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Studies of the Biomimetic Synthesis of Plumarellide

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A thesis submitted to the University of Nottingham for Master's Degree

Abstract

Part 1 provides an overview of marine natural products, emphasizing the significance of polycyclic cerium diterpenes, specifically furanobutenolide-based cembranoids (FBCs), due to their unique structures and diverse biological activities. These compounds, often found in corals, are of great research interest, but their limited natural sources hinder extensive study. Thus, the total synthesis of FBCs is crucial. Researchers have explored various methods, including biomimetic synthesis, computational chemistry, and organic synthetic chemistry, to address this challenge.

Part 2 introduces one FBCs molecule, plumarellide, which remains unsynthesized. Plumarellide is distinct with a central cyclohexene ring linked to a substituted cyclohexane and an oxybridged cyclohexene. It is related to three other natural product molecules also isolated from corals. Multiple research groups have attempted to synthesize plumarellide, simulating its biosynthetic pathway and proposing thermodynamically favorable synthetic routes using computational chemistry. However, full synthesis has not yet been achieved.

Part 3 presents a new approach to the total synthesis of plumarellide. This method involves the organic synthesis of a key precursor, 24, followed by biomimetic synthesis and computational chemistry-assisted transformations leading to the final product. The article provides detailed explanations of the implemented synthesis steps and their significance in the context of plumarellide synthesis.

Part 4 outlines the future research endeavors. While a potential full synthesis route has been designed, it requires further experimentation and refinement. If the attempt to fully synthesize plumarellide proves successful, this achievement will serve as a valuable foundation for synthesizing three other related natural products found within the same organism. Additionally, research into structural modifications of these natural products and subsequent biological activity testing holds promising prospects. The article looks ahead to these exciting possibilities in the field of natural product synthesis and modification.

Acknowledgement

I would like to take this opportunity to convey my sincere gratitude to numerous individuals and institutions that have played crucial roles in my academic and personal development throughout the past year. At the forefront of my appreciation is Professor Bencan Tang, my esteemed mentor, whose unwavering guidance and unwavering support have been indispensable in shaping my academic and research journey. Professor Tang's mentorship has not only facilitated my smooth transition into this new academic milieu but has also propelled me toward substantial advancements in my scientific pursuits. I am profoundly appreciative of the encouragement and aid extended to me by Professor Tang and my fellow colleagues within our research cohort.

Additionally, I would like to acknowledge and thank the University of Nottingham Ningbo China (UNNC). My experience on this campus has introduced me to new people, diverse experiences, and a beautiful environment. Despite the relatively small campus, the tranquil surroundings have been a source of solace, particularly during evening walks that offer respite from the demands of my studies. Ningbo, with its unhurried pace of life, has become an oasis of calm for me. One of my favorite pastimes here is cycling, and there's nothing quite like riding a bike along the coast, with the sea breeze providing a refreshing escape from the rigors of academic life. The only minor drawback has been my adjustment to the local cuisine, as I have not yet mastered the art of cooking.

I also want to extend my gratitude to Professor Gao Zhanghua from Zhejiang University and his research group. Their support, guidance, and access to their excellent laboratory facilities have been indispensable in my research achievements over the past year. I must particularly thank Teacher Jiang Zhijiang for his outstanding mentorship. His imaginative thinking and profound knowledge in chemistry have been a great source of inspiration for me. I look forward to continuing our collaboration as I embark on my doctoral studies.

Lastly, but certainly not least, I want to express my deep appreciation to my family. Despite the physical distance that separates us, their unwavering care and support have been a constant presence in my life. Our monthly phone calls serve as a lifeline, providing warmth and encouragement that fortify my resolve to persevere. It is with their support that I have been able to pursue and attain a master's degree, and I recognize that their contributions have been immeasurable. The democratic approach to communication within our family and my sister's stern reprimands have played a significant role in helping me interact effectively with others.

While my master's degree is but a small chapter in the grand tapestry of life, I am committed to continued dedication and learning as I step into the next exciting phase of my journey. I am eager to embrace new challenges, expand my horizons, and work toward new milestones in my academic and personal growth.

Table of Contents

1 Introduction

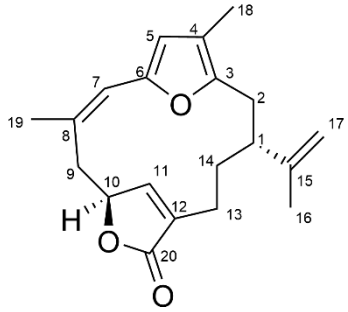
1.1 Marine natural product: polycyclic cembranoid diterpenes

Marine natural products exhibit diverse biological activities and possess unique structures, making them one of the most active research areas in the fields of natural product separation, drug development, and organic synthesis.

Cembranoid natural products are widely distributed as marine and terrestrial diterpene secondary metabolites in nature, and they can be found in gorgonian octocorals and various soft coral species. Researchers have identified these structures as exhibiting strong cytotoxicity. Isolation and investigation of this diverse and highly oxidized class of compounds have led to the discovery of a series of structurally diverse compounds.

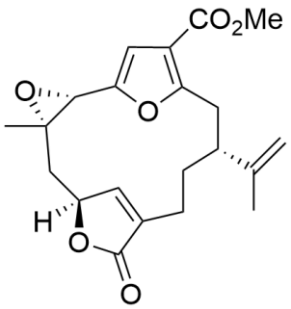
Furanobutenolide-based cembranoids (FBCs) are among the most biologically active members of the cembranoid family. The first characterized furanobutenolide-based cembranoid, named pukalide **2**, was discovered by Scheuer et al. in 1975 from the soft coral Sinularia abrupta. Following this discovery, a class of compounds known as furanobutenolide-based cembranoids has been gradually isolated from various coral species. These compounds share a common core structure known as rubifolide **1**. They belong to a larger family of 14-membered ring diterpenes derived from geranyl pyrophosphate, a structure that accommodates furan rings between C3–C6 and butenolide ring systems encompassing C10–C12.[1]

One of the most representative members of this family is bipinnatin J (**3**). Lophotoxin **4**, on the other hand, is a potent neurotoxin that functions as an irreversible antagonist of the nicotinic acetylcholine receptor. Acerosolide **5** exhibits the *E*-configuration at the alkene bond, while most other FBCs compounds exhibit the opposite configuration at the same alkene bond. Additionally, enedione-based cembranoids, such as coralloidolide E (**6**) resulting from oxidative cleavage of the furan rings in FBCs, and isomeric structures with 12-membered rings, known as pseudopterolides or kallolides (e.g., kallolide B (**7**)), are commonly found alongside FBCs in corals.[2]



1

Rubifolide



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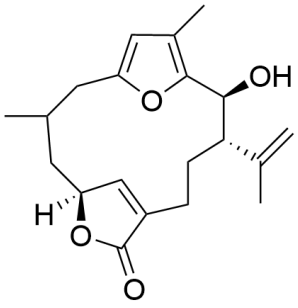
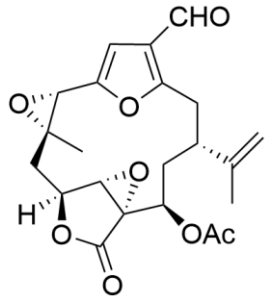
Pukalide



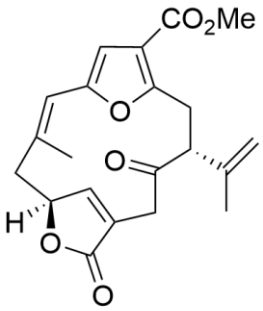
3

Bipinnatin J



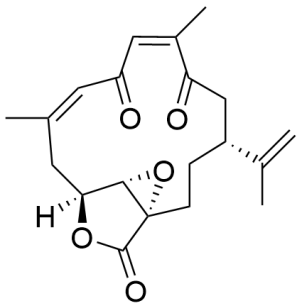
4

Lophotoxin



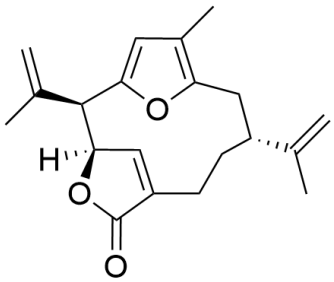
5

Acerosolide



6

Coralloidolide E



7

kallolide B

Figure 1. Some furanobutenolide-based cembranoids, (FBCs), and oxidized and

rearranged relatives isolated from corals.

By far the most exciting FBC-related metabolites to be found in corals, however, are a variety of highly oxygenated and complex ring-fused diterpene metabolites, represented by bielschowskysin **8**, plumarellide **9**, rameswaralide **10**, and intricarene **11** (Figure 2). In addition, a number of related C19 norditerpenes, which also have highly complex ring-fused systems, e. g. ineleganolide **12**, sinulochromodin C (**13**) and dissectolide **14**, have been isolated from corals and clearly have their origins in FBC precursors.[3]

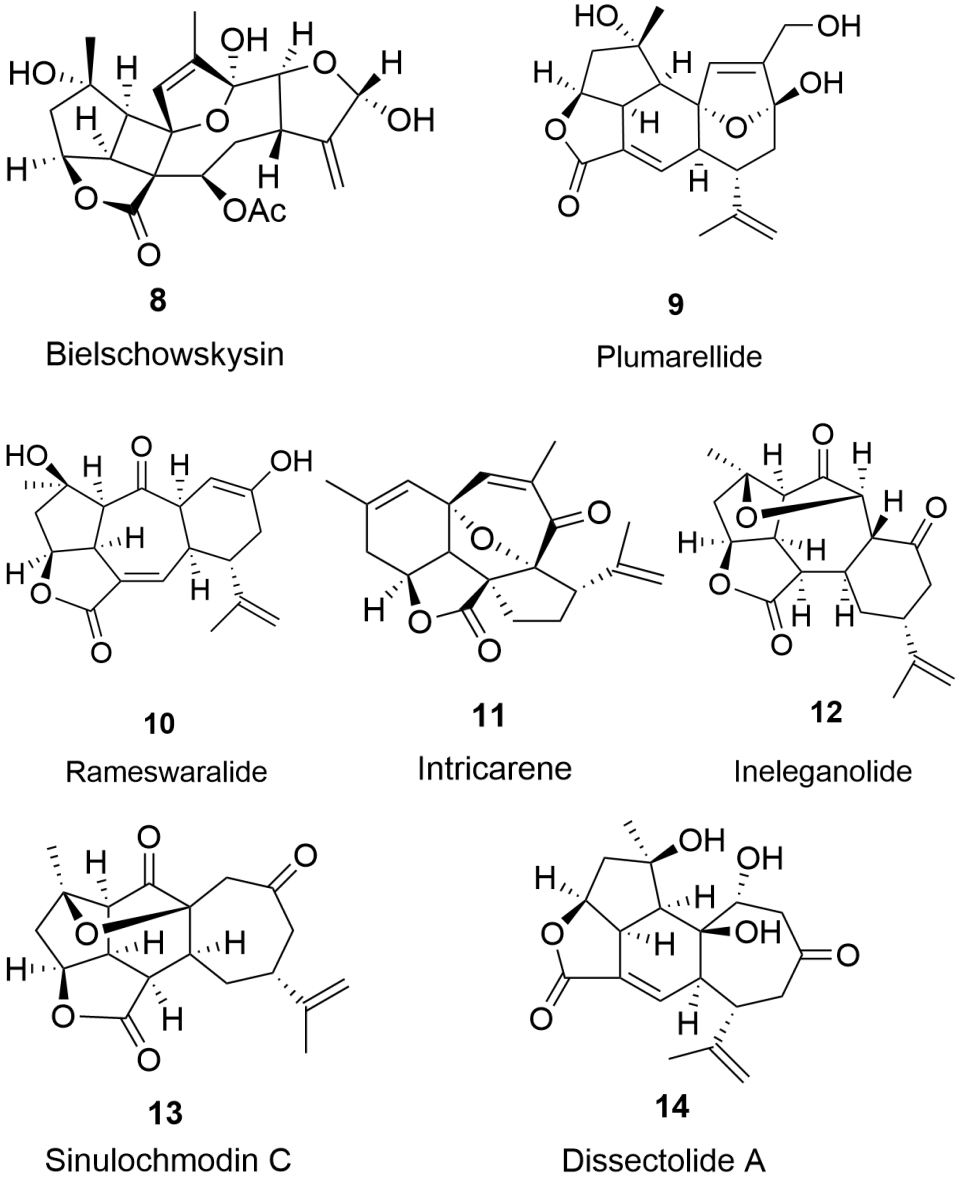


Figure 2. Representative highly oxygenated and complex ring-fused diterpene metabolites.

1.2 Research progress of polycyclic cembranoid diterpenes

FBCs can be divided into two types. One type is cembranoid containing 20 carbon atoms, and its precursor (**15**) has a branched chain connected to the 10th carbon atom of the furan ring. The corresponding norcembranoid (**16**) only contains 19 carbon atoms, which is speculated to be due to the easy loss of C18 during the oxidation and hydrolysis process of the compound. These two types of structures also have the same three-dimensional structure, which contain the isopropenyl and butenolide groups in the C1-(*R*)- and C10-(*S*)-configurations.

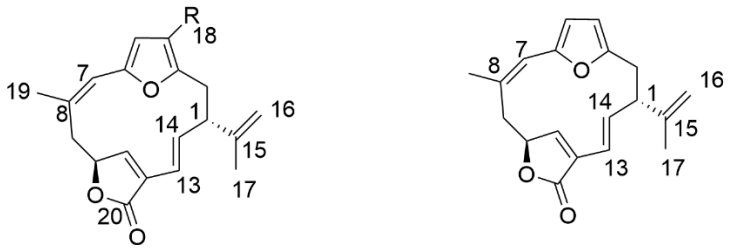


Figure 3. Cembranoid and norcembranoid furanobutenolide scaffolds.

Among these two types of compounds, we pay more attention to Cembranoid. There are some known polycyclic furanobutenolide-derived cembranoids, including macrocycles BSK **8**, rameswaralide **10**, intricarene **11**, and verrillin **13,** polycycles and the closely related plumarellide **9**, mandapamate **17,** isomandapamate **18** (Figure 3).

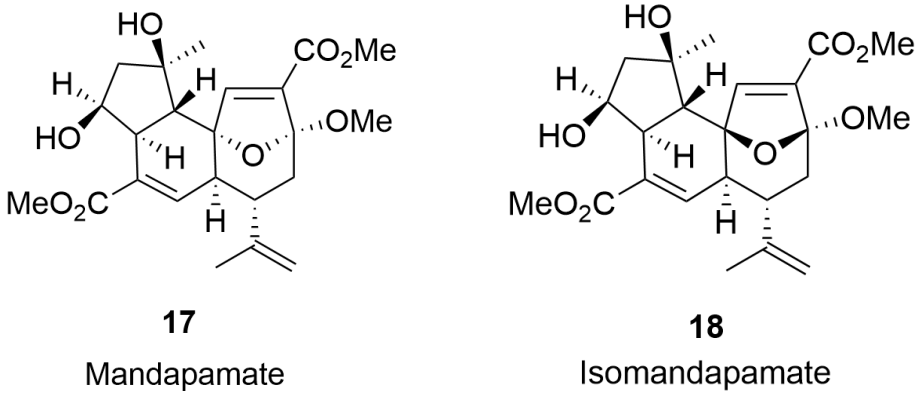


Figure 4. Mandapamate and isomandapamate.

These structures have been isolated from corals and clearly have their origins in FBC precursors. The amazing nature products, combined with the unusual

fusion of rings with complex oxy-substitution patterns and stereochemistry in the polycyclic structures. Decorated by a variety of oxygenation states and patterns, these diterpenes display a variety of complex, highly compact, stereochemically dense architectures.[3]

1.3 Biomimetic synthesis of polycyclic cembranoid diterpenes

Natural products are compounds or substances produced by naturally existing living organisms. They can also be prepared through chemical synthesis, including semisynthetic and total synthesis. Natural products play a fundamental role in the development of organic chemistry by providing challenging synthesis goals. The synthesis of natural products remains highly significant today for several reasons.

First, natural products represent the most important source of research and development for new drugs. Over the past 30 years, approximately half of the 1,000 new drugs approved by the US FDA have been either natural products, derivatives of natural products, or synthetic drugs based on natural product structures.[4]

Second, natural product synthesis is crucial for protecting the natural environment. Many natural products are rare in nature, and obtaining them from their natural sources can lead to environmental damage. For instance, consider paclitaxel, an anticancer drug found in yew trees, where its content is less than 0.01%. In the pursuit of this drug, human activities have nearly decimated yew forests.

Third, the synthesis of natural products has driven research into new theories, reactions, and reagents, thus advancing the entire field of chemistry.

Total synthesis of natural products is an effective means of obtaining these molecules through chemical methods. Due to the complexity and importance of the research, natural product synthesis is considered one of the most challenging and vital directions in synthetic chemistry. It plays an irreplaceable role in promoting the development of synthetic chemistry, fostering innovative drug development, and nurturing cutting-edge chemical talents. The key characteristic of natural product synthesis lies in the structural complexity of the target molecules and the associated synthetic challenges. For a long time, the primary challenge in this field has been achieving the efficient synthesis of complex natural

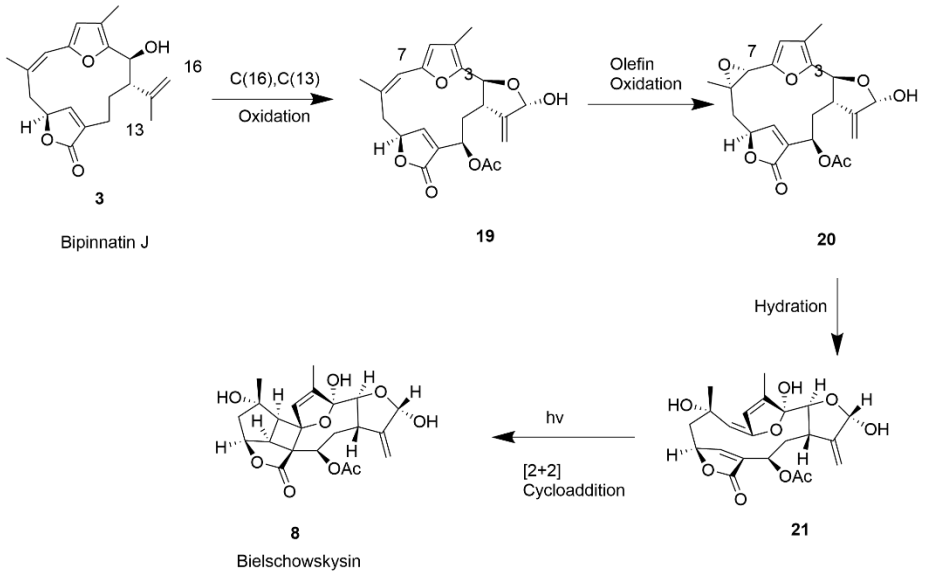
products. Nature is known as the greatest "molecular maker," often synthesizing complex natural products with great precision and efficiency. Therefore, one effective approach to efficient synthesis is to draw inspiration from nature by simulating key elements in the biogenic synthesis of natural products, such as substrate structure, enzyme function, bond-breaking mechanisms, and reaction conditions.

Natural products have been and will continue to be a significant source for drug discovery. Approximately half of existing drugs are either natural products or their derivatives, yet many undiscovered natural products remain to be explored. For example, compared to terrestrial natural products, the diversity and quantity of natural compounds in the sea are much greater, but only a small fraction of them has been studied. Marine natural products represent a promising frontier in drug development and are poised to become the next treasure trove of valuable compounds.

Bielschowskysin (BSK, **8**) is a rare polycyclic lambdoid diterpene associated with EKVX non-small cell lung cancer (GI50<0.01 μM) and CAKI-1 renal cell carcinoma (GI50=0.51 μM), exhibiting notable cytotoxicity and antiplasmodial activity. As a result, much of the research focused on the synthesis of polycyclic furanobutenolide-derived cembranoids has been directed towards the synthesis of BSK.[5]

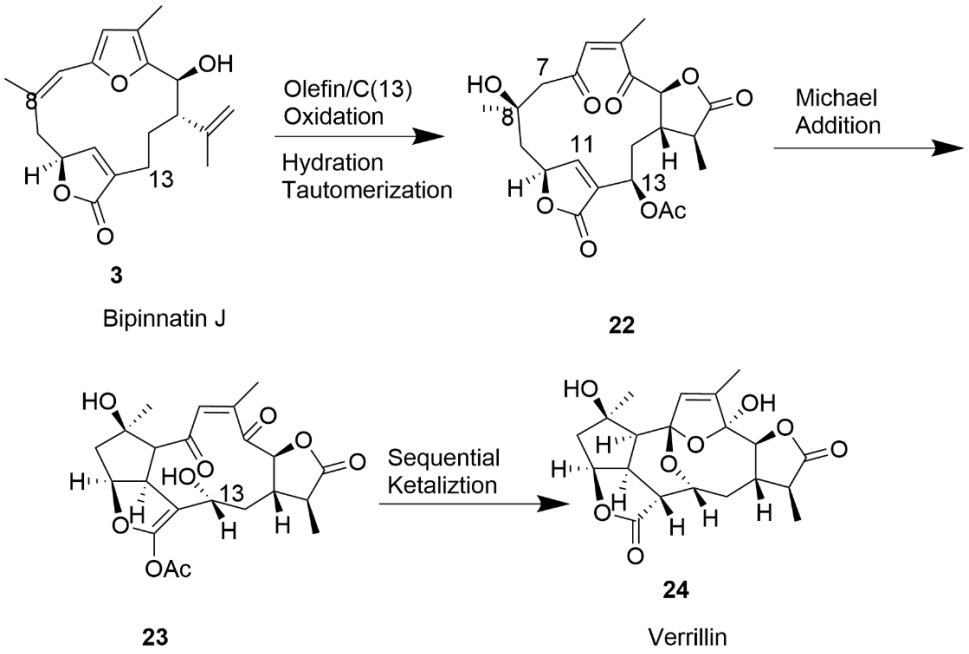
Most approaches to synthesizing BSK **8** rely on light-induced [2+2] cycloaddition to create the fused cyclobutane structural elements. While a complete synthesis of BSK **8** has yet to be reported, substantial advancements have been made in functionalizing BSK **8**.[6]

In terms of biosynthesis, BSK **8** is believed to originate from bipinnatin J (**3**). Oxidation at positions C13 and C16, followed by intramolecular emulsification, results in acetic acid **19**. Subsequently, $\Delta^{7,8}$ bonds oxidize to form epoxide **20**, followed by a double grape-like hydration reaction on the furan ring to yield hydroxyfuran **21**. This positions butenolide **21** for photoinduced [2+2] cycloaddition, forming the characteristic cyclobutane ring and completing the synthesis of BSK **8**.[7]



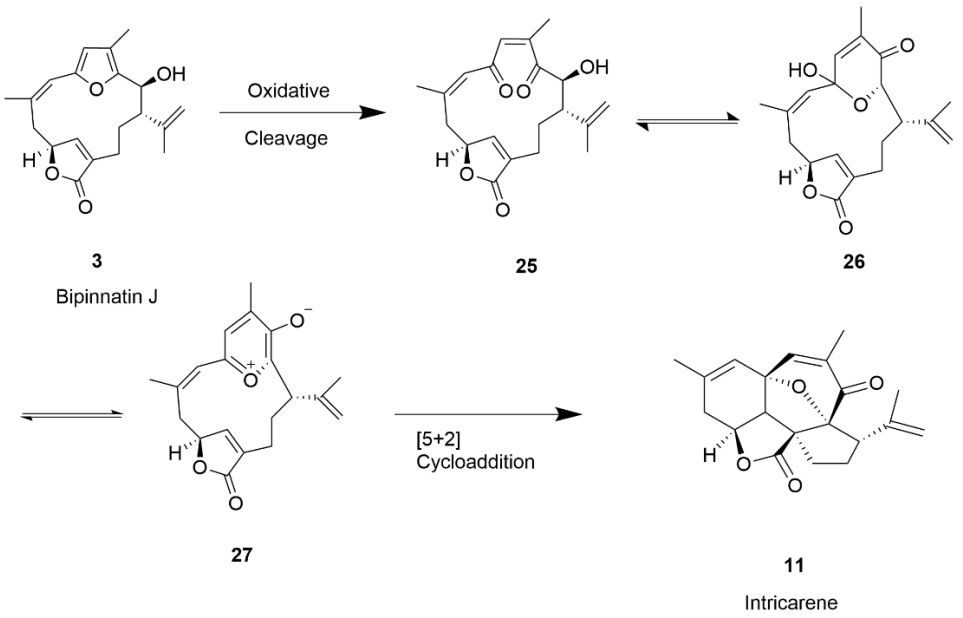
Scheme 1. Biosynthetic proposal for the construction of bielschowskysin (BSK).[6]

Verrillin **24**, derived from furanbutene lactone and also based on the central ether-bridged macrocycle, may also trace its origins back to bipinnatin J (**3**, as shown in Scheme 2). The selective oxidation of butanolide **3** serves a dual purpose, targeting not only the oxidation of C13 and isopropenyl groups but also introducing a stereochemical change at C8 through the epoxidation of the $\Delta^{7,8}$ bonds. Subsequent to the double-grape-like hydration reaction of the furan ring and isomerization, grape-like diketone **22** is generated. An intramolecular Michael addition within the molecule of grape ketone **22** forms a C7– C11 bond, leading to the creation of a polycyclic compound **23** after the migration of the acetic acid group. Compound **23** exhibits an oxygen anion at C13. [8]Ultimately, the continuous ketonization of diol **23**, involving a grape-like ketone system and hydrolysis of the acetic enol portion, yields verrillin **24**. Notably, there are currently no successful total synthesis examples of verrillin **24** using biomimetic synthesis routes. Instead, the sole successful total synthesis route for verrillin **24** begins with furfural.[9]



Scheme 2. Proposed biosynthesis of verrillin **24**.[8]

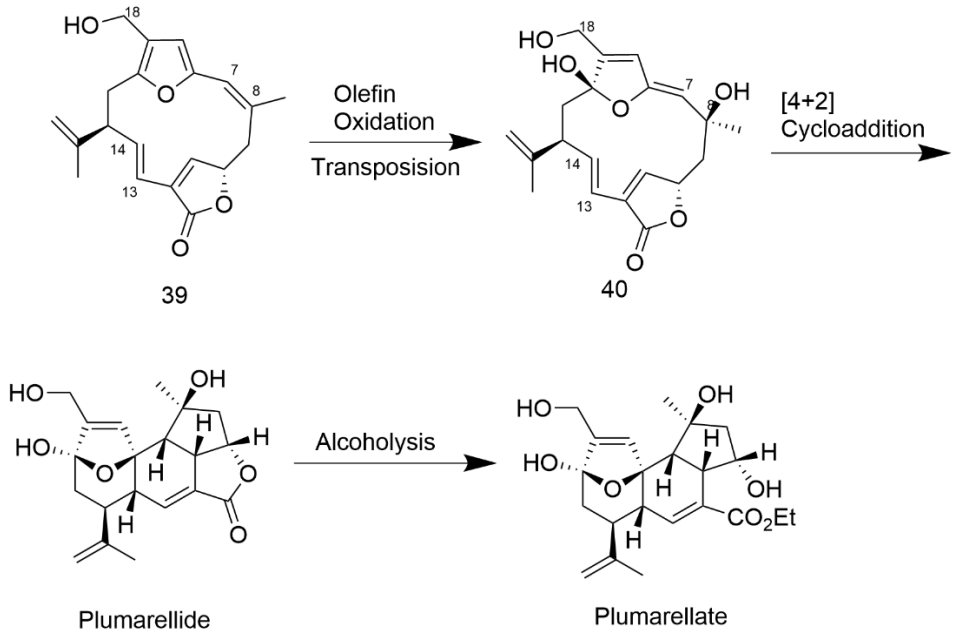
Drawing from the experimental work conducted by the Pattenden and Trauner laboratories, along with computational research carried out by the Tantillo laboratory, it appears highly likely that intracarene **11**, a pentacyclic cytotoxic cembranoid, is a biosynthetic precursor with intriguing contrasts. The process begins with the oxidative cleavage of the furan ring in bipinnatin J (**3**), resulting in the formation of homoallylic alcohol **25** (as shown in Scheme 3). An equilibrium between hydroxypyrone **26** and alcohol **25** leads to the creation of oxidopyrylium **27**. It is proposed that the charge-separated, simple aromatic ring within the macrocycle **27** plays a pivotal role in an intramolecular [5+2] cycloaddition event, giving rise to a furan-bridged cycloheptanone ring. This step completes the biosynthesis of intracarene **11**. Remarkably, this represents a rare and successful example of total synthesis within the realm of polycyclic cembranoid diterpenes.[3]



Scheme 3. Biosynthetic speculation concerning the formation of intricarene 11.[3]

However, it is important to note that bipinnatin J (**3**) is not the precursor for all polycyclic furanobutenolide-derived cembranoids. In contrast to Bipinnatin J (**3**), Macrocycle **28** undergoes oxidation at C18 rather than C2, and it possesses an additional unsaturated unit between C13 and C14. This makes it a precursor for hemolytic membrane plumarellide **9** and plumarellate (**30**, as illustrated in Scheme 4).[10]

The process involves the oxidation of the Δ7,8 bonds followed by olefin translocation, resulting in the intermediate hemiketal **29**. Diene **29** can intramolecularly participate in a [4+2] reaction with the *trans*-cyclic enol segment, ultimately forming the central cyclohexene ring and completing the synthesis of plumarellide **15**.[1] Additionally, the alcoholysis of lactones with ethanol yields a tetracyclic derivative known as plumarellate **30**. A more detailed exploration of plumarelide will be provided in Part 2.



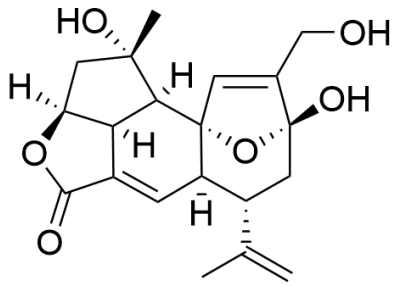
Scheme 4. Proposed biosynthetic construction of the plumarellides.[1]

2 Plumarellide

2.1 Structure of plumarellide

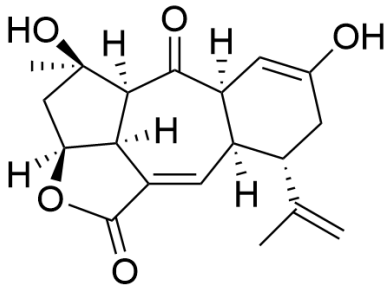
In 2002, plumarellide **9** was discovered in gorgonian coral of the *Plumarella sp.* species, thriving in the Kuri Island region of the Pacific Ocean. Its distinctive features include a central cyclohexene ring connected to a substituted cyclopentane and an oxybridged cycloheptene. This compound shares structural similarities with mandapamates **17** and **18**, previously found in soft corals of the *Sinularia genus*. The main structural differences lie in whether they are lactones or contain -CO2Me at C18, as well as epimerism at C8. On the other hand, rameswaralide **10** boasts a central cycloheptene ring flanked by substituted cyclopentane and cyclohexene rings. It coexists with mandapamates **17** and **18** in *Sinularia dissecta*. There was an earlier suggestion that rameswaralide might be derived from the expansion of a 6-membered ring in a mandapamate through a novel vinylogous α-ketol rearrangement.

The four metabolites, namely **9**, **10**, **17**, and **18**, exhibit subtle variations in the orientations of their C7 and C8 centers within their structures. Plumarellide **9** features an α-oriented OH group at C8, while in metabolites **10**, **17**, and **18**, this OH group is β-oriented. Furthermore, the bridged C7–H center in 9 and 10 is α-oriented, whereas in mandapamates **17** and **18**, it exhibits the alternative β-H stereochemistry. These distinctions hold significance in terms of understanding the biosynthetic origins of these four metabolites.



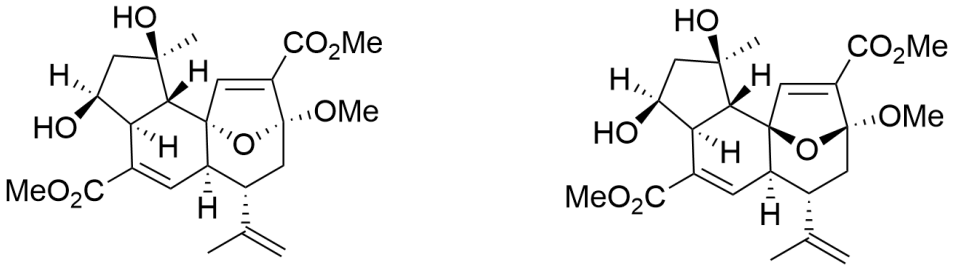
9

Plumarellide



10

Rameswaralide



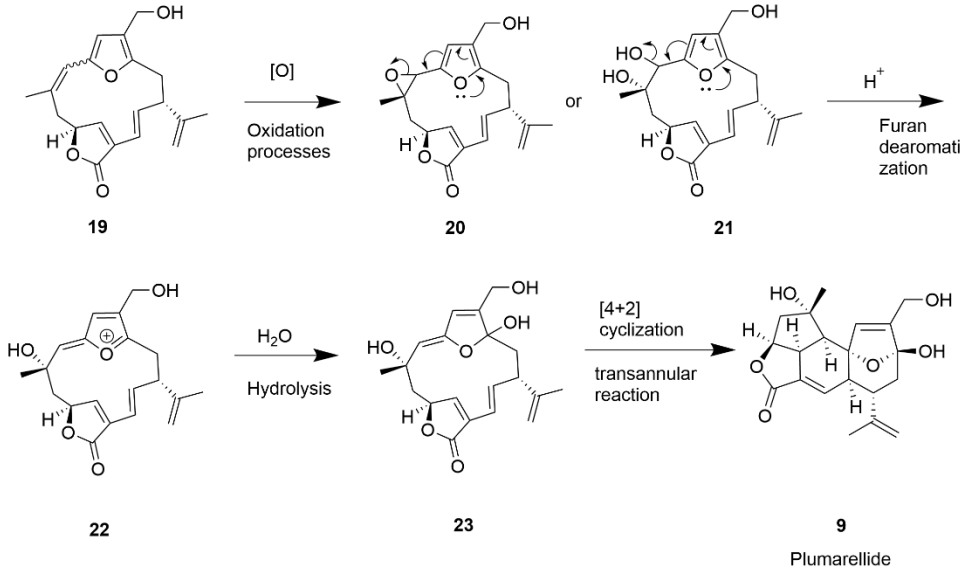
17
Mandapamate

18
Isomandapamate

Figure 5. Plumarellide, rameswaralide, mandapamate and isomandapamate.

In accordance with proposals set forth by Pattenden and other researchers, it has been suggested that the ring structures observed in compounds **9**, **10**, **17**, and **18** originate from furanobutenolide-based macrocyclic cembranoids, specifically compound **19**. This transformation is facilitated through a series of oxidative processes that give rise either to epoxides, denoted as **20**, or to vicinal diols, represented as **21**. Subsequently, these intermediates undergo hydrolysis, resulting in the formation of furanoxonium ions, along with enol ether and cyclic hemiketal intermediates, identified as **22** and **23**, respectively.[11]

In the context of plumarellide, it is hypothesized that intermediate **23** undergoes a transannular cyclization reaction of the [4+2] type, leading to the formation of the intricate polycyclic ring system characteristic of this natural product (Scheme 5). This synthetic process provides insight into the formation of the polycyclic cyclohexene ring-based compound, plumarellide **9**, based on the previously mentioned conjectures regarding its biosynthesis.[12]



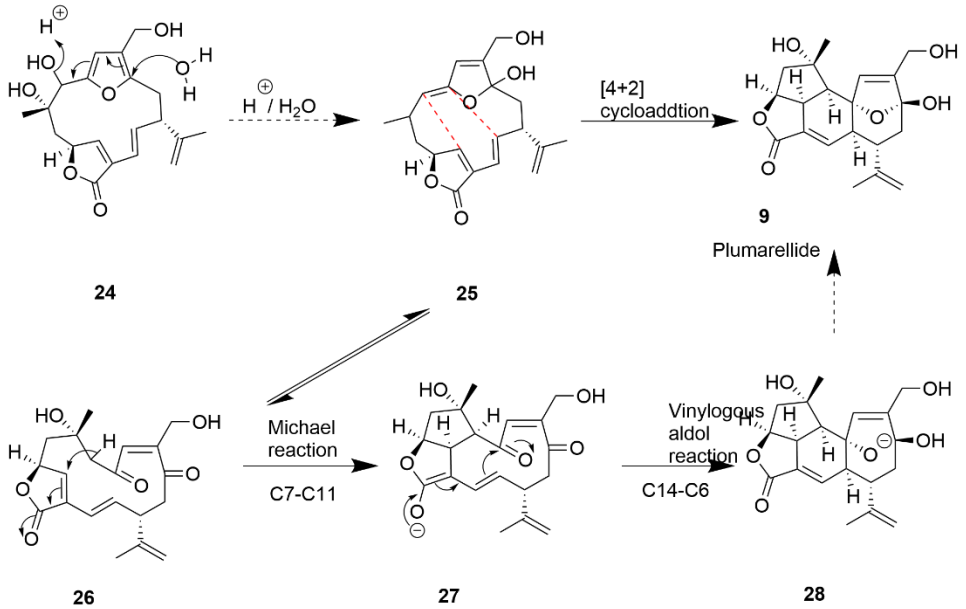
Scheme 5. Potential biosynthesis pathway of plumarellide. [13]

2.2 Synthetic progress of plumarellide

Presently, two prominent research groups have undertaken comprehensive investigations into the synthesis of plumarellide, contributing valuable synthetic routes. By comprehending and enhancing these routes, a deeper understanding of the complexities and challenges inherent in plumarellide synthesis can be achieved.

To begin, the Pattenden research group stands as a pioneering force in the total synthesis of plumarellide. Their pioneering work has had significant implications for the synthesis of plumarellide, offering multiple prospective solutions. The primary focus of their initial scheme is the proposal of plumarellide synthesis *via* a [4+2] cycloaddition reaction employing precursor **24**. Additionally, an alternative route was suggested, involving the intermediate 25 undergoing a Michael reaction between C7-C11 and C14-C6, akin to a vinylogical aldol reaction.[2]

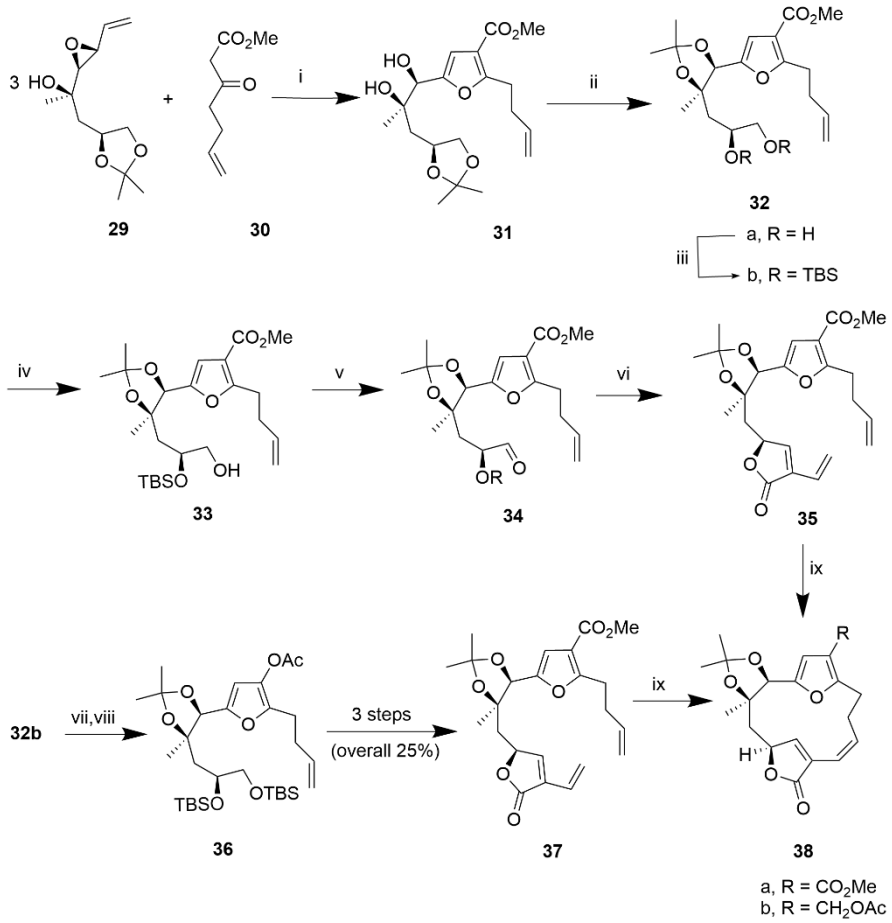
The first scheme's [4+2] cycloaddition route was substantiated through comparison with the natural synthesis pathway of the compound and computational chemistry calculations, making it the route that has garnered the most research effort. Nonetheless, current synthetic endeavors have not yet reached the critical [4+2] cycloaddition step, leaving both schemes unverified experimentally. [13]The Pattenden group's research has thus encountered challenges, particularly in the synthesis of precursor **24**.[14]



Scheme 6. The plumarellide synthesis route with [4+2] cycloaddition as the key step.[13]

Scheme 7 represents a relatively comprehensive endeavor by the Pattenden

group to synthesize precursor **24**. [1]Initially, researchers in the Pattenden group connected precursor molecules **29** and **30**, forming the distinctive furan ring. Subsequently, they continued to synthesize the pivotal lactone ring, aiming to maximize molecular efficiency within the route. However, during the final RCM (Ring-Closing Metathesis) ring closure reaction, *cis*-structured products were unexpectedly obtained at critical olefin positions.[15, 16]

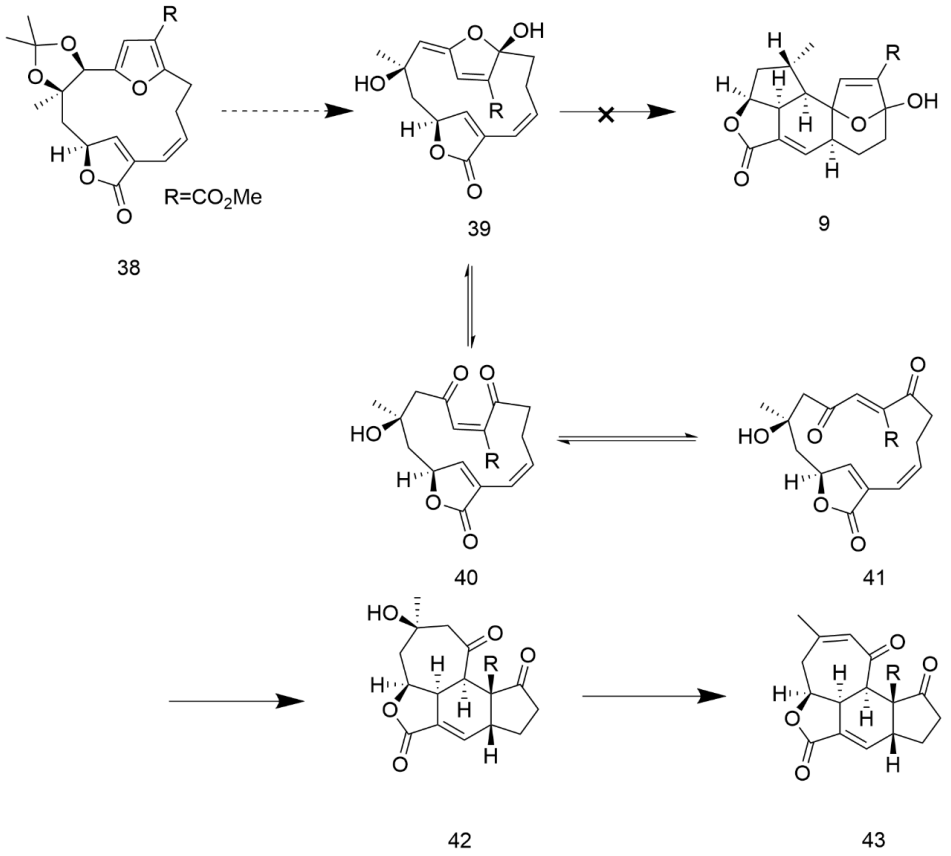


Reagents and conditions: (i) piperidine–HOAc, 55 ℃, overnight, 45%; (ii) Me2C(OMe)2, PPTS, reflux, 1 h, 35% over two steps; then HOAc–H2O (10:1), 50 ℃, 2.5 h, 90%; (iii) TBSCl, Im, DMF, rt, 12 h, 87%; (iv) HF–pyridine, THF–pyridine, rt, 5 h, 65%; (v) DMP, NaHCO3, C H2Cl2, rt, 1 h, 80%; (vi) MeCH=CHCO2Et, LiHMDS–HMPA, THF, - 78 ℃ to - 20 ℃ over 2 h, 25%; (vii) $LiAlH_4$, THF, rt; (viii) Ac2O, pyridine, rt, 2 h, 70% over two steps; (ix) Hoveyda–Grubbs II, toluene, 70 ℃, 15 h, 68–72%.

Scheme 7. The plumarellide synthesis route with RCM reaction as the key step.[17]

During subsequent investigations concerning intermediate **38**, which possessed a *cis*-olefin structure, it was observed that this configuration did not undergo the anticipated [4+2] cycloaddition reaction to yield Plumarellide as expected.[14] Instead, another multi-ring product, referred to as **43**, was obtained following the pathway outlined in Scheme 8. It is evident that the formation of the cyclohexene ring in the newly formed compound **43** occurs through a transannular [4+2] cycloaddition reaction involving the 1,3-diene moiety within the macrocycle **38**. However, it is noteworthy that the component participating in this cycloaddition is not the enol ether alkene bond found in the initially assumed intermediate 39. Rather, it is the alkene bond associated with the listener **42** of **39**

(as depicted in Scheme 7). [17]If an intramolecular [4+2] cycloaddition reaction was to occur in **39a**, involving its enol ether alkene bond, it would be expected to result in the formation of the structure resembling plumarellide, encompassing the plumarellide ring system.[18]



Scheme 8. Potential biosynthesis pathway of plumarellide.[17]

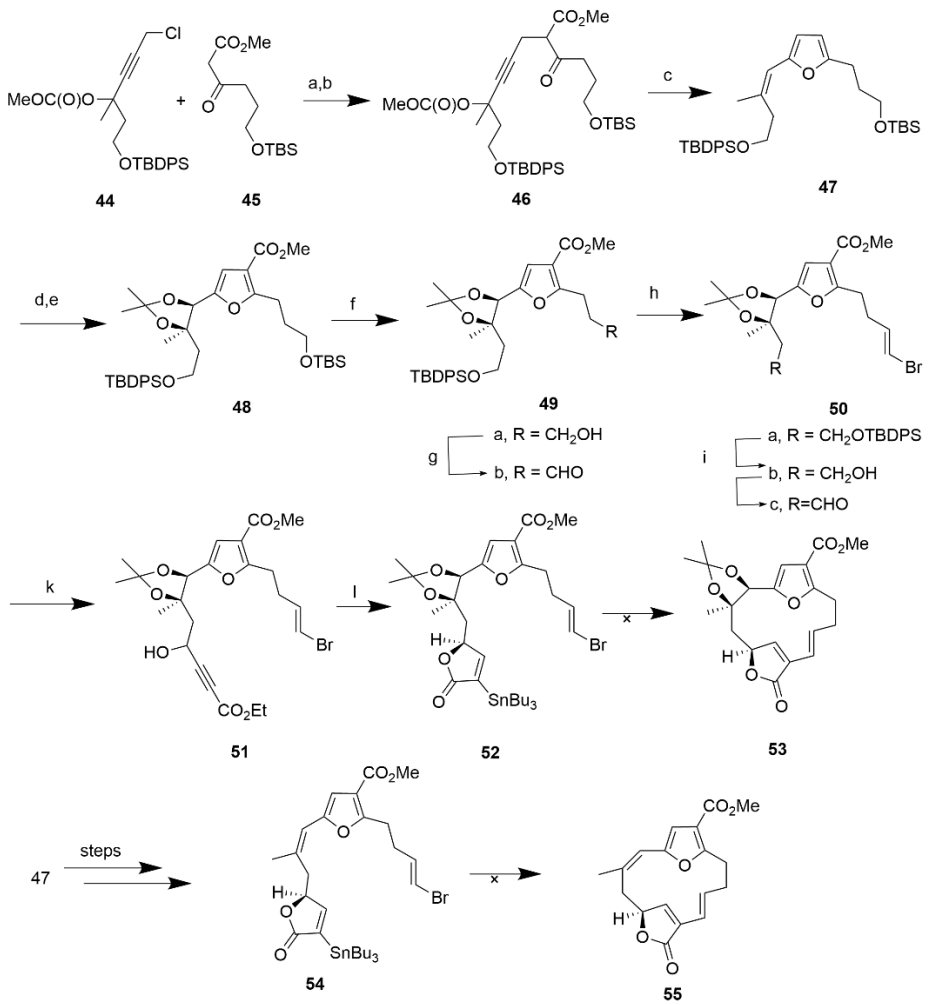
Pattenden's subsequent investigation aimed to synthesize the *E*-macrocycle **24**, with the intramolecular Stille coupling reaction of vinylstannane-vinyl bromide **42** as the pivotal step. The synthetic process commenced with the production of substituted furan 54. This was achieved by initiating a condensation reaction between propargyl chloride **49** and β-keto ester **45** in the presence of sodium hydride, yielding gketoacetylene **46** (as illustrated in Scheme 8). Subsequently, treatment of **46** with Pd(ddpf)-K_2CO_3 in acetonitrile-water at 75 ℃ resulted in a 1:1 mixture of *Z*- and *E*-isomers of the substituted furan **47**. Notably, when the palladium catalyst was omitted, and the reaction was conducted in DMF at 90 ℃, the *Z*:*E* ratio of **47** shifted to 2:1.

The next step involved treating **47** with AD-mix-a to produce the corresponding vicinal diol, which was subsequently protected as its acetonide **48**. After removing the TBS protecting group from **48**, the resulting alcohol **49a** underwent oxidation using Desse-Martin periodinane, leading to the formation of aldehyde **49b**. When aldehyde **49b** was treated with $CHBr_3$ and $CrCl_3$ under Takai conditions, it unsurprisingly yielded a 2:1 mixture of *E*/*Z*-vinyl bromides **50a**.

Further steps included the removal of the TBDPS protecting group in **50a** and the oxidation of alcohol **50b** to produce aldehyde **50c**. The reaction of aldehyde **50c** with the anion derived from ethyl propionate ultimately furnished the substituted propargyl alcohol **51**.

However, when a solution of **51** in acetonitrile was subjected to a reaction with Bu_3SnH in the presence of $Pd(PPh_3)_4$, the major product obtained was the vinylstannane-vinyl bromide **54** (in yields ranging from 27% to 35%). This was accompanied by small quantities of a compound resulting from the concurrent reduction of the vinyl bromide moiety in **54**. Unfortunately, despite their efforts, Pattenden's team was unable to isolate the anticipated macrocyclic *E*-diene **24** from this reaction.

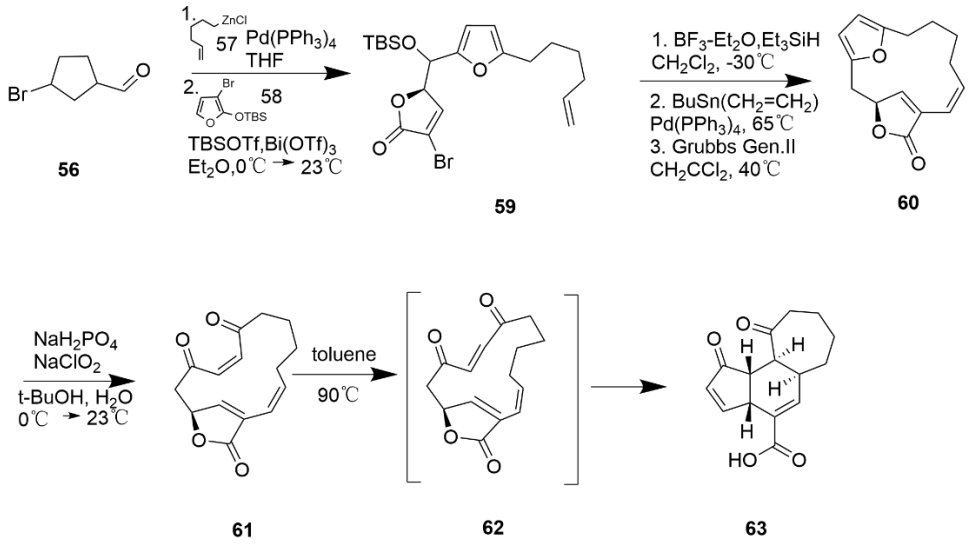
Subsequent attempts included the preparation of butenolide-based stannane-vinyl bromide **53**, structurally related to **54** but lacking the protected vicinal diol functionality. However, similar to previous efforts, their endeavors to effect an intramolecular Stille reaction from this substrate, leading to macrocycle **55**, were met with challenges. Consequently, they decided to discontinue their pursuit of synthesizing the macrocyclic *E*-vinylbutenolide **24** at this stage and shifted their focus to converting the corresponding macrocyclic *Z*-vinylbutenolide **38** into the plumarellide ring system **9** in the presence of aqueous acid.



44 45 46 47 48 49 50 51 52 53 54 55

Reagents and conditions: a) NaI, Aceto ne, reflux; b) NaH, THF, 68% over two steps; c) K_2CO_3, Pd (dppf) , MeCN : H_2O, 75 ºC, 55 %; d) AD-mix-α, t-BuOH: H_2O, 59% ; e) 2,2-DMP, pTSA, Acetone, 93% ; f) P y.pTSA MeOH, 82 %; g) De ss-Martin pe riodina ne, $NaHCO_3$, DCM; h) $CHBr_3$, $CrCl_3$, 68% over two steps; i) TBAF, THF, -78 ºC to rt, 84% ; j) Dess-Martin periodin ane, $NaHCO_3$, DCM; k) ethyl prop yno ate, n-B uLi, THF , - 78 ° C , 43 % over two step s ; l) Bu_3SnH, $Pd(PPh_3)_4$ then CuI

Scheme 9. The route of plumarellide synthesis Stille reaction.[3]



Scheme 10. Mehta's research of plumarellide.[3]

Synthetic advancement began with furfural derivative **56** (Scheme 9). A Negishi coupling of alkyl zinc reagent **57** followed by nucleophilic addition of bromide **58** into the aldehyde moiety of heterocycle **56** provided butenolide **59** in 47% yield over two steps. Sequential reduction, Stille coupling, and ring-closing metathesis yielded macrocycle **60** in 14% yield over three steps. Advancement of *cis*-macrocycle **60** by oxidative cleavage of the furan moiety provided *cis*-vinylogous diketone **61** in excellent yield. Diene **61** was then heated in toluene to induce an intramolecular Diels-Alder cycloaddition.

Under the specific reaction conditions applied, the *cis*-dienophile **61** experienced isomerization, resulting in the formation of the *trans*-vinylogous diketone **62**. This transformation is evident from the observed *trans* stereochemistry within tricycle **63**, which was isolated as the exclusive product following the simultaneous opening of the lactone. Regrettably, the core scaffold **63** does not exhibit the appropriate relative stereochemistry at C7 when compared to plumarellides **9** and dissectolide **14**. Furthermore, it deviates from the required configuration at C11 for plumarellides **9**, mandapamates **17** and **18**, and dissectolide **14**.

While it is conceivable to envision an epimerization process for altering the configuration at C7, correcting the anti-relationship between C11 and C14 to achieve the desired *syn* configuration poses a nontrivial challenge. This anti relationship is primarily governed by the *cis*-configuration of the $\Delta^{13,14}$ bond formed during the macrocyclization of butenolide **59** *via* ring-closing metathesis. Consequently, establishing an alternative method for the formation of macrocycle **60** becomes imperative if this synthetic route is to be further explored in the pursuit of polycyclic furanobutenolide-derived natural products. Currently, tricycle **63** stands as the most advanced intermediate disclosed by Mehta and co-workers in their research efforts.

2.3 Advance of research

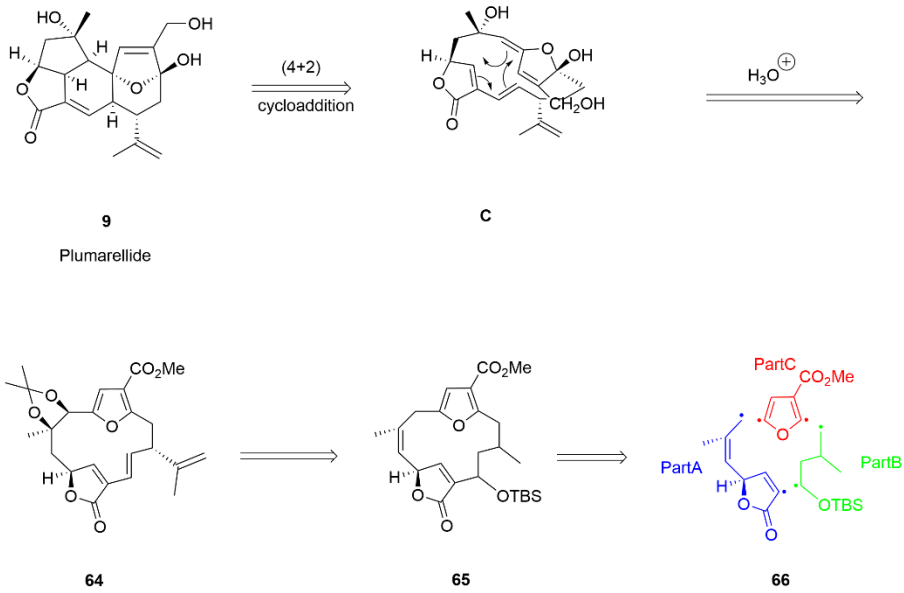
B. Lygo et al through DFT calculations probing potential (4 + 2) and (4 + 3) cycloaddition pathways leading to the polycyclic ring systems found in the coral secondary metabolites plumarellide, mandapamate and rameswaralide are described. Formation of plumarellide and mandapamate via stepwise intramolecular cycloaddition of a furanoxonium ion onto a 1,3-diene is shown to be viable. The calculations also predict the outcome of related cyclisations involving model systems.[19] The calculation of plumarellide starts with a key furan macrocyclic precursor 64, which is also where my current research focuses. After the successful synthesis of this key precursor, research has entered the most

exciting part. Combining the achievements of computational chemistry and biomimetic synthesis, I will gradually perform cyclic addition reactions on key precursors to obtain the target natural product. Although there is already a large amount of theoretical data to support this part, it is still the first time to conduct specific experimental verification. Regardless of whether the final total synthesis is successful or not, such attempts are highly valuable for scientific research.

3 Synthesis and characterization of plumarellide

3.1 Synthesis of plumarellide

3.1.1 Retrosynthetic analysis



Scheme 11. Retrosynthetic analysis of compound **64**.

Through research on computational chemistry and biomimetic synthesis, it is highly likely that plumarellide was obtained through the [4+2] cycloaddition reaction of intermediate **C**. And this intermediate is obtained by processing the key precursor 64, so the main focus of the first stage of this study will be on synthesizing the key precursor **64**. Due to many attempts to achieve full synthesis of plumarellide through similar methods, I have many routes to learn from and attempt to synthesize the key precursor **64**.

Currently, two primary types of synthesis routes are available for consideration. One approach involves creating iconic furan rings by combining small molecules, while the other focuses on pre-synthesizing structures containing furan rings for subsequent assembly. After careful evaluation, I have opted for the latter route, which involves synthesizing molecules with furan rings in advance and then proceeding with the subsequent synthesis.[20]

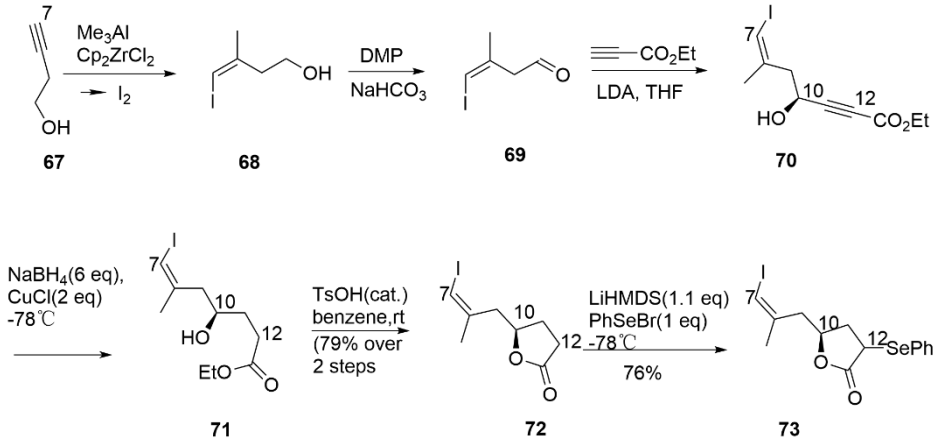
To tackle this process effectively, I have divided the target compound **64** into

three distinct parts. I synthesized these three smaller molecules individually and subsequently combined them to form the larger ring structure. Among these, Part A stands out as the most complex and challenging to synthesize. Part B, on the other hand, boasts a relatively simple structure with no isomerism, making it a suitable intermediate between the three molecules. It acts as the connecting element between the other two molecules, facilitating the final cyclization reaction.[21]

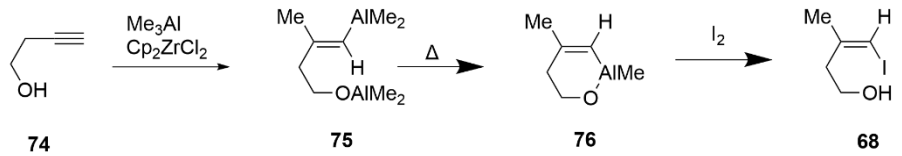
While the molecular structure of Part B may appear straightforward, it plays a crucial role in the overall ring formation process. Past studies in similar synthesis endeavors have often encountered difficulties in achieving successful ring closure between Part A and Part B. Therefore, enhancing the synthesis in this particular section represents a vital aspect of my research process.

This part of the work will only serve as a prerequisite for obtaining plumarellide through the cycloaddition reaction of precursor **64**.

3.1.2 Synthesis of compound A



Scheme 12. Plan A of synthesis of compound A.

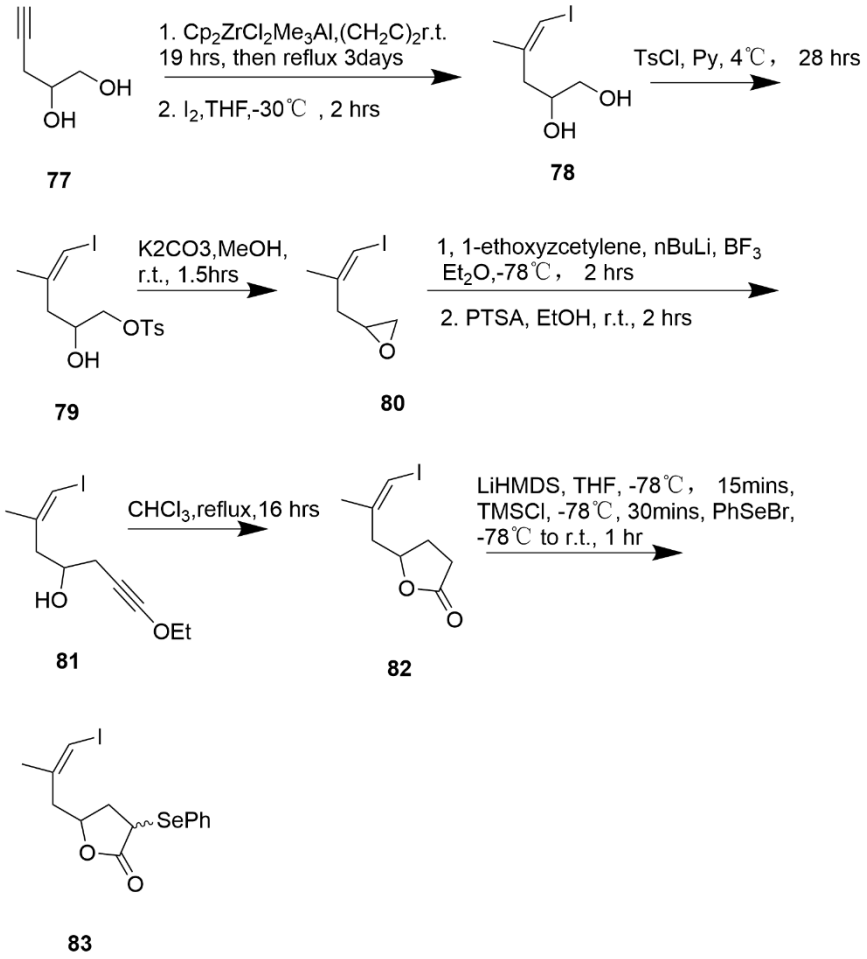


Scheme 13. Mechanism of part A step 1.[21]

Part A initiates with the readily available raw material alkynol **67** (Scheme **12** and **13**). Through a well-established synthesis pathway, Me_3Al catalyzed by Cp_2ZrCl_2 is employed to introduce a methyl branch at C2, while another Me_3Al molecule reacts with hydroxyl groups.[22] Following a period of heating and reflux, the

configuration at the double bond is altered, and the addition of I2 at -30 ℃ leads to the formation of the *trans* configuration of alcohol **68**. [23]Subsequently, DMP is utilized to convert alcohol **68** into aldehyde **69**, and after concentration, the alkyne ester is directly treated with LDA, reacting with the aldehyde group to yield compound **70**.[24] This compound is then reduced using $NaBH_4$ and CuCl, resulting in ketone **71**. [25]A cyclization using TsOH produces lactone **72**, which is further treated with LiHMDS to introduce a SePh group at C12, preparing it for subsequent cyclization.[26]

However, several challenges were encountered during the actual synthesis process. Firstly, Part A step 1 involves a prolonged reaction time, and the subsequent processing is rather intricate. As the initial step in a series of syntheses, this consumes significant energy to repeat. Additionally, Part A steps 2 and 3 are combined because the product stability of Part A step 2, aldehyde **69**, is notably poor. During the post-treatment process following DMP oxidation, aldehyde **69** undergoes rapid deterioration, gradually transforming from a light-yellow liquid to a red liquid. This transformation has been confirmed through GC-MS detection. The resulting products of aldehyde 69 are highly disordered, and ideal products cannot be obtained during the subsequent reaction process. After encountering numerous failures, I have opted to abandon this uncontrollable reaction and explore an alternative synthesis route.



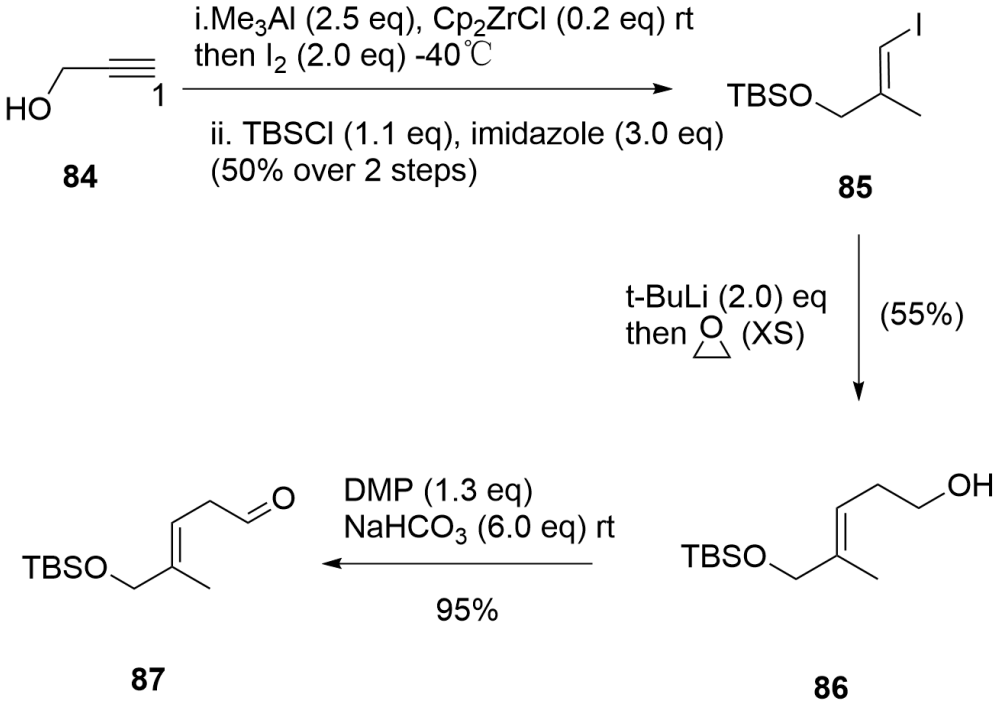
Scheme 14. Plan B of synthesis of compound A.[27]

The synthesis commenced with the introduction of ethylene glycol **77** as the raw material (Scheme 14), followed by stirring at room temperature for 19 hrs and subsequent refluxing for 3 days. The reaction was then quenched with iodine in THF at a temperature of -30 ℃, yielding the anti-methylalumination product **78**.

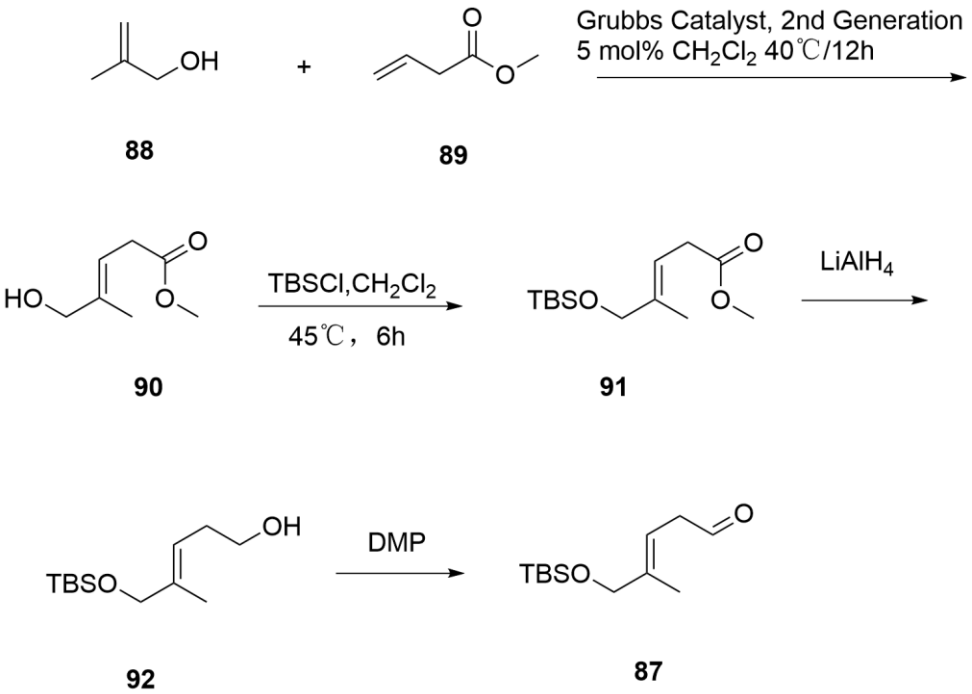
The next step involved the selective tosylation of the primary hydroxy group in diol **78**, followed by treatment with potassium carbonate. This sequence of reactions led to the formation of epoxide **79**, which was subsequently treated with the lithium salt derived from 1-ethoxyacetylene, followed by PTSA, resulting in the formation of lactone **82**.

To further modify the molecule, the phenylselanyl group was introduced to the lactone moiety **82**. This was achieved by first deprotonating the compound, then trapping the resulting anion with trimethylsilyl chloride, and finally quenching the reaction with phenylselenium bromide. These steps collectively produced the phenylselanyl lactone **83**.

3.1.3 Synthesis of compound B



Scheme 15. Plan A of synthesis of compound B.[21]



Scheme 16. Plan B of synthesis of compound B.[28]

The synthesis of aldehyde **87** commenced with propargyl alcohol **84**, as outlined in Scheme 15. The process involved methyl zirconation followed by iodination,

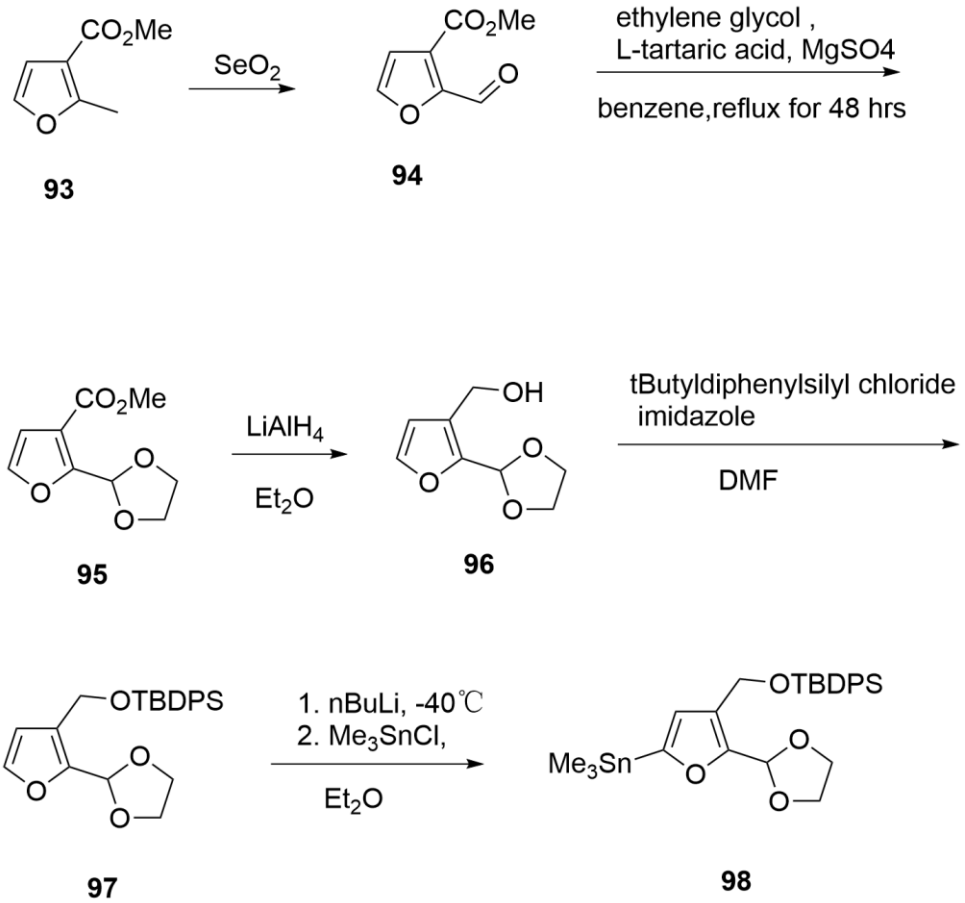
resulting in compound **85**. Subsequently, the pendant allylic alcohol was protected.[29] The resulting vinyl iodide was lithiated, and the reaction was quenched with oxirane, resulting in the formation of **86**. This compound was then oxidized using Dess–Martin periodinane, yielding b, c-unsaturated aldehyde **87**, which was utilized without requiring additional purification.

In the initial step of this plan, the same method employed in Part A, Step 1, was utilized to treat alkynol **84**. However, as subsequent steps involve the use of more hazardous reagents such as *n*-butyl lithium, I am contemplating optimizing the synthesis route for Part B.

Firstly, I address the source of the *trans* double bonds in compound **87**. I opt to utilize an olefin metathesis reaction to obtain *trans* olefin **90**, where the *Z*:*E* ratio is 7:3. Enol **88** is reacted with enol 89 using Grubbs Catalyst, 2nd Generation catalysis, at 40 ℃ overnight. This step achieves a 60% yield and features mild reaction conditions, straightforward post-processing, and fewer side reactions.

Subsequently, hydroxyl groups are protected using TBSCl,[30] and $LiAlH_4$ is employed for reduction. Following this reduction, DMP oxidation is performed to obtain aldehyde **87**, with a two-step combined yield of 95%. [31]It's worth noting that DIBAL-H is not used in this context to reduce the ester group to an aldehyde in one step. Experimental findings have indicated that it is challenging to selectively control the reaction with DIBA-H to achieve the desired aldehyde product. At low temperatures, DIBA-H has minimal reactivity with this structure, and as the temperature rises to 0 ℃, the reaction yields alcohol **86**. Therefore, opting for two mild, high-yield reactions instead of employing DIBA-H for a one-step aldehyde synthesis proves to be more efficient. [32]

3.1.4 Synthesis of compound C



Scheme 17. Synthesis of compound C.[27]

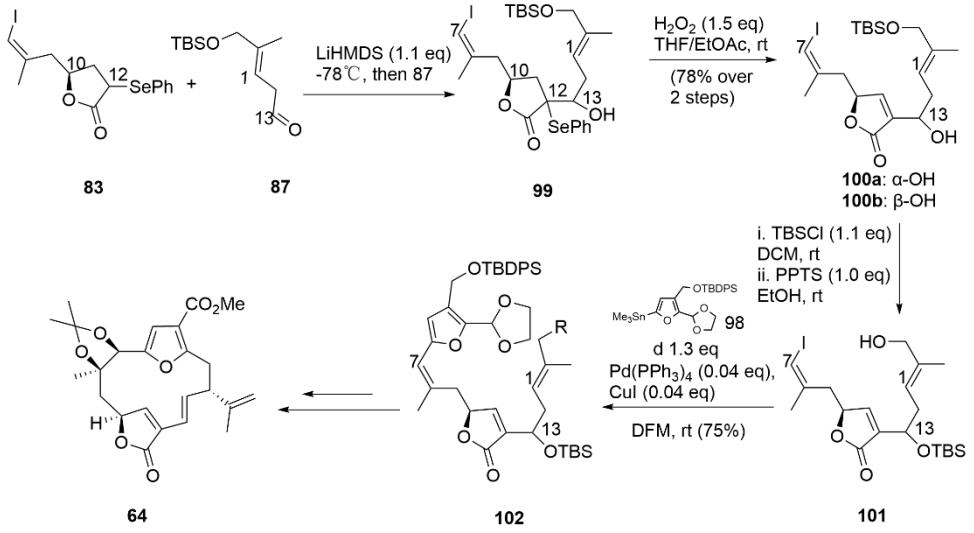
The synthesis of Part C proceeded smoothly and without significant operational difficulties or low-yield reactions. This route relied on well-established reaction types, resulting in a pleasant synthesis experience throughout. The synthesis commenced with compound **93** and involved the use of SeO_2 to introduce aldehyde groups in a single step.[33] This approach, compared to the previous method of replacing methyl bromide with hydroxyl groups and subsequent oxidation to form aldehyde groups, streamlined the process and yielded a 63% yield.[34]

Next, conventional protection of aldehyde groups with ethylene glycol led to the formation of compound **95**. This compound was then reduced using $LiAlH_4$ to yield alcohol **96**.[35] The hydroxyl group was protected with TBDPSCl, and compound **97** was subjected to a reaction with *n*-butyl lithium, enabling it to be connected with a Me_3Sn group for subsequent coupling with compound **83** obtained from Part A.

It's important to note that Me_3SnCl used in this step is a highly toxic

compound, necessitating the use of personal protective equipment and proper ventilation. Additionally, the Me_3Sn group in compound **98** is not stable and is unsuitable for long-term storage. Therefore, it is advisable to keep the route at compound **97** during the preparation process and only synthesize compound **98** when needed for subsequent reactions to prevent deterioration.

3.1.5 Synthesis of precursor 64



Scheme 18. Synthesis of precursor **64**.

Upon completing the synthesis of the three precursor compounds, the exciting macrocyclic synthesis can commence. Firstly, compounds **83** and **87** are assembled. Compound **83** is treated with LiHMDS at -78 ℃ to connect it to C13 of compound **87**, yielding intermediate product **99**. Next, H_2O_2 is utilized to remove the SePh group at room temperature, resulting in compound **100**. At this stage, the hydroxyl groups at C13 exhibit isomerism. TBSCl is then used to protect the hydroxyl group at C13, while PPTS is employed to remove the protective group from another hydroxyl group, leading to compound **101**. Subsequently, $Pd(PPh_3)_4$ and CuI catalyze the synthesis of compound 98 with compound **101**, producing compound **102**.

Following this, the protection of aldehyde groups on the furan ring is removed to initiate the ring closure reaction. After the ring formation, the target compound **64** can be obtained by modifying the macrocyclic compound as needed. Importantly, this route avoids the ring closure reaction at C12 and C13, resulting in a *cis* structure of the double bonds at C13 and C14.

This study provides a valuable reference route for the synthesis of plumarellide and holds great promise for achieving the first complete synthesis of

plumarellide in future research endeavors.

4 Future work

4.1 Total synthesis of plumarellide

During my one-year graduate studies and research, I first gained knowledge about biomimetic synthesis of natural products. I developed an understanding of successful research on compounds related to FBCs (Furanobutenolide-based cembranoids). With the guidance of my mentor, I started delving into the challenging topic of total synthesis of plumarellide. However, one year is too short to fully explore the complexities of total synthesis of natural products. In my doctoral stage, I plan to dedicate more time and energy to this subject.

The successful synthesis of precursor **64** not only provides hope for the complete synthesis of plumarellide but also opens the possibility for the total synthesis of mandapamate and isomandapamate. These two natural products share homology with plumarellide, making this achievement all the more enticing.

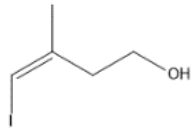
Currently, the synthesis of the three precursor compounds in the project is nearing completion, and compounds 87 and 97 have been successfully obtained. Part A has faced some delays due to a change in the route, but significant progress has been made in overcoming the challenging steps of the predetermined route in the previous approach. Therefore, I am confident that this route can be expedited once we resume work on it. After completing the synthesis of the three precursor compounds, we will enter the most exciting phase of this project. The groundwork laid in previous research will be crucial in this part. This phase is undoubtedly challenging, as all previous attempts to synthesize plumarellide have been unsuccessful. I am well aware of the difficulties that lie ahead. Nevertheless, I believe that overcoming these challenges, if successful in the end, will significantly contribute to advancing research in this field. Even in the event of failure, the research will not be in vain, as future researchers can learn from these setbacks and eventually achieve success.

4.2 Structural derivation and physiological activity testing of plumarellide

If the complete synthesis of plumarellide is achieved, my subsequent research will involve the modification and derivatization of the plumarellide ring structure, as well as the evaluation of the biological activity of these derived compounds. These studies hold the potential to provide valuable insights for the development of new drugs. Research in this field necessitates interdisciplinary collaboration, potentially involving cooperation with experts in drug structure screening and computational chemistry from within the research group, as well as collaboration with experts in biological activity testing from other research groups. The investigation of plumarellide and its related compounds is still in its early stages, with numerous promising research directions on the horizon. We eagerly anticipate the outcomes of future research endeavors.

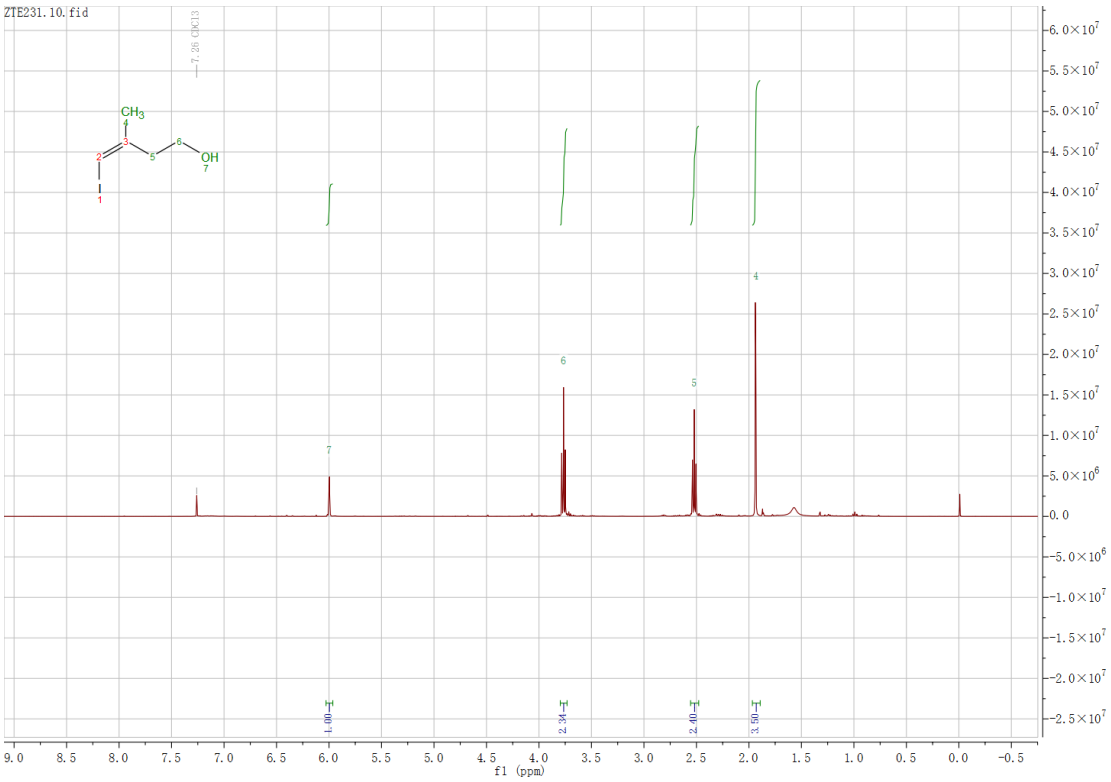
Experimental details

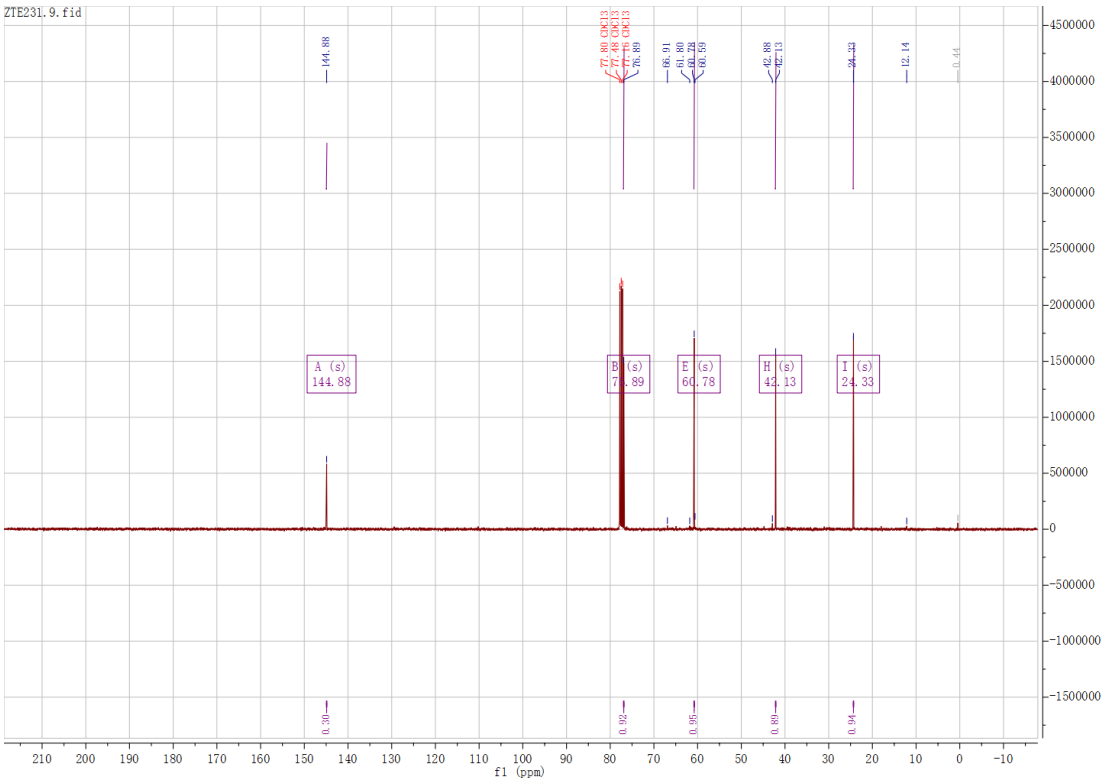
(*Z*)-4-iodo-3-methylbut-3-en-1-ol (68)



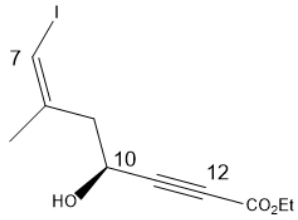
68

A solution of trimethylaluminium (2.0 M) in hexane (43.5 ml, 87.0 mmol) was added dropwise over 10 minutes to a stirred solution of bis(cyclopentadienyl)zirconium dichloride (1.41 g, 4.83 mmol) in anhydrous $ClCH_2CH_2Cl$ (20 ml) under an argon atmosphere. The mixture was stirred at room temperature for 10 minutes. A solution of (S)-pent-4-yne-1,2-diol 207 (1.93 g, 19.3 mmol) in anhydrous $ClCH_2CH_2Cl$ (60 ml) was cautiously added dropwise *via* a syringe over 10 minutes (slowly), there is white fog generation. The resulting yellow solution was stirred at room temperature for 19 hrs and then refluxed for 3 days, resulting in the formation of a red solution. The mixture was subsequently cooled to -30 ^oC, and a solution of iodine (10.1 g, 40.0 mmol) in anhydrous THF (50 ml) was added dropwise *via* a syringe over 10 minutes. The dark/red solution was stirred at -30 ^oC for 10 minutes and then allowed to warm to room temperature over 2 hrs. The mixture was carefully quenched by adding a saturated solution of aqueous Rochelle's salt (2.5 ml) at 0 ^oC and then poured into a mixture of a saturated solution of aqueous Rochelle's salt (190 ml) and ethyl acetate (190 ml). The resulting mixture was stirred vigorously overnight, and the organic layer was subsequently separated. The aqueous layer was further extracted with ethyl acetate (3 × 150 ml), and the combined organic extracts were dried with Na_2SO_4 and evaporated under vacuum. The resulting residue (3.99 g) was purified by silica chromatography, using an elution mixture of petroleum and ethyl acetate (5:1). This purification process yielded vinyl iodide 68 as a red viscous oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.00 (q, *J* = 1.5 Hz, 1H), 3.77 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 1.94 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 144.88, 76.89, 60.78, 42.13, 24.33.


ZTE231.10.fid
7.26 CDCl3
CH3
OH
1
2
3
4
5
6
7
1.00
2.34
2.40
3.50
f1 (ppm)


ZTE231.9.fid
144.88
77.80 CDCl3
77.48 CDCl3
77.16 CDCl3
76.89
66.91
61.80
60.78
60.59
42.88
42.13
24.33
12.14
0.44
A (s)
144.88
B (s)
76.89
E (s)
60.78
H (s)
42.13
I (s)
24.33
0.30
0.92
0.95
0.89
0.94
f1 (ppm)

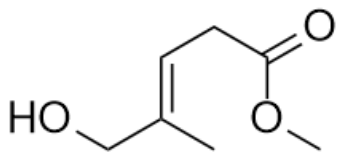
Ethyl (*S*,*Z*)-4-hydroxy-7-iodo-6-methylhept-6-en-2-ynoate (70)



70

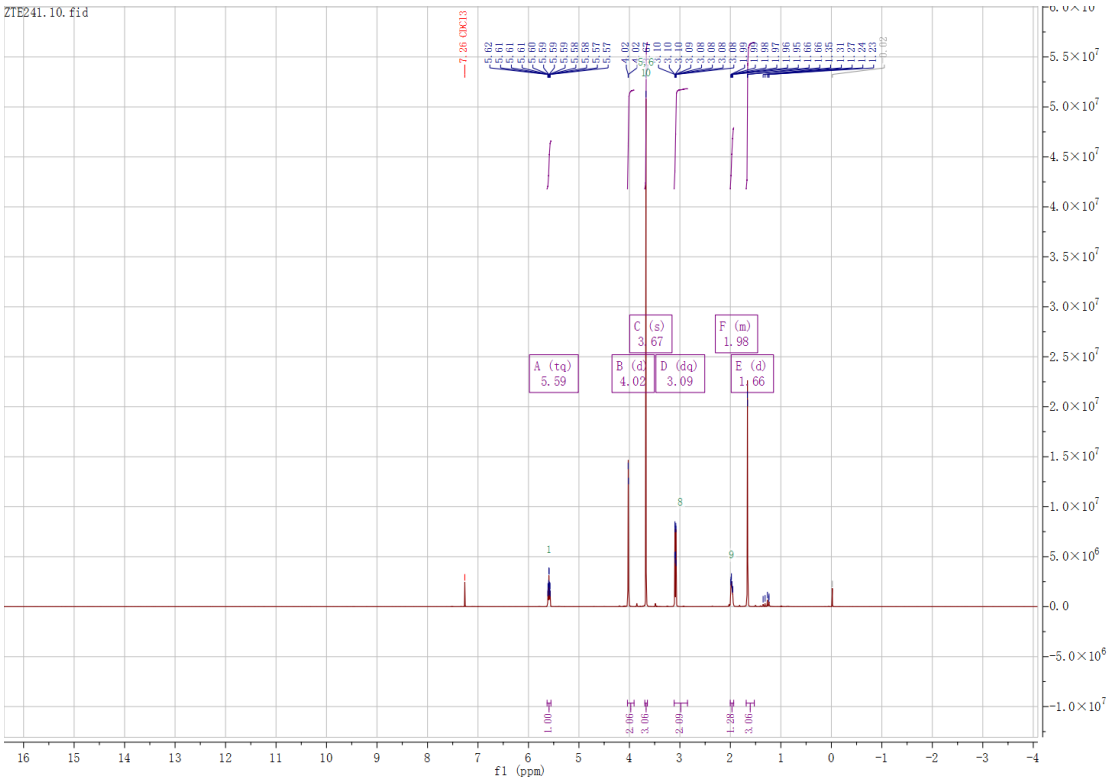
To an oven-dried flask was added dry HMDS (bis(trimethylsilyl)amine) (19.93 mL, 94 mmol, 3 eq) and THF (95 mL). The solution was cooled to -78 °C and *n*-BuLi (1.6M in hexanes, 56.7 mL, 91 mmol, 2.9 eq) was added dropwise. The solution turned yellow and was then warmed up to 0 °C and stirred for 20 minutes. The reaction was cooled back down to -78 °C and a solution of ethyl propiolate (9.51 mL, 94 mmol, 3 eq) in THF (60 mL) was added dropwise over 30 minutes. The solution remained pale yellow. The reaction was stirred at -78 °C for 1 hr. During this time, to a solution of the alcohol 68 (6.63 g, 31.3 mmol) in CH_2Cl_2 (156 mL) at rt was added $NaHCO_3$ (15.76 g, 188 mmol, 6 eq) followed by Dess-Martin periodinate (17.24 g, 40.7 mmol, 1.3 eq) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of aq. sat. $Na_2S_2O_3$, aq. sat. $NaHCO_3$ and water (160 mL) was added slowly to the CH_2Cl_2 solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure at rt to yield aldehyde which was used without further purification. The aldehyde was then taken up in dry THF (50 mL) and was cooled to -78 °C in a separate cooling bath. The cold aldehyde solution was added *via* cannula quickly to the solution of the alkyne at -78 °C. The solution turned dark red and was stirred for 30 minutes at -78 °C. The reaction was then quenched with sat. NH_4Cl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with Brine, dried over $MgSO_4$ and concentrated under reduced pressure. According to GC-MS and other methods, it was found that no target compound was generated. It is inferred that product **69** is too unstable and deteriorated before the reaction, resulting in experimental failure.

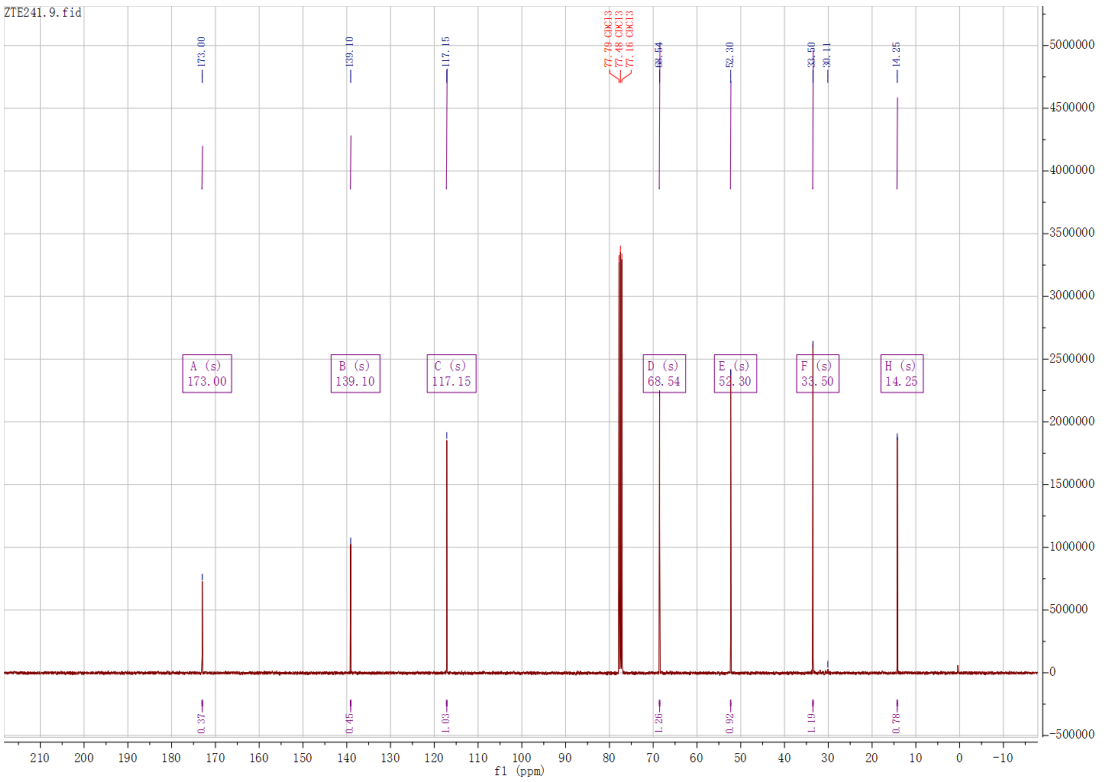
Methyl (*E*)-5-hydroxy-4-methylpent-3-enoate (90)

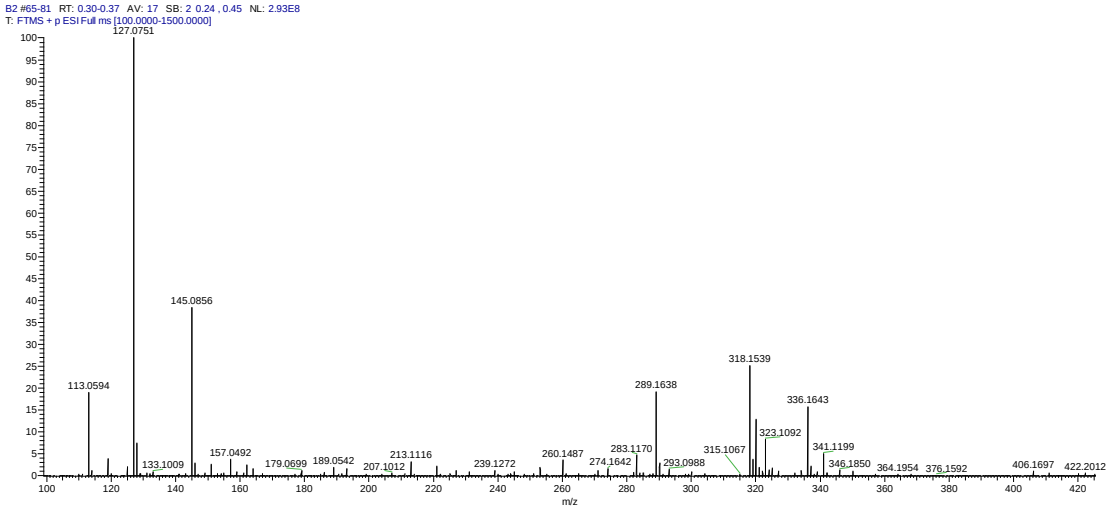


90

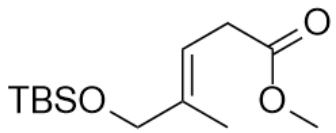
2-methylprop-2-en-1-ol (1.1 mL, 10 mmol) and methyl but-3-enoate (1.7 mL, 20 mmol) were simultaneously added *via* syringe to a stirring solution of Grubbs Catalyst, 2nd Generation (200 mg, 0.24 mmol, 4.8 mol %) in CH_2Cl_2 (25 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 5 mL and purified directly on a silica gel column, eluting with 10:1 hexane:ethyl acetate. A brown oil was obtained (830 mg, 60% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.59 (tq, *J* = 7.2, 1.4 Hz, 1H), 4.02 (d, *J* = 1.6 Hz, 2H), 3.67 (s, 3H), 3.09 (dq, *J* = 7.2, 1.1 Hz, 2H), 2.00 – 1.93 (m, 1H), 1.66 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.00, 139.10, 117.15, 68.54, 52.30, 33.50, 14.25. HRMS (ESI) found 145.0856 ($M+H^+$, $C_7H_{13}O_3^+$ requires 145.0859).




ZTE241.9.fid
173.00
139.10
117.15
77.48 CDCl3
77.16 CDCl3
68.54
52.30
33.50
30.11
14.25
A (s) 173.00
B (s) 139.10
C (s) 117.15
D (s) 68.54
E (s) 52.30
F (s) 33.50
H (s) 14.25
0.37
0.45
1.03
1.26
0.92
1.19
0.78
f1 (ppm)

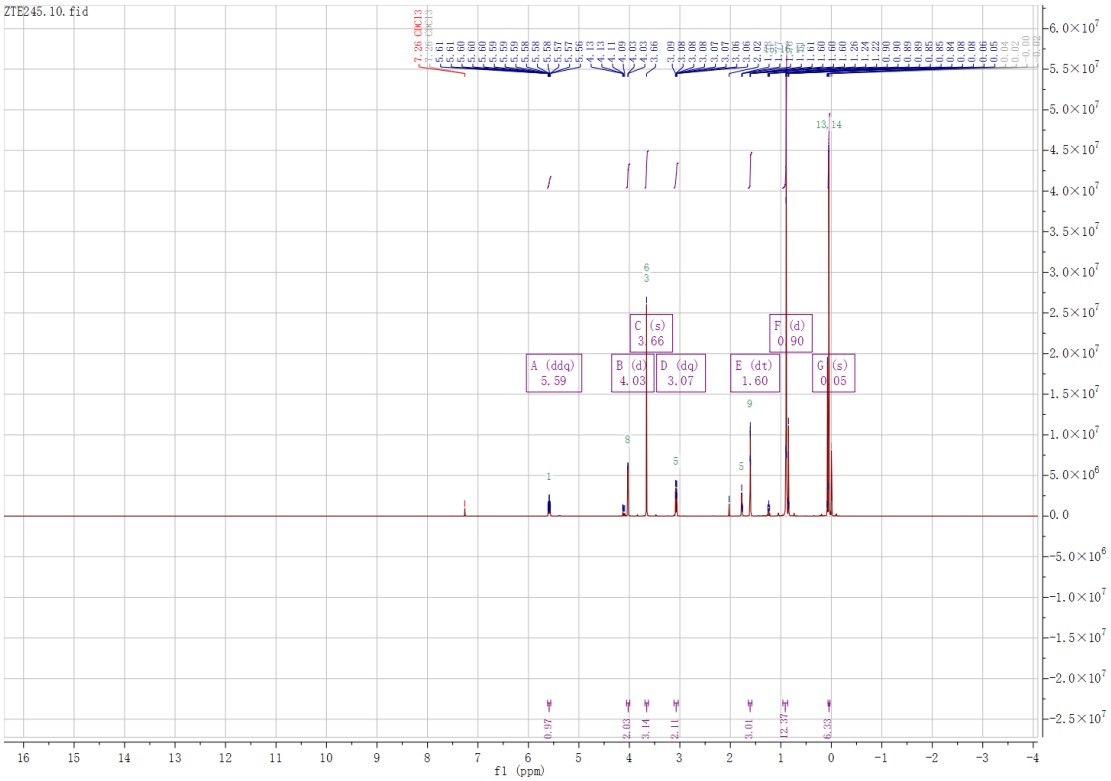

B2 #65-81 RT: 0.30-0.37 AV: 17 SB: 2 0.24 , 0.45 NL: 2.93E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]
127.0751
145.0856
113.0594
318.1539
289.1638
336.1643
323.1092
341.1199
157.0492
133.1009
283.1170
315.1067
346.1850
179.0699
189.0542
213.1116
207.1012
239.1272
260.1487
274.1642
293.0988
364.1954
376.1592
406.1697
422.2012
m/z

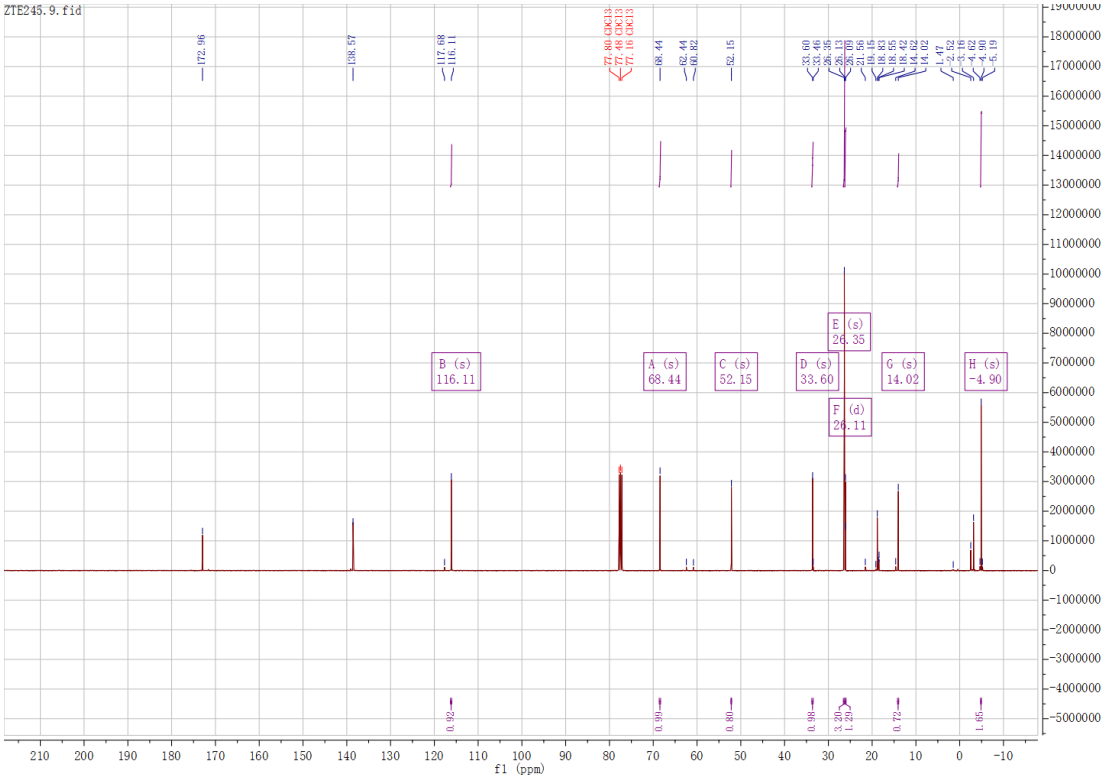
Methyl (*E*)-5-((tert-butyldimethylsilyl) oxy)-4-methylpent-3-enoate (91)

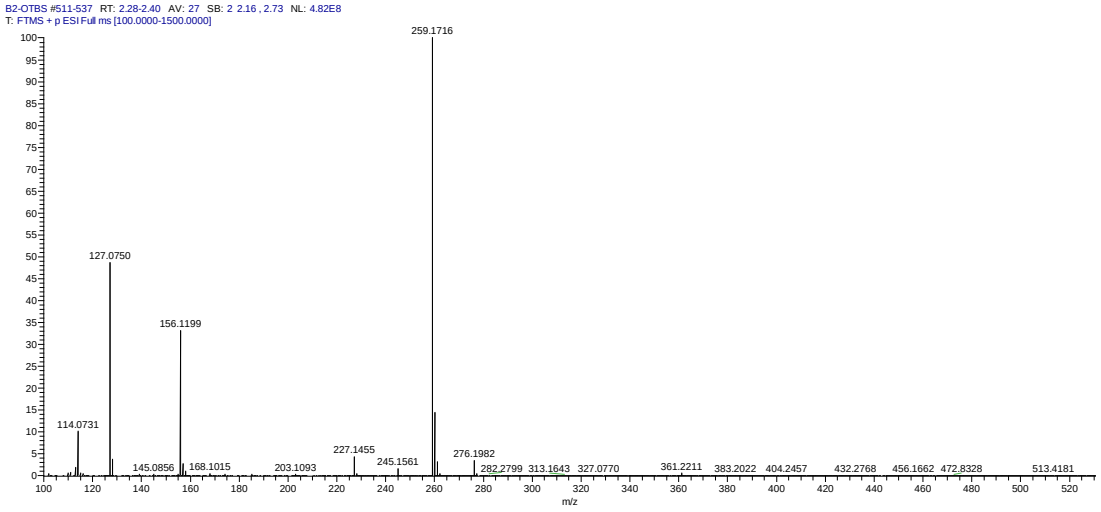


91

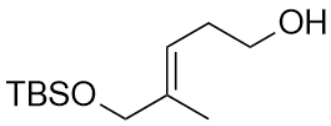
TBSCl (10.0 g, 36.4 mmol) and imidazole (2.70 g, 39.7 mmol) were added to a stirred solution of the alcohol 90 (4.35 g, 30.0 mmol) in DMF (11 ml). The mixture was stirred at 40 ℃ for 12 h before it was diluted with ether (10 ml). The mixture was then evaporated with silica (ca. 10.0 g) before it was purified by chromatography on silica, eluting with light petroleum-diethyl ether (10: 1), to give ether 91 (10.0 g, 74%) as a colourless solid,^{1}H NMR (400 MHz, Chloroform-d) δ 5.59 (ddq, *J* = 7.2, 5.8, 1.5 Hz, 1H), 4.03 (d, *J* = 1.8 Hz, 2H), 3.66 (s, 3H), 3.07 (dq, *J* = 7.3, 1.1 Hz, 2H), 1.60 (dt, *J* = 1.5, 0.8 Hz, 3H), 0.90 (d, *J* = 1.1 Hz, 12H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 116.11, 68.44, 52.15, 33.60, 26.35, 26.11 (d, *J* = 4.1 Hz), 14.02, -4.90. HRMS (ESI) found 259.1716 ($M+H^+$, $C_{13}H_{27}O_3Si^+$ requires 259.1724）.




ZTE245.9.fid
B (s) 116.11
A (s) 68.44
C (s) 52.15
D (s) 33.60
E (s) 26.35
F (d) 26.11
G (s) 14.02
H (s) -4.90
f1 (ppm)

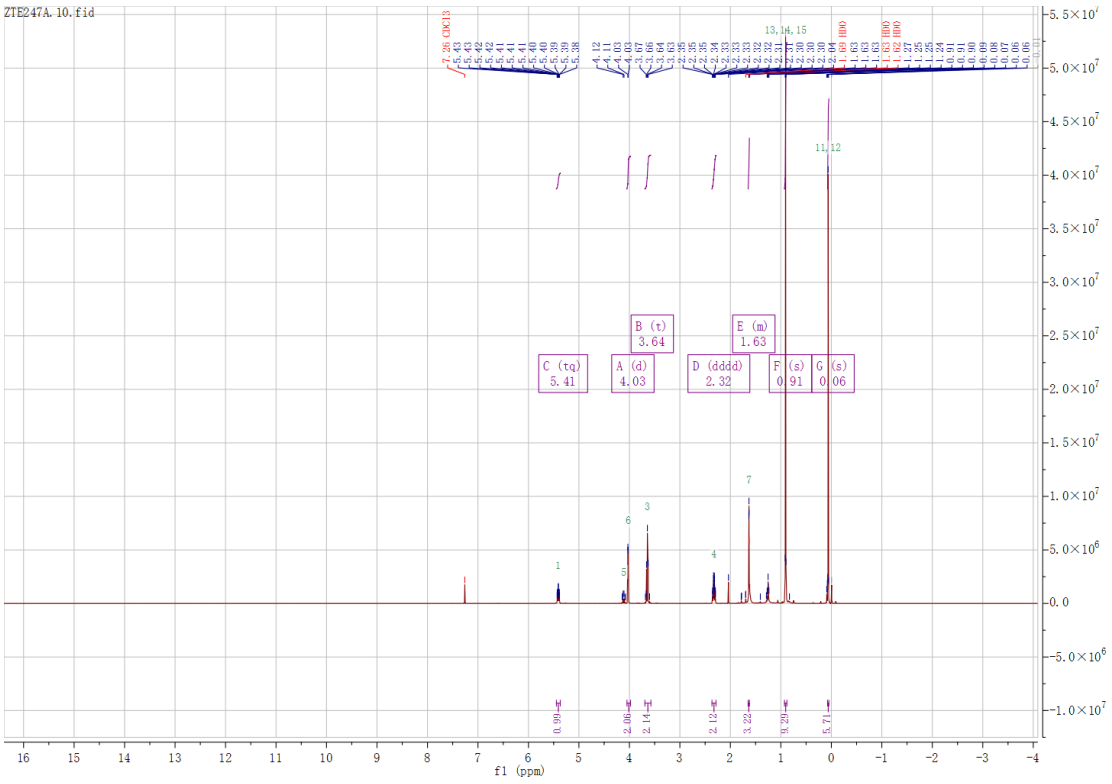

B2-OTBS #511-537 RT: 2.28-2.40 AV: 27 SB: 2 2.16 , 2.73 NL: 4.82E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]
259.1716
127.0750
156.1199
114.0731
227.1455
245.1561
276.1982
m/z

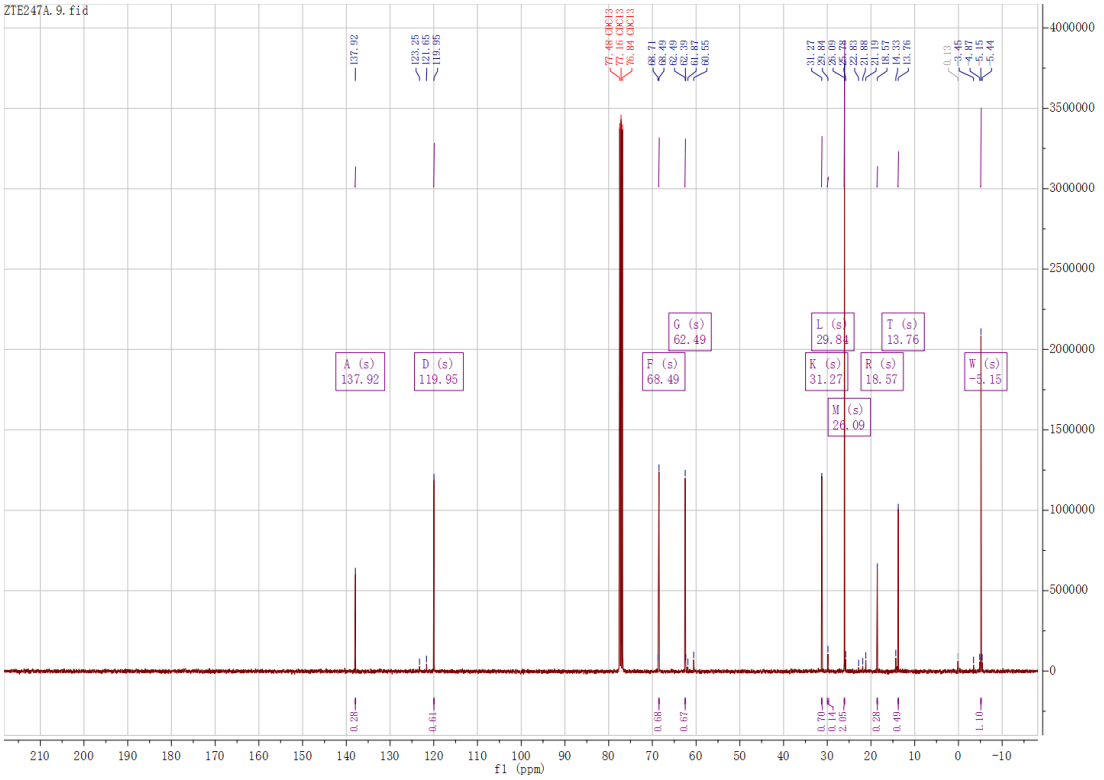
(*E*)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-3-en-1-ol (92)

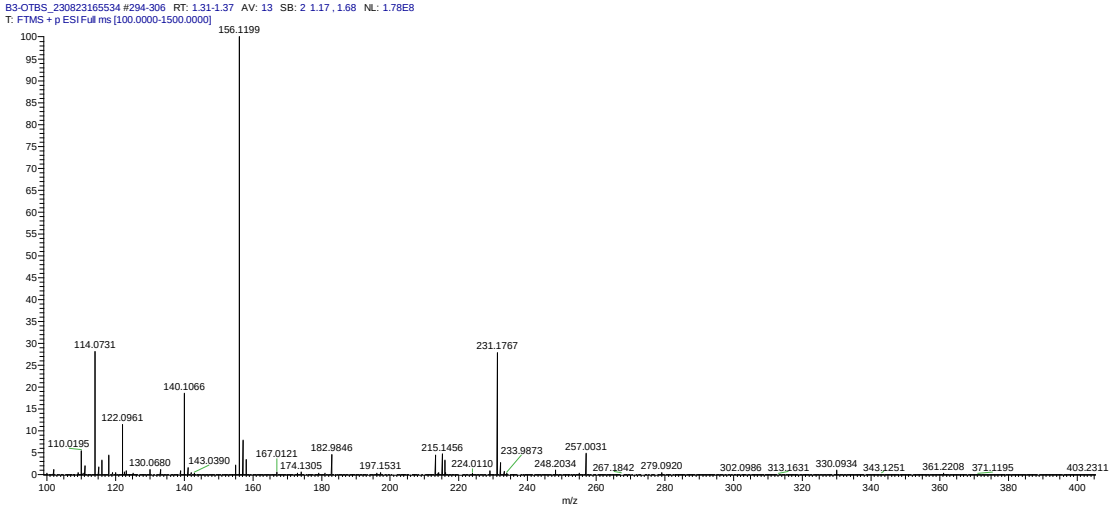


92

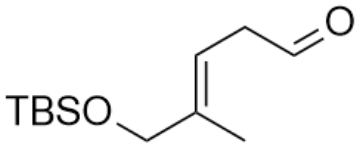
A solution of the ester 91 (2.59 g, 10.0 mmol) in anhydrous Et_2O (27 ml) was added dropwise, over 10 mins, to maintain a steady reflux, to a stirred suspension of lithium aluminium hydride (671 mg, 17.7 mmol) in anhydrous Et_2O (44 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, and then quenched carefully with water (0.67 ml), followed by aqueous NaOH (20% w/w, 0.67 ml) and water (3 x 0.67 ml). The mixture was stirred at room temperature for a further 1 h and then filtered. The filtrate was dried (Na_2SO_4) and concentrated in vacuo to leave the alcohol (2.05 g, 89 %) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.41 (tq, *J* = 7.4, 1.5 Hz, 1H), 4.03 (d, *J* = 1.7 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.32 (dddd, *J* = 7.5, 6.5, 5.6, 1.0 Hz, 2H), 1.65 – 1.62 (m, 3H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.92, 119.95, 68.49, 62.49, 31.27, 29.84, 26.09, 18.57, 13.76, -5.15. HRMS (ESI) found 231.1767($M+H^+$, $C_{12}H_{27}O_2Si^+$ requires 231.1775)




ZTE247A.9.fid
A (s)
137.92
D (s)
119.95
G (s)
62.49
F (s)
68.49
L (s)
29.84
K (s)
31.27
M (s)
26.09
R (s)
18.57
T (s)
13.76
W (s)
-5.15
f1 (ppm)

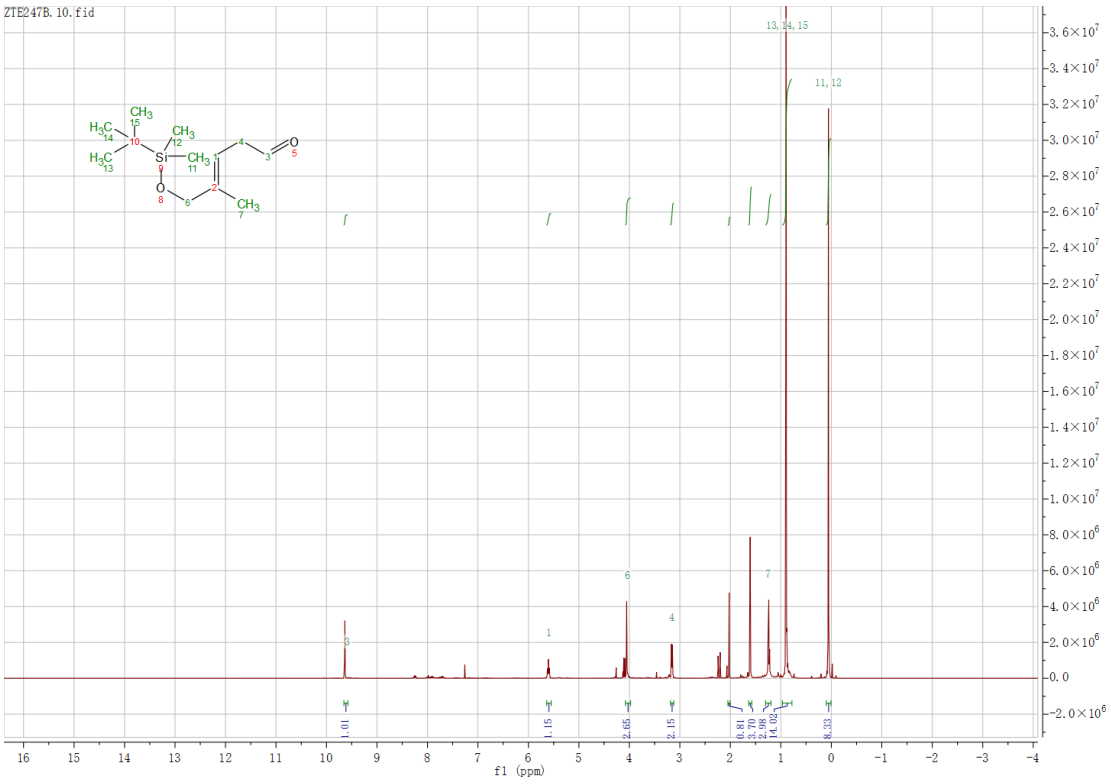

B3-OTBS_230823165534 #294-306 RT: 1.31-1.37 AV: 13 SB: 2 1.17 , 1.68 NL: 1.78E8
T: FTMS + p ESI Full ms [100.0000-1500.0000]
156.1199
114.0731
231.1767
140.1066
122.0961
110.0195
130.0680
143.0390
167.0121
174.1305
182.9846
197.1531
215.1456
224.0110
233.9873
248.2034
257.0031
267.1842
279.0920
302.0986
313.1631
330.0934
343.1251
361.2208
371.1195
403.2311
m/z

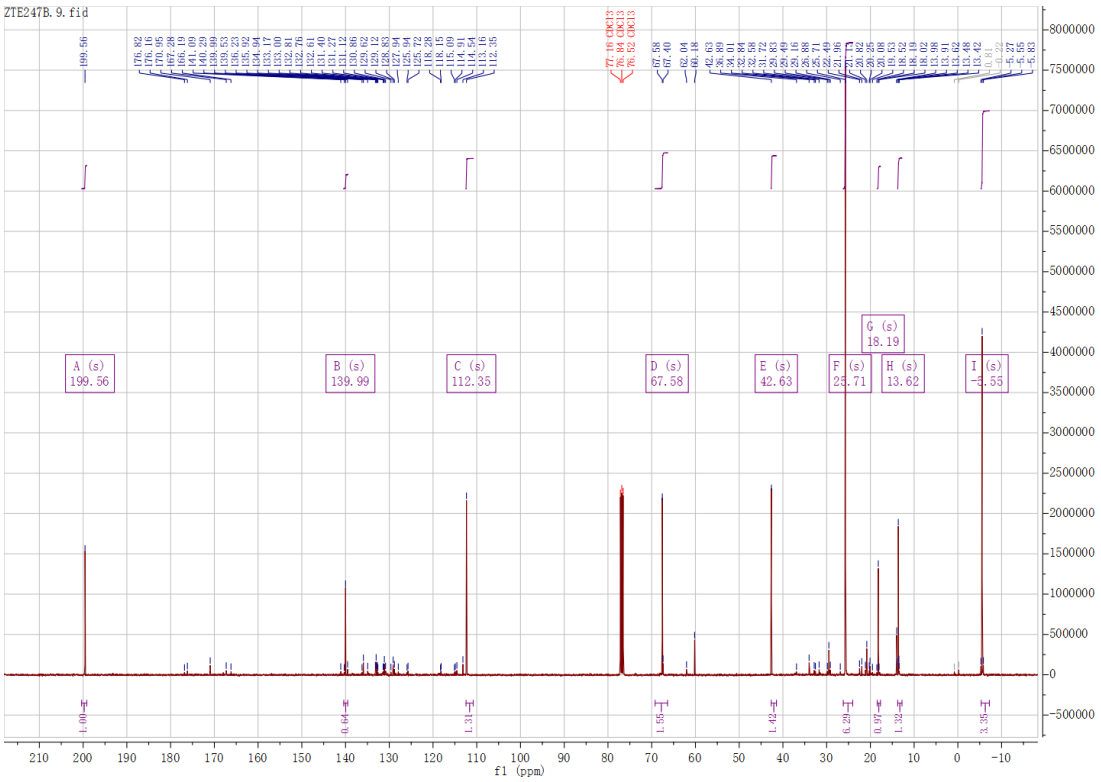
(*E*)-5-((tert-butyldimethylsilyl)oxy)-4-methylpent-3-enal (87)

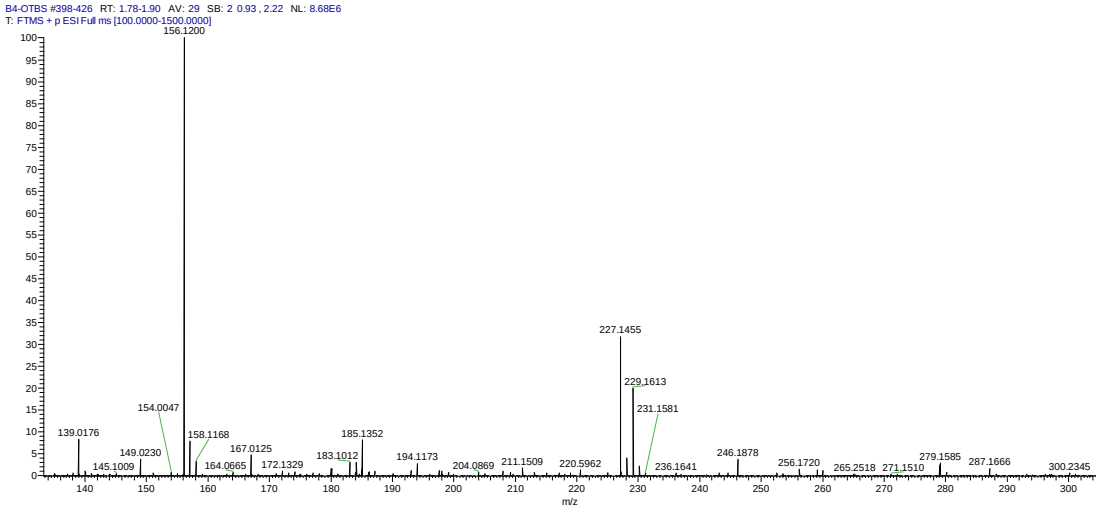


87

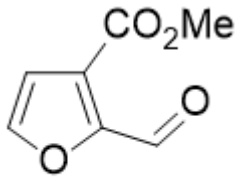
To a solution of the alcohol 92(2.31 g, 10 mmol) in CH_2Cl_2 (156 mL) at rt was added Dess-Martin periodinate (17.24 g, 40.7 mmol) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of aq. sat. Na2S2O3, aq. sat. $NaHCO_3$ and water (160 mL) was added to the CH_2Cl_2 solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure eave the aldehyde 87(95% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (t, *J* = 2.1 Hz, 1H), 5.60 (ddp, *J* = 8.7, 5.8, 1.5 Hz, 1H), 4.08 – 3.98 (m, 3H), 3.16 (ddq, *J* = 7.3, 2.1, 1.1 Hz, 2H), 2.02 (s, 1H), 1.61 (dt, *J* = 1.5, 0.7 Hz, 4H), 1.30 – 1.19 (m, 3H), 0.90 (s, 14H), 0.06 (s, 8H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.20, 140.63, 112.99, 68.22, 43.27, 26.34, 18.83, 14.26, -4.92. HRMS (ESI) found 229.1613(M+H$^+$, $C_{12}H_{25}O_2Si^+$ requires 229.1618)




ZTE247B.9.fid
A (s) 199.56
B (s) 139.99
C (s) 112.35
D (s) 67.58
E (s) 42.63
F (s) 28.71
G (s) 18.19
H (s) 13.62
I (s) 0.55
f1 (ppm)


B4-OTBS #398-426 RT: 1.78-1.90 AV: 29 SB: 2 0.93 , 2.22 NL: 8.68E6
T: FTMS + p ESI Full ms [100.0000-1500.0000]
156.1200
227.1455
229.1613
231.1581
154.0047
139.0176
158.1168
167.0125
149.0230
145.1009
164.0665
172.1329
183.1012
185.1352
194.1173
204.0869
211.1509
220.5962
236.1641
246.1878
256.1720
265.2518
271.1510
279.1585
287.1666
300.2345
m/z

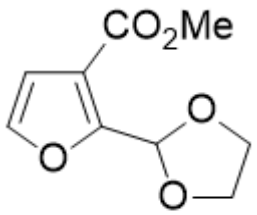
Methyl 2-formylfuran-3-carboxylate (94)



94

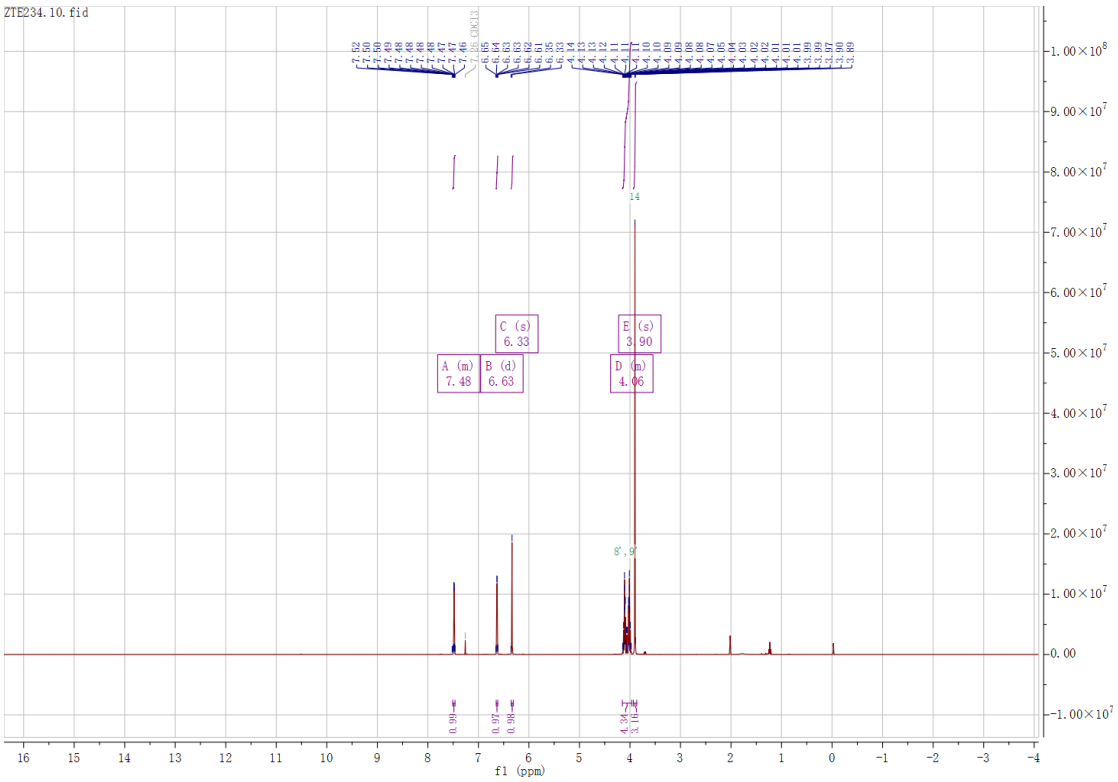
SeO_2 (1.58 g, 14.24 mmol) was introduced to a stirred solution of compound **93** (1.0 g, 7.14 mmol) in anisole (20 ml). The resulting mixture was then heated to reflux temperature and maintained at this temperature for 18 hrs. Once the reaction was completed, the mixture underwent filtration, followed by washing with H2O (50 ml) and AcOEt (370 ml). Subsequently, the combined organic extract was subjected to drying with $MgSO_4$, and the solvent was subsequently evaporated. The resulting crude product was subjected to purification through column chromatography (using SiO_2 and a hexane/AcOEt mixture with a ratio of 5:1), leading to the isolation of compound 11 as a yellow solid in a yield of 40%. he isolated compound is identified as methyl 2-(1,3-dioxolan-2-yl)furan-3-carboxylate. ^{1}HNMR (CDCl3): 10.23 (d, 1H); 7.64 (dd, 1H); 6.89 (d, 1H); 3.95 (s, 3H). ^{13}CNMR ($CDCl_3$): 178.8; 162.0; 152.4; 146.6; 126.2; 112.9; 52.5.

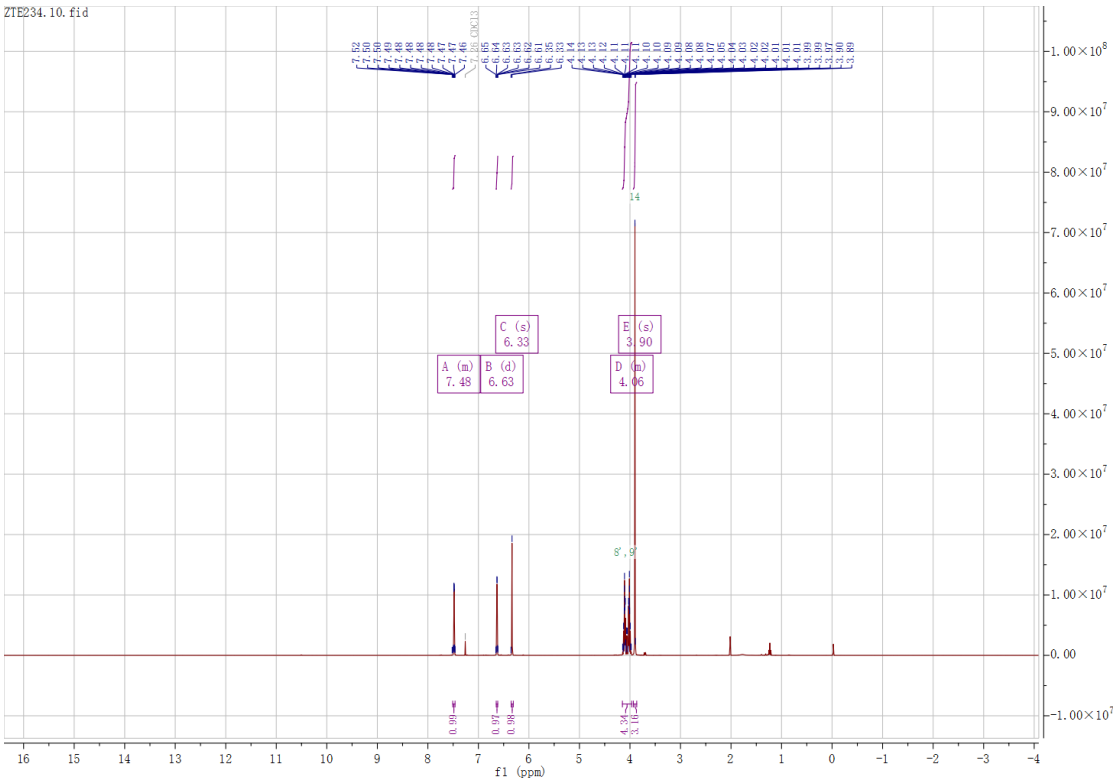
(2-(1,3-dioxolan-2-yl)furan-3-yl)methanol (95)



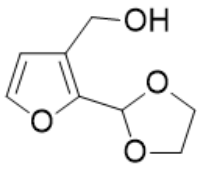
95

Ethylene glycol (3.47 g, 55.9 mmol) was added dropwise, over 10 mins, to a vigorously stirred solution of the aldehyde 307 (2.15 g, 14.0 mmol), L-tartaric acid (52 mg, 0.35 mmol) and anhydrous $MgSO_4$ (3.35 g, 27.9 mmol) in benzene (49 ml) in a 100 ml flash, equipped with a Dean-Stark adaptor and a condenser. The mixture was heated under reflux for 48 h. The mixture was cooled to room temperature. Solid $NaHCO_3$ (44 mg) was added, and the resulting mixture was stirred for 0.5 h before it was filtered through a thin layer of $NaHCO_3$, and washed with DCM (150 ml). The filtrate was evaporated in vacuo to leave the dioxolane (2.69 g, 97 %) as an oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.46 (m, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 6.33 (s, 1H), 4.15 – 3.97 (m, 4H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.04, 145.35, 141.62, 131.96, 111.07, 97.13, 65.55, 52.18.


ZTE234.10.fid
C (s)
6.33
E (s)
3.90
A (m)
7.48
B (d)
6.63
D (m)
4.06
f1 (ppm)


ZTE234.10.fid
C (s)
6.33
E (s)
3.90
A (m)
7.48
B (d)
6.63
D (m)
4.06
f1 (ppm)

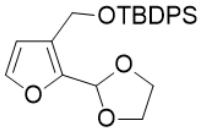
((2-(1,3-dioxolan-2-yl)furan-3-yl)methoxy)(tert-butyl)diphenylsilane (96)



96

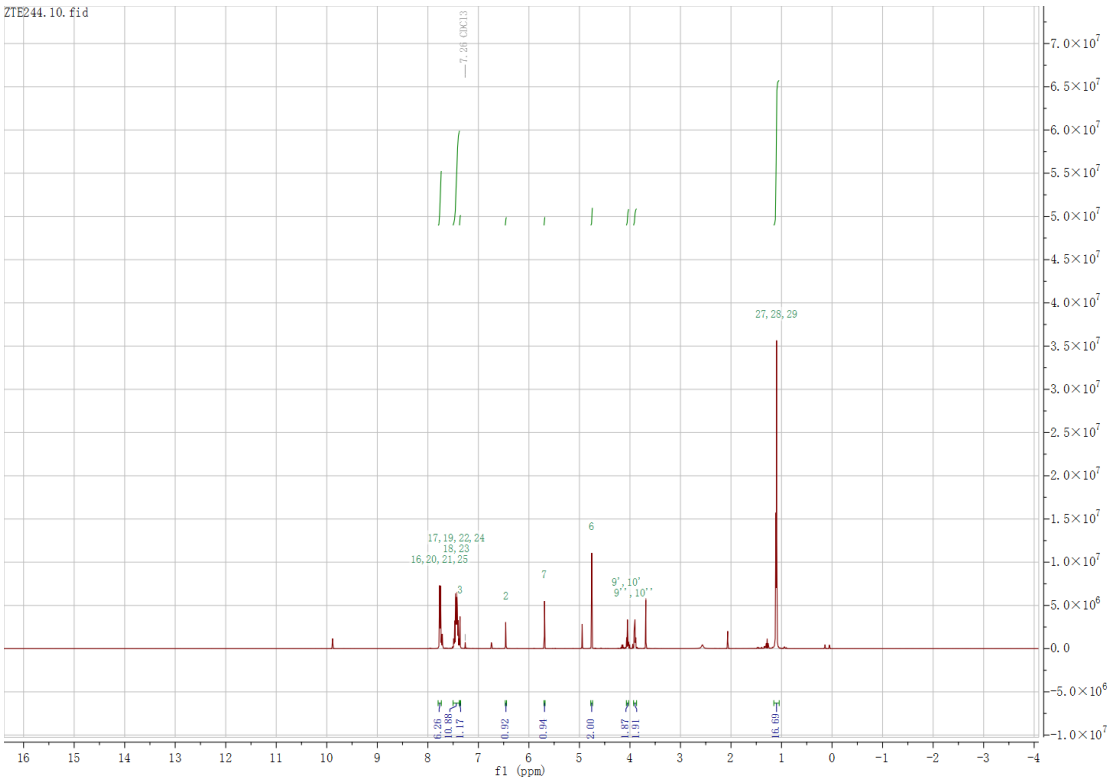
A solution of the ester 308 (2.69 g, 13.6 mmol) in anhydrous Et2O (27 ml) was added dropwise, over 10 mins, to maintain a steady reflux, to a stirred suspension of lithium aluminium hydride (671 mg, 17.7 mmol) in anhydrous Et2O (44 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 hr, and then quenched carefully with water (0.67 ml), followed by aqueous NaOH (20% w/w, 0.67 ml) and water (3 x 0.67 ml). The mixture was stirred at room temperature for a further 1 hr and then filtered. The filtrate was dried (Na_2SO_4) and concentrated in vacuo to leave the alcohol (2.05 g, 89 %) as a yellow oil. vmax (film)/cm-1 3385; 1H (400 MHz; $CDCl_3$) 7.36 (1 H, br s, fur-H), 6.40 (1 H, br s, fur-H), 5.96 (1 H, s, OCHO), 4.56 (2 H, br s, CH2OH), 4.19-4.11 (2 H, m, CH2), 4.06-3.97 (2 H, m, CH2), 2.46 (1 H, br s, OH); ^{13}C(90 MHz; CDCl3) 146.2 (s), 142.5 (d), 124.2 (s), 111.5 (d), 97.3 (d), 65.2 (2 x t), 55.8 (t).

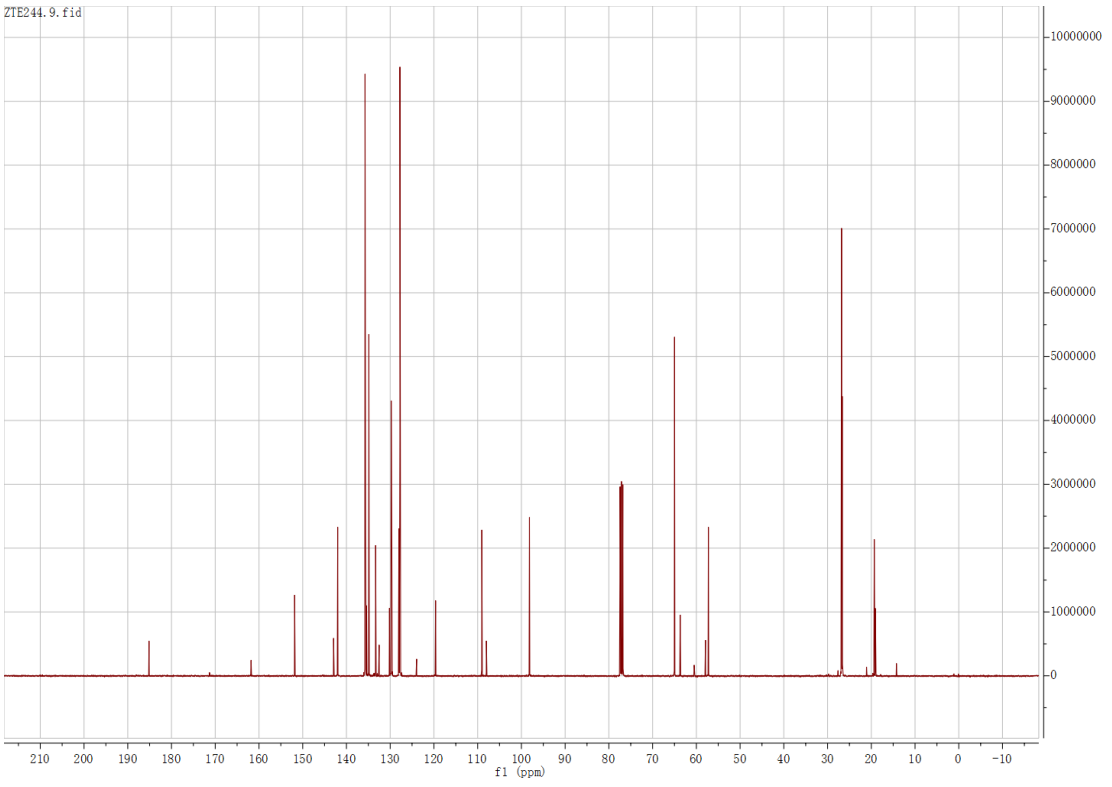
((2-(1,3-dioxolan-2-yl)furan-3-yl)methoxy)(tert-butyl)diphenylsilane (97)



97

^{t}Butyldiphenylsilyl chloride (10.0 g, 36.4 mmol) and imidazole (2.70 g, 39.7 mmol) were added to a stirred solution of the alcohol 96 (5.62 g, 33.1 mmol) in DMF (11 ml) at 0 ºC. The mixture was stirred at 0 ºC for 10 mins and then at room temperature for 20 mins before it was diluted with ether (10 ml). The mixture was then evaporated with silica (ca. 10.0 g) before it was purified by chromatography on silica, eluting with light petroleum-diethyl ether (9: 1), to give the ^{t}butyldiphenylsilyl ether (10.0 g, 74%) as a colourless solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.73 (m, 6H), 7.50 – 7.37 (m, 11H), 7.37 (d, *J* = 1.9 Hz, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 5.69 (s, 1H), 4.76 (s, 2H), 4.07 – 4.03 (m, 2H), 3.93 – 3.87 (m, 2H), 1.15 – 1.05 (m, 17H). ^{13}C NMR (125 MHz, Common NMR Solvents) δ 145.69, 143.51, 143.46, 143.41, 143.36, 135.83, 135.81, 135.77, 135.76, 135.74, 134.00, 129.27, 129.22, 129.21, 129.19, 129.15, 127.99, 127.97, 127.96, 127.94, 114.96, 100.96, 100.93, 100.90, 66.41, 66.37, 61.12, 61.09, 26.92, 19.24.


ZTE244.10.fid
7.26 CHCl3
27, 28, 29
17, 19, 22, 24
18, 23
16, 20, 21, 25
3
2
7
6
9', 10'
9'', 10''
6.26
10.88
1.17
0.92
0.94
2.00
1.87
1.91
16.69
f1 (ppm)


ZTE244.9.fid
f1 (ppm)

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