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Aurélien Brion, Luc Neuville and Géraldine Masson

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Review article

# Stereoselective strategies to access spirotetronate natural products

Aurélien Brion<sup>✉, a</sup>, Luc Neuville<sup>✉, a, b</sup> and Géraldine Masson<sup>✉, \*, a, b</sup>

<sup>a</sup> Institut de Chimie des Substances Naturelles (ICSN), CNRS UPR 2301, Université Paris-Saclay, 1 Avenue de la Terrasse, Gif-sur-Yvette Cedex 91198, France

<sup>b</sup> HitCat, Seqens-CNRS Joint Laboratory, Seqens'Lab, 8 Rue de Rouen, Porcheville 78440, France

E-mail: geraldine.masson@cnrs.fr (G. Masson)

**Abstract.** Spirotetronates constitute a large family of natural products that have attracted significant attention due to their intriguing structures and broad biological activities. These compounds share a common spirocyclic 4-hydroxy-1-oxaspiro[4.5]deca-3,7-dien-2-one unit, whose synthesis has been actively pursued by chemists. In this review, we highlight various approaches to accessing diversely substituted spirotetronates, including methods that enable the total synthesis of selected natural targets. The Diels–Alder/Dieckmann route originally reported has been extensively developed and encompasses various diastereoselective processes. Although enantioselective transformations have been reported, they remain scarce. Additionally, although less explored, alkylation of ketones has been employed for the synthesis of alkoxyfuran-2(5*H*)-one scaffolds, and selected ring-forming strategies have been investigated to construct pre-functionalized cyclohexyl backbones.

**Keywords.** Spirotetronates, Diels–Alder reaction, Stereoselective synthesis, Total synthesis.

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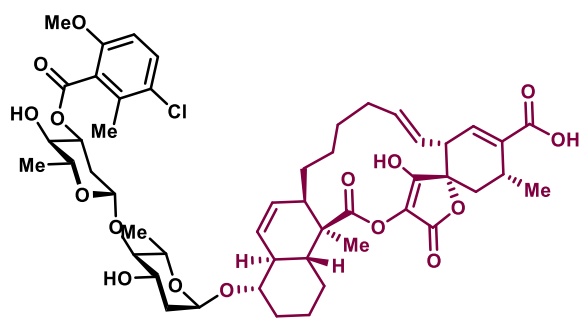
## 1. Introduction

Spirotetronates are a remarkable class of macrocyclic natural products isolated predominantly from *actinomycetes*, a phylum of gram-positive bacteria. Since the discovery of chlorothricin in 1969, the first isolated spirotetronate [1] (Figure 1), numerous related compounds have been structurally characterized [2,3] such as spirohexenolide A and B [4], abyssomicin C [5], quartromicins [6], versipelostatins [7], streptaspirotonates A–C [8], glenthmycins A–M [9], and others [10–20]. These compounds have attracted substantial interest due to their diverse and potent biological activities, including antibacterial, antiviral, and antitumoral properties. Their fascinating structures and significant pharmacological

potential have made spirotetronates central to ongoing synthetic and pharmaceutical research.

Structurally, spirotetronates feature a characteristic tetronic acid (4-hydroxy-[5*H*]furan-2-one) moiety that is spiro-linked to a cyclohexene ring at the C-4 position, a distinctive motif within this family (Figure 1). The spirotetronate core consists of a five-membered lactone ring with a high degree of oxidation and unsaturation. This structural unit is typically substituted at the C-2 position by an acyl group or, in rare cases, by an acyloxy chain, such as in chlorothricolide (Figure 1). Adjacent to the spiro-linkage at the C-5 position of the cyclohexene ring is another stereocenter, which can lead to two diastereoisomeric arrangements: the *endo* configuration, where the higher alkyl chain is *cis* relative to C-3 of the spirotetronate (highlighted in blue), and the *exo* configuration, where these groups are *trans* (highlighted in red). Both diastereomers have been

\*Corresponding author



1, Chlorothricin  
2, Chlorothricolide (in purple)

**Figure 1.** Structure of chlorothricin and its aglycon chlorothricolide.

observed in spirotetronates, posing a key synthetic challenge in achieving diastereoselective access to the desired configuration (Figure 2A).

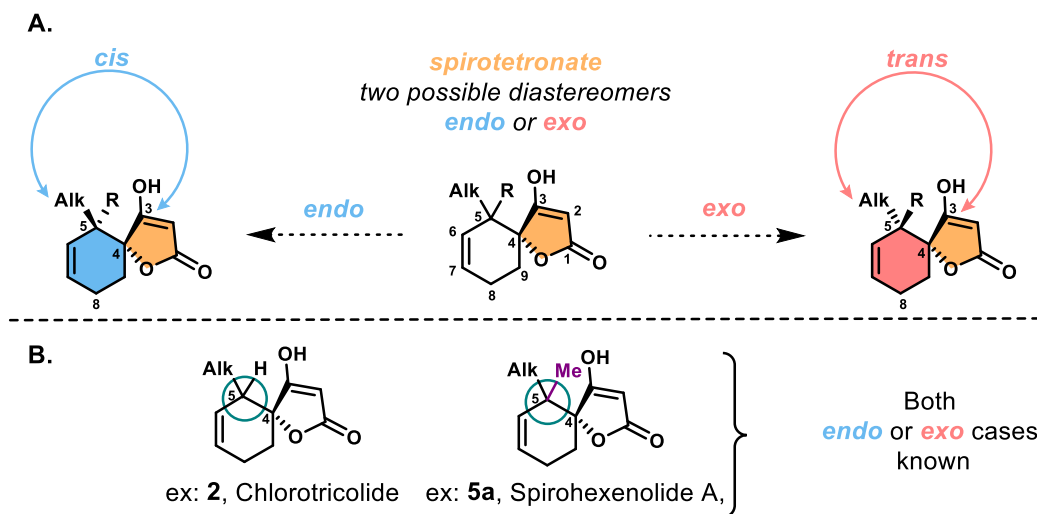
This stereocenter at the C-5 position of the cyclohexene ring can be quaternary, which is a significant structural feature in some spirotetronates (Figure 2B). In these cases, a methyl group replaces a hydrogen, as seen in compounds such as in spirohexenolides **5a** and **5b**, maklamicin **6**, and quartromicins **9–14**. This modification dramatically increases the complexity of the synthesis by introducing steric hindrance in the form of adjacent quaternary stereocenters. The presence of these bulky neopentyl carbons restricts functionalization and adds strain to the cyclohexene ring, making these molecules even more challenging targets for synthetic chemists.

In addition to the tetronic acid core and the stereocenters at C-5, spirotetronates exhibit diverse modifications at the C-7 and C-8 positions of the cyclohexene ring. These substituents vary from simple methyl groups, as seen in okilactomycin **4** or spirohexenolides **5a–b**, to more complex, oxidized alkyl chains in compounds like maklamicin **6** and chlorothricolide **2** (Figure 3). The oxidation state and size of these side chains contribute to the structural diversity of spirotetronates and influence their biological activities. In some cases, such as abyssomicin C (compound **3**), the cyclohexene ring is further oxidized to form vicinal diols.

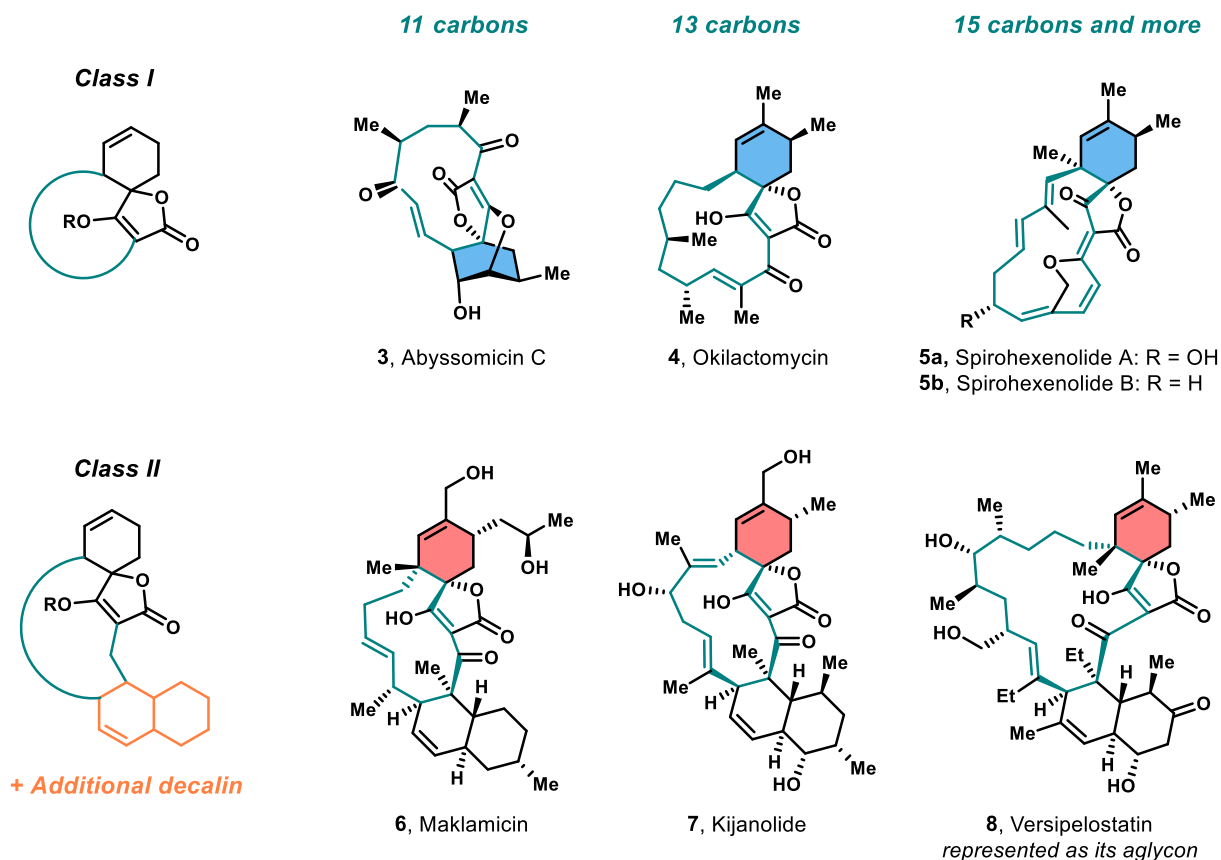
A key feature of spirotetronates is their macrocyclic structure, which links the tetronic acid to the cyclohexene ring (C2–C5). The size and substitution of the macrocycle vary, resulting in three subclasses: small spirotetronates with 11-carbon macrocycles, medium-sized with 13 carbons, and larger structures with 15 carbons or more. These macrocycles can range from simple structures to those bearing conjugated alkenes, alcohols, or ketones. Additionally, some members of the spirotetronate family contain a *trans*-decalin ring system within the macrocycle, further increasing structural complexity (Figure 3). Based on these features, spirotetronates are divided into two main classes: Class I, containing a single spirotetronate moiety in the macrocycle, and Class II, which incorporates a decalin ring system in addition to the spirotetronate.

Perhaps one of the most intriguing subclasses within the spirotetronates is the quartromicin family, which lies outside of the conventional Class I and Class II designations. Unlike the typical members of the spirotetronate family, quartromicins (first isolated in 1991 from a strain of *Amycolatopsis orientalis*) [6,21] contain four spirotetronate units within their scaffold (Figure 4). These compounds exhibit strong metal-ion-binding affinity and are a 32-carbon macrocycle, which contributes to their highly symmetrical C<sub>2</sub> axial structure.

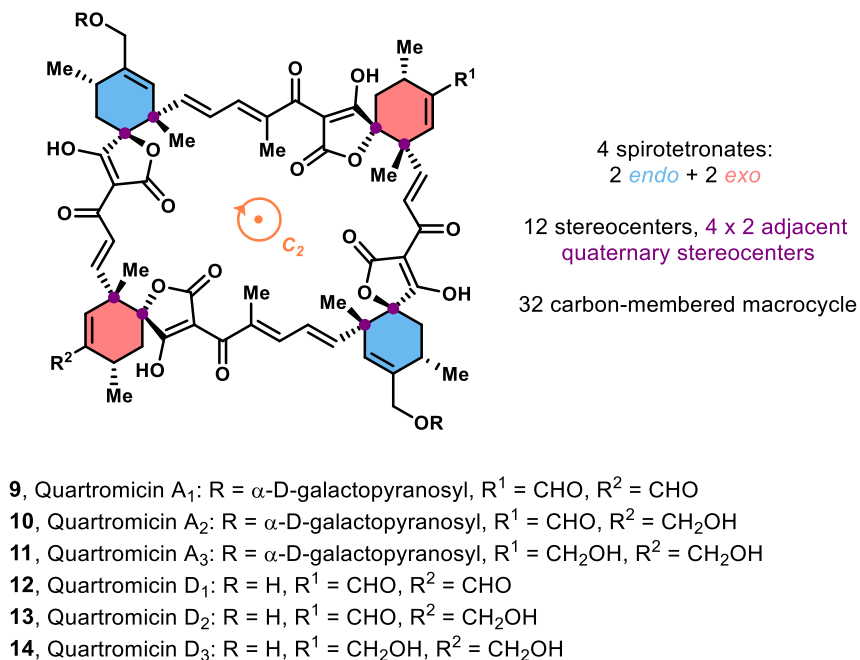
Spirotetronates, with their fascinating structures, have captured significant interest due to their diverse biological activities [2,3,22]. For example, chlorothricin **1** inhibits pyruvate carboxylase, an enzyme crucial for bacterial metabolism, making it an effective antibacterial agent against gram-positive bacteria [23]. The abyssomicin family, known for inhibiting the growth of *Mycobacterium tuberculosis* and *Staphylococcus aureus*, has also been extensively studied [24]. Abyssomicin C specifically targets the chorismate pathway, which is vital for the production of aromatic amino acids in microorganisms [25]. This compound works by acting as a double Michael acceptor, irreversibly modifying a cysteine residue in an enzyme involved in this pathway, showcasing the importance of its enone group and strained macrocyclic structure. In contrast, quartromicins are recognized for their potent antiviral effects, including against HIV and HSV-1 [21,26]. Although their exact mechanisms are still under investigation, their interactions with metal ions and their



**Figure 2.** (A) Structure of the two different diastereomers. (B) Spirotetrone derivatives harnessing a quaternary stereocenter at C<sub>5</sub>.



**Figure 3.** Diverse structures of Class I and Class II spirotetrone derivatives.



**Figure 4.** General structure of quartromicins and their structural characteristics.

complex macrocyclic structures suggest they might employ novel modes of action.

The intricate structures and significant biological activities of spirotetronates have fascinated synthetic chemists for decades. Previous reviews have covered their biological activities, biosynthesis, and total syntheses in detail, often focusing on the macrocycle and decalin components [2,3,22,27,28]. However, they often overlook the construction of the spirotetronate core—a crucial element with significant stereoselective challenges. The synthesis of this spiro-linked tetrone acid, in particular, remains complex, requiring precise stereocontrol and functionalization. This review aims to explore the methods developed for constructing spirotetronates, highlighting both successful strategies and ongoing challenges. By focusing on the stereochemical and synthetic difficulties, we seek to provide a thorough understanding of the progress made in synthesizing this intriguing class of natural products.

## 2. Synthetic strategies to access spirotetronates

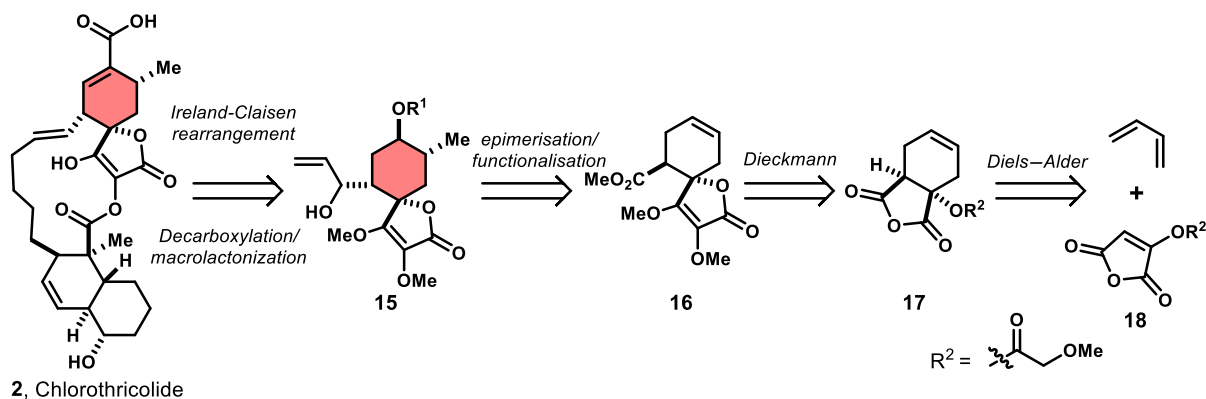
We will discuss the key disconnections investigated up to date and their drawbacks as well as their

benefits. However, except when deemed useful, we will not discuss the construction of the macrocycle and the decalin moieties, as these have been reviewed and studied elsewhere and are not the purpose of this review [2,3,22,27–35].

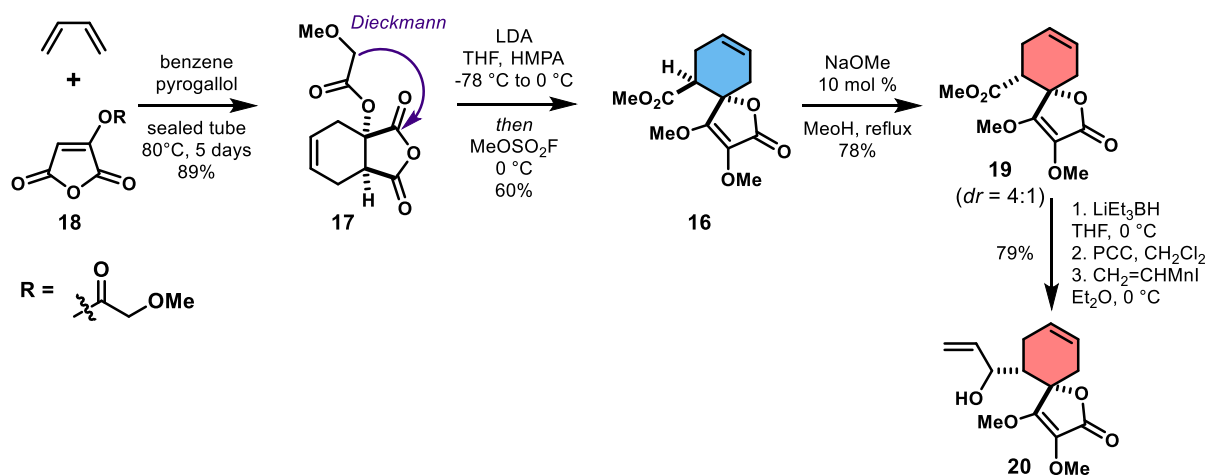
### 2.1. Seminal works established the Diels–Alder reaction as a preferred strategy

One of the earliest synthetic studies on spirotetronates was conducted by Ireland and co-workers in 1979, focusing on the synthesis of chlorothricin (**2**), the aglycon of chlorothricolide [36]. This molecule features an *exo*-type spirotetronate moiety, a functionalized decalin, and a macrocyclic structure with a single unsaturation. Based on a retrosynthetic analysis, the authors assumed that an Ireland–Claisen rearrangement could be key in forming the macrocyclic backbone and therefore the first requirement would be to build the advanced spirotetronate intermediate **15** (Scheme 1).

For constructing such a spirotetronate moiety, the authors proposed a Diels–Alder reaction between maleic anhydride derivative **18** and butadiene. The maleic anhydride was chosen not only for



**Scheme 1.** Retrosynthetic analysis to access chlorothricolide **2** by Ireland and co-workers.

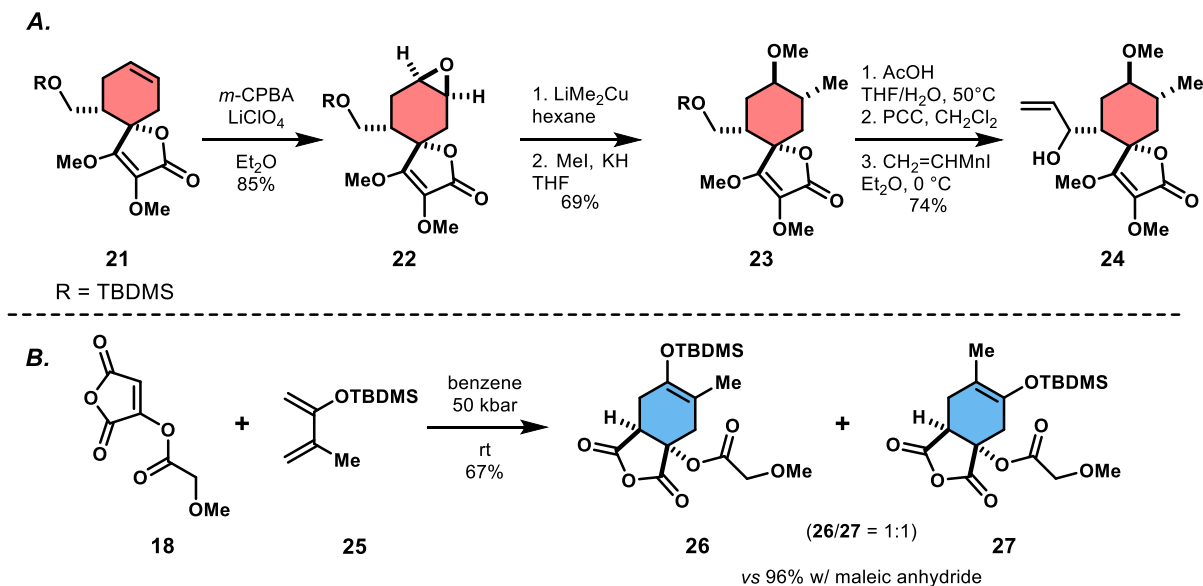


its dienophilic properties but also because it enabled an intramolecular Dieckmann condensation to form the tetronic acid moiety.

Although efficient, the Diels–Alder reaction between **18** and butadiene produced an unfunctionalized diastereo- and regioisomeric adduct of the desired spiro-tetronate backbone, requiring therefore post-manipulation of the cyclohexene ring. Scheme 2 outlines the high-pressure, high-temperature reaction of **18** with butadiene, leading to cycloadduct **17** in 89% yield (Scheme 2). Subsequent Dieckmann cyclization and methylation produced **16** in 60% yield. An epimerization event using sodium methoxide resulted in the desired diastereomer **19**. Following a series of redox manipulations and the addition of vinyl manganese iodide, the

authors obtained intermediate **20** (79% yield over three steps).

The functionalization of the cyclohexene ring in **19** required incorporation of a methyl and a carboxylate group, and regioselective formation of an endocyclic double bond. The approach, started from silyl-protected alcohol **21** and led to epoxide **22**, which was transformed to intermediate **23** (Scheme 3A). Further transformations produced intermediate **24**, which allowed further functionalization of the spiro-tetronate. Despite significant progress, Ireland's group was unable to complete the synthesis of chlorothricin due to difficulties in the final stages, particularly in further functionalizing the cyclohexene ring. This first synthetic access to a functionalized spiro-tetronate was notable



**Scheme 3.** (A) Post-functionalization of the cyclohexene ring. (B) Reactivity of **18** toward substituted dienes.

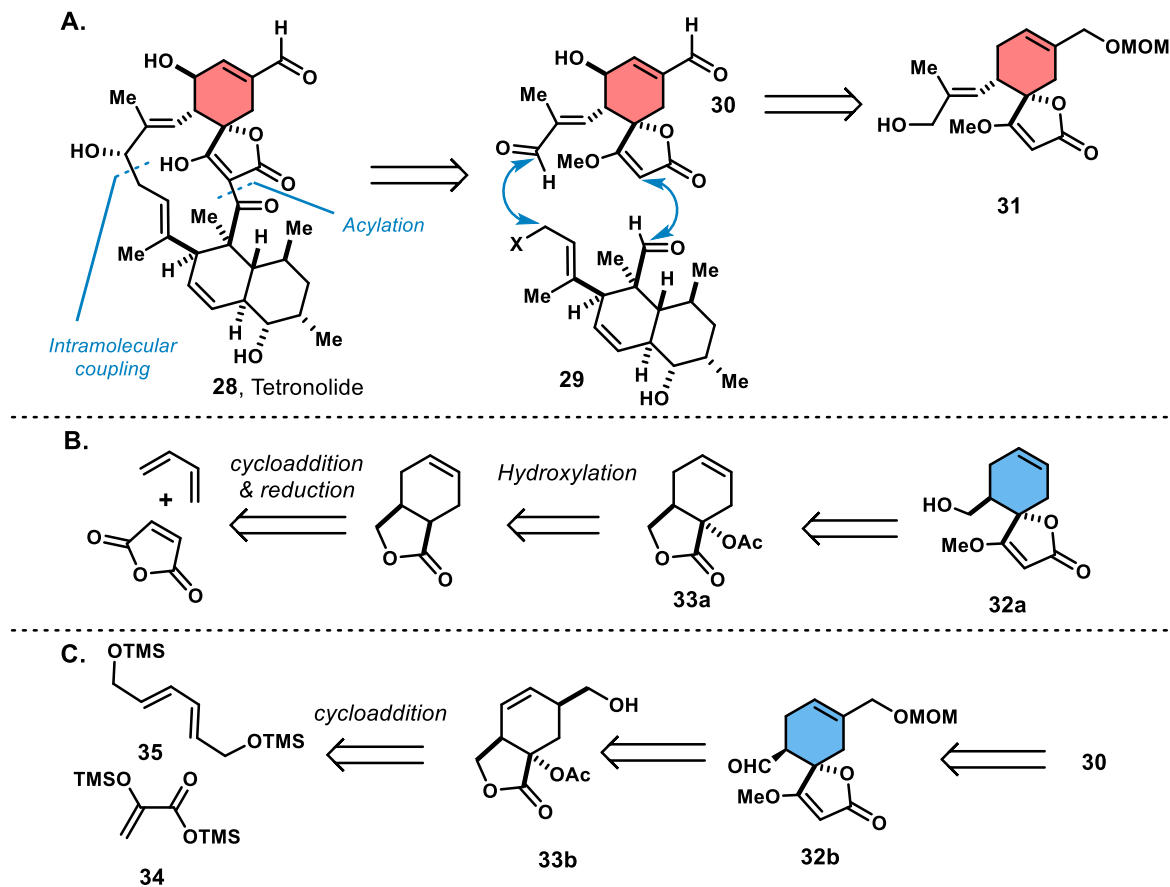
but burdened by many protecting-group manipulations, redox steps, and moderate selectivities. Attempts to improve the strategy by using an already pre-functionalized butadiene analogue as a reactive dienophile in the Diels–Alder reaction, namely activated silyl enol ether **25**, was largely unsuccessful due to poor regioselectivity (**26/27** = 1:1; 67% overall yield) observed during cycloaddition (Scheme 3B). Nevertheless, this research laid the groundwork for future synthetic efforts by demonstrating the utility of a cycloaddition and a Dieckmann condensation for constructing the bicyclic tetrone ring, a key feature in spirotetronate synthesis.

Yoshii's group adopted a related Diels–Alder/Dieckmann cyclization route during their effort toward the synthesis of tetronolide **28**, a structurally related spirotetronate with anticancer and antibacterial activity [37]. The synthesis relied on the construction of a cyclohexene fused lactone that could subsequently undergo a Dieckmann condensation to reveal an advance spirotetronate (Scheme 4A). In a model study, it was demonstrated that tetrahydrophthalide (obtained from maleic anhydride/butadiene cycloaddition and reduction) could be hydroxylated and converted to spirotetronate **32a** (Scheme 4B). In the second approach, diverging from Ireland and co-workers'

reported work, 2-hydroxyacrylate derivative **34** rather than maleic anhydride was used as the coupling partner in the Diels–Alder reaction and opposed to symmetrical diene **35**, avoiding regioselectivity issues. This allowed the progress toward a more functionalized spirotetronate (Scheme 4C).

Yoshii *et al.*'s second strategy began with diene **35** and acrylate **34**, which upon Diels–Alder cycloaddition and heating in methanol delivered bicyclic lactone **36** in 61% yield (Scheme 5). After several steps, including protection/deprotection, acylation, and redox manipulations, the Dieckmann condensation led to the desired regioisomeric cyclohexene spirotetronate **41**. Next, oxidation of the terminal alcohol to the aldehyde allows the epimerization event to take place, leading to **42** as a 5:1 mixture of *exo/endo* diastereomers. Further post-transformations were then conducted to install the required side chain on the cyclohexene [38]. This sequence, although more efficient than Ireland and co-workers' approach, still required 17 steps with an overall yield of less than 2%, due in part to extensive protecting group manipulations [39].

Despite these challenges, Yoshii *et al.*'s work represented the first use of an acrylate derivative in a Diels–Alder reaction to access spirotetronates. It was found to be particularly well suited to spirotetronate



**Scheme 4.** Retrosynthetic analysis toward tetronolide by Yoshii and co-workers.

synthesis, allowing the installation of both carboxyl and acyloxy groups, critical to the tetronate ring formation.

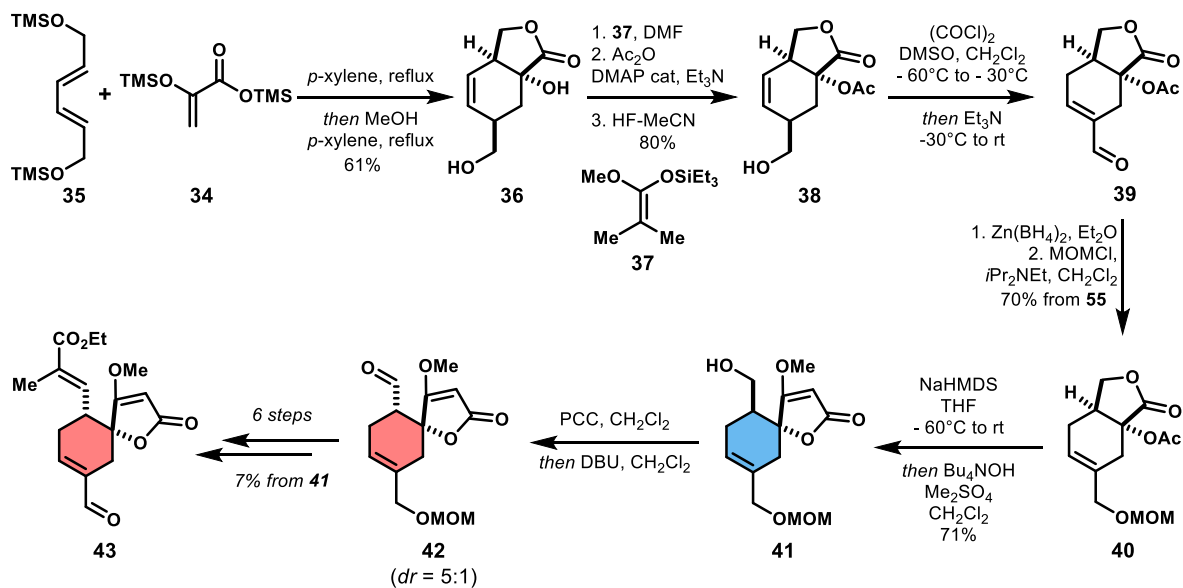
Both Ireland *et al.* and Yoshii *et al.* studies underscore the centrality of the Diels–Alder reaction and Dieckmann condensation in spirotetronate synthesis despite the challenges in achieving regio- and stereoselective control. Within such a strategy, the use of an acrylate derivative in a Diels–Alder reaction was largely pursued in subsequent work. Since costly post-functionalization remained a bottleneck, efforts undertaken subsequently have increasingly focused on designing more functionalized dienes and dienophiles to simplify the overall synthetic routes. The biosynthetic insights gained over the past decade have further reinforced the suitability of the Diels–Alder strategy, providing a pathway for future advancements in the synthesis of this complex class of natural products.

## 2.2. Acrylates and acrolein derivatives as privileged dienophiles in the synthesis of spirotetronates

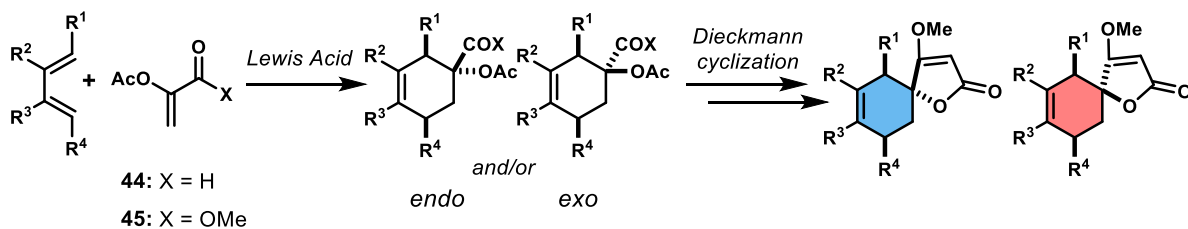
As mentioned above, the utilization of deactivated alkenes such as  $\alpha$ -acyloxy acrolein **44** and acrylate **45** and substituted dienes in [4+2]-cycloadditions has proven to be a significant strategy in the synthesis of spirotetronates (Scheme 6). These dienophiles lead to intermediates containing essential functional groups required for subsequent Dieckmann condensation, while also establishing the requisite endocyclic double bond and desired substituents.

Acrolein derivatives and  $\alpha$ -substituted acrylates are characterized by their enhanced reactivity as dienophile partners, attributed to the presence of electron-withdrawing groups. Their reactivity under thermal conditions has been well documented with simple cyclopentadiene or activated dienes





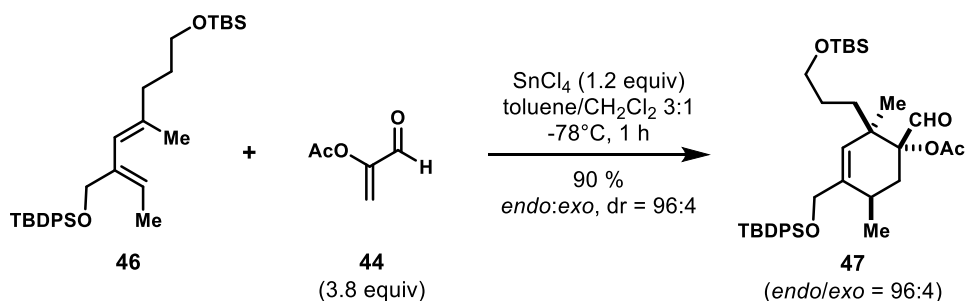
**Scheme 5.** Synthetic access to spirotetronate precursor **70** by a Diels–Alder strategy with an acrylate and a symmetrical diene.



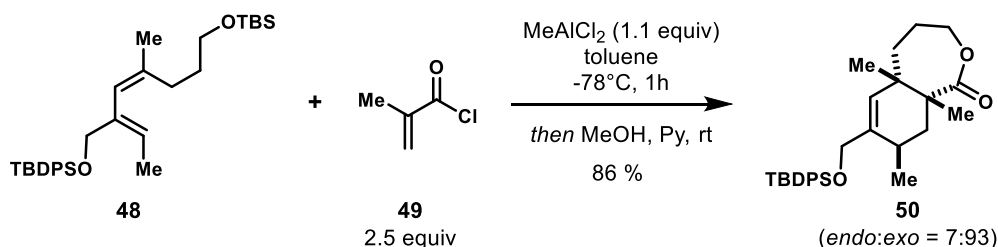
**Scheme 6.** Diastereoselective outcome of a Diels–Alder reaction using an acrolein or an acrylate as the dienophile.

analogous to Danishefsky's diene [40–42]. However, the interaction of these dienophiles with inactivated, highly substituted, in particular  $\alpha,\alpha'$  di-substituted acyclic dienes, was scarcely explored until Roush *et al.* reported the use of Lewis acids to promote such reactivity in 1997 [43]. Their findings demonstrated that aluminum(III) or tin(IV) based Lewis acids could facilitate [4+2]-cycloadditions between hindered, inactivated acyclic dienes and  $\alpha$ -acyloxy acrolein, yielding good to excellent selectivity. As shown in Scheme 7, diene **46** reacted with **44** upon exposure to stoichiometric amounts of  $\text{SnCl}_4$  at  $-78^\circ\text{C}$ , leading to cycloadduct **47** bearing two vicinal quaternary carbons with excellent regio- and diastereoselectivity in favor of the *endo* diastereomer.

Further evaluations of various dienophiles, including  $\alpha$ -bromoacrolein and methacrolein, indicated that  $\text{MeAlCl}_2$  could promote these reactions effectively even if longer reaction times were observed for certain dienophiles. Importantly, the application of  $\text{MeAlCl}_2$  in these cycloadditions resulted in cycloadducts exhibiting complete regioselectivity and good to excellent diastereoselectivities (*endo/exo* < 85:15) in favor of the *endo* cycloadduct. It should be mentioned that the  $\alpha$ -substituent of the acrylate residue has a strong influence on the outcome of the reaction; indeed, the use of acryloyl and methacryloyl chlorides leads to the *exo* adduct or poor diastereoselectivity. An example is illustrated in Scheme 8, where *exo*-selective cycloaddi-



**Scheme 7.** Lewis acid-promoted Diels-Alder reaction with hindered acyclic dienes.



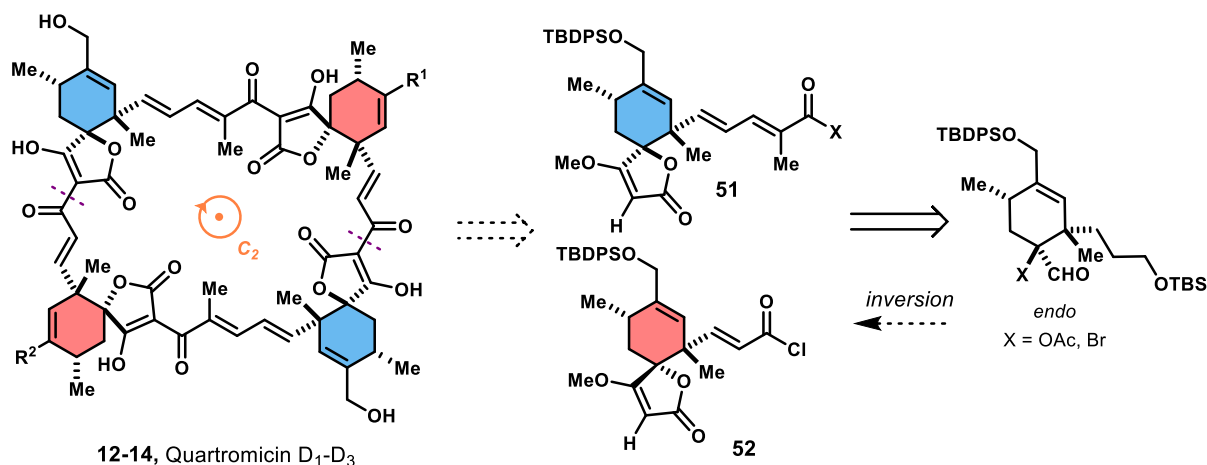
**Scheme 8.** Diastereoselective outcome between diene 1.66 and acryloyl chloride.

tion achieved from compound **48** was followed by a methanol/pyridine treatment to facilitate the formation of *trans*-fused lactones **50**. The successful application of Lewis acids not only demonstrated the ability to achieve stereoselective outcomes that are often challenging under thermal conditions but also highlighted their utility in promoting the Diels-Alder reaction involving acrolein derivatives and acyclic dienes.

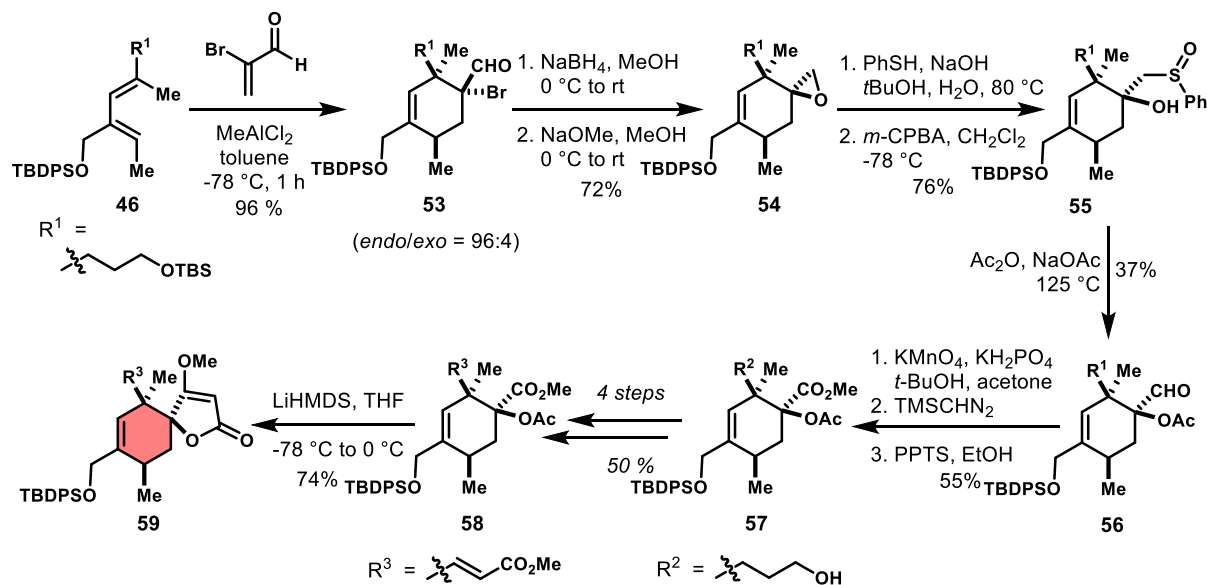
In 2002, Roush's group employed this strategy to devise a diastereoselective synthesis of both *exo* and *endo* spirotetronate fragments of quartromicins [44]. Capitalizing on the C<sub>2</sub> axial symmetry of quartromicins, they reasoned that the tetramer could result from an incremental twofold dimerization of *endo* and *exo* spirotetronates (Scheme 9). Specifically, this strategy could be accessible from a coupling reaction between tetronates **51** and **52**, which should be feasible by Diels-Alder cycloadditions between **46** and an appropriate acrolein derivative. The reaction with acrolein **44**, upon activation by a Lewis acid, would lead to the *endo* spirotetronate. For the *exo* spirotetronate, they relied on an *endo*-selective Diels-Alder reaction of  $\alpha$ -bromoacrolein and **46**, followed by a subsequent inversion of configuration of the quaternary stereocenter described below [45].

Indeed, the reaction of **46** with  $\alpha$ -bromoacrolein in the presence of MeAlCl<sub>2</sub> produced cycloadduct **53** as the single *endo* diastereomer (Scheme 10). Then, a series of five synthetic steps enabled the conversion of cycloadduct **53** to the spiroepoxide **54**, which was obtained in 72% yield. This involved the reduction of aldehyde **53** to the corresponding alcohol, followed by an alkoxide-mediated inversion of the quaternary stereocenter. Although spiroepoxide **54** displayed reluctance to react with oxygen-based nucleophiles, it was successfully opened by sodium thiophenolate, yielding sulfoxide **55** upon oxidation with *m*-CPBA. The subsequent reaction with Ac<sub>2</sub>O and NaOAc produced the desired intermediate **56** via Pummerer rearrangement and acylation of the tertiary alcohol. After further oxidation of the aldehyde using KMnO<sub>4</sub> and conversion to the methyl ester with TMSCHN<sub>2</sub>, the TBS-protected hydroxyl group was deprotected using pyridinium *p*-toluenesulfonate. This allowed for further functionalization to obtain the  $\alpha,\beta$ -unsaturated ester **58**, ultimately leading to the classical Dieckmann condensation that produced spirotetronate **59** in good yield.

For the construction of the *endo* spirotetronate, diene **46** was made to react with  $\alpha$ -acyloxy acrolein to generate cycloadduct **60**, followed by functional



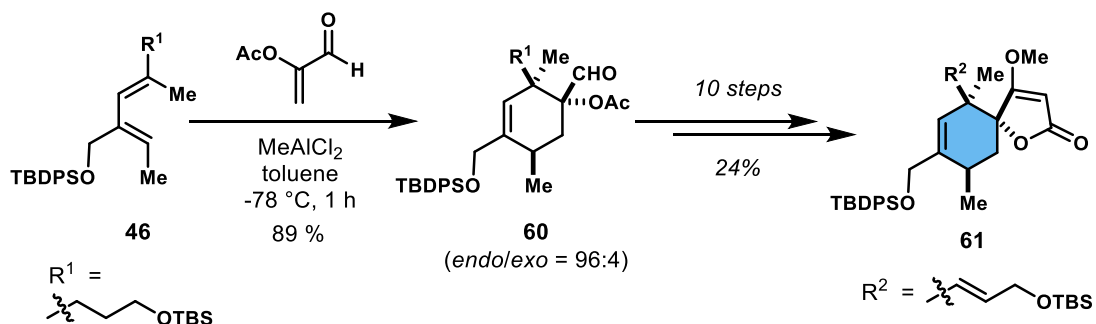
**Scheme 9.** Retrosynthetic analysis to access quartromicins by Roush and co-workers.



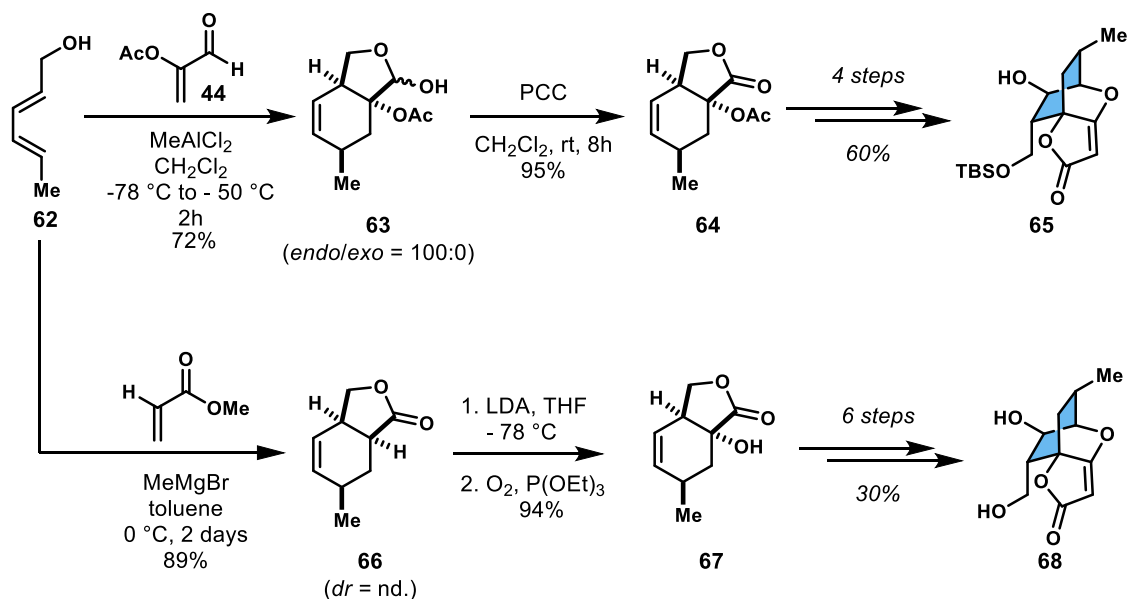
**Scheme 10.** Inversion of a quaternary stereocenter to access *exo* spirotetronate **78**.

group interconversion and redox manipulations to access the desired *endo* product in 10 steps (24% yield; Scheme 11). These synthetic sequences highlight the versatility of acrylates and acroleins as privileged dienophiles, underscoring their significance in the efficient construction of complex spirocyclic architectures relevant to biologically active compounds. Further advance in the synthesis was undertaken [46], but the total synthesis of quartromicins remained incomplete.

Lewis acid-promoted cycloadditions of functionalized dienes with acrolein derivatives or acrylates have proven effective for synthesizing various *endo* diastereocontrolled spirotetronates. Several studies [47–49] have highlighted this approach, particularly in the context of abyssomicin C. Two independent studies published in 2005 reported the synthesis of the spirotetronate moiety using diene **62**, which contains an unprotected allylic alcohol (Scheme 12). The reaction with  $\alpha$ -acyloxyacrolein **44**



**Scheme 11.** Synthesis of the *endo* spirotetronate moiety en route to quartromicins.

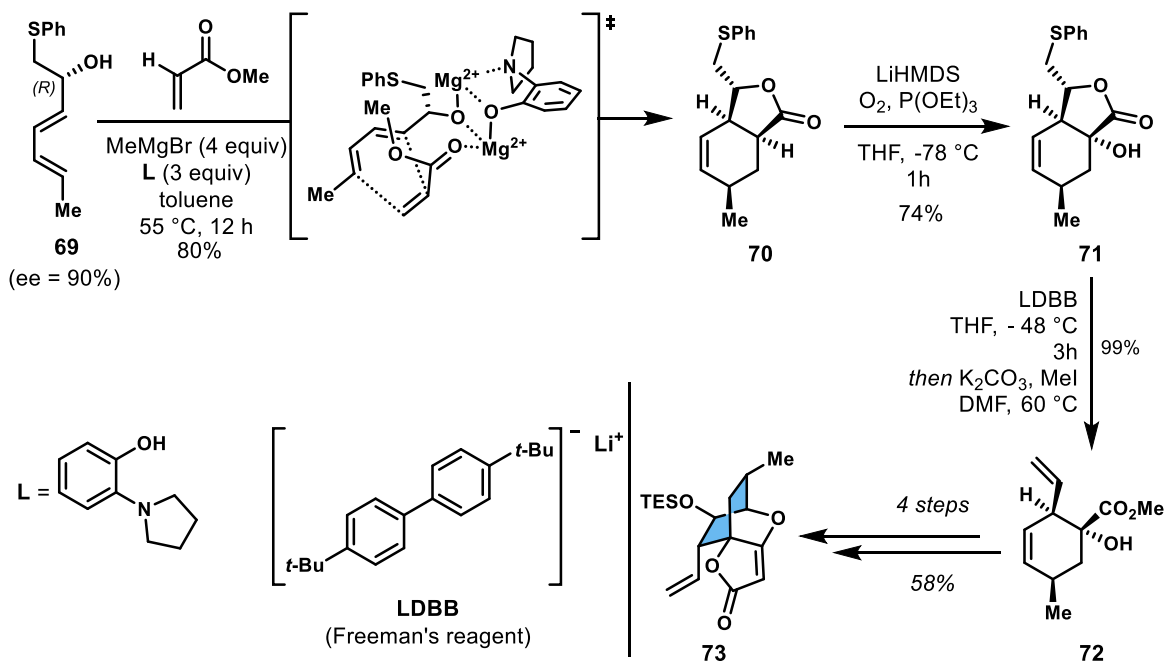


**Scheme 12.** Synthetic access to the spirotetronate moiety of abyssomicin C.

produced cycloadduct **63** as the sole *endo* diastereomer [48]. The fused lactol was subsequently oxidized to lactone **64** and engaged in a Dieckmann condensation that first required a TBSCl protection of the terminal alcohol to prevent recyclization to the lactone. Attempts to achieve enantioselectivity through aluminum/BINOL complexes during the cycloaddition were unsuccessful. In the second study, methyl acrylate served as the dienophile, leading to the fused lactone **66**, necessitating an additional hydroxylation step to introduce the acetate group required for the spirotetronate formation [49]. Both studies ended with the formation of compounds **65** or its deprotected variant **68**, without completing the total synthesis of abyssomicin C.

Burkart's group mimicked this method to access the core structure of spirohexenolides **5a** and **5b**, previously isolated compounds exhibiting antitumoral activity [4]. They achieved a regio- and diastereoselective cycloaddition between a hindered triene and  $\alpha$ -acyloxyacrolein **44** [50], but encountered the undesired deacylation of the tertiary alcohol during aldehyde oxidation, necessitating additional protection/deprotection steps and reducing the overall synthetic efficiency.

Nicolaou and co-workers implemented this strategy in a diastereoselective process during their synthesis of enantioenriched spirotetronate moiety of abyssomicin C [51,52]. Engaging enantioenriched diene **69** bearing a chiral secondary alkoxy



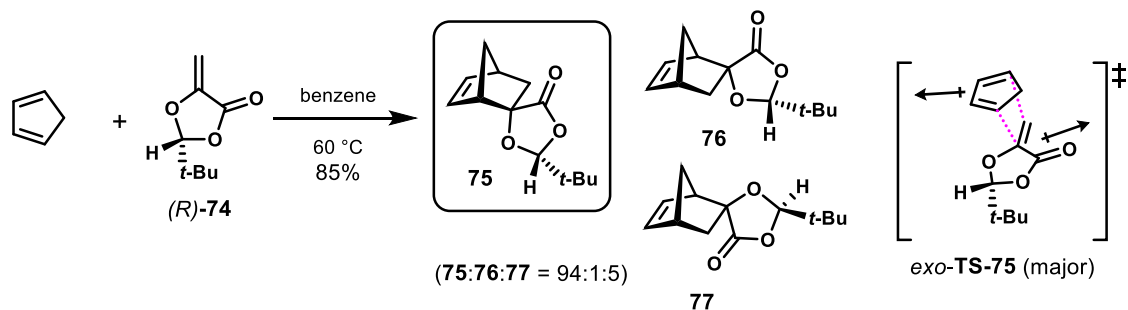
**Scheme 13.** Enantioselective access to the spiro-tetronate moiety of abyssomicin C.

side chain with methyl acrylate in a Diels–Alder reaction, they managed to isolate lactone **70** as a single diastereoisomer in 80% yield (Scheme 13). This magnesium-promoted reaction used 2-(pyrrolidin-1-yl)phenol as a ligand, which enhanced the reaction rate by facilitating a favorable spatial arrangement between the magnesium ions and the dienophile. The cycloadduct underwent further transformations, including  $\alpha$ -hydroxy ester formation, lithium–sulfur exchange, epoxidation, and Dieckmann cyclization, ultimately yielding *endo* spiro-tetronate intermediate **73**. Final macrocyclization was achieved through ring-closing metathesis (RCM) using a Hoveyda–Grubbs catalyst, culminating in the successful synthesis of abyssomicin C and its atropisomer alongside numerous analogues, helping in understanding the structure–activity relationship.

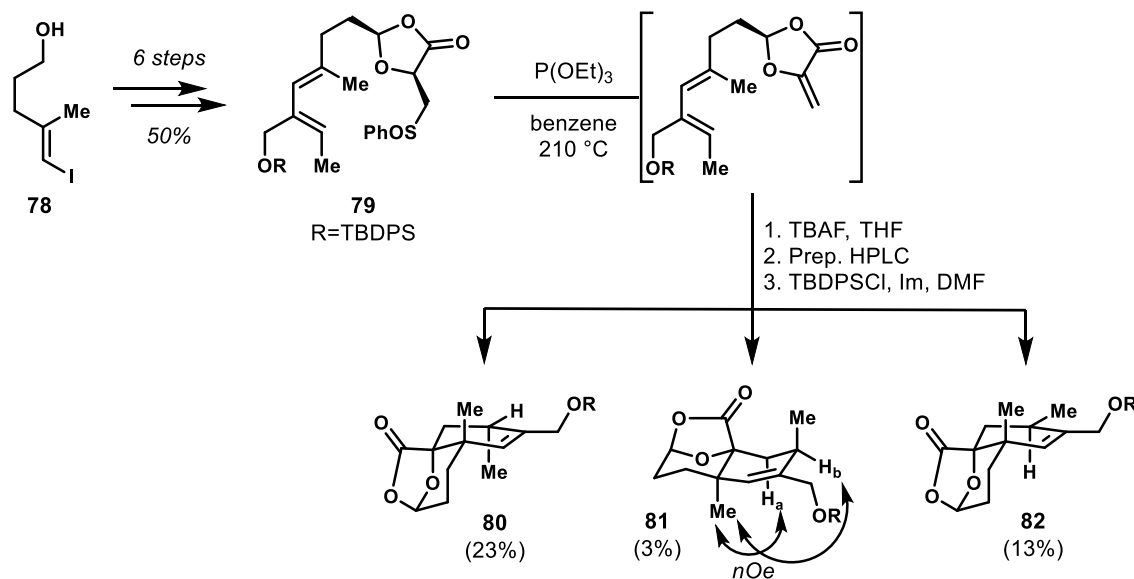
Exploration of chiral dienophiles to induce diastereoselectivity and obtained enantioenriched cycloadducts have also been reported. Roush *et al.* demonstrated that 2-alkyl-5-methylene-1,3-dioxolan-4-ones participate in Diels–Alder reactions involving cyclobutene via an *exo* transition state [53–56], leading essentially to one diastereomer with an *exo* configuration. In particular,

2-(*tert*-butyl)-5-methylene-1,3-dioxolan-4-one **74** with its bulky *tert*-butyl substituent predominantly forms product **75** from *exo*-**TS-75**, with selectivity attributed to the constrained *s-cis* conformation of the dienophile and steric interactions influencing the transition states (Scheme 14).

Utilizing this diastereoselective *exo*-selective approach, Roush and co-workers implemented an intramolecular Diels–Alder (IMDA) strategy to access diverse diastereomers of spiro-tetronates relevant to quartromicins [57]. The synthesis of the sulfone precursor **79** was achieved in six steps from a known vinyl iodide **78**, yielding an overall 50% yield. The IMDA reaction conducted at  $210^\circ\text{C}$  generated cycloadducts **80**, **81**, and **82**, albeit with low yields and poor stereoselectivity (Scheme 15). The absolute configurations of products **80** and **82** were confirmed through crystallographic analysis, while nOe correlations determined the relative configuration of **81** [58,59]. Ring opening of the lactone was achieved using ethanedithiol to reveal the key  $\alpha$ -hydroxy ester motif subsequently used to build the tetronate. This IMDA strategy has proven effective in the total synthesis of chlorothricolide [60,61], tetronolide [62,63], and kijanolide [64,65],



**Scheme 14.** Diastereoselective Diels–Alder cycloaddition of (*R*)-74 with cyclopentadiene.



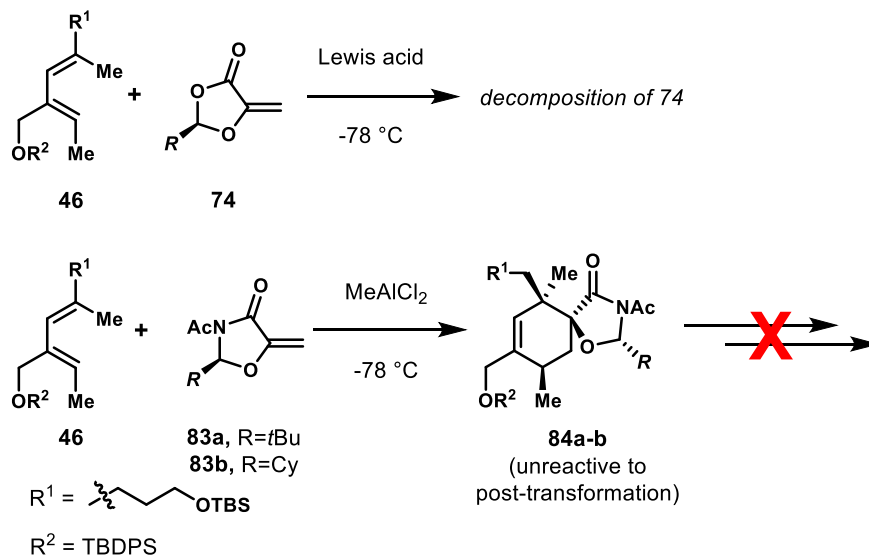
**Scheme 15.** Diastereoselective outcome of the intramolecular Diels–Alder reaction applied to **79**.

showcasing the potential of spirotrienone derivatives.

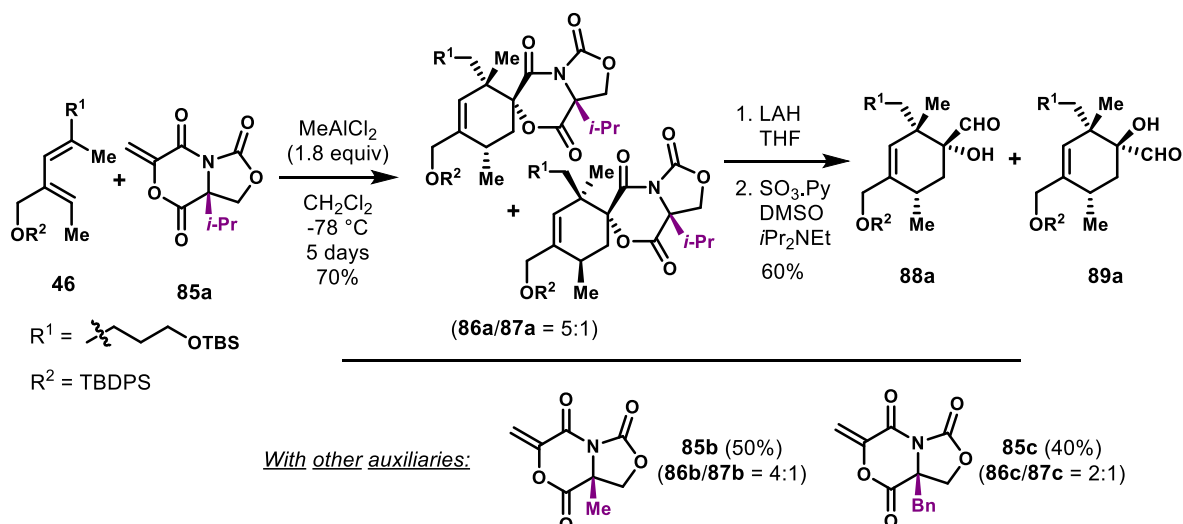
Although 5-methylene-1,3-dioxolan-4-one derivatives were demonstrated to be competent partners in Diels–Alder reactions, their reactivity remained low, and even under quite forcing conditions, furnished low yield and limited selectivity. To improve the outcome, Roush's group explored the reactivity of 1,3-oxazolidine-4-one analogues **83a–b** under Lewis acid activation to facilitate an intermolecular Diels–Alder reaction. However, the reaction between dienophile **74** and diene **46** exhibited extensive decomposition at cryogenic temperatures in the presence of a Lewis acid (Scheme 16). An aza analogue of 1,3-oxazolidine-4-one, in the form

of oxazolidinone **83**, was more robust as a dienophile and underwent the cycloaddition smoothly. Unfortunately, efforts to subsequently cleave the lactam were unsuccessful [66].

To improve the strategy without struggling with low yields and decomposition and for subsequent handling, Roush's group turned its attention toward bicyclic oxazolidinone based dienophiles **85a–c**, each featuring substituents such as methyl, isopropyl, or benzyl groups, designed to enantioselectively access the spirotrienone moieties of quartromicins (Scheme 17) [66]. These chiral building blocks proved to be effective in the anticipated Lewis acid-activated Diels–Alder reaction even if the reaction was specially slow (5 days).



**Scheme 16.** Reactivity issues posed by the chiral auxiliaries developed by Roush *et al.*

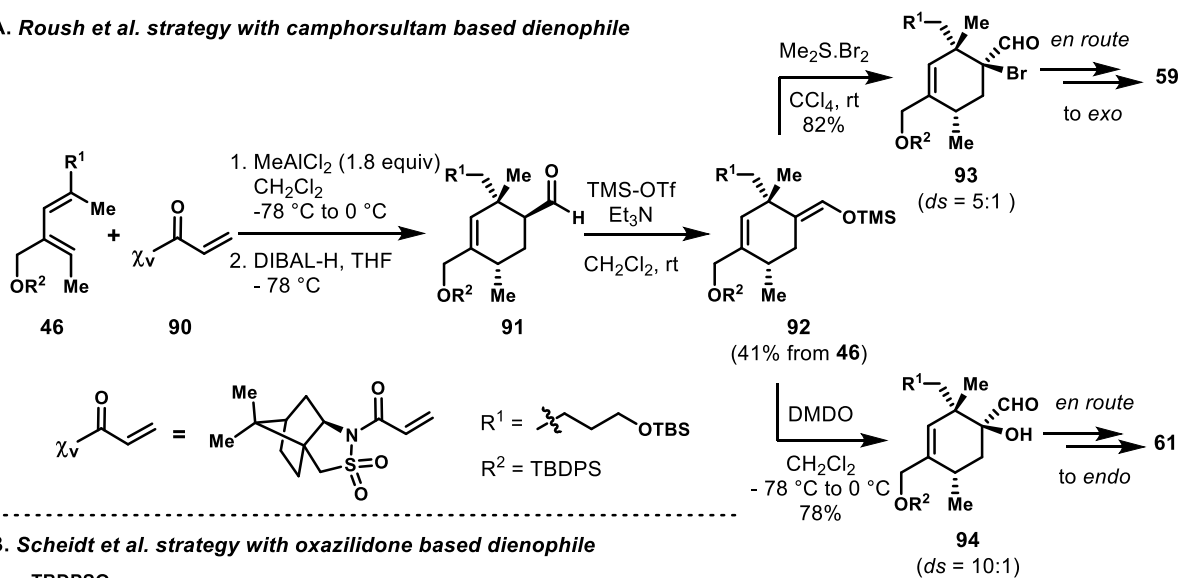
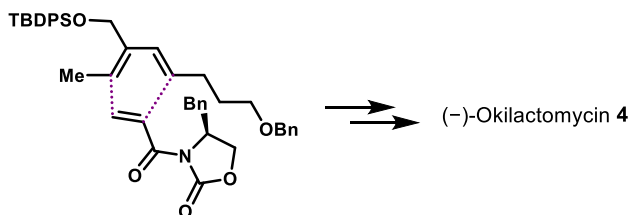


**Scheme 17.** Bicyclic chiral oxazolidinone enables access to the *exo* and the *endo* fragments of quartromicins.

Among the dienophiles tested, **85a** provided the most promising results leading to a 5:1 ratio with a total yield of 70% for the *exo* adduct. Subsequent transformations involved the cleavage of the chiral auxiliary using lithium aluminum hydride followed by oxidation of the primary alcohol with DMSO, yielding the enantioenriched precursors **88a** and **89a**. Despite the advancements achieved with these bicyclic oxazolidinone dienophiles, their relatively

low diastereoselectivity in the Diels–Alder reaction (*exo* vs *endo* ratio) highlights the limitations of this approach. Although other chiral auxiliaries based on acrylates and acrolein derivatives have been explored for spirotronate synthesis, they generally encounter similar challenges related to post-functionalization [67,68].

Roush and co-workers also examined a Lewis acid-promoted Diels–Alder reaction using

A. Roush *et al.* strategy with camphorsultam based dienophileB. Scheidt *et al.* strategy with oxazolidone based dienophile

**Scheme 18.** (A) Use of camphorsultam-based auxiliary to access both *endo* and *exo* spirotetronates of quartromicins by Roush *et al.* (B) Scheidt *et al.* strategy displaying a *N*-acryloyl oxazolidinone.

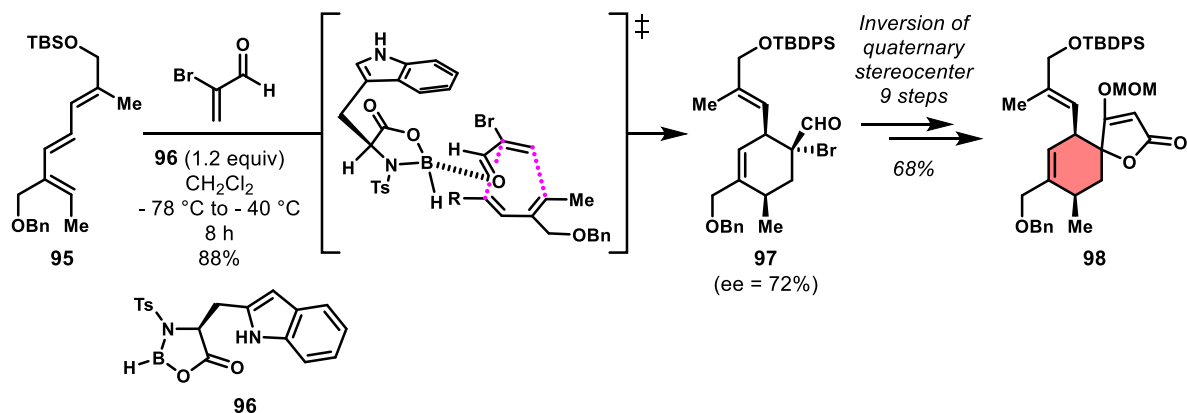
*N*-acryloyl camphorsultam **90** and diene **46**, achieving a diastereomeric ratio of *exo/endo* 7:1 (Scheme 18A) [44]. Despite this stereoselectivity, the approach did not provide direct access to the required quaternary hydroxy carbon, thereby diminishing its relevance. Post-manipulations nevertheless allowed building suitable spirotetronate precursors. Subsequent attempts to utilize  $\alpha$ -substituted *N*-acryloyl camphorsultams were unsuccessful, prompting further investigations.

In a related approach, Scheidt and co-workers successfully utilized a chiral *N*-acryloyl oxazolidinone [69] in the synthesis of the *endo* spirotetronate of (-)-okilactomycin, demonstrating that this strategy could be extended to complex natural products (Scheme 18B) [70].

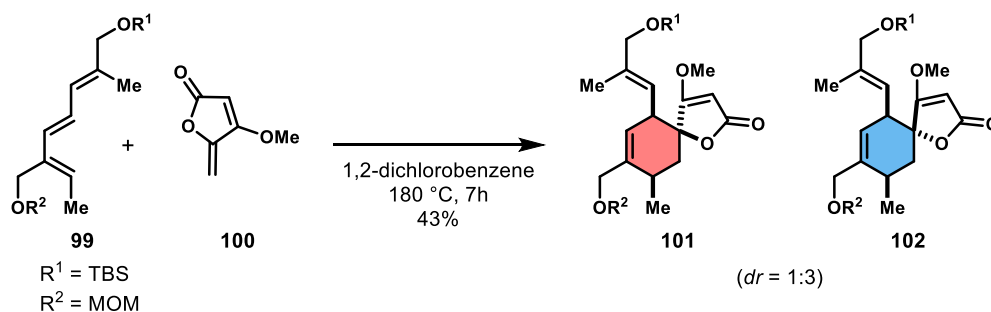
Given the challenges with chiral dienophiles, it would be advantageous to achieve enantioenriched intermediates from achiral substrates by controlling the enantioselectivity of the Diels–Alder reaction through the use of chiral promoters or catalysts. In

the synthesis of spirotetronates, this approach remains underexplored, with the only successful example reported by Marshall and Xie in 1992 [45]. They leveraged an enantioselective Diels–Alder reaction using reactive dienes and acrolein derivatives, promoted by the Corey–Bakshi–Shibata (CBS) catalyst, a boron-based oxazaborolidine. They conducted the reaction between functionalized triene **95**, synthesized in eight steps from glycolaldehyde, and  $\alpha$ -bromoacrolein, using one equivalent of the CBS catalyst **96**. This reaction led to the formation of the *endo* diastereomer **97** with moderate enantiocontrol (*ee* = 72%) but impressive regioselectivity (Scheme 19). The choice of bromo-substituted acrolein was driven by its reactivity toward dienes when activated by the oxazaborolidine catalyst and the requirement to invert the quaternary stereocenter to access the *exo* spirotetronate. Although the authors did not provide a detailed mechanism, a plausible transition state based on Corey and Loh's earlier work was proposed in Scheme 19 [71]. The key inversion





**Scheme 19.** Enantioselective Diels–Alder reaction with achiral substrates with the use of CBS catalyst.



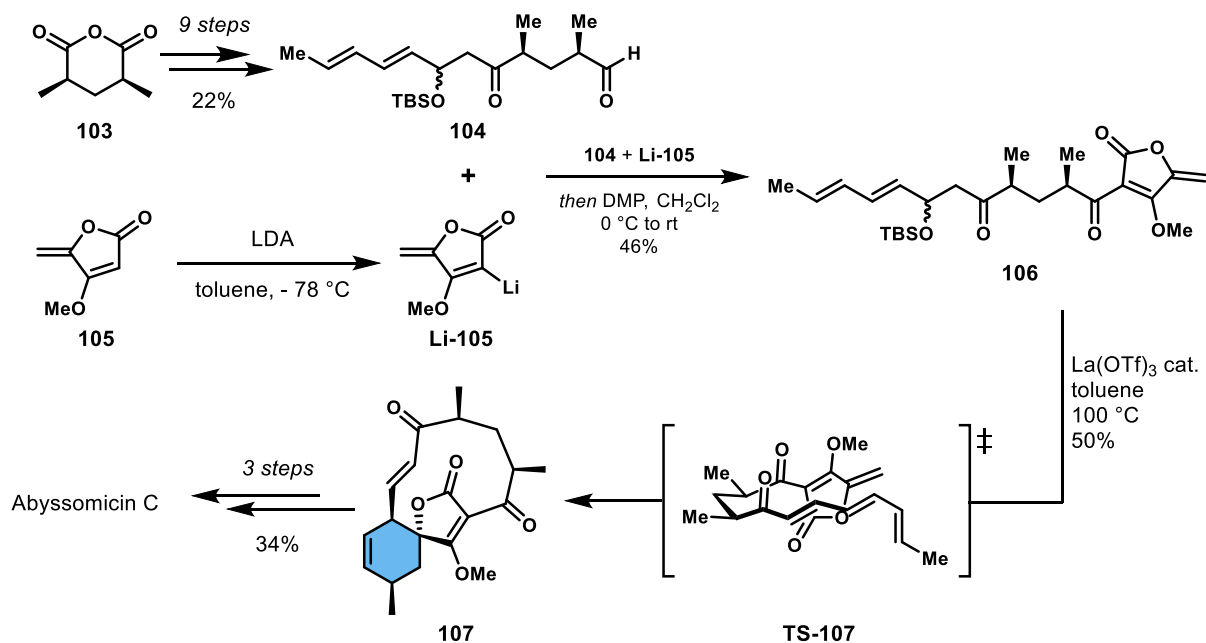
**Scheme 20.** First example of intermolecular Diels–Alder reaction using a tetronate dienophile.

of the stereocenter followed a sequence similar to that previously outlined by Roush *et al.*, involving an epoxide intermediate, sulfide ring opening, oxidation of the sulfoxide, and a Pummerer rearrangement. Following this, a classical acylation of the tertiary alcohol and a subsequent Dieckmann cyclization were used to form the spirocyclic intermediate **98** in nine steps from **97** (overall yield 68%). Despite the moderate enantiomeric excess and the stoichiometric use of the oxazaborolidine catalyst, this regio- and diastereoselective cycloaddition represents a rare example of spirotetronate synthesis not relying on chiral dienophiles.

### 2.3. Emergence and use of tetronate-derived dienophile in Diels–Alder reactions

The use of Diels–Alder reactions to access spirotetronates has been predominantly based on acrolein derivatives or acrylates, both chiral and

achiral. However, some studies have explored alternative dienophiles, such as 5-methylenetetronate **100** (Scheme 20), which bypass the need for post-functionalization steps required for Dieckmann condensation [72]. Yoshii's group successfully synthesized **100** in just three steps starting from 4-methoxyfuran-2(5*H*)-one. They were the first to apply this dienophile in an intermolecular Diels–Alder reaction with triene **99** at high temperatures (180 °C in 1,2-dichlorobenzene), obtaining a modest diastereoselectivity (dr = 1:3) and yield (43%). The reaction favored the undesired *endo* diastereomer **102**, considering that targeted kijanolide contains an *exo*-type spirotetronate. Despite the low yield and selectivity, the reaction showcased the ability of tetronate dienophiles to form spirocycles in a single step. Following this work, the same group explored  $\alpha$ -acyloxy derivatives of **100**, synthesized in two steps from **100**, to access the spirotetronate moiety of chlorothricolide [73]. Although the reaction conditions were

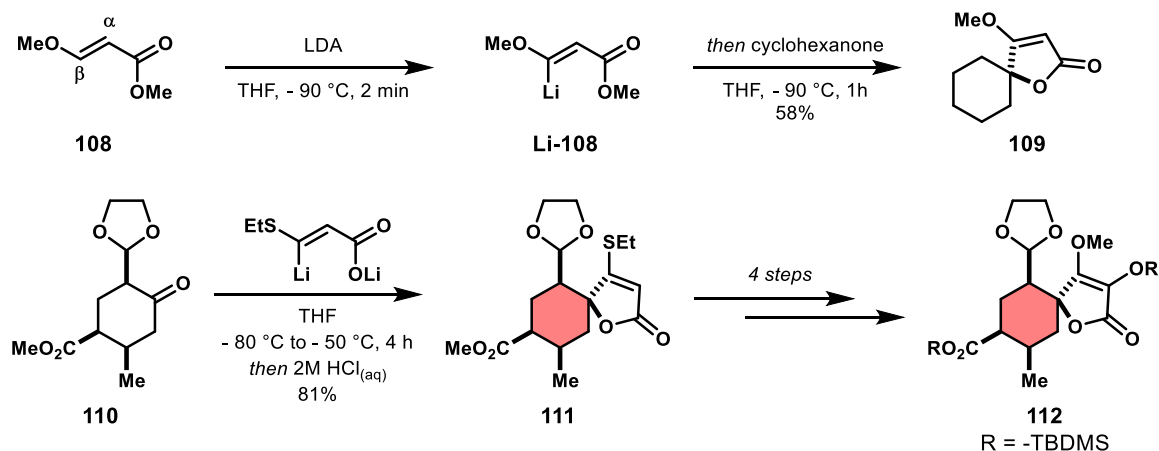


**Scheme 21.** Enantio- and diastereoselective access to abyssomicin C via a biomimetic strategy by Sorensen and co-workers.

less severe (140–150 °C in chlorobenzene), the outcome was again a diastereomeric mixture favoring the *endo*-type spirotetronate along with regioisomeric products. These results highlight the limitations of 5-methylenetetronate in terms of regio- and diastereoselectivity, yet its use circumvents extensive post-reaction functionalization.

The use of tetronate-derived dienophile as a synthetic precursor to spirotetronate was illustrated by Sorensen and co-workers (2005) [74], who achieved the enantioselective and diastereoselective synthesis of abyssomicin C. Sorensen *et al.*'s approach relied on a biomimetic IMDA reaction that constructs the spirotetronate and the macrocyclic ring in a single step (Scheme 21). The synthesis began with *meso*-anhydride **103**, which was accessible from diethyl methylmalonate in three steps on a large scale. After several key transformations, including stereoselective hydrolysis and aldolization with *trans,trans*-2,4-hexadienal, aldehyde **104** was obtained in nine steps from **103** with a 22% overall yield. A critical step in the sequence was the addition of deprotonated tetronate **105** to aldehyde **104**, followed by oxidation of the resulting secondary alcohol using the Dess–Martin periodinane, generating interme-

diate **106**. Initially, the authors attempted to eliminate the protected alcohol and initiate the Diels–Alder reaction by using scandium(III) triflate, but this approach produced an unstable polyene intermediate. They subsequently found that treating **106** with lanthanum(III) triflate triggered both polyene formation and intramolecular cycloaddition in one step, furnishing the key intermediate **107** in 50% yield. Notably, this step was completely diastereoselective, a significant improvement over previous methods employing tetronate dienophiles. The Diels–Alder reaction proceeded through a favorable transition state (**TS-107**) as confirmed by computational studies. Further transformations, including epoxidation of the cyclohexene ring and nucleophilic attack of the deprotected tetronic acid, completed the synthesis of abyssomicin C. This strategy not only provided the first enantioselective synthesis of abyssomicin C but also closely mirrored the natural biosynthetic pathway, which involves a similar IMDA reaction with a tetronate dienophile. In addition to abyssomicin C, this method has been extended to the synthesis of abyssomicin C analogues and okilactomycin, further demonstrating the versatility of the IMDA reaction with tetronate dienophiles [75,76]. These efforts have



**Scheme 22.** Alkylation of cyclohexanone with a  $\beta$ -lithiated acrylate.

significantly expanded the scope of spirotetronate synthesis, offering a powerful tool for accessing complex natural products with spirocyclic cores.

### 3. Other strategies

As illustrated previously, the main strategies to access spirotetronates rely on two key disconnections: a Diels–Alder reaction to build the cyclohexene ring and a Dieckmann condensation to form the tetronate unit. However, alternative retrosynthetic disconnections have been explored to address the synthesis of this challenging spirotetronate motive.

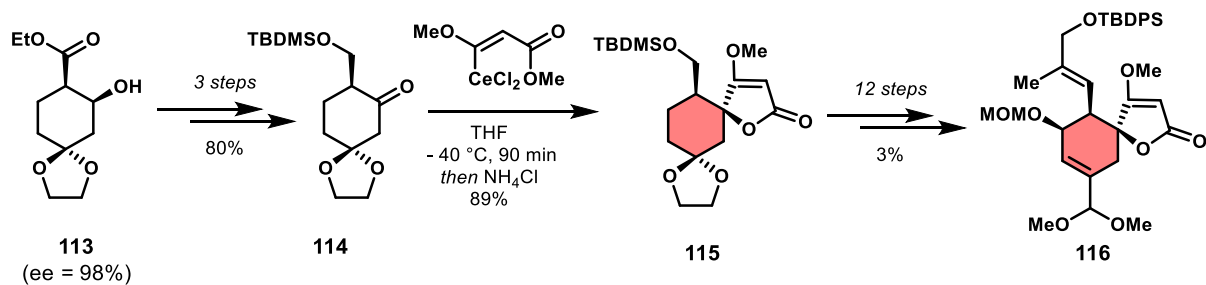
#### 3.1. Alkylation of cyclic ketones

The conversion of ketone with  $\beta$ -lithiated acrylates has been reported as an alternative to the Dieckmann condensation in the context of spirotetronate natural compound synthesis. For instance, selective  $\beta$ -lithiation of  $\beta$ -methoxyacrylate **108** under kinetic control and subsequent addition to cyclohexanone produced unfunctionalized spirotetronate **109** (Scheme 22) [77,78]. Schmidt and Hirsenkorn used this method in the synthesis of chlorothricolide [79,80], and showed that  $\beta$ -ethylthioacrylate improved yields compared to methoxyacrylate, while both nucleophiles provided the same diastereoselectivity. The resulting sulfide **111** could be further converted into a methoxy derivative and  $\alpha$ -hydroxylated to yield intermediate **112**, useful in chlorothricolide synthesis.

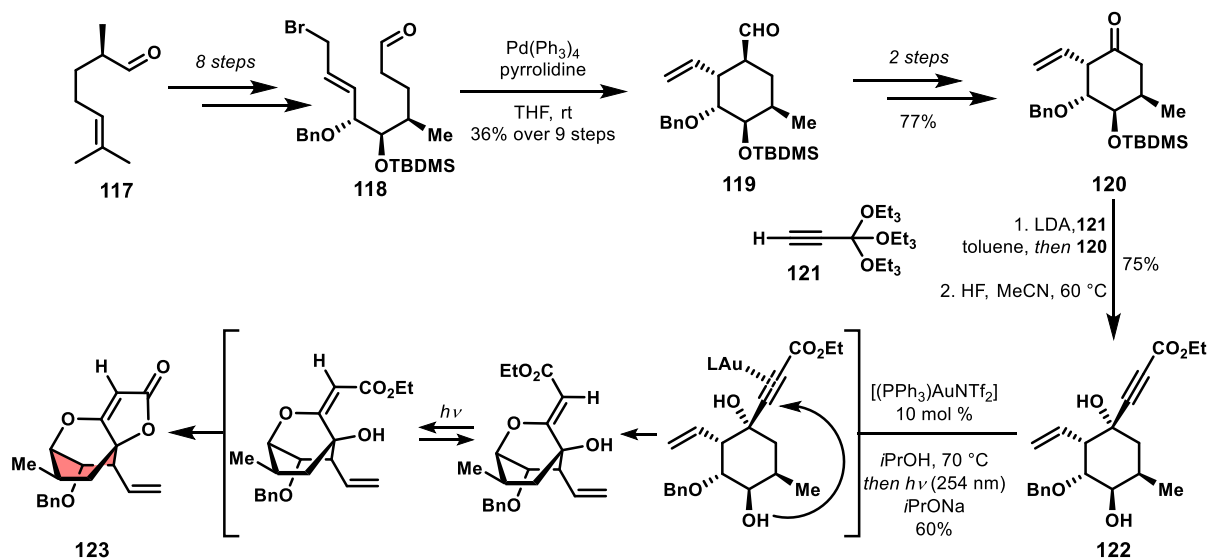
Yoshii and co-workers also took advantage of this strategy in several studies toward kijanolide and tetronolide [81,82]. They found that using a cerium(III) derivative of **Li-108** allowed better compatibility with enolizable ketones due to the nucleophilicity of organocerium compounds, which are poor bases [83]. Their synthesis of tetronolide started with enantioenriched cyclohexanol **113** [84] and proceeded to cyclohexanone **114** in three steps with 80% yield. Addition of  $\beta$ -dichlorocerium salt of **108** provided the spirotetronate intermediate **115** as the *exo* diastereomer (Scheme 23).

Other notable efforts include the total synthesis of (-)-atrop-abyssomicin C by Bihelovic and Saicic, relying on a gold-catalyzed step to form the bridged spirotetronate (Scheme 24) [85]. This approach involved the addition of a lithium derivative of ethyl orthopropiolate to a cyclic ketone that occurred with high diastereoselectivity, providing compound **122** in 75% yield [86]. A gold-catalyzed hydroxyl addition to the alkyne was subsequently performed, leading to a tricyclic (*Z*)-3-alkoxyacrylate. Photochemical (*Z*)-(E) isomerization did then offer the suitable conformation for tetronate formation.

Interestingly in Bihelovic and Saicic's work, the synthesis of the functionalized cyclohexanone precursor was not established by a cycloaddition strategy (see *vide infra*) but was achieved through a dual organo/metal-catalyzed Tsuji–Trost cyclization of linear allyl–aldehyde **118** [87]. This key cyclization involves a transient enamine formation that undergoes a cyclative  $\pi$ -allyl palladium



**Scheme 23.** Enantioselective access to an *exo* spirotetronate by alkylation of a cyclohexanone with a cerium salt.



**Scheme 24.** Synthetic access to an intermediate in the synthesis of (-)-atrop-abysomicin by Saicic *et al.*

displacement. The resulting cyclic aldehyde was next transformed through an oxidation into desired cyclohexanone **120**.

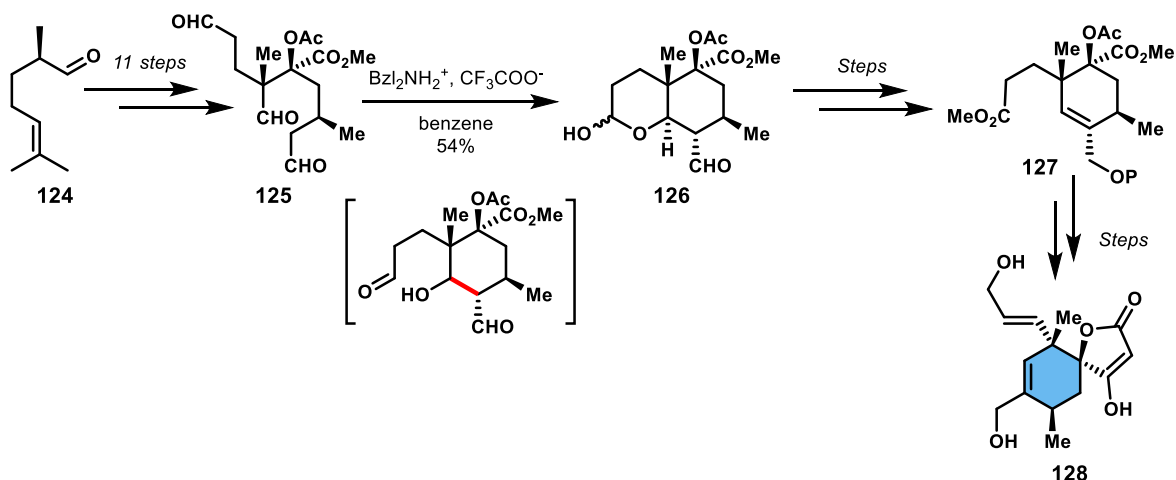
### 3.2. Alternatives to Diels–Alder reaction for cyclohexene ring construction

The Dieckmann condensation of 1-acetoxycyclohexene-1-carboxylate derivatives was largely used when targeting spirotetronates, and the Diels–Alder reaction has been found to be particularly well suited to prepare these precursors. Selected ring-forming approaches, bypassing cycloaddition strategies, were nevertheless also reported.

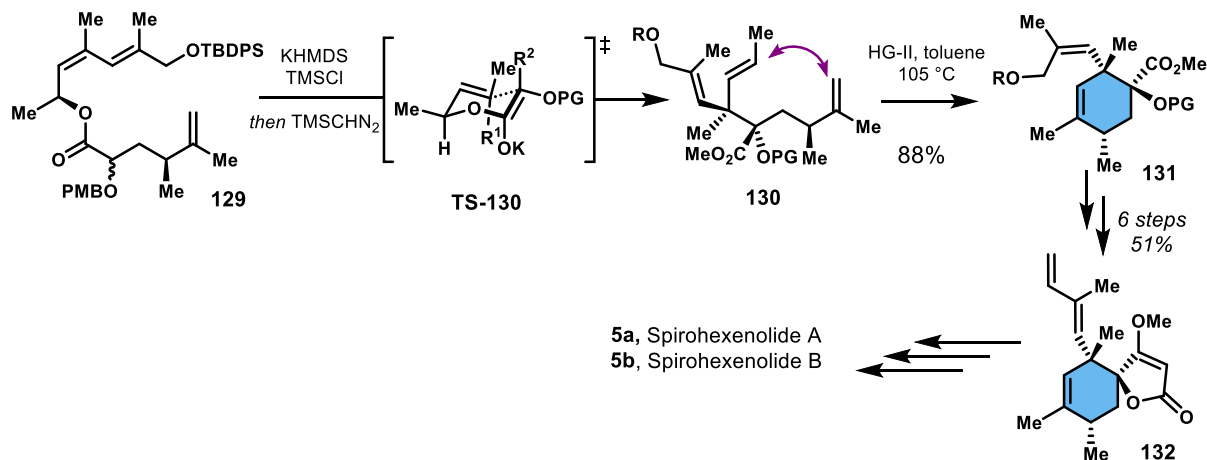
Roush's work related to quartromicins is a notable example of such an alternative strategy, wherein

enantioselective access to a functionalized cyclohexene precursor is achieved through an intramolecular aldol reaction [88]. The synthesis involves trialdehyde **125** (obtained in 11 steps), which undergoes an intramolecular aldol reaction, transiently forming a cyclohexanol that is trapped by the third aldehyde leading to bicyclic lactol **126** in 54% yield. Elimination of the hydroxy after several steps furnished an entry into the unsaturated cyclohexene that was finally converted through a Dieckmann condensation to spirotetronate (Scheme 25).

Retrosynthetic disconnections employing RCM have been explored in a few reports, demonstrating their utility in synthesizing functionalized cyclohexenes. In the context of spirotetronates, RCM requires the formation of a  $\beta$ -unsaturated ester,



**Scheme 25.** Enantioselective synthesis of an *endo* spirotetronate via an intramolecular aldolization step.



**Scheme 26.** Ireland–Claisen rearrangement followed by an RCM step *en route* to spirohexenolides.

typically synthesized via a Claisen rearrangement. An example of this strategy is found in the work of Bedel and co-workers, who used an Ireland–Claisen/metathesis sequence to generate precursors for quartromicins [89]. More recently, an enantioselective total synthesis of spirohexenolides A and B (**5a** and **5b**) utilized the same strategy, further illustrating the power of this approach [90]. In this synthesis, enantiopure ester **129** undergoes an Ireland–Claisen rearrangement with high yield and diastereoselectivity, driven by a chair-like transition state (Scheme 26). Two adjacent quaternary centers are formed in this step. The subsequent RCM

proceeded efficiently, achieving an 88% yield using the Hoveyda–Grubbs second-generation catalyst (HG-II). The succeeding steps included a Dieckmann cyclization to form spirotetronate **132**, another RCM to construct the macrocyclic backbone, and an elimination to introduce the unsaturation into the macrocycle [91–93]<sup>1</sup>. An alternative RCM-based strategy targeting versipelostatatin involved the formation of

<sup>1</sup>We encourage the interested reader to refer to the study for this last step, as it constitutes an elegant access to a bent  $\pi$ -conjugated macrocyclic system. For other examples of bent- $\pi$  macrocycle synthesis, see refs [91–93].

a cyclohexenone, followed by the stereoselective addition of a deprotonated alkyne to the ketone [94].

#### 4. Conclusion

Among the strategies discussed, the Diels–Alder cycloaddition between a diene and an acrolein derivative stands out as the most versatile and widely studied approach for spirotronate synthesis. The ease with which functionalized dienes can be accessed through reactions like Wittig olefination and vinyl lithium addition, combined with the utility of substituted acroleins, makes this method highly efficient for constructing spirotronate frameworks. However, enantioselective control remains a key challenge. Although asymmetric variants have been developed, they often require pre- and post-functionalization steps to manipulate chiral auxiliaries, adding complexity to the overall synthesis. The reported enantioselective Diels–Alder reaction achieving 72% enantiomeric excess using achiral substrates demonstrates progress, but further refinement is needed to increase both efficiency and stereocontrol.

The diastereoselective IMDA variants, particularly those leveraging biomimetic approaches with tetronate-type dienophiles, show promise for applications. Meanwhile, alternative strategies like the addition of acrylates to cyclohexanone and the use of RCM have shown potential but require further optimization, particularly in improving the selectivity and overall step economy of the synthesis. The recent successes in spirohexenolide synthesis highlight the potential of these methods when effectively applied, but they also underscore the significant challenges related to step count, diastereoselectivities, and enantioselectivities.

Looking ahead, future research should focus on improving the enantioselective control in Diels–Alder reactions by exploring new chiral catalysts or reagents that can enhance selectivity without necessitating multiple auxiliary steps. Additionally, integrating biomimetic strategies with catalytic approaches may offer new avenues to streamline the synthesis of spirotronates, particularly for complex natural products like spirohexenolides. Further investigation into RCM and the development of novel organocatalytic systems could provide more efficient routes to construct these intricate molecular

architectures. Ultimately, the goal will be to reduce the synthetic burden while achieving greater precision in stereoselectivity, enabling broader access to spirotronate-based natural products and their analogues.

#### Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

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