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Towards the Total Synthesis of Garsubellin A
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Towards the Total Synthesis of Garsubellin A

by

Marie-Christine Brochu

B.Sc., Laval Unversity, 2005

Thesis submitted to the Faculty of Graduate & Postdoctoral Studies
In partial fulfillment of the requirements for the
M. Sc. degree in chemistry

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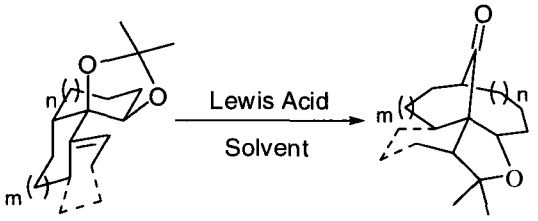
À mon père

Abstract

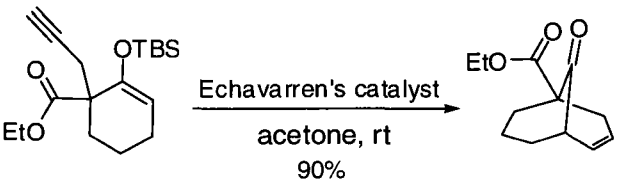
Our laboratory reported a novel method to prepare highly oxygenated and functionalized bicyclo[m.n.1]alkanones from acetals using a Lewis acid mediated Prins-pinacol cationic cascade[1]. This allows us to access complex bridgehead ketone frameworks encountered in many natural products. Garsubellin A is an example of highly functionalized bicyclo[3.3.1]alkanone that we expect to synthesized using the Prins-pinacol methodology. For instance, we were able to prepare diastereoselectively an advanced intermediate for the total synthesis of garsubellin A using this method. Even if the Lewis acid mediated Prins-pinacol cationic cascade appears to be a powerfull method to access complex bridgehead ketone frameworks, we are presently envisaging a second method for the preparation of the garsubellin A core. This method consists in a gold catalyzed Conia-ene reaction. It was already demonstrated in our laboratory that unsubstituted bicyclo[3.3.1]alkanone can be prepared using the gold catalyzed Conia-ene reaction. We want to apply this new methodology to the total synthesis of garsubellin A.

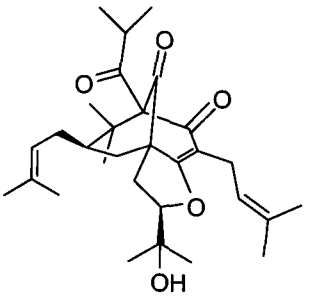
Prins-pinacol



yield 44-96%
m, n = 0-2

Gold Catalyzed Conia-ene





Garsubellin A

Remerciements

Je voudrais premièrement remercier mon superviseur de recherches, Professeur Louis Barriault, de m'avoir confié un projet aussi audacieux. Merci de m'avoir fait confiance et de m'avoir aidé à développer mon autonomie au laboratoire. Merci également à mes collègues de laboratoire pour leur conseils et leur soutien dans les jours plus tristes. Merci à Dr Irina Denisova pour l'aide à la correction de ce mémoire. Merci à mon ami Éric Beaulieu. On est passé en même temps aux mêmes endroits. À deux, ça va deux fois mieux. Merci à mon voisin de hotte Jason Poulin pour ses bons conseils. Merci à Christiane Grisé, la maman du laboratoire, pour avoir partagé si patiemment sa grande expérience avec nous. Merci à Francis Barabé, mon coéquipier de Conia-ene. Lâche pas Francis, on va les avoir les PPAPs. Merci à tous les autres que j'ai côtoyés, passés et présents : Patric Ang, Dr Steve Arns, Dr Rachel Beingessner, Anik Chartrand, Mélina Girardin, Kassandra Lepack, Dr Minaruzzaman, Dr Maxime Riou, Dr Effiette Sauer. Bonne chance aux « undergrads » qui mettent de la vie dans le labo.

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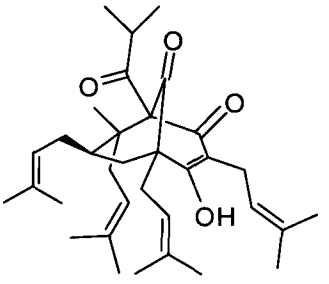
1

Introduction

In 1971, Kolosov *et al.*[1] isolated hyperforin (**1.1**) from *Hypericum perforatum*, a folk remedy used by the ancient Greeks for its antibacterial and antidepressive properties. The same group assigned the chemical structure of this natural product in 1975.[2] Hyperforin (**1.1**) is one of the first compounds to be isolated from the family called polyprenylated acylphloroglucinols (PPAP's). Many more members have since been reported.[3, 4]



Hyperforin
1.1

Figure 1.1 – Structure of Hyperforin

PPAP's are generally highly oxygenated bicyclo[3.3.1]nonane-2,4,9-trione densely substituted with prenyl or geranyl subunits. There are more then 100 PPAP's known to date; they are divided into three classes depending on the relative position of the acyl substituent (Scheme 1.1). Structures bearing an acyl group at the C-6 bridgehead position (type A) represent the most abundant PPAP's found in nature. Type B and type C structures bear their acyl group at C-2 and C-4 respectively.

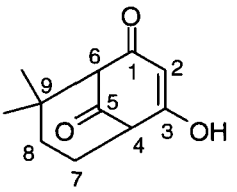
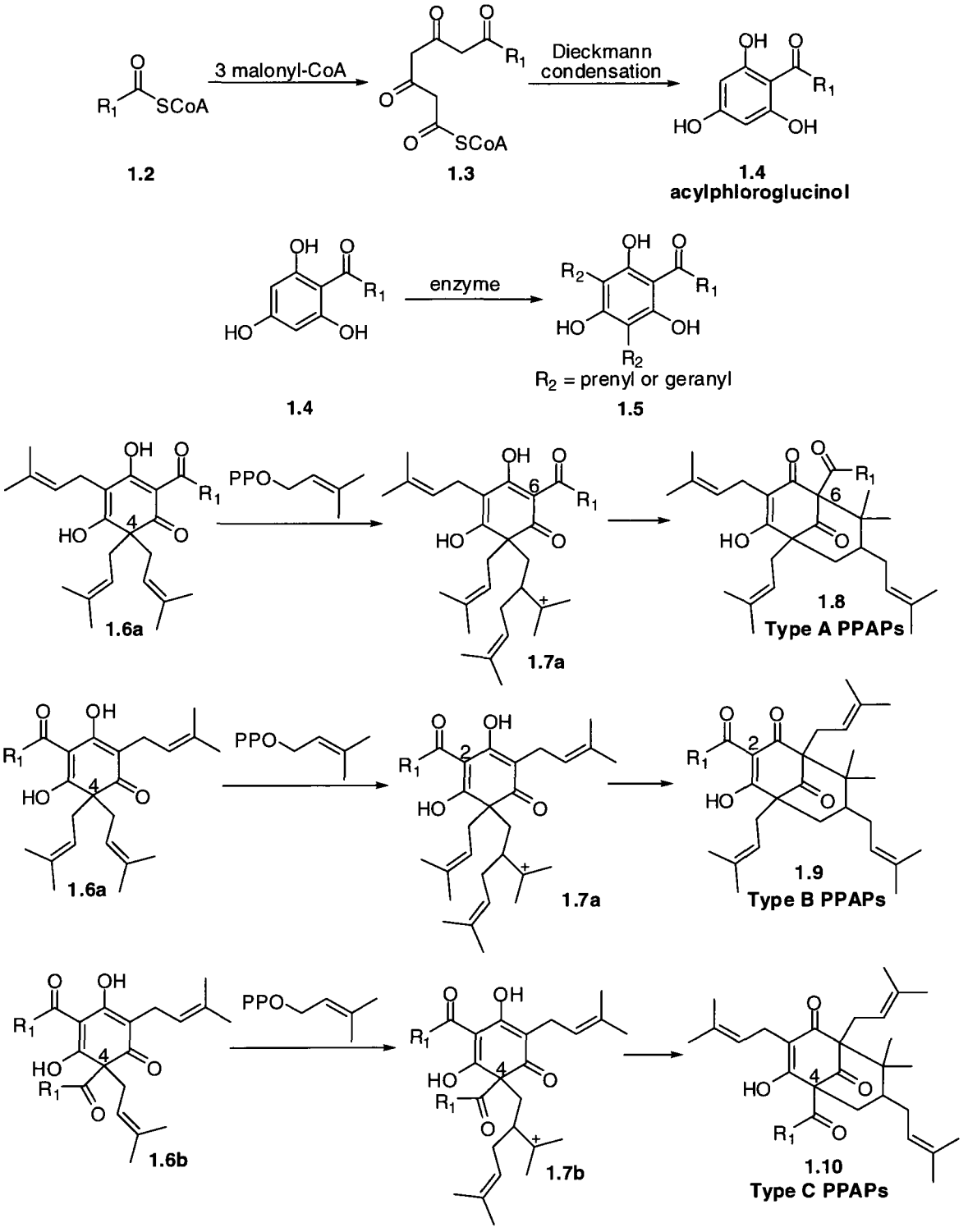


Figure 1.2 – Bicyclo[3.3.1]nonane-2,4,9-trione core of PPAP's

1.1 Biosynthesis of PPAP's

The biosynthesis of PPAP's[3, 4] involves condensation of three molecules of malonyl-coenzyme A and one molecule of acyl-coenzyme A (**1.2**) (Scheme 1.2). Dieckmann condensation of the resulting compound **1.3** affords acylphloroglucinol **1.4** which then undergoes enzyme-catalyzed prenylations or geranylations to give compound **1.5**. It was proposed[3, 4] that type A and type B PPAP's are obtained through the same intermediate **1.6a** which is a result of prenylation of compound **1.5** *meta* to the acyl group. Further prenylation of one of the prenyl side chain attached at C4 gives cationic intermediate **1.7a**. Cyclization of intermediate **1.7a** by either attack from the carbon bearing the acyl or the prenyl substituent leads to type A (**1.8**) and type B (**1.9**) structures respectively. Synthesis of type C structures occurs through a different intermediate (**1.6b**) which is obtained by prenylation of compound **1.5** at the carbon bearing the acyl group. Further prenylation of the prenyl side chain attached at C4 (intermediate **1.7b**) followed by cyclization of intermediate **1.7b** leads to type C structures (**1.10**).



Scheme 1.1 – Biosynthesis of PPAP's

1.2 Biological activity of some PPAP's

Many PPAP's possess interesting biological activity. Hyperforin (**1.1**) inhibits the synaptosomal reuptake of many neurotransmitters (serotonin, dopamine and norepinephrine) *in vitro* at concentration from 80 to 200 nM.[5] It has also been demonstrated that hyperforin (**1.1**) shows antibacterial activity[6] against multiresistant *Staphylococcus aureus* and other gram positive bacteria. Other studies[7] have reported that hyperforin (**1.1**) inhibits the growth of tumour cells by induction of apoptosis. Nemorosone[8] (**1.11**) is another PPAP found in the resins and latex of Clusiaceae plant species. This compound features cytotoxicity against four different cancer cell lines.[9] It also showed an EC_{50} of 0.8 μM against C8166 human T lymphoblastoid cells infected with HIV-1_{MN}.[10]

Another PPAP member, garsubellin A (**1.12**) was isolated[11] from the bark of *Garsinia subelliptica* found on the Okinawa islands of Japan. It has been reported to increase the activity of the choline acetyltransferase (ChaT) by 154% at 10 μM in P10 rat septal neurons.[11] Thus, it could be potentially employed in the development of new treatment for Alzheimer's disease. The promising biological properties of garsubellin A combined with its challenging architecture have prompted many research groups to develop their synthetic approaches to this molecule.

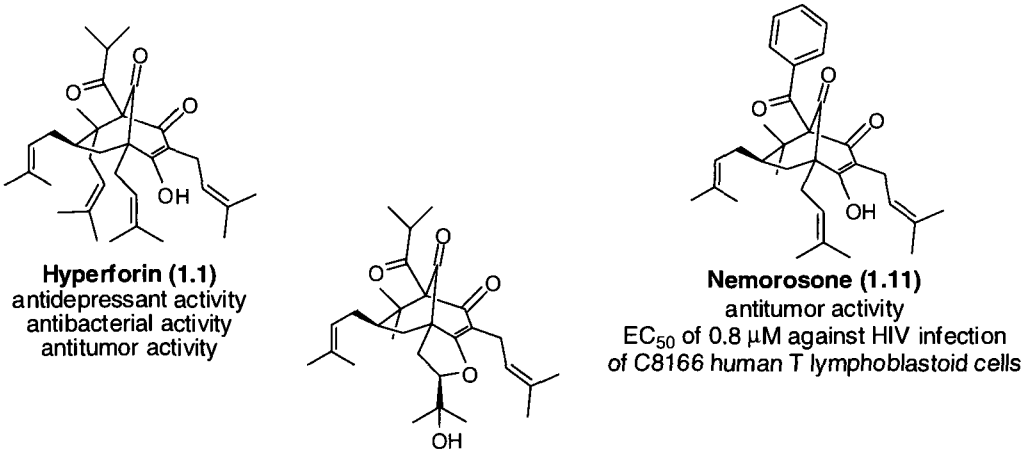
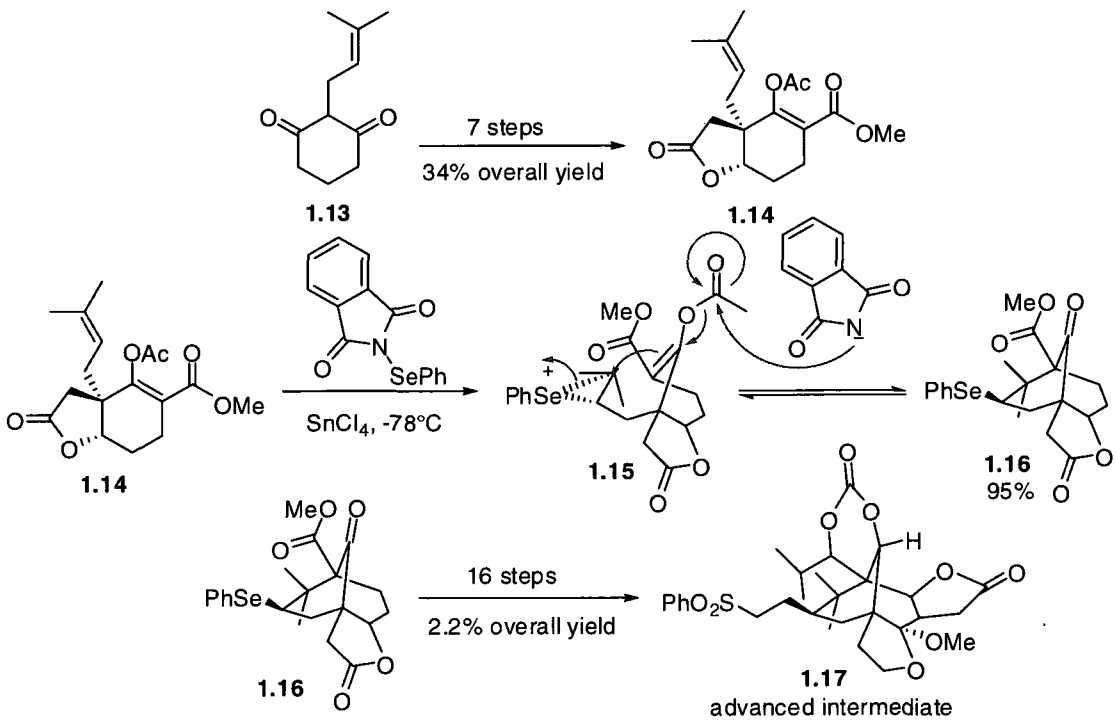


Figure 1.3 – Some examples of PPAP's presenting biological activity

1.3 Synthetic Efforts toward PPAP's

1.3.1 Nicolaou's Selenium-Mediated Electrophilic Cyclization Approach

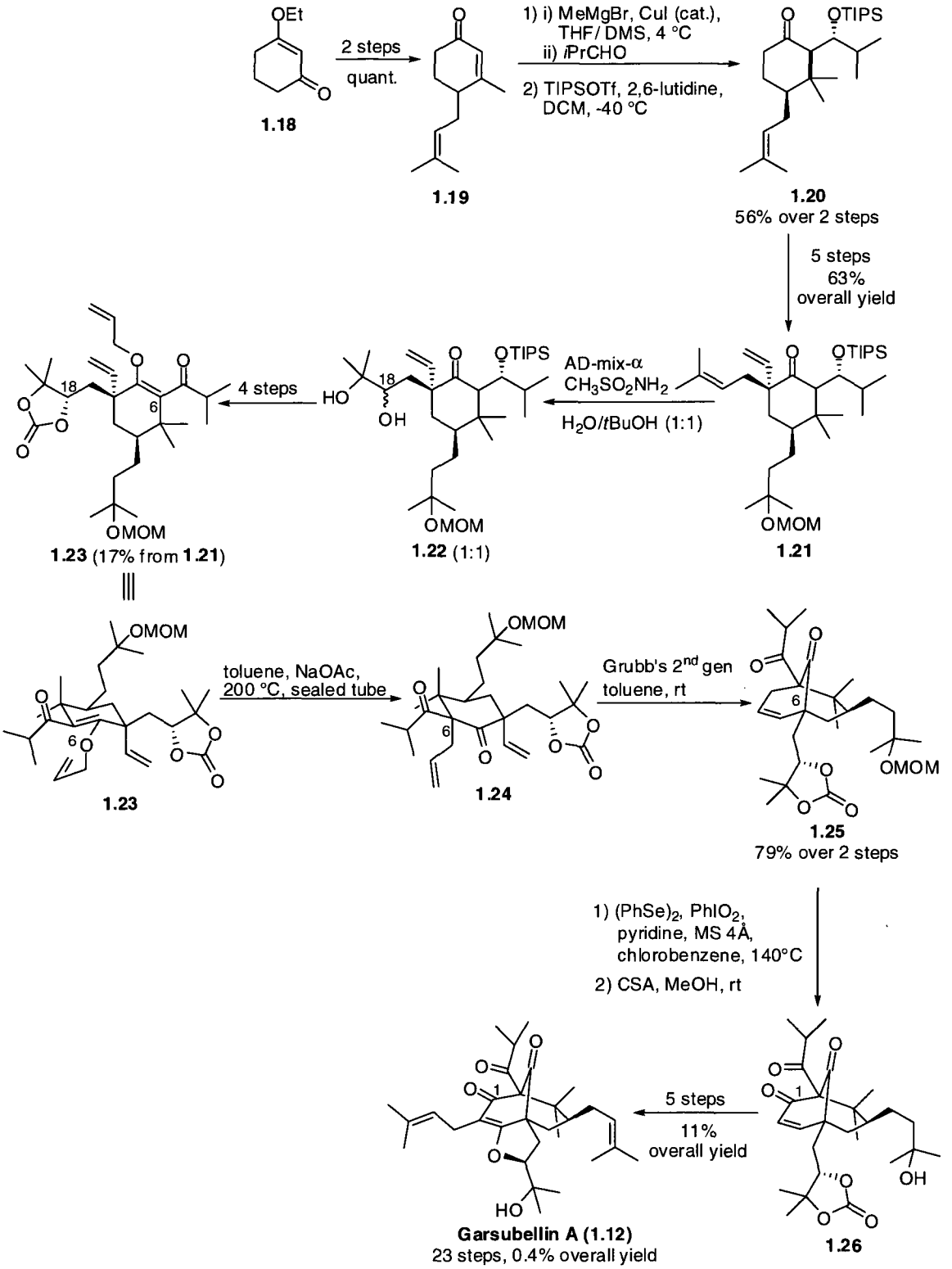
The first efforts toward the total synthesis of (±)garsubellin A were reported by Nicolaou and co-workers.[12] Their strategy towards constructing bicyclo[3.3.1]nonanone core (**1.16**) employed a selenium mediated electrophilic cyclization methodology[13] developed in their laboratory. The key step precursor **1.14** was readily prepared in 7 steps from 2-prenyl-1,3-cyclodienone (**1.13**). Compound **1.14** underwent a selenium-mediated electrophilic cyclization to give **1.16** in excellent yield. They were able to convert advanced intermediate **1.16** into highly functionalized intermediate **1.17**. However, the completed total synthesis of garsubellin A has never been published by this group.



Scheme 1.2 - Nicolaou's selenium-mediated electrophilic cyclization approach

1.3.2 Shibasaki's Claisen and Ring Closing Metathesis Approach

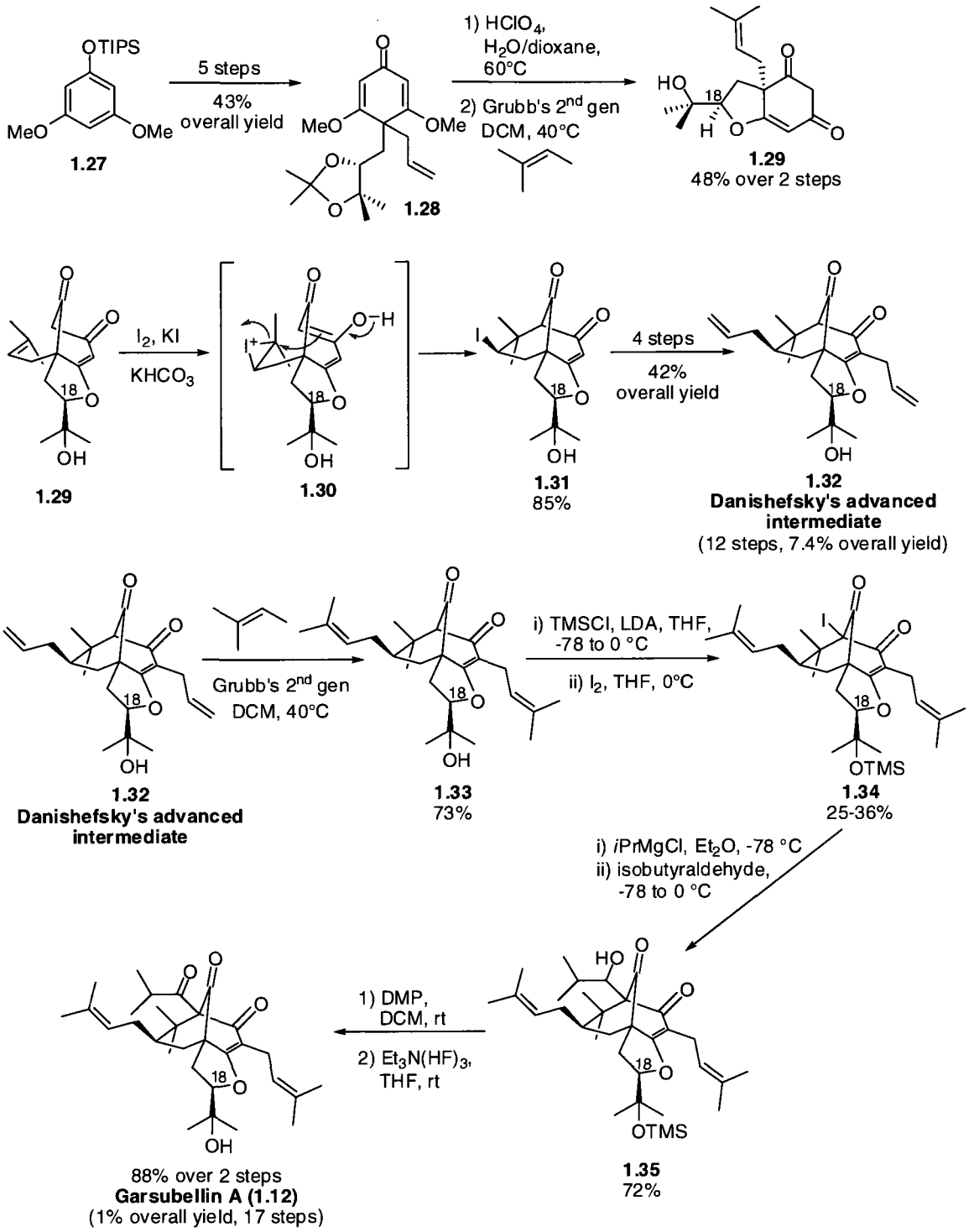
In 2005, the first total synthesis of (±)garsubellin A was reported by Shibasaki *et al.*[14] (Scheme 1.3). The core (**1.25**) of garsubellin A was accessed in 2 steps from **1.23**. Claisen rearrangement on substrate **1.23** afforded **1.24** with complete stereocontrol at C6. Compound **1.24** was further converted to **1.25** by ring closing metathesis. Preparation of the Claisen rearrangement precursor **1.23** from enone **1.19** necessitated 12 steps. Important transformations along this 12 steps sequence are the installation of the isobutyryl group and the formation of the stereogenic center in the tetrahydrofuran ring. The isobutyryl side chain attached at C6 was installed by quenching the enolate resulting from the conjugate addition to enone **1.19** with isobutyraldehyde. The resulting alcohol was protected with TIPSOTf to afford compound **1.20** in 56% yield over 2 steps. Compound **1.20** was converted into **1.21** in 5 steps and 63% overall yield. Sharpless dihydroxylation of **1.21** led to diol **1.22** as a 1:1 mixture of diastereoisomers. The newly formed stereocenter (C18) corresponds to the one present in the tetrahydrofuran ring of the final product. The ketone at C1 was installed by allylic oxidation of the ring closing metathesis product **1.25**. Shibasaki *et al.* were able to synthesize garsubellin A in 23 steps and 0.4% overall yield starting from **1.18**. In the same paper, the authors reported the synthesis of enone **1.19** as a single enantiomer. However, the enantioselective synthesis of garsubellin A has never been completed. Therefore, the absolute configuration of the natural product has not been determined yet.



Scheme 1.3 - Shibasaki's RCM approach

1.3.3 Danishefsky's Iodine-Mediated Electrophilic Cyclization Approach

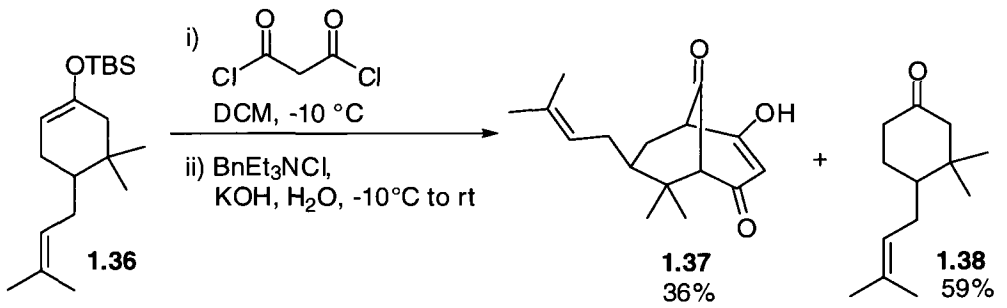
The second total synthesis of (±)garsubellin A was reported by Danishefsky *et al.*[15]. The bicyclo[3.3.1]nonanone skeleton of garsubellin A was prepared using iodocarbocyclization reminiscent of a biomimetic approach. The synthesis of the precursor **1.29** started from protected phloroglucinol derivative **1.27**. Compound **1.27** was converted into **1.28** in 5 steps (43% overall yield). In comparison with Shibasaki's synthesis, the dihydroxylation step is not problematic because there is no diastereoselectivity issue. The relative stereochemistry at C18 is controlled in the next step. Treatment of compound **1.28** with $HClO_4$ followed by cross-metathesis gave **1.29** in 48% yield. Iodocarbocyclization of compound **1.29** afforded **1.31** in 85% yield. The latter was converted into intermediate **1.32** in 4 steps and 42% overall yield. This key intermediate underwent Grubb's cross-metathesis followed by iodination to give **1.34**. Halogen-metal exchange followed by addition of isobutyraldehyde led to alcohol **1.35**. The lather was oxidized using Dess-Martin reagent. Final deprotection afforded (±)garsubellin A in 88% yield from **1.35**. Thus, Danishefsky *et al.* were able to synthesize garsubellin A from **1.27** in 17 steps and 1% overall yield.



Scheme 1.4 - Danishefsky's iodine-mediated electrophilic cyclization approach

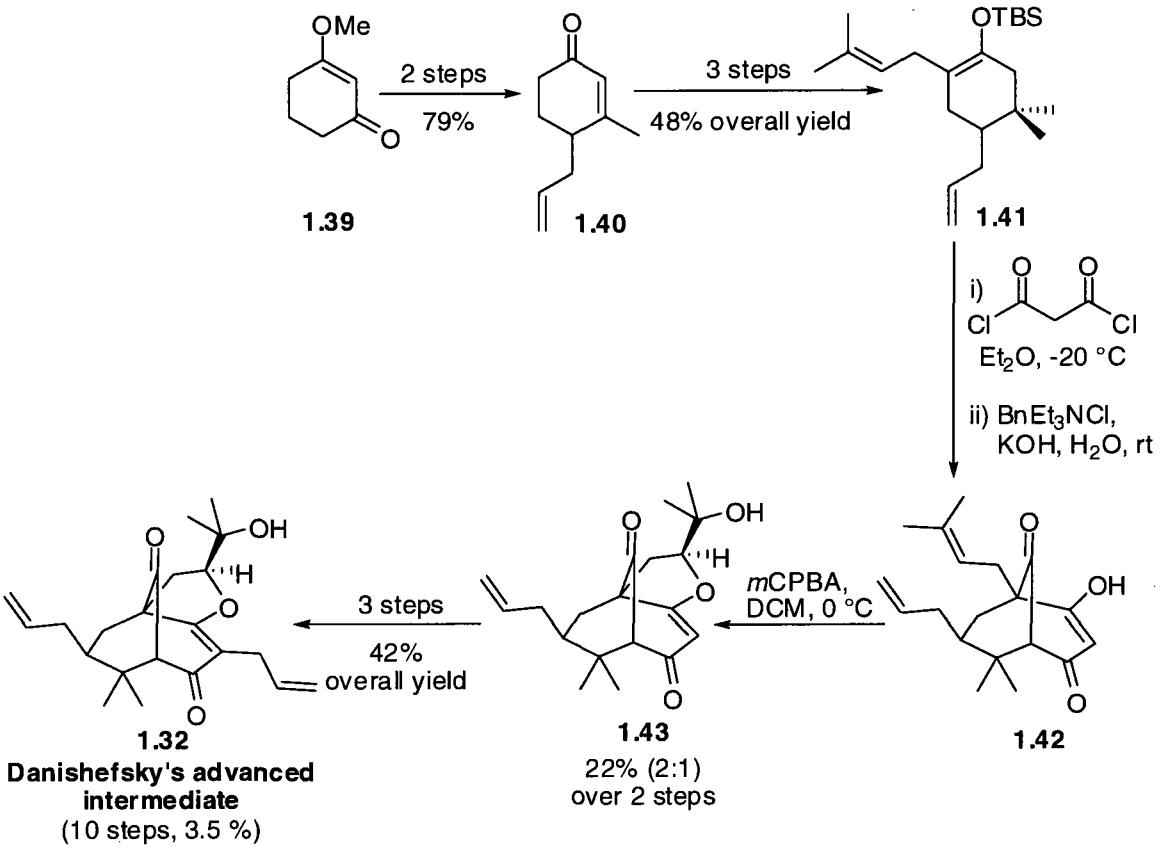
1.3.4 Stolz's Approach – Effenberger's Cyclization

Stolz *et al.* reported[16] the synthesis of garsubellin A core **1.37** using the Effenberger's cyclization in 36% yield starting from **1.36** (Scheme 1.5). Although the yield of the reaction is low, compound **1.38** is recovered can be re-converted to **1.36**.



Scheme 1.5 – Synthesis of the garsubellin A core using the Effenberger's cyclization

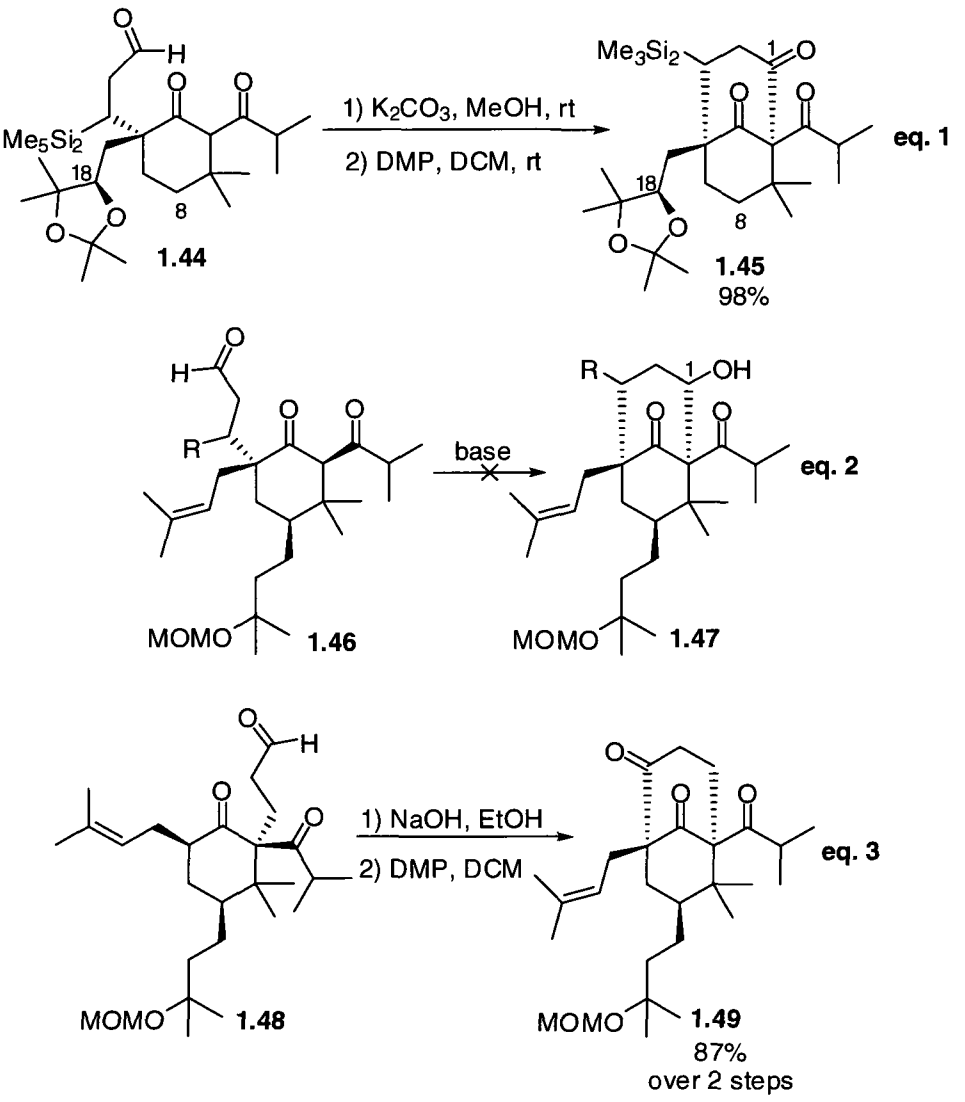
Drawing inspiration from the work of Stolz, Simpkins[17] *et al.* utilized Effenberger's cyclization to obtain Danishefsky's advanced intermediate **1.32** (Scheme 1.6). Effenberger's cyclization precursor **1.41** was prepared in 3 steps from easily accessible enone **1.40**. Effenberger's cyclization on compound **1.41** led to bridgehead ketone **1.42** that was further oxidized to **1.43** in 22% yield over 2 steps. Compound **1.42** was finally converted to Danishefsky's advanced intermediate **1.32** in 42% yield over 3 steps.



Scheme 1.6 – Simpkin's formal synthesis of garsubellin A

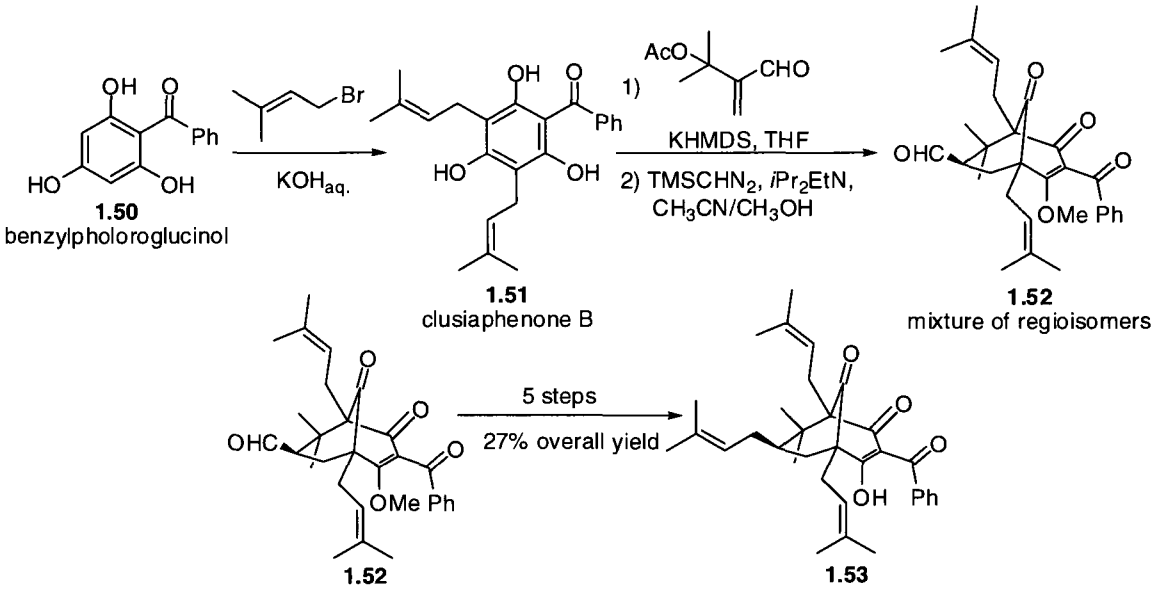
1.3.5 Other Approaches

There are several other approaches reported in the literature for the synthesis of PPAP's. For example, Shibasaki *et al.*[18] reported a different methodology for the synthesis of garsubellin A (Scheme 1.7) prior to publishing the RCM approach described earlier in this chapter (Scheme 1.3). Model substrate **1.44** was subjected to intramolecular aldol condensation and the resulting alcohol was oxidized to ketone **1.45** in 98% yield (eq. 1). However, **1.45** possesses the wrong relative stereochemistry at C18 and has no prenyl side chain at C8. The alcohol generated upon aldol condensation served as a synthetic handle for the introduction of the ketone at C1. Unfortunately, this method failed when it was applied to the fully functionalized substrate **1.46** (eq. 2). The authors were able to overcome the problem by performing the cyclization from the other side of the ketone (eq. 3).



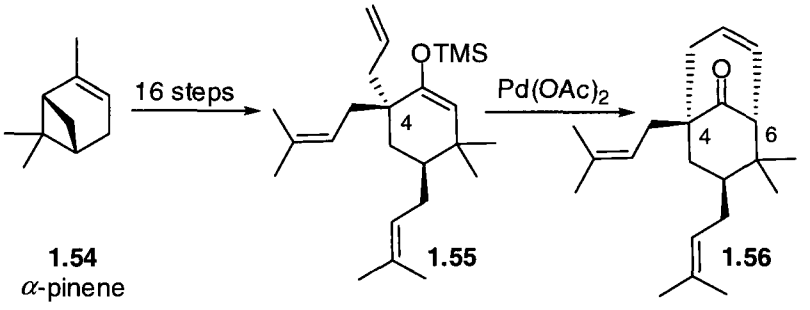
Scheme 1.7 – Shibasaki's aldol condensation approach

Recently, a biomimetic approach to the synthesis of type C PPAP's was reported by Porco *et al.*[19] (Scheme 1.8). The authors achieved the construction of the Clusianone core **1.52** by Michael addition-elimination-Michael addition cascade on compound **1.51**. The resulting bicyclic product was further methylated to afford compound **1.52** as a mixture of regioisomers. Compound **1.52** was converted to Clusianone (**1.53**) in 5 steps and 27% yield.



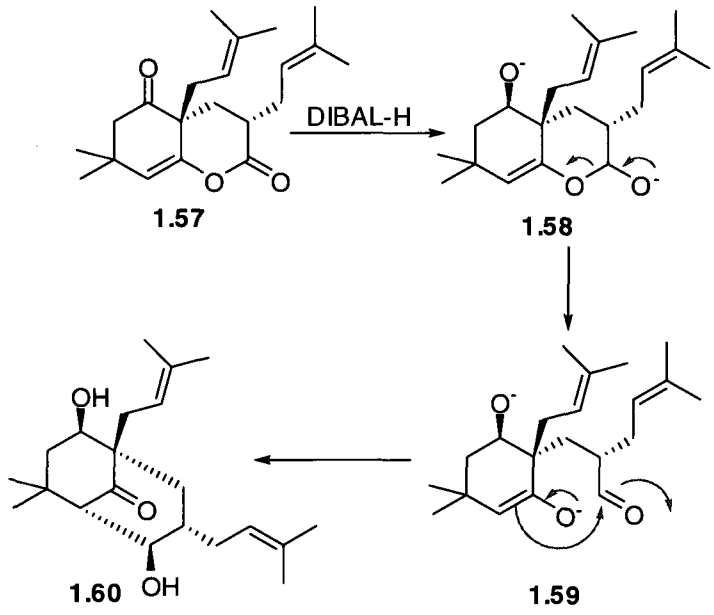
Scheme 1.8 – Porco's total synthesis of clusianone

Mehta *et al.*[20, 21] were able to prepare advanced intermediate **1.56** *via* palladium-mediated oxidative cyclization[20] (Scheme 1.9). Precursor **1.55** was obtained starting from α-pinene (**1.54**) thus allowing for eq. to enantiospecific synthesis of garsubellin A. However, the preparation of **1.55** from α-pinene is synthetically demanding and necessitates 16 steps. Conversion of **1.56** into garsubellin A would require either selective dihydroxylation or epoxydation of prenyl chain at C4 and consequent introduction of the isobutyryl group at C6.



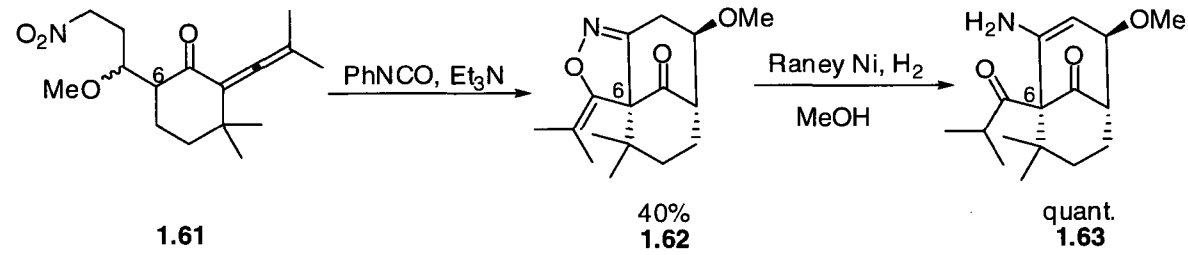
Scheme 1.9 - Mehta's palladium-mediated oxidative cyclization approach

Mehta *et al.* also published another method[21] for the formation of PPAP's skeleton starting from lactone **1.57** (Scheme 1.10). Lactone **1.57** was reduced to hemiacetal **1.58** which then opened and underwent aldol condensation to give diol **1.60**.



Scheme 1.10 - Mehta's reduction-aldol approach

Young *et al.*[22] reported an interesting method for the simultaneous formation of the bicyclo[3.3.1]nonanone core and the introduction of the isobutyryl at C6 (Scheme 1.11). Model substrate **1.61** underwent intramolecular allene-nitrile oxide cycloaddition to give compound **1.62** in 40% yield. Further reduction of the N-O bond afforded diketone **1.63** in quantitative yield.



Scheme 1.11 – Young's intramolecular allene-nitrile oxide cycloaddition approach

According to literature precedents, in addition to synthesis of the bicyclo[3.3.1]nonanone core of PPAP's, there exist other important synthetic challenges in the total synthesis of this class of natural products. As we discussed previously, many groups reported different effective approaches to advanced substituted bicyclo[3.3.1]nonanone core characteristic to this class of

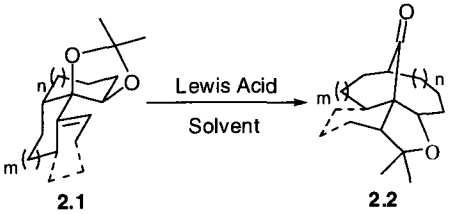
compound. On the other hand, the introduction of the isobutyryl at C6 does present a challenge according to several reported syntheses. Selectivity problems also arise from the presence of several prenyl groups in those molecules. In the specific case of garsubellin A, one of this prenyl group has to be further converted to a fused tetrahydrofuran ring possessing a chiral center (at C18). The high relative stereocontrol at this center (C18) was achieved in only one of the three synthesis of garsubellin A published to date. Thus, synthesis of PPAP's still represents an important challenge and inspires new synthetic approaches.

2

Application of the Prins-pinacol Methodology to the Total Synthesis of Garsubellin A

2.1 Introduction

As discussed in the introduction, the construction of bicyclo[3.3.1]nonanone core encountered in PPAP's presents a significant synthetic challenge. Our laboratory has recently reported[23] a novel methodology to generate highly oxygenated and functionalized bicyclo[m.n.1]alkanones fused to a tetrahydrofuran ring from various acetals *via* a Lewis acid mediated Prins-pinacol cationic cascade (Scheme 2.1). This approach allows for rapid access to complex bridgehead ketone frameworks including bicyclo[3.3.1]nonanone featured in PPAP's.



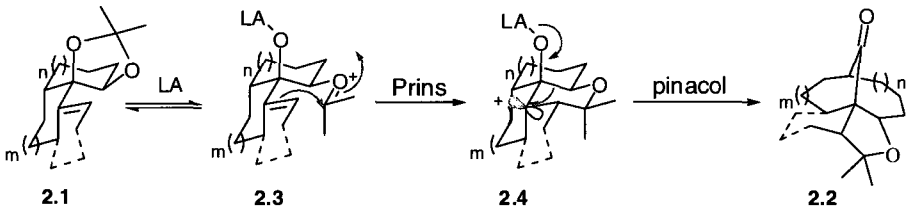
2.1 **2.2**

yield 44-96%
m, n = 0-2

Scheme 2.1 – Prins-pinacol methodology developed in our laboratories

The proposed mechanism for the Prins-pinacol cascade is illustrated in Scheme 2.2. Under acidic conditions, the acetal **2.1** opens to afford oxacarbenium intermediate **2.3** that is

poised to undergo Prins cyclization, resulting in **2.4**. Carbocationic intermediate **2.4** possess an empty *p* orbital aligned periplanar to the bond highlighted in blue, thus allowing this bond to migrate to form the bicyclic bridged system fused to a tetrahydrofuran ring.



Scheme 2.2 – Proposed mechanism for the Prins-pinacol rearrangement

Our group has been interested in further applying this new methodology to a total synthesis of a natural product from PPAP family. Thus, garsubellin A (**2.5**) was selected as our synthetic target (figure 2.1). As described in the introduction, garsubellin A is a complex natural product which, in addition to challenges associated with its core, features a fused tetrahydrofuran ring bearing a chiral center. Several total syntheses have been recently reported, however, enantioselective synthesis of garsubellin A has never been achieved and the absolute configuration of the natural product has not been determined.

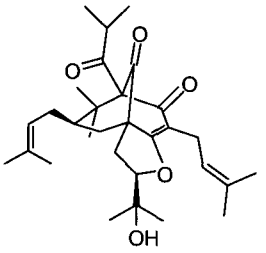
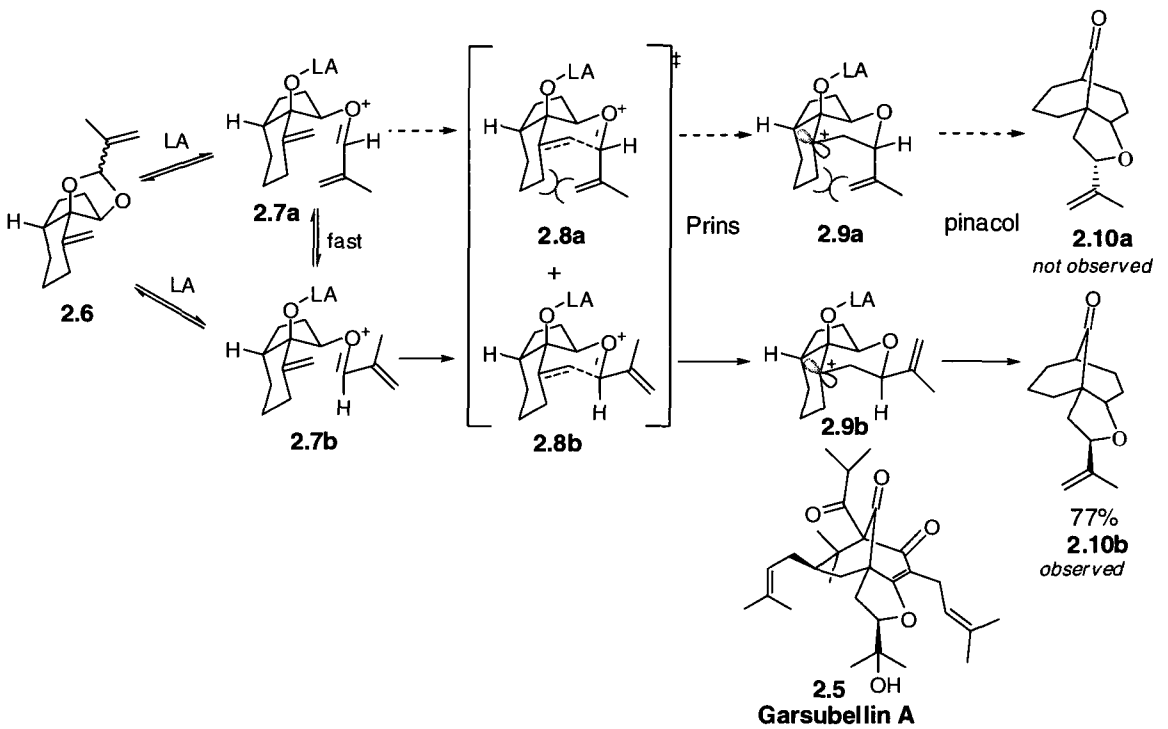


Figure 2.1 – Structure of garsubellin A

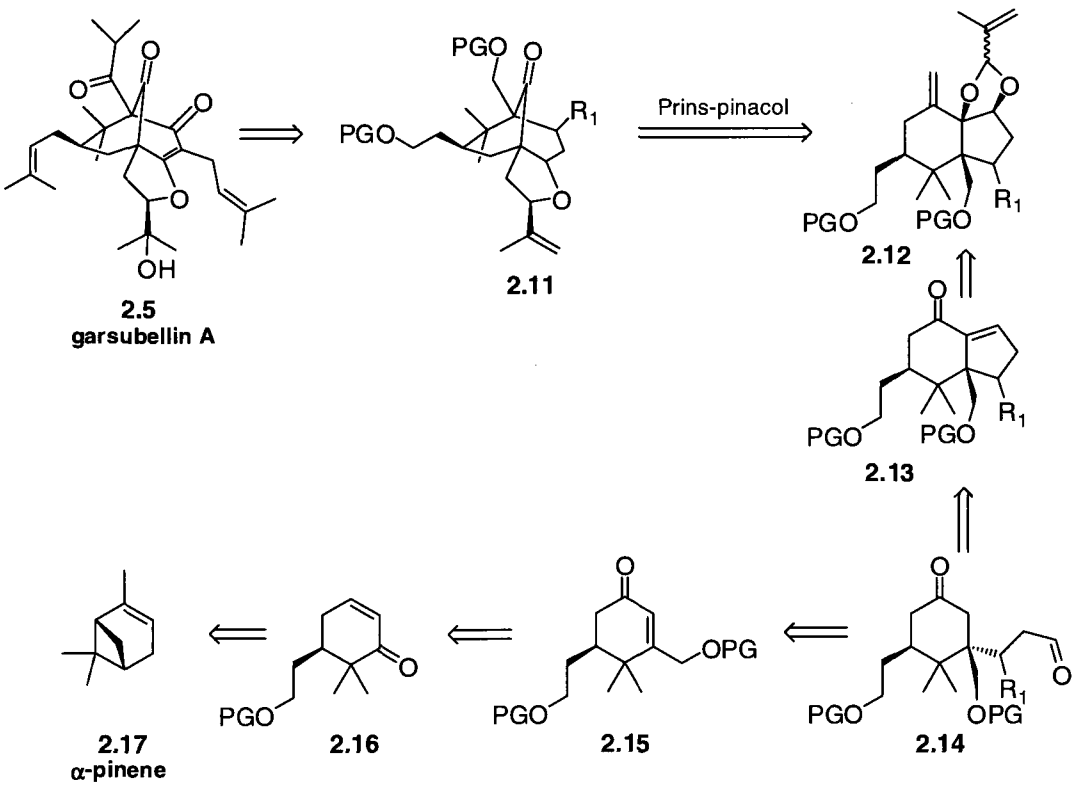
Our studies toward the total synthesis of garsubellin A began from a model study performed by Mélina Girardin[24] on acetal **2.6** (Scheme 2.3) in order to evaluate feasibility of generating bicyclo[3.3.1] ketone with a fused tetrahydrofuran ring bearing a chiral center. It was expected that the stereochemistry at the carbon bearing the isopropenyl side chain in product of Prins-pinacol cascade **2.10** would be controlled during the reaction process. The acetal **2.6** would open under acidic conditions to afford the oxacarbenium intermediates **2.7a** and **2.7b** that would then undergo the Prins reaction. There are two possible transition states for the Prins reaction, one having the isopropenyl substituent at the pseudoaxial position (**2.8a**) and one having the isopropenyl substituent at the pseudoequatorial position (**2.8b**). The transition state **2.8a** is disfavoured because of the steric hindrance arising from 1,3-diaxial interactions between the isopropenyl group and the six membered ring. Thus, if the equilibrium between oxoniums **2.7a** and **2.7b** is fast and the Prins reaction is slow (Curtin–Hammett conditions), only carbocationic intermediate **2.9b** would be formed to further undergo pinacol rearrangement. This would allow for the stereocontrol at the carbon α to the oxygen in the tetrahydrofuran ring, the relative stereochemistry of this center corresponding to the one present in garsubellin A. Indeed, when substrate **2.6** was treated in the presence of $SnCl_4$, only product **2.10b** was observed, confirming the initial hypothesis. The synthesis of garsubellin A was then attempted.



Scheme 2.3 – Attempted Prins-pinacol rearrangement on an unfunctionalized substrate

2.2 First Retrosynthetic Analysis

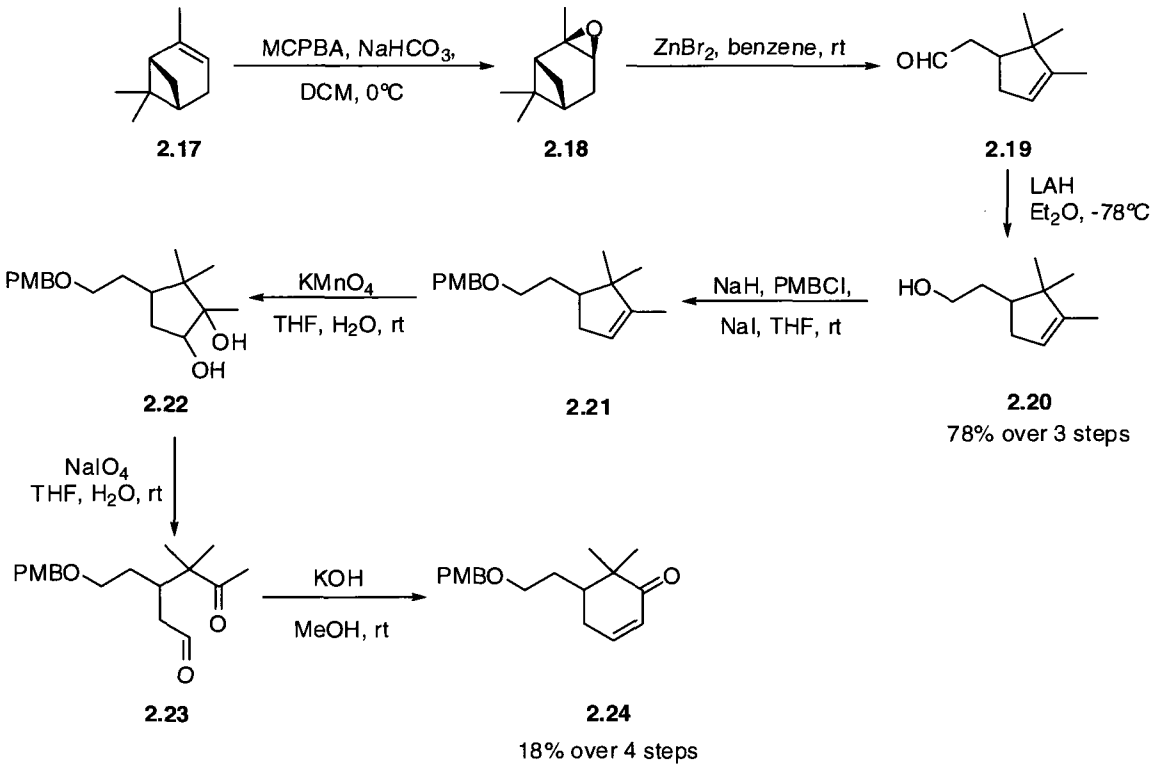
Barriault's group[24] proposed that tricycle core **2.11** of garsubellin A could be generated from the corresponding acetal precursor **2.12** (Scheme 2.4) *via* the Prins-pinacol cascade. In this turn, the Prins-pinacol precursor **2.12** could be synthesized starting from α-pinene **2.17**. This would allow for the enantiospecific synthesis of garsubellin A. Enone **2.16** would be first prepared from α-pinene (**2.17**) and then be converted to enone **2.15**. Conjugate addition on enone **2.11** was chosen to introduce the aldehyde side chain needed for the consequent intramolecular aldol condensation. At the same time, a functional group R1 would be introduced in order to be converted to a ketone later in the synthesis. Intramolecular aldol condensation of **2.14** would give bicyclic enone **2.13** that would be further converted to the Prins-pinacol precursor **2.12** within a few steps. The Prins-pinacol rearrangement of **2.12** would afford advanced intermediate **2.11** that could be transformed to the target garsubellin A using conventional chemistry.



Scheme 2.4 – Retrosynthetic analysis of the total synthesis of garsubellin A applying the Prins-pinacol methodology

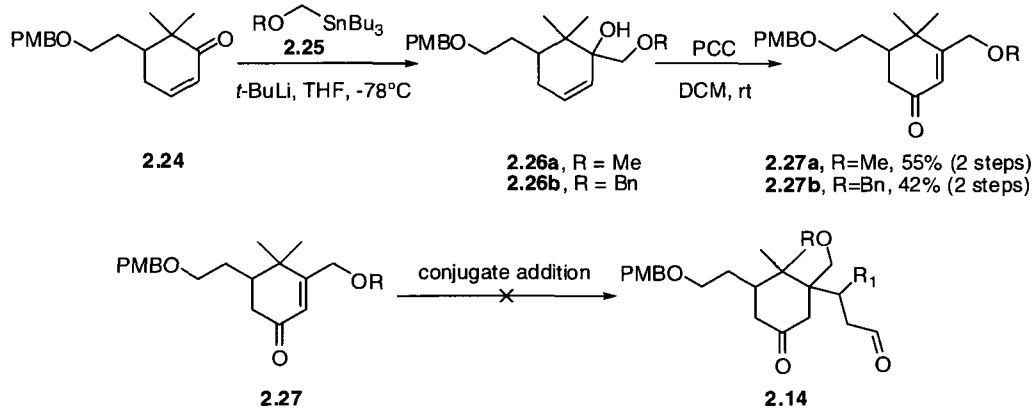
2.3 Synthesis of the Prins-pinacol Precursor using Aldol Condensation

Synthesis of enone **2.24** from α-pinene (**2.17**) was first developed by Melina Girardin[24] (Scheme 2.5). Commercially available (Aldrich) α-pinene (**2.17**) was oxidized using *m*-CPBA to provide epoxide (**2.18**). Rearrangement of epoxide **2.18** in the presence of zinc bromide gave aldehyde **2.19** that was then reduced using $LiAlH_4$ to give primary alcohol **2.20** in 78% yield over 3 steps. The alcohol was protected with PMBCl to give compound **2.21**. Dihydroxylation followed by oxidative cleavage of compound **2.21** led to keto-aldehyde **2.23**. Finally, intramolecular aldol condensation of **2.23** afforded enone **2.24** in 18% yield over 4 steps or 14% overall yield from α-pinene.



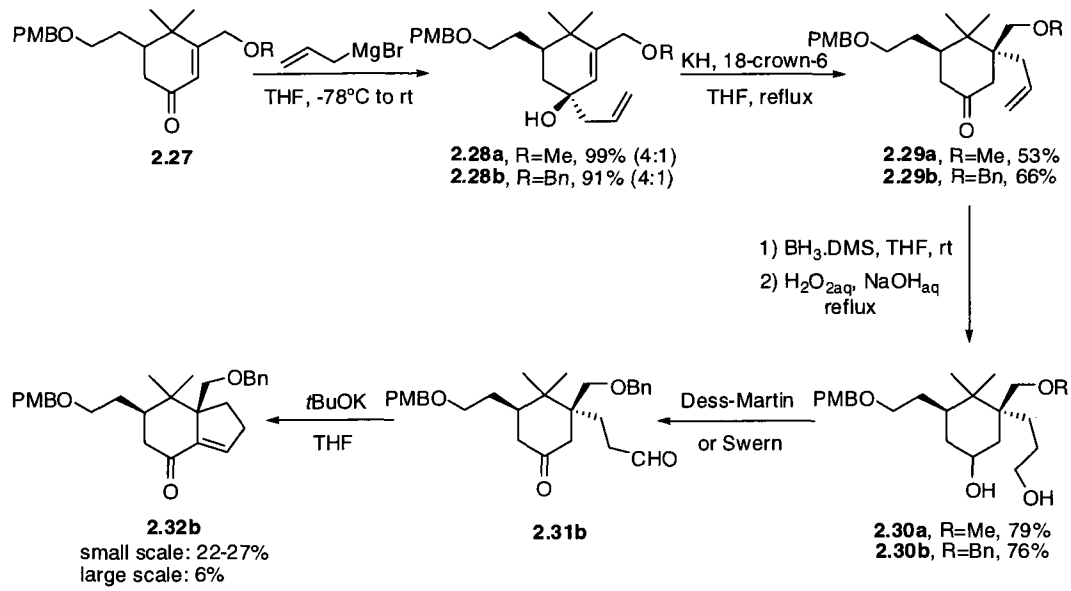
*Scheme 2.5 – Preparation of enone **2.24** from α-pinene*

Scheme 2.6 illustrates the sequence developed by Melina Girardin towards model substrate **2.13** starting from **2.24**. Compound **2.24** was subjected to 1,2-addition of alkyl lithium species generated *in situ* from **2.25** *via trans*-metallation to obtain **2.26**. The yield of this reaction is highly dependant on the quality of *t*-BuLi reagent. It is essential to use a newly opened bottle. An excess of **2.25** had to be employed to ensure that all *t*-BuLi was reacted *prior to* substrate addition. PCC oxidative rearrangement of compounds **2.26** (**a** and **b**) gave **2.27** (**a** and **b**) in 55% and 42% yield over 2 steps respectively. Unfortunately, all attempts to perform conjugate addition on **2.27** failed. Thus, it was decided to install the desired quaternary center *via* an anionic oxy-Cope rearrangement as shown on Scheme 2.7.



*Scheme 2.6 – Preparation of enone **2.27** from enone **2.24***

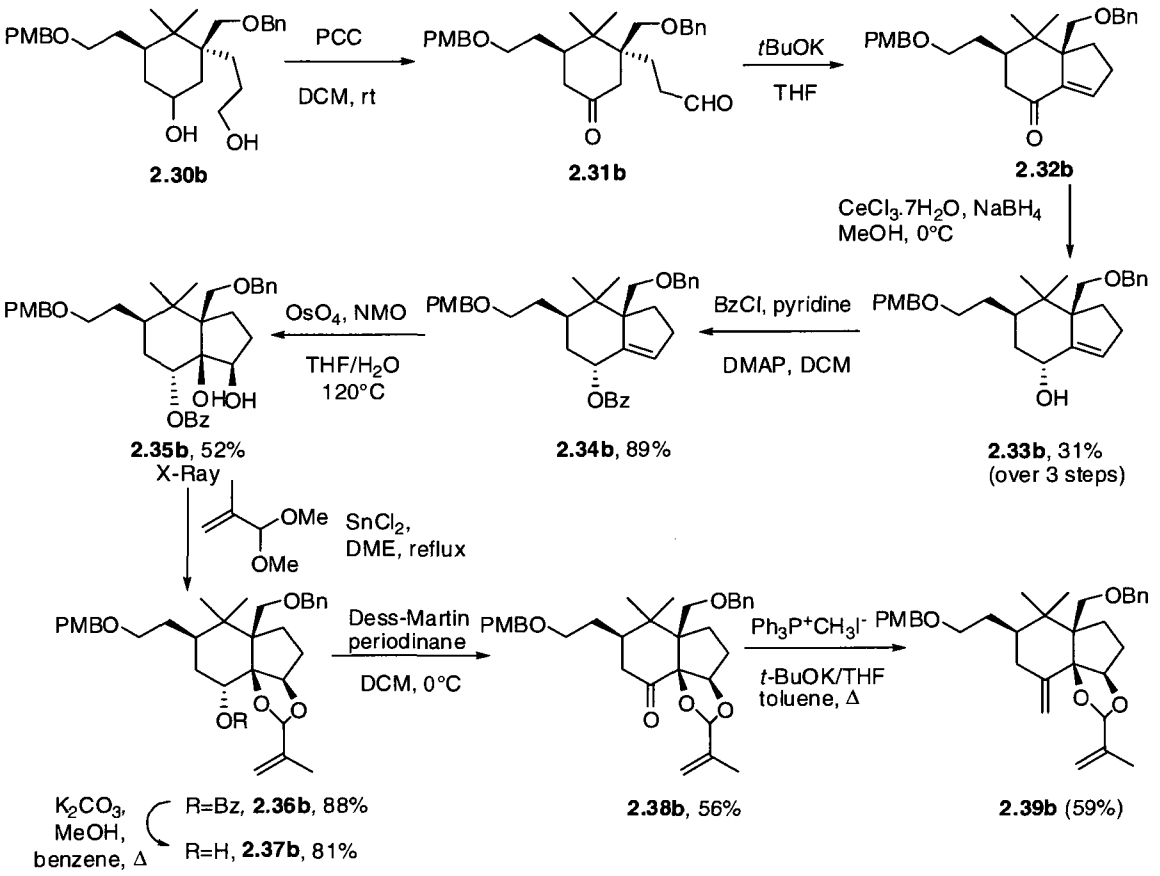
Grignard addition to enone **2.27** afforded tertiary allylic alcohol **2.28** in 86-91 % yield as a 4:1 mixture of diastereoisomers, the major one being the desired one. Compound **2.28** underwent anionic oxy-Cope rearrangement to give ketone **2.29** in 66% yield. Diol **2.30** was then prepared from ketone **2.29** *via* hydroboration of the terminal olefin in good yield. Double oxidation of **2.30b** provided aldehyde **2.31b** which was then transformed to **2.32b** *via* aldol reaction. This condensation however poses a problem. We observed that when the reaction was performed on a smaller than 500 mg scale, the yield varied between 20-30%. However, the yield dropped as low as 6% when the reaction was performed on a larger scale (> 500 mg). Furthermore, aldol precursor **2.31** as well as aldol product **2.32** are unstable and should not be purified and stored for longer than one day.



Scheme 2.7 – Preparation of bicyclic enone ***2.32b*** *via aldol condensation*

In order to maximize the yield of the aldol condensation step, the starting material was divided into 13 fractions of 100 mg each. Thirteen condensations were then performed simultaneously. The sequence started from first oxidizing diol **2.30b** to keto aldehyde **2.31b** using PCC. Originally Dess-Martin reagent or Swern oxidation conditions were used, however we observed that the reaction is cleaner and more reproducible under PCC oxidation conditions (Scheme 2.7). The crude material obtained from the oxidation was then divided into fractions which were simultaneously subjected to optimized aldol conditions previously established by Mélina Girardin. Upon completion, the reaction mixtures were combined for a work-up and the crude material was converted to alcohol **2.33b** using Luche reduction conditions. Alcohol **2.33b** was obtained in 31% overall yield from diol **2.30b**. This approach is only practical on a scale smaller than 1g. Obviously, dividing large quantities of starting material into 100 mg fractions would prove to be a tedious task. Nevertheless, it allowed us to generate enough material to attempt the Prins-pinacol cascade key step. Alcohol **2.33b** was protected as a benzoate and was dihydroxylated using osmium tetraoxide to give diol **2.35b** in moderate 52% yield. We were able to obtain X-Ray structure of **2.35b** which allowed us unambiguously assign stereochemistry at this stage (Figure 2.1). Diol **2.35b** was then converted to the corresponding methacrolein acetal **2.36b** in 88% yield. Finally, deprotection of the alcohol followed by oxidation and Wittig

olefination afforded Prins-pinacol precursor **2.39b** in 27% overall yield starting from acetal **2.36b**.



Scheme 2.8 – Preparation of the Prins-pinacol precursor ***2.39b***

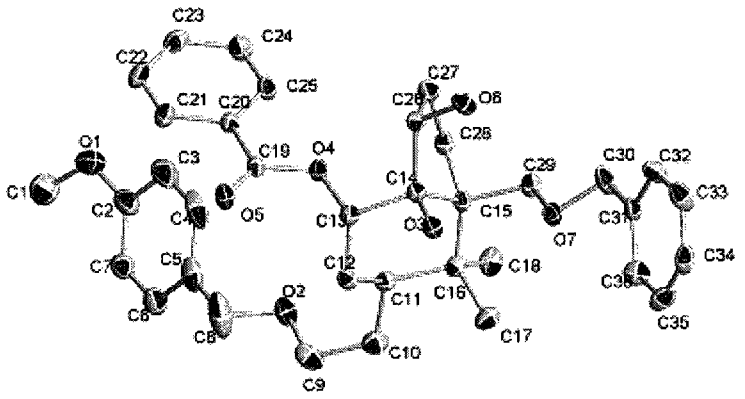
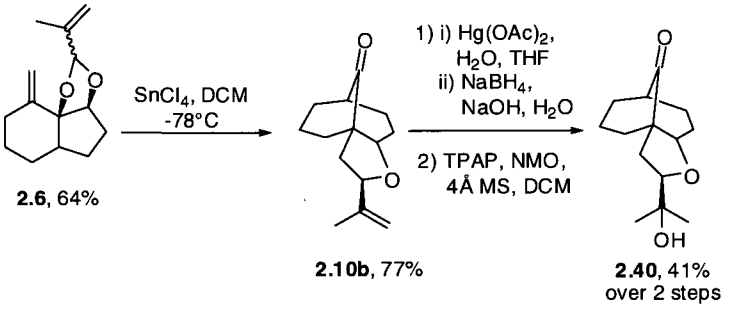


Figure 2.2 – X-Ray of compound ***2.35b***

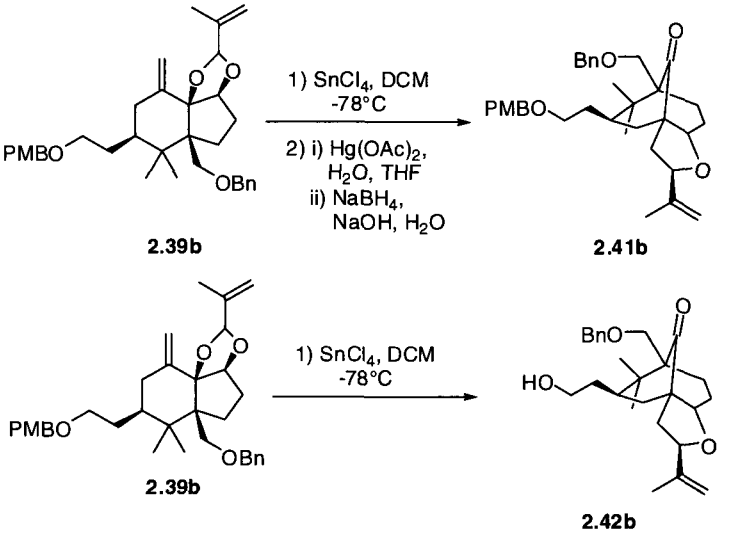
Original study[24] by Mélina Girardin on compound **2.6** demonstrated that best conditions for the Prins-pinacol rearrangement was using $SnCl_4$ in DCM at -78 °C (Scheme 2.9). Furthermore, Prins-pinacol product **2.10b** was found to be unstable and was converted to **2.40** without purification.



Scheme 2.9 - First attempt of the Prins-pinacol reaction on unfunctionalized substrate ***2.6***

Taking this into account, we applied the optimized Prins-pinacol conditions to highly functionalized substrate **2.39** (Scheme 2.10). The crude material recovered after the reaction was not purified and was immediately subjected to oxymercuration. However, after flash chromatography, only one compound, tentatively assigned as **2.41b**, was isolated as a single diastereoisomer. We then decided to repeat Prins-pinacol reaction and purify the product *prior to* oxymercuration. As a result, compound **2.42b** (tentatively assigned) was isolated. In both cases,

only one diastereoisomer was observed. Unfortunately, we were not able to determine the yield, as the reactions were performed on a very small scale.



Scheme 2.10 – Attempts of the Prins-pinacol reaction on a highly functionalized substrate

Careful ^{1}H NMR analysis revealed that special features previously observed in the ^{1}H NMR spectrum of compound **2.10b** were also present in the spectrum of compound **2.42b** (see Table 2.1). For comparison, proton shifts of the two olefin protons of the isobutyryl side chain are shown in entries 4 and 5. The chemical shifts of the protons α to oxygen in the tetrahydrofuran ring are demonstrated in entries 8 and 9. H-6 shift (eq. 13) is characteristic of the bicyclo[3.3.1] alkanone fused to a tetrahydrofuran ring. The chemical shift of this proton is larger than that of a normal aliphatic proton because of its position in the anisotropy cone of the bridgehead ketone. Eq. 14 shows chemical shift corresponding to the methyl of the isobutyryl side chain. Furthermore, HMBC spectrum of compound **2.42b** shows the presence of ketone carbon at 214 ppm.

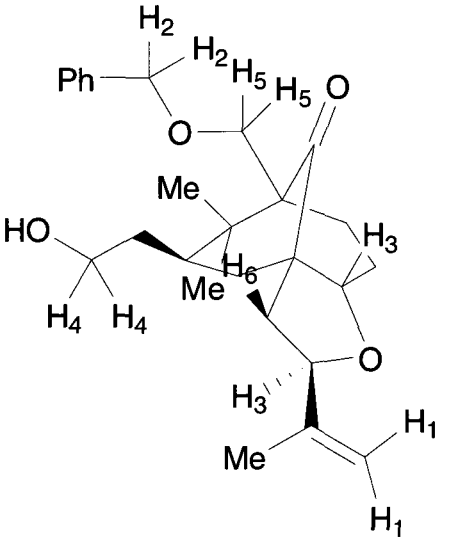


*Figure 2.3 – Compound **2.42b***

Table 2.1 Comparison of ^{1}H NMR spectra of compound **2.10b** and **2.42b**

entry	compound **2.10b**	compound **2.42b**	correspounding fonctionality
1	-	7.32 - 7.30 (m, 2H)	Ph
2	-	7.17 - 7.14 (m, 2H)	Ph
3	-	7.08 - 7.06 (m, 1H)	Ph
4	5.17 - 5.15 (m, 1H)	5.17 (br s, 1H)	H1
5	4.87 - 4.85 (m, 1H)	4.85 (br s, 1H)	H1
6	-	4.48 (d, *J* = 12.1 Hz, 1H)	H2
7	-	4.35 (d, *J* = 12.1 Hz, 1H)	H2
8	4.08 (dd, *J* = 10.4, 5.8 Hz, 1H)	4.16 (dd, *J* = 11.4, 5.0 Hz, 1H)	H3
9	3.80 (dd, *J* = 9.0, 5.4 Hz, 1H)	3.99 (dd, *J* = 11.3, 5.1 Hz, 1H)	H3
10	-	3.92 (d, *J* = 9.0 Hz, 1H)	H5
11	-	3.42 (d, *J* = 9.0 Hz, 1H)	H5
12	-	3.31 - 3.20 (m, 2H)	H4
13	2.75 (dd, *J* = 12.6, 10.4 Hz, 1H)	2.81 (dd, *J* = 12.6, 11.5 Hz, 1H)	H6
14	1.76 (s, 3H)	1.72 (s, 3H)	Me
15	-	0.80 (s, 3H)	Me
16	-	0.55 (s, 3H)	Me
17	12 other aliphatic protons	11 other aliphatic protons	

Our comparison table shows that all the characteristic protons are present in the Prins-pinacol product **2.42b**. Furthermore, all the chemical shifts of these protons are strikingly similar to those of the unfunctionalized substrate **2.10b**.

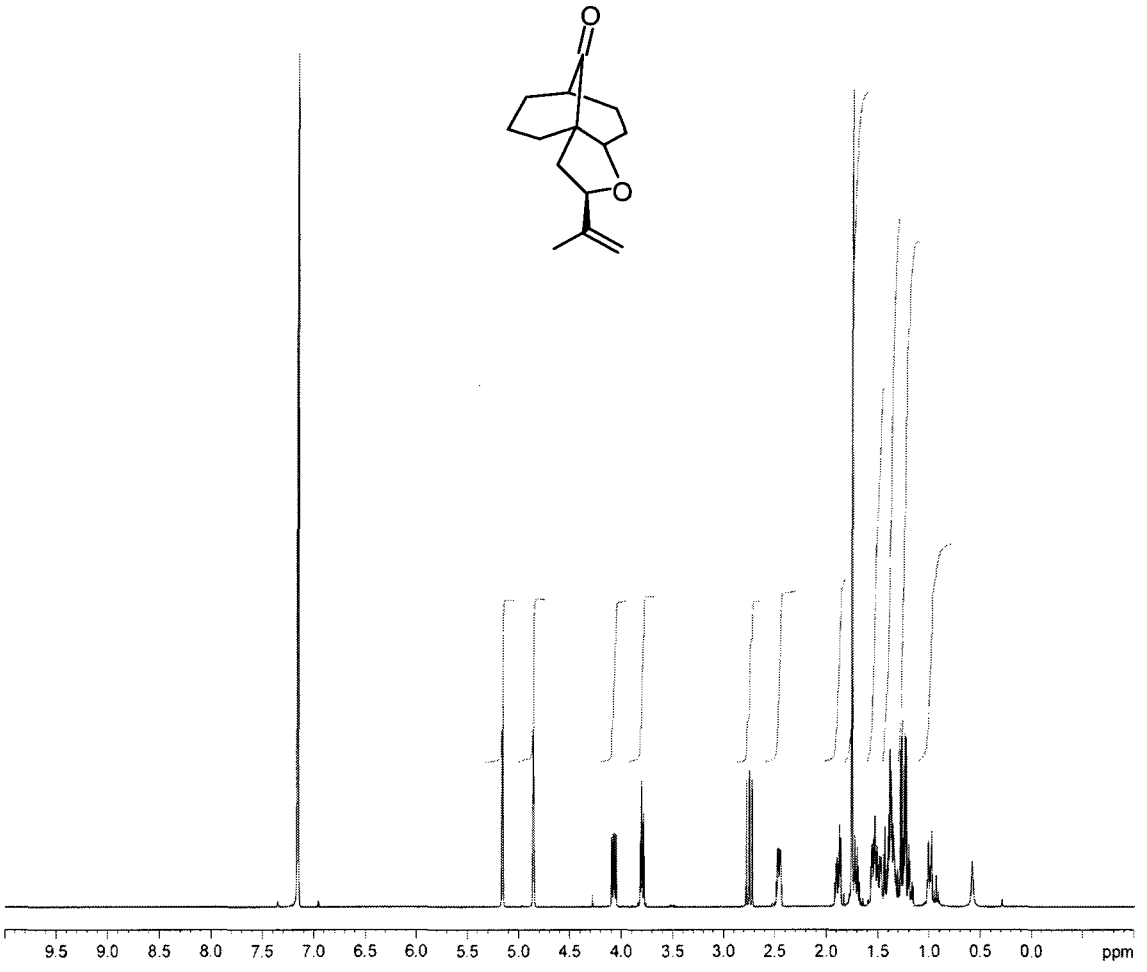


*Figure 2.4 – ^{1}H NMR spectra of compound **2.10b***

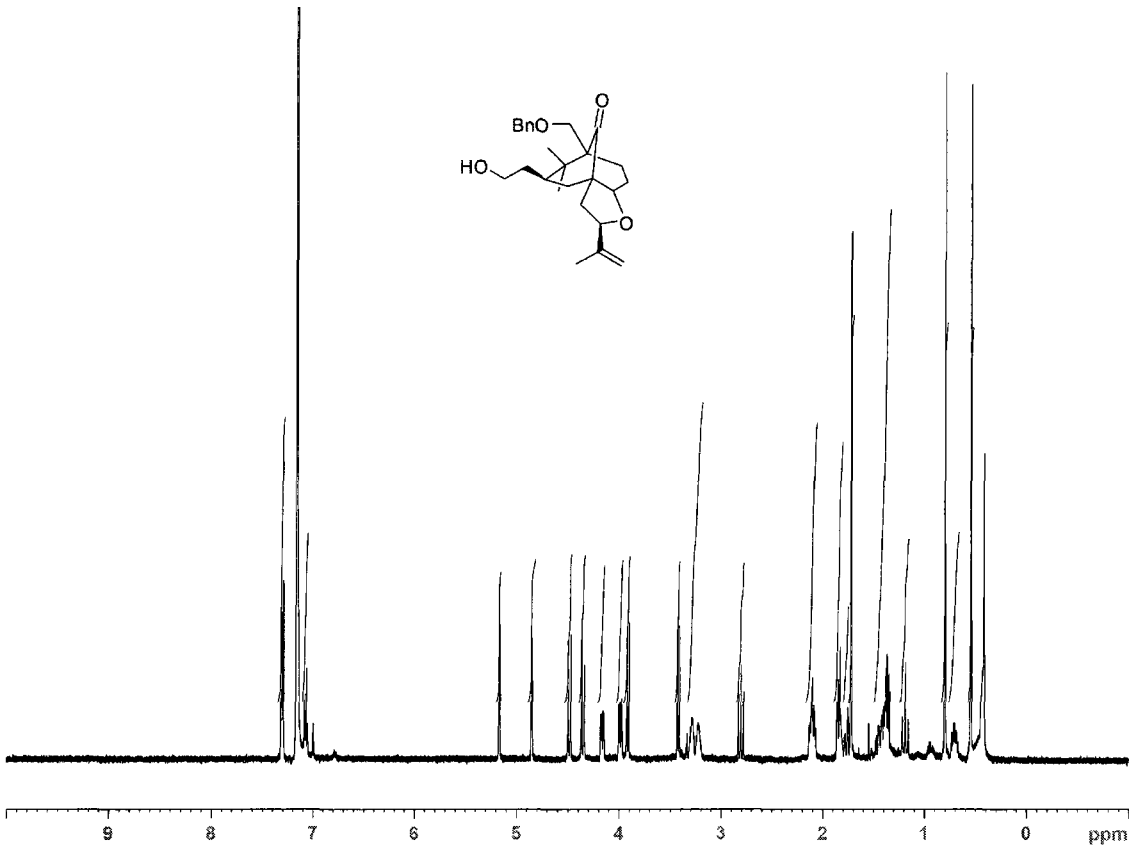
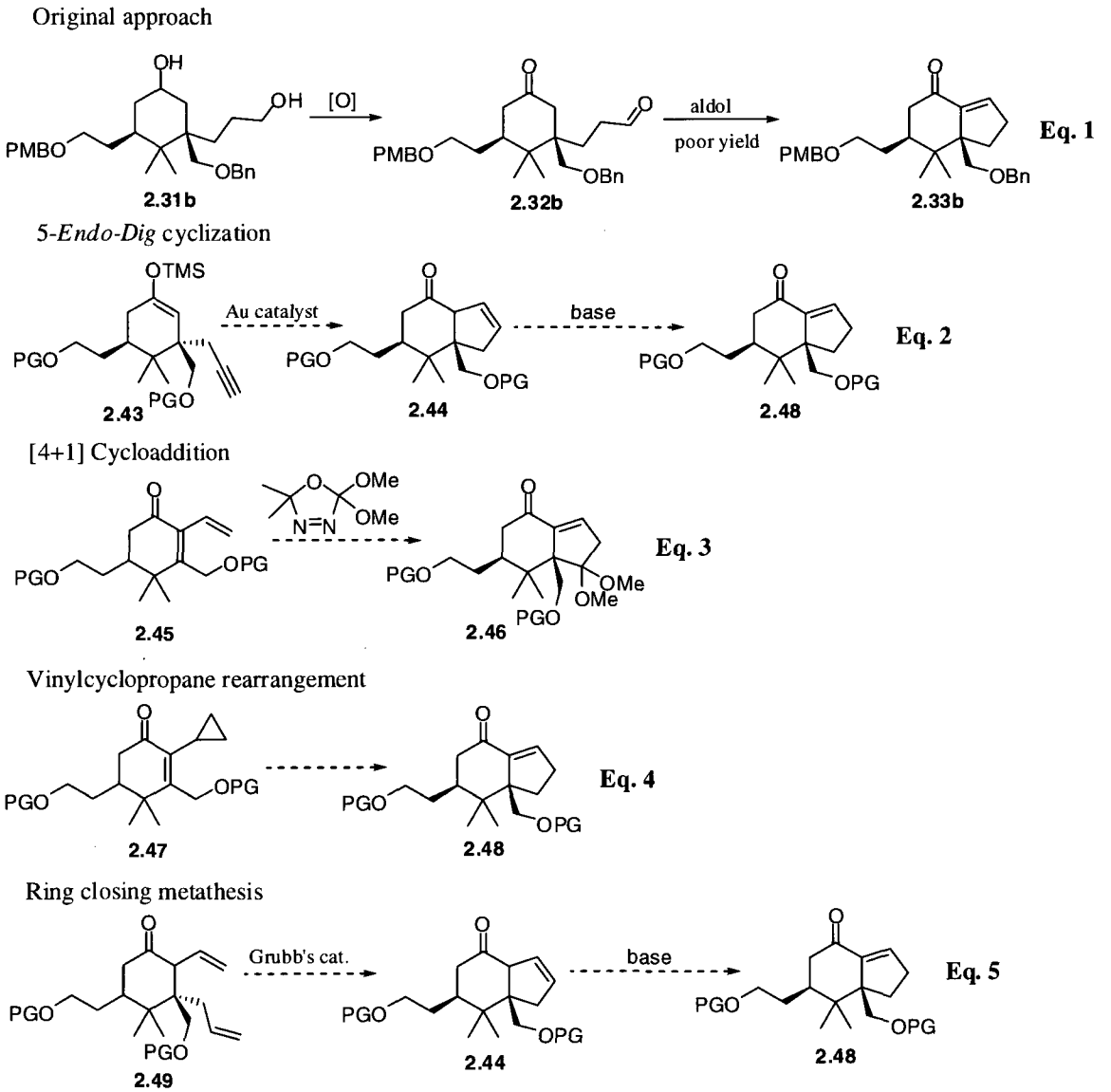


Figure 2.5 – ^{1}H NMR spectra of compound ***2.42b***

To our disappointment, we were unable to obtain sufficient quantities of either **2.41b** or **2.42b** for extensive NMR analysis in order to confirm the relative stereochemistry. We were also unable to obtain these compounds in a crystalline form suitable for X-Ray analysis. Reacting **2.42b** with *p*-nitrobenzoyl chloride led to recovery of starting material (we further realized the poor quality of the *p*-nitrobenzoyl chloride). Subjecting **2.42b** to hydrogenation conditions resulted in reduction of the olefin while leaving benzyl protecting group intact.

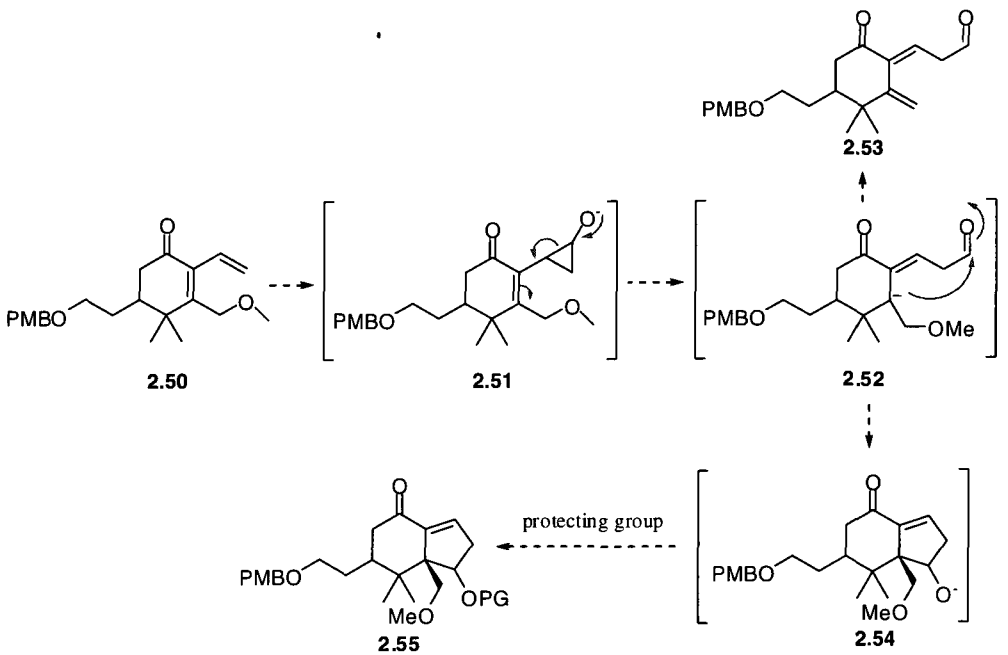
2.4 Strategies for the Formation of the Fused 5-Member ring

Our preliminary results obtained from the Prins-pinacol rearrangement of **2.39b** were strongly encouraging. However, in order to proceed with the synthesis of garsubellin A, large quantity of the Prins-pinacol precursor **2.39b** was needed. Thus, finding an alternative to the aldol condensation (Scheme 2.11, eq. 1) to obtain **2.33b** became our priority. Four different strategies were then proposed as outlined in Scheme 2.11.



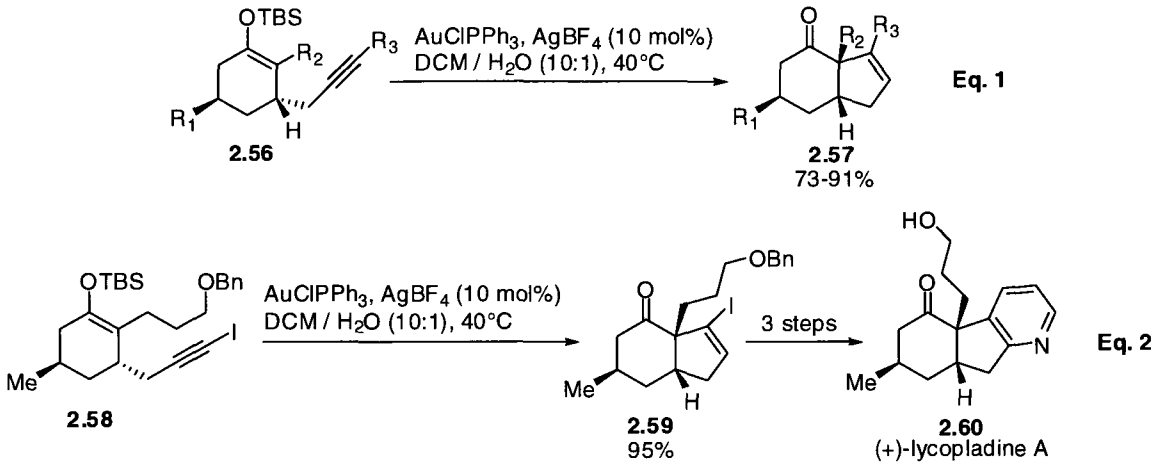
Scheme 2.11 – Alternative strategies to the aldol condensation for the formation of the fused five-membered ring of the Prins-pinacol precursor

Our first strategy was to use the gold catalyzed 5-*endo-dig* cyclization methodology developed by Toste *et al.*[25] to obtain compound **2.44** (Scheme 2.11, eq. 2). Migration of the endocyclic double bond to the conjugated position would further afford desired bicyclic enone **2.48**. Another approach was to employ the [4+1] cycloaddition developed by Spino *et al.*[26] to access compound **2.46** (Scheme 2.11, eq. 3). This strategy presents an advantage of introducing the desired ketone α to the gem-dimethyls protected as an acetal. The third approach was to generate compound **2.48** *via* vinylcyclopropane rearrangement, inspired by the work of Danheiser *et al.*[27] (Scheme 2.11, eq. 4). The proposed mechanism of this transformation is shown in Scheme 2.12. Rearrangement of vinyl alkoxy cyclopropane **2.51** under basic condition would give anionic intermediate **2.52**. Methoxy group could then eliminate to give undesired product **2.53**. However, another possibility would be the intramolecular attack of the carbanion on a newly formed aldehyde leading to the formation of the desired five-membered-ring (intermediate **2.54**). The latter possesses an alcohol functionality that could be then transformed into a ketone. This alcohol could be protected upon formation by adding a desired protecting group to intermediate **2.54** *prior to* work-up. The fourth approach was to form the five-membered ring using the ring closing metathesis and isomerization of the double bond position (Scheme 2.11, eq. 5).



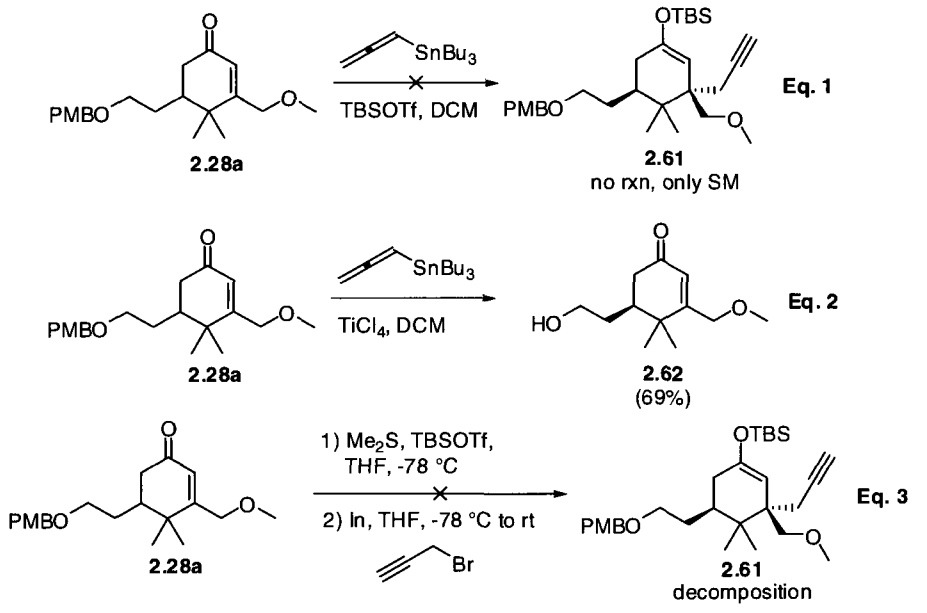
Scheme 2.12 – Third strategy to form the fused five-membered ring: alkoxy vinyl cyclopropane rearrangement

We first investigated the possibility of the gold catalyzed 5-*endo-dig* cyclization to generate the desired five-membered ring. Toste *et al.*[25] have recently reported formation of bicyclo[4.3.0]nonanones using the gold catalyzed 5-*endo-dig* cyclization of alkynes (Scheme 2.13, eq. 1). Furthermore, this methodology was successfully applied to the total synthesis of (+)-lycopladine (**2.60**)[25] (Scheme 2.13, eq. 2).



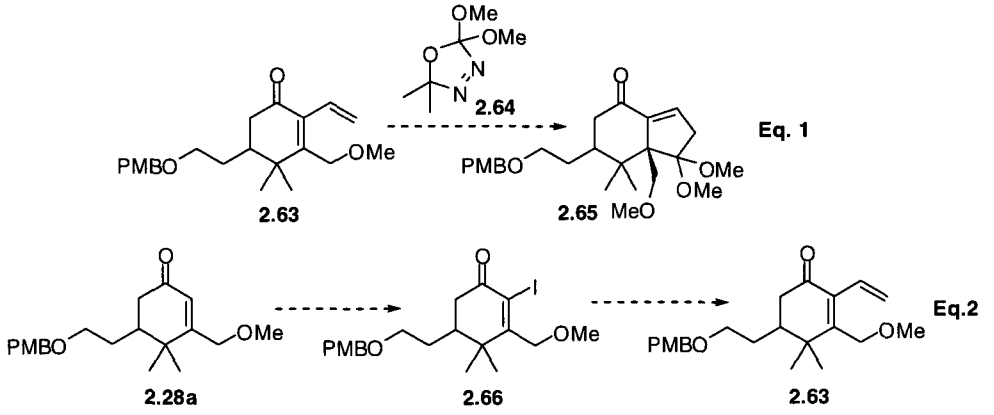
Scheme 2.13 – Toste's gold catalyzed 5-endi-dig cyclization and application of this methodology to the total synthesis of (+)-lycopladine A

We began our study by trying to prepare 5-*endo-dig* cyclization precursor **2.61** starting from enone **2.28a** (Scheme 2.14). Unfortunately, all attempts of propargyl conjugate addition on enone **2.28a** using conditions previously described in the literature failed. Thus, when enone **2.28a** was treated with allenyl tributyltin in the presence of TBSOTf [25] (eq. 1), only starting material was recovered at the end of the reaction. Allenyl tributyltin[29] had to be synthesized since it was not commercially available. When enone **2.28a** was treated with allenyl tributyltin in the presence of $TiCl_4$,[28] the acid-labile PMB protecting group was removed and no conjugate addition occurred (eq. 2). Using conditions reported by Lee[30] resulted in the recovery of starting material (eq. 3). One can propose that geminal methyl groups shield a site of nucleophilic attack thus rending ketone **2.28a** unreactive towards a 1,4-addition. Similar observation[24] was previously made when 1,4-addition on enone **2.28a** using alkyl species was attempted.



Scheme 2.14 – Attempts of propargyl conjugate addition on enone ***2.28a***

Thus we moved to our second approach inspired by the work of Spino *et al.*[26] We envisaged to form the fused five-membered-ring *via* [4+1] cycloaddition of carbene (Scheme 2.15, eq. 1). First, we prepared our substrate diene **2.63** from **2.28a** by converting **2.28a** to vinyl iodide **2.66** followed by corresponding Stille coupling (eq. 2).

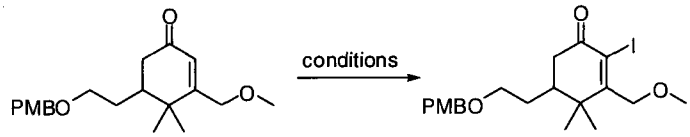


Scheme 2.15 – Formation of the fused five-membered ring by [4+1] cycloaddition

The iodination step required optimization (Table 2.2). When enone **2.28a** was treated under usual iodination conditions (eq. 1), no reaction was observed. Addition of DMAP to the reaction mixture was not effective (eq. 2). It was previously reported in the literature that a

presence of a substituent β to the ketone as well as a quaternary center in γ-position significantly retards the iodination of α,β-unsaturated ketones.[31, 32, 33] Enone **2.28a** possesses both of these features, which might explain why no iodination reaction is observed. It has been proposed[32] that reaction occurs *via* Baylis-Hillman type mechanism. The presence of substituents in β and γ position of the enone could hinder the conjugate addition of pyridine (or DMAP) and therefore prevent the reaction from occurring. Sha *et al.*[33] have reported that using of $TMSN_3$ allows to overcome this hurdle. Azide is a much smaller nucleophile then either pyridine or DMAP, which facilitates the first conjugate addition step of the proposed mechanism. We were pleased to see formation of vinyl iodide **2.66** using the Sha's iodination conditions (eq. 3), although the reaction did not go to completion. We then varied the reaction time (eq. 4) and the reaction temperature (eq. 5). Unfortunately, only increased decomposition was observed. The best results were obtained when number of equivalents of $TMSN_3$ was increased from 2 to 4 equivalents (eq. 6). We were able to obtain 63% yield and 23% of starting material was recuperated.

Table 2.2 Optimization of the iodination step



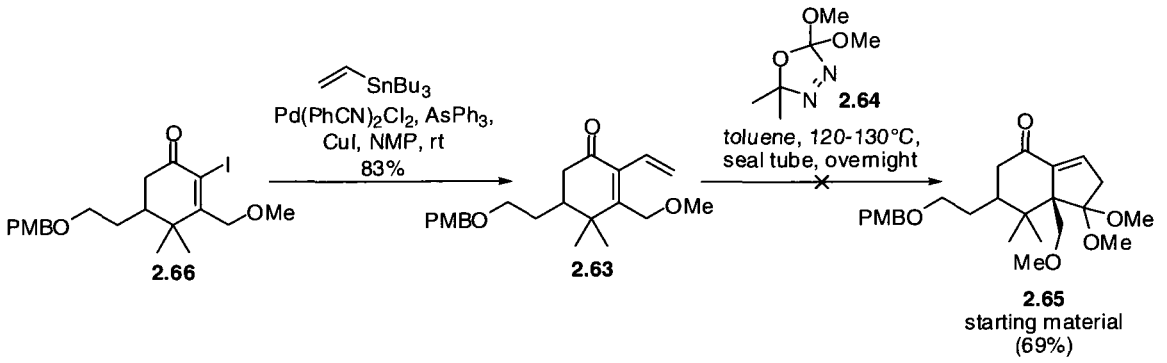
2.28a **2.66**

entry	conditions	yield (SM)*
1	**I_2, Et_2O/Pyridine** (1:1), 0 °C, o/n	only SM
2	I_2, Et_2O/Pyridine (1:1), **DMAP**, 0 °C to rt, o/n	only SM
3	1) **$TMSN_3$ (2 equiv)**, DCM, 0°C 2) I_2, DCM/pyridine (1:1), **0 °C to rt, o/n**	32% (60%)
4	1) **$TMSN_3$ (2 equiv)**, DCM, 0°C 2) I_2, DCM/pyridine (1:1), **0 °C to rt, 3x o/n**	44% (35%)
5	1) **$TMSN_3$ (2 equiv)**, DCM, 0°C 2) I_2, DCM/pyridine (1:1), 0 °C to **65 °C, o/n**	35% (20%)
6	1) **$TMSN_3$ (4 equiv)**, DCM, 0°C 2) I_2, DCM/pyridine (1:1), **0 °C to rt**	63% (23%)

* yield of starting material recovered at the end of the reaction

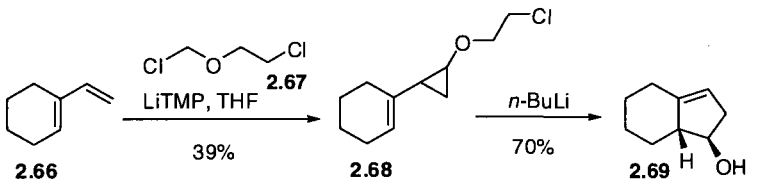
Vinyl iodide **2.66** was then subjected to Stille cross-coupling[34] in the presence of tributylvinyl tin to afford diene **2.63** in 83% yield (Scheme 2.16). The next step was to react **2.63** with **2.64** under [4+1] cycloaddition conditions. 2,2-Dialkoxy-Δ^3-1,3,4-oxadiazolin (**2.64**) was

prepared according to literature procedure.[35] Unfortunately, when diene **2.63** was heated in toluene in the presence of the dimethoxy carbene precursor, no reaction occurred and only starting material was recovered at the end of the reaction. Thus, this approach was also abandoned.



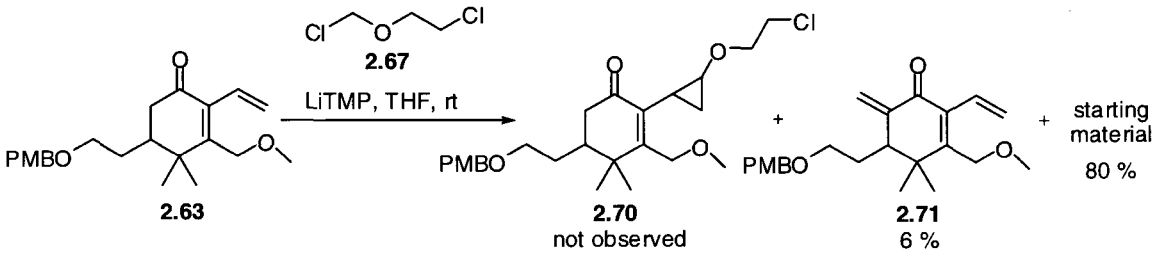
Scheme 2.16 – Attempts to apply the [4+1] cycloaddition of carbene methodology to synthesis of the Prins-pinacol precursor

Our third approach was inspired by the work of Danheiser *et al.*[27] The authors reported the synthesis of various cyclopentene derivatives using alkoxy vinyl cyclopropane rearrangement. For example, bicyclic compound **2.69** was prepared starting from diene **2.66** (Scheme 2.17).



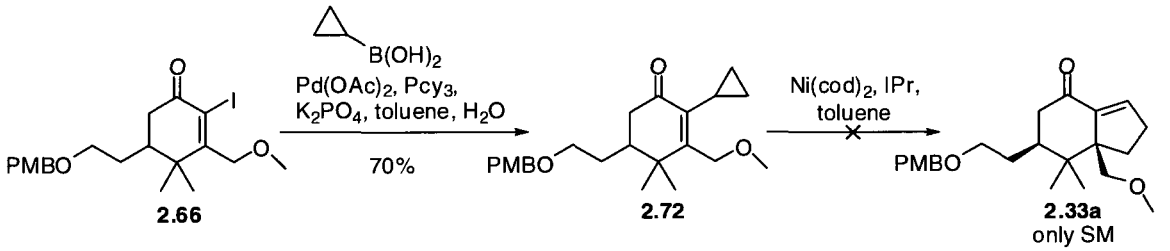
Scheme 2.17– Literature precedent on the synthesis of bicyclo[4.3.0]nonanone core using alkoxy vinyl cyclopropane rearrangement

We then tried to perform the same reaction on diene **2.63** to generate **2.70** (Scheme 2.18). Compound **2.67** was prepared according to literature precedents.[36] Unfortunately, most of the starting material and a small amount of the undesired product **2.71** were recovered at the end of the reaction.



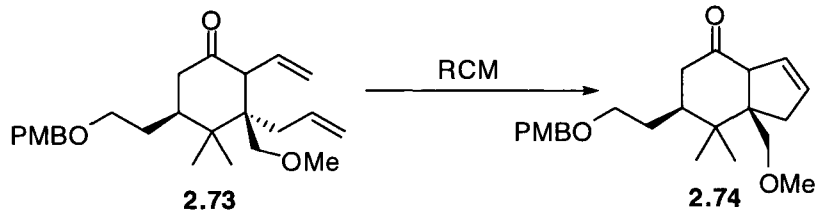
Scheme 2.18 – Attempts to form the fused five-membered ring via alkoxy vinyl cyclopropane rearrangement

We then turned our attention to the rearrangement of unsubstituted vinylcyclopropane **2.72** (Scheme 2.19). This second approach was inspired by the work of Louie *et al.*[37] The authors reported a few examples of nickel(0) catalyzed isomerization of unactivated vinyl cyclopropanes to cyclopentenes. We prepared vinyl cyclopropane **2.72** starting from vinyl iodide **2.63** and using Suzuki cross-coupling with the corresponding cyclopropane boronic acid.[38] Unfortunately, no reaction occurred when compound **2.72** was treated under nickel(0) catalyzed isomerization conditions. Thermal rearrangement of unactivated vinylcyclopropane has been reported in the literature[39] but it involves very high temperature pyrolysis. Therefore, we decided to move to our fourth approach.



Scheme 2.19 – Attempts to form the fused five-membered ring via unsubstituted vinyl cyclopropane rearrangement

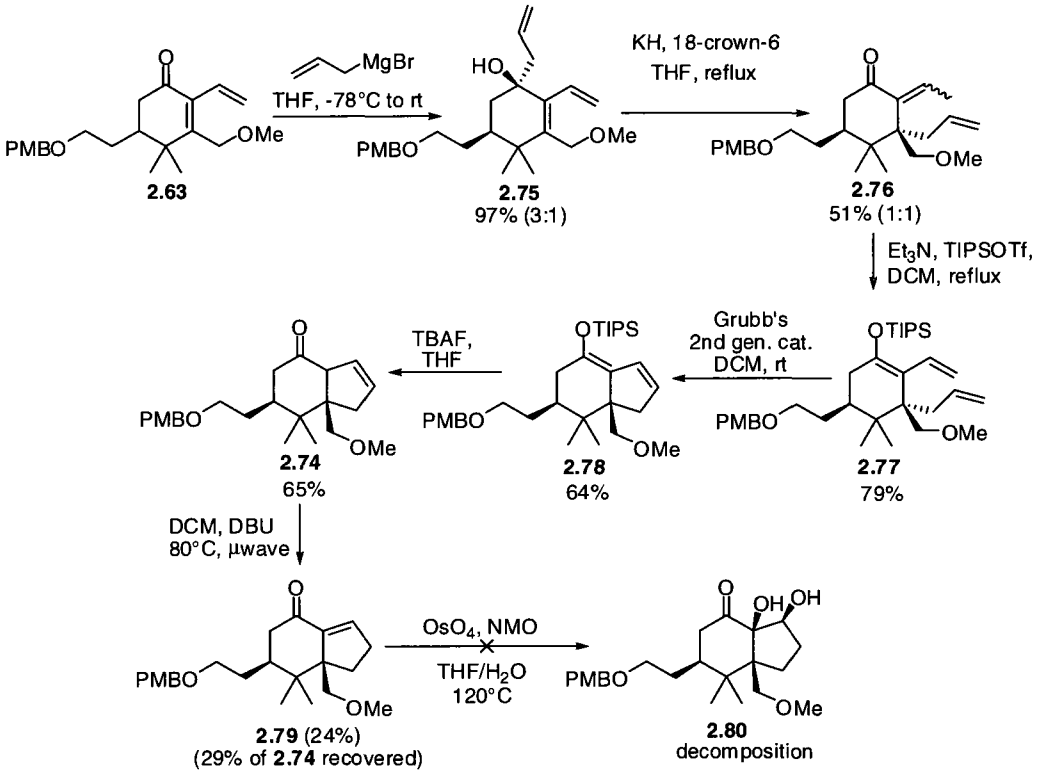
The last approach to the desired five-membered-ring was to apply ring closing metathesis to compound **2.73** (Scheme 2.20).



2.73 **2.74**

Scheme 2.20 – Last approach toward the formation of the fused five-membered ring: ring closing metathesis

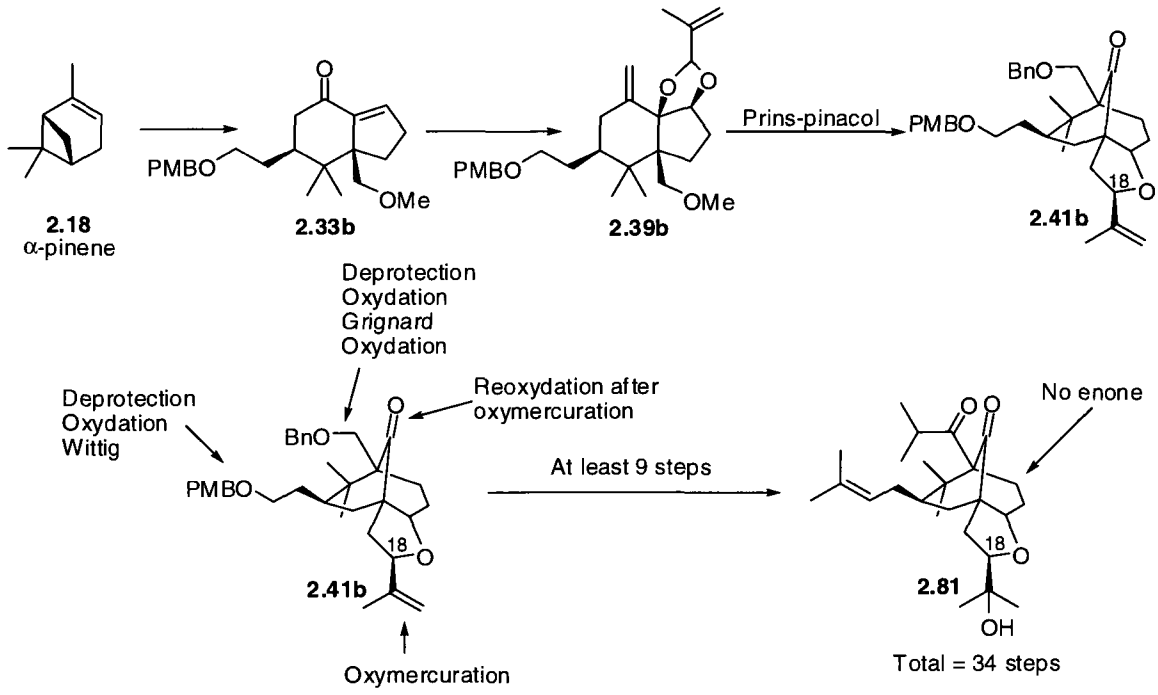
We started the synthesis of compound **2.73** from diene **2.63** (previously prepared, Scheme 2.19). Grignard addition on diene **2.63** afforded the tertiary alcohol **2.75** in 97% yield as a 3:1 mixture of diastereoisomers. (Scheme 2.21) The anionic oxy-Cope rearrangement was found to be the only way to form the quaternary center adjacent to the gem-dimethyls. However, during anionic oxy-Cope rearrangement, the migration of double bond occurred to generate conjugated ketone **2.76** in 51% yield as a 1:1 mixture of *E/Z* isomers. In order to regenerate the terminal olefin required for the RCM, thermodynamic silyl enol ether **2.77** was then prepared. RCM of compound **2.77** proceeded smoothly to afford bicyclic compound **2.78** in 64% yield. Deprotection using TBAF led to unconjugated ketone **2.74**. Migration of the double bond to the conjugated position under basic conditions afforded a mixture of the desired enone (**2.79**) and the starting material (**2.74**). The recovered starting material can be reacted again under the same conditions. Direct dihydroxylaiton of enone **2.79** led to decomposition. In order to overcome this problem, enone **2.79** would have to be reduced under Luche conditions and resulting allylic alcohol would have to be protected before the dihydroxylation step (as it was previously shown in Scheme 2.8). Unfortunately, we were not able to further continue the synthesis due to the lack of material at this stage.



Scheme 2.21 – Synthesis of the bicyclo[4.3.0]nonanone core of the Prins-pinacol precursor using ring closing metathesis

2.5 Conclusion

Model studies previously performed in our laboratory demonstrate that the Prins-pinacol methodology is a powerful tool to construct bicyclo[3.3.1]alkanone fused to a tetrahydrofuran ring from various acetals. The reaction is diastereoselective and epimeric mixture of acetals can be used. The observed relative stereochemistry of the Prins-pinacol products corresponds to the one present in garsubellin A. Preliminary results from Prins-pinacol reaction of a highly functionalized substrate (**2.39b**) are very promising. Unfortunately, the lack of material did not allow us performing extensive NMR studies and X-Ray crystallographic study on the Prins-pinacol product (**2.41b**). The synthesis of the Prins-pinacol precursor (**2.39b**) appears to be difficult and remains the major challenge in this approach. Different strategies for the preparation of the bicyclo[4.3.0] core of the Prins-pinacol precursor were employed. The aldol condensation strategy was found to be the fastest way to access the bicyclic enone **2.33b**. However, it proved to be problematic on a large scale. Other strategies were also explored. The most promising one appeared to be the ring closing metathesis. The synthesis of the Prins-pinacol precursor requires 24 steps and a shorter sequence is strongly desirable. Starting from intermediate **2.41b**, at least 9 steps are foreseen in order to convert the side chain functionalities into those present in garsubellin A. Furthermore, compound **2.81** remains a model substrate since we had to sacrifice our synthetic handle needed for the introduction of the endocyclic enone present in the natural product. Thus, we have chosen to abandon the Prins-pinacol approach and have turned our attention to development of a novel synthetic strategy toward the total synthesis of garsubellin A.



Scheme 2.22 – Towards the total synthesis of garsubellin A using the Prins-pinacol methodology – an overview

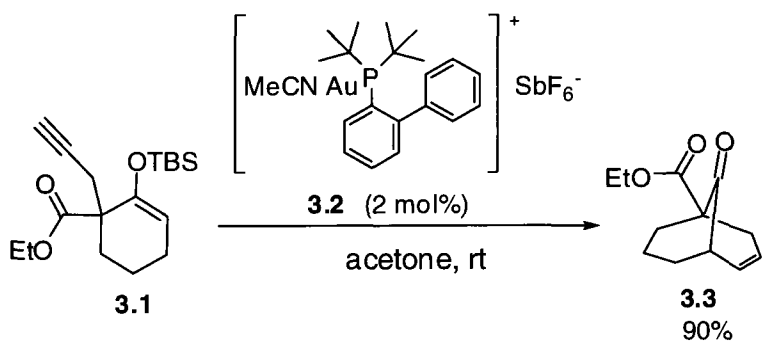
3

Application of the Gold Catalyzed Conia-ene Methodology to the Total Synthesis of Garsubellin A

3.1 Introduction

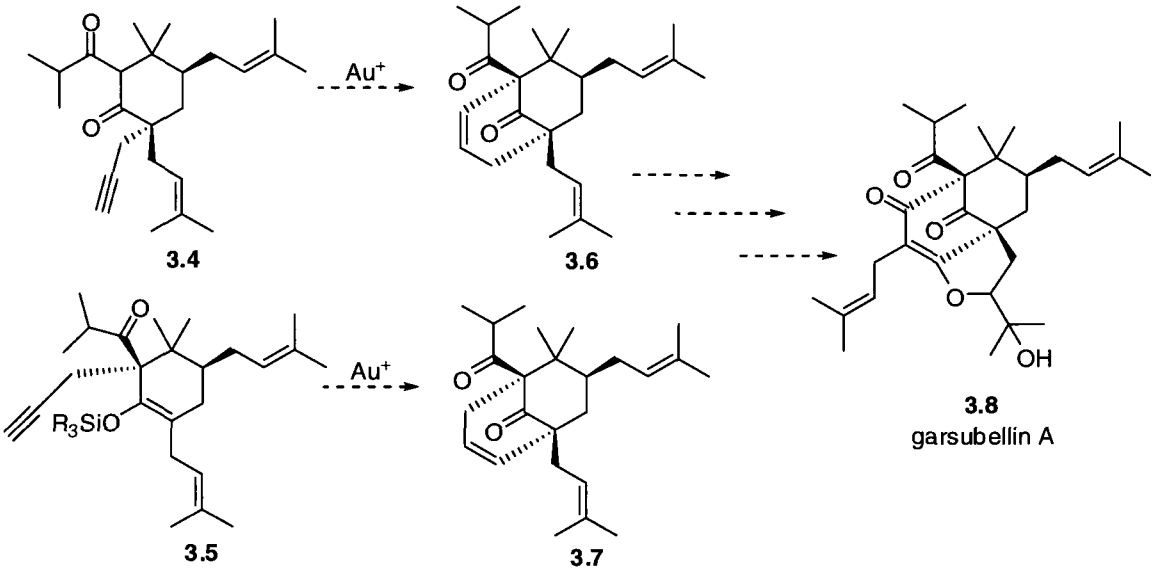
As we discussed at the end of Chapter 2, difficulties encountered during the synthesis of the Prins-pinacol precursor led us to review our strategy toward the total synthesis of garsubellin A. To this end, we have proposed to apply a novel gold catalyzed Conia-ene reaction recently developed in our laboratory to prepare the [3.3.1]nonanone core of garsubellin A.

Francis Barabé, a graduate student in the Barriault's laboratory, has recently demonstrated that cationic gold(I) catalyzes the 6-*endo-dig* cyclization of silyl enol ether **3.1** to form **3.3** (Scheme 3.1). After solvents and catalysts screening, the best yield was obtained using the Echavaren's catalyst[40] (**3.2**) in acetone at room temperature.



Scheme 3.1 – Gold catalyzed Conia-ene reaction – optimal conditions

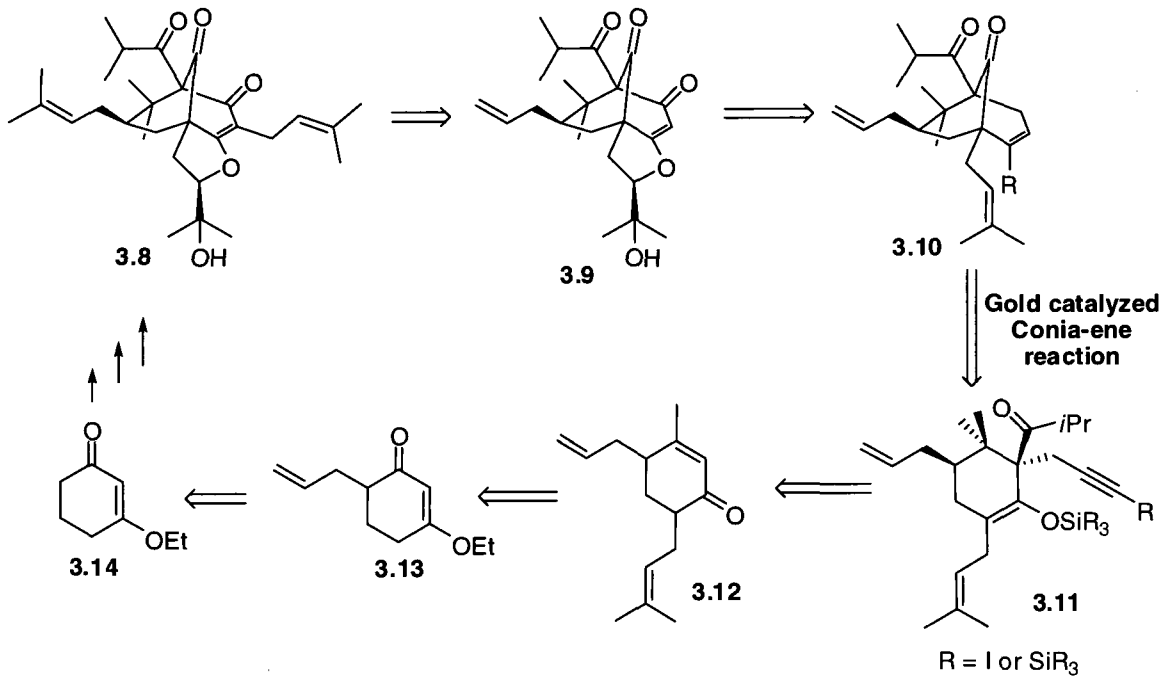
This finding has inspired us to propose a retrosynthesis of garsubellin A using gold-catalyzed Conia-ene cyclization of **3.5** as a key step (Scheme 3.2). Thus, one can imagine that the core of garsubellin A (**3.6** or **3.7**) could be generated *via* cyclization of either compound **3.4** or compound **3.5** respectively.



Scheme 3.2 – Second strategy for the construction of the garsubellin A core

3.2 Retrosynthetic Analysis

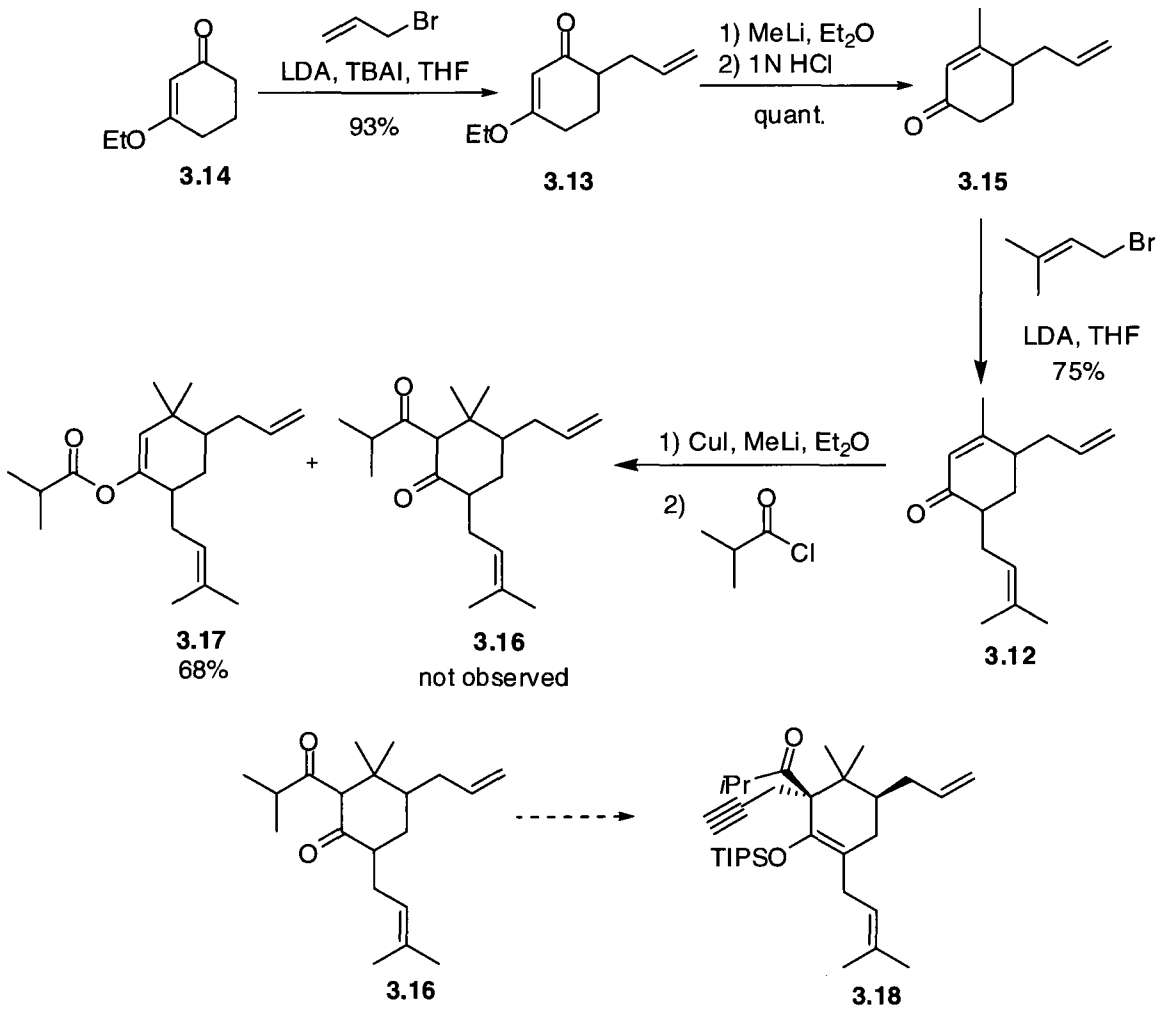
A closer retrosynthetic analysis reveals that the Conia-ene precursor (**3.11**) could be derived from ethoxy cyclohexenone **3.14** (Scheme 3.3). The latter would be converted to compound **3.12** through enone **3.13** by two subsequent alkylations. Cuprate addition on enone **3.13** followed by quenching of the resulting enolate would afford the desired *β*-dicarbonyl. The latter could be converted to **3.11** *via* treatment with a strong base and propargyl bromide. Gold catalyzed Conia-ene reaction would lead to advanced intermediate **3.10**. We also needed to install a synthetic handle R (R = I or SiR_3) that would help us to differentiate the endocyclic double bond in **3.10** from the other double bonds. Allylic oxidation of the endocyclic double bond would lead to the corresponding enone. Regio and diastereoselective dihydroxylation of the most substituted prenyl side chain would give **3.9**. The last prenyl side chain would be introduced using Shibasaki's method[14].



Scheme 3.3 - Retrosynthetic analysis of the total synthesis of garsubellin A applying the gold catalyzed Conia-ene methodology

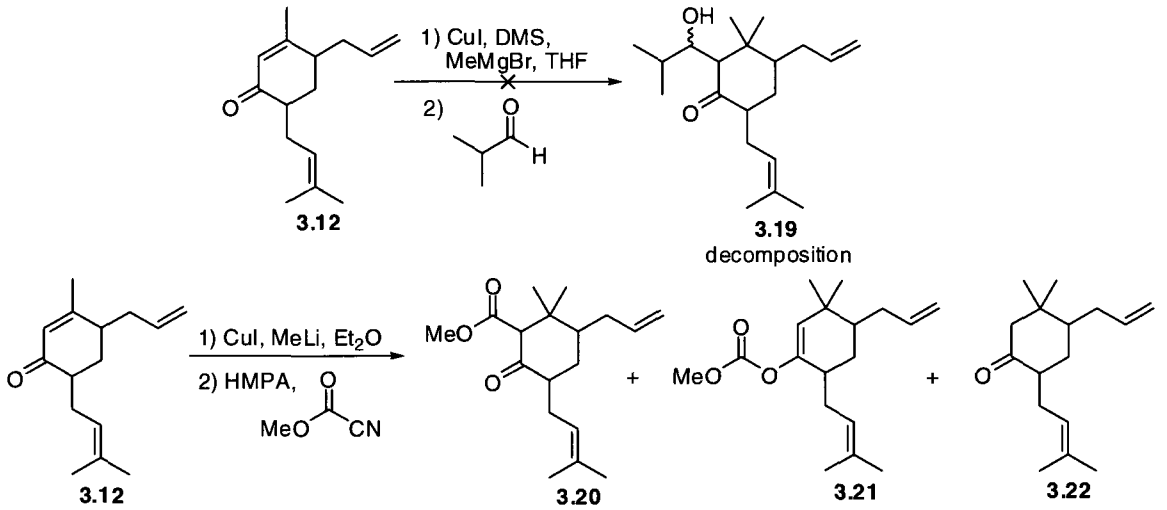
3.3 Synthesis of the Precursor for the Gold Catalyzed Conia-ene Reaction

The proposed synthesis of compound **3.16** starting from commercial ethoxy cyclohexenone (**3.14**) is shown in Scheme 3.4. Generation of lithium enolate followed by alkylation with allyl bromide afforded compound **3.13** in 93% yield. Addition of methyl lithium followed by an acid-catalyzed rearrangement gave enone **3.15** in quantitative yield. Compound **3.15** was treated with LDA and then prenyl bromide to generate **3.12** in 63% yield. Conjugate addition on enone **3.12** using Me_2CuLi and subsequent trapping of the resulting enolate intermediate with isobutyryl chloride resulted in the *O*-acylation product **3.12** in 68% yield. Desired compound **3.16** was not observed in the crude reaction mixture.



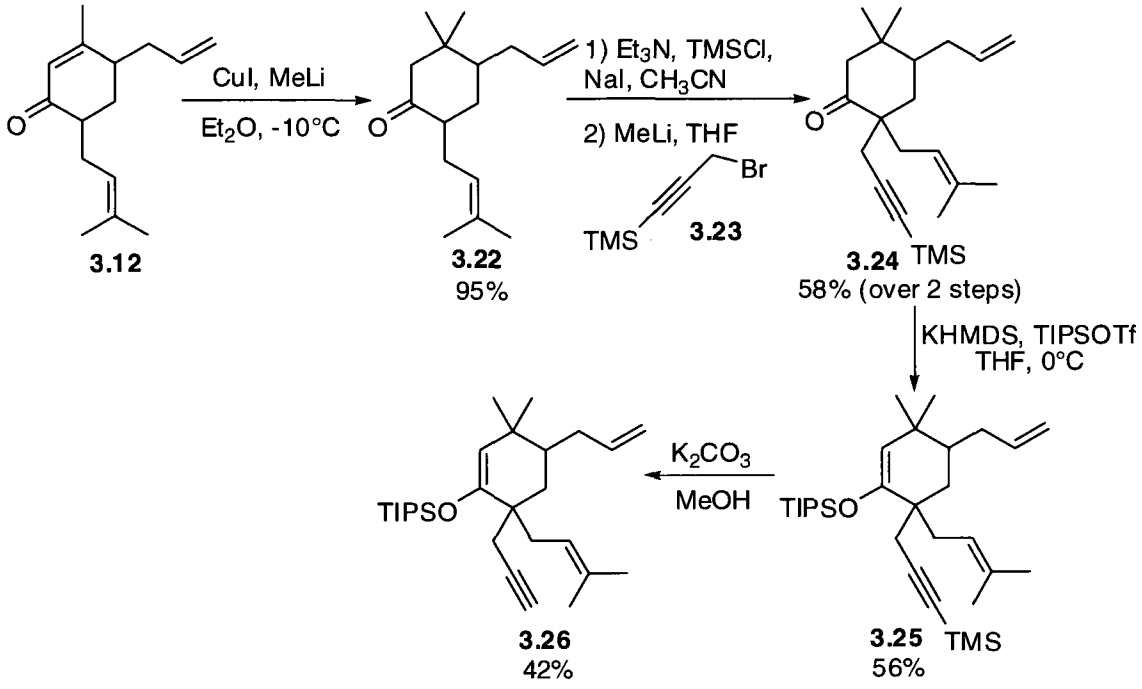
*Scheme 3.4 – First attempts on total synthesis of the Conia-ene precursor **3.18***

We then repeated the same reaction using isobutyraldehyde which is a softer electrophile compared to acid chloride (see Scheme 3.5). Unfortunately, a complex mixture of products was obtained. When the enolate was trapped with Mander's reagent, a mixture of non-acylated (**3.22**), *O*-acylated (**3.21**) and *C*-acylated (**3.20**) product was obtained (ratios not determined). The reaction proved to be not reproducible. We therefore realized that the introduction of the isobutyryl subsistent would be more challenging than originally thought. Thus, we decided to first perform model studies on the substrate devoid of the isobutyryl substituent.



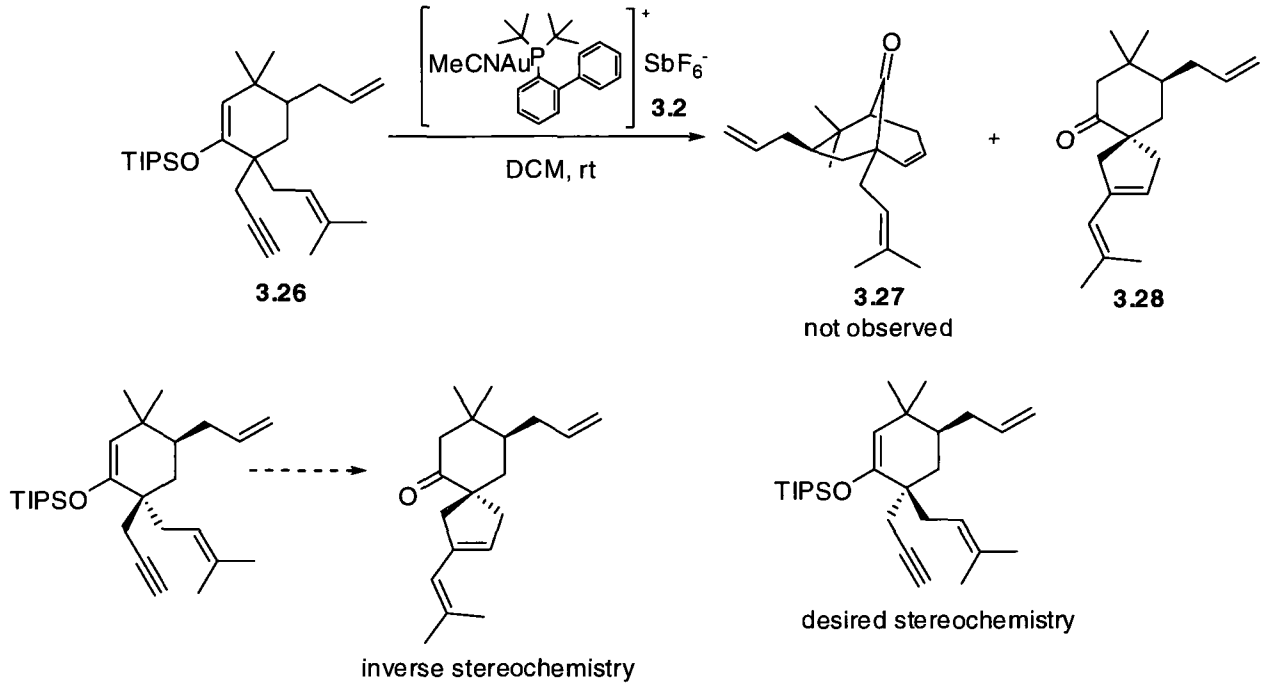
Scheme 3.5 – Attempts to trap the enolate resulting from the cuprate addition

The synthesis of model substrate **3.26** started from compound **3.12** (Scheme 3.6). Methyl cuprate addition on enone **3.12** afforded ketone **3.22** in 95%. Formation of the thermodynamic silyl enol ether followed by silicon-metal exchange and alkylation of the resulting enolate with TMS protected propargyl bromide (**3.23**) yielded compound **3.24** in 58% yield over two steps. TIPS enol ether **3.25** was then prepared using KHMDS and TIPSOTf in 56% yield. Originally, we prepared the TMS enol ether. However, when it was treated under cyclization conditions, compound **3.24** was mostly recovered thereby demonstrating that the silyl enol ether has to be stable under the slightly acidic conditions. Thus, we exchanged the TMS for a TIPS enol ether. Selective deprotection of the triple bond afforded precursor **3.26** in 42% yield.



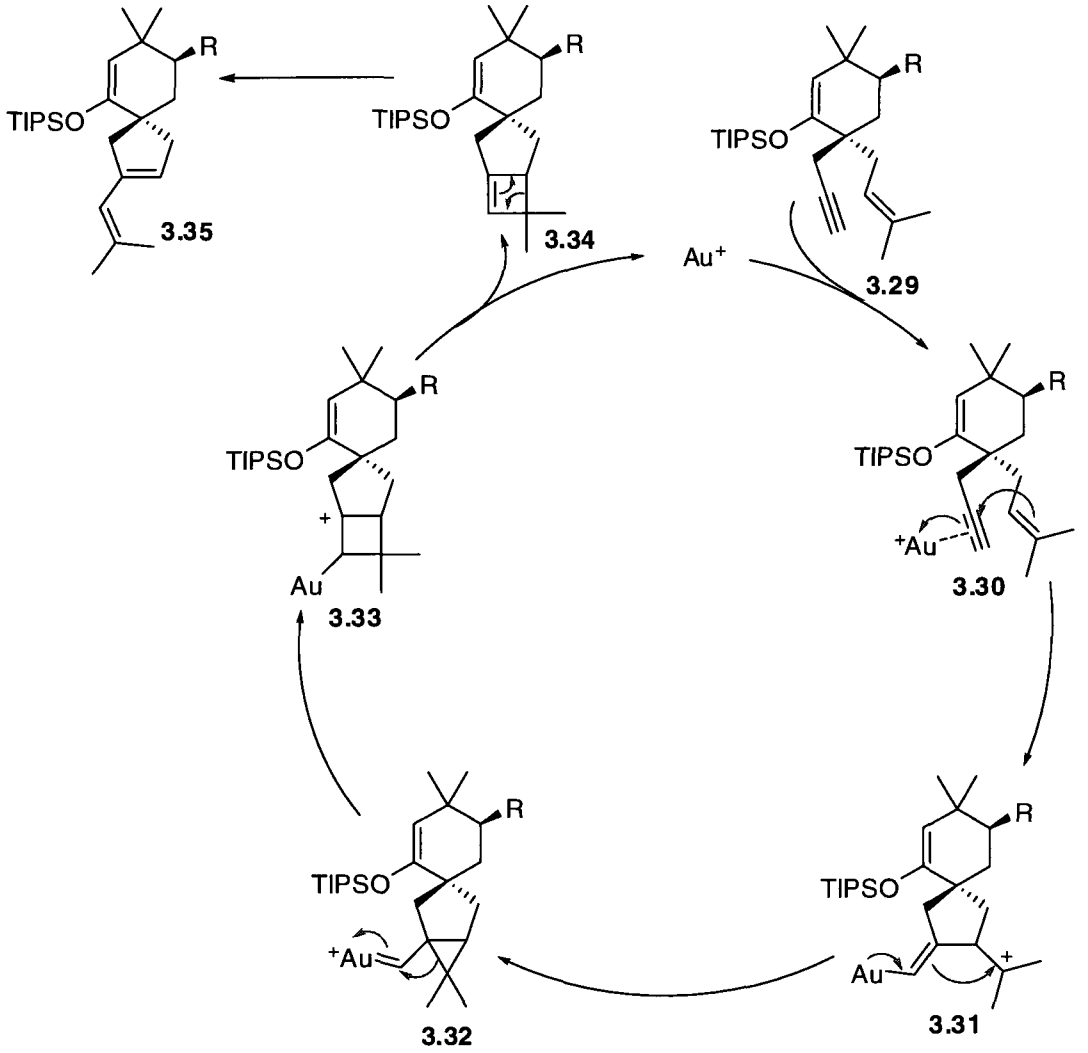
Scheme 3.6 – Preparation of the model substrate ***3.26***

Unfortunately, when compound **3.26** was treated under our optimized Conia-ene reaction conditions, only product **3.28** was obtained resulting from cycloisomerization (Scheme 3.7). The formation of compound **3.28** allowed us to determine the relative stereochemistry in the starting material **3.26** (see Experimental part). Unfortunately, the opposite stereochemistry was obtained.



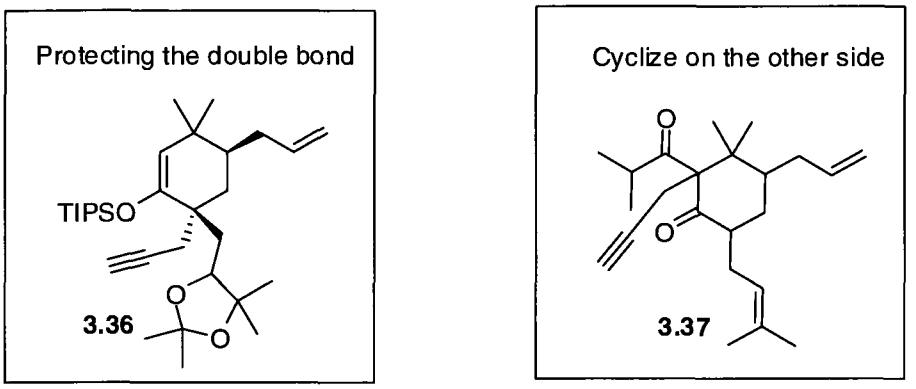
Scheme 3.7 - First attempt on the gold catalyzed Conia-ene reaction on a highly functionalized substrate

Echavarren has previously proposed a mechanism of gold catalyzed cycloisomerization of enynes of **3.29** type (Scheme 3.8).[41] The proposed mechanism is depicted in Scheme 3.8. First, coordination of the cationic gold catalyst to the alkyne gives **3.30**. The activated alkyne **3.30** undergoes a nucleophilic attack by the alkene to give a spiro five-membered ring **3.31**. Back-donation of electrons from gold provides cyclopropane carbene **3.32**. Ring expansion of **3.32** affords cationic intermediate **3.33**. Protodemetallation regenerates the active cationic gold catalyst and forms cyclobutene intermediate **3.34** which undergoes a 4πe conrotatory electrocyclization to produce diene **3.35**.



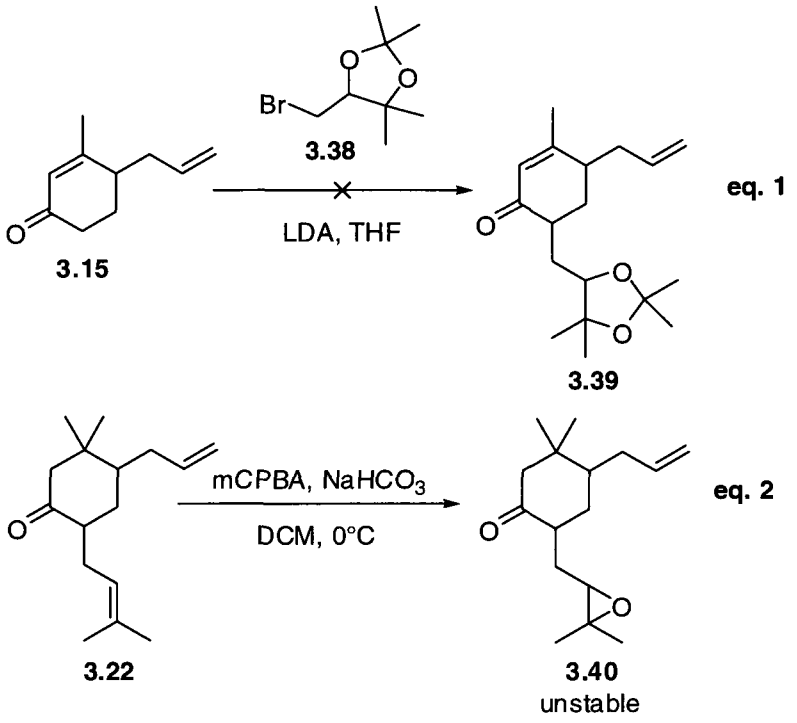
Scheme 3.8 - Mechanism proposed by Echavarren for cycloisomerization of alkynes

We proposed two general strategies to avoid the cycloisomerization (Scheme 3.9). The first strategy would be to protect the double bond of the prenyl side chain by dihydroxylation which otherwise would have to be performed later on in the synthesis. The second strategy to overcome the cycloisomerization problem would be to perform cyclization on **3.37** in which the triple bond is installed on the other side of the ketone.



Scheme 3.9 – Strategies to solve the cycloisomerization problem

We envisioned that enone **3.15** could be directly alkylated with the protected dihydroxy side chain (Scheme 3.10, eq. 1). Enantiomerically pure bromide **3.38** can be prepared from either L-serine or D-mannitol giving access to both enantiomers[42]. Separation of the resulting diastereoisomers could be performed after the alkylation in order to obtain an enantioselective synthesis of garsubellin A. Unfortunately, the alkylation of compound **3.15** with bromide **3.38** led to recovery of the starting material. Regioselective epoxidation of **3.22** with *m*-CPBA (Scheme 3.10, eq. 2) gave epoxide **3.40**. However, this epoxide proved to be unstable and therefore could not be used as a protecting group.



Scheme 3.10 – First attempts to solve the cycloisomerization problem

3.4 Conclusion

In conclusion, we have attempted the gold catalyzed Conia-ene reaction to highly functionalized model substrate **3.26** and we observed a competitive cycloisomerization reaction (Scheme 3.7). Treatment of compound **3.26** with gold(I) catalyst resulted exclusively in undesired cycloisomerization product. The synthesis of functionalized substrate **3.18** (Scheme 3.4) was not completed since we were not able to install the isobutyryl side chain. Future efforts will be directed towards circumventing those problems.

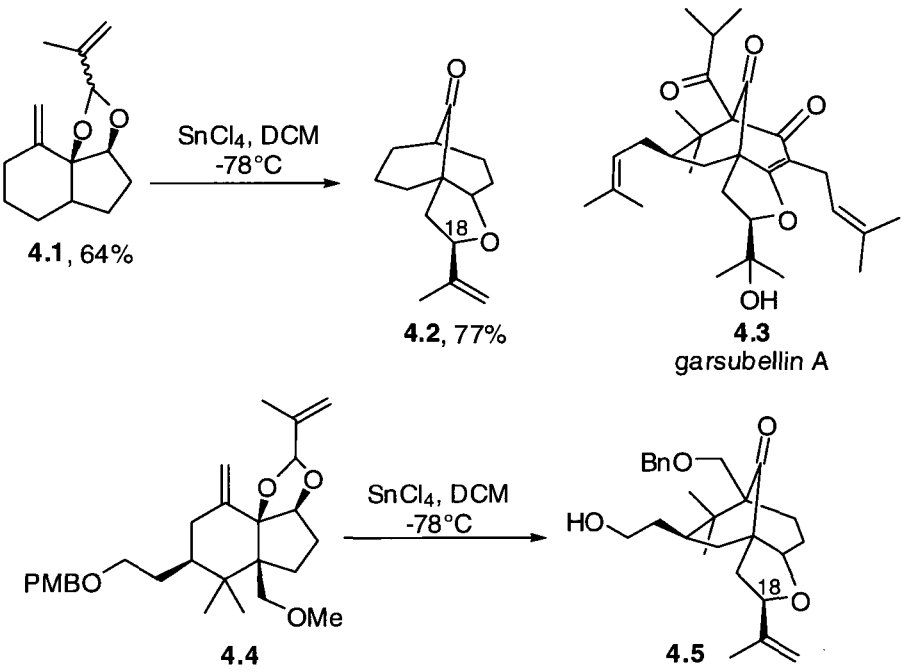
4

General Conclusion

4.1 Summary

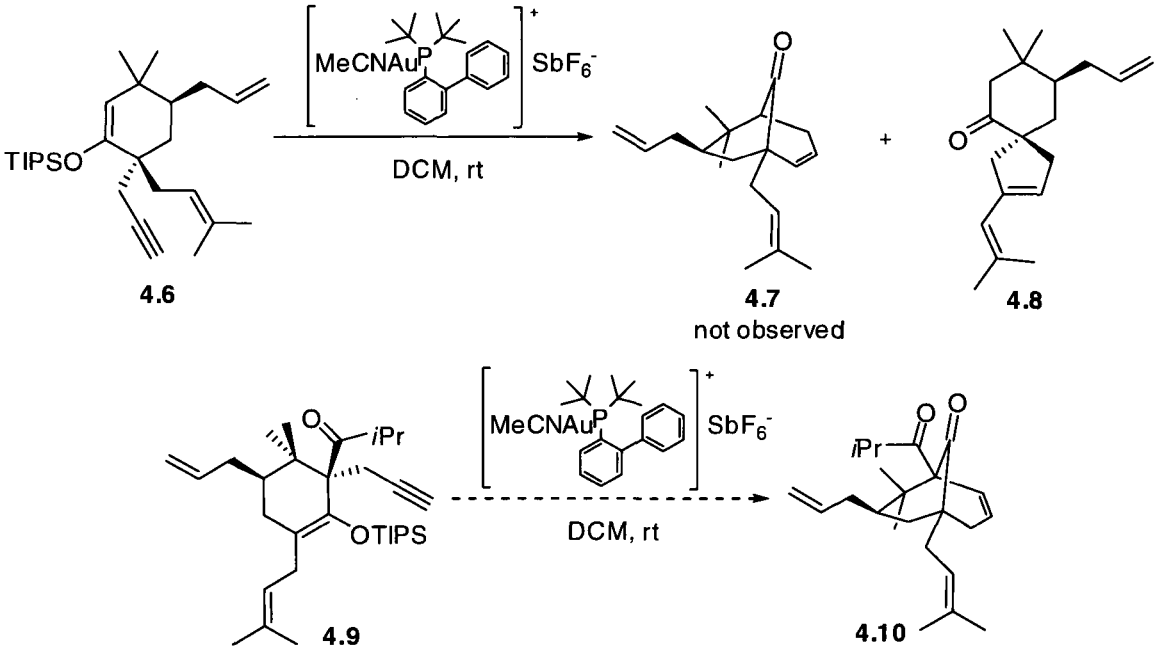
In the course of our studies, we have investigated two different approaches toward the total synthesis of garsubellin A, a complex natural product from PPAP family.

Our first strategy involved using the Prins-pinacol cationic cascade previously developed in our laboratory as a key step to construct tricyclic core of garsubellin A. As shown by our model studies on substrate **4.1**, this strategy allows for complete stereocontrol at C18 center, thus potentially providing a solution to one of the main synthetic challenges in the total synthesis of garsubellin A. Based on the literature, only Danishefski's group has been able to achieve a high stereocontrol at this center in their total synthesis of garsubellin A. Preliminary results on Prins-pinacol reaction of a highly functionalized substrate (**4.4**) are very promising. Unfortunately, the lack of material did not allow us performing extensive NMR studies and X-Ray crystallographic study on the Prins-pinacol product (**4.5**). The synthesis of the Prins-pinacol precursor (**4.4**) appears to be difficult and remains the major challenge in this approach.



Scheme 4.1 – Highlights on the Prins-pinacol approach

Our second approach utilized the gold catalyzed Conia-ene reaction also developed in the Barriault's group. Unfortunately, preliminary model studies on substrate **4.6** revealed formation of undesired cycloisomerization product **4.8** instead of expected **4.7**. The future work will be dedicated to eliminate competing cycloisomerisation reaction pathway. One of the solution would be protection of the prenyl side chain. Cyclization on **4.9** could also be performed.



Scheme 4.2 – Highlights on the gold catalyzed Conia-ene approach

4.2 Claims to Original Research

1. Progress in the synthesis of garsubellin A using the Prins-pinacol methodology developed in our laboratory
2. Progress in the synthesis of garsubellin A using the gold catalyzed Conia-ene methodology developed in our laboratory

4.3 Poster and OralPresentations

1- **Brochu, M.-C.**; Girardin, M.; Barriault, L. *Progress Towards the Total Synthesis of Garsubellin A: Application of Prins-Pinacol Cationic Cascade* QOMSBOC, **2007**, Montréal, Québec, Canada, November 9th – 11th

2- **Brochu, M.-C.**; Girardin, M.; Barriault, L. *Progress Towards the Total Synthesis of Garsubellin A: Application of Prins-Pinacol Cationic Cascade* Synthesis Day, **2007**, Ottawa, Ontario, Canada, June 18th

3- **Brochu, M.-C.**; Barabé, F.; Barriault, L. *Progress Towards the Total Synthesis of Polycyclic Polyprenylated Acylphloroglucinols (PPAP's)* Synthesis Day, **2008**, Ottawa, Ontario, Canada, June 16th

4- **Brochu, M.-C.**; Barriault, L. *Progress Towards the Total Synthesis of Garsubellin A* Boehringer Ingelheim, **2008**, Laval, Québec, Canada, June 18th

5- **Brochu, M.-C.**; Barriault, L. *Progress Towards the Total Synthesis of Garsubellin A* Aegera Therapeutics Inc., **2008**, Montréal, Québec, Canada, July 22th

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. Anhydrous solvents and some liquid reagents were freshly distilled prior to use: acetonitrile (CaH_2), dichloromethane (CaH_2), *N,N*-Diisopropylamine (CaH_2), diethyl ether ($LiAlH_4$, then sodium / benzophenone), 1,2-dimethoxyethane (LAH), hexamethylphosphoramide (CaH_2 (X3)), NMP (CaH_2, pump), pyridine (CaH_2), tetrahydrofuran (sodium / benzophenone), triethylamine (CaH_2), trimethylsilyl chloride (CaH_2), TMP (CaH_2), toluene (CaH_2). 18-Crown-6 was dried under high vacuum overnight in a dessicator with phosphorus pentoxide. NaH (60% dispersion in mineral oil) was washed 3 times with freshly distilled pentane (CaH_2).

All commercial reagents were used without purification unless otherwise indicated. 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, *p*-anisaldehyde staining solution. Flash chromatography was carried out on 230-400 mesh silica gel 60.

^1H 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.

Titration of alkyl lithium reagents solutions: The titration was performed under an argon atmosphere in flame-dried glassware. THF was distilled over sodium and benzophenone. To a solution of 2,6-di(*t*-butyl)-4-methoxy phenol (150 mg) in THF (1 mL) was added a small amount of fluorene. The alkyl lithium solution was added dropwise until the mixture became yellow.

Titration of Grignard reagents solutions: The titration was performed under an argon atmosphere in flame-dried glassware. THF was distilled over sodium and benzophenone. To a solution of 2-((2-phenylhydrazono)methyl)phenol (50 mg) in THF (1 mL) was added the Grignard reagent solution until the mixture became orange.

Purification of CuI: To a mixture of CuI (40.34 g, 212 mmol, 1.0 equiv) and KI (402 g, 2.42 mol, 11.4 equiv) in 320 mL of distilled water was added 8.90 g of activated charcoal. The yellow mixture was stirred overnight at room temperature in the dark. The mixture was filtrated through a pad of Celite. 2800 mL of distilled water was added to the filtrate. A white precipitate was formed. The solid was recuperated by filtration and dried over high vacuum overnight (34.1 g, 85% recovery).

Preparation of methyltriphenylphosphonium iodide: The reaction was performed under inert atmosphere using flame dried flasks. To a solution of triphenylphosphine (20.0 g, 76.3 mmol, 1.0 equiv) in benzene (700 mL) was added MeI (4.8 mL, 76.3 mmol, 1 equiv). The mixture was stirred overnight at room temperature protected from light. The mixture was filtrated. The white solid was washed 4 times with benzene and dried overnight under high vacuum (24.15g, 78% yield).

Preparation of 4-methoxybenzyl chloride: To a solution of 4-methoxybenzyl alcohol (87 mL, 630 mmol, 1 equiv) in 640 mL of Et_2O were added concentrated HCl (200 mL). The mixture was stirred for 4 hours at room temperature. The layers were separated. The organic layer was washed

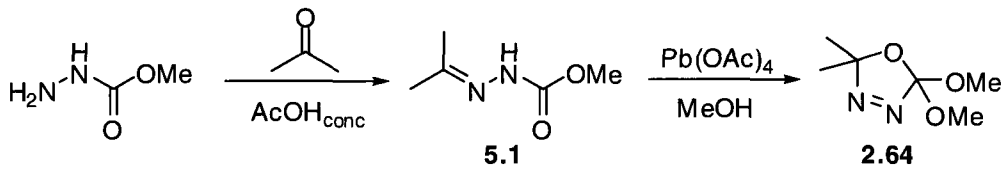
with brine (x2) and dried over Na_2CO_3. K_2CO_3 was added to the filtrate that was then concentrated under reduced pressure. The resulting residue was distilled over K_2CO_3 under reduced pressure (high vacuum) to afford the product as a colorless liquid (the yield was not calculated). The product was stored in the refridgerator in a big bottle over K_2CO_3 (no screw-on cap). The product may decompose or polymerize in the fridge (it becomes pink before it polymerizes).

Preparation of (methyloxymethyl)tributyl stannane (**2.25a**)[43]: To a solution diisopropylamine (10.3 mL, 73.6 mmol, 1.1 equiv) in THF (135 mL) at 0 °C was added a solution of *n*-BuLi in pentane (1.77 M, 37.8 mL, 66.9 mmol, 1 equiv) dropwise. The mixture was stirred for 15 minutes at 0 °C followed by a dropwise addition of tributyltin hydride (18 mL, 66.9 mmol, 1 equiv). (It is important to use tributyltin hydride from Alfa Aesar). The mixture was stirred for an extra 30 minutes at 0 °C and was cooled to -78 °C. The reaction mixture turned yellow and the magnetic stiring bar became black. Chloromethyl methyl ether (5.1 mL, 66.9 mmol, 1 equiv) was then added dropwise. The mixture was stirred for 30 minutes at -78 °C and for 1.5 hour at room temperature followed by addition of hexanes. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-5% EtOAc/hexanes) as eluent. The recovered material was distilled over $MgSO_4$ under reduced pressure (high vacuum) to give **2.25a** as a colorless liquid. No yield was calculated. This reagent was kept in the refridgerator.

Preparation of methacrolein dimethylacetal: To a solution of methacrolein (3.00 g, 42.8 mmol, 1.0 equiv) in MeOH (60 mL) was added a catalytic amount of PTSA. The mixture was heated at reflux for 4 hours, cooled down to room temperature and then diluted with Et_2O (300 mL). The organic layer was washed with sat $NaHCO_3$, with water, with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was distilled at 760 mmHg to give methacrolein dimethylacetal as a colorless liquid.

(3-bromoprop-1-ynyl)trimethylsilane was prepared according to literature precedents.[44]

Preparation of 2,2-Dialkoxy-Δ^3-1,3,4-oxadiazolin (**2.64**)[35]



To a solution of methyl hydrazinecarboxylate (5.0 g, 56 mmol, 1equiv)in acetone (10 mL) was added a few drops of concentrated acetic acid. The mixture was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting residue was recristallized using a mixture of methanol and hexanes to give **5.1** as a white solid. No yield calculated.

To a solution of **5.1** (2.0 g, 15.4 mmol, 1.0 equiv) in methanol (50 mL) was added $Pb(OAc)_4$ (7.49 g, 16.9 mmol, 1.1 equiv) in small portions at 0 °C. The mixture was stirred 3 hours at 0°C and was diluted with DCM. The organic layer was washed with sat NaHCO3, dried over anhydrous MgSO4 and concentrated under reduced pressure. The resulting residue is a yellow solid and was purified by distillation at 760 mmHg. **2.64** was contaminated. It was purified again by flash chromatography on silica gel without success. It was used without any further purification.

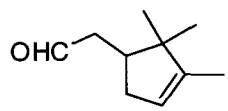
Preparation of 1-chloro-2-(chloromethoxy)ethane (**2.67**)[36]: A solution of 1,3,5-trioxane (6.2 g, 68.3 mmol, 0.37 equiv) in 2-chloroethanol (17 mL, 0.106 mmol, 1 equiv) was prepared. The solution was heated with heat gun to help dissolution. Gaseous HCl (prepared by mixing concentrated H_2SO_4 and brine) was bubbled in the solution for 4 hours at 0 °C. The flask was sealed and the mixture was stirred overnight at room temperature. The layers were separated. The bottom layer was dried over freshly grinded $CaCl_2$ and distilled over $CaCl_2$.

Experimental Procedures and Characterization

α-pinene oxide (2.18)

To a suspension of *m*-CPBA (98.70 g, 440 mmol, 1.2 equiv) and $NaHCO_3$ (46.25 g, 550 mmol, 1.5 equiv) in 900 mL of DCM was slowly added a solution of α-pinene (50 g, 367 mmol, 1 equiv) in 100 mL of DCM at 0 °C. The mixture was stirred (mechanical stirring) for 1.5 hour at 0 °C. 500 mL of an aqueous Na_2SO_3 solution (10% w/w) was added and the mixture was stirred at room temperature until two clear layers appeared. The layers were separated and the aqueous layer was extracted once with DCM. The combined organic layer was washed once with sat $NaHCO_3$, once with brine and dried over anhydrous $MgSO_4$. DCM was removed under reduced pressure to give a crude product as colorless oil. It was used in the next step without further purification.

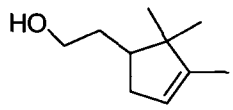
2-(2,2,3-trimethylcyclopent-3-enyl)acetaldehyde (2.19)



To a flame-dried flask filled with argon was added $ZnBr_2$ (from Alfa Aesar). It was flame-dried under vaccum until it was melted. The flask was refilled with argon and allowed to cool to room temperature. 600 mL of benzene were added to the flask. A solution of compound **2.18** (53.45 g, 351 mmol, 1 equiv) in 100 mL of benzene was prepared in a separate flask and was slowly added *via* cannula to a suspension of $ZnBr_2$. The mixture was stirred overnight at room temperature. 10% v/v aqueous acetic acid solution (100 mL) was added to the reaction mixture followed by Et_2O. The layers were separated. The organic layer was washed once with distilled water, once with sat $NaHCO_3$, once with brine and dried over anhydrous $MgSO_4$. The solvents were removed

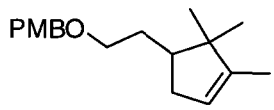
under reduced pressure. It is important to not to put the recovered material under high vacuum because it seems to be volatile. The resulting crude **2.19** was directly used for the next step. The product can be purified by flash chromatography on silica gel using a slow gradient (0 to 40% EtOAc/hexanes) as eluent.

2-(2,2,3-Trimethylcyclopent-3-enyl)ethanol (2.20)



To a solution of crude **2.19** in Et_2O (1.5 L) was added $LiAlH_4$ (11.14 g, 294 mmol, 0.8 equiv) portionwise at -78 °C. The mixture was then stirred for 45 minutes at -78 °C. The reaction was slowly quenched with 200 mL of isopropanol at -78 °C followed by addition of 1 M NaOH (400 mL). The mixture was slowly warmed to room temperature and was filtered. The layers were separated. The aqueous layer was extracted with Et_2O (x3). The combined organic fractions were washed with brine (x2) and dried over anhydrous $MgSO_4$. Et_2O was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel using a slow gradient (0 to 30% EtOAc/hexanes) as eluent to afford the product as a colorless oil (44.26 g, 78% yield over 3 steps). ^1H NMR was identical to previously reported on literature[24].

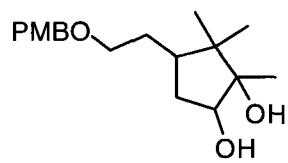
1-Methoxy-4-{[2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethoxy]methyl}benzene (2.21)



To a solution of compound **2.20** (6.21 g, 40.2 mmol, 1 equiv) in 210 mL of THF was added NaH (60% dispersion in mineral oil, 4.02 g, 100 mmol, 2.5 equiv) portionwise. NaH was washed 3 times with fresly distilled pentane (over CaH_2) before introducing it in the reaction mixture. The mixture was stirred for 15 minutes at room temperature. 4-methoxybenzyl chloride (6.5 mL, 48 mmol, 1.2 equiv) and sodium iodide (1.20 g, 8.04 mmol, 0.2 equiv) were then added. The mixture was stirred overnight at room temperature. The reaction was not complete according to

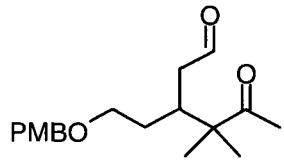
the TLC. The reaction was diluted with Et_2O and was quenched with sat NH_4Cl. The organic solvents were removed under reduced pressure. The resulting material was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The reaction was repeated twice (overall = 3 times). The resulting residue was passed through a pad of silica gel using 40% DCM/hexanes as an eluent. Once the desired product is out of the column (fractions containing the desired product are not clean), the latter was flushed with 40:30:30 hexanes/EtOAc/DCM mixture to recover the starting material. The recovered starting material was reacted again following the same procedure. The reaction still didn't go to completion. Therefore, the remaining starting material was recovered and reacted again for the third time following the same procedure. The fractions containing the desired product are dirtier as long as the recovered starting material was reacted again and again. All fractions containing the desired product were combined together and divided into two parts for the next step. The obtained material was used in the next step without further purification. Previous experiments[24] showed that a repeated purification leads to the decomposition of the product. Increasing the scale of the reaction leads to decomposition.

4-(2-(4-methoxybenzyloxy)ethyl)-1,5,5-trimethylcyclopentane-1,2-diol (2.22)



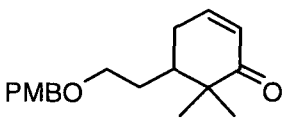
To a solution of crude **2.21** (half of the material recovered from the previous step, the reaction was performed twice) in THF (640 mL) was added aqueous $KMnO_4$ (0.14 M, 640 mL) over 1 hour. The mixture was kept under 20 °C (monitored by inserting a thermometer directly in the reaction mixture) during the addition using an ice bath. The mixture was stirred for 1 hour below 20 °C (the ice bath was kept). The mixture was first filtered through a filtering paper (long filtration, about 3 hours) and than through a pad of Celite. The recovered aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed once with brine and dried over anhydrous $MgSO_4$. EtOAc was evaporated under reduced pressure. The resulting residue was directly used for the next step.

3-{2-[(4-methoxybenzyl)oxy]ethyl}-4,4-dimethyl-5-oxohexanal (2.23)



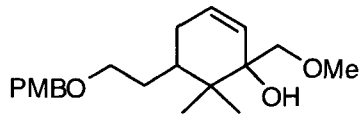
To a mixture of crude **2.22** (half of the material recovered from the previous step, the reaction was performed twice) in a 4:1 mixture of THF/water (740 mL) was added sodium periodate (18.85 g, 88.11 mmol, 1.5 equiv). The mixture was stirred overnight at room temperature. The reaction was quenched with a sat $NaHCO_3$. The mixture was filtrated and the filtrate was concentrated under reduced pressure. The resulting material was extracted Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was used in the next step without further purification.

5-[2-(4-Methoxybenzyloxy)ethyl]-6,6-dimethylcyclohex-2-enone (2.24)



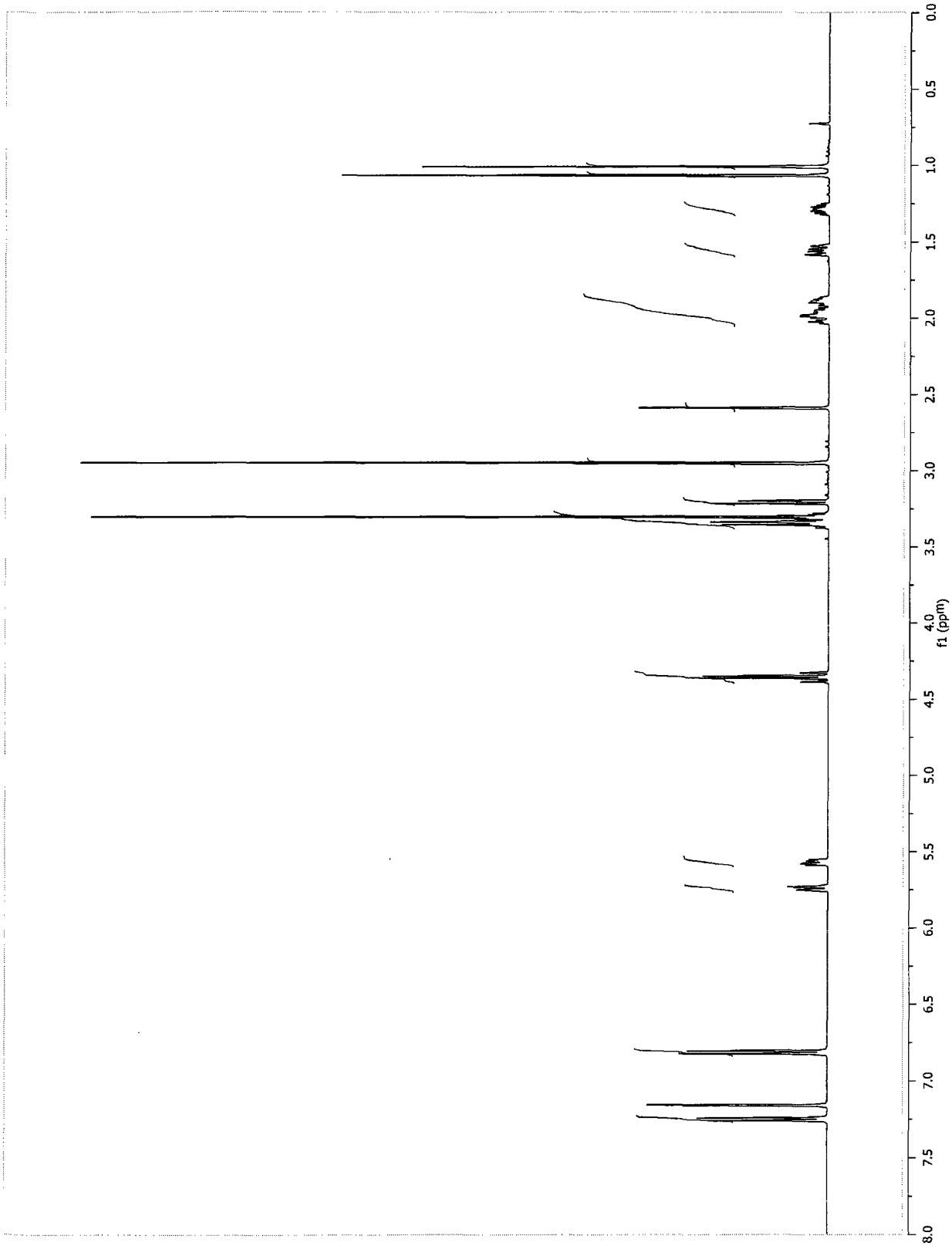
Crude **2.23** (half of the material recovered from the previous step, the reaction was performed twice) was dissolved in a 1:1 mixture of MeOH / aq. NaOH (1M) (575 mL). The mixture was stirred overnight at room temperature. Distilled water and brine were added to the mixture. MeOH was removed under reduced pressure. Water was added to the resulting residue and the mixture was extracted with Et_2O (x3). The combined organic fractions were washed with brine (x3), dried over anhydrous $MgSO_4$ and concentrated. The reaction was performed again using the same conditions. The combined crude material was purified by flash chromatography on silica gel using a gradient (0-30% EtOAc/hexanes) as eluent to give **2.24** (6.39 g, 18% overall yield starting from **2.20** (18.63 g)). The purification is difficult and there are a lot of mixed fractions. ^1H NMR was identical to previously reported on literature[24].

1-(Methyloxymethyl)-5-[2-(4-methoxybenzyloxy)ethyl]-6,6-dimethylcyclohex-2-enol (2.26a)



To a solution of (methyloxymethyl)tributyl stannane (**2.25a**) (3.84 g, 11.4 mmol, 3.3 equiv) in THF (15 mL) at -78 °C was added dropwise a solution of *t*-BuLi in pentane (1.54 M, 6.76 mL, 10.4 mmol, 3 equiv). The mixture was stirred for 1 hour at -78 °C and became yellow. A solution of dry (aseotropal removal of H_2O using dry benzene) compound **2.24** (1.00 g, 3.47 mmol, 1.0 equiv) in 15 mL of THF was prepared in a separate flask and was cooled to -78 °C. This solution was added dropwise *via* cannula cooled by dry ice wrapped in foil. The flask was rinsed twice with 2.5 mL of THF. It is important to not let the reaction mixture warm. The mixture was stirred for 1 hour at –78 °C. Sat NH_4Cl (150 mL) was added in order to quench the reaction. The mixture was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-40% EtOAc/hexanes) as eluent to give **2.26a** as a white solid (0.940 g, 81% yield). Note: It is important to use an excess of (methyloxymethyl)tributyl stannane (1.1 equiv relative to *t*-BuLi) and to employ *t*-BuLi instead of *n*-buLi in order to reduce the competitive *n*-BuLi addition reaction.

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.25 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.74 (ddd, J = 10.2, 2.4, 1.8 Hz, 1H), 5.57 (ddd, J = 10.2, 4.4, 2.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.34 (d, J = 11.7 Hz, 1H), 3.38 – 3.28 (m, 2H), 3.35 (d, J = 8.8 Hz, 1H), 3.31 (s, 3H), 3.21 (d, J = 8.8 Hz, 1H), 2.95 (s, 3H), 2.59 (s, 1H), 2.04 – 1.93 (m, 2H), 1.89 (tdd, J = 10.3, 5.6, 3.3 Hz, 1H), 1.56 (ddt, J = 18.2, 10.0, 2.6 Hz, 1H), 1.29 (dddd, J = 10.9, 8.5, 4.5, 4.0 Hz, 1H), 1.07 (s, 3H), 1.01 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.7 (C), 133.3 (CH), 131.4 (C), 129.4 (CH), 126.2 (CH), 114.1 (CH), 78.1 (CH_2), 75.1 (C), 72.8 (CH_2), 68.6 (CH_2), 58.9 (CH_3), 54.8 (CH_3), 39.0 (C), 37.2 (CH), 30.2 (CH_2), 29.1 (CH_2), 21.8 (CH_3), 17.3 (CH_3) **IR** (neat, cm^{-1}) 3527 (s), 2973 (m), 2918 (m), 1610 (m), 1515 (m), 1243 (s), 1087 (m), 1037 (m) **HRMS** (EI) m/z $(M-C_8H_{11}O_2)^+$ calculated for $C_{12}H_{19}O_2$ 195.1385, found 195.1395 (1.2%)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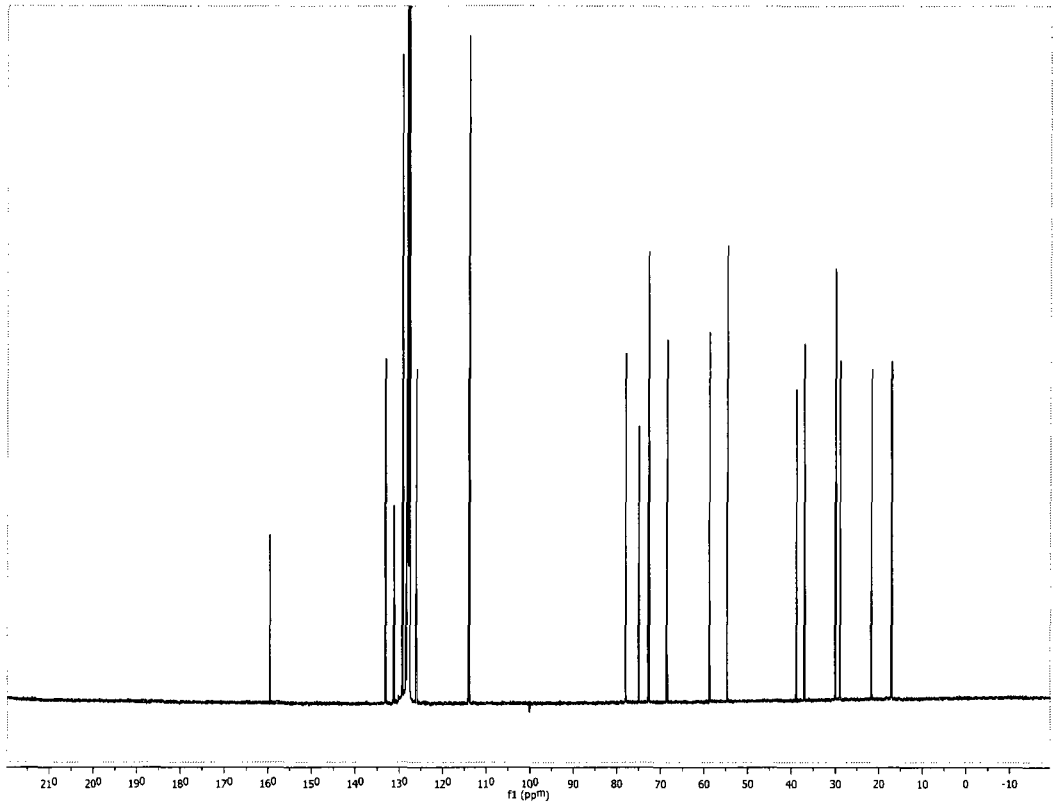
f1 (ppm)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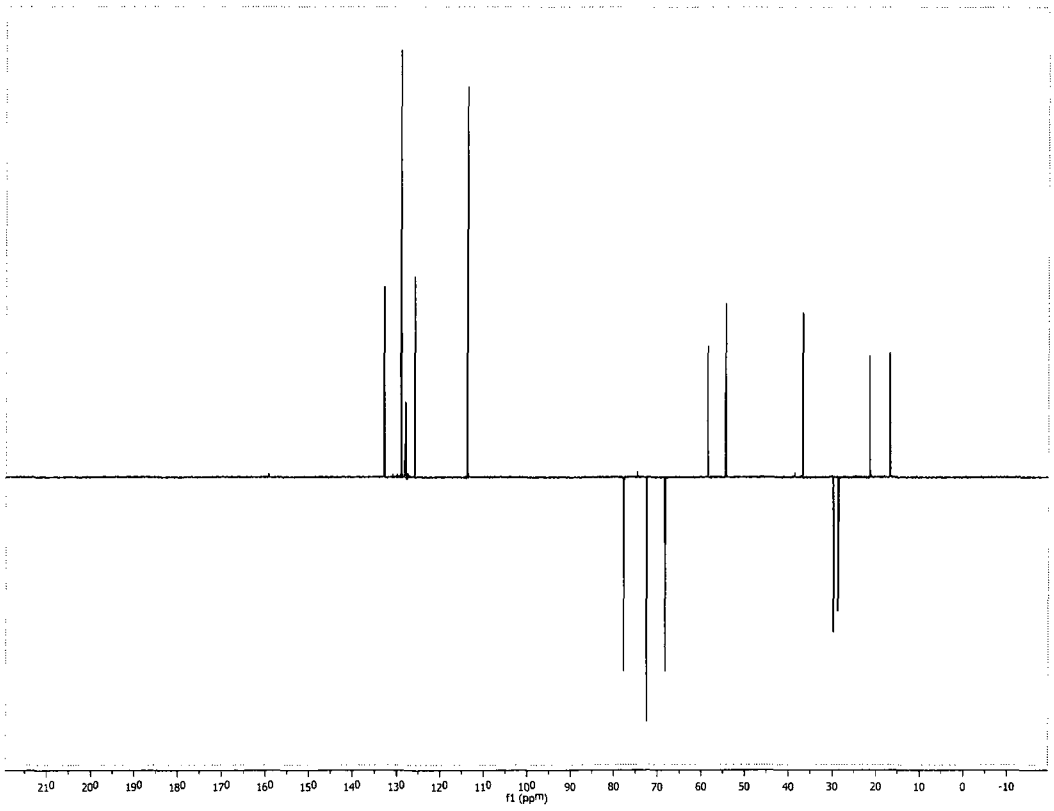
f1 (ppm)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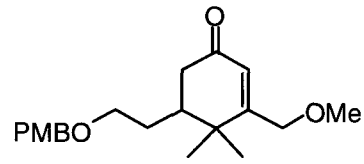
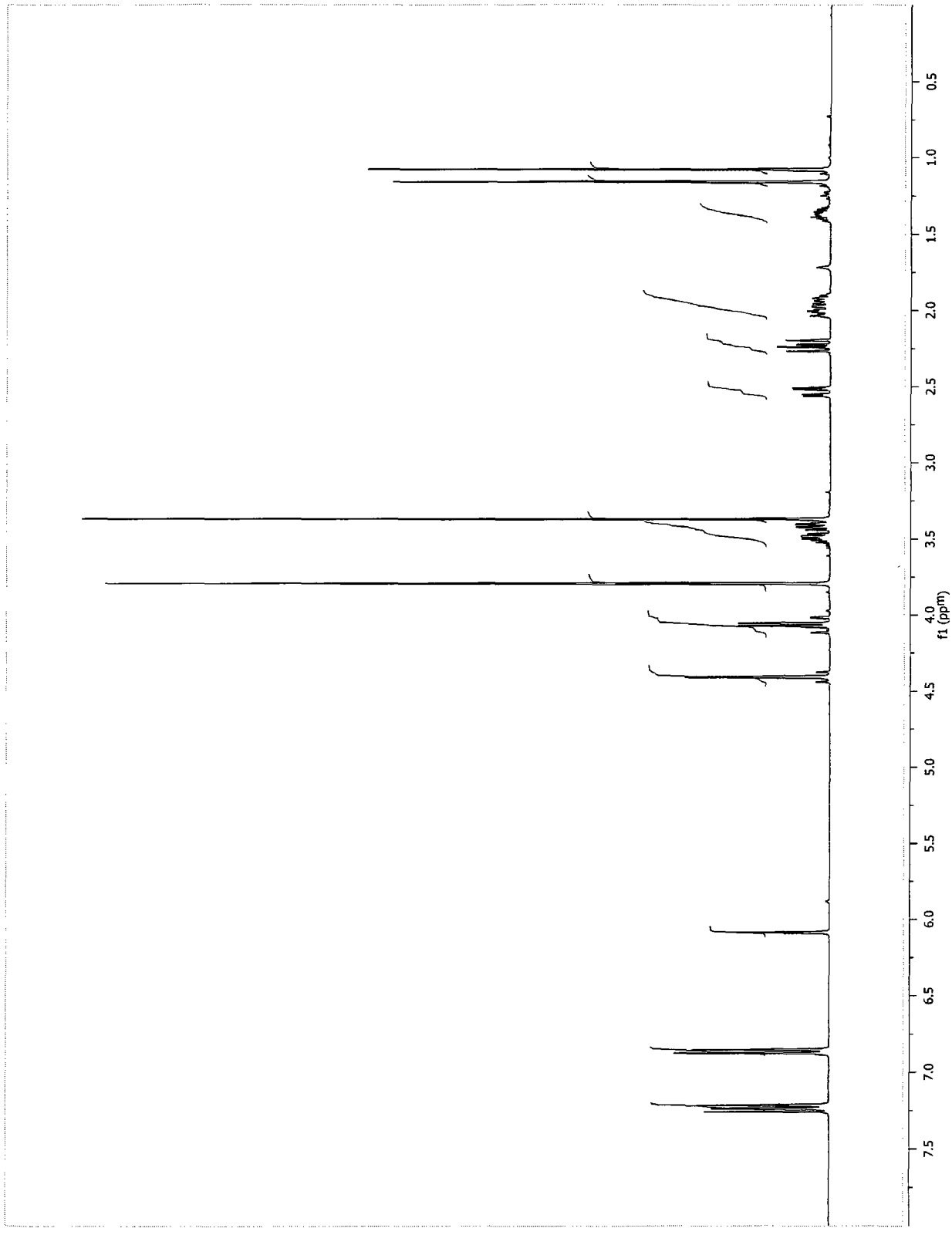
f1 (ppm)

3-(Methyloxymethyl)-5-[2-(4-methoxybenzyloxy)ethyl]-4,4-dimethylcyclohex-2-enone (2.27a)



To a suspension of PCC (2.75 g, 12.8 mmol, 5 equiv) in DCM (20 mL) was added a solution of compound **2.26a** (0.854 g, 2.55 mmol, 1 equiv) in 20 mL of DCM *via* canula. The mixture was stirred for 2 days at room temperature and was diluted with Et_2O. The mixture was filtered through a pad of Celite. Silica gel was added to the filtrate before solvent evaporation and the mixture was concentrated. The resulting product (pre-adsorbed on silica gel) was purified by flash chromatography on silica gel using a gradient (20-40% EtOAc/hexanes) as eluent to afford **2.27a** as a white solid (577 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.09 (br s, 1H), 4.42 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.09 (dd, J = 16.0, 1.7 Hz, 1H), 4.04 (dd, J = 16.0, 1.6 Hz, 1H), 3.80 (s, 3H), 3.50 (ddd, J = 9.3, 7.2, 4.8 Hz, 1H), 3.41 (ddd, J = 9.1, 8.3, 6.3 Hz, 1H), 3.37 (s, 3H), 2.54 (dd, J = 17.2, 4.3 Hz, 1H), 2.23 (dd, J = 17.2, 11.1 Hz, 1H), 2.04 – 1.90 (m, 2H), 1.37 (dddd, J = 13.6, 10.8, 6.1, 4.7 Hz, 1H), 1.16 (s, 3H), 1.08 (s, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 198.9 (C), 167.3 (C), 159.3 (C), 130.4 (C), 129.4 (CH), 123.6 (CH), 133.9 (CH), 72.9 (CH_2), 71.4 (CH_2), 68.0 (CH_2), 58.8 (CH_3), 55.4 (CH_3), 41.8 (CH), 39.3 (CH_2), 37.7 (C), 29.7 (CH_2), 24.6 (CH_3), 20.8 (CH_3) **IR** (neat, cm^{-1}) 2934 (m), 2872 (m), 1667 (s), 1613 (m), 1513 (m), 1248 (m), 1094 (m), 820 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{20}H_{28}O_4$ 332.1988, found 332.1999 (1.7%)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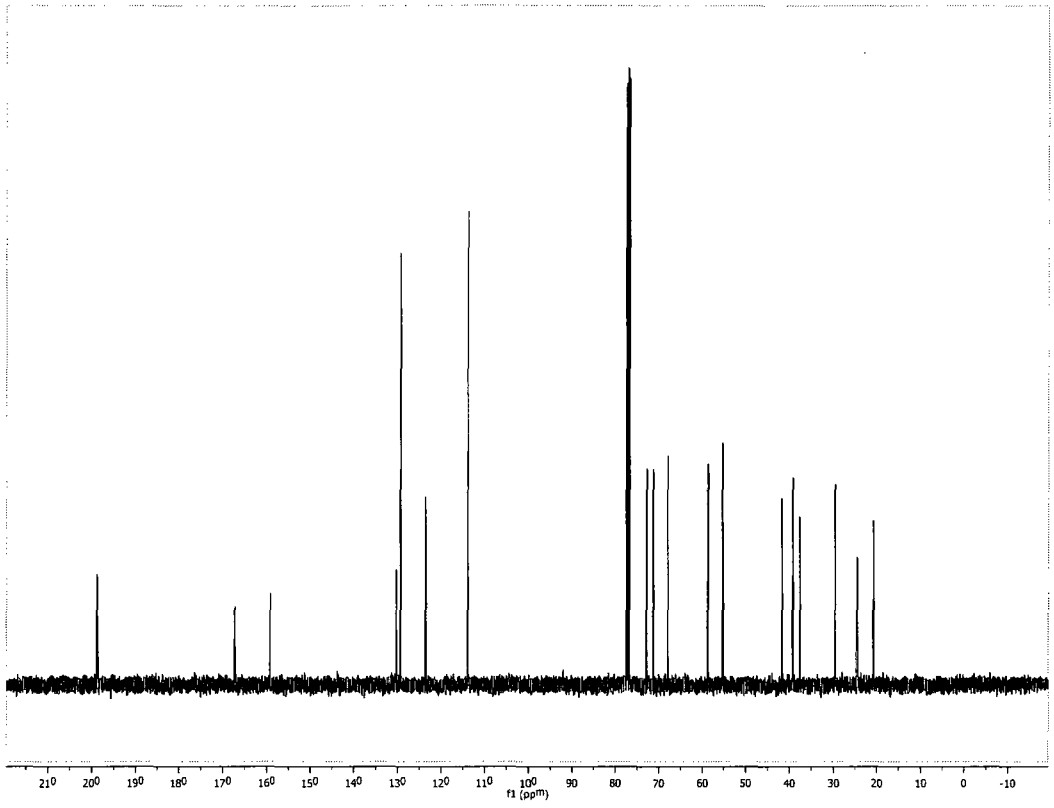
f1 (ppm)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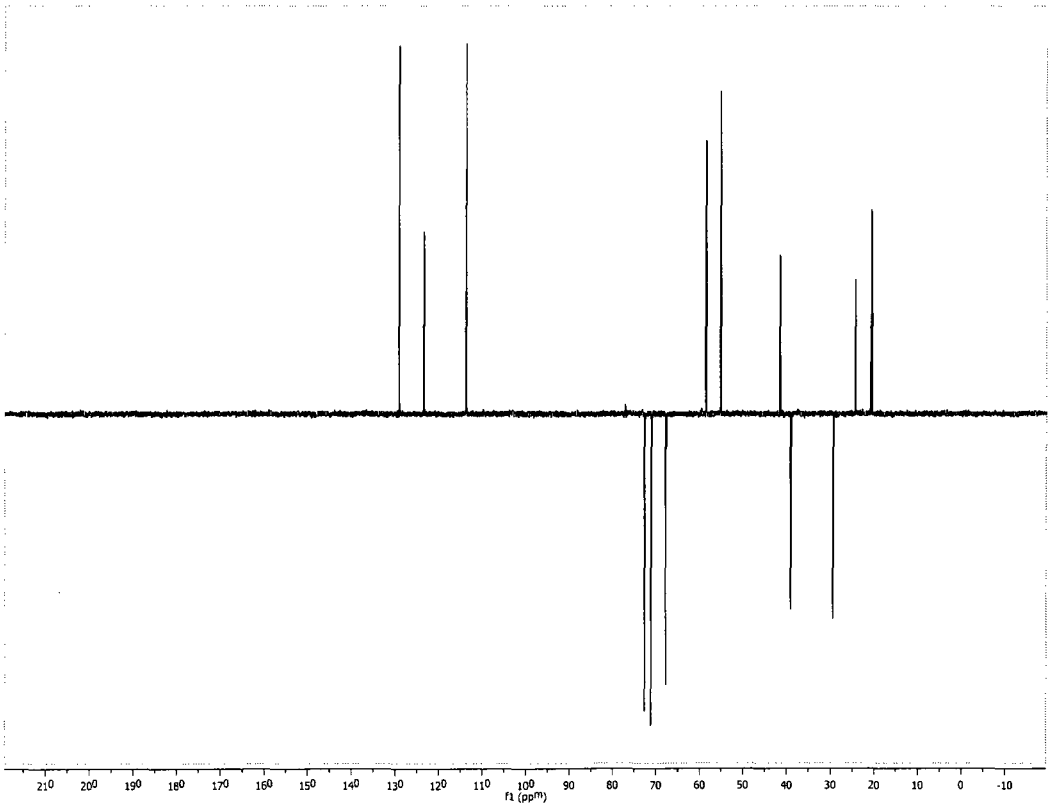
f1 (ppm)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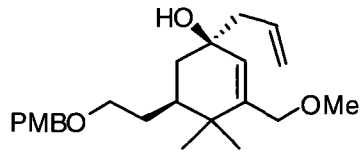
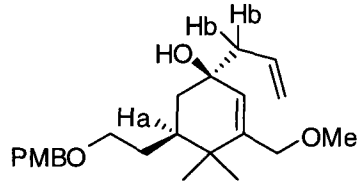
f1 (ppm)

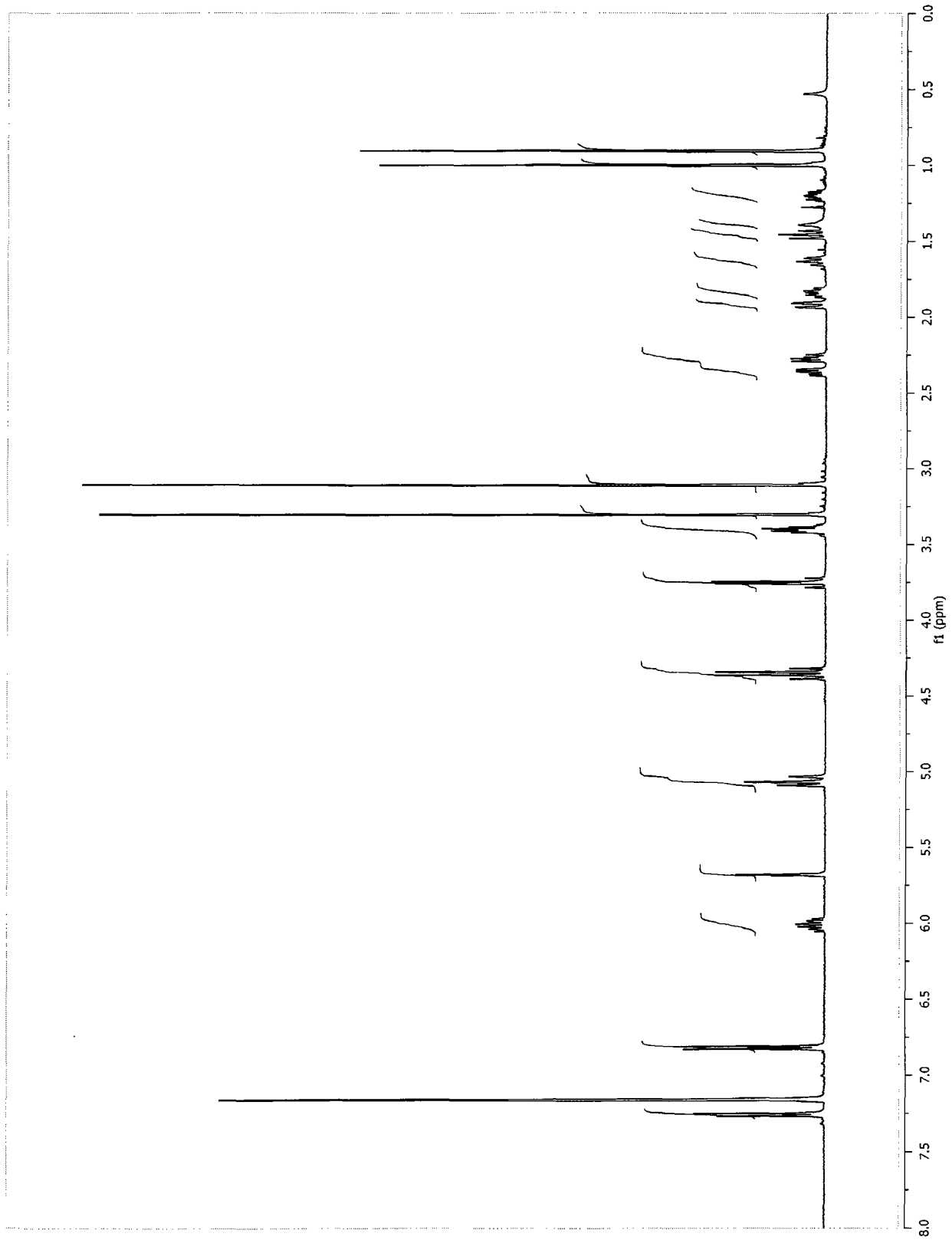
1-Allyl-3-(menzyloxymethyl)-5-[2-(4-methoxybenzyloxy)ethyl]-4,4-dimethylcyclohex-2-enol (2.28)



To a solution of compound **2.27a** (0.400 g, 1.20 mmol, 1 equiv) in THF (10 mL) at -78 °C was added dropwise a solution of allyl magnesium bromide in Et_2O (1.0 M, 3.6 mL, 3.6 mmol, 3 equiv). The mixture was stirred for 1 hour at -78 °C and was slowly warmed to room temperature. Sat NH_4Cl was added in order to quench the reaction. The mixture was extracted with Et_2O (x3). The combined organic fractions were washed with brine (x2), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-40% EtOAc/hexanes) as eluent to afford **2.28a** as colorless oil (447 mg, 99%) The relative stereochemistry was assigned by NOESY experiment. There is a correlation between proton Ha and Hb.



major **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.24 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.01 (dddd, *J* = 17.0, 10.2, 8.0, 6.8 Hz, 1H), 5.68 (br s, 1H), 5.09 – 5.03 (m, 2H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 3.77 (dd, *J* = 12.5, 1.2 Hz, 1H), 3.74 (dd, *J* = 12.5, 1.2 Hz, 1H), 3.42 – 3.37 (m, 2H), 3.30 (s, 3H), 3.11 (s, 3H), 2.36 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.27 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.92 (ddd, *J* = 13.2, 2.7, 1.5 Hx, 1H), 1.84 (dddd, *J* = 13.6, 8.6, 6.7, 1.9 Hz, 1H), 1.63 (tt, *J* = 11.4, 2.3 Hz, 1H), 1.45 (t, *J* = 12.6 Hz), 1.39 (br s, 1H), 1.20 (dddd, *J* = 13.7, 10.6, 5.2, 5.2 Hz, 1H), 1.00 (s, 3H), 0.90 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.8 (C), 142.2 (C), 134.7 (CH), 131.3 (C), 131.2 (CH), 129.4 (CH), 118.2 (CH_2), 114.1 (CH), 73.4 (CH_2), 72.9 (CH_2), 70.6 (C), 68.9 (CH_2), 57.6 (CH_3), 54.8 (CH_3), 46.5 (CH_2), 40.5 (CH), 37.2 (C), 37.0 (CH_2), 30.2 (CH_2), 25.3 (CH_3), 21.2 (CH_3) **IR** (neat, cm^{-1}) 3435 (s), 2937 (s), 2868 (s), 1610 (m), 1515 (m), 1245 (s), 1089 (s) **HRMS** (EI) m/z $(M-C_3H_5)^+$ calculated for $C_{20}H_{29}O_4$ 333.2066, found 333.2049 (1.1%)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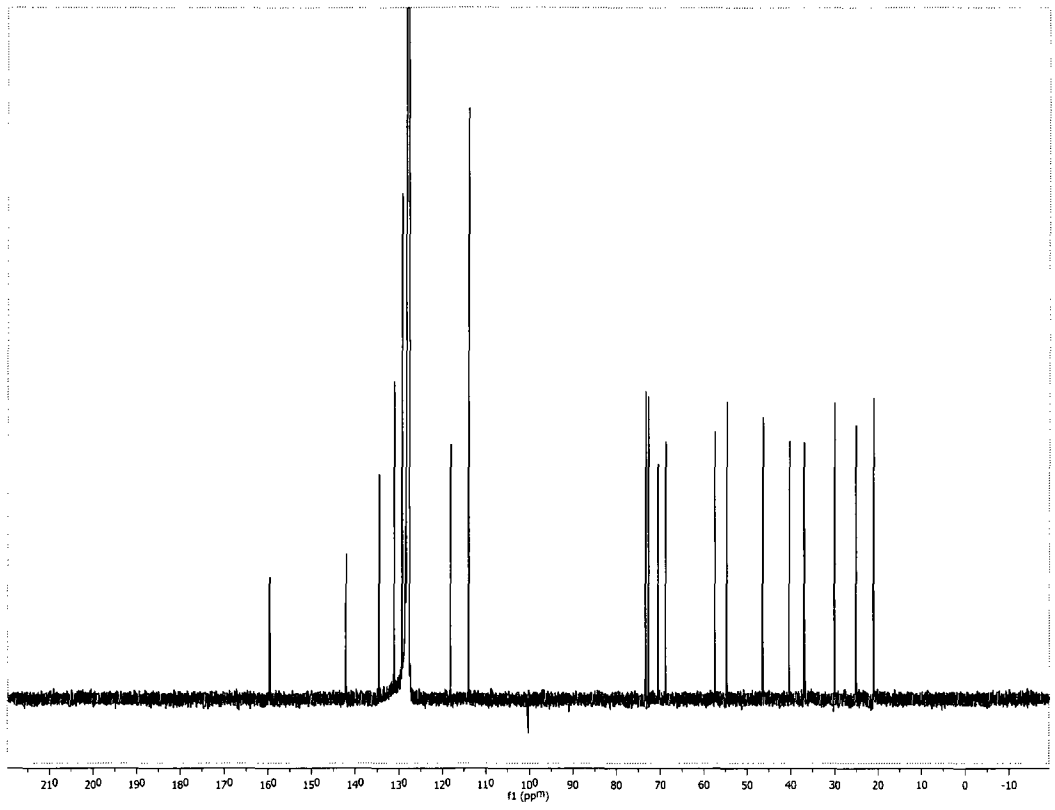
f1 (ppm)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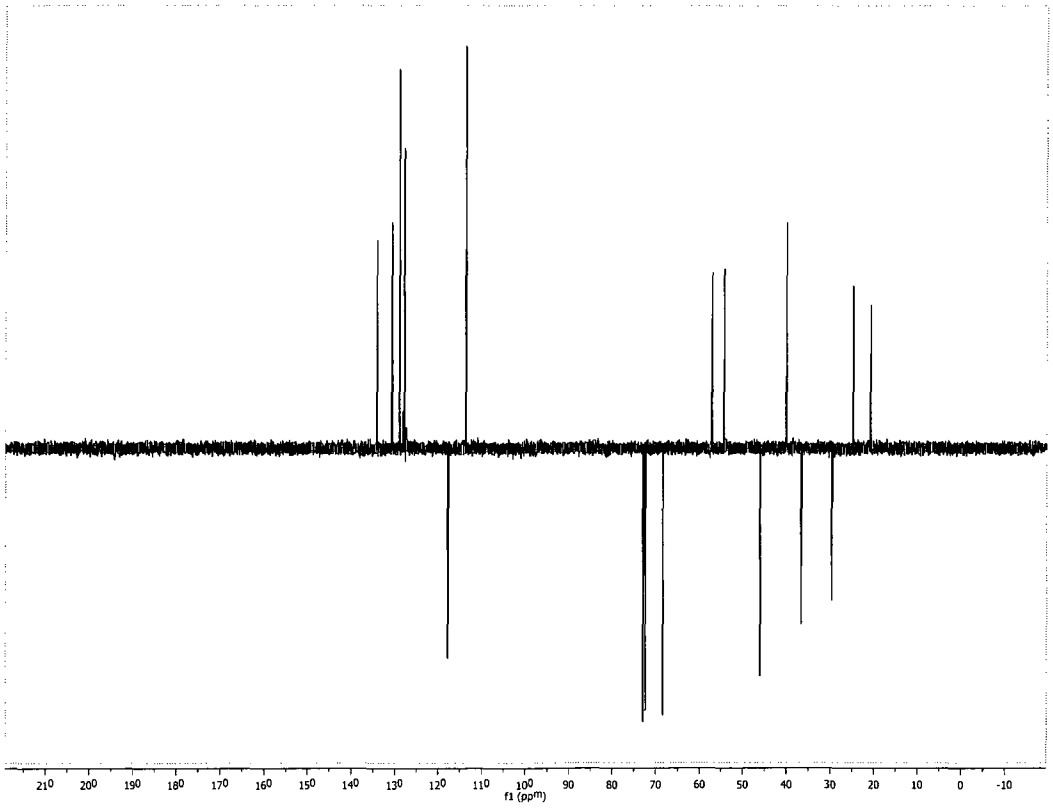
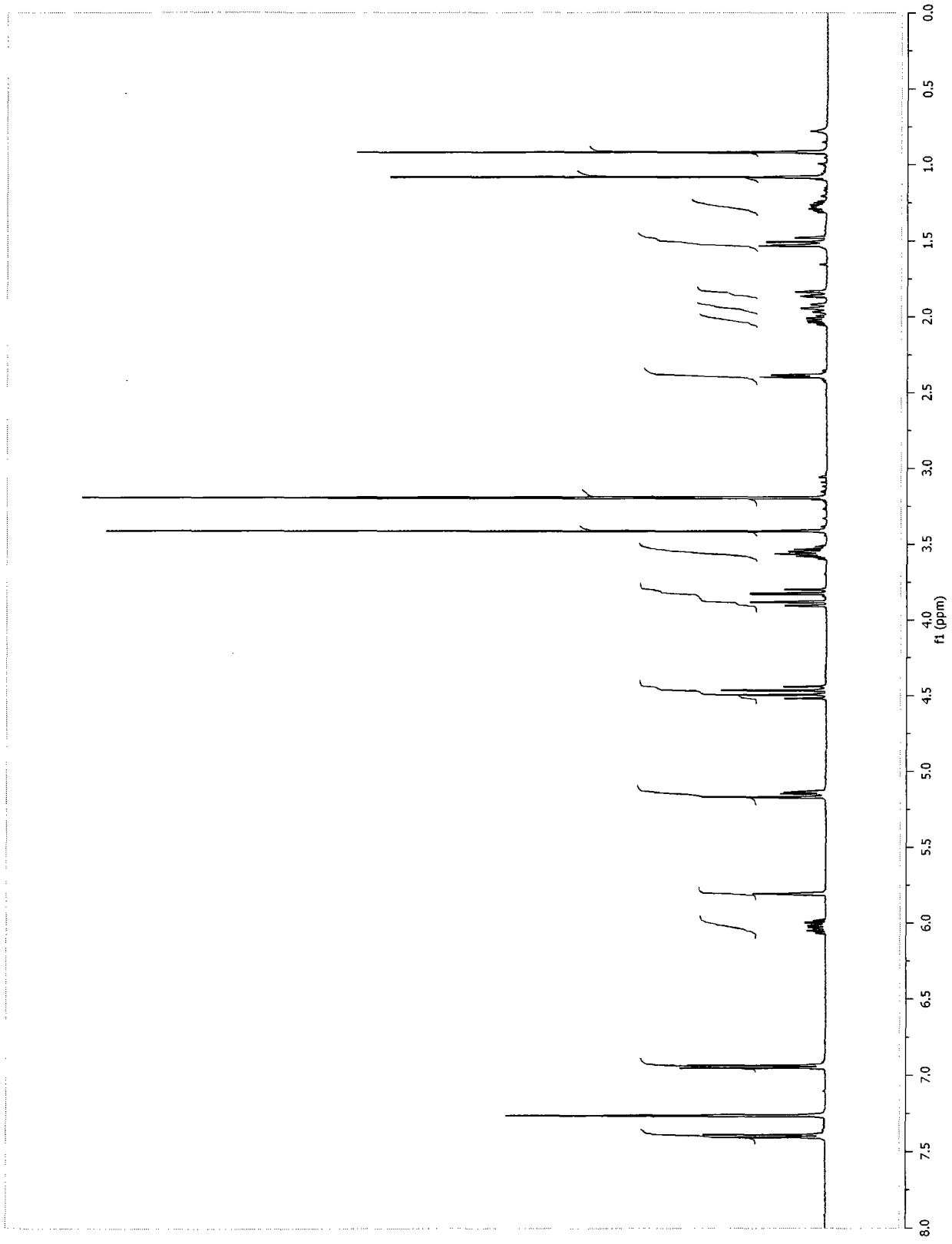
f1 (ppm)


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

minor **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.30 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.92 (dddd, *J* = 16.0, 11.4, 7.4, 7.3 Hz, 1H), 5.70 (d, *J* = 1.5 Hz, 1H), 5.06 (br s, 1H), 5.05 – 5.02 (m, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 3.79 (dd, *J* = 12.7, 1.3 Hz, 1H), 3.71 (dd, *J* = 12.7, 1.3 Hz, 1H), 3.49 – 3.41 (m, 2H), 3.31 (s, 3H), 3.09 (s, 3H), 2.30 – 2.27 (m, 2H), 1.92 (dddd, *J* = 13.6, 7.7, 7.7, 1.8 Hz, 1H), 1.84 (dddd, *J* = 13.0, 10.6, 2.4, 2.4 Hz, 1H), 1.74 (ddd, *J* = 13.9, 2.8, 1.9 Hz, 1H), 1.40 (t, *J* = 13.5 Hz, 1H), 1.41 (br s, 1H), 1.17 (dddd, *J* = 13.5, 10.7, 6.1, 4.7 Hz, 1H), 0.98 (s, 3H), 0.81 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.7 (C), 145.0 (C), 134.7 (CH), 131.5 (C), 129.4 CH), 128.7 (CH), 118.0 (CH_2) 114.1 (CH), 73.4 (CH_2), 72.8 (CH_2). 69.1 (CH_2), 69.0 (C), 57.7 (CH_3), 54.8 (CH_3), 48.0 (CH_2), 37.7 (CH), 37.6 (CH_2), 37.0 (C), 30.3 (CH_2), 24.2 (CH_3), 20.0 (CH_3) **IR** (neat, cm^{-1}) 3438 (s), 2937 (s), 2872 (s), 1610 (m), 1511 (m), 1245 (s), 1093 (s) **HRMS** (EI) m/z $(M-H_2O)^+$ calculated for $C_{23}H_{32}O_3$ 356.2351, found 356.2333 (1.2%)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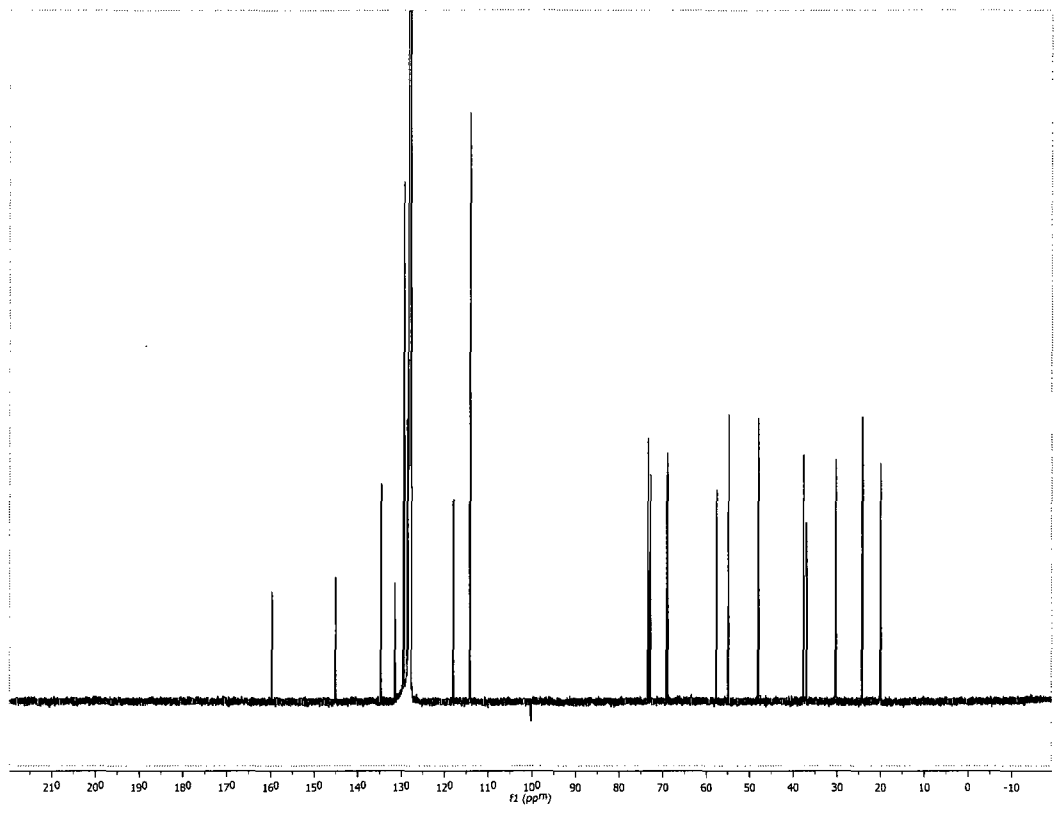
f1 (ppm)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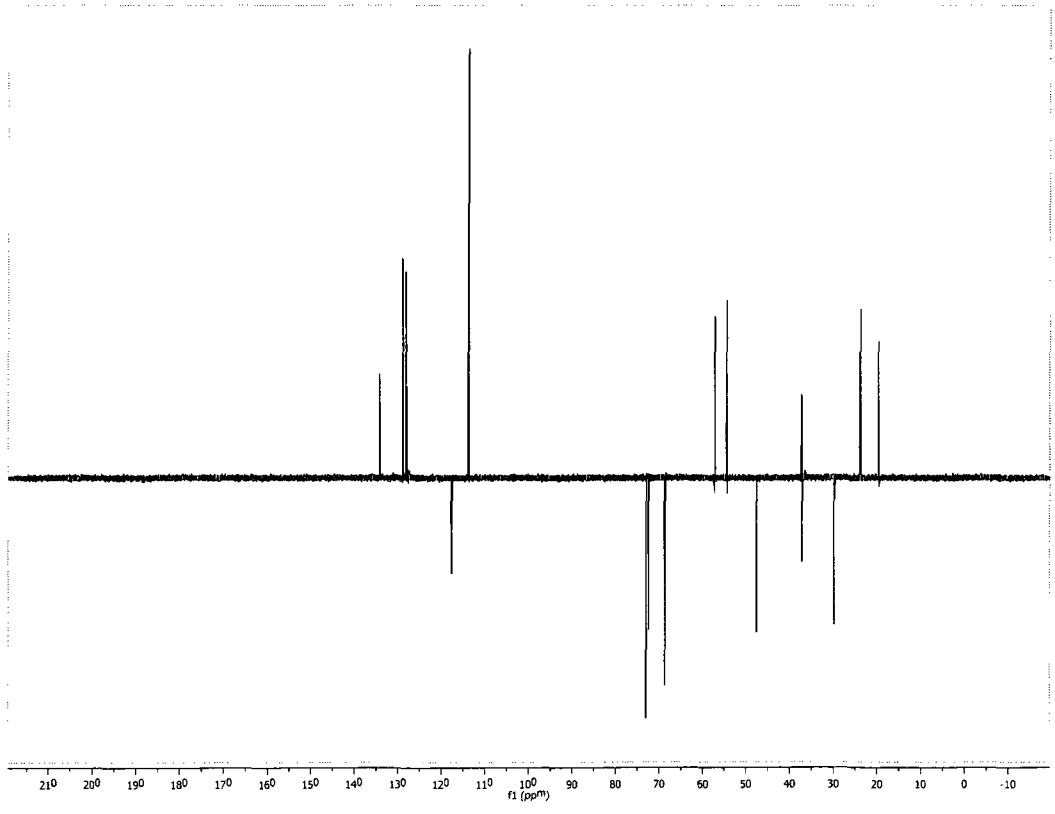
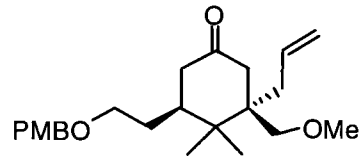
f1 (ppm)

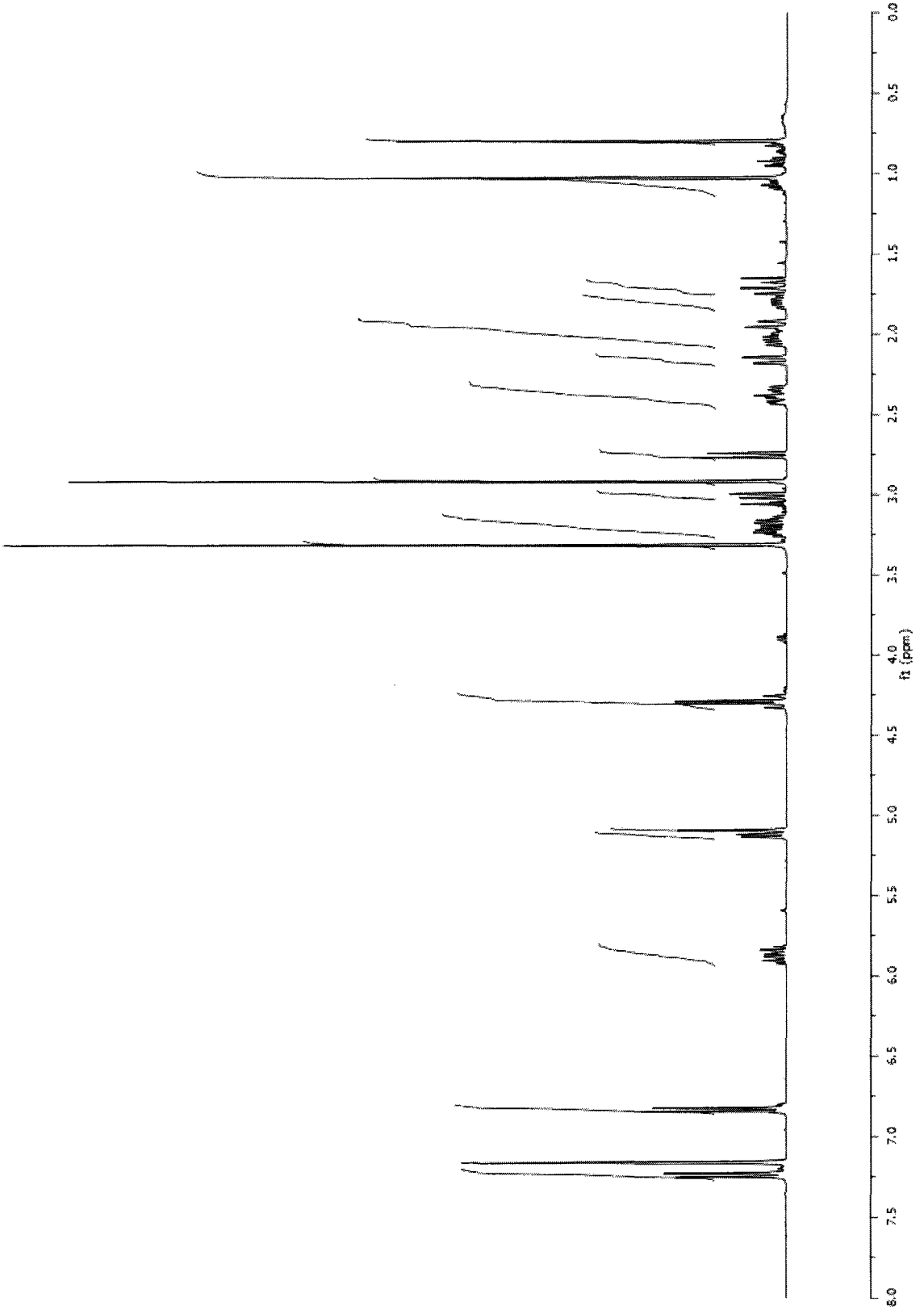

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

3-allyl-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethylcyclohexanone (2.29a)



KH was washed 3 times with freshly distilled pentane (over CaH_2). Compound **2.28a** was co-evaporated 3 times with freshly distilled benzene (over CaH_2). To a suspension of KH (30% dispersion in mineral oil, 0.650 g, 4.86 mmol, 5 equiv) in 8 mL of THF was added *via* canula a solution of compound **2.28a** (0.400 g, 0.97 mmol, 1 equiv, mixture of diatereoisomers) and 18-crown-6 (1.29 g, 4.86 mmol, 5 equiv) in THF (8 mL). The mixture was heated for 30 minutes at reflux. The mixture was then cooled to room temperature. MeOH was added in order to quench the reaction followed by sat NH_4Cl. The mixture was extracted with Et_2O (3x). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-30% EtOAc/hexanes) to afford **2.29a** as a colorless oil (211 mg, 53%).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.24 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.87 (dddd, J = 16.4, 10.7, 7.5, 7.5 Hz, 1H), 5.14 – 5.11 (m, 1H), 5.09 (br s, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.28 (d, J = 11.7 Hz, 1H), 3.31 (s, 3H), 3.23 (ddd, J = 9.2, 6.9, 5.0 Hz, 1H), 3.17 (ddd, J = 9.1, 8.1, 5.9 Hz, 1H), 3.01 (d, J = 10.0 Hz, 1H), 2.92 (s, 3H), 2.75 (d, J = 10.0 Hz, 1H), 2.41 (ddd, J = 14.3, 4.5, 2.3 Hz, 1H), 2.35 (dd, J = 13.6, 7.6, Hz, 1H), 2.16 (dd, J = 14.2, 2.3 Hz, 1H), 2.04 (dd, J = 13.3, 7.0 Hz, 1H), 2.02 – 1.96 (m, 1H), 1.94 (dd, J = 14.2, 0.9 Hz, 1H), 1.80 (dddd, J = 13.5, 8.2, 7.1, 2.2 Hz, 1H), 1.71 (dd, J = 13.9, 13.9 Hz, 1H), 1.11 – 1.02 (m, 1H), 1.03 (s, 3H), 0.80 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 208.6 (C), 159.8 (C), 134.9 (CH), 131.2 (C), 129.4 (CH), 119.0 (CH_2), 114.2 (CH), 75.8 (CH_2), 72.9 (CH_2), 68.5 (CH_2), 58.4 (CH_3), 54.8 (CH_3), 47.9 (C), 44.0 (CH_2), 43.7 (CH_2), 40.8 (CH), 38.9 (C), 35.1 (CH_2), 31.1 (CH_2), 23.1 (CH_3), 17.5 (CH_3) **IR** (neat, cm^{-1}) 2922 (s), 2875 (s), 1709 (s), 1611 (m), 1513 (m), 1247 (s), 1094 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{23}H_{34}O_4$ 374.2457, found 374.2457 (1.1%)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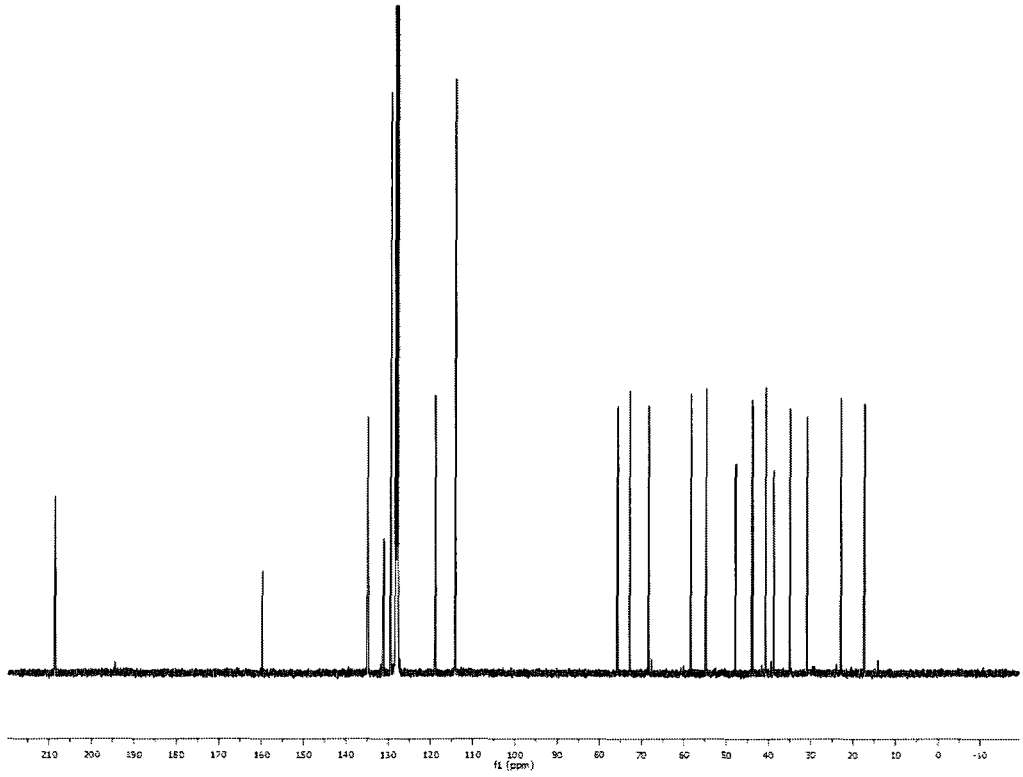
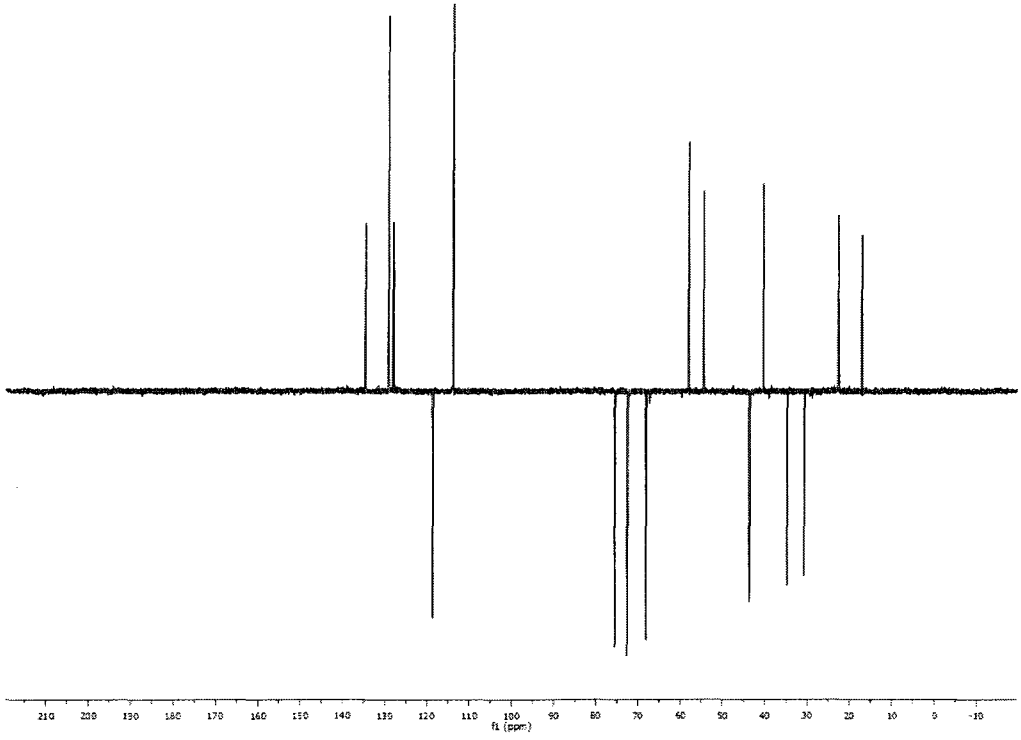
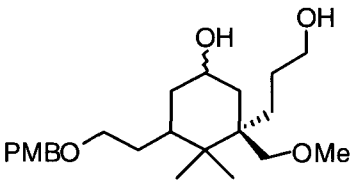
f1 (ppm)


f1 (ppm)

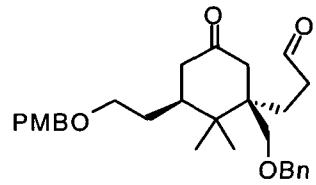

f1 (ppm)

3-(3-hydroxypropyl)-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethylcyclohexanol (2.30a)



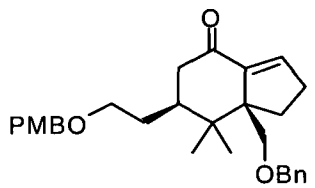
Compound **2.29a** was co-evaporated twice with freshly distilled benzene (over CaH_2). To a solution of compound **2.29a** (0.226g, 0.603 mmol, 1 equiv) in THF (6 mL) was added $BH_3 \cdot Me_2S$ (86 µL, 0.905 mmol, 1.5 equiv) dropwise. The mixture turned yellow upon addition. The mixture was stirred at room temperature for 1 hour. A 1:1 mixture (28 mL) of 30% (w/w) aqueous hydrogen peroxide and 3M aqueous NaOH was added dropwise at 0 °C followed by 4 mL of THF. The mixture was then heated at reflux for 1 hour, cooled to room temperature and extracted with Et_2O (x4). Combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a slow gradient (50-80% EtOAc/hexanes) as eluent to give **2.30a** (188 mg, 79%, 1:1 mixture of diastereoisomers) as a colorless oil. The compound was contaminated and could not be purified even after multiple flash chromatographies. Thus, it was used in the next step without full characterization

3-(1-(benzyloxymethyl)-3-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl-5-oxocyclohexyl)propanal (2.31b)



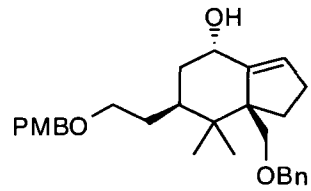
To a mixture of compound **2.30b** (1.33 g, 2.83 mmol, 1.0 equiv) in DCM (30 mL) was added PCC (2.44 g, 11.3 mmol, 4.0 equiv). The mixture was stirred for 1 hour at room temperature, diluted with Et_2O and filtered through a pad of Celite. The solvents were evaporated and the resulting residue was directly used in the next step without further purification.

(6S,7aS)-7a-(benzyloxymethyl)-6-(2-(4-methoxybenzyloxy)ethyl)-7,7-dimethyl-5,6,7,7a-tetrahydro-1H-inden-4(2H)-one (2.32b)



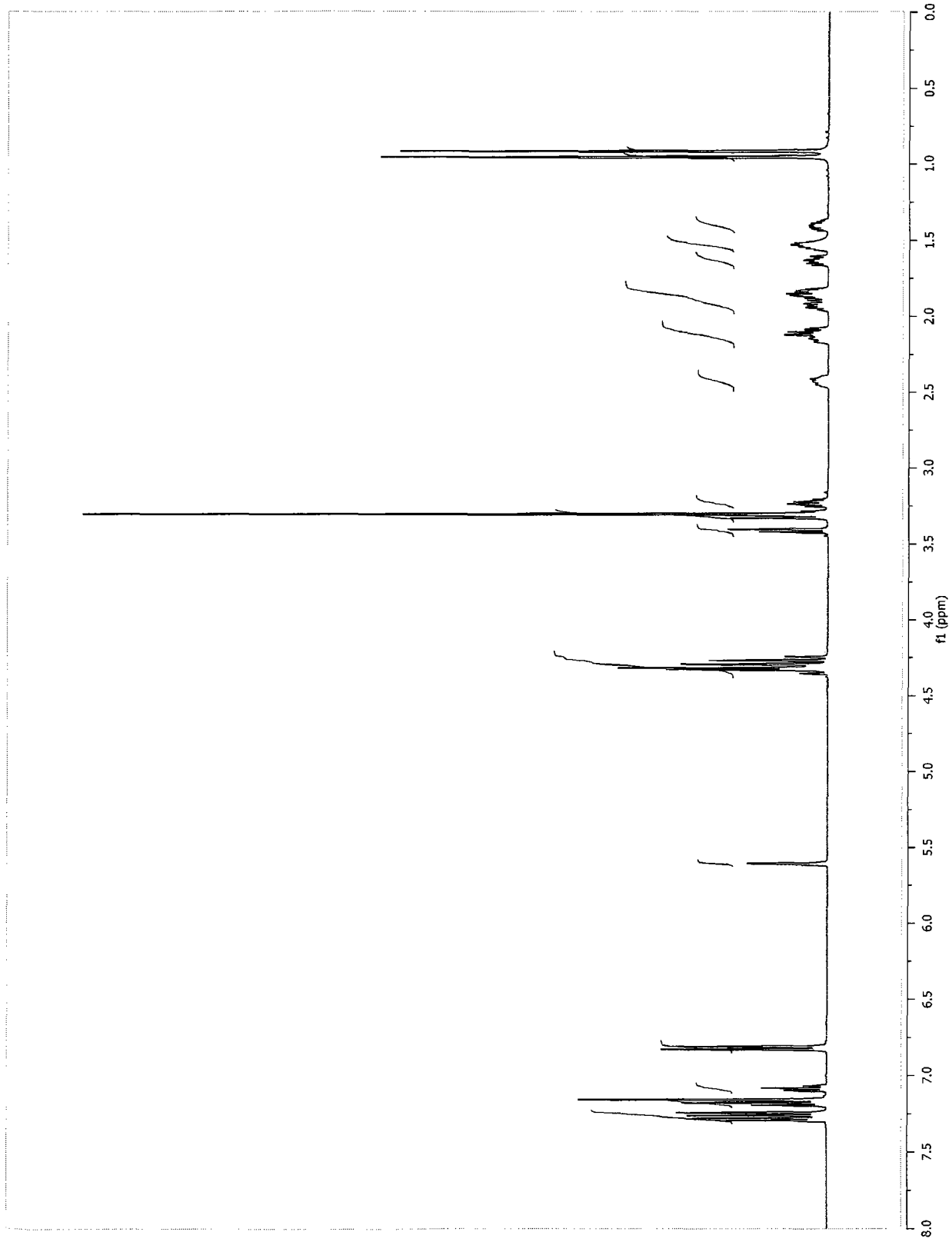
A solution of crude **2.31b** in THF (26 mL) was prepared and was divided in 13 fractions of 2 mL each. To each fraction was added 2 mL of a KO*t*Bu solution in THF (prepared from 1.68 g of KO*t*Bu and 28 mL of THF). Each flask was sealed with a cap and parafilm. The reaction mixtures were stirred overnight at room temperature and quenched by addition of sat NH_4Cl. The mixture were combined for the work-up. The aqueous phase was extracted Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure and the resulting residue was used in the next step without further purification.

7a-(benzyloxymethyl)-6-(2-(4-methoxybenzyloxy)ethyl)-7,7-dimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-ol (2.33b)



To a mixture of crude **2.32b** in MeOH (30 mL) was added $CeCl_3 \cdot 7H_2O$ (1.012 g, 2.71 mmol, 1.0 equiv) at 0 °C. The mixture was stirred for 5 minutes followed by addition of $NaBH_4$ (0.257 g, 6.77 mmol, 2.5 equiv) in small portions. The resulting mixture was stirred at 0 °C for 2 hours and quenched with sat NH_4Cl. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (20-30% EtOAc/hexanes) as eluent to afford **2.33b** as a colorless oil (0.381g, 31% yield over 3 steps). See **2.34b** for the relative stereochemistry assignment.

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.29 (d, J = 7.2 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 5.61 (d, J = 2.0 Hz, 1H), 4.34 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 12.2 Hz, 1H), 4.26 (d, J = 12.2 Hz, 1H), 3.41 (d, J = 9.1 Hz, 1H), 3.32 (d, J = 9.1 Hz, 1H), 3.31 (s, 3H), 3.31 – 3.28 (m, 1H), 3.23 (dd, J = 16.0, 7.3 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.18 – 2.08 (m, 2H), 1.96 – 1.82 (m, 3H), 1.62 (ddd, J = 12.7, 10.2, 5.9 Hz, 1H), 1.56 – 1.52 (m, 2H), 1.44 – 1.37 (m, 1H), 0.95 (s, 3H), 0.92 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.7 (C), 149.3 (C), 139.5 (C), 131.4 (C), 129.4 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 120.7 (CH), 114.1 (CH), 73.9 (CH_2), 73.4 (CH_2), 72.8 (CH_2), 70.2 (CH_2), 65.8 (CH), 59.5 (C), 54.8 (CH_3), 43.1 (CH), 39.7 (C), 37.7 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 27.3 (CH_3), 21.9 (CH_3) **IR** (neat, cm^{-1}) 3426 (s), 2933 (s), 2851 (s), 1610 (m), 1513 (m), 1246 (s), 1094 (s) **HRMS** (EI) m/z $(M-C_8H_9O)^+$ calculated for $C_{21}H_{29}O_3$ 329.2117, found 329.2110 (3.6%)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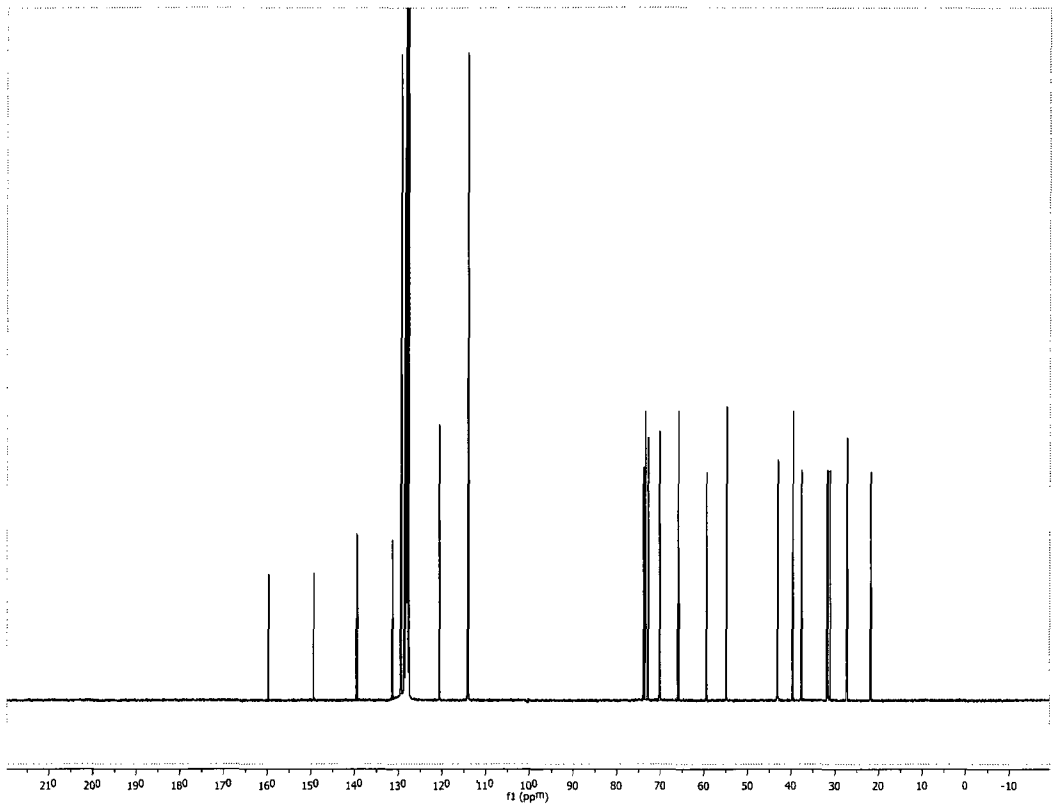
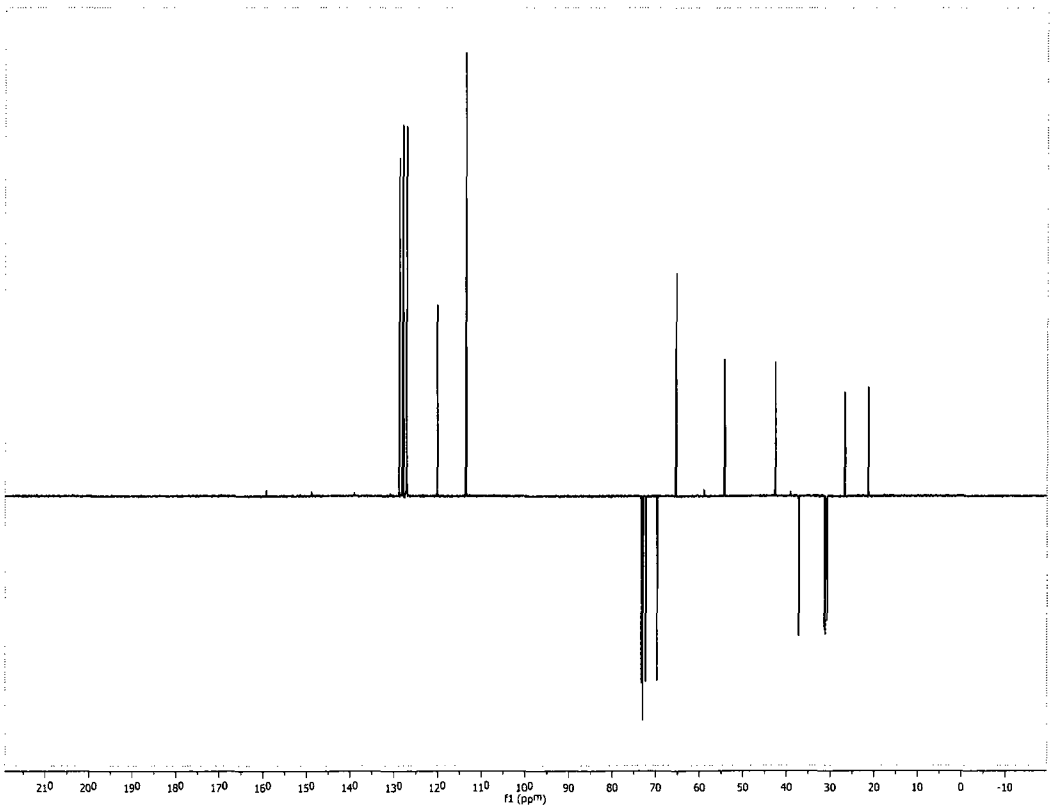
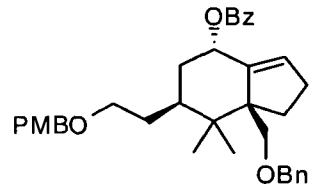
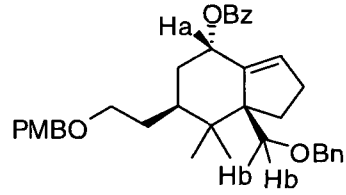

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


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

7a-(benzyloxymethyl)-6-(2-(4-methoxybenzyloxy)ethyl)-7,7-dimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-4-yl benzoate (2.34b)

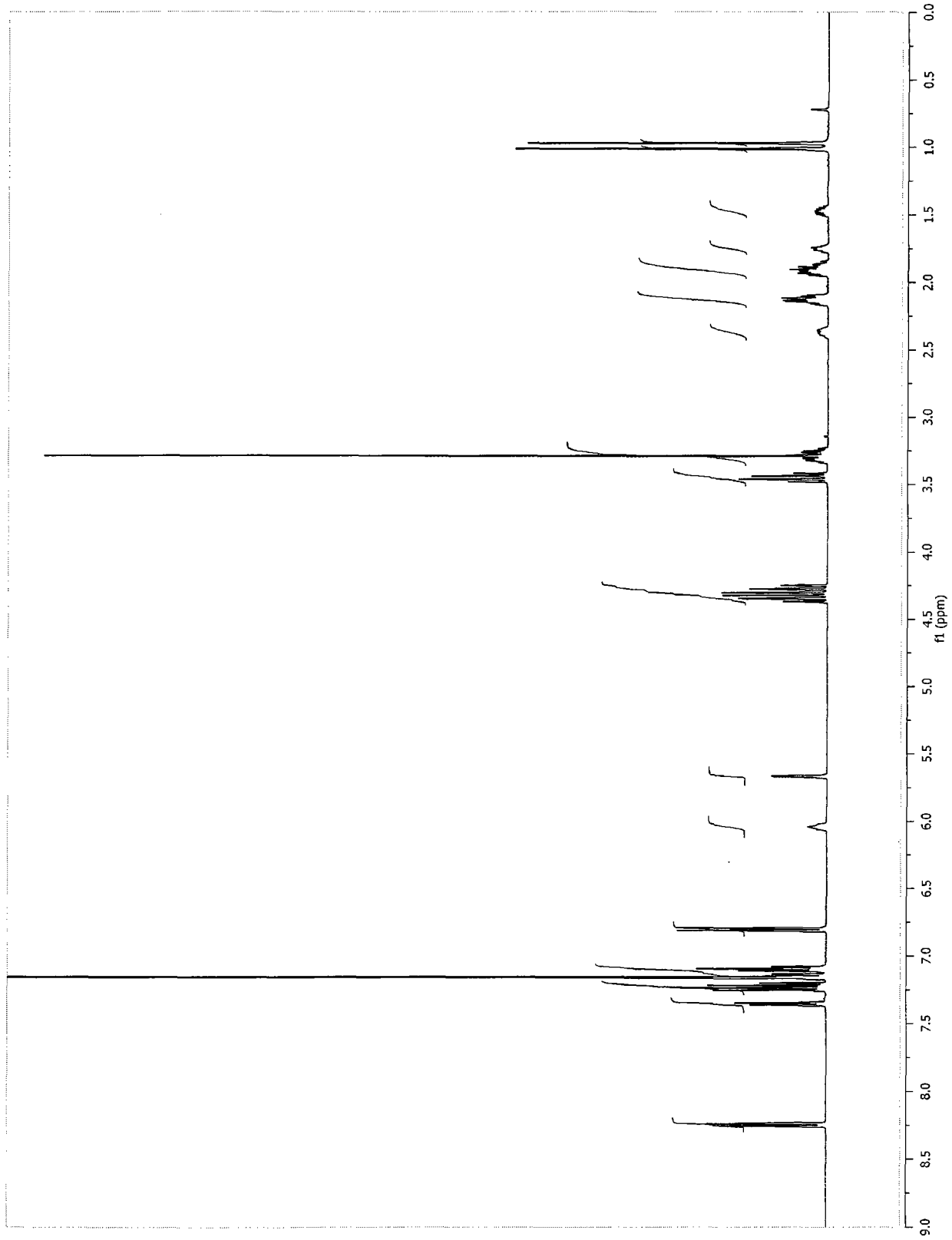


To a mixture of compound **2.33b** (0.373 g, 0.828 mmol, 1.0 equiv) in DCM (8 mL) were sequentially added benzoyl chloride (0.15 mL, 1.24 mmol, 1.5 equiv), pyridine (0.20 mL, 2.48 mL, 3.0 equiv) and DMAP (0.010 g, 0.083 mmol, 0.1 equiv). The reaction mixture was stirred overnight at room temperature and was then quenched with sat NH_4Cl. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with sat $NaHCO_3$, with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/ benzene) to afford **2.34b** as a colorless oil (0.366 g, 89% yield). The relative stereochemistry was assigned by NOESY experiment. There is a correlation between proton Ha and Hb.



^{1}H NMR (500 MHz, C_6D_6) δ ppm 8.26 – 8.24 (m, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.26 – 7.20 (m, 4H), 7.15 – 7.13 (m, 1H), 7.11 – 7.08 (m, 3H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.06 – 6.02 (m, 1H), 5.67 (d, *J* = 2.2 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.26 (d, *J* = 12.1 Hz, 1H), 3.47 (d, *J* = 9.3 Hz, 1H), 3.43 (d, *J* = 9.3 Hz, 1H), 3.32 (ddd, *J* = 9.1, 6.7, 5.0 Hz, 1H), 3.26 (ddd, *J* = 8.7, 8.7, 5.9 Hz, 1H), 3.29 (s, 3H), 2.41 – 2.35 (m, 1H), 2.17 – 2.09 (m, 3H), 1.94 – 1.84 (m, 3H), 1.75 (dtd, *J* = 10.4, 5.8, 1.8 Hz, 1H), 1.47 (dddd, *J* = 13.5, 10.6, 5.4, 5.4 Hz, 1H), 1.01 (s, 3H), 0.97 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 165.7 (C), 159.7 (C), 144.5 (C), 139.5 (C), 132.9 (CH), 131.4 (C), 130.0 (CH), 129.4 (CH), 128.62

(CH), 128.60 (C), 128.58 (CH), 127.8 (CH), 127.6 (CH), 122.1 (CH), 114.1 (CH), 73.4 (CH_2), 73.2 (CH_2), 72.7 (CH_2), 69.7 (CH), 69.5 (CH_2), 59.6 (C), 54.8 (CH_3), 42.2 (CH), 39.4 (C), 34.4 (CH_2), 31.5 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 26.9 (CH_3), 21.5 (CH_3) **IR** (neat, cm^{-1}) 2951 (s), 2855 (s), 1718 (s), 1609 (m), 1512 (m), 1273 (s), 1246 (s), 1111 (s), 711 (s) **HRMS** (EI) m/z (M-$C_{15}H_{15}O_3$)$^+$ calculated for $C_{21}H_{27}O_2$ 311.2011, found 311.1986 (8.6%)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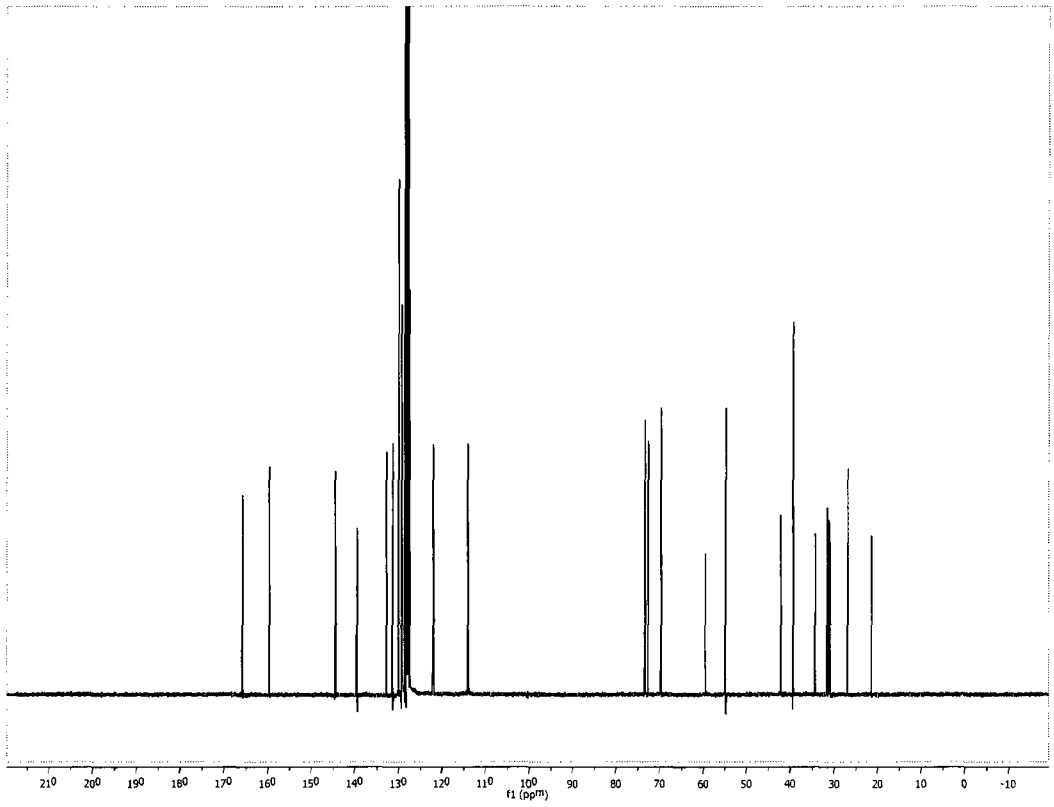
9.0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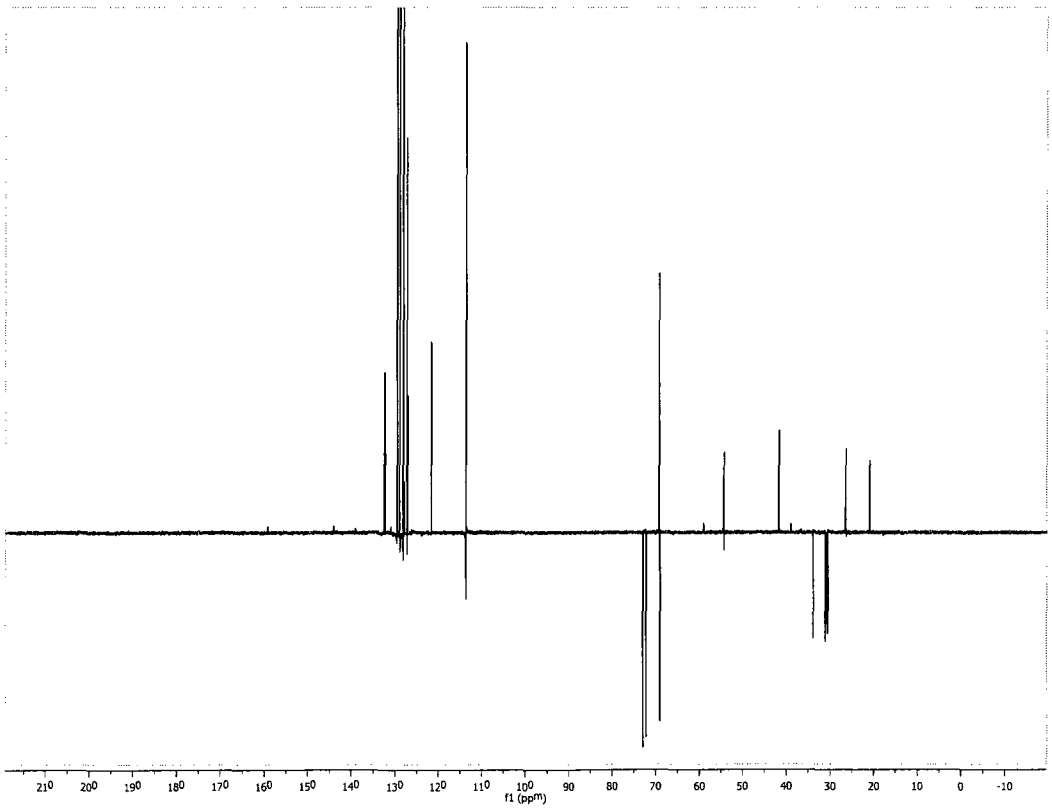
f1 (ppm)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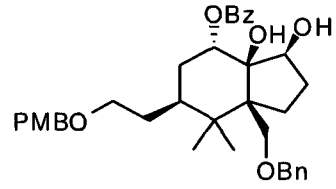
f1 (ppm)

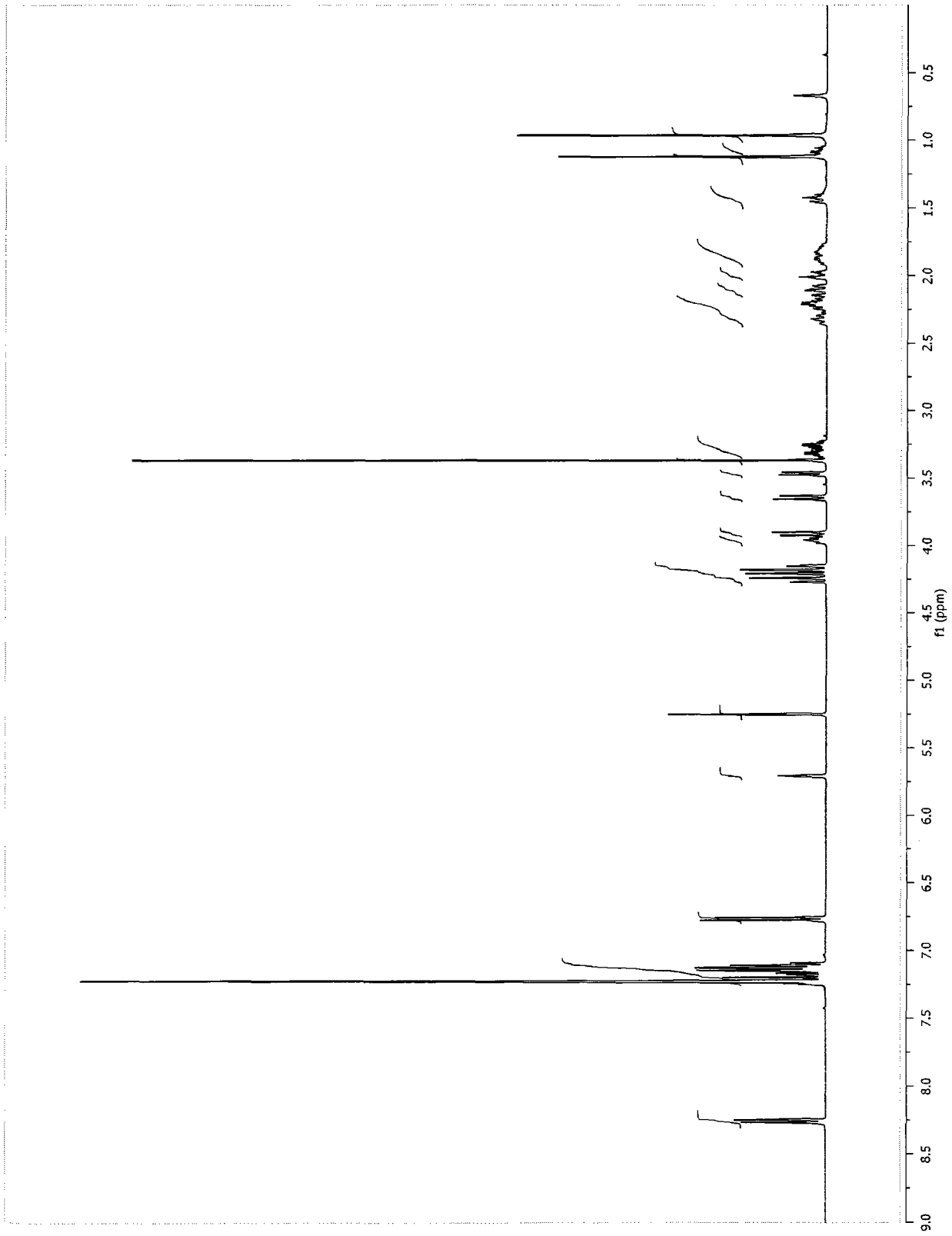
7a-(benzyloxymethyl)-3,3a-dihydroxy-6-(2-(4-methoxybenzyloxy)ethyl)-7,7-dimethyloctahydro-1H-inden-4-yl benzoate (2.35b)



The reaction was performed in a sealed tube. To a solution of **2.34b** (0.366 g, 0.660 mmol, 1.0 equiv) and NMO (0.155g, 1.32 mmol, 2.0 equiv) in a 3:1 mixture of THF and water (5 mL) was added a 4% w/w aqueous solution of OsO_4 (0.16 mL, 0.026 mmol, 0.04 equiv). The mixture was stirred overnight at 140°C in the dark. The mixture was cooled down to room temperature. Additional NMO (0.155g, 1.32 mmol, 2.0 equiv) and a 4% w/w aqueous solution of OsO_4 (0.16 mL, 0.026 mmol, 0.04 equiv) were then added and the mixture was stirred at 120°C for 5 hours. The reaction was quenched by addition of sat Na_2SO_3. The aqueous phase was extracted with EtOAc (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 20% EtOAc/hexanes as eluent to afford **2.35b** as a white crystalline solid (0.202 g, 52% yield). Starting material (0.085 g, 23%) was also recovered.

^{1}H NMR (500 MHz, C_6D_6) δ ppm 8.21 – 8.18 (m, 2H), 7.18 – 7.02 (m, 10H), 6.70 (d, J = 8.8 Hz, 2H), 5.64 (t, J = 2.9 Hz, 1H), 5.20 (s, 1H), 4.17 (dd, J = 17.0, 11.7 Hz, 2H), 4.09 (dd, J = 11.7, 2.9 Hz, 2H), 3.91 – 3.88 (m, 1H), 3.84 (d, J = 9.8 Hz, 1H), 3.57 (d, J = 9.8 Hz, 1H), 3.42 (d, J = 6.3 Hz, 1H), 3.30 (s, 3H), 3.25 (ddd, J = 9.2, 6.0, 4.2 Hz, 1H), 3.18 (ddd, J = 9.4, 9.4, 4.5 Hz, 1H), 2.25 (ddt, J = 12.3, 10.3, 2.3 Hz, 1H), 2.19 – 2.08 (m, 2H), 2.04 (ddd, J = 15.0, 12.8, 2.6 Hz, 1H), 1.92 (dt, J = 14.6, 3.2 Hz, 1H), 1.81 (dddd, J = 13.8, 9.5, 5.9, 1.8 Hz, 1H), 1.77 – 1.71 (m, 1H), 1.38 – 1.33 (m, 1H), 1.05 (s, 3H), 1.01 (dddd, J = 14.3, 10.3, 4.3, 4.3 Hz, 1H), 0.89 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 165.6 (C), 159.5 (C), 137.7 (C), 133.0 (CH), 131.41 (C), 131.35 (C), 129.8 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 114.0 (CH), 81.1 (C), 77.0 (CH), 76.8 (CH), 73.9 (CH_2), 73.8 (CH_2), 72.8 (CH_2), 68.6 (CH_2), 54.8 (CH_3), 52.1 (C), 37.7 (C), 33.5 (CH), 31.3 (CH_2), 30.4 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 24.0

(CH_3), 18.4 (CH_3) **IR** (neat, cm^{-1}) 3384 (s), 2952 (s), 2858 (s), 1715 (s), 1512 (m), 1271 (s), 1249 (s), 1094 (s), 710 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{36}H_{44}O_7$ 588.3087, found 588.3080 (2.3%)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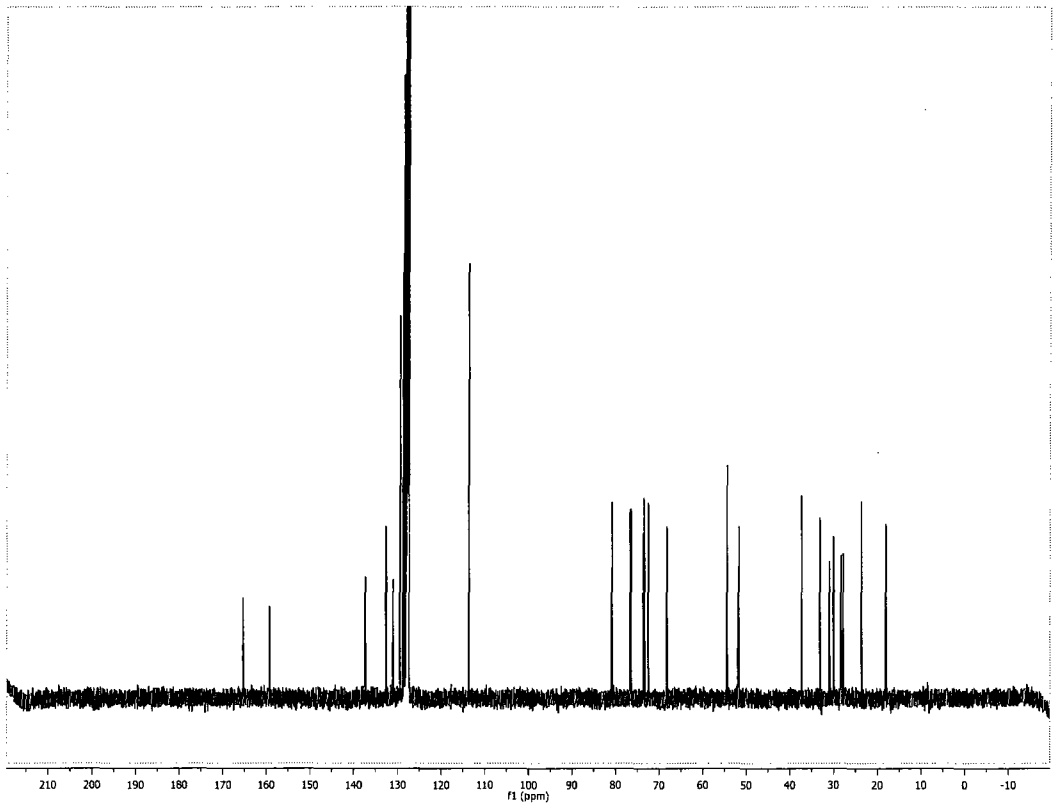
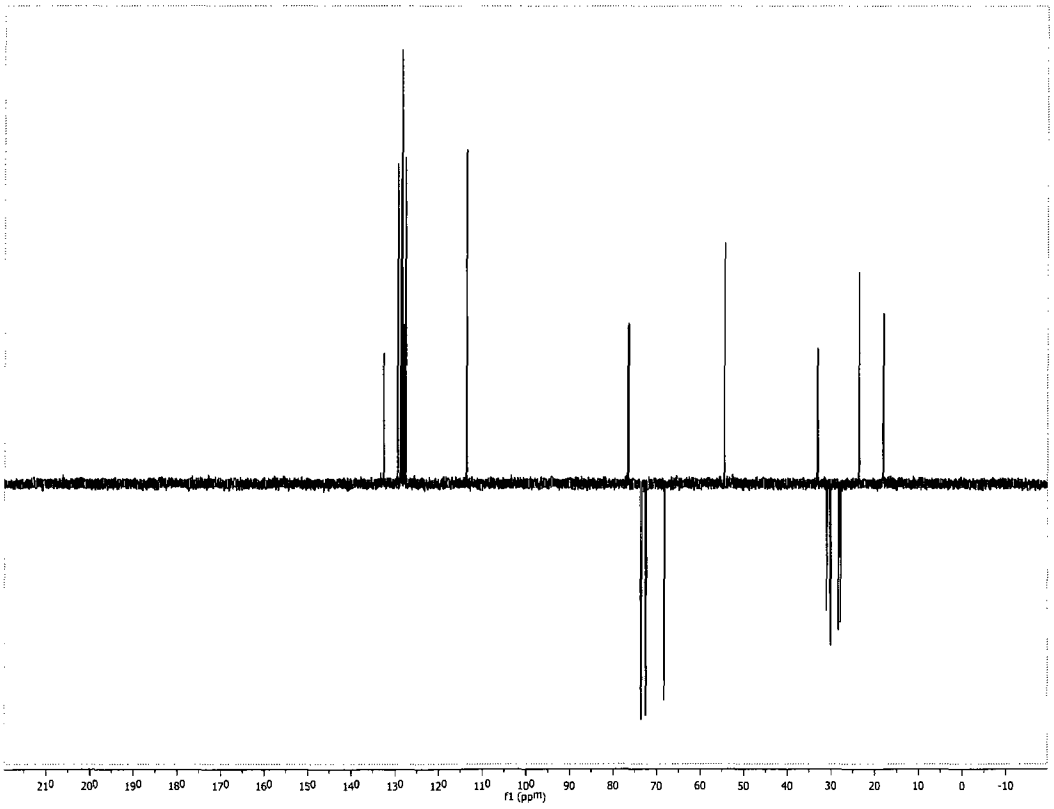
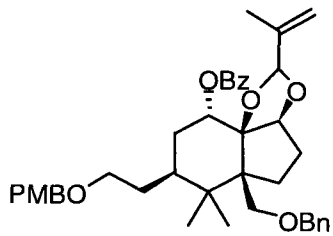
1.5
1.0
0.5


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


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

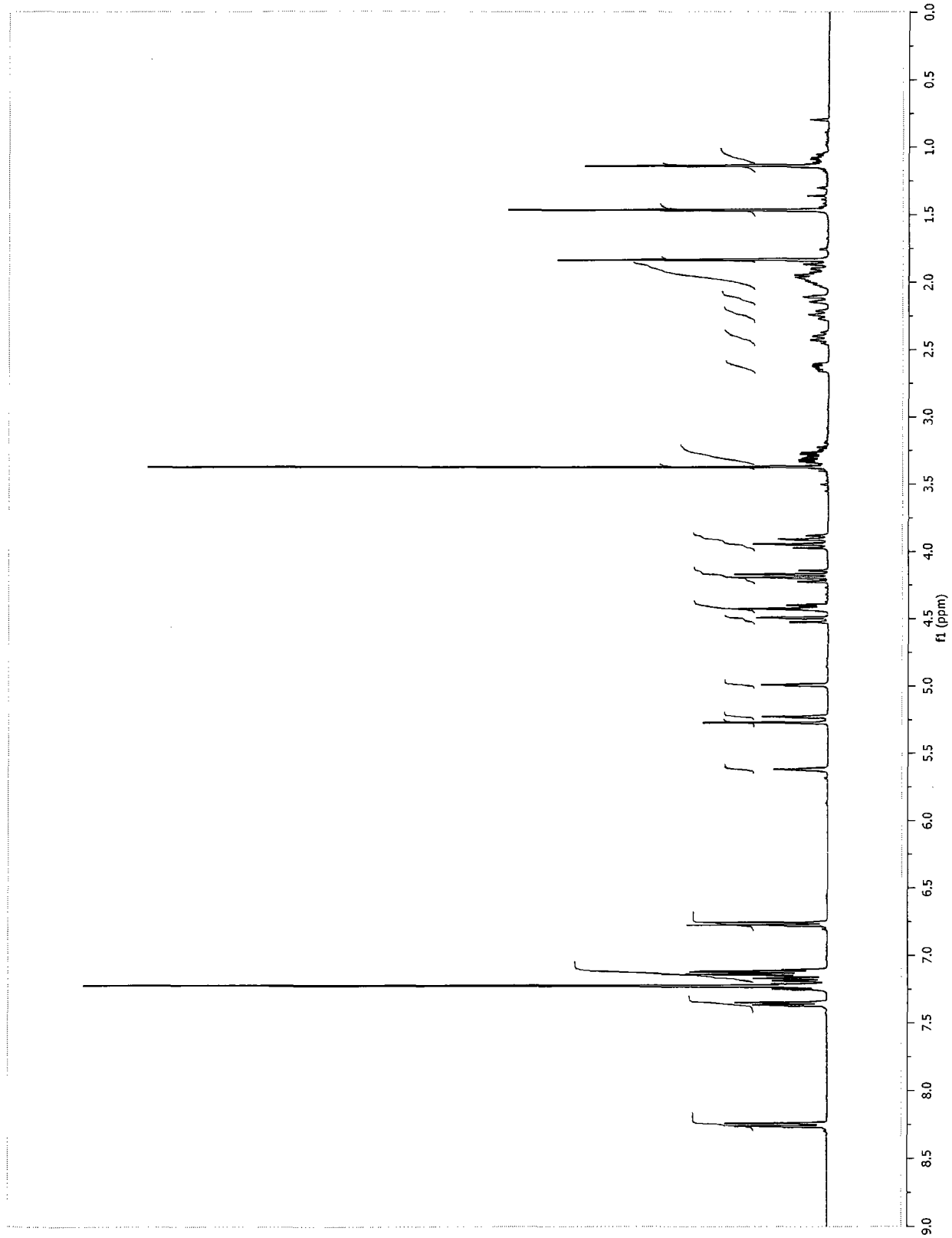
5a-(benzyloxymethyl)-7-(2-(4-methoxybenzyloxy)ethyl)-6,6-dimethyl-2-(prop-1-en-2-yl)octahydroindeno[1-d][1,3]dioxol-9-yl benzoate (2.36b)



To a solution of compound **2.35b** (0.135 g, 0.229 mmol, 1.0 equiv) in DME (2 mL) was added a solution of methacrolein dimethylacetal (0.053 g, 0.459 mmol, 2.0 equiv) in 3 mL of DME *via* canula. Tin(II) chloride (4 mg, 23 mmol, 0.1 equiv) was then added. The resulting mixture was stirred 1.5 hour at reflux and cooled to room temperature. The reaction was quenched by addition of sat $NaHCO_3$. Et_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (pretreated with Et_3N) using a gradient (0%-5%-10% EtOAc/hexanes) as eluent to give compound **2.36b** (130 mg, 88% yield)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 8.20 – 8.18 (m, 2H) 7.29 (d, *J* = 7.0 Hz, 2H), 7.19 - 7.04 (m, 8H), 6.70 (d, *J* = 8.7 Hz, 2H), 5.56 (t, *J* = 2.8 Hz, 1H), 5.21 (s, 1H), 5.16 (s, 1H), 4.93 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.44 (d, *J* = 12.1 Hz, 1H), 4.36 (dd, *J* = 7.3, 4.7 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 11.7 Hz, 1H), 4.09 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.83 (d, *J* = 10.9 Hz, 1H), 3.31 (s, 1H), 3.29 -3.16 (m, 2H), 2.57 (ddd, *J* = 12.6, 7.1, 1.9 Hz, 1H), 2.35 (ddd, *J* = 10.8, 10.8, 10.8 Hz, 1H), 2.18 (dd, *J* = 10.6, 12.1 Hz, 1H), 2.06 (dt, *J* = 14.7, 2.8 Hz, 1H), 1.96 – 1.77 (m, 4H), 1.77 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H), 1.01 (ddt, *J* = 14.1, 10.0, 4.7 Hz, 1H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 165.6 (C), 159.5 (C), 140.6 (C), 139.4 (C), 133.2 (CH), 131.3 (C), 131.0 (C), 129.8 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 115.7 (CH_2), 114.0 (CH), 107.7 (CH), 90.1 (C), 86.7 (CH), 75.2 (CH), 73.9 (CH_2), 72.7 (CH_2), 71.9 (CH_2), 68.9 (CH_2), 54.8 (CH_3), 52.8, (C), 37.3 (C), 33.8 (CH), 31.5 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 25.4 (CH_3), 18.9 (CH_3), 17.7 (CH_3). **IR** (neat, cm^{-1}) 2959 (s), 2855 (s), 1718

(s), 1512 (m), 1268 (s), 1248 (s), 1094 (s), 1078 (s), 712 (s). **HRMS** (EI) m/z $(M\text{-}C_7H_7)^+$ calculated for $C_{33}H_{41}O_7$ 549.2852, found 549.2879 (1.6%)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7.5
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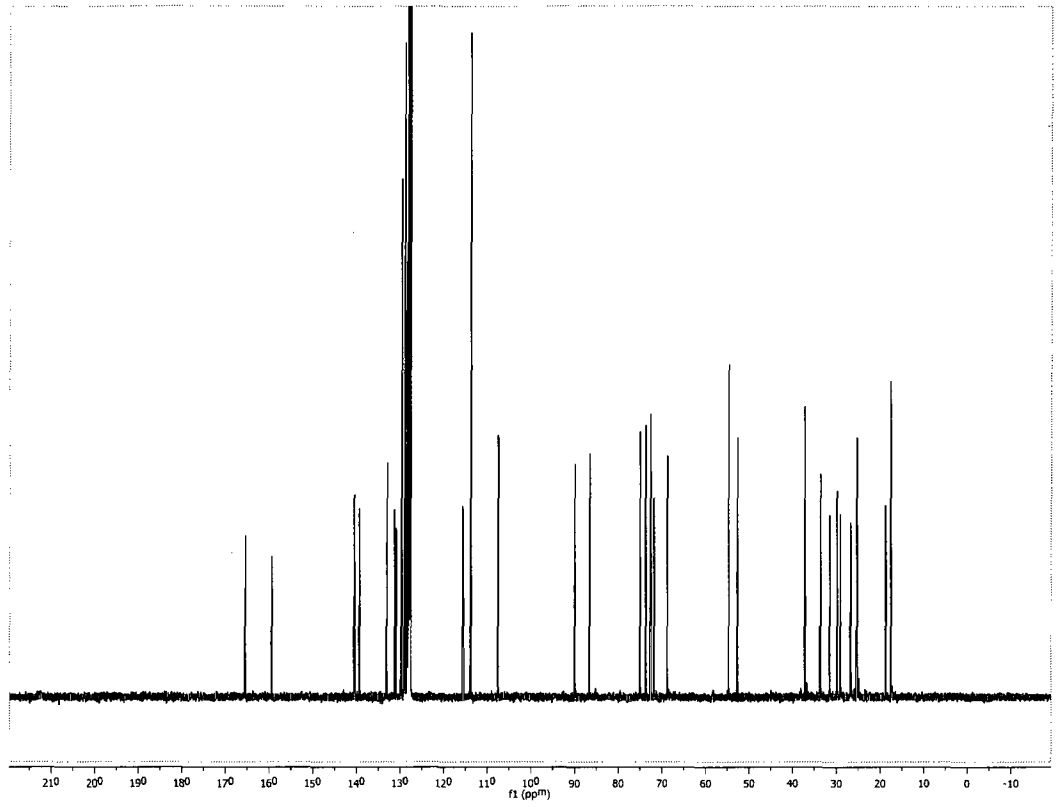
8.5
9.0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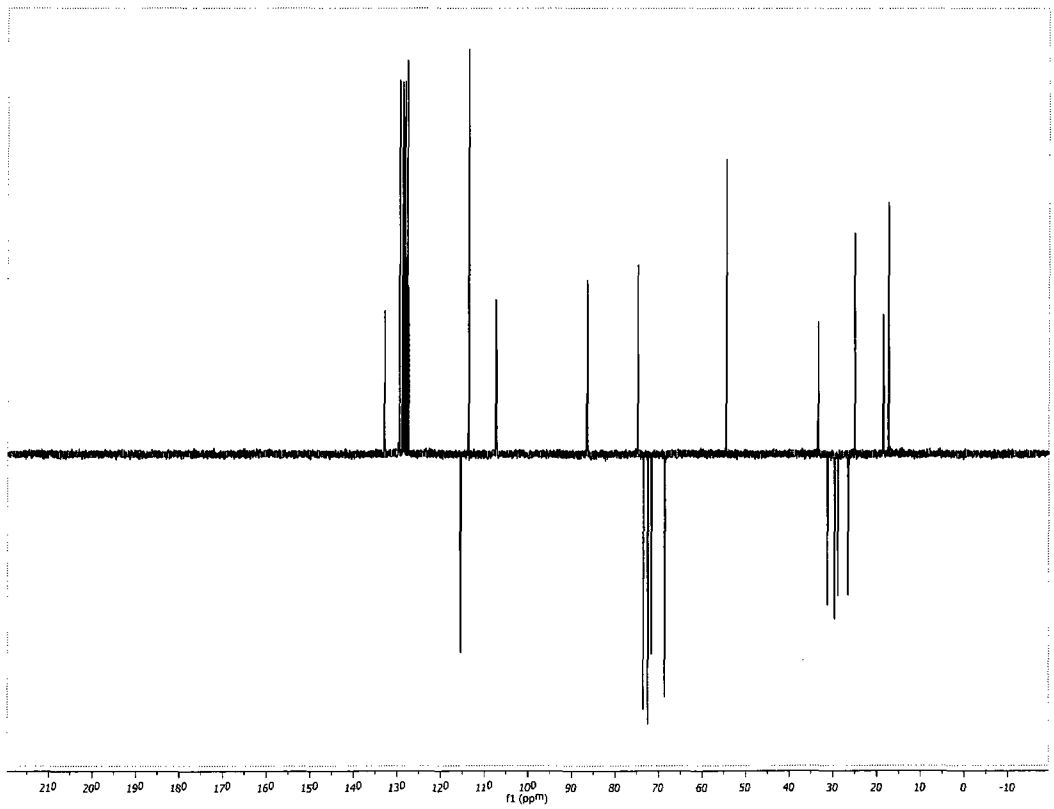
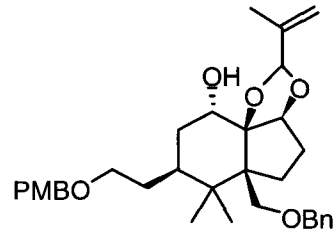
f1 (ppm)

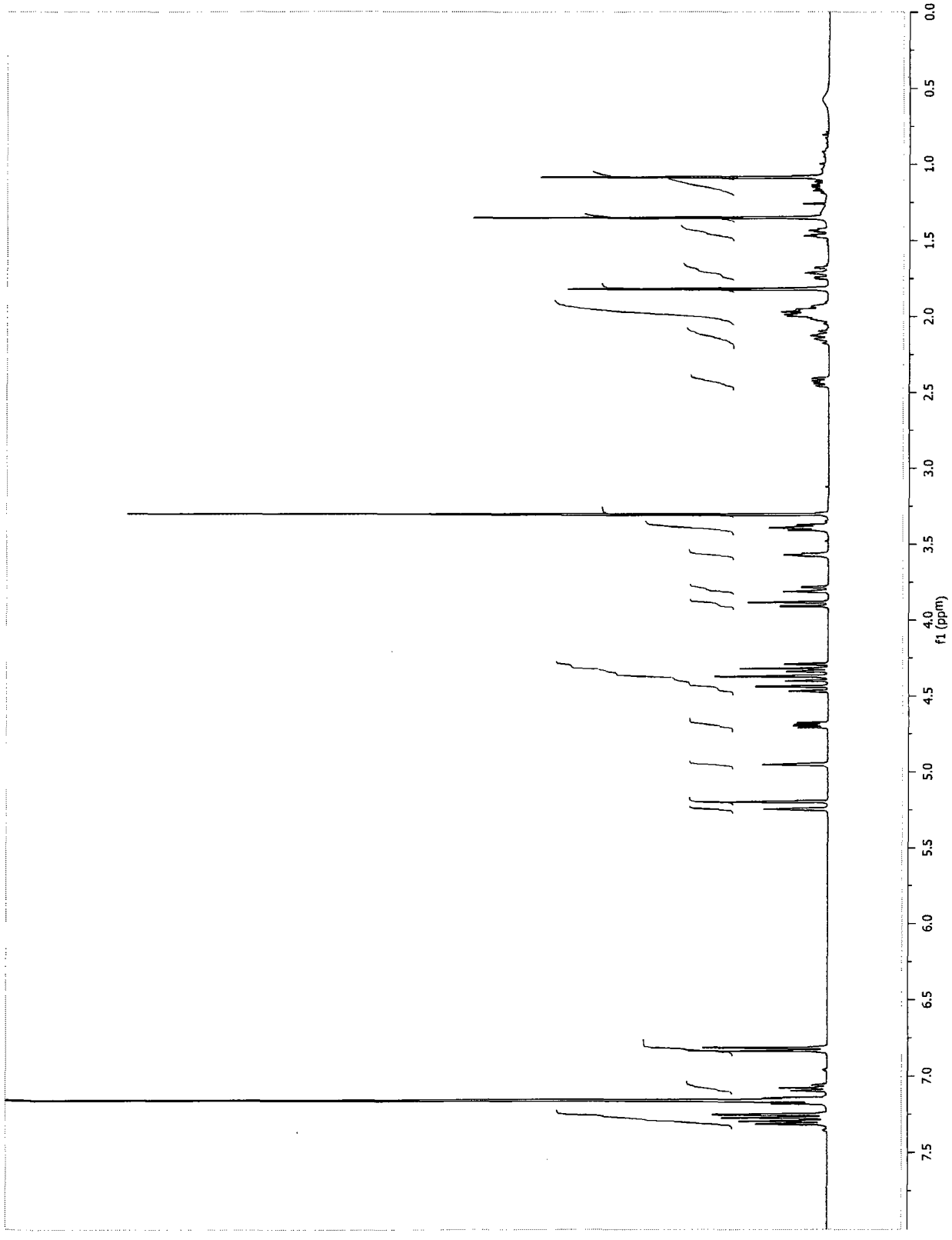

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5a-(benzyloxymethyl)-7-(2-(4-methoxybenzyloxy)ethyl)-6,6-dimethyl-2-(prop-1-en-2-yl)octahydroindeno[1-d][1,3]dioxol-9-ol (2.37b)



To a solution of **2.36b** (0.130 g, 0.203 mmol, 1.0 equiv) in MeOH (3 mL) was added K_2CO_3 until saturation followed by addition of benzene (3 mL). The resulting mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl was added. The aqueous layer was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 20% EtOAc/hexanes to afford **2.37b** as a white solid (0.088 mg, 81% yield).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.30 (d, *J* = 7.0 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.18 – 7.14 (m, 2H), 7.10 – 7.06 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.25 (br s, 1H), 5.20 (s, 1H), 4.95 (t, *J* = 1.6 Hz, 1H), 4.69 (dd, *J* = 7.6, 4.2 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.80 (dd, *J* = 10.8, 1.0 Hz, 1H), 3.57 (t, *J* = 3.1 Hz, 1H), 3.41 – 3.37 (m, 2H), 3.30 (s, 3H), 2.43 (ddd, *J* = 12.2, 7.4, 1.7 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.03 – 1.93 (m, 4H), 1.82 (s, 3H), 1.71 (ddd, *J* = 13.3, 13.3, 2.7, 1H), 1.45 (dt, *J* = 14.0, 3.3 Hz, 1H), 1.35 (s, 3H), 1.19 – 1.09 (m, 1H), 1.09 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 159.8 (C), 141.3 (C), 139.6 (C), 131.4 (C), 129.4 (CH), 128.5 (CH), 128.0 (CH), 127.6 (CH), 115.2 (CH_2), 114.2 (CH), 107.3 (CH), 91.1 (C), 86.2 (CH), 73.8 (CH_2), 72.6 (CH_2), 72.3 (CH_2), 71.6 (CH), 69.4 (CH_2), 54.8 (CH_3), 52.7 (C), 37.4 (C), 32.97 (CH), 32.91 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 27.3 (CH_2), 25.6 (CH_3), 19.0 (CH_3), 17.7 (CH_3) **IR** (neat, cm^{-1}) 3438 (s), 2956 (s), 2858 (s), 1512 (m), 1248 (s), 1082 (s). **HRMS** (EI) m/z $(M-C_{15}H_{17}O_2)^+$ calculated for $C_{18}H_{27}O_4$ 307.1909, found 307.1926 (2.2%)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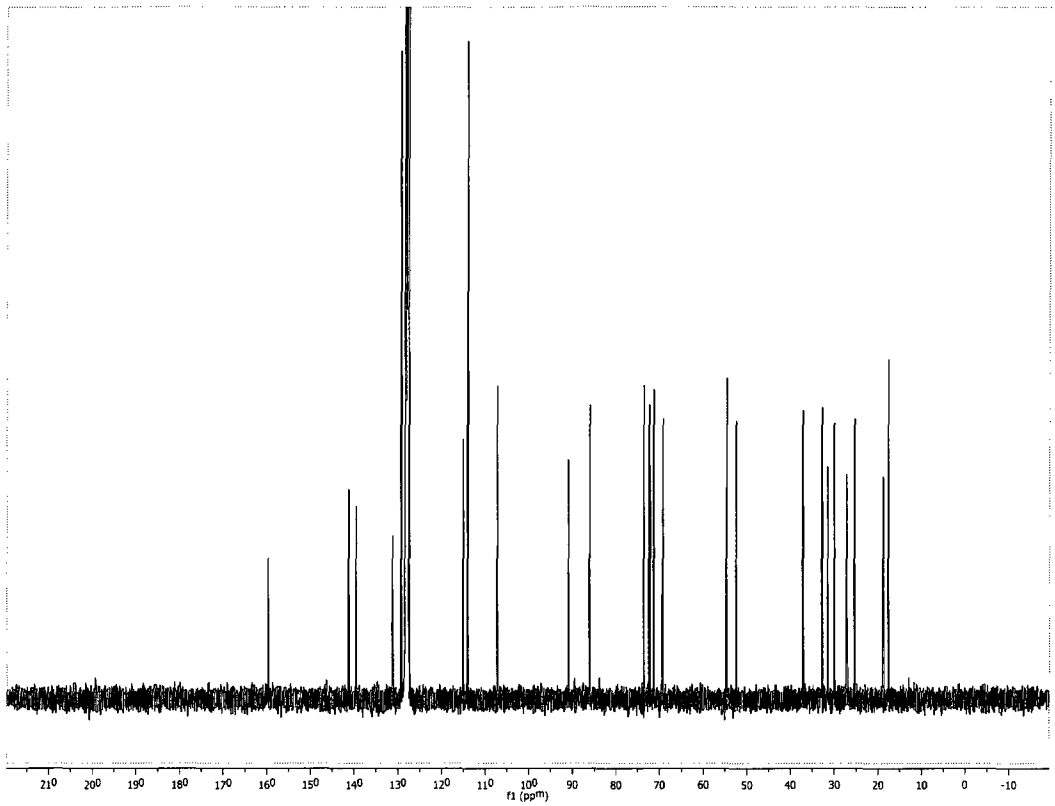
7.5
f1 (ppm)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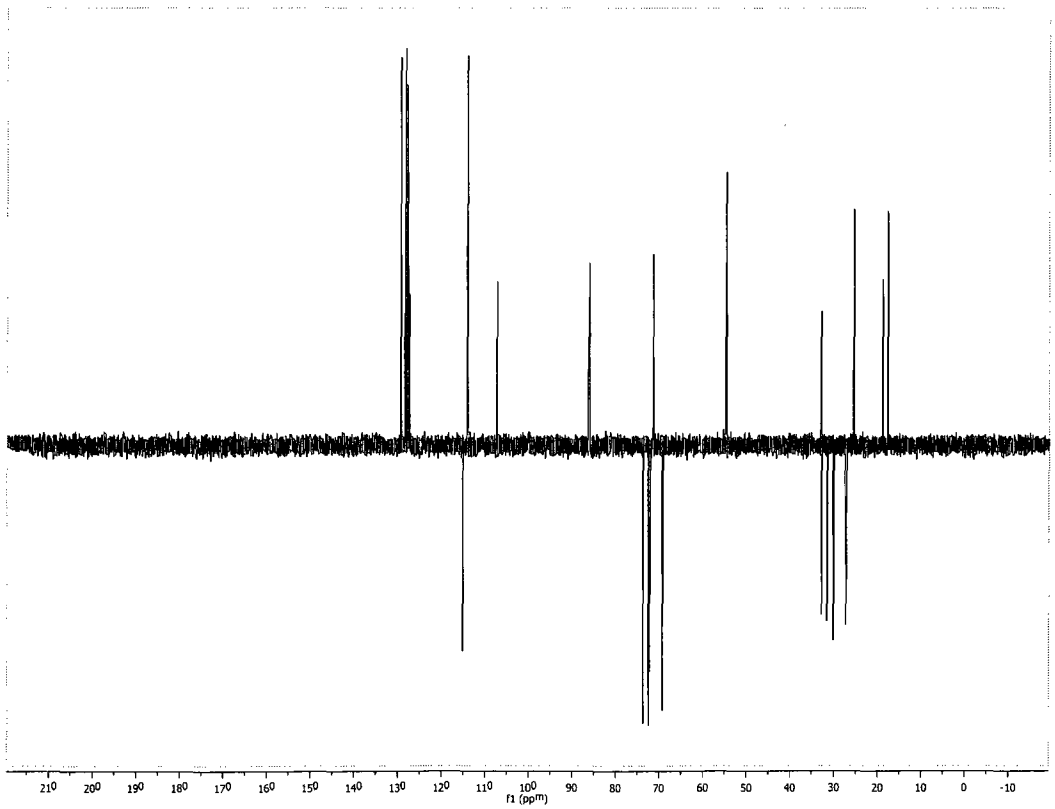
f1 (ppm)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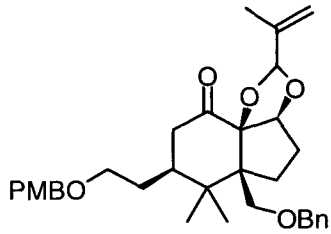
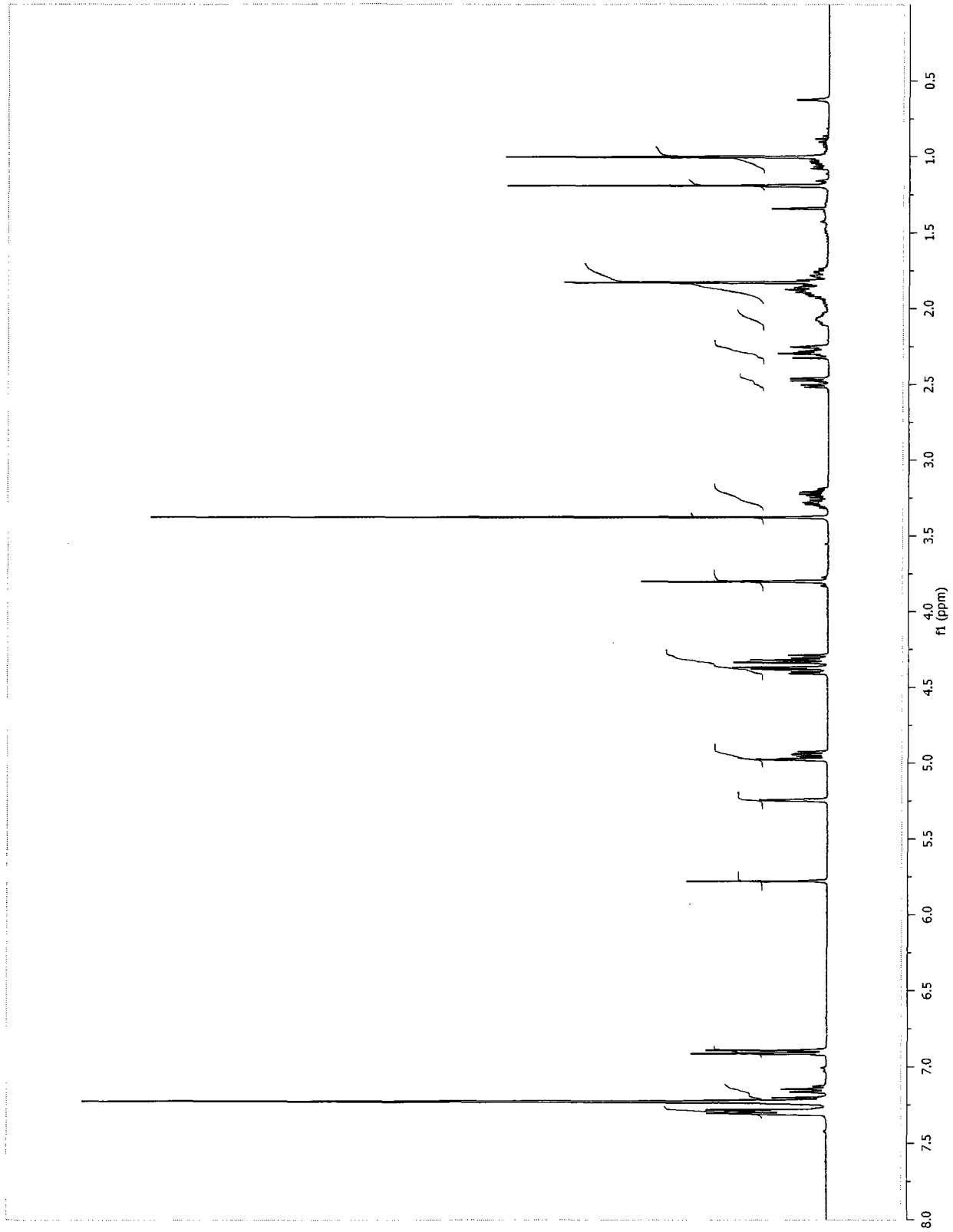
f1 (ppm)

5a-(benzyloxymethyl)-7-(2-(4-methoxybenzyloxy)ethyl)-6,6-dimethyl-2-(prop-1-en-2-yl)hexahydroindeno[1-d][1,3]dioxol-9(3aH)-one (2.38b)



To a solution of **2.37b** (0.088 g, 0.164 mmol, 1.0 equiv) in DCM (2 mL) at 0 °C was added Dess-Martin periodinane (0.417 g, 0.984 mmol, 6.0 equiv). The mixture was stirred overnight at room temperature. The reaction was quenched with a 1:1 mixture of saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with DCM (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 5% EtOAc/hexanes to afford **2.38b** as a colorless oil (0.049 g, 56% yield).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.24 – 7.05 (m, 7H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.71 (s, 1H), 5.18 (br s, 1H), 4.91 (t, *J* = 1.6 Hz, 1H), 4.88 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.32 (dd, *J* = 11.8, 4.2 Hz, 2H), 4.25 (dd, *J* = 11.8, 6.8 Hz, 2H), 3.73 (s, 2H), 3.31 (s, 3H), 3.22 (ddd, *J* = 9.3, 6.1, 4.5 Hz, 1H), 3.15 (ddd, *J* = 9.2, 9.2, 5.0 Hz, 1H), 2.42 (dd, *J* = 16.8, 5.7 Hz, 1H), 2.26 – 2.19 (m, 2H), 2.00 (dddd, *J* = 12.4, 10.0, 5.5, 2.6 Hz, 1H), 1.87 – 1.67 (m, 4H), 1.76 (s, 3H), 1.13 (s, H), 1.10 – 0.95 (m, 1H), 0.95 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 207.7 (C), 159.9 (C), 141.3 (C), 139.1 (C), 131.1 (C), 129.5 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 116.3 (CH_2), 114.2 (CH), 109.3 (CH), 94.1 (C), 85.5 (CH), 73.7 (CH_2), 72.9 (CH_2), 71.9 (CH_2), 67.9 (CH_2), 57.0 (C), 54.8 (CH_3), 40.7 (CH_2), 38.3 (C), 37.0 (CH), 31.7 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 24.5 (CH_3), 18.7 (CH_3), 17.0 (CH_3) **IR** (neat, cm^{-1}) 2963 (s), 2870 (s), 1715 (s), 1513 (m), 1248 (s), 1082 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{33}H_{42}O_6$ 534.2981, found 534.2962 (0.8 %)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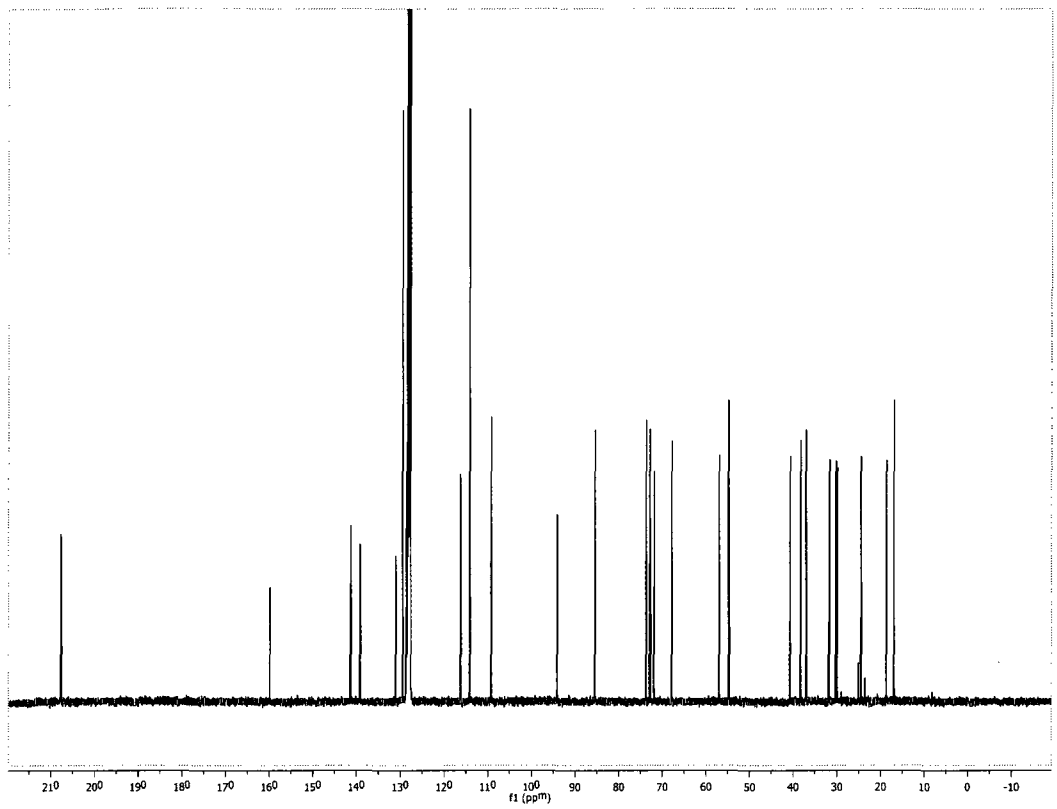
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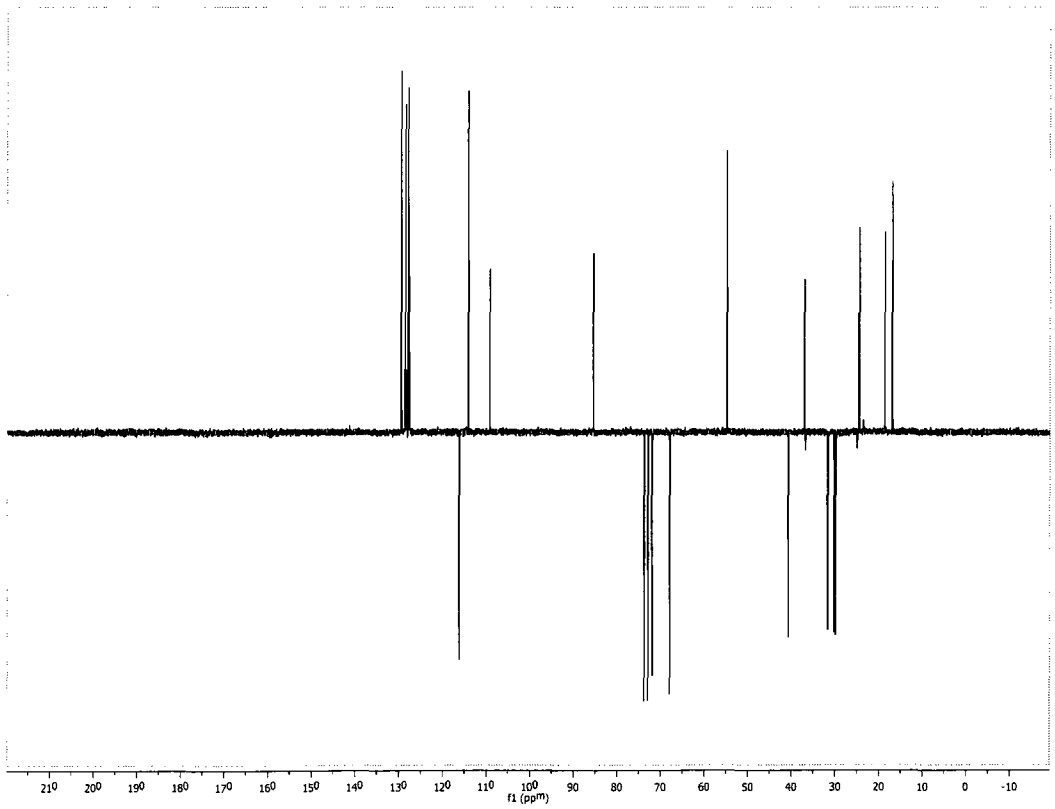
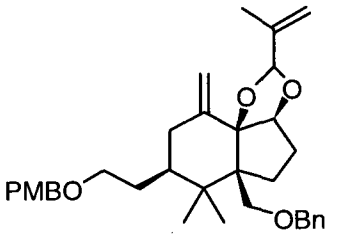
f1 (ppm)

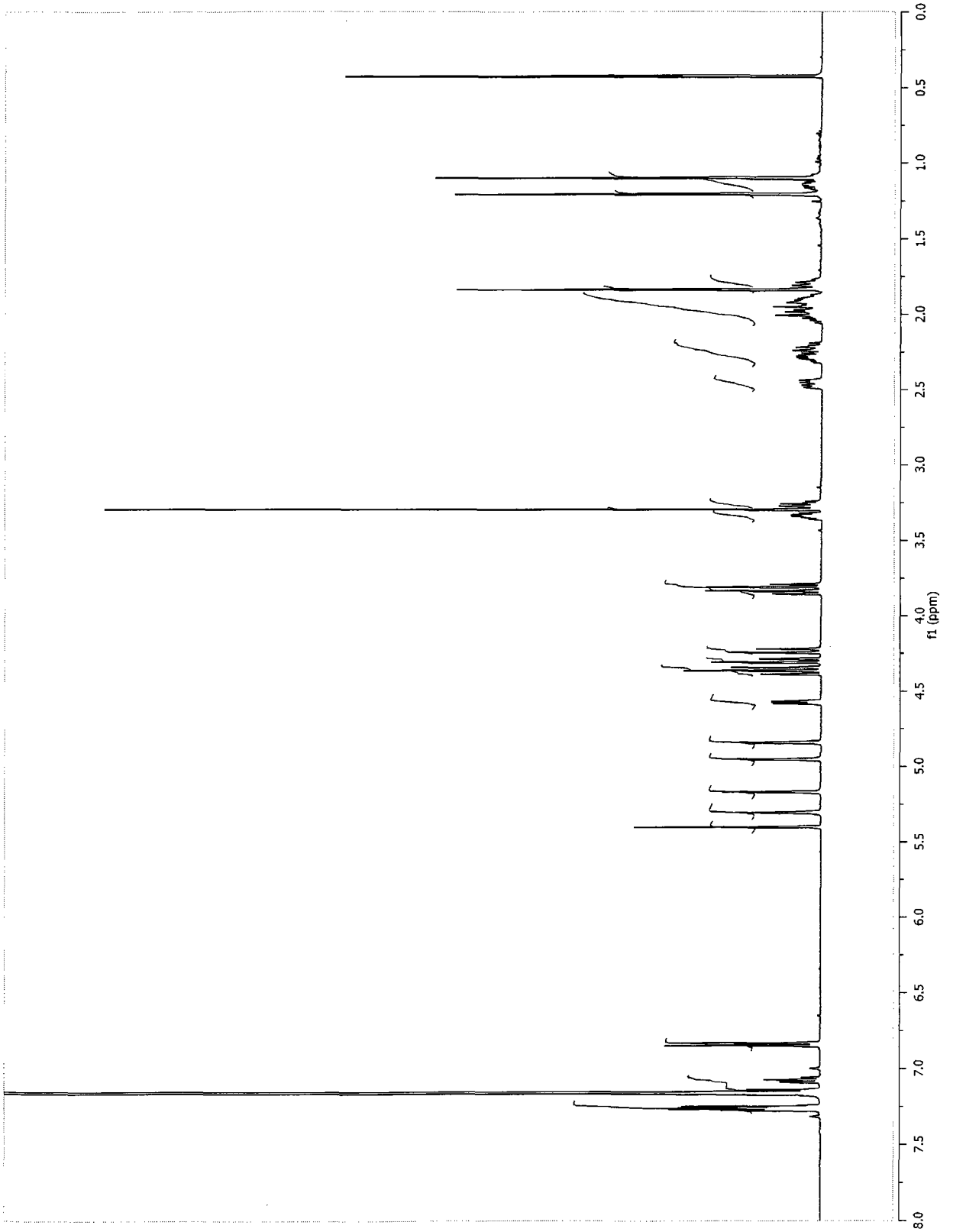

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5a-(benzyloxymethyl)-7-(2-(4-methoxybenzyloxy)ethyl)-6,6-dimethyl-9-methylene-2-(prop-1-en-2-yl)octahydroindeno[1-d][1,3]dioxole (2.39b)



To a suspension of methyltriphenylphosphonium iodide (0.500 g, 1.24 mmol, 20.0 equiv) in toluene (2 mL) was added KO*t*Bu in THF (1.36 mL, 1M, 1.36 mmol, 22.0 equiv). The resulting bright yellow mixture was stirred for 20 minutes at room temperature. A solution of dry (aesotropal removal of H_2O using benzene) compound **2.38b** (0.033 g, 0.062 mmol, 1.0 equiv) in toluene (2 mL) was then added *via* canula. The mixture was stirred for 4 hours at reflux, cooled to room temperature and saturated aqueous NH_4Cl was added. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/hexanes) as eluent to afford **2.39b** as a colorless oil (0.022 g, 67% yield).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.27 – 7.25 (m, 4H), 7.16 – 7.06 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.40 (s, 1H), 5.31 (br s, 1H), 5.17 (br s, 1H), 4.95 (br s, 1H), 4.84 (br s, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 4.23 (d, *J* = 12.1 Hz, 1H), 3.84 (d, *J* = 9.7 Hz, 1H), 3.80 (d, *J* = 9.7 Hz, 1H), 3.34 (ddd, *J* = 9.1, 6.6, 4.3 Hz, 1H), 3.29 (s, 3H), 3.29 – 3.24 (m, 1H), 2.46 (ddt, *J* = 16.2, 7.5, 2.3 Hz, 1H), 2.29 (ddd, J = 13.6, 7.6, 3.7 Hz, 1H), 2.22 (ddd, J = 13.7, 10.6, 8.6 Hz, 1H), 2.05 – 1.86 (m, 4H), 1.84 (s, 3H), 1.84 – 1.77 (m, 1H), 1.21 (s, 3H), 1.17 – 1.10 (m, 1H), 1.10 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.8 (C), 145.5 (C), 142.4 (C), 139.5 (C), 131.3 (C), 129.4 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 115.9 (CH_2), 114.2 (CH), 107.9 (CH_2), 105.8 (CH), 95.4 (C), 87.6 (CH), 75.8 (CH_2), 73.7 (CH_2), 72.8 (CH_2), 68.3 (CH_2), 57.5 (C), 54.8 (CH_3), 39.5 (C), 37.4 (CH), 34.6 (CH_2), 33.5 (CH_2), 33.0 (CH_2), 31.0 (CH_2), 26.5 (CH_3), 19.3 (CH_3), 16.3 (CH_3) **IR** (neat, cm^{-1}) 2956 (s), 2850 (s), 1513 (m), 1248 (s), 1094 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{34}H_{44}O_5$ 532.3189, found 532.3180 (2.7 %)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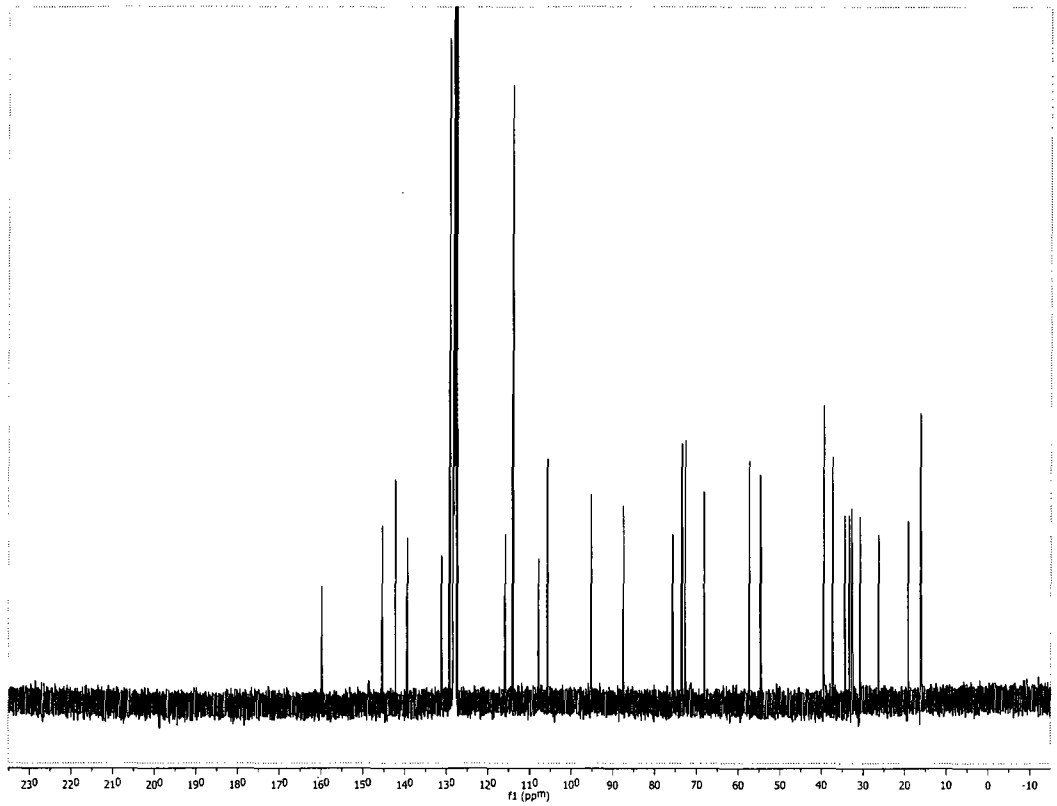
f1 (ppm)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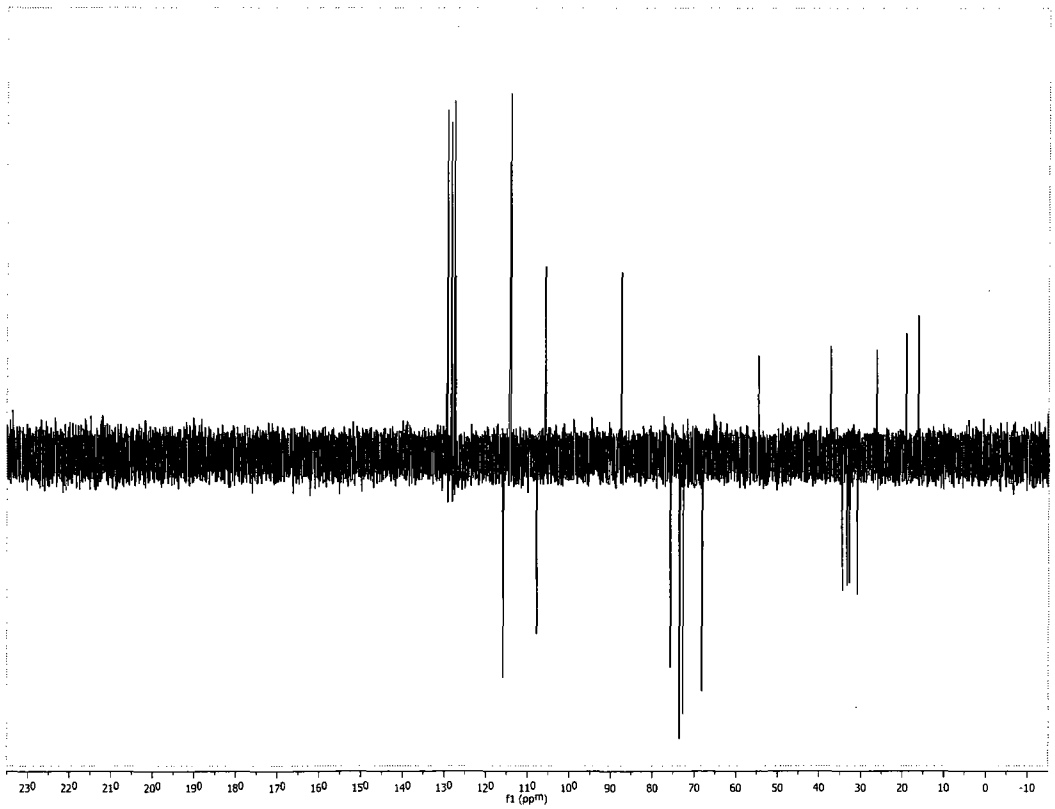
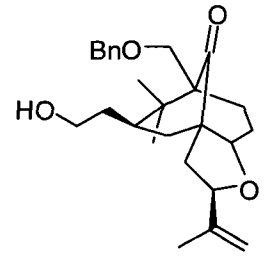
f1 (ppm)

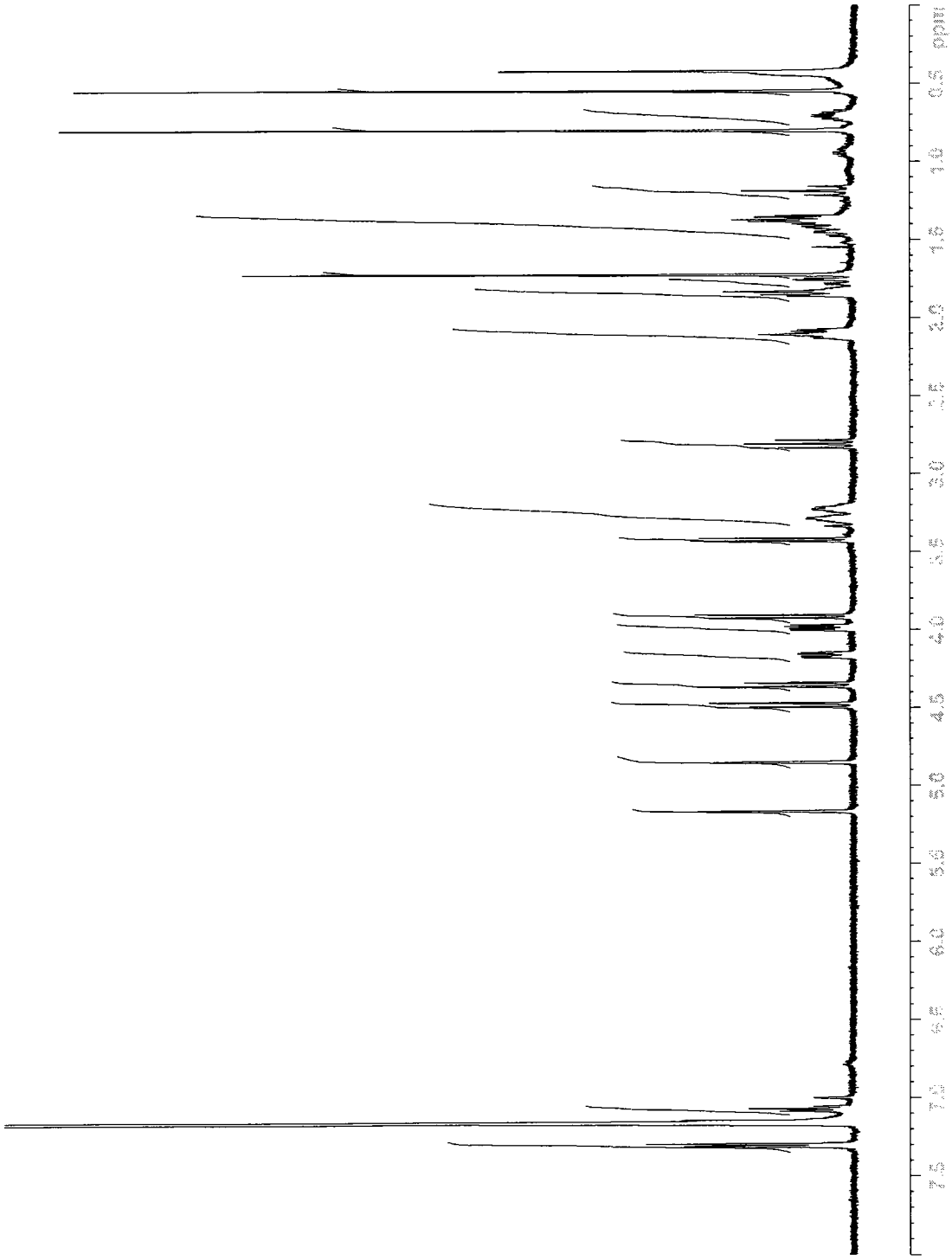

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

3-Isopropenyl-8-(benzyloxymethyl)-9,9-dimethyl-10-(2-(4-methoxybenzyloxy)ethyl)-4-oxatricyclo[6.3.1.$0^{1,5}$]dodecan-12-one (2.42b)



To a solution of **2.39b** (about 14 mg) in DCM (1 mL) was added a few drops of a solution of tin(IV) chloride in DCM at -78 °C. The reaction was stirred for 45 minutes and quenched with sat $NaHCO_3$. The aqueous phase was extracted with DCM (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/hexanes) as eluent to afford **2.42b** (a few milligrams).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.32 – 7.30 (m, 2H), 7.17 – 7.14 (m, 2H), 7.08 – 7.06 (m, 1H), 5.17 (br s, 1H), 4.85 (br s, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.35 (d, *J* = 12.1 Hz, 1H), 4.16 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.99 (dd, *J* = 11.3, 5.1 Hz, 1H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.42 (d, *J* = 9.0 Hz, 1H), 3.31 – 3.20 (m, 2H), 2.81 (dd, *J* = 12.6, 11.5 Hz, 1H), 2.14 – 2.07 (m, 2H), 1.87 – 1.75 (m, 3H), 1.72 (s, 3H), 1.49 – 1.35 (m, 4H) 1.19 (t, *J* = 14.2 Hz, 1H), 0.80 (s, 3H), 0.55 (s, 3H)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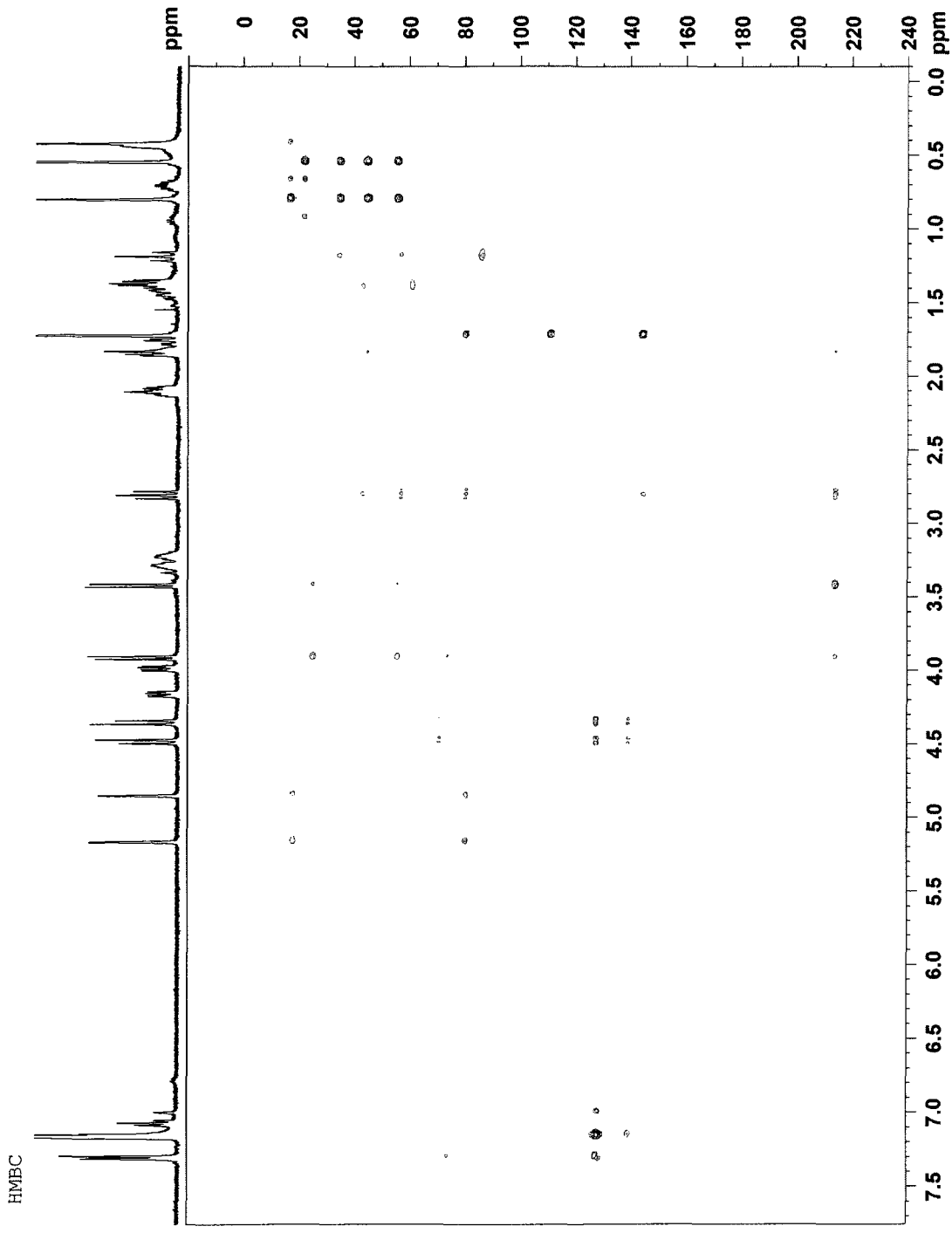
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ppm
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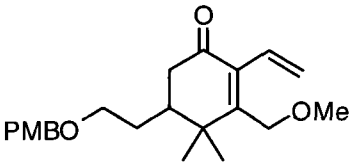
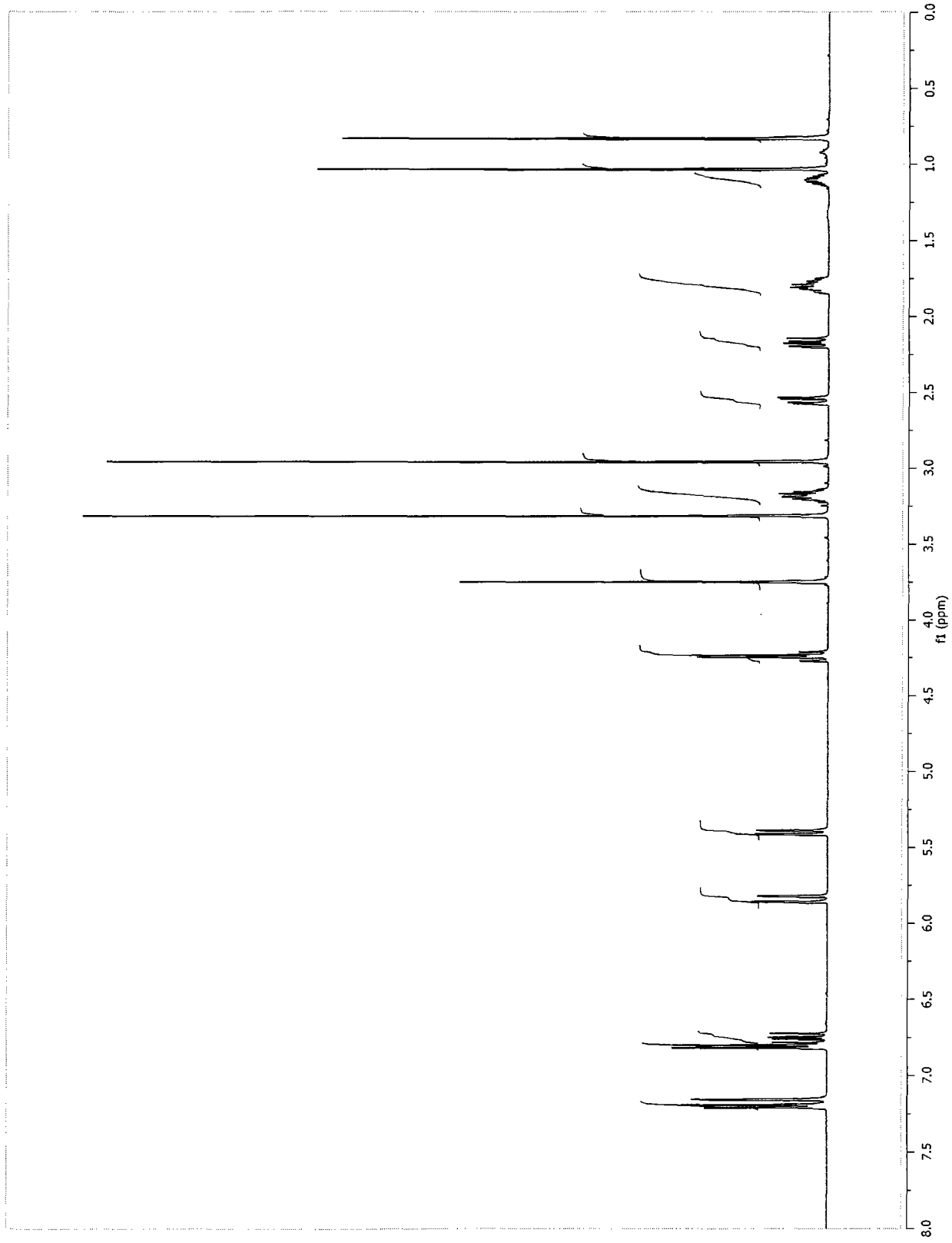
7.5

5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethyl-2-vinylcyclohex-2-enone (2.63)



To a solution of $Pd(PhCN)_2Cl_2$ (0.028 g, 0.073 mmol, 0.05 equiv), $AsPh_3$ (0.044 g, 0.15 mmol, 0.1 equiv) and CuI (0.028 g, 0.15 mmol, 0.1 equiv) in NMP (5 mL) was added a solution of compound **2.66** (0.665 g, 1.45 mmol, 1.0 equiv) in NMP (5 mL) and then a solution of tributyl(vinyl)tin (0.42 mL, 1.45 mmol, 1.0 equiv) in NMP (5 mL). The reaction was stirred over night at room temperature and was quenched by addition of water. The aqueous phase was extracted EtOAc (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-30% EtOAc/hexanes) as eluent. The product is a colorless oil (0.429 g, 83%).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.20 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.75 (dd, *J* = 17.7, 11.6 Hz, 1H), 5.84 (dd, *J* = 17.7, 2.6 Hz, 1H), 5.40 (dd, *J* = 11.7, 2.5 Hz, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 4.23 (d, *J* = 11.6 Hz, 1H), 3.75 (s, 2H), 3.32 (s, 3H), 3.20 (ddd, *J* = 9.2, 6.6, 4.9 Hz, 1H), 3.16 (ddd, *J* = 8.7, 8.7, 5.8 Hz, 1H), 2.96 (s, 3H), 2.56 (dd, *J* = 16.9, 4.3 Hz, 1H), 2.17 (dd, *J* = 16.9, 11.0 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.14 – 1.07 (m, 1H), 1.03 (s, 3H), 0.83 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 197.4 (C), 159.8 (C), 157.9 (C), 136.5 (C), 131.4 (CH), 131.2 (C), 129.4 (CH), 120.8 (CH_2), 114.1 (CH), 72.9 (CH_2), 70.1 (CH_2), 68.1 (CH_2), 57.8 (CH_3), 54.8 (CH_3), 41.0 (CH), 39.8 (CH_2), 39.2 (C), 30.1 (CH_2), 25.6 (CH_3), 20.8 (CH_3) **IR** (neat, cm^{-1}) 2923 (m), 2870 (m), 1674 (s), 1612 (m), 1513 (m), 1247 (m), 1091 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{22}H_{30}O_4$ 358.2144, found 358.2134 (2.1%)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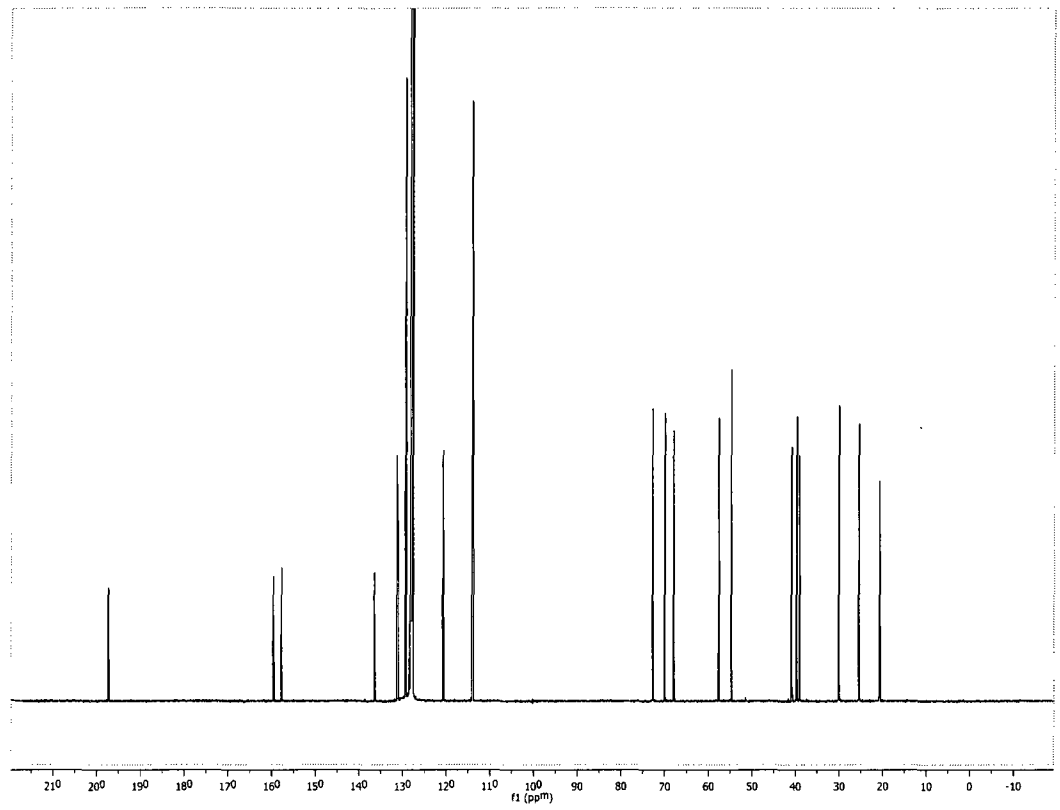
f1 (ppm)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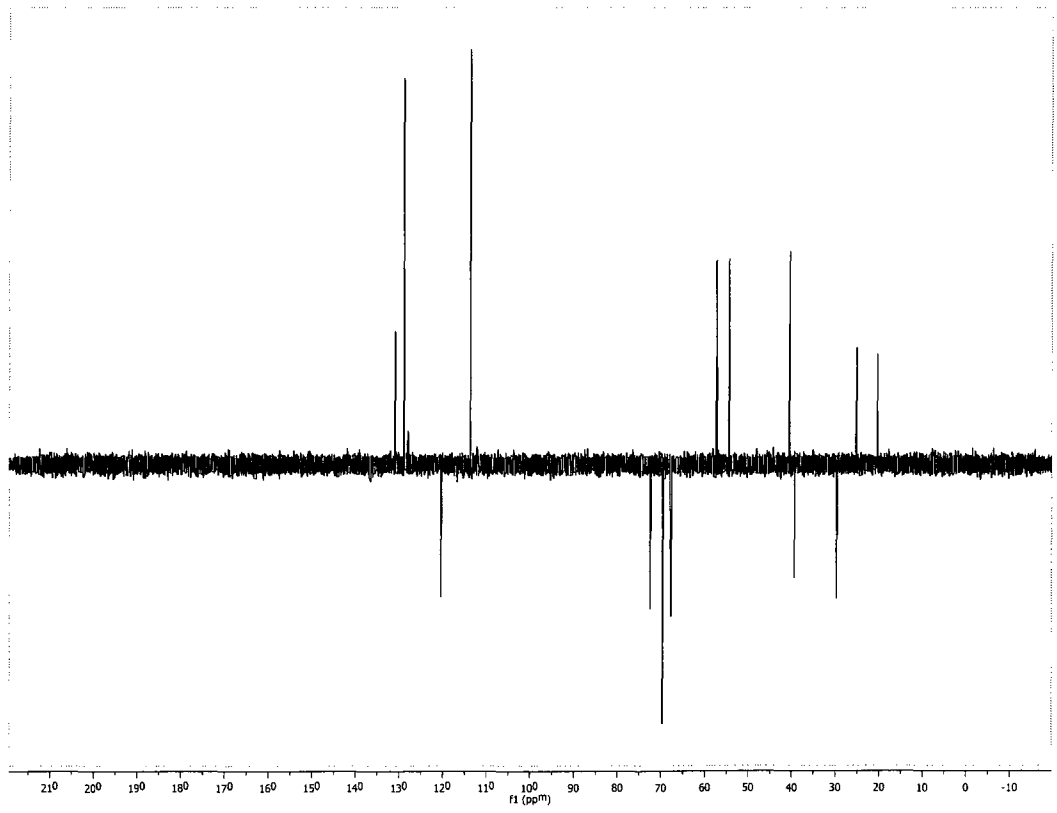
f1 (ppm)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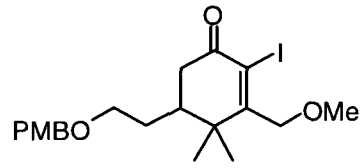
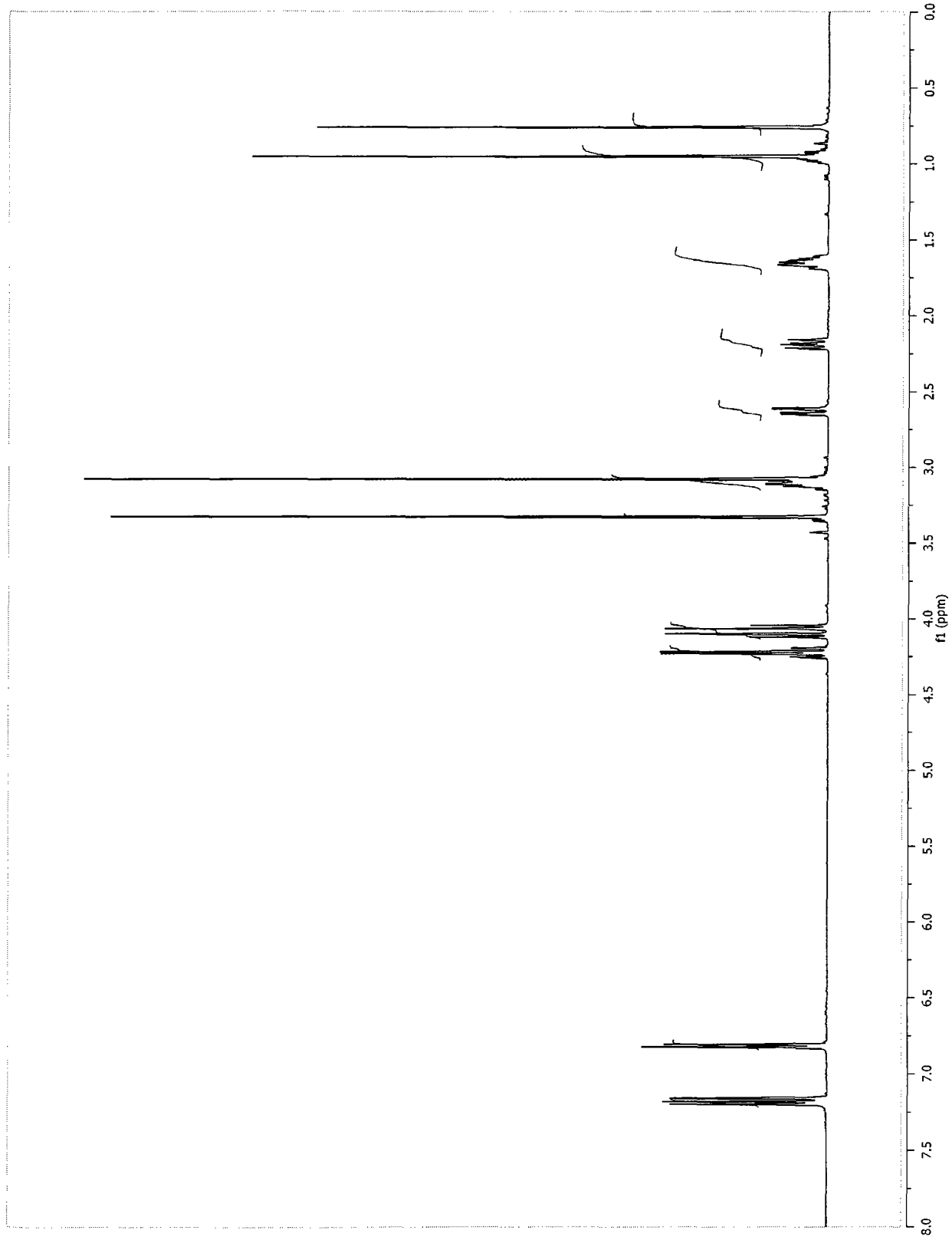
f1 (ppm)

2-iodo-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethylcyclohex-2-enone (2.66)



To a solution of **2.28a** (3.14 g, 9.44 mmol, 1.0 equiv), in DCM (15 mL) was added $TMSN_3$ (5.0 mL, 37.7 mmol, 4.0 equiv) at 0 °C. The mixture was stirred for 2 hours and a solution of iodine (4.79 g, 18.9 mmol, 2.0 equiv) in 1:1 pyridine/DCM (30 mL) was added *via* canula. The reaction was warmed to room temperature, stirred over night and diluted with Et_2O. The organic layer was washed with 2N HCl (x2), with sat Na_2SO_3 (x2), with sat $NaHCO_3$, with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (20%-40% EtOAc/hexanes) as eluent to afford **2.66** as a yellow oil (2.62 g, 63%). Starting material (0.717 g, 23%) was also recovered.

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.19 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.24 (d, J = 11.6 Hz, 1H), 4.21 (d, J = 11.6 Hz, 1H), 4.11 (d, J = 10.7 Hz, 1H), 4.06 (d, J = 10.7 Hz, 1H), 3.33 (s, 3H), 3.14 – 3.06 (m, 2H), 3.08 (s, 3H), 2.63 (dd, J = 16.8, 4.0 Hz, 1H), 2.19 (dd, J = 16.8, 10.9 Hz, 1H), 1.69 – 1.60 (m, 2H), 0.99 – 0.92 (m, 1H), 0.95 (s, 3H), 0.76 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 191.0 (C), 167.3 (C), 159.8 (C), 131.0 (C), 129.5 (CH), 114.1 (CH), 113.4 (C), 78.7 (CH_2), 72.9 (CH_2), 67.7 (CH_2), 58.6 (CH_3), 54.9 (CH_3), 42.5 (C), 41.5 (CH), 38.2 (CH_2), 29.7 (CH_2), 25.4 (CH_3), 20.7 (CH_3) **IR** (neat, cm^{-1}) 2929 (s), 2867 (m), 1683 (s), 1610 (m), 1513 (m), 1247 (m), 1093 (m) **HRMS** (EI) m/z $(M\text{-}CH_4O)^+$ calculated for $C_{19}H_{23}IO_3$ 426.0692, found 426.0671 (4.4 %)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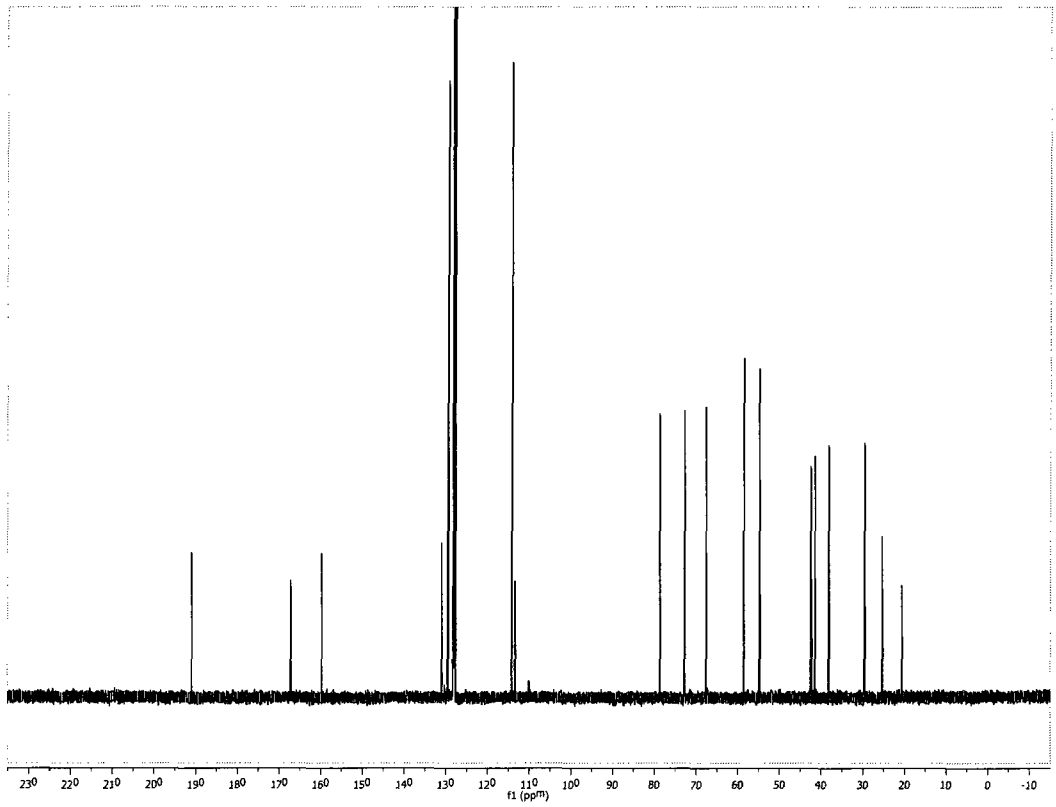
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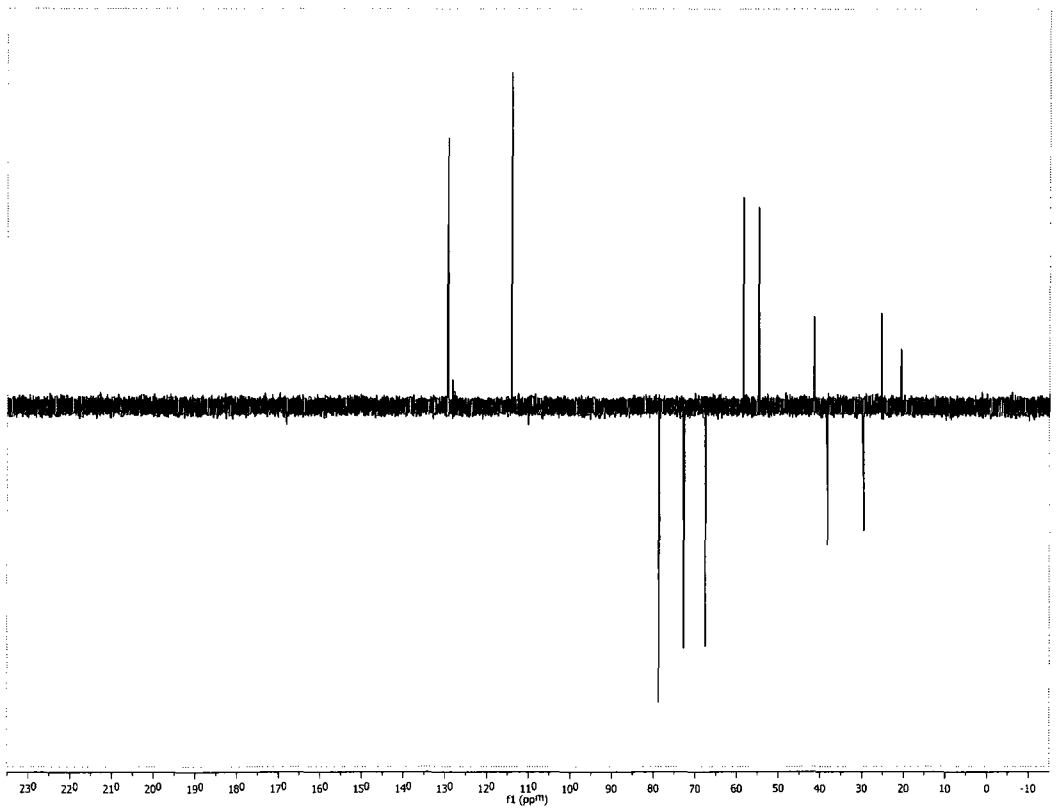
f1 (ppm)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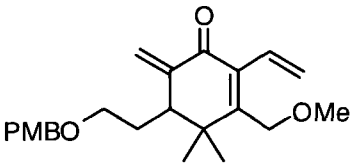
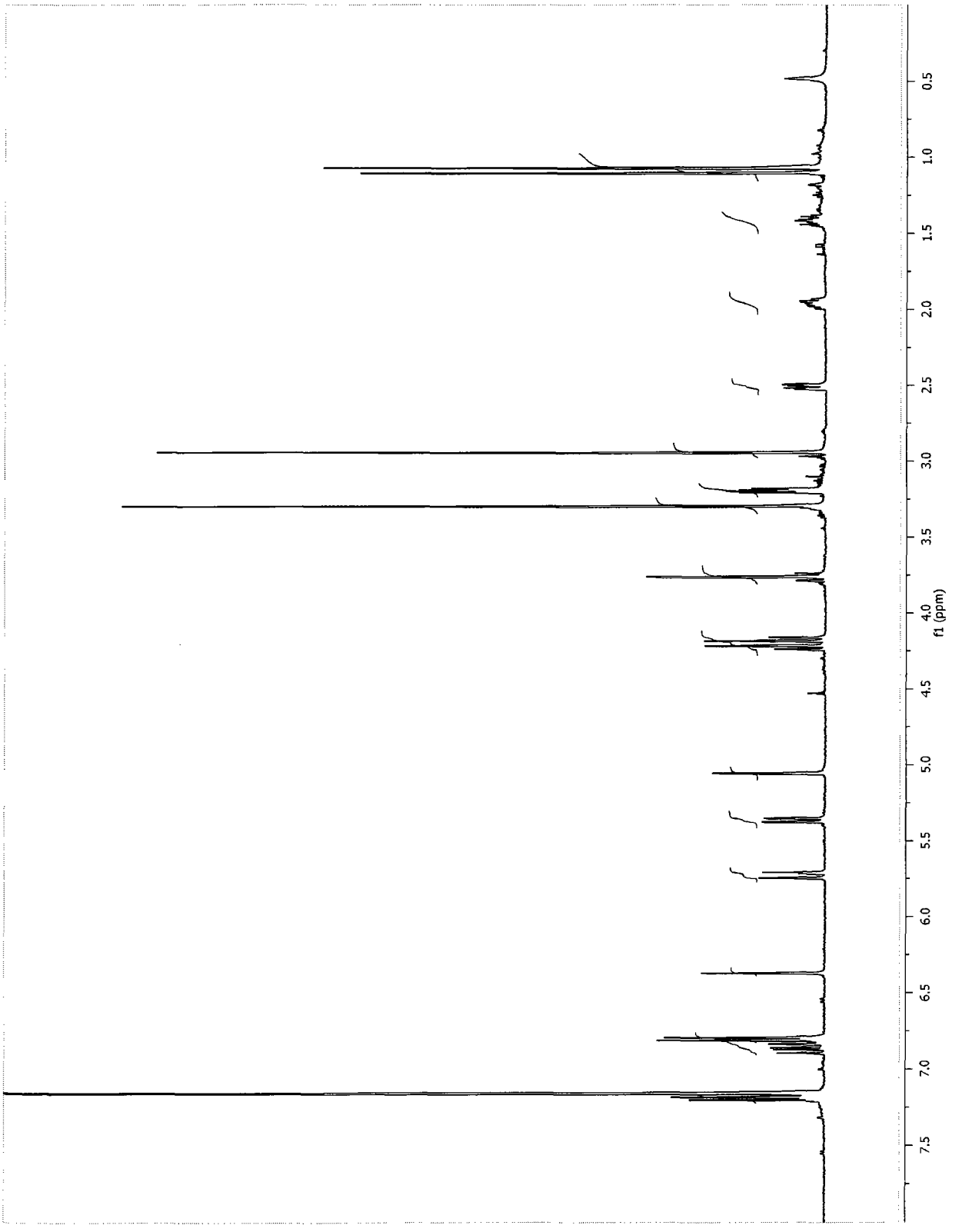
f1 (ppm)

5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethyl-6-methylene-2-vinylcyclohex-2-enone (2.71)



A solution of LiTMP was prepared by mixing TMP (0.45 mL, 2.67 mmol, 1 equiv) and *n*-BuLi (in pentanes) (1.86 M, 1.43 mL, 2.66 mmol, 1 equiv) in Et_2O (5 mL). This solution was titrated (using the same method as for *n*-BuLi titration) to know the exact concentration (0.22 M). To a solution of dry (aseotropal removal of H_2O using dry benzene) **2.63** (0.100 g, 0.279 mmol, 1.0 equiv) and 1-chloro-2-(chloromethoxy)ethane (0.054 g, 0.418 mmol, 1.5 equiv) in Et_2O (1 mL) was added slowly a solution of LiTMP in Et_2O (1.91 mL, 0.22 M, 1.5 equiv) at 0 °C. The reaction mixture was warmed to room temperature, stirred 4h and quenched by addition of a 5% w/w aqueous citric acid solution. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (pretreated with Et_3N) using a gradient (0-20% EtOAc/hexanes) as eluent. The product is a colorless oil (0.008 g, 6%).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.19 (d, *J* = 8.5 Hz, 2H), 6.87 (dd, *J* = 17.7, 11.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.37 (d, *J* = 2.2 Hz, 1H), 5.73 (dd, *J* = 17.7, 2.1 Hz, 1H), 5.36 (dd, *J* = 11.5, 2.2 Hz, 1H), 5.06 (d, *J* = 2.4 Hz, 1H), 4.22 (d, *J* = 11.5 Hz, 1H), 4.18 (d, *J* = 11.5 Hz, 1H), 3.77 (d, *J* = 9.7 Hz, 1H), 3.75 (d, *J* = 9.7 Hz, 1H), 3.30 (s, 3H), 3.19 (dd, *J* = 8.0, 4.5 Hz, 2H), 2.94 (s, 3H), 2.51 (dd, *J* = 11.4, 3.4 Hz, 1H), 1.96 (dddd, *J* = 13.8, 7.8, 7.8, 3.4, 1H), 1.42 (ddt, *J* = 14.0, 11.5, 4.4, 1H), 1.10 (s, 3H), 1.07 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ 187.1 (C), 159.8 (C), 156.6 (C), 144.9 (C), 137.0 (C), 131.34 (CH), 131.31 (C), 129.6 (CH), 122.0 (CH_2), 120.8 (CH_2), 114.1 (CH), 72.9 (CH_2), 70.2 (CH_2), 67.6 (CH_2), 57.7 (CH), 54.8 (CH_3), 51.0 (CH_3), 39.5 (C), 30.6 (CH_3), 29.4 (CH_2), 23.8 (CH_3) **IR** (neat, cm^{-1}) 2929 (m), 2869 (m), 1669 (s), 1613 (m), 1513 (m), 1248 (m), 1113 (m), 1089 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{23}H_{30}O_4$ 370.2144, found 370.2131 (1.2%)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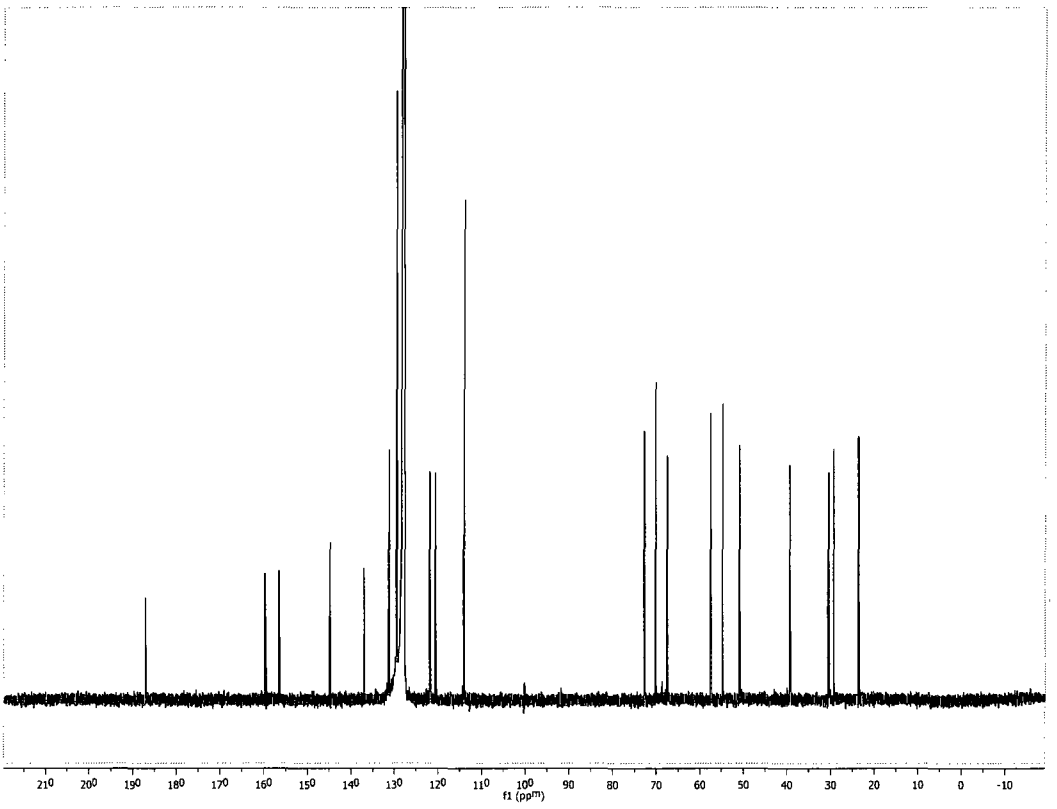
f1 (ppm)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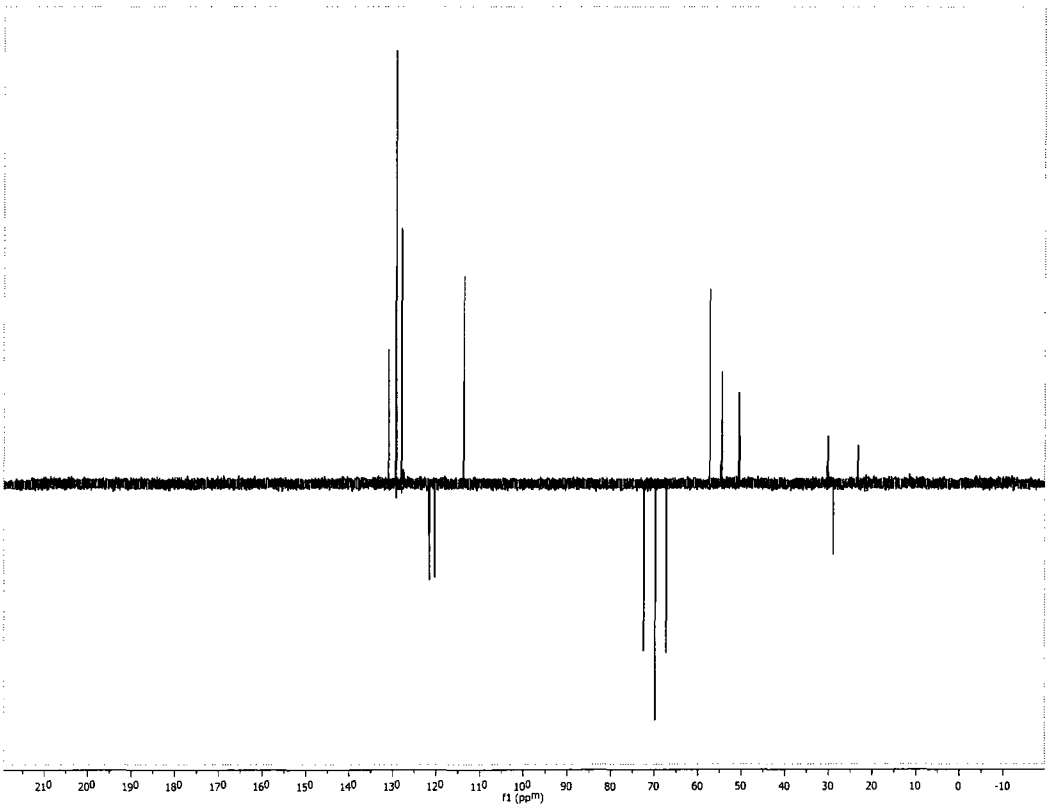
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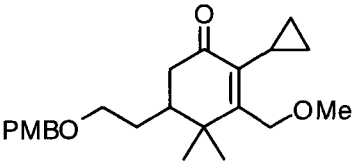
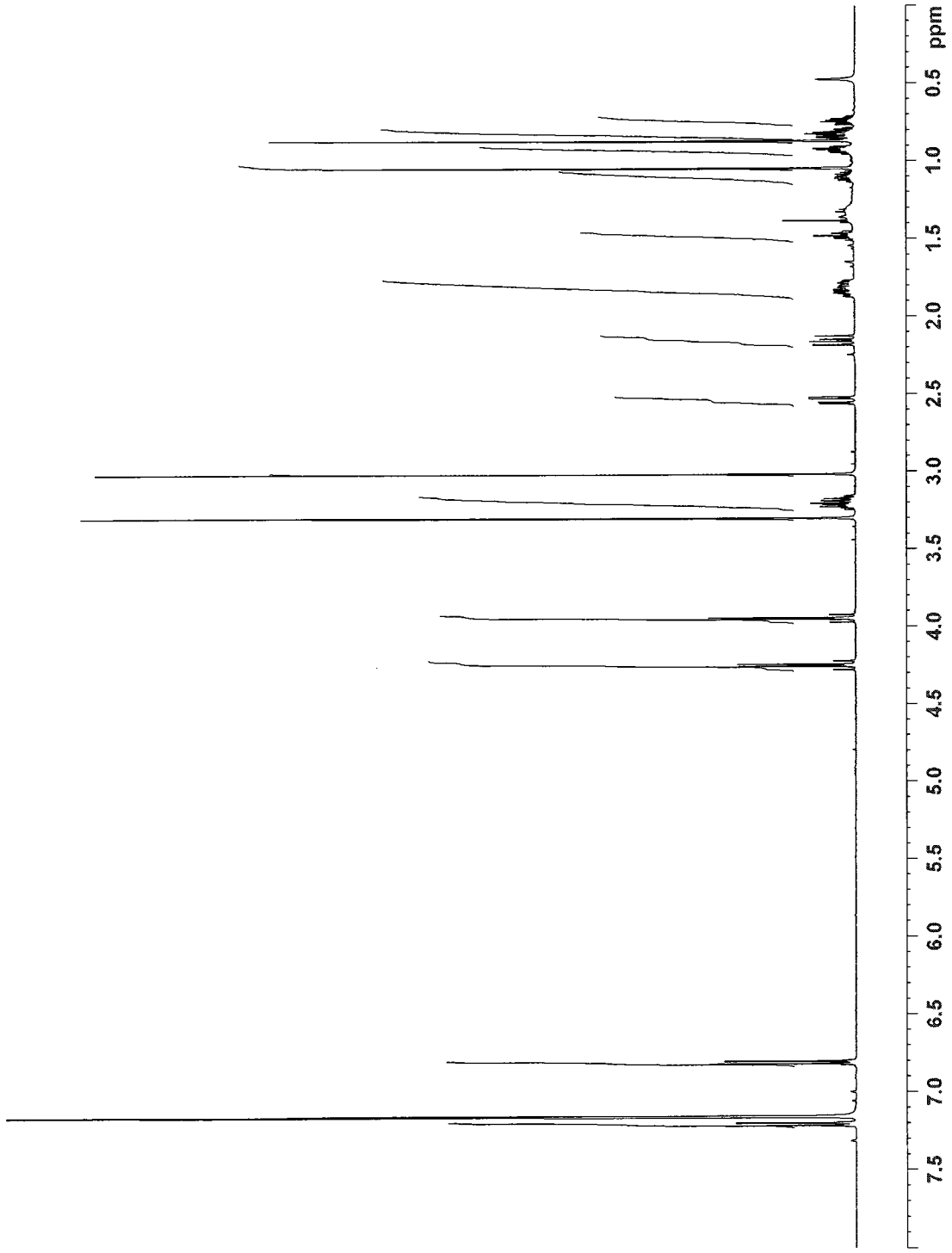
f1 (ppm)

2-cyclopropyl-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethylcyclohex-2-enone (2.72)



To a mixture of cyclopropylboronic acid (0.074 g, 0.860 mmol, 1.3 equiv), K_3PO_4 (0.486 g, 2.29 mmol, 3.5 equiv) and tricyclohexylphosphine (0.037 g, 0.131 mmol, 0.2 equiv) was added a solution of compound **2.66** (0.300 g, 0.655 mmol, 1.0 equiv) in toluene (3 mL). Palladium(II) acetate (0.015 g, 0.0655 mmol, 0.1 equiv) and then water (0.15 mL) were added. The mixture was degassed for 15 minutes with argon. The mixture was stirred at 100 °C in the microwave for 3 hours. Water was added and the aqueous phase was extracted with EtOAc (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (10-15% EtOAc/hexanes) as eluent. The product is a yellow oil (0.172 g, 70%).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.21 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.26 (d, *J* = 11.6 Hz, 1H), 4.24 (d, *J* = 11.6 Hz, 1H), 3.96 (d, *J* = 10.2 Hz, 1H), 3.94 (d, *J* = 10.2 Hz, 1H), 3.30 (s, 3H), 3.23 (ddd, *J* = 9.1, 6.6, 4.7 Hz, 1H), 3.18 (ddd, *J* = 8.7, 8.7, 5.6 Hz, 1H), 3.02 (s, 3H), 2.54 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.16 (dd, *J* = 17.1, 11.0 Hz, 1H), 1.85 (ddt, *J* = 10.7, 4.3, 2.7 Hz, 1H), 1.80 (dddd, *J* = 13.6, 8.3, 6.8, 2.6 Hz, 1H), 1.48 (ddt, *J* = 8.6, 8.6, 5.7 Hz, 1H), 1.10 (dddd, *J* = 13.7, 10.4, 5.5, 5.0 Hz, 1H), 1.05 (s, 3H), 0.96 – 0.91 (m, 1H), 0.87 (s, 3H), 0.87 – 0.79 (m, 2H), 0.74 (tdd, *J* = 8.6, 6.2, 3.7 Hz, 1H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 197.9 (C), 159.8 (C), 159.3 (C), 138.4 (C), 131.2 (C), 129.4 (CH), 114.1 (CH), 72.9 (CH_2), 69.6 (CH_2), 68.1 (CH_2), 58.3 (CH_3), 54.8 (CH_3), 41.3 (CH), 40.1 (CH_2), 39.1 (C), 30.2 (CH_2), 25.5 (CH_3), 20.9 (CH_3), 10.1 (CH), 7.0 (CH_2), 6.9 (CH_2) **IR** (neat, cm^{-1}) 2922 (m), 2855 (m), 1673 (s), 1513 (m), 1247 (m), 1094 (m) **HRMS** (EI) m/z $(M-C_8H_9O)^+$ calculated for $C_{15}H_{23}O_3$ 251.1642, found 251.1645 (1.7%)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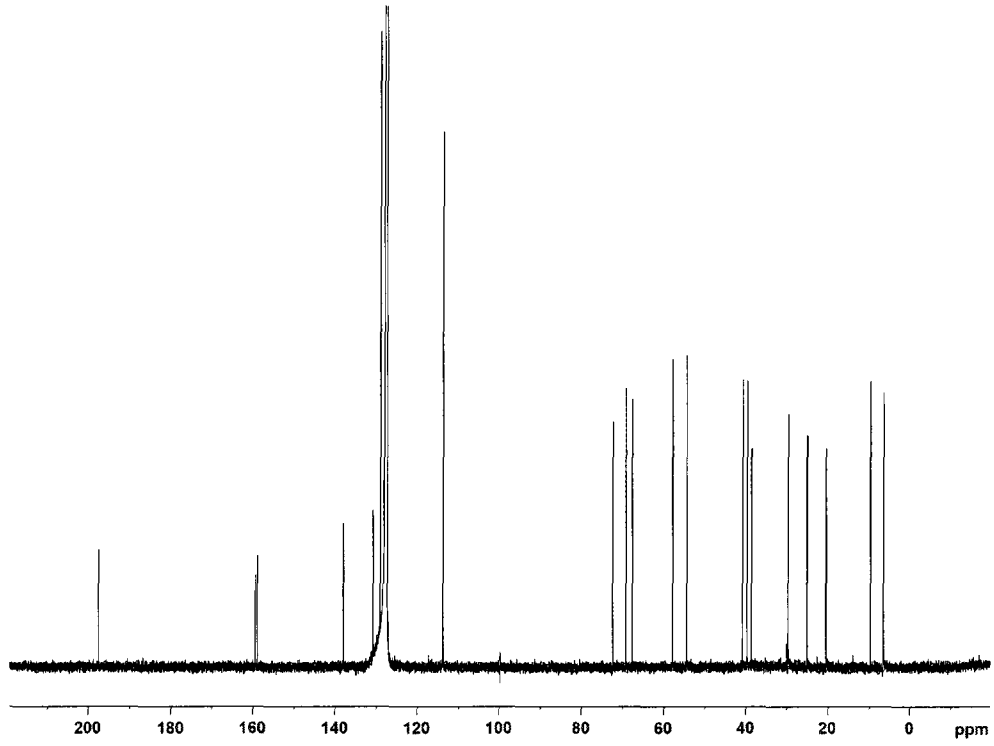
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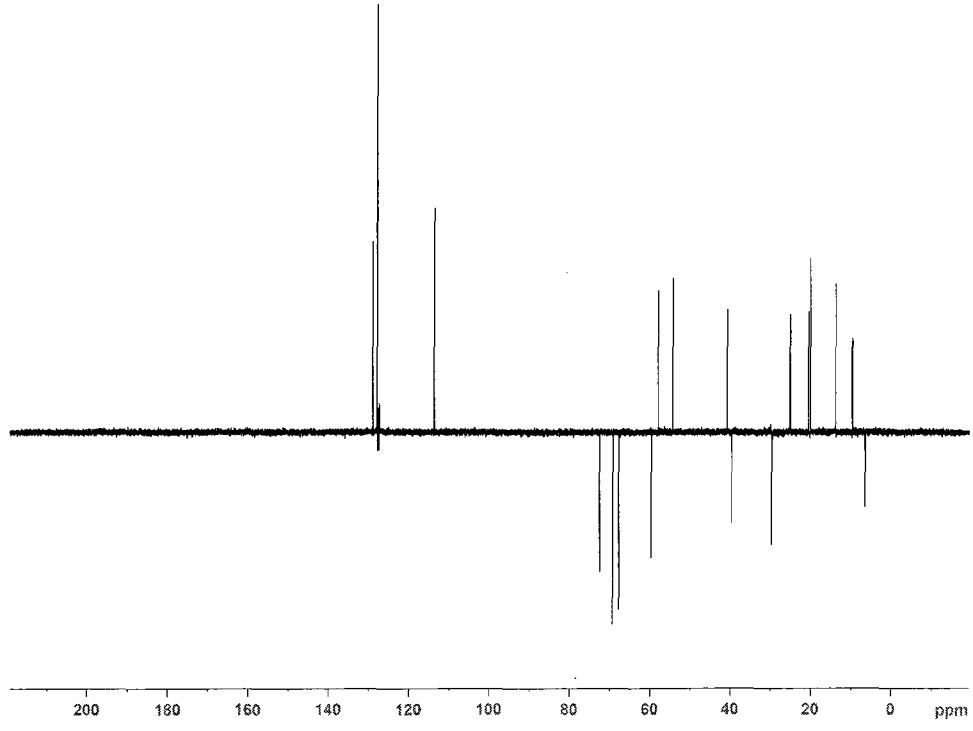
ppm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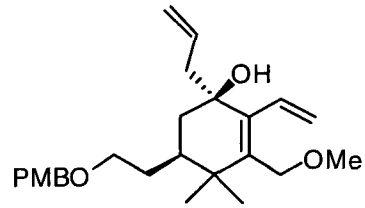
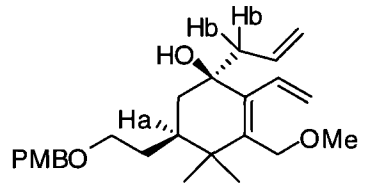
***trans*-1-allyl-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethyl-2-vinylcyclohex-2-enol (2.75)**

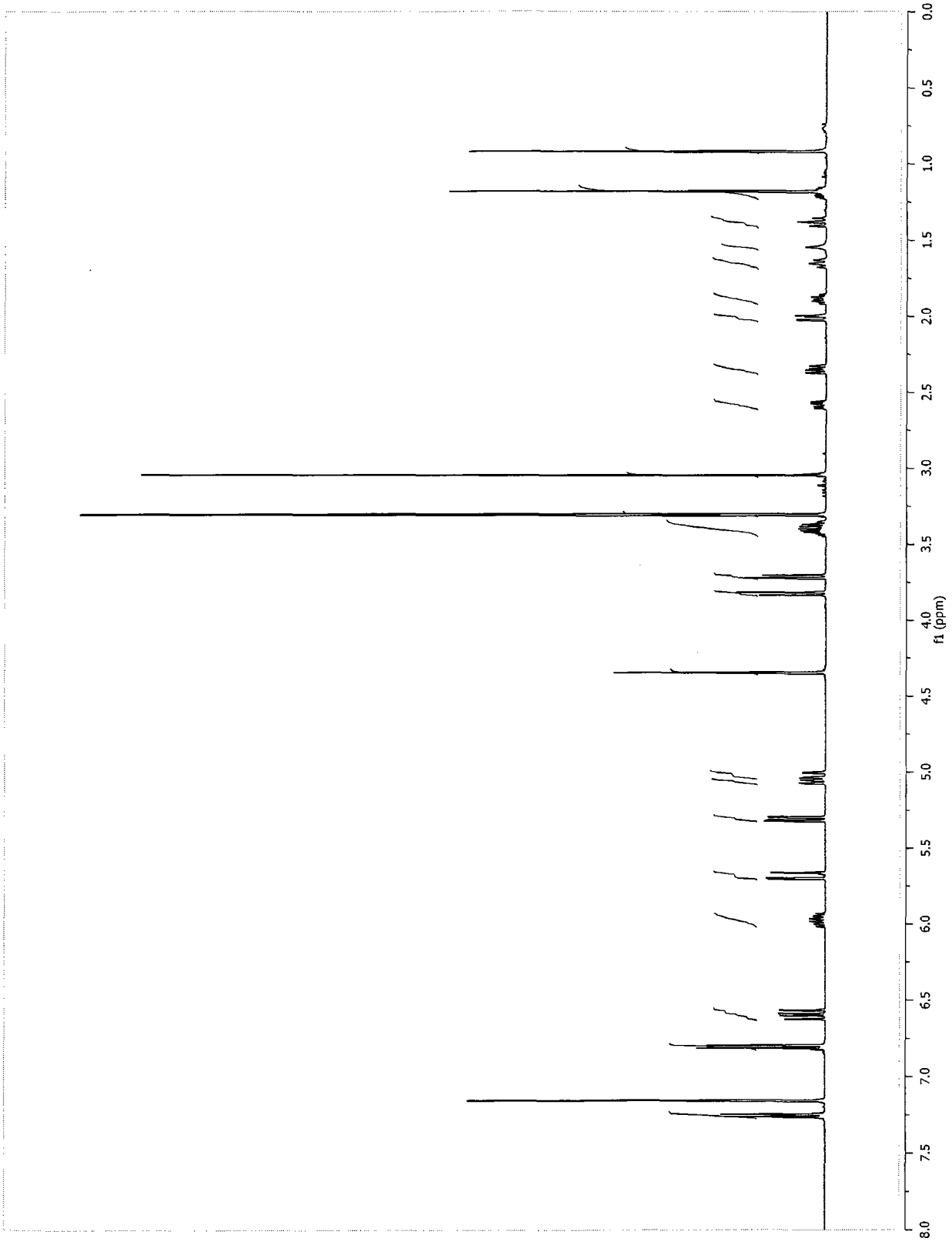


To a solution of **2.63** (2.0 g, 5.58 mmol, 1.0 equiv) in THF (80 mL) was added a 1M solution of allyl magnesium bromide in Et_2O (16.7 mL, 16.7 mmol, 3.0 equiv) dropwise at -78 °C. The mixture was stirred 1 hour at -78 °C, was slowly warmed to room temperature and was quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (x3). The combined organic fractions were washed with brine (x2), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/hexanes) as eluent to afford **2.75** a colorless oil (2.19 g, 98%). The product is a 3:1 mixture of diastereoisomers. The major one is drawn at the top. The relative stereochemistry was assigned by NOESY experiment. There is a correlation between proton Ha and Hb.



major product **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.25 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.60 (dd, *J* = 17.7, 11.7 Hz, 1H), 5.97 (dddd, *J* = 17.1, 10.2, 8.4, 6.4 Hz, 1H), 5.68 (dd, J = 17.7, 2.9 Hz, 1H), 5.31 (dd, *J* = 11.7, 2.9 Hz, 1H), 5.06 (ddt, *J* = 10.2, 2.2, 1.0 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.5, 1.3 Hz, 1H), 4.35 (s, 2H), 3.82 (d, *J* = 9.4 Hz, 1H), 3.71 (d, *J* = 9.4 Hz, 1H), 3.42 (ddd, *J* = 9.1, 6.6, 4.8 Hz, 1H), 3.38 (ddd, *J* = 9.0, 8.4, 5.5 Hz, 1H), 3.30 (s, 3H), 3.04 (s, 3H), 2.58 (ddq, *J* = 14.1, 6.3, 1.3 Hz, 1H), 2.35 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.01 (dd, *J* = 13.1, 2.6 Hz, 1H), 1.89 (dddd, *J* = 13.6, 8.4, 6.7, 1.7 Hz, 1H), 1.65 (ddt, *J* = 12.6, 10.6, 2.1 Hz, 1H), 1.54 (br s, 1H), 1.38 (ddd, *J* = 12.7, 12.7, 1.1 Hz, 1H), 1.22 – 1.15 (m, 1H), 1.18 (s, 3H), 0.92 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.7 (C), 143.0 (C), 139.8 (C), 134.9 (CH), 134.3 (CH), 131.3

(C), 129.4 (CH), 119.9 (CH_2), 118.1 (CH_2), 114.1 (CH), 72.8 (CH_2), 72.7 (C), 70.6 (CH_2), 69.0 (CH_2), 57.3 (CH_3), 54.8 (CH_3), 44.6 (CH_2), 38.9 (CH), 38.6 (C), 36.7 (CH_2), 30.6 (CH_2), 26.1 (CH_3), 21.4 (CH_3) **IR** (neat, cm^{-1}) 3446 (s), 2970 (m), 2870 (m), 1513 (m), 1247 (m), 1090 (m) **HRMS** (EI) m/z $(M-C_3H_5)^+$ calculated for $C_{22}H_{31}O_4$ 359.2222, found 359.2234 (6.3%)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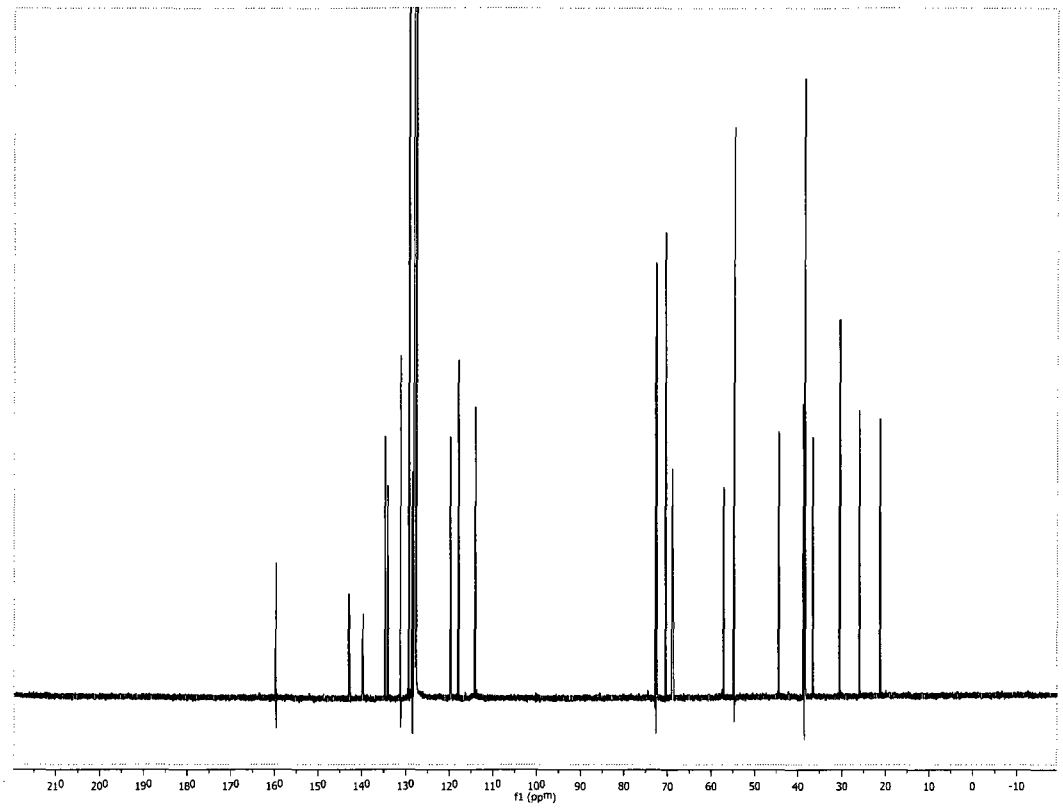
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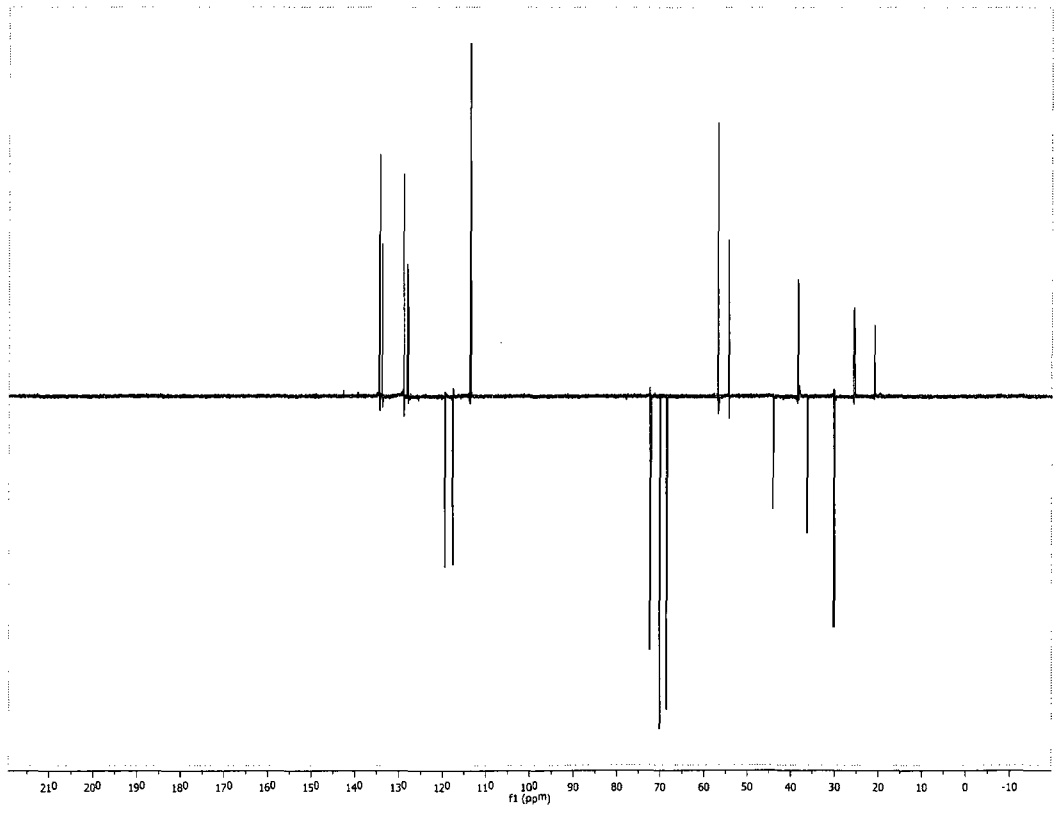
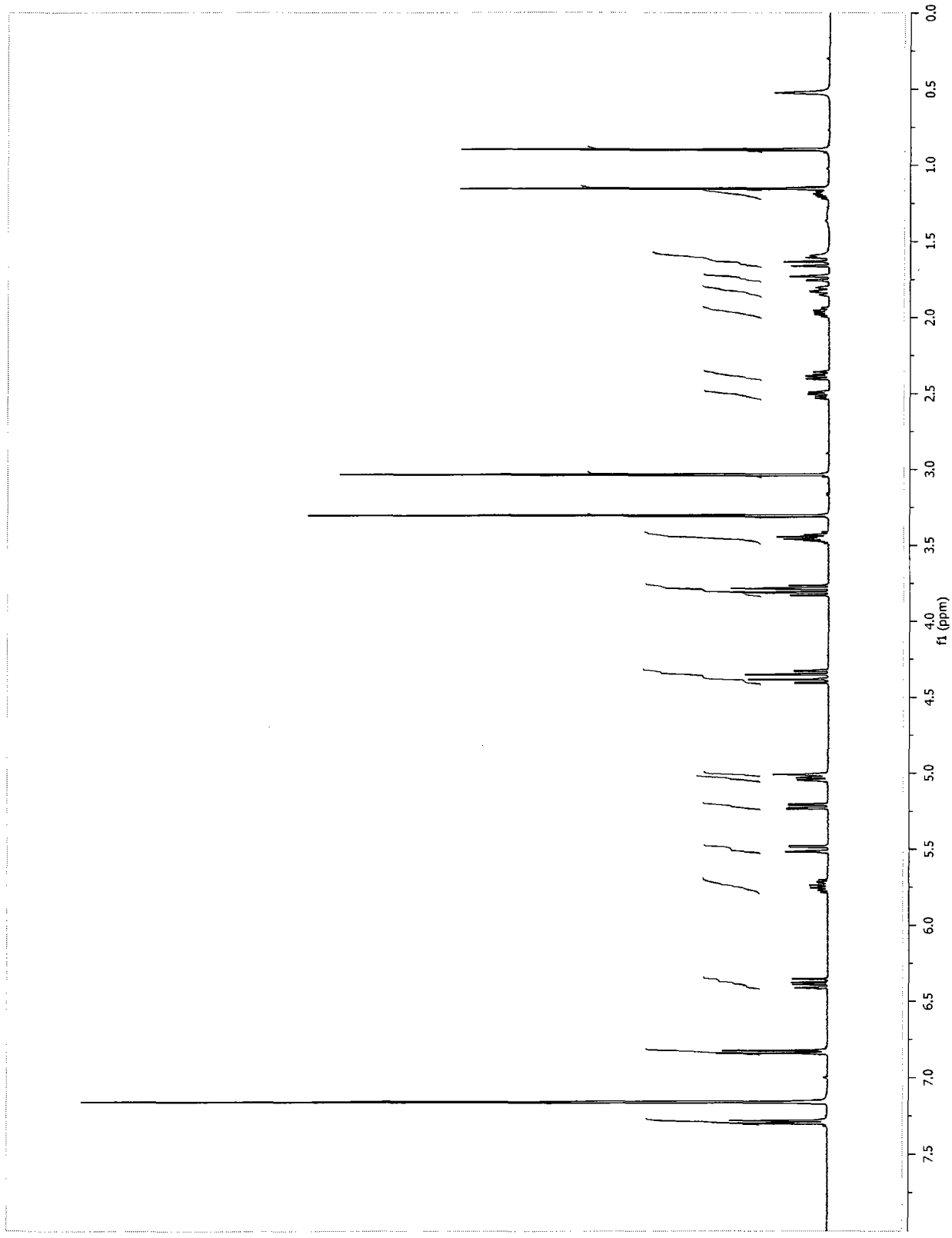

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

minor product **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.29 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.38 (dd, *J* = 17.6, 11.5 Hz, 1H), 5.74 (dddd, *J* = 16.9, 10.4, 8.0, 6.5 Hz, 1H), 5.50 (dd, *J* = 17.6, 2.8 Hz, 1H), 5.22 (dd, *J* = 11.5, 2.8 Hz, 1H), 5.05 – 5.02 (m, 1H), 5.02 – 5.00 (m, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 11.7, 1H), 3.81 (d, *J* = 9.8 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 1H), 3.49 – 3.41 (m, 2H), 3.30 (s, 3H), 3.03 (s, 3H), 2.51 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.38 (dd, *J* = 13.8, 8.1 Hz, 1H), 1.96 (dtd, *J* = 13.7, 7.7, 1.8 Hz, 1H), 1.83 (ddt, *J* = 12.8, 10.8, 2.5 Hz, 1H), 1.74 (dd, *J* = 14.0, 2.9 Hz, 1H), 1.63 (dd, *J* = 13.6, 13.6 Hz, 1H), 1.59 (br s, 1H), 1.22 – 1.15 (m, 1H), 1.15 (s, 3H), 0.90 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 159.7 (C), 142.6 (C), 140.1 (C), 134.9 (CH), 134.5 (CH), 131.5 (C), 129.4 (CH), 119.8 (CH_2), 117.8 (CH_2), 114.1 (CH), 72.8 (CH_2), 71.6 (C), 70.4 (CH_2), 69.0 (CH_2), 57.4 (CH_3), 54.8 (CH_3), 46.2 (CH_2), 38.3 (C), 37.5 (CH_2), 36.6 (CH), 30.6 (CH_2), 25.1 (CH_3), 20.3 (CH_3) **IR** (neat, cm^{-1}) 3430 (s), 2913 (m), 2850 (m), 1512 (m), 1246 (m), 1086 (m) **HRMS** (EI) m/z $(M-C3H5)^{+}$ calculated for C22H31O4 359.2222, found 359.2230 (3.2%)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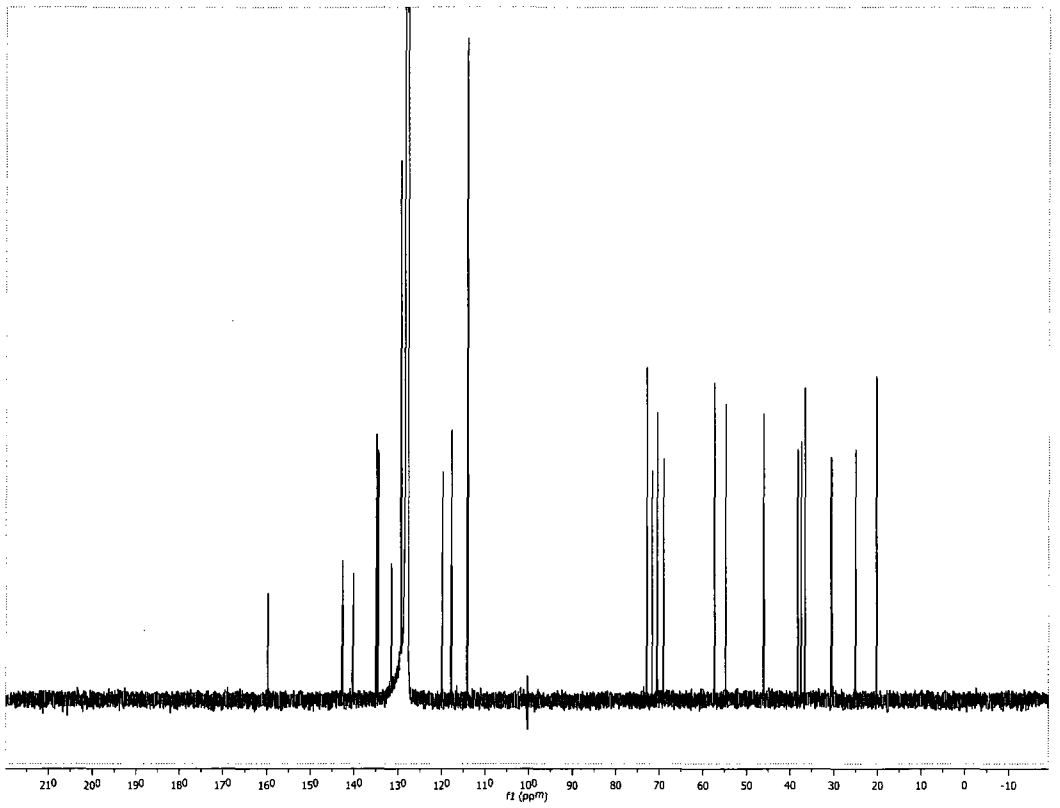
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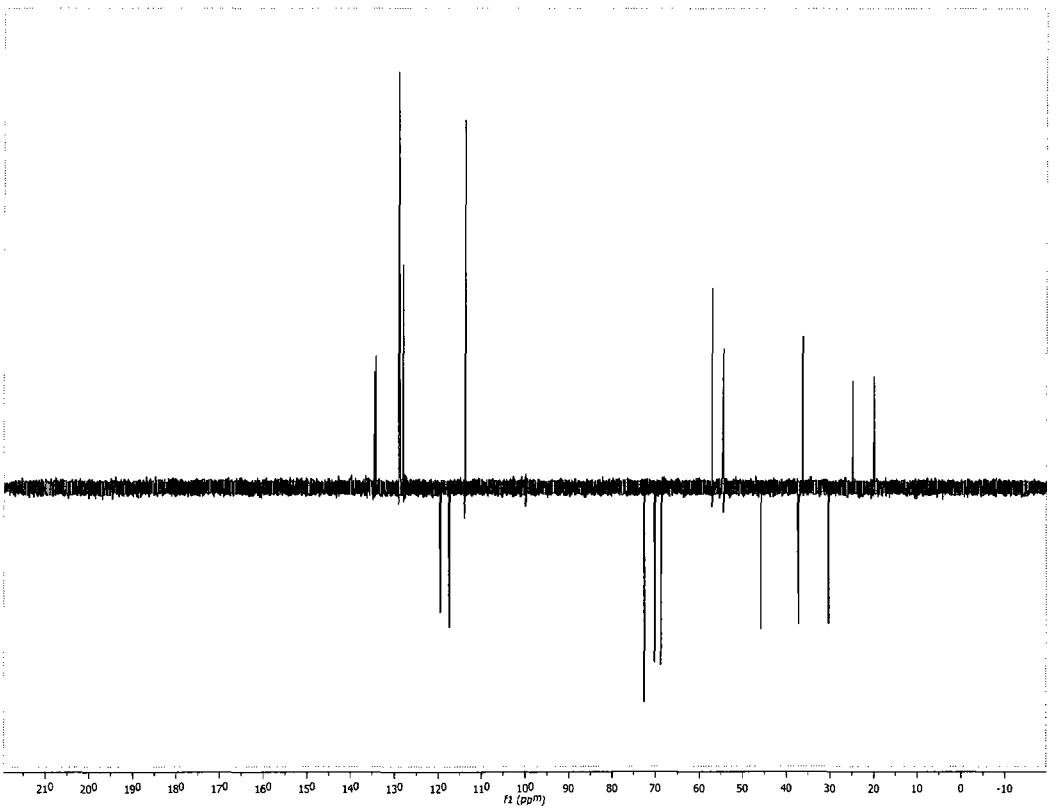
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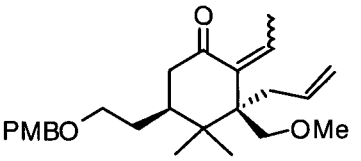
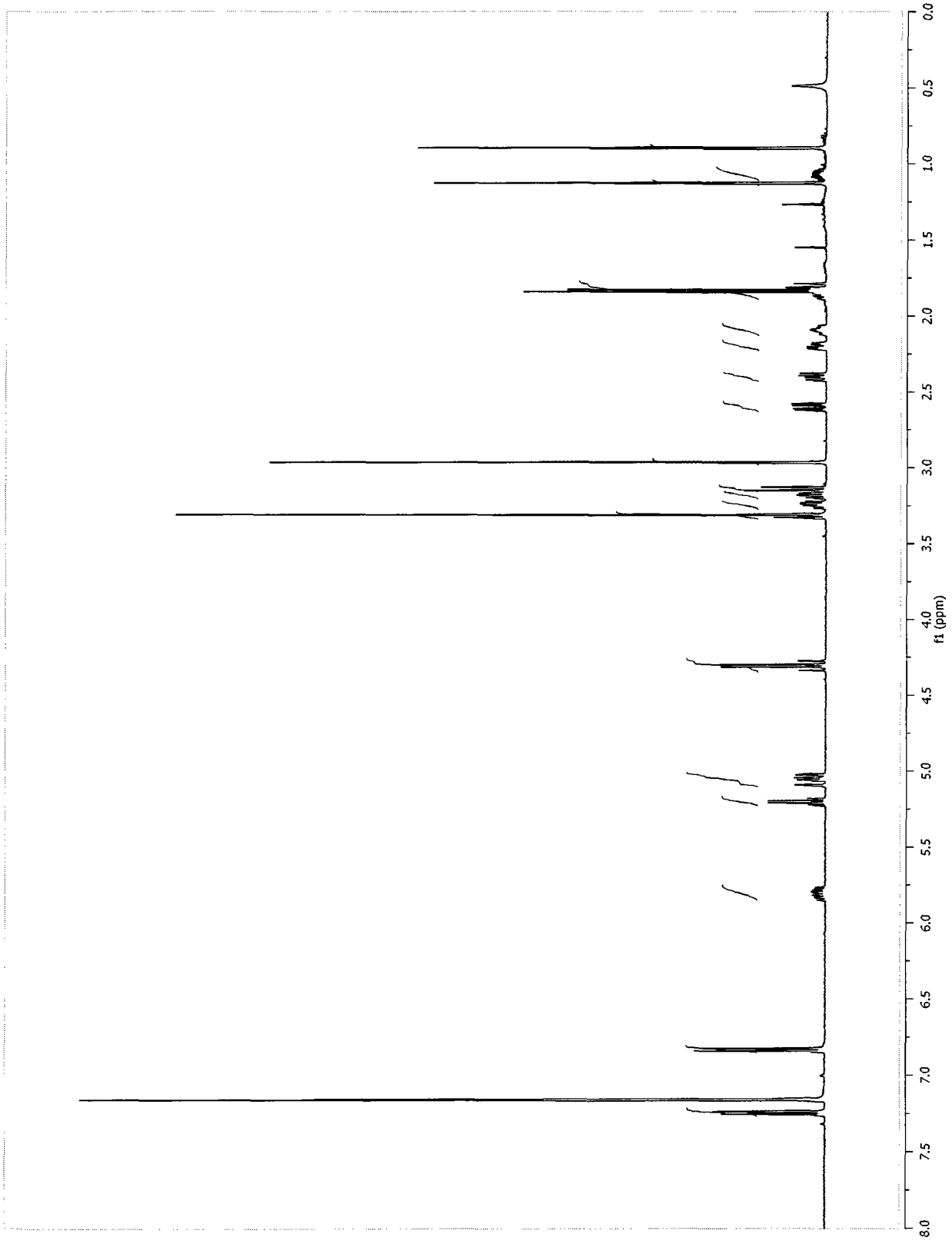
f1 (ppm)

3-allyl-2-ethylidene-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethylcyclohexanone (2.76)



KH was washed 3 times with freshly dried pentane (distilled over calcium hydride). To a suspension of KH (30% dispersion in mineral oil, 2.74 g, 4.86 mmol, 5 equiv) in THF (40 mL) was added a solution of dry (aseotropal removal of H_2O using dry benzene) **2.75** (1.64 g, 4.10 mmol, 1.0 equiv) and 18-crown-6 (5.42 g, 20.5 mmol, 5.0 equiv) in THF (40 mL) *via* cannula. The mixture was stirred for 30 minutes at reflux. The mixture was cooled to room temperature and the reaction was quenched by addition of MeOH and saturated aqueous NH_4Cl. The aqueous phase was extracted Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (10–20% EtOAc/hexanes) as eluent to afford **2.76** as a colorless oil (1.14 g, 70%). The product is a 1:1 mixture of E/Z isomers.

isomer 1 **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.25 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.81 (dddd, *J* = 17.0, 10.0, 8.9, 5.8 Hz, 1H), 5.20 (q, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.32 (d, *J* = 11.8 Hz, 1H), 4.29 (d, *J* = 11.8 Hz, 1H), 3.32 (d, *J* = 9.5 Hz, 1H), 3.31 (s, 3H), 3.24 (ddd, *J* = 9.1, 6.9, 5.0 Hz, 1H), 3.17 (ddd, *J* = 8.3, 8.3, 6.1 Hz, 1H), 3.14 (d, *J* = 10 Hz, 1H), 2.96 (s, 3H), 2.60 (dd, *J* = 15.5, 5.3 Hz, 1H), 2.40 (dd, *J* = 13.6, 8.9 Hz, 1H), 2.19 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.09 (dddd, *J* = 12.5, 10.0, 5.1, 2.5 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.83 (d, *J* = 7.0 Hz, 3H), 1.81 (dd, *J* = 15.5, 12.5 Hz, 1H), 1.12 (s, 3H), 1.10 – 1.03 (m, 1H), 0.89 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 203.7 (C), 159.8 (C), 143.6 (C), 135.2 (CH), 131.2 (C), 129.5 (CH), 126.2 (CH), 117.5 (CH_2), 114.2 (CH), 74.3 (CH_2), 72.9 (CH_2), 68.4 (CH_2), 58.5 (CH_3), 54.8 (CH_3), 51.8 (C), 45.4 (CH_2), 40.4 (C), 38.7 (CH), 35.6 (CH_2), 31.3 (CH_2), 22.4 (CH_3), 18.3 (CH_3), 15.1 (CH_3) **IR** (neat, cm^{-1}) 2972 (m), 2878 (m) 1693 (s), 1513 (m), 1247 (m), 1115 (m), 1093 (m) **HRMS** (EI) m/z $(M)^+$ calculated for C25H36O4 400.2614, found 400.2612 (1.5%)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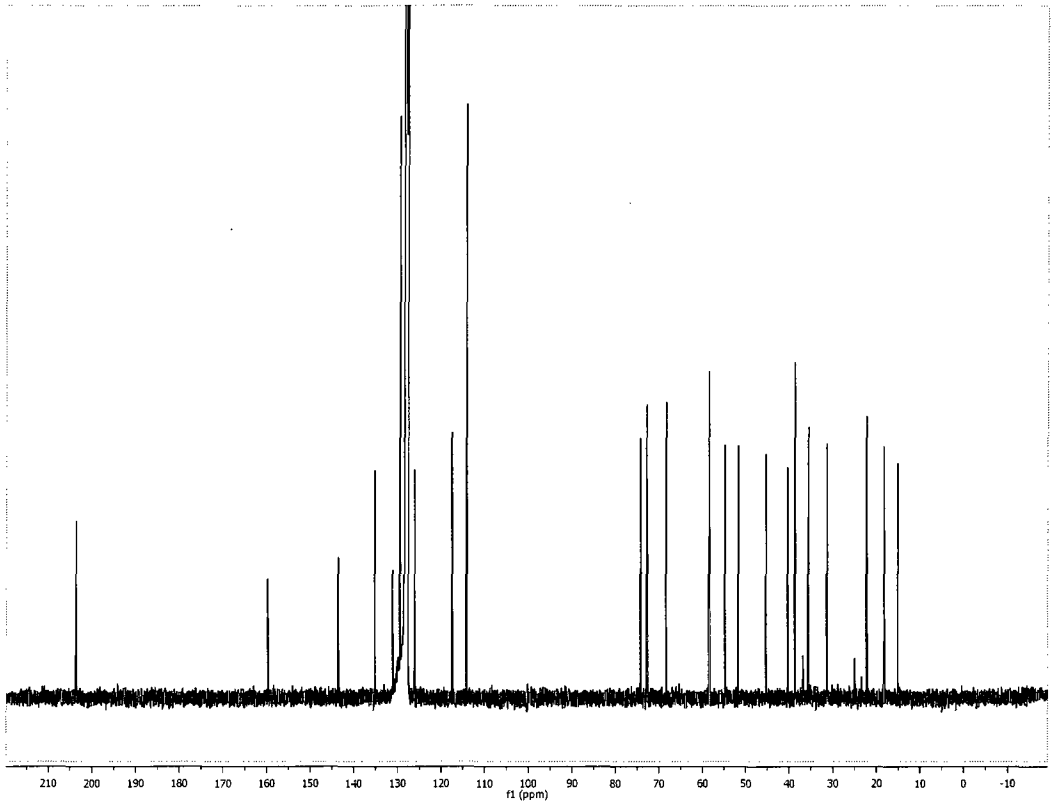
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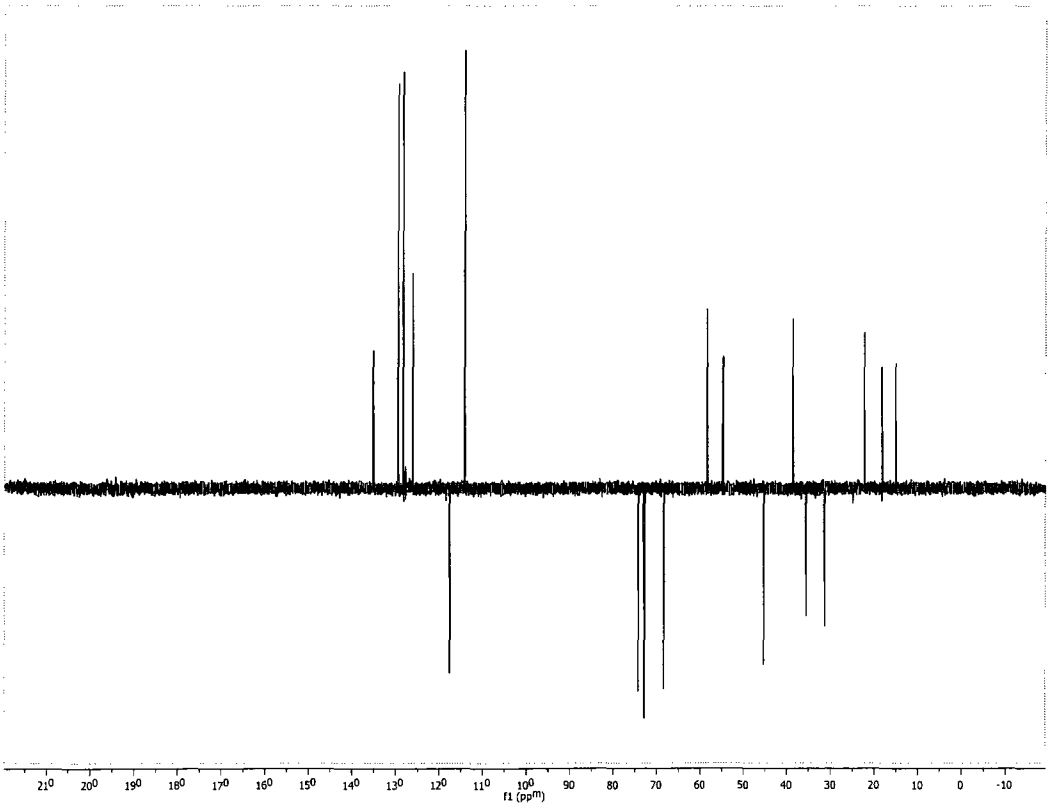
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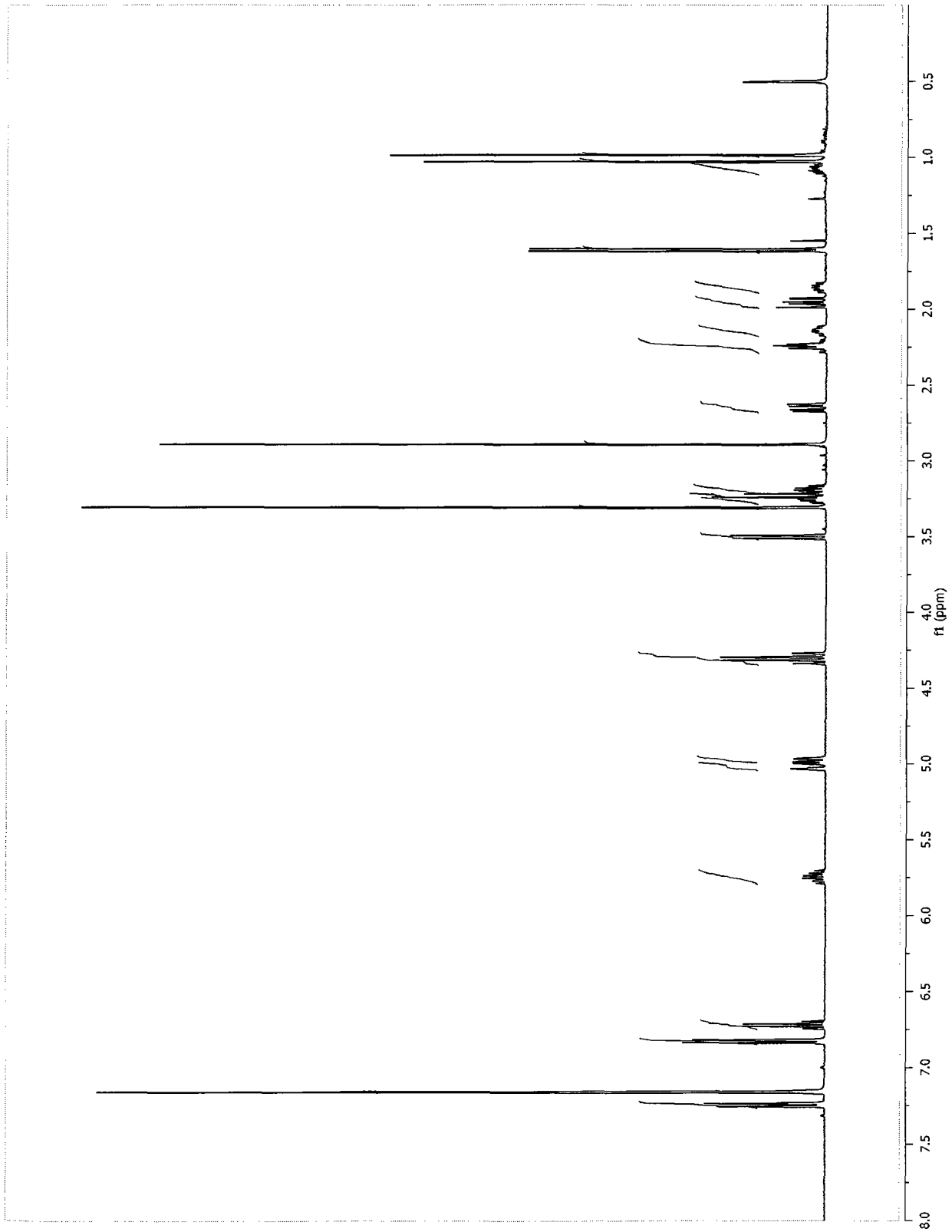
f1 (ppm)

isomer 2 **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 7.24 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.72 (q, *J* = 7.7 Hz, 1H), 5.75 (dddd, *J* = 17.0, 10.2, 7.9, 6.7 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.3, 1.2 Hz, 1H), 4.97 (ddt, *J* = 10.1, 2.1, 1.0 Hz, 1H), 4.32 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 3.50 (d, *J* = 10.3 Hz, 1H), 3.31 (s, 3H), 3.26 (ddd, *J* = 9.1, 6.9, 4.7 Hz, 1H), 3.23 (d, J = 10.3 Hz, 1H), 3.18 (ddd, *J* = 8.8, 8.8, 6.0 Hz, 1H), 2.89 (s, 3H), 2.65 (dd, *J* = 17.6, 6.3 Hz, 1H), 2.28 - 2.20 (m, 2H), 2.17 – 2.11 (m, 1H), 1.96 (dd, *J* = 17.6, 11.5 Hz, 1H), 1.86 (dddd, *J* = 13.3, 8.5, 7.1, 2.4 Hz, 1H), 1.61 (d, *J* = 7.7 Hz, 3H), 1.07 (dddd, J = 13.5, 10.4, 5.7, 4.8 Hz, 1H), 1.03 (s, 3H), 0.98 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 202.2 (C), 159.8 (C), 142.9 (C), 135.4 (CH), 132.7 (CH), 131.3 (C), 129.5 (CH), 117.2 (CH_2), 114.2 (CH), 75.4 (CH_2), 72.9 (CH_2), 68.2 (CH_2), 57.9 (CH_3), 54.8 (CH_3), 52.3 (C), 42.9 (CH_2), 40.2 (C), 38.0 (CH_2), 36.5 (CH), 31.2 (CH_2), 21.7 (CH_3), 19.2 (CH_3), 14.5 (CH_3) **IR** (neat, cm^{-1}) 2935 (m), 1686 (s), 1613 (m), 1513 (m), 1247 (m), 1114 (m), 1094 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{25}H_{36}O_4$ 400.2614, found 400.2601 (2.5%).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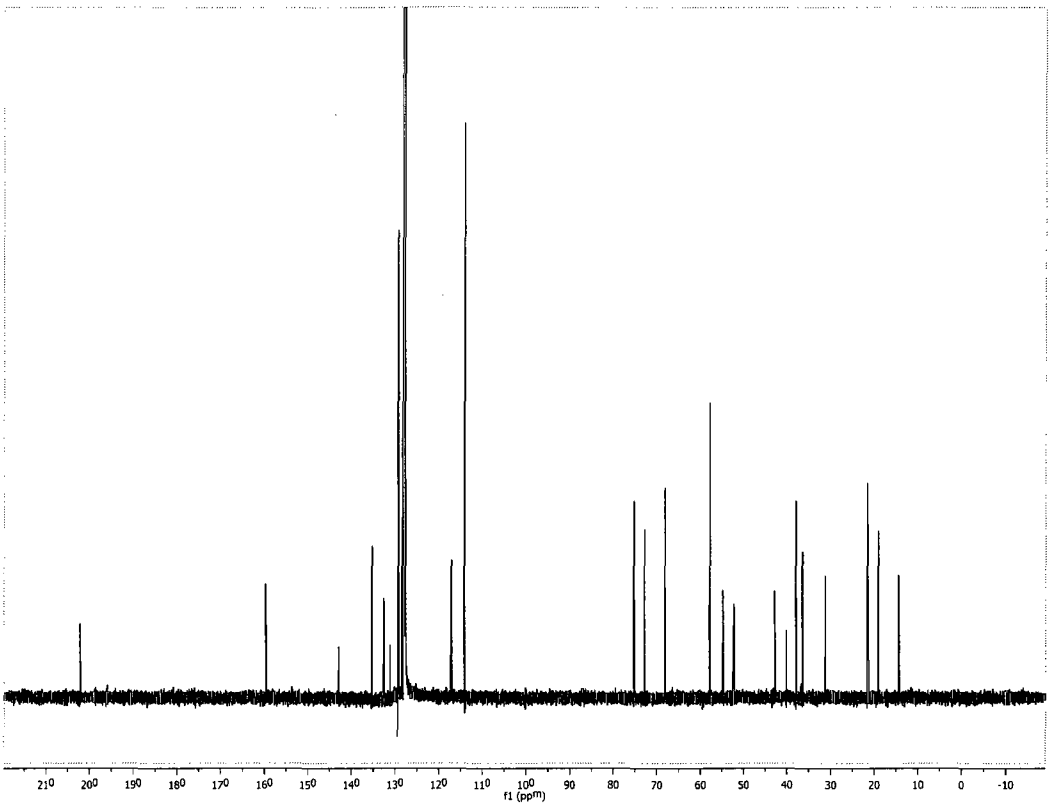
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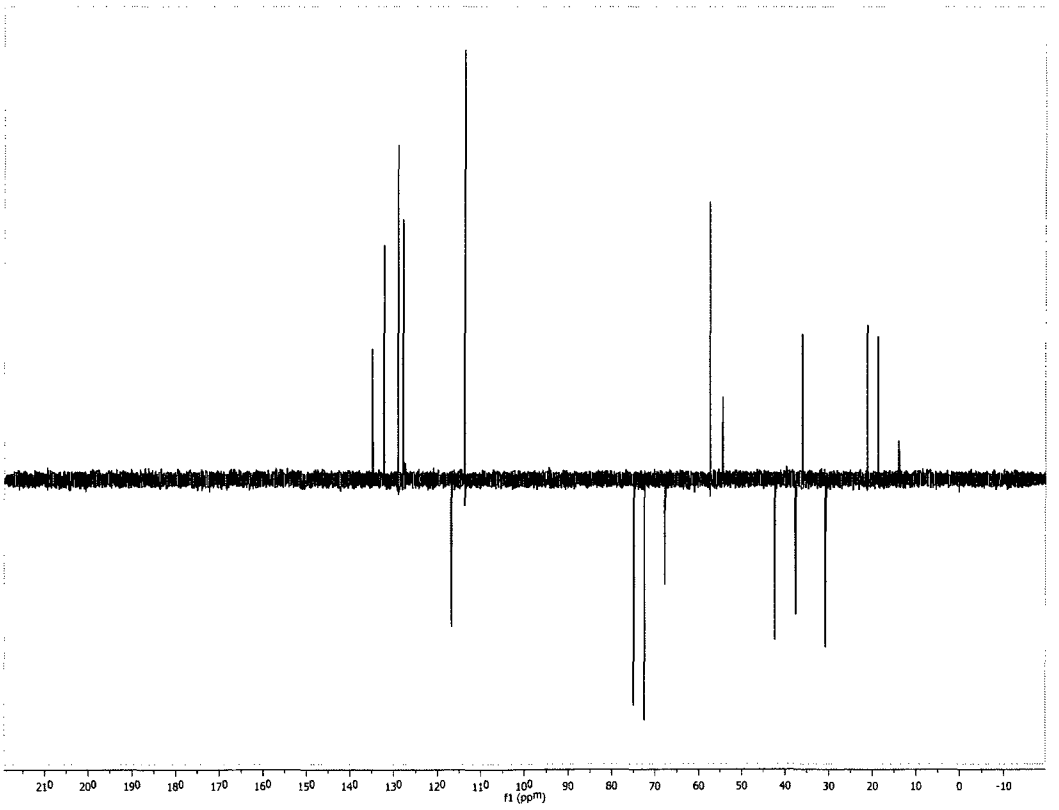
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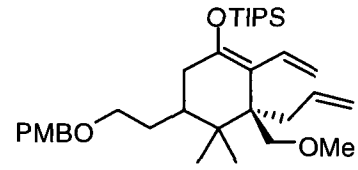
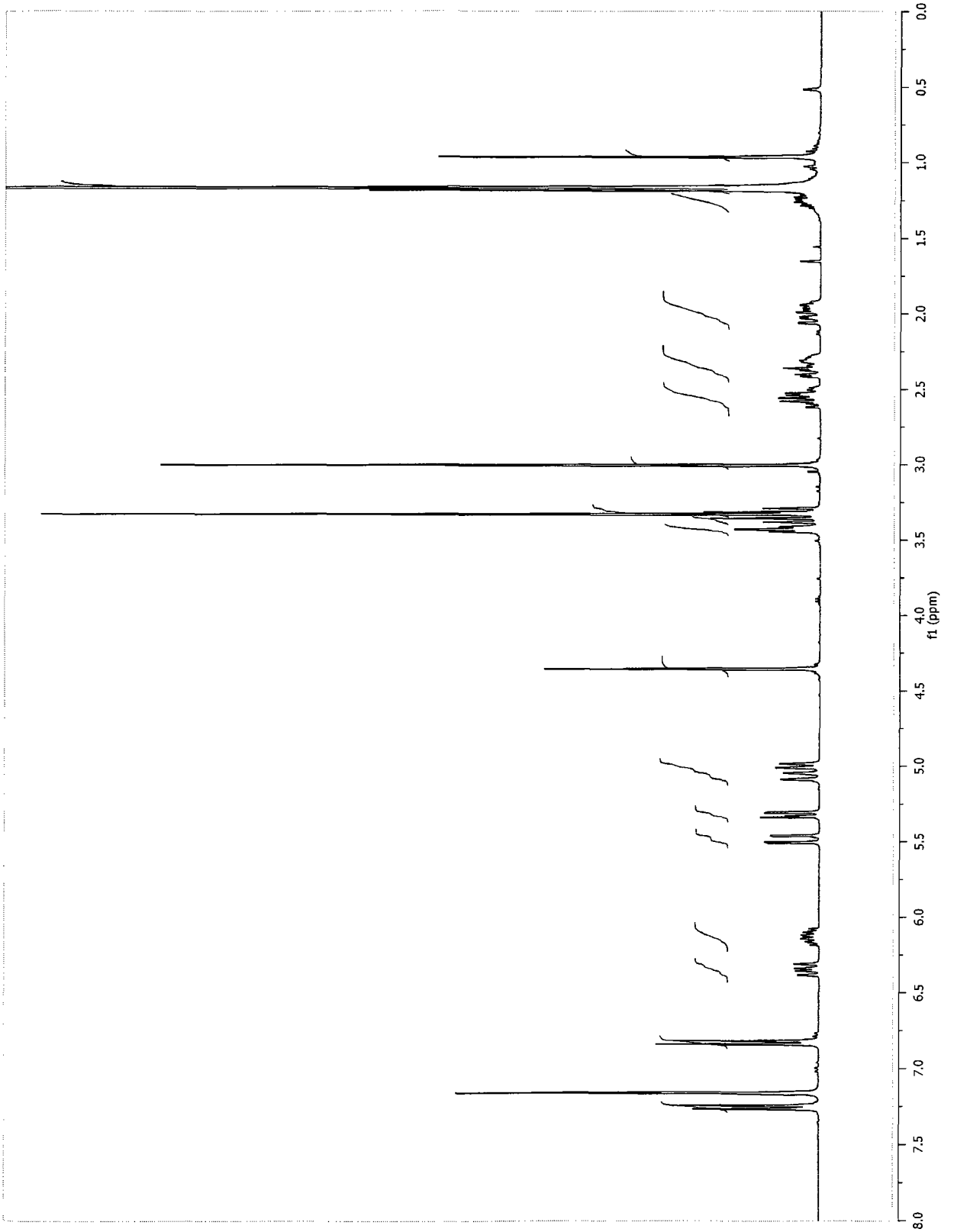
f1 (ppm)

(3-allyl-5-(2-(4-methoxybenzyloxy)ethyl)-3-(methoxymethyl)-4,4-dimethyl-2-vinylcyclohex-1-enyloxy)triisopropylsilane (2.77)



To a solution of compound **2.76** (0.050 g, 0.125 mmol, 1.0 equiv) in DCM (3 mL) was added Et_3N (0.1 mL, 0.750 mmol, 6.0 equiv) and TIPSOTf (0.05 mL, 0.187 mmol, 1.5 equiv). The mixture was stirred at reflux for 1 hour and saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with DCM (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 5% EtOAc/hexanes to afford **2.77** as a colorless oil (0.055 g, 79%).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.26 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7, 2H), 6.35 (dd, *J* = 17.8, 11.5 Hz, 1H), 6.13 (dddd, *J* = 17.0, 9.9, 9.1, 5.9 Hz, 1H), 5.49 (dd, *J* = 17.9, 2.7 Hz, 1H), 5.32 (dd, *J* = 11.5, 2.7 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.99 (dt, *J* = 10.0, 1.6 Hz, 1H), 4.36 (s, 2H), 3.44 (d, *J* = 5.7 Hz, 1H), 3.45 – 3.41 (m, 1H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.33 (s, 3H), 3.30 (d, *J* = 9.8 Hz, 1H), 3.00 (s, 3H), 2.59 (dd, *J* = 14.8, 8.9 Hz, 1H), 2.51 (ddt, *J* = 14.8, 5.7, 1.8 Hz, 1H), 2.39 (dd, *J* = 16.7, 5.0 Hz, 1H), 2.35 – 2.28 (m, 1H), 2.03 (ddd, *J* = 16.6, 11.4, 1.7 Hz, 1H), 1.95 (ddd, *J* = 13.9, 6.9, 3.1 Hz, 1H), 1.30 – 1.18 (m, 1H), 1.18 (s, 3H), 1.16 (s, 21H), 0.96 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 159.7 (C), 147.6 (C), 138.6 (CH), 134.1 (CH), 131.4 (C), 129.3 (CH), 117.7 (CH_2), 117.4 (C), 115.4 (CH_2), 114.1 (CH), 78.1 (CH_2), 72.9 (CH_2), 69.3 (CH_2), 58.3 (CH_3), 54.8 (CH_3), 48.8 (C), 39.5 (CH_2), 38.7 (C), 36.3 (CH), 34.9 (CH_2), 29.8 (CH_2), 23.4 (CH_3), 18.53 (CH_3), 18.46 (CH_3), 13.8 (CH) **IR** (neat, cm^{-1}) 2944 (m), 2866 (m), 1513 (m), 1248 (m), 1211 (m), 1100 (m). **HRMS** (EI) m/z $(M-C_8H_9O)^+$ calculated for $C_{26}H_{47}O_6Si$ 435.3294, found 435.3297 (6.5%).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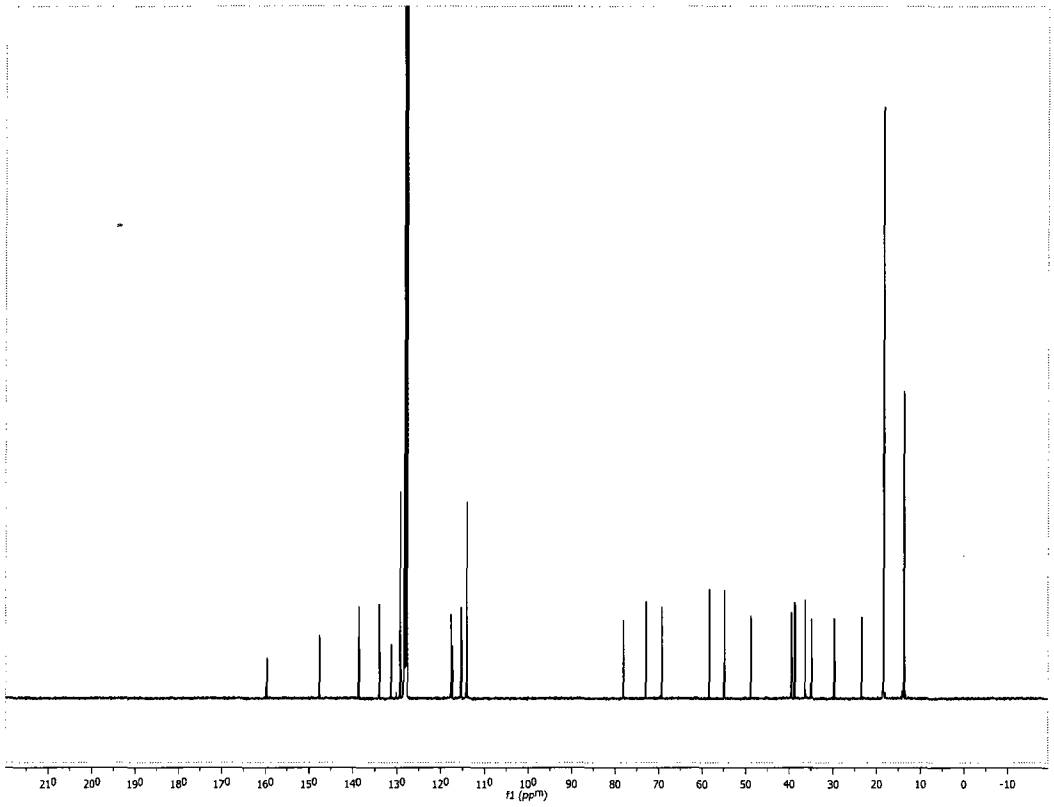
f1 (ppm)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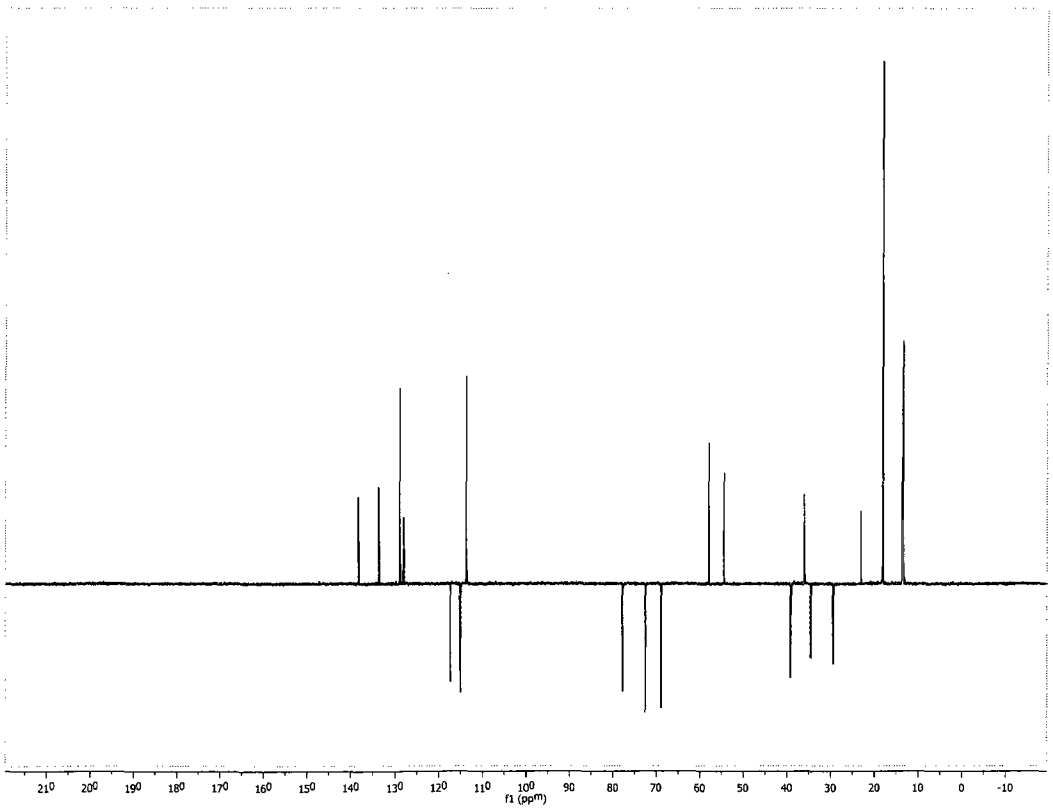
f1 (ppm)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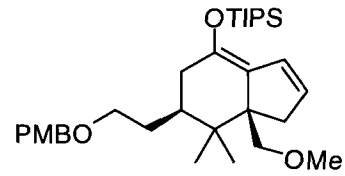
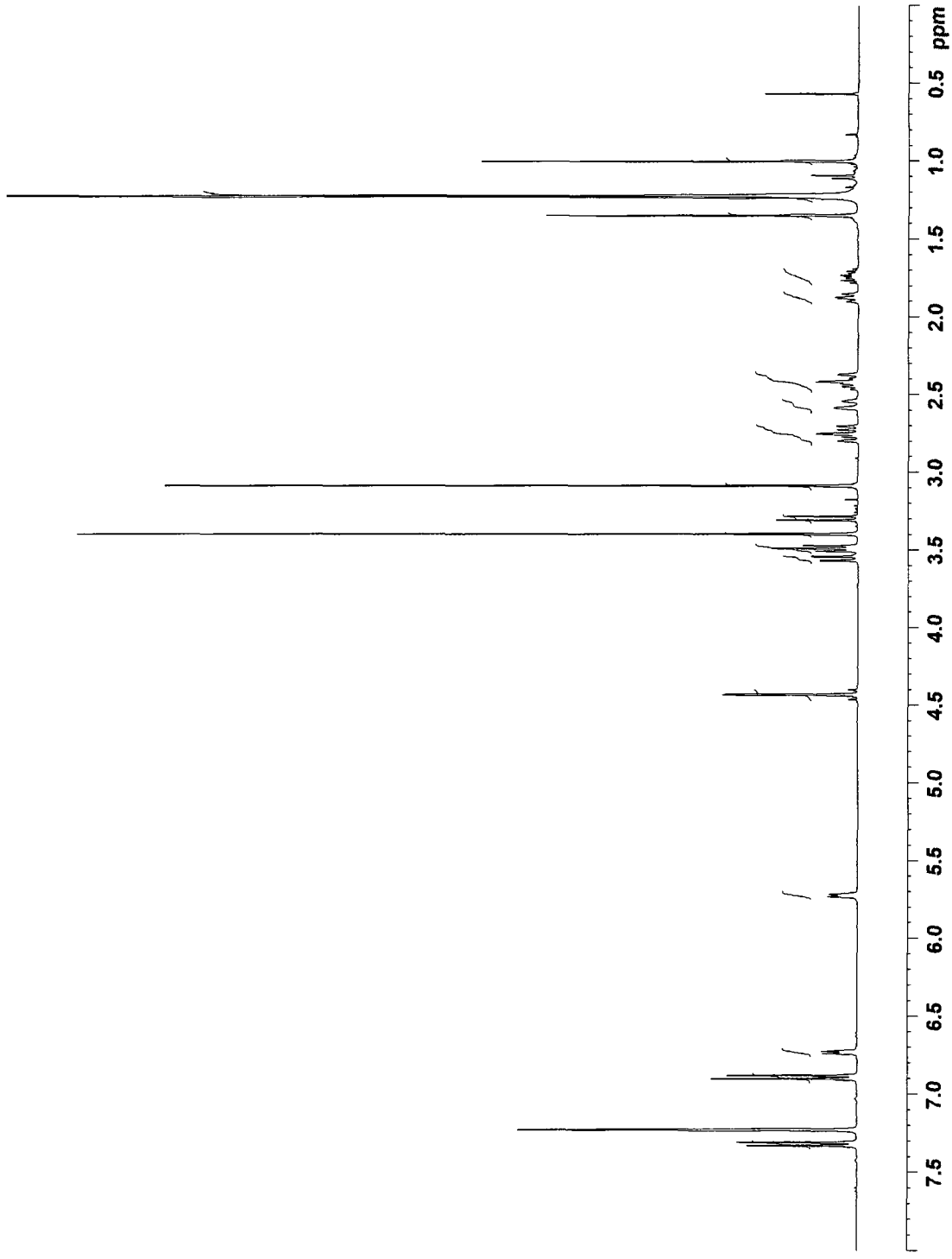
f1 (ppm)

triisopropyl((6,7a)-6-(2-(4-methoxybenzyloxy)ethyl)-7a-(methoxymethyl)-7,7-dimethyl-5,6,7,7a-tetrahydro-1H-inden-4-yloxy)silane (2.78)



To a solution of compound **2.77** (0.813 g, 1.46 mmol, 1.0 equiv) in DCM (150 mL) was added Grubb's 2nd generation catalyst (0.062 g, 0.073 mmol, 0.05 equiv). The mixture was bubbled with argon for 20 minutes and stirred overnight at room temperature. Grubb's 2nd generation catalyst (0.050 g) was added, the mixture was stirred for 24 hours at room temperature and the reaction was quenched by bubbling air into the mixture for 20 minutes. DCM was evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0% to 5% EtOAc in hexanes) as eluent to afford **2.78** as a colorless oil (0.387 g, 50%). Starting material (0.089 g, 11%) was also recovered.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.25 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.66 (dt, *J* = 5.7, 2.0 Hz, 1H), 5.65 (dt, *J* = 5.4, 2.6 Hz, 1H), 4.37 (d, *J* = 11.7, Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.49 (dd, *J* = 9.6, 0.9 Hz, 1H), 3.43 (d, *J* = 6.1 Hz, 1H), 3.41 (d, *J* = 6.3 Hz, 1H), 3.33 (s, 3H), 3.23 (d, *J* = 9.6 Hz, 1H), 3.02 (s, 3H), 2.71 (dt, *J* = 18.2, 2.3 Hz, 1H), 2.67 (dd, *J* = 18.2, 8.9 Hz, 1H), 2.50 (d, *J* = 17.4 Hz, 1H), 2.40 – 2.30 (m, 2H), 1.81 (ddt, *J* = 10.4, 8.7, 2.2 Hz, 1H), 1.67 (dddd, *J* = 13.4, 10.3, 5.8, 5.8 Hz, 1H), 1.28 (s, 3H), 1.16 (s, 21H), 0.93 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 159.7 (C), 140.0 (C), 131.4 (C), 129.9 (CH), 129.3 (CH), 128.9 (CH), 127.3 (C), 114.1 (CH), 79.0 (CH_2), 72.9 (CH_2), 70.9 (CH_2), 58.5 (CH_3), 54. 8 (CH_3), 53.0 (C), 43.4 (CH), 38.8 (CH_2), 38.7 (C), 35.6 (CH_2), 35.5 (CH_2), 30.4 (CH_3), 23.7 (CH_3), 18.4 (CH_3), 13.5 (CH) **IR** (neat, cm^{-1}) 2944 (m), 2866 (m), 1513 (m), 1358 (m), 1248 (m), 1108 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{32}H_{52}O_4Si$ 528.3635, found 528.3659 (8.4%)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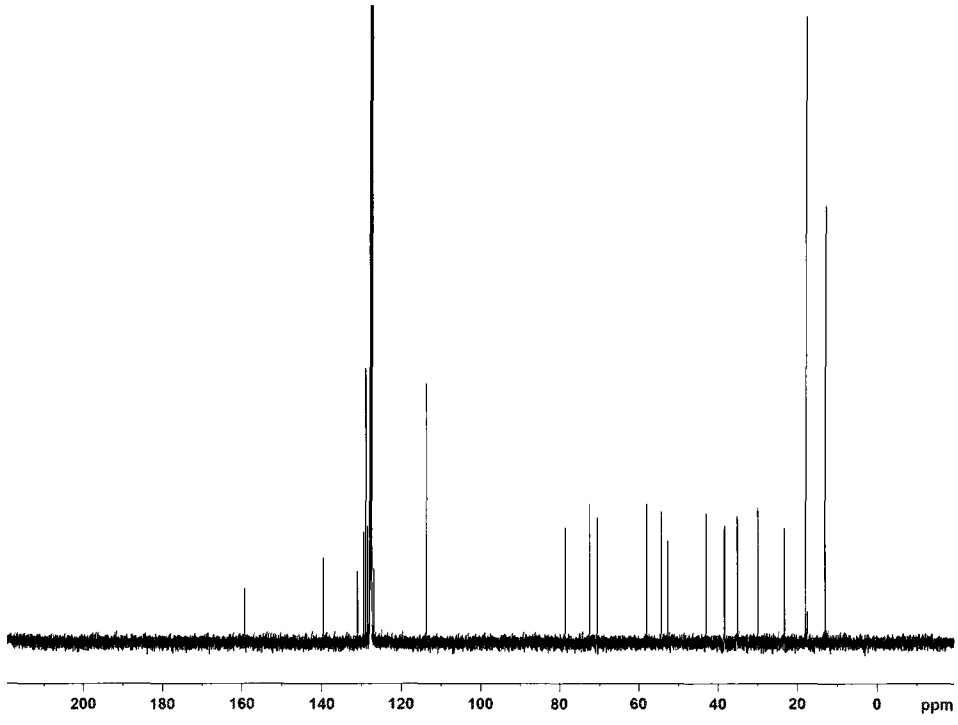
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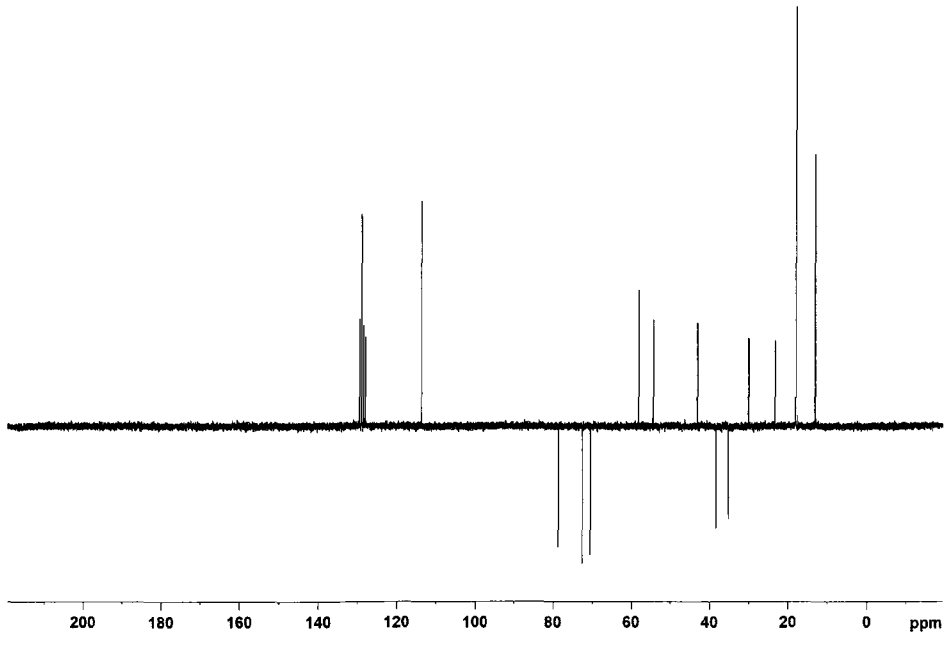
ppm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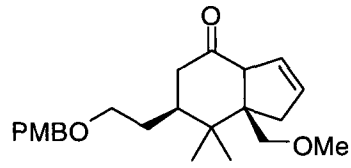
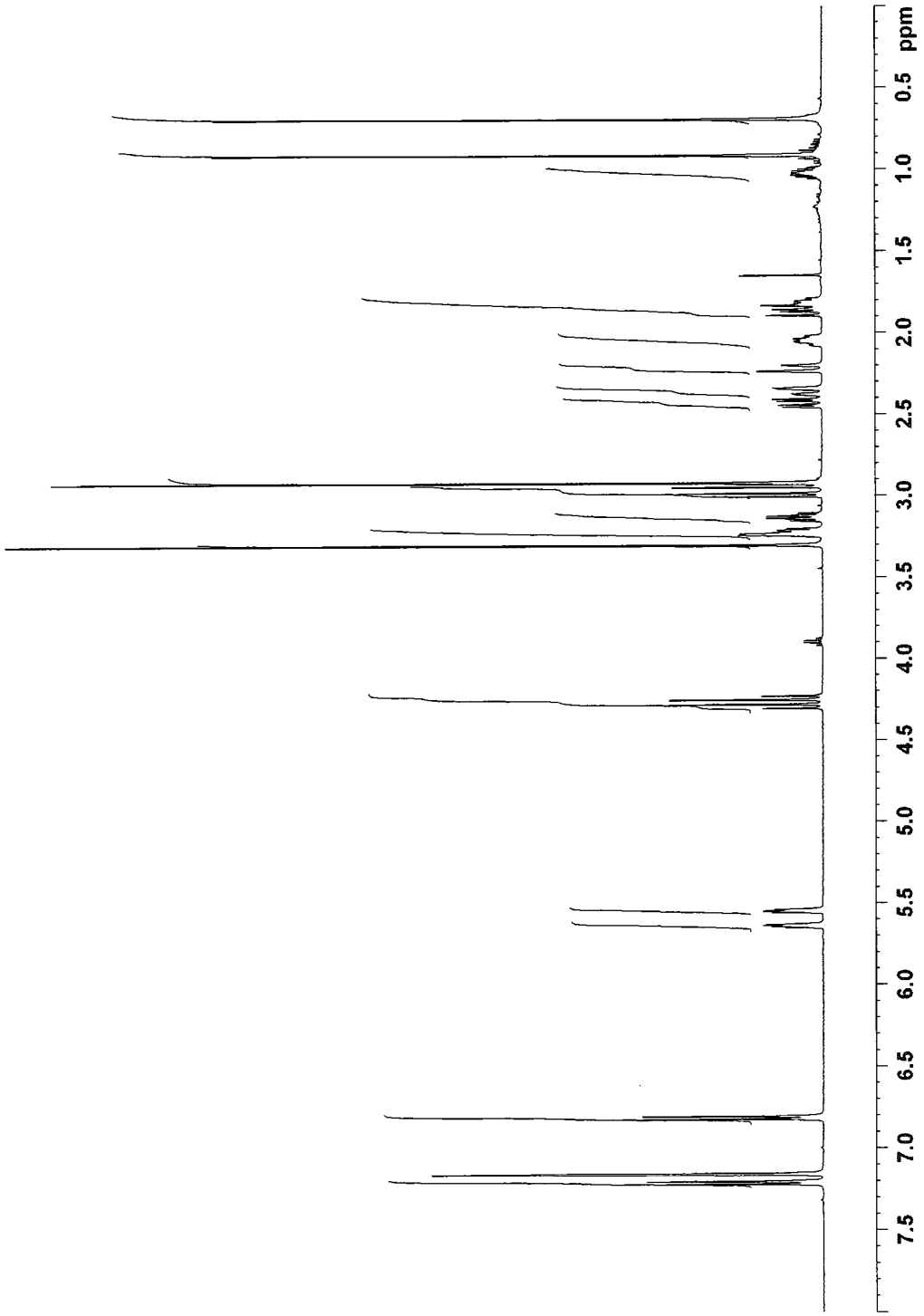
0
ppm

6-(2-(4-methoxybenzyloxy)ethyl)-7a-(methoxymethyl)-7,7-dimethyl-5,6,7,7a-tetrahydro-1H-inden-4(3aH)-one (2.74)



To a solution **2.78** (0.387 g, 0.732 mmol, 1 equiv) in THF (7 mL) was added TBAF (1M solution in THF, 1.1 mL, 1.10 mmol, 1.5 equiv). The mixture was stirred at room temperature for 2 hours. THF was evaporated under reduced pressure and the resulting residue was purified by flash chromatography on silica gel (pretreated with Et_3N) using 20% EtOAc/hexanes to afford **2.74** (0.179 g, 65%).

^{1}H NMR (500 MHz, C_6D_6) δ ppm 7.21 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.64 (dd, *J* = 5.5, 2.7 Hz, 1H), 5.55 (dd, *J* = 5.4, 2.6 Hz, 1H), 4.29 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 3.31 (s, 3H), 3.24 – 3.20 (m, 2H), 3.13 (ddd, *J* = 8.8, 8.8, 5.9 Hz, 1H), 3.00 (d, *J* = 9.2 Hz, 1H), 2.94 (d, *J* = 9.2 Hz, 1H), 2.93 (s, 3H), 2.43 (dd, *J* = 18.2, 6.3 Hz, 1H), 2.36 (ddt, *J* = 17.6, 2.6, 2.6 Hz, 1H), 2.22 (d, *J* = 17.6 Hz, 1H), 2.08 – 2.02 (m, 1H), 1.87 (dd, *J* = 18.3, 11.9 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.02 (ddd, *J* = 18.7, 10.8, 5.4 Hz, 1H), 0.92 (s, 3H), 0.69 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 210.3 (C), 159.8 (C), 133.0 (CH), 131.2 (C), 129.6 (CH), 129.4 (CH), 114.2 (CH), 77.9 (CH_2), 72.8 (CH_2), 68.0 (CH_2), 62.3 (CH_3), 58.7 (CH_3), 54.8 (CH), 54.1 (C), 40.6 (CH_2), 39.6 (CH_2), 37.4 (C), 36.1 (CH), 30.1 (CH_2), 23.2 (CH_3), 18.9 (CH_3) **IR** (neat, cm^{-1}) 2969 (m), 2873 (m), 1701 (s), 1513 (m), 1247 (m), 1094 (m) **HRMS** (EI) m/z $(M-C_8H_9O)^+$ calculated for $C_{15}H_{23}O_3$ 251.1647, found 251.1651 (12.1%)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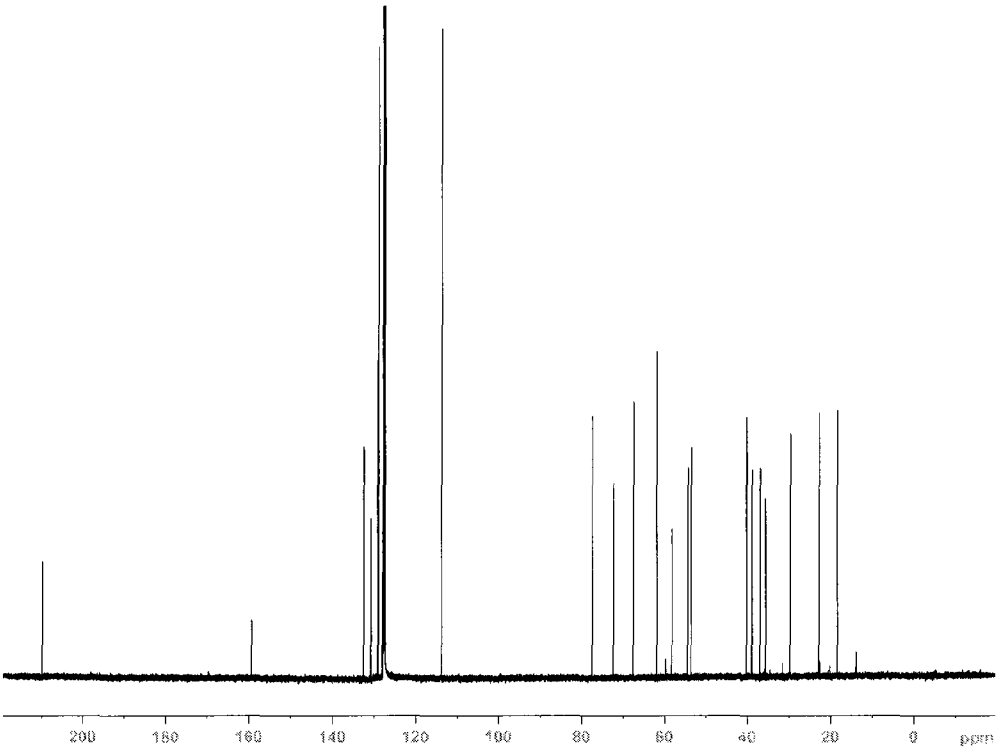
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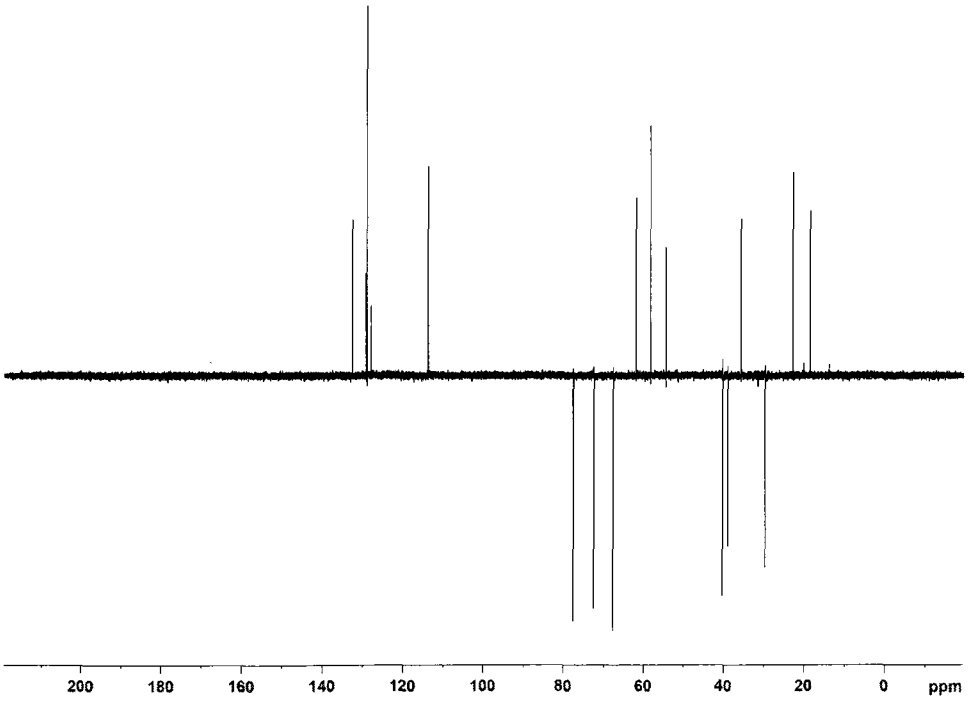
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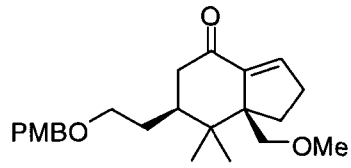
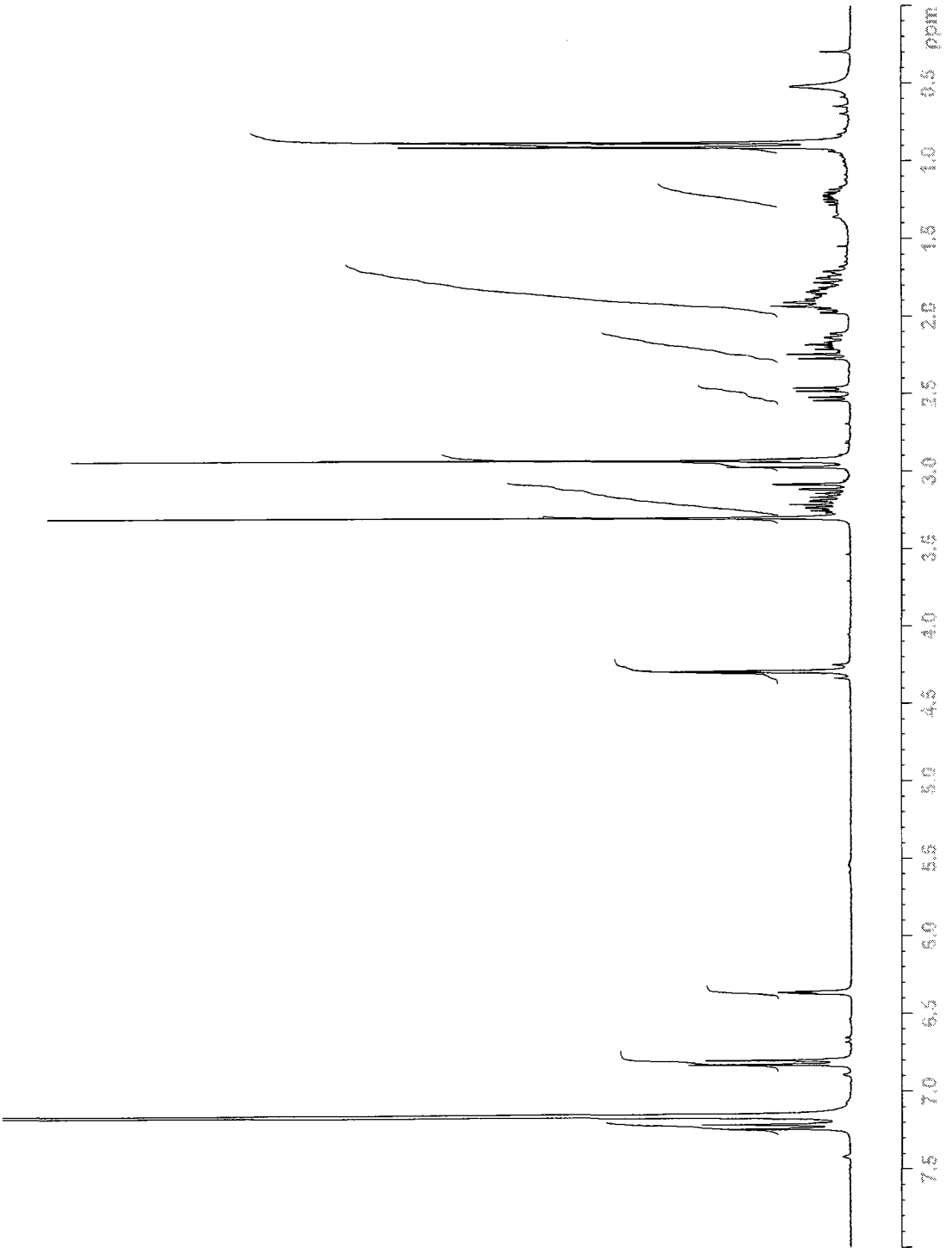
ppm

6-(2-(4-methoxybenzyloxy)ethyl)-7a-(methoxymethyl)-7,7-dimethyl-5,6,7,7a-tetrahydro-1H-inden-4(2H)-one (2.79)



To a solution of 2.74 (0.051 g, 0.137 mmol, 1 equiv) in DMF (1 mL) was added DBU (a few drops). The mixture was stirred at 80 °C in the microwave for 5 hours and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine (x3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-15% EtOAc/hexanes) as eluent to afford 2.79 (0.012 g, 24%). Starting material was also recovered (0.015 g, 29%).

^{1}H NMR (300 MHz, C_6D_6) δ ppm 7.23 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.37 (dd, *J* = 3.5, 2.1 Hz, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 4.27 (d, *J* = 11.6 Hz, 1H) 3.30 (s, 3H), 3.25 (ddd, *J* = 8.8, 6.3, 4.5 Hz, 1H), 3.20 – 3.14 (m, 1H), 3.10 (dd, *J* = 9.6, 1.0 Hz, 1H), 2.96 (d, *J* = 9.6 Hz, 1H), 2.93 (s, 3H), 2.50 (dd, *J* = 18.3, 6.3 Hz, 1H), 2.23 (dd, *J* = 18.3, 8.9 Hz, 1H), 2.24 – 2.11 (m, 1H), 1.98 (m, 5H), 1.23 (ddt, *J* = 13.4, 10.6, 5.3 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 198.9 (C), 159.8 (C), 147.4 (C), 137.3 (CH), 131.2 (C), 129.5 (CH), 114.2 (CH), 76.3 (CH_2), 72.9 (CH_2), 68.9 (CH_2), 58.6 (CH_3), 58.3 (C), 54.8 (CH_3), 42.6 (CH_2), 40.4 (CH), 38.1 (C), 32.7 (CH_2), 31.4 (CH_2), 30.8 (CH_2), 27.1 (CH_3), 20.1 (CH_3) **IR** (neat, cm^{-1}) 2922 (m), 2851 (m), 1685 (s), 1610 (m), 1513 (m), 1247 (m), 1106(m) **HRMS** (EI) m/z $(M-C_8H_9O)^+$ calculated for $C_{15}H_{23}O_3$ 252.1647, found 251.1643 (6.2 %)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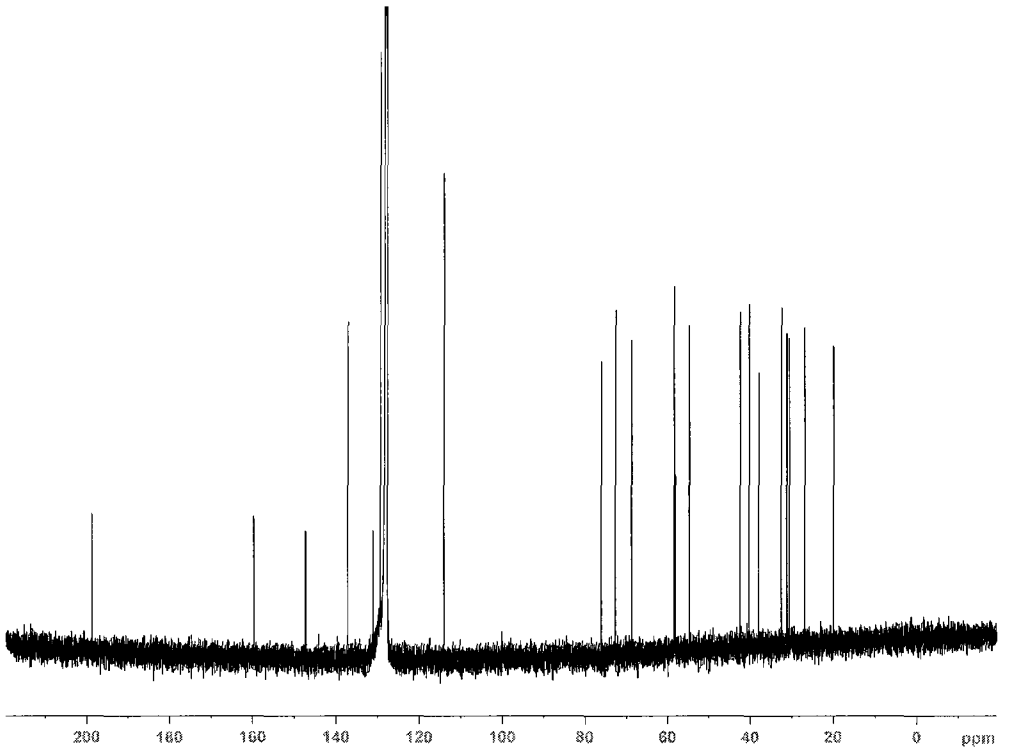
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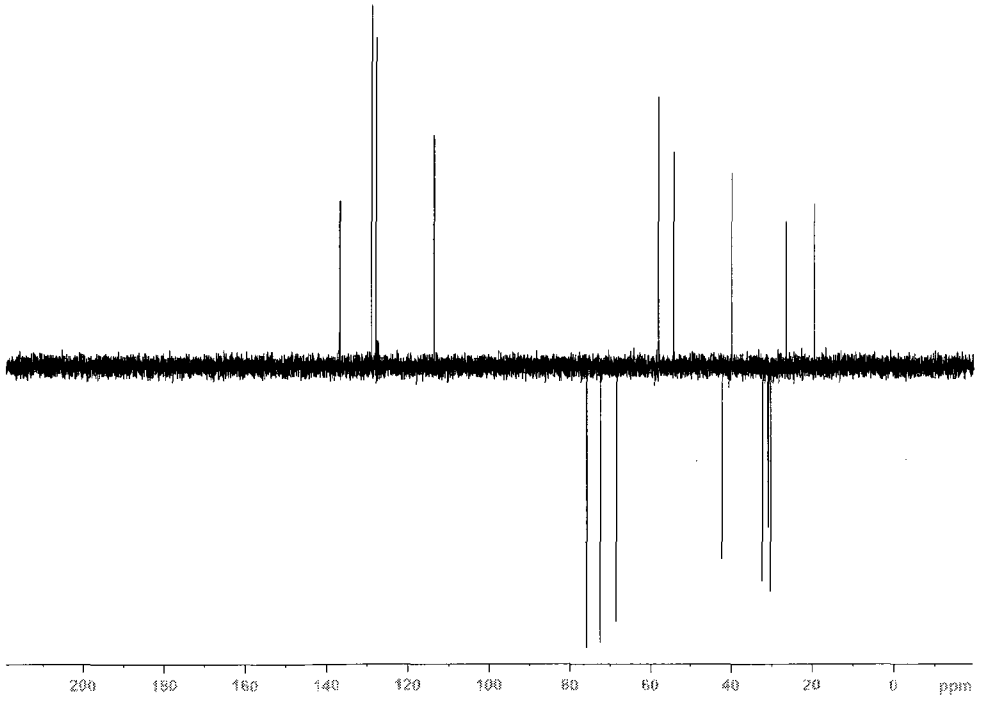
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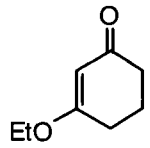
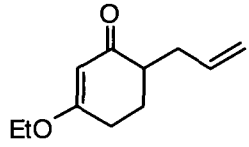
3-ethoxycyclohex-2-enone (3.14)



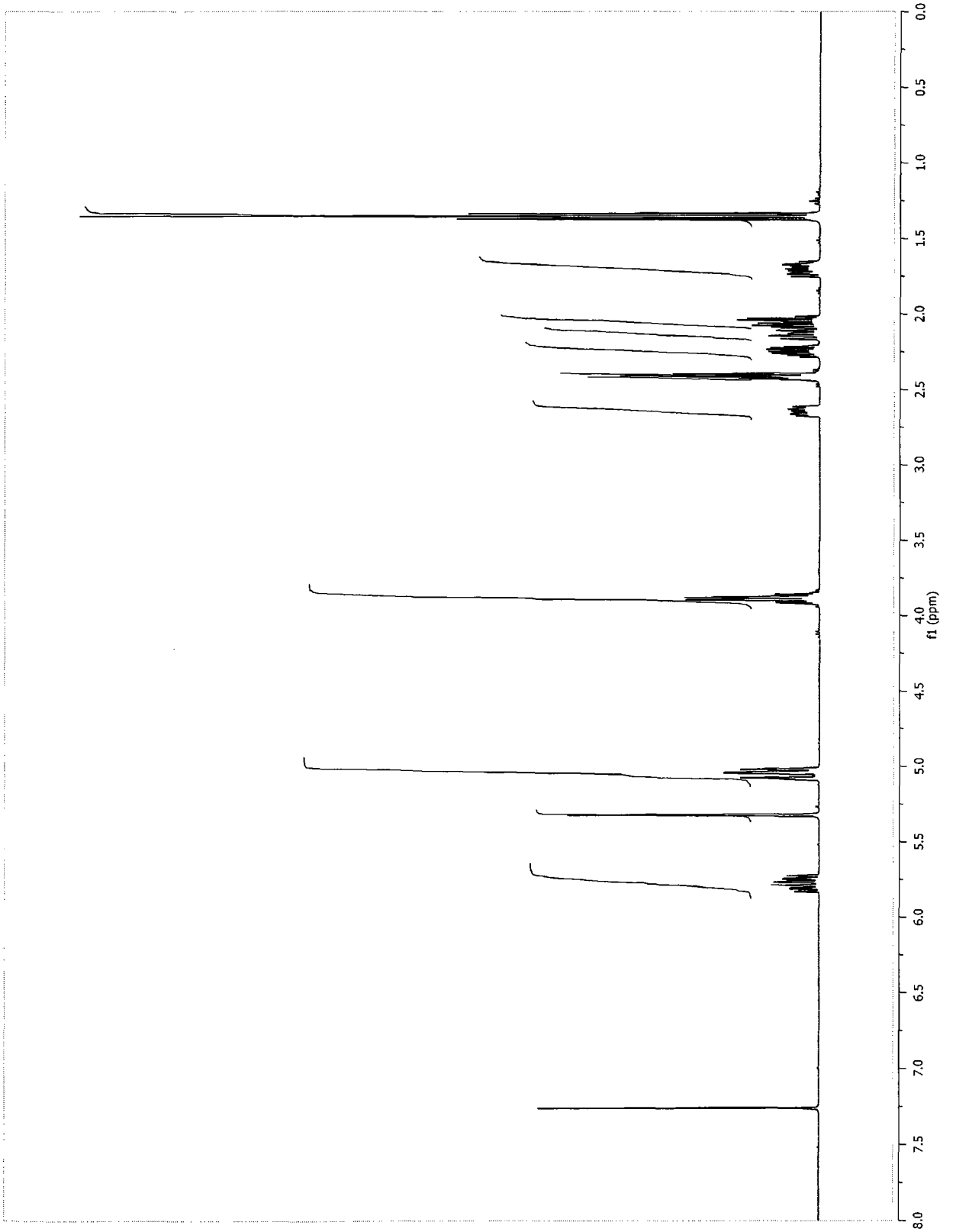
To a solution of 1,3-cyclohexanedione (20.0 g, 178 mmol, 1 equiv) in EtOH (99%, 200 mL) was added a catalytic amount of concentrated sulfuric acid (2 mL). The mixture was stirred at reflux overnight. A few pellets of KOH were added and EtOH was evaporated under reduced pressure. Water was added and the aqueous phase was extracted Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concetrated under reduced pressure. The resulting residue (14.63 g, 59%) was used in the next step without further purification. Decomposition of the product occurs if the mixture stays to long on the rotavap during EtOH evaporation. It is important to not completely evaporate EtOH. This product was not characterized because it is commercially available from Aldrich.

6-allyl-3-ethoxycyclohex-2-enone (3.13)



A solution of LDA was prepared by mixing DIPA (18.6 mL, 133 mmol, 1.27 equiv) and *n*-BuLi (in pentanes) (61.5 mL, 1.95 M, 120 mmol, 1.15 equiv) in THF (280 mL) at -78 °C. A solution of compound **3.14** (14.63 g, 104 mmol, 1 equiv) in THF (80 mL) was added to the LDA solution over 15 minutes and *via* canula. The mixture was warmed to 0 °C, stirred for 45 minutes and cooled down to -78 °C. TBAI (19.28 g, 52.2 mmol, 0.5 equiv) followed by allyl bromide (9.9 mL, 115 mmol, 1.1 equiv) were added. The reaction was stirred 45 minutes at -78 °C, 45 minutes at -15 °C, 30 minutes at 0 °C and quenched by adding saturated aqueous NH_4Cl. The aqueous phase was extracted Et_2O (x2). The combined organic fractions were washed with sat $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 30% EtOAc/hexanes as eluent to afford **3.13** as a yellow oil (17.52 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.78 (dddd, *J* = 16.9, 10.2, 7.8, 6.5 Hz, 1H), 5.32 (s, 1H), 5.08 – 5.01 (m, 2H), 3.88 (qd, *J* = 7.0, 2.0 Hz, 2H), 2.64 (dddt, *J* = 13.9, 6.3, 4.3, 1.5 Hz, 1H), 2.43 – 2.41 (m, 1H), 2.40 (d, *J* = 5.0 Hz, 1H), 2.28 – 2.21 (m, 1H), 2.12 (dddt, *J* = 14.0, 8.9, 7.9, 1.0 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.70 (dddd, *J* = 13.3, 10.5, 8.5, 6.5 Hz, 1H) **^{13}C NMR** (100 Hz, $CDCl_3$) δ ppm 200.6 (C), 177.1 (C), 136.5 (CH), 116.7 (CH_2), 102.4 (CH), 64.3 (CH_2), 44.8 (CH), 34.1 (CH_2), 28.2 (CH_2), 25.9 (CH_2), 14.2 (CH_3) **IR** (neat, cm^{-1}) 2981 (m), 2941 (m), 1653 (s), 1608 (s) 1191 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{11}H_{16}O_2$ 180.1150, found 180.1159 (100 %).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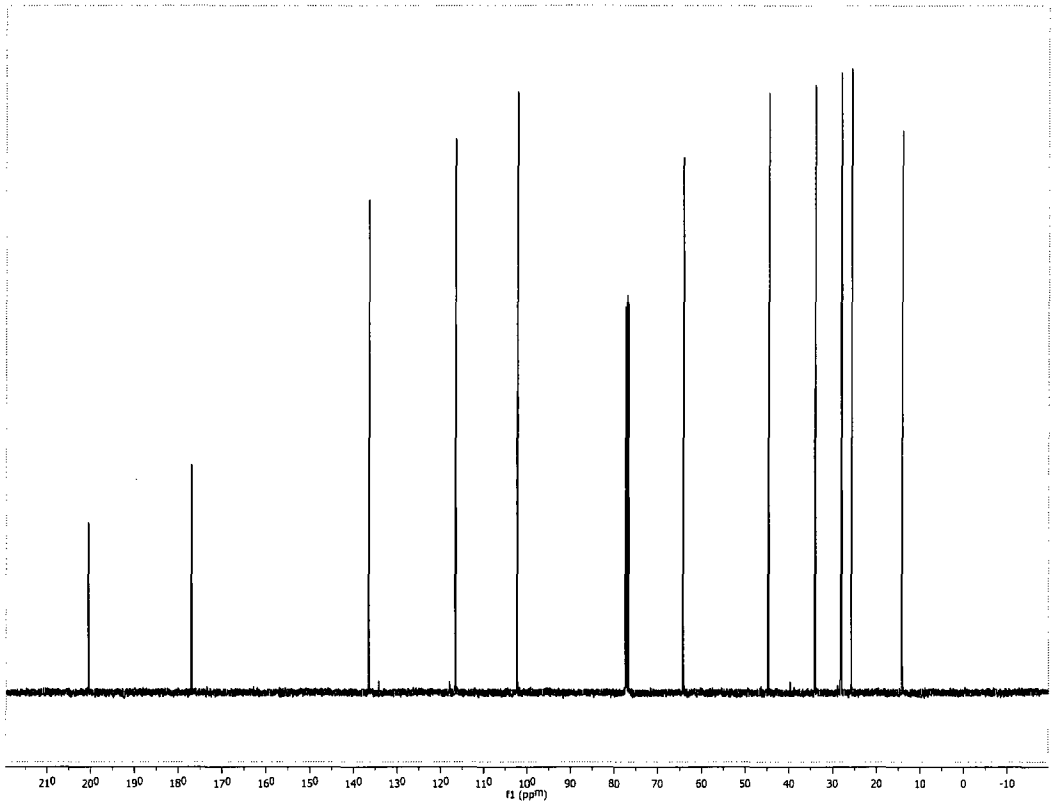
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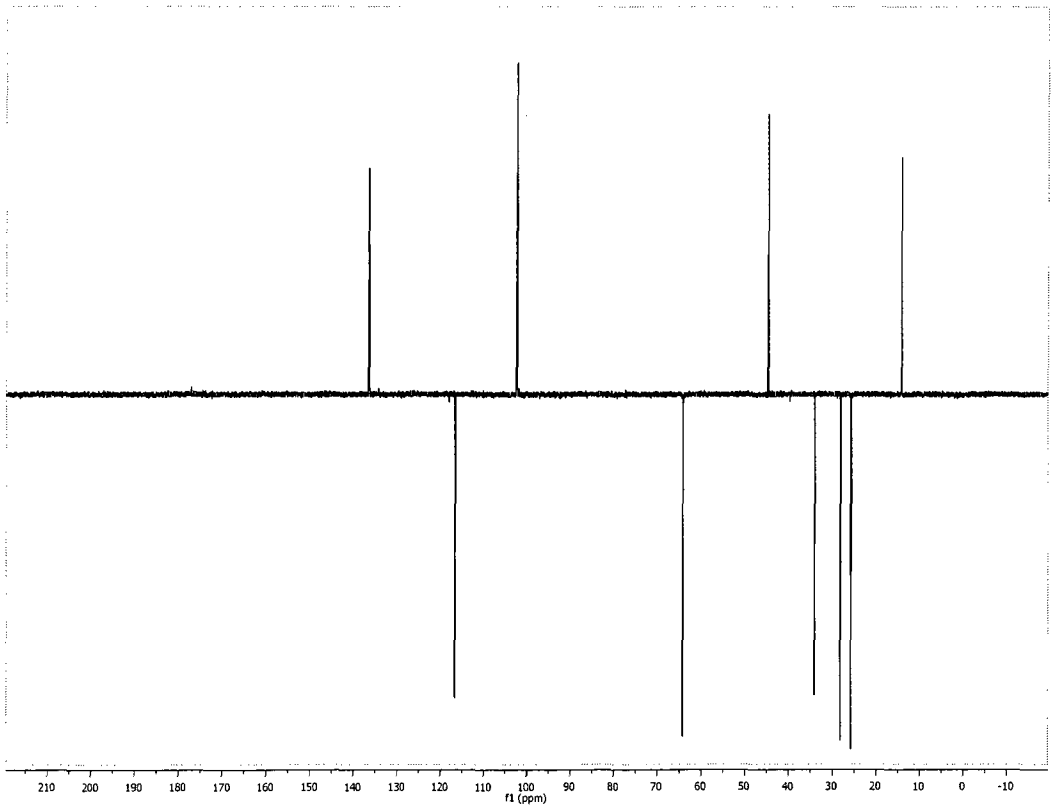
f1 (ppm)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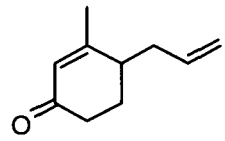
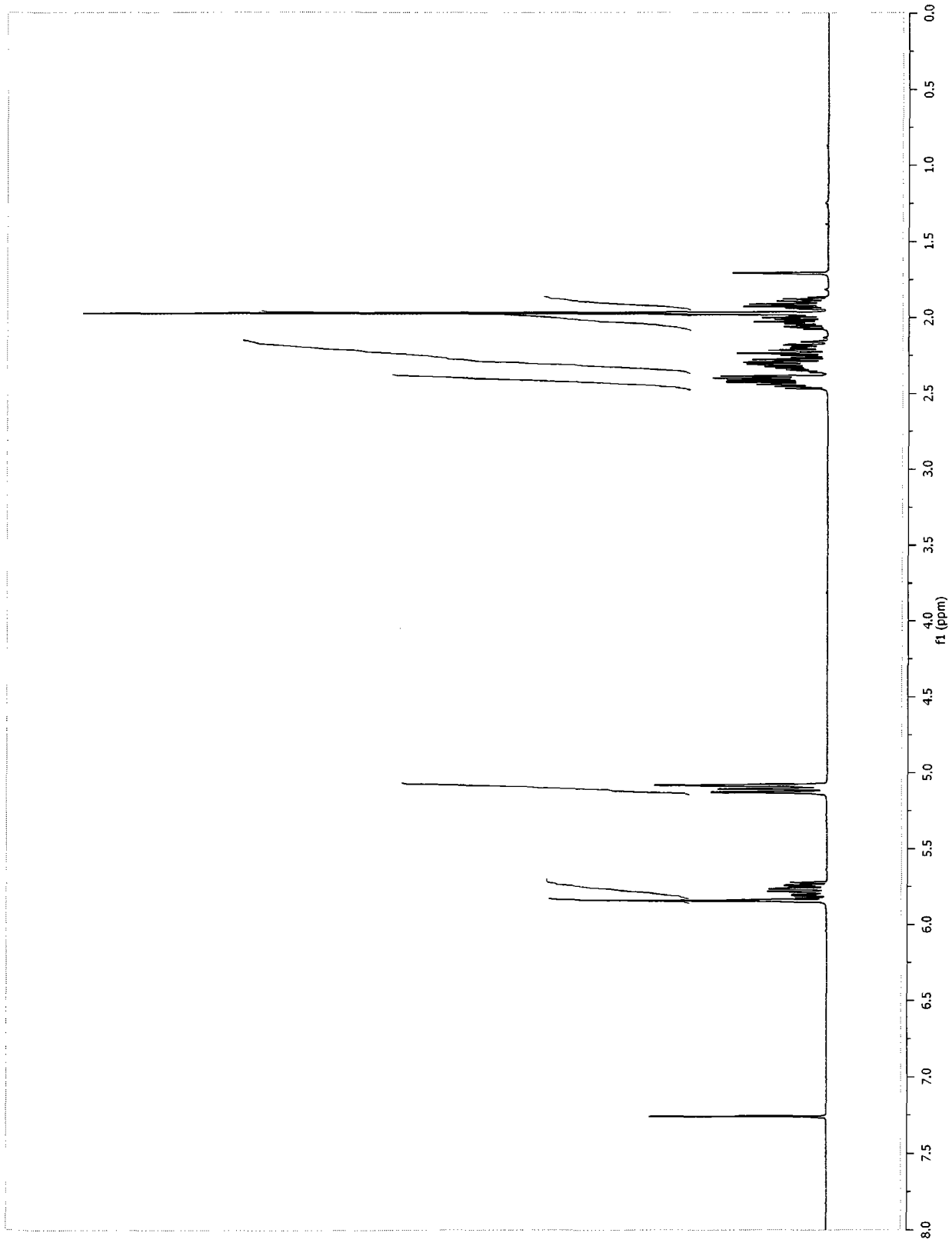
f1 (ppm)

4-allyl-3-methylcyclohex-2-enone (3.15)



To a solution of compound **3.13** (17.52 g, 97.2 mmol, 1.0 equiv) at -78 °C was added MeLi (70 mL, 1.38 M solution in Et_2O, 97.2 mmol, 1 equiv) dropwise. The mixture was stirred 1 hour, was warmed to 0 °C, 1N HCl_{aq} (243 mL) was slowly added and the mixture was stirred for an extra 15 minutes. Layers were separated. The aqueous layer was extracted Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 20% EtOAc/hexanes as eluent to afford **3.15** as a light yellow oil (13.72 g, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.84 (br s, 1H), 5.78 (dddd, J = 16.8, 10.3, 7.8, 6.4 Hz, 1H), 5.14 – 5.08 (m, 2H), 2.43 (ddd, J = 17.2, 10.7, 5.1 Hz), 2.36 – 2.16 (m, 3H), 2.08 – 1.97 (m, 1H), 1.97 (s, 3H), 1.90 (dddd, J = 13.6, 6.4, 5.1, 5.1 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 199.5 (C), 165.1 (C), 136.2 (CH), 127.2 (CH), 117.4 (CH_2), 39.3 (CH), 35.8 (CH_2), 33.9 (CH_2), 26.5 (CH_2), 23.1 (CH_3) **IR** (neat, cm^{-1}) 2925 (m), 1669 (s), 1442 (m), 1380 (m), 1250 (m), 910 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{10}H_{14}O$ 150.1045, found 150.1048 (31.1 %)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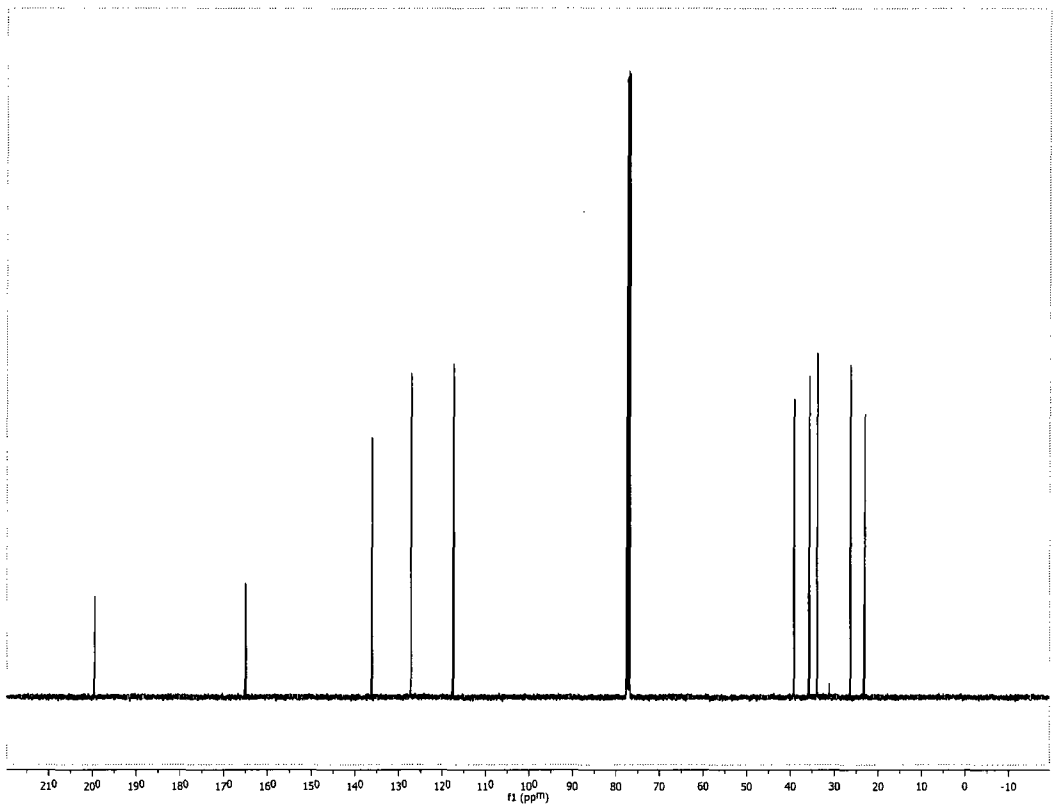
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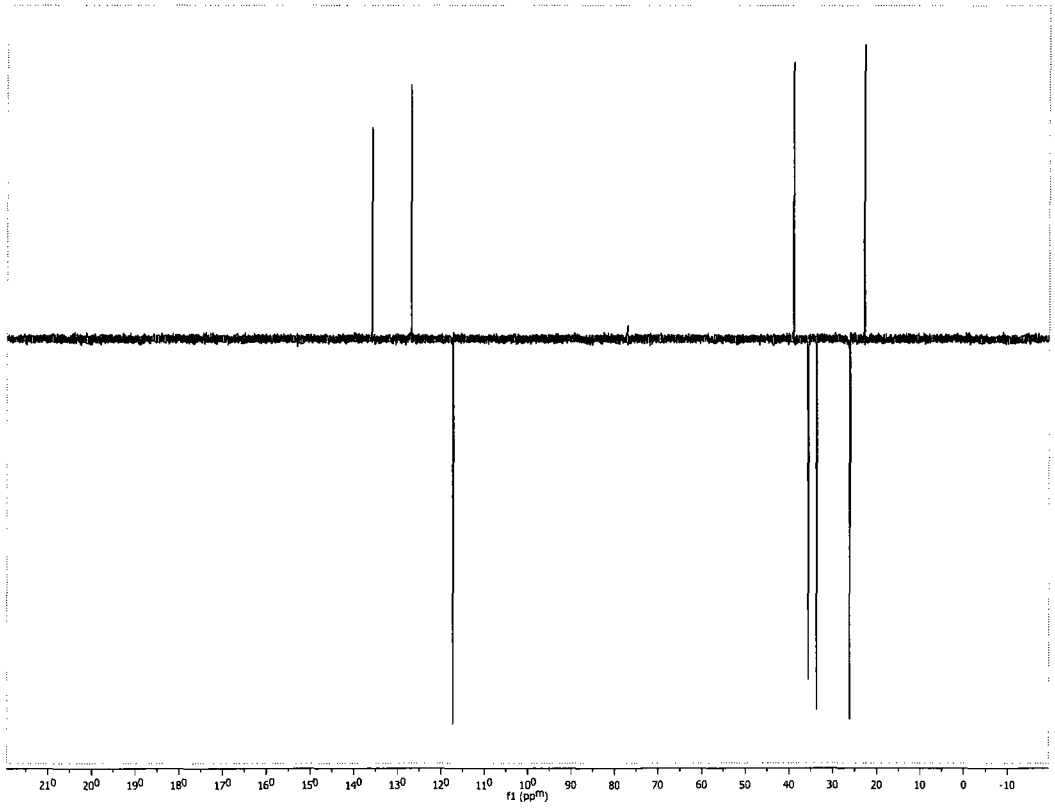
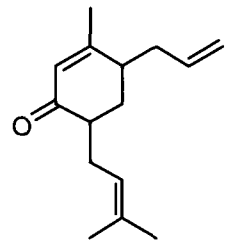
f1 (ppm)

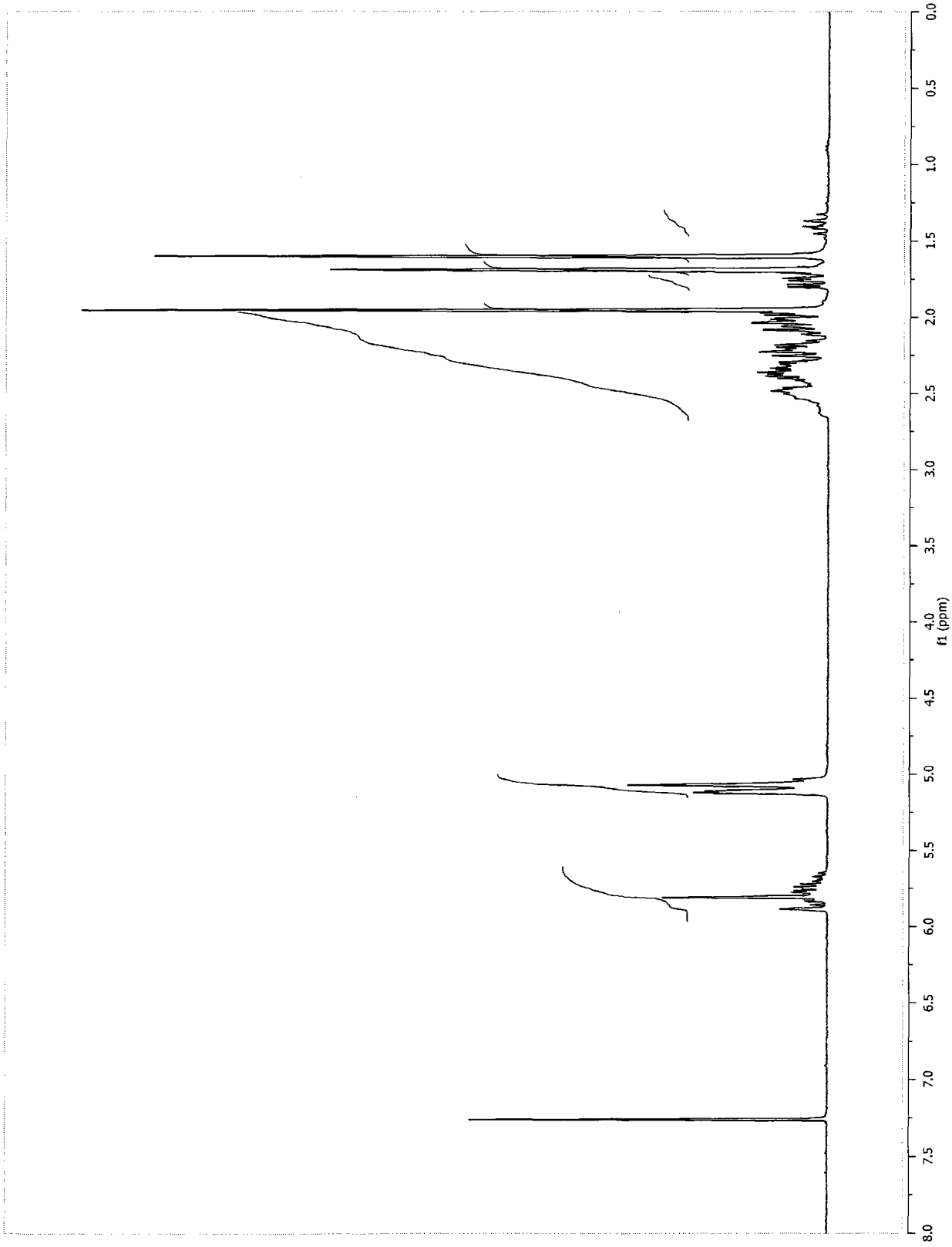

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

4-allyl-3-methyl-6-(3-methylbut-2-enyl)cyclohex-2-enone (3.12)



To a solution of DIPA (17.4 mL, 124 mmol, 1.27 equiv) in THF (250 mL) was added *n*-BuLi (58 mL, 1.93 M solution in pentanes, 112 mmol, 1.15 equiv) dropwise at -78 °C. The mixture was stirred for 30 minutes and a solution of **3.15** (14.66 g, 97.6 mmol, 1.0 equiv) in THF (60 mL) was slowly added *via* canula. The mixture was warmed to 0 °C, stirred 30 minutes and cooled down to –78 °C. TBAI (18.02 g, 48.8 mmol, 0.5 equiv) followed by prenyl bromide (12.4 mL, 107 mmol, 1.1 equiv) were finally added. The reaction was stirred for 1 hour at -78 °C, for 1 hour at -15°C, for 30 minutes at 0°C and was quenched with saturated aqueous NH_4Cl. The layers were separated. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/hexanes) to afford **3.12** as a light yellow oil (15.97 g, 75%). The product is a mixture of inseparable diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.89 – 5.65 (m, 2H), 5.12 – 5.03 (m, 3H), 2.64 – 1.97 (m, 7H), 1.95 (br s, 3H), 1.75 (ddd, *J* = 17.8, 16.1, 6.1 Hz, 0.6 H), 1.69 (br s, 3H), 1.60 (br s, 3H), 1.39 (ddd, *J* = 18.1, 18.1, 14.6 Hz, 0.4 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 200.9 (C), 200.8 (C), 163.9 (C), 162.8 (C), 136.3 (CH), 135.2 (CH), 133.3 (C), 133.2 (C), 128.2 (CH), 126.7 (CH), 121.9 (CH), 121.7 (CH), 177.5 (CH_2), 177.1 (CH_2), 46.6 (CH), 41.6 (CH), 39.8 (CH), 38.9 (CH), 36.8 (CH_2), 35.7 (CH_2), 33.4 (CH_2), 31.2 (CH_2), 28.0 (CH_2), 27.5 (CH_2), 25.83 (CH_3), 25.79 (CH_3), 22.8 (CH_3), 21.9 (CH_3), 17.8 (CH_3) **IR** (neat, cm^{-1}) 2976 (m), 2921 (m), 1673 (s), 1442 (m), 1380 (m), 1211 (m), 914 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_5H_{22}O$ 218.1671, found 218.1668 (42.1 %).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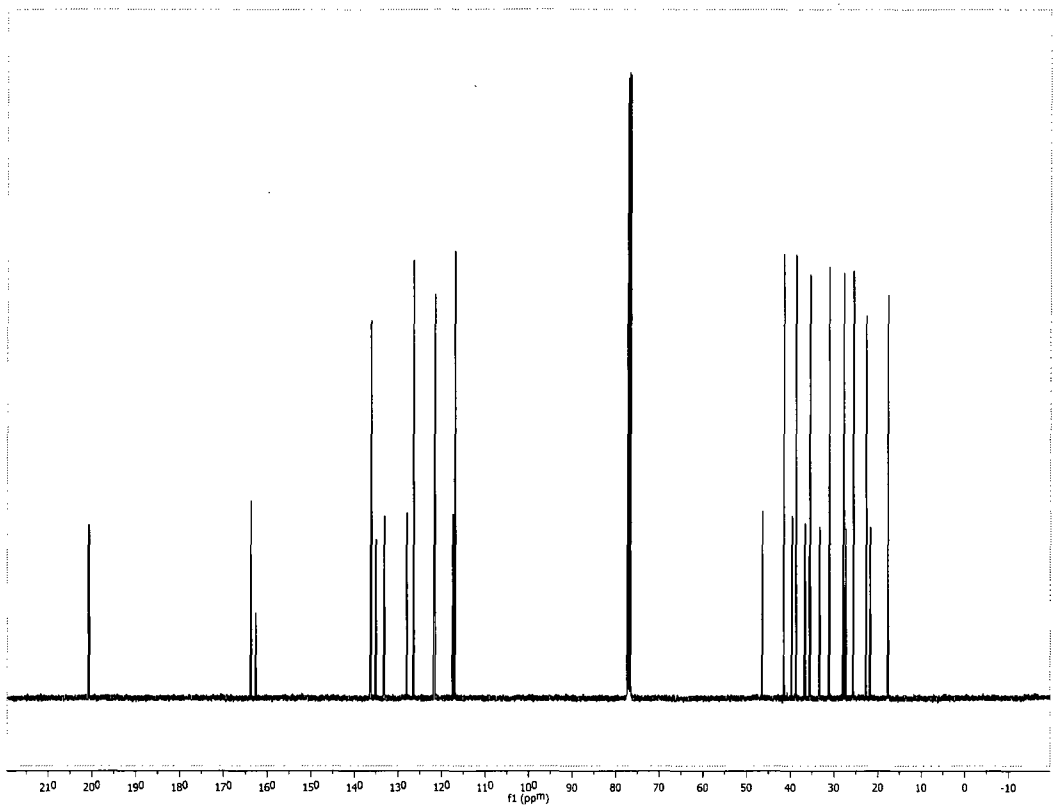
7.5
8.0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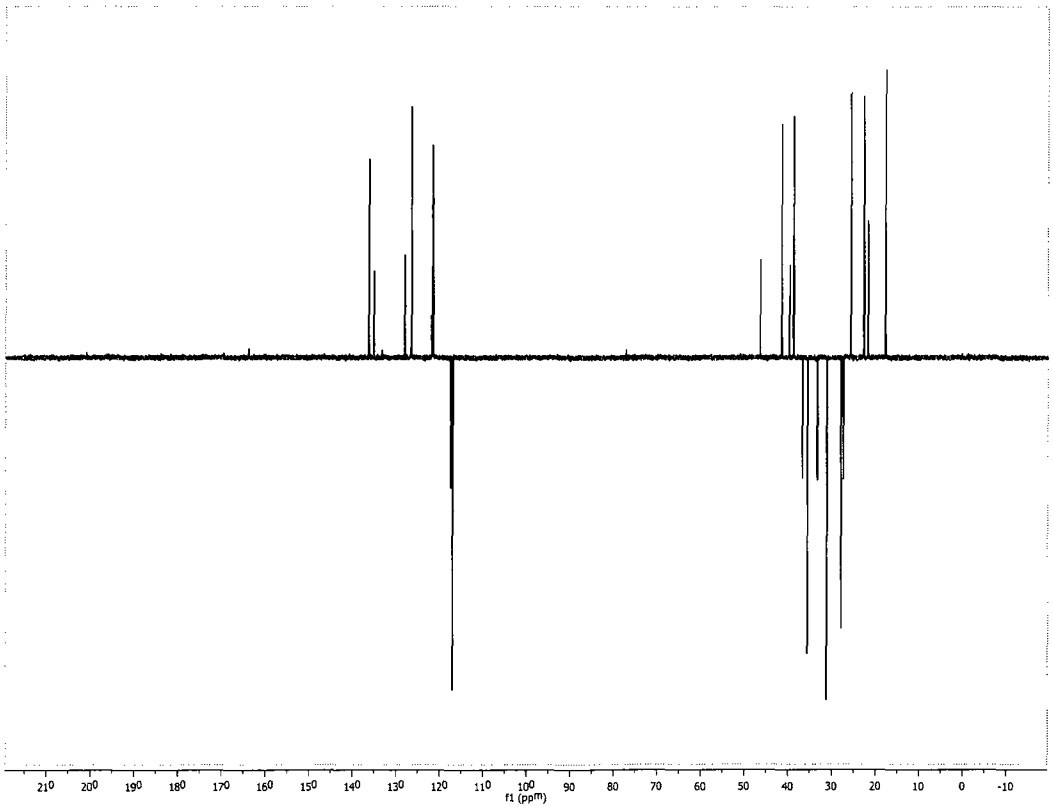
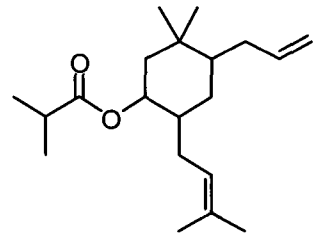
f1 (ppm)

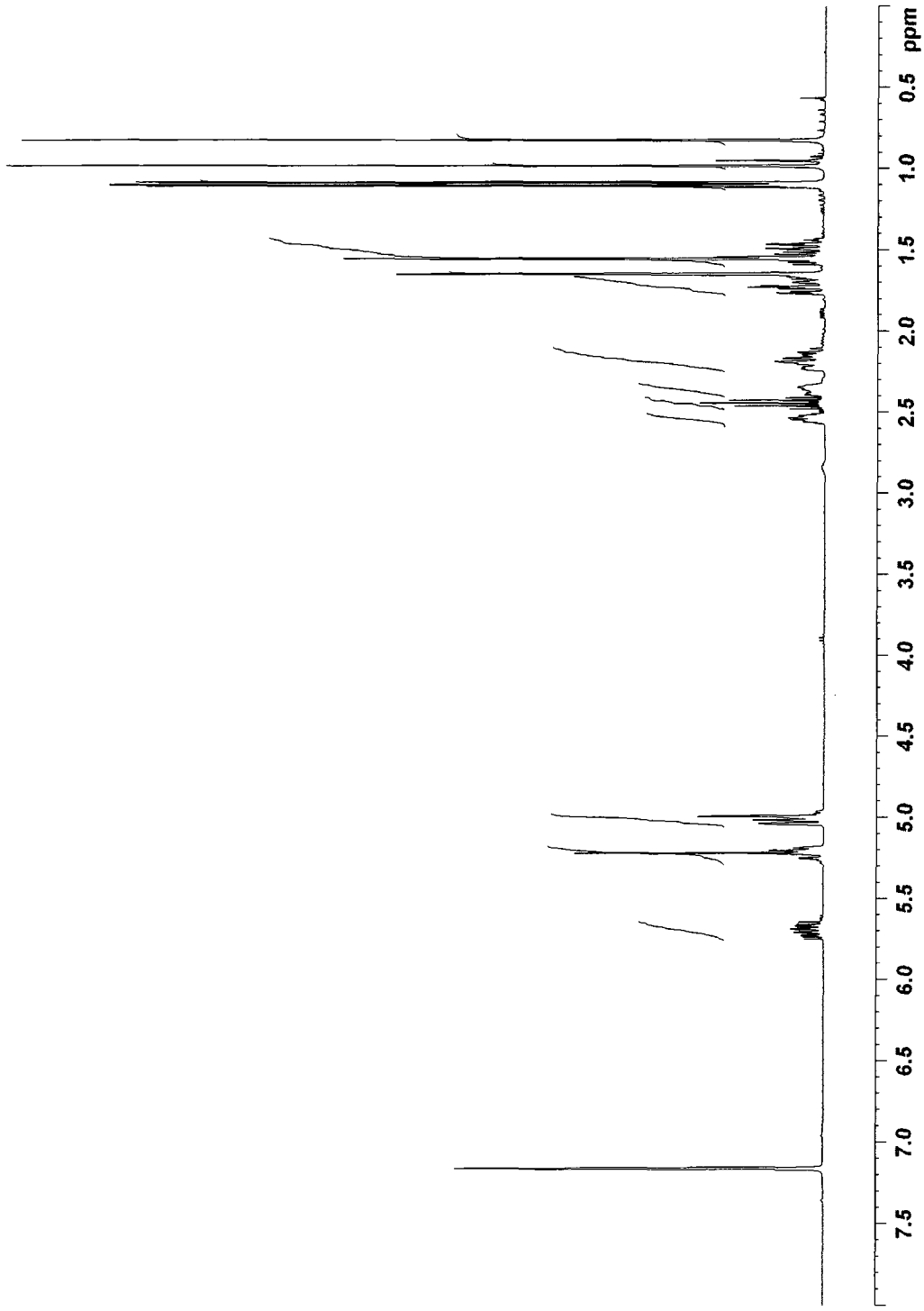

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

4-allyl-5,5-dimethyl-2-(3-methylbut-2-enyl)cyclohexyl isobutyrate (3.17)



To a suspension of CuI (0.174 g, 0.916 mmol, 2.0 equiv) in Et_2O (2.5 mL) was added MeLi (1.15 mL, 1.6 M solution in Et_2O, 1.83 mmol, 4.0 equiv) dropwise at -10 °C. A solution of **3.12** (0.100 g, 0.458 mmol, 1.0 equiv) in Et_2O (1 mL) was added *via* canula and the mixture was stirred for 30 minutes. Isobutyryl chloride (0.24 mL, 2.29 mmol, 5 equiv) was finally added. The reaction was stirred for an extra 10 minutes and was quenched with a buffer pH 8. The layers were separated. The aqueous phase was extracted with Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAC/hexanes) as eluent to afford **3.17** (94 mg, 68%)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.70 (dddd, J = 16.8, 10.3, 8.4, 5.7 Hz, 1H), 5.27 – 5.18 (m, 1H), 5.22 (d, J = 0.9 Hz, 1H), 5.05 – 4.99 (m, 2H), 2.57 – 2.51 (m, 1H), 2.45 (sept, J = 7.0 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.24 – 2.11 (m, 2H), 1.75 (dt, J = 13.6, 2.8 Hz, 1H), 1.70 – 1.65 (m, 1H), 1,65 (s, 3H), 1.59 – 1.43 (m, 2H), 1.56 (s, 3H), 1.11 (d, J = 2.5 Hz, 3H), 1.09 (d, J = 2.4 Hz, 3H), 0.98 (s, 3H), 0.83 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 174.8 (C), 149.9 (C), 138.6 (CH), 132.7 (C), 125.6 (CH), 123.4 (CH), 115.9 (CH_2), 39.7 (CH), 36.7 (CH), 35.3 (C), 34.6 (CH_2), 34.4 (CH), 31.1 (CH_2), 29.4 (CH_3), 28.0 (CH_2), 26.0 (CH_3), 23.6 (CH_3), 19.2 (CH_3), 19.0 (CH_3), 18.1 (CH_3) **IR** (neat, cm^{-1}) 2969 (m), 2929 (m) 1747 (s), 1137 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{20}H_{32}O_2$ 304.2402, found 304.2383 (6.5 %)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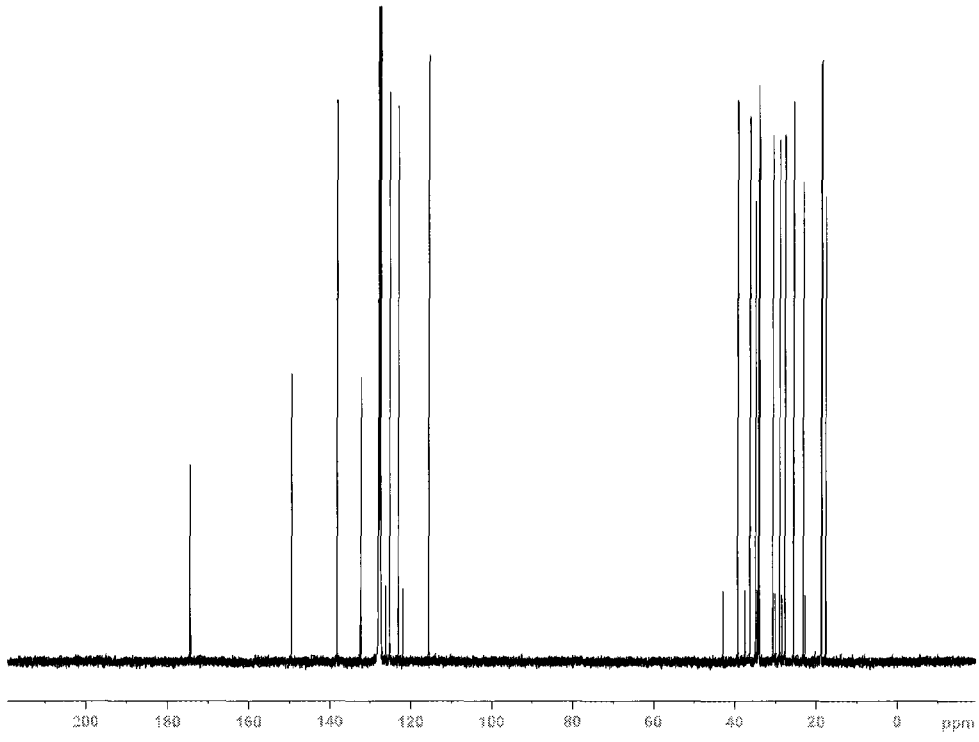
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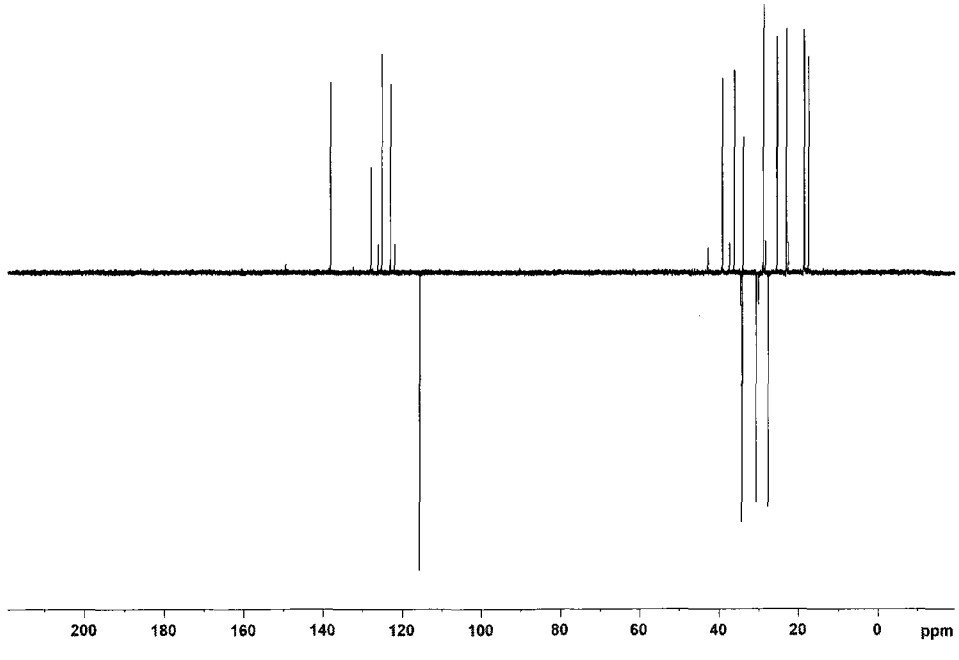
ppm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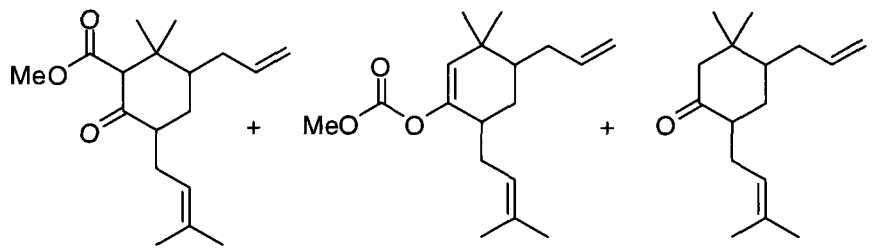
ppm

methyl 3-allyl-2,2-dimethyl-5-(3-methylbut-2-enyl)-6-oxocyclohexanecarboxylate (3.20), 4-allyl-3,3-dimethyl-6-(3-methylbut-2-enyl)cyclohex-1-enyl methyl carbonate (3.21), 4-allyl-5,5-dimethyl-2-(3-methylbut-2-enyl)cyclohexanone (3.22)



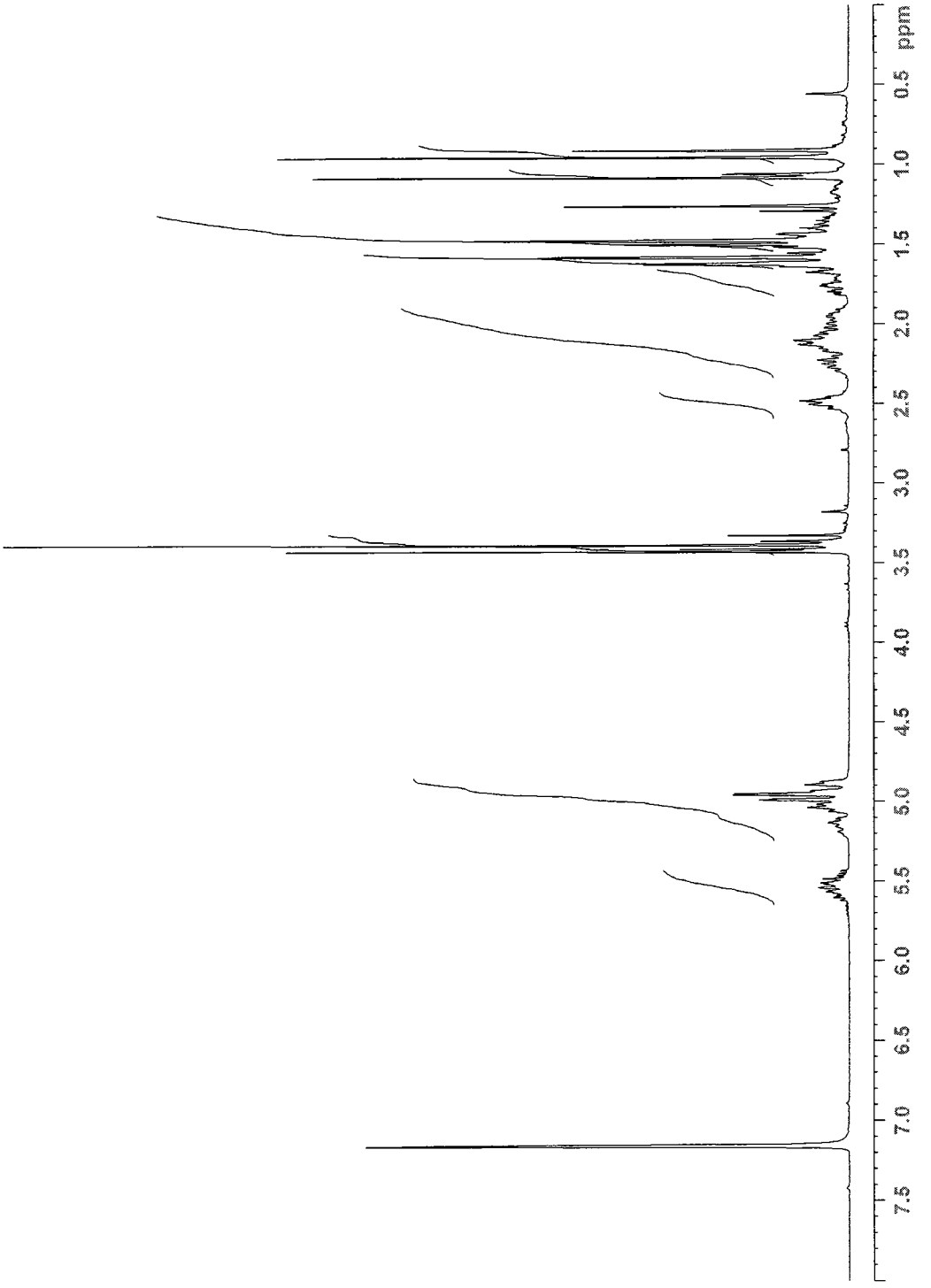
3.20 **3.21** **3.22**

To a suspension of CuI (0.174 g, 0.916 mmol, 2 equiv) in Et_2O (2 mL) was added MeLi (1.53 mL, 1.20 M solution in Et_2O, 1.83 mmol, 4 equiv) dropwise at -10°C. The mixture was stirred for 5 minutes and a solution of **3.12** (0.100 g, 0.458 mmol, 1 equiv) in Et_2O (1 mL) was added *via* canula. The mixture was stirred for 15 minutes, HMPA (0.58 mL, 3.34 mmol, 7.3 equiv) was added dropwise and it was cooled down to -78°C. Mander's reagent (0.22 mL, 2.75 mmol, 6.0 equiv) was finally added. The reaction was stirred for 1 hour at -78°C, for 30 minutes at -15°C, was slowly warmed to room temperature was quenched with a buffer pH 8. The layers were separated. The aqueous phase was extracted with Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a slow gradient (0-10% EtOAC/hexanes) as eluent to afford a mixture of **3.20**, **3.21** and **3.22** (yield and ratio not determined)

methyl 3-allyl-2,2-dimethyl-5-(3-methylbut-2-enyl)-6-oxocyclohexanecarboxylate (3.20) as a 1.2:1 mixture of diastereoisomers

^{1}H NMR (300 MHz, C_6D_6) δ ppm 5.62 – 5.44 (m, 1H), 5.22 – 4.88 (m, 3H), 3.42 – 1.64 (s, 3H), 3.41 and 3.33 (s, 1H), 2.55 – 2.46 (m, 1H), 2.30 – 1.91 (m, 3H), 1.82 – 1.32 (m, 4H), 1.62 and 1.58 (s, 3H), 1.50 and 1.48 (s, 3H), 1.26 and 1.08 (s, 3H), 0.96 and 0.91 (s, 3H) **^{13}C NMR** (75.7 MHz, C_6D_6) δ ppm 207.3, 205.7, 169.4, 169.0, 138.0, 137.8, 133.9, 132.9, 122.4, 121.5, 116.3, 116.2, 64.9, 62.8, 51.2, 51.2, 51.2, 49.5, 45.1, 44.7, 42.4, 41.8, 41.7, 34.0, 32.3, 31.4, 30.9, 30.7,

28.1, 27.3, 25.9, 25.8, 25.2, 18.0, 17.9, 16.6 **IR** (neat, cm^{-1}) 2972 (m), 2929 (m), 1752 (s), 1709 (s), 1434 (m), 1341 (m), 1130 (m) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{18}H_{28}O_3$ 292.2038, found 292.2041 (6.7 %) No DEPT for this experiment.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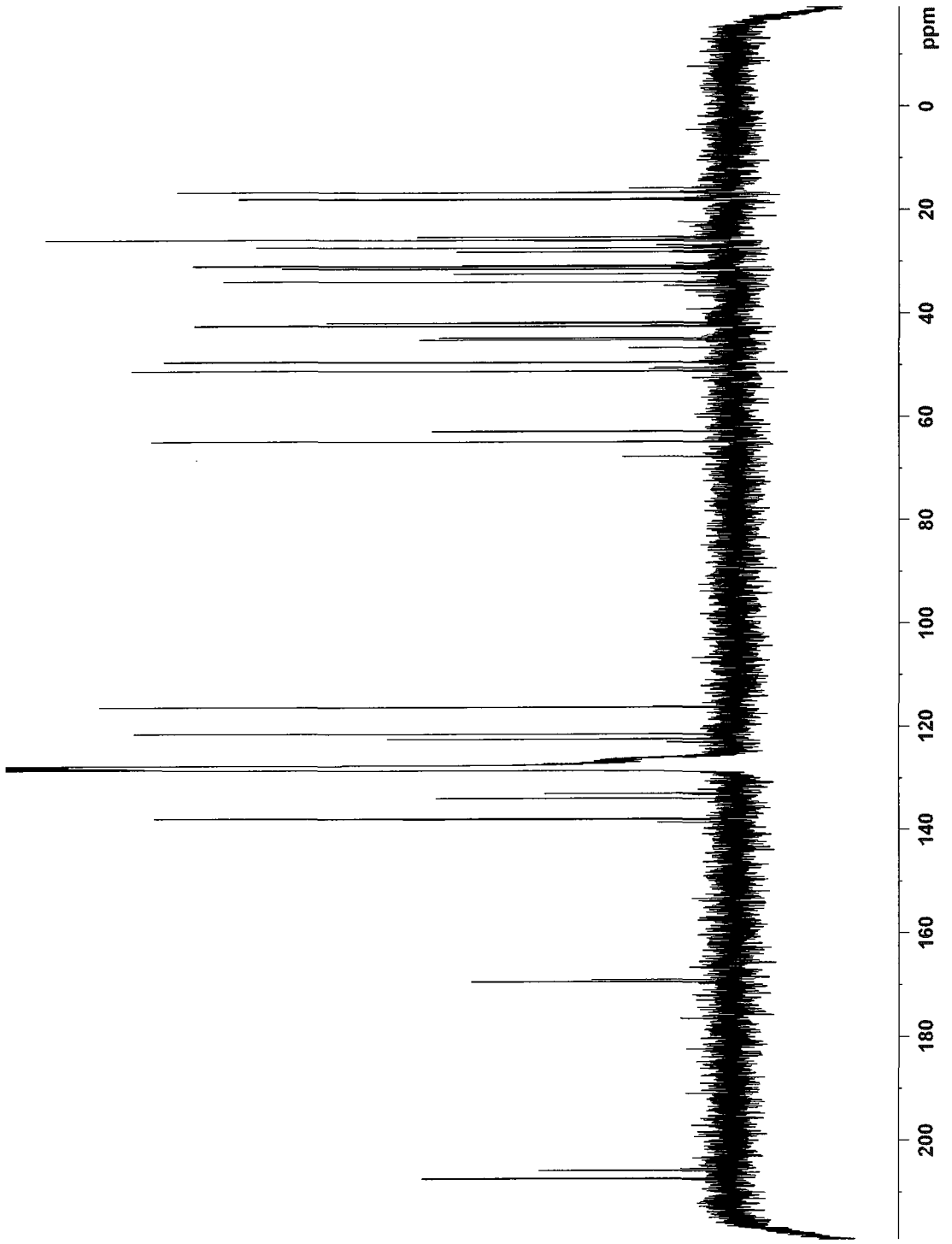
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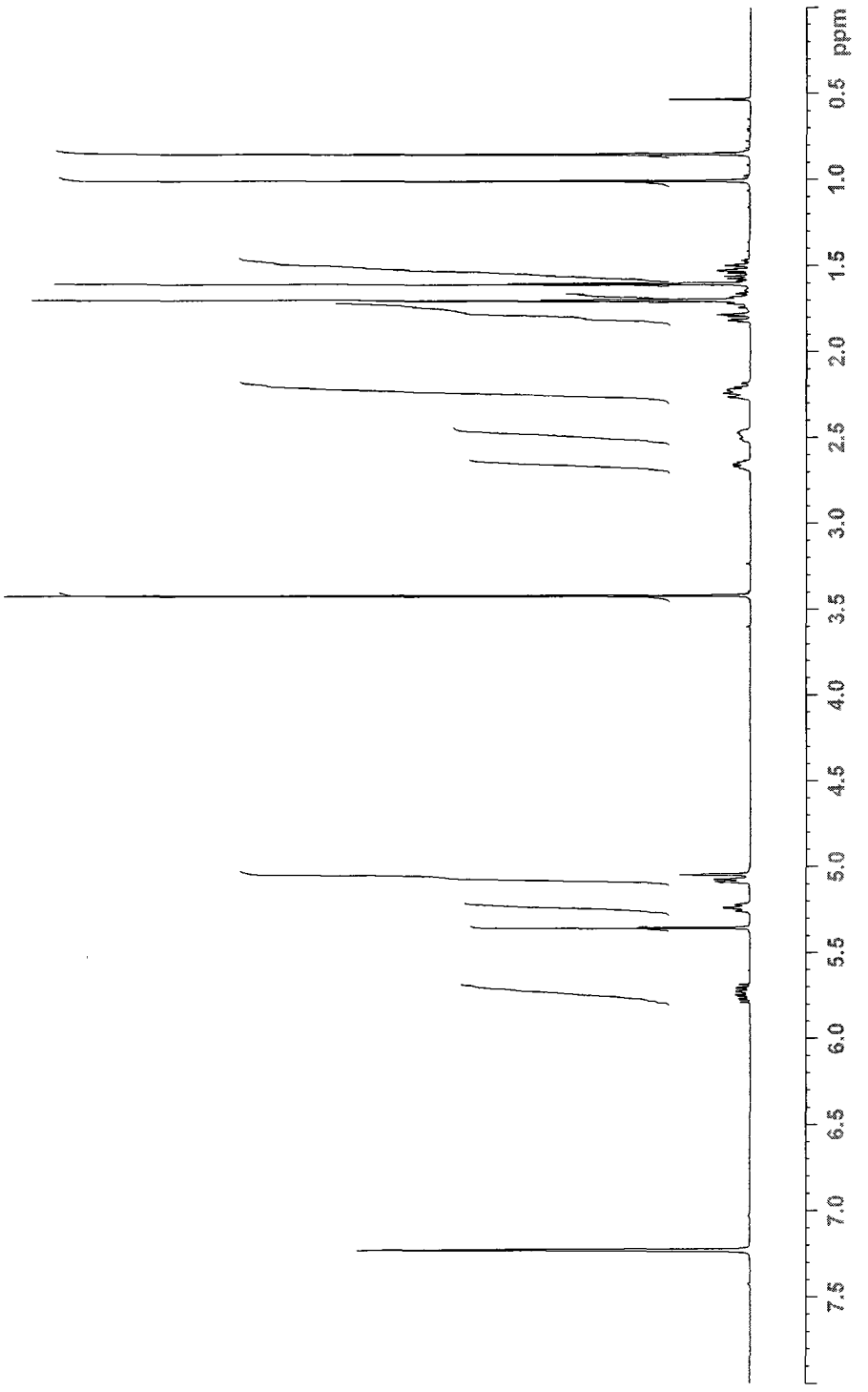
180
200

4-allyl-3,3-dimethyl-6-(3-methylbut-2-enyl)cyclohex-1-enyl methyl carbonate (3.21)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.72 – 5.62 (m, 1H), 5.29 (d, *J* = 0.8 Hz, 1H), 5.17 (ddt, *J* = 8.2, 6.7, 1.4 Hz, 1H), 5.03 – 5.00 (m, 1H), 4.98 (dd, *J* = 1.5, 0.8 Hz, 1H), 3.35 (s, 3H), 2.62 – 2.57 (m, 1H), 2.45 – 2.40 (m, 1H), 2.21 – 2.11 (m, 2H), 1.73 (dt, *J* = 13.4, 2.4 Hz, 1H), 1.67 – 1.57 (m, 1H), 1.63 (s, 3H), 1.54 (s, 3H) 1.52 – 1.40 (m, 2H), 0.94 (s, 3H), 0.78 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 154.7 (C), 150.4 (C), 138.5 (CH), 132.8 (C), 125.6 (CH), 123.2 (CH), 116.0 (CH_2), 54.3 (CH_3), 39.6 (CH), 36.5 (CH), 35.2 (C), 34.5 (CH_2), 31.0 (CH_2), 29.2 (CH_3), 28.1 (CH_2), 25.9 (CH_3), 23.3 (CH_3), 18.1 (CH_3) **IR** (neat, cm^{-1}) 2960 (m), 2930 (m), 1760 (s), 1441 (m), 1269 (s), 1259 (s), 1244 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{18}H_{28}O_3$ 292.2038, found 292.2049 (10.4 %)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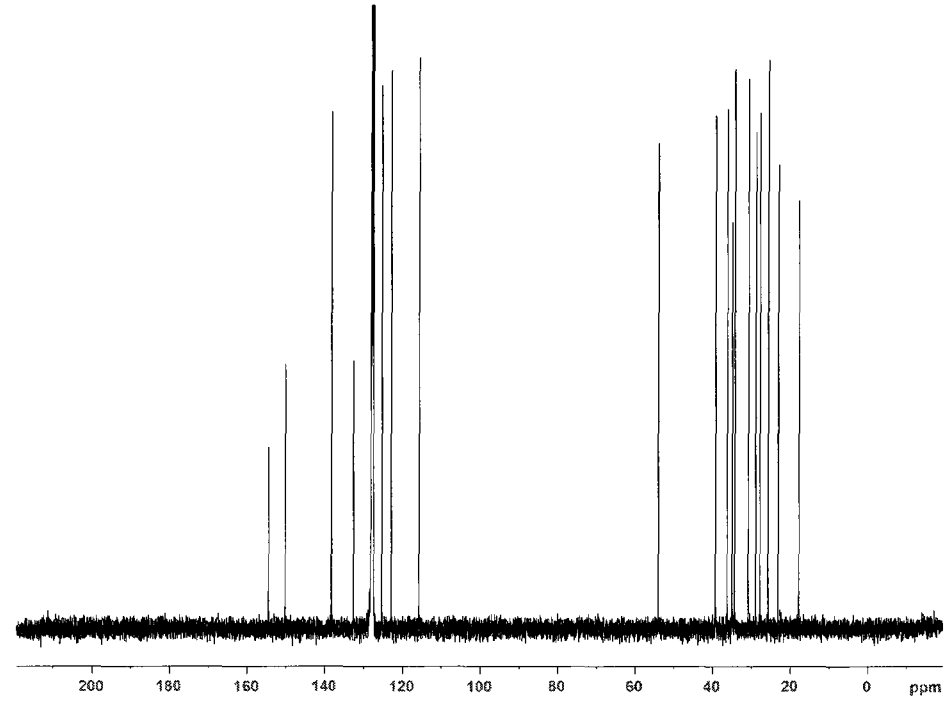
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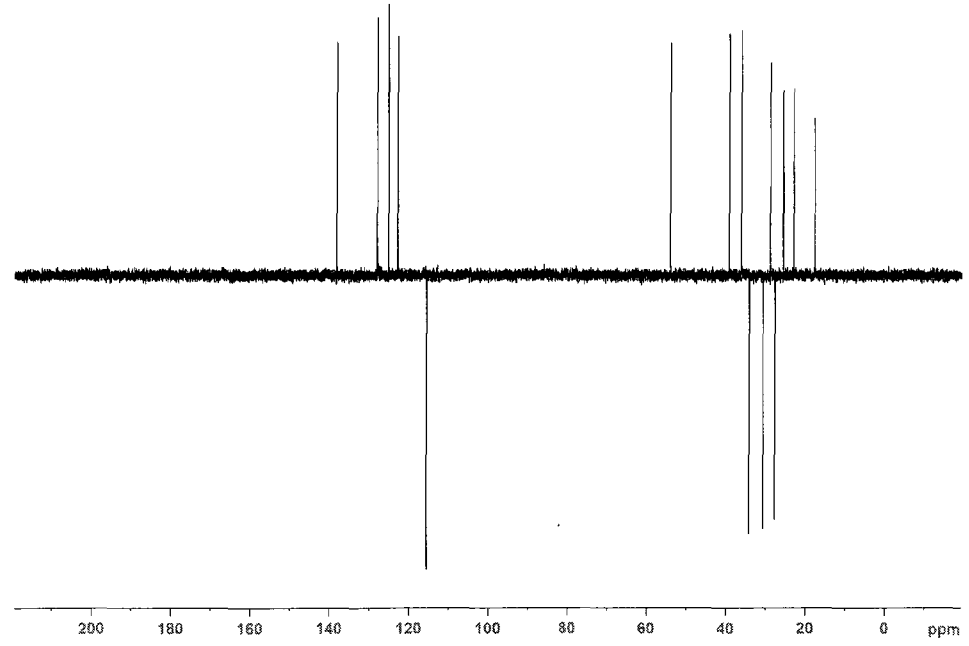
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180
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120
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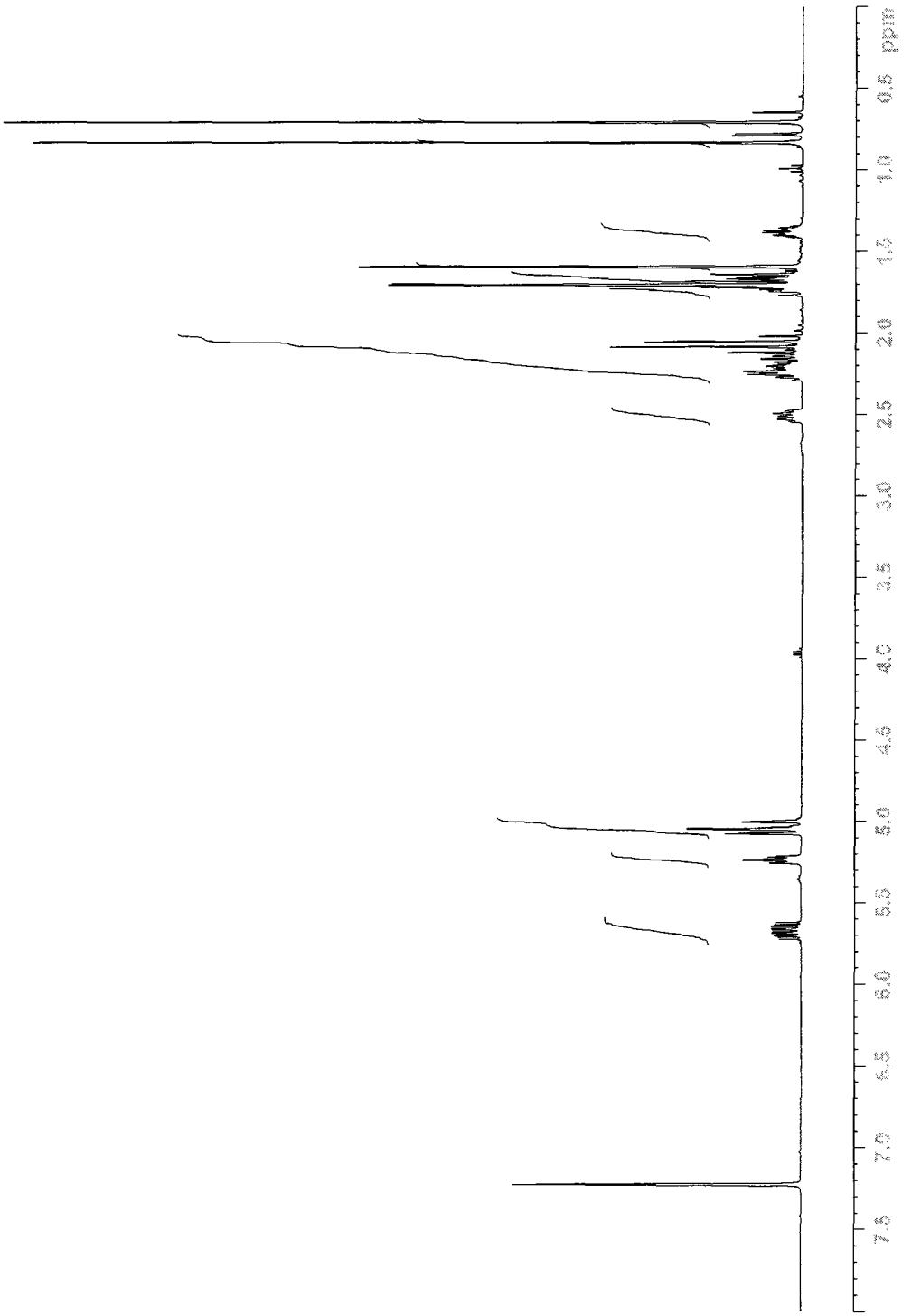
80
60
40
20
0
ppm

4-allyl-5,5-dimethyl-2-(3-methylbut-2-enyl)cyclohexenone (3.22)

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.61 (dddd, *J* = 16.9, 10.1, 8.7, 5.5 Hz, 1H), 5.17 (ddt, *J* = 8.0, 6.6, 1.4 Hz, 1H), 5.01 – 4.93 (m, 2H), 2.44 (dt, *J* = 15.1, 5.6 Hz, 1H), 2.22 – 2.04 (m, 3H), 2.04 (d, *J* = 13.6 Hz, 1H), 1.97 (d, *J* = 14.0 Hz, 1H), 1.70 – 1.54 (m, 3H), 1.64 (s, 3H), 1.53 (s, 3H), 1.31 (ddt, *J* = 10.9, 6.8, 4.1 Hz, 1H), 0.77 (s, 3H), 0.64 (s, 3H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 210.6 (C), 138.2 (CH), 132.8 (C), 122.7 (CH), 116.0 (CH_2), 51.9 (CH_2), 47.1 (CH), 41.9 (CH), 38.6 (C), 33.6 (CH_2), 31.5 (CH_2), 29.2 (CH_3), 29.2 (CH_2), 25.9 (CH_3), 24.7 (CH_3), 17.9 (CH_3) **IR** (neat, cm^{-1}) 2966 (m), 2929 (m), 1711 (s), 1443 (m), 910 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{16}H_{26}O$ 234.1984, found 234.1969 (37.9 %)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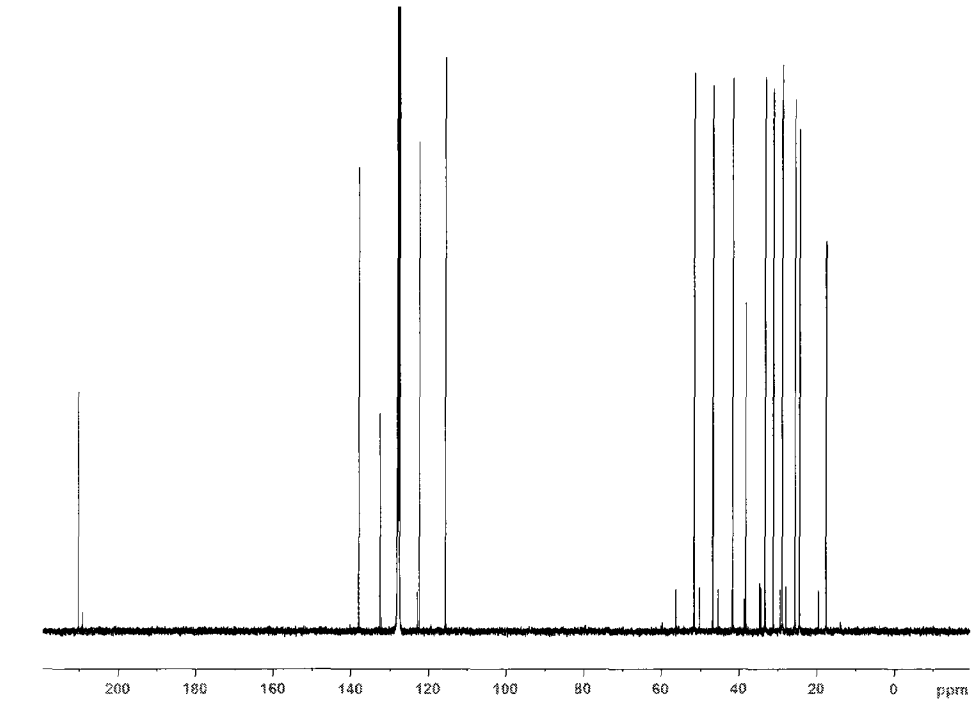
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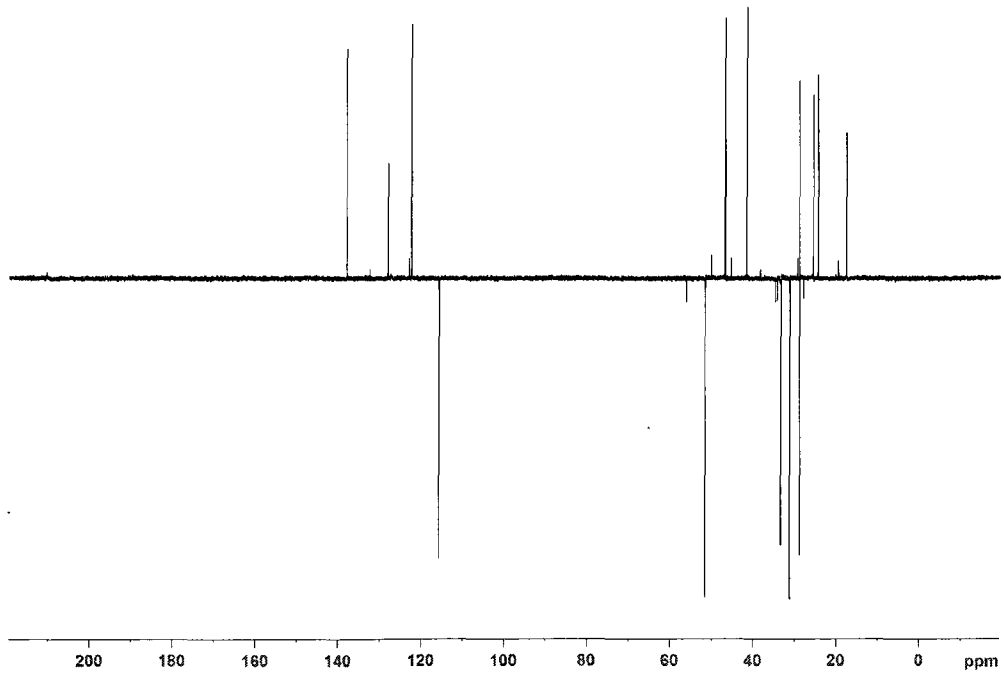
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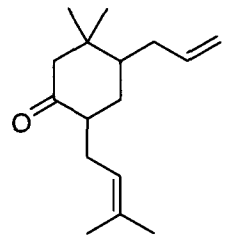
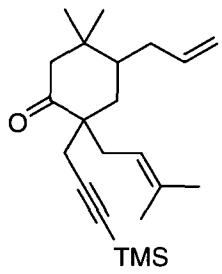
ppm

4-allyl-5,5-dimethyl-2-(3-methylbut-2-enyl)cyclohexenone (3.22)



To a suspension of CuI (8.72g, 45.8 mmol, 2.0 equiv) in Et_2O (140 mL) was added MeLi (57 mL, 1.6 M solution in Et_2O, 91.6 mmol, 4.0 equiv) dropwise at -10°C. The mixture was stirred for 5 minutes and a solution of **3.12** (5.0 g, 22.9 mmol, 1.0 equiv) in Et_2O (20 mL) was added *via* canula. The reaction was stirred for 15 minutes and was quenched with saturated aqueous NH_4Cl. The mixture was stirred for 30 minutes and was filtered. The layers were separated. The aqueous phase was extracted with Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using 10% EtOAC/hexanes as eluent to afford **3.22** (5.12 g, 95%).

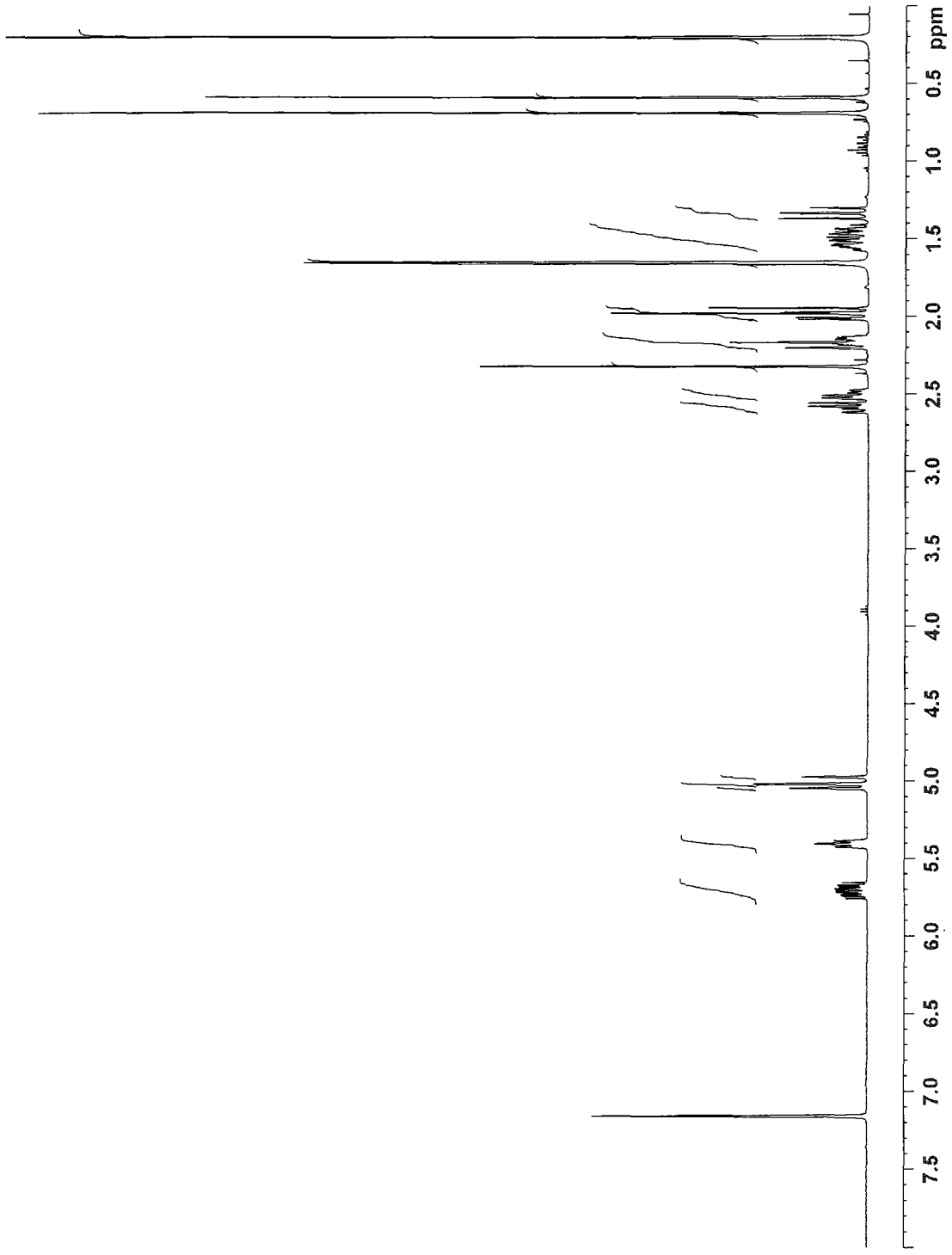
4-allyl-5,5-dimethyl-2-(3-methylbut-2-enyl)-2-(3-(trimethylsilyl)prop-2-ynyl)cyclohexenone (3.24)



To a solution of **3.22** (0.244 g, 1.04 mmol, 1.0 equiv) in acetonitrile (4 mL) was sequentially added Et_3N (0.29 mL, 2.08 mmol, 2.0 equiv), TMSCl (0.26 mL, 2.08 mmol, 2.0 equiv) and NaI (0.312 g, 2.08 mmol, 2 equiv). The mixture was stirred for 1 hour at room temperature and was quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

To a solution of the resulting residue in THF (4 mL) was added MeLi (0.71 mL, 1.46 M solution in Et2O, 1.04 mmol, 1 equiv) dropwise at -78 °C. The mixture was stirred for 15 minutes, warmed to 0 °C, stirred for 45 minutes and a solution of (3-bromoprop-1-ynyl)trimethylsilane (0.398 g, 2.08 mmol, 2.0 equiv) in THF (2 mL) was added *via* canula. The reaction was warmed to room temperature, stirred for 30 minutes and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (x2). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using hexanes as eluent to afford **3.24** (210 mg, 58%).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.71 (dddd, *J* = 16.9, 10.2, 8.0, 5.5 Hz, 1H), 5.41 (ddt, *J* = 8.2, 6.7, 1.4 Hz, 1H), 5.05 (m, 2H), 2.59 (dd, *J* = 14.3, 8.7 Hz, 1H), 2.50 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.32 (d, *J* = 1.0 Hz, 2H), 2.19 (dd, *J* = 13.9, 0.6 Hz, 1H), 2.19 – 2.13 (m, 1H), 1.98 (dd, *J* = 14.4, 3.5 Hz, 1H), 1.96 (d, *J* = 14.0 Hz, 1H), 1.65 (br s, 6H), 1.58 – 1.41 (m, 2H), 1.34 (dd, *J* = 14.2, 12.5, 1H), 0.69 (s, 3H), 0.59 (s, 3H), 0.20 (s, 9H) **^{13}C NMR** (100 MHz, C_6D_6) δ ppm 210.7 (C), 138.2 (CH), 134.4 (C), 120.9 (CH), 116.0 (CH2), 103.5 (C), 88.5 (C), 53.5 (CH_2), 51.9 (C), 41.4 (CH), 38.4 (C), 36.7 (CH_2), 34.6 (CH_2), 34.3 (CH_2), 29.4 (CH_3), 27.7 (CH_2), 26.2 (CH_3), 20.2 (CH_3), 18.1 (CH_3), 0.19 (CH_3) **IR** (neat, cm^{-1}) 2961 (m), 2925 (m) 1710 (s), 1250 (m), 842 (s) **HRMS** (EI) m/z $(M)^+$ calculated for $C_{22}H_{36}O$ 344.2535, found 344.2554 (18.6 %)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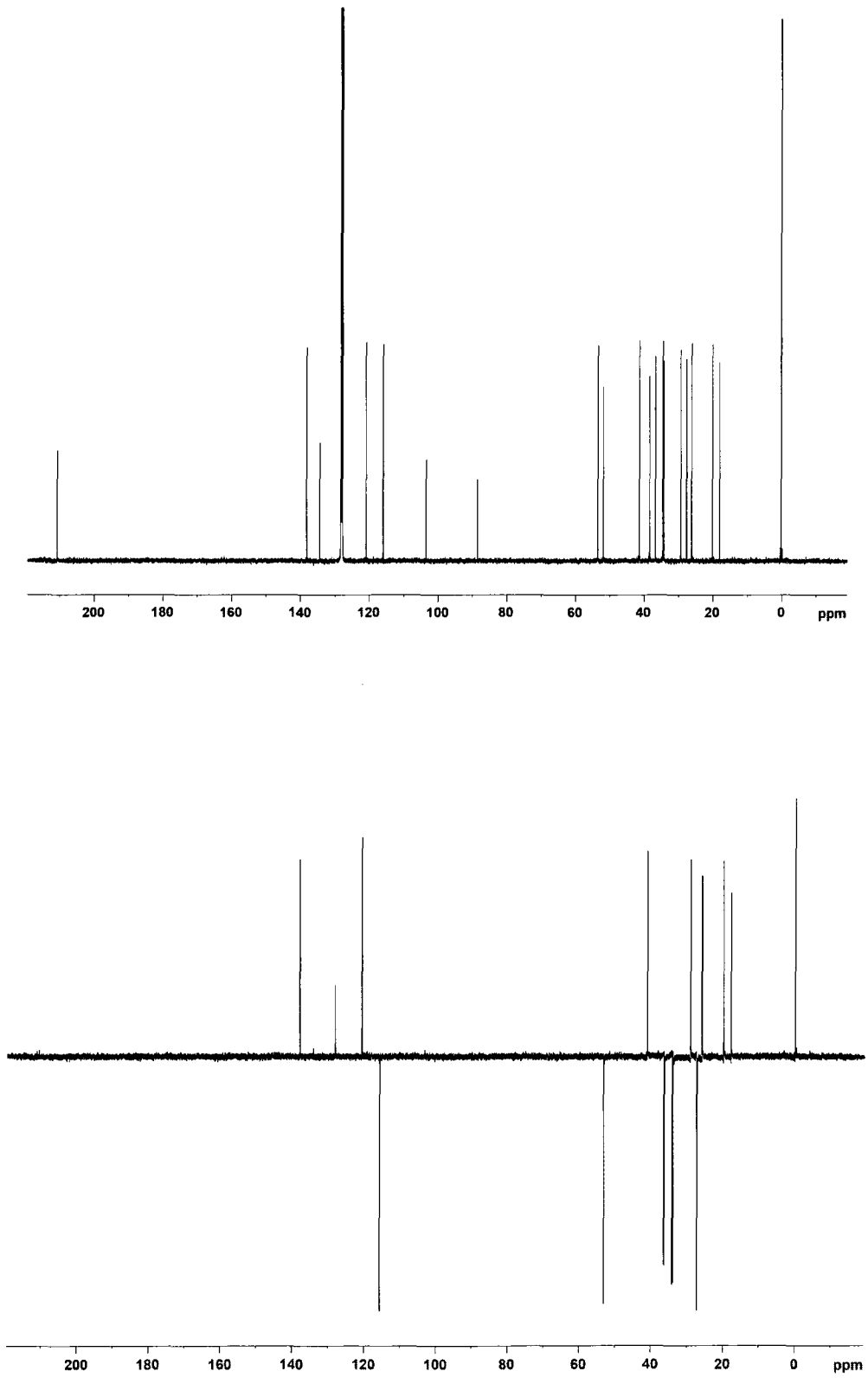
7.5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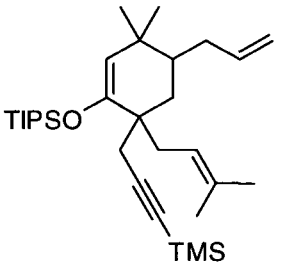
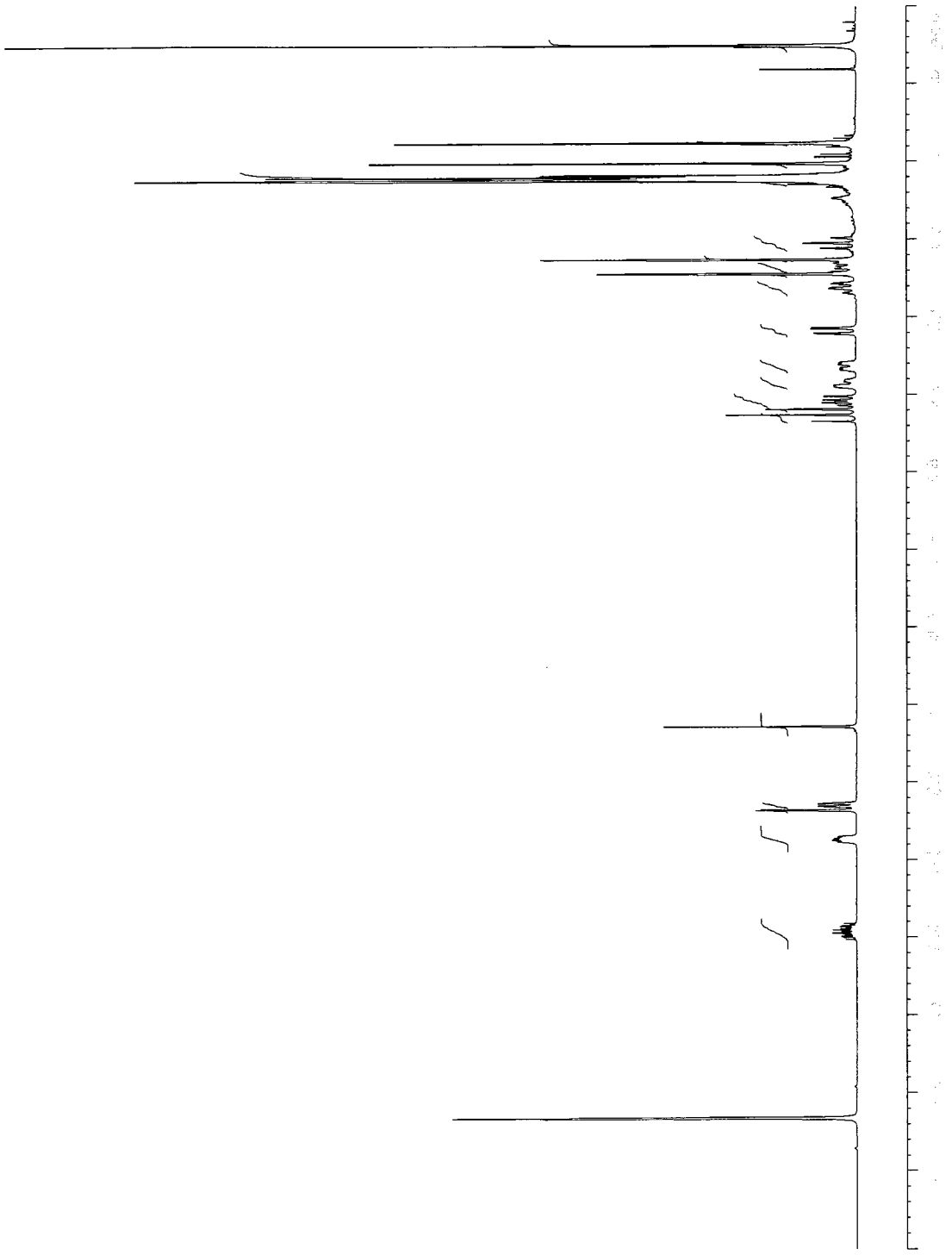
ppm

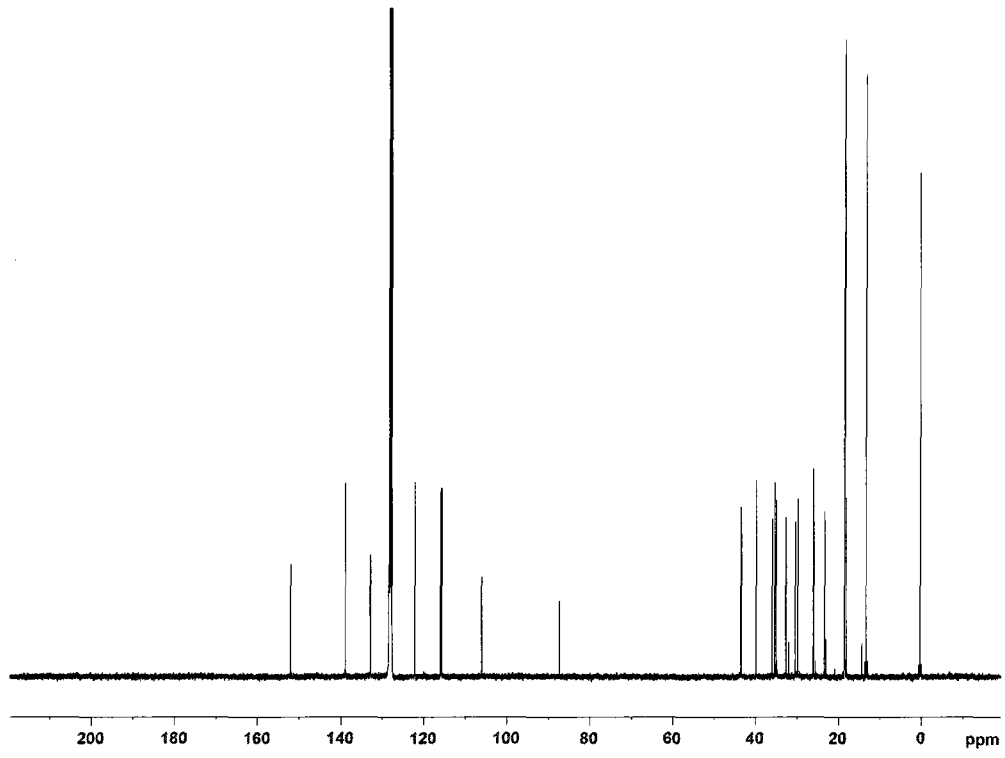
4-allyl-3,3-dimethyl-6-(3-methylbut-2-enyl)-6-(3-(trimethylsilyl)prop-2-ynyl)cyclohex-1-enyloxy)triisopropylsilane (3.25)



To a solution of **3.24** (0.044 g, 0.128 mmol, 1 equiv) in THF (1 mL) was added a solution of KHMDS (0.051 g, 0.255 mmol, 2.0 equiv) in THF (1 mL) followed by TIPSOTf (0.09 mL, 0.319 mmol, 2.5 equiv) at 0 °C. The reaction was stirred for 1 hour and was quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O (x3). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using hexanes as eluent to afford **3.25** (36 mg, 56%).

^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.96 (dddd, *J* = 16.3, 10.8, 8.0, 5.5 Hz, 1H), 5.37 (ddt, *J* = 9.2, 4.9, 1.4 Hz, 1H), 5.18 (br s, 1H), 5.16 - 5.13 (m, 1H), 4.64 (s, 1H), 2.65 (d, *J* = 16.8 Hz, 1H), 2.58 (d, *J* = 17.2 Hz, 1H), 2.54 (dd, *J* = 14.3, 9.2 Hz, 1H), 2.43 (ddd, *J* = 14.2, 3.2, 1.4 Hz, 1H), 2.32 (ddq, *J* = 12.1, 5.5, 1.7 Hz, 1H), 2.09 (dd, *J* = 13.9, 2.9, 1H), 1.81 (ddt, *J* = 13.0, 10.8, 2.5 Hz, 1H), 1.72 (s, 3H), 1.71-1.64 (m, 1H), 1.63 (s, 3H), 1.53 (t, *J* = 13.6 Hz, 1H), 1.12-1.09 (m, 21H), 1.01 (s, 3H), 0.88 (s, 3H), 0.25 (s, 9H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 152.0 (C), 138.9 (CH), 132.9 (C), 122.2 (CH), 115.9 (CH), 115.7 (CH_2), 106.1 (C), 87.3 (C), 43.5 (C), 39.9 (CH), 36.0 (CH_2), 35.4 (C), 35.0 (CH_2), 32.7 (CH_2), 30.4 (CH_2), 29.8 (CH_3), 26.1 (CH_3), 23.4 (CH_3), 18.6 (CH_3), 18.4 (CH_3), 13.3 (CH), 0.3 (CH_3). **IR** (neat, cm^{-1}) 2957 (m), 2871 (m), 2174 (w), 1658 (w), 1462 (m), 1247 (m), 1161 (m), 840 (s). **HRMS** (EI) m/z $(M)^+$ calculated for $C_{31}H_{56}OSi_2$ 500.3870, found 500.3897 (12.9 %)

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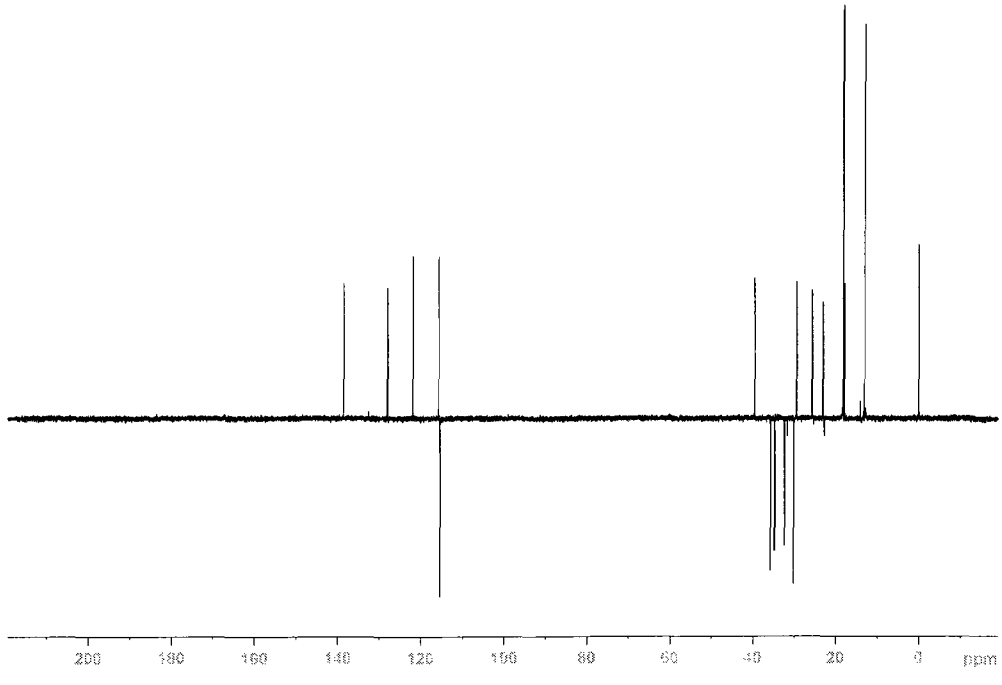
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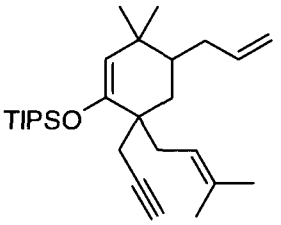
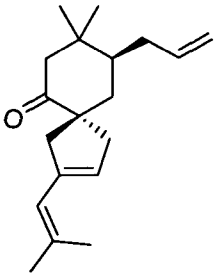
(4-allyl-3,3-dimethyl-6-(3-methylbut-2-enyl)-6-(prop-2-ynyl)cyclohex-1-enyloxy)triisopropylsilane (3.26)

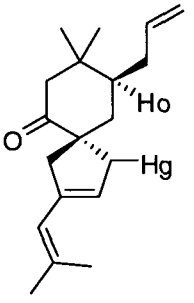


To a solution of **3.25** (0.027 g, 0.059 mmol, 1.0 equiv) in MeOH (1 mL) was added K_2CO_3 (0.019 g, 0.100 mmol, 2.0 equiv). The mixture was stirred overnight at room temperature. MeOH was evaporated and the resulting residue was purified by flash chromatography on silica gel using hexanes as eluent to afford **3.26** (9.6 mg, 42%). The product was not clean enough for characterization.

9-allyl-8,8-dimethyl-2-(2-methylprop-1-enyl)spiro[4.5]dec-2-en-6-one (3.28)



To a solution of **3.26** (0.010 g, 0.022 mmol, 1 equiv) in DCM (0.5 mL) was added a catalytic amount of Echavarren's catalyst (**3.2**). The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a gradient (0-10% EtOAc/hexanes) as eluent to afford **3.28** (no yield calculated). The relative stereochemistry was assigned by NOESY experiment. There is a correlation (6.3% nOe) between proton Ha and Hb.

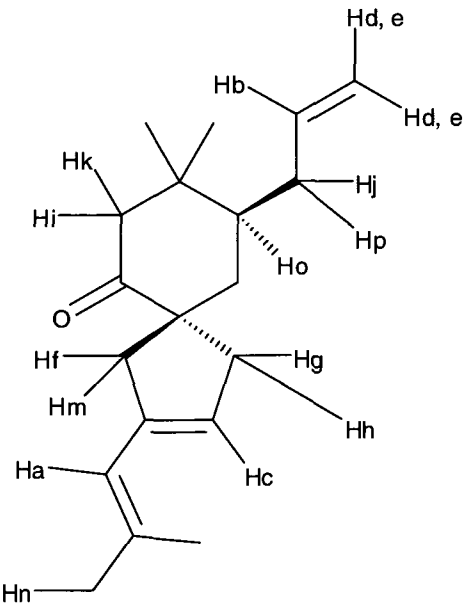


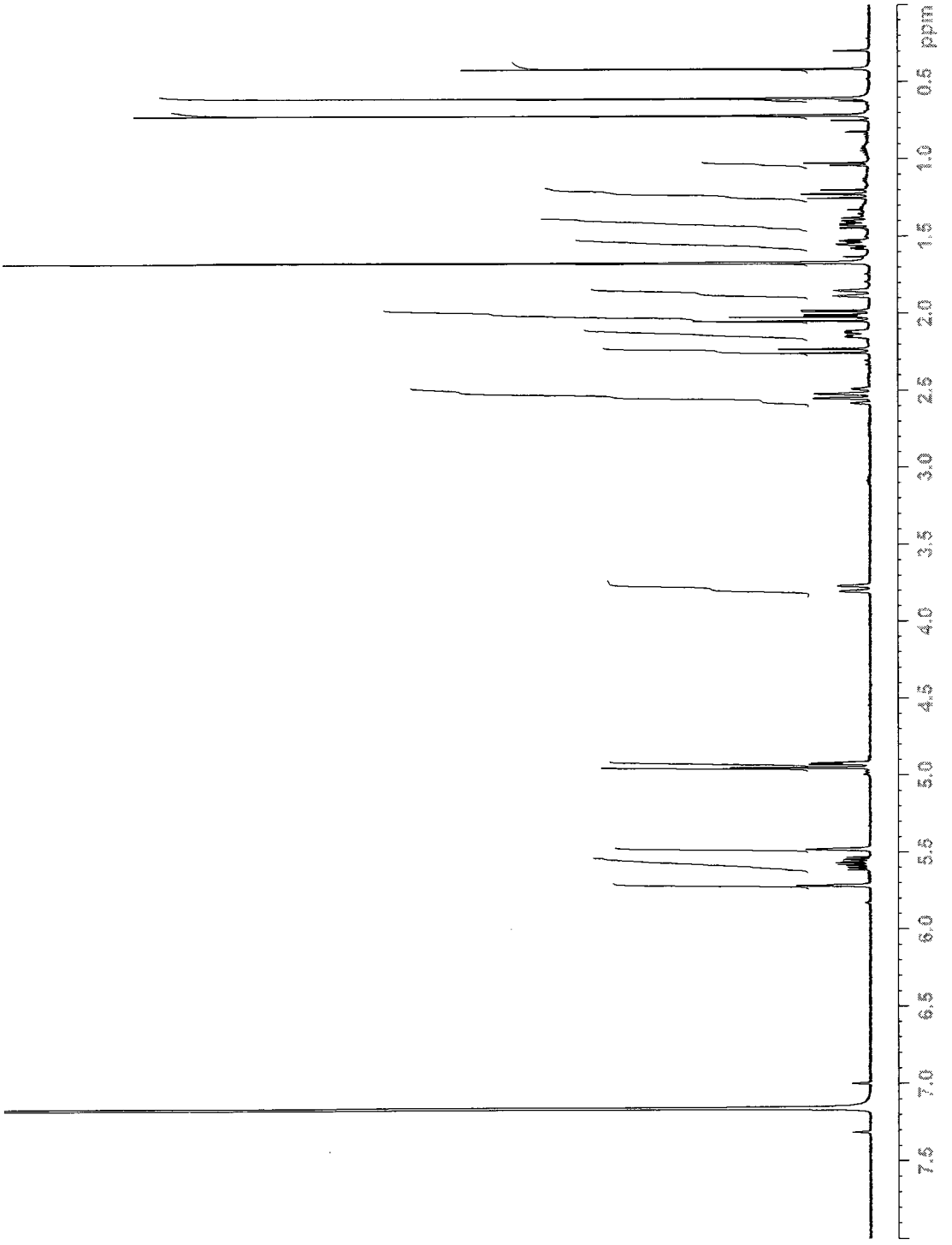
^{1}H NMR (400 MHz, C_6D_6) δ ppm 5.72 (br s, 1H), 5.57 (dddd, *J* = 17.8, 9.4, 8.4, 5.8 Hz, 1H), 5.48 (br s, 1H), 4.95 – 4.91 (m, 2H), 3.79 (d, *J* = 17.6 Hz, 1H), 2.57 (d, *J* = 15.6 Hz, 1H), 2.51 (dd, *J* = 15.7, 2.2 Hz, 1H), 2.24 (dd, *J* = 13.1, 0.8 Hz, 1H), 2.13 (dddt, *J* = 13.7, 5.8, 2.9, 1.5 Hz, 1H), 2.04 (d, *J* = 13.3 Hz, 1H), 2.00 (dd, *J* = 14.0, 3.7 Hz, 1H), 1.87 (d, *J* = 17.4 Hz, 1H), 1.67 (s, 6H), 1.58 – 1.52 (m, 1H), 1.45 – 1.38 (m, 1H), 1.23 (dd, *J* = 14.0, 13.0 Hz, 1H), 0.72 (s, 3H), 0.61 (s, 3H) **^{13}C NMR** (125.8 MHz, C_6D_6) δ ppm 210.0 (C), 138.0 (CH), 136.8 (C), 134.1 (C), 127.7 (CH), 122.2 (CH), 116.1 (CH_2), 55.8 (C), 53.8 (CH_2), 47.0 (CH_2), 42.8 (CH), 42.4 (CH_2), 40.4 (CH_2), 38.4 (C), 34.4 (CH_2), 29.6 (CH_3), 27.1 (CH_3), 19.9 (CH_3), 19.7 (CH_3) **IR** (neat, cm^{-1}) 2965 (m), 2826 (m), 1709 (s), 910 (m). **HRMS** (EI) m/z $(M)^+$ calculated for $C_{19}H_{28}O$ 272.2140, found 272.2135 (58.8 %)

COSY

	peak description	correlation with
A	5.72 (br s, 1H)	N
B	5.57 (dddd, J = 17.8, 9.4, 8.4, 5.8 Hz, 1H)	D, E, J
C	5.48 (br s, 1H)	F, H, M
D and E	4.95 – 4.91 (m, 2H)	B
F	3.79 (d, J = 17.6 Hz, 1H)	C, G, H, M
G	2.57 (d, J = 15.6 Hz, 1H)	C, F, H, M
H	2.51 (dd, J = 15.7, 2.2 Hz, 1H)	C, F, G, M
I	2.24 (dd, J = 13.1, 0.8 Hz, 1H)	K
J	2.13 (dddt, J = 13.7, 5.8, 2.9, 1.5 Hz, 1H)	P
K	2.04 (d, J = 13.3 Hz, 1H)	I
L	2.00 (dd, J = 14.0, 3.7 Hz, 1H)	O, Q
M	1.87 (d, J = 17.4 Hz, 1H)	C, F, G, H
N	1.67 (s, 6H)	A, F
O	1.58 – 1.52 (m, 1H)	L, Q
P	1.45 – 1.38 (m, 1H)	J
Q	1.23 (dd, J = 14.0, 13.0 Hz, 1H)	L, O
R	0.72 (s, 3H)	none
S	0.61 (s, 3H)	none

According to the HMQC experiment, the following protons are on the same carbon: F and M, G and H, I and K, P and J, O, L and Q. There is a correlation between proton A and F in the NOESY experiment.

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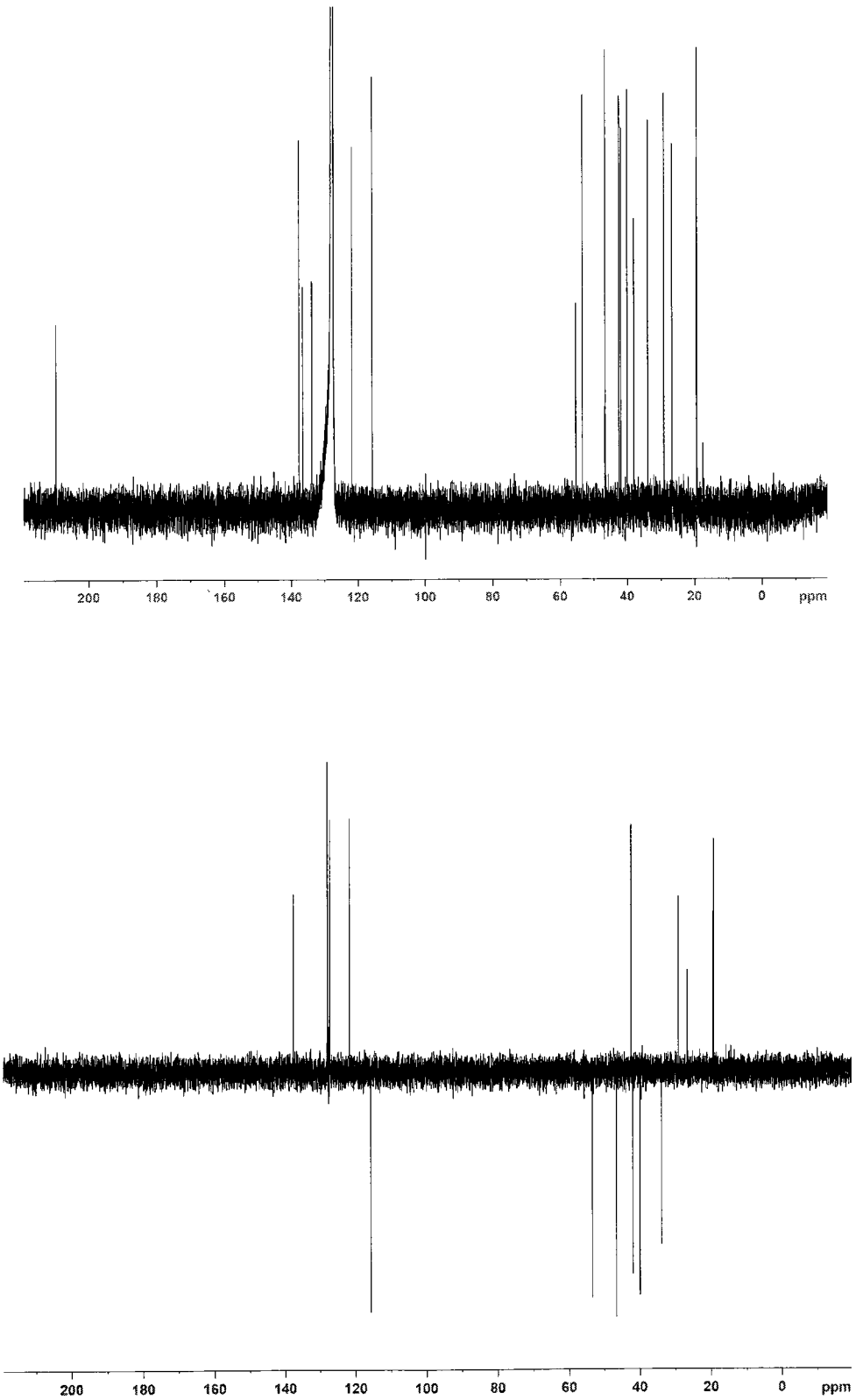
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X-Ray crystallography of compound 2.35b

Crystals of $C_{36}H_{44}O_7$ were grown from a solution of hexane/CH_2Cl_2. A single colorless prism suitable for X-ray diffraction measurements was mounted on a glass fibre. Unit cell measurements and intensity data collections were performed on a Bruker-AXS SMART 1 k CCD diffractometer at 202K using graphite monochromatized Mo K_α radiation (λ = 0.71073 Å). The data reduction included a correction for Lorentz and polarization effects, with an applied multi-scan absorption correction (SADABS). The crystal data and refinement parameters for $C_{36}H_{44}O_7$ are listed in Table 1. Interatomic distances and angles are listed in Table 3. The reflection data were consistent with a triclinic system; P-1.

The crystal structure was solved and refined using the SHELXTL program suite. Direct methods yielded all non-hydrogen atoms. All hydrogen atom positions were either located from the difference Fourier map or were calculated geometrically and were riding on their respective carbon atoms. The terminal OCH_3 group was disordered and modeled as a 65:35 mixture. With the exception of the minor portion of the disordered OCH_3 molecule, all non-hydrogen atoms were refined with anisotropic thermal parameters. The largest residual electron density peak (0.214 e/Å^3) was associated with the C8 atom. Full-matrix least-squares refinement on F^2 gave R_1 = 0.0563 and wR_2 = 0.1225 at convergence.

Table 1. Crystal data and structure refinement for 07066.

Identification code	07066	
Empirical formula	C36 H44 O7	
Formula weight	588.71	
Temperature	201(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.2570(15) Å	α= 109.215(2)°.
	b = 13.0180(17) Å	β= 113.902(2)°.
	c = 13.1836(18) Å	γ= 101.211(2)°.
Volume	1543.0(4) $Å^3$	
Z	2	
Density (calculated)	1.267 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	632	
Crystal size	0.15 x 0.12 x 0.10 mm^3	
Theta range for data collection	2.14 to 25.35°.	
Index ranges	-13<=h<=13, -15<=k<=15, -15<=l<=15	
Reflections collected	12597	
Independent reflections	5577 [R(int) = 0.0459]	
Completeness to theta = 25.35°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9914 and 0.9871	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5577 / 33 / 520	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0563, wR2 = 0.1225	
R indices (all data)	R1 = 0.1226, wR2 = 0.1478	
Largest diff. peak and hole	0.214 and -0.206 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 07066. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5826(6)	9344(5)	5925(6)	74(2)
C(1)	5897(8)	10398(7)	6749(8)	79(2)
O(1A)	5928(13)	9177(11)	6271(11)	69(3)
C(1A)	6093(19)	10243(15)	7241(15)	89(5)
O(2)	11067(2)	8169(2)	5772(2)	54(1)
O(3)	11464(2)	4495(2)	1248(2)	34(1)
O(4)	8991(2)	5571(2)	1823(2)	33(1)
O(5)	9052(2)	7092(2)	1362(2)	41(1)
O(6)	9105(2)	2483(2)	-334(2)	41(1)
O(7)	11869(2)	2792(2)	1878(2)	37(1)
C(2)	7062(4)	9270(3)	6026(3)	63(1)
C(3)	6923(5)	8284(3)	5091(3)	79(1)
C(4)	8087(6)	8209(3)	4993(4)	76(1)
C(5)	9409(5)	9103(3)	5835(4)	64(1)
C(6)	9511(5)	10051(3)	6768(4)	58(1)
C(7)	8363(4)	10146(3)	6874(3)	53(1)
C(8)	10664(5)	9109(4)	5684(5)	98(2)
C(9)	12370(4)	8326(3)	5784(4)	57(1)
C(10)	12617(4)	7199(3)	5474(3)	50(1)
C(11)	11563(3)	6192(3)	4176(3)	35(1)
C(12)	11518(3)	6539(3)	3169(3)	35(1)
C(13)	10331(3)	5620(2)	1884(3)	31(1)
C(14)	10381(3)	4400(2)	1557(2)	29(1)
C(15)	10637(3)	4019(2)	2612(3)	32(1)
C(16)	11786(3)	5007(2)	3956(3)	36(1)
C(17)	13271(3)	5165(3)	4162(3)	49(1)
C(18)	11668(4)	4640(3)	4924(3)	50(1)
C(19)	8483(3)	6362(2)	1575(2)	31(1)
C(20)	7170(3)	6262(2)	1618(2)	33(1)
C(21)	6560(3)	7070(3)	1428(3)	44(1)
C(22)	5353(3)	7013(3)	1477(3)	50(1)

C(23)	4725(3)	6166(3)	1695(3)	47(1)
C(24)	5322(4)	5369(3)	1888(3)	51(1)
C(25)	6534(3)	5420(3)	1853(3)	44(1)
C(26)	8951(3)	3462(2)	421(3)	33(1)
C(27)	8129(3)	3052(3)	990(3)	38(1)
C(28)	9126(3)	3624(3)	2407(3)	35(1)
C(29)	10870(4)	2851(3)	2289(3)	38(1)
C(30)	11641(4)	1589(3)	1249(4)	54(1)
C(31)	12685(3)	1459(2)	830(3)	38(1)
C(32)	12239(4)	553(3)	-306(3)	48(1)
C(33)	13183(4)	383(3)	-707(4)	57(1)
C(34)	14550(4)	1123(3)	13(4)	51(1)
C(35)	15008(4)	2031(4)	1146(4)	52(1)
C(36)	14081(4)	2199(3)	1551(3)	48(1)

Table 3. Bond lengths [Å] and angles [°] for 07066.

O(1)-C(2)	1.369(7)
O(1)-C(1)	1.405(9)
O(1A)-C(2)	1.431(13)
O(1A)-C(1A)	1.46(2)
O(2)-C(8)	1.408(4)
O(2)-C(9)	1.434(4)
O(3)-C(14)	1.430(3)
O(4)-C(19)	1.339(3)
O(4)-C(13)	1.465(3)
O(5)-C(19)	1.215(3)
O(6)-C(26)	1.427(3)
O(7)-C(30)	1.423(3)
O(7)-C(29)	1.437(3)
C(2)-C(7)	1.371(5)
C(2)-C(3)	1.385(5)
C(3)-C(4)	1.385(5)
C(4)-C(5)	1.393(5)
C(5)-C(6)	1.371(5)
C(5)-C(8)	1.503(5)
C(6)-C(7)	1.379(5)
C(9)-C(10)	1.501(5)
C(10)-C(11)	1.526(4)
C(11)-C(12)	1.523(4)
C(11)-C(16)	1.564(4)
C(12)-C(13)	1.515(4)
C(13)-C(14)	1.522(3)
C(14)-C(26)	1.551(4)
C(14)-C(15)	1.564(3)
C(15)-C(29)	1.543(4)
C(15)-C(28)	1.559(4)
C(15)-C(16)	1.570(4)
C(16)-C(17)	1.540(4)
C(16)-C(18)	1.546(4)
C(19)-C(20)	1.484(4)

C(20)-C(25)	1.382(4)
C(20)-C(21)	1.398(4)
C(21)-C(22)	1.375(4)
C(22)-C(23)	1.367(4)
C(23)-C(24)	1.378(4)
C(24)-C(25)	1.373(4)
C(26)-C(27)	1.528(4)
C(27)-C(28)	1.538(4)
C(30)-C(31)	1.502(4)
C(31)-C(32)	1.373(4)
C(31)-C(36)	1.378(4)
C(32)-C(33)	1.389(4)
C(33)-C(34)	1.354(5)
C(34)-C(35)	1.368(5)
C(35)-C(36)	1.374(4)

C(2)-O(1)-C(1)	117.5(5)
C(2)-O(1A)-C(1A)	115.4(11)
C(8)-O(2)-C(9)	109.6(3)
C(19)-O(4)-C(13)	118.0(2)
C(30)-O(7)-C(29)	108.3(2)
O(1)-C(2)-C(7)	124.9(4)
O(1)-C(2)-C(3)	115.2(4)
C(7)-C(2)-C(3)	119.4(4)
O(1)-C(2)-O(1A)	22.5(5)
C(7)-C(2)-O(1A)	121.3(6)
C(3)-C(2)-O(1A)	116.9(6)
C(2)-C(3)-C(4)	119.9(4)
C(3)-C(4)-C(5)	121.1(4)
C(6)-C(5)-C(4)	117.3(4)
C(6)-C(5)-C(8)	120.0(4)
C(4)-C(5)-C(8)	122.5(4)
C(5)-C(6)-C(7)	122.4(4)
C(2)-C(7)-C(6)	119.9(4)
O(2)-C(8)-C(5)	113.2(3)
O(2)-C(9)-C(10)	111.4(3)

C(9)-C(10)-C(11)	116.4(3)
C(12)-C(11)-C(10)	111.2(3)
C(12)-C(11)-C(16)	111.3(2)
C(10)-C(11)-C(16)	113.9(2)
C(13)-C(12)-C(11)	111.8(2)
O(4)-C(13)-C(12)	108.8(2)
O(4)-C(13)-C(14)	109.0(2)
C(12)-C(13)-C(14)	113.1(2)
O(3)-C(14)-C(13)	101.9(2)
O(3)-C(14)-C(26)	111.3(2)
C(13)-C(14)-C(26)	110.0(2)
O(3)-C(14)-C(15)	114.56(19)
C(13)-C(14)-C(15)	114.2(2)
C(26)-C(14)-C(15)	105.1(2)
C(29)-C(15)-C(28)	101.9(2)
C(29)-C(15)-C(14)	111.3(2)
C(28)-C(15)-C(14)	100.3(2)
C(29)-C(15)-C(16)	113.1(2)
C(28)-C(15)-C(16)	114.3(2)
C(14)-C(15)-C(16)	114.5(2)
C(17)-C(16)-C(18)	107.3(2)
C(17)-C(16)-C(11)	110.5(2)
C(18)-C(16)-C(11)	108.7(2)
C(17)-C(16)-C(15)	110.8(2)
C(18)-C(16)-C(15)	109.1(2)
C(11)-C(16)-C(15)	110.3(2)
O(5)-C(19)-O(4)	123.5(3)
O(5)-C(19)-C(20)	124.0(2)
O(4)-C(19)-C(20)	112.5(2)
C(25)-C(20)-C(21)	118.5(3)
C(25)-C(20)-C(19)	123.1(2)
C(21)-C(20)-C(19)	118.3(3)
C(22)-C(21)-C(20)	119.9(3)
C(23)-C(22)-C(21)	120.9(3)
C(22)-C(23)-C(24)	119.5(3)
C(25)-C(24)-C(23)	120.3(3)

C(24)-C(25)-C(20)	120.8(3)
O(6)-C(26)-C(27)	109.4(2)
O(6)-C(26)-C(14)	112.2(2)
C(27)-C(26)-C(14)	104.6(2)
C(26)-C(27)-C(28)	107.8(2)
C(27)-C(28)-C(15)	105.6(2)
O(7)-C(29)-C(15)	115.3(2)
O(7)-C(30)-C(31)	111.4(3)
C(32)-C(31)-C(36)	118.5(3)
C(32)-C(31)-C(30)	118.8(3)
C(36)-C(31)-C(30)	122.7(3)
C(31)-C(32)-C(33)	120.4(3)
C(34)-C(33)-C(32)	120.1(4)
C(33)-C(34)-C(35)	120.1(3)
C(34)-C(35)-C(36)	120.0(4)
C(35)-C(36)-C(31)	120.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 07066. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	52(3)	63(3)	85(4)	35(3)	20(3)	8(2)
C(1)	73(4)	78(5)	95(6)	36(4)	49(4)	36(3)
O(2)	73(2)	42(1)	58(2)	23(1)	41(1)	27(1)
O(3)	38(1)	34(1)	43(1)	19(1)	29(1)	15(1)
O(4)	35(1)	34(1)	41(1)	20(1)	23(1)	19(1)
O(5)	52(1)	37(1)	51(1)	27(1)	33(1)	24(1)
O(6)	44(1)	33(1)	44(1)	10(1)	27(1)	9(1)
O(7)	40(1)	34(1)	51(1)	20(1)	31(1)	19(1)
C(2)	69(3)	44(2)	56(2)	15(2)	23(2)	15(2)
C(3)	95(3)	45(2)	52(2)	7(2)	15(2)	18(2)
C(4)	147(4)	46(2)	47(2)	25(2)	51(3)	50(3)
C(5)	105(3)	54(2)	67(3)	42(2)	54(3)	44(3)
C(6)	66(3)	48(2)	60(3)	25(2)	29(2)	24(2)
C(7)	61(3)	44(2)	45(2)	15(2)	24(2)	19(2)
C(8)	161(5)	90(3)	151(4)	89(3)	125(4)	89(3)
C(9)	74(3)	41(2)	40(2)	7(2)	31(2)	10(2)
C(10)	48(2)	55(2)	37(2)	14(2)	20(2)	18(2)
C(11)	31(2)	40(2)	34(2)	14(1)	19(2)	15(2)
C(12)	38(2)	31(2)	40(2)	15(2)	24(2)	13(2)
C(13)	34(2)	34(2)	33(2)	18(1)	21(1)	15(1)
C(14)	31(2)	31(2)	33(2)	16(1)	21(1)	12(1)
C(15)	33(2)	35(2)	42(2)	23(1)	25(1)	19(1)
C(16)	37(2)	47(2)	35(2)	22(2)	22(2)	22(2)
C(17)	38(2)	60(2)	42(2)	18(2)	16(2)	24(2)
C(18)	63(2)	62(2)	43(2)	30(2)	33(2)	34(2)
C(19)	40(2)	28(2)	24(2)	10(1)	14(1)	15(1)
C(20)	35(2)	34(2)	25(2)	11(1)	14(1)	15(1)
C(21)	44(2)	52(2)	49(2)	32(2)	25(2)	27(2)
C(22)	43(2)	62(2)	57(2)	36(2)	24(2)	32(2)
C(23)	37(2)	57(2)	43(2)	18(2)	20(2)	21(2)
C(24)	52(2)	50(2)	66(2)	30(2)	39(2)	23(2)

C(25)	48(2)	39(2)	58(2)	25(2)	33(2)	23(2)
C(26)	35(2)	34(2)	34(2)	15(1)	19(1)	15(1)
C(27)	35(2)	35(2)	51(2)	19(2)	27(2)	13(2)
C(28)	39(2)	39(2)	44(2)	24(2)	28(2)	22(2)
C(29)	42(2)	42(2)	48(2)	26(2)	32(2)	23(2)
C(30)	68(3)	36(2)	86(3)	30(2)	57(2)	28(2)
C(31)	45(2)	30(2)	57(2)	25(2)	33(2)	22(2)
C(32)	44(2)	35(2)	62(2)	16(2)	30(2)	11(2)
C(33)	74(3)	39(2)	71(3)	21(2)	51(2)	25(2)
C(34)	58(3)	57(2)	80(3)	45(2)	51(2)	41(2)
C(35)	35(2)	72(3)	59(2)	39(2)	25(2)	22(2)
C(36)	51(2)	52(2)	45(2)	22(2)	28(2)	16(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 07066.

	x	y	z	U(eq)
H(1A)	4948	10339	6580	119
H(1B)	6319	11051	6632	119
H(1C)	6473	10539	7609	119
H(1A1)	5259	10100	7327	133
H(1A2)	6205	10885	7013	133
H(1A3)	6925	10458	8034	133
H(3O)	11750(30)	3940(30)	1350(30)	70(12)
H(6O)	9710(40)	2780(30)	-490(30)	72(13)
H(3)	6032	7661	4517	95
H(4)	7981	7535	4341	91
H(8A)	10445	9070	4862	117
H(8B)	11463	9859	6332	117
H(17A)	13380	5393	3557	73
H(17B)	13407	4423	4050	73
H(17C)	13971	5779	5008	73
H(18A)	10732	4531	4820	75
H(18B)	12382	5254	5766	75
H(18C)	11815	3900	4801	75
H(6)	10410(30)	10650(30)	7340(30)	60(11)
H(7)	8480(30)	10800(30)	7540(30)	65(10)
H(9A)	12380(30)	8630(20)	5230(30)	44(9)
H(9B)	13150(30)	9000(30)	6650(30)	56(9)
H(10A)	12690(30)	7010(30)	6110(30)	52(10)
H(10B)	13590(40)	7380(30)	5610(30)	65(10)
H(11)	10710(30)	6060(20)	4130(20)	41(8)
H(12A)	11350(20)	7270(20)	3300(20)	28(7)
H(12B)	12420(30)	6640(20)	3160(30)	56(9)
H(13)	10320(20)	5806(18)	1240(20)	16(6)
H(21)	6960(30)	7570(30)	1190(30)	68(11)
H(22)	4930(30)	7570(20)	1350(20)	42(8)

H(23)	3870(30)	6100(20)	1700(20)	36(8)
H(24)	4820(40)	4740(30)	1970(30)	86(12)
H(25)	6950(30)	4840(20)	1930(20)	38(8)
H(26)	8460(20)	3839(19)	-90(20)	21(6)
H(27A)	7330(30)	3310(20)	820(20)	48(8)
H(27B)	7780(30)	2190(30)	620(20)	45(8)
H(28A)	9000(20)	4340(20)	2860(20)	19(6)
H(28B)	9020(30)	3060(20)	2760(20)	39(7)
H(29A)	11220(30)	2730(20)	3040(20)	35(7)
H(29B)	9960(30)	2220(20)	1590(30)	37(8)
H(30A)	11790(30)	1240(20)	1840(20)	43(8)
H(30B)	10550(40)	1130(30)	430(30)	89(12)
H(32)	11270(30)	40(30)	-770(30)	65(10)
H(33)	12810(40)	-330(30)	-1530(30)	77(11)
H(34)	15180(30)	1030(20)	-230(20)	44(9)
H(35)	15950(30)	2570(30)	1680(30)	54(10)
H(36)	14380(30)	2830(30)	2310(30)	71(11)

Glossary and Abbreviations

±	racemic
Ac	acetate
aq.	aqueous
Bn	benzyl
br	broad
Bz	benzoyl
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
decomp.	decomposition
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DPS	*tert*-butyldiphenylsilyl
EI	electron ionization
eq.	equivalents
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate

HMBC	heteronuclear multiple bond correlations
HRMS	high resolution mass spectrometry
i-Pr	isopropyl
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
PA	*p*-anisaldehyde
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PTSA	*p*-toluene sulphonic acid
q	quartet
quant.	quantitative yield
Rf	retention factor
r.t.	room temperature
s	singlet or strong
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl

n-Bu	*n*-butyl
t-Bu	*tert*-butyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
w	weak

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