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Synthesis of α-*exo*-Methylene-γ-butyrolactone: Recent Developments and Applications in Natural Product Synthesis

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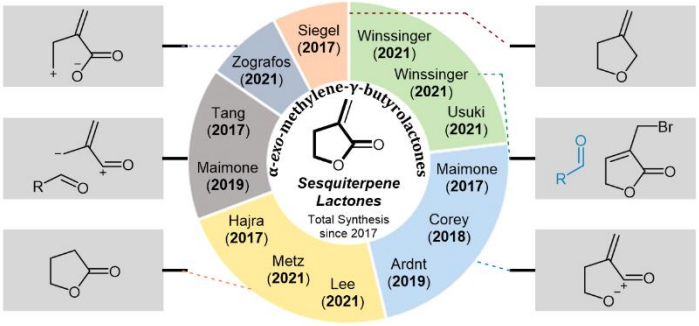


Abstract The α-exo-methylene-γ-butyrolactone moiety is present in a vast array of structurally diverse natural products and is often central to their biological activity. In this review, we summarize new approaches to α-exo-methylene-γ-butyrolactones developed over the past decade as well as their applications in total synthesis.

Key words natural product, α-exo-methylene-γ-butyrolactone, total synthesis, sesquiterpene lactone, lignan

1 Introduction

The α-*exo*-methylene-γ-butyrolactone moiety is preponderant in sesquiterpenes. Over 5800 α-*exo*-methylene-γ-butyrolactone containing natural products have been included in encyclopedic Dictionary of Natural Products (DNP) database, constituting 1/7 of natural occurring unsaturated ester and 2% of natural product repertoire.[1] The α-*exo*-methylene-γ-butyrolactone moiety frequently acts as a warhead, resulting in a covalently engagement with its target proteins. The unique electrophilicity profile makes it an important Michael acceptor[2] amongst covalent inhibitors.[3] Significantly, despite the commonality of this motif in numerous natural products, detailed investigations have shown that their biological activity is very diverse and the same Michael acceptor has been found to engage structurally and functionally diverse target protein. For example, studies into the mode of action and target of parthenolide,[4] helenalin,[5] ainsliadimer A,[6] deoxyelephantopin,[7] xanthatin,[8] and goyazensolide[9] have shown selective engagement of transcription factors, kinases, and an importin (Figure 1). The biological activity of these natural products coupled to the resurging interest in covalent inhibition is bringing renewed focus on the rapid construction of α-*exo*-methylene-γ-butyrolactone as well as total synthesis of natural products bearing this motif.

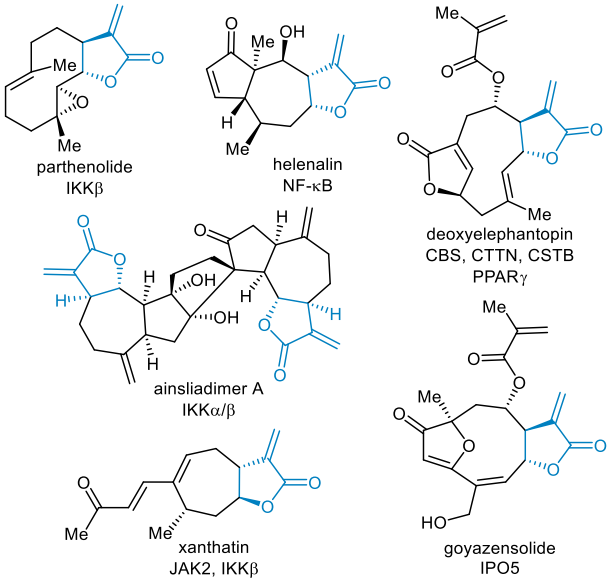


Figure 1 Structures of representative sesquiterpene lactones

The synthesis of α-*exo*-methylene-γ-butyrolactones has been well reviewed[10] but the renaissance of interest has yielded impressive progresses and applications in the past 10 years. In this review, we summarize the developments in the synthesis of α-*exo*-methylene-γ-butyrolactones, especially enantioselective syntheses and newly developed strategies, as well as their applications in natural products total synthesis ranging from January 2009 to June 2021.

2 Approaches to α-*exo*-Methylene-γ-butyrolactones

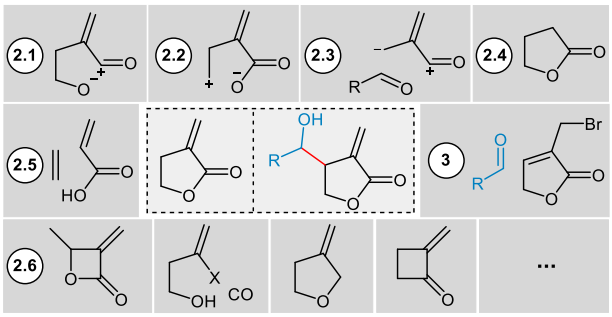
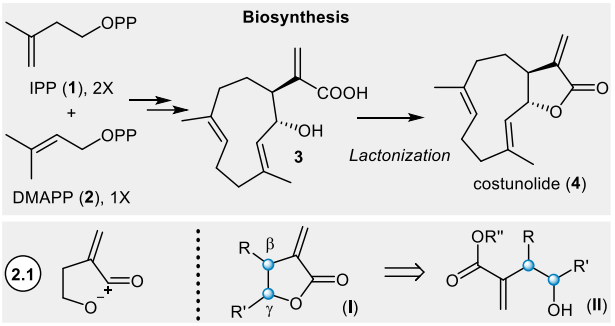


Figure 2 Formation of α-exo-methylene-γ-butyrolactone

The possible retrosynthetic disconnections of the α-*exo*-methylene-γ-butyrolactone are shown in Figure 2 (each given a number from corresponding to the section of discussion 2.1, 2.2... to 3). With the remarkable advances in synthetic methodologies, including organo-catalysis[11] and C–H functionalization,[12] the repertoire of synthetic methodologies to access α-*exo*-methylene-γ-butyrolactone continues to grow. These include the enantioselective synthesis via lactonization (2.1)/halolactonization (2.2), enantioselective synthesis through Barbier allylation (2.3), C–H insertion/olefination sequence (2.4), alkene cyclization (2.5) as well as newly developed strain-driven dyotropic rearrangements (2.6). Amongst the >5800 α-*exo*-methylene-γ-butyrolactone containing natural products, over half members contain β-hydroxymethylalkyl substitutions. Hence, methods for the direct synthesis of β-hydroxymethylalkyl-α-exo-methylene-γ-butyrolactones are given in Section 3.

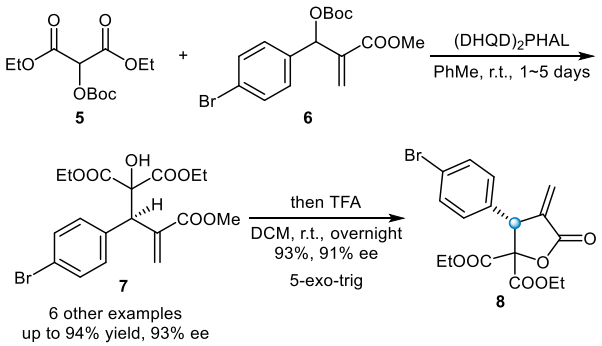
2.1 Enantioselective Synthesis via Lactonization Approach

Lactonization approach, which is also the biosynthetic route (Scheme 1), has been widely used and well covered in previous reviews.[10] Biogenetically, the formation of costunolide (**4**) derives from lactonization of its biosynthetic precursor **3**.[13] Following the biosynthetic route, the formation of chiral intermediates **II** can be used to gain access to optically active β/γ-substituted α-*exo*-methylene-γ-butyrolactones (Scheme 1, **I**).



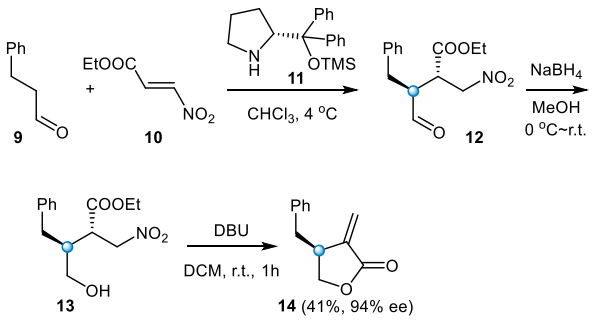
Scheme 1 Synthesis via lactonization approach

The lactonization can be combined with clever methodology to access intermediate **II** for a one-pot operation. For instance, Rios and co-workers reported a highly enantioselective one-pot organocatalytic synthesis of α-*exo*-methylene-γ-butyrolactones via a Morita–Baylis–Hillman reaction / lactonization sequence (Scheme 2).[14] In the presence of catalytic amount of a Lewis base [(DHQD)$_2$PHAL], the Morita–Baylis–Hillman carbonate **6** undergoes a double S$_N$2' reaction yielding the coupling product **7**. A subsequent acid-catalyzed 5-*exo*-trig cyclization performed in the same reaction vessel delivered chiral α-*exo*-methylene-γ-butyrolactone **8**.



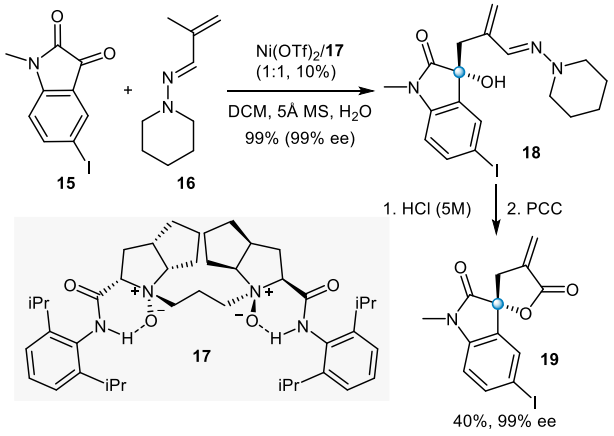
Scheme 2 Rios's one-pot organocatalytic synthesis of α-*exo*-methylene-γ-butyrolactones

There are also some recent examples of stepwise synthesis of α-*exo*-methylene-γ-butyrolactones via β/γ-stereocenter construction (**II**, Scheme 1) followed by lactone formation (**I**). In 2017, Jørgensen and co-workers developed a one-pot α-alkenylation/reduction/lactonization process for the preparation of α-*exo*-methylene-γ-butyrolactones in a highly enantioselective manner (Scheme 3).[15] After the organocatalized reaction of aldehyde **9** with nitroacrylate **10**, a NaBH$_4$ reduction of **12** was carried out in a one-pot manner to give alcohol **13**. DBU treatment along with transesterification and elimination of the nitro group provides **14** in 41% overall yield and 94% ee.



Scheme 3 Jørgensen's stepwise synthesis of optically active α-*exo*-methylene-γ-butyrolactones

In 2018, Feng, Cao and co-workers reported the construction of chiral α-*exo*-methylene-γ-butyrolactones via catalytic enantioselective ene-type reactions (Scheme 4).[16] The catalytic asymmetric ene-type reaction between isatin **15** and hydrazone **16** was accomplished by using chiral N,N'-dioxide (**17**)–nickel complex as catalyst with excellent yield (99%) and ee (99%). Further two-step transformation (hydrolysis and oxidation) from **18** gave rise to bioactive spiro-fused 2-oxindole-α-*exo*-methylene-γ-butyrolactone **19** in moderate yield.

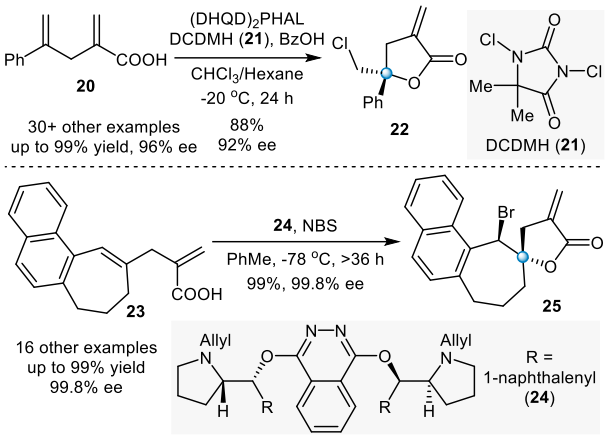


Scheme 4 Feng and Cao's stepwise synthesis of optically active α-*exo*-methylene-γ-butyrolactones

2.2 Enantioselective Halolactonizations

Historically, halolactonization is an important approach to lactones in racemic or diastereomeric versions.[17] Accordingly, it has also been applied to the construction α-*exo*-methylene-γ-butyrolactones as documented in previous reviews.[10] However, the emergence of asymmetric counter anion directed catalysis has now enabled asymmetric syntheses of α-*exo*-methylene-γ-butyrolactones.

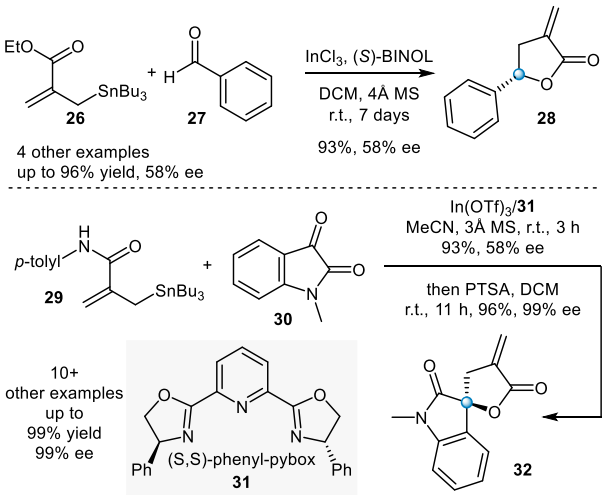
As shown in Scheme 5, an organocatalytic halolactonization approach was utilized by Jiang's research group in their synthesis of enantioenriched α-*exo*-methylene-γ-butyrolactones.[18] Prochiral dienoic acids (**20** as an example) can be employed as starting materials and the γ-disubstituted α-*exo*-methylene-γ-butyrolactone **22** was obtained by using $(DHQD)_2PHAL$ as catalyst and 1,3-dichloro-5,5-dimethyl-hydantoin (DCDMH, **21**) as electrophilic chlorine source. In another example spiro α-*exo*-methylene-γ-butyrolactone **25** was obtained using phthalazine catalyst **24** with high yield and ee from precursor **23**.



Scheme 5 Jiang's organocatalytic halolactonization

2.3 Enantioselective Barbier-type Allylation

Schmidt first demonstrated the one pot synthesis of α-*exo*-methylene-γ-butyrolactone from bromomethylacrylic ester and aldehyde or ketone using a Barbier allylation in 1970.[19] This reaction was subsequently adapted with chiral auxiliaries to set the desired stereochemsitry[10] with a variety of different metal reagents including zinc as in the original Barbier allylation or boron, silicon, chromium, tin, indium and nickel. The reactions proceed through a Zimmerman Taxler transition state[20] affording the expected *syn*/*anti* selectivity based on the alkene geometry. In the past decade, a series of novel catalytic methods to obtain chiral γ-substituted α-*exo*-methylene-γ-butyrolactones have been reported.

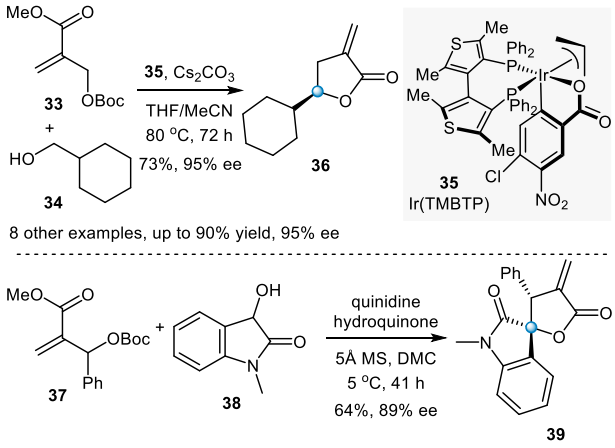


Scheme 6 Yoda's enantioselective allylation of aldehydes with β-carbonyl allyltributylstannanes

Yoda's group used an ethylacrylate ester substituted at the allylic position with a tributylstannane (**26**) in the presence of $InCl_3$/BINOL for a catalytic enantioselective allylation of aldehydes, affording the product in high yield (Scheme 6).[21] Although only modest enantioselectivities was observed, this method benefits from being catalytic and enantioselective without employing chiral auxiliaries. When the β-alkoxycarbonyl

allyltributylstannanes (for example **26**) was replaced with N-substituted β-amido allyltributylstannanes (ex. **29**), the two steps transformation-allylation/lactonization gave higher *ee* (up to 79% ee).[21] Further exploration of chiral ligands for the Lewis acid resulted in near perfect enantioselectivity. For example, the use of (*S*,*S*)-phenyl-pybox **31** as ligand and N-methyl isatin **30** as substrate resulted in the formation of spiro α-*exo*-methylene-γ-butyrolactone **32** in 99% ee (Scheme 6).[22] The reaction scope could be further extended to α-ketoesters, generating γ-disubstituted α-*exo*-methylene-γ-butyrolactones with excellent performance.[23]

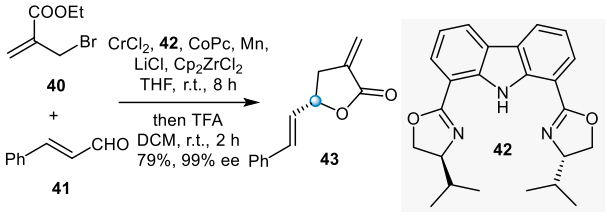
Krische and co-workers applied the elegant transfer hydrogenative C-C coupling methodology pioneered by his group *en route* to enantiomerically enriched γ-substituted α-*exo*-methylene-γ-butyrolactones (Scheme 7).[24] Upon exposure of acrylic ester **33** to alcohol **34** in the presence of Ir(TMBTP) (**35**), desired butyrolactone **36** in good yield with 95% ee. Similar results were obtained with more substrates with good to excellent and high enantioselectivities ranging from 82 to 95% ee. Subsequently, they extended their methodology to synthesize spiro/ γ-disubstituted α-*exo*-methylene-γ-butyrolactones from vicinal diols and hydroxyl-substituted methacrylate.[25]



Scheme 7 Krische's and Wang's synthesis of α-*exo*-methylene-γ-butyrolactones

A related approach was reported by Wang's group using organocatalysis with quinidine as the chiral oraganocatlyst and hydroquinone as the organic oxidant. The sequential allylic alkylation/cyclization of phenyl acrylic ester (**37** as an example) and 3-hydroxyoxindoles (**38** as an example) afforded spiro α-*exo*-methylene-γ-butyrolactones in good yields and with excellent diastereo- and enantioselectivities.[26]

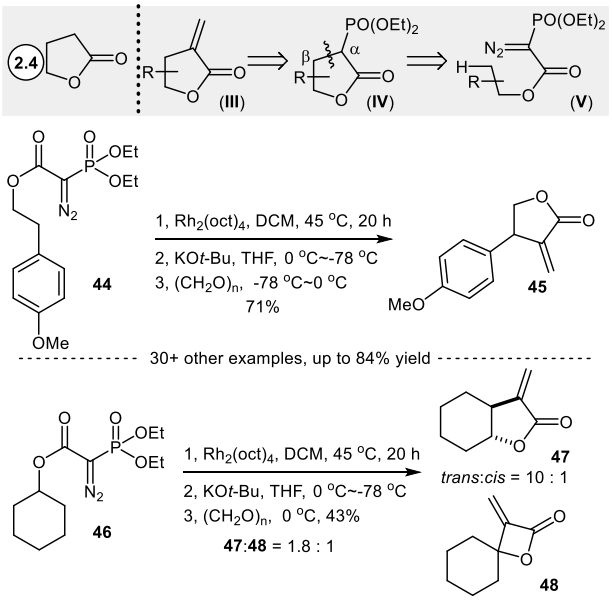
In 2015, Zhang and co-workers reported a highly enantioselective allylation approach based on chromium and carbazole-based bisoxazoline ligand (Scheme 8).[27] The reaction was shown to have good substrate scope with broad tolerance to sensitive functionalities. A variety of γ-substituted α-*exo*-methylene-γ-butyrolactones were obtained with excellent yield and enantioselectivity. As an example, α-*exo*-methylene-γ-butyrolactone **43** was generated from cinnamaldehyde **41** and ethyl 2-(bromomethyl) acrylate **40** in 79% yield and 99% ee.



Scheme 8 Zhang's synthesis of α-*exo*-methylene-γ-butyrolactones

2.4 C–H Insertion/Olefination Sequence

The field of C-H functionalization has grown tremendously during last two decades and rhodium-catalyzed intramolecular insertion of a carbene into a C–H bond is a powerful approach.[12] This methodology has been cleverly applied to the synthesis of α-*exo*-methylene-γ-butyrolactones. The α,β-position disconnection (Scheme 9, **IV**) could result in a sp3 carbon and reactive carbonyl position (**V**) which is poised for carbene insertion.



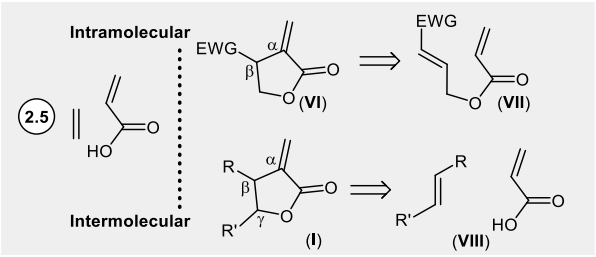
Scheme 9 C–H Insertion/olefination sequence

In 2014, a one-pot C–H insertion/olefination sequence for the conversion of α-diazo-α-(dialkoxyphosphoryl)acetates into α-alkylidene-γ-butyrolactones was reported by Taylor, Unsworth and co-workers (Scheme 9).[28] Heating diazophosphonate **44** in the presence of 2 mol % of $Rh_2(oct)_4$ furnished the desired C-H insertion product with only nitrogen gas as byproduct. The subsequent Horner–Wadsworth–Emmons (HWE) olefination resulted in the formation of α-methylene-γ-butyrolactone **45** in good overall yield and the sequence could be carried out in one pot. Bicyclic ring scaffolds were also tested, employing cyclic alcohol as starting material (Scheme 9).[28b,29] The α-*exo*-methylene-γ-butyrolactone **47** was formed in a 10:1 trans/cis ratio and insertion took place predominantly into the equatorial C-H bond, along with spiro analogue **48** as by-product. Finally,

this methodology has also been used in total synthesis of lignans and eudesmanolides (*vide infra*, section 4).

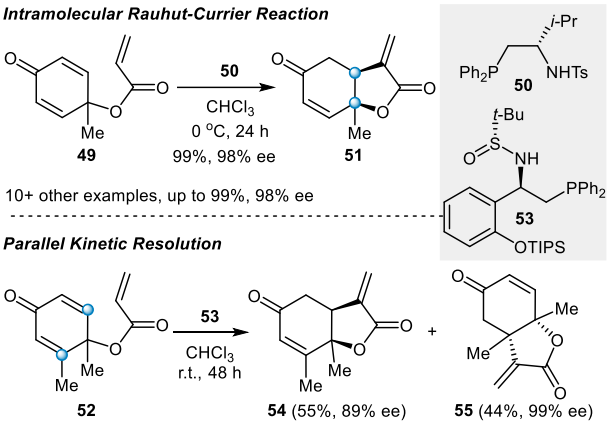
2.5 Alkene Cyclization

Another α,β-disconnection of α-*exo*-methylene-γ-butyrolactones can be envisioned with intramolecular Rauhut–Currier reaction (Scheme 10). Intermediate **VII** undergoes a vinylogous Marita-Baylis-Hillman addition to make the α-position of the acrylate (latent enolate) attack to β-position, resulting in the formation of bicyclic α-*exo*-methylene-γ-butyrolactones. Intermolecularly, further disconnection of the γ-C-O bond reveals readily available acrylic acid and various alkenes (Scheme 10, **VIII**).



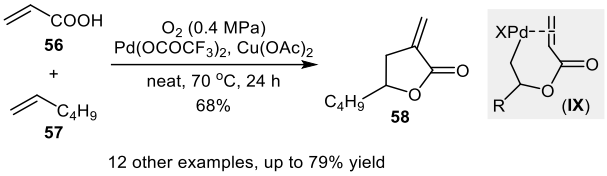
Scheme 10 Alkene cyclization approach

In 2012, a highly chemo-, diastereo-, and enantioselective organocatalytic Rauhut–Currier reaction was reported by Sasai and co-workers.[30] The prochiral dienone **49** (Scheme 11), easily accessible from readily available phenol, was successfully cyclized in the presence of chiral acid-based organocatalyst **50**. The enantioselective Rauhut–Currier process produced the highly functionalized α-*exo*-methylene-γ-butyrolactone **51** as a single diastereomer with 98% ee. Shortly after, Zhang's group performed this reaction with Xiao-Phos catalyst **53**.[31] Moreover, kinetic resolution and parallel kinetic resolution were also realized. For example, parallel kinetic resolution of *rac*-**52** afforded enantioenriched (+)-**54** and (+)-**55** with great efficiency.



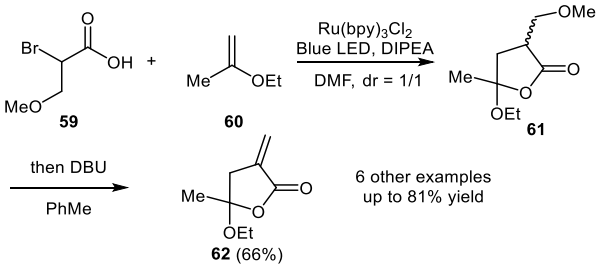
Scheme 11 Rauhut–Currier approach from Sasai and Zhang.

The alkene cyclization can also be performed in an intermolecular manner. Yonehara and co-workers developed a novel palladium catalyzed aerobic intermolecular cyclization of acrylic acid with alkenes to afford α-*exo*-methylene-γ-butyrolactones from the simplest starting materials (Scheme 12).[32] The catalytic system $Pd(OAc)_2/Cu(OCOCF_3)_2$ was very effective to transform acrylic acid **56** with 1-hexene **57** to the desired product in good isolated yield (68%). During this process, palladium (II) selectively complexing olefin **57** followed by an addition of the acid on the more substituted carbon yielding oxypalladation intermediate **IX** poised to undergo a Heck coupling to give α-*exo*-methylene-γ-butyrolactone **58**. Oxidation of the resulting Pd (0) back to Pd (II) completes the catalytic cycle.



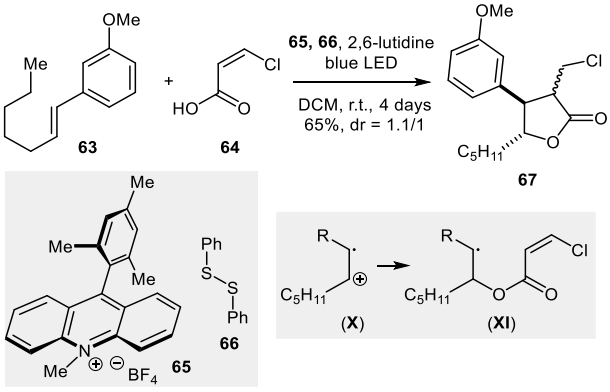
Scheme 12 Yonehara's intermolecular cyclization of acrylic acid with alkene

Similar transformations using organic photoredox catalyst[33] system were also reported. Very recently, a consecutive visible-light photoredox-catalyzed formal [3+2] cycloaddition/ β-elimination process was reported by Tang and co-workers (Scheme 13).[34] Using 2-bromo-3-methoxy propionic acid **59** and 2-ethoxypropene **60** as reaction pairs, [3+2] cycloaddition was achieved in the presence of $Ru(bpy)_3Cl_2$ with blue LED as light source, yielding **61**. A subsequent β-elimination with DBU to afforded α-*exo*-methylene-γ-butyrolactone **62** in 66% yield**.**



Scheme 13 Tang's intermolecular cyclization of acrylic acid with alkene

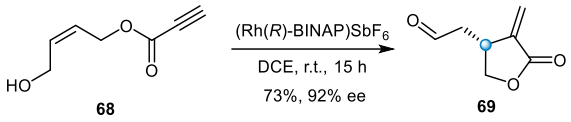
Another example was reported by Nicewicz and co-workers. A polar radical crossover cycloaddition system was applied to synthesis of γ-butyrolactones, which can act as precursor of α-*exo*-methylene-γ-



Scheme 14 Nicewicz's intermolecular cyclization of acrylic acid with alkene

butyrolactones (Scheme 14).[35] In the presence of cridinium photooxidant **65** and cocatalyst **66**, the alkene **63** is oxidized to a radical cation (**X**) which undergoes an addition of carboxylic acid **64** to radical **XI** *en route* to a 5-exo-trig radical cyclization. Lactone **67** could be obtained in good yield and a 1.1:1 dr. Further treatment of **67** with mild basic conditions to promote the chloride elimination would afford the desired α-*exo*-methylene-γ-butyrolactone.

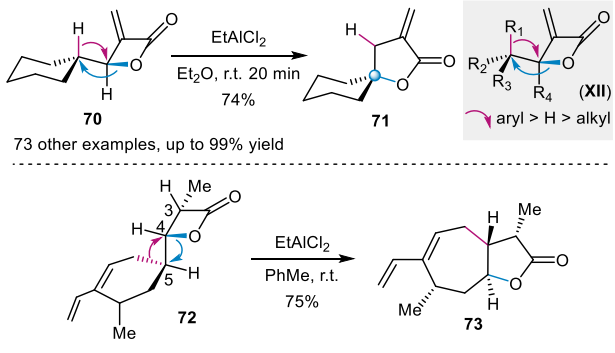
An interesting variant is the enyne cycloisomerization developed by Hodgson's group (Scheme 15).[36] Rhodium(I) catalysis using [Rh((*R*)-BINAP)]SbF_6 gave desired product **69** in 73% yield and 92% ee from terminal alkynyl ester **68**. This reaction act as a key step in their total synthesis of (+)-anthecotulide (*vide infra*, section 4).[36]



Scheme 15 Hodgson's enyne cycloisomerization

2.6 Strain-Driven Dyotropic Rearrangement

Dyotropic reaction, a new class of pericyclic reactions in which two σ-bonds simultaneously migrate intramolecularly, has attracted the curiosity of the synthetic community since its discovery in 1972.[37] β-lactones bearing different substitution patterns have been widely used in such rearrangement.[38] For α-methylene-β-lactones, an unprecedented strain-driven dyotropic rearrangement has been realized by Tang's group, which enabled efficient access to a wide range of α-*exo*-methylene-γ-butyrolactones (Scheme 16).[39]

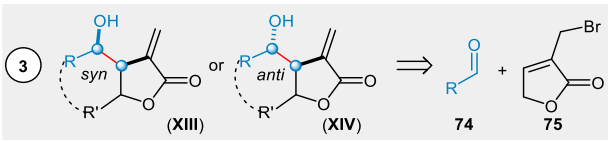


Scheme 16 Strain-Driven dyotropic rearrangement

A broad range of α-methylene-β-lactones (over 70 substrates) has been tested and remarkable structural diversity have been accessed. For example, the rearrangement of β-lactone **70** smoothly produced **71** in the presence of $EtAlCl_2$ with 74% yield. More importantly, the stereospecific dyotropic rearrangement renders the reaction predictable and controllable (migration aptitude of R_1: aryl>H>alkyl, **XII**). The reaction mechanism was further examined by computational studies, indicating an asynchronous concerted mechanism.[39] This is distinct from the previously reported dyotropic reactions. 3,4-*cis*-disubstituted β-lactone **72** underwent a different rearrange pathway with alkyl migration instead of C5-H to give lactone **73**.[40]

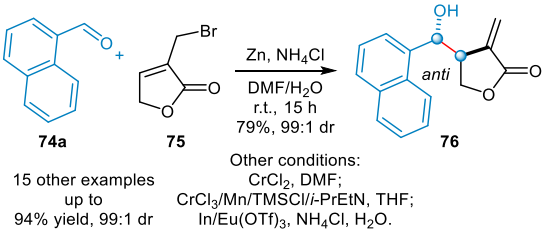
3 β-(Hydroxymethylalkyl)-α-*exo*-methylene-γ-butyro-lactones

A significant portion of natural product endowed with α-*exo*-methylene-γ-butyrolactone (*ca.* half) contain a hydroxyl group adjacent to the γ-butyrolactone (Scheme 17). This β-hydroxyl group is present in both diastereoisomeric relationship with respect to γ-butyrolactone, i.e. *syn*-**XIII** /*anti*-**XIV** configurations of these contiguous stereo centers are present amongst natural products. Direct access to β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactones from readily available reactants is of great interest and have attracted significant attention from the synthetic community. The diastereoselective aldehyde allylation using bromolactone **75** affords a rapid entry into this privileged structures (Scheme 17).



Scheme 17 Formation of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

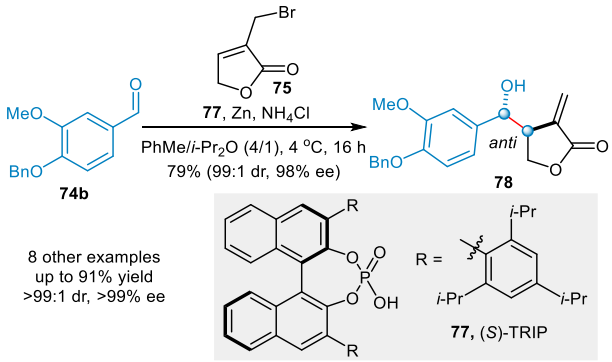
Hodgson and co-workers recognized the potential of this strategy and explored the scope of the chemistry (Scheme 18).[41] Bromolactone **75**, was conveniently prepared from commercially available tulipalin A in two steps with only one purification step. The use of zinc (Zn^0/NH_4Cl), chromium (Cr^{2+}), or indium (In/Eu(OTf)$_3$) gave in all cases one major *anti*-diastereoisomer (for example **74a**+**75**→**76**) based on a Zimmerman–Traxler transition state.[20] Good yields and high diastereoselectivities were observed with different aromatic or nonaromatic aldehydes. Conditions using chromium ($CrCl_3$/Mn/TMSCl) were found to be more effective for nonaromatic aldehydes. This methodology was further demonstrated in their concise syntheses of natural products (*vide infra*, section 4). A parallel report from Xu's group focused on zinc or indium-mediated Barbier-type allylation in aqueous media, providing an efficient, operationally simple route to α-*exo*-methylene-γ-butyrolactones.[42]



Scheme 18 Hodgson's synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

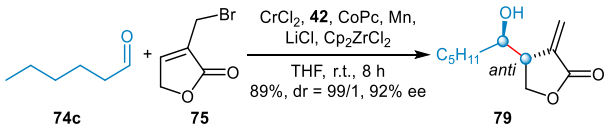
For asymmetric allylation, a chiral BINOL-derived phosphoric acid (TRIP, **77**) was employed[43] as exemplified in Scheme 19. The allylzinc species generated from bromolactone **75** can react with various aldehydes (for example, **74b**), leading to optically active β-(hydroxymethylalkyl)-α-*exo*-

methylene-γ-butyrolactones (**78**) in high isolated yields and almost perfect enantio- and diastereoselectivities. The computational study revealed that the chiral phosphate acted as a counterion for the Lewis acidic zinc ion for the activation of the aldehyde.[43c]



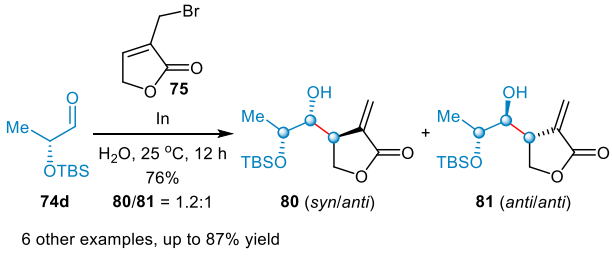
Scheme 19 Asymmetric synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

The system used for construction of optically active α-*exo*-methylene-γ-butyrolactones developed by Zhang's group[27] is also suitable for bromolactone **75** and hexanal **74c** (Scheme 20). In their reaction, the corresponding β-substituted lactone **79** was obtained in 89% yield with 99/1 dr and 92% ee.



Scheme 20 Zhang's synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

Barbier allylation can yield excellent diastereoselectivity with chiral substrates (both aldehyde and bromolactone have been explored as chiral precursors). Thus, capitalizing on pre-installed stereocenters provides an alternative route to biologically important α-*exo*-methylene-γ-butyrolactones. While excellent diastereoselectivities have been observed with chiral bromolactones, poorer diasteroselectivity are obtained with chiral aldehydes. For example, α-chiral aldehyde **74d** did not afford meaningful diastereoselectivity (Scheme 21).[44] However, more functionalized, and sterically differentiated aldehydes yielded better *anti*/*anti*-diastereomer ratios (*vide infra*, section 4).

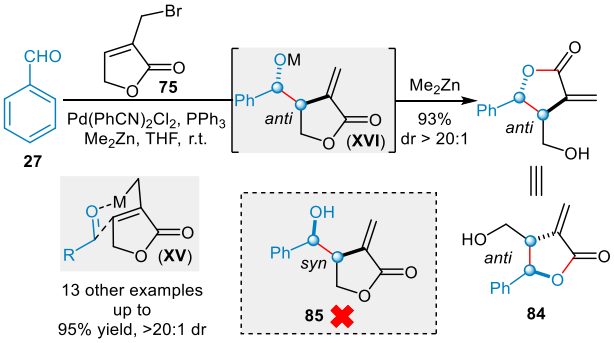


Scheme 21 Xu's synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

In the context of our study of deoxyelephantopin, we used the zinc-mediated Barbier allylation of chiral bromolactones with a γ-substituent, which led to coupling products with three contiguous stereocenters with high diastereoselectivity induced by the first γ-stereocentre.[7,45] For example, zinc-mediated Barbier coupling of **82** with aldehyde **74e** provided secondary alcohol **83** with high *anti*/*anti* diastereoselectivity (Scheme 22). Subsequently, our group developed a rapid and scalable route to chiral bromolactones as enabling precursors in the synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactones.[46]

Scheme 22 Winssinger's synthesis of β-(hydroxymethylalkyl)-α-*exo*-methylene-γ-butyrolactone

It is generally accepted that the aldehyde allylation with bromolactone proceeds through on a Zimmerman–Traxler transition state and results in *anti*-configuration for the newly formed stereocenters (Scheme 23, **XV**). There is a demand for methodologies affording the *syn*-configuration. A pioneering work was reported by Xu and co-workers in 2013.[47] In this publication, a diastereoselective Pd-catalyzed allylation of aromatic and aliphatic aldehydes with **75** was developed with the aim of accessing a *syn*-configuration in the newly formed stereocenters. However, when we revisited this methodology, we found that the transformation with 1 equiv, or a slight excess, of dimethyl zinc afforded the *trans*-configuration (as shown in **XVI**, scheme 23), and the use of an excess of dimethyl zinc simply promoted a further translactonization to give β-hydroxymethyl-α-*exo*-methylene-γ-butyrolactones (Scheme 23, **84**).[48] However, this investigation revealed that *syn*-**85** was unavailable from this palladium chemistry. This palladium catalyzed Barbier allylation/translactonization cascade reaction was exploited for the rapid construction of β, γ-disubstituted α-methylene-γ-butyrolactones. This sequence was further harnessed for the successful syntheses of paraconic acids and 1,10-*seco*-guaianolides (*vide infra*, Section 4).



Scheme 23 Winssinger's synthesis of β,γ-disubstituted-α-*exo*-methylene-γ-butyrolactone

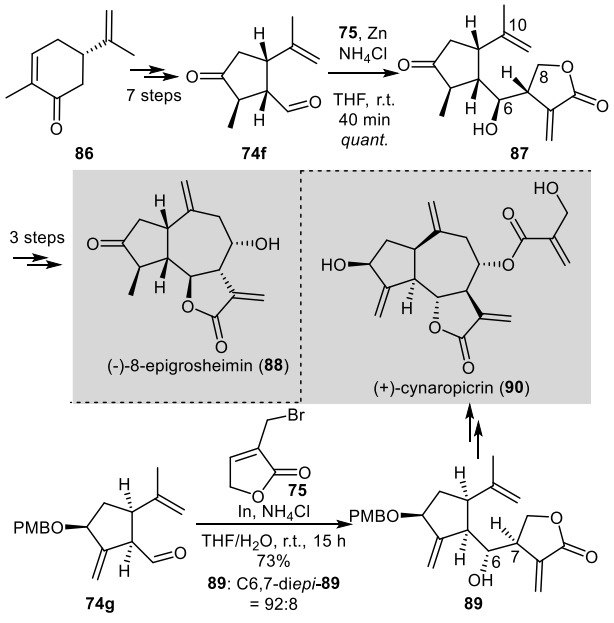
Finally, an intramolecular version of Barbier-type allylation was investigated and applied in a total synthesis of several sesquiterpene lactones (*vide infra*, Section 4).

4 Applications in Total Synthesis

The α-*exo*-methylene-γ-butyrolactone substructure is most abundant in sesquiterpene lactones[49] but can be found in other natural products such as cembranolides,[50] avenaciolides,[51] paraconic acids[52] as well as other monocyclic compounds. The applications of different synthetic approaches in total synthesis have been well covered in earlier reviews;[10] this section will thus focus on the applications of methodologies discussed above. Beyond terpenes, lignans[53] also count numerous members with α-substituted-γ-butyrolactones intermediates and their synthesis has harnessed the chemistry of α-*exo*-methylene-γ-butyrolactone.

4.1 Sesquiterpene Lactones

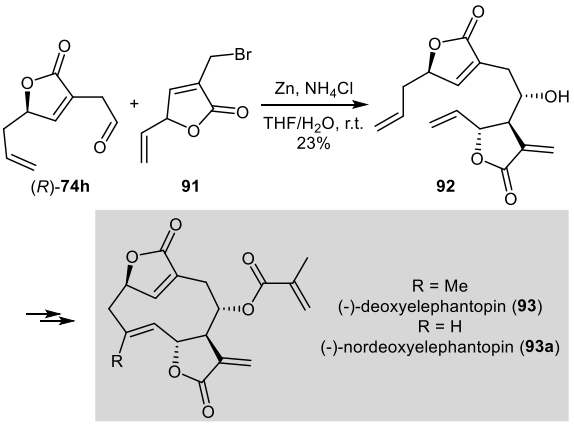
(+)-8-Epigrosheimin was initially isolated as an amoebicidal and antibiotic guaianolide.[54] In 2011, Xu's group reported a highly diastereoselective and efficient total synthesis of its enantiomer, (−)-8-epigrosheimin (**88**), which showed promising antitumor activities (Scheme 24).[55] One of the key steps of the synthesis is the stereo- and regioselective allylation with bromolactone **75**. Using (*S*)-carvone (**86**) as starting material, aldehyde **74f** was



Scheme 24 Total syntheses of (−)-8-epigrosheimin by Xu and (+)-cynaropicrin by Usuki

synthesized in 7 steps. The zinc reagent generated from bromolactone **75**, reacted smoothly with the α-branched aldehyde **74f** to give the anticipated lactone **87** as a sole product. With **87** in hand, further transformations including C6-C8 translactonization, oxidation of the primary alcohol and aldehyde-ene cyclization (C8-C10) affording (−)-8-epigrosheimin (**88**) in 11 steps. Very recently, a similar application was reported by Usuki and co-workers for the total synthesis of bitter-tasting (+)-cynaropicrin (**90**, Scheme 24).[56] After optimization of the reaction conditions, it was found that In(0) was the best metal for the Barbier-type reaction. Key intermediate **89** was successfully obtained in 73% yield with high diastereoselectivity.

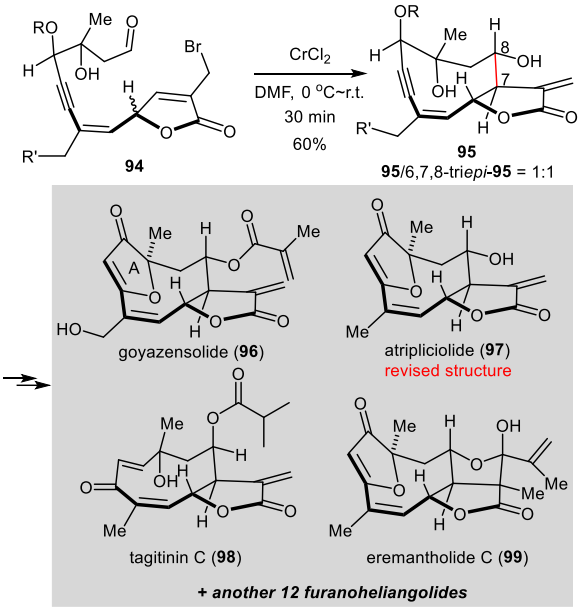
Our interest in covalent inhibitors led us to investigate deoxyelephantopin and goyazensolide. In the context of our study of (-)-deoxyelephantopin (**93**), a substrate controlled Barbier-type allylation was used (Scheme 25).[7] In this reaction, enantiomerically enriched (*R*)-**74h** was prepared using an enantioselective allylic alkylation of cyclic dienol carbonates,[57] that was then subjected to a reaction with bromolactone **91** using zinc activation. The anticipated diastereomer **92** was successfully isolated thus enabling the synthesis of (-)-nordeoxyelephantopin (**93a**). Using alkyne-tagged cellular probes, we found that deoxyelephantopin is a potent covalent antagonist of PPARγ, targeting its zinc-finger motif.[7]



Scheme 25 Winssinger's synthesis of (-)-nordeoxyelephantopin

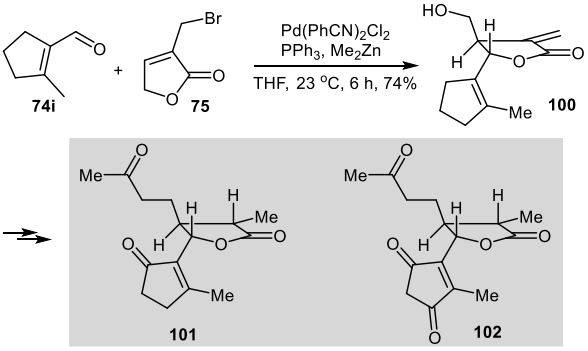
In the context of our study of goyazensolide (Scheme 26, **96**), we relied on an intramolecular substrate controlled Barbier-type allylation.[9] The key intermediate **94** was prepared using a Sonogashira coupling followed by a PBr_3 treatment to unmask the aldehyde and form the bromolactone. The use of stoichiometric $CrCl_2$ afforded a clean transformation to the challenging strained germacrene lactone **95**. This is the first example merging the closure of a 10-membered germacrene framework with the α-methylene-γ-butyrolactone formation. Germacrene lactone **95** was further derivatized for the total synthesis of sesquiterpene lactones. The furano A ring was constructed with gold-catalyzed transannulation. Overall, this strategy enabled the total synthesis of 16 structurally diverse natural products including goyazensolide (**96**), tagitinin C (**98**) and erementholide C (**99**). Our studies also revised the stereochemical assignment of atripliciolide (**97**).

Using an alkyne-tagged cellular probe, we discovered that goyazensolide covalently targets the oncoprotein importin-5 (IPO5), inhibiting its interaction with cargo proteins. It was further demonstrated that goyazensolide inhibits the translocation of RASAL-2, providing a rational for its antitumor activity.



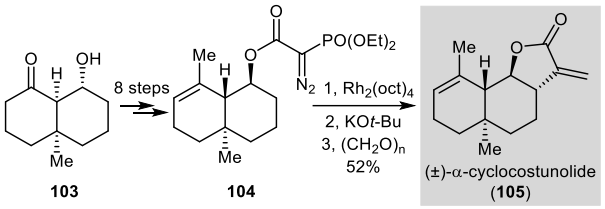
Scheme 26 Winssinger's syntheses of 16 sesquiterpene lactones

Another application of Barbier-type allylation comes from our total synthesis of 1,10-*seco*-guaianolides.[48] Building upon our investigation on Pd-catalyzed Barbier-type allylation, we harnessed the allylation/translactonization cascade in total synthesis of various natural products. As shown in Scheme 27, treatment of aldehyde **74i** with bromolactone **75** under the palladium allylation condition cleanly afforded the anticipated transesterified product **100**. Subsequent adjustment of oxidation state and proline-catalyzed aldol condensation[58] completed the 6-steps racemic synthesis of two 1,10-*seco*-guaianolides: 3-deshydroxy-iso-*seco*-tanapartholide (**101**) and 1,10-dioxo-1,10-deoxy-1,10-secogorgonolide (**102**).



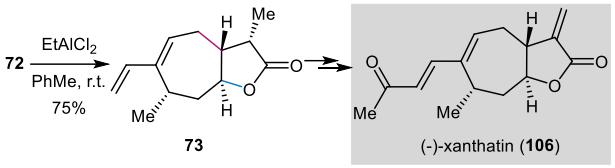
Scheme 27 Winssinger's synthesis of 1,10-*seco*-guaianolides

α-Cyclocostunolide (Scheme 28, **105**) is a *trans*-decalin eudesmanolide natural product with anti-trypanosomal and anti-coagulant activities.[59] In 2016, Taylor, Unsworth and co-workers reported the total synthesis of (±)-α-cyclocostunolide with the help C–H insertion/olefination sequence (2.4).[60] Starting from cis β-hydroxyketone **103**, diazophosphonate **104** was obtained in 8 steps (Scheme 28). Subsequently, α-cyclocostunolide (**105**) was isolated as the sole product under one-pot C–H insertion/olefination conditions.



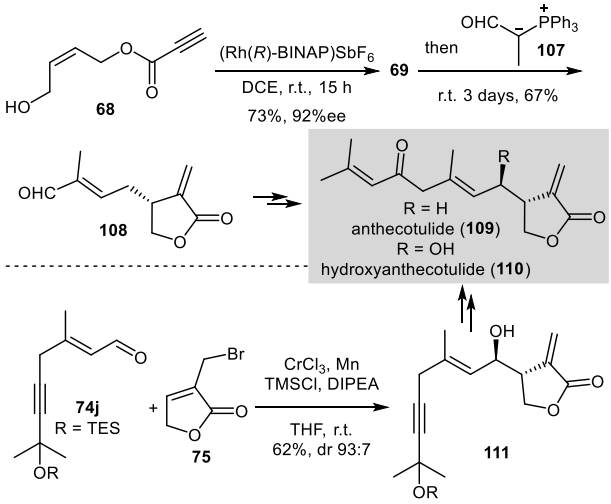
Scheme 28 Total synthesis of (±)-α-cyclocostunolide by Taylor and Unsworth

In 2012, Tang and co-workers reported the collective total synthesis of bioactive xanthanolides isolated from the genus *Xanthium* (Scheme 29).[40] Controllable dyotropic rearrangement product **73** was obtained as illustrated in Scheme 16 and was used in their formal synthesis of (-)-xanthatin (**106**).



Scheme 29 Tang's formal synthesis of (-)-xanthatin

Anthecotulide (**109**) and hydroxyanthecotulide (**110**) are bioactive linear sesquiterpene lactones (Scheme 30).[61] The irregular structures demonstrated antibacterial, antimalarial, trypanocidal, and leishmanicidal activity. In 2011, Hodgson's group reported the six-step synthesis of (+)-anthecotulide employing asymmetric enyne rearrangement (2.5, Scheme 15) to construct the α-*exo*-methylene-γ-butyrolactone core **108**.[36] In a follow-up publication, (±)-hydroxyanthecotulide **110** was achieved in 7 steps, involving a stereoselective Cr(II)-catalysed synthesis of **111** from allylation reaction between bromolactone **75** and aldehyde **74j**.[62]



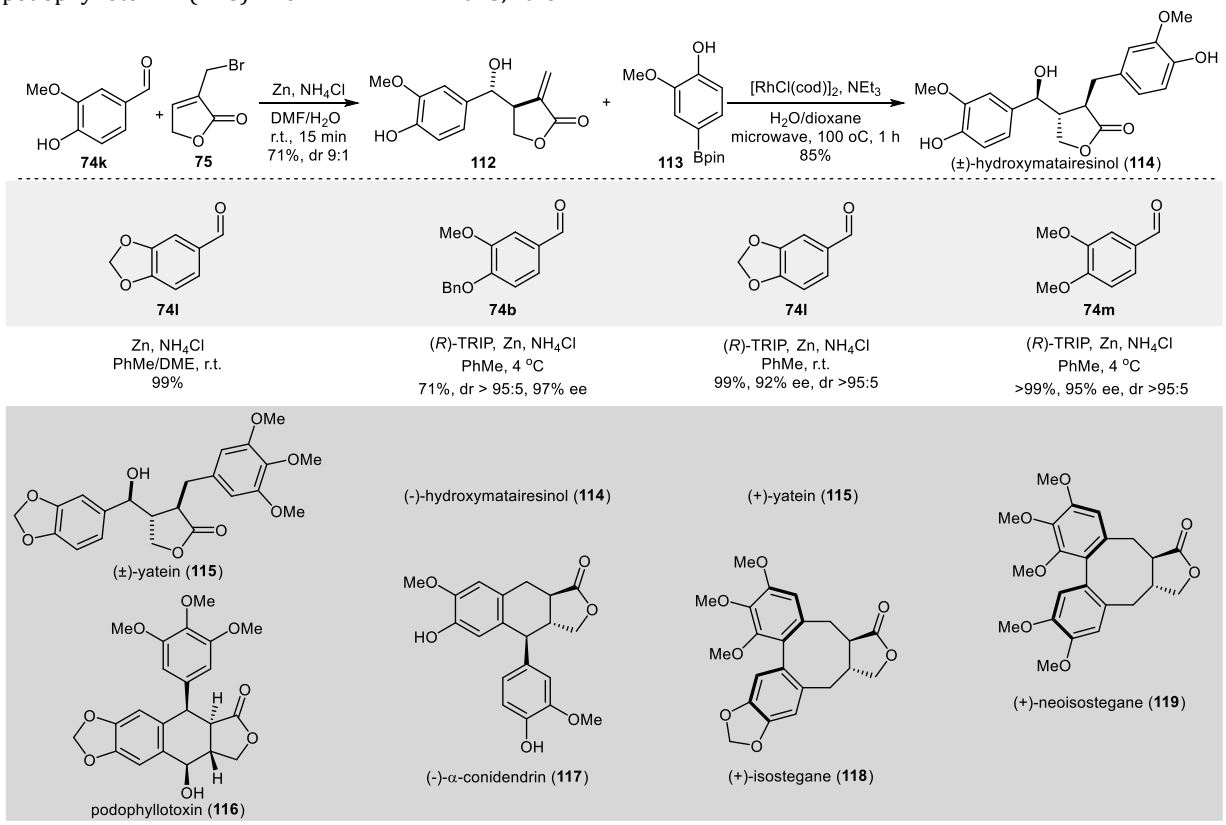
Scheme 30 Hodgson's syntheses of anthecotulide and hydroxyanthecotulide

4.2 Lignans

Lignans are a group of secondary metabolites consisting of dimeric phenylpropanes, linked at the C8 carbon.[53] Butyrolactone are frequently found in this class of natural products and their synthesis lend

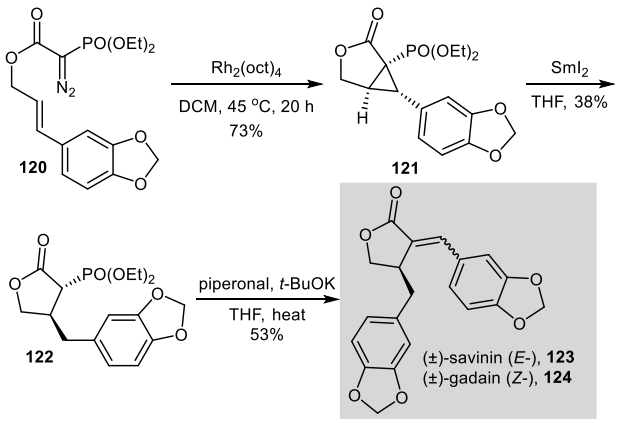
themselves to 1,4-addition reactions onto α-*exo*-methylene-γ-butyrolactones.

In Hodgson's synthesis of antitumor (±)-hydroxymatairesinol (**114**, Scheme 31), the synthetic utility of metal mediated allylation of aldehydes using bromolactone **75** was further demonstrated. The electron-rich vanillin **74k** reacted smoothly in the presence of zinc. Subsequent rhodium catalyzed 1,4-addition of aryl borane **113** resulted in a concise, protecting group-free synthesis of (±)-hydroxymatairesinol (**114**).[41] In addition, the zinc-mediated Barbier-type allylation was also used in the total synthesis of (±)-yatein (**115**) and podophyllotoxin (**116**) from **74l**.[63] In 2013, the synthesis of (*S*)-(-)-hydroxymatairesinol (**114**) was reported by Orthaber, Faber and co-workers from benzyl protected vanillin **74b** as illustrated in Scheme 31 (see also Scheme 19).[43a] Using a similar reaction sequence as Hodgson's followed by benzyl deprotection gave rise to desired lignan. The applicability of the TRIP-assistant asymmetric allylation methodology was further demonstrated in the total synthesis of (−)-α-conidendrin (**117**) from **74b**, (+)-yatein (**115**) and (+)-isostegane (**118**) from **74l**, and (+)-neoisostegane (**119**) from **74m**.[43b] The syntheses of lignans by means of Barbier-type allylation with bromolactone **75** are summarized in Scheme 31.



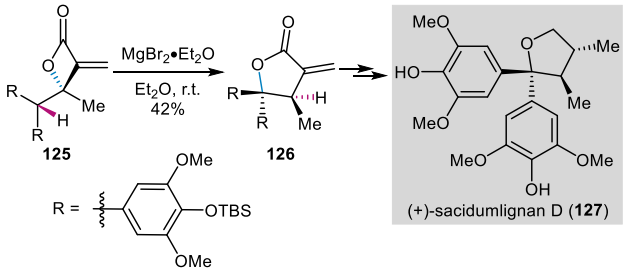
Scheme 31 Syntheses of lignans using Barbier-type allylation

In 2016, Taylor, Unsworth and co-workers reported the total synthesis of (±)-savinin (**123**) and (±)-gadain (**124**) by means of extension of their C–H insertion/olefination sequence (Scheme 32).[64] With α-diazo-α-(diethoxyphosphoryl) acetate **120** derived from allylic alcohol as starting material, the C–H insertion step is replaced by a rhodium(II)-catalysed cyclopropanation reaction. Subsequent reductive ring-opening and Horner–Wadsworth–Emmons olefination of cyclopropane **121** furnished lignans **123** and **124**. The same reaction sequence was also applied for (±)-peperomin E.[64]



Scheme 32 Taylor and Unsworth's syntheses of lignans using C–H insertion/olefination

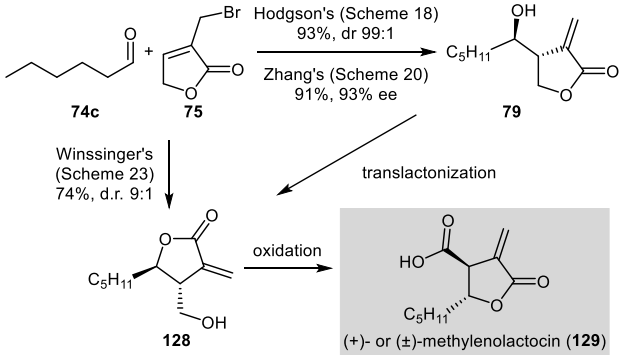
The formal synthesis of sacidumlignan D (**127**, Scheme 33) by Tang and co-workers exemplifies the synthetic potential of the dyotropic rearrangement.[39] Rearrangement of enantiopure α-methylene-β-lactone **125** provided the key intermediate α-*exo*-methylene-γ-butyrolactone **126**, which could be further derivatized into natural lignan (+)-sacidumlignan D.



Scheme 33 Formal synthesis of sacidumlignan D by Tang's group

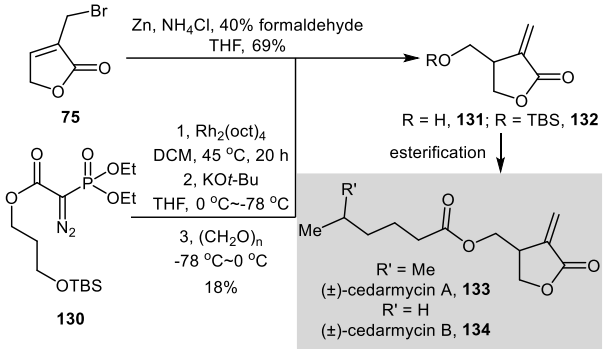
4.3 Other Monocyclic Natural Products

Paraconic acids, usually found in *Lichen* symbionts, are medicinally important molecules possessing varied bioactivities such as antibiotic and antitumor properties.[52] The characteristic β-carboxylic acid group substitution and the frequent presence of α-*exo*-methylene-γ-butyrolactone predispose these compounds for synthesis *via* Barbier allylation. For instance, antibacterial methylenolactocin (**129**) could be obtained from Barbier allylation followed by translactonization and Jones oxidation (Scheme 34). Anticipated alcohol **79** was synthesized from bromolactone **75** and hexanal **74c** employing Hodgson's catalytic Cr(II) conditions (see also Scheme 18).[41] Optically active **79** was generated from Zhang's chromium catalysis (see also Scheme 20).[27] Finally, the allylation/ tranlactonization can be achieved in one pot using palladium catalysis with $ZnMe_2$ (see also Scheme 23).[48]



Scheme 34 Synthesis of methylenolactocin

Cedarmycins A and B (**133** and **134** respectively, Scheme 35) are antibiotics isolated from actinomycete *Streptomyces sp.* TP-A0456.[65] In 2009, Xu's group reported the first total synthesis of (±)-cedarmycin B using zinc mediated Barbier allylation.[66] Bromolactone **75** was engaged in a reaction with formaldehyde to yield **131**. Subsequent esterification of **131** was used to complete the synthesis of (±)-cedarmycin B. A similar strategy was applied by Unsworth and co-workers with the help of their one-pot C-H insertion/olefination.[28b] TBS protected alcohol **132** was synthesized from α-diazo-α-(diethoxyphosphoryl)acetate **130**, thereby resulting the synthesis of (±)-cedarmycins A and B.



Scheme 35 Synthesis of cedarmycins A and B

4.4 Choice of Methodology in Recent Total Syntheses

While the discussion of total syntheses in section 4 focused on examples making use of recently developed methodologies, we analyzed the choice of methodology for constructing the α-*exo*-methylene-γ-butyrolactone in recent total syntheses, irrespectively of their coverage in the present or a previous review. In particular, we analyzed sesquiterpene lactone syntheses from 2017.[67] To the best of our knowledge, there are 13 publications covering guaianolides (Maimone 2017,[68] Siegel 2017,[69] Hajra 2017,[70] Maimone 2019,[71] Metz 2021,[72] Usuki 2021[56]), germacranolides (Corey 2018,[73] Ardnt 2019[74]), furanoheliangolides (Winssinger 2021),[9] 1,10-*seco*-guaianolides (Winssinger 2021),[48] xanthanolides (Tang 2017),[75] rearranged germacranolide (Lee 2021),[76] and sesquiterpene lactone scaffolds (Zografos 2021).[77]

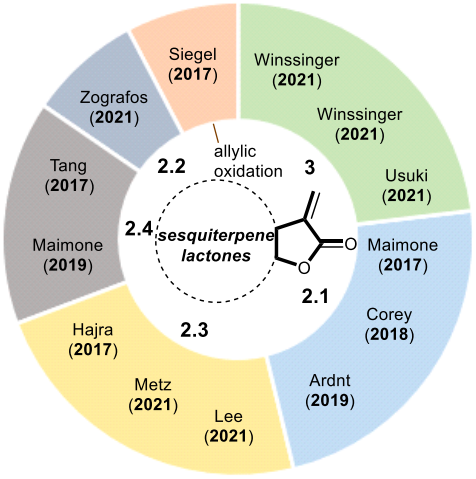


Figure 3 Statistics of methodologies for sesquiterpene lactone synthesis since 2017

As shown in Figure 3, representative works are divided into different categories distinguished by colours for the different bond breaking strategies. Formation of the α-*exo*-methylene-γ-butyrolactone moiety and construction of the core skeleton are two essential elements for sesquiterpene lactone synthesis. This analysis clearly shows that the wealth of methodologies greatly benefits the synthesis of sesquiterpene lactones without a clear domination from one method. It goes without saying that different methodologies have been tactically used based on specific target molecule as well as synthetic strategies.

5 Summary and Outlook

The α-*exo*-methylene-γ-butyrolactone is a vital substructural motif in bioactive natural products and medicinal chemistry. Its presence endows small molecules with a mildly reactive functionalities that can engage with a nucleophilic residue in their target proteins. Assembly of the α-*exo*-methylene-γ-butyrolactone has challenged synthetic chemists to develop novel methodologies that facilitates their access. Even though the structure is relatively simple, significant advances have been achieved by embracing recently developed chemistries enabling novel disconnections as well as better diastereo- or enantioselectivities. This short review updates recent progresses in this field and showcases their tactical application in total synthesis.

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Acknowledgment

We thank our collaborators in the area of sesquiterpene lactone synthesis. This perspective is not intended to be comprehensive but instead aims to highlight recent studies, and we apologize for arbitrary omissions.

References

(1) Dictionary of Natural Products (DNP). http://dnp.chemnetbase.com (accessed February 27, 2021).

(2) (a) Jackson, P. A.; Widen, J. C.; Harki, D. A.; Brummond, K. M. *J. Med. Chem.,* **2017,** *60*, 839. (b) Mayer, R. J.; Allihn, P. W.; Hampel, N.; Mayer, P.; Sieber, S. A.; Ofial, A. R. *Chem. Sci.*, **2021**, *12*, 4850.

(3) (a) Tian, C.; Sun, R.; Liu, K.; Fu, L.; Liu, X.; Zhou, W.; Yang, Y.; Yang, J. *Cell Chem. Bio.*, **2017,** *24*, 1416. (b) Lagoutte, R.; Winssinger, N. *CHIMIA* **2017,** *71*, 703.

(4) Kwok, B. H.; Koh, B.; Ndubuisi, M. I.; Elofsson, M.; Crews, C. M. *Chem. Bio.,* **2001,** *8*, 759.

(5) Lyß, G.; Knorre, A.; Schmidt, T. J.; Pahl, H. L.; Merfort, I. *J. Bio. Chem.,* **1998,** *273*, 33508.

(6) Dong, T.; Li, C.; Wang, X.; Dian, L.; Zhang, X.; Li, L.; Chen, S.; Cao, R.; Li, L.; Huang, N.; He, S.; Lei, X. *Nat. Commun.,* **2015,** *6*, 6522.

(7) Lagoutte, R.; Serba, C.; Abegg, D.; Hoch, D. G.; Adibekian, A.; Winssinger, N. *Nat. Commun.,* **2016,** *7*, 12470.

(8) Liu, M.; Xiao, C.; Sun, M.; Tan, M.; Hu, L.; Yu, Q. *J. Cell. Mol. Med.* **2019,** *23*, 4301.

(9) Liu, W.; Patouret, R.; Barluenga, S.; Plank, M.; Loewith, R.; Winssinger, N. *ACS Cent. Sci.*, **2021**, 7, 954.

(10) (a) Hoffmann, H.; Rabe, J. *Angew. Chem., Int. Edit.,* **1985,** *24*, 94. (b) Kitson, R. R.; Millemaggi, A.; Taylor, R. J. *Angew. Chem., Int. Edit.,* **2009,** *48*, 9426. (c) Elford, T. G.; Hall, D. G. *Synthesis* **2010,** *2010*, 893.

(11) (a) Seayad, J.; List, B. *Org. Bimol. Chem.,* **2005,** *3*, 719. (b) MacMillan, D. W. *Nature* **2008,** *455*, 304.

(12) (a) Davies, H. M.; Beckwith, R. E., *Chem. Rev.,* **2003,** *103*, 2861. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Hartwig, J. F. *J. Am. Chem. Soc*., **2016**, *138*, 2-24.

(13) De Kraker, J.-W.; Franssen, M. C.; Joerink, M.; De Groot, A.; Bouwmeester, H. J. *Plant physiol.,* **2002,** *129*, 257.

(14) Companyó, X.; Mazzanti, A.; Moyano, A.; Janecka, A.; Rios, R., *Chem. Commun.* **2013,** *49*, 1184.

(15) Li, Y.; Ibsen, L.; Jørgensen, K. A. *Org. Lett.,* **2017,** *19*, 1200.

(16) Zhang, H.; Yao, Q.; Cao, W.; Ge, S.; Xu, J.; Liu, X.; Feng, X. *Chem. Commun.,* **2018,** *54*, 12511.

(17) Nolsøe, J. M.; Hansen, T. V. *Eur. J. Org. Chem.,* **2014,** *2014*, 3051.

(18) (a) Gan, M.; Wang, W.; Wang, H.; Wang, Y.; Jiang, X. *Org. Lett.,* **2019,** *21*, 8275. (b) Wang, W.; He, H.; Gan, M.; Wang, H.; Wang, Y.; Jiang, X. *Adv. Syn. Cat.* **2019,** *361*, 4797.

(19) Öhler, E.; Reininger, K.; Schmidt, U., *Anyew. Chem. Int. Ed.*, **1970**, *9*, 457.

(20) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.,* **1957**, *79*, 1920.

(21) Suzuki, T.; Atsumi, J.-i.; Sengoku, T.; Takahashi, M.; Yoda, H. *J. Organomet. Chem.,* **2010,** *695*, 128.

(22) (a) Murata, Y.; Takahashi, M.; Yagishita, F.; Sakamoto, M.; Sengoku, T.; Yoda, H. *Org. Lett.,* **2013,** *15*, 6182. (b) Takahashi, M.; Murata, Y.; Yagishita, F.; Sakamoto, M.; Sengoku, T.; Yoda, H. *Chem. Eur. J.,* **2014,** *20*, 11091.

(23) Takahashi, M.; Murata, Y.; Ishida, M.; Yagishita, F.; Sakamoto, M.; Sengoku, T.; Yoda, H. *Org. Bimol. Chem.,* **2014,** *12*, 7686.

(24) Montgomery, T. P.; Hassan, A.; Park, B. Y.; Krische, M. J. *J. Am. Chem. Soc*., **2012,** *134*, 11100.

(25) McInturff, E. L.; Mowat, J.; Waldeck, A. R.; Krische, M. J. *J. Am. Chem. Soc*., **2013,** *135*, 17230.

(26) Wang, Q.-L.; Peng, L.; Wang, F.-Y.; Zhang, M.-L.; Jia, L.-N.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2013,** *49*, 9422.

(27) Chen, W.; Yang, Q.; Zhou, T.; Tian, Q.; Zhang, G. *Org. Lett.,* **2015**, *17*, 5236.

(28) (a) Lloyd, M. G.; Taylor, R. J.; Unsworth, W. P. *Org. Lett.,* **2014,** *16*, 2772. (b) Lloyd, M. G.; D'Acunto, M.; Taylor, R. J.; Unsworth, W. P. *Tetrahedron* **2015,** *71*, 7107.

(29) Shie, J.-Y.; Zhu, J.-L. *Tetrahedron* **2016,** *72*, 1590-1601.

(30) (a) Takizawa, S.; Nguyen, T. M. N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Edit.,* **2012,** *51*, 5423. (b) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Suzuki, M.; Enders, D.; Sasai, H. *Tetrahedron* **2013,** *69*, 1202.

(31) Su, X.; Zhou, W.; Li, Y.; Zhang, J. *Angew. Chem., Int. Edit.,* **2015,** *54*, 6874.

(32) Tang, Y., Guo, Z., Bao, R., Li, Y., Li, Y., Zhang, J., Tang, Y. *Angew. Chem., Int. Edit.,* **2021,** *60*, 14545-14553.

(33) (a) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D.W. C., *Science,* **2007**, *316*, 582. (b) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D.W. C., *J. Am. Chem. Soc.,* **2009**, 131, 11640.

(34) Yonehara, K.; Miyoshi, Y.; Tsukajima, A.; Akatsuka, T.; Saito, M. *Adv. Syn. Cat.,* **2011,** *353*, 1071.

(35) Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.,* **2014,** *16*, 4810.

(36) Hodgson, D. M.; Talbot, E. P.; Clark, B. P. *Org. Lett.,* **2011,** *13*, 5751.

(37) (a) Reetz, M. T. *Angew. Chem., Int. Edit.,* **1972,** *11*, 129. (b) Reetz, M. T. *Angew. Chem., Int. Edit.,* **1972,** *11*, 130.

(38) (a) Fernandez, I.; Cossio, F. P.; Sierra, M. A. *Chem. Rev.,* **2009,** *109*, 6687. (b) Hugelshofer, C. L.; Magauer, T. *Nat. Prod. Rep.,* **2017,** *34*, 228.

(39) Lei, X.; Li, Y.; Lai, Y.; Hu, S.; Qi, C.; Wang, G.; Tang, Y. *Angew. Chem., Int. Edit.,* **2021**, 60, 4221.

(40) Ren, W.; Bian, Y.; Zhang, Z.; Shang, H.; Zhang, P.; Chen, Y.; Yang, Z.; Luo, T.; Tang, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 6984.

(41) Hodgson, D. M.; Talbot, E. P.; Clark, B. P. *Org. Lett.* **2011**, *13*, 2594.

(42) Y.; Wang, X.; Sun, L.; Xie, L.; Xu, X. *Org. Biomol. Chem.*, **2012**, *10*, 3991.

(43) (a) Fuchs, M.; Schober, M.; Orthaber, A.; Faber, K. *Adv. Synth. Catal.* **2013**, *355*, 2499. (b) Hartmann, P.; Lazzarotto, M.; Steiner, L.; Cigan, E.; Poschenrieder, S.; Sagmeister, P.; Fuchs, M. *J. Org. Chem.* **2019**, *84*, 5831. (c) Hartmann, P. E.; Lazzarotto, M.; Pletz, J.; Tanda, S.; Neu, P.; Goessler, W.; Kroutil, W.; Boese, A. D.; Fuchs, M. *J. Org. Chem.* **2020**, *85*, 9672.

(44) Zhang, F.; Liu, Y.; Xie, L.; Xu, X. *RSC Adv.,* **2014,** *4*, 17218.

(45) Lagoutte, R.; Serba, C.; Winssinger, N. *J. Antibiot.,* **2018,** *71*, 248.

(46) Lagoutte, R.; Pastor, M.; Berthet, M.; Winssinger, N. *Tetrahedron* **2018**, *74*, 6012.

(47) Zhang, F. H.; Yang, Y. X.; Xie, L. G.; Xu, X. H. *Chem. Commun.* **2013**, *49*, 4697.

(48) Liu, W.; Yu, Z.; Winssinger, N. *Org. Lett.* **2021**, *23*, 3, 969.

(49) Albrecht, Ł.; Albrecht, A.; Janecki, T., In Lactones and Lactams: Synthesis, Occurrence and Biological ActivityJanecki, T., Ed.; Wiley-VCH: Weinheim,**2013**, 147.

(50) Berrue, F.; Kerr, R. G., *Nat. Prod. Rep.,* **2009,** *26*, 681.

(51) Martinez, S. A.; Gillard, M.; Chany, A.-C.; Burton, J. W., *Tetrahedron* **2018,** *74*, 5012.

(52) Fernandes, R. A.; Chaudhari, D. A.; Jha, A. K. *Asian J. Org. Chem.* **2020**, *9*, 1478.

(53) Peng, Y. Lignans, Lignins, and Resveratrols. In From Biosynthesis to Total Synthesis: Strategies and Tactics for Natural Products; Zografos, A. L., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, **2016**; pp 331–379.

(54) Barbetti, P.; Casinovi, C. G.; Santurbano, B.; Longo, R. Collect. *Czech. Chem. Commun.* **1979**, *44*, 3123.

(55) Yang, H.; Gao, Y.; Qiao, X.; Xie, L.; Xu, X. *Org. Lett.* **2011**, *13*, 3670.

(56) Nakamura, T.; Pitna, D. B.; Kimura, K.; Yoshimoto, Y.; Uchiyama, T.; Mori, T.; Kondo, R.; Hara, S.; Egoshi, Y.; Yamaguchi, S.; Suzuki, N.; Suzuki, Y.; Usuki, T. *Org. Biomol. Chem.*, **2021**, *19*, 6038.

(57) (a) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 1257. (b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.*, **2009**, *131*, 18343.

(58) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(59) Kulkarni, G.; Kelkar, G.; Bhattacharyya, S. *Tetrahedron* **1964,** *20*, 2639.

(60) Lloyd, M. G.; D'Acunto, M.; Taylor, R. J.; Unsworth, W. P. *Org. Biomol. Chem.*, **2016,** *14*, 1641.

(61) (a) Bohlmann, F.; Zdero, C.; Grenz, M.; *Tetrahedron Lett.*, **1969**, 2417. (b) Theodori, R.; Karioti, A.; Rančić, A.; Skaltsa, H. *J. Nat. Prod.* **2006**, *69*, 662.

(62) Hodgson, D. M.; Talbot, E. P.; Clark, B. P. *Chem. Commun.*, **2012**, *48*, 6349.

(63) Lazzarotto, M.; Hammerer, L.; Hetmann, M.; Borg, A.; Schmermund, L.; Steiner, L.; Hartmann, P.; Belaj, F.; Kroutil, W.; Gruber, K. A*ngew. Chem., Int. Ed.* **2019**, *58*, 8226.

(64) Lloyd, M. G.; Taylor, R. J.; Unsworth, W. P. *Org. Bimol. Chem.,* **2016,** *14*, 8971.

(65) Sasaki, T.; Igarashi, Y.; Saito, N.; Furumai, T. *J. Antibiot.,* **2001,** *54*, 567.

(66) Yang, H.; Qiao, X.; Cui, Q.; Xu, X. *Chin. Chem. Lett.* **2009**, *20*, 1023.

(67) For reviews on sesquiterpene lactone synthesis, see: (a) Fraga, B. M., *Nat. Prod. Rep.,* **2013**, *30*, 1226. (b) Santana, A.; González Molinillo, J. M.; Macías Domínguez, F. A., *Eur. J. Org. Chem.* **2015**, 2093. (c) Dey, S.; Bajaj, S. O., *Synth. Commun.*, **2018**, *48*, 1. (d) Barbero, M.; Prandi, C., *Nat. Prod. Commun.* **2018,** *13*, 241.

(68) Hu, X.; Xu, S.; Maimone, T. J., *Angew. Chem., Int. Edit.,* **2017,** *56*, 1624.

(69) Johnson, T. C.; Chin, M. R.; Siegel, D., *J. Org. Chem.,* **2017,** *82*, 4640.

(70) Hajra, S.; Acharyya, S.; Mandal, A.; Maity, R., *Org. Bimol. Chem.,* **2017,** *15*, 6401.

(71) Hu, X.; Musacchio, A. J.; Shen, X.; Tao, Y.; Maimone, T. J., *J. Am. Chem. Soc.*, **2019,** *141*, 14904.

(72) Kaden, F.; Metz, P., *Org. Lett.,* **2021,** *23*, 1344.

(73) Reddy, D. S.; Corey, E., *J. Am. Chem. Soc.*, **2018,** *140*, 16909.

(74) Freund, R. R.; Gobrecht, P.; Rao, Z.; Gerstmeier, J.; Schlosser, R.; Görls, H.; Werz, O.; Fischer, D.; Arndt, H.-D., *Chem. Sci.,* **2019,** *10*, 7358.

(75) Feng, J.; Lei, X.; Bao, R.; Li, Y.; Xiao, C.; Hu, L.; Tang, Y. *Angew. Chem. Int. Ed.*, **2017**, *56*, 16323.

(76) Lee, S.; Kim, B.-G.; Geum, S.; Kim, J.; Lee, H.-Y. *Org. Lett.,* **2021**. *23*, 4651-4656.

(77) Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A., *Org. Biomol. Chem.,* **2021**,*19,* 8687-8690.

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