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Studies Toward the Total Synthesis of Penostatin F

by

Eric Beaulieu

B.Sc. (Honours), University of Ottawa, 2006

Thesis submitted to the Faculty of Graduate & Postdoctoral Studies
In partial fulfillment of the requirements for the
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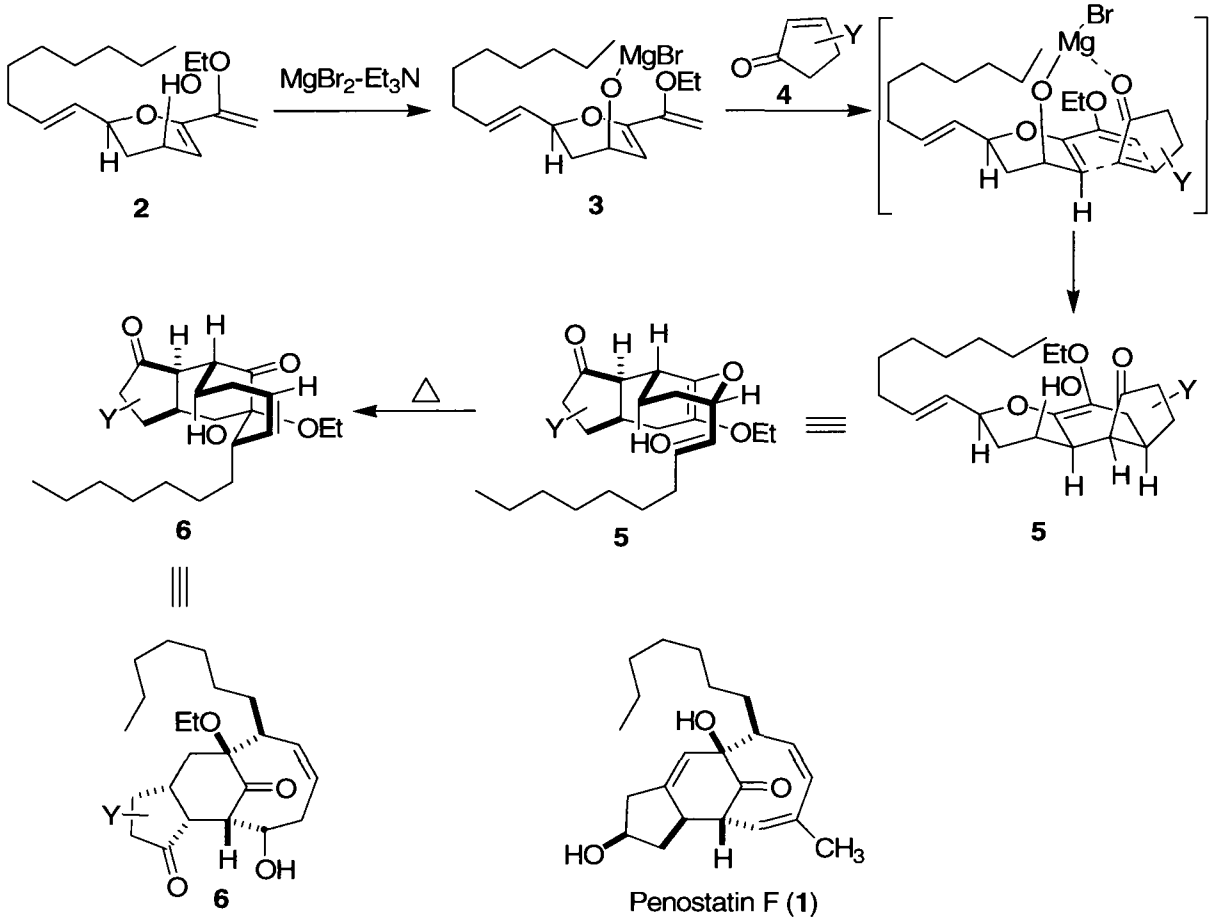
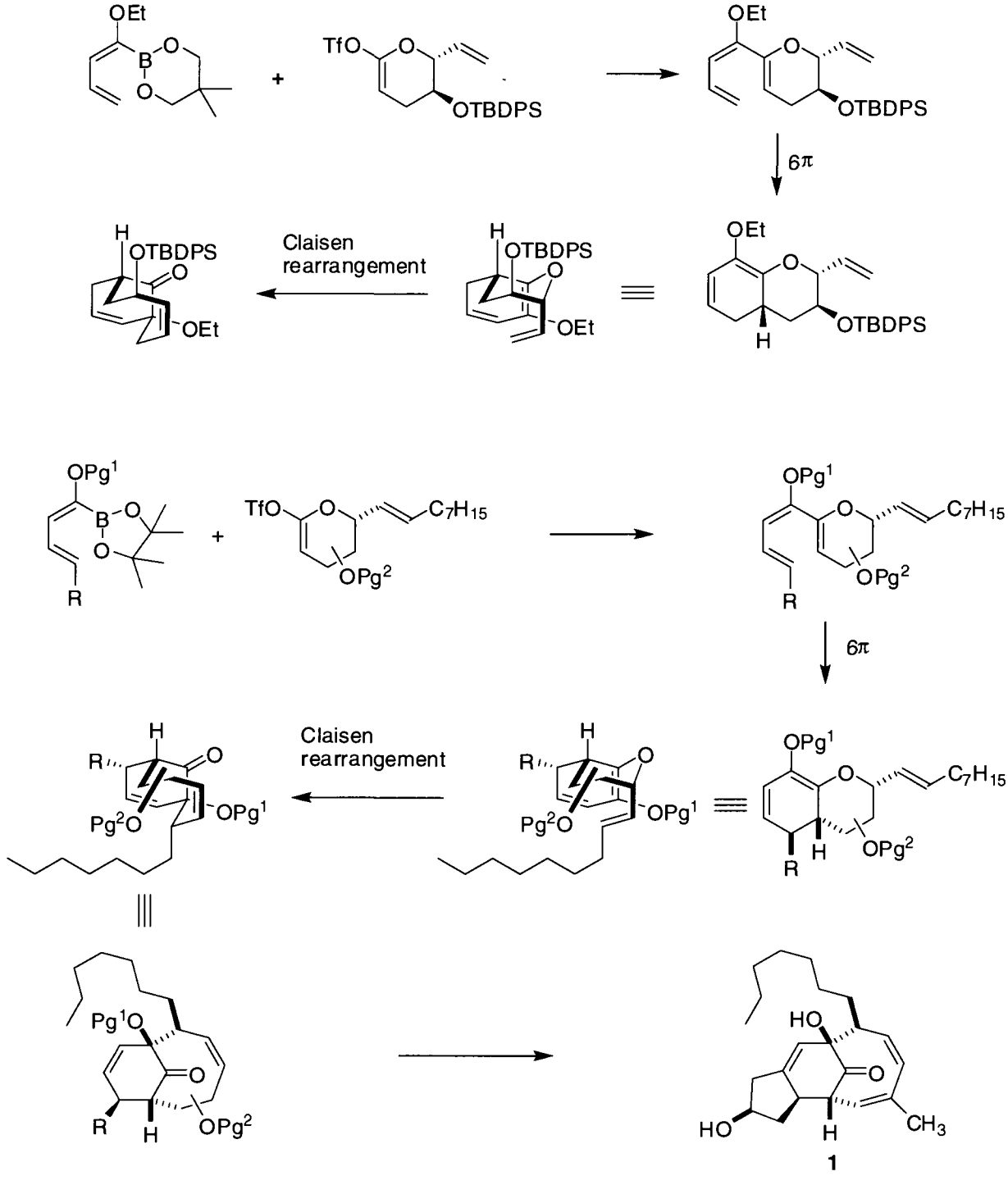
Dédié à Tommy Beaulieu

Abstract

The total synthesis of penostatin F (**1**) has been a goal in our laboratory for the last 6 years. Our first approach developed by Patrick Ang and Roch Lavigne (Scheme 1) involved a hydroxy-directed Diels-Alder (HDDA) reaction between diene **2** and dienophile **4** through the formation of a magnesium alkoxide **3**. The single resulting Diels-Alder adduct **5** is then poised to undergo a Claisen rearrangement upon heating, to rapidly afford the bicyclo[5.3.1]undecenone core of penostatin F. Unfortunately, numerous attempts to employ this strategy to complete the synthesis have failed.



This thesis discusses a new approach towards the total synthesis of penostatin F. The key step involves a 6π electrocyclization of a triene precursor followed by a Claisen rearrangement, as depicted below. Following a successful key step model study, the syntheses of a functionalized alkoxydienyl boronic ester and an enol triflate dihydropyran as coupling partners are described. Issues surrounding the electrocyclization are discussed and possible solutions are presented.



Acknowledgements

First, I would like to thank Professor Louis Barriault for welcoming me in his group and offering me this exciting and challenging project. I appreciate the guidance, the encouragement and ideas he has given me over the last two years. I have gained a great deal of knowledge from our discussions and from group meetings (as well as a few interesting stories during group activities).

I would also like to thank my parents and grandparents who were always there to support me in every way and to remind me to take a break once in a while. On that note, I wish to thank my close friends and Priscille for being available whenever some distracting was of the essence.

I would like to take this occasion to thank Professor André Beauchemin for allowing me to use his photochemistry equipment, for the discussions we have had concerning this project, for giving me the opportunity to work in his laboratory as an undergrad student and for writing reference letters for scholarships and job applications. Similarly, I wish to thank Professor William Ogilvie for his reference letter and for answering my NMR related questions. I would also like to express my gratitude to all of the professors who have given the graduate courses I have taken during my master's degree.

Finally, I would like to acknowledge my lab mates for making this learning experience so enjoyable. I am especially grateful to Christiane, Steve, Max, and Rachel who I knew I could always turn to when I had questions, particularly when I was starting. Thanks to Jason, Marie, Dan, Genevieve and Anne-Catherine with who I loved to share a laugh. I want to thank Minaruzzaman and wish him the best of luck with the continuation of this project. Thanks to all the other students who have been in our group or in other groups, who have made these years go by so fast!

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Introduction

General Information on the Penostatin Family

In an effort to discover new antitumor metabolites, Numata and co-workers have isolated many new compounds from microorganisms found in the marine environment, and have elucidated their structure. Among them, they have discovered the penostatin class, which they have extracted from *Penicillium* sp. OUPS-79. This fungal strain was separated from the marine alga *Enteromorpha intestinalis*.[1] The penostatin class is composed of nine members (A to I) (Figure 1.1) These have been screened in a cell culture assay to determine their respective cytotoxic activity against the P388 lymphocytic leukemia cell line, according to a procedure developed by the same researchers.[2] All of the penostatins show cytotoxicity (ED_{50} ~ 1 μg/ml) except penostatin D (**1.4**).

It is interesting to note that the absolute stereochemistry at C5 is always the same (*R*), even between pairs of stereo-isomers (i.e.: between **1.1** and **1.2**, **1.6** and **1.9**) whereas the stereochemistry of the other asymmetric centres vary depending on the compound. Penostatin E does not possess the pyran ring found in penostatins A – E, instead, it seems to have been opened through the incorporation of a molecule of water. Penostatins F – I have different ring systems such as the bicyclo[5.3.1]undecenone found in **1.6** and **1.9** or the lactone ring found in **1.7** and **1.8**. Uniting characteristics found in all of the members are a *n*-heptyl chain and a six-membered ring fused to a five-membered ring.

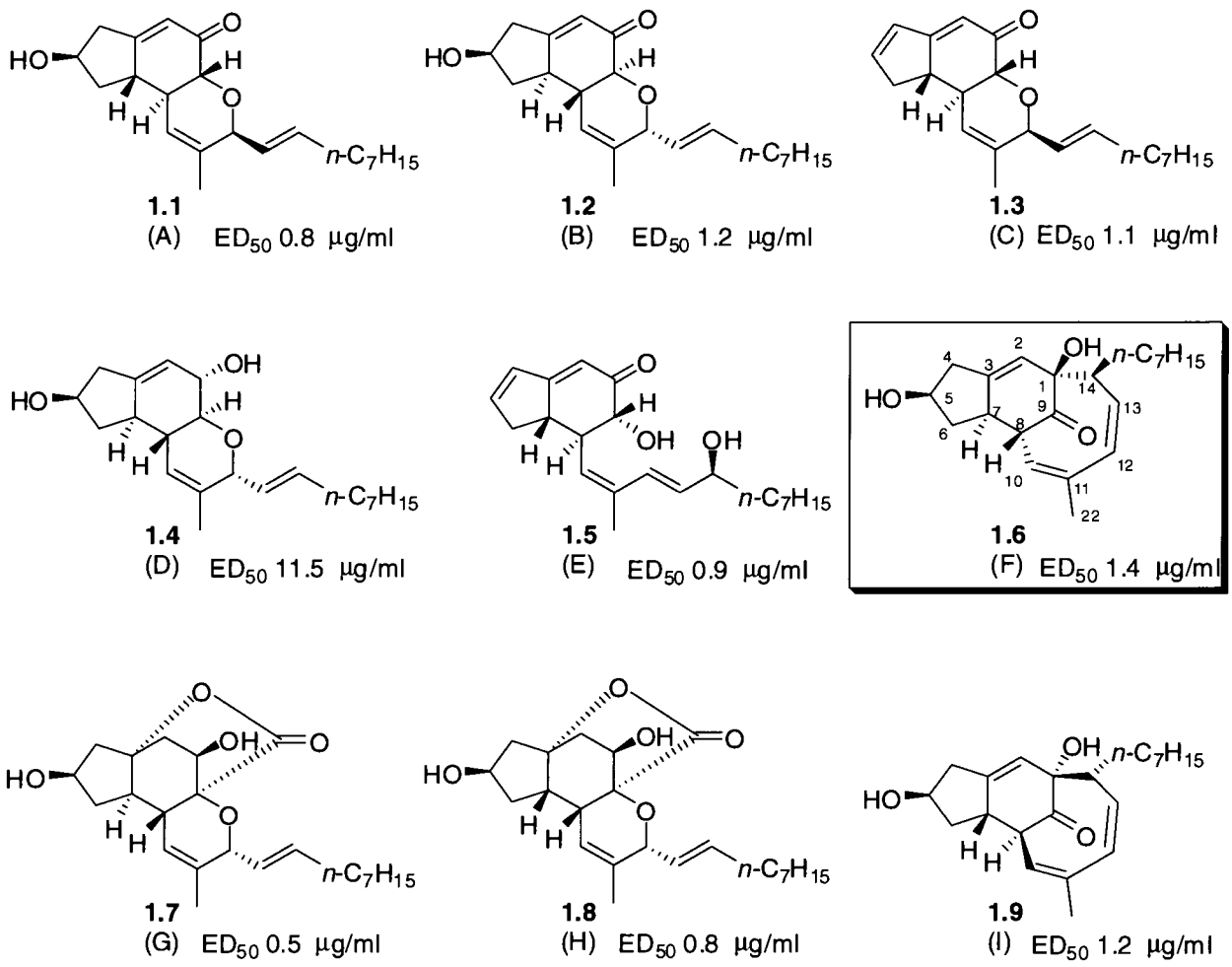
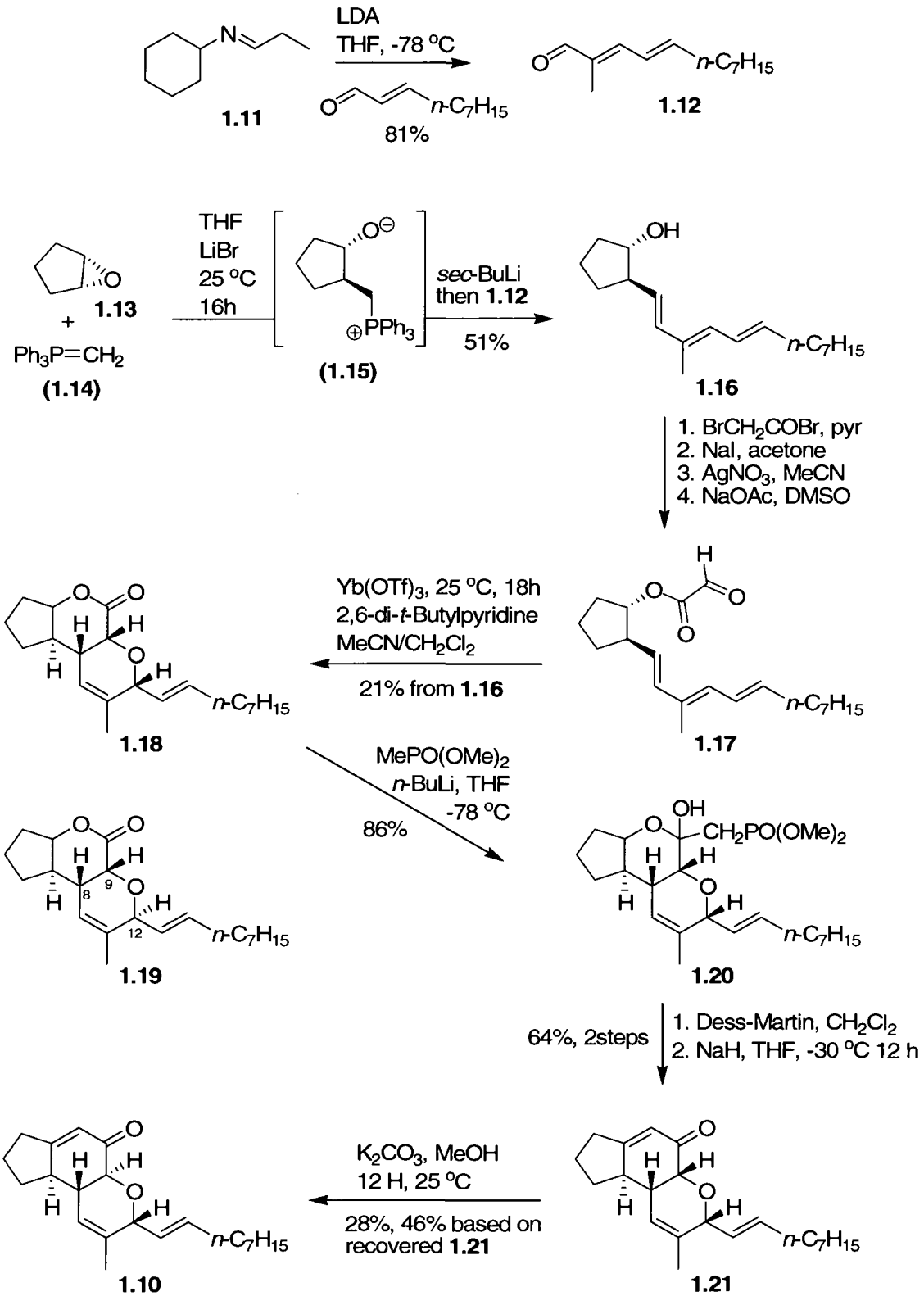


Figure 1.1 The Nine Members of the Penostatin Family (A to I)[1]

Previous Synthetic Efforts Towards Members of the Penostatin Family

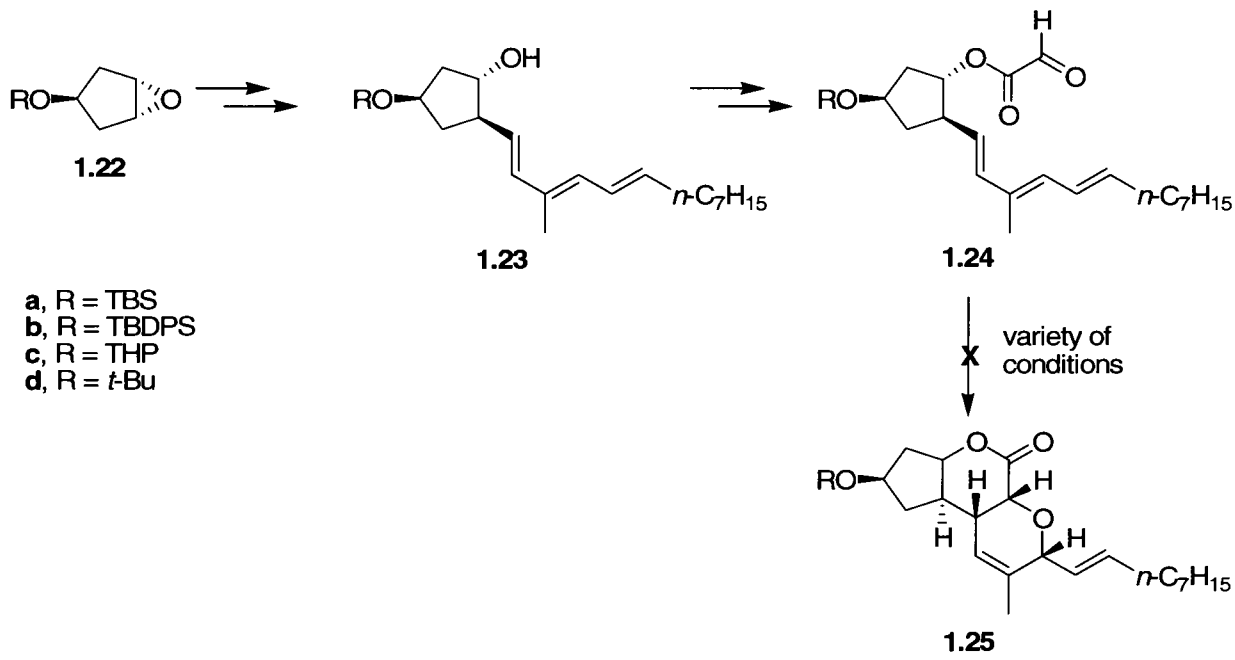
Only two groups have reported an attempt to tackle a member of the penostatin family as a synthetic target, including our own. The first report of such an effort was in 2000 by Snider and Liu.[3] They described their rapid construction of (±)-deoxypenostatin A (**1.10**) and discuss their unfruitful approaches to penostatins A and B (**1.1** and **1.2**). Their synthesis of (±)-deoxypenostatin A (**1.10**) started with the treatment of bromomethyltriphenylphosphonium bromide with 1 equivalent of *sec*-BuLi to generate ylid **1.14** and LiBr (Scheme 1.1). Addition of epoxide **1.13** gave betain **1.15**[4] which was treated with a second equivalent of *sec*-BuLi followed by aldehyde **1.12**, to give **1.16** in 51% yield.[5,6]



*Scheme 1.1 Snider's Synthesis of (±)-deoxypenostatin A (**1.10**)*[3]

The Kornblum procedure[7] was necessary to generate the glyoxylate ester **1.17** in its partially hydrated form, as other methods were not tolerated. Treatment of this aldehyde with 0.2 equivalents of ytterbium triflate in the presence of 0.15 equivalents of 2,6-di-*tert*-butylpyridine afforded the intramolecular Diels-Alder (IMDA) product **1.18** in 21% yield from **1.16**. Interestingly, if no base was added, the major product of the reaction was **1.19**. This product can only arise from epimerization at C12 due to acid catalyzed opening of the pyran ring, forming a doubly allylic carbocation. **1.19** could not arise simply from the Diels-Alder reaction since hydrogens at C8 and C12 would have to be *cis*. This acid catalyzed pyran ring opening could explain the formation of penostatin E (**1.5**) by the incorporation of water at the distal carbon of such a pentadienyl cation from penostatin C (**1.3**).

The synthesis of (±)-deoxypenostatin A (**1.10**) was completed by the addition of the anion of dimethyl methylphosphonate to lactone **1.18** then subsequent oxidation to a di-ketone intermediate which undergwent an intramolecular Horner-Emmons Wittig olefination, affording enone **1.21** in 55% yield over 3 steps. Base induced epimerization at C9 of this unstable enone gave (±)-deoxypenostatin A in modest yield.

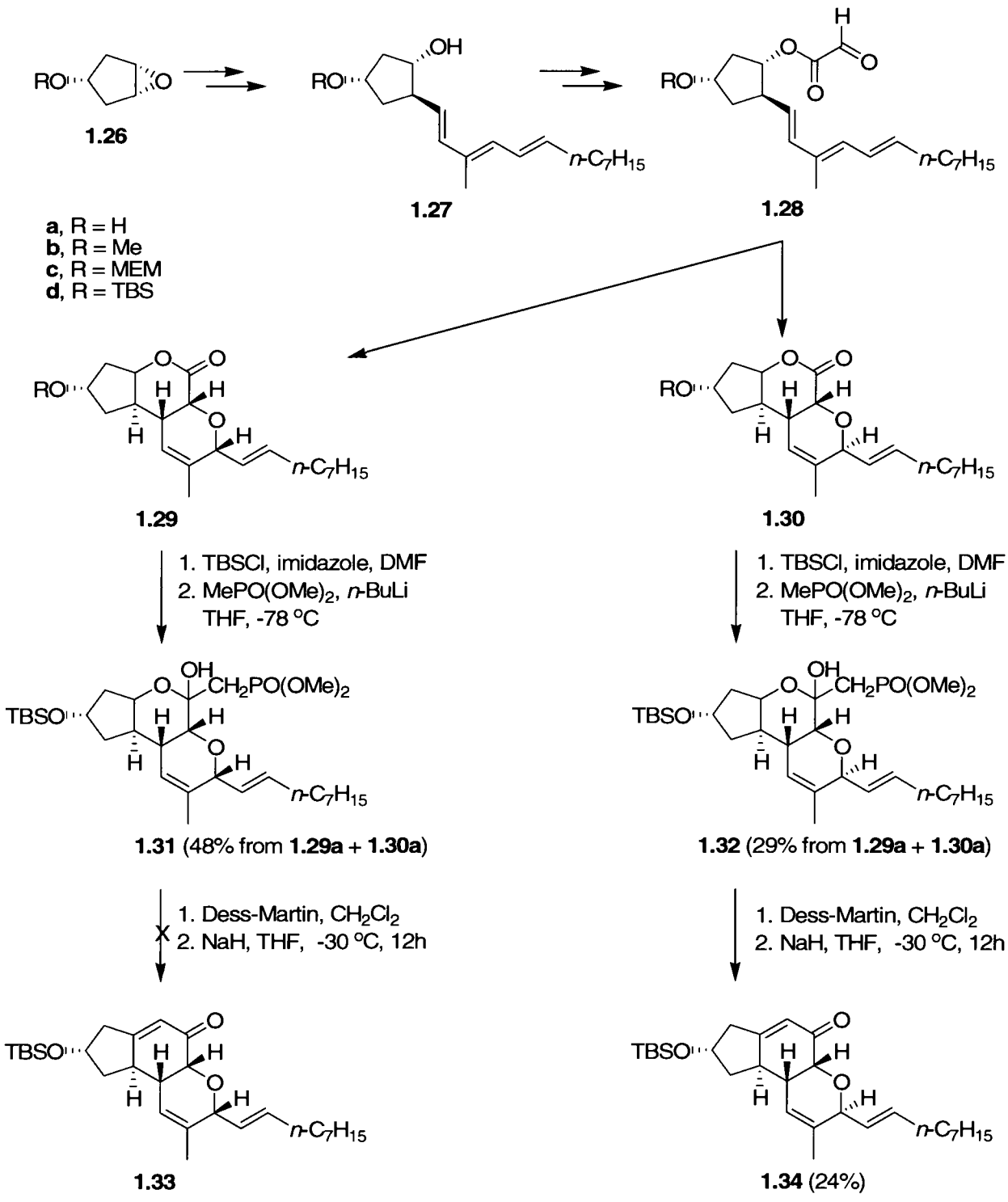


Scheme 1.2 IMDA Attempts at Synthesizing Penostatin B (1.2)[3]

Having demonstrated that the intramolecular Diels-Alder reaction strategy is a viable approach and, out of two possible *endo* products, it leads only to the one having all of the same relative stereochemistry as the penostatins except at C9, the authors turned their attention to the synthesis of penostatins A and B. In the case of penostatin B (**1.2**), a trans-epoxide such as **1.22** (Scheme 1.2) was necessary to initiate the synthesis. It was elaborated to glyoxylate **1.24** the same way as **1.17**. However, after many attempts, the Diels-Alder reaction failed to produce any of the desired cycloadduct. Even after trying various conditions and different hydroxyl protecting groups, only decomposition or polymerization was observed.

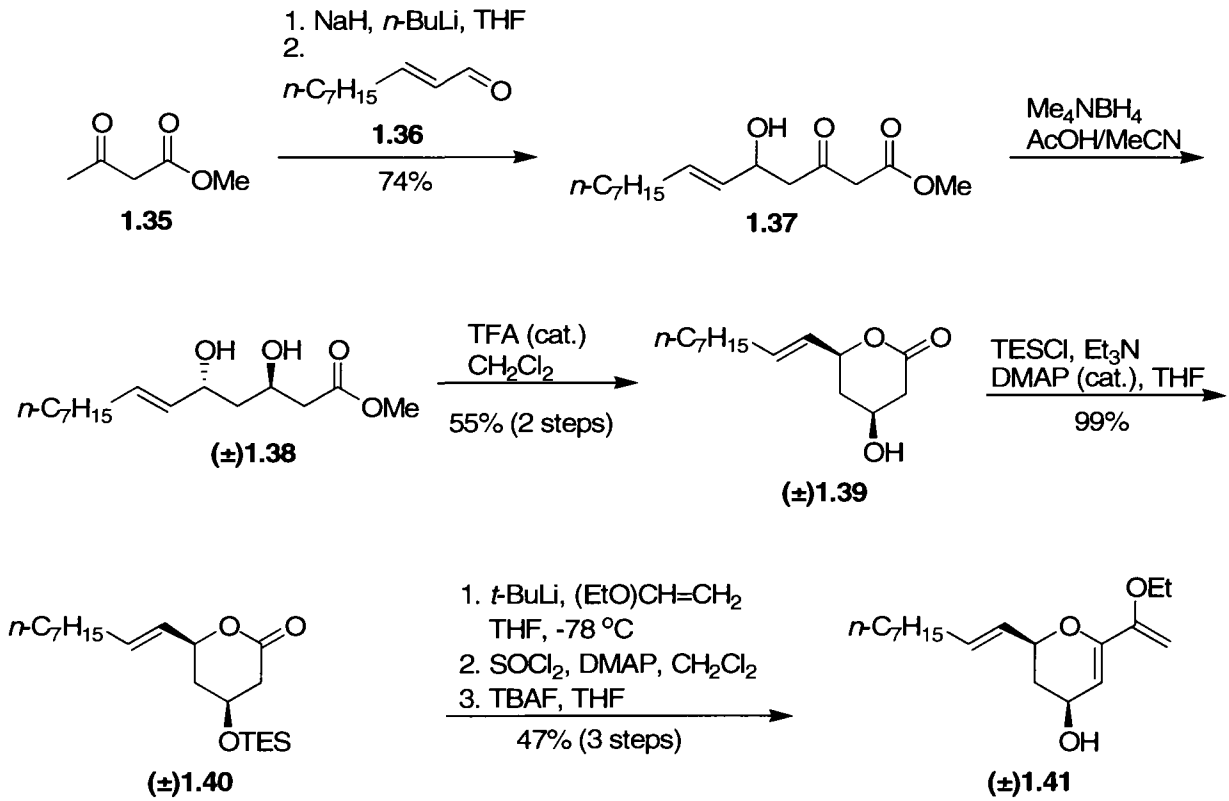
This unfortunate result did not discourage Snider from trying his methodology on the construction of penostatin A (**1.1**). For this, a cis-epoxide (**1.26a**, Scheme 1.3) was produced from the oxidation of 3-cyclopentenol with *tert*-butyl hydroperoxide and a catalytic amount of $VO(acac)_2$. It was first protected with a methyl group (**1.26b**) then converted to the crude glyoxylate **1.28b** in the usual fashion. Treatment with 0.6 equivalents of ytterbium triflate and 0.7 equivalents of 2,6-di-*tert*-butylpyridine led to the formation of an inseparable 1:1 mixture of cycloadducts **1.29b** and **1.30b** in 10% yield from **1.27**. Even with the use of more than one equivalent of base relative to the catalyst, epimerization at C12 could not be avoided. Encouraged by this result but worried that the conditions necessary to remove the methyl protecting group might be too harsh, Snider and Liu opted to introduce a more labile protecting group on the epoxide, such as a MEM ether (**1.26c**). From crude glyoxylate **1.28c**, still, an inseparable 3:2 mixture of cycloadducts **1.29a** and **1.30a** were obtained in 16% yield from **1.27c**. The MEM protecting group was hydrolysed under the IMDA reaction conditions and was therefore replaced by a TBS ether. Attack of the corresponding lactones by $LiCH_2PO(OMe)_2$ afforded the separable hydroxy keto phosphonate hemiacetals **1.31** and **1.32**. **1.31** would lead to (±) penostatin A after Dess-Martin oxidation, intramolecular olefination, epimerization at C12 and deprotection of the TBS ether. Unfortunately, enone **1.33** remained elusive as the diketone intermediate decomposed under the olefination conditions. Strangely, the diketone intermediate produced from **1.32** was sturdy enough to generate **1.34** in 24% yield after 2 steps, as the TBS protected bis-epi-penostatin A.

A major drawback of this approach is the instability of many of the intermediates and low yields for numerous steps. This strategy however demonstrates the power of the Diels-Alder reaction to quickly generate key carbon-carbon or carbon-oxygen bonds stereoselectively.



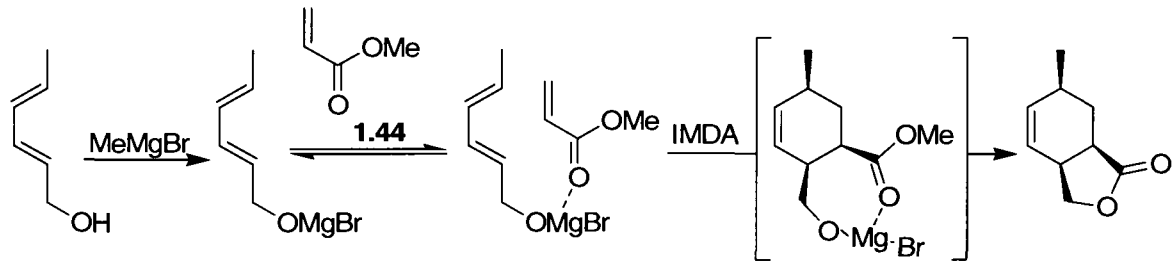
Scheme 1.3 IMDA Attempts at Synthesizing Penostatin A (1.2)[3]

In 2004, Barriault and coworkers have reported an efficient and stereoselective approach for the construction of the bicyclo[5.3.1]undecenone core of penostatin F (**1.6**).[8] As of yet, there are still no reported total syntheses of this natural product. The key feature of their strategy involved a hydroxy-directed Diels-Alder (HDDA) reaction followed by a Claisen rearrangement. They began their synthesis of the core by the 1,2-addition of the Weiler dianion[9] of methylacetoacetate (**1.35**) to (*E*)-2-decenal, which yielded racemic alcohol **1.37** (Scheme 1.4). This was followed by a diastereoselective reduction of the β-hydroxy ketone to the 1,3-*anti* diol[10] **1.38**. The 1,3-*anti* relationship of the diol allowed the formation of lactone **1.39** upon treatment with a catalytic amount of TFA, where the alkyl chain and the hydroxyl are *syn*. This is essential for the proper relative stereochemistry in the ensuing steps. The hydroxyl group was then protected as a triethylsilyl ether. Addition of lithiated ethyl vinyl ether to lactone **1.40** followed by a treatment with thionyl chloride and deprotection of the hydroxyl gave the necessary diene **1.41**, in 47% over 3 steps, with a free hydroxyl to direct the Diels-Alder reaction.



*Scheme 1.4 Synthesis of Diene **1.41***[8]

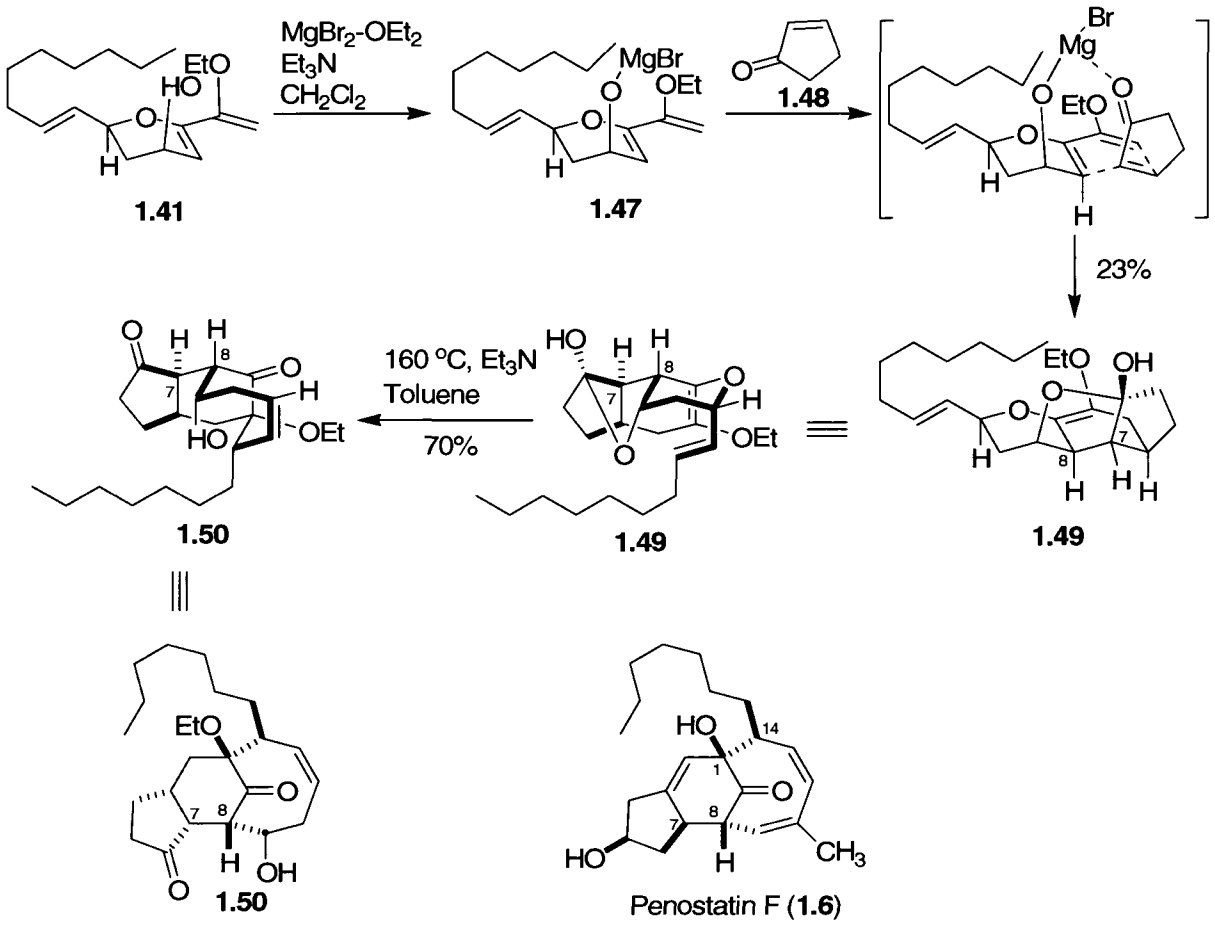
The use of tethers and temporary (or disposable) metal tethers to direct the facial and/or regio-selectivity of cycloaddition reactions is well documented.[11,12] As an illustrative example, Ward and Abaee[13] have demonstrated that dienes having a free allylic alcohol (**1.42**), placed in the presence of methylmagnesium bromide generated a magnesium alkoxide (**1.43**) which when treated with a dienophile conjugated to a carbonyl, such as methyl acrylate (**1.44**), resulted in the exclusive formation of the *endo* product where the hydroxyl and carbonyl are regioselectively both on the same portion of the cyclohexene ring (**1.45**, Scheme 1.5). This demonstrates that the magnesium atom of the alkoxide coordinates to the carbonyl of the dienophile to activate and direct it in an intramolecular fashion.



Scheme 1.5 Selectivity in the Diels-Alder Reaction using a Magnesium Alkoxide Tether[13]

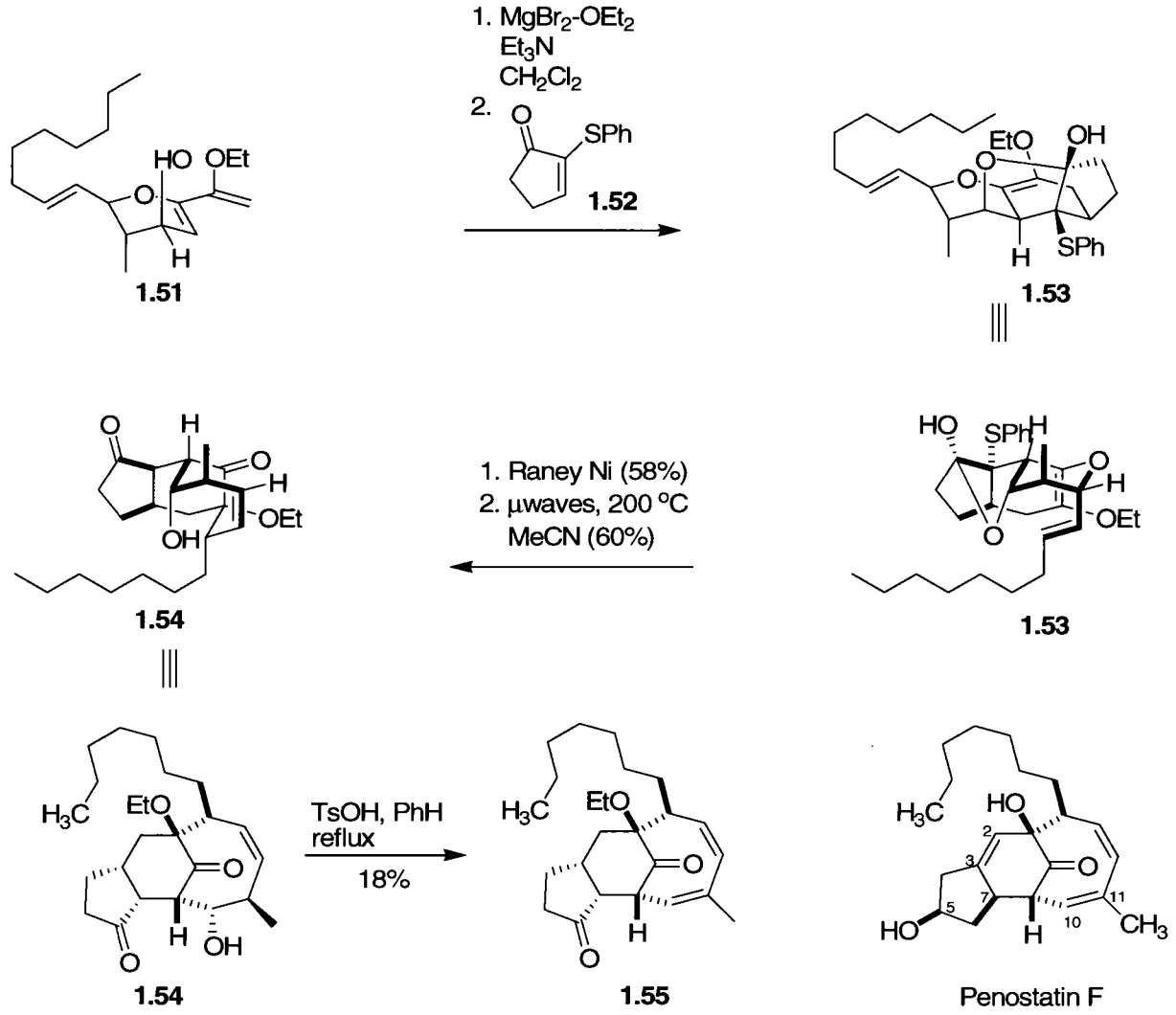
With this precedent in mind, Barriault and coworkers[8] subjected diene **1.41** to $MgBr_2$-OEt_2[14] in the presence of triethylamine in dichloromethane which generated the corresponding alkoxide **1.47** (Scheme 1.6). Upon treatment with 2-cyclopentene-1-one (**1.48**), the Diels-Alder product **1.49** was obtained in albeit 23% yield as the only diastereomer, with the dienophile portion attached on the same side of the ring as the hydroxyl group, in an *endo* fashion. The selectivity of the Diels-Alder reaction is crucial to obtain the proper stereochemistry at C8, which would otherwise be difficult to adjust.

As we can see, **1.49** can adopt a chair conformation where the olefinic side chains are oriented in such a fashion that a Claisen rearrangement can take place upon heating, with a chairlike transition state (Scheme 1.6). When **1.49** was heated at 160 °C in toluene in the presence of a trace of triethylamine, the desired rearranged product **1.50** was obtained in 70% yield. **1.50** possesses the tricyclic ring system found in penostatin F with the proper stereochemistry at C1, C8 and C14.



Scheme 1.6 Hydroxy-Directed Diels Alder (HDDA) /Claisen Rearrangement Sequence to the Bicyclo[5.3.1]undecenone Core of Penostatin F[8]

Having demonstrated the efficiency with which the HDDA / Claisen rearrangement sequence strategy can afford the tricyclic core of penostatin F, efforts were then turned at solving the remaining issues of this strategy to complete the synthesis.[15] The first of which being the installation of the methyl group at C11. It was thought that installation of this methyl group at the very beginning of the synthesis would most likely be preferable and could help in the elimination of the hydroxyl group at C10 to install the double bond at the desired position. For these reasons, lactone **1.51** (Scheme 1.7) with the desired methyl group was constructed. Due to low yields of the hydroxy-directed Diels-Alder reaction between **1.51** and 2-cyclopentene-1-one (**1.48**), a more reactive dienophile was sought after. It was found that 1-phenylthio-2-cyclopenten-1-one (**1.52**) could be used with satisfactory yields, to generate cycloadduct **1.53**.

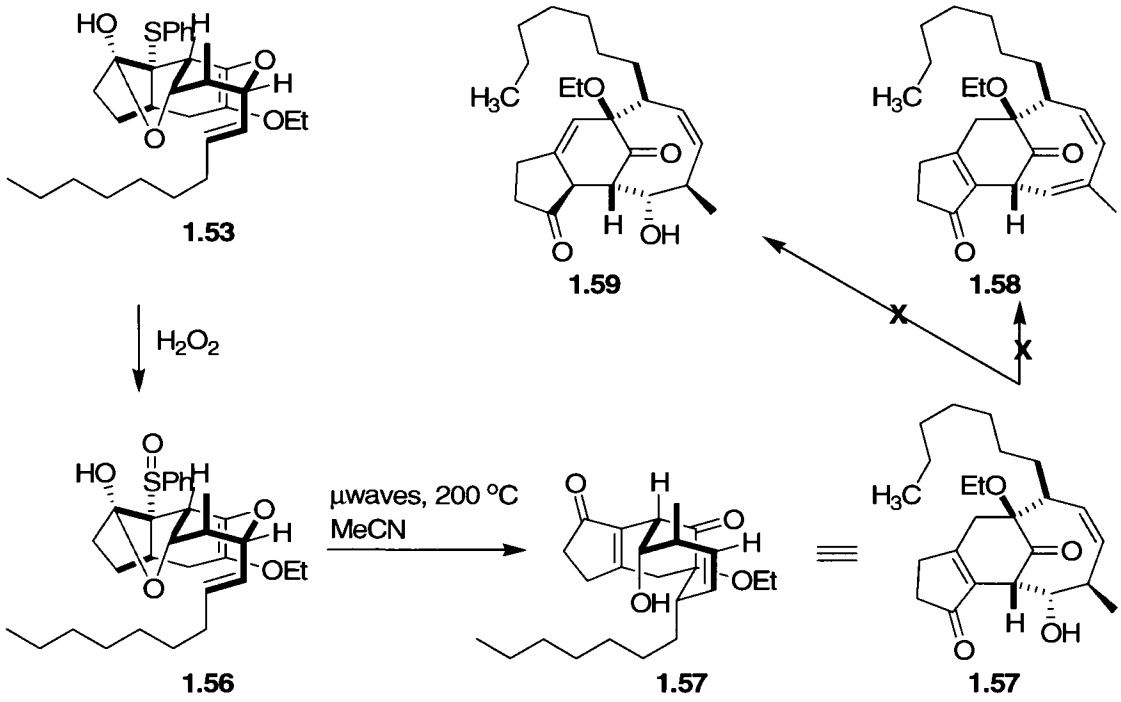


Scheme 1.7 Installation of the Methyl group at C11 and the Insaturation Between C10 and C11[15]

Desulfurization with Raney nickel followed by the microwave assisted Claisen rearrangement proceeded smoothly and gave the tricyclic core **1.54**. After many attempts, the desired dehydrated product **1.55** could only be obtained in 18% yield, it however seemed to be a significant step towards the completion of the natural product.

With the carbonyl moiety at C6 in **1.55**, it was hoped that epimerization at C7 could take place, giving the proper stereochemistry at that center relative to penostatin F. It was expected that this epimerization would be favored, bringing the substituents on C7 and C8 of the cyclohexanone ring in a *trans* relationship. Unfortunately, attempts to accomplish this transformation in either acidic or basic conditions were unsuccessful. Similarly, attempts to

transpose the oxygen on C6 to C5 met with failure. Finally, given the fact that no appropriate handles were present on **1.55** to install the double bond between C2 and C3, it was determined that this molecule could not be used as a precursor to complete the synthesis. On a similar note, it was found that sulfoxide **1.56** obtained from the treatment of **1.53** with hydrogen peroxide, affords enone **1.57** when submitted to the Claisen rearrangement conditions (Scheme 1.8). The change in conformation induced by the extra insaturation now completely prevented the elimination of the hydroxyl at C10 from taking place. Also, unsurprisingly, efforts to deconjugate the double bond in the 5-membered ring to have it migrate in the cyclohexyl ring were not fruitful. Due to these seemingly insurmountable hurdles, a different strategy was necessary to complete the synthesis of this natural product.



*Scheme 1.8 Final Attempts with Precursor **1.53***

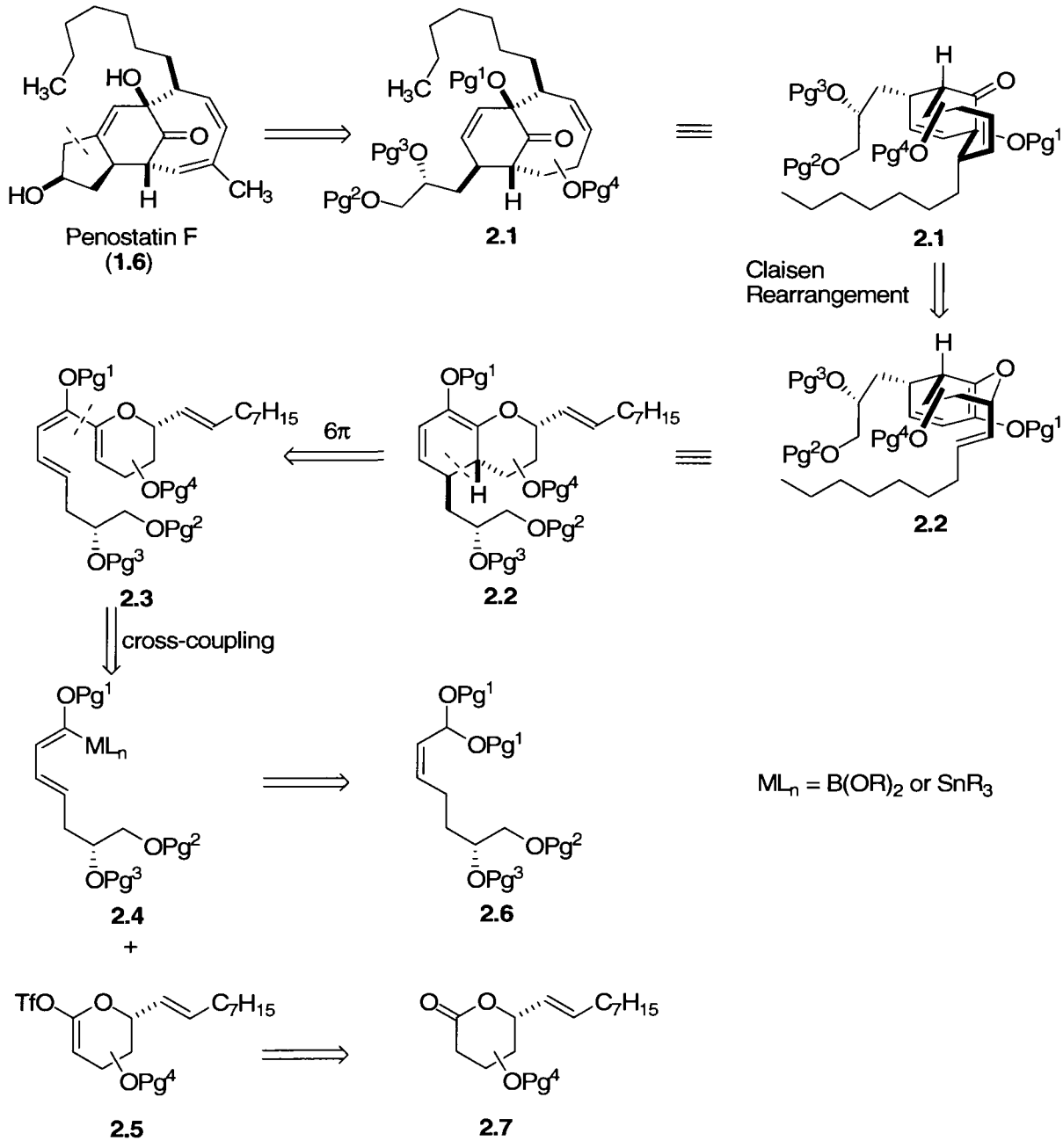
2

First Attempt at Generating a Model Triene for a 6π Electrocyclization / Claisen Rearrangement

General approach

Given the efficiency with which the Claisen rearrangement can generate the desired bicyclo[5.3.1]undecenone core,[8] which constitutes the major part of the structural complexity of penostatin F, we believed that this step should not be discarded yet. Our focus was then to work out some of the previous problems around this key step. By looking at the general retrosynthetic analysis depicted in Scheme 2.1, one can see that the five-membered ring could be opened at the C3-C4 junction. With the appropriate functional groups present, this bond could be formed using Fu's modified Heck reaction.[16,17] Intermediate **2.1** could arise from the Claisen rearrangement of **2.2**. Diene **2.2** could come from a 6π electrocyclization of intermediate triene **2.3** which in turn could be obtained through a metal catalyzed cross-coupling reaction between enol triflate **2.5** and an appropriate alkoxydienyl-metal coupling partner such as **2.4**. Alkoxydienylstannanes and alkoxydienylboronates can be derived from α,β-unsaturated acetals such as **2.6**.[18a,b,d-f] The enol triflate should be easily obtained from the corresponding lactone **2.7** where the oxygen substituent would eventually serve as a handle to install the double bond between C10 and C11 and the methyl group on C11. This new plan addresses the issue of inserting the double bond

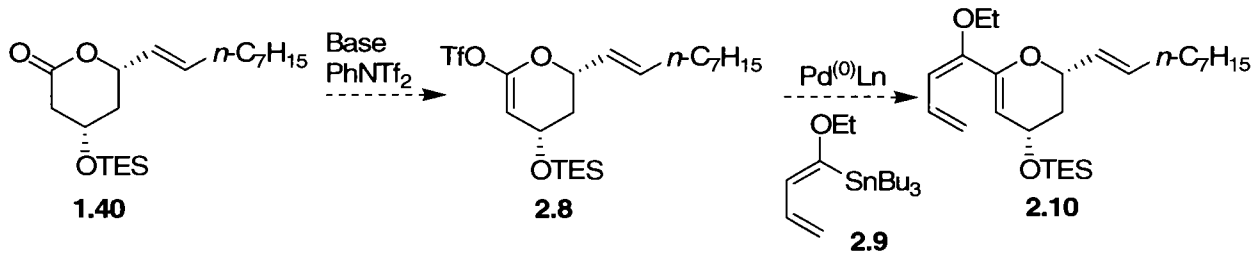
between C2 and C3 which proved to be a major drawback of the previous HDDA / Claisen rearrangement strategy.[15]



Scheme 2.1 General Retrosynthetic Analysis for the Proposed Approach

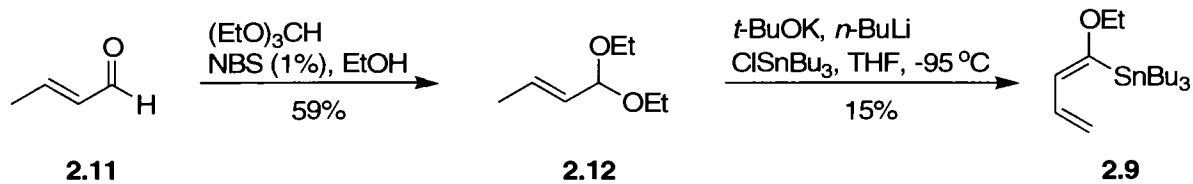
Attempts Towads a First Model Study Key Step Precursor

To launch this project, it was thought that it might be preferable to attempt the key step (the 6π electrocyclization / Claisen rearrangement) on a more easily accessible and simpler model. Previous research in our laboratory has enabled the rapid construction of lactone **1.40** in 4 steps[8] which does not possess the methyl group corresponding to the one found at C11 on penostatin F. This lactone could serve to form an enol triflate such as **2.8** (Scheme 2.2) which could then be coupled to alkoxydienylstannane **2.9** to produce triene **2.10**. This triene could then serve as a model precursor for the key step.



Scheme 2.2 First Approach to a Model Key Step Precursor

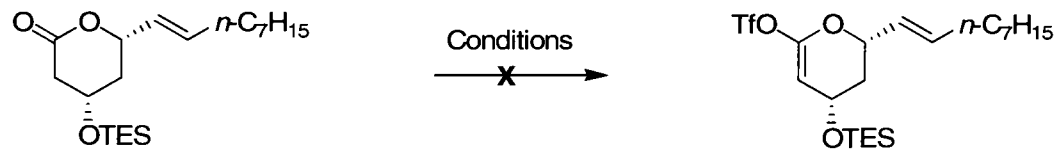
Believing that the construction of the alkoxydienylstannane such as **2.9** might be more difficult than deriving an enol triflate from lactone **1.40**, we started by the former. Following literature precedent[19] crotonaldehyde was converted to its diethylacetal **2.12**. Treatment of **2.12** with 2 equivalents of Schlosser's base[20] and subsequent trapping with chlorotributyltin afforded the desired stannane **2.9**[18a,b,d-f] which proved to be unstable on silica gel, even if triethylamine is present. Since only two steps are necessary, the scale of the reaction could be adjusted to obtain sufficient amounts of this product.



*Scheme 2.3 Synthesis of Alkoxydienylstannane **2.9***

With the desired alkoxydienylstannane in hand, all that was needed for the projected Stille[21] cross-coupling reaction leading to the key step precursor was the enol triflate arising from lactone **1.40**. General procedures[18c, 22] to generate this type of species were tried and mostly starting lactone was recovered, with no trace of the desired enol triflate (Table 2.1). In order to determine if deprotonation and formation of an enolate was occurring, we treated the lactone with base and quenched the reaction mixture with deuterium oxide to evaluate whether or not incorporation of deuterium such as in **1.40***, was observed (Table 2.2). When treated with KHMDS in the presence of HMPA, only starting lactone was recovered with some decomposition observed. No incorporation of deuterium could be noticed in the proton NMR of the recovered starting material. This indicated that no enolate formation took place. When lactone **1.40** was treated with the stronger and less sterically hindered base LDA at various temperatures, some starting material was recovered with no signs of incorporation of deuterium, and also product **2.13**. These results indicate that as soon as deprotonation takes place, an E1cb type of elimination ensues, ejecting the OTES group. To validate this, the lactone was treated with LDA in the presence of phenyltriflimide in the hopes of trapping the enolate before the elimination takes place, however, the same mixture of starting material and **2.13** was obtained.

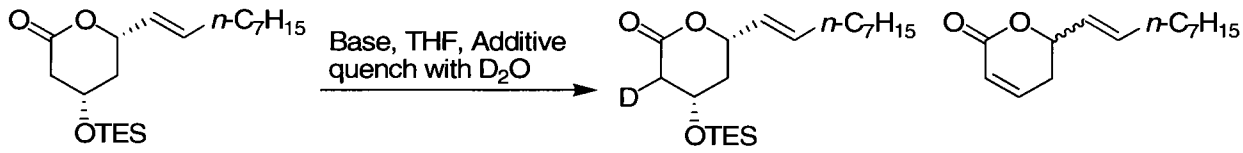
*Table 2.1 Attempts at Generating an Enol Triflate from Lactone **1.40***



1.40 **2.8**

Entry	Solvent	Base	Additive	Temperature (°C)	Triflating reagent	Result
1	THF	LiHMDS	HMPA	-78 to r.t.	$PhNTf_2$ (Aldrich™)	**1.40** recovered and some decomp.
2	THF	KHMDS	--	-78 to r.t.	$PhNTf_2$ (prepared)	**1.40** recovered and some decomp..

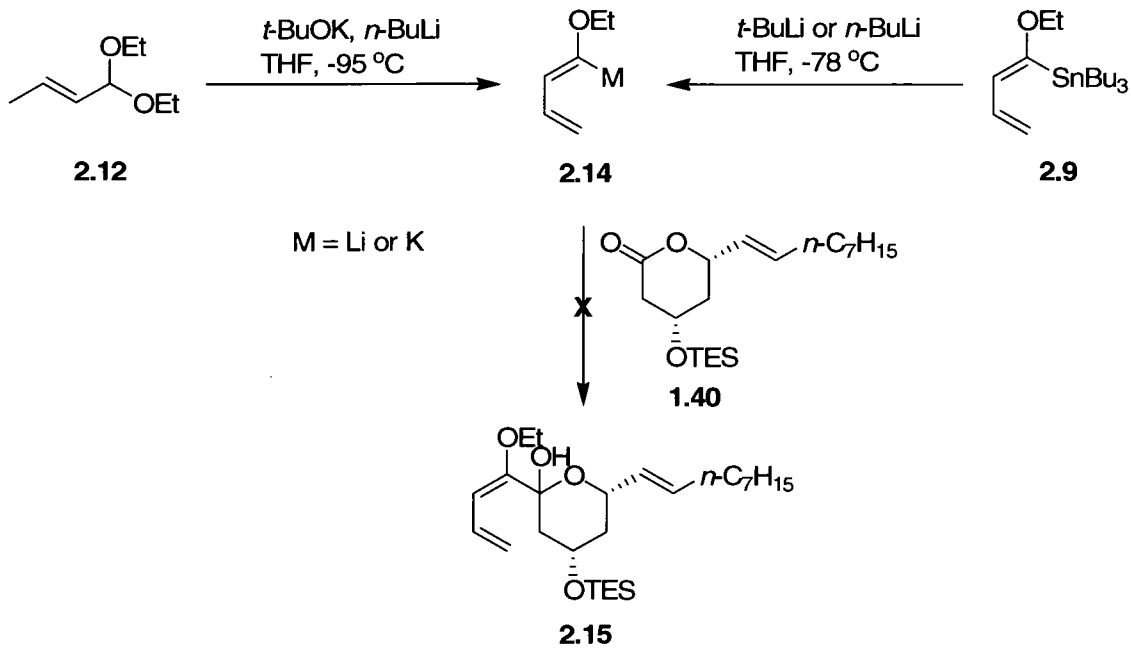
Table 2.2 Enolate Trapping Experiments



1.40 **1.40*** **2.13**

Entry	Base	Additive	Temperature (°C)	Result
1	KHMDS	HMPA	-78 to r.t.	**1.40** recovered and some decomp.
2	LDA	--	-78	**1.40** (25%), **2.13** (46%)
3	LDA	--	-40	**1.40** (20%), **2.13** (48%)
4	LDA	--	0	**1.40** (< 5%), **2.13** (52%)

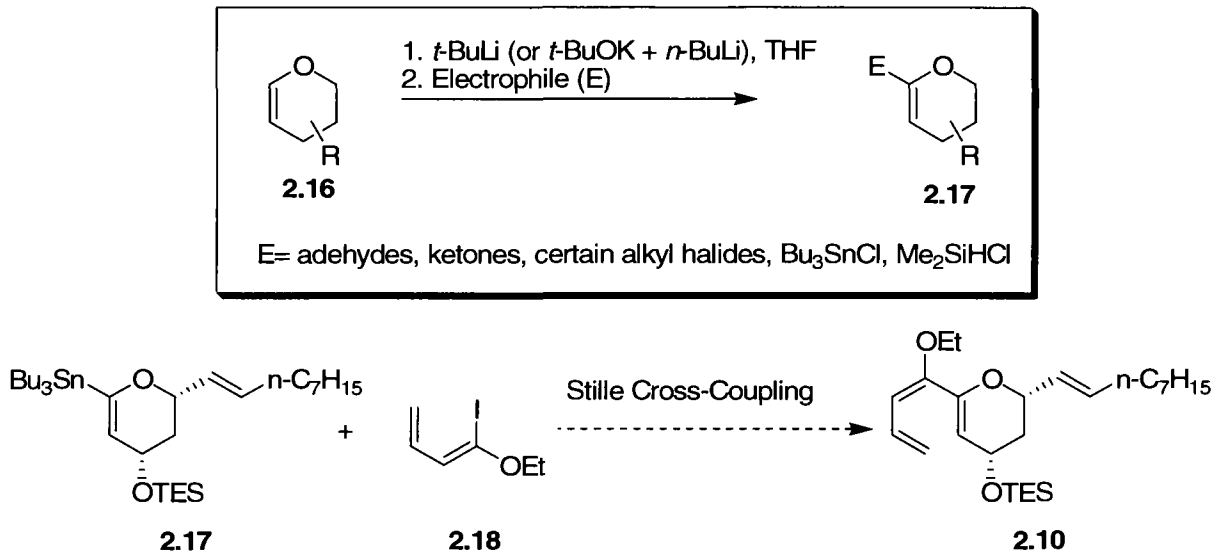
Due to the reluctance of lactone **1.40** to generate an enol triflate, a different method of coupling the alkoxydienyl fragment to the 6-membered ring had to be devised. Our first attempts to do so were to generate a metallated diene such as **2.14** by either treatment of diethylacetal **2.12** with Schlosser's base or by transmetallation of stannane **2.9** with *t*-BuLi or *n*-BuLi, followed by the addition of lactone **1.40** in the hopes of obtaining the corresponding lactol **2.15** (Scheme 2.4). Unfortunately, these reactions only led to complex mixtures from which no desired product could be isolated. Once again, a different strategy was required.



*Scheme 2.4 Attempts at Alkylating Lactone **1.40** with Dienyl Anion **2.14***

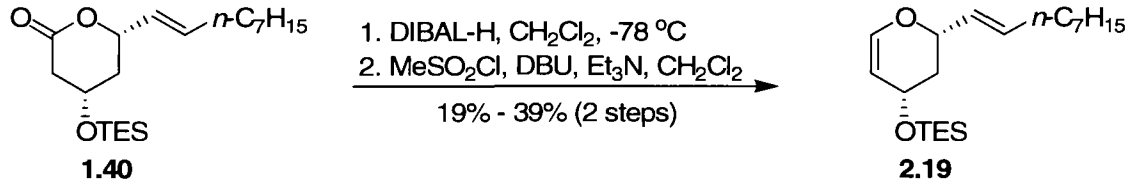
Attempts at Generating a Stannylated Dihydropyran as Coupling Partner

A quick survey of the literature revealed that dihydropyrans such as **2.16** could be metallated at the sp^2 carbon α to the oxygen with either Schlosser's base or *t*-BuLi. The resulting species could then be trapped by various electrophiles such as aldehydes,[23] ketones, [23] certain alkyl halides,[23] chlorotributyltin[24] and chlorodimethylsilane.[25] By converting lactone **1.40** into the corresponding dihydropyran, it should be possible to t it to the corresponding vinyllithium species and trap it with chlorotributyltin to generate stannane **2.17**. This stannane could then be coupled through a Stille cross-coupling reaction with iodide **2.18**, which should be obtainable from stannane **2.9** through a metal-halogen exchange, to form the desired key step precursor **2.10**.



Scheme 2.5 α-Metallation of Dihydropyran and Projected use for the Synthesis of Triene ***2.10***

The required dihydropyran **2.19** was obtained in two steps from lactone **1.40** in yields ranging from 19% to 39% (Scheme 2.6). Different conditions were screened for the dehydration of the intermediate crude lactol, however, none proved to be higher yielding. Although the yields were low, sufficient amounts of the desired product were obtained to attempt the metalation / stannylation step. Compound **2.19** was treated with either Schlosser's base in pentane in the presence of TMEDA[24c] or with *t*-BuLi in THF[26] at -78 °C then chlorotributyltin was added. In both cases, only starting material was recovered.

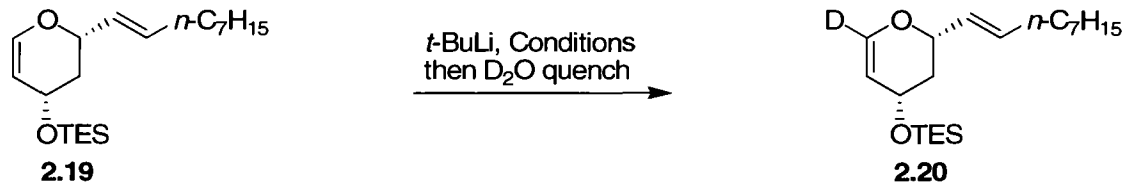


Scheme 2.6 Formation of Dihydropyran ***2.19***

In order to determine if metallation was taking place, the dihydropyran was treated with various amounts of *t*-BuLi in different solvents and at different temperatures (Table 2.3) then the reaction mixture was quenched by the addition of deuterium oxide. Under no set of conditions,

even with a large excess of *t*-BuLi, was the incorporation of deuterium noticeable by proton NMR of the crude reaction mixtures. Only intact starting material was recovered.

Table 2.3 Metallation / Deuteration Experiments on Dihydropyran ***2.19***

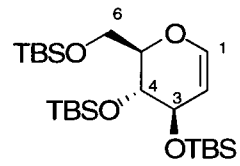


2.19 **2.20**

Entry	Solvent	Base (# equiv.)	Metallation Temperature (°C)	D_2O Quench Temperature (°C)	% Deuterium incorporation
1	THF	*t*-BuLi (3.5)	-78 to -15	-78 to r.t.	0
2	THF	*t*-BuLi (4)	-78 to 0	0	0
3	Et_2O	*t*-BuLi (10)	-78 to -20	-20 to r.t.	0
4	Hexanes	*t*-BuLi (15)	-78 to -10	-10 to r.t.	0
5	Hexanes	*t*-BuLi (20)	-78 to 0	-78 to r.t.	0

Friesen and coworkers[26] have reported difficulties in obtaining high yields of α-stannylated glycals with oxygen substituents protected with the *tert*-butyldimethylsilane (TBS) protecting group and noticed that stannylation was also occurring on the methyls of the protecting groups. However, using deuteration experiments, they have demonstrated that metallation mostly takes place on the C6 oxygen protecting group, and to a lesser extent, on the C4 oxygen protecting group. The metallation / deuteration process was never observed on the C3 oxygen protecting group (Figure 2.1).[26c] Also, they do not report observing any metallation on carbons α to silicon with any other silyl protecting group. Given that we did not notice deuteration or stannylation on carbons of the triethylsilyl (TES) protecting group of dihydropyran

2.19, this phenomenon was ruled out as the probable cause of our problems. We believed instead that the bulkiness of the TES protecting group might be to blame, hindering the approach of the already bulky base, *t*-BuLi.



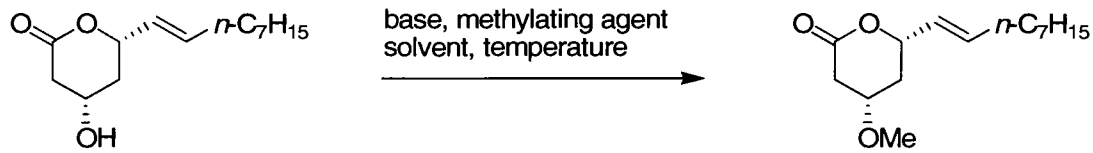
2.21

Figure 2.1 Friesen's model glycal

In order to relieve steric hindrance possibly caused by the triethylsilyl protecting group on **2.19**, we decided to replace it by a much smaller methyl protecting group. Oddly, installing a methyl group on the hydroxyl of lactone **1.39** was not as easy as expected. Typical conditions (Table 2.4, entry 1 and 2) either afforded complex mixtures of products or no reaction occurred. Evans and coworkers[27] have described the methylation of a similar alcohol using 10 equivalents of Proton Sponge™ and 10 equivalents of Meerwein's salt (Me_3OBF_4) at 0 °C for 24 hours. These conditions provided the desired methylated product; however, due to the large excess in reagents used, the work-up became tedious, especially on a larger scale. For this reason, the use of fewer equivalents of reagents was evaluated (Table 2.4, entries 3 and 4). It was found that using 5 equivalents of Proton Sponge™ with 5 equivalents of Meerwein's salt was practically just as good. Fewer equivalents of Meerwein's salt resulted in lower yields and the reaction became sluggish.

Once the methyl protecting group was installed, lactone **2.22** could be reduced with DIBAL-H and the resulting crude intermediate lactol was dehydrated using similar conditions as those used for the formation of dihydropyran **2.19**. In this case, the use of toluene as solvent proved to be slightly better than dichloromethane, although the yield of the dihydropyran product **2.23** was still quite low (28% over 2 steps).

*Table 2.4 Methylation of **1.39***



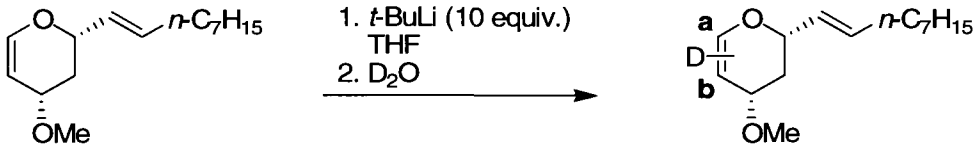
1.39 **2.22**

Entry	Solvent	Base (# equiv.)	Methylating Agent (# equiv.)	Temperature (°C)	Result or Yield (%)
1	DMF : THF (1 : 3)	NaH (1.2)	MeI (1.2)	0 to r.t.	Complex mixture
2	DCM	2,6-lutidine (15)	MeOTf (3.3)	0 to r.t.	No reaction
3	DCM	Proton Sponge™ (10)	Me_3OBF_4 (10)	0	76
4	DCM	Proton Sponge™ (5)	Me_3OBF_4 (5)	0	70
5	DCM	Proton Sponge™ (5)	Me_3OBF_4 (2.5)	0	42 (sluggish)

With dihydropyran **2.23** in hand, we immediately evaluated its propensity to form the desired lithiated species (Table 2.5, position **a**). This was done by treating **2.23** with excess *t*-BuLi in THF at different temperatures then quenching the reaction with D_2O. The crude reaction mixture was then analyzed by proton NMR to evaluate the degree of deuteration. When the reaction mixture was maintained at -78 °C, no deuterium was incorporated (Table 2.5, entry 4) suggesting that the temperature has to rise somewhat for the metallation to take place. If the temperature was allowed to warm to -40 °C during the metallation step (entries 2 and 3), deuterium incorporation was observed, however, it was mostly at position **b** rather than position **a** (~75% deuteration vs. ~ 50% deuteration). This was deduced from the integrals of the corresponding remaining protons (Figure 2.2). When the reaction mixture was allowed to warm

to 0 °C before the addition of deuterium oxide, no incorporation of deuterium was observed (entry 1). This result is most likely explained by the deprotonation of THF by the metallated species at higher temperatures, before the D_2O quench.

Table 2. 5 Metallation / Deuteration Experiments on Dihydropyran ***2.23***



2.23 **2.24**

Entry	Metallation Temperature (°C)	Quench Temperature (°C)	Result
1	-78 to 0	0	No deuteration
2	-78 to -40	-40	~50% deuteration at position **a**, ~75% deuteration at position **b**
3	-78 to -40	-78	~50% deuteration at position **a**, ~75% deuteration at position **b**
4	-78	-78	No deuteration

Metallation at position **b** was unexpected but it can possibly be explained by the substitution of the TES protecting group by the small methyl group. The decrease in steric hinderance around this oxygen may allow it to direct the approach of the base, such as depicted in Figure 2.3. In any case, these results demonstrate that the formation of a stannylated dihydropyran using this approach is most likely destined to fail on this substrate.

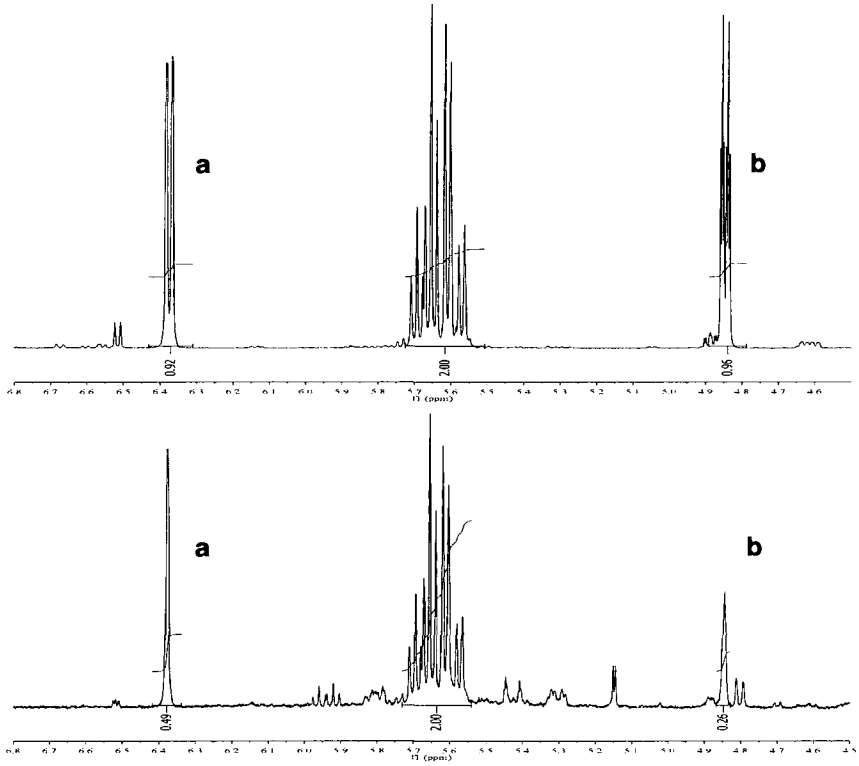


Figure 2.2 ^1H NMR of Dihydropyran 2.23 Before Treatment with t-BuLi then D_2O (top) and After (bottom) for entry 2 in Table 2.5

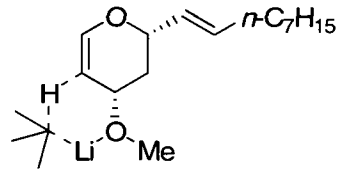


Figure 2.3 Possible Oxygen Directed Deprotonation at Position 5 of the Dihydropyran Ring through a 6-Membered Ring Transition State

Summary

We have envisioned the construction of the model key step precursor, triene **2.10**, through a cross-coupling strategy between a diene and a dihydropyran counterpart. The permutation of the metal-containing fragment and the X–group-containing fragment (X = iodide or OTf) for this cross-coupling has been investigated. In both cases, the formation of an appropriate dihydropyran coupling partner was not possible due to the position of the oxygen substituent on the ring. For this reason, the substitution pattern of the dihydropyran portion needs to be reassessed.

3

Generation of a Model Study Key Step Precursor and Efforts Towards Deoxypenostatin F

Introduction

Efforts to derive a useful cross-coupling partner from lactone **3.1** were unfruitful. For both routes outlined in Figure 3.1, the major problem was due to the position of the oxygen substituent on the dihydropyran ring. Direct formation of an enol triflate such as **3.2** was not possible due to an E1cb elimination of the protected hydroxyl group when the lactone was treated with a strong enough base. When lactone **3.1** was transformed to the corresponding dihydropyran **3.3**, metalation of **3.3** did not take place when a large protecting group was present on the same hydroxyl. Alternately, there was no selectivity as to which carbon of the dihydropyran double bond would get metallated, when a small protecting group was present. Due to these issues, we decided to change the position of the oxygen substituent on the ring. It is important to note that this oxygen would eventually serve as a handle to introduce the exocyclic methyl group and the C10 – C11 insaturation on an actual precursor to penostatin F.

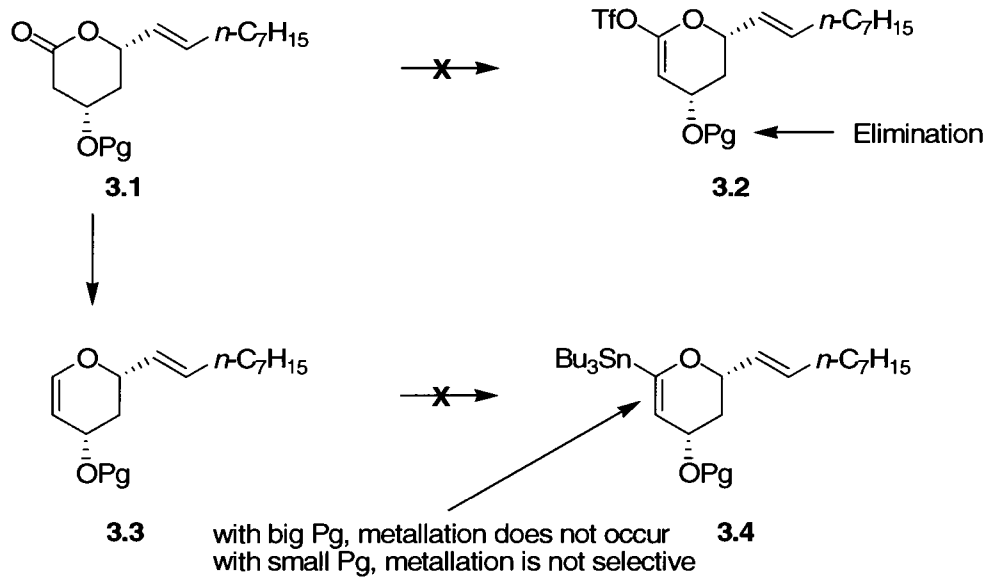
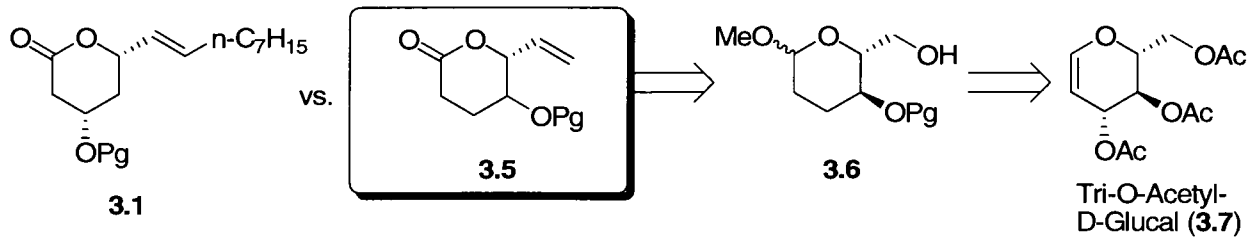


Figure 3.1 Failed Attempts at Generating a Useful Cross-coupling Partner from Lactone ***3.1***

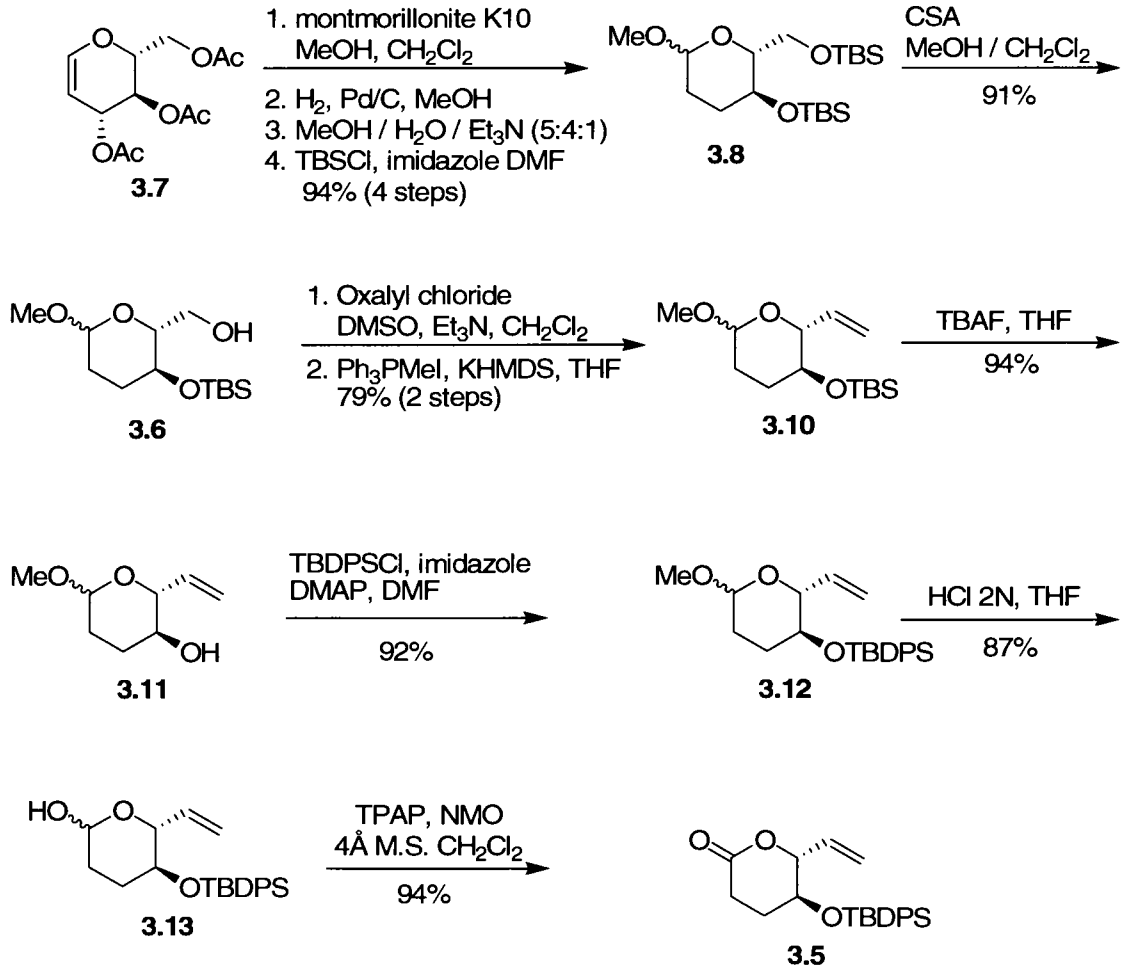
At that point, we had decided to move the oxygen by one carbon on the lactone, as depicted in Scheme 3.1. Also, for the purpose of simply trying the 6π electrocyclization followed by a Claisen rearrangement, the *n*-heptyl chain was truncated, leaving us with **3.5** as our new target lactone for our model study. The formation of an enol triflate cross-coupling partner from **3.5** should not be an issue since the position of the oxygen substituent does not allow it to undergo an E1cb type of elimination. This lactone could be derived from the known acetal **3.6** (where Pg = *tert*-butyldimethylsilane)[28] which in turn comes from commercially available and optically pure tri-*O*-acetyl-D-glucal (**3.7**). Starting with this material could lead to an enantiospecific synthesis of penostatin F.



Scheme 3.1 New Lactone for the Construction of a Model Study Triene

Synthesis of the New Model Study Key Step Precursor

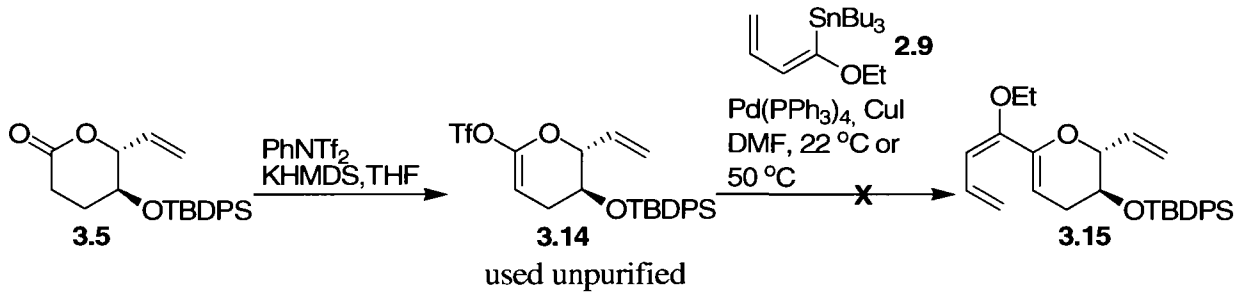
As previously mentioned, the synthesis of alcohol **3.6** en route to the new target lactone **3.5**, has previously been reported by the Nakata group[28] for their total synthesis of brevetoxin-B. The only step which was not followed was the acetate hydrolysis, which was done using a procedure described by Pougny and co-workers[29] on the same substrate. The use of a methanol, water and triethylamine mixture proved to be a higher yielding process compared to potassium carbonate in methanol, as prescribed by Nakata. The first four steps can be carried out without chromatographic purification, which allows quick access to the bis-TBS protected



*Scheme 3.2 Synthesis of Lactone **3.5***

intermediate **3.8** in high yield on a large scale. The primary alcohol was selectively deprotected using camphorsulfonic acid in methanol and dichloromethane at 0 °C affording the mono-protected TBS ether **3.6** which was oxidized using the Swern[30] protocol to the corresponding aldehyde **3.9**. This aldehyde was used immediately for the subsequent Wittig reaction leading to **3.10** in 79% yield over 2 steps. Attempts to hydrolyze the methoxy group on **3.10** afforded a complex mixture of products from which no desired lactol was observed. This was attributed to the acid lability of the TBS protecting group. As a consequence, the TBS protecting group was substituted for the more acid-stable TBDPS. Hydrolysis of the methoxy group on **3.12** using aqueous HCl in THF smoothly afforded the desired lactol **3.13** in 87% yield which underwent Ley[31] oxidation to cleanly produce lactone **3.5** in 94% yield (Scheme 3.2).

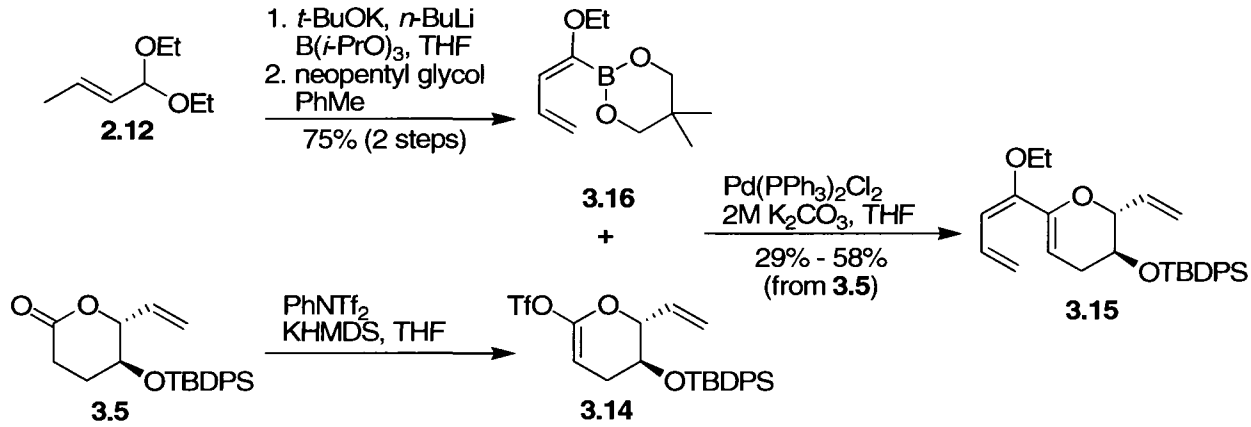
With lactone **3.5** in our hands, we were ready to attempt the Stille coupling reaction between its derived enol triflate and alkoxydienylstannane **2.9**. We were pleased to notice that treatment of the lactone with KHMDS and phenyl triflimide yielded the corresponding enol triflate (Scheme 3.3). Due to the unstable nature of this species, it was immediately used after aqueous work-up for the subsequent cross-coupling reaction. Unfortunately, initial attempts to couple the enol triflate with the alkoxydienylstannane using standard conditions[32] afforded complex mixtures of products from which no desired triene could be isolated.



*Scheme 3.3 Unsuccessful Stille Cross-Coupling for the Synthesis of Triene **3.15***

Prandi and coworkers[18b-e] have described the synthesis of similar trienes via a Suzuki[33] cross-coupling reaction. Encouraged by her work, we set off to synthesize alkoxydienyl boronic ester **3.16** in an analogous fashion to the synthesis of the corresponding stannane (Scheme 3.4). Diethylacetal **2.12** was treated with 2 equivalents of Schlosser's base and the generated dienyl anion was quenched with triisopropylborate. The unstable boronic acid obtained after aqueous

work-up was condensed with neopentyl glycol to give boronic ester **3.16** which was used as such after aqueous work-up in the next reaction. The cross-coupling reaction between boronic ester **3.16** and enol triflate **3.14** finally provided us with the desired model key step precursor **3.15** in yields varying from 29% to 58% from lactone **3.5**. The modest yields are due to many factors such as the instability of the triene on silica, the instability of the triflate and the fact that both coupling partners must be used without purification to avoid their decomposition.



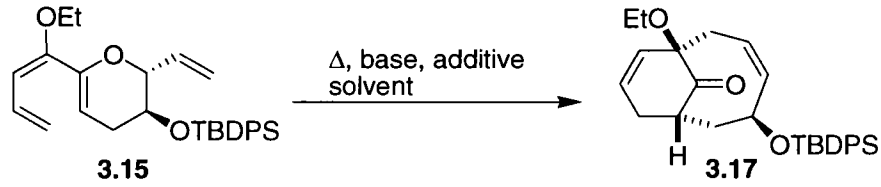
*Scheme 3.4 Synthesis of Model Study Triene **3.15***

Regardless of the yield of the coupling reaction, the stage was set to attempt the key electrocyclization/Claisen step. The first attempts were conducted in a sealed tube in a wax bath preheated to the desired temperature. The first try (entry 1, Table 3.1) was done without the presence of base at 180 °C which quickly led to decomposition. When 2% of the solvent was triethylamine, a new major spot along with other minor spots could be noticed by thin layer chromatography. To our delight, it was determined that this new product was the desired bicyclo[5.3.1]undecenone **3.17** (Figure 3.2) which was confirmed by NOESY and COSY experiments. The other products arising from this reaction were not obtained in sufficient quantity and purity for their identification.

In order to reduce the amount of time necessary for the complete consumption of the starting material, the reactions were run in the microwave (20h vs. 2h 20min, entry 2 and 3, Table 3.1). Shorter reaction periods at these temperatures are preferable to decrease the amount

of decomposition. We then tried reducing the temperature to 160 °C in toluene and the reaction was monitored by TLC. However, after 4 hours mostly starting material was observed therefore the reaction was completed at 185 °C for another 2 hours (entry 4). At that point, we also started adding BHT in our reaction mixture which would serve as a radical scavenger to try to eliminate possible decomposition pathways. The addition of BHT did not seem to have a significant impact on the yield.

Table 3.1 Model Key Step Optimization



Entry	Base (amt.)	Solvent	Additive (# equiv.)	Temperature (°C)	Time	Yield
1[a]	none	Toluene	none	180	10 min.	decomp.
2[a]	Et_3N (2% solvent)	Toluene	none	180	20h	14%
3	Et_3N (2% solvent)	Toluene	none	180	2h 20 min.	24%
4	Et_3N (2% solvent)	Toluene	BHT (5 mol%)	160 to 185	6h	13%
5	Et_3N (2% solvent)	PhCl[b]	BHT (5 mol%)	160	2h	19%
6	Et_3N (2% solvent)	DMF	BHT (5 mol%)	160	2h	decomp.
7	DBU (2% solvent)	PhCl[b]	BHT (5 mol%)	150	2.5h	24%
8	DBU (2% solvent)	PhCl[b]	BHT (5 mol%)	140	5h	21%
9	DBU (1% solvent)	PhCl[b]	BHT (5 mol%)	150	2.5h	14%

Reactions were run in a microwave vessel in degassed solvent, containing a carboflon and irradiated in the microwave until no more starting material could be observed by TLC
[a]Reactions were run in a sealed tube in a wax bath, [b]No carboflon was necessary.

We investigated the use of other solvents such as DMF and chlorobenzene. DMF proved to be not suitable for this reaction, leading only to decomposition. Chlorobenzene did not require the use of a carboflon and product was obtained when it was used as solvent. Also, in this solvent, the temperature could be decreased to 150 °C with a relatively short reaction time (2.5h, entry 7) when compared with toluene. At 140 °C, the reaction time was doubled which was accompanied with a small decrease in yield. Changing the base from triethylamine to DBU did not seem to make a significant difference (entry 5 and entry 7). In summary, under the conditions tried, the highest yield is 24% (entries 3 and 7). The only advantage to using chlorobenzene instead of toluene is the possibility of decreasing the reaction temperature. Finally, in one experiment, the Suzuki cross-coupling reaction and the thermal electrocyclization / Claisen rearrangement were done sequentially, in a sealed tube. Unfortunately, very little desired product (< 8% yield) was obtained from the messy reaction mixture.

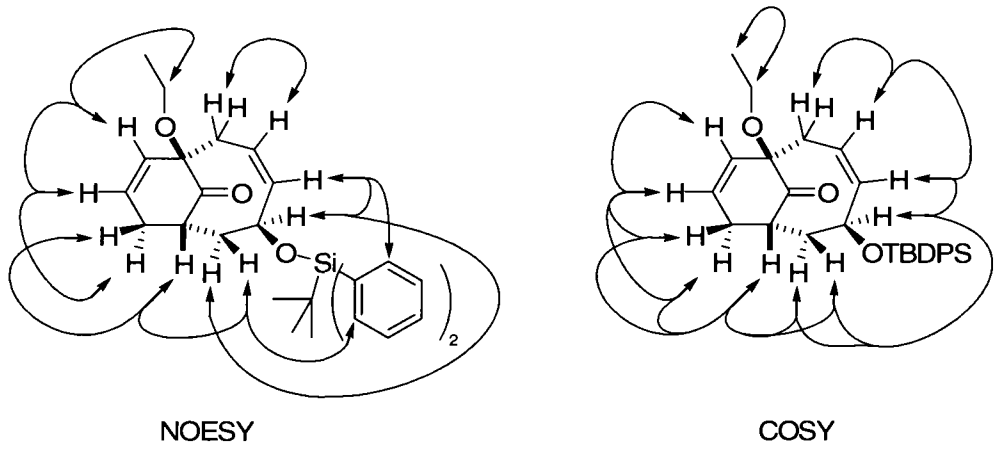
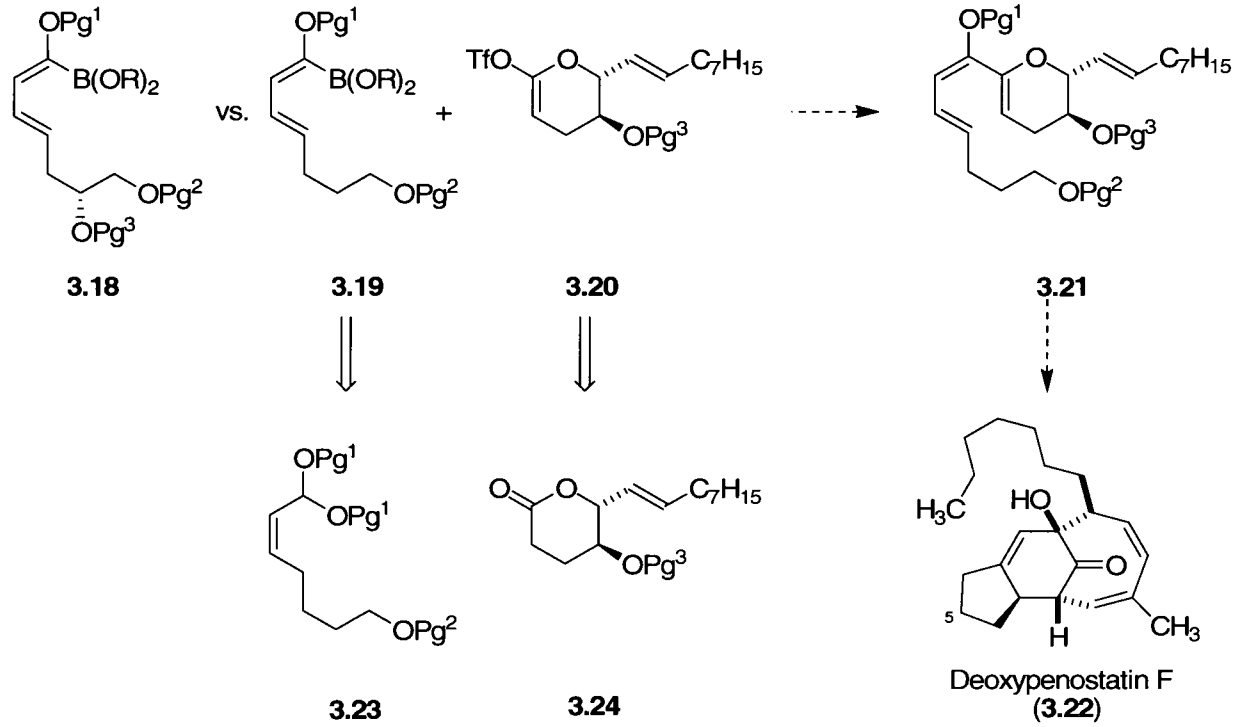


Figure 3.2 Structure Elucidation of ***3.17*** *by 2D NMR Experiments*

Efforts Towards Deoxypenostatin F

Once we knew that the electrocyclization / Claisen rearrangement was possible on the simplified model substrate **3.17**, we wanted to turn our attention to the synthesis of penostatin F.

However, we believed that constructing a boronic ester such as **3.18** with the chiral secondary hydroxyl, under conditions analogous to those used to produce our previous boronic ester (**3.16**), might be difficult and time consuming. Instead, we fixed our aim on the total synthesis of deoxypenostatin F (**3.22**), which would not possess the hydroxyl at C5.

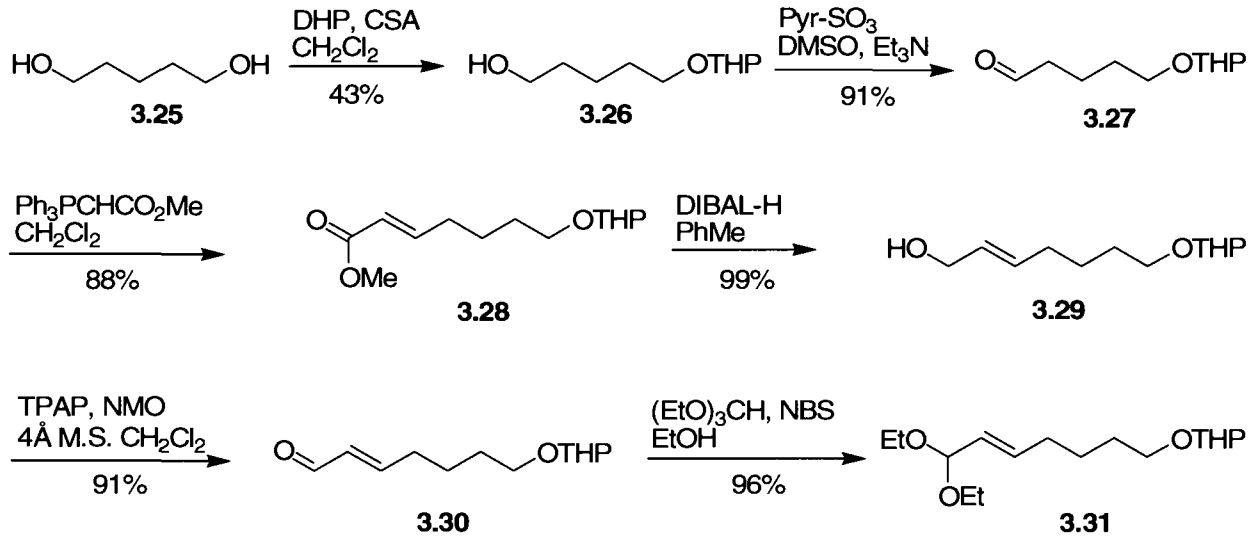


Scheme 3.5 Towards Deoxypenostatin F

In order to build a triene such as **3.21**, which could serve as the precursor to the key step towards deoxypenostatin F, we would need to couple a boronic ester such as **3.19** and an enol triflate such as **3.20**. Once again, one can conceive that the enol triflate could come from the corresponding lactone **3.24**, and the boronic ester from the acetal **3.23**.

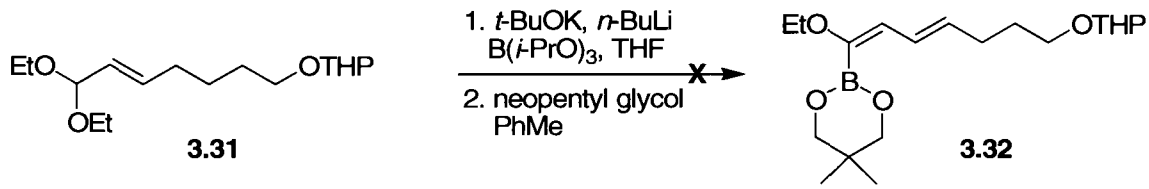
The first steps of the synthesis of the desired acetal, up to the allylic alcohol, were done according to the procedure described by Clasby and coworkers (Scheme 3.6).[34] The synthesis began with the mono-protection of 1,5-pentanediol with DHP and CSA in dichloromethane. The mono-protected diol **3.26** was oxidized using pyridine-SO_3 in DMSO in the presence of triethylamine. The resulting aldehyde was then treated with Ph_3PCHCO_2Me to afford ester **3.28** in 88% yield which was then reduced to the corresponding allylic alcohol **3.29**. The latter

underwent Ley[31] oxidation to give enal **3.30** in high yield followed by the NBS catalyzed acetalization[19] to afford **3.31** in 96% yield.



*Scheme 3.6 Synthesis of Diethylacetal **3.31***

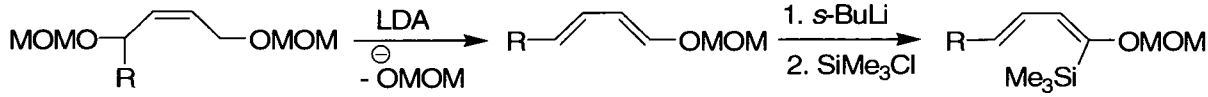
The conversion of diethyl acetal **3.31** to the corresponding boronic ester under the same conditions as those employed to generate boronic ester **3.16** afforded a complex mixture in which only trace amounts of unsaturated products were noticeable by proton NMR (Scheme 3.7). Varying the amount of Schlosser's base, the temperature, the reaction time or the diol proved to be fruitless. We therefore needed another method at accessing this type of boronic ester.



*Scheme 3.7 Unsuccessful Conversion of Acetal **3.31** to Boronic Ester **3.32***

McDougal and Rico had reported the *trans* stereoselective synthesis of 1-alkoxy polyenes, there α-lithiation and subsequent trapping with an electrophile (Scheme 3.8).[35] The alkoxy group is a methoxymethyl enol ether which is preferable in our case given the milder

conditions necessary for the eventual removal a MOM group rather than an ethyl group, which would have been the case with boronic ester **3.32**. The presence of the MOM group has a second advantage which is that it facilitates the α-lithiation of the polyene. Schlosser's base is no longer necessary, *sec*-butyllithium is now sufficient for this purpose.



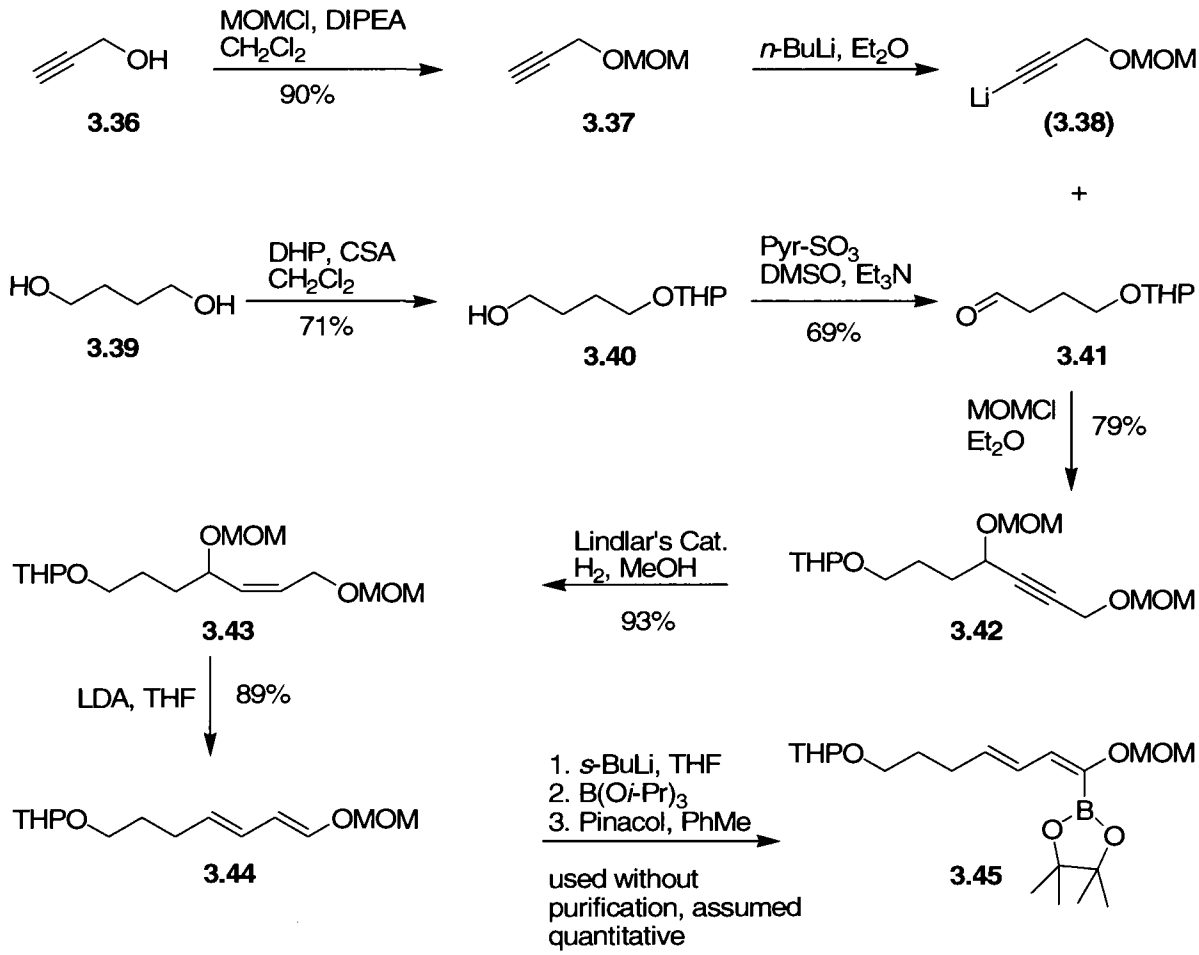
3.33 **3.34** **3.35**

Scheme 3.8 McDougal and Rico's Synthesis of E,E-*Alkoxydienes and their Subsequent Metallation*[35]

For the reasons outlined above, we undertook the synthesis of boronic ester **3.45** as depicted in Scheme 3.9. It started by the installation of a MOM group on propargyl alcohol (**3.36**) under standard conditions[36] to afford alkyne **3.37** in 90% yield. This alkyne was then treated with *n*-butyllithium followed by the addition of aldehyde **3.41**, which was prepared similarly as aldehyde **3.27** from 1,4-butanediol (**3.39**). The resulting intermediate alkoxide was trapped with methoxymethyl chloride to afford the bisMOM-ether **3.42** in 79% yield. Reduction of the triple bond with Lindlar's catalyst followed by treatment of the resulting *cis*-alkene with 6 equivalents of LDA furnished the 1-alkoxydiene **3.44** having the *trans-trans* double bond geometry, in 89% yield. **3.44** underwent a metallation reaction with *sec*-butyllithium to give the corresponding α-lithiated intermediate which was then trapped with triisopropyl borate. After aqueous work-up, the resulting boronic acid was condensed with pinacol in toluene to afford the desired boronic ester **3.45**. Due to its unstable nature on silica, this boronic ester had to be used without further purification, the yield was assumed to be quantitative.

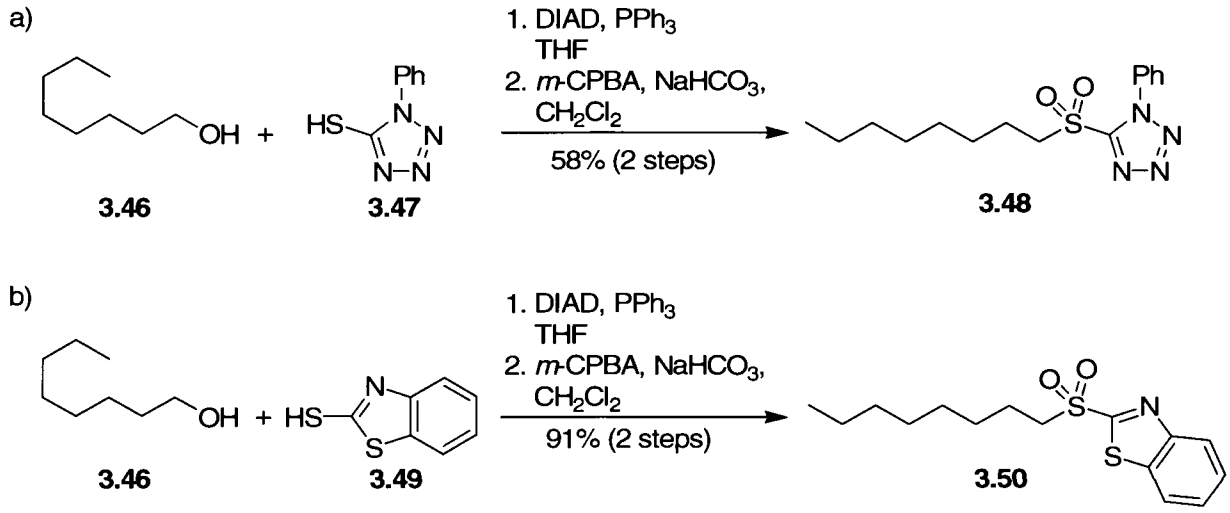
With the boronic ester in hand, we then turned our attention to the synthesis of a lactone such as **3.24** (Scheme 3.5). The installation of the *E* alkene proved to be more challenging than it was originally planed. We initially looked at the use of the Julia-Kocienski olefination which is a well known method for obtaining *E* double bonds.[37] For this purpose, we first synthesized the 1-phenyl-1*H*-tetrazol-5-yl sulfone **3.48** (PT-sulfone) which apparently provides better yields than its benzothiazolyl sulfone (BT-sulfone) **3.50** counterpart according to the authors of the original

publication. This was done through a Mitsunobu[38] reaction between 1-octanol and 1-phenyl-1*H*-tetrazole-5-thiol which was followed by the oxidation of the resulting crude mixture of the intermediate sulfide with *m*-CPBA (Scheme 3.10 a).



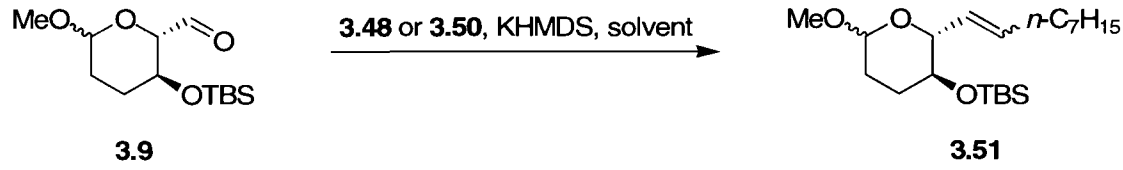
Scheme 3.9 Synthesis of Boronic Ester ***3.45***

Olefination of aldehyde **3.9** with PT-sulfone **3.48** in DME with KHMDS as base afforded the alkene in low yield, where the undesired *Z* isomer was the major product (Table 3.2). The *E* alkene could be obtained as the major isomer by changing the solvent to DMF however in even lower yields, with reproducibility issues. For this reason, the BT-sulfone **3.50** was prepared such as **3.48** (Scheme 11 b), unfortunately it failed to generate any alkene product.



Scheme 3.10 Construction of the BT and PT-Sulfones

Table 3.2 Julia-Kocienski Olefination

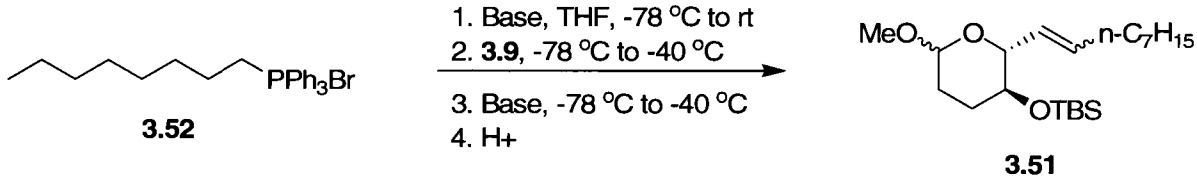


Entry	Sulfone (equiv.)	Solvent	Conditions	Yield (%)	*E/Z*
1	**3.48** (1.5)	DME	KHMDS + sulfone, -60 °C, 0.5h then **3.9**, -60 °C, 3h to rt, o.n.	28	5/9
2	**3.48** (1.5)	DMF	KHMDS + sulfone, -60 °C, 0.5h then **3.9**, -60 °C, 3h to rt, o.n.	0	--
3	**3.48** (1.5)	DMF	KHMDS + sulfone, -60 °C, 1h then **3.9**, -60 °C, 1h to rt, o.n.	10	6/1
4	**3.50** (1.5)	DMF	KHMDS + sulfone, -60 °C, 1h then **3.9**, -60 °C, 1h to rt, o.n.	0	--

Another method of selectively accessing *E* alkenes is through the use of Schlosser's[39] modification of the Wittig reaction. In an attempt to exploit this reaction,

octyltriphenylphosphonium bromide (**3.52**) was prepared and treated with either *s*-BuLi[39d] or phenyllithium[39b,c] to generate the corresponding ylid (Table 3.3). After the usual procedure, the *Z* product was still predominantly formed.

Table 3.3 Schlosser's Modified Wittig



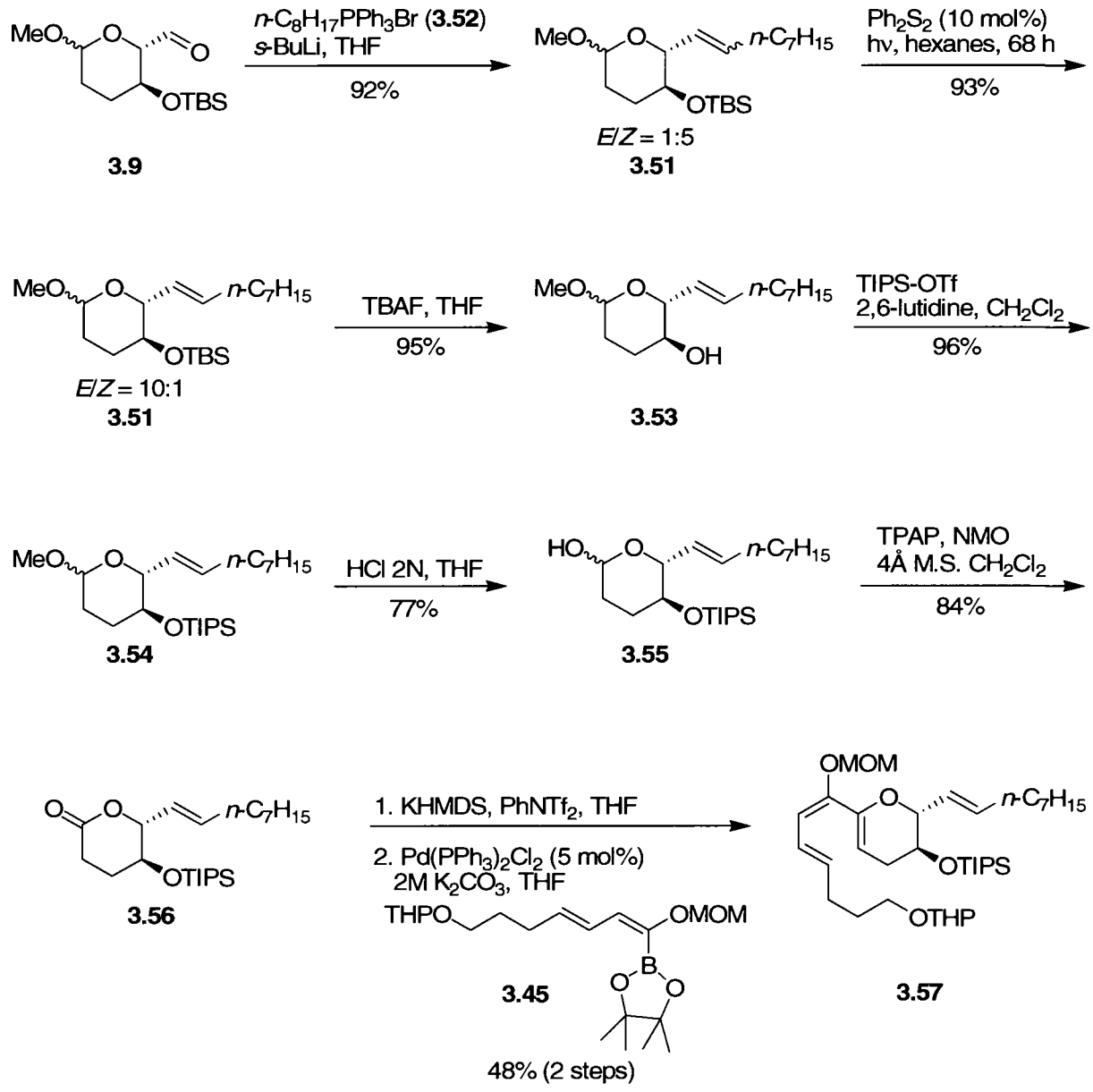
3.52 **3.51**

Entry	Base	Yield (%)	*E/Z*
1	*s*-BuLi	64	1/5
2	PhLi	54	2/5

At that point, a more efficient method was necessary to obtain the thermodynamically favored *E* alkene. A survey of the literature revealed that a similar secondary *E* alkene bound to an unsubstituted aliphatic chain and to a tetrahydropyran had been synthesized.[40] This had been achieved through a simple Wittig reaction between the corresponding aldehyde and alkyl-phosphonium bromide followed by a light induced isomerization of the olefin in the presence of diphenyldisulphide. This sequence was therefore attempted with aldehyde **3.9** and octyltriphenylphosphonium bromide **3.52**. The Wittig reaction afforded the alkene in excellent yield as a 1:5 *E/Z* mixture. Subsequent irradiation of the mixture with light (300W lamp) in the presence of 10mol % of diphenyldisulphide in hexanes provided the alkene as a 10:1 *E/Z* mixture in 93% yield (Scheme 3.11). It was found that irradiation for 68 hours was necessary to reach the thermodynamic equilibrium. Prolonged irradiation after the addition of another 10 mol% of diphenyldisulphide did not increase the *E/Z* ratio.

Satisfied by the efficiency of the olefination / isomerization procedure, we then turned our attention to the remaining steps of the synthesis of the desired triene. As for intermediate **3.10**, a less acid-labile protecting group had to be installed in place of the TBS group present on **3.51**. The TBS protecting group was removed with TBAF. At that point, the *E/Z* stereoisomers

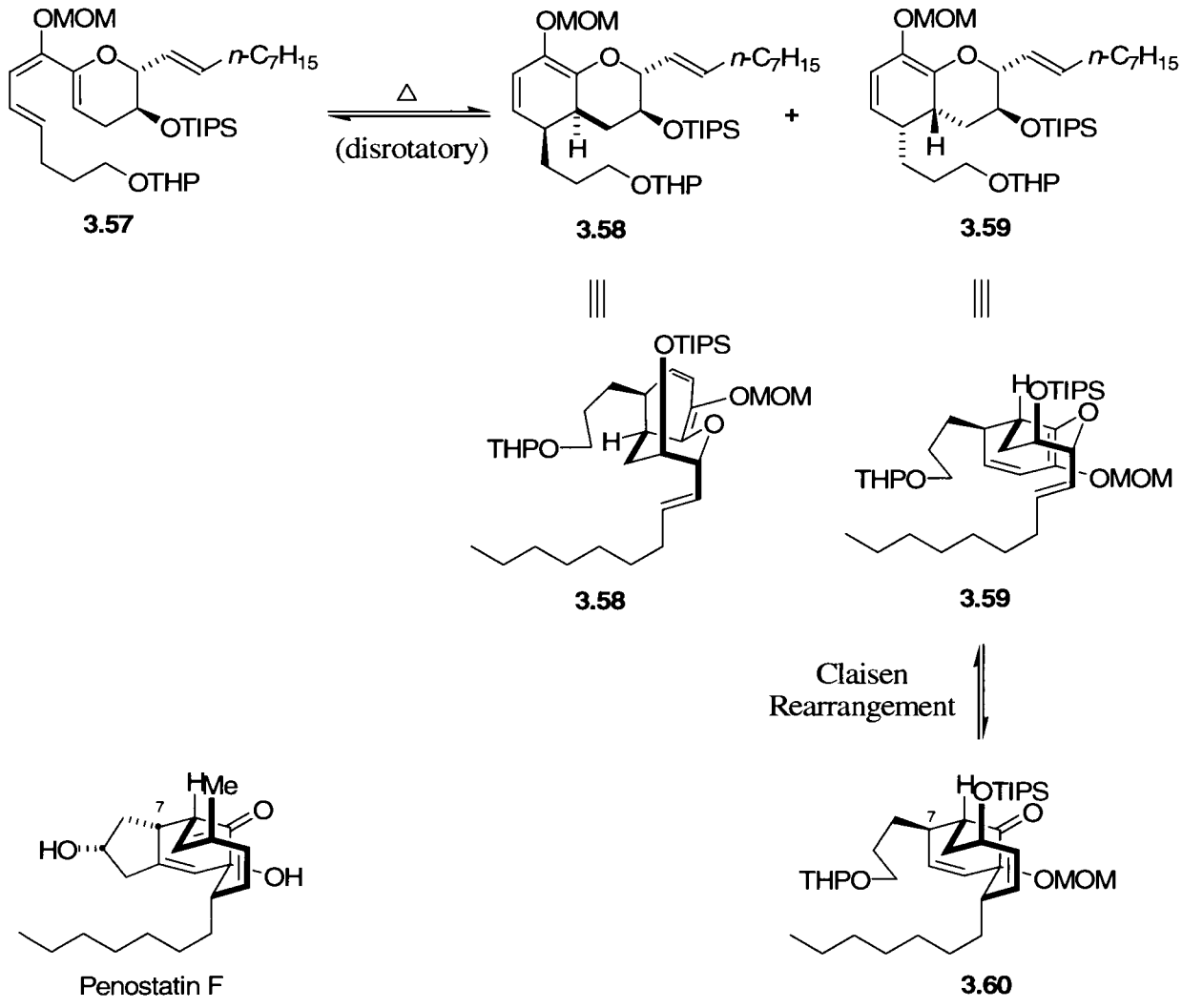
could be separated more easily. The free alcohol was reprotected by a TIPS in high yield. The hydrolysis of the methoxy group proceeded smoothly (77% yield) followed by the oxidation of the resulting lactol **3.55** to the lactone **3.56** in 84% yield. Formation of the enol triflate from this lactone was accomplished in the same manner as with lactone **3.5**. Once again, the unstable enol triflate was used without further purification for the subsequent coupling reaction with boronic ester **3.45**. The desired key step precursor, triene **3.57** was obtained in 48% yield over two steps.



*Scheme 3.11 Synthesis of Triene **3.57***

Projected Outcomes for the 6π Electrocyclization / Claisen Rearrangement

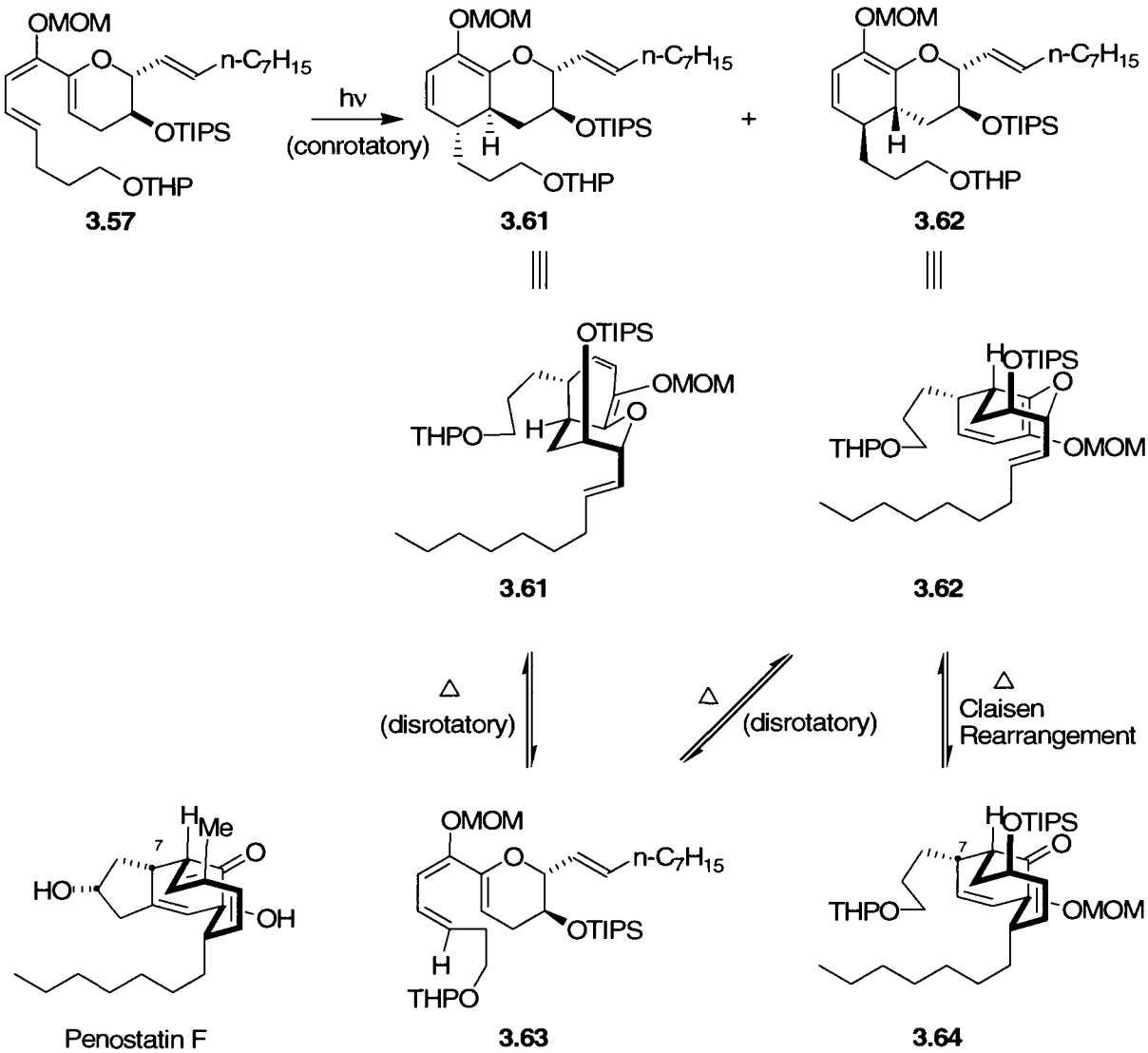
Having triene **3.57** in our hands, we were ready for the 6π electrocyclization / Claisen rearrangement key step. If this triene were to be heated, a disrotatory 6π electrocyclization would be expected,[41] theoretically leading to stereoisomers **3.58** and **3.59**. As depicted in Scheme 3.12, isomer **3.58** cannot adopt a conformation allowing for a Claisen rearrangement to occur. On the other hand, compound **3.59** is poised to undergo the [3,3] rearrangement leading to **3.60**. Since electrocyclizations are reversible, we hypothesized that **3.58** could return to the starting triene **3.57** and furnish both electrocyclization isomers which could, in principle, enable



Scheme 3.12 Expected Thermal 6π Electrocyclization / Claisen Rearrangement

the complete conversion of triene **3.57** to the Claisen rearranged product **3.60**. However, when looking closely at **3.60**, one will notice that the stereochemistry at C7 is opposite to that found in penostatin F.

To obtain the proper stereochemistry at C7, we must look at an initial photo-induced 6π electrocyclization (Scheme 3.13). If **3.57** were irradiated with light, a conrotatory electrocyclization would be expected,[41] leading to stereoisomers **3.61** and **3.62**. If the resulting mixture were heated, **3.62** could undergo a Claisen rearrangement affording **3.64**, with the desired bicyclo[5.3.1]undecenone core found in penostatin F. Isomer **3.61** cannot adopt the proper conformation for the Claisen rearrangement, however, upon heating, it could undergo a



Scheme 3.13 Expected Photochemical 6π Electrocyclization / Claisen Rearrangement

disrotatory electrocyclic ring opening, leading to **3.63** with the distal double bond relative to the dihydropyran ring having the *Z* conformation. This intermediate could now go through a thermal disrotatory electrocyclization, leading to **3.61** and **3.62**. Once again, this should allow for both products of the initial electrocyclization to be converted to the desired Claisen rearranged product **3.64**.

Attempts Towards a Photochemical 6π Electrocyclization Initiated Key Step

Photochemical 6π electrocyclizations of hexatrienes (and the reverse reactions) were first recognized during studies on vitamin D (Figure 3.3)[41b, 42] and stilbene (Figure 3.4).[41b, 43] There are relatively few applications of this reaction in organic synthesis.[44] Nonetheless, in order to

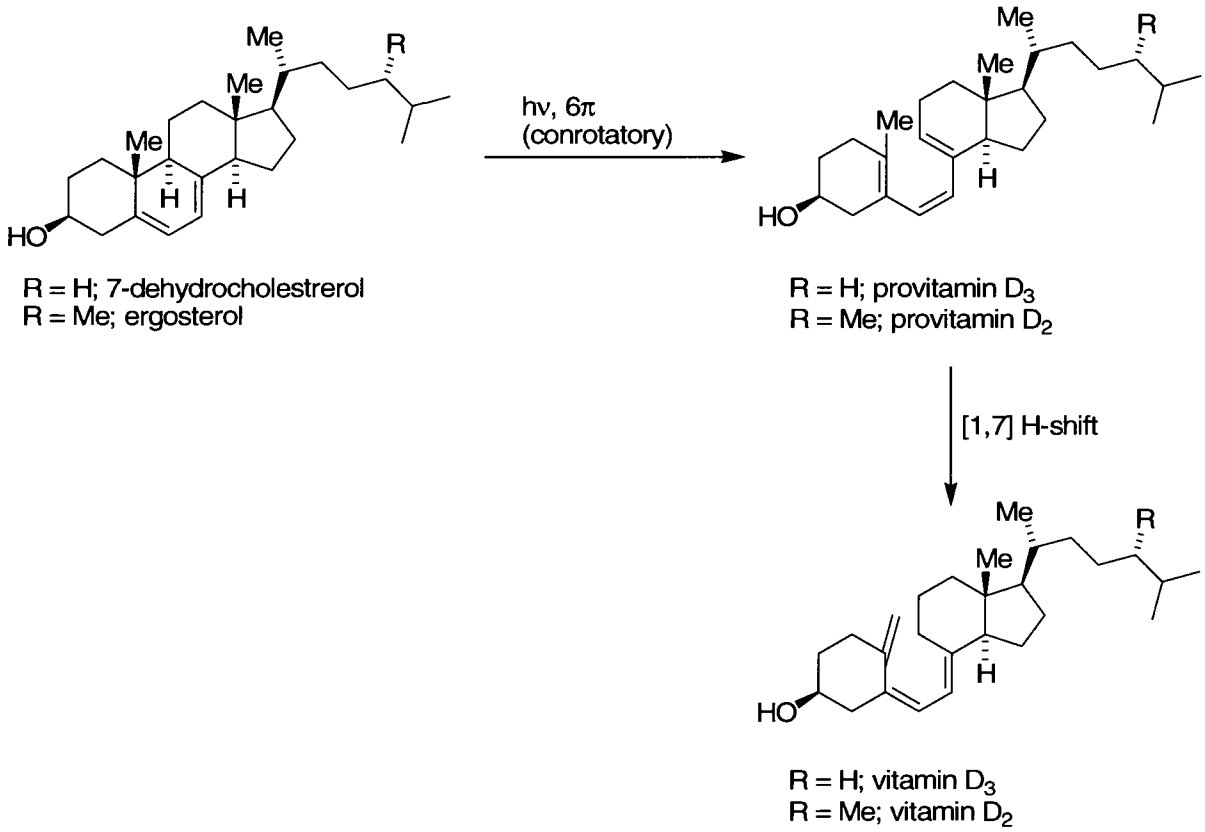


Figure 3.3 Role of the Light Induced 6π Conrotatory Electrocyclic Ring Opening of Precursors of Vitamin D_2 and D_3

Figure 3.4 Light Induced 6π Conrotatory Electrocyclization of cis-*Stilbene*

obtain the desired stereochemistry at C7 of the natural product, photochemical electrocyclizations of triene **3.57** to **3.61** and **3.62** were investigated. To have an idea at which wavelength the triene absorbed UV light the most, its absorption spectrum was recorded between 200 nm and 600 nm (Figure 3.5). There is a strong but narrow absorbance at 203 nm followed by a "hump" between 250 nm and 300 nm. For this reason, most of the electrocyclization attempts were carried out using UVB (281 – 315 nm) and UVC (235 – 280 nm) lamps instead of UVA (316 – 400 nm) lamps.

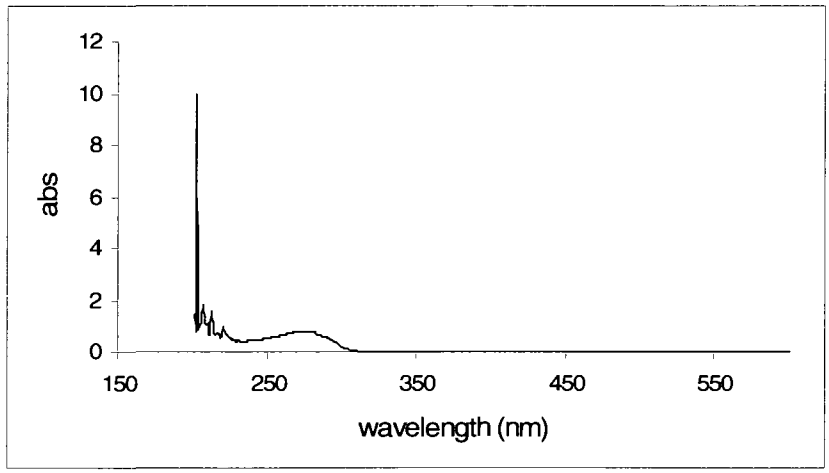
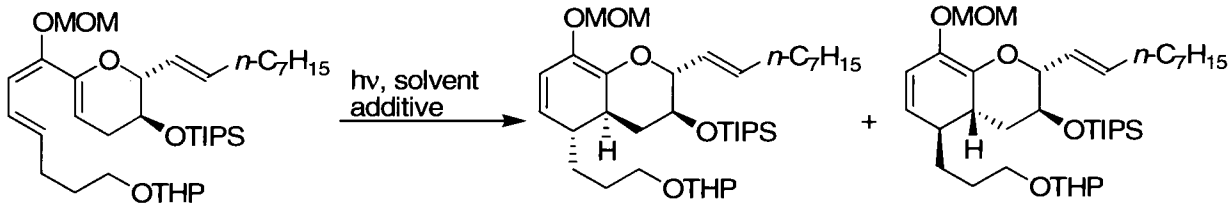


Figure 3.5 UV Absorption Spectrum of Triene ***3.57***

As depicted in Table 3.4, no electrocyclization products have been obtained from irradiation of the triene with various light sources. All reactions in hexanes led to decomposition over various amounts of time. The use of methanol as solvent led to no reaction at all. The

Table 3.4 Photochemical Electrocyclization Attempts



3.57 **3.61** **3.62**

Entry	Wavelength	Solvent	Additive	Result
1[a]	UVA	hexanes	--	decomp. over 2 days
2[a]	UVB	hexanes	--	decomp. over 2 days
3[a]	UVB	hexanes	$MgBr_2$-OEt_2	decomp. over 4h
4[a]	UVB	hexanes	LiCl	decomp. overnight
5[a]	UVB	hexanes	LiCl, Et_3N	decomp. overnight
6[a]	UVB	methanol	--	no reaction after 5 days
7[a]	UVB	methanol	LiCl	no reaction after 5 days
8[a]	UVB	methanol	LiCl, Et_3N	no reaction after 5 days
9[a]	UVC	hexanes	LiCl, Et_3N	decomp. overnight
10[a]	UVC	hexanes	$PhCO_2Me$	decomp. overnight
11[a]	UVC	EtOAc	$PhCO_2Me$	decomp. overnight
12[a]	UVC	hexanes	acetophenone	decomp. after 18h
13[a]	UVC	hexanes	benzophenone	decomp. after 18h
14[b]	sunlight	methanol	--	no reaction after 7 days
15[c]	Hanovia high-pressure Hg-lamp (no filter)	hexanes	--	s.m. and decomp. after 11h

[a] Reactions were run in 10 mL quartz tubes between two Luzchem exposure panels having 5 12" long 8 watt lamps each. [b] Reaction run in a 10 mL Pyrex flask in direct sunlight. [c] Reaction run in a 10 mL quartz tube placed 30 cm from an unfiltered refrigerated Hanovia high-pressure Hg-lamp.

addition of certain metal salts such as lithium chloride and magnesium bromide was investigated. The reasoning behind this was that the metal might be used as a tether coordinating between the oxygens on C1 and C9, locking the C1-C9 bond in a s-*cis* conformation, in the hopes of facilitating the electrocyclic reaction (Figure 3.6). In certain cases, a base was added to ensure no acid species would be present, which could lead to decomposition. Unfortunately the addition of these metal species had no influence on the reactions.

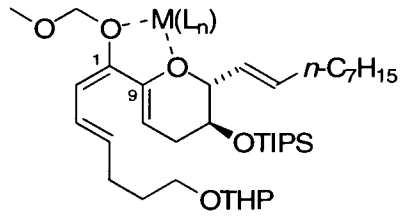


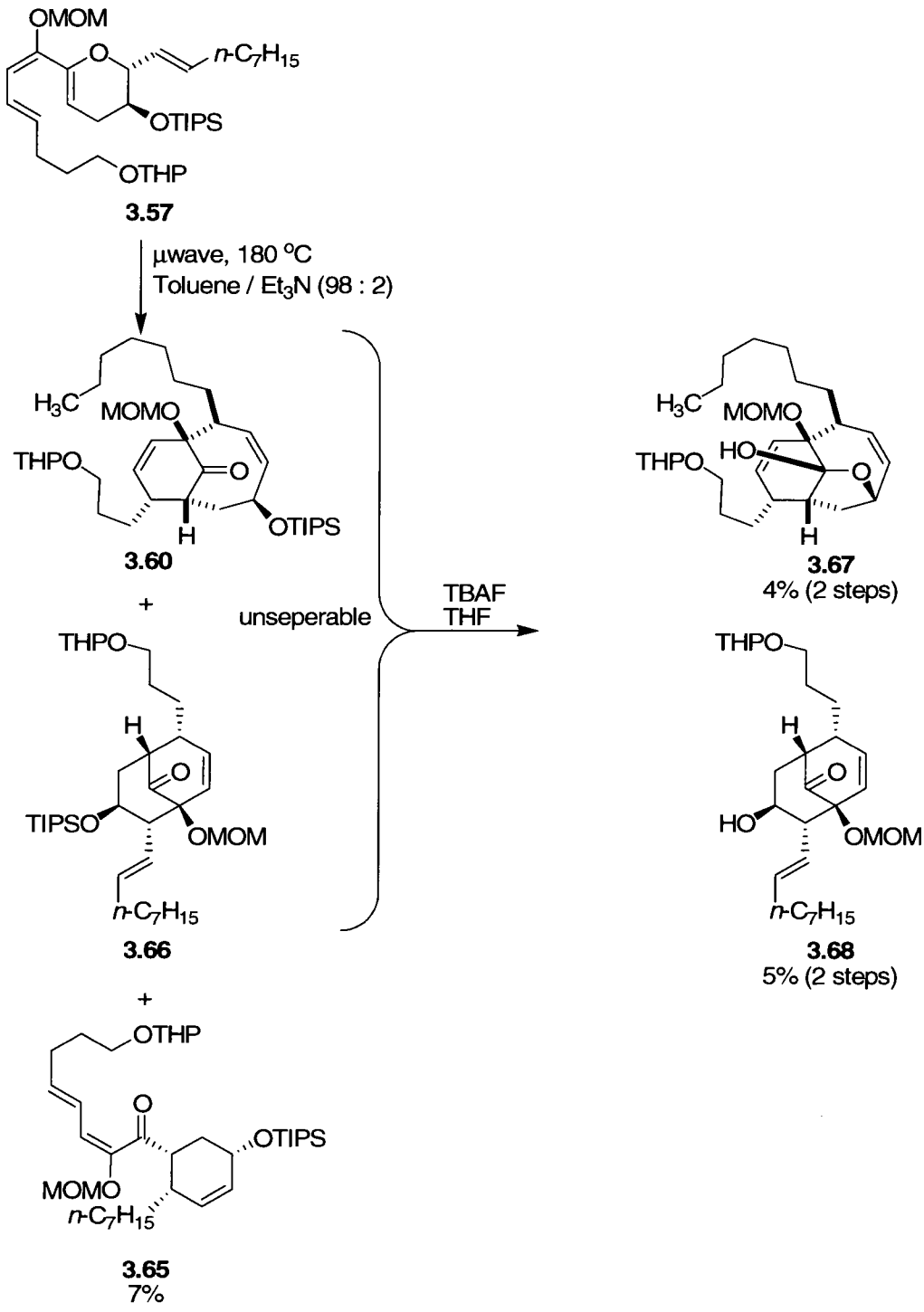
*Figure 3.6 Locking of the C1-C9 Bond in a s-*cis *Conformation by a Metal Tether*

The use of additives such as methyl benzoate, acetophenone and benzophenone, which could potentially serve as photosensitizers for this reaction, was also investigated. Once again their presence did not seem to have an effect on the outcome of the reaction. Moses and coworkers[45] have recently describe a photochemical 6π electrocyclization of a hexatriene as the key step of their synthesis of (±)-tridachiahydropyrone in methanol under direct sunlight. These conditions were reproduced with our triene (entry 14). Unfortunately, keeping true to the other reactions in methanol, no reaction was observed after 7 days. Finally, in a last attempt, thinking that a brighter light source might be necessary to drive the desired reaction, **3.57** was irradiated with a Hanovia high-pressure Hg-lamp for 11 hours (entry 15). By that time mostly decomposition was observed along with a small amount of starting material.

Results for the Thermal Key Step

Discouraged by our lack of success at promoting a light induced electrocyclization with triene **3.57** we decided to look at the completely thermal pathway (Scheme 3.12) which could

eventually lead to epi-deoxypenostatin F. When the triene was heated in the microwave at 180 °C in toluene for 1 hour, two new spots were visible by TLC along with some decomposition. The starting triene had also been completely consumed. Both spots were separated. From the proton NMR of the fractions obtained after chromatography, it was determined that the least polar spot corresponded to a single product (**3.65**) while the more polar spot corresponded to a mixture of two co-eluting products (**3.60** and **3.66**) in a ratio of 1.0 to 0.8. In order to separate them, the mixture was treated with TBAF in THF (Scheme 3.14) which afforded the separable hemiacetal **3.67** and alcohol **3.68**. These structures were confirmed by 2D NMR experiments (Figures 3.7 and 3.8). Product **3.67** must come from intermediate **3.60** after an acetalization following the removal of the TIPS protecting group. The formation of this product demonstrates that the desired thermal 6π electrocyclization does take place and is followed by a Claisen rearrangement, as predicted in Scheme 3.12 in albeit 4% after 2 steps. The low yield is once again in part due to the instability of the product on silica. An attempt to purify this product a second time on silica gel in the presence of triethylamine led to its complete decomposition.



Scheme 3.14 Products Arising from the Microwave Irradiation of Triene ***3.57***

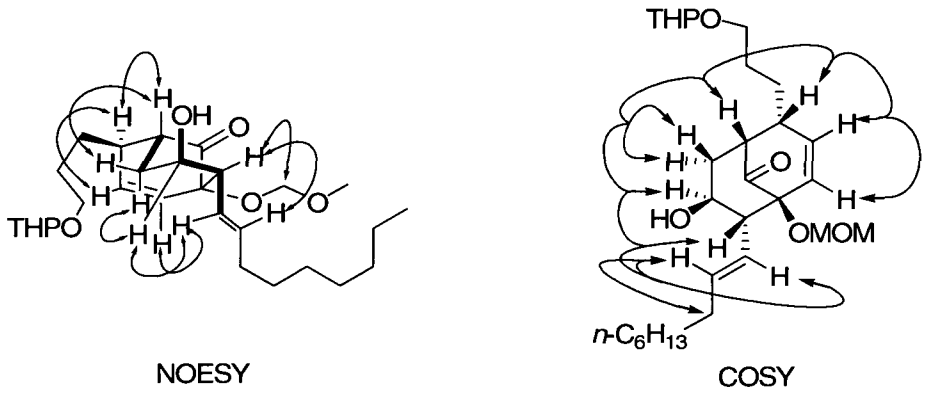


Figure 3.7 Structure Elucidation of ***3.68*** *by 2D NMR Experiments*

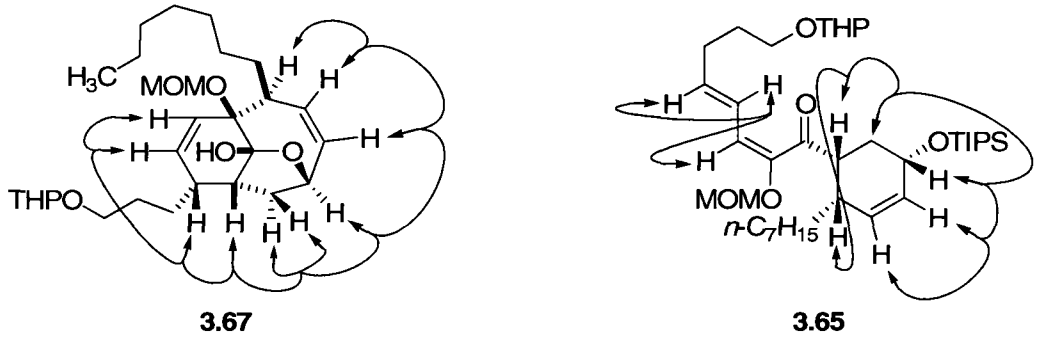


Figure 3.8 Structure Elucidation of ***3.67*** *and* ***3.65*** *by COSY Experiments*

Another obvious reason for the low yield of the desired product is the formation of byproducts. The presence of product **3.65** can be explained by an undesired Claisen rearrangement of the triene before the desired electrocyclization, as depicted in Figure 3.9. The other byproduct arising from this reaction is compound **3.66**. Its presence can be accounted for by a [1,3] rearrangement of the cyclized intermediate **3.59** (Figure 3.10). The analogous [1,3] rearrangement product that would arise from the other possible electrocyclization intermediate (**3.58**) was not observed. This could mean that either the electrocyclization is torquoselective and **3.58** is not formed, or, the transition state for the [1,3] rearrangement of this intermediate is too high in energy and does not occur. Either way, the formation of the observed byproducts is necessarily detrimental to the yield of the desired product. Avoiding their formation is therefore beneficial.

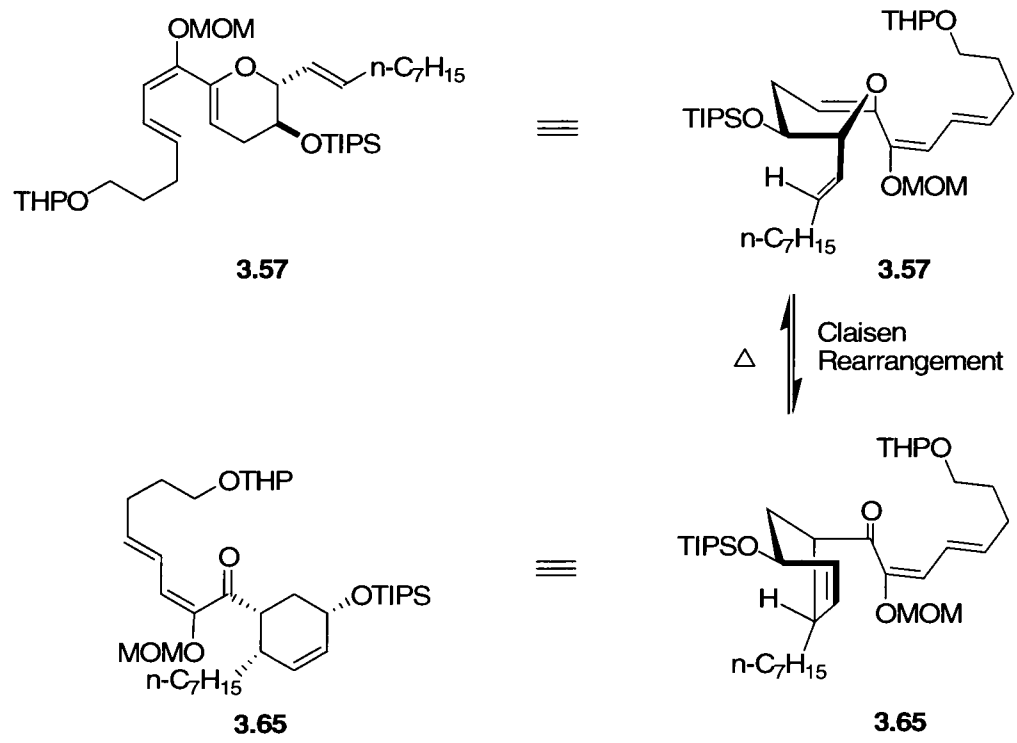


Figure 3.9 Undesired Claisen Rearrangement of Triene ***3.57***

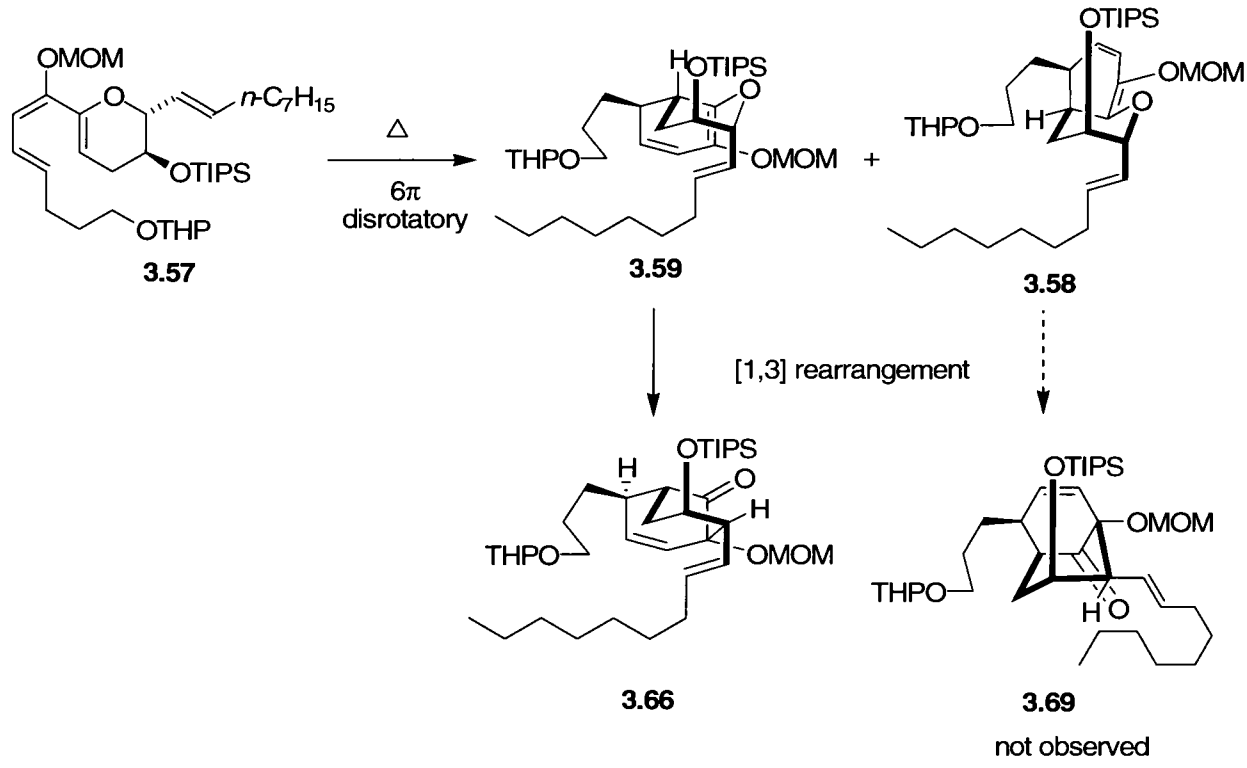


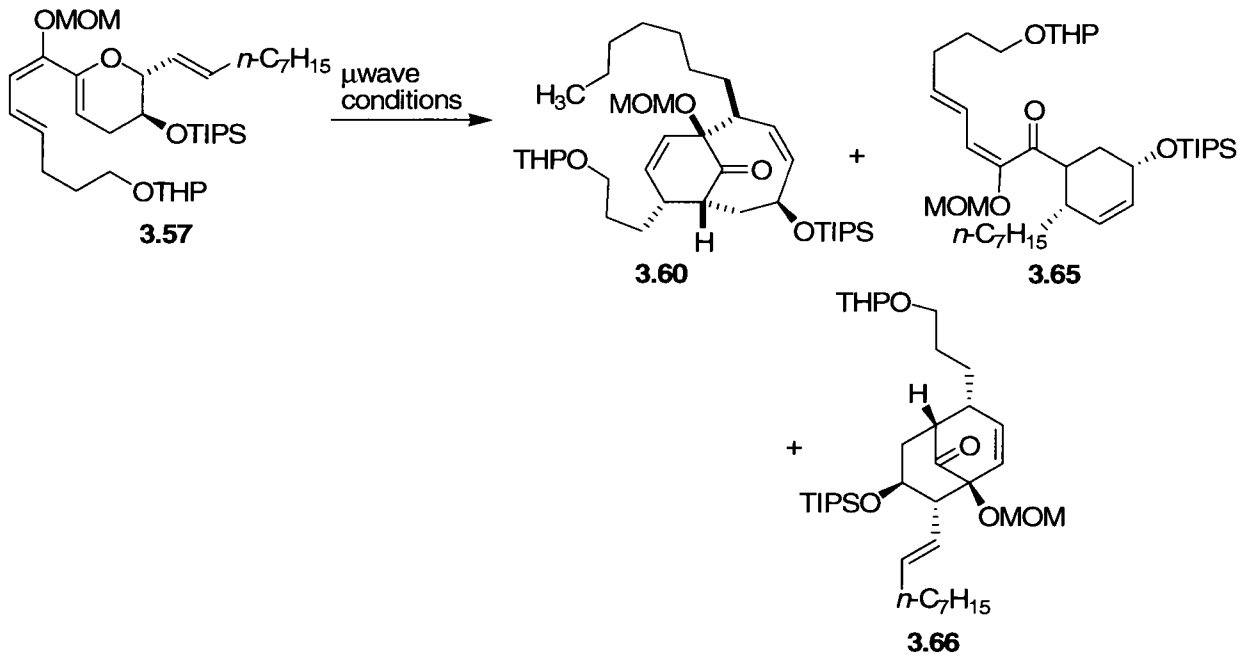
Figure 3.10 Undesired [1,3] Rearrangement Leading to ***3.66***

In an effort to increase the yield of the desired bicyclo[5.3.1]undecenone **3.60** produced from the thermal electrocyclization / Claisen rearrangement of triene **3.57**, optimization of the reaction conditions was investigated (Table 3.5). Due to the fact that the desired product could not be separated from **3.66** without removal of the silyl protecting group, and subsequently, purification could lead to various amounts of decomposition, we decided to look at the proton NMR of the unpurified reaction mixture after the key step. Doing so was also advantageous since the amount of triene available for this optimization was limited. Certain signals from the proton NMR of the mixture of **3.66** and **3.60** could clearly be attributed to one of the two compounds, indentifying them in the unpurified reaction mixture. Isolated signals belonging to each of the three compounds could be integrated and compared to the signal arising from the addition of a known amount of an internal standard (methyl 4-methylbenzoate). The yields of the three compounds were then calculated.

The conditions for the first entry of Table 3.5 are essentially the same conditions as those used in the first experiment when the products were isolated. The calculated yield of undesired Claisen rearrangement product is in good agreement with the isolated yield. Based on this, 12% of the desired product and a similar amount of the [1,3]-rearrangement product (**3.66**) were formed. We then looked at decreasing the temperature. After 5 hours at 140 °C in toluene, some starting material remained and a small increase in the calculated yield of the desired product (**3.60**) was noticed. What was more noticeable was the decrease in the formation of the other two byproducts, especially **3.66**.

At that point, we started investigating the use of more polar solvents (MeCN, MeOH) in the hopes that the polarity of the solvent might stabilize the dipole generated in the molecule as the oxygen substituents on C1 and C9 become aligned to adopt the s-*cis* conformation necessary for the electrocyclization (see Figure 3.6). However, results in acetonitrile were almost identical to those in toluene (entries 1 and 2 compared to entries 3 and 4 respectively). The use of chlorobenzene seemed to be detrimental to the yield of the desired product (entry 6). Once again, we started looking at the use of additives for the same reason as we did for our attempts at promoting a photochemical electrocyclization. This time, these reactions were run in acetonitrile to improve the solubility of the additives. Unfortunately, none of the additives tried increased the yield of the desired product. Magnesium bromide proved to be incompatible with this reaction as

Table 3.5 Thermal Key Step Optimization



Entry	Solvent	Temp (°C)	Time (h)	Additive (equiv.)	**3.60** (%)	**3.65** (%)	**3.66** (%)	**3.57** (%)
1[a]	PhMe	180	0.75	--	12	6	13	0
2[a]	PhMe	140	5	--	16	3	3	15
3	MeCN	180	0.75	--	12	9	9	0
4	MeCN	140	5	--	14	7	3	8
5	MeOH	160	1	--	16	10	8	0
6	PhCl	180	0.75	--	6	6	18	0
7	MeCN	180	0.75	$CaCO_3$ (3)	13	7	7	0
8	MeCN	180	0.75	$ZnBr_2$ (3)	7	1	11	0
9	MeCN	180	0.75	$MgBr_2$-OEt_2 (3)	0	0	0	0
10	MeCN	140	5	$MgBr_2$-OEt_2 (3)	0	11	0	4
11	MeCN	140	5	$PdCl_2$ (0.05)	12	4	0	34

Typical conditions: In a flame-dried microwave tube, the **3.57** was weighed and dissolved in the specified solvent (0.005 M) and triethylamine (1% of solvent volume) was added followed by the additive. A stream of argon was bubbled through the reaction mixture for 10 minutes then the

tube was sealed and the mixture was irradiated in the microwave for the specified amount of time at the corresponding temperature. [a] A carboflon was present in the reaction tube and the concentration of the S.M. was 0.01 M.

no desired product was observed in its presence. Finally, palladium chloride was tried (entry 11) to see if we could activate one or more of the double bonds, and possibly favor the desired reaction. This was not the case since a larger amount of starting material remained after 5 hours at 140 °C compared to when no palladium chloride was added. This result is somewhat strange since only 5 mol% of palladium chloride was present.

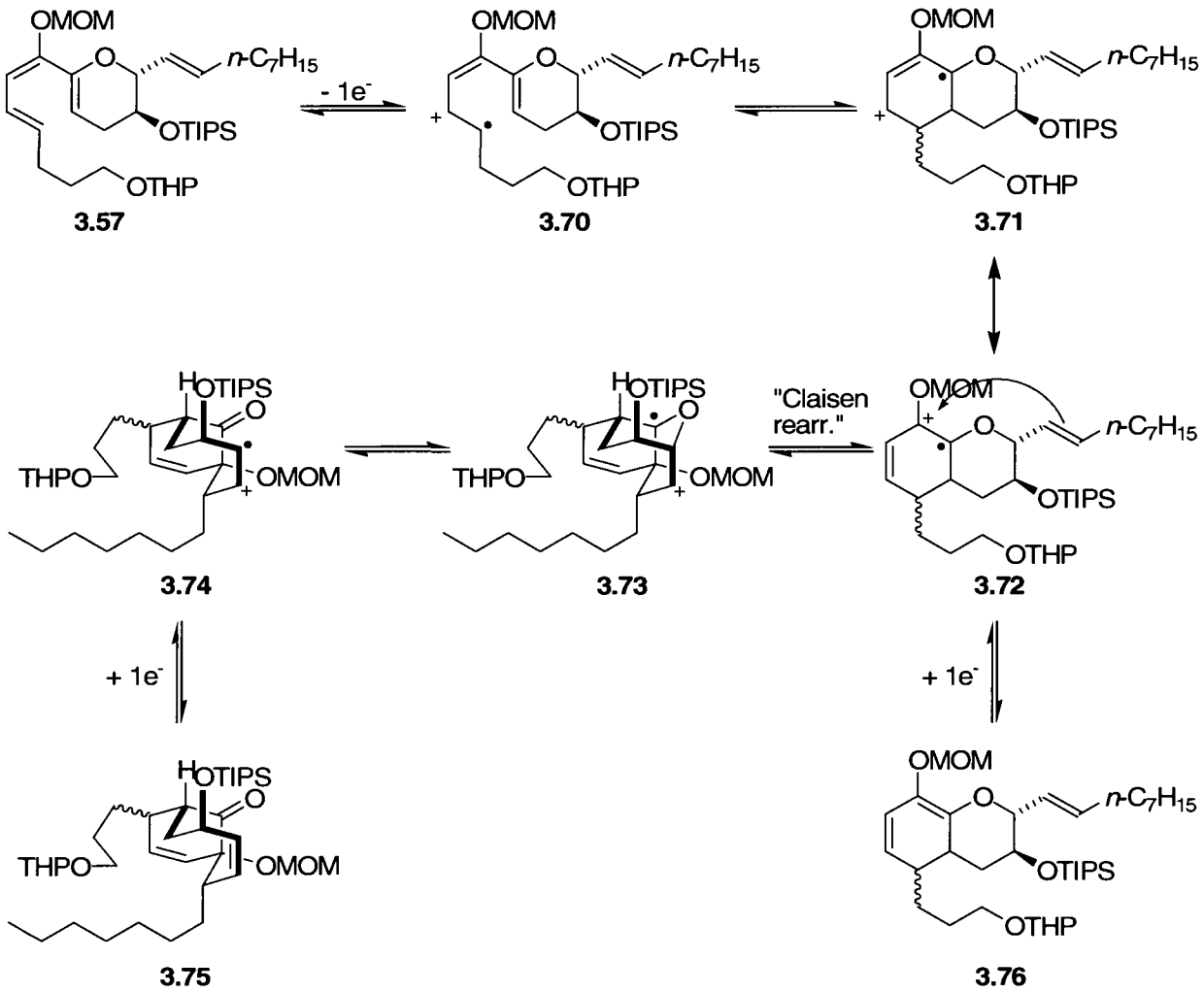
In summary, the best conditions found for the thermal key step are the use of toluene as solvent at 140 °C for 5 hours. The remaining starting material can be recovered and resubmitted to the reaction conditions. We noticed than leaving the reaction at that temperature for a longer period of time to convert all of the starting material leads to lower yields. This is probably due to product decomposition.

Single Electron Transfer

The low yield of the thermal key step combined with the instability of the desired desilylated product and the shortage of triene prevented us from proceeding towards the synthesis of epi-deoxypenostatin F. We decided instead to invest the remaining triene into finding better conditions to promote the electrocyclization / Claisen rearrangement key step. Since triene **3.57** is very electron rich, we believed that removing a single electron from it should be feasible (Scheme 3.15). By doing so, an intermediate such as **3.70** could be formed and provoke a cyclization through the participation of the dihydropyran double bond affording **3.71** which can be shown as its resonance structure **3.72**. At this point, **3.72** could recover the lost electron affording a formal electrocyclization product such as **3.76** which can be heated to promote a Claisen rearrangement. Another possibility is the participation of the olefin on the right hand side of the bicyclic intermediate **3.72** which could eventually lead to a formal Claisen rearrangement product (**3.75**) after the recapture of an electron.

Triarylaminium reagents are known to be effective single electron oxidants for cycloaddition reactions.[46] Photoredox catalysts such as $Ru(bpy)_3^{2+}$ are also known to abstract an

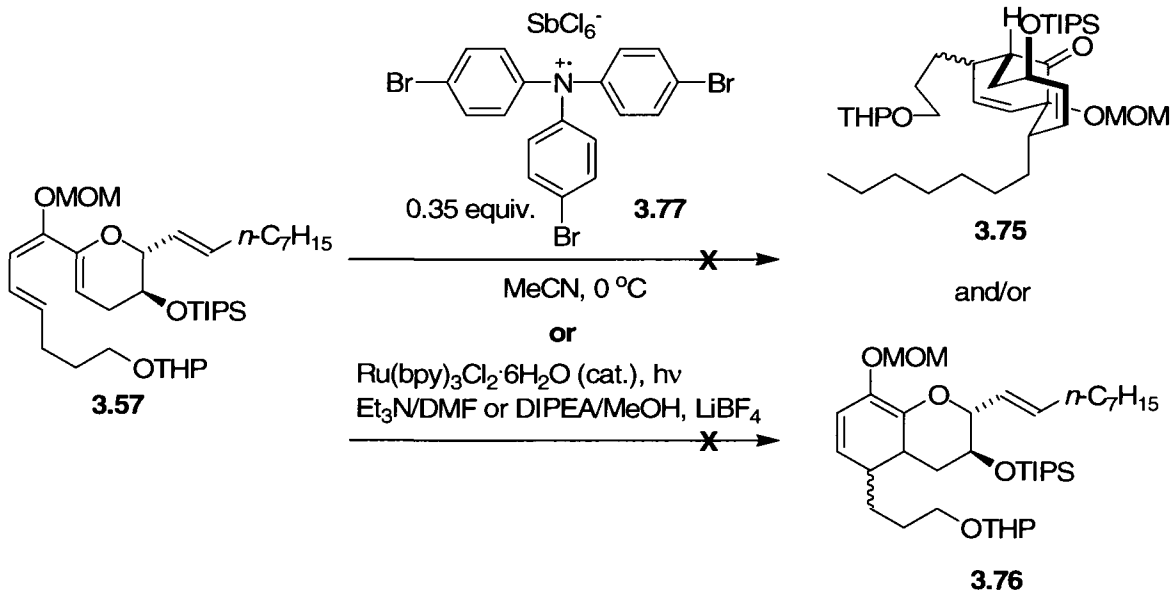
electron from electron rich systems when irradiated with light.[47] With this in mind, we decided to submit triene **3.57** to both types of reagents (Scheme 3.16). With triarylaminium **3.77** in acetonitrile at 0 °C, 15 minutes after the addition of the catalyst, no more starting triene could be observed by TLC analysis. Unfortunately, the proton NMR of the reaction mixture after aqueous work-up revealed a complex mixture in which no traces of the desired products were apparent.



*Scheme 3.15 Possible Single Electron Transfer Outcome with Triene **3.57***

When a solution of triene **3.57** in either DMF with triethylamine or methanol with diisopropyl ethylamine and lithium tetrafluoroborate, was irradiated with a 300 W lamp, in the presence of photoredox catalyst $Ru(bpy)_3Cl_2$-$6H_2O$, no reaction was apparent until the eventual

decomposition of the starting material over several days. Due to these results, further attempts to generate products **3.75** or **3.76** under single electron oxidation conditions were abandoned.



*Scheme 3.16 Reactions of Triene **3.57** with Single Electron Transfer Reagents*

Summary

In order to generate an enol triflate cross-coupling partner, the location of the oxygen substituent on the precursor lactone had to be displaced by one position relative to its position on the previous lactone (**1.40**). Doing so enabled the construction of our first model study triene (**3.15**). This triene successfully underwent a tandem thermal 6π electrocyclization / Claisen rearrangement to prove that this strategy was viable for the construction of the bicyclo[5.3.1]undecenone core of penostatin F. Subsequently, a functionalized triene was constructed that could lead to deoxypenostatin F through a photochemical 6π electrocyclization / Claisen rearrangement key step. Unfortunately, conditions allowing a successful photo-induced electrocyclization were not found. However, a thermal tandem 6π electrocyclization / Claisen rearrangement did lead to the formation of the bicyclo[5.3.1]undecenone unit which could allow

for the synthesis of epi-deoxypenostatin F. Some optimization of the thermal key step was performed but the best calculated yield (16%) is still less than ideal. The formation of either a formal electrocyclization product or a formal Claisen rearrangement product through a single electron redox processes was investigated as an alternative but failed to deliver any useful compound.

4

General Conclusion

Summary

The hydroxy-directed Diels-Alder / Claisen strategy previously developed in our laboratory[8] efficiently allowed the construction of the tricyclic core of penostatin F. However it presented certain challenges that could not be surmounted which prevented the completion of the total synthesis of the natural product. Such hurdles include the absence of the hydroxyl group on C5, the stereochemistry of C7 and the installation of the double bond in the six-membered ring between C2 and C3. In order to address these problems, a new strategy was elaborated where the Claisen rearrangement was retained but the Diels-Alder portion was substituted by a cross-coupling reaction and a 6π electrocyclization.

After some time and effort, it was determined that the lactone employed by Pat Ang and Roch Lavigne for the construction of their key step precursor was inappropriate for the formation of an enol triflate cross-coupling partner. Changing the position of the hydroxyl substituent in the ring successfully enabled the synthesis of the desired triflate. A Suzuki-Miyaura cross-coupling reaction between this enol triflate and an appropriate alkoxydienyl boronic ester provided a simplified model triene on which the key step was tested. This model study allowed us to determine that a tandem thermal 6π electrocyclization followed by a Claisen rearrangement was a viable approach to the construction of the desired bicyclo[5.3.1]undecenone core of penostatin F.

Following this, the synthesis of a more elaborate triene which could lead to deoxypenostatin F was achieved. It was determined that a photochemical 6π electrocyclization was necessary to initiate the key step in order to obtain the desired stereochemistry at C7.

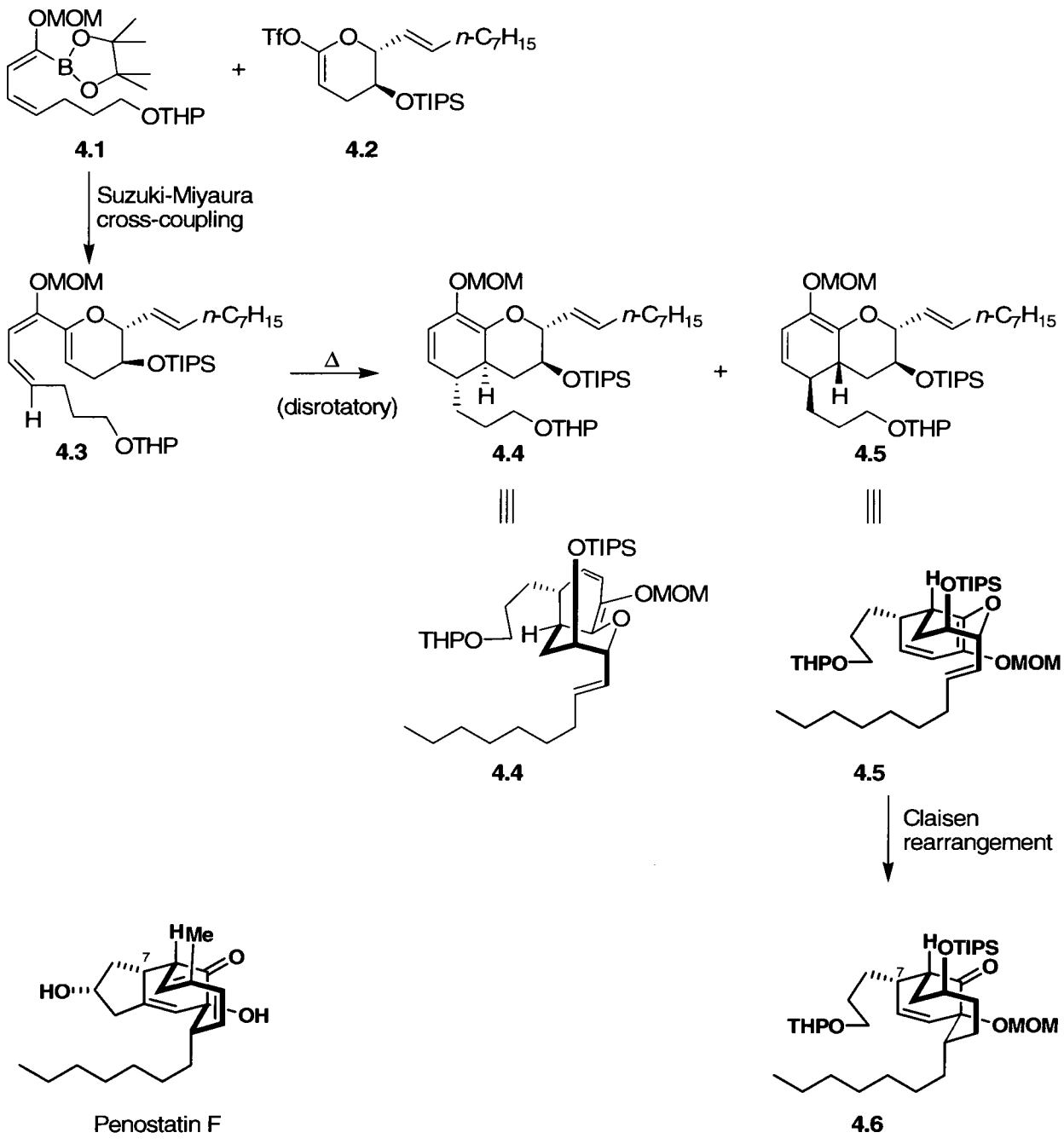
Unfortunately, after many attempts, no photochemical electrocyclization product was observed after the irradiation of the triene with light under various conditions. On the other hand, the completely thermal key step did allow the formation of an intermediate possessing a bicyclo[5.3.1]undecenone core structure which could lead to epi-deoxypenostatin F.

The work outlined in this thesis has allowed to solve one of the major problems associated with the previous strategy towards penostatin F, which is the installation of the double bond between C2 and C3 of the bicyclo[5.3.1]undecenone core. This is an important contribution since solutions to the other two problems, which are the installation of a hydroxyl group on C5 and the proper stereochemical configuration at C7, are conceivable and discussed below.

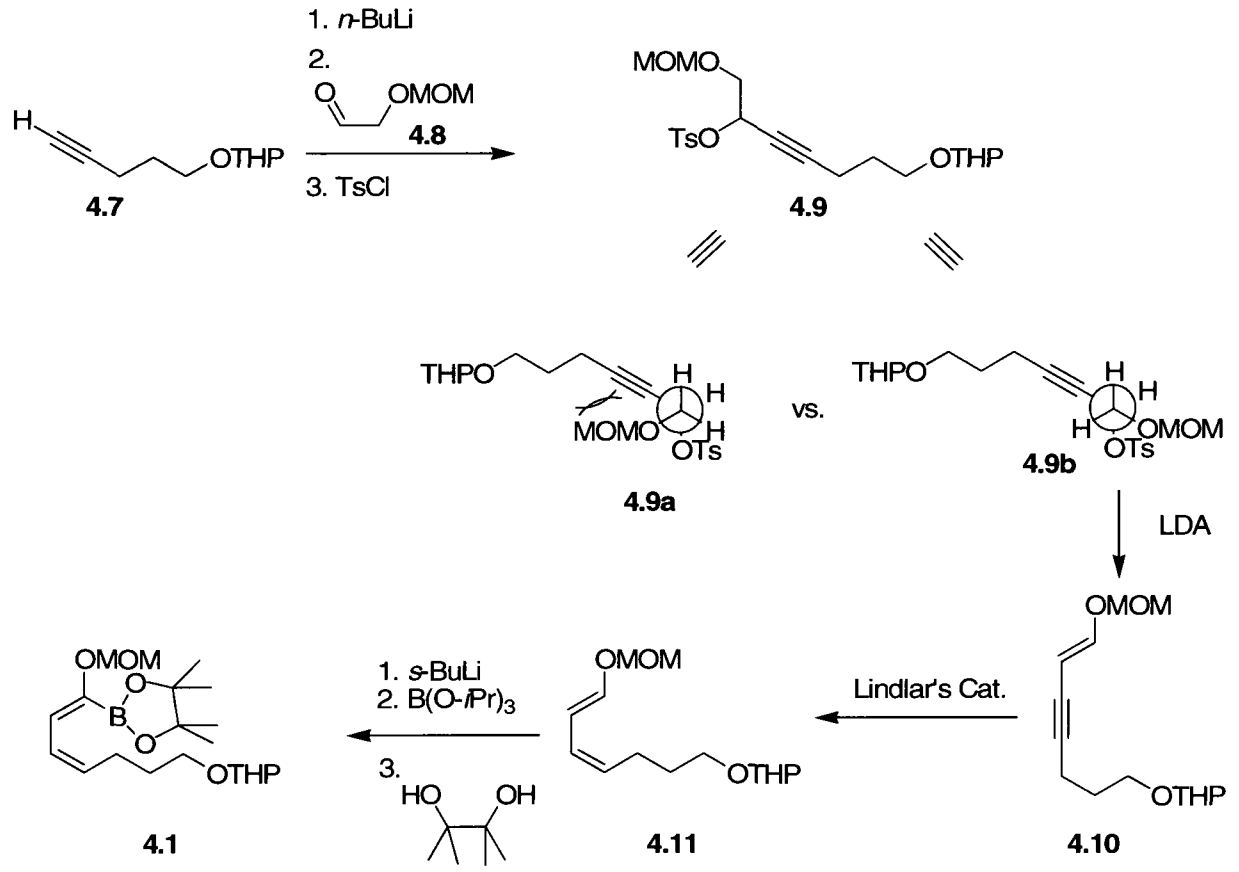
Outlook

In order to obtain the proper stereochemistry at C7 of Penostatin F, two solutions are possible. The first would be the construction of an alkoxydienyl boronic ester with a *E,Z*-configuration of the diene fragment such as **4.1**. After an analogous Suzuki-Miyaura coupling reaction to the one previously performed, triene **4.3** would be obtained. Heating this triene would afford the disrotatory electrocyclization isomers **4.4** and **4.5**. Once again, only one of the two can undergo the Claisen rearrangement (**4.5**) whereas the other (**4.4**) can reopen to the starting triene. Now, the Claisen rearranged product **4.6** has the desired stereochemistry at C7, avoiding a photochemical 6π electrocyclization (Scheme 4.1).

The construction of a boronic ester such as **4.1** is proposed in Scheme 4.2. Alkyne **4.7** could be deprotonated and treated with an aldehyde such as **4.8** generating the corresponding alkoxide which could then be trapped with tosyl chloride. Elimination of the tosylate of **4.9** should be preferred on conformer **4.9b** in order to relieve steric strain, leading to the *trans*-enyne **4.10**. Hydrogenation of this compound using Lindlar's catalyst would then afford the *E,Z*-diene **4.11**. Treatment of this diene with *s*-BuLi followed by boron triisopropoxide and pinacol should produce the desired boronic ester in the same way as the previous one.



Scheme 4.1 Proposed Solution to the Stereochemistry Problem at C7 through a New Boronic Ester

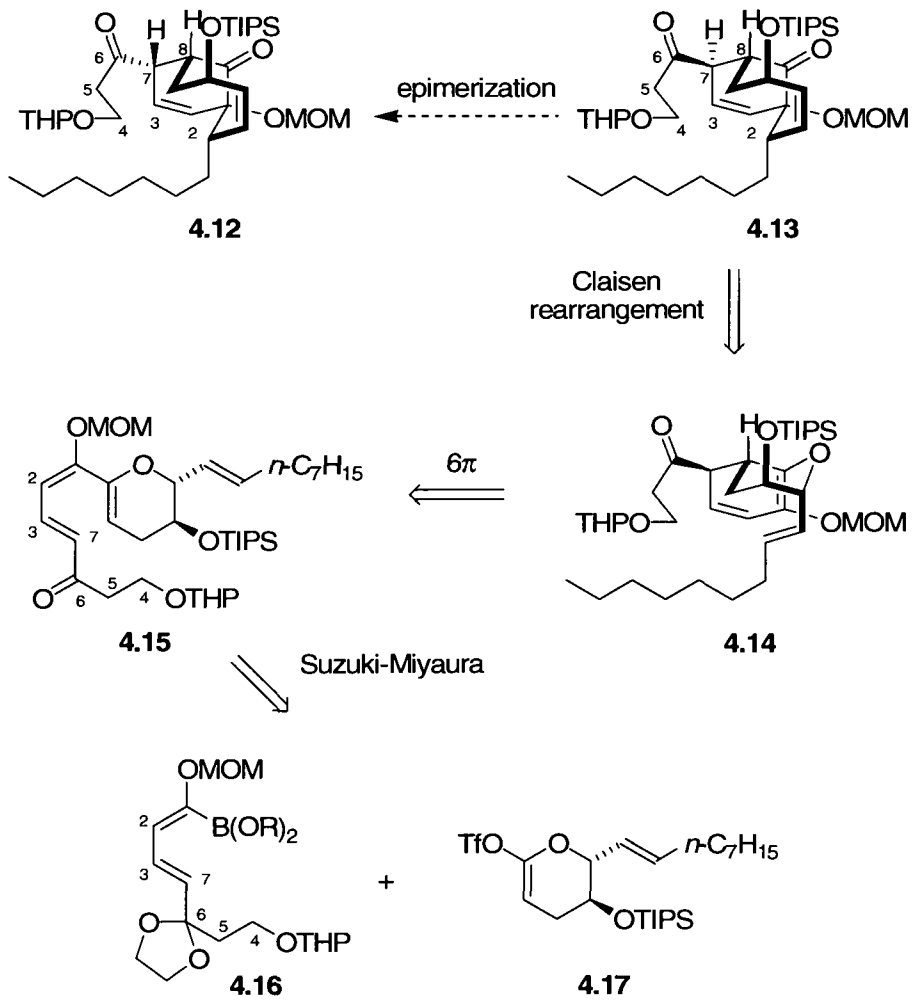


*Scheme 4.2 Proposed Synthesis of Boronic Ester **4.1***

Should the formation of the proposed boronic ester **4.1** or the steps ensuing not work, a second possibility for obtaining the correct stereochemistry at C7 would be through an epimerization step at some point after the Claisen rearrangement. To do so, an appropriate functional group next to C7 would be necessary to permit such an epimerization. It is conceivable that a carbonyl on C6 could allow the desired transformation. We predict that the desired epimer should be thermodynamically preferred since the alkyl substituents on C7 and C8 are further apart (Scheme 4.3). Although an epimerization of this center has been attempted on the tricyclic core arising from the previous hydroxy-directed Diels-Alder / Claisen strategy, it may be feasible on a substrate where the five-membered ring is absent. Also, an interesting aspect of this strategy is that the carbonyl on C6 can serve as a handle to introduce the hydroxyl at C5 of Penostatin F.

The necessary epimerization precursor **4.13** would have to come from a Claisen rearrangement of **4.14** which in turn arises from the thermal 6π electrocyclization of **4.15**. Finally, triene **4.15** could be obtained from the cross-coupling of enol triflate **4.17** and boronic ester **4.16**.

The proposed solutions could allow us to solve the stereochemistry problem at C7 and eventually lead us to the completion of the total synthesis of penostatin F.



Scheme 4.3 Epimerization at C7 Strategy

Claims to Original Research

1. Successfully obtained the bicyclo[5.3.1]undecenone core of penostatin F from a simplified triene through a tandem thermal 6π electrocyclization / Claisen rearrangement.
2. Investigated a photochemical 6π electrocyclization of a functionalized triene in order to obtain the proper stereochemistry at C7 of penostatin F.
3. Successfully obtained a functionalized bicyclo[5.3.1]undecenone through a tandem thermal 6π electrocyclization / Claisen rearrangement which could possibly lead to epi-deoxypenostatin F.

Poster and Oral Presentations

Beaulieu, E.; Barriault, L. "Studies Towards the Total Synthesis of Penostatin F"

1. Poster presentation, presented at *Synthesis Day* in June 2007 at the University of Ottawa, Ontario, Canada.
2. Oral presentation, presented at the *Québec-Ontario Mini Symposium of Bioorganic and Organic Chemistry (QOMSBOC)* in November 2007 at l'Université de Montréal, Québec, Canada.
3. Poster presentation, presented at *Synthesis Day* in June 2007 at the University of Ottawa, Ontario, Canada.

5

Experimental

General Experimental

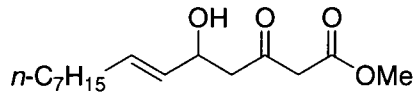
All reactions were performed under an argon atmosphere in flame-dried glassware equipped with a magnetic stirbar and a rubber septum unless otherwise indicated. Solvents used were freshly distilled prior to use: ether, THF and 1,2-dimethoxyethane (DME) over sodium and benzophenone; dichloromethane, toluene and DMF over calcium hydride. All other commercial reagents were used without purification.

Reactions were monitored by TLC analysis using glass plates precoated (250 μm thickness) with silica gel 60 F_{254} (E. Merck). TLC plates were viewed using UV light, *para*-anisaldehyde staining solution or potassium permanganate staining solution. Flash chromatography was carried out on 230-400 mesh silica gel 60.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz, Bruker Avance 400 MHz, Bruker Avance 500 MHz or Varian INOVA 500 MHz spectrometers in the specified deuterated solvent. IR spectra were recorded on a Bomen Michaelson 100 FT-IR spectrometer. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer, and melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.

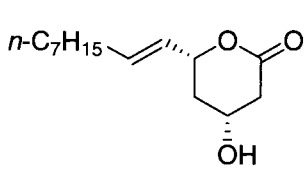
Experimental Procedures, Characterization and Spectra

5-Hydroxy-3-oxo-tetradec-6-enoic acid methyl ester ((±)1.37)



To a suspension of sodium hydride (60% in mineral oil, 9.49 g, 0.237 mol) cooled to 0° C was added methylacetoacetate (17.1 mL, 0.158 mol) dropwise (evolution of gas was observed). Once the addition was complete, the mixture was stirred 30 minutes at 0 °C then cooled to -78 °C. *n*-BuLi (1.92 M in Hexanes, 90.6 mL, 0.174 mol) was added dropwise along the inside wall of the flask over 1 hour. The resulting yellow solution was allowed to stir for 2 hours at -78 °C before neat *trans*-2-decenal (14.5 mL, 0.079 mol) was added dropwise. After 1 hour at -78 °C, TLC analysis showed no presence of the aldehyde. The reaction was therefore quenched at this temperature by the slow addition of a saturated aqueous solution of ammonium chloride. Upon warming to room temperature, diethyl ether was added and the layers were separated. The aqueous layer was completely neutralized as indicated by pH paper with concentrated HCl. It was then extracted 3 times with diethyl ether. The combined organic extracts were washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography using a gradient elution from 100% hexanes to 30% ethyl acetate 70% hexanes to afford **(±)1.37** (16.3 g, 76%) as a light yellow oil. ^{1}H NMR spectrum was in agreement with the previously reported data.[8]

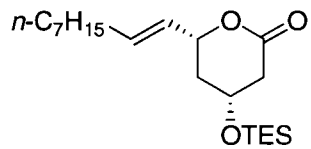
4-Hydroxy-6-non-1-enyl-tetrahydro-pyran-2-one ((±)1.39)



To a mixture of acetic acid (20 mL) and acetonitrile (20 mL) cooled to 0 °C was added tetramethylammonium borohydride (2.58 g, 29.0 mmol) slowly (evolution of gas was observed). The resulting mixture was stirred at this temperature for 20 minutes then cooled to -78 °C, at which time a solution of **(±)1.37** (1.96 g, 7.26 mmol) in 3 mL of acetic acid and 3 mL of acetonitrile was added dropwise to the frozen mixture via syringe. The flask containing the reaction mixture was then placed in a refrigerator set to -25 °C and left there for 24 hours with occasional swirling. At this time, no more starting material was apparent by TLC analysis. The mixture was quenched while still at -25 °C by the addition of 60 mL of a 0.5 N aqueous solution of potassium sodium tartrate. The resulting solution was allowed to warm to room temperature

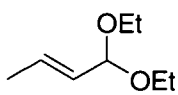
then diluted with DCM. A saturated aqueous solution of sodium bicarbonate was added and the layers were separated. The organic layer was washed consecutively with two more portions of the sodium bicarbonate solution. The combined aqueous layers were extracted twice with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness. The resulting oil was dissolved in DCM (60 mL) and trifluoroacetic acid (0.10 ml, 1.3 mmol) was added at room temperature. After 48 hours, solid potassium carbonate was added until the mixture was no longer acidic, as indicated by pH paper. $MgSO_4$ was added and the solid material was filtered out. The mixture was concentrated to dryness and the resulting residue was purified by flash column chromatography using a gradient elution from 20% ethyl acetate 80% hexanes to 60% ethyl acetate 40% hexanes to afford 784 mg of the desired lactone. Remaining diol was also isolated and resubmitted to the lactonization conditions to afford another 555 mg of product (1.34 g total, 77%) as a colorless oil. ^{1}H NMR spectrum was in good accordance with that of the previously reported product.[8]

6-Non-1-enyl-4-triethylsilanyloxy-tetrahydro-pyran-2-one ((±)1.40)



To a solution of **(±)1.39** (780 mg, 3.25 mmol) in THF (30 mL) at room temperature was added triethylamine (1.81 mL, 13.0 mmol), 4-dimethylaminopyridine (39.6 mg, 0.325 mmol) and chlorotriethylsilane (1.63 mL, 9.74 mmol). A white precipitate was formed and the reaction was stirred for 16 hours at room temperature. It was then quenched by the addition of a saturated aqueous solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with two more portion of diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography using a gradient elution from 10% hexanes to 15% EtOAc and 85% hexanes, afforded **(±) 1.40** as a colorless oil (0.909 g, 79%). ^{1}H NMR was in accordance with that of the previously reported compound.[8]

Crotonaldehyde diethyl acetal (2.12)

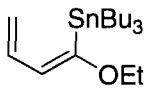


Procedure adapted from Karimi and coworkers[19]

To a solution of crotonaldehyde (2.00 mL, 24.1 mmol) and triethyl orthoformate

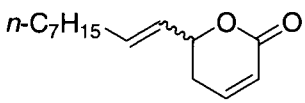
(4.22 mL, 25.3 mmol) in absolute ethanol at room temperature was added N-bromosuccinimide (43 mg, 0.24 mmol). The mixture was stirred at room temperature for 30 minutes then sodium sulfate was added and filtered out. To the filtrate was added solid sodium carbonate and the product was fractionally distilled through a Vigreux column to afford 2.04 g (59%) of acetal **2.12** as a colorless liquid with a sweet odor (bp = 146-150 °C at 1 atm). ^{1}H NMR spectrum was in accordance to that of the previously reported compound.[48]

(*Z*)-1-(Tri-*n*-butylstannyl)-1-ethoxybuta-1,3-diene (2.9)



To a solution of freshly sublimed potassium *tert*-butoxide (312 mg, 2.78 mmol) in THF cooled to -95 °C (acetone / liquid nitrogen slush bath) was added a solution of acetal **2.12** (160 mg, 1.11 mmol) in 1.5 mL of THF dropwise via syringe followed by *n*-butyllithium (1.89 M in pentane, 1.47 mL, 2.78 mmol). The solution became dark red and was stirred for 2 hours at -95 °C at which time neat chlorotributyltin was added and the resulting mixture was stirred for another 2 hours at -95 °C. The reaction was then quenched at the same temperature by the slow addition of a 1 : 1 aqueous solution of THF. Upon warming to room temperature, diethyl ether was added and the layers were separated. The aqueous layer was extracted with two more portions of diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and filtered. Flash column chromatography on silica gel pretreated with Et_3N using hexanes as eluent afforded pure stannane **2.9** as a colorless oil (65 mg, 15%). Spectral data was in accord with that previously reported.[18a]

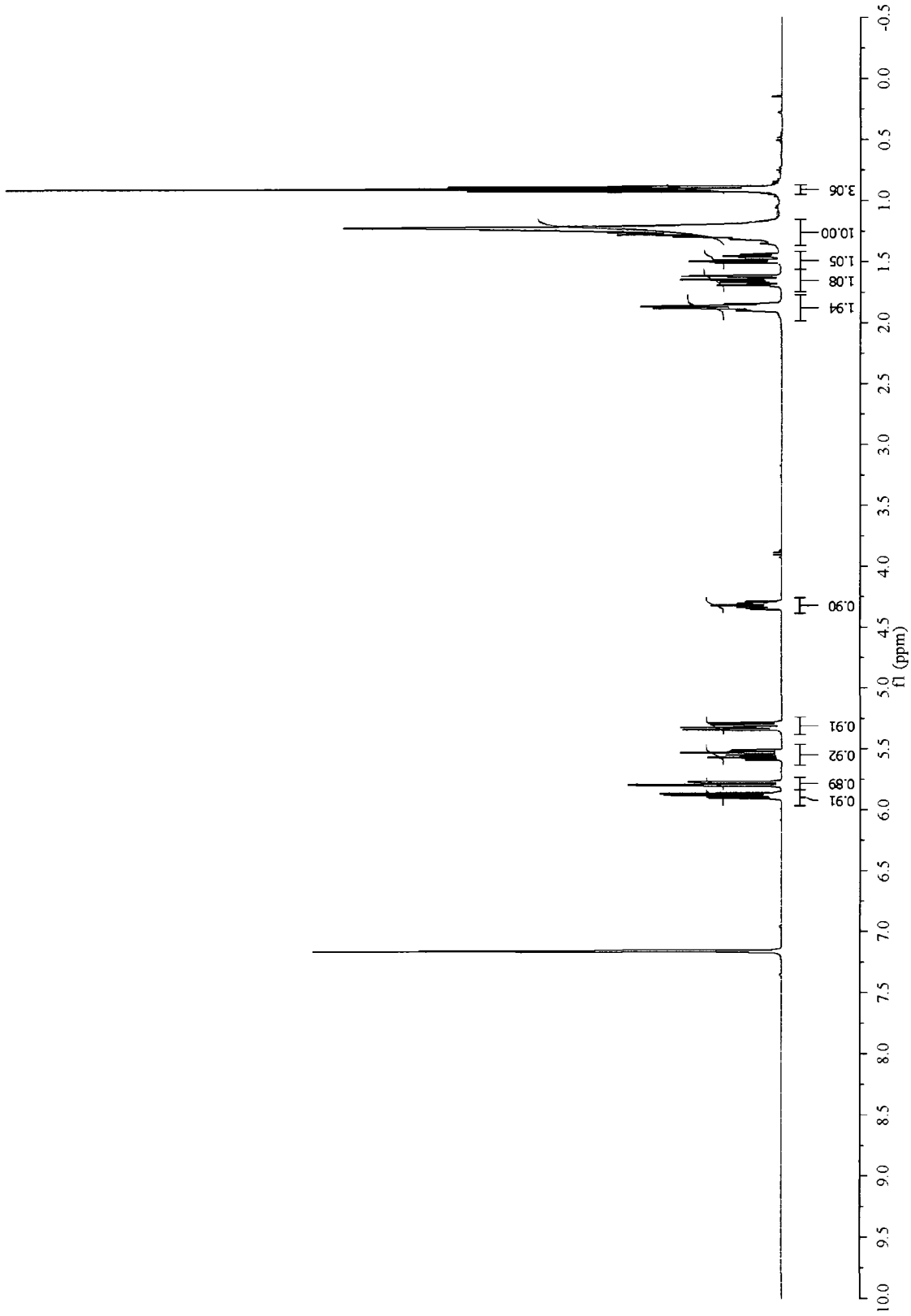
5,6-dihydro-6-(non-1-enyl)pyran-2-one ((±)2.13)



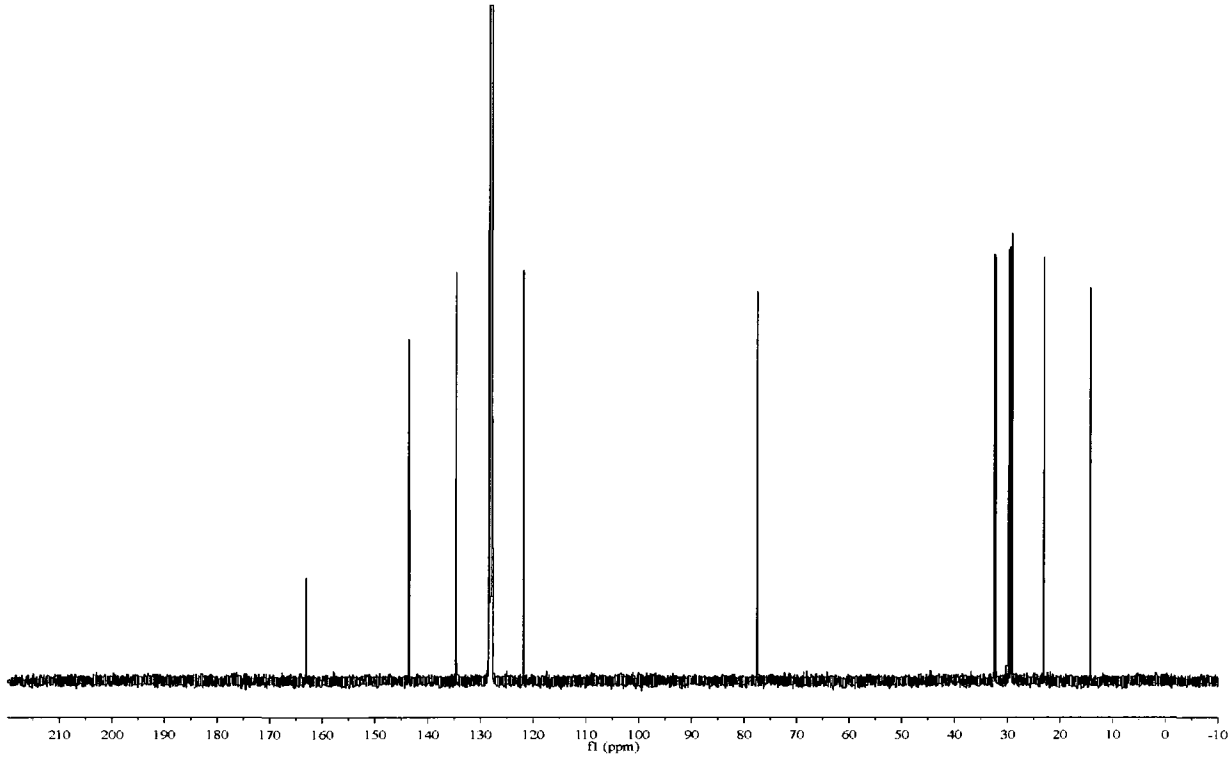
To a solution of lactone (±)**1.40** (100 mg, 0.282 mmol) in THF (2.5 mL) at the specified temperature was added a freshly prepared solution of LDA (367μL (1.0 M), 0.367 mmol) dropwise. The mixture was stirred at -78°C for 30 minutes then the reaction was quenched by the addition of D_2O. Ether was added and the layers were separated. The aqueous layer was extracted 3 times with ether and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was purified by flash chromatography on silica gel using a gradient elution (5% to 20% EtOAc in Hexanes) to afford 25 mg of the starting lactone (25%) and the elimination product (29 mg, 46%) as a colorless oil. ^{1}H NMR (400 MHz, benzene D_6): δ 5.88 (ddd, J = 9.7, 5.6, 2.6 Hz, 1H), 5.79

(ddd, J = 9.8, 2.4, 1.0 Hz, 1H), 5.56 (dtd, J = 15.4, 6.8, 1.1 Hz, 1H), 5.32 (ddt, J = 15.4, 6.5, 1.4 Hz, 1H), 4.32 (ddddd, J = 10.9, 5.9, 4.1, 1.6, 0.7 Hz, 1H), 1.88 (dt, J = 6.9, 6.9 Hz, 2H), 1.65 (dddd, J = 18.2, 10.9, 2.5, 2.5 Hz, 1H), 1.47 (dddd, J = 18.2, 5.5, 4.1, 1.0 Hz, 1H), 1.35 – 1.18 (m, 10H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 163.1 (C), 143.6 (CH), 134.7 (CH), 127.5 (CH), 121.9 (CH), 77.6 (CH), 32.5 (CH_2), 32.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 23.1 (CH_2), 14.3 (CH_3); IR (neat): υmax 2956 (s), 2926 (s), 2855 (s), 1733 (s), 1467 (m), 1421 (w), 1383 (s), 1245 (s), 1149 (w), 1058 (m), 1019 (m), 969 (m), 916 (w), 870 (w), 817 (s), 724 (w), 662 (w); HRMS (EI) *m/z* M^+ ($C_{14}H_{22}O_2$) calculated 222.1614, found 222.1549.

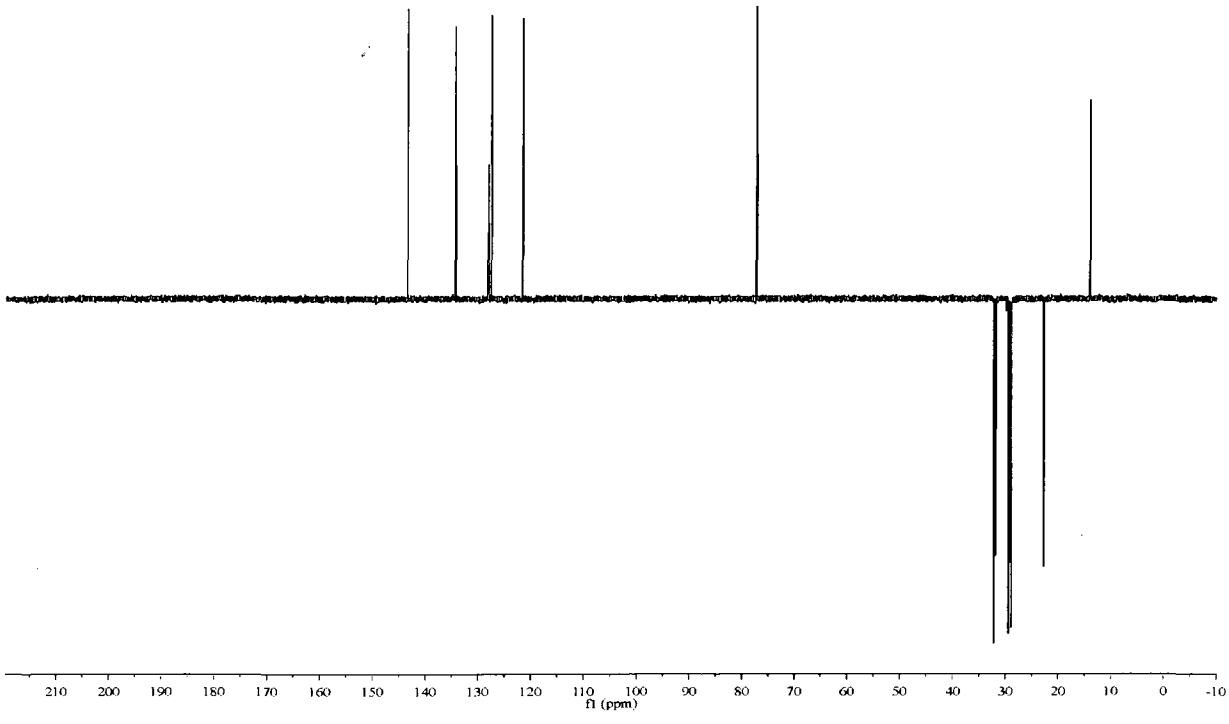
^{1}H NMR (400 MHz, C_6D_6)



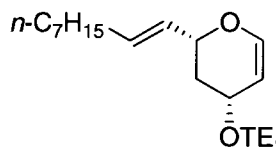
^{13}C NMR(100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)

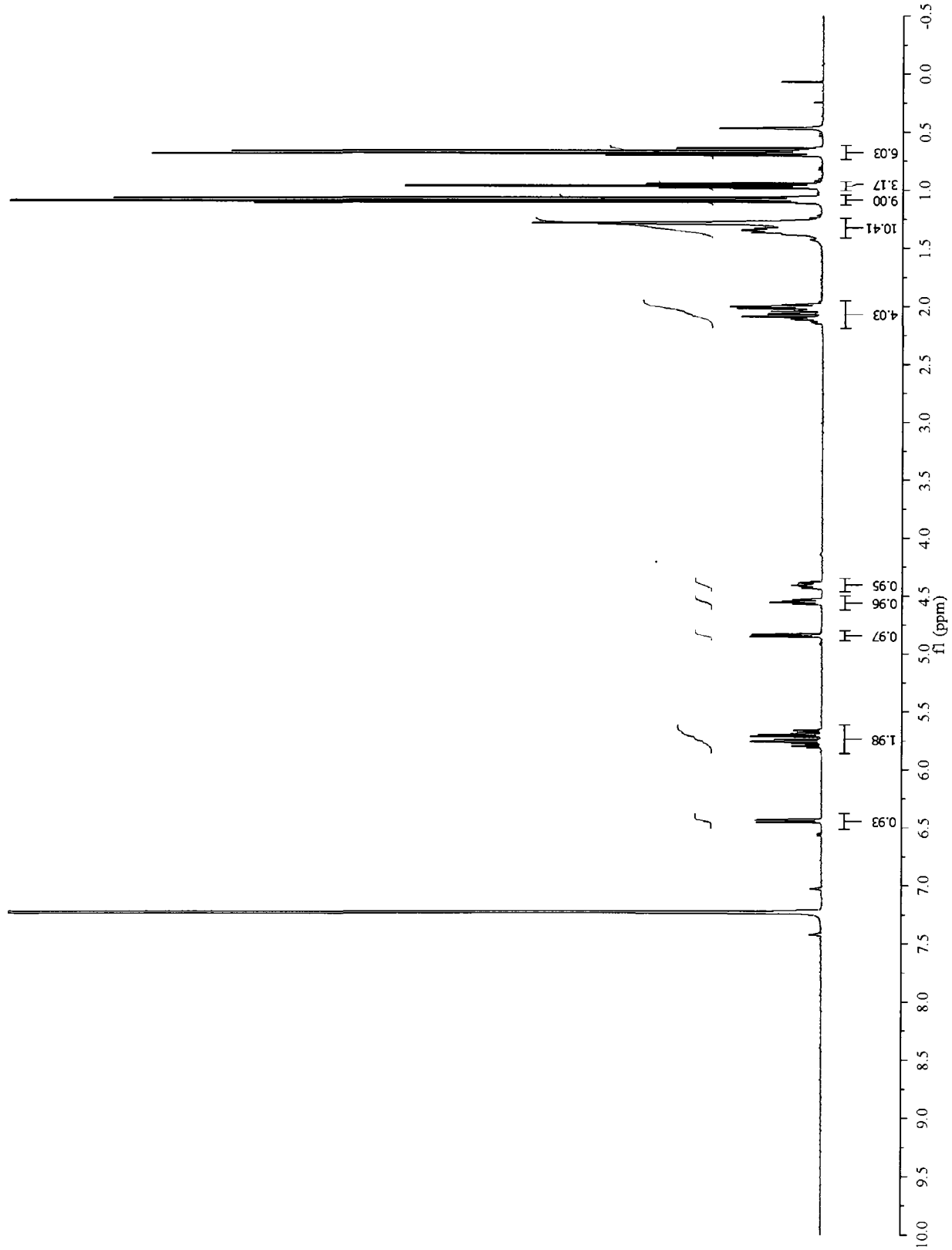


3,4-Dihydro-2-((*E*)-non-1-enyl)-2*H*-pyran-4-yloxy)triethylsilane ((±)2.19)

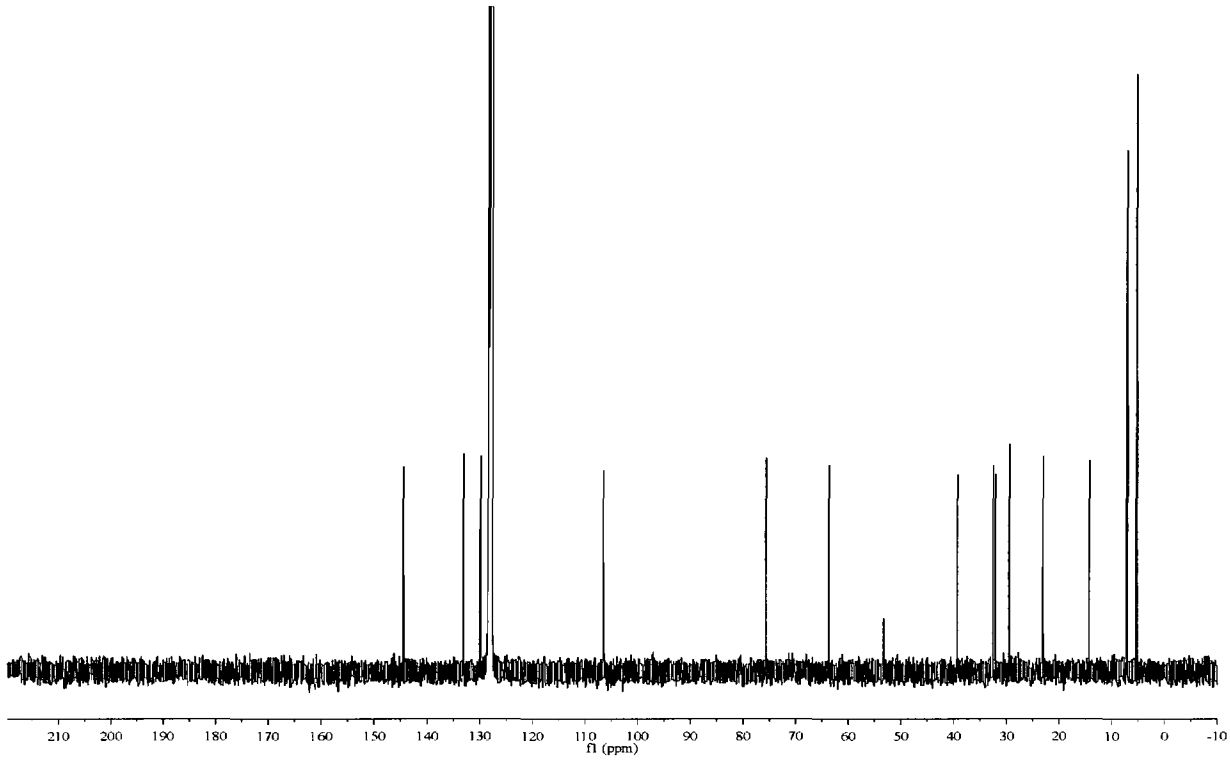


To a solution of **(±)1.40** (152 mg, 0.429 mmol) in DCM (3 mL) at -78 °C was added a solution of diisobutylaluminum hydride (1 M in DCM, 2.15 mL, 2.15 mmol) dropwise. The mixture was stirred at -78 °C for 30 minutes at which time the reaction was complete as indicated by TLC. The reaction was quenched by slow addition of a saturated aqueous solution of potassium sodium tartrate at -78 °C. The mixture was then allowed to warm to room temperature and ethyl acetate was added. The resulting gel was filtered on a pad of celite which was flushed with ethyl acetate. Water was added to the filtrate and the layers were separated. The aqueous layer was extracted with ethyl acetate two more times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was filtered through a plug of silica pretreated with Et_3N using a mixture of 3% ethyl acetate and 97% DCM as eluent. This material was then concentrated to dryness (122 mg) and dissolved in DCM (2 mL). Et_3N (0.17 ml, 1.2 mmol) was added to the solution followed by methanesulfonyl chloride (80 µL, 1.0 mmol) (freshly distilled over calcium hydride) at room temperature. After 3 hours of stirring, DBU (154 µL, 1.03 mmol) was added and the yellow solution was stirred for another hour at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel pretreated with Et_3N using hexanes as eluent to afford glycal **(±)2.19** as a light yellow oil (43.6 mg, 30% from **(±)1.40**). ^1H NMR (400 MHz, benzene D_6): δ 6.38 (dd, J = 6.3, 1.1 Hz, 1H), 5.75 – 5.59 (m, 2H), 4.78 (ddd, J = 6.3, 1.9, 1.9 Hz, 1H), 4.49 (dddd, J = 8.8, 6.6, 2.0, 1.6 Hz, 1H), 4.35 (ddd, J = 10.0, 6.4, 2.8 Hz, 1H), 2.08 – 1.92 (m, 4H), 1.36 – 1.22 (m, 10H), 1.02 (t, J = 7.9 Hz, 9H), 0.90 (t, J = 7.0 Hz, 3H), 0.60 (q, J = 7.9 Hz); ^{13}C NMR (100 MHz, benzene D_6): δ 144.6 (CH), 133.1 (CH), 130.0 (CH), 106.6 (CH), 75.7 (CH), 63.7 (CH), 39.3 (CH_2) 32.6 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2) 23.1 (CH_2), 14.3 (CH_3), 7.2 (CH_3 (3C)), 5.4 (CH_2 (3C)); IR (neat) 2956 (s), 2925 (s), 2878 (m), 2858 (m), 1637 (m), 1461 (w), 1230 (m) 1121 (m), 1078 (s), 1007 (m), 964 (w), 890 (w), 831(w)722 (m); HRMS (EI) *m/z* M^+ ($C_{20}H_{38}O_2Si$) calculated 338.2641, found 338.2637, $M^+ - C_2H_5$ ($C_{18}H_{33}O_2Si$) calculated 309.2250, found 309.2262.

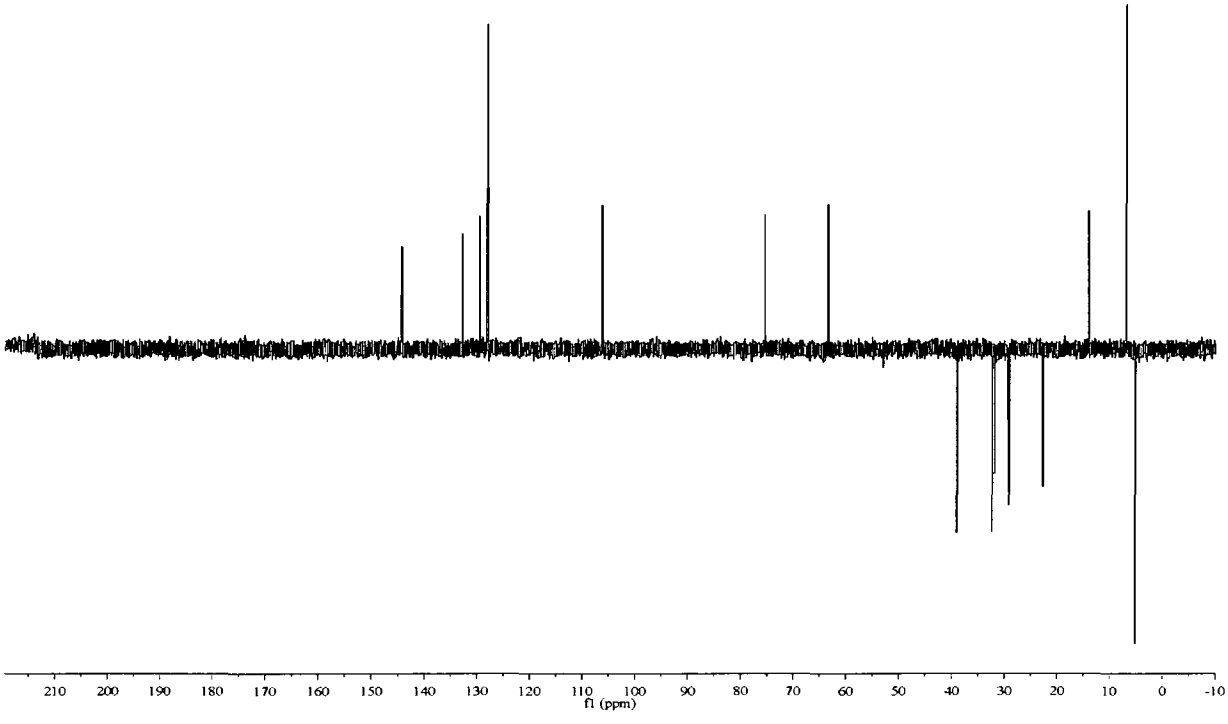
^{1}H NMR (400 MHz, C_6D_6)



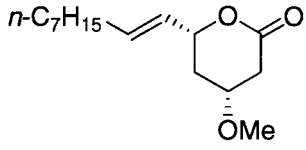
^{13}C NMR(100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)

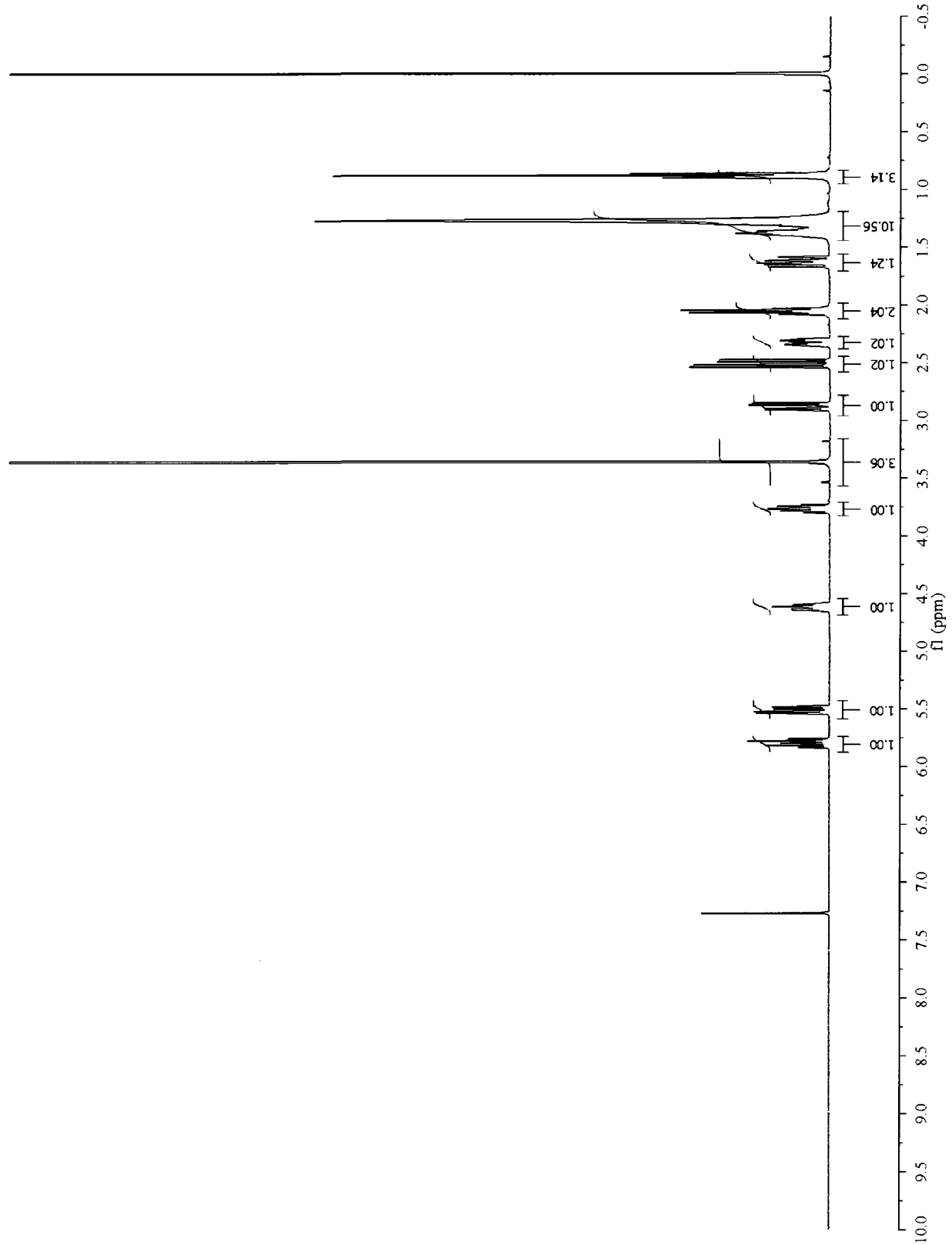


3,4-dihydro-4-methoxy-2-((*E*)-non-1-enyl)-2*H*-pyran ((±)2.22)

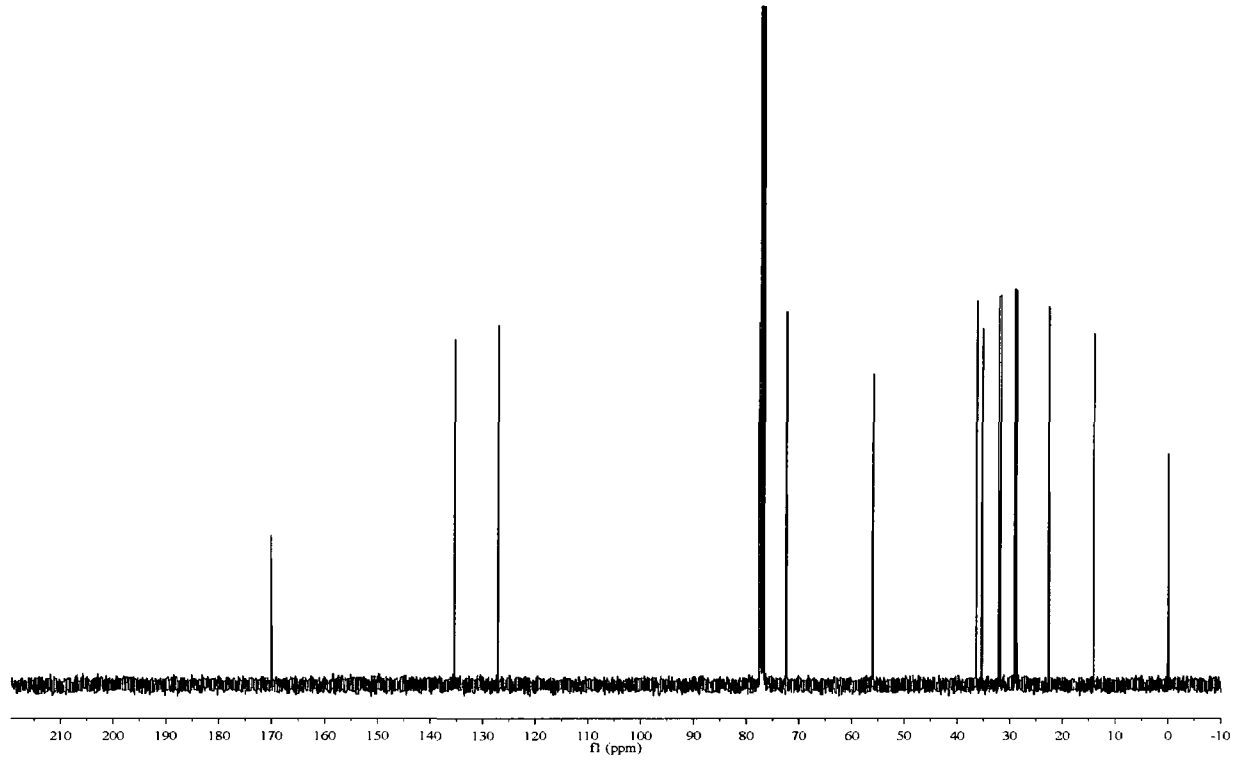


To a solution of lactone **(±)1.39** (1.00 g, 4.16 mmol) in DCM was added Proton Sponge™ (4.46 g, 20.8 mmol) at room temperature. The solution was cooled to 0 °C then trimethyloxonium tetrafluoroborate (3.08 g, 20.8 mmol) was added. The resulting suspension was stirred at 0 °C for 6 hours then placed in a refrigerator set to -25 °C for 16 hours. TLC analysis showed very little starting lactone remained therefore the mixture was then brought back to 0 °C and quenched by the slow addition of isopropanol (2.5 mL). Upon warming to room temperature, a saturated aqueous solution of sodium bicarbonate was added and the mixture was diluted with DCM. The remaining solid material was filtered out using a Büchner funnel. The layers were separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting suspension was taken up in diethyl ether and filtered again using a Büchner funnel. The filtrate was washed with a 1 N solution of HCl and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using a gradient elution from 10% ethyl acetate, 90% hexanes to 30% ethyl acetate, 70% hexanes to afford 0.736 g (70%) of **(±)2.22** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddd, J = 15.4, 6.7, 0.7 Hz, 1H), 5.52 (ddt, J = 15.4, 7.0, 1.4 Hz, 1H), 4.62 (ddd, J = 10.7, 7.0, 2.9 Hz, 1H), 3.77 (ddt, J = 8.9, 7.6, 5.7 Hz, 1H), 3.36 (s, 3H), 2.89 (ddd, J = 17.1, 5.9, 1.2 Hz, 1H), 2.51 (dd, J = 17.2, 7.6 Hz, 1H), 2.33 (dddd, J = 13.8, 3.1, 2.0, 1.3 Hz, 1H), 2.06 (q, J = 7.1 Hz, 2H), 1.63 (ddd, J = 13.9, 11.6, 9.0 Hz, 1H), 1.41 – 1.27 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C), 135.4 (CH), 127.1 (CH), 77.7 (CH), 72.4 (CH), 56.0 (CH_3), 36.4 (CH_2), 35.3 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 29.1(CH_2), 29.1 (CH_2), 28.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (neat): υmax 2956 (m), 2926 (s), 2855 (m), 1745 (s), 1673 (w), 1465 (w), 1379 (w), 1353 (w), 1233 (m), 1160 (w), 109 (m), 1032 (w) 969 (w); HRMS (EI) *m/z* M^+ ($C_{15}H_{26}O_3$) calculated 254.1882, found 254.1882.

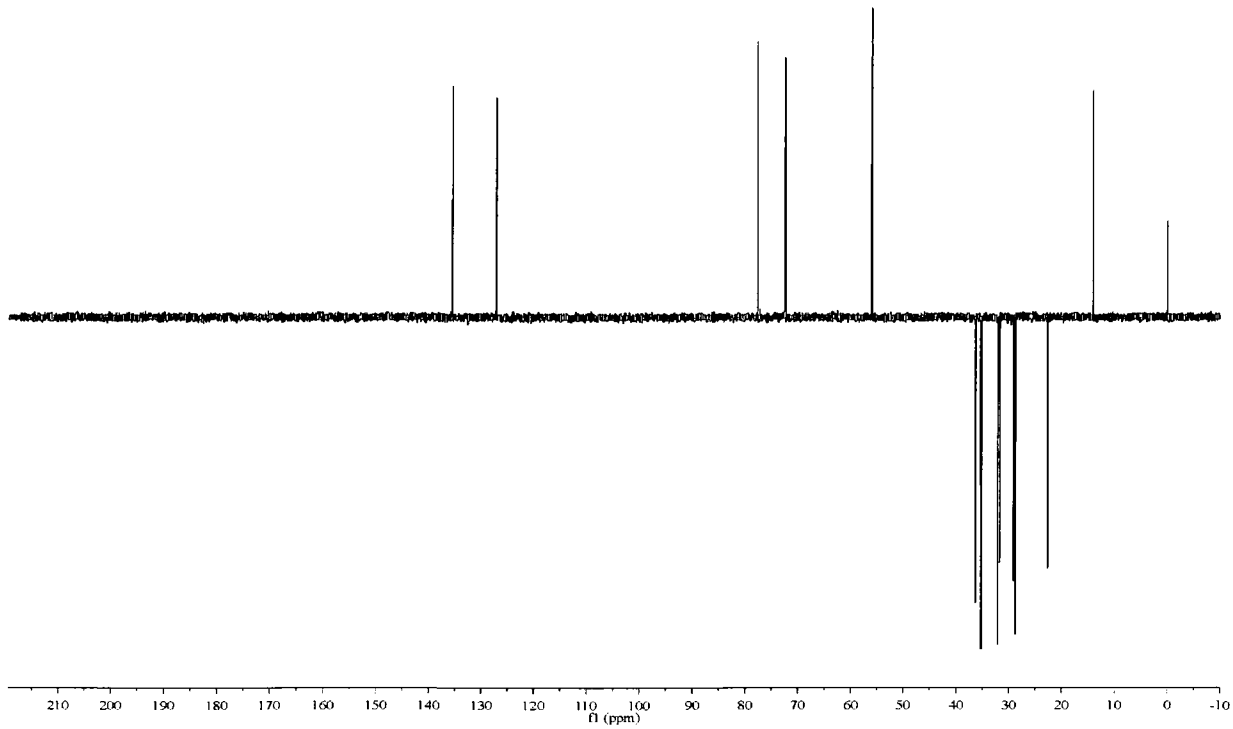
^{1}H NMR (400 MHz, $CDCl_3$)



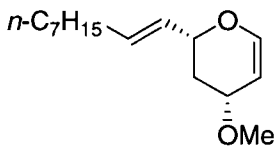
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT135 (100 MHz, $CDCl_3$)

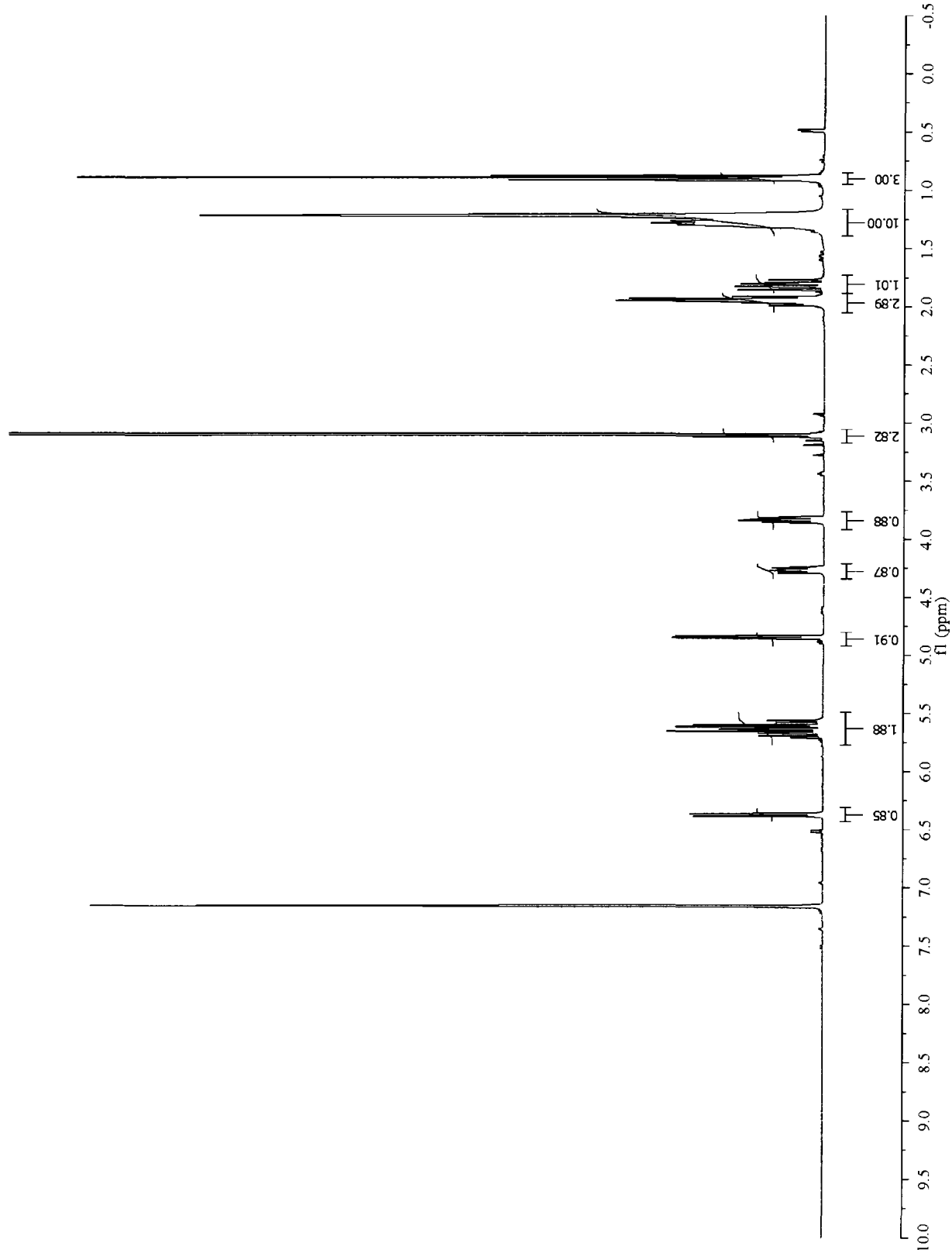


(±)-3,4-dihydro-4-methoxy-2-((*E*)-non-1-enyl)-2*H*-pyran ((±)2.23)

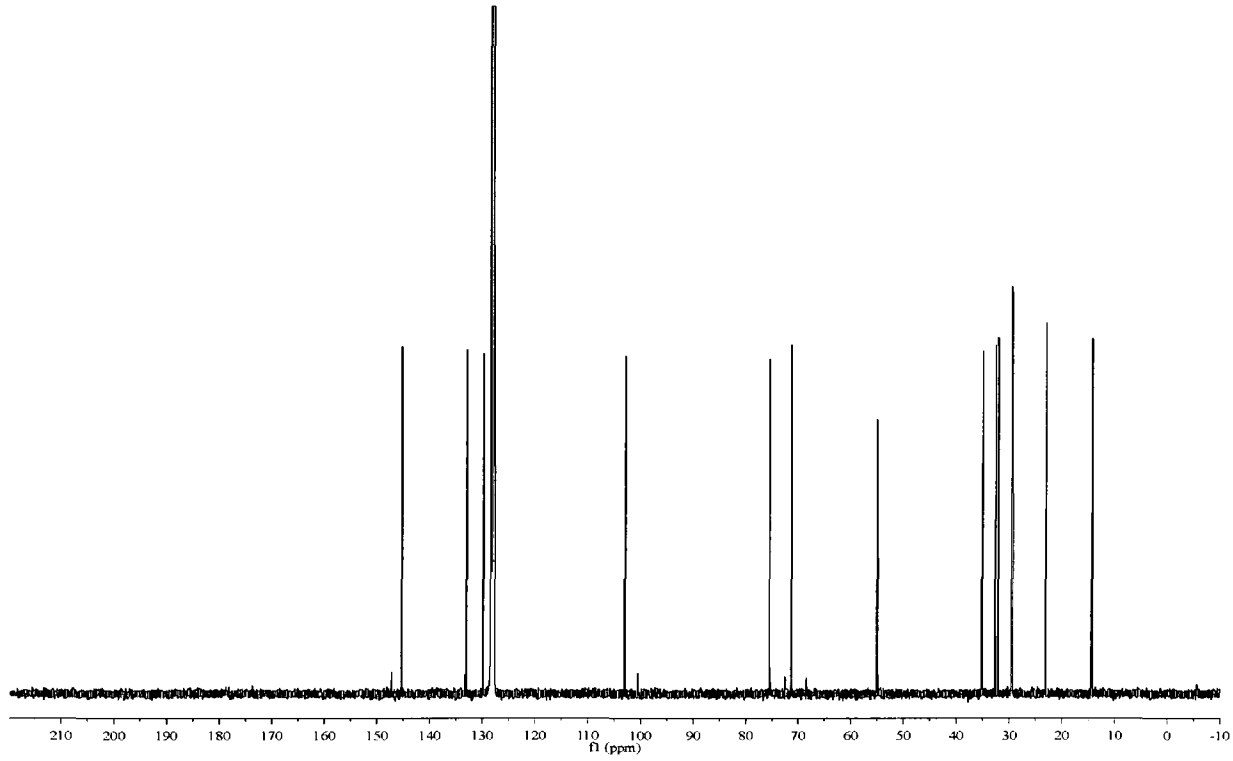


To a solution of **(±)2.22** (521 mg, 2.05 mmol) in toluene (10 mL) at -78 °C was added a solution of diisobutylaluminum hydride (1 M in toluene, 10.3 mL, 10.3 mmol) dropwise. The mixture was stirred at -78 °C for 30 minutes at which time the reaction was complete as indicated by TLC. The reaction was quenched by slow addition of a saturated aqueous solution of potassium sodium tartrate at -78 °C. The mixture was then allowed to warm to room temperature and ethyl acetate was added. The resulting gel was filtered on a pad of celite which was flushed with ethyl acetate. Water was added to the filtrate and the layers were separated. The aqueous layer was extracted with ethyl acetate two more times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was filtered through a plug of silica pretreated with Et_3N using a mixture of 3% ethyl acetate and 97% DCM as eluent. This material was then concentrated to dryness (520 mg) and dissolved in toluene (15 mL). Et_3N (2.86 ml, 20.5 mmol) was added to the solution which was cooled to 0 °C, followed by methanesulfonyl chloride (635 µL, 8.20 mmol) (freshly distilled over calcium hydride). After 1 hour of stirring, DBU (1.23 mL, 8.20 mmol) was added and the yellow solution was stirred for another hour at 0 °C then allowed to warm to room temperature, at which temperature it was stirred overnight. At that time, 10 ml of a $1M_{aq}$ solution of K_2CO_3 was added followed by EtOAc. The layers were separated and the aqueous layer was extracted two more times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel pretreated with Et_3N using hexanes as eluent to afford glycal **(±)2.23** as a light yellow oil (137 mg, 28% from **(±)2.22**). ^1H NMR (400 MHz, benzene D_6): δ 6.37 (dd, J = 6.3, 1.1 Hz, 1H), 5.66 (dt, J = 15.5, 6.4 Hz, 1H), 5.59 (dd, J = 15.4, 6.3 Hz, 1H), 4.85 (ddd, J = 6.4, 1.9, 1.9 Hz, 1H), 4.27 (ddd, J = 10.8, 6.4, 2.1 Hz, 1H), 3.84 (dddd, J = 8.7, 6.3, 1.8, 1.8 Hz, 1H), 3.10 (s, 3H), 1.97 (dddd, J = 13.0, 6.2, 1.9, 1.9 Hz, 1H), 1.94 (dt, J = 6.7, 6.7 Hz, 2H), 1.81 (ddd, J = 13.0, 11.1, 9.0 Hz, 1H), 1.36 – 1.20 (m, 10H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 145.3 (CH), 133.1 (CH), 129.8 (CH), 103.0 (CH), 75.6 (CH), 71.4 (CH), 55.1 (CH_3), 35.1 (CH_2), 32.6 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 23.1 (CH_2), 14.4 (CH_3); IR (neat): υmax 2955 (s), 2926 (s), 2855 (s), 1644 (m), 1465 (w), 1395 (w), 1235 (m), 1191 (w), 1096 (m), 1043 (w), 967 (m), 870 (w), 758 (w), 733 (w); HRMS (EI) *m/z* M^+ ($C_{15}H_{26}O_2$) calculated 238.1933, found 238.1937.

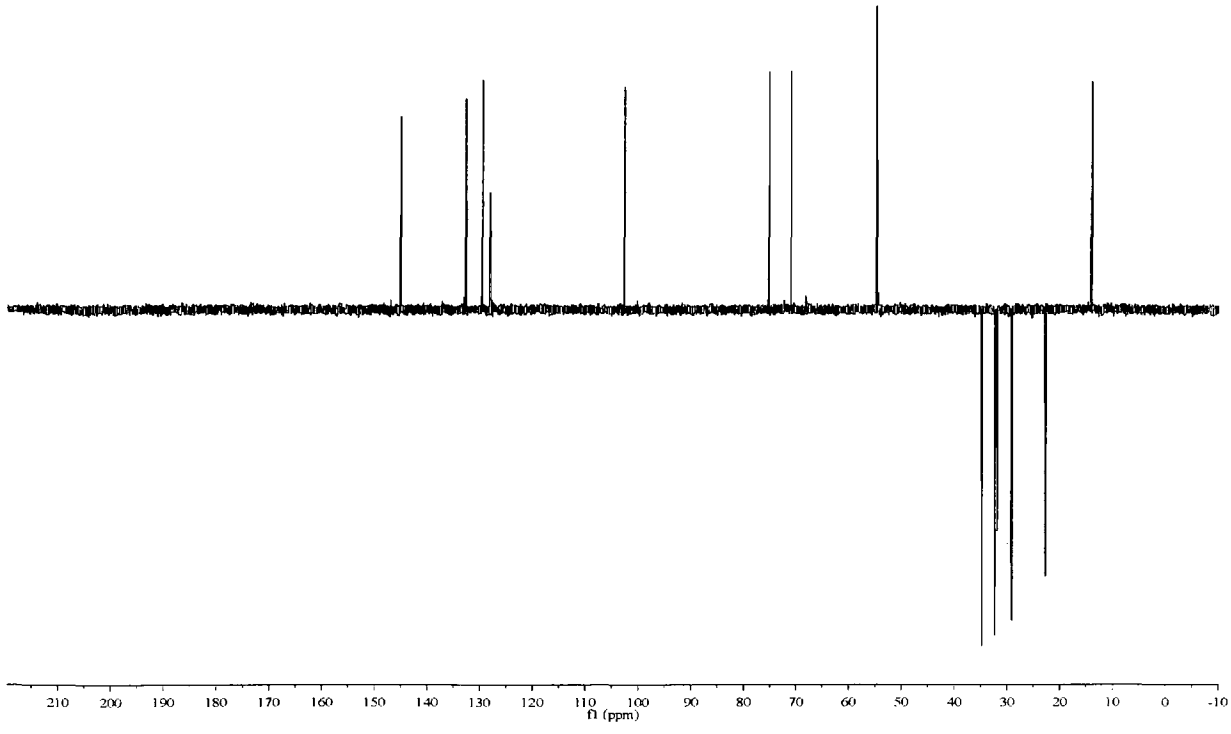
^{1}H NMR (400 MHz, C_6D_6)



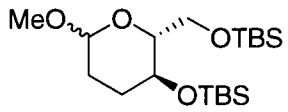
^{13}C NMR(100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)



(2*R*,3*S*)-tetrahydro-2-(*tert*-butyldimethylsilyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-6-methoxy-2*H*-pyran (3.8)

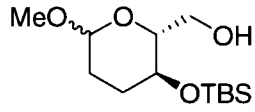


Note: the procedure for the first two steps as well as the TBS protection step were adapted from the procedure described by Nakata and co-workers[28] *with the exception of the acetate hydrolysis which was carried out according to the procedure by Pougny and co-workers.*[29]

To a solution of Tri-O-acetyl-D-glucal (20.0 g, 73.5 mmol) in dry dichloromethane (200 mL) was added montmorillonite K10 (6.0 g). Methanol (4.47 mL, 110.3 mmol) was then added to the mixture. The resulting slurry was then stirred at reflux for 1 hour at which time, an aliquot was filtered through celite and NMR analysis revealed no more starting material remained. The mixture was allowed to cool to room temperature and filtered through celite using dichloromethane as eluent. The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in 200 mL of methanol in a flask equipped with a magnetic stirbar. 1.8 g of 10% Pd/C was added and the mixture was purged 3 times with hydrogen (vacuum / hydrogen cycles). The resulting suspension was then stirred vigorously under an atmosphere of hydrogen at room temperature overnight. At this time NMR analysis of an aliquot showed no presence of olefin peaks therefore the mixture was filtered through celite using dichloromethane as eluent. The filtrate was concentrated under reduced pressure and the resulting colorless viscous oil was dissolved in 100 mL of methanol to which was added 80 mL of water. To the stirred solution at room temperature was added triethylamine (20 mL). The reaction mixture became warm and was allowed to stir at room temperature overnight. TLC analysis showed no starting material remained. The resulting mixture was concentrated under reduced pressure and azeotropically dried with toluene (40 mL, 3 times) then placed under high vacuum for 3 hours. The resulting viscous oil was dissolved in DMF (80 mL) and *tert*-butyldimethylsilyl chloride (33.3 g, 221 mmol) was added followed by imidazole (20.0 g, 294 mmol). The reaction mixture was then stirred at 50 °C for 4 hours (the mixture becomes cloudy as the reaction progresses). It was then allowed to cool to room temperature and diluted with diethyl ether and water. The layers were separated and the aqueous layer was extracted three more times with diethyl ether. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered and concentrated. The filtrate was purified by flash column chromatography on silica gel using a gradient elution from hexanes to 7% diethyl ether in hexanes to afford 27.1 g (94%) of the

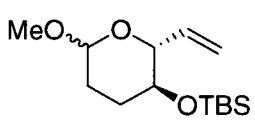
desired product as a colorless oil. Spectral data were in accord with that of the previously reported product.[49]

(2*R*,3*S*)-tetrahydro-2-(hydroxymethyl)-3-(*tert*-butyldimethylsilyloxy)-6-methoxy-2*H*-pyran (3.6)



To a solution of the diTBS ether (**3.8**) (3.56 g, 9.11 mmol) in a 1:1 methanol/dichloromethane mixture (50 mL) at 0 °C was added camphorsulfonic acid (212 mg, 0.911 mmol). After 1 hr at 0 °C, only traces of starting material could be seen by TLC therefore triethylamine (254 μL, 1.82 mmol) was added and the mixture was allowed to warm to room temperature. It was then concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using gradient elution from 95:5 hexanes/ethyl acetate to 85:15 hexanes/ethyl acetate to afford 2.30 g (91%) of the desired product. Spectral data were in accord with that of the previously reported product.[28]

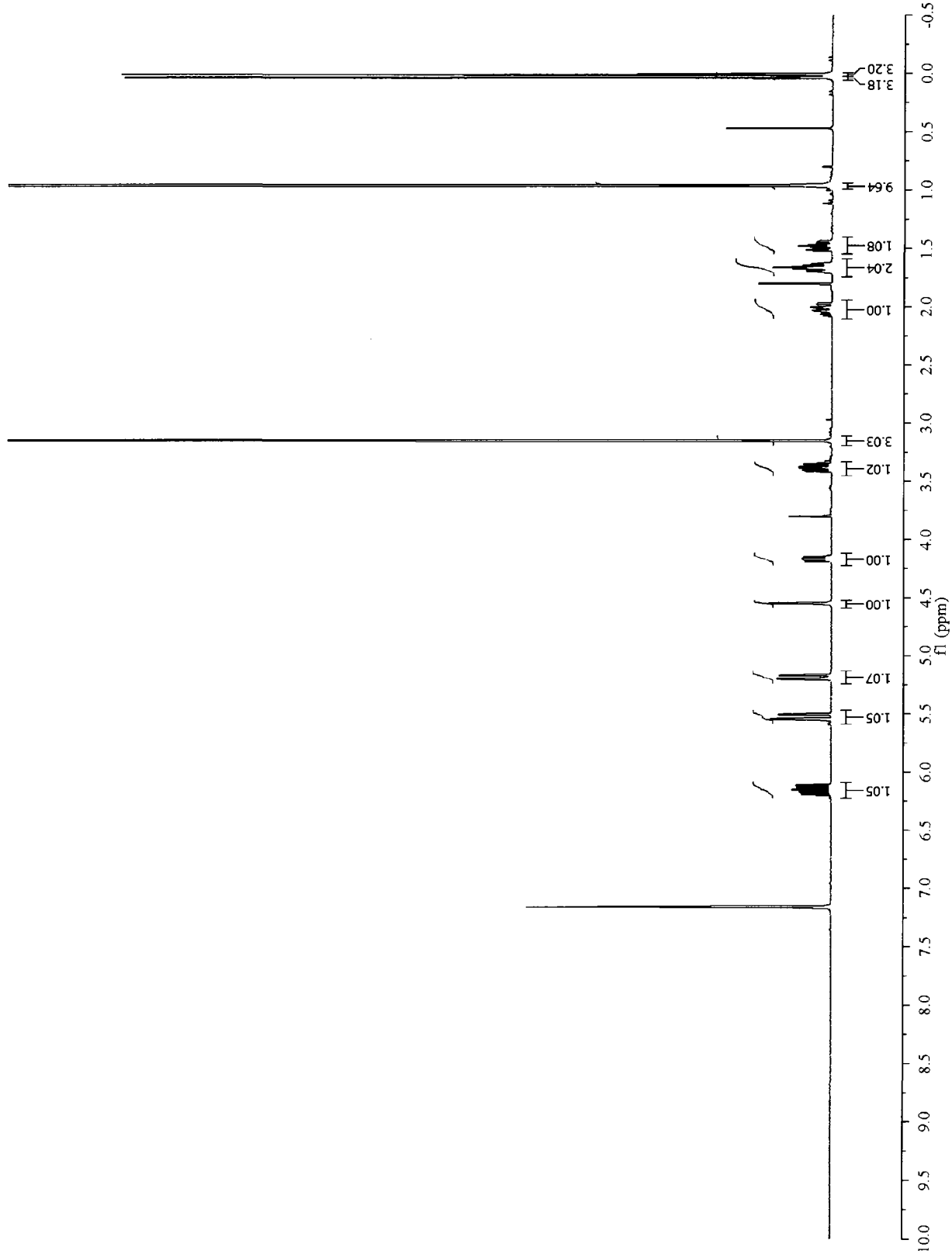
(2*R*,3*S*)-tetrahydro-6-methoxy-3-(*tert*-butyldimethylsilyloxy)-2-vinyl-2*H*-pyran (3.10)



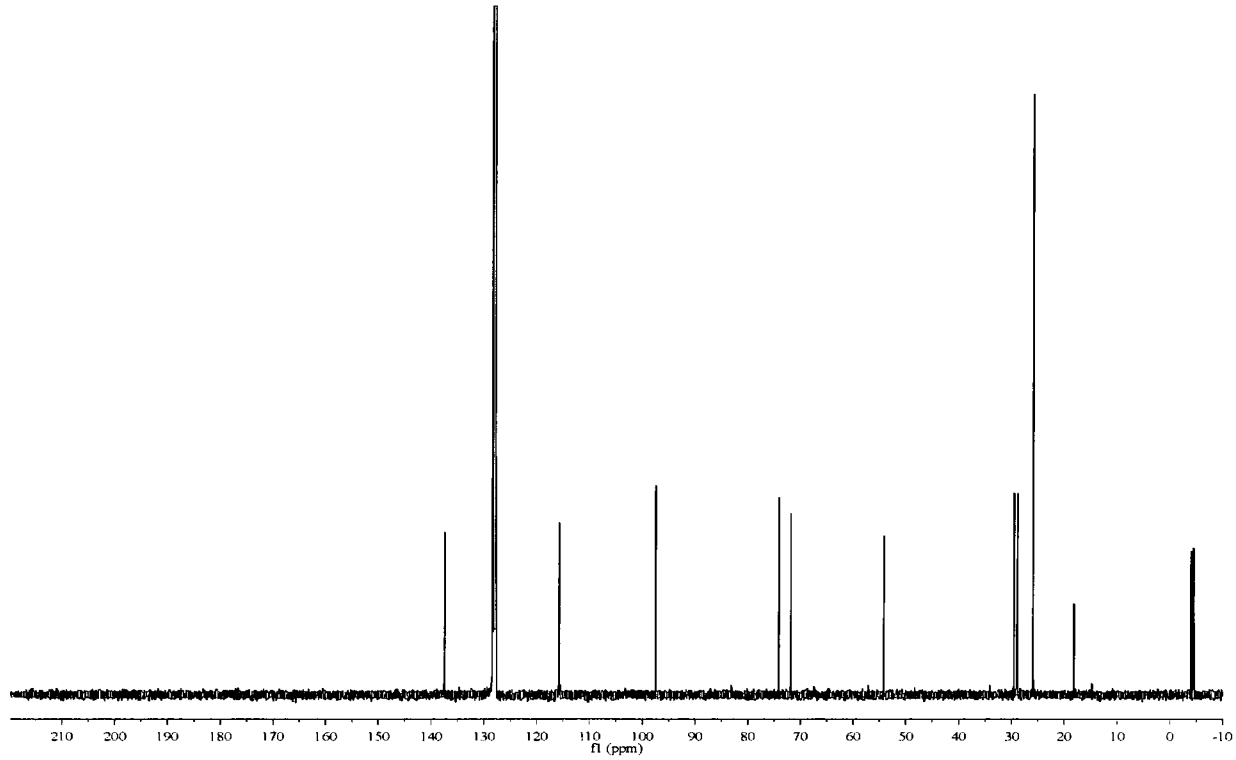
To a cold solution (-78 °C) of oxalyl chloride (3.55 mL, 41.3 mmol) in 50 mL of dry dichloromethane was added a solution of DMSO (6.46 mL, 90.9 mmol) in 10 mL of dichloromethane dropwise. The resulting mixture was stirred at this temperature for 5 minutes then a solution of alcohol **3.8** (2.29 g, 8.27 mmol) in 10 mL of dichloromethane (with an extra 10 mL for rinse) was added dropwise. After another 15 minutes at the same temperature, neat triethylamine (26.5 mL, 190 mmol) was added dropwise. The reaction mixture was then stirred another 15 minutes at -78 °C then allowed to slowly warm to -30 °C at which time a saturated solution of ammonium chloride, water and diethyl ether were added. Upon warming to room temperature, the layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with water then brine then dried over Na_2SO_4, filtered and concentrated. The resulting residue was quickly passed through a short pad of silica pretreated with triethylamine using dichloromethane as eluent. After concentration, the aldehyde was diluted in 10 mL of dry THF. In a separate flask, methyltriphenylphosphonium iodide ($MePPh_3I$, 10.2 g, 25.1 mmol) was suspended in 70 mL of dry THF at 0 °C. To this suspension was added a solution of KHMDS (4.68 g, 23.5 mmol), in 35 mL of dry THF dropwise. The resulting yellow suspension was stirred at 0 °C for 15 minutes

then the solution of the aldehyde was added dropwise. The mixture was stirred another 35 minutes at the same temperature at which time TLC analysis no longer showed the presence of the aldehyde. A saturated solution of ammonium chloride was added and the yellow color was immediately discharged. Diethyl ether was added and the layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed once with brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel using a gradient elution from hexanes to 95:5 hexanes/ethyl acetate to afford 1.78 g (79%) of the desire alkene as a colorless, viscous oil. An aliquot was repurified to afford the pure major anomer (α anomer): ^{1}H NMR (400 MHz, benzene D_6): δ 6.16 (ddd, J = 17.2, 10.6, 5.6 Hz, 1H), 5.53 (ddd, J = 17.3, 2.2, 1.5 Hz, 1H), 5.19 (ddd, J = 10.6, 2.2, 1.3 Hz, 1H), 4.56 (d, J = 3.4 Hz, 1H), 4.17 (dddd, J = 9.1, 5.6, 1.5, 1.5 Hz, 1H), 3.39 (ddd, J = 10.9, 9.2, 4.5 Hz, 1H), 3.16 (s, 3H), 2.03 (dddd, J = 14.9, 13.2, 10.8, 4.6 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.48 (dddd, J = 13.7, 13.7, 5.1, 3.5 Hz, 1H), 0.96 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 137.5 (CH), 115.8 (CH_2), 97.5 (CH), 74.1 (CH), 71.8 (CH), 54.2 (CH_3), 29.7 (CH_2), 28.9 (CH_2), 26.0 (CH_3 (3C)), 18.2 (C), -4.0 (CH_3), -4.4 (CH_3); IR (neat): υmax 2954 (s), 2930 (s), 2894 (s), 2858 (s), 1473 (m), 1373 (m), 1258 (m), 1225 (w), 1207 (w), 1129 (s), 1060 (s), 1023 (m), 1006 (m), 954 (m), 923 (w), 866 (m), 837 (s), 776 (s), 670 (w) ; HRMS (EI) *m/z* M^+ not found, M^+ - C_4H_9 ($C_{10}H_{19}O_3Si$) calculated 215.1098, found 215.1091; $[\alpha]^{22}_D$ +130.3°, *c* 14.0 mg/mL (CH_2Cl_2).

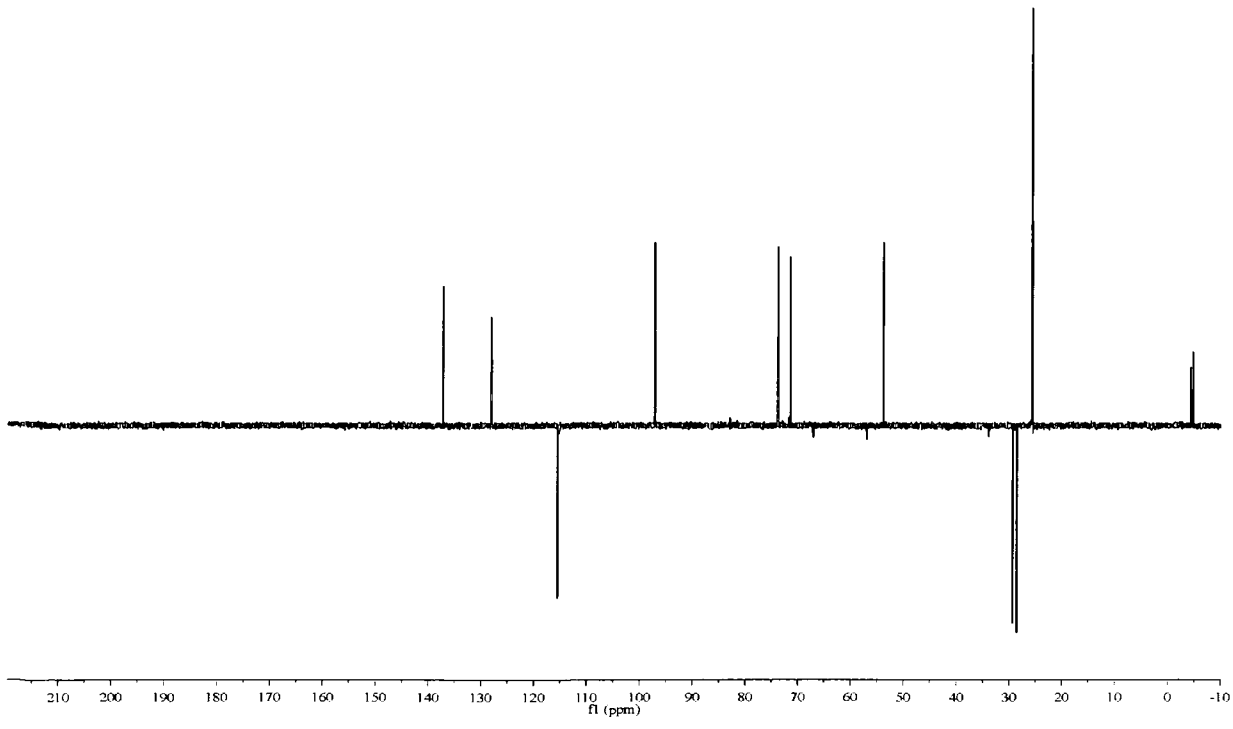
^{1}H NMR (400 MHz, benzene D_6)



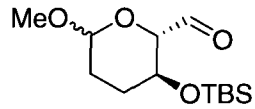
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, C_6D_6)

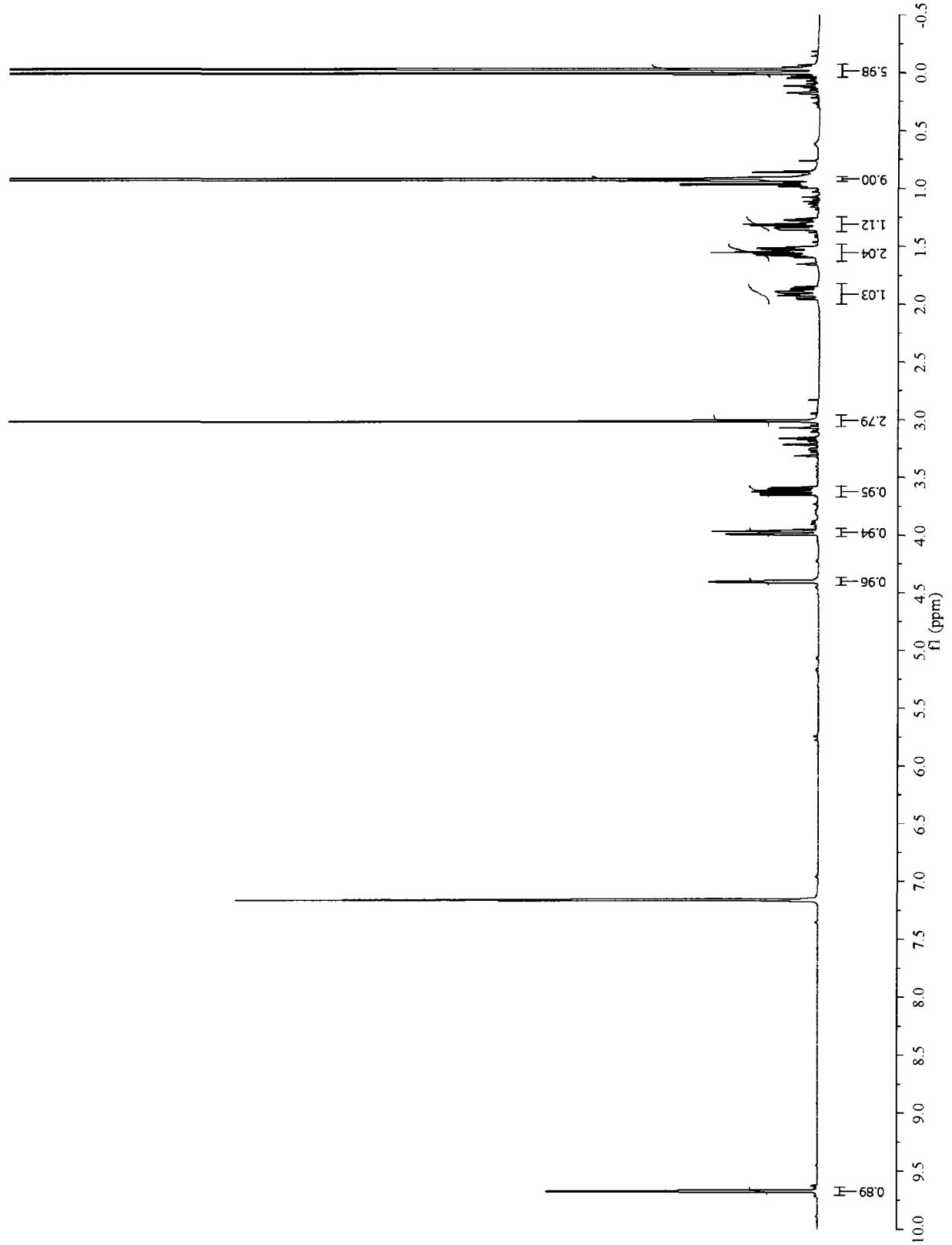


(2*S*,3*S*)-tetrahydro-3-(*tert*-butyldimethylsilyloxy)-6-methoxy-2*H*-pyran-2-carbaldehyde (3.9) (alternative procedure)

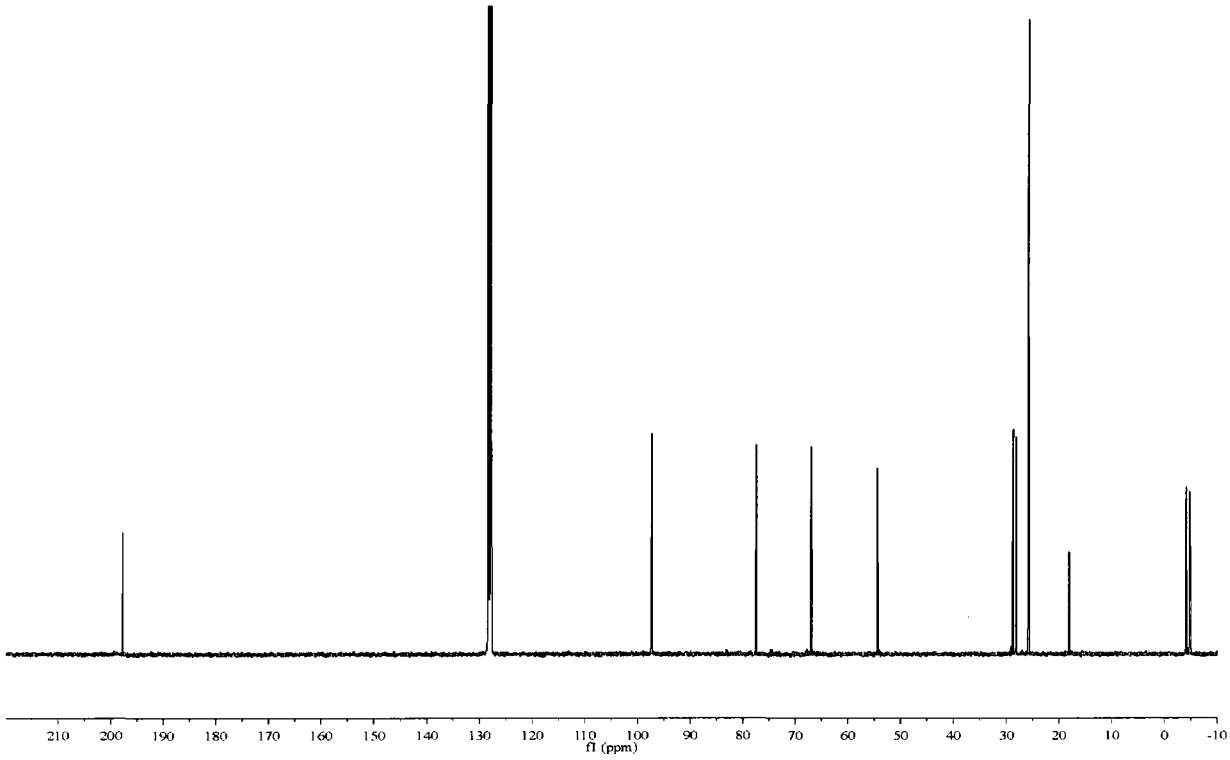


To a solution of alcohol **3.8** (400 mg, 1.45 mmol) in 14 mL of dry dichloromethane was added 300 mg of activated 4Å molecular sieves followed by NMO (339 mg, 2.89 mmol). The flask was protected from light and cooled to 0 °C then TPAP (25.4 mg, 0.072 mmol) was added. The flask was then allowed to warm to room temperature and stirred for one hour at which time TLC analysis demonstrated that the reaction was complete. The mixture was filtered through a pad of celite using dichloromethane as eluent. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (15 % ethyl acetate in hexanes) to afford 285 mg (72 %) of the desired aldehyde as a colorless oil. Major anomer (α anomer): ^{1}H NMR (400 MHz, benzene D_6): δ 9.68 (d, J = 2.1 Hz, 1H), 4.41 (d, J = 2.4 Hz, 1H), 3.98 (dd, J = 9.4, 2.0 Hz, 1H), 3.62 (ddd, J = 10.6, 9.4, 4.7 Hz, 1H), 3.02 (s, 3H), 1.91 (dddd, J = 14.5, 13.1, 10.7, 4.5 Hz, 1H), 1.60 – 1.51 (m, 2H), 1.31 (dddd, J = 13.9, 13.9, 5.0, 3.4 Hz, 1H), 0.92 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 197.8 (CH), 97.3 (CH), 77.4 (CH), 67.0 (CH), 54.5 (CH_3), 28.8 (CH_2), 28.3 (CH_2), 25.9 (CH_3 (3C)), 18.1 (C), -4.1 (CH_3), -4.8 (CH_3); IR (neat): υmax 3473 (w), 2954 (s), 2931 (s), 2898 (m), 2858 (s), 1744 (s), 1473 (m), 1374 (m), 1257 (m), 1225 (w), 1209 (w), 1133 (s), 1096 (s), 1057 (s) 954 (m), 837 (s), 777 (s), 667 (w); HRMS (EI) *m/z* M^+ not found, M^+ - C_4H_9 ($C_9H_{17}O_4Si$) calculated 217.0891, found 217.0907; $[\alpha]^{22}_D$ +140.2°, *c* 12.0 mg/mL (CH_2Cl_2).

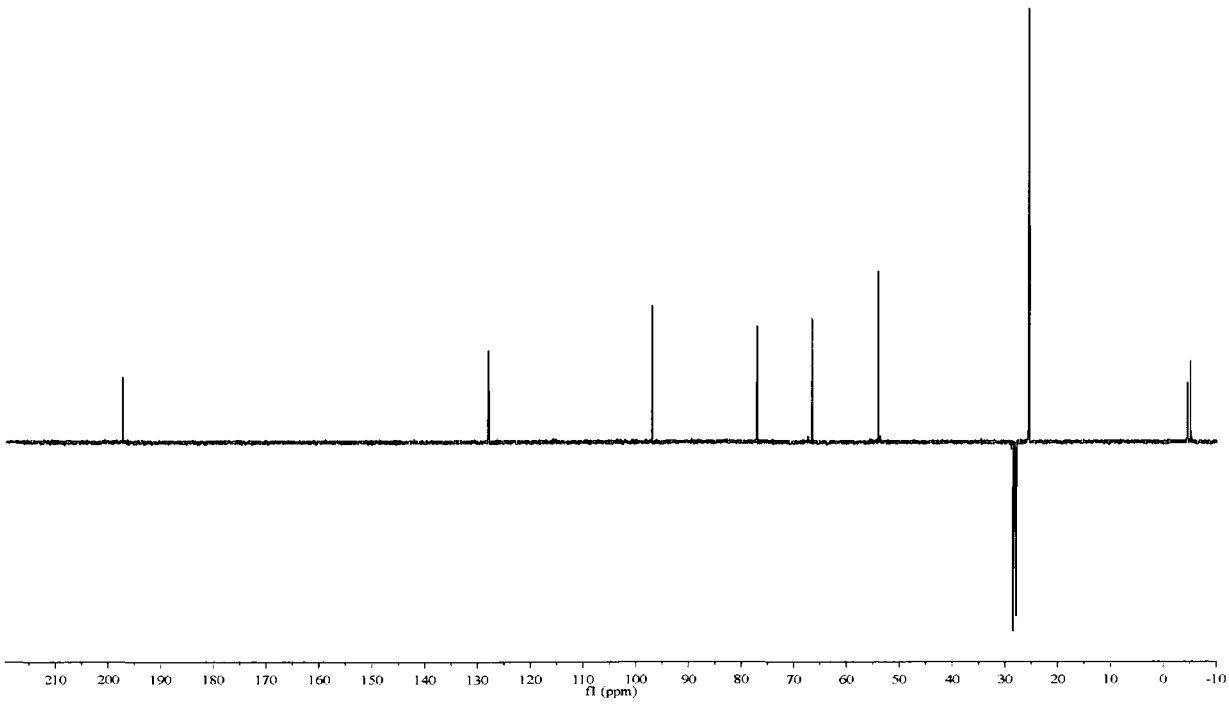
^{1}H NMR (400 MHz, benzene D_6)



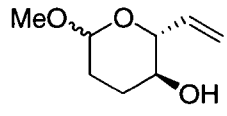
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, C_6D_6)

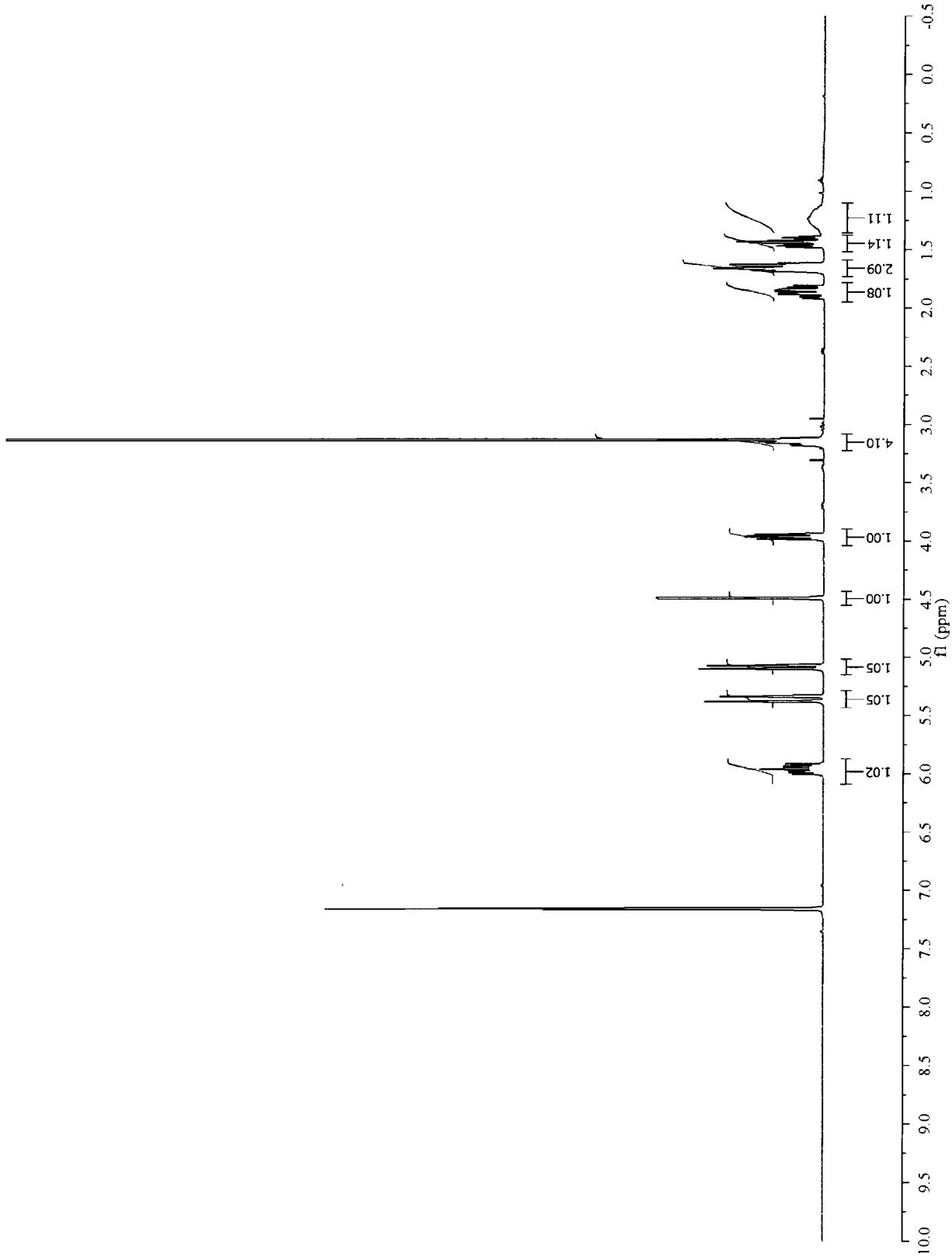


(2*R*,3*S*)-tetrahydro-6-methoxy-2-vinyl-2*H*-pyran-3-ol (3.11)

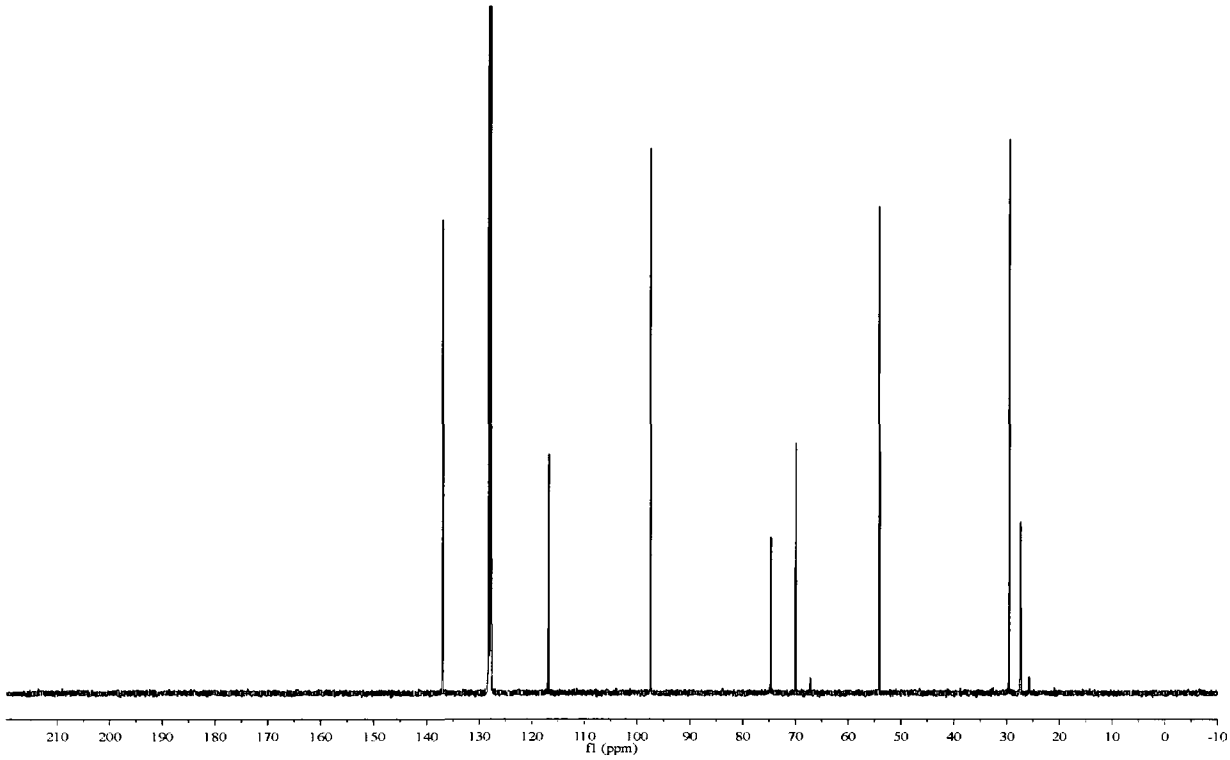


To a solution of TBS ether **3.10** (300 mg, 1.10 mmol) in 5 mL of dry THF was added a 1M solution of tetrabutylammonium fluoride (1.32 mL, 1.32 mmol) at room temperature. The mixture was stirred for 2 hours at which time TLC analysis no longer showed the presence of the starting material. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel using a gradient elution from 10% ethyl acetate in hexanes to 35% ethyl acetate in hexanes to afford 150 mg (94%) of the desired alcohol as a colorless viscous oil. A second purification of an aliquot by flash chromatography afforded the pure major anomer (α). ^{1}H NMR (400 MHz, benzene D_6): δ 5.97 (ddd, J = 17.1, 10.6, 6.3 Hz, 1H), 5.36 (ddd, J = 17.3, 2.0, 1.3 Hz, 1H), 5.09 (ddd, J = 10.6, 2.0, 1.1 Hz, 1H), 4.50 (d, J = 3.3 Hz, 1H), 3.97 (dd, J = 8.5, 7.1 Hz, 1H), 3.19 – 3.12 (m, 1H), 3.14 (s, 3H), 1.92 – 1.81 (m, 1H), 1.69 – 1.62 (m, 2H), 1.44 (dddd, J = 13.8, 13.8, 4.7, 3.8 Hz, 1H), 1.24 (s, br, 1H); ^{13}C NMR (100 MHz, benzene D_6): δ 137.0(CH), 116.9 (CH_2), 97.5 (CH), 74.8 (CH), 70.0 (CH), 54.3 (CH_3), 29.7 (CH_2), 27.4 (CH_2); IR (neat): υmax 3422 (s), 2939(s), 2897 (s), 2834 (m), 1646 (m), 1440 (m), 1371 (m), 1207 (m), 1128 (s), 1056 (s), 1020 (s), 1003 (s), 944 (s), 868 (m), 854 (m); HRMS (EI) *m/z* M^+ not found, M^+ - MeOH ($C_7H_{10}O_2$) calculated 126.0681, found 126.0667; $[\alpha]^{22}_D$ +164.9°, *c* 13.2 mg/mL (CH_2Cl_2).

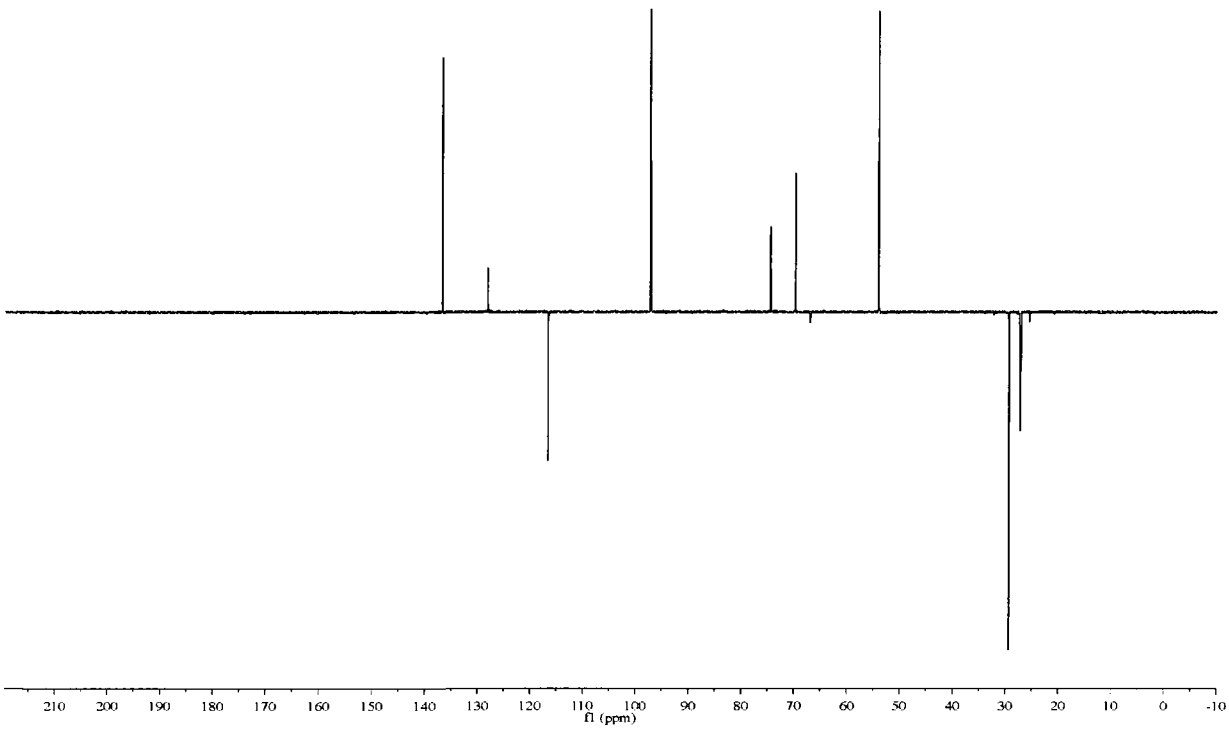
^{1}H NMR (400 MHz, benzene D_6)



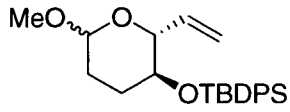
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, C_6D_6)

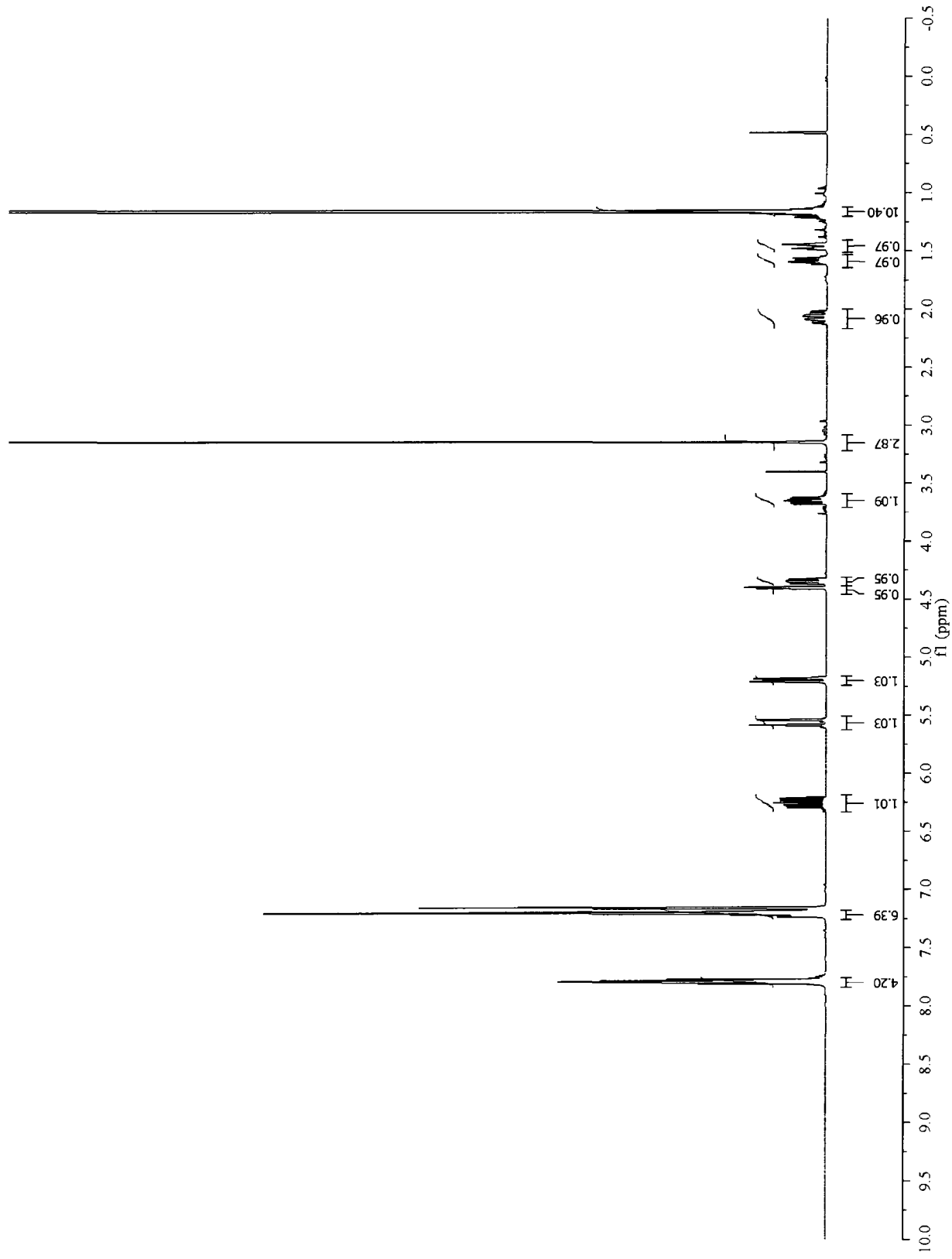


(2*R*,3*S*)-tetrahydro-6-methoxy-3-(*tert*-butyldiphenylsilyloxy)-2-vinyl-2*H*-pyran (3.12)

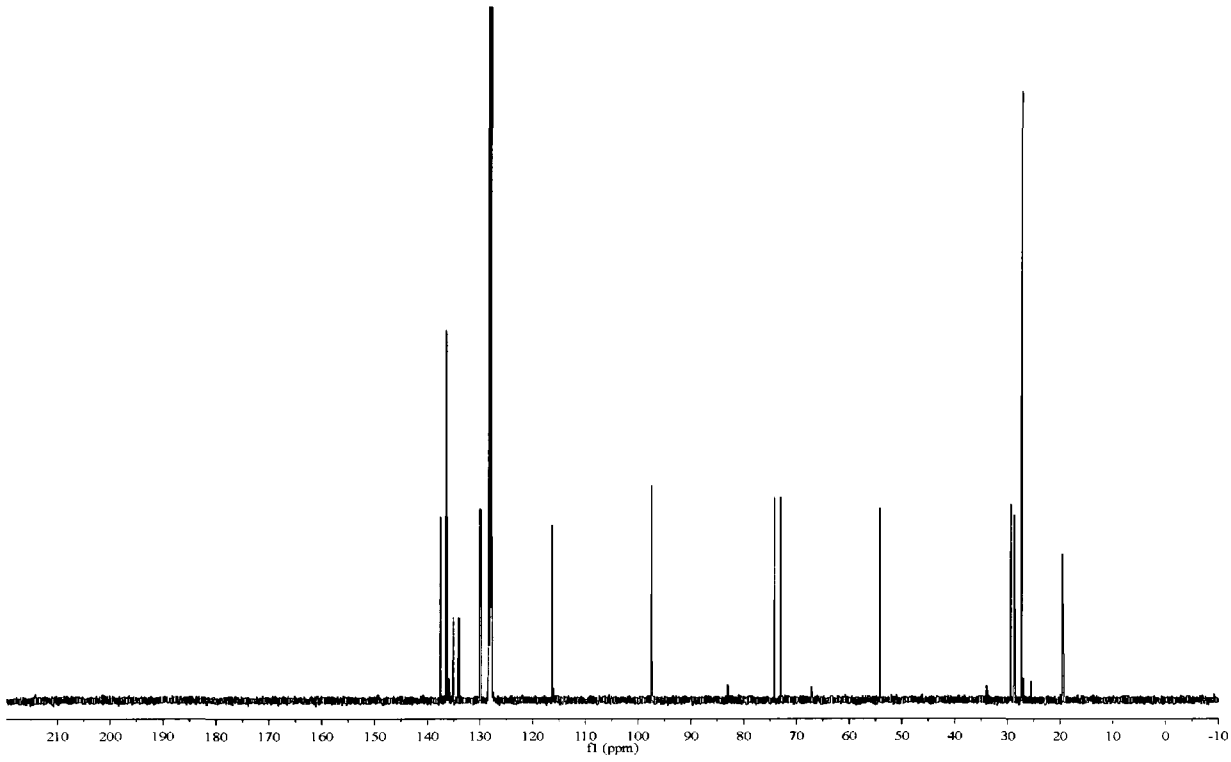


To a solution of the alcohol **3.11** (261 mg, 1.65 mmol), DMAP (10 mg, 0.08 mmol) and imidazole (673 mg, 9.90 mmol) in 10 mL of DMF was added *tert*-butyldiphenylsilyl chloride (1.27 mL, 4.95 mmol). The reaction mixture was stirred at 120 °C for 4 hours at which time TLC analysis showed only trace amounts of the starting alcohol remained. The reaction mixture was allowed to cool to room temperature and stirred overnight. 1 mL of water was added and the mixture was stirred another 15 minutes before it was diluted with diethyl ether and brine. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic extracts were washed once with a 1 N aqueous HCl solution then with brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel using a gradient elution from hexanes to 7 % ether in hexanes to afford 578 mg (92 %) of the desired TBDPS ether as a colorless oil. ^{1}H NMR (400 MHz, benzene D_6): δ 7.82 – 7.78 (m, 4H), 7.23 – 7.19 (m, 6H), 6.26 (ddd, J = 17.2, 10.6, 5.7 Hz, 1H), 5.57 (ddd, J = 17.3, 2.2, 1.5 Hz, 1H), 5.20 (ddd, J = 10.6, 2.2, 1.3 Hz, 1H), 4.41 (d, J = 3.1 Hz, 1H), 4.35 (dddd, J = 9.1, 5.8, 1.4, 1.4 Hz, 1H), 3.66 (ddd, J = 10.9, 9.2, 4.5 Hz, 1H), 3.15 (s, 3H), 2.08 (dddd, J = 13.8, 12.4, 11.1, 4.3 Hz, 1H), 1.58 (dddd, J = 12.2, 4.5, 4.5, 3.2 Hz, 1H), 1.46 (dddd, J = 13.7, 4.1, 3.1, 1.0 Hz, 1H), 1.23 – 1.14 (m, 10H with a singlet at 1.17 ppm); ^{13}C NMR (100 MHz, benzene D_6): δ 137.6 (CH), 136.5(CH (2C)), 136.4 (CH (2C)), 135.1 (C), 134.1 (C), 130.1 (CH) 129.9 (CH), 128.0 (CH (2C)), 127.9 (CH (2C)), 116.3 (CH_2), 97.5 (CH), 74.2 (CH), 73.1 (CH), 54.2 (CH_3), 29.4 (CH_2), 28.8 (CH_2), 27.3 (CH_3 (3C)), 19.6 (C); IR (neat): υmax 3072 (w), 2932 (s), 2893 (s), 2858 (s), 1473 (m), 1428 (s), 1373 (m), 1208 (w), 1112 (s), 1059 (s), 1024 (m), 1007 (m), 953 (m), 902 (w), 864 (w), 823 (m), 809 (m), 702(s), 613 (w); HRMS (EI) *m/z* M^+ not found, M^+ - C_4H_9 ($C_{20}H_{23}O_3Si$) calculated 339.1411, found 339.1383; $[\alpha]^{22}_D$ +72.5°, *c* 14.2 mg/mL (CH_2Cl_2).

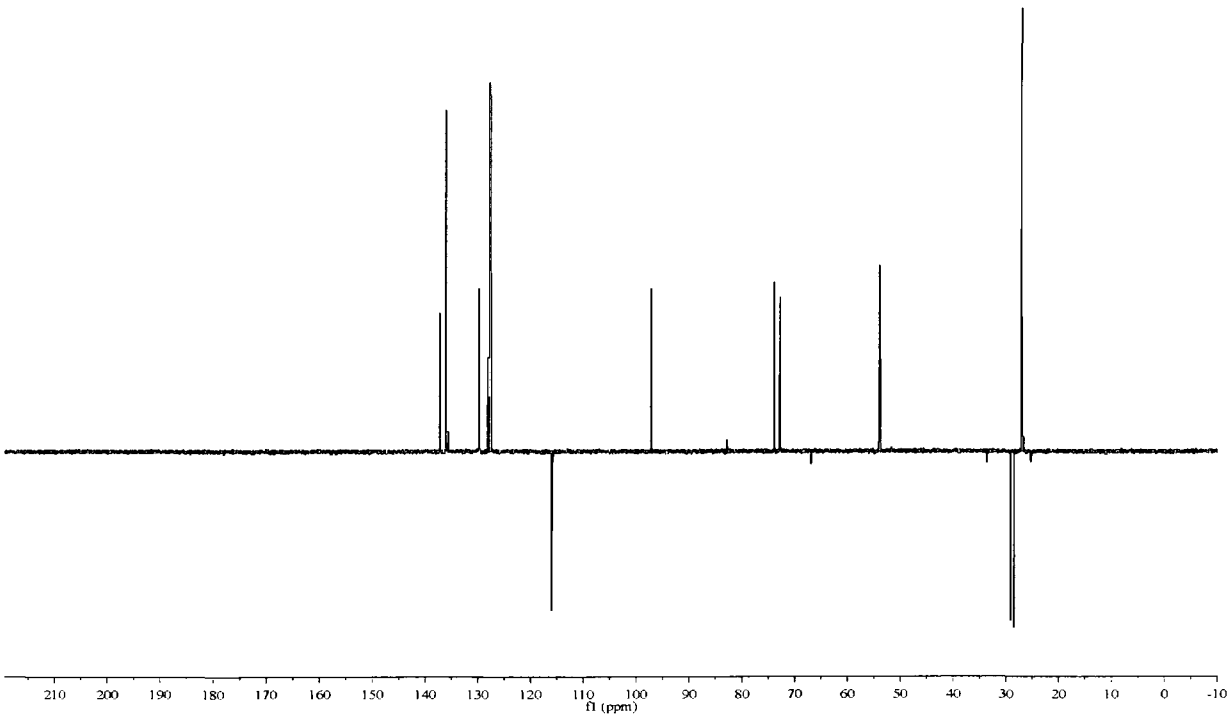
^{1}H NMR (400 MHz, benzene D_6)



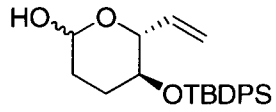
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, C_6D_6)

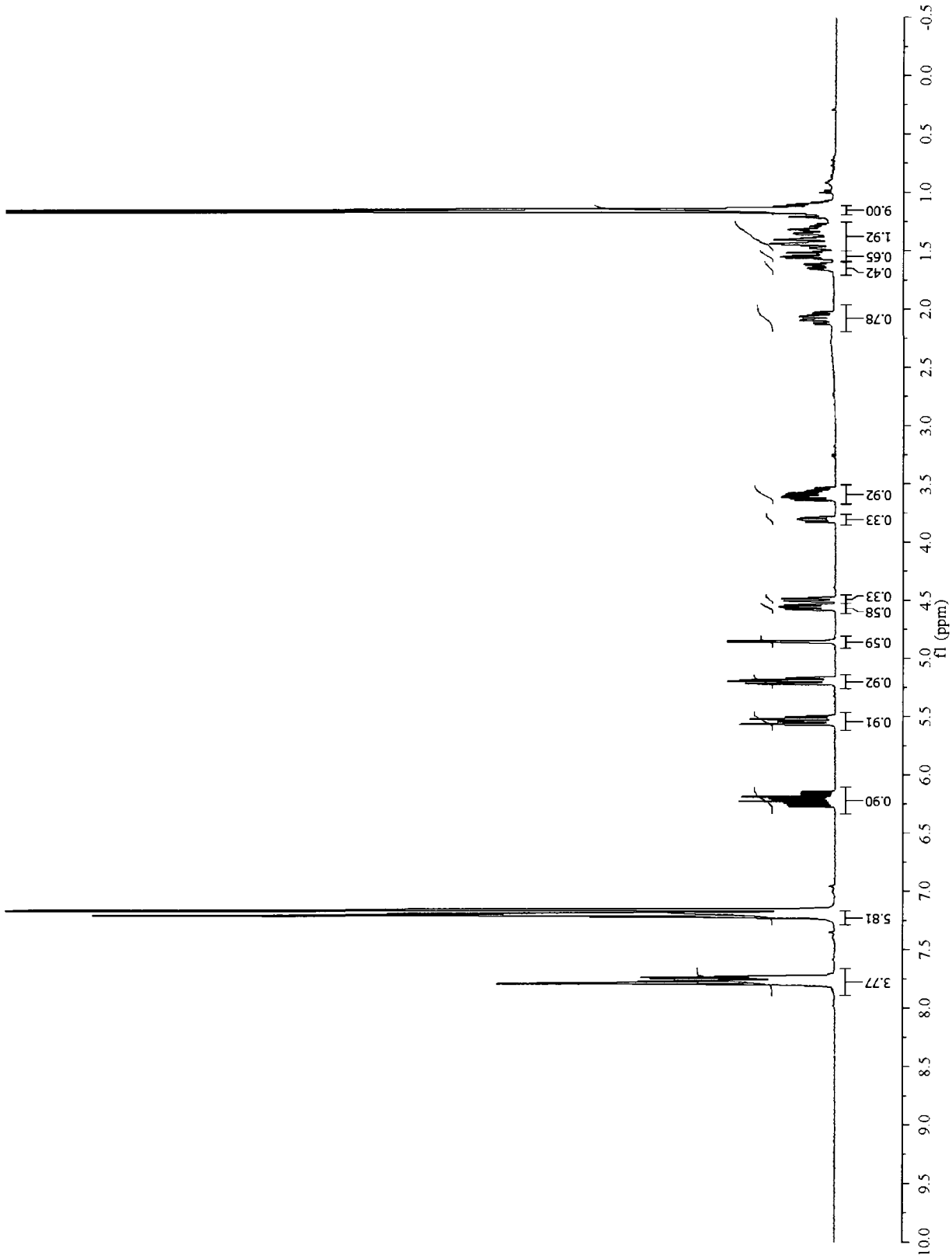


(2*R*,3*S*)-tetrahydro-6-hydroxy-3-(*tert*-butyldiphenylsilyloxy)-2-vinyl-2*H*-pyran (3.13)

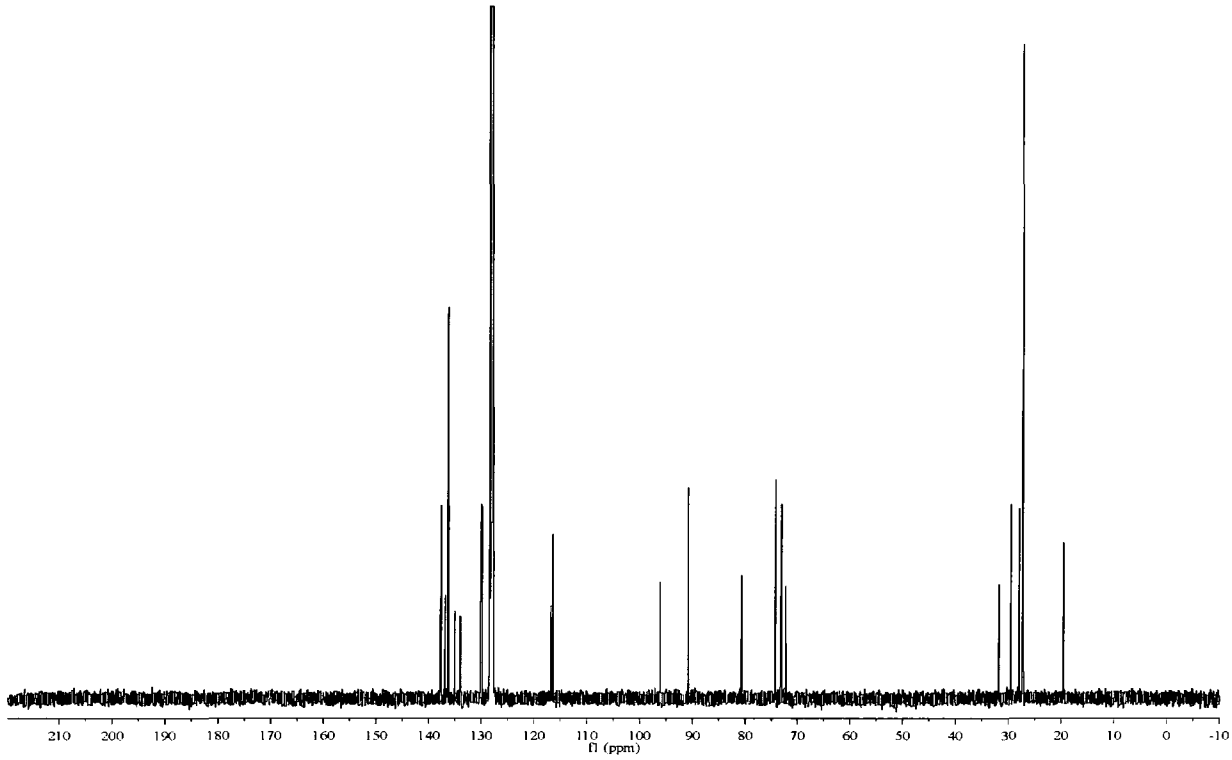


To a solution of the TBDPS ether **3.12** (560 mg, 1.47 mmol) in 25 mL of THF was added a 2N aqueous solution of HCl (3.68 mL, 7.36 mmol). The mixture was brought to reflux and stirred for 3 hours. At that time, TLC analysis revealed that starting material remained but decomposition was starting to occur. The mixture was therefore allowed to cool to room temperature and solid $NaHCO_3$ was slowly added until the mixture was saturated. Ether and water were added and the layers were separated. The aqueous layer was extracted 3 times with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel pretreated with triethylamine using a gradient elution from hexanes to 20% ethyl acetate in hexanes to afford 489 mg (87%) of the desired lactol as a 65 : 35 mixture of inseparable α and β anomers respectively, in the form of a colorless oil. 67 mg (12%) of starting material was also recovered. α and β anomer mixture: IR (neat): υmax 3407 (m), 3070 (w), 2932 (s), 2858 (s), 1473 (m), 1428 (s), 1362 (w), 1112 (s), 1007 (m), 931 (m), 873 (w), 823 (m), 740 (m), 702 (s), 612 (w); HRMS (EI) *m/z* M^+ not found, M^+ - H_2O ($C_{23}H_{28}O_2Si$) calculated 364.1853, found 364.1866; $[\alpha]^{22}_D$ +33.1°, *c* 10.6 mg/mL (CH_2Cl_2). Major anomer (α): ^1H NMR (400 MHz, benzene D_6): δ 7.81 – 7.73 (m, 4H), 7.25 – 7.18 (m, 6H), 6.23 (ddd, J = 16.5, 10.6, 5.8 Hz, 1H), 5.55 (ddd, J = 17.3, 2.1, 1.5 Hz, 1H), 5.21 (ddd, J = 10.5, 2.1, 1.3 Hz, 1H), 4.86 (d, J = 2.6 Hz, 1H), 4.56 (dd, J = 8.9, 5.9 Hz, 1H), 3.61 (ddd, J = 10.8, 9.0, 4.4 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.54 (dddd, J = 12.2, 4.2, 4.2, 4.2 Hz, 1H), 1.49 – 1.39 (m, 1H), 1.36 – 1.27 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, benzene D_6): δ 137.7 (CH), 136.4 (CH (2C)), 136.4 (CH (2C)), 135.1 (C), 134.1 (C), 130.1 (CH), 129.9 (CH), 128.0 (CH (2C)), 127.9 (CH (2C)), 116.4 (CH_2), 90.8 (CH), 74.3 (CH), 73.2 (CH), 29.5 (CH_2), 28.0 (CH_2), 27.3 (CH_3 (3C)), 19.6 (C). Minor anomer (β): ^1H NMR (400 MHz, benzene D_6): δ 7.81 – 7.73 (m, 4H), 7.25 – 7.18 (m, 6H), 6.19 (ddd, J = 16.4, 10.6, 5.6 Hz, 1H), 5.52 (ddd, J = 17.3, 1.9, 1.5 Hz, 1H), 5.19 (ddd, J = 10.6, 2.0, 1.3 Hz, 1H), 4.50 (dd, J = 9.2, 2.1 Hz, 1H), 3.81 (dddd, J = 10.0, 5.6, 1.2, 1.2 Hz, 1H), 3.57 (ddd, J = 10.4, 8.8, 4.6 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.64 (dddd, J = 12.4, 4.0, 4.0, 4.0 Hz, 1H), 1.49 – 1.39 (m, 1H), 1.36 – 1.27 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, benzene D_6): δ 136.9 (CH), 136.4 (CH (2C)), 136.3 (CH (2C)), 135.0 (C), 133.9 (C), 130.1 (CH), 130.0 (CH), 128.0 (CH (2C)), 127.9 (CH (2C), 116.7 (CH_2), 96.2 (CH), 80.7 (CH), 72.4 (CH), 31.9 (CH_2), 31.8 (CH_2), 27.3 (CH_3 (3C)), 19.6 (C).

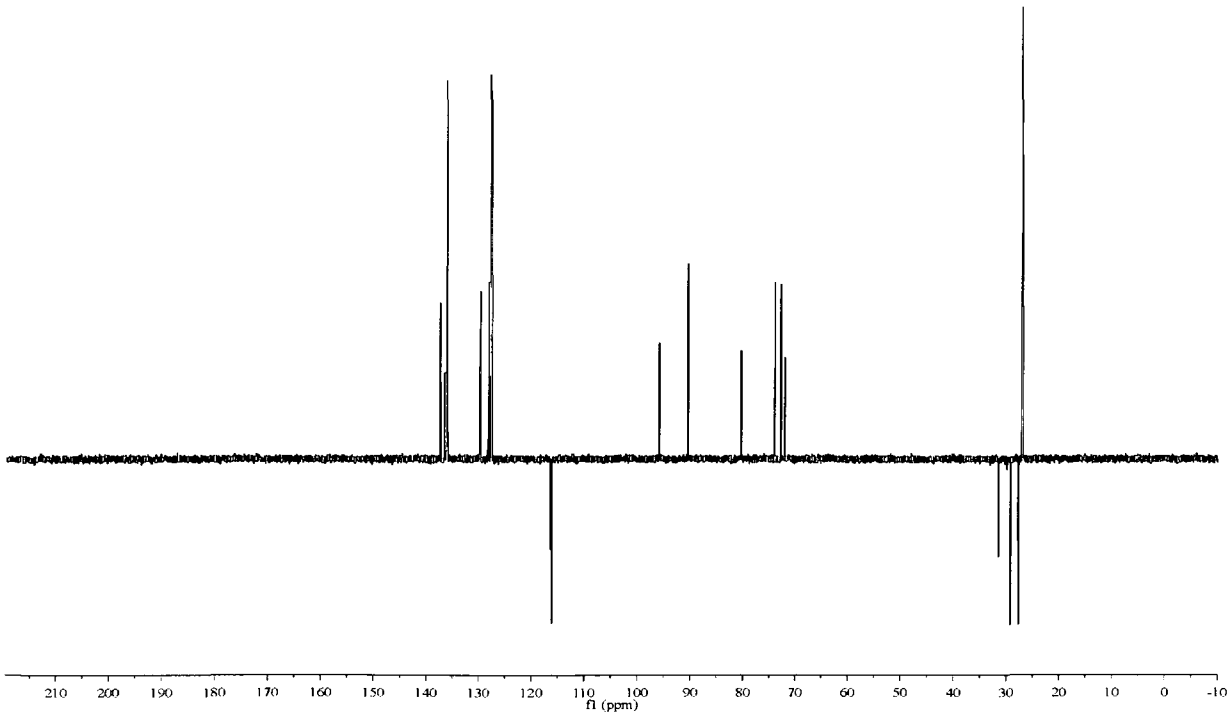
^{1}H NMR (400 MHz, benzene D_6)



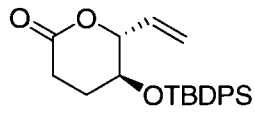
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, C_6D_6)

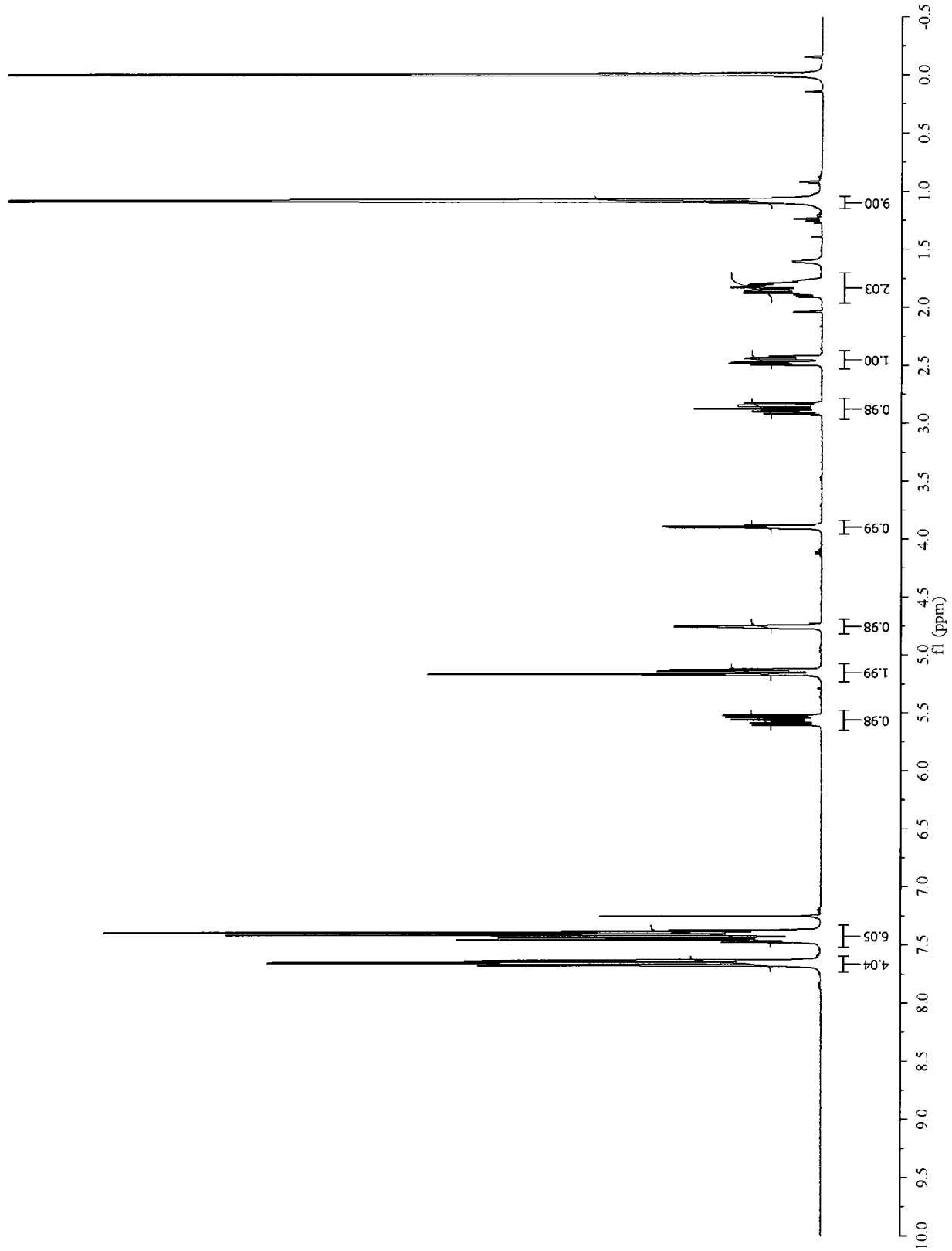


(5*S*,6*R*)-tetrahydro-5-(*tert*-butyldiphenylsilyloxy)-6-vinylpyran-2-one (3.5)

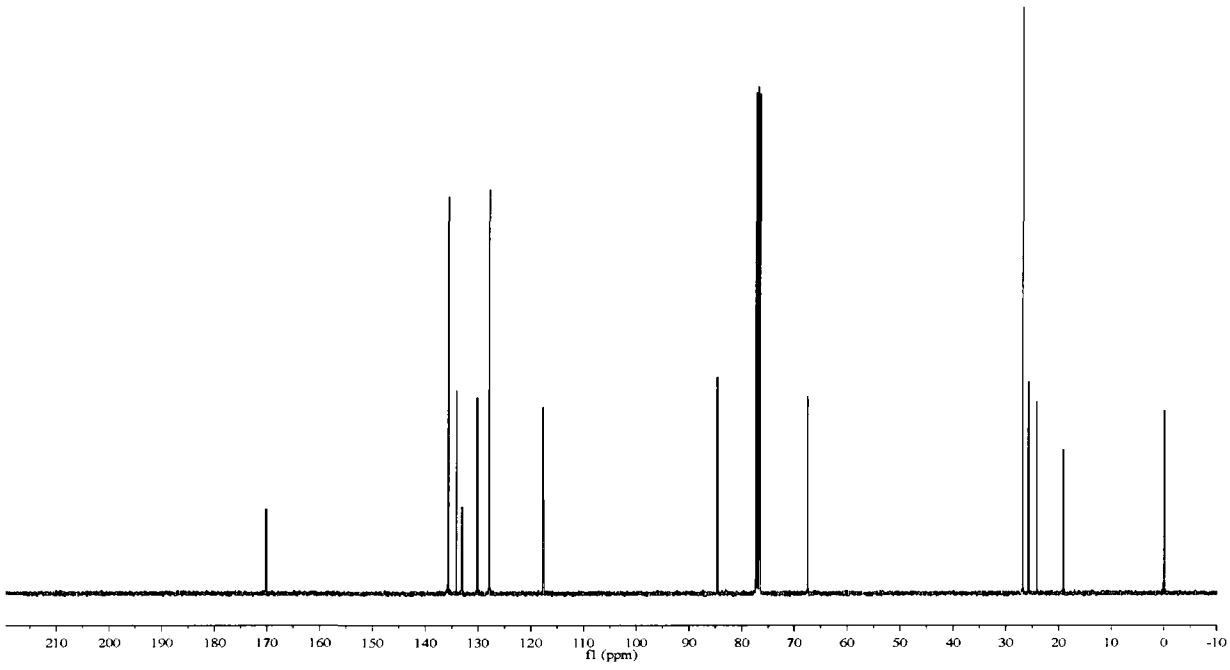


To a solution of lactol **3.13** (489 mg, 1.28 mmol) in 9 mL of dry dichloromethane was added 50 mg of activated 3Å molecular sieves followed by NMO (225 mg, 1.92 mmol). The flask was protected from light and cooled to 0 °C then TPAP (23 mg, 0.065 mmol) was added. The flask was then allowed to warm to room temperature and stirred for one hour at which time TLC analysis demonstrated that the reaction was complete. The mixture was filtered through a pad of celite using dichloromethane as eluent. The filtrate was concentrated and the resulting residue was purified by flash column chromatography on silica gel (1:4 ethyl acetate / hexanes) to afford 457 mg (94%) of the desired lactone as a colorless oil which solidified to a colorless solid upon standing in the fridge. Mp: 54 – 55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (td, J = 7.8, 1.3 Hz, 4H), 7.49 – 7.38 (m, 6H), 5.57 (dddd, J = 17.7, 11.6, 4.8, 1.3 Hz, 1H), 5.17 (d, J = 1.6 Hz, 1H), 5.14 (ddd, J = 6.1, 1.3, 1.0 Hz, 1H), 4.77 – 4.75 (m, 1H), 3.90 (dt, J = 4.5, 2.9 Hz, 1H), 2.88 (ddd, J = 18.2, 11.0, 7.6 Hz, 1H), 2.46 (ddd, J = 18.1, 6.4, 3.2 Hz, 1H), 1.92 – 1.76 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (C), 135.7 (CH (2C)), 135.7 (CH (2C)), 134.2 (CH), 133.1 (C), 133.1 (C), 130.2 (CH), 130.1 (CH), 127.9 (CH (2C)), 127.9 (CH (2C)), 117.8 (CH_2), 84.7 (CH), 67.5 (CH), 26.9 (CH_3 (3C)), 25.7 (CH_2), 24.2 (CH_2), 19.2 (C); IR (neat): υmax 3071 (w), 2931 (m), 2857 (m), 1742 (s), 1472 (w), 1427 (m), 1111 (s), 1009 (m), 928 (m), 822 (m), 703 (s); HRMS (EI) *m/z* M^+ ($C_{23}H_{28}O_3Si$) calculated 380.1808, found 380.1789, M^+ - C_4H_9 ($C_{19}H_{19}O_3Si$) calculated 323.1098, found 323.1106; $[\alpha]^{22}_D$ +28.5°, *c* 13.5 mg/mL (CH_2Cl_2).

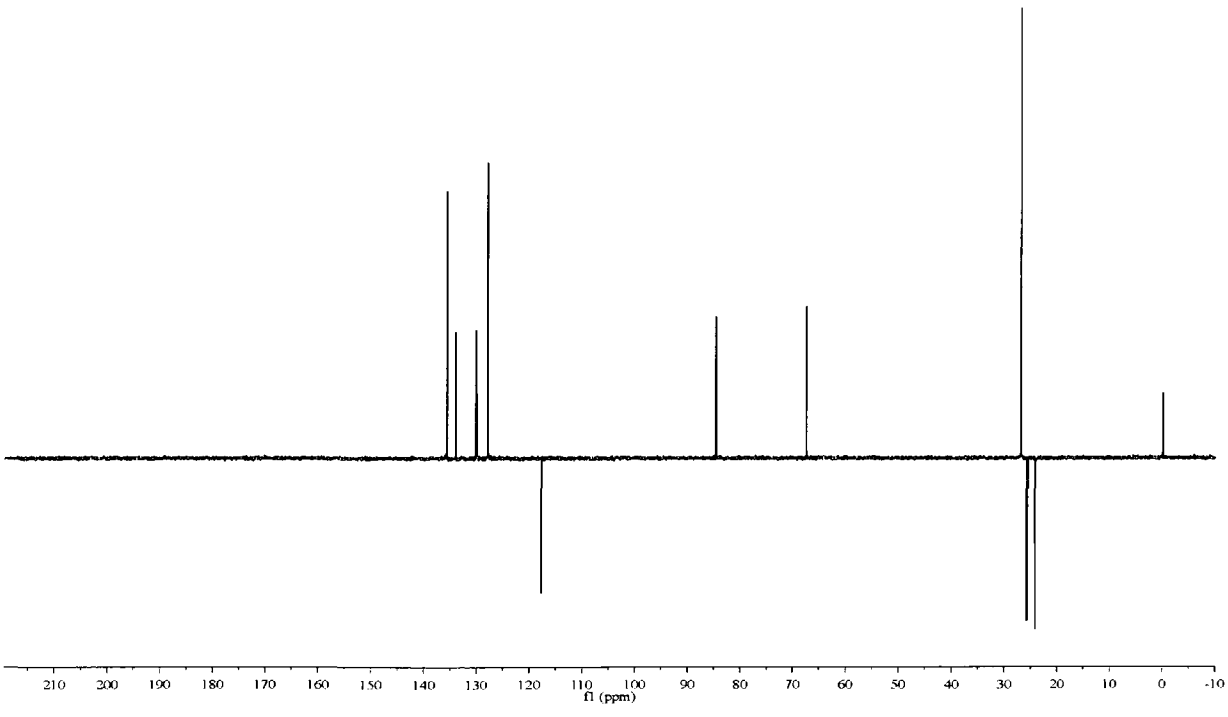
^{1}H NMR (400 MHz, $CDCl_3$)



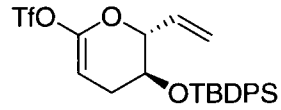
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT 135 (100 MHz, $CDCl_3$)

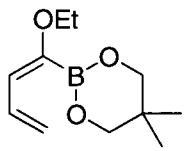


((2*R*,3*S*)-6-((trifluoromethansulfonyl)-3,4-dihydro-2-vinyl-2*H*-pyran-3-yloxy)(tert-butyl)diphenylsilane (3.14)



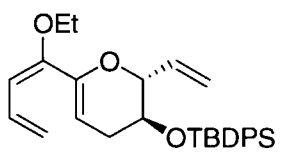
To a solution of lactone **3.5** (250 mg, 0.657 mmol) and phenyltriflimide (329 mg, 0.920 mmol) in 8.0 mL of dry THF at -78 °C was added a solution of KHMDS (406 mg, 2.04 mmol) in 4.0 mL of THF dropwise over one hour. The resulting yellow solution was stirred another 30 minutes while warming to -60 °C. It was then quenched at that temperature by the slow addition of water. Upon warming to room temperature the mixture was diluted with ether and water and the layers were separated. The aqueous layer was extracted three times with ether and the combined organic layers were washed with water then brine. They were then dried over K_2CO_3 and Na_2SO_4, filtered and concentrated. The resulting yellow residue was used as such for the coupling reaction. *Note: Once concentrated, the unpurified triflate was quickly diluted in the solvent used for the coupling reaction and used immediately as it is unstable, especially when concentrated.*

(*E*)-2-[(1-ethoxy)buta-1,3-dienyl]-5,5-dimethyl-[1,3,2]-dioxaborinane (3.16)



Synthesized from diethylacetal **2.12** according to Prandi's procedure.[18b] Used without further purification, yield was assumed quantitative. Spectral data in accord with those reported.

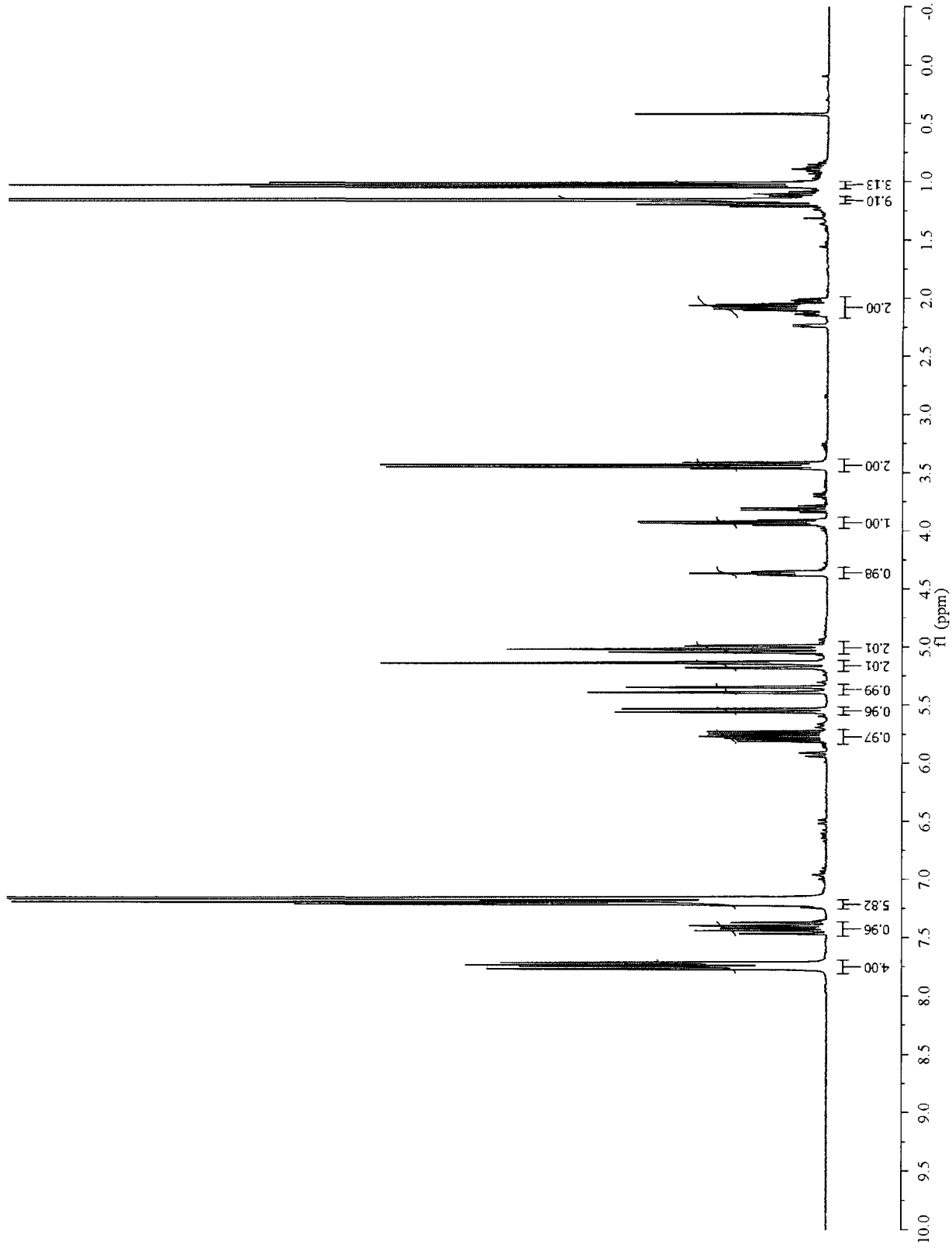
((2*R*,3*S*)-6-((*E*)-1-ethoxybuta-1,3-dienyl)-3,4-dihydro-2-vinyl-2*H*-pyran-3-yloxy)(*tert*-butyl)diphenylsilane (3.15)



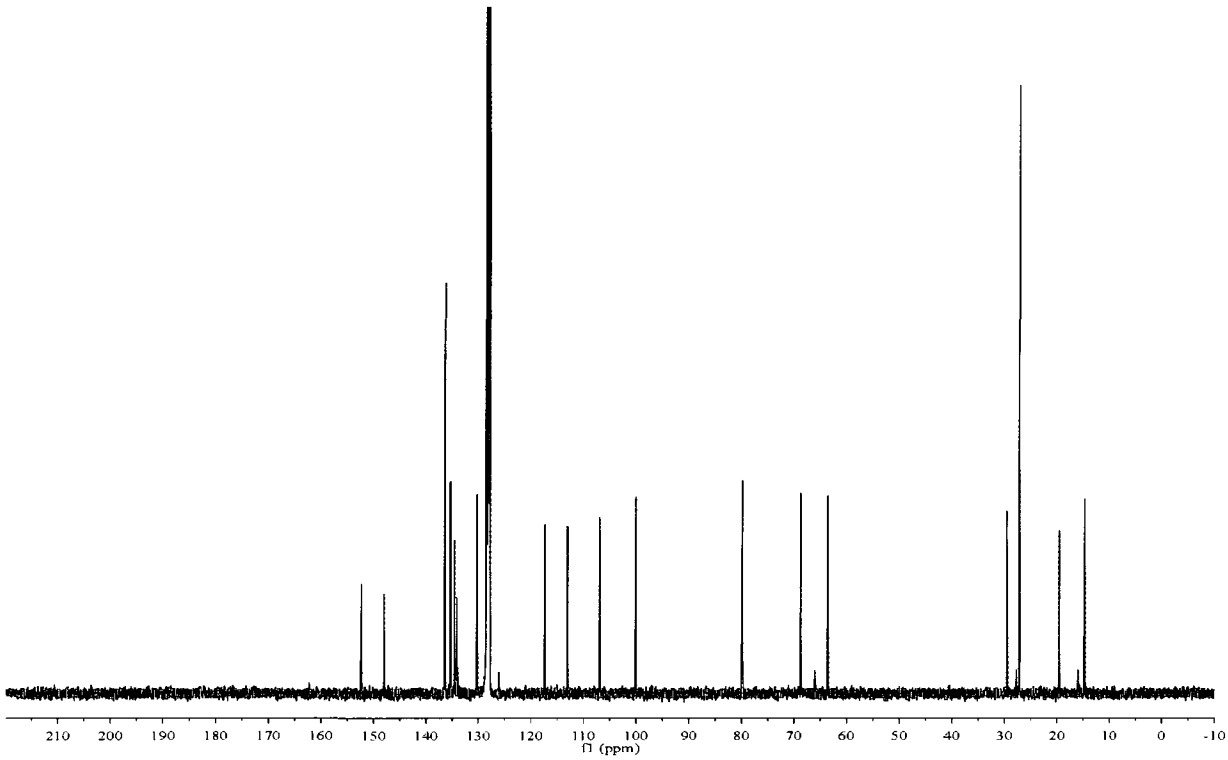
To a solution of the unpurified triflate **3.14** (ca. 0.657 mmol) in 10.0 mL of THF was added a solution of the boronic ester **3.16** (221 mg, 1.05 mmol) in 2.0 mL of THF. To the mixture was added a 2 M aqueous solution of K_2CO_3 (1.31 mL, 2.63 mmol). The mixture was purged 3 times (vacuum / argon cycles) with argon then $Pd(PPh_3)_2Cl_2$ (23.0 mg, 0.033 mmol) was added. After being purged three more times with argon, the mixture was stirred vigorously at room temperature overnight. Water and ether were added and the layers were separated. The aqueous layer was extracted with ether 3 times and the combined organic layers were washed with water then brine. They were then dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified on silica gel pretreated with triethylamine using a gradient elution from 100% hexanes to 10% benzene

and 90% hexanes to afford 176 mg (58% yield over 2 steps calculated from lactone **3.5**) of the desired triene as a light yellow oil. ^{1}H NMR (400 MHz, benzene D_6): δ 7.77 – 7.71 (m, 4H), 7.42 (ddd, J = 17.0, 10.7, 10.3 Hz, 1H), 7.22 – 7.18 (m, 6H), 5.77 (ddd, J = 17.2, 10.7, 5.5 Hz, 1H), 5.55 (d, J = 10.8 Hz, 1H), 5.37 (ddd, J = 17.3, 1.7, 1.7 Hz, 1H), 5.16 (ddd, J = 16.9, 2.1, 0.6 Hz, 1H), 5.14 (dd, J = 4.0, 4.0 Hz, 1H), 5.03 (ddd, J = 10.6, 1.6, 1.6 Hz, 1H), 5.01 (dd, J = 9.9, 1.8 Hz, 1H), 4.36 (dddd, J = 5.7, 5.7, 2.2, 1.4 Hz, 1H), 3.93 (ddd), J = 5.7, 5.7, 5.7 Hz, 1H), 3.44 (q, J = 7.0 Hz, 2H), 2.11 (dddd, J = 17.8, 5.4, 4.2, 0.8 Hz, 1H), 2.04 (ddd, J = 17.6, 5.2, 4.2 Hz, 1H), 1.15 (s, 9H), 1.03 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 152.2 (C), 147.9 (C), 136.3 (CH (2C)), 136.3 (CH (2C)), 135.2 (CH), 134.6 (C), 134.5 (CH), 134.1 (C), 130.1 (CH), 130.1 (CH), 128.1 (CH (2C)), 128.0 (CH (2C)), 117.2 (CH_2), 112.9 (CH_2), 106.8 (CH), 100.1 (CH), 79.9 (CH), 68.7 (CH), 63.6 (CH_2), 29.5 (CH_2), 27.2 (CH_3 (3C)), 19.5 (C), 14.7 (CH_3); IR (neat): υmax 3072 (m), 2931 (s), 2858 (s), 1617 (s), 1472 (m), 1427 (s), 1363 (w), 1112 (s), 929 (w), 882 (m), 740 (s), 702 (s), 612 (w); HRMS (EI) *m/z* M^+ ($C_{29}H_{36}O_3Si$) calculated 460.2434, found 460.2437; $[\alpha]^{22}_D$ +5.2°, *c* 11.0 mg/mL (CH_2Cl_2).

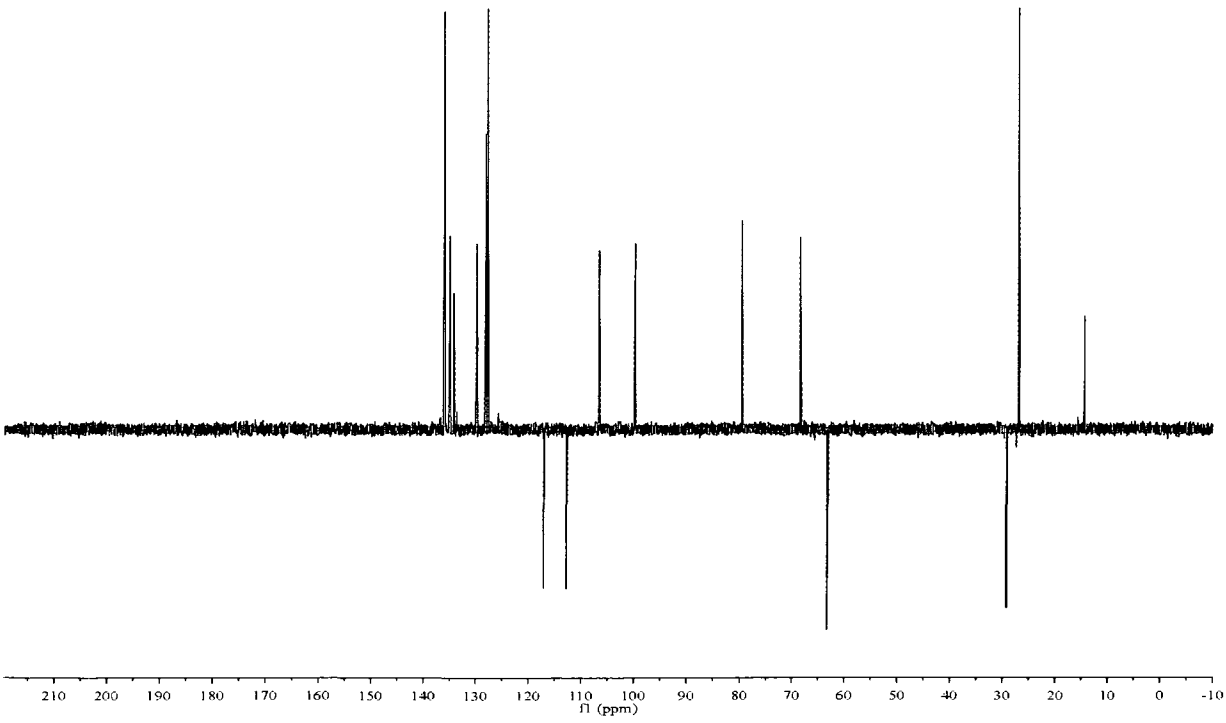
^{1}H NMR (400 MHz, benzene D_6)



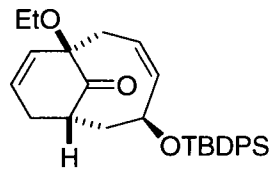
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

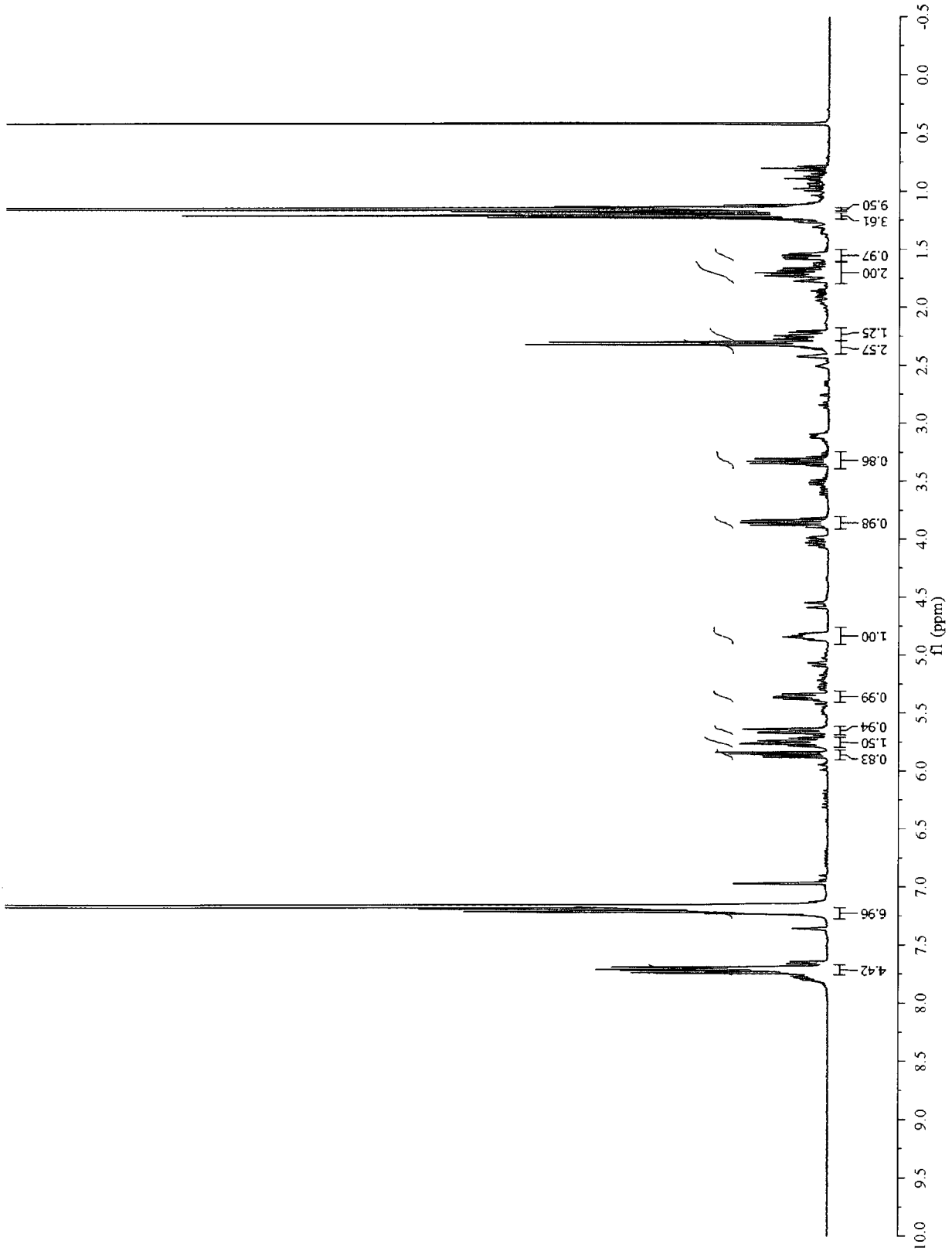


(1*R*,5*S*,7*S*,*Z*)-5-(*tert*-butyldiphenylsilyloxy)-1-ethoxybicyclo[5.3.1]undeca-3,9-dien-11-one (3.17)

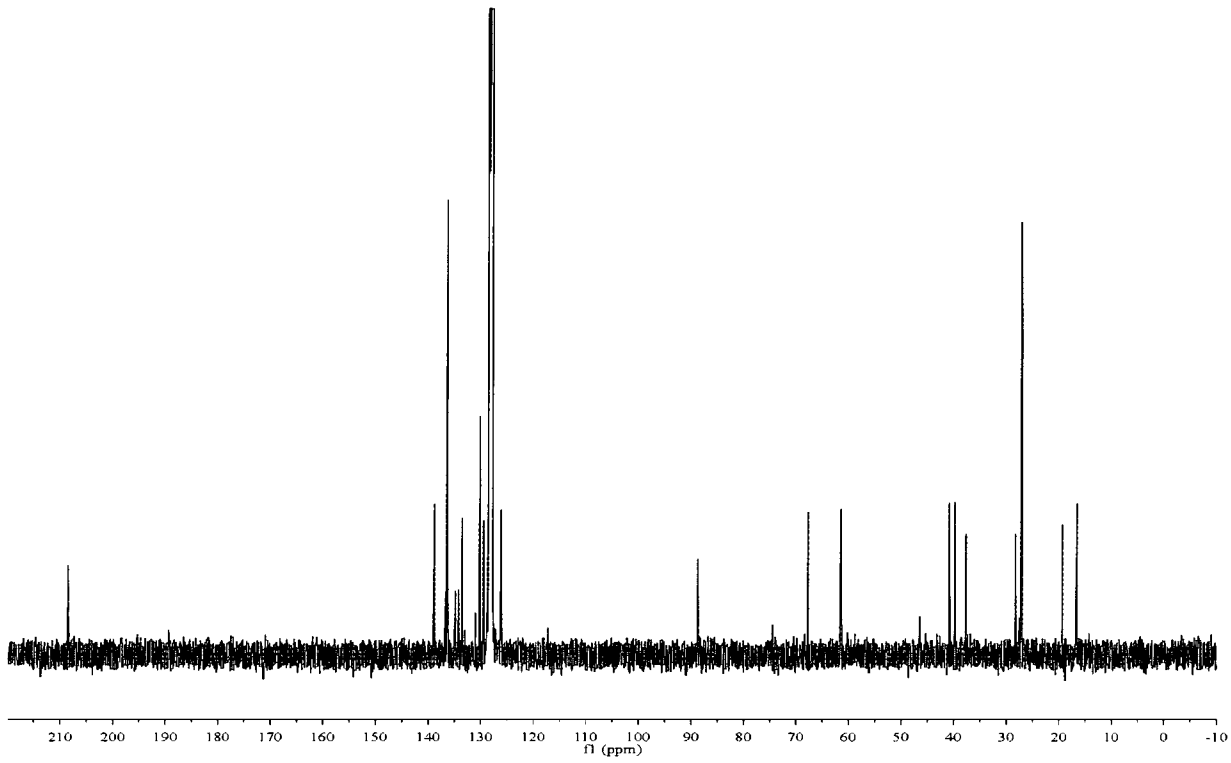


In a flame dried microwave tube containing a carboflon was loaded triene **3.15** (5.0 mg, 0.011 mmol) and toluene (2.5 mL) followed by triethylamine (50 μL). Argon was bubbled through the mixture for 10 minutes then the tube was sealed and irradiated in the microwave at 180 °C for 2h 20min. Once the mixture had cooled to room temperature, it was concentrated and purified by flash chromatography on silica gel pretreated with triethylamine using a gradient elution (0% to 5% Et_2O in hexanes) to afford 1.2 mg (24% yield) of the desired product as a light yellow oil. Other byproducts were observed by TLC analysis but could not be obtained in sufficient amount and purity for characterization. Rf = 0.37 with 5% Et_2O in hexanes as eluent (TLC plate pretreated with triethylamine); ^1H NMR (400 MHz, benzene D_6): δ 7.75 – 7.69 (m, 4H), 7.23 – 7.18 (m, 6H), 5.86 (dd, J = 10.9, 5.8 Hz, 1H), 5.75 (ddd, J = 10.5, 8.5, 1.8 Hz, 1H), 5.66 (dd, J = 9.9, 2.5 Hz, 1H), 5.36 (ddd, J = 9.8, 5.8, 2.8 Hz, 1H), 4.87 – 4.81 (m, 1H), 3.86 (dq, J = 8.9, 7.0 Hz, 1H), 3.33 (dq, J = 9.0, 7.0 Hz, 1H), 2.36 – 2.30 (m, 2H), 2.31 (d, J = 8.5 Hz, 1H), 2.24 (ddd, J = 13.5, 11.0, 4.6 Hz, 1H), 1.73 (dddd, J = 18.2, 7.3, 2.9, 2.9 Hz, 1H), 1.67 (ddd, J = 18.4, 8.6, 5.9 Hz, 1H), 1.56 (ddd, J = 13.4, 5.3, 2.8 Hz, 1H), 1.21 (t, J = 7.0 Hz, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, benzene D_6): δ 208.4 (C), 138.8 (CH), 136.3 (CH (4C)), 134.7 (C), 134.1 (C), 133.4 (CH), 130.1 (CH (2C)), 129.4 (CH), 128.2 (CH (2C)), 127.9 (CH (2C)), 126.0 (CH), 88.7 (C), 67.7 (CH), 61.4 (CH_2), 40.9 (CH), 39.8 (CH_2), 37.7 (CH_2), 28.2 (CH_2), 27.1 (CH_3 (3C), 19.4 (C), 16.6 (CH_3); IR (neat): υmax 3027 (w), 2931 (s), 2857 (m), 1724 (s), 1472 (m), 1427 (m), 1391 (w), 1112 (s), 1072 (s), 822 (m), 763 (w), 741 (w), 702 (s), 613 (w); HRMS (EI) *m/z* M^+ ($C_{29}H_{36}O_3Si$) calculated 460.2434, found 460.2422; $[\alpha]^{22}_D$ -45.8°, *c* 4.1 mg/mL (CH_2Cl_2).

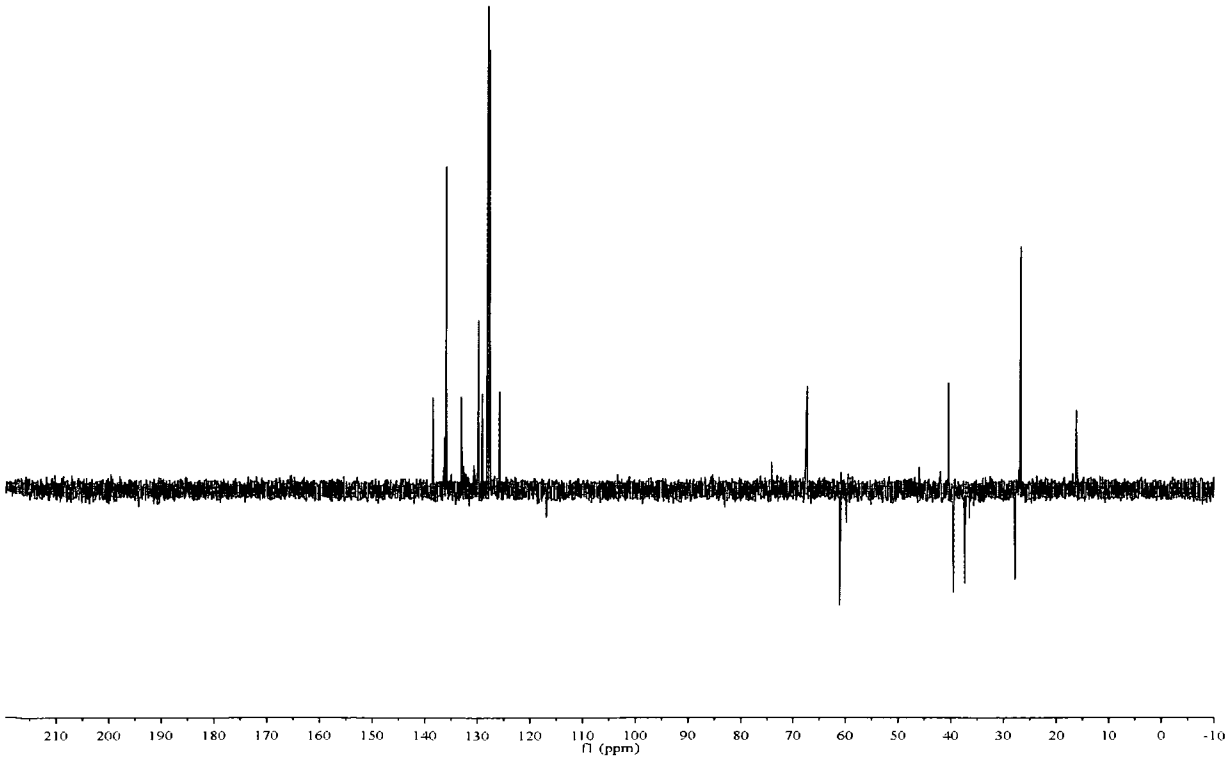
^{1}H NMR (400 MHz, benzene D_6)



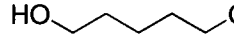
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

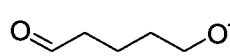


5-(tetrahydro-2*H*-pyran-2-yloxy)pentan-1-ol (3.26)



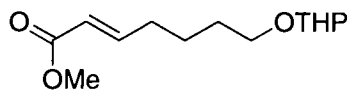
To a biphasic mixture of 1,5-pentanediol (15.1 g, 145 mmol) and DCM (170 mL) was added camphorsulfonic acid (3.37 g, 14.5 mmol) at room temperature followed by 2,3-dihydropyran (13.2 mL, 145 mmol). Upon completion of the addition of DHP, the mixture became homogenous. It was stirred overnight then diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$ (2 times) then with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel pretreated with triethylamine, using a gradient elution from 9:1 Hexanes / diethyl ether to 4:1 diethyl ether / Hexanes. 11.8 g (43% yield) of the desired mono-protected diol were obtained as a colorless oil. Its spectral data was in accord of those of the previously reported compound.[34]

5-(tetrahydro-2*H*-pyran-2-yloxy)pentanal (3.27)



To a solution of alcohol **3.26** (9.54 g, 50.7 mmol) in 120 mL of DMSO was added triethylamine (70.6 mL, 507 mmol). To the resulting vigorously stirred biphasic mixture at room temperature was added a solution of pyridine-SO_3 (26.6 g, 167 mmol) in DMSO (120 mL). After 10 minutes, TLC analysis showed no more starting material present. The mixture was poured in 500 mL of water and extracted three times with diethyl ether. The combined organic extracts were washed three times with a saturated aqueous copper sulfate solution, then with water and finally with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel pretreated with triethylamine using a gradient elution from 10% diethyl ether in hexanes to 60% diethyl ether in hexanes to afford 8.56 g (91% yield) of the desired aldehyde as a colorless oil. Spectral data were in accord with those of the previously reported compound.[34]

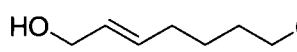
(*E*)-methyl 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-enoate (3.28)



To a solution of aldehyde **3.27** (1.55 g, 8.32 mmol) in 23 mL of DCM was added a solution of Ph_3PCHCO_2Me (3.90 g, 11.7 mmol) in 22 mL of DCM at room temperature. The resulting mixture was stirred for two days. It was then concentrated and taken up in a 1:1 mixture of hexanes and diethyl ether. The solid material was filtered out and the filtrate was concentrated again. The resulting residue was purified by

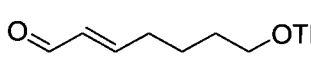
flash column chromatography on silica gel using a gradient elution from hexanes to 30% diethyl ether in hexanes to afford 1.77 g (88% yield) of the desired product as a colorless oil. Spectral data were in accord with those of the previously reported compound.[34]

(*E*)-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-en-1-ol (3.29)



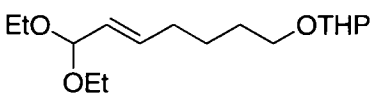
To a solution of ester **3.28** (0.70 g, 2.89 mmol) in 16 mL of toluene at – 78 °C was added a 1.0 M solution of DIBAL-H in toluene (8.67 mL, 8.67 mmol) dropwise. The mixture was stirred at -78 °C for one hour at which time TLC analysis showed no more starting material remained. Water (3.5 mL) was carefully added to the mixture and it was allowed to warm to room temperature at which time it was diluted with ethyl acetate. The resulting viscous mixture was stirred vigorously while solid $NaHCO_3$ was added. The resulting granular solid was filtered out and washed with ethyl acetate. The filtrate was concentrated and purified by flash column chromatography on silica gel using a gradient elution from 40% diethyl ether in hexanes to diethyl ether afforded 614 mg (99% yield) of the desired allylic alcohol as a colorless oil. Spectral data were in accord with those of the previously reported compound.[34]

(*E*)-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-enal (3.30)



To a solution of allylic alcohol **3.29** (8.19 g, 38.2 mmol) in 240 mL of DCM was added 8.5 g of activated powdered 4 Å molecular sieves followed by NMO (6.72 g, 57.3 mmol). The flask was cooled to 0 °C and protected from light before TPAP (336 mg, 0.96 mmol) was added. The reaction mixture was then allowed to warm to room temperature and stirred overnight at which time TLC analysis showed no more starting alcohol remained. The mixture was filtered through a short pad of silica using DCM as eluent then concentrated. The filtrate was purified by flash column chromatography on silica gel using a gradient elution from 5% diethyl ether in hexanes to 30% diethyl ether in hexanes to afford 7.41 g (91% yield) of the desired enal as a colorless oil. Spectral data were in accord with those of the previously reported compound.[34]

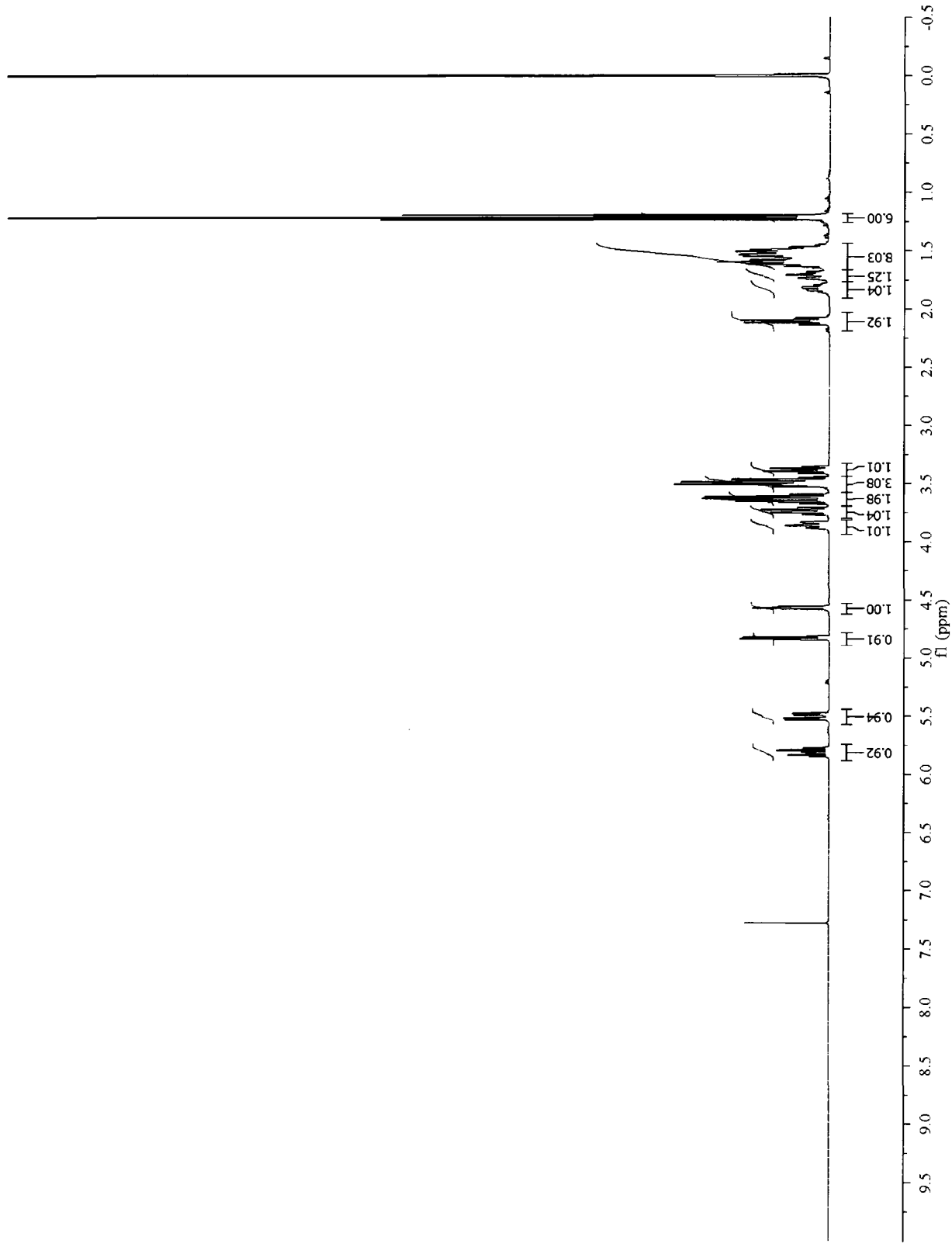
2-((*E*)-7,7-diethoxyhept-5-enyloxy)-tetrahydro-2*H*-pyran (3.31)



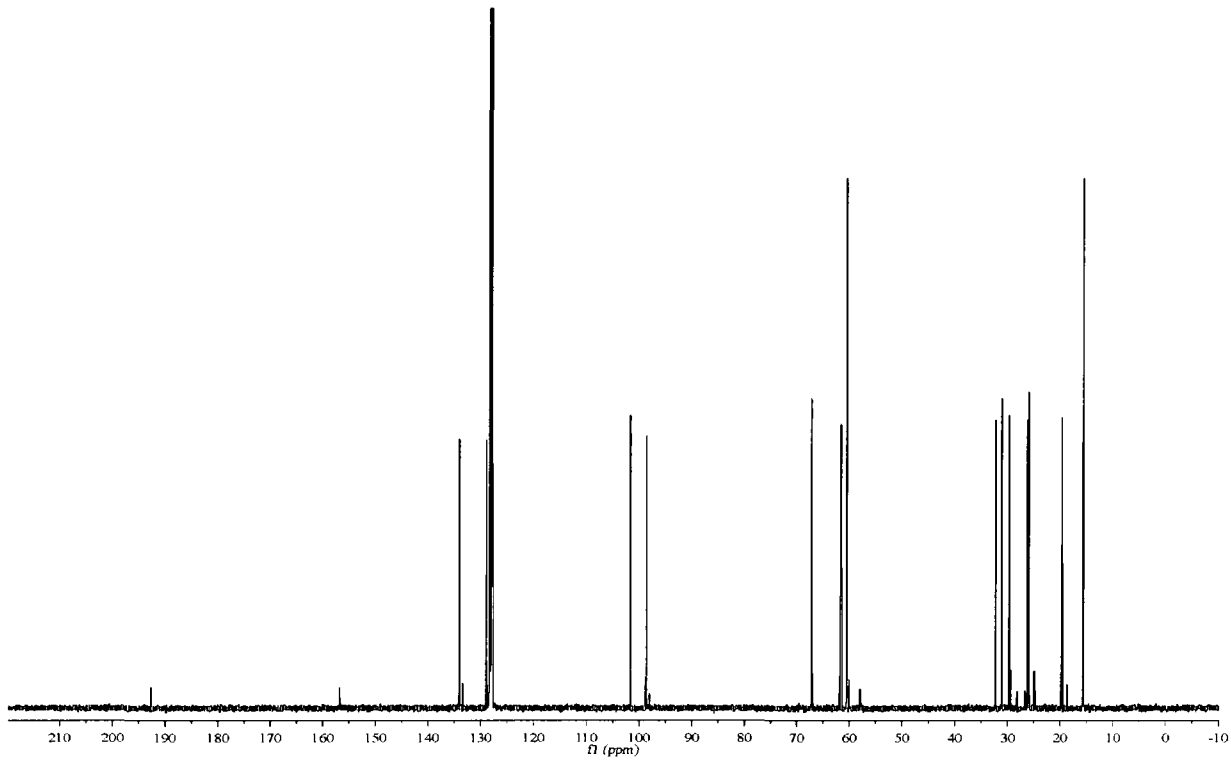
To a solution of enal **3.30** (100 mg, 0.471 mmol) in 2 mL of 99% ethanol was added triethyl orthoformate (82 μL, 0.495 mmol).

The flask was protected from light and NBS (0.8 mg, 0.005 mmol) was added. After 1 hour, no more starting enal could be detected by TLC. Solid K_2CO_3 was added (~10 mg) and the mixture was concentrated. The resulting residue was purified by flash column chromatography on silica gel pretreated with triethylamine with a 10% diethyl ether in hexanes mixture as eluent. 130 mg (96% yield) of the desired acetal was obtained as a colorless oil which decomposed rapidly back to the aldehyde in the presence of moisture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (dt, J = 15.6, 6.7 Hz, 1H), 5.51 (ddt, J = 15.6, 5.6, 1.5 Hz, 1H), 4.84 (d, J = 5.6 Hz, 1H), 4.58 (dd, J = 4.3, 2.6 Hz, 1H), 3.87 (ddd, J = 11.1, 7.6, 3.4 Hz, 1H), 3.74 (dt, J = 9.6, 6.6 Hz, 1H), 3.65 (q, J = 7.1 Hz, 1H), 3.63 (q, J = 7.1 Hz, 1H), 3.53 – 3.45 (m, 3H), 3.39 (dt, J = 9.6, 6.4 Hz, 1H), 2.11 (q, J = 7.0 Hz, 2H), 1.86 – 1.79 (m, 1H), 1.75 – 1.68 (m, 1H), 1.65 – 1.45 (m, 8H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, benzene D_6): δ 134.1 (CH), 128.9 (CH), 101.7 (CH), 98.6 (CH), 67.3 (CH_2), 61.6 (CH_2), 60.5 (CH_2 (2C)), 32.3 (CH_2), 31.1 (CH_2), 29.7 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 19.7 (CH_2), 15.6 (CH_3); IR (neat): υmax 2938 (s), 2871 (s), 1694 (m), 1446 (m), 1350 (m), 1125 (s), 1035 (s), 993 (s), 906 (w), 871 (w) 813 (w); HRMS (EI) *m/z* M^+ not found, $M^+ - C_2H_5O$ ($C_{14}H_{25}O_3$) calculated 241.1798, found 241.1826.

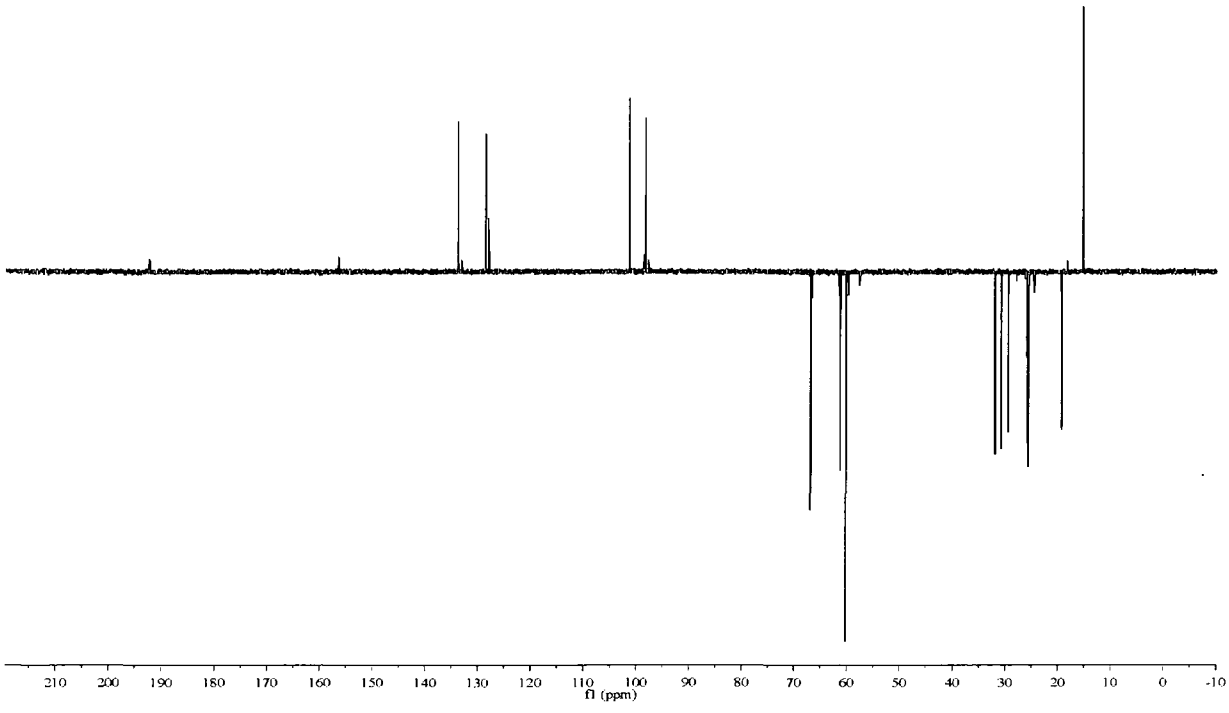
^{1}H NMR (400 MHz, $CDCl_3$)



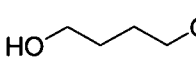
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

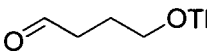


4-(tetrahydro-2*H*-pyran-2-yloxy)butan-1-ol (3.40)



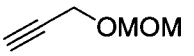
To a biphasic mixture of 1,4-butanediol (10.0 mL, 113 mmol) and DCM (110 mL) was added camphorsulfonic acid (1.31 g, 5.63 mmol) at room temperature followed by 2,3-dihydropyran (5.13 mL, 56.26 mmol). Upon completion of the addition of DHP, the mixture became homogenous. It was stirred overnight then diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$ (2 times) then with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel pretreated with triethylamine, using a gradient elution from 9:1 Hexanes / diethyl ether to 4:1 diethyl ether / Hexanes. 6.92 g (71% yield) of the desired mono-protected diol were obtained as a colorless oil. Its spectral data was in accord of those of the previously reported compound.[34]

4-(tetrahydro-2*H*-pyran-2-yloxy)butanal (3.41)



Same procedure as for aldehyde **3.27**. Obtained 4.70 g (69% yield) of the desired aldehyde as a colorless oil. Spectral data for this compound were in accord with those previously reported.[34]

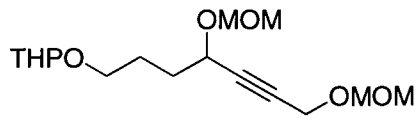
3-(methoxymethoxy)prop-1-yne (3.37)



Procedure adapted from Piers and Tillyer[36]

To a solution of propargyl alcohol (3 mL, 51.5 mmol) in 100 mL of dichloromethane was added N,N'-diisopropylethylamine (18.0 mL, 103 mmol). The mixture was cooled to 0 °C then chloromethyl methyl ether (7.44 mL, 97.9 mmol) was added dropwise (white fumes are generated). The resulting mixture was stirred for four hours at 0 °C then allowed to warm to room temperature while stirring overnight. At that time, a saturated aqueous solution of $NaHCO_3$ was added to the yellow mixture and the layers were separated. The organic layer was washed with 10 mL of a 5% HCl solution (2 times) followed by brine. It was then dried over $MgSO_4$, filtered and concentrated to ~15 mL. The product was then distilled with a short (6 cm) Vigreux apparatus (100 to 110 °C at atmospheric pressure) to afford 4.64 g (90% yield) of the desired product as a colorless liquid. Spectral data was in accord with that previously reported.[50]

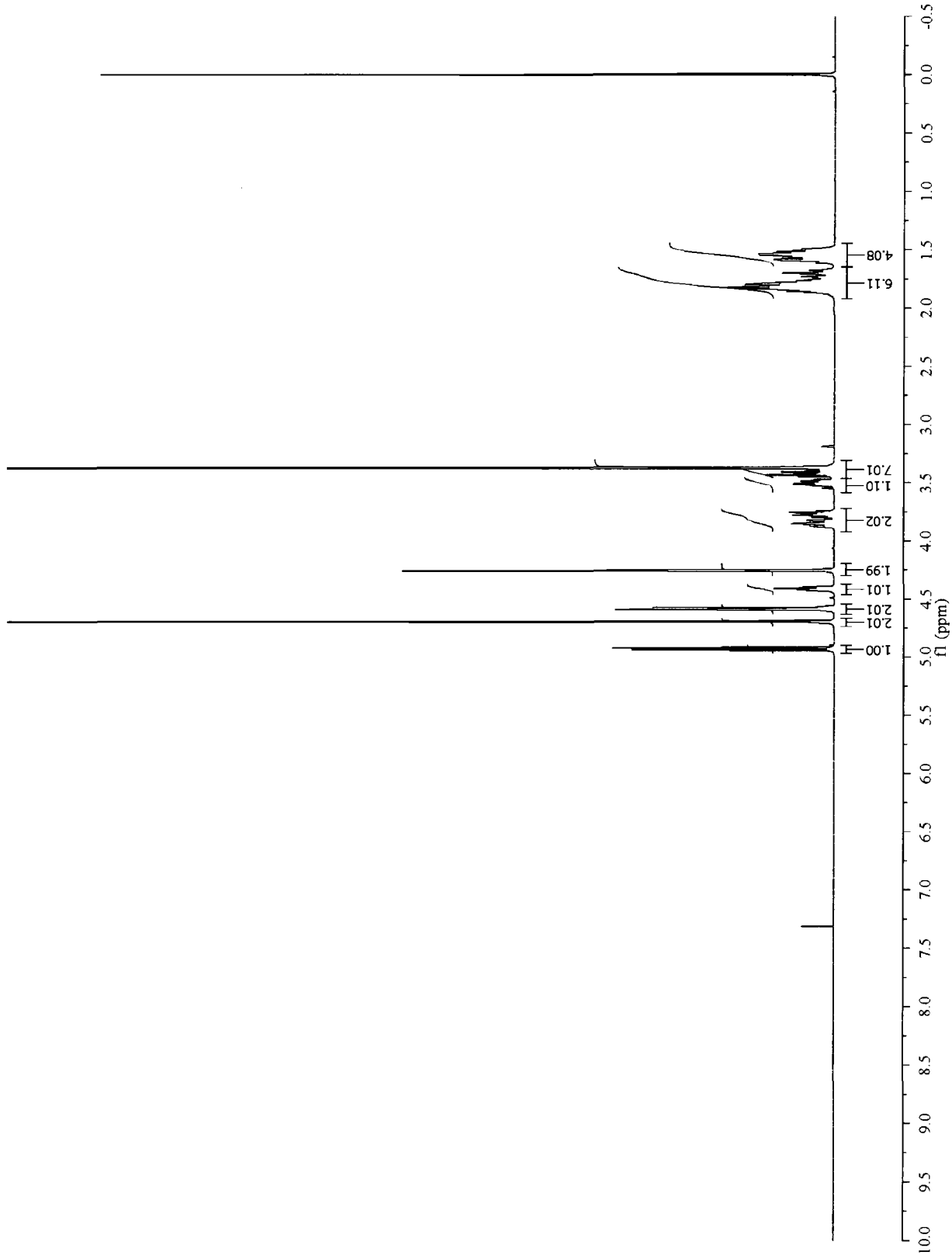
2-(4,7-bis(methoxymethoxy)hept-5-ynyloxy)-tetrahydro-2*H*-pyran (3.42)



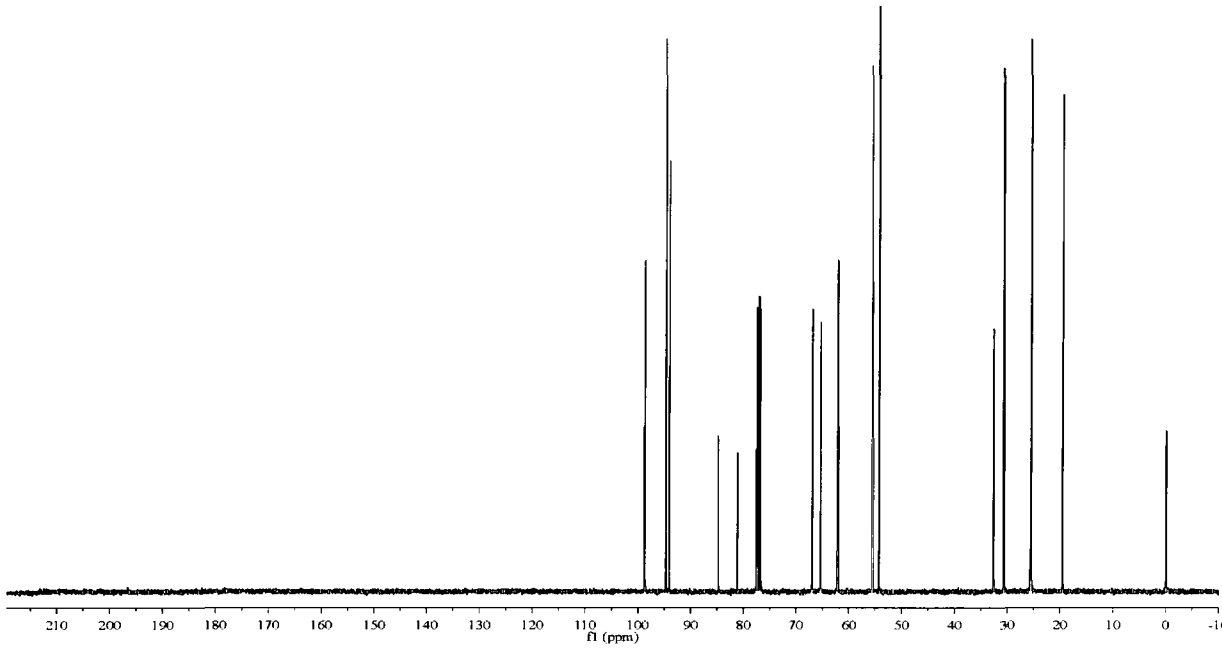
Procedure adapted from Wasserman and Pearce[51]

To a solution of alkyne **3.37** (0.60 g, 5.99 mmol) in 15 mL of diethyl ether at -78 °C was added *n*-BuLi (1.75 M in pentane, 3.77 mL, 6.59 mmol) dropwise. After 30 minutes at -78 °C, a solution of aldehyde **3.41** (1.14 g, 6.59 mmol) in 3 mL of diethyl ether was added dropwise to the resulting white suspension. The mixture was stirred for another hour at this temperature before allowing it to gradually warm to room temperature (the white suspension becomes a colorless clear solution upon warming). Once the mixture had warmed to room temperature, TLC analysis showed that no more aldehyde remained therefore the reaction mixture was cooled to -10 °C and chloromethyl methyl ether (0.59 mL, 7.79 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for another hour (the clear, colorless solution becomes milky white). At that time, it was diluted with diethyl ether and quenched with water. The layers were separated and the aqueous layer extracted 2x with diethyl ether. The combined organic extracts were washed with brine then dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel using a gradient elution from hexanes to 4 : 6 diethyl ether/hexanes to afford 1.50 g (79% yield) of the desired product as a 1 : 1 mixture of diasteromers in the form of a colorless oil. ^{1}H NMR(400 MHz, $CDCl_3$): δ 4.94 (d, J = 6.8 Hz, 1H), 4.70 (s, 2H), 4.59 (d, J = 6.7 Hz, 2H), 4.42 (dd, J = 6.2, 6.2 Hz, 1H), 4.26 (d, J = 1.6 Hz, 2H), 3.88 – 3.83 (m, 1H), 3.80 – 3.75 (m, 1H), 3.55 – 3.48 (m, 1H), 3.45- 3.40 (m, 1H), 3.38 (s, 6H), 1.88 – 1.68 (m, 6H), 1.62 – 1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.7 (CH), 94.7 (CH_2), 94.1 (CH_2), 84.8 (C), 81.2 (C), 67.0 (CH_2), 65.4 (CH), 62.2 (CH_2), 55.6 (CH_3), 55.5 (CH_3), 54.3 (CH_2), 32.6 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 19.5 (CH_2); IR (neat): υmax 2944 (s), 2888 (s), 1443 (m), 1353 (m), 1201 (m), 1152 (s), 1102 (s), 1035 (s), 990 (s), 922 (s), 869 (m), 814 (w); HRMS (EI) *m/z* M^+ not found.

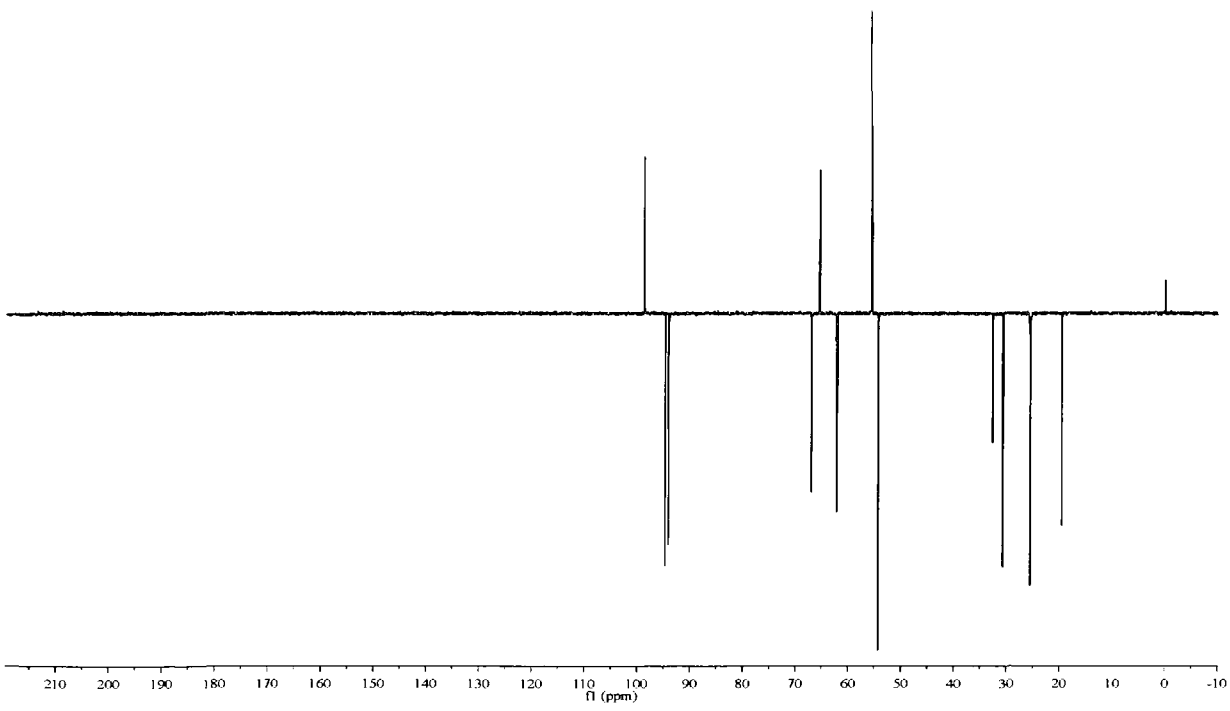
^{1}H NMR(400 MHz, $CDCl_3$)



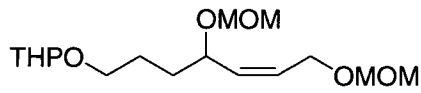
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT 135 (100 MHz, $CDCl_3$)

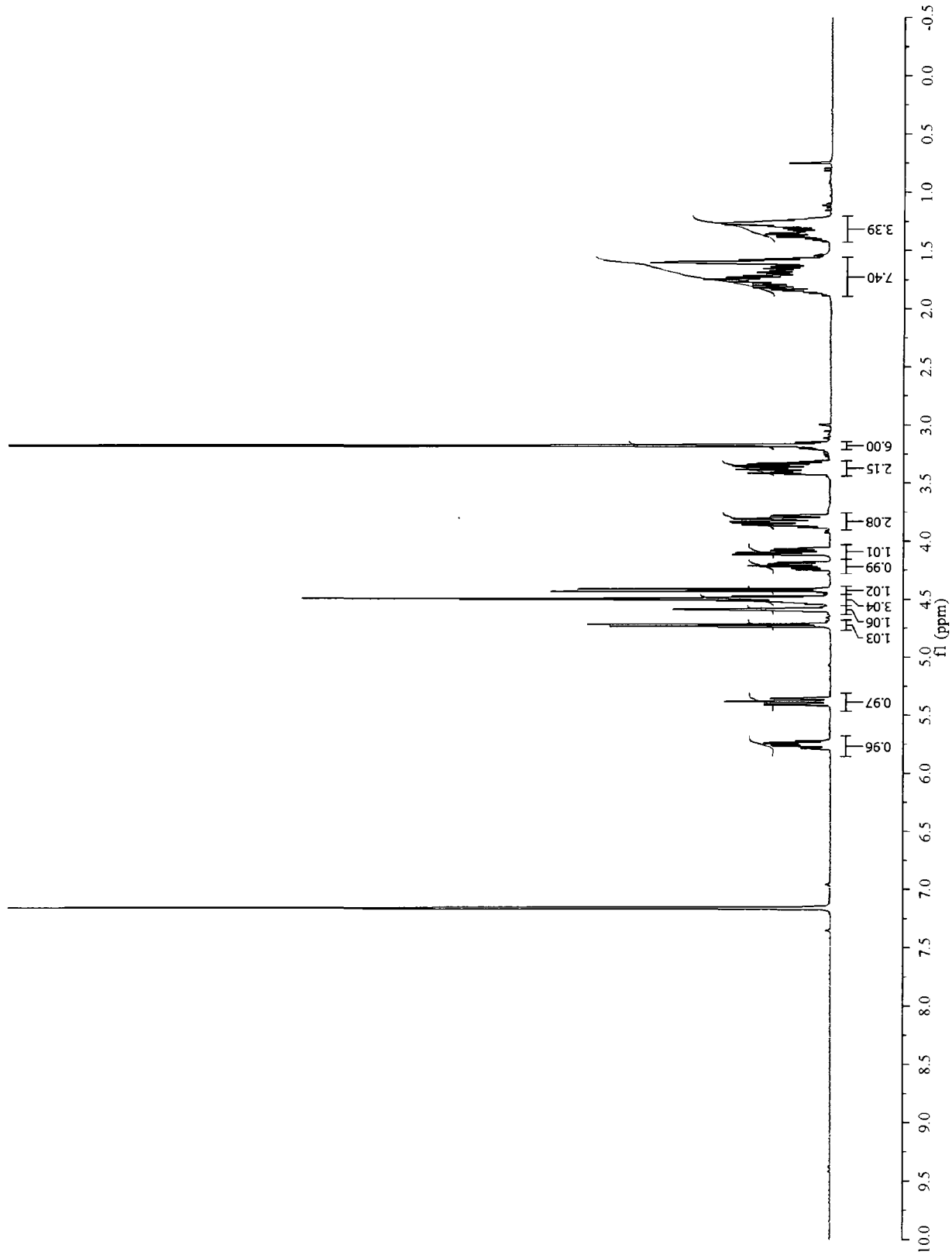


2-((*Z*)-4,7-bis(methoxymethoxy)hept-5-enyloxy)-tetrahydro-2*H*-pyran (3.43)

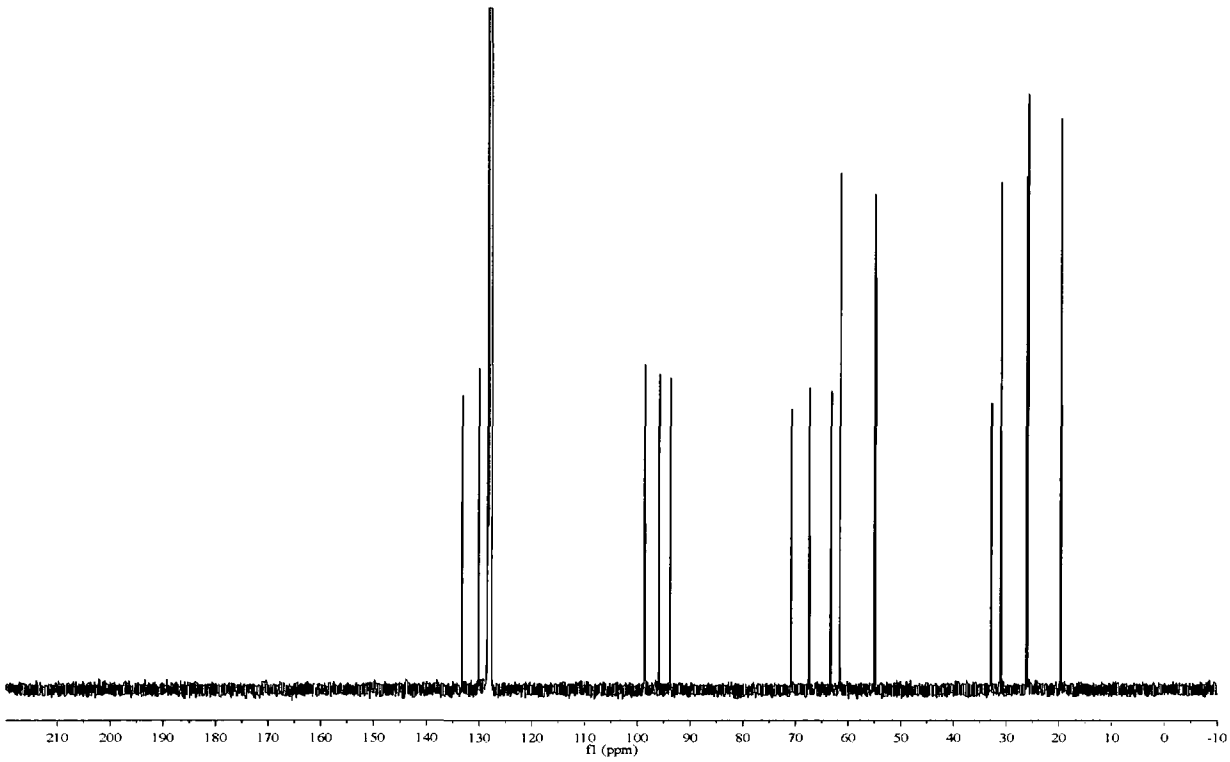


To a solution of the alkyne **3.42**(0.41 g, 1.30 mmol) in 10 mL of dry methanol was added Lindlar's catalyst (5% Pd wt, 138 mg, 0.068 mmol). The mixture was purged with hydrogen (3 times) then stirred under an atmosphere of hydrogen for 4 hours. The mixture was then diluted with diethyl ether and filtered through a pad of celite then concentrated to afford the desired alkene as an inseparable 1 : 1 mixture of diastereomers in the form of a colorless oil (382 mg, 93% yield). ^{1}H NMR (400 MHz, benzene D_6): δ 5.76 (dt, J = 11.6, 5.9 Hz, 1H), 5.39 (dd, J = 10.3, 10.3 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 4.59 (dd, J = 3.2, 3.2 Hz, 1H), 4.55 – 4.48 (m, 3H), 4.43 (d, J = 6.7 Hz, 1H), 4.21 (dddd, J = 12.6, 7.2, 4.4, 1.4 Hz, 1H), 4.10 (ddt, J = 12.6, 5.9, 1.9 Hz, 1 H), 3.89 – 3.78 (m, 2H), 3.43 – 3.32 (m, 2H), 3.18 (s, 3H), 3.18 (s, 3H), 1.89 – 1.57 (m, 7H), 1.43 – 1.23 (m, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 133.3 (CH), 130.1 (CH), 98.7 (CH), 96.0 (CH_2), 93.8 (CH_2), 70.8 (CH), 67.4 (CH_2), 63.3 (CH_2), 61.6 (CH_2), 55.1 (CH_3), 54.9 (CH_3), 32.9 (CH_2), 31.1 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 19.7 (CH_2); IR (neat): υmax 2941 (s), 2882 (s), 2064 (w), 1466 (m), 1446 (m), 1399 (w), 1348 (w), 1258 (w), 1200 (m), 1023 (s), 914 (s), 863 (m), 812 (m), 742 (w); HRMS (EI) *m/z* M^+ not found.

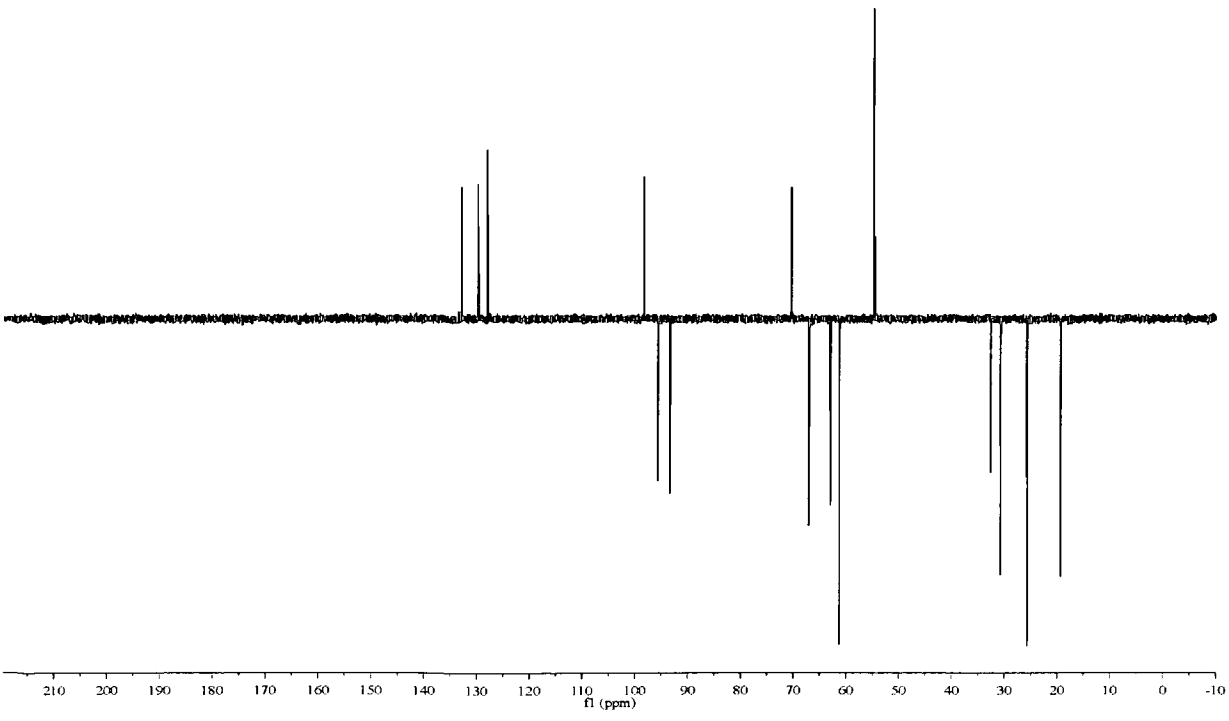
^{1}H NMR (400 MHz, benzene D_6)



^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

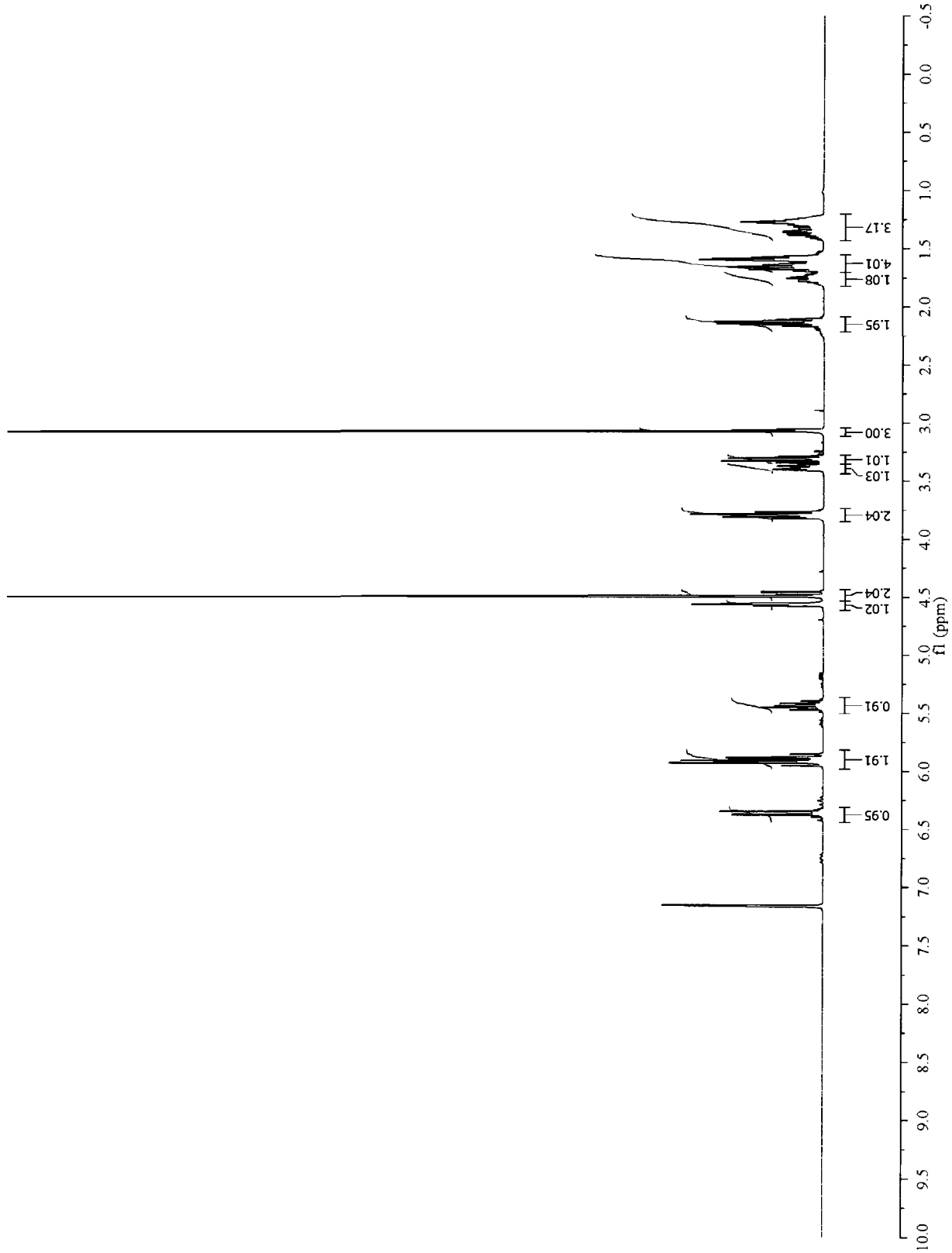


2-((4*E*,6*E*)-7-(methoxymethoxy)hepta-4,6-dienyloxy)-tetrahydro-2*H*-pyran (3.44)

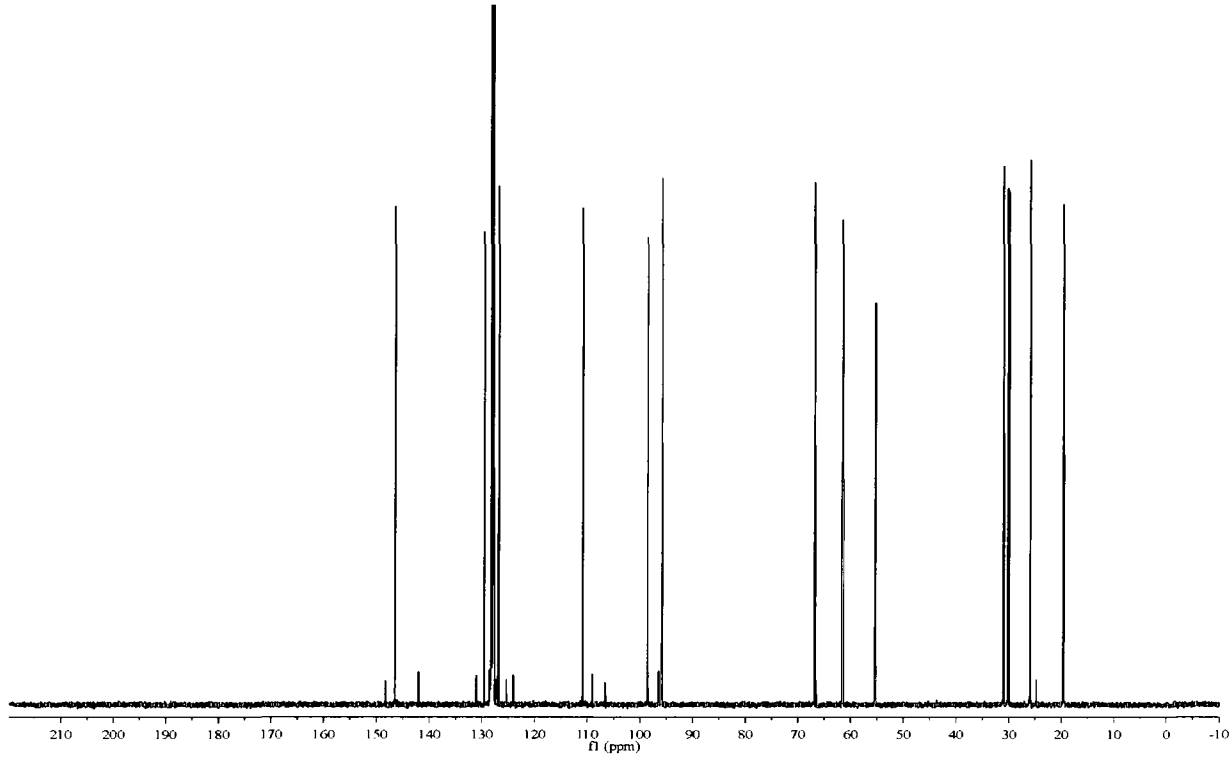
Procedure adapted from McDougal and Rico[52]

To a freshly prepared solution of LDA (11.3 mmol) in 17 mL of THF was added a solution of alkene **3.43** (0.60 g, 1.88 mmol) in 3 mL of THF dropwise at -78 °C. The resulting solution was stirred for two hours at this temperature then allowed to warm to room temperature gradually over one hour. Upon warming, the colorless solution becomes yellow then orange. The mixture was diluted with diethyl ether and water was added. The layers were separated and the aqueous layer extracted with diethyl ether 3 times. The combined organic extracts were washed with brine then dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel pretreated with triethylamine using a gradient elution from hexanes to 15 : 85 diethyl ether/hexanes to afford 432 mg (89% yield) of the desired diene as a colorless oil. ^{1}H NMR (400 MHz, benzene D_6): δ 6.36 (d, J = 11.4 Hz, 1H), 5.96 – 5.86 (m, 2H), 5.49 – 5.39 (m, 1H), 4.57 (dd, J = 3.4, 3.4 Hz, 1H), 4.50 (s, 2H), 3.83 – 3.77 (m, 2H), 3.39 (dddd, J = 11.1, 4.4, 4.4, 1.3 Hz, 1H), 3.32 (ddd, J = 9.6, 6.4, 6.4 Hz, 1H), 3.07 (s, 3H), 2.14 (dt, J = 7.0, 7.0 Hz, 2H), 1.80 – 1.71 (m, 1H), 1.70 – 1.63 (m, 2H), 1.62 – 1.56 (m, 2H), 1.43 – 1.33 (m, 1H), 1.32 – 1.23 (m, 2H); ^{13}C NMR (100 MHz, benzene D_6): δ 149.5 (CH), 129.6 (CH), 126.9 (CH), 110.9 (CH), 98.6 (CH), 95.9 (CH_2), 66.9 (CH_2), 61.6 (CH_2), 55.4 (CH_3), 31.1 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 26.0 (CH_2), 19.7 (CH_2); IR (neat): υmax 2941 (s), 2788 (w), 1666 (s), 1627 (s), 1466 (w), 1452 (w), 1441 (m), 1353 (m), 1156 (s), 1046 (s), 972 (s), 923 (s), 869 (m), 814 (m); HRMS (EI) *m/z* M^+ ($C_{14}H_{24}O_4$) calculated 256.1675, found 256.1687.

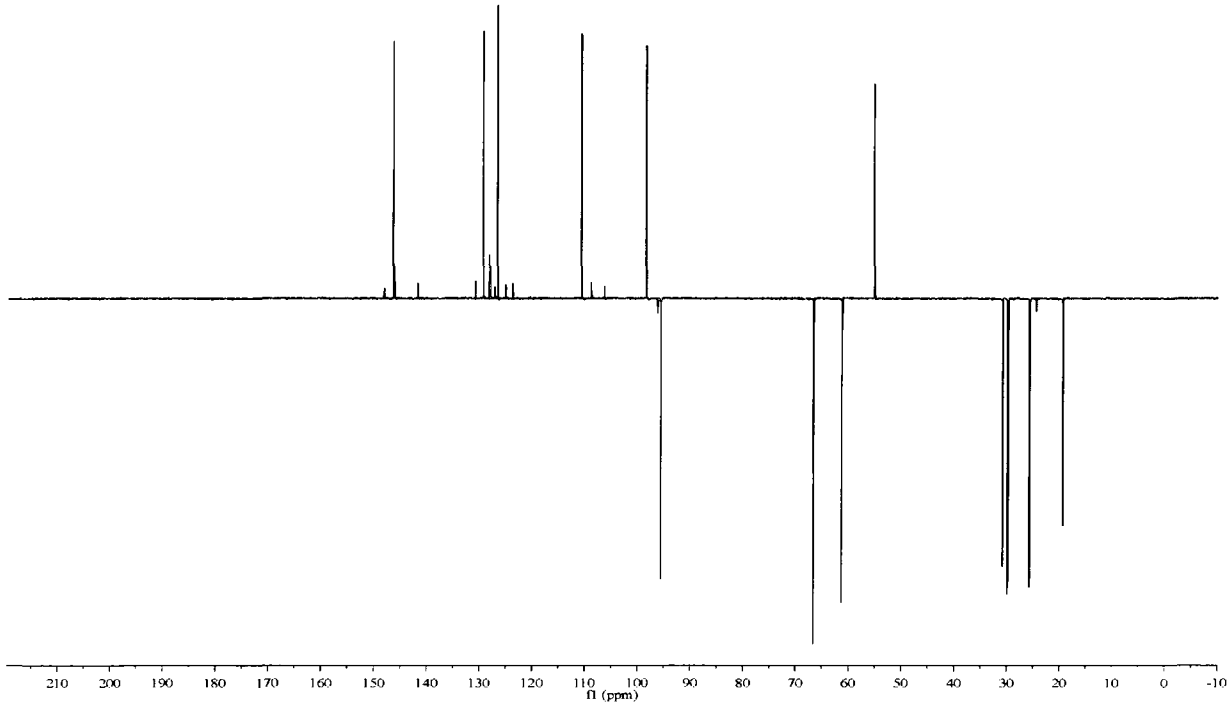
^{1}H NMR (400 MHz, benzene D_6)



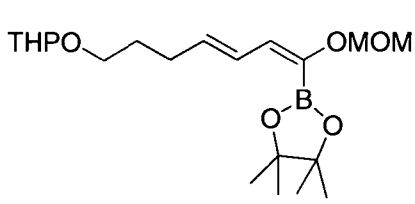
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

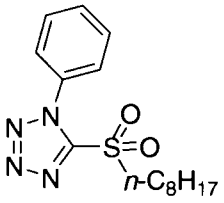


2-((1*E*,3*E*)-1-(methoxymethoxy)-7-(tetrahydro-2*H*-pyran-2-yloxy)hepta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.45)



To a solution of 1-alkoxydiene **3.44** (125 mg, 0.488 mmol) in 3 mL of THF at -78 °C was added a solution of *sec*-BuLi (1.32 M in hexanes, 0.48 mL, 0.634 mmol) dropwise. The mixture became light yellow upon stirring at this temperature for two hours. At that time, triisopropyl borate (168 μL, 0.732 mmol) was added and the flask was removed from the cold bath. Once the mixture had warmed to room temperature, (it becomes cloudy) a saturated aqueous solution of ammonium chloride was added and the mixture was diluted with diethyl ether. The layers were separated and the aqueous layer was extracted 3 times with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was then taken up in 3 mL of dry toluene and pinacol (63.4 mg, 0.536 mmol) was added. The mixture was stirred at room temperature overnight then diluted with ether and washed once with water then brine, dried over Na_2SO_4, filtered and concentrated. Purification on silica gel, with or without Et_3N, led to decomposition therefore the product (light yellow oil) was used as such and the yield was assumed to be quantitative.

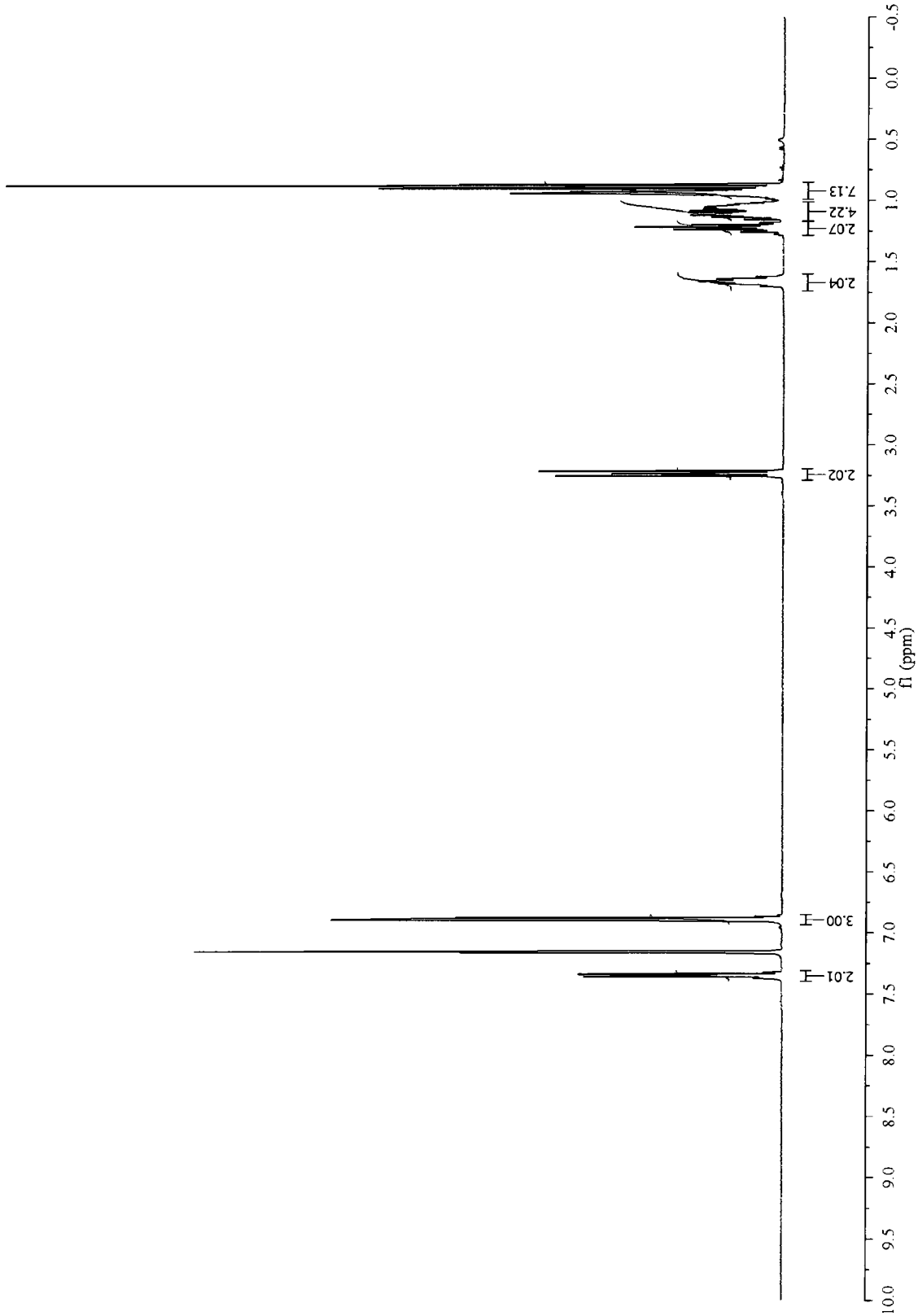
5-(octylsulfonyl)-1-phenyl-1*H*-tetrazole (3.48)



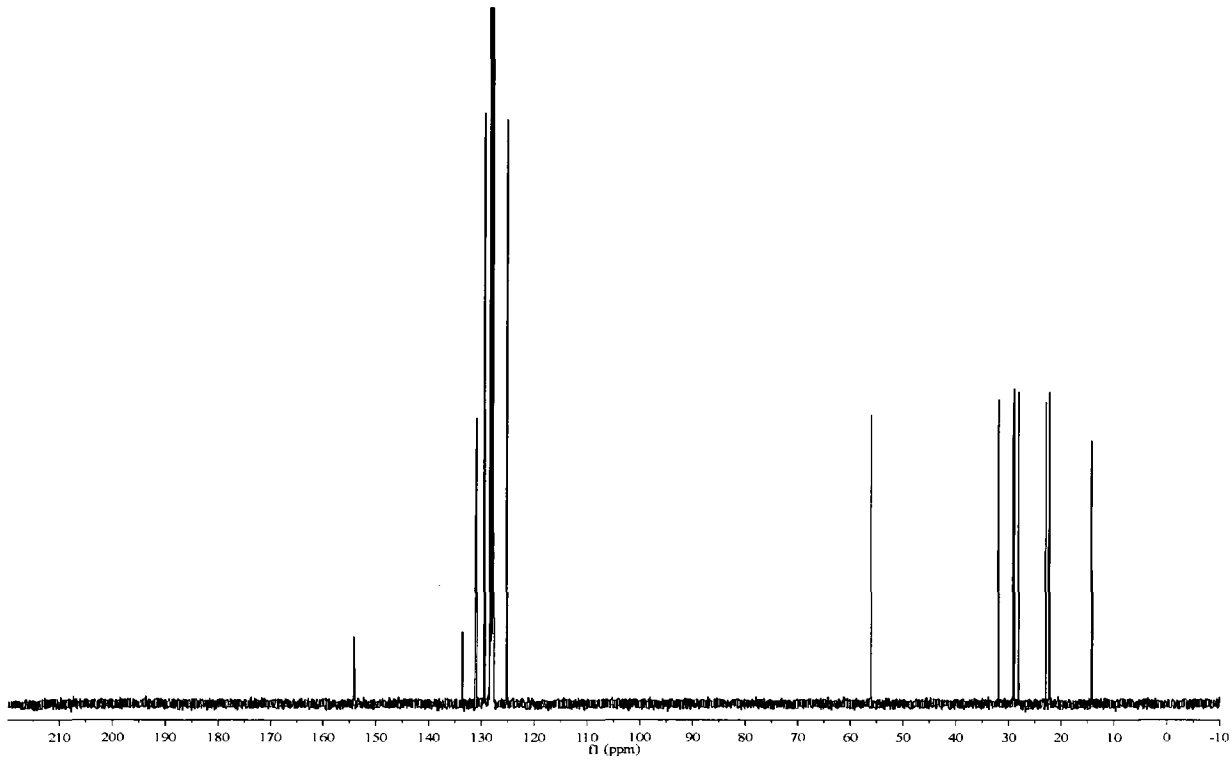
To a solution of triphenylphosphine (4.37 g, 16.7 mmol), 1-octanol (2.5 mL, 15.9 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.97 g, 16.7 mmol) in 150 mL of dry THF at 0 °C in a flask protected from light was added DIAD (3.75 mL, 19.1 mmol) dropwise over a period of 45 minutes. The resulting solution was stirred for another hour at 0 °C then allowed to warm to room temperature while stirring overnight. The mixture was then concentrated under reduced pressure and the resulting residue was taken up in diethyl ether with a small amount of hexanes and placed in the fridge for 3 hours. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate was concentrated and diluted in 120 mL of dichloromethane. To this solution was added $NaHCO_3$ (3.33 g, 39.7 mmol) and 77% *m*-CPBA (8.90 g, 39.7 mmol). The resulting suspension was stirred overnight at room temperature then 50 mL of a 1M solution of $NaHCO_3$ was added and the mixture was stirred for another hour before being diluted with dichloromethane. The layers were then separated and the aqueous layer was extracted three times with dichloromethane. The

combined organic layers were washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel using a gradient elution from hexanes to 15% ethyl acetate in hexanes to afford 2.97 g (58%) of the desired sulfone which crystallized (white needles) upon storing in the fridge. Mp: 44 – 45°C; ^{1}H NMR (400 MHz, benzene D_6): δ 7.38 – 7.34 (m, 2H), 6.92 – 6.88 (m, 3H), 3.26 – 3.22 (m, 2H), 1.67 (quint, J = 7.6 Hz, 2H), 1.28 – 1.18 (m, 2H), 1.16 – 1.02 (m, 4H), 0.97 – 0.93 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 154.3 (C), 133.6 (C), 131.0 (CH), 129.5 (CH (2C)), 125.3 (CH (2C)), 56.1 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.2 (CH_2), 23.0 (CH_2), 22.3 (CH_2), 14.3 (CH_3); IR (KBr): υmax 2918 (s), 2847 (s), 1763 (s), 1595 (s), 1498 (s), 1465 (s) 1424 (s), 1400 (s), 1292 (w), 1259 (w), 1153 (m), 1051 (m), 1017 (m), 984 (m), 919 (s), 812 (w), 776 (s), 733 (s), 632 (s), 520 (s); HRMS (EI) *m/z* M^+ not found, M^+ - $C_8H_{17}O_2S$ ($C_7H_5N_4^+$) calculated 145.0509, found 145.0514.

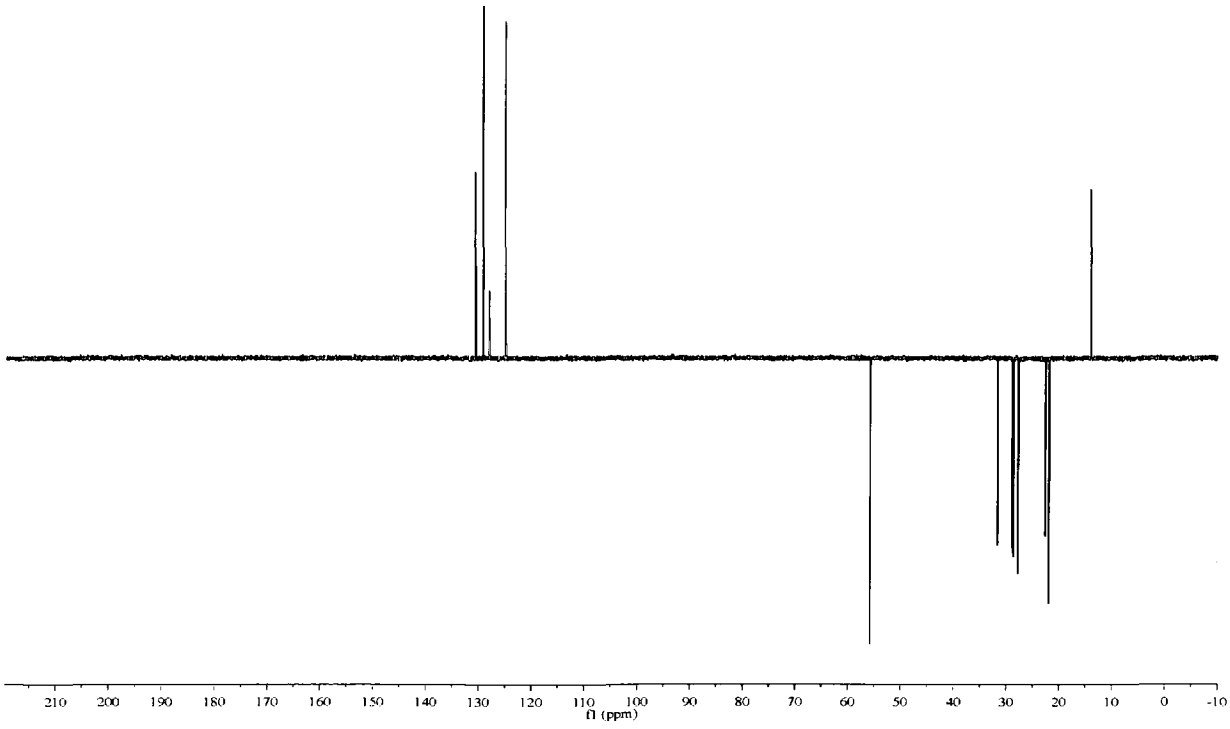
^{1}H NMR (400 MHz, benzene D_6)



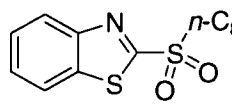
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

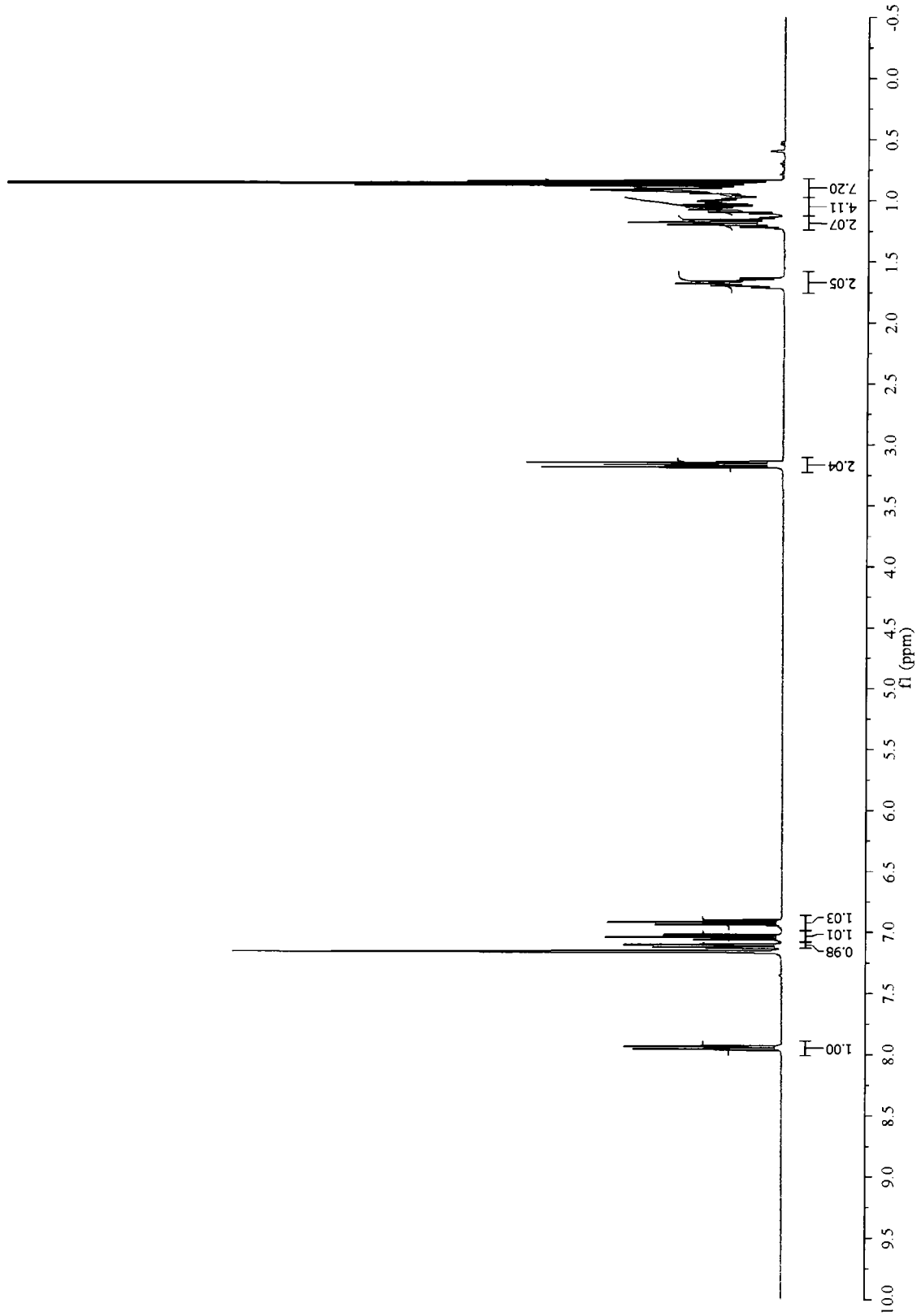


2-(octylsulfonyl)benzothiazole (3.50)

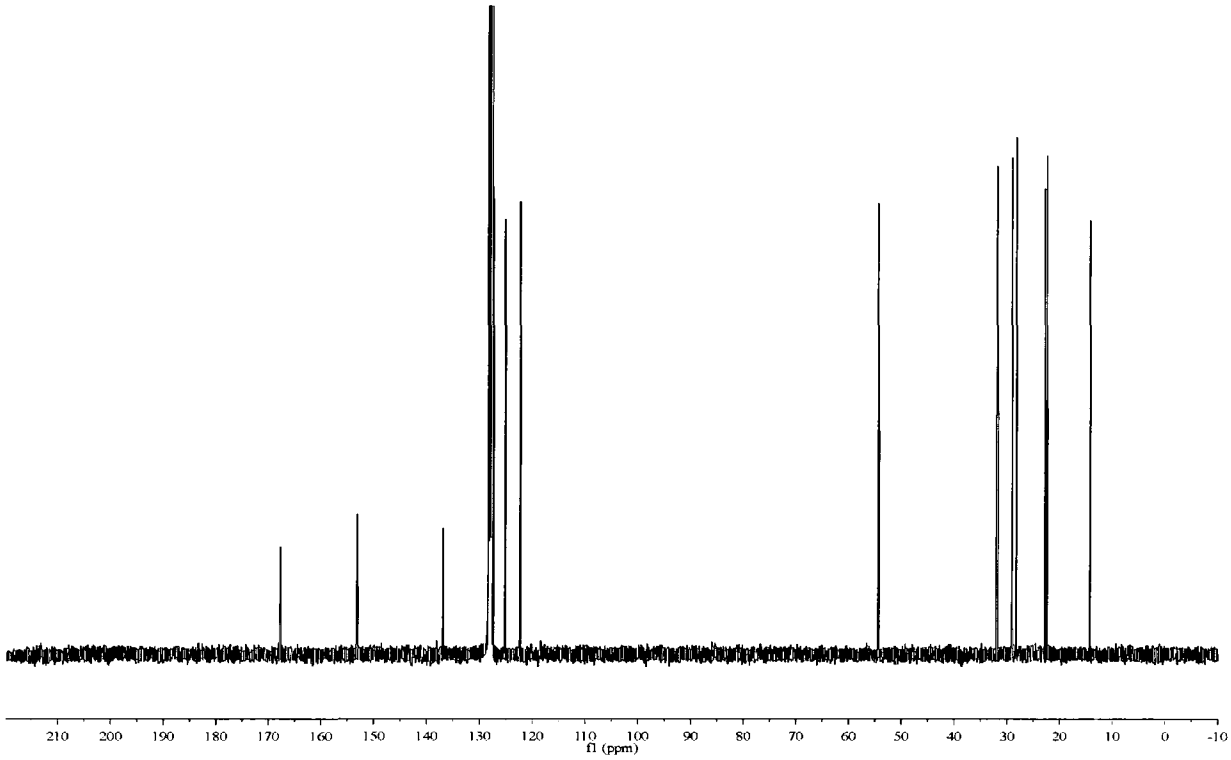


To a solution of triphenylphosphine (4.37 g, 16.7 mmol), 1-octanol (2.5 mL, 15.9 mmol) and 2-benzothiazolethiol (2.79 g, 16.7 mmol) in 150 mL of dry THF in a flask protected from light at 0 °C was added DIAD (3.75 mL, 19.1 mmol) dropwise over a period of 45 minutes. Once the addition was complete, the mixture was stirred another hour at 0 °C then allowed to warm to room temperature while stirring overnight. The solvent was removed under reduced pressure and the residue was taken up in diethyl ether with a small amount of hexanes. The mixture was placed in the fridge (-20 °C) for 3 hours and the precipitated triphenylphosphine oxide was removed by filtration. The filtrate was concentrated then diluted in dichloromethane (120 mL) and $NaHCO_3$ (8.0 g, 95.3 mmol) was added followed by 77% *m*-CPBA (8.19 g, 36.5 mmol). The resulting suspension was stirred 24 hours at room temperature. 50 mL of a 1M solution of $NaHCO_3$ was added and the mixture stirred for another hour before being diluted with dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography on silica gel using a gradient elution from hexanes to 8% ethyl acetate in hexanes to afford 4.52 g (91%) of the desired product which crystallized (white needles) upon storing in the fridge. Mp: 33 - 34 °C; ^{1}H NMR (400 MHz, benzene D_6): δ 7.95 (ddd, J = 8.3, 0.9, 0.7 Hz, 1H), 7.12 (ddd, J = 8.2, 1.1, 0.7 Hz, 1H), 7.05 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 6.93 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H) 3.19 - 3.15 (m, 2H), 1.68 (dddd, J = 8.0, 7.9, 7.6, 7.1 Hz, 2H), 1.23 – 1.14 (m, 2H), 1.11 – 0.89 (m, 8H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, benzene D_6): δ 167.8 (C), 153.2 (C), 136.9 (C), 127.6 (CH), 127.4 (CH), 125.2 (CH), 122.4 (CH), 54.5 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 29.1(CH_2), 28.3 (CH_2), 22.9 (CH_2), 22.6 (CH_2), 14.3 (CH_3); IR (KBr): υmax 2945 (w), 2855 (w), 1469 (s), 1427 (s), 1324 (s) 1237 (w), 1138 (s), 1026 (s), 982 (w), 868 (w), 852 (s), 763 (s), 735 (s), 723 (m), 686 (s), 599 (w), 567 (s), 538 (s); HRMS (EI) *m/z* M^+ not found, $M^+ - C_8H_{17}O_2S$ ($C_7H_4NS^+$) calculated 134.0059, found 134.0054.

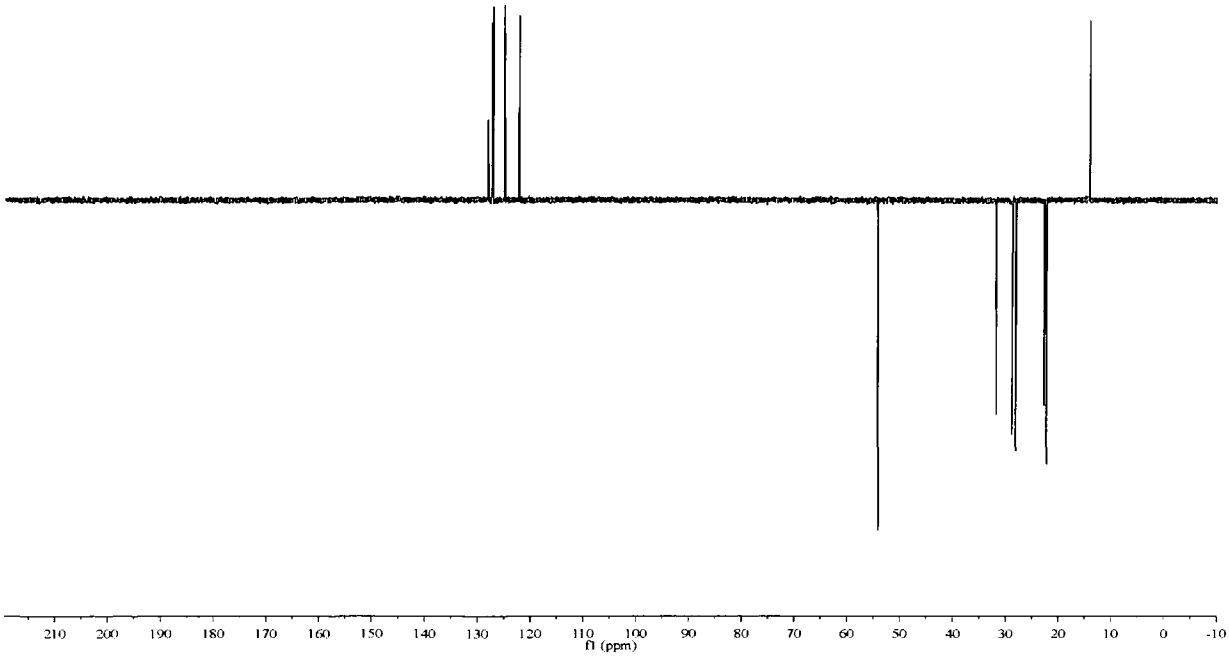
^{1}H NMR (400 MHz, benzene D_6)



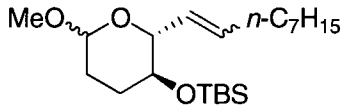
^{13}C NMR (100 MHz, benzene D_6)



DEPT 135 (100 MHz, benzene D_6)

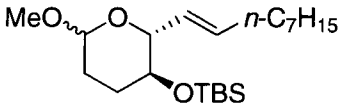


((2*R*,3*S*)-tetrahydro-6-methoxy-2-(non-1-enyl)-2*H*-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (3.51)



To a cold solution (-78 °C) of the phosphonium salt **3.52** (365 mg, 0.802 mmol) in 2.5 mL of dry THF was added *s*-BuLi (1.24 M, 0.59 mL, 0.73 mmol) dropwise. The orange, heterogeneous mixture was then allowed to warm to room temperature and stirred for 30 minutes at which time it became a clear red solution. It was cooled to -78 °C again and a solution of the aldehyde **3.9** (100 mg, 0.364 mmol) in 1.5 mL of dry THF was added dropwise. Once the addition was complete, the mixture was slowly allowed to warm to room temperature (over one hour) then stirred for another hour. At this time, no more starting aldehyde was apparent by TLC analysis therefore ether (10 mL) and water (5 mL) were added and the layers were separated. The aqueous layer was extracted three times with ether and the combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel using a gradient elution (0% to 6% ether in hexanes) to afford 124 mg (92% yield) of the desired alkene as a 1:5 ratio of *E* and *Z* isomers, in the form of a colorless oil.

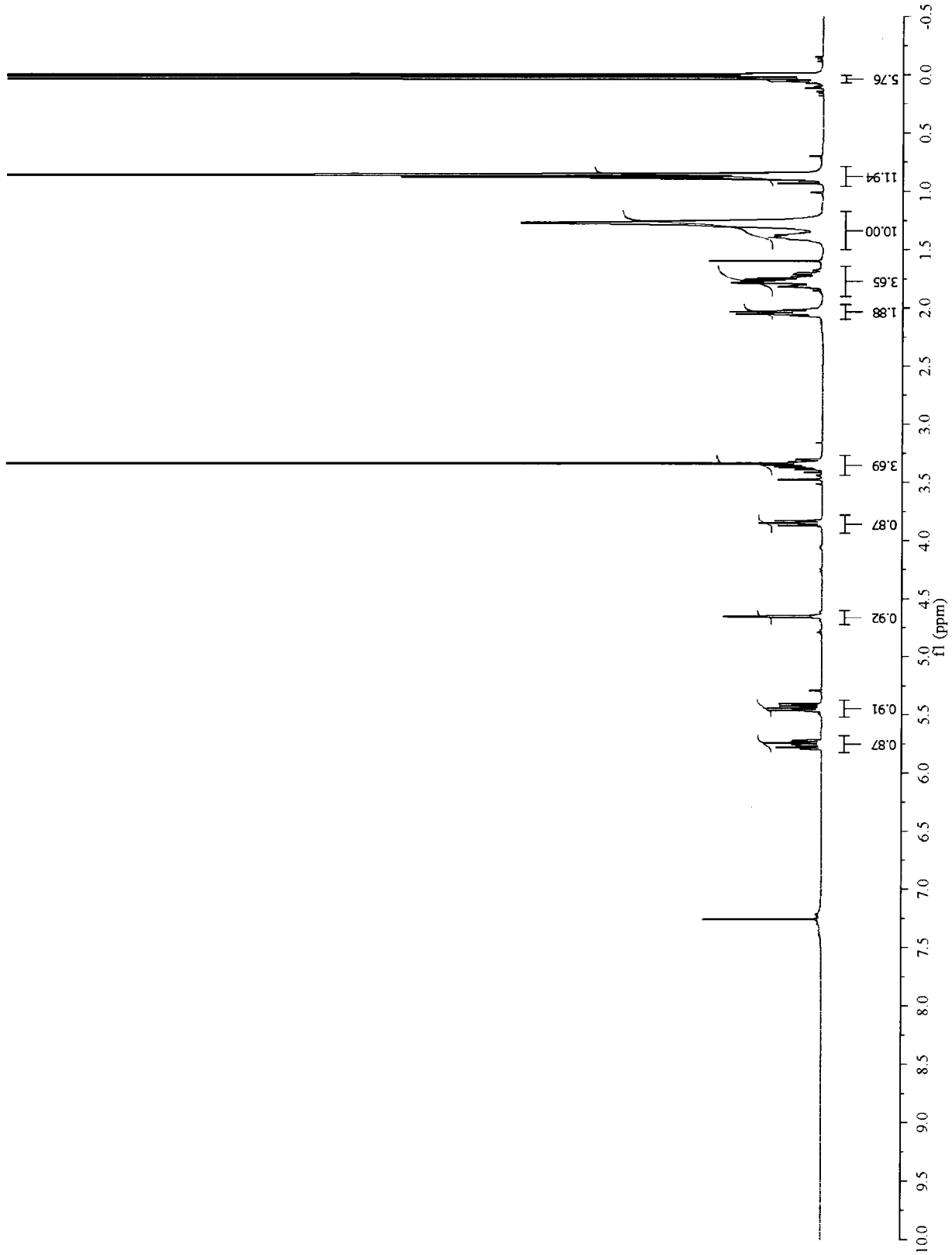
((2*R*,3*S*)-tetrahydro-6-methoxy-2-((*E*)-non-1-enyl)-2*H*-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (3.51 (*E*))



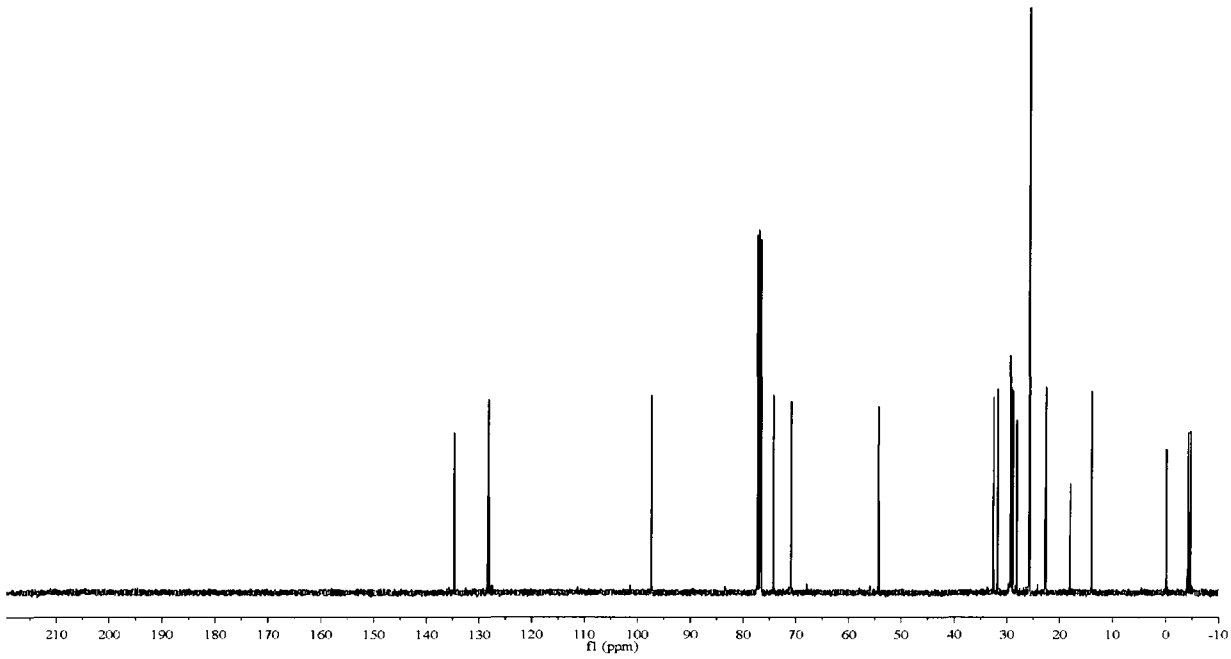
To a solution of the 1:5 *E/Z* mixture of **3.51** (533 mg, 1.44 mmol) in 25 mL of hexanes was added diphenyldisulphide (31.4 mg, 0.144 mmol). The flask was equipped with a condenser and a stream of argon was bubbled through the solution for 10 minutes. The mixture was then irradiated with a 300 W lamp under argon for 68 hours. The mixture was then concentrated under reduced pressure and purified by flash chromatography using a gradient elution (0% to 4% ether in hexanes) to afford the desire product as a 10:1 mixture of *E* and *Z* isomers respectively (496 mg, 93%) yield. For characterization purposes, an aliquot was purified two more times by flash chromatography to obtain the pure *E* isomer. Major anomer (α): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (dtd, J = 15.3, 6.6, 0.7 Hz, 1H), 5.44 (ddt, J = 15.4, 7.3, 1.5 Hz, 1H), 4.66 (d, J = 2.8 Hz, 1H), 3.86 (t, J = 8.2 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.34 (s, 3H), 2.04 (qd, J = 6.8, 1.3 Hz, 2H), 1.84 – 1.70 (m, 4H), 1.44 – 1.36 (m, 2H), 1.32 – 1.27 (m, 8H), 0.94 – 0.85 (m, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7 (CH), 128.3 (CH), 97.4 (CH),

74.4 (CH), 71.0 (CH), 54.4 (CH_3), 32.5 (CH_2), 31.8, (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 25.8 (CH_3 (3C)), 22.7 (CH_2), 18.0 (C), 14.1 (CH_3), -4.2 (CH_3), -4.6 (CH_3); IR (neat): υmax 2955 (s), 2928 (s), 2856 (s), 1463 (m), 1256 (m), 1129 (s), 1060 (s), 1060 (s), 1021 (s), 954 (m), 837 (s), 775 (s), 669 (w); HRMS (EI) *m/z* M^+ ($C_{21}H_{42}O_3Si$) calculated 370.2903, found 370.2910, M^+ - C_4H_9 ($C_{17}H_{33}O_3Si$) calculated 313.2194, found 313.2165; $[\alpha]^{22}_D$ +83.0°, *c* 11.6 mg/mL (CH_2Cl_2).

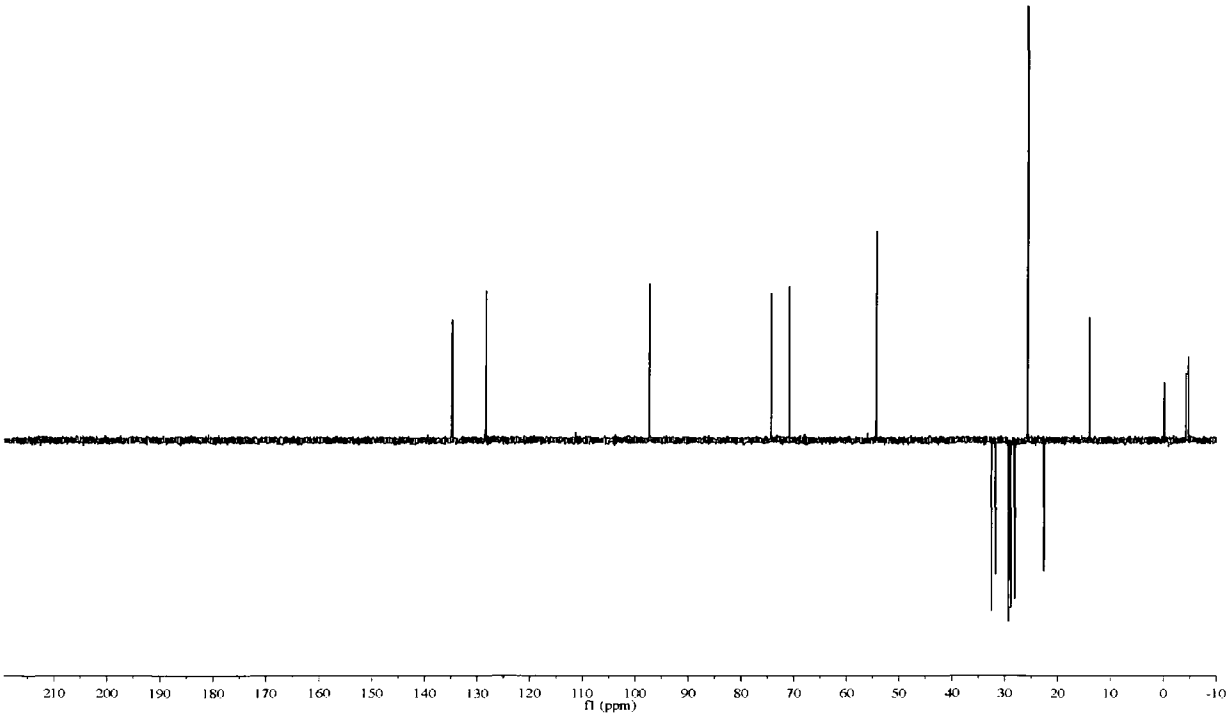
^{1}H NMR (400 MHz, $CDCl_3$)



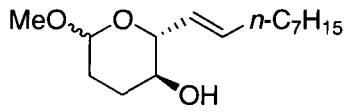
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT 135 (100 MHz, $CDCl_3$)

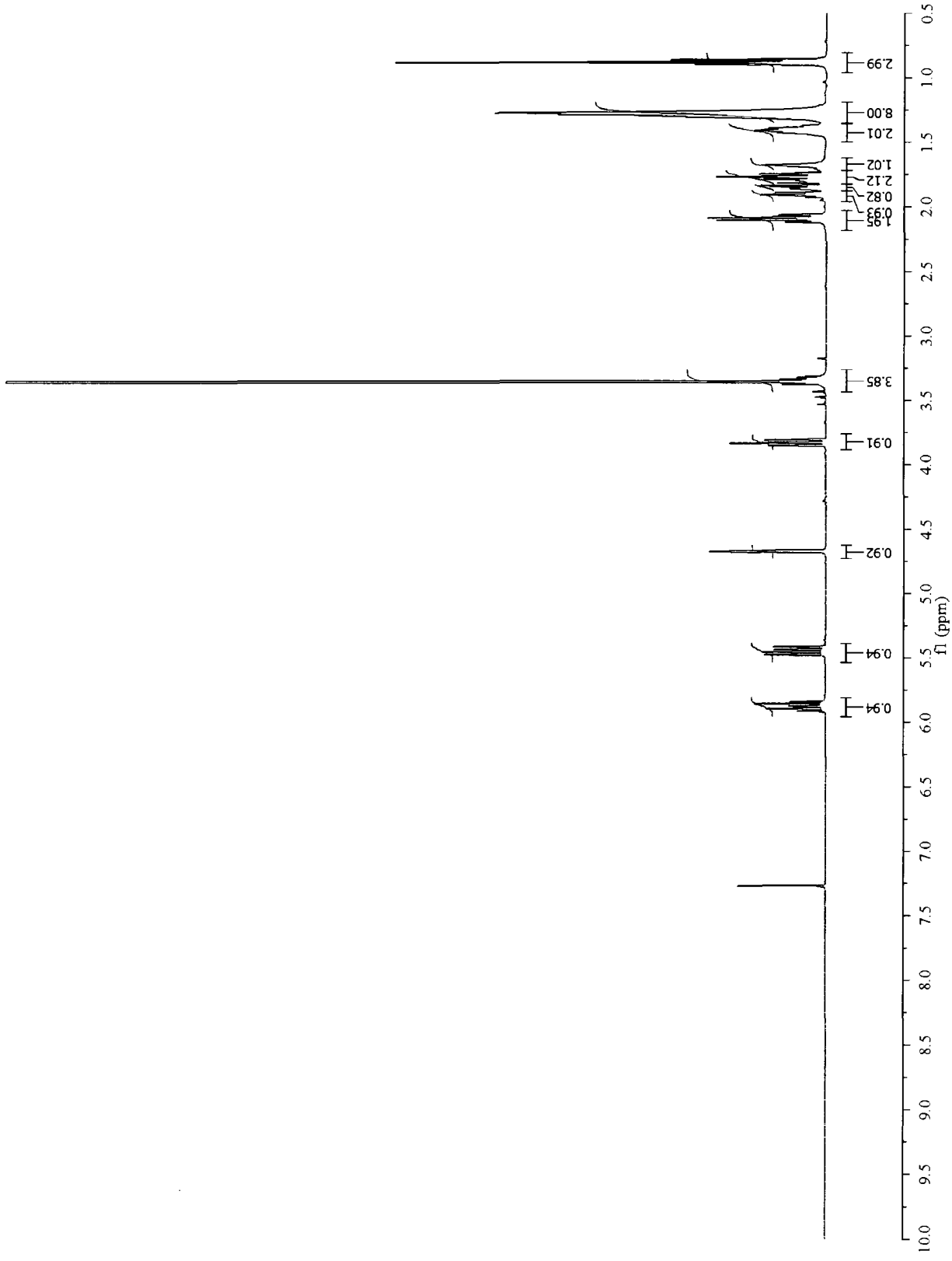


(2*R*,3*S*)-tetrahydro-6-methoxy-2-((*E*)-non-1-enyl)-2*H*-pyran-3-ol (3.53)

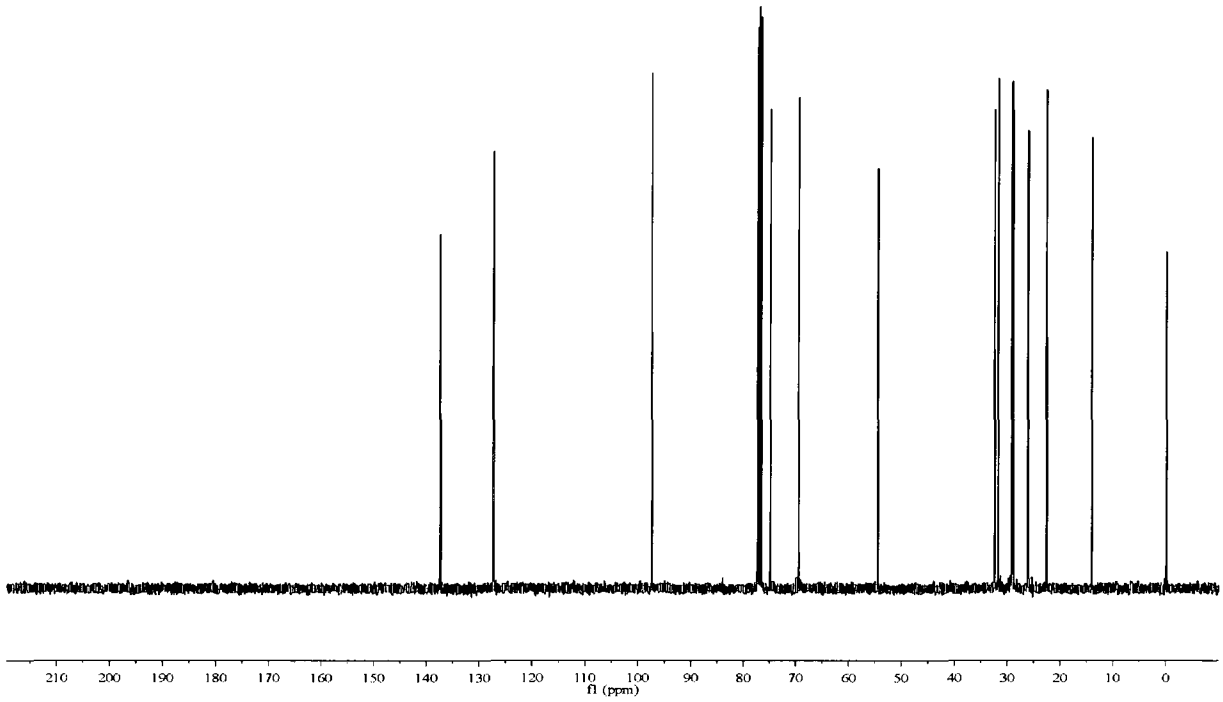


To a solution of the silyl ether **3.51** (185 mg, 0.499 mmol), in 3 mL of dry THF at room temperature was added a 1 M tetrabutylammonium fluoride solution in THF (0.70 mL, 0.70 mmol). The resulting yellow solution was stirred overnight at which time the color had become dark brown and no more starting material was apparent by TLC analysis. The mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (15% EtOAc in hexanes) to afford 30.0 mg of the major anomer and 92.2 mg of the mixed anomers (total 122.2 mg, 95% yield) as a colorless oil. Major anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (dt, J = 15.4, 6.6 Hz, 1H), 5.45 (ddt, 15.5, 8.0, 1.4 Hz, 1H), 4.68 (d, J = 2.0 Hz, 1H), 3.83 (t, J = 8.6 Hz, 1H), 3.38 – 3.31 (m, 1H), 3.36 (s, 3H), 2.09 (qd, J = 7.1, 1.3 Hz, 2H), 1.93 – 1.89 (m, 1H), 1.87 – 1.83 (m, 1H), 1.82 – 1.75 (m, 2H), 1.68 (s, br, 1H), 1.45 – 1.38 (m, 2H), 1.32 – 1.27 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4 (CH), 127.3 (CH), 97.5 (CH), 75.0 (CH), 69.5 (CH), 54.6 (CH_3), 32.5 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (neat): υmax 3432 (w), 2927 (s), 1459 (w), 1368 (w), 1206 (w), 1128 (s), 1060 (s), 1018 (s), 947 (s); HRMS (EI) *m/z* M^+ not found, M^+ - MeOH ($C_{14}H_{24}O_2$) calculated 224.1765, found 224.1724; $[\alpha]^{22}_D$ +87.9°, *c* 10.0 mg/mL (CH_2Cl_2).

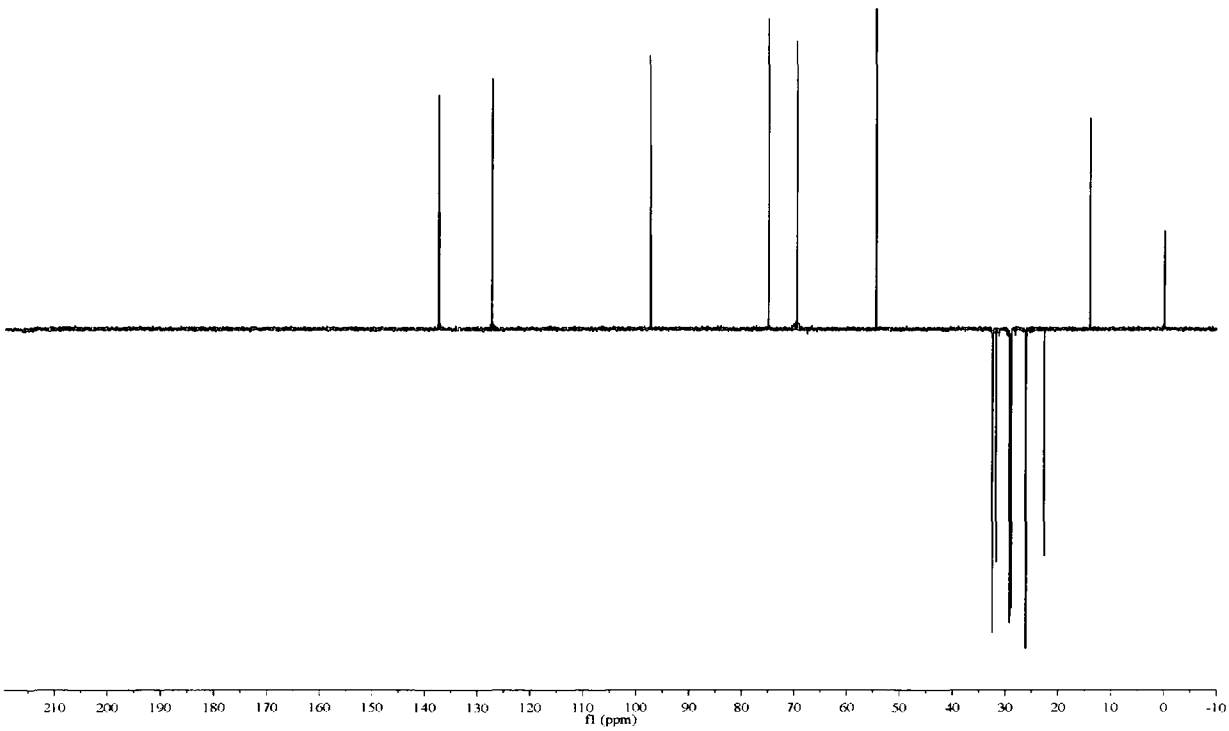
^{1}H NMR (400 MHz, $CDCl_3$)



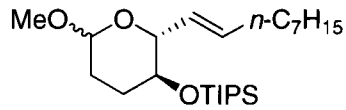
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT (100 MHz, $CDCl_3$)

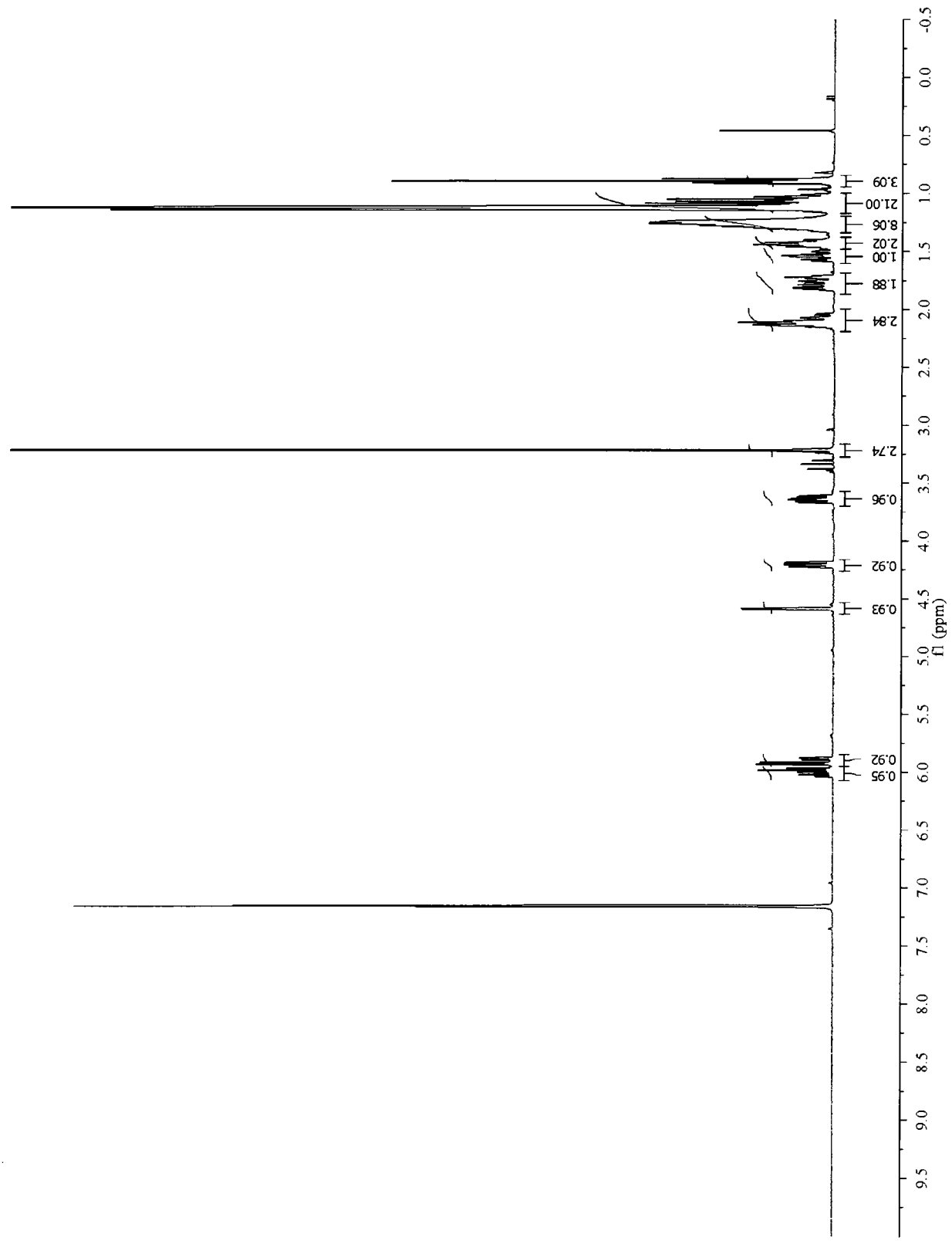


((2*R*,3*S*)-tetrahydro-6-methoxy-2-((*E*)-non-1-enyl)-2*H*-pyran-3-yloxy)triisopropylsilane (3.54)

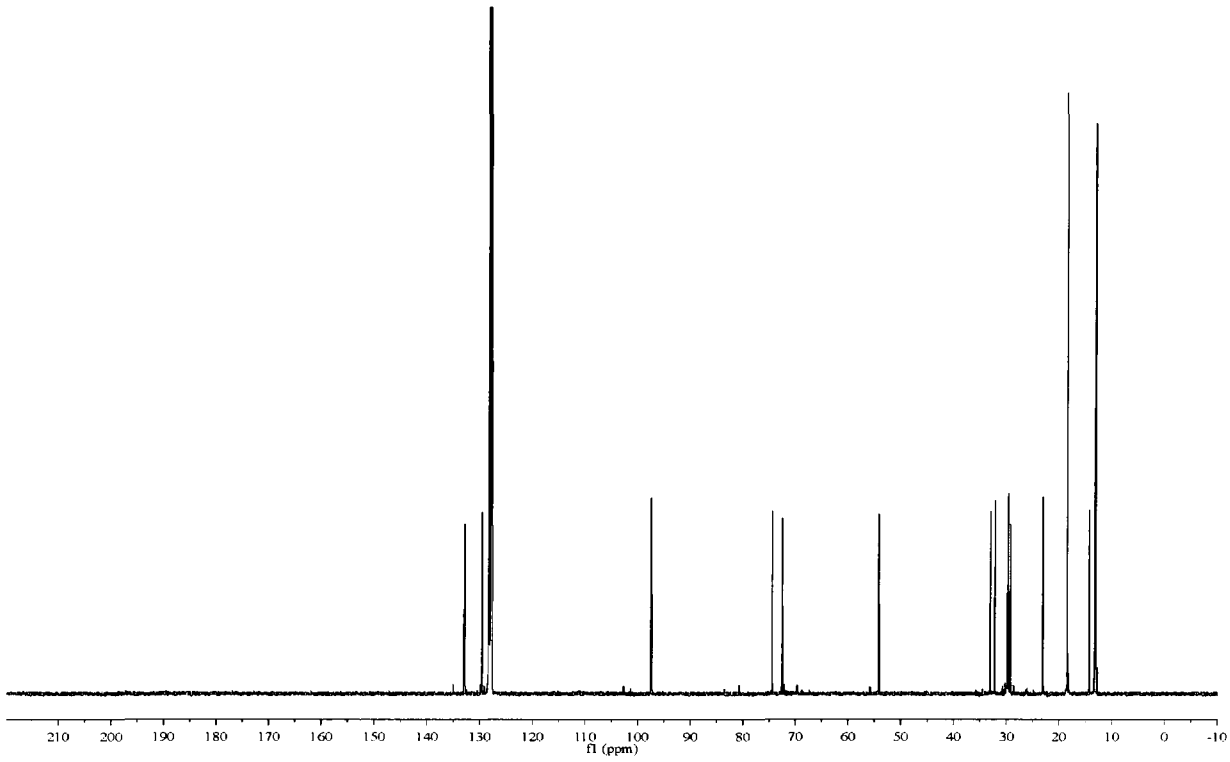


To a solution of alcohol **3.53** (92.0 mg, 0.359 mmol) and 2,6-lutidine (104 μL, 0.897 mmol) in 3 mL of dry CH_2Cl_2 at 0 °C was added triisopropylsilyl trifluoromethansulfonate (125 μL, 0.467 mmol) dropwise. The resulting clear, colorless solution was stirred for one hour at 0 °C then water (3 mL) and CH_2Cl_2 (5 mL) was added. The layers were separated and the aqueous layer was extracted 2 more times with CH_2Cl_2. The combined organic extracts were washed with brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel using a gradient elution (0% to 3% ether in hexanes) to afford 141.6 mg (96% yield) of the desired product as a colorless oil. An aliquot was purified once more for characterization purposes to afford the major anomer: ^{1}H NMR (400 MHz, C_6D_6): δ 6.01 (dtd, J = 15.5, 6.4, 0.8 Hz, 1H), 5.89 (dddd, J = 15.4, 6.0, 1.2, 1.2 Hz, 1H), 4.59 (d, 3.0 Hz, 1H), 4.21 (dd, J = 9.0, 6.0, Hz, 1H), 3.64 (ddd, J = 10.8, 9.0, 4.4 Hz, 1H), 3.22 (s, 3H), 2.15 – 2.04 (m, 3H), 1.84 – 1.72 (m, 2H), 1.54 (tt, J = 13.6, 4.0, 1H), 1.44 (quint., 7.3 Hz, 2H), 1.31 – 1.23 (m, 8H), 1.14 – 1.01 (m, 21 H), 0.65 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 132.9 (CH), 129.7 (CH), 97.5 (CH), 74.5 (CH), 72.6 (CH), 54.3 (CH_3), 33.1 (CH_2), 32.2 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 23.1 (CH_2), 18.5 and 18.4 (CH_3 (6C)), 14.4 (CH_3), 13.1 (CH (3C)); IR (neat): υmax 2927 (s), 2867 (s), 1465 (m), 1372 (w), 1129 (s), 1061 (s), 1019 (m), 954 (m), 883 (m), 802 (m), 679 (m); HRMS (EI) *m/z* M^+ ($C_{24}H_{48}O_3Si$) calculated 412.3373, found 412.3401, M^+ - C_3H_7 ($C_{21}H_{41}O_3Si$) calculated 369.2820, found 369.2833; $[\alpha]^{22}_D$ +89.3°, *c* 13.0 mg/mL (CH_2Cl_2).

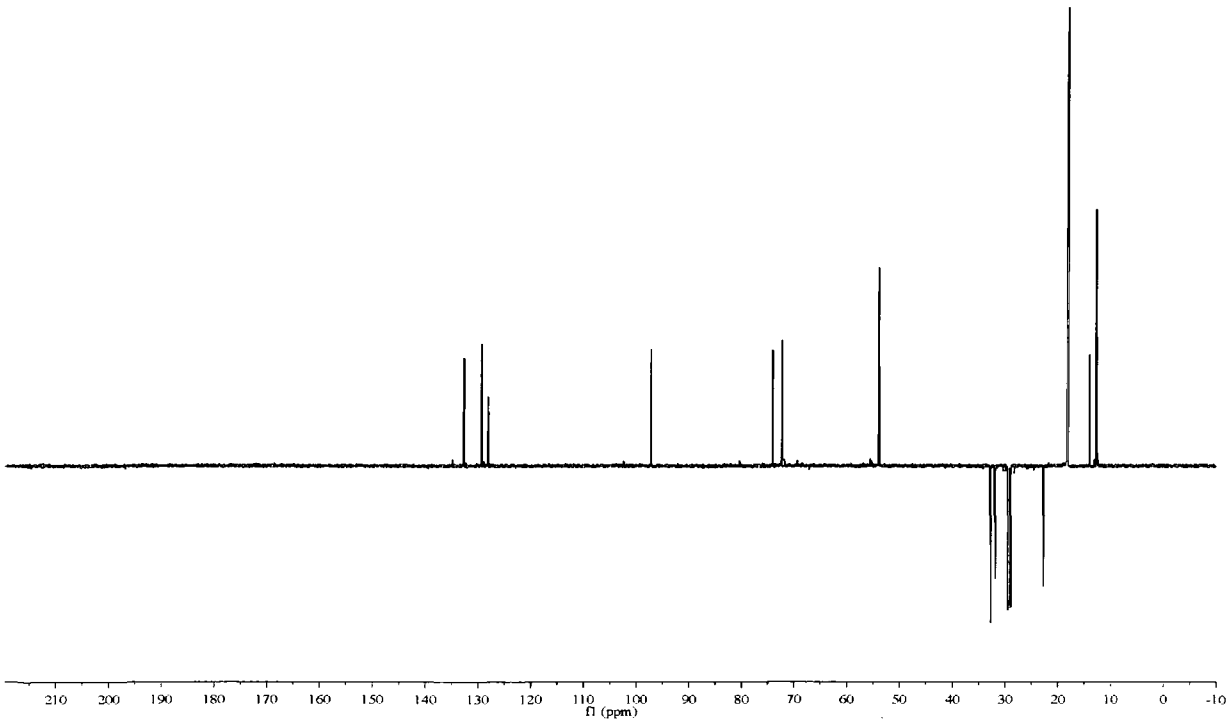
^{1}H NMR (400 MHz, C_6D_6)



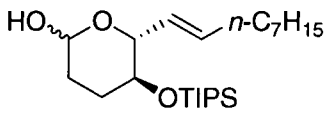
^{13}C NMR (100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)

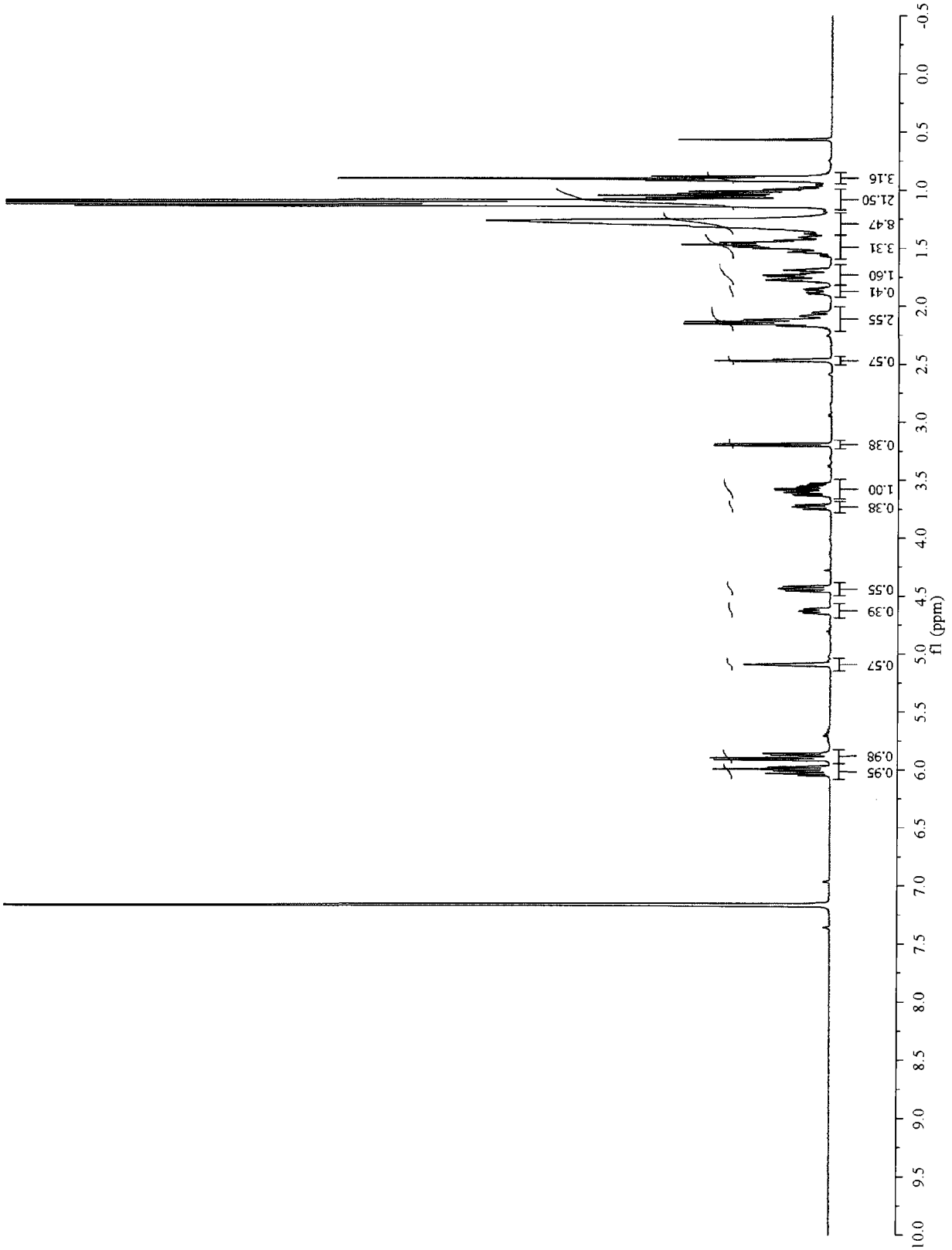


(5*S*,6*R*)-6-((*E*)-non-1-enyl)-5-(triisopropylsilyloxy)tetrahydro-2*H*-pyran-2-ol (3.55)

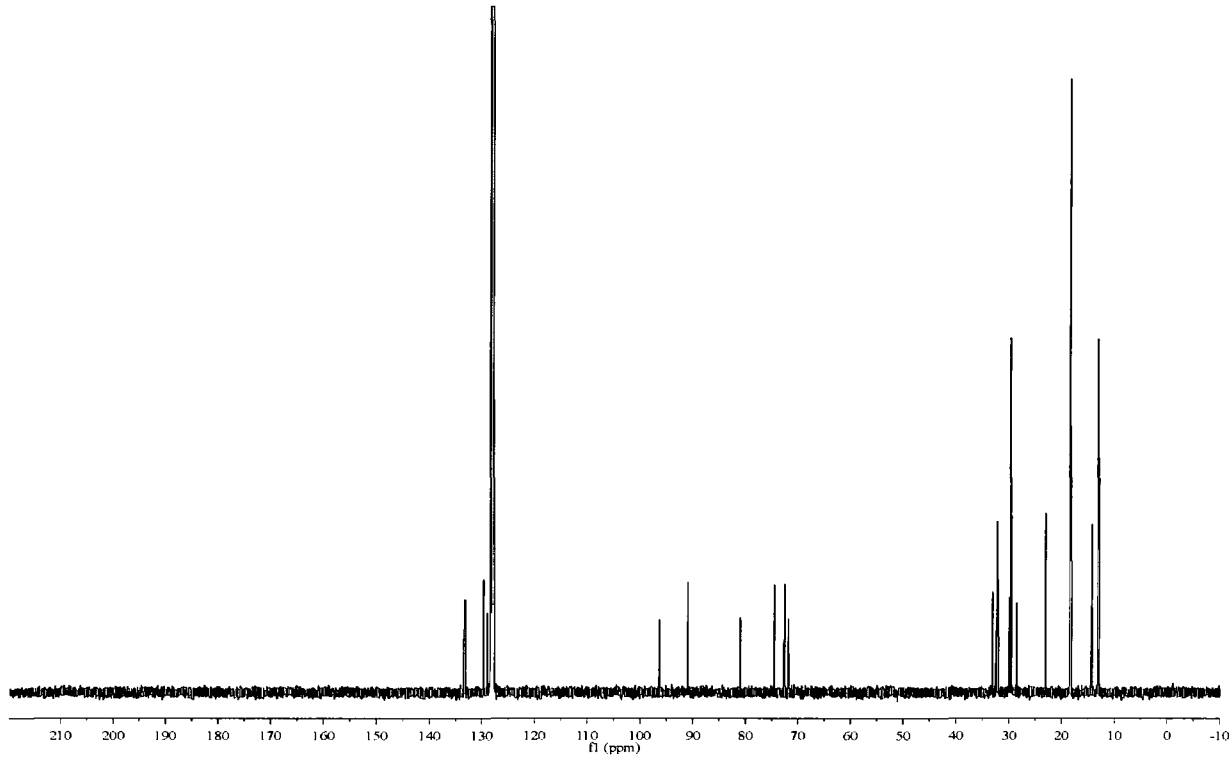


To a solution of **3.54** (13.9 g, 33.7 mmol) in 500 mL of THF was added 84.2 mL of a $2N_{aq}$ HCl solution. The flask was equipped with a reflux condenser and the mixture refluxed for 3 hours then allowed to cool to room temperature. Solid $NaHCO_3$ was slowly added until a neutral pH was obtained. Water and ether were added and the layers separated. The aqueous layer was extracted 3 times with ether and the combined organic extracts were washed with brine. They were then dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford 10.4 g (77% yield) of the desired lactol as an inseparable mixture of the major (α) and minor (β) anomers, 60 : 40 respectively, in the form of a colorless oil. IR (neat): υmax 3411 (m), 2927 (s), 2866 (s), 1464 (m), 1380 (w), 1364 (w), 1220 (w), 1121 (s), 1069 (m), 1024 (w), 983 (m), 884 (m), 803 (m), 680 (m); HRMS (EI) *m/z* M^+ not found, M^+ - H_2O ($C_{23}H_{44}O_2Si$) calculated 380.3111, found 380.3120; $[\alpha]^{22}_D$ +54.4°, *c* 12.5 mg/mL (CH_2Cl_2). Major anomer (α): ^1H NMR (400 MHz, C_6D_6): δ 6.00 (dtd, J = 15.4, 6.7, 0.9 Hz, 1H), 5.89 (ddt, J = 15.4, 6.1, 1.3 Hz, 1H), 5.09 (dd, J = 2.4, 2.4 Hz, 1H), 4.44 (dd, J = 8.8, 6.3 Hz, 1H), 3.60 (ddd, J = 10.7, 8.9, 4.3 Hz, 1H), 2.47 (dd, J = 3.0, 2.1 Hz, 1H), 2.14 (dt, J = 7.2, 7.2 Hz, 2H), 2.14 – 2.05 (m, 1H), 1.76 (dddd, J = 16.7, 4.2, 4.2, 4.2 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.50 – 1.40 (m, 3H), 1.37 – 1.26 (m, 8H), 1.14 – 0.99 (m, 21H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 133.2 (CH), 129.8 (CH), 91.0 (CH), 74.6 (CH), 72.7 (CH), 33.1 (CH_2), 32.3 (CH_2), 30.0 (CH_2), 29.7 (CH_2 (2C)), 29.7 (CH_2), 28.5 (CH_2), 23.1 (CH_2), 18.4 (CH_3 (6C)), 14.4 (CH_3), 13.1 (CH (3C)). Minor anomer (β): ^1H NMR (400 MHz, C_6D_6): δ 6.00 (dtd, J = 15.4, 6.7, 0.9 Hz, 1H), 5.89 (ddt, J = 15.4, 6.1, 1.3 Hz, 1H), 4.63 (ddd, J = 9.0, 5.2, 2.2 Hz, 1H), 3.73 (dd, J = 8.4, 6.2 Hz, 1H), 3.56 (ddd, J = 10.1, 8.6, 4.4 Hz, 1H), 3.20 (d, J = 5.2 Hz, 1H), 2.14 (dt, J = 7.2, 7.2 Hz, 2H), 1.87 (dddd, J = 12.3, 4.0, 4.0, 4.0 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.57 – 1.51 (m, 1H), 1.50 – 1.40 (m, 3H), 1.37 – 1.26 (m, 8H), 1.14 – 0.99 (m, 21H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 133.4 (CH), 129.0 (CH), 96.3 (CH), 81.1 (CH), 71.9 (CH), 33.1 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 29.7 (CH_2 (3C)), 29.6 (CH_2), 23.1 (CH_2), 18.4 (CH_3 (6C)), 14.4 (CH_3), 13.0 (CH (3C)).

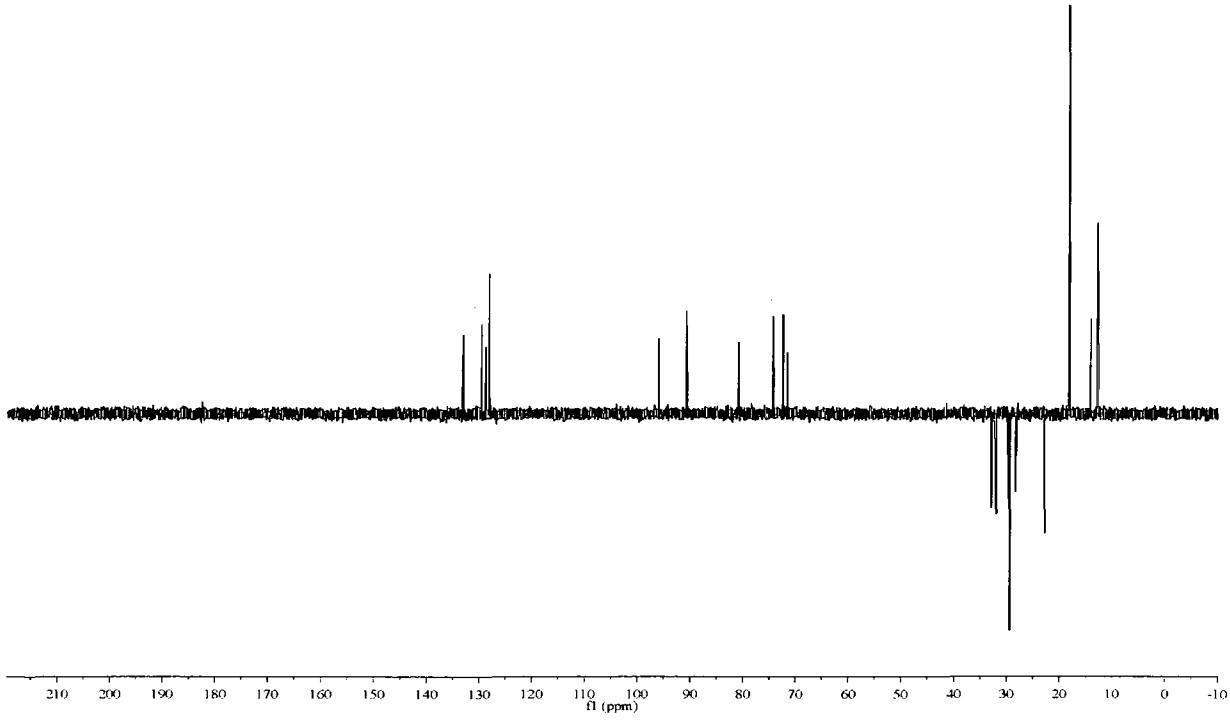
^{1}H NMR (400 MHz, C_6D_6)



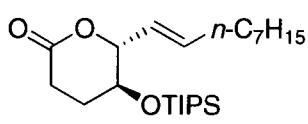
^{13}C NMR (100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)

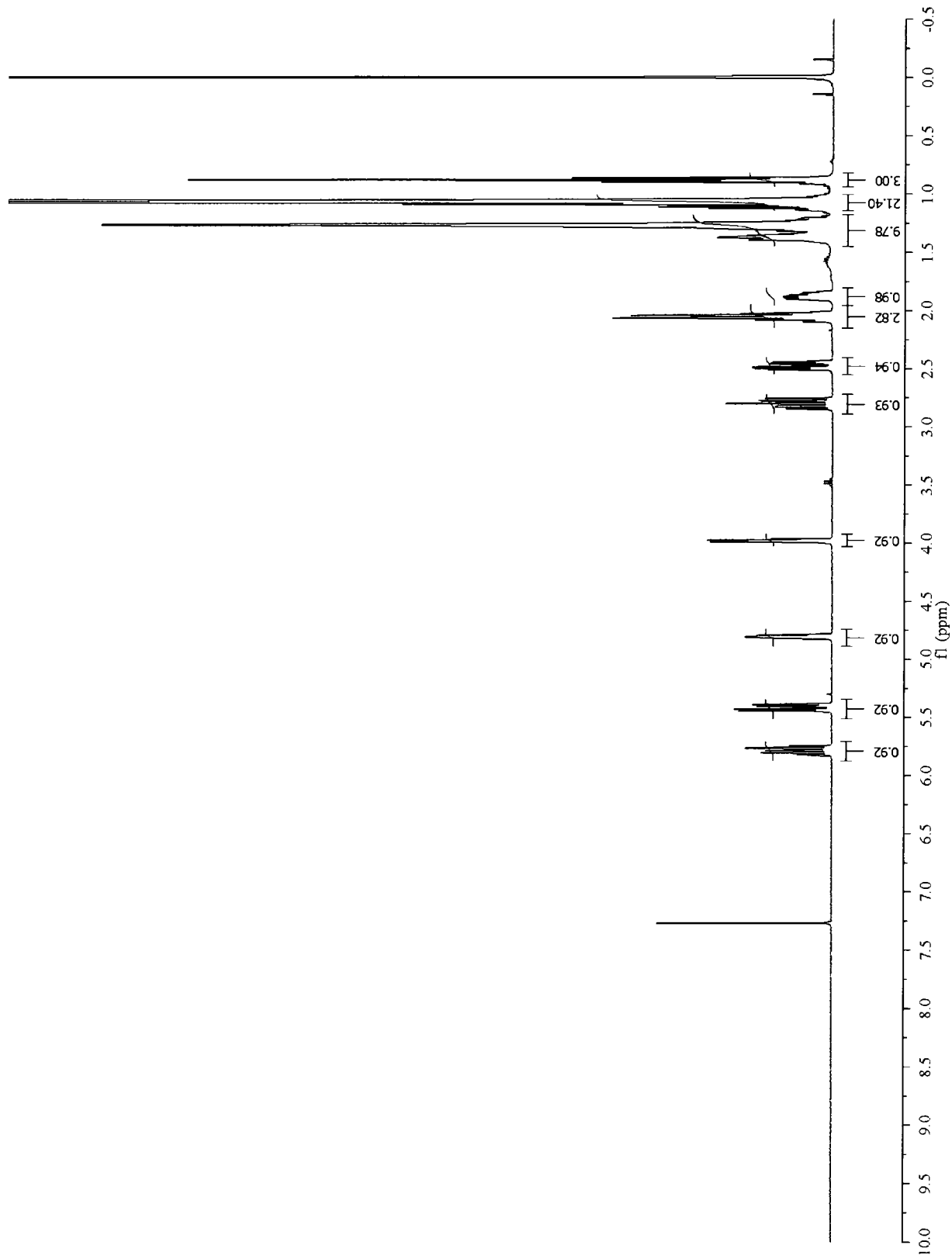


(5*S*,6*R*)-6-((*E*)-non-1-enyl)-5-(triisopropylsilyloxy)tetrahydro-2*H*-pyran-2-one (3.56)

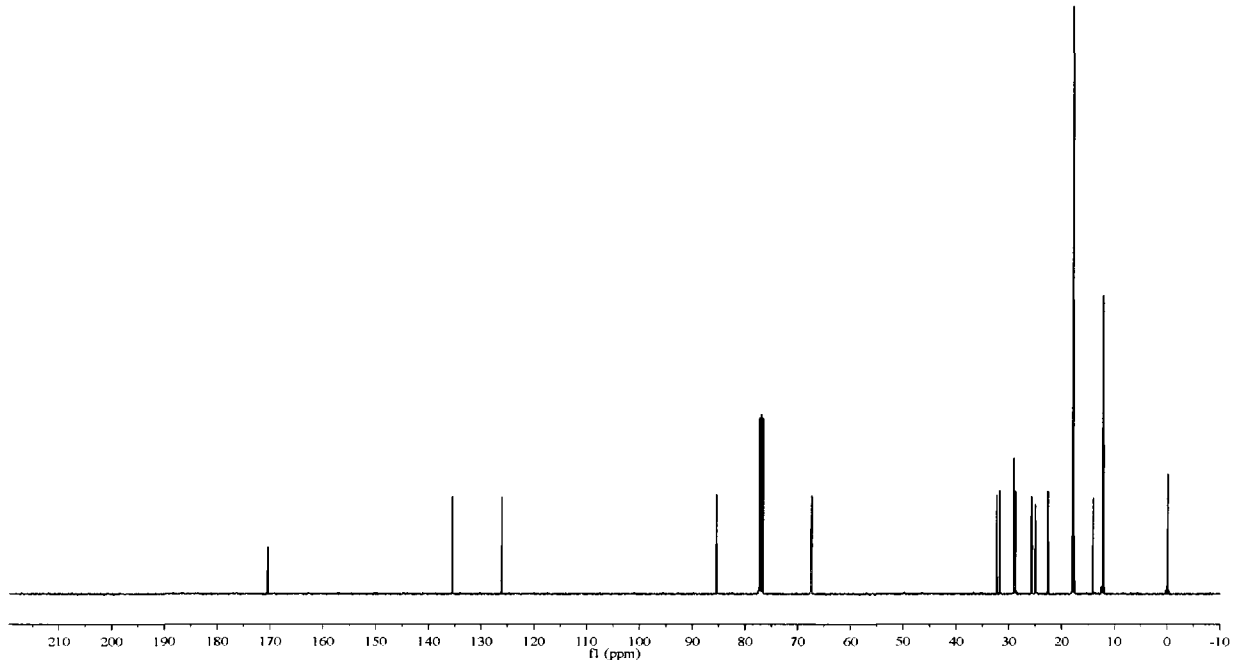


To a solution of lactol **3.55** (358 mg, 0.898 mmol) in dry CH_2Cl_2 (7 mL) was added activated 4Å molecular sieves (300 mg) followed by NMO (210 mg, 1.80 mmol). The flask was protected from light and cooled to 0 °C. Tetrapropylammonium perruthenate (15.8 mg, 0.045 mmol) was added and the flask was allowed to warm to room temperature. After one hour of stirring, the mixture was concentrated under reduced pressure. The resulting residue was taken up in ether and the dark suspension filtered through a celite pad. The filtrate was concentrated and the residue purified by flash column chromatography on silica gel using a gradient elution (0% to 7% EtOAc in hexanes) to afford 302 mg (84% yield) of the desired lactone as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (td, J = 6.8, 1.3 Hz, 1H), 5.42 (ddt, J = 15.4, 6.0, 1.4 Hz, 1H), 4.82 – 4.80 (m, 1H), 3.99 (ddd, J = 4.8, 3.0, 3.0 Hz, 1H), 2.81 (ddd, J = 18.2, 11.1, 7.3 Hz, 1H), 2.48 (ddd, J = 18.0, 6.5, 3.3 Hz, 1H), 2.10 – 2.01 (m, 3H), 1.91 – 1.84 (m, 1H), 1.38 (quint., J = 6.9 Hz, 2H), 1.32 – 1.21 (m, 8H), 1.13 – 1.04 (m, 21 H), 0.88 (t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (C), 135.5 (CH), 126.1 (CH), 85.5 (CH), 67.4 (CH), 32.3(CH_2), 31.8 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 18.0 (CH_3) and 17.7 (CH_3) (TIPS (6C)), 14.1 (CH_3), 12.3 (CH (3C)); IR (neat): υmax 2927 (s), 2867 (s), 1744 (s), 1464 (m), 1106 (m), 1013 (m), 883 (m), 825 (w), 682 (m); HRMS (EI) *m/z* M^+ not found, M^+ - C_3H_7 ($C_{20}H_{37}O_3Si$) calculated 353.2507, found 353.2500; $[\alpha]^{22}_D$ +52.4°, *c* 12.1 mg/mL (CH_2Cl_2).

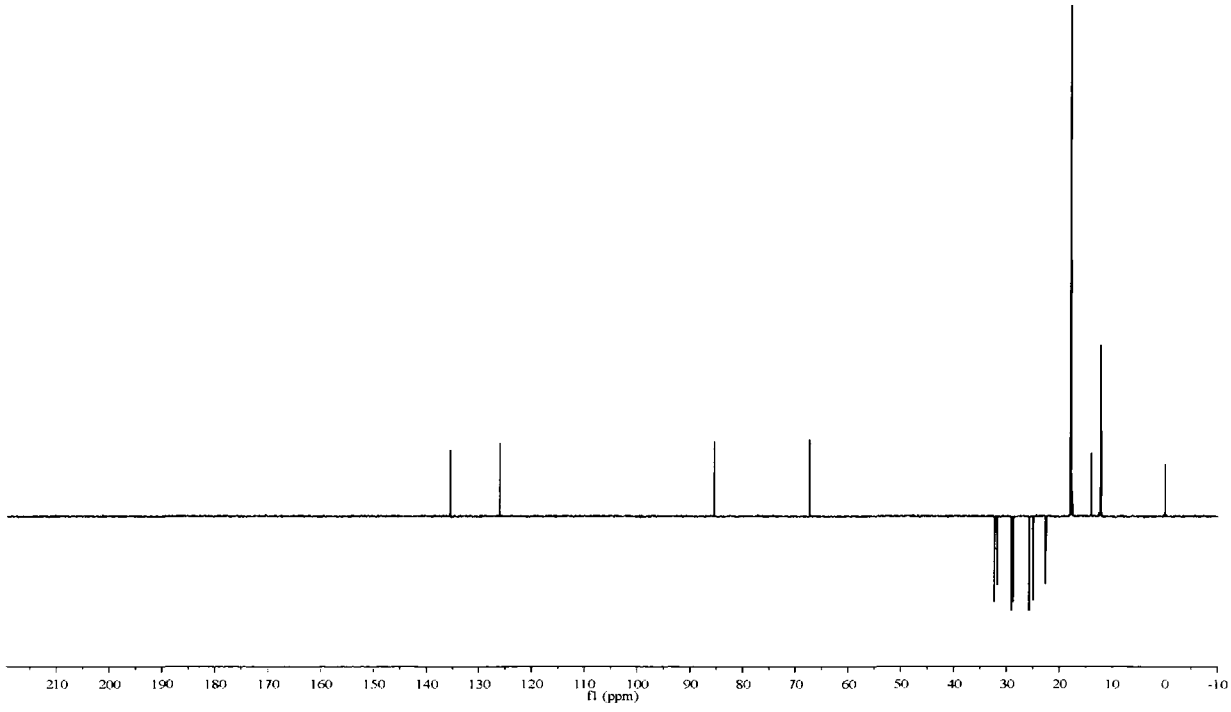
^{1}H NMR (400 MHz, $CDCl_3$)



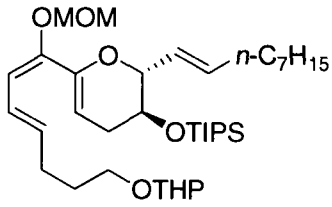
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT 135 (100 MHz, $CDCl_3$)



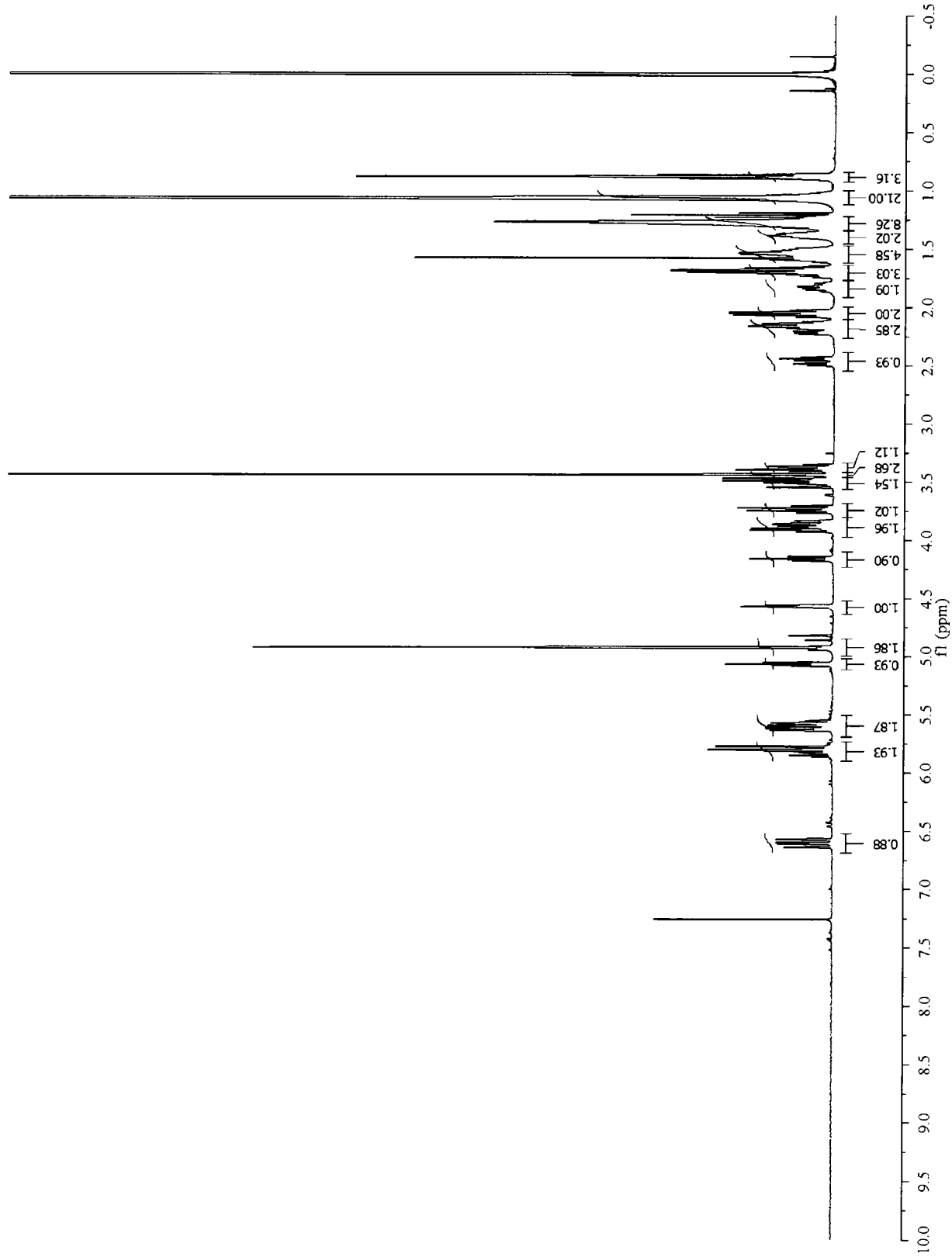
Triisopropyl((2*R*,3*S*)-6-((1*E*,3*E*)-1-(methoxymethoxy)-7-(tetrahydro-2*H*-pyran-2-yloxy)hepta-1,3-dienyl)-2-((*E*)-non-1-enyl)-3,4-dihydro-2*H*-pyran-3-yloxy)silane (3.57)



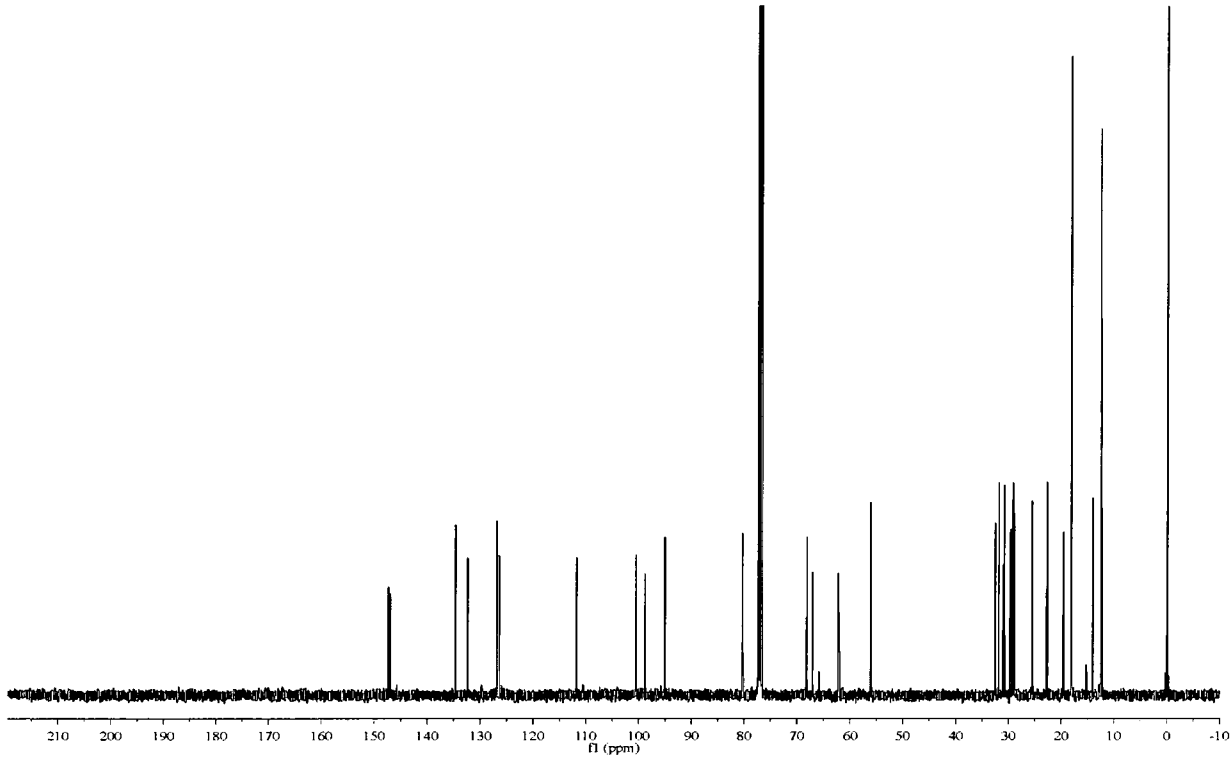
To a solution lactone **3.56** (50.0 mg, 0.126 mmol) and phenyltriflimide (63.0 mg, 0.176 mmol) in THF (2.0 mL) at -78 °C was added a solution of KHMDS (77.9 mg, 0.390 mmol) in THF (1.0 mL) over a period of one hour. The resulting mixture was stirred for another 30 minutes at that temperature then quenched by the addition of water. Ether was added and the layers were separated. The aqueous layer was extracted with ether three times. The combined organic extracts were washed with water then brine, dried over Na_2SO_4, filtered and concentrated to dryness. The crude triflate was then quickly taken up in THF (1.5 mL). To it was added a solution of the boronic ester **3.45** (131.0 mg, 0.343 mmol) in THF (1.5 mL). A 2 M solution of K_2CO_3 (0.25 mL, 0.50 mmol) was then added. The resulting biphasic mixture was purged with argon 3 times and the catalyst was added. The mixture was purged with argon 3 more times then stirred vigorously overnight at room temperature. Water and ether were added and the layers separated. The aqueous layer was extracted with ether 3 times. The combined organic extracts were washed with water then brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel pretreated with triethylamine using a gradient elution (0% to 5% ether in hexanes) to afford 37.4 mg (48 % based on the starting lactone) of the desired triene as a light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (ddt, J = 15.2, 10.9, 1.4 Hz, 1H), 5.83 (dtd, J = 15.5, 6.6, 1.0 Hz, 1H), 5.79 (d, J = 11.0 Hz, 1H), 5.64 – 5.56 (m, 2H), 5.07 (dd, J = 4.4, 3.7 Hz, 1H), 4.93 (s, 2H), 4.57 (dd, J = 4.2, 2.7 Hz, 1H), 4.16 (dd, J = 6.9, 6.8 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.74 (ddd, J = 9.6, 9.6, 6.7 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.44 (s, 3H), 3.38 (ddd, J = 9.7, 6.2, 6.2, 1H), 2.47 (dt, J = 17.5, 5.1 Hz, 1H), 2.23 – 2.13 (m, 3H), 2.06 (q, J = 7.0 Hz, 2H), 1.87 – 1.79 (m, 1H), 1.74 – 1.65 (m, 3H), 1.61 – 1.49 (m, 4H), 1.40 – 1.34 (m, 2H), 1.32 – 1.24 (m, 8H), 1.10 – 1.04 (m with s at 1.07, 21 H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3 (C), 147.0 (C), 134.7 (CH), 132.4 (CH), 126.9 (CH), 126.5 (CH), 111.9 (CH), 100.5, (CH), 98.8 (CH), 95.1 (CH_2), 80.3 (CH), 68.2 (CH), 67.1 (CH_2), 62.2 (CH_2), 56.1(CH_3), 32.5 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 19.6 (CH_2), 18.1 (CH_3 (6C)), 14.1 (CH_3), 12.5 (CH (3C)); IR (neat): υmax 2927 (s), 2867 (s), 1583

(w), 1465 (m), 1136 (s), 1120 (s), 1063 (s), 971 (s), 883 (m), 815 (w), 681 (m); HRMS (EI) *m/z* M^+ not found; $[\alpha]^{22}_D$ +42.4°, *c* 10.6 mg/mL (CH_2Cl_2).

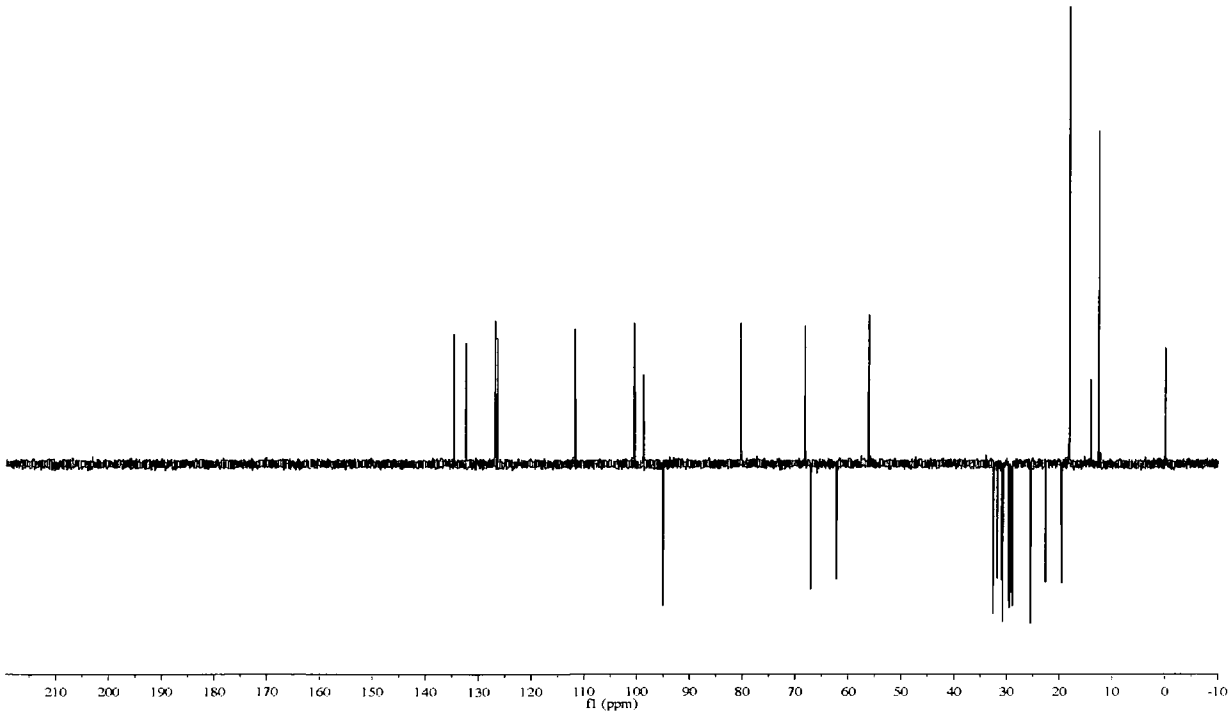
^{1}H NMR (400 MHz, $CDCl_3$)



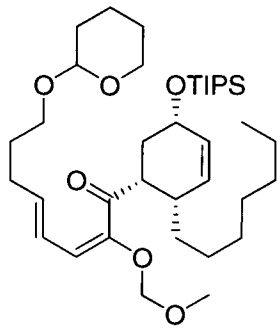
^{13}C NMR (100 MHz, $CDCl_3$)



DEPT 135 (100 MHz, $CDCl_3$)

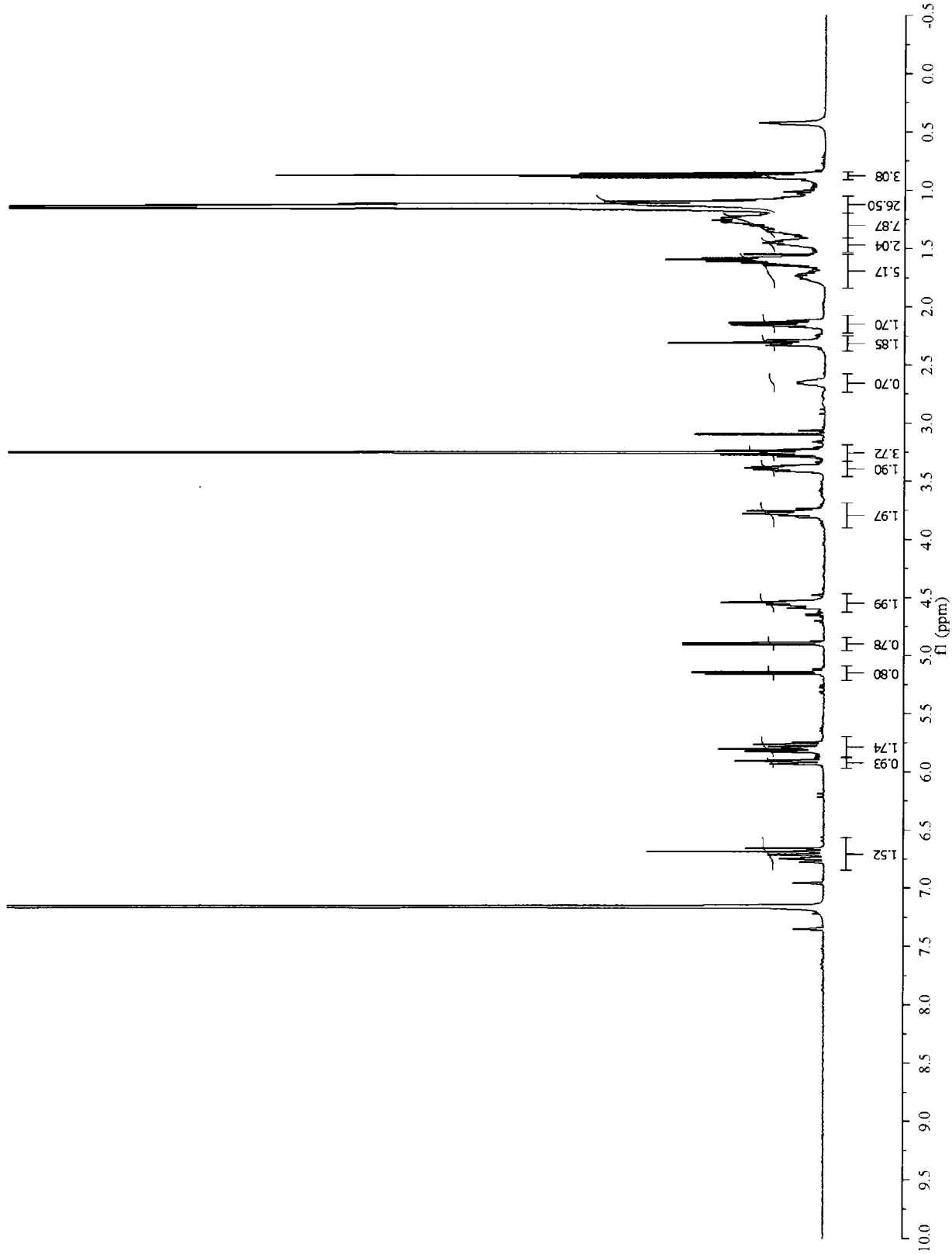


(2*E*,4*E*)-1-((1*R*,2*S*,5*S*)-2-heptyl-5-(triisopropylsilyloxy)cyclohex-3-enyl)-2-(methoxymethoxy)-8-(tetrahydro-2*H*-pyran-2-yloxy)octa-2,4-dien-1-one (3.65)

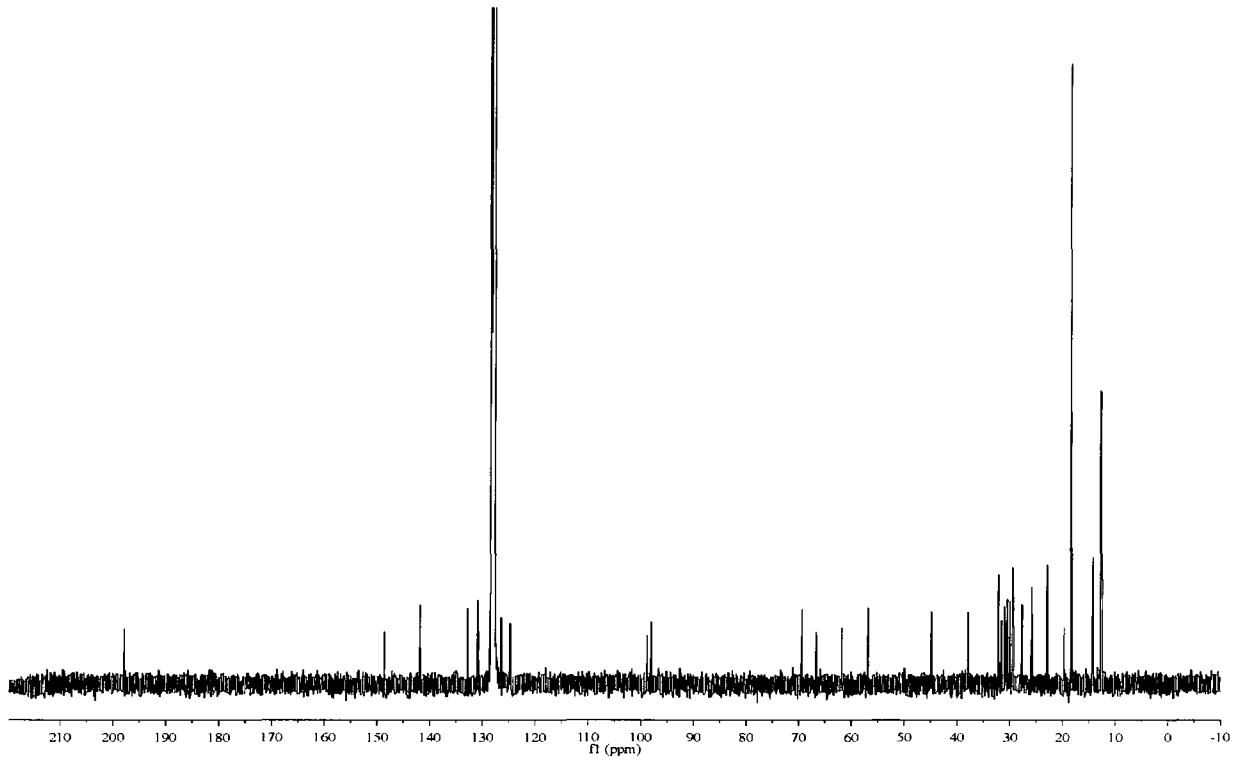


Four microwave tubes containing a carboflon were flame dried and loaded with 50 mg (0.079 mmol X 4) each of the triene **3.57** followed by the addition of 2.5 mL of toluene and 25 μL of triethylamine. They were degased by bubbling argon through the solution for 10 minutes then sealed. Each tube was irradiated in the microwave at 180 °C for 1h and the four resulting reaction mixtures were combined and concentrated. A first flash chromatography on silica gel pretreated with triethylamine was performed using a 0% to 30% Et_2O in hexanes gradient and the least polar compound was isolated ((**3.65**) 14.1 mg, 7%, pink spot when revealed with PA stain, Rf = 0.51 (30% Et_2O in hexanes, tlc plate pretreated with triethylamine)). 50 mg of a mixture of two impure products also was isolated witch appeared as only one spot by tlc (dark blue to black when revealed with PA stain, Rf = 0.23 with 30% Et_2O in hexanes, TLC plate pretreated with triethylamine). Another flash chromatography was performed but failed to separate the two products. 28 mg of this mixture remained. ^{1}H NMR (400 MHz, C_6D_6): δ 6.75 (ddd, J = 14.8, 10.9, 0.7 Hz, 1H), 6.68 (d, J = 10.9 Hz, 1H), 5.92 (br d, J = 10.1 Hz, 1H), 5.82 (ddd, J = 10.2, 4.6, 1.7 Hz, 1H), 5.79 (dt, J = 14.7, 7.3 Hz, 1H), 5.16 (dd, J = 6.1, 1.1 Hz, 1H), 4.91 (dd, J = 6.0, 0.6 Hz, 1H), 4.60 – 4.54 (m, 2H), 3.82- 3.74 (m, 2H), 3.42 – 3.37 (m, 2H), 3.30 – 3.24 (m, 1H), 3.26 (d, J = 0.6 Hz, 3H), 2.66 (ddt, J = 10.1, 5.1, 5.1 Hz, 1H), 2.31 (dd, J = 8.7, 8.7 Hz, 1H), 2.31 (dd, J = 7.0, 7.0 Hz, 1H), 2.15 (dt, J = 7.2, 7.2 Hz, 2H), 1.78 – 1.68 (m, 1H), 1.66 – 1.55 (m, 4H), 1.48 – 1.42 (m, 2H), 1.40- 1.21 (m, 8H), 1.18 – 1.08 (m, 26H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 197.9 (C), 148.6 (C), 141.9 (CH), 132.9 (CH), 131.0 (CH), 126.5 (CH), 124.8 (CH), 98.8 (CH), 98.0 (CH_2), 69.4 (CH), 66.7 (CH_2), 61.8 (CH_2), 56.9 (CH_3), 44.9 (CH), 38.0 (CH), 32.2 (CH_2), 31.6 (CH_2), 31.1 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 25.9 (CH_2), 23.0 (CH_2), 19.8 (CH_2), 18.4 (CH_3 (6C)), 14.4 (CH_3), 12.8 (CH (3C)); IR (neat): υmax 2941 (s), 2866 (s), 1734 (w), 1671 (m), 1632 (w), 1465 (m), 1389 (w), 1352 (w), 1259 (w), 1201 (m), 1094 (s), 1022 (s), 996 (m), 883 (m), 815 (w), 681 (w); HRMS (EI) *m/z* M^+ not found, M^+ - *i*-Pr and CH_3OCH_2 ($C_{32}H_{54}O_5Si$) calculated 546.3741, found 546.3754; $[\alpha]^{22}_D$ +44.6°, *c* 5.3 mg/mL (CH_2Cl_2).

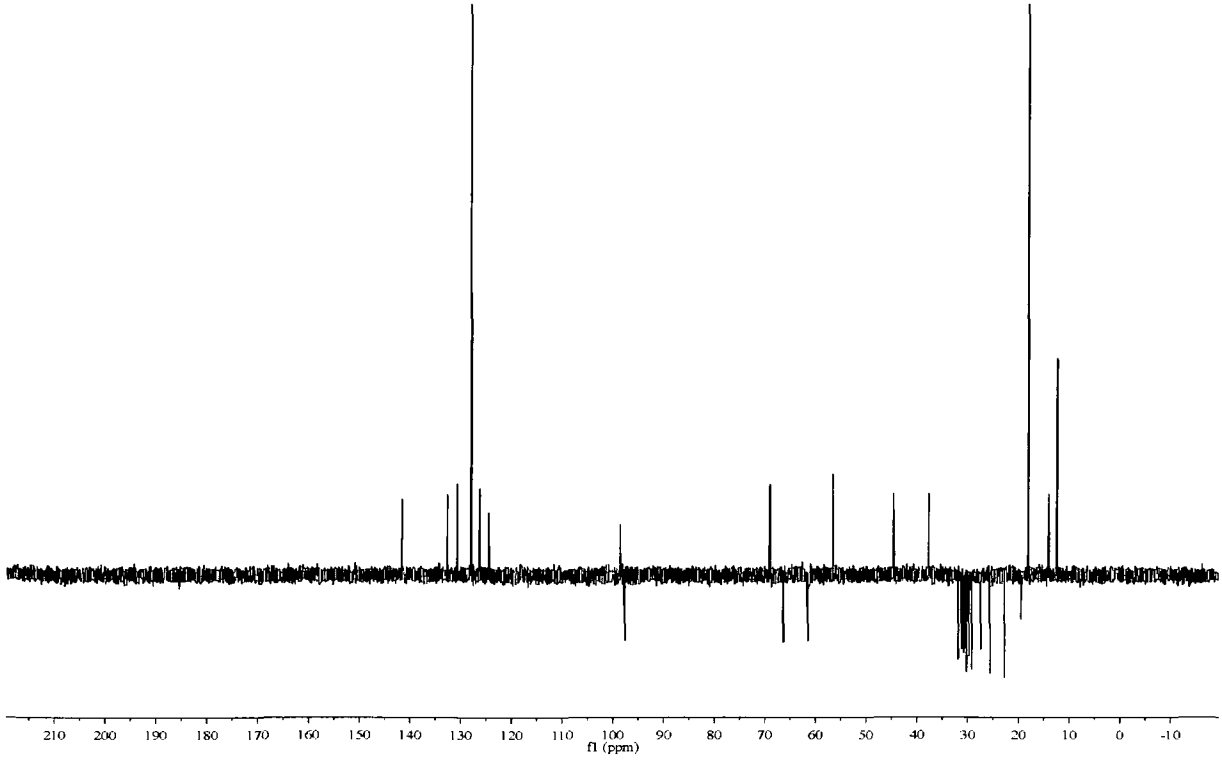
^{1}H NMR (400 MHz, C_6D_6)



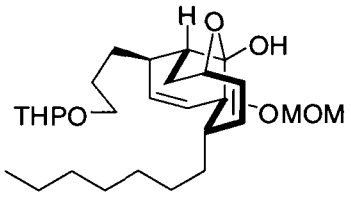
^{13}C NMR (100 MHz, C_6D_6)



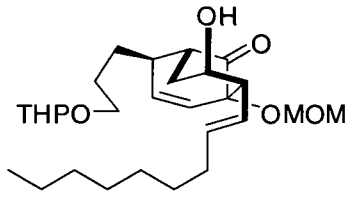
DEPT 135 (100 MHz, C_6D_6)



Lactol 3.67 and (4*R*,5*R*,7*R*,8*R*)-7-hydroxy-1-(methoxymethoxy)-8-((*E*)-non-1-enyl)-4-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)bicyclo[3.3.1]non-2-en-9-one (3.68)



3.67

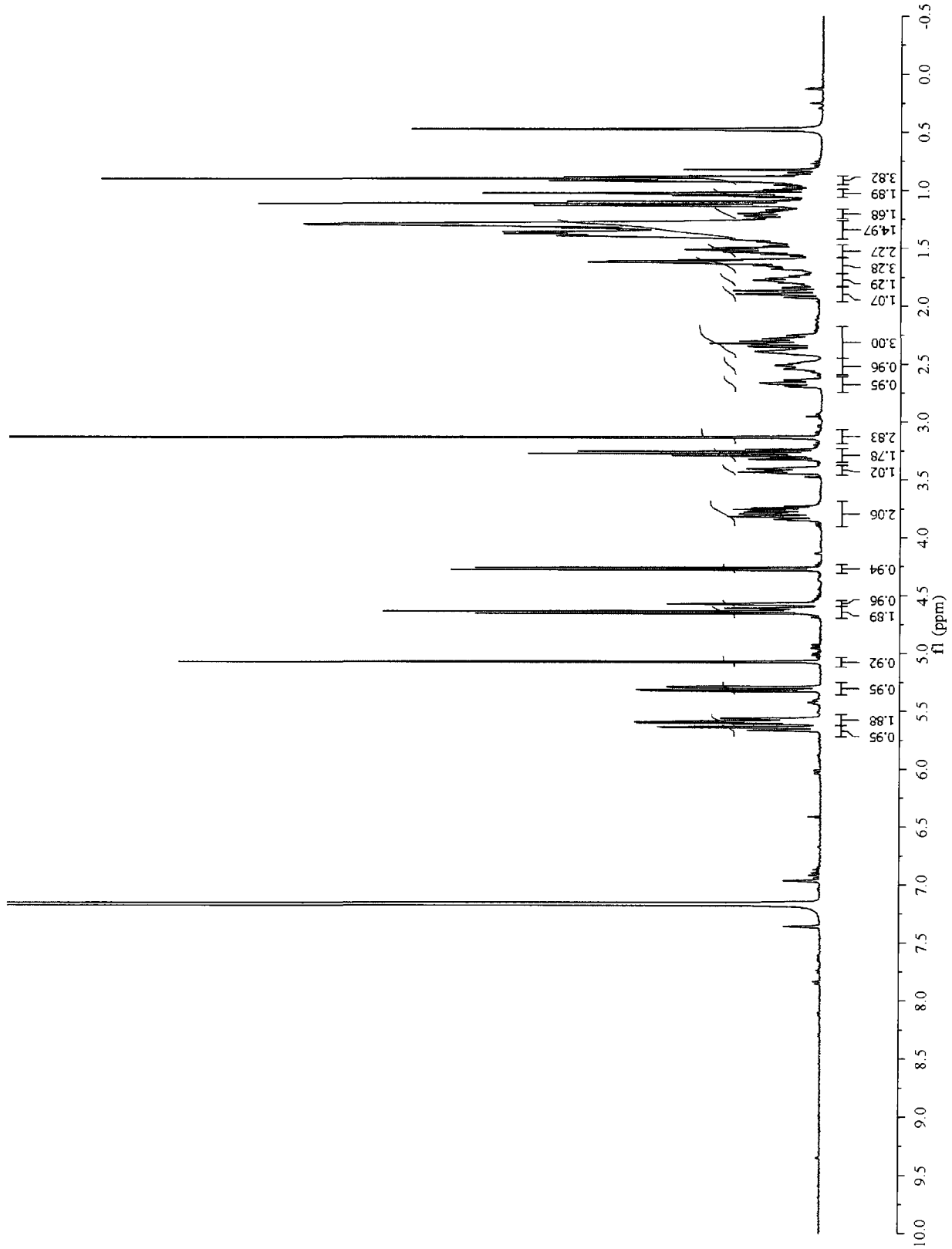


3.68

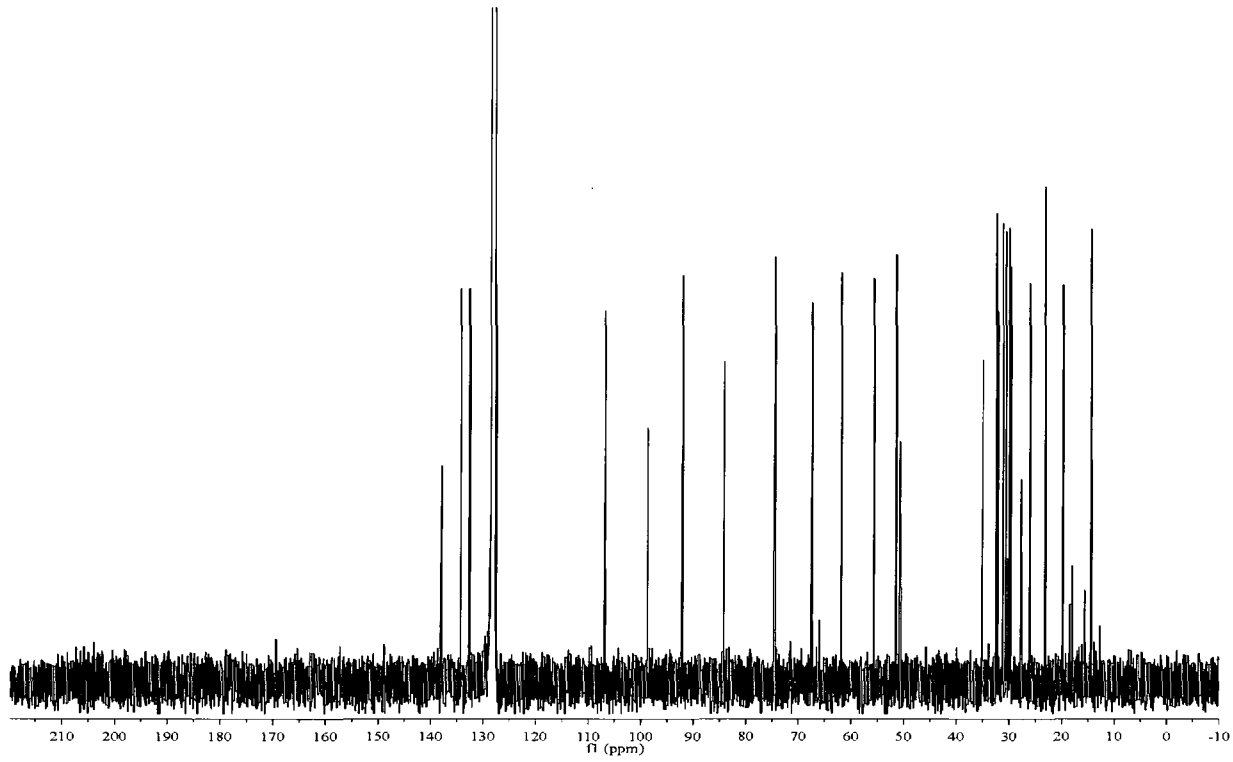
The impure mixture of two products described above (28 mg) was dissolved in THF 0.6 mL. Triethylamine (23 μL, 0.17 mmol) was added at room temperature followed by a 1M solution of TBAF in THF (50 μL, 50 μmol). The resulting yellow solution was stirred for 1h then concentrated to dryness. Two new products were observed by TLC analysis and isolated by flash column chromatography on silica gel pretreated with triethylamine using a gradient elution (0% to 30% EtOAc in hexanes).

3.67: light yellow oil (6.3 mg, 4% yield from triene **3.57**): Rf = 0.25 (20% EtOAc in hexanes, TLC plate pretreated with triethylamine); ^{1}H NMR (400 MHz, C_6D_6): δ 5.64 (ddd, J = 10.1, 2.9, 1.4 Hz, 1H), 5.59 (dd, J = 10.0, 2.8 Hz, 1H), 5.58 (ddd, J = 10.9, 8.6, 0.5 Hz, 1H), 5.30 (dd, J = 11.0, 3.8 Hz, 1H), 5.07 (s, 1H), 4.65 (d, J = 6.9 Hz, 1H), 4.63 (ddd, J = 9.6, 3.7, 3.7, Hz, 1H), 4.57 (ddd, J = 3.2, 3.2, 0.9 Hz, 1H), 4.27 (d, J = 6.8 Hz, 1H), 3.82 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 3.76 (dddd, J = 9.9, 6.6, 6.6, 4.3 Hz, 1H), 3.42 (ddd, J = 11.0, 4.0, 4.0 Hz, 1H), 3.32 – 3.25 (m, 1H), 3.13 (s, 3H), 2.67 (ddd, J = 8.7, 8.7, 3.9Hz, 1H), 2.57 – 2.47 (m, 1H), 2.42 – 2.36 (m, 1H), 2.34 (dd, J = 8.9, 3.3 Hz, 1H), 2.33 – 2.24 (m, 1H) 1.88 (dddd, J = 11.6, 11.6, 9.6, 1.9 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.68 – 1.59 (m, 3H), 1.57 – 1.48 (m, 2H), 1.45 – 1.26 (m, 13H), 1.24 – 1.17 (m, 1H), 1.06 – 1.00 (m, 1H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 137.9 (CH), 134.2 (CH), 132.6 (CH), 127.5 (CH), 106.8 (C), 98.7 (CH), 92.1 (CH_2), 84.2 (C), 74.5 (CH), 67.3 (CH_2), 61.8 (CH_2), 55.6 (CH_3), 51.4 (CH), 50.7 (CH), 35.0 (CH), 32.4 (CH_2), 32.1 (CH_2), 31.1 (CH_2), 31.1 (CH_2), 30.7 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 27.7 (CH_2), 26.0 (CH_2), 23.1 (CH_2), 19.8 (CH_2), 14.4 (CH_3); IR (neat): υmax 3481 (s), 2922 (m), 2855 (w), 2096 (w), 1645 (s), 1458 (w), 1352 (w), 1079 (w), 1020 (w); HRMS (EI) *m/z* M^+ not found, M^+ - $C_2H_6O_2$ ($C_{26}H_{40}O_4$) calculated 416.2927, found 416.2884; $[\alpha]^{22}_D$ +38.6°, *c* 4.8 mg/mL (CH_2Cl_2).

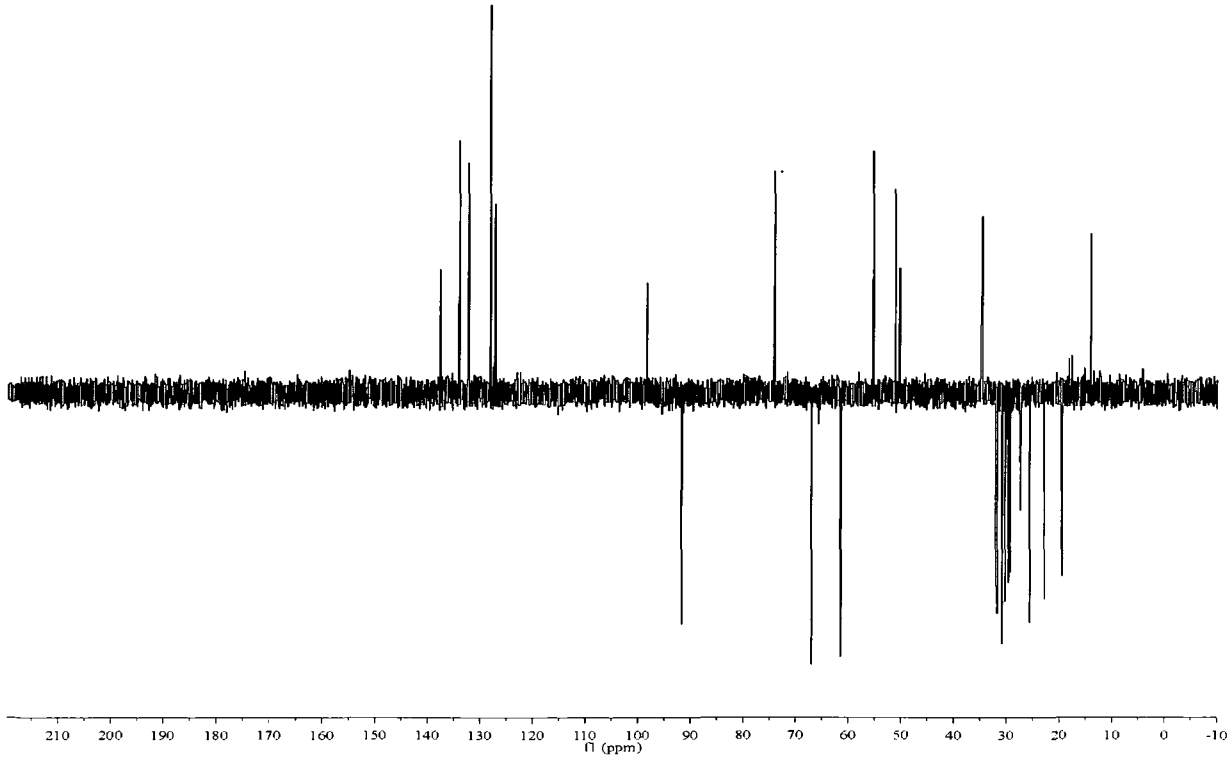
^{1}H NMR (400 MHz, C_6D_6)



^{13}C NMR (100 MHz, C_6D_6)

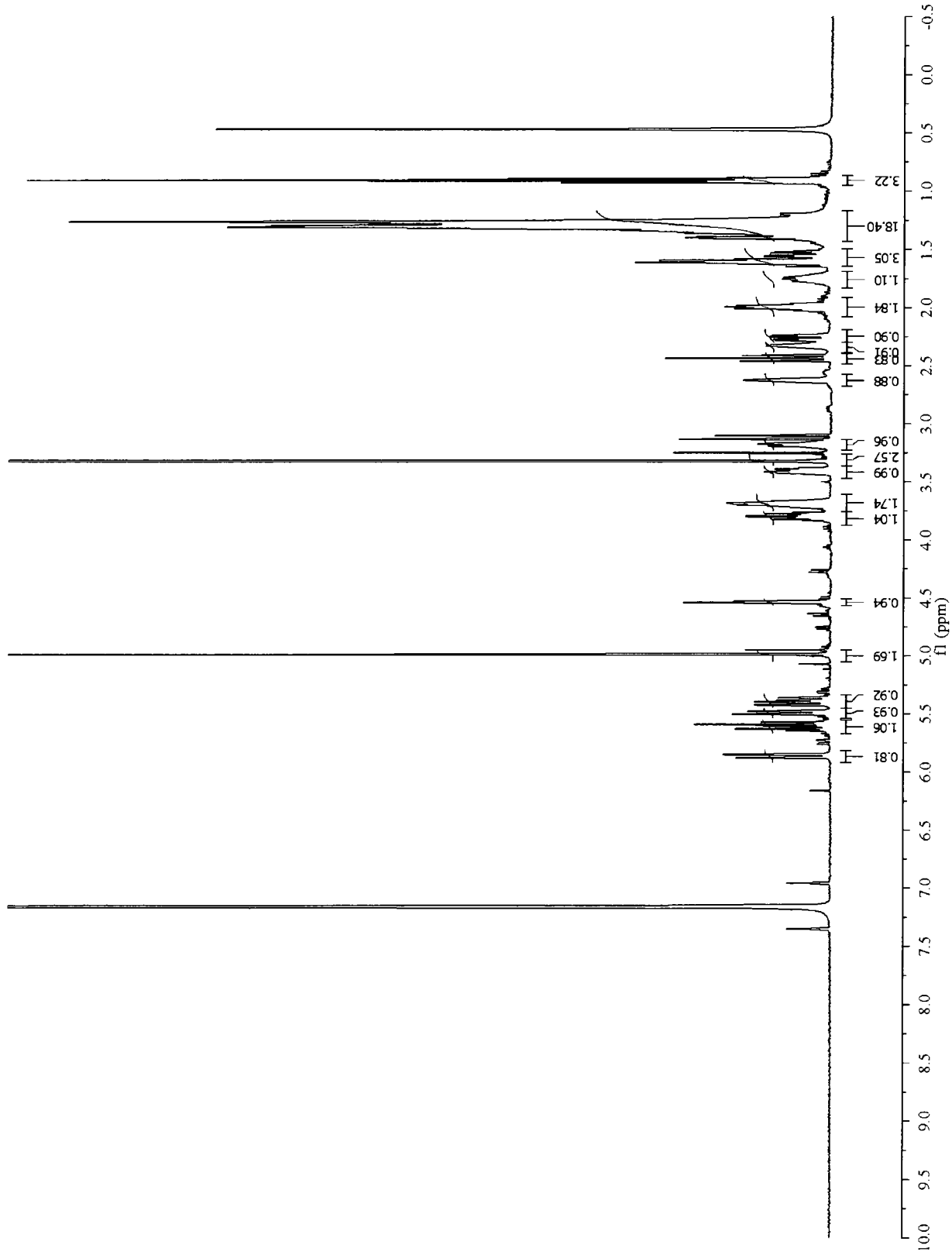


DEPT 135 (100 MHz, C_6D_6)

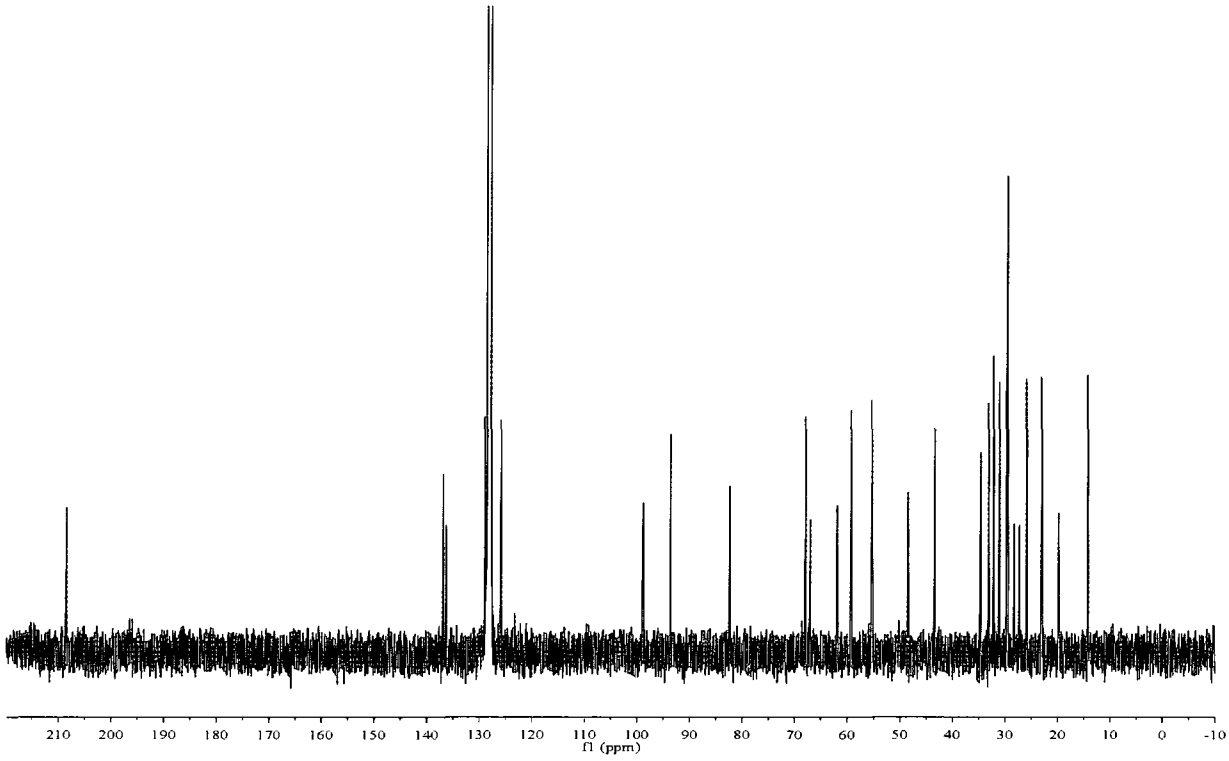


3.68: light yellow oil, (7.0 mg, 5% yield from triene **3.57**): Rf = 0.13 (20% EtOAc in hexanes, TLC plate pretreated with triethylamine); ^{1}H NMR (400 MHz, C_6D_6): δ 5.87 (ddd, J = 10.6, 2.8, 0.9 Hz, 1H), 5.61 (dt, J = 15.3, 6.8 Hz, 1H), 5.49 (dddd, J = 10.2, 3.4, 2.4, 1.2 Hz, 1H), 5.40 (dddt, J = 15.3, 8.9, 2.8, 1.3 Hz, 1H), 4.99 (br s, 2H), 4.54 (ddd, J = 3.3, 3.3, 3.3 Hz, 1H), 3.8 (dddd, J = 11.7, 8.8, 3.1, 3.1 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.44 – 3.38 (m, 1H), 3.33 (d, J = 0.3 Hz, 3H), 3.21 – 3.15 (m, 1H), 2.63 (dd, J = 5.0, 5.0 Hz, 1H), 2.44 (dd, J = 9.3, 9.3 Hz, 1H), 2.35 – 2.32 (m, 1H), 2.26 (ddd, J = 13.9, 5.2, 2.3 Hz, 1H), 2.00 (dt, J = 11.0, 6.9 Hz, 2H), 1.79 – 1.72 (m, 1H), 1.63 – 1.59 (m, 2H), 1.56 (ddd, J = 13.9, 11.7, 5.1 Hz, 1H), 1.41 – 1.19 (m, 18H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 208.4 (C), 136.8 (CH), 136.2 (CH), 128.8 (CH), 125.8 (CH), 98.9 (CH), 93.7 (CH_2), 82.5 (C), 67.9 (CH), 67.1 (CH_2), 62.0 (CH_2), 59.3 (CH), 55.4 (CH_3), 48.5 (CH), 43.4 (CH), 34.7 (CH_2), 33.2 (CH_2), 32.2 (CH_2), 31.1 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 25.9 (CH_2), 23.1 (CH_2), 19.9 (CH_2), 14.3 (CH_3); IR (neat): υmax 3466 (w), 2926 (s), 2855 (m), 1735 (s), 1466 (w), 1161 (w), 1120 (m), 1074 (m), 1033 (s), 985 (m), 918 (w); HRMS (EI) *m/z* M^+ ($C_{28}H_{46}O_6$) calculated 478.3294, found 478.3266; $[\alpha]^{22}_D$ -27.8°, *c* 5.4 mg/mL (CH_2Cl_2).

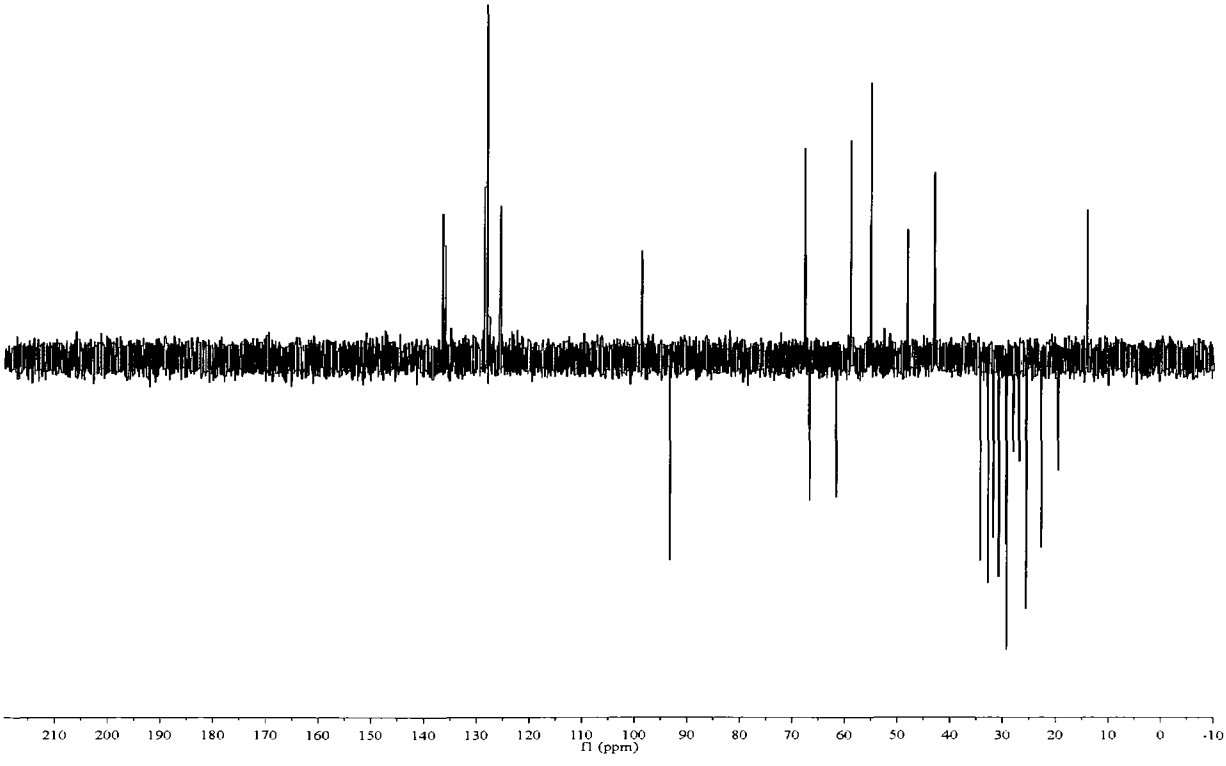
^{1}H NMR (400 MHz, C_6D_6)



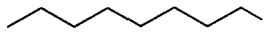
^{13}C NMR (100 MHz, C_6D_6)



DEPT 135 (100 MHz, C_6D_6)



Octyltriphenylphosphonium bromide (3.53)



Procedure adapted from Pettit and Duffield.[39c]

To a solution of triphenylphosphine (31.9 g, 122 mmol) in dry toluene (135 mL) was added 1-bromooctane (20.0 mL, 116 mmol) at room temperature. The flask was equipped with a reflux condenser and the reaction mixture was stirred at reflux over 3 days. Upon cooling two layers could be observed. The mixture was concentrated under reduced pressure and to the resulting gum was added 100 mL of ether. The sticky gum was stirred manually with a spatula with the ether for 5 minutes then the ether was decanted. The gum was similarly washed with ether two more times (100 mL each) then dried under high vacuum to afford the desired phosphonium bromide as a glassy solid (49.0 g, 93% yield). *Note: this compound must be handled rapidly as it is very hygroscopic and quickly becomes a sticky oil.* Spectral data was in accord with those previously reported.[53]

Glossary and Abbreviations

±	*racemic*
Ac	*acetate*
aq.	*aqueous*
br	*broad*
COSY	*correlation spectroscopy*
CSA	*camphorsulphonic acid*
d	*doublet*
DBU	*1,8-diazobicyclo[5.4.0]undec-7-ene*
DCE	*1,2-dichloroethane*
DCM	*dichloromethane*
decomp.	*decomposition*
DHP	*3,4-dihydro-2H-pyran*
DMAP	*4-dimethylaminopyridine*
DME	*1,2-dimethoxyethane*
DMF	N,N-*dimethylformamide*
DMSO	*dimethylsulfoxide*
EI	*electron ionization*
eq.	*equivalents*
Et	*ethyl*
Et_2O	*diethyl ether*
Et_3N	*triethylamine*
EtOAc	*ethyl acetate*
HMPA	*hexamethylphosphoramide*
HRMS	*high resolution mass spectrometry*
IR	*infrared*

J	*coupling constant*
KHMDS	*potassium hexamethyldisilazane*
m	*multiplet or medium*
M^+	*molecular ion*
m-CPBA	*3-chloroperoxybenzoic acid*
Me	*Methyl*
MOM	*methoxymethyl ether*
MS	*molecular sieves*
NMO	N-*methylmorpholine* N-*oxide*
NMR	*nuclear magnetic resonance*
NOE	*nuclear Overhauser effect*
NOESY	*nuclear Overhauser effect spectroscopy*
o.n.	*over night*
PA	para-*anisaldehyde*
Pg	*protecting group*
Ph	*Phenyl*
ppm	*parts per million*
PTSA	para-*toluene sulphonic acid*
q	*Quartet*
quant.	*quantitative yield*
Rf	*retention factor*
r.t.	*room temperature*
s	*singlet or strong*
t	*Triplet*
TBAF	*tetrabutylammonium fluoride*
TBDPS	tert-*butyldiphenylsilyl*
TBS	tert-*butyldimethylsilyl*
t-Bu	tert-*butyl*
TES	*Triethylsilyl*
Tf	*Trifluoromethylsulfone*
TFA	*trifluoroacetic acid*

THF	*Tetrahydrofuran*
TIPS	*Triisopropylsilyl*
TLC	*thin layer chromatography*
TMS	*Trimethylsilyl*
w	*Weak*

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