.305
1.048
0.883
0.858
0.776
0.752
0.059
0.047
0.024

TBDPSO
Me
TBSO
Me
OTBS
F'
E'
D'
C'
Me
Me
Me
OH
OH
2
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
135.719
134.331
134.302
129.630
127.724
86.246
83.125
83.096
79.965
77.380
77.294
77.160
76.949
74.872
74.508
74.000
73.273
71.358
62.760
61.362
53.079
38.756
36.180
35.845
34.849
33.681
33.327
27.055
26.088
26.050
21.713
21.511
19.376
18.256
18.151
16.379
16.006
-3.488
-3.833
-4.542

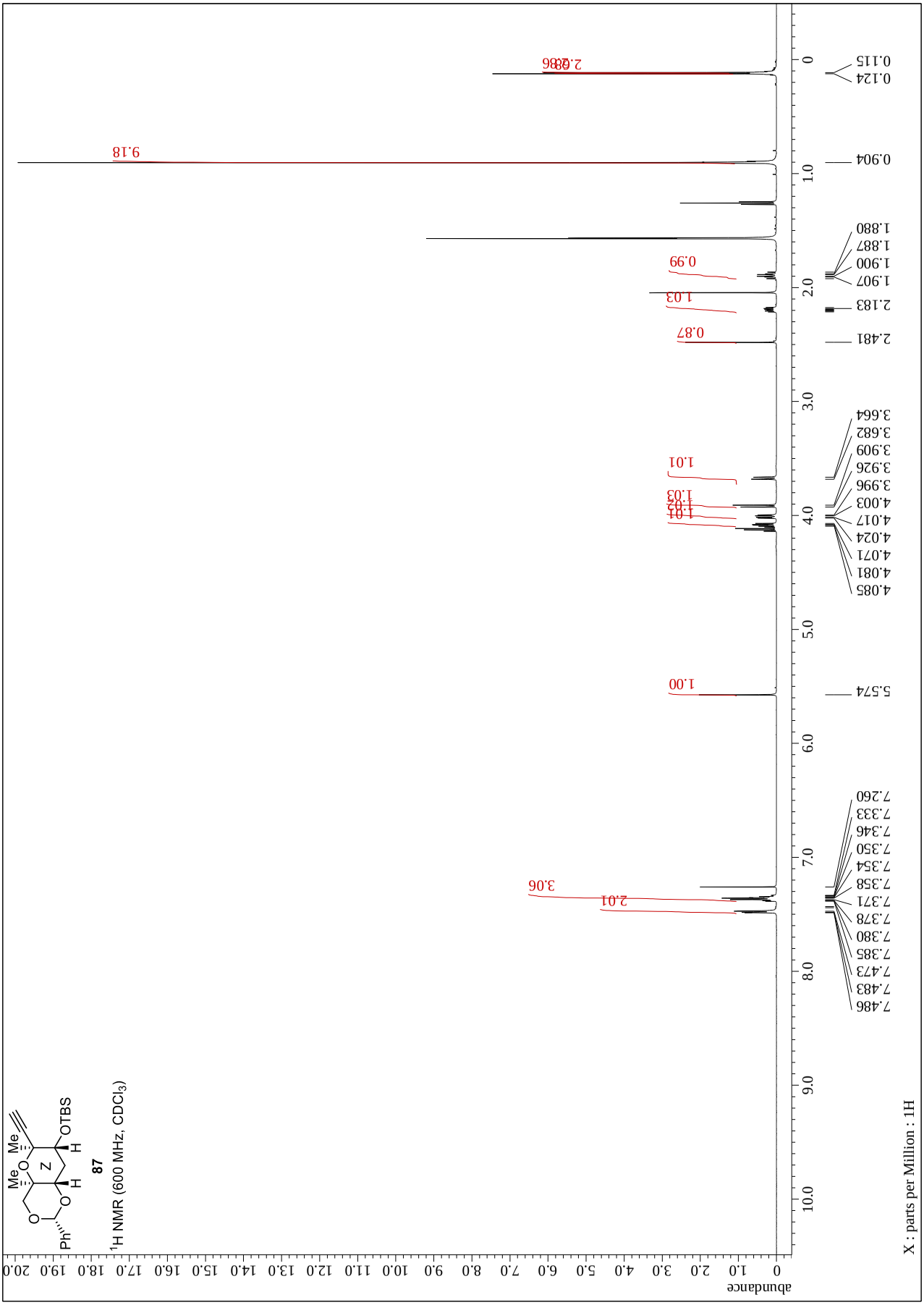

78
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H

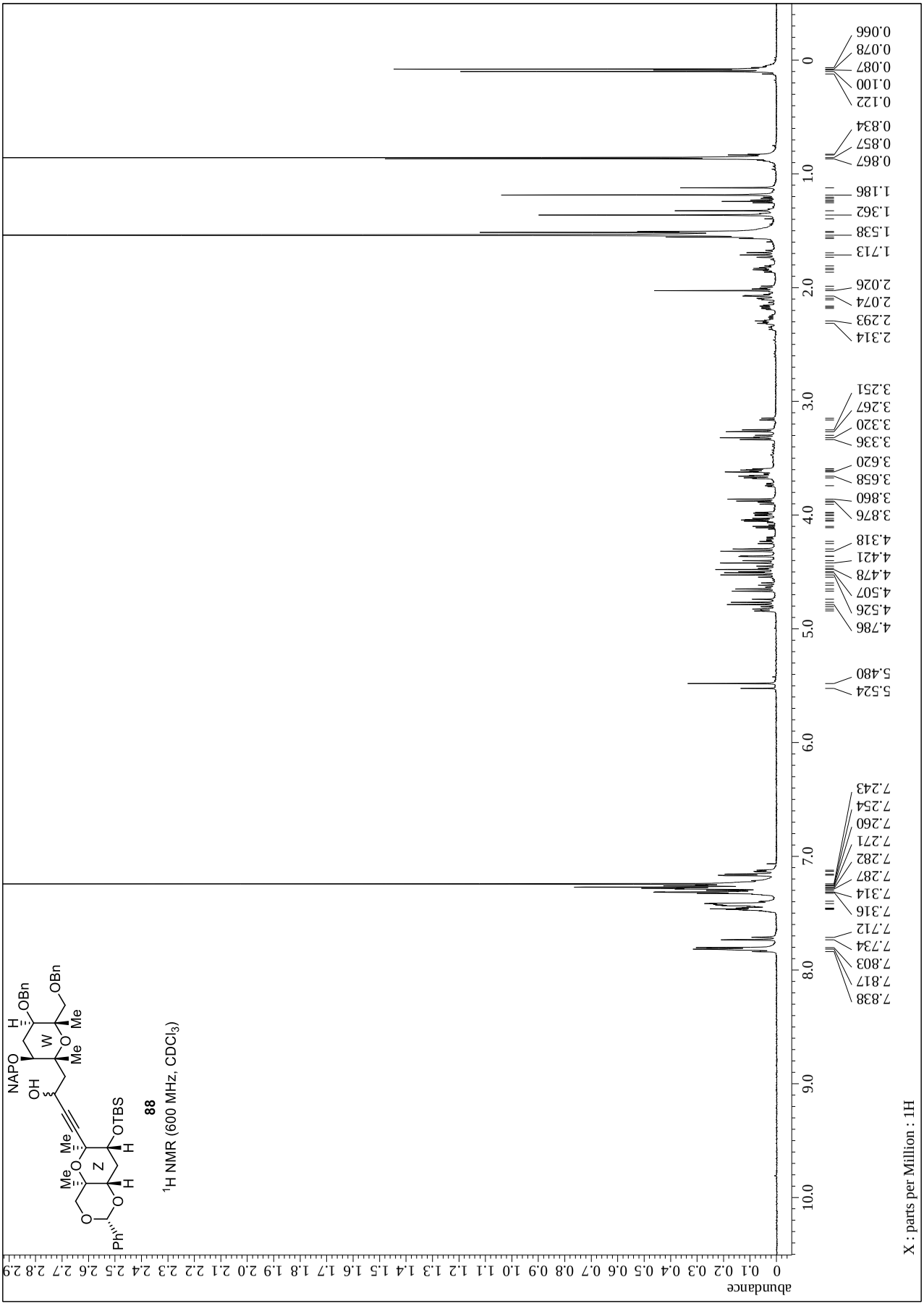

79
^{1}H NMR (600 MHz, $CDCl_3$)
abundance
X : parts per Million : 1H
13.92
3.87
3.41
3.14
2.59
2.20
1.95
1.26
1.22
1.05
1.00
0.99
7.951
7.865
7.858
7.851
7.844
7.839
7.831
7.823
7.353
7.347
7.342
7.313
7.300
7.260
7.251
5.728
4.647
4.626
4.609
4.527
4.507
4.424
3.978
3.961
3.653
3.464
3.446
3.380
3.363
2.329
2.321
2.316
2.309
1.960
1.939
1.611
1.304
1.298

NAPO
H
H
OBn
W
HO
O
OBn
Me
Me
80
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

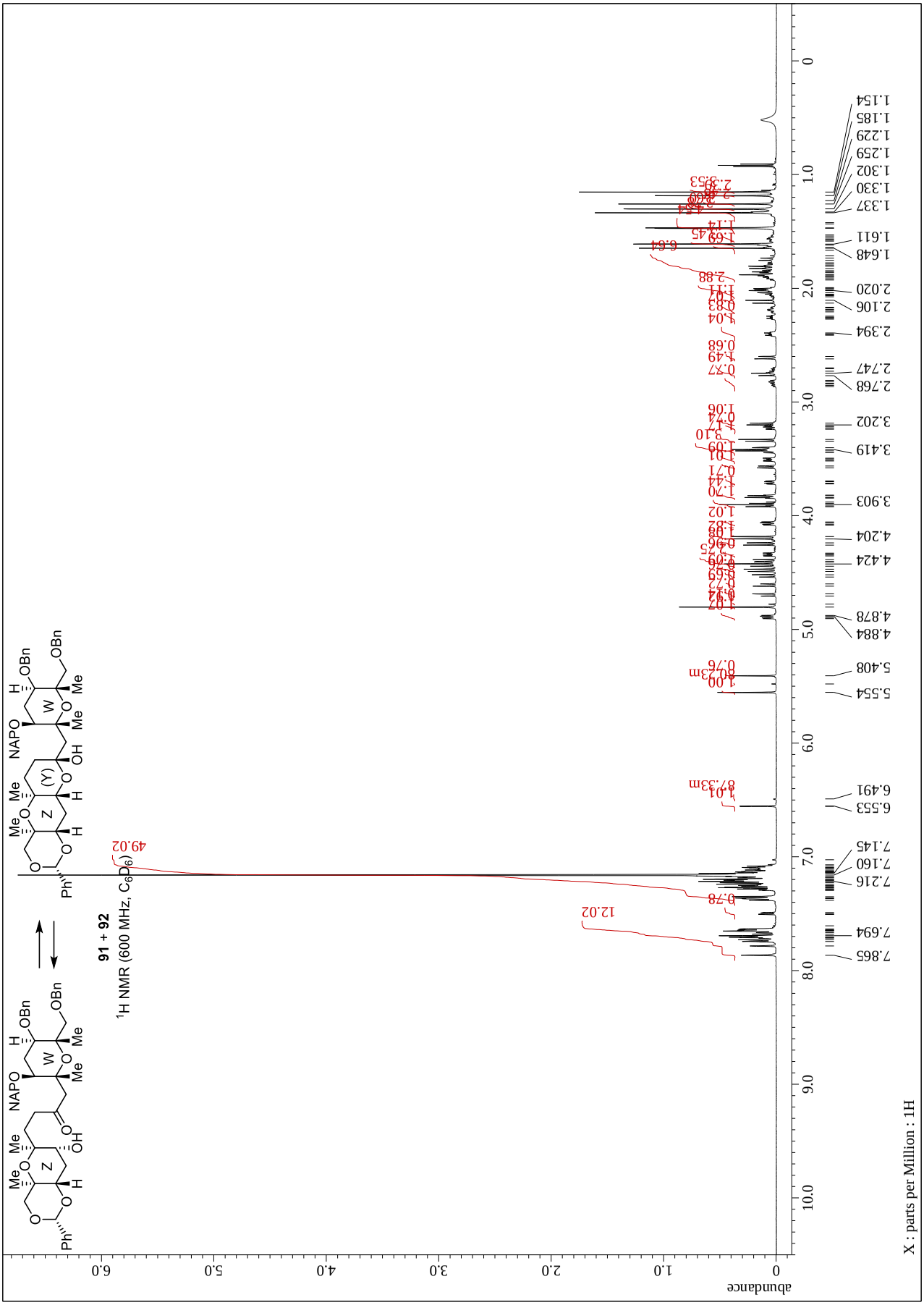
NAPO
H
H
OBn
W
NC
O
OBn
Me
Me
82
1H NMR (600 MHz, CDCl3)
15.66
4.56
4.33
0.94
1.17
1.01
0.95
0.97
0.94
2.87
2.94
abundance
X : parts per Million : 1H

NAPO
H
H
OBn
W
OBn
O
O
Me
Me
83
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H


Me
Me
O
Z
OTBS
H
H
O
O
Ph
87
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
0.115
0.124
0.904
1.880
1.887
1.900
1.907
2.183
2.481
3.664
3.682
3.909
3.926
3.996
4.003
4.017
4.024
4.071
4.081
4.085
5.574
7.260
7.333
7.346
7.350
7.354
7.358
7.371
7.378
7.380
7.385
7.473
7.483
7.486
9.18
0.87
0.99
1.00
1.01
1.03
2.01
3.06

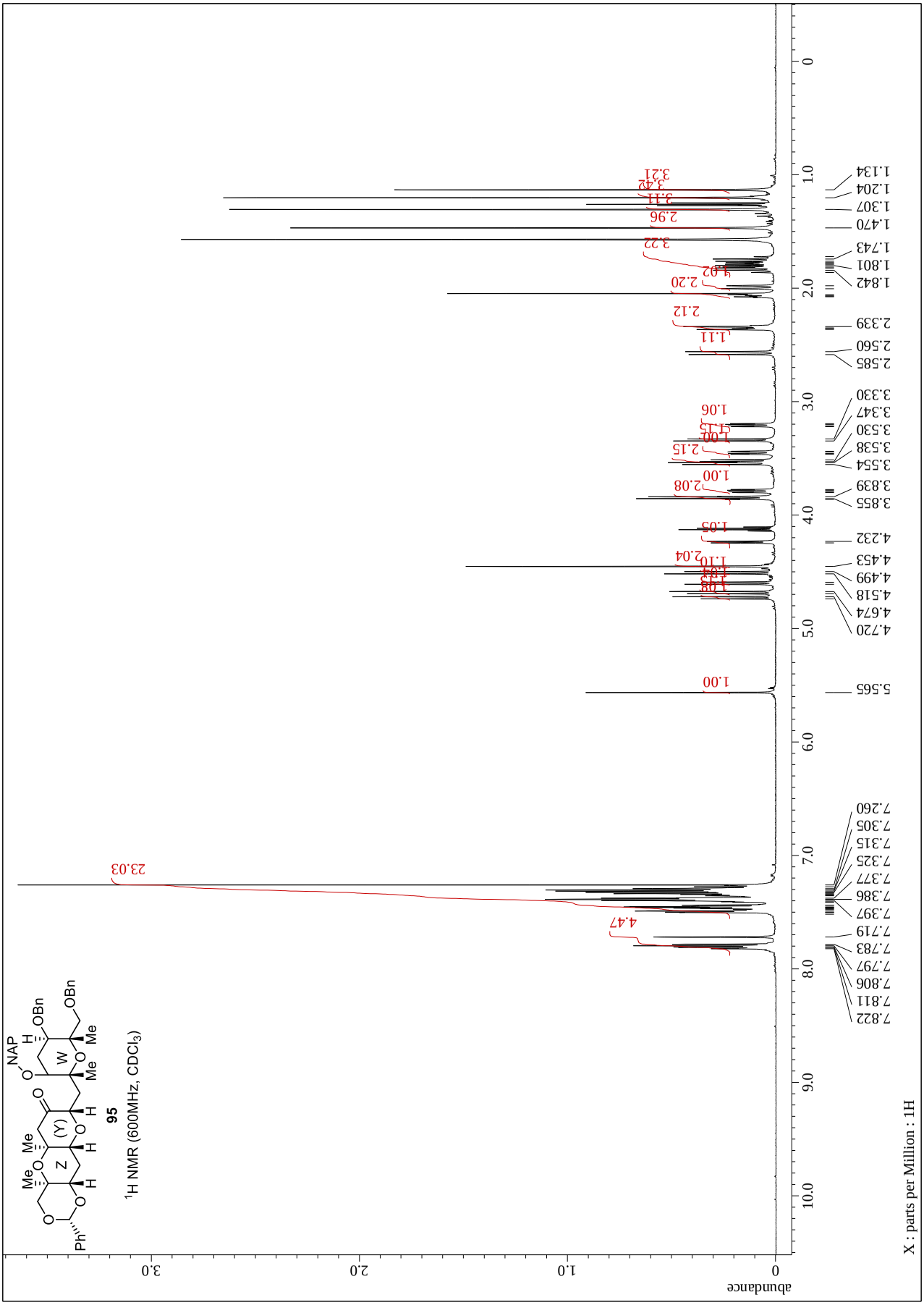

88
^{1}H NMR (600 MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

Me
Me
NAPO
H
OBn
Z
W
OBn
Ph
O
H
O
TBS
Me
Me
90
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

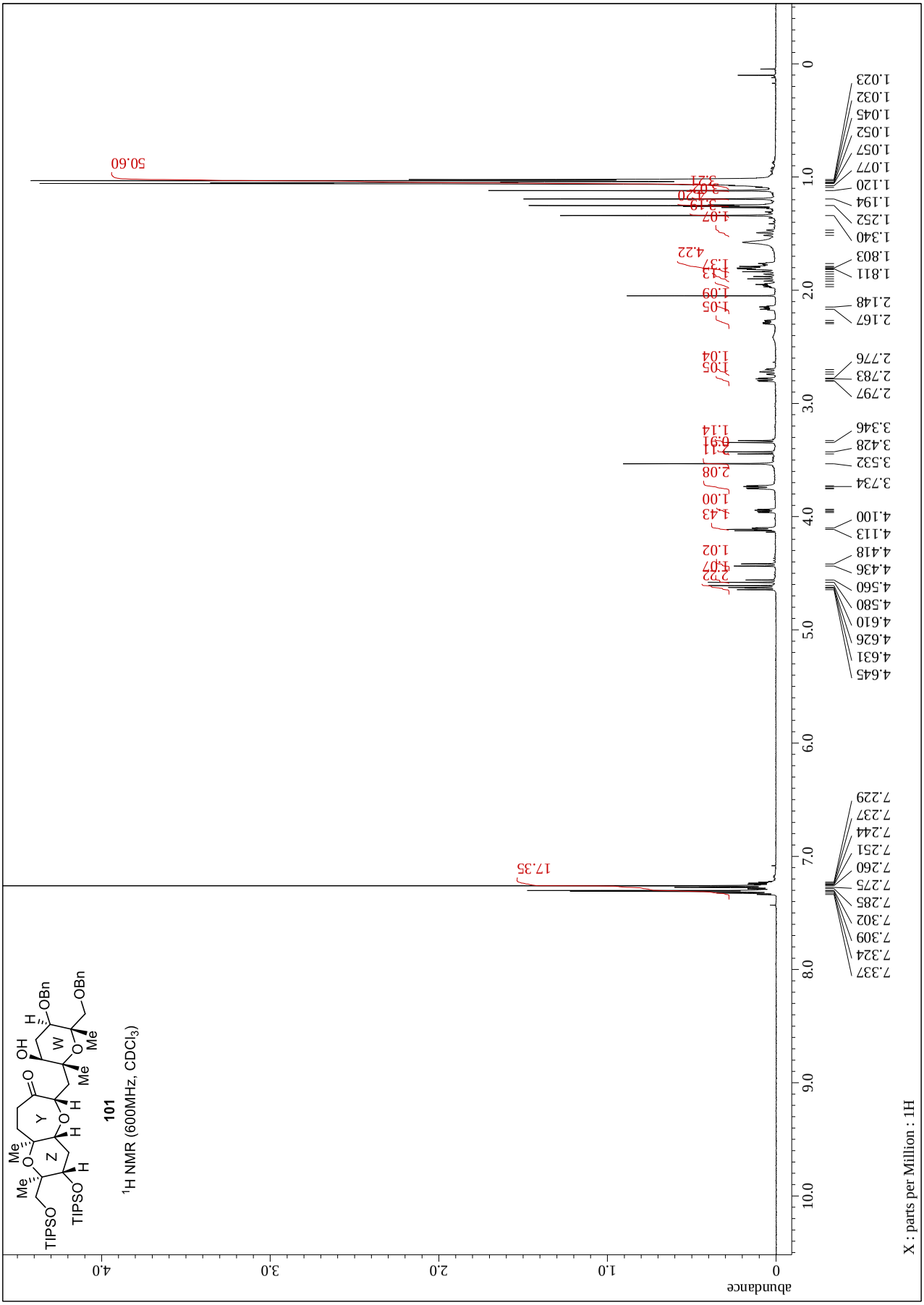

91 + 92
^{1}H NMR (600 MHz, C_6D_6)
abundance
X : parts per Million : 1H

93
1H NMR (600MHz, C6D6)
abundance
X : parts per Million : 1H

94
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H

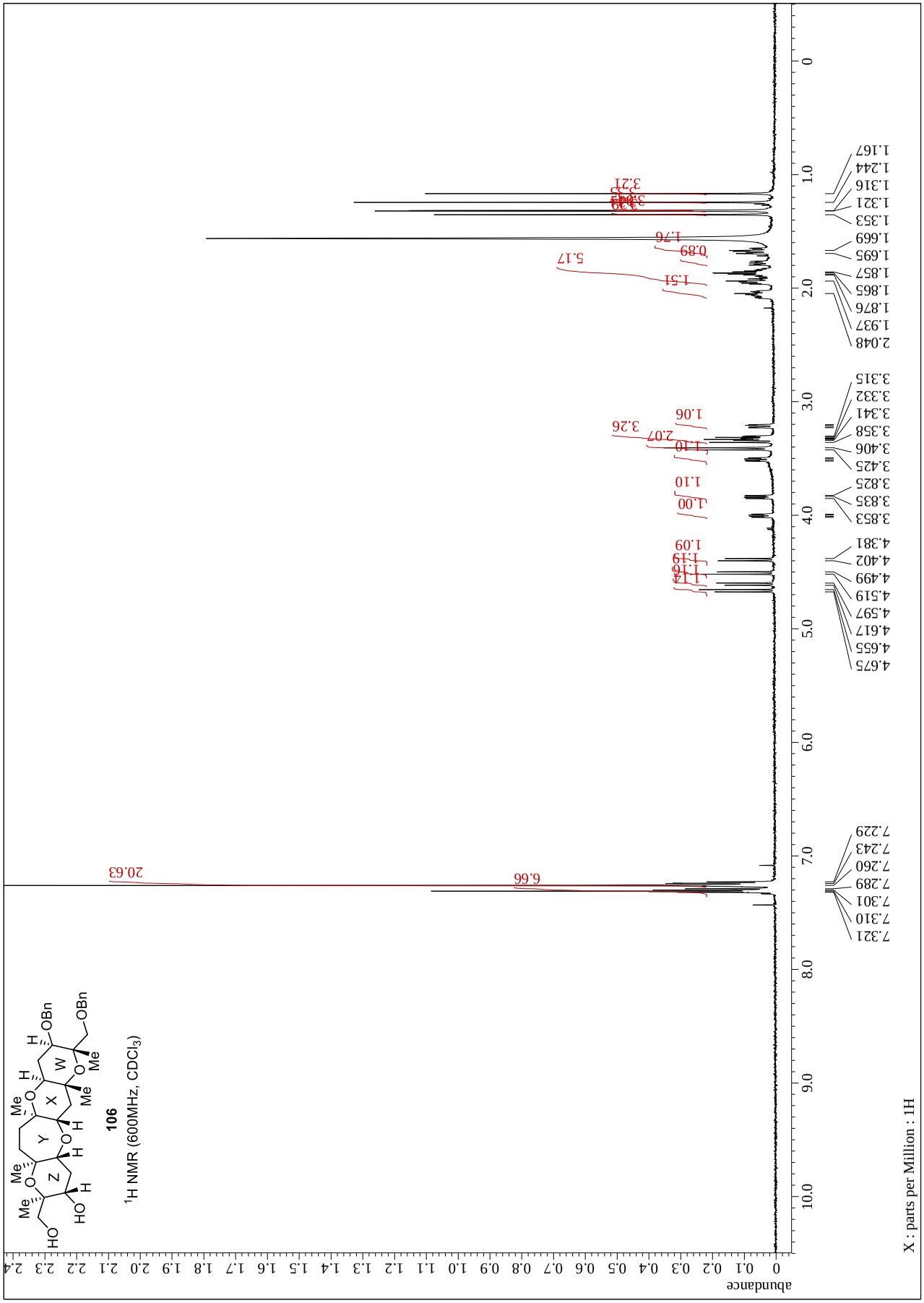

95
^{1}H NMR (600MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

NAP
Me
Me
O
O
HO
Z
Y
W
H
OBn
HO
H
H
O
H
Me
O
Me
OBn
97
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H

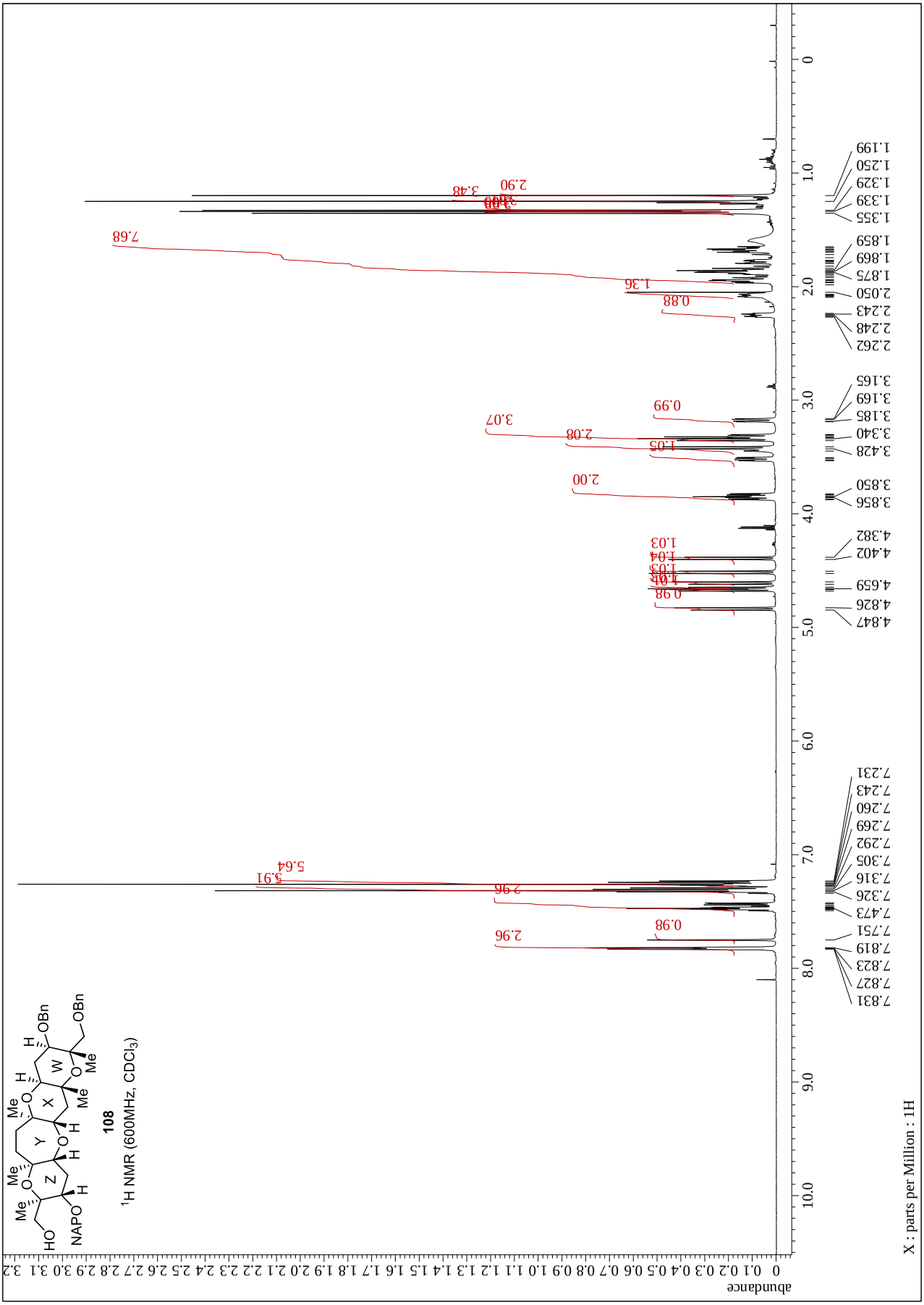

101
^{1}H NMR (600MHz, CDCl$_3$)
abundance
X : parts per Million : 1H
17.35
50.60
4.22
7.337
7.324
7.309
7.302
7.285
7.275
7.260
7.251
7.244
7.237
7.229
4.645
4.631
4.626
4.610
4.580
4.560
4.436
4.418
4.113
4.100
3.734
3.532
3.428
3.346
2.797
2.783
2.776
2.167
2.148
1.811
1.803
1.340
1.252
1.194
1.120
1.077
1.057
1.052
1.045
1.032
1.023

Me
Me
SEt
H
H
TIPSO
Z
Y
X
W
OBn
TIPSO
H
H
H
Me
O
Me
OBn
102
1H NMR (600MHz, CDCl3)
abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7 2.8 2.9 3.0
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
7.371 7.360 7.337 7.325 7.312 7.297 7.284 7.274 7.260 7.254 7.249 7.244 7.237
4.776 4.757 4.578 4.538 4.127 4.115 3.870 3.528 3.478 3.469 3.152 3.144
2.440 2.348 2.336 2.315 2.046 1.934 1.755 1.545 1.260 1.094 1.085 1.070 1.057 1.051 1.033 1.009
X : parts per Million : 1H

105
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H


106
^{1}H NMR (600MHz, CDCl$_3$)
X : parts per Million : 1H
abundance
20.63
6.66
5.17
3.26
1.76
1.51
1.10
1.09
1.00
0.89
7.321
7.310
7.301
7.289
7.260
7.243
7.229
4.675
4.655
4.617
4.597
4.519
4.499
4.402
4.381
3.853
3.835
3.825
3.425
3.406
3.358
3.341
3.332
3.315
2.048
1.937
1.876
1.865
1.857
1.695
1.669
1.353
1.321
1.316
1.244
1.167

107
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H


108
^{1}H NMR (600MHz, CDCl$_3$)
X : parts per Million : 1H
abundance

109
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H

3
1H NMR (600MHz, CDCl3)
abundance
X : parts per Million : 1H

TBDPSO
Me
TBSO
OTBS
F'
E'
D'
C'
CN
ONAP
OH
OBn
OBn
Y
X
W
Z
112
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

TBDPSO
Me
TBSO
Me
OTBS
F'
E'
D'
C'
Me
Me
Me
Me
Me
Me
Me
Me
Y
X
W
Z
OBn
OBn
CN
ONAP
OH
112
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
138.994
138.975
138.544
135.643
128.356
127.667
120.333
118.877
86.237
86.199
85.490
84.849
84.753
77.371
77.160
76.949
73.598
64.904
62.597
61.161
52.888
52.792
46.128
38.037
33.585
26.969
26.021
21.473
21.004
19.778
19.300
18.419
18.074
-3.507
-3.795
-3.862
-4.618

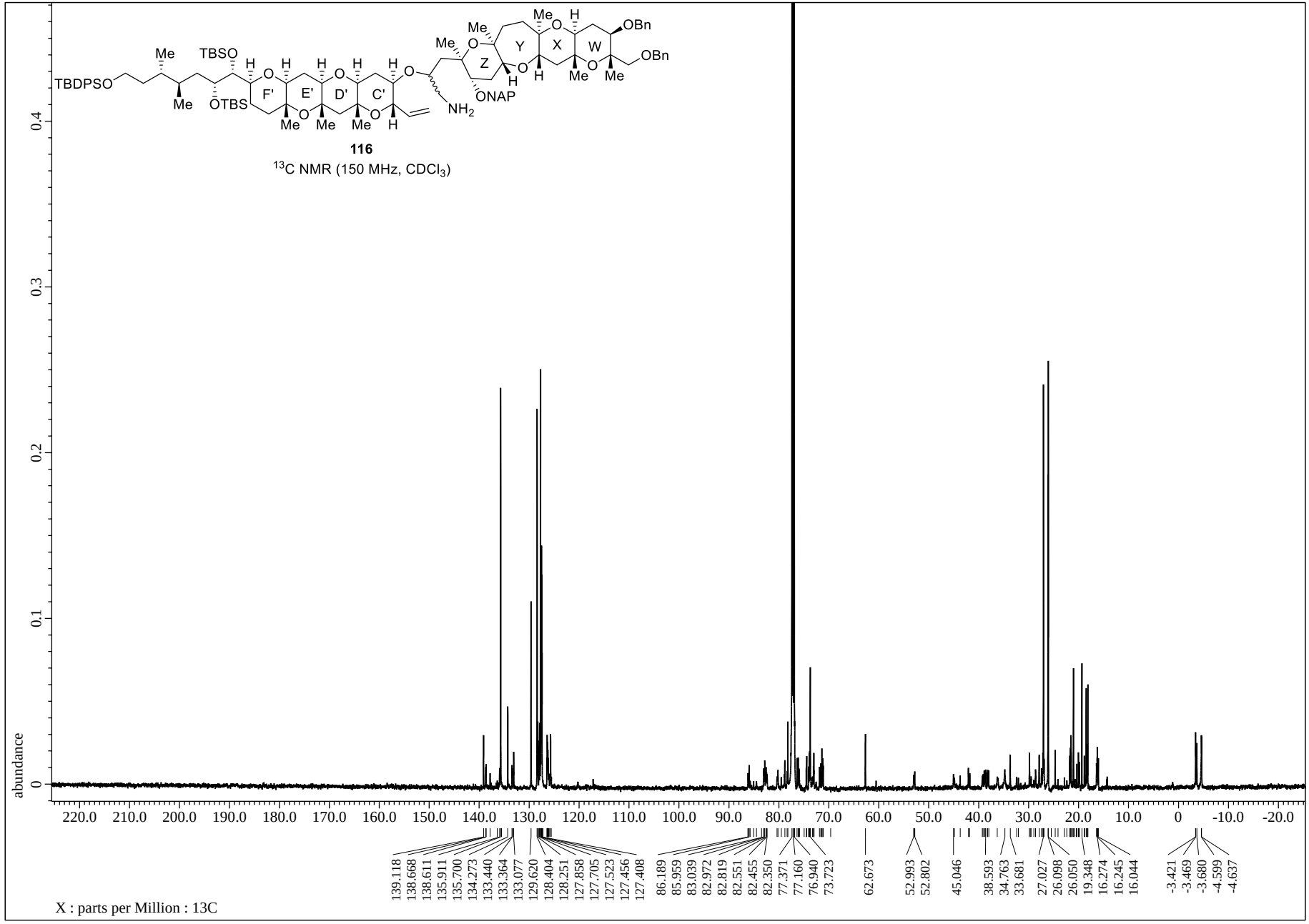
TBDPSO
Me
TBSO
Me
OTBS
F'
E'
D'
C'
CN
ONAP
Me
Me
Y
X
W
Z
OBn
OBn
Me
Me
Me
Me
Me
Me
Me
H
114
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

114
13CNMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
139.042
138.630
135.671
134.254
128.366
127.686
127.428
120.256
118.734
118.485
117.920
86.237
85.624
84.906
78.165
77.371
77.160
76.940
73.952
73.665
65.345
62.673
62.041
52.917
52.840
46.032
45.018
42.001
38.124
33.652
27.017
26.059
26.012
21.473
21.014
19.817
19.328
18.438
18.112
15.891
-3.488
-3.507
-3.776
-3.843
-4.570

115
1H NMR (600 MHz, CDCl3)
X : parts per Million : 1H

115
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
200.435
200.186
139.051
138.640
136.619
136.342
136.026
135.671
134.245
133.326
133.067
128.423
128.375
127.686
117.987
86.141
83.039
82.694
78.165
77.371
77.160
76.949
76.729
76.030
73.943
73.665
71.578
71.147
62.673
52.898
44.299
42.930
41.992
38.669
27.017
26.059
21.674
21.473
21.014
19.836
19.328
18.448
18.112
16.427
15.910
-3.498
-3.776
-4.580

116
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H


116
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C

117
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

117
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
139.032
138.620
138.592
137.002
136.591
136.284
136.016
135.662
134.216
128.366
127.676
118.868
118.360
117.518
117.154
116.924
116.780
116.598
86.103
85.988
85.835
85.586
85.260
85.174
83.039
78.146
77.371
77.160
76.949
73.646
62.664
52.965
52.878
46.664
42.001
39.005
33.633
26.998
26.059
26.012
19.309
18.112
16.389
16.035
15.968
15.872
-3.469
-3.527
-3.718
-3.843
-4.561
-4.647

TBDPSO
Me
TBSO
OTBS
Me
F'
E'
D'
C'
B'
Me
Me
Me
H
OH
ONAP
Me
Me
Z
Y
X
W
OBn
OBn
Me
Me
118
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

118
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
139.051
138.592
135.662
134.206
129.591
128.395
127.973
127.686
127.590
127.504
127.447
126.432
78.749
78.165
77.457
77.371
77.160
76.949
76.700
76.059
73.905
73.665
73.589
71.587
71.157
68.390
62.654
60.509
52.936
52.850
48.531
46.885
42.011
38.114
33.662
26.998
26.031
19.328
18.132
14.321
-3.450
-3.488
-3.737
-3.814
-4.570
-4.676

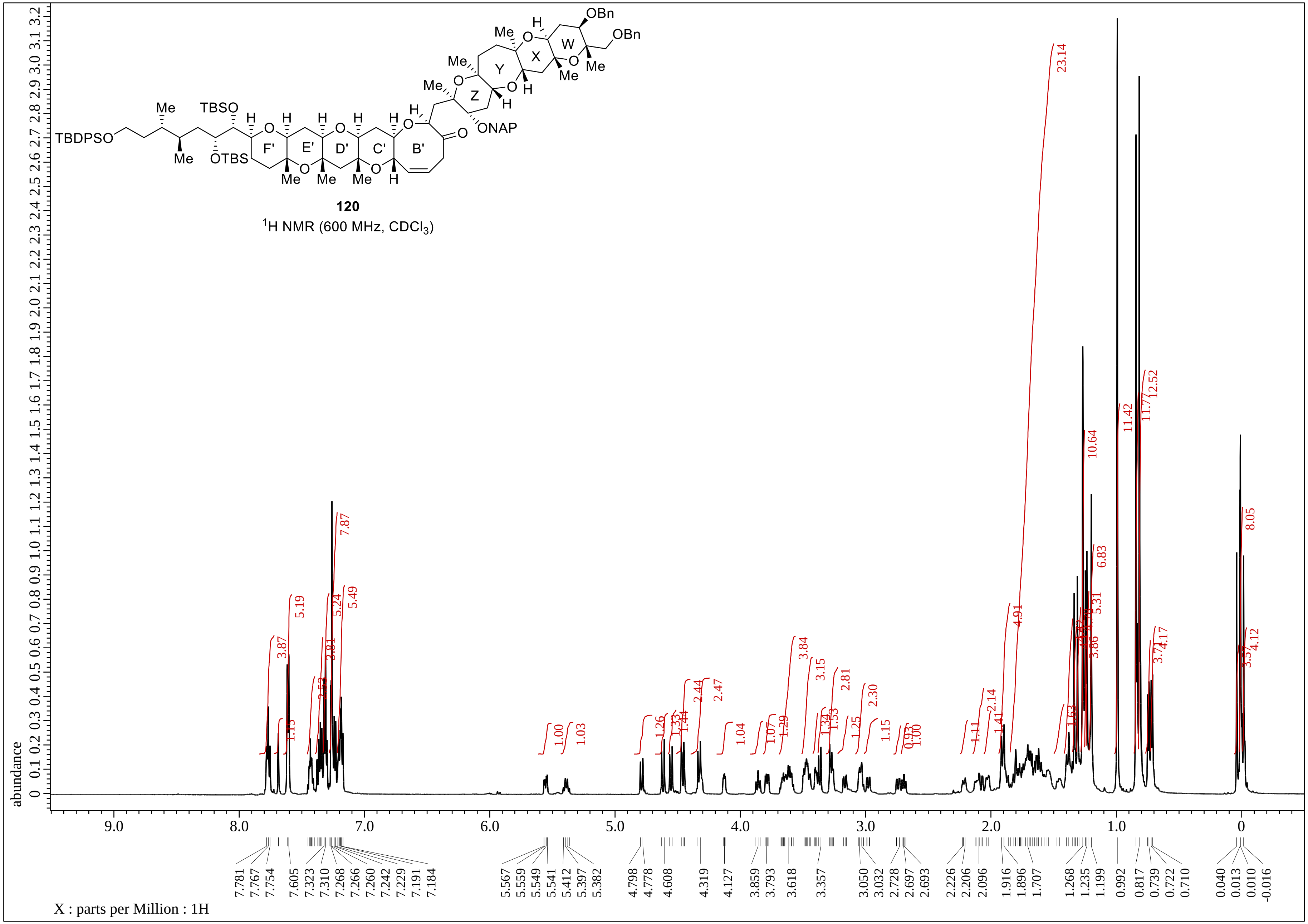
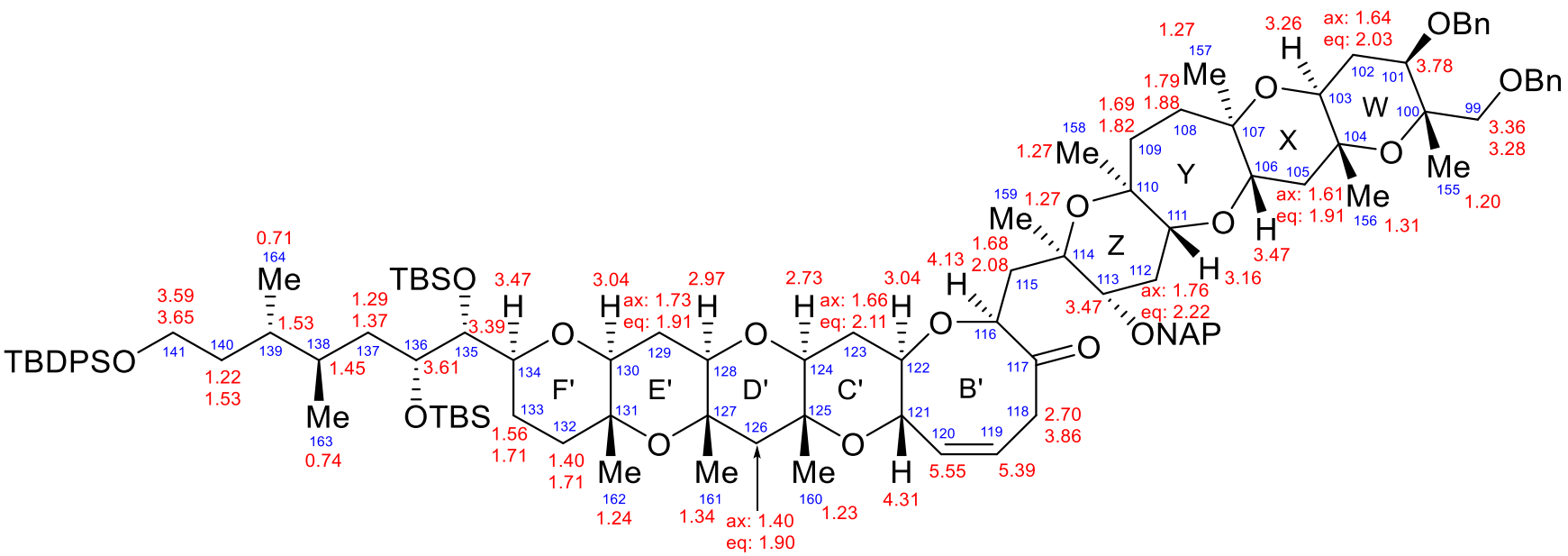
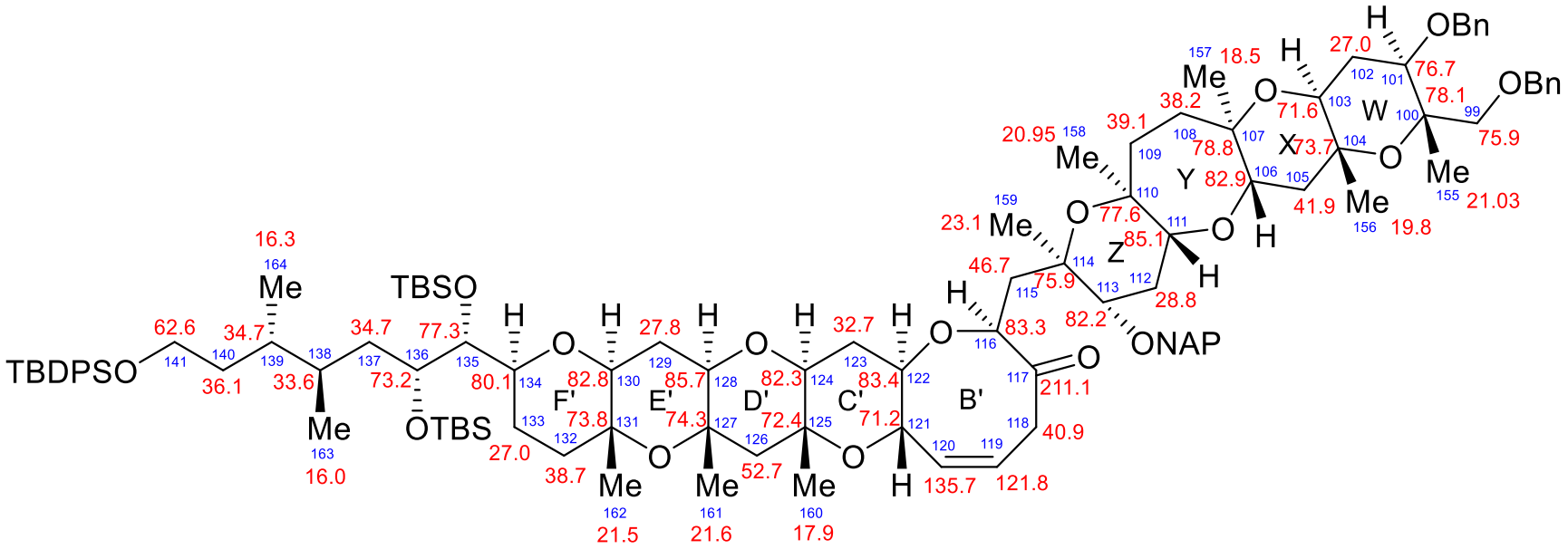

TBDPSO
Me
TBSO
OTBS
Me
F'
E'
D'
C'
B'
ONAP
OBn
OBn
W
X
Y
Z
120
¹H NMR (600 MHz, CDCl₃)
abundance
X : parts per Million : 1H
7.781
7.767
7.754
7.605
7.323
7.310
7.268
7.266
7.260
7.242
7.229
7.191
7.184
5.567
5.559
5.549
5.541
5.412
5.397
5.382
4.798
4.778
4.608
4.319
4.127
3.859
3.793
3.618
3.357
3.050
3.032
2.728
2.697
2.693
2.226
2.206
2.096
1.916
1.896
1.707
1.268
1.235
1.199
0.992
0.817
0.739
0.722
0.710
0.040
0.013
0.010
-0.016

Figure S1. Assignment of ^{1}H NMR of ketone **120**.

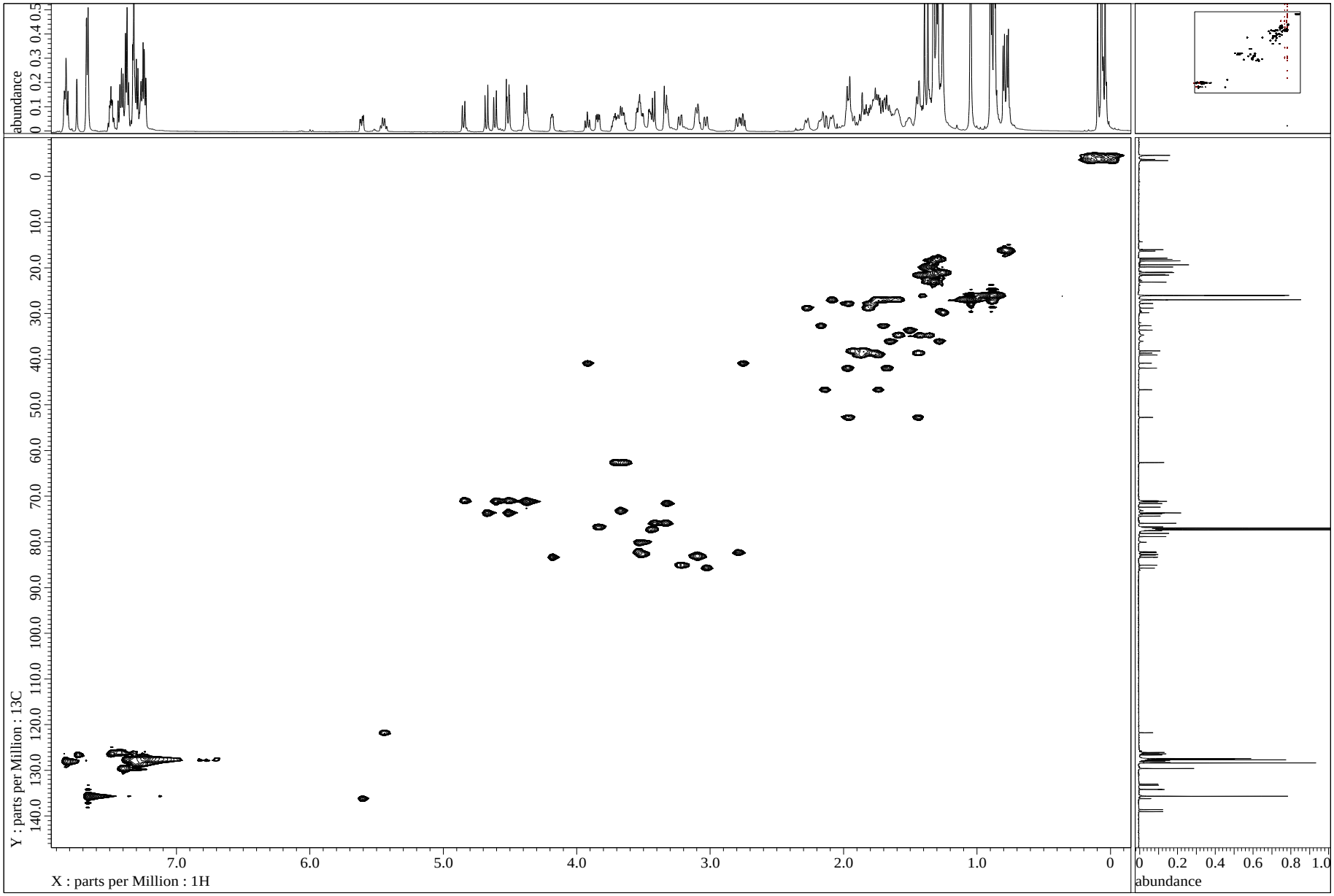


120
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
211.149
139.042
138.592
136.188
135.662
134.178
134.159
133.259
133.019
128.375
127.696
121.769
78.836
78.137
77.371
77.160
76.940
76.700
75.925
73.704
73.636
71.587
71.109
62.626
52.735
46.684
41.944
39.072
38.172
33.624
26.988
26.012
21.033
20.956
19.798
19.328
18.476
-3.479
-3.737
-4.628

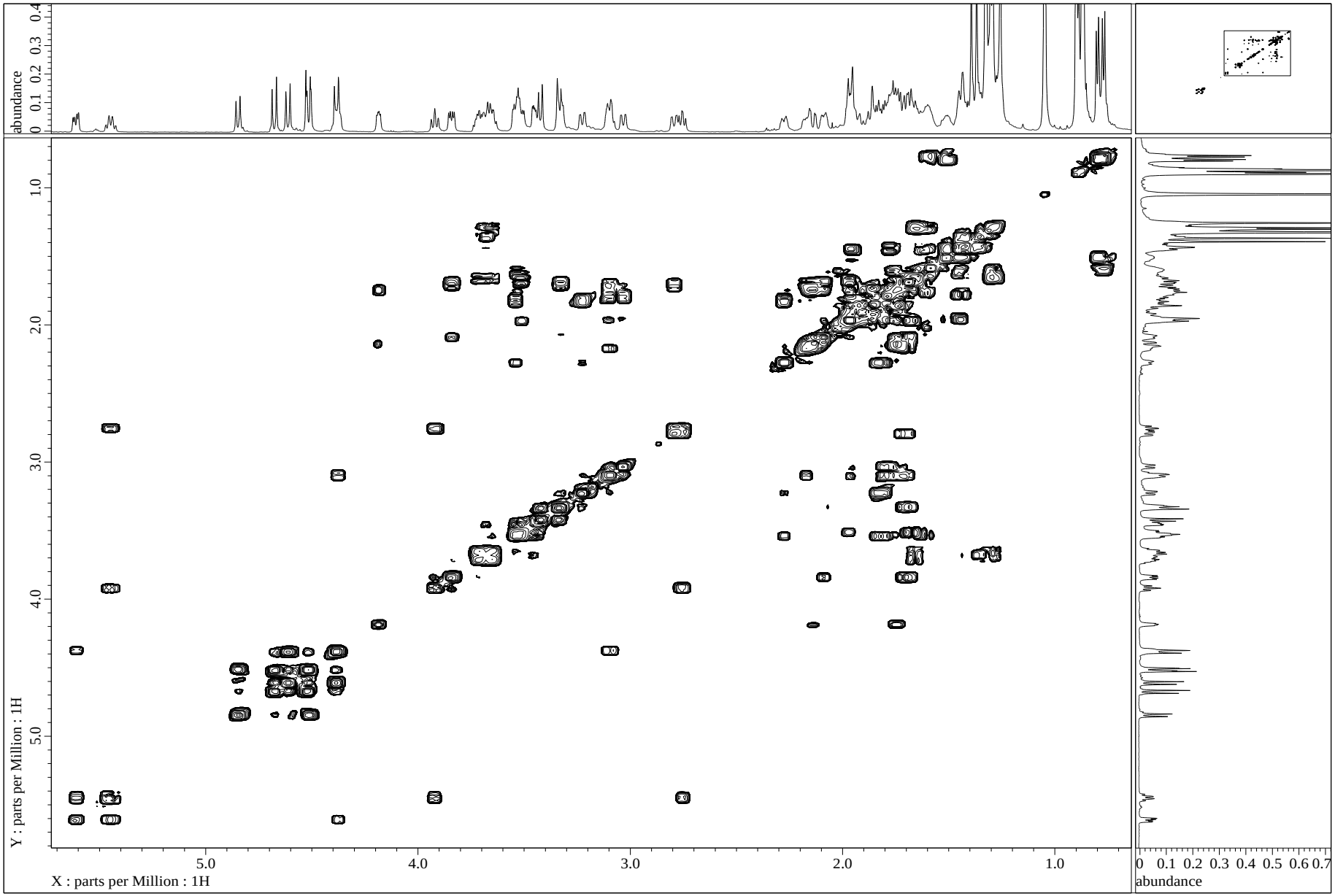
Figure S2. Assignment of ^{13}C NMR of ketone **120**.



HSQC spectrum of ketone **120**.



DQF–COSY spectrum of ketone **120**.



HSQC–TOCSY spectrum of ketone **120**.

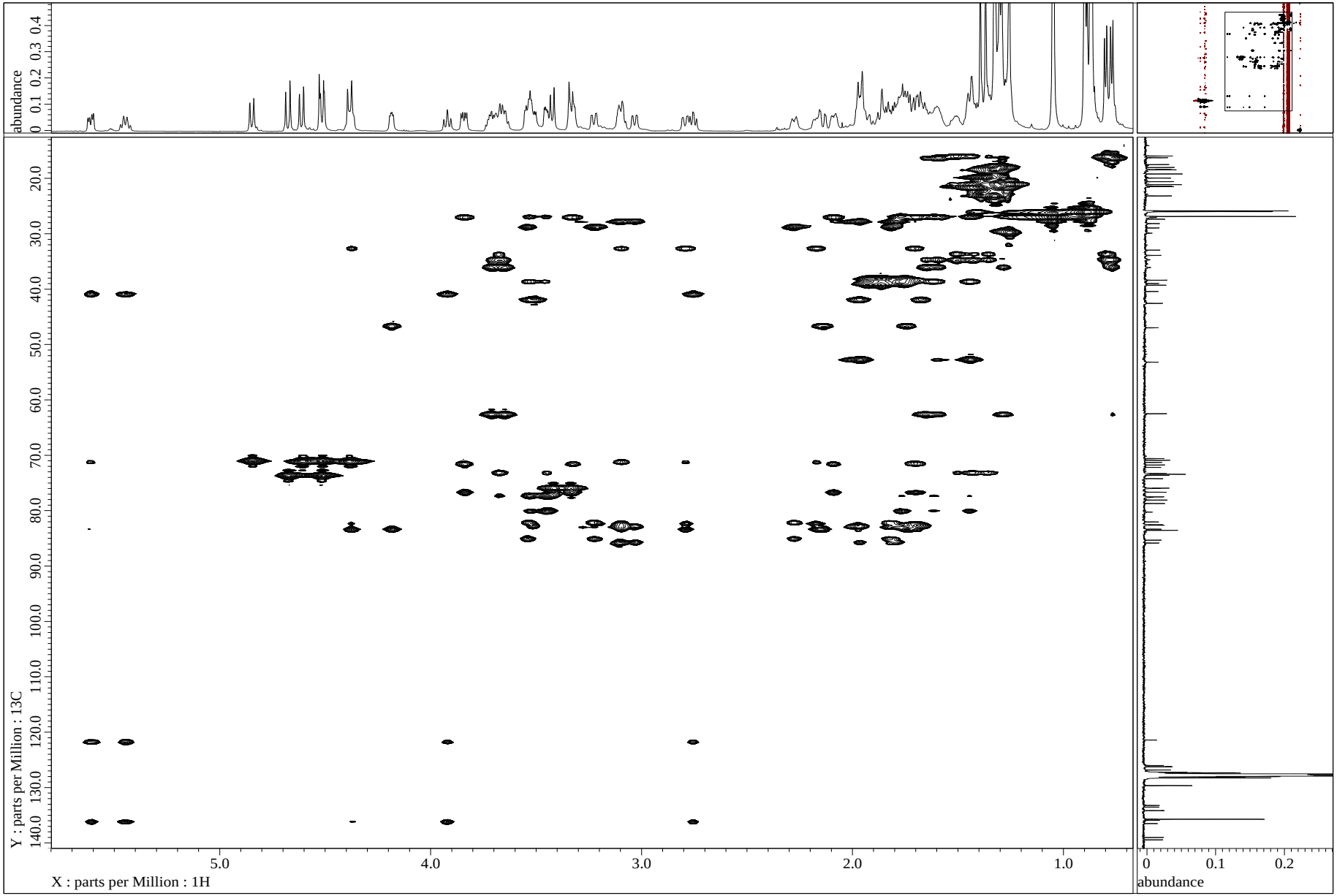
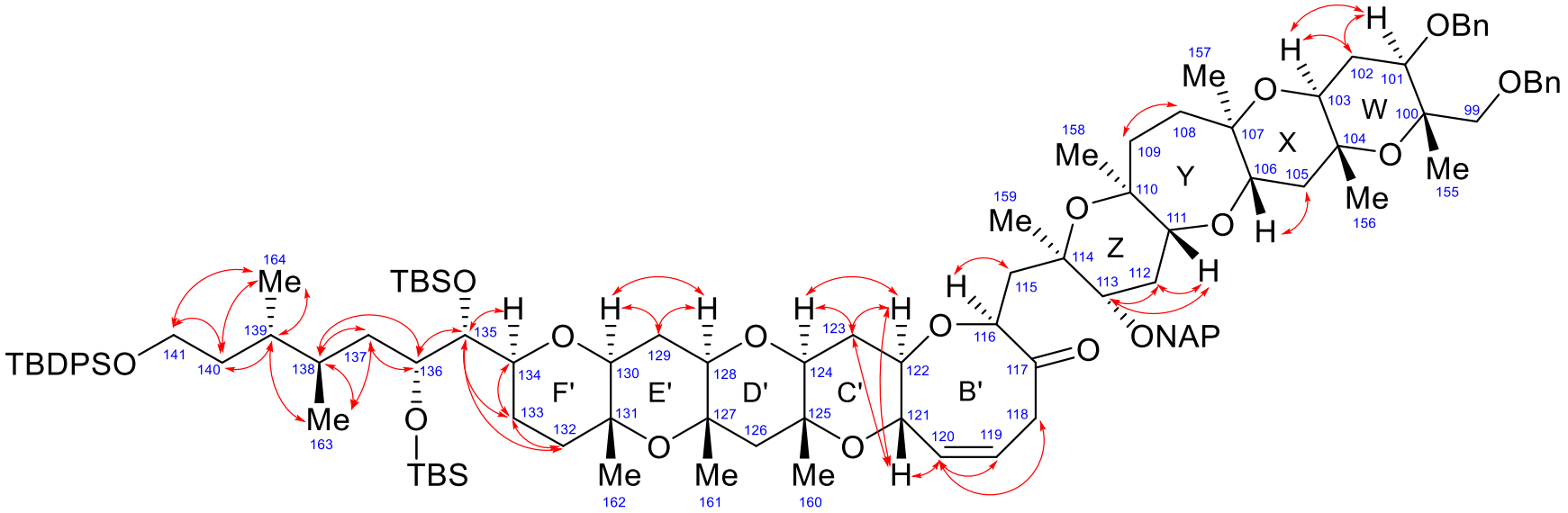


Figure S3. Key COSY and HSQC–TOCSY correlation of ketone **120**.



HMBC spectrum of ketone **120**.

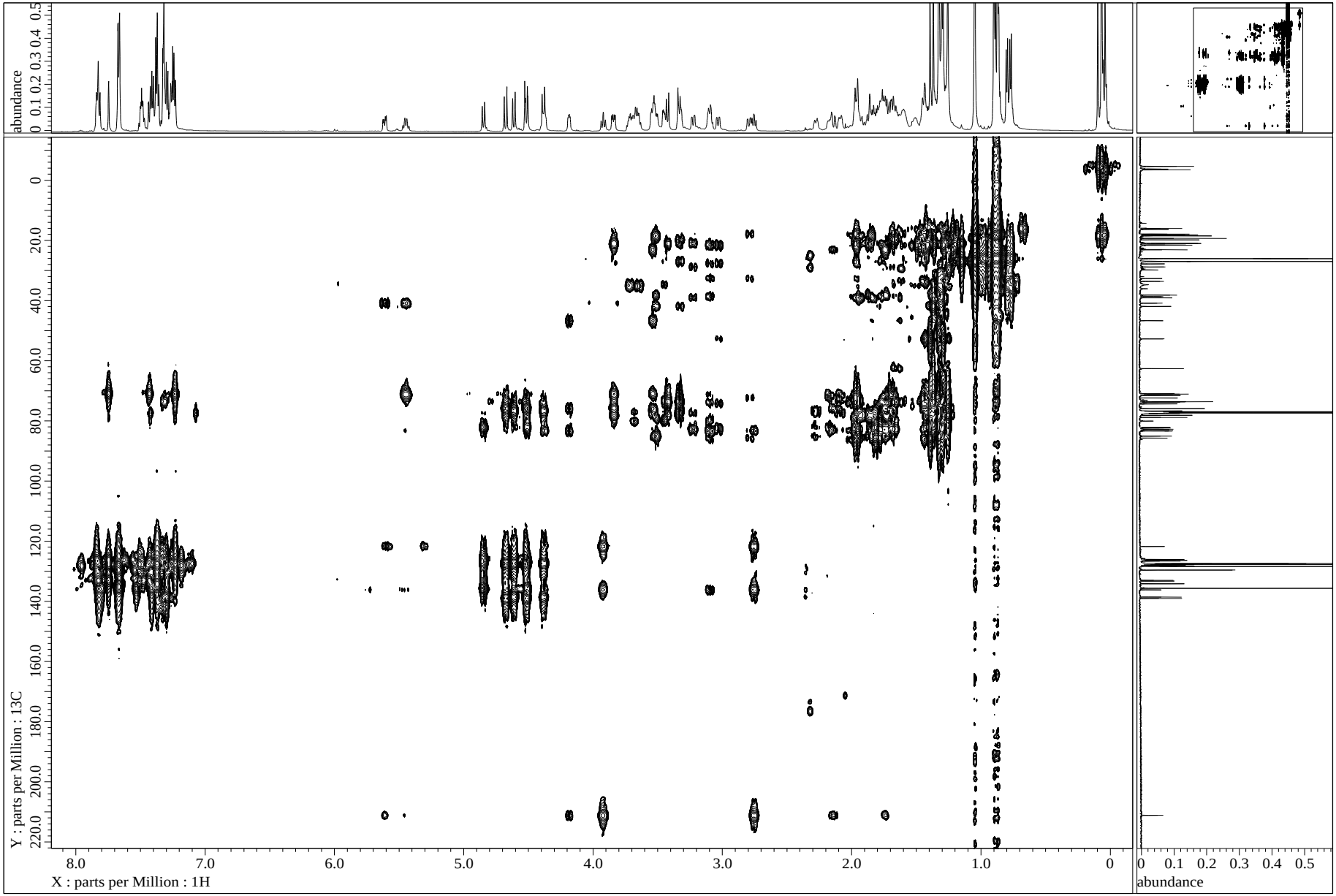
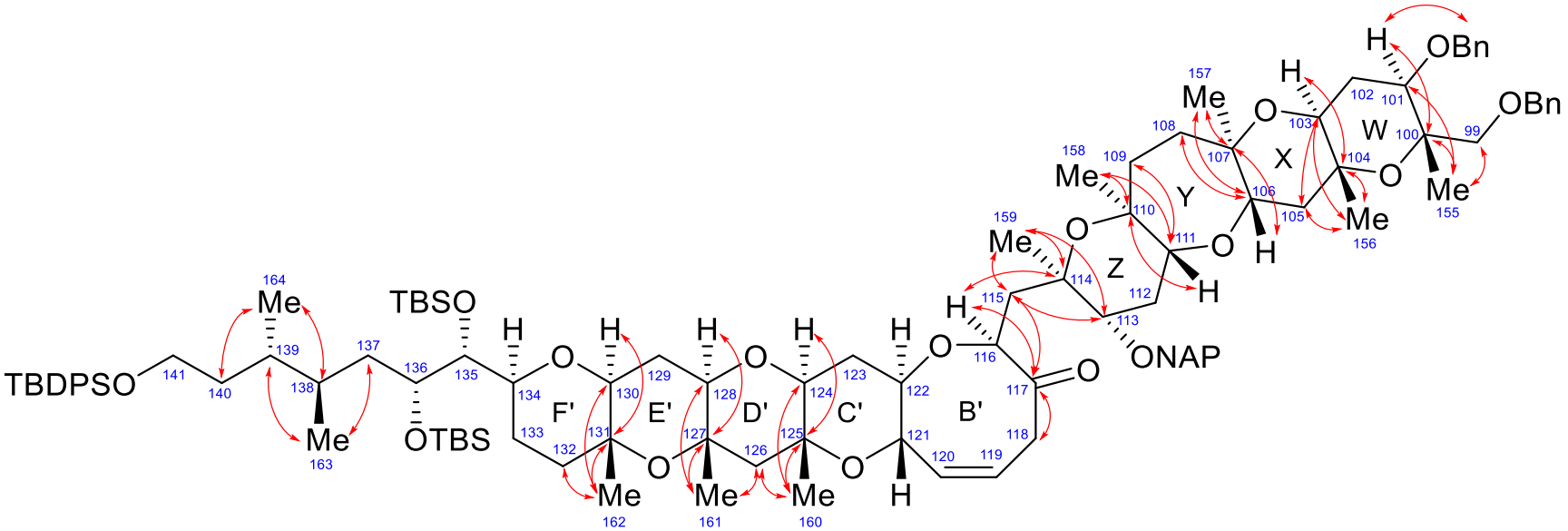
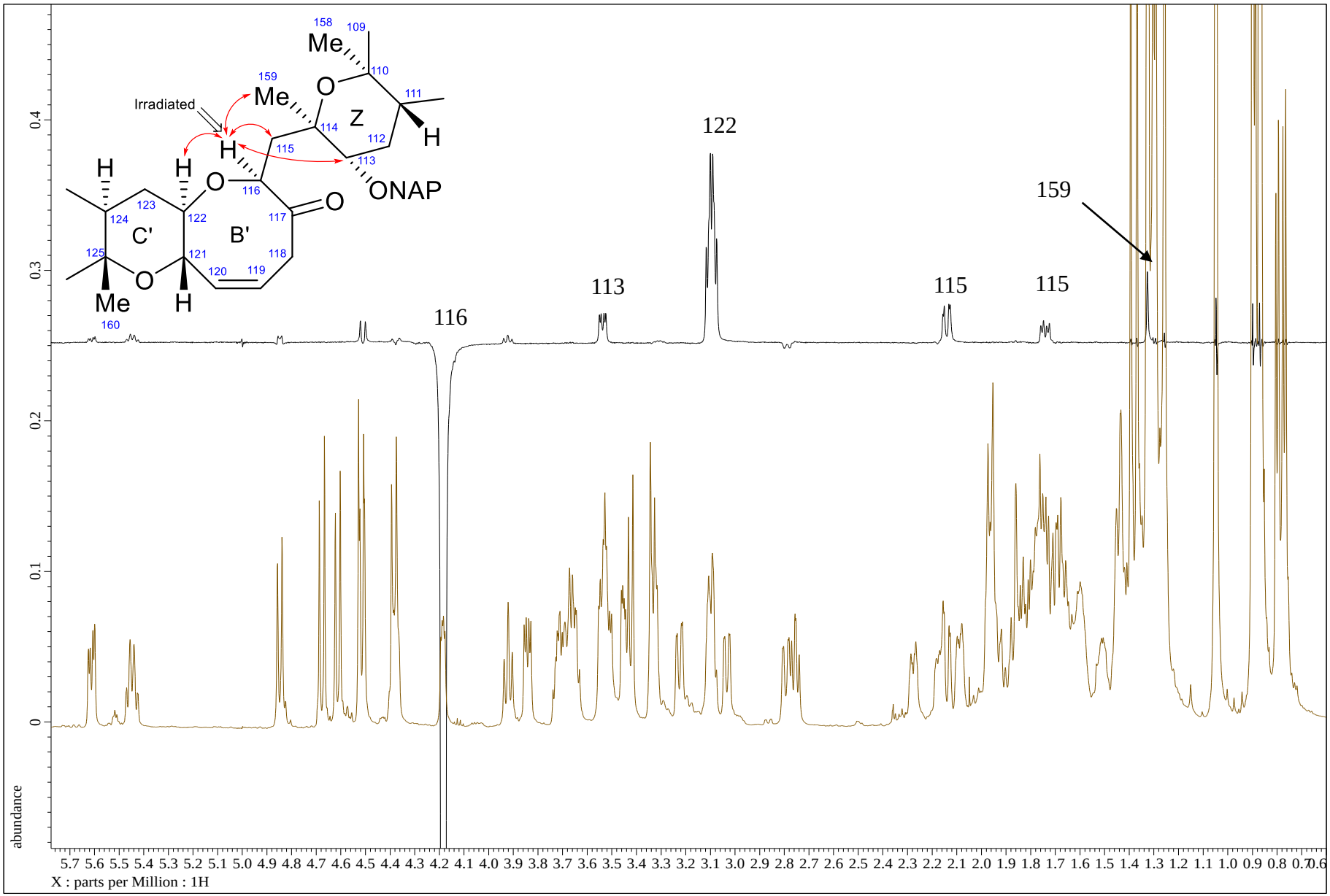


Figure S4. Key HMBC correlation of ketone **120**



1D–ROE experiment of ketone **120**.



121
^{1}H NMR (600 MHz, CDCl$_3$)
122
^{1}H NMR (600 MHz, CDCl$_3$)
abundance
X : parts per Million : 1H

121
^{13}C NMR (150 MHz, $CDCl_3$)
122
^{13}C NMR (150 MHz, $CDCl_3$)
abundance
X : parts per Million : 13C
210.766
139.137
138.697
136.466
135.710
134.293
128.385
127.715
121.941
100.321
87.357
86.323
84.121
83.144
77.380
77.160
76.949
73.972
73.742
62.740
52.993
46.291
42.040
38.746
38.411
33.681
27.055
26.050
21.502
21.042
19.367
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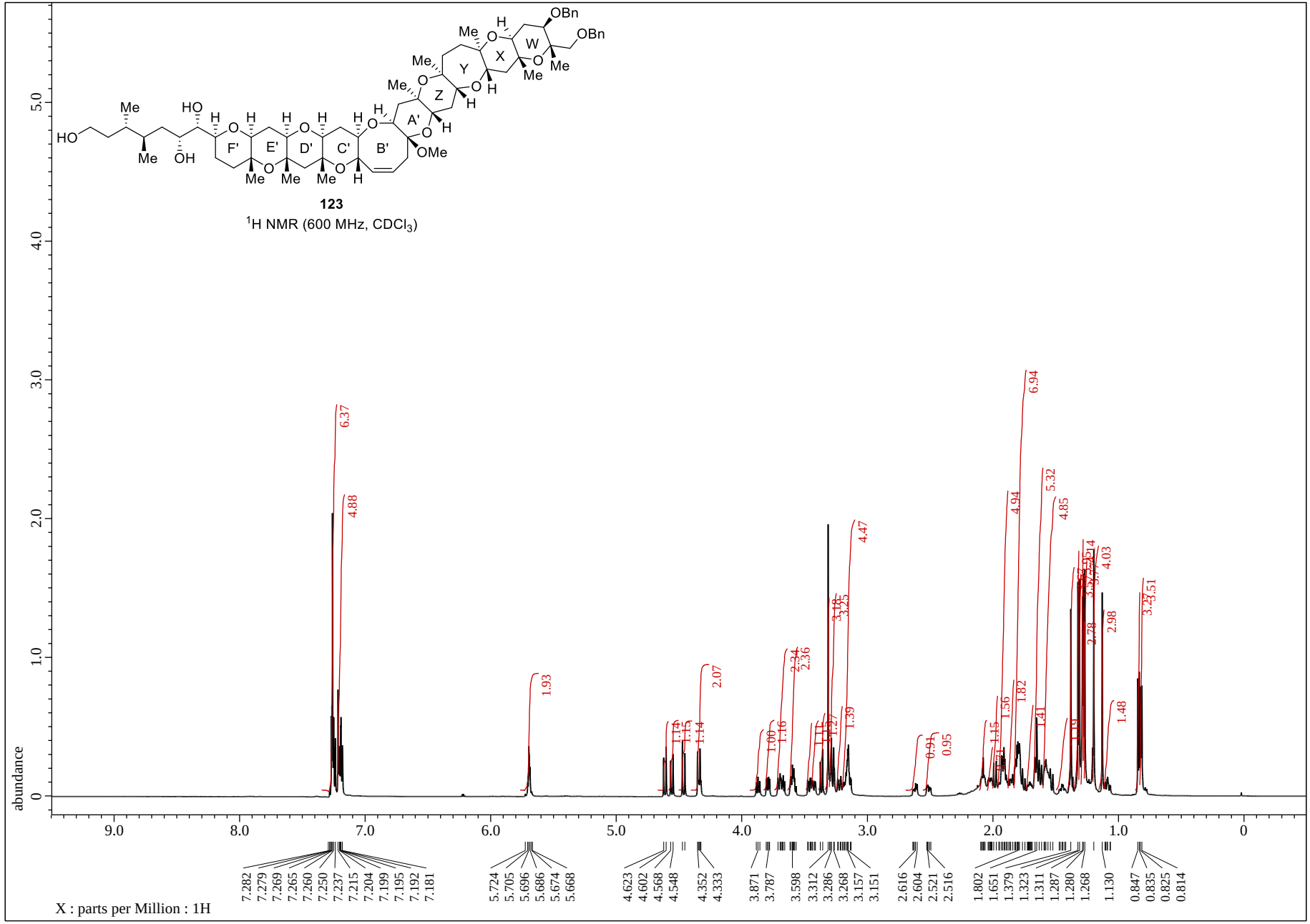
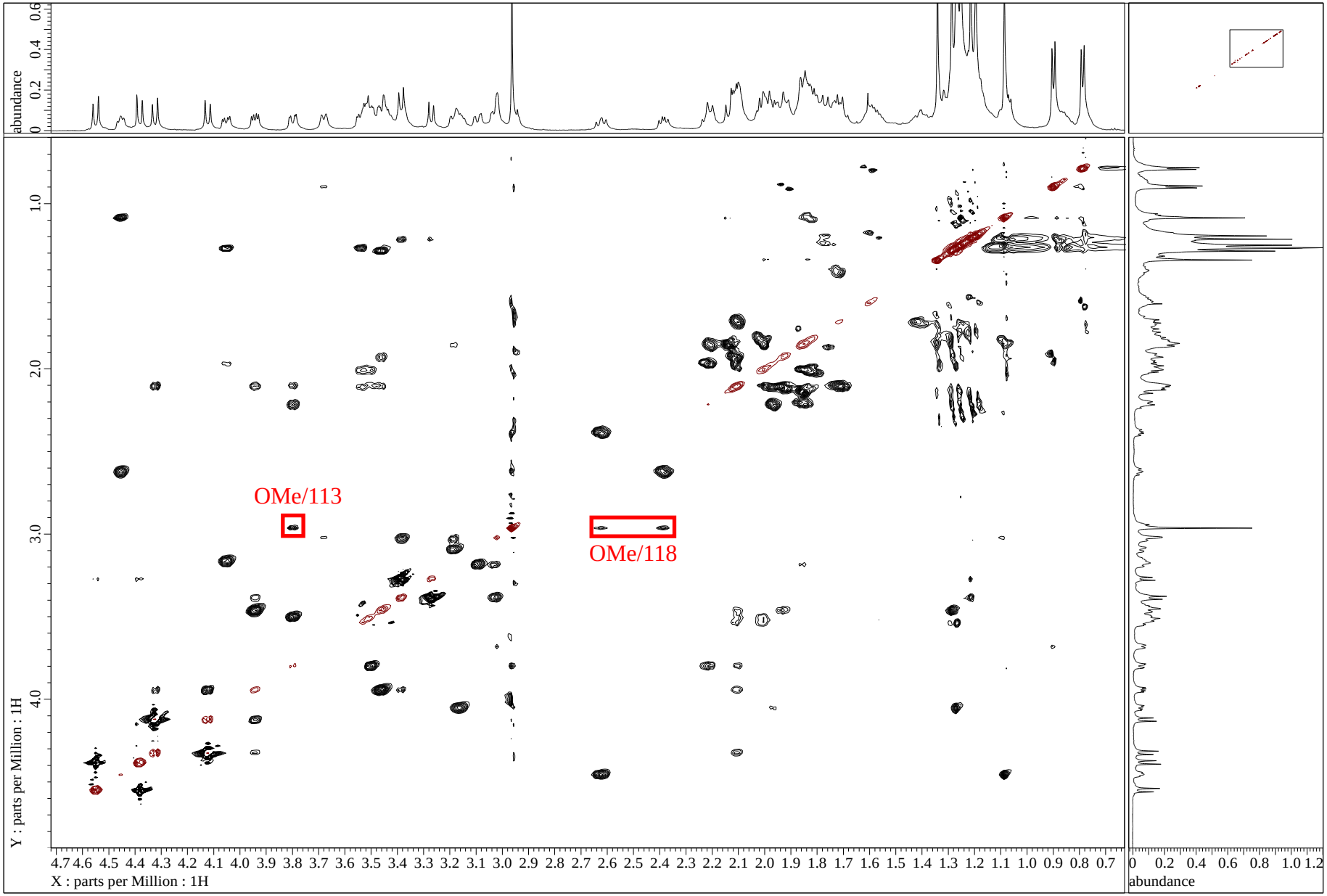
18.141
16.399
-3.479
-3.756
-3.843
-4.551


123
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

123
1H NMR (600 MHz, C6D6)
abundance
X : parts per Million : 1H

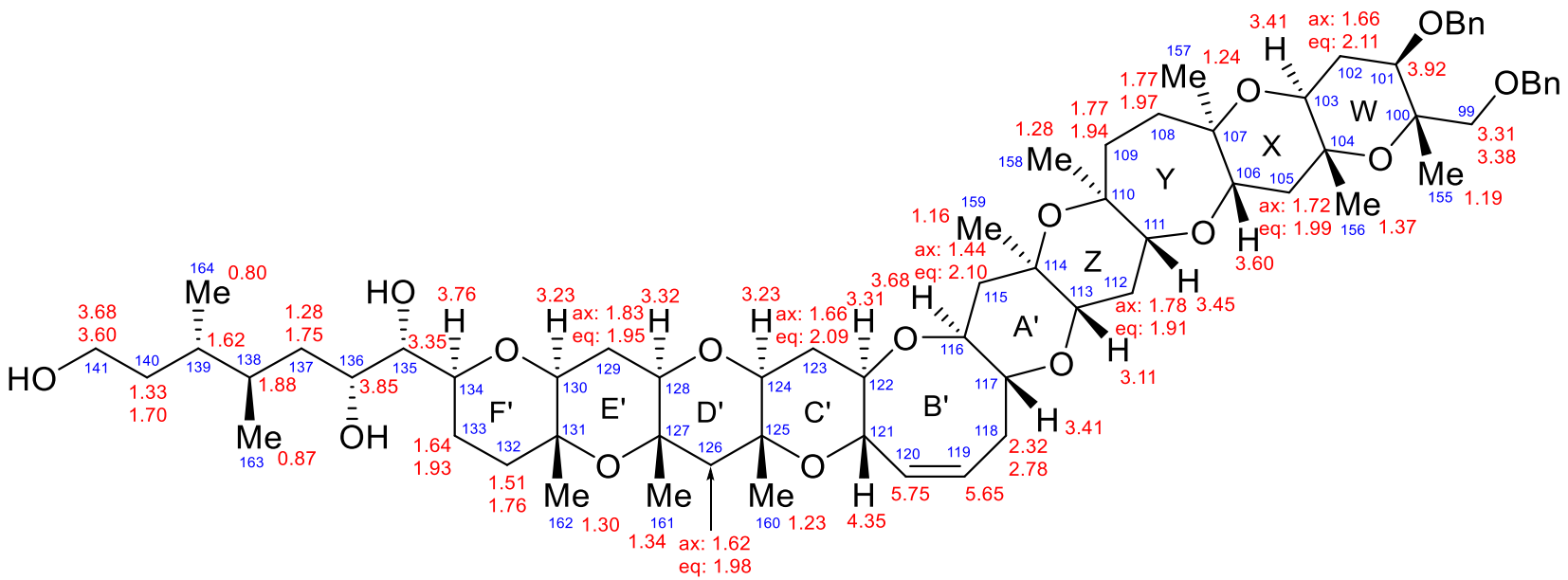
123
13C NMR (150 MHz, CDCl3)
abundance
X : parts per Million : 13C
139.099
138.668
136.351
128.404
128.385
127.590
127.514
127.447
126.738
103.175
77.371
77.160
77.074
76.949
76.815
73.790
73.704
73.225
72.775
71.597
71.224
61.754
52.907
47.832
41.973
39.636
38.411
37.157
36.008
34.610
33.375
27.180
23.503
21.636
21.224
21.052
20.171
19.865
18.160
17.959
16.370
16.312

ROESY spectrum of methyl acetal **123** (600 MHz, C_6D_6).



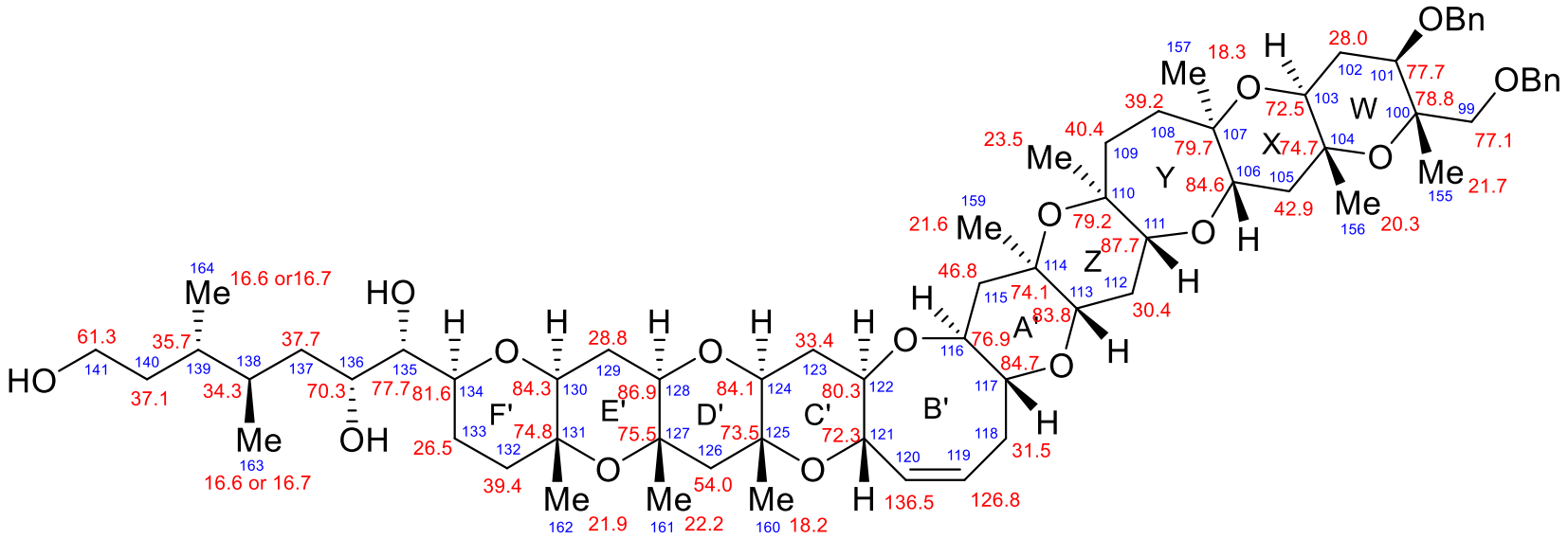
129
1H NMR (600 MHz, CD3OD/C5D5N = 1/1)
abundance
X : parts per Million : 1H

Figure S5. Assignment of ^{1}H NMR of triol **129**.

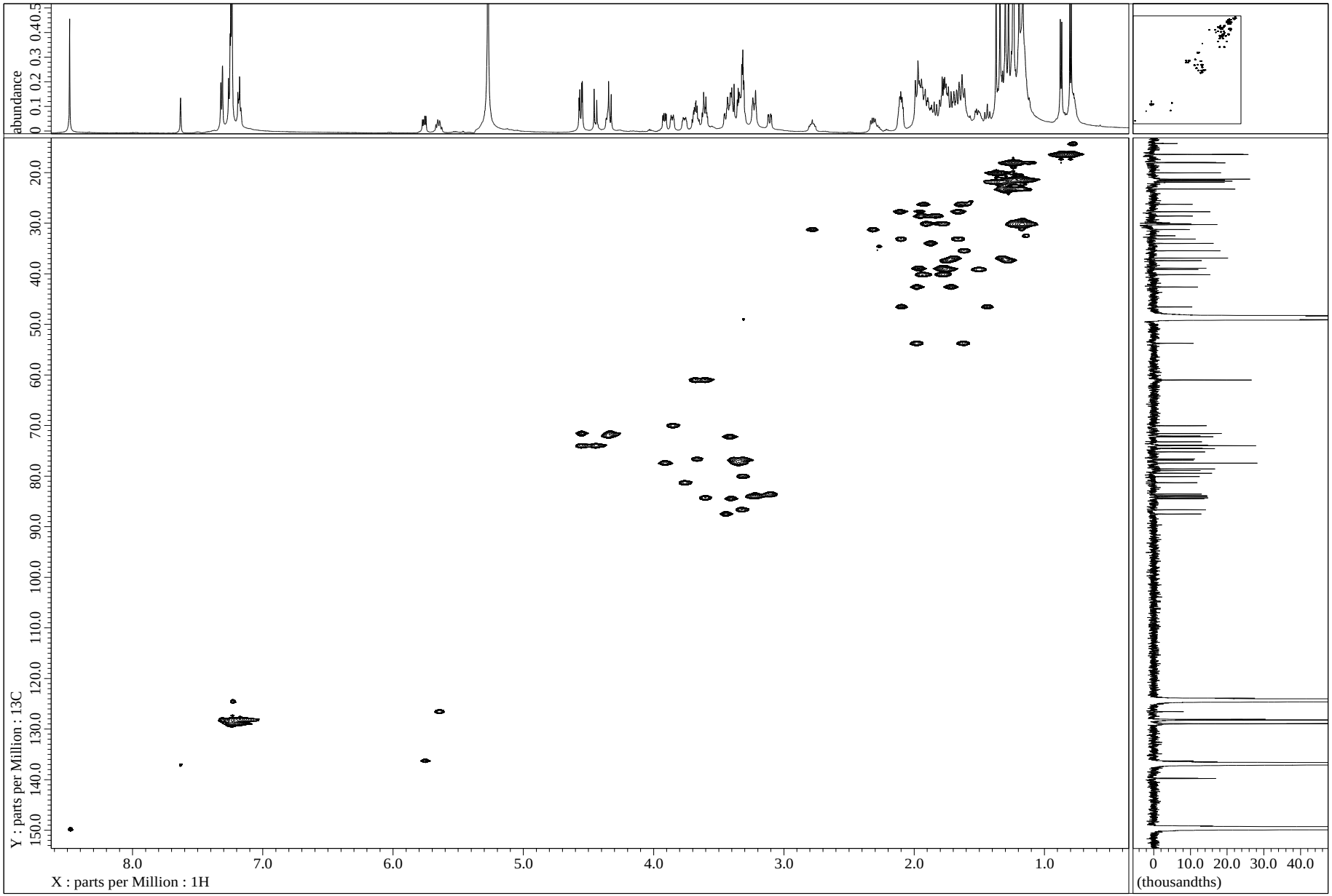


129
13C NMR (150 MHz, CD3OD/C5D5N = 1/1)
abundance
X : parts per Million : 13C
149.944
149.772
149.590
140.015
139.948
137.056
136.894
129.195
129.167
128.487
128.449
128.315
126.792
124.676
124.504
124.341
86.894
84.548
84.252
84.108
79.675
78.823
77.674
75.452
74.801
74.227
74.112
72.456
71.824
70.282
61.253
53.976
49.084
48.940
40.418
39.145
37.661
37.144
35.698
34.252
27.981
23.500
22.169
21.939
21.709
21.556
20.292
18.310
16.673
16.644

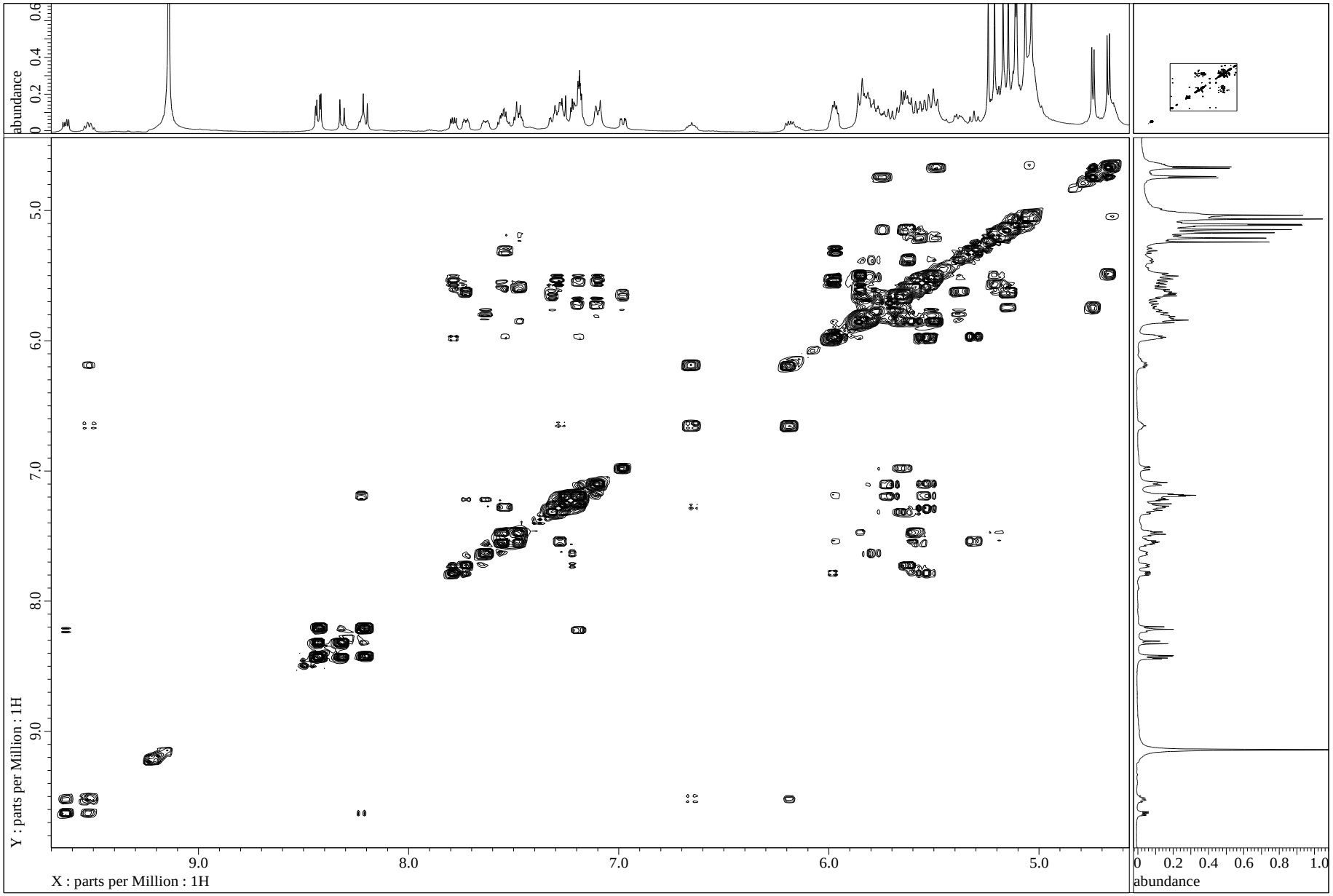
Figure S6. Assignment of ^{13}C NMR of triol **129**.



HSQC spectrum of triol **129**.



DQF–COSY spectrum of triol **129**.



HSQC–TOCSY spectrum of triol **129**.

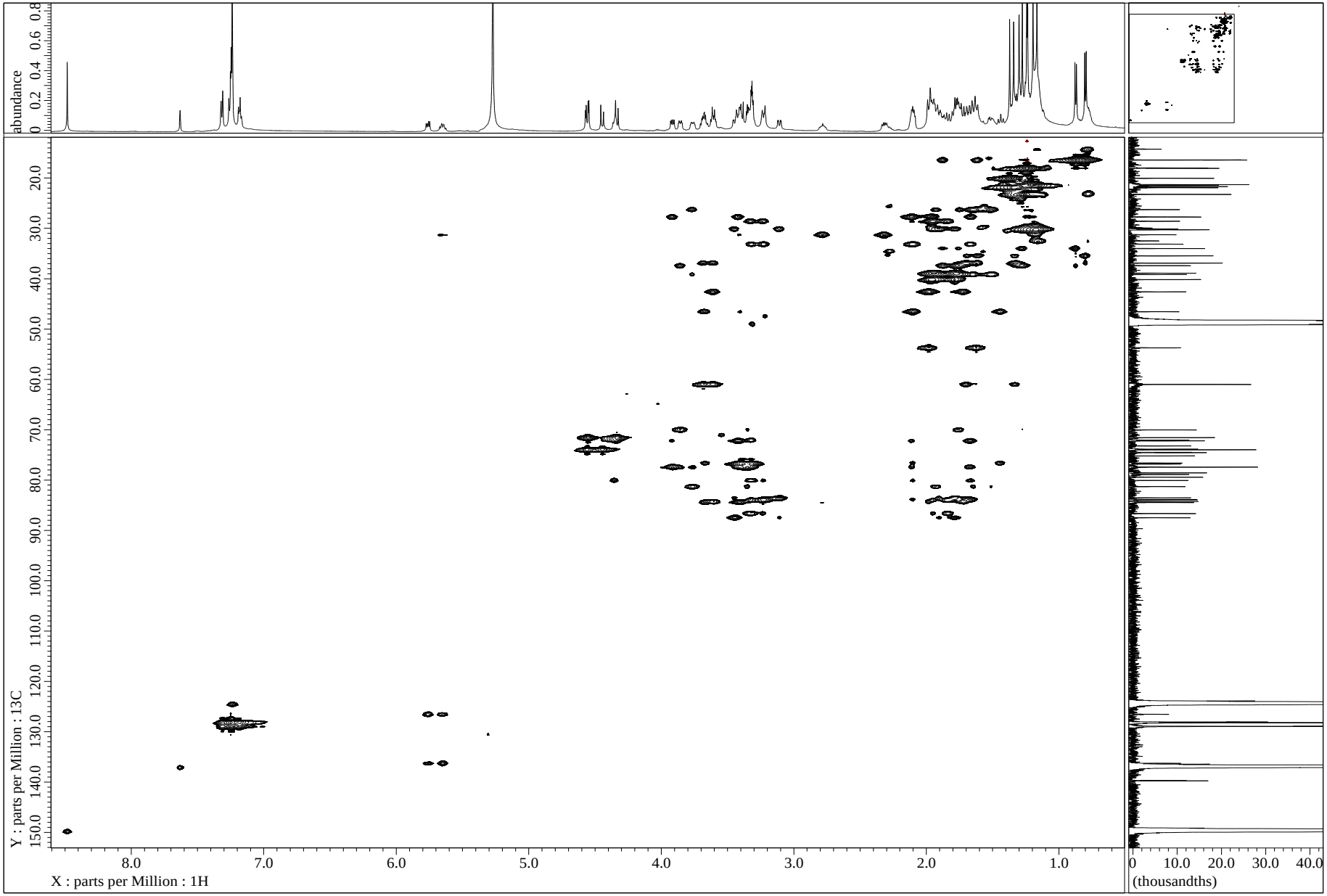
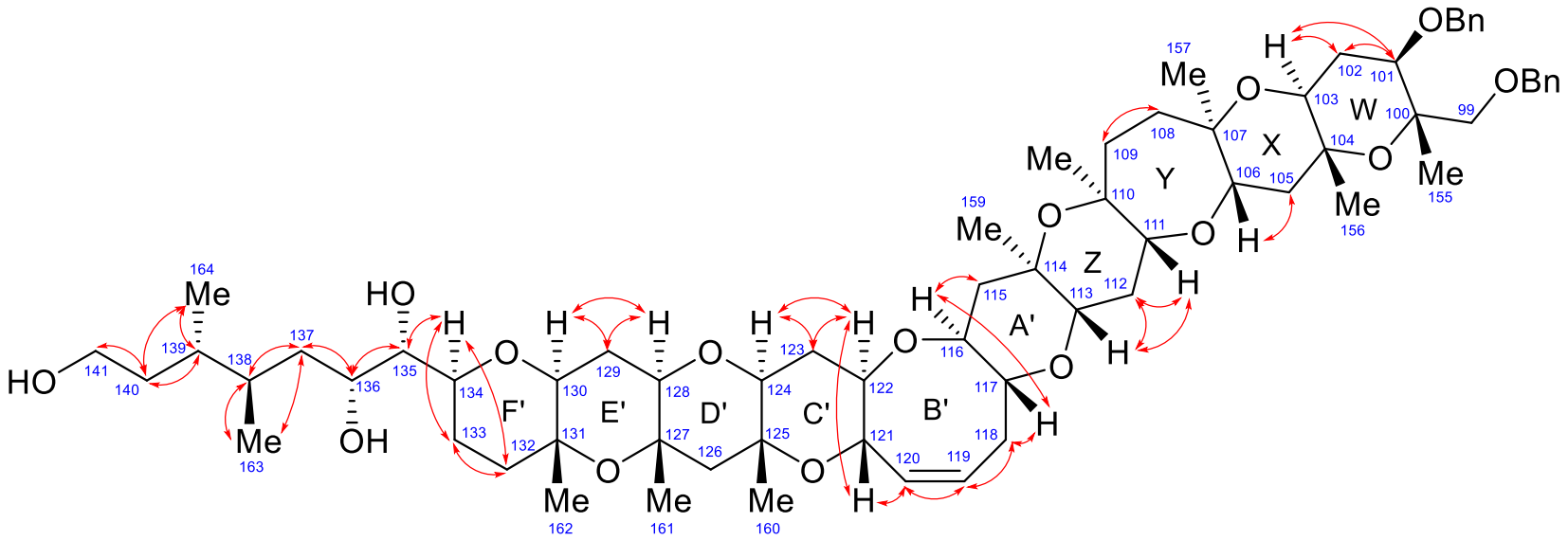


Figure S7. Key COSY and HSQC–TOCSY correlation of triol **129**.



HMBC spectrum of triol **129**.

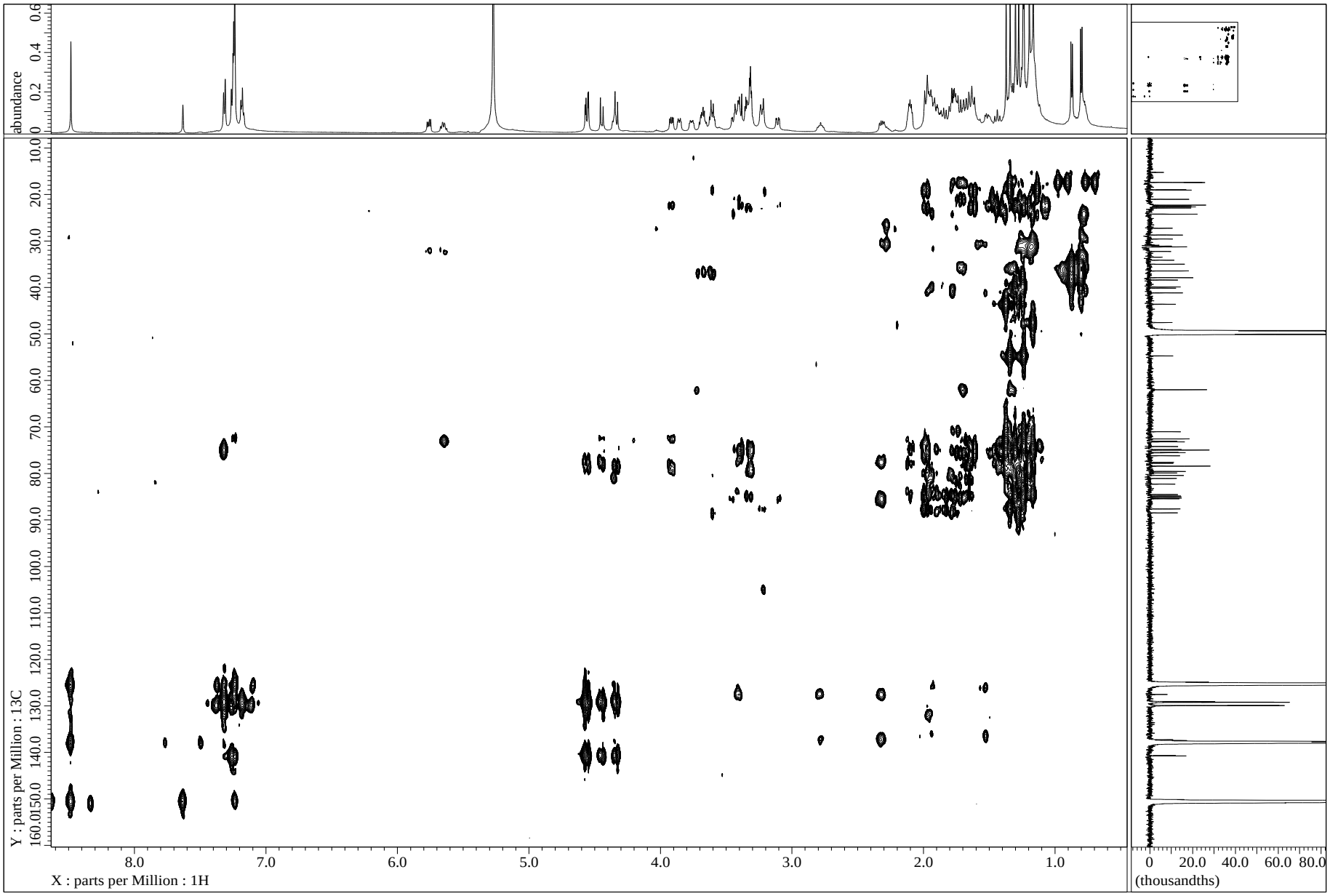
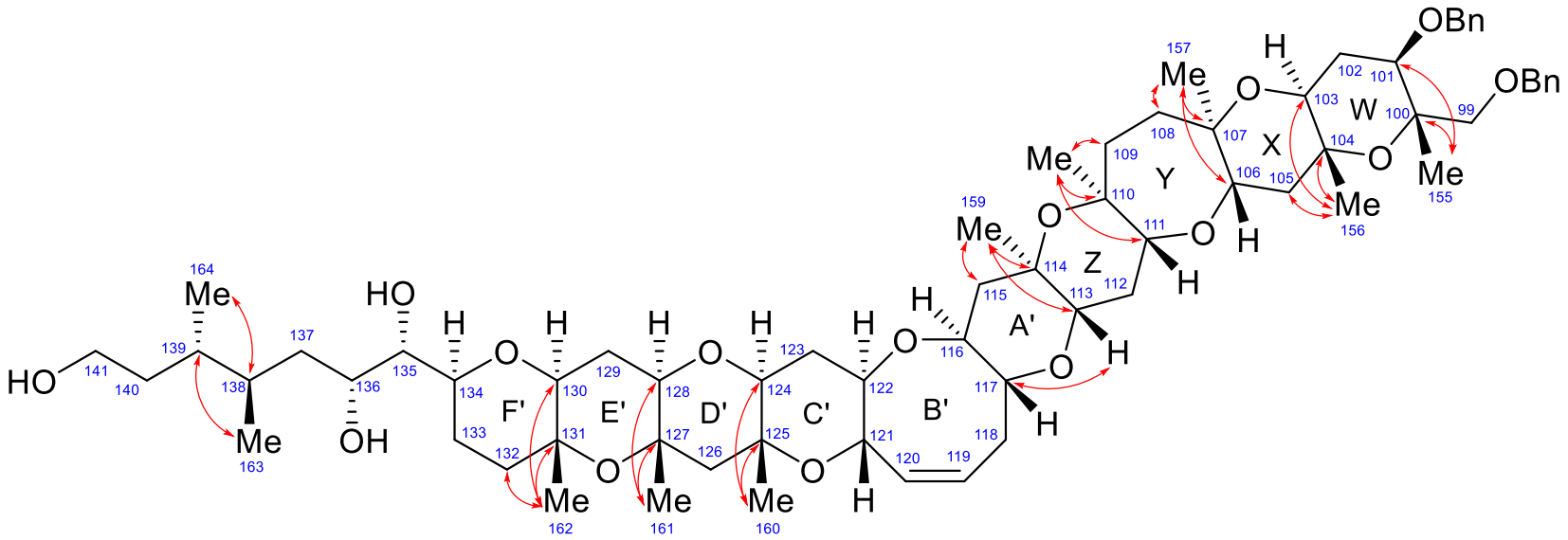
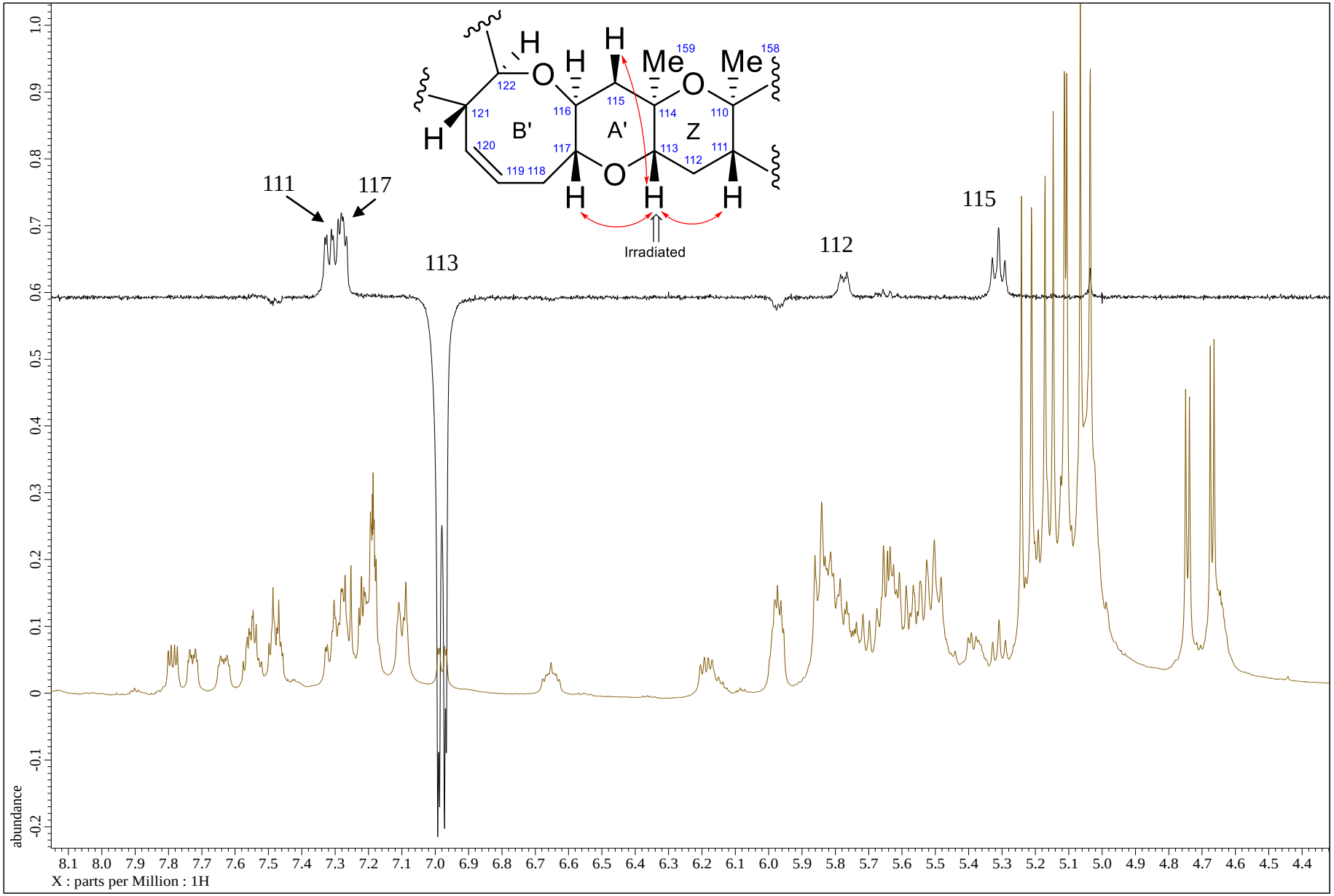


Figure S8. Key HMBC correlation of triol **129**.



1D–ROE experiment of triol **129**.

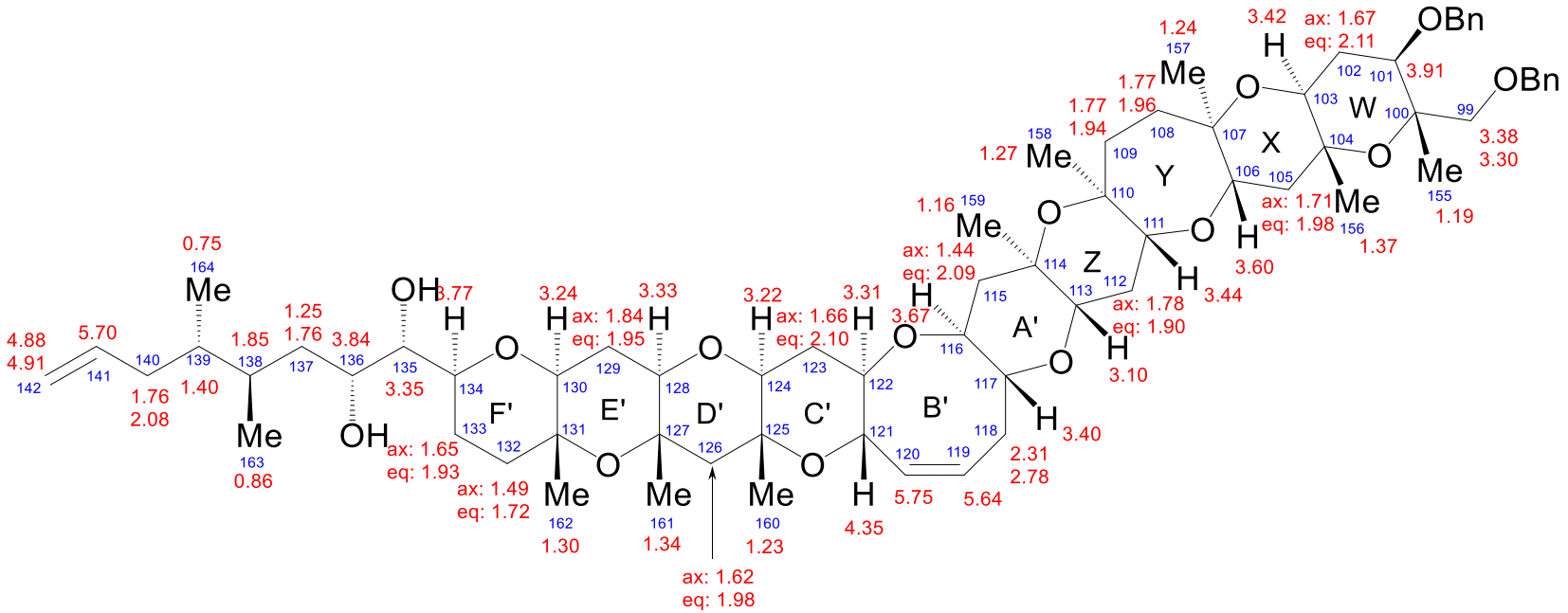


133
1H NMR (600 MHz, CDCl3)
abundance
X : parts per Million : 1H

133
13C NMR (150 MHz, CDCl3)
(thousandths)
X : parts per Million : 13C
139.128
138.697
138.295
135.269
128.423
128.404
127.523
127.466
115.574
109.015
87.281
83.738
83.470
83.412
83.135
83.077
78.883
77.371
77.160
76.940
76.825
73.751
71.252
52.993
45.927
38.401
38.172
37.779
34.016
29.506
27.611
27.208
26.998
23.034
21.722
21.349
21.301
21.042
19.826
18.017
16.217
16.025

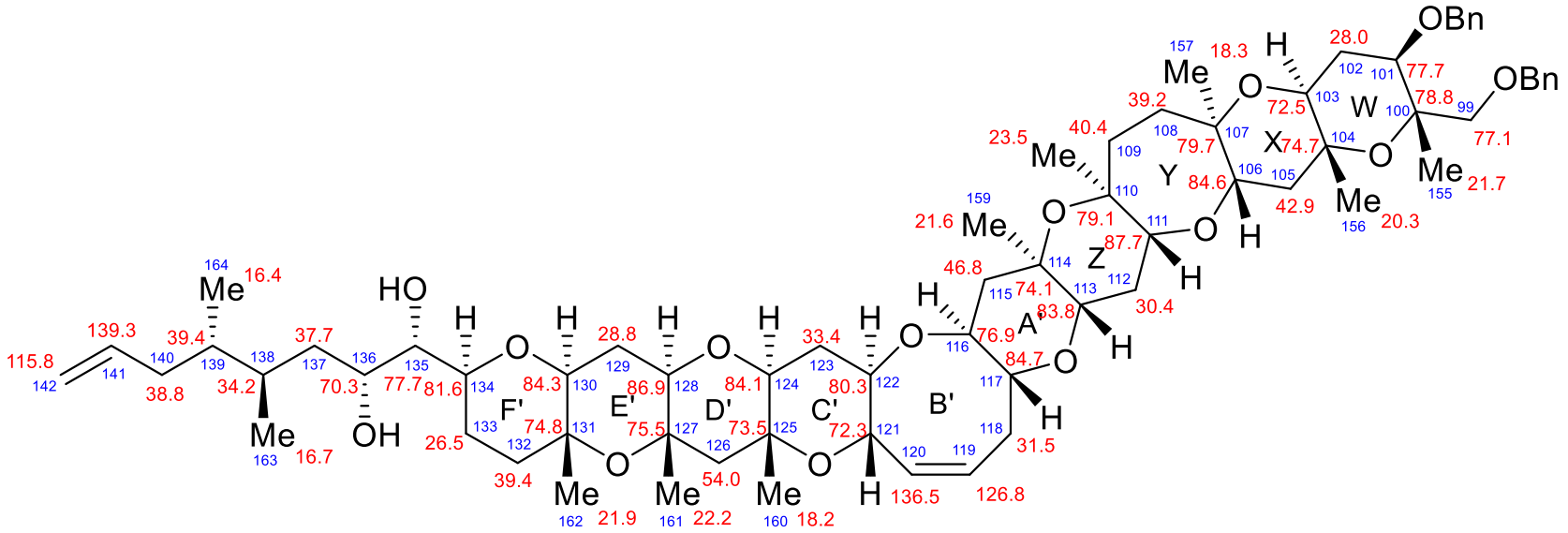
1
1H NMR (600 MHz, CD3OD/C5D5N=1/1)
abundance
X : parts per Million : 1H

Figure S9. Assignment of ^{1}H NMR of WXYZA'B'C'D'E'F' ring segment **1**.

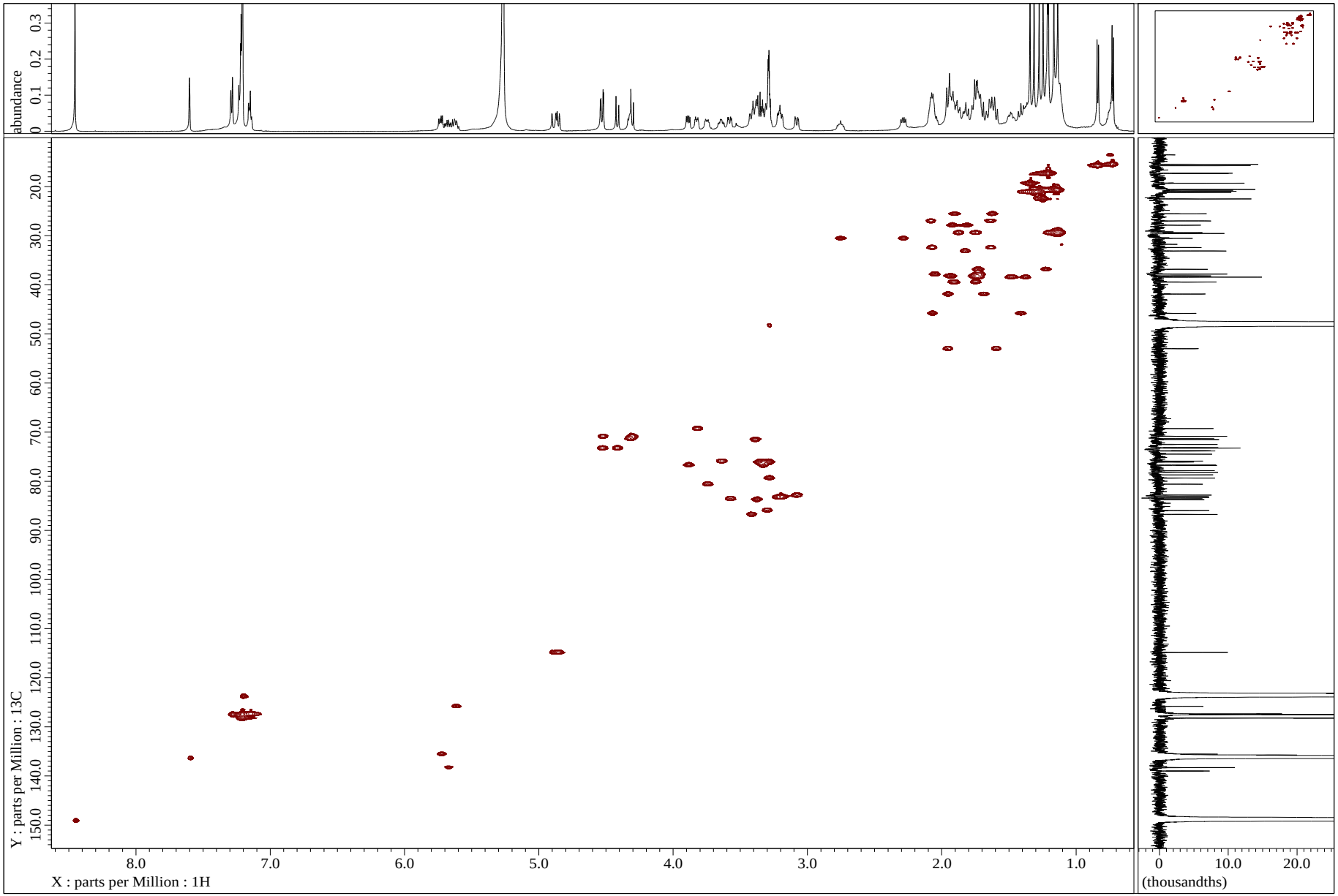


1
13C NMR (150 MHz, CD3OD/C5D5N=1/1)
(thousandths)
X : parts per Million : 13C
150.098
149.944
149.762
149.580
137.229
137.057
136.894
136.702
124.791
124.676
124.514
124.341
115.820
87.727
80.317
79.139
78.813
77.731
77.674
74.801
74.217
74.112
73.461
72.456
72.312
71.814
70.234
53.976
48.940
48.796
42.850
39.413
38.791
34.090
30.518
27.971
23.490
22.159
21.939
21.709
21.556
20.292
18.243
16.711
16.443

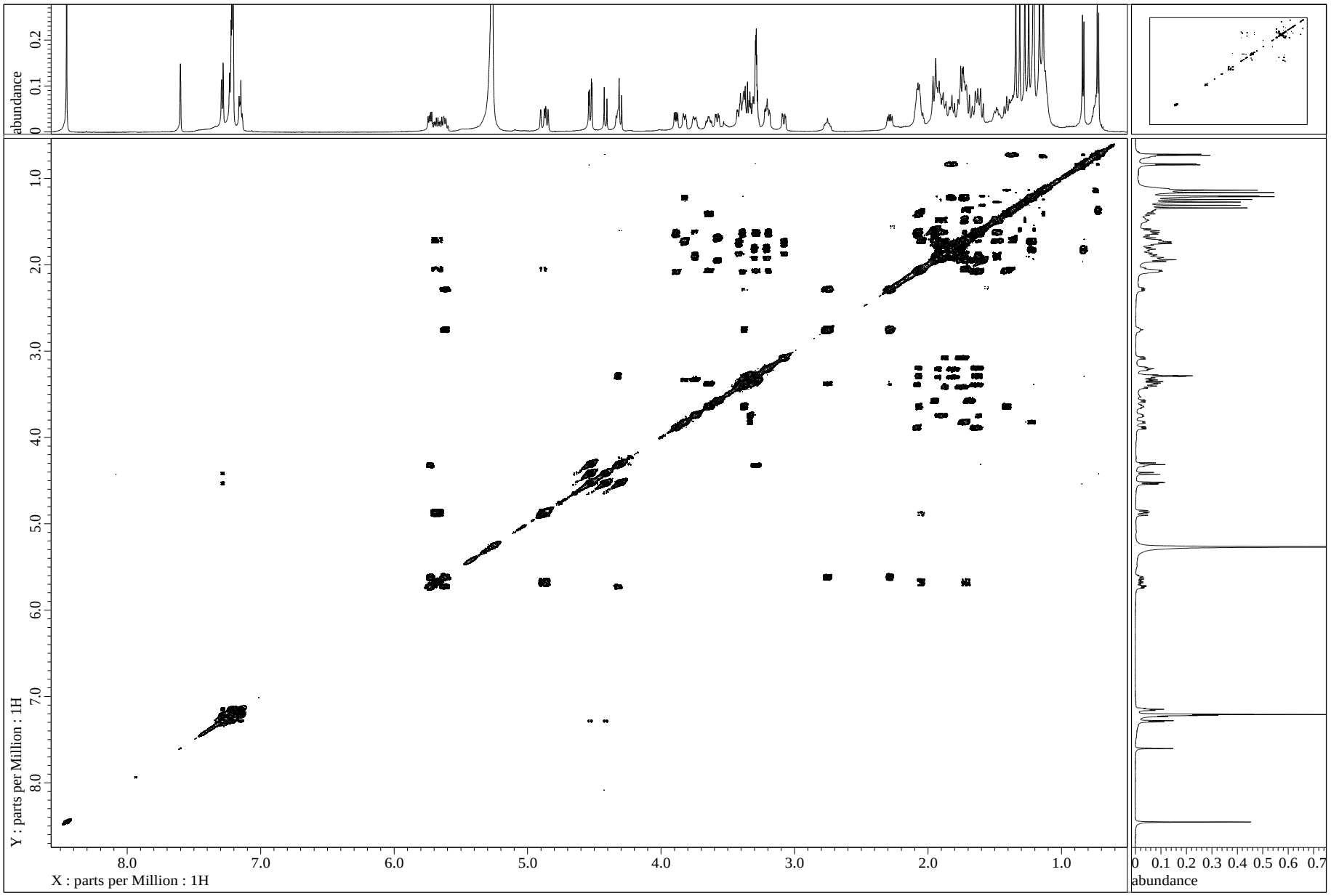
Figure S10. Assignment of ^{13}C NMR of WXYZA'B'C'D'E'F' ring segment **1**.



HSQC spectrum of WXYZA'B'C'D'E'F' ring segment **1**.



DQF–COSY spectrum of WXYZA’B’C’D’E’F’ ring segment **1**.



HSQC–TOCSY spectrum of WXYZA’B’C’D’E’F’ ring segment **1**.

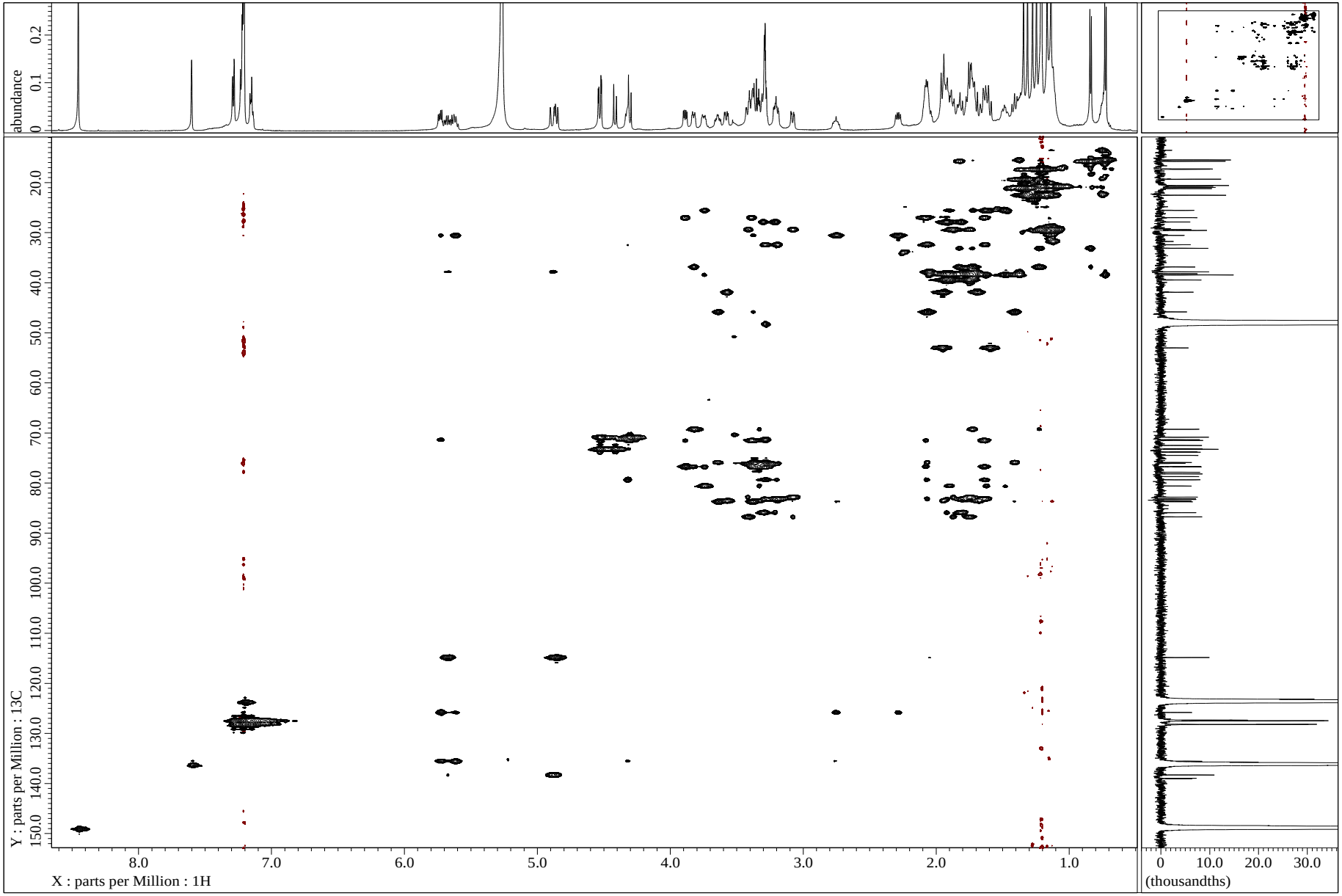
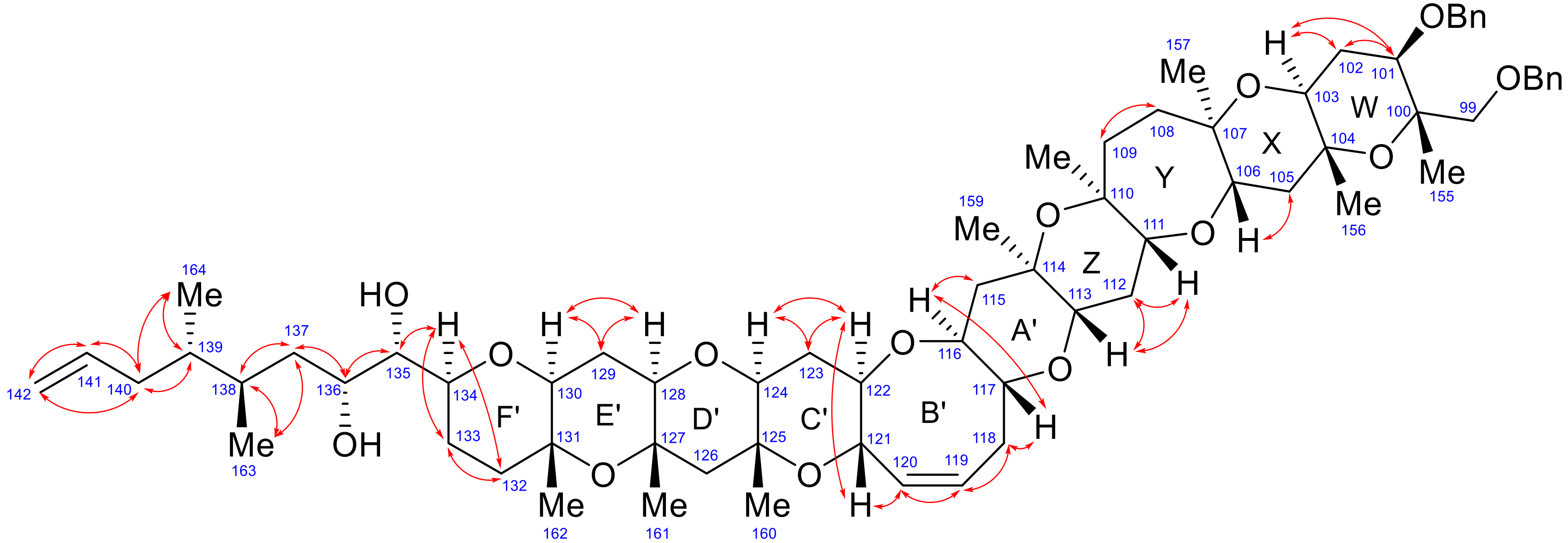


Figure S11. Key COSY and HSQC–TOCSY correlation of WXYZA'B'C'D'E'F' ring segment **1**.



HMBC spectrum of WXYZA'B'C'D'E'F' ring segment **1**.

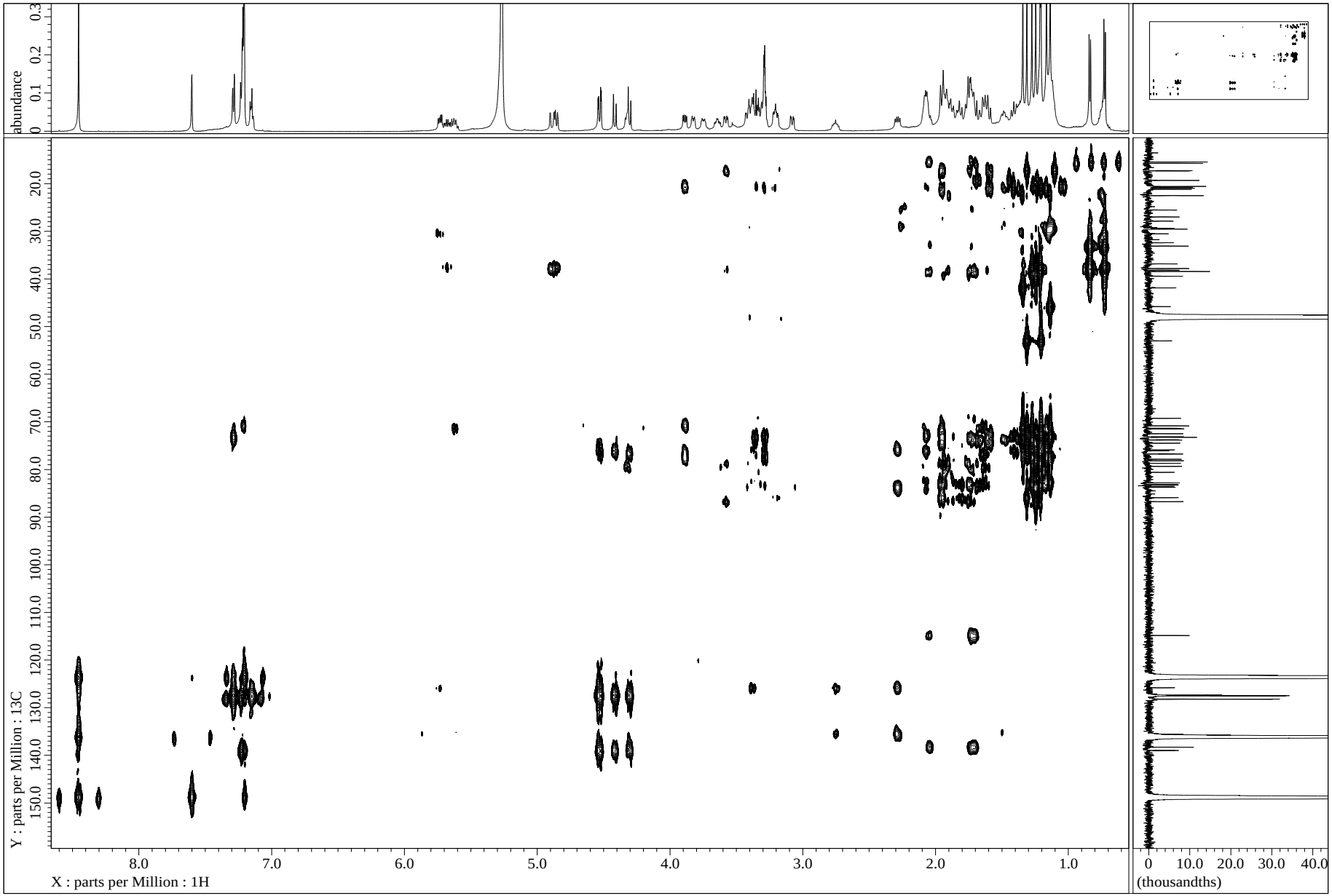
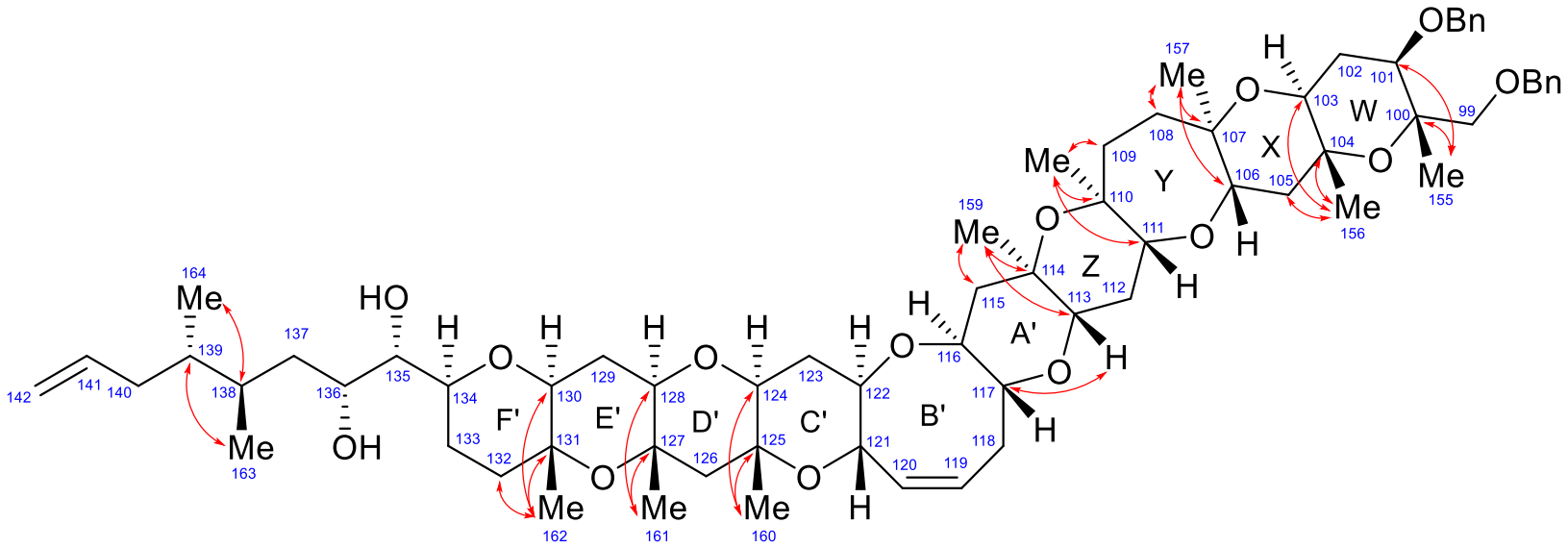


Figure S12. Key HMBC correlation of WXYZA'B'C'D'E'F' ring segment **1**.



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This research has been carried out under the direction of Professor Tohru Oishi at the Department of Chemistry, Graduate School of Sciences, Kyushu University.

I would first like to thank Professor Tohru Oishi for giving me a chance to study this field, encouragements, guidance and supports on this dissertation for three years.

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I would like to thank Associate Professor Keiichi Konoki (Tohoku University). He performed activity evaluations and gave me valuable data.

I would like to thank each and every one of the members in Oishi's laboratory for their advice and discussion to this study. I would like to thank all members at the Department of Chemistry, Graduate school of Science, Kyushu University. They made my study life meaningful.

Finally, I would like to give a special note of thanks to my family. They have always been supportive and no matter what I have ever done they have always been there help me along the way.

Keitaro Umeno

Fukuoka, Japan
March 2023

List of publications

1. Synthesis and Stereochemistry of the C30–C63 section of Karlotoxin 2
   K. Umeno, T. Oishi, *Asian J. Org. Chem.* **2020**, *9*, 1597.

2. Convergent Synthesis of the WXYZA'B'C'D'E'F' Ring Segment of Maitotoxin
   K. Umeno, H. Onoue, K. Konoki, K. Torikai, Y. Yasuno, M. Satake, T. Oishi, *Bull. Chem. Soc. Jpn.* **2022**, *95*, 325.

3. マイトトキシンの WXYZA'B'C'D'E'F'環部の合成研究
   梅野圭太郎, 大石徹, 有機合成化学協会誌 **2023**, *81*, 35.