Studies on the Total Synthesis of Gymnocin B

by

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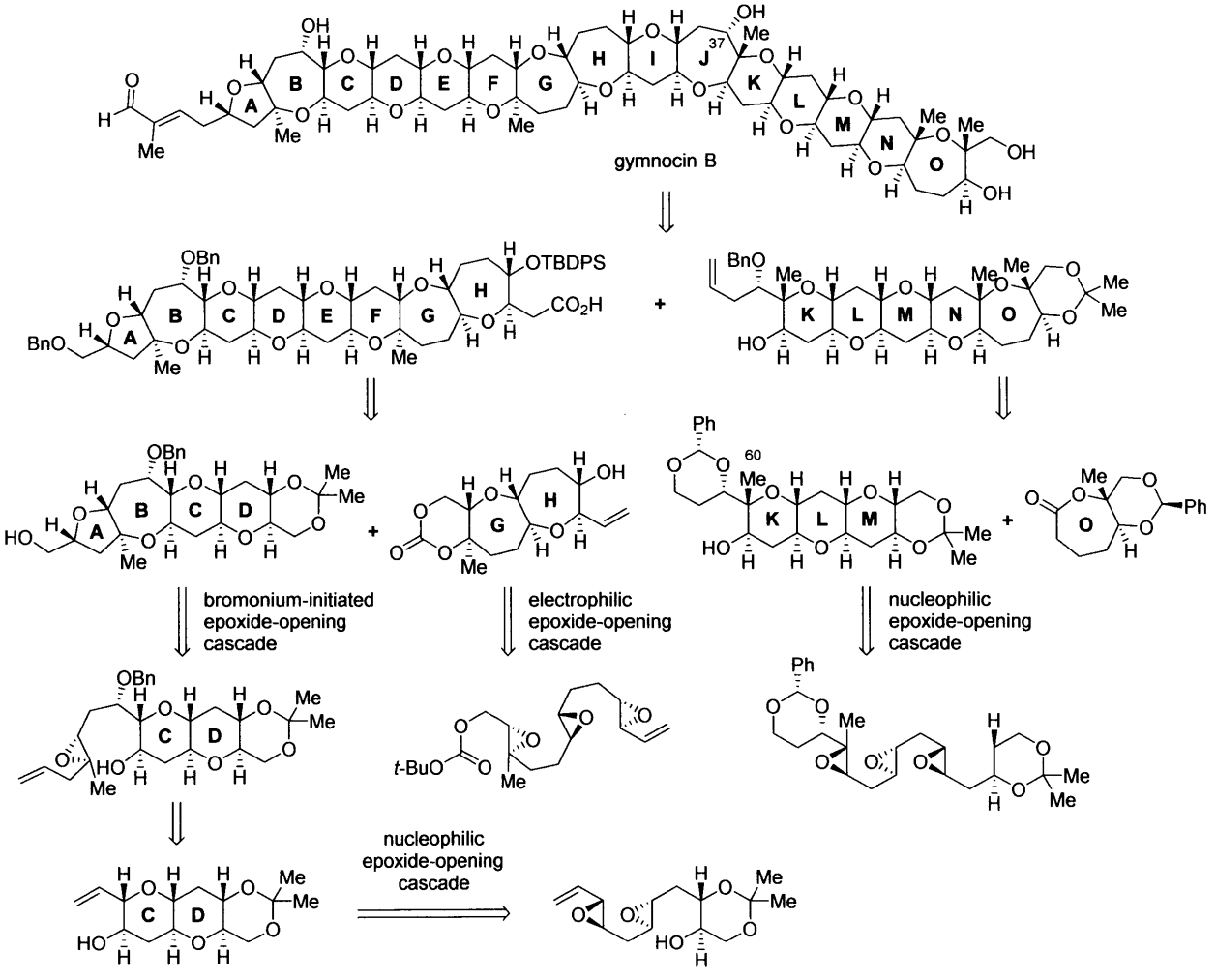
In Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

Abstract

Progress toward the biomimetic total synthesis of gymnocin B is described. Synthesis of the *ABCDEFGH* fragment has been completed in 30 steps longest linear sequence, using three different types of epoxide-opening cascades and one fragment coupling. Synthesis of the *KLMNO* fragment has been completed in 27 steps longest linear sequence, using one epoxide-opening cascade and one fragment coupling. The completion plan of gymnocin B is also detailed.



Thesis Supervisor: Timothy F. Jamison
Title: Professor of Chemistry

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Abbreviations

$[\alpha]_D$	specific rotation at 589 nm (sodium D line)
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Ar	generic aryl substituent
B:	generic base
Bn	benzyl
Boc	*tert*-butoxy carbonyl
brsm	based on recovered starting material
cat.	catalyst or catalytic (quantity)
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	day(s)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylanimopyridine
DMF	*N*,*N*-dimethylformamide
DMM	dimethoxymethane
DMP	dimethoxypropane
DMPU	1,3-dimethyltetrahydropyrimin-2(1*H*)-one (*N*,*N*'-dimethylpropyleneurea)
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E^+	generic electrophile
EDA	ethylenediamine
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ESI	electron spray ionization
Et	ethyl
GC	gas chromatography
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	bis(trimethylsilyl)amine (hexamethyldisilazane)
HMPA	hexamethylphosphoramide
HPLC	his-performance liquid chromatography
HRMS	high-resolution mass spectrometry
imid	imidazole
i-Pr	isopropyl
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide (potassium hexamethyldisilazane)
KP_i	potassium phosphate

LA	Lewis acid
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
MS	molecular sieves
n-Bu	*n*-butyl
NaP_i	sodium phosphate
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonace
NOESY	nuclear Overhauser effect spectroscopy
Nu	generic nucleophile
PG	generic protecting group
Ph	phenyl
P_i	phosphate
PIDA	(diacetoxyiodo)benzene
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PT	5-phenyltetrazole
Piv	trimethylacetate (pivalate)
pyr.	pyridine
R	generic carbon substituent
R_f	retention factor
rr	regioisomeric ratio
sat.	saturated
Sharpless AE	Sharpless asymmetric epoxidation
Shi AE	Shi asymmetric epoxidation
SiO_2	silica gel
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl radical
t-Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
THF	tetrahydropfuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMANO	trimethylamine-*N*-oxide
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl (tosyl)
X	generic heteroatom substituent

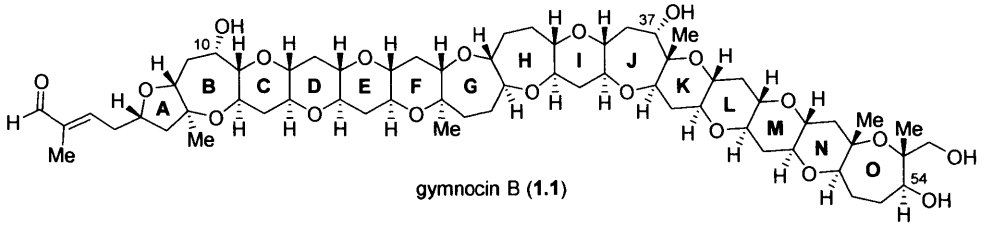
CHAPTER I

Introduction to Gymnocin B and Its Retrosynthetic Analysis

A. Introduction to Gymnocin B

Isolated in 2005 from a culture of red tide dinoflagellate, *Karenia* (formerly *Gymnodinium*) *mikimotoi*, gymnocin B (**1.1**, Figure 1) is the second largest contiguous marine ladder polyether discovered to date.[1] Despite structural similarities to other toxic marine ladder polyethers, **1.1** is only weakly ichthyotoxic presumably due to its low water solubility in laboratory assays. In addition, **1.1** exhibited cytotoxic activity against P388 murine leukemia cells at 1.7 μg/mL. An absolute configuration determination method was specifically developed for **1.1** since all three sterically encumbered hydroxyl groups, namely C10, C37 and C54, were not applicable to the conventional Mosher protocol.[2] To this end, *p*-(meso-triphenylporphyrin)-cinnamate groups were introduced at the hindered C10 and C37 hydroxyl groups. In addition to its massive size, five flexible seven-membered oxepanes embedded in **1.1** necessitated an extensive conformational campaign. Determination of C10 and C37 configuration was based on a long-distance porphyrin/porphyrin circular dichroism exciton-coupled interaction, establishing the absolute configuration of **1.1** to be (*S*)-10 and (*S*)-37.

Figure 1. Structure of gymnocin B.

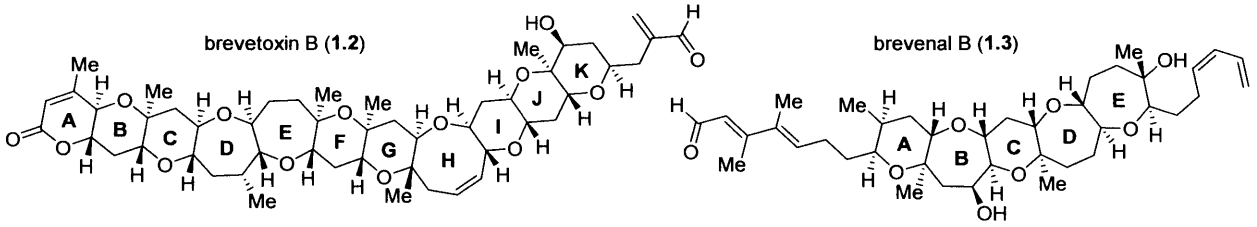


[1] Satake, M.; Tanaka, Y.; Ishikura, Y.; Oshima, Y.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **2005**, *46*, 3537.
[2] Tanaka, K.; Itagaki, Y.; Satake, M.; Naoki, H.; Yasumoto, T.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2005**, *127*, 9561.

B. Marine Ladder Polyethers: Biological Properties and Structural Features

Gymnocin B belongs to a large group of natural products called marine ladder polyethers (MLPs). MLPs are associated with harmful algal blooms, commonly known as red tides. Caused by an explosive growth and accumulation of algae, these phenomena often culminate in massive fish kills, mammalian poisoning and death, and disruption of fishery and tourism.[3] Since the isolation and structural elucidation of brevetoxin B (**1.2**, Figure 2) in 1981,[4] more than 50 MLPs have been isolated.[5]

Figure 2. Structures of brevetoxin B and brevenal.



Marine ladder polythers display a wide range of biological activities. Their main targets of binding are voltage-gated sodium, calcium, or potassium ion transport channel proteins. For instance, binding of **1.2** to voltage-gated sodium ion channels causes depolarization of nerve cells and eventually leads to human neurotoxic shellfish poisoning.[6] In spite of the notorious toxicity associated with MLPs, some members exhibit biological properties that are beneficial to humans. Isolated in 2005 from dinoflagellate *Karenia brevis*, brevenal (**1.3**) acts as a nontoxic competitive inhibitor of brevetoxins, protecting fish from harmful neurotoxic effects.[7] Furthermore, **1.3** has

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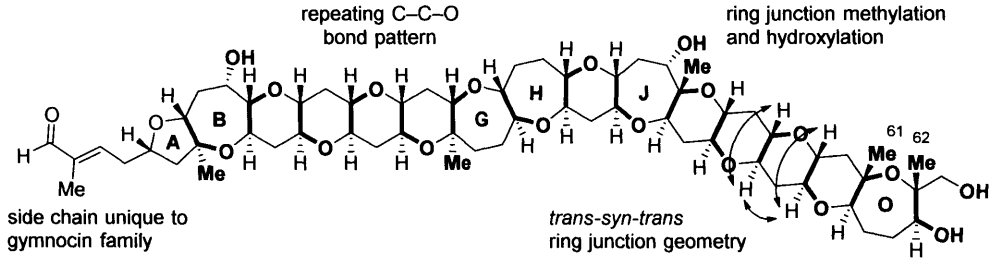
[3] Sellner, K. G.; Doucette, G. J.; Kirkpatrick, G. J.; *J. Ind. Microbol. Biotechnol.* **2003**, *30*, 383.
[4] Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
[5] Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J.; *Angew. Chem., Int. Ed.* **2008**, *47*, 7182.
[6] Watkins, S. M.; Reich, A.; Fleming, L. E.; Hammond, R. *Mar. Drugs* **2008**, *6*, 431.
[7] (a) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.; Baden, D. G. *Nat. Prod.* **2005**, *68*, 2. (b) Bourdelais, A. J.; Campbell, S.; Jacocks, H.; Naar, J.; Wright, J. L. C.; Carsi, J.; Baden, D. G. *Cell. Mol. Neurobiol.* **2004**, *24*, 553.

shown promise for treating cystic fibrosis, a disease caused by malfunctioned sodium voltage-gated ion channels.[8]

Equally as impressive as their myriad biological activities are the unique MLP structures that have piqued the interest of the synthetic community for decades.[5,9] The most distinctive features are the sequences of fused cyclic ether rings and the strictly conserved *trans-syn-trans* ring junction geometry that give rise to the ladder-like structures (Figure 3). Each MLP may comprise up to four ladders, each containing four to seventeen cyclic ethers. The ring sizes range from five-membered tetrahydrofurans (THFs) to nine-membered oxonanes, with six-membered tetrahydropyrans (THPs) being the most prevalent. In some cases, degrees of unsaturation are observed in seven- to nine-membered ether rings.

In addition to the intricate ladder-like topography, from which MLPs derive their name, another key characteristic of MLPs is the repeating C–C–O bond pattern that can be traced throughout each ladder, regardless of ring numbers and sizes. Methyl groups are the only substituents other than hydrogens found at ring junctions, while the polycyclic core may be decorated with hydroxyl or methyl groups elsewhere. MLP side chains vary in functional groups from simple alcohols to charged sulfates.

Figure 3. Structural features of **1.1**.



[8] Abraham, W. M.; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. *G. Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.
[9] Nakata, T. *Chem. Rev.* **2005**, *105*, 4314.

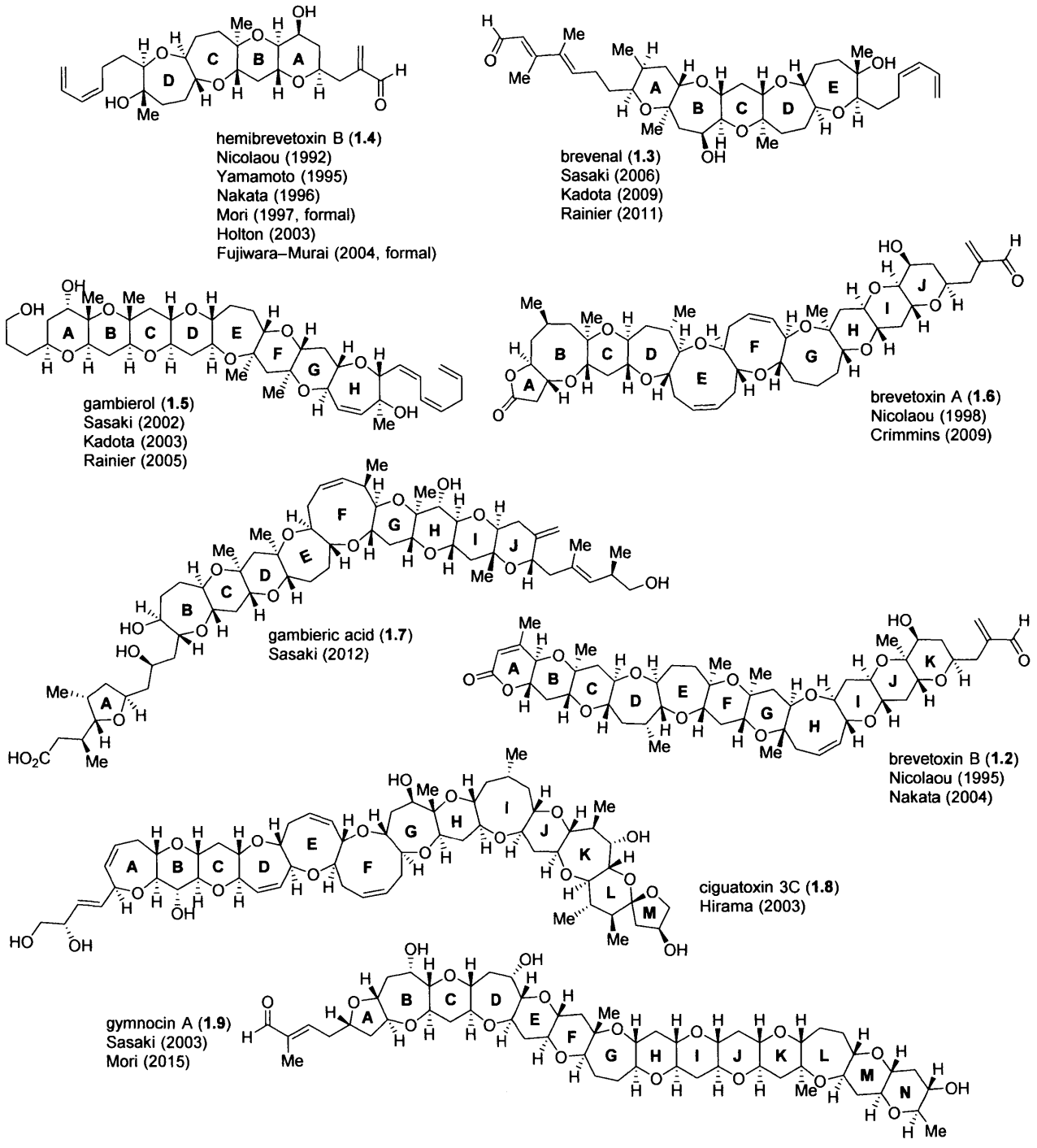
To date, **1.1** has remained the second largest member of the MLPs since its isolation in 2005, containing fifteen contiguous cyclic ethers. One-third of these rings are seven-membered oxepanes (ring *B*, *G*, *H*, *J* and *O*), which confer a high degree of conformational flexibility. Four hydroxyl groups decorate the polycyclic core, while a unique 2-methyl-2-butenal side chain adorns the terminal THF *A* ring. Five methyl groups are situated at ring junctions, with Me61 and Me62 flanking the oxepane *O* ring being the most recognizable feature.

C. Perspective

Structural complexity and profound biological activities of marine ladder polyethers (MLPs) have attracted much attention from the synthetic community for more than three decades.[5,9] Due to the low natural abundance and challenges associated with dinoflagellate culturing,[10] chemical synthesis has emerged as an alternative tool to gain access to this class of natural products. Creative ring forming and fragment coupling strategies have been developed to enhance the efficiency as well as reduce the number of synthetic operations.[5,9] With innovative methods and tenacious efforts from various laboratories, members of MLPs have begun to succumb to total synthesis. Depicted in Figure 4 are the MLPs that have been constructed by total synthesis along with the corresponding laboratories and years.

[10] Garcia Camacho, F.; Gallardo Rodríguez, J.; Sánchez Mirón, A.; Cerón García, M. C.; Belarbi, E. H.; Chisti, Y.; Grima Molina, E. *Biotechnol. Adv.* **2007**, *25*, 176.

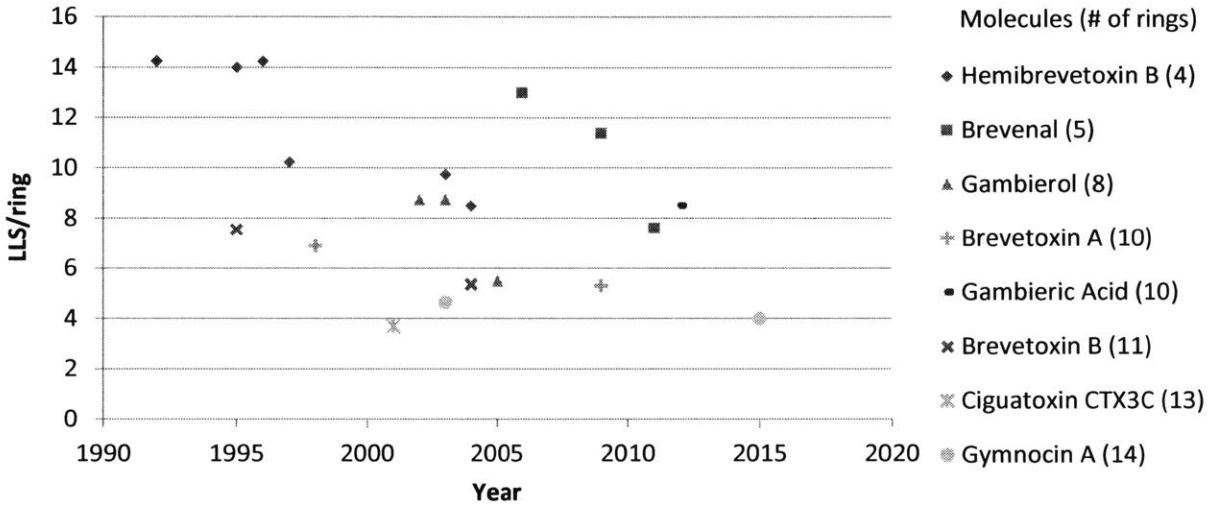
Figure 4. MLPs synthesized to date. [5,9,11]



[11] (a) Crimmins, M. T.; Zuccarello, J. L.; Ellis, J. M.; McDougall, P. J.; Haile, P. A.; Parrish, J. D.; Emmitte, K. A. *Org. Lett.* **2009**, *11*, 489. (b) Sakai, T.; Matsushita, S.; Arakawa, S.; Mori, K.; Tanimoto, M.; Tokumasu, A.; Yoshida, T.; Mori, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14513. (c) Takamura, H.; Kikuchi, S.; Nakamura, Y.; Yamagami, Y.; Kishi, T.; Kadota, I.; Yamamoto, Y. *Org. Lett.* **2009**, *11*, 2531. (d) Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 3208. (e) Fuwa, H.; Ishigai, K.; Hashizume, K.; Sasaki, M. *J. Am. Chem. Soc.* **2012**, *134*, 11984.

To better understand the longstanding history of MLP synthesis, we use the number of cyclic ethers in each MLP as a normalizing factor. The timeline of normalized longest linear sequences of relevant syntheses is shown in Figure 5. One obvious trend is that the longest linear sequence per ring (LLS/ring) has shrunk significantly over time.

Figure 5. Timeline of longest linear sequence per ring (LLS/ring) of MLP synthesis



Since its isolation in 1989,[12] hemibrevetoxin B (**1.4**, Figure 4) has been the most targeted MLP, prompting greater than nine synthetic reports.[5] Containing four cyclic ethers, **1.4** represented an attractive target for testing synthetic methods so far developed. The first three syntheses feature completely linear approaches with an LLS/ring value above fourteen. Although linear, Mori's synthesis by means of couplings between sulfonyl-stabilized oxiranyl anions and triflates followed by *endo*-clyclizations significantly lowered LLS/ring parameter to about ten.[13] With the introduction of a more convergent approach, Holton[14] and Fujiwara–Murai[15] were able to achieve a synthesis with fewer than 10 steps LLS/ring.

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[12] Krishna Prasad, A. V.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 64876.
[13] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.
[14] Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.
[15] Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243.

Convergent synthesis has become a common practice in the synthesis of larger MLPs. Consequently, inventive yet practical fragment coupling methods have been realized.[16] Convergent strategies have improved the synthesis of MLPs as reflected by the apparent trend of LLS/ring (Figure 5). However, even with various fragment coupling methods at our disposal, the synthesis of each individual fragment still needs to be advanced. In pursuit of a more efficient approach, synthetic chemists have drawn inspiration from the proposed biosynthetic pathway involving a polyepoxide cascade.

D. Nakanishi Hypothesis and Baldwin Rules

Regarding their biosynthetic origins, much remains unknown about the biogenesis of MLPs. However, carbon labeling and feeding experiments have confirmed their polyketide origins.[17] Besides the source of its carbon backbone, how such complicated molecules are assembled in nature remains unsolved. Despite the lack of conclusive evidence, a number of remarkable MLP biosynthetic proposals have been put forth.[18]

Shortly after the structure elucidation of brevetoxin B (**1.2**, Figure 2) was completed, Nakanishi put forth a biosynthetic pathway that accounts for the profound regularity found in all MLPs.[18a] In the Nakanishi hypothesis, the C–C–O repeating units as well as the reserved *trans-syn-trans* ring junction geometry can be explained in two straightforward chemical steps (Scheme 1). Starting from a linear polyene precursor (**1.10**), stereoselective epoxidation installs all epoxides with the same absolute configuration [all (*S*,*S*) shown]. Subsequently, a single dramatic epoxide-opening cascade of polyepoxide **1.11** culminates in the construction of the polyether core of **1.1**.

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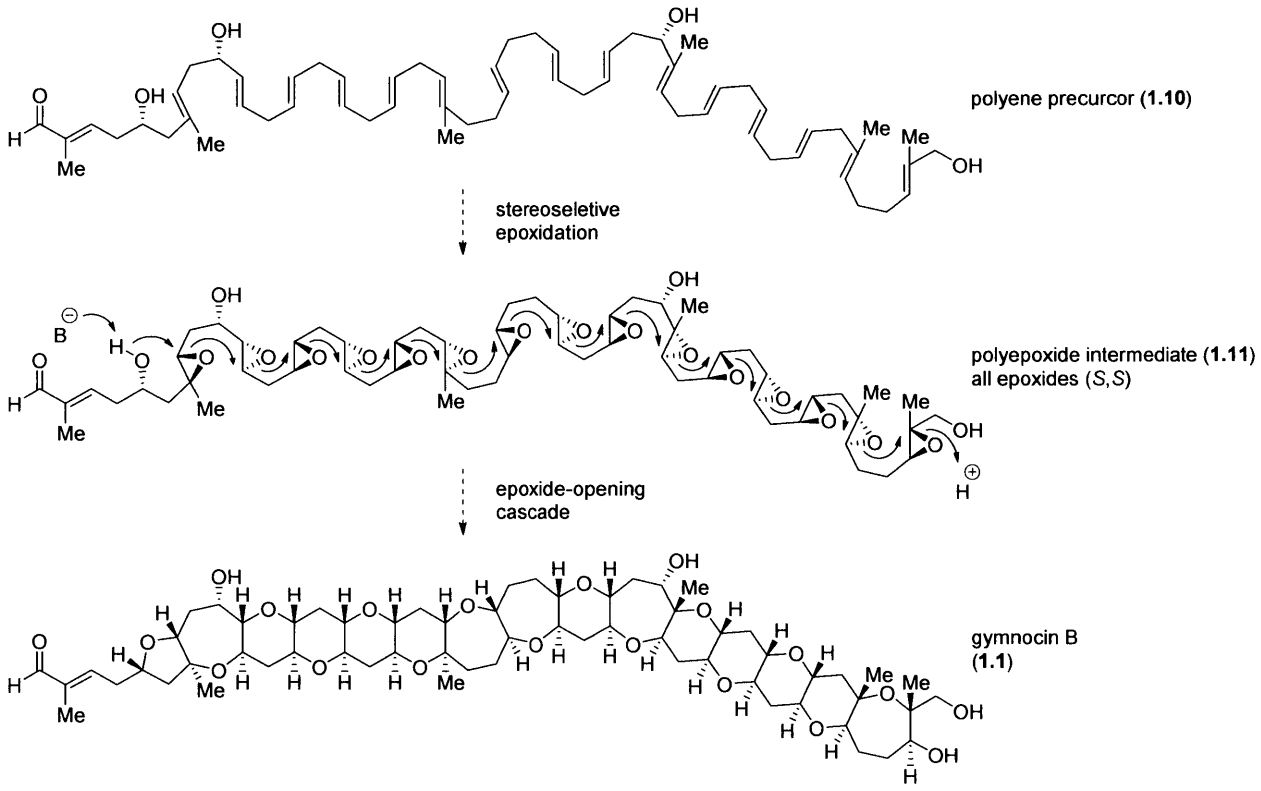
[16] Inoue, M. *Chem. Rev.* **2005**, *105*, 4379.
[17] (a) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234.
[18] (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473. (b) Giner, J.-L.; Li, X.; Mullins, J. J. *J. Org. Chem.* **2003**, *68*, 10079.

The three atoms constituting each epoxide unit contribute to the observed C–C–O patterns. Moreover, if each epoxide opening proceeds stereospecifically with inversion of configuration, the unique *trans-syn-trans* topography can be explained mechanistically by conservation of epoxide configuration.

Scheme 1. The proposed Nakanishi hypothesis of the biosynthesis of gymnocin B.



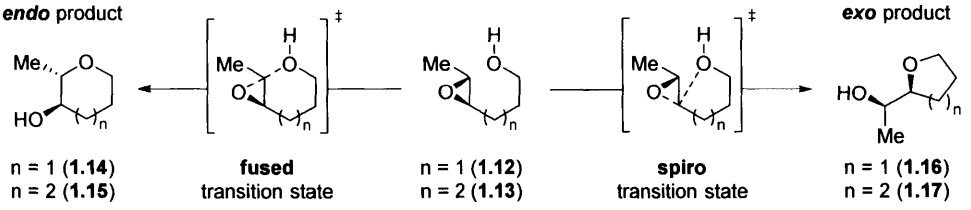
Despite its intellectual appeal, the Nakanishi hypothesis still lacks in experimental evidence. A single enzyme responsible for stereoselective epoxidation has never been identified. No polyene or polyepoxide intermediates have been isolated. Still, the Nakanishi hypothesis has inspired a multitude of synthetic efforts toward this class of natural products.[19]

[19] Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250.

Attempts to emulate the Nakanishi hypothesis in the laboratory are challenged by an intrinsic regioselectivity dilemma. With the advent of stereoselective epoxidation by Sharpless[20] and Shi,[21] synthetic chemists have developed tools to access polyepoxide cascade precursors. However, achieving high degree of regioselectivity in a single epoxide-opening event is non-trivial, let alone multiple events in the proposed biosynthetic cascades.

Cyclization of epoxy alcohols can proceed via two different pathways, giving rise to two regioisomeric products (Scheme 2). Borrowing terminology from the Baldwin rules,[22] the *endo* cyclization proceeds through fused transition state to furnish larger-ring products, while the *exo* pathway leads to smaller ring size via a spiro transition state. These epoxy alcohol cyclizations are kinetically controlled, and, as predicted by the Baldwin rules, the desired *endo*-tet cyclizations are energetically unfavorable in the cases of THF vs. THP (**1.12**) and THP vs. oxepane (**1.13**). Indeed, experimental results strongly support this trend.[23] For electronically unbiased *trans*-disubstituted epoxy alcohols, *exo* products are favored under all conditions.

Scheme 2. Regioselectivity in epoxide-opening cyclizations.



substrates	Conditions	*exo*:*endo*
1.12	$BF_3{\cdot}OEt_2$, CH_2Cl_2	84:16
1.12	Cs_2CO_3, MeOH	83:17
1.12	H_2O, 60 °C	86:14
1.13	$BF_3{\cdot}OEt_2$, CH_2Cl_2	>95:5

[20] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

[21] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

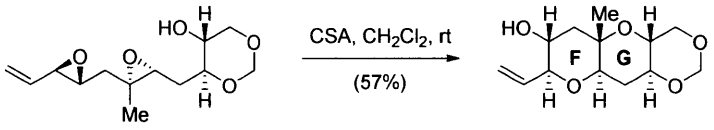
[22] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[23] (a) Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521. (b) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, *75*, 2681. (c) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem*, **2008**, *73*, 2270.

E. Epoxide-Opening Cascades in Chemical Synthesis

In order to mimic the proposed biosynthetic epoxide-opening cascade, ingenious methods have been developed to overcome this intrinsic obstacle. The most common solution has been the use of directing groups. Due to their ability to stabilize any incipient positive charge accumulation during the transition state, additional alkyl and vinyl groups have been incorporated into epoxide-opening cascade precursors to bias the desired *endo* pathway. For instance, both methyl and vinyl groups were used in the epoxide-opening cascade of diepoxy alcohol **1.18** en route to the *FG* rings of gambierol (Figure 6).[24] This type of cascade often requires activation of epoxides by Brønsted or Lewis acids.

Figure 6. A directing group assisted, *endo*-selective electrophilic epoxide-opening cascade.



1.18 **1.19**

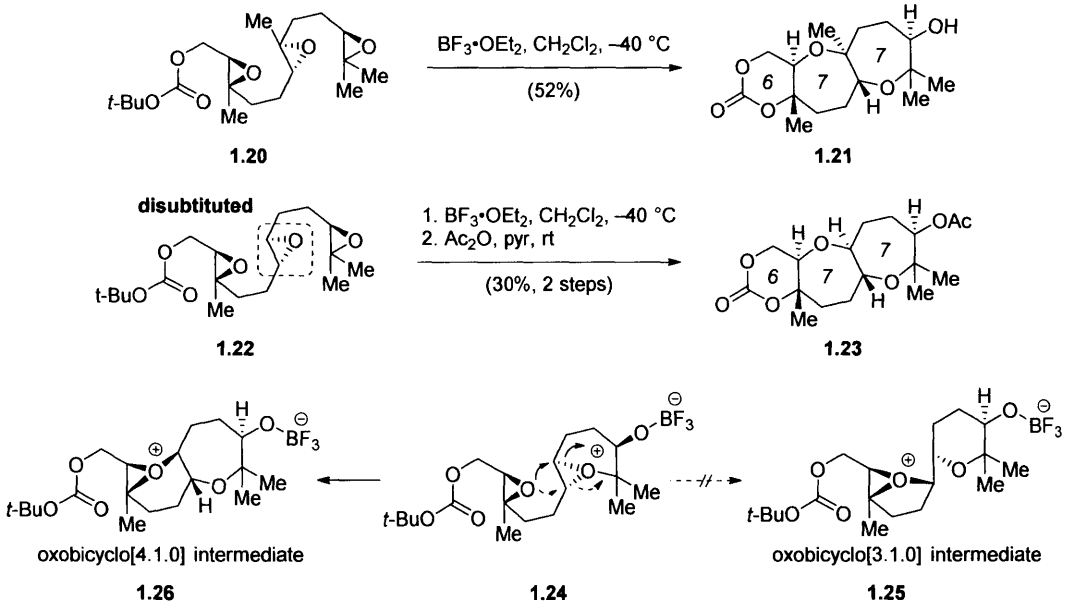
FG rings of gambierol

Despite their utility, limitations arise with the use of directing groups. First, alkyl groups are limited to methyl groups since they are the only substituents besides hydrogens found at ring junctions. Second, the majority of rings in MLPs are hypothetically derived from disubstituted epoxides. Thus, from a synthetic standpoint, incorporation of alkyl groups is best used when they end up in the final targets. Likewise, with the advantage of functional group interconversion, vinyl groups can only be placed at the terminus of the cascade precursors.

[24] Van Dyke, A. R. Ph.D. Thesis. Massachusetts Institute of Technology, Cambridge, MA, 2009.

Several examples of electrophilic epoxide-opening cascades are depicted in Scheme 3.[25] Each trisubstituted epoxide in cascade precursor **1.20** is electronically biased by the presence of additional methyl groups. A more useful strategy is when directing groups are not required at every epoxide but rather at the proximal and distal epoxides with respect to the trapping nucleophile as shown in the cascade of triepoxide **1.22**. The epoxide in between can be electronically neutral. The observed outcome was proposed to stem from the highly strained oxobicyclo[3.1.0] intermediate **1.25** prohibiting the cascade to proceed through the undesired *exo* pathway. Interestingly, the electrophilic cascades can often accommodate different ring sizes in one transformation as seen in a *6,7,7* motif embedded in **1.21** and **1.23**.

Scheme 3. Electrophilic epoxide-opening cascades utilizing electronic and conformational bias techniques.

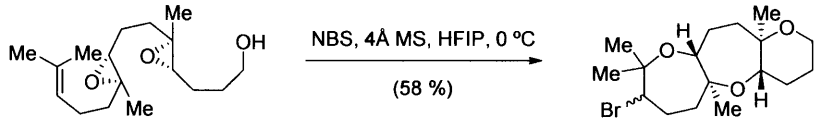


Electrophilic epoxide-opening cascades also find utility in the synthesis of other classes of polyether natural products. One such example is the total synthesis of *ent-*

[25] (a) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (b) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.

dioxepandehydrothyrsiferol, a squalene-derived terpenoid polyether.[26] The main difference in this methodology is the use of a bromonium species to activate the pendant alkenes as an electrophile. This mode of activation allows for selective point of initiation, thus, tolerating a wide range of trapping nucleophiles such as an alcohol (**1.27**, Figure 7).

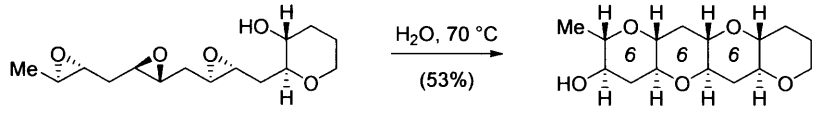
Figure 7. Alcohol as a trapping nucleophile in a bromonium-initiated epoxide-opening cascade.



1.27 **1.28**

Continued efforts in the area of epoxide-opening cascades have led to directing group free transformations. Our laboratory has shown that a combination of a pre-installed THP template and water as a promoter is critical to mimic the polyepoxide openings as described in the Nakanishi hypothesis.[27] In a single operation, the cascade reaction of **1.29** generates tetracycle **1.30** that contains three newly formed THPs, the most prevalent ring size encountered in MLPs (Figure 8). Mechanistic studies support a step-wise mechanism and reveal that the rate and *endo* selectivity increase as the cascade proceeds.[28] Based on these observations, we often refer to this type of transformation as nucleophilic epoxide-opening cascades, facilitating a rapid access to polyTHP subunits.

Figure 8. Water-promoted *endo*-selective nucleophilic epoxide-opening cascade.

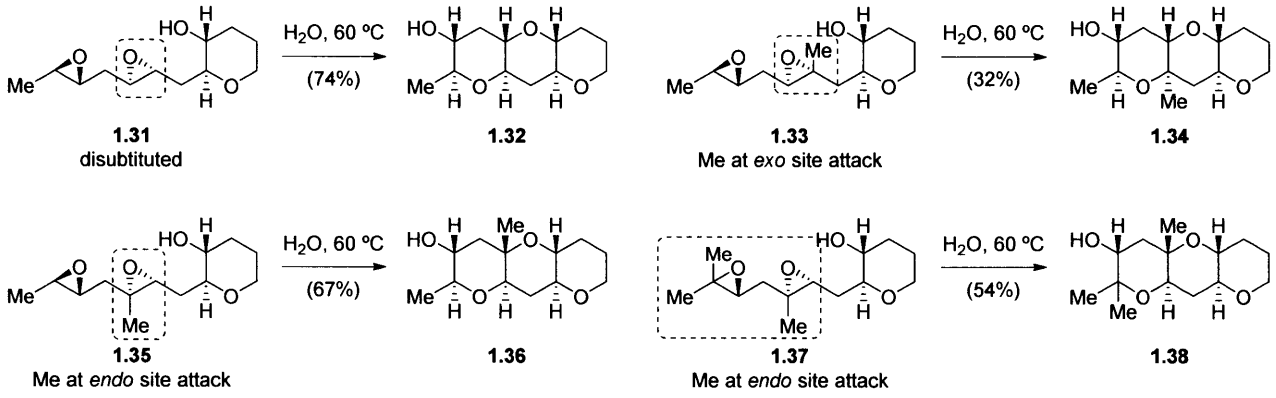


1.29 **1.30**

[26] Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.
[27] (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383.
[28] Morten, C. J.: Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 1902.

The ability to accommodate different methyl substitution patterns is crucial for epoxide-opening cascades to be implemented in practical synthesis of MLPs. Our laboratory has shown that the combination of water as reaction solvent and a THP template can also accomplish this challenging task.[29] Scheme 4 depicts a variety of epoxide-opening cascade precursors. Methyl groups at the *exo* (**1.33**) and *endo* (**1.35**, **1.37**) sites are well tolerated, delivering the desired polyTHP products (**1.34**, **1.36** and **1.38**, respectively) in good yields. Most importantly, the ability to incorporate methyl groups at the *exo* position in **1.33** illustrates that the developed methodology can overcome the directing group effects. In addition, a 1,3-dioxane template has been demonstrated to exhibit very high *endo* selectivity in epoxy alcohol cyclizations.[30] This new synthetically versatile scaffold has found applications in the synthesis of MLPs.[31]

Scheme 4. Water-promoted epoxide-opening cascades of differentially methyl-substituted polyepoxides.



Attempts to emulate the Nakanishi hypothesis have stimulated the development of many epoxide-opening cascade methods. Armed with this knowledge, we were ready to embark upon the total synthesis of gymnocin B.

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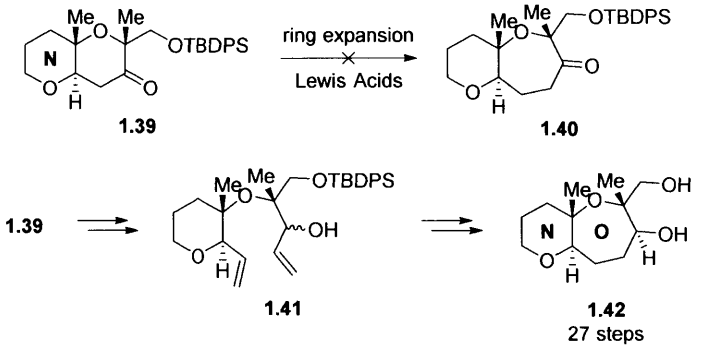
[29] Morten, C. J.; Jamison, T F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.
[30] Mousseau, J. J.; Morten, C. J.; Jamison, T. F. *Chem. Eur. J.* **2013**, *19*, 10004.
[31] (a) Morten, C. J. Ph.D. Thesis. Massachusetts Institute of Technology. Cambridge, MA 2011. (b) Halkina, T. Ph.D. Thesis. Massachusetts Institute of Technology. Cambridge, MA 2016.

F. Previous Synthetic Attempts of Gymnocin B

Gymnocin B (**1.1**) has not yet succumbed to total synthesis since its isolation in 2005. Only one synthetic attempt has been reported.[32] Instead of aiming to access the whole structure, the Sasaki group targeted the more simplified *NO* ring model system. The challenge in synthesizing this system resides in the construction of the oxepane *O* ring containing pseudoaxial methyl groups. Sasaki's initial approach hinged upon ring expansion strategy (Scheme 5). However, attempts to conduct ring expansion of ketone **1.39** to ketone **1.40** by a variety of Lewis acids were unsuccessful, presumably due to severe steric congestion of the axial methyl groups at the α-position of the carbonyl. An alternative route featured ring-closing metathesis (RCM) to construct the *O* ring. Diene **1.41**, synthesized in several steps from ketone **1.39**, underwent RCM as the key ring forming step. In the end, the *NO* ring model **1.42** was synthesized in 27 linear steps.

Scheme 5. Synthesis of *NO* ring model system by Sasaki.



G. Retrosynthetic Analysis of Gymnocin B

Given the molecular size and complexity of **1.1**, we designed a convergent synthesis that could incorporate epoxide-opening cascades and utilize well-established fragment coupling

[32] Tsukano, C.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4617.

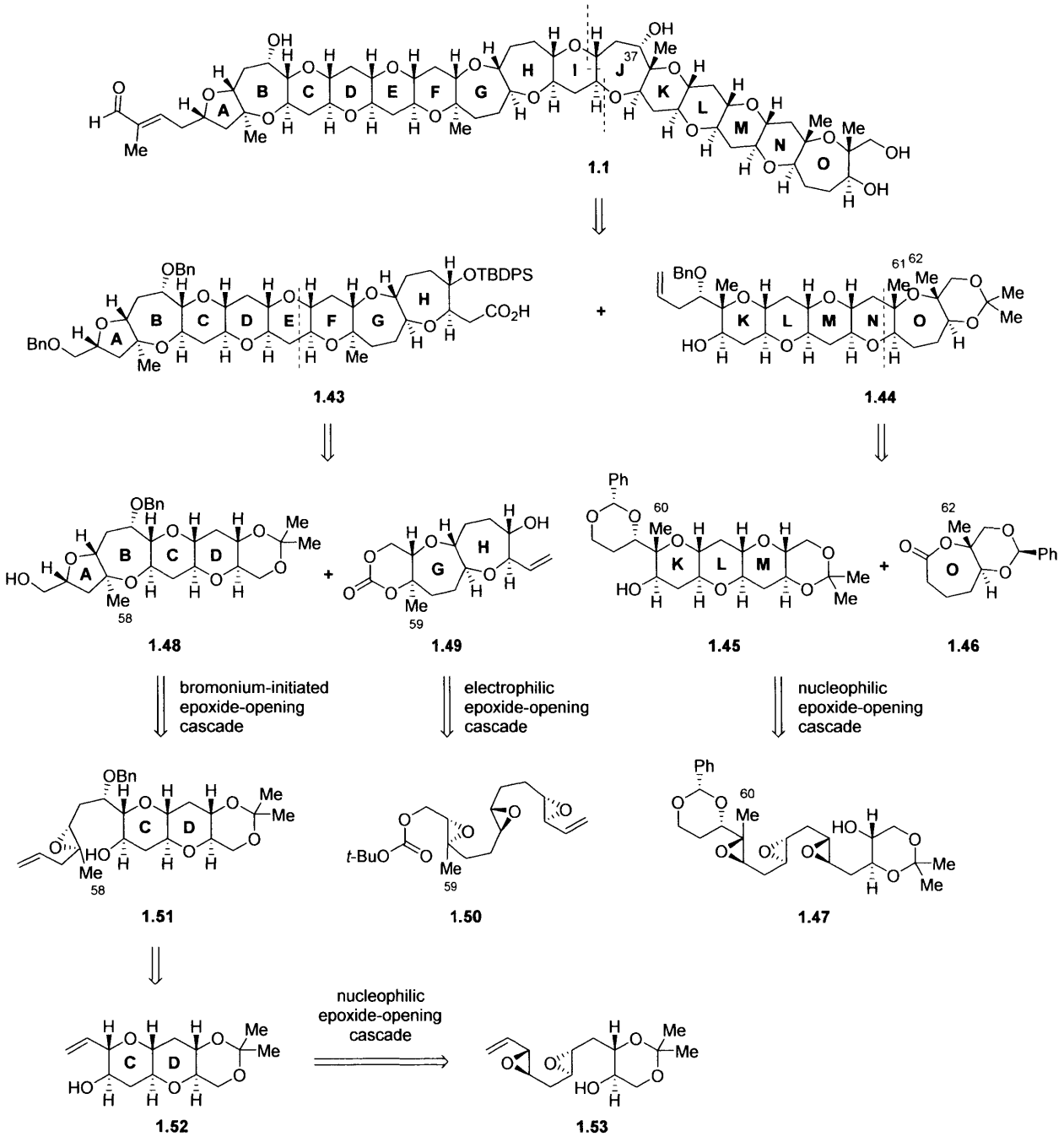
strategies. In a retrosynthetic plan, our initial point of disconnection centered on C37 alcohol as shown in Scheme 6. By splitting its core along *IJ* ring junction, **1.1** was simplified to two smaller fragments: western *ABCDEFGH* acid **1.43** and eastern *KLMNO* alcohol **1.44**. We envisioned that the latter could be assembled via the union of *KLM* fragment **1.45** and known lactone **1.46**.[33] To install the challenging pseudoaxial Me61, we planned to take advantage of the axial Me62 group already present in **1.46**. Regarding the *KLM* fragment, we believed that a polyTHP motif in **1.45** could be readily derived from a nucleophilic epoxide-opening cascade of triepoxy alcohol **1.47** bearing a dimethyl acetal moiety as a template. Under this type of cascade, Me60 in **1.45** should be well tolerated. The cascade precursor **1.47** also contained stereodefined C37 secondary alcohol masked within a bezylidene acetal moiety. Similarly, *ABCDEFGH* acid **1.43** could be disconnected in a convergent manner through ring *E*, giving rise to *ABCD* alcohol **1.48** and *GH* cyclic carbonate **1.49**. Containing two *trans* fused oxepanes embedded in a *6,7,7* motif, tricycle **1.49** maps nicely onto the product of an electrophilic epoxide-opening cascade of triepoxide **1.50**. We postulated that the presence of Me59 and a vinyl group in **1.50** would sufficiently guide the cascade into the desired *endo*-selective direction due to their positive-charge stabilizing ability.

Comprising all THF, THP, and oxepane rings in a single fragment, *ABCD* **1.48** posed a challenging target. Consequently, we decided to target *AB* and *CD* portions separately and use two different cascades to construct each subunit. For the unique fused THF-oxepane *AB* rings, we turned our attention to a bromonium-initiated electrophilic cascade due to its ability to tolerate varied ring size in a single transformation. We believed that epoxide Me58 in **1.51** would bias the epoxide opening toward the desired *endo* direction. Finally, we arrived at our last retrosynthetic target, polyTHP **1.52**. We posited that this fragment would be readily derived from another

[33] Kuranaga, T.; Satake, M.; Baden, D. G.; Wright, J. L. C.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 4673.

nucleophilic epoxide-opening cascade of diepoxide **1.53**. The choice of a vinyl group in **1.53** was two-fold regarding its directing ability and functional group convertibility.

Scheme 6. Retrosynthetic analysis of gymnocin B (**1.1**).



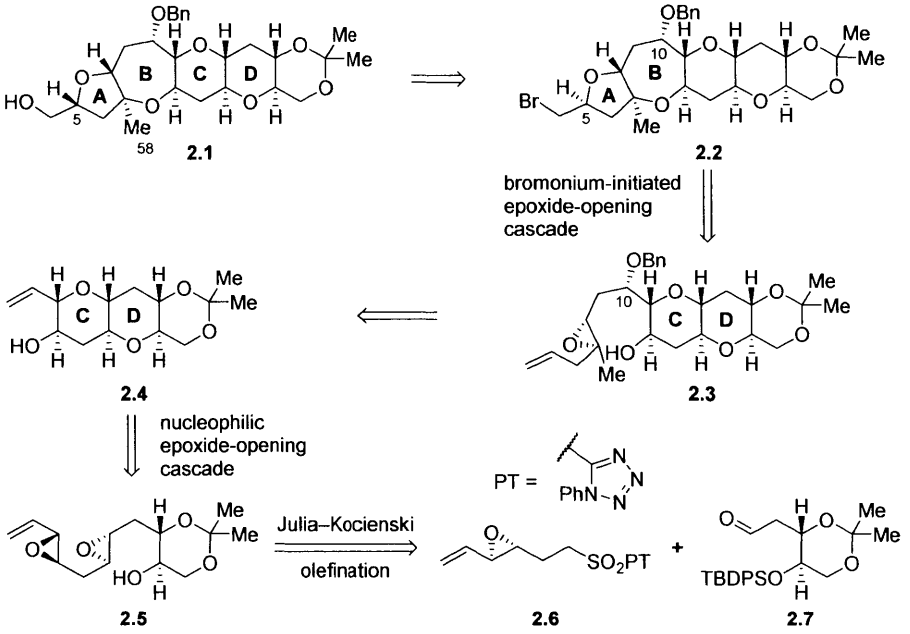
CHAPTER II

Synthesis of the *ABCD* Fragment of Gymnocin B

A. Retrosynthetic Analysis of *ABCD* Fragment

Due to varied ring sizes, we chose two different types of epoxide-opening cascades to construct *ABCD* fragment **2.1** as shown in Scheme 1. Retrosynthetically, we envisioned that alcohol **2.1** could be derived from bromide **2.2**. Pseudoaxial Me58 would play a significant role in setting correct stereochemical configuration at C5. In turn, the *AB* portion in **2.2** could be assembled via a bromonium-initiated epoxide-opening cascade of epoxyalcohol **2.3**. This type of cascade was chosen due to its ability to tolerate different ring sizes.[1] Cascade precursor **2.3** could be elaborated from alcohol **2.4** containing a polyTHP *CD* unit. During elaboration steps, C10 configuration would be installed diastereoselectively. The polyTHP unit in **2.4** could be derived from a nucleophilic epoxide-opening cascade of diepoxyalcohol **2.5** bearing a dimethyl acetal moiety as a template. Lastly, Julia–Kocienski olefination[2] between sulfone **2.6** and aldehyde **2.7** would furnish cascade precursor **2.5**.

Scheme 1. Retrosynthetic analysis of *ABCD* fragment **2.1**.

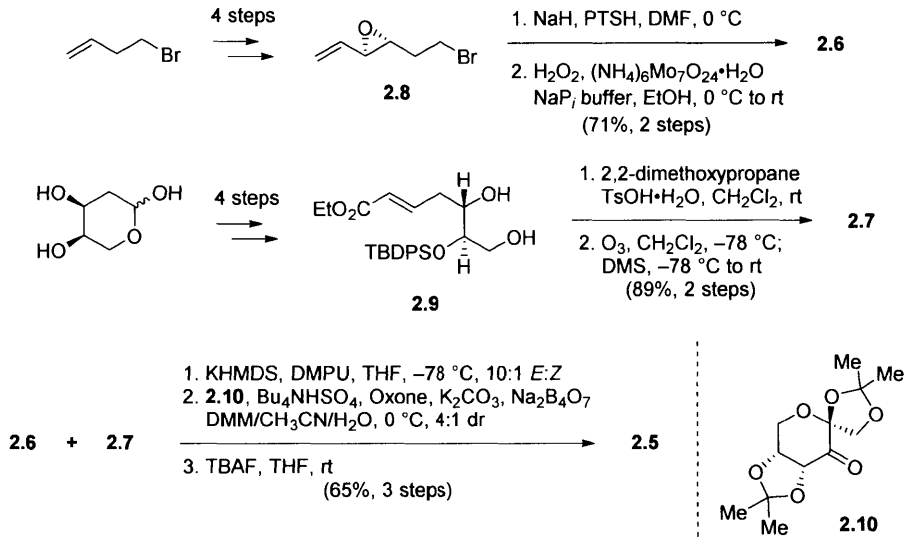


[1] Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.
[2] Blakemore, P. R.; Cole. W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

B. Synthesis of *ABCD* Fragment

The synthesis of **2.1** commenced with known bromoepoxide **2.8**[3] as depicted in Scheme 2. Conversion to the requisite sulfone **2.6** was achieved via nucleophilic substitution with 1-phenyl-1*H*-tetrazole-5-thiol followed by selective sulfur oxidation. Buffered conditions were necessary to circumvent epoxide solvolysis. The aldehyde coupling partner was synthesized from known diol **2.9**.[4] Dimethyl acetal formation followed by ozonolysis furnished aldehyde **2.7**. Julia–Kocienski olefination between **2.6** and **2.7** proceeded uneventfully with 10:1 *E*:*Z* ratio. Asymmetric Shi epoxidation[5] with ketone **2.10**, followed by desilylation, afforded diepoxy alcohol **2.5** with 4:1 dr.

Scheme 2. Synthesis of diepoxy alcohol **2.5**.



With cascade precursor **2.5** in hand, we began our investigation into the key epoxide-opening cascade. We envisioned that acidic aqueous conditions would result in undesired premature opening of the vinyl epoxide. Consequently, our initial attempts were focused on employing basic conditions. After considerable experimentation, it was determined that subjecting

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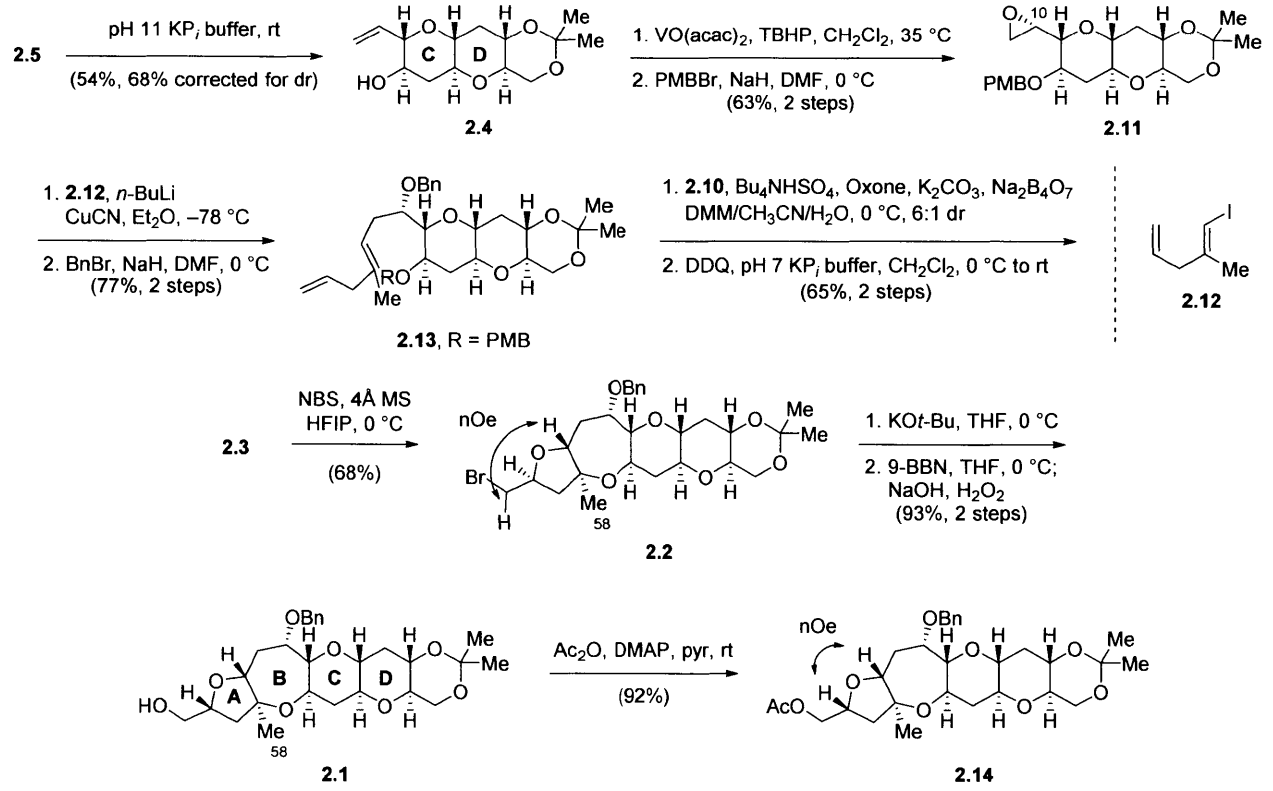
[3] Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.–Eur. J.* **2009**, *15*, 11490.
[4] Morten, C. J.; Jamison, T F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.
[5] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

2.5 to pH 11 aqueous phosphate buffer at ambient temperature delivered tricycle **2.4** at an optimal yield (68% yield corrected for dr, 82% yield per ring formation) as shown in Scheme 3. Inorganic bases and acidic additives proved to be less effective. This cascade represented the first example of a successful nucleophilic epoxide-opening cascade at basic pH. Tricycle **2.4**, containing the *CD* rings found in gymnocin B, was synthesized in 10 steps longest linear sequence.

Our next challenge was to elaborate the *CD* fragment to the full *ABCD* tetracycle **2.1**. To this end, **2.4** underwent Sharpless diastereoselective epoxidation,[6] followed by subsequent alcohol protection as a PMB ether to furnish epoxide **2.11**. From vinyliodide **2.12**,[7] cuprate addition to epoxide **2.11** provided homoallylic alcohol, which was converted to benzyl ether **2.13**. Asymmetric Shi epoxidation,[5] followed by PMB removal, delivered epoxy alcohol **2.3** as the key substrate for the bromonium-initiated epoxide-opening cascade.

[6] Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061.
[7] Zhu, G.; Negishi, E. *Chem.–Eur. J.* **2008**, *14*, 311.

Scheme 3. Synthesis of *ABCD* fragment **2.1**.

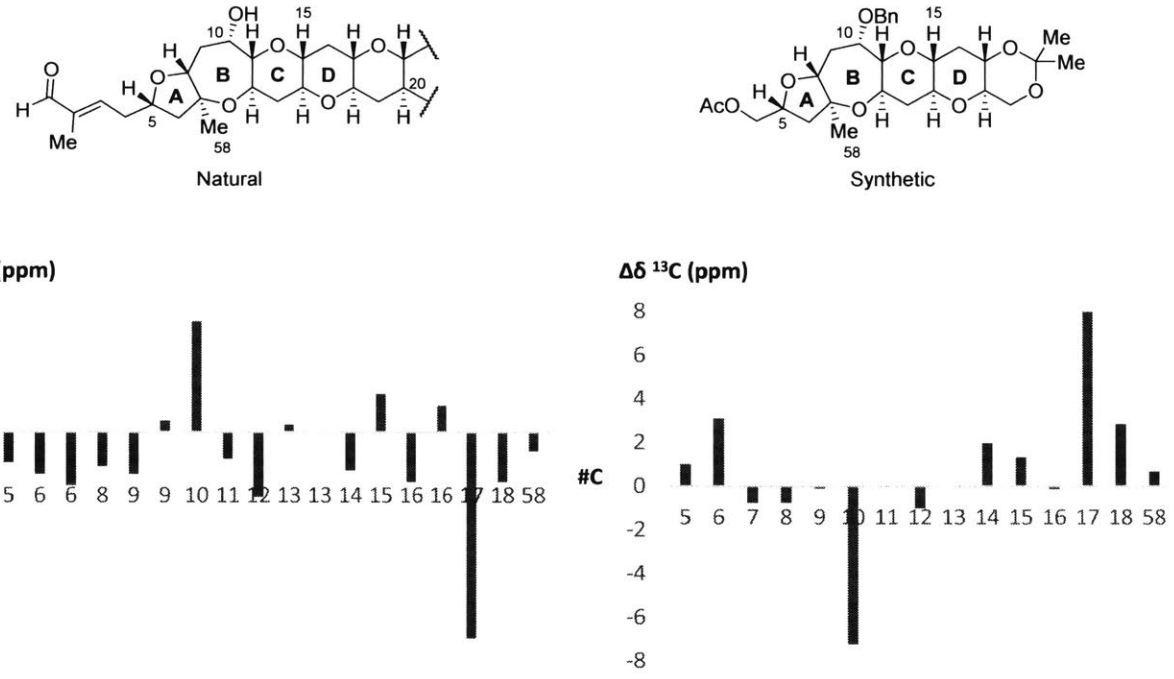


To form the *AB* rings, we investigated an unprecedented 7-*endo*-5-*exo* epoxide-opening cascade. As shown in previous studies,[1] the choice of bromonium initiator had no significant effect on the reaction yields. The choice of solvent was critical as acetonitrile proved ineffective for our system. A combination of NBS as an initiator with HFIP as solvent effected the desired transformation. The cascade proceeded with high regio- and diastereoselectivity, however, with incorrect C5 stereochemistry as confirmed by nOe experiments of bromide **2.2**. This discrepancy could be corrected via a two-step reaction sequence. To this end, elimination of **2.2** provided exocyclic enol ether, which immediately underwent hydroboration/oxidation to furnish alcohol **2.1** with complete facial selectivity, thus, completing the synthesis of *ABCD* fragment **2.1**.

Strategically, ring junction Me58 served two purposes. First, it electronically biases 7-*endo* epoxide opening during the cascade event. Second, it sterically shields the bottom face of **2.2**, thus, enabling the installation of correct C5 configuration as confirmed by nOe experiments of acetate

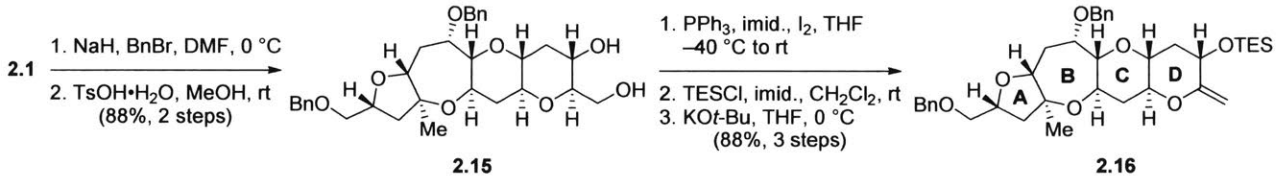
derivative **2.14**. The ^{1}H and ^{13}C chemical shifts of **2.14** were compared to those of the natural product (Figure 1). In general, good agreement was observed. As expected, significant deviation arose at the edges of the fragment and at C10 where the hydroxyl group in gymnocin B was protected as a benzyl ether in fragment **2.14**.

Figure 1. Chemical shift comparison between natural and synthetic *ABCD* fragments.



Elaboration of alcohol **2.1**, in preparation for the next fragment coupling step, is shown in Scheme 4. After protection of primary alcohol in **2.1** as a benzyl ether, acetonide removal under acidic conditions revealed diol **2.15**. Selective iodination of the primary alcohol, silylation of the secondary alcohol, and elimination of the alkyl iodide furnished exocyclic methylene **2.16**.

Scheme 4. Synthesis of *ABCD* fragment coupling partner **2.16**.



In conclusion, the *ABCD* fragment **2.1** was synthesized in 19 steps longest linear sequence. The synthesis featured two different types of epoxide-opening cascades to assemble the multi-cyclic core of **2.1**. The nucleophilic cascade at basic pH delivered the *CD* rings, eventually followed by a 7-*endo*-5-*exo* bromonium-initiated cascade to furnish the *AB* rings of **2.1**. Diasteroselective epoxidation of homoallylic **2.4** set C10 configuration. The incorrect C5 configuration generated during the 7-*endo*-5-*exo* cascade could be inverted via an elimination and hydroboration/oxidation procedure. This *ABCD* fragment **2.1** was further elaborated to exocyclic methylene **2.16** for the ensuing fragment coupling step.

C. Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Dichloromethane, THF, Et_2O, toluene, DMSO, DMF, and trimethylamine, pyridine, acetonitrile, and benzene were purified via an SG Water USA solvent system. Ti(O*i*-Pr)$_4$, HMPA, and DMPU were distilled from CaH_2 and stored over molecular sieves under argon. Reactions in water used deionized water without further purification. All other reagents and solvents were used as obtained, without further purification.

Chiral ketone **2.10**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers[8].

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), CAM, $KMnO_4$, or *p*-anisaldehyde stain. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh) or Biotage Isolera flash purification system on SNAP KP-Sil, HP-Sil, or Ultra columns. Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^{1}H NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-125 MHz spectrometer, a Bruker AVANCE-100 MHz spectrometer, or a Bruker AVANCE-150 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard residual $CHCl_3$ in $CDCl_3$ (7.26 ppm) or C_6HD_5 in C_6D_6 (7.16 ppm). Data are reported as follows: chemical shifts, multiplicity (s =singlet, d =doublet, t = triplet, q = quartet, and m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm), on the δ scale.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR and are reported in terms of frequency absorption (cm^{-1}). High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumental Facility. Optical rotations were measured on a Jasco Model 1010 digital polarimeter at 589 nm.

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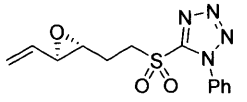
[8] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.



2.6

Sulfone 2.6: To a solution of 1-phenyltetrazole-5-thiol (17.82 g, 100 mmol) in 1:1 THF/DMF (240 mL) at 0 °C was added NaH (60% in mineral oil, 4.0 g, 100 mmol) in three portions. The suspension was warmed to rt over 15 min and then cooled to 0 °C. To this was added a solution of bromide **2.8** (16.1 g, 91 mmol) in THF (60 mL). The solution was allowed to warm to rt over 90 min, at which point the reaction was quenched by addition of sat. $NH_4Cl_{(aq)}$ (90 mL) at 0 °C. The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude sulfide as a yellow oil (R_f = 0.37 (30% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

To a solution of the crude sulfide in EtOH (300 mL) was added aq. NaH_2PO_4 (1 M, 200 mL, 200 mmol), and the resulting solution was cooled to 0 °C. 30% $H_2O_{2(aq)}$ (15.3 g, 46 mL, 450 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (22.5 g, 18.2 mmol) were then added. The reaction was stirred vigorously and allowed to warm to rt slowly overnight. The reaction was quenched by addition of brine (90 mL). The aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 60% EtOAc in hexanes) to afford **2.6** as a colorless oil (21.8 g, 71 mmol, 71% over two steps, R_f = 0.37 (30% EtOAc in hexanes)).

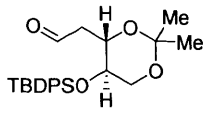
$[\alpha]^{22}_D$ = +26.67 (*c* = 0.78, $CHCl_3$)

IR (ATR): 3084, 2991, 2925, 2253, 2184, 2004, 1732, 1595, 1498, 1340, 1149, 986, 910, 880, 761, 727, 687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.73–7.54 (m, 5H), 5.60–5.42 (m, 2H), 5.29 (dd, *J* = 9.3, 2.2 Hz, 1H), 3.88 (t, *J* = 7.6 Hz, 2H), 3.20 (dd, *J* = 6.7, 2.0 Hz, 1H), 3.02 (ddd, *J* = 6.5, 4.2, 2.0 Hz, 1H), 2.42 (dtd, *J* = 15.3, 7.6, 4.3 Hz, 1H), 2.13 (dq, *J* = 14.6, 7.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 134.4, 133.0, 131.6, 129.8, 125.2, 120.4, 58.9, 57.4, 52.8, 25.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}N_4O_3S$ $[M+H]^+$: 307.0859, found 307.0861.



2.7

Aldehyde 2.7: To a solution of diol **2.9** (60 g, 136 mmol) in CH_2Cl_2 (150 mL) was added 2,2-dimethoxypropane (36.8 mL, 31.2 g, 300 mmol) and $TsOH{\cdot}H_2O$ (1.90 g, 10 mmol). The solution was stirred 30 min at rt and then quenched by addition of sat. $NaHCO_{3(aq)}$ (30 mL). The aqueous

layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude acetonide as a pale yellow oil (R_f = 0.57 (20% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

The crude acetonide was dissolved in CH_2Cl_2 (100 mL), and the resulting solution was cooled to –78 °C. A stream of ozone was bubbled through until a pale blue color evolved, about 4-5 h. Argon was bubbled through the solution to remove residual ozone, and then DMS (11 mL, 9.3 g, 150 mmol) was added, at which point the cold bath was removed, and the reaction was allowed to warm to rt overnight. The solution was then concentrated *in vacuo* and purified by column chromatography (gradient 0% to 40% EtOAc in hexanes) to provide aldehyde **2.7** as a colorless oil (50 g, 121 mmol, 89% over two steps, R_f = 0.54 (20% EtOAc in hexanes))

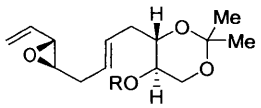
$[\alpha]^{22}_D$ = –15.42 (*c* = 2.65, $CHCl_3$)

IR (ATR): 3072, 2996, 2955, 2935, 2895, 2859, 2733, 1727, 1590, 1472, 1428, 1378, 1275, 1259, 1231, 1199, 1165, 1103, 1062, 998, 984, 909, 858, 842, 820, 732, 700 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 9.65 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.63 (td, *J* = 8.0, 1.5 Hz, 4H), 7.45 (dddt, *J* = 6.9, 5.4, 2.9, 1.5 Hz, 2H), 7.40 (ddd, *J* = 8.2, 6.8, 5.3 Hz, 4H), 4.28 (td, *J* = 9.1, 2.8 Hz, 1H), 3.66 (dd, *J* = 11.3, 9.5 Hz, 1H), 3.61 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.55 (td, *J* = 9.3, 5.3 Hz, 1H), 2.69 (ddd, *J* = 16.4, 2.9, 1.5 Hz, 1H), 2.31 (ddd, *J* = 16.3, 9.1, 2.8 Hz, 1H), 1.48 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 201.1, 135.9, 135.9, 133.6, 133.0, 130.3, 130.2, 128.1, 128.0, 98.8, 70.4, 68.3, 65.1, 46.1, 28.7, 27.1, 19.4, 19.3.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{32}O_4Si$ $[M+H]^+$: 430.2408, found 430.2426.



2.17, R = TBDPS

Olefin 2.17: To a solution of aldehyde **2.7** (28.9 g, 70 mmol) and sulfone **2.6** (21.8 g, 71 mmol) in THF (200 ml) was added DMPU (34 ml, 280 mmol). The resulting solution was cooled to –78 °C. A solution of KHMDS (15.4 g, 77 mmol) in THF (80 mL) was added over 15 min. The reaction mixture was stirred at –78 °C for 30 min, at which point the reaction was quenched by addition of brine (50 mL) and allowed to warm to rt over 1 h. The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 20% EtOAc in hexanes) to afford **2.17** as a colorless oil (29.7 g, 60.2 mmol, 86%, 10:1 *E*/*Z*, R_f = 0.31 (10% EtOAc in hexanes)).

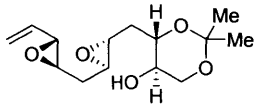
$[\alpha]^{22}_D$ = –8.64 (*c* = 3.35, $CHCl_3$)

IR (ATR): 3073, 2993, 2934, 2896, 2859, 1472, 1428, 1378, 1260, 1200, 1163, 1101, 973, 910, 845, 821, 735, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.65 (ddd, J = 13.4, 8.0, 1.5 Hz, 4H), 7.48–7.35 (m, 6H), 5.59 (ddd, J = 17.7, 10.3, 7.6 Hz, 1H), 5.52 (dt, J = 15.5, 6.8 Hz, 1H), 5.46 (dd, J = 17.3, 1.5 Hz, 1H), 5.38 (dt, J = 15.4, 6.8 Hz, 1H), 5.27 (dd, J = 10.2, 1.6 Hz, 1H), 3.74 (td, J = 8.4, 2.7 Hz, 1H), 3.62–3.48 (m, 3H), 3.12 (dd, J = 7.6, 2.2 Hz, 1H), 2.85 (td, J = 5.3, 2.1 Hz, 1H), 2.53–2.46 (m, 1H), 2.31 (dt, J = 12.9, 6.2 Hz, 1H), 2.27–2.20 (m, 1H), 2.02 (dt, J = 14.7, 7.3 Hz, 1H), 1.45 (s, 3H), 1.29 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 136.0, 135.9, 135.9, 134.0, 133.5, 130.04, 130.02, 129.5, 127.9, 127.8, 126.3, 119.0, 98.5, 74.4, 68.5, 65.1, 59.8, 58.2, 35.1, 35.0, 28.8, 27.2, 19.5, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{40}O_4Si$ $[M+NH_4]^+$: 510.3034, found 510.3024.



2.5

Diepoxy alcohol 2.5: To a solution of olefin **2.17** (18 g, 36.5 mmol) in 2:1 DMM:MeCN (360 mL) were added a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M Na_2EDTA (220 mL), *n*-Bu_4HSO_4 (3.72 mg, 11 mmol), and chiral ketone **2.10** (2.35 g, 9.1 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 90 min via syringe pumps, a solution of Oxone (44.9 g, 73 mmol) in 4×10^{-4} M Na_2EDTA (220 mL) and a 0.89 M solution of aq. K_2CO_3 (220 mL). Over this period, additional chiral ketone **2.10** (2.35 g, 9.1 mmol) was added in two portions. After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred for an additional 1 h and allowed to warm to rt, at which point it was diluted with EtOAc (150 mL) and water (100 mL). The aqueous layer was separated and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude silyl ether diepoxide as a yellow oil (R_f = 0.43 (20% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

To a solution of crude diepoxide in THF (60 mL) was added TBAF (1 M solution in THF, 60 mL, 60 mmol).The reaction was stirred at rt for 45 min, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 10% MeOH in EtOAc) to afford diepoxy alcohol **2.5** as a colorless oil (6.4 g, 23.7 mmol, 65% over two steps as a 4:1 mixture of diastereomers, R_f of all diastereomers = 0.40 (70% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +19.5 (c = 0.7, $CHCl_3$)

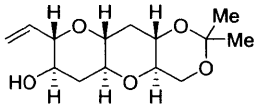
IR (ATR): 3436, 2992, 2922, 1643, 1486, 1408, 1372, 1270, 1225, 1198, 1165, 1126, 1066, 986, 959, 926, 863, 820, 734, 702, 676 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 5.57 (ddd, J = 17.3, 10.0, 7.4 Hz, 1H), 5.49 (dd, J = 17.2, 1.6 Hz, 1H), 5.30 (dd, J = 10.0, 1.6 Hz, 1H), 3.90 (dd, J = 10.8, 5.0 Hz, 1H), 3.75 (ddd, J = 9.4, 5.5, 4.1 Hz, 1H), 3.72–3.65 (m, 1H), 3.61 (dd, J = 10.9, 9.3 Hz, 1H), 3.17 (dd, J = 7.3, 2.1 Hz, 1H), 3.01

(tdd, J = 6.9, 4.2, 2.2 Hz, 2H), 2.94 (ddd, J = 6.8, 4.8, 2.3 Hz, 1H), 2.34–2.29 (m, 1H), 2.03 (dt, J = 14.9, 4.0 Hz, 1H), 1.91–1.74 (m, 3H), 1.47 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 135.2, 119.8, 98.8, 72.0, 66.8, 64.8, 58.7, 57.3, 55.5, 55.2, 35.0, 34.7, 28.8, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{22}O_5$ $[M+H]^+$: 271.1540, found 271.1554.



2.4

Tricycle 2.4: Triepoxy alcohol **2.5** (5 g, 18.5 mmol, 4:1 dr) was dissolved in pH 11 buffer (0.1 M potassium phosphate, 370 mL), and the resulting suspension was stirred at rt for 3 d. The reaction solution was extracted with EtOAc (5×100 mL). The combined organic layers were concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 10% MeOH in EtOAc) to afford tricycle **2.4** as a white solid (2.7 g, 10 mmol, 54%, R_f = 0.51 (70% EtOAc in hexanes)).

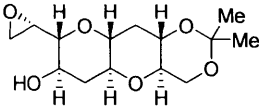
$[\alpha]^{22}_D$ = –0.165 (c = 0.385, $CHCl_3$)

IR (ATR): 3441, 2993, 2940, 2877, 1373, 1271, 1198, 1105, 1074, 1054, 859, 734, 702 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.84 (ddd, J = 17.7, 10.6, 7.3 Hz, 1H), 5.44 (dt, J = 17.4, 1.3 Hz, 1H), 5.37 (dd, J = 10.5, 1.5 Hz, 1H), 3.90 (dd, J = 10.9, 5.2 Hz, 1H), 3.70 (t, J = 10.6 Hz, 1H), 3.64 (ddd, J = 11.7, 9.3, 4.2 Hz, 1H), 3.56 (t, J = 8.2 Hz, 1H), 3.45 (ddd, J = 11.3, 9.0, 4.6 Hz, 1H), 3.23 (td, J = 9.9, 5.2 Hz, 1H), 3.20–3.14 (m, 2H), 2.43 (dt, J = 11.6, 3.9 Hz, 1H), 2.28 (dt, J = 11.3, 3.8 Hz, 1H), 1.59–1.48 (m, 2H), 1.50 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.4, 120.2, 99.5, 84.2, 76.8, 76.7, 74.9, 69.5, 68.9, 62.8, 37.34, 35.3, 29.3, 19.2.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{22}O_5$ $[M+H]^+$: 271.1540, found 271.1551.



2.18

Epoxy alcohol 2.18: To a solution of tricycle **2.4** (4 g, 14.8 mmol) in CH_2Cl_2 (100 mL) was added $VO(acac)_2$ (48 mg, 0.3 mmol) and TBHP (5.5 M in decane, 8 mL, 44.4 mmol). The resulting dark purple solution was stirred at 35 °C overnight. The reaction solution was concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 20% MeOH in EtOAc) to afford tricycle **2.18** as a white solid (2.87 g, 10 mmol, 68%, R_f = 0.54 (100% EtOAc)).

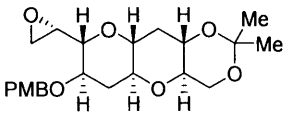
$[\alpha]^{22}_D = -9.5$ ($c = 0.2$, $CHCl_3$)

IR (ATR): 3458, 2922, 2927, 2880, 1730, 1375, 1273, 1109, 1079, 1033, 861, 832, 754 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 3.90 (dd, J = 10.8, 5.2 Hz, 1H), 3.84 (dddd, J = 11.3, 9.0, 4.9, 2.9 Hz, 1H), 3.69 (t, J = 10.6 Hz, 1H), 3.63 (ddd, J = 11.3, 9.3, 4.1 Hz, 1H), 3.23 (ddd, J = 10.4, 9.2, 5.2 Hz, 1H), 3.18–3.09 (m, 3H), 3.00 (dd, J = 9.2, 5.7 Hz, 1H), 2.84 (dd, J = 5.0, 4.0 Hz, 1H), 2.77 (dd, J = 5.0, 2.7 Hz, 1H), 2.47 (d, J = 3.1 Hz, 1H), 2.43 (dt, J = 11.9, 4.3 Hz, 1H), 2.26 (dt, J = 11.1, 4.0 Hz, 1H), 1.55–1.43 (m, 2H), 1.49 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 99.5, 80.5, 76.7, 76.4, 75.0, 69.5, 69.2, 62.8, 53.1, 45.7, 37.7, 35.2, 29.3, 19.3.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{22}O_6$ $[M+H]^+$: 287.1489, found 287.1504.



2.11

PMB ether 2.11: To a solution of epoxy alcohol **2.18** (2.8 g, 9.8 mmol) and freshly prepared PMBBr (4.02 g, 2.88 mL, 20 mmol) in DMF (30 mL) at 0 °C was added 60% NaH (2.4 g, 20 mmol) in one portion. The resulting slurry was stirred at 0 °C for 30 min and warmed to rt over 1 h. The reaction solution was quenched by addition of sat. $NH_4Cl_{(aq)}$ (30 mL) at 0 °C. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 60% EtOAc in hexanes) to afford **2.11** as a colorless oil (3.66 g, 9.0 mmol, 92%, R_f = 0.31 (30% EtOAc in hexanes)).

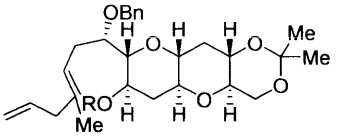
$[\alpha]^{22}_D = -48.23$ ($c = 2.185$, $CHCl_3$)

IR (ATR): 2995, 2941, 2877, 1612, 1586, 1513, 1458, 1373, 1302, 1248, 1199, 1178, 1154, 1079, 1034, 910, 860, 821, 727 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.28–7.24 (m, 2H), 6.90–6.85 (m, 2H), 4.59 (d, J = 11.3 Hz, 1H), 4.44 (d, J = 11.3 Hz, 1H), 3.87 (dd, J = 10.8, 5.1 Hz, 1H), 3.79 (s, 3H), 3.68 (t, J = 10.6 Hz, 1H), 3.60 (ddd, J = 11.3, 9.2, 4.1 Hz, 1H), 3.47–3.36 (m, 2H), 3.22–3.16 (m, 2H), 3.14–3.08 (m, 1H), 3.04 (ddd, J = 11.5, 9.1, 4.0 Hz, 1H), 2.82 (dd, J = 5.5, 2.7 Hz, 1H), 2.68 (dd, J = 5.6, 4.1 Hz, 1H), 2.54 (dt, J = 11.7, 4.2 Hz, 1H), 2.24 (dt, J = 11.3, 4.2 Hz, 1H), 1.51–1.43 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5, 129.8, 129.6, 114.0, 99.4, 78.2, 76.6, 76.4, 74.8, 74.1, 70.6, 69.4, 62.7, 55.4, 52.2, 44.0, 35.2, 35.1, 29.3, 19.2.

HR-MS (ESI) *m/z* calcd for $C_{22}H_{30}O_7$ $[M+NH_4]^+$: 424.2330, found 424.2309.



2.13, R = PMB

Benzyl ether 2.13: To a solution of vinyliodide **2.12** (3.74 g, 18 mmol) in Et_2O (20 mL) at –78 °C was added *n*-BuLi (2.5 M in hexane, 7.2 mL, 18 mmol) slowly. The resulting cloudy solution was stirred at –78 °C for 1 h with exclusion of light and then added via cannulation to a slurry of CuCN (1.79 g, 20 mmol) in Et_2O (20 mL) at –78 °C. The resulting slurry was stirred at –25 °C for 2 h with exclusion of light and then cooled to –78 °C, at which point the solution of epoxide **2.11** (3.66 g, 9 mmol) in Et_2O (20 mL) was added via cannulation. The resulting solution was allowed to warm to rt over 3 h and quenched with addition of sat. $NH_4Cl_{(aq)}$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude homoallylic alcohol as a pale yellow oil (R_f = 0.46 (50% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

To a solution of the crude alcohol and BnBr (3.08 g, 2.14 mL, 18 mmol) in DMF (16 mL) at 0 °C was added 60% NaH (960 mg, 24 mmol) in one portion. The resulting slurry was warmed to rt over 1 h. The reaction was quenched at 0 °C by addition of sat. $NH_4Cl_{(aq)}$ (20 mL). The aqueous layer was separated and extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford benzyl ether **2.13** as a colorless oil (4.01 g, 6.9 mmol, 77% over two steps, R_f = 0.51 (30% EtOAc in hexanes)).

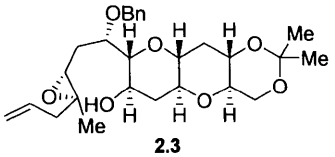
$[\alpha]^{22}_D$ = –10.92 (*c* = 0.25, $CHCl_3$)

IR (ATR): 2994, 2935, 2875, 1612, 1514, 1456, 1373, 1303, 1200, 1178, 1082, 1038, 994, 912, 862, 821, 738, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 7.19–7.12 (m, 2H), 6.86–6.80 (m, 2H), 5.75 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 5.04–4.97 (m, 2H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 3.89 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.80 (s, 3H), 3.74–3.66 (m, 2H), 3.62 (ddd, *J* = 11.4, 9.2, 4.1 Hz, 1H), 3.53–3.46 (m, 2H), 3.21 (td, *J* = 9.8, 5.1 Hz, 1H), 3.11 (ddd, *J* = 11.1, 8.7, 4.2 Hz, 1H), 3.00 (td, *J* = 10.5, 8.8, 3.9 Hz, 1H), 2.67 (d, *J* = 6.9 Hz, 2H), 2.50 (dd, *J* = 9.8, 5.9 Hz, 1H), 2.36 (dt, *J* = 14.7, 7.4 Hz, 1H), 2.31 (dt, *J* = 11.3, 4.1 Hz, 1H), 2.25 (dt, *J* = 14.3, 6.5 Hz, 1H), 1.56–1.48 (m, 1H), 1.55 (s, 3H), 1.49 (s, 3H), 1.48–1.39 (m, 1H), 1.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 159.5, 139.1, 137.1, 134.9, 130.2, 129.6, 128.3, 128.1, 127.5, 122.8, 115.7, 114.0, 99.4, 82.1, 79.0, 76.8, 74.9, 72.7, 72.0, 70.6, 69.6, 62.9, 55.4, 44.4, 35.5, 29.5, 29.4, 19.3, 16.4.

HR-MS (ESI) *m/z* calcd for $C_{35}H_{46}O_7$ $[M+H]^+$: 579.3316, found 579.3327.



2.3

Epoxy alcohol 2.3: To a solution of olefin **2.13** (4 g, 6.9 mmol) in 2:1 DMM:MeCN (70 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M Na_2EDTA (45 mL), *n*-Bu_4HSO_4 (703 mg, 2.07 mmol), and chiral ketone **2.10** (356 mg, 1.38 mmol). The biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 60 min via syringe pumps, a solution of Oxone (12.73 g, 20.7 mmol) in 4×10^{-4} M Na_2EDTA (45 mL) and a 0.89 M solution of aq. K_2CO_3 (45 mL, 40 mmol). Over this period, additional chiral ketone **2.10** (178 mg, 0.69 mmol) was added in two portions. After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred for an additional 1 h and allowed to warm to rt, at which point it was diluted with EtOAc (30 mL) and water (30 mL). The aqueous layer was separated and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude epoxide xx as a yellow oil (R_f = 0.37 (30% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

To a biphasic solution of crude PMB ether in CH_2Cl_2 (80 mL) and pH 7 buffer (0.1 M aq. potassium phosphate, 8 mL) at 0 °C was added DDQ (2.35 g, 10.3 mmol). The biphasic solution was stirred at 0 °C for 15 min and warmed to rt over 1 h, at which point the solution was quenched by addition of sat. $NaHCO_{3(aq)}$ (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 90% EtOAc in hexanes) to afford **2.3** as a colorless oil (2.13 g, 4.49 mmol, 65% over two steps as a 6:1 mixture of diastereomers, R_f of all diastereomers = 0.51 (50% EtOAc in hexanes)).

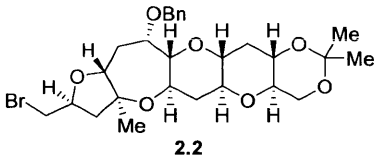
$[\alpha]^{22}_D$ = –23.1 (*c* = 0.15, $CHCl_3$)

IR (ATR): 3488, 3054, 2927, 2857, 1456, 1382, 1304, 1265, 1200, 1178, 1108, 1079, 1029, 920, 733, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.31 (m, 5H), 5.78 (ddt, *J* = 19.4, 9.7, 7.1 Hz, 1H), 5.16–5.06 (m, 2H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.93–3.86 (m, 2H), 3.76 (dt, *J* = 8.4, 4.4 Hz, 1H), 3.72–3.58 (m, 3H), 3.31 (t, *J* = 8.5 Hz, 1H), 3.25–3.16 (m, 1H), 3.16–3.03 (m, 2H), 2.99 (dd, *J* = 7.7, 4.2 Hz, 1H), 2.41–2.31 (m, 2H), 2.28–2.17 (m, 2H), 2.13 (dt, *J* = 15.2, 4.4 Hz, 1H), 1.89 (ddd, *J* = 15.2, 7.7, 4.2 Hz, 1H), 1.56–1.48 (m, 1H), 1.48 (s, 3H), 1.48–1.39 (m, 1H), 1.40 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 137.1, 133.5, 128.9, 128.5, 128.4, 118.2, 99.4, 81.2, 81.0, 76.7, 76.7, 74.9, 72.1, 69.9, 69.5, 62.9, 60.0, 59.4, 43.1, 37.5, 35.4, 30.5, 29.3, 19.7, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{38}O_7$ $[M+H]^+$: 475.2690, found 475.2683.



2.2

Bromide 2.2: To a solution of epoxy alcohol **2.3** (800 mg, 1.69 mmol) and 500 mg of activated 4Å MS in HFIP (10 mL) at 0 °C was added *N*-bromosuccinimide (450 mg, 2.5 mmol) in one portion with vigorous stirring with exclusion of light. After 20 min, to the reaction was added Et_3N (0.5 g, 0.7 mL, 5 mmol) and filtered through celite. To the filtrate was added Et_2O (10 mL) and sat. $Na_2S_2O_{3(aq)}$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford bromide **2.2** as a colorless oil (634 mg, 1.15 mmol, 68%, R_f = 0.37 (30% EtOAc in hexanes)).

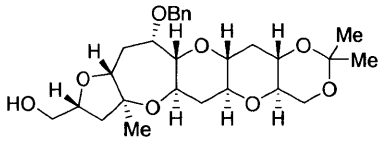
$[\alpha]^{22}_D$ = +16 (*c* = 0.12, $CHCl_3$)

IR (ATR): 2930, 2878, 1455, 1374, 1313, 1266, 1198, 1179, 1104, 1063, 1042, 940, 861, 807, 733, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 3H), 7.29–7.24 (m, 2H), 4.66 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 12.3 Hz, 1H), 4.22 (dq, *J* = 9.5, 6.2 Hz, 1H), 4.16 (ddd, *J* = 10.9, 8.8, 5.5 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.91 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.79 (dd, *J* = 11.9, 6.0 Hz, 1H), 3.70 (t, *J* = 10.6 Hz, 1H), 3.63 (ddd, *J* = 11.4, 9.2, 4.1 Hz, 1H), 3.45 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.40 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.29–3.18 (m, 2H), 3.08 (ddd, *J* = 11.6, 8.9, 4.0 Hz, 1H), 3.01 (ddd, *J* = 10.9, 8.9, 4.3 Hz, 1H), 2.40 (ddd, *J* = 15.4, 9.8, 6.0 Hz, 1H), 2.37–2.28 (m, 1H), 2.22 (dt, *J* = 11.2, 4.2 Hz, 1H), 2.14 (dd, *J* = 12.3, 6.7 Hz, 1H), 2.33 (dt, *J* = 12.0, 4.7 Hz, 1H), 1.70 (ddd, *J* = 14.9, 11.9, 0.9 Hz, 1H), 1.57–1.44 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.1, 128.4, 127.6, 127.5, 99.4, 82.6, 81.9, 81.8, 76.7, 76.2, 75.7, 75.5, 74.9, 73.4, 69.6, 65.8, 62.9, 46.9, 36.8, 36.4, 35.6, 31.5, 29.4, 19.3, 17.1.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{37}BrO_7$ $[M+Na]^+$: 575.1615, found 575.1638.



2.1

Alcohol 2.1: To a solution of bromide **2.2** (600 mg, 1.08 mmol) in THF (5 mL) at 0 °C was added a solution of KO*t*-Bu (243 mg, 2.17 mmol) in THF (50 mL) via cannulation. The resulting solution was stirred at 0 °C for15 min and quenched by addition of sat. $NH_4Cl_{(aq)}$ (50 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered through a short plug of neutral alumina, and

concentrated *in vacuo* to provide unstable olefin (R_f = 0.26 (20% EtOAc in hexanes)), which was carried onto the next step without further purification.

To a solution of crude olefin in THF (5 mL) at 0 °C was added 9-BBN (0.5 M in THF, 4.4 mL, 2.2 mmol). The resulting solution was stirred at 0 °C for 30 min and warmed to rt over 2 h, at which point the solution was cooled to 0 °C and quenched by slow addition of $NaOH_{(aq)}$ (2 M, 2 mL) and 30% $H_2O_{2(aq)}$ (340 mg, 1 mL, 10 mmol). The resulting solution was warmed to rt over 1 h. The aqueous layer was separated and extracted with EtOAc (3×7 mL). The combined organic layers were washed with brine (7 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 40% EtOAc in hexanes) to afford alcohol **2.1** as a colorless oil (495 mg, 1.01 mmol, 93% over two steps, R_f = 0.40 (70% EtOAc in hexanes)).

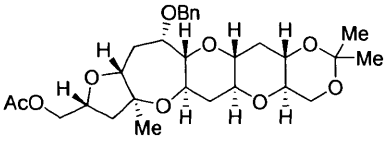
$[\alpha]^{22}_D$ = +0.57 (*c* = 0.3, $CHCl_3$)

IR (ATR): 3461, 2925, 2856, 1456, 1377, 1272, 1200, 1180, 1106, 1082, 1064, 941, 861, 735, 697 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.33–7.29 (m, 3H), 7.29–7.24 (m, 2H), 4.66 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.14 (dtd, *J* = 10.5, 5.7, 3.1 Hz, 2H), 3.98 (d, *J* = 9.9 Hz, 1H), 3.91 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.70 (t, *J* = 10.6 Hz, 1H), 3.67–3.61 (m, 2H), 3.54 (dt, *J* = 11.3, 5.1 Hz, 1H), 3.31 (dd, *J* = 8.8, 1.7 Hz, 1H), 3.23 (td, *J* = 9.9, 5.1 Hz, 1H), 3.08 (ddd, *J* = 12.1, 8.9, 4.0 Hz, 1H), 3.01 (ddd, *J* = 11.1, 8.9, 4.3 Hz, 1H), 2.40 (ddd, *J* = 15.3, 9.8, 5.8 Hz, 1H), 2.33 (dt, *J* = 12.0, 4.7 Hz, 1H), 2.22 (dt, *J* = 11.3, 4.2 Hz, 1H), 2.17 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.89 (d, *J* = 6.3 Hz, 1H), 1.81–1.71 (m, 2H), 1.57–1.45 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.1, 128.4, 127.5, 127.5, 99.4, 83.1, 82.8, 81.9, 77.0, 76.7, 76.2, 75.8, 74.8, 73.3, 69.6, 65.9, 65.4, 62.9, 43.9, 36.8, 35.5, 30.9, 29.4, 19.3, 18.7.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{38}O_8$ $[M+Na]^+$: 513.2459, found 513.2470.



2.14

Acetate 2.14: To a solution of alcohol **2.1** (5 mg, 0.01 mmol) in pyridine (0.5 mL) was added DMAP (2 crystals) and acetic anhydride (216 mg, 0.2 mL, 2.1 mmol). The solution was stirred at rt for 1 h and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 90% EtOAc in hexanes) to afford acetate **2.14** as a colorless oil (5 mg, 0.0094 mmol, 92%, R_f = 0.37 (50% EtOAc in hexanes)).

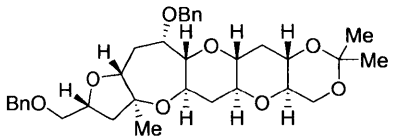
$[\alpha]^{22}_D$ = +19.09 (*c* = 0.25, $CHCl_3$)

IR (ATR): 3005, 2941, 2878, 1739, 1455, 1373, 1234, 1180, 1105, 1080, 1062, 860, 749, 697, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.29 (m, 3H), 7.29–7.24 (m, 2H), 4.66 (d, J = 12.3 Hz, 1H), 4.62 (d, J = 12.3 Hz, 1H), 4.26 (dddd, J = 10.1, 7.1, 5.6, 3.1 Hz, 1H), 4.20–4.10 (m, 2H), 4.04–3.95 (m, 2H), 3.91 (dd, J = 10.8, 5.1 Hz, 1H), 3.70 (t, J = 10.6 Hz, 1H), 3.67–3.60 (m, 2H), 3.30 (dd, J = 8.8, 1.6 Hz, 1H), 3.23 (ddd, J = 10.4, 9.3, 5.2 Hz, 1H), 3.08 (ddd, J = 11.6, 8.9, 4.0 Hz, 1H), 3.01 (ddd, J = 11.0, 8.9, 4.3 Hz, 1H), 2.41 (ddd, J = 15.3, 9.8, 5.8 Hz, 1H), 2.36–2.30 (m, 1H), 2.27–2.18 (m, 2H), 2.09 (s, 3H), 1.83–1.75 (m, 1H), 1.72 (dd, J = 13.0, 5.6 Hz, 1H), 1.58–1.45 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 139.0, 128.4, 127.5, 127.5, 99.4, 83.1, 82.5, 81.5, 76.6, 76.0, 75.5, 74.7, 74.0, 73.1, 69.5, 66.6, 65.8, 62.8, 44.2, 36.7, 35.4, 30.7, 29.3, 21.1, 19.2, 18.6.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{40}O_9$ $[M+Na]^+$: 555.2565, found 555.2588.



2.19

Benzyl ether 2.19: To a solution of alcohol **2.1** (480 mg, 0.98 mmol) in DMF (2 mL) was added BnBr (513 mg, 0.36 mL, 3 mmol) and cooled to 0 °C. NaH (60% in mineral oil, 120 mg, 3 mmol) was added in one portion, and the resulting slurry was warmed to rt over 1 h. The reaction was quenched at 0 °C by addition of sat. $NH_4Cl_{(aq)}$ (3 mL). The aqueous layer was separated and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford benzyl ether **2.19** as a colorless oil (563 g, 0.97 mmol, 99%, R_f = 0.23 (30% EtOAc in hexanes)).

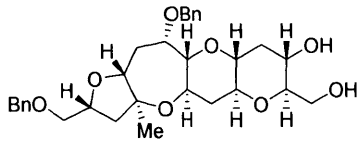
$[\alpha]^{22}_D$ = +10.25 (c = 0.4, $CHCl_3$)

IR (ATR): 2991, 2937, 2874, 1454, 1373, 1271, 1199, 1180, 1104, 1080, 1060, 939, 860, 733, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 6H), 7.30–7.24 (m, 4H), 4.66 (d, J = 12.3 Hz, 1H), 4.63–4.58 (m, 2H), 4.54 (d, J = 12.2 Hz, 1H), 4.24 (dtd, J = 10.1, 5.9, 4.4 Hz, 1H), 4.14 (ddd, J = 10.8, 8.8, 5.4 Hz, 1H), 4.00–3.94 (m, 1H), 3.91 (dd, J = 10.8, 5.2 Hz, 1H), 3.70 (t, J = 10.6 Hz, 1H), 3.67–3.58 (m, 2H), 3.50–3.42 (m, 2H), 3.31 (dd, J = 8.9, 1.6 Hz, 1H), 3.23 (ddd, J = 10.4, 9.2, 5.1 Hz, 1H), 3.08 (ddd, J = 11.6, 8.9, 4.0 Hz, 1H), 3.00 (ddd, J = 10.9, 8.9, 4.3 Hz, 1H), 2.42 (ddd, J = 15.3, 9.8, 5.8 Hz, 1H), 2.36–2.28 (m, 1H), 2.25–2.13 (m, 2H), 1.80 (ddd, J = 14.8, 12.2, 1.0 Hz, 1H), 1.72 (dd, J = 12.8, 5.6 Hz, 1H), 1.55–1.44 (m, 2H), 1.50 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.2, 138.3, 128.5, 128.4, 127.9, 127.8, 127.5, 127.5, 127.4, 99.4, 83.0, 82.7, 81.7, 76.7, 76.1, 75.8, 75.6, 74.8, 73.5, 73.2, 72.8, 69.6, 65.8, 62.9, 44.6, 36.8, 36.8, 35.5, 30.9, 29.4, 19.3, 18.8.

HR-MS (ESI) *m/z* calcd for $C_{34}H_{44}O_8$ $[M+Na]^+$: 603.2928, found 603.2910.



2.15

Diol 2.15: To a solution of benzyl ether **2.19** (555 g, 0.96 mmol) in CH_2Cl_2/MeOH (1:1, 20 mL total) was added *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) at rt. After 1 h, the reaction was quenched by addition of Et_3N (0.5 g, 0.7 mL, 5 mmol)), concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 40% MeOH in EtOAc) to afford diol **2.15** as a colorless oil (460 mg, 0.85 mmol, 89%, R_f = 0.29 (100% EtOAc)).

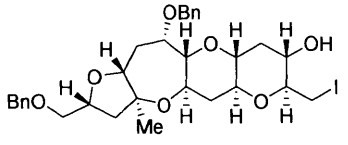
$[\alpha]^{22}_D$ = +14.75 (*c* = 0.16, $CHCl_3$)

IR (ATR): 3431, 2934, 2865, 1497, 1454, 1363, 1287, 1186, 1108, 1043, 907, 848, 726, 696 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.30 (m, 8H), 7.30–7.24 (m, 2H), 4.68–4.57 (m, 3H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.28–4.21 (m, 1H), 4.13 (ddd, *J* = 9.2, 7.2, 3.8 Hz, 1H), 3.97 (d, *J* = 9.8 Hz, 1H), 3.85 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.79 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.69 (ddd, *J* = 11.2, 9.2, 4.7 Hz, 1H), 3.62 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.51–3.43 (m, 2H), 3.30 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.22 (dt, *J* = 9.0, 4.4 Hz, 1H), 3.03 (ddd, *J* = 12.3, 8.8, 4.2 Hz, 1H), 2.91 (ddd, *J* = 11.2, 8.9, 4.2 Hz, 1H), 2.71 (s, 1H), 2.42 (ddd, *J* = 15.2, 9.7, 5.8 Hz, 1H), 2.38–2.30 (m, 1H), 2.18 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.81 (dd, *J* = 14.9, 12.2 Hz, 1H), 1.72 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.52–1.42 (m, 2H), 1.43 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.2, 138.3, 128.5, 128.3, 127.9, 127.7, 127.4, 83.0, 82.4, 81.7, 81.2, 76.0, 75.9, 75.5, 75.4, 73.5, 73.2, 72.8, 66.8, 65.7, 63.1, 44.5, 38.4, 36.8, 30.8, 29.7, 18.7.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{40}O_8$ $[M+Na]^+$: 563.2615, found 563.2616.



2.20

Iodide 2.20: To a solution of diol **2.15** (400 mg, 0.74 mmol) in THF (3 mL) was added imidazole (151 mg, 2.22 mmol) and PPh_3 (291 mg, 1.11 mmol) at rt. The reaction mixture was cooled to –40 °C and added I_2 (282 mg, 1.11 mmol). The reaction solution was allowed to warm to rt over 1 h with exclusion of light and quenched with sat. $Na_2S_2O_{3(aq)}$ (3 mL). The aqueous layer was separated and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column

chromatography (gradient 0% to 100% EtOAc in hexanes) to afford iodide **2.20** as a colorless oil (455 mg, 0.7 mmol, 95%, R_f = 0.31 (50% EtOAc in hexanes)).

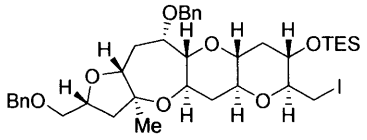
$[\alpha]^{22}_D$ = +7.41 (*c* = 0.17, $CHCl_3$)

IR (ATR): 3447, 3030, 2933, 2864, 1496, 1453, 1378, 1286, 1109, 1047, 979, 909, 851, 732, 697 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.30 (m, 8H), 7.30–7.24 (m, 2H), 4.69–4.57 (m, 3H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.28–4.21 (m, 1H), 4.18–4.10 (m, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.62 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.57–3.44 (m, 3H), 3.37 (dd, *J* = 10.7, 5.7 Hz, 1H), 3.31 (d, *J* = 8.7 Hz, 1H), 3.07 (ddd, *J* = 12.4, 8.8, 4.2 Hz, 1H), 2.98–2.85 (m, 2H), 2.48–2.29 (m, 2H), 2.24–2.11 (m, 2H), 1.81 (dd, *J* = 15.2, 12.5 Hz, 1H), 1.72 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.58–1.46 (m, 2H), 1.43 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.2, 138.2, 128.4, 128.3, 127.8, 127.7, 127.4, 127.4, 83.0, 82.4, 81.6, 80.0, 76.0, 75.5, 75.3, 73.5, 73.2, 72.8, 69.8, 65.6, 44.5, 38.4, 36.7, 30.8, 18.7, 7.7.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{39}IO_7$ $[M+Na]^+$: 673.1633, found 673.1632.



2.21

TES ether 2.21: To a solution of iodide **2.20** (440 mg, 0.68 mmol) in CH_2Cl_2 (3 mL) were added imidazole (138 mg, 2.03 mmol) and TESCl (153 mg, 0.17 mL, 1.01 mmol) at rt. The resulting solution was stirred at rt for 2 h and quenched by addition of brine (2 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×3mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 30% EtOAc in hexanes) to afford TES ether **2.21** as a colorless oil (497 mg, 0.65 mmol, 97%, R_f = 0.34 (20% EtOAc in hexanes)).

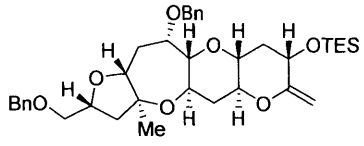
$[\alpha]^{22}_D$ = +41.08 (*c* = 0.24, $CHCl_3$)

IR (ATR): 2954, 2876, 1496, 1454, 1410, 1377, 1284, 1239, 1186, 1060, 1008, 907, 821, 727, 696 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.30 (m, 8H), 7.30–7.24 (m, 2H), 4.70–4.58 (m, 3H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.25 (dq, *J* = 10.8, 5.6 Hz, 1H), 4.14 (ddd, *J* = 10.9, 8.7, 5.4 Hz, 1H), 3.96 (d, *J* = 9.7 Hz, 1H), 3.63 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.57–3.43 (m, 4H), 3.37–3.27 (m, 2H), 3.09 (ddd, *J* = 12.2, 8.8, 4.1 Hz, 1H), 2.96–2.87 (m, 2H), 2.43 (ddd, *J* = 15.2, 9.7, 5.8 Hz, 1H), 2.38 (dt, *J* = 12.0, 4.8 Hz, 1H), 2.28 (dt, *J* = 11.6, 4.4 Hz, 1H), 2.18 (dd, *J* = 12.8, 10.0 Hz, 1H), 1.82 (dd, *J* = 14.9, 12.2 Hz, 1H), 1.73 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.58–1.49 (m, 2H), 1.43 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.66 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.2, 138.3, 128.5, 128.3, 127.8, 127.7, 127.4, 127.4, 83.0, 82.4, 81.6, 80.2, 76.1, 76.0, 75.6, 75.4, 73.5, 73.2, 72.8, 70.5, 65.7, 44.6, 39.0, 36.8, 30.9, 18.70, 8.2, 7.0, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{37}H_{53}IO_7Si$ $[M+Na]^+$: 787.2497, found 787.2480.



2.16

Exocyclic methylene 2.16: To a solution of iodide **2.21** (460 mg, 0.60 mmol) in THF (3 mL) at 0 °C was added KO*t*-Bu (135 mg, 1.20 mmol) in THF (3 mL). The resulting solution was stirred at 0 °C for 20 min, quenched by addition of sat. $NH_4Cl_{(aq)}$ (3 mL). The aqueous layer was separated and extracted with Et_2O (3×4mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 30% EtOAc in hexanes) to afford olefin **2.16** as a colorless oil (363 mg, 0.57 mmol, 95%, R_f = 0.34 (20% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +15.27 (*c* = 0.41, $CHCl_3$)

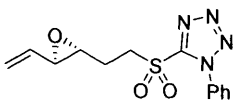
IR (ATR): 2956, 2876, 1660, 1454, 1413, 1379, 1223, 1133, 1087, 1054, 1005, 907, 863, 837, 726, 695 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.30 (m, 8H), 7.30–7.24 (m, 2H), 4.71 (d, *J* = 1.8 Hz, 1H), 4.66–4.60 (m, 4H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.30–4.23 (m, 1H), 4.21–4.12 (m, 2H), 3.98 (d, *J* = 9.7 Hz, 1H), 3.64 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.52–3.45 (m, 2H), 3.35 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.25–3.18 (m, 1H), 3.12 (ddd, *J* = 11.0, 9.1, 4.3 Hz, 1H), 2.50–2.40 (m, 2H), 2.35–2.27 (m, 1H), 2.21 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.83 (dd, *J* = 14.9, 12.2 Hz, 1H), 1.74 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.66–1.55 (m, 2H), 1.44 (s, 3H), 1.01 (t, *J* = 8.0 Hz, 9H), 0.67 (q, *J* = 7.9 Hz, 6H).

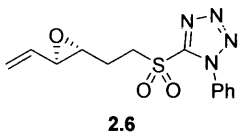
^{13}C NMR (151 MHz, $CDCl_3$): δ 161.9, 139.1, 138.3, 128.5, 128.3, 127.8, 127.7, 127.4, 127.4, 92.9, 83.0, 82.5, 81.7, 77.5, 76.0, 75.6, 75.0, 73.5, 73.3, 72.8, 66.9, 65.6, 44.6, 39.7, 37.0, 30.9, 18.7, 6.9, 4.9.

HR-MS (ESI) *m/z* calcd for $C_{37}H_{52}O_7Si$ $[M+Na]^+$: 659.3375, found 659.3387.

D. ^{1}H and ^{13}C NMR Spectra

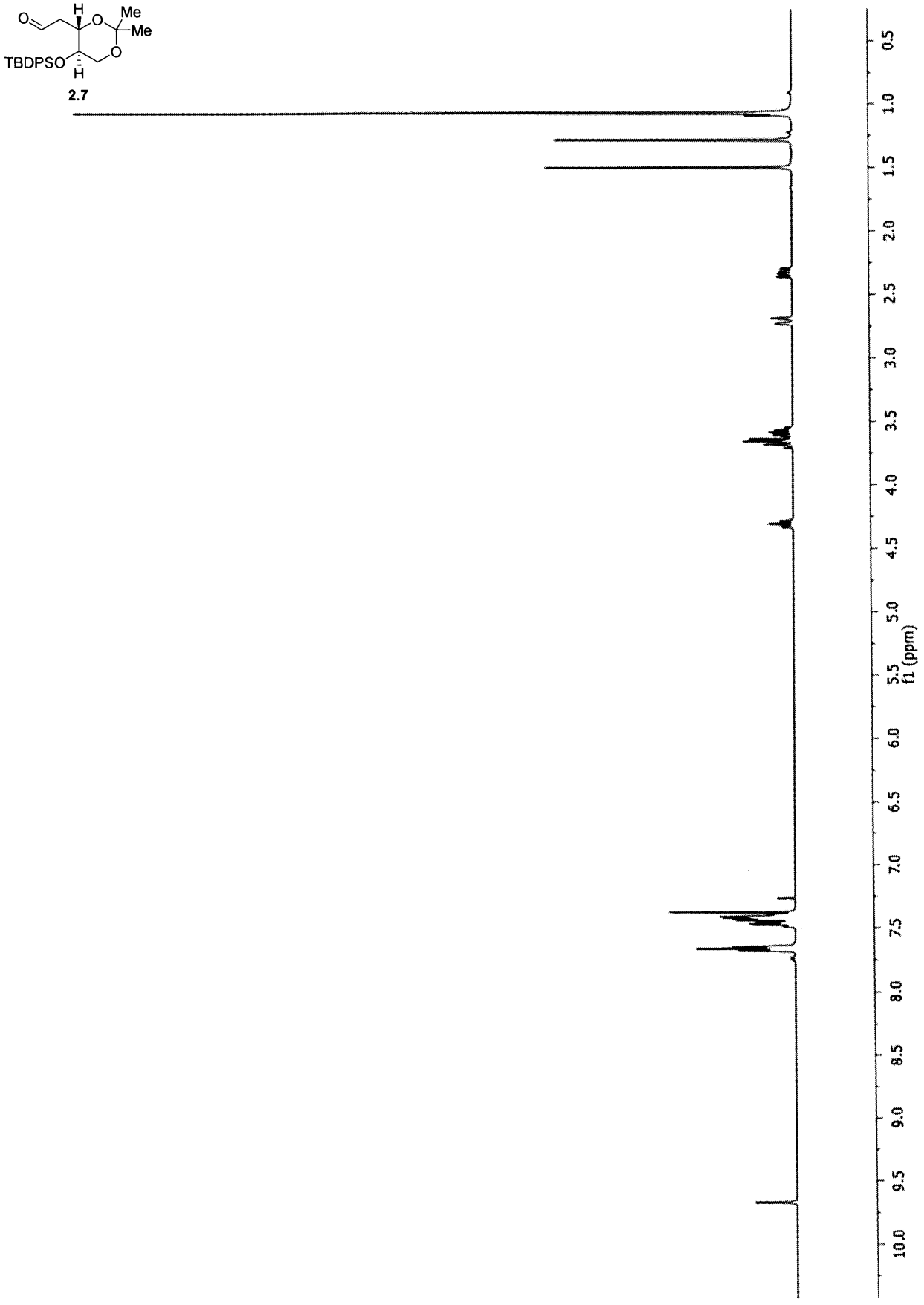


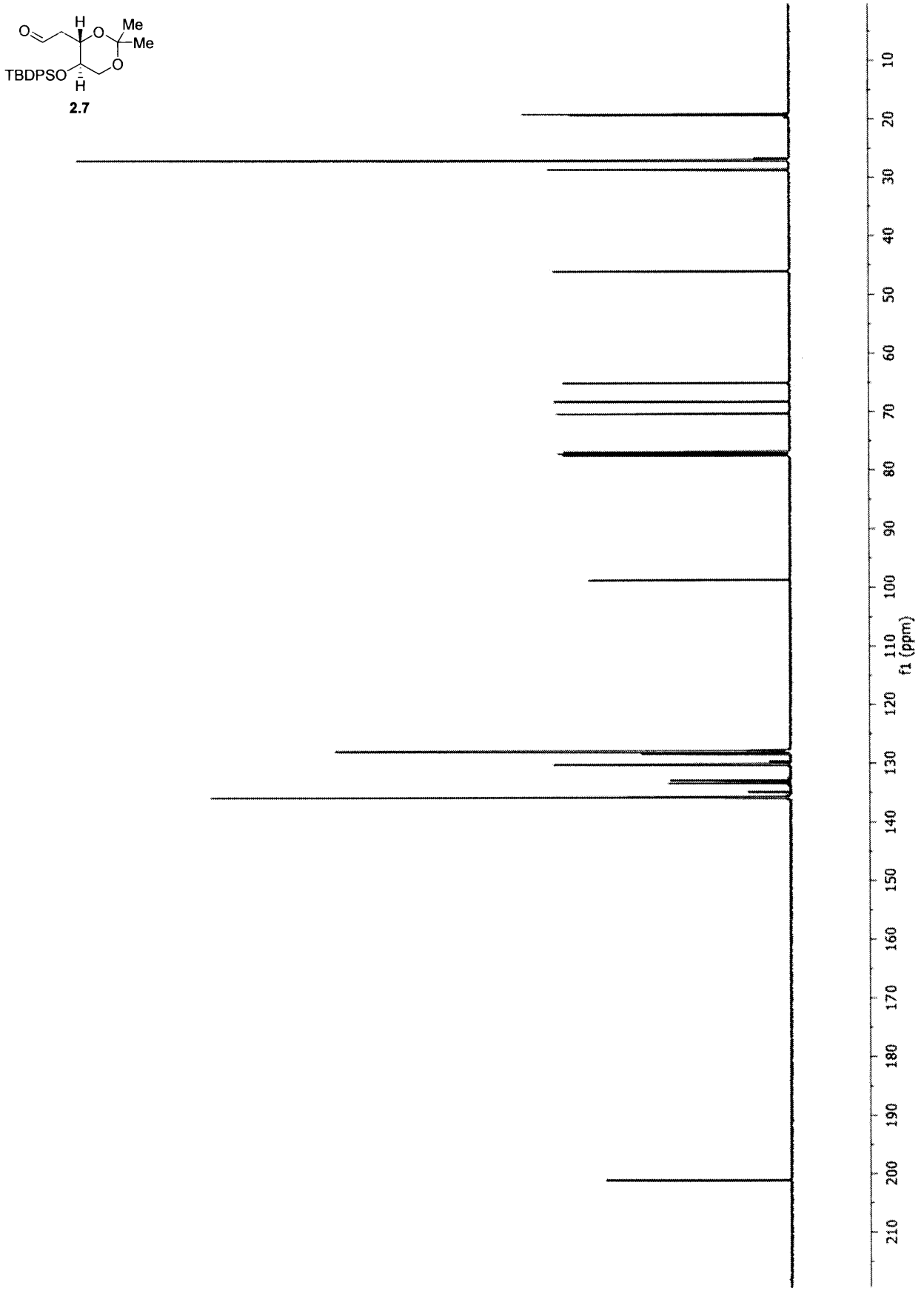
2.6

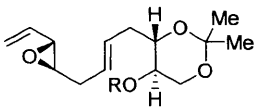

O
N
N
N
S
O
O
N
Ph

2.6

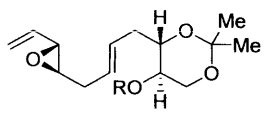
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)


O
H
O
Me
Me
O
TBDPSO
H
2.7
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
f1 (ppm)


O
H
O
Me
Me
O
TBDPSO
H
2.7
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

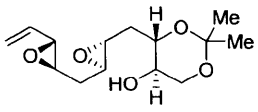


2.17, R = TBDPS

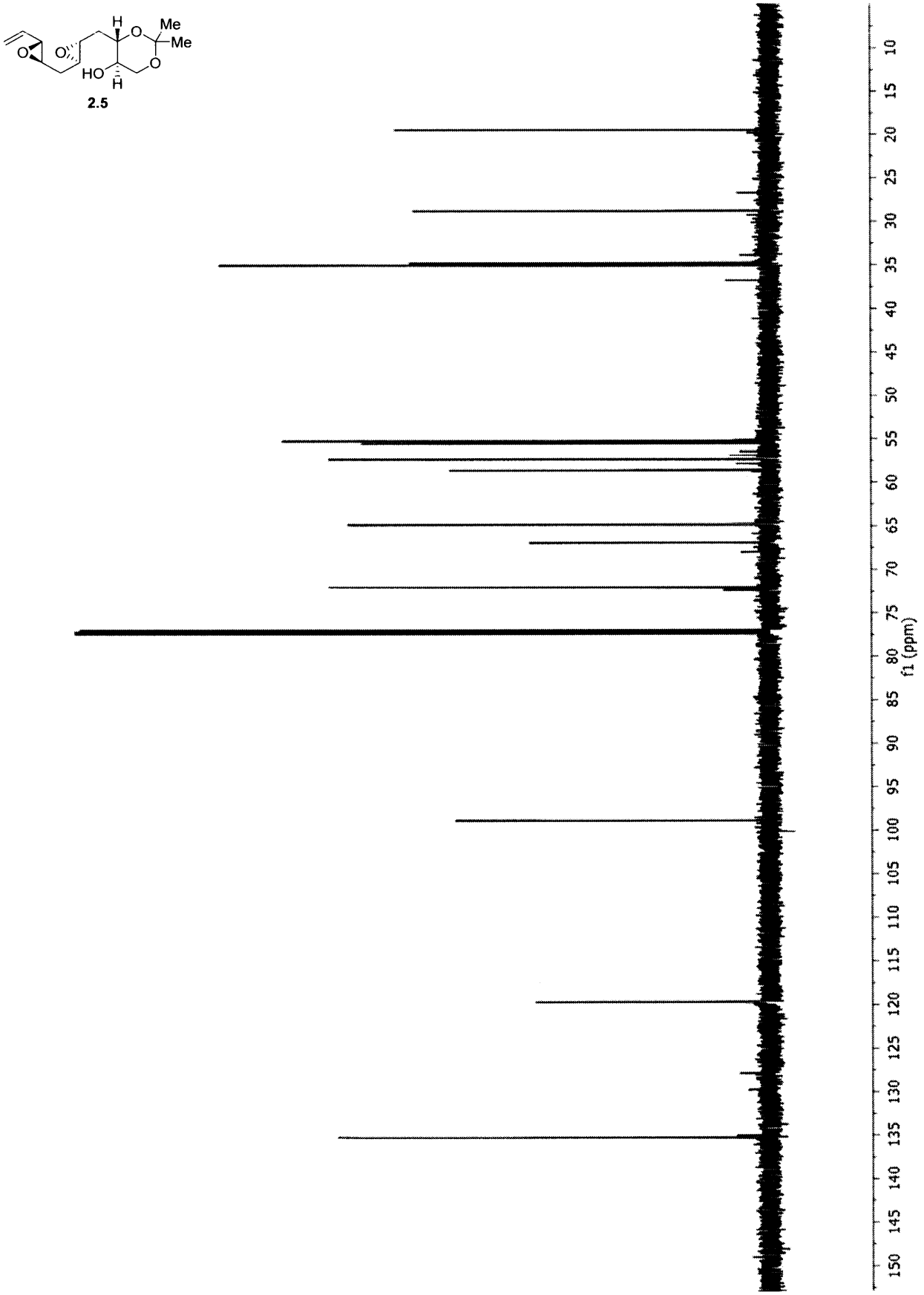

H
O
Me
Me
O
O
RO
H

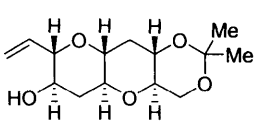
2.17, R = TBDPS

50
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)



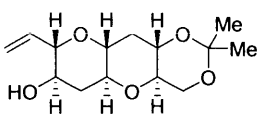
2.5


H
O
Me
Me
O
O
HO
H
2.5
f1 (ppm)


H
H
H
O
O
Me
Me
HO
H
H
O
H
O

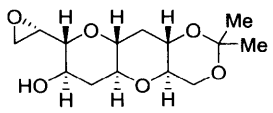
2.4

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


H
H
H
O
Me
Me
HO
H
H
O
H
O
O

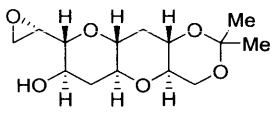
2.4

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)


O
H
H
H
O
O
Me
Me
HO
H
H
O
H
O

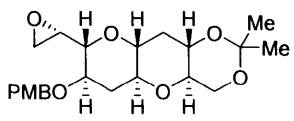
2.18

7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)


O
H
H
H
O
Me
Me
HO
H
H
O
H
O

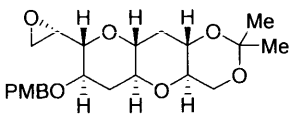
2.18

10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
f1 (ppm)

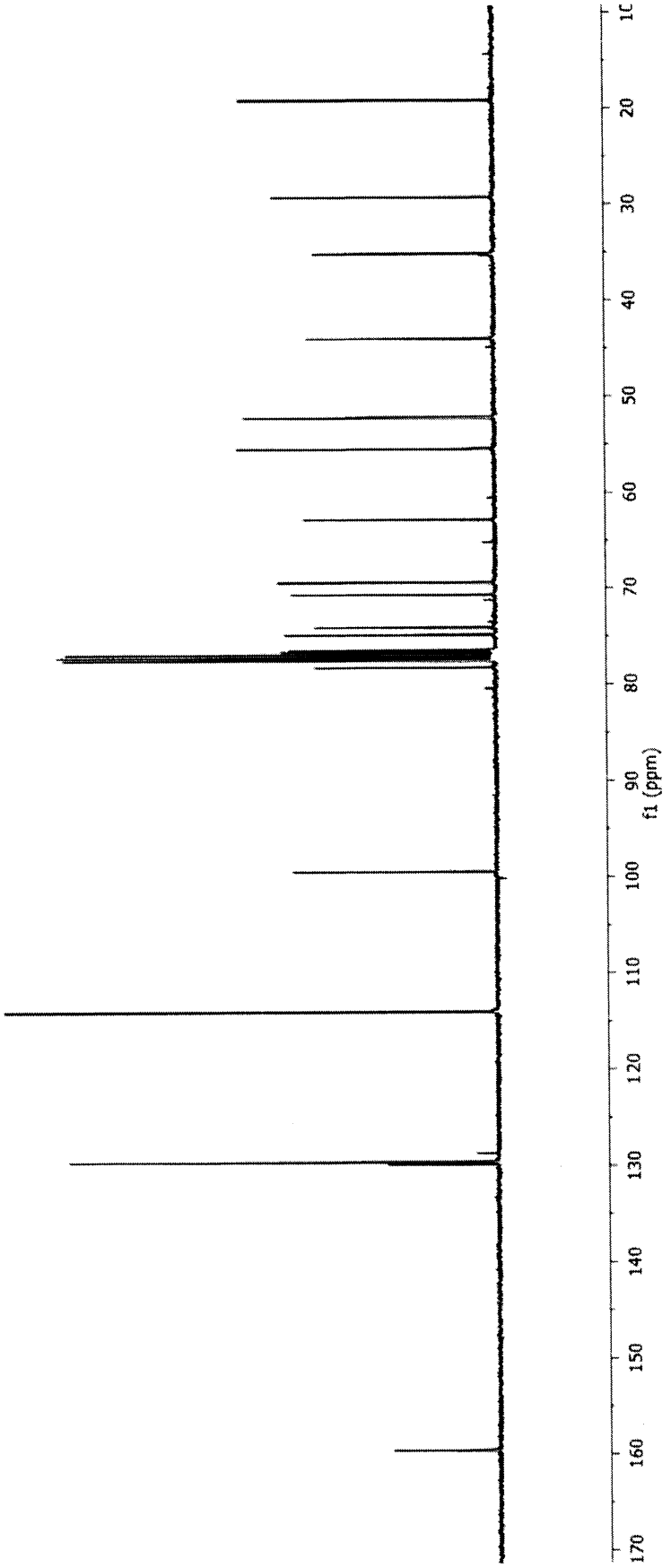

O
H
H
H
O
O
Me
Me
PMBO
H
H
O
H
O

2.11

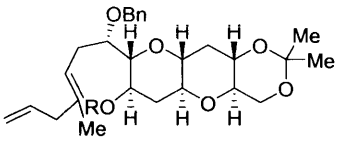
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.
f1 (ppm)


O
H
H
H
O
Me
Me
O
PMBO
H
O
H
H
O

2.11


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

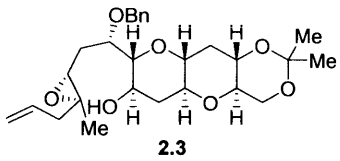
OBn
RO
Me
H
O
Me
Me
2.13, R = PMB
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OBn
H
O
H
H
O
Me
Me
O
RO
H
H
O
H
Me

2.13, R = PMB

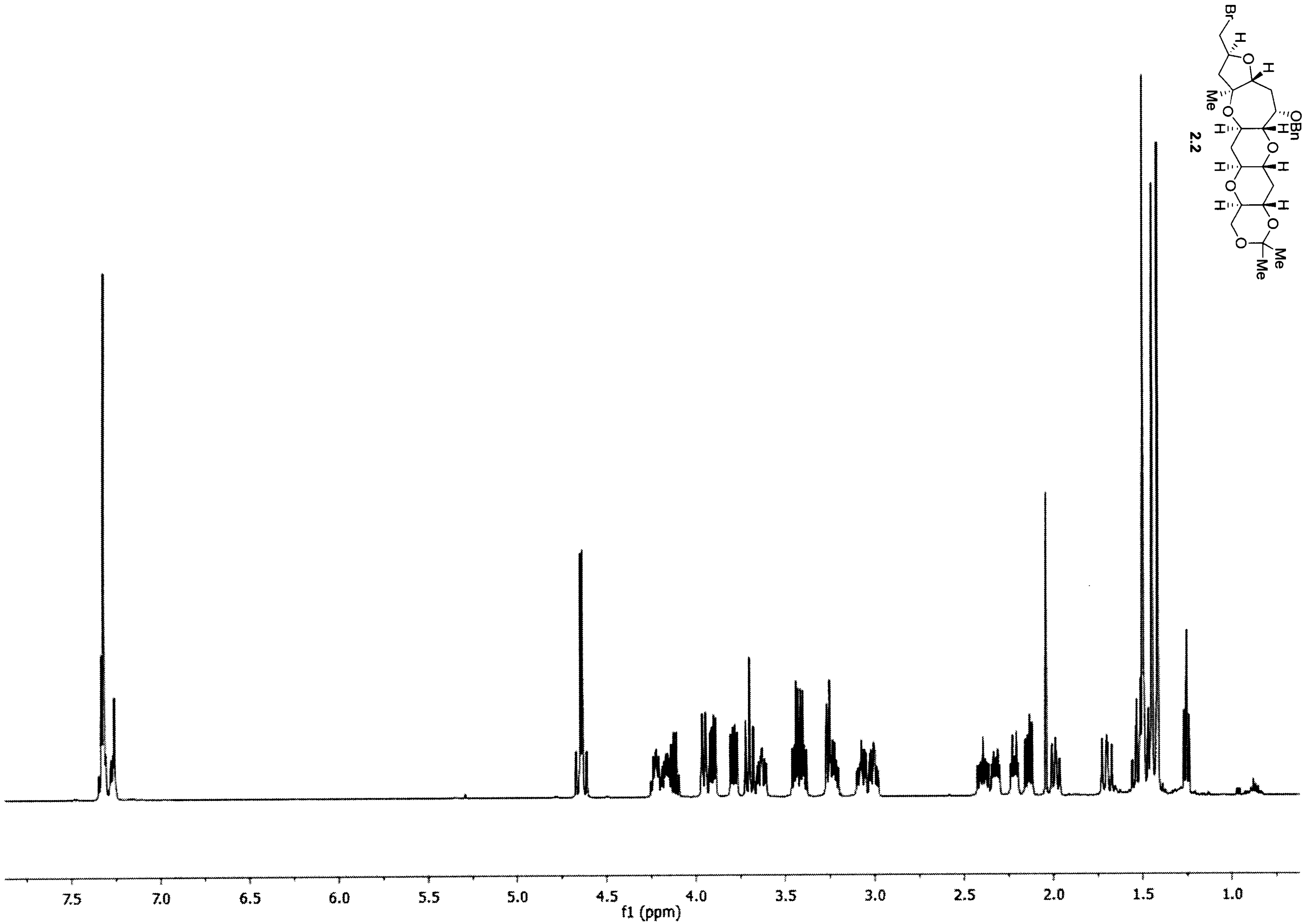
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

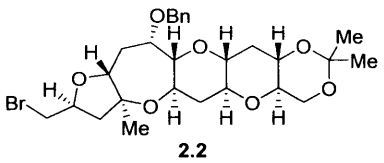
OBn
Me
HO
H
O
H
Me
Me
2.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OBn
H
H
H
O
O
Me
Me
O
O
HO
H
H
H
Me

2.3

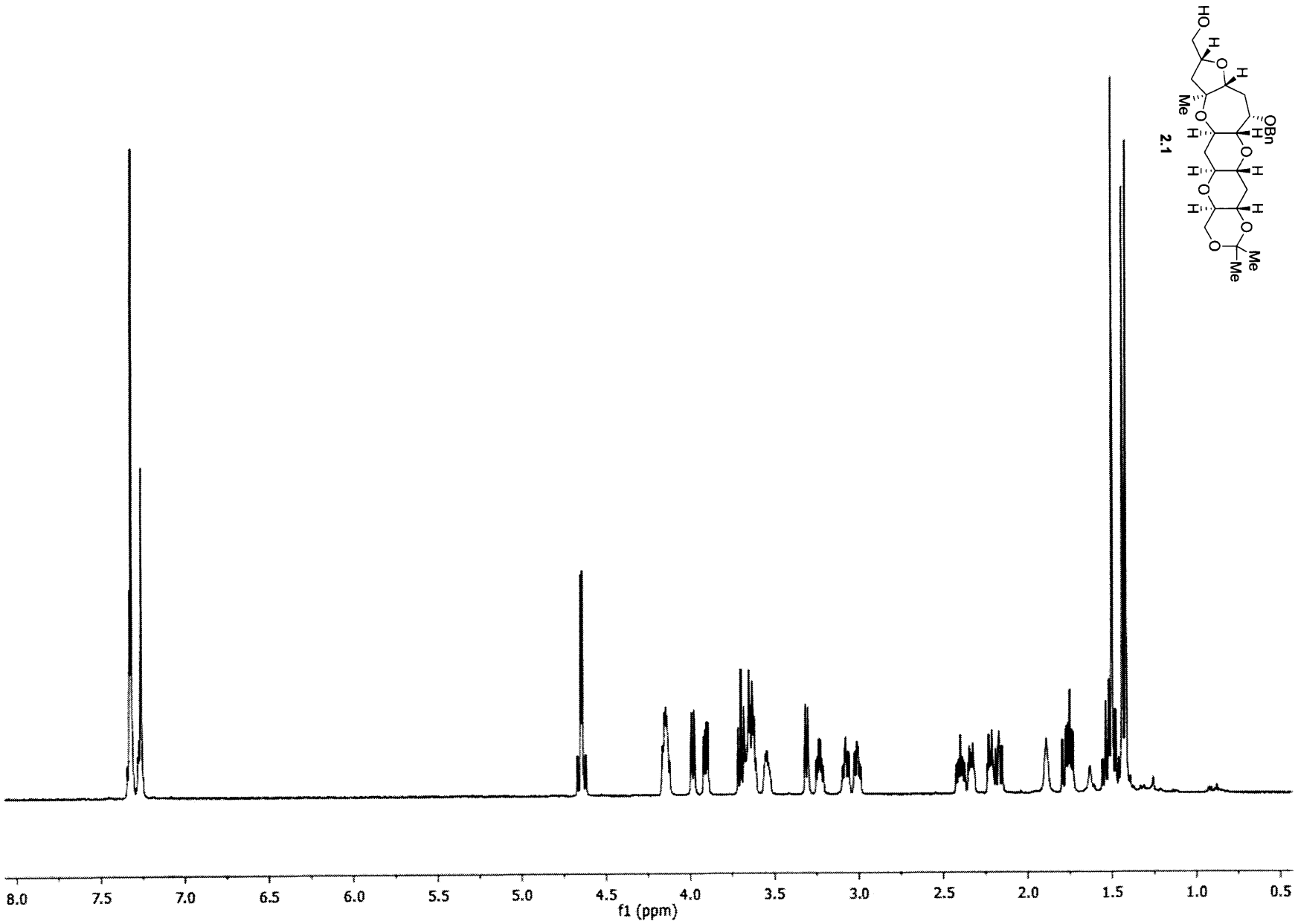
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)


2.2
Br
H
O
Me
OBn
Me
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

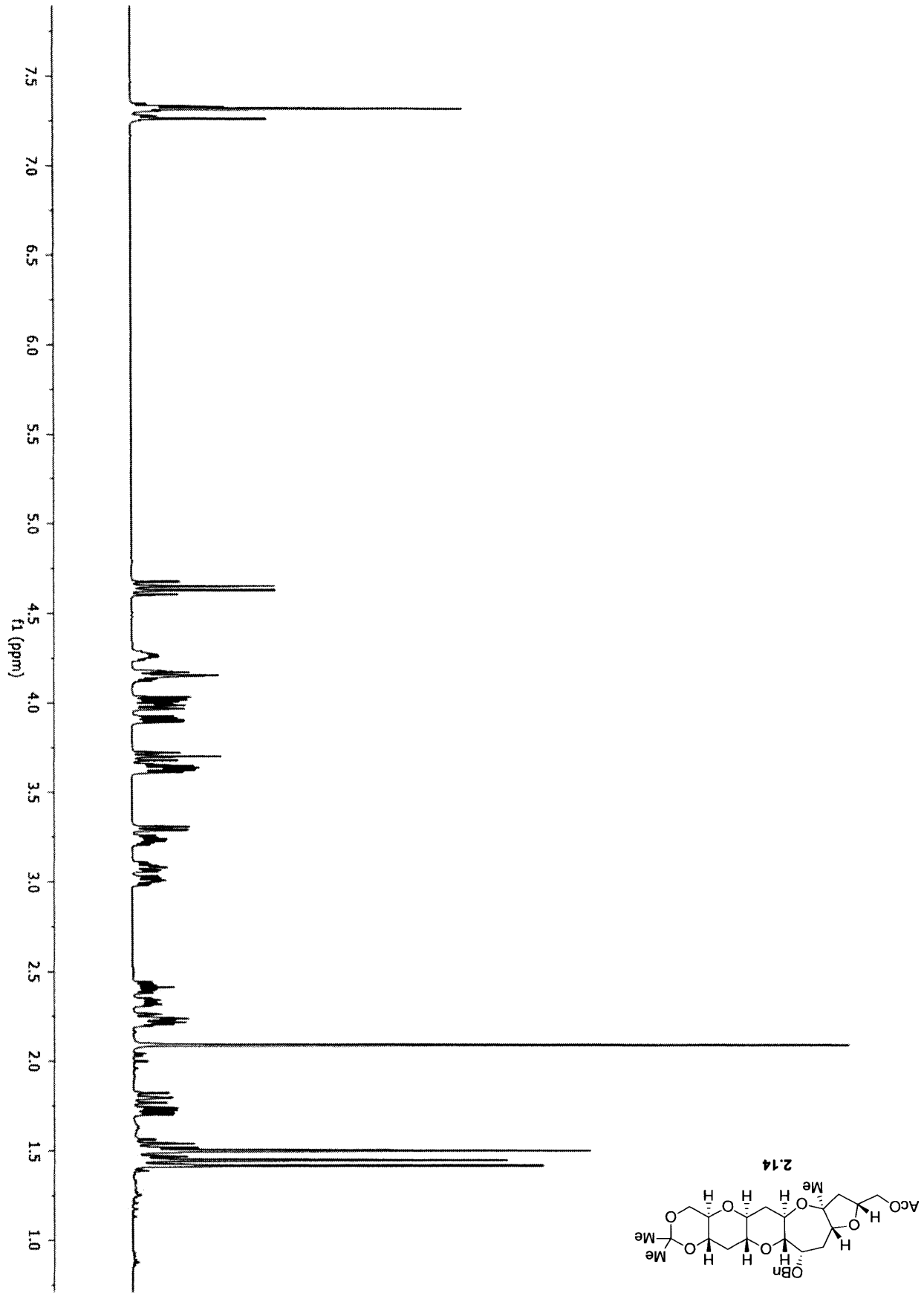

OBn
H
H
H
H
O
O
Me
Me
O
O
H
O
Br
O
H
H
H
Me

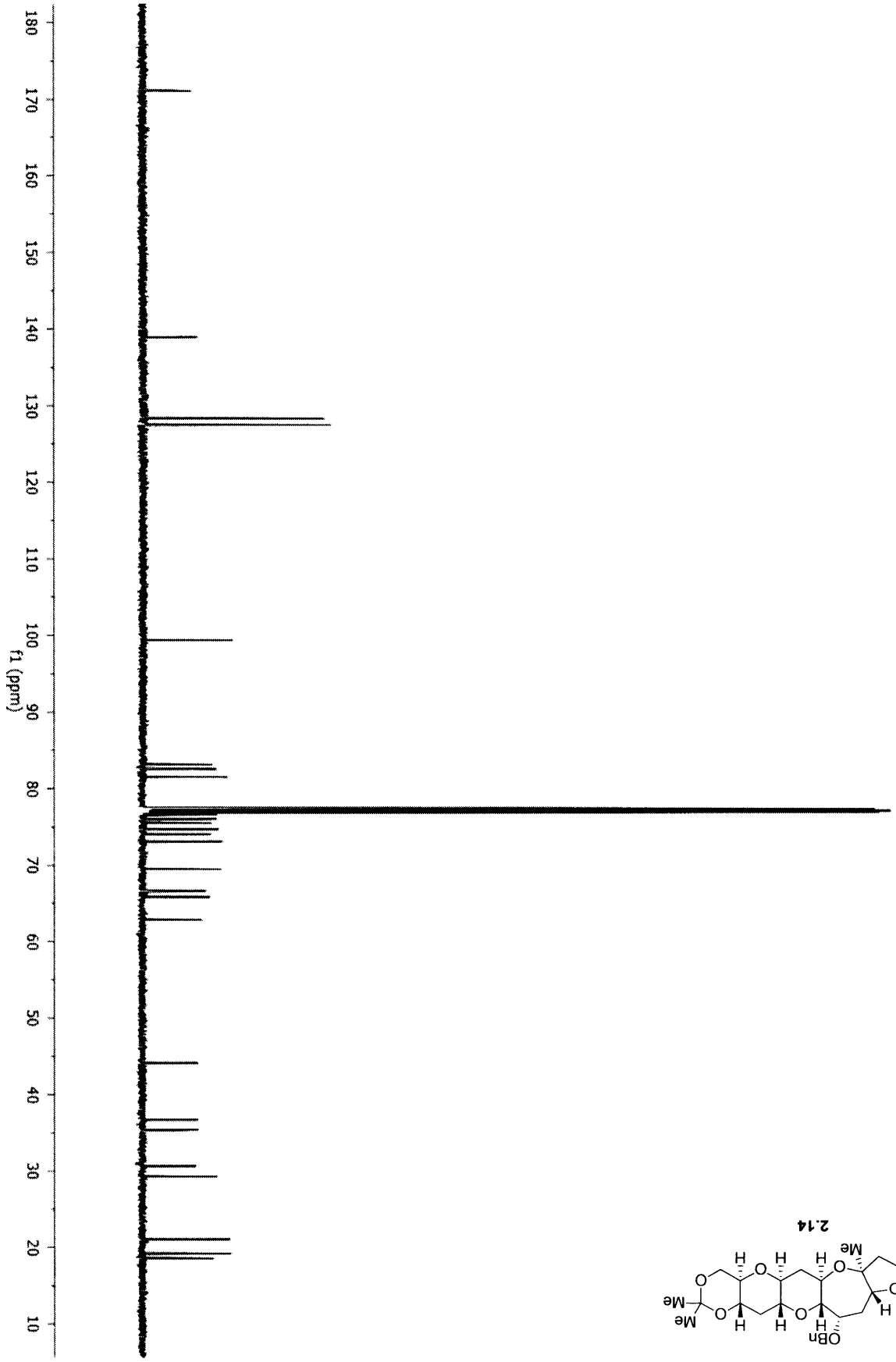
2.2

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


HO
H
O
H
Me
O
H
OBn
H
O
H
H
O
H
H
O
O
Me
Me
2.1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

HO
H
O
H
Me
O
H
OBn
H
O
H
H
O
H
H
O
H
O
O
Me
Me
2.1
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

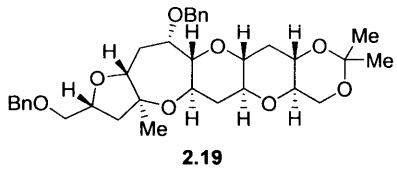

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
2.14
OBn
Me
Me
Me
AcO


f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

2.14

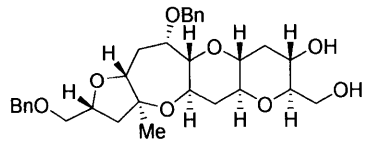
OBn
Me
Me
AcO

BnO
H
O
H
Me
O
H
OBn
H
O
H
H
O
H
H
O
H
O
Me
Me
O
2.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OBn
H
H
H
H
O
O
O
O
O
O
Me
Me
BnO
Me

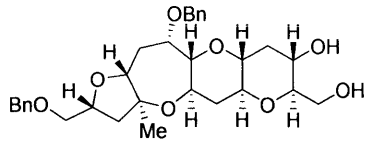
2.19

f1 (ppm)
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150

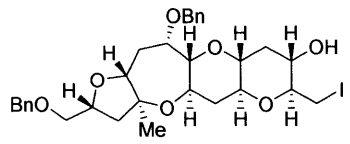

OBn
H
H
H
OH
H
O
O
O
H
BnO
O
H
H
O
H
OH
Me

2.15

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

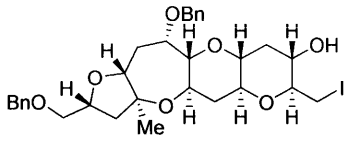


2.15


OBn
H
H
H
H
OH
O
O
O
O
H
H
H
H
H
BnO
I
Me

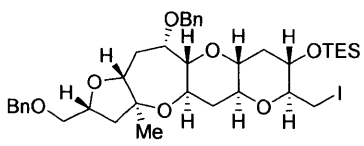
2.20

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


OBn
H
H
O
H
H
OH
H
O
H
BnO
O
H
H
O
I
Me

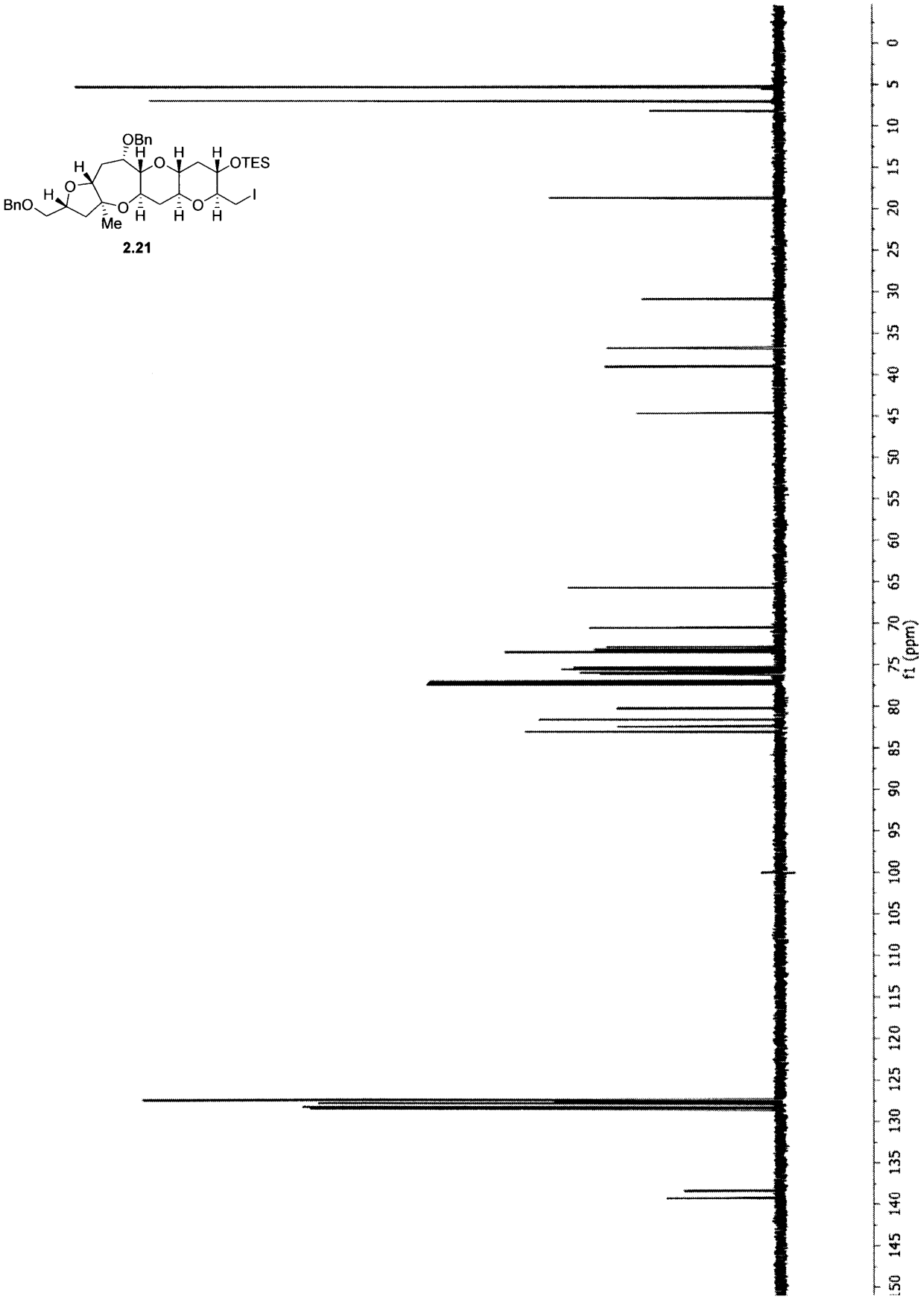
2.20

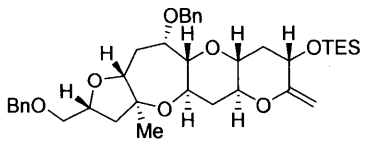
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)


OBn
H
H
H
H
O
O
OTES
BnO
O
H
H
H
O
I
Me

2.21

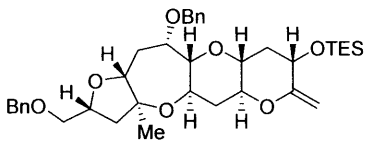
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


OBn
H
H
H
H
OTES
BnO
H
O
O
O
O
H
H
H
H
Me
I
2.21
f1 (ppm)


OBn
H
H
H
H
OTES
BnO
O
O
O
O
Me

2.16

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


OBn
H
H
H
H
OTES
BnO
O
O
O
O
Me

2.16

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

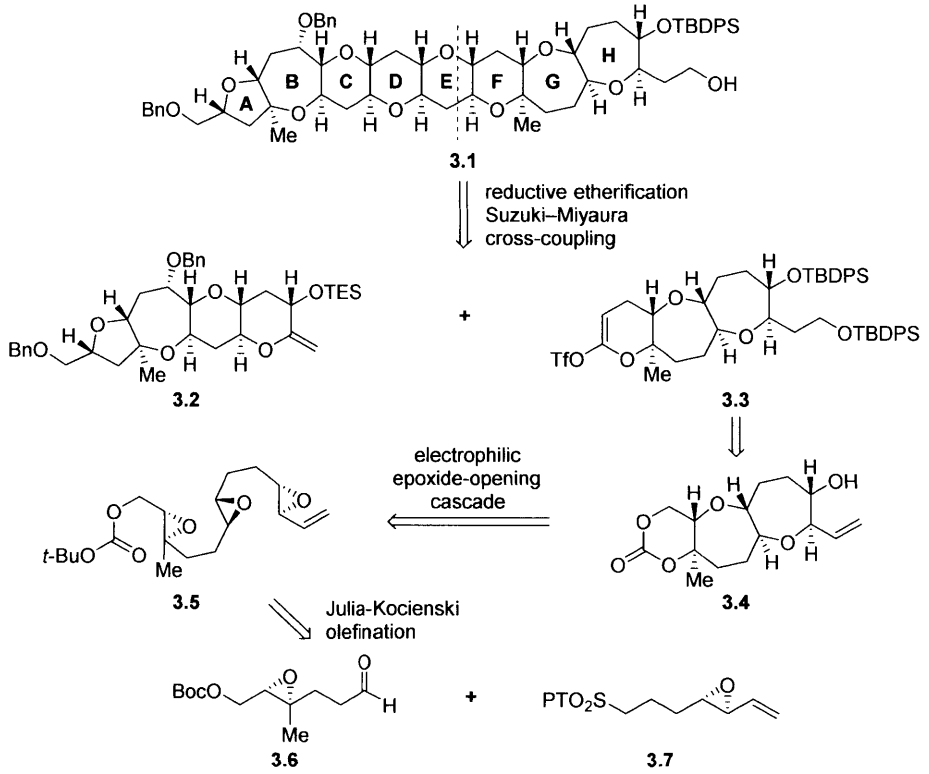
CHAPTER III

Synthesis of the *ABCDEFGH* Fragment of Gymnocin B

A. Retrosynthetic Analysis of *ABCDEFGH* Fragment

In order to complete the western portion of gymnocin B, we envisioned a convergent disconnection along the *E* ring of alcohol **3.1** to lead to exocyclic methylene **3.2**, whose synthesis was described in the previous chapter, and enol triflate **3.3**. We expected that using a well-established Suzuki–Miyaura cross-coupling would unite the two fragments.[1] Subsequent reductive etherification would forge the remaining *E* ring. We believed that **3.3** could be accessed from cyclic carbonate **3.4**, which would be the product of an electrophilic epoxide-opening cascade of triepoxide **3.5**. Our approach would amount to the first use of this type of electrophilic cascades in total synthesis. Lastly, Julia–Kocienski olefination[2] between sulfone **3.6** and aldehyde **3.7** would furnish cascade precursor **3.5**.

Scheme 1. Retrosynthetic analysis of *ABCDEFGH* fragment **3.1**.

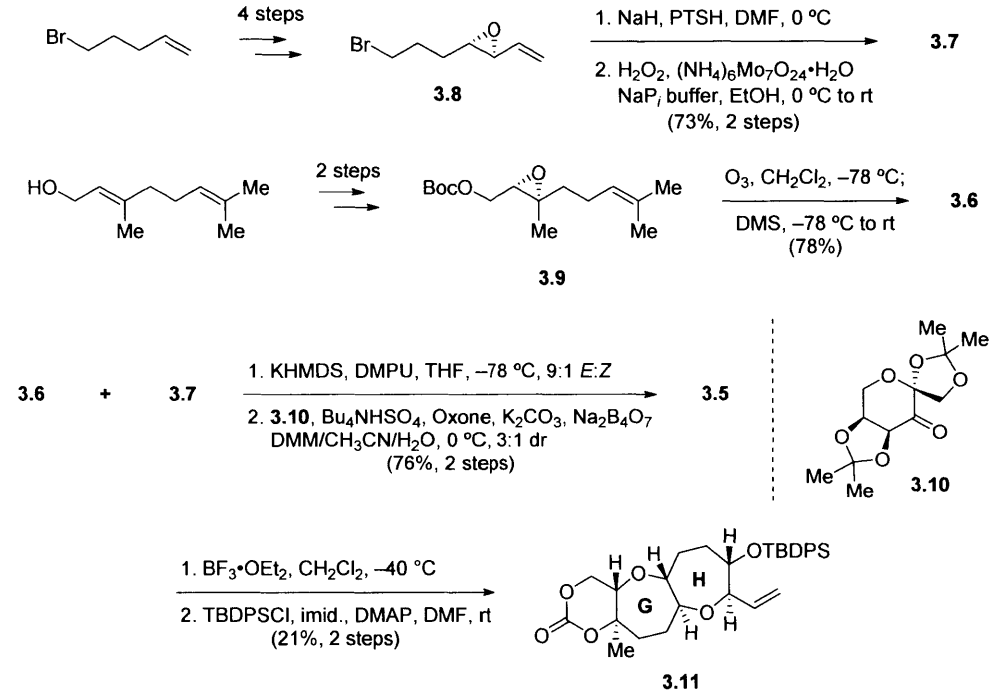


[1] Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851.
[2] Blakemore, P. R.; Cole. W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

B. Synthesis of *FGH* Fragment

The synthesis of **3.4** commenced with known bromovinylepoxide **3.8**[3] as depicted in Scheme 2. Following the same reaction sequence as sulfone **2.6** (Chapter II, Scheme 2), we arrived at the requisite sulfone **3.7**. The aldehyde coupling partner **3.6** was synthesized from known epoxide **3.9**[4] with addition of an ozonolysis step. Julia–Kocienski olefination between **3.6** and **3.7** proceeded uneventfully with a 9:1 ratio of *E*:*Z* isomers. Asymmetric Shi epoxidation[5] with *ent* Shi ketone **3.10** afforded triepoxide **3.5** with 3:1 dr.

Scheme 2. Synthesis of *GH* fragment **3.11**.



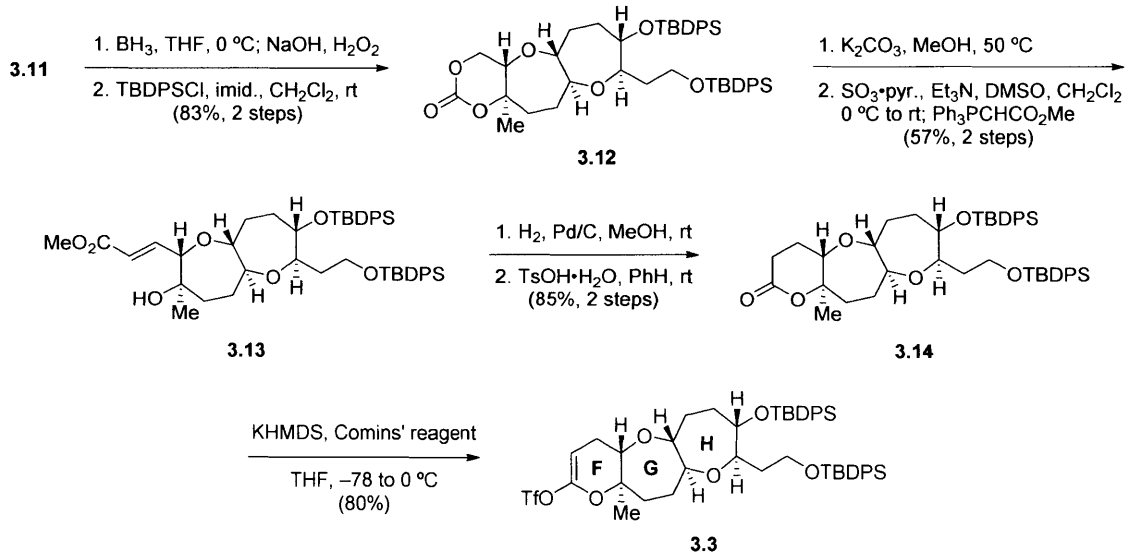
With cascade precursor **3.5** in hand, we began our investigation into the key electrophilic epoxide-opening cascade. Initially, we adapted conditions reported by McDonald for similar types

[3] Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.–Eur. J.* **2009**, *15*, 11490.
[4] Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.
[5] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

of cascades.[6] Among a variety of Lewis acids tested, $BF_3 \cdot OEt_2$ proved to be most effective, delivering the highest yield of the desired cascade product. More satisfactory and reproducible yields were obtained when reactions were performed at dilute concentration (<0.025 M). We believe that dilute conditions were necessary to avoid nonproductive, intermolecular reaction pathways. The cascade product was then silylated to afford TBDPS ether **3.11**.

Our next task was to elaborate the *GH* fragment to enol triflate **3.3** (Scheme 3) as a fragment coupling component. To this end, **3.11** underwent hydroboration/oxidation to furnish, after silylation of the newly formed primary alcohol, bisTBDPS ether **3.12**. To construct the *F* ring, carbonate removal under basic conditions revealed a diol, whose primary alcohol was oxidized and homologated to hydroxy enoate **3.13**. Hydrogenation and acid-catalyzed lactonization then revealed δ-lactone **3.14**, which was converted to enol triflate **3.3** with Comins' reagent, giving the requisite *FGH* fragment in 17 steps longest linear sequence.

Scheme 3. Elaboration of cyclic carbonate **3.11** to enol triflate *FGH* **3.3**.



[6] Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487.

C. Synthesis of *ABCDEFGH* Fragment

With both olefin **3.2** (Chapter II, Scheme 4) and enol triflate **3.3** in hand, we investigated the crucial Suzuki-Miyaura fragment coupling step. To this end, hydroboration of **3.2** with 9-BBN, followed by cross-coupling with **3.3**, furnished desired adduct **3.15** in good yield (Scheme 4). Interestingly, attempts to use an enol phosphate analog of **3.3** were met with no success, similar to what was reported in Sasaki's total synthesis of gymnocin A.[7] Hydroboration/oxidation of glycal **3.15** afforded predominantly alcohol **3.16** with incorrect C20 stereochemical configuration. The observed facial selectivity was due to the sterically encumbered Me59 shielding the bottom face of the molecule. After oxidation of **3.16** to the corresponding ketone, C20 stereochemical discrepancy was corrected via base-catalyzed epimerization to the more thermodynamically stable epimer **3.17**. Attempts to synthesize ketone **3.17** directly from glycal **3.15** via glycal-epoxide rearrangements[8] were unsuccessful.

Reductive etherification of ketone **3.17** proceeded smoothly to complete the synthesis of the entire *ABCDEFGH* core in 29 steps longest linear sequence. Notably, selective removal of the primary TBDPS ether in **3.17** allowed for exhaustive oxidation to carboxylic acid **3.18**, the substrate for the final union event.

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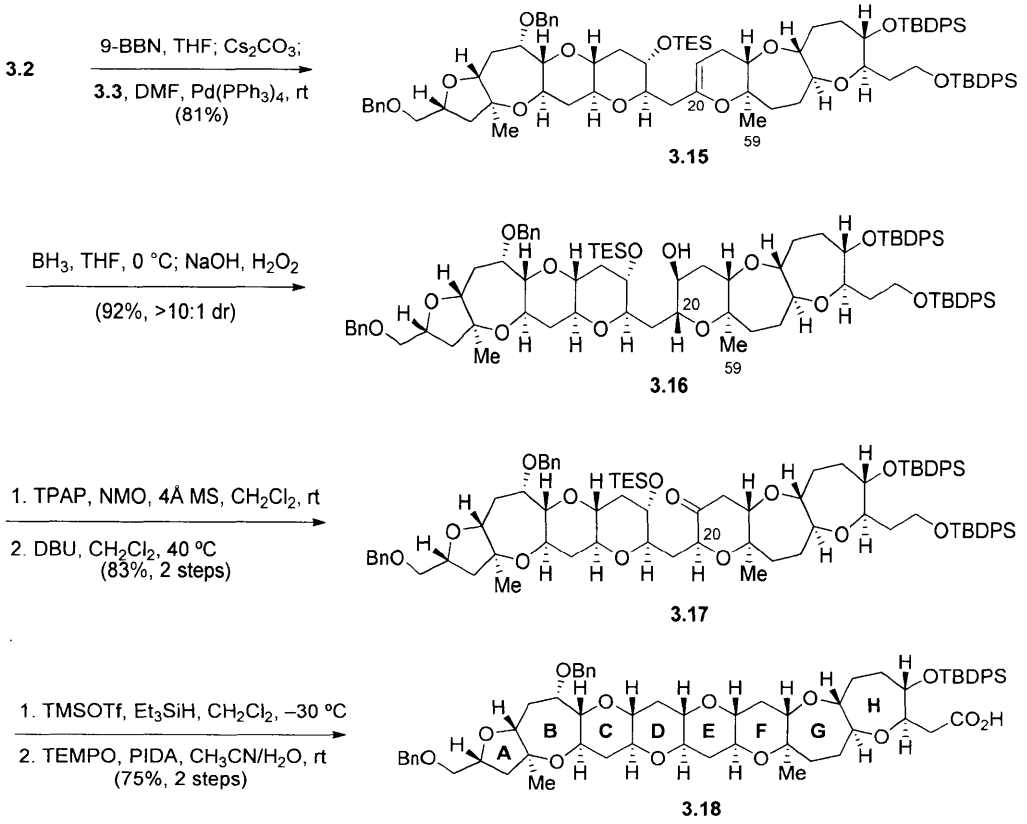
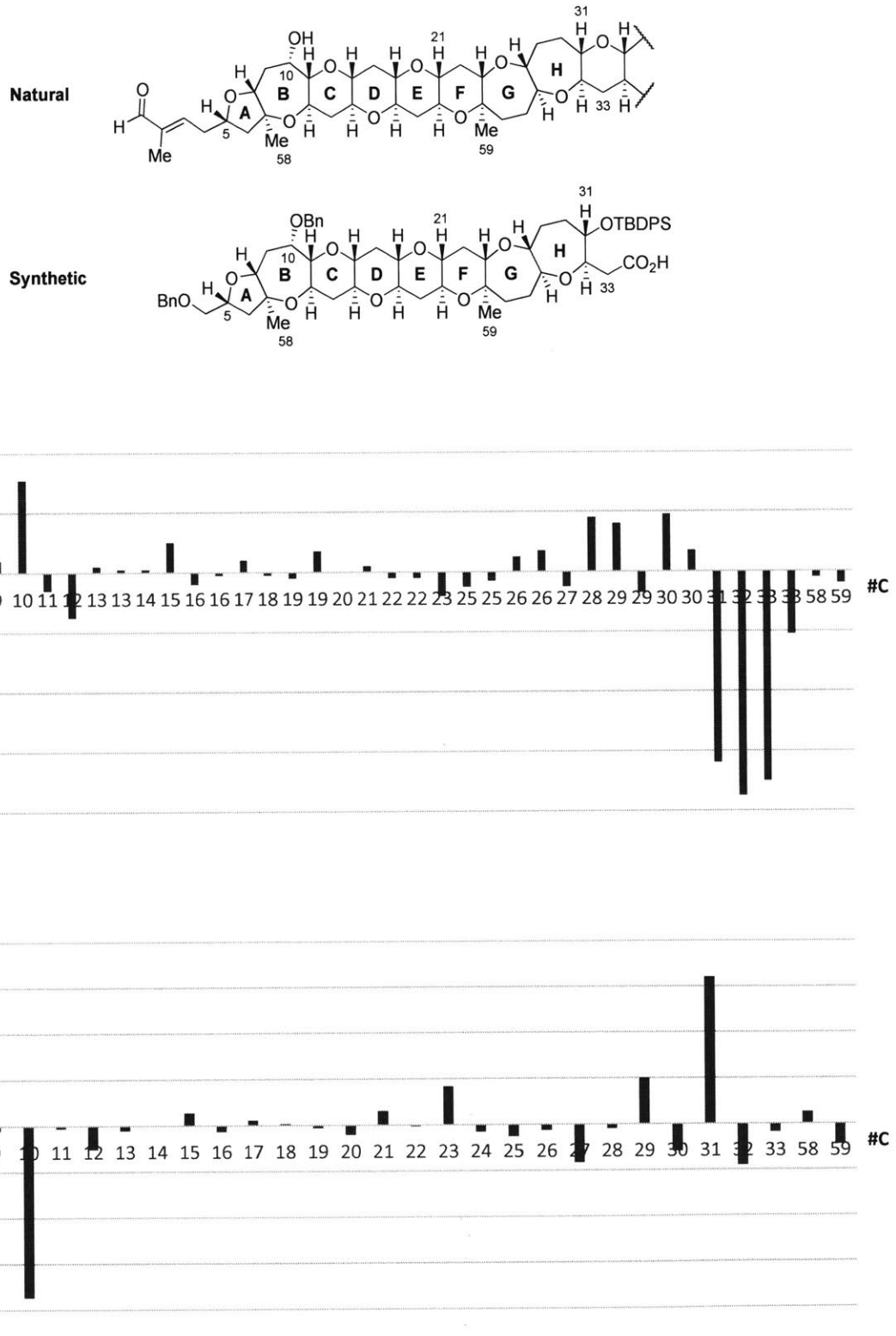
[7] Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326.
[8] Akoto, C. O.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8055.

Scheme 4. Completion of *ABCDFGH* fragment **3.18**.



As a comparison, the differences in ^{1}H and ^{13}C chemical shifts of synthetic **3.18** vs. natural product are shown in Figure 1. Good agreement was observed throughout the rigid polyTHP *CDEF* core, including the newly formed C21 stereocenter during the reductive cyclization. As expected, significant deviation arose at the edges of the fragment, especially around *GH* rings where flexible fused oxepanes are located.

Figure 1. Chemical shift comparison between natural and synthetic *ABCDFGH* fragments



In conclusion, the *ABCDEFGH* acid **3.18** was synthesized in 30 steps longest linear sequence. In addition to two epoxide-opening cascades used to construct the *ABCD* fragment, the synthesis featured an electrophilic epoxide-opening cascade to assemble the *trans* fused *GH* oxepanes. Our approach represents the first use of this type of electrophilic cascades in total synthesis. Furthermore, Suzuki–Miyaura cross-coupling proved reliable for complex fragment union. Reductive etherification completed the entire multi-cyclic core of **3.1**. Lastly, carboxylic acid **3.18** was accessed in order to engage in the final fragment coupling step.

D. Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Dichloromethane, THF, Et_2O, toluene, DMSO, DMF, and trimethylamine, pyridine, acetonitrile, and benzene were purified via an SG Water USA solvent system. $Ti(OiPr)_4$, HMPA, and DMPU were distilled from CaH_2 and stored over molecular sieves under argon. Reactions in water used deionized water without further purification. Cs_2CO_3 was oven-dried overnight before use. All other reagents and solvents were used as obtained, without further purification.

Chiral ketone **3.10**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[9]

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), CAM, $KMnO_4$, or *p*-anisaldehyde stain. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh) or Biotage Isolera flash purification system on SNAP KP-Sil, HP-Sil, or Ultra columns. Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-125 MHz spectrometer, a Bruker AVANCE-100 MHz spectrometer, or a Bruker AVANCE-150 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard residual $CHCl_3$ in $CDCl_3$ (7.26 ppm) or C_6HD_5 in C_6D_6 (7.16 ppm). Data are reported as follows: chemical shifts, multiplicity (s =singlet, d =doublet, t = triplet, q = quartet, and m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm), on the δ scale.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR and are reported in terms of frequency absorption (cm^{-1}). High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumental Facility. Optical rotations were measured on a Jasco Model 1010 digital polarimeter at 589 nm.

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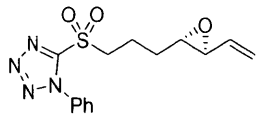
[9] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.



3.7

Sulfone 3.7: To a solution of 1-phenyltetrazole-5-thiol (19.6 g, 110 mmol) in THF/DMF (3:1, 150 mL) at 0 °C was added sodium hydride (60% in mineral oil, 4.4 g, 110 mmol) in three portions over 10 min. The slurry was stirred at 0 °C until gas evolution subsided and then warmed to rt over 1 h. The slurry was cooled to 0 °C and added a solution of bromide **3.8** (20.1 g, 105 mmol) in THF (70 mL) over 15 min. The resulting solution was warmed to rt over 2 h, at which point it was quenched by addition of sat. $NH_4Cl_{(aq)}$ (50 mL). The aqueous layer was separated and extracted with Et_2O (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude sulfide (R_f = 0.40 (30% EtOAc in hexanes)), which was carried onto the next step without further purification.

To a solution of the crude sulfide in EtOH (300 mL) was added aq. NaH_2PO_4 (1 M, 200 mL, 200 mmol), and the resulting solution was cooled to 0 °C. 30% $H_2O_{2(aq)}$ (17.9 g, 54 mL, 525 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (26 g, 21 mmol) were then added. The reaction was stirred vigorously and allowed to warm to rt overnight. The reaction was quenched by addition of brine (100 mL). The aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 60% EtOAc in hexanes) to afford sulfone **3.7** as a white solid (25.9 g, 80.9 mmol, 73% over two steps, R_f = 0.26 (20% EtOAc in hexanes)).

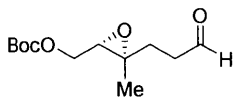
$[\alpha]^{22}_D$ = –19.12 (*c* = 1.00, $CHCl_3$)

IR (ATR): 3020, 2921, 1595, 1498, 1340, 1217, 1149, 928, 880, 748, 687, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.65–7.59 (m, 2H), 7.55 (td, *J* = 5.9, 2.8 Hz, 3H), 5.49 (ddd, *J* = 16.9, 9.8, 7.1 Hz, 1H), 5.41 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.22 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.84–3.66 (m, 2H), 3.14 (dd, *J* = 7.1, 2.1 Hz, 1H), 2.88 (ddd, *J* = 6.5, 4.0, 2.1 Hz, 1H), 2.16–2.02 (m, 2H), 1.91 (dddd, *J* = 14.5, 8.1, 6.4, 4.0 Hz, 1H), 1.60 (dq, *J* = 14.6, 7.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5, 135.1, 133.1, 131.6, 129.9, 125.2, 119.9, 59.2, 58.3, 55.7, 30.3, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}N_4O_3S$ $[M+H]^+$: 321.1016, found 321.1034.



3.6

Aldehyde 3.6: Epoxide **3.9** (25 g, 92.5 mmol) was dissolved in CH_2Cl_2 (120 mL), and the resulting solution was cooled to –78 °C. A stream of ozone was bubbled through until a pale blue color evolved, about 3 h. Argon was bubbled through the solution to remove residual ozone, and then PPh_3 (26.2 g, 100 mmol) was added, at which point the cold bath was removed, and the reaction

was allowed to warm to rt over 90 min. The solution was then concentrated *in vacuo* and chromatographed (gradient 0% to 60% EtOAc in hexanes) to provide aldehyde **3.6** as a colorless oil (17.5 g, 72 mmol, 78%, R_f = 0.37 (30% EtOAc in hexanes))

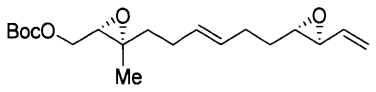
$[\alpha]^{22}_D$ = –17.97 (*c* = 0.7, $CHCl_3$)

IR (ATR): 2983, 2933, 2727, 1738, 1457, 1369, 1275, 1253, 1157, 1088, 1037, 961, 936, 856, 792, 766 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 9.74 (s, 1H), 4.17 (dd, *J* = 11.9, 4.9 Hz, 1H), 4.09 (dd, *J* = 11.9, 6.1 Hz, 1H), 2.99 (dd, *J* = 6.1, 4.9 Hz, 1H), 2.50 (td, *J* = 7.5, 1.3 Hz, 2H), 1.93 (dt, *J* = 14.9, 7.5 Hz, 1H), 1.86 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.46 (s, 9H), 1.29 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.9, 153.3, 82.7, 65.3, 59.7, 59.3, 39.0, 29.9, 27.8, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $[M+NH_4]^+$: 262.1649, found 262.1659.



3.19

Olefin 3.19: To a solution of aldehyde **3.6** (15.7 g, 64.5 mmol) and sulfone **3.7** (19.7 g, 61.4 mmol) in THF (160 ml) was added DMPU (29.6 ml, 245 mmol). The resulting solution was cooled to –78 °C. A solution of KHMDS (13 g, 65 mmol) in THF (90 mL) was added over 15 min. The reaction mixture was stirred at –78 °C for 30 min, at which point the reaction was quenched by addition of brine (50 mL) and allowed to warm to rt over 1 h. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 40% EtOAc in hexanes) to afford **3.19** as a colorless oil (17.8 g, 52.6 mmol, 86%, 9.0:1 *E*:*Z*, R_f = 0.51 (20% EtOAc in hexanes)).

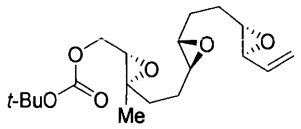
$[\alpha]^{22}_D$ = –8.35 (*c* = 0.39, $CHCl_3$)

IR (ATR): 2984, 2932, 2856, 1742, 1370, 1265, 1160, 1092, 927, 858, 733, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 5.56 (ddd, *J* = 17.5, 10.1, 7.5 Hz, 1H), 5.50–5.37 (m, 3H), 5.25 (dd, *J* = 10.1, 1.7 Hz, 1H), 4.20 (dd, *J* = 11.9, 4.7 Hz, 1H), 4.11 (dd, *J* = 11.9, 6.2 Hz, 1H), 3.09 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.00 (dd, *J* = 6.2, 4.9 Hz, 1H), 2.83 (td, *J* = 5.6, 2.3 Hz, 1H), 2.25–2.02 (m, 3H), 1.74–1.59 (m, 3H), 1.57–1.45 (m, 2H), 1.49 (s, 9H), 1.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5, 135.9, 130.1, 129.8, 119.1, 82.7, 65.7, 60.6, 60.1, 59.6, 58.9, 38.2, 32.0, 29.0, 28.2, 27.9, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{19}H_{30}O_5$ $[M+NH_4]^+$: 356.2431, found 356.2428.



3.5

Triepoxide 3.5: To a solution of olefin **3.19** (12 g, 35.5 mmol) in 2:1 DMM:MeCN (350 mL) was added a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M Na_2EDTA (210 mL), *n*-Bu_4HSO_4 (3.62 g, 10.7 mmol), and chiral ketone xx (2.29 g, 8.8 mmol). This biphasic mixture was stirred rigorously at 0 °C. To this mixture was added, simultaneously over 1 h via syringe pumps, a solution of Oxone (43.7 g, 71 mmol) in 4×10^{-4} M Na_2EDTA (210 mL) and a 0.89 M solution of K_2CO_3 (210 mL). Over this period, additional chiral ketone **3.10** (2.29 g, 8.8 mmol) was added in three portions. After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 1 h, at which point it was diluted with EtOAc (120 mL) and water (80 mL). The aqueous layer was separated and extracted with EtOAc (3×80 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 60% EtOAc in hexanes) to afford **3.5** as a colorless oil (9.5 g, 26.8 mmol, 76% as a 3:1 mixture of diastereomers, R_f of all diastereomers = 0.34 (30% EtOAc in hexanes)).

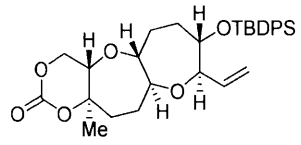
$[\alpha]^{22}_D = -21$ (c = 0.4, $CHCl_3$)

IR (ATR): 2979, 2927, 2857, 1739, 1644, 1457, 1369, 1278, 1253, 1092, 986, 925, 857, 792, 766, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 5.56 (ddd, J = 17.5, 10.2, 7.6 Hz, 1H), 5.46 (dd, J = 17.2, 1.8 Hz, 1H), 5.27 (dd, J = 10.1, 1.7 Hz, 1H), 4.19 (dd, J = 12.1, 5.0 Hz, 1H), 4.13 (dd, J = 11.9, 6.3 Hz, 1H), 3.12 (dd, J = 7.4, 2.2 Hz, 1H), 3.02 (t, J = 5.6 Hz, 1H), 2.90–2.84 (m, 1H), 2.77–2.67 (m, 2H), 1.81–1.53 (m, 8H), 1.49 (s, 9H), 1.31 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 153.5, 135.7, 119.3, 82.7, 65.5, 60.2, 59.8, 59.3, 58.8, 58.2, 58.1, 34.2, 28.4, 28.4, 27.9, 27.5, 17.1.

HR-MS (ESI) *m/z* calcd for $C_{19}H_{30}O_6$ $[M+NH_4]^+$: 372.2381, found 372.2365.



3.11

Tricycle 3.11: To a solution of triepoxide **3.5** (5 g, 14.1 mmol) in CH_2Cl_2 (700 mL) cooled to –40 °C was added $BF_3{\cdot}OEt_2$ (2.1 g, 1.79 mL, 14.1 mmol). The resulting solution was stirred at –40 °C for 15 min, quenched with sat. $NaHCO_{3(aq)}$ (250 mL), and allowed to warm to rt over 1 h with rigorous stirring. The aqueous layer was separated and extracted with CH_2Cl_2 (3×120 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to provide crude tricycle **3.4** as a yellow oil (R_f = 0.37 (70% EtOAc in hexanes)), which was carried onto the next step without further purification.

To a solution of crude tricycle **3.4** in DMF (20 mL) were added imidazole (14.4 g, 21.2 mmol), DMAP (172 mg, 1.41 mmol) and TBDPSCl (4.26 g, 4.03 mL, 15.5 mmol) at rt. The resulting solution was stirred at 40 °C overnight and quenched by addition of sat. $NH_4Cl_{(aq)}$ (15 mL). The aqueous layer was separated and extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford TBDPS tetracycle **3.11** as a white solid (1.59 g, 2.96 mmol, 21 % over two steps, R_f = 0.43 (30% EtOAc in hexanes)).

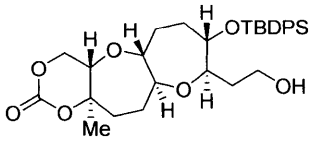
$[\alpha]^{22}_D$ = +22.03 (*c* = 0.35, $CHCl_3$)

IR (ATR): 2932, 2889, 2858, 1800, 1760, 1472, 1428, 1388, 1362, 1304, 1251, 1205, 1105, 1043, 1005, 928, 823, 769, 741, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (td, *J* = 7.9, 1.5 Hz, 4H), 7.46–7.40 (m, 2H), 7.40–7.33 (m, 4H), 5.50 (ddd, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.01 (dt, *J* = 17.2, 1.7 Hz, 1H), 4.94 (dt, *J* = 10.6, 1.7 Hz, 1H), 4.36 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.13 (t, *J* = 10.7 Hz, 1H), 4.01 (td, *J* = 3.4, 1.6 Hz, 1H), 3.92 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.90–3.86 (m, 1H), 3.76 (td, *J* = 8.5, 6.2 Hz, 1H), 3.42 (td, *J* = 9.6, 5.0 Hz, 1H), 2.25–2.15 (m, 1H), 2.11–1.94 (m, 3H), 1.91–1.81 (m, 1H), 1.81–1.73 (m, 1H), 1.65–1.49 (m, 2H), 1.47 (s, 3H), 1.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 136.8, 136.0, 135.9, 133.9, 133.6, 130.0, 129.9, 127.8, 127.8, 115.4, 85.9, 85.6, 82.6, 82.0, 75.6, 73.5, 66.4, 36.1, 29.6, 27.3, 27.2, 25.6, 21.0, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{40}O_6Si$ $[M+Na]^+$: 559.2486, found 559.2498.



3.20

Alcohol 3.20: To a solution of olefin **3.11** (1.3 g, 2.42 mmol) in THF (25 mL) at 0 °C was added a solution of 9-BBN (0.5 M in THF, 5.81 mL, 2.91 mmol). The resulting solution was stirred to rt over 4 h, at which point it was cooled to 0 °C and quenched by slow addition of $NaOH_{(aq)}$ (2 M, 1 mL, 2 mmol) and 30% $H_2O_{2(aq)}$ (0.34 g, 1 mL, 10 mmol). The resulting solution was stirred at 0 °C for 15 min. The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 80% EtOAc in hexanes) to afford alcohol **3.20** as a colorless oil (1.22 g, 2.2 mmol, 91%, R_f = 0.34 (50% EtOAc in hexanes)).

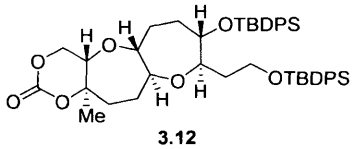
$[\alpha]^{22}_D$ = +17.68 (*c* = 0.25, $CHCl_3$)

IR (ATR): 3487, 2934, 2859, 1755, 1472, 1428, 1388, 1308, 1253, 1207, 1103, 1065, 939, 856, 822, 740, 703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (td, J = 7.7, 1.5 Hz, 4H), 7.48–7.41 (m, 2H), 7.38 (ddd, J = 8.3, 6.4, 1.7 Hz, 4H), 4.36 (dd, J = 10.4, 6.4 Hz, 1H), 4.12 (t, J = 10.4, 1H), 3.89 (dd, J = 11.1, 6.4 Hz, 1H), 3.73 (td, J = 3.6, 1.7 Hz, 1H), 3.69–3.57 (m, 2H), 3.56–3.46 (m, 2H), 3.39 (td, J = 9.4, 4.8 Hz, 1H), 2.24–2.13 (m, 1H), 2.11–1.51 (m, 7H), 1.46 (s, 3H), 1.41–1.24 (m, 2H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 136.0, 135.9, 133.8, 133.7, 130.1, 130.0, 127.9, 127.8, 86.3, 85.4, 83.2, 82.5, 75.9, 73.5, 66.4, 61.1, 36.3, 36.1, 29.6, 27.4, 27.2, 26.5, 21.0, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{42}O_7Si$ $[M+Na]^+$: 577.2592, found 577.2602.



3.12

BisTBDPS ether 3.12: To a solution of alcohol **3.20** (1.2 g, 2.16 mmol) in CH_2Cl_2 (5 mL) were added imidazole (265 mg, 3.9 mmol) and TBDPSCl (712 g, 0.67 mL, 2.59 mmol) at rt. The resulting solution was stirred at rt for 2 h and quenched by addition of sat. $NH_4Cl_{(aq)}$ (3 mL). The aqueous layer was separated and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford bisTBDPS ether **3.12** as a colorless oil (1.62 g, 2.04 mmol, 95%, R_f = 0.31 (20% EtOAc in hexanes)).

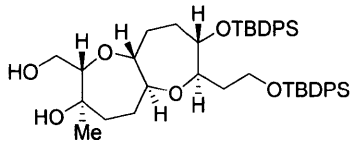
$[\alpha]^{22}_D$ = +12.2 (c = 0.25, $CHCl_3$)

IR (ATR): 2932, 2858, 1757, 1472, 1428, 1388, 1361, 1307, 1265, 1203, 1091, 940, 822, 769, 735, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.61 (m, 8H), 7.48–7.30 (m, 12H), 4.34 (dd, J = 10.5, 6.4 Hz, 1H), 4.11 (t, J = 10.7 Hz, 1H), 3.89–3.76 (m, 2H), 3.74–3.58 (m, 3H), 3.48 (dt, J = 9.2, 6.7 Hz, 1H), 3.33 (td, J = 9.4, 4.6 Hz, 1H), 2.18–1.96 (m, 2H), 1.87–1.66 (m, 4H), 1.65–1.46 (m, 3H), 1.44 (s, 3H), 1.32–1.20 (m, 1H), 1.10 (s, 9H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 136.0, 135.9, 135.7, 135.7, 134.3, 134.0, 134.0, 133.6, 129.9, 129.8, 129.8, 129.7, 127.8, 127.8, 127.7, 127.7, 85.8, 83.8, 82.7, 82.7, 76.3, 73.6, 66.5, 60.2, 37.1, 36.3, 29.2, 27.6, 27.3, 27.2, 27.0, 20.9, 19.4, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{47}H_{60}O_7Si2$ $[M+Na]^+$: 815.3770, found 815.3790.



3.21

Diol 3.21: To a solution of tricycle **3.12** (1.3 g, 1.64 mmol) in MeOH (30 mL) was added K_2CO_3 (0.34 g, 2.46 mmol). The resulting solution was stirred at 50 °C for 1 h. The reaction solution was concentrated *in vacuo* and partitioned between EtOAc (20 mL) and sat. $NH_4Cl_{(aq)}$ (10 mL). The aqueous layer was separated and extracted with EtOAc (5×5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 100% EtOAc in hexanes) to afford diol **3.21** as a colorless oil (1.10 g, 1.43 mmol, 87%, R_f = 0.31 (50% EtOAc in hexanes)).

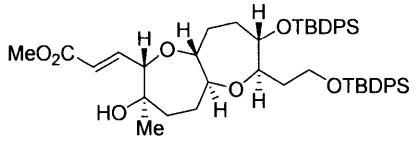
$[\alpha]^{22}_D$ = +6.13 (*c* = 0.15, $CHCl_3$)

IR (ATR): 3390, 2933, 2858, 1472, 1428, 1390, 1110, 1078, 822, 739, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.61 (m, 8H), 7.46–7.28 (m, 12H), 3.84 (dt, *J* = 10.5, 3.1 Hz, 1H), 3.80–3.70 (m, 2H), 3.65 (td, *J* = 9.3, 8.7, 3.5 Hz, 2H), 3.58 (ddd, *J* = 9.9, 6.2, 3.5 Hz, 1H), 3.54–3.44 (m, 2H), 3.23 (td, *J* = 10.5, 4.3 Hz, 1H), 2.17–1.95 (m, 2H), 1.86–1.65 (m, 5H), 1.65–1.37 (m, 4H), 1.33–1.22 (m, 1H), 1.18 (s, 3H), 1.10 (s, 9H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.1, 135.9, 135.7, 135.7, 134.3, 134.1, 134.1, 133.8, 129.9, 129.8, 129.7, 129.7, 127.8, 127.7, 87.9, 86.4, 84.7, 82.3, 76.4, 74.5, 62.6, 60.4, 38.9, 37.4, 28.8, 27.9, 27.3, 27.0, 24.3, 19.4, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{46}H_{62}O_6Si_2$ $[M+Na]^+$: 789.3977, found 789.3983.



3.13

Enoate 3.13: To a solution of diol **3.21** (1 g, 1.3 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.40 g, 0.55 mL, 3.9 mmol) and DMSO (0.41 g, 0.37 mL, 5.2 mmol). The resulting solution was cooled to 0 °C and added SO_3·pyr. (0.42 g, 0.26 mmol) in two portions. After addition, the reaction was warmed to rt until complete consumption of the diol was observed, about 2 h (R_f of hydroxy aldehyde intermediate = 0.43 (30% EtOAc in hexanes)). At this point, (methoxycarbonylmethylene)triphenylphosphorane (0.52 g, 1.56 mmol) was added. The solution was stirred at rt for 2 h and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 40% EtOAc in hexanes) to afford hydroxy enoate **3.13** as a colorless oil (0.69 g, 0.84 mmol, 65%, R_f = 0.57 (30% EtOAc in hexanes)).

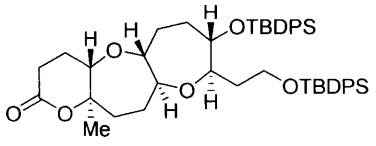
$[\alpha]^{22}_D$ = –7.86 (*c* = 0.22, $CHCl_3$)

IR (ATR): 3460, 2931, 2858, 1705, 1653, 1472, 1428, 1390, 1212, 1084, 998, 939, 906, 822, 737, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.61 (m, 8H), 7.46–7.28 (m, 12H), 6.21 (dd, J = 11.8, 8.4 Hz, 1H), 5.95 (dd, J = 11.9, 1.1 Hz, 1H), 4.90 (dd, J = 8.4, 1.1 Hz, 1H), 4.03 (s, 1H), 3.85 (dt, J = 10.5, 2.9 Hz, 1H), 3.79–3.75 (m, 1H), 3.74 (s, 3H), 3.64 (dt, J = 9.6, 4.9 Hz, 1H), 3.57 (ddd, J = 8.8, 5.5, 3.0 Hz, 1H), 3.51 (dt, J = 6.7, 4.3 Hz, 1H), 3.22 (td, J = 10.2, 4.4 Hz, 1H), 2.10 (dd, J = 25.6, 13.2 Hz, 1H), 1.92–1.84 (m, 2H), 1.79–1.65 (m, 4H), 1.57–1.39 (m, 2H), 1.32–1.21 (m, 1H), 1.14 (s, 3H), 1.10 (s, 9H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 148.8, 136.1, 136.0, 135.7, 135.7, 134.5, 134.2, 134.1, 133.8, 129.9, 129.8, 129.7, 129.6, 127.8, 127.7, 127.7, 127.7, 87.8, 84.7, 83.2, 82.1, 76.6, 76.5, 60.4, 52.2, 38.1, 37.5, 28.7, 27.9, 27.3, 27.0, 25.1, 19.4, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{49}H_{64}O_7Si_2$ $[M+Na]^+$: 843.4083, found 843.4083.



3.14

Lactone 3.14: To a solution of hydroxy enoate **3.13** (660 mg, 0.80 mmol) in MeOH (2 mL) was added Pd/C (10%, 80 mg). The black suspension was stirred under an H_2 atmosphere overnight. The slurry was filtered and concentrated *in vacuo* to provide crude hydroxy methylester (R_f = 0.31 (30% EtOAc in hexanes)). This crude material was dissolved in benzene (3 mL) and added *p*-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol). The reaction solution was stirred at rt 24 h, quenched with addition of Et_3N (1 mL), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford enoate **3.14** as a colorless oil (538 mg, 0.68 mmol, 85%, R_f = 0.43 (30% EtOAc in hexanes)).

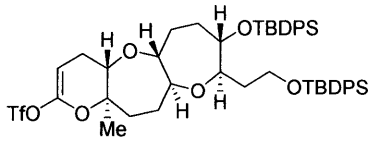
$[\alpha]^{22}_D$ = +12.42 (c = 0.12, $CHCl_3$)

IR (ATR): 2933 2858, 1738, 1472, 1428, 1390, 1297, 1260, 1210, 1111, 1081, 986, 941, 823, 739, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.61 (m, 8H), 7.46–7.28 (m, 12H), 3.84–3.77 (m, 1H), 3.75–3.70 (m, 1H), 3.70–3.55 (m, 3H), 3.55–3.46 (m, 1H), 3.30 (td, J = 9.7, 4.6 Hz, 1H), 2.82–2.56 (m, 2H), 2.15–2.01 (m, 2H), 2.01–1.87 (m, 2H), 1.82–1.69 (m, 4H), 1.69–1.55 (m, 2H), 1.5 –1.44 (m, 1H), 1.37 (s, 3H), 1.34–1.20 (m, 1H), 1.09 (s, 9H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 136.1, 136.0, 135.7, 135.7, 134.4, 134.0, 133.7, 129.9, 129.8, 129.7, 129.7, 127.8, 127.7, 127.7, 127.7, 85.8, 84.1, 83.5, 82.4, 79.1, 76.4, 60.3, 37.2, 37.0, 29.1, 28.5, 27.9, 27.3, 27.2, 27.0, 22.6, 22.0, 19.4, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{48}H_{62}O_6Si_2$ $[M+Na]^+$: 813.3977, found 813.3977.



3.3

Enol triflate 3.3: To a solution of lactone **3.14** (400 mg, 0.51 mmol) in THF (5 mL) was added HMPA (453 mg, 0.44 mL, 2.53 mmol). The solution was cooled to –78 °C, and a solution of KHMDS (303 mg, 1.52 mmol) in THF (5 mL) was added via cannulation. After 20 min at –78 °C, a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (496 mg, 1.26 mmol) in THF (5 mL) was added via cannulation. The resultant solution was stirred at –78 °C for 10 min, allowed to warm to 0 °C, and stirred at 0 °C for 1 h. The mixture was treated with pH 7 aqueous phosphate buffer (19 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*. The crude mixture was purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 15% EtOAc in hexanes) to afford enol triflate **3.3** as a colorless oil (379 mg, 0.41 mmol, 80%, R_f = 0.66 (20% EtOAc in hexanes)).

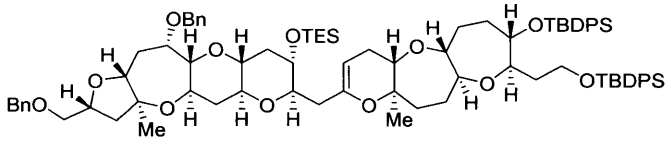
$[\alpha]^{22}_D$ = +22.35 (*c* = 0.2, C_6H_6)

IR (ATR): 2933, 2858, 1695, 1472, 1426, 1330, 1211, 1137, 1104, 1077, 938, 910, 854, 816, 737, 700 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ 7.85–7.69 (m, 8H), 7.31–7.17 (m, 12H), 4.15 (dd, *J* = 4.8, 2.7 Hz, 1H), 3.97–3.78 (m, 3H), 3.74 (ddd, *J* = 9.9, 6.3, 3.5 Hz, 1H), 3.53 (td, *J* = 8.4, 5.3 Hz, 1H), 3.16 (dd, *J* = 9.8, 6.5 Hz, 1H), 2.95 (td, *J* = 9.5, 4.1 Hz, 1H), 2.20–2.08 (m, 1H), 1.93–1.74 (m, 3H), 1.74–1.53 (m, 3H), 1.46 (ddd, *J* = 14.6, 11.3, 2.2 Hz, 1H), 1.40–1.28 (m, 2H), 1.21 (s, 9H), 1.19 (s, 9H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 148.5, 136.4, 136.2, 136.0, 136.0, 134.7, 134.4, 134.4, 134.1, 130.2, 130.1, 130.1, 130.0, 128.6, 128.2, 128.1, 86.0, 85.2, 84.2, 84.1, 82.7, 77.9, 77.0, 60.9, 37.8, 36.0, 29.3, 28.2, 27.6, 27.4, 27.2, 25.1, 19.6, 16.9.

HR-MS (ESI) *m/z* calcd for $C_{49}H_{61}F_3O_8SSi$ $[M+H]^+$: 923.3651, found 923.3659.



3.15

Coupling product 3.15: Exocyclic enol ether **3.2** (255 mg, 0.4 mmol) in THF (1 mL) was treated with 9-BBN (0.5 M in THF, 2.4 mL, 1.2 mmol). The resultant solution was stirred at rt for 2 h, at which point it was treated with $Cs_2CO_{3(aq)}$ (3 M, 0.8 mL, 2.4 mmol) and stirred at rt for 15 min. To this mixture were added a solution of enol triflate **3.3** (369 mg, 0.4 mmol) in DMF (3 mL) and a solution of $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) in DMF (1 mL) via cannulation. The resultant mixture was stirred at rt for 2 h and quenched with addition of water (4 mL). The aqueous layer was

separated and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*. The crude mixture was purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 45% EtOAc in hexanes) to afford coupling product **3.15** as a colorless oil (458 mg, 0.324 mmol, 81%, R_f = 0.40 (20% EtOAc in hexanes)).

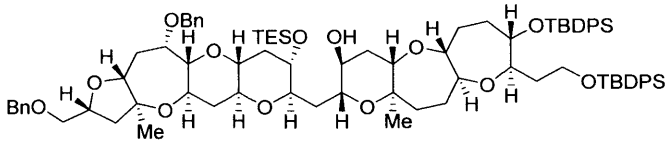
$[\alpha]^{22}_D$ = +38.12 (*c* = 0.25, C_6H_6)

IR (ATR): 2933, 2857, 1674, 1455, 1428, 1377, 1362, 1265, 1187, 1076, 1007, 977, 822, 734, 699 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ 7.87–7.72 (m, 8H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.31–7.14 (m, 18H), 7.13–7.06 (m, 2H), 4.68–4.61 (m, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.36 (s, 2H), 4.22 (dq, *J* = 7.5, 4.6, 2.6 Hz, 2H), 3.97 (dt, *J* = 10.3, 3.5 Hz, 1H), 3.91–3.84 (m, 2H), 3.82 (d, *J* = 5.7 Hz, 1H), 3.73 (ddd, *J* = 9.5, 6.0, 3.4 Hz, 1H), 3.71–3.65 (m, 1H), 3.63–3.53 (m, 4H), 3.38 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.33 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.24–3.15 (m, 2H), 2.96 (ddd, *J* = 11.8, 8.8, 4.0 Hz, 1H), 2.90 (ddd, *J* = 12.9, 8.7, 4.1 Hz, 1H), 2.81 (d, *J* = 14.7 Hz, 1H), 2.55 (dt, *J* = 10.2, 4.6 Hz, 1H), 2.44 (dt, *J* = 11.8, 4.0 Hz, 1H), 2.38–2.19 (m, 4H), 2.19–2.11 (m, 1H), 1.98–1.64 (m, 7H), 1.57 (s, 3H), 1.50 (t, *J* = 13.5 Hz, 1H), 1.36 (td, *J* = 9.9, 4.2 Hz, 1H), 1.29 (s, 3H), 1.24–1.18 (m, 18H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (151 MHz, C_6D_6): δ 150.6, 139.7, 139.1, 136.4, 136.3, 136.1, 136.0, 134.8, 134.5, 134.4, 134.2, 130.1, 130.0, 129.9, 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 127.8, 127.8, 127.7, 127.5, 95.0, 85.2, 85.1, 83.3, 82.9, 82.6, 81.9, 80.7, 79.8, 78.4, 77.3, 76.7, 76.2, 76.1, 75.9, 73.5, 73.4, 73.2, 71.0, 66.1, 61.0, 45.0, 41.5, 40.3, 37.9, 37.8, 37.4, 36.8, 31.5, 29.9, 28.6, 28.0, 27.4, 27.2, 27.1, 19.6, 18.9, 17.8, 7.2, 5.5.

HR-MS (ESI) *m/z* calcd for $C_{85}H_{114}O_{12}Si_3$ $[M+Na]^+$: 1433.7510, found 1433.7494.



3.16

Alcohol 3.16: To a solution of enol ether **3.15** (420 mg, 0.297 mmol) in THF (2 mL) at 0 °C was added BH_3·THF (1 M in THF, 0.15 mL, 0.15 mmol). The resultant solution was stirred at 0 °C for 10 min and then allowed to warm to rt. After 2 h, the mixture was cooled to 0 °C and treated with 2 M $NaOH_{(aq)}$ (0.2 mL, 0.4 mmol) followed by 30% $H_2O_{2(aq)}$ (340 mg, 1 mL, 1 mmol). The resultant mixture was stirred at rt 1 h. The aqueous layer was separated and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford alcohol **3.16** as a colorless oil (391 mg, 0.273 mmol, 92%, >10:1 dr, R_f = 0.37 (30% EtOAc in hexanes)).

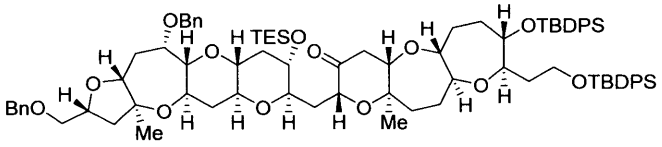
$[\alpha]^{22}_D$ = +37.73 (*c* = 0.15, $CHCl_3$)

IR (ATR): 3456, 2933, 2874, 2858, 1455, 1428, 1378, 1361, 1265, 1187, 1080, 1052, 1005, 822, 734, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.73–7.62 (m, 8H), 7.47–7.26 (m, 22H), 4.70–4.50 (m, 4H), 4.30–4.20 (m, 1H), 4.14 (ddd, J = 10.8, 8.9, 5.7 Hz, 1H), 4.00–3.93 (m, 1H), 3.91–3.76 (m, 3H), 3.72 (td, J = 10.1, 4.0 Hz, 1H), 3.68–3.57 (m, 2H), 3.53–3.35 (m, 5H), 3.31 (td, J = 10.1, 8.9, 1.8 Hz, 2H), 3.20 (td, J = 9.3, 4.1 Hz, 1H), 3.03 (ddd, J = 12.1, 8.8, 4.1 Hz, 1H), 2.96–2.84 (m, 2H), 2.43 (ddd, J = 15.1, 9.7, 5.8 Hz, 1H), 2.36–2.22 (m, 2H), 2.22–1.94 (m, 5H), 1.93–1.43 (m, 10H), 1.41 (s, 3H), 1.33–1.22 (m, 2H), 1.19 (s, 3H), 1.08 (s, 18H), 0.98 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 138.2, 136.1, 136.0, 135.6, 134.5, 134.1, 134.0, 133.8, 129.8, 129.7, 129.7, 129.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.5, 127.4, 86.4, 84.4, 83.0, 82.5, 82.3, 81.6, 80.0, 78.1, 76.4, 76.0, 75.9, 75.5, 75.2, 75.2, 73.5, 73.1, 72.8, 72.6, 72.0, 70.8, 65.6, 60.3, 44.5, 39.4, 37.9, 37.1, 36.8, 35.2, 33.3, 31.7, 30.8, 28.9, 28.1, 27.2, 27.0, 24.6, 19.4, 18.7, 7.0, 5.2.

HR-MS (ESI) *m/z* calcd for $C_{85}H_{116}O_{13}Si_3$ $[M+H]^+$: 1429.7796, found 1429.7815.



3.22

Ketone 3.22: To a mixture of alcohol **3.16** (380 mg, 0.266 mmol) and 4 Å MS (30 mg) were added CH_2Cl_2 (2 mL), *N*-methylmorpholine *N*-oxide (93 mg, 0.797 mmol), and tetrapropylammonium perruthenate (9.3 mg, 0.027 mmol). The resultant slurry was stirred at rt for 90 min, at which point it was filtered through a plug of celite, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 30% EtOAc in hexanes) to afford ketone **3.22** as a colorless oil (365 mg, 0.256 mmol, 96%, R_f = 0.57 (30% EtOAc in hexanes)).

$[\alpha]^{22}_D$ =+32.05 (c = 0.18, $CHCl_3$)

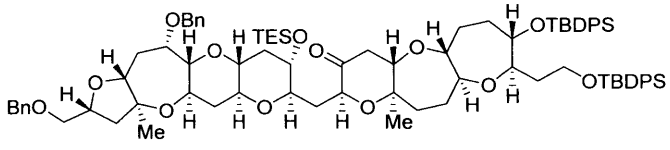
IR (ATR): 2933, 2875, 2858, 1732, 1455, 1428, 1378, 1266, 1239, 1081, 1060, 1007, 948, 822, 734, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.73–7.62 (m, 8H), 7.47–7.26 (m, 22H), 4.79–4.47 (m, 4H), 4.33–4.10 (m, 3H), 3.98 (d, J = 9.7 Hz, 1H), 3.89 (dd, J = 11.8, 5.9 Hz, 1H), 3.83 (ddd, J = 10.4, 5.0, 2.4 Hz, 1H), 3.76–3.59 (m, 4H), 3.58–3.29 (m, 6H), 3.25 (td, J = 9.4, 4.3 Hz, 1H), 3.02 (ddd, J = 12.1, 8.6, 4.0 Hz, 1H), 2.91 (ddd, J = 11.2, 8.8, 4.2 Hz, 1H), 2.76–2.56 (m, 2H), 2.45 (ddd, J = 15.2, 9.7, 5.8 Hz, 1H), 2.30 (tt, J = 11.6, 4.5 Hz, 2H), 2.24–1.97 (m, 3H), 1.97–1.46 (m, 9H), 1.44 (s, 3H), 1.35–1.22 (m, 1H), 1.21 (s, 3H), 1.11 (s, 9H), 1.10 (s, 9H), 0.98 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.9, 139.2, 138.3, 136.1, 136.0, 135.6, 134.4, 134.1, 134.0, 133.8, 129.8, 129.8, 129.7, 129.7, 128.5, 128.3, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 86.0,

84.2, 83.0, 82.6, 82.2, 81.6, 77.4, 77.3, 76.4, 76.1, 75.7, 75.6, 75.5, 73.9, 73.5, 73.1, 72.8, 70.8, 65.8, 60.4, 44.5, 41.8, 39.6, 37.2, 36.9, 35.9, 34.5, 30.8, 30.6, 28.1, 28.0, 27.2, 27.0, 22.3, 19.4, 19.4, 18.8, 7.0, 5.2.

HR-MS (ESI) *m/z* calcd for $C_{85}H_{114}O_{13}Si_3$ $[M+Na]^+$: 1449.7459, found 1449.7412.



3.17

Epimer 3.17: To a solution of ketone **3.22** (345 mg, 0.242 mmol) in CH_2Cl_2 (10 mL) was added DBU (110 mg, 0.11 mL, 0.725 mmol). The resultant solution was refluxed at 50 °C overnight, at which point it was concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 30% EtOAc in hexanes) to afford ketone **3.17** as a colorless oil (297 mg, 0.208 mmol, 86%, R_f = 0.57 (30% EtOAc in hexanes)).

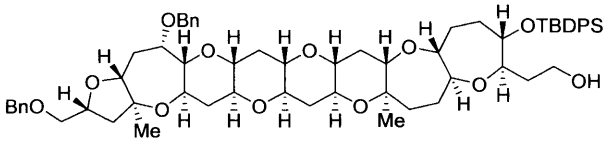
$[\alpha]^{22}_D$ = +31.18 (*c* = 0.33, $CHCl_3$)

IR (ATR): 2933, 2874, 2858, 1719, 1455, 1428, 1379, 1266, 1240, 1188, 1079, 1007, 822, 734, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.73–7.62 (m, 8H), 7.47–7.26 (m, 22H), 4.73–4.52 (m, 4H), 4.31–4.22 (m, 1H), 4.16–4.03 (m, 2H), 3.99–3.90 (m, 1H), 3.84 (ddd, *J* = 10.6, 5.0, 2.6 Hz, 1H), 3.78–3.67 (m, 3H), 3.63 (ddd, *J* = 12.1, 6.0, 3.8 Hz, 2H), 3.57–3.38 (m, 4H), 3.32 (td, *J* = 9.3, 4.4 Hz, 1H), 3.26 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.01–2.74 (m, 3H), 2.49–2.28 (m, 2H), 2.21 (dtd, *J* = 16.0, 9.7, 9.1, 4.1 Hz, 3H), 2.14–1.87 (m, 3H), 1.87–1.61 (m, 7H), 1.61–1.43 (m, 2H), 1.41 (s, 3H), 1.32–1.23 (m, 1H), 1.22 (s, 3H), 1.12 (s, 9H), 1.10 (s, 9H), 0.99 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.3, 138.2, 136.1, 136.0, 135.7, 135.7, 135.6, 134.4, 134.1, 134.0, 133.7, 129.8, 129.7, 129.7, 129.6, 128.5, 128.3, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.4, 85.2, 85.2, 82.9, 82.6, 82.2, 81.6, 78.7, 77.4, 76.5, 76.2, 76.0, 75.8, 75.4, 75.4, 74.3, 73.4, 73.0, 72.7, 70.9, 65.7, 60.3, 44.5, 42.1, 39.5, 37.5, 37.2, 36.5, 34.8, 30.7, 29.7, 28.1, 28.0, 27.2, 27.0, 19.4, 19.4, 18.7, 16.9, 7.0, 5.1.

HR-MS (ESI) *m/z* calcd for $C_{85}H_{114}O_{12}Si_3$ $[M+Na]^+$: 1449.7459, found 1449.7479.



3.1

Alcohol 3.1: To a solution of ketone **3.17** (280 mg, 0.196 mmol) in CH_2Cl_2 (5 mL) at –78 °C were added triethylsilane (456 mg, 0.63 mL, 3.92 mmol) and TMSOTf (218 mg, 0.18 mL, 0.98 mmol).

The resultant solution was stirred at –30 °C for 1 h, quenched with sat. $NaHCO_{3(aq)}$ (3 mL), and allowed to warm to rt over 20 min. The aqueous layer was separated and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 90% EtOAc in hexanes) to afford alcohol **3.1** as a colorless oil (170 mg, 0.16 mmol, 82%, R_f = 0.40 (50% EtOAc in hexanes)).

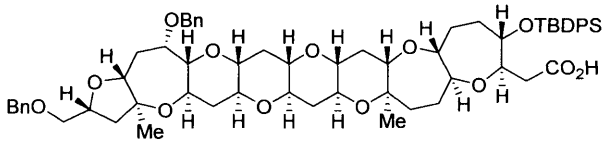
$[\alpha]^{22}_D$ = +9.7 (*c* = 0.21, $CHCl_3$)

IR (ATR): 3502, 2933, 2859, 1455, 1428, 1377, 1340, 1288, 1188, 1062, 822, 738, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.63 (ddt, *J* = 8.0, 6.7, 1.5 Hz, 4H), 7.45–7.40 (m, 2H), 7.37 (ddt, *J* = 8.2, 6.7, 1.5 Hz, 4H), 7.32 (dd, *J* = 8.6, 5.2 Hz, 8H), 7.29–7.26 (m, 2H), 4.69–4.50 (m, 4H), 4.24 (dq, *J* = 10.4, 5.6 Hz, 1H), 4.12 (td, *J* = 10.2, 5.4 Hz, 1H), 3.96 (d, *J* = 9.9 Hz, 1H), 3.68–3.50 (m, 5H), 3.50–3.42 (m, 3H), 3.37–3.24 (m, 4H), 3.14–3.05 (m, 2H), 3.04–2.92 (m, 3H), 2.45–2.35 (m, 2H), 2.35–2.28 (m, 2H), 2.24–2.13 (m, 2H), 2.09 (dt, *J* = 11.6, 4.2 Hz, 1H), 2.06–1.98 (m, 1H), 1.93–1.84 (m, 1H), 1.84–1.61 (m, 5H), 1.52–1.44 (m, 1H), 1.42 (s, 3H), 1.25 (s, 3H), 1.05 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.1, 138.3, 136.0, 136.0, 134.0, 133.8, 123.0, 129.9, 128.5, 128.3, 127.9, 127.8, 127.8, 127.5, 127.4, 86.9, 84.5, 84.2, 83.0, 82.5, 81.7, 81.1, 78.5, 77.4, 77.2, 77.2, 76.6, 76.2, 75.9, 75.8, 75.6, 73.5, 73.0, 72.8, 69.4, 65.8, 61.6, 44.5, 37.8, 36.8, 36.2, 35.8, 35.5, 32.8, 30.8, 30.4, 28.1, 27.6, 27.2, 19.4, 18.8, 17.5.

HR-MS (ESI) *m/z* calcd for $C_{63}H_{82}O_{12}Si$ $[M+Na]^+$: 1081.5468, found 1081.5475.



3.18

Carboxylic acid 3.18: A mixture of diacetoxyiodobenzene (122 mg, 0.378 mmol) and alcohol **3.1** (160 mg, 0.151 mmol) was suspended in 1:1 acetonitrile/water (4 mL). This mixture was sonicated for 3 min until the reagents were completely dissolved. TEMPO (4.7 mg, 0.03 mmol) was added to the reaction vessel. The reaction mixture was stirred at rt overnight. The aqueous layer was separated and extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes) to afford alcohol **3.18** as a colorless oil (149 mg, 0.139 mmol, 92%, R_f = 0.17 (50% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +28 (*c* = 0.06, $CHCl_3$)

IR (ATR): 3060, 2931, 2858, 1708, 1455, 1428, 1376, 1339, 1266, 1058, 822, 734, 699 cm^{-1}.

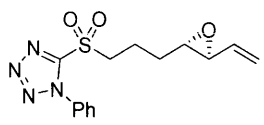
^1H NMR (600 MHz, $CDCl_3$): δ 7.66–7.59 (m, 4H), 7.43 (dd, *J* = 8.3, 6.3 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 4H), 7.35–7.29 (m, 7H), 7.29–7.24 (m, 3H), 4.71–4.50 (m, 4H), 4.23 (dq, *J* = 10.7, 5.4 Hz, 1H), 4.12 (td, *J* = 9.7, 5.2 Hz, 1H), 3.96 (d, *J* = 9.8 Hz, 1H), 3.87 (td, *J* = 8.3, 7.5, 3.8 Hz, 1H),

3.61 (dd, J = 12.1, 5.8 Hz, 1H), 3.56–3.50 (m, 2H), 3.49–3.42 (m, 2H), 3.34–3.22 (m, 4H), 3.15–3.05 (m, 2H), 3.05–2.92 (m, 3H), 2.49 (dd, J = 15.5, 2.8 Hz, 1H), 2.41 (ddd, J = 15.1, 9.8, 5.7 Hz, 1H), 2.37–2.27 (m, 2H), 2.25–1.92 (m, 5H), 1.86–1.55 (m, 8H), 1.54–1.36 (m, 3H), 1.42 (s, 3H,), 1.23 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.2, 139.1, 138.2, 136.0, 135.9, 133.9, 133.4, 130.0, 129.9, 128.5, 128.3, 127.9, 127.9, 127.7, 127.5, 127.4, 85.3, 84.2, 83.5, 82.9, 82.4, 81.8, 81.7, 78.4, 77.6, 77.3, 77.1, 76.6, 75.9, 75.8, 75.7, 75.5, 73.5, 73.0, 72.7, 69.3, 65.8, 44.4, 39.6, 37.5, 36.8, 36.8, 35.6, 35.4, 32.8, 30.7, 29.6, 28.9, 28.5, 27.1, 19.4, 18.7, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{63}H_{80}O_{13}Si$ $[M+Na]^+$: 1095.5260, found 1095.5240.

E. ^{1}H and ^{13}C NMR Spectra



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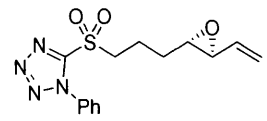

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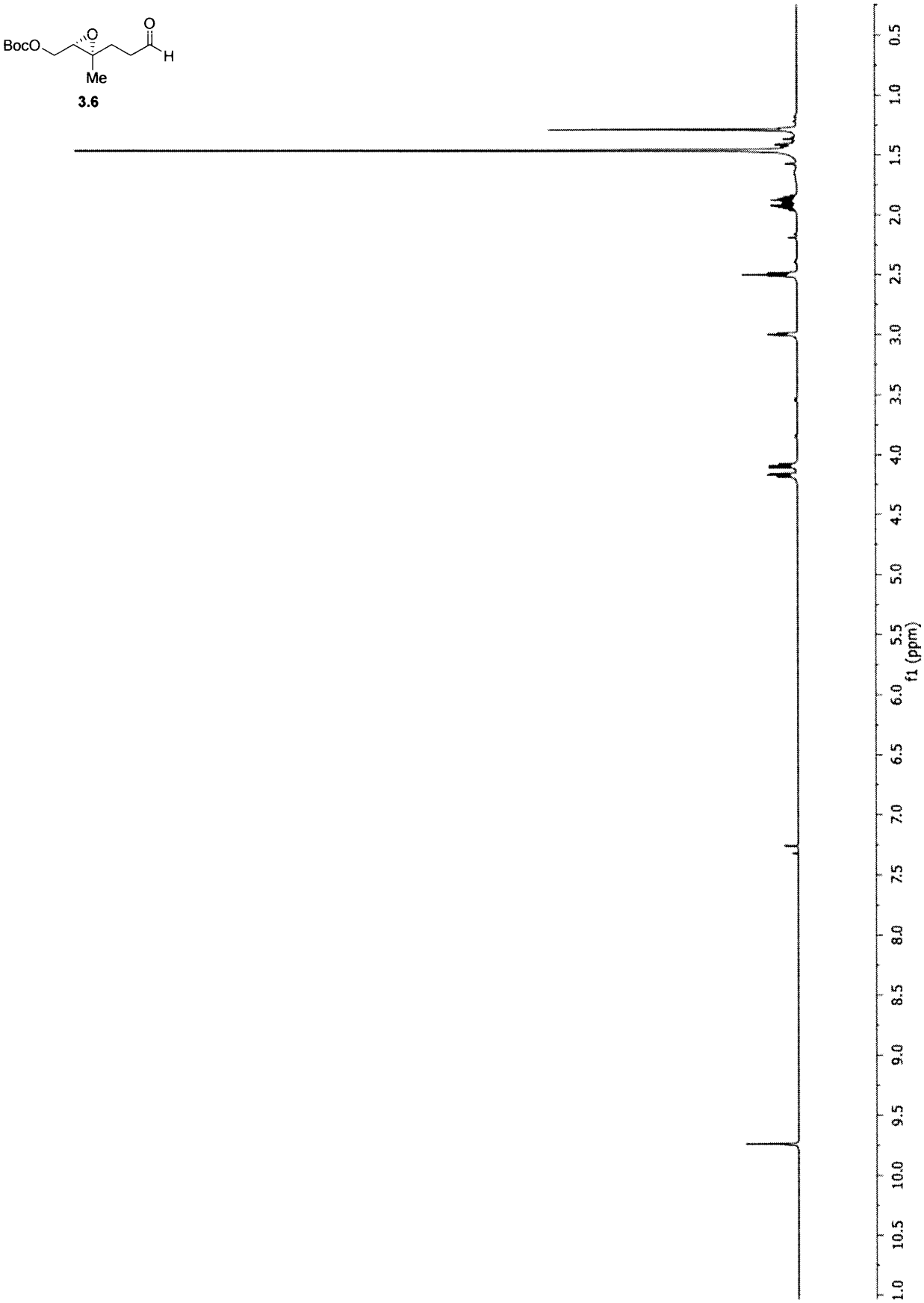
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Me
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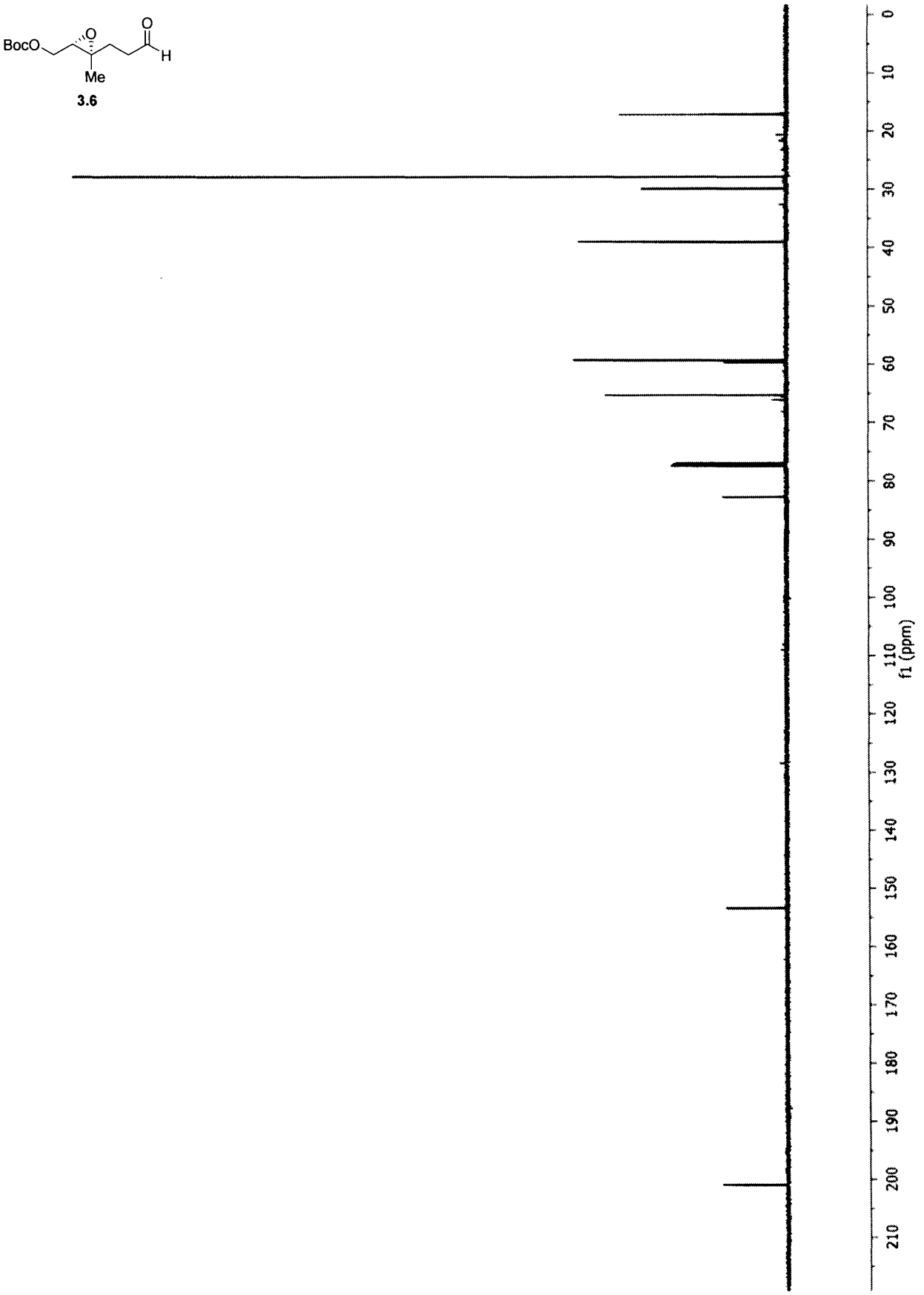
f1 (ppm)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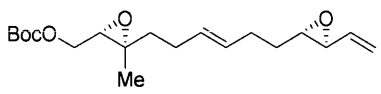
f1 (ppm)



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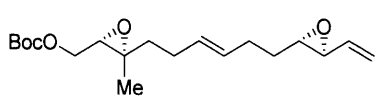
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Me

3.19

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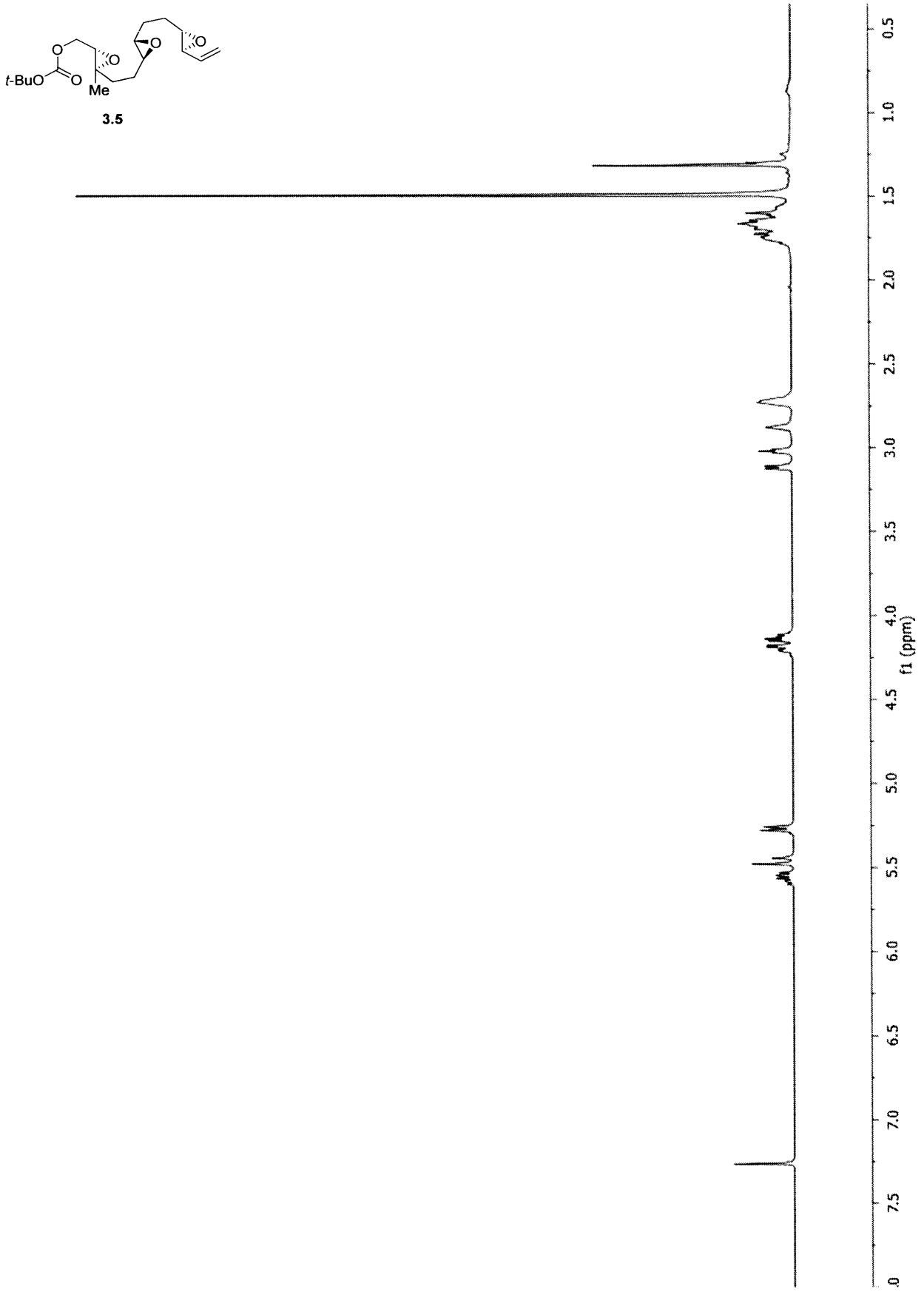
f1 (ppm)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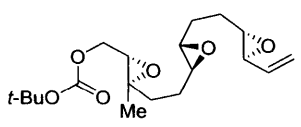
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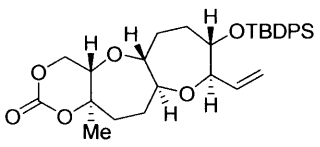
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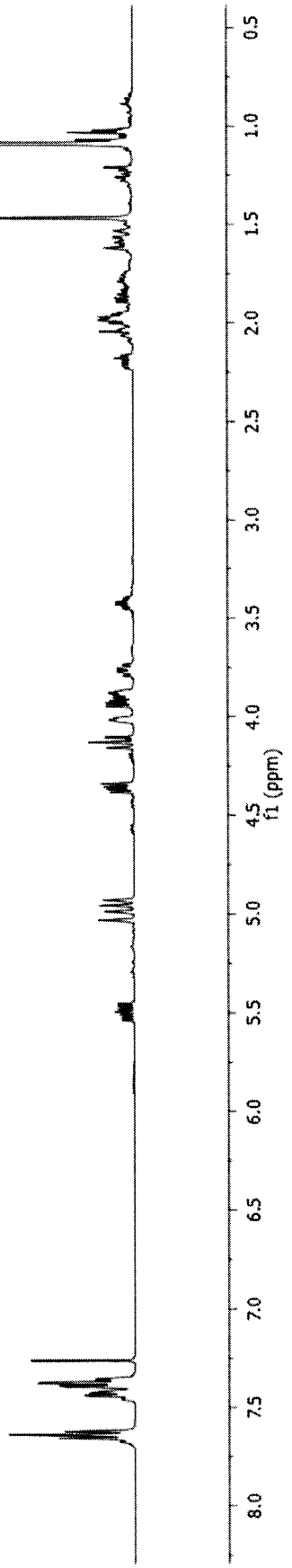
3.11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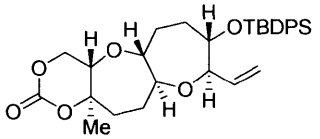
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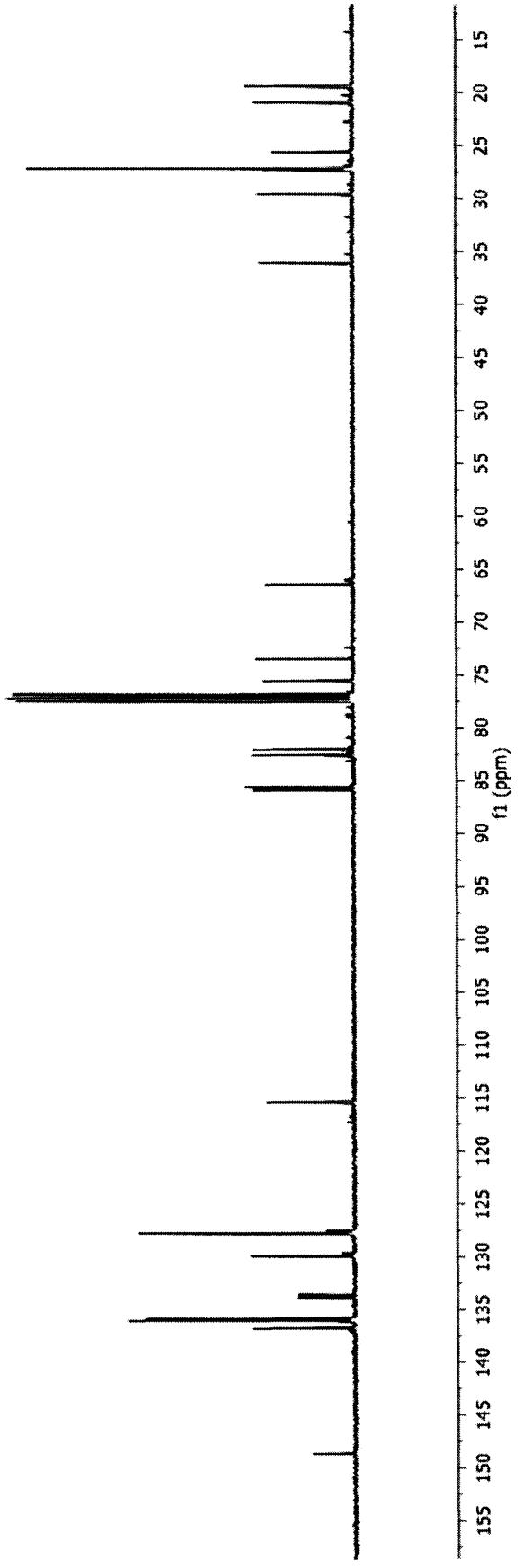
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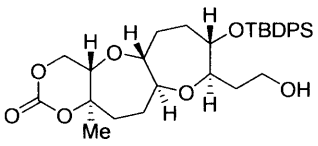
f1 (ppm)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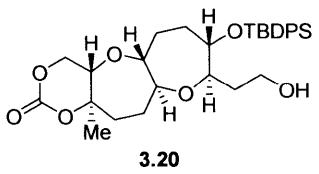
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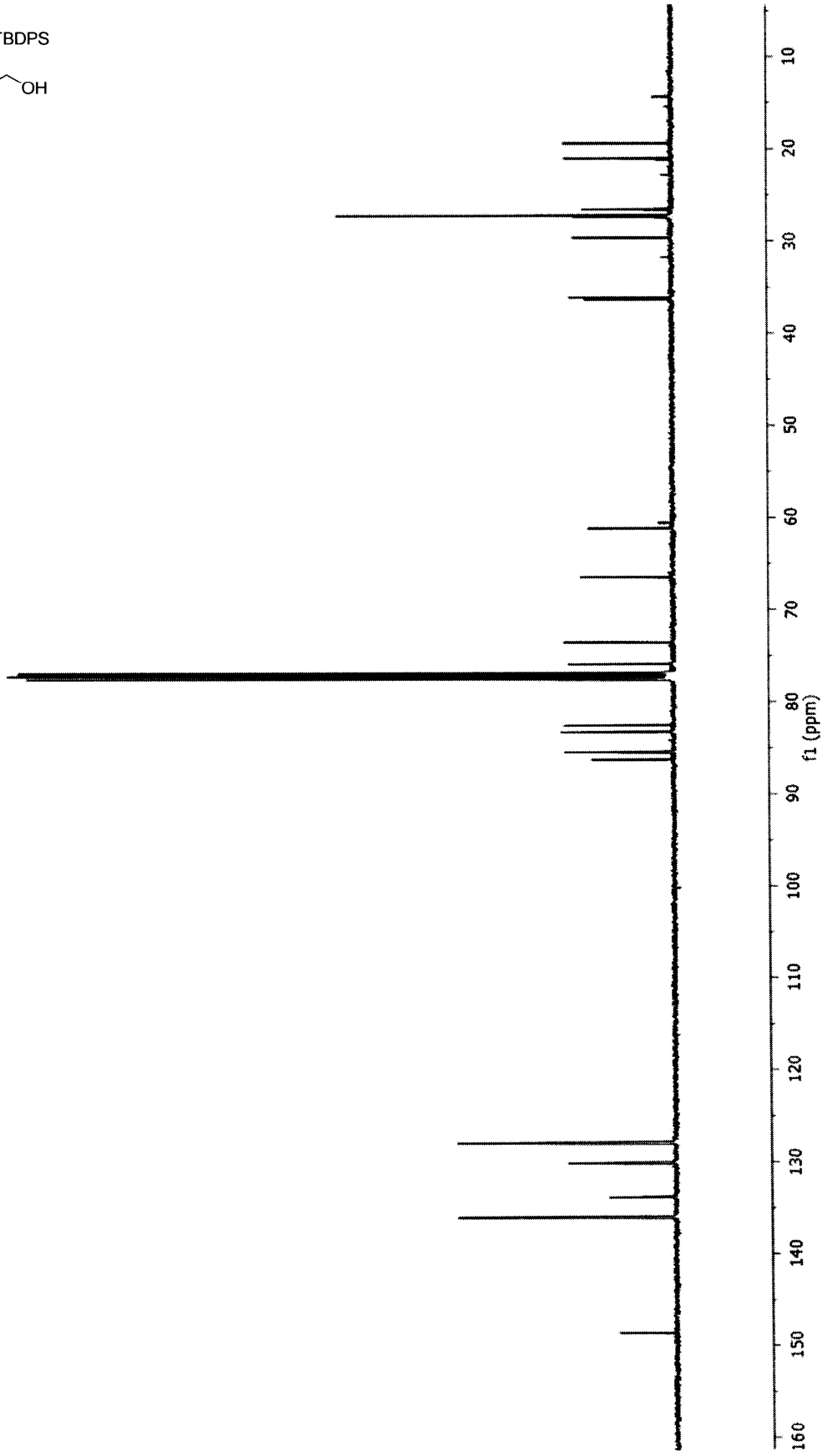
Me

3.20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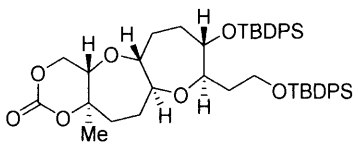
160
f1 (ppm)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H
H
OTBDPS
O
O
O
O
H
OTBDPS
Me

3.12

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1.0
1.5
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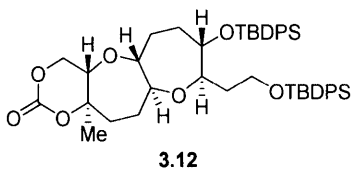
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)



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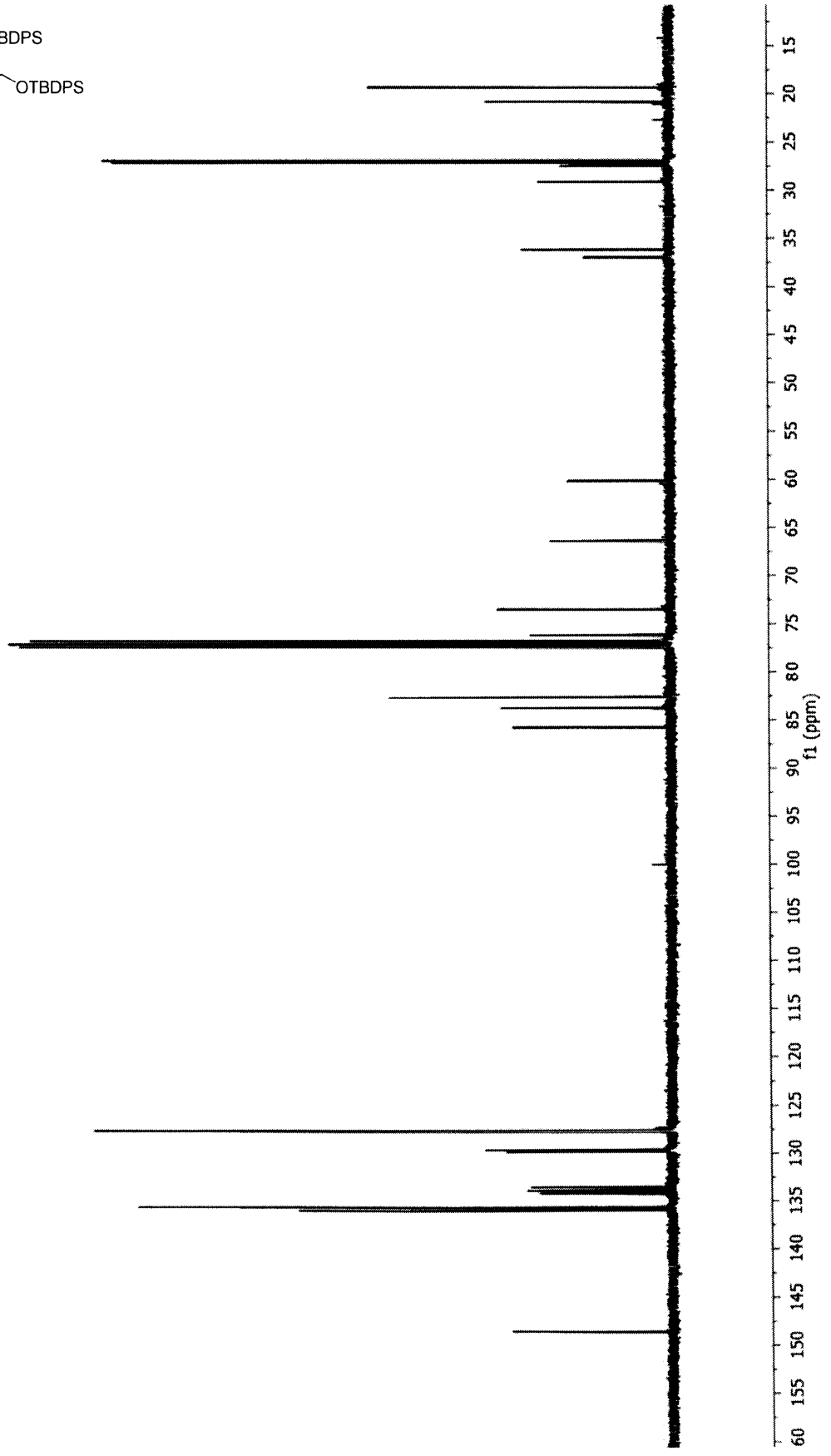
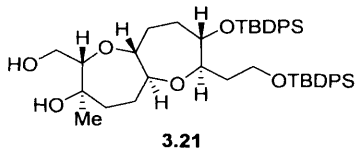
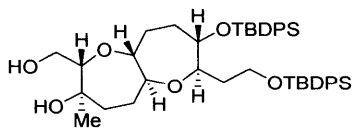



HO
H
H
O
H
OTBDPS
HO
Me
O
H
H
OTBDPS

3.21

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)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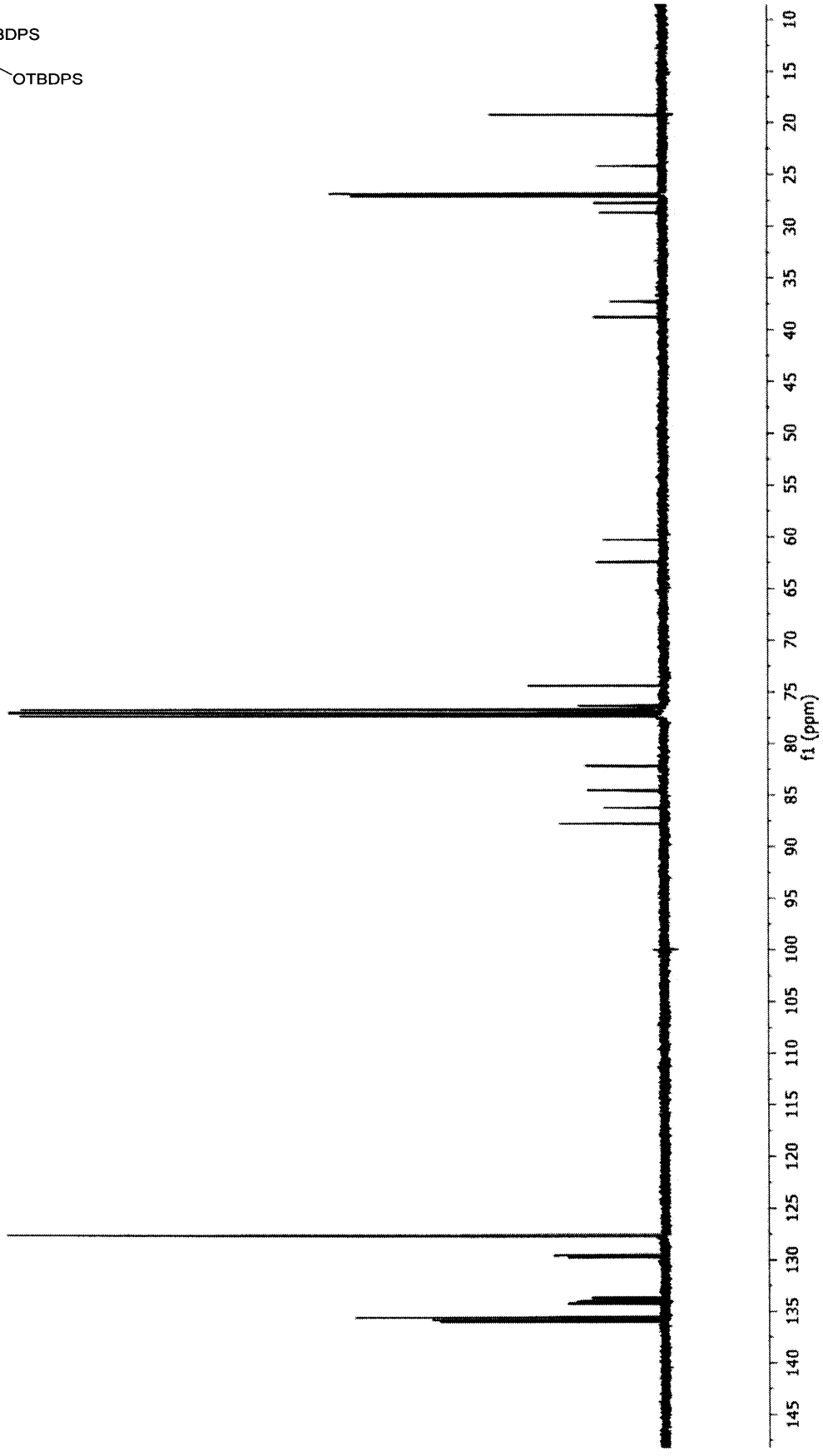
H
H
OTBDPS
HO
O
O
OTBDPS
H
HO
Me

3.21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15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
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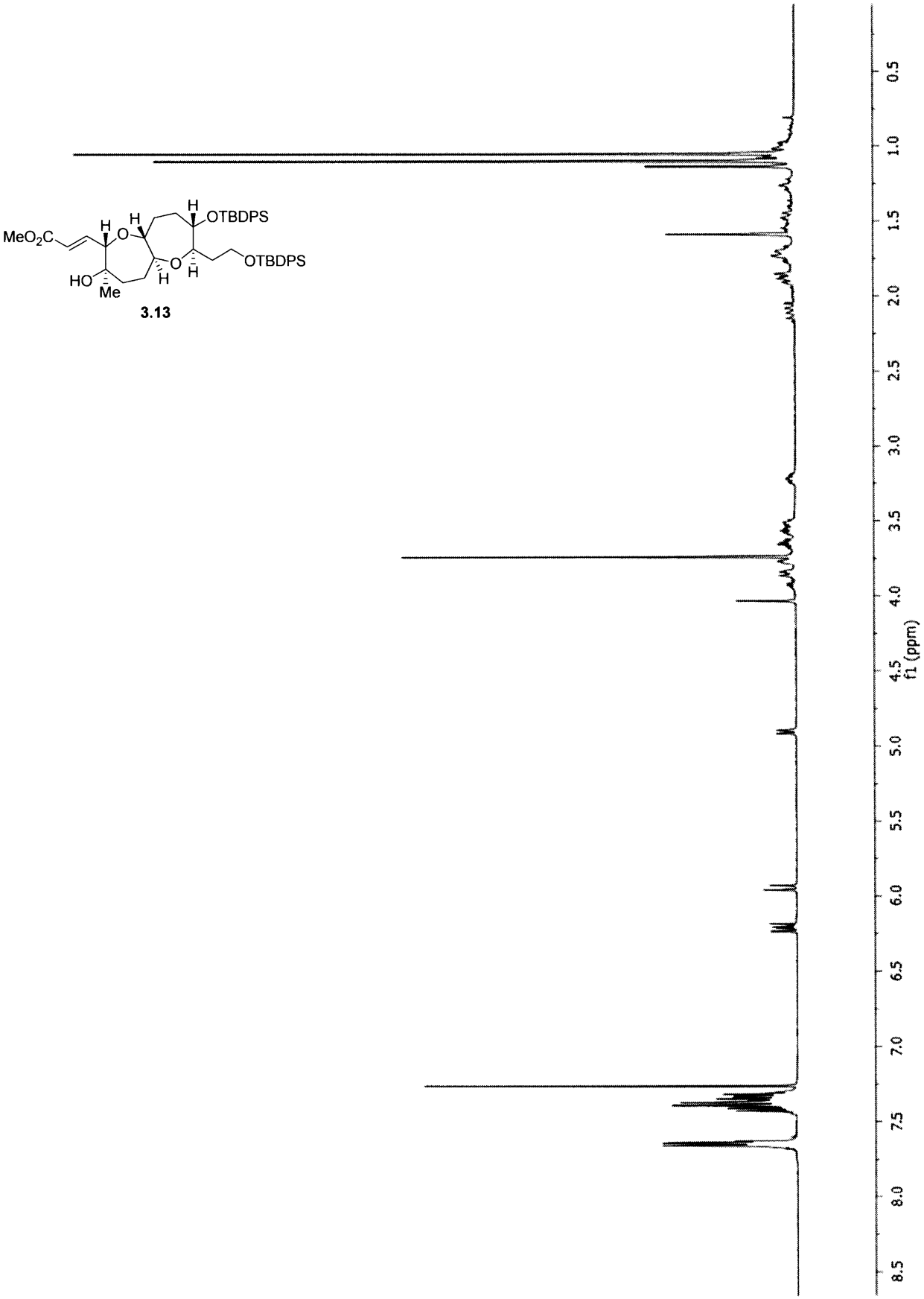
115
120
125
130
135
140
145
f1 (ppm)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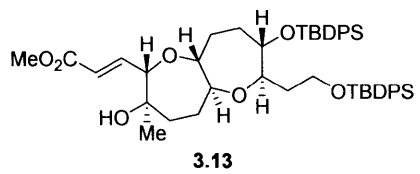
H
O
H
H
OTBDPS
OTBDPS
HO
Me
O
H
H
3.13
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


MeO2C
H
H
O
H
OTBDPS
O
H
H
OTBDPS
HO
Me

3.13

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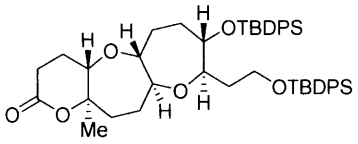
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)


H
OTBDPS
H
O
H
O
H
OTBDPS
O
O
Me

3.14

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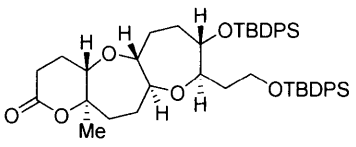
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
5.0
5.5
6.0
6.5
7.0
7.5
8.0


H
H
H
OTBDPS
O
O
O
H
H
OTBDPS
O
Me

3.14

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30
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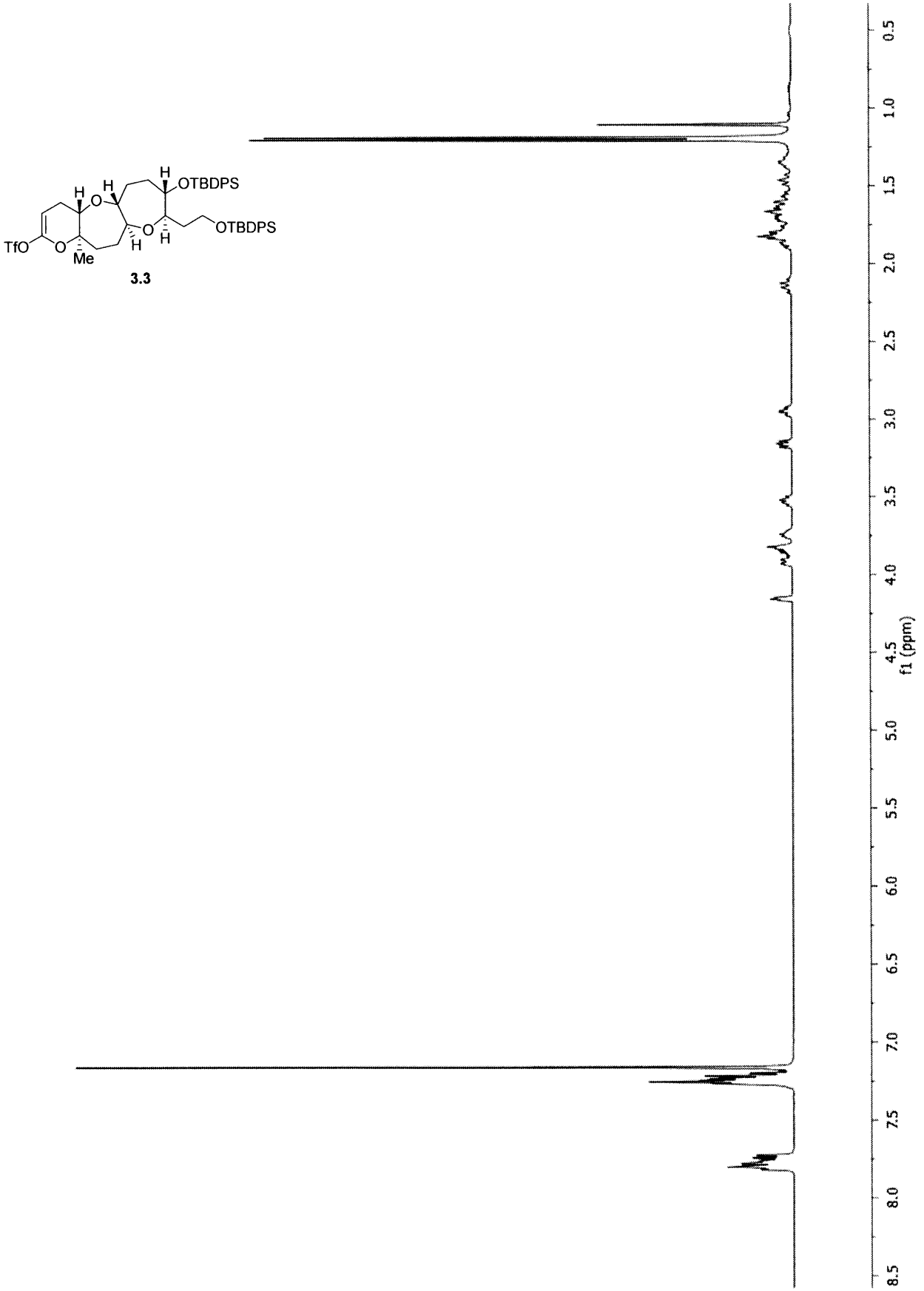
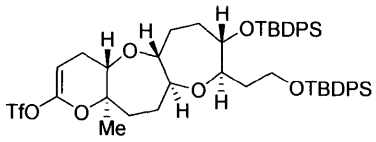
120
130
140
150
160
170
180
f1 (ppm)


H
H
H
OTBDPS
O
O
O
H
H
OTBDPS
TfO
O
Me
3.3
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


H
H
O
H
OTBDPS
TfO
O
Me
O
H
H
OTBDPS

3.3

10
15
20
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30
35
40
45
50
55
60
65
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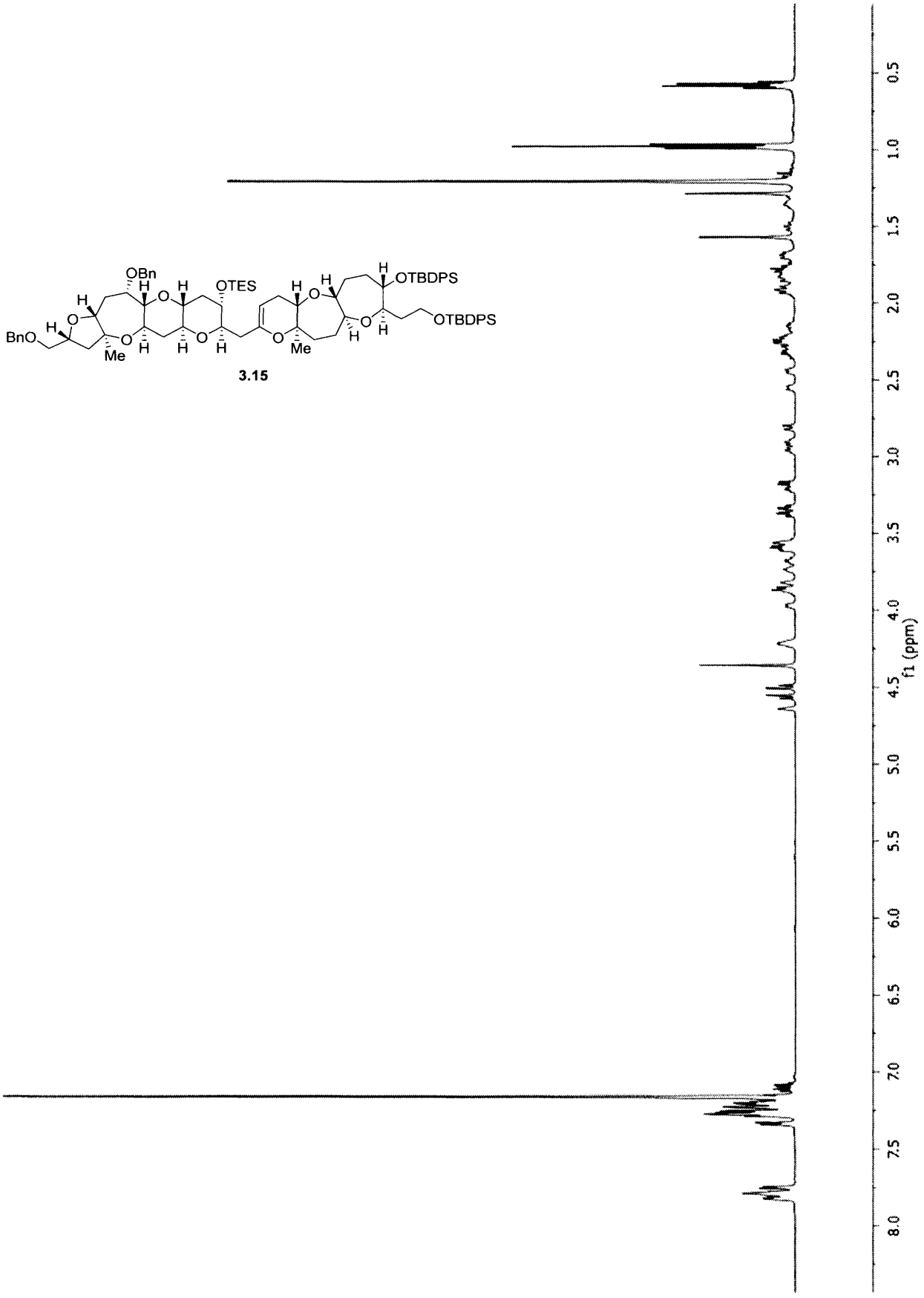
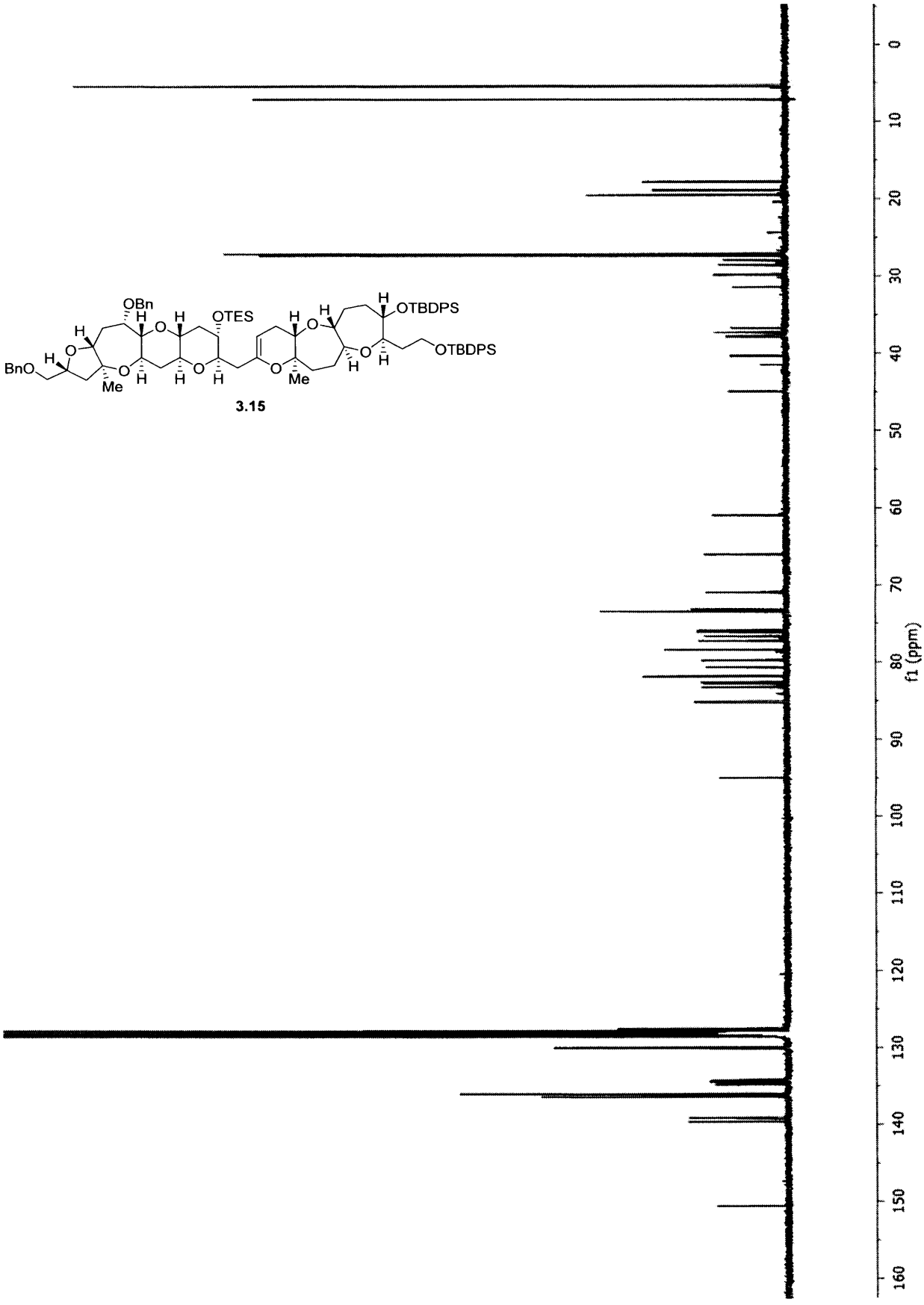
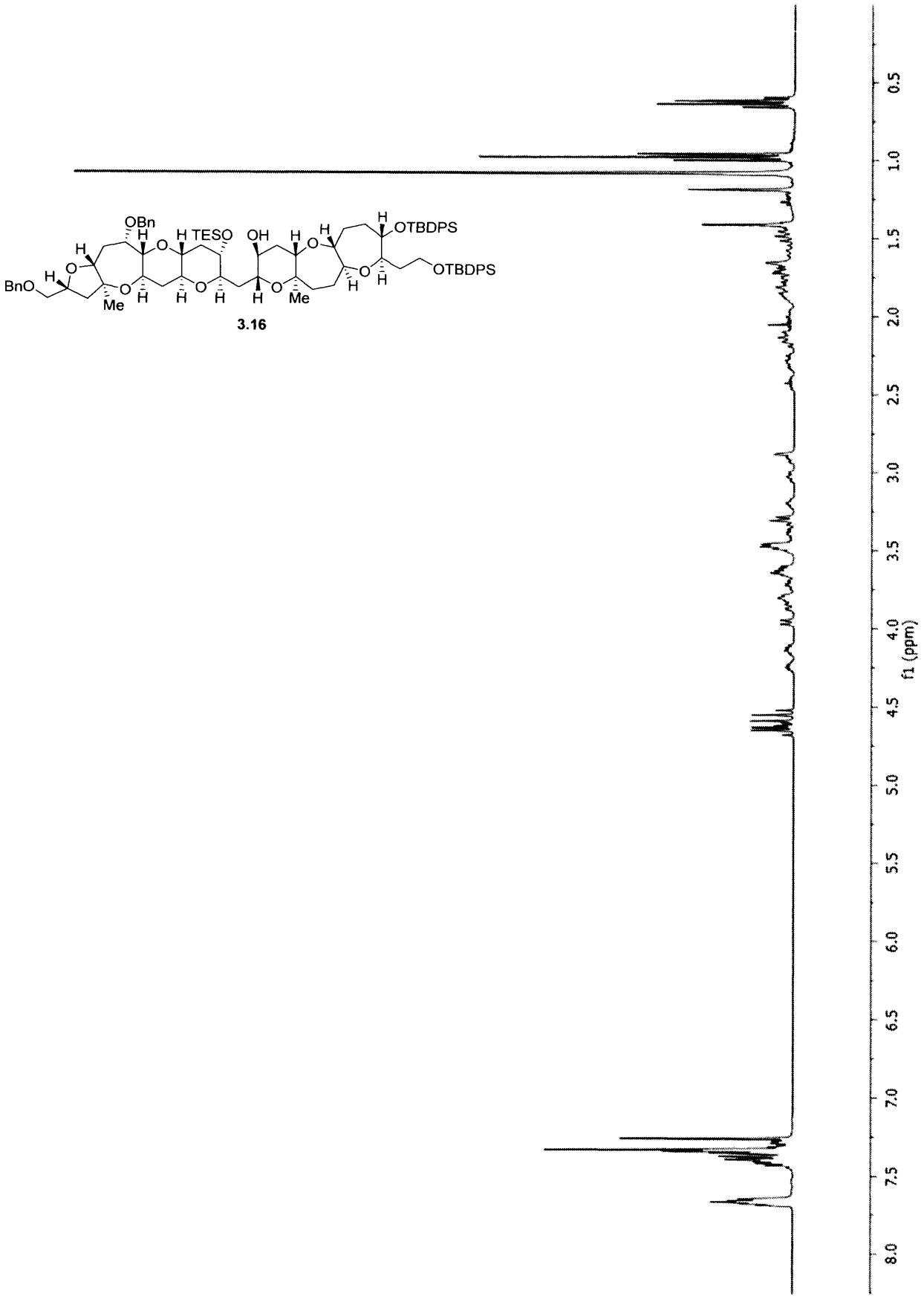
130
135
140
145
150
155
f1 (ppm)


OBn
OTES
OTBDPS
OTBDPS
BnO
Me
Me
3.15
f1 (ppm)


OBn
OTES
OTBDPS
OTBDPS
BnO
Me
Me
3.15
f1 (ppm)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H TESO
OH
OTBDPS
OTBDPS
BnO
Me
Me
3.16
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1.0
1.5
2.0
2.5
3.0
3.5
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4.5
5.0
5.5
6.0
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7.0
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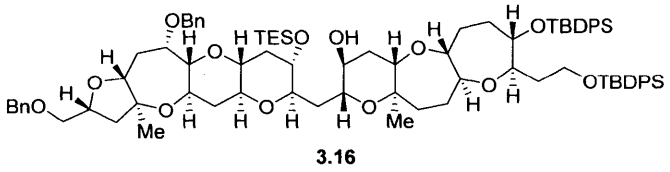
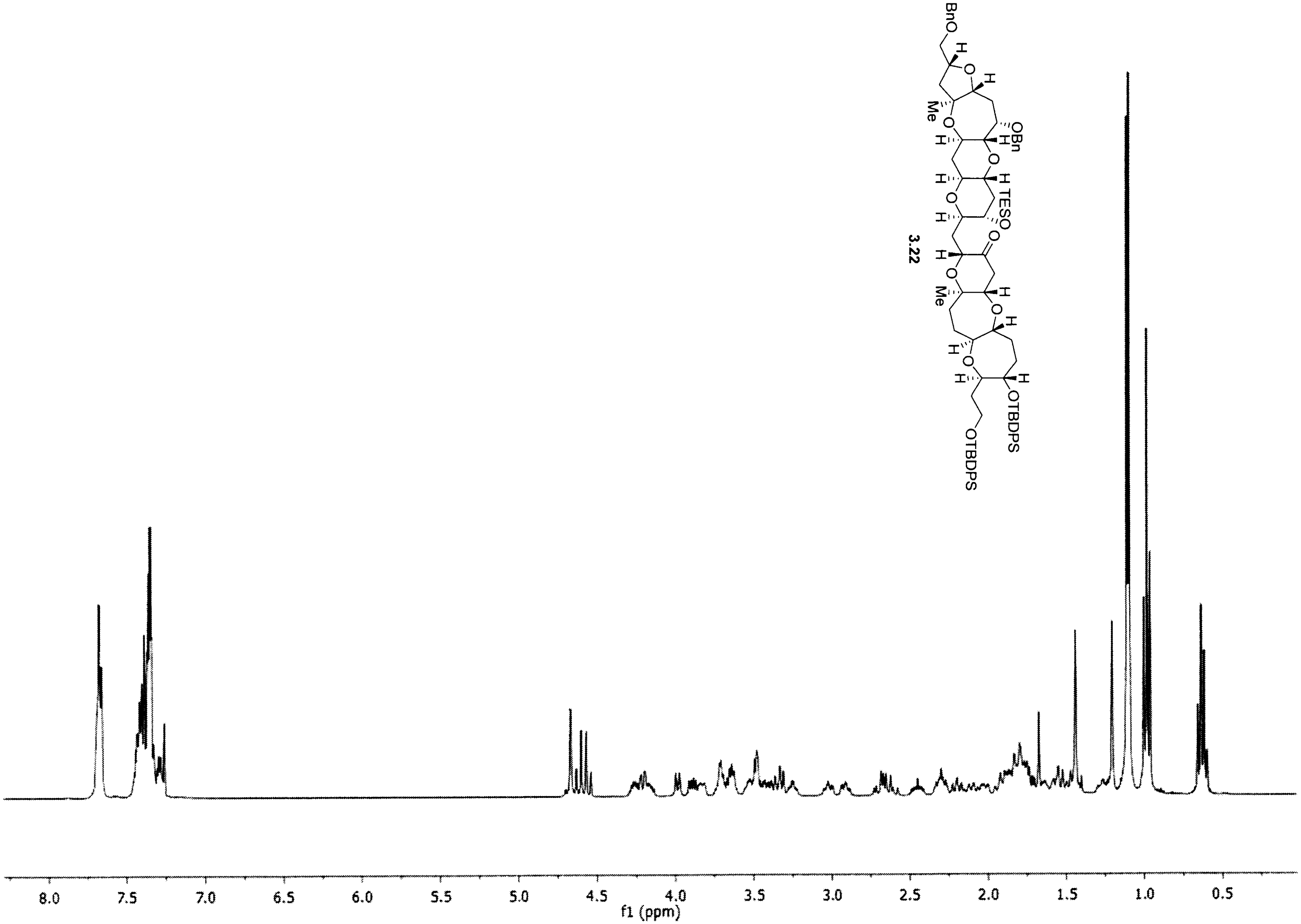
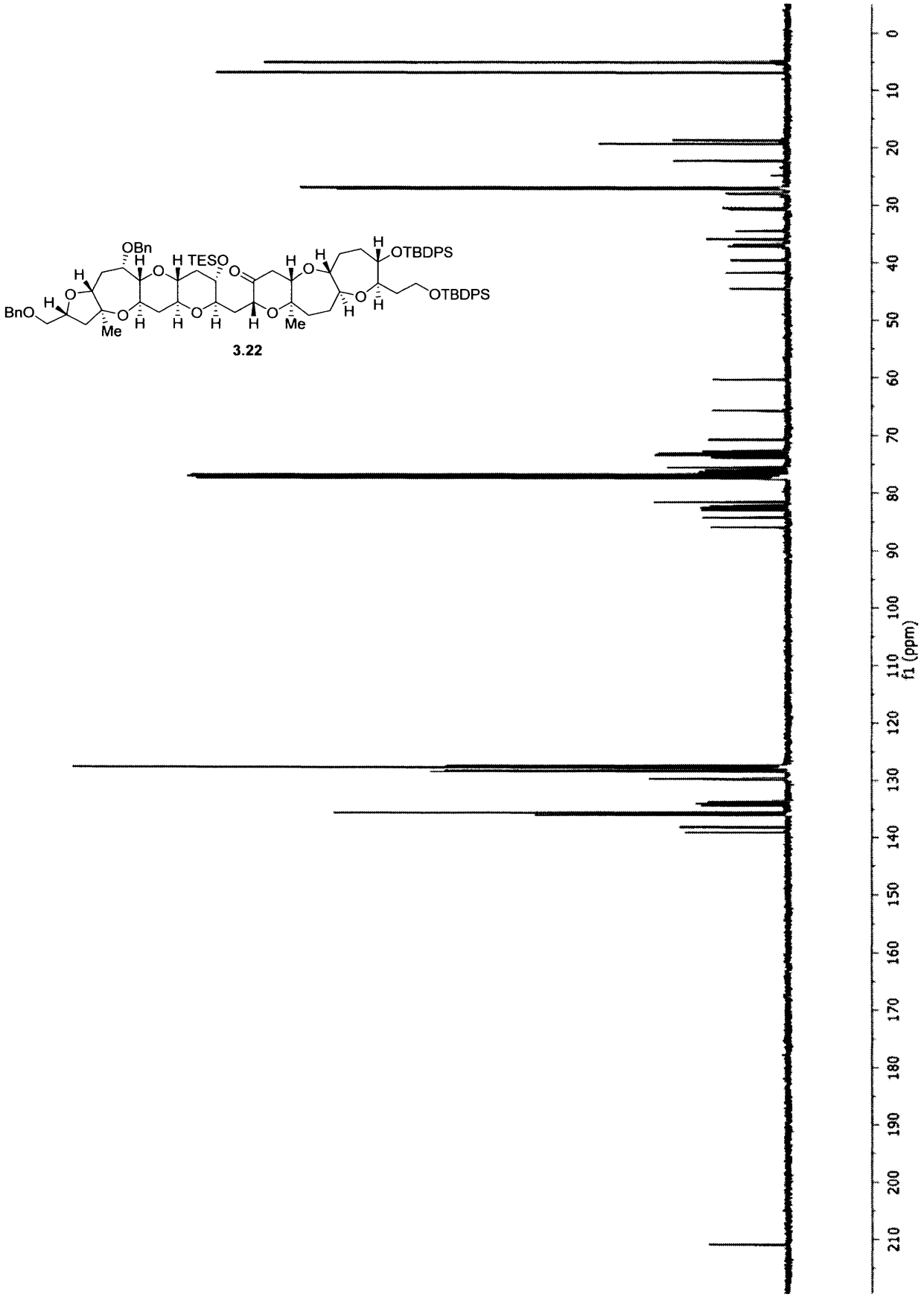
8.0
f1 (ppm)


OBn
H
H TESO
OH
H
H
H
OTBDPS
OTBDPS
BnO
H
O
O
H
H
O
H
H
O
H
O
H
Me
Me

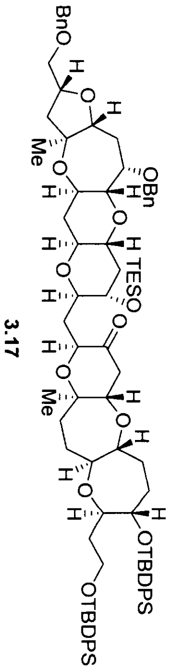
3.16

0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)

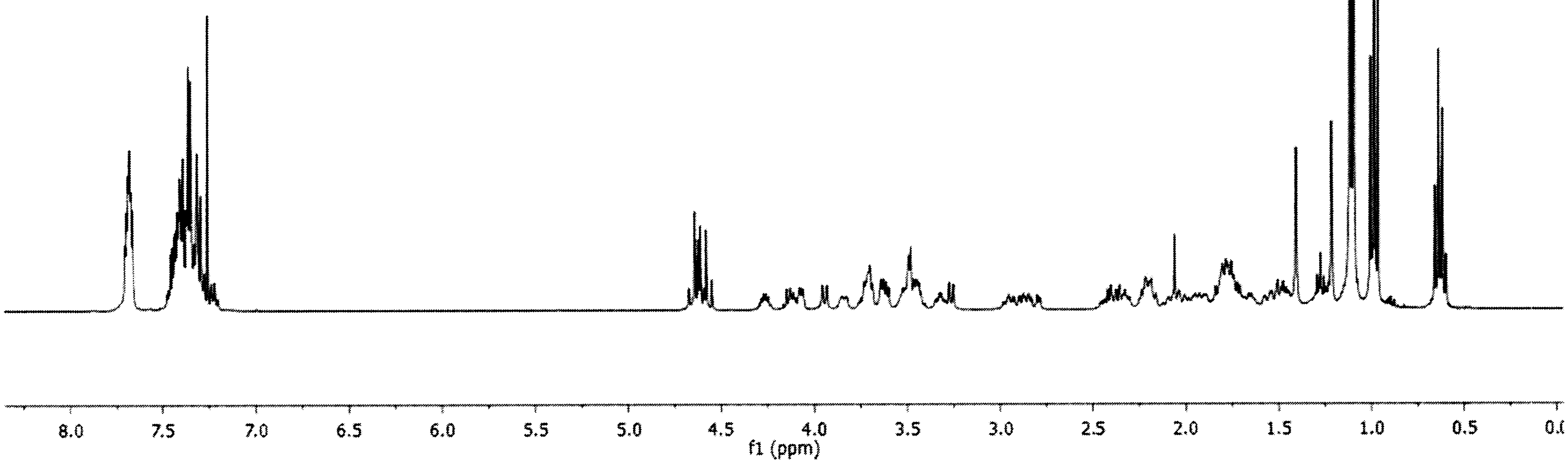

BnO
H
O
H
Me
O
OBn
H
H
O
H
H
TESO
O
H
H
O
H
O
Me
H
O
H
H
O
H
H
OTBDPS
OTBDPS
3.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

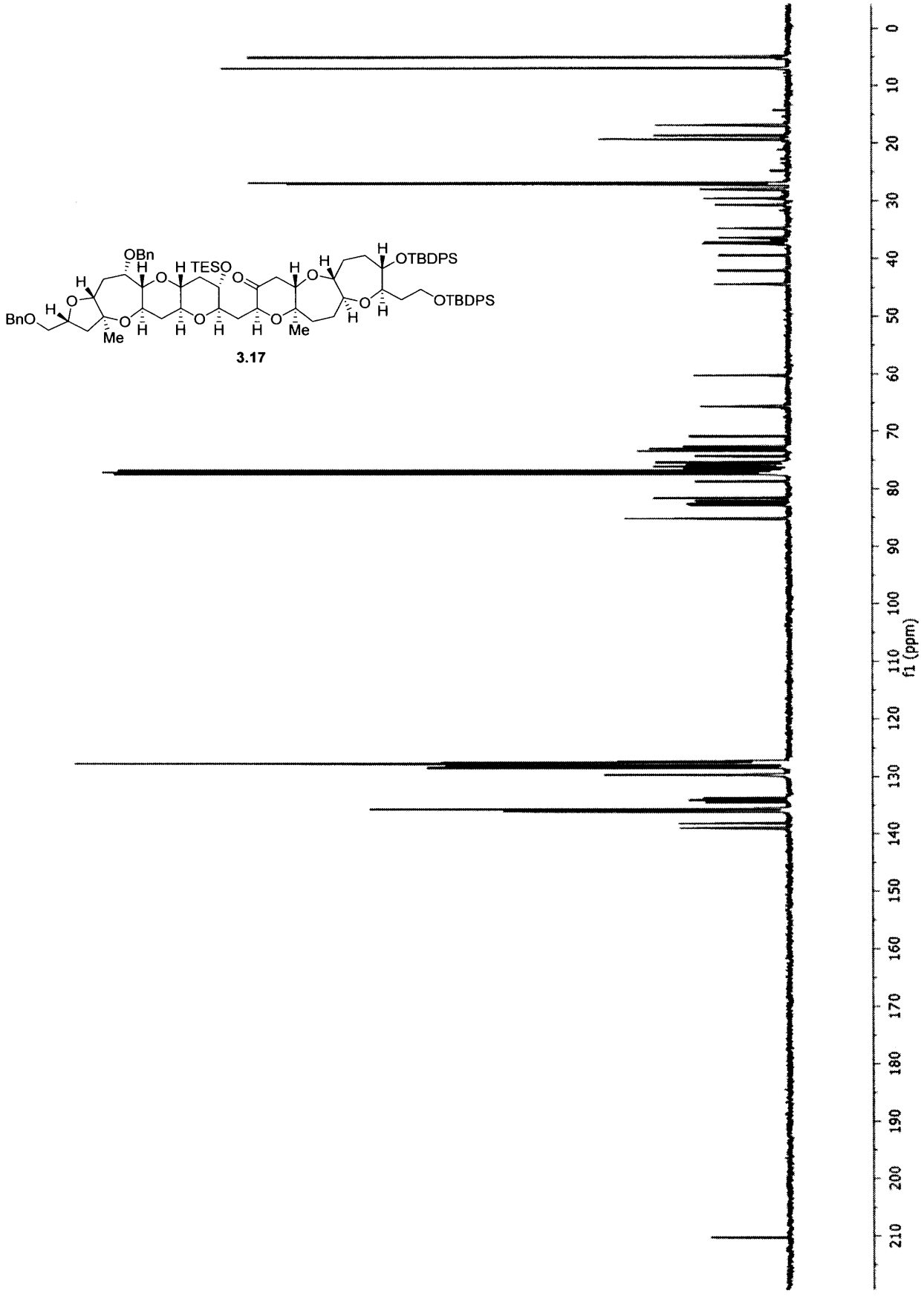


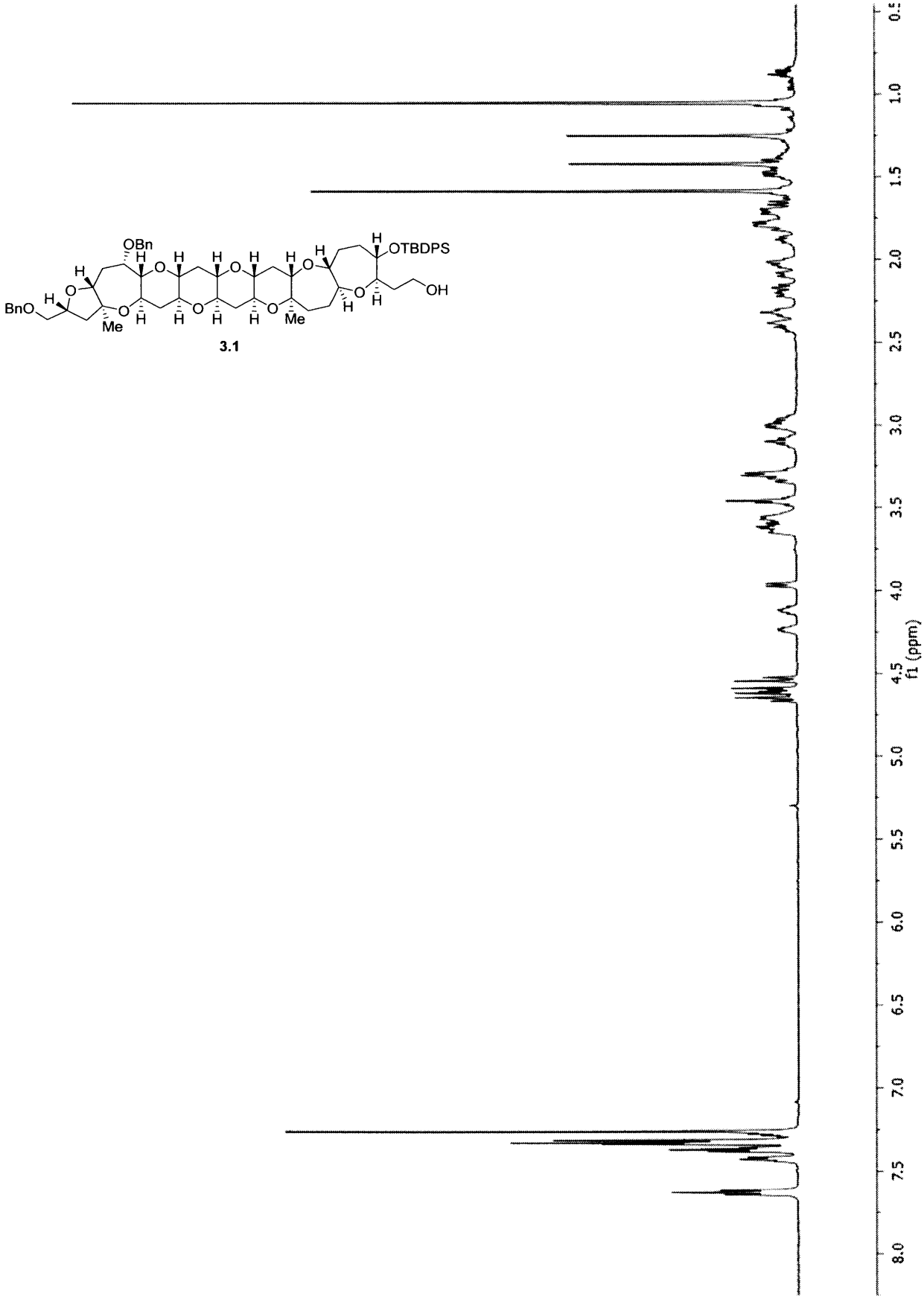
3.22


BnO
OBn
TESO
Me
OTBDPS
OTBDPS

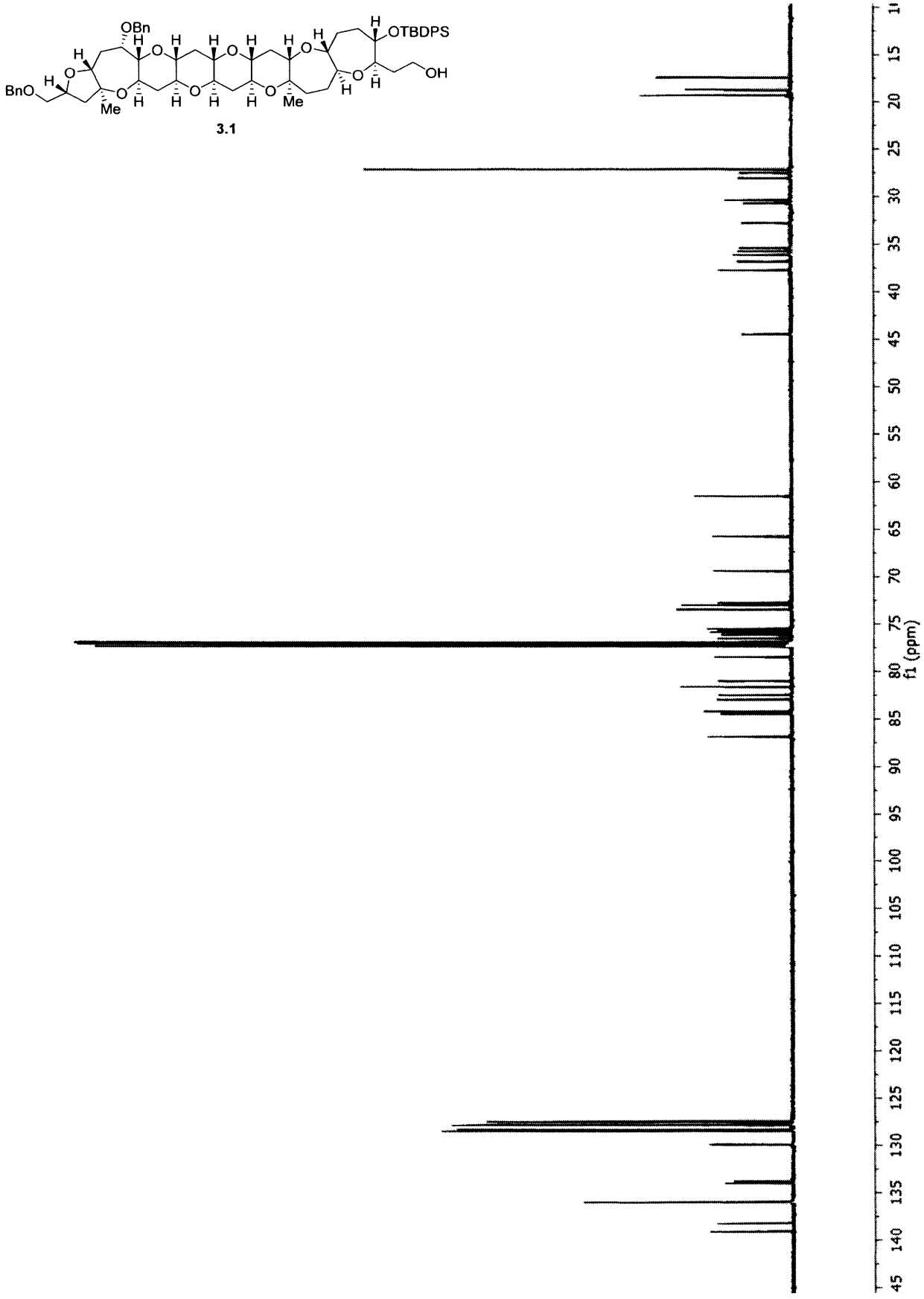
3.17

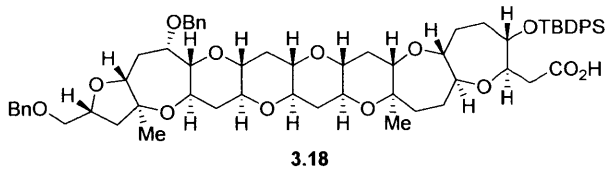

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OBn
H TESO
OTBDPS
OTBDPS
BnO
Me
Me
3.17
f1 (ppm)

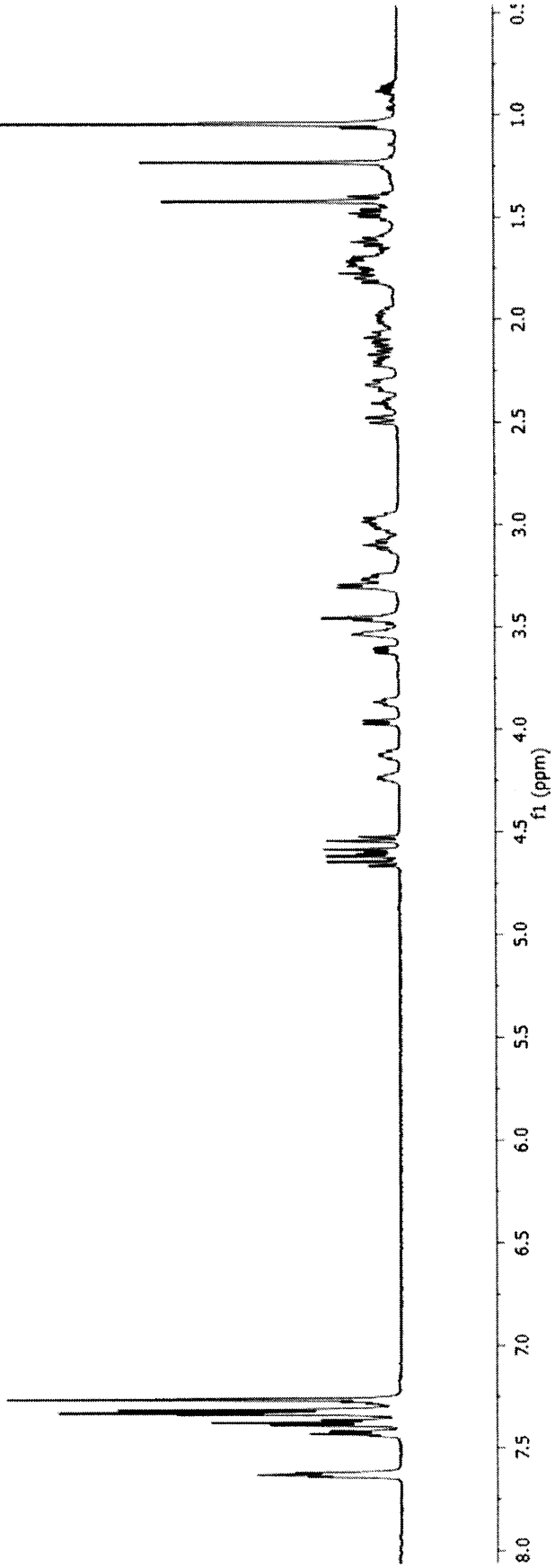


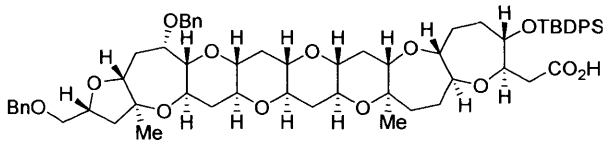
3.1


OBn
OTBDPS
OH
BnO
Me
Me
3.1
f1 (ppm)


OBn
OTBDPS
CO2H
BnO
Me
Me

3.18


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


OBn
OTBDPS
CO2H
BnO
Me
Me

3.18

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

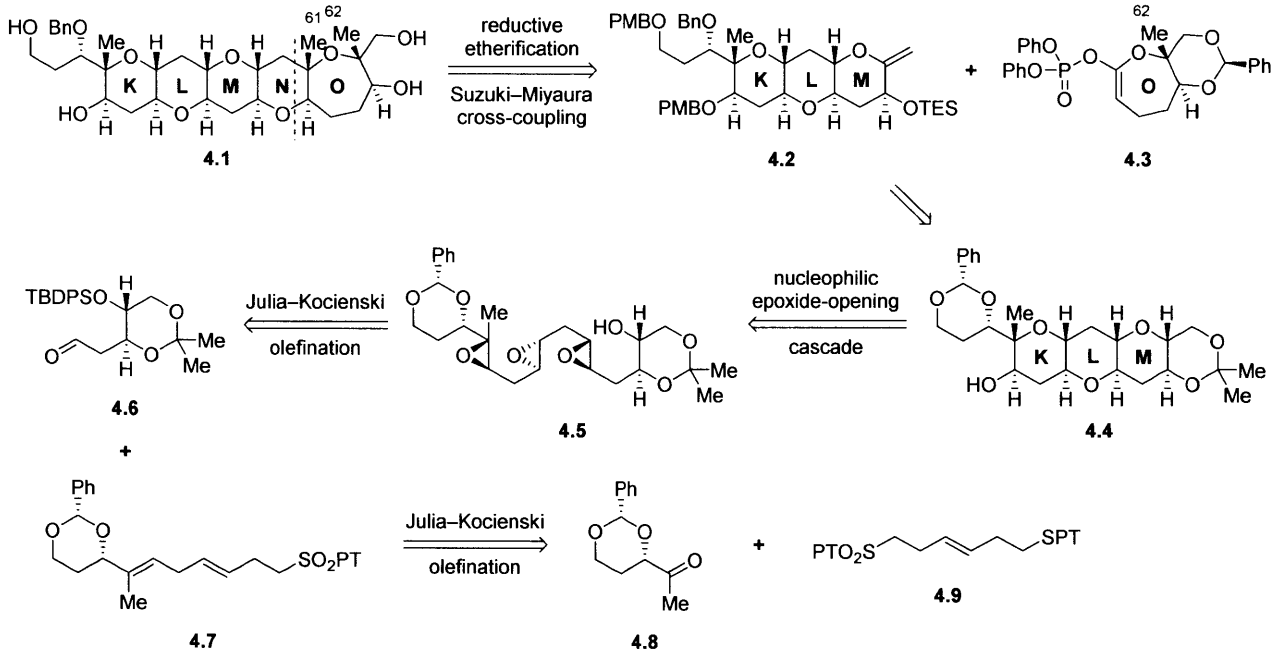
CHAPTER IV

Synthesis of the *KLMNO* Fragment of Gymnocin B

A. Retrosynthetic Analysis of *KLMNO* Fragment

In order to complete the eastern portion of gymnocin B, we envisioned a disconnection along the THP *N* ring of tetraol **4.1**, simplifying our synthetic targets to exocyclic methylene **4.2** and known ketene acetal phosphate **4.3**.[1] Encouraged by the synthesis of the *ABCDEFGH* fragment (Chapter III), we hoped to rely on a similar Suzuki–Miyaura cross-coupling and reductive etherification strategy to complete the polycyclic core of **4.1**.[2] Moreover, Me61 would be installed in a stereoselective fashion by taking advantage of the unique molecular framework encompassing the oxepane *O* ring. In turn, the *KLM* **4.2** could be derived from polyTHP **4.4**, a product of an epoxide-opening cascade of triepoxide **4.5**. Julia–Kocienski olefination[3] of aldehyde **4.6** (Chapter II, Scheme 2) and sulfone **4.7** would lead to **4.4**. Lastly, olefination between ketone **4.8** and mixed sulfide sulfone **4.9** would afford diene **4.7**.

Scheme 1. Retrosynthetic analysis of *KLMNO* fragment **4.1**.

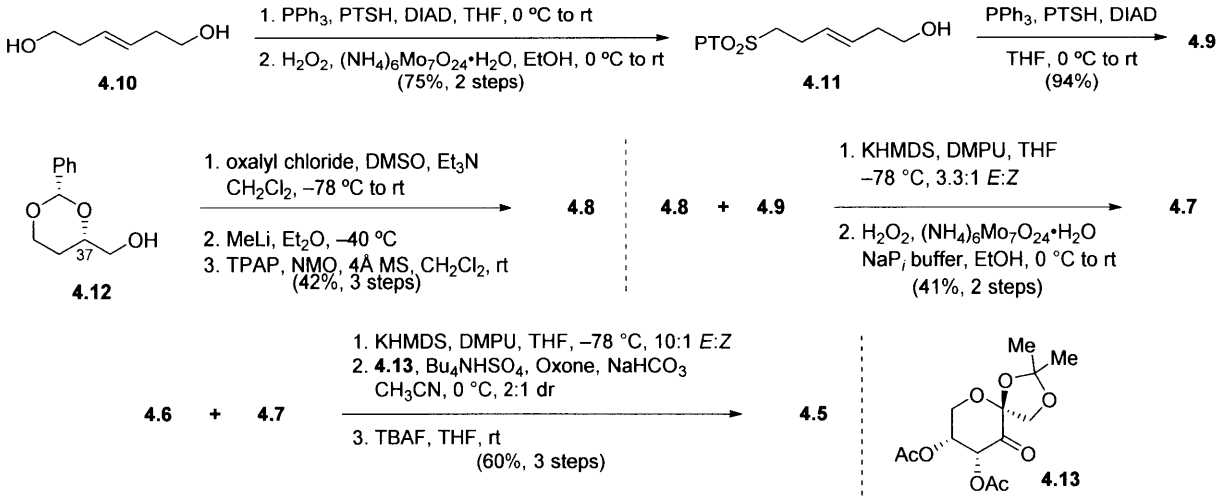


[1] Kuranaga, T.; Satake, M.; Baden, D. G.; Wright, J. L. C.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 4673.
[2] Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851.
[3] Blakemore, P. R.; Cole. W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

B. Synthesis of *KLM* Fragment

The synthesis of **4.1** commenced with known enediol[4] **4.10** as depicted in Scheme 2. Monofunctionalization of **4.10** was achieved via Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol, followed by selective sulfur oxidation to afford sulfone **4.11**. Another Mitsunobu reaction completed the synthesis of sulfide **4.9**. The ketone coupling partner was accessed from known alcohol **4.12**[5] with pre-installed C37 stereocenter. An oxidation-alkylation-oxidation sequence furnished methyl ketone **4.8**. Julia–Kocienski olefination of **4.8** and **4.9** proceeded with moderate *E*:*Z* ratio of the newly formed trisubstituted alkene. Attempts to use an LDA/$CeCl_3$ combination[6] resulted in a 1:1.4 ratio of *E*:*Z* isomers. Subsequent sulfur oxidation under buffered condition delivered sulfone **4.7**. Julia–Kocienski olefination between **4.7** and aldehyde **4.6** (Chapter II, Scheme 2) proceeded uneventfully with a 10:1 ratio of *E*:*Z* isomers. Asymmetric Shi epoxidation[7] with activated ketone **4.13**,[8] followed by desilylation, afforded triepoxy alcohol **4.5** with 2:1 dr.

Scheme 2. Synthesis of triepoxy alcohol **4.5**.

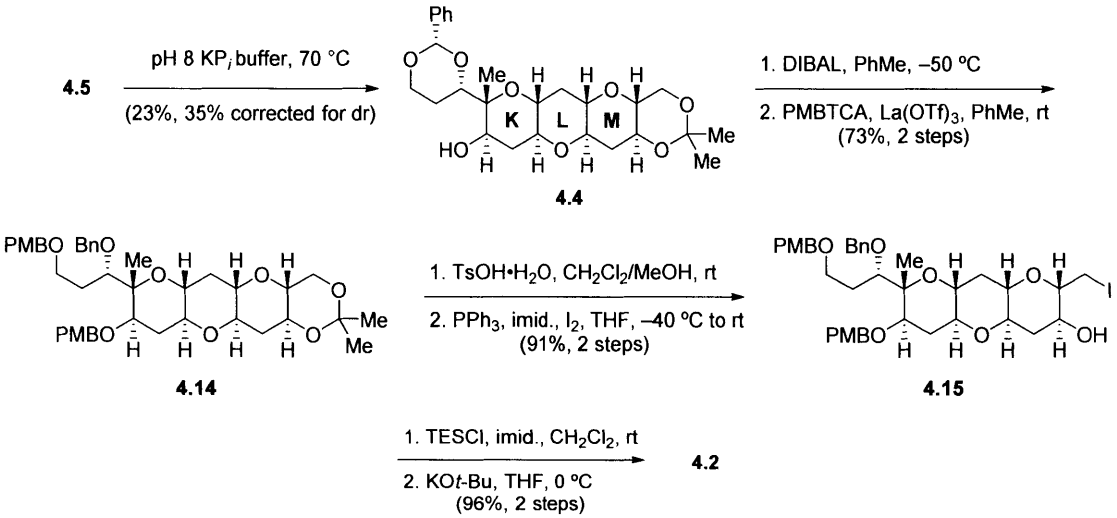


[4] McNaughton, B. R.; Bucholtz, K. M.; Camaaño-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733.
[5] Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896.
[6] Fuwa, H.; Ishigai, K.; Hashizume, K.; Sasaki, M. *J. Am. Chem. Soc.* **2012**, *134*, 11984.
[7] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
[8] Wang, B.; Wu, X.-Y.; Wong, O. A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986.

With cascade precursor **4.5** in hand, we began our investigation into the key epoxide-opening cascade. Initial pH screening revealed that the benzylidene and dimethyl acetals did not tolerate aqueous acidic conditions. In addition, elevated temperatures were necessary for sufficient solubility of **4.5** in aqueous media. After considerable experimentation, it was determined that subjecting **4.5** to pH 8 aqueous phosphate buffer at 70 °C delivered tricycle **4.4** at an optimal yield (35% yield corrected for dr, 70% yield per ring formation) as shown in Scheme 3. Tetracycle **4.4**, containing the *KLM* rings found in gymnocin B, was synthesized in 10 steps longest linear sequence.

Our next task was to elaborate the *KLM* fragment in preparation for the Suzuki–Miyaura cross-coupling step. To this end, chemo- and regioselective reduction of benzylidene acetal in **4.4** revealed a 1,5-diol, which was protected as bisPMB ether **4.14**. Acetonide removal under acidic conditions liberated a diol, whose primary alcohol underwent selective iodination to afford iodide **4.15**. Silylation of the secondary alcohol and elimination of the alkyl iodide furnished exocyclic methylene **4.2** in 16 steps longest linear sequence.

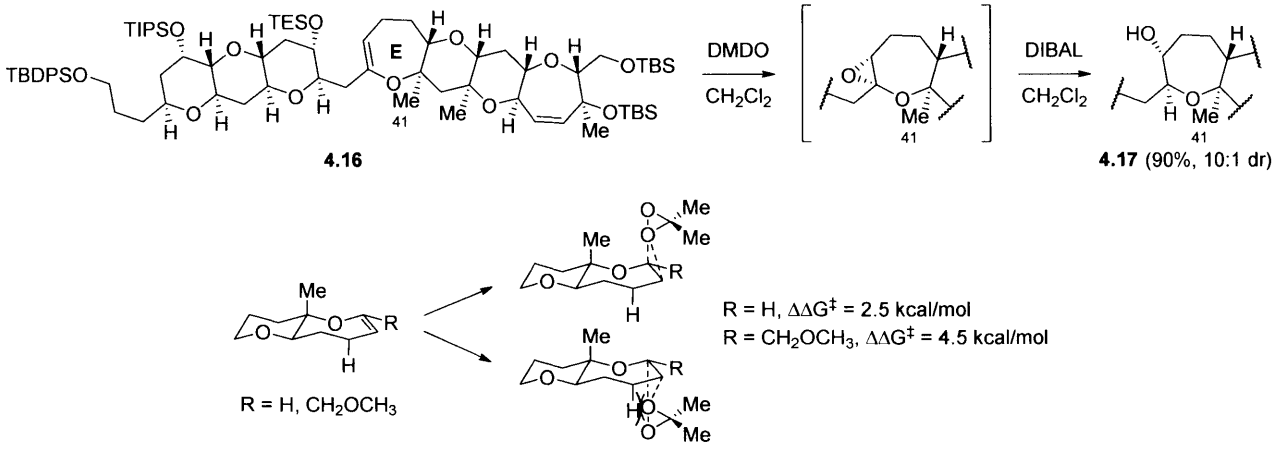
Scheme 3. Synthesis of *KLM* fragment **4.2**.



C. Synthesis of *KLMNO* Fragment

Our next challenge was to construct the highly decorated *O* ring. To accomplish this, we were inspired by Rainier's total synthesis of gambierol.[9] Their elaboration of oxepene *E* ring is shown in Scheme 4. Epoxidation of glycal **4.16** with DMDO proceeded preferentially from the bottom face in spite of the presence of Me41 residing at a nearby ring junction. Nevertheless, subsequent reduction with DIBAL furnished the desired alcohol **4.17** in good yield and dr. Computational studies showed that steric demand exerted by pseudoaxial allylic hydrogen governed the trajectory of DMDO epoxidation.[10] This observation was due to the constraint imposed by the unique molecular framework.

Scheme 4. Elaboration of gambierol *E* ring by Rainier and computational studies.

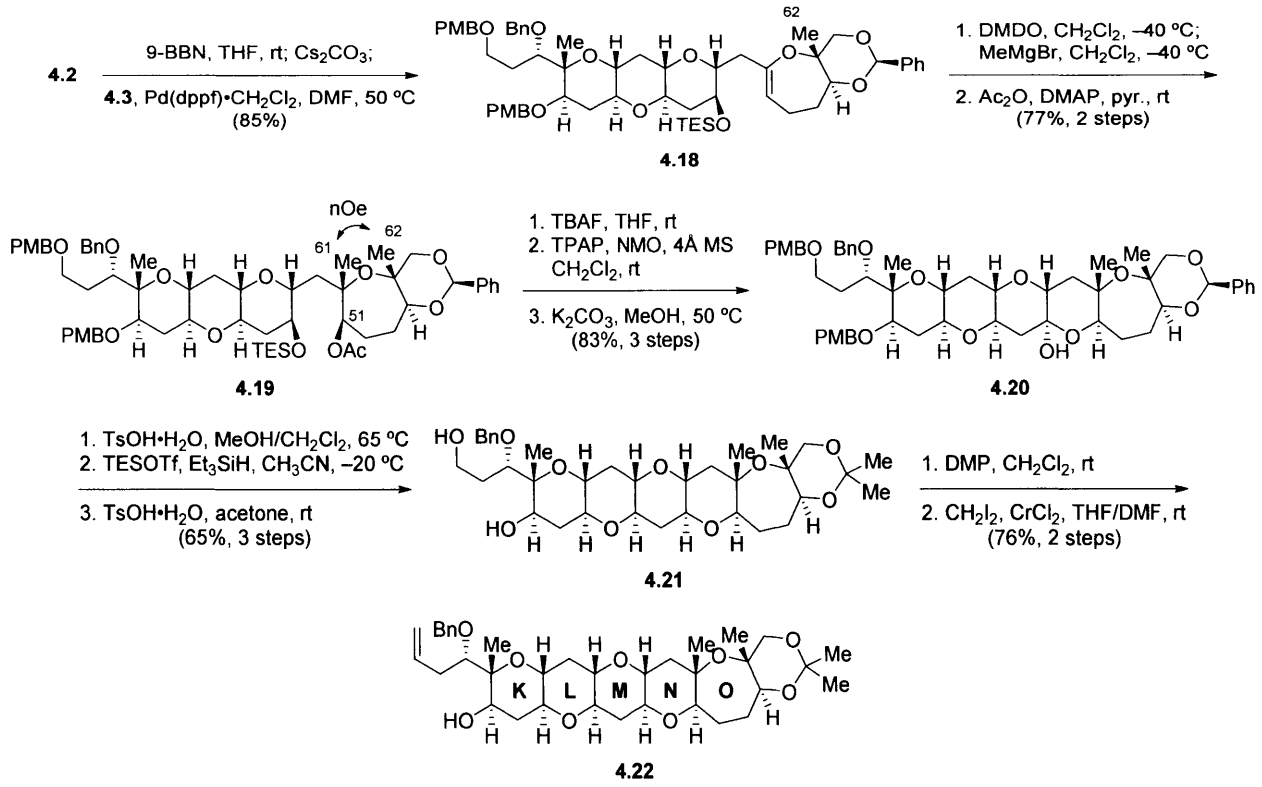


In order to implement our strategies for *O* ring elaboration, we first investigated the crucial Suzuki-Miyaura fragment coupling step. To this end, hydroboration of **4.2** with 9-BBN, followed by cross-coupling with phosphate **4.2**,[1] furnished desired adduct **4.18** in good yield (Scheme 5). Due to the similarity in molecular framework, we posited that glycal **4.18** would undergo the same transformation as glycal **4.16**, while retaining a high level of selectivity during the epoxidation

[9] Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.
[10] Orendt, A. M.; Roberts, S. W.; Rainier, J. D. *J. Org. Chem.* **2006**, *71*, 5565.

step. However, instead of reduction of epoxide with DIBAL, incorporation of an alkylating reagent would directly install Me62 diastereoselectively by relying on directed addition as observed in Rainier's synthesis. Thus, glycal **4.18** underwent DMDO epoxidation followed by treatment with methylmagnesium bromide. Indeed, after acylation of the newly formed alcohol, the *syn* relationship of Me61 and Me62 was confirmed by NOE experiments of acetate **4.19**. The choice of alkylating agents was critical as trimethylaluminum resulted in lower yields. In a one-pot operation, two stereocenters were set, including C51 and formidable pseudoaxial methyl groups flanking the *O* ring.[11]

Scheme 5. Synthesis of *KLMNO* fragment coupling partner**4.22**.



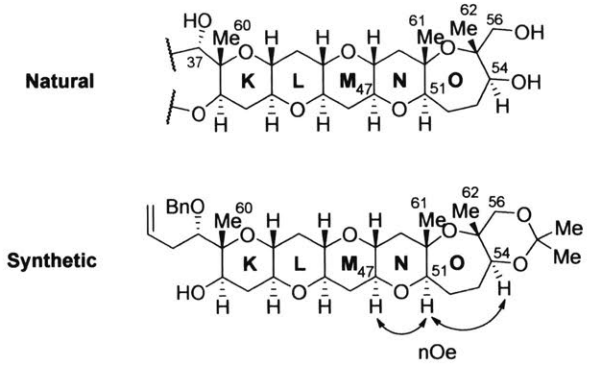
With the fully elaborated *O* ring in hand, we continued the completion of *KLMNO* fragment **4.1**. To this end, desilylation, alcohol oxidation, and deacylation furnished hemiacetal **4.20**. Our

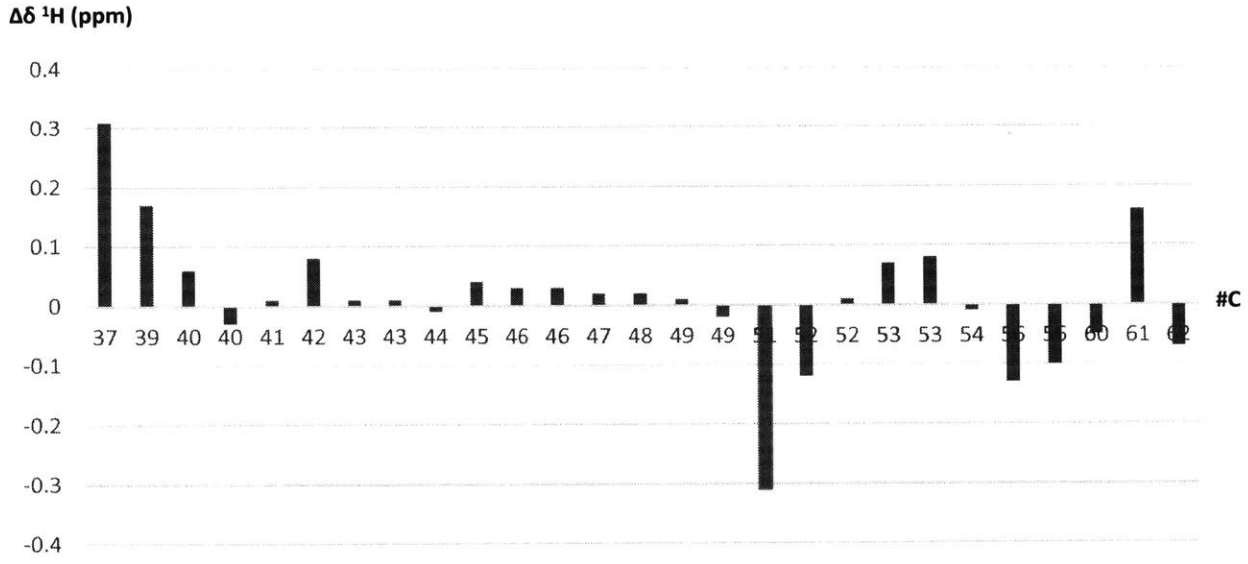
[11] Tsukano, C.; Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4617.

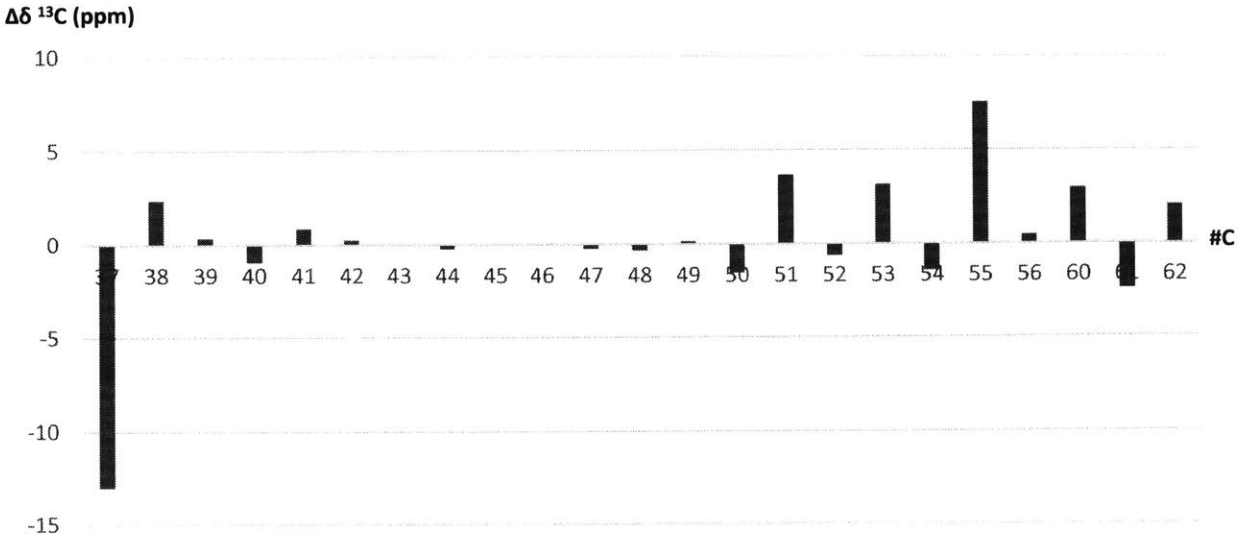
previous studies had shown that benzylidene acetal could lead to complication during the reductive cyclization. Consequently, **4.20** underwent acid-catalyzed acetal removal. Subsequent reductive cyclization proceeded smoothly using a combination of TESOTf and TESH with acetonitrile as the solvent. The 1,3-diol moiety in the cyclized product was selectively protected as an acetonide, giving rise to diol **4.21**. Partial oxidation of 1,5-diol **4.21**, followed by mild Takai–Utimoto olefination, furnished olefin **4.22**. As expected, attempts to use basic Wittig olefination resulted in rapid elimination of benzyl alcohol and exclusive formation of conjugated diene.

As a comparison, the differences in ^{1}H and ^{13}C chemical shifts of synthetic **4.22** vs. natural product are shown in Figure 1. Good agreement was observed throughout the rigid polyTHP *KLMN* core, including the newly formed C47 stereocenter during the reductive cyclization. As expected, significant deviation arose at the edges of the fragment, especially around flexible oxepane *O* ring where the 1,3-diol is protected as an acetonide. One alarming discrepancy in chemical shifts is located at C51, whose stereochemistry was derived from the DMDO epoxidation/methylation step. Thus, nOe experiments were conducted to confirm the C51 stereochemical configuration. As shown in Figure 1, C51 indeed contains the correct stereochemistry, thus, highlighting the excellent selectivity during the DMDO epoxidation.

Figure 1. Chemical shift comparison between natural and synthetic *KLMNO* fragments







In conclusion, the *KLMNO* hydroxy olefin **4.22** was synthesized in 27 steps longest linear sequence. The synthesis featured a nucleophilic epoxide-opening cascade of a highly functionalized substrate to assemble *KLM* rings found in gymnocin B. Suzuki–Miyaura cross-coupling incorporated the *O* ring, which was fully elaborated by the epoxidation/alkylation strategy. Reductive etherification completed the multi-cyclic *KLMNO* core, which was further functionalized to olefin **4.22**, another substrate for the final fragment coupling step.

D. Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Dichloromethane, THF, Et_2O, toluene, DMSO, DMF, and trimethylamine, pyridine, acetonitrile, and benzene were purified via an SG Water USA solvent system. $Ti(O\textit{i}\text{-}Pr)_4$, HMPA, and DMPU were distilled from CaH_2 and stored over molecular sieves under argon. Reactions in water used deionized water without further purification. All other reagents and solvents were used as obtained, without further purification.

Chiral ketone **4.13**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[12]

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), CAM, $KMnO_4$, or *p*-anisaldehyde stain. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh) or Biotage Isolera flash purification system on SNAP KP-Sil, HP-Sil, or Ultra columns. Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ or C_6D_6, unless otherwise noted, on a Varian Inova-125 MHz spectrometer, a Bruker AVANCE-100 MHz spectrometer, or a Bruker AVANCE-150 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard residual $CHCl_3$ in $CDCl_3$ (7.26 ppm) or C_6HD_5 in C_6D_6 (7.16 ppm). Data are reported as follows: chemical shifts, multiplicity (s =singlet, d =doublet, t = triplet, q = quartet, and m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm), on the δ scale.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR and are reported in terms of frequency absorption (cm^{-1}). High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumental Facility. Optical rotations were measured on a Jasco Model 1010 digital polarimeter at 589 nm.

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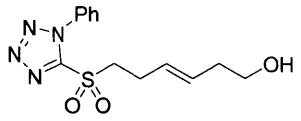
[12] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.



4.11

Sulfone 4.11: PPh_3 (29.8 g, 114 mmol) and 1-phenyltetrazole-5-thiol (20.25 g, 114 mmol) were added to a solution of diol **4.10** (12 g, 103 mmol) in THF (90 mL). The resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (19.8 g, 17.8 mL, 114 mmol) was added slowly over 15 min to provide a pale yellow solution. The reaction was stirred at 0 °C for 10 min and warmed to rt over 45 min. It was quenched by addition of brine (30 mL). The aqueous layer was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude sulfide as a yellow oil (R_f = 0.29 (50% EtOAc in hexanes)). The crude material was carried onto the next step without further purification.

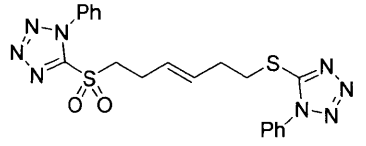
The crude sulfide was dissolved in EtOH (150 mL), and the resulting solution was cooled to 0 °C. 30% $H_2O_{2(aq)}$ (17.5 g, 52 mL, 515 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25.5 g, 20.6 mmol) were then added. The reaction was stirred vigorously and allowed to warm to rt overnight. The reaction was quenched by addition of brine (50 mL). The aqueous layer was separated and extracted with EtOAc (3×80 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 90% EtOAc in hexanes) to afford **4.11** as a white solid (24 g, 78 mmol, 75% over two steps, R_f = 0.29 (50% EtOAc in hexanes)).

IR (ATR): 3393, 3062, 2925, 1594, 1497, 1338, 1149, 1043, 970, 761, 733, 687 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.67 (m, 2H), 7.66–7.58 (m, 3H), 5.66–5.52 (m, 2H), 3.84–3.80 (m, 2H), 3.65 (app q, J = 6.0 Hz, 2H), 2.76–2.69 (m, 2H), 2.28 (app qd, J = 6.3, 0.8 Hz, 2H), 1.49–1.42 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 153.6, 133.1, 131.7, 130.8, 129.9, 127.5, 125.2, 61.9, 55.8, 35.9, 25.5.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{16}N_4O_3S$ $[M+H]^+$: 309.1016, found 309.1018.



4.9

Sulfide 4.9: PPh_3 (22 g, 83.8 mmol) and 1-phenyltetrazole-5-thiol (14.9 g, 83.8 mmol) were added to a solution of sulfone **4.11** (23.5 g, 76.2 mmol) in THF (80 mL). The resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (14.6 g, 13.2 mL, 83.8 mmol) was added over 5 min to provide a yellow solution. The reaction was stirred at 0 °C for 10 min and warmed to rt over 45 min. It was quenched by addition of brine (30 mL). The aqueous layer was separated and extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over

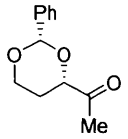
Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 10% EtOAc in dichloromethane to remove byproduct from diisopropyl azodicarboxylate and then gradient 5% to 55% EtOAc in hexanes) to afford **4.9** as a colorless oil (33.4 g, 71.3 mmol, 94%, R_f = 0.20 (30% EtOAc in hexanes)).

IR (ATR): 3057, 2922, 2851, 1595, 1497, 1340, 1150, 1014, 972, 759, 734, 685 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.65 (m, 2H), 7.65–7.51 (m, 8H), 5.64 (app dt, *J* = 15.4, 6.6 Hz, 1H), 5.56 (app dt, *J* = 15.4, 6.4 Hz, 1H), 3.80–3.73 (m, 2H), 3.42 (t, *J* = 7.2 Hz, 2H), 2.72–2.64 (m, 2H), 2.56 (app q, *J* = 7.2 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 154.2, 153.5, 133.8, 133.1, 131.7, 131.0, 130.3, 123.0, 129.9, 127.5, 125.2, 124.0, 55.6, 32.8, 32.0, 25.4.

HR-MS (ESI) *m/z* calcd for $C_{20}H_{20}N_8O_2S_2$ $[M+H]^+$: 469.1223, found 469.1222.



SI-29

Ketone 4.8: To a solution of oxalyl chloride (23.53 g, 15.9 mL, 185 mmol) in CH_2Cl_2 (300 mL) at –78 °C was added DMSO (18.1 g, 16.5 mL, 232 mmol) over 20 min. The resulting solution was stirred at –78 °C for 30 min, at which point a solution of alcohol **4.12** (30 g, 154 mmol) in CH_2Cl_2 (90 mL) was added via cannulation. After stirring at –78 °C for 1 h, triethylamine (62.5 g, 86 mL, 618 mmol) was added, and the solution was allowed to warm to rt over 2 h. The reaction was quenched by addition of sat. $NaHCO_{3(aq)}$ (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude aldehyde (R_f = 0.43, 50% EtOAc in hexanes), which was carried onto the next step without further purification.

The crude aldehyde was dissolved in Et_2O (250 mL) and cooled to –40 °C. MeMgBr (3 M in Et_2O, 77 mL, 232 mmol) was added over 15 min, and the resulting solution was stirred at –40 °C for 1 h. The reaction was quenched by addition of sat. $NH_4Cl_{(aq)}$ (90 mL) at –40 °C and allowed to warm to rt over 30 min. The aqueous layer was separated and extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude alcohol (R_f = 0.49, 50% EtOAc in hexanes), which was carried onto the next step without further purification.

To a solution of the crude alcohol in CH_2Cl_2 (150 mL) were added 4 Å molecular sieves (15 g), *N*-methylmorpholine *N*-oxide (45.1 g, 385 mmol), and tetrapropylammonium perruthenate (1.08 g, 3.08 mmol) at rt. After stirring at rt for 2 h, the slurry was filtered through a plug of celite, washed with CH_2Cl_2 (3×50 mL), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 55% EtOAc in hexanes) to afford ketone **4.8** as a colorless oil (13.4 g, 65 mmol, 42% over three steps, R_f = 0.46 (30% EtOAc in hexanes)).

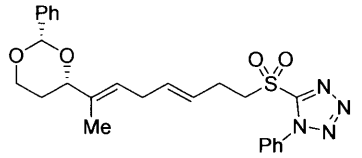
$[\alpha]^{22}_D = -49.56$ (c = 1.29, $CHCl_3$)

IR (ATR): 2974, 2930, 2860, 1718, 1356, 1240, 1127, 1100, 1026, 994, 752, 669 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2H), 7.43–7.35 (m, 3H), 5.57 (s, 1H), 4.35 (ddd, J = 11.5, 5.0, 1.4, 1H), 4.30 (dd, J = 11.5, 1.4, 1H), 4.02 (td, J = 11.9, 2.8, 1H), 2.31 (s, 3H), 1.99–1.89 (m, 1H), 1.88–1.81 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 138.1, 129.2, 128.5, 126.2, 100.1, 81.7, 67.0, 27.4, 26.0.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{14}O_3$ $[M+NH_4]^+$: 224.1281, found 224.1287.



4.7

Sulfone 4.7: To a solution of ketone **4.8** (10.7 g, 52 mmol) and sulfone **4.9** (23.4 g, 50 mmol) in THF (100 mL) was added DMPU (35.8 g, 35 mL, 200 mmol). The resulting solution was cooled to –78 °C. A solution of KHMDS (10.4 g, 52 mmol) in THF (60 mL) was added over 15 min via cannulation. The reaction mixture was stirred at –78 °C for 30 min, at which point the reaction was quenched by addition of brine (50 mL) and allowed to warm to rt over 1 h. The aqueous layer was separated and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude diene sulfide (R_f = 0.57 (30% EtOAc in hexanes)), which was carried onto the next step without further purification.

To a solution of the crude diene sulfide in EtOH (200 mL) was added aq. NaH_2PO_4 (1 M, 100 mL, 100 mmol), and the resulting solution was cooled to 0 °C. 30% $H_2O_{2(aq)}$ (6.8 g, 200 mL, 200 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (12.4 g, 10 mmol) were then added. The reaction was stirred vigorously and allowed to warm to rt overnight. The reaction was quenched by addition of brine (70 mL). The aqueous layer was extracted with EtOAc (3×80 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 45% EtOAc in hexanes) to afford **4.7** as a colorless oil (9.9 g, 20.6 mmol, 41% over two steps, ~3.3:1 *E*:*Z* at the newly formed alkene, R_f = 0.34 (20% EtOAc in hexanes)).

$[\alpha]^{22}_D = +9.27$ (c = 0.22, $CHCl_3$)

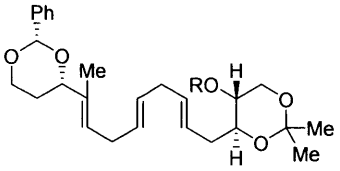
IR (ATR): 3060, 3037, 2966, 2922, 2852, 1596, 1498, 1453, 1341, 1267, 1241, 1153, 1098, 1015, 972, 760, 734, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 8.1, 1.8 Hz, 2H), 7.63–7.55 (m, 3H), 7.51 (dt, J = 7.8, 1.9 Hz, 2H), 7.40–7.31 (m, 3H), 5.64–5.55 (m, 2H), 5.52–5.37 (m, 2H), 4.33–4.28 (m, 1H), 4.24 (dd, J = 11.8, 2.0 Hz, 1H), 4.01 (ddd, J = 12.4, 11.4, 2.5 Hz, 1H), 3.80–3.74 (m, 2H), 2.76 (t, J =

6.9 Hz, 2H), 2.66 (dddt, J = 9.1, 6.8, 5.6, 1.2 Hz, 2H), 2.07–1.95 (m, 1H), 1.71 (d, J = 1.4 Hz, 3H), 1.60–1.52 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 138.9, 136.4, 132.5, 131.6, 129.9, 128.9, 128.3, 126.3, 125.2, 124.6, 123.3, 101.4, 81.8, 67.3, 55.9, 30.7, 30.2, 25.4, 12.8.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{28}N_4O_4S$ $[M+NH_4]^+$: 498.2170, found 498.2178.



4.23, R = TBDPS

Triene 4.23: To a solution of aldehyde **4.6** (8.5 g, 20.6 mmol) and sulfone **4.7** (9 g, 18.7 mmol) in THF (90 ml) was added DMPU (13.4 g, 13 ml, 75 mmol). The resulting solution was cooled to –78 °C. A solution of KHMDS (4.1 g, 20.6 mmol) in THF (40 mL) was added over 15 min via cannulation. The reaction mixture was stirred at –78 °C for 90 min, at which point the reaction was quenched by addition of brine (40 mL) and allowed to warm to rt over 1 h. The aqueous layer was separated and extracted with Et_2O (3×40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 30% EtOAc in hexanes) to afford **4.23** as a colorless oil (10.6 g, 15.9 mmol, 85%, >10:1 *E*:*Z* at the newly formed alkene, R_f = 0.63 (20% EtOAc in hexanes)).

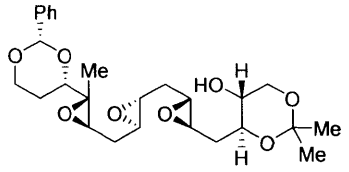
$[\alpha]^{22}_D$ = +2.46 (c = 0.13, $CHCl_3$)

IR (ATR): 3050, 2960, 2932, 2859, 1463, 1428, 1376, 1265, 1100, 972, 845, 821, 734, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (td, J = 7.4, 6.8, 1.6 Hz, 4H), 7.55–7.48 (m, 2H), 7.39 (dddd, J = 24.0, 13.6, 8.6, 6.8 Hz, 10H), 5.60–5.51 (m, 2H), 5.47–5.30 (m, 4H), 4.30 (ddd, J = 11.4, 5.0, 1.4 Hz, 1H), 4.27–4.21 (m, 1H), 4.01 (td, J = 11.9, 2.5 Hz, 1H), 3.73 (td, J = 8.2, 2.7 Hz, 1H), 3.60–3.47 (m, 3H), 2.77 (t, J = 5.8 Hz, 2H), 2.66 (t, J = 4.6 Hz, 2H), 2.48 (dt, J = 13.9, 3.9 Hz, 1H), 2.03 (ddt, J = 13.0, 8.2, 3.7 Hz, 2H), 1.73 (s, 3H), 1.61–1.47 (m, 1H), 1.44 (s, 3H), 1.29 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 136.0, 135.9, 134.9, 134.0, 133.4, 130.7, 130.0, 130.0, 129.3, 128.9, 128.7, 128.3, 127.9, 127.8, 126.8, 126.3, 124.7, 101.5, 98.4, 82.1, 74.6, 68.5, 67.3, 65.1, 35.8, 35.0, 30.9, 30.1, 28.8, 27.2, 26.7, 19.5, 19.4, 12.7.

HR-MS (ESI) *m/z* calcd for $C_{42}H_{54}O_5Si$ $[M+NH_4]^+$: 684.4079, found 684.4098.



4.5

Triepoxy alcohol 4.5: To a solution of triene **4.23** (10 g, 15 mmol) in CH_3CN (225 mL) was added chiral diacetate ketone **4.13** (9.1 g, 30 mmol), Bu_4NHSO_4 (1.53 g, 4.5 mmol), and a 4 x 10^{-4} M aqueous solution of Na_2EDTA (150 mL). The resulting biphasic mixture was cooled to 0 °C and stirred vigorously. $NaHCO_3$ (41.1 g, 489 mmol) and Oxone (92.4 g, 150 mmol) were thoroughly mixed, and this solid mixture was added over 4 h in nine portions. The aqueous layer was separated and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude triepoxide (R_f = 0.26 (30% EtOAc in hexanes)). The crude mixture was carried onto the next step without further purification.

To a solution of crude triepoxide in THF (30 mL) was added TBAF (1 M solution in THF, 50 mL, 50 mmol). The reaction was stirred at rt for 90 min, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 10% MeOH in EtOAc) to afford triepoxy alcohol **4.5** as a colorless oil (5.1 g, 10.7 mmol, 71% over two steps as a 2.0:1 overall mixture of diastereomers, R_f of all diastereomers = 0.26 (70% EtOAc in hexanes)).

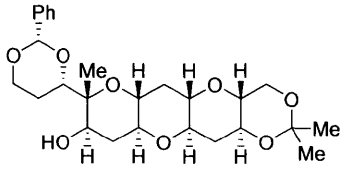
$[\alpha]^{22}_D$ = +17.33 (*c* = 0.045, $CHCl_3$)

IR (ATR): 3455, 2058, 2992, 2930. 2866, 1456, 1372, 1269, 1199, 1166, 1128, 1070, 1022, 978, 732, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 7.40–7.32 (m, 3H), 5.51 (s, 1H), 4.30 (ddd, *J* = 11.4, 5.1, 1.4 Hz, 1H), 4.01–3.90 (m, 1H), 3.8 –3.79 (m, 1H), 3.76 (ddd, *J* = 9.4, 5.4, 4.3 Hz, 1H), 3.70 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.66–3.53 (m, 2H), 3.18 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.01 (ddd, *J* = 6.7, 4.7, 2.3 Hz, 1H), 2.92 (dqd, *J* = 17.5, 5.4, 2.2 Hz, 3H), 2.45 (d, *J* = 5.6 Hz, 1H), 2.02–1.90 (m, 2H), 1.90–1.74 (m, 5H), 1.65 (s, 3H), 1.52 (dtd, *J* = 13.1, 2.5, 1.4 Hz, 1H), 1.46 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.4, 129.0, 128.3, 126.3, 101.3, 98.8, 80.9, 72.0, 66.9, 66.8, 64.8, 61.9, 56.7, 55.9, 55.5, 55.3, 35.0, 34.9, 31.4, 28.8, 26.8, 19.4, 13.5.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{36}O_8$ $[M+NH_4]^+$: 494.2748, found 494.2731.



4.4

Tetracycle 4.4: Triepoxy alcohol **4.5** (5 g, 10.5 mmol, in 2.0:1 overall dr) was dissolved in pH 8

aqueous buffer (0.1 M KP_i, 420 mL, 0.025 M), and the resulting suspension was heated to 70 °C for 7 d. The reaction solution was cooled to rt and extracted with EtOAc (6×100 mL). The combined organic layers were concentrated *in vacuo* without drying. The crude cascade product was purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 10% MeOH in EtOAc) to provide the desired tatracycle **4.4** as a white solid (1.15 g, 2.41 mmol, 23%, R_f = 0.43 (50% EtOAc in hexanes)).

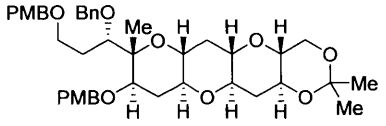
$[\alpha]^{22}_D$ = +39.16 (*c* = 0.5, $CHCl_3$)

IR (ATR): 3523, 2989, 2947, 2863, 1375, 1084, 988, 857, 736, 697 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 7.43–7.39 (m, 2H), 7.38–7.32 (m, 3H), 5.59 (s, 1H), 4.32 (ddd, *J* = 11.4, 4.9, 1.4 Hz, 1H), 3.98 (td, *J* = 12.0, 2.4 Hz, 1H), 3.93–3.87 (m, 2H), 3.84 (ddd, *J* = 11.6, 4.9, 1.1 Hz, 1H), 3.70 (t, *J* = 10.6 Hz, 1H), 3.64 (ddd, *J* = 11.3, 9.3, 4.1 Hz, 1H), 3.34 (d, *J* = 1.1 Hz, 1H), 3.30–3.11 (m, 4H), 3.02 (ddd, *J* = 11.9, 9.2, 4.3 Hz, 1H), 2.27 (dt, *J* = 11.1, 3.9 Hz, 1H), 2.23–2.16 (m, 2H), 2.00 (dddd, *J* = 13.5, 12.2, 11.4, 5.0 Hz, 1H), 1.68 (dtd, *J* = 13.5, 2.3, 1.3 Hz, 1H), 1.62 (q, *J* = 11.9 Hz, 1H), 1.50 (s, 3H), 1.55 (q, *J* = 11.2 Hz, 1H), 1.42 (s, 3H), 1.38 (q, *J* = 11.2 Hz, 1H), 1.32 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 129.4, 128.6, 126.0, 101.8, 99.5, 86.6, 77.5, 77.3, 77.3, 76.5, 75.1, 74.2, 69.5, 69.0, 67.5, 62.8, 35.5, 35.3, 33.1, 29.3, 24.8, 19.2, 11.7.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{36}O_8$ $[M+H]^+$: 477.2483, found 477.2477.



4.14

BisPMB 4.14: To a solution of tetracycle **4.5** (1 g, 2.1 mmol) in toluene (20 mL) at –50 °C was added a solution of DIBAL (1 M in toluene, 42 mL, 42 mmol) over 10 min. The resulting solution was stirred at –50 °C for 8 h. Upon completion as monitored by TLC analysis, the reaction was quenched by dropwise addition of MeOH (15 mL) and then sat. Rochelle's salt solution (100 mL) followed by vigorous stirring for 2 h. The aqueous layer was separated and extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude diol (R_f = 0.37 (100% EtOAc)). The crude mixture was carried onto the next step without further purification.

To a solution of $La(OTf)_3$ (2.46 g, 4.2 mmol) in toluene (30 mL) was added a solution of crude diol in toluene (20 mL) via cannulation. A solution of *p*-methoxybenzyl-2,2,2-trichloroacetimidate (3.56 g, 2.62 mL, 10.5 mmol) in toluene (16 mL) was added over 1 h via syringe pump. The resulting slurry was stirred at rt 2 h, quenched by addition of sat. $NaHCO_{3(aq)}$ (30 mL). The aqueous layer was separated and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford **4.14** as a colorless oil (1.10 g, 1.53 mmol, 73% over two steps, R_f = 0.31 (30% EtOAc in hexanes)).

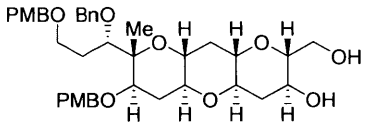
$[\alpha]^{22}_D = -34.52$ ($c = 2$, $CHCl_3$)

IR (ATR): 2993, 2947, 2878, 1612, 1513, 1457, 1373, 1357, 1301, 1246, 1200, 1174, 1073, 1034, 860, 821, 733, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 7.26–7.22 (m, 2H), 7.21–7.16 (m, 2H), 6.89–6.80 (m, 4H), 4.75 (d, J = 11.4 Hz, 1H), 4.51 (d, J = 4.8 Hz, 1H), 4.49 (d, J = 4.9 Hz, 1H), 4.44–4.31 (m, 3H), 3.91 (dd, J = 10.8, 5.1 Hz, 1H), 3.84–3.78 (m, J = 4.6 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.73–3.59 (m, 3H), 3.56–3.44 (m, 2H), 3.35 (ddd, J = 11.0, 9.2, 4.1 Hz, 1H), 3.28–3.08 (m, 3H), 2.91 (ddd, J = 11.8, 9.2, 4.0 Hz, 1H), 2.37 (dt, J = 11.5, 4.4 Hz, 1H), 2.31–2.21 (m, 2H), 1.88 (dddd, J = 19.6, 14.6, 9.0, 5.1 Hz, 2H), 1.56 (q, J = 11.2 Hz, 2H), 1.50 (s, 3H), 1.43 (s, 3H), 1.39 (q, J = 11.1 Hz, 1H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.2, 139.3, 130.8, 130.5, 129.4, 129.2, 128.3, 128.0, 127.4, 113.8, 99.4, 81.5, 81.0, 77.5, 77.3, 75.1, 75.0, 74.0, 72.6, 70.3, 69.5, 69.0, 67.3, 62.7, 55.3, 35.7, 35.3, 31.1, 30.8, 29.3, 19.2, 14.2.

HR-MS (ESI) *m/z* calcd for $C_{42}H_{54}O_{10}$ $[M+Na]^+$: 741.3609, found 741.3613.



4.24

Diol 4.24: To a solution of the bisPMB **4.14** (1.05 g, 1.46 mmol) in 1:1 CH_2Cl_2/MeOH (60 mL) was added *p*-toluenesulfonic acid monohydrate (56 mg, 0.29 mmol) at rt. After 1 h, the reaction was quenched by addition of Et_3N (51 mg, 0.07 mL, 0.5 mmol), concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 20% MeOH in EtOAc) to afford diol **4.24** as a colorless oil (932 mg, 1.37 mmol, 94%, R_f = 0.49 (100% EtOAc)).

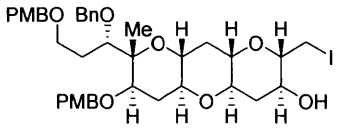
$[\alpha]^{22}_D = -33.22$ ($c = 0.83$, $CHCl_3$)

IR (ATR): 3400 2937, 2872, 1612, 1513, 1456, 1346, 1302, 1246, 1173, 1057, 1029, 820, 733, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.26–7.22 (m, 2H), 7.21–7.16 (m, 2H), 6.89–6.80 (m, 4H), 4.75 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 6.2 Hz, 1H), 4.49 (d, J = 6.4 Hz, 1H), 4.44–4.31 (m, 3H), 3.84–3.72 (m, 8H), 3.66 (ddd, J = 12.9, 9.6, 3.8 Hz, 2H), 3.56–3.45 (m, 2H), 3.33 (ddd, J = 11.0, 9.1, 4.1 Hz, 1H), 3.19 (dt, J = 9.0, 4.3 Hz, 1H), 3.11 (ddd, J = 11.1, 8.9, 4.2 Hz, 1H), 3.01 (ddd, J = 11.3, 9.0, 4.0 Hz, 1H), 2.90 (ddd, J = 11.6, 9.2, 4.0 Hz, 1H), 2.41–2.31 (m, 2H), 2.26 (dt, J = 11.2, 4.1 Hz, 1H), 1.97–1.80 (m, 2H), 1.61–1.44 (m, 2H), 1.36 (q, J = 11.3 Hz, 1H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.1, 139.2, 130.7, 130.5, 129.5, 129.2, 128.3, 128.0, 127.5, 113.8, 81.4, 80.9, 77.2, 76.7, 76.4, 75.0, 74.0, 72.6, 70.3, 69.0, 67.3, 66.8, 63.0, 55.3, 38.2, 35.6, 31.0, 30.8, 14.1.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{50}O_{10}$ $[M+Na]^+$: 701.3296, found 701.3281.



4.15

Iodide 4.15: To a solution of diol **4.24** (920 mg, 1.36 mmol) in THF (10 mL) were added imidazole (277 mg, 4.07 mmol) and PPh_3 (711 mg, 2.71 mmol) at rt. The reaction mixture was cooled to –40 °C and added I_2 (688 mg, 2.71 mmol). The reaction solution was allowed to warm to rt over 1 h with exclusion of light and quenched with sat. $Na_2S_2O_{3(aq)}$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 90% EtOAc in hexanes) to afford iodide **4.15** as a white solid (1.04 g, 1.31 mmol, 97%, R_f = 0.54 (50% EtOAc in hexanes)).

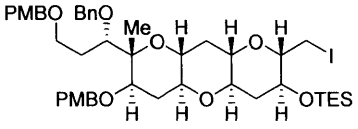
$[\alpha]^{22}_D$ = –19.65 (*c* = 0.4, $CHCl_3$)

IR (ATR): 3438, 2938, 2872, 1611, 1586, 1512, 1455, 1302, 1245, 1173, 1055, 1030, 819, 733, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.26–7.22 (m, 2H), 7.21–7.16 (m, 2H), 6.89–6.80 (m, 4H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 5.5 Hz, 1H), 4.50 (d, *J* = 5.7 Hz, 1H), 4.44 – 4.32 (m, 3H), 3.84 (dd, *J* = 11.5, 4.7 Hz, 1H), 3.794 (s, 3H), 3.793 (s, 3H), 3.68 (dd, *J* = 9.7, 2.9 Hz, 1H), 3.58–3.43 (m, 4H), 3.34 (dt, *J* = 10.5, 5.1 Hz, 2H), 3.16 (ddd, *J* = 11.2, 9.0, 4.2 Hz, 1H), 3.04 (ddd, *J* = 11.4, 9.0, 4.0 Hz, 1H), 2.97–2.84 (m, 2H), 2.44–2.22 (m, 4H), 1.89 (dtt, *J* = 14.6, 9.6, 5.5 Hz, 2H), 1.66–1.36 (m, 3H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 159.1, 139.3, 130.7, 130.5, 129.4, 129.2, 128.3, 127.9, 127.4, 113.8, 81.5, 81.0, 80.3, 76.9, 76.4, 75.0, 74.0, 72.6, 70.3, 69.7, 69.0, 67.3, 55.3, 38.3, 35.5, 31.1, 30.9, 14.1.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{49}IO_9$ $[M+Na]^+$: 811.2313, found 811.2307.



4.25

TES ether 4.25: To a solution of iodide **4.15** (1 g, 1.27 mmol) in CH_2Cl_2 (6 mL) were added imidazole (155 mg, 2.28 mmol) and TESCl (230 mg, 0.26 mL, 1.52 mmol) at rt. The resulting

solution was stirred at rt for 2 h and quenched by addition of brine (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 30% EtOAc in hexanes) to afford TES ether **4.25** as a colorless oil (1.14 g, 1.26 mmol, 99%, R_f = 0.51 (20% EtOAc in hexanes)).

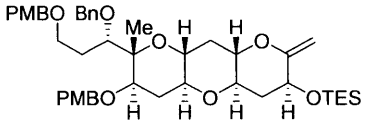
$[\alpha]^{22}_D$ = –7.21 (*c* = 0.75, $CHCl_3$)

IR (ATR): 2952, 2876, 1612, 1513, 1456, 1353, 1302, 1246, 1173, 1075, 1036, 907, 820, 726, 697 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 7.27–7.23 (m, 2H), 7.21–7.16 (m, 2H), 6.91–6.79 (m, 4H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 1H), 4.43–4.32 (m, 3H), 3.84 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.67 (dd, *J* = 10.1, 2.6 Hz, 1H), 3.61–3.46 (m, 4H), 3.37–3.28 (m, 2H), 3.19 (ddd, *J* = 11.3, 8.9, 4.2 Hz, 1H), 3.05 (ddd, *J* = 12.6, 9.0, 4.0 Hz, 1H), 2.97–2.86 (m, 2H), 2.40–2.26 (m, 3H), 1.89 (dqd, *J* = 30.0, 10.1, 9.3, 5.4 Hz, 2H), 1.63–1.50 (m, 2H), 1.44 (q, *J* = 11.4 Hz, 1H), 1.26 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.65 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.1, 139.4, 130.8, 130.5, 129.4, 129.2, 128.3, 127.9, 127.4, 113.8, 81.6, 81.0, 80.5, 77.2, 76.9, 76.4, 75.0, 74.0, 72.6, 70.5, 70.4, 69.0, 67.3, 55.3, 38.8, 35.6, 31.2, 31.0, 14.1, 8.0, 7.0, 5.2.

HR-MS (ESI) *m/z* calcd for $C_{45}H_{63}IO_9Si$ $[M+Na]^+$: 925.3178, found 925.3187.



4.2

Exocyclic methylene 4.2: To a solution of iodide **4.25** (1.11 g, 1.23 mmol) in THF (5 mL) at 0 °C was added KO*t*-Bu (276 mg, 2.46 mmol) in THF (5 mL). The resulting solution was stirred at 0 °C for 20 min, quenched by addition of sat. $NH_4Cl_{(aq)}$ (5 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 30% EtOAc in hexanes) to afford olefin **4.2** as a colorless oil (924 mg, 1.19 mmol, 97%, R_f = 0.51 (20% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = –35.59 (*c* = 1, CH_2Cl_2)

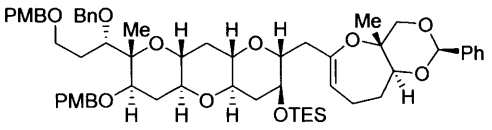
IR (ATR): 2957, 2877, 1660, 1612, 1513, 1457, 1362, 1302, 1247, 1173, 1079, 1051, 1035, 831, 732, 700 cm^{-1}.

^1H NMR (400 MHz, C_6D_6) δ 7.42 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.27–7.21 (m, 4H), 7.21–7.10 (m, 5H), 6.78 (dd, *J* = 8.6, 1.9 Hz, 4H), 5.00–4.91 (m, 2H), 4.89 (d, *J* = 1.7 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.28 (dd,

J = 11.3 Hz, 1H), 4.26–4.20 (m, 1H), 4.01 (dd, J = 11.5, 4.7 Hz, 1H), 3.94 (dd, J = 9.2, 3.7 Hz, 1H), 3.67 (td, J = 8.9, 5.8 Hz, 1H), 3.53 (dt, J = 9.1, 5.0 Hz, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.25 (td, J = 11.5, 9.4 Hz, 1H), 3.22 (td, J = 11.5, 9.4 Hz, 1H), 3.09 (ddd, J = 11.2, 9.2, 4.3 Hz, 1H), 2.86 (ddd, J = 11.8, 9.1, 4.0 Hz, 1H), 2.50–2.34 (m, 3H), 2.21–2.05 (m, 2H), 1.85 (q, J = 11.3 Hz, 1H), 1.63 (q, J = 11.2 Hz, 2H), 1.32 (s, 3H), 0.99 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H).

^{13}C NMR (101 MHz, C_6D_6) δ 162.6, 159.8, 159.7, 140.5, 131.4, 131, 129.6, 129.6, 128.6, 128.5, 127.4, 114.1, 114.1, 93.0, 82.5, 81.5, 78.6, 77.6, 76.4, 75.5, 74.3, 72.9, 70.6, 69.4, 67.6, 67.4, 54.8, 40.2, 36.5, 32.1, 31.5, 14.3, 7.1, 5.2.

HR-MS (ESI) *m/z* calcd for $C_{45}H_{62}O_9Si$ $[M+Na]^+$: 797.4055, found 797.4031.



4.18

Coupling product 4.18: Exocyclic enol ether **4.2** (915 mg, 1.18 mmol) in THF (2 mL) was treated with 9-BBN (0.5 M in THF, 7.1 mL, 3.54 mmol). The resultant solution was stirred at rt for 2 h, at which point it was treated with $Cs_2CO_{3(aq)}$ (3 M, 2.4 mL, 7.1 mmol) and stirred at rt for 15 min. To this mixture were added a solution of enol phosphate **4.3** (584 mg, 1.18 mmol) in DMF (3 mL) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (96 mg, 0.12 mmol). The resultant mixture was stirred at 50 °C for 1 h and quenched with addition of water (3 mL). The aqueous layer was separated and extracted with Et_2O (3×7 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (pretreated with 2% Et_3N in hexanes, gradient 0% to 35% EtOAc in hexanes) to afford coupling product **4.18** as a colorless oil (1.02 g, 1 mmol, 85%, R_f = 0.49 (20% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +0.89 (c = 0.35, CH_2Cl_2)

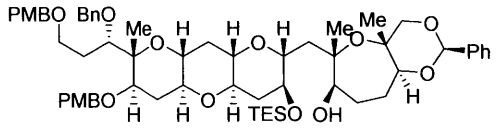
IR (ATR): 2931, 2876, 1612, 1513, 1453, 1412, 1385, 1340, 1265, 1247, 1211, 1171, 1081, 1061, 1036, 1007, 973, 908, 822, 733, 699 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6) δ 7.63–7.58 (m, 2H), 7.41 (dd, J = 7.9, 1.3 Hz, 2H), 7.28–7.09 (m, 10H), 6.77 (dd, J = 8.6, 3.0 Hz, 4H), 5.40 (s, 1H), 5.09 (dd, J = 9.0, 3.3 Hz, 1H), 4.98 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.3 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.6 Hz, 1H), 4.11 (d, J = 10.4 Hz, 1H), 4.02 (dd, J = 11.5, 4.7 Hz, 1H), 3.91 (dd, J = 9.4, 3.4 Hz, 1H), 3.85 (d, J = 10.5 Hz, 1H), 3.71–3.62 (m, 2H), 3.62–3.55 (m, 1H), 3.55 – 3.49 (m, 1H), 3.44 (ddd, J = 10.6, 8.9, 4.6 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 3.20 (td, J = 10.8, 4.0 Hz, 1H), 3.03–2.84 (m, 3H), 2.77 (d, J = 14.2 Hz, 1H), 2.51–2.37 (m, 2H), 2.27 (dt, J = 11.0, 3.9 Hz, 1H), 2.22–2.04 (m, 2H), 1.85 (ddt, J = 15.5, 8.6, 3.9 Hz, 1H), 1.80–1.51 (m, 4H), 1.59 (s, 3H), 1.43–1.22 (m, 3H), 1.32 (s, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H).

^{13}C NMR (151 MHz, C_6D_6) δ 159.8, 159.8, 152.5, 140.5, 139.0, 131.5, 131.1, 129.6, 129.6, 128.9, 128.5, 128.4, 127.4, 126.9, 114.2, 114.1, 109.8, 102.1, 85.8, 82.6, 81.4, 80.4, 77.7, 77.1, 77.1, 77.0,

75.4, 74.5, 73.3, 72.9, 71.2, 70.8, 70.6, 69.7, 67.6, 54.8, 54.8, 40.6, 40.2, 36.6, 32.4, 32.1, 31.7, 27.6, 26.7, 22.5, 22.4, 15.2, 14.3, 7.2, 5.6.

HR-MS (ESI) *m/z* calcd for $C_{60}H_{80}O_{12}Si$ $[M+Na]^+$: 1043.5311, found 1043.5301.



4.26

Alcohol 4.26: To a solution of enol ether **4.18** (700 mg, 0.69 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added a solution of acetone-free DMDO (0.12 M, 6.9 mL, 0.82 mmol) slowly. The resulting yellow solution was stirred at –40 °C for 30 min and quenched by addition of 3,4-dihydropyran (922 mg, 0.1 mL, 1.1 mmol). The resulting clear solution was warmed to rt and evacuated until dryness, about 30 min. The crude material was dissolved in CH_2Cl_2 (20 mL) and cooled to –78 °C. To this was added a solution of MeMgBr (3 M in Et_2O, 4.6 mL, 13.7 mmol) slowly. After stirring at –40 °C for 1 h, the reaction was quenched by slow addition of sat. $NH_4Cl_{(aq)}$ (15 mL) and allowed to warm to rt. The aqueous layer was separated and extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 45% EtOAc in hexanes) to afford alcohol **4.26** as a colorless oil (556 g, 0.53 mmol, 78%, R_f = 0.51 (30% EtOAc in hexanes)).

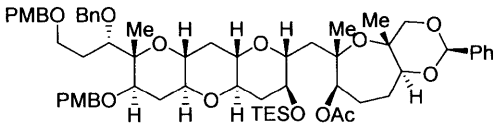
$[\alpha]^{22}_D$ = +2.92 (*c* = 0.24, $CHCl_3$)

IR (ATR): 3483, 2951, 2876, 1612, 1513, 1456, 1374, 1301, 1247, 1079, 1056, 1035, 821, 733, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.39–7.29 (m, 5H), 7.28–7.21 (m, 5H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.86–6.80 (m, 4H), 5.46 (s, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.50–4.45 (m, 2H), 4.42–4.31 (m, 3H), 3.85–3.76 (m, 8H), 3.73 (d, *J* = 10.7 Hz, 1H), 3.64 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.55–3.41 (m, 5H), 3.35 (ddd, *J* = 11.5, 8.8, 3.8 Hz, 2H), 3.17 (td, *J* = 11.5, 10.3, 4.2 Hz, 1H), 3.01 (ddd, *J* = 12.6, 8.9, 4.0 Hz, 1H), 2.89 (ddd, *J* = 12.5, 9.1, 4.0 Hz, 1H), 2.33 (dq, *J* = 10.5, 4.8 Hz, 2H), 2.27 (dt, *J* = 11.3, 4.2 Hz, 1H), 2.04 (d, *J* = 14.8 Hz, 1H), 2.01–1.79 (m, 5H), 1.59–1.50 (m, 4H), 1.49 (s, 3H), 1.34 (q, *J* = 11.4 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 159.2, 139.5, 138.2, 130.8, 130.6, 129.5, 129.3, 129.1, 128.5, 128.3, 127.8, 127.4, 126.4, 113.9, 101.9, 82.2, 81.7, 81.7, 81.1, 79.2, 77.6, 77.2, 76.7, 76.4, 74.9, 74.0, 72.7, 72.2, 71.8, 70.4, 69.7, 69.0, 67.4, 55.4, 44.3, 39.4, 35.81 31.2, 31.0, 25.5, 24.6, 22.6, 19.1, 14.2, 7.0, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{61}H_{84}O_{13}Si$ $[M+Na]^+$: 1075.5573, found 1075.5547.



4.19

Acetate 4.19: To a solution of alcohol **4.26** (740 mg, 0.7 mmol) in pyridine (2 mL) were added DMAP (8.6 mg, 0.07 mmol) and acetic anhydride (211 mg, 0.2 mL, 2.1 mmol). The resulting solution was stirred at rt overnight and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 40% EtOAc in hexanes) to afford alcohol **4.26** as a colorless oil (769 mg, 0.7 mmol, 99%, R_f = 0.54 (30% EtOAc in hexanes)).

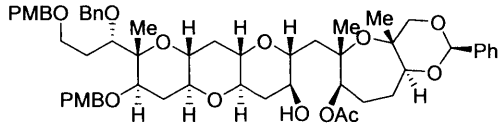
$[\alpha]^{22}_D = -3.26$ (c = 0.175, $CHCl_3$)

IR (ATR): 2945, 2875, 1740, 1612, 1586, 1513, 1455, 1372, 1302, 1247, 1098, 1034, 822, 745, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H), 7.39–7.29 (m, 5H), 7.29–7.21 (m, 5H), 7.19–7.15 (m, 2H), 6.88–6.79 (m, 4H), 5.47 (s, 1H), 5.18 (d, J = 6.4 Hz, 1H), 4.76 (d, J = 11.4 Hz, 1H), 4.52–4.43 (m, 2H), 4.42–4.31 (m, 3H), 3.84–3.73 (m, 8H), 3.64 (td, J = 12.5, 11.3, 3.3 Hz, 2H), 3.55 (d, J = 10.6 Hz, 1H), 3.53–3.46 (m, 2H), 3.37–3.26 (m, 3H), 3.08–2.97 (m, 1H), 2.89 (ddd, J = 12.8, 9.1, 4.1 Hz, 1H), 2.35–2.28 (m, 2H), 2.23 (dt, J = 11.4, 4.1 Hz, 1H), 2.11 (s, 3H), 2.02 (d, J = 14.2 Hz, 1H), 1.97–1.75 (m, 4H), 1.61 (s, 3H), 1.57–1.50 (m, 3H), 1.34 (q, J = 11.3 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.9, 159.2, 159.2, 139.5, 138.2, 130.9, 130.6, 129.5, 129.3, 129.1, 128.5, 128.3, 128.0, 127.4, 126.4, 113.9, 101.9, 84.8, 81.7, 81.0, 80.7, 79.4, 78.0, 77.2, 76.6, 76.5, 75.7, 75.1, 74.0, 72.7, 72.1, 70.4, 70.2, 69.1, 67.4, 55.4, 45.4, 39.5, 35.9, 31.2, 31.0, 25.6, 25.1, 24.5, 21.3, 17.1, 14.2, 7.0, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{63}H_{86}O_{14}Si$ $[M+Na]^+$: 1117.5679, found 1117.5696.



4.27

Alcohol 4.27: To a solution of acetate **4.19** (755 mg, 0.69 mmol) in THF (1.5 mL) was added TBAF (1 M solution in THF, 1 mL, 1 mmol). The reaction was stirred at rt for 1 h, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 90% EtOAc in hexanes) to afford alcohol **4.27** as a colorless oil (656 mg, 0.69 mmol, 97%, R_f = 0.26 (50% EtOAc in hexanes)).

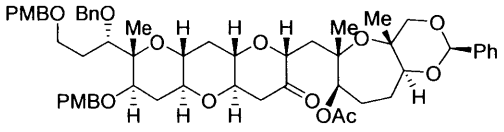
$[\alpha]^{22}_D = -12.4$ (c = 0.15, $CHCl_3$)

IR (ATR): 3486, 2942, 2870, 1736, 1612, 1586, 1513, 1456, 1372, 1303, 1247, 1172, 1093, 1056, 1030, 821, 735, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.44 (m, 2H), 7.40–7.21 (m, 10H), 7.21–7.14 (m, 2H), 6.89–6.78 (m, 4H), 5.47 (s, 1H), 5.19 (d, J = 5.8 Hz, 1H), 4.76 (d, J = 11.4 Hz, 1H), 4.53–4.45 (m, 2H), 4.43–4.30 (m, 3H), 3.87–3.74 (m, 8H), 3.68 (ddd, J = 12.7, 10.2, 3.3 Hz, 2H), 3.61–3.44 (m, 3H), 3.40–3.29 (m, 2H), 3.25 (ddd, J = 9.1, 6.2, 2.5 Hz, 1H), 3.10–2.97 (m, 2H), 2.89 (ddd, J = 12.8, 9.1, 4.1 Hz, 1H), 2.35–2.28 (m, 2H), 2.24 (dt, J = 11.8, 3.9 Hz, 1H), 2.10 (s, 3H), 2.04–1.97 (m, 1H), 1.89 (ddt, J = 20.7, 9.6, 3.9 Hz, 5H), 1.81–1.70 (m, 3H), 1.62 (s, 3H), 1.55 (q, J = 11.7 Hz, 2H), 1.32 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 159.2, 159.2, 139.4, 138.0, 130.8, 130.5, 129.4, 129.2, 129.1, 128.4, 128.3, 128.0, 127.4, 126.4, 113.8, 101.9, 83.9, 81.6, 81.2, 81.0, 78.7, 77.6, 77.2, 76.7, 76.6, 75.1, 74.7, 74.0, 72.9, 72.6, 70.3, 69.9, 69.1, 67.4, 55.4, 46.4, 38.7, 35.7, 31.1, 30.9, 24.8, 24.7, 24.3, 21.3, 17.4, 14.2.

HR-MS (ESI) *m/z* calcd for $C_{57}H_{72}O_{14}$ $[M+Na]^+$: 1003.4815, found 1003.4810.



4.28

Ketone 4.28: To a mixture of alcohol **4.27** (642 mg, 0.65 mmol) and 4 Å MS (30 mg) were added CH_2Cl_2 (2 mL), *N*-methylmorpholine *N*-oxide (230 mg, 1.96 mmol), and tetrapropylammonium perruthenate (23 mg, 0.065 mmol). The resultant slurry was stirred at rt for 90 min, at which point it was filtered through a plug of celite, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford ketone **4.28** as a colorless oil (617 mg, 0.63 mmol, 96%, R_f = 0.23 (30% EtOAc in hexanes)).

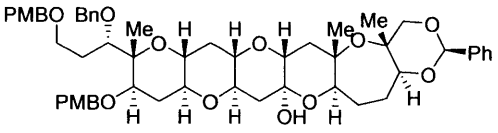
$[\alpha]^{22}_D$ = –23.52 (c = 0.125, $CHCl_3$)

IR (ATR): 2940, 2860, 1734, 1612, 1586, 1513, 1456, 1371, 1302, 1245, 1082, 1029, 917, 820, 734, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 7.41–7.21 (m, 10H), 7.21–7.14 (m, 2H), 6.89–6.79 (m, 4H), 5.45 (s, 1H), 5.09–5.02 (m, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.54–4.47 (m, 2H), 4.44–4.30 (m, 3H), 3.97 (dd, J = 6.3, 2.9 Hz, 1H), 3.87–3.71 (m, 8H), 3.68 (dd, J = 9.5, 3.1 Hz, 1H), 3.61 (dt, J = 6.2, 4.0 Hz, 1H), 3.55–3.46 (m, 3H), 3.46–3.32 (m, 3H), 2.95 (ddd, J = 12.1, 9.9, 4.7 Hz, 2H), 2.53–2.30 (m, 3H), 2.24 (dd, J = 14.9, 2.8 Hz, 1H), 2.10 (s, 3H), 1.99–1.74 (m, 7H), 1.68–1.39 (m, 6H), 1.28 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 169.9, 159.2, 139.4, 138.0, 130.8, 130.5, 129.5, 129.3, 129.1, 128.5, 128.3, 128.0, 127.5, 126.4, 113.9, 113.9, 101.9, 84.5, 81.6, 81.1, 80.7, 80.2, 77.8, 77.0, 76.8 , 76.1, 75.8, 75.1, 74.0, 72.7, 72.6, 70.5, 68.8, 67.3, 55.4, 45.0, 41.9, 35.7, 31.2, 30.8, 25.1, 24.9, 24.1, 21.3, 17.0, 14.2.

HR-MS (ESI) *m/z* calcd for $C_{57}H_{70}O_{14}$ $[M+Na]^+$: 1001.4658, found 1001.4638.



4.20

Hemiacetal 4.20: To a solution of alcohol **4.28** (600 mg, 0.61 mmol) in MeOH (3 mL) was added K_2CO_3 (254 mg, 1.84 mmol). The resultant slurry was stirred at 50 °C for 60 min, at which point it was concentrated *in vacuo*. The crude mixture was quenched by addition of sat. $NH_4Cl_{(aq)}$ (4 mL) and extracted with EtOAc (3×8 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford alcohol **4.20** as a colorless oil (511 mg, 0.55 mmol, 89%, R_f = 0.26 (30% EtOAc in hexanes)).

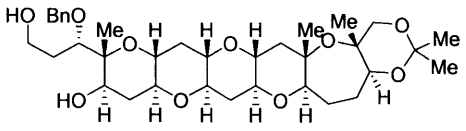
$[\alpha]^{22}_D$ = –6.67 (*c* = 0.09, $CHCl_3$)

IR (ATR): 3426, 2929, 2857, 1735, 1612, 1513, 1456, 1373, 1301, 1247, 1173, 1082, 1029, 821, 751, 735, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.38–7.30 (m, 4H), 7.29–7.21 (m, 6H), 7.19–7.14 (m, 2H), 6.88–6.80 (m, 4H), 5.44 (s, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.51–4.46 (m, 2H), 4.41–4.31 (m, 3H), 4.09 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.85 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.78 (s, 8H), 3.65 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.54–3.44 (m, 3H), 3.39–3.28 (m, 2H), 3.23 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.20–3.13 (m, 1H), 2.94–2.86 (m, 1H), 2.42 (s, 1H), 2.37–2.31 (m, 1H), 2.31–2.25 (m, 1H), 2.20 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.99 (d, *J* = 16.3 Hz, 2H), 1.96–1.76 (m, 5H), 1.63–1.42 (m, 5H), 1.38 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 139.4, 138.0, 130.9, 130.5, 129.5, 129.3, 129.1, 128.5, 128.4, 128.1, 127.5, 126.8, 113.9, 113.9, 101.9, 93.5, 81.5, 81.5, 81.1, 78.5, 78.5, 77.7, 77.3, 77.2, 75.1, 74.1, 73.0, 72.7, 72.4, 70.4, 69.2, 67.3, 55.4, 55.4, 41.5, 40.0, 35.7, 31.2, 30.9, 24.2, 23.7, 20.3, 19.3, 14.2.

HR-MS (ESI) *m/z* calcd for $C_{55}H_{68}O_{13}$ $[M+Na]^+$: 959.4552, found 959.4570.



4.21

Diol 4.21: To a solution of hemiacetal **4.20** (347 mg, 0.37 mmol) in 1:4 CH_2Cl_2/MeOH (5 mL) was added *p*-toluenesulfonic acid monohydrate (14 mg, 0.074 mmol). The resulting solution was refluxed at 65 °C for 1 h, cooled to rt, quenched by addition of Et_3N (20 mg, 0.03 mL, 0.2 mmol)), and concentrated *in vacuo*. The crude material was partitioned between EtOAc (5 ml) and sat. $NaHCO_{3(aq)}$ (3 mL). The aqueous layer was separated and extracted with EtOAc (6×3 mL). The

combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude diol (R_f = 0.43 (70% EtOAc)). The hemiacetal in **4.20** was fully converted to methoxy acetal as confirmed by NMR experiment and mass spectrometry. The crude mixture was carried onto the next step without further purification.

To a solution of crude methoxy aetal in acetonitrile (9 mL) at –20 °C were added triethylsilane (861 mg, 1.18 mL, 7.4 mmol) and TESOTf (293 mg, 0.25 mL, 1.11 mmol). The resulting solution was stirred at –20 °C 30 min, quenched by addition of sat. $NaHCO_{3(aq)}$ (3 mL), and warmed to rt over 15 min. The aqueous layer was separated and extracted with EtOAc (6×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude tetraol **4.1** (R_f = 0.23 (100% EtOAc)). The crude mixture was carried onto the next step without further purification.

To a solution of crude tertraol in acetone (5 mL) was added *p*-toluenesulfonic acid monohydrate (14 mg, 0.074 mmol). The resulting solution was stirred at rt for 30 min, quenched by addition of Et_3N (20 mg, 0.03 mL, 0.2 mmol)), and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 0% to 100% EtOAc in hexanes then 0% to 15% MeOH in EtOAc)) to afford diol **4.21** as a colorless oil (152 mg, 0.24 mmol, 65%, R_f = 0.70 (100% EtOAc)).

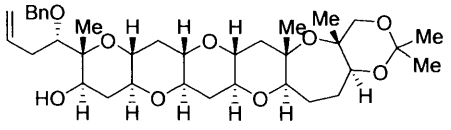
$[\alpha]^{22}_D$ = +9.25 (*c* = 0.2, $CHCl_3$)

IR (ATR): 3472, 2950, 2877, 1456, 1380, 1339, 1264, 1199, 1081, 1036, 863, 736, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 11.1 Hz, 1H), 3.85–3.74 (m, 2H), 3.74–3.63 (m, 3H), 3.56 (dd, *J* = 7.0, 4.7 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 1H), 3.41 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.35 (d, *J* = 11.1 Hz, 1H), 3.27 (ddd, *J* = 11.2, 9.1, 4.2 Hz, 1H), 3.13–2.93 (m, 4H), 2.44 (s, 1H), 2.31 (dt, *J* = 11.1, 3.5 Hz, 1H), 2.24–21.3 (m, 2H), 2.10–1.89 (m, 3H), 1.88–1.45 (m, 5H), 1.42 (s, 3H), 1.45–1.32 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.0, 128.9, 128.5, 128.3, 98.5, 86.6, 81.7, 78.6, 77.8, 77.4, 77.0, 76.8, 76.6, 73.8, 73.4, 72.4, 70.8, 69.2, 60.7, 45.7, 35.4, 35.3, 33.4, 32.6, 29.5, 24.5, 24.3, 21.0, 18.9, 18.7, 11.5.

HR-MS (ESI) *m/z* calcd for $C_{35}H_{52}O_{10}$ $[M+Na]^+$: 655.3453, found 655.3439.



4.22

Alkene 4.22: To a solution of diol **4.21** (124 mg, 0.196 mmol) in CH_2Cl_2 (4 mL) was added Dess-Martin periodinane (100 mg, 0.235 mmol). The resulting solution was stirred at rt for 90 min, and quenched with sat. $Na_2S_2O_{3(aq)}$ (3 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in*

vacuo to provide crude hemiacetal (R_f = 0.34 (50% EtOAc in hexanes)). The crude mixture was carried onto the next step without further purification.

To a slurry of CH_2I_2 (525 mg, 0.16 mL, 1.96 mmol) and $CrCl_2$ (120 mg, 0.98 mmol) in 1:4 DMF/THF (5 mL) was added a solution of the crude hemiacetal in THF (2 mL) via cannulation. The resulting slurry was stirred at rt overnight, at which point it was quenched with addition of brine (3 mL). The aqueous layer was separated and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (gradient 0% to 50% EtOAc in hexanes) to afford olefin **4.22** as a colorless oil (93.6 mg, 0.149 mmol, 76% over two steps, R_f = 0.23 (30% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +48.5 (*c* = 0.185, $CHCl_3$)

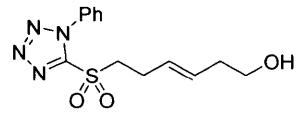
IR (ATR): 3513, 2988, 2949, 2877, 1456, 1379, 1339, 1264, 1198, 1076, 1035, 912, 862, 734, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 5.98 (dddd, *J* = 17.1, 10.1, 8.4, 5.8 Hz, 1H), 5.16 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.06 (dt, *J* = 10.0, 1.8 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 3.81 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.72–3.66 (m, 2H), 3.52–3.46 (m, 2H), 3.41 (dd, *J* = 10.7, 3.9 Hz, 1H), 3.35 (d, *J* = 11.1 Hz, 1H), 3.21 (ddd, *J* = 11.2, 9.1, 4.2 Hz, 1H), 3.13–2.92 (m, 5H), 2.65 (dtt, *J* = 13.1, 3.8, 1.9 Hz, 1H), 2.4–2.26 (m, 2H), 2.21–2.11 (m, 2H), 2.07 (dd, *J* = 12.3, 3.6 Hz, 1H), 2.00–1.91 (m, 1H), 1.88–1.67 (m, 2H), 1.61–1.30 (m, 17H), 1.21 (s, 3H).

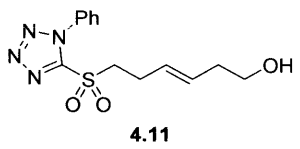
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 136.9, 128.8, 128.3, 128.3, 116.7, 98.5, 87.9, 81.7, 78.6, 77.8, 77.5, 77.4, 77.2, 76.6, 73.8, 73.8, 73.7, 73.4, 70.8, 69.0, 45.8, 35.6, 35.3, 35.0, 33.3, 29.5, 24.5, 24.3, 21.0, 18.9, 18.7, 11.4.

HR-MS (ESI) *m/z* calcd for $C_{36}H_{52}O_9$ $[M+Na]^+$: 651.3504, found 651.3486.

E. ^{1}H and ^{13}C NMR Spectra



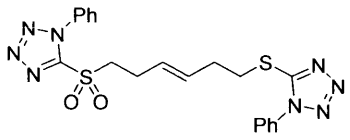
4.11


Ph
N
N
N
S
O
O
OH

4.11

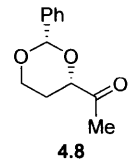
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)

4.9
Ph
Ph
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

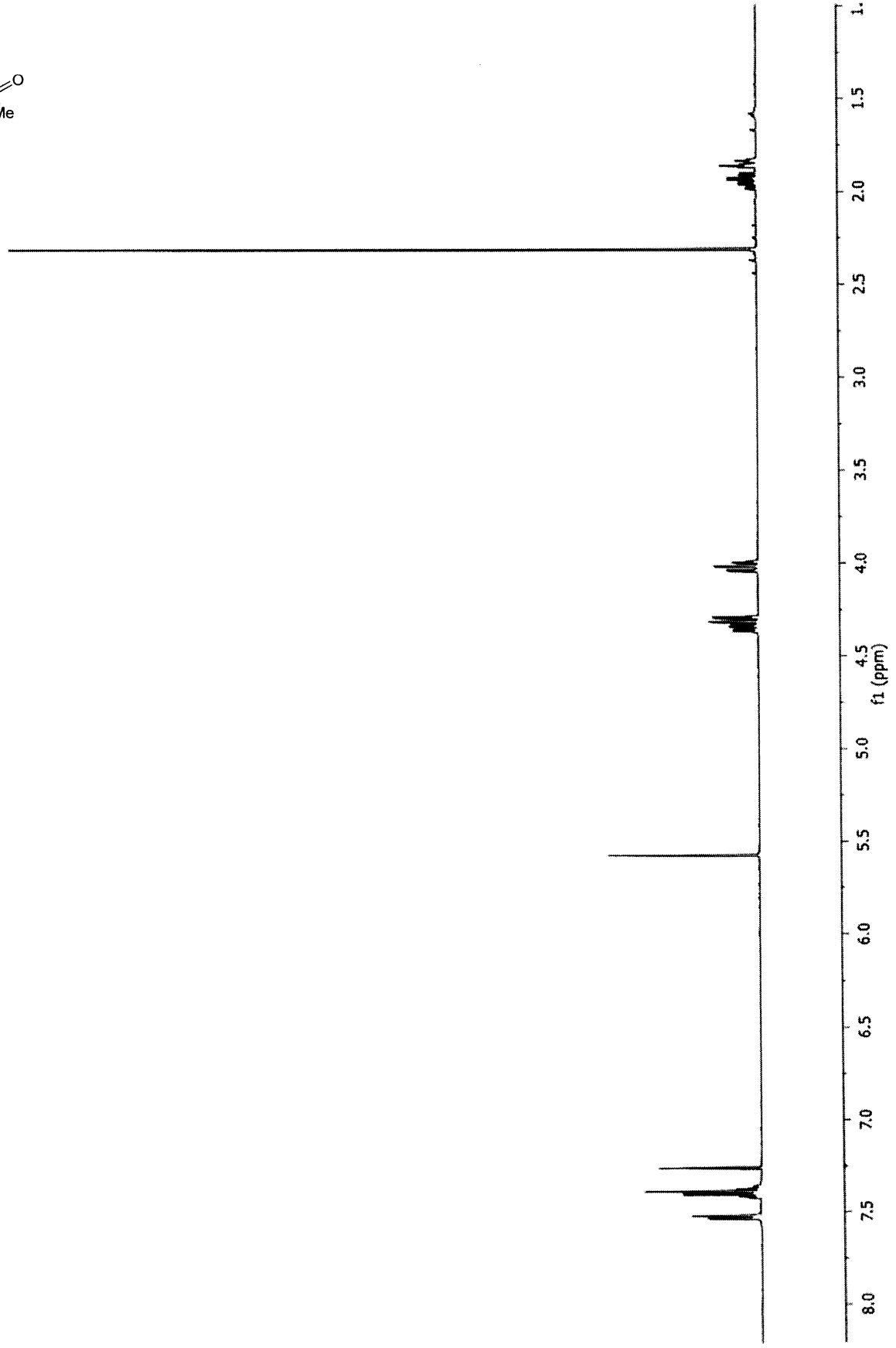

Ph
N
N
N
S
O
O
S
N
N
N
Ph

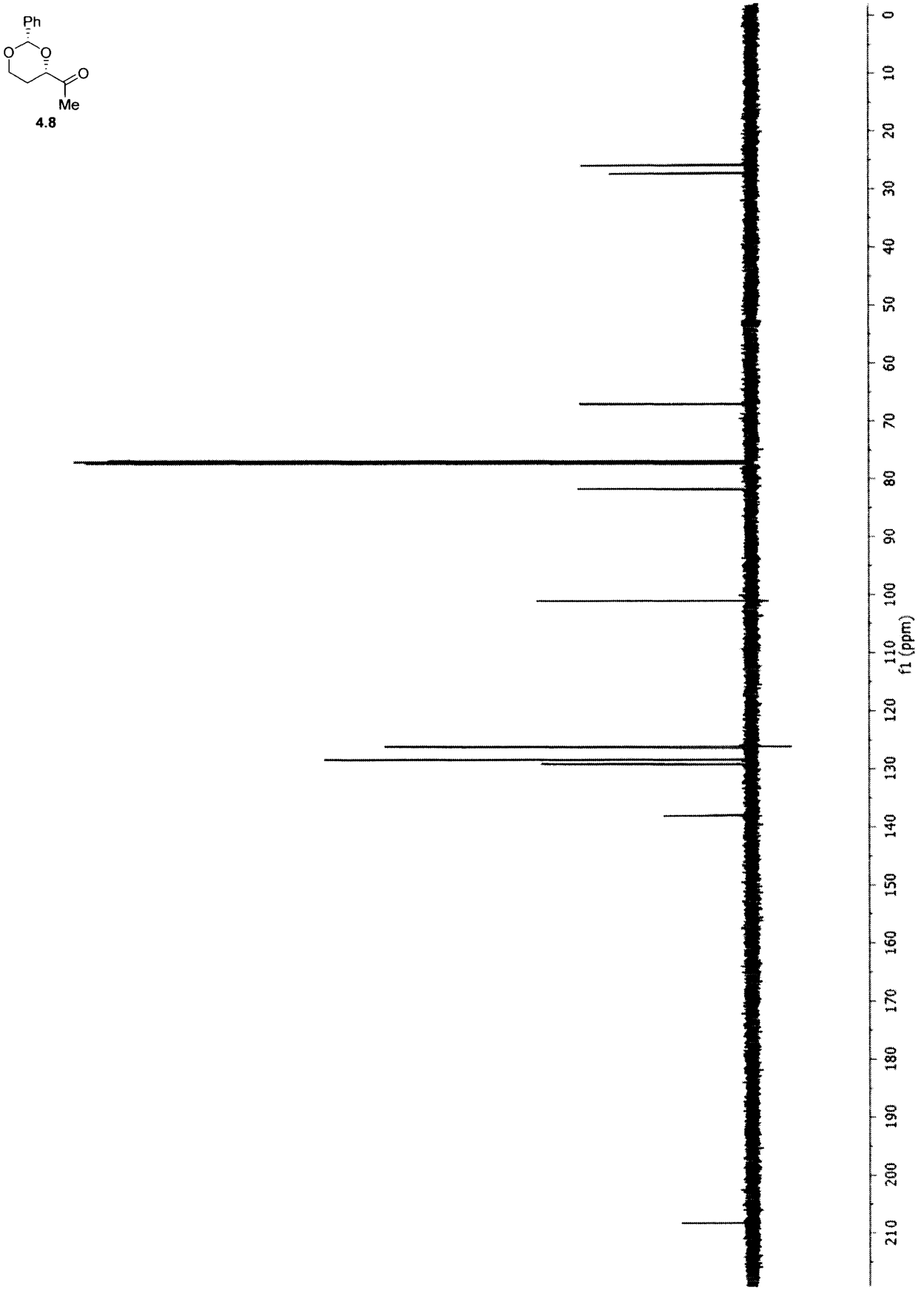
4.9

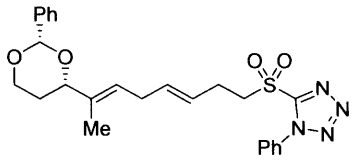
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)



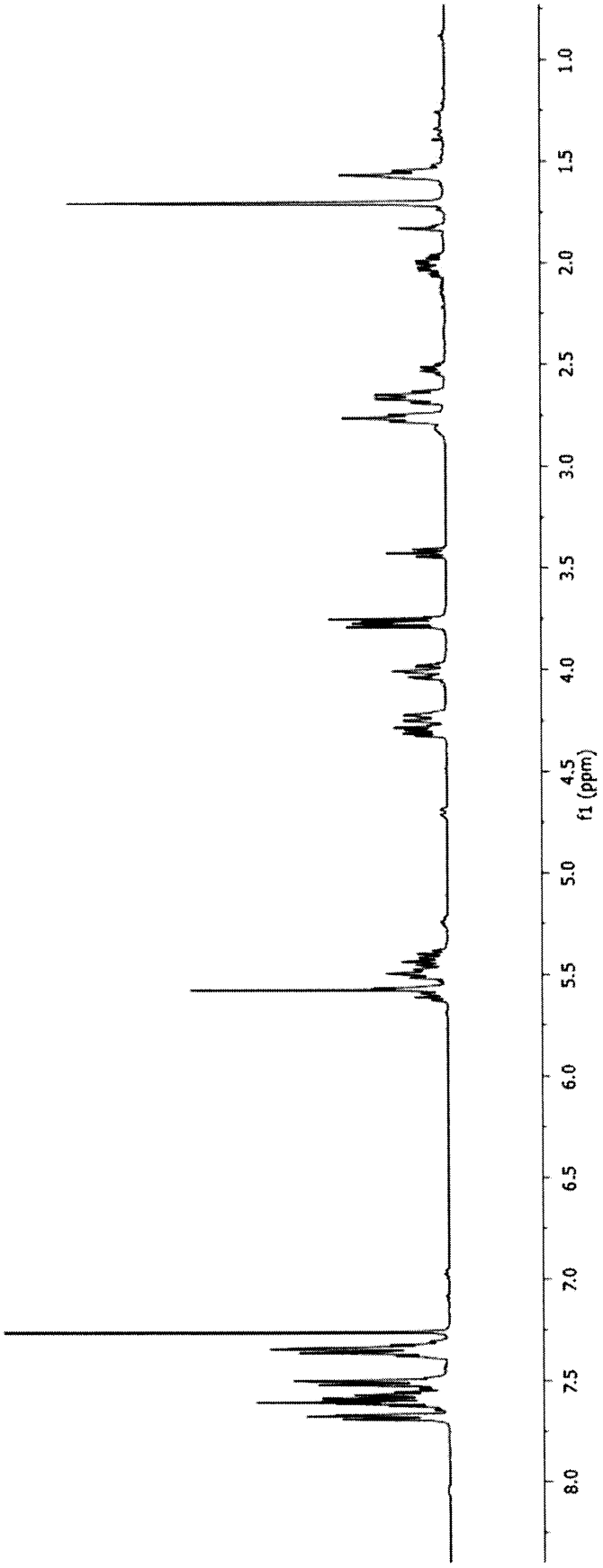
4.8

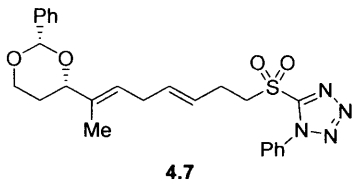



Ph
O
O
O
Me
4.8
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)


Ph
O
O
Me
O
O
S
N
N
N
N
Ph

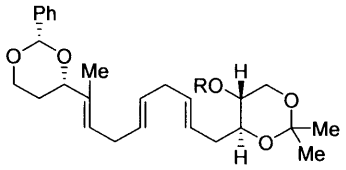
4.7


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


Ph
O
O
Me
O
O
S
N
N
N
N
Ph

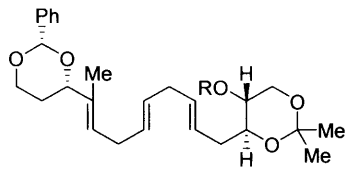
4.7

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)


Ph
O
O
Me
RO
H
O
Me
Me
O
H

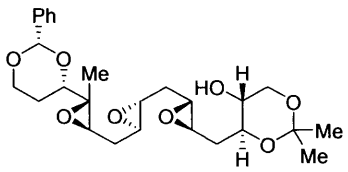
4.23, R = TBDPS

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
5.0
5.5
6.0
6.5
7.0
7.5
8.0


Ph
O
O
Me
RO
H
O
Me
Me
O
H

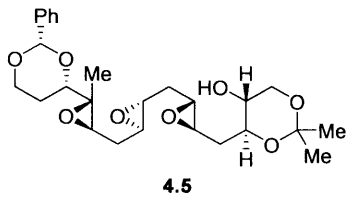
4.23, R = TBDPS

10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)


Ph
O
O
Me
O
O
O
HO
H
O
Me
Me
O
H

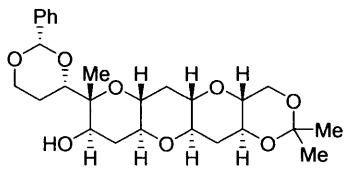
4.5

7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)


Ph
O
O
Me
O
O
O
HO
H
O
Me
O
Me
H

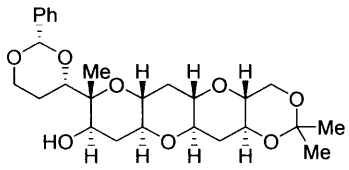
4.5

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)


Ph
O
O
Me
O
H
H
O
H
O
Me
HO
H
H
O
H
H
O
Me

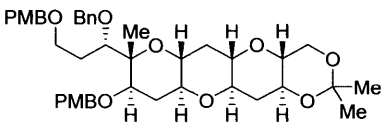
4.4

0.
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0


Ph
O
O
Me
O
H
H
O
H
O
Me
HO
H
H
O
H
O
Me

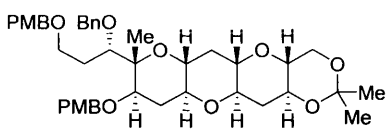
4.4

0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
f1 (ppm)

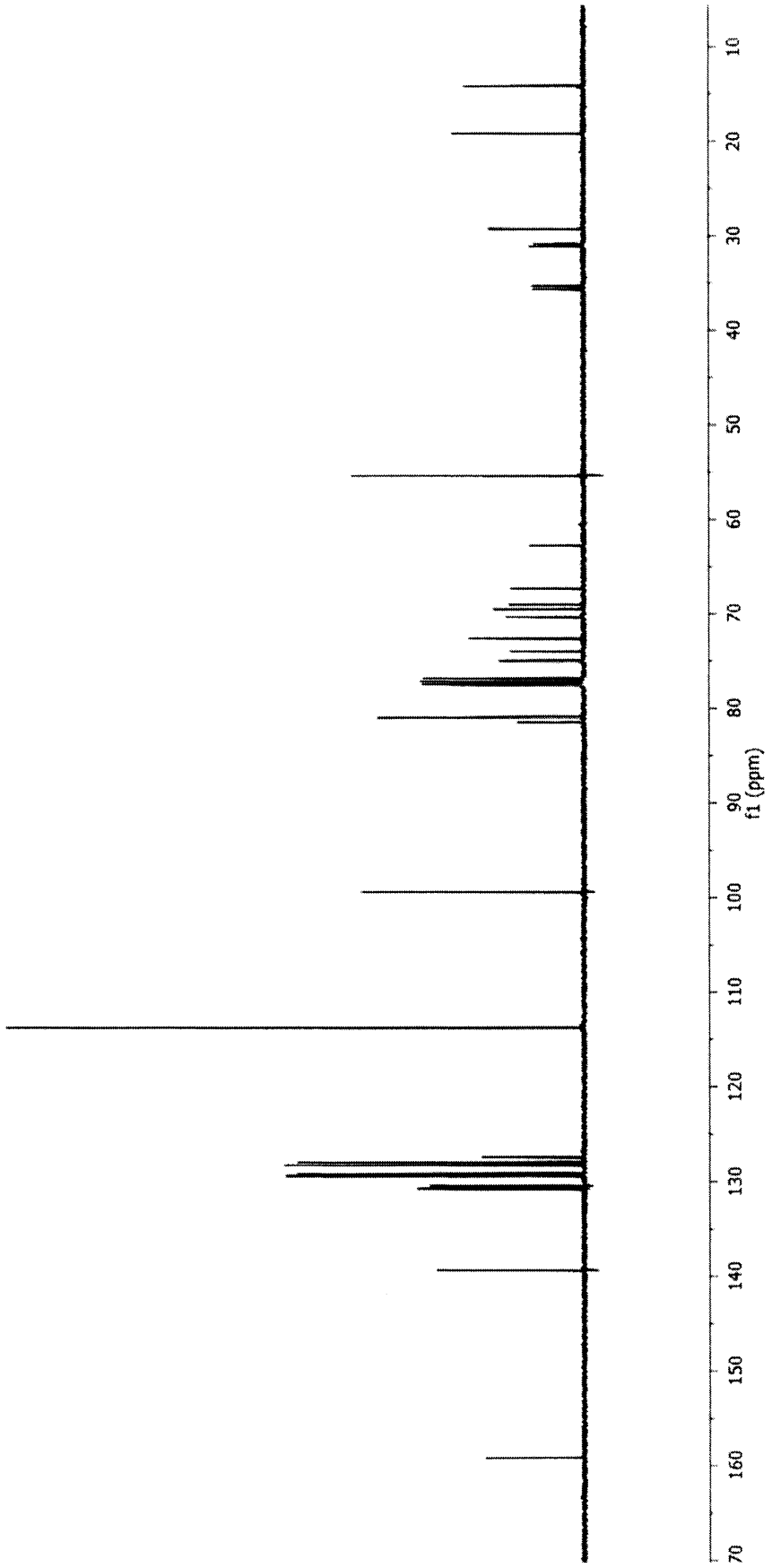

PMBO
BnO
Me
H
H
H
O
O
O
O
O
Me
Me
PMBO
H
H
H
H

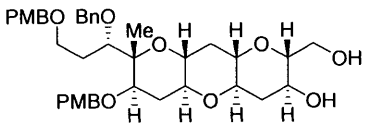
4.14

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


PMBO
BnO
Me
H
H
H
O
O
O
O
O
Me
Me
PMBO
H
H
H
H

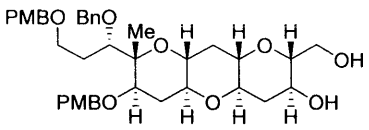
4.14


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)


PMBO
BnO
Me
O
H
H
O
H
OH
PMBO
H
H
O
H
H
OH

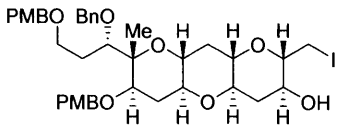
4.24

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
5.0
5.5
6.0
6.5
7.0
7.5


PMBO
BnO
Me
H
H
H
O
O
O
O
OH
PMBO
OH
H
H
H
H

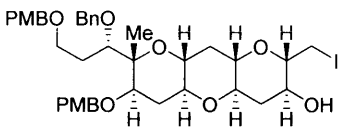
4.24

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)

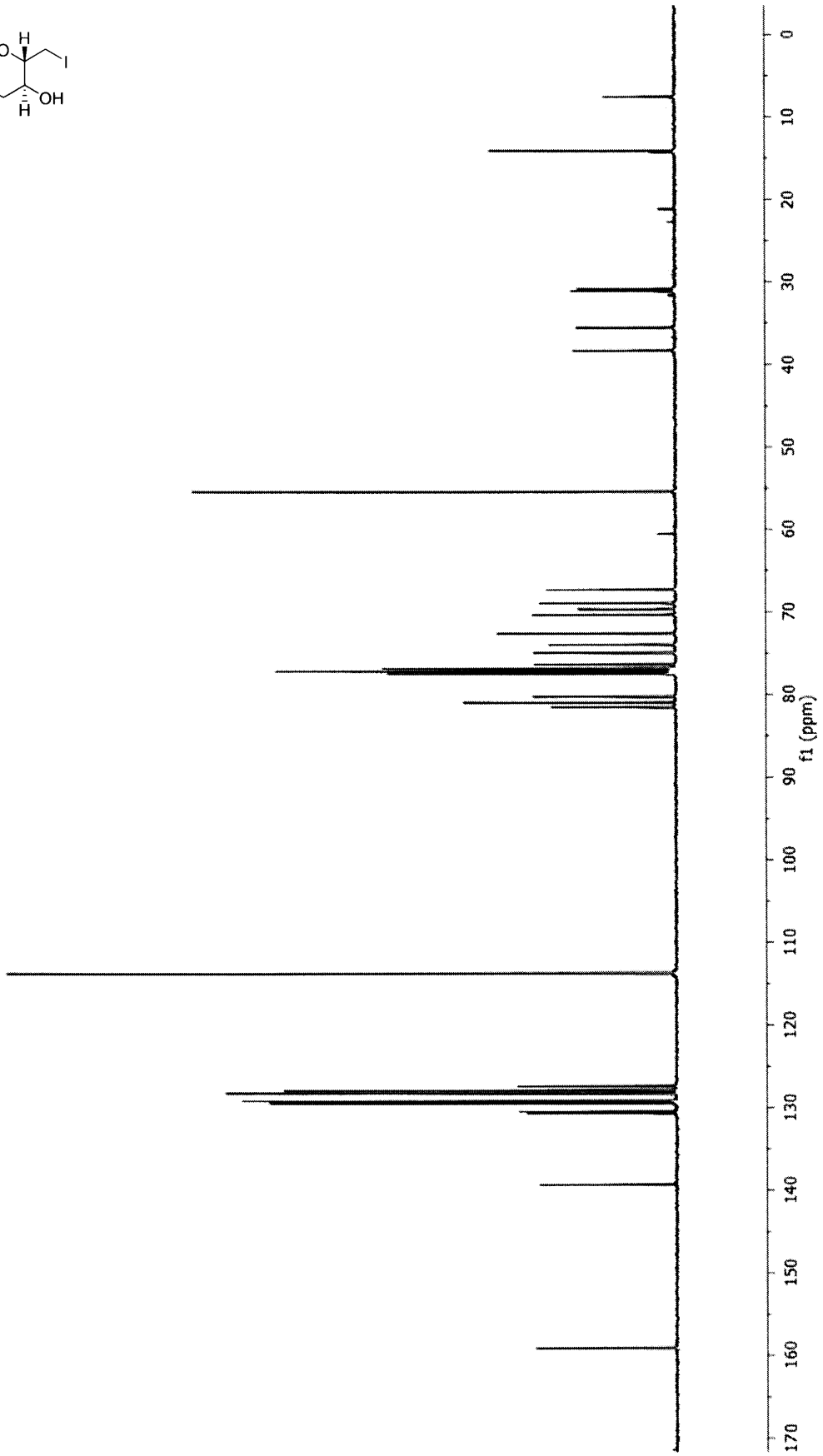

PMBO
BnO
Me
H
H
H
O
O
I
PMBO
H
H
O
H
H
OH

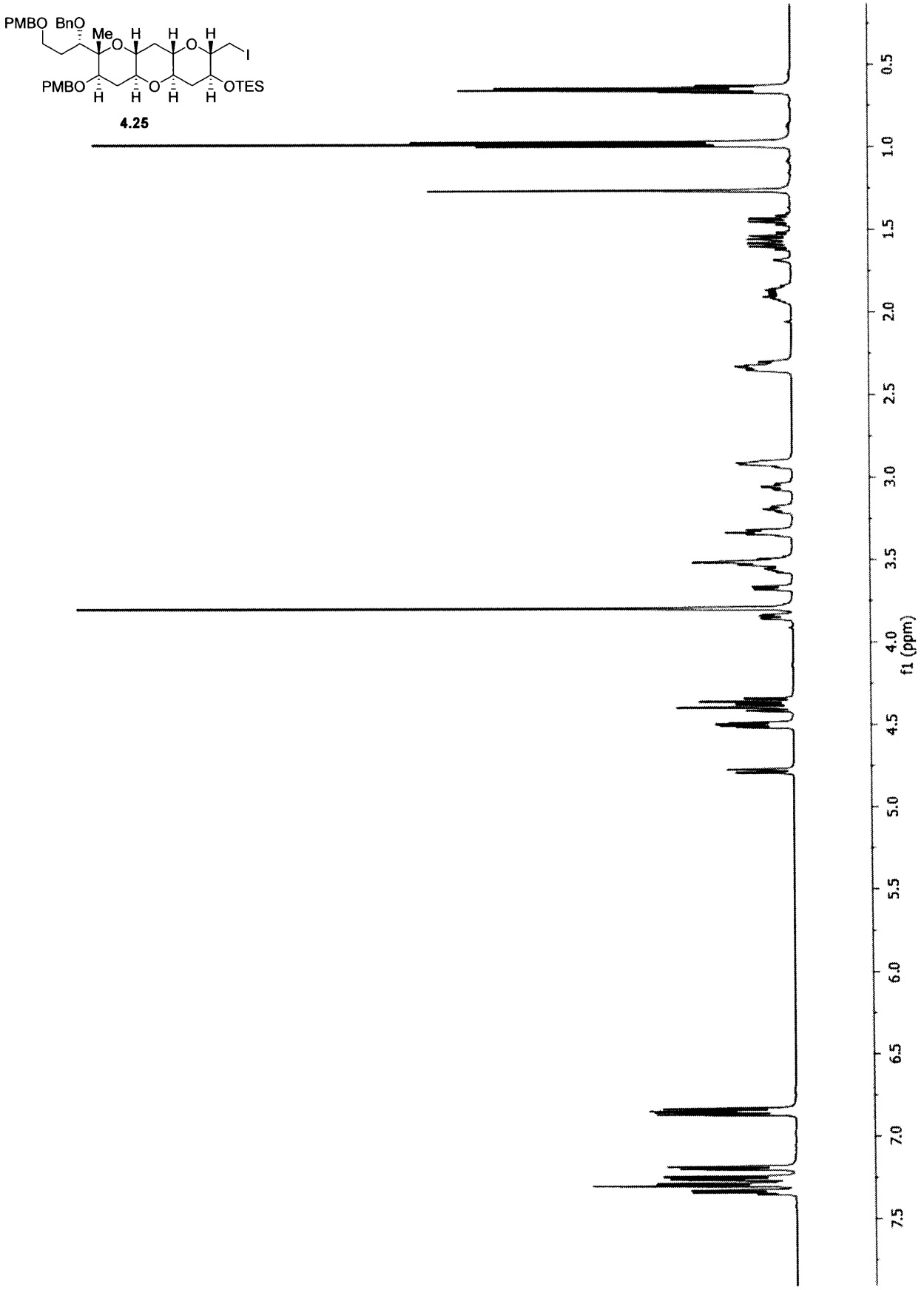
4.15

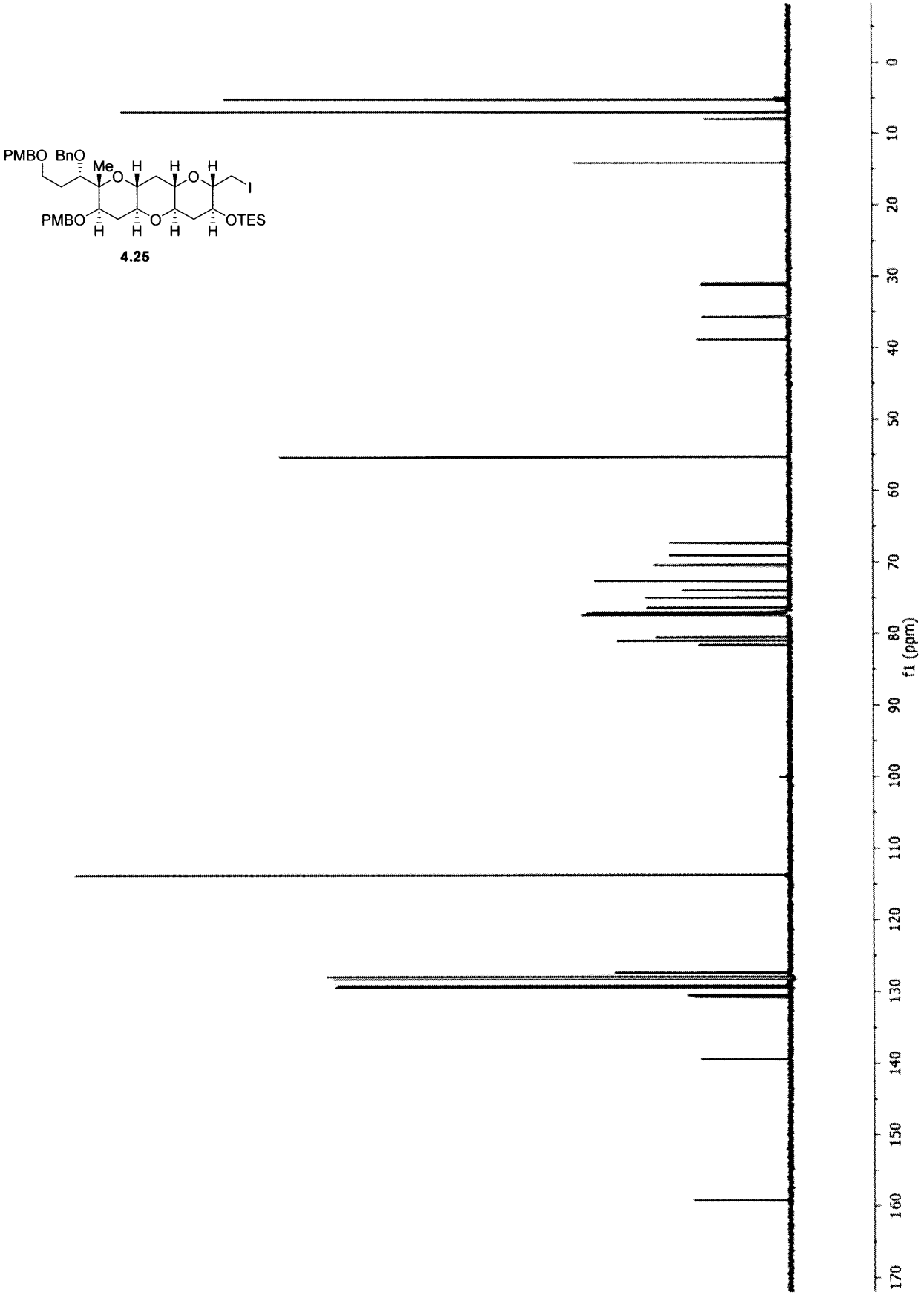
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

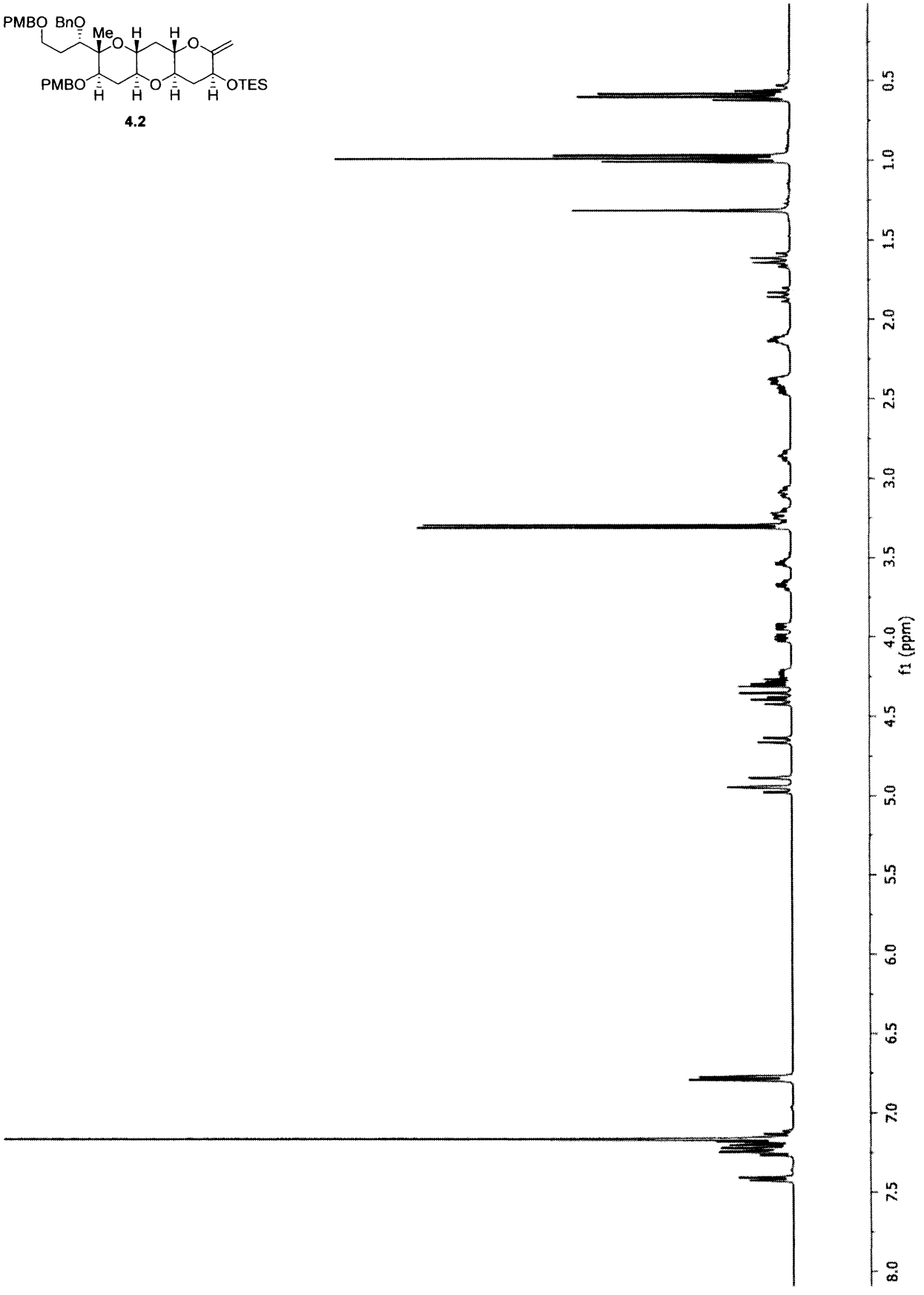

PMBO
BnO
Me
H
H
H
O
O
O
I
PMBO
H
H
O
H
H
OH

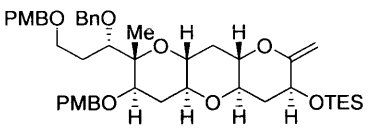
4.15


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)


PMBO
BnO
Me
H
H
H
O
O
I
PMBO
H
H
O
H
H
OTES
4.25
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

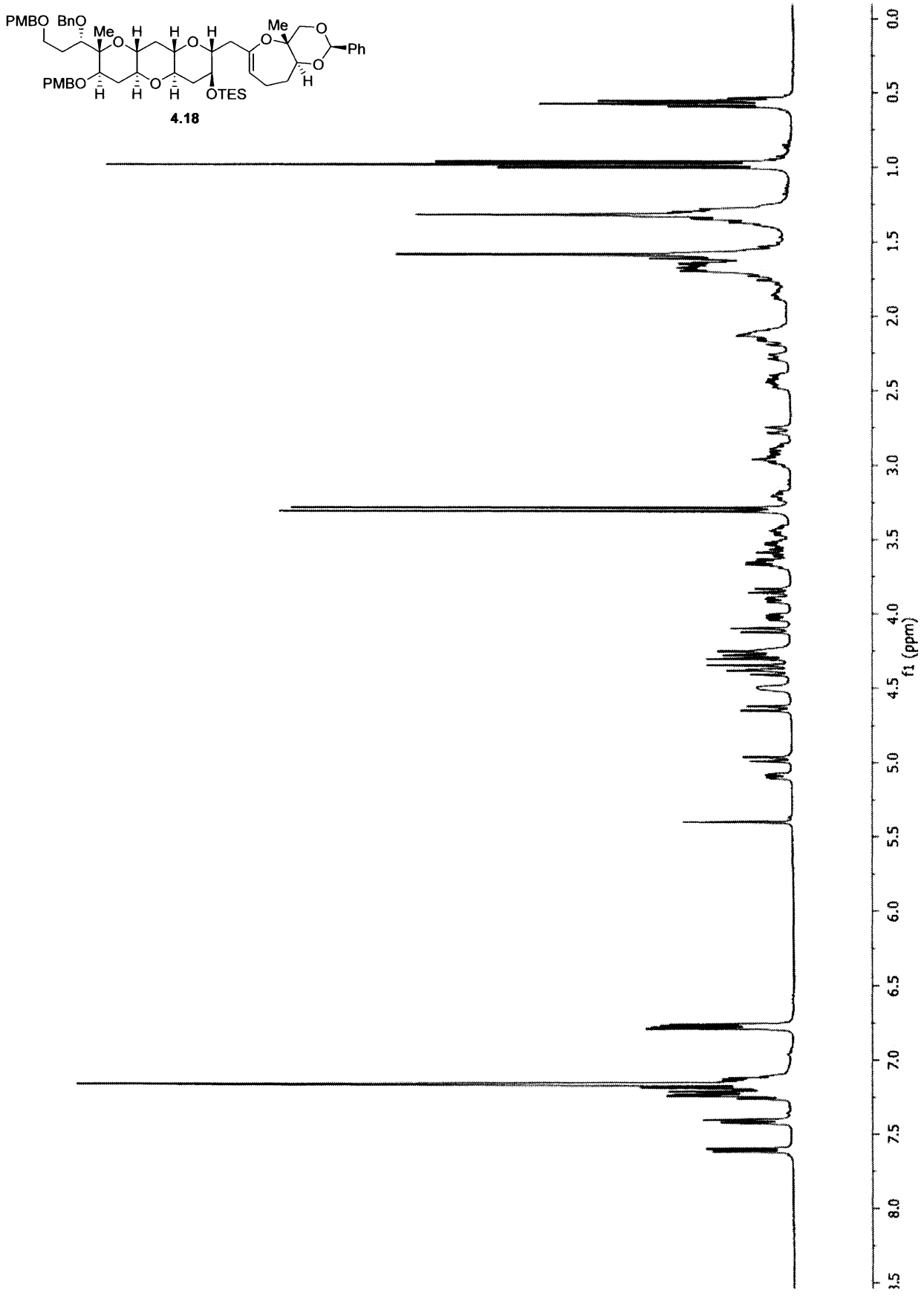

PMBO
BnO
Me
H
H
H
O
O
O
I
PMBO
H
H
O
H
H
OTES
4.25
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

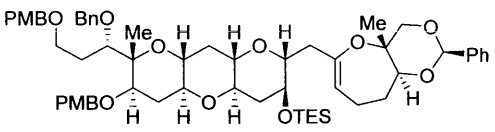

PMBO
BnO
Me
H
H
O
PMBO
H
H
O
H
H
OTES
4.2
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


PMBO
BnO
Me
H
H
O
O
PMBO
H
H
O
H
H
OTES

4.2

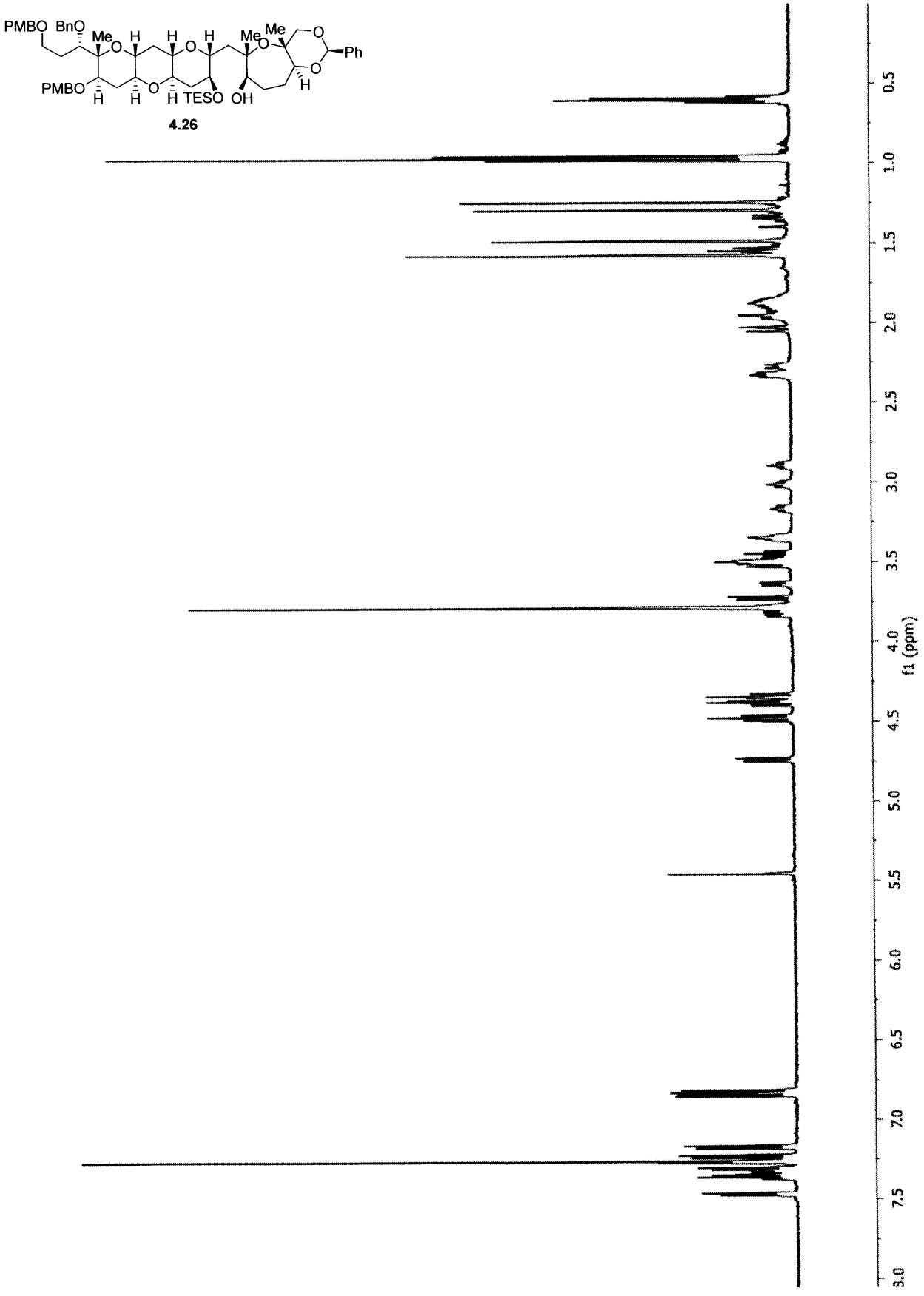
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

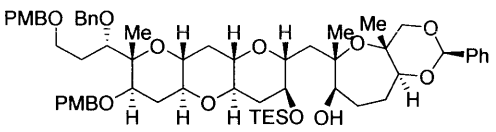

PMBO
BnO
Me
H
H
H
Me
O
Ph
PMBO
H
H
H
OTES
H
4.18
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
O
Ph
PMBO
H
H
H
OTES
H

4.18

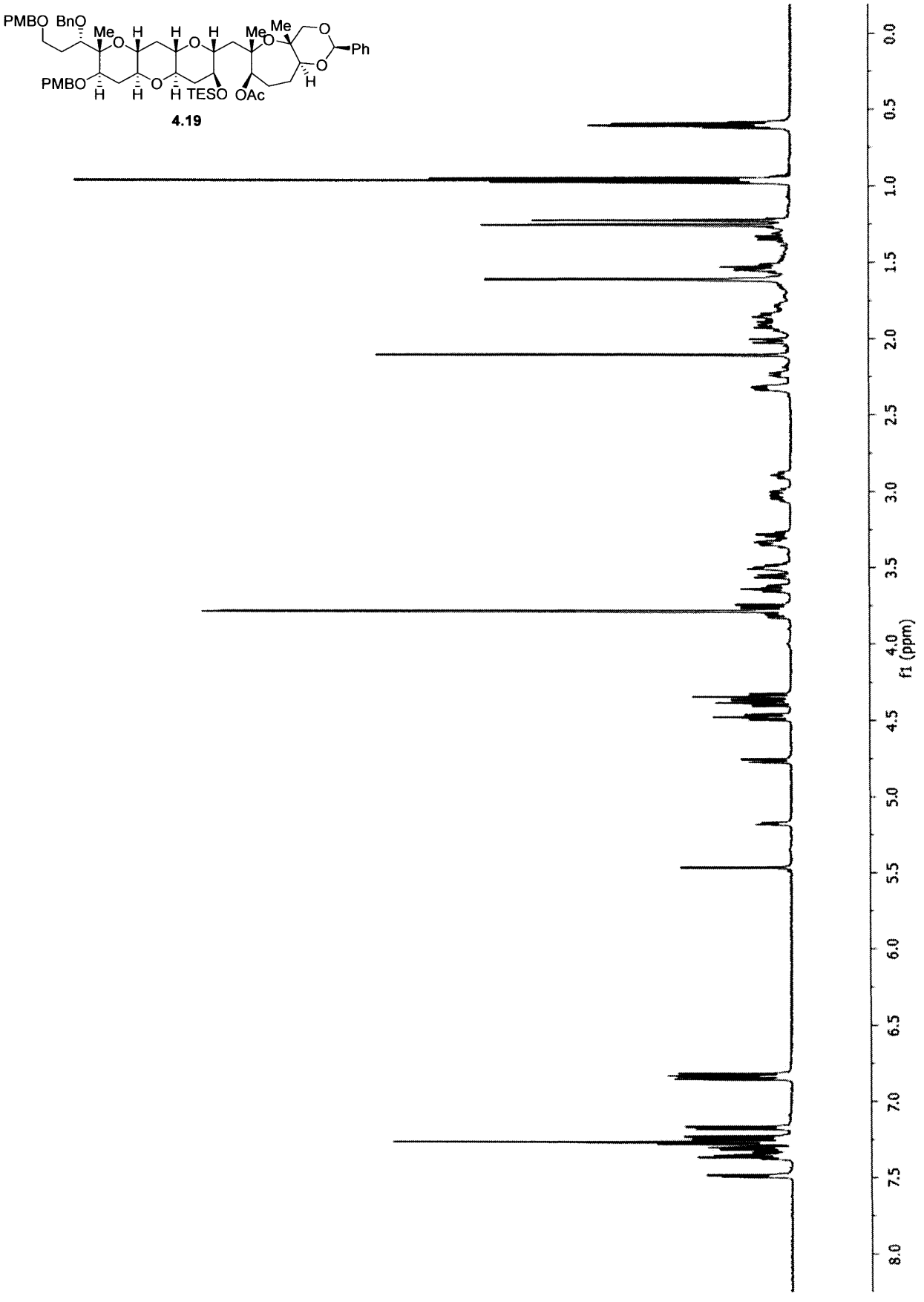
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

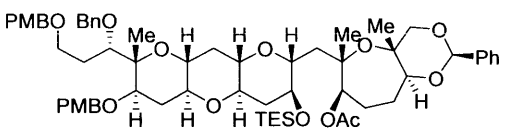

PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
TESO
OH
H
4.26
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
TESO
OH
H

4.26

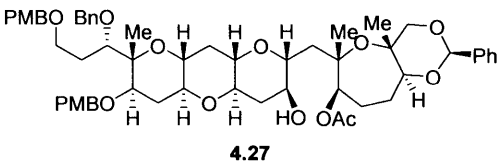
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
O
H
TESO
OAc
H
4.19
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
TESO
OAc
H

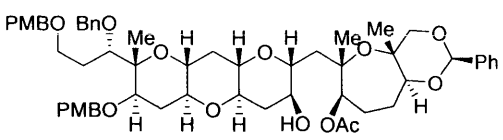
4.19

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
HO
OAc
H

4.27

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)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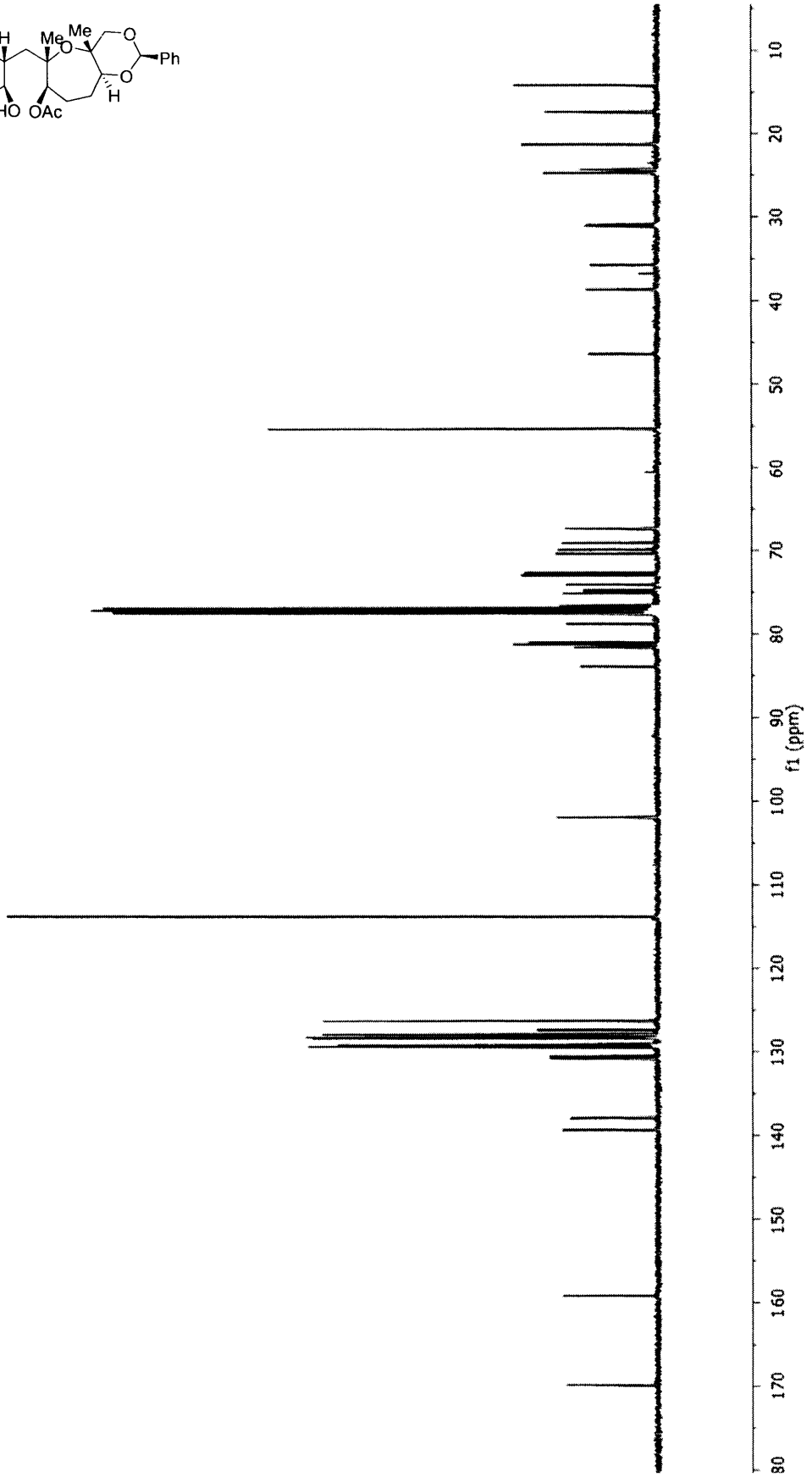
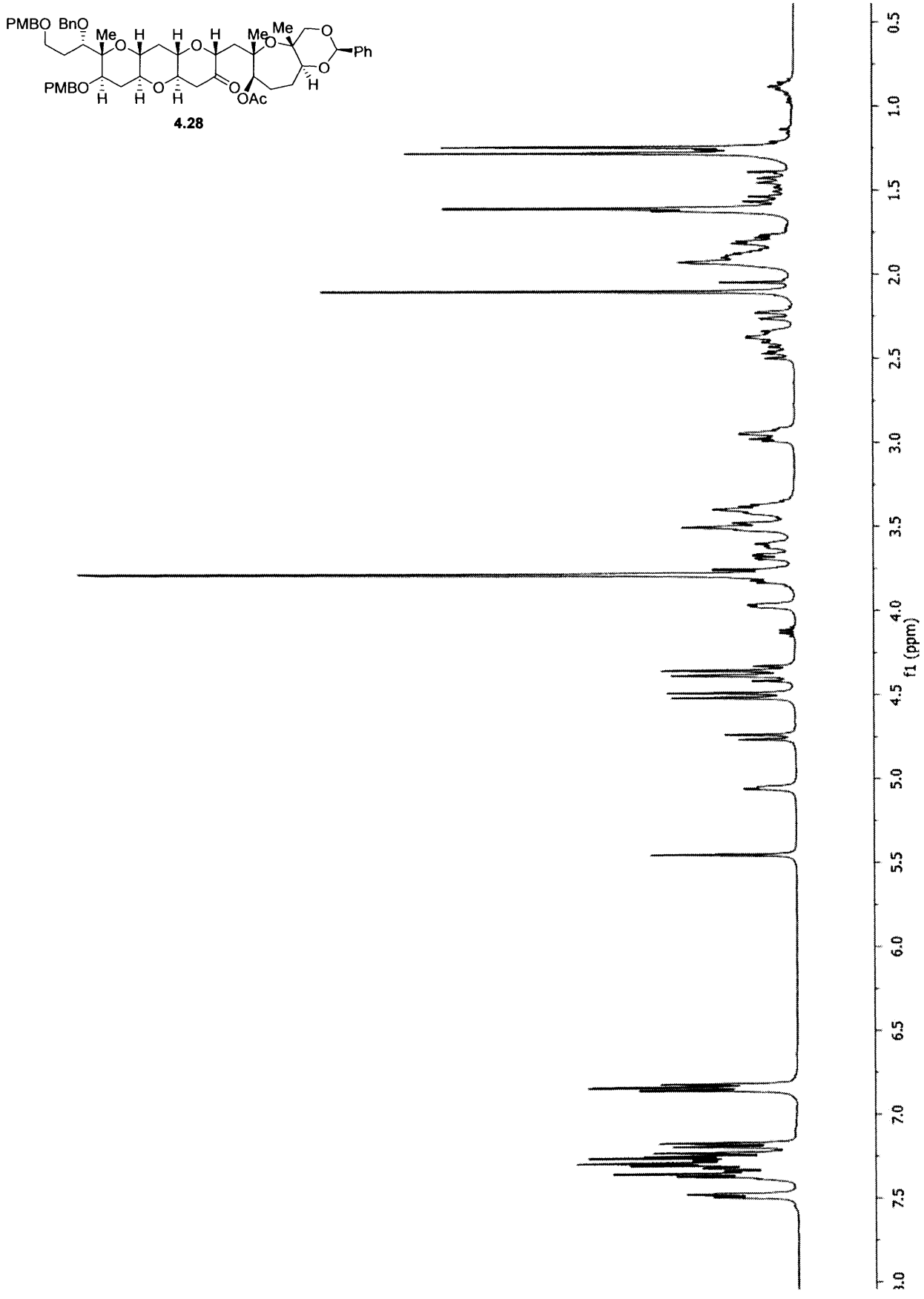
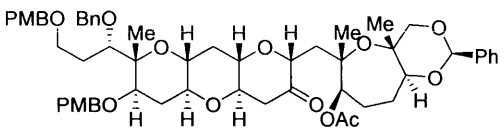
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
HO
OAc
H

4.27

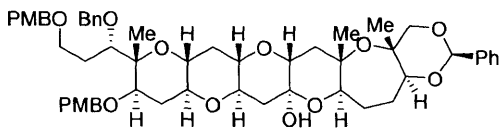

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
OAc
H
4.28
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
O
OAc
H

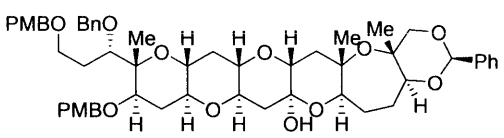
4.28

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
OH
H
H

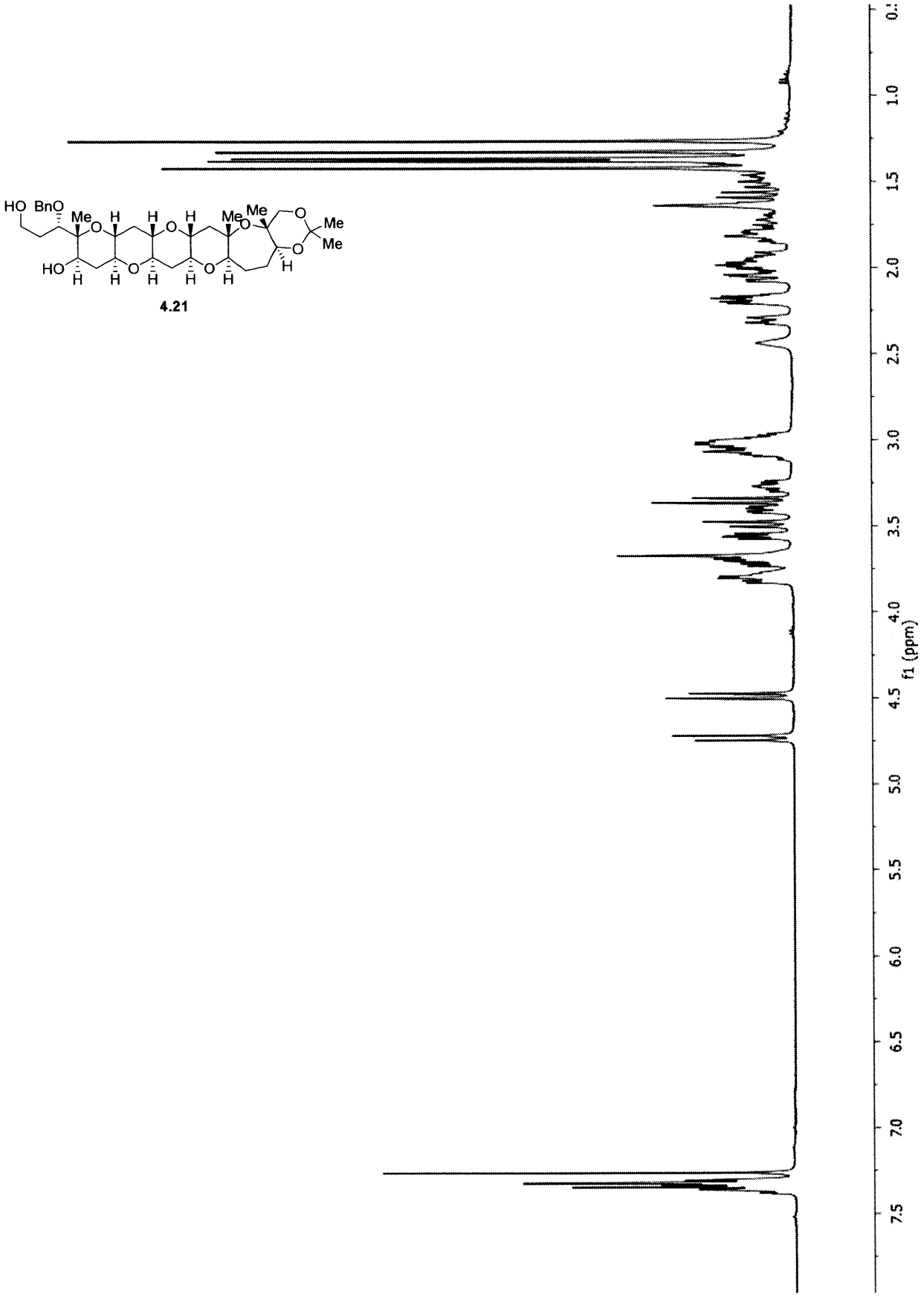
4.20

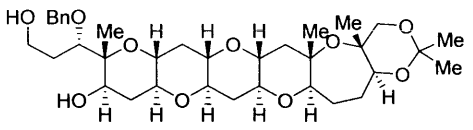
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
5.0
5.5
6.0
6.5
7.0
7.5
.0


PMBO
BnO
Me
H
H
H
Me
Me
O
Ph
PMBO
H
H
H
OH
H
H

4.20

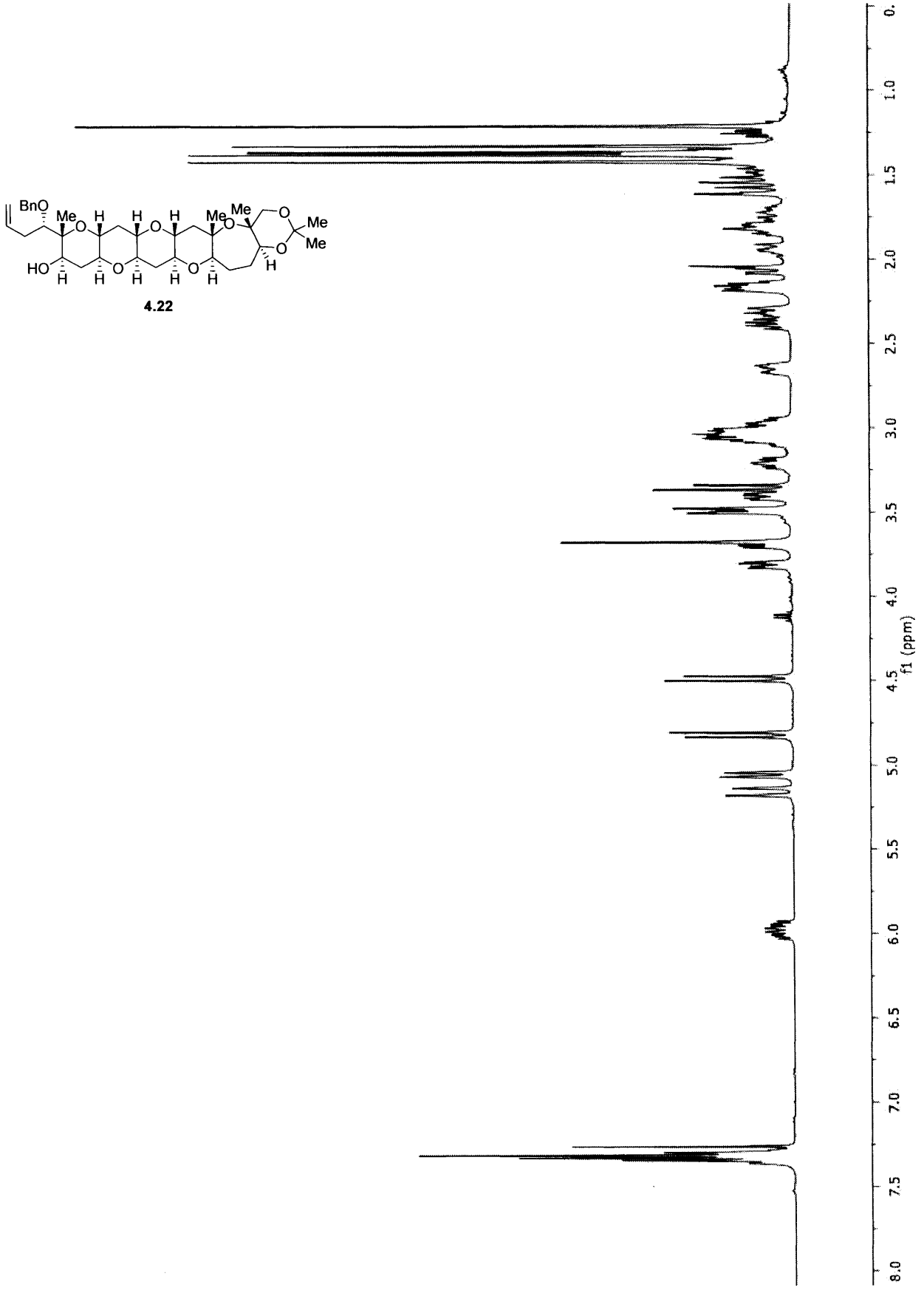
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)


HO
BnO
Me
H
H
H
Me
Me
O
Me
Me
HO
H
H
H
H
H
H
4.21
f1 (ppm)

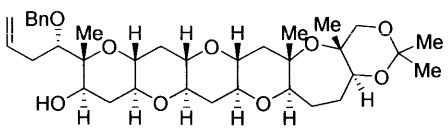

HO
BnO
Me
O
H
H
O
H
Me
Me
O
O
Me
Me
HO
H
H
O
H
O
H
O
H

4.21

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
f1 (ppm)



4.22


BnO
Me
H
H
H
Me
Me
O
Me
Me
HO
H
H
H
H
H
O
O
O
O
O
O
O
H

4.22

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
f1 (ppm)

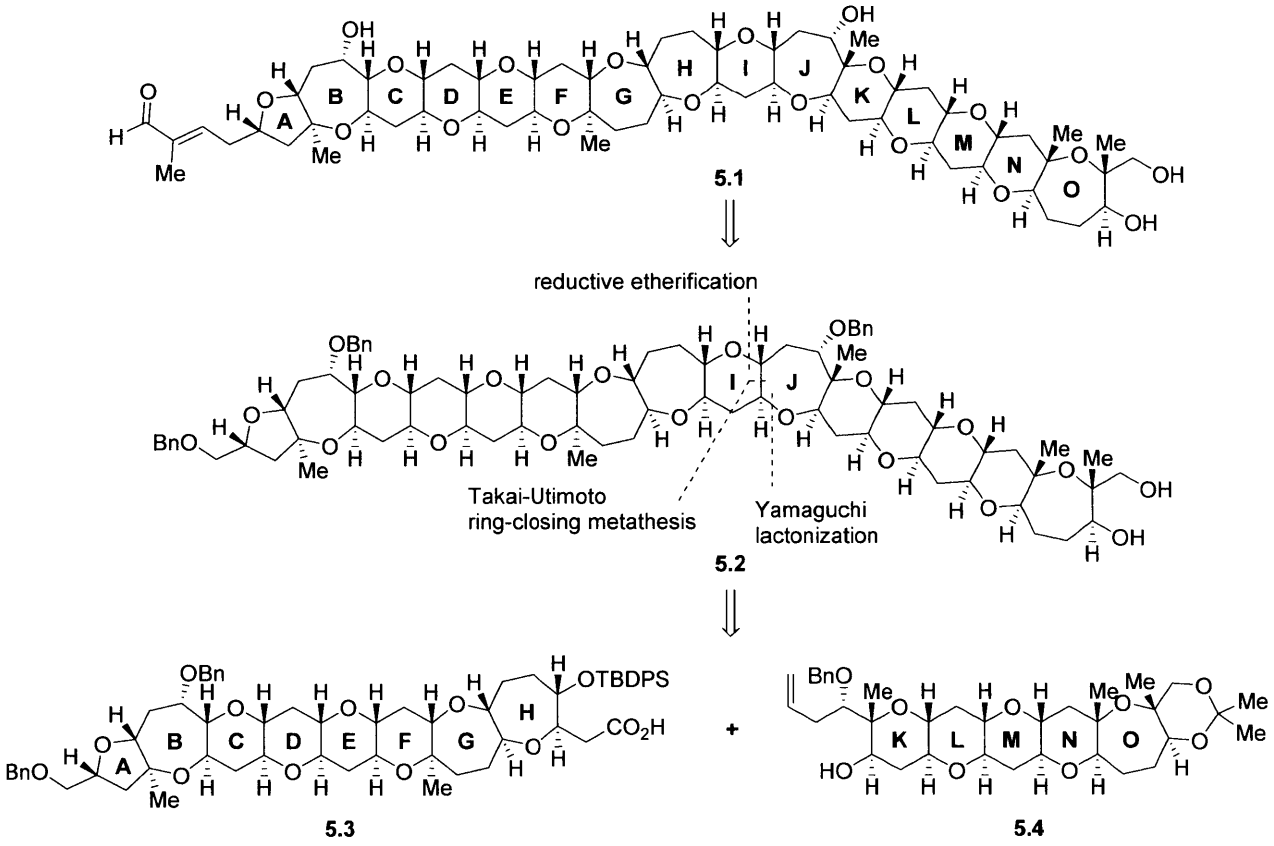
CHAPTER V

Completion Plan

A. Retrosynthetic Analysis: the Last Fragment Union

To complete the synthesis of gymnocin B (**5.1**), we envisioned installation of the 2-methyl-2-butenal side chain to be the last objective (Scheme 1). The polycyclic core of **5.2** would be completed by reductive etherification to forge the remaining tetrahydropyran *I* ring. En route to diol **5.2** was the fragment union between carboxylic acid **5.3** and alcohol **5.4** through Yamaguchi esterification. Takai–Utimoto ring-closing metathesis would then assemble the 7-membered *J* ring.

Scheme 1. Retrosynthetic analysis of **5.1**.

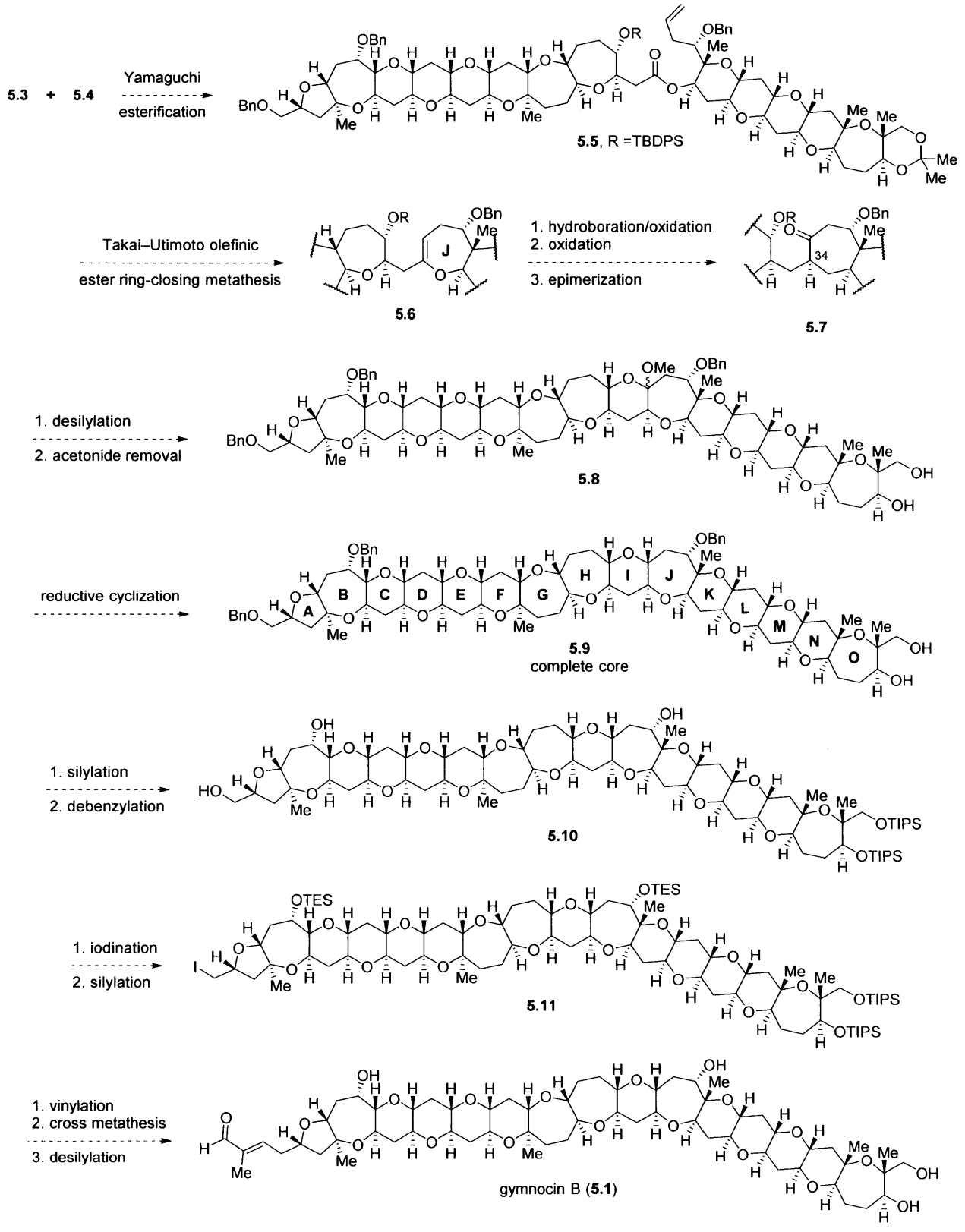


B. Synthetic Plan

Our synthetic plan will commence with Yamaguchi esterification between **5.3** and **5.4** (Scheme 2). Takai–Utimoto ring-closing metathesis[1] of olefinic ester **5.5** will forge the oxepene *J* ring. Hydroboration/oxidation of glycal **5.6** will furnish an alcohol, which will be oxidized to the corresponding ketone. Previous model studies revealed that hydroboration/oxidation of glycals similar to **5.6** was nonselective, giving a 1:1 mixture of diastereomers.[2] However, the same model system also showed that the stereochemical discrepancy at C34 could be corrected via simple epimerization. Desilylation followed by acetonide removal will furnish methoxy acetal **5.8**, which will undergo reductive etherification to forge the entire multi-cyclic core of **5.1**, 15 ether rings in total. Elaboration of diol **5.9** will begin with silylation and exhaustive debenzylation to give triol **5.10**. Selective iodination of the primary alcohol, followed by silyation of the remaining two secondary alcohols, will afford iodide **5.11**. Vinyl cuprate substitution and cross metathesis with methacrolein will install the characteristic butenal side chain. Finally, global deprotection will presumably reveal **5.1**. We anticipate that the total synthesis of **5.1** will be 45 steps longest linear sequence.

[1] Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604.
[2] Sittihan, S.; Jamison, T. F. Unpublished results.

Scheme 2. Completion plan of **5.1**.



At the onset of this project, we formulated three ambitious goals. The first was to complete the total synthesis of gymnocin B. The second was to use epoxide-opening cascades as the primary ring-forming strategies. Lastly, the longest linear sequence should not exceed 45 steps, which amounts to three steps longest linear sequence per ring (LLS/ring). We have achieved our second goal by incorporating four different epoxide-opening cascades in our synthesis. Two nucleophilic epoxide-opening cascades to assemble the polyTHP *CD* and *KLM* units. Two electrophilic epoxide-opening cascades to assemble the fused oxepane *GH* and THF-oxepane *AB* units. The remaining two goals will be achieved in due course. The projected total synthesis of gymnocin B with the anticipated three steps LLS/ring with be a testament to the utility of bioinspired epoxide-opening cascades in the synthesis of MLPs.