SPIRODIEPOXIDES: MECHANISM STUDIES AND APPLICATIONS IN SYNTHESIS

By

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Dr. Lawrence J. Williams Ph.D.

And approved by

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ABSTRACT OF THE DISSERTATION

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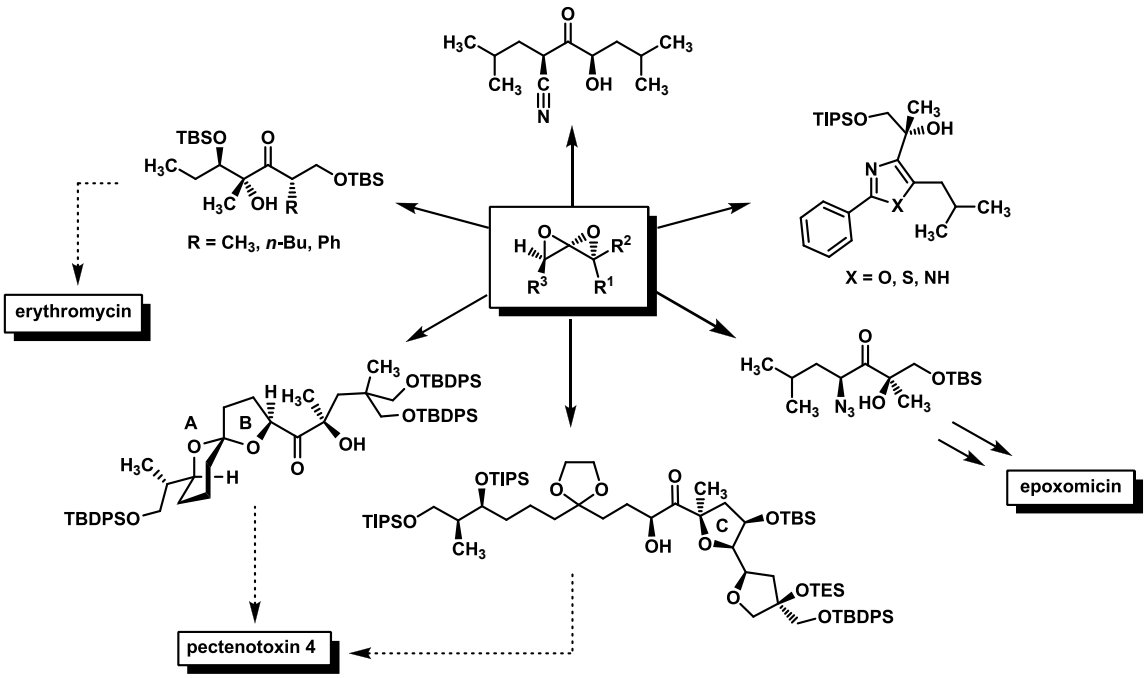
By Stephen Dominic Lotesta

Dissertation Director

Dr. Lawrence J. Williams Ph.D.



Disclosed are studies on the mechanism and reactivity of spirodiepoxides (SDE) and their applications in synthesis. Experimental and computational data led to the

establishment of three discernable mechanisms for nucleophilic opening of SDEs. New SDE-based methodologies have also been developed including the formation of functionalized azoles in a single flask from allenes and the addition of carbon nucleophiles to generate useful precursors to complex polyketides (i.e. erythromycin). Heteroatom additions to SDEs have been identified in the studies towards the potent proteasome inhibitor, epoxomicin. Syntheses of the AB spiroketal and C ring systems of the anticancer natural product, pectenotoxin 4, have also been achieved using SDE-based methods.

Acknowledgements

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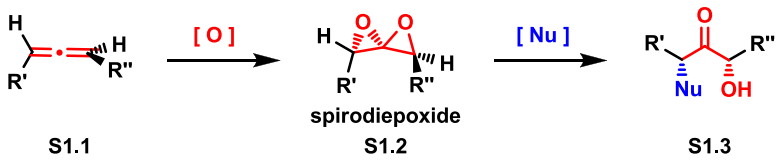
Chapter 1

Background on Spirodiepoxides (SDEs)

I. Introduction to Spirodiepoxides

Described here are studies on the structure and reactivity of the spirodiepoxide (SDE) functional group (**S1.2**, Scheme 1, pg. 1). Unlike the reactivity of epoxides, SDEs can be opened by nucleophiles to give a product with a new ketone, alcohol, and substituent corresponding to the nucleophile (see below **S1.1→S1.2→S1.3**, Scheme 1, pg. 1). Arising from the double epoxidation of allenes, this single flask process stereoselectively converts the chiral axis of the allene into two centers of chirality that flank the carbonyl.

Scheme 1 Formation and Reactivity of SDEs



S1.1 S1.2 S1.3

SDE transformations can be categorized as cascade reactions. Cascade reactions, also known as domino reactions, provide a means for the concise introduction of molecular complexity by multiple bond breaking and bond making events in a single operation.[1] These types of reactions are among the most powerful transformations in organic synthesis as they offer shorter and more efficient routes to complex molecules.

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

The cascade reactivity of SDEs allows direct entry into densely functionalized structures, including both cyclic and acyclic motifs.

New methods that use SDEs enable the conversion of unfunctionalized allene hydrocarbons into highly oxygenated motifs found in an array of biomedically relevant natural products. Structural motifs found in the natural products epoxomicin,[2] 9-*(S)*-dihydroerythronolide A,[3] and pectenotoxin 4[4] were studied and will be discussed (Figure 1, pg. 3). Since SDE-based methods simultaneously establish multiple connectivities, this approach influences complex molecule strategic design. Figure 1 indicates portions of molecules that might be derived from SDEs and their corresponding nucleophilic counterparts, as indicated in red and blue respectively.

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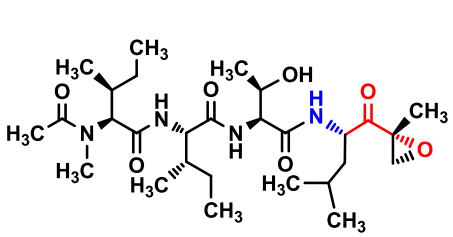
(2) For epoxomicin isolation papers see: (a) Hanada, H.; Sugawara, K.; Kaneta, K.; Toda, S.; Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1746. (b) Meng, L.; Mohan, R.; Kwok, B. H. B.; Elofsson, M.; Sin, N.; Crews, C. M. *Proc. Natl. Acad. Sci. U.S.A.*, **1999**, *96*, 10403. For a previous synthesis of epoxomicin see: Sin, N.; Kim, K. B.; Elofsson, M.; Meng, L.; Auth, H.; Kwok, B. H. B.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2283.

(3) For structural and synthetic studies related to erythromycin, erythronolide A, and 9-(*S*)-dihydroerythronolide A see: (a) Peng, Z.; Woerpel, K. A. *J. Am. Chem. Soc*. **2003**, *125*, 6018. (b) Muri, D.; Fraefel-Lohse, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *117*, 4104 and references cited therein.

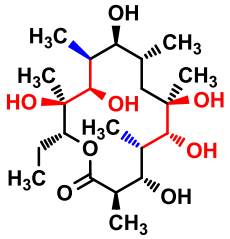
(4) For pectenotoxin 4 isolation papers see: (a) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.,* **1998**, *63*, 2475. (b) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron.* **1985**, *41*, 1019. For pectenotoxin synthetic studies see: (c) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4569. (d) Evans, D. A.; Rajapakse, H. A.; Chiu, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4573. (e) Kolakowski, R. V.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 4761. (f) Vellucci, D.; Rychnovsky, S. *Org. Lett.* **2007**, *9*, 711. (g) D. Fujiwara, K.; Aki, Y.; Yamamoto, F.; Kawamura, M.; Kobayashi, M.; Okano, A.; Awakura, D.; Shiga, S.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2007**, *48*, 4523. (h) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659. (i) Fujiwara, K.; Kobayashi, M.; Yamamoto, F.; Aki, M.; Kawamura, M.; Awakura, D.; Amano, S.; Okano, A.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 5067. (j) Bondar, D.; Liu, J.; Muller, T.; Paquette L. A. *Org. Lett.* **2005**, *7*, 1813 (k) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron*, **2004**, *60,* 9589. (l) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849. (m) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.*, **2002**, *4*, 937. (n) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (o) Awakura, D.; Fujiwara, K.; Murai, A. *Syn. Lett.* **2000**, 1733. (p) Amano, S.; Fujiwara, K.; Murai, A. *Syn Lett*. **1997**, 1300. (q) O'Connor, P. D.; Knight, C. K.; Friedrich, D.; Peng, X.; Paquette, L. A. *J. Org. Chem.* 2007, *72*, 1747. For a review on pectenotoxin synthetic studies see: (r) Halim, R.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 4048.

Since their initial discovery in 1968,[5] SDEs have emerged as a synthetically useful functional group only within the last 4 years.[6] Up until 2004, less than 25 reports pertaining to SDEs existed,[5,7-13] unlike epoxides, which have been referenced in over

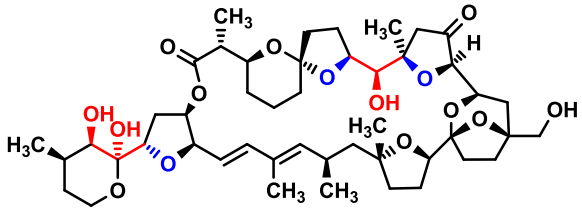
Figure 1 Natural Products Studied Using SDE-Based Methods



epoxomicin (F1.1)



9-(S)-dihydroerythronolide A (F1.2)



pectenotoxin 4 (F1.3)

(5) (a) Crandall, J. K.; Machleder, W. H., *J. Am. Chem. Soc.* **1968**, *90*, 7292. see also: (b) Reeves, W. P.; Stroebel, G. G. *Tetrahedron Lett*. **1971**, *12*, 2946. (c) Greibrokk, T.; Skattebol, L. *Acta Chem. Scand.* **1973**, *27*, 1421.

(6) (a) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett*, submitted. (b) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869. (c) Lotesta, S. D.; Kiren, S. K.; Sauers, R. R.; Williams, L. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 15. (d) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (e) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (f) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc*. **2004**, *126*, 15348, and references cited therein.

(7) (a) Crandall, J. K.; Machleder, W. H.; Thomas, M. J., *J. Am. Chem. Soc.*, **1968**, *90*, 7346. (b) Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347. (c) Crandall, J. K.; Machleder, W. H. *J. Het. Chem.* **1969**, *6*, 777. (d) Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723. (e) Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338. (f) Crandall, J. K.; Batal, D. J. *Tetrahedron Lett.* **1988**, *29*, 4791. (g) Crandall. J. K.; Rambo, E. *J. Org. Chem.* **1990**, *55*, 5929. (h) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Ling, F. *J. Org. Chem*. **1991**, *56*, 1153. (i) Crandall, J. K.; Batal, D. J.; Lin, F.; Riex, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427. (j) Crandall, J. K.; Rambo, E. *Tetrahedron Lett*. **1994**, *35*, 1489. (k) Crandall, J. K.; Reix, T. *Tetrahedron Lett*. **1994**, *35*, 2513. (l) Crandall, J. K.; Rambo, E. *Tetrahedron* **2002**, 7027.

(8) (a) Boeseken, J., *Rec. Trav. Chim. Pays-Bas*. **1935**, *54*, 657. (b) Pansevich-Kolyada; Idelchik, Z. B.; *J. Gen. Chem. USSR*, **1954**, *24*, 1601.

(9) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem*. **2002**, *67*, 1339.

(10) Krause, N.; Laux, M. *Synlett* **1997**, 765.

(11) Andrews, D. R.; Giusto, R. A.; Sudhakar, A. R. *Tetrahedron Lett.* **1996**, *37*, 3417.

(12) Marshall, J. A.; Tang, Y. *J. Org. Chem*. **1994**, *59*, 1457.

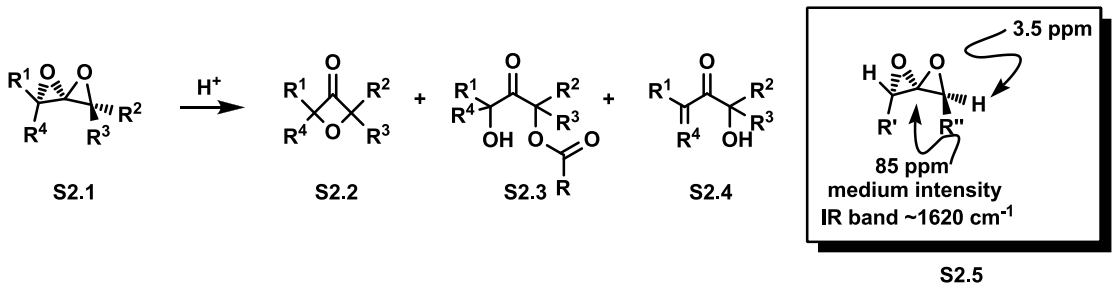
(13) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1993**, *58*, 3233.

55,000 literature citations.[14] Crandall was the primary contributor of the early studies on SDE formation and reactivity. He studied relatively simple and unfunctionalized systems. A more thorough mechanistic and structural investigation on the reactivity of SDEs was recently established by our group along with applications in complex molecule synthesis. The following section will give an overview on the background of SDE formation and reactivity.

II. Background of Spirodiepoxide Formation and Reactivity

SDEs were initially formed by allene oxidation using peracid oxidants such as m-CPBA. However, in the presence of acid (i.e. carboxylic acids) SDEs rapidly decompose and lead to the formation of oxetanones (**S2.2**, Scheme 2, pg. 4), hydroxy ketones (**S2.3**), and elimination products (**S2.4**).[5,7a-h] Since the by-product of an m-CPBA oxidation is a carboxylic acid (m-CBA), this peracid oxidant is not well suited for formation and characterization of SDEs. In order to allow for the formation and characterization of a

Scheme 2 SDE Instability Towards Acid

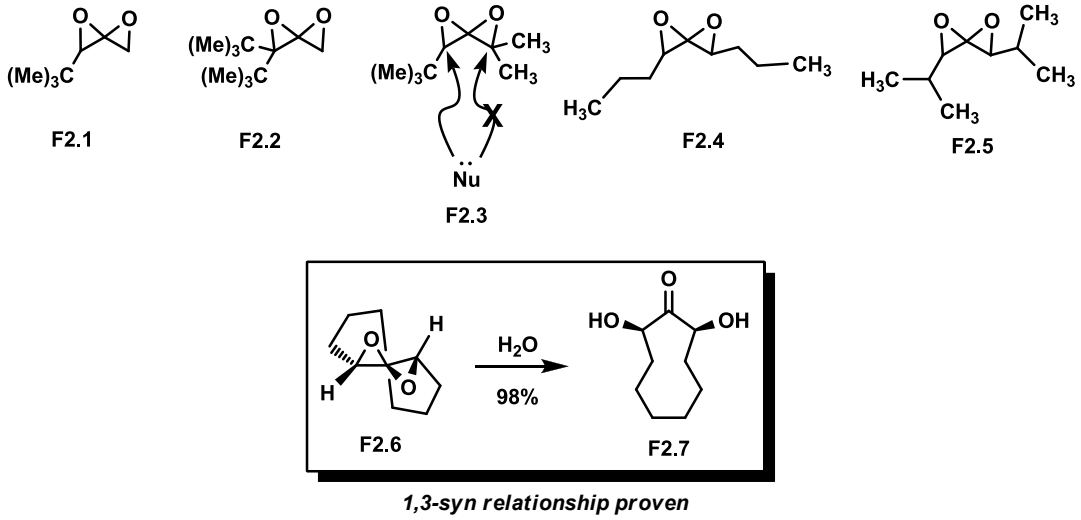


(14) Scifinder Scholar, Version: 2007, general epoxide structure search with a total synthesis keyword refinement.

SDE, a neutral oxidant such as dimethyl dioxirane (DMDO)[15] is used to avoid SDE decomposition.[7e] SDEs give characteristic IR and NMR signals[7h] at 1620 cm^{-1} and 3.5 ppm (^{1}H) and 85 ppm (^{13}C) respectively (**S2.5**).

Most SDEs studied by Crandall were derived from unfunctionalized, achiral, and symmetric allenes (**F2.1-F2.5**, Figure 2, pg. 5). Both inter- and intramolecular nucleophilic additions were studied and gave yields between 17-95% (typically near 50%).[7h] For the intermolecular additions heteroatom nucleophiles such as water, alcohols, acetic acid and amines were studied as well as a few examples of imidazole, thiophenol, fluoride and chloride additions. These intermolecular additions were shown to occur at the most accessible site of the SDE, with neopentyl sites favored over tertiary sites (**F2.3**). Nucleophilic addition of primary alcohols was efficient, however, a secondary

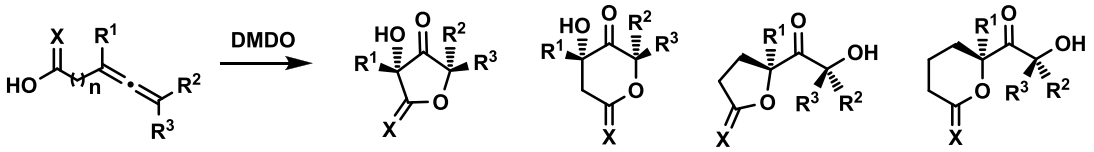
Figure 2 Previously Studied SDE Systems



(15) For the original procedure to prepare DMDO in acetone see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. For a procedure to prepare DMDO in chloroform see: (b) Gilbert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron*, **1997**, *53*, 8643. (c) Ferrer, M.; Gilbert, M.; Sandez-Baeza, F.; Messeguer, A. *Tetrahedron Lett.*, **1996**, *37*, 3585. (d) For our modified procedure to prepare DMDO see Experimental Data (Chapter 8, pg. 108).

alcohol proceeded in low yield and no additions of tertiary alcohols were reported. In the instance of water addition to a 9-membered SDE containing compound (**F2.6**) the stereochemistry of the corresponding keto-diol (**F2.7**) was proven to be syn.[7h] This was the only instance, prior to our work, where the stereochemistry was proven for nucleophilic addition to a SDE. A stereochemical model for SDE formation will be discussed in Chapter 2.

Scheme 3 Intramolecular Additions of Alcohols and Acids to SDEs

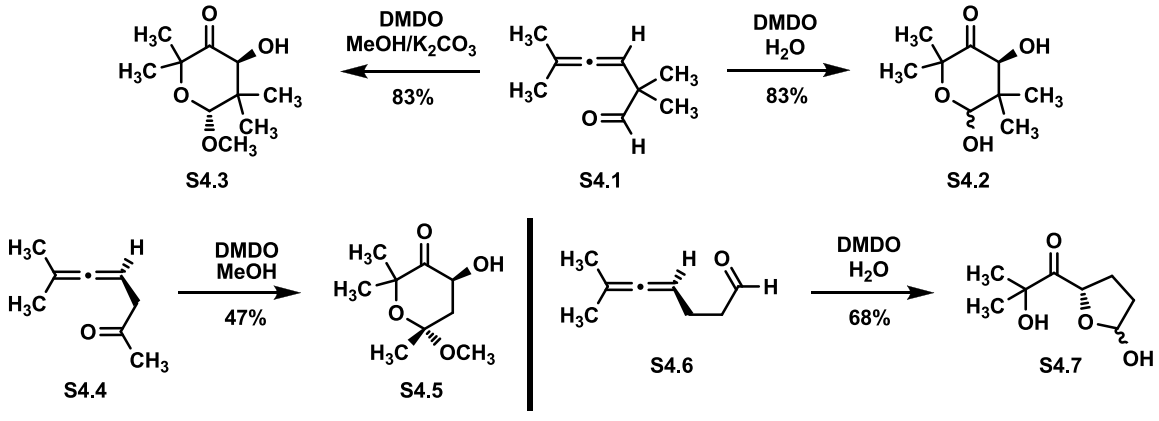


For intramolecular additions to SDEs, allenes tethered with both alcohols and carboxylic acids were investigated (Scheme 3, pg. 6). For this study, relatively simple allenes were used having either CH_3 or H substituents at R^1, R^2 and R^3 (**S3.1**). Two furanones (**S3.2**), six pyranones (**S3.3**), and three acyl-substituted furans (**S3.4**) were prepared from the corresponding allenic alcohols.[7f,7i] A single example of the formation of an oxepanyl ketone (X = H_2, n = 5) was also reported. Five intramolecular couplings with carboxylic acids were shown to give the corresponding substituted lactones (X = O, **S3.3** – **S3.5**).[7g,7k] In contrast to intermolecular reactions, both primary and tertiary alcohols were shown to react intramolecularly with no secondary alcohol additions reported. The presence of a carbon substituent at the site of nucleophilic attack was allowed and appeared to be required for 5-endo-tet cyclizations (**S3.1**→**S3.2**, X=H_2).[7i]

Presumably, this "Baldwin disallowed"[16] cyclization occurs via development of partial cationic character on the attacked SDE carbon which would alleviate the otherwise poor transition state geometry required for cyclization. This partial ionization would be stabilized by alkyl substitution (R^2 and R^3).

Crandall also reported examples of intramolecular additions of aldehydes and ketones to SDEs.[7j] Since DMDO is capable of oxidizing aldehydes to acids,[15a] the oxidation of allenic aldehydes was initially examined in order to access lactones (Scheme 3, **S3.3-S3.5**, X=O). However, aldehyde oxidation is generally slower than allene oxidation and therefore products were obtained from nucleophilic opening of SDEs by aldehydes and ketones (Scheme 4, pg. 7). Oxidation of **S4.1** using wet DMDO gave an 83% yield of a 1:1 mixture of anomers from the 6-endo-tet cyclization (**S4.2**). In the presence of methanol and K_2CO_3, the SDE derived from **S4.1** afforded cyclic acetal **S4.3** in high yield (83%). 5-exo-tet cyclizations of aldehydes were also demonstrated by formation of **S4.7** from **S4.6** upon exposure to wet DMDO. A ketone was also shown to

Scheme 4 Intramolecular Additions of Aldehydes and Ketones to SDEs



(16) Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734.

add intramolecularly to a SDE. Thus, oxidation of keto-allene **S4.4** in the presence of methanol gave cyclic acetal **S4.5** (47%).

In many of these earlier reports only a limited number of nucleophiles and allenes were studied. Since SDEs were thought to be highly unstable, substrates for the intramolecular reactions were designed to rapidly cyclize upon SDE formation. Symmetrical allenes were used, which avoided the possibility of forming diastereomeric mixtures. Where diastereomeric mixtures were possible, the stereoselectivity was usually stereorandom. In more complex and unsymmetrical allene systems the stereoselectivity of DMDO oxidation becomes important. Thus, a stereochemical model for allene oxidation needed to be established. The following chapter will discuss a stereochemical model for allene oxidation based on our current research and is consistent with all relevant previously reported SDE data.

Chapter 2

Stereochemical Model for Allene Oxidations

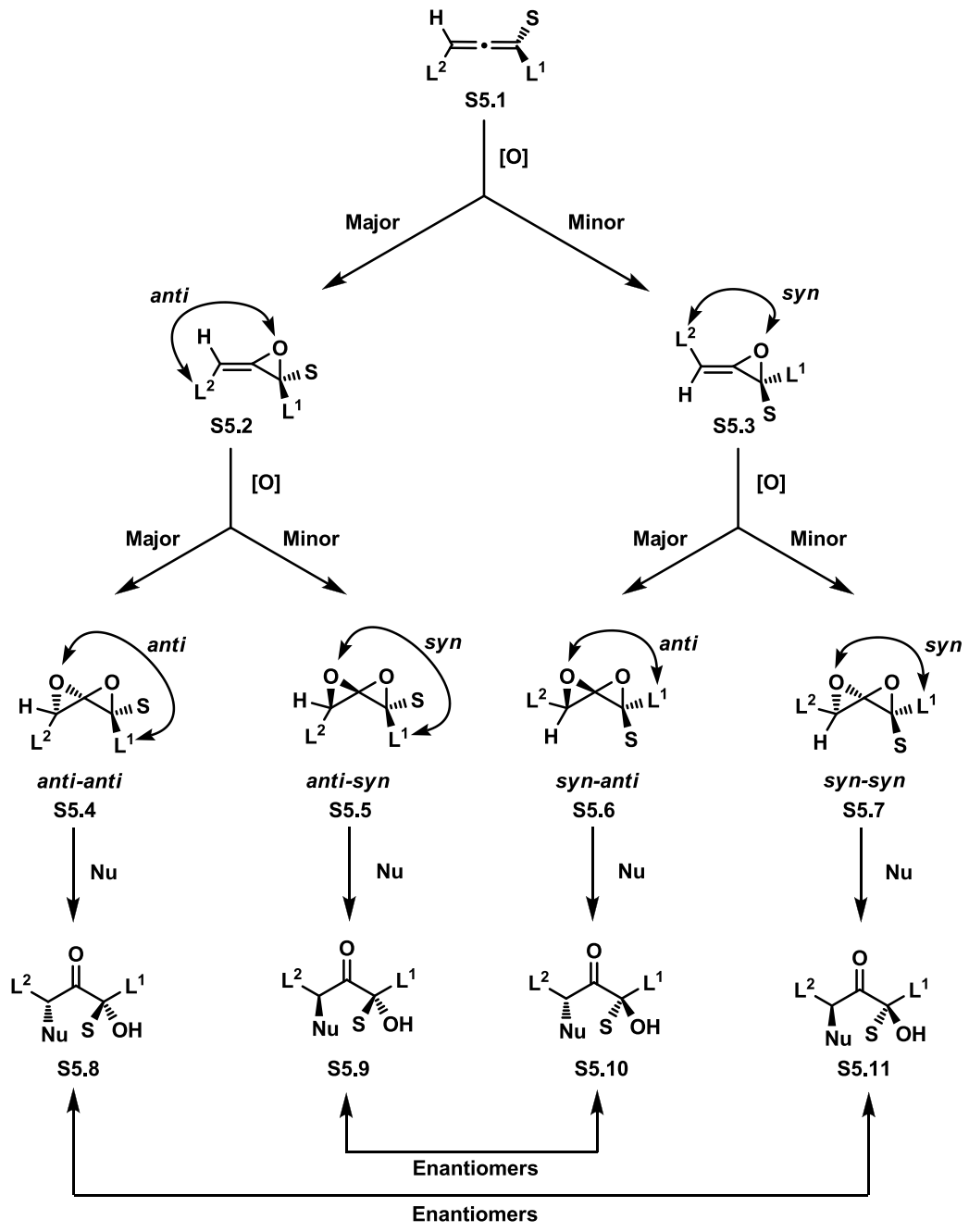
I. Steric Effects in Allene Oxidations

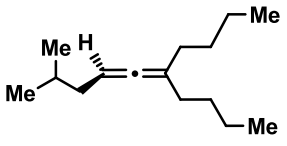
Allene oxidation is considered intrinsically diastereoselective. Allenes may possess an axis of chirality and even may be C_2 symmetric. This chirality is ultimately relayed to the corresponding SDE. Delivery of oxidant is expected to occur on the π-face anti to the large substituent of the non-reacting allene terminus (Scheme 5, pg. 10). In the case of a trisubstituted allene (**S5.1**, S = small substituent, L^1, L^2 = large substituents), the first oxidation would be expected to occur on the more electron rich double bond with good selectivity and give rise to allene oxide **S5.2**.

Oxidation of the allene oxide is expected to be fast and therefore may be significantly less selective than allene oxidation. Hence, a mixture of two products would be expected to form (**S5.4**, anti-anti / **S5.5**, anti-syn). Rapid oxidation of the allene oxide intermediate is traceable to its electron-rich nature, similar to that of an enol ether.[17] This oxidation may also relieve strain associated with an epoxide bearing an exocyclic olefin. Regioselective nucleophilic opening of SDE **S5.4** would lead to the syn-substituted ketone (**S5.8**) as the major product (**F2.6→F2.7**, Figure 2, pg. 5). Importantly, the extent to which the anti product (**S5.9**) is formed reflects the degree of selectivity of the allene oxide oxidation. The antipodal syn and anti SDEs (**S5.6** and **S5.7**) may not be observed

(17) Yamamoto, H.; Tsuda, M.; Sakaguchi, S.; Ishi, Y. *J. Org. Chem.* **1997**, *62*, 7174 and references cited therein.

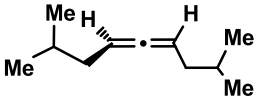
Scheme 5 Stereochemical Model for Allene Oxidation





S5.12

10 : 1 DMDO/acetone
>20 : 1 DMDO/$CHCl_3$



S5.13

1 : 1 DMDO/acetone
2 : 1 DMDO/$CHCl_3$

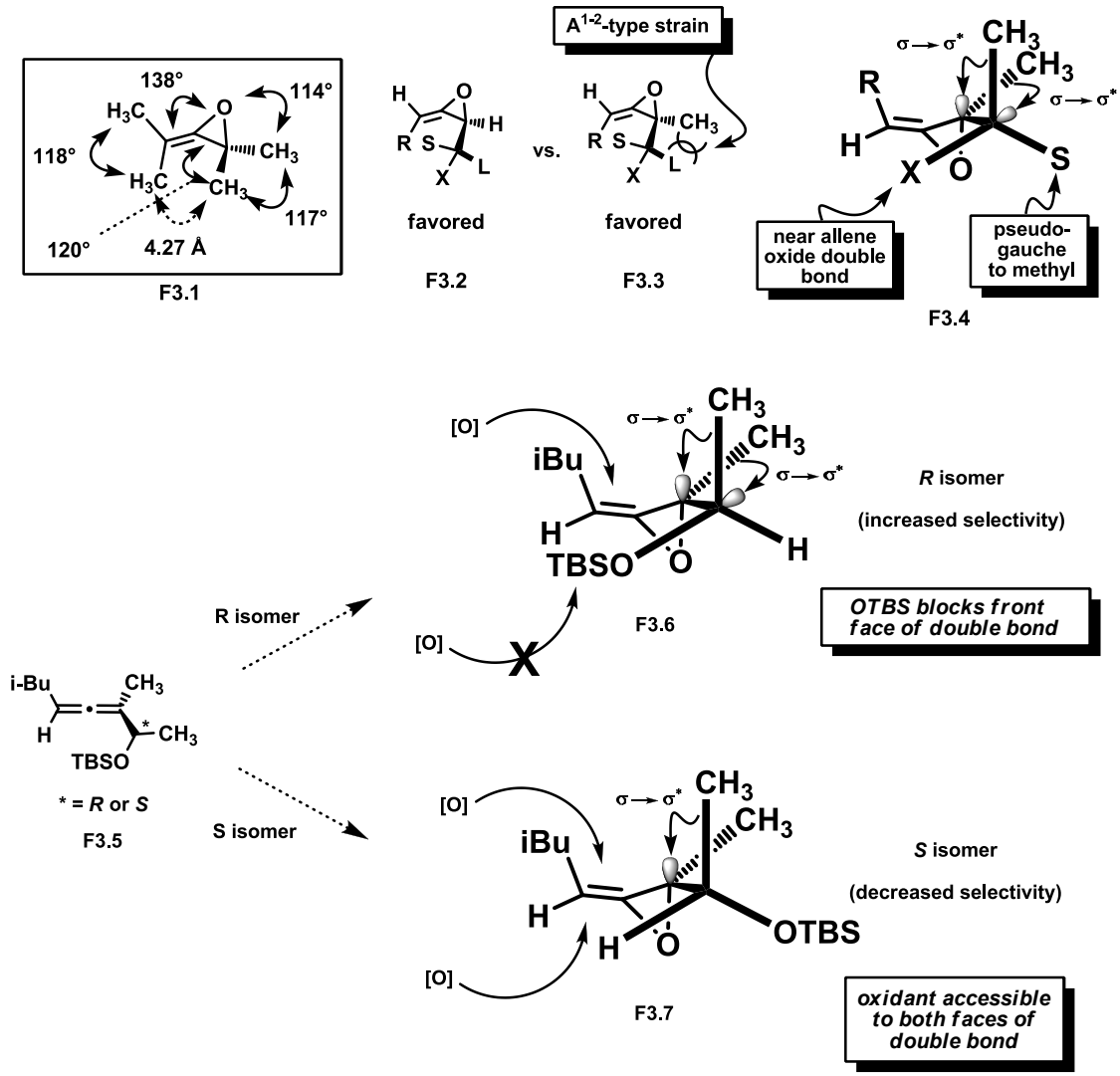
provided the stereo- and regioselectivity of the first oxidation (**S5.1→S5.2**) is high. If the first oxidation is stereoselective (e.g. 10:1) and the second oxidation is modestly stereoselective (e.g. 2:1), the reaction will give the syn (**S5.8**) as the major product after nucleophilic addition and **S5.9** as the minor product. The diastereomeric ratio of **S5.8**:**S5.9** would be 2:1. Although **S5.9** would be obtained in only 5:1 er, the major diastereomer **S5.8** would be obtained in a synthetically useful 20:1 er. When L^1, L^2 = alkyl and S = hydrogen, the first oxidation is selective[7h] (~10:1, DMDO/acetone) and the second oxidation is often not (~1:1). The second ratio improves with branching alpha to the allene (~2:1, for L^1, L^2 = *i*-propyl) and is high in the specific case of L^1, L^2 = *t*-butyl (9:1 dr). Our preliminary findings demonstrated that SDE formation in DMDO/chloroform solutions significantly improved oxidation selectivity. Thus, the use of DMDO in chloroform[15b,c] increased the selectivity of the first oxidation from ~10:1 to >20:1. This high selectivity of the first oxidation was proven when allene **S5.12** was oxidized using DMDO/chloroform to give a >20:1 dr of SDEs. This SDE diastereomer ratio is reflective of the first oxidation at the most substituted side of the allene due to the two faces of the adjacent double bond being identical. Even in the simplest case with a symmetrical disubstituted allene (**S5.13**) the ratio of SDEs increased from 1:1 to 2:1 when switching oxidation solvent from acetone to chloroform.

II. Stereoelectronic Effects in Allene Oxidations

As shown in Figure 3 (pg. 12), the bond angle[18] between the 1,1-substituents of

(18) (a) The calculations were carried out in collaboration with R. R. Sauers. The Gaussian 03 package was used and calculations were performed at the level: B3LYP 6-311G 2d,2p Gaussian 03, Revision C.02, M. J. Frisch, *et. al.* Gaussian, Inc., Wallingford CT, 2004. (b) Molecular dynamics were conducted using HyperChem release 7.5. Langevin dynamics, followed by optimization of final structure using DFT-B3LYP 6-31G 2d, 2p.

Figure 3 Stereoelectronic Effects in Allene Oxidations



an allene oxide (**F3.1**) is ~117°; much closer to an apparent sp^2 hybridization than sp^3. This may lead to a destabilizing A^{1-2}-type strain when both substituents are CH_3 or larger (compare **F3.2** to **F3.3**). The allene oxide may be stabilized by $\sigma \rightarrow \sigma^*$ interactions when electron-donating groups, such as methyl, are antiperiplanar to the allene oxide C-O bond (**F3.4**). Such conformers will place the other substituents near the allene oxide double bond and pseudo-gauche to the methyl substituent on the allene oxide. Steric effects should favor larger groups near the allene oxide double bond. For electronegative atoms

directly attached to the substituent (**F3.4**, X=O) another $\sigma \rightarrow \sigma^*$ stabilizing interaction may become important when the methyl substituent on the allene oxide is antiperiplanar to the C-X bond. When the carbon bearing the electronegative atom is stereogenic, the conformational effects may enhance or suppress the selectivity of the second oxidation. For example, since alkyl substituents will likely contribute greater $\sigma \rightarrow \sigma^*$ stabilization than hydrogen, diastereomers of **F3.5** would be expected to display differing oxidation selectivities. In the case of diastereomer **F3.6**, the bulkier OTBS group should block the front face of the double bond from oxidation and epoxidation should occur predominately from the back face. In **F3.7**, a hydrogen is positioned in front of the allene oxide double bond thus the two faces of the double bond should be equally accessible to oxidation. In this case, the stereoselectivity of the oxidation should decrease. Yue Zhang, a graduate student in the Williams group, has demonstrated that the *R* diastereomer (**F3.6**) shows increased selectivity (5:1) in comparison to the *S*-diastereomer (**F3.7,** 1:1 dr) upon DMDO oxidation. This interesting finding becomes relevant in our study towards the stereotetrad of erythromycin using carbon nucleophile additions to SDEs (Chapter 5).

In this section, a stereochemical model for allene oxidation was discussed. This model will be used to predict the stereochemical outcome for allene oxidations and is therefore useful in our synthetic applications employing SDEs. The next chapter will discuss our synthesis of epoxomicin, the first use of SDEs in total synthesis.

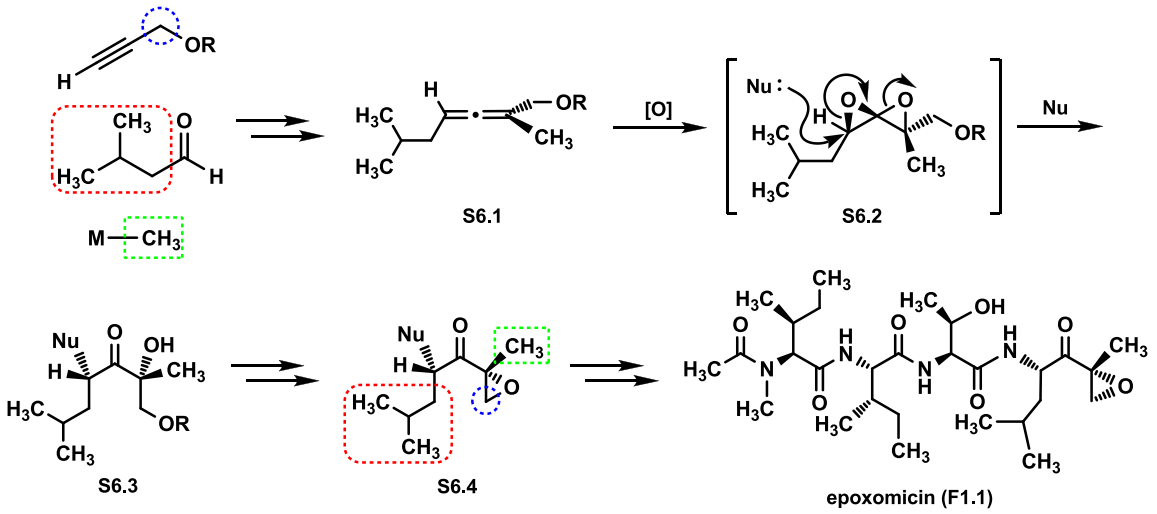
Chapter 3

Total Synthesis of Epoxomicin

I. Epoxomicin Background and Synthetic Plan

The first use of SDEs in total synthesis was demonstrated by our research group in synthesizing the potent proteasome inhibitor epoxomicin[6f] (**F1.1**, Scheme 6, pg. 14). Proteasome targeting has emerged as a new mode for the treatment of diseases ranging from malaria to cancer.[19] The importance of understanding and controlling proteasome function led us to design new approaches to **F1.1**. By exploiting SDE chemistry, **S6.3** would, in principle, be concisely synthesized by introducing the appropriate functionality and stereochemistry in a single flask (**S6.1**→**S6.3**, via **S6.2**).

Scheme 6 Synthetic Plan Towards Epoxomicin



(19) For proteasome structure, biology and application lead references, see: Kloetzel, P. M. *Nat. Rev. Mol. Cell. Biol.* **2001**, *2*, 179.

This methodology would also provide flexibility as modifications in the highlighted portions of **S6.4** would not encumber the synthetic route. Thus, appropriately protected **S6.1** would be readily prepared using aldehyde, alkyne and organometallic precursors all of which are indicated by the highlighted portions.

II. Studies Towards the Total Synthesis of Epoxomicin

A series of hydroxy-allenes with various O-protecting groups (**S6.1**, R=TBS, TMS, TIPS, TBDPS) were prepared in enantiomerically pure form starting from isovaleraldehyde (**S7.1**, Scheme 7, pg. 16). Zinc-mediated asymmetric alkynylation[20] using alkyne **S7.2** employing conditions developed by Carreira afforded propargyl alcohol **S7.3** (93%) as a single enantiomer determined by ^{19}F NMR analysis of the Mosher ester.[21] The room temperature reaction conditions in toluene proved to be more efficient than mild heating (~60^{o}C) which resulted in shorter reaction times with a slight decrease in ee (89%). The alcohol was converted to the mesylate and subsequently transformed into allene **S7.4** upon copper-mediated[22] S_N2' displacement (91%) with no racemization observed by ^{19}F NMR analysis of the corresponding Mosher ester[21] (**S6.1**, R=MTP). This reaction sequence proved to be highly efficient as allene **S7.4** was routinely prepared in multi-gram quantities. A deprotection/protection sequence was employed at this stage to access the various O-protecting groups of allene **S6.1**. All of the silyl protecting groups were stable to DMDO oxidation and the ratios obtained for the corresponding SDEs were all approximately 2:1 as determined by ^{1}H NMR analysis.

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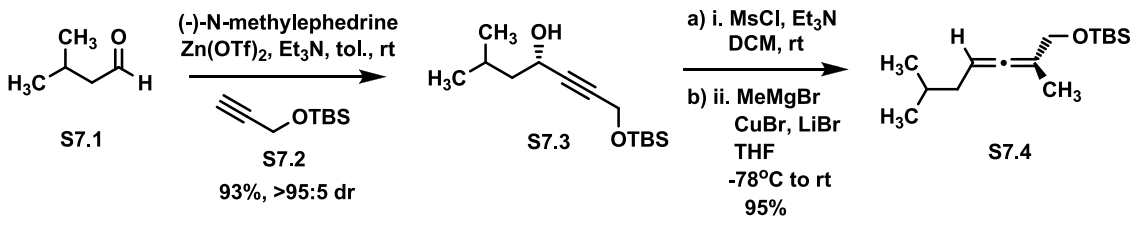
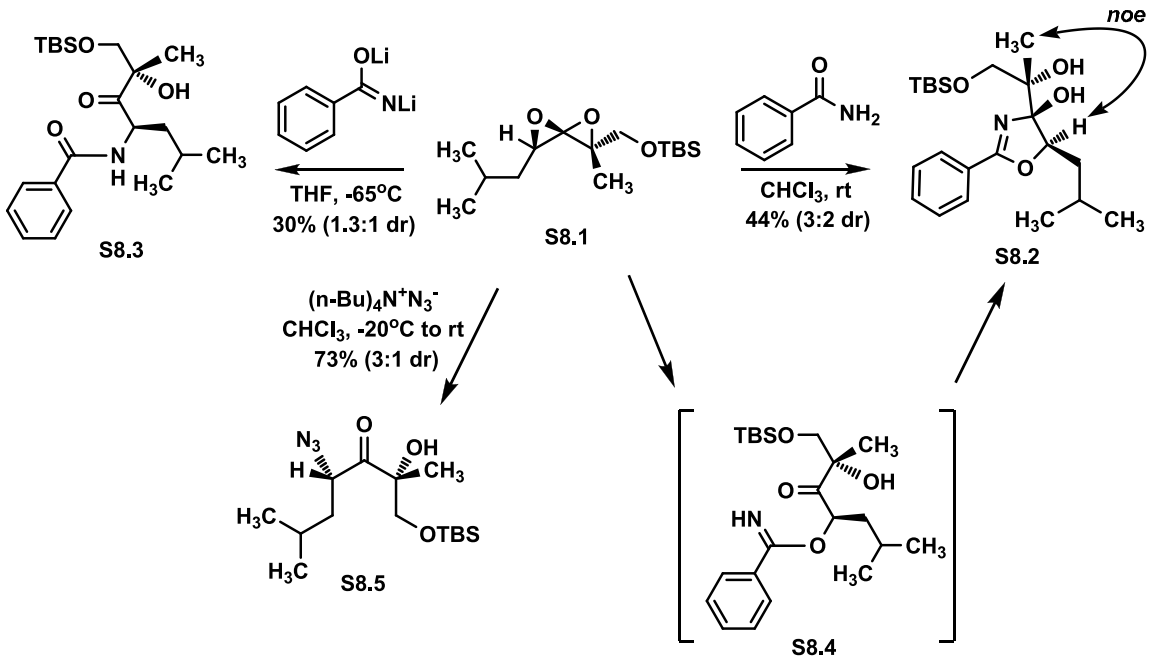
(20) Frantz, D.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(22) (a) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. (b) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1984**, *49*, 1649.

Scheme 7 Synthesis of Allene S7.4 from Isovaleraldehyde



Suitable nitrogen nucleophiles were identified and reacted with SDE **S8.1** (Scheme 8, pg. 16). Upon exposure to benzamide, addition took place at room temperature to furnish oxazoline **S8.2** and not the corresponding *N*-alkylated product **S8.3**, which was the desired product for our study towards epoxomicin. Apparently, *O*-alkylation occured to form imidate **S8.4** followed by spontaneous cyclization to afford **S8.2**. The trans stereochemical assignment for the diastereomers was based on NMR data

Scheme 8 Nucleophilic Additions to SDE S8.1



showing an NOE between the primary methyl group and the methine proton on the oxazoline ring (**S8.2,** see arrow). The *N*-alkylated product was obtained (**S8.1→S8.3**), albeit in low yield (30%), from addition of the dianion of benzamide after *n*-BuLi deprotonation. Unfortunately this product was only obtained as a 1.3:1 mixture of diastereomers due to epimerization from the basic reaction conditions.

We thought that a more feasible approach would be to prepare α-azido ketone **S8.5** in order to install the tetrapeptide of **F1.1** by way of our thioacid-azide amidation.[23] Therefore, nucleophilic addition to SDE **S8.1** using azides was investigated. While sodium azide added slowly, tetrabutylammonium azide added rapidly even at low temperature to give **S8.5** in 73% yield (3:1 dr). As previously suggested (Scheme 5 and Figure 2), the stereochemistry of the major diastereomer was expected to be syn. This was proven since **S8.5** was taken on to prepare epoxomicin by Dr. Sreenivas Katukojvala, a former post-doc in the Williams group, and Kristin Barlett, a former graduate student in the group. The compound was shown to match identically, by ^{1}H, ^{13}C and optical rotation, to the natural product.[2a]

The next chapter will discuss mechanistic insights on SDEs structure and reactivity based on our observations during the course of this total synthesis.

(23) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754-7755.

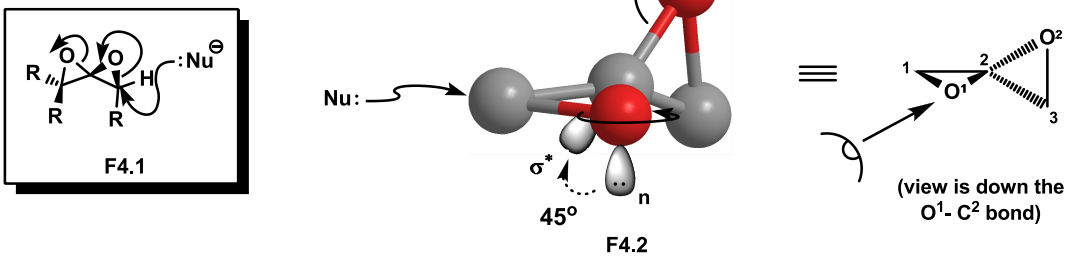
Chapter 4

Mechanistic Insight on Nucleophilic SDE Opening

I. Introduction

Despite the mechanistic rationales suggested by others,[7-13] the structure of the SDE, along with certain other observations, led us to hypothesize that SDE opening proceeds such that both epoxides open in a concerted fashion (**F4.1**, Figure 4, pg. 18). This hypothesis is consistent with the mild reaction conditions under which SDEs react and is stereoelectronically reasonable. A structural model of a SDE (**F4.2**) suggests that the dihedral angle of the non-bonded electrons on the oxygen are approximately 45° to the σ^* orbital of the adjacent C-O bond in the ground state. Upon nucleophilic addition this dihedral angle approches 0° and thereby could lead to the asynchronous concerted opening of the SDE (see arrows in **F4.2**).

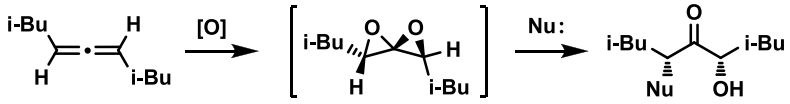
Figure 4 Mechanism for Concerted SDE Opening



II. Intermolecular Nucleophilic Additions to Spirodiepoxides

Anionic and neutral nucleophiles have been shown to add to SDEs efficiently under non-acidic conditions, including deprotonated benzenesulfonamide, lithium benzimidate, azide,[6f] certain aliphatic alkoxides, phenyl thiolate, chloride, fluoride,[7h] along with ammonia, and a limited number of secondary amines.[7h] We examined a series of other related nucleophiles, a key subset of which is shown in Table 1 (pg. 19) (**T1.1→T1.3**). Cyanide, an anionic carbon nucleophile, as well as acetate[24] and phenoxide, anionic oxygen nucleophiles, added to give the corresponding products in

Table 1 Intermolecular Additions to a SDE



T1.1 T1.2 T1.3

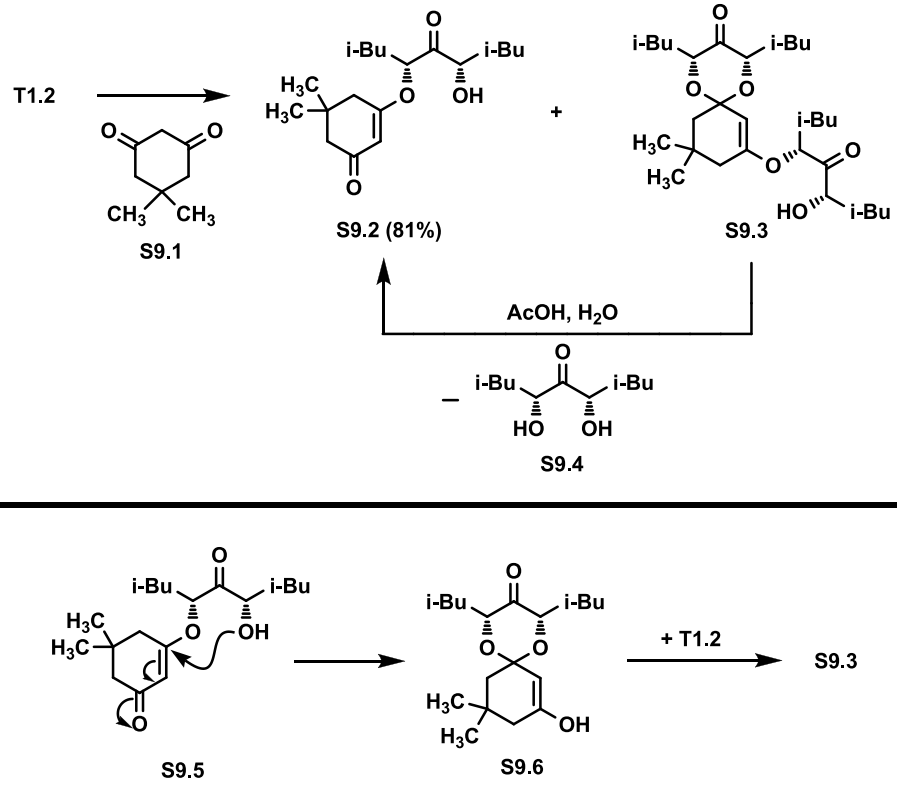
Entry	Nucleophile	Solvent	Time (h)	Yield (%)[c]
1[a]	$(n\text{-}Bu)_4N^+CN^-$	$CHCl_3$	1	77
2[a]	$(n\text{-}Bu)_4N^+OAc^-$	$CHCl_3$	1	70
3[b]	PhO^-	THF	4	65[d,f]
4[b]	PhOH	$CHCl_3$	12	0
5[b]	3,5-dimethoxy-PhOH	$CHCl_3$	12	0
6[b]	3,5-dimethoxy-PhO^-	THF	5	78[e,f]

Conditions: 3.0 equiv. of DMDO. [a]1.1 equiv of nucleophile. [b]1 equiv of nucleophile. [c]Yield after chromatography based on SDE except where noted. [d]1 equiv PhOH, 1.1 equiv K_2CO_3, 10 mol% 18-crown-6 in THF. [e]1 equiv 3,5-dimethoxy-PhOH, 1.1 equiv K_2CO_3, 10 mol% 18-crown-6 in THF. [f]Yield after chromatography based on nucleophile.

(24) Under non-acidic conditions, only acetate addition is observed. In contrast, exposure of an SDE to acetic acid in DCM gives oxetanone, enone, and acetate addition products as previously mentioned in Scheme 2,, pg. 4 (cf. ref. 5).

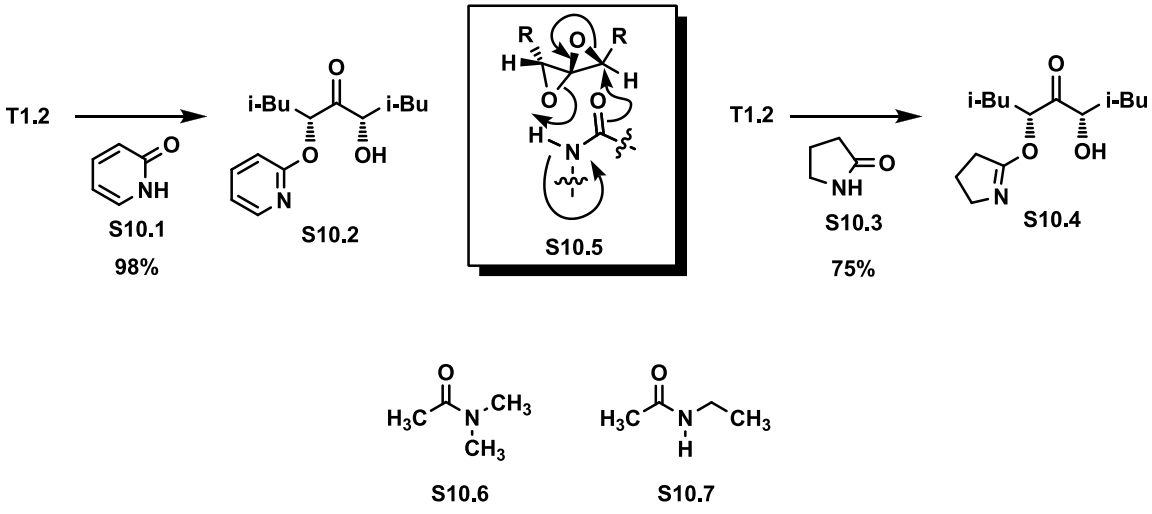
good yield (entries 1-3). Stoichiometric quantities of water, aliphatic alcohols, and phenol do not add at useful rates to SDEs under neutral conditions (e.g. entries 4 and 5). When used as a solvent or co-solvent, however, water,[7h] methanol, and ethanol, but not *t*-butanol, were found to add efficiently to SDEs (data not shown). The addition of 3,5-dimethoxyphenol proved to be similar to phenol addition, as basic conditions were required for addition to take place (Table 1, entries 5 and 6). Upon exposure of dimedone (**S9.1**, Scheme 9, pg. 20) to SDE **T1.2** O-alkylation occurred in high yield under neutral conditions to give **S9.2** (81%) along with a side product which was presumed to be **S9.3** (formed via **S9.5→S9.6→S9.3**). **S9.3** was converted back to **S9.2** after acid hydrolysis and loss of **S9.4**.

Scheme 9 Addition of Dimedone to a SDE



Surprisingly, one equivalent of 2-hydroxypyridine added smoothly under neutral conditions to give the *O*-alkylated product (**T1.2→S10.2**, Scheme 10, pg. 21). One explanation for this facile addition of 2-hydroxypyridine invokes the amide tautomer (**S10.1**) in which a general acid catalyzed mechanism is operative. Thus, the oxygen of the distal epoxide hydrogen bonds to the hydrogen of the NH, thereby activating the SDE and facilitating addition of the oxygen to the proximal epoxide (**S10.5**). This type of reaction is similar to the previously mentioned case of benzamide adding to a SDE to form an oxazoline ring (**S8.1→S8.2**, Scheme 8, pg. 16). In order for this mechanism to be operative a cis amide conformation would be required. Consequently, the reactivity of a series of amides was examined under identical conditions. Virtually no reaction took place between SDEs and *N,N*-dimethyl acetamide (**S10.6**), which contains no amide hydrogens or *N*-ethyl acetamide (**S10.7**), whose amide structure exists in the trans conformation. However, upon exposure of cis amide 2-pyrrolidinone (**S10.3**) *O*-

Scheme 10 Cis Amide Addition to a SDE

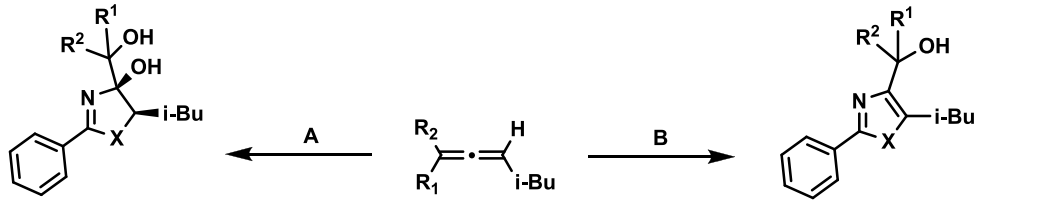


alkylation occurred rapidly to give the corresponding imidate in good yield (**T1.2→S10.4**). Indeed a cis amide structure seemed to be required for this mild and facile addition of an amide to a SDE under neutral conditions.

III. Synthesis of Heterocycles from Spirodiepoxides

It was at this stage that the addition of primary amides was revisited in order to identify the scope of such an unprecedented transformation. Table 2 (pg. 23) illustrates that thiobenzamide and benzamidine also add to SDEs; this constitutes a novel entry to heterocycles from allenes. Benzamide added very slowly (entries 1 and 3). Nevertheless, even in the presence of 5 equivalents of water, a potentially competitive nucleophile, only the oxazoline product was obtained. Thiobenzamide (entries 2 and 4) and benzamidine (entries 7 and 10) added more rapidly to SDEs than benzamide, consistent with the expected increased nucleophilicity of these reagents. SDE stereochemistry was assigned based on analogy to earlier models; the first oxidation is highly selective, the second oxidation is less selective, and the product ratios matched the SDE ratios. Although spontaneous formation of imidazoles from the imidazolines complicated imidazoline isolation, thiazolines and oxazolines were readily obtained in pure form. As previously mentioned in Scheme 8 (pg. 16), NOE analysis allowed trans assignment of the carbinol and the alkyl substutuents of the azolines (**T2.2** and **T2.3**), as expected based on thermodynamic considerations. In a separate step, dehydration to the corresponding imidazoles, thiazoles, and oxazoles was readily achieved. Ultimately, oxazoles, imidazoles, and thiazoles were conveniently prepared in a single flask from the allene without isolation of intermediates (entries 5-10).

Table 2 One-Pot Heterocycle Synthesis from Allenes



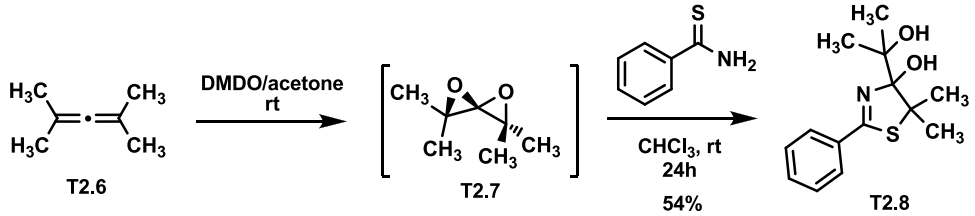
T2.2: R^1 = H, R^2 = *i*-Bu
T2.3: R^1 = CH_3, R^2 = CH_2OTIPS

T1.1: R^1 = H, R^2 = *i*-Bu
T2.1: R^1 = CH_3, R^2 = CH_2OTIPS

T2.4: R^1 = H, R^2 = *i*-Bu
T2.5: R^1 = CH_3, R^2 = CH_2OTIPS

Entry	Allene	Amide	Condition	Time	Product	Yield
1	T1.1	$C_6H_5CONH_2$	A	24	T2.2 (X=O)	74
2	T1.1	$C_6H_5CSNH_2$	A	12	T2.2 (X=S)	80
3	T2.1	$C_6H_5CONH_2$	A	84	T2.3 (X=O)	81
4	T2.1	$C_6H_5CSNH_2$	A	17	T2.3 (X=S)	76
5	T1.1	$C_6H_5CONH_2$	B	48	T2.4 (X=O)	66
6	T1.1	$C_6H_5CSNH_2$	B	24	T2.4 (X=S)	83
7	T1.1	$C_6H_5CNHNH_2$	A	60	T2.4 (X=NH)	83
8	T2.1	$C_6H_5CONH_2$	B	72	T2.5 (X=O)	47
9	T2.1	$C_6H_5CSNH_2$	B	35	T2.5 (X=S)	60
10	T2.1	$C_6H_5CNHNH_2$	B	21	T2.5 (X=NH)	78

Condition A: DMDO, –40 ^oC, 1h, 5 equiv nucleophile, $CHCl_3$, rt.
Condition B: DMDO, –40 ^oC, 1h; 5 equiv amide, $CHCl_3$, rt, then 10 mol% p-TsOH, reflux.



T2.6 T2.7 T2.8

The addition of thiobenzamide to a tetrasubstituted SDE was also demonstrated in our group (bottom of Table 2, **T2.6→T2.8**). The crystalline and sublimable SDE (**T2.7**) was formed upon subjection of **T2.6** to DMDO. Exposure of **T2.7** to 5 equivalents of thiobenzamide gave thiazoline **T2.8**, albeit at a slow rate, in 54% yield.

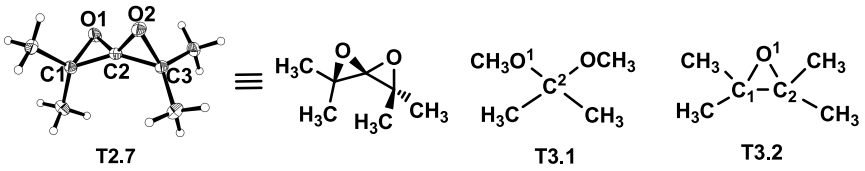
IV. Computational Data on Spirodiepoxide Structure and Reactivity

To further evaluate this proposal, we gathered additional structural and computational data. Table 3 (pg. 25) presents the first crystal structure of a SDE (**T2.7**, Table 2) which was synthesized by Sezgin Kiren, a graduate student in the Williams group, and crystallographically analyzed by Dr. Tom Emge. Observed key bond lengths are tabulated and compared to the calculated values. Importantly, molecular mechanics based methods (e.g. MM2, MM3, MM4) do not provide accurate optimization of SDEs. PM3 or higher level computations, which incorporate quantum effects, appear necessary for accurate SDE modeling (e.g DFT, HF, MP2). The C2-O1/O2 bond lengths of **T2.7** are shorter than those of simple acetals (**T3.2**). The C2-C1/C3 and C2-O1/O2 bond lengths of **T2.7** are shorter than those of epoxides (**T3.3**); however, the C1-O1 and C3-O2 bonds are longer than the average length of C-O bonds of epoxides.

In collaboration with Professor Ron Sauers, reaction pathways consistent with models **F4.1** and **S10.5** have been identified by Density Functional (DFT)[18,25] calculations as highly exothermic transformations wherein both epoxides open in concert, yet, in an asynchronous fashion. Transition state geometries for nucleophilic addition by water, amide, and chloride are very similar. Key atomic distances of reactants and transition

(25) (a) Becke, A. D. *J. Chem. Phys*. **1992**, *98*, 1372. (b) Miehlich, B.; Savin, A.; Stoll, H.; Pruess, H. *Chem. Phys. Lett.* **1989**, *157*, 200. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B*. **1988**, *37*, 785.

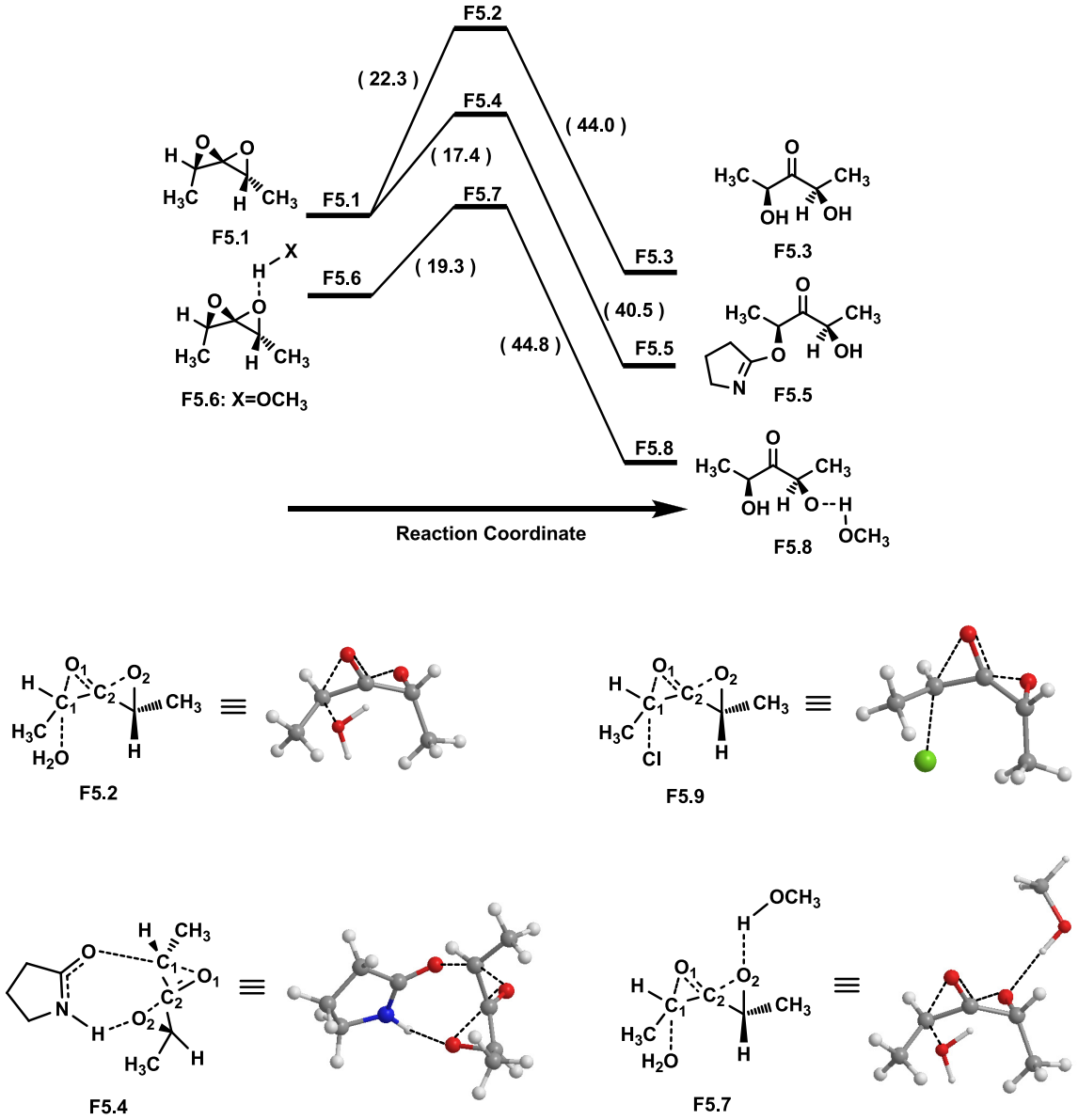
Table 3 Key Bond Lengths for SDE and Proposed Transition States



	Bond Lengths (Angstroms)						
	Structure	**C1-O1**	**C2-O1**	**C2-O2**	**C3-O2**	**C2-C1**	**C2-C3**
Crystal	T2.7	1.517	1.393	1.393	1.517	1.446	1.446
Calculated	T2.7	1.495	1.398	-	-	1.454	-
	T3.1	-	1.429	-	-	-	-
	T3.2	-	1.446	-	-	1.489	-
	F5.1	1.490	1.390	-	-	-	-
	F5.2	2.010	1.270	1.750	-	-	-
	F5.4	2.079	1.280	1.607	-	-	-
	F5.6	1.489	1.384	1.397	-	-	-
	F5.7	1.910	1.260	1.960	-	-	-
	F5.9	1.929	1.331	1.439	-	-	-

structures are included for comparison in Table **3**. We focused our computational analysis on the addition of water and related nucleophiles to SDEs (Figure 5, pg. 26). A single transition barrier (**F5.2**) connects water and the SDE (**F5.1**) with the substituted ketone (**F5.3**). Stable hydrogen-bonded complexes of weak acids, such as methanol, to O2 of SDE **F5.1** (→**F5.6**) were also identified. Addition of water to C1 of **F5.6** (→**F5.8**) was found to proceed by way of a lower enthalpy of activation (19.3 kcal/mol) than addition to **F5.1** (22.3 kcal/mol). The alternative pathway, where water attacks C3 of **F5.6**, represents a higher enthalpic barrier (~1 kcal/mol).

Figure 5 Calculations of Relative Enthalpies of Activation (kcal/mol)



The simultaneous coordination of 2-pyrrolidinone to a proximal SDE oxygen (O1) and attack at the proximal carbon (C1) is not geometrically feasible. Nonetheless, a transition structure for 2-pyrrolidinone-induced SDE opening was found (**F5.1→F5.4→F5.5**) and proved closely related to the other addition reactions of this study. This transition state structure features attack by the carbonyl lone pair at the proximal carbon (C1) and cis-amide hydrogen coordination to the distal oxygen (O2).

Three classes of nucleophiles that add to SDEs have been identified. First, SDE opening is readily achieved by anionic carbon, nitrogen, oxygen, sulfur, and halide nucleophiles. As with other nucleophilic openings, SDE opening takes place with inversion at the least substituted site. Second, weakly acidic reagents, e.g. water, methanol, and phenol, open SDEs very slowly under neutral conditions. Consequently, a large excess of reagent is required for reasonable reaction times. Third, there is a structural requirement for certain nucleophiles to add to SDEs under neutral conditions. Amides, amidines, and thioamides add to SDEs to give oxazoles and oxazolines, imidazoles and imidazolines, and thiazoles and thiazolines, respectively (Table 2). Evidently, alkylation of these nucleophiles is followed by addition of the nitrogen to the carbonyl. The structural requirement appears to be an NH cis to the amide carbonyl, or its analogue.

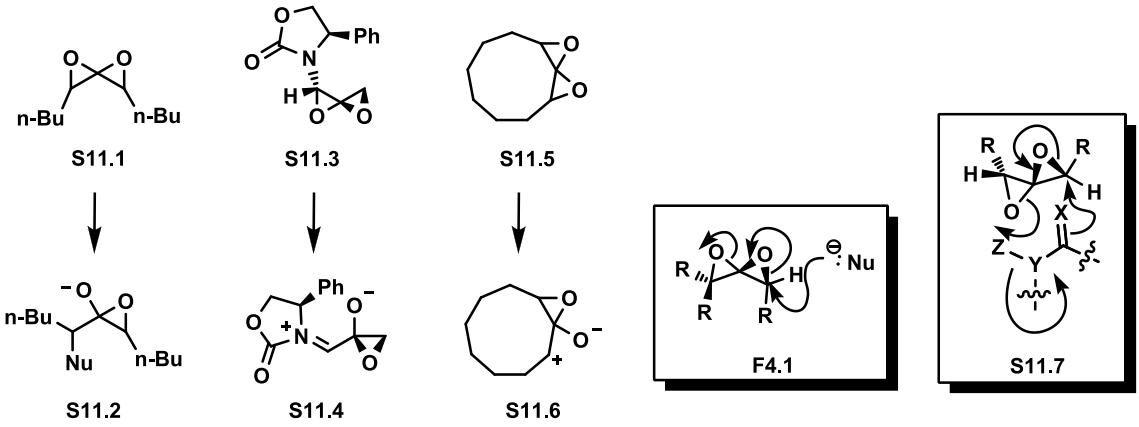
Computational studies reveal strikingly similar transition states for the three classes of nucleophile. The angle of nucleophilic attack (Nu-C1-O1: **F5.2** = 158°, **F5.4** = 168°, **F5.7** = 161°, **F5.9** = 170°, Table 3) reflects a degree of cationic character at C1.[26] For all nucleophiles in this study, the C1-O1 bond lengthens, the O1-C2 bond shortens, and the C2-O2 bond lengthens upon nucleophilic attack of the SDE, although the epoxide-opening occurs at different rates (compare **F5.2**, **F5.4**, **F5.7**, and **F5.9**, Table 3). Hydrogen bonding, by solvent or by the attacking nucleophile, to the SDE oxygen that is destined to become the hydroxyl facilitates SDE opening by stabilizing the transition state. Taken together, the analysis supports a mechanistic framework wherein

(26) This observation is also consistent with observations discussed in ref. 7i.

nucleophilic addition to SDEs involves concerted, asynchronous opening of both epoxides.

The structural dependence and generality of these findings are difficult to reconcile with earlier models of SDE opening. Previous models suggest that each epoxide of the SDE opens sequentially (**S11.1→S11.2**,[7h] **S11.3→S11.4**,[9] **S11.5→S11.6**,[5b] Scheme 11, pg. 28). A mechanism wherein both epoxides open in concert could account for the new findings and is consisistent with the earlier data as well (Scheme 11, compare **F4.1** with **S11.7**, X = O, N, S; Y = N; Z = H).

Scheme 11 Previously Suggested SDE Mechanisms



Anionic reagents are excellent nucleophiles for SDE opening, although side reactions can be problematic. Even though many neutral reagents are not good nucleophiles, SDEs can be activated in the presence of hydroxylic reagents.[6b,d] Coordination to the distal SDE oxygen (O2, **F5.6**) lowers the barrier for attack at the proximal SDE carbon (C1, **F5.6**). In this way, hydrogen bond activation, and presumably Lewis or Brønsted acid activation in general, acts synergistically to relieve ring strain in

both epoxides upon SDE opening. The remarkable finding that amides, amidines, and thioamides give heterocycles upon addition to SDEs is readily understood; certain nucleophiles are able to act simultaneously as hydrogen bonding-activators and as nucleophiles.

The new mechanistic model presented here is consistent with all the available data. Nucleophilic SDE opening involves the concerted, asynchronous opening of both epoxides. This process is facilitated by coordination to the oxygen destined to become the hydroxyl.

The next chapter will discuss our recently developed methodology for the nucleophilic addition of cuprates to SDEs.

Chapter 5

Nucleophilic Addition of Cuprates to SDEs

I. Introduction

In the previous section a mechanistic framework for SDE reactivity was established. Since SDEs are unstable in the presence of Brønsted acid,[5a,7a-h] as previously mentioned (see Scheme 2, pg. 4), the possibilities of transition metal-mediated reactions seem limited. However, if such reactions were attainable, the transformation (**S12.1→S12.2→S12.3**, Scheme 12, pg. 31) would set two stereocenters, install two oxygen atoms, and one C-C bond, and thus result in the formation of a vicinal triad composed of hydroxyl, ketone, and syn-substituted carbon substituent. Moreover, the anti product (**S12.4→S12.5→S12.6**) would be available as well by using R^2 as the nucleophile and R^1 as the allene substituent. This motif, and the closely related motif wherein the carbonyl is replaced with hydroxyl, is found in a myriad of biomedically relevant natural products including cytochalasin D[27] (**S12.8**), oligomycin F[28] (**S12.7**) and 9-(*S*)-dihydroerythronolide (**F1.2**), a direct precursor of erythromycin,[3] among others.

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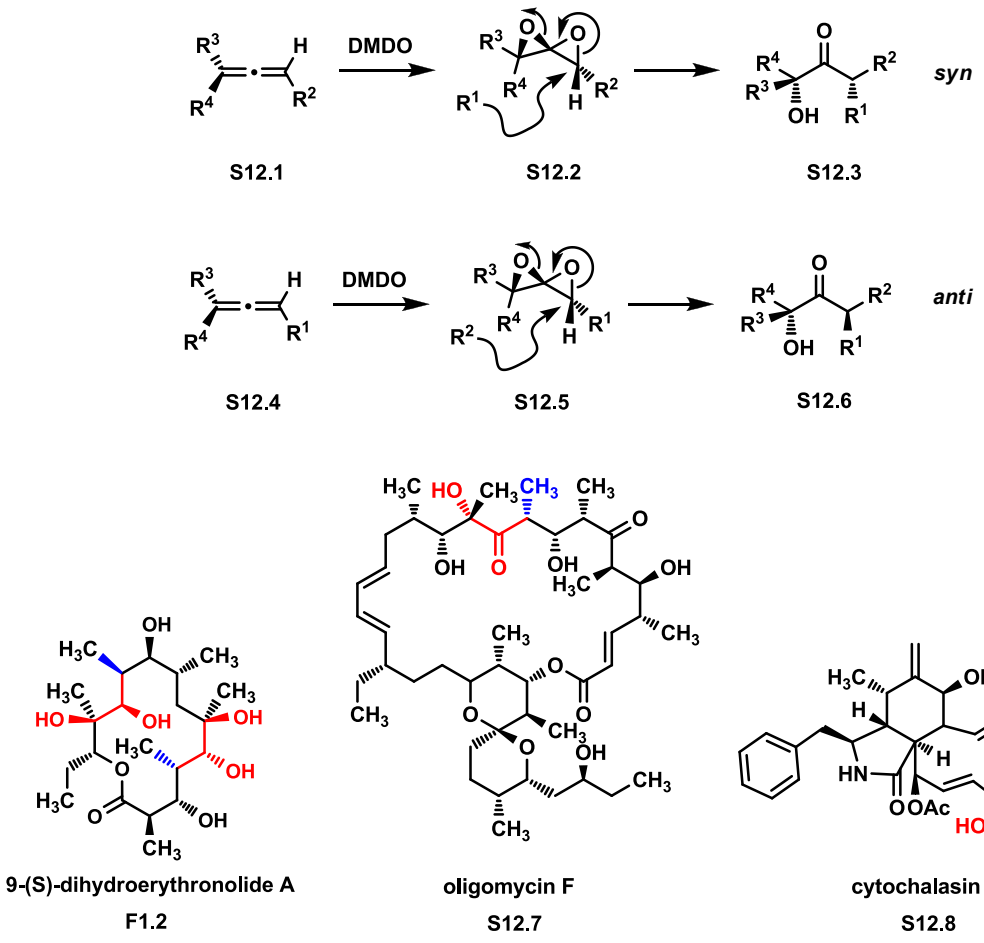
(27) Aldridge, D. C.; Turner, W. B. *J. Antibiot.* **1969**, 22, 170.

(28) H.; Kellner, M.; Wolf, G.; Lee Y, S.; Hansske, F.; Konetschny-Rapp, S.; Pessara, U.; Scheuer, W.; Stockinger, H.; *J. Antibiotics*. **1993**, *46*, 1334.

(29) Lipshutz, B. H. in *Organometallics in Synthesis: A Manual*; Schlosser, M., Hegedus, L. S., Lipshutz B. H., Marshall, J. A., Nakamura, E., Negishi, E., Reetz, M. T., Semmelhack, M. F., Smith, K., Yamamoto, H. Eds.; Wiley: England, 2004; Vol. VI, pp 665- 816 and references cited therein.

Scheme 12 Carbon Nucleophile Addition to SDE and Potential Applications

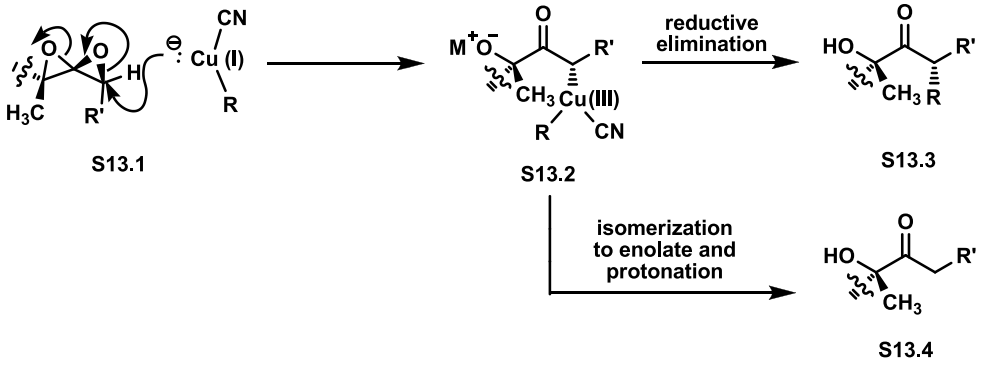


II. Development of Carbon Nucleophile Methodology

Our study focused on organocuprates, owing to the advantages of these mild reagents.[29] After an extensive screening of cuprates by Partha Ghosh, a graduate student in the Williams group, a methodology for the preparation of α-hydroxy ketone motifs was developed. Lower order cyano cuprates generated from alkyl lithium species were found to give the highest yields for carbon nucleophile addition. Presumably, the Cu(I) reagent adds to the SDE (**S13.1,** Scheme 13, pg. 32) to form an α-keto-Cu(III) species **S13.2** followed by reductive elimination to give **S13.3**. However in some instances the

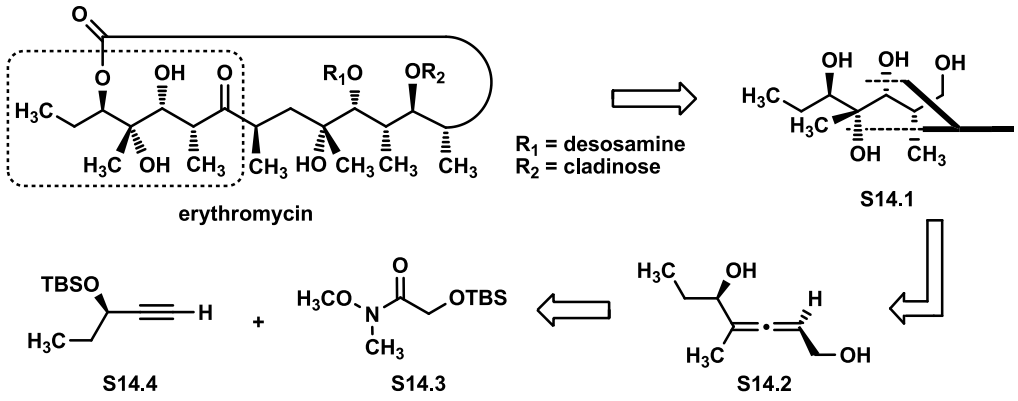
corresponding reduction product (**S13.4**) was observed. The mechanism for this transformation is presumably isomerization of **S13.2** to an enolate which upon acidic workup gives **S13.4**.

Scheme 13 Possible Mechanism for Cuprate Addition to SDE



We recognized that the backbone of erythromycin possessed two identical stereotetrad units as indicated in the highlighted portion of Scheme 14. More importantly, it seemed reasonable that a moiety of this sort could be prepared by utilizing our carbon nucleophile methodology. Thus, a concise synthetic plan to stereotetrad **S14.1** was put forth (Scheme 14, pg. 32).

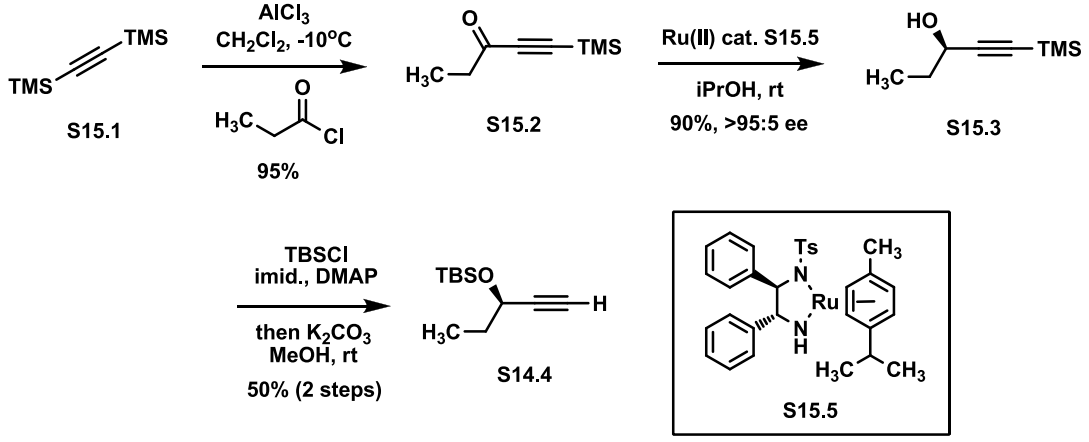
Scheme 14 Plan Towards Stereotetrad of Erythromycin



III. Synthesis of the Stereotetrad of Erythromycin

Known propargyl alcohol[30] **S14.4** was prepared starting from commercially available bis-TMS acetylene **S15.1** (Scheme 15, pg. 33). $AlCl_3$-promoted acylation (95%) followed by Noyori asymmetric transfer hydrogenation[31] gave **S15.3** in 90% yield as a single enantiomer determined by ^{19}F NMR analysis of the MTPA ester.[21] This Meerwein-Ponndorf-Verley-type reduction[32] employs the use of a Ru based catalyst (**S15.5**) and iPrOH as the hydride source. This highly efficient, practical and robust reaction has been employed numerous times in our research group in preparing various complex propargyl alcohols as allene precursors. The asymmetric induction for the Noyori reduction is governed by the chiral geometry from the 5-membered chelate ring on the Ru from the TsDPEN ligand (**F6.1→F6.2→F6.3,** Figure 6, pg. 34).[33] In aryl systems (bottom of Figure 6), this asymmetric induction is reinforced by a CH/π attraction between the π

Scheme 15 Synthesis of Known Alkynol S14.4



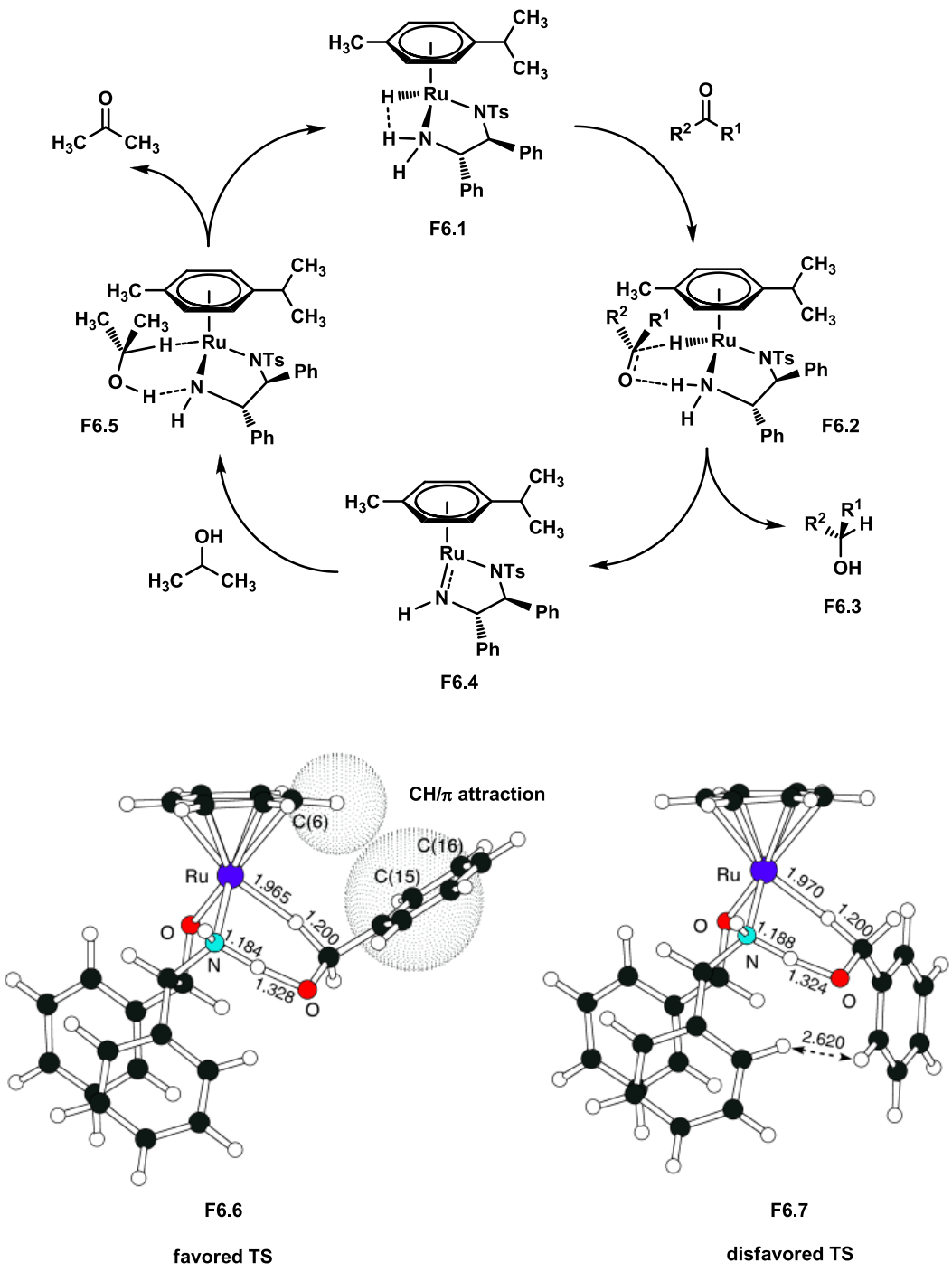
(30) The enantiomer of **S14.4** is known. See: Xu, L.; Wu, X.; Zheng, G. R.; Cai, J.C. *Chinese Chem. Lett.* **2000**, *11*, 213.

(31) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(32) For a review on the MPV-reduction see: Creyghton, E. J.; Van Der Waal, J. C. *Fine Chemicals through Heterogeneous Catalysis* **2001**, *438*

(33) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coordination Chem. Rev.* **2004***, 248*, 2201.

Figure 6 Noyori Asymmetric Transfer Hydrogenation



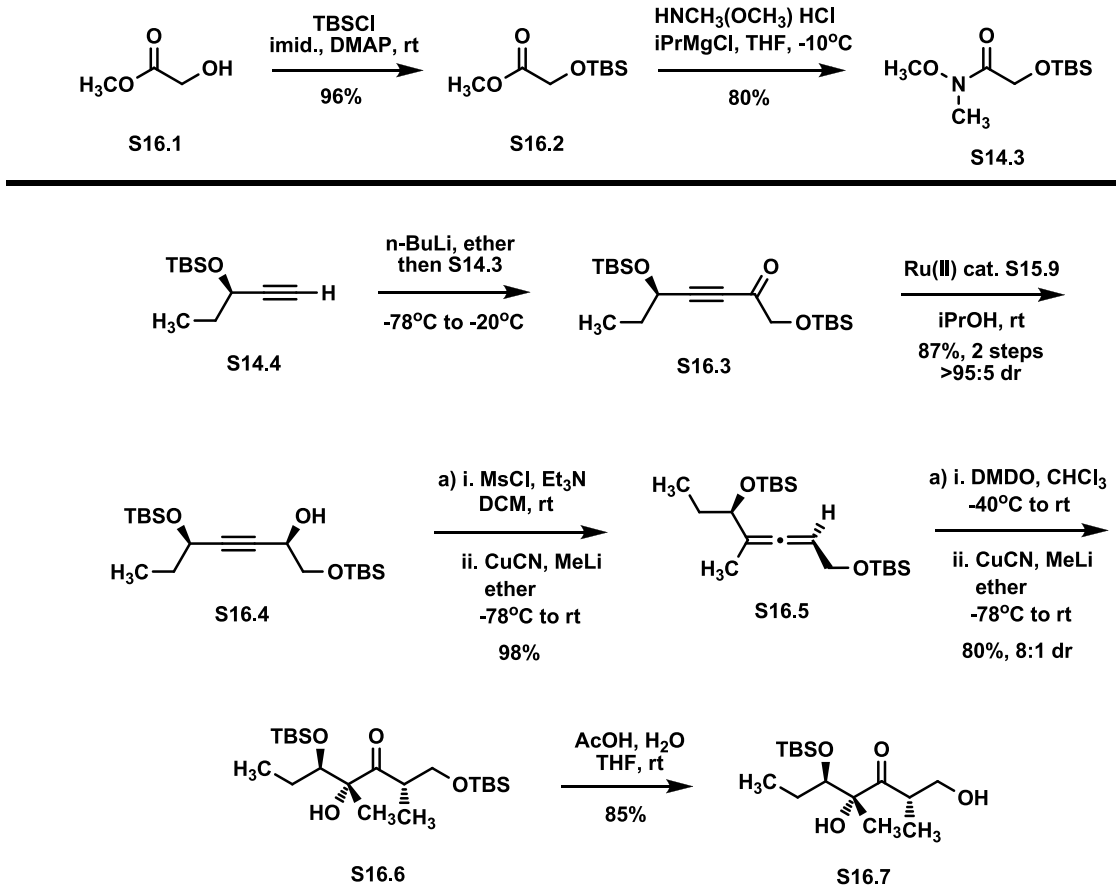
system of the aryl group and the CH bond of the *p*-cymene ligand (**F6.6**).[34] TBS protection of the corresponding alcohol followed by deprotection of TMS using K_2CO_3 in

(34) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2818.

MeOH afforded known propargyl alcohol **S14.4** in a 50% yield overall for the 2 steps. Isolation of **S14.4** was problematic due to volatility issues, which explains the moderate yield obtained for the protecion/deprotection sequence.

Known Weinreb amide[35] **S14.3** was prepared from commercially available methyl propiolate **S16.1** in a 2 step sequence (Scheme 16, pg. 35). TBS protection followed by conversion of the methyl ester to the Weinreb amide using a procedure developed by the Merck labs[36] employing Weinreb amine salt and i-PrMgCl gave **S14.3**. Alkynylation with

Scheme 16 Synthesis of α-Hydroxy Ketone S16.7



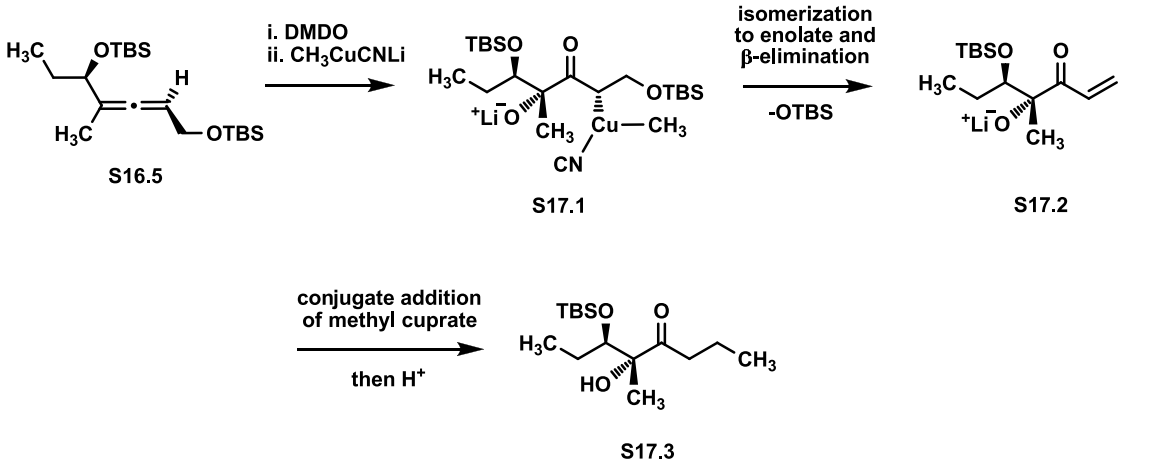
(35) Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331.

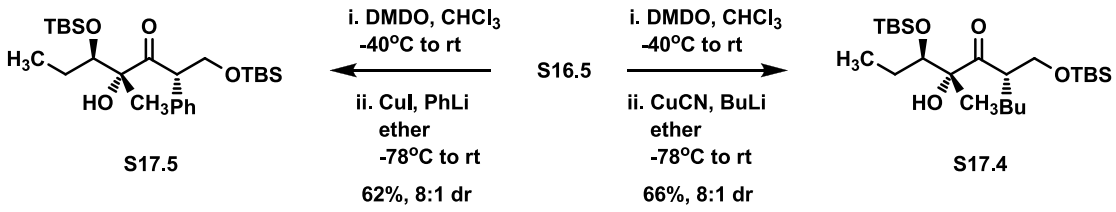
(36) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

S14.4 and then reduction[27] to the propargyl alcohol under Noyori conditions afforded **S16.4** in 87% yield (2 steps) as a single diastereomer. **S16.4** was exposed to mesyl chloride and the crude mesylate was converted to allene **S16.5** (98%). Subjection of **S16.5** to oxidation/organocuprate addition furnished the desired syn α-hydroxy-α'-methyl ketone **S16.6** (80%, 8:1 dr). A high degree of selectivity was predicted for this reaction based on our stereochemical model (discussed in Chapter 2), which incorporates stereoelectronic effects. The R isomer of the OTBS stereogenic center (**S16.5**) is analogous to **F3.6** (Figure 3, pg. 12) which we expected would give rise to the enhanced selectivity. We attributed the slight enhancement of selectivity of **S16.3** (8:1 dr) over that observed for **F3.6** (5:1 dr) to the presence of the TBS protected primary alcohol. We expected the oxidation of the allene oxide to be slightly attenuated by the electron-withdrawing nature of the adjacent protected primary alcohol, thus giving a higher degree of selectivity.

In order to achieve this organocuprate addition in excellent yield, a rigorous optimization process took place that included variations in solvent, temperature, addition rates and equivalencies of CuCN and MeLi. The optimal conditions included the use of rigorously dried ether and 5 equivalents of both CuCN (activated under vacuum using a gentle flame) and MeLi. Hydroxy ketone **S17.3** (Scheme 17, pg. 37) was observed as a side product of this reaction. This product is presumably formed via the reduction pathway. For example, SDE opening with Cu(I) (→Cu(III), **17.1**) followed by isomerization to the corresponding enolate and then β-elimination of the OTBS would form enone **S17.2**. Conjugate addition to the enone by methyl cuprate gives rise to **S17.3**.

Scheme 17 Formation of Side Product S17.3



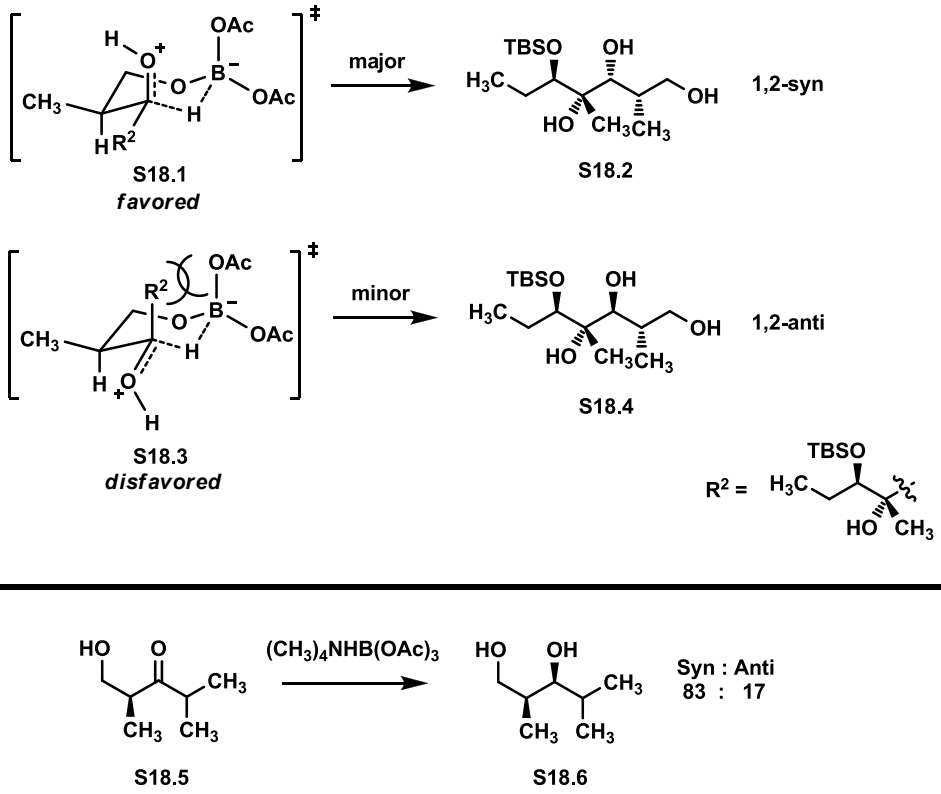


Subsequently, n-butyl and phenyl cuprate additions were also found to take place to the SDE derived from allene **S16.5** and furnished α-hydroxy ketones **S17.4** and **S17.5** in 66% and 62% yield respectively (bottom, Scheme 17, pg. 37). With these fast transferring ligands no reduced product or products analogous to **S17.3** were observed. This is consistent with the notion that **S17.3** is formed via the enolate since for, fast transferring ligands, the Cu(III) species would not be likely.

The diastereomers of **S16.6** were readily separated by FCC after removal of the primary silyl group to give **S16.7** in 85% yield. Reduction,[37] directed by the primary alcohol using $(CH_3)_4NHB(OAc)_3$, furnished **S18.2** (90%, 6:1 dr). This reduction involves

(37) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

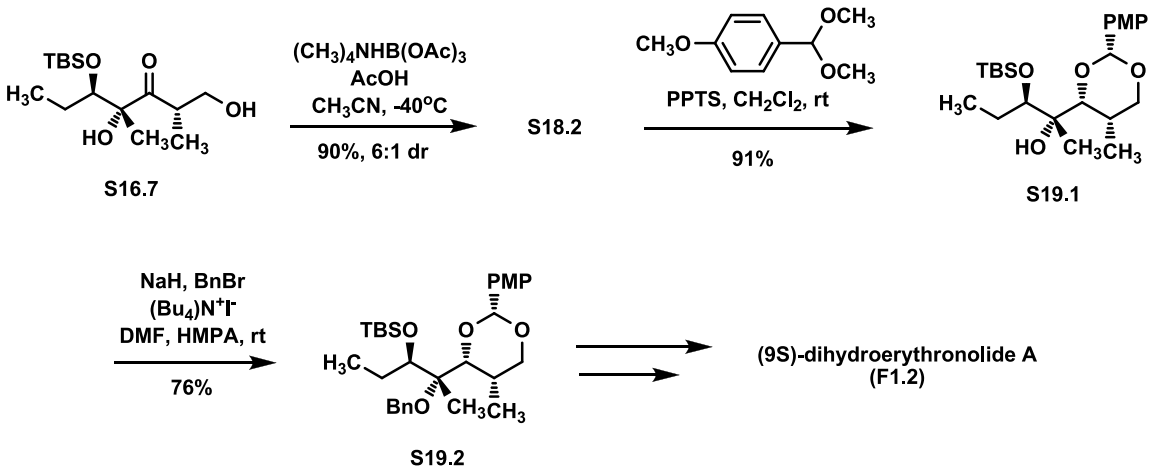
Scheme 18 Transition States for $(CH_3)_4NHB(OAc)_3$ Reduction



an acid-promoted ligand exchange of acetate for the primary alcohol to form a borohydride intermediate (**S18.1**, Scheme 18, pg. 38). This intermediate then reduces the ketone by an intramolecular delivery of hydride. Scheme 18 depicts the favored and disfavored 6-membered transition states, which give rise to this selective reduction. To our knowledge, this is the first example of a $(CH_3)_4NHB(OAc)_3$ reduction with a β-keto primary alcohol and an α-keto tertiary alcohol in the same system. The observed 6:1 dr in this system is analogous to the selectivity achieved by Evans in a similar system (**S18.5→S18.6**).

Proof of stereochemical assignment was established by preparing **S19.2** (Scheme 19, pg. 39), an intermediate previously synthesized by Woerpel in his recent synthesis of (9*S*)-dihydroerythronolide A (**F1.2**), a precursor of erythromycin. Selective conversion of

Scheme 19 Synthesis of Known Intermediate S19.2



S18.2 to the *p*-methoxy benzylidine (**S19.1**) followed by formation of the benzyl ether gave the known protected tetrol.[3a] Protection of the sterically encumbered tertiary alcohol was achieved by incorporating HMPA into the standard NaH/BnBr reaction conditions. Thus, this oxygenated polypropionate stereotetrad was prepared in a short, efficient, and selective route. This marked the first example of a transition metal-mediated transformation of SDEs used in synthesis.

The following chapter will discuss the background of pectenotoxin 4 as well as our synthetic efforts towards this natural product using SDE chemistry to access the functionalized cyclic ethers.

Chapter 6

The Pectenotoxin Family of Natural Products

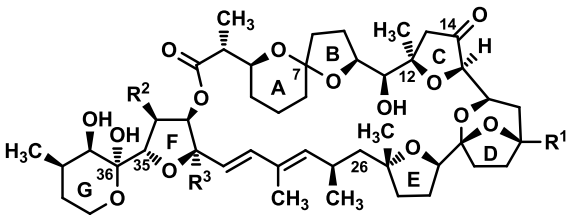
I. Isolation and Biological Activity of the Pectenotoxin Family

While addition of carbon nucleophiles to SDEs gives densely functionalized α-hydroxy ketone motifs related to polyketides as discussed in Chapter 5, intramolecular addition of oxygen nucleophiles would give highly functionalized cyclic ethers and related ring systems present in an array of biomedically relevant substances, including the pectenotoxins (Figure 7, pg. 41).

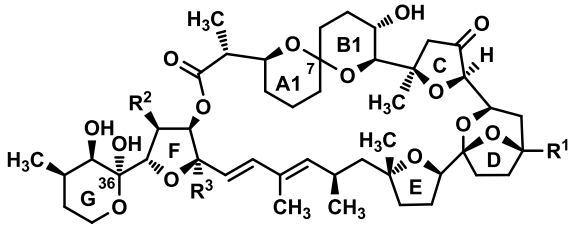
Pectenotoxins (PTXs) 1-5 were isolated in 1985 by Yasumoto and Clardy from the toxic sea scallop *Patinopecten yesseonesses*.[4a,b,r] Since then, eleven other PTXs have been isolated and characterized. These highly oxygenated marine natural products consist of 19 stereocenters and a 34-membered macrolide which houses seven oxygen-containing ring systems, including three tetrahydrofuran rings, a spiroketal, and one bicyclic ketal. The members of the PTX family have five distinct structural variations including; the oxidation state of C43 which varies from methyl to carboxylic acid; the AB spiroketal ring system, of which both the [6,5] and [6,6] variants are known; the configuration of the anomeric spiroketal at C7; structural variations in the FG ring system; and the seco acid form.

The PTXs are classified as causative agents for diarrhetic shellfish poisoning (DSP), which has been known to cause stomach pain and severe diarrhea. Biological studies showed that the PTXs are hepatotoxic, tumor promoters and cause apoptosis in rat

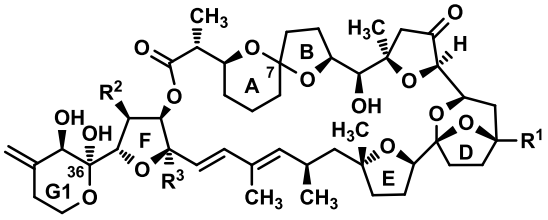
Figure 7 The Pectenotoxin Family of Natural Products



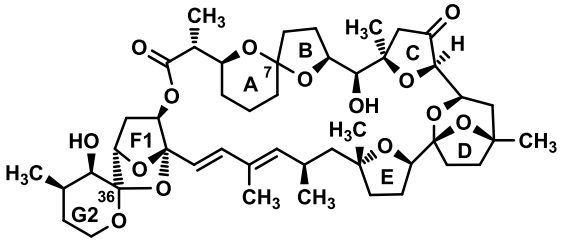
	R1	R2	R3	C-7	C-36
PTX 1	CH_2OH	H	H	*R*	α-OH
PTX 2	CH_3	H	H	*R*	α-OH
PTX 3	CHO	H	H	*R*	α-OH
PTX 4	CH_2OH	H	H	*S*	α-OH
PTX 6	COOH	H	H	*R*	α-OH
PTX 7	COOH	H	H	*S*	α-OH
PTX 11	CH_3	OH	H	*R*	α-OH



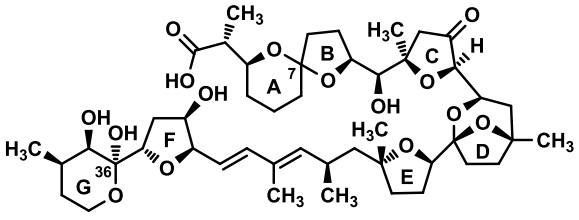
	R1	R2	R3	C-7	C-36
PTX 8	CH_2OH	H	H	*S*	α-OH
PTX 9	COOH	H	H	*S*	α-OH



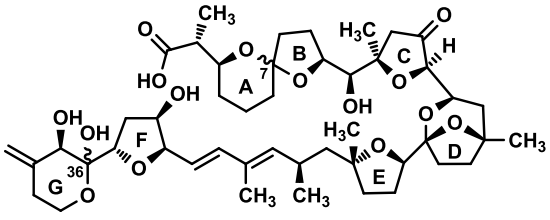
	R1	R2	R3	C-7	C-36
36S-PTX 12	CH_3	H	H	*R*	α-OH
36R-PTX 12	CH_3	H	H	*R*	β-OH
PTX 13	CH_3	H	OH	*R*	α-OH



	C-7
PTX 14	*R*



	C-7
PTX 2-SA	*R*
7-epi-PTX 2-SA	*S*



	C-7	C-36
PTX 12-SA	*R/S*	*R/S*

Table 4 Cytotoxicity of PTX2 Against Human Tumor Cell Lines

Panel	Cell Line	LC_{50} (molar)
Non-Small Cell Lung Cancer	**EKVX**	**6.20×10^{-8}**
	HOP-62	**2.51×10^{-8}**
	HOP-92	**8.07×10^{-7}**
Colon Cancer	**COLO 205**	**7.82×10^{-9}**
	HCT-116	**7.33×10^{-8}**
CNS Cancer	**SF-268**	**1.54×10^{-7}**
	SF-295	**7.77×10^{-8}**
Melanoma	**MALME-3M**	**1.23×10^{-7}**
	M14	**4.73×10^{-6}**
	SK-MEL-28	**4.23×10^{-8}**
	SK-MEL-5	**5.52×10^{-8}**
Ovarian Cancer	**IGROV1**	**6.73×10^{-8}**
	OVCAR-3	**6.16×10^{-8}**
Renal Cancer	**A498**	**3.41×10^{-8}**
	CAKI-1	**1.91×10^{-8}**
	RXF-393	**3.00×10^{-8}**
	TK-10	**7.25×10^{-8}**
	UO-31	**5.63×10^{-8}**
	HS-578T	**7.79×10^{-8}**
	BT-549	**6.27×10^{-8}**

and salmon hepatocytes.[4b,38]

PTX2 is the most biologically active member, and has shown cytotoxicity towards several lines of ovarian, renal, lung, colon, melanoma, and breast cancer with LC_{50} values in the nanomolar range (Table 4, pg. 42).[39a] Three seco acids of the PTX family have also

(38) (a) Miles, C. O. *et. al. Toxicon* **2004**, *43*, 1. (b) Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* **1986**, *50*, 2693. (c) Fladmark, K.; Serres, M. H.; Larsen, N. L.; Yasumoto, T.; Aune, T.; Doskeland, S. O. *Toxicon*, **1998**, *36*, 1101.

(39) (a) Jung, J. H.; Sim, C. J.; Lee, C. O. *J. Nat. Prod.* **1995**, *58*, 1722. (b) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; MacKenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, *653*.

been isolated but appear to be less toxic than their parent compounds indicating the importance of the macrocyclic structure. For example, PTX2 was found to be cytotoxic against KB cells at a dose of 0.05 μg/ml, while its seco acid analogue failed to show any cytotoxicity towards KB cells at a dose of 1.8 μg/ml.[39b]

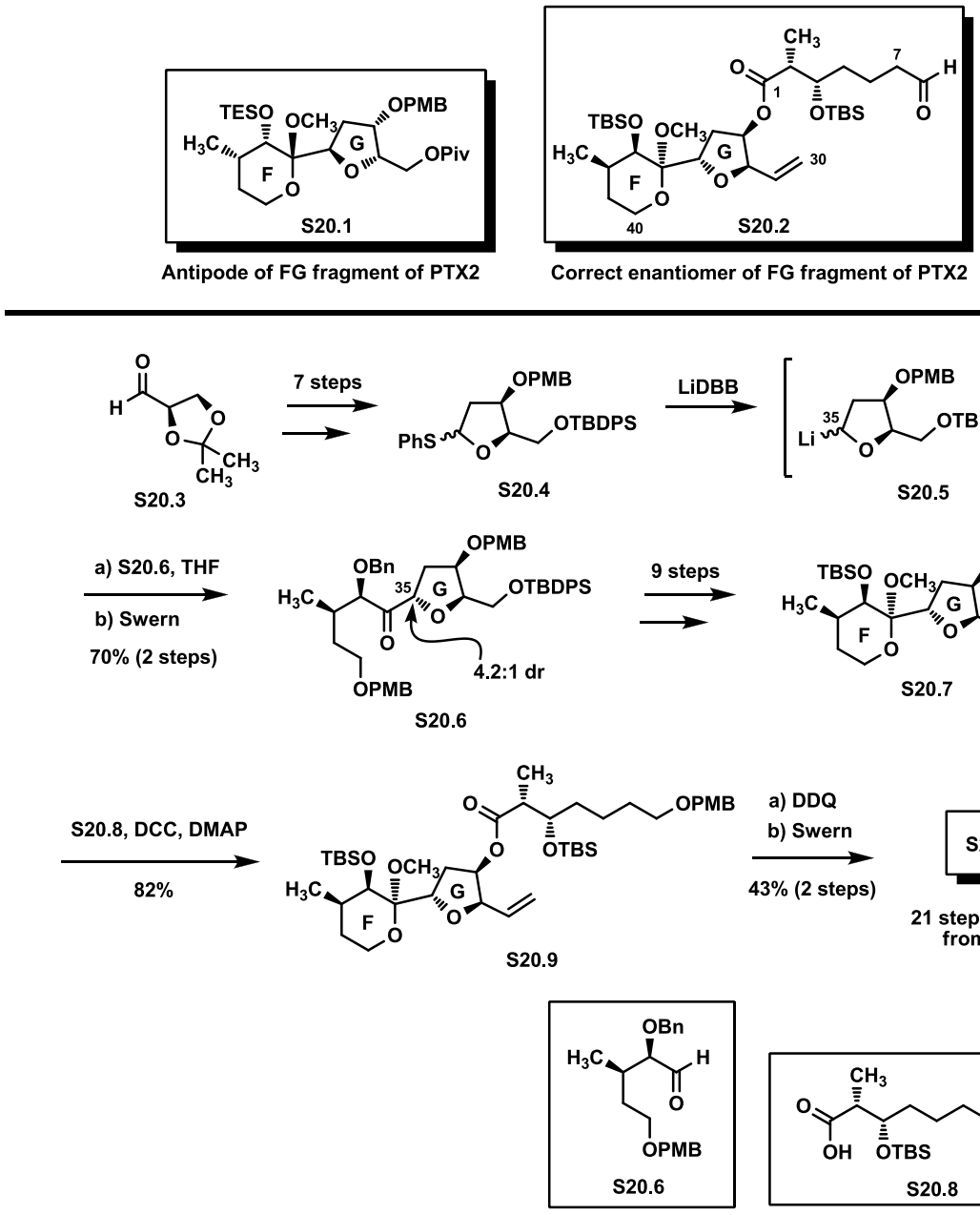
II. Previous Synthetic Studies of the Pectenotoxins

The PTXs have been the focus of intense research with only one total synthesis achieved.[4r] The structural complexities of the PTXs make this family of natural products synthetically challenging targets. Since their initial isolation, over a decade past before Murai and Fujiwara reported the first synthesis of the FG ring system of PTX2 (**S20.1**, Scheme 20, pg. 44).[4p] Although this was antipodal to that of PTX2, they recently reported the correct enantiomer of this fragment (**S20.2**).[4i] Both syntheses used similar methodologies employing the selective generation of an α-lithiated tetrahydrofuran at C35 from the corresponding phenythioacetal (**S20.4→S20.5**). Compound **S20.6** was obtained as a 4.2:1 mixture of diastereomers at C35 with the desired diastereomer as the major product. Formation of acetal **S20.7** followed by a DCC/DMAP promoted coupling with **S20.8** and deprotection/oxidation gave **S20.2** in a 21 step sequence from **S20.3**.

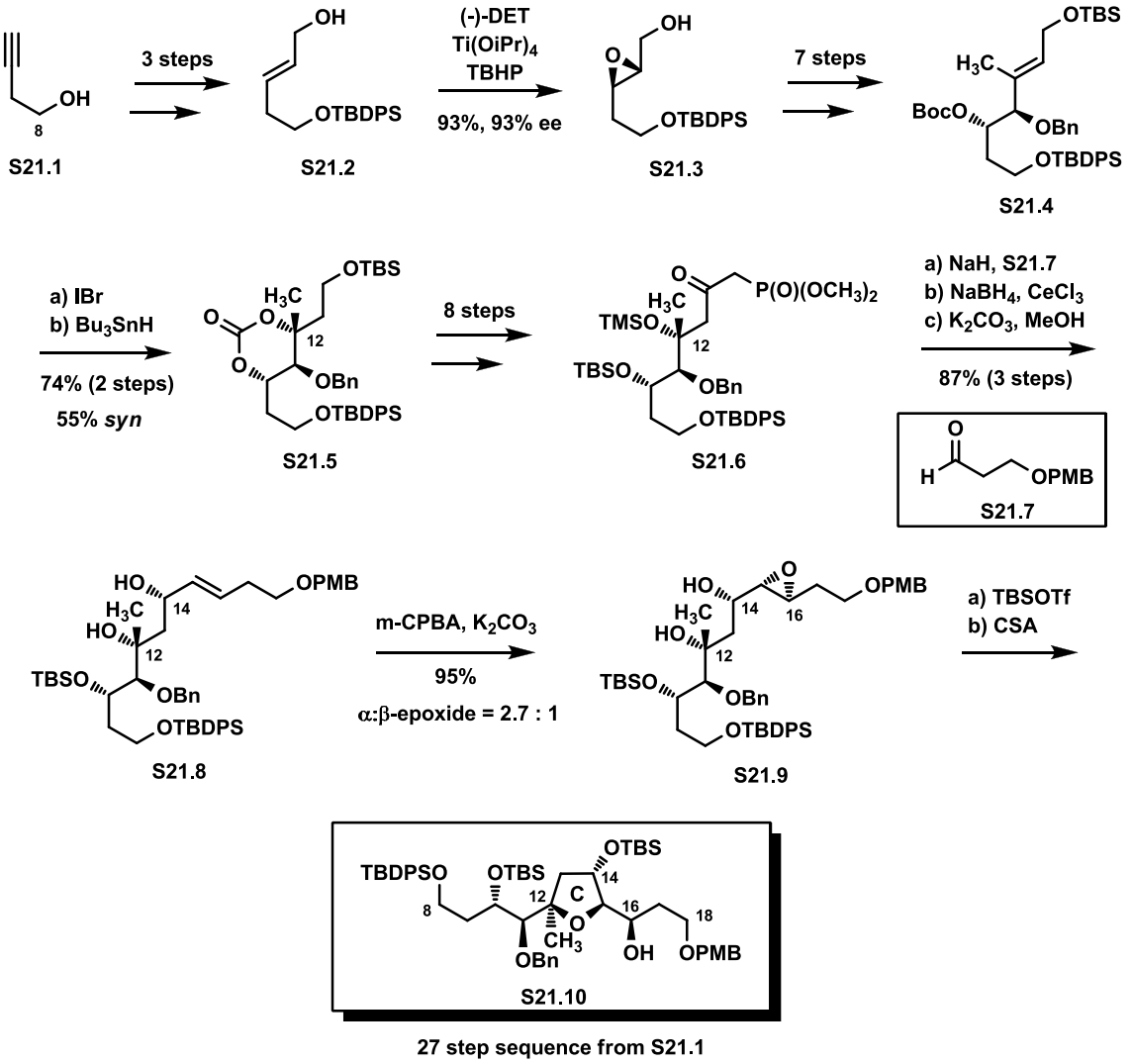
In 2000, Murai and Fujiwara also reported a synthesis of the C8-C18, which included the C ring system of PTX2 (**S21.10**, Scheme 21, pg. 45).[4o] Starting from alkynol **S21.1**, **S21.10** was prepared utilizing proximal chirality to introduce the stereocenters sequentially. Key steps of this synthesis included iodocarbonate cyclization to establish the stereochemistry at C12 (**S21.4→S21.5**), Horner-Wadsworth-Emmons olefination, substrate-controlled stereoselective Luche reduction setting C14 (**S21.6→S21.8**), and a

hydroxyl directed epoxidation using m- CPBA (**S21.8→S21.9**). Final acid-induced C ring formation afforded **S21.10** in a 27 step sequence from **S21.1**.

Scheme 20 Murai and Fujiwara's Route to FG Ring System



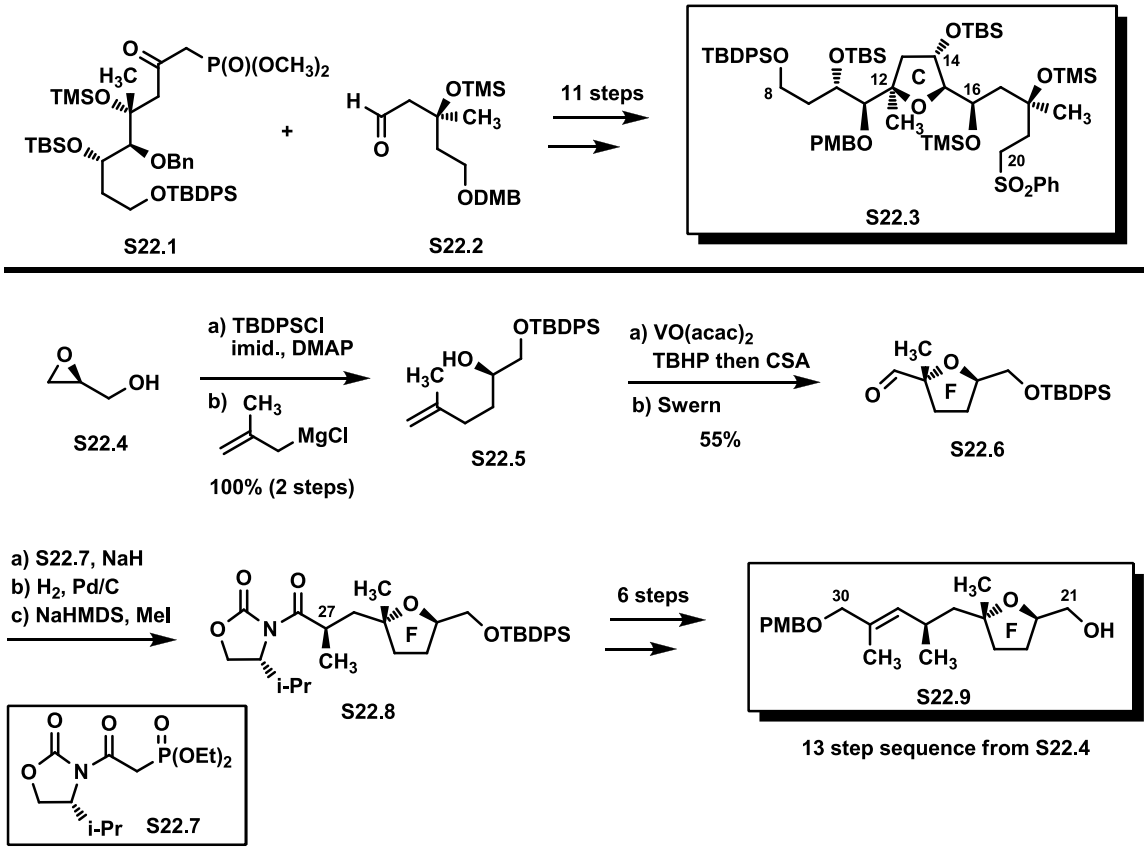
Scheme 21 Murai and Fujiwara's Route to the C Ring System



A second generation route to the C8-C20 C ring fragment, along with a synthesis of the C21-C30 segment of PTX2 was recently disclosed by Fujiwara (Scheme 22, pg. 46).[4g] The strategy for the C8-C20 segment was analogous to his previous strategy for the C8-C18 route in Scheme 21. A Horner-Wadsworth-Emmons reaction using a more functionalized aldehyde (**S22.2**) afforded **S22.3** after a series of protecting group manipulations and modification of the C20 carbon. The C21-C30 fragment was

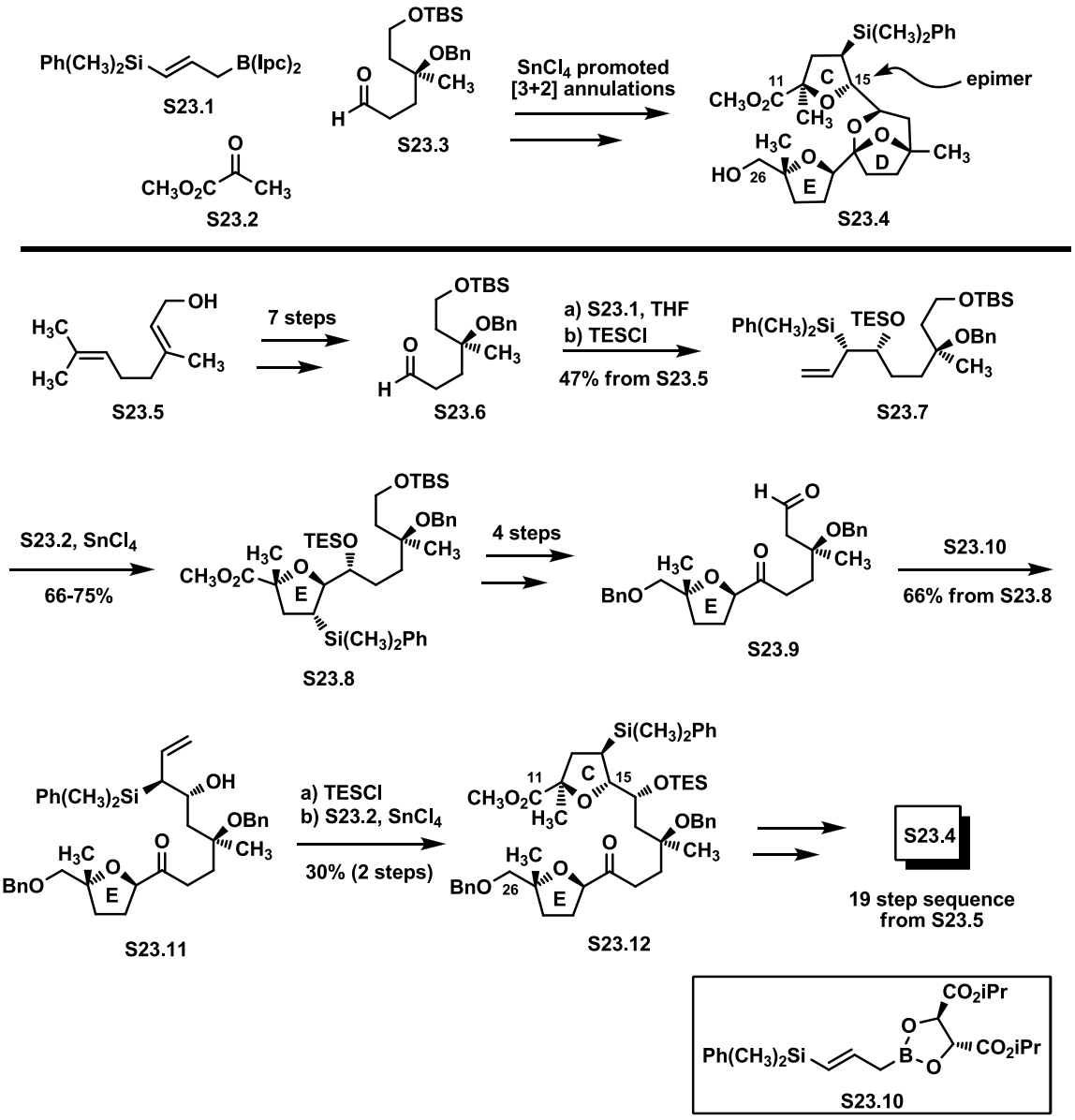
assembled in 13 steps (**S22.4→S22.9**) from (*S*)-glycidol via a route involving E ring formation by 5-*exo-tet* epoxide opening and stereoselective methylation at C27 using Evans' chiral auxiliary.

Scheme 22 Fujiwara's 2nd Generation Route to the C and F Ring Systems



Roush reported an alternative route to the C ring of PTX2 and had also synthesized the D and E ring systems to establish the C11-C26 carbon skeleton (Scheme 23, pg. 47).[4n] In this synthesis, a three-component coupling sequence via a [3+2]-annulation using a chiral γ-allylsilane was employed to construct the C ring system. The Roush group recognized early on that this strategy would ultimately give rise to the epimer of PTX2 at C15 (**S23.4**, see arrow). However, they reasoned that this issue would

Scheme 23 Roush's Synthesis of the CDE Ring System

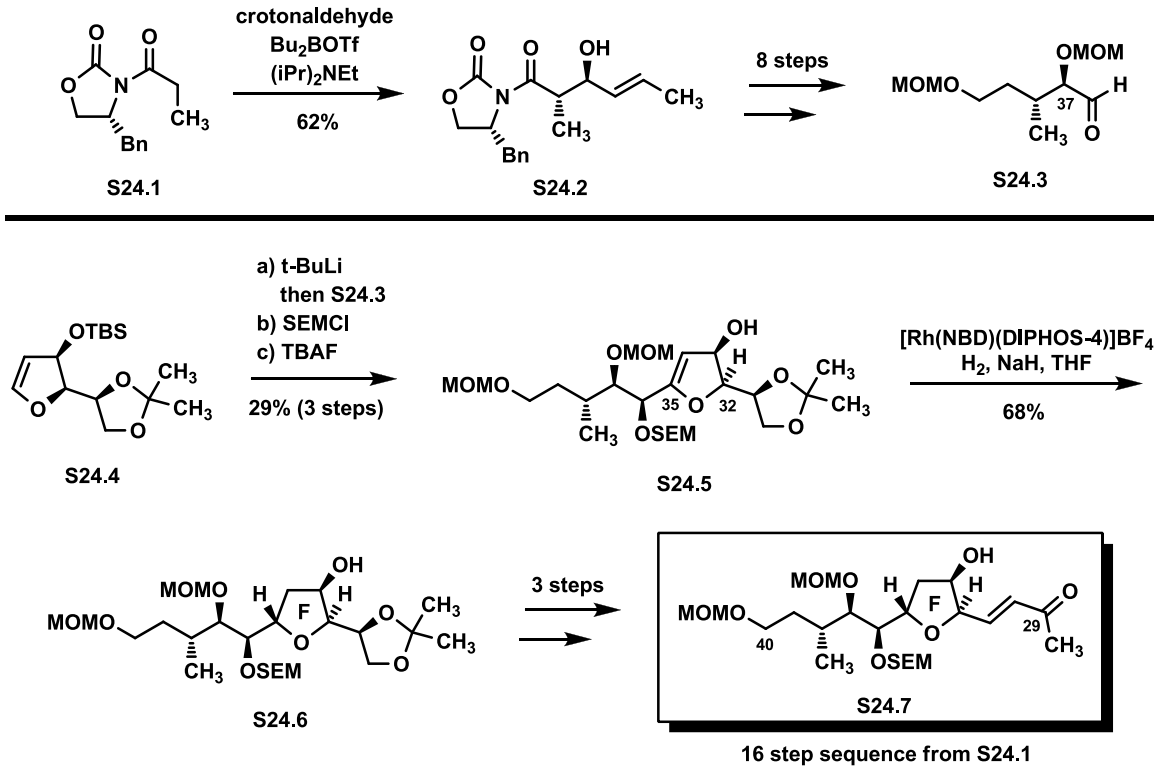


be addressed at a later stage by a base-promoted epimerization. The E ring system was constructed in a 10 step sequence starting from commercially available **S23.5**. Thus, conversion to **S23.6** in 7 steps was followed by an asymmetric silylboration to give allylsilane **S23.7** (47% from **S23.5**). Chelation-controlled $SnCl_4$-promoted [3+2]

annulation with methyl pyruvate (**S23.2**) afforded the desired E ring system **S23.8** in excellent yield (66-75%, >20:1 dr). The same strategy was then used to form the C ring system. With aldehyde **S23.9** in hand, the allylation/[3+2] annulation sequence was achieved to ultimately furnish the target CDE ring fragment (**S23.4**), in 19 steps, after bicyclic ketal formation.

In 2002, Paquette reported a synthesis of the C29-C40 FG fragment of PTX2 (Scheme 24, pg. 48) based on a hydroxyl-directed hydrogenation of **S24.5** to form the substituted F ring.[4k,m] Starting from oxazolidinone **S24.1** an Evans' *anti*-aldol reaction (62%) was followed by a series of steps to give aldehyde **S24.3**. Addition of the lithiated

Scheme 24 Paquette's Route to the C29-C40 Fragment

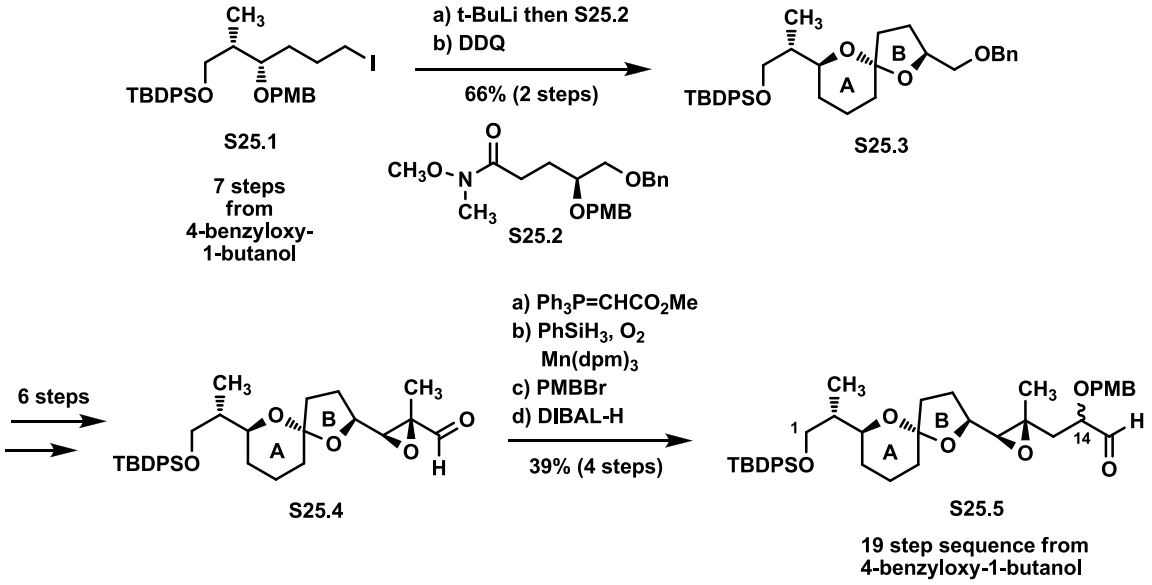


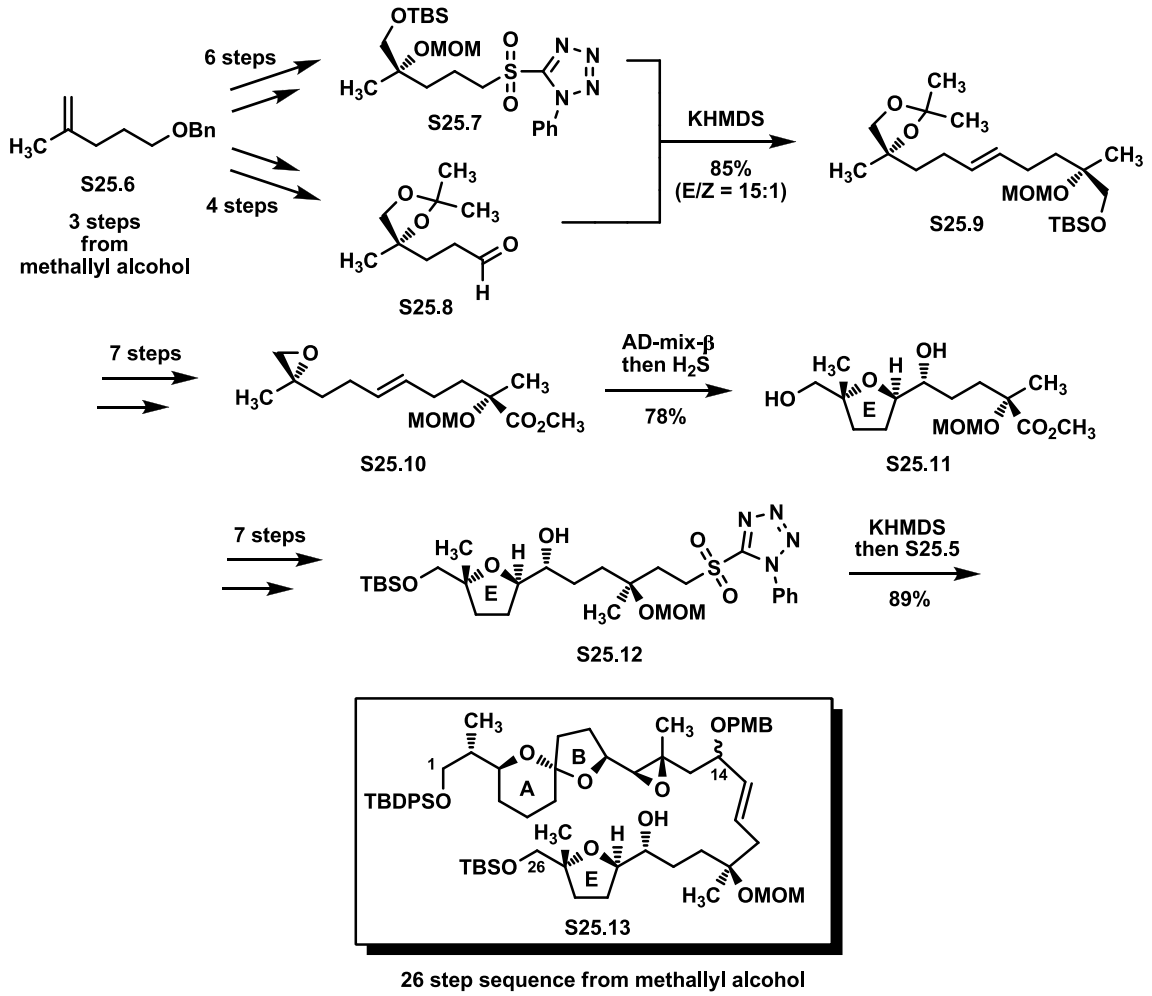
anion derived from dihydrofuran **S24.4** to **S24.3** afforded coupling product **S24.5** after a protection/deprotection sequence (29%, 3 steps). Hydroxyl-directed hydrogenation using the cationic catalyst [Rh(NBD)(DIPHOS-4)BF_4] was achieved using the sodium salt of **S24.5** to avoid elimination of water (68%). This capped a 16 step sequence to the C29-C40 FG fragment from **S24.1**.

Paquette also reported a synthesis of the C1-C26 fragment of PTX2, a precursor to the ABCDE ring systems (Scheme 25, pg. 50).[4j] Addition of the organolithium derivative of **S25.1**, available in 7 steps from 4-benzyloxy-1-butanol, with Weinreb amide **S25.2** followed by PMB removal using DDQ afforded spiroketal **S25.3** in 66% yield over the 2 steps. After a chain extension and introduction of a chiral epoxide, the C14 and C15 functionalized carbons were introduced using a Wittig reaction followed by a Mn^{3+}-catalyzed oxidation to give the C1-C15 fragment (**S25.5**).

The C16-C26 phenyltetrazole sulfone was efficiently constructed from benzyl ether **S25.6**, readily available from methallyl alcohol in 3 steps. Both **S25.7** and **S25.8** were constructed via Sharpless dihydroxylation. Julia olefination was achieved in 85% yield (15:1 E/Z ratio) and subsequent manipulations on **S25.9** furnished epoxide **S25.10** in seven steps. Subjection to Sharpless asymmetric dihydroxylation conditions followed by exposure to acid afforded the tetrahydrofuran E ring (**S25.11**) in 78% yield. Seven additional steps gave phenyltetrazole sulfone **S25.12** which was coupled with aldehyde **S25.5** under the Julia olefin nation conditions to generate exclusively the *E* isomer of **S25.13** (89%) in a 26 step sequence from methallyl alcohol. However, attempts to assemble the C and D rings were unsuccessful.

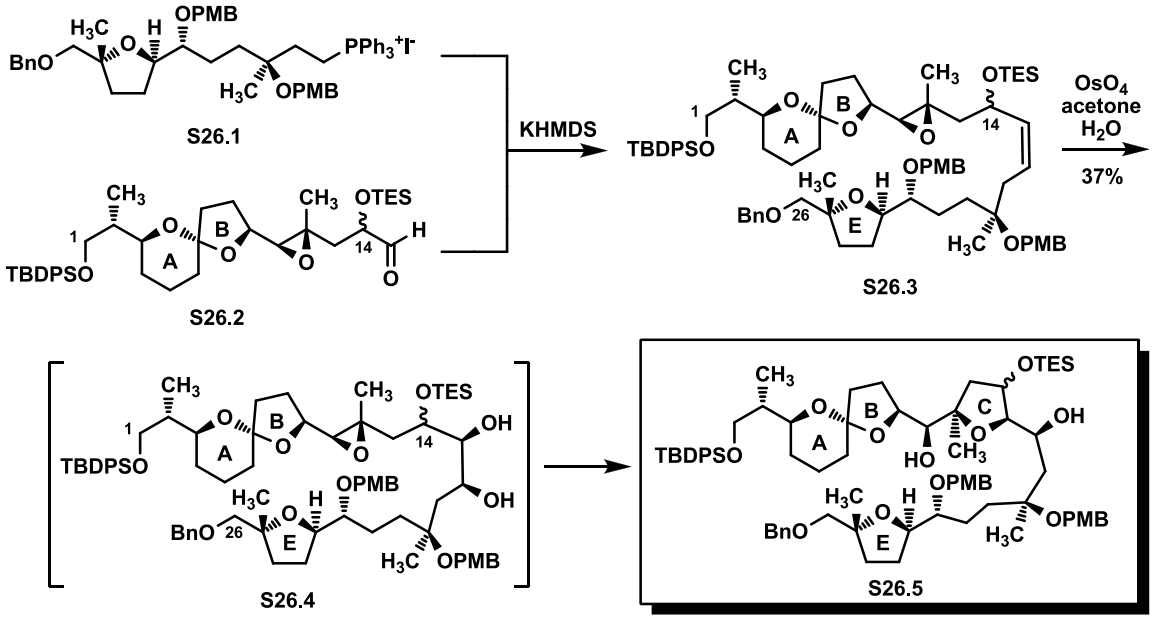
Scheme 25 Paquette's Synthesis of the C1-C2 Fragment





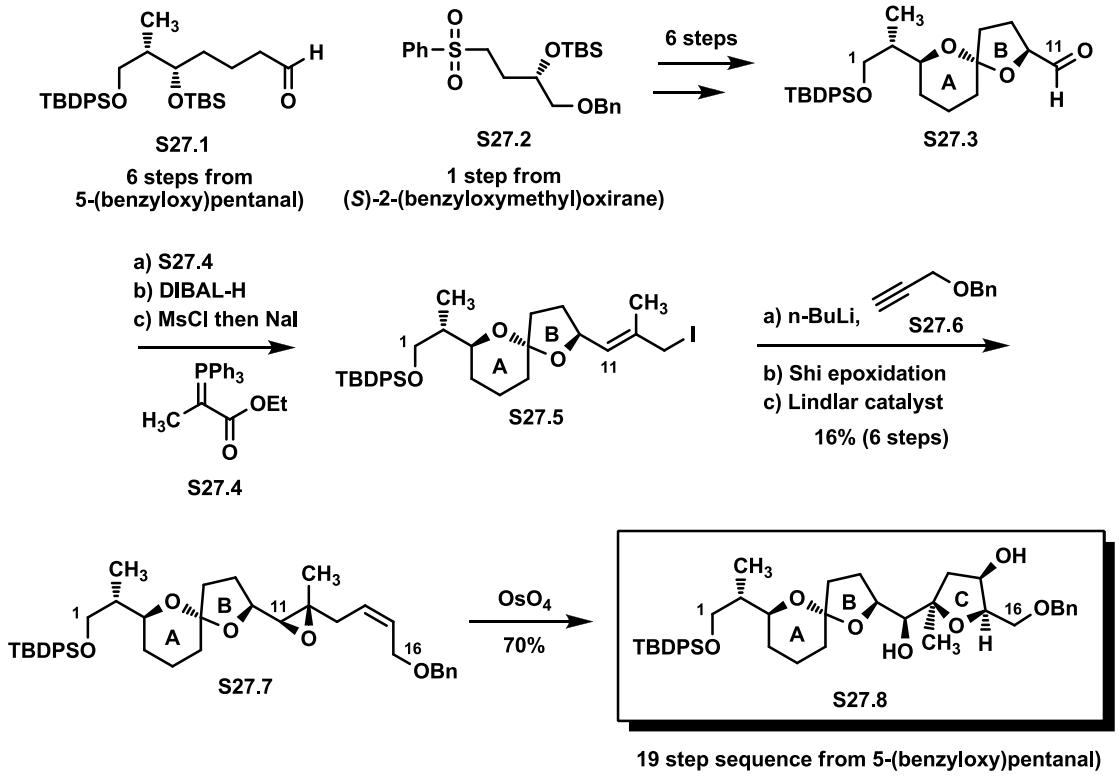
Paquette recently reported a second generation route to the C1-C26 fragment which also included the C ring system (Scheme 26, pg. 51).[4q] This route was similar to his previous route with the exception of the protecting groups and coupling strategy. A Wittig reaction was employed **(S26.1 + S26.2)** for the key coupling step which gave the *Z* isomer of the C15/C16 olefin (**S26.3**). Dihydroxylation of the olefin (→**S26.4)** led to spontaneous cyclization to form the C ring (**S26.5**) in 37% yield.

Scheme 26 Paquette's 2nd Generation Route to the C21-C26 Fragment



In 2005, Brimble published a synthesis of the C1-C16 ABC spiroketal fragment of PTX2 (Scheme 27, pg. 52).[4h] The synthesis began from readily available aldehyde **S27.1** (6 steps from 5-(benzyloxy)pentanal) and sulfone **S27.2** (1 step from (*S*)-2-(benzyloxymethyl)oxirane). The C1-C11 AB spiroketal system was assembled in a 6 step sequence. Introduction of the remaining C12-C16 carbon chain was achieved via Wittig reaction using ylide **S27.4** and a subsequent 3 step sequence converted the ester to the

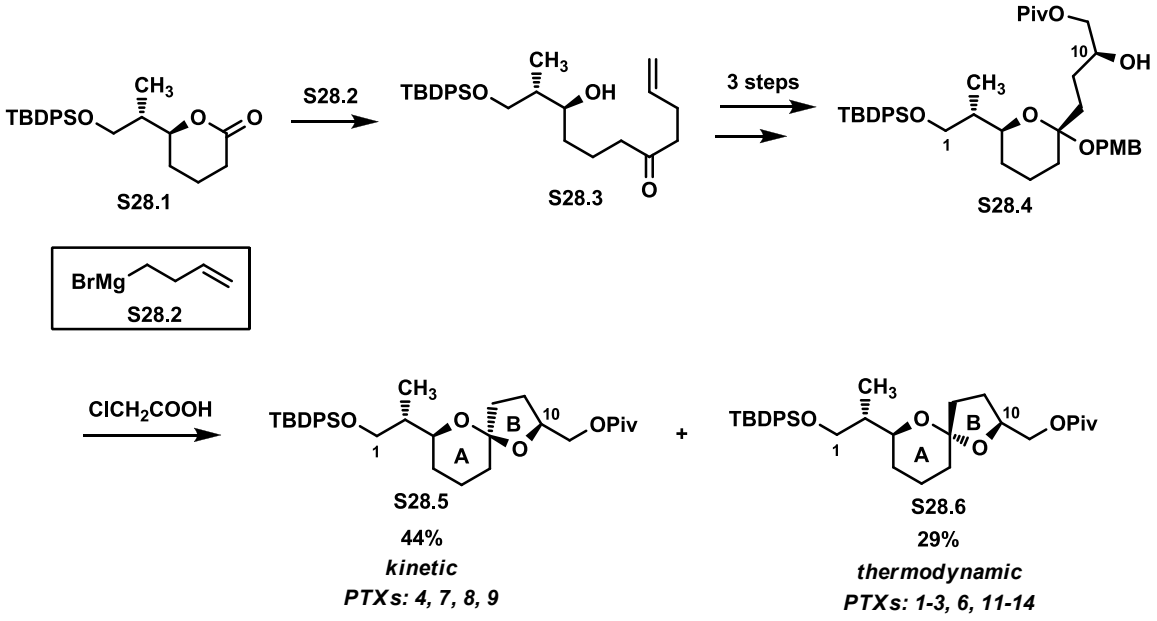
Scheme 27 Brimble's Synthesis of the C1-C16 AB Spiroketal Ring System



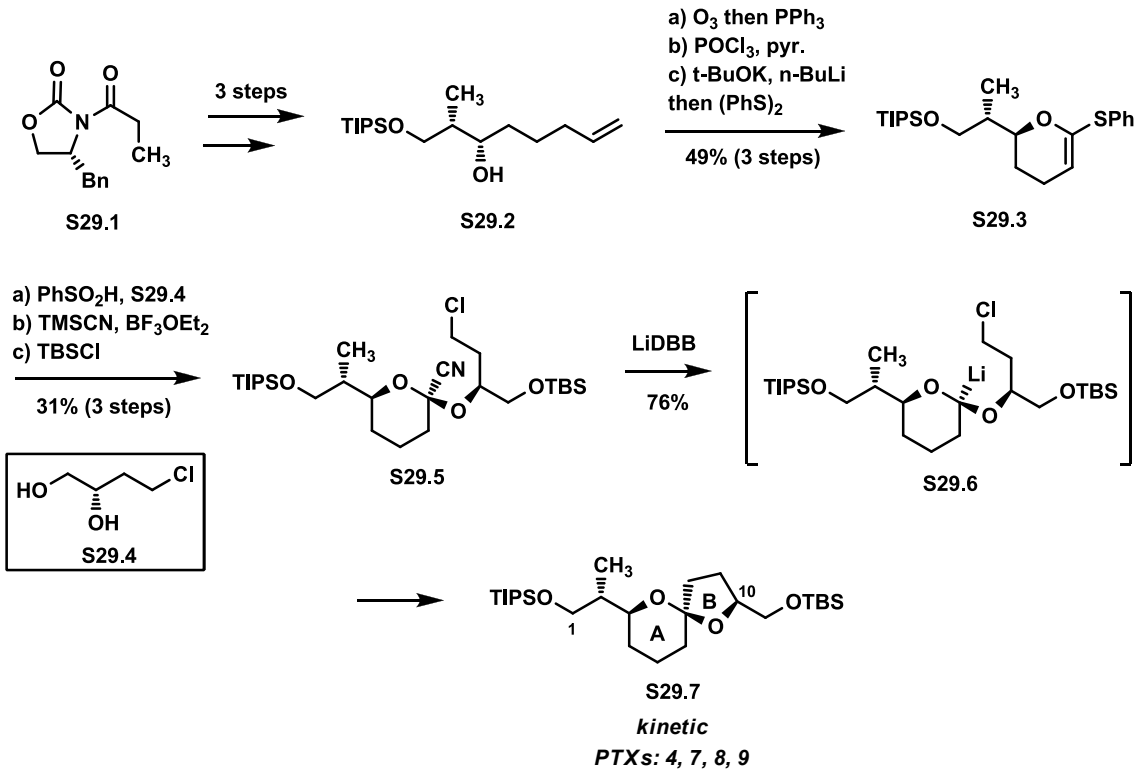
corresponding primary iodide (**S27.5**). Displacement of the iodide using the lithium acetylide derivative of **S27.6** was followed by Shi epoxidation (5.5:1 dr) and Lindlar reduction to afford **S27.7** (16%, 6 steps). Dihydroxylation of the corresponding olefin led to spontaneous cyclization to form the C ring system (**S27.8**) in a 70% yield thus completing the C1-C16 spiroketal-containing ABC fragment in an 19 step sequence from 5-(benzyloxy)pentanal.

Synthetic approaches to access both spiroketal anomers of PTX2 have been reported by both Pihko[4l] and more recently, Rychnovsky.[4f] Pihko prepared spirocyclic precursor **S28.3** (Scheme 28, pg. 53) via Sharpless dihydroxylation of the C10/C11 terminal olefin. The spiroketalization was performed in the presence of several acids. Although stronger acids (i.e. p-TsOH) gave rise to the more stable doubly-anomeric

Scheme 28 Pihko's Approach to the Nonanomeric AB Spiroketal Ring System



Scheme 29 Rychnovsky's Approach to the Nonanomeric AB Spiroketal



product (**S28.6**), chloroacetic acid effected the formation of nonanomeric spiroketal **S28.5** in a 44% yield. Thus, these studies established a method to obtain both isomers of the AB ring system of the PTXs.

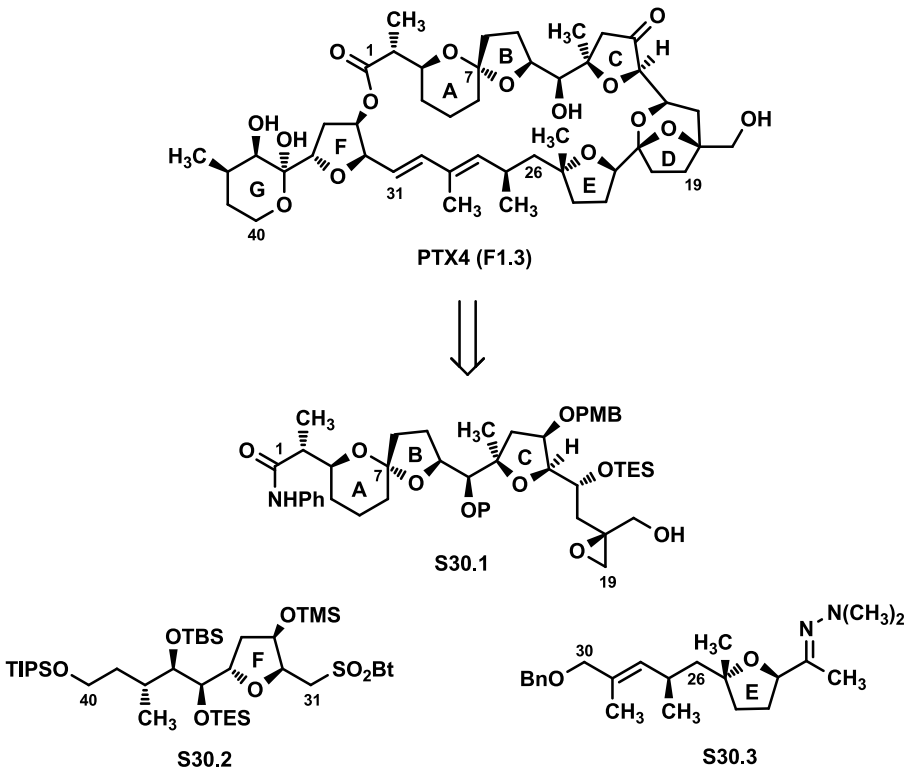
Rychnovsky also reported a synthesis of the nonanomeric AB spiroketal ring system using a reductive cyclization reaction (Scheme 29, pg. 53).[4f] Cyanoacetal **S29.5** was prepared in a 10 step sequence from Evans' chiral auxiliary **S29.1**. Axial-selective reductive lithiation employing LiDBB gave intermediate **S29.6** which then cyclized to afford the desired AB spiroketal system (**S29.7**) in 76% yield.

III. Evans Total Synthesis of Pectenotoxins 4 and 8

Although several research groups have constructed various subunits of the PTXs, only one total synthesis has been achieved, and that was by the Evans group.[4c,d] The retrosynthetic strategy that they employed for this elegant synthesis is illustrated in Scheme 30 (pg. 55) wherein three intermediates were prepared.

Synthesis of subunit **S30.1** began by constructing the AB spiroketal ring system. A Wittig reaction between phosphonium salt **S31.2** (4 steps from 5-hexenol) and aldehyde **S31.3** (3 steps from ethyl glyoxylate) followed by acid treatment gave the corresponding anomeric spiroketal (Scheme 31, pg. 56). Chain elongation and further manipulations afforded epoxy diol **S31.5** which underwent a 5-exo-tet cyclization upon exposure to PPTS. Barton deoxygenation and subsequent protection/deprotection furnished **S31.6**. The C17-C19 chain was incorporated by an asymmetric allylation under Felkin control to give **S31.7**, which was converted to intermediate **S30.1** under Sharpless epoxidation conditions (22 step sequence from 5-hexenol).

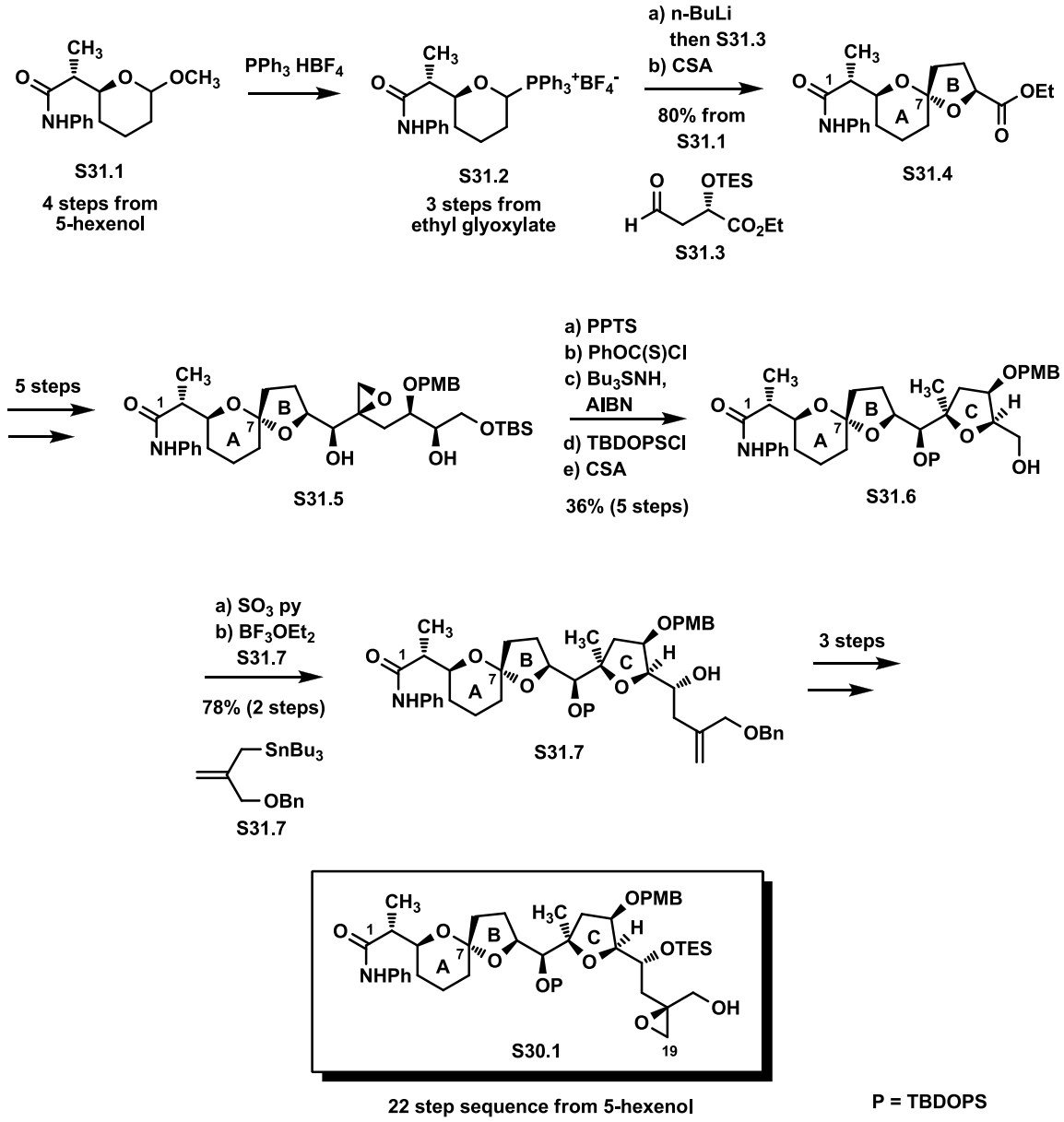
Scheme 30 Evans' Retrosynthetic Analysis Towards PTX4



Intermediate **S30.3** was prepared starting from Evans' syn-aldol product **S32.1** (Scheme 32, pg. 57). Conversion to enol ether **S32.2** was followed by a Claisen rearrangement and then chelation controlled reduction to afford alcohol **S32.3**. The E ring was prepared by iodoetherification of **S32.3** to give the corresponding iodide which was subsequently removed using Bu_3SnH and AIBN. Thus, the C20-C30 fragment was prepared in 17 steps from **S32.1**.

The synthesis of the C31-C40 F ring fragment was achieved in 17 steps using a different approach from the methods employed by other groups as described herein. The key step in the synthesis of this segment involved the coupling of the C31-C35 phosphonium salt **S33.2** (Scheme 33, pg. 57) with C36-C40 aldehyde **S33.4** to form *Z*-

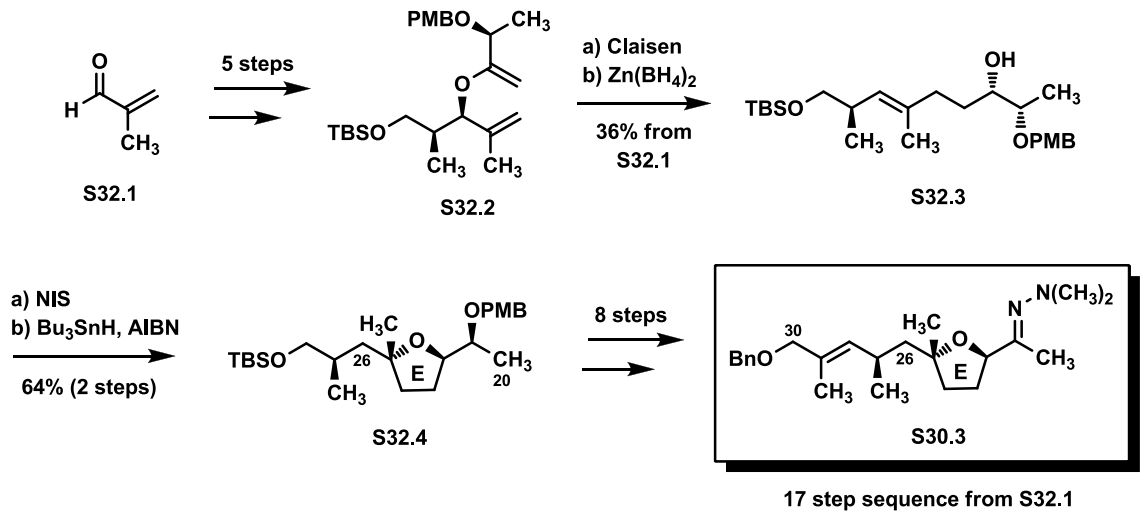
Scheme 31 Synthesis of Intermediate S30.1



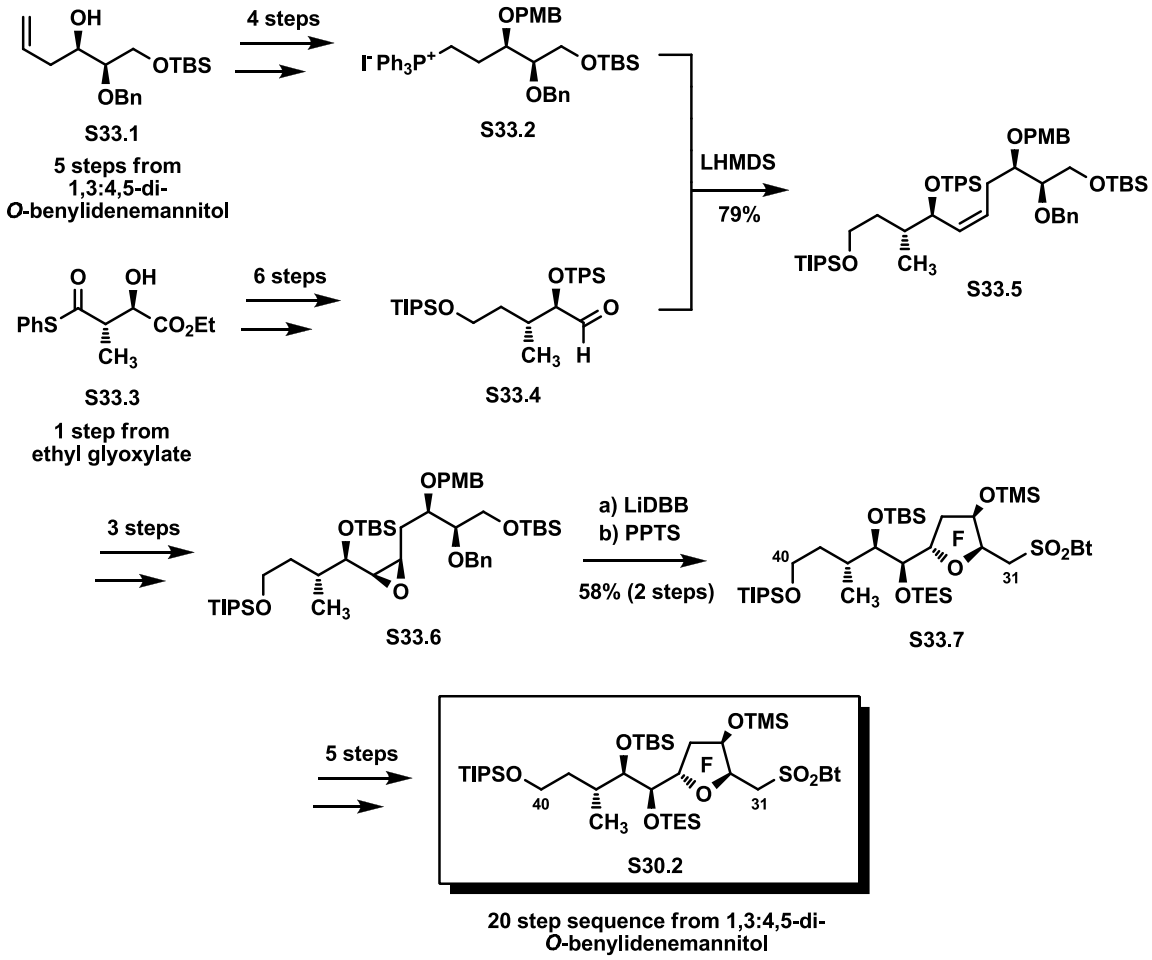
olefin (**S33.**5). Epoxidation and protecting group manipulations gave epoxide **S33.6**. Benzyl deprotection using LiDBB was accompanied by exposure of the corresponding epoxy alcohol to acid to affect a 5-exo-tet cyclization, thus establishing the F ring system (**S33.7**). A series of 5 steps followed to afford the final key intermediate (**S30.2**) in a 20 step sequence from commercially available 1,3:4,5-di-*O*-benylidenemannitol.

With all three intermediates prepared, completion of the synthesis began by the

Scheme 32 Synthesis of Intermediate S30.3

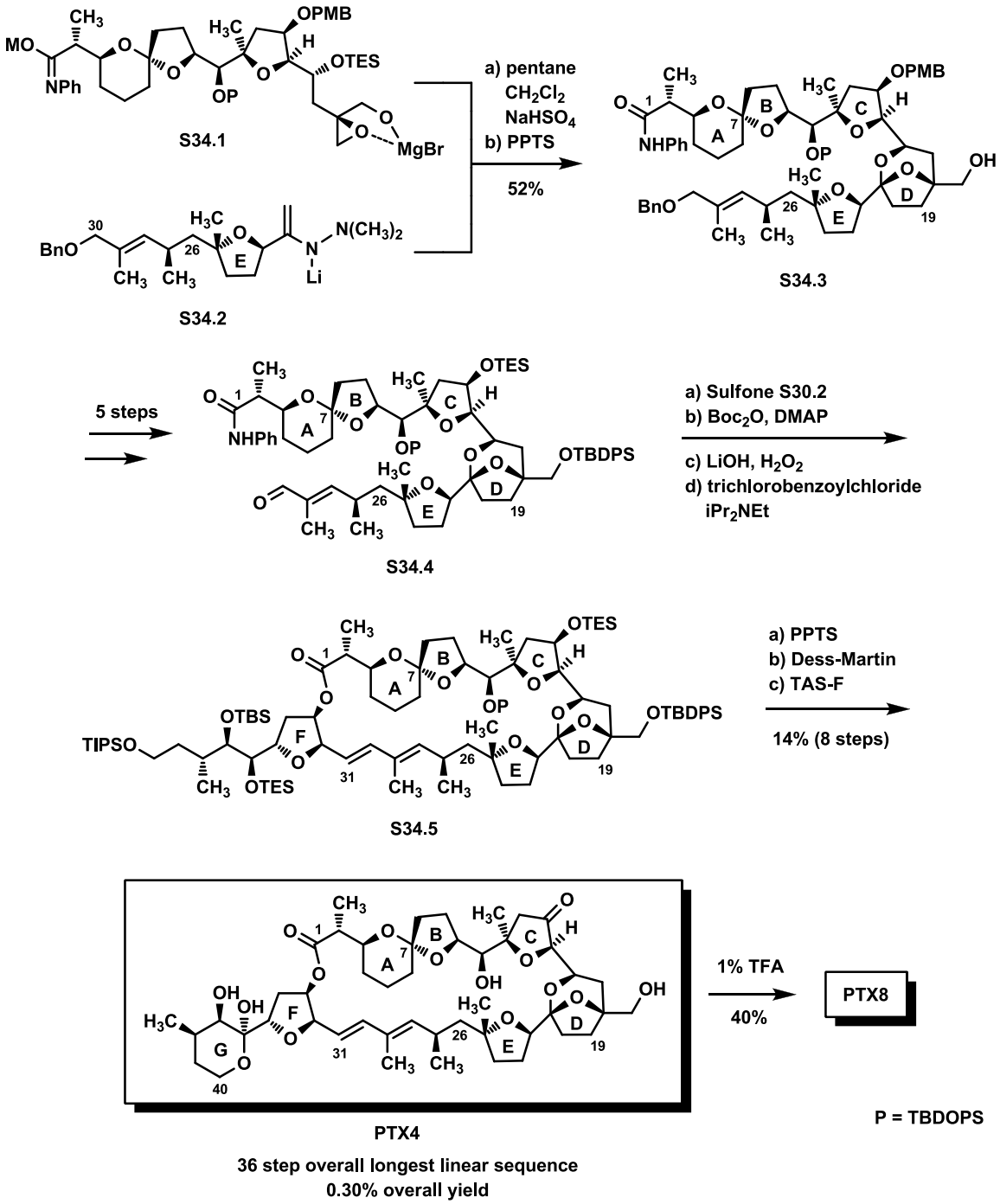


Scheme 33 Synthesis of Intermediate S30.2



coupling of the C1-C19 fragment with the C20-C30 fragment. This union was achieved by formation of the metalloenamine **S34.2** (Scheme 34, pg. 58, derived from **S30.3**) and

Scheme 34 Final Coupling and Completion of Total Synthesis



then subsequent reaction with $MgBr_2$-activated epoxide **S34.1**. Acidolysis of the corresponding hydrazinyl lactol (not shown) afforded the C1-C30 ABCDE subunit (**S34.3**). Incorporation of intermediate **S30.2** was accomplished via Julia olefination with aldehyde **S34.4** followed by macrolactonization under Yamaguchi conditions to furnish the C1-C40 carbon skeleton of PTX4 (**S34.5**). Further deprotection and oxidation at C14 and C36 effected the formation of the final G ring. Global deprotection using TAS-F gave PTX4 in 36 steps (longest linear sequence) and 0.3% overall yield. PTX8 was obtained from PTX4 upon exposure to TFA to effect isomerization of the AB spiroketal ring system.

The following chapter will describe our synthetic efforts towards the pectenotoxins, which utilized SDE chemistry. This will be followed by a proposed synthetic route for the total synthesis of PTX4.

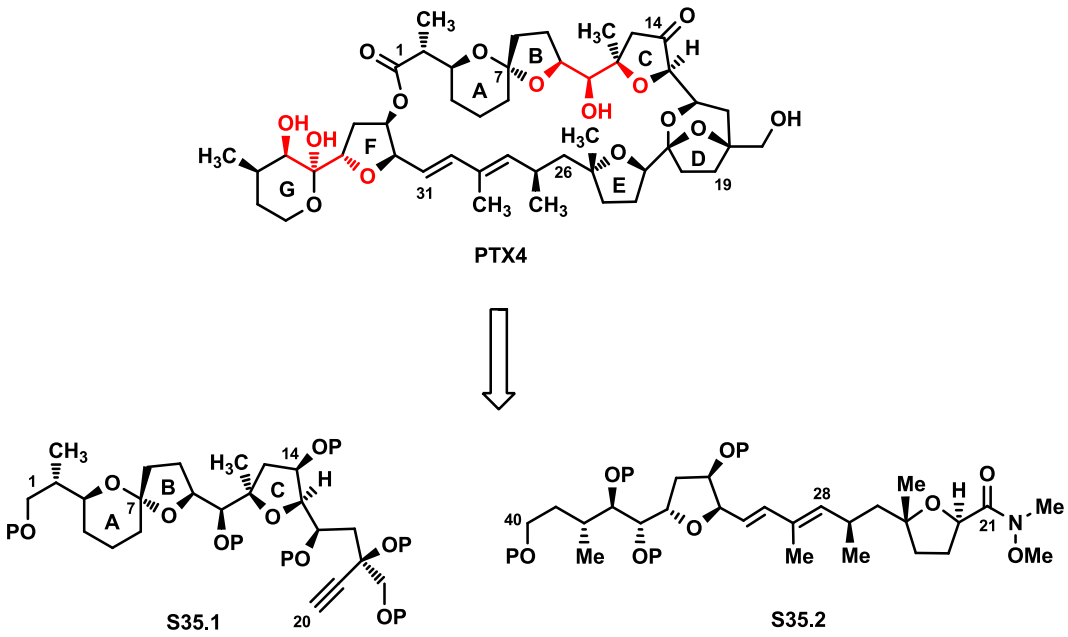
Chapter 7

Studies Towards Pectenotoxin 4 (PTX4)

I. Strategy for Spirodiepoxide Approach to Pectenotoxin 4

In principle, SDEs can provide access to the three tetrahydrofurans of PTX4, as well as the oxygenated substituents that are directly attached to these rings, and thereby facilitate the synthesis of this highly complex polyketide (see colored bonds in PTX4, Scheme 35).

Scheme 35 Key Coupling Strategy Towards PTX4



There are several challenges that must be addressed in order to confidently proceed with this total synthesis. The primary concerns are: (1) intermediate stability to reaction and isolation conditions; (2) selective construction of each stereocenter; (3)

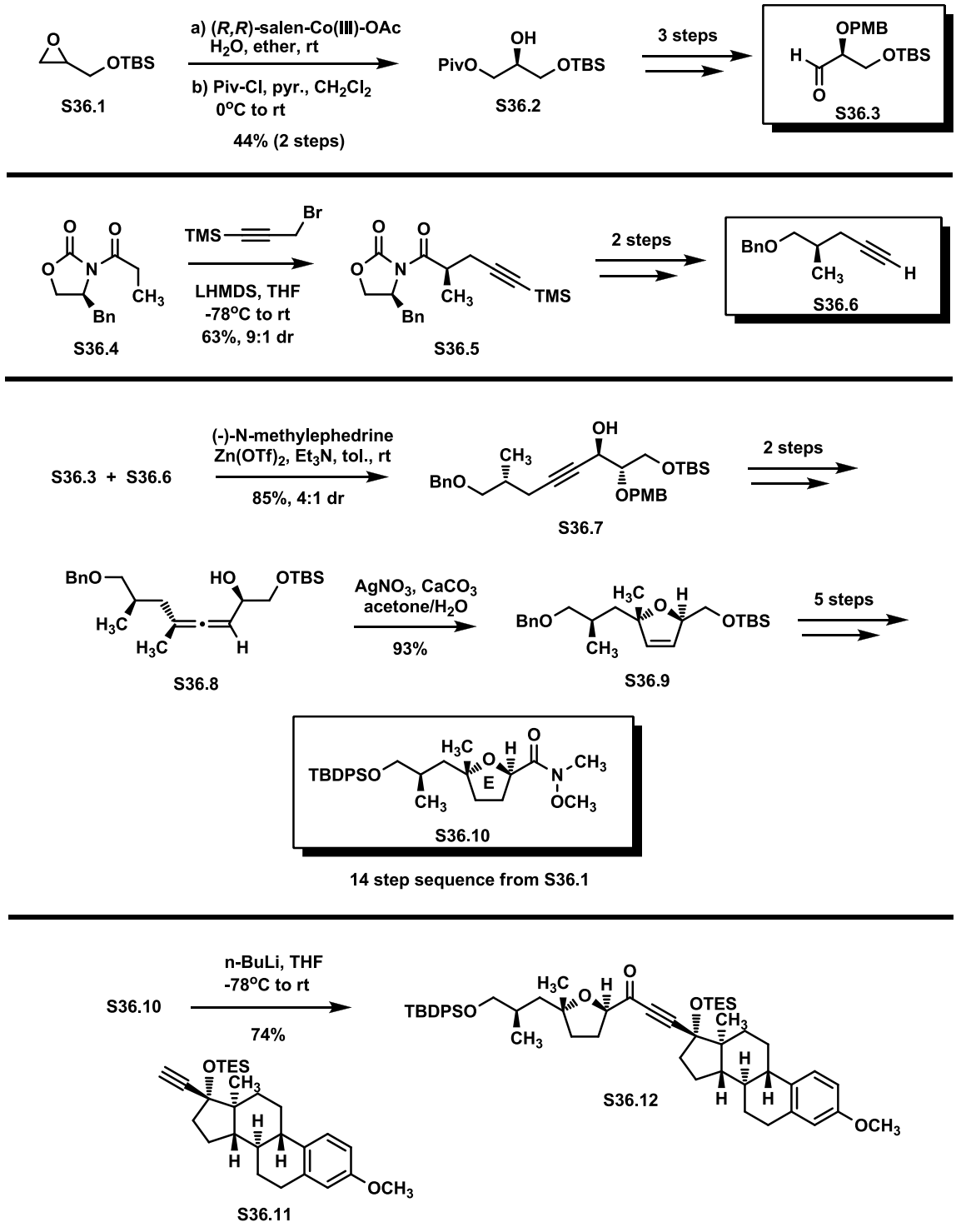
overall brevity via convergency; and (4) synchronized and unencumbered protecting group strategy. The primary goals are to develop superior strategies and direct methods in the synthetic endeavor, including, but not limited to, SDE-based transformations. Our synthetic plan focused on the late-stage union of C1-C20 (ABC fragment, **S35.1**) with C21-C40 (EF fragment, **S35.2**) via an alkyne/Weinreb amide coupling (Scheme 35). We pursued these precursors as a preliminary test of the viability of our SDE chemistry. This section describes our studies towards these segments and is focused on C1-C20. This discussion is followed by a full synthetic plan to PTX4 based on these studies.

II. Previous Synthesis of the C21-C28 Fragment of Pectenotoxin 4[4e]

Rob Kolakowski, a graduate student in the Williams group, recently reported a synthesis of the C21-C28 E ring segment of PTX4 (**S36.10**, Scheme 36, pg. 62).[4e] Starting from commercially available glycidol **S36.1**, Jacobsen hydrolytic kinetic resolution[40] followed by selective protection of the resultant primary alcohol with PivCl afforded **S36.2** (44%, 2 steps). A protection/deprotection and subsequent oxidation gave aldehyde **S36.3**. Alkyne **S36.6** was prepared in a 3 step sequence from Evans' oxazolidinone **S36.4**. Thus, alkylation with TMS-propargyl bromide (63%, 9:1 dr) followed by oxazolidinone reduction and benzyl protection furnished alkyne **S36.6**. Propargyl alcohol **S36.7** was obtained from an asymmetric Zn alkynylation of **S36.3** with **S36.6** under the Carreira conditions.[20] Upon conversion to allene **S36.8**, dihydrofuran **S36.9** was prepared by using Marshall cyclization conditions,[41] which employ $AgNO_3$ and $CaCO_3$ in acetone/H_2O (93%). Five subsequent steps afforded the C21-C28 E ring

(40) (a) Tokunga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *936*, 277. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776.
(41) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

Scheme 36 Synthesis of the C21-C28 Fragment of PTX4



fragment of PTX4. The longest linear sequence to this fragment is 14 steps from commercially available **S36.1**.

In order to test the feasibility of our approach to PTX4, a series of complex and easily accessible alkynes were coupled to Weinreb amide **S36.10**.[42] For example, the union of alkynyl steroid **S36.11** with **S36.10** proceeded smoothly in a 74% yield, which argued well for our planned C1-C20 / C21-C40 coupling.

III. A Spirodiepoxide Strategy to the AB Spiroketal Ring System of Pectenotoxin 4[6b]

Among the potential strategies for accessing the northern hemisphere of PTX-4, we were intrigued by the possibility of forming the AB spiroketal ring system by way of an intramolecular ketone addition to a SDE followed by trapping the oxocarbenium ion with the resident alcohol (**S37.1→S37.3→S37.6**, Scheme 37). Alternatively, the AB spiroketal could form by lactol-initiated SDE opening (**S37.1→S37.4→S37.6**).[8j] The stereochemical outcome of each potential pathway was of interest. For this study we were aware that isomerization to the more stable spiroketal matches the structure of PTX-4 and would be readily achieved by the action of Brønsted acid.[4l,38a] While the data presented does not allow one to discern the operative pathway to **S37.6**, suitable target systems and their oxidative cyclization products were prepared.

The C1-C7 fragment was prepared as shown in Scheme 38 (pg. 65). Known syn aldol product[43] **S38.1** was reduced with lithium borohydride and gave **S38.2** along with the cleaved oxazolidinone as an inseparable mixture after FCC. This contaminant failed attempts to selectively mask the primary alcohol as the TBDPS ether. Consequently,

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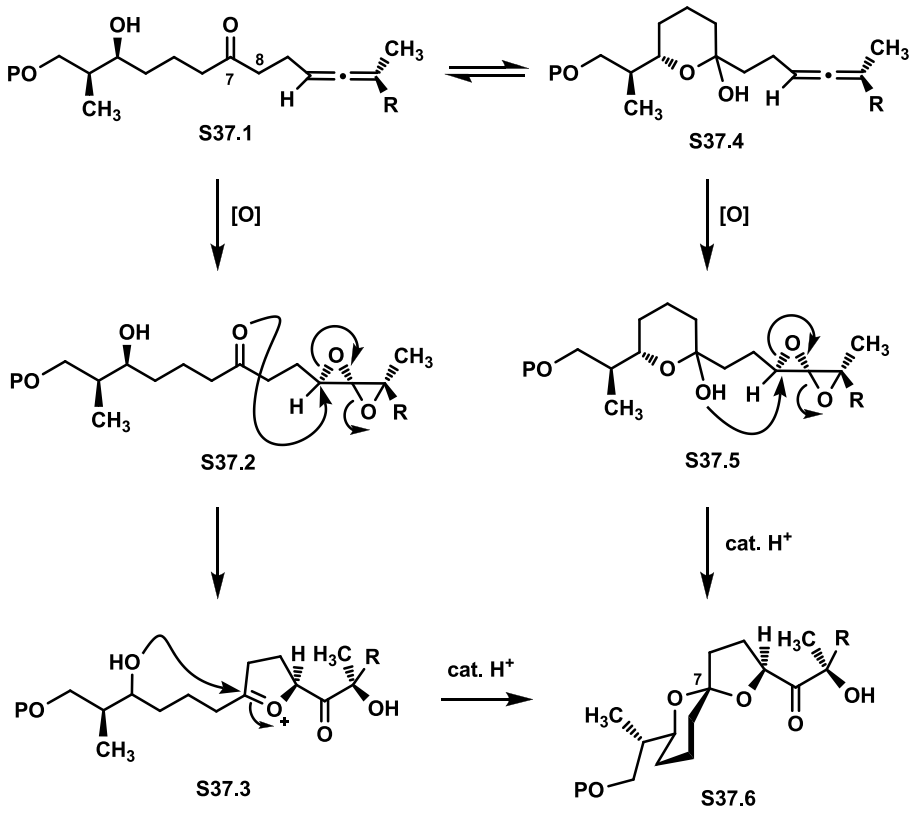
(42) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22,* 3815.

(43) **S38.1** was prepared on multigram scale in 2 steps from commercially available 5-hexenol according to ref. 4c.

Scheme 37 Plan for the SDE-Based Approach to the AB Spiroketal System



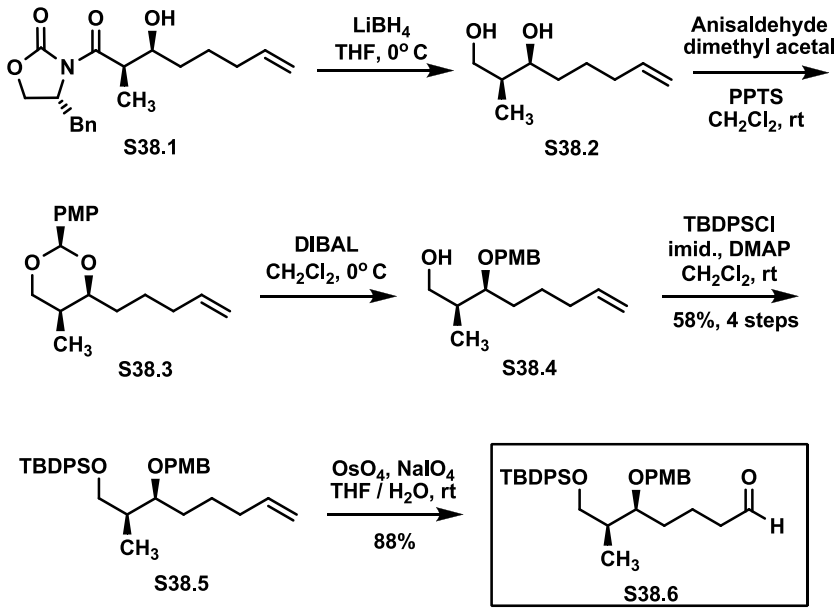
S38.2 was converted to the PMP acetal, reduced with DIBAL, and then protected with TBDPS to afford alkene **S38.5** in 58% yield over 4 steps. At each point in this sequence (**S38.2-S38.4**) rigorous purification was hampered by the presence of inseparable by-products. However, **S38.5** was readily purified and obtained in good overall yield (87% average per step). Although ozonolysis of related systems is documented,[44] Lemieux-Johnson[45a,b] oxidation of **S38.5** proved to be superior for this substrate and furnished **S38.6** (88%).

Trisubstituted allenes containing no α-branching on the more substituted double

(44) (a) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583. (b) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.

(45) (a) Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. (b) Ozonolysis of **S38.5** led to a complex mixture of products even when an OTES group was used at C3 instead of a PMB group. Hence, the problems from ozonolysis of **S38.5** were not directly related to the presence of the OPMB group.

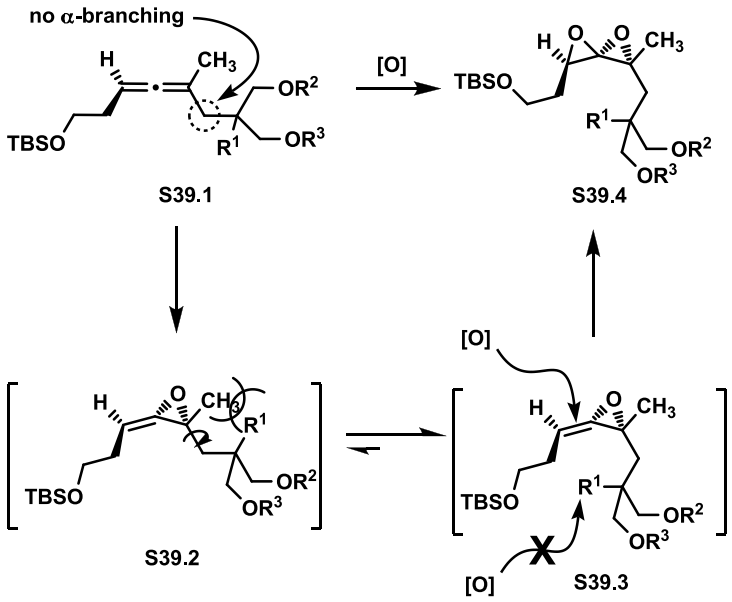
Scheme 38 Synthesis of the C1-C7 Aldehyde



bond typically give rise to low diastereomeric ratios of SDEs (~1.5:1) based on previous studies in our group (Chapter 2). Therefore, the possibility of a synthetically useful, stereoselective substrate-controlled oxidation using β-branching seemed unlikely. Analysis of **S39.1**, however, suggested that allene oxide (**S39.2**, Scheme 39, pg. 65) would suffer destabilizing syn-pentane interactions between the neopentyl-like side chain and the methyl substituent on the epoxide. We reasoned that the allene oxide would avoid the destabilizing syn pentane interactions expected for conformers closely related to **S39.2** and therefore would prefer to populate conformers approximated by structure **S39.3**. In this case, the oxidant should prefer approach from the top face of the double bond, since the neopentyl group would effectively block attack from the bottom face (**S39.3**, see arrows).

Ideally R^1, OR^2 and OR^3 in S39.1 would be orthogonally protected alcohols to allow further functionalization en route to the C1-C15 portion of PTX-4. Initial oxidation

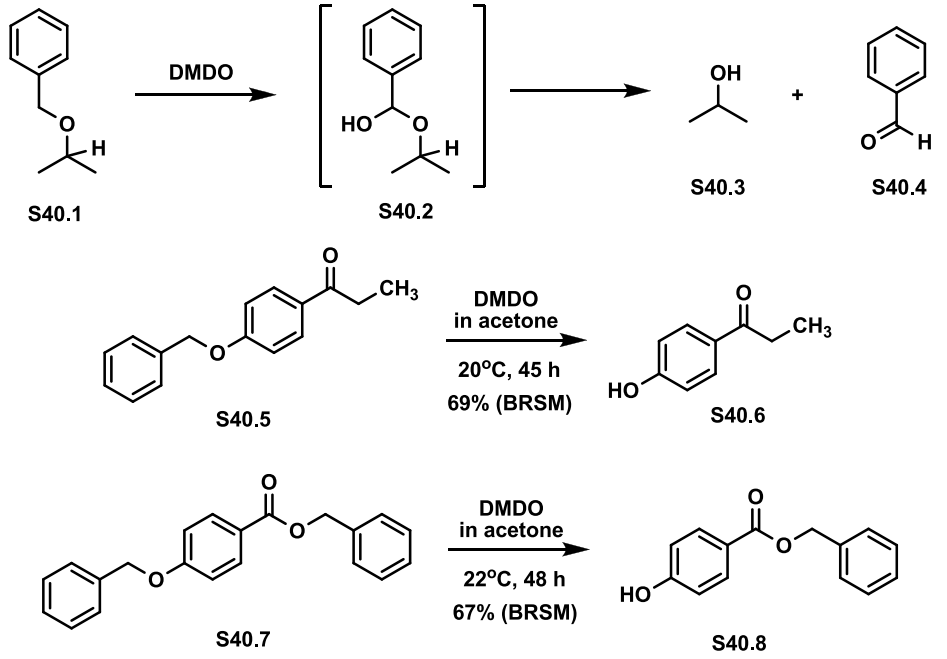
Scheme 39 Plan for Substrate Controlled Allene Oxidation Using β-Branching



studies of this system (**S39.1,** R^1 = OTBS, OMOM, OCH_3 / R^2, R^3 = TBDPS and Bn) gave only ~1:1 SDE ratios. Moreover, for R^2=R^3=Bn, partial cleavage of these groups was observed under DMDO in chloroform conditions. Presumably, oxidative insertion into the benzylic C-H bond occurs to form the hemi-acetal (**S40.2**, Scheme 40, pg. 67), which collapses to liberate the alcohol (**S40.3**) and eject benzaldehyde (**S40.4**). Indeed, this type of transformation was first reported by Marples for para-substituted benzyl ethers (**S40.5→S40.6, S40.7→S40.8**).[46] However, for the Marples systems the reactions had to be stirred at room temperature for up to 48 hours using 3-4 equivalents of DMDO in acetone. Based on our results, DMDO is a more potent oxidant in chloroform, since benzyl cleavage is much more rapid and occurs at lower temperatures. Thus, the use of benzyl ethers as protecting groups had to be avoided at this stage of our synthesis.

(46) Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett*. **1992**, 646.

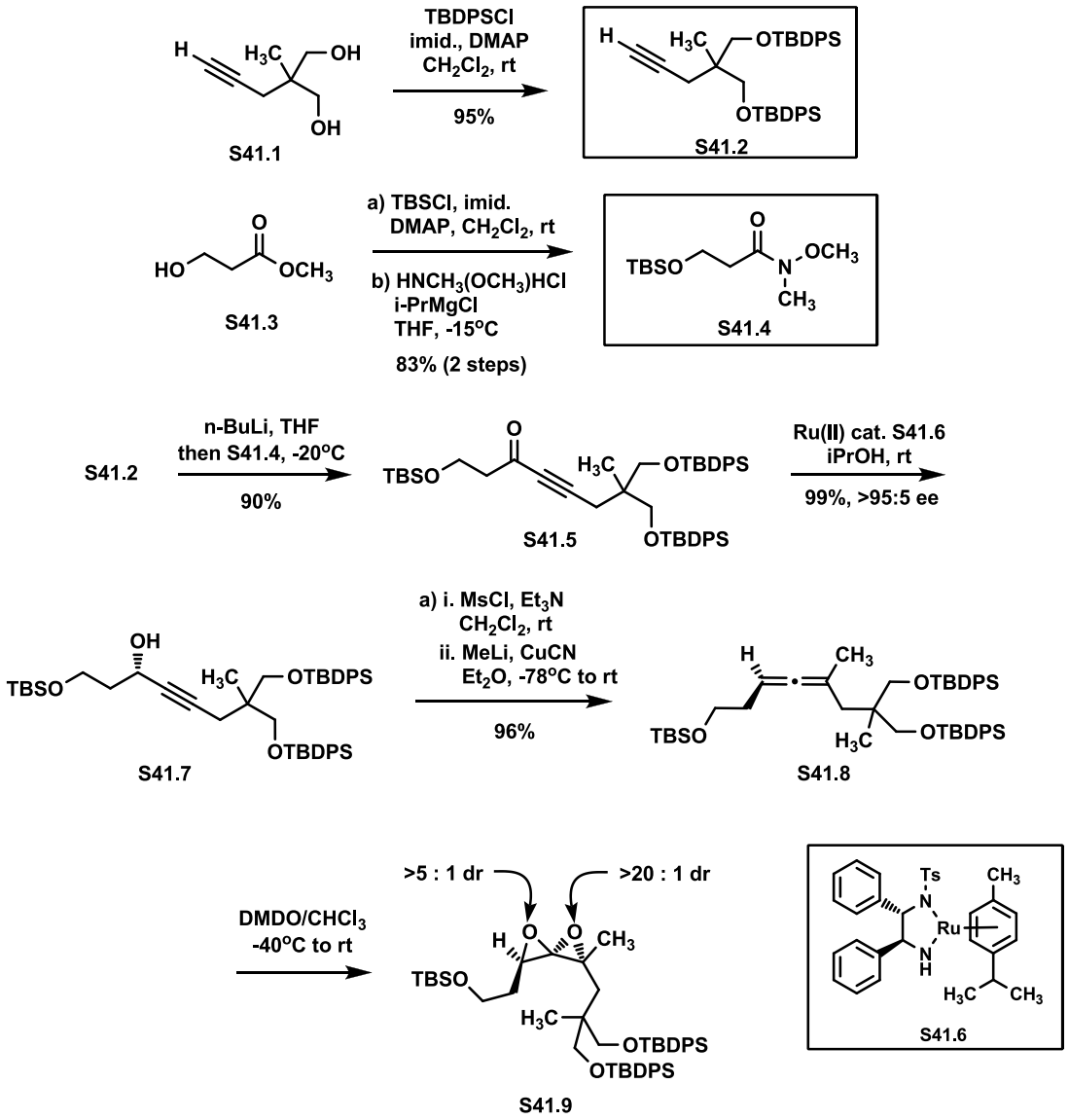
Scheme 40 Marples' Studies on Benzyl Cleavage Using DMDO



Although we were able to isolate a stable SDE using a fully persilylated compound, the issue of oxidation stereoselectivity remained. One possible explanation for low selectivity is that for R^1=OP a syn-pentane orientation is not as destabilizing, and therefore conformers related to **S39.2** may not be energetically unfavorable. We reasoned that for R^1=CH_3 the destabilizing interaction between the two methyl groups would be much more unfavorable and may lead to the desired conformational properties (**S39.2**→**S39.3**). Therefore, we set out to prepare **S41.8** (Scheme 41, pg. 68).

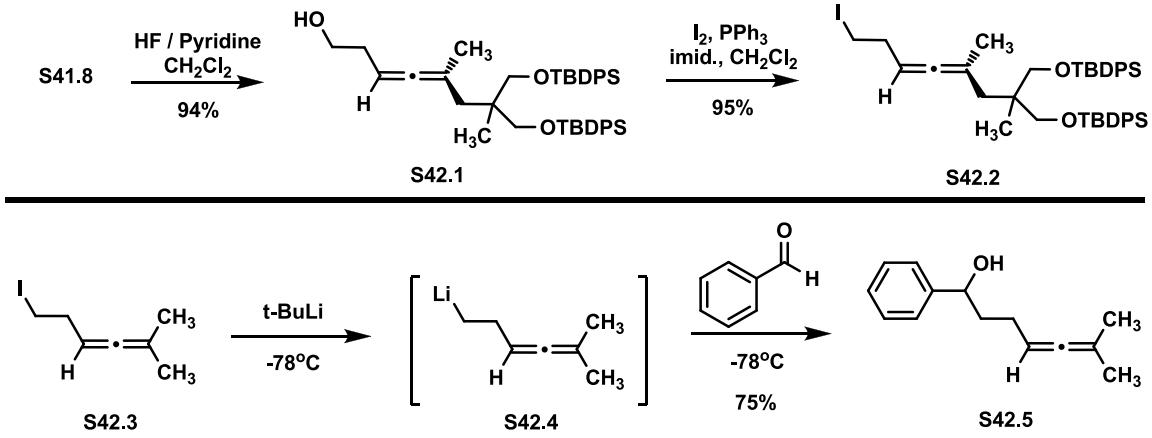
The synthesis of the C8-C15 fragment (**S41.8**) began with bis-protection of known alkyne diol **S41.1** (95% yield) which was prepared in a two step sequence from diethylmethyl malonate. Weinreb amide **S41.4** was synthesized in a 2 step sequence from commercially available β-hydroxy ester **S41.3**. TBS protection of **S41.3** followed by conversion of the methyl ester to the corresponding Weinreb amide under conditions developed in the Merck labs[36] gave **S41.4** (83% yield, 2 steps). Alkynylation of **S41.4**

Scheme 41 Preparation of Allene S41.8



with **S41.2** gave the expected alkynone in 90% yield. Subjection to Noyori reduction[31] gave alkynol **S41.7** (99% yield) as a single enantiomer as suggested by Mosher ester analysis.[21] Conversion of the propargyl alcohol to the mesylate and then to allene **S41.8** proceeded in 96% yield. To our delight, exposure of **S41.8** to a solution of DMDO in chloroform gave predominantly a single stable SDE to which we assigned structure **S41.9**. The ^{1}H-NMR signals for the diastereomeric SDEs were not baseline resolved.

Scheme 42 Synthesis of Iodoallene S42.2 and Crandall's Allenyl Anion Studies



However, the signals that correspond to the erstwhile allenic methyl groups approached baseline resolution. Thus, we conservatively estimated SDE **S41.9** to be >5:1 dr.

With routes to fragments **S38.6** and **S41.8** secured, and with the supportive evidence that allenes of type **S41.8** would oxidize selectively, we proceeded with our synthesis. The primary TBS group of **S41.8** (Scheme 42, pg. 69) was removed (94% yield) and the resultant hydroxyl was then converted to iodide **S42.2** using Appel conditions (91%).[47] Conversion of the primary iodide to the corresponding anion followed by nucleophilic addition to an aldehyde was then investigated. β-Allenyl iodides (**S42.3**, bottom of Scheme 42) had been shown to undergo lithium-halogen exchange at -78°C to form alkyl lithium species **S42.4**.[48] This anion proved to be stable at -78°C and was subsequently trapped using benzaldehyde to generate allenol **S42.5** in 75% yield.

Accordingly, lithium halogen exchange of **S42.2** followed by addition of aldehyde **S38.6** under rigorously dry and oxygen-free conditions gave γ-hydroxy allene **S43.1**

(47) Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801.
(48) Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993.

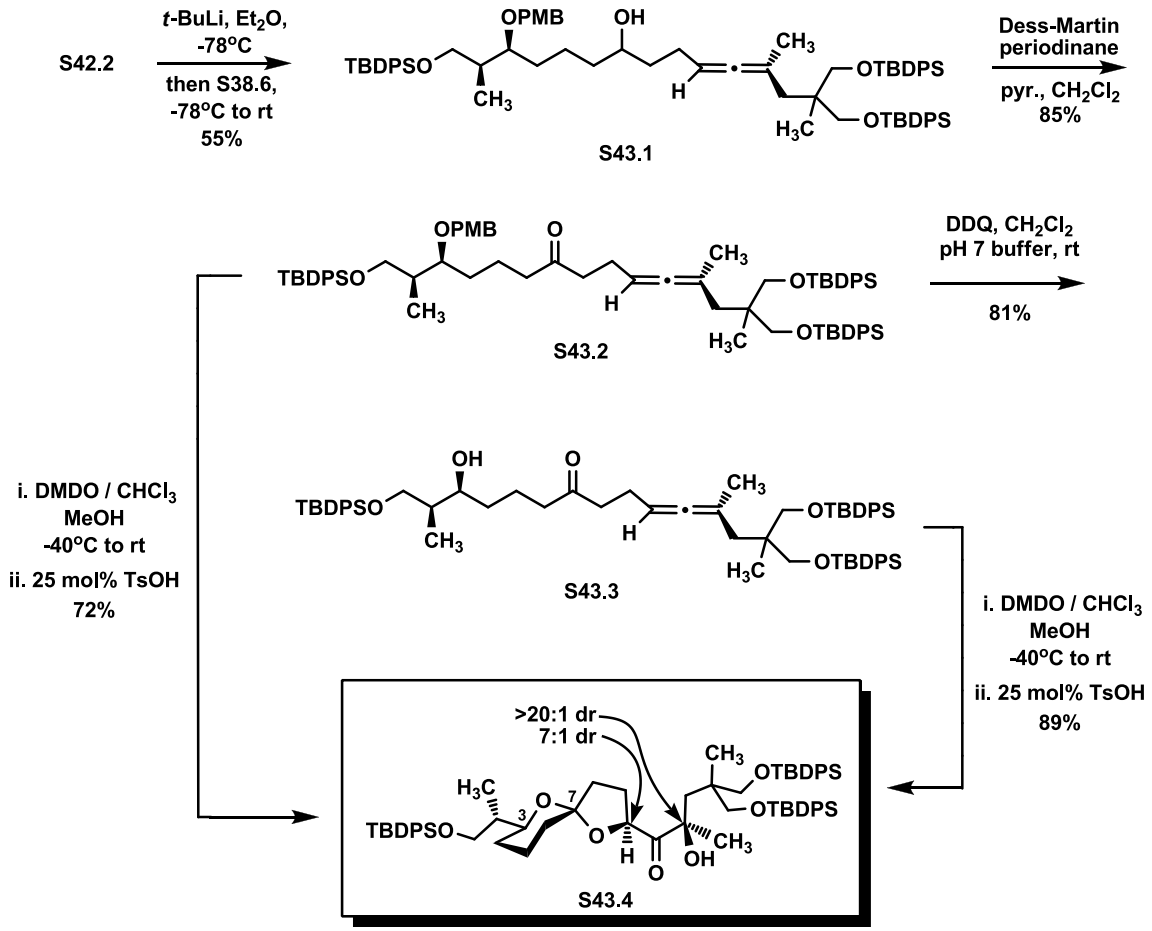
(Scheme 43, pg. 71) in a 52% yield. Yongquan Hou, a former graduate student in the Williams group, was responsible for optimizing this key coupling reaction to generate a significant amount of **S43.1**. Solvent effects were not extensively studied, and it seems likely that the use of pentane or pentane/Et_2O mixtures would improve the efficiency of this reaction. Dess-Martin oxidation[49] (85%) and subsequent PMB removal with DDQ[50] (81%) gave **S43.3**, which existed as the α-hydroxy ketone in $CDCl_3$ and no evidence of the lactol isomer (cf. S37.5) was observed. ^{1}H NMR analysis showed a multiplet at 2.5 ppm corresponding to 4 protons, indicative of two methylenes flanking a ketone. ^{13}C showed no signals in the 100-110 ppm region otherwise expected for a quaternary lactol carbon, instead a peak at 210 ppm, indicative of a ketone, was observed.

Upon DMDO oxidation in $CHCl_3$, **S43.3** gave a product mixture that upon careful examination included the desired bicycle as well as isomeric compounds. A separate experiment established that oxidation of **S43.3** followed by addition of water in THF predominantly gave the corresponding diol (not shown). Treatment of the diol with TsOH gave **S43.4** (68%[51]). Upon further evaluation we arrived at a single-flask procedure for the conversion of **S43.3** to **S43.4**, wherein addition of MeOH to the DMDO oxidation, followed by addition of acid at room temperature, smoothly converted allene **S43.3** to spiroketal **S43.4** (89%, dr: 7:1).

The product ratio is consistent with our earlier observations for the oxidation of allene **S41.8** to **S41.9**. Thus, the first oxidation at the more substituted double bond of the allene is highly selective (>20:1) while the oxidation of the second double bond is, in this

(49) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(50) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron*. **1986**, *42*, 3021.
(51) Two isomers were apparent in a ratio of 7:1.

Scheme 43 Key Coupling and AB Spiroketal Formation via SDE



case, 7:1.[52] Acid-induced isomerization is known to give the doubly anomeric spiroketal corresponding to **S43.4** in acyclic PTX-type systems.[4c,h,l] Comparison of key signals in the ^{13}C NMR with the PTXs and similar systems supports this assignment (Figure 8, pg.

(52) Trace quantities of a third compound was also observed. The A-B spiroketal shown corresponds to the spiroketal of PTX-4 and related compunds (see refs. 4c,h,l) which forms selectively under acidic conditions. That the minor isomer is not the diastereomeric A-B spiroketal cannot be ruled out. Hence, we conservatively estimate the selectivity at this center as >10:1.

73).[53] The ^{13}C NMR signals for the C3 and C7 carbons of **S43.4** were compared with closely related synthetic systems and the pectenotoxins. The corresponding ^{13}C NMR signals for the desired spiroketals of compounds **F8.1**[4h], **F8.2**[4c], and **F8.3**[4l] correlate well with **S43.4** and, importantly, signals for the undesired spiroketal of compound **F8.4**[4l] do not. In addition, the C3 carbon signal of **S43.4** is in good agreement with the C3 signal of PTX-4 bearing the desired spiroketal and is in poor agreement with PTXs 1, 2, and 2-seco acid, which houses the undesired spiroketal.[4b,54]

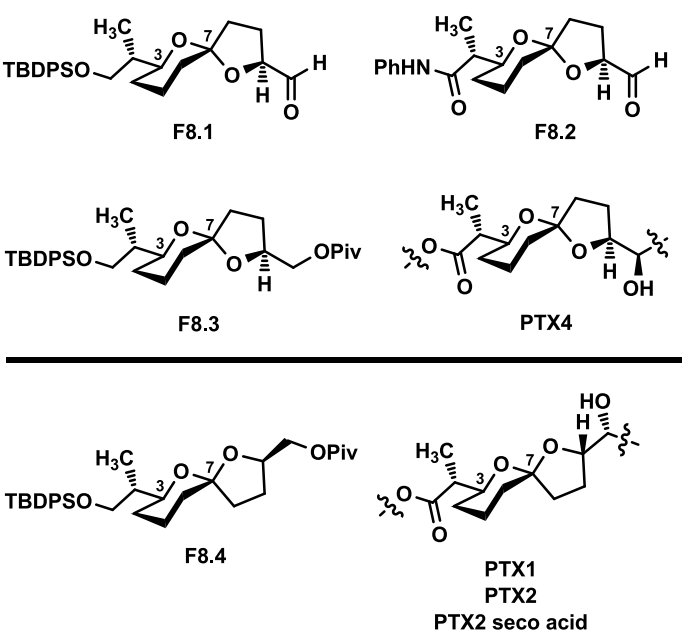
While the ability to control allene epoxidation and to predict SDE cyclization has enabled a short synthesis of **S43.4**, our final experiment constitutes an even more direct route to the target. As previously mentioned, DMDO in chloroform cleaves benzyl ethers at low temperature (Scheme 40, pg. 67). We therefore sought to effect the direct conversion of **S43.2** to **S43.4** and found that treament of **S43.2** under the conditions shown effected its conversion to the targeted spiroketal in a 72% yield, which, as before, was obtained as a 7:1 mixture of isomers (Scheme 43, pg. 71). Thus in an excellent overall yield, the PMB group was removed, the allene was selectively converted to a SDE (and thereby two stereocenters that appear in the final target were introduced), the SDE was opened to give the C12 tertiary hydroxyl and the C11 carbonyl, and the A-B spiroketal was assembled.

---

(53) The ^{13}C chemical shifts of C3 (72.3 ppm) and C7 (107.2 ppm) in **S43.4** correlate well with PTX-4 and other reported PTX spiroketals with this configuration ($\Delta\delta$ = 0.2-1.2 ppm), whereas PTX-1 and related compounds with the alternative spiroketal configuration do not ($\Delta\delta$ = 2.3-3.9 ppm), cf. refs. 4a,c,l,38a.

(54) Comparison of the C7 carbon in **S43.4** with compounds **F8.3**, **F8.4**, and the PTXs was inconclusive. Compounds **F8.3**, **F8.4**, and the PTXs showed ^{13}C NMR shifts for C7 between 106.3 – 109.4 ppm in CD_3OD, C_5D_5N, and CD_3CN. Compound **S43.4** showed ^{13}C NMR shifts for C7 between 107.5 – 108.6 ppm with the same solvents.

Figure 8 NMR Comparison of S43.4 With Related Systems



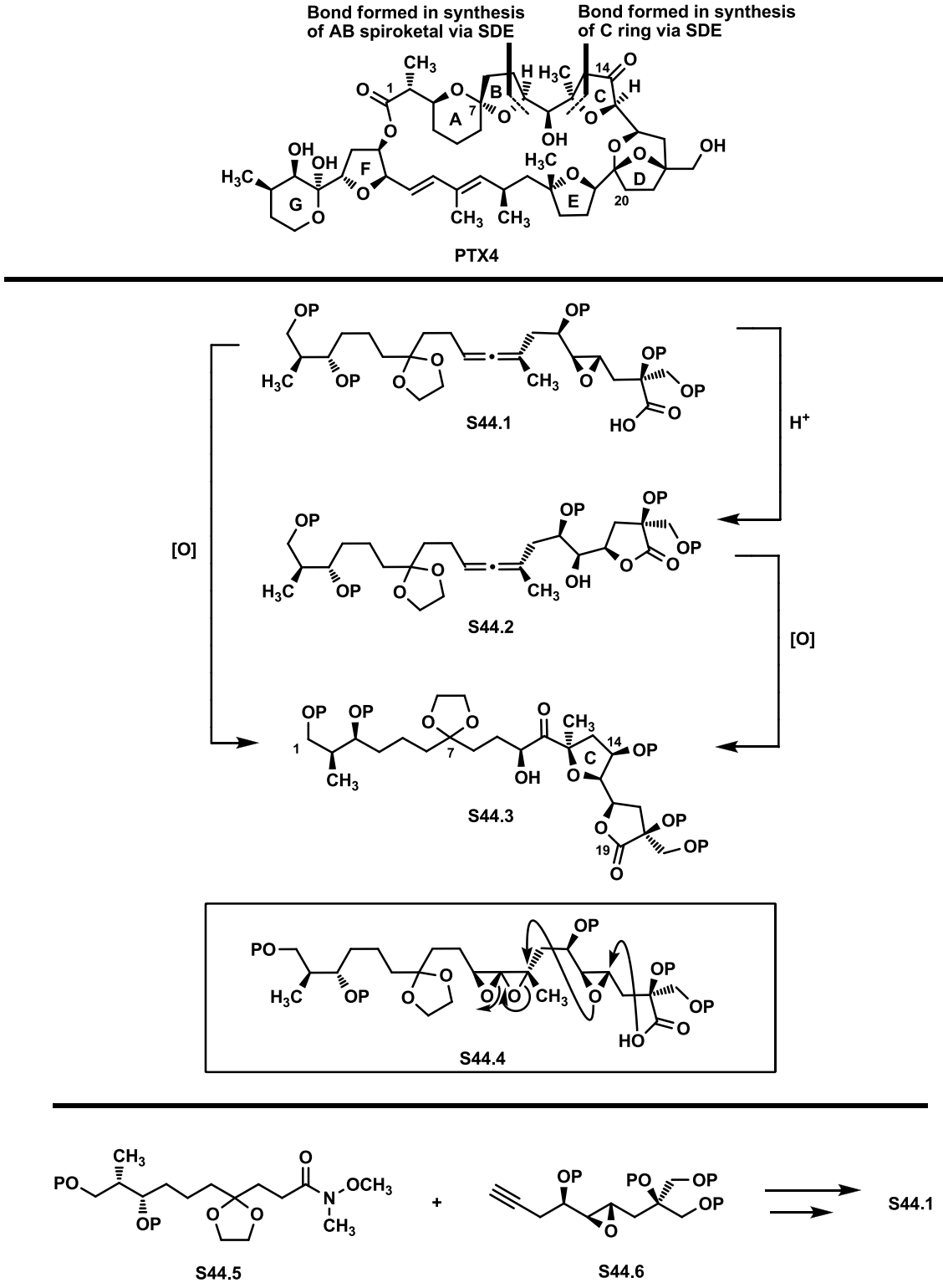
S43.4 vs. related systems	Carbon	Δδ (ppm)	Matches
F8.1	C3	1.2	✓
F8.1	C7	0.2	✓
F8.2	C3	0.6	✓
F8.2	C7	0.8	✓
F8.3	C3	1.2	✓
PTX4	C3	0.3	✓
F8.4	C3	2.4	X
PTX1	C3	4.0	X
PTX2	C3	4.1	X
PTX2 (seco acid)	C3	4.0	X

IV. A Spirodiepoxide Strategy to the Pectenotoxin 4 C1-C20 C Ring Segment

Although our preparation of the AB spiroketal ring system via SDEs was highly efficient, we desired to use SDE chemistry to access the more challenging tetrasubstituted C ring system in route to establishing the C1-C20 northern hemisphere of PTX4. We recognized that oxidation of an allene of type **S44.2** (Scheme 44, pg. 74) would, in principle, give the fully substituted C ring system **S44.3**. This allene would be prepared from **S44.1** by acid-induced intramolecular epoxide opening. We also wondered whether a suitably positioned epoxide (e.g. **S44.1**) would be a viable SDE nucleophile and enable an extended cascade reaction (e.g. **S44.4**).[55] Thus, treatment of **S44.1** under our optimized

(55) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.

Scheme 44 Synthetic Plan for the Synthesis of the PTX4 C Ring System



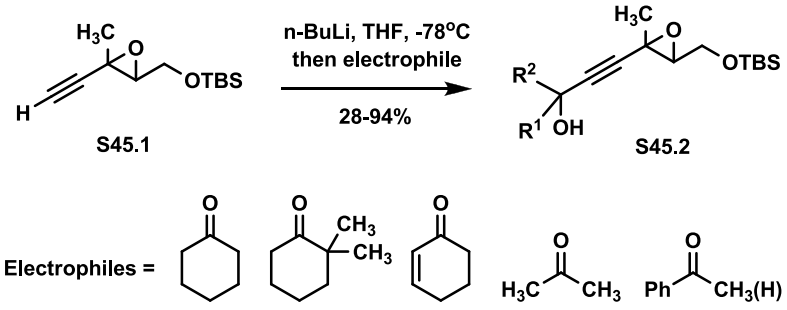
oxidation conditions would give rise to the SDE, which the epoxide could well attack. The carboxylate would then affect opening of the activated epoxide to give **S44.3**.

We recognized that a late-stage stereoselective installment of the C15/C16 epoxide in the presence of an allene would not be a trivial task. Aside from the fact that a Shi epoxidation[56] is unprecedented in the presence of an allene, achieving a high level of stereoselectivity (>95:5 ee) for this oxidation was not guaranteed. Thus, a Sharpless epoxidation[57] using an unprotected alcohol at C14 was considered. Late-stage selective deprotection of this C14 alcohol to enable epoxidation seemed cumbersome. Therefore, early installation of the epoxide was envisioned. Ideally, a fully functionalized epoxy alkyne (**S44.6**, bottom of Scheme 44) could be used to couple with a Weinreb amide (**S44.5**) in order to gain access to a fully functionalized epoxy allene (**S44.1**) in a highly convergent manner. The possibility of such a coupling, however appealing, could be challenging due to potential problems associated with alkyne deprotonation and nucleophilic addition, both of which would be required in the presence of an epoxide. The closest precedent appeared to by a report by Krause that demonstrated the addition of epoxy acetylides to ketones and aldehydes by n-BuLi deprotonation and subsequent low temperature nucleophilic addition (Scheme 45, pg. 76).[58]

Based on this report, we were hopeful that the acetylide derived from **S44.6** could be generated without significant epoxide decomposition. However, since the addition of acetylides to Weinreb amides generally occur at ~0^{o}C, the proposal seemed ambitious not to mention the comparatively considerable complexity of the epoxy acetylide partner. Nonetheless, we investigated this coupling

(56) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
(57) Pfenninger, A. *Synthesis* **1986**, 89.
(58) Hoffmann-Roder, A.; Krause, N. *Helv. Chim. Acta.* **2002**, *85*, 3176.

Scheme 45 Krause's Previously Reported Epoxy Acetylide Additions

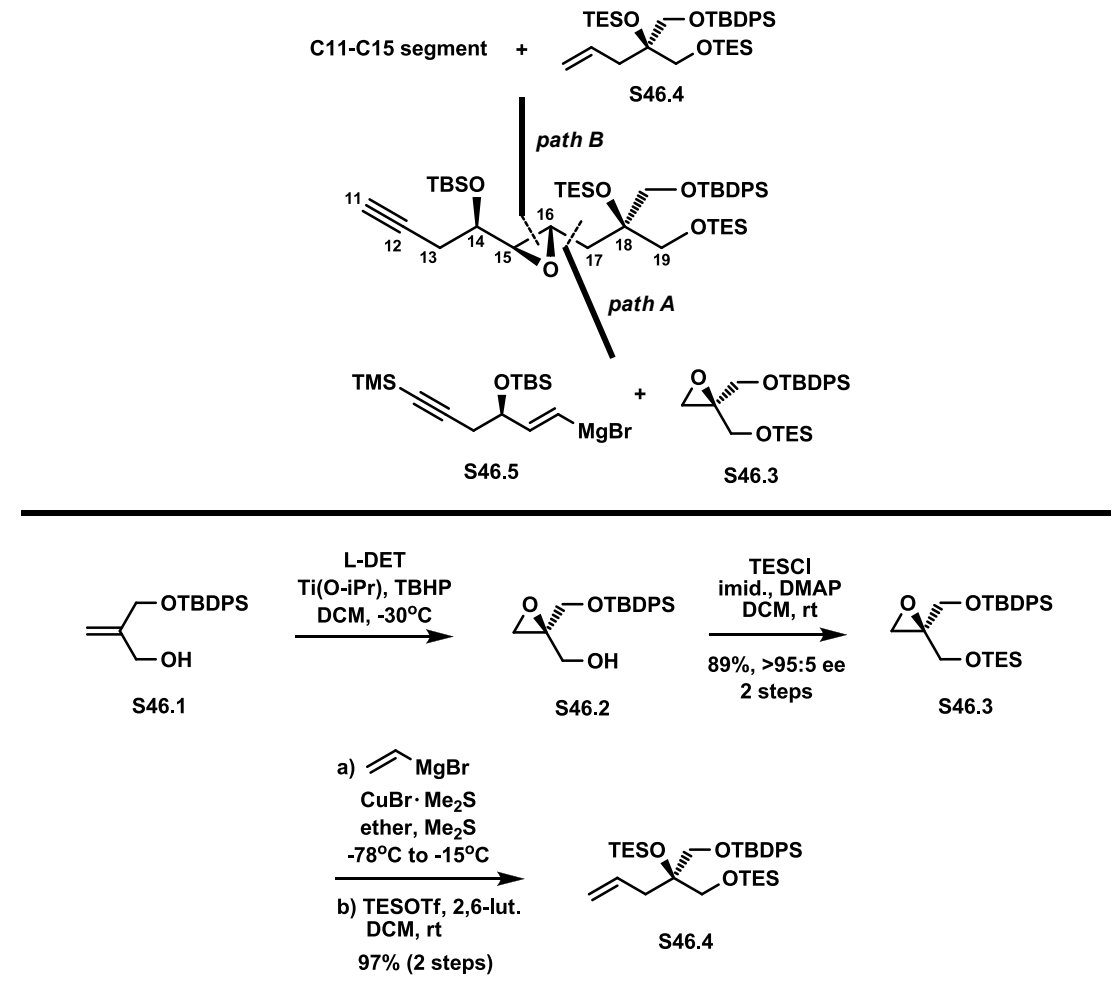


The synthesis of the C11-C19 fragment began from known monoprotected diol **S46.1**[59] (Scheme 46, pg. 76). Sharpless epoxidation[57] using L-DET followed by TES protection gave fully protected epoxy diol **S46.3** (89%, >95:5 ee, 2 steps). Our original synthetic plan involved epoxide opening of **S46.3** with vinyl Grignard **S46.5** (Path A, top of Scheme 46). Unfortunately, efforts to prepare **S46.5** were inefficient and impractical due to problems with protecting group manipulations. We then considered the addition of a suitable nucleophile to an epoxide (**S46.3**) that would provide alternatives for obtaining the remaining C11-C15 portion (Path B). Thus, addition of the higher order vinyl cuprate generated from vinyl Grignard and CuBr•Me_2S smoothly converted **S46.3** to terminal olefin **S46.4** after TES protection of the resultant tertiary alcohol. Due to a small amount of primary TES cleavage being observed from this cuprate reaction, the crude material was taken on without purification and TES protected to obtain **S46.4** in excellent yield from **S46.3** (97%, 2 steps).

A one-pot ozonolysis/Horner-Wadsworth-Emmons reaction was achieved to give the corresponding ester (not shown). Subsequent DIBAL reduction afforded allylic

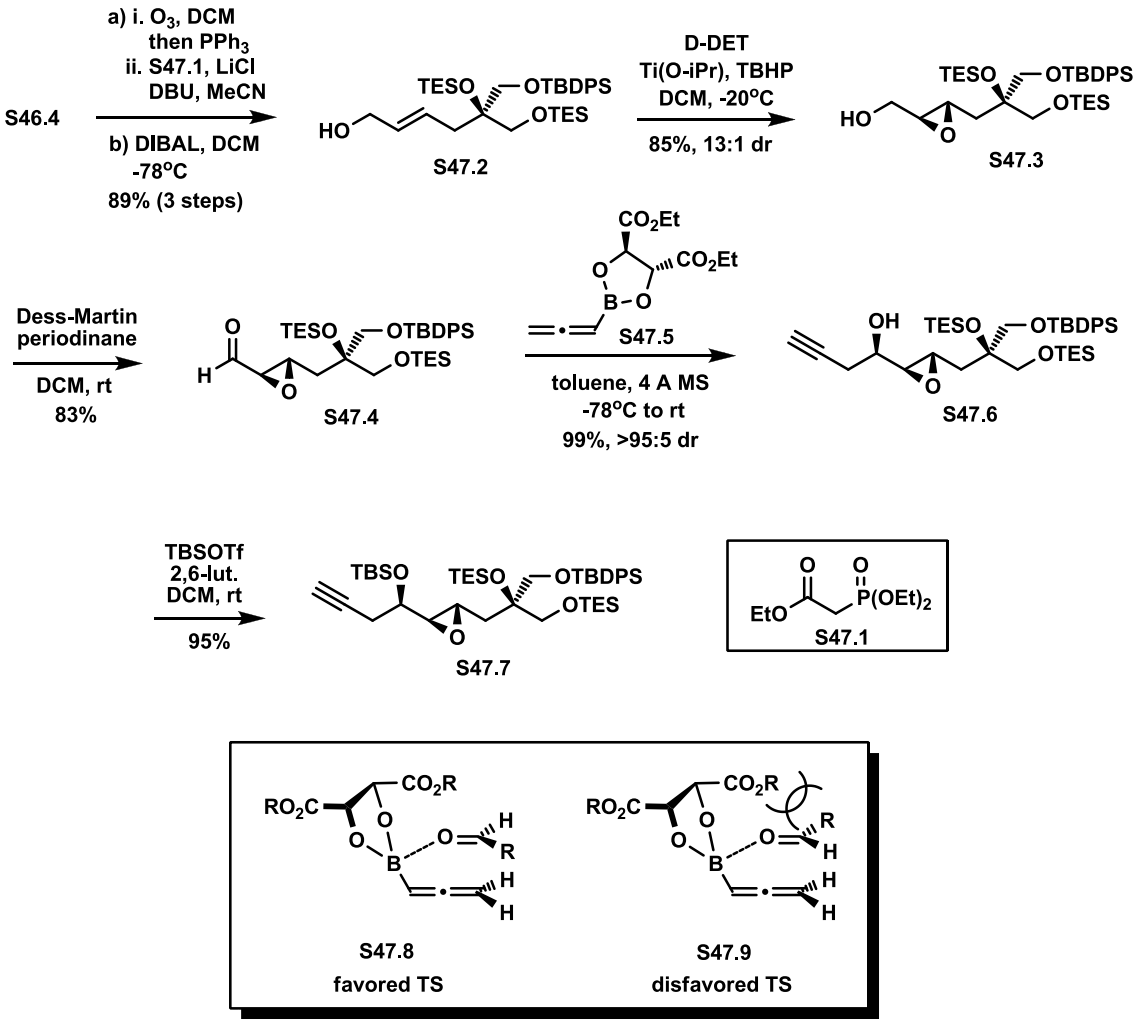
(59) Faveau, C.; Mondon, M.; Gesson, J.; Mahnke, T.; Gebhardt, S.; Koert, U. *Tetrahedron Lett.* **2006**, *47*, 8305.

Scheme 46 Plan for Synthesis of C11-C19 Alkyne



alcohol **S47.2** (Scheme 47, pg. 78) in 89% yield from **S46.4.** It is noteworthy that Me_2S failed to convert the ozonide intermediate of **S46.4** (not shown) into the desired aldehyde. This stable ozonide could be isolated by chromatography. However, this intermediate was readily converted to the aldehyde after subjection with PPh_3. Sharpless epoxidation[57] (85%, 13:1 dr) and subsequent Dess-Martin oxidation[49] furnished epoxy aldehyde **S47.4** (83%). The 13:1 dr of products obtained from the Sharpless epoxidation proved to be inseparable and was subsequently carried through the remainder of the synthesis.

Scheme 47 Synthesis of Epoxy Acetylene S47.7



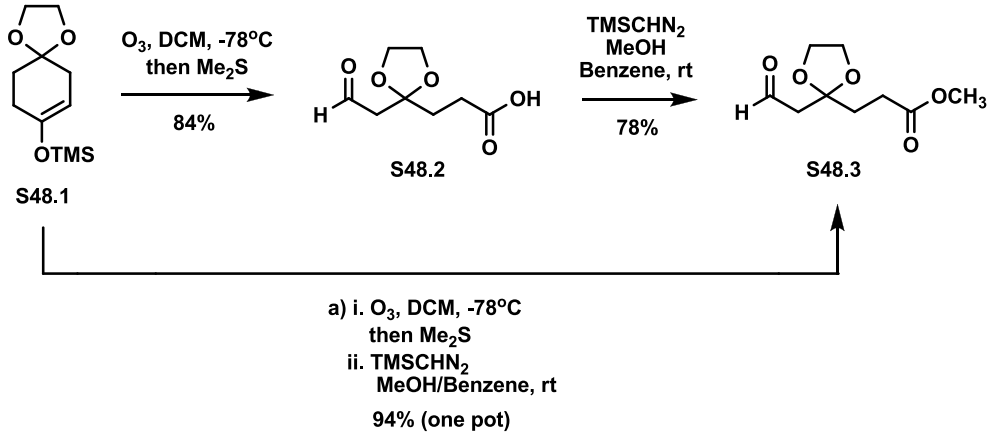
Yamamoto asymmetric homopropargylation conditions[60] stereoselectively converted **S47.4** to alkynol **S47.6** in excellent yield (99%, >95:5 dr). While not widely used, this transformation appears to be highly efficient and robust and employs the use of allenyl boronic acid and D-DET for the in situ preparation of allenyl chiral boronate **S47.5.** Moreover, the method proved compatible with the epoxide and silyl protecting groups of **S47.4**. The favored and disfavored transistion states for this reaction, originally formulated by Yamamoto, are shown in **S47.8** and **S47.9** (bottom of Scheme 47). Final

(60) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.

TBS protection of the resultant alcohol under TBSOTf conditions gave the fully protected C11-C19 alkyne subunit (**S47.7**) in 95% yield.

Originally, we planned to use a dithiane at C7 to build the C1-C10 subunit based on the work of Smith.[61] However, we recognized that the C5-C10 fragment could arise from ozonolysis of a cyclohexanone derived enol ether to give the proper oxidation state at C10 as well as the aldehyde at C5. Thus, ozonolysis of known silyl enol ether **S48.1**[62] (Scheme 48, pg. 79) afforded acid aldehyde **S48.2** in an 84% yield. The use of MeOH as a solvent was superior to CH_2Cl_2, which led to a significant amount of side products. Conditions employing MeI to methylate the carboxylic acid were unsuccessful. However, in situ formation of diazomethane using $TMSCHN_2$[63] in methanol and benzene smoothly converted **S48.2** to **S48.3** in 78% yield. This ozonoylsis/$TMSCHN_2$ sequence was ultimately achieved in a one pot procedure to furnish **S48.3** in excellent yield (94%) from **S48.1**.

Scheme 48 Preparation of Ester Aldehyde S48.3



(61 For a review on dithiane-based strategies see: Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.

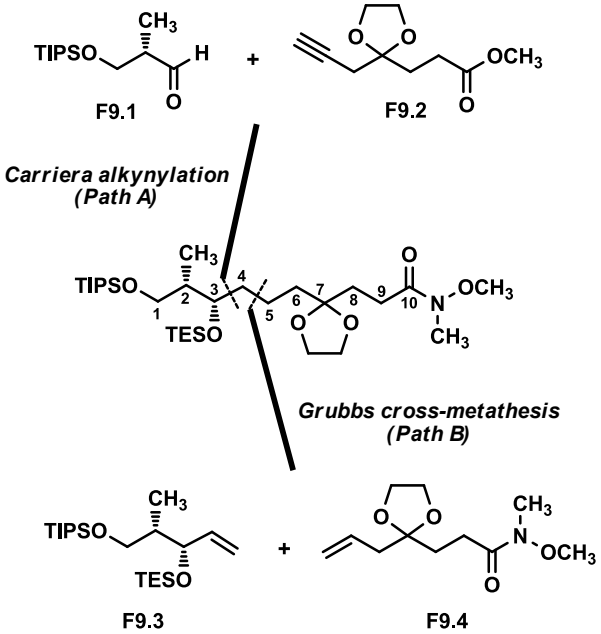
(62) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

(63) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

Our original synthetic plan was to convert **S48.3** to alkyne **F9.2** (Figure 9, pg. 80) and set the alcohol at C3 by way of Carreira's asymmetric alkynylation,[20] which was shown to give excellent selectivities with β-branched aldehydes (Path A, Figure 9). Unfortunately, only a 1:1 mixture of diastereomers at C3 was obtained for this reaction. Presumably, unwanted coordination of the acetal oxygen or amide of the alkyne to zinc compete with coordination by the chiral ligand and thereby compromise selective alkynylation.

Upon further analysis, we considered a coupling between the C4 and C5 carbons. In principle, alkenes **F9.3** and **F9.4** would serve well in a Grubbs cross-metathesis (Path B, Figure 9). According to the Grubbs categorization,[64] alkene **F9.3** is characterized as a type II olefin which undergoes slow homodimerization and alkene **F9.4** as a type I olefin,

Figure 9 Plan for Synthesis of C1-C10 Weinreb Amide

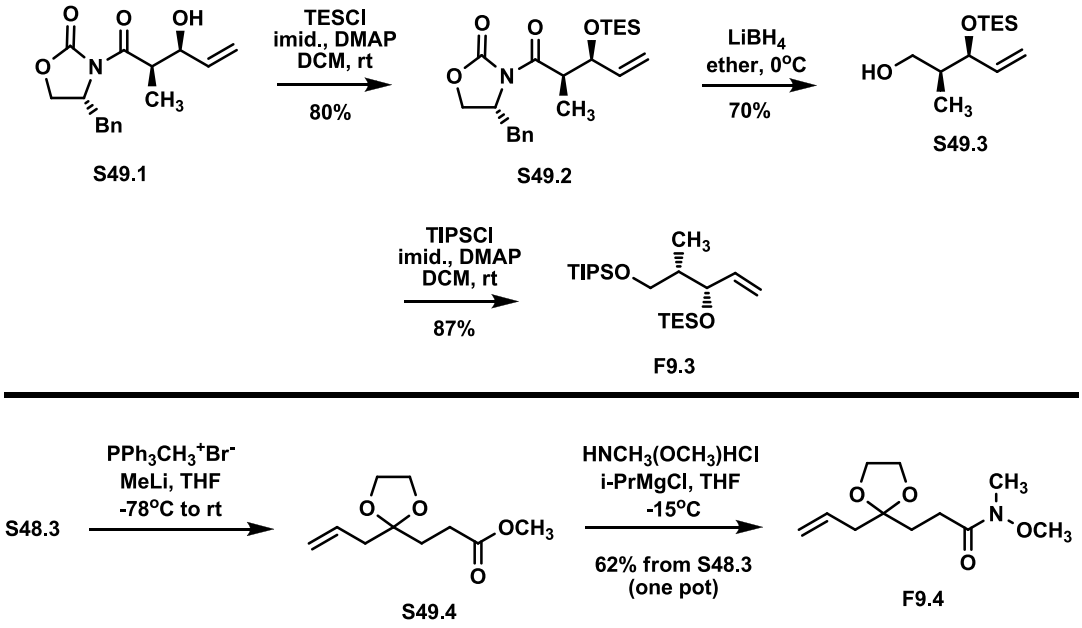


(64) Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

which undergoes fast homodimerization. Thus, these two subunits were good candidates for a cross metathesis.

Synthesis of the type II olefin (**F9.3**) began from the known Evans syn-aldol product **S49.1**[65] (Scheme 49, pg. 81)**.** TES protection (80%) was followed by $LiBH_4$ reduction to cleave the oxazolidinone and afford **S49.3** (70%). TIPS protection of the resultant primary alcohol gave protected diol **F9.3** in an 87% yield. Weinreb amide **F9.4** was synthesized from aldehyde ester **S48.3**. Wittig methylenation of the aldehyde ester to give the corresponding terminal olefin resulted in low yields (30%) due to volatility of this substance. Therefore, the direct one pot conversion of **S48.3** to **F9.4** was investigated. Upon formation of the terminal olefin the reaction mixture was cooled and subjected directly to the Merck Weinreb amidation conditions[36] to afford **F9.4** in a 62% yield from **S48.3**.

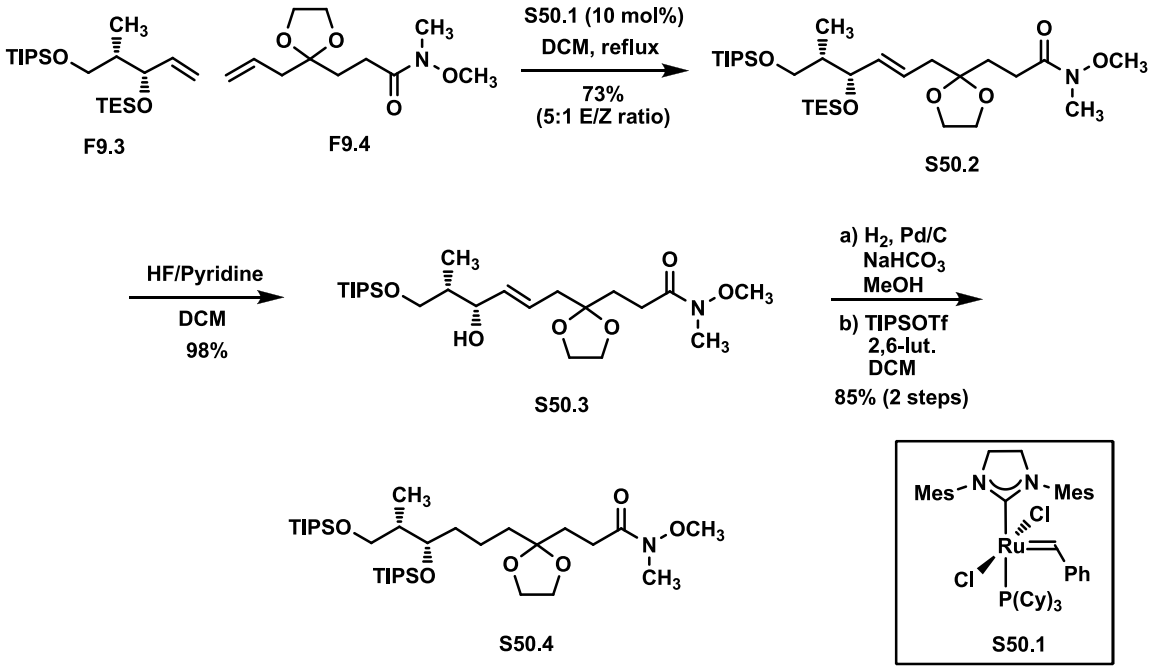
Scheme 49 Synthesis of Alkenes F9.3 and F9.4



(65) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425.

Early studies on the cross-metathesis showed only trace amounts of product with the standard Grubbs second generation catalyst conditions (**S50.1**, Scheme 50, pg. 82) [in refluxing DCM or benzene with a 2:1 ratio of **F9.4** to **F9.3**]. However, in benzene we observed a much more rapid homodimerization of alkene **F9.4**. Fortuitously we discovered that the use of bulk DCM was superior to the anhydrous DCM obtained from our alumina-based solvent purification system. Thus, 10 mol% of **S50.1** with a 2:1 ratio of **F9.4** to **F9.3** in refluxing bulk DCM afforded a 73% yield of the desired coupling product (**S50.2**) obtained as a 5:1 E/Z isomeric mixture.

Scheme 50 Grubbs Cross Metathesis and Preparation of Weinreb Amide S50.4



Hydrogenation of **S50.2** to obtain the fully saturated compound was unsuccessful and was eventually traced to the presence of residual ruthenium from the Grubbs catalyst.

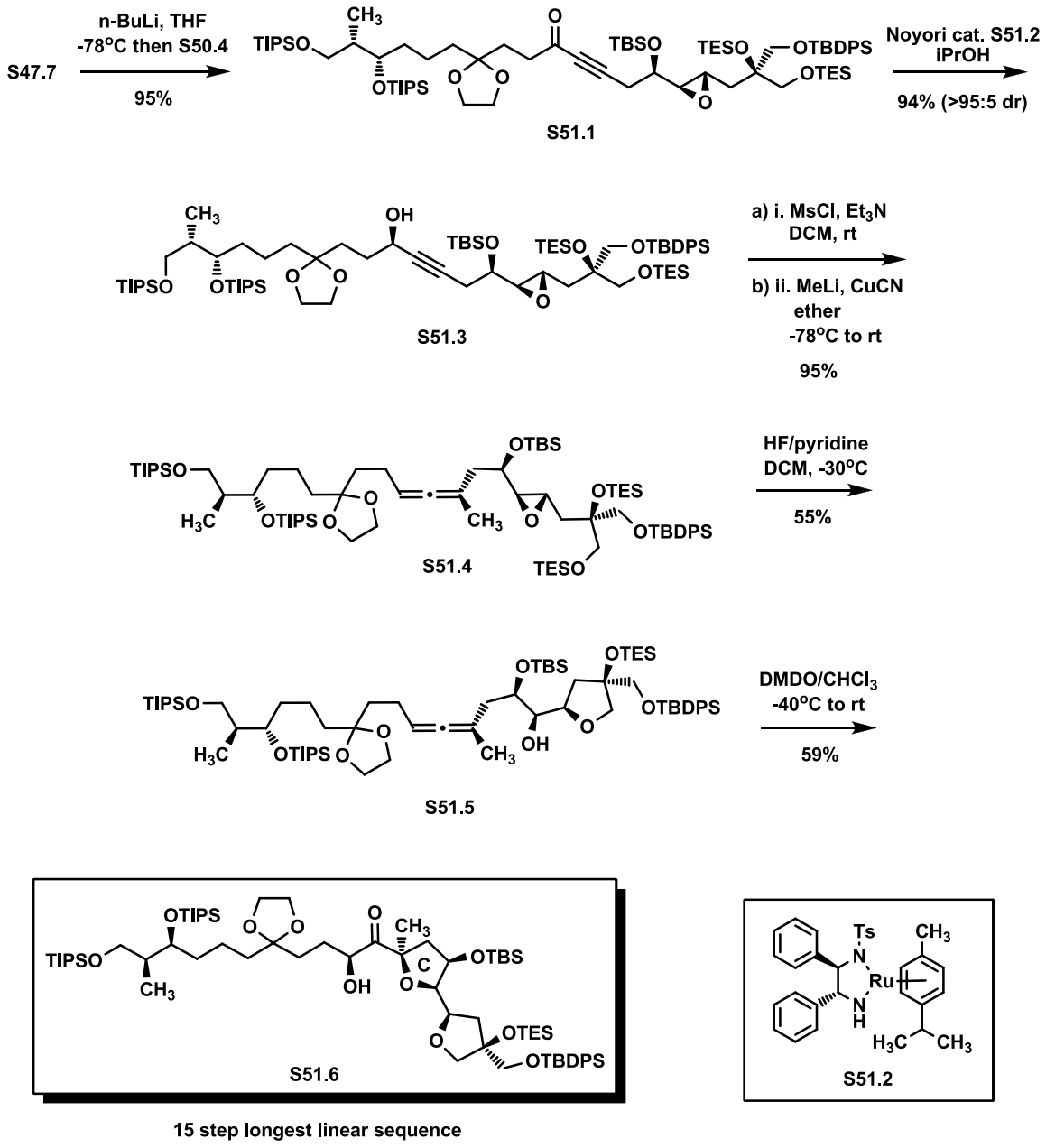
Only after removing the trace metals, according to a procedure by Kim[66], was the double bond hydrogenated. However, incorporation of $NaHCO_3$ in the MeOH was critical for the efficiency of the hydrogenation. Performing the reaction in the absence of $NaHCO_3$ led predominately to TES deprotection and hydrogenation of the olefin. Based on the peculiar lability of the OTES group at C3 we anticipated potential problems in our protecting group scheme and therefore decided to protect this alcohol with a much less labile group for the purposes of this study. Therefore, cross-metathesis product **S50.2** was subjected to HF/pyridine conditions to cleave the TES group in a 98% yield. Hydrogenation of the resultant allylic alcohol followed by protection with TIPS proceeded smoothly to furnish **S50.4** in an 85% yield (2 steps).

The stage was now set for coupling of Weinreb amide **S50.4** with epoxy acetylene **S47.7**. Remarkably, conversion of **S47.7** to the corresponding epoxy acetylide at -78^{o}C followed by addition of Weinreb amide **S50.4** and warming to 0^{o}C cleanly afforded epoxy alkynone **S51.1** (Scheme 51, pg. 84) in a 95% yield!

Noyori reduction[31] (94%, >95:5 dr) followed by mesylation and S_N2' displacement using MeLi derived lower order cyano cuprate gave allene **S51.4** (95%). Deprotection of the primary TES protected alcohol at C19 proved to be problematic presumably due to sterics. Various conditions (i.e. HF/pyridine and Brønsted acids) only led to mixtures of products. Presumably these products were formed from TBS cleavage at C14 and TES cleavage at C19 (both not shown) in addition to formation of **S51.5** via

(66) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531.

Scheme 51 Alkyne/Weinreb Amide Coupling and C Ring Formation



epoxide opening by the unmasked C19 alcohol. In the end, **S51.5** was obtained in a 55% yield from **S51.4** after subjection with HF/pyridine at low temperature. Although this compound lacked the desired lactone ring system (**S44.2**), it was a good candidate to test the feasibility of the SDE transformation (**S44.2→S44.3**). To our delight, exposure to

DMDO in chloroform at -40^{o}C and subsequent warming to room temperature smoothly converted allene **S51.5** into α-furanyl-α′-hydroxy ketone **S51.6** in a 59% yield. An inseparable trace amount of another product was detected by ^{1}H and ^{13}C analysis which we believe is from the 13:1 dr obtained from the earlier Sharpless epoxidation (→**S47.3**).

In summary, this section described our efforts towards the C1-C19 northern hemisphere of PTX4 using SDE chemistry to access the tetrasubstituted tetrahydrofuran C ring system. This route enables the rapid assembly of the C1-C19 fragment in 15 steps (longest linear sequence from **S46.1**) using a highly convergent approach. Key steps in the synthesis included a Grubbs cross metathesis to obtain the C1-C10 fragment, Yamamoto asymmetric homopropargylation reaction in the presence of an epoxide to set C14, unprecedented addition of an epoxy acetylide to a Weinreb amide, and intramolecular addition to a SDE forming the tetrasubstituted C ring system and establishing the stereochemistry at C10 and C12.

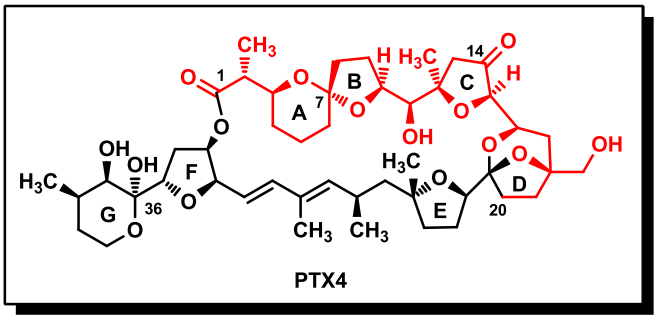
In the next section a full synthetic route to PTX4 is proposed based on these findings.

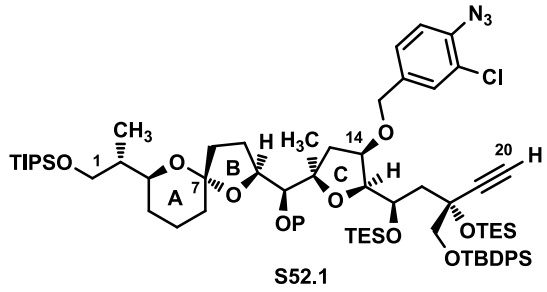
V. Proposed Synthetic Route to Pectenotoxin 4

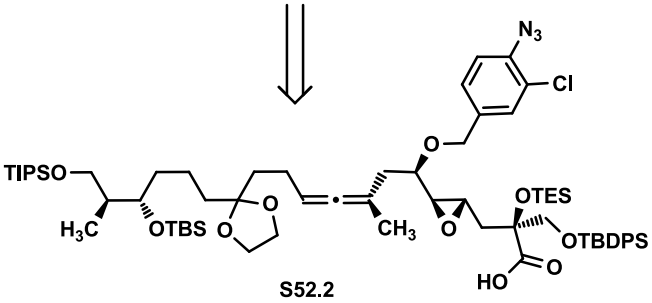
In the previous three sections of this chapter SDE-based approaches to the northern hemisphere of PTX4 were discussed. In this section a full synthetic route to PTX4 is proposed based on these studies, including a full protecting group strategy.

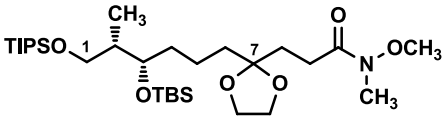
As shown in Schemes 52-64, the proposed strategy is a refined approach based on the studies presented here. The C1-C20 fragments (**S52.1** and **S52.2**, Scheme 52, pg. 86) will be prepared from suitably protected precursors (**S52.3** and **S52.4**) as described in

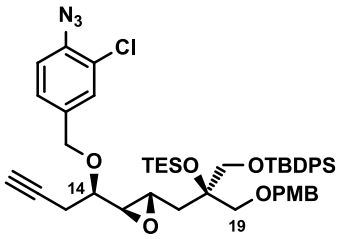
Scheme 52 Synthetic Plan Towards C1-C20 Alkyne Subunit





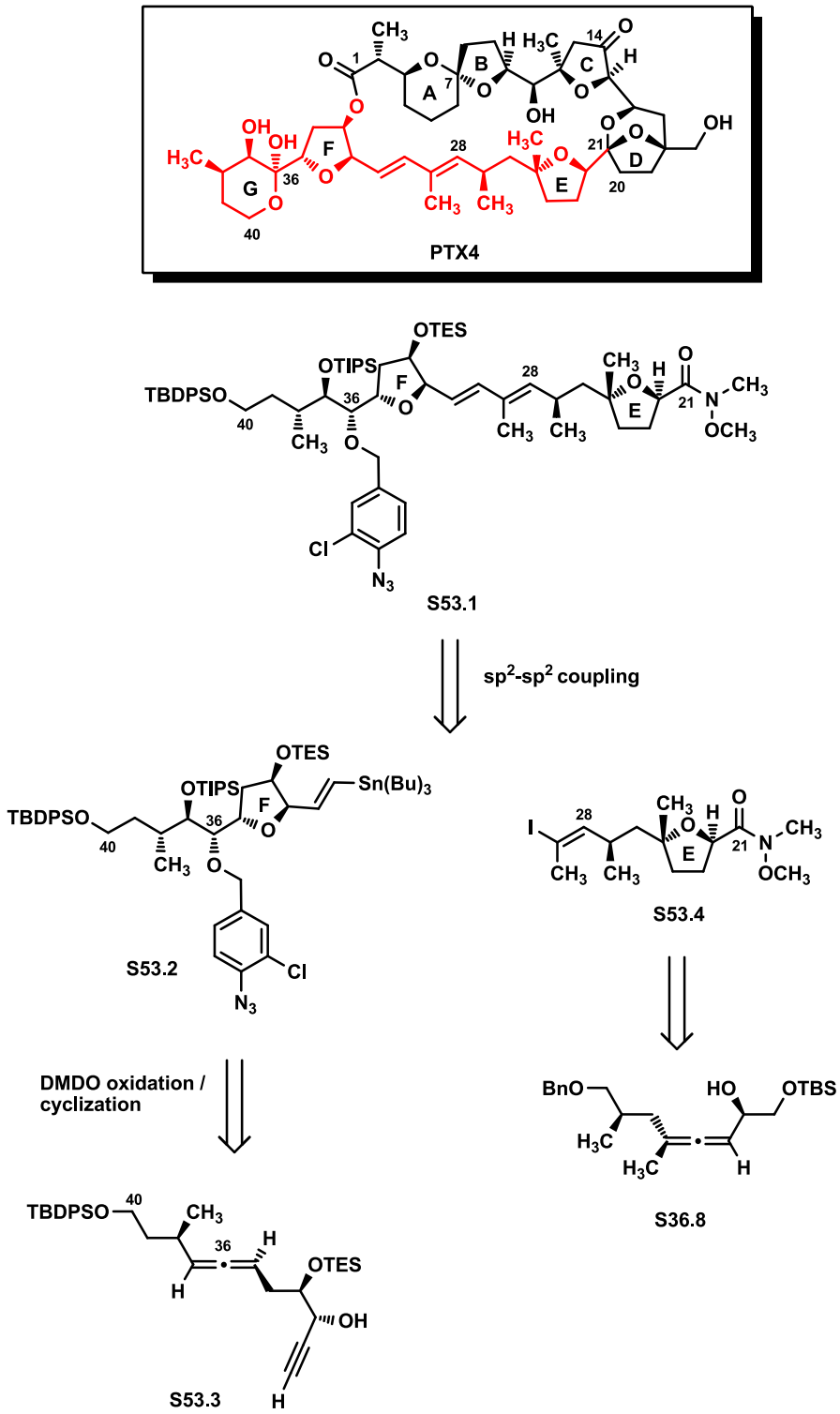




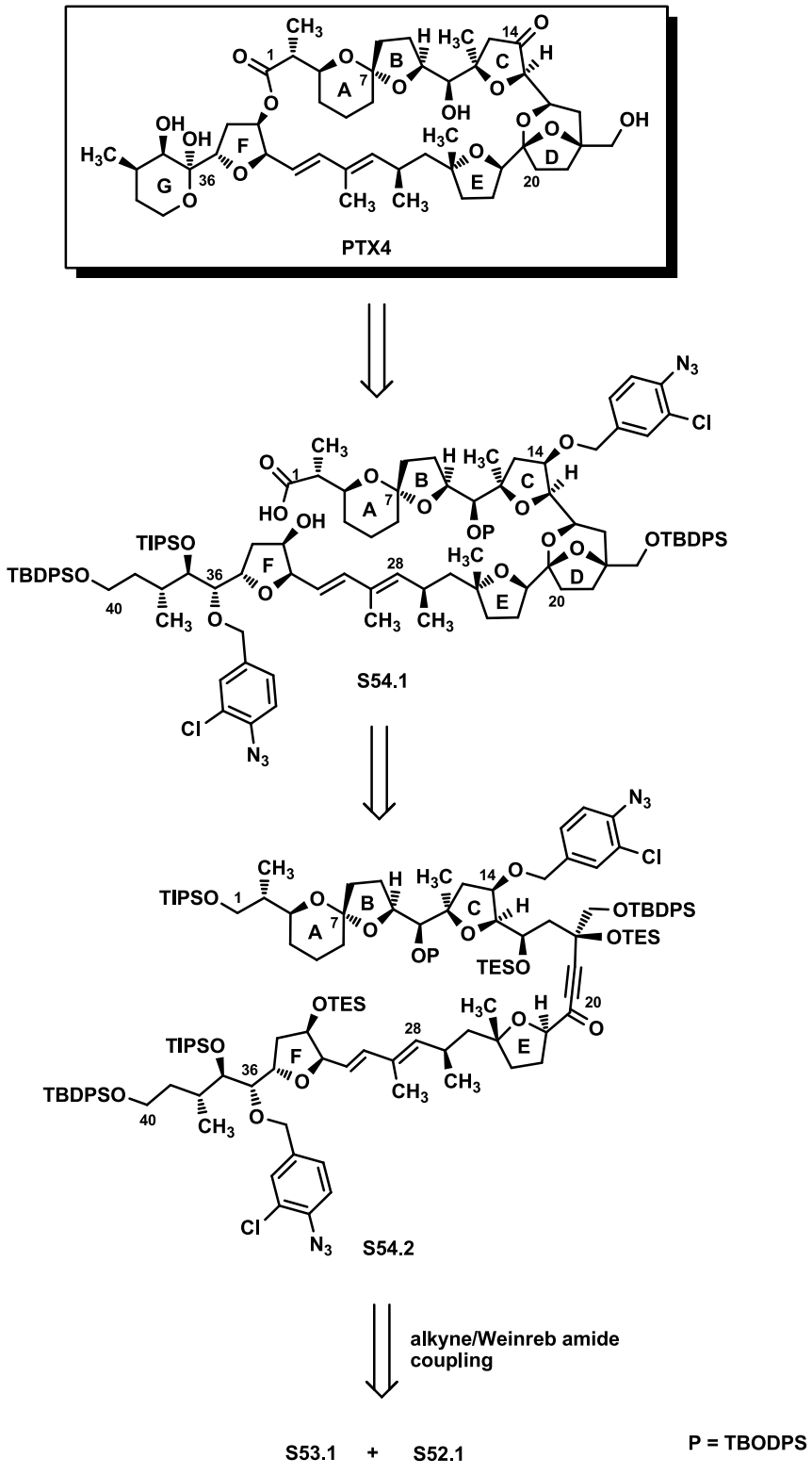


P = TBODPS

Scheme 53 Synthetic Plan Towards C21-C40 Weinreb Amide Subunit



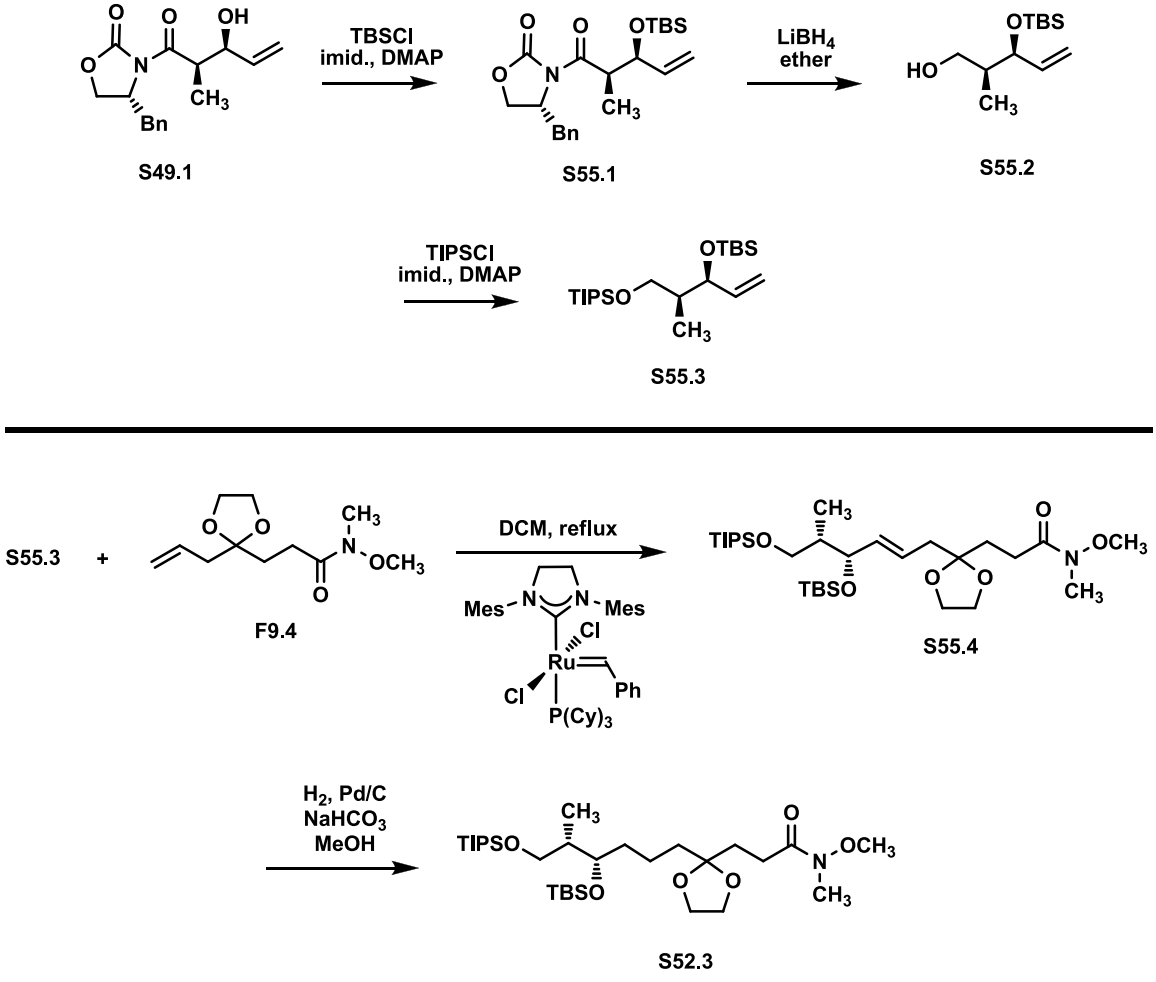
Scheme 54 Plan for Union of the Top and Bottom Fragments



detail. Parallel construction of a C21-C40 fragment (**S53.1**, Scheme 53, pg. 87) from properly protected precursors **S53.2** and **S53.4** also follows a convergent route. **S53.4** will be accessed via a route analogous to earlier studies (cf. **S36.8**) and **S53.2** will be prepared from allene **S53.3**.

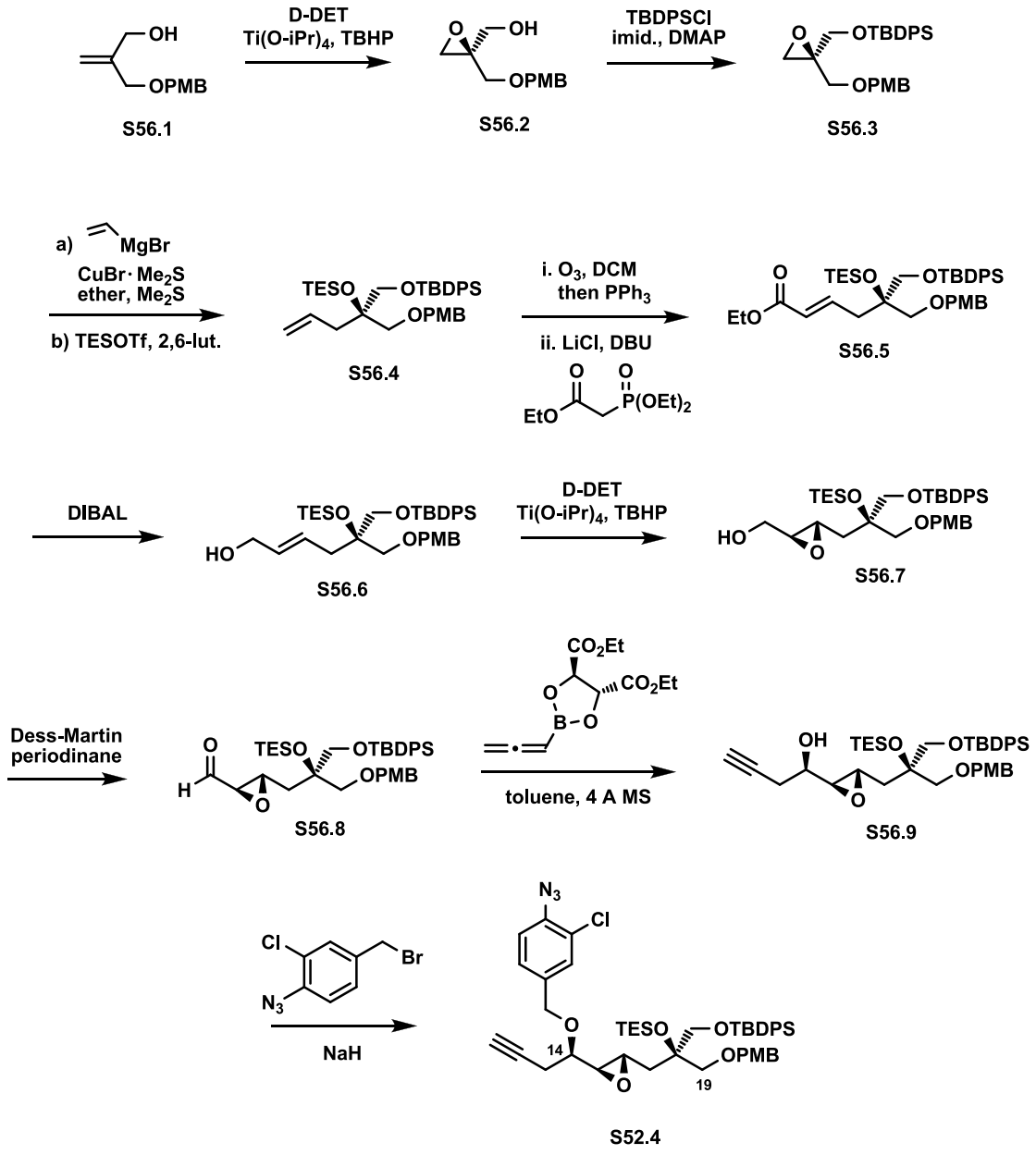
The convergent coupling of alkyne **S52.1** with Weinreb amide **S53.1** will assemble the entire C1-C40 carbon backbone of PTX4 (Scheme 54, pg. 88). Bicyclic D ring formation followed by macrolactonization and protecting group manipulations should furnish PTX4.

Scheme 55 Proposed Route to Weinreb Amide S52.3



The synthesis of the C1-C10 portion will begin from known syn-aldol product **S49.1**[65] (Scheme 55, pg. 89). We reasoned that a TBS ether would be a suitable protecting group for the C3 alcohol owing to the unusual lability of a TES ether as previously discussed. Hence, TBS protection followed by $LiBH_4$ reduction to the corresponding primary alcohol (**S55.2**) then TIPS protection will afford alkene **S55.3**.

Scheme 56 Proposed Route to Epoxy Acetylene S52.4



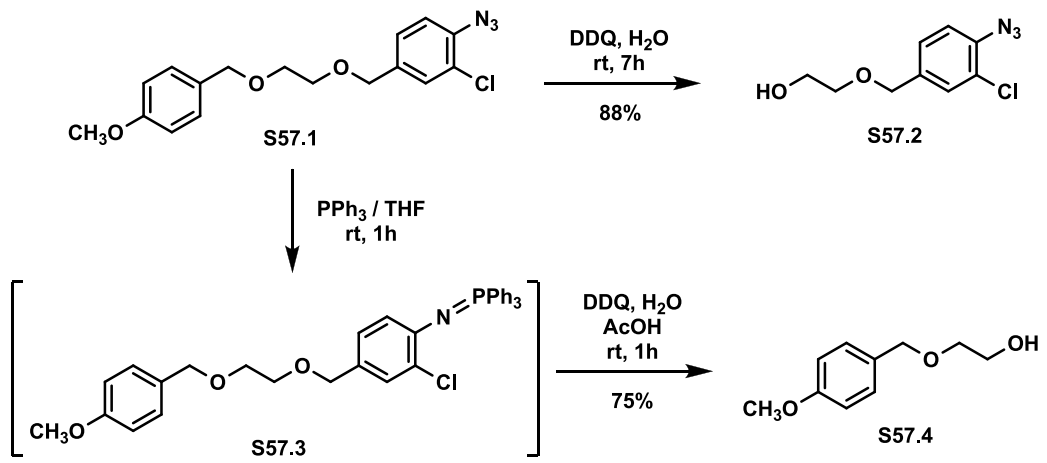
Weinreb amide **F9.4** will be prepared as previously discussed in our model study (Scheme 49, pg. 81). Grubbs cross metathesis[64] of **S55.3** with **F9.4** and subsequent hydrogenation under the basic conditions employed previously (Scheme 50, pg. 82) should furnish the fully saturated Weinreb amide (**S52.3**).

Epoxy acetylide **S52.4** will be synthesized using the conditions from our earlier approach starting from known monoprotected diol **S56.1**[67] (Scheme 56, pg. 90). Sharpless epoxidation[57] and TBDPS protection will give epoxy diol **S56.3**. Vinyl cuprate addition will be followed by TES protection of the resultant tertiary alcohol to afford alkene **S56.4**. A one pot ozonolysis/Horner-Wadsworth- Emmons sequence and subsequent ester reduction using DIBAL will furnish allylic alcohol **S56.6**. Epoxy aldehyde **S56.8** will be obtained by Sharpless epoxidation[57] followed by Dess-Martin[49] oxidation. **S56.8** will be subjected to Yamamoto asymmetric homopropargylation[60] conditions to afford epoxy acetylene **S56.9**.

Choosing a suitable protecting group for the C14 alcohol is critically important. This group must be stable to acid, DDQ, and DMDO/$CHCl_3$ conditions. More importantly, this protecting group will have to be selectively removed in the presence of multiple silyl groups, an ester (lactone), and the C28-C31 diene. The resultant C14 alcohol will then be oxidized to a ketone prior to the final global deprotection step. We propose that the 4-azido-3-chloro benzyl protecting group can satisfy these criteria. This under-utilized functional group is stable to DDQ and acidic conditions but is rapidly cleaved using DDQ if first converted to the corresponding iminophosphorane (Scheme 57

(67) Min, S.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2199.

Scheme 57 The 4-Azido-3-Chloro Benzyl Protecting Group



pg. 92).[68] Importantly, cleavage of a PMB group using DDQ[50] was achieved in the presence of the 4-azido-3-chloro benzyl group (**S57.1→S57.2**), whereas treatment of **S57.1** first with PPh_3 and then DDQ rapidly cleaved this protecting group and left the PMB ether intact. It was noted in Evans' PTX4 synthesis that attempts to remove a PMB ether at C14 resulted in allylic oxidation of the C28-C31 diene.[4c,4d,69] It seems likely that the enhanced reactivity of the iminophosphorane towards DDQ will promote the cleavage of this group in the presence of the C28-C31 diene. The stability of the 4-azido-3-chloro benzyl group towards DMDO has not been studied. Partha Ghosh recently discovered, however, that 3-fluoro benzyl ethers are stable to allene oxidation with DMDO/$CHCl_3$. Thus, the 4-azido-3-chloro benzyl group seems to be an excellent candidate for this approach. The C14 alcohol will be masked accordingly.

Coupling of the lithium acetlyide derivative of **S52.4** with Weinreb amide **S52.3**, as previously demonstrated in our model study, should give alkynone **S58.1** (Scheme 58,, pg. 93). Noyori reduction[31] and conversion of the corresponding alcohol to the mesylate

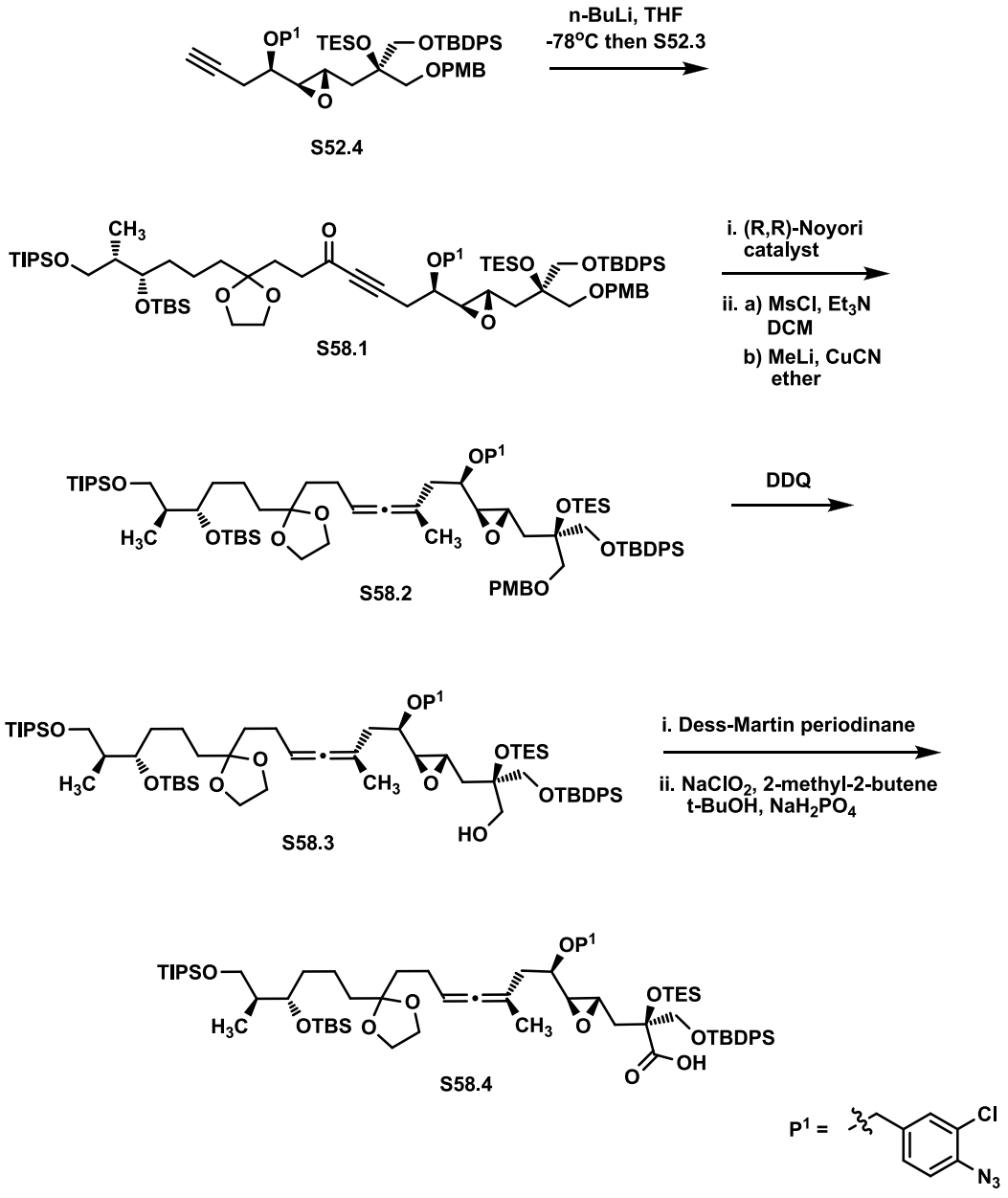
(68) Egusa, K.; Fukase, K.; Kusumoto, S. *Synlett* **1997**, 675.

(69) For successful deprotections of PMB ethers with DDQ in the presence of allylic dienes see: (a) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291. (b) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099.

followed by displacement with methyl cuprate in an S_N2' fashion should furnish allene **S58.2**. Epoxy acid **S58.4** will be obtained by selective deprotection of PMB using DDQ[50] followed by a Dess-Martin[49] and Pinnick[70] oxidation sequence.

The resultant carboxylic acid may spontaneously cyclize on the epoxide to afford

Scheme 58 Proposed Synthesis of Allene S58.4



(70) Bal, B.S.; Childers, W. E.; Pinnick, H.W. *Tetrahedron.* **1981**, *37*, 2091.

lactone **S59.1** (Scheme 59, pg. 95). In this case, **S59.1** will be subjected to DMDO/chloroform conditions to obtain α-hydroxy ketone **S59.2**. If **S59.1** does not form under Pinnick conditions, **S58.4** will be subjected to the DMDO/chloroform conditions to give the same α-hydroxy ketone product (**S59.2**) and thus provide the opportunity to study this cascade reaction sequence, as previously mentioned in our model study (**S44.4**, Scheme 44). $Zn(BH_4)_2$[71] reduction to the 1,2-anti diol (**S59.3**) and subsequent exposure to p-TsOH should effect TBS deprotection, acetal cleavage[72] and anomeric AB spiroketal formation. Acid induced isomerization to the desired 6,5- spiroketal is favored.[73] Possible isomeric structures for the spirocycle that involve the C11 hydroxyl (i.e. a 6,6-spirocycle) appear to be disfavored due to destabilizing 1,3-diaxial interactions or lack of anomeric stabilization. Standard protecting groups to mask the C11 hydroxyl were found to be problematic according to Evans report,[4c,4d] however, the TBODPS group proved uniquely effective. Thus, the C11 alcohol will be protected accordingly to give **S59.5**.

The lactone ring of **S59.5** will be opened using $HNCH_3(OCH_3)$-HCl and iPrMgCl[36] to afford Weinreb amide **S60.1** (Scheme 60, pg. 96). TES protection and DIBAL reduction of the Weinreb amide to aldehyde **S60.2** will be followed by Ohira-Bestmann conditions[74] to convert the aldehyde into alkyne **S52.1**. The longest linear sequence for the proposed synthesis of the C1-C20 fragment of PTX4 is 23 steps from **S56.1**.

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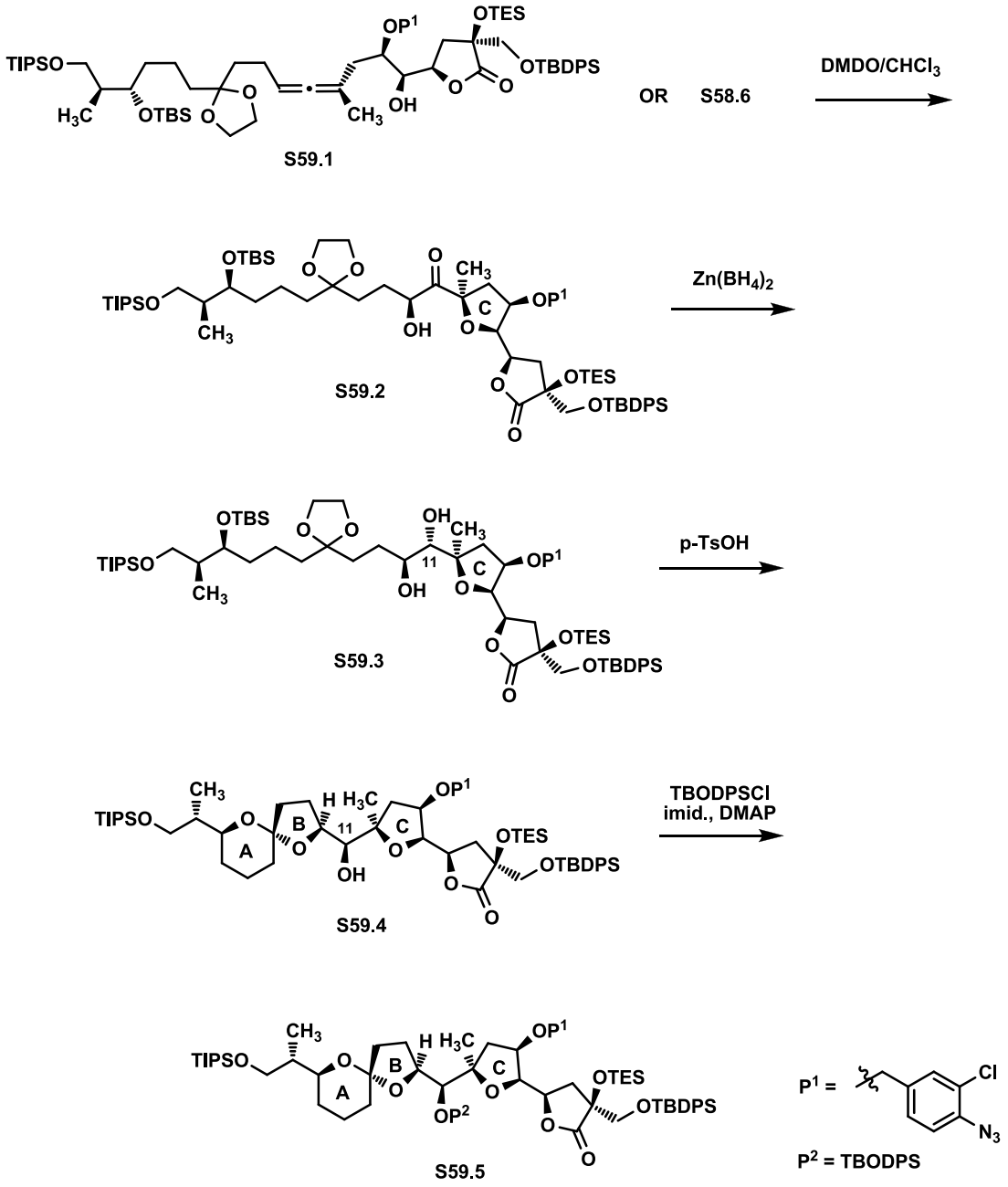
(71) Evans, D.A.; Ratz, A.M.; Huff, B.E.; Sheppard, G.S. *J. Am. Chem. Soc.* **1995**, *117*, 3448.

(72) For examples of acetal cleavage see: (a) Shanmugham, M.S.; White, J.D. *Chem. Commun.* **2004**, 44. (b) Trost, B.M.; Rudd, M.T. *J. Am. Chem. Soc.* **2005**, *127*, 4763.

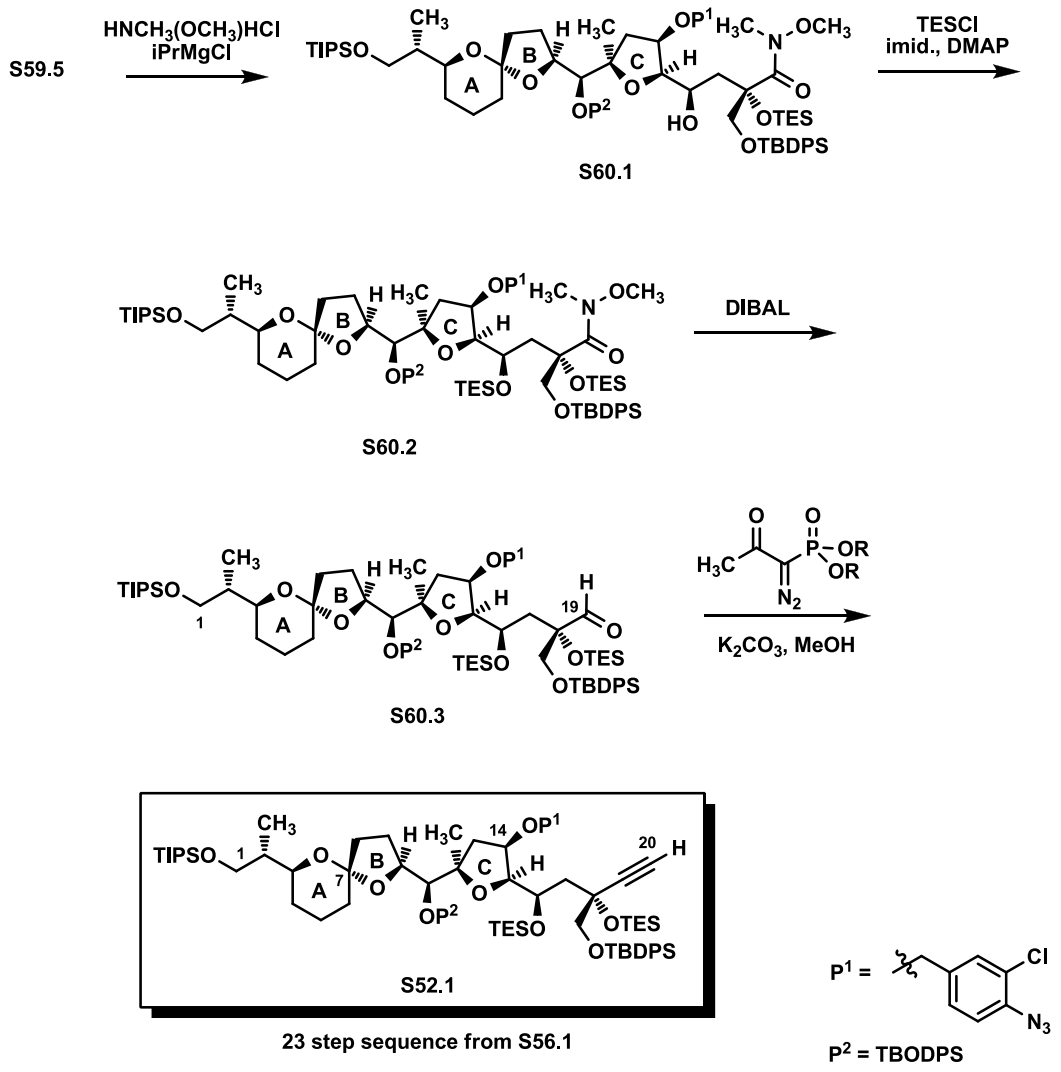
(73) The 5,6-spirocyclic ketal and 5,6-bicyclic ketal substructures have been shown to be stable to mild acid. The 5,6-bicyclic ketal appears to be stable in both the macrolide, seco form, and precursors. The 5,6-spirocyclic ketal (shown) is the thermodynamic product and is apparently the only isomer formed from acid-induced isomerization. See references: 4 and Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; MacKenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, 653.

(74) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

Scheme 59 Proposed Synthesis of the ABC Ring System of PTX4



Scheme 60 Proposed Synthesis of Alkyne S52.1

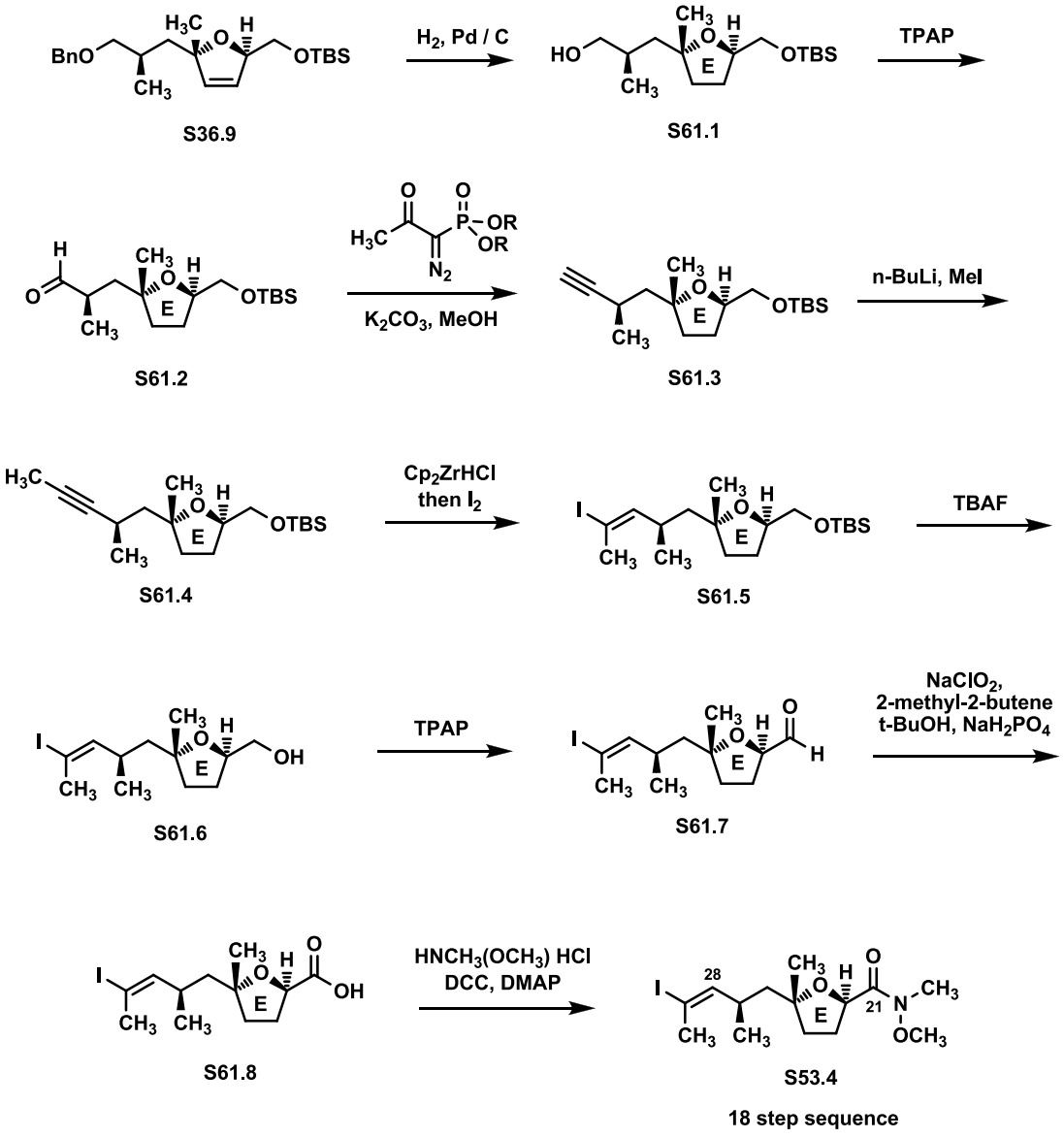


The C21-C29 E ring portion (**S53.4**) will be prepared from dihydrofuran **S36.9**, which we previously synthesized in 9 steps from commercially available glycidol **S36.1** (Scheme 36, pg. 62). Hydrogenation of the double bond and concomitant cleavage of the benzyl group should afford the furan E ring of PTX4 (**S61.1**, Scheme 61, pg. 97). Ley oxidation[75] followed by Ohira-Bestmann[74] reaction will convert the primary alcohol of **S61.1** into terminal alkyne **S61.3**. Vinyl iodide **S61.5** will be installed by methylation of

(75) Griffith, W. P.; Ley, S. V. Whitcombe, G. P. White, A. D. *J. Chem. Soc., Chem. Comm.* **1987**, 1625.

the terminal alkyne and a hydrozirconation/iodination sequence.[76] TBS deprotection and subsequent oxidation[75] should furnish aldehyde **S61.7**, which will be converted to the

Scheme 61 Proposed Route to Weinreb Amide S53.4



(76) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

corresponding Weinreb amide by a Pinnick oxidation[70] followed by a DCC/DMAP promoted amidation. Thus, the preparation of Weinreb amide **S53.4** will be achieved in an 18 step sequence from **S36.1**.

The synthesis of the C30-C40 F ring fragment will begin from commercially available enyne **S62.1** (Scheme 62, pg. 99). Sharpless dihydroxylation,[77] selective mesylation of the primary alcohol and PMP acetal formation should give protected triol **S62.3**. Displacement of the primary mesylate with lithium acetylide should afford diyne **S62.4**. Formation of allene **S62.7** will be achieved by asymmetric alkynylation[20] of **S62.4** with known aldehyde **S62.5**,[78] followed by subjection of this product to PPh_3, DIAD and *o*-$NO_2C_6H_4SO_2NHNH_2$.[79] Exposure of **S62.7** to DMDO in chloroform should oxidize the allene to the SDE and cleave the PMP acetal[80] to the corresponding diol, which will then add to the SDE to yield α-hydroxy-α′-furanyl ketone **S62.8**. The 5-exo-tet cyclization of the C32 alcohol on the SDE should be favored over the 6-endo-tet cyclization of the C33 alcohol.[16] This strategy is worth investigating since no SDE-based studies have been reported involving a 5-exo-tet vs. 6-endo-tet cyclization in the same system. TES protection of the less sterically encumbered C33 alcohol with concomitant TMS-alkyne deprotection upon K_2CO_3/MeOH workup will be followed by protection of the remaining C37 alcohol as the TIPS ether (**S62.10**). Chelation-controlled reduction of the ketone, directed by the α-furan,[71] should furnish alcohol **S62.12**. Installation of the 4-azido-3 chloro benzyl ether at C36 and conversion of the terminal alkyne to the vinyl stannane

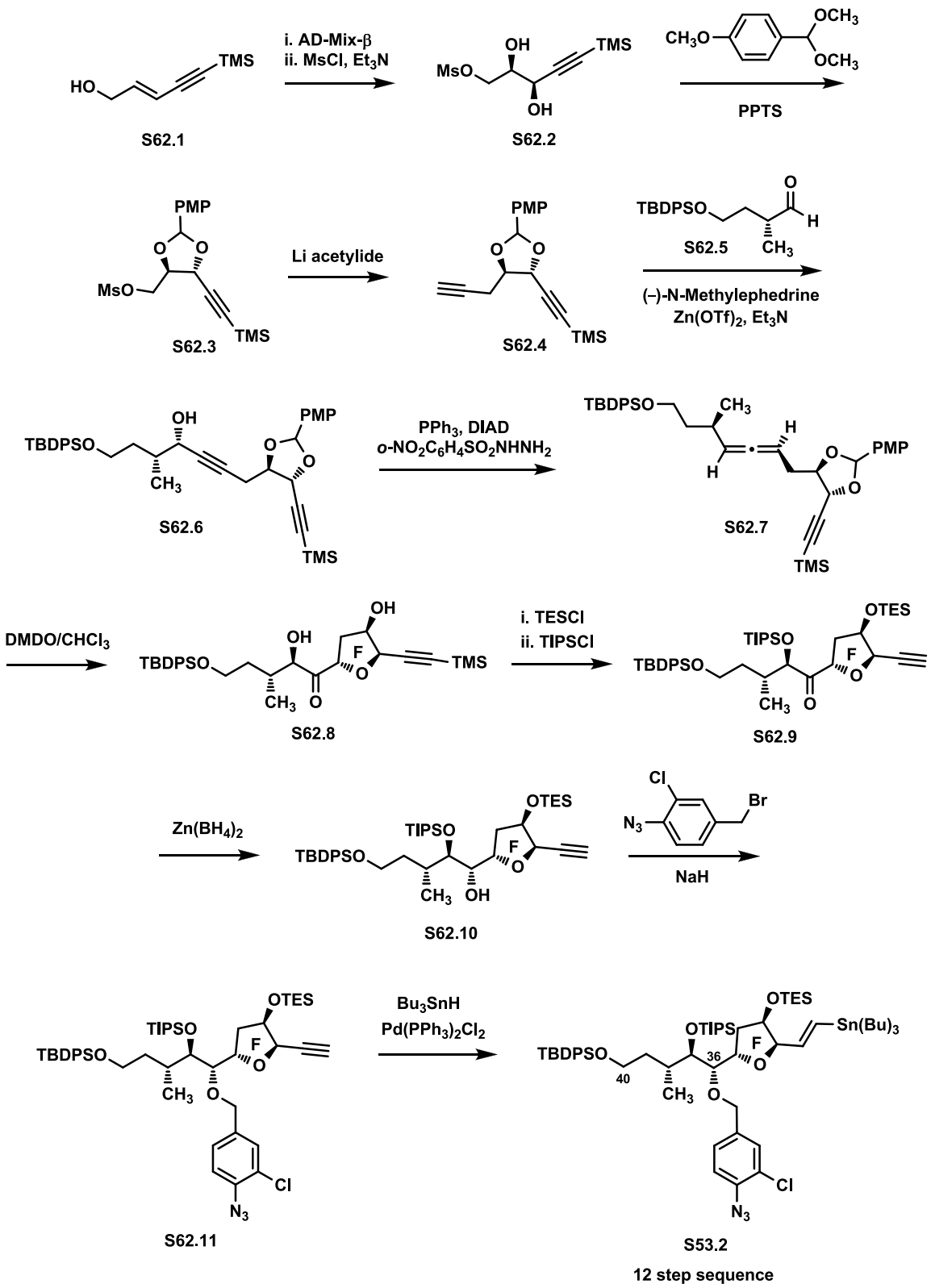
(77) For a review on the Sharpless dihydroxylation see: Beller, M.; Sharpless, K. B. *Applied Homogeneous Catalysis with Organometallic Compounds (2nd Edition)* **2002**, *3*, 1149.

(78) Enders, D.; Vicario, J. L.; Job, A.; Wolberg, M.; Muller, M. Chemistry--A European Journal **2002**, *8*, 4272

(79) Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(80) See ref. 6b for an example of PMB cleavage by DMDO

Scheme 62 Proposed Route to Vinyl Stannane S53.2



using Pd(0) and Bu_3SnH[81] should provide **S53.2** in 12 steps from **S62.1**.

Assembly of the C21-C40 southern hemisphere of PTX4 will be accomplished using Stille coupling conditions[82] (Scheme 63, pg. 101) to give Weinreb amide **S53.1**. Conversion of **S52.1** to the lithium acetylide derivative and exposure to Weinreb amide **S53.1** will be performed for the union of the top and bottom subunits which represents the entire C1-C40 carbon framework of PTX4. The Stryker copper hydride reagent will be used to reduce the alkynone to **S63.1**. Exposure of **S63.1** to TFA, should convert the C16-C21 portion into the bicyclic ketal D ring and remove the silyl groups at C1[83] and C33. Selective TEMPO oxidation of the primary alcohol at C1 followed by Pinnick oxidation should furnish carboxylic acid **S54.1**.[70]

Macrolactionization[84] of **S54.1** to **S64.1** (Scheme 64, pg. 102) will be achieved under Yamaguchi conditions**.** At this stage the 4-azido-3-chloro benzyl ethers on the C14 and C36 alcohols will be selectively removed by treatment with PPh_3 followed by DDQ in the presence of silica gel[68] to unmask the corresponding diol (**S64.2**). Doering oxidation[85] to diketone **S64.3** and subsequent global deprotection using TAS-F[4d] should afford PTX4 in 32 steps overall (longest linear sequence).

This synthesis features the extensive use of alkynes, propargyl alcohol derivatives, and allenes, as well as the use of SDEs to prepare the functionalized furans and to control the 19 stereocenters of this target in the context of a highly convergent and flexible strategy. The route compares well with partial but innovative routes reported by

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(81) (a) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1987**, *60*, 3468. (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

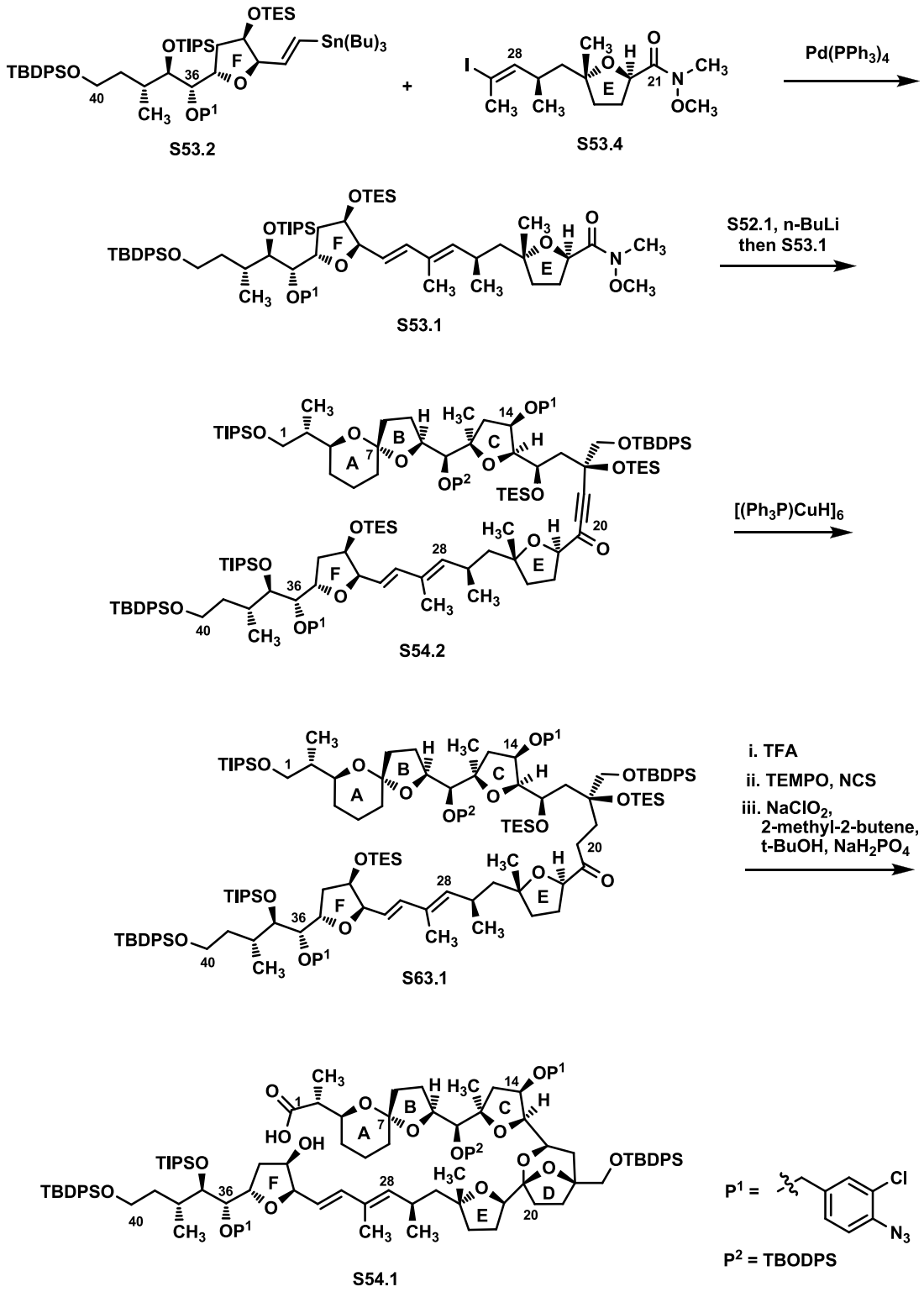
(82) For a recent review on the Stille coupling see: De Souza, M. V. N. *Curr. Org. Syn.* **2006**, *3*, 313.

(83) For an example of the cleavage of a primary TIPS groups using TFA see: Crimmins, M. T.; Zuccarello, J. L.; Cleary, P. A.; Parrish, J. D. *Org. Lett.* **2006**, *8*, 159.

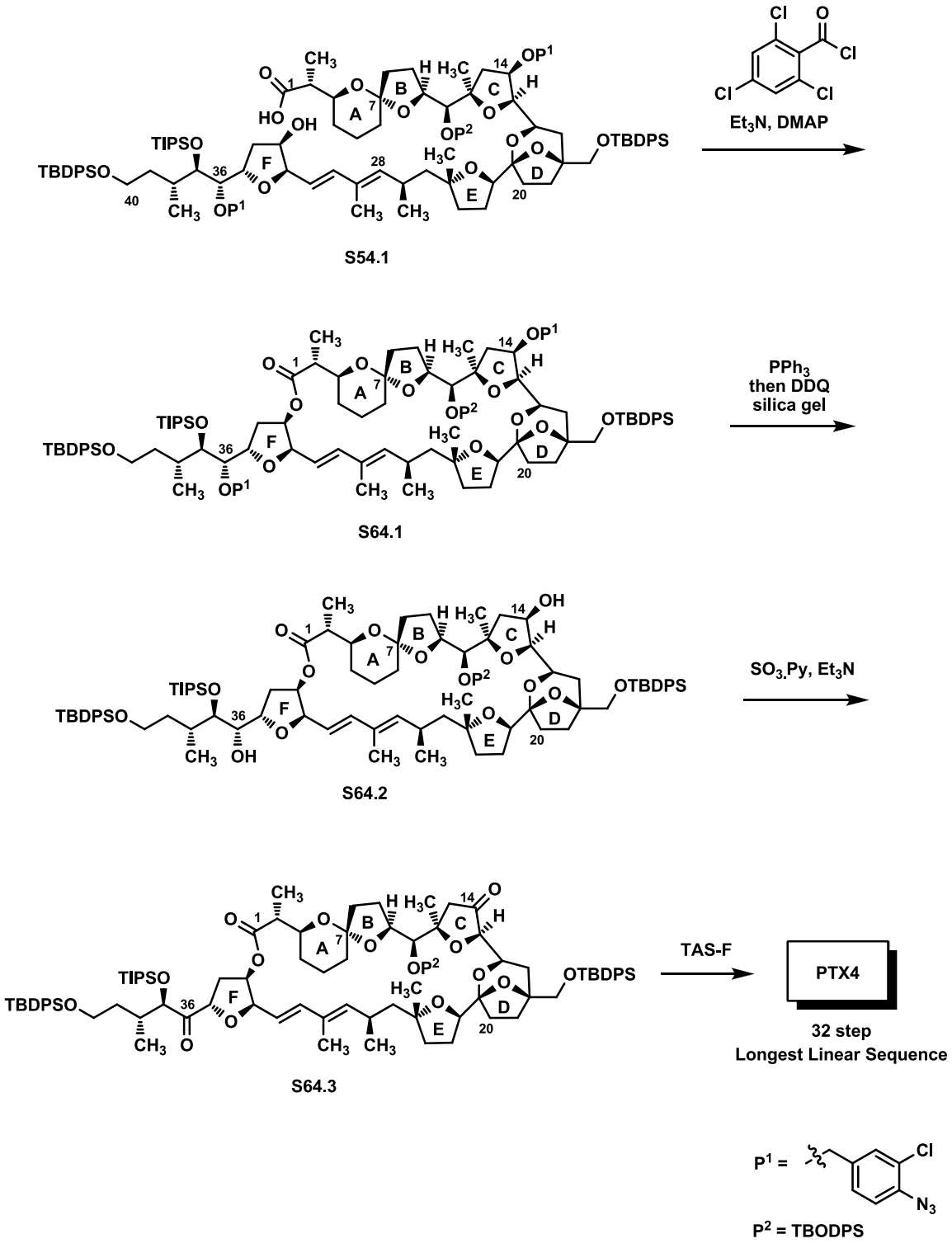
(84) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(85) Parikh, J. R.; Von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Scheme 63 Proposal for the Assembly of the Top and Bottom Fragments



Scheme 64 Proposed Macrolactonization and Synthesis of PTX4



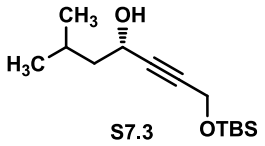
Roush (19 steps to C11-C26), Paquette (26 steps to C1-C26 and 14 steps to C29-C40), Murai (27 steps to C8-C18), Fujiwara (13 steps to C20-C30) and Brimble (19 steps to C1-C16), as discussed in Chapter 6, as well as the pioneering and remarkably concise total synthesis by Evans (36 steps overall).[4c,d]

Chapter 8

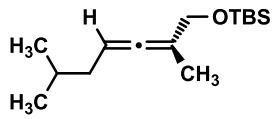
Experimental Section

General: Starting materials, reagents and solvents were purchased from commercial suppliers (Aldrich and Fischer) and used without further purification. Anhydrous THF, Et_2O, $CHCl_3$, and DCM were obtained from a solvent purification system consisting of alumina based columns. All reactions were conducted in oven-dried (135 ^oC) glassware under an inert atmosphere of dry nitrogen. The progress of reactions were monitored by silica gel thin layer chromatography (tlc) plates (mesh size 60Å with fluorescent indicator, Sigma-Aldrich), visualized under UV and charred using cerium or anisaldehyde stain. Products were purified by flash column chromatography (FCC) on 120-400 mesh silica gel (Fisher). Infrared (FTIR) spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on either a Varian-300 instrument (300 MHz), Varian-400 instrument (400 MHz), or a Varian-500 instrument (500 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Data is reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constants (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on either a Varian-300 instrument (75 MHz), Varian-400 instrument (100 MHz) or a Varian-500 instrument (125 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. Optical rotations were recorded at 25^oC using the sodium D line (589 nm), on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

Chapter 3: Total Synthesis of Epoxomicin



To a mixture of activated $Zn(OTf)_2$ (1.431 g, 3.936 mmol) and (-)-*N*-methylephedrine (770 mg, 4.294 mmol) in dry toluene (10 ml) was added Et_3N (434 mg, 4.294 mmol) dropwise and stirred under argon atmosphere at room temperature for 2 h. To the resulting milky–white slurry was added dropwise a solution of TBS protected propargyl ether **S7.2** (730 mg, 4.294 mmol) in dry toluene (8 ml) and stirred for 15 min. Distilled isovaleraldehyde (**S7.1**) (308 mg, 384 µl, 3.578 mmol) was added dropwise and stirred at rt for 14 h. The reaction mixture was extracted with (100 ml) toluene and washed with saturated aqueous NH_4Cl solution (20 ml x 4) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave nearly pure alcohol, which upon further purification using 5% ethyl acetate-hexanes furnished the (*S*)-alcohol **S7.3** (852 mg, 93%) as a clear viscous liquid in >95% ee as determined by ^{19}F NMR of MTPA esters. $[\alpha]_D$ -9.6 (*c* 2.72, $CHCl_3$). IR ν_{max}(neat)/cm^{-1} 3366, 2949; δ_H (300 MHz, $CDCl_3$) 4.44 (1H, tt, J=7.7, 1.5 Hz), 4.34 (2H, d, J=1.8 Hz), 1.91-1.77 (1H, m), 1.71 (1H, s), 1.67-1.49 (2H, m), 0.94 (3H, d, J=4.5 Hz), 0.91 (3H, d, J=4.5 Hz), 0.91 (9H, s), 0.12 (6H, s); δ_C (50 MHz, $CDCl_3$) 86.1, 83.5, 61.1, 51.7, 46.8, 25.8, 24.7, 22.54, 22.47, 18.3, -5.1; *m/z* (ESIMS) 257 $(M+1)^+$.



S7.4

To a solution of alcohol **S7.3** (3.25 g, 12.7 mmol) in dry DCM (30 ml) was added Et_3N (2.48 ml, 17.78 mmol) dropwise and cooled to -65^oC. MsCl (1.28 ml, 16.5 mmol) was added dropwise and stirred for 2 h (-65^oC to rt). The reaction mixture was extracted with DCM and washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue was dried under vacuum. The crude mesylate was used as such for the next step without further purification.

In a 100 ml flask CuBr (2.0 g, 13.97 mmol) and LiBr (1.21 g, 13.97 mmol) were taken under argon and THF was added (30 ml). The resulting green solution was degassed with argon for 2 minutes and cooled to -10^oC (acetone-ice mixture). MeMgBr solution (14 ml in butyl ether, 13.97 mmol) was added dropwise and the resulting canary yellow suspension was stirred for 1 h at -10^oC then cooled to -65^oC. A solution of above mesylate in dry THF (10 ml) was added dropwise and stirred under argon for 2 h (-65 to 10^oC). The reaction was quenched with saturated aqueous NH_4Cl solution (10 ml) and extracted with ether (200 ml), washed with saturated aqueous NH_4Cl solution (30 ml x 3), water (50 ml), brine (50 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a nearly pure compound, which upon further purification using 2% ethyl acetate-hexanes gave allene **S7.4** (2.94 g, 91%) as a clear viscous liquid. $[\alpha]_D$ +31.7 (*c* 1.01, $CHCl_3$). IR ν_{max}(neat)/cm^{-1} 2954, 1968; δ_H (400 MHz, $CDCl_3$) 5.06-5.02 (1H, m), 4.09 (2H, d, J=2.4 Hz), 1.87 (2H, t, J=6.4 Hz), 1.69 (3H, d, J=2.8 Hz), 1.67-1.61 (1H, m), 0.91 (6H, d, J=6.4 Hz), 0.90 (9H, s), 0.07 (6H, s); δ_C (100 MHz, $CDCl_3$) 201.6, 98.6, 89.5, 65.7, 38.4, 28.5, 25.9, 22.2, 22.1, 18.4, 15.7, -5.22, -5.24; *m/z* (ESIMS) 254$(M)^+$.

General Procedure for Preparation of DMDO

*Note – This setup is shown on a bench top but reaction should be run inside of a hood

To the 5 L 3-neck flask was added 360 g (4.3 mol) $NaHCO_3$, 660 ml water, and 480 ml (6.55 mol) acetone. The contents were mixed thoroughly by swirling the flask by hand for 5 minutes. 750 g (1.22 mol) of OXONE® was slowly added to avoid excessive bubbling. After complete addition, the rubber tubing from the cold finger was attached to the reaction flask. The other two necks of the flask were then closed off. The vacuum pump was immediately turned on and the pressure was brought down to ~500 torr. The

pressure of the reaction was carefully monitored due to the excessive bubbling that occurred. As the reaction and the bubbling subsided, the pressure was gradually decreased to as low as ~200 torr. The complete reaction time was about 30 minutes. After removing the collection flask from the dewar, anhydrous $MgSO_4$ was added to it. After filtration gave ~300 ml of a clear yellow solution. The concentration of dimethyldioxirane in acetone was ~0.05 M. For the procedure to extract DMDO into $CHCl_3$ see ref. 15b,c (pg. 4).

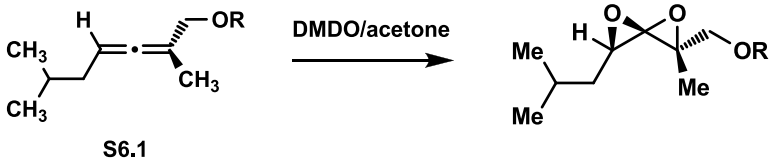
General Procedure for Preparation of Spirodiepoxides (SDEs) from Allenes

To the allene was added a 0.05 M solution of dimethyldioxirane (DMDO) in acetone at -40°C dropwise over 1 minute. The reaction mixture stirred under inert atmosphere at -40°C for 1 h and was let to warm to rt over 1 h. At rt, the reaction was monitored by tlc for the disappearance of allene. Upon completion of the reaction, the solvent was evaporated and the resulting SDE was dried under vacuum and used for the next step without further purification.

Determination of ratios of SDEs derived from allenes S6.1:

Allenes **S6.1 (R = TBS, TMS, TIPS, TBDPS)** were oxidized with DMDO according to the general procedure. ^{1}H-NMR analysis of the crude material was used to

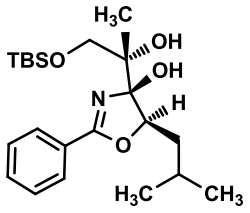
determine the diastereomeric ratios of spirodiepoxides. [Based on Crandall, J.K.; Batal, D.J.; Sebesta, D.P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153, the signals at or near 3.8 ppm correspond to the methine proton of the spirodiepoxide.] The ^{1}H-NMR signals were not baseline resolved and hence represent only approximate diastereomeric ratios. The methyl signals (singlets at ~1.5 ppm), which were also not baseline resolved, indicated a ratio of approximately 2:1. While four diastereomeric spirodiexpoxides are possible, only two signals were observed for the methine residues. Similarly, only two signals were observed for the methyl residues. The stereoisomers are discussed below.



S6.1

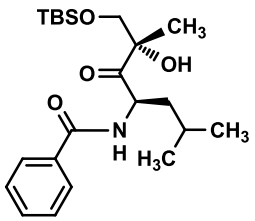
Allene	Approximate ratios of corresponding SDEs
R = TBS	2 : 1
R = TIPS	2 : 1
R = TBDPS	2 : 1
R = TMS	2 : 1

*^{1}H-NMR signals were not baseline resolved and hence represent only approximate diastereomeric ratios.



S8.2

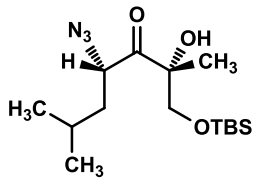
To the allene **S7.4** (56 mg, 0.221 mmol) cooled to -40°C was added DMDO (9 ml of a 0.05 M solution in acetone) and stirred under argon for 2 h (-40°C to rt). Solvent was evaporated and the crude SDE was dried. A mixture of the SDE and benzamide (53 mg, 0.441 mmol) in $CDCl_3$ (1 ml) was stirred at rt under argon atmosphere for 24 h. Solvent was evaporated and FCC using 12% ethyl acetate-hexanes afforded oxazolines **S8.2** (40 mg, 44%, dr 3:2) as a clear liquid. Spectral data for major diastereomer: IR ν_{max}(neat)/cm^{-1} 3435, 1644, 1581; δ_H (400 MHz, $CDCl_3$) 8.01(2H, d, J=7.2 Hz), 7.50 (1H, t, J=7.2 Hz), 7.41 (2H, t, J=7.6 Hz), 4.96 (1H, s), 4.76 (1H, dd, J=11.2, 2.0 Hz), 4.17 (1H, d, J=9.6 Hz), 3.58 (1H, d, J=9.2 Hz), 1.97 (1H, brs), 2.20-1.91 (1H, m), 1.89-1.81 (1H, m), 1.56-1.49 (1H, m), 1.30 (3H, s), 1.07 (3H, d, J=3.2 Hz), 1.05 (3H, d, J=3.2 Hz), 0.95 (9H, s), 0.17 (3H, s), 0.15 (3H, s); δ_C (100 MHz, $CDCl_3$) 166.1, 131.8, 128.7, 128.2, 127.6, 102.6, 81.6, 73.1, 69.3, 38.3, 26.0, 25.9, 23.7, 21.8, 18.8, 18.2, -5.5; *m/z* (ESIMS) 430 $(M+23)^+$. Spectral data for minor diastereomer: IR ν_{max}(neat)/cm^{-1} 3435, 1644, 1581; δ_H (400 MHz, $CDCl_3$) 7.99 (2H, d, J=7.2 Hz), 7.50 (1H, t, J=7.6 Hz), 7.41 (2H, t, J=7.6 Hz), 4.85 (1H, dd, J=10.8, 2.4 Hz), 4.79 (1H, s), 4.07 (1H, dd, J=9.6, 2.4 Hz), 3.61 (1H, d, J=10.0 Hz), 2.86 (1H, br), 1.99-1.89 (1H, m), 1.82-1.75 (1H, m), 1.56-1.49 (1H, m), 1.17 (3H, s), 1.05 (3H, d, J=3.2 Hz), 1.04 (3H, d, J=3.6 Hz), 0.94 (9H, s), 0.15 (3H, s), 0.12 (3H, s); δ_C (100 MHz, $CDCl_3$) 165.1, 131.7, 128.7, 128.2, 127.7, 102.4, 81.9, 74.4, 69.1, 38.4, 25.8, 23.6, 22.0, 19.4, 18.2, -5.6; *m/z* (ESIMS) 408 $(M+1)^+$.



S8.3

To the allene **S7.4** (60 mg, 0.236 mmol) was added DMDO (0.59 mmol, 11.8 ml of 0.05 M solution in acetone) and stirred under argon atmosphere at rt. After 1 h, solvent was evaporated and the residue was dried. The crude SDE was used as such for the next step. In a separate flask, to a solution of benzamide (34 mg, 0. 283 mmol) in dry THF (2 ml) cooled to -65^{o}C was added n-BuLi (0.566 mmol, 0.353 ml of 1.6 M solution in hexanes) and stirred under argon for 10 min. To the resulting yellow solution was added a solution of above SDE in dry THF (1 ml) and stirred for 3 h (-65^{o}C to rt). The reaction was quenched with water (0.5 ml) and extracted with ethyl acetate (20 ml). The organic phase was washed with water (5 ml), brine (5 ml) and dried over Na_2SO_4. Solvent was evaporated and FCC using 5% ethyl acetate/hexanes then 10% ethyl acetate/hexanes furnished **S8.3** (28 mg, 30%, 1.3:1 dr) as a white solid. Spectral data for major isomer: IR ν_{max}(neat)/cm-1 3346, 3061, 2954, 1714, 1640; δ_H (300 MHz, $CDCl_3$) 7.79 (2H, d, J=5.7 Hz), 7.51 (1H, t, J=5.4 Hz), 7.44 (2H, t, J=5.7 Hz), 6.99 (1H, d, J=6.3 Hz), 5.47 (1H, t, J=6.6 Hz), 3.96 (1H, d, J=7.2 Hz), 3.69 (1H, s), 3.47 (1H, d, J=7.2 Hz), 1.86-1.72 (2H, m), 1.48-1.40 (1H, m), 1.33 (3H, s), 1.07 (3H, d, J=4.5 Hz), 0.95 (3H, d, J=4.8 Hz), 0.84 (9H, s), 0.04 (3H, s), 0.02 (3H, s); δ_C (75 MHz, $CDCl_3$) 214.0, 166.4, 134.0, 131.4, 128.3 (2 C), 126.8 (2 C), 80.0, 69.0, 53.2, 41.2, 25.7 (3 C), 25.1, 23.5, 21.9, 21.5, 18.1, -5.52, -5.54; *m/z* (ESIMS) 408 $(M+1)^+$. Spectral data for minor isomer: IR ν_{max}(neat)/cm^{-1} 3364, 3064, 1716, 16420; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, J=7.2 Hz), 7.50 (1H, t, J=7.2 Hz), 7.42 (2H, t, J=7.2 Hz), 6.52 (1H, d, J=8.4 Hz), 5.56-5.51 (1H, m), 4.04 (1H, d, J=10.0

Hz), 3.50 (1H, s), 3.46 (1H, d, J=9.6 Hz), 1.84-1.76 (1H, m), 1.70-1.64 (1H, m), 1.38-1.30 (1H, m), 1.31 (3H, s), 1.05 (3H, d, J=6.4 Hz), 0.95 (3H, d, J=6.4 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.03 (3H, s); δ_C (100 MHz, $CDCl_3$) 213.9, 167.0, 134.0, 131.7, 128.6, 127.1, 80.2, 68.2, 51.8, 40.6, 25.8, 25.3, 23.6, 21.8, 21.5, 18.2, -5.5, -5.6; *m/z* (ESIMS) 408 $(M+1)^+$.

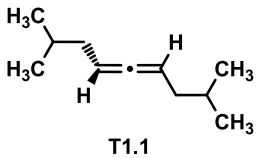


S8.5

To the allene **S7.4** (660 mg, 2.6 mmol) cooled to -40°C was added DMDO (104 ml of 0.05 M solution in acetone) and stirred for 1.5 h (-40°C to rt). Solvent was evaporated and the residue was dried under vacuum. The crude SDE was dissolved in dry $CHCl_3$ (5 ml) and cooled to -20°C. A solution of tetrabutylammonium azide (740 mg, 2.6 mmol) in dry $CHCl_3$ (5 ml) was added and stirred for 1 h (-20°C to rt). The solvent was evaporated at rt under vacuum and the yellow residue was extracted with ether (100 ml), washed with water (25 ml x 2), brine (25 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a mixture of azido alcohols, which upon purification using 3% ethyl acetate-hexanes as the eluent gave the desired azido alcohol **S8.5** (462 mg, 54%) as a clear viscous liquid. $[\alpha]_D$ +126.4 (*c* 1.21, $CHCl_3$). IR ν_{max}(neat)/cm^{-1} 3540, 2109, 1722; δ_H (400 MHz, $CDCl_3$) 4.25 (1H, dd, J=10.4, 4.0 Hz), 3.92 (1H, d, J=10.0 Hz), 3.45 (1H, s), 3.44 (1H, d, J=10.0 Hz), 1.85-1.54 (3H, series of m), 1.27 (3H, s), 0.99 (3H, d, J=5.2 Hz), 0.97 (3H, d, J=5.2 Hz), 0.88 (9H, s), 0.07 (3H, s), 0.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 211.4, 79.9, 69.1, 61.1, 38.0, 25.7, 25.3, 23.1, 21.6, 21.3, 18.2, -5.55, -5.6;

m/z (ESIMS) 330 (M+1)+. Continued elution gave the minor diastereomer (162 mg, 19%). IR ν_{max}(neat)/cm-1 3550, 2106, 1724; δ_H (300 MHz, $CDCl_3$) 4.39 (1H, t, J=8.2 Hz), 4.01 (1H, d, J=9.6 Hz), 3.43 (1H, d, J=9.6 Hz), 3.36 (1H, s), 1.87-1.81 (1H, m), 1.56 (2H, t, J=6.9 Hz), 1.27 (3H, s), 0.99 (3H, d, J=4.2 Hz), 0.97 (3H, d, J=4.2 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 211.6, 80.0, 68.4, 60.3, 38.6, 26.1, 25.6, 23.4, 22.0, 21.7, 18.5, -5.1, -5.2; *m/z* (ESIMS) 330 $(M+1)^+$.

Chapter 4: Mechanistic Insight on Nucleophilic SDE Opening

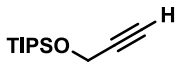


T1.1

To a solution of commercially available 5-methyl-1-hexyn-3-ol (600 mg, 5.357 mmol) in dry CH_2Cl_2 (10 ml) was added Et_3N (1.10 ml, 8.00 mmol). The solution was cooled to 0^oC and MsCl (0.62 ml, 8.036 mmol) was added dropwise over 1 minute and the reaction stirred for 1 h at 0^oC. The reaction was quenched by the addition of water (3 ml). The organic layer was separated, washed with water (2 x 10 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude mesylate was dried under vacuum and used for the next step without further purification.

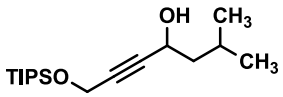
To a separate flask was added CuBr (1.049 g, 7.30 mmol, used from commercial source without further drying or purification), LiBr (633 mg, 7.30 mmol, used from commercial source without further drying or purification) and dry THF (30 ml). The resulting green solution was degassed with argon for 2 minutes and cooled to -10^oC. A 2.0 M solution of isobutylmagnesium bromide (3.65 ml in THF, 7.30 mmol) was added dropwise over 5 minutes and the resulting dark red suspension was stirred for 1 h at -10^oC then cooled to -78^oC. A solution of the above mesylate in dry THF (5 ml) was added dropwise over 5 minutes and stirred under argon for 5 h (-78^oC to rt). The reaction was quenched with a sat. NH_4Cl solution (10 ml) and extracted with ether (150 ml), washed with a sat. NH_4Cl solution (20 ml x 3), water (50 ml), brine (50 ml), and dried over anhydrous $MgSO_4$. Evaporation of solvent gave a nearly pure compound, which upon further purification by FCC using hexane gave 692 mg (85%) of allene **T1.1**

as a clear colorless oil. IR ν_{max} (neat) / cm^{-}1 2958, 2933, 2900, 2872, 1960, 1466, 1388, 1368, 874; δ_H (400 MHz, $CDCl_3$) 4.95-4.90 (2H, m), 1.87-1.74 (4H, m), 1.62-1.52 (2H, m), 0.84 (12 H, d, J=6.8 Hz); δc (100 MHz, $CDCl_3$) 205.0, 88.7, 38.6, 28.4, 22.2, 22.1; *m/z* (ESIMS) 152.8 $(M)^+$.



T2.1a

To a solution of propargylic alcohol (2.55 g, 45.49 mmol) in 100 ml of DMF was added imidazole (3.387 g, 49.75 mmol) and TIPS-Cl (10.646 ml, 49.75 mmol) in one portion at rt. The reaction stirred for 15 h at rt and was then diluted with 150 ml of hexane and washed with water (2 x 50 ml). The aqueous layer was extracted with hexane (3 x 100 ml). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated to give 9.741 g (99%) of known alkyne[88] **T2.1a** as a clear colorless oil. No further purification was necessary.

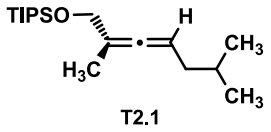


T2.1b

To a solution of alkyne **T2.1a** (8.565 g, 40.33 mmol) in 100 ml of dry THF was added a 1.6 M solution of n-BuLi in hexane (38.00 ml, 60.80 mmol) dropwise over 5 minutes at -78^{o}C. The reaction stirred for 15 min at -78^{o}C and was allowed to warm to rt at which point stirring continued for 15 minutes. The reaction was then cooled back down to -78^{o}C and a solution of isovaleraldehyde (4.738 ml, 44.12 mmol) in 10 ml of dry

(88) Magnus, P.; Matthews, K.S. *J. Am. Chem. Soc.* **2005**, *127*, 12476.

THF was added dropwise over 5 minutes. The reaction stirred for 1 h at -78°C and was allowed to warm to rt over 1 h. Upon completion by tlc, the reaction was quenched with sat. NH_4Cl (50 ml) and 100 ml of ether was added. The organic layer was washed with water (2 x 50 ml). The aqueous layers were combined and extracted with ether (2 x 100 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 10% ethyl acetate-hexane gave 11.42 g (95%) of alcohol **T2.1b** as a clear colorless oil. IR ν_{max} (neat) / cm^{-1} 3372, 2944, 2866, 1464, 1367, 1261, 1150, 1117, 1067, 882; δ_H (400 MHz, $CDCl_3$) 4.38 (1H, t, J=7.1 Hz), 4.35 (2H, d, J=1.6 Hz), 1.83-1.71 (1H, m), 1.66 (1H, br), 1.59-1.52 (1H, m), 1.51-1.44 (1H, m), 1.10-0.97 (3H, m), 1.01 (18H, d, J=5.5 Hz), 0.86 (6H, t, J=6.6 Hz); δc (100 MHz, $CDCl_3$) 85.8, 83.6, 61.1, 51.9, 46.7, 24.7, 22.5, 17.9, 11.9; *m/z* (ESIMS) 321.7 $(M+23)^+$.

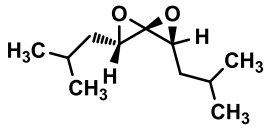


T2.1

To a solution of alcohol **T2.1b** (1.097 g, 3.68 mmol) in dry CH_2Cl_2 (10 ml) was added Et_3N (0.835 ml, 5.99 mmol). The solution was cooled to 0°C and MsCl (0.431 ml, 5.57 mmol) was added dropwise over 5 minutes and the reaction stirred for 1 h at 0°C. The reaction was quenched by the addition of water (5 ml). The organic layer was separated, washed with water (2 x 15 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude mesylate was dried under vacuum and used for the next step without further purification.

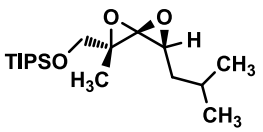
To a separate flask was added CuBr (0.581 g, 4.05 mmol, used from commercial source without further drying or purification), LiBr (0.352 g, 4.05 mmol, used from

commercial source without further drying or purification) and dry THF (10 ml). The resulting green solution was degassed with argon for 2 minutes and cooled to -10°C. A 1.0 M solution of methylmagnesium bromide (4.05 ml in ether, 4.05 mmol) was added dropwise and the resulting yellow suspension was stirred for 1 h at -10°C then cooled to -78°C. A solution of the above mesylate in dry THF (3.0 ml) was added dropwise over 5 minutes and the reaction was allowed to warm to rt over 5 h. Upon completion by tlc, the reaction was quenched with sat. NH_4Cl (10 ml), extracted with ether (150 ml), washed with sat. NH_4Cl (20 ml x 3), water (50 ml), brine (50 ml), and dried over anhydrous $MgSO_4$. Evaporation of solvent gave a nearly pure compound (>95%) as judged by ^1H NMR, which upon further purification by FCC using hexane gave 1.080 g (99%) of allene **T2.1** as a clear colorless oil. IR ν_{max} (neat) / cm^{-1} 2933, 2868, 1965, 1462, 1372, 1082, 1066, 878, 686; δ_H (400 MHz, $CDCl_3$) 4.99-4.94 (1H, m), 4.09 (2H, d, J=2.0 Hz), 1.79 (2H, dd, J=6.8, 7.2 Hz), 1.65 (3H, d, J=2.8 Hz), 1.61-1.51 (1H, m), 1.06-0.98 (3H, m), 1.00 (18H, d, J=4.8 Hz), 0.84 (6H, d, J=6.4 Hz); δc (100 MHz, $CDCl_3$) 201.4, 98.9, 89.6, 65.6, 38.5, 28.5, 22.2, 22.1, 18.0 (2), 12.0; *m/z* (ESIMS) 296.0 $(M)^+$.



T1.1a

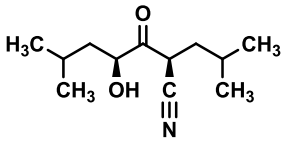
DMDO oxidation of allene **T1.1** gave a 1:1 mixture of SDE diastereomers **T1.1a**. IR ν_{max} (neat) / cm^{-1} 2962, 2864, 1626, 1471, 1364, 1082, 997; δ_H (400 MHz, $CDCl_3$) 3.74-3.52 (2H, m), 1.92-1.46 (6H, m), 0.99-0.93 (12H, m); δc (125 MHz, $CDCl_3$) 85.8, 85.3, 60.4, 59.4, 58.7, 39.2, 38.8, 37.7, 26.2, 26.1, 25.9, 22.9, 22.8, 22.7, 22.4, 22.2 (2).



T2.1a

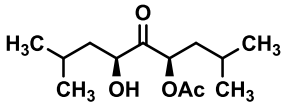
DMDO oxidation of allene **T2.1** gave approximately a 2:1 mixture of SDE diastereomers **T2.1a**. IR ν_{max} (neat) / cm^{-1} 2929, 2864, 1626, 1462, 1111, 1008, 882; δH (500 MHz, $CDCl_3$) 3.96 (0.8H, s), 3.89 (1.2H, s), 3.79(0.6H, dd, J=9.3, 3.5 Hz), 3.73(0.4H, dd, J=6.75, 5.0 Hz), 1.92-1.82 (1H, m), 1.73-1.44 (5H, m), 1.14-1.02 (21H, m), 0.99 (6H, d, J=6.5 Hz); δc (125 MHz, $CDCl_3$) 88.4, 88.0, 65.5, 65.4, 65.2, 64.9, 61.0, 59.8, 39.3, 38.7, 26.1, 26.0, 22.8 (2), 22.4, 22.2, 17.9, 16.3, 15.6, 11.9 (2).

Experimental Data for Table 1

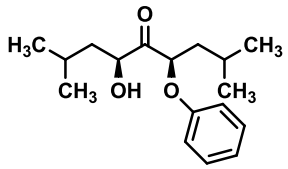


To a solution of 52 mg (0.283 mmol) of SDE derived from allene **T1.1** in 3 ml of dry $CHCl_3$ was added 97 mg (0.362 mmol) of tetrabutylammonium cyanide in 3 ml of dry $CHCl_3$ dropwise over a 2 min period at -40°C. The reaction mixture stirred at -40°C for 1 h and was allowed to warm to rt over 30 min. Upon completion by tlc, the reaction was quenched with 10 ml of water and an additional 10 ml of $CHCl_3$ was added. The organic layer was separated and washed twice with 10 ml of water. The organic layer was dried using $MgSO_4$, filtered, and evaporated to give an orange-yellow residue. FCC using 15% ethyl acetate-hexane gave 46 mg (77%, 1:1 dr) of α-hydroxy ketone as a clear

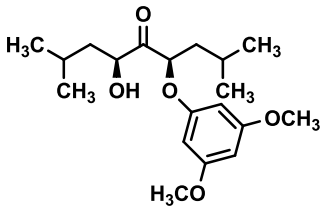
colorless oil. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3427, 2959, 2205, 1730, 1651, 1469, 1370, 1069; δ_H (400 MHz, $CDCl_3$) 4.52-4.48 (0.5H, m), 4.41-4.36 (0.5H, m), 3.71-3.62 (1H, m), 2.77 (0.5H, d, J=6.3 Hz), 2.69 (0.5H, d, J=5.9 Hz), 1.94-1.67 (4H, m), 1.65-1.54 (1H, m), 1.46-1.35 (1H, m), 0.97-0.89 (12H, m); δ_c (100 MHz, $CDCl_3$) 204.2, 204.1, 116.9, 116.7, 74.8, 74.7, 42.9, 42.5, 38.4, 38.1, 37.5, 36.9, 26.3, 26.1, 24.8 (2), 23.5, 22.7, 22.6, 21.2 (2), 21.0 (2); *m/z* (ESIMS) 210.1 $(M-1)^-$.



To a solution of 47 mg (0.255 mmol) of SDE derived from allene **T1.1** in 3 ml of dry $CHCl_3$ was added 85 mg (0.281 mmol) of tetrabutylammonium acetate in 3 ml of dry $CHCl_3$ dropwise over a 2 min period at -40°C. The reaction mixture stirred at -40°C for 1 h and was allowed to warm to rt over 30 min. Upon completion by tlc, the solvent was removed by rotovap. FCC using 10% ethyl acetate-hexane gave 43.5 mg (70%, 1:1 dr) of α-hydroxy ketone as a clear colorless oil. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3481, 2954, 2864, 1748, 1724, 1466, 1368, 1074; δ_H (400 MHz, $CDCl_3$) 5.38 (0.5H, dd, J=9.2, 3.6 Hz), 5.31 (0.5H, dd, J=10.4, 2.8 Hz), 4.42 (0.5H, dd, J=10.0, 3.2 Hz), 4.29 (0.5H, dd, J=10.6, 2.4 Hz), 3.11 (0.5H, br), 2.94 (0.5H, br), 2.14 (1.5H, s), 2.12 (1.5H, s), 2.00-1.87 (1H, m), 1.82-1.49 (4H, m), 1.45-1.33 (1H, m), 0.99-0.93 (12H, m); δ_c (100 MHz, $CDCl_3$) 210.5, 209.9, 170.5, 170.4, 74.3, 73.8, 73.6, 72.9, 43.2, 42.6, 39.7, 39.2, 24.9, 24.7(2), 24.6, 23.6, 23.2, 23.1, 21.4, 21.3, 21.1(2), 20.6, 20.5; *m/z* (ESIMS) 267.5 $(M+23)^+$.

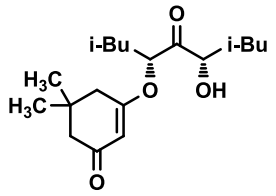


To a solution of 60.5 mg (0.329 mmol) of SDE derived from allene **T1.1** in 2 ml of dry THF was added 25 mg (0.266 mmol) of phenol in 2 ml of dry THF, 40 mg (0.290 mmol) of K_2CO_3, and 4 mg (0.015 mmol) of 18-crown-6 at rt in one portion. After stirring for 3 h at rt, 15 ml of DCM was added and the reaction was quenched with 10 ml of water. The organic layer was washed once with 10 ml of water. The aqueous layer was extracted once using 10 ml of DCM. The organic layers were combined, dried using $MgSO_4$, filtered, and evaporated to give an orange-yellow residue. FCC using 10% ethyl acetate-hexane gave 48 mg (65%, 1:1 dr) of α-hydroxy ketone as a clear colorless liquid. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3468, 2957, 1715, 1598, 1494, 1386, 1236, 1078, 752, 690; δ_H (400 MHz, $CDCl_3$) 7.25-7.19 (2H, m), 6.92 (1H, t, J=7.1 Hz), 6.81 (1H, d, J=8.0 Hz), 6.75 (1H, d, J=8.0 Hz), 4.82 (0.5H, dd, J=4.8, 2.4 Hz), 4.75 (0.5H, dd, J=6.5, 3.4 Hz), 4.58 (0.5H, d, J=9.5 Hz), 4.27 (0.5H, d, J=10.9 Hz), 3.07 (0.5H, d, J=5.2 Hz), 2.88 (0.5H, d, J= 5.2 Hz), 1.88-1.50 (4H, m), 1.35-1.12 (2H, m), 0.93-0.76 (12H, m); δ_c (100 MHz, $CDCl_3$) 214.5, 213.2, 157.7, 157.3, 129.9 (2), 129.7 (2), 121.9 (2), 121.7 (2), 115.1, 114.8, 114.7, 114.5, 80.3, 80.1, 73.4 (2), 72.8, 72.6, 43.0, 42.9, 42.7, 42.3, 42.1, 41.9, 40.6, 40.5, 40.2, 25.0, 24.9 (2), 24.7 (2), 24.4 (2), 23.7, 23.5, 23.4, 23.1, 22.2 (2), 21.4 (2), 21.1 (2), 20.9 (2); *m/z* (ESIMS) 277.3 $(M-1)^-$.



To a solution of 60.5 mg (0.329 mmol) of SDE derived from allene **T1.1** in 2 ml of dry THF was added 39 mg (0.253 mmol) of 3,5-Dimethoxyphenol in 2 ml of dry THF, 35 mg (0.254 mmol) of K2CO3, and 6 mg (0.023 mmol) of 18-crown-6 at rt. After stirring for 5 hours at rt, 15 ml of DCM was added and the reaction was quenched with 10 ml of water. The organic layer was washed twice with 10 ml of water. The aqueous layer was extracted twice using 10 ml of DCM. The organic layers were combined, dried using MgSO4, filtered, and evaporated to give an orange-yellow residue. FCC using 10% ethyl acetate-hexane gave 66 mg (78%) of a 1:1 mixture of diastereomers as a clear colorless liquid; IR vmax (neat) / cm-1 3468, 2957, 1721, 1599, 1475, 1206, 1154, 1068, 820; δH (400 MHz, CDCl3) 6.05-6.03 (1H, m), 5.98-5.97 (1H, d, J=2.0 Hz), 5.92-5.91 (1H, d, J=1.8 Hz), 4.80-4.77 (0.05H, dd, J=4.8, 2.2 Hz), 4.73-4.70 (0.05H, dd, J=6.7, 3.5 Hz), 4.57-4.54 (0.50H, d, J=9.2 Hz), 4.29-4.27 (0.05H, d, J=10.4 Hz), 3.69-3.68 (6H, d, J=4.4 Hz), 3.07 (0.05H, br), 2.88 (0.05H, br), 1.93-1.51 (4H, m), 1.37-1.14 (2H, m), 0.93-0.78 (12H, m); δc (100 MHz, CDCl3) 214.2, 212.9, 161.7 (2), 159.6, 159.2, 93.9, 93.8, 93.6, 80.1, 79.4, 73.3, 72.8, 55.3 (2), 42.9, 42.7, 42.0, 40.4, 24.9, 24.8 (2), 24.4, 23.8, 23.5, 23.0 (2), 22.2, 21.4, 21.1, 20.9; m/z (ESIMS) 361 (M+23)+.

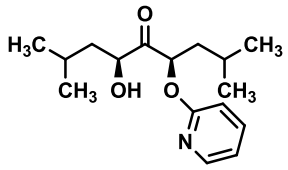
Experimental Data from Scheme 9



S9.2

To a solution of 60.5 mg (0.326 mmol) of SDE derived from allene **T1.1** in 3 ml of dry DCM was added 37 mg (0.264 mmol) of dimedone (**S9.1**) in 2 ml of dry DCM. The reaction mixture stirred at rt for 10 hours. FCC using 25% ethyl acetate-hexane gave 66 mg (81%, 1:1 dr) of **S9.2** as a clear colorless liquid; IR ν_{max} (neat) / cm^{-1} 3362, 2962, 2868, 1732, 1642, 1605, 1470, 1376, 1217, 1151; δ_H (400 MHz, $CDCl_3$) 5.46 (0.50H, s), 5.35 (0.50H, s), 5.20-5.17 (0.50H, dd, J=5.6, 2.6 Hz), 5.09-5.06 (0.50H, dd, J=7.1, 2.8 Hz), 4.46-4.45 (0.50H, d, J=5.4 Hz), 4.30-4.20 (1.50H, m), 2.37-2.09 (4H, m), 1.91-1.60 (4H, m), 1.51-1.31 (2H, m), 1.02-1.00 (6H, d, J=6.4 Hz), 0.91-0.84 (12H, m); δ_c (100 MHz, $CDCl_3$) 211.2, 210.4, 200.3, 200.2, 175.9 (2), 102.3, 79.5, 79.0, 74.1, 73.5, 50.5 (2), 43.1, 42.8 (2), 42.0, 39.9, 39.4, 32.6, 28.2, 28.1 (2), 27.9, 25.1, 24.9, 24.5, 24.3, 23.5, 23.0 (2), 21.5, 21.1 (2), 20.9; *m/z* (ESIMS) 347 $(M+23)^+$.

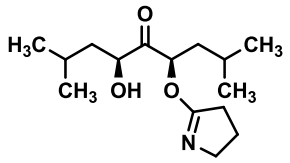
Experimental Data from Scheme 10



S10.2

To a solution of 60 mg (0.326 mmol) of SDE derived from allene **T1.1** in 3 ml of dry $CHCl_3$ was added 25 mg (0.263 mmol) of 2-hydroxypyridine in 3 ml of dry $CHCl_3$.

The reaction mixture stirred at rt for 12 h. FCC using 8% ethyl acetate-hexane gave 69.5 mg (98%, 1:1 dr) of α-hydroxy ketone as a clear colorless liquid. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3468, 2958, 2859, 1724, 1597, 1568, 1474, 1433, 1286, 1062, 988, 780; δ_H (400 MHz, $CDCl_3$) 8.03- 8.02 (1H, m), 7.63-7.59 (1H, m), 6.89 (1H, t, J=6.0 Hz), 6.82 (1H, t, J=7.9 Hz), 5.69 (0.5H, dd, J=5.9, 3.3 Hz), 5.62 (0.5H, dd, J=7.5, 3.0 Hz), 4.59-4.55 (0.5H, m), 4.32-4.28 (0.5H, m), 3.85 (0.5H, d, J=4.9 Hz), 3.71 (0.5H, d, J=6.6 Hz), 1.98-1.83 (3H, m), 1.76-1.32 (3H, m), 1.01-0.89 (12H, m); δ_c (100 MHz, $CDCl_3$) 213.2, 212.5, 162.4, 162.2, 146.3, 146.1, 139.2 (2), 117.5 (2), 111.2, 111.0, 74.8, 74.0 (2), 73.8, 43.2, 42.5, 40.8, 39.9, 25.0, 24.7 (3), 23.6 (2), 23.3, 23.2, 21.7, 21.4, 21.2, 21.1; *m/z* (ESIMS) 280.1 $(M+1)^+$.



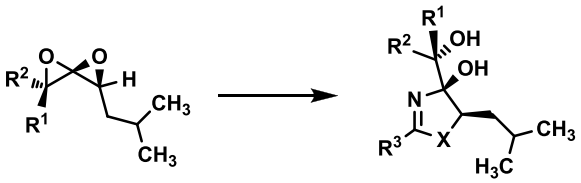
S10.4

To 60 mg (0.329 mmol) of SDE derived from allene **T1.1** was added 140 mg of 2-pyrrolidinone (1.645 mmol) in 1.5 ml of $CDCl_3$ in one portion at rt. After 45 minutes the reaction was complete by ^1H NMR monitoring. 5 ml of $CHCl_3$ was added and the reaction mixture was washed with water (5 x 5 ml). The organic layer was dried using Na_2SO_4, filtered and evaporated to give 66 mg (75%, 1:1 dr) of α-hydroxy ketone as a clear pale yellow oil. This material was unstable and hydrolyzed upon standing and when subjected to FCC to give the corresponding α,α'-ketone diol and 2-pyrrolidinone. IR ν_{max} (neat) / cm^{-1} 3405, 2956, 1728, 1645, 1469, 1369, 1307, 1078; δ_H (400 MHz, $CDCl_3$) 5.78 (0.5H, br), 5.45 (0.5H, dd, J=15.4, 9.2 Hz), 5.44 (0.5H, dd, J=14.2, 9.2 Hz), 5.32 (0.5H, br), 4.12 (0.5H, dd, J=10.4, 4 Hz), 4.11 (0.5H, dd, J=7.8, 3.6 Hz), 3.57-3.44 (2H,

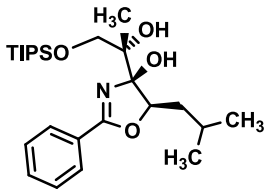
m), 2.45-2.39 (2H, m), 2.00-1.92 (2H, m), 1.86-1.62 (3H, m), 1.58-1.50 (1H, m), 1.45-1.38 (1H, m), 1.32-1.24 (1H, m), 0.93-0.83 (12H, m); δ_C (100 MHz, $CDCl_3$) 213.9, 212.4, 173.3, 173.1, 75.7, 75.3, 74.2 (2), 54.2 (2), 42.5, 41.9, 40.5, 39.9, 30.5, 30.4, 24.7, 24.6, 24.5, 24.3, 23.6, 23.4, 23.2, 23.1 (2), 23.0, 21.9, 21.6, 21.5, 21.3; *m/z* (ESIMS) 270.2 $(M+1)^+$.

Experimental Data for Table 2

General Procedure for Preparation of Oxazolines and Thiazolines from SDEs



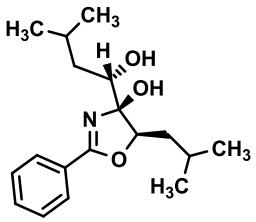
To a stirred solution of SDE in dry $CHCl_3$ (or dry THF), was added the amide or thioamide in dry $CHCl_3$ (or dry THF) at rt. The reaction mixture was stirred at rt and monitored by tlc. Upon completion by tlc, the solvent was evaporated and the residue was dried under vacuum. The product was purified by FCC using ethyl acetate/hexane as the eluent.



T2.3 (X = O)

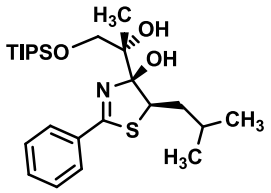
The reaction was carried out following the general procedure, using 110 mg (0.335 mmol) of SDE derived from allene **T2.1** in 5 ml of a 50/50 mixture of dry

THF/$CHCl_3$ and 200 mg (1.653 mmol) of benzamide in 5 ml of a 50/50 mixture of dry THF/$CHCl_3$. The reaction stirred at rt for 3.5 days. FCC using 7% ethyl acetate-hexane gave 122 mg (81%, 3:2 dr) of oxazoline **T2.3 (X=O)** as a clear colorless oil. The diastereomers were readily separable by FCC under the same conditions. The trans stereochemical assignment for the diastereomers was based on NMR data showing an NOE between the 3^o methyl group and the methine proton on the oxazoline ring; IR ν_{max} (neat) / cm^{-1} 3428, 2956, 2866, 1642, 1581, 1463, 1366, 1289, 1105, 702; δ_H (400 MHz, $CDCl_3$) Diastereomer 1: 7.93 (2H, d, J=7.5 Hz), 7.43 (1H, t, J=7.6 Hz), 7.41 (2H, t, J=7.6 Hz), 5.05 (1H, s), 4.70 (1H, dd, J=9.5, 1.7 Hz), 4.21 (1H, d, J=9.3 Hz), 3.59 (1H, d, J=8.9 Hz), 1.92-1.75 (3H, m), 1.48-1.42 (1H, m), 1.28 (3H, s), 1.19-1.05 (21H, m), 0.98 (6H, dd, J=4.4, 1.9 Hz); Diastereomer 2: 7.91 (2H, d, J=7.6 Hz), 7.42 (1H, t, J=7.2 Hz), 7.33 (2H, t, J=7.6 Hz), 4.86 (1H, br), 4.78 (1H, dd, J=8.4, 2.0 Hz), 4.14 (1H, d, J=10.0 Hz), 3.63 (1H, d, J=9.6 Hz), 2.88 (1H, br), 1.91-1.81 (1H, m), 1.75-1.67 (1H, m), 1.49-1.43 (1H, m), 1.09-1.02 (21H, m), 0.99-0.95 (6H, m); δ_c (100 MHz, $CDCl_3$) Diastereomer 1: 166.0, 131.8, 128.8, 128.2, 127.8, 102.7, 81.6, 73.0, 70.0, 38.4, 26.0, 23.7, 21.9, 18.8, 17.9, 11.8; Diastereomer 2: 164.9, 131.6, 128.6, 128.2, 127.9, 102.5, 81.9, 74.6, 69.7, 38.5, 25.8, 23.6, 22.0, 19.5, 17.9, 11.8; *m/z* (ESIMS) 450.2 $(M+1)^+$.



T2.2 (X = O)

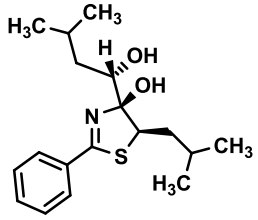
The reaction was carried out following the general procedure, using 52 mg (0.283 mmol) of SDE derived from allene **T1.1** in 2.5 ml of dry $CHCl_3$ and 120 mg (0.987 mmol) of benzamide in 2.5 ml of dry $CHCl_3$. The reaction stirred at rt for 24 h. FCC using 20% ethyl acetate-hexane gave 64 mg (74%, 1:1 dr) of oxazoline **T2.2 (X=O)** as a clear colorless oil. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3358, 2949, 2868, 1634, 1576, 1446, 1364, 1282, 1070, 710; δ_H (400 MHz, $CDCl_3$) 7.86 (0.5 H, d, J=7.5 Hz), 7.81 (0.5 H, d, J=7.7 Hz) (2H, J=7.2 Hz), 7.44-7.37 (1H, m), 7.33-7.25 (2H, m), 4.59 (0.5H, dd, J=8.3, 2.5 Hz), 4.43 (0.5H, dd, J=8.0, 2.6 Hz), 3.79 (0.5H, d, J=10.2 Hz) 3.69 (0.5H, d, J=10.1 Hz), 1.89-1.71 (3H, m), 1.51-1.33 (2H, m), 1.28-1.19 (1H, m), 1.10-1.03 (1H, m), 0.97 (6H, d, J=6.5 Hz), 0.88-0.75 (6H, m); δ_c (100 MHz, $CDCl_3$) 166.6, 165.6, 132.0 (2), 128.7, 128.3 (2), 127.2, 127.0, 99.8, 99.7, 82.2, 81.6, 74.8, 73.7, 38.8, 38.7, 38.3, 38.0, 25.8 (2), 24.7, 24.5, 23.9, 23.5, 21.9 (2), 21.4, 21.3; *m/z* (ESIMS) 306.2 $(M+1)^+$.



T2.3 (X = S)

The reaction was carried out following the general procedure, using 28 mg (0.085 mmol) of SDE derived from allene **T2.1** in 2.5 ml of dry $CHCl_3$ and 116 mg (0.847 mmol) of thiobenzamide in 2.5 ml of dry $CHCl_3$. The reaction stirred at rt for 17 h. FCC using 5% ethyl acetate-hexane gave 60 mg (76%, 3:2 dr) of thiazoline **T2.3 (X=S)** as a clear slightly yellow liquid. The diastereomers were readily separable by FCC under the same conditions; IR ν_{max} (neat) / cm^{-1} 3419, 2945, 2868, 1601, 1576, 1470, 1384, 1241,

1086, 1062, 886, 686; δ_H (400 MHz, $CDCl_3$) Diastereomer 1: 7.87 (2H, d, J=7.5 Hz), 7.47 (1H, t, J=7.0 Hz), 7.39 (2H, t, J=7.6 Hz), 5.33 (1H, s), 4.37 (1H, dd, J=9.6, 2.5 Hz), 4.32 (1H, d, J=9.0 Hz), 3.73 (1H, d, J=9.0 Hz), 1.99-1.92 (2H, m), 1.82-1.75 (1H, m), 1.60-1.54 (1H, m), 1.41 (3H, s), 1.24-1.17 (3H, m), 1.14 (18H, t, J=6.0 Hz), 1.04 (3H, d, J=12.9 Hz), 1.01 (3H, d, J=6.5 Hz); Diastereomer 2: 7.86 (2H, d, J=7.2 Hz), 7.47 (1H, t, J=7.2 Hz), 7.40 (2H, t, J=7.2 Hz), 5.27 (1H, s), 4.39 (1H, d, J=9.7 Hz), 4.35 (1H, d, J=8.1 Hz), 3.70 (1H, d, J=9.9 Hz), 3.12 (1H, br), 1.90-1.83 (2H, m), 1.65-1.55 (1H, m), 1.21-1.10 (21H, m), 1.01 (3H, d, J=2.4 Hz), 0.99 (3H, d, J=2.4 Hz); δ_C (100 MHz, $CDCl_3$) Diastereomer 1: 170.3, 133.2, 131.6, 128.4, 128.3, 110.9, 74.9, 71.2, 52.7, 40.3, 29.6, 24.1, 21.1, 19.4, 17.9, 11.7; Diastereomer 2: 168.7, 133.4, 131.5, 128.3, 110.5, 75.7, 71.3, 53.3, 40.1, 29.0, 24.0, 21.1, 19.5, 17.9, 11.7; *m/z* (ESIMS) 488.3 $(M+23)^+$

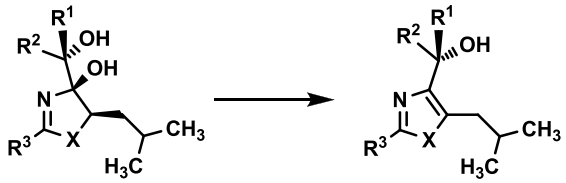


T2.2 (X = S)

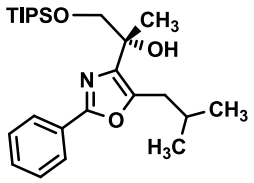
The reaction was carried out following the general procedure, using 60 mg (0.326 mmol) of SDE derived from allene **T1.1** in 2.5 ml of dry $CHCl_3$ and 90 mg (0.657 mmol) of thiobenzamide in 2.5 ml of dry $CHCl_3$. The reaction stirred at rt for 12 h. FCC using 10% ethyl acetate-hexane gave 84 mg (80%, 1:1 dr) of thiazoline **T2.2(X=S)** as a clear slightly yellow oil. The diastereomers were inseparable by FCC; IR ν_{max} (neat) / cm^{-1} 3365, 2958, 2868, 1596, 1572, 1468, 1448, 1368, 1244, 1065, 953, 761; δ_H (400 MHz, $CDCl_3$ with D_2O) 7.85-7.81 (2H, m), 7.50-7.46 (1H, m), 7.42-7.37 (2H,m), 4.09-4.05

(1H, m), 3.84 (0.5H, dd, J=8.2, 2.1 Hz), 3.80 (0.5H, dd, J=6.9, 2.9 Hz), 1.97-1.69 (3H, m), 1.66-1.56 (1H, m), 1.48-1.26 (2H, m), 1.01-0.92 (12H, m); δ_C (100 MHz, $CDCl_3$) 170.9, 170.5, 132.8, 131.8 (2), 128.4, 128.3 (2), 108.2, 108.1, 74.9, 74.2, 52.5 (2), 40.1, 39.4, 39.2, 28.8, 28.7, 24.7 (2), 23.9 (2), 23.8 (2), 21.4 (2), 21.2, 21.1; (ESIMS) 322.2 $(M+1)^+$

General Procedure for Preparation of Oxazoles and Thiazoles from the corresponding azolines.



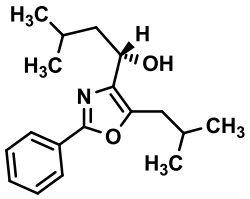
To a stirred solution of oxazoline or thiazoline in dry $CHCl_3$ was added 10 mol% of p-toluenesulfonic acid. The reaction mixture was stirred and refluxed under inert atmosphere and monitored by tlc. Upon completion by tlc, the solvent was evaporated and the residue was dried under vacuum. The product was purified by FCC using ethyl acetate/hexane as the eluent.



T2.5 (X = O)

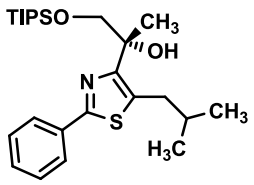
The reaction was carried out following the general procedure, using 48 mg (0.107 mmol) of oxazoline **T2.3(X=O)** in 5 mL of dry $CHCl_3$ and 2 mg (0.011 mmol) of p-

toluenesulfonic acid. The reaction was refluxed for 24 h. FCC using 6% ethyl acetate-hexane gave 32 mg (70%) of oxazole **T2.5(X=O)** as a clear colorless oil; IR ν_{max} (neat) / cm^{-1} 3538, 2945, 2864, 1634, 1556, 1462, 1384, 1094, 1078, 886, 800, 682; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, dd, J=6.0, 2.0 Hz), 7.37-7.32 (3H, m), 4.02 (1H, d, J=9.2 Hz), 3.67 (1H, d, J=8.8 Hz), 3.17 (1H, s), 2.79-2.68 (2H, m), 2.04-1.94 (1H, m), 1.44 (3H, s), 1.04-0.90 (27H, m); δ_c (100 MHz, $CDCl_3$) 158.5, 148.2, 139.9, 129.6, 128.6, 127.9, 126.0, 72.7, 70.6, 34.8, 28.5, 24.9, 22.5 (2), 17.9 (2), 11.9; *m/z* (ESIMS) 432.2 $(M+1)^+$.



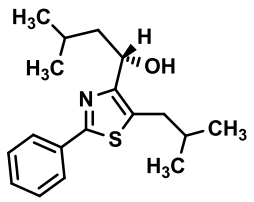
T2.4 (X = O)

The reaction was carried out following the general procedure, using 20 mg (0.066 mmol) of oxazoline **T2.2(X=O)** in 3 mL of dry $CHCl_3$ and 1 mg (0.005 mmol) of p-toluenesulfonic acid. The reaction was refluxed for 24 h. FCC using 20% ethyl acetate-hexane gave 15 mg (80%) of oxazole **T2.4(X=O)** as a clear colorless oil; IR ν_{max} (neat) / cm^{-1} 3370, 2958, 2929, 2868, 1625, 1556, 1482, 1462, 1446, 1364, 1074, 771, 690; δ_H (400 MHz, $CDCl_3$) 7.92-7.90 (2H, m), 7.36-7.32 (3H, m), 4.60 (1H, br), 2.50 (2H, d, J=7.0 Hz), 2.45 (1H, br), 2.00-1.91 (1H, m), 1.86-1.79 (1H, m), 1.71-1.63 (1H, m), 1.56-1.49 (1H, m), 0.90 (12H, dd, J=6.9, 4.4 Hz); δ_c (100 MHz, $CDCl_3$) 159.9, 146.9, 139.1, 129.9, 128.6, 127.6, 126.1, 64.6, 46.2, 33.8, 28.1, 24.6, 23.1, 22.3, 22.2; *m/z* (ESIMS) 288.4 $(M+1)^+$.



T2.5 (X = S)

The reaction was carried out following the general procedure, using 47 mg (0.101 mmol) of thiazoline **T2.2(X=S)** in 5 mL of dry $CHCl_3$ and 2 mg (0.010 mmol) of p-toluenesulfonic acid. The reaction was refluxed for 18 h. FCC using 2% ethyl acetate-hexane gave 33 mg (73%) of thiazole **T2.5(X=S)** as a clear pale yellow oil; IR ν_{max} (neat) / cm^{-1} 3534, 2958, 2864, 1470, 1376, 1278, 1102, 1070, 992, 886, 767, 686; δ_H (400 MHz, $CDCl_3$) 7.87 (2H, d, J=6.4 Hz), 7.42-7.34 (3H, m), 4.24 (1H, d, J=9.2 Hz), 3.83 (1H, d, J=9.2 Hz), 3.54 (1H, br), 3.09-2.94 (2H, m), 2.00-1.90 (1H, m), 1.58 (3H, s), 1.14-1.00 (27H, m); δ_c (100 MHz, $CDCl_3$) 162.4, 154.9, 134.9, 133.9, 129.3, 128.7, 126.1, 75.9, 71.4, 35.8, 31.7, 25.7, 22.5 (2), 17.8 (2), 11.9; *m/z* (ESIMS) 470.4 $(M+23)^+$.

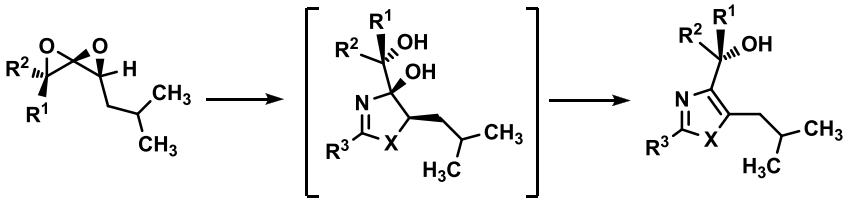


T2.4 (X = S)

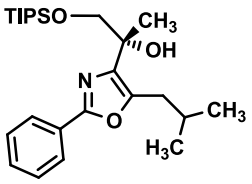
The reaction was carried out following the general procedure, using 49 mg (0.153 mmol) of thiazoline **T2.2(X=S)** in 5 mL of dry $CHCl_3$ and 3 mg (0.016 mmol) of p-toluenesulfonic acid. The reaction was refluxed for 12 h. FCC using 5% ethyl acetate-hexane) gave 41 mg (89%) of thiazole **T2.4(X=S)** as a clear pale yellow oil; IR ν_{max} (neat) / cm^{-1} 3432, 2953, 2868, 1536, 1499, 1466, 1388, 1364, 1070, 976, 767, 690; δ_H (400 MHz, $CDCl_3$) 7.91 (2H, d, J=7.9 Hz), 7.42-7.36 (3H, m), 4.81 (1H, dd, J=7.7, 4.9

Hz). 2.86 (1H, d, J=7.8 Hz), 2.72-2.62 (2H, m), 1.96-1.81 (3H, m), 1.61-1.54 (1H, m), 1.02-0.98 (12H, m); δ_c (100 MHz, $CDCl_3$) 164.9, 155.5, 133.7, 132.2, 129.5, 128.7, 126.2, 66.4, 47.4, 35.0, 31.0, 24.6, 23.4, 22.4, 22.2, 22.1; *m/z* (ESIMS) 304.2 $(M+1)^+$.

General Procedure for a One-Pot Preparation of Oxazoles, Thiazoles and Imidazoles from SDEs



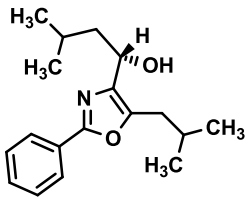
To a stirred solution of SDE in dry $CHCl_3$ (or dry THF), was added the amide or amidine in dry $CHCl_3$ at rt. The reaction mixture was stirred and monitored by tlc. After complete formation of the azoline product, 10 mol% of p-toluenesulfonic acid was added. The reaction mixture was stirred and refluxed while being monitored by tlc. Upon completion of the reaction, the solvent was evaporated and the residue was dried under vacuum. The product was purified by FCC using ethyl acetate/hexane as the eluent.



T2.5 (X = O)

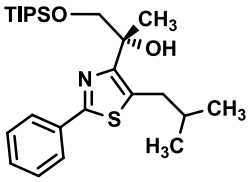
The reaction was carried out following the general procedure, using 55 mg (0.168 mmol) of SDE derived from allene **T2.1** in 5 ml of dry $CHCl_3$ and 102 mg (0.843 mmol) of benzamide in 5 ml of dry $CHCl_3$. The reaction stirred at rt for 2 days. 3 mg (0.016 mmol) of p-toluenesulfonic acid was added and reaction stirred under reflux for 24 h.

FCC using 6% ethyl acetate-hexane gave 34 mg (47%) of oxazole **T2.5(X=O)** as a clear colorless oil.



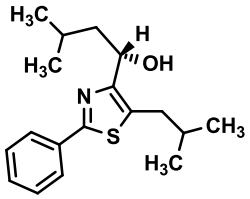
T2.4 (X = O)

The reaction was carried out following the general procedure, using 55 mg (0.297 mmol) of SDE derived from allene **T1.1** in 2 ml of dry $CHCl_3$ and 200 mg (1.653 mmol) of benzamide in 2 ml of dry $CHCl_3$. The reaction stirred at rt for 24 h. 5 mg (0.026 mmol) of p-toluenesulfonic acid was added and reaction stirred under reflux for 24 h. FCC using 10% ethyl acetate-hexane gave 56 mg (66%) of oxazole **T2.4(X=O)** as a clear colorless oil.



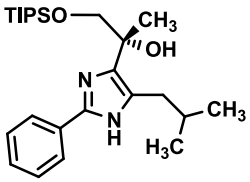
T2.5 (X = S)

The reaction was carried out following the general procedure, using 55 mg (0.168 mmol) of SDE derived from allene **T2.1** in 5 ml of dry $CHCl_3$ and 115 mg (0.843 mmol) of thiobenzamide in 5 ml of dry $CHCl_3$. The reaction stirred at rt for 15 h. 4 mg (0.021 mmol) of p-toluenesulfonic acid was added and reaction stirred under reflux for 18 h. FCC using 2% ethyl acetate-hexane gave 45 mg (60%) of thiazole **T2.5(X=S)** as a clear colorless oil.



T2.4 (X = S)

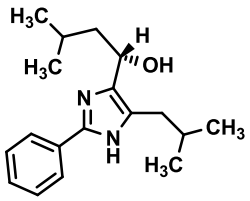
The reaction was carried out following the general procedure, using 54.5 mg (0.296 mmol) of SDE derived from allene **T1.1** in 2 ml of dry $CHCl_3$ and 200 mg (1.653 mmol) of thiobenzamide in 2 ml of dry $CHCl_3$. The reaction stirred at rt for 12 h. 5 mg (0.026 mmol) of p-toluenesulfonic acid was added and reaction stirred under reflux for 12 h. FCC (silica gel, 10% ethyl acetate-hexane) gave 74.5 mg (83%) of thiazole **T2.4(X=S)** as a clear colorless oil.



T2.5 (X = NH)

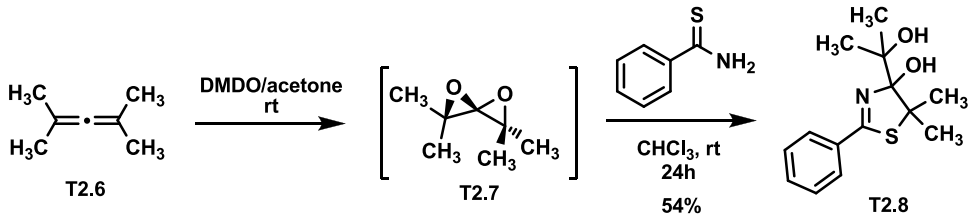
The reaction was carried out following the general procedure, using 55 mg (0.168 mmol) of SDE derived from allene **T2.1** in 5 ml of dry $CHCl_3$ and 100 mg (0.833 mmol) of benzamidine in 5 ml of dry $CHCl_3$. The reaction stirred at rt for 12 h. 3 mg (0.016 mmol) of p-toluenesulfonic acid was added and reaction stirred under reflux for 9 h. FCC using 12% ethyl acetate-hexane gave 56 mg (78%) of imidazole **T2.5(X=NH)** as a clear colorless oil; IR ν_{max} (neat) / cm^{-1} 3240, 2945, 2868, 1576, 1462, 1384, 1364, 1111, 878, 804, 690; δ_H (400 MHz, CD3OD) 7.80 (2H, d, J=7.2 Hz), 7.40 (2H, t, J=7.2 Hz), 7.33 (1H, t, J=7.2 Hz), 3.87 (2H, dd, J=10.8, 9.6 Hz), 2.67 (2H, d, J=7.6 Hz), 2.08-1.97 (1H,

m), 1.59 (3H, s), 1.11-1.00 (21H, m), 0.96 (6H, dd, J=5.2, 1.6 Hz); δ_c (100 MHz, $CDCl_3$) 143.1, 130.4, 128.7, 128.1, 124.9, 76.5, 71.1, 29.4, 25.5, 22.6 (2), 17.9 (2), 11.9; *m/z* (ESIMS) 431.4 $(M+1)^+$.



T2.4 (X = NH)

The reaction was carried out following the general procedure, using 29 mg (0.158 mmol) of SDE derived from allene **T1.1** in 2 ml of dry $CHCl_3$ and 100 mg (0.833 mmol) of benzamidine in 2 ml of dry $CHCl_3$. The reaction stirred at rt for 2.5 days. FCC using 50% ethyl acetate-hexane gave 37.3 mg (83%) of imidazole **T2.4(X=NH)** as a colorless foam; IR ν_{max} (KBr) / cm^{-1} 3197, 3070, 2954, 2869, 1466, 1405, 1350, 1105, 988, 686; δ_H (400 MHz, CD3OD) 7.86 (2H, d, J=7.6 hz), 7.43 (2H, t, J=7.2 Hz), 7.35 (1H, t, J=7.2 Hz), 4.82-4.79 (1H, m), 2.53 (2H, d, J=7.6 Hz), 2.06-1.87 (2H, m), 1.75-1.64 (2H, m), 1.00-0.95 (12H, m); δ_c (100 MHz, $CDCl_3$) 144.7, 130.4, 128.8, 128.4, 125.1, 65.2, 47.2, 34.5, 29.2, 24.9, 23.2, 22.5, 22.4, 22.2; *m/z* (ESIMS) 287.2 $(M+1)^+$.



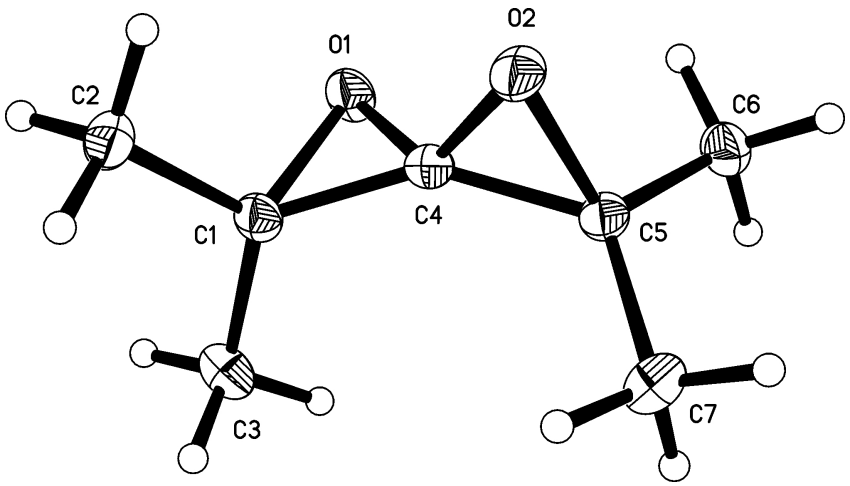
T2.6 **T2.7** **T2.8**

42 mg (0.330 mmol) of SDE **T2.7** (derived from allene **T2.6**) was formed using the general procedure. The solvent was carefully removed under vacuum. To the crude

SDE was added 225 mg of thiobenzamide (1.64 mmol) in 5 ml of $CHCl_3$ in one portion at rt. The reaction stirred for 24 h at rt after which point the $CHCl_3$ was removed under vacuum. FCC using 15% ethyl acetate-hexanes gave 47 mg (54%) of **T2.8** as a clear colorless oil. δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, J=7.2 Hz), 7.47 (1H, t, J=7.6 Hz), 7.40 (2H, t, J=7.6 Hz), 3.9 (1H, br), 2.86 (1H, s), 1.75 (3H, s), 1.65 (3H, s), 1.51 (3H, s), 1.44 (3H, s); δ_c (100 MHz, $CDCl_3$) 171.2, 133.5, 131.7, 128.4, 128.1, 106.8, 76.5, 64.1, 29.6, 25.8, 23.7.

SDE Crystal Structure Data from Table 3

CCDC 649708 (Deposition # from the Cambridge Crystallographic Data Centre)



Crystal data and structure refinement for SDE

Identification code	epoxy1_b	
Empirical formula	C7 H12 O2	
Formula weight	128.17	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 10.7367(6) Å	α= 90°.
	b = 10.7367(6) Å	β= 90°.
	c = 25.6705(15) Å	γ = 90°.
Volume	2959.2(8) $Å^3$	
Z	16	
Density (calculated)	1.151 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	1120	
Crystal size	.60 x .51 x .10 mm^3	
Theta range for data collection	2.06 to 30.50°.	
Index ranges	-15<=h<=14, -15<=k<=15, -36<=l<=36	
Reflections collected	17976	
Independent reflections	2270 [R(int) = 0.0280]	
Completeness to theta = 30.50°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9999 and 0.8614	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2270 / 0 / 130	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1058	
R indices (all data)	R1 = 0.0520, wR2 = 0.1128	
Largest diff. peak and hole	0.503 and -0.150 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for SDE. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
O(1)	6904(1)	5028(1)	806(1)	20(1)
O(2)	7527(1)	4403(1)	1695(1)	20(1)
C(1)	8314(1)	4994(1)	767(1)	16(1)
C(2)	8816(1)	3740(1)	621(1)	22(1)
C(3)	8875(1)	6102(1)	501(1)	22(1)
C(4)	7640(1)	5140(1)	1250(1)	15(1)
C(5)	7494(1)	5814(1)	1733(1)	16(1)
C(6)	6240(1)	6316(1)	1879(1)	22(1)
C(7)	8602(1)	6375(1)	1999(1)	22(1)

Bond lengths [Å] and angles [°] for SDE

O(1)-C(4)	1.3934(10)	C(3)-H(3B)	0.962(16)
O(1)-C(1)	1.5168(10)	C(3)-H(3C)	0.946(14)
O(2)-C(4)	1.3932(10)	C(4)-C(5)	1.4440(12)
O(2)-C(5)	1.5177(10)	C(5)-C(7)	1.4975(12)
C(1)-C(4)	1.4455(12)	C(5)-C(6)	1.4986(12)
C(1)-C(3)	1.4978(12)	C(6)-H(6A)	0.959(14)
C(1)-C(2)	1.4981(12)	C(6)-H(6B)	0.944(16)
C(2)-H(2A)	0.961(14)	C(6)-H(6C)	0.974(14)
C(2)-H(2B)	0.959(17)	C(7)-H(7A)	0.960(15)
C(2)-H(2C)	0.976(14)	C(7)-H(7B)	0.960(17)
C(3)-H(3A)	0.952(14)	C(7)-H(7C)	0.963(13)
C(4)-O(1)-C(1)	59.38(5)	O(2)-C(4)-C(1)	133.25(7)
C(4)-O(2)-C(5)	59.30(5)	O(1)-C(4)-C(1)	64.56(6)
C(4)-C(1)-C(3)	120.41(8)	C(5)-C(4)-C(1)	147.79(7)
C(4)-C(1)-C(2)	119.46(8)	C(4)-C(5)-C(7)	120.46(8)
C(3)-C(1)-C(2)	117.10(8)	C(4)-C(5)-C(6)	119.47(8)
C(4)-C(1)-O(1)	56.05(5)	C(7)-C(5)-C(6)	117.06(8)
C(3)-C(1)-O(1)	114.37(7)	C(4)-C(5)-O(2)	56.05(5)
C(2)-C(1)-O(1)	113.42(7)	C(7)-C(5)-O(2)	114.41(7)
C(1)-C(2)-H(2A)	108.6(8)	C(6)-C(5)-O(2)	113.37(7)
C(1)-C(2)-H(2B)	110.0(8)	C(5)-C(6)-H(6A)	108.9(8)
H(2A)-C(2)-H(2B)	107.2(12)	C(5)-C(6)-H(6B)	110.5(8)
C(1)-C(2)-H(2C)	111.3(8)	H(6A)-C(6)-H(6B)	106.5(12)
H(2A)-C(2)-H(2C)	109.5(11)	C(5)-C(6)-H(6C)	110.9(8)
H(2B)-C(2)-H(2C)	110.1(12)	H(6A)-C(6)-H(6C)	110.3(11)
C(1)-C(3)-H(3A)	110.0(8)	H(6B)-C(6)-H(6C)	109.6(11)
C(1)-C(3)-H(3B)	110.0(9)	C(5)-C(7)-H(7A)	109.8(8)
H(3A)-C(3)-H(3B)	110.7(12)	C(5)-C(7)-H(7B)	110.0(9)
C(1)-C(3)-H(3C)	108.5(9)	H(7A)-C(7)-H(7B)	111.4(13)
H(3A)-C(3)-H(3C)	109.6(12)	C(5)-C(7)-H(7C)	108.2(8)
H(3B)-C(3)-H(3C)	108.0(12)	H(7A)-C(7)-H(7C)	109.6(12)
O(2)-C(4)-O(1)	124.93(7)	H(7B)-C(7)-H(7C)	107.8(12)
O(2)-C(4)-C(5)	64.65(6)		
O(1)-C(4)-C(5)	133.29(7)		

Anisotropic displacement parameters ($Å^2 x\ 10^3$) for spirodiepoxide. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	12(1)	30(1)	18(1)	-3(1)	-1(1)	-1(1)
O(2)	29(1)	12(1)	18(1)	1(1)	2(1)	-1(1)
C(1)	12(1)	19(1)	17(1)	-1(1)	-1(1)	0(1)
C(2)	21(1)	21(1)	24(1)	-7(1)	2(1)	1(1)
C(3)	18(1)	24(1)	24(1)	5(1)	4(1)	1(1)
C(4)	14(1)	14(1)	17(1)	1(1)	-1(1)	-1(1)
C(5)	19(1)	12(1)	17(1)	1(1)	1(1)	0(1)
C(6)	21(1)	21(1)	24(1)	-2(1)	6(1)	0(1)
C(7)	23(1)	19(1)	24(1)	-4(1)	-5(1)	1(1)

Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for SDE

	x	y	z	U(eq)
H(2A)	9702(13)	3741(13)	676(6)	30(3)
H(2B)	8678(13)	3586(13)	258(7)	32(3)
H(2C)	8436(13)	3081(13)	829(6)	31(3)
H(3A)	8498(13)	6847(13)	626(6)	31(3)
H(3B)	8775(13)	6031(13)	130(6)	30(3)
H(3C)	9738(13)	6118(13)	575(6)	29(3)
H(6A)	6238(13)	7201(13)	1827(5)	27(3)
H(6B)	6081(13)	6184(13)	2237(6)	30(3)
H(6C)	5586(12)	5928(13)	1672(5)	29(3)
H(7A)	9352(13)	5997(13)	1871(6)	33(4)
H(7B)	8527(14)	6279(14)	2370(7)	34(4)
H(7C)	8612(12)	7254(13)	1924(5)	26(3)

Torsion angles [°] for SDE

C(4)-O(1)-C(1)-C(3)	-111.40(8)
C(4)-O(1)-C(1)-C(2)	110.76(8)
C(5)-O(2)-C(4)-O(1)	-126.48(9)
C(5)-O(2)-C(4)-C(1)	147.10(10)
C(1)-O(1)-C(4)-O(2)	-126.39(9)
C(1)-O(1)-C(4)-C(5)	147.04(10)
C(3)-C(1)-C(4)-O(2)	-144.50(9)
C(2)-C(1)-C(4)-O(2)	15.23(13)
O(1)-C(1)-C(4)-O(2)	115.03(10)
C(3)-C(1)-C(4)-O(1)	100.47(8)
C(2)-C(1)-C(4)-O(1)	-99.80(8)
C(3)-C(1)-C(4)-C(5)	-31.55(18)
C(2)-C(1)-C(4)-C(5)	128.19(13)
O(1)-C(1)-C(4)-C(5)	-132.02(15)
O(2)-C(4)-C(5)-C(7)	100.49(8)
O(1)-C(4)-C(5)-C(7)	-144.42(9)
C(1)-C(4)-C(5)-C(7)	-31.59(18)
O(2)-C(4)-C(5)-C(6)	-99.72(8)
O(1)-C(4)-C(5)-C(6)	15.37(13)
C(1)-C(4)-C(5)-C(6)	128.20(13)
O(1)-C(4)-C(5)-O(2)	115.09(10)
C(1)-C(4)-C(5)-O(2)	-132.08(15)
C(4)-O(2)-C(5)-C(7)	-111.44(8)
C(4)-O(2)-C(5)-C(6)	110.80(8)

Experimental Data for Figure 5

Computational Methodology

All structures were fully optimized by analytical gradient methods using the Gaussian03 suite[89] and density functional (DFT) calculations at the 6-31+G(d) level, the exchange functional of Becke[25a] and the correlation functional of Lee, Yang and Parr.[25b,c] Vibrational analyses established the nature of all stationary points as energy minima (no imaginary frequencies).

(89) *[Full citation to reference 18a] Gaussian 03, Revision B.02*. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J.R.; Montgomery, J. A. Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian,H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen,W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.: Gaussian, Inc.: Pittsburgh, 2003.

All calculations carried out at B3LYP/6-31+G(d) level unless specified otherwise. Solvent simulations used the SCIPCM protocol incorporated in Gaussian03 RevB.02.

Transition State F5.4 for 2-Pyrrolidinone Reaction with SDE F5.1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.540033	0.398282	-0.448081
2	8	0	0.662663	1.093340	-1.024801
3	7	0	1.346162	-0.470231	0.540441
4	6	0	3.021305	0.462532	-0.788860
5	1	0	3.422640	1.404605	-0.391979
6	1	0	3.170232	0.476999	-1.871795
7	6	0	3.603402	-0.777385	-0.080045
8	1	0	3.652737	-1.618345	-0.780193
9	1	0	4.608587	-0.614163	0.317555
10	6	0	2.576246	-1.088713	1.036131
11	1	0	2.426871	-2.160948	1.194072
12	1	0	2.861806	-0.641642	1.997633
13	1	0	0.376031	-0.679659	0.879784
14	8	0	-3.053733	0.814001	0.210916
15	6	0	-1.950629	0.204725	-0.056446
16	6	0	-1.153888	1.423486	-0.319960
17	8	0	-1.303654	-0.855756	0.914640
18	6	0	-1.718095	-1.190450	-0.446060
19	6	0	-0.789154	2.334183	0.816873
20	1	0	-0.051006	3.071458	0.489917
21	1	0	-1.689572	2.864604	1.140402
22	1	0	-0.405133	1.770417	1.672126
23	1	0	-0.872955	-1.417959	-1.106295
24	1	0	-1.378934	1.892925	-1.271217
25	6	0	-2.876465	-2.149059	-0.560096
26	1	0	-3.184690	-2.245794	-1.609175
27	1	0	-2.590517	-3.142619	-0.193222
28	1	0	-3.727970	-1.786535	0.022523

imaginary frequency --- -375.7902 cm**-1
Zero-point correction= 0.234511
(Hartree/Particle)
Thermal correction to Energy= 0.248244
Thermal correction to Enthalpy= 0.249189
Thermal correction to Gibbs Free Energy= 0.194147
Sum of electronic and zero-point Energies= -632.113075
Sum of electronic and thermal Energies= -632.099341
Sum of electronic and thermal Enthalpies= -632.098397
Sum of electronic and thermal Free Energies= -632.153439

Single point calculation in acetone: HF= -632.369817748

IRC calculation 50 steps on Transition State F5.4:

Forward trajectory

Last Point Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.477758	0.375109	-0.358981
2	8	0	0.514061	1.130453	-0.914406
3	7	0	1.297892	-0.509445	0.547422
4	6	0	2.938030	0.521590	-0.795871
5	1	0	3.346789	1.450603	-0.375114
6	1	0	3.048296	0.582680	-1.882766
7	6	0	3.573394	-0.743787	-0.162827
8	1	0	3.636246	-1.543983	-0.908961
9	1	0	4.581643	-0.569422	0.224131
10	6	0	2.561329	-1.129699	0.942289
11	1	0	2.426427	-2.211188	1.048232
12	1	0	2.852801	-0.742027	1.928276
13	1	0	-0.173564	-0.955044	0.896107
14	8	0	-3.071864	0.779792	0.221218
15	6	0	-2.007283	0.375804	-0.215809
16	6	0	-0.859822	1.446328	-0.346681
17	8	0	-1.166070	-1.119750	0.937243
18	6	0	-1.688855	-1.085145	-0.402872
19	6	0	-0.723155	2.275627	0.924702
20	1	0	-0.048521	3.119898	0.749537
21	1	0	-1.709707	2.659005	1.196639
22	1	0	-0.348671	1.673944	1.757717
23	1	0	-0.894318	-1.260485	-1.140941
24	1	0	-1.211744	2.091272	-1.156942
25	6	0	-2.842703	-2.058544	-0.607486
26	1	0	-3.161105	-2.062491	-1.657193
27	1	0	-2.513725	-3.068515	-0.339473
28	1	0	-3.697272	-1.785796	0.017562

IRC calculation 50 steps on Transition State F5.4:

Reverse trajectory

Last Point Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.369059	.124621	-.691430
2	8	0	-1.283827	.170730	.579882
3	7	0	-.372018	.104795	-1.505920
4	6	0	-2.687392	.104477	-1.470854
5	1	0	-3.130417	1.094631	-1.413008
6	1	0	-3.392238	-.594310	-1.039917
7	6	0	-2.234638	-.255092	-2.901962
8	1	0	-2.349431	-1.319624	-3.071241
9	1	0	-2.799298	.264982	-3.665222
10	6	0	-.742191	.120529	-2.914746
11	1	0	-.130590	-.580248	-3.465691
12	1	0	-.570784	1.109737	-3.325136
13	1	0	.626997	.058637	-1.099360
14	8	0	1.855537	.143271	2.989692
15	6	0	1.365468	-.121169	1.932540
16	6	0	.011802	.642942	1.770706
17	8	0	1.892717	-.007134	-.273993
18	6	0	2.008566	-.857440	.772517
19	6	0	.218780	2.119509	1.562832
20	1	0	-.715819	2.611013	1.329593
21	1	0	.589041	2.512273	2.504610
22	1	0	.953905	2.300618	.792591
23	6	0	1.376906	-2.242536	.563256
24	1	0	1.534068	-2.897580	1.417824
25	1	0	.308948	-2.175101	.376785
26	1	0	1.839070	-2.697399	-.306861
27	1	0	-.672745	.381787	2.552087
28	1	0	3.044985	-1.009753	1.083694

2-Pyrrolidinone

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.904431	0.001873	-0.007214
2	8	0	-2.126763	-0.012223	-0.039024
3	7	0	-0.086755	-1.096882	-0.076377
4	6	0	0.006530	1.224724	0.136002
5	1	0	-0.076618	1.583540	1.170544
6	1	0	-0.331559	2.032749	-0.517979
7	6	0	1.416283	0.694718	-0.185228
8	1	0	1.633597	0.830917	-1.250606
9	1	0	2.209412	1.187797	0.384201
10	6	0	1.329707	-0.817857	0.132095
11	1	0	1.954231	-1.423149	-0.533391
12	1	0	1.629662	-1.030819	1.169310
13	1	0	-0.485875	-2.025824	-0.029175

Low frequencies --- -21.4023 -11.5592 -7.0528 -0.0008 -0.0005
0.0002

Zero-point correction= 0.111256
(Hartree/Particle)
Thermal correction to Energy= 0.116667
Thermal correction to Enthalpy= 0.117611
Thermal correction to Gibbs Free Energy= 0.082418
Sum of electronic and zero-point Energies= -286.533120
Sum of electronic and thermal Energies= -286.527709
Sum of electronic and thermal Enthalpies= -286.526764
Sum of electronic and thermal Free Energies= -286.561957

Single point calculation in acetone: HF= -286.6607634

SDE F5.1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.075292	-1.114012	-0.609849
2	6	0	0.000119	-0.481669	-0.000528
3	6	0	-1.326584	-0.091166	0.440027
4	8	0	1.075382	-1.113517	0.610259
5	6	0	1.327310	-0.091553	-0.439929
6	6	0	2.027840	1.165308	0.003174
7	1	0	1.958546	1.932191	-0.778524
8	1	0	1.585988	1.560700	0.923083
9	1	0	3.090167	0.965419	0.186787
10	1	0	1.686280	-0.544393	-1.365429
11	6	0	-2.028605	1.164824	-0.003345
12	1	0	-1.960459	1.931575	0.778416
13	1	0	-1.587147	1.560787	-0.923070
14	1	0	-3.090476	0.963184	-0.187091
15	1	0	-1.684106	-0.543705	1.366150

Low frequencies --- -10.0102 -9.2305 -0.0016 -0.0015 -0.0013
1.429

Zero-point correction= 0.123051
(Hartree/Particle)
Thermal correction to Energy= 0.130450
Thermal correction to Enthalpy= 0.131394
Thermal correction to Gibbs Free Energy= 0.091824
Sum of electronic and zero-point Energies= -345.602713
Sum of electronic and thermal Energies= -345.595315
Sum of electronic and thermal Enthalpies= -345.594371
Sum of electronic and thermal Free Energies= -345.633940

Single point calculation in acetone: HF= -345.736065

Product F5.5 from SDE F5.1 and 2-Pyrrolidinone

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.422628	0.502047	-0.079550
2	8	0	-0.582415	1.541235	-0.045283
3	7	0	-1.123075	-0.685390	-0.458840
4	6	0	-2.852262	0.743401	0.344140
5	1	0	-3.368374	1.329496	-0.428386
6	1	0	-2.907891	1.313810	1.276436
7	6	0	-3.373051	-0.705280	0.450181
8	1	0	-3.361124	-1.032311	1.495720
9	1	0	-4.394696	-0.823620	0.077310
10	6	0	-2.336580	-1.518836	-0.374155
11	1	0	-2.092654	-2.482382	0.085380
12	1	0	-2.691599	-1.727002	-1.392815
13	1	0	0.556232	-1.337623	-1.204185
14	8	0	1.470674	0.449534	1.633377
15	6	0	1.469680	0.278030	0.429534
16	6	0	0.778870	1.313112	-0.493743
17	8	0	1.519397	-1.337658	-1.409710
18	6	0	2.194286	-0.905019	-0.236817
19	1	0	0.742940	0.938550	-1.518888
20	6	0	2.454128	-2.044788	0.748839
21	1	0	3.044101	-1.701494	1.604250
22	1	0	1.507994	-2.447752	1.127123
23	1	0	2.994543	-2.845176	0.234146
24	1	0	3.162390	-0.508921	-0.585587
25	6	0	1.488822	2.658305	-0.417892
26	1	0	1.516044	3.014261	0.616376
27	1	0	2.516990	2.563742	-0.785485
28	1	0	0.967785	3.393433	-1.039796

Low frequencies --- -5.6462 0.0004 0.0010 0.0011 8.0508 10.4336

Zero-point correction= 0.238680 (Hartree/Particle)
Thermal correction to Energy= 0.252186
Thermal correction to Enthalpy= 0.253131
Thermal correction to Gibbs Free Energy= 0.198296
Sum of electronic and zero-point Energies= -632.186718
Sum of electronic and thermal Energies= -632.173211
Sum of electronic and thermal Enthalpies= -632.172267
Sum of electronic and thermal Free Energies= -632.227102

Single point calculation in acetone: HF= -632.4264691

Transition state F5.9 for Reaction of Chloride Ion with SDE F5.1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.384359	1.753410	-0.336691
2	6	0	0.975292	0.489218	-0.260562
3	6	0	-0.392494	1.016028	-0.182834
4	1	0	-0.797545	1.367455	-1.120216
5	8	0	1.438789	-0.540159	-1.153894
6	6	0	1.664036	-0.692996	0.282473
7	1	0	2.712914	-0.530753	0.555971
8	17	0	-2.219379	-0.718174	-0.381258
9	6	0	-0.930718	1.574651	1.107666
10	1	0	-0.411076	2.511564	1.341832
11	1	0	-2.003010	1.760681	1.020952
12	1	0	-0.771861	0.870577	1.931302
13	6	0	0.999842	-1.876680	0.942864
14	1	0	1.082968	-1.799710	2.037042
15	1	0	-0.057654	-1.928050	0.667574
16	1	0	1.493770	-2.810133	0.633972

Low frequencies --- -284.0059 -10.8629 -0.0015 0.0004 0.0026
4.7547

HF=-806.0006657

Zero-point correction= 0.121822
(Hartree/Particle)
Thermal correction to Energy= 0.130976
Thermal correction to Enthalpy= 0.131920
Thermal correction to Gibbs Free Energy= 0.087386
Sum of electronic and zero-point Energies= -805.878843
Sum of electronic and thermal Energies= -805.869690
Sum of electronic and thermal Enthalpies= -805.868746
Sum of electronic and thermal Free Energies= -805.913280

Single point energy in acetone: -806.091314066

Product from Reaction of Chloride Ion with SDE F5.1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.896325	-0.926222	-0.857428
2	6	0	-0.388735	-0.335205	0.642890
3	6	0	-1.798516	-0.019844	0.162678
4	8	0	-0.102138	-0.845397	1.725460
5	6	0	0.677467	-0.256353	-0.469107
6	6	0	1.448830	-1.547996	-0.660136
7	1	0	2.252231	-1.431115	-1.397254
8	1	0	1.872585	-1.882635	0.291788
9	1	0	0.736091	-2.301776	-1.014423
10	1	0	0.234215	0.096125	-1.395688
11	6	0	-2.039327	1.451514	-0.251681
12	1	0	-1.944606	2.146725	0.598355
13	1	0	-1.339979	1.762269	-1.038900
14	1	0	-3.055850	1.529019	-0.662360
15	1	0	-2.472522	-0.226193	1.028155
16	17	0	1.900425	1.101637	0.005777

Low frequencies --- -14.5721 -9.2334 -4.5203 -0.0035 -0.0024 0.0018

HF=-806.0336296

Zero-point correction= 0.122933 (Hartree/Particle)
Thermal correction to Energy= 0.132327
Thermal correction to Enthalpy= 0.133271
Thermal correction to Gibbs Free Energy= 0.087993
Sum of electronic and zero-point Energies= -805.910697
Sum of electronic and thermal Energies= -805.901303
Sum of electronic and thermal Enthalpies= -805.900359
Sum of electronic and thermal Free Energies= -805.945637

Single point energy in acetone: -806.121490729

Transition State F5.2 for Reaction of Water with SDE F5.1

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.508422	-1.969420	-0.353919
2	6	0	-0.039469	-0.840146	-0.145165
3	6	0	1.218790	-0.092372	-0.182010
4	8	0	-1.204905	-0.023505	-1.158128
5	6	0	-1.414765	-0.470284	0.184803
6	6	0	-1.808088	0.559939	1.229151
7	1	0	-1.902091	0.091333	2.216839
8	1	0	-1.086014	1.380121	1.309312
9	1	0	-2.781198	0.990097	0.962663
10	1	0	-2.072380	-1.347535	0.225226
11	6	0	2.054613	0.149932	1.028035
12	1	0	2.795918	0.928414	0.826699
13	1	0	1.452907	0.416599	1.901766
14	1	0	2.599853	-0.774802	1.258347
15	1	0	1.709332	-0.118322	-1.146122
16	8	0	0.589123	1.835729	-0.853664
17	1	0	0.334452	2.507412	-0.200505
18	1	0	-0.258380	1.341838	-1.117422

Low frequencies --- -430.0223 -13.5297 -8.1487 0.0008 0.0011
0.0011

Zero-point correction= 0.146066
(Hartree/Particle)
Thermal correction to Energy= 0.155816
Thermal correction to Enthalpy= 0.156760
Thermal correction to Gibbs Free Energy= 0.111963
Sum of electronic and zero-point Energies= -421.967177
Sum of electronic and thermal Energies= -421.957428
Sum of electronic and thermal Enthalpies= -421.956484
Sum of electronic and thermal Free Energies= -422.001281

Product F5.3 from Reaction of Water with SDE 7

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.288832	1.854595	-0.116530
2	6	0	-0.064686	0.665585	-0.257305
3	6	0	-1.195702	-0.380442	-0.255720
4	8	0	1.453621	-1.196920	-0.847309
5	6	0	1.379249	0.156976	-0.421229
6	6	0	2.198976	0.423064	0.850542
7	1	0	2.157691	1.482986	1.121648
8	1	0	1.819009	-0.169042	1.692377
9	1	0	3.241048	0.137956	0.674878
10	1	0	1.807789	0.741851	-1.243705
11	6	0	-2.571507	0.212687	-0.000395
12	1	0	-3.323696	-0.582759	-0.004046
13	1	0	-2.606255	0.738062	0.961693
14	1	0	-2.824327	0.943026	-0.775101
15	1	0	-1.173920	-0.895244	-1.222803
16	8	0	-0.852841	-1.411163	0.699891
17	1	0	-1.073082	-1.092300	1.590619
18	1	0	1.002184	-1.743850	-0.179340

Low frequencies --- -0.0013 -0.0008 0.0007 5.2750 15.1679 18.5141

Zero-point correction= 0.151305 (Hartree/Particle)
Thermal correction to Energy= 0.160729
Thermal correction to Enthalpy= 0.161673
Thermal correction to Gibbs Free Energy= 0.117172
Sum of electronic and zero-point Energies= -422.072616
Sum of electronic and thermal Energies= -422.063193
Sum of electronic and thermal Enthalpies= -422.062249
Sum of electronic and thermal Free Energies= -422.106749

Methanol complex with SDE F5.6

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.605303	-1.395966	-0.441430
2	6	0	-0.701645	-0.119460	0.085855
3	6	0	-1.752236	-1.053692	0.444266
4	8	0	0.295645	0.531058	0.815922
5	6	0	-0.313537	1.200392	-0.376103
6	6	0	-1.096190	2.455010	-0.101309
7	1	0	-1.685760	2.728547	-0.985192
8	1	0	-1.774449	2.322263	0.747050
9	1	0	-0.415968	3.285127	0.120850
10	1	0	0.389536	1.234760	-1.208995
11	6	0	-3.116334	-1.069731	-0.191624
12	1	0	-3.845269	-0.582996	0.468213
13	1	0	-3.110244	-0.548574	-1.153817
14	1	0	-3.447153	-2.101581	-0.357652
15	1	0	-1.664979	-1.533255	1.420084
16	1	0	2.195670	0.312696	0.365333
17	6	0	3.644813	-0.939677	-0.078783
18	1	0	4.568008	-0.876615	-0.662164
19	1	0	3.901912	-1.252395	0.944741
20	1	0	2.996614	-1.705086	-0.530484
21	8	0	3.047515	0.349915	-0.107213

Low frequencies --- -8.7743 0.0014 0.0015 0.0016 2.1870 4.9995

Zero-point correction= 0.176156 (Hartree/Particle)
Thermal correction to Energy= 0.188486
Thermal correction to Enthalpy= 0.189430
Thermal correction to Gibbs Free Energy= 0.135104
Sum of electronic and zero-point Energies= -461.283344
Sum of electronic and thermal Energies= -461.271014
Sum of electronic and thermal Enthalpies= -461.270070
Sum of electronic and thermal Free Energies= -461.324396

Transition state F5.7 for Reaction of Water with Methanol Complex F5.6

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.712061	-1.534934	-1.240445
2	6	0	-0.730731	-0.401689	-0.692549
3	6	0	-1.731273	-0.891096	0.243385
4	8	0	0.646688	0.482855	0.391757
5	6	0	0.068631	0.825821	-0.844595
6	6	0	-0.630379	2.178421	-0.924723
7	1	0	-1.062199	2.343307	-1.920010
8	1	0	-1.425407	2.273430	-0.176895
9	1	0	0.111397	2.962574	-0.735941
10	1	0	0.773361	0.709345	-1.682073
11	6	0	-3.193639	-0.844192	-0.024923
12	1	0	-3.710625	-0.684108	0.926977
13	1	0	-3.467687	-0.060059	-0.734811
14	1	0	-3.525468	-1.814960	-0.414217
15	1	0	-1.359464	-1.560935	1.007459
16	1	0	2.434277	0.361627	0.214995
17	6	0	3.871756	-0.971020	0.365559
18	1	0	4.923065	-1.027095	0.064461
19	1	0	3.816626	-1.134938	1.453959
20	1	0	3.325505	-1.785952	-0.136160
21	8	0	3.391386	0.307034	-0.008737
22	8	0	-1.388318	0.497951	2.054433
23	1	0	-1.766634	1.376072	2.217010
24	1	0	-0.494493	0.640975	1.606266

Low frequencies --- -352.8999 -7.8384 -4.3397 -3.4995 -0.0010 -0.0005

Zero-point correction= 0.198852 (Hartree/Particle)
Thermal correction to Energy= 0.213716
Thermal correction to Enthalpy= 0.214660
Thermal correction to Gibbs Free Energy= 0.154441
Sum of electronic and zero-point Energies= -537.652828
Sum of electronic and thermal Energies= -537.637964
Sum of electronic and thermal Enthalpies= -537.637020
Sum of electronic and thermal Free Energies= -537.697239

Product F5.8 from Reaction of Water with Methanol Complex F5.6

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-2.030455	1.556458	-0.775500
2	6	0	-1.365230	0.595880	-0.434480
3	6	0	-1.994748	-0.796939	-0.236107
4	8	0	0.825674	-0.504841	-0.124427
5	6	0	0.142829	0.752124	-0.175971
6	6	0	0.405564	1.612400	1.068158
7	1	0	-0.091698	2.582851	0.970422
8	1	0	0.034069	1.117853	1.974059
9	1	0	1.482791	1.770232	1.178633
10	1	0	0.550308	1.264119	-1.054345
11	6	0	-3.512696	-0.790906	-0.320573
12	1	0	-3.895204	-1.806335	-0.176372
13	1	0	-3.949798	-0.129597	0.437528
14	1	0	-3.840879	-0.422655	-1.296916
15	1	0	-1.574369	-1.457666	-1.003741
16	1	0	2.683042	-0.270042	0.108329
17	6	0	4.481562	-0.665171	-0.597096
18	1	0	5.494649	-0.320035	-0.370272
19	1	0	4.450408	-1.757666	-0.464245
20	1	0	4.264347	-0.433427	-1.651272
21	8	0	3.602374	0.007150	0.291319
22	8	0	-1.513604	-1.353834	1.008981
23	1	0	-2.035451	-0.983888	1.739929
24	1	0	0.412179	-1.037537	0.581694

Low frequencies --- -13.5253 -7.3946 -0.0010 -0.0008 -0.0003 3.7927

Zero-point correction= 0.204535 (Hartree/Particle)
Thermal correction to Energy= 0.218832
Thermal correction to Enthalpy= 0.219777
Thermal correction to Gibbs Free Energy= 0.160479
Sum of electronic and zero-point Energies= -537.754475
Sum of electronic and thermal Energies= -537.740178
Sum of electronic and thermal Enthalpies= -537.739234
Sum of electronic and thermal Free Energies= -537.798531

Transition state for Reaction of Water with Methanol Complex F5.6: (Proximal epoxide complexation followed by water addition to proximal epoxide)

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.591335	-0.553642	-1.294177
2	6	0	0.407444	-0.414151	-0.480710
3	6	0	0.196660	1.008199	-0.134578
4	8	0	0.681223	-1.303520	0.775911
5	6	0	1.600751	-1.261977	-0.355017
6	6	0	3.028002	-0.829615	-0.103620
7	1	0	3.582037	-0.799982	-1.049817
8	1	0	3.106131	0.160145	0.358599
9	1	0	3.526759	-1.552353	0.554375
10	1	0	1.534248	-2.176534	-0.949749
11	6	0	0.809399	2.124327	-0.909089
12	1	0	0.678729	3.077575	-0.389091
13	1	0	1.866048	1.952068	-1.135600
14	1	0	0.266978	2.193603	-1.861388
15	1	0	-0.774802	1.185060	0.317528
16	8	0	0.965425	1.121308	1.735516
17	1	0	1.893743	1.401515	1.799542
18	1	0	0.960392	0.116688	1.749392
19	1	0	-2.262776	-0.111265	-0.635926
20	6	0	-3.850738	-0.602092	0.432469
21	1	0	-4.572003	-0.055393	1.047809
22	1	0	-4.403179	-1.146630	-0.348280
23	1	0	-3.330055	-1.332975	1.069246
24	8	0	-2.957983	0.353396	-0.120171

Low frequencies --- -361.8064 -10.9162 -2.7974 -0.0005 0.0002 0.0003

Zero-point correction= 0.200200 (Hartree/Particle)
Thermal correction to Energy= 0.214271
Thermal correction to Enthalpy= 0.215215
Thermal correction to Gibbs Free Energy= 0.158248
Sum of electronic and zero-point Energies= -537.651619
Sum of electronic and thermal Energies= -537.637549
Sum of electronic and thermal Enthalpies= -537.636604
Sum of electronic and thermal Free Energies= -537.693571

Product from Transition State for Reaction of Water with Methanol Complex F5.6: (Proximal epoxide complexation followed by water addition to proximal epoxide)

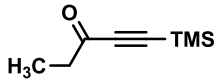
Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.644672	-0.805464	0.206644
2	6	0	-0.433297	-0.298509	-0.063816
3	6	0	-0.543434	1.216253	-0.302337
4	8	0	-2.565994	-0.718354	-1.216013
5	6	0	-1.678029	-1.186339	-0.210045
6	6	0	-2.363315	-1.384598	1.151886
7	1	0	-1.667257	-1.820841	1.877407
8	1	0	-2.736104	-0.434365	1.548236
9	1	0	-3.209479	-2.067624	1.022799
10	1	0	-1.309446	-2.152144	-0.568828
11	6	0	0.484885	2.032265	0.473564
12	1	0	0.353135	3.098883	0.250915
13	1	0	0.363066	1.884073	1.551597
14	1	0	1.505031	1.756722	0.194068
15	1	0	-0.385474	1.350603	-1.385714
16	8	0	-1.893154	1.604103	0.026495
17	1	0	-1.982193	2.560559	-0.106187
18	1	0	-2.871206	0.166038	-0.942390
19	1	0	2.506417	-0.275174	0.122564
20	6	0	4.370412	-0.832535	-0.199561
21	1	0	5.318245	-0.306097	-0.343880
22	1	0	4.469639	-1.495279	0.673166
23	1	0	4.174570	-1.447755	-1.090678
24	8	0	3.370441	0.157611	-0.004778

Zero-point correction= (Hartree/Particle)	0.204297
Thermal correction to Energy=	0.218654
Thermal correction to Enthalpy=	0.219598
Thermal correction to Gibbs Free Energy=	0.160369
Sum of electronic and zero-point Energies=	-537.753619
Sum of electronic and thermal Energies=	-537.739262
Sum of electronic and thermal Enthalpies=	-537.738318
Sum of electronic and thermal Free Energies=	-537.797547

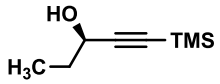
Chapter 5: Nucleophilic Addition of Cuprates to SDEs

Experimental Data for Route to S19.2



S15.2

To a suspension of $AlCl_3$ (10.09 g, 76.43 mmol) in CH_2Cl_2 (200 ml) was added a mixture of bis[trimethylsilyl]acetylene (10.00 g, 58.82 mmol) and propionyl chloride (5.11 ml, 58.82 mmol) in CH_2Cl_2 (10 ml) dropwise at -10°C. The reaction was allowed to warm to rt and stirred for an additional 1 h. After cooling to -78°C, 1 N HCl (50 ml) was added dropwise and the reaction was allowed to warm to rt. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were combined, dried using Na_2SO_4, and evaporated to give 8.60 g of known alkynone[90] **S15.2** (95%) as a yellow oil. This material was used for the next step without further purification.

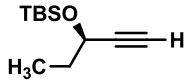


S15.3

In a glove bag, 50 mg of dichloro(p-cymene)ruthenium (II) dimer (0.082 mmol), 60 mg of (1R,2R)-(+)-N-p-tosyl-1,2-diphenylethylenediamine (0.164 mmol), and 65 mg of potassium hydroxide (1.16 mmol) were added to a flask followed by addition of 2 mL of anhydrous CH_2Cl_2. The orange colored reaction was removed from the glove bag and

(90) Denmark, S. E.; Yang, S. *J. Am. Chem. Soc.* **2004**, *126*, 12432.

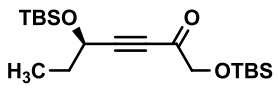
stirred for 5 min. after which time a purple colored appeared (Note: On some occasions the reaction turned purple immediately upon addition of CH_2Cl_2). 2 mL of water and 2 mL of CH_2Cl_2 were added to the reaction. The CH_2Cl_2 layer was separated and washed again with 2 mL of water. The CH_2Cl_2 layer was dried using CaH, filtered, and evaporated to give 100 mg of the Noyori catalyst as dark purple crystals. To this catalyst was added 25 mL of anhydrous isopropanol at rt. Upon complete dissolution of the catalyst the solution was dark orange in color. **S15.2** in 8 mL of anhydrous isopropanol was added in 0.5 mL portions based on the color change in the reaction. Upon addition of one portion of the alkynone the reaction immediately went from dark orange to dark purple and back to dark orange. At this time another portion of alkynone in isopropanol was added. This process was repeated until all alkynone was added (approximately 20 min.). Upon completion of the reaction by tlc, the isopropanol was evaporated to give a dark brown crude oil. FCC using 10% ethyl acetate-hexanes gave 1.93 g of known propargyl alcohol[90] **S15.3** (90%) as a pale yellow oil (R_f = 0.20 in 10% ethyl acetate-hexanes). Mosher ester analysis of the alcohol showed a single isomer indicating >95:5 ee.



S14.4

To a solution of **S15.3** (3.70 g, 23.70 mmol) in 100 ml CH_2Cl_2 was added imidazole (2.23 g, 32.70 mmol), DMAP (133 mg, 1.08 mmol) and TBSCl (3.65 g, 24.17 mmol) at rt. The reaction stirred at rt and was monitored by tlc. Upon completion of the reaction by tlc, 100 ml of a sat. solution of K_2CO_3 in MeOH was added. The reaction stirred for 2 h at rt followed by addition of 50 ml of water. The CH_2Cl_2 layer was

separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The organic layers were combined and dried using $NaSO_4$. The solvent was slowly removed by rotovap in order to avoid loss of the volatile product. FCC using pentane gave 2.35 g of TBS-protected propargyl alcohol **S14.4** (50%) as a clear colorless oil (R_f = 0.80 in pentane). Enantiomer of **S14.4** is a known compound. See: Xu, L.; Wu, X.; Zheng, G.R.; Cai, J.C. *Chinese Chem. Lett.* **2000**, *11*, 213-216. $[\alpha]_D$ +41.5 (*c* = 0.020, MeOH). IR ν_{max} (neat) / cm^{-1} 2962, 2929, 2859, 1471, 1249, 1082, 837; δH (400 MHz, $CDCl_3$) 4.28 (1H, td, J=6.4, 2.0 Hz), 2.37 (1H, d, J= 2.0 Hz), 1.74-1.65 (2H, m), 0.98 (3H, t, J=7.2 Hz), 0.91 (9H, s), 0.14 (3H, s), 0.11 (3H, s); δc (100 MHz, $CDCl_3$) 85.5, 71.9, 64.0, 31.7, 25.8, 18.2, 9.5, -4.6, -5.1; *m/z* (ESIMS) 221.4 $(M+23)^+$.

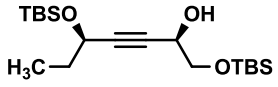


S16.3

To a solution of 2.39 g of **S14.4** (12.070 mmol) in 40 mL of anhydrous Et_2O was added 6.86 mL of 1.6M n-BuLi (10.976 mmol) at –78°C. The reaction stirred at –78°C for 20 min. and was allowed to warm to rt. Reaction stirred at rt for 30 min. before cooling back down to -78°C. 2.34 g of known Weinreb amide **S14.3**[91] (10.043 mmol) in 10 mL of anhydrous Et_2O was added dropwise at –78°C. The reaction was placed in a –20°C freezer overnight. 25 mL of saturated aq. NH_4Cl was added to the reaction at –20°C and was let to warm to rt. The Et_2O layer was separated and the aqueous layer was extracted twice using 10 mL of Et_2O. The Et_2O layers were combined, dried using

(91) Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331.

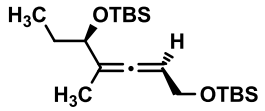
$MgSO_4$, and evaporated to give alkynone **S16.3** as a pale yellow oil. This crude material was taken onto the next step without further purification (R_f = 0.65 in 5% ethyl acetate-hexanes). $[\alpha]_D$ +24.5 (*c* = 0.011, MeOH). IR ν_{max} (neat) / cm^{-1} 2953, 2952, 2859, 2210, 1703, 1679, 1462, 1254, 1143, 1111; δH (400 MHz, $CDCl_3$) 4.44 (1H, t, J=6.4 Hz), 4.34 (2H, s), 1.78-1.71 (2H, m), 0.99 (3H, t, J=7.2 Hz), 0.92 (9H, s), 0.91 (9H, s), 0.14 (3H, s), 0.11 (3H, s), 0.10 (6H, s); δc (100 MHz, $CDCl_3$) 186.0, 96.0, 80.9, 70.5, 64.0, 31.0, 25.8, 25.7, 18.4, 18.2, 9.5, -4.6, -5.1, -5.4 (2); *m/z* (ESIMS) 371.1 $(M+1)^+$.



S16.4

In a glove bag, 150 mg of dichloro(p-cymene)ruthenium (II) dimer (0.245 mmol), 180 mg of (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylenediamine (0.492 mmol), and 195 mg of potassium hydroxide (3.480 mmol) were added to a flask followed by addition of 4 mL of anhydrous CH_2Cl_2. The orange colored reaction was removed from the glove bag and stirred for 5 min. after which time a purple colored appeared. (Note: On some occasions the reaction turned purple immediately upon addition of CH_2Cl_2) 5 mL of water and 5 mL of CH_2Cl_2 were added to the reaction. The CH_2Cl_2 layer was separated and washed again with 5 mL of water. The CH_2Cl_2 layer was dried using CaH, filtered, and evaporated to give 300 mg (0.500 mmol) of the Noyori catalyst as dark purple crystals. To this catalyst was added 60 mL of anhydrous isopropanol at rt. Upon complete dissolution of the catalyst the solution was dark orange in color. **S16.3** in 10 mL of anhydrous isopropanol was added in 1 mL portions based on the color change in the reaction. Upon addition of one portion of the alkynone the reaction immediately went

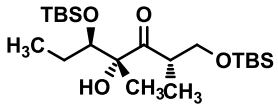
from dark orange to dark purple and back to dark orange. At this time another portion of alkynone in isopropanol was added. This process was repeated until all alkynone was added (approximately 20 min.). Upon completion of the reaction by tlc, the isopropanol was evaporated to give a dark brown crude oil. FCC using first hexanes than 3% ethyl acetate-hexanes gave 3.25 g of propargyl alcohol **S16.4** (87% over 2 steps, >95:5 dr) as a pale yellow oil (R_f = 0.50 in 5% ethyl acetate-hexanes). $[\alpha]_D$ +25.2 (*c* = 0.088, MeOH). IR ν_{max} (neat) / cm^{-1} 3374, 2953, 2929, 2855, 2218, 1719, 1679, 1454, 1254, 1082; δ_H (400 MHz, $CDCl_3$) 4.45-4.40 (1H, m), 4.31 (1H, td, J=6.4, 1.6 Hz), 3.75 (1H, dd, J=10.0, 4.0 Hz), 3.62 (1H, dd, J=8.4, 7.6 Hz), 2.51 (1H, br), 1.70-1.63 (2H, m), 0.96 (3H, t, J=7.2 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.12 (3H, s), 0.10 (3H, s), 0.09 (6H, s); δc (100 MHz, $CDCl_3$) 87.1, 81.7, 67.0, 64.2, 63.1, 31.7, 25.8 (2), 18.3, 18.2, 9.7, -4.5, -4.9, -5.3, -5.4; *m/z* (ESIMS) 397.8 $(M+23)^+$.



S16.5

To a solution of 1.21g (3.253 mmol) of **S16.4** and 0.59 mL (4.240 mmol) of triethylamine in 50 mL of CH_2Cl_2 was added 0.30 mL (3.895 mmol) of methanesulfonyl chloride dropwise at –78°C. The reaction was slowly allowed to warm to rt over 1 h and stirred for 30 min. at rt. 25 mL of water was added and the CH_2Cl_2 layer was separated and washed again with 25 mL of water. The CH_2Cl_2 layer was separated, dried using Na_2SO_4 and evaporated. The crude pale yellow oil was used for the next step without purification.

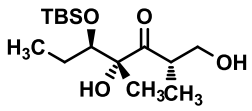
In a separate flask, 579 mg (6.465 mmol) of CuCN (activated by a gentle flame under high vacuum) in 40 mL of anhydrous Et_2O was degassed for 10 min with argon. This suspension was cooled to –20°C and 4.00 mL (6.400 mmol) of 1.6 M MeLi in ether was added dropwise. The suspension went from a bright canary yellow color to a homogeneous clear colorless solution. A solution of the above mesylate in 10 mL of anhydrous Et_2O was added dropwise to the reaction at –20°C. The reaction immediately formed a bright canary yellow precipitate and was allowed to warm to rt over 1 h. Upon completion by tlc, the reaction was quenched at rt using 30 mL of saturated aq. NH_4Cl. The ether layer was separated and washed again with 30 mL of saturated aq. NH_4Cl. The aqueous layers were combined and extracted using Et_2O (2 x 20 mL). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 1% ether-pentane gave 1.18g of allene **S16.5** (98%, >95:5 dr) as a colorless oil (R_f = 0.90 in 5% ethyl acetate-hexanes). $[\alpha]_D$ +20.8 (*c* = 0.024, MeOH). IR ν_{max} (neat) / cm^{-1} 2962, 2917, 2888, 2859, 1969, 1470, 1462, 1254, 1090; δ_H (400 MHz, $CDCl_3$) 5.17-5.12 (1H, m), 4.22-4.12 (2H, m), 4.02 (1H, t, J=6.8 Hz), 1.63 (3H, d, J=2.8 Hz), 1.62-1.48 (2H, m), 0.91 (9H, s), 0.89 (9H, s), 0.84 (3H, t, J=7.4 Hz), 0.08 (6H, s), 0.04 (6H, s); δc (100 MHz, $CDCl_3$) 200.4, 102.9, 91.2, 75.7, 62.2, 29.1, 26.0, 25.9, 18.4, 18.2, 12.8, 10.2, -4.6, -5.0 (2), -5.1; *m/z* (ESIMS) 393.4 $(M+23)^+$.



S16.6

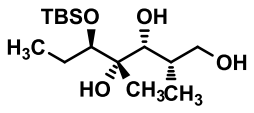
Allene **S16.5** (506 mg, 1.367 mmol) was converted to the SDE using the general procedure. To CuCN (601 mg, 6.710 mmol) (activated by a gentle flame under high

vacuum) was added 50 mL of anhydrous Et_2O. The suspension was degassed for 10 min using argon. The suspension was then cooled to –78°C and 4.20 ml (6.720 mmol) of 1.6 M MeLi in Et_2O was added dropwise. The reaction was warmed to 0°C over 10 min and stirred at 0°C for 5 min. The reaction had gone from heterogeneous to a clear pale yellow homogeneous solution at 0°C. The reaction was then recooled to –78°C and the above spirodiepoxide in 5 mL of anhydrous Et_2O was added dropwise. A bright canary yellow precipitate immediately formed and the reaction was let to warm to rt over 1.5 h and stirred at rt for 4 h. Upon completion of the reaction by tlc saturated aq. NH_4Cl (20 ml) was added. The Et_2O layer was separated and washed again with saturated aq. NH_4Cl (2 x 15 ml). The aqueous layers were combined and extracted with Et_2O (3 x 20 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 5% ethyl acetate-hexanes gave 456 mg of α-hydroxy ketone **S16.6** (80%, 8:1 dr) as a clear colorless oil (R_f = 0.70 in 10% ethyl acetate-hexanes). Spectral data for major isomer: IR ν_{max} (neat) / cm^{-1} 3469, 2949, 2856, 1712, 1467, 1251, 1100, 843; δ_H (400 MHz, $CDCl_3$) 3.76 (1H, s), 3.68-3.57 (4H, m), 1.58-1.36 (2H, m), 1.23 (3H, s), 0.97 (3H, d, J=6.4 Hz), 0.93-0.86 (21H, m), 0.14 (3H, s), 0.09 (3H, s), 0.06 (3H, s), 0.04 (3H, s); δc (100 MHz, $CDCl_3$) 217.5, 82.5, 79.5, 66.7, 43.4, 29.7, 26.1, 25.9, 24.0, 18.4, 18.3, 12.9, 11.2, -3.7, -4.3, -5.5, -5.7; *m/z* (ESIMS) 419.0 $(M+1)^+$. Reduction product **S17.3** was also isolated as the major side product. δ_H (300 MHz, $CDCl_3$) 3.69 (1H, dd, J=6.5, 1.8 Hz), 3.24 (1H, bs), 2.67-2.50 (2H, m), 1.66-1.41 (4H, m), 1.27 (3H, s), 0.94-0.87 (15H, m), 0.09 (6H, s).



S16.7

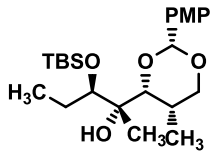
97 mg (0.232 mmol) of **S16.6** (8:1 dr) in 2.5 mL of acetic acid, 0.9 mL of water, and 0.9 mL of THF were stirred at rt for 12h. 10 ml of water and 15 ml of CH_2Cl_2 were added. The CH_2Cl_2 layer was separated and washed again with 10 mL of water. The aqueous layers were combined, dried using Na_2SO_4 and evaporated. FCC using 15% ethyl acetate-hexane gave 60 mg of diol (8:1 dr) as a clear colorless oil. At this stage the isomers were readily separable by FCC under the same conditions to give **S16.7** as a single diastereomer (85%) (R_f = 0.30 in 20% ethyl acetate-hexanes). Spectral data for **S16.7**: $[\alpha]_D$ +58.1 (*c* = 0.016, MeOH). IR ν_{max} (neat) / cm^{-1} 3423, 2953, 2929, 2888, 2855, 1707, 1462, 1254, 1123, 1017, 1008; δ_H (400 MHz, $CDCl_3$) 3.76-3.64 (3H, m), 3.55-3.46 (1H, m), 3.39 (1H, s), 2.57 (1H, br), 1.60-1.49 (2H, m), 1.31 (3H, s), 1.05 (3H, d, J=6.8 Hz), 0.93 (3H, t, J=7.6 Hz), 0.92 (9H, s), 0.14 (3H, s), 0.12 (3H, s); δc (100 MHz, $CDCl_3$) 218.0, 83.0, 79.6, 65.8, 43.7, 26.2, 26.0, 24.2, 18.3, 13.3, 11.2, -4.0, -4.1; *m/z* (ESIMS) 305.0 $(M+1)^+$.



S18.2

To a solution of 418 mg (1.589 mmol) of tetramethylammonium triacetoxyborohydride in 0.8 mL of acetic acid and 1.3 mL of acetonitrile was added 100 mg (0.329 mmol) of **S16.7** at –40°C. The reaction stirred at –40°C for 12h and was let to warm to rt. Upon completion of the reaction by TLC, 2 mL of saturated aq. $NaHCO_3$ and 10 mL of CH_2Cl_2 were added. The CH_2Cl_2 layer was separated and washed again with 5 mL of sat. $NaHCO_3$. The aqueous layers were combined and extracted with CH_2Cl_2 (2 x

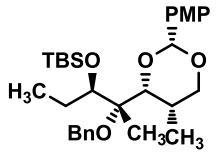
5 mL). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 20% ethyl acetate-hexane gave 91 mg of the triol (90%, 6:1 dr) as a clear colorless oil (R_f = 0.50 in 50% ethyl acetate-hexanes). Careful separation by FCC under the same conditions gave the major isomer **S18.2**. Spectral data for **S18.2**: $[\alpha]_D$ +13.5 (*c* = 0.023, MeOH). IR ν_{max} (neat) / cm^{-1} 3403, 2958, 2925, 2884, 2859, 1470, 1462, 1249, 1098, 1045, 837; δ_H (300 MHz, $CDCl_3$) 4.11 (1H, d, J=1.5 Hz), 3.74 (1H, dd, J=10.6, 3.9 Hz), 3.64 (1H, dd, J=10.5, 6.0 Hz), 3.50 (1H, dd, J= 7.8, 3.3 Hz), 1.86-1.79 (1H, m), 1.69-1.42 (2H, m), 1.09 (3H, d, J=6.9 Hz), 1.07 (3H, s), 1.00 (3H, t, J=7.5 Hz), 0.93 (9H, s), 0.18 (3H, s), 0.14 (3H, s); (75 MHz, $CDCl_3$) 85.7, 74.8, 74.3, 68.3, 36.2, 26.5, 26.1, 21.0, 18.3, 12.1, 10.6, -4.0, -4.3; *m/z* (ESIMS) 308.2 $(M+1)^+$.



S19.1

To a solution of 39 mg (0.127 mmol) of **S18.2** in 1 mL of CH_2Cl_2 was added 54 µL (0.320 mmol) of anisaldehyde dimethyl acetal and 1 mg of pyridinium p-toluenesulfonate (PPTS) at rt. Reaction stirred for 30 min. at rt. 2 mL of saturated aq. $NaHCO_3$ and 10 mL of CH_2Cl_2 was added. The CH_2Cl_2 layer was separated, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-hexane gave 49 mg of PMP acetal **S19.1** (91%) as a clear colorless oil (R_f = 0.40 in 10% ethyl acetate-hexanes) (R_f = 0.60 in 20% ethyl acetate-hexanes). $[\alpha]_D$ -6.6 (*c* = 0.029, MeOH). IR ν_{max} (neat) / cm^{-1} 3566, 2953, 2929, 2851, 1617, 1519, 1466, 1380, 1249, 1111, 1041; δ_H (400 MHz, $CDCl_3$) 7.42 (2H, d, J=11.6 Hz), 6.92 (2H, d, J=11.2 Hz), 5.58 (1H, s), 4.11 (1H, d, J=3.2 Hz), 4.06-

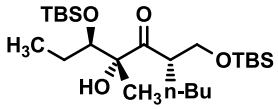
3.97 (2H, m), 3.82 (3H, s), 3.62 (1H, dd, J=8.0, 6.0 Hz), 2.20 (1H, br), 1.93-1.71 (2H, m), 1.45-1.30 (1H, m), 1.35 (3H, d, J=9.2 Hz), 0.95 (3H, t, J=10.0 Hz), 0.92 (9H, s), 0.11 (3H, s), 0.09 (3H, s); (100 MHz, $CDCl_3$) 160.0, 131.2, 127.4, 113.6, 101.7, 78.6, 76.5, 75.8, 75.1, 55.3, 30.3, 26.1, 24.8, 18.2, 14.7, 13.0, 12.3, -3.3, -4.4; *m/z* (ESIMS) 449.0 $(M+23)^+$.



S19.2

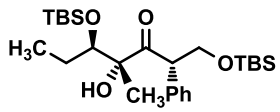
To a suspension of 6 mg (0.261 mmol) of sodium hydride in 2 mL of anhydrous DMF was added 21 mg (0.049 mmol) of **S19.1** at 0^oC. The reaction was let to warm to rt over 10 minutes and stirred at rt for 30 minutes. 0.05 ml (0.420 mmol) of benzyl bromide (purified using basic alumina column), 17 mg (0.045 mmol) of tetrabutylammonium iodide and 0.5 mL of HMPA were added at rt. After stirring for 4 h, 5 mL of water and 10 mL of CH_2Cl_2 were added. The CH_2Cl_2 layer was separated and washed again using 5 mL of water. The aqueous layers were combined and extracted using CH_2Cl_2 (2 x 5 mL). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-hexane gave 19 mg of **S19.2** (76%) as a clear colorless oil (R_f = 0.50 in 10% ethyl acetate-hexanes). $[\alpha]_D$ +7.1 (*c* = 0.007, $CDCl_3$). ^1H and ^{13}C NMR matched identically to the known Woerpel intermediate.[3a]

Experimental Data for Scheme 17



S17.4

Allene **S16.5** (50 mg, 0.135 mmol) was converted to the SDE using the general procedure. In a separate flask, a suspension of CuCN (60 mg, 0.674 mmol) (activated by a gentle flame under vacuum) in 5 ml of Et_2O was degassed for 5 min using argon. The suspension was then cooled to -78^oC and a 1.6 M solution of n-BuLi in hexanes (0.42 ml, 0.674 mmol) was added dropwise. The suspension was warmed to -20^oC at which point a homogeneous solution was formed. The solution was then cooled to -78^oC and the above SDE in 1 ml of Et_2O was added dropwise. The reaction was slowly allowed to warm to rt over 1 hr and stirred at rt for 6 h. Upon completion of the reaction by tlc, saturated aq. NH_4Cl (2 ml) was added. The Et_2O layer was separated and washed again with saturated aq. NH_4Cl (2 x 5 ml). The aqueous layers were combined and extracted with Et_2O (3 x 10 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 1% ethyl acetate-hexanes gave 41 mg (66%, 8:1 dr) of **S17.4** as a clear colorless oil (R_f = 0.80 in 10% ethyl acetate-hexanes). Spectral data for major isomer: IR ν_{max} (neat) / cm^{-1} 3444, 2949, 2929, 2851, 1711, 1474, 1254, 1106, 841; δ_H (500 MHz, $CDCl_3$) 3.89-3.66 (4H, m), 3.48-3.43 (1H, m), 1.59-1.22 (6H, m), 1.24 (3H, s), 0.94-0.86 (26H, m), 0.14 (3H, s), 0.11 (3H, s), 0.06 (3H, s), 0.04 (3H, s); (125 MHz, $CDCl_3$) 216.9, 82.6, 79.5, 65.0, 49.2, 29.6, 27.7, 26.2, 25.9, 25.8, 24.3, 23.0, 18.4, 18.3, 13.9, 11.3, -3.7, -4.2, -5.5, -5.6; *m/z* (ESIMS) 461.0 $(M+1)^+$

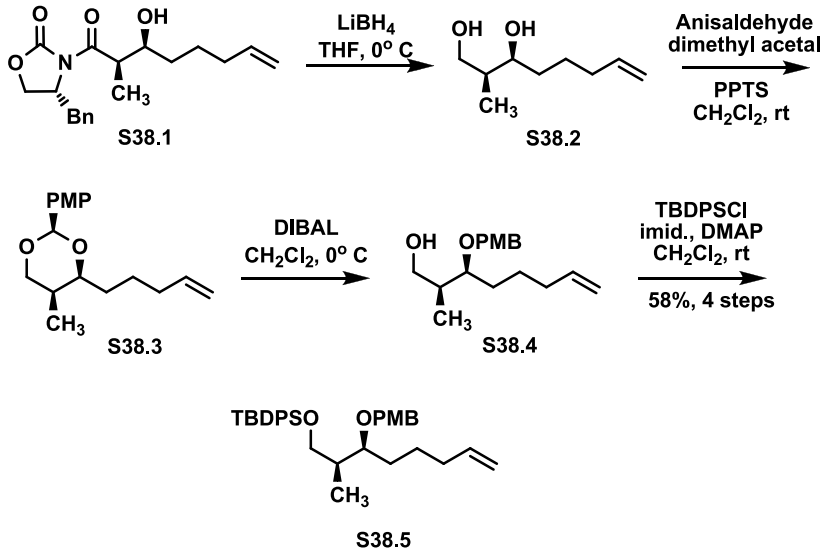


S17.5

Allene **S16.5** (30 mg, 0.081 mmol) was converted to the SDE using the general procedure. In a separate flask, a suspension of CuI (104 mg, 0.547 mmol) (activated by a gentle flame under vacuum) in 3 ml of Et_2O was degassed for 5 min using argon. The suspension was then cooled to -78^oC and a 2.0 M solution of PhLi in dibutylether (0.54 ml, 1.08 mmol) of was added dropwise. The suspension was warmed to 0^oC at which point the reaction mixture turned dark and a black precipitate was formed. This heterogeneous mixture was stirred for 5 min at 0^oC and was then cooled to -78^oC. The above spirodiepoxide in 1 ml of Et_2O was added dropwise at -78^oC. The reaction was slowly allowed to warm to rt over 3 hr and stirred at rt for 2 h. Upon completion of the reaction by tlc, saturated aq. NH_4Cl (2 ml) was added. The Et_2O layer was separated and washed again with saturated aq. NH_4Cl (2 x 2 ml). The aqueous layers were combined and extracted with Et_2O (3 x 5 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 5% EtOAc/Hexanes gave 24 mg (62%, 8:1 dr) of **S17.5** as a clear colorless oil (R_f = 0.75 in 10% ethyl acetate-hexanes). Spectral data for major isomer: IR ν_{max} (neat) / cm^{-1} 3497, 2953, 2925, 2855, 1716, 1470, 1258, 1095, 833, 776; δ_H (400 MHz, $CDCl_3$) 7.29-7.19 (5H, m), 4.66 (1H, dd, J=9.6, 4.8 Hz), 4.19 (1H, t, J=9.6 Hz), 3.79 (1H, dd, J=6.0, 1.6 Hz), 3.65 (1H, dd, J=9.4, 4.4 Hz), 3.02 (1H, s), 1.24-1.16 (2H, m), 1.21 (3H, s), 0.86 (9H, s), 0.84 (9H, s), 0.63 (3H, t, J=7.6 Hz), 0.05 (6H, s), -0.03 (3H, s), -0.01 (3H,s); (125 MHz, $CDCl_3$) 212.3, 135.3, 128.9, 128.5, 127.3, 83.1, 77.7, 65.8, 55.2, 26.0, 25.9, 25.8, 24.6, 18.3 (2), 10.5, -3.9, -4.1, -5.5, -5.6; *m/z* (ESIMS) 503.4 $(M+23)^+$

Chapter 7: Studies Towards Pectenotoxin 4 (PTX4)

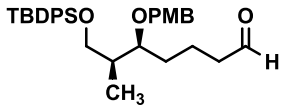
Experimental Data for Route to S43.4



To a solution of known syn α-hydroxyimide **S38.1** (3.97 g, 12.0 mmol) in Et_2O (50 ml) and H_2O (0.30 ml) was added a 2.0 M solution of $LiBH_4$ in THF (6.6 ml, 13.2 mmol) dropwise at 0°C. The reaction was stirred for 1 h at 0°C followed by addition of 1.0 N aq. NaOH (10 ml). The mixture was warmed to rt, and H_2O (40 ml) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated to give a mixture of diol **S38.2** and chiral oxazolidinone. To a solution of this mixture in CH_2Cl_2 (50 ml) was added anisaldehyde dimethylacetal (2.3 ml, 13.2 mmol) and PPTS (300 mg, 10 mol%) at rt. The reaction stirred at rt for 1 h followed by addition of saturated aq. $NaHCO_3$ (50 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 3% ethyl acetate-hexanes gave an

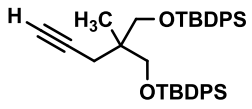
inseparable mixture of benzylidene acetal **S38.3** and anisaldehyde. To a solution of this mixture in CH_2Cl_2 (50 ml) was added a 1.0 M solution of DIBAL in hexanes (30 ml, 30.0 mmol) dropwise at 0^oC. The reaction was stirred at 0^oC for 30 min and was quenched by the addition of MeOH (10 ml). The mixture was allowed to warm to rt followed by addition of saturated aq. Rochelle's salt (10 ml). After 30 min of stirring, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 10% ethyl acetate-hexanes gave an inseparable mixture of the desired primary alcohol (**S38.4**) and the regioisomeric 2° alcohol (not shown). To a solution of this mixture in CH_2Cl_2 (50 ml) was added imidazole (1.22 g, 17.9 mmol), DMAP (87 mg, 10 mmol%) and TBDPSCl (2.25 ml, 8.64 mmol) in one portion at 0oC. The reaction was allowed to warm to rt and monitored by tlc. Upon completion by tlc, H2O (10 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 1% ethyl acetate-hexanes gave 3.58 g (58%, >95:5 dr, 4 steps) of alkene **S38.5** as a clear colorless oil: $[\alpha]_D$ -14.0 (*c* = 0.01, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3068, 2929, 2856, 1618, 1520, 1466, 1425, 1300, 1250, 1176, 1111, 1086, 1041, 825, 739, 698, 612; δ_H (500 MHz, $CDCl_3$) 7.65 (4H, d, J= 7.0 Hz), 7.43-7.33 (6H, m), 7.19 (2H, d, J= 8.5 Hz), 6.83 (2H, d, J= 8.5 Hz), 5.83-5.75 (1H, m), 4.99 (1H, dd, J = 17.1, 1.7 Hz), 4.94 (1H, dd, J = 10.2, 1.7 Hz), 4.42 (2H, dd, J= 11.1, 29.4 Hz), 3.78 (3H, s), 3.70 (1H, dd, J = 7.0, 9.9 Hz), 3.59-3.56 (1H, m), 3.54 (1H, dd, J = 6.5, 10Hz), 2.04(2H, td, J = 6.7, 7.1 Hz), 1.90-1.85 (1H, m), 1.64-1.33 (4H, m), 1.06 (9H, s), 0.90 (3H, d, J= 6.9 Hz); δc (125

MHz, $CDCl_3$) 158.9, 138.8, 135.6, 133,9, 131.4, 129.5, 129.1, 127.6, 114.5, 113.6, 79.0, 71.8, 66.0, 55.2, 38.9, 33.8, 30.8, 26.9, 25.3, 19.3, 11.5. *m/z* (ESIMS) 539.4 $(M+23)^+$.



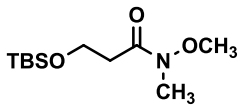
S38.6

To a solution of the alkene **S38.5** (1.24 g, 2.40 mmol) in dioxane-H_2O (3:1, 20 ml) was added 2,6-lutidine (0.56 ml, 4.81 mmol), a 2.5 wt% solution of OsO_4 in 2-methyl-2-propanol (0.48 ml, 0.048 mmol), and $NaIO_4$ (2.05 g, 9.61 mmol) at rt. The reaction stirred at rt and was monitored by tlc. Upon completion by tlc, H_2O (20 ml) and CH_2Cl_2 (40 ml) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 10% ethyl acetate-hexanes gave 1.09 g (88%, >95:5 dr) of aldehyde **S38.6** as a clear colorless oil. $[\alpha]_D$ - 5.3 (*c* = 0.013, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 2958, 2929, 2859, 1724, 1614, 1511, 1466, 1422, 1246, 1111, 1082, 1046, 825, 702; δ_H (500 MHz, $CDCl_3$) 9.72 (1H, s), 7.65 (4H, d, J= 7.2 Hz), 7.44-7.34 (6H, m), 7.18 (2H, d, J= 8.5 Hz), 6.83 (2H, d, J= 8.5 Hz), 4.42 (2H, s), 3.79 (3H, s), 3.70 (1H, dd, J1= 6.8 Hz, J2= 9.9 Hz), 3.58-3.52 (2H, m), 2.38(2H, t, J= 7.3 Hz), 1.93-1.85 (1H, m), 1.73-1.43 (4H, m), 1.06 (9H, s), 0.91 (3H, d, J= 6.9 Hz); δ_C (125 MHz, $CDCl_3$) 202.5, 159.1, 135.6, 133.9, 131.1, 129.6, 129.2, 127.6, 113.7, 78.9, 71.9, 65.8, 55.3, 43.9, 38.9, 31.0, 26.9, 19.3, 18.7, 11.7. *m/z* (ESIMS) 541.3 $(M+23)^+$.



S41.2

To a solution of the known diol **S41.1**[92] (1.30 g, 10.1 mmol) in CH_2Cl_2 (50 ml) was added imidazole (3.45 g, 50.8 mmol), DMAP (248 mg, 2.03 mmol) and TBDPSCl (6.50 ml, 25.4 mmol) in one portion at 0^oC. The solution was allowed to warm to rt and monitored by tlc. Upon completion by tlc, H_2O (30 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 0.1% ethyl acetate-hexanes gave 5.83 g (95%) of alkyne **S41.2** as a clear colorless oil. IR υ_{max} (neat) /cm^{-1} 3305, 3068, 2962, 2925, 2852, 2120, 1471, 1421, 1385, 1115, 1078, 829, 739, 702; δ_H (500 MHz, $CDCl_3$) 7.65 (8H, d, J= 6.5 Hz), 7.41-7.37 (4H, m), 7.34-7.31 (8H, m), 3.58 (4H, dd, J1= 9.7 Hz, J2= 15.2 Hz), 2.32 (2H, d, J= 2.6 Hz), 1.87 (1H, t, J= 2.6 Hz), 1.03 (18H, s), 0.99 (3H, s); δc (125 MHz, $CDCl_3$) 135.7, 133.5, 129.5, 127.6, 81.9, 70.0, 67.1, 41.3, 26.9, 23.7, 19.4, 18.6; *m/z* (ESIMS) 605.4 $(M+1)^+$.

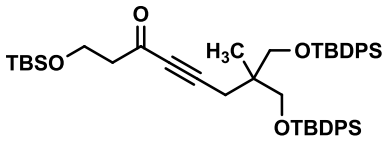


S41.4

To a solution of commercially available β-hydroxyester **S41.3** (5.00 g, 48.1 mmol) in CH_2Cl_2 (50 ml) was added imidazole (12.2 g, 179 mmol), DMAP (732 mg, 6.00 mmol) and TBSCl (9.07 g, 60.1 mmol) in one portion at rt. The reaction was stirred at rt and was monitored by tlc. Upon completion by tlc, H_2O (30 ml) was added. The organic

(92) Findeis, R. A.; Gade, L. H. *Journal of the Chemical Society, Dalton Transactions* **2002**, *21*, 3952.

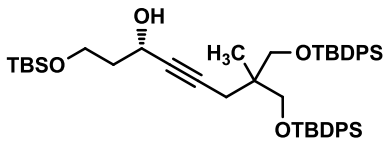
layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated to give the crude ester which was used for the next step without further purification. To a suspension of the crude ester (above) and $HNCH_3(OCH_3)\cdot HCl$ (7.07 g, 72.2 mmol) in THF (200 ml) was added a 2.0 M solution of iPrMgCl in THF (72 ml, 144.3 mmol) over a 1 min period at -20°C. The reaction stirred at -20°C for 5 min, was allowed to warm to -15°C over 5 min, and monitored by tlc. Upon completion by tlc, saturated aq. NH_4Cl (20 ml) and Et_2O (30 ml) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 40 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 10% ethyl acetate-hexanes gave 9.87 g (83%, 2 steps) of Weinreb amide **S41.4** as a clear colorless oil. IR υ_{max} (neat) /cm^{-1} 1659, 1250, 1091, 833, 780; δ_H (500 MHz, $CDCl_3$) 3.94 (2H, t, J= 7.0 Hz), 3.70 (3H, s), 3.18 (3H, s), 2.66 (2H, t, J= 7.0 Hz), 0.88 (9H, s), 0.06 (6H, s); δc (125 MHz, $CDCl_3$) 172.5, 61.3, 59.3, 35.1, 31.9, 25.9, 18.3, -5.4; *m/z* (ESIMS) 270.2 $(M+23)^+$.



S41.5

To a solution of alkyne **S41.2** (10.02 g, 16.59 mmol) in dry Et_2O (100 ml) was added n-BuLi dropwise at -78°C. The reaction was allowed to warm to rt, stirred for 20 min then cooled back down to -78°C. Weinreb amide **S41.4** (3.15g, 12.8 mmol) in dry Et_2O (20 ml) was added dropwise at -78°C and the reaction was placed in a -30°C freezer overnight (12 h). Saturated aq. NH_4Cl (20 ml) was added at -30°C, and the reaction was allowed to warm to rt. The Et_2O layer was separated, and aqueous layer was extracted

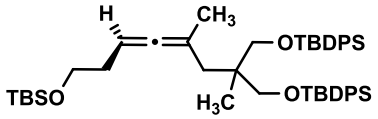
with Et_2O (2 × 40 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 1% ethyl acetate-hexanes gave 9.07 g (90%) of alkynone **S41.5** as a clear colorless oil. IR υ_{max} (neat) /cm^{-1} 2958, 2929, 2210, 1674, 1471, 1426, 1258, 1107, 825, 702; δ_H (500 MHz, $CDCl_3$) 7.63-7.61 (8H, m), 7.42-7.31 (12H, m), 3.87 (2H, t, J= 6.4 Hz), 3.55 (4H, s), 2.61 (2H, t, J= 6.4 Hz), 2.51 (2H, s), 1.02 (18 H, s), 1.00 (3H, s), 0.86 (9H, s), 0.03 (6H, s); δ_C (125 MHz, $CDCl_3$) 185.8, 135.6, 133.3, 129.7, 127.7, 92.3, 82.8, 67.1, 58.3, 48.6, 41.8, 26.9, 25.8, 24.2, 19.4, 18.8, 18.2, -5.4. *m/z* (ESIMS) 813.4 $(M+23)^+$.



S41.7

In a glove bag, 150 mg of dichloro(p-cymene)ruthenium (II) dimer (452 mg, 0.739 mmol), (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylenediamine (542 mg, 1.48 mmol), and potassium hydroxide (588 mg, 10.5 mmol) were added to a flask followed by addition of 4 mL of anhydrous CH_2Cl_2. The orange colored reaction was removed from the glove bag and stirred for 5 min. after which time a purple colored appeared. (Note: On some occasions the reaction turned purple immediately upon addition of CH_2Cl_2) 5 mL of water and 5 mL of CH_2Cl_2 were added to the reaction. The CH_2Cl_2 layer was separated and washed again with 5 mL of water. The CH_2Cl_2 layer was dried using CaH, filtered, and evaporated to give 300 mg (0.500 mmol) of Noyori catalyst **S41.6** as dark purple crystals. To this catalyst was added 60 mL of anhydrous isopropanol at rt. Upon complete dissolution of the catalyst the solution was dark orange in color. Alkynone

S41.5 (9.07 g, 11.5 mmol) in 20 mL of anhydrous isopropanol was added in 1 mL portions based on the color change in the reaction. Upon addition of one portion of the alkynone the reaction immediately went from dark orange to dark purple and back to dark orange. At this time another portion of alkynone in isopropanol was added. This process was repeated until all alkynone was added (approximately 20 min.). Upon completion of the reaction by tlc, the isopropanol was evaporated to give a dark brown crude oil. FCC using first hexanes than 3% ethyl acetate-hexanes gave 9.00 g (99%) of propargyl alcohol **S41.7** as a clear colorless oil**.** Mosher ester analysis of the alcohol showed a single isomer indicating >95:5 ee. $[\alpha]_D$ - 5.7 (*c* = 0.045, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3452, 2958, 2929, 2852, 2239, 1471, 1430, 1254, 1115, 1074, 829, 706; δ_H (500 MHz, $CDCl_3$) 7.66-7.63 (8H, m), 7.41-7.38 (4H, m), 7.35-7.31 (8H, m), 4.50-4.47 (1H, m), 3.91-3.86 (1H, m), 3.73-3.68 (1H, m), 3.61-3.55 (4H, m), 2.92 (1H, d, J= 5.7 Hz), 2.34 (2H, s), 1.85-1.78 (1H, m), 1.73-1.67 (1H, m), 1.02 (18 H, s), 0.97 (3H, s), 0.88 (9H, s), 0.05 (6H, s); δ_C (125 MHz, $CDCl_3$) 135.7, 133.6, 129.5, 127.6, 82.8, 82.5, 67.2, 61.7, 61.0, 41.4, 39.3, 26.9, 25.9, 24.1, 19.4, 18.7, 18.2, -5.5; *m/z* (ESIMS) 815.5 $(M+23)^+$.

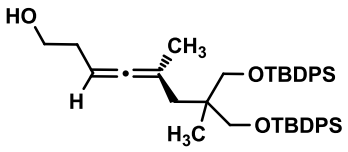


S41.8

To a solution of propargyl alcohol **S41.7** (8.80 g, 11.1 mmol) in CH_2Cl_2 (100 ml) was added Et_3N (4.64 ml, 33.3 mmol) and MsCl (1.37 ml, 16.7 mmol) dropwise at -78^oC. The reaction was allowed to warm to rt over 1 h, and stirred at rt for 30 min. The reaction was quenched by addition of H_2O (20 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 ml). The organic layers were combined,

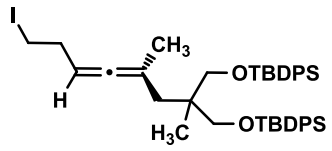
dried using Na_2SO_4, filtered and evaporated to give the crude mesylate which was used for the next step without further purification.

In a separate round-bottom flask, a suspension of CuCN (4.95 g, 55.6 mmol, activated by a gentle flame under high vacuum) in anhydrous Et_2O (20 ml) was degassed for 2 min with argon. The suspension was cooled to -78^oC and a solution of 1.6 M MeLi in Et_2O (34.3 ml, 55.0 mmol) was added dropwise. The reaction mixture was warmed to 0^oC at which point it became a colorless homogeneous solution. The solution was cooled back to –78^oC and the mesylate (above) in anhydrous Et_2O (2 ml) was added dropwise. The reaction was allowed to warm to rt over 1 h and monitored by tlc. Upon completion by tlc, saturated aq. NH_4Cl (50 ml) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 1% ethyl acetate-hexanes gave 8.42 g (96%) of allene **S41.8** as a clear colorless oil. $[\alpha]_D$ +13.7 (*c* = 0.114, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 2954, 2933, 2856, 1961, 1475, 1422, 1254, 1111, 841, 702; δ_H (500 MHz, $CDCl_3$) 7.67-7.65 (8H, m), 7.43-7.40 (4H, m), 7.36-7.32 (8H, m), 4.73 (1H, br), 3.61 (2H, s), 3.59 (2H, s), 3.57-3.49 (2H, m), 2.09-2.02 (2H, m), 2.02-1.93 (2H, m), 1.62 (3H, d, J= 2.8 Hz), 1.06 (18 H, s), 0.96 (3H, s), 0.90 (9H, s), 0.04 (6H, s); δ_C (125 MHz, $CDCl_3$) 203.8, 135.7, 133.9, 129.5, 127.5, 95.3, 85.6, 68.0, 67.8, 63.1, 42.1, 38.2, 33.0, 27.0, 26.0, 22.1, 19.4, 18.8, 18.3, -5.3; *m/z* (ESIMS) 813.6 (M+23)$^+$.



S42.1

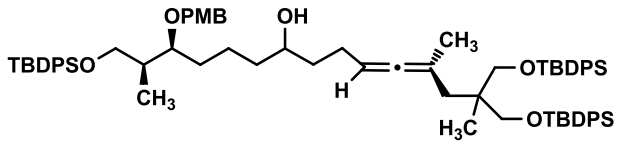
To a solution of allene **S41.8** (7.61 g, 9.63 mmol) in CH_2Cl_2 (50 ml) and pyridine (10 ml) was added HF/Pyridine (30 ml) dropwise at 0°C. The reaction was stirred at 0°C and monitored by tlc. Upon completion by tlc, H_2O (30 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 15% ethyl acetate-hexanes gave 6.70 g (94%) of alcohol **S42.1** as a clear colorless oil. $[\alpha]_D$ +14.4 (*c* = 0.009, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3342, 2962, 2933, 2852, 1965, 1471, 1430, 1111, 1078, 829, 735, 689, 612; δ_H (500 MHz, $CDCl_3$) 7.64-7.62 (8H, m), 7.41-7.38 (4H, m), 7.34-7.30 (8H, m), 4.68-4.64 (1H, m), 3.58 (2H, s), 3.56 (2H, s), 3.52-3.44 (2H, m), 2.04 (2H, d, J= 1.9 Hz), 1.94 (2H, q, J= 6.5 Hz), 1.61 (3H, d, J= 2.9 Hz), 1.03 (18 H, s), 0.94 (3H, s); δ_C (125 MHz, $CDCl_3$) 204.1, 135.7, 133.8, 129.5, 127.6, 96.2, 85.2, 68.0, 67.7, 62.1, 42.1, 38.3, 32.5, 27.0, 22.2, 19.4, 19.0. *m/z* (ESIMS) 699.4 $(M+23)^+$.



S42.2

To a solution of PPh_3 (452 mg, 1.72 mmol) and imidazole (335 mg, 4.92 mmol) in anhydrous CH_2Cl_2 (50 ml) was added I_2 (437 mg, 1.72 mmol) in one portion at 0°C. The reaction mixture stirred at 0°C until a colorless homogeneous solution was formed. Allenyl alcohol **S42.1** (1.11 g, 1.64 mmol) in 5 ml of CH_2Cl_2 was added slowly to the solution at 0°C. The reaction was allowed to warm to rt, and stirred for 2 h at rt. Saturated aq. $NaHCO_3$ (10ml) and H_2O (30 ml) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 ml). The organic layers were

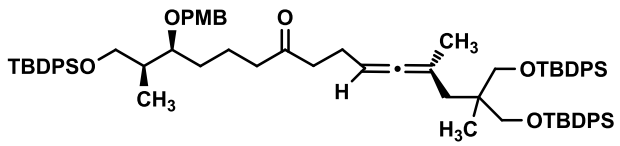
combined, dried using Na_2SO_4, filtered and evaporated. FCC using 0.5% ethyl acetate-hexanes gave 1.17 g (91%) of iodoallene **S42.2** as a clear colorless oil. $[\alpha]_D$ +20.5 (*c* = 0.037, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3048, 2962, 2925, 2852, 1956, 1471, 1422,1111, 1086, 820, 743, 698, 616; δ_H (500 MHz, $CDCl_3$) 7.64-7.62 (8H, m), 7.41-7.38 (4H, m), 7.34-7.31 (8H, m), 4.66-4.62 (1H, m), 3.57 (2H, s), 3.56 (2H, s), 2.99 (2H, t, J= 7.2 Hz), 2.22 (2H, q, J= 7.0 Hz), 2.08 (1H, dd, J = 2.2, 14.6 Hz), 2.03 (1H, dd, J = 2.0, 14.4 Hz), 1.63 (3H, d, J= 2.8 Hz), 1.03 (18 H, s), 0.92 (3H, s); δ_C (125 MHz, $CDCl_3$) 203.6, 135.7, 133.8, 129.5, 127.6, 97.1, 88.4, 67.9, 67.8, 42.1, 38.1, 33.2, 27.0, 22.0, 19.4, 19.0, 5.4. *m/z* (ESIMS) 809.6 $(M+23)^+$.



S43.1

In a flame-dried round-bottom flask, iodoallene **S42.2** (610 mg, 0.776 mmol / azeotroped with benzene) in anhydrous Et_2O (10 ml) was degassed for 10 min with argon. The solution was cooled to -78^oC and a solution of 1.7 M t-BuLi in Et_2O (0.91 ml, 1.55 mmol) was added dropwise. The reaction was stirred at -78^oC for 20 min, and then aldehyde **S38.6** (518 mg, 0.749 mmol, azeotroped with benzene) in anhydrous Et_2O (3 ml / degassed with argon) was added dropwise over 15 min. The reaction was allowed to warm to rt over 2 h and monitored by tlc. Upon completion by tlc, saturated aq. NH_4Cl (10 ml) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 10 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 8% ethyl acetate-hexanes gave 462 mg (55%, 1:1 dr) of alcohol **S43.1** as a clear colorless oil. IR υ_{max} (neat) /cm^{-1} 3444, 2933, 2856, 1953, 1520,

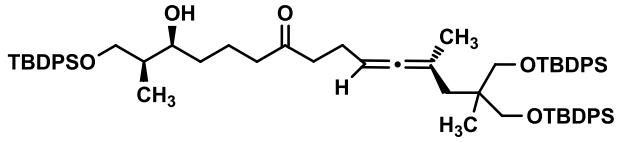
1471, 1430, 1246, 1115, 1078, 829, 739, 698; δ_H (500 MHz, $CDCl_3$) 7.66-7.62 (12H, m), 7.41-7.29 (18H, m), 7.18 (2H, d, J= 8.2 Hz), 6.82 (2H, d, J= 8.2 Hz), 4.68 (1H, br), 4.42 (2H, dd, J = 11.0, 22.9 Hz), 3.77 (3H, s), 3.71 (1H, t, J= 8.4 Hz), 3.59 (2H, s), 3.57 (2H, s), 3.55-3.51 (2H, m), 3.48 (1H, br), 2.03 (2H, s), 1.91-1.74 (3H, m), 1.59 (3H, s), 1.47-1.15 (8H, m), 1.05 (9H, s), 1.03 (18 H, s), 0.93 (3H, s), 0.89 (3H, d, J= 6.8 Hz); δ_C (100 MHz, $CDCl_3$) 203.0, 159.0, 135.8, 135.7, 134.0, 133.9, 133.8, 131.4, 129.5, 129.2, 127.6, 127.5, 113.7, 95.9, 88.9, 79.2, 71.9, 71.5, 68.0, 67.7, 66.0, 55.3, 42.1, 39.0, 38.2, 37.5, 37.0, 31.5, 27.0, 26.9, 25.5, 22.3, 22.2, 19.4, 19.3, 18.9, 11.5. *m/z* (ESIMS) 1202.6 $(M+23)^{+\cdot}$



S43.2

To a suspension of Dess-Martin periodinane (330 mg, 0.780 mmol) in anhydrous CH_2Cl_2 (20 ml) was added pyridine (0.1 ml, 0.78 mmol) at rt. After stirring for 5 min, alcohol **S43.1** (460 mg, 0.390 mmol) in anhydrous CH_2Cl_2 (2 ml) was added dropwise at 0^oC. The reaction was allowed to warm to rt, and monitored by tlc. Upon completion by tlc, a mixture of saturated aq. $NaHCO_3$ and $Na_2S_2O_3$ solution (1:1, 10 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 10% ethyl acetate-hexanes gave 390 mg (85%) of ketone **S43.2** as a clear colorless oil. $[\alpha]_D$ +13.6 (*c* = 0.011, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3068, 2958, 2933, 2852, 1957, 1716, 1516, 1471, 1426, 1246, 1111, 1082, 821, 739, 702, 612; δ_H (500 MHz,

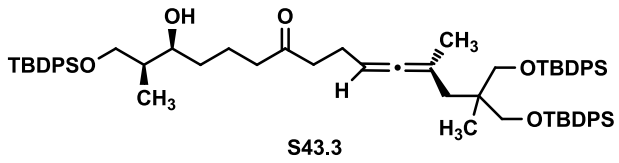
$CDCl_3$) 7.65-7.61 (12H, m), 7.41-7.29 (18H, m), 7.17 (2H, d, J= 8.4 Hz), 6.81 (2H, d, J= 8.5 Hz), 4.68 (1H, br), 4.41 (2H, dd, J = 10.9, 21.1 Hz), 3.77 (3H, s), 3.70 (1H, dd, J = 7.0, 9.9 Hz), 3.57 (2H, s), 3.55 (2H, s), 3.54-3.51 (2H, m), 2.34-2.21 (4H, m), 2.05-1.94 (4H, m), 1.91-1.86 (1H, m), 1.57 (3H, d, J= 2.7 Hz), 1.51-1.37 (4H, m), 1.05 (9H, s), 1.03 (18 H, s), 0.92 (3H, s), 0.88 (3H, d, J= 6.9 Hz); δ_C(125 MHz, $CDCl_3$) 210.0, 203.0, 159.0, 135.7, 135.6, 133.9, 133.8, 131.2, 130.0, 129.5, 129.2, 127.6, 127.5, 113.6, 96.7, 88.1, 78.9, 71.8, 68.0, 67.6, 65.9, 55.3, 42.7, 42.1, 41.8, 38.9, 38.2, 31.0, 27.0, 26.9, 23.2, 22.2, 20.3, 19.4, 19.3, 18.9, 11.5. *m/z* (ESIMS) 1199.5 $(M+23)^+$.



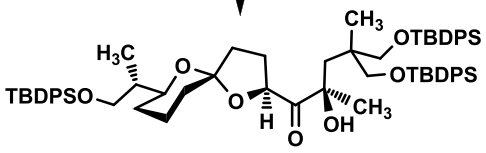
S43.3

To a solution of ketone **S43.2** (350 mg, 0.297 mmol) in a mixture of CH_2Cl_2 and phosphate buffer solution pH 7 (20:1, 20 ml) was added DDQ (101 mg, 0.445 mmol) in one portion at 0°C. The reaction was stirred at 0°C and monitored by tlc. Upon completion by tlc, saturated aq. Na_2CO_3 (10 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated. FCC using 5% ethyl acetate-hexanes gave 253 mg (81 %) of keto alcohol **S43.3** as a clear colorless oil. $[\alpha]_D$ +28.0 (*c* = 0.003, $CHCl_3$). IR υ_{max} (neat) /cm^{-1} 3526, 2962, 2933, 2856, 1961, 1716, 1426, 1389, 1111, 1078, 825, 743, 698, 612; δ_H (500 MHz, $CDCl_3$) 7.67-7.62 (12H, m), 7.45-7.30 (18H, m), 4.68 (1H, br), 3.82 (1H, br), 3.73 (1H, dd, J = 4.0, 10.0 Hz), 3.65 (1H, dd, J = 6.0, 9.9 Hz), 3.57 (2H, s), 3.55 (2H, s), 2.82 (1H, br), 2.38-2.23 (4H, m), 2.06-1.93

(4H, m), 1.75-1.65 (1H, m), 1.57 (3H, d, J= 2.5 Hz), 1.49-1.30 (4H, m), 1.05 (9H, s), 1.03 (18 H, s), 0.92 (3H, s), 0.89 (3H, d, J= 7.0 Hz); δ_C (125 MHz, $CDCl_3$) 210.3, 202.9, 135.7, 135.6, 133.8, 133.1, 129.9, 129.5, 127.8, 127.5, 96.8, 88.1, 73.8, 68.6, 68.0, 67.7, 42.6, 42.1, 41.8, 39.1, 38.2, 33.7, 27.0, 26.9, 23.2, 22.1, 20.4, 19.4, 19.2, 18.9, 10.2. *m/z* (ESIMS) 1079.3 $(M+23)^+$.



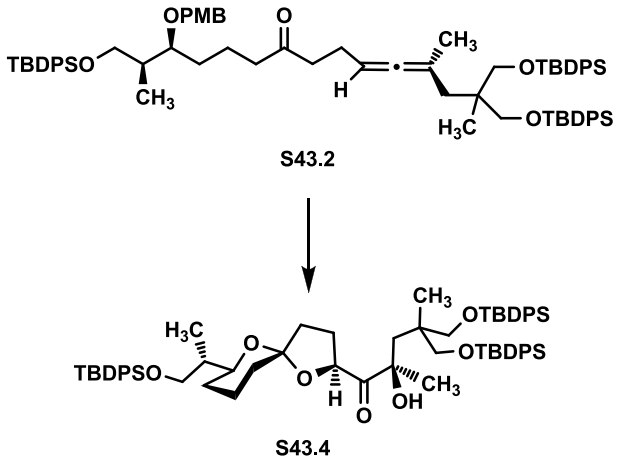
S43.3



S43.4

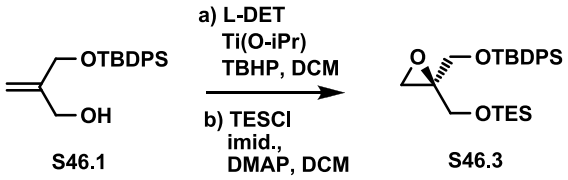
To a solution of **S43.3** (32 mg, 0.0303 mmol) in MeOH (1 ml) and $CDCl_3$ (2 ml) was added a solution of DMDO (~0.20 M) in $CHCl_3$ (0.50 ml, 0.10 mmol) dropwise at -40^{o}C. Over the course of 1 h, the reaction was allowed to warm to rt and monitored by tlc. Upon disappearance of the allene, a 0.1 M solution of TsOH in MeOH was added (0.08 mL, 25 mol%). The reaction was stirred for 1.5 h and then quenched by the addition of sat. aq. $NaHCO_3$ (1 ml). The organic layer was separated, dried using $MgSO_4$, and evaporated to give 29.3 mg of spiroketal **S43.4** (89%, 7:1 dr) as a nearly pure compound by ^{1}H and ^{13}C NMR. The isomers were inseparable by FCC. Spectral data for the major isomer: IR ν_{max} (neat) / cm^{-1} 3362, 3072, 3047, 2929, 2855, 1723, 1478, 1425, 1098, 825; δ_H (500 MHz, $CDCl_3$) 7.66-7.25 (7:1; 30H : 4H, m), 5.02 (1H, dd, J = 3.0, 8.75 Hz), 4.77

(1H, s), 3.65-3.56 (7:1; 4H : 0.6H, m), 3.49 (1H, dd, J = 3.5, 10.0 Hz), 3.39 (1H, d, J = 9.5 Hz), 3.30 (1H, d, J = 10.0 Hz), 2.42-2.34 (1H, m), 2.09 (1H, d, J = 15.0 Hz), 1.94-1.50 (7:1; 11H : 1.6H, m), 1.32 (3H, s), 1.05-0.96 (7:1; 30H : 4H, m), 0.90-0.84 (3H, s); δ_C (125 MHz, CDCl3) 214.9, 135.8, 135.7 (2), 135.6 (3), 133.9 (2), 133.4, 133.2, 133.0, 132.9, 129.7 (2), 129.5 (2), 127.7, 127.6 (2), 107.2, 79.5, 79.1, 72.3, 70.3, 69.7, 65.8, 45.0, 41.6, 40.8, 37.0, 32.6, 29.2, 28.3, 27.8, 26.9 (2), 20.4, 19.3 (2), 18.9, 13.5; *m/z* (ESIMS) 1089.3 $(M+1)^+$.



To a solution of **S43.2** (15 mg, 0.0127 mmol) in MeOH (0.5 ml) and $CDCl_3$ (1 ml) was added a 0.20 M solution of DMDO in $CHCl_3$ (1.27 ml, 0.255 mmol) dropwise at -40^{o}C. The reaction was allowed to warm to rt over 1 h and stirred at rt for 1 h. A 0.1 M solution of TsOH in MeOH (0.02 mL, 25 mol%) was added at rt. The reaction stirred for 1 h and was quenched by the addition of sat. aq. $NaHCO_3$ (0.5 ml). The organic layer was separated, dried using $MgSO_4$, and evaporated. FCC using 10% ethyl acetate-hexanes with 1% Et_3N gave 9.8 mg of spiroketal **S43.4** (71%, 7:1 dr).

Experimental Data for Route to S51.6



A suspension of 4 Å MS (3.5 g, activated by a gentle flame under vacuum) in CH_2Cl_2 (100 ml) was cooled to -40°C. L-diethyl tartrate (317 mg, 1.54 mmol) and Ti(O-iPr)$_4$ (437 mg, 1.54 mmol) were added and the reaction stirred at -40°C for 1 h. A 3.0 M solution of TBHP in CH_2Cl_2 (13 ml, 38.35 mmol) was added and the reaction stirred for an additional 1 h at -40°C. A solution of **S46.1**[59b] (5.0 g, 15.34 mmol) in CH_2Cl_2 (10 ml) was added at -40°C and the reaction was placed in a -30°C freezer. After 24 h, H_2O (30 ml) was added and the reaction was allowed to warm to rt. A solution of 30% aq. NaOH/NaCl (50 ml) was added at rt and stirring continued for 1 h. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. This material was taken on without further purification. Mosher ester analysis of this material revealed a >95:5 ee.

To a solution of crude epoxy alcohol in CH_2Cl_2 (100 ml) was added imidazole (2.61 g, 38.38 mmol), DMAP (936 mg, 7.67 mmol) and TESCl (3.45 g, 23.01 mmol) at 0°C. The reaction was allowed to warm to rt and monitored by tlc. Upon completion of the reaction, MeOH (20 ml) was added followed by H_2O (20 ml). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 2% ethyl acetate-

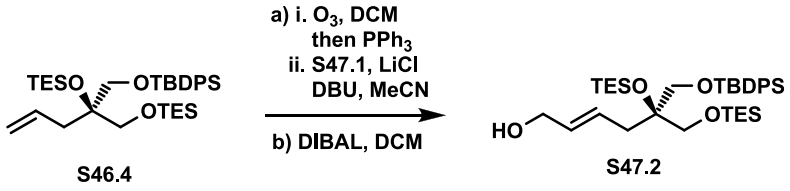
hexanes gave 6.23 g (89%, 2 steps) of **S46.3** as a clear colorless oil. $[\alpha]_D$ +1.1 (*c* = 0.042, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3068, 2953, 2925, 2876, 1425, 1102; δ_H (500 MHz, $CDCl_3$) 7.68-7.66 (4H, m), 7.44-7.36 (6H, m), 3.87-3.77 (4H, m), 2.75 (1H, d, J=5.5 Hz), 2.68 (1H, d, J=5.0 Hz), 1.05 (9H, s), 0.94 (9H, t, J=8.0 Hz), 0.59 (6H, q, J=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 135.6 (2), 133.3 (2), 129.7, 127.7, 63.8, 62.7, 60.0, 48.8, 26.8, 19.3, 6.7, 4.4; *m/z* (ESIMS) 479.2 $(M+23)^+$

S46.3 S46.4

To a suspension of CuBr•Me_2S (1.81 g, 8.77 mmol) in Et_2O (50 ml) and Me_2S (2 ml) was added a 1.0 M solution of vinyl MgBr in Et_2O (21.93 ml, 21.93 mmol) at -40°C. The dark green solution stirred at -40°C for 30 min and was cooled to -78°C. A solution of **S46.3** (1.0 g, 2.19 mmol) in Et_2O (5 ml) was added dropwise at -78°C. The reaction was allowed to warm to -15°C over 30 min and monitored by tlc. Upon completion of the reaction, saturated aq. NH_4Cl (20 ml) was added and reaction was allowed to warm to rt. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (3 x 20 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. The crude product was used for the next step without further purification.

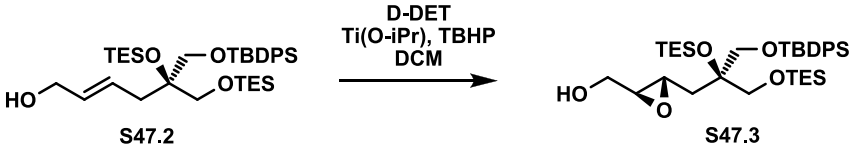
To a solution of crude alkene in CH_2Cl_2 (100 ml) was added 2,6-lutidine (2.54 ml, 21.93 mmol) and TESOTf (2.48 ml, 10.97 mmol) at rt. The reaction stirred at rt and was monitored by tlc. Upon completion of the reaction (1 h), H_2O (25 ml) was added and the CH_2Cl_2 layer was separated, dried using Na_2SO_4 and evaporated. FCC using hexanes

gave 1.27 g (97%, 2 steps) of **S46.4** as a clear colorless oil. $[\alpha]_D$ +4.3 (*c* = 0.023, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3068, 2953, 2876, 1462, 1425, 1106, 1004; δ_H (500 MHz, $CDCl_3$) 7.68-7.65 (4H, m), 7.43-7.35 (6H, m), 5.89-5.80 (1H, m), 5.02 (1H, d, J=15.0 Hz), 5.00 (1H, d, J=7.5 Hz), 3.62 (1H, d, J=9.5 Hz), 3.53 (2H, dd, J=12.5, 10.0 Hz), 3.47 (1H, d, J=10.0 Hz), 2.40-2.29 (2H, m), 1.06 (9H, s), 0.94 (9H, t, J=8.0 Hz), 0.877 (9H, t, J=8.0 Hz), 0.61-0.52 (12H, m); δ_C (125 MHz, $CDCl_3$) 136.0 (2), 134.8, 133.8, 129.8, 127.8, 117.2, 78.6, 67.0, 66.7, 39.6, 27.2, 19.5, 7.4, 7.1, 6.9, 4.6; *m/z* (ESIMS) 621.3 $(M+23)^+$



A solution of **S46.4** (1.88 g, 3.14 mmol) in CH_2Cl_2 (200 ml) was cooled to -78°C and O_3 was bubbled into the reaction. Upon completion by tlc, argon was bubbled into the reaction for 10 min at -78°C. PPh_3 (8.22 g, 31.39 mmol) was added and the reaction was allowed to warm to rt over 2 h. Stirring continued for an additional 24 h at rt before the solvent was evaporated. The crude aldehyde was taken up in MeCN (200 ml) followed by the addition of LiCl (396 mg, 9.42 mmol), DBU (1.43 g, 9.42 mmol) and phosphonate **S47.1** (2.11 g, 9.42 mmol). The reaction stirred at rt and was monitored by tlc. Upon completion of the reaction (~12 h), FCC (dry-loaded using silica gel) using 10% ethyl acetate-hexanes gave a mixture of product and PPh_3. This material was taken onto the next step without further purification. To a solution of crude ester in CH_2Cl_2 (150 ml) was added a 1.0 M solution of DIBAL in hexanes (7.85 ml, 7.85 mmol) dropwise at -78°C. The reaction stirred for 20 min at -78°C and was quenched by the

addition of sat. aq. Rochelle salt (50 ml). Upon warming to rt, the CH_2Cl_2 layer was separated, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-hexanes gave 1.76 g (89%, 3 steps) of **S47.2** as a clear colorless oil. $[\alpha]_D$ +6.6 (*c* = 0.009, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3379, 2949, 2872, 1466, 1421, 1090, 1004; δ_H (500 MHz, $CDCl_3$) 7.66 (4H, d, J=6.5 Hz), 7.42 (2H, t, J=7.0 Hz), 7.37 (4H, t, J=7.5 Hz), 5.70-5.60 (2H, m), 4.01 (2H, t, J=5.0 Hz), 3.61 (1H, d, J=10.0 Hz), 3.53 (2H, dd, J=10.0, 4.0 Hz), 3.44 (1H, d, J=10.0 Hz), 2.36-2.29 (2H, m), 1.06 (9H, s), 0.95 (9H, t, J=8.0 Hz), 0.87 (9H, t, J=8.0 Hz), 0.62-0.52 (12H, m); δ_C (125 MHz, $CDCl_3$) 136.0 (2), 133.7, 131.8, 129.8 (2), 129.2, 127.8 (2), 78.7, 66.8, 66.7 64.2, 37.7, 27.2, 19.4, 7.4, 7.1, 6.9, 4.6; *m/z* (ESIMS) 651.3 $(M+23)^+$

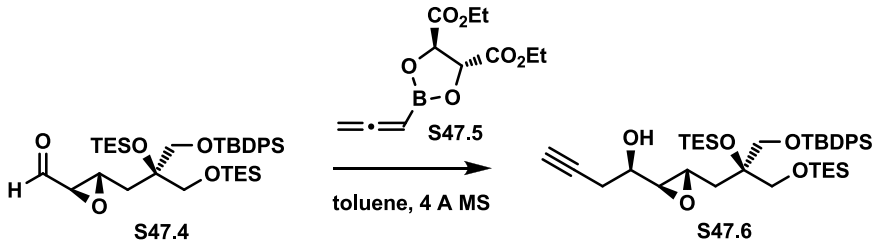


A suspension of 4 Å MS (500 mg, activated by a gentle flame under vacuum) in CH_2Cl_2 (30 ml) was cooled to -40°C. D-diethyl tartrate (270 mg, 1.31 mmol) and Ti(O-iPr)$_4$ (267 mg, 0.940 mmol) were added and the reaction stirred at -40°C for 1 h. A 3.0 M solution of TBHP in CH_2Cl_2 (1.75 ml, 5.2 mmol) was added and the reaction stirred for an additional 1 h at -40°C. A solution of **S47.2** (1.61 g, 2.56 mmol) in CH_2Cl_2 (5 ml) was added at -40°C and the reaction was placed in a -30°C freezer. After 24 h, H_2O (10 ml) was added and the reaction was allowed to warm to rt. A solution of 30% aq. NaOH/NaCl (10 ml) was added at rt and stirring continued for 1 h. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-

hexane gave 1.41 g (85%, 13:1 dr / inseparable mixture) of **S47.3** as a clear colorless oil. $[\alpha]_D$ +5.5 (*c* = 0.057, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3440, 2958, 2872, 1462, 1429, 1098, 1008; δ_H (500 MHz, $CDCl_3$) 7.68-7.63 (4H, m), 7.44-7.36 (6H, m), 3.83 (1H, ddd, J=12.0, 3.5, 2.5 Hz), 3.64 (2H, t, J=9.5 Hz), 3.55 (2H, t, J=9.5 Hz), 3.49 (1H, ddd, J=12.0, 3.5, 2.5 Hz), 3.04 (1H, td, J=6.0, 2.5, 1.5 Hz), 2.89-2.87 (1H, m), 1.96 (1H, dd, J=14.0, 5.5 Hz), 1.72 (1H, dd, J=14.0, 5.5 Hz), 1.63-1.60 (1H, m), 1.07 (9H, s), 0.93 (9H, t, J=8.0 Hz), 0.88 (9H, t, J=8.0 Hz), 0.61-0.53 (12H, m); δ_C (125 MHz, $CDCl_3$) 136.0 (2), 133.6, 133.5, 129.9 (2), 127.8 (2), 78.4, 67.2, 67.0, 62.0, 58.7, 52.3, 37.4, 27.2, 19.5, 7.3, 7.1, 6.8, 4.6; *m/z* (ESIMS) 667.3 $(M+23)^+$

To a solution of **S47.3** (1.30 g, 2.02 mmol) in CH_2Cl_2 (50 ml) was added pyridine (1 ml) and Dess-Martin periodinane (2.57 g, 6.06 mmol) at rt. Upon completion of the reaction by tlc, 1 M aq. Na_2SO_3 (10 ml) and sat. aq. $NaHCO_3$ (10 ml) were added and reaction stirred at rt for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-hexanes gave 1.08 g (83%) of **S47.4** as a clear colorless oil. $[\alpha]_D$ -8.1 (*c* = 0.029, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2949, 2876, 1736, 1466, 1433, 1098, 1012; δ_H (500 MHz, $CDCl_3$) 8.89 (1H, d, J=6.5 Hz), 7.66 (4H, t, J=8.5 Hz), 7.43 (2H, t, J=7.0 Hz), 7.38 (4H, t, J=7.0 Hz), 3.62 (2H, t, J=10.0 Hz), 3.57 (1H, d, J=10.0 Hz), 3.51 (1H, d, J=10.0 Hz), 3.31 (1H, td, J=8.0, 6.5, 1.5 Hz), 3.09 (1H,

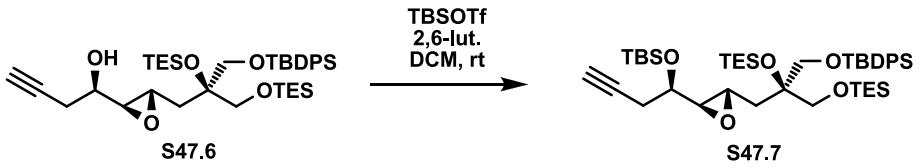
dd, J=6.5, 1.5 Hz), 1.94 (1H, dd, J=14.25, 6.5 Hz), 1.86 (1H, dd, J=14.5, 5.5 Hz), 1.07 (9H, s), 0.93 (9H, t, J=8.0 Hz), 0.86 (9H, t, J=8.0 Hz), 0.60-0.52 (12H, m); δ_C (125 MHz, $CDCl_3$) 198.8, 136.0, 135.9, 133.4 (2), 130.0 (2), 127.9 (2), 78.3, 67.2, 67.0, 59.3, 53.8, 36.7, 27.2, 19.5, 7.3, 7.0, 6.8, 4.5; *m/z* (ESIMS) 665.3 $(M+23)^+$



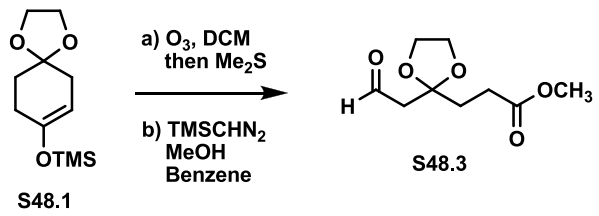
To a solution of allenyl boronic acid (700 mg, 8.33 mmol)[92] in dry toluene (30 ml) was added D-diethyl tartrate (2.08 g, 10.09 mmol), and 4 Å MS pellets (500 mg) at rt. The reaction stirred for 24 h at rt for the formation of allenyl boronate **S47.5**. After cooling the reaction to -78°C a solution of **S47.4** (1.02 g, 1.59 mmol) in toluene (5 ml) was added dropwise. The reaction stirred at -78°C for 12 h and was slowly allowed to warm to rt over 12 h. Upon warming to rt the reaction was complete by tlc. FCC (dry-loaded using silica gel) using 5% ethyl acetate-hexanes gave 1.07 g (99%, >95:5 dr) of **S47.6** as a clear colorless oil. $[\alpha]_D$ +1.3 (*c* = 0.013, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3432, 3301, 2945, 2872, 2120, 1470, 1425, 1106, 1000; δ_H (400 MHz, $CDCl_3$) 7.68-7.64 (4H, m), 7.44-7.33 (6H, m), 3.79-3.72 (1H, m), 3.67 (2H, dd, J=10.0, 5.6 Hz), 3.58 (2H, dd, J=10.0, 0.4 Hz), 3.16 (1H, td, J=5.8, 2.4, 2.0 Hz), 2.86 (1H, dd, J=4.2, 2.4 Hz), 2.45-2.43 (2H, m), 2.03 (1H, t, J=2.8 Hz), 2.00 (1H, d, J=3.6 Hz), 1.84 (2H, qd, J=14.2, 8.4, 6.0 Hz), 1.06 (9H, s), 0.93 (9H, t, J=8.0 Hz), 0.88 (9H, t, J=8.0 Hz), 0.62-0.54 (12H, m); δ_C (125 MHz, $CDCl_3$) 136.0, 135.9, 133.7, 133.6, 129.9, 129.8, 127.8, 80.0, 78.5, 71.1, 68.5,

(92) For the preparation of allenyl boronic acid as a suspension in hexanes see ref. 60

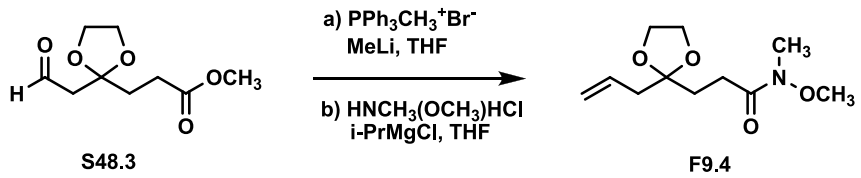
67.3, 66.9, 59.5, 52.9, 37.5, 27.2, 24.0, 19.5, 7.3, 7.1, 6.9, 4.6; *m/z* (ESIMS) 705.3 $(M+23)^+$



A solution of **S47.6** (1.04 g, 1.53 mmol) and 2,6-lutidine (1.06 ml, 9.15 mmol) in CH_2Cl_2 (30 ml) was cooled to -78°C. TBSOTf (1.40 ml, 6.10 mmol) was added dropwise at -78°C and the reaction was allowed to warm to rt over 15 min. Upon completion of the reaction by tlc, H_2O (10 ml) was added. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 3% ethyl acetate-hexanes gave 1.16 g (95%) of **S47.7** as a clear colorless oil. $[\alpha]_D$ +3.7 (*c* = 0.009, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3301, 2945, 2929, 2872, 2124, 1462, 1115; δ_H (500 MHz, $CDCl_3$) 7.68 (4H, t, J=8.0 Hz), 7.42-7.34 (6H, m), 3.82-3.79 (1H, m), 3.70 (1H, d, J=10.0 Hz), 3.66-3.61 (2H, m), 3.56 (1H, d, J=10.0 Hz), 3.16-3.14 (1H, m), 2.78 (1H, dd, J=3.5, 2.0 Hz), 2.38 (2H, dd, J=6.0, 2.5 Hz), 1.97 (1H, t, J=3.0 Hz), 1.93 (1H, d, J=4.5 Hz), 1.67 (1H, dd, J=14.5, 7.5 Hz), 1.05 (9H, s), 0.95-0.87 (27H, m), 0.61-0.54 (12H, m), 0.07 (3H, s), 0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 136.0, 135.9, 133.8, 133.7, 129.8, 129.7, 127.8, 81.1, 78.7, 70.4, 69.9, 67.3, 66.9, 59.6, 52.3, 37.7, 27.2, 26.0, 25.4, 19.5, 18.4, 7.4, 7.1, 6.9, 4.6, -4.4, -4.7; *m/z* (ESIMS) 820.4 $(M+23)^+$

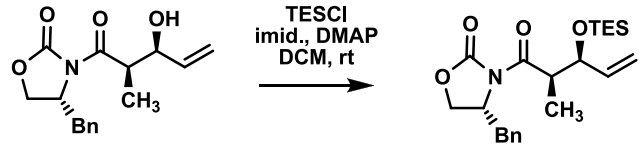


A solution of **S48.1** (5.59 g, 24.52 mmol) in CH_2Cl_2 (200 ml) was cooled to -78°C and O_3 was bubbled into the reaction. Upon completion by tlc (30 min), argon was bubbled into the reaction for 10 min at -78°C. Me_2S (25 ml) was added at -78°C and the reaction was slowly allowed to warm to rt over 2 hr. Stirring continued at rt for an additional 1 h before the solvent was evaporated. The crude residue was taken up in MeOH (25 ml) and benzene (50 ml) and a 2.0 M solution of $TMSCHN_2$ in ether (13.49 ml, 26.97 mmol) was added dropwise over the course of 30 min. Upon completion of the reaction by tlc, a small amount (~1 ml) of AcOH was added to quench the excess $TMSCHN_2$. The solvent was evaporated and FCC using 20% ethyl acetate-hexanes gave 4.66 g (94%, 2 steps) of **S48.3** as a pale yellow oil. IR ν_{max} (neat) / cm^{-1} 2953, 2892, 2851, 1732, 1450, 1307, 1037; δ_H (400 MHz, $CDCl_3$) 9.74 (1H, t, J=3.5 Hz), 4.01 (4H, s), 3.68 (3H, s), 2.68 (2H, d, J=3.5 Hz), 2.41 (2H, t, J=9.0 Hz), 2.10 (2H, t, J=9.5 Hz); δ_C (125 MHz, $CDCl_3$) 200.0, 173.7, 108.7, 65.4, 51.9, 50.9, 33.5, 28.5; *m/z* (ESIMS) 225.1 $(M+23)^+$



To a solution of $PPh_3CH_3^+Br^-$ (1.77 g, 4.95 mmol) in dry THF (20 ml) was added a 1.6 M solution of MeLi in Et_2O (3.02 ml, 4.83 mmol) dropwise at -78°C. The reaction

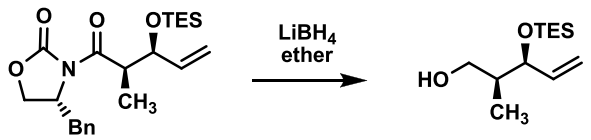
stirred at -78°C for 10 min and was let to warm to rt. After stirring at rt for 30 min the reaction was cooled to -20°C and a solution of **S48.3** (500 mg, 2.48 mmol) in dry THF (5 ml) was added dropwise. Stirring continued at 0°C for 2.5 h followed by an additional 1 h at rt. Upon consumption of **S48.3** by tlc, the reaction mixture was cooled to -15°C and $HNCH_3(OCH_3)$ HCl (364 mg, 3.71 mmol) was added followed by the dropwise addition of a 2.0 M solution of iPrMgCl in THF (3.71 ml, 7.43 mmol). The reaction stirred was allowed to warm to -10°C over a 5 min period and was quenched by the addition of sat. aq. NH_4Cl (10 ml). 40 ml of Et_2O was added and the Et_2O layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 70% Et_2O-pentane then 100% ether gave 349 mg (62%, 2 steps) of **F9.4** after slow evaporation of the volatile product. IR ν_{max} (neat) / cm^{-1} 3088, 2962, 2904, 1675, 1425, 1090, 1045, 996; δ_H (500 MHz, $CDCl_3$) 5.87-5.79 (1H, m), 5.14-5.09 (2H, m), 3.97 (4H, s), 3.69 (3H, s), 3.18 (3H, s), 2.51 (2H, t, J=7.5 Hz), 2.40 (2H, d, J=7.5 Hz), 2.01 (2H, t, J=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 174.6, 133.3, 118.5, 110.6, 65.3, 61.4, 42.3, 31.8; *m/z* (ESIMS) 230.1 $(M+1)^+$



S49.1 **S49.2**

To a solution of known syn α-hydroxyimide **S49.1**[65] (2.86 g, 9.90 mmol) in CH_2Cl_2 (75 ml) was added imidazole (1.68 g, 24.74 mmol), DMAP (302 mg, 2.47 mmol) and TESCl (1.86 g, 12.37 mmol) at rt. Upon completion of the reaction by tlc (1 h), MeOH (10 ml) and H_2O (20 ml) were added. The CH_2Cl_2 layer was separated and the

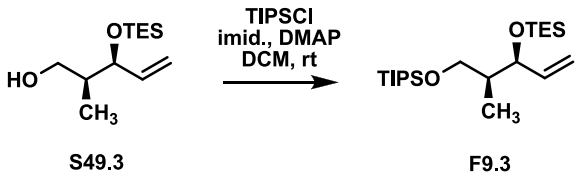
aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 5% ethyl acetate-hexanes gave 3.18 g (80%) of **S49.2** as a clear colorless oil. $[\alpha]_D$ -60.0 (*c* = 0.013, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2949, 2868, 1781, 1695, 1376, 1213, 1017; δ_H (500 MHz, $CDCl_3$) 7.33 (2H, t, J=7.0 Hz), 7.27 (1H, t, J=7.5 Hz), 7.22 (2H, d, J=7.0 Hz), 5.87 (1H, ddd, J=10.5, 6.5 Hz), 5.19 (1H, d, J=17.0 Hz), 5.10 (1H, d, J=10.5 Hz), 4.63-4.58 (1H, m), 4.32 (1H, t, J=6.5 Hz), 4.17-4.11 (2H, m), 4.05-3.99 (1H, m), 3.28 (1H, dd, J=13.5, 3.0 Hz), 2.77 (1H, dd, J=13.25, 9.5 Hz), 1.22 (3H, d, J=7.0 Hz), 0.94 (9H, t, J=8.0 Hz), 0.58 (6H, q, J=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 174.9, 153.4, 139.4, 135.6, 129.7, 129.1, 127.5, 116.0, 75.7, 66.2, 55.9, 44.3, 38.1, 13.0, 7.0, 5.1; *m/z* (ESIMS) 426.1 $(M+23)^+$



S49.2 **S49.3**

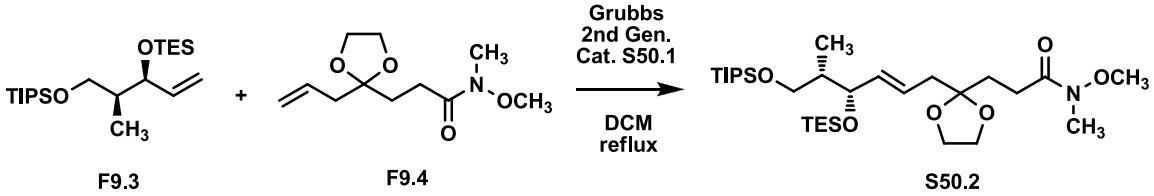
To a solution of **S49.2** (3.18 g, 7.90 mmol) in Et_2O (100 ml) and H_2O (1 ml) was added a 2.0 M solution of $LiBH_4$ in Et_2O (7.46 ml, 14.92 mmol) dropwise at 0^oC. The reaction was warmed to rt and monitored by tlc. Upon completion of the reaction (30 min), saturated aq. $NaHCO_3$ (30 ml) was added at rt. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 5% ethyl acetate-hexanes gave 1.28 g (70%) of **S49.3** as a clear colorless oil. $[\alpha]_D$ -11.8 (*c* = 0.010, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3366, 2945, 2876, 1462, 1405, 1237, 1029; δ_H (500 MHz, $CDCl_3$) 5.89 (1H, ddd, J=10.5, 6.5 Hz), 5.23 (1H, d, J=17.0 Hz), 5.19 (1H, d, J=10.5 Hz), 4.25 (1H, t, J=5.0 Hz), 3.66 (1H, ddd, J=8.5, 3.0, 2.0 Hz), 3.49 (1H, ddd, J=7.25, 4.5, 4.0 Hz), 2.95 (1H, dd,

J=7.25, 3.5 Hz), 2.06-1.98 (1H, m), 0.96 (9H, t, J=8.0 Hz), 0.81 (3H, d, J=7.0 Hz), 0.61 (6H, q, J=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 137.7, 116.3, 78.1, 66.0, 41.0, 12.7, 7.0, 5.0; *m/z* (ESIMS) 230.1 $(M)^+$



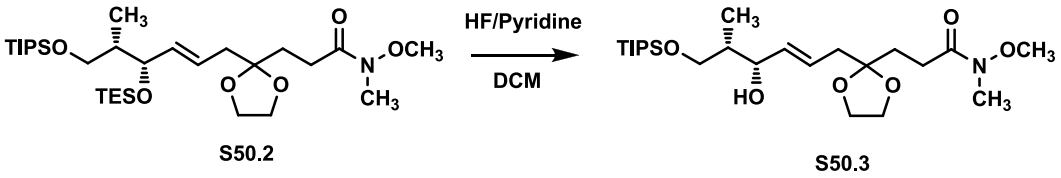
S49.3 **F9.3**

To a solution of **S49.3** (1.24 g, 5.39 mmol) in CH_2Cl_2 (30 ml) was added imidazole (733 mg, 10.78 mmol), DMAP (165 mg, 1.35 mmol, and TIPSCl (1.20 g, 6.19 mmol) at rt and the reaction was monitored by tlc. Upon completion of the reaction, H_2O (10 ml) was added and the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 ml) and the CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using hexanes gave 1.80 g (87%) of **F9.3** as a clear colorless oil. $[\alpha]_D$ -5.4 (*c* = 0.056, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2949, 2859, 1462, 1233, 1102, 1066, 1008; δ_H (500 MHz, $CDCl_3$) 5.82 (1H, ddd, J=10.5, 6.5 Hz), 5.14 (1H, d, J=17.5 Hz), 5.50 (1H, d, J=10.0 Hz), 4.24 (1H, t, J=5.5 Hz), 3.68 (1H, dd, J=9.75, 6.5 Hz), 3.49 (1H, dd, J=9.5, 6.5 Hz), 1.71-1.63 (1H, m), 1.10-1.01 (21H, m), 0.95 (9H, t, J=8.0 Hz), 0.89 (3H, d, J=7.0 Hz), 0.59 (6H, q, J=8.0 Hz); δ_C (125 MHz, $CDCl_3$) 140.9, 114.4, 74.3, 65.4, 43.0, 18.3, 12.3, 11.7, 7.1, 5.2; *m/z* (ESIMS) 387.0 $(M+1)^+$



F9.3 **F9.4** **S50.2**

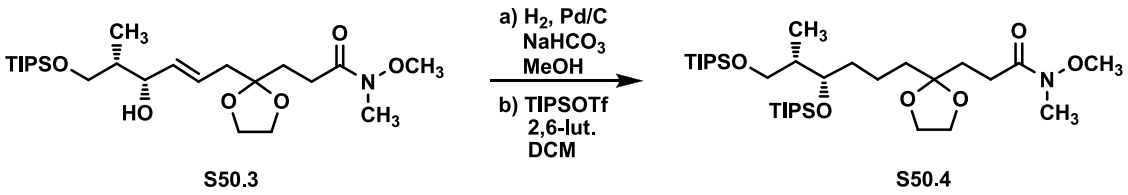
To a solution of **F9.3** (1.21 g, 3.13 mmol) and **F9.4** (1.50 g, 6.55 mmol) in bulk CH_2Cl_2 (30 ml) was added Grubbs 2nd generation catalyst **S50.1** (260 mg, 0.30 mmol). The reaction was refluxed for 24 h. FCC (dry-loaded using silica gel) using 20% then 35% ethyl acetate-hexanes gave 1.34 g (73%, 5:1 E/Z) of **S50.2** as a pale orange oil. The trace metals in this material were removed using a procedure reported by Kim employing activated charcoal.[66] $[\alpha]_D$ -0.6 (*c* = 0.025, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2949, 2872, 1675, 1470, 1254, 1102, 1049, 1012; δ_H (400 MHz, $CDCl_3$) 5.59-5.49 (2H, m), 4.21 (1H, t, J=4.4 Hz), 3.94 (4H, s), 3.71-3.67 (4H, m), 3.46 (1H, dd, J=9.6, 6.4 Hz), 3.17 (3H, s), 2.49 (2H, d, J=8.0 Hz), 2.44-2.32 (2H, m), 1.99 (2H, d, J=8.0 Hz), 1.69-1.64 (1H, m), 1.09-1.02 (21H, m), 0.93 (9H, t, J=8.0 Hz), 0.88 (3H, d, J=6.8 Hz), 0.58 (6H, t, J=8.0 Hz); δ_C (100 MHz, $CDCl_3$) 174.5, 136.3, 124.7, 110.7, 73.8, 65.4, 65.3, 65.2, 61.4, 43.3, 40.7, 31.9, 18.3, 12.2, 11.8, 7.1, 5.2; *m/z* (ESIMS) 610.4 $(M+23)^+$



S50.2 S50.3

To a solution of **S50.2** (77 mg, 0.13 mmol) and pyridine (0.10 ml) in CH_2Cl_2 (5 ml) was added HF/pyridine (0.10 ml) at 0°C. The reaction stirred at 0°C and was monitored by tlc. Upon completion of the reaction, H_2O (1 ml) was added and the CH_2Cl_2 layer was separated, dried using Na_2SO_4 and evaporated. FCC using 40% ethyl acetate-hexanes gave 61 mg (98%) of **S50.3** as a clear colorless oil. $[\alpha]_D$ +0.70 (*c* = 0.026, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3460, 2949, 2868, 1666, 1466, 1102; δ_H (500 MHz, $CDCl_3$) 5.73-5.59 (2H, m), 4.30-4.24 (1H, m), 3.96 (4H, s), 3.79-3.74 (2H, m), 3.69 (3H, s), 3.34 (1H, d, J=5.0 Hz), 3.17 (3H, s), 2.50 (2H, t, J=7.5 Hz), 2.46-2.36 (2H, m), 2.01 (2H, t,

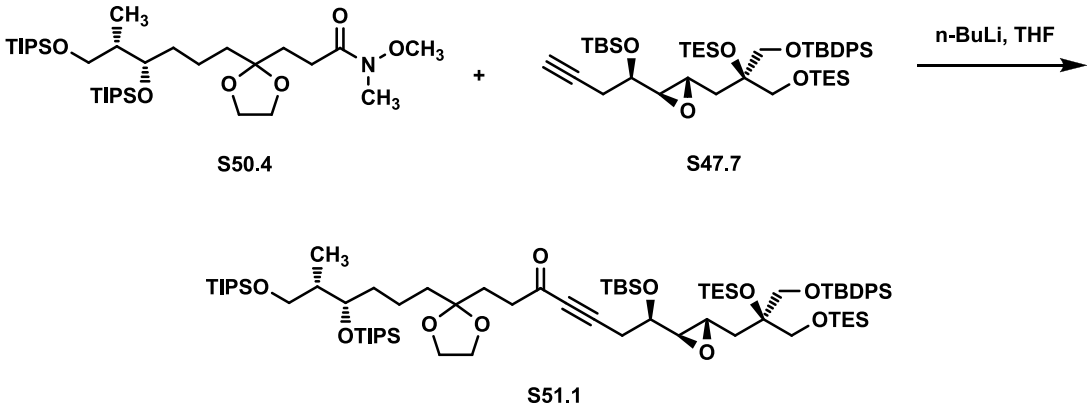
J=7.0 Hz), 1.95-1.89 (1H, m), 1.14-1.06 (21H, m), 0.88 (3H, d, J=7.0 Hz); δ_C (125 MHz, $CDCl_3$) 174.6, 134.5, 126.0, 110.7, 75.8, 67.9, 65.3, 61.4, 40.9, 40.2, 31.9, 18.2 (2), 12.0, 11.5; *m/z* (ESIMS) 496.3 $(M+23)^+$



S50.3 **S50.4**

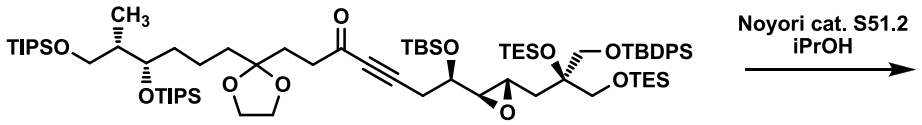
A suspension of **S50.3** (460 mg, 0.97 mmol), $NaHCO_3$ (60 mg, 0.71 mmol) and 10 wt. % palladium on activated carbon (30 mg, 0.09 mmol) in MeOH (5 ml) was stirred at rt under a balloon filled with H_2. Upon completion by tlc (12 h), the reaction was filtered through a pad of celite and the MeOH was evaporated. To a solution of the crude alcohol in CH_2Cl_2 (10 ml) was added 2,6-lutidine (0.37 ml, 3.22 mmol) and the solution was cooled to -78°C. TIPSOTf (0.39 ml, 1.45 mmol) was added dropwise at -78°C and the reaction was allowed to warm to rt. Upon completion by tlc at rt, the reaction was quenched by the addition of MeOH (1 ml) then H_2O (5 ml). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 30% ethyl acetate-hexanes gave 521 mg (85%, 2 steps) of **S50.4** as a clear colorless oil. $[\alpha]_D$ +4.7 (*c* = 0.009, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2937, 2864, 1671, 1466, 1380, 1102, 1049; δ_H (400 MHz, $CDCl_3$) 3.99-3.87 (5H, m), 3.72 (1H, dd, J=9.6, 6.8 Hz), 3.69 (3H, s), 3.53 (1H, dd, J=9.4, 7.2 Hz), 3.18 (3H, s), 2.50 (2H, t, J=7.6 Hz), 1.97 (2H, t, J=8.4 Hz), 1.78-1.70 (1H, m), 1.62 (1H, dd, J=10.0, 6.8 Hz), 1.57-1.18 (5H, m), 1.09-0.94 (42H, m), 0.85 (3H, d,

J=6.8 Hz); δ_C (125 MHz, $CDCl_3$) 174.5, 111.0, 72.5, 66.0, 65.0, 61.2, 40.0, 37.5, 34.9, 31.7, 20.0, 18.3 (2), 18.1 (2), 17.9 (2), 13.0, 12.0, 10.2; *m/z* (ESIMS) 654.4 $(M+23)^+$

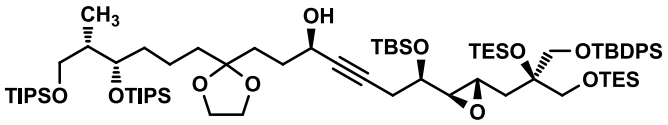


To a solution of **S47.7** (1.17 g, 1.47 mmol) in dry THF (40 ml) was added a 1.6 M solution on n-BuLi in hexanes (0.78 ml, 1.25 mmol) at -78°C. After stirring for 30 min at -78°C, **S50.4** (494 mg, 0.78 mmol) in dry THF (3 ml) was added dropwise. The reaction was allowed to warm to 0°C over a 20 min period and was monitored by tlc. Upon completion at 0°C, saturated aq. NH_4Cl (10 ml) and Et_2O (50 ml) were added and the reaction was allowed to warm to rt. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 ml). The Et_2O layers were combined, dried using $MgSO_4$ and evaporated. FCC using 3% ethyl acetate-hexanes gave 1.02 g (95%) of **S51.1** as a clear colorless oil. $[\alpha]_D$ +5.8 (*c* = 0.007, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2949, 2929, 2868, 2218, 1679, 1458, 1254, 1111, 1017; δ_H (500 MHz, $CDCl_3$) 7.69-7.66 (4H, m), 7.42-7.35 (6H, m), 3.98-3.96 (1H, m), 3.91 (4H, s), 3.76-3.67 (3H, m), 3.63 (2H, dd, J=16.75, 10.5 Hz), 3.53 (1H, d, J=10.0 Hz), 3.54-3.49 (1H, m), 3.11-3.10 (1H, m), 2.69 (1H, dd, J=4.5, 2.0 Hz), 2.59 (2H, t, J=7.5 Hz), 2.55-2.54 (2H, m), 2.02-1.98 (3H, m), 1.77-1.72 (1H, m), 1.63-1.13 (7H, m), 1.05-0.99 (51H, m), 0.96-0.84 (30H, m), 0.61-0.54 (12H, m), 0.09

(3H, s), 0.07 (3H, s); δ_C (125 MHz, $CDCl_3$) 187.3, 136.0, 135.9, 133.8, 133.7, 129.8, 127.8 (2), 110.9, 90.4, 82.3, 78.6, 72.8, 70.2, 67.3, 67.0, 66.2, 65.4, 59.3, 53.2, 40.4, 40.3, 38.1, 37.4, 35.2, 31.5, 29.9, 27.2, 26.0, 25.9, 20.3, 19.5, 18.6, 18.5, 18.4, 18.3 (2), 18.2, 13.3, 12.3, 10.5, 7.4, 7.1, 6.9, 4.6, -4.3, -4.7; *m/z* (ESIMS) 1390.3 $(M+23)^+$



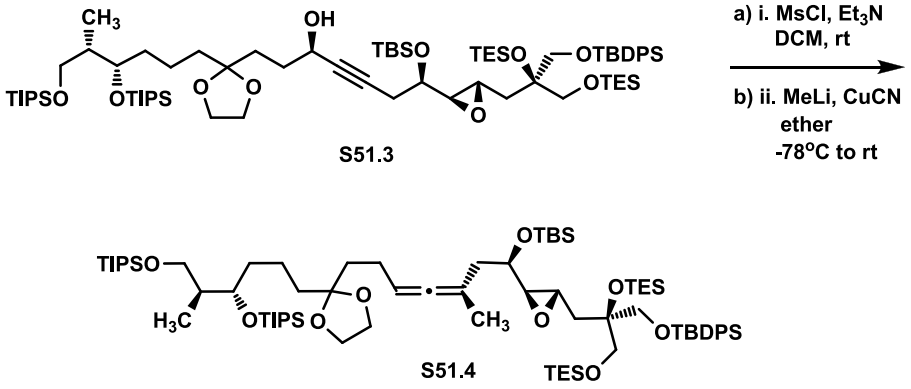
S51.1



S51.3

Noyori catalyst **S51.2** (88 mg, 0.15 mmol) was prepared according to the procedure used in Chapter 5 (pg. 160). To **S51.2** was added dry isopropanol (30 ml) at rt. Upon complete dissolution of the catalyst, **S51.1** (987 mg, 0.72 mmol) in dry isopropanol (5 ml) was added in 0.5 ml portions over a 30 min period at rt. Upon completion of the reaction by tlc (1 h), the isopropanol was evaporated. FCC using 8% ethyl acetate-hexanes gave 931 mg (94%, >95:5 dr) of **S51.3** as a clear colorless oil. $[\alpha]_D$ +4.7 (*c* = 0.011, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 3407, 2949, 2933, 2868, 1462, 1254, 1086; δ_H (500 MHz, $CDCl_3$) 7.69-7.66 (4H, m), 7.42-7.35 (6H, m), 4.38-4.34 (1H, m), 3.98-3.90 (5H, m), 3.75-3.72 (2H, m), 3.70 (1H, d, J=9.5 Hz), 3.64 (2H, s), 3.55 (1H, d, J=10.5 Hz), 3.52 (1H, dd, J=9.5, 7.0 Hz), 3.13-3.11 (1H, m), 2.74 (1H, dd, J=4.0, 2.0 Hz), 2.42-2.40 (2H, m), 1.97 (1H, dd, J=14.5, 3.5 Hz), 1.83-1.14 (13H, m), 1.10-0.99 (51H, m), 0.96-0.84 (30H, m), 0.61-0.53 (12H, m), 0.07 (3H, s), 0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 136.0,

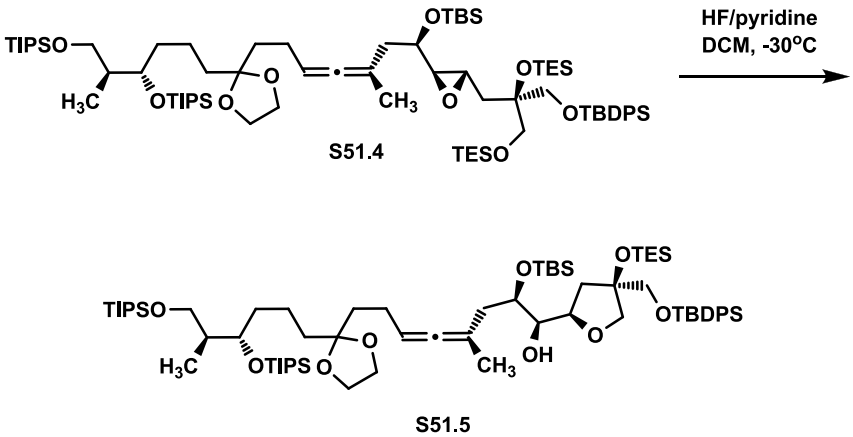
135.9, 133.8, 133.7, 129.8, 127.8, 111.6, 83.0, 82.0, 78.7, 72.7, 70.3, 67.2, 66.9, 66.2, 65.2, 62.8, 59.6, 52.4, 40.3, 37.7, 37.6, 35.1, 33.0, 32.4, 29.9, 27.2, 25.9, 25.8, 20.3, 19.5, 18.6, 18.5, 18.4, 18.3, 18.2, 13.2, 12.2, 10.5, 7.4, 7.1, 6.9, 4.6, -4.3, -4.7; *m/z* (ESIMS) 1392.6 $(M+23)^+$



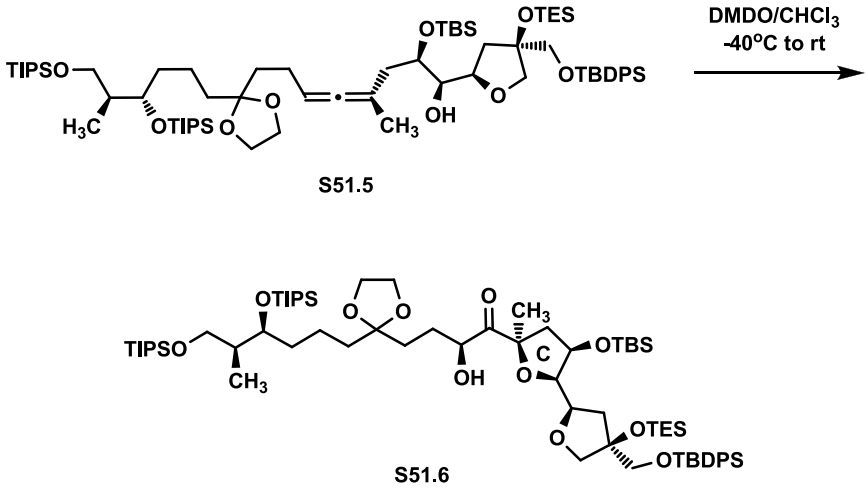
To a solution of propargyl alcohol **S51.3** (913 mg, 0.67 mmol) in CH_2Cl_2 (30 ml) was added Et_3N (0.46 ml, 3.33 mmol) and MsCl (0.16 ml, 2.0 mmol) dropwise at -78°C. The reaction was allowed to warm to rt over 1 h, and stirred at rt for 30 min. The reaction was quenched by addition of H_2O (5 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 ml). The organic layers were combined, dried using Na_2SO_4, filtered and evaporated to give the crude mesylate which was used for the next step without further purification.

In a separate round-bottom flask, a suspension of CuCN (297 mg, 3.33 mmol, activated by a gentle flame under high vacuum) in anhydrous Et_2O (30 ml) was degassed for 2 min with argon. The suspension was cooled to -78°C and a solution of 1.6 M MeLi in Et_2O (2.08 ml, 3.33 mmol) was added dropwise. The reaction mixture was warmed to

0^{o}C at which point it became a colorless homogeneous solution. The solution was cooled back to -78^{o}C and the mesylate (above) in anhydrous Et_2O (2 ml) was added dropwise. The reaction was allowed to warm to rt over 1 h and monitored by tlc. Upon completion by tlc, saturated aq. NH_4Cl (10 ml) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 ml). The organic layers were combined, dried using $MgSO_4$, filtered and evaporated. FCC using 5% ethyl acetate-hexanes gave 862 mg (95%) of **S51.4** as a clear colorless oil. $[\alpha]_D$ -17.6 (*c* = 0.006, $CHCl_3$). IR ν_{max} (neat) / cm^{-1} 2933, 2868, 1965, 1458, 1249, 1094, 1012; δ_H (500 MHz, $CDCl_3$) 7.70-7.67 (4H, m), 7.42-7.34 (6H, m), 5.04-4.98 (1H, m), 3.99-3.96 (1H, m), 3.91-3.89 (4H, m), 3.86-3.83 (1H, m), 3.71 (1H, dd, J=10.0, 7.0 Hz), 3.71 (1H, d, J=10.0 Hz), 3.64 (2H, s), 3.56 (1H, d, J=10.0 Hz), 3.53 (1H, dd, J=10.0, 7.0 Hz), 3.15-3.14 (1H, m), 2.65 (1H, t, J=2.5 Hz), 2.18 (1H, dd, J=13.75, 7.0 Hz), 2.10 (1H, dd, J=15.0, 8.0 Hz), 2.04-1.97 (2H, m), 1.97 (1H, dd, J=15.0, 8.0 Hz), 1.78-1.26 (10H, m), 1.68 (3H, d, J=3.0 Hz), 1.08-1.00 (51H, m), 0.96-0.84 (30H, m), 0.60-0.55 (12H, m), 0.02 (3H, s), 0.01 (3H, s); δ_C (125 MHz, $CDCl_3$) 202.7, 136.0, 135.9, 133.8, 133.7, 129.7, 127.8, 111.6, 96.4, 89.9, 78.7, 72.7, 69.4, 67.3, 66.9, 66.1, 65.3, 60.4, 51.5, 40.3, 40.2, 37.8, 37.7, 37.2, 35.1, 27.1, 26.0, 23.8, 20.2, 20.1, 19.5, 18.6, 18.5, 18.4, 18.3(2), 18.1, 13.2, 12.2, 10.4, 7.4, 7.1, 6.9, 4.6, -4.3, -4.9; *m/z* (ESIMS) 1390.5 $(M+23)^+$



To a solution of **S51.4** (30 mg, 0.02 mmol) in CH_2Cl_2 (5 ml) was added HF/pyridine (0.1 ml) dropwise over a 10 min period at -30°C. The reaction was slowly allowed to warm to -25°C over 1 h and was monitored by tlc. Upon completion of the reaction, saturated aq. $NaHCO_3$ (1 ml) was added. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 ml). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated. FCC using 3% ethyl acetate-hexanes gave 15 mg (55%) of **S51.5** as a clear colorless oil. $[\alpha]_D$ -9.5 (*c* = 0.023, $CHCl_3$); IR ν_{max} (neat) / cm^{-1} 3444, 2945, 1964, 1640, 1465, 1249, 1098, 1057; δ_H (500 MHz, $CDCl_3$) 7.65 (4H, d, J=7.0 Hz), 7.44-7.36 (6H, m), 5.04-4.98 (1H, m), 4.21-4.17 (1H, m), 4.10 (1H, d, J=9.0 Hz), 3.99-3.94 (2H, m), 3.92-3.87 (4H, m), 3.76-3.74 (1H, m), 3.72 (1H, dd, J=10.0, 7.0 Hz), 3.62-3.54 (3H, m), 3.52 (1H, dd, J=10.0, 7.0 Hz), 2.25-2.12 (4H, m), 2.04-2.00 (2H, m), 1.87 (1H, dd, J=10.0, 7.0 Hz), 1.78-1.67 (3H, m), 1.69 (3H, d, J=3.0 Hz), 1.62-1.11 (6H, m), 1.08-0.99 (51H, m), 0.89-0.84 (21H, m), 0.51 (6H, q, J=8.0 Hz), 0.08 (3H, s), 0.07 (3H, s); δ_C (125 MHz, $CDCl_3$) 202.8, 135.9, 133.5 (2), 129.9, 127.9, 111.6, 96.4, 89.9, 84.5, 78.8, 76.2, 75.7, 72.8, 72.0, 66.9, 66.2, 65.3, 40.4, 38.9, 38.7, 37.6, 37.2, 35.2, 27.1, 26.2, 26.1, 23.9, 20.3, 19.9, 19.5, 18.6, 18.5, 18.3(2), 18.1, 13.3, 12.3, 10.5, 7.2, 6.6, -4.3, -4.4; *m/z* (ESIMS) 1275.6 $(M+23)^+$



To a solution of **S51.5** (40 mg, 0.03 mmol) in $CDCl_3$ (1 ml) was added a solution of DMDO (~0.20 M) in $CHCl_3$ (0.50 ml, 0.10 mmol) dropwise at -40°C. The reaction was slowly allowed to warm to rt over the course of 1 h. Upon completion of the reaction by tlc, the solvent was evaporated. FCC using 3% ethyl acetate-hexanes gave 24 mg (59%) of **S51.6** as an inseparable 13:1 dr of products. $[\alpha]_D$ +5.3 (*c* = 0.008, $CHCl_3$); IR ν_{max} (neat) / cm^{-1} 3456, 2929, 2859, 1711, 1630, 1461, 1249, 1098, 1053; δ_H (500 MHz, $CDCl_3$) 7.67 (4H, d, J=7.0 Hz), 7.48-7.40 (6H, m), 4.76-4.73 (1H, m), 4.32 (1H, d, J=3.5 Hz), 4.02 (1H, d, J=9.0 Hz), 3.99-3.96 (1H, m), 3.91-3.85 (6H, m), 3.73 (1H, dd, J=10.0, 7.0 Hz), 3.63-3.57 (3H, m), 3.54 (1H, dd, J=10.0, 7.0 Hz), 3.24 (1H, d, J=6.0 Hz), 2.42 (1H, d, J=13.0 Hz), 2.19-2.03 (2H, m), 1.96-1.91 (2H, m), 1.79-1.16 (10H m), 1.43 (3H, s), 1.10-0.94 (51H, m), 0.90-0.83 (21H, m), 0.53 (6H, q, J=8 Hz), 0.02 (6H, s); δ_C (125 MHz, $CDCl_3$) 218.1, 135.9, 135.8, 133.4, 133.3, 130.1, 127.9, 111.6, 91.3, 89.3, 84.4, 79.6, 76.6, 74.4, 73.7, 72.8, 66.6, 66.3, 65.2 , 47.7, 40.6, 40.3, 37.9, 35.2, 32.5, 29.9, 28.3, 27.2, 25.8, 25.7, 20.1, 19.5, 18.6, 18.5, 18.3, 18.1, 13.2, 12.4, 10.4, 7.2, 6.6, -4.8, -4.9; *m/z* (ESIMS) 1307.7 $(M+23)^+$

Appendix 1

List of Abbreviations

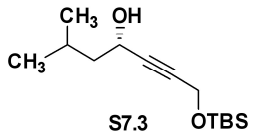
^{o}C	degrees Celsius
2,6-lut.	2,6-lutidine
Ac	acetate
acac	acetylacetonate
AIBN	azobis(isobutyronitrile)
Bn	benzyl
Boc	*t*-butyloxycarbonyl
Bu	butyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
δ	chemical shift (parts per million)
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-bezoquinone
DET	diethyl tartrate
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
diphos	1,2-bis(diphenylphosphino)ethane
DMAP	4-(*N,N*-dimethylamino)pyridine

DMDO	dimethyldioxirane
DMF	dimethylformamide
ee	enantiomeric excess
FCC	flash column chromatography
h	hour(s)
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphorus triamide
Hz	hertz
i	iso
imid.	imidazole
LC_{50}	concentration that will eliminate 50% of a given population when administered as a single dose
LiDBB	lithium di-*tert*-butyldiphenylide
m	multiplet
M	molar (moles/liter)
m/z	mass to charge ratio
m-CBA	meta-chlorobenzoic acid
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minutes
ml	milliliters
mol	moles
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
MTP	methoxytrifluoromethylphenyl

n-BuLi	n-butyllithium
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Nu	nucleophile
[O]	oxidant
OTf	trifluoromethanesulfonyl
P	protecting group (generic)
p	para
Pd/C	palladium on carbon
Ph	phenyl
Piv	pivaloyl
PMB	(4-methoxy)benzyl
PMP	4-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTX	pectenotoxin
R	rectus (Cahn-Inglod-Prelog system)
R	alkyl group (generic)
rt	room temperature
s	singlet
S	sinister (Cahn-Inglod-Prelog system)
SDE	spirodiepoxide
SEM	2-trimethylsilylethoxymethoxy

t	tertiary
t	triplet
TAS-F	tris(dimethylamino)sulfur(trimethylsilyl)difluoride
TBAF	terta(*n*-butyl)ammonium fluoride
TBAI	terta(n-butyl)ammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBODPS	*tert*-butoxydiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-BuLi	*tert*-butyllithium
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-n-propylammonium perruthenate
TsDPEN	N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine

Appendix 2: Spectral Data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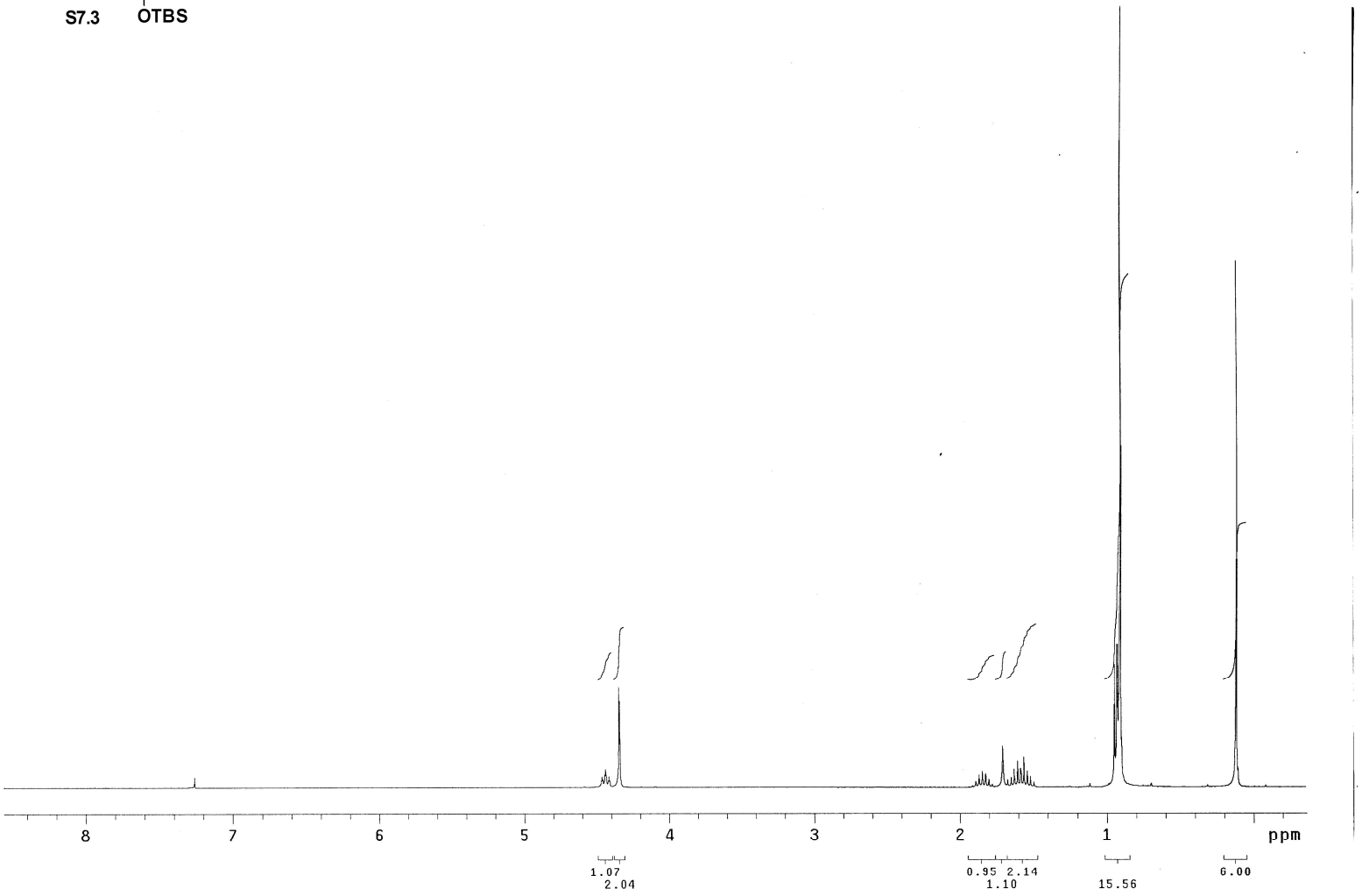
CH3
S7.3
OTBS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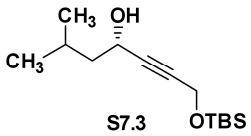
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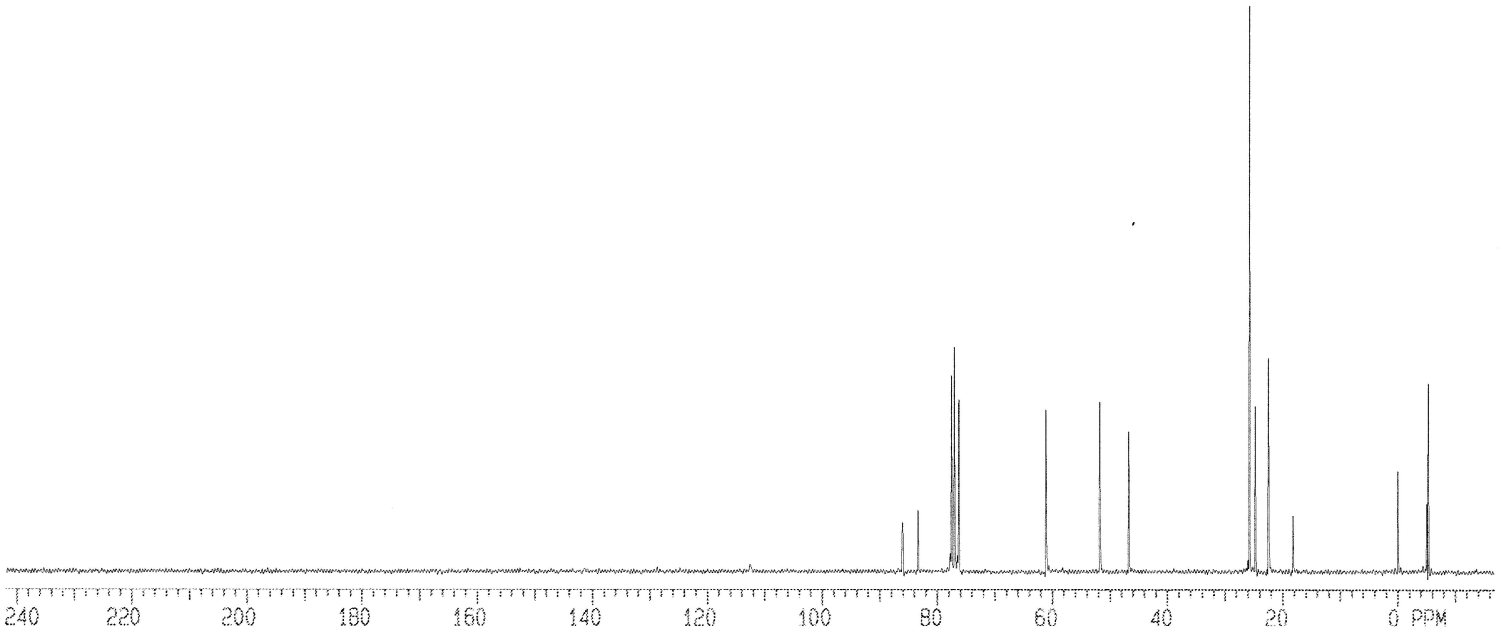
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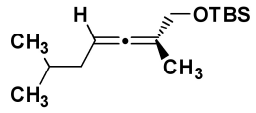

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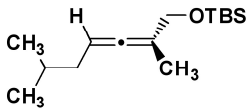

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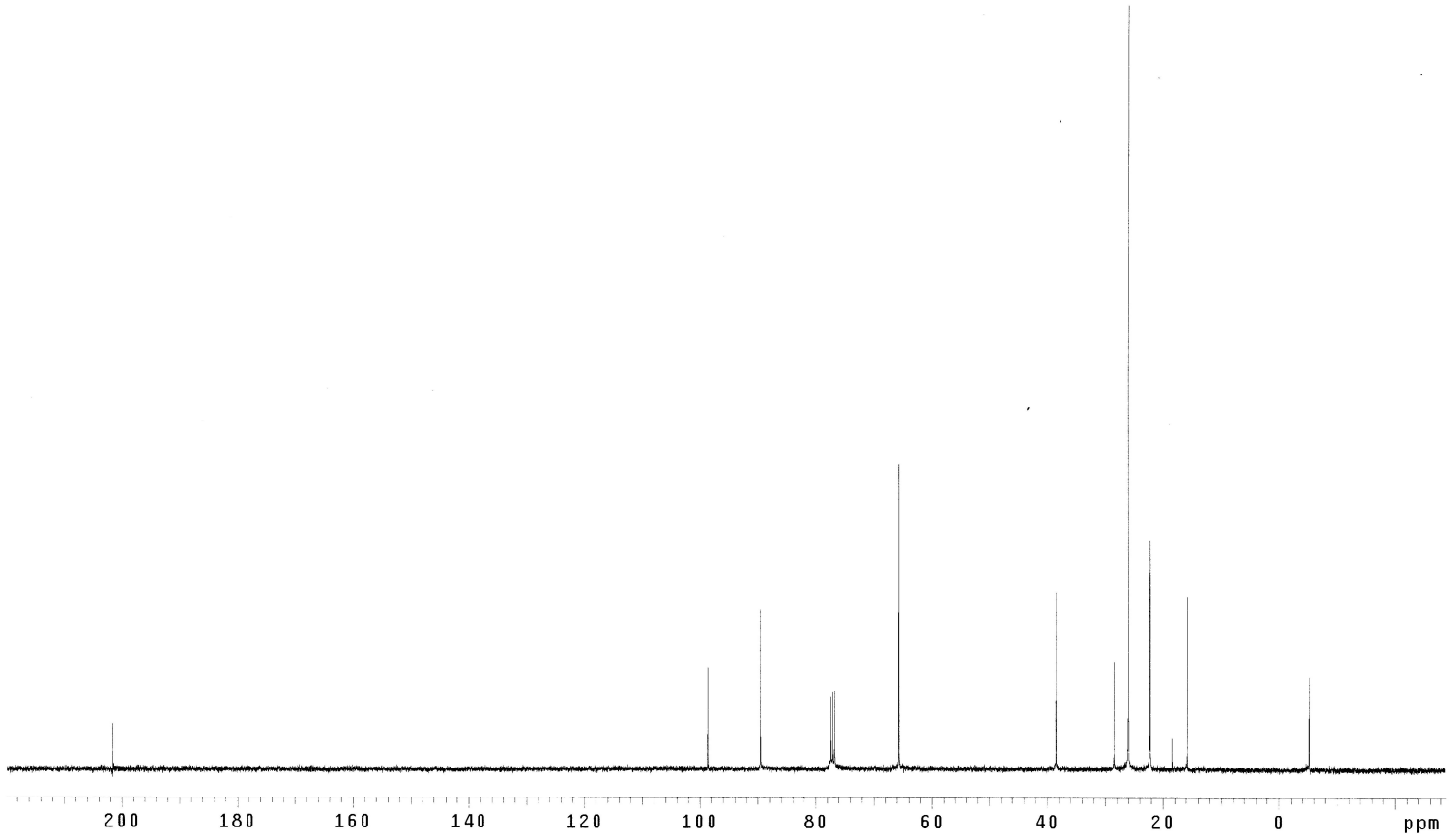
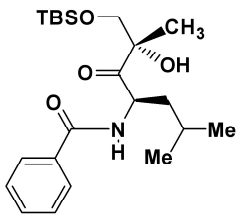
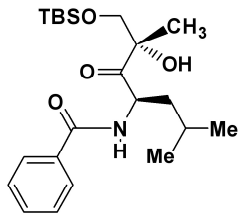


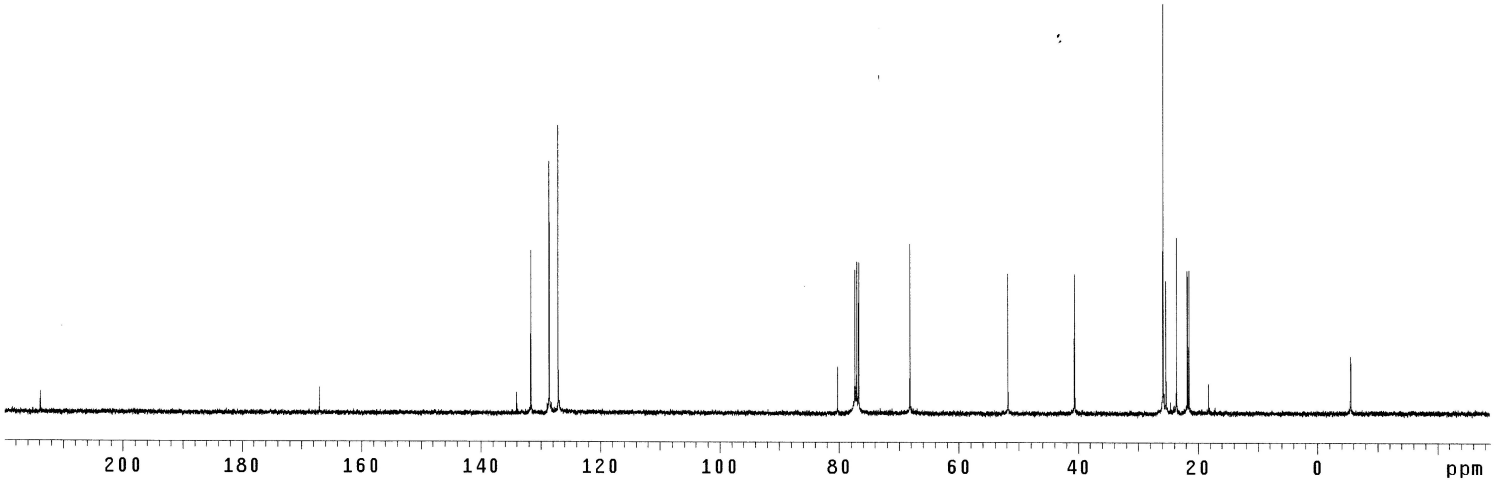

TBSO
CH3
OH
O
O
N
H
Me
Me

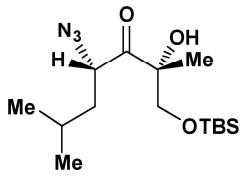
S8.3

10
9
8
7
6
5
4
3
2
1
-0
ppm
1.88
3.16
1.00
0.85
1.10
1.79
3.67
4.46
16.67
6.03



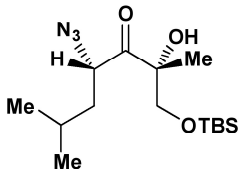
S8.3



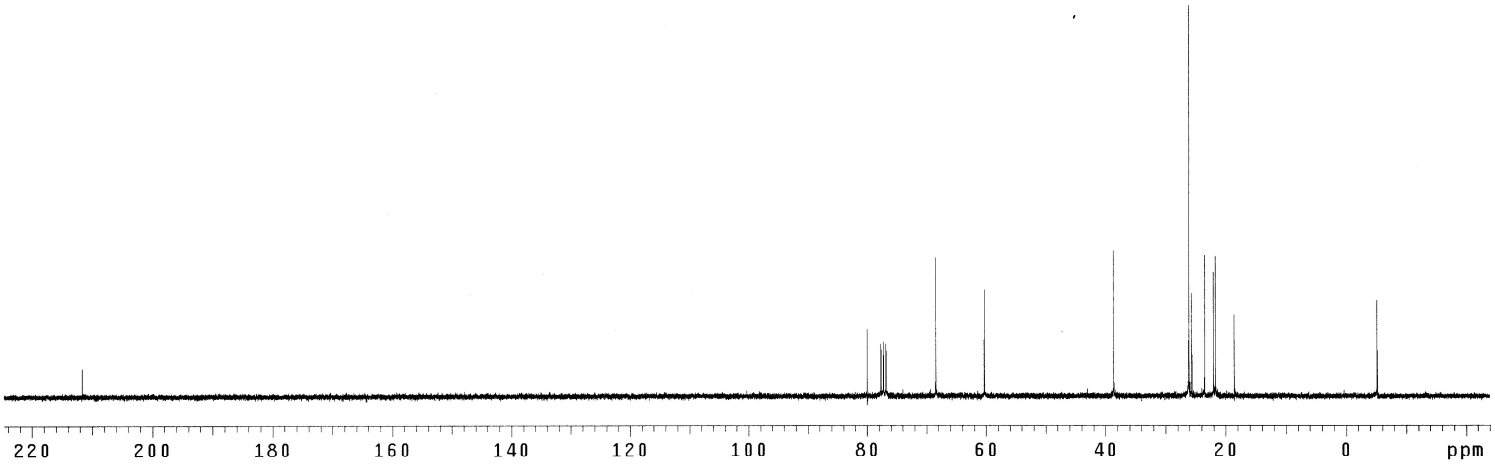

O
N3
H
OH
Me
Me
OTBS
Me

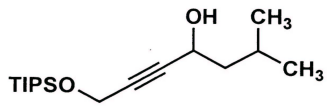
S8.5

10
9
8
7
6
5
4
3
2
1
-0
ppm
0.87
1.00
1.90
3.20
3.25
15.65
5.44

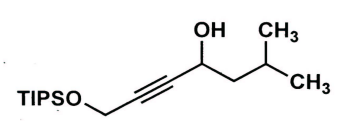


S8.5



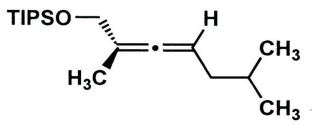


T2.1b

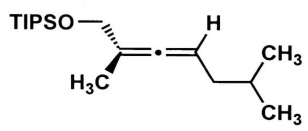

OH
CH3
CH3
TIPSO

T2.1b

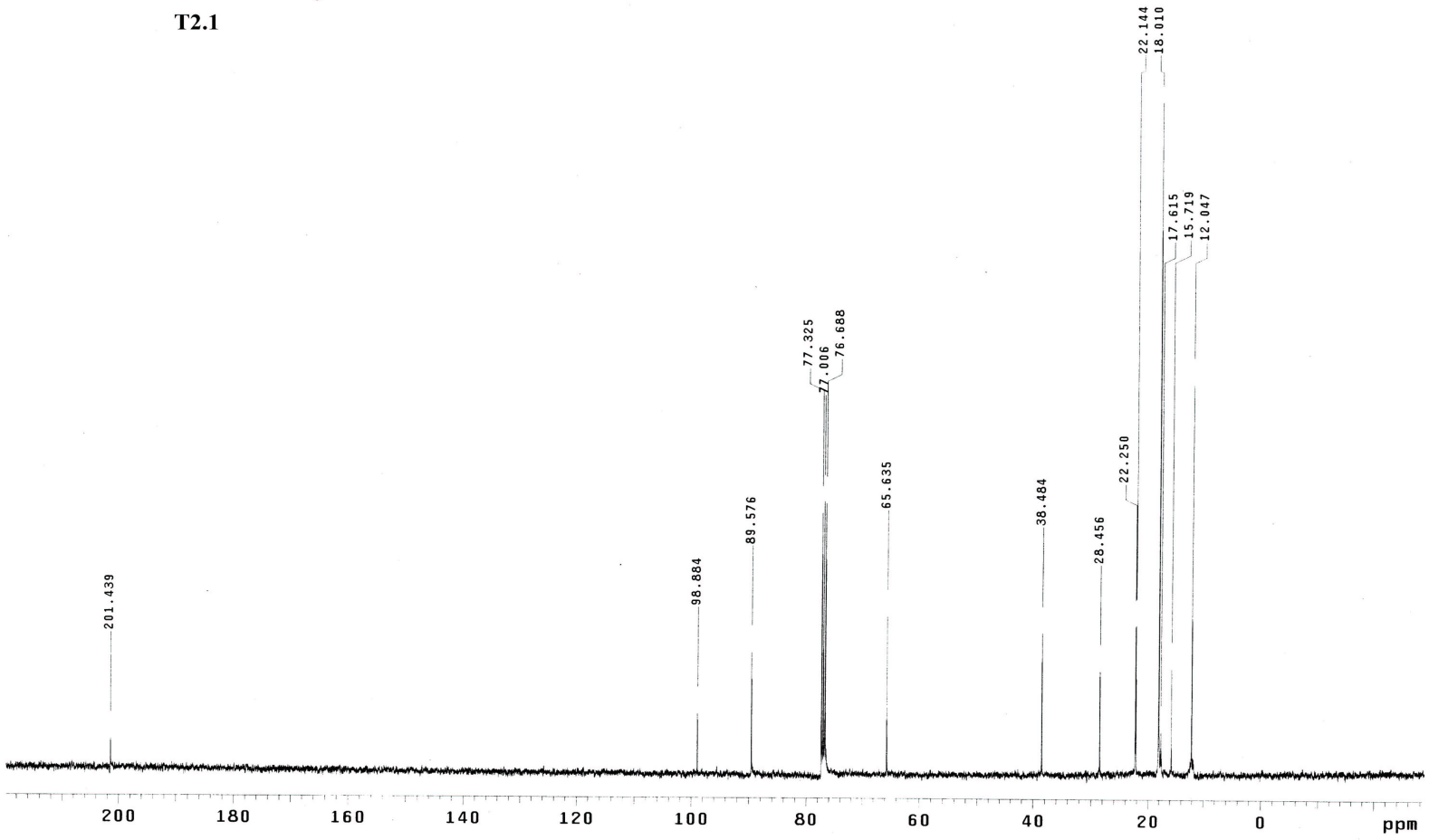
85.783
83.568
77.325
77.006
76.688
61.106
51.950
46.730
24.701
22.478
17.904
11.971
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

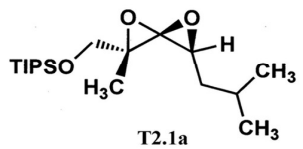


T2.1

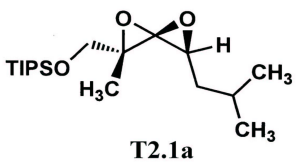

TIPSO
H
CH3
H3C
CH3

T2.1


201.439
98.884
89.576
77.325
77.006
76.688
65.635
38.484
28.456
22.250
22.144
18.010
17.615
15.719
12.047
200
180
160
140
120
100
80
60
40
20
0
ppm

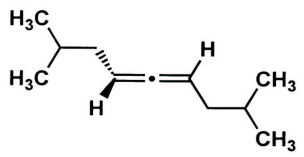


T2.1a

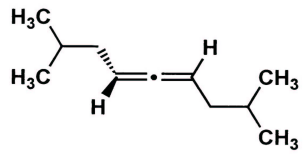

O
O
H
TIPSO
H3C
CH3
CH3

T2.1a

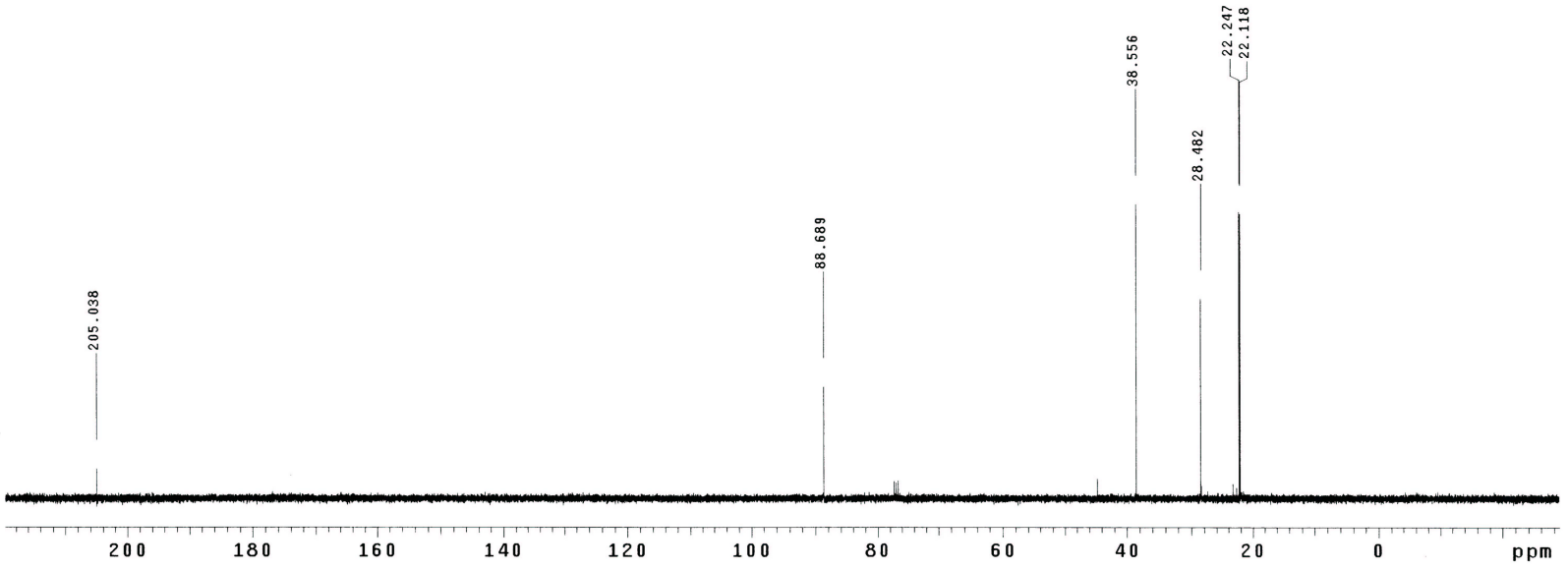
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

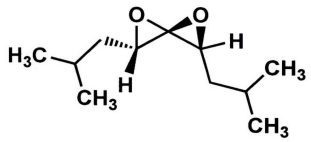


T1.1

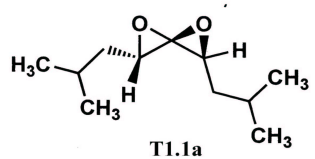

H3C
H3C
H
H
CH3
CH3

T1.1

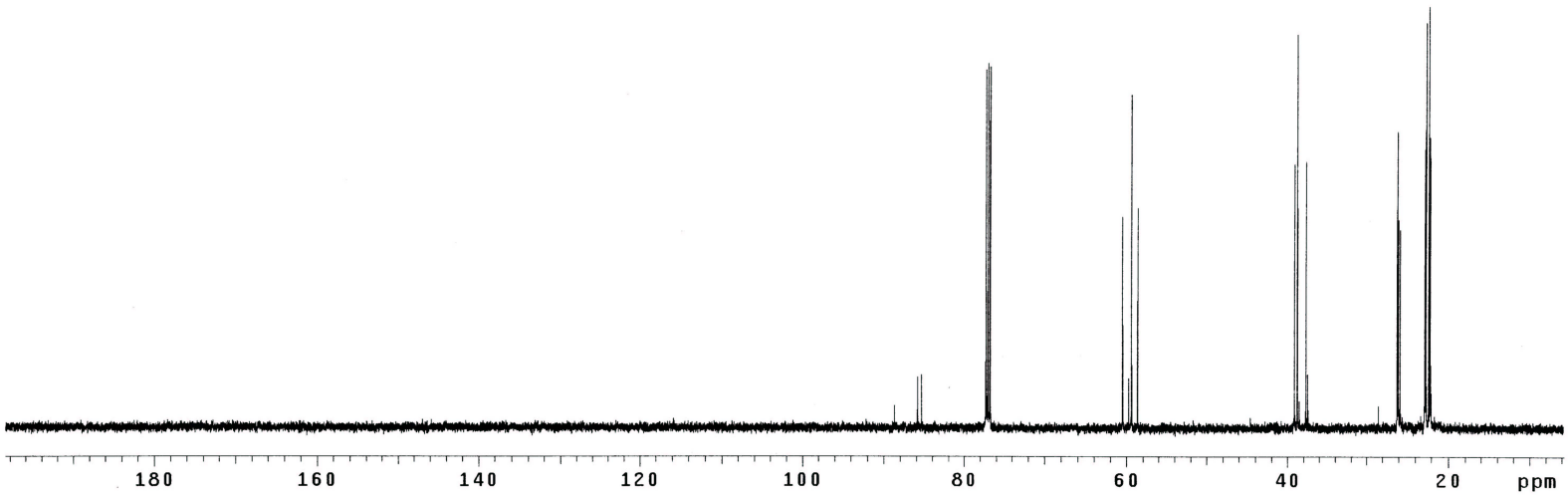

205.038
88.689
38.556
28.482
22.247
22.118
200
180
160
140
120
100
80
60
40
20
0
ppm

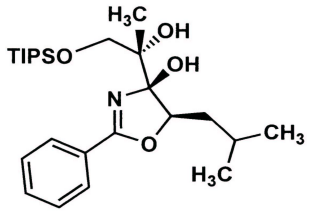


T1.1a



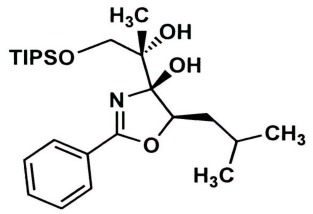
T1.1a





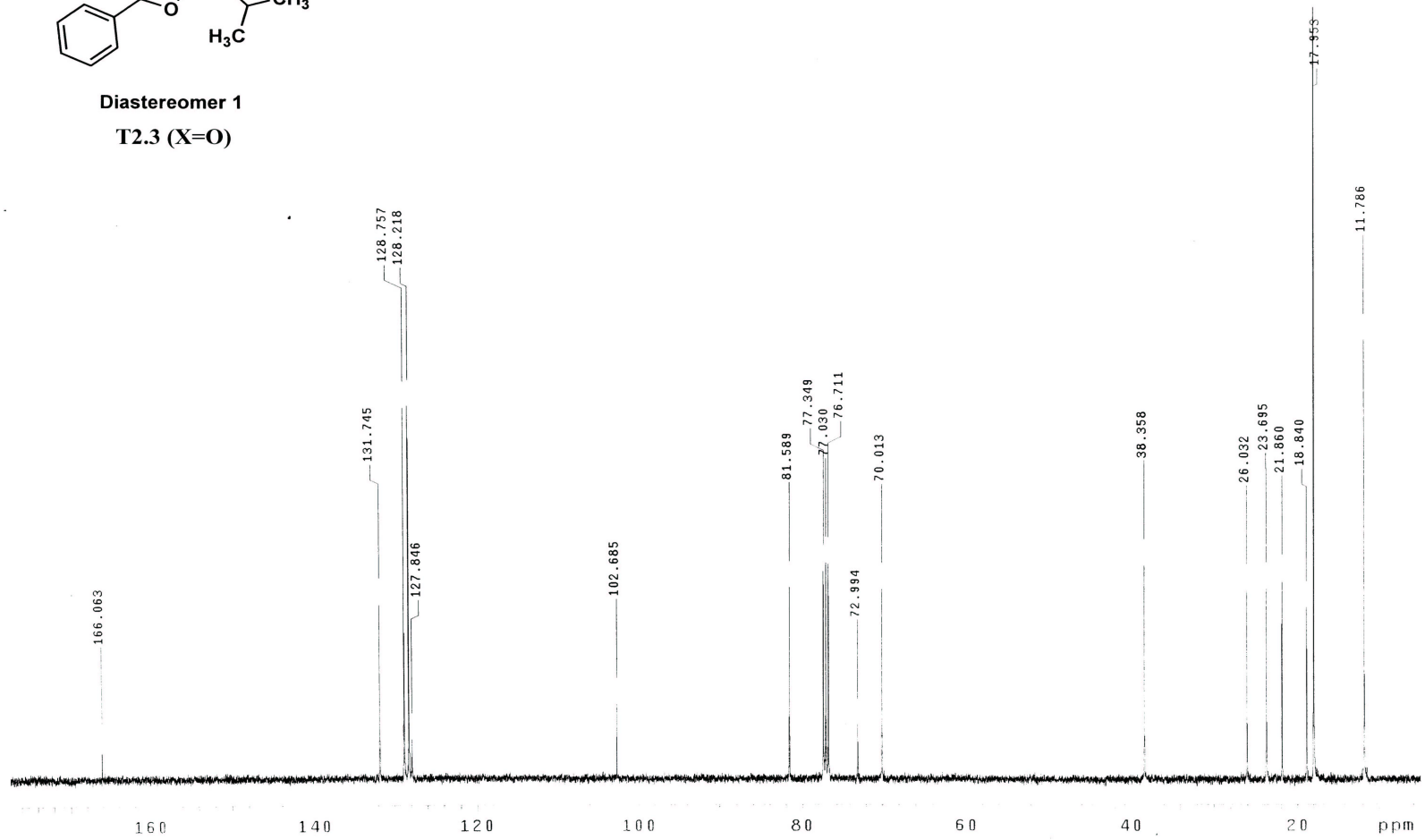
Diastereomer 1

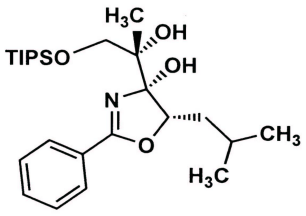
T2.3 (X=O)



Diastereomer 1

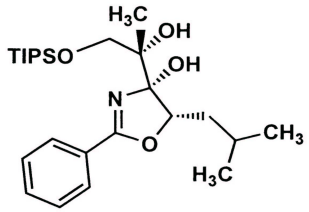
T2.3 (X=O)





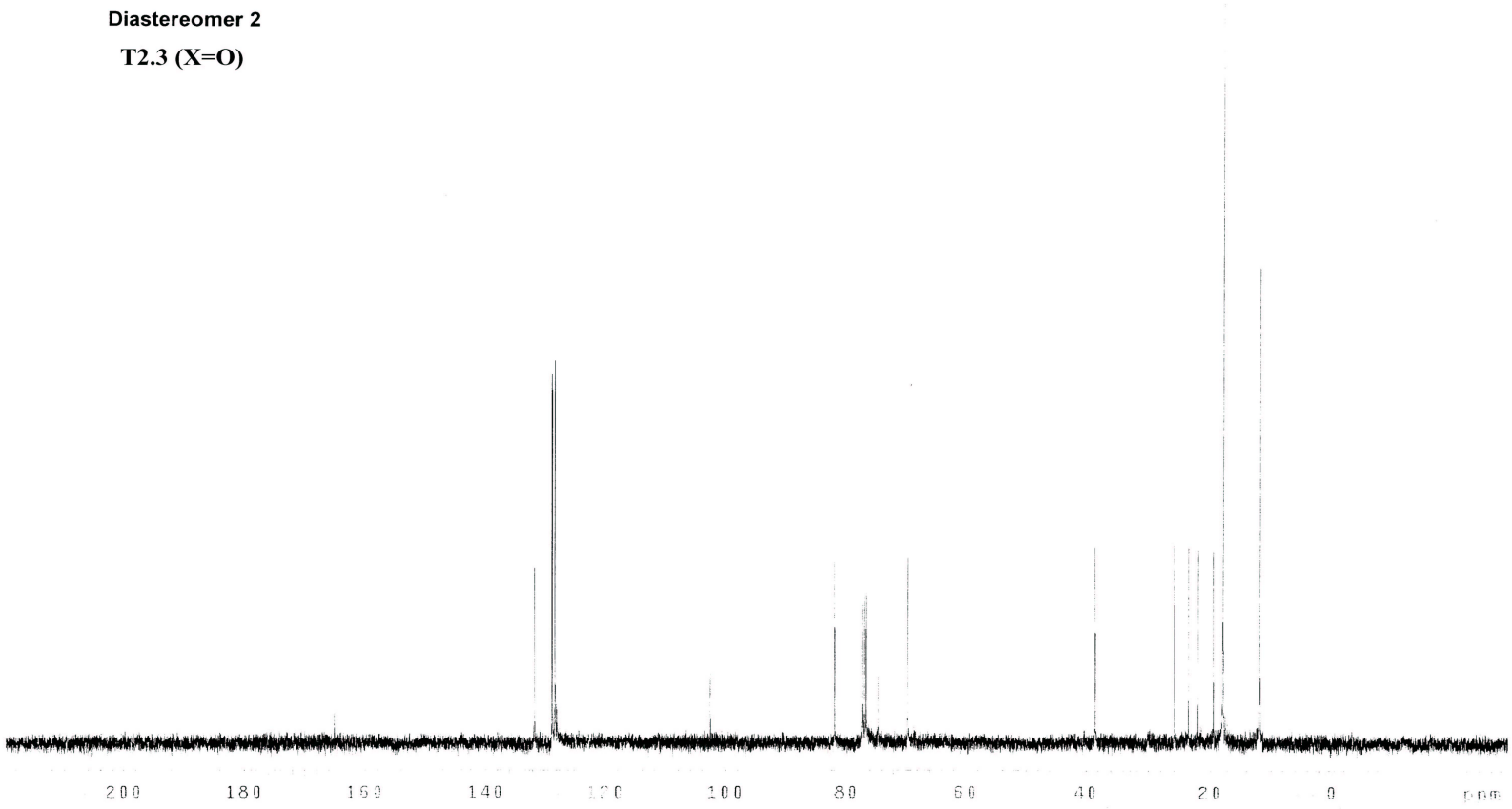
Diastereomer 2

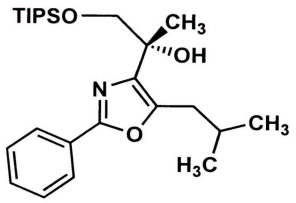
T2.3 (X=O)



Diastereomer 2

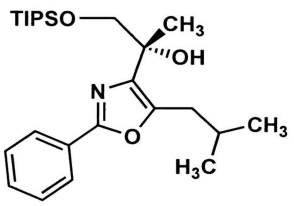
T2.3 (X=O)



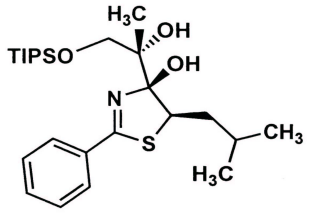

TIPSO
CH3
OH
N
O
CH3
H3C

T2.5 (X=O)

9
8
7
6
5
4
3
2
1
ppm
1.46
2.47
1.00
0.97
0.87
2.00
1.16
2.47
25.43

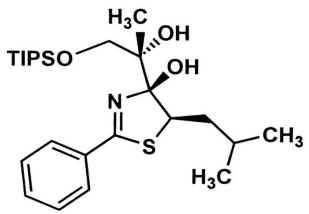


T2.5 (X=O)



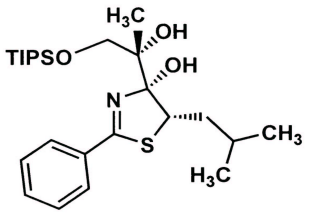
Diastereomer 1

T2.3 (X=S)



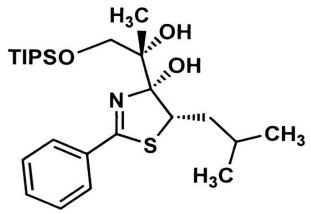
Diastereomer 1

T2.3 (X=S)



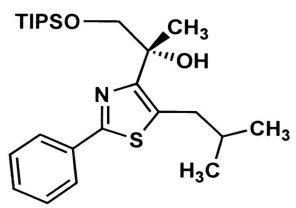
Diastereomer 2

T2.3 (X=S)



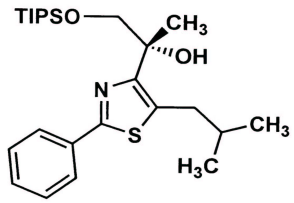
Diastereomer 2

T2.3 (X=S)

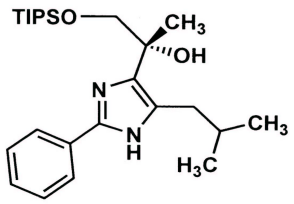

TIPSO
CH3
OH
N
S
CH3
H3C

T2.5 (X=S)

9
8
7
6
5
4
3
2
1
0
ppm
1.54
2.62
1.03
1.00
0.77
2.19
0.93
2.86
26.77

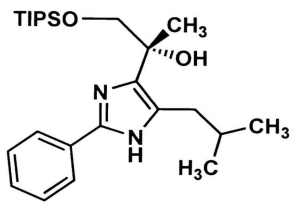


T2.5 (X=S)


TIPSO
CH3
OH
N
N
H
CH3
H3C

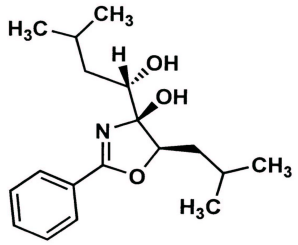
T2.5 (X=NH)

10
9
8
7
6
5
4
3
2
1
ppm
1.45
0.78
1.66
2.07
2.00
1.03
2.90
5.24
19.61


TIPSO
CH3
OH
N
N
H
CH3
H3C

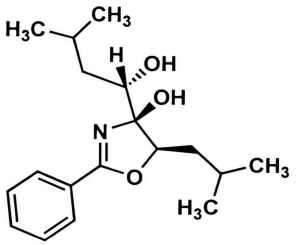
T2.5 (X=NH)

17.908
17.885
11.885
128.719
124.919
77.311
76.992
76.681
128.112
25.456
22.634
22.550
130.365
76.454
71.144
143.116
29.393
12.181
160
140
120
100
80
60
40
20
ppm

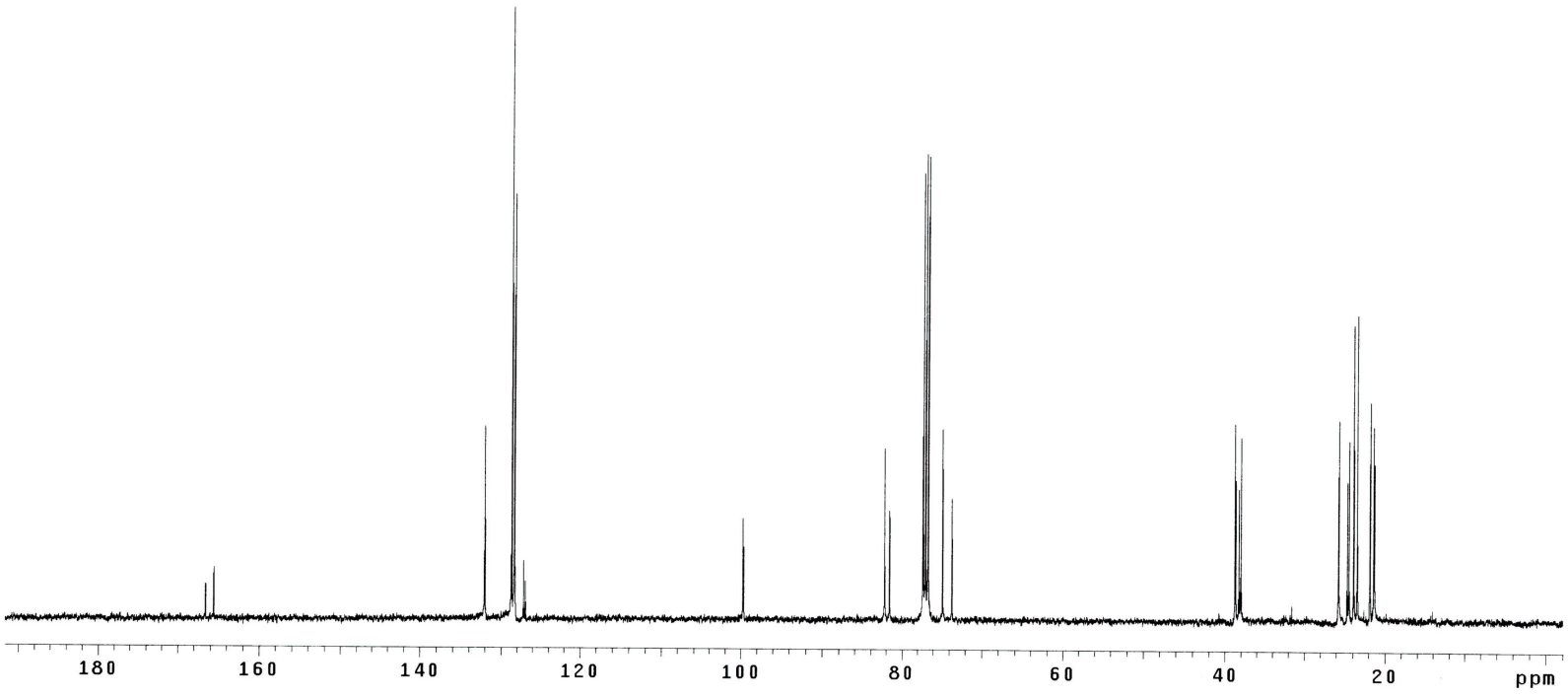

H3C
CH3
H
OH
OH
N
O
CH3
H3C

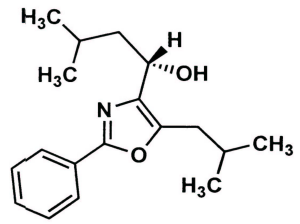
T2.2 (X=O)

11
10
9
8
7
6
5
4
3
2
1
-0
ppm
2.00
3.01
0.74
1.04
3.21
3.63
6.50
6.63

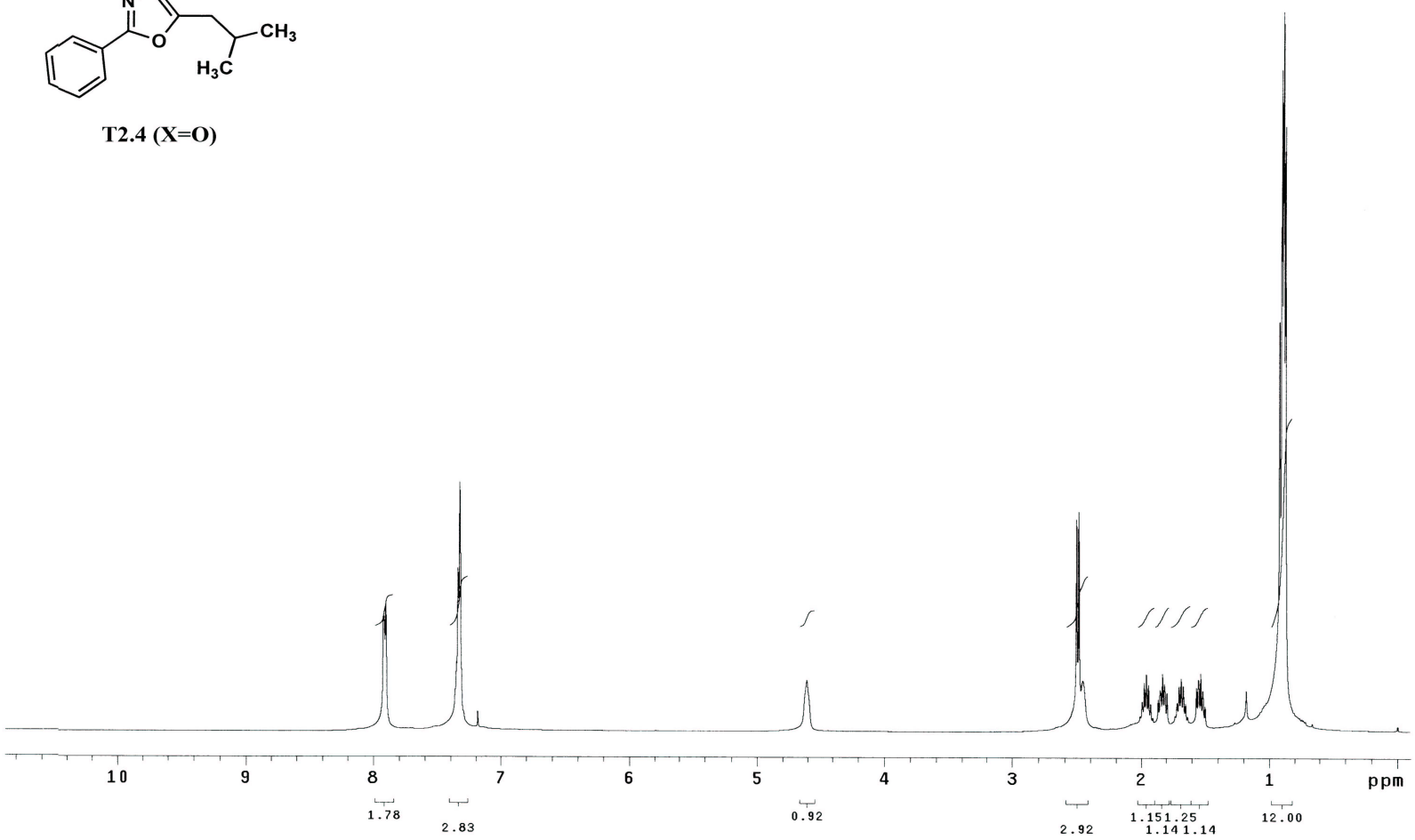


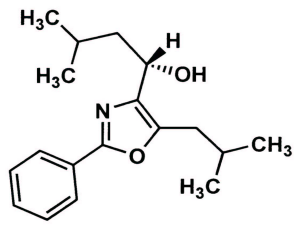
T2.2 (X=O)



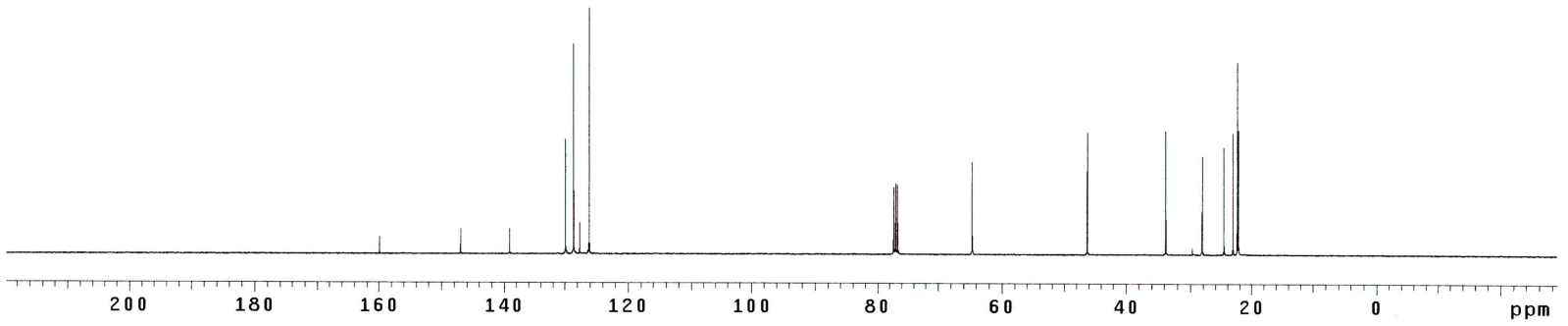

H3C
H
H3C
OH
N
O
CH3
H3C

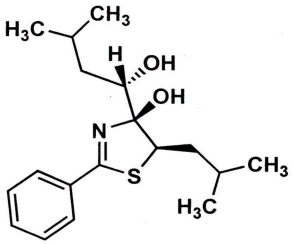
T2.4 (X=O)


10
9
8
7
6
5
4
3
2
1
ppm
1.78
2.83
0.92
2.92
1.15
1.25
1.14
1.14
12.00

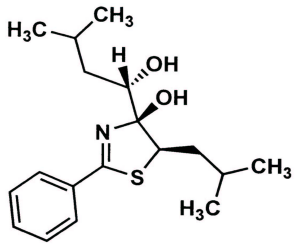


T2.4 (X=O)

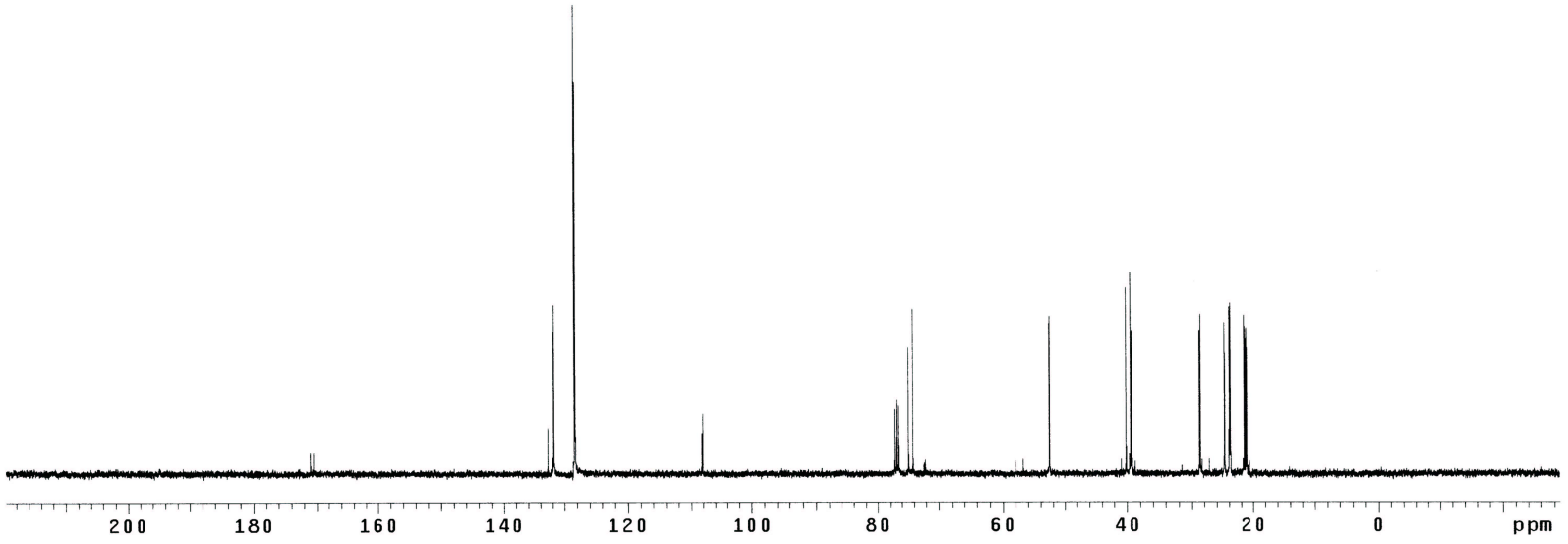


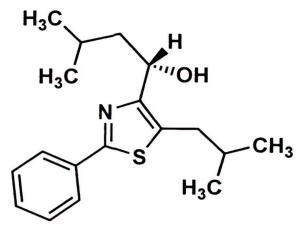


T2.2 (X=S)

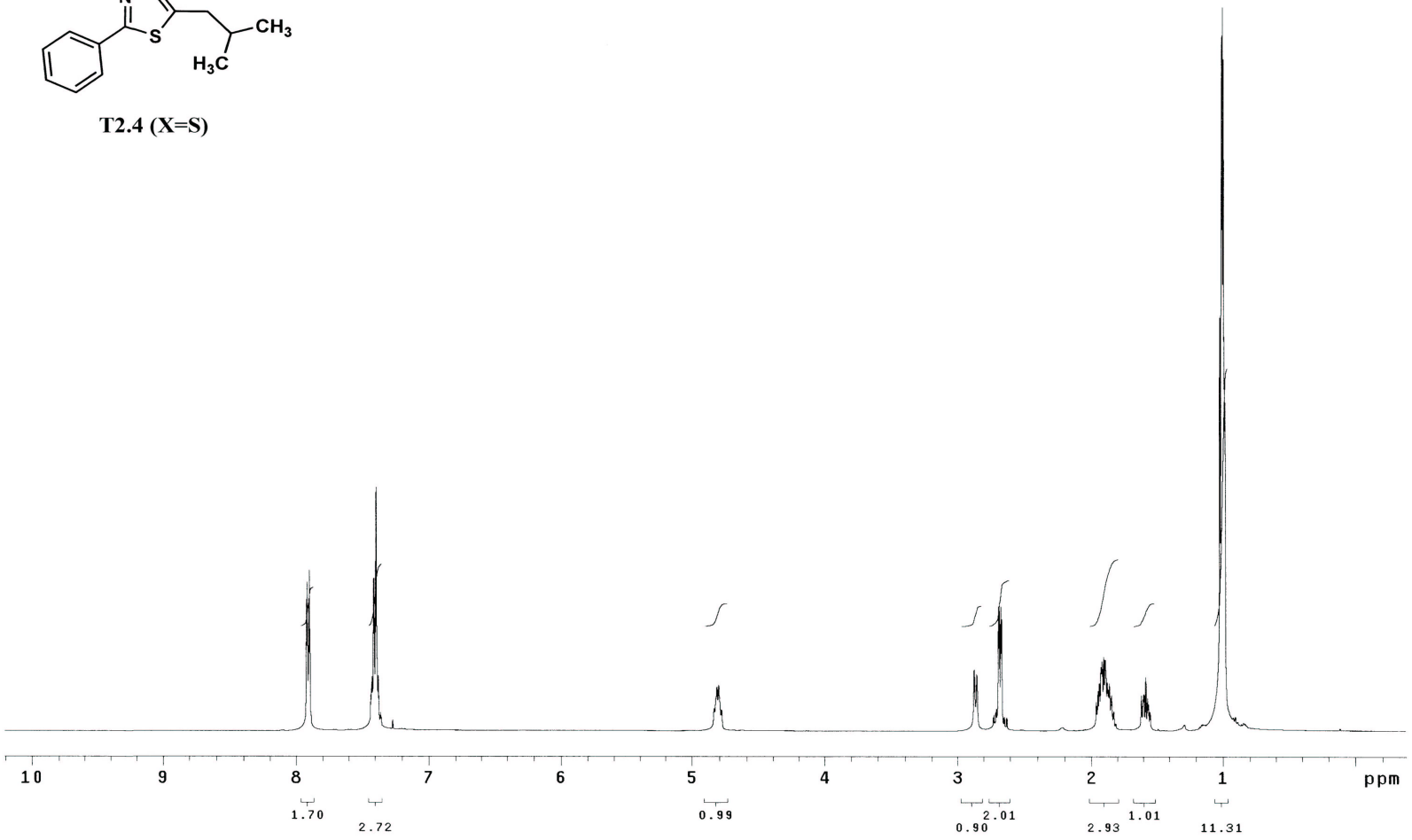


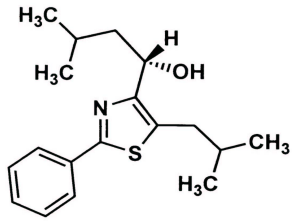
T2.2 (X=S)



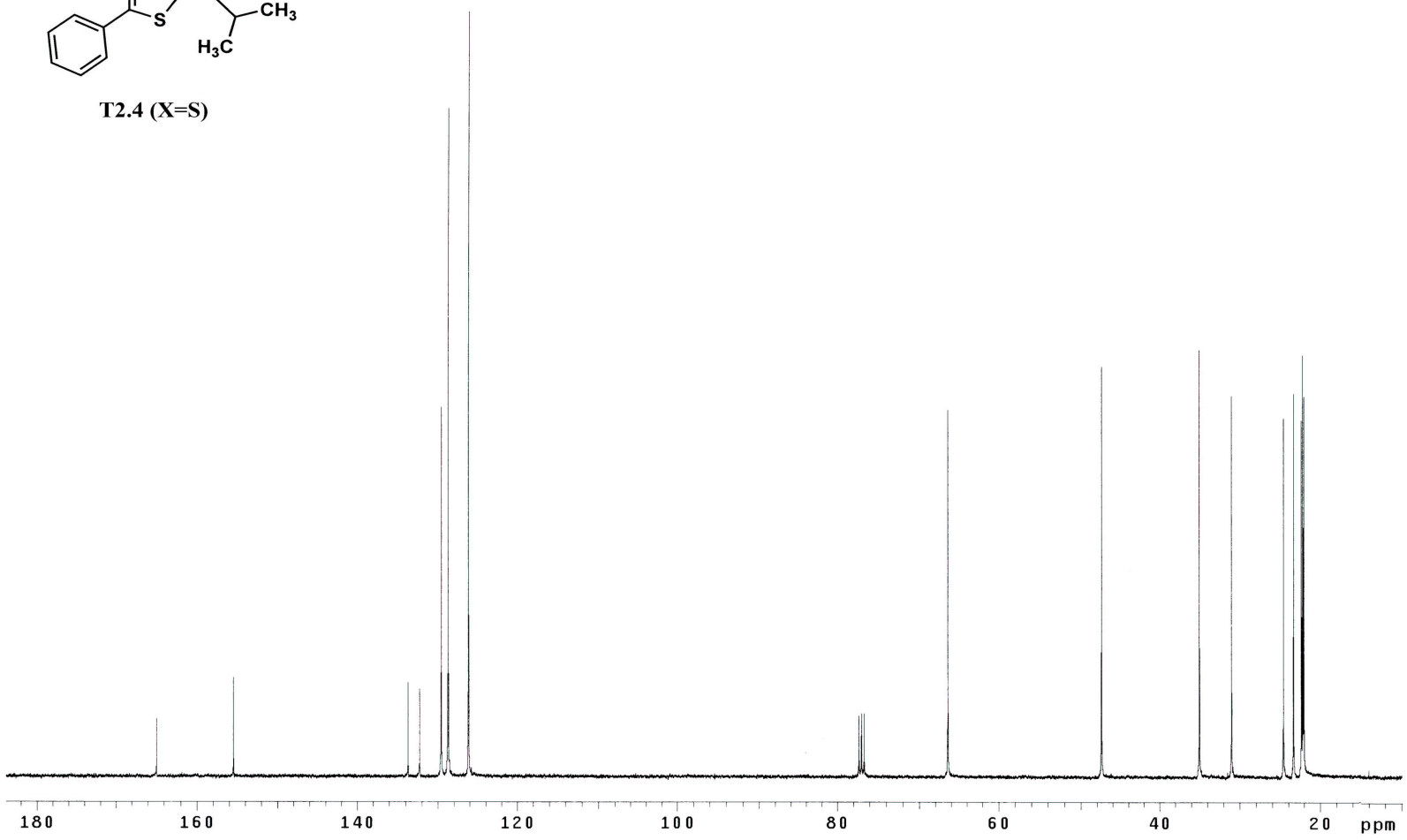

H3C
H
H3C
OH
N
S
CH3
H3C

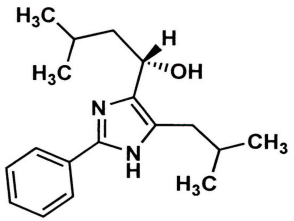
T2.4 (X=S)


10
9
8
7
6
5
4
3
2
1
ppm
1.70
2.72
0.99
0.90
2.01
2.93
1.01
11.31

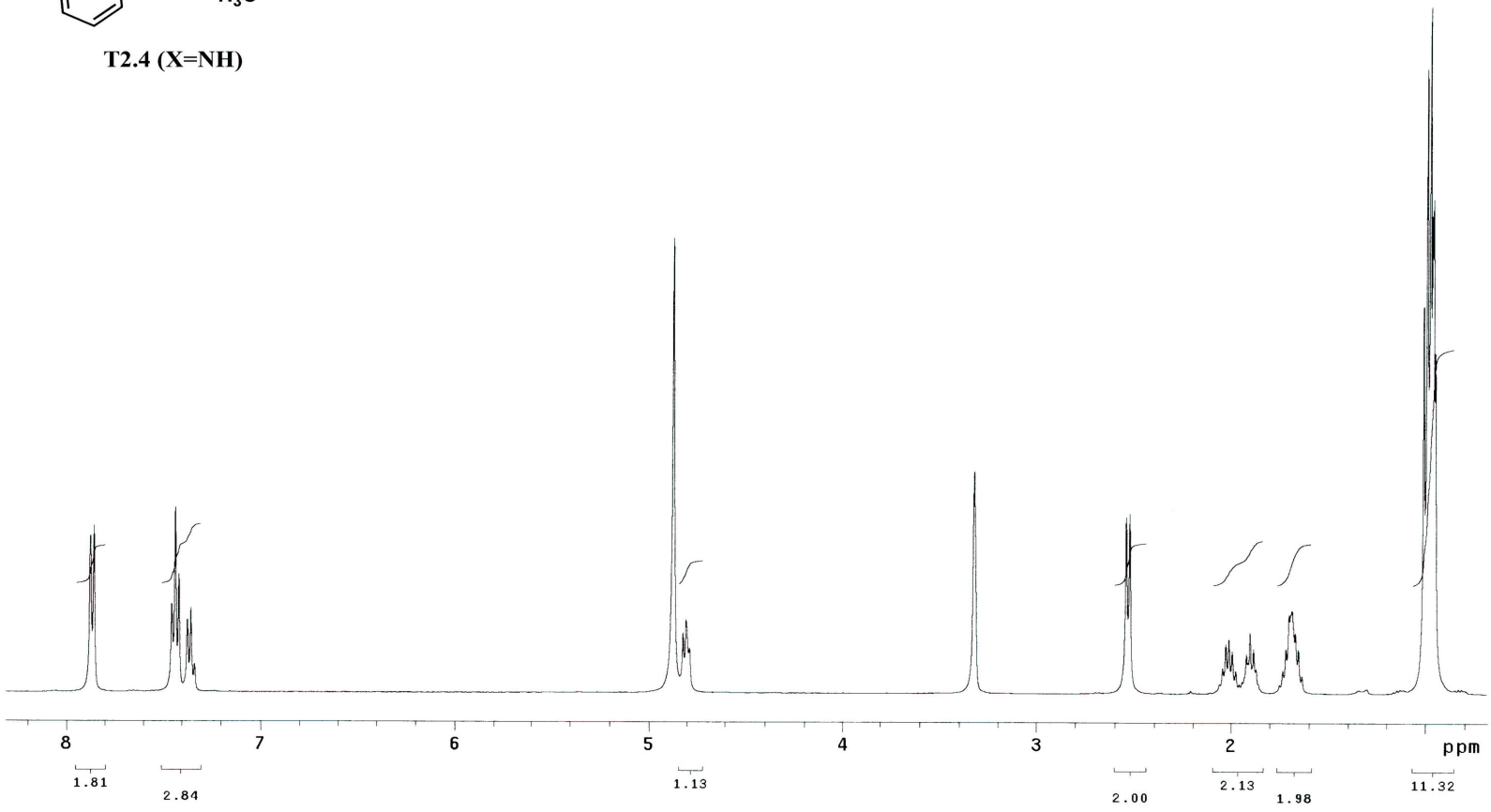


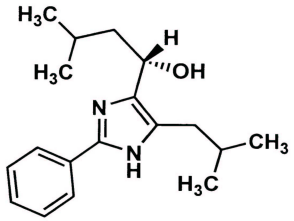
T2.4 (X=S)



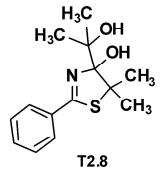

H3C
H
H3C
OH
N
N
H
CH3
H3C

T2.4 (X=NH)

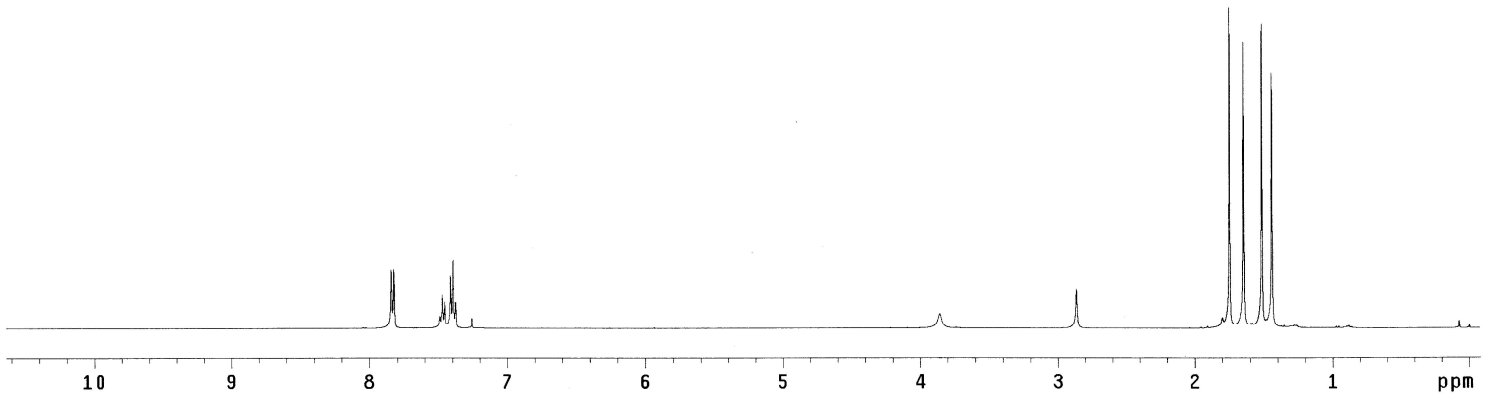

8
7
6
5
4
3
2
ppm
1.81
2.84
1.13
2.00
2.13
1.98
11.32

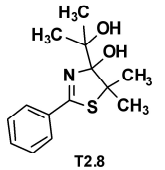


T2.4 (X=NH)

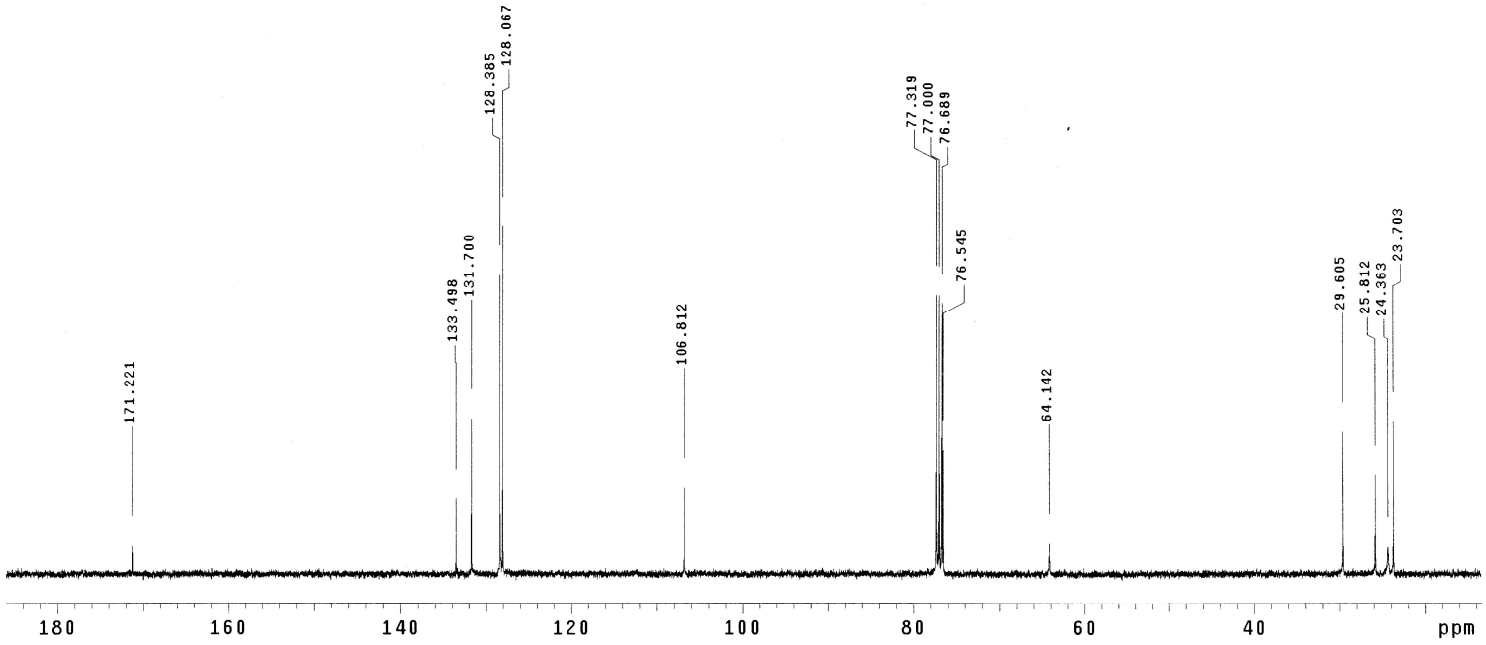


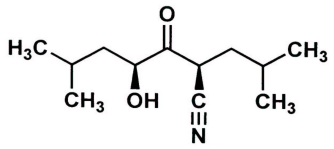
T2.8

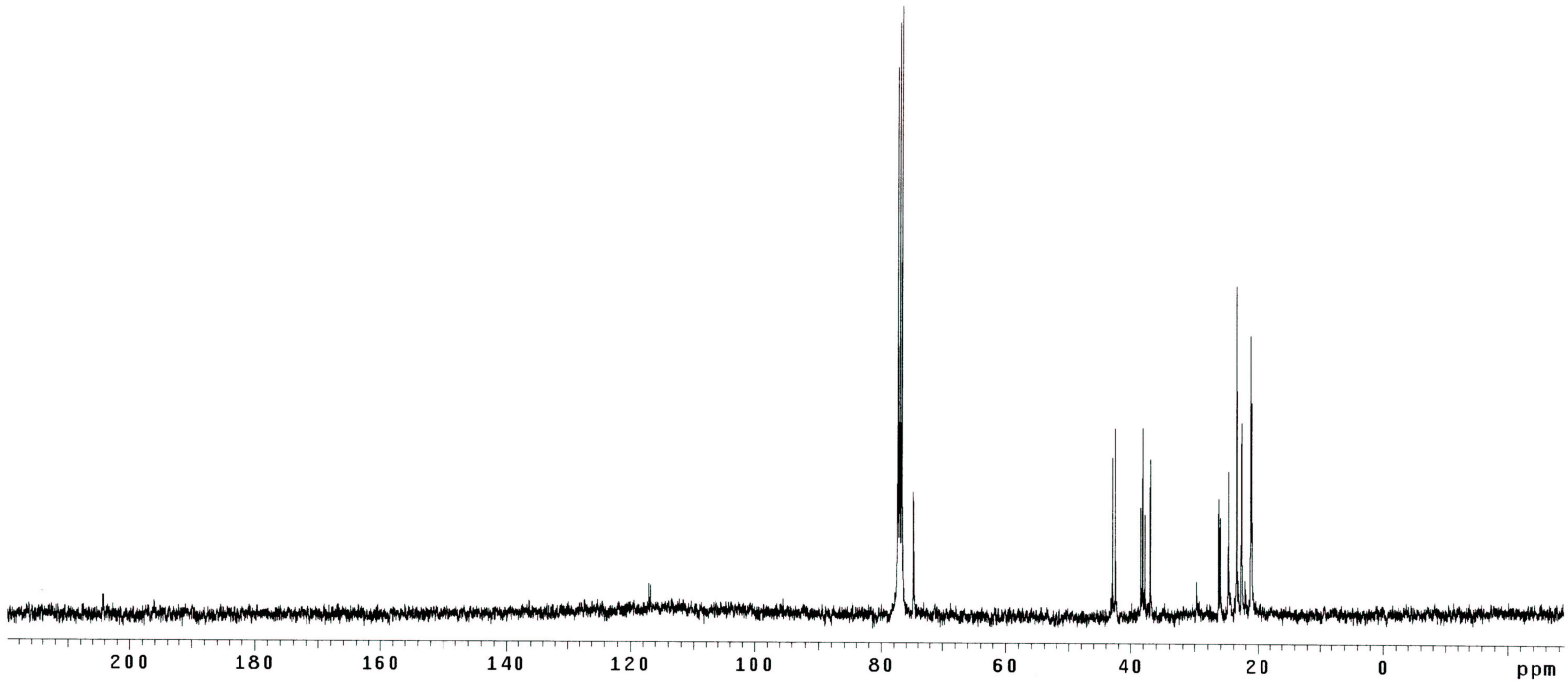


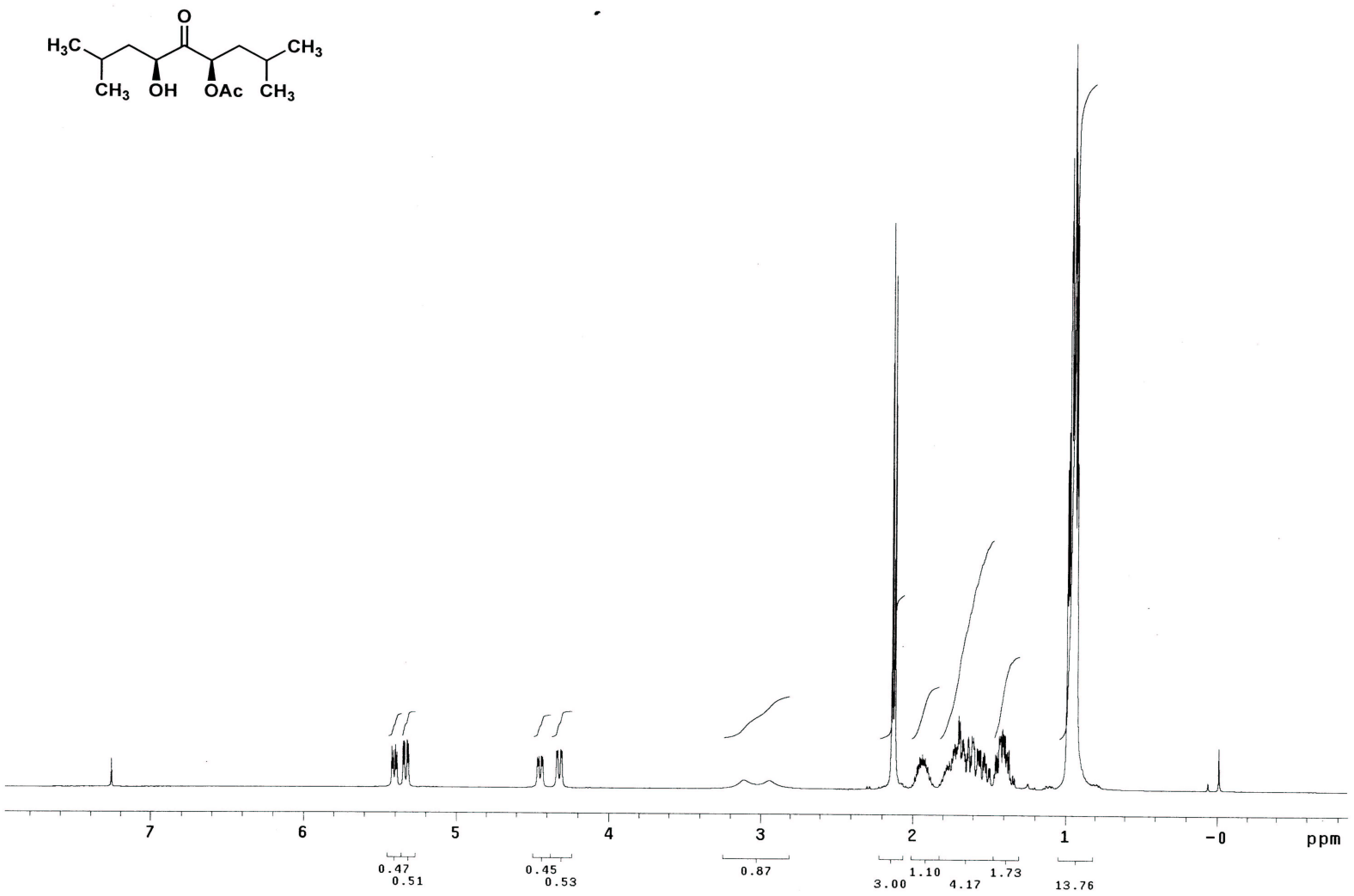

H3C
OH
H3C
OH
N
CH3
S
CH3

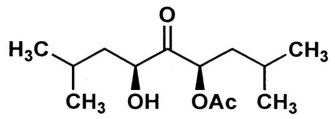
T2.8

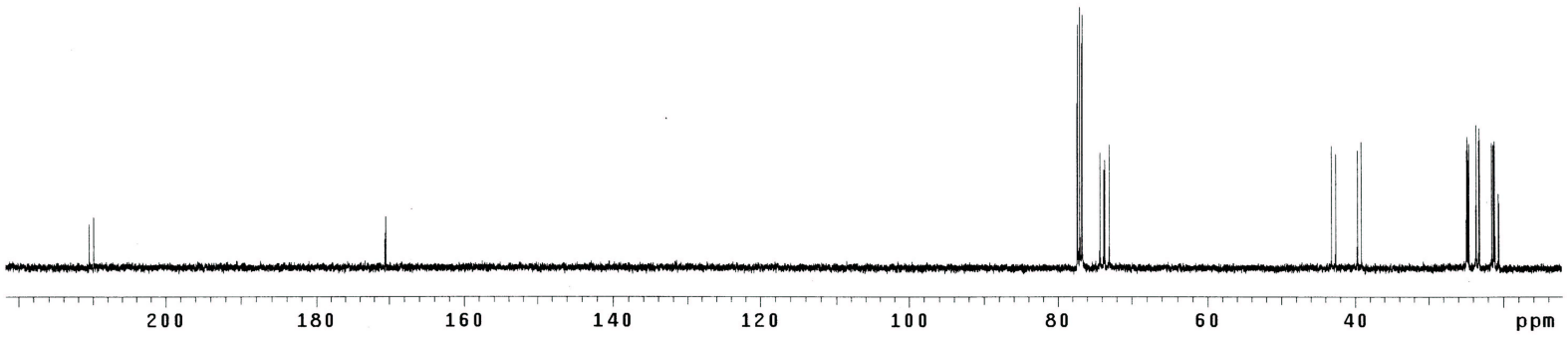

171.221
133.498
131.700
128.385
128.067
106.812
77.319
77.000
76.689
76.545
64.142
29.605
25.812
24.363
23.703
180
160
140
120
100
80
60
40
ppm

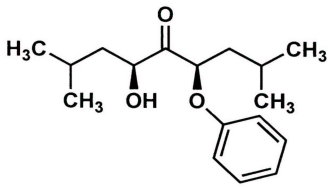

O
H3C
CH3
CH3
OH
C
N
CH3


200
180
160
140
120
100
80
60
40
20
0
ppm

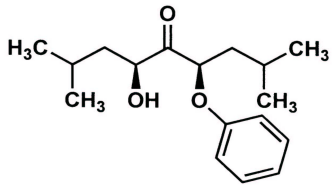

O
H3C
CH3
CH3
OH
OAc
CH3
7
6
5
4
3
2
1
-0
ppm
0.47
0.51
0.45
0.53
0.87
3.00
1.10
4.17
1.73
13.76

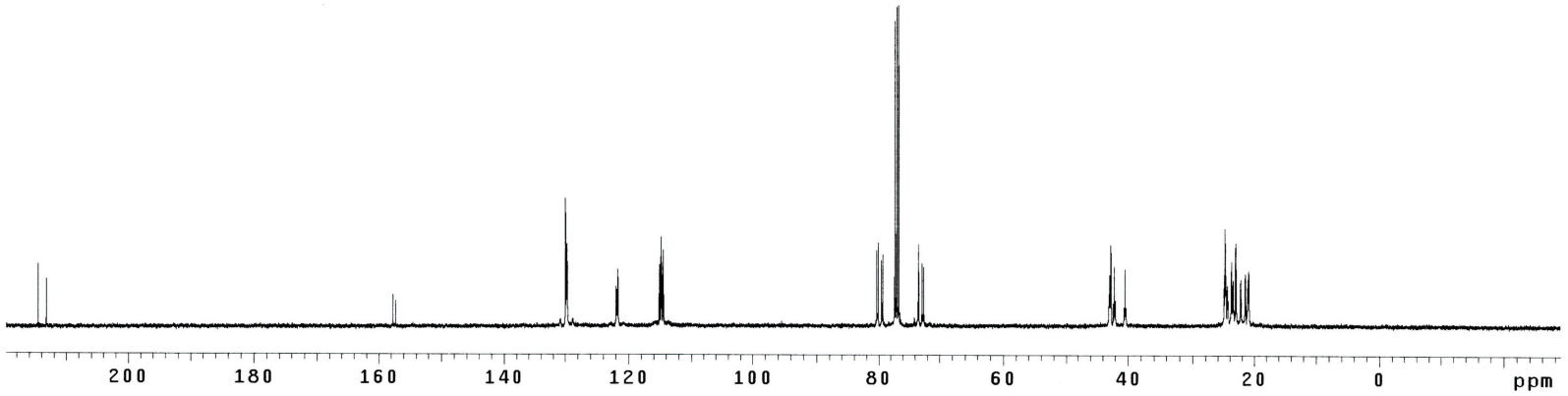

O
H3C
CH3
CH3
OH
OAc
CH3

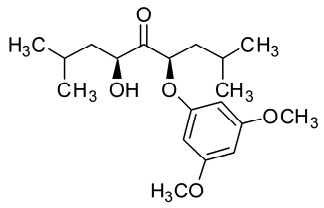

200
180
160
140
120
100
80
60
40
ppm

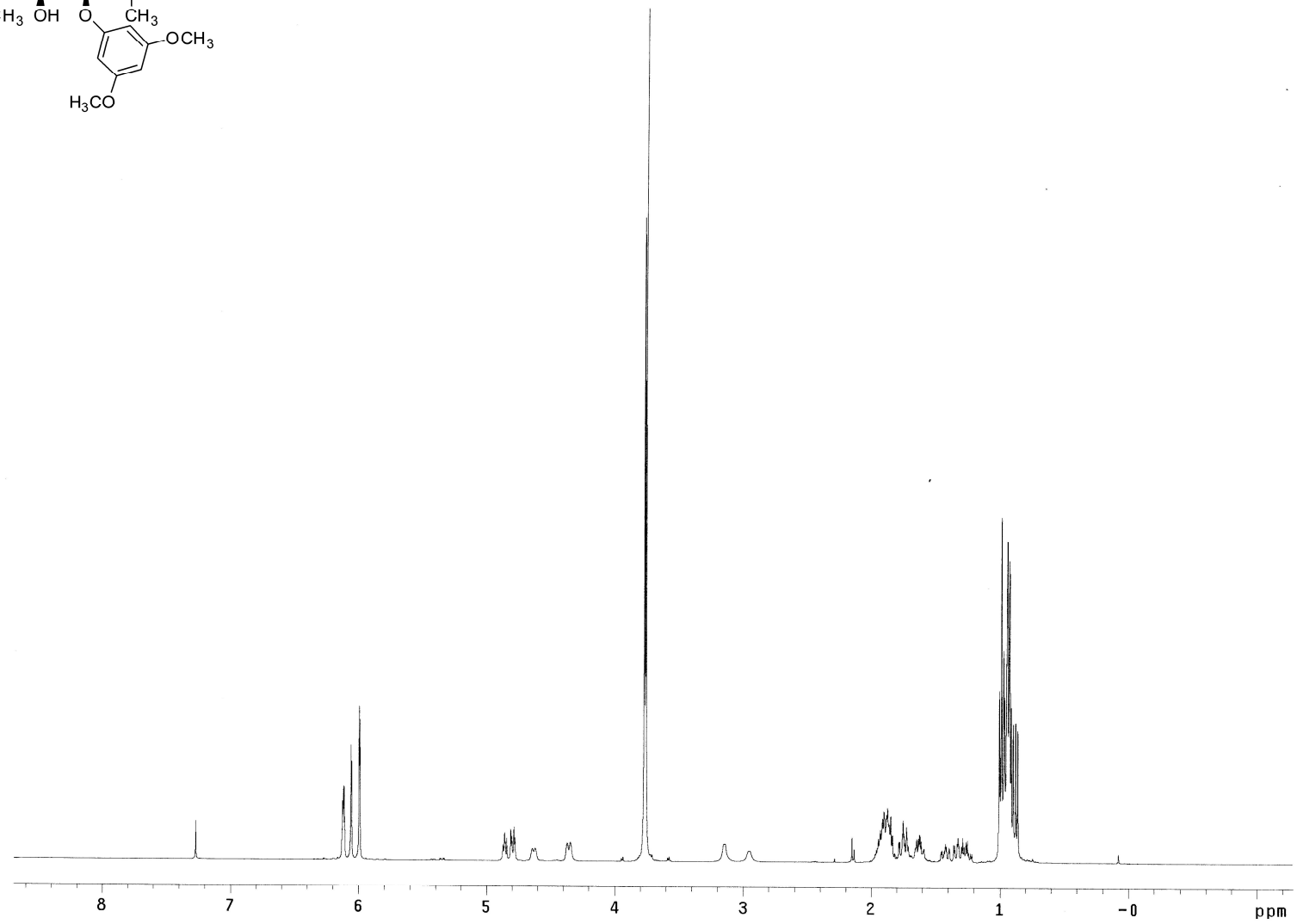

O
H3C
CH3
CH3
OH
O
CH3

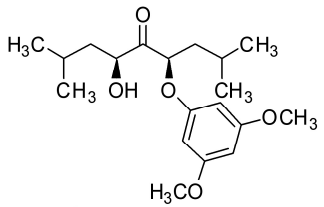
9
8
7
6
5
4
3
2
1
ppm
2.26
1.97
1.00
0.65
0.47
0.45
0.65
0.54
0.40
1.23
3.14
1.31
1.85
12.91

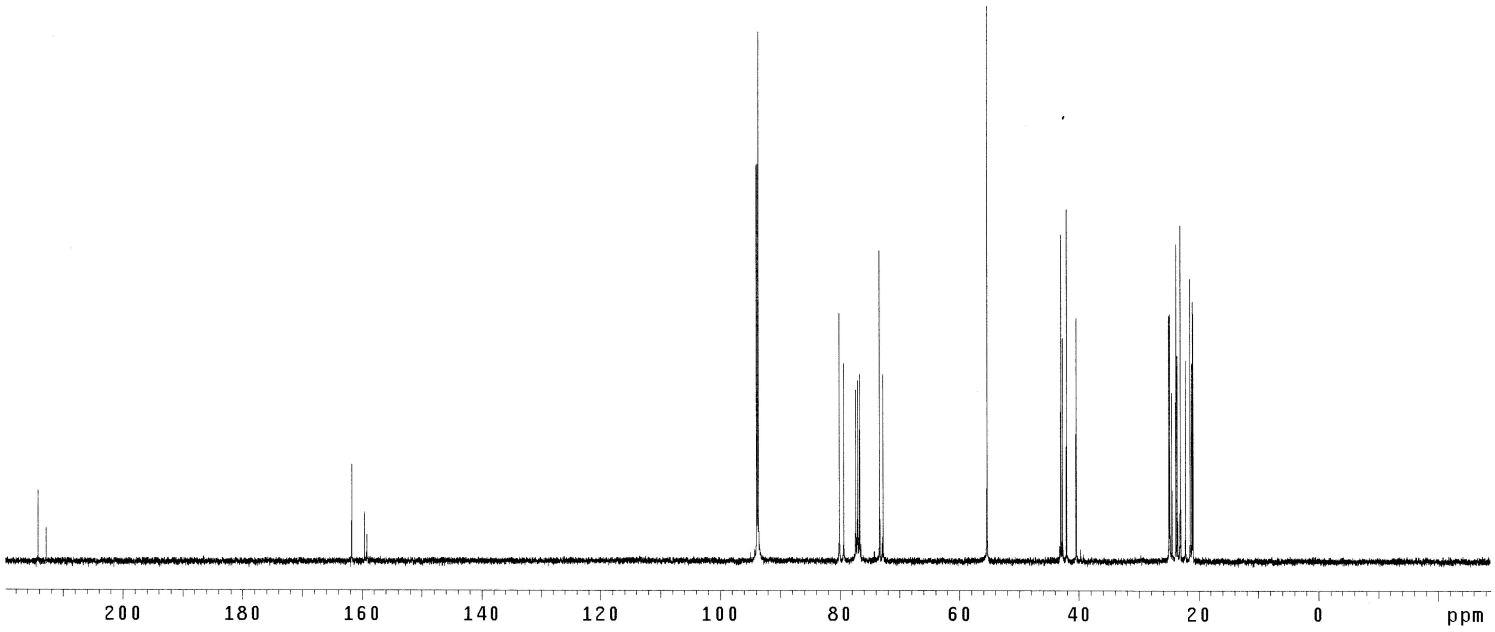

O
H3C
CH3
CH3
OH
O
CH3

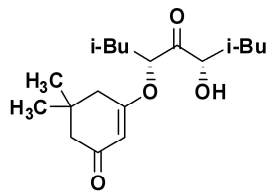

200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
CH3
CH3
OH
O
CH3
OCH3
H3CO

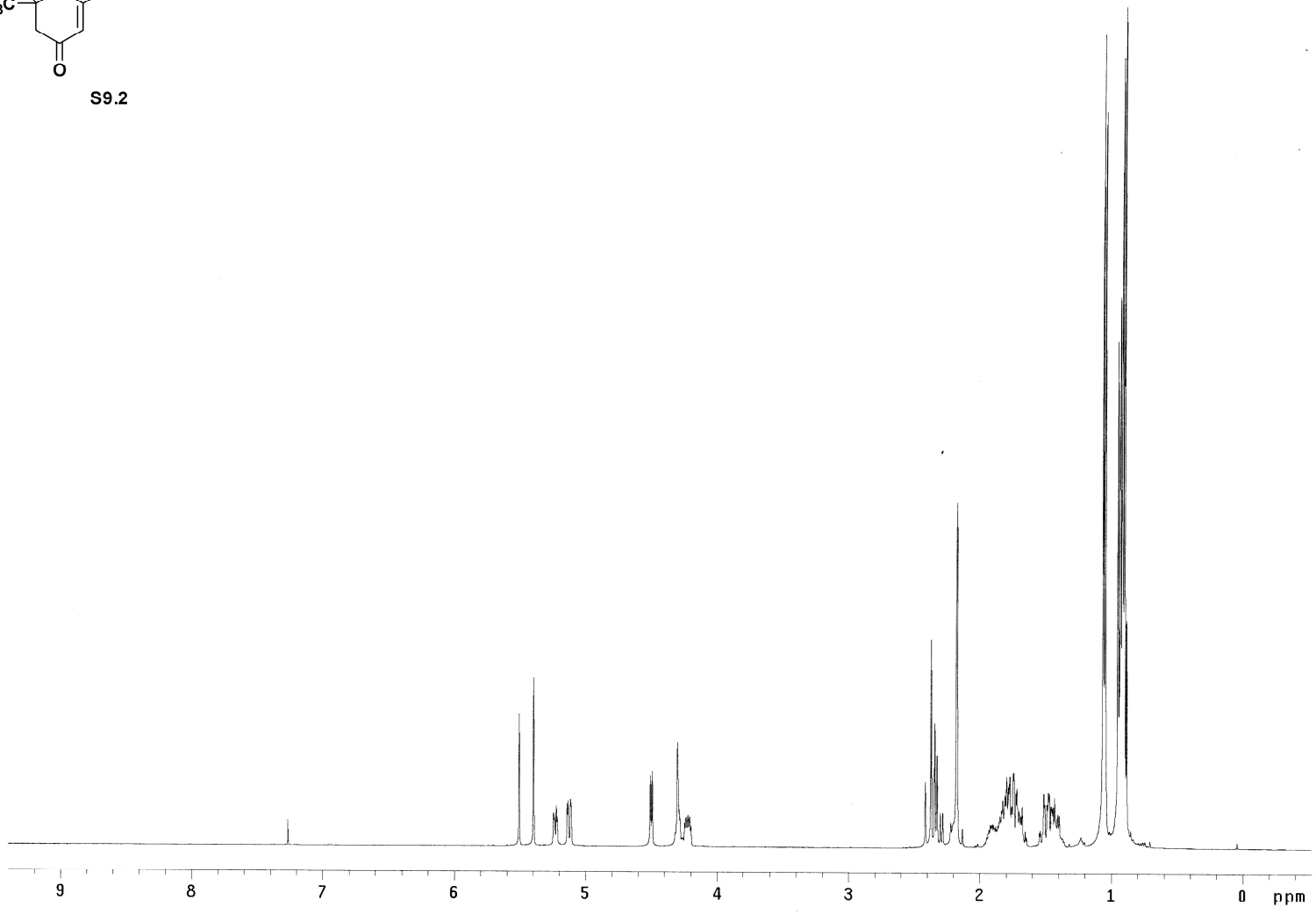

8
7
6
5
4
3
2
1
-0
ppm

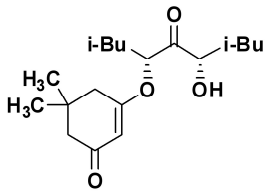

O
H3C
CH3
CH3
OH
O
CH3
OCH3
H3CO


200
180
160
140
120
100
80
60
40
20
0
ppm

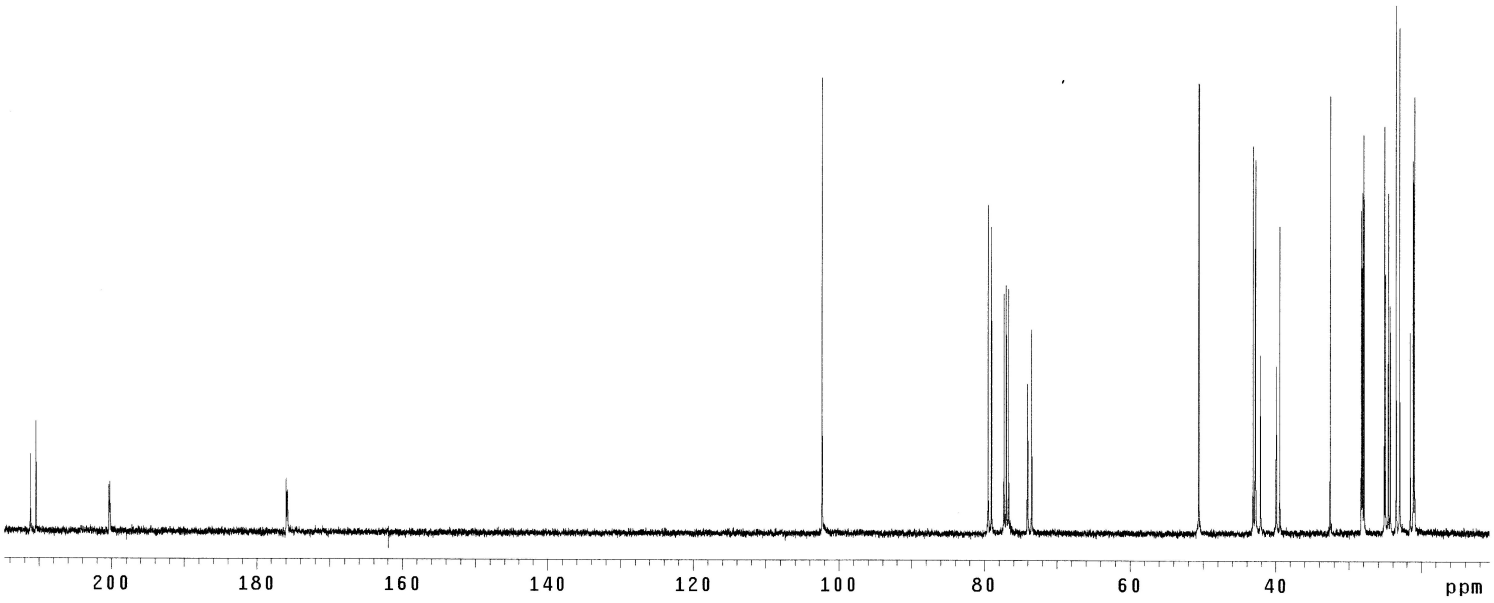


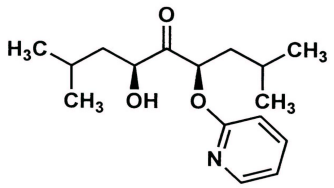
S9.2





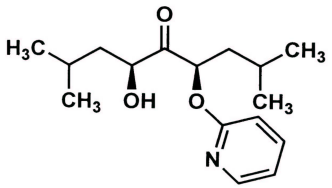
S9.2



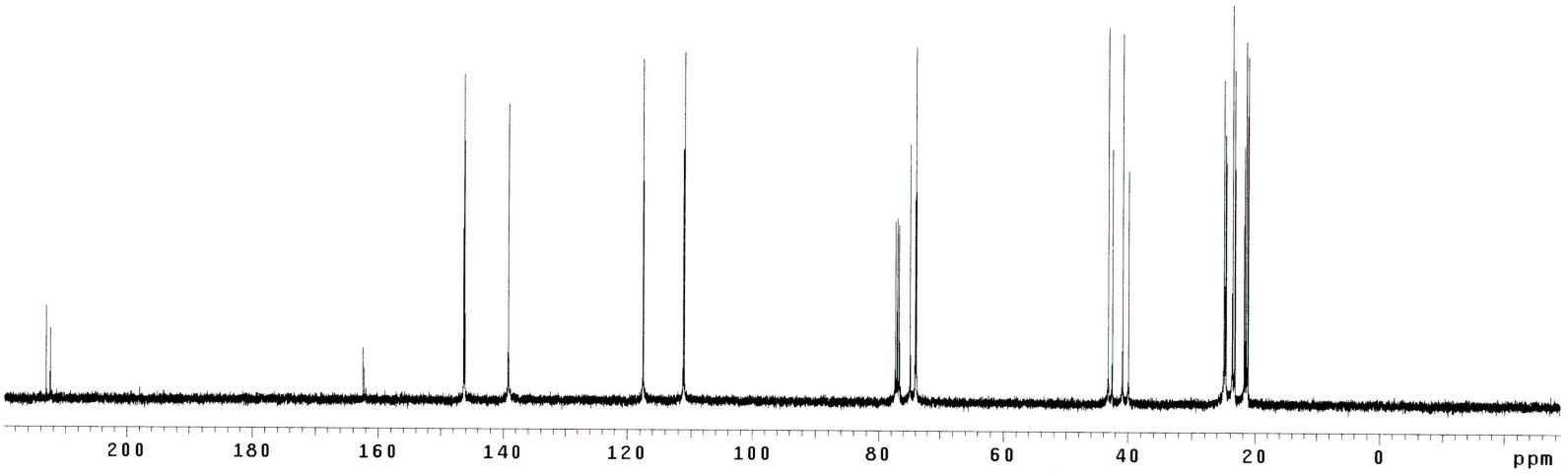

O
H3C
CH3
CH3
OH
O
CH3
N

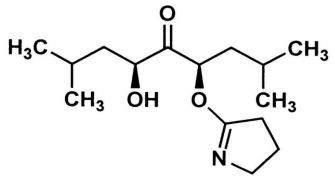
S10.2

11
10
9
8
7
6
5
4
3
2
1
-0
ppm
0.84
0.92
1.76
1.00
0.41
0.53
0.51
0.38
2.95
3.68
12.38



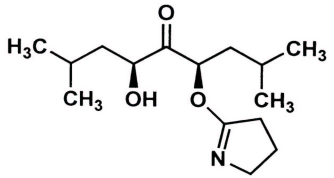
S10.2



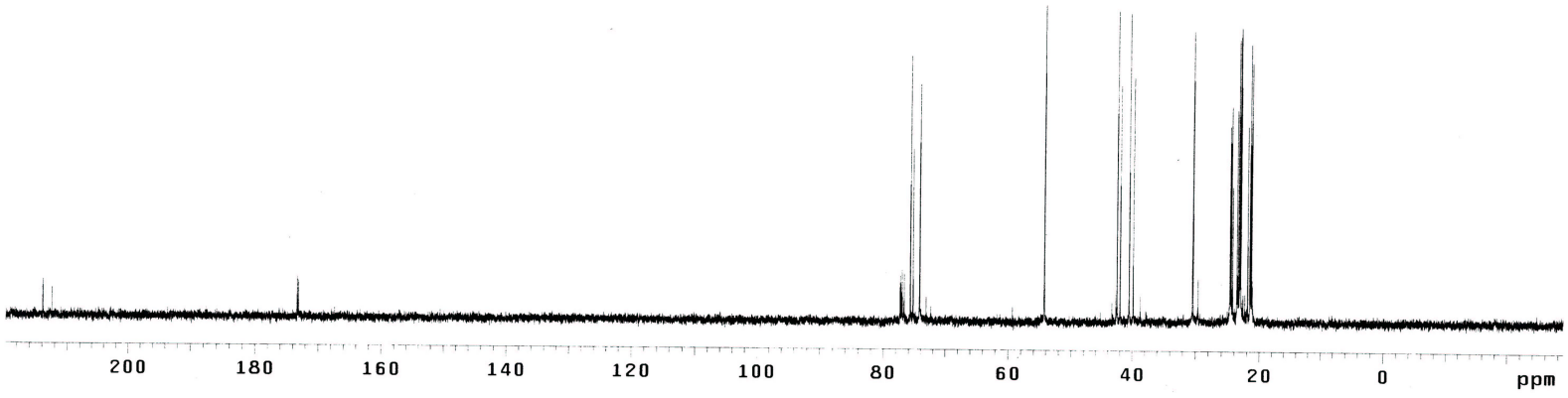

O
H3C
CH3
CH3
OH
O
CH3
N

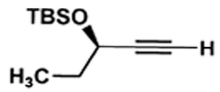
S10.4

7
6
5
4
3
2
1
ppm
0.52
1.05
0.90
2.00
2.00
1.99
3.28
3.94
14.05

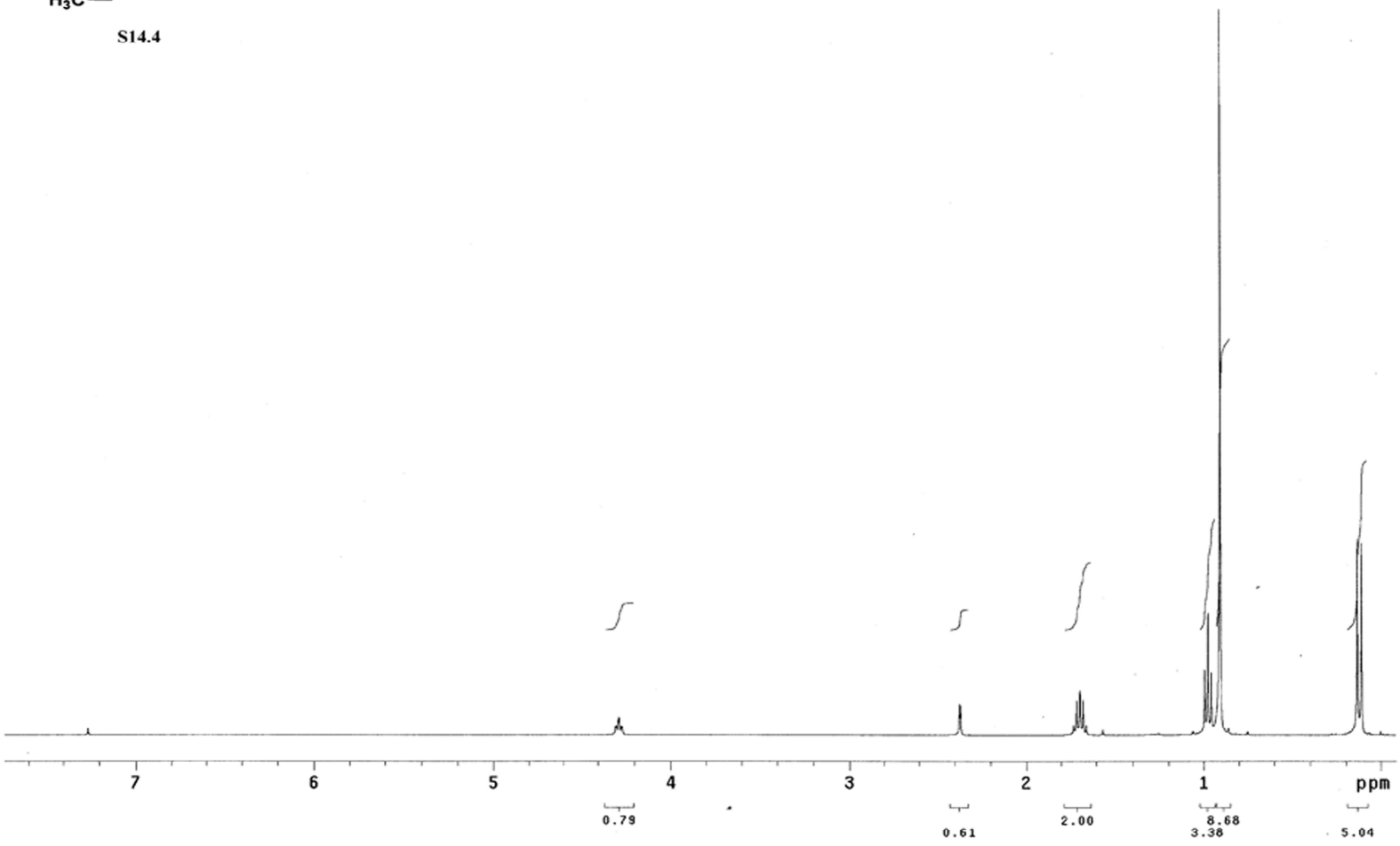


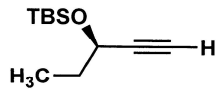
S10.4





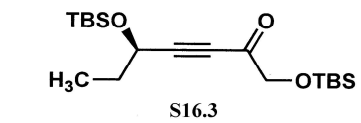
S14.4



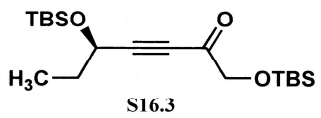

TBSO
H
H3C

S14.4

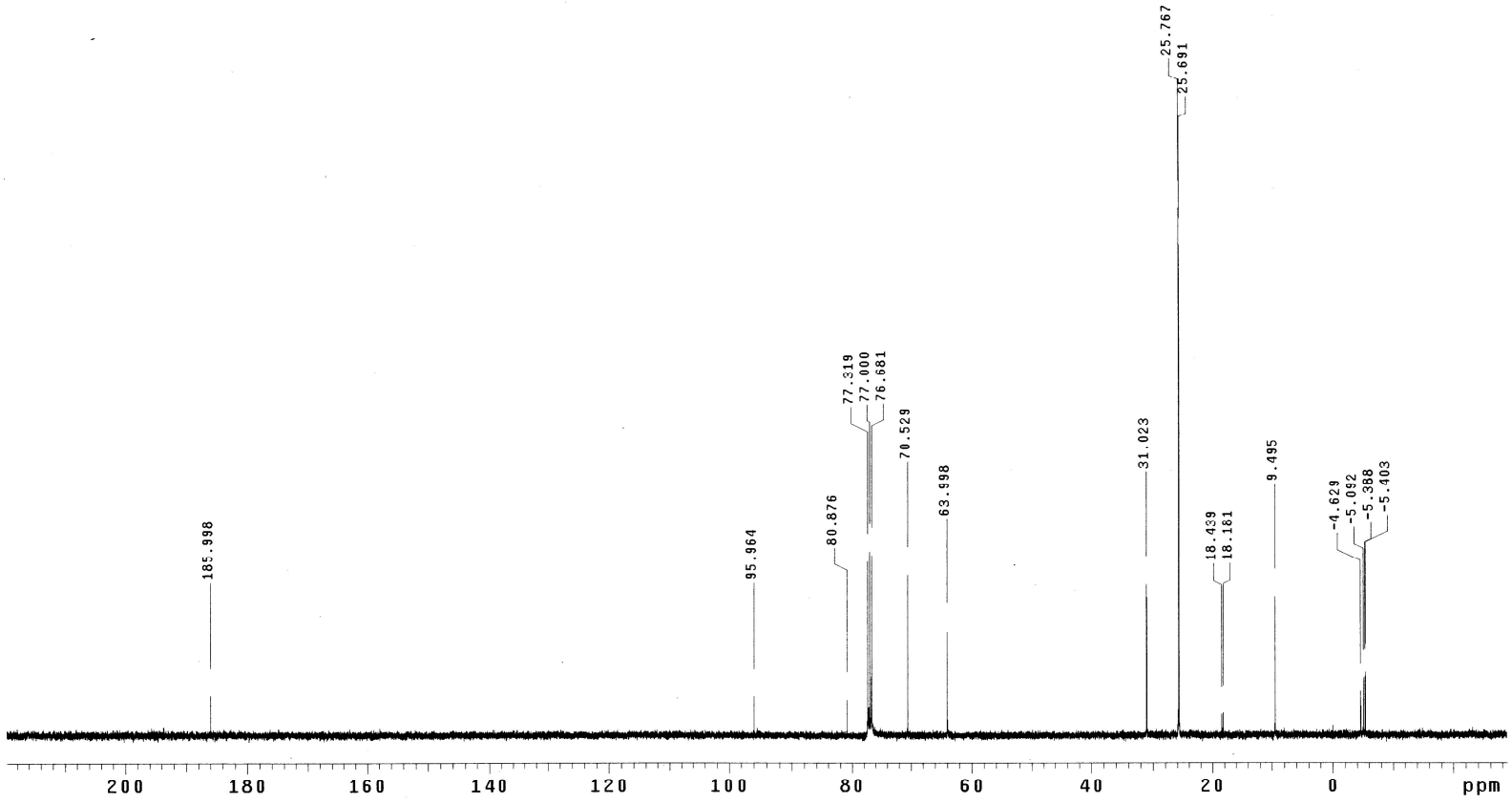
25.767
85.519
77.319
77.000
76.681
71.865
64.006
31.683
18.242
9.511
-4.614
-5.077
200
180
160
140
120
100
80
60
40
20
0
ppm

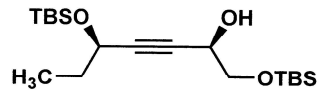


S16.3

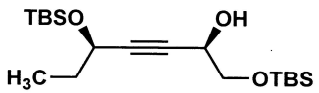

TBSO
O
H3C
OTBS

S16.3

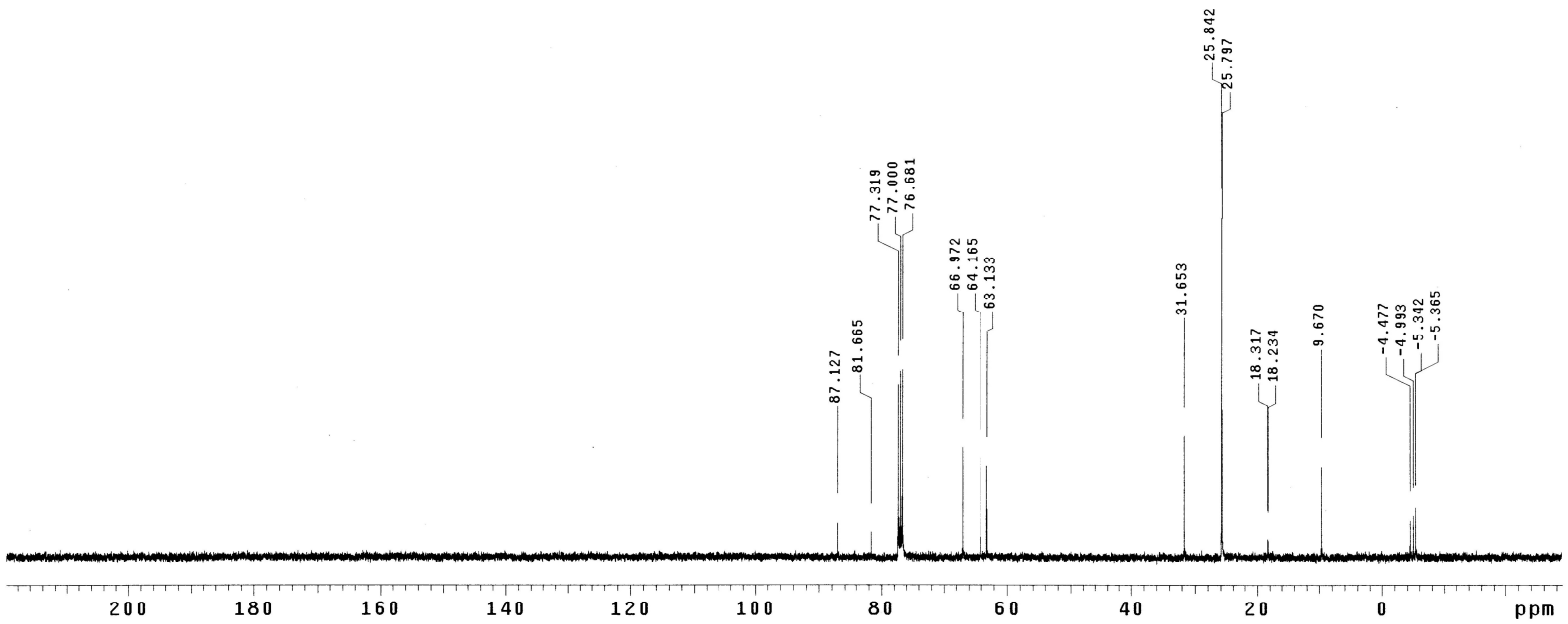

185.998
95.964
80.876
77.319
77.000
76.681
70.529
63.998
31.023
25.767
25.691
18.439
18.161
9.495
-4.629
-5.052
-5.388
-5.403
200
180
160
140
120
100
80
60
40
20
0
ppm

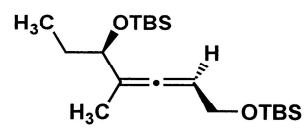


S16.4


TBSO
OH
H3C
OTBS

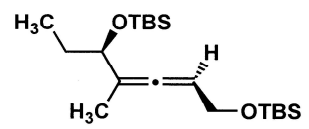
S16.4


87.127
81.665
77.319
77.000
76.681
66.472
64.165
63.133
31.653
25.842
25.797
18.317
18.234
9.670
-4.477
-4.993
-5.342
-5.365
200
180
160
140
120
100
80
60
40
20
0
ppm

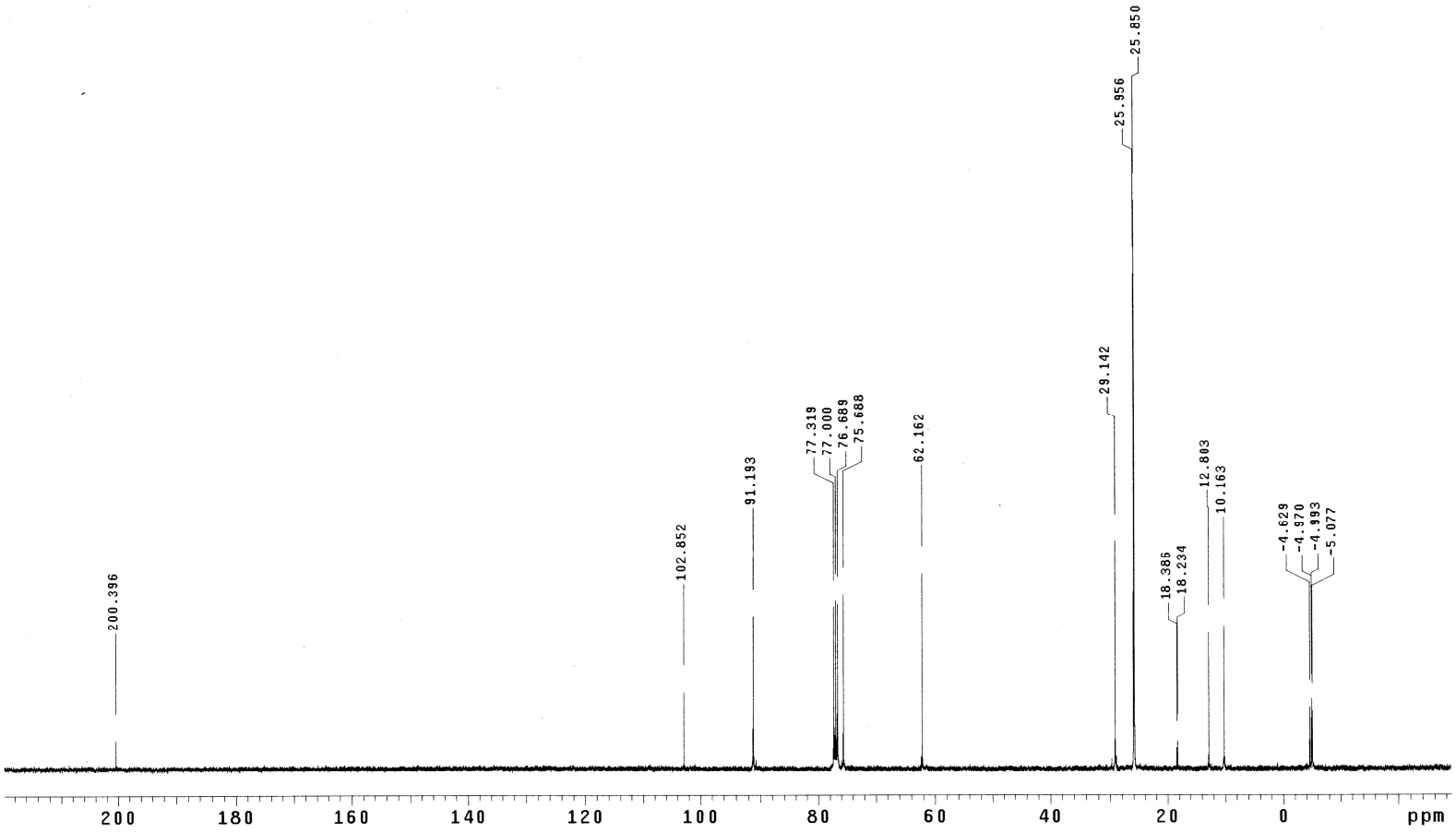

H3C
OTBS
H
H3C
OTBS

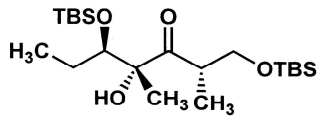
S16.5

10
9
8
7
6
5
4
3
2
1
-0
ppm
0.84
1.00
2.14
2.51
3.07
3.33
18.66
10.71


H3C
OTBS
H
H3C
OTBS

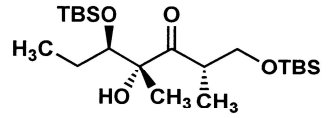
S16.5


200.396
102.852
91.193
77.319
77.000
76.689
75.688
62.162
29.142
25.956
25.850
18.386
18.234
12.803
10.163
-4.629
-4.870
-4.993
-5.077
200
180
160
140
120
100
80
60
40
20
0
ppm

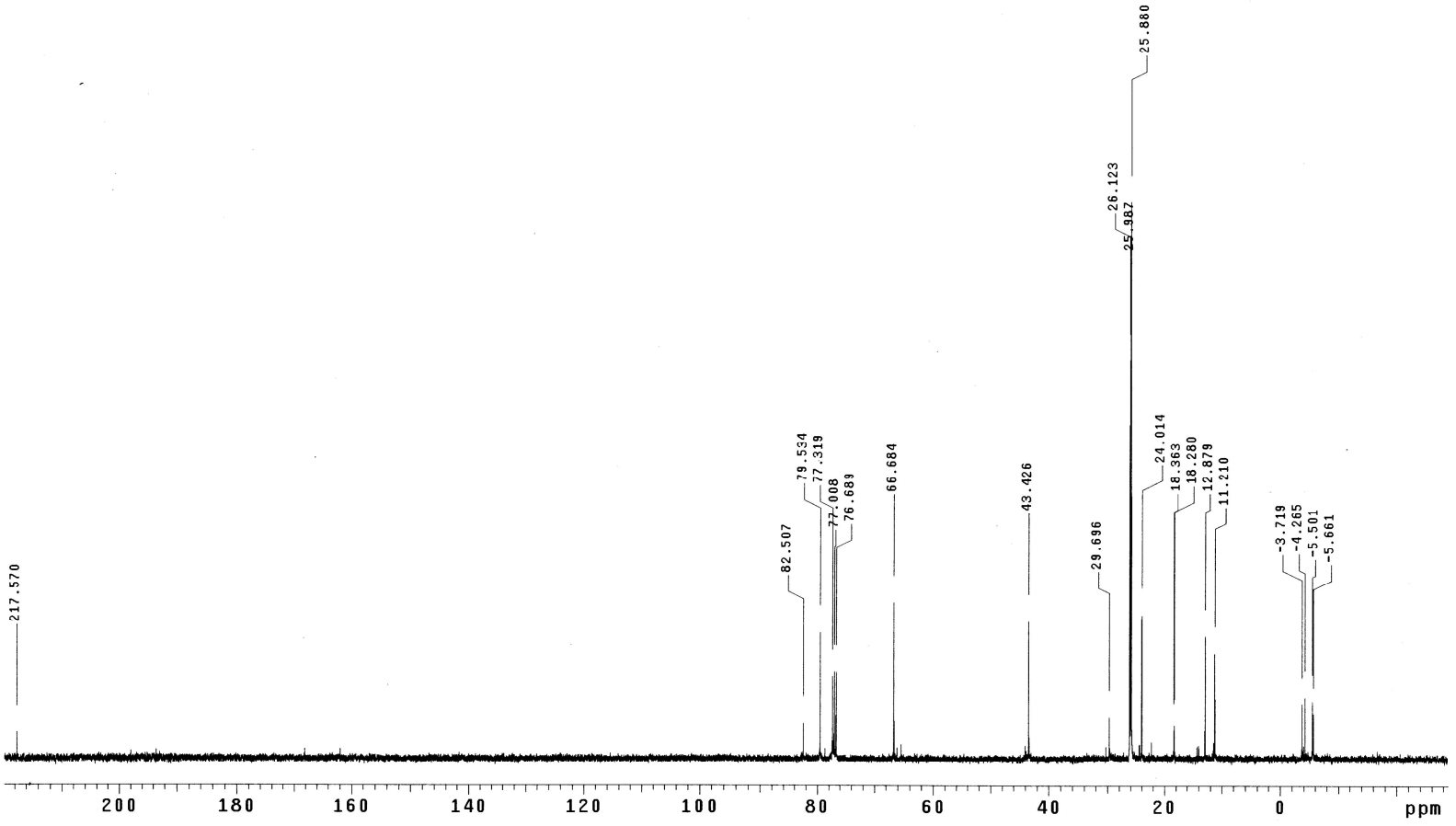

TBSO
O
H3C
OTBS
HO
CH3
CH3

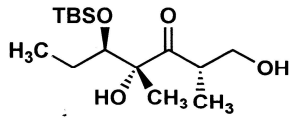
S16.6

7
6
5
4
3
2
1
ppm
0.91
4.48
2.84
3.00
3.63
0.35
0.52
4.67
13.07

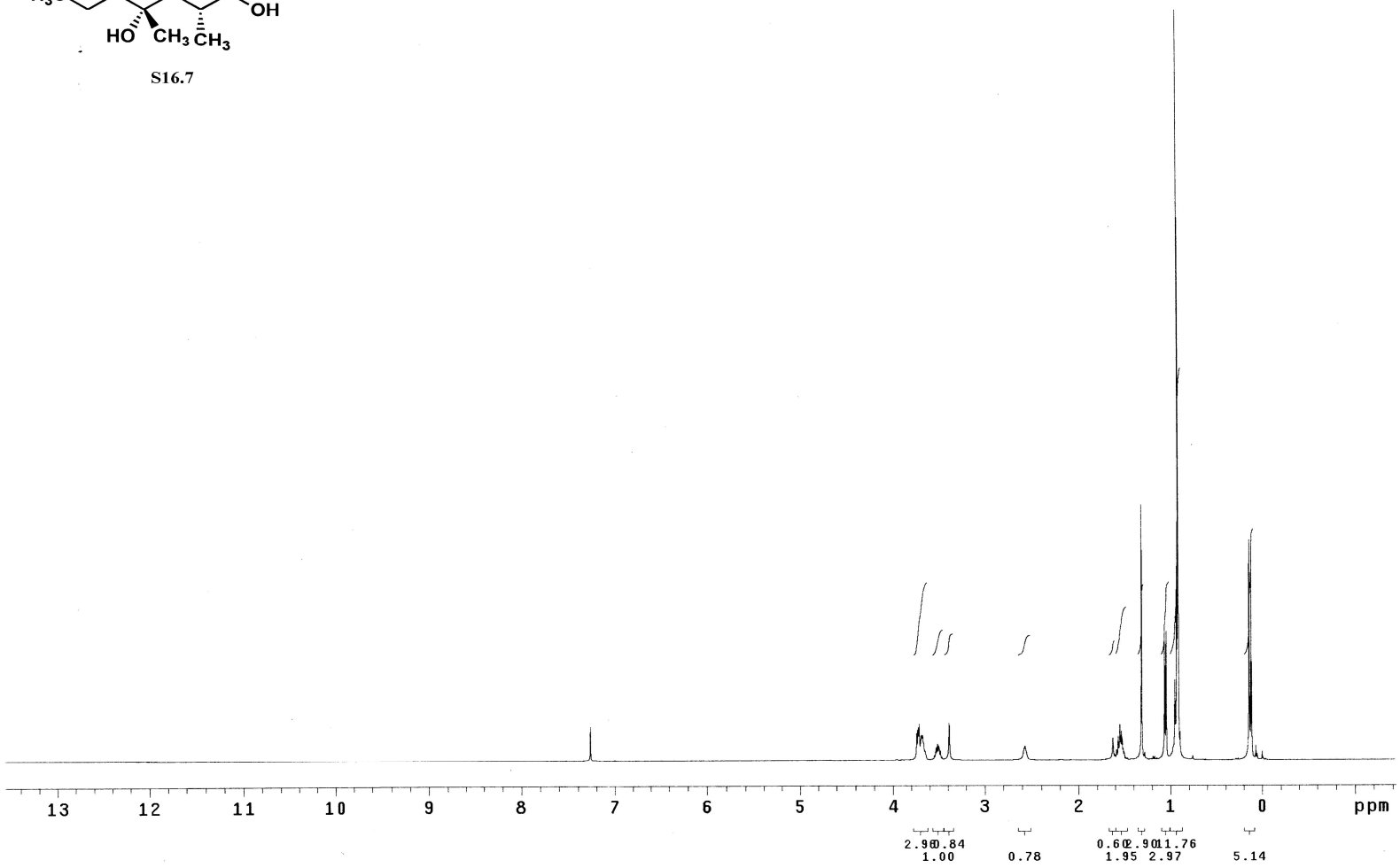

TBSO
O
H3C
OTBS
HO
CH3
CH3

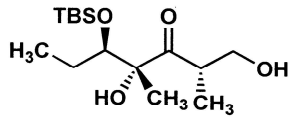
S16.6


217.570
82.507
79.534
77.319
77.008
76.689
66.684
43.426
29.696
26.123
25.987
25.880
24.014
18.363
18.280
12.879
11.210
-3.719
-4.265
-5.501
-5.661
200
180
160
140
120
100
80
60
40
20
0
ppm

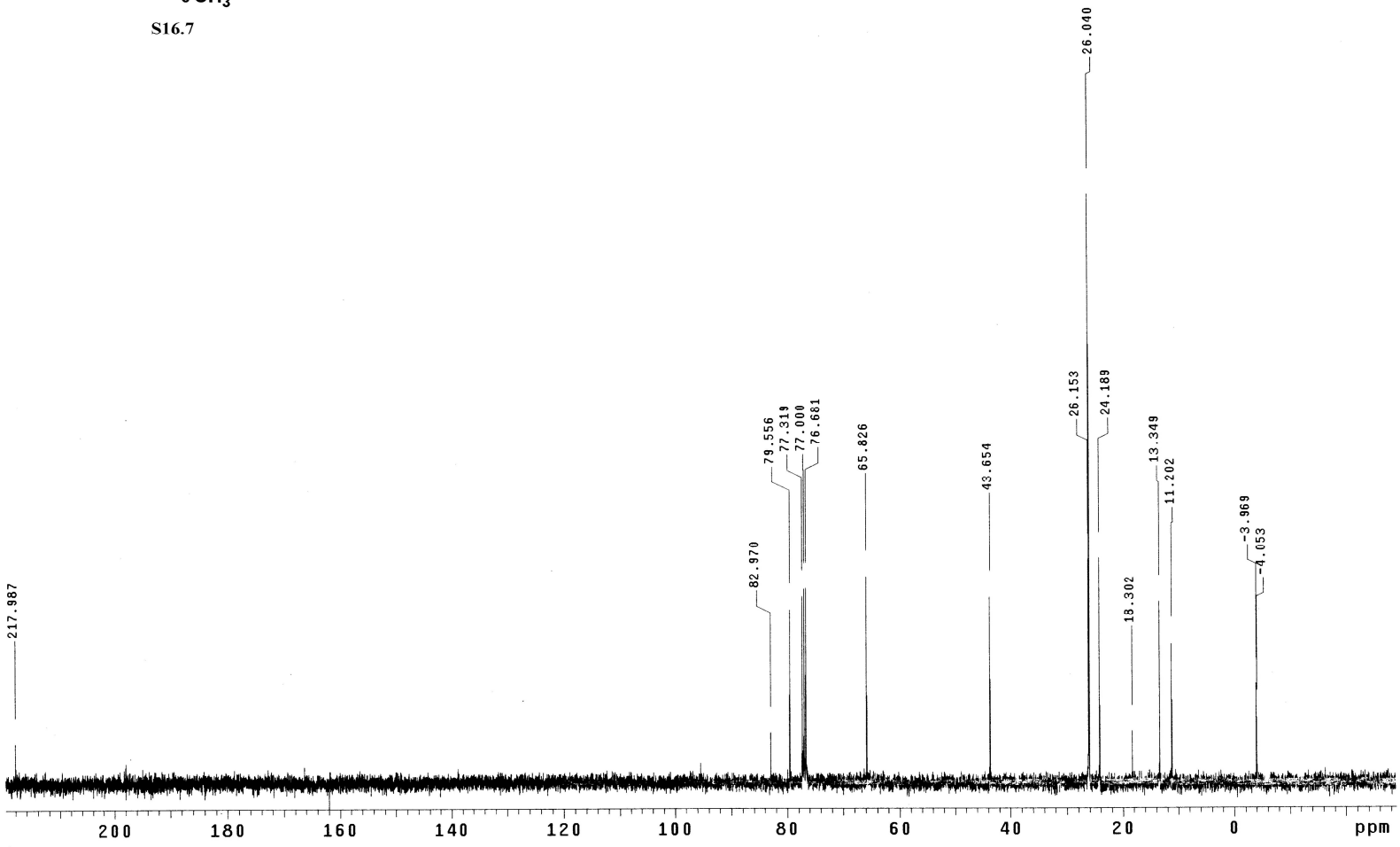

TBSO
O
H3C
OH
HO
CH3
CH3

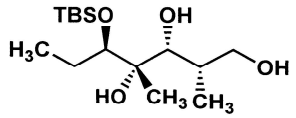
S16.7


13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.96
0.84
1.00
0.78
0.60
2.90
1.76
1.95
2.97
5.14


TBSO
O
H3C
OH
HO
CH3
CH3

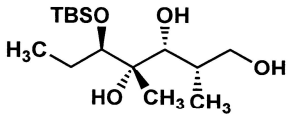
S16.7


217.987
82.970
79.556
77.319
77.000
76.681
65.826
43.654
26.153
26.040
24.189
13.349
13.302
11.202
-3.969
-4.053
200
180
160
140
120
100
80
60
40
20
0
ppm

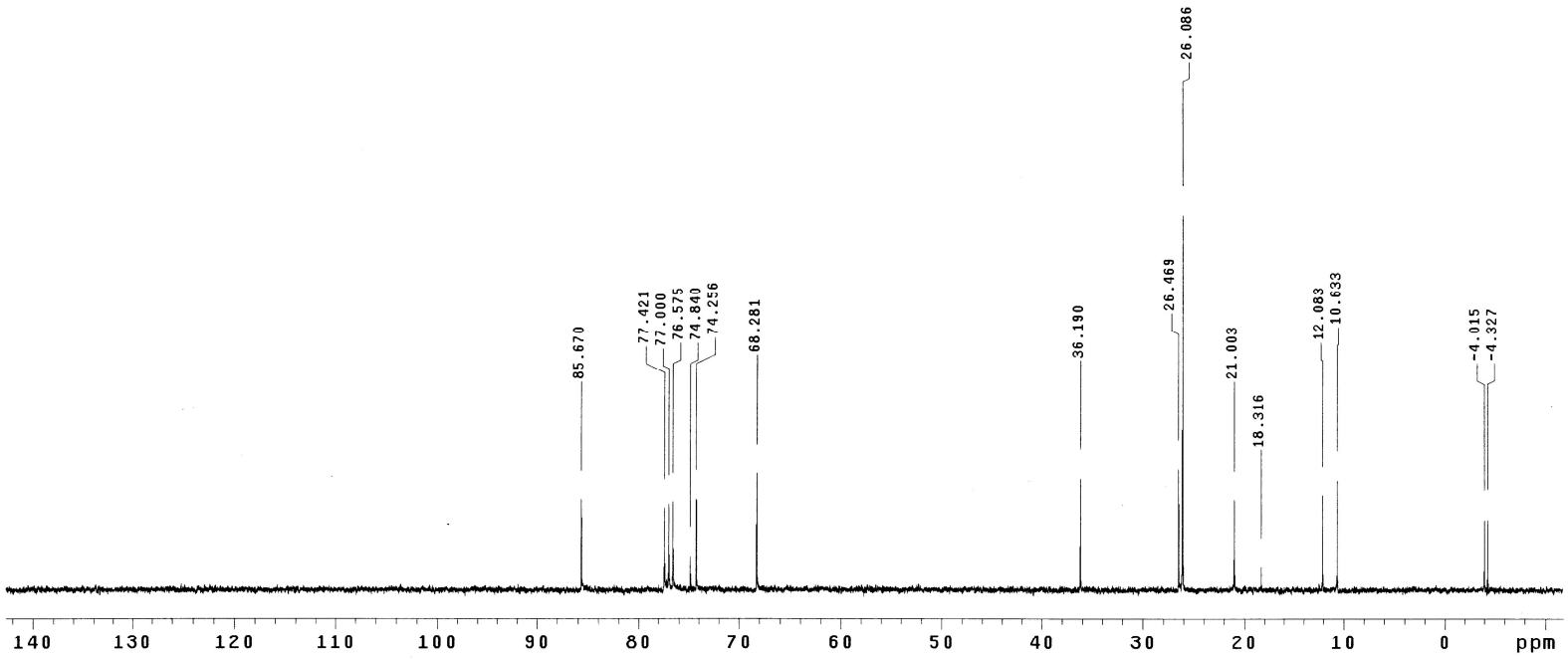

TBSO
OH
H3C
OH
HO
CH3
CH3

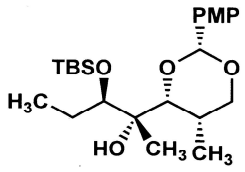
S18.2

12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.00
1.09
0.93
1.90
3.23
5.18

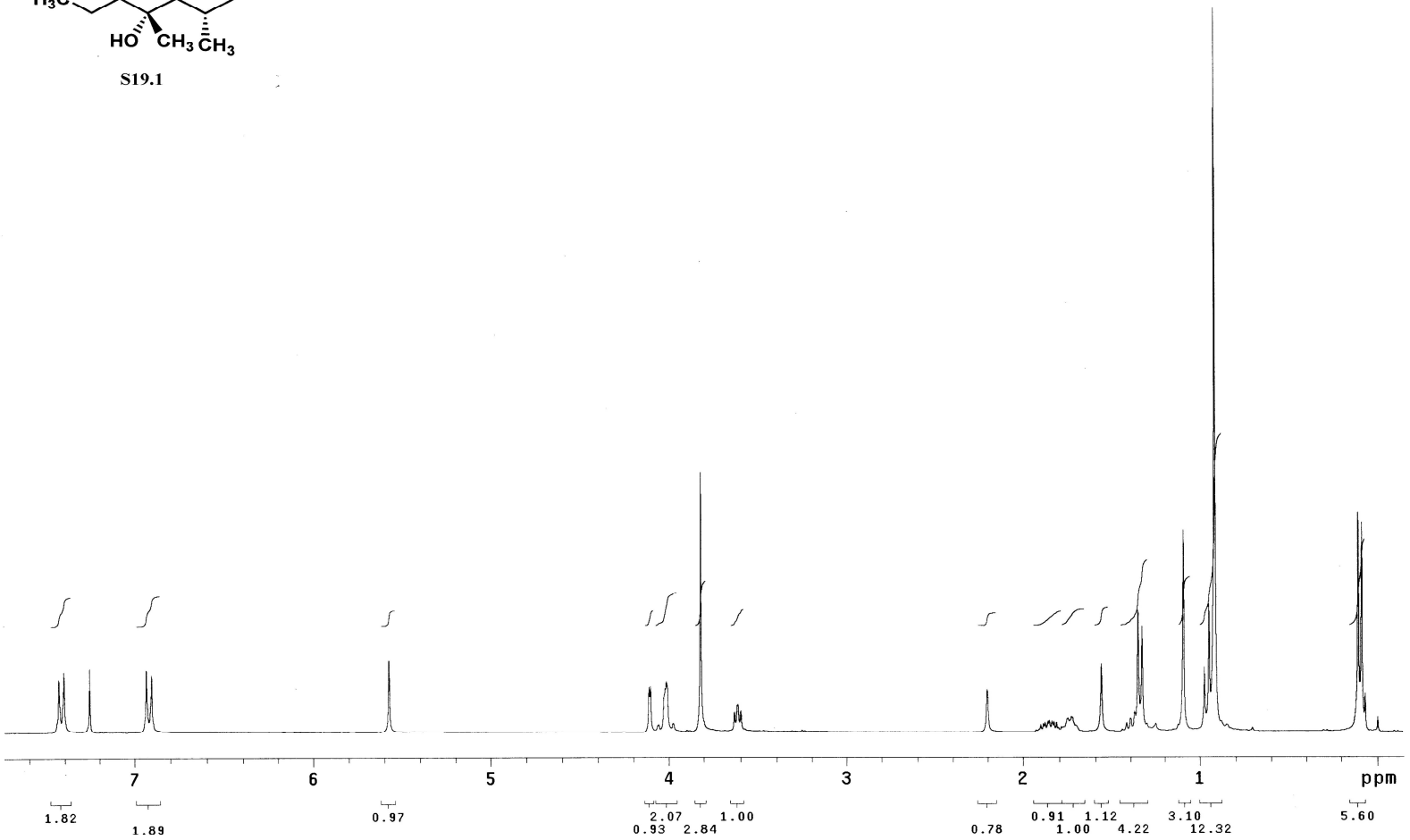

TBSO
OH
H3C
OH
HO
CH3
CH3

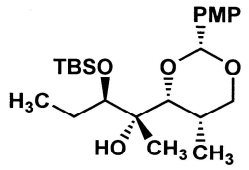
S18.2


85.670
77.421
77.000
76.575
74.840
74.256
68.281
36.190
26.469
26.086
21.003
18.316
12.083
10.633
-4.015
-4.327
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

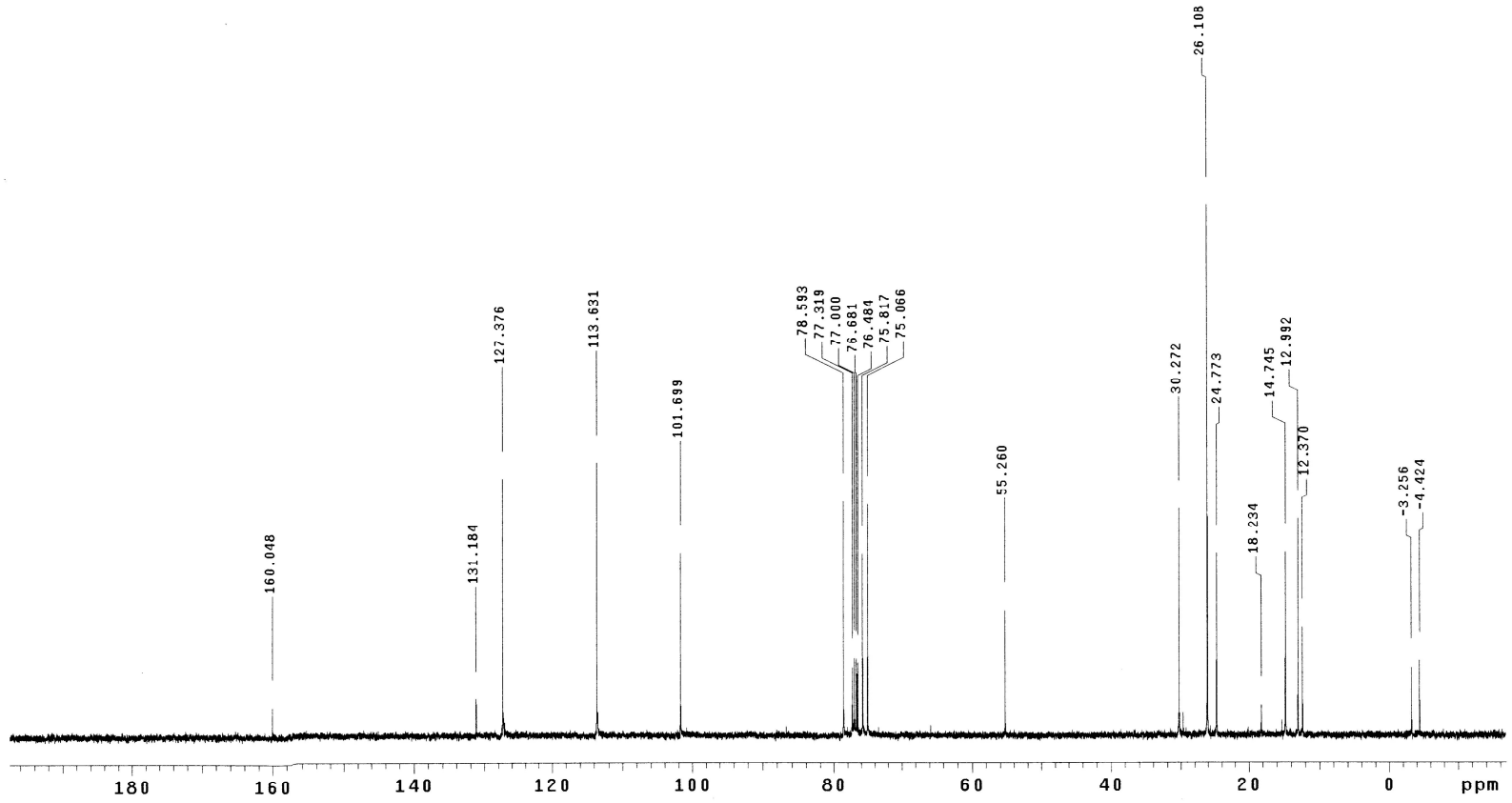

PMP
TBSO
O
O
H3C
HO
CH3
CH3

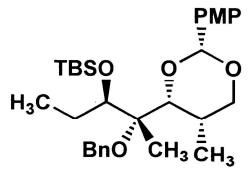
S19.1


7
6
5
4
3
2
1
ppm
1.82
1.89
0.97
2.07
0.93
2.84
1.00
0.78
0.91
1.00
1.12
4.22
3.10
12.32
5.60


PMP
TBSO
O
O
H3C
HO
CH3
CH3

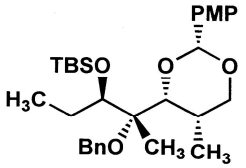
S19.1


160.048
131.184
127.376
113.631
101.699
78.593
77.319
77.000
76.681
76.484
75.817
75.066
55.260
30.272
26.108
24.773
18.234
14.745
12.992
12.370
-3.256
-4.424
180
160
140
120
100
80
60
40
20
0
ppm

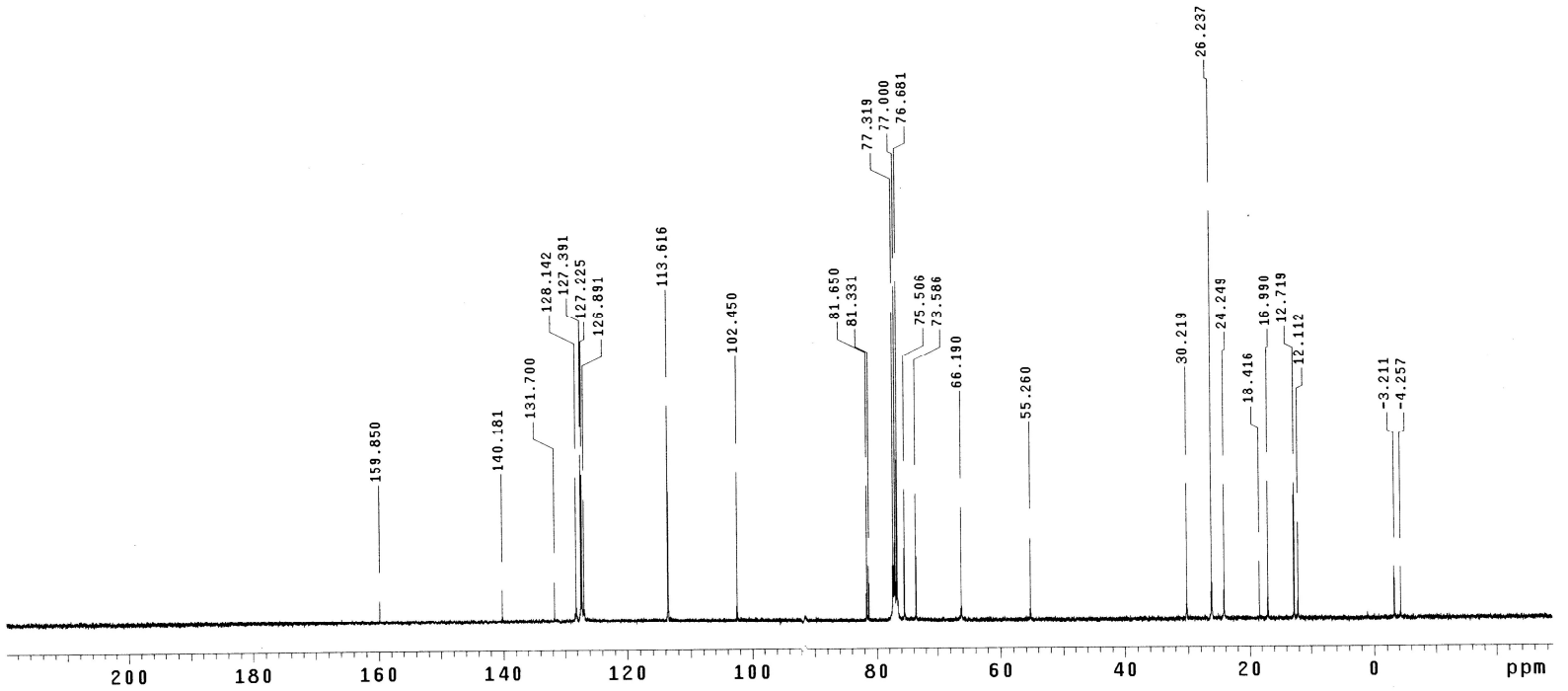

PMP
TBSO
O
O
H3C
BnO
CH3
CH3

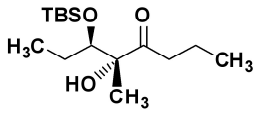
S19.2

8
7
6
5
4
3
2
1
-0
ppm
1.85
0.89
4.09
1.84
1.03
1.05
1.06
2.12
1.83
2.91
2.00
3.85
2.79
8.45
3.05
5.54

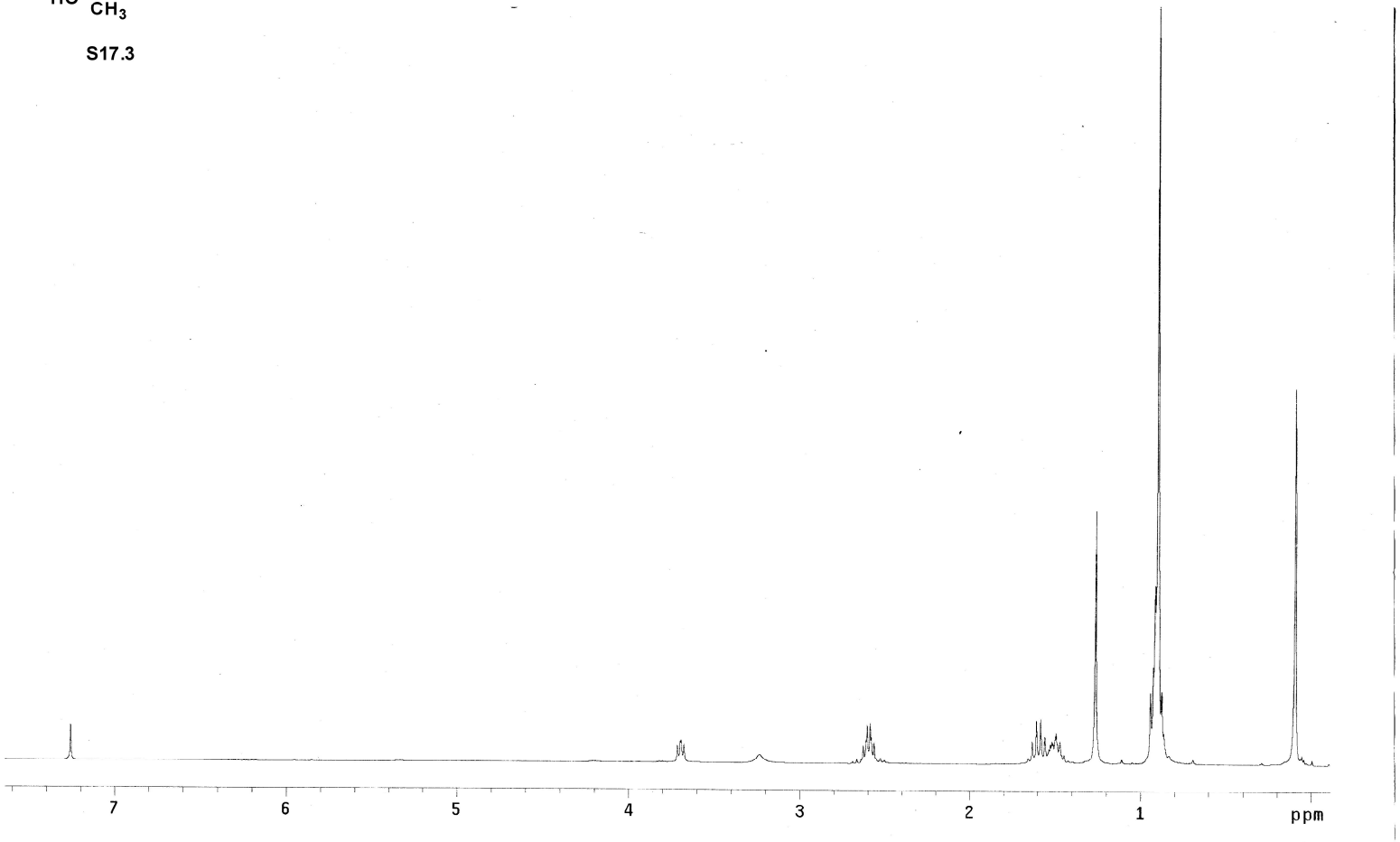

PMP
TBSO
O
O
H3C
BnO
CH3
CH3

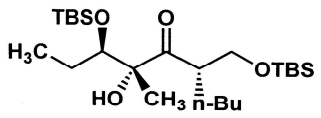
S19.2


159.850
140.181
131.700
128.142
127.391
127.225
126.891
113.616
102.450
81.650
81.331
77.319
77.000
76.681
75.506
73.586
66.190
55.260
30.219
26.237
24.249
18.416
16.990
12.719
12.112
-3.211
-4.257
200
180
160
140
120
100
80
60
40
20
0
ppm

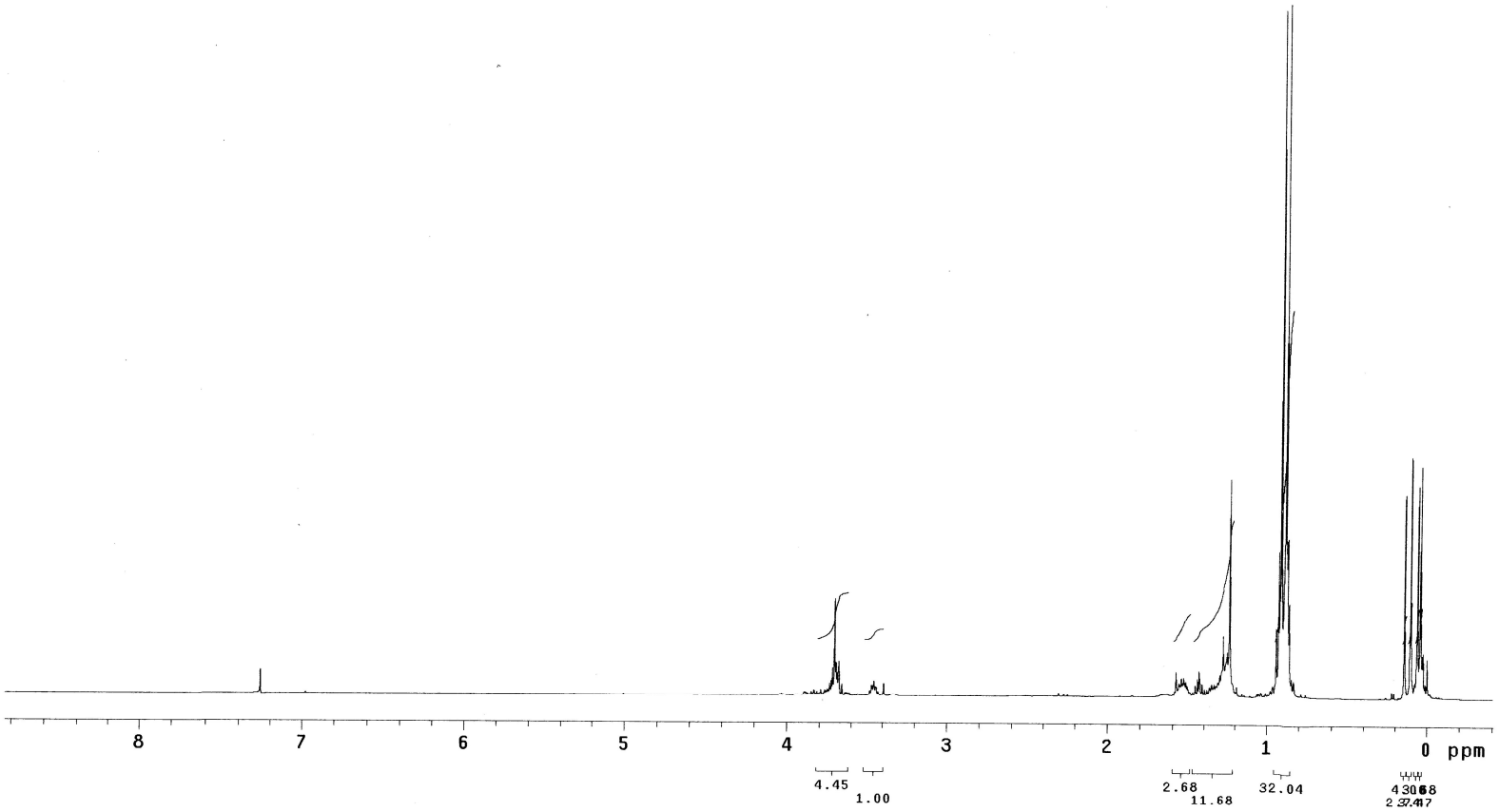


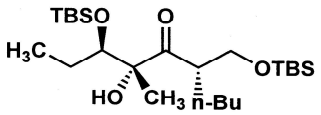
S17.3



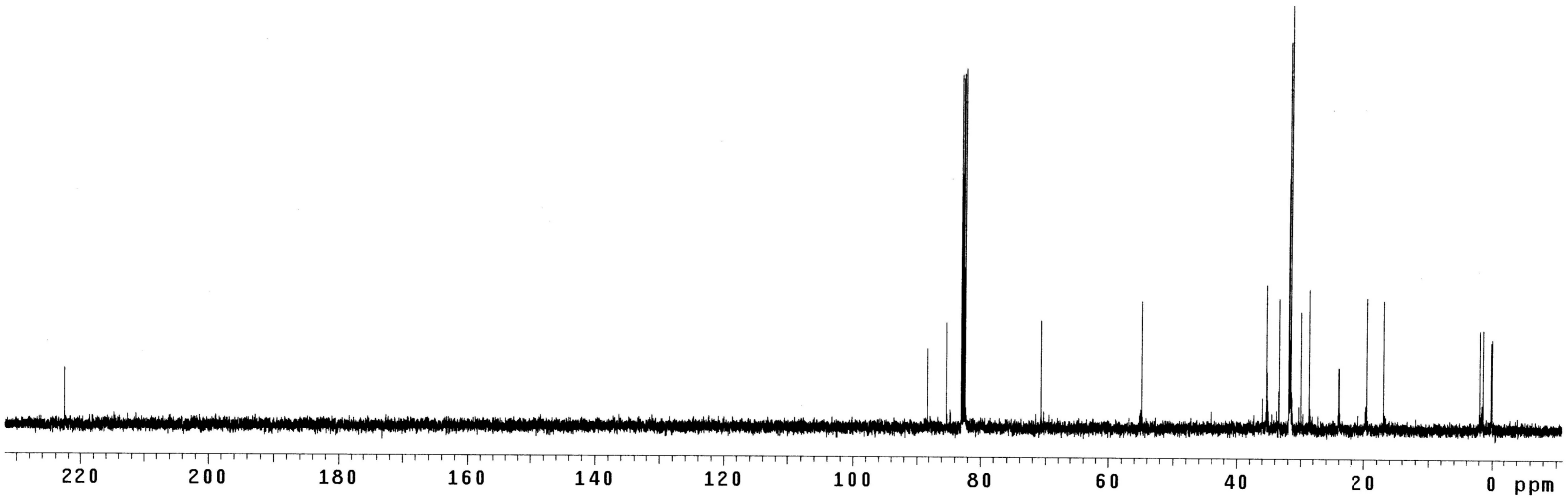

TBSO
O
H3C
OTBS
HO
CH3
n-Bu

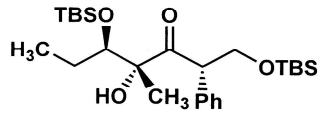
S17.4


8
7
6
5
4
3
2
1
0 ppm
4.45
1.00
2.68
11.68
32.04
43068
23741

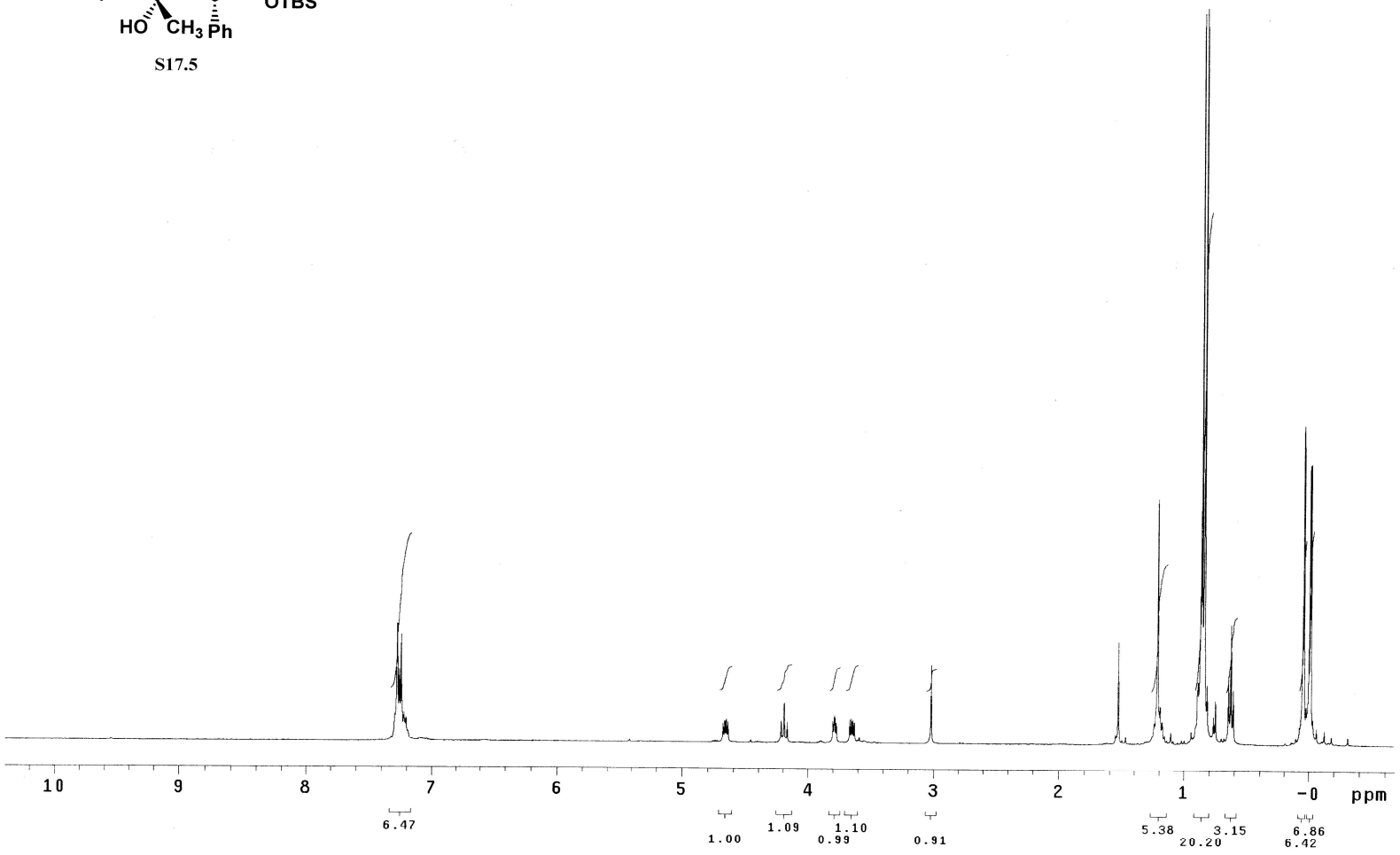

TBSO
O
H3C
OTBS
HO
CH3
n-Bu

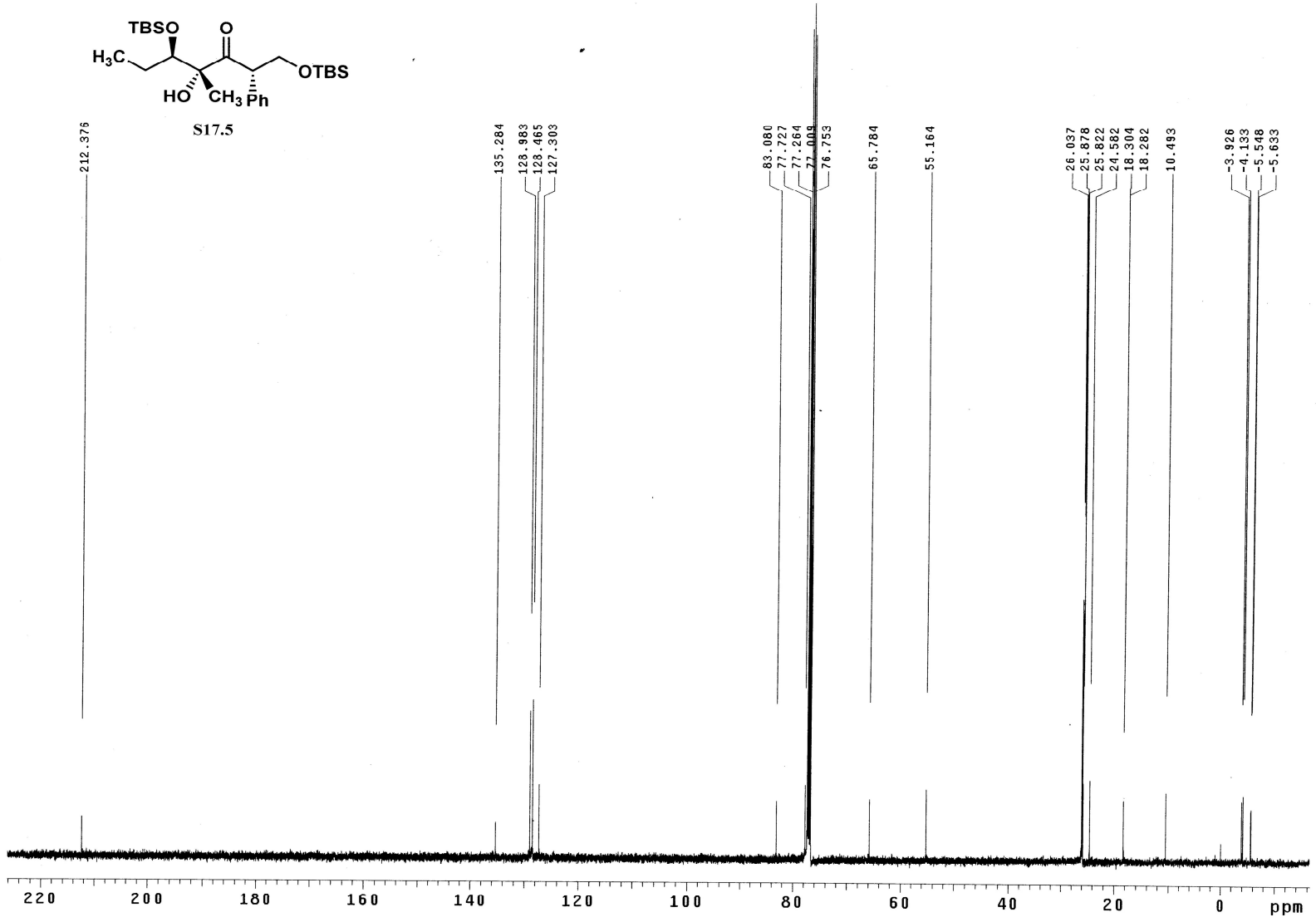
S17.4

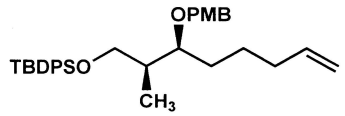

220
200
180
160
140
120
100
80
60
40
20
0 ppm


TBSO
O
H3C
OTBS
HO
CH3
Ph

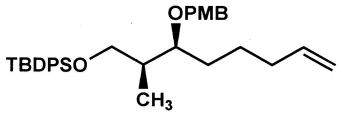
S17.5


10
9
8
7
6
5
4
3
2
1
-0
ppm
6.47
1.00
1.09
0.99
1.10
0.91
5.38
20.20
3.15
6.86
6.42

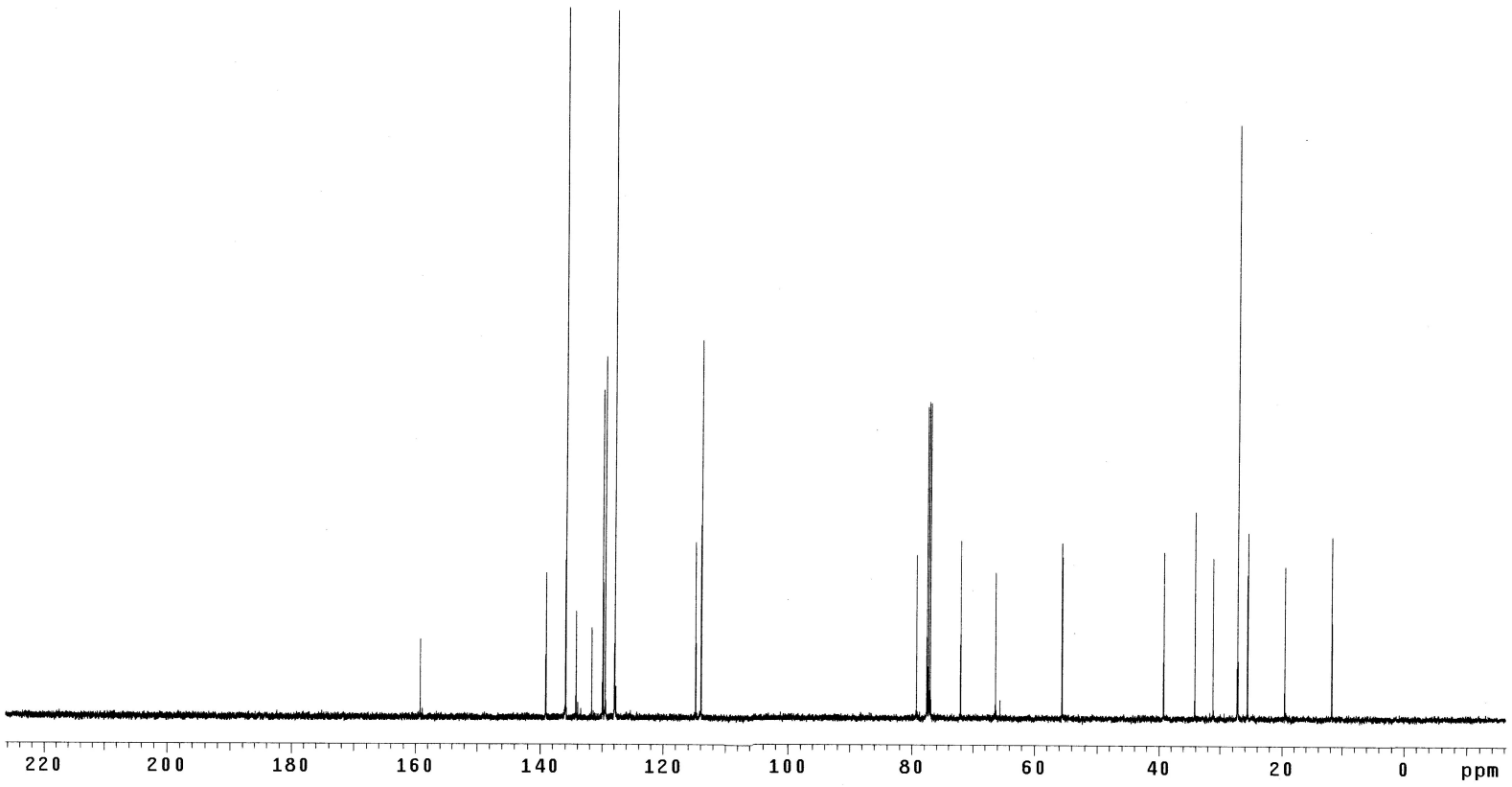

TBSO
O
H3C
OTBS
HO
CH3
Ph
S17.5
212.376
135.284
128.983
128.465
127.303
83.080
77.727
77.264
77.009
76.753
65.784
55.164
26.037
25.878
25.822
24.582
18.304
18.282
10.493
-3.926
-4.133
-5.548
-5.633
220
200
180
160
140
120
100
80
60
40
20
0
ppm

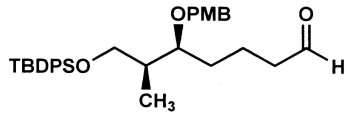


S38.5

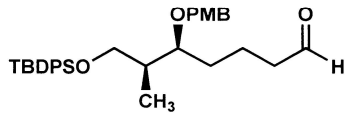


S38.5

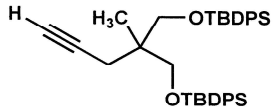




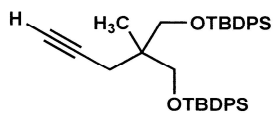
S38.6



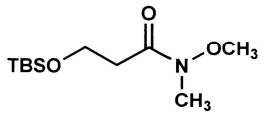
S38.6



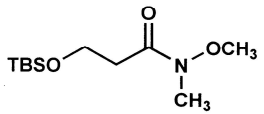
S41.2



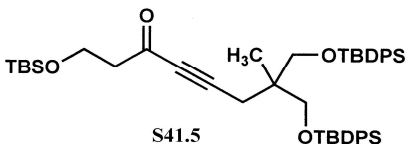
S41.2



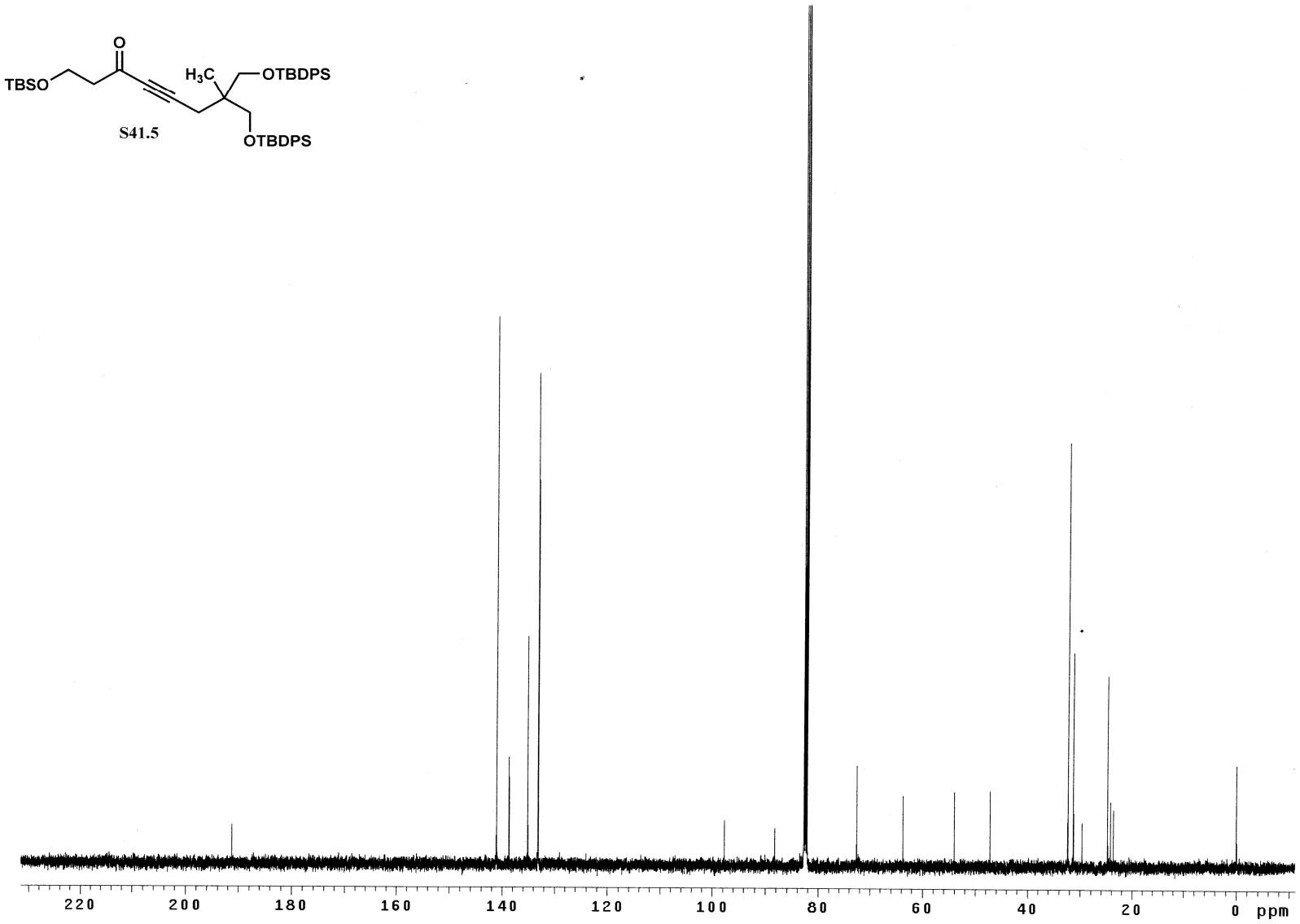
S41.4

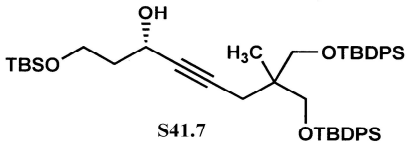


S41.4

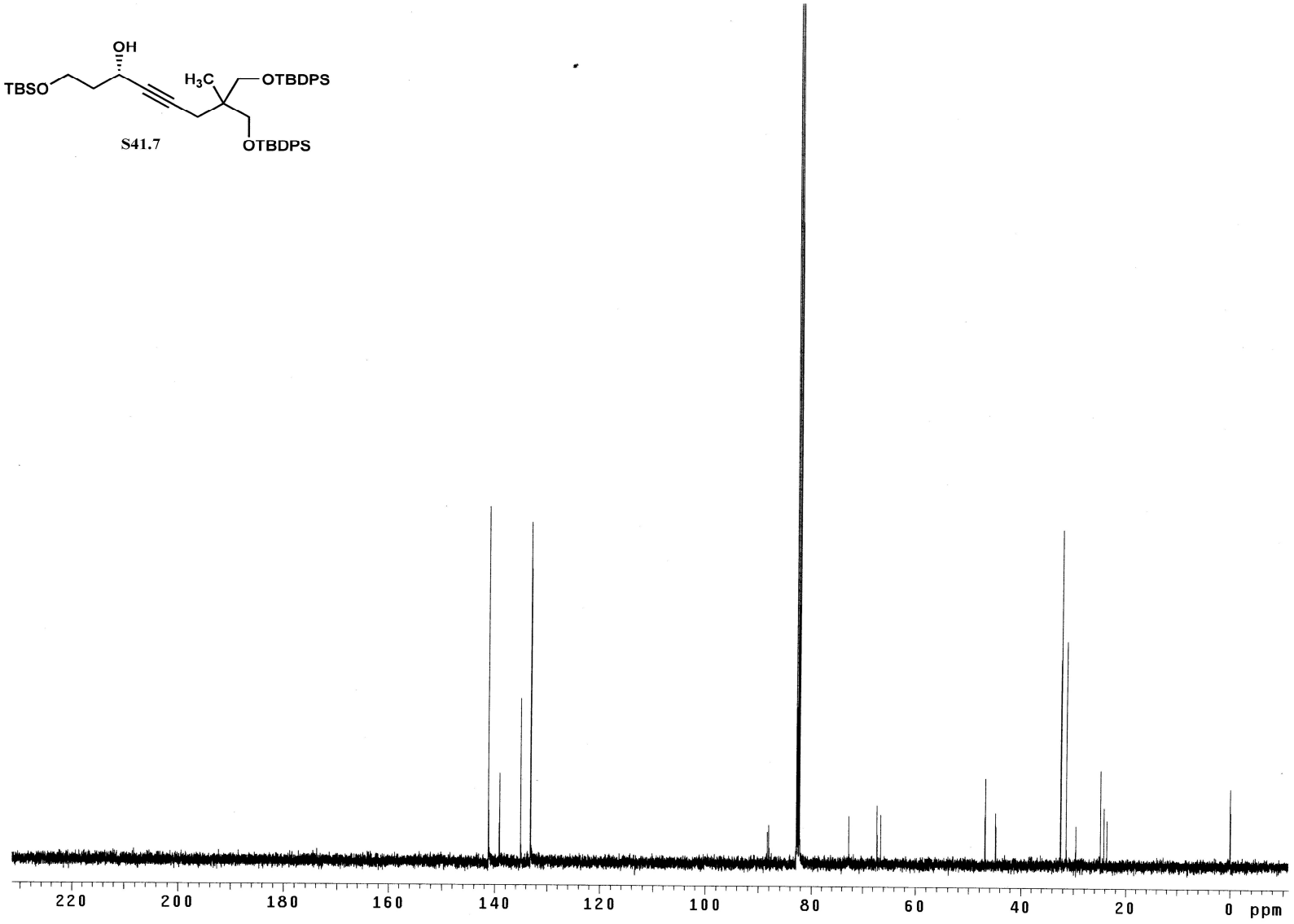


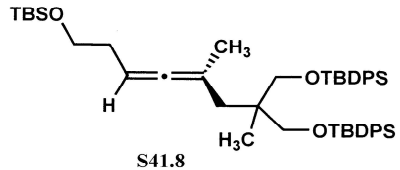
S41.5


O
TBSO
H3C
OTBDPS
OTBDPS
S41.5
220
200
180
160
140
120
100
80
60
40
20
0
ppm

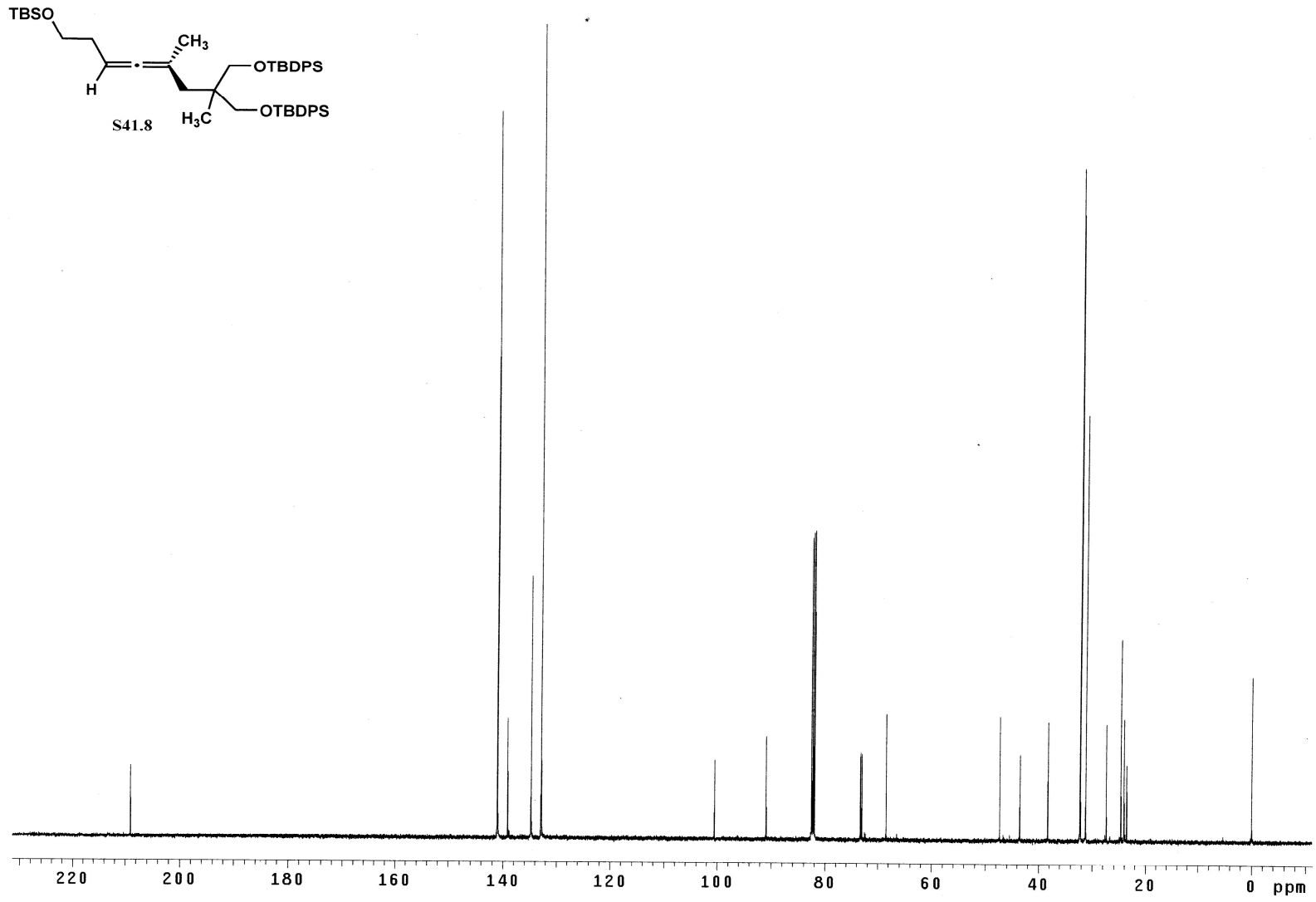


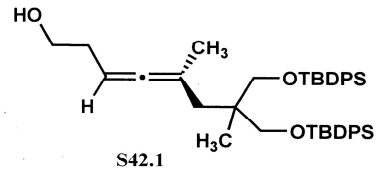
S41.7


OH
TBSO
H3C
OTBDPS
OTBDPS
S41.7
220
200
180
160
140
120
100
80
60
40
20
0 ppm

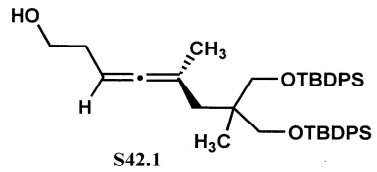


S41.8

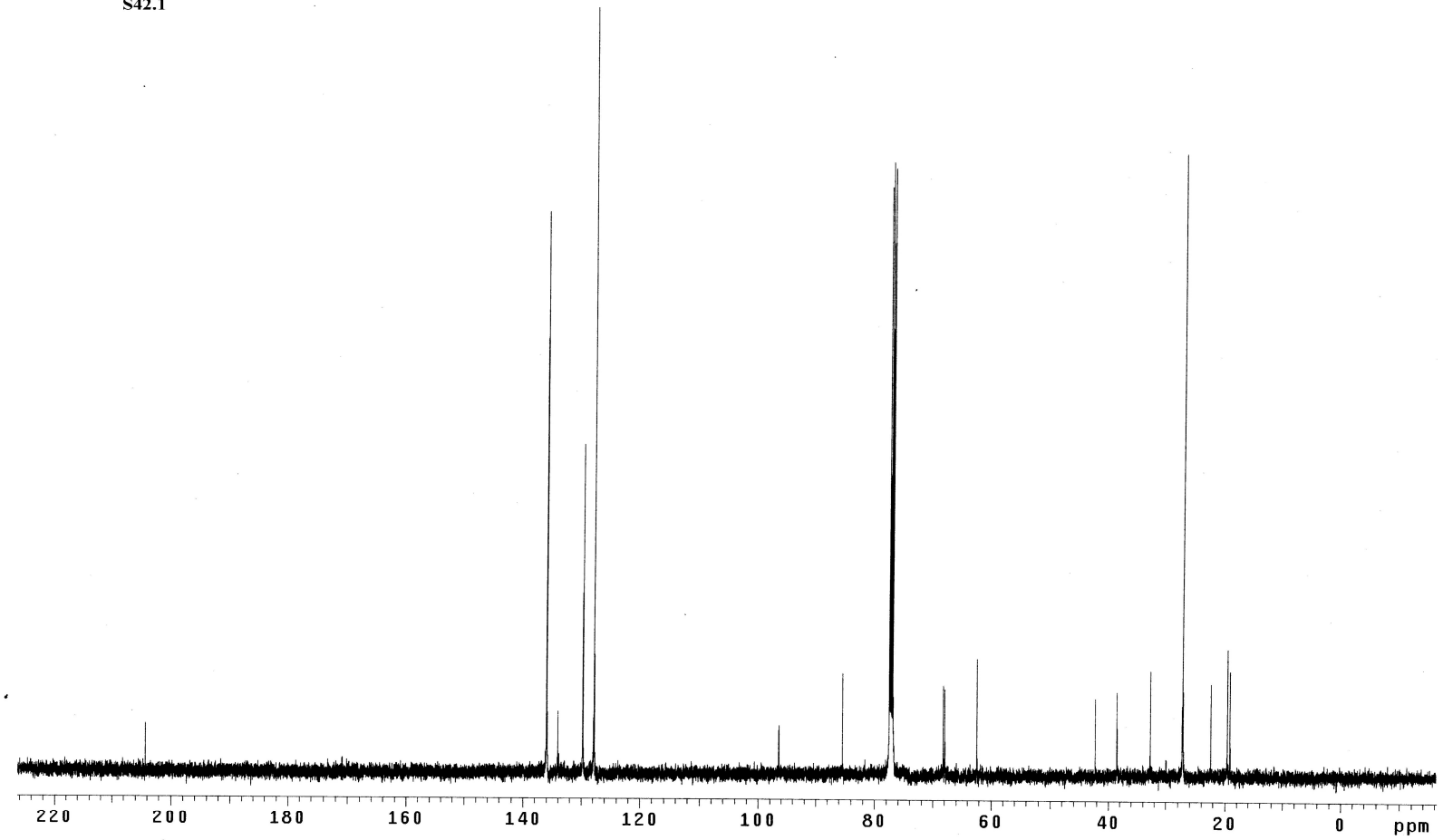

TBSO
CH3
OTBDPS
H
H3C
OTBDPS
S41.8
220
200
180
160
140
120
100
80
60
40
20
0
ppm

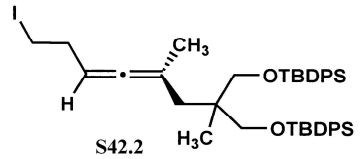


S42.1

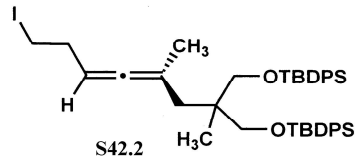

HO
CH3
OTBDPS
H
H3C
OTBDPS

S42.1


220
200
180
160
140
120
100
80
60
40
20
0
ppm

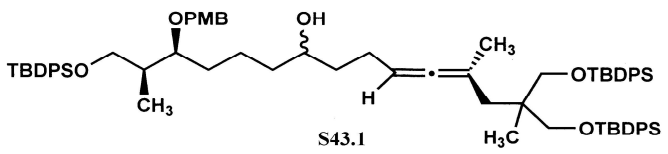


S42.2

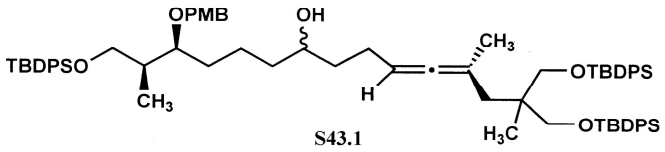

I
CH3
OTBDPS
H
H3C
OTBDPS

S42.2

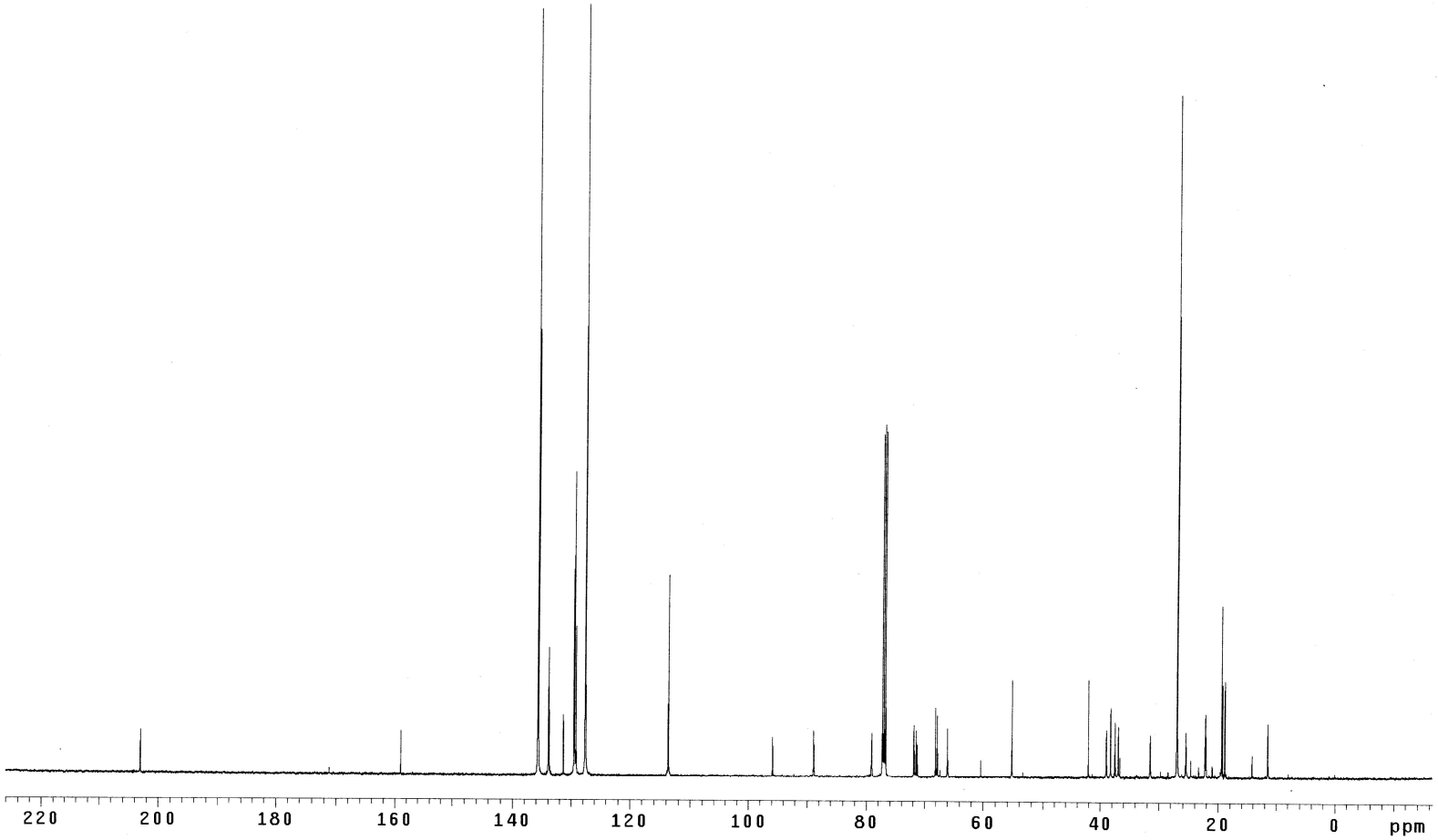
220
200
180
160
140
120
100
80
60
40
20
0
ppm

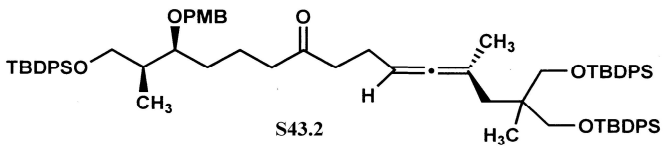


S43.1

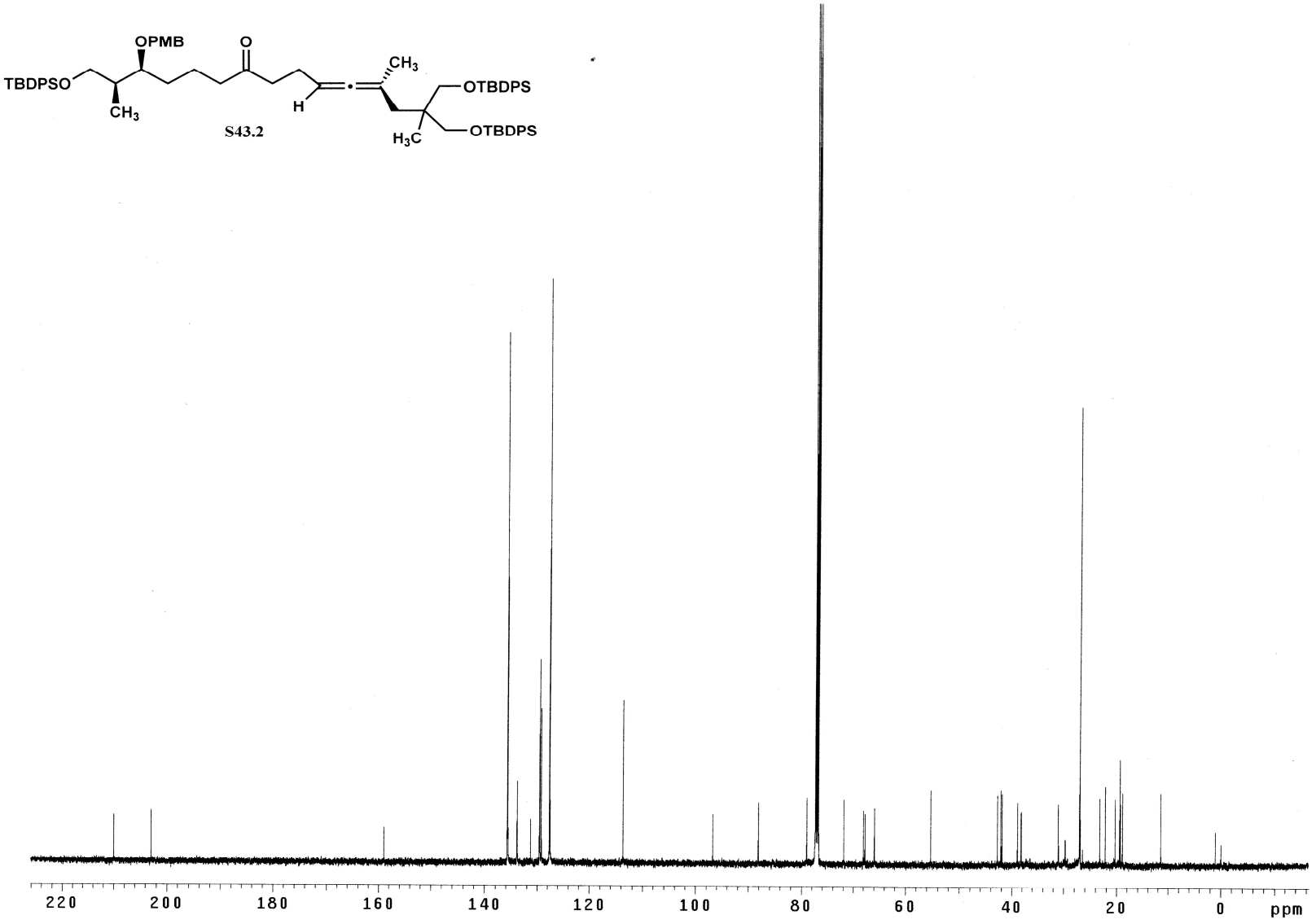

OPMB
OH
TBDPSO
CH3
H
CH3
OTBDPS
OTBDPS
H3C

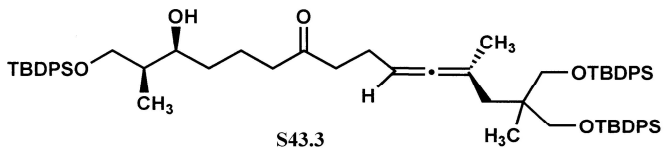
S43.1


220
200
180
160
140
120
100
80
60
40
20
0
ppm

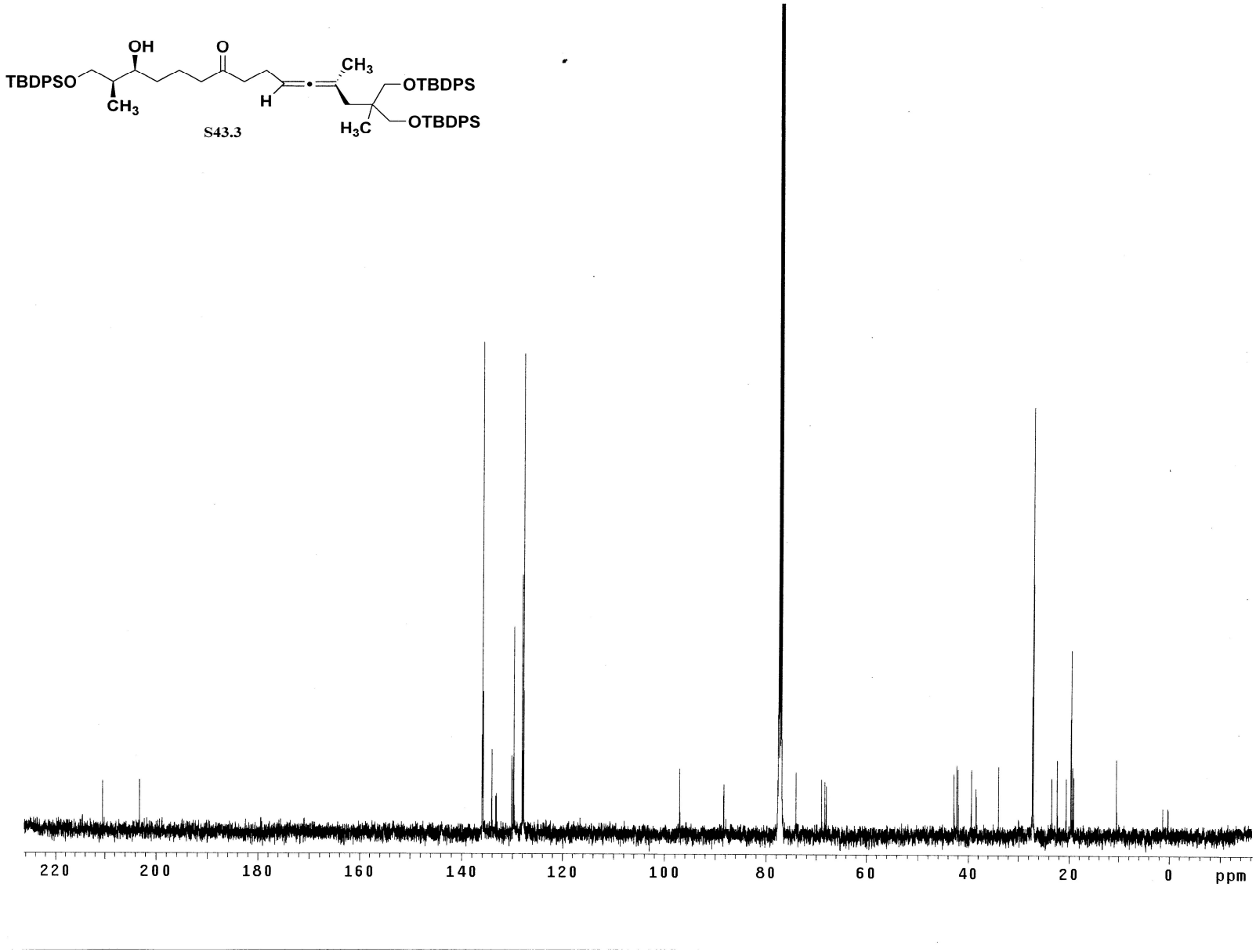


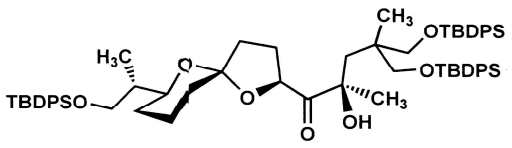
S43.2


OPMB
O
TBDPSO
CH3
H
CH3
OTBDPS
OTBDPS
H3C
S43.2
220
200
180
160
140
120
100
80
60
40
20
0
ppm

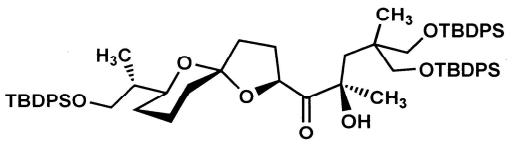


S43.3


OH
O
TBDPSO
CH3
CH3
H
OTBDPS
H3C
OTBDPS
S43.3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

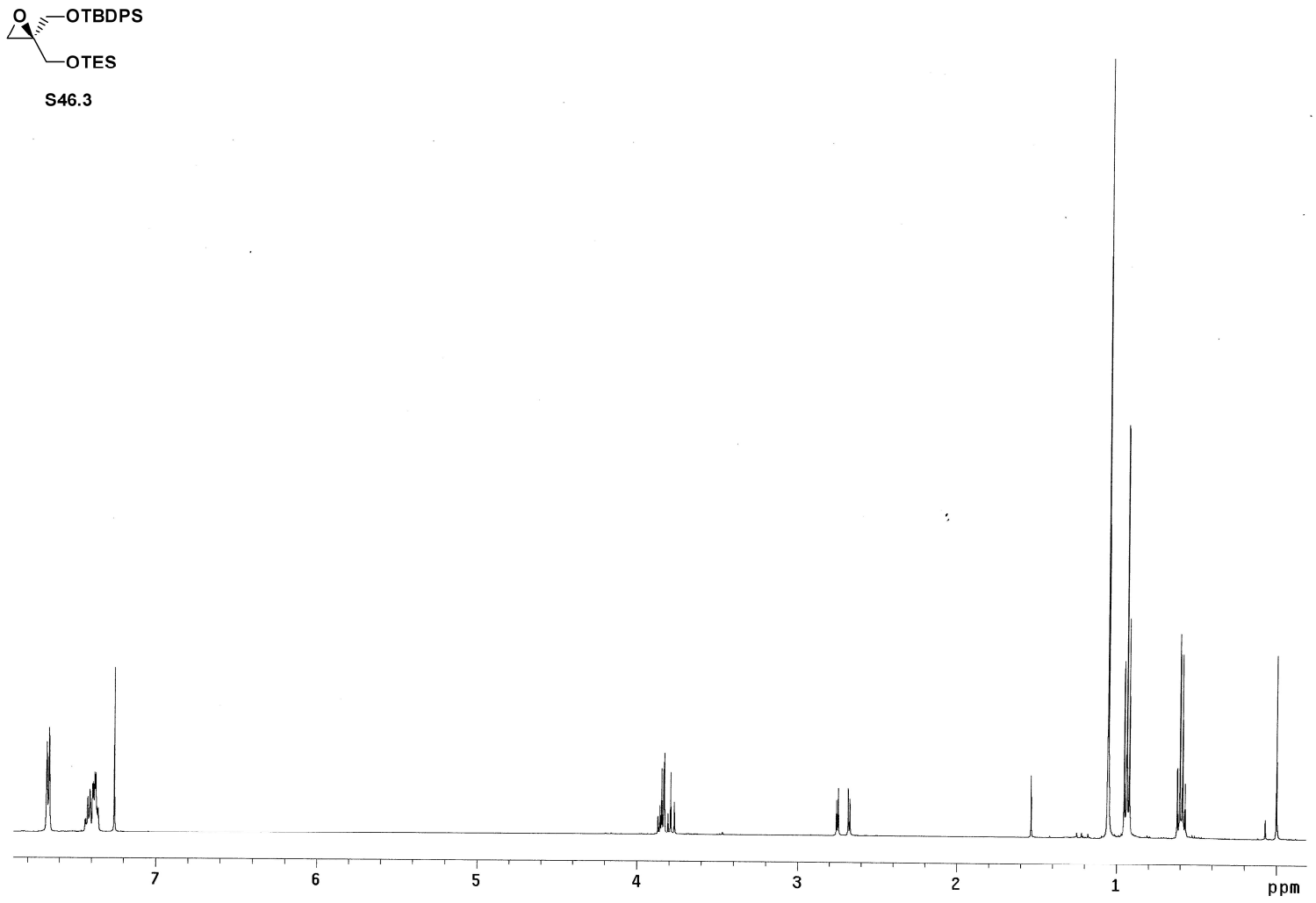


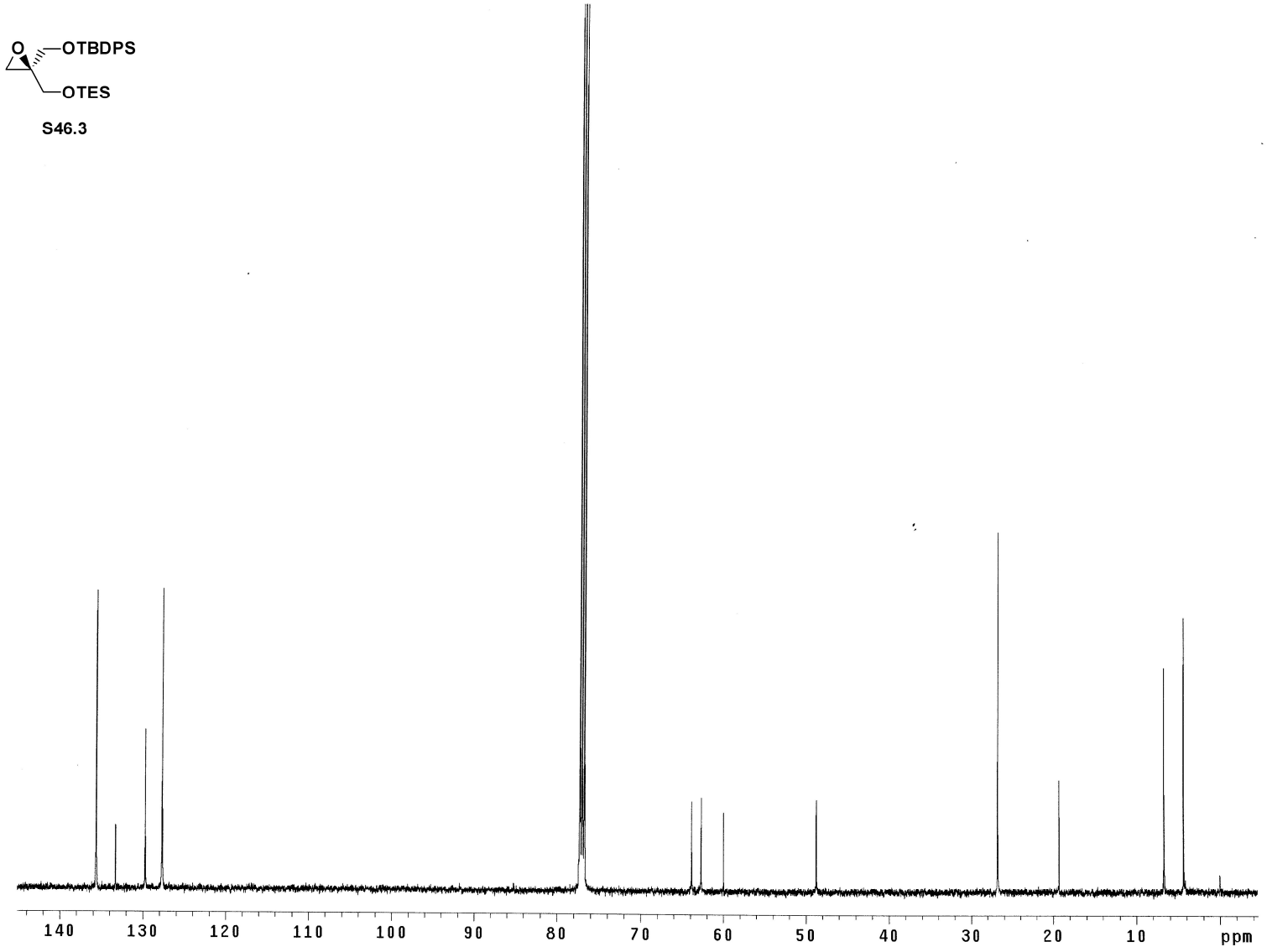
S43.4

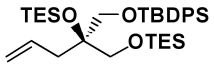

CH3
OTBDPS
H3C
O
OTBDPS
TBDPSO
O
CH3
O
OH

S43.4

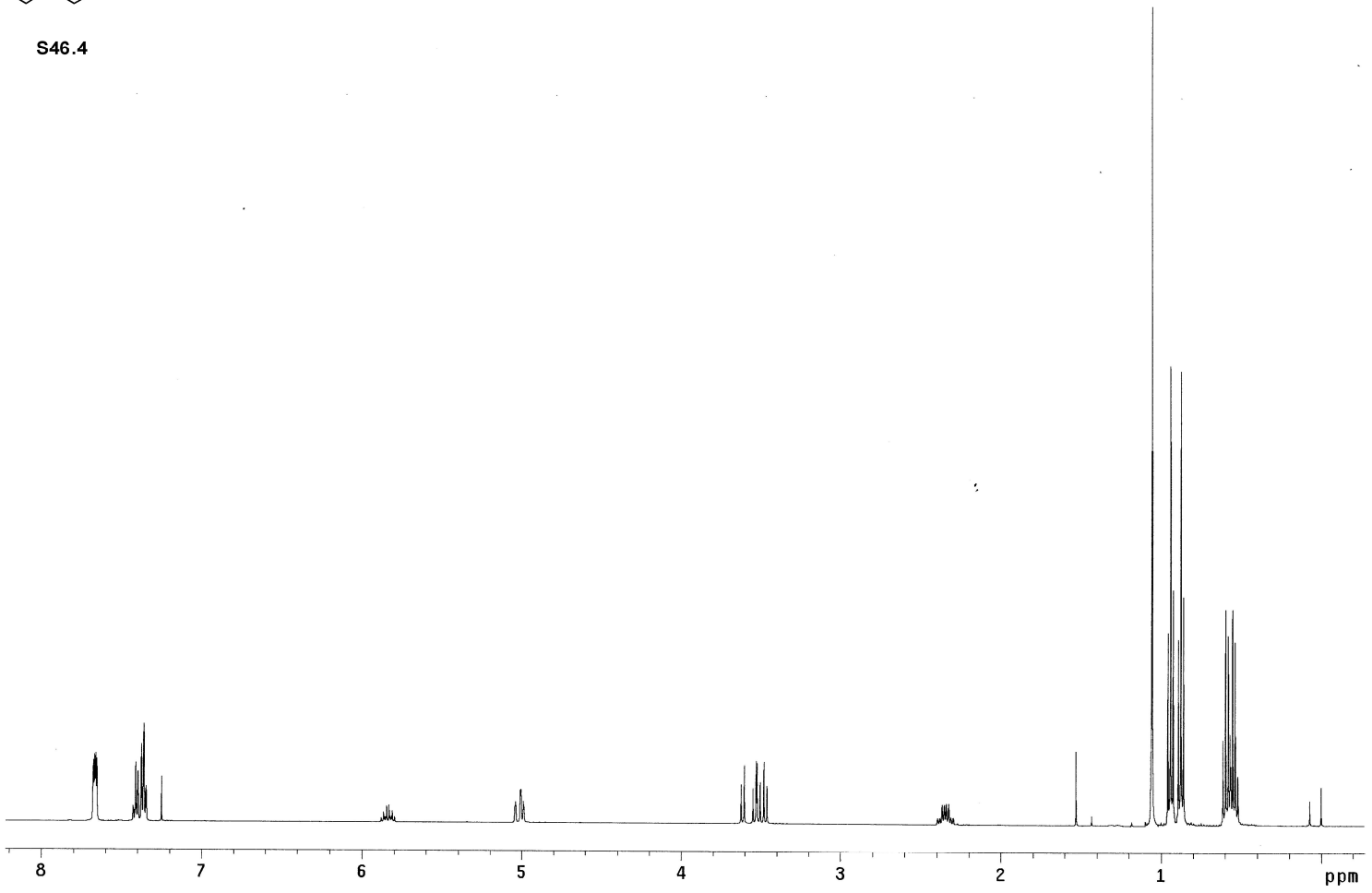
220
200
180
160
140
120
100
80
60
40
20
0
ppm

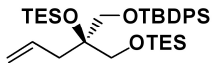

OTBDPS
OTES
S46.3
7
6
5
4
3
2
1
ppm


O
OTBDPS
OTES
S46.3
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

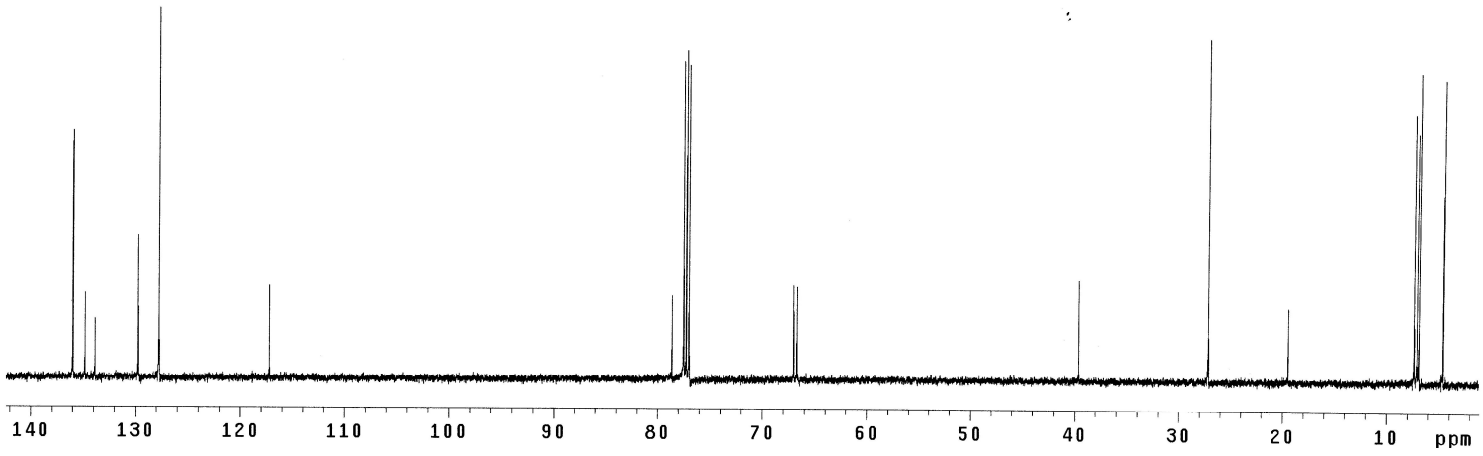


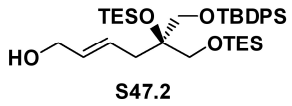
S46.4



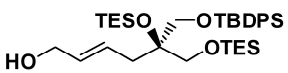

TESO
OTBDPS
OTES

S46.4

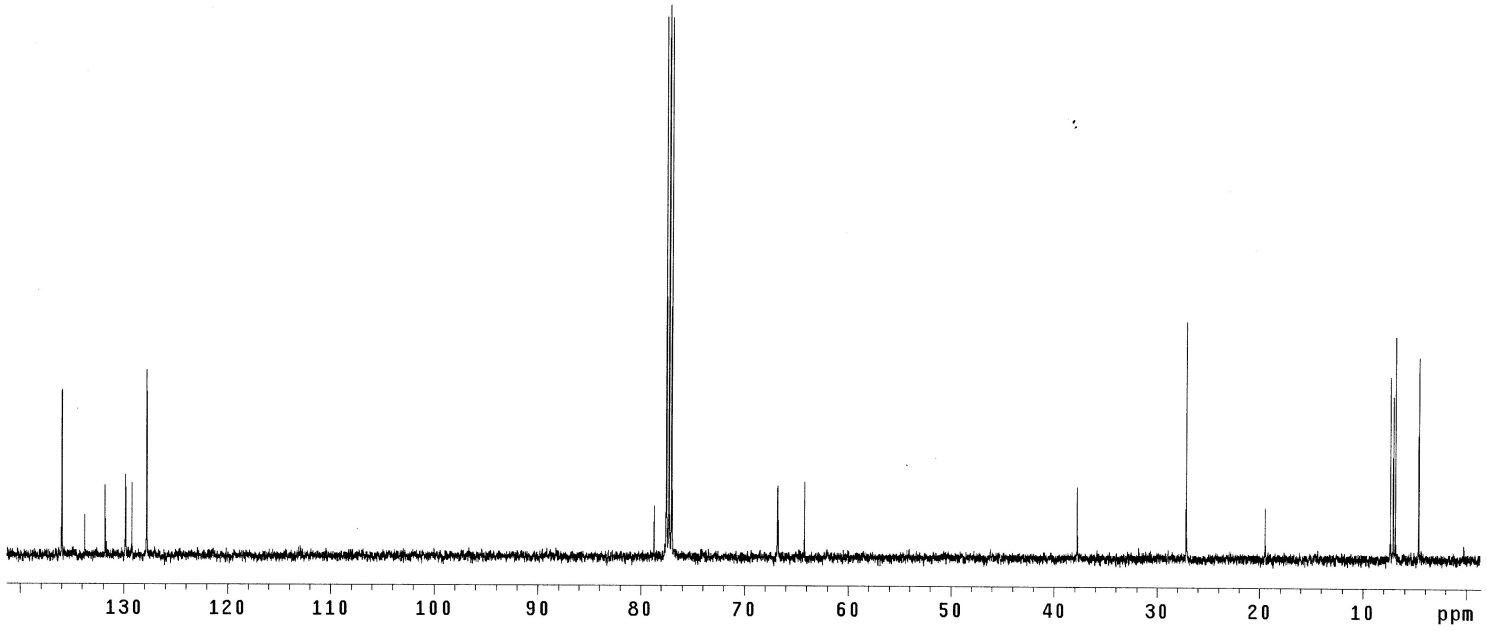

140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

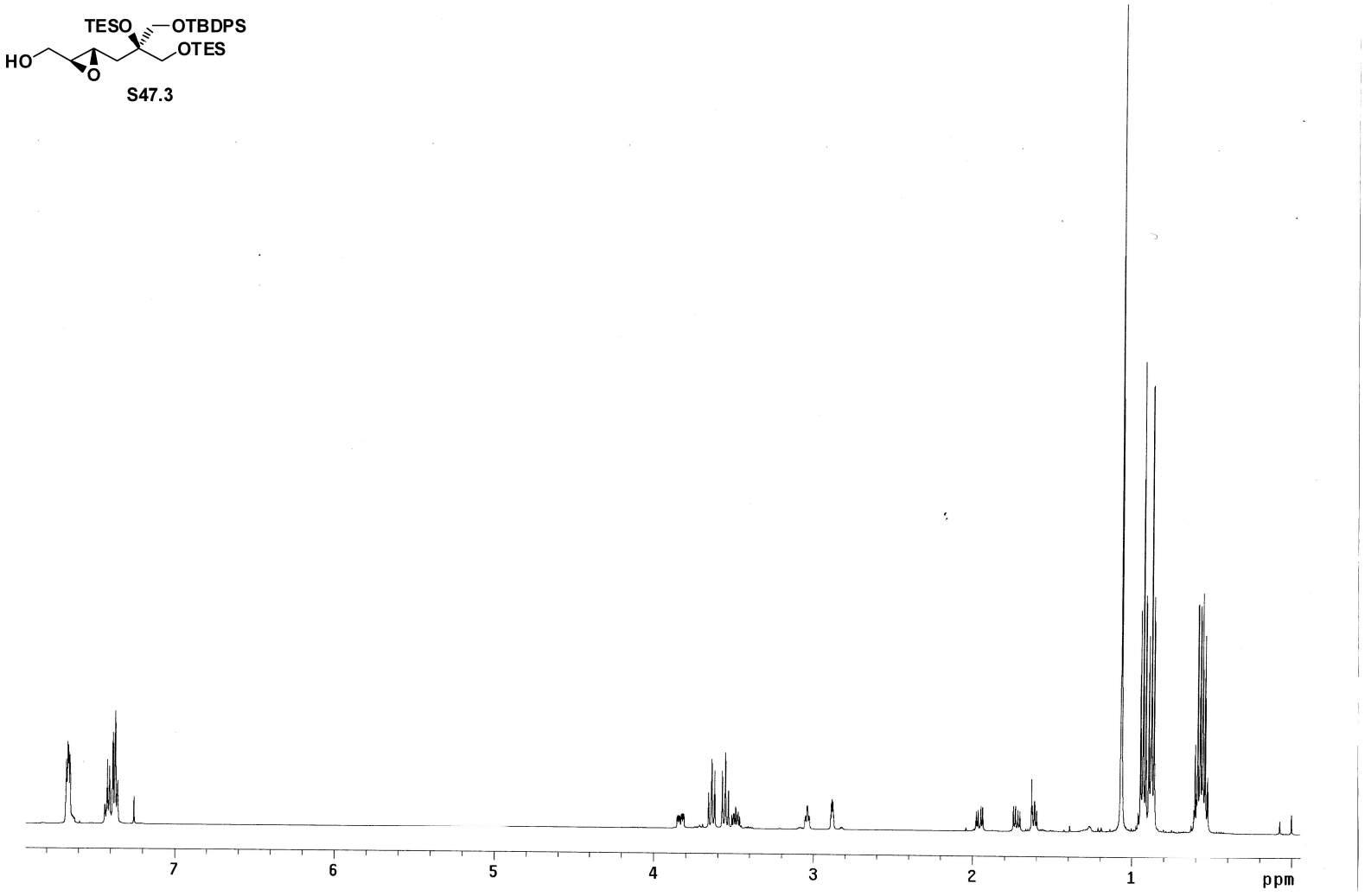


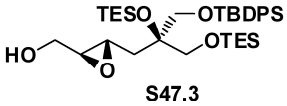
S47.2



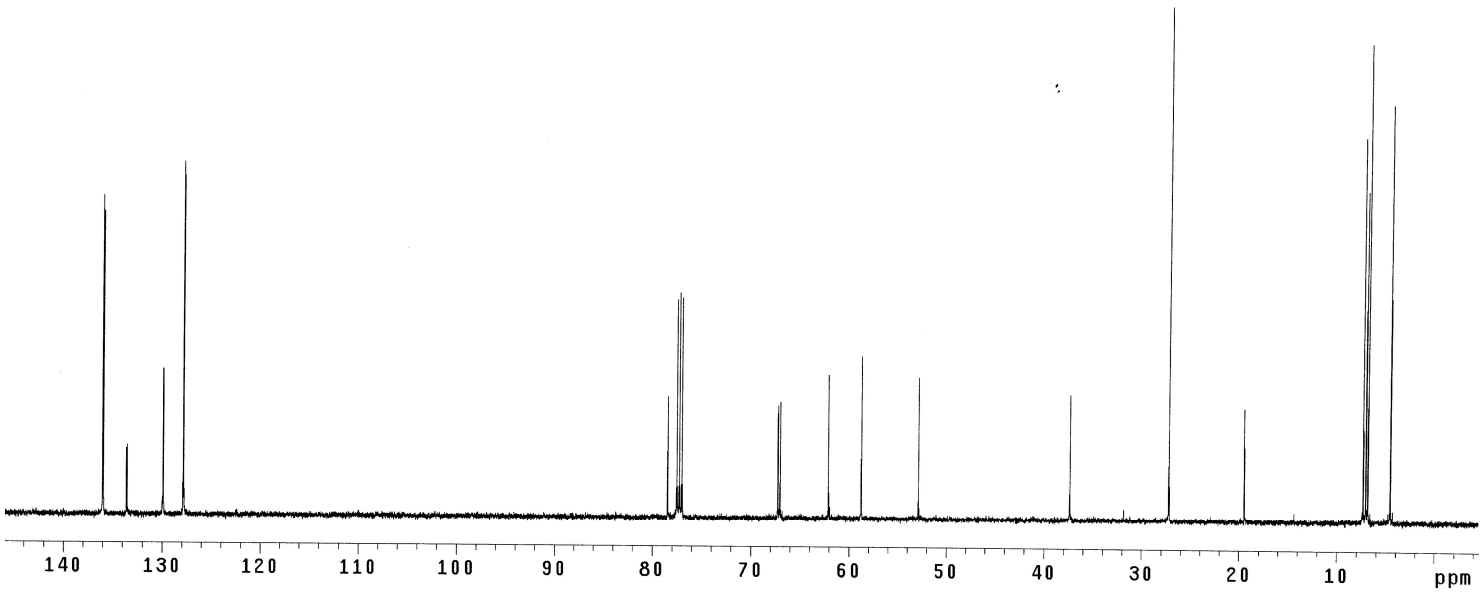
S47.2

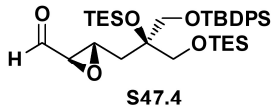



TESO
OTBDPS
OTES
HO
O
S47.3
7
6
5
4
3
2
1
ppm

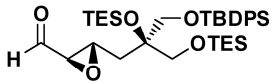

TESO
OTBDPS
HO
OTES
O

S47.3

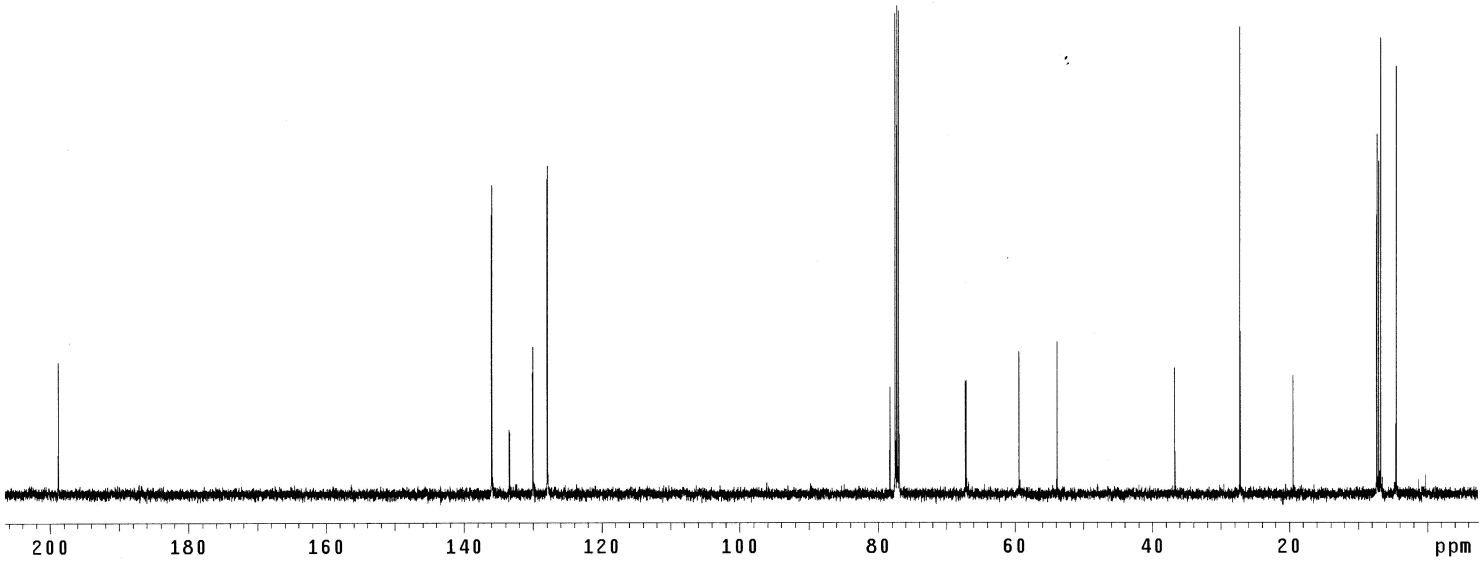

140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

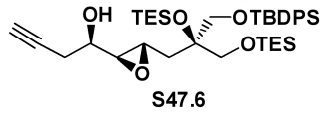


S47.4

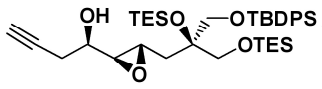


S47.4

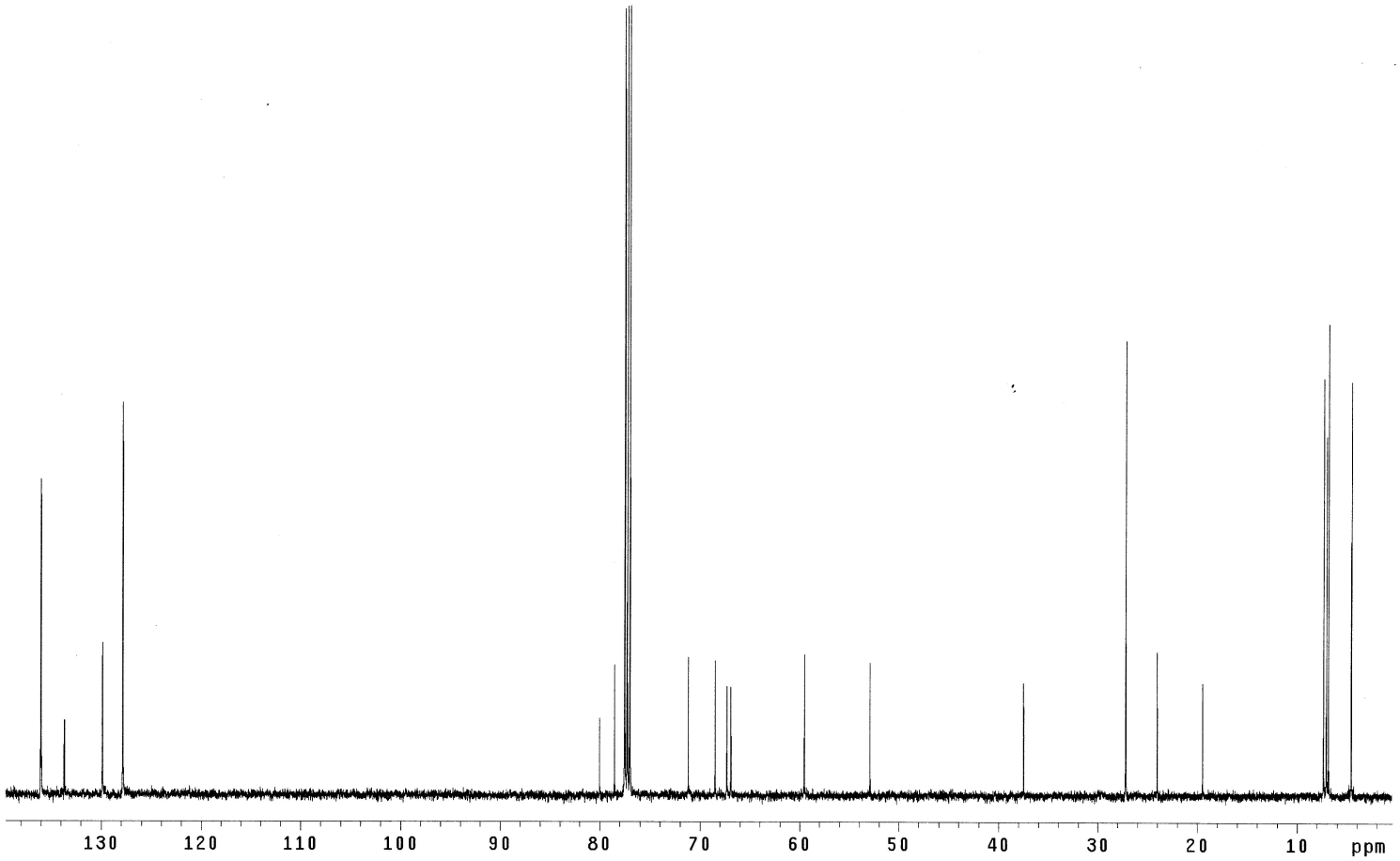


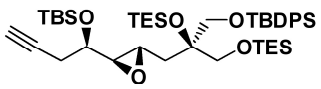


S47.6

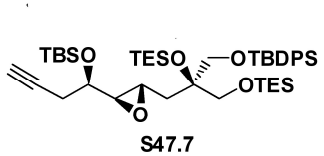

OH
TESO
OTBDPS
OTES
O

S47.6

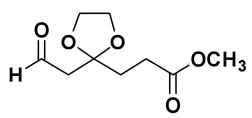

130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



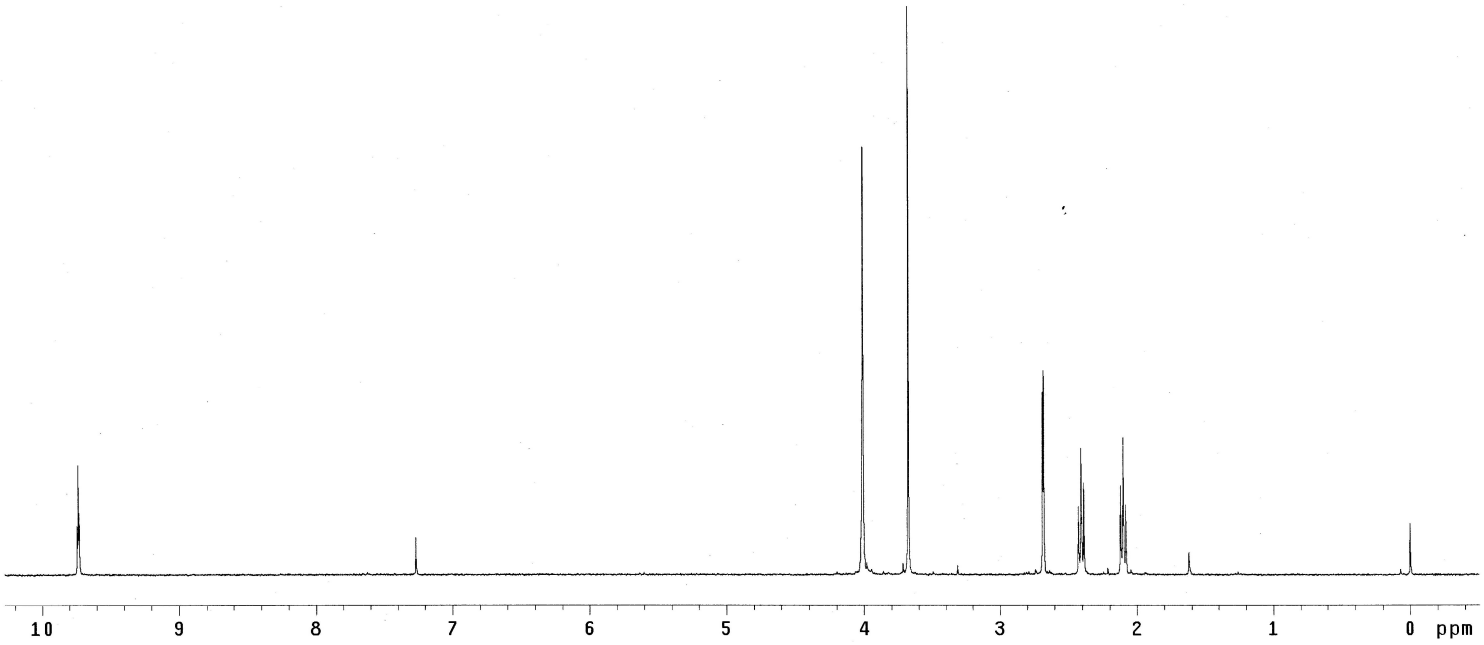
S47.7

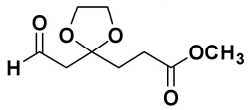


S47.7

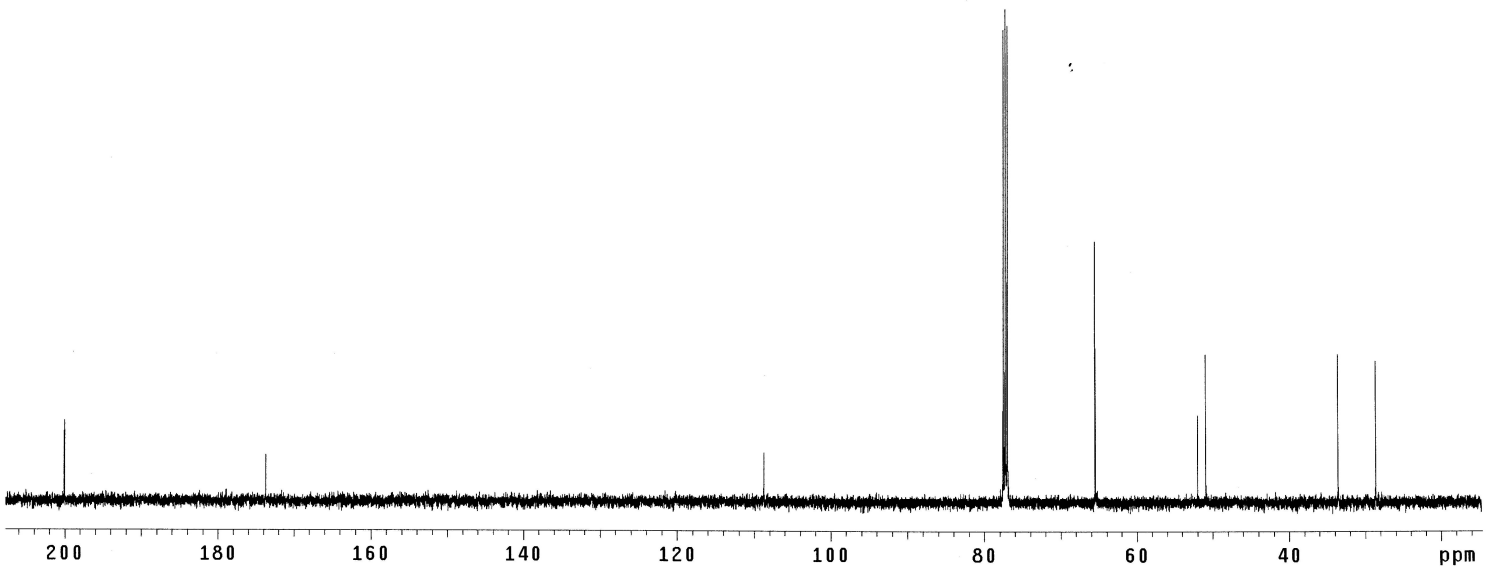


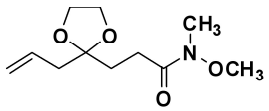
S48.3



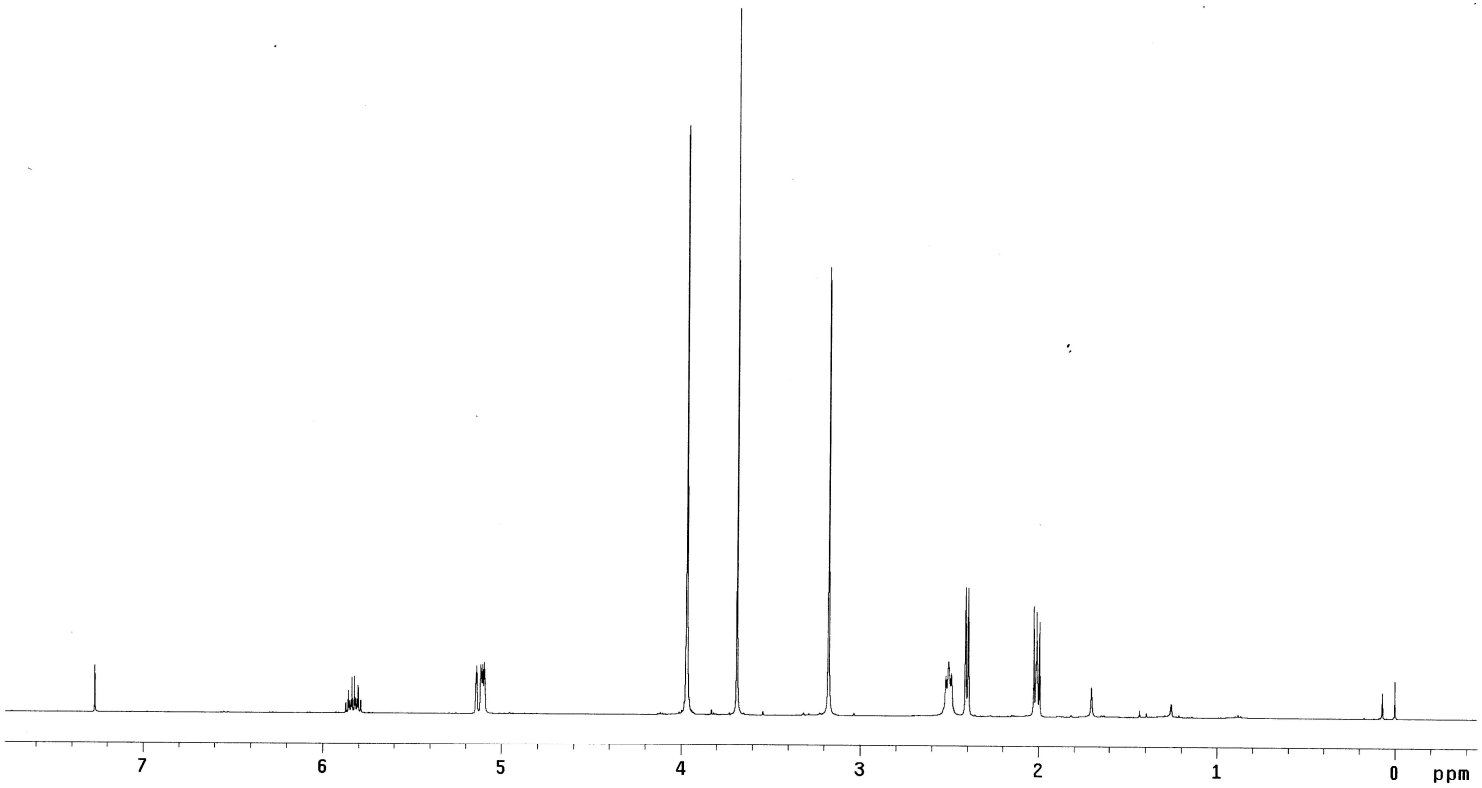


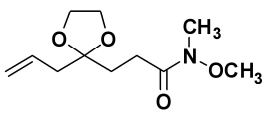
S48.3





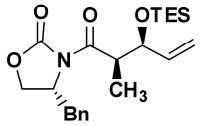
F9.4



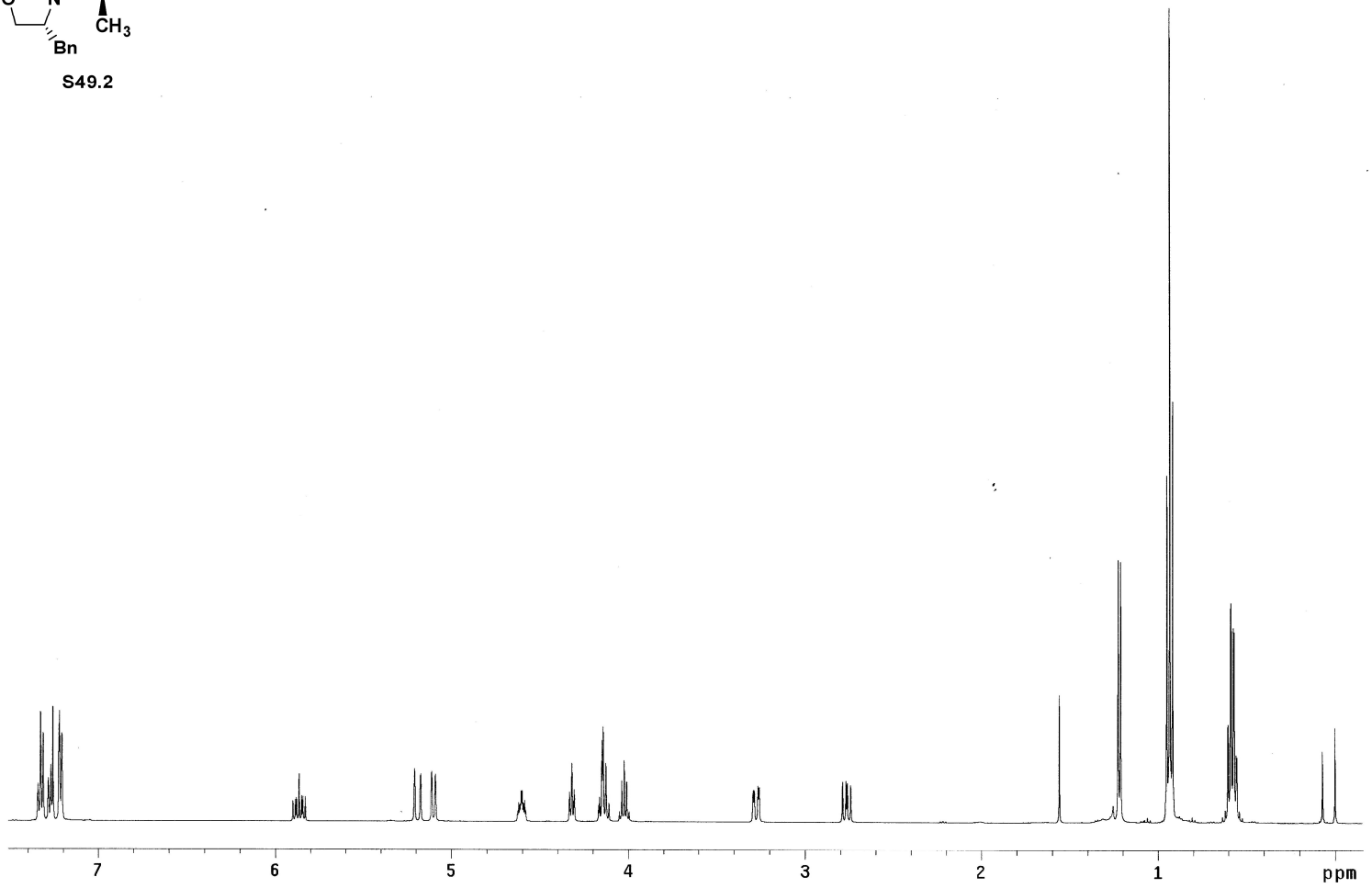

O
O
CH3
N
OCH3
O

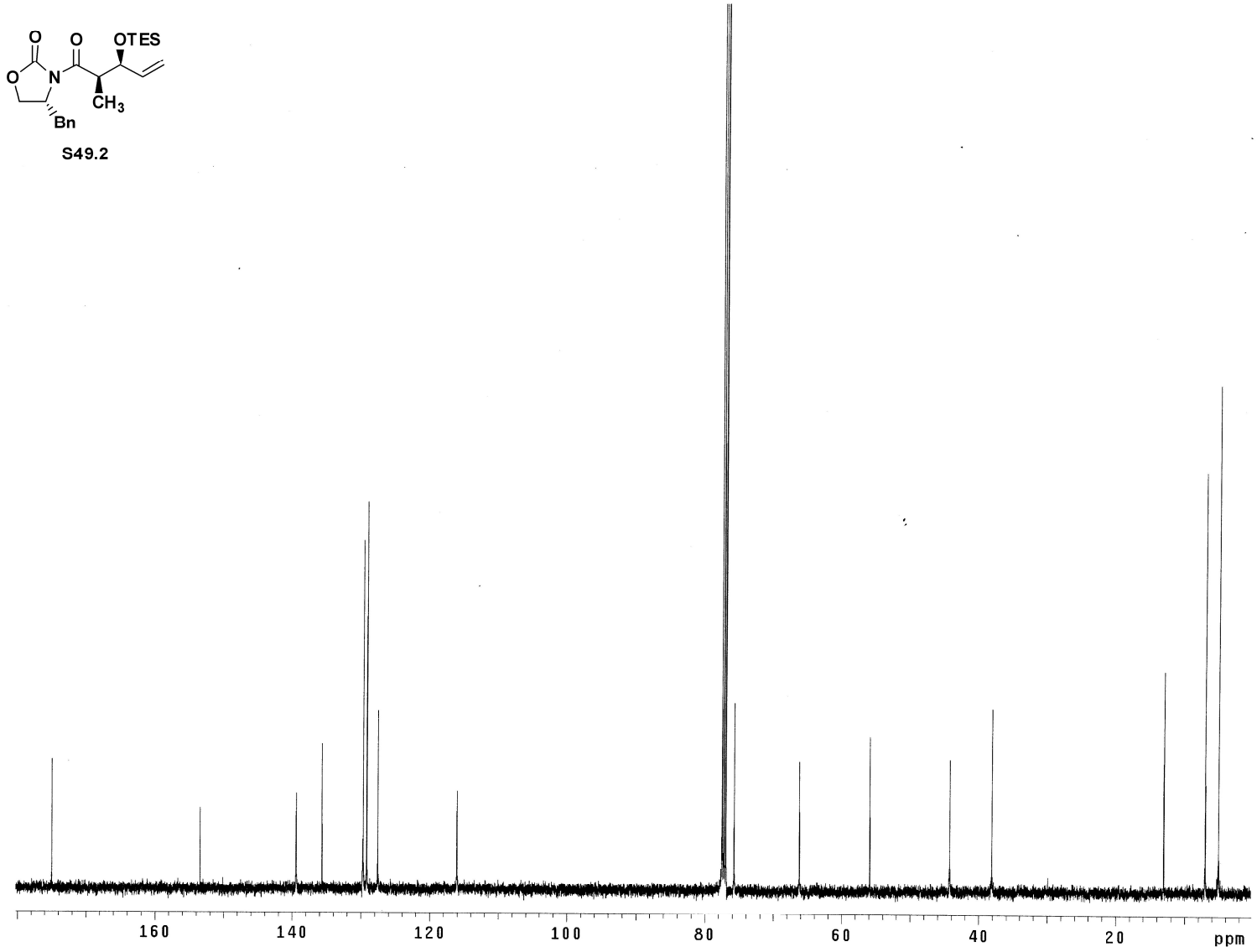
F9.4

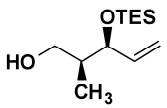
133.244
174.565
180
170
160
150
140
130
160
140
120
100
80
60
40
ppm



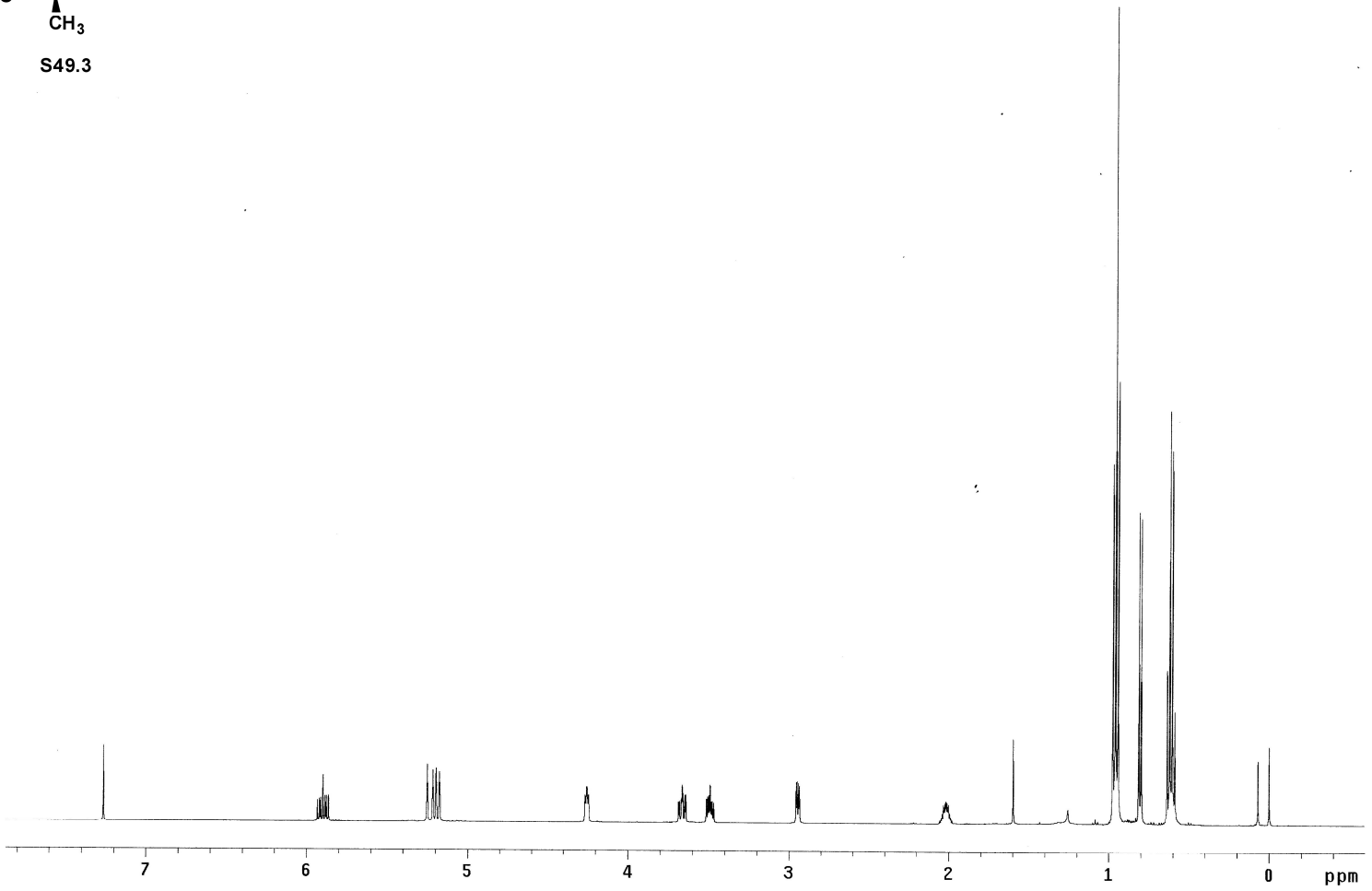
S49.2

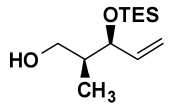



O
O
OTES
O
N
CH3
Bn
S49.2
160
140
120
100
80
60
40
20
ppm

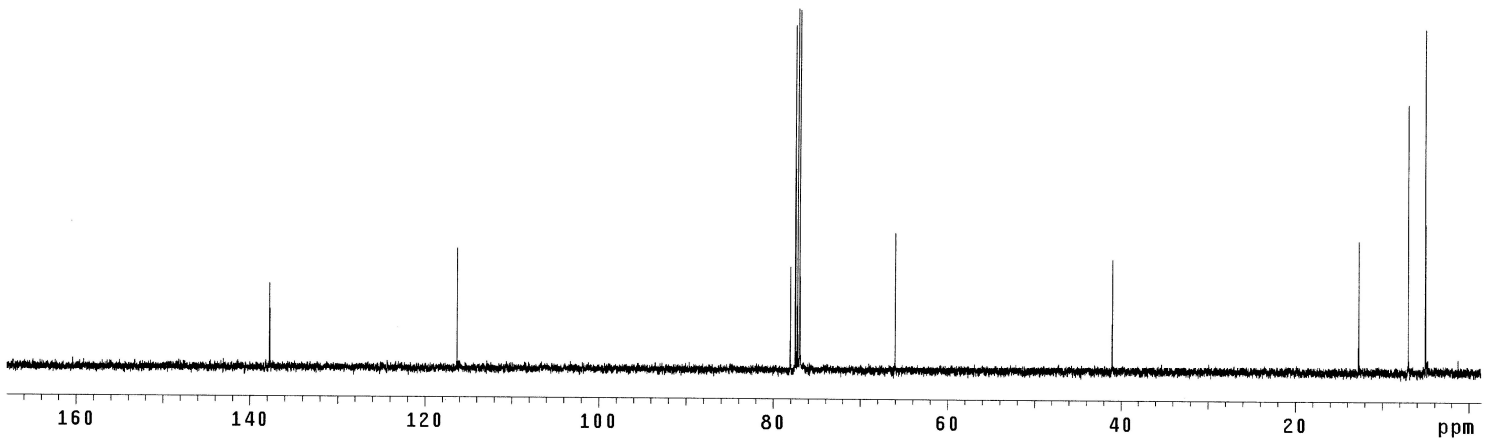


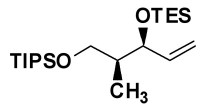
S49.3



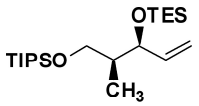


S49.3

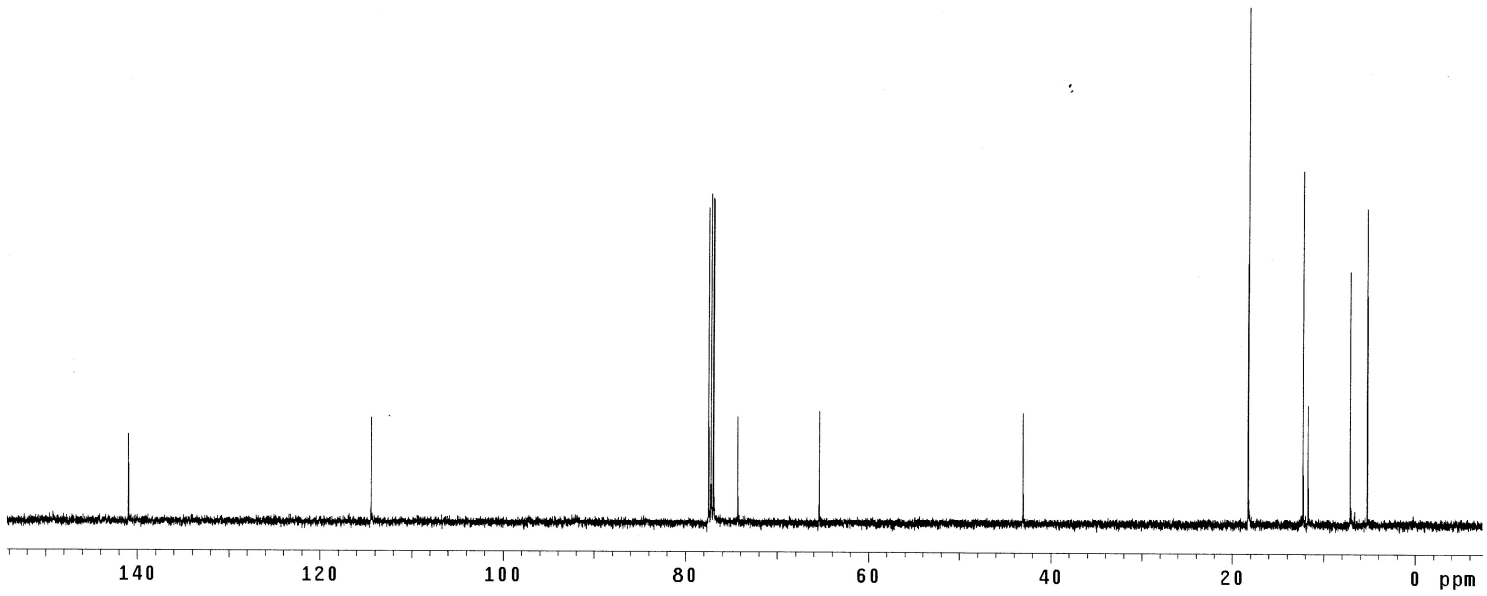


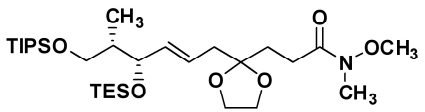


F9.3

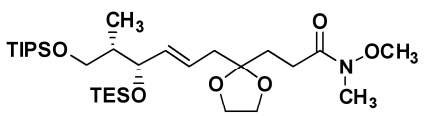


F9.3



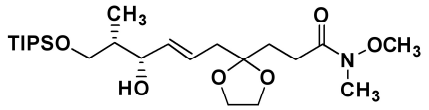


S50.2

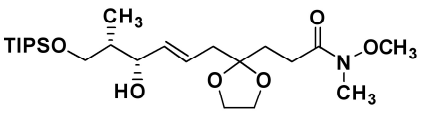

CH3
TIPSO
TESO
O
O
O
N
OCH3
CH3

S50.2

136.348
174.524
175
170
165
160
155
150
145
140
135
13
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

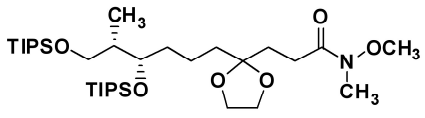


S50.3

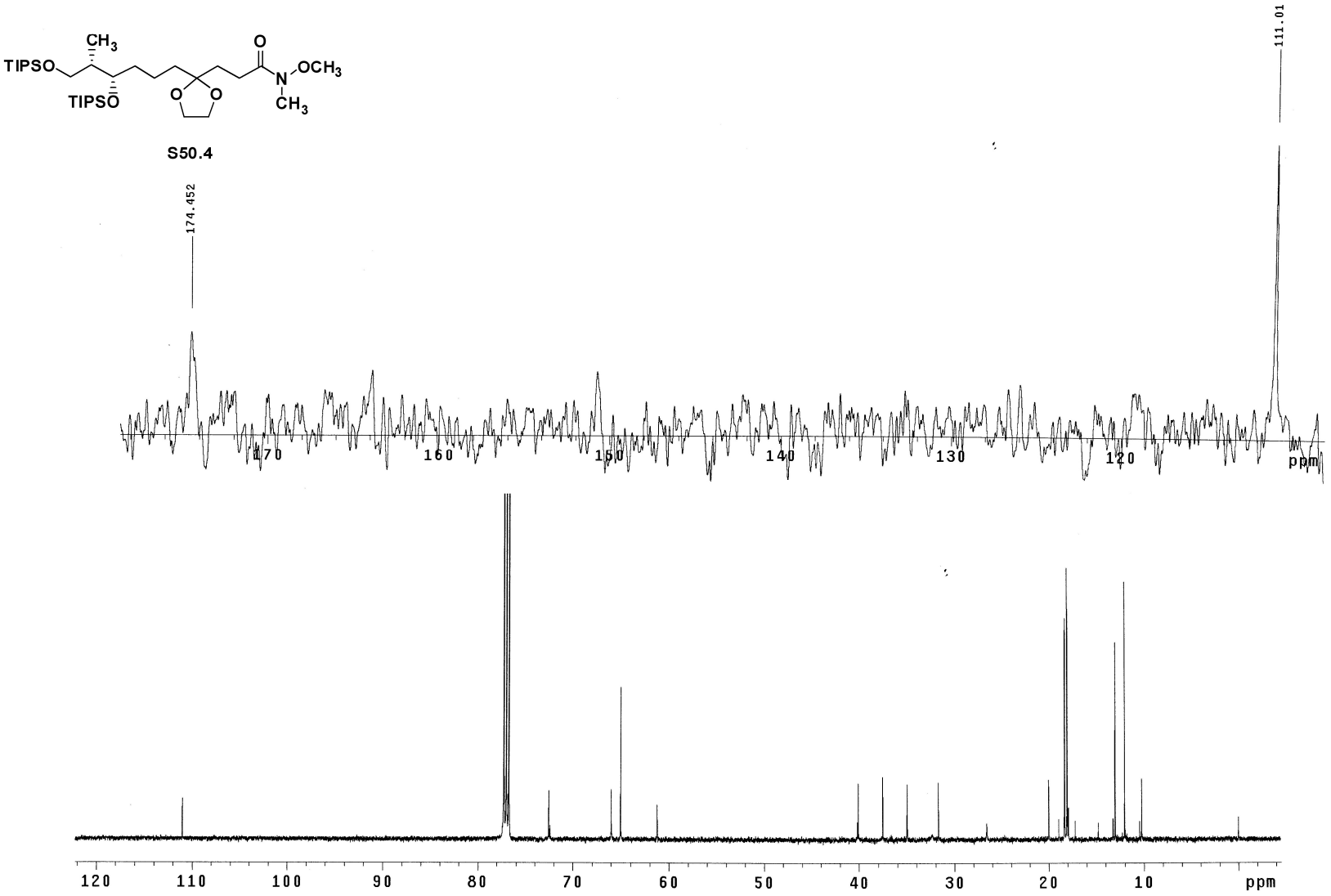

CH3
TIPSO
O
N
OCH3
HO
O
O
CH3

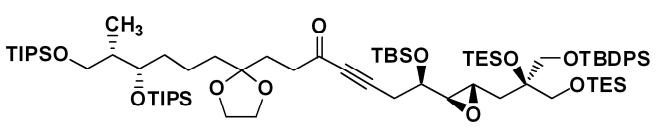
S50.3

134.549
174.551
170
160
150
140
130
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

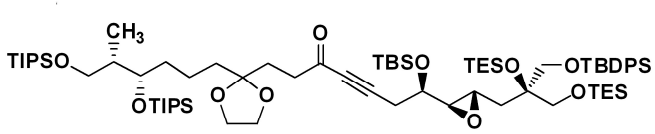


S50.4


TIPSO
CH3
TIPSO
O
N
OCH3
CH3
O
O
S50.4
174.452
111.01
170
160
150
140
130
120
ppm
120
110
100
90
80
70
60
50
40
30
20
10
ppm

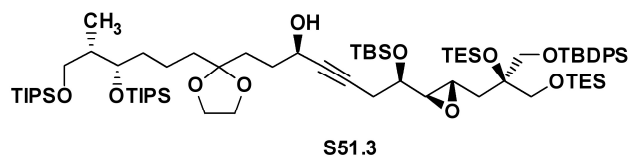


S51.1

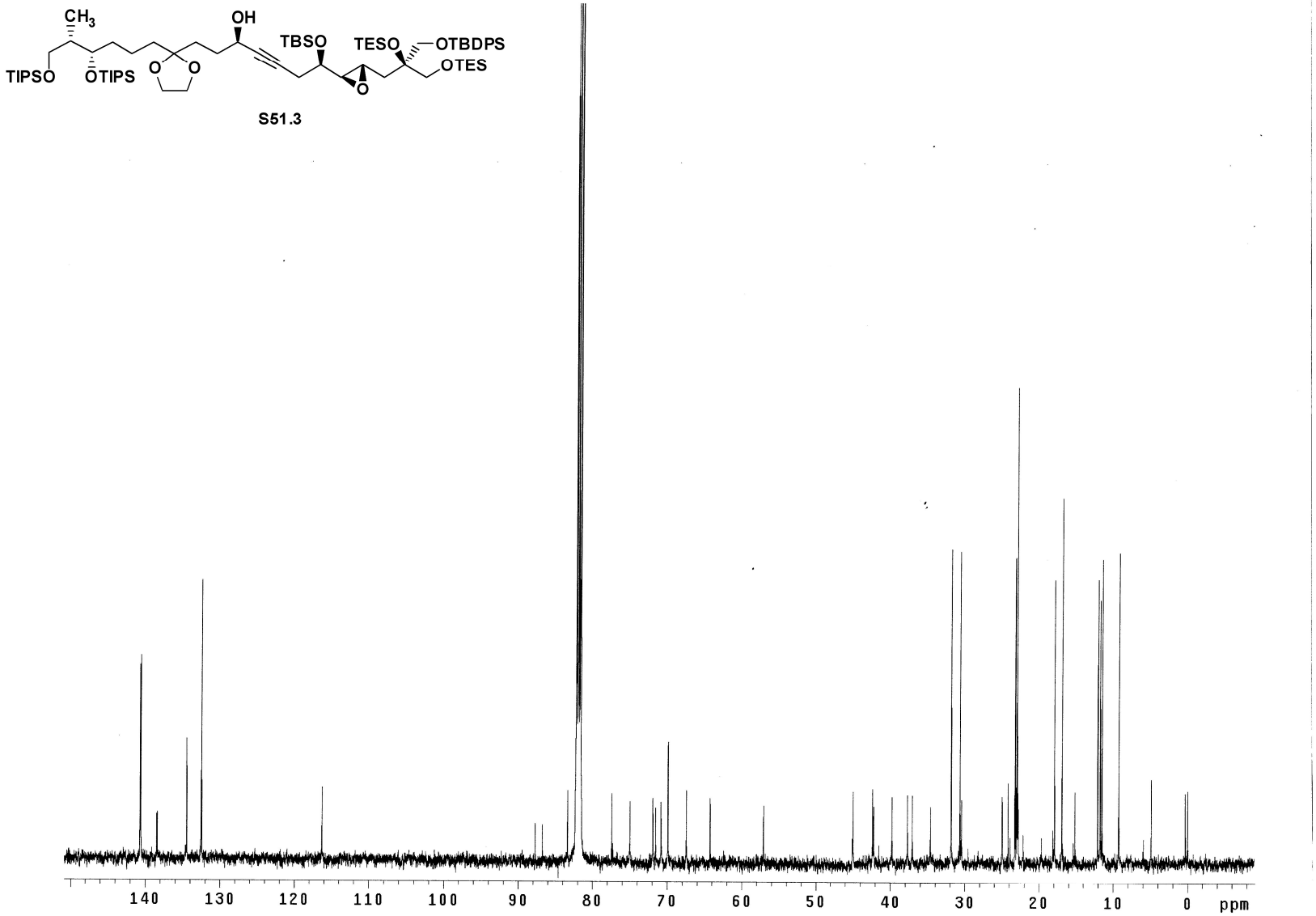

CH3
TIPSO
OTIPS
O
O
O
TBSO
TESO
OTBDPS
OTES
O

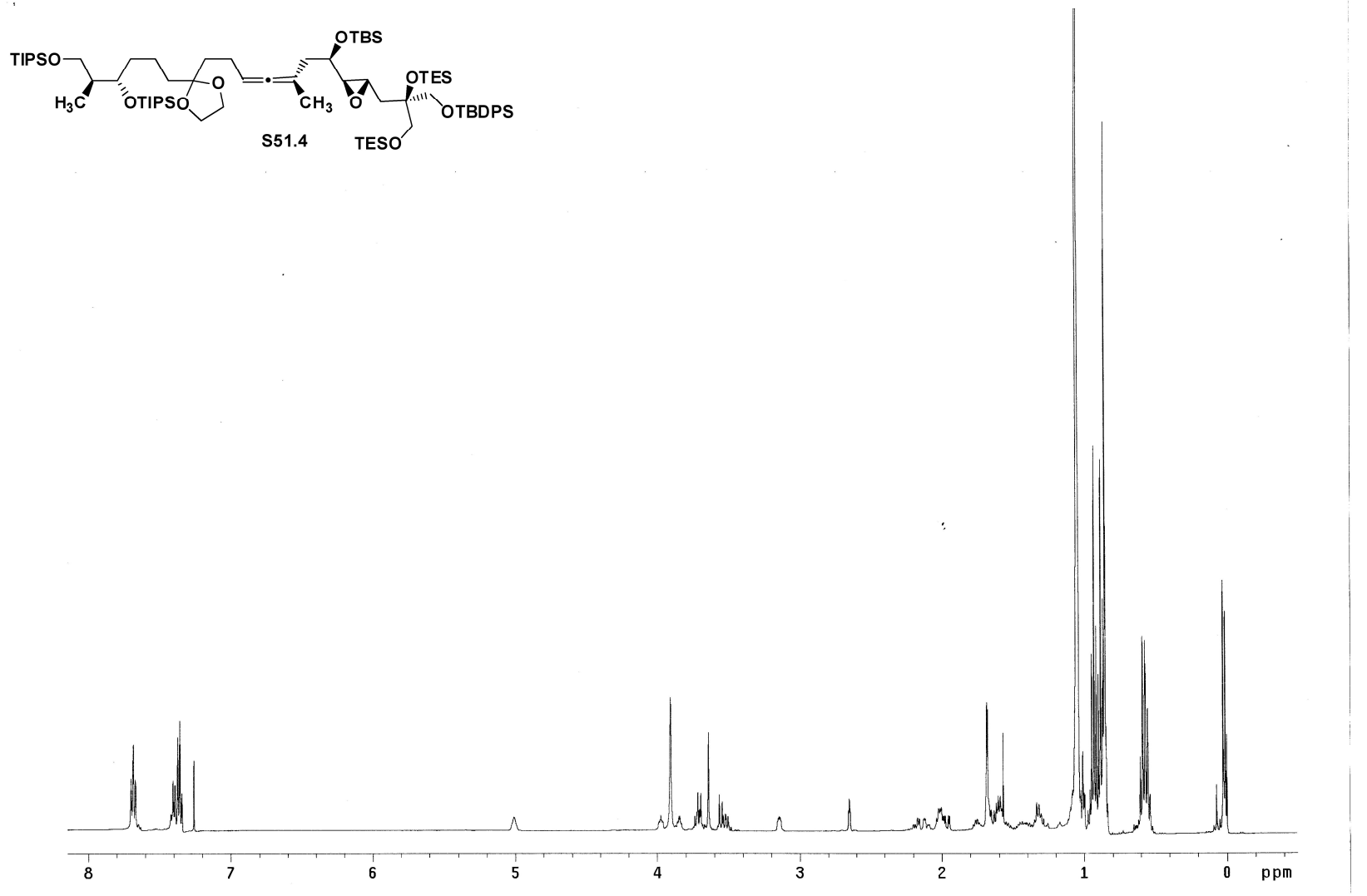
S51.1

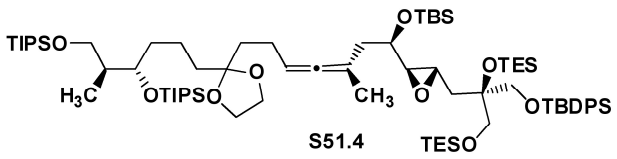
180
160
140
120
100
80
60
40
20
0
ppm



S51.3

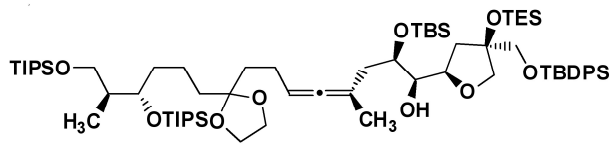

CH3
OH
TBSO
TESO
OTBDPS
OTES
TIPSO
OTIPS
O
O
O
S51.3
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


TIPSO
H3C
OTIPSO
O
CH3
OTBS
O
OTES
OTBDPS
TESO
S51.4
8
7
6
5
4
3
2
1
0
ppm

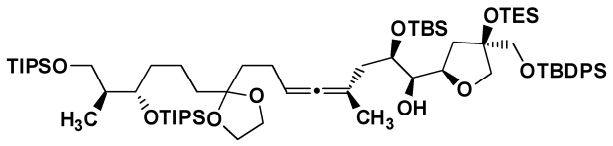

TIPSO
H3C
OTIPSO
O
CH3
OTBS
O
OTES
OTBDPS
TESO

S51.4

200
180
160
140
120
100
80
60
40
20
ppm

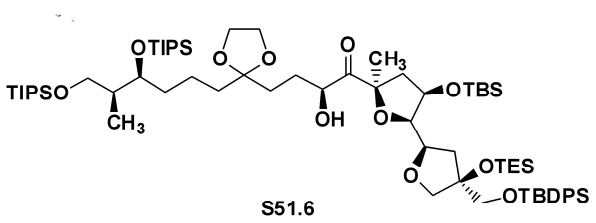


S51.5

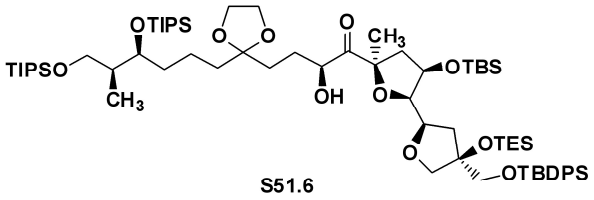

TIPSO
OTBS
OTES
OTBDPS
O
O
OH
H_3C
OTIPSO
CH_3

S51.5

200
180
160
140
120
100
80
60
40
20
ppm



S51.6


OTIPS
TIPSO
CH3
O
O
O
CH3
OTBS
OH
O
O
OTES
OTBDPS

S51.6

220
200
180
160
140
120
100
80
60
40
20
0
ppm

Curriculum Vita

Stephen Dominic Lotesta

September 1997 - May 2002 Fairleigh-Dickinson University, Madison, NJ
Subject: Chemistry
Degree Earned: B.S.

Awards and Honors:

Undergraduate scholarship (September 1997- May 2002)
Honor's List - GPA 3.5+ (1997-2002)
Phi Zeta Kappa Honor Society (1999)
Phi Omega Epsilon Honor Society (2000)
David Hart Award for Achievement in Chemistry (2002)
ACS Polymer Education Division Award for Achievement in Organic Chemistry (2002)

September 2002 – January 2008 Rutgers, The State University of New Jersey
New Brunswick, NJ
Subject: Chemistry
Degree Earned: Ph.D.

Awards and Honors:

GAAN Fellowship (May 2003 - August 2006)
Damle Graduate Fellowship for Excellence in Graduate Research (May 2003-August 2006)
Reid Graduate Award for Outstanding Achievement in Research (September 2006)

Publications:

Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 15. "Spirodiepoxides: Heterocycle Synthesis and Mechanistic Insight."

Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. "Spirodiepoxide Reaction with Cuprates."

Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869. "A Spirodiepoxide-Based Strategy to the A-B Ring System of Pectenotoxin 4."

Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. "Spirodiepoxides in Total Synthesis: Epoxomicin."