

Chapter 2

Model Study of Maoecrystal V

2.1 Model Study of Maoecrystal V: Synthesis Strategy

Maoecrystal V is a C-19 diterpenoid natural product with rare caged skeleton. The main difficulties of synthesis were forecasted through structure analysis: (1) construction of highly compact five-membered ring; (2) installing continuous quaternary carbon chiral center; and (3) construction of [2.2.2] bridge ring. For these reasons, total synthesis of Maoecrystal V should conquer enormous challenges in both strategic design and practical reaction exploration. Exploring meritorious methods for basic skeleton construction of Maoecrystal V is the foundation of total synthesis. It is necessary to build up a model in order to provide worthy information for further total synthesis study.

We decided to omit the oxa-bridge subunit in model study. Introducing oxa-bridge is the most challenging step of the total synthesis of Maoecrystal V, we planned to solve this problem in the late stages of total synthesis. Although the similar cycloalkene ketone fragment (right side) has been reported in the literature, the methyl groups, double bond, and ketone group were deleted in our final scheme, which means the replacement of right synthetic fragment with commercially available cyclohexanone. The efficiency would be significantly improved by the simplification. Cyclohexanone kept the oxygen atom of oxa-bridge, which maintained the feasibility of constructing oxa-bridge structure. Based on the analysis, natural product Maoecrystal V was simplified to model compound 2.1.1 (Fig. 2.1) for early study.

2.2 The Model Synthesis of Maoecrystal V

Figure 2.2 depicts the retro-synthesis analysis of Maoecrystal V. Intramolecular Diels–Alder (IMDA) reaction was utilized as a key reaction in our retro-synthesis of Maoecrystal V to construct the main skeleton [2.2.2] caged scaffold. The IMDA

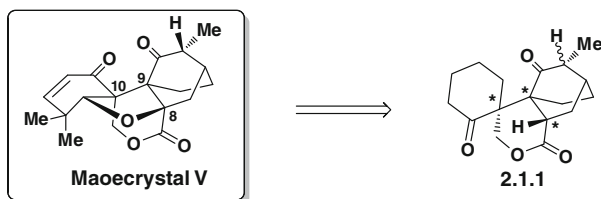


Fig. 2.1 Model study of Maoecrystal V

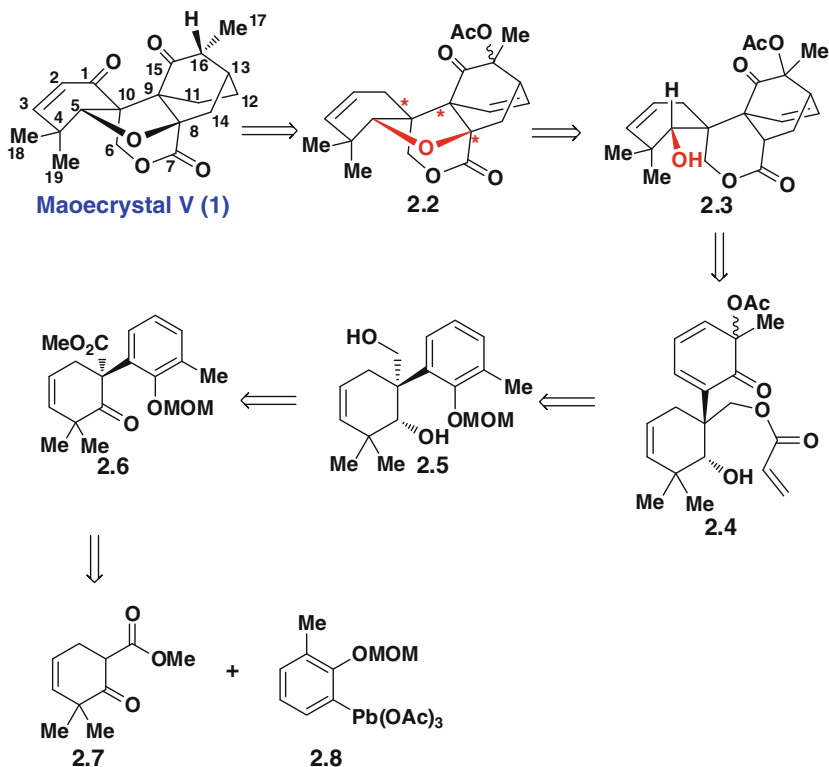


Fig. 2.2 The retro-synthetic analysis of Maoecrystal V

precursor could be disconnected to diol 2.5, which could be obtained by 2.6 after several conversion steps. The construction of 2.6 was based on the arylation reaction of 1,3-dicarbonyl substrate 2.7 and organic lead compound 2.8. The design and key reactions will be briefly introduced in the following sections.

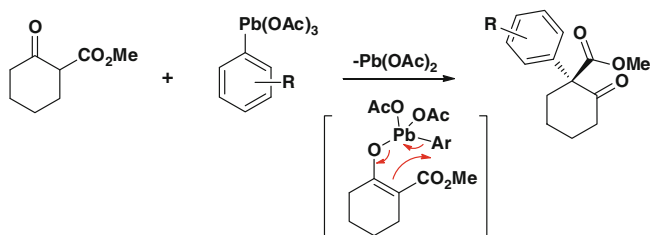


Fig. 2.3 Pinhey arylation

2.2.1 Pinhey Arylation

In the retro-synthetic analysis of Maoecrystal V, α -arylation reaction was used in 1,3-dicarbonyl compound. The conversion could be achieved through the Pinhey arylation reaction (Fig. 2.3). Pinhey reaction was found and developed by Pinhey's group in the 1970s. The α -arylation reaction occurred between a tetravalent organic lead reagent and 1,3-dicarbonyl compound. Although its mechanism was still not fully understood, Pinhey speculated that it might be a process of reductive elimination. It could realize the coupling of soft carbon nucleophilic reagent and strong aryl lead reagent.

2.2.2 The Development and Synthetic Application of Diels–Alder Reaction

2.2.2.1 A Brief Introduction to Diels–Alder Reaction

Diels–Alder reaction [1, 2] (Fig. 2.4) happens between conjugated dienes and double bond substrates to form substituted cyclohexene system. Even if the atoms in some positions are non-carbon heteroatoms, the reaction still can occur normally. The reaction was first discovered by Otto Paul Hermann Diels and Kurt Alder in 1928. They won the 1950 Nobel Prize for chemistry because of this discovery.

Diels–Alder reaction has several significant features [1, 2]: First of all, Diels–Alder reaction is a thermal driving reaction, usually triggered by heating. Secondly, the reaction is widely used in constructing a new six-membered ring structure. In the process of the conversion, 3 π bond systems are opened to form 2 new C–C σ bonds and a new C–C π bond. All the fractures and formations of chemical bonds are finished in one-step transformation.

The dienes of Diels–Alder reaction: Dienes can be either chain or circular structure and may contain different substituent groups. The limitation is that diene must contain *s-cis* configuration. Bulky substituent groups may affect the most stable conformation of diene, which leads to the failure of the reaction. For cricoid

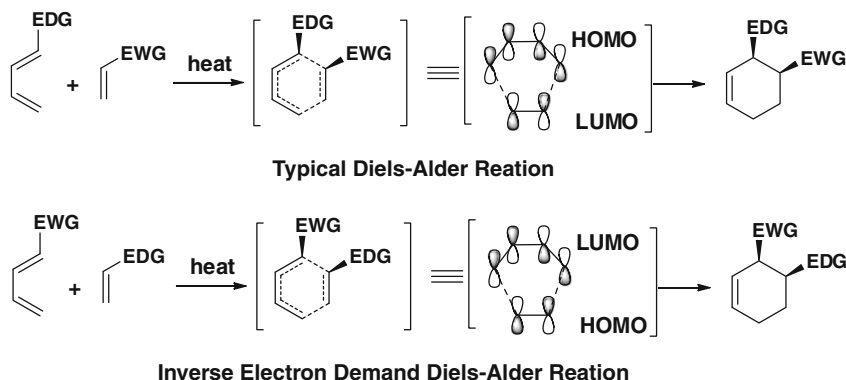


Fig. 2.4 Mechanism of Diels–Alder reaction [1, 2]

dienes, most of them are *s-cis* configurations. Chemist developed various Diels–Alder reactions by artful designs, which produced a series of dienes with unique characteristics, such as the famous Danishefsky’s diene and dendralenes [1, 2].

Dienophile: In a typical Diels–Alder reaction, dienophile (double bond) has to connect electrophilic functional groups. The strong electron-withdrawing ability of the substituent, and the quantity of substitutional groups, both have positive effect on Diels–Alder reaction. In some cases, Diels–Alder reaction cannot be triggered. It means that Lewis acid was needed to activate the reaction [1, 2].

Reaction rules: (1) Syn-addition principle: Diels–Alder reaction is triggered by overlapping dienophile and the p track of π bond in diene. Therefore, Diels–Alder reaction is a stereospecific reaction, and the initial latent chiral center substituent remains unchanged. (2) Endo-addition principle: In the cycloaddition reaction, the electron-withdrawing group of dienophile heads to the internal direction of diene. It can be explained by the secondary track overlap, but there are some limitations, so this rule is not suitable for all cases [1, 2].

The regioselectivity of Diels–Alder reaction [1, 2]: If the diene contains strong electronic group in the normal Diels–Alder reaction, and dienophile contains strong electron-withdrawing group, the product will obtain high regioselectivity (Fig. 2.5).

2.2.2.2 Intramolecular Diels–Alder Reaction

Intramolecular Diels–Alder (IMDA) reaction is a common type of Diels–Alder reaction. This is one of the powerful methods in the synthesis of polycyclic compounds and has been widely applied in the synthesis of complex natural products.

Intramolecular Diels–Alder is an important method to construct bicyclic system. Because IMDA can construct two rings in one-step conversion, it is a highly efficient method.

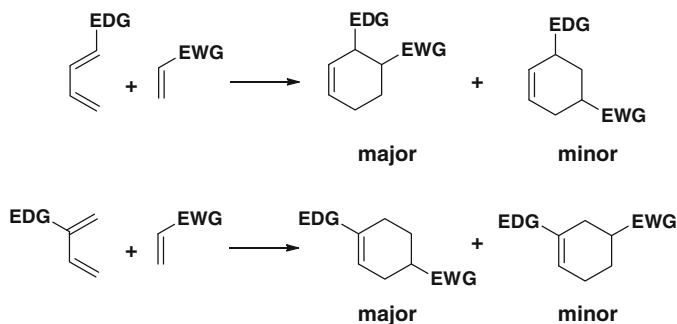


Fig. 2.5 The regioselectivity of Diels–Alder reaction [1, 2]

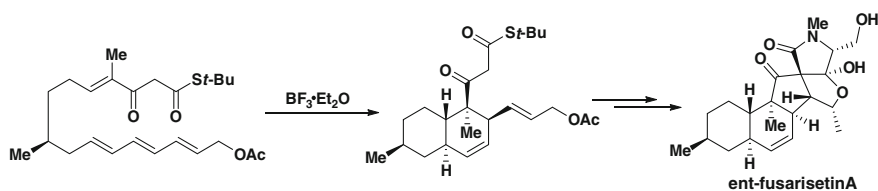


Fig. 2.6 *Ent*-fusarisetin A construction from Ang Li's group via IMDA [3]

In 2011, Prof. Ang Li from SIOC finished the first total synthesis of the enantiomer of fusarisetin A [3] (Fig. 2.6). In their report, intramolecular Diels–Alder was used as a key reaction to construct 6,6-bicyclic system. After several steps, they successfully obtained the enantiomer of the natural product and thereby corrected the absolute configuration of natural product.

Taber's group [4] also used IMDA (Fig. 2.7) in the construction of natural product *trans*-dihydroconfertifolin. Through heating the inseparable *E/Z* isomer 2.2.1, the IMDA reaction was triggered and gave target compounds 2.2.2 and 2.2.3, which could be separated through the column chromatography and recrystallized with the proportion of 4:1. Taber and his colleagues constructed the key 6,6-bicyclic systems with IMDA. From the transition-state analysis (2.2.6 and 2.2.7), the target product should be obtained from *E* type. Double bond in compound 2.2.2 was transformed into propane structure under Simmons–Smith reaction, and the yielded 2.2.4 was hydrogenated with PtO_2 to open propane ring, giving target compound *trans*-dihydroconfertifolin 2.2.5. Accordingly, the usage of IMDA reaction to construct bicyclic system can significantly improve the efficiency and quickly construct the target structure.

Transannular Diels–Alder reaction is also one of the most prominent synthetic methods of intramolecular Diels–Alder reaction. The applications of transannular Diels–Alder reaction are mostly found in biomimetic synthesis. The reasonable use of transannular Diels–Alder strategy can significantly simplify the synthesis route and improve the artistic quality of synthesis, and at the same time, it can also provide a meaningful reference for the speculation of the routes of biosynthetic

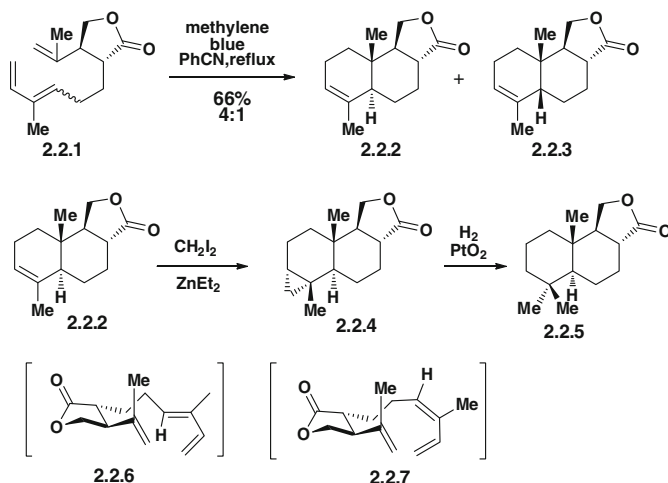


Fig. 2.7 The *trans*-dihydroconfertifolin bicyclic system constructed by Taber's group via Diels–Alder reaction (Reprinted with the permission from Ref. [4]. Copyright 2002 American Chemical Society)

transformation. One of the representative synthesis works was from Evans [5, 6], that is, the synthesis of molecular FR182877 (Fig. 2.8). They utilized Suzuki coupling reaction, firstly connected (E)-vinylboronic acid fragment and vinyl dibromide, and then closed the macro-ring using intramolecular $\text{S}_{\text{N}}2$ reaction. They got two isomeric products with different substitutes at α -position of ester. Without separation, they put the mixture into the next reaction of constructing the double bond and got transannular Diels–Alder product in one single step.

The multiple conversions, including a configured double bond, a carbon Diels–Alder reaction, and a hetero-Diels–Alder reaction, were completed in one step, and the basic molecular skeleton was completed efficiently. Later, Evans et al. completed the total synthesis of FR182877 through a simple transformation of functional groups. Interestingly, Sorensen group [7, 8] also completed the total synthesis of the same molecule, and the strategy they used shows almost no difference compared with that used by Evans. It shows that chemists have remarkably similar understanding toward this molecule [9].

2.2.2.3 Construction of [2.2.2] System via Diels–Alder Reaction

Another application of Diels–Alder reaction is to construct [2.2.2] system. Generally speaking, the [2.2.2] ring system is either the core structure of target molecular or one important precursor, which undergoes a series of rearrangement and ring opening reaction to construct the target skeleton.

A typical example is the construction of vinigrol, which was done by Professor Baran [10] from Scripps Research Institute, San Diego.

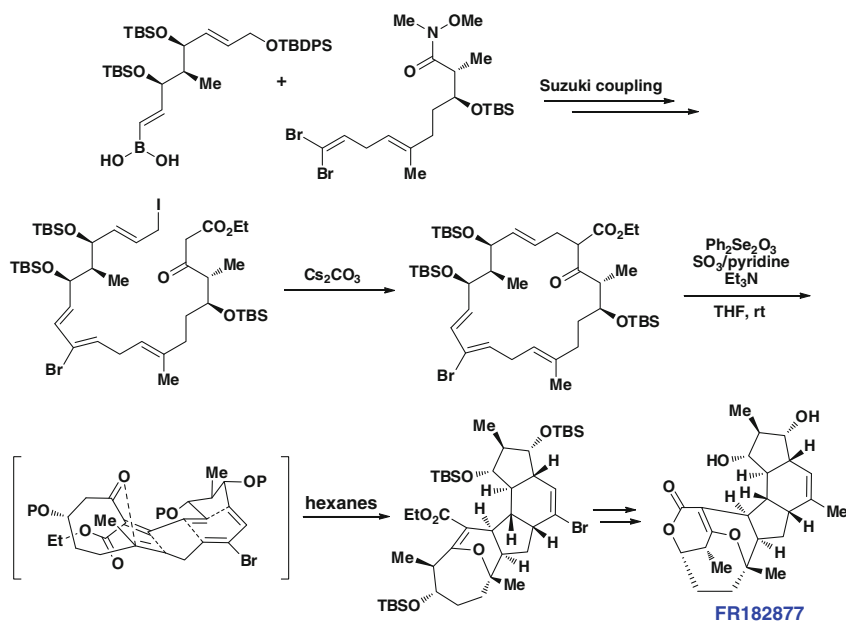


Fig. 2.8 The application of transannular Diels–Alder reaction in total synthesis (Reprinted with the permission from Ref. [6]. Copyright 2003 American Chemical Society)

As shown in Fig. 2.9, in their total synthesis of vinigrol, Baran used Diels–Alder reaction to construct [2.2.2] system at the first step and then successfully completed the synthesis of vinigrol via functionalization and rearrangement. The [2.2.2] bridge ring that was constructed by Diels–Alder reaction was used in the rearrangement process. It played an important role in the construction of octatomic ring, which had large ring tension in vinigrol skeleton.

In the synthesis of natural product connatusin A, Banwell and his colleagues [11] also used Diels–Alder reaction to construct [2.2.2] ring system at the initial steps in the preparation of starting material (Fig. 2.10). After getting the caged scaffold precursor, they successfully obtained the target product connatusin A via multiple transformations such as rearrangement. Therefore, after constructing [2.2.2] ring system by Diels–Alder reaction, we can use rearrangement to significantly improve the synthesis efficiency and quickly obtain the desired natural product.

2.2.3 Construction of [2.2.2] System via Sequential Oxidative Dearomatization/IMDA Reaction

Oxidative dearomatization reaction can start from ortho-substituted phenol and quickly construct dienes structure after oxidation. It is often used to design Diels–Alder reaction.

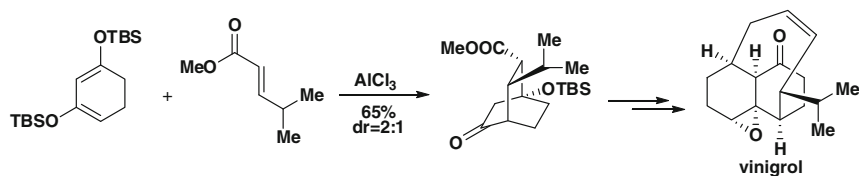


Fig. 2.9 The construction of [2.2.2] ring system by Baran's group via Diels–Alder reaction (Reprinted with the permission from Ref. [10]. Copyright 2008 Wiley–VCH Verlag GmbH & Co. KGaA, Weinheim)

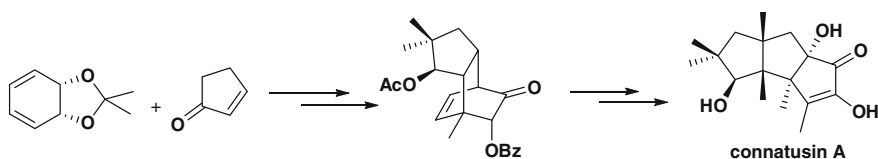


Fig. 2.10 The construction of [2.2.2] ring system by Banwell's group via Diels–Alder reaction

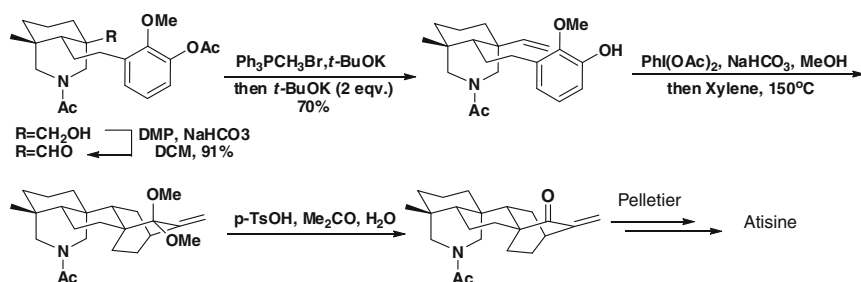


Fig. 2.11 Synthesis of atisine by Prof. Fengpeng Wang

Prof. Fengpeng Wang from Sichuan University utilized oxidative dearomatization reaction to construct the precursor of intramolecular Diels–Alder reaction in the synthesis of atisine [12]. As shown in Fig. 2.11, after Diels–Alder reaction, the core structure of atisine could be obtained. After several steps of functional group conversion, they obtained the common precursor of the synthesis used by Prof. Pelletier and completed the formal total synthesis.

Danishefsky's group [13] utilized sequential oxidative dearomatization/IMDA reaction to finish the total synthesis of natural product 11-O-debenzoyltashironin. As shown in Fig. 2.12, after undergoing oxidative dearomatization, the phenol substrate formed ten-membered ring skeleton. Under microwave heating, the core structure of natural product was obtained. This step could also be seen as trans-annular Diels–Alder reaction. After several conversions, Danishefsky's group obtained the natural product 11-O-debenzoyltashironin.

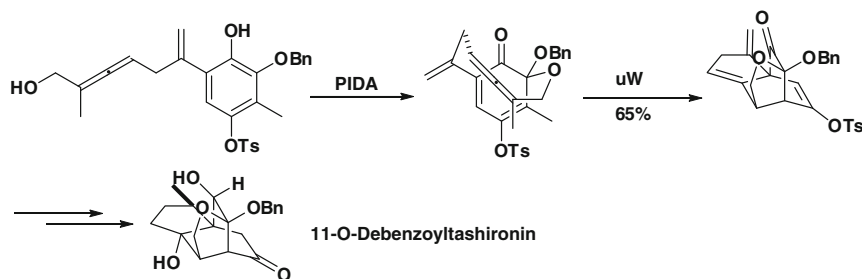


Fig. 2.12 The synthetic research of 11-O-debenzoyltashironin from Danishefsky's group (Reprinted with the permission from Ref. [13]. Copyright 2006 American Chemical Society)

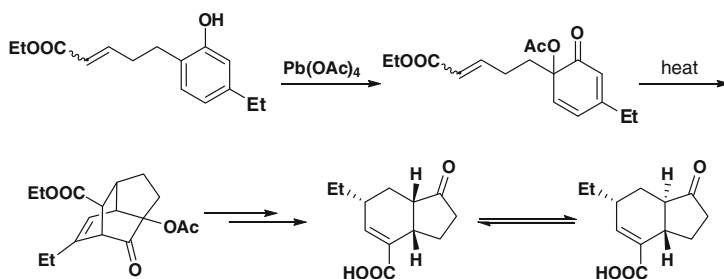


Fig. 2.13 The synthesis of coronafacic acid by Macas's group

Macas also utilized sequential oxidative dearomatization/IMDA reaction strategy in the synthesis of coronafacic acid [14]. As shown in Fig. 2.13, first of all, it triggered oxidative dearomatization of phenol substrate as well as connected the side chains, and then, it underwent intramolecular Diels–Alder reaction and obtained the intermediate containing [2.2.2] structure. After several conversions such as rearrangement, they obtained the target natural product coronafacic acid. Interestingly, the final products existed as tautomers.

Liao's group [15] used the masked benzoquinone to trigger intramolecular Diels–Alder reaction and completed a series of total synthesis (Fig. 2.14). In the total synthesis of bilosespens A and bilosespens B, they used oxidative dearomatization to construct masked benzoquinone. With the allyl alcohol, they triggered oxidative dearomatization of the phenol substrate using iodosobenzene diacetate. At the same time, they completed the allyl alcohol protection to benzoquinone. And the intramolecular Diels–Alder reaction happened between the double bond of side chain and the diene in bone structure, and [2.2.2] caged scaffold system was constructed.

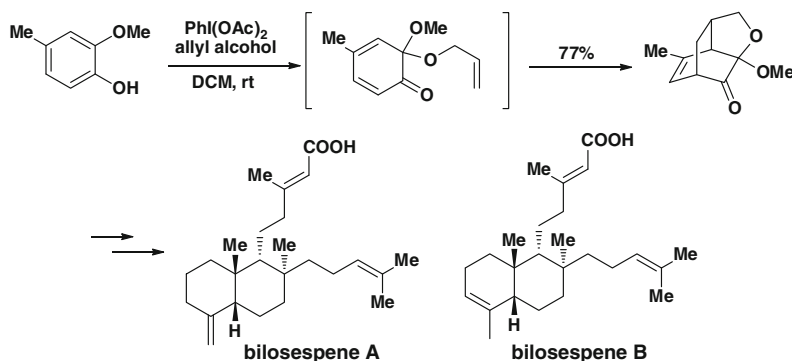


Fig. 2.14 The application of oxidative dearomatization and Diels–Alder reaction in total synthesis (Reprinted with the permission from Ref. [15]. Copyright 2003 American Chemical Society)

2.2.4 The Model Study of Maoecrystal V

The investigation and survey of the literature hinted us that the application of intramolecular Diels–Alder to construct the core structure of Maoecrystal V was a wise choice. By analyzing the structure of the target molecule, we found the [2.2.2] system was especially suitable to be constructed using IMDA. The usage of Diels–Alder reaction was powerful to introduce the quaternary carbon on [2.2.2] bridge. According to Liao's work [15], we found that the carbonyl structure existing on the caged scaffold of Maoecrystal V was suitable to be constructed by oxidative dearomatization. Thus, the molecule was disconnected to compound 2.3, and the intermediate could be obtained through 2.6. Intermediate 2.6 can be obtained through the Pinhey arylation (Fig. 2.15).

Model compound 2.1.1 was designed to test key reactions, which may be applied to the total synthesis, such as intramolecular Diels–Alder reaction, Wessely oxidative dearomatization reaction, and Pinhey arylation. The synthetic strategy of model research is shown in Fig. 2.16; compound 2.1.1 could be constructed from the precursor 2.1.2 after IMDA. Compound 2.1.2 could be prepared from compound 2.1.3 through esterification. Compound 2.1.3 could be obtained from 2.1.4 by reduction. Compound 2.1.4 was designed to be obtained by Pinhey arylation between 1,3-keto ester compounds 2.1.5 and organic lead compound 2.1.6. The advantage of this model system is that it contains three key reactions in total synthesis design, which can effectively supply the synthetic information for the total synthesis.

The feasibility of Pinhey arylation (Fig. 2.17) was tested in the initial stage. Starting from the o-methoxy bromobenzene 2.2.8, under the condition of butyl lithium, quenched with tributyltin chloride, organic tin compound 2.2.9 was obtained with 85 % yield. Compound 2.2.9 under lead(IV) acetate/mercuriacetate condition gave Pb(IV) compound 2.2.10 with 72 % yield. According to the

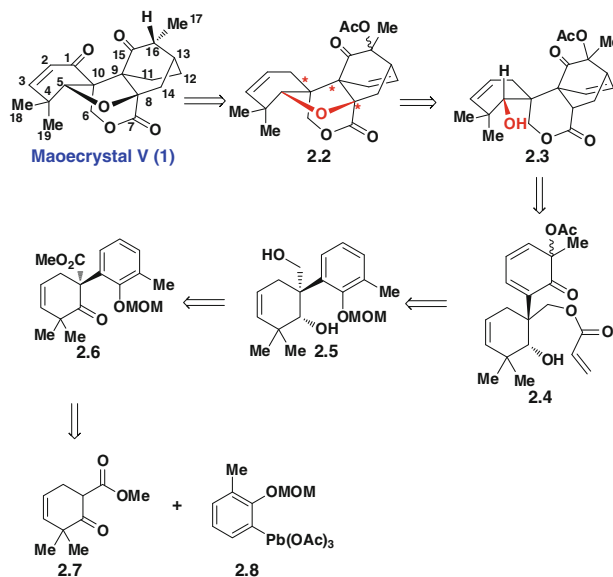


Fig. 2.15 The synthetic strategy of Maoecrystal V

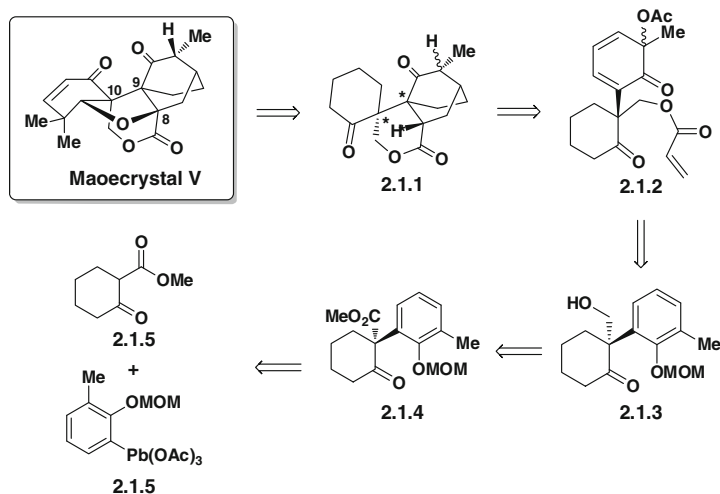


Fig. 2.16 The model synthetic strategy of Maoecrystal V

literature, Pinhey arylation triggered by organic lead reagent 2.2.10 and 1,3-dicarbonyl compound 2.2.10 can give coupling product 2.2.12 with 95 % yield. We made this progress at the early stage of research, which proved the feasibility of Pinhey arylation. More importantly, Pinhey arylation can be scaled

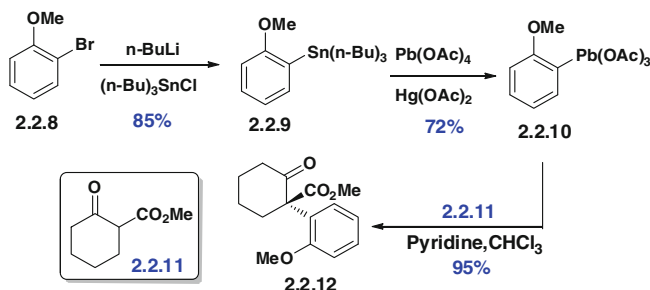


Fig. 2.17 The implementation of Pinhey arylation

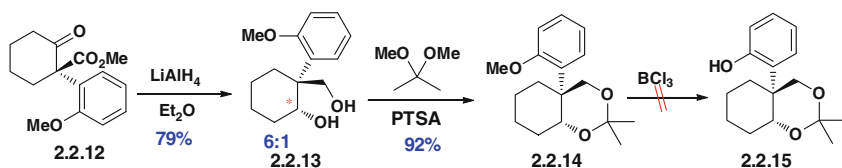


Fig. 2.18 Attempt to remove the methoxyl group on phenol

up to a few hundred grams, which is advantageous for the future preparation of starting material for total synthesis.

After obtaining 2.2.12 from coupling reaction, lithium aluminum hydride was used to reduce carbonyl and ester group simultaneously to give diol 2.2.13 as a mixture with the proportion 6:1 and 79 % yield. Then, 2,2-dimethoxypropane was used to protect 1,3-diol and gave 2.2.14 with 92 % yield (Fig. 2.18). The choice of protecting group was extremely critical. The removal of methoxyl group was firstly tested in the model. The deprotection product could not be obtained from compound 2.2.14 with excess boron trichloride, and only diol 2.2.13 was produced. Methoxyl group in diol 2.2.13 could not be removed to give phenolic hydroxyl group, so the methyl protection was not a good choice for this substrate.

MOM was considered as an excellent protecting group for phenol according to the literature. MOM group has the following advantages: (1) The conditions of removing or protecting are relatively mild; (2) MOM is resistant to alkali, and it is stable under strong basic conditions; (3) MOM can also act as the directing group to functionalize the ortho position of benzene.

As shown in Fig. 2.19, starting from *o*-cresol 2.2.16, with NBS ortho-bromination and then MOM protection of phenolic hydroxyl group, compound 2.2.17 was obtained in two steps with 55 % overall yield. Reacted in butyl lithium and then quenched with trimethyl borate, arylboronic acid ester was obtained. The boric acid ester was in situ hydrolyzed to boric acid compound 2.2.18 with diluted HCl to give 45 % yield. Compound 2.2.18 was reacted with lead (IV) acetate/mercury (II) acetate to convert the boric acid into lead reagent 2.2.19. Without

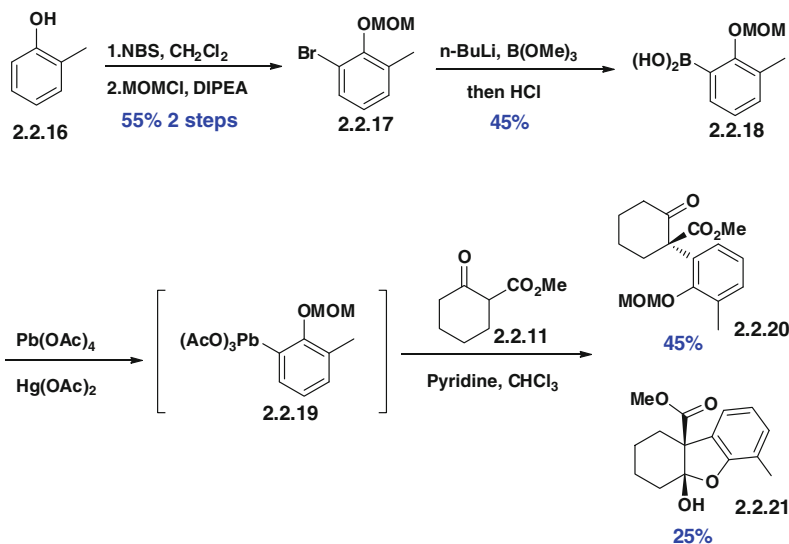


Fig. 2.19 The utilization of MOM group as Pinhey arylation substrate

further separation and directly added pyridine and dicarbonyl fragment 2.2.11, 2.2.20 was obtained as a coupling product with 45 % yield. The coupling process was not stable to repeat the yield. MOM deprivation was always observed after quenching to produce 2.2.21. And a hemiketal structure was formed between phenolic hydroxyl group and adjacent carbonyl group on the cyclohexanone fragment. A large amount of concentrated sulfuric acid was needed in the quenching step to precipitate divalent lead, but MOM was easily removed under this strong acid condition. The quenching process should be handled carefully. The usage of acid, the stirring time, and temperature should be strictly controlled to avoid the removal of MOM group under acid conditions.

Though MOM deprivation product 2.2.21 was accidentally obtained, it was still useful to test two key reactions for total synthesis: Wessely oxidative dearomatization reaction and intramolecular Diels–Alder reaction (Fig. 2.20). A pair of diethyl phthalate derivative 2.2.22 with the ratio of 2:1 and 95 % yield could be obtained from phenol 2.2.21 in acetic acid solvent with the presence of lead tetraacetate at room temperature after 5 min. Then, we tried intermolecular Diels–Alder reaction. Unfortunately, both substrate 2.2.22 and dimethyl acetylene dicarboxylate were not producing Diels–Alder product 2.2.23 under toluene refluxing or sealing tube heating conditions, only gave the results of raw material recovery.

Although intermolecular Diels–Alder reaction was failed, Wessely oxidative dearomatization was satisfactorily successful. Thus, functionalizing the coupling product 2.2.20 with side chain and trying intramolecular Diels–Alder reaction were necessary. As shown in Fig. 2.21, intermediate 2.2.20 was dissolved in THF.

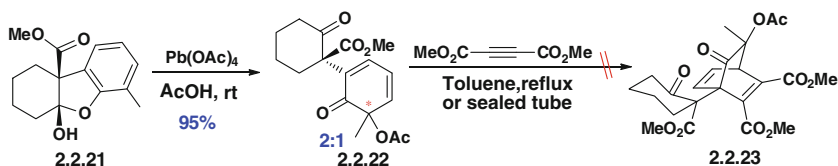


Fig. 2.20 The first attempt of Wessely oxidative dearomatization and Diels–Alder reaction

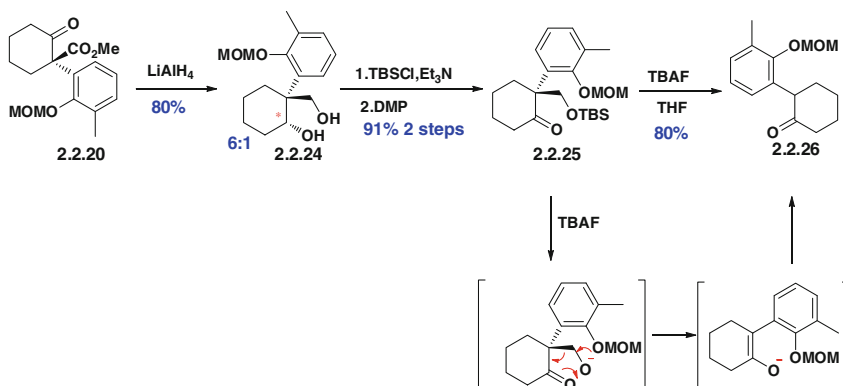
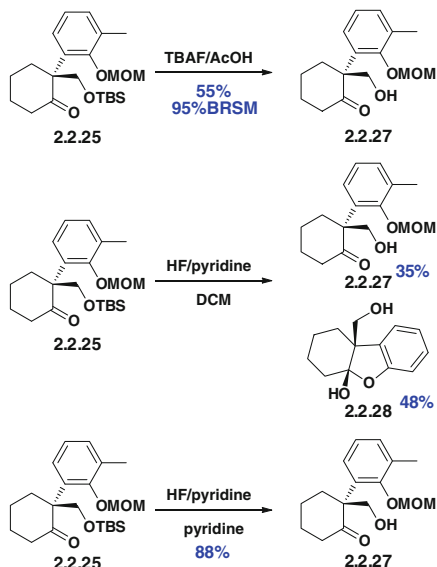


Fig. 2.21 The possible mechanism for retro-aldol condensation

Ketone and ester in the substrate were reduced with excess lithium aluminum hydride. Then, a pair of diol product 2.2.24 was generated at 6:1 ratio with 80 % yield. The diol compounds were solid, and the crystal was obtained. The X-ray structure confirmed that the side chain of primary hydroxyl group and secondary hydroxyl group were in different positions of cyclohexane six-membered ring. The main product had *trans*-diol structure. TBSCl/pyridine selectively protected primary hydroxyl group, Dess–Martin oxidized the secondary hydroxyl group, and then transformed it into ketone to get 2.2.25. The overall yield of the two steps was 91 %. The following step was to remove TBS protecting group.

In order to get the target compounds, we tried various methods (Fig. 2.22), including diluting reaction concentration, using anhydrous TBAF, etc., but all of them were not good enough. Finally, we fortunately found that the substrate 2.2.25 could be transformed to de-TBS product 2.2.27 under TBAF/AcOH condition with 55 % yield. Using HF/pyridine to react in CH_2Cl_2 solvent, the reaction gave product 2.2.27 with 35 % yield, together with the main MOM-removed product hemiketal 2.2.28 (48 % yield). If taking pyridine as the solvent and adding HF/pyridine as the reagent to remove TBS, TBS was specifically removed and retro-aldol reaction did not happen (88 % yield). The inference was that TBAF was strong alkaline and the specificity of the target product structure might easily trigger retro-aldol reaction. The condition of HF/pyridine was acid, which actively suppress retro-aldol process.

Fig. 2.22 Conditions screened to remove TBS protection group



After the removal of TBS group, the primary hydroxyl group in compound 2.2.27 was connected with acrylic side chain through the condensation with EDC/DMAP and gave compound 2.2.29 with 71 % yield. TMSBr was used for the removal of the MOM group and could get the target product at -78°C with a good yield. However, the product was different from what we expected. After careful analysis, it was shown that once the MOM group was removed, the phenolic hydroxyl and ketone carbonyl group on cyclohexanone formed hemiketal structure (95 % yield), giving the [6-5-6] bicyclic product 2.2.30. Under similar conditions, compound 2.2.27 was reacted with bromo-acrylic ester derivatives 2.2.31, giving 29 % yield. MOM protection group was removed by TMSBr, which produced hemiketal 2.2.32 with 95 % yield. A bromine atom was introduced on the dienophile side chain in order to keep an active site for constructing tetrahydrofuran oxa-bridge after IMDA (Fig. 2.23).

There were no examples of aryl ketal compounds' oxidative dearomatization could be found in the literature of earlier research, so it was unknown whether it could be converted successfully to give the desired oxidative dearomatization. Iodobenzene diacetate analogs were first used as the antioxidant; unfortunately, this type of oxidizing agent could not gain the expected target product. However, when $\text{Pb}(\text{OAc})_4$ was used as the oxidizing agent, the oxidative aromatization products 2.2.33 and 2.2.34 could be obtained with a high yield and good regioselectivity (Fig. 2.24). After comparison, we believed that the difference between $\text{Pb}(\text{OAc})_4$ and iodosodiacetate and its analogs was as follows: (1) $\text{Pb}(\text{OAc})_4$ reacted in an acidic system; hence, a certain proportion of the ketal could exist in the form of opening intermediate; (2) $\text{Pb}(\text{OAc})_4$ had a better oxidation performance; therefore, it could effectively capture the raw materials in

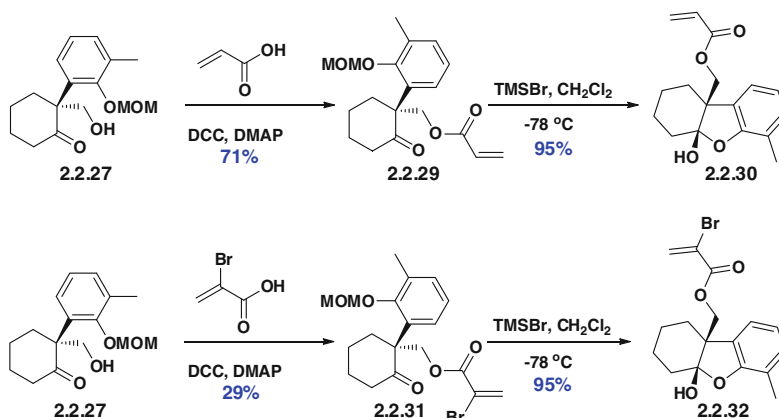


Fig. 2.23 The synthesis of hemiketal 2.2.30 and 2.2.32

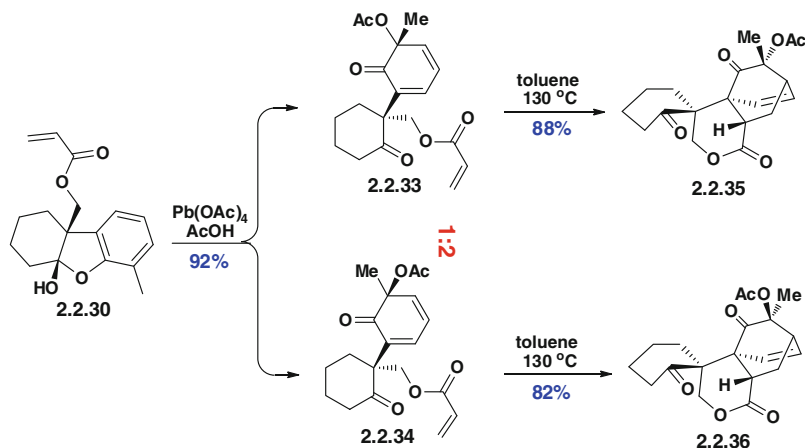
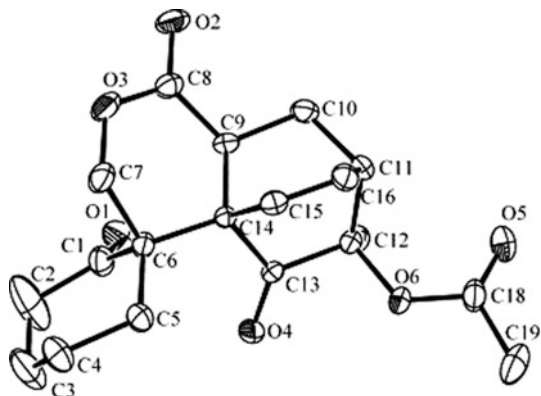


Fig. 2.24 Wessely oxidation and intramolecular Diels–Alder reaction of model study

ketal opening form, pulling the reaction equilibrium to the target product until it was fully converted.

Via separation and identification, it was found that the oxidative dearomatization did not supply sole product; instead, it obtained a pair of isomers at acetyl position. If the two isomers underwent the key IMDA reaction separately, two IMDA products 2.2.35 and 2.2.36 were obtained. The structure of the product with smaller R_f value was confirmed by single-crystal X-ray diffraction experiments (Fig. 2.25). The stereochemistry of resulting quaternary carbon center was identical to target natural product. This was the most relevant information in terms of the total synthesis. However, we were still concerned whether the IMDA result of the other isomer 2.2.35 was consistent with the structure of Maoecrystal V.

Fig. 2.25 Single-crystal diffraction diagram of IMDA product 2.2.35



As shown in Fig. 2.26, the other IMDA precursor 2.2.32 also underwent Wessely oxidative dearomatization to create a pair of separable 2:1 products 2.2.37 and 2.2.38 with 92 % total yield. Unfortunately, the precursors could not be transformed into IMDA products under the same conditions. It was speculated that the steric hindrance of the bromine atom blocked the activity of the reaction.

With successfully constructed [2.2.2] bicyclic product in hand, since two IMDA isomers were already obtained, it was inferred if IMDA product 2.2.36 could be identified to have the same structure with another X-ray confirmed product after several conversions, the relative configuration on molecular skeleton of the two isomers would be same. Therefore, the two IMDA products were subjected to the same functional group conversions (Fig. 2.27). The unsaturated double bond of IMDA product 2.2.35 (with X-ray identification) was reduced under Pd/C hydrogenation. The compound 2.2.41 was obtained in the yield of 90 %. Acetoxy group was removed through SmI_2 reduction, and 2.2.43 and 2.2.44 were obtained with 2:1 proportion in methyl position giving 68 % total yield, which could be separated by column chromatography. On the other hand, the IMDA product 2.2.36 (without X-ray identification) could be transformed into a pair of separable 3:1 isomers with the same procedure of Pd/C hydrogenation and samarium di-iodide reduction. Compared with the NMR of the isolated compounds, it was found that the spectrums of the compounds from two different IMDA were the same (two isomers of the final products could be compared separately). Therefore, the quaternary carbon chiral centers at the key position in the basic skeleton of the two IMDA isomers were identical. The only difference of the isomers was at the acetyl position. Thus, the oxidative dearomatization/IMDA reaction was perfectly applied in the model construction and appeared highly efficient in constructing the skeleton of Maoecrystal V. The IMDA selectivity has concerned us in the early stage since it was difficult to predict the facial selectivity of IMDA. However, the model experiment gave us the skeleton structure identical to Maoecrystal V. There was no clear and definite explanation for the selectivity. Computational chemistry was also used to explain the selectivity of IMDA. Unfortunately, so far no reasonable explanation has been obtained for the result.

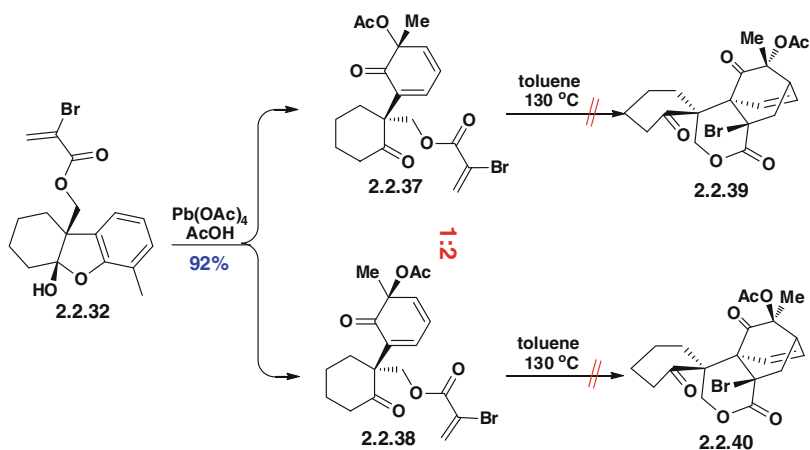


Fig. 2.26 Failure attempt on intramolecular Diels–Alder reaction

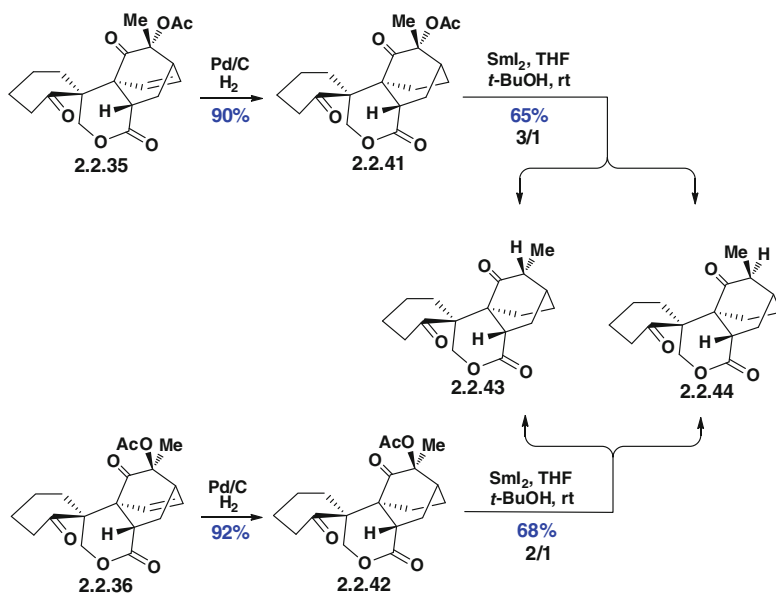


Fig. 2.27 The structure proof for intramolecular Diels–Alder product 2.2.36

A different route for removing acetyl oxygen group through SmI_2 reduction is shown in Fig. 2.28, and acetoxyl group of 2.2.41 was dislodged under the potassium carbonate/methanol condition. Compound 2.2.45 was obtained with 95 % yield; the structure was confirmed by single-crystal X-ray diffraction experiment. The hydroxyl group of compound 2.2.45 was removed to produce 2.2.43 and 2.2.44 with 3.8:1 ratio under SmI_2 reduction to give 84 % yield. The results of this

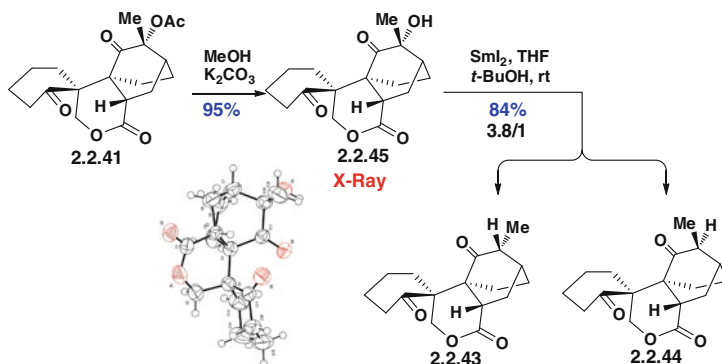


Fig. 2.28 The structure of intramolecular Diels–Alder product 2.2.36

experiment were just contrary to what Molander's group reported. Their result showed that acetoxymethyl substrate would give better yield and diastereoselectivity. However, the α -hydroxyl carbonyl substrate 2.2.45 showed a better result, indicating the reaction had a strong relationship with the substrates.

In the process of coupling reaction, as described previously, the usage of dilute acid leads to the by-product 2.2.21. After removal of the MOM group, the newly formed five-membered hemiketal ring was quite stable. The by-product could not be reprotected with MOM to give the desired one. The protection would first happen at the hemiketal hydroxyl position. At the beginning of our model synthesis, this result caused great trouble because it significantly reduced the efficiency of preparing the precursors. However, dearomatization can be successfully carried on even with the removal of the MOM group and formation of hemiketal structure. Hemiketal structure did not affect the key dearomatization, which was proved by our research. Therefore, the structure could be used to redesign the route (Fig. 2.29). The target was to utilize the stability of hemiketal intermediate to protect carbonyl group in cyclohexanone from reduction and only convert ester to primary alcohol to connect with the side chain. The synthetic route would be significantly simplified. The coupling was handled with relatively strong acid; thus, the coupling product was further converted to the hemiketal structure. The hemiketal hydroxyl group of compound 2.2.46 was protected using TMSCl, which could survive in the next DIBAL reduction of the ester. Hydrochloric acid was added for dislodging TMS after reduction reaction, which produced diol compound 2.2.47. EDCI/DMAP realized condensation of the hydroxyl group and acrylic acid, which completed the construction of 2.2.30.

Intermediate 2.2.30 was the same as the one in early synthetic research. Comparing the two routes, the new synthetic method clearly showed the higher efficiency. Seven steps were used in early attempts to get 2.2.30, including those strict requirements, for example the controlling of the acid strength in coupling step and the removal of the TBS with retro-aldol by-product. The total yield was 29 %. Based on the analysis of the transformation, a four-step conversion was obtained

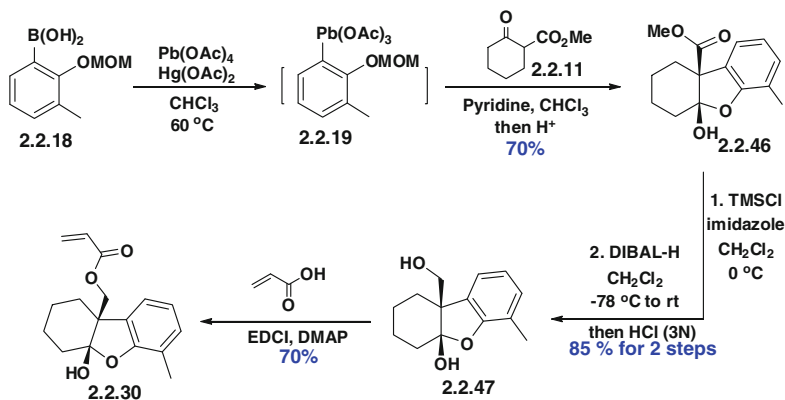


Fig. 2.29 The optimized synthesis route of compound 2.2.30

with reasonable simplification. The two synthetic routes ultimately started from the same material, the simplified route achieved high efficiency, easy operation, and up to 41 % total yield, therefore maximally optimized the original route.

2.3 Experimental Section

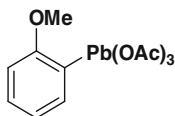
2.3.1 Experimental Materials and Equipment

Benzene and toluene were dried by sodium metal; ether and THF were dried from sodium and benzophenone ketone; dichloromethane and acetonitrile were dried through CaH_2 ; methanol and ethanol were redistilled from MgI_2 ; if not particularly mentioned, other solvents were analytically pure. Flash column chromatography silica gel (200–300 mesh) was purchased from Qingdao Ocean Chemical; the boiling point of petroleum ether is 60–90 °C; the thin layer chromatography plate GF254 and efficient plate were purchased from Qingdao Ocean Chemical Plant in China.

All NMR spectral data (^1H -NMR and ^{13}C -NMR) were measured by US Bruker Avance 500 Spectrometer or US Bruker Avance 300 Spectrometer instruments, generally using CDCl_3 or CD_3OD as the solvent. Tetramethylsilane (TMS) was added as the internal standard. Coupling constant used Hz as the unit. Some of the abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = single broad peak; high-resolution mass spectrometry (HRMS) data were measured by the US Bruker Apex IV FTICRMS instrument; low-resolution mass spectrometry (MS) data were measured by the British Micromass ZAB-HS MMS instrument; specific rotation data were measured by US Perkin Elmer 341 LC polarimeter instrument, which used Na light source, and the data are expressed as $[\alpha]_D^{25}$ (cg/100 mL, solvent). Melting point (mp)

was measured by Microprocessor melting point apparatus (Tektronix instrument Co., Ltd). Chromatographic data (HPLC) were measured by the Hewlett-Packard Agilent 1100 Series HPLC instrument.

2.3.2 Experimental Process and NMR Data of Model Study



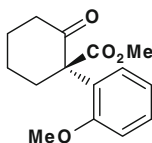
2.2.10

Synthesis and NMR data of compound 2.2.10:

Under the protection of nitrogen, 2-bromo-anisole 2.2.8 (3.8 g, 20 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to -78°C . *n*-BuLi (10 mL, 22 mmol) was slowly added dropwise. The reaction was stirred at -78°C for 0.5 h, and tributyltin chloride tin (7.2 mL, 24 mmol) was slowly added dropwise within 10 min under stirring. TLC showed that the reaction was completed. Saturated ammonium chloride solution (50 mL) was added to quench the reaction. After separation, the aqueous phase was extracted with ethyl acetate (3×50 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure, and the resulting crude product was isolated and purified by flash column chromatography (PE/EA = 15:1, R_f = 0.8) to give 6.7 g colorless liquid 2.2.9, yield 85 %.

Under a nitrogen atmosphere, the compound 2.2.9 (6.7 g, 17 mmol) was dissolved in chloroform (40 mL) and the $\text{Pb}(\text{OAc})_4$ (9.1 g, 21 mmol) and $\text{Hg}(\text{OAc})_2$ (320 mg, 1 mmol) were added at room temperature. The reaction was heated to 40°C and stirred for 2 h. After TLC determination, the reaction was cooled down to room temperature. The solvent was removed by rotary evaporator under reduced pressure, and then, *n*-hexane (50 mL) was added to precipitate a solid. The solids were washed with *n*-hexane (3×10 mL) and recrystallized in chloroform and *n*-hexane (10 mL:100 mL) to give 5.5 g white solid, yield 72 %.

^1H NMR (500 MHz, CDCl_3): δ 7.81–7.79 (m, 1H), 7.49–7.46 (m, 1H), 7.23–7.19 (m, 1H), 7.07 (d, J = 8.1 Hz, 1H), 3.82 (s, 3H), 2.10 (s, 9H).

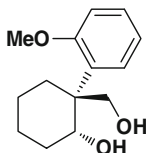


2.2.12

Synthesis and NMR data of compound 2.2.12:

Under the nitrogen protection, 2-oxo-cyclohexane carboxylate 2.2.11 (1.4 g, 9 mmol) was dissolved in chloroform (30 mL) at room temperature, pyridine (2.5 mL, 31 mmol) was slowly added, and the reaction was stirred. The substrate 2.2.10 (4.5 g, 9 mmol) was dissolved in chloroform (30 mL) and added to the reaction dropwise. The reaction was heated to 40 °C for 3 h. Then, TLC showed that the reaction was completed. The reaction was cooled to 0 °C using the ice water bath, and then, 2 N H₂SO₄ (20 mL) was slowly added. After vacuum filtration through Celite and liquid separation, the aqueous phase was extracted with chloroform (3 × 50 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporator under reduced pressure, and the resulting crude product was separated and purified by flash column chromatography (PE/EA = 5:1), the desired product was obtained as 2.2 g white solid (*R_f* = 0.20 PE/EA = 15:1), yield 95 %.

¹H NMR (500 MHz, CDCl₃): δ 7.32–7.28 (m, 1H), 7.12–7.10 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 1H), 6.99–6.93 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.68–2.51 (m, 4H), 1.94–1.83 (m, 2H), 1.75–1.69 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 206.1, 171.9, 157.4, 128.9, 127.8, 120.9, 112.3, 64.6, 55.6, 52.4, 40.4, 35.2, 27.3, 21.8.



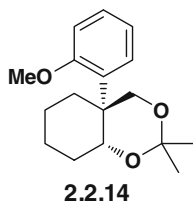
2.2.13

Synthesis and NMR data of compound 2.2.13:

Under a nitrogen atmosphere, LiAlH₄ (0.97 g, 25.5 mmol) was added to anhydrous diethyl ether (30 mL), which had already been cooled to 0 °C. The substrate 2.2.12 (2.2 g, 8.5 mmol) was dissolved in anhydrous diethyl ether (30 mL) and introduced into the reaction flask under stirring. The reaction was stirred for 3 h at room temperature. TLC determined that the reaction was completed. Cooled to 0 °C, 3 N NaOH (5 mL) was added dropwise. After vacuum filtration through Celite and liquid separation, the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was separated and purified by flash column chromatography (PE/EA = 5:1) to give 1.6 g colorless liquid (*R_f* = 0.60, and PE/EA = 1:1), yield 79 %.

¹H NMR (500 MHz, CDCl₃): δ 8.16 (dd, *J* = 27.7 Hz, *J* = 7.8 Hz, 0.85H), 7.59 (d, *J* = 1.5 Hz, 0.14H), 7.24–7.20 (m, 1H), 6.98–6.93 (m, 1H), 6.90–6.88 (m, 1H), 4.68 (s, 0.14H), 4.35 (d, *J* = 5.8 Hz, 0.88H), 4.03–4.01 (m, 1H), 3.86–3.75 (m, 1H), 3.81 (s, 3H), 2.15–2.12 (m, 1H), 1.95–1.75 (m, 2H), 1.70–1.60 (m, 2H), 1.60–1.45 (m, 2H), 1.40–1.30 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 158.3,

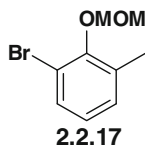
158.1, 131.8, 131.2, 129.9, 129.1, 128.1, 127.7, 120.9, 120.8, 112.1, 111.7, 66.5, 55.1, 55.1, 49.5, 30.7, 29.4, 28.1, 21.7, 21.6, 21.5, 14.1.



Synthesis and NMR data of compound 2.2.14:

Under the protection of nitrogen, the substrate **2.2.13** (320 mg, 1.36 mmol) and 2,2-dimethoxypropane (0.34 mL, 2.72 mmol) were added to acetone (10 mL), which was cooled to 0 °C. Monohydrate *p*-toluenesulfonic acid (26 mg, 0.136 mmol) was added, and the reaction was stirred at room temperature for 0.5 h. TLC showed that the reaction was completed. The reaction was cooled to 0 °C. Then, saturated NaHCO₃ (5 mL) was added dropwise. The acetone solvent was removed by vacuum rotary evaporator, and ethyl acetate (50 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure, and the resulting crude product was separated and purified by flash column chromatography (PE/EA = 10:1). 300 mg desired product was obtained as a white solid (*R_f* = 0.80, PE/EA = 5:1), yield 92 (%).

¹H NMR (500 MHz, CDCl₃): δ 8.16 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H), 7.23–7.20 (m, 1H), 6.94–6.89 (m, 2H), 4.29 (d, *J* = 11.1 Hz, 1H), 3.98 (dd, *J* = 12.5 Hz, *J* = 4.0 Hz, 1H), 3.87 (s, 3H), 3.73 (d, *J* = 11.1 Hz, 1H), 2.91 (d, *J* = 10.6 Hz, 1H), 2.29–2.26 (m, 1H), 1.78–1.71 (m, 2H), 1.78 (d, *J* = 13.1 Hz, 1H), 1.63 (s, 3H), 1.36 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 157.9, 1133.8, 127.0, 119.5, 111.7, 99.2, 78.6, 70.5, 54.7, 43.2, 30.8, 29.6, 27.9, 26.2, 21.9, 18.9.



Synthesis and NMR data of compound 2.2.17:

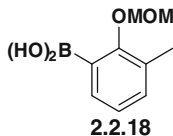
Under the protection of nitrogen, the substrate *o*-cresol (10.8 g, 100 mmol) and diisopropylamine (1.4 mL, 10 mmol) were added to –78 °C dichloromethane (100 mL). NBS (35.6 g, 200 mmol) dissolved in dichloromethane (500 mL) was added under stirring condition. The reaction was heated to room temperature and stirred for 1 h. TLC determination showed that the reaction was completed. After cooled to 0° C, 1 N diluted hydrochloric acid was slowly added dropwise to adjust

$pH = 1$. Dichloromethane (500 mL) was added for liquid separation, and the aqueous phase was extracted with dichloromethane (3×100 mL). The organic phases were combined, washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by vacuum distillation, collected the 120°C distillate, and obtained 11.6 g 2-bromo-6-methyl phenol as colorless liquid ($R_f = 0.80$, PE/EA = 5:1), yield 62 %.

^1H NMR (500 MHz, CDCl_3): δ 7.31 (d, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 7.4$ Hz, 1H), 6.74 (t, $J = 7.8$ Hz, 1H), 5.56 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 150.3, 130.3, 129.3, 125.9, 121.2, 110.1, 16.6.

Under the protection of nitrogen, the substrate 2-bromo-6-methyl phenol (30.0 g, 160 mmol) and diisopropyl ethyl amine (82.9 mL, 480 mmol) were added to 0°C dichloromethane (600 mL). Under the stirring condition, MOMCl (18.1 g, 240 mmol) was added, heated to room temperature, and reacted for 3 h. TLC showed that the reaction was completed. 1 N diluted hydrochloric acid (200 mL) was slowly added dropwise at 0°C to adjust $pH = 7$. Dichloromethane (200 mL) was added to the system. The aqueous phase was extracted with dichloromethane (3×200 mL). The organic phases were combined, washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The resulting crude product was separated and purified by flash column chromatography (PE/EA = 100:1) to give 32 g colorless liquid ($R_f = 0.80$, PE/EA = 10:1), 89 % yield.

^1H NMR (500 MHz, CDCl_3): δ 7.41 (d, $J = 7.1$ Hz, 1H), 7.14 (d, $J = 7.5$ Hz, 1H), 6.92 (t, $J = 7.8$ Hz, 1H), 5.10 (s, 2H), 3.66 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 153.2, 133.8, 131.1, 130.3, 125.4, 117.4, 99.5, 57.7, 17.3.

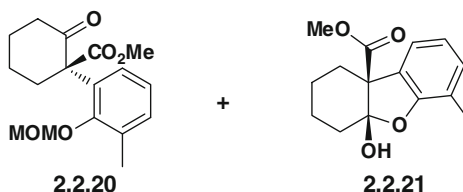


Synthesis and NMR data of compound 2.2.18:

Under the protection of nitrogen, substrate 2.2.17 (33.0 g, 140 mmol) was cooled to -78°C in tetrahydrofuran (150 mL), and then, *n*-butyl lithium (76.0 mL, 168 mmol) was added. The reaction was stirred for 1 h, and then, trimethyl borate (21.1 mL, 182 mmol) was slowly added dropwise at -78°C within 1.5 h and stirred for another 1 h. The reaction was heated to room temperature for 10 h. TLC showed that the reaction was completed. Then, the solution was cooled to 0°C by ice water bath, slowly 1 N diluted hydrochloric acid (150 mL) was added dropwise to adjust $pH = 1$. Then, ether (1 L) was added for liquid separation. The aqueous phase was extracted with ether (3×200 mL). The organic phases were combined, washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary

evaporator under reduced pressure. The resulting crude product was dissolved in petroleum ether (150 mL) at 0 °C and stirred for 0.5 h. The solid was collected by filtration to give 12.3 g white solid, 45 % yield.

¹H NMR (500 MHz, CDCl₃) δ 7.73–7.60 (m, 1H), 7.31 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.06 (s, 2H), 3.56 (s, 3H), 2.31 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 160.9, 134.6, 133.9, 129.7, 124.6, 100.0, 77.1, 76.9, 76.6, 57.9, 16.7.

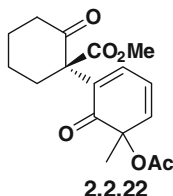


Synthesis and NMR data of compounds 2.2.20 and 2.2.21:

Under the protection of nitrogen, the boric acid (10.6 g, 53.8 mmol) was dissolved in chloroform (100 mL), and then, lead tetraacetate (26.3 g, 59.1 mmol) and mercuric acetate (3.4 g, 10.8 mmol) were added at the temperature of 40 °C. The reaction was heated to 60 °C and stirred for 2 h. Compound 2.2.11 (8.4 g, 53.8 mmol) was dissolved in pyridine (15.2 mL) and added at 60 °C. After stirred for 1 h, the reaction was kept at room temperature overnight. TLC showed that the reaction was completed. The solid was removed by filtration and washed with chloroform (100 mL). Dilute sulfuric acid (3 N, 100 mL) was used to quench the reaction. After liquid separation, the aqueous phase was extracted with chloroform (3 × 100 mL). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was isolated and purified by flash column chromatography (PE/EA = 10:1) to obtain 7.4 g white solid 2.2.20, yield 45 %, and 3.6 g white solid 2.2.21, yield 25 %.

Compound 2.2.20, white solid, $R_f = 0.6$ (PE/EA = 5:1), ^1H NMR (500 MHz, CDCl_3) δ 7.18 (dd, $J = 6.7, 1.5$ Hz, 1H), 7.08–7.03 (m, 2H), 4.80 (dd, $J = 12.3, 5.6$ Hz, 2H), 3.70 (s, 3H), 3.50 (s, 3H), 2.71–2.65 (m, 2H), 2.50–2.39 (m, 2H), 2.35 (s, 3H), 1.88–1.80 (m, 2H), 1.68–1.56 (m, 1H), 1.55–1.53 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 206.5, 172.0, 154.9, 132.3, 132.0, 131.5, 124.6, 124.2, 99.9, 64.5, 56.9, 52.2, 40.2, 35.6, 28.3, 21.3, 17.3. HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 329.1365; found: 329.1448.

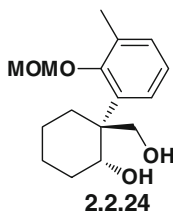
Compound 2.2.21, white solid, $R_f = 0.4$ (PE/EA = 5:1), ^1H NMR (300 MHz, CDCl_3) δ 7.01 (d, $J = 7.3$ Hz, 1H), 6.95–6.74 (m, 2H), 5.17 (s, 1H), 3.85 (qd, $J = 11.5, 6.1$ Hz, 2H), 2.70 (dd, $J = 6.9, 5.4$ Hz, 1H), 2.23 (s, 3H), 2.10–1.76 (m, 3H), 1.71–1.42 (m, 4H), 1.42–1.16 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 130.4, 130.0, 120.7, 120.3, 120.1, 112.4, 77.4, 77.0, 76.5, 66.6, 51.5, 33.6, 30.3, 20.2, 19.4, 15.1. HRMS-ESI Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 285.1103; found: 285.1100.



Synthesis and NMR data of compound 2.2.22:

Under the protection of nitrogen, the compound 2.2.21 (270 mg, 1.0 mmol) was dissolved in acetic acid (5 mL), and then, tetraacetate lead (1.3 g, 3.0 mmol) was added at 0 °C. The reaction was heated to 60 °C and stirred for 1 h. TLC showed that the reaction was completed. The solid was removed by filtration and washed with ethyl acetate (20 mL). The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by flash column chromatography (PE/EA = 8:1) to obtain 300 mg white solid (R_f = 0.40, PE/EA = 3:1) with a ratio of 2:1, yield 95 %.

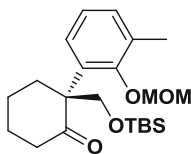
^1H NMR (500 MHz, CDCl_3) δ 6.74–6.73 (m, 1H), 6.23–6.22 (m, 2H), 3.73 (s, 1H), 3.65 (s, 2H), 2.44–2.38 (m, 3H), 2.06–2.02 (m, 4H), 1.90–1.60 (m, 4H), 1.47 (s, 2H), 1.42 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 205.9, 204.8, 197.1, 196.7, 171.0, 170.7, 169.4, 169.0, 137.0, 136.7, 136.4, 135.7, 120.9, 120.8, 79.9, 64.1, 62.3, 53.3, 52.6, 52.2, 40.7, 40.5, 34.8, 34.7, 27.0, 26.2, 23.7, 23.4, 22.5, 22.0, 21.2, 20.3.



Synthesis and NMR data of compound 2.2.24:

Under the protection of nitrogen, the compound 2.2.20 (4.7 g, 16 mmol) was dissolved in diethyl ether (100 mL), and lithium aluminum hydride (1.8 g, 48 mmol) was then added at 0 °C. The reaction was heated to room temperature and stirred for 1 h. TLC showed that the reaction was completed. Water (5 mL) and saturated sodium hydroxide solution (10 mL) were slowly added to quench the reaction. Diethyl ether (100 mL) was added for liquid separation, and the aqueous phase was extracted with ether (3 × 100 mL). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporator under reduced pressure. The resulting crude product was isolated and purified by flash column chromatography (PE/EA = 3:1, R_f = 0.2) to give 3.4 g colorless liquid (R_f = 0.2, PE/EA = 4:1), 80 % yield.

^1H NMR (500 MHz, CDCl_3) δ 7.48 (d, $J = 7.8$ Hz, 1H), 7.12 (d, $J = 6.6$ Hz, 1H), 7.08 (t, $J = 7.7$ Hz, 1H), 5.06 (dd, $J = 12.7, 5.2$ Hz, 2H), 4.66 (d, $J = 8.0$ Hz, 1H), 4.35 (d, $J = 11.2$ Hz, 1H), 4.24 (d, $J = 11.3$ Hz, 1H), 3.60 (s, 3H), 3.28 (s, 1H), 3.08 (s, 1H), 2.34 (s, 3H), 2.13–2.08 (m, 1H), 1.88–1.79 (m, 4H), 1.65–1.55 (m, 1H), 1.45–1.39 (m, 3H), 0.89–0.84 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 154.7, 136.4, 131.5, 130.4, 127.6, 124.4, 99.5, 74.1, 65.5, 57.5, 48.6, 33.3, 30.7, 23.6, 21.64, 18.1. HRMS-ESI Calcd for $\text{C}_{16}\text{H}_{25}\text{O}_4$ $[\text{M} + \text{H}]^+$: 281.1675; found: 281.1774.

**2.2.25**

Synthesis and NMR data of compound 2.2.25:

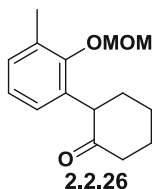
Under the protection of nitrogen, the compound 2.2.24 (1.5 g, 5.3 mmol) and triethylamine (1.1 mL, 7.9 mmol) were dissolved in dichloromethane (50 mL). TBSCl (1.1 g, 6.9 mmol) was slowly added at 0 °C. The reaction was heated to room temperature and stirred for 8 h. TLC showed that the reaction was completed. Saturated ammonium chloride solution (50 mL) was added to quench the reaction. Dichloromethane (100 mL) was added for liquid separation. The aqueous phase was extracted with ether (3 × 100 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was isolated and purified by flash column chromatography (PE/EA = 10:1), to give 2.0 g colorless liquid, which is a hydroxy monoprotected product (PE/EA = 6:1, $R_f = 0.6$), yield 95 %.

^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, $J = 7.8$ Hz, 1H), 7.08 (t, $J = 7.7$ Hz, 1H), 5.01 (d, $J = 6.2$, 1H), 4.96 (d, $J = 5.2$ Hz, 1H), 4.83 (br, 1H), 4.37 (t, $J = 11.4$ Hz, 2H), 4.01 (d, $J = 9.7$, 1H), 3.63 (s, 3H), 2.33 (s, 3H), 2.30 (s, 1H), 1.82–1.80 (m, 2H), 1.71–1.70 (m, 2H), 1.48–1.47 (m, 2H), 1.35–1.35 (m, 2H), 0.91 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.5, 135.6, 131.4, 130.3, 128.0, 123.6, 99.1, 72.9, 68.3, 57.2, 47.9, 30.5, 25.7, 25.6, 21.8, 18.2, 17.9, 3.6, –5.7, –5.8. HRMS-ESI Calcd for $\text{C}_{22}\text{H}_{39}\text{O}_4\text{SiNa}$ $[\text{M} + \text{Na}]^+$: 417.2437; found: 417.2440.

Under the protection of nitrogen, the hydroxy monoprotected product (1.60 g, 4.06 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C. DMP (2.60 g, 6.10 mmol) was added, and the reaction was stirred for 1 h at 0 °C. TLC showed that the reaction was completed. The reaction was quenched by adding a saturated sodium thiosulfate (10 mL). DCM (100 mL) was added for liquid

separation. The aqueous phase was extracted with ether (3×20 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was separated and purified by flash column chromatography (PE/EA = 20:1) to give 1.56 g colorless liquid (R_f = 0.7, PE/EA = 6:1), yield 96 %.

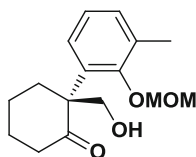
^1H NMR (500 MHz, CDCl_3) δ 7.22 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 12.7 Hz, 1H), 4.76 (d, J = 5.5, 1H), 4.71 (d, J = 5.5 Hz, 1H), 3.86 (d, J = 10.2, 1H), 3.69 (d, J = 10.2, 1H), 3.50 (s, 3H), 2.88 (d, J = 10.9, 1H), 2.60–2.54 (m, 1H), 2.33 (s, 3H), 2.27 (d, J = 12.3, 1H), 1.92–1.90 (m, 1H), 1.64–1.51 (m, 4H), 0.78 (s, 9H), -0.14 (s, 3H), -0.24 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 212.4, 153.9, 134.2, 131.1, 130.4, 127.3, 123.5, 99.5, 68.5, 57.1, 56.8, 40.5, 36.6, 29.5, 25.8, 21.4, 18.2, 17.3, -5.8 , -5.8 . HRMS-ESI Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$: 415.2281; found: 415.2305



Synthesis and NMR data of compound 2.2.26:

Under the protection of nitrogen, the compound 2.2.25 (1.44 g, 3.67 mmol) was dissolved in dichloromethane (50 mL). TBAF (11 mL, 11 mmol) was then slowly added at 0 °C. The reaction was allowed to warm to room temperature and stirred for 8 h. TLC showed that the reaction was completed. Saturated ammonium chloride solution (20 mL) was added to quench the reaction. After adding diethyl ether (100 mL) for liquid separation, the aqueous phase was extracted by ether (3×50 mL). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by flash column chromatography (PE/EA = 5:1) to give 730 mg colorless liquid (R_f = 0.2, PE/EA = 6:1), yield 80 %.

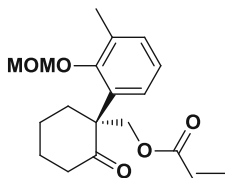
^1H NMR (500 MHz, CDCl_3) δ 7.11–7.10 (m, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H), 4.90 (d, J = 5.6, 1H), 4.84 (d, J = 5.5 Hz, 1H), 4.20 (dd, J = 12.6 Hz, J = 5.0 Hz, 1H), 3.56 (s, 3H), 2.57–2.47 (m, 2H), 2.30 (s, 3H), 2.24–2.17 (m, 2H), 2.03–1.90 (m, 2H), 1.80–1.65 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 210.2, 154.3, 132.4, 130.6, 129.8, 126.8, 124.2, 99.4, 57.1, 50.9, 42.3, 34.8, 27.7, 25.8, 16.9.

**2.2.27**

Synthesis and NMR data of compound 2.2.27:

Under the protection of nitrogen, the compound 2.2.25 (78 mg, 0.2 mmol) was dissolved in pyridine (2 mL) and cooled to 0 °C. HF/pyridine (0.152 mL, 1 mmol) was added, heated to room temperature, and stirred for 7 h. TLC showed that the reaction was completed. The reaction was quenched by adding saturated sodium bicarbonate (1 mL), and the solution was separated by adding diethyl ether (10 mL). The aqueous phase was extracted with ether (3 × 10 mL). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was separated and purified by flash column chromatography (PE/EA = 5:1), to give 49 mg colorless liquid (R_f = 0.3, PE/EA = 4:1), yield 88 %.

^1H NMR (500 MHz, CDCl_3) δ 7.20 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 4.81 (dd, J = 12.9, J = 5.0, 2H), 3.55 (s, 3H), 3.45–3.44 (m, 1H), 3.15 (br, 1H), 2.65–2.55 (m, 1H), 2.55–2.45 (m, 1H), 2.40–2.25 (m, 1H), 2.31 (s, 3H), 2.10–2.01 (m, 1H), 1.85–1.97 (m, 1H), 1.70–1.20 (m, 6H), 0.90–0.90 (m, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 214.9, 154.6, 133.7, 131.7, 131.0, 124.9, 124.6, 99.8, 69.7, 57.5, 57.3, 40.8, 35.1, 29.5, 21.1, 17.5. HRMS-ESI Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 301.1416; found: 301.1414.

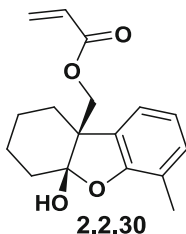
**2.2.29**

Synthesis and NMR data of compound 2.2.29:

Under the protection of nitrogen, the compound 2.2.27 (180 mg, 0.65 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. DCC (402 mg, 1.95 mmol), DMAP (277 mg, 2.27 mmol), and acrylic acid (0.134 mL, 1.95 mmol) were then added, heated to room temperature, and stirred for 24 h. TLC showed that the reaction was completed. Saturated ammonium chloride solution (10 mL) was added to quench the reaction. DCM (10 mL) was added for liquid separation. The aqueous phase was extracted with ether (3 × 10 mL). The

organic phases were combined, washed with saturated brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by flash column chromatography (PE/EA = 10:1), to give 153 mg colorless liquid (R_f = 0.7, PE/EA = 5:1), yield 71 %.

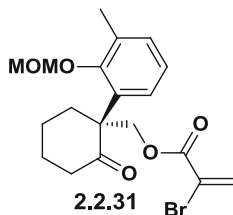
^1H NMR (500 MHz, CDCl_3) δ 7.20 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H), 6.28 (dd, J = 17.3, J = 1.3, 1H), 6.02 (dd, J = 17.3, J = 10.5, 2H), 5.75 (dd, J = 10.3, J = 1.2, 1H), 4.83 (dd, J = 13.2, J = 5.5, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 3.52 (s, 3H), 2.82 (dd, J = 14.3, J = 2.9, 1H), 2.62–2.56 (m, 1H), 2.5–2.31 (m, 1H), 2.34 (s, 3H), 1.96–1.92 (m, 1H), 1.73–1.54 (m, 5H). ^{13}C NMR (125 MHz, CDCl_3) δ 210.6, 165.6, 154.3, 132.7, 131.7, 131.2, 130.4, 128.2, 126.0, 124.0, 99.5, 68.9, 57.2, 55.2, 40.1, 36.5, 29.3, 21.1, 17.4. HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 355.1521; found: 355.1533.



Synthesis and NMR data of compound 2.2.30:

Under the protection of nitrogen, the compound 2.2.29 (120 mg, 0.36 mmol) was dissolved in dichloromethane (20 mL) and cooled to $-78\text{ }^\circ\text{C}$. TMSBr (0.122 mL, 0.9 mmol) was slowly added dropwise under stirring condition. The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 3 h. TLC showed that the reaction was completed. Saturated sodium bicarbonate solution (10 mL) was added to quench the reaction. DCM (10 mL) was added for liquid separation. The aqueous phase was extracted with DCM ($3 \times 20\text{ mL}$). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was isolated and purified by flash column chromatography (PE/EA = 3:1) to give 110 mg colorless liquid (R_f = 0.5, PE/EA = 3:1), yield 96 %.

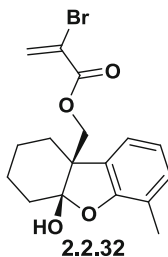
^1H NMR (500 MHz, CDCl_3): δ 7.01 (d, J = 7.4 Hz, 2H), 6.83 (t, J = 7.5 Hz, 1H), 6.39 (d, J = 17.3 Hz, 1H), 6.14 (dd, J = 17.4 Hz, J = 10.4 Hz, 1H), 5.86 (d, J = 10.5 Hz, 1H), 4.51 (s, 2H), 3.52 (s, 1H), 2.23 (s, 3H), 2.19–2.08 (m, 1H), 1.99–1.88 (m, 2H), 1.70–1.62 (m, 1H), 1.61–1.46 (m, 3H), 1.44–1.32 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ 166.1, 155.0, 132.2, 131.1, 130.0, 128.2, 121.0, 120.6, 120.5, 110.1, 66.4, 50.5, 33.9, 32.7, 21.7, 20.5, 15.0; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 311.1259; found: 311.1270.



Synthesis and NMR data of compound 2.2.31:

Under the protection of nitrogen, the compound 2.2.27 (1.39 g, 5.0 mmol) was dissolved in dichloromethane (60 mL) and cooled to 0 °C. Under stirring condition, DCC (3.1 g, 15 mmol), DMAP (1.9 g, 2.27 mmol), and 2-bromo-acrylic acid (2.3 g, 15 mmol) were added, then heated to room temperature, and stirred for 0.5 h. TLC showed that the reaction was completed. Saturated ammonium chloride solution (20 mL) was added to quench the reaction, and dichloromethane was added (100 mL) for liquid separation. The aqueous phase was extracted with ether (3 × 50 mL). The organic phases were combined, washed with saturated brine (40 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by flash column chromatography (PE/EA = 10:1) to give 600 mg colorless liquid (R_f = 0.6, PE/EA = 5:1), yield 29 %.

^1H NMR (500 MHz, CDCl_3) δ 7.27 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 1.5, 1H), 6.17 (d, J = 1.5, 1H), 4.82 (s, 2H), 4.48 (dd, J = 19.1, J = 11.4, 2H), 3.51 (s, 3H), 2.91 (dd, J = 14.2, J = 2.7, 1H), 2.60–2.53 (m, 1H), 2.33–2.29 (m, 1H), 2.33 (s, 3H), 1.95–1.92 (m, 2H), 1.80–1.54 (m, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 210.6, 161.4, 154.3, 132.1, 131.7, 131.4, 130.4, 126.3, 124.0, 121.0, 99.4, 71.2, 57.2, 55.2, 39.9, 36.6, 32.3, 30.4, 29.3, 26.2, 21.1, 17.4. HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{23}\text{O}_5\text{NaBr}$ $[\text{M} + \text{Na}]^+$: 433.0627; found: 433.0626.

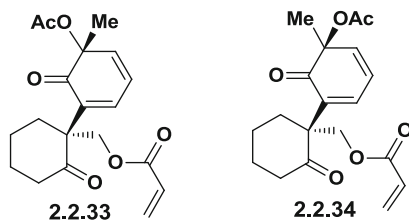


Synthesis and NMR data of compound 2.2.32:

Under the protection of nitrogen, the compound 2.2.31 (600 mg, 1.46 mmol) was dissolved in dichloromethane (50 mL) and cooled to −78 °C. TMSBr (0.491 mL, 3.65 mmol) was slowly added dropwise. The reaction was stirred at −78 °C for 1 h.

TLC showed that the reaction was completed. Saturated sodium bicarbonate solution (10 mL) was added to quench the reaction, and dichloromethane (50 mL) was added for liquid separation. The aqueous phase was extracted with DCM (3×20 mL). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure. The resulting crude product was purified by flash column chromatography (PE/EA = 10:1) to give 480 mg colorless liquid (R_f = 0.5, PE/EA = 5:1), yield 90 %.

^1H NMR (500 MHz, CDCl_3): δ 7.05 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 3.21 (s, 1H), 2.23 (s, 3H), 2.15–2.12 (m, 1H), 2.02–1.55 (m, 8H). ^{13}C NMR (125 MHz, CDCl_3): δ 161.8, 155.0, 132.0, 130.9, 130.0, 121.2, 120.8, 120.7, 120.5, 109.8, 68.6, 50.5, 33.9, 32.8, 32.3, 30.5, 26.2, 24.6, 21.6, 20.3, 15.0. HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{19}\text{O}_4\text{NaBr}$ $[\text{M} + \text{Na}]^+$: 389.0364; found: 389.0354.

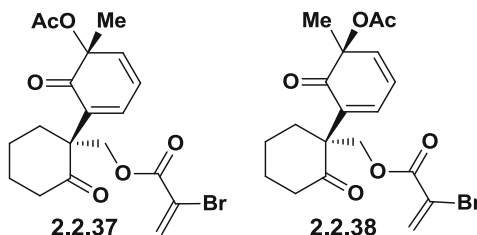


Synthesis and NMR data of compounds 2.2.33 and 2.2.34:

Under the protection of nitrogen, the compound 2.2.31 (2.09 g, 7.3 mmol) was dissolved in AcOH (60 mL), and then, $\text{Pb}(\text{OAc})_4$ (19.3 g, 43.5 mmol) was added at 0 °C. The reaction was stirred for 1 h. TLC showed that the reaction was completed. The solid was filtered off and washed with ethyl acetate (250 mL), and the retained organic phase was washed with saturated sodium bicarbonate (3×100 mL). The water phase was extracted with ethyl acetate (3×50 mL), and the combined organic phase was dried over anhydrous sodium sulfate. After filtration, the solvent was removed by rotary evaporator under reduced pressure, and the resulting crude product was isolated and purified by flash column chromatography (PE/EA = 5:1) to give 2.2.33 (1.53 g) and 2.2.34 (792 mg) as white solid, total yield rate of 92 %.

Compound 2.2.33, white solid (R_f = 0.68, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 7.00 (m, 1H), 6.39–6.26 (m, 3H), 6.08 (dd, J = 17.4 Hz, J = 10.5 Hz, 1H), 5.79 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.23 (d, J = 11.3 Hz, 1H), 2.52–2.45 (m, 1H), 2.38–2.29 (m, 1H), 2.26–2.15 (m, 1H), 2.08–1.95 (m, 5H), 1.80–1.65 (m, 5H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 209.4, 197.6, 169.2, 165.7, 142.3, 138.8, 135.9, 130.5, 128.5, 121.3, 79.0, 67.0, 54.8, 40.4, 34.9, 28.5, 23.9, 21.1, 20.2; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 369.1314; found: 369.1315.

Compound 2.2.34, white solid ($R_f = 0.79$, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 6.93 (m, 1H), 6.35–6.28 (m, 2H), 6.26 (d, $J = 9.45$ Hz, 1H), 6.05 (dd, $J = 17.3$ Hz, $J = 10.5$ Hz, 1H), 5.81 (d, $J = 10.4$ Hz, 1H), 4.59 (d, $J = 11.5$ Hz, 1H), 4.23 (d, $J = 11.5$ Hz, 1H), 2.49–2.35 (m, 2H), 2.30–2.24 (m, 1H), 2.12–1.98 (m, 5H), 1.97–1.89 (m, 1H), 1.78–1.51 (m, 6H), 1.41–1.28 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 209.9, 197.4, 169.7, 165.6, 141.4, 137.6, 136.4, 130.8, 128.3, 121.5, 79.4, 67.0, 54.3, 40.4, 35.2, 28.2, 23.6, 21.0, 20.4; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 369.1314; found: 369.1316.

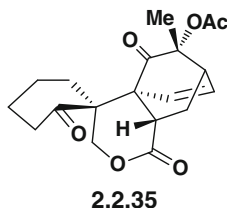


Synthesis and NMR data of compounds 2.2.37 and 2.2.38:

Under the protection of nitrogen, the compound 2.2.30 (500 mg, 1.36 mmol) was dissolved in AcOH (10 mL), and then, $\text{Pb}(\text{OAc})_4$ (3.1 g, 6.8 mmol) was added at 0 °C. The reaction was stirred for 1 h at 0 °C. TLC showed that the reaction was completed. Ethylene glycol (5 mL) was added to quench the reaction. The solid was filtered off and washed with ethyl acetate (100 mL). The organic phase was reserved and washed with saturated sodium bicarbonate (3×50 mL). The water phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate. After filtration, the solvent was removed by a rotary evaporator, and the resulting crude product was isolated and purified by flash column chromatography (PE/EA = 5:1) to give 2.2.37 (275 mg) and 2.2.38 (135 mg) as white solid, total yield 92 %.

Compound 2.2.37, white solid ($R_f = 0.20$, PE/EA = 3:1); ^1H NMR (500 MHz, CDCl_3): δ 7.10 (d, $J = 5.9$ Hz, 1H), 6.91 (s, 1H), 6.38–6.30 (m, 2H), 6.19 (s, 1H), 4.52 (d, $J = 11.3$ Hz, 1H), 4.27 (d, $J = 11.3$ Hz, 1H), 2.62 (d, $J = 10.0$ Hz, 1H), 2.34 (d, $J = 12.3$ Hz, 1H), 2.23–2.17 (m, 1H), 2.02 (s, 4H), 1.80–1.60 (m, 4H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 209.4, 197.6, 169.1, 161.3, 142.3, 139.4, 134.8, 130.6, 121.3, 121.0, 78.7, 69.2, 54.6, 40.4, 35.2, 28.8, 23.8, 20.9, 20.1. HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_6\text{NaBr}$ $[\text{M} + \text{Na}]^+$: 447.0419; found: 447.0396.

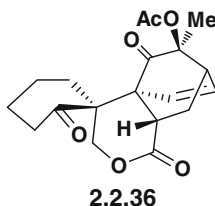
Compound 2.2.38, white solid ($R_f = 0.30$, PE/EA = 3:1); ^1H NMR (500 MHz, CDCl_3): δ 7.00 (d, $J = 5.4$ Hz, 1H), 6.89 (s, 1H), 6.36–6.33 (m, 1H), 6.26–6.22 (m, 2H), 4.59 (d, $J = 11.3$ Hz, 1H), 4.35 (d, $J = 11.3$ Hz, 1H), 2.56 (d, $J = 11.7$ Hz, 1H), 2.42 (d, $J = 12.8$ Hz, 1H), 2.28–2.26 (m, 1H), 2.06 (s, 4H), 1.80–1.60 (m, 5H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 209.8, 197.4, 169.7, 161.4, 141.6, 138.4, 135.2, 130.8, 121.4, 120.8, 79.2, 69.2, 54.2, 40.3, 35.3, 28.6, 23.5, 20.8, 20.3. HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_6\text{NaBr}$ $[\text{M} + \text{Na}]^+$: 447.0419; found: 447.0412.



Synthesis and NMR data of compound 2.2.35:

Under the protection of nitrogen, compound 2.2.33 (128 mg, 0.370 mmol) was dissolved in toluene (40 mL) in a sealed tube, and then, the reaction was heated to 130 °C and stirred for 24 h. TLC showed that the reaction was completed. The reaction was cooled to room temperature, the solvent was removed by rotary evaporator, and the resulting crude product was purified by flash column chromatography (PE/EA = 5:1) and obtained 113 mg white solid (R_f = 0.71, PE/EA = 1:1), yield 88 %.

^1H NMR (500 MHz, CDCl_3): δ 6.70–6.62 (m, 1H), 6.03 (d, J = 8.4 Hz, 1H), 4.68 (d, J = 12.4 Hz, 1H), 4.35 (dd, J = 9.8 Hz, J = 6.6 Hz, 1H), 4.26 (d, J = 12.4 Hz, 1H), 3.89 (m, 1H), 2.69–2.52 (m, 2H), 2.28–2.18 (m, 2H), 2.16–2.02 (m, 4H), 2.00–1.85 (m, 4H), 1.72–1.59 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 209.4, 199.3, 172.2, 169.9, 140.5, 124.5, 79.0, 71.7, 56.3, 47.4, 39.8, 39.7, 38.1, 31.5, 26.2, 24.7, 21.8, 21.4, 21.0; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 369.1314; found: 369.1320.

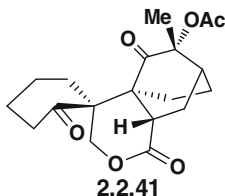


Synthesis and NMR data of compound 2.2.36:

Under the protection of nitrogen, the compound 2.2.34 (243 mg, 0.702 mmol) was dissolved in toluene (20 mL) in a sealed tube, and then, the reaction was heated to 130 °C and stirred for 24 h. TLC showed that the reaction was completed. The reaction was cooled to room temperature, the solvent was removed by rotary evaporator, and the resulting crude product was purified by flash column chromatography (PE/EA = 5:1) and obtained 200 mg white solid (R_f = 0.71, PE/EA = 1:1) in 82 % yield.

^1H NMR (500 MHz, CDCl_3): δ 6.56 (t, J = 8.2 Hz, J = 6.8 Hz, 1H), 6.02 (d, J = 8.2 Hz, 1H), 4.61 (d, J = 12.5 Hz, 1H), 4.25 (d, J = 12.4 Hz, 1H), 4.13–4.01 (m, 1H), 4.10 (dd, J = 3.1 Hz, J = 1.6 Hz, 1H), 4.61–4.46 (m, 2H),

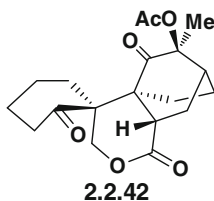
2.34–2.15 (m, 3H), 2.06–1.78 (m, 11H), 1.48–1.69 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 210.0, 201.2, 171.9, 169.5, 139.3, 123.7, 79.1, 71.8, 56.9, 47.4, 39.7, 38.3, 37.2, 31.4, 26.7, 24.5, 21.7, 21.2, 20.1; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 369.1314; found: 369.1318.



Synthesis and NMR data of compound 2.2.41:

Pd/C catalyst (13 mg) was added in methanol (5 mL), and then, the compound 2.2.35 (80 mg, 0.231 mmol) dissolved in methanol (5 mL) was added at room temperature. The reaction was stirred for 10 min at room temperature in the H_2 atmosphere. TLC showed that the reaction was completed. The reaction solution was filtered by silica gel and washed with ethyl acetate (20 mL). The solvent was removed by rotary evaporator, and the resulting crude product was purified by flash column chromatography (PE/EA = 5:1) to give 74 mg white solid (R_f = 0.71, PE/EA = 2:1), yield 92 %.

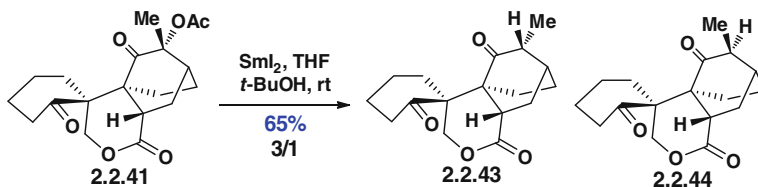
^1H NMR (300 MHz, CDCl_3): δ 4.61 (d, J = 12.6 Hz, 1H), 4.27–4.15 (m, 2H), 2.97 (s, 1H), 2.70–2.51 (m, 2H), 2.39–2.13 (m, 3H), 2.10 (s, 3H), 2.09–1.98 (m, 3H), 1.98–1.20 (m, 7H) 1.71–1.62 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 210.4, 206.2, 173.4, 169.8, 83.2, 71.3, 49.9, 49.0, 39.6, 37.8, 34.0, 31.5, 24.7, 24.1, 22.3, 21.8, 21.2, 17.5; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_6$ $[\text{M} + \text{Na}]^+$: 371.1471; found: 371.1460.



Synthesis and NMR data of compound 2.2.42:

Pd/C catalyst (13 mg) was added to methanol (13 mL), and then, compounds 2.2.36 (120 mg, 0.346 mmol) in methanol (5 mL) was added at room temperature. The reaction was stirred for 10 min at room temperature in the H_2 atmosphere. TLC showed that the reaction was completed. The reaction solution was filtered by silica gel and washed with ethyl acetate (20 mL). The solvent was removed by rotary evaporator, and the resulting crude product was purified by flash column chromatography (PE/EA = 5:1) to give 109 mg white solid (R_f = 0.75, PE/EA = 2:1), yield 90 %.

^1H NMR (300 MHz, CDCl_3): δ 4.59 (d, $J = 12.5$ Hz, 1H), 4.26 (d, $J = 12.6$ Hz, 1H), 4.19–4.17 (m, 1H), 3.00–2.90 (m, 1H), 2.61–2.58 (m, 1H), 2.52–2.40 (m, 1H), 2.33–2.19 (m, 2H), 2.08–2.02 (m, 3H), 2.02–1.91 (m, 3H), 1.89–1.84 (m, 1H), 1.81–1.70 (m, 2H), 1.68–1.55 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 210.4, 206.2, 173.4, 169.8, 83.3, 71.3, 49.9, 48.9, 39.6, 37.8, 34.0, 31.5, 24.7, 24.1, 22.3, 21.8, 21.2, 17.5; HRMS-ESI Calcd for $\text{C}_{19}\text{H}_{25}\text{O}_6$ $[\text{M} + \text{H}]^+$: 349.1651; found: 349.1661.

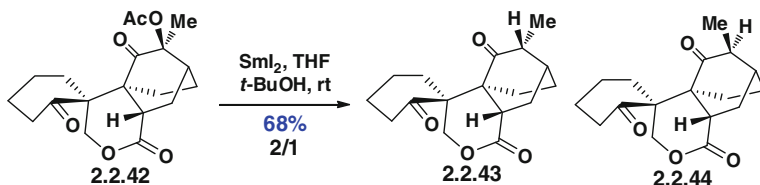


Synthesis and NMR data of compounds 2.2.43 and 2.2.44 (synthesis from compound 2.2.41):

Under the protection of nitrogen, the compound 2.2.41 (25 mg, 0.072 mmol) was dissolved in THF (2 mL), and tert-butanol (13 μL , 0.14 mmol) and SmI_2 (0.1 M in THF, 1.4 mL, 0.14 mmol) were added at room temperature. The reaction was stirred at room temperature for 10 min. TLC showed that the reaction was completed. The reaction was quenched with saturated NH_4Cl (5 mL). Dichloromethane (10 mL) was added for liquid separation, and the water phase was extracted with dichloromethane (10 mL). The combined organic phase was dried over Na_2SO_4 , the solvent was removed by rotary evaporator, and the residue was purified by flash column chromatography (PE/EA = 5:1). Compounds 2.2.43 (10.5 mg) and 2.2.44 (3.5 mg) were obtained in 65 % overall yield.

Compound 2.2.43, white solid ($R_f = 0.81$, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.52 (d, $J = 12.5$ Hz, 1H), 4.22 (d, $J = 12.5$ Hz, 1H), 3.98–3.95 (m, 1H), 2.60–2.57 (m, 1H), 2.50–2.39 (m, 3H), 2.30–2.21 (m, 2H), 2.00–1.81 (m, 3H), 1.79–1.57 (m, 6H), 1.14 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 215.0, 211.4, 174.1, 71.5, 50.7, 49.7, 47.0, 39.8, 38.2, 33.3, 31.5, 28.8, 24.6, 24.1, 21.2, 20.8, 12.7. HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1410.

Compound 2.2.44, white solid ($R_f = 0.79$, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.50 (d, $J = 12.5$ Hz, 1H), 4.22 (d, $J = 12.5$ Hz, 1H), 4.08–4.04 (m, 1H), 2.68–2.63 (m, 1H), 2.49–2.31 (m, 2H), 2.32–2.11 (m, 5H), 2.05–1.65 (m, 8H), 1.22 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 213.8, 211.4, 173.7, 71.9, 51.6, 48.2, 47.3, 39.9, 38.0, 31.8, 31.5, 26.0, 24.1, 22.6, 22.3, 21.1, 14.4; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1422.

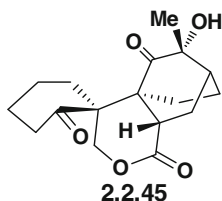


Synthesis and NMR data of compounds 2.2.43 and 2.2.44 (synthesis from compound 2.2.42):

Under the protection of nitrogen, the compound 2.2.42 (30 mg, 0.086 mmol) was dissolved in THF (2 mL), and tert-butanol (25 μ L, 0.26 mmol) and SmI_2 (0.1 M in THF, 2.6 mL, 0.26 mmol) were added at room temperature. The reaction was stirred at room temperature for 10 min. TLC showed that the reaction was completed. The reaction was quenched with saturated NH_4Cl (5 mL). Dichloromethane (10 mL) was added for liquid separation, and the water phase was extracted with dichloromethane (10 mL). The combined organic phase was dried over Na_2SO_4 , the solvent was removed by rotary evaporator, and the residue was purified by flash column chromatography (PE/EA = 5:1); compounds 2.2.43 (11.3 mg) and 2.2.44 (5.7 mg) were obtained in 68 % overall yield.

Compound 2.2.43, white solid (R_f = 0.81, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.52 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 12.5 Hz, 1H), 3.98–3.95 (m, 1H), 2.60–2.57 (m, 1H), 2.50–2.39 (m, 3H), 2.30–2.21 (m, 2H), 2.00–1.81 (m, 3H), 1.79–1.57 (m, 6H), 1.14 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 215.0, 211.4, 174.1, 71.5, 50.7, 49.7, 47.0, 39.8, 38.2 33.3, 31.5, 28.8, 24.6, 24.1, 21.2, 20.8, 12.7. HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1410.

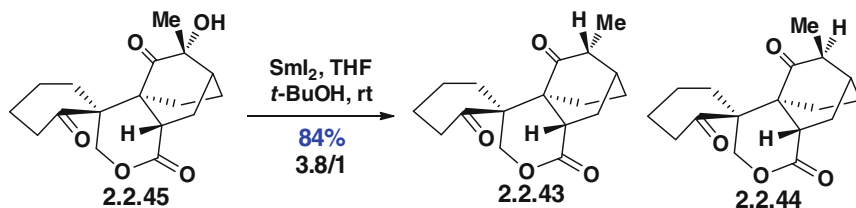
Compound 2.2.44, white solid (R_f = 0.79, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.50 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 12.5 Hz, 1H), 4.08–4.04 (m, 1H), 2.68–2.63 (m, 1H), 2.49–2.31 (m, 2H), 2.32–2.11 (m, 5H), 2.05–1.65 (m, 8H), 1.22 (d, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 213.8, 211.4, 173.7, 71.9, 51.6, 48.2, 47.3, 39.9, 38.0 31.8, 31.5, 26.0, 24.1, 22.6, 22.3, 21.1, 14.4; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1422.



Synthesis and NMR data of compound 2.2.45:

Under the protection of nitrogen, the compound 2.2.41 (81 mg, 0.233 mmol) was dissolved in methanol (5 mL), and then, potassium carbonate (32 mg, 0.233 mmol) in methanol (5 mL) solution was added at room temperature. After 5 min at room temperature, TLC showed that the reaction was completed. The solution was filtered by silica gel and washed with ethyl acetate (20 mL). The solvent was removed by rotary evaporator, and the resulting crude product was purified by flash column chromatography (PE/EA = 5:1) to give 68 mg white solid (R_f = 0, PE/EA = 1:1), yield 95 %.

^1H NMR (300 MHz, CDCl_3): ^1H NMR (500 MHz, CDCl_3): δ 4.62 (d, J = 12.6 Hz, 1H), 4.26 (d, J = 12.6 Hz, 1H), 3.93–3.84 (m, 1H), 2.79 (s, 1H), 2.58–2.41 (m, 3H), 2.39–2.28 (m, 1H), 2.18–2.11 (m, 1H), 2.10–2.02 (m, 3H), 1.95–1.55 (m, 8H), 1.44 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 216.6, 210.8, 173.4, 76.5, 71.4, 50.2, 49.8, 39.6, 37.6, 37.2, 31.7, 25.3, 25.2, 24.6, 23.7, 21.2, 20.6; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 329.1365; found: 329.1351.



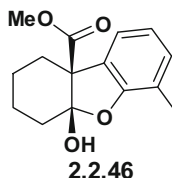
Synthesis and NMR data of compounds 2.2.43 and 2.2.44 (synthesis from compounds 2.2.45):

Under the protection of nitrogen, the compound 2.2.45 (60 mg, 0.196 mmol) was dissolved in THF (2 mL), and then, *tert*-butanol (37 μL , 0.39 mmol) and SmI_2 (0.1 M in THF, 3.9 mL, 0.39 mmol) were added at room temperature. The reaction was stirred at room temperature for 5 min. TLC showed that the reaction was completed. The reaction was quenched with saturated NH_4Cl (5 mL). Dichloromethane (10 mL) was added for liquid separation, and the water phase was extracted with dichloromethane (10 mL). The combined organic phase was dried over Na_2SO_4 , the solvent was removed by rotary evaporator, and the residue was purified by flash column chromatography (PE/EA = 5:1). Compounds 2.2.43 (38 mg) and 2.2.44 (10 mg) were obtained in 84 % overall yield.

Compound 2.2.43, white solid (R_f = 0.81, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.52 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 12.5 Hz, 1H), 3.98–3.95 (m, 1H), 2.60–2.57 (m, 1H), 2.50–2.39 (m, 3H), 2.30–2.21 (m, 2H), 2.00–1.81 (m, 3H), 1.79–1.57 (m, 6H), 1.14 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 215.0, 211.4, 174.1, 71.5, 50.7, 49.7, 47.0, 39.8, 38.2, 33.3, 31.5, 28.8, 24.6, 24.1, 21.2, 20.8, 12.7. HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1410.

Compound 2.2.44, white solid (R_f = 0.79, PE/EA = 1:1); ^1H NMR (500 MHz, CDCl_3): δ 4.50 (d, J = 12.5 Hz, 1H), 4.22 (d, J = 12.5 Hz, 1H), 4.08–4.04 (m,

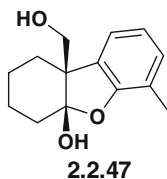
1H), 2.68–2.63 (m, 1H), 2.49–2.31 (m, 2H), 2.32–2.11 (m, 5H), 2.05–1.65 (m, 8H), 1.22 (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 213.8, 211.4, 173.7, 71.9, 51.6, 48.2, 47.3, 39.9, 38.0 31.8, 31.5, 26.0, 24.1, 22.6, 22.3, 21.1, 14.4; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 313.1416; found: 313.1422.



Synthesis and NMR data of compound 2.2.46:

Under the protection of nitrogen, the boric acid compound (10.6 g, 53.8 mmol) was dissolved in chloroform (100 mL), and then, lead tetraacetate (26.3 g, 59.1 mmol) and mercuric acetate (3.4 g, 10.8 mmol) were added at 40 °C. The reaction was heated to 60 °C and stirred for 2 h. Compound 2.2.11 (8.4 g, 53.8 mmol) dissolved in pyridine (30 mL) was added under constant stirring at 60 °C for 1 h. The reaction was stirred overnight. The TLC showed that the reaction was completed. The solid was removed by filtration and washed with chloroform (100 mL). Dilute sulfuric acid (3 N, 500 mL) was added to quench the reaction. After liquid separation, the aqueous phase was extracted with chloroform (2×150 mL). The organic phases were combined. The solvent was removed under reduced pressure, and the residue was dissolved in ether (200 mL). Diluted sodium hydroxide solution (3 N, 250 mL) was added at 0 °C, then washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure, and the resulting crude product was purified by flash column chromatography (PE/EA = 10:1) to obtain 9.9 g colorless liquid ($R_f = 0.6$, PE/EA = 5:1), yield 70 %.

^1H NMR (500 MHz, CDCl_3): δ 7.13 (d, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 7.5$ Hz, 1H), 6.85 (t, $J = 7.5$ Hz, 1H), 5.28 (s, 1H), 3.75 (s, 3H), 2.23 (s, 3H), 2.19–2.14 (m, 1H), 2.07–1.99 (m, 2H), 1.89–1.83 (m, 1H), 1.69–1.63 (m, 2H), 1.61–1.53 (m, 1H), 1.35–1.45 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 174.1, 155.3, 130.4, 129.5, 122.0, 121.0, 109.6, 57.2, 52.4, 33.6, 21.6, 20.8, 15.0; HRMS-ESI Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 285.1103; found: 285.1100.



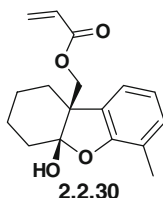
Synthesis and NMR data of compound 2.2.47:

Under the protection of nitrogen, the compound **2.2.46** (9.01 g, 34.4 mmol) was dissolved in dichloromethane (100 mL), and then, imidazole (3.51 g, 51.5 mmol) and TMSCl (5.2 mL, 41.3 mmol) were added at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. TLC showed that the reaction was completed, and saturated ammonium chloride solution (40 mL) was slowly added. After liquid separation, the aqueous phase was extracted with ethyl acetate (3 × 60 mL). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure, and the resulting crude product was isolated and purified by flash column chromatography (PE/EA = 30:1) to give TMS-protected product as 10.57 g colorless liquid (R_f = 0.8, PE/EA = 10:1), yield 92 %.

^1H NMR (500 MHz, CDCl_3): δ 7.19 (d, J = 7.4 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 3.74 (s, 3H), 2.36–2.26 (m, 5H), 2.14–2.07 (m, 1H), 1.77–1.75 (m, 2H), 1.50–1.48 (m, 1H), 1.39–1.30 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 172.3, 155.2, 131.7, 129.3, 122.7, 121.0, 119.8, 109.5, 60.6, 51.4, 36.1, 33.6, 21.3, 19.5, 15.1, 1.2; HRMS-ESI Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4\text{Si}$ [$\text{M} + \text{Na}$] $^+$: 357.1498; found: 357.1513.

Under the protection of nitrogen, the TMS-protected product (6.78 g, 20.3 mmol) was dissolved in dichloromethane (100 mL), and DIBAL (44, 0.7 mL, 44.7 mmol) was added at –78 °C under stirring over 5 min and then stirred for 2 h. Saturated sodium potassium tartrate solution (100 mL) was slowly added to quench the reaction. The aqueous phase was extracted with ether (3 × 100 mL). The solvent was removed by rotary evaporator under reduced pressure, and diethyl ether (100 mL) was added to dissolve the residue. Hydrochloric acid solution (3 N, 70 mL) was added to dilute the mixture. The aqueous phase was extracted with ether (3 × 60 mL). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporator under reduced pressure, and the resulting crude product was separated and purified by flash column chromatography (PE/EA = 10:1), to give 4.39 g colorless liquid (R_f = 0.4, PE/EA = 3:1), yield 93 %.

^1H NMR (300 MHz, CDCl_3): δ 7.01 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 6.3 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 5.17 (s, 1H), 3.92–3.778 (m, 2H), 2.70 (dd, J = 6.9 Hz, J = 5.4 Hz, 1H), 2.23 (s, 3H), 2.00–1.81 (m, 3H), 1.58–1.41 (m, 4H), 1.35–1.19 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 155.8, 130.5, 130.1, 120.8, 120.4, 120.1, 112.5, 66.6, 51.5, 33.6, 30.3, 20.2, 19.5, 15.2; HRMS-ESI Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 257.1154; found: 257.1155.



Synthesis and NMR data of compound **2.2.30**:

Under the protection of nitrogen, compound **2.2.47** (3.23 g, 13.8 mmol) was dissolved in dichloromethane (60 mL) at 0 °C, then DMAP (2.02 g, 16.6 mmol) and EDCI (3.18 g, 16.6 mmol) were added, and then, acrylic acid (1.4 mL, 20.7 mmol) was added. The reaction was then allowed to warm to room temperature and stirred for 24 h. TLC showed that the reaction was completed. The reaction was quenched with saturated NH_4Cl (30 mL) and then extracted with EtOAc (3×40 mL). The organic phases were combined and dried with anhydrous Na_2SO_4 . The organic phase was removed by rotary evaporator, and the resulting crude product was isolated and purified by flash column chromatography (PE/EA = 15:1) to give 2.80 g colorless liquid (R_f = 0.65, PE/EA = 5:1), yield 70 %.

^1H NMR (500 MHz, CDCl_3): δ 7.01 (d, J = 7.4 Hz, 2H), 6.83 (t, J = 7.5 Hz, 1H), 6.39 (d, J = 17.3 Hz, 1H), 6.14 (dd, J = 17.4 Hz, J = 10.4 Hz, 1H), 5.86 (d, J = 10.5 Hz, 1H), 4.51 (s, 2H), 3.52 (s, 1H), 2.23 (s, 3H), 2.19–2.08 (m, 1H), 1.99–1.88 (m, 2H), 1.70–1.62 (m, 1H), 1.61–1.46 (m, 3H), 1.44–1.32 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 166.1, 155.0, 132.2, 131.1, 130.0, 128.2, 121.0, 120.6, 120.5, 110.1, 66.4, 50.5, 33.9, 32.7, 21.7, 20.5, 15.0; HRMS-ESI Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 311.1259; found: 311.1270.

2.4 Summary

In this chapter, we completed the model study of Maoecrystal V. The synthesis route is shown briefly in Fig. 2.30.

Model study constructed four rings of the pentacyclic system of natural products Maoecrystal V (Fig. 2.31) and laid the foundation for the future total synthesis work. The major progresses made in our model study are as follows:

1. We developed the synthesis strategy for a convergence model and successfully synthesized the core structure of natural product Maoecrystal V.
2. Arylation of organolead reagents to 1,3-keto ester, oxidative dearomatization reaction, and intramolecular Diels–Alder reaction were applied as the key reactions to successfully construct the tetracyclic structure of natural product Maoecrystal V and two consecutive quaternary carbons.
3. The model study is highly efficient, and the route is short with only 8 steps in total. The total yield is 20 %.
4. Compared the structure of the model compound **2.2.43** with the natural product, we found the most significant difference between them was the tetrahydrofuran oxa-bridge. Therefore, stereoselectively construction of tetrahydrofuran oxa-bridge structure would be the most difficult problem in later total synthesis study.

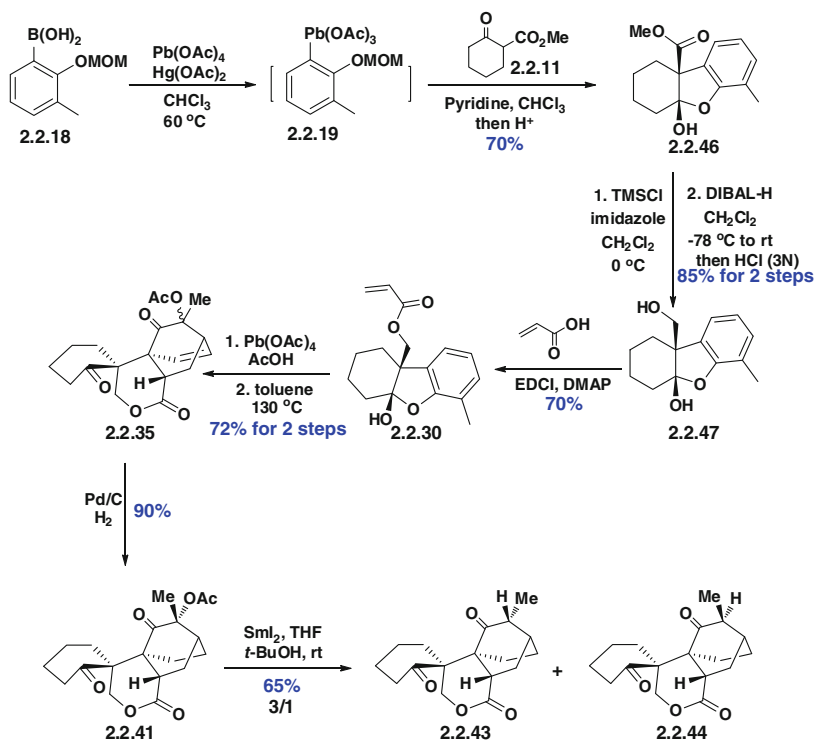
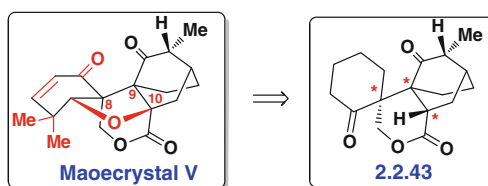


Fig. 2.30 The final synthesis route of model study

Fig. 2.31 The construction of model synthesis system



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Gong, J.

2014, XII, 137 p. 177 illus., 1 illus. in color., Hardcover

ISBN: 978-3-642-54303-6