Butyrolactones

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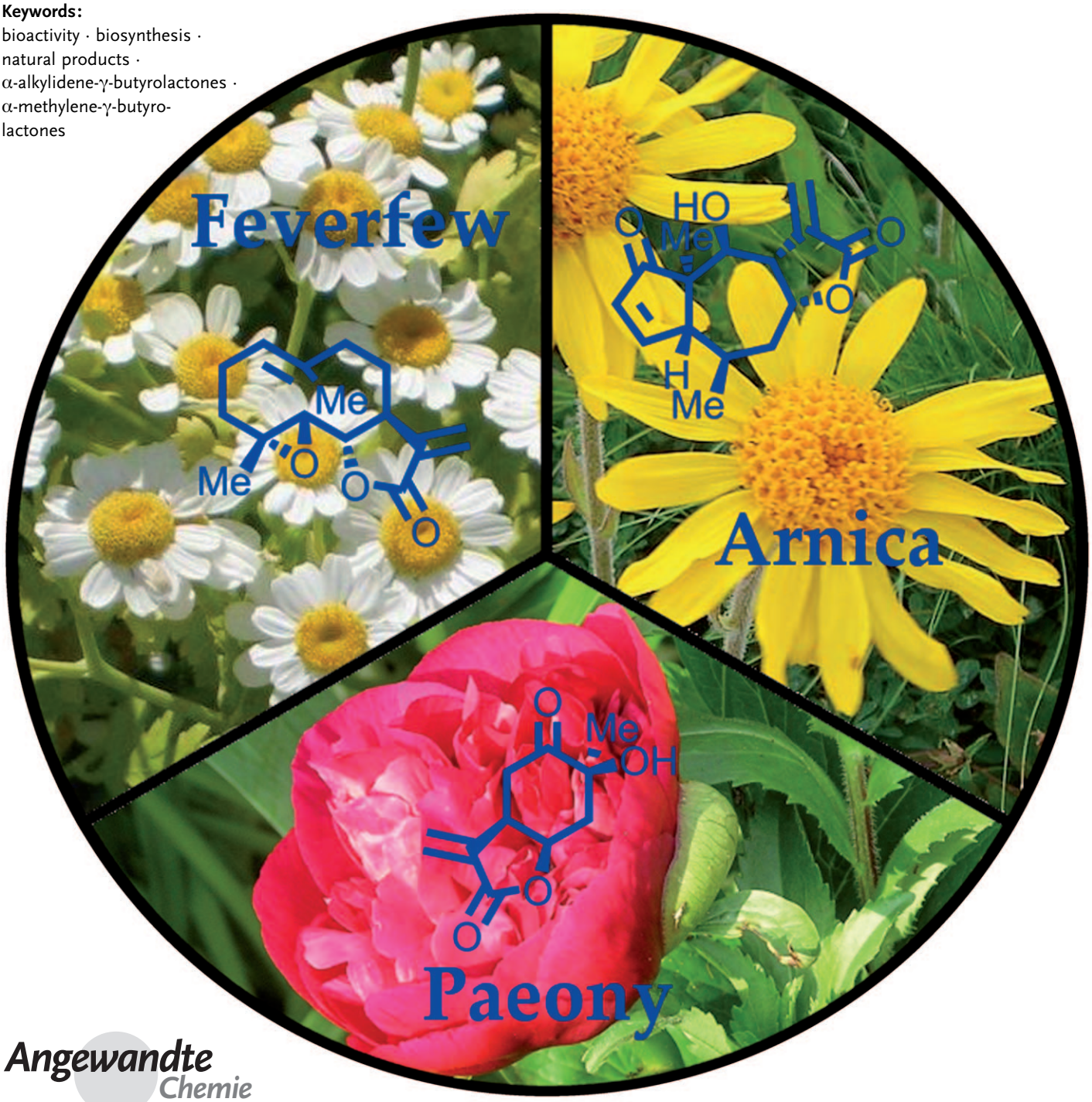
The Renaissance of α-Methylene-γ-butyrolactones: New Synthetic Approaches**

*Russell R. A. Kitson, Alessia Millemaggi, and Richard J. K. Taylor**

Keywords:
bioactivity · biosynthesis · natural products · α-alkylidene-γ-butyrolactones · α-methylene-γ-butyrolactones

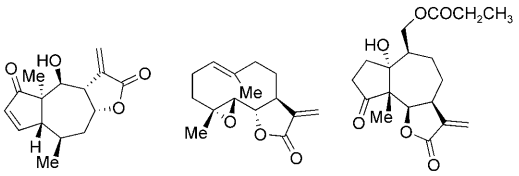


The amount of research activity concerning α-methylene-γ-butyrolactones and α-alkylidene-γ-butyrolactones has increased dramatically in recent years. This Review summarizes the structural types, biological activities, and biosynthesis of these compounds, concentrating on publications from the past 10 years. Traditional approaches to α-methylene-γ-butyrolactones and α-alkylidene-γ-butyrolactones are then reviewed together with novel approaches, including those from our own research group, reported more recently.

From the Contents

1. Introduction

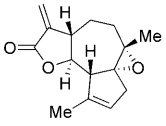
The α-methylene-γ-butyrolactone structural motif is found in a vast array of synthetically challenging and biologically significant natural products, many of which possess useful biological activities (e.g. anticancer, antimalarial, antiviral, antibacterial, antifungal, anti-inflammatory).[1,2] Of particular significance are natural products such



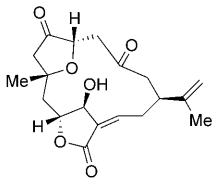
Helenalin **1**
Anti-inflammatory

Parthenolide **2**
Anti-inflammatory
Anticancer
Antiviral

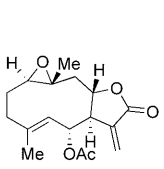
Hispitolide A **3**
Antiviral



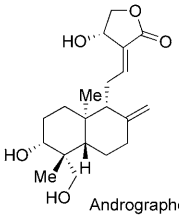
Arglabin **4**
Tumor Inhibitor



Scabrolide E **5**
Cytotoxic



Pyrethrosin **6**



Andrographolide **7**
α-Glucosidase inhibitor

as helenalin (**1**),[3] the anti-inflammatory active ingredient of Arnica, which is widely used in liniments and ointments for the treatment of strains, sprains, and bruises;[4] parthenolide (**2**),[5] a sesquiterpene lactone isolated from the medicinal herb feverfew, which possesses interesting anti-inflammatory, anticancer and antiviral properties;[6] the hispitolides (e.g. hispitolide A, **3**), a newly discovered family of compounds exhibiting activity against the hepatitis C virus (HCV);[7] and arglabin (**4**),[8] a tumor inhibitor that was the subject of an elegant total synthesis in 2007.[9]

In addition, many α-alkylidene-γ-butyrolactones are known, as illustrated by the recently discovered scabrolides (e.g. scabrolide E, **5**),[10] an interesting family of macrocyclic α-alkylidene-γ-butyrolactones exhibiting potent cytotoxicity against liver and pharynx/nasal cell lines.

The first α-methylene-γ-butyrolactone to be isolated was probably pyrethrosin (**6**) in 1891,[11] and the first alkylidene example was andrographolide (**7**) in 1911.[12] Since then this family has grown inexorably; in addition to reports describing the isolation of α-methylene- and α-alkylidene-γ-butyrolactones, there have been numerous publications covering their biosynthesis, biological properties, and medical applications. The α-methylene-γ-butyrolactone area was reviewed several times in the period 1977–1986[1,2,13,14] and was briefly covered in two more-recent reviews.[15,16] At the time of the seminal review by Hoffmann and Rabe in 1985,[1] there were approximately 2000 α-methylene and α-alkylidene-γ-butyrolactone natural products and this grew to over 5000 by 2009 (ca. 3% of all known natural products contain the α-methylene-γ-butyrolactone grouping; data from Beilstein CrossFire). When synthetic analogues are included, over 14000 α-methylene- and α-alkylidene-γ-butyrolactones have been reported in total.

In the past ten years or so, there has been a renaissance of interest in the isolation and biological screening of α-

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methylene- and α-alkylidene-γ-butyrolactones as well as the development of new and improved synthetic approaches. The main purpose of the current Review is to collate and outline the various synthetic methods used for the synthesis of these compounds, with particular emphasis on the period 1986–2008. However, we will first provide a condensed overview of newly isolated α-methylene- and α-alkylidene-γ-butyrolactones, their biological activity, and their biosynthesis. One particular aim of this Review is to provide detailed coverage of α-alkylidene-γ-butyrolactones (namely, examples in which the methylene group is further substituted), as this class of natural products has not been well reviewed to date.

2. Novel Structures

Since the earlier reviews in this area,[1,14] there have been almost 4000 α-methylene- and α-alkylidene-γ-butyrolactones isolated from natural sources. Given that the majority of these are α-methylene-γ-butyrolactone sesquiterpenes, we will first group novel structures into the standard[2] sesquiterpene categories (Figure 1): germacranolides (with a 10-membered ring), eudesmanolides (with a 6/6-fused bicyclic frame), and guaianolides and pseudoguaianolides (both with a fused 5/7-bicyclic system). The fifth category contains cembranolide diterpenes, and the sixth category contains α-alkylidene-γ-butyrolactones which are not sesqui- or diterpenes.

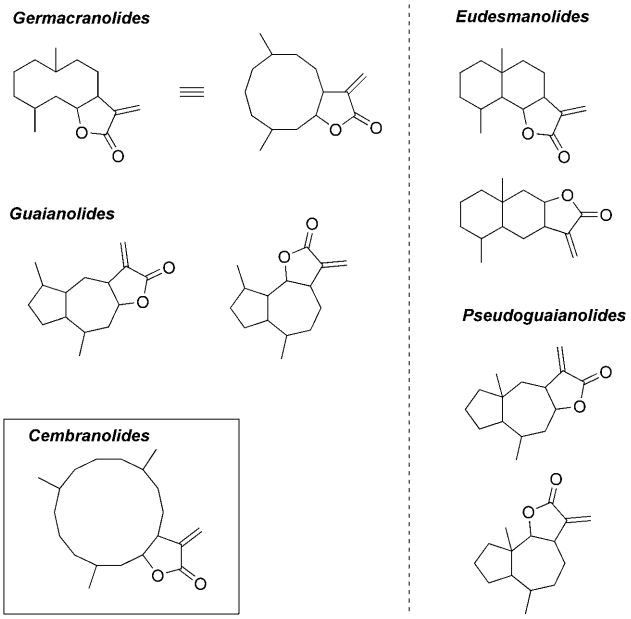
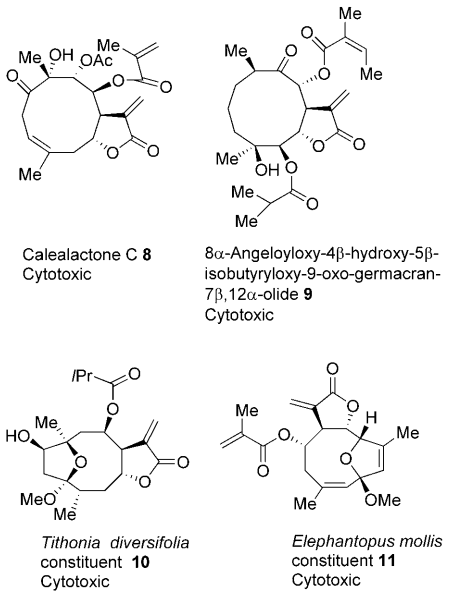


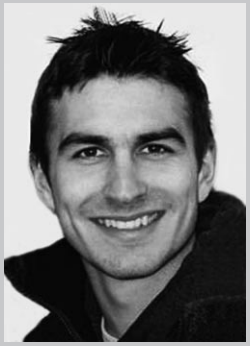
Figure 1. Terpene structures that contain α-methylene-γ-butyrolactone rings.

2.1. Germacranolides

Among the germacranolide sesquiterpene lactones to be discovered recently is calealactone C (**8**) which was isolated from *Calea urticifolia* in 2004 and exhibited cytotoxic effects against U937 human leukaemia cells.[17] The structurally



related 9-oxo-germacranolide **9** was isolated from the seeds of *Carpesium triste* in 2007 and shown to possess significant cytotoxicity against human leukaemia cells.[18] Also in 2007, several sesquiterpene α-methylene-γ-butyrolactones (including **10**) were isolated from the aerial parts of *Tithonia diversifolia* and shown to exhibit cytotoxic activity against



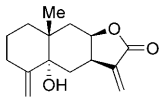
Russ Kitson carried out his undergraduate studies and obtained an M.Chem. (Hons.) at the University of Leeds in 2006 (carrying out a research project under the supervision of Dr. Stephen Marsden). After an industrial placement at AstraZeneca Pharmaceuticals, Charnwood, he then joined the research group of Prof. Richard Taylor at the University of York to undertake a PhD, investigating one-pot approaches to α-alkylidene-γ-butyrolactones from phosphonate-tethered enones and the application of this methodology to natural product syntheses.

Alessia Millemaggi conducted her undergraduate studies at the University of Bologna, where she received her laurea in 2004. She stayed at the University of Bologna to join the research group of Dr. Mauro Panunzio, working on the synthesis of 1,3-aminols by hetero Diels–Alder reactions. In 2006, she joined DSM Research, Geleen, The Netherlands, working on the resolution of enantiomeric mixtures by preferential crystallization. She is currently undertaking her PhD within the group of Prof. Richard Taylor at the University of York, working on the development of tandem reactions and their application in natural product synthesis.

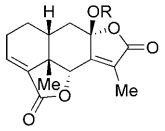
human leukaemia cells.[19] Finally, several structurally interesting dihydrofurans (e.g. **11**) were obtained from *Elephantopus mollis* in 2007 and shown to induce apoptosis in neuroblastoma cells.[20]

2.2. Eudesmanolides

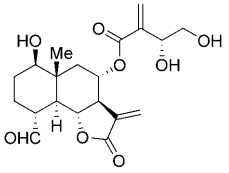
Eudesmanolides usually exist as either a linear fusion of the two 6-membered rings and lactone or with the methylene lactone fused in the α-position to the bridgehead of the 6/6-ring. An example of the former class reported in 2007 is 5α-hydroxy-eudesma-4,11-dien-12,8β-olide (**12**),[21] a compound isolated in 2007 from the Chinese herbs *Carpesium macrocephalum* and *Carpesium cernuum* and shown to be cytotoxic to human ovarian cell lines. In addition, the eremophilane-type sesquiterpenes **13**, isolated from the roots of *Ligularia lapathifolia*, possess a novel tetracyclic diolide structure in which one γ-butyrolactone is fused across the two 6-membered rings (**13**, R = Me, exhibited moderate activity against human hepatoma cell lines).[22]



5α-Hydroxy-eudesma-4,11-dien-12,8β-olide **12**
Cytotoxic, telomerase inhibitor

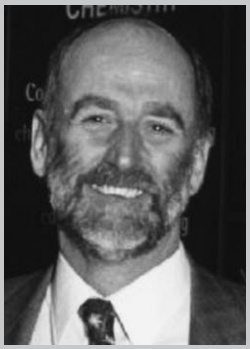


Diolides **13** (R = H, Me, Et)
Cytotoxic



8α-*O*-(3,4-dihydroxy-2-methylenebutanoyloxy)-sonchucarpolide **14**
Low antibacterial activity

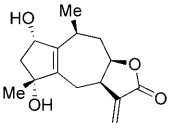
An example of the latter class is the sonchucarpolide derivative **14**,[23] which was isolated from *Centaurea spinosa* and shown to possess antibacterial activity, but at a low level.



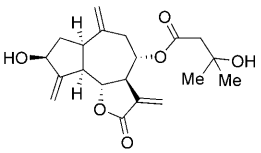
Richard Taylor obtained BSc and PhD (Dr. D. Neville Jones) from the University of Sheffield. Postdoctoral periods with Dr. Ian Harrison and Prof. Franz Sondheimer were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to the Chair of Organic Chemistry at the University of York. His research interests center on the synthesis of bioactive natural products and the development of new synthetic methods. His awards include the Royal Society of Chemistry's Pedler Lectureship (2007). He is the current President of the International Society of Heterocyclic Chemistry, a past-President of the RSC Organic Division, and an Editor of Tetrahedron.

2.3. Guaianolides

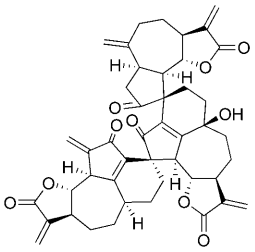
Three novel α-methylene-γ-butyrolactone guaianolides were reported in the past two years. In 2008, compounds **15** and **16** were isolated from *Pulicaria crispa*[24] and *Saussurea pulchella*,[25] respectively. Then in 2009, two remarkable guaianolide sesquiterpene trimers, ainsliatrimer A (**17**) and B, and a related dimer, ainsliadimer B, were isolated from *Ainsliaea fulvioides* and shown to possess potent cytotoxic activity.[26]



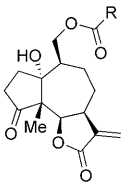
2α,4α-Dihydroxy-7αH,8αH,10αH-guaia-1(5),11(13)-dien-8β,12-olide **15**



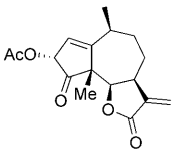
8α-*O*-(3'-Hydroxy-3'-methylbutyryl)-desacylcynaropicrin **16**



Ainsliatrimer A **17**
Cytotoxic



Hispitolides **18**
(*e.g.* Hispitolide A (**3**), R = Et)
Antiviral



Parthenium hysterophorus constituent **19**
Cytotoxic

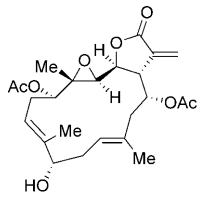
2.4. Pseudoguaianolides

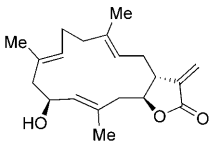
Pseudoguaianolides are closely related to guaianolides in structural terms, differing only in the position of the one-carbon substituent on the cyclopentane ring. In guaianolides the substituent is at the α position to the ring junction, whereas in pseudoguaianolides it is located at the ring junction itself. Recently isolated bioactive pseudoguaianolides include the hispitolide family **18**,[7] which exhibit potent activity against the hepatitis C virus, and cytotoxic parthenin analogues such as **19** isolated from *Parthenium hysterophorus*.[27]

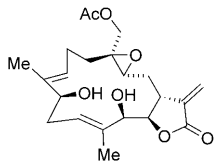
2.5. Cembranolides

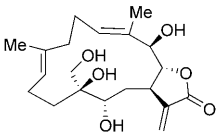
There is a growing family of α-methylene-γ-butyrolactones based on the cembrane diterpene family known as cembranolides. These natural products, which are believed to be produced as defence chemicals, have mainly been isolated from marine soft corals of the genera *Lobophytum*, *Sinularia*,

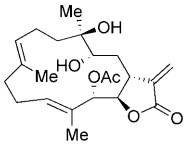
and *Sarcophyton*, and from gorgonians of the genus *Eunicea*. Soft coral of the genus *Lobophytum* has proved to be a particularly rich source of cembranolides. Recently isolated examples include michaolide A (**20**; plus 11 related family members) isolated from *Lobophytum michaelae* in 2007[28] and crassumolide A (**21**) isolated in 2008 from *Lobophytum crassum* together with four related novel compounds.[29] Both **20** and **21** display cytotoxic properties (e.g. against human colon and leukaemia cell lines). Durumolide A (**22**), isolated along with related compounds from *Lobophytum durum* in 2006, also possesses the α-methylene-γ-butyrolactone ring *trans*-fused to a 14-membered ring and exhibits potent antibacterial activity.[30] The sinularolide family of cembranolides, for example sinularolide A (**23**), were isolated from *Sinularia gibberosa*,[31] and the crassocolides A–F (e.g. crassocolide A, **24**) were isolated from *Sarcophyton crassocaule*.[32] Crassolide A is cytotoxic against breast, liver, and lung cancer cell lines.[32]

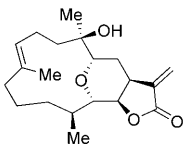

Michaolide A **20**
Cytotoxic


Crassumolide A **21**
Cytotoxic


Durumolide A **22**
Antibacterial


Sinularolide A **23**

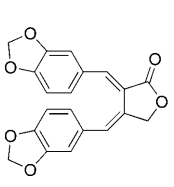

Crassocolide A **24**
Cytotoxic

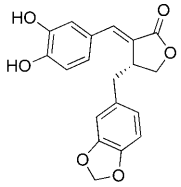

Eunicea constitutent **25**
Cytotoxic

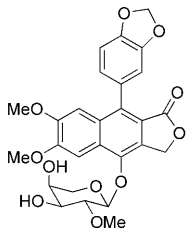
Many bioactive cembranolides have also been extracted from gorgonian octocorals of the genus *Eunicea*. Particularly interesting from a biosynthetic viewpoint (see Section 4) is the cembranolide **25** which was isolated in 2006 from *Eunicea mammosa* and found to possess moderate cytotoxic activity against a panel of cell lines.[33] It should be noted that, in contrast to the metabolites **20**–**24** isolated from *Lobophytum* and *Sinularia* sp., compounds such as **25** obtained from *Eunicea* contain α-methylene-γ-butyrolactones that are *syn* disposed with respect to the 14-membered ring.

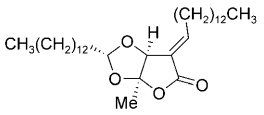
2.6. Other α-Alkylidene-γ-butyrolactones

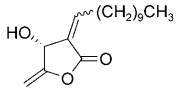
A large number of non-terpenoid, naturally occurring α-alkylidene-γ-butyrolactones are also known. Lignan representatives are growing in number and are illustrated by compounds **26**–**28**. Taiwanin A (**26**) was isolated from *Taiwania cryptomerioides* and shown to inhibit the growth of three

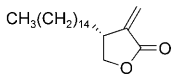

Taiwanin A **26**
Tumor inhibition

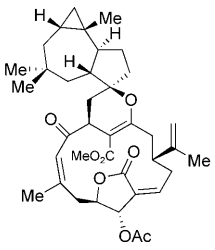

Piperphilippinin IV **27**
Anticoagulant


Acutissimalignan A **28**
Cytotoxic


Kotolactone A **29**


Subamolide D (*Z*),
Subamolide E (*E*) **30**
Anticancer


3-Methylene-4-pentadecyl-
dihydrofuran-2-one **31**
Antifungal


Polymaxenolide **32**

types of human tumor cell;[34] more recent studies investigated the mode of action (induces cell-cycle arrest at the G2M phase and p53-dependant apoptosis).[35] The structurally related piperphilippinin family of lignans (e.g. piperphilippinin IV, **27**), were obtained from *Piper philippinum* in 2007,[36] and several members were found to possess antiplatelet aggregation activity. Similar compounds were isolated from *Phyllanthus acutissima*,[37] with acutissimalignan A (**28**) being the most noteworthy in a structural sense in view of its naphthaleno-γ-lactone tricyclic nucleus.

Several fairly simple naturally occurring α-alkylidene-γ-butyrolactones such as **29**–**31** have been isolated in the past five years. A family of novel compounds, including kotolactone A (**29**), were isolated from the stem wood of *Cinnamomum kotoense*,[38] and in 2008, two new monocyclic butanolides named subamolides D and E (**30**)[39] were isolated from the leaves of *Cinnamomum subavenium* and found to possess potent activity against a strain of colon cancer. In 2009, another monocyclic example was reported when 3-methylene-4-pentadecyldihydrofuran-2-one (**31**) was isolated from the juice of the ripe fruit of *Artabotrys odoratissimus* and found to possess good antifungal activity.[40] It was proposed that the C_{20} natural product **31** was produced by a mixed isoprene/fatty acid biosynthetic pathway.[40] A mixed biosynthesis was also proposed for polymaxenolide (**32**) which was isolated from the hybrid soft coral *Sinularia maxima*/*Sinularia*

polydactyla. The authors suggest that polymaxenolide (**32**) is probably formed by the condensation of a cembranolide diterpene precursor with an africanane-type sesquiterpene.[41]

3. Biological Activity

A literature search (Beilstein CrossFire) on the α-methylene/α-alkylidene-γ-butyrolactone fragment, limiting the results to natural products isolated since the earlier reviews (1986) and exhibiting biological activity, gives almost 900 hits, of which the majority are α-methylene systems, but over 80 are substituted alkylidene examples. The biological activities are wide-ranging and often potent. Of the newly discovered natural products there are numerous examples of compounds with cytotoxic/anticancer activity.[5,6,8,10,17–22,26–29,31–35,37,39] Anti-inflammatory,[4,6] antibacterial,[23,30] anticoagulant[36] and antifungal[40] properties have also been found. Recently, the antiviral activity of α-methylene-γ-butyrolactones has been reported; for example, parthenolide **2**[6d] and the hispitolides **18**,[7] both of which are active against the hepatitis C virus. In addition, the antiprotozoal, antiparasitic, and insect antifeedant activities of sesquiterpene α-methylene-γ-butyrolactones have been reviewed.[2]

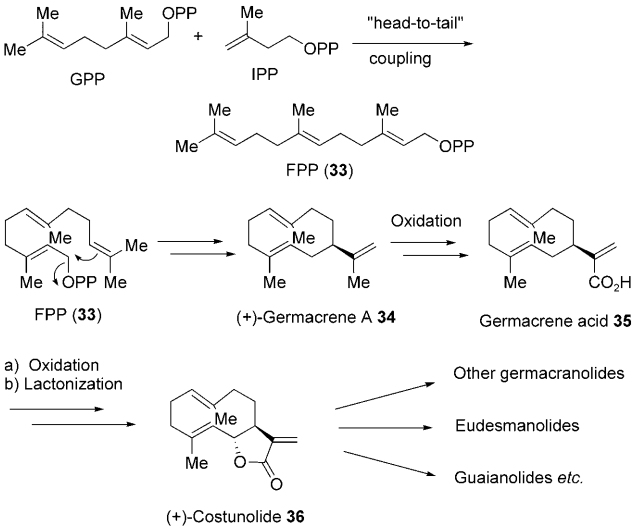
The allergenic properties of α-methylene-γ-butyrolactones, which are often present in pollen, should also be noted. Such compounds can cause allergenic contact dermatitis (ACD)[42] and photodermatosis.[43] It has been proposed that the α-methylene-γ-butyrolactones react with skin proteins in a Michael-type reaction, thereby forming antigenic compounds within epidermal cells.[43] α-Methylene-γ-butyrolactones are excellent conjugate acceptors and this is believed to provide the basis of many of their biological activities (e.g. reaction with L-cysteinyl residues in proteins/enzymes).[43,44]

Finally, the over-the-counter herbal remedies arnica (treatment of strains, sprains, and bruises)[4] and feverfew (anti-inflammatory, anticancer, and antiviral properties)[6] deserve to be mentioned again in this section, as does arglabin (**4**), which in the prodrug form of the hydrochloride salt of the dimethylamino adduct, has been used against breast, lung, and liver cancer strains in Kazakhstan.[8b]

4. Biosynthesis

The biosynthesis of sesquiterpenoid α-methylene-γ-butyrolactones proceeds along the terpene biosynthetic pathway via geranyl pyrophosphate (GPP) and then "head-to-tail" coupling with isopentenylpyrophosphate (IPP) to produce farnesyl pyrophosphate (FPP, **33**; Scheme 1). In standard sesquiterpenoid α-alkylidene-γ-lactone biosynthesis, FPP (**33**) then undergoes cyclization to (+)-germacrene A (**34**) and oxidative elaboration giving germacrene acid (**35**; Scheme 1). This topic has been extensively covered in the early reviews,[1] and reprised by Schall and Reiser in a 2008 microreview.[16]

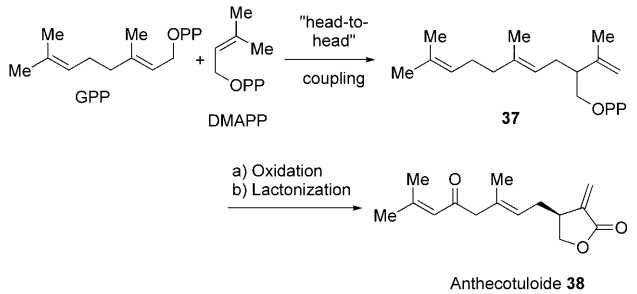
More recently, extensive studies have been carried out by de Kraker and co-workers concerning the biosynthesis of sesquiterpene lactones in chicory (Scheme 1).[45] They



Scheme 1.

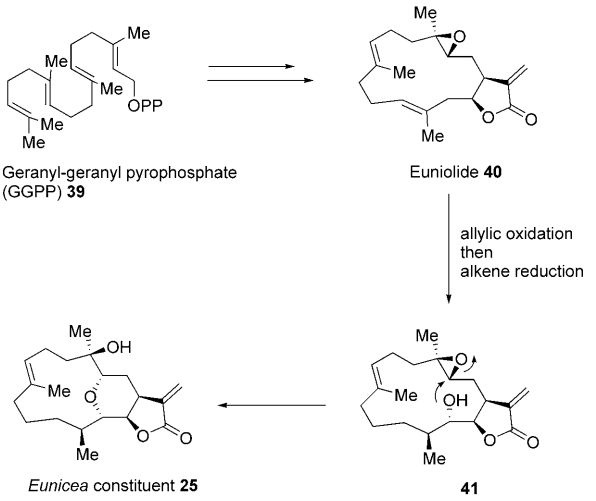
obtained an enzyme from chicory roots and demonstrated that it converts germacrene acid (**35**) into costunolide (**36**). Structurally, costunolide (**36**) is the simplest naturally occurring germacranolide, and it is further elaborated biosynthetically to give more complex germacranolides, as well as eudesmanolides and guaianolides. This area was reviewed in more detail in 2009,[46] and a theoretical study was carried out to clarify the mechanism of the biosynthetic cyclization process which converts germacranolides into guaianolides and pseudoguaianolides.[46]

A non-FPP biosynthetic route is also possible and has been proposed for the biosynthesis of anthecotuloide (**38**),[47] an "irregular" sesquiterpene α-methylene-γ-butyrolactone isolated from *Anthemis cotula* and other members of the *Asteracea* family. The carbon skeleton of anthecotuloide seems to be incompatible with biosynthesis via FPP, and van Klink et al. have recently carried out extensive labeling studies, which confirmed that anthecotuloide (**38**) is formed via the intermediacy of the pyrophosphate **37**, derived from 3-hydroxymethyl-2,6,10-trimethylundeca-1,5,9-triene. It is proposed that pyrophosphate **37** results from a "head-to-head" coupling of geranyl pyrophosphate (GPP) with dimethylallylpyrophosphate (DMAPP). Subsequent oxidation of **37** followed by lactonization produces anthecotuloide (**38**; Scheme 2).[47]



Scheme 2. PP = pyrophosphate.

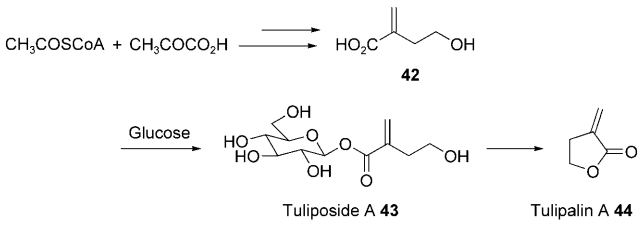
Biosynthetic studies have also been conducted to elucidate the metabolic origin of the cembranolide **25** discussed earlier.[33] Labeling, metabolite isolation, and synthetic studies indicated that the pathway shown in Scheme 3 provides a



Scheme 3.

plausible sequence. Thus, both euniolide (**40**) and its hydroxylated derivative **41** were isolated along with compound **25**, and it was suggested that GGPP (**39**) was converted into euniolide (**40**). Allylic oxidation and alkene reduction of **40** would produce alcohol **41**. Cyclization of alcohol **41** as shown would be expected to give the ether-bridged product **25**, and indeed this could be carried out chemically by the treatment of alcohol **41** with *p*-toluenesulfonic acid.[33,48]

One other biosynthetic study concerns the biosynthesis of α-methylene-γ-butyrolactone (**44**) itself (Scheme 4).[49]



Scheme 4.

Hutchinson and Leete studied the biosynthesis of tuliposide A (**43**), a 1-acylglucoside found in tulips, which is believed to undergo hydrolysis to generate α-methylene-γ-butyrolactone (tulipalin A, **44**) to protect the tulip bulbs from fungal infection. Using labeled pyruvate, they established that an initial condensation between pyruvate and acetyl coenzyme A ultimately generated γ-hydroxy-α-methylene-butanoic acid (**42**), the tuliposide A precursor.

For some natural products resulting from "mixed" biosynthetic pathways, see Section 2.6.

5. Synthesis of α-Alkylidene-γ-butyrolactones

The synthesis of α-methylene-γ-butyrolactones has been extensively studied and well reviewed up to 1986.[1,13,14] However, a wide array of new methods has been developed more recently. The aim of this Review is to summarize these new approaches and to illustrate their use in more complex α-alkylidene-γ-butyrolactone natural product synthesis.

The synthetic approaches used for the construction of the α-methylene- and α-alkylidene-γ-butyrolactone motif have been classified into six main groups (Figure 2), plus a miscellaneous section, and these will be described in turn.

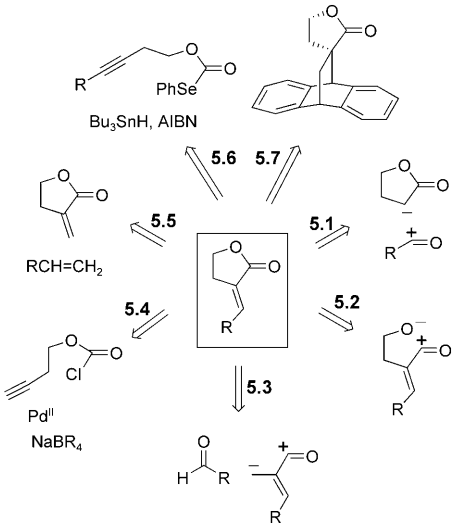
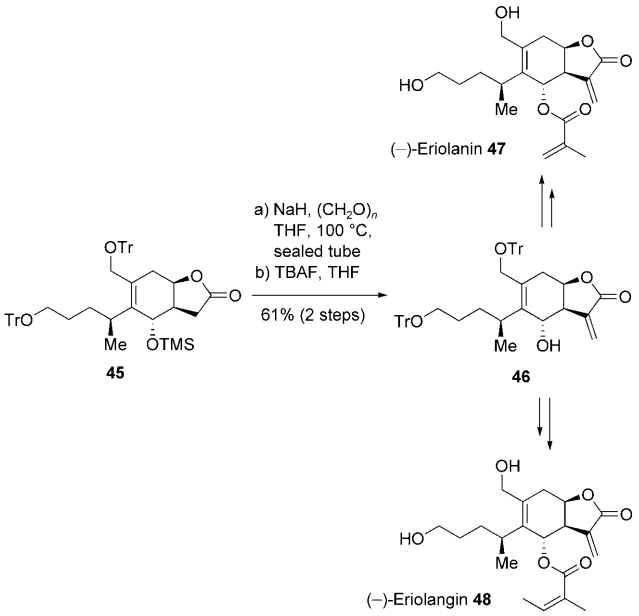


Figure 2. Organization of Section 5 according to synthetic approaches.

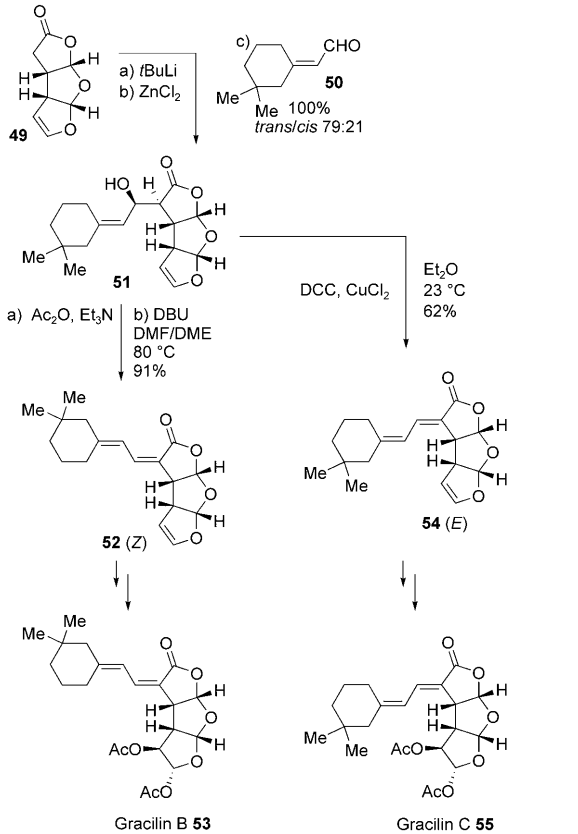
5.1. By Alkylidenation of γ-Butyrolactones

One of the most commonly-used methods for the preparation of α-methylene-γ-butyrolactones, well-covered in earlier reviews,[1,13,14] involves the reaction of the γ-butyrolactone enolate or enolate equivalent with formaldehyde (or a formate ester followed by reduction) and subsequent dehydration of the resulting α-(hydroxymethyl)-γ-lactone, often by base-mediated elimination of a derived sulfonate ester. Metz and co-workers observed the spontaneous elimination of water when employing this method for their syntheses of the antileukaemia agents (−)-eriolanin (**47**) and (−)-eriolangin (**48**; Scheme 5).[50] Treatment of γ-butyrolactone **45** with NaH followed by paraformaldehyde and heating to 100 °C in THF in a sealed tube gave the α-methylene unit directly. Similar approaches using LDA and gaseous formaldehyde have recently been described by the the research groups of Danishefsky (total synthesis of spirotenuipesines A and B)[51] and Mukai (total synthesis of (+)-achalensolide).[52]

α-Alkylidene-γ-butyrolactones can be prepared in a similar manner, as demonstrated by Corey and Letavic in their total synthesis of gracilins B (**53**) and C (**55**; Scheme 6).[53] Treatment of lactone **49** with *t*BuLi followed



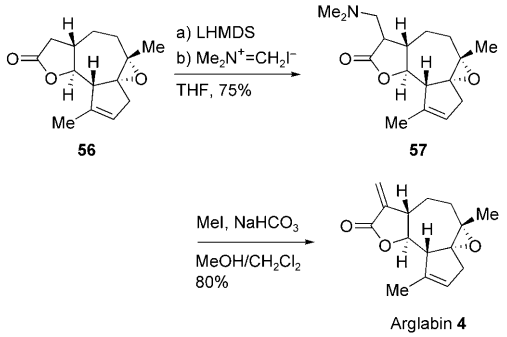
Scheme 5.



Scheme 6.

by $ZnCl_2$ formed the zinc enolate which was trapped with aldehyde **50** in quantitative yield and reasonable selectivity. β-Hydroxy-γ-lactone **51** was then manipulated to give either the *E* or *Z* configuration about the *exo*-alkylidene unit by either stereoselective dehydration with DCC/$CuCl_2$ to give the *Z* configuration **52** in 62% yield, or acetylation and elimination to give the *E* configuration **54** in 91% yield. These products were further elaborated to give gracilins B (**53**) and C (**55**), respectively.

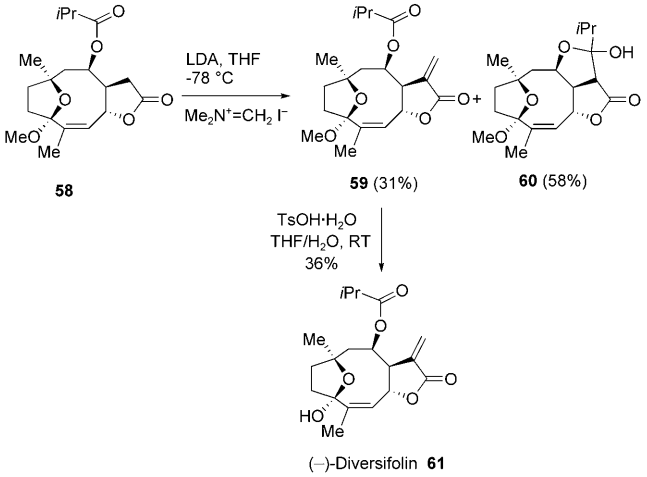
Eschenmoser's salt can be employed in place of formaldehyde and this approach was utilized by Reiser and coworkers in the total synthesis of the guaianolide arglabin (**4**), a farnesyl transferase inhibitor and promising antitumor agent (Scheme 7).[9] The lithium enolate derived from γ-lactone **56**



Scheme 7.

was trapped with Eschenmoser's salt to afford the tertiary amine **57** in good yield. Methylation and Hofmann elimination proceeded smoothly to give arglabin (**4**) in 80% yield.

In 2009, Kobayashi's research group utilized the deprotonation/Eschenmoser's salt methylenation route (Scheme 8)

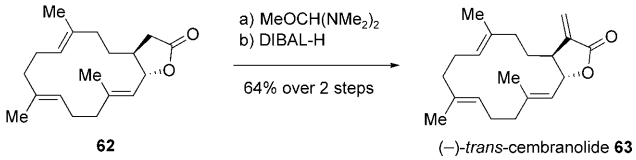


Scheme 8.

in the first total synthesis of the germacrane (−)-diversifolin (**61**), an inhibitor of the transcription factor NF-κβ.[54] Thus, lactone **58** was prepared by a route which employed Grubbs ring-closing metathesis to construct the 10-membered ring. Deprotonation with LDA followed by treatment with Eschenmoser's salt gave the expected α-methylene-γ-butyrolactone **59**, but the major product was hemiketal **60** resulting from an intramolecular Claisen condensation. It is noteworthy that elimination to give the α-methylene-γ-butyrolac-

tone occurred spontaneously (addition of MeI to promote Hofmann elimination was not required).[55] Hydrolysis of methyl ketal **59** was then accomplished using acidic conditions to give (−)-diversifolin (**61**) in 36% yield. A related example employed the Cope elimination to reveal the α-methylene-γ-butyrolactone moiety.[56]

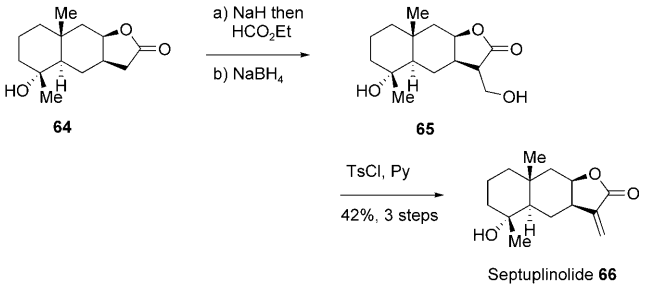
Some time ago, Ziegler and Piwinski reported a related variant based on the use of Bredereck's reagent [bis(dimethylamino)methoxymethane], with subsequent reduction of the resultant aminoalkene.[57] This procedure was utilized in 1997 by Taber and Song for their total synthesis of (−)-*trans*-cembranolide (**63**; Scheme 9).[58] Thus, γ-lactone **62** was



Scheme 9.

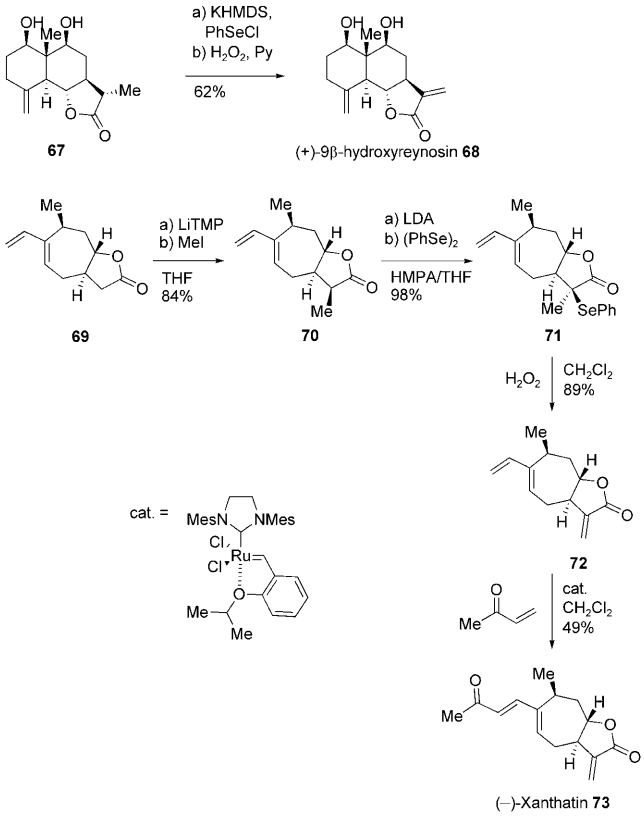
treated with Bredereck's reagent (no additional base or solvent required) followed by DIBAL-H to afford (−)-*trans*-cembranolide (**63**) in 64% yield over the 2 steps.

The formate ester trapping approach, referred to earlier, was employed by Tada and co-workers in the synthesis of the eudesmanolide septuplinolide (**66**; Scheme 10).[59] The enolate of γ-butyrolactone **64** was generated using sodium hydride and trapped with ethyl formate, and the resulting aldehyde was reduced to the α-(hydroxymethyl)-γ-butyrolactone **65** with sodium borohydride. Without purification, alcohol **65** was treated with tosyl chloride and base to give septuplinolide (**66**) in 42% yield over the 3 steps.



Scheme 10.

Another well-known route to α-methylene-γ-butyrolactones commences with an α-methyl lactone, and then utilizes a regioselective elimination reaction to introduce unsaturation. The most common variant of this type of approach proceeds by oxidation of an intermediate α-phenylselenide and subsequent β-elimination. This approach was recently utilized by Oltra and co-workers in their synthesis of the eudesmanolide (+)-9β-hydroxyreynosin (**68**; Scheme 11).[60] The enolate derived from γ-lactone **67** was treated with phenylselenyl chloride; subsequent oxidation of the resulting selenide and selenoxide elimination afforded (+)-9β-hydroxyreynosin (**68**) in 62% yield over the 2 steps.

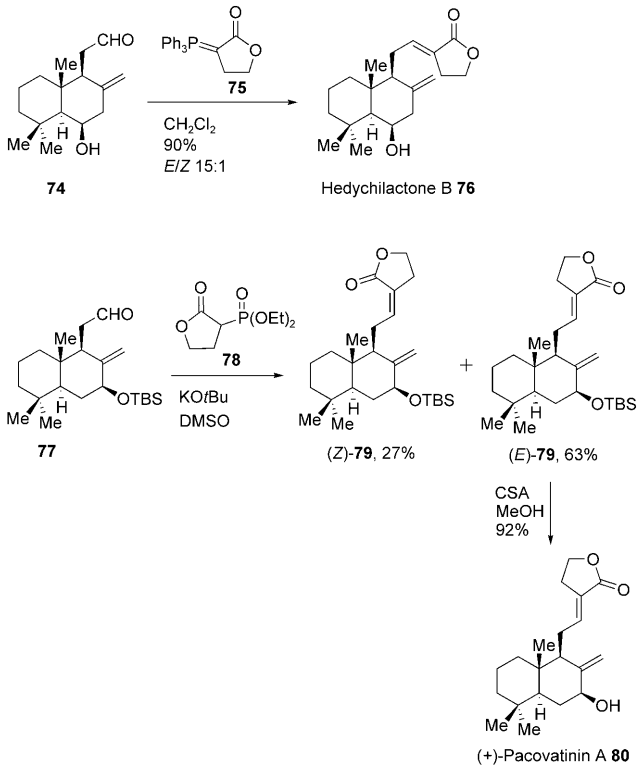


Scheme 11.

The selenation approach has been utilized in several recent syntheses.[61–64] For example, in 2008, Shishido and co-workers employed selenium chemistry in their synthesis of the antibacterial sesquiterpenoid (−)-xanthatin (**73**; Scheme 11).[64] Thus, α-methyl-γ-butyrolactone **70** was treated with LDA and the enolate was trapped with diphenyldiselenide in near-quantitative yield. This was oxidized and underwent elimination to afford α-methylene-γ-butyrolactone **72** in 89% yield. Subsequent cross-metathesis with methyl vinyl ketone, employing the Hoveyda–Grubbs second generation catalyst, gave (−)-xanthatin (**73**) in 49% yield. It is noteworthy that the metathesis was achieved in the presence of the α-methylene-γ-butyrolactone.

A different approach to α-alkylidene-γ-butyrolactones involves the direct alkylidation of an activated γ-lactone. Early examples involved Wittig and Horner–Wadsworth–Emmons (HWE) olefinations of α-phosphoranyl- or α-phosphono-γ-lactones with paraformaldehyde,[1] and these methods have since been utilized frequently.[65,66] The Wittig procedure was recently used by Jung and Murakami in their total synthesis of (±)-hedychilactone B (**76**; Scheme 12).[67] The aldehyde **74** was treated with α-(triphenylphosphoranyl)-γ-butyrolactone (**75**) to complete the total synthesis in 90% yield.

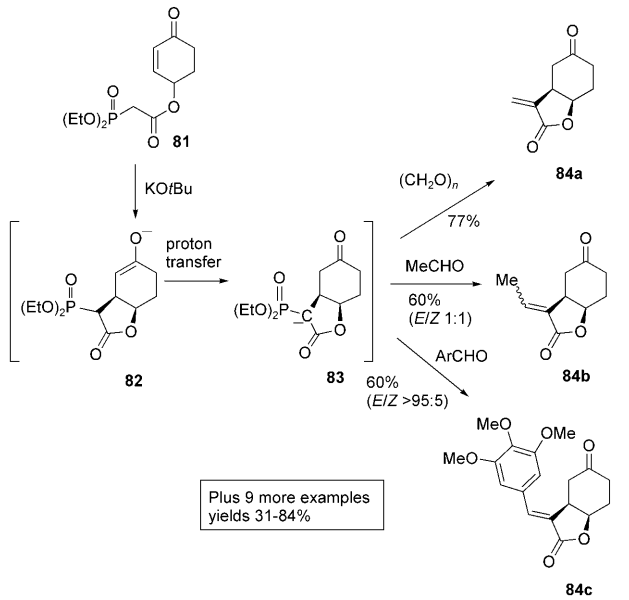
The phosphonate approach was employed by Akita and co-workers in the endgame of their total synthesis of (+)-pacovatinin (**80**; Scheme 12).[68] HWE olefination of aldehyde



Scheme 12.

77 with α-(diethylphosphono)-γ-butyrolactone (**78**) and KO*t*Bu in DMSO gave a 63% yield of the desired isomer (*E*)-**79**, with 27% of the undesired (*Z*)-**79**. Cleavage of the TBS group in (*E*)-**79** was achieved with camphorsulfonic acid (CSA) in 92% yield and completed the total synthesis of (+)-pacovatinin (**80**).

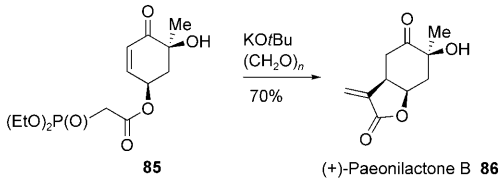
The HWE approach has recently been incorporated into an efficient telescoped intramolecular Michael/olefination (TIMO) sequence by Taylor and co-workers (Scheme 13).[69]



Scheme 13.

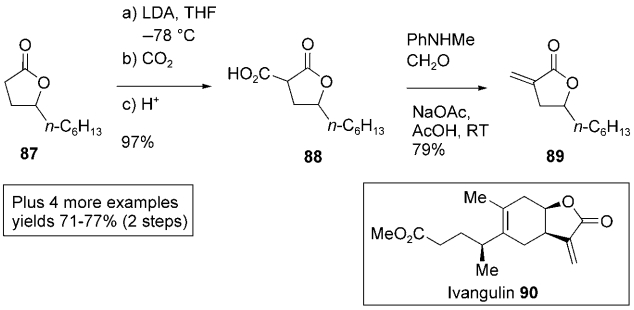
Thus, the anion of the α-phosphono-γ-lactone **83** was generated in situ by an intramolecular Michael/proton-transfer process; subsequent addition of paraformaldehyde then gave the *cis*-fused α-methylene-γ-butyrolactone **84a** in 77% yield. Aromatic and aliphatic aldehydes could also be employed in this telescoped methodology, thereby generating, for example, the α-alkylidene-γ-butyrolactones **84b** and **84c**.

This TIMO methodology was then utilized as the cornerstone of a concise synthesis of (+)-paeonilactone B (**86**; Scheme 14).[69] It is noteworthy that this telescoped sequence is compatible with an unprotected tertiary alcohol.



Scheme 14.

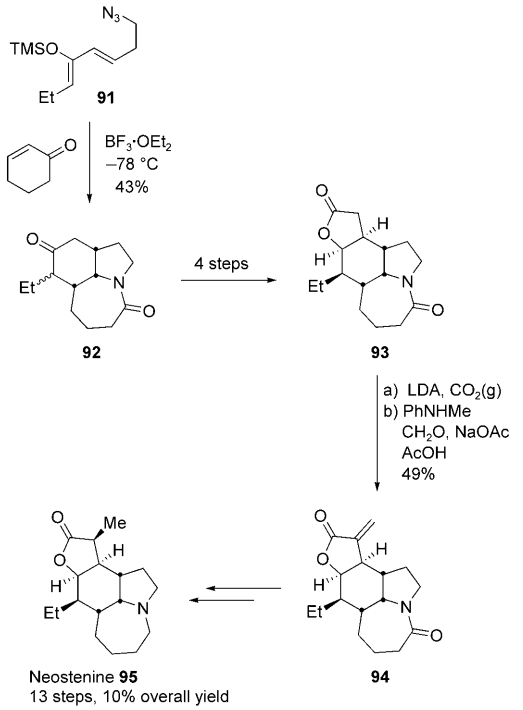
A related non-phosphorus-based procedure for the α-methylenation of γ-lactones was published by Greene and co-workers in 1993.[70] This utilizes initial α-carboxylation followed by a Mannich/decarboxylation process (Scheme 15). Thus, treatment of the LDA-generated enolate



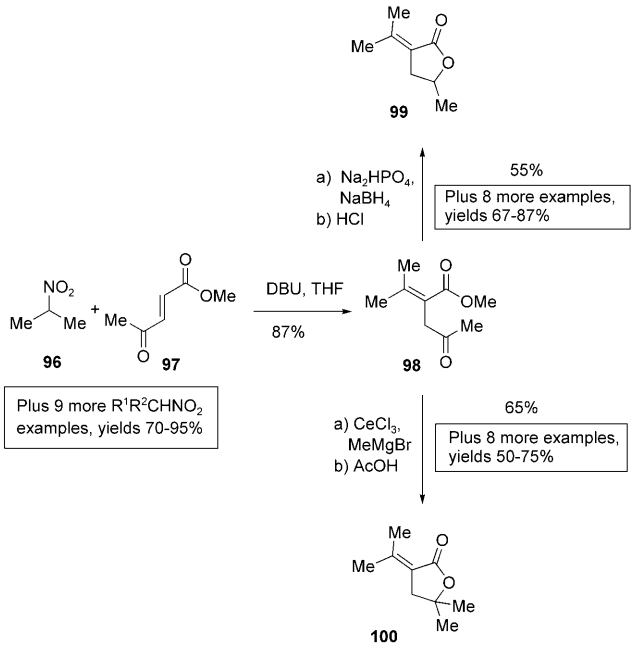
Scheme 15.

of **87** with gaseous carbon dioxide gave acid **88** after protonation. Subsequent reaction of compound **88** with a mixture of aqueous formaldehyde and *N*-methylaniline in buffered acetic acid generated the α-methylene-γ-butyrolactone **89** in yields of up to 77% over the two steps. In a slight variation, Metz et al. used methoxymagnesium carbonate to carboxylate a γ-butyrolactone and then the standard Greene Mannich/decarboxylation procedure, en route to the seco-eudesmanolide ivangulin (**90**).[71]

The Greene approach has been employed in many total syntheses.[71–75] For example, Aubé and co-workers utilized the Greene procedure in their synthesis of the *stemona* alkaloid (±)-neostenine (**95**) published in 2008 (Scheme 16).[75] An elegant, tandem Diels–Alder/azido-Schmidt reaction between azido-silyl enol ether **91** and cyclohexenone afforded selectively the *endo*-adduct **92** in 43% yield. Further manip-



Scheme 16.



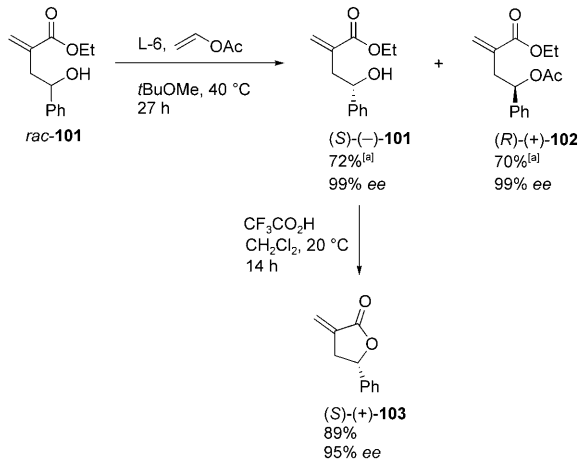
Scheme 17.

ulations afforded γ-lactone **93**, which was subjected to the Greene procedure to give α-methylene-γ-butyrolactone **94**. Diastereoselective hydrogenation using Adams' catalyst, followed by reduction of the amide with P_2S_{10} and Raney Nickel gave neostenine (**95**). This synthesis illustrates the value of α-methylene-γ-butyrolactones as precursors to the corresponding α-methyl-γ-butyrolactones in natural product synthesis.

5.2. Lactonization Approaches

The construction of the α-methylene-γ-butyrolactone core by lactonization has been widely used and is well-covered in earlier reviews.[1,13,14] An interesting variant has been developed by Ballini and co-workers[76] which commences with the conjugate addition of a nitroalkane (e.g. **96**) to enone **97** to give adducts such as **98** in a regioselective manner (Scheme 17). Adducts **98** were then reduced with sodium borohydride in the presence of 12.5 mol% of sodium hydrogenphosphate dodecahydrate to afford, after acidic work up, the α-alkylidene-γ-butyrolactones **99** in good yield. Ballini and co-workers also examined the reaction of the Michael adduct **98** with Grignard reagents. The use of anhydrous cerium(III) chloride was fundamental to avoid competing reactions. A range of Grignard reagents were added to a suspension of ketone **98** and cerium(III) chloride at −70 °C, thereby affording, after acidic work up, α-alkylidene-γ-butyrolactones such as **100** in good yield.

Adam and co-workers developed an effective method for the preparation of optically active α-alkylidene-γ-butyrolactones by a lipase-catalyzed kinetic resolution (Scheme 18).[77] They submitted racemic γ-hydroxy esters *rac*-**101**, to enzyme-

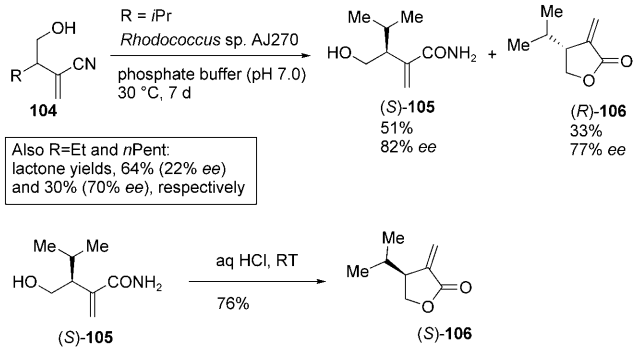


Scheme 18. [a] Yields normalized to 100% conversion.

catalyzed acetylation in the presence of lipase Chirazyme L-6. Excellent kinetic resolution was achieved, furnishing the ester (*S*)-(−)-**101** and the acetate (*R*)-(+)-**102** with excellent enantioselectivity at 50% conversion. Cyclization of the optically active hydroxy ester (*S*)-(−)-**101** with trifluoroacetic acid afforded the α-methylene-γ-butyrolactone (*S*)-(+)-**103** in 89% yield (95% *ee*).

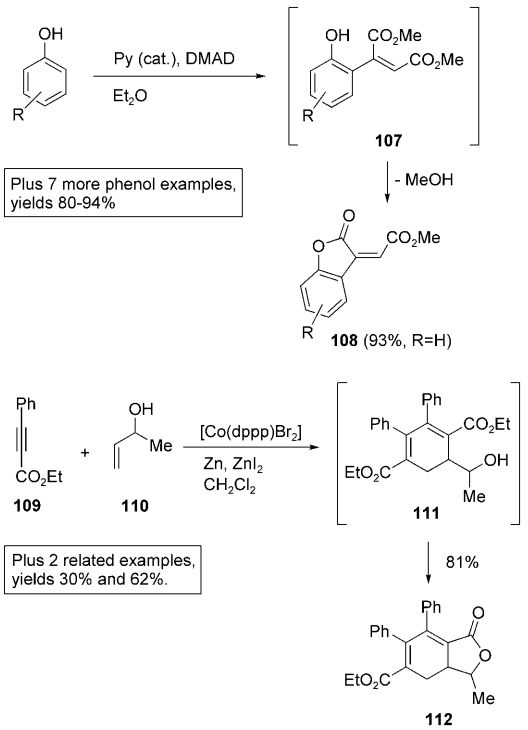
In 2002, Wang and Zhao reported the preparation of optically active β-alkyl-α-methylene-γ-butyrolactones by the enantioselective biotransformation of nitriles.[78] They studied the enantioselective hydrolysis of the readily available nitriles **104** catalyzed by *Rhodococcus* sp. AJ270 whole cells, a powerful nitrile hydratase/amidase-containing microorganism. The best example used **104** (R = *i*Pr), which underwent enantioselective hydrolysis/cyclization to give the (*R*)-α-methylene-γ-butyrolactone **106** in 33% yield and 77% *ee*,

although the transformation was very slow (Scheme 19). In addition, the (*S*)-amide **105** was obtained in 51% yield (82% *ee*). Chemical hydrolysis/cyclization of (*S*)-amide **105** could be carried out in hydrochloric acid giving the (*S*)-α-methylene-γ-butyrolactone **106** in modest yield.



Scheme 19.

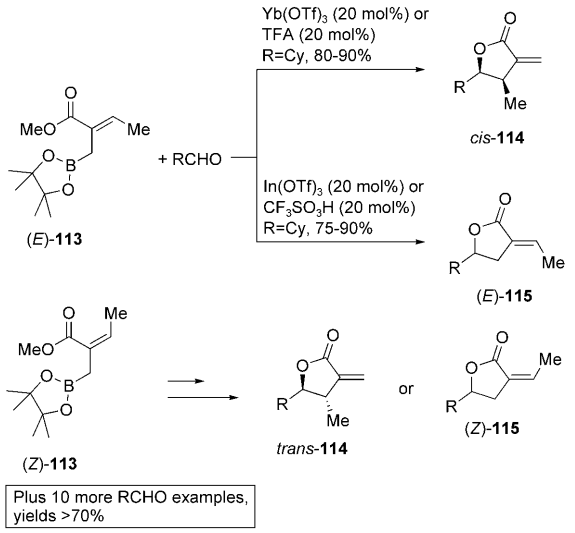
Yavari and Hossaini recently developed a method for the synthesis of aryl-fused α-methylene-γ-butyrolactone derivatives **108** through the reaction of dimethyl acetylenedicarboxylate (DMAD) with phenols in the presence of a catalytic amount of pyridine (Scheme 20).[79] Initial addition of pyridine to DMAD formed an activated species which underwent addition of phenol to form the corresponding nitrogen ylide, giving intermediate **107** after proton transfer and spontaneous elimination of pyridine. Intramolecular lactonization gave the fused α-methylene-γ-butyrolactones **108** in high yields.



Scheme 20. dppp = 1,3-bis(diphenylphosphanyl)propane.

A related process was developed by Hilt and co-workers to prepare fused α-alkylidene-γ-butyrolactones such as **112** (Scheme 20).[80] They studied a [2+2+2] cycloaddition between a substituted alkynoate and an allylic alcohol in the presence of catalytic amount of $[Co(dppp)Br_2]$. A regioselective cycloaddition was observed with phenylpropynoate (**109**) and 1-methyl-2-propen-1-ol (**110**) generating the 1,3-cyclohexadiene intermediate **111**, which underwent lactonization in situ to give α-alkylidene-γ-butyrolactone **112** in 81% yield.

In 2007, Ramachandran and Pratihar extended the methodology initially developed by Hall and Kennedy[81] to provide a selective synthesis of β,γ-disubstituted-α-methylene-γ-butyrolactones **114** or γ-substituted-α-alkylidene-γ-butyrolactones **115** (Scheme 21).[82] Thus, with the reagent

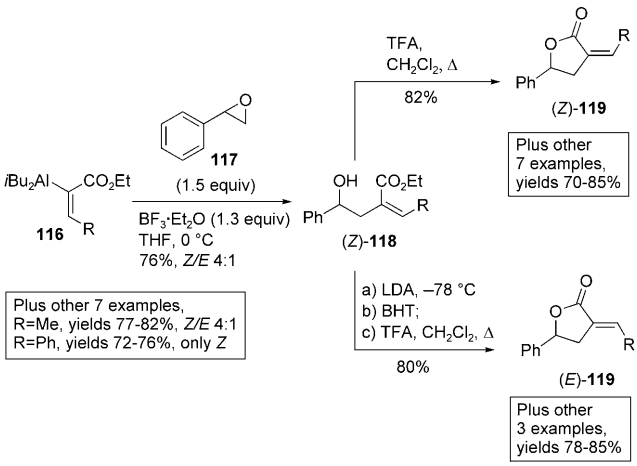


Scheme 21.

(*E*)-**113** in the presence of 20 mol% of $Yb(OTf)_3$ or TFA, aldehydes were converted into *cis*-β,γ-disubstituted-α-methylene-γ-butyrolactones **114** by initial crotylboration followed by lactonization. The use of stronger Lewis or Brønsted acids such as $In(OTf)_3$ or triflic acid produced the (*E*)-α-alkylidene-γ-substituted-γ-butyrolactones **115** via the formation of an oxonium ion intermediate, which underwent an oxonia-Cope rearrangement, followed by lactonization. In a similar manner, (*Z*)-**113** was employed to access the isomeric products *trans*-**114** and (*Z*)-**115**. This method is limited to the preparation of γ-alkyl derivatives, since γ-aryl derivatives undergo a carbocation-mediated rearrangement to provide *cis*- or *trans*-β,γ-disubstituted-α-methylene-γ-butyrolactones.[83] A similar approach has been recently used by Chataigner and co-workers for the stereocontrolled synthesis of γ-substituted-α-methylene-γ-butyrolactones.[84]

Subsequently, Ramachandran and co-workers extended their methodology to the synthesis of (*Z*)-α-alkylidene-γ-aryl-γ-butyrolactones **119** by alkenylalumination of the corresponding 2-aryloxirane **117**.[85] Reaction of the readily prepared [α-(ethoxycarbonyl)alkenyl]diisobutylaluminium **116** with styrene oxide (**117**) in the presence of $BF_3{\cdot}Et_2O$ provided

the homoallylic alcohol **118** in 76% yield (*Z*/*E* 4:1; Scheme 22). Purification, followed by lactonization, gave the (*Z*)-α-alkylidene-γ-phenyl-γ-butyrolactone **119** in 82%



Scheme 22. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

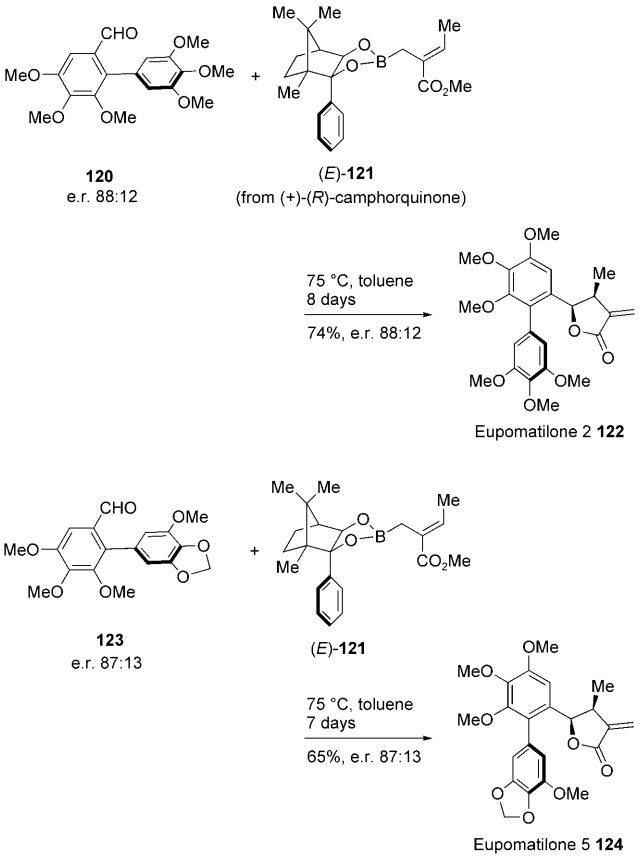
yield and as a single isomer. The synthesis of the (*E*)-α-alkylidene-γ-aryl-γ-butyrolactone **119** was achieved in high yield by base-mediated isomerization of the homoallylic alcohol **118** and subsequent lactonization.

An efficient diastereoselective thermal carbomethoxycrotylboration of biaryl aldehydes was employed by Coleman and co-workers in their total synthesis of the lignans eupomatilone 2 (**122**) and eupomatilone 5 (**124**; Scheme 23).[86] The natural products were obtained in good yield and high enantioselectivity, although the reactions were very slow.

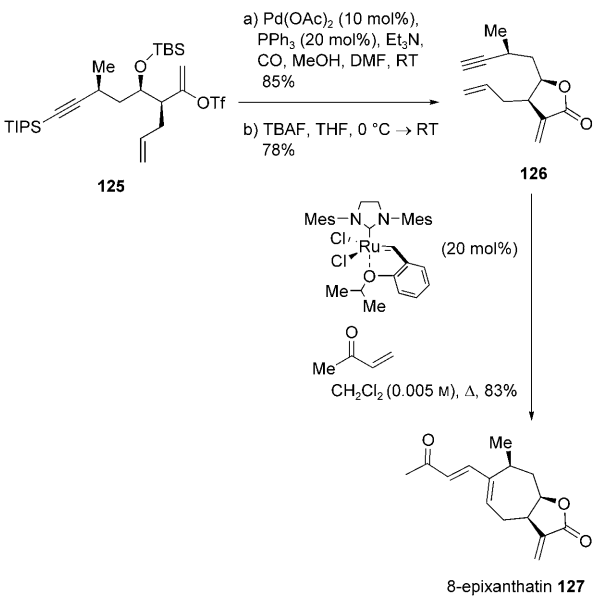
In 2005, Martin and co-workers achieved the first total synthesis of (+)-8-epixanthatin (**127**), a sesquiterpene lactone particularly known for its antimalarial and antitumor activity (Scheme 24).[87] The α-methylene-γ-butyrolactone **126** was prepared in high yield from the corresponding vinyl triflate **125** by a palladium-catalyzed carbonylation/lactonization sequence. Subsequent domino enyne ring-closing metathesis/cross-metathesis in the presence of 20 mol% of the Hoveyda–Grubbs second generation catalyst provided the natural product in 83% yield.

In 2008, Spilling and co-workers synthesized two diastereomers of a phosphonate analogue of cyclophostin, the acetylcholinesterase (AChE) inhibitor (Scheme 25).[88] Selective mono-demethylation and protonation of phosphonate **128** generated the corresponding phosphonic acid, which underwent cyclization to afford compound **129** in 73% yield over three steps, as a mixture of diastereomers. Selective debenzylation led to the formation of the primary alcohol, which cyclized spontaneously to give the phosphonate analogue **130** of cyclophostin as a mixture of diastereomers in quantitative yield.

Finally in this section, examples are presented in which unsaturated carboxylic acid derivatives are generated oxidatively and then undergo lactonization in situ. Markó and co-workers prepared γ-hydroxy aldehydes such as **132** from

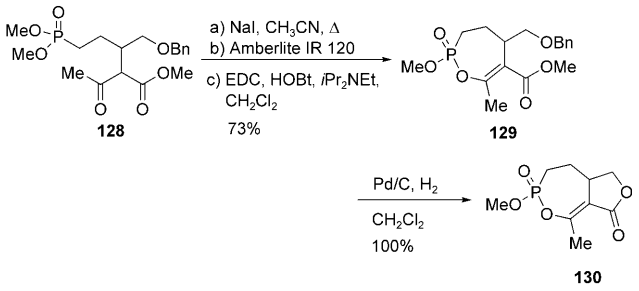


Scheme 23.

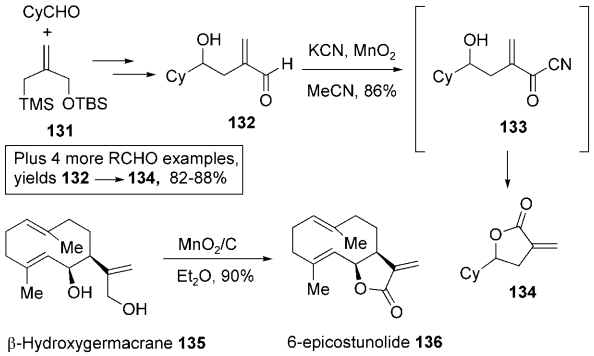


Scheme 24.

simple aldehydes and allylsilane **131** (Scheme 26).[89] They then applied Corey's MnO_2/cyanide procedure to efficiently generate the substituted α-methylene-γ-butyrolactone (e.g. **134**) by way of the intermediate cyanohydrin, which was oxidized to the acyl cyanide intermediate **133** and then underwent in situ lactonization. However, in 2008 in their



Scheme 25.



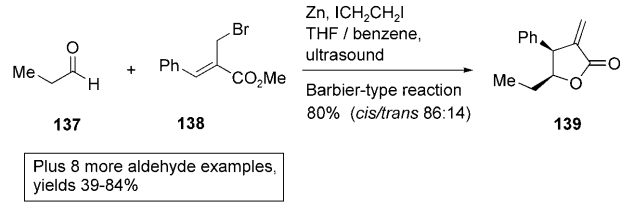
Scheme 26.

preparation of 6-epicostunolide (**136**), Massanet and co-workers demonstrated that cyanide is not always required for such oxidative lactonizations (Scheme 26).[90]

5.3. The Dreiding–Schmidt Organometallic Approach

In 1970, Dreiding et al. and Schmidt et al. developed a one-pot methodology for the preparation of α-methylene-γ-butyrolactones, which involved the treatment of 2-bromomethylacrylic esters with zinc to provide a functionalized organometallic reagent; addition of an aldehyde, followed by spontaneous cyclization produced α-methylene-γ-butyrolactones. The reaction proceeds via a six membered chair transition state and is *cis*-selective. This method provides one of the simplest and most direct methods for the preparation of α-methylene-γ-butyrolactones and it has been widely used and well reviewed.[1] Dreiding-Schmidt variants producing α-methylene-γ-butyrolactones have also been reported using chromium,[91] tin,[92] indium,[93] and Cu/Zn[94] (see also Scheme 56 for a [Cp_2TiCl]-mediated radical variant of the Dreiding–Schmidt reaction).

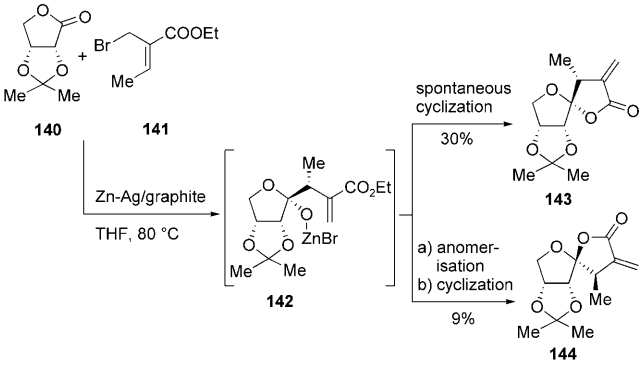
An interesting variation of the Dreiding–Schmidt approach has been reported by Chu and co-workers for the preparation of 3,4-disubstituted α-methylene-γ-butyrolactones **139** (Scheme 27).[95] Addition of 3-phenylallyl bromide **138** to propanal (**137**) using sonochemical Barbier-type conditions gave the expected addition followed by in situ cyclization to produce the 3,4-disubstituted-α-methylene-γ-butyrolactone **139** in 80% yield. The choice of solvent was crucial to the success of the reaction; a mixture of THF and



Scheme 27.

benzene gave α-methylene-γ-butyrolactone **139** as the only product, whereas in DMF, lactonization did not occur and the acyclic allylation product was observed.

Csuk and co-workers utilized the Dreiding-Schmidt procedure with a highly reactive zinc–silver/graphite-derived organometallic reagent to prepare spiro-anellated carbohydrate-derived α-methylene-γ-butyrolactones **143** and **144**, which possess an additional stereogenic center in the β-position (Scheme 28).[96] The reaction proceeds through the

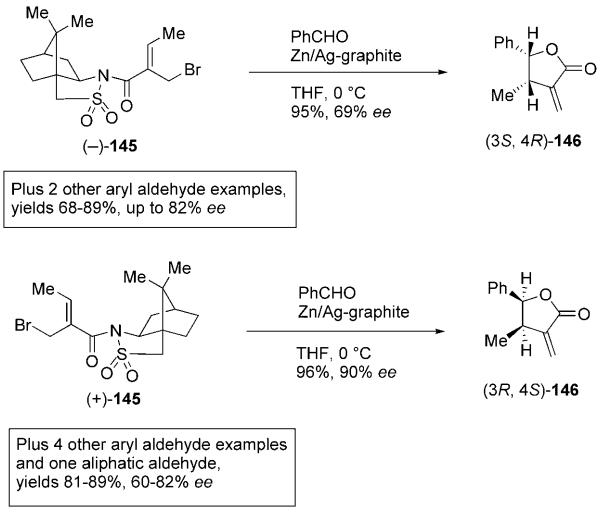


Scheme 28.

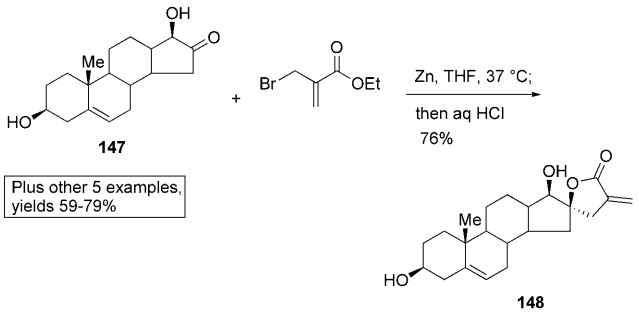
formation of the alkoxide intermediate **142**, which cyclizes spontaneously to give **143** in 30% yield. Anomerization followed by cyclization leads to the isomeric product **144** in 9% yield.

Csuk's research group went on to develop an enantioselective Dreiding–Schmidt variant, based on Oppolzer sultam methodology, for the asymmetric preparation of α-methylene-γ-butyrolactones **146** (Scheme 29).[97] Reaction between the enantiopure 2-bromomethyl-sultamamide **145** and a range of aldehydes using the zinc-silver/graphite reagent gave β-methyl-α-methylene-γ-butyrolactones such as **146** in high yields and moderate enantioselectivity. Similar examples were reported that produce the β-unsubstituted analogues.[97]

Finally, the classical Dreiding–Schmidt process is still widely used. Trivedi and co-workers employed it in a highly stereoselective synthesis of steroid-derived spiro-α-methylene-γ-butyrolactones (Scheme 30).[98] A range of steroidal α-hydroxyketones were utilized, and it was established that the α-hydroxy group was fundamental for the stereoselectivity, as the reaction proceeded via a transition state involving a chelate intermediate in which zinc is coordinated to both the hydroxy and carbonyl oxygen atoms. As an example, α-hydroxyketone **147** gave the spiro-α-methylene-γ-butyrolactone **148** in 76% yield as a single diastereomer.



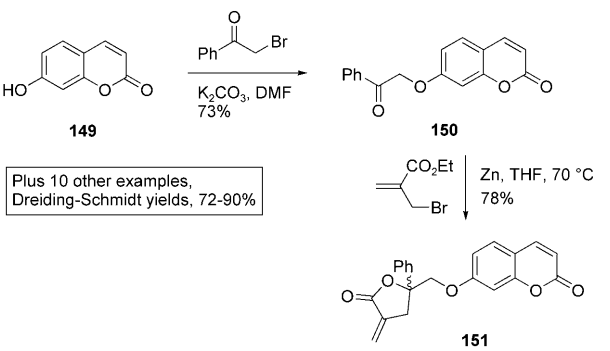
Scheme 29.



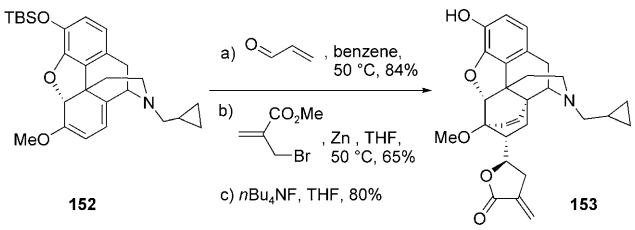
Scheme 30.

Tzeng and co-workers prepared a range of coumarin, naphthalene and quinoline derivatives, all containing the α-methylene-γ-butyrolactone moiety, in the search for new compounds with anticoagulant, antiplatelet, or vasorelaxing activities.[99] For example (Scheme 31), 7-hydroxycoumarin (**149**) was easily converted into ketone **150** which was subjected to the Dreiding–Schmidt reaction to give α-methylene-γ-butyrolactone **151**, which exhibited strong antiplatelet activity.[99]

Nelson and co-workers used the classical Dreiding–Schmidt methodology for the synthesis of the α-methylene-γ-butyrolactone **153** which is related to the potent opioid etorphine (Scheme 32).[100] A Diels–Alder reaction of dienol ether **152** with acrolein followed by the Dreiding-Schmidt



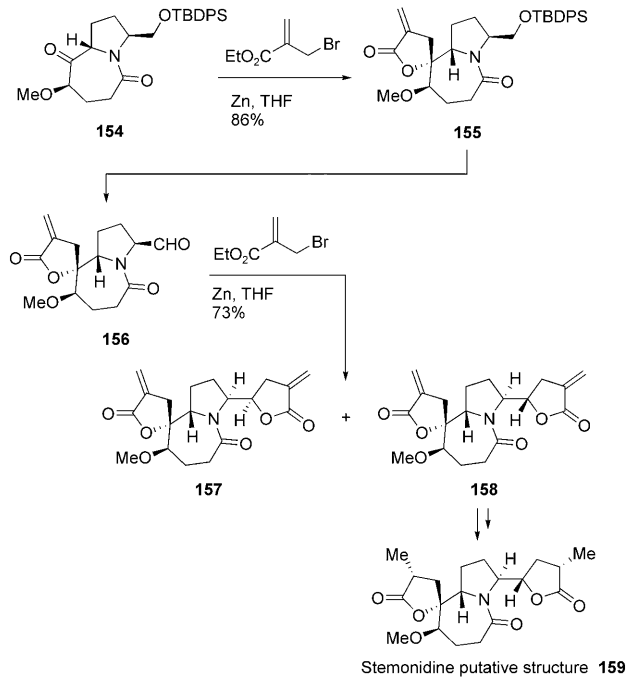
Scheme 31.



Scheme 32.

reaction and deprotection afforded the opioid candidate **153** as a single diastereomer.

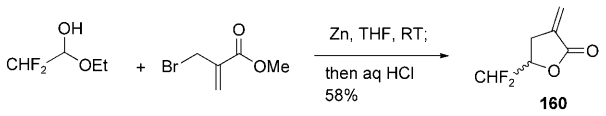
In 2007, Figueredo and co-workers applied the Dreiding–Schmidt reaction in the synthesis of the putative structure **159** of the alkaloid stemonidine (Scheme 33).[101] Treatment of



Scheme 33.

precursor **154** with ethyl bromoethylacrylate and zinc in THF afforded the spiro-α-methylene-γ-butyrolactone **155** with complete facial selectivity in 86% yield. Deprotection and further oxidation led to the formation of the aldehyde **156**, which underwent a second Dreiding–Schmidt reaction to give a 1:1 mixture of bislactones **157** and **158** in 73% overall yield. Further manipulation of the bislactone **158** led to the formation of compound **159**, which was shown to be a diastereomer of stemonidine.

Finally, Scheme 34 illustrates an interesting application of the Dreiding–Schmidt reaction reported by Kitazume and co-workers.[102] By using difluoroacetaldehyde ethyl hemiacetal

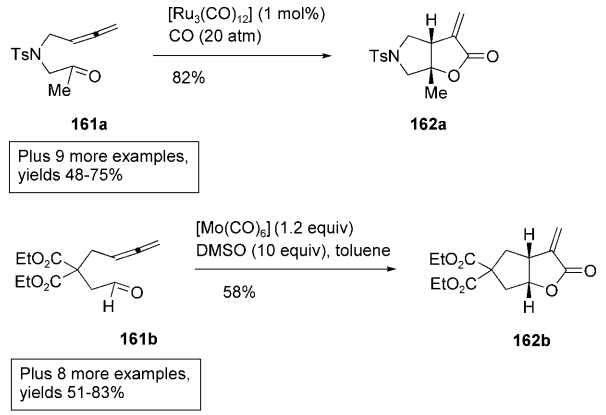


Scheme 34.

they prepared the antitumor agent γ-difluoromethyl-α-methylene-γ-butyrolactone (**160**) in 58% yield.

5.4. Other Metal-Promoted Approaches

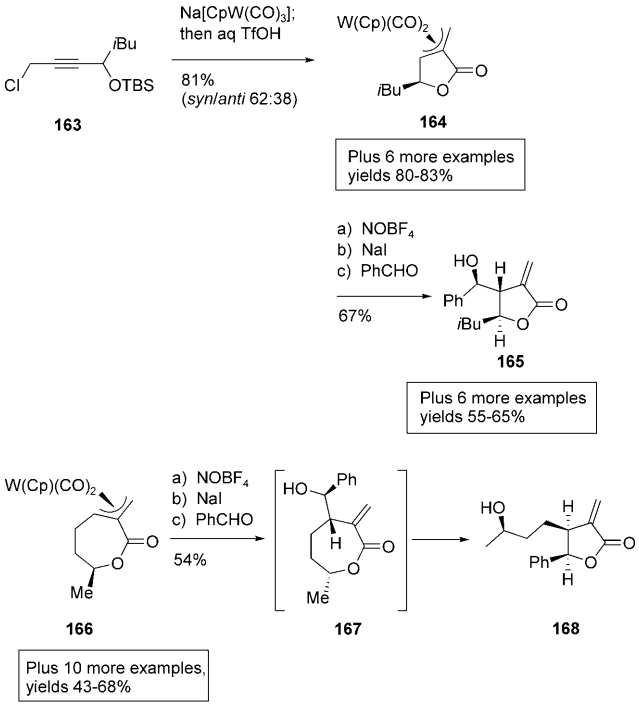
In addition to the Dreiding–Schmidt and metathesis procedures discussed, a number of other organometallic approaches to α-alkylidene-γ-butyrolactones have been reported,[1] and there have been many advances in this area in recent years. In 2002, Kang and co-workers reported a ruthenium-catalyzed [2+2+1]-carbonylative hetero-Pauson–Khand-type cyclization of allenyl aldehydes and ketones **161a** to give the *cis*-fused bicyclic α-methylene-γ-butyrolactones **162a** in good to excellent yields (Scheme 35).[103] They



Scheme 35.

proposed a mechanistic pathway involving the concerted cyclization of the allene, carbonyl, and {Ru(CO)$_4$}, followed by insertion of CO and subsequent reductive elimination. Subsequently, Yu and co-workers reported that the same transformation could be performed using stoichiometric quantities of [Mo(CO)$_6$] in DMSO, thus eliminating the need for an atmosphere of CO (e.g. Scheme 35, **161b**→**162b**).[104] A [Co$_2$(CO)$_8$]/thiourea-catalyzed carbonylative Pauson–Khand reaction of enynes was described more recently by Chen, Yang, and co-workers in which tetrasubstituted α-alkylidene-γ-butyrolactones were formed in good yield.[105]

A tungsten-promoted intramolecular alkoxycarbonylation approach to α-methylene-γ-butyrolactones was reported by Liu and co-workers (Scheme 36).[106] Treatment of propargyl chloride **163** with Na[CpW(CO)$_3$], followed by protonation under controlled conditions, gave the isolable η^3-γ-lactone **164** in 81% yield (*syn*/*anti* 62:38). A mechanistic proposal was presented to explain the observed products and

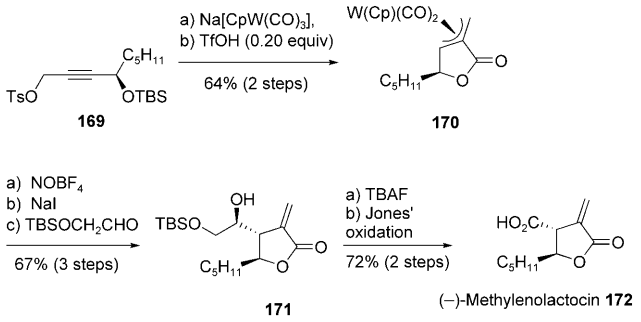


Scheme 36.

stereoselectivity. The separated *syn*-η^3-tungsten intermediate **164** was then transformed into the corresponding α-methylene-γ-butyrolactone **165** by sequential treatment with nitrosonium tetrafluoroborate and sodium iodide (to generate the η^3-W(Cp)(NO)I species), followed by addition of an aldehyde. The aldehyde adds selectively at the γ-position to give, with benzaldehyde, the *anti*-disubstituted-γ-lactone **165** in 67% yield and with complete diastereoselectivity. This same methodology was also applied to larger ring η^3-lactone intermediates **166**. When treated with nitrosonium tetrafluoroborate and sodium or lithium iodide followed by an aldehyde, the initial product **167** rearranges to form the more stable γ-lactone product **168** in 54% yield (Scheme 36).[106]

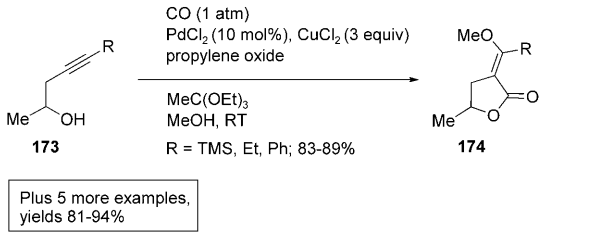
Subsequently, Liu's group utilized their methodology as the cornerstone of a concise total synthesis of the antibacterial and antitumor agent (−)-methylenolactocin (**172**; Scheme 37).[107] Thus, reaction of propargyl tosylate **169** with Na[CpW(CO)$_3$] afforded the corresponding η^1-propargyl tungsten complex, which, on treatment with triflic acid underwent intramolecular alkoxycarbonylation to afford the *syn*-η^3-tungsten species **170** in 64% yield (two steps). Treatment with NOBF$_4$ and NaI, followed by in situ trapping with TBS-protected 2-hydroxyacetaldehyde gave α-methylene-γ-butyrolactone **171** in 67% yield over the three steps. Cleavage of the silyl group and oxidation to the acid afforded (−)-methylenolactocin (**172**) in good yield.

Although this section commenced with ruthenium and tungsten examples, palladium- and nickel-catalyzed routes to α-alkylidene-γ-butyrolactones are more common. In 1991, Tamaru and co-workers devised a palladium-catalyzed double carbonylation procedure for the stereoselective conversion of substituted 3-butyn-1-ols **173** into 1-substituted-1-methoxy-



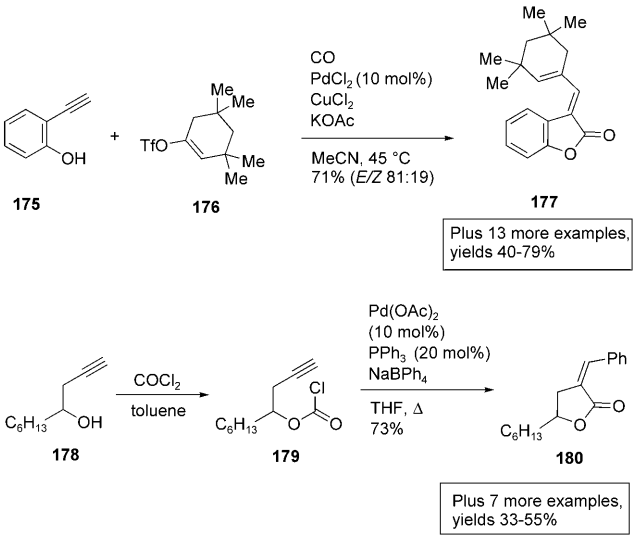
Scheme 37.

lated α-alkylidene-γ-butyrolactones **174** (Scheme 38).[108] The addition of propylene oxide (to quench HCl) and ethyl orthoacetate (to remove any water) were essential to obtain high yields.



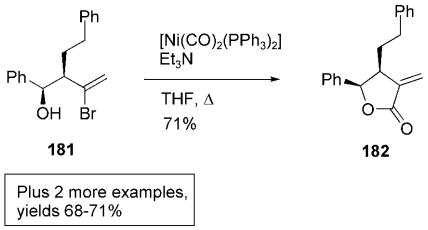
Scheme 38.

Similar palladium-catalyzed alkyne carbonylations have been employed to prepare monosubstituted α-alkylidene-γ-butyrolactones (Scheme 39).[109,110] Arcadi, Cacchi, and coworkers started from *o*-ethynylphenol (**175**) and trapped the resulting vinylpalladium species with vinyl triflates such as **176** to afford 3-alkylidene-2-coumaranones such as **177** stereoselectively and in good yield (Scheme 39).[109] More recently, Grigg and Savic devised a similar approach which avoided the use of carbon monoxide. Instead the corresponding chloroformate **179** was employed with cyclization-anion capture giving the (*Z*)-α-arylidene-γ-butyrolactone product **180** in a stereoselective manner (Scheme 39).[110] Other palladium-catalyzed cyclization routes to α-alkylidene-γ-butyrolactones have also been reported.[111,112]



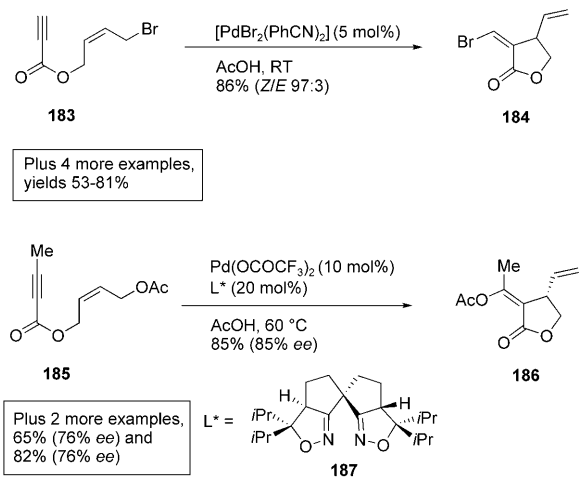
Scheme 39.

In 2003, Uenishi and Ohmi reported the conversion of hydroxylated vinyl bromides such as **181** (prepared by a Sakurai reaction of the corresponding 2-bromo-allylsilane and an aldehyde) into α-methylene-γ-butyrolactones **182** (Scheme 40).[113] The transformation was mediated by stoichiometric amounts of $[Ni(CO)_2(PPh_3)_2]$ and proceeded by a standard oxidative addition/CO insertion/reductive elimination sequence, with the nickel complex acting as the source of CO. The relative configuration of the starting material is retained in the product.



Scheme 40.

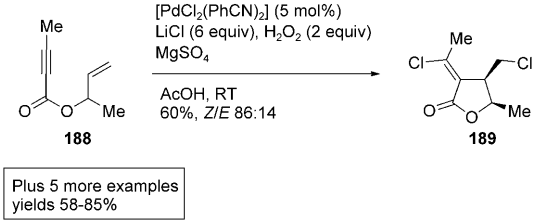
Moving on from carbonylation approaches, palladium-catalyzed enyne cyclization processes have also provided useful routes to α-methylene-γ-butyrolactones. In 1990, Ma and Lu reported the palladium(II)-catalyzed stereoselective synthesis of α-halomethylene-γ-butyrolactones **184** from 1,6-enynes **183** in yields up to 86% (Scheme 41).[114] The proposed mechanism involves initial *trans*-alkyne halopalladation followed by addition to the alkene and subsequent dehalopalladation giving the *Z*-alkenyl product **184**. More recently, Lu's research group reported the use of iminopyridines as efficient ligands for related palladium-catalyzed enyne cyclization



Scheme 41.

processes.[115] Sasai and co-workers have developed an enantioselective palladium-catalyzed enyne cyclization process (**185**→**186**) employing catalytic $Pd(OCOCF_3)_2$ and a chiral spiro-bis(isoxazoline) ligand **187** with enantiomeric excesses of up to 85% being obtained (Scheme 41).[116]

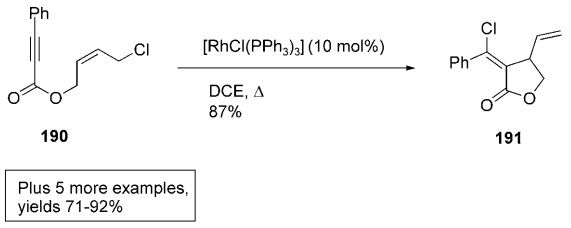
In 2008, Liu and Yin reported the Pd-catalyzed oxidative cyclization of similar enyne substrates (Scheme 42).[117] β-Chloro-α-methylene-γ-butyrolactones **189** were obtained in



Scheme 42.

good to excellent yields predominantly as the *Z* stereoisomers. It is noteworthy that when **188** was substituted at the allylic position (e.g. the methyl group), the *cis* product was obtained exclusively, as shown.

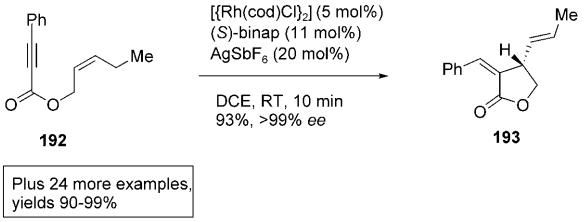
Recently, a rhodium(I)-catalyzed variant of this cyclization process has been reported by Tong et al. (Scheme 43).[118] In these examples, however, it is noteworthy that the



Scheme 43.

E-alkenyl products (e.g. **191**) are produced stereoselectively. To rationalize the stereochemical outcome, the formation of a π-allyl rhodium intermediate was proposed with subsequent *syn* addition to the alkyne (with concomitant intramolecular halogen shift) and then reductive elimination.

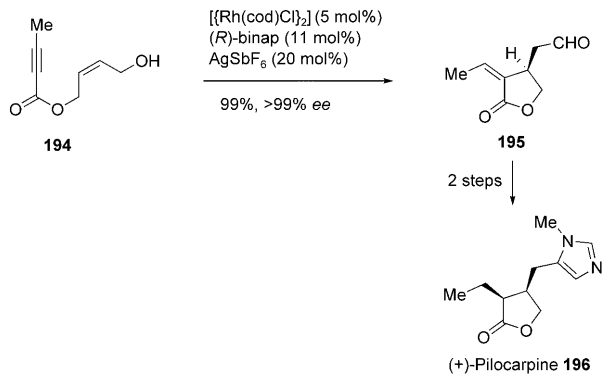
An enantioselective rhodium(I)-catalyzed intramolecular Alder-ene route to α-alkylidene- and α-arylidene-γ-butyrolactones **193** from simple 1,6-enynes **192** has been described by Zhang and co-workers (Scheme 44).[119] The α-alkylidene-



Scheme 44.

γ-butyrolactone products **193** were obtained in yields of up to 99%, and remarkable enantioselectivities were observed with the use of (*R*)- or (*S*)-binap as the chiral ligand.

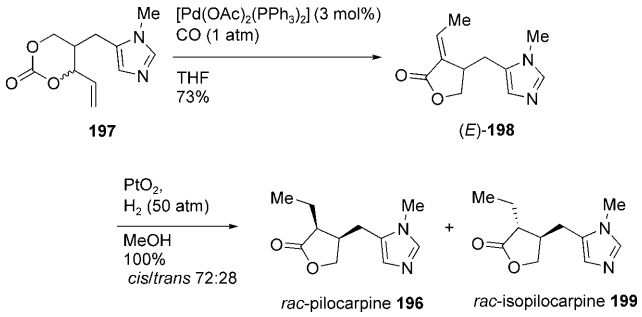
This enyne methodology was used as the cornerstone of a short, enantioselective formal synthesis of the muscarinic alkaloid (+)-pilocarpine (**196**; Scheme 45). Thus, the Rh^I



Scheme 45.

methodology was employed to convert enyne **194** into aldehyde **195** in one step and with complete enantiocontrol.[119] Büchi's two step procedure[120] was used to complete the synthesis of (+)-pilocarpine (**196**). This example once again highlights the value of α-alkylidene-γ-lactones as building blocks in natural product synthesis.

Finally in this section, racemic pilocarpine (**196**) and isopilocarpine (**199**) were prepared by the Davies research group (Scheme 46).[121] A diastereomeric mixture (1:1) of



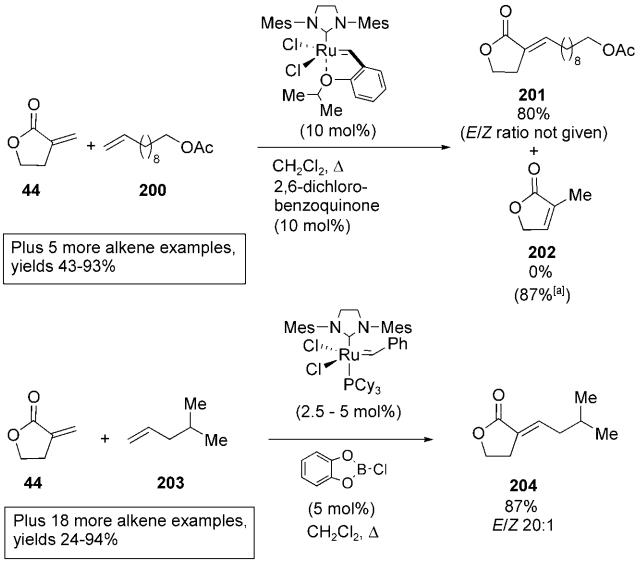
Scheme 46.

carbonates **197** was subjected to $[Pd(OAc)_2(PPh_3)_2]$ under an atmosphere of carbon monoxide to afford exclusively the (*E*)-α-alkylidene-γ-butyrolactone **198** in 73% yield. Hydrogenation with the Adams catalyst gave a 72:28 mixture of pilocarpine (**196**) and isopilocarpine (**199**) in quantitative combined yield.

5.5. Elaboration of Existing α-Methylene-γ-butyrolactones

The elaboration of simple α-methylene-γ-butyrolactones to give more complex α-alkylidene-γ-butyrolactone systems

has been explored before,[14] but there have been major advances in this area in recent years. One of the most valuable methods for the construction of carbon–carbon bonds is by olefin cross-metathesis,[122] and recently the groups of Howell and Cossy have extended the methodology to encompass exocyclic enone substrates.[123,124] In 2007, Howell's research group reported the coupling of α-methylene-γ-butyrolactone **44** with a range of terminal olefins (e.g. **200**) in the presence of 10 mol% Hoveyda–Grubbs second generation catalyst and 10 mol% 2,6-dichlorobenzoquinone to give cross-metathesis products such as **201** in excellent yields (Scheme 47).[123]

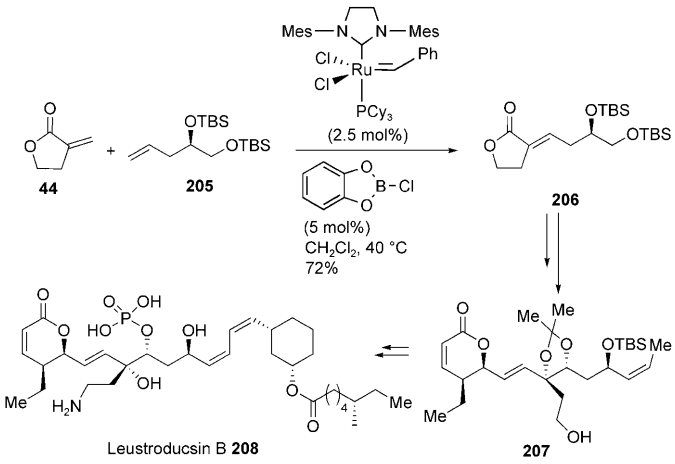


Scheme 47. [a] In the absence of 2,6-dichlorobenzoquinone.

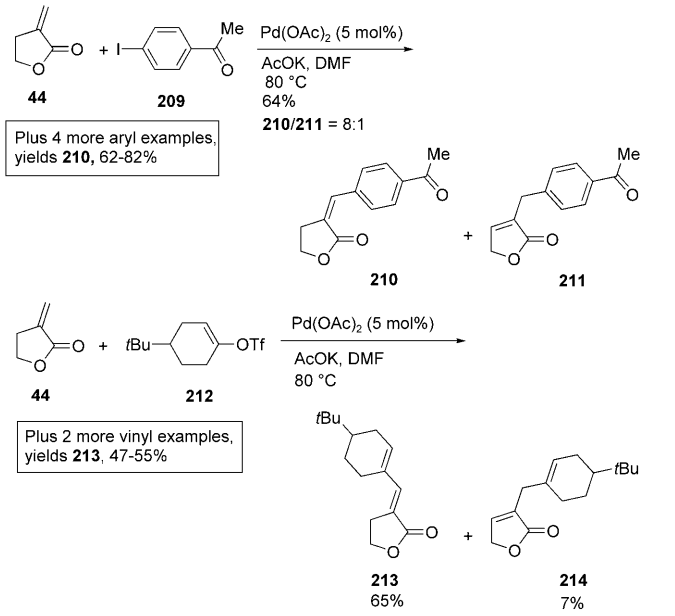
Electron-deficient benzoquinones are essential additives as they prevent the formation of the undesired isomerized product **202**.

A similar approach has been reported by Cossy's research group.[124] They developed a highly efficient cross-metathesis between α-methylene-γ-butyrolactone **44** and a large range of olefinic partners (Scheme 47). The products (e.g. **204**) were obtained in moderate to excellent yields and with high *E* stereoselectivity using a low loading (2.5 to 5 mol%) of the Grubbs second generation catalyst; again, an additive was required to minimize production of **202**, and chlorocatechol-borane proved most effective. Furthermore, Cossy, Arseniyadis, and co-workers successfully used their methodology in a formal synthesis of leustroducsin B, an α,β-unsaturated-δ-lactone, known for its potent protein phosphatase inhibition activity (Scheme 48).[125] Alkene **205** was subjected to the optimized cross-metathesis conditions to give α-alkylidene-γ-butyrolactone **206** in 72% yield. Further transformations led to the formation of intermediate **207**, a precursor of leustroducsin B (**208**).

Arcadi and co-workers investigated the Heck reactions of aryl iodide **209** with α-methylene-γ-butyrolactone **44** to stereoselectively prepare substituted α-benzylidene-γ-butyrolactone **210** (Scheme 49).[126] The reaction, which presumably proceeded through the β-elimination of a hydridopalladium



Scheme 48.



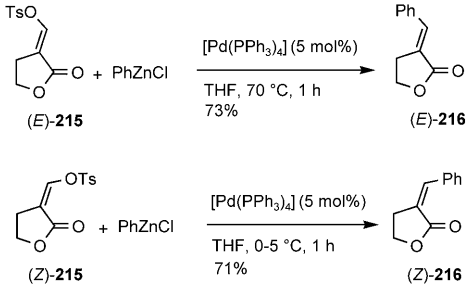
Scheme 49.

intermediate, generates α-benzylidene-γ-butyrolactone **210** in moderate yield as an 8:1 mixture with 3-benzylfuran-2-(5*H*)-one **211** (with triethylamine as base, **211** predominates). Somewhat surprisingly, this process is highly stereoselective in favor of the (*Z*)-alkylidene lactone **210**.

Subsequently, the Arcadi research group extended the methodology by using vinyl iodides and vinyl triflates such as **212** to prepare vinyl-substituted α-alkylidene-γ-butyrolactones **213** (Scheme 49).[127] In these examples, the *E* isomer **213** of the vinyl-substituted α-alkylidene-γ-butyrolactone is formed without contamination by the corresponding *Z* isomer. The *E* stereoselectivity in these examples was ascribed to the formation of an intermediate π-allylpalladium complex[128] which isomerized to give the thermodynamically favored stereoisomer.

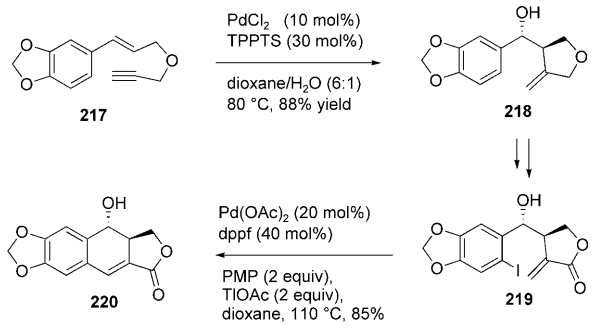
A related method for the synthesis of α-alkylidene-γ-butyrolactones was reported by Mazal and Castulík in

2000.[129] They developed a cross-coupling reaction of *E*- and *Z*-tosylate derivatives of α-hydroxymethylene-γ-butyrolactones with aryl-, heteroaryl-, alkyl-, and alkynylzinc chlorides, using catalytic tetrakis(triphenylphosphine)palladium(0). The reactions were carried out in THF at 70 °C for the *E* isomer. For the *Z* isomer, the temperature was kept between 0–5 °C, to avoid isomerization and achieve a satisfactory stereoselectivity. The most promising results for the coupling reaction were obtained with arylzinc and heteroarylzinc reagents, where excellent stereoselectivity and complete retention of configuration was observed (Scheme 50).



Scheme 50.

A palladium-catalyzed route was employed by Michelet and Genêt for the preparation of the aryltetralin moiety of podophyllotoxin, a lignan known for its antineoplastic and antiviral properties (Scheme 51).[130] Initial carbohydroxypalladation led diastereoselectively to the formation of dihydrofuran **218**, which was further elaborated, to give iodo derivative **219**. Then, a second palladium-catalyzed reaction was employed to effect intramolecular cyclization to give the podophyllotoxin skeleton **220** in 85 % yield.

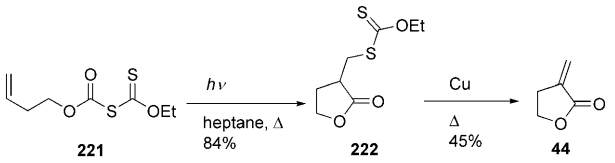


Scheme 51.

Finally in this section, it should be noted that naturally occurring α-methylene-γ-lactones have been further elaborated to provide novel compounds for bioassay. For example, euniolide (**40**) has been converted into a range of novel analogues by oxidation/dehydration/halogenation sequences (all of which preserved the α-methylene-γ-lactones unit to a certain extent).[131]

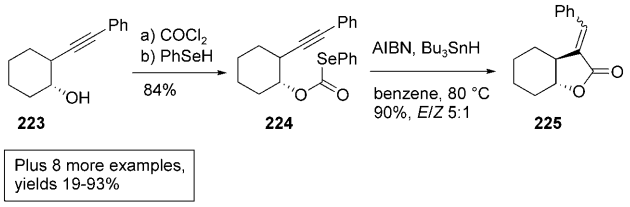
5.6. Radical Cyclization Approaches

Since the earlier synthetic reviews,[1,13,14] there have been major advances in radical approaches to α-alkylidene-γ-butyrolactones. In 1990, Zard and Forbes described the use of (*S*)-alkoxycarbonyl dithiocarbonates **221** to prepare α-methylene-γ-butyrolactone (**44**, tulipalin A) in a yield of 38 % over two steps (Scheme 52).[132] (*S*)-Alkoxycarbonyl dithiocarbonate **221**, derived from the corresponding homoallylic alcohol, phosgene, and $EtOCS_2K$, was irradiated with visible light in heptane under reflux. Fragmentation/decarboxylation followed by 5-*exo*-radical cyclization and then radical recombination generated xanthate **222** in high yield. Elimination of the xanthate group was achieved by heating under vacuum in the presence of copper powder, which produced α-methylene-γ-butyrolactone (**44**).



Scheme 52.

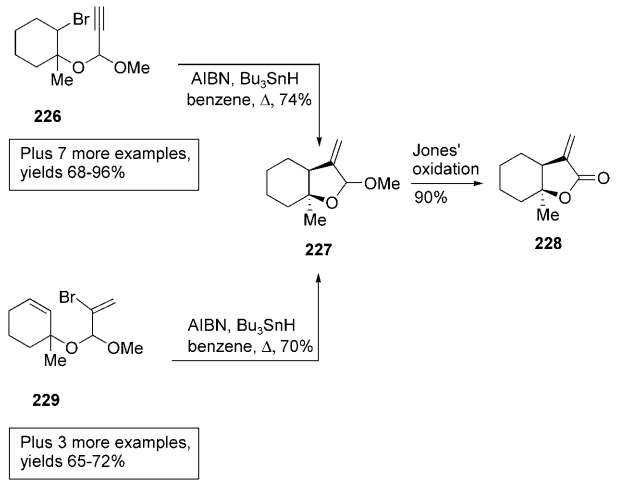
In 1992, Bachi and Bosch reported a synthetic approach to α-methylene-γ-butyrolactones **225** by a radical-induced cyclization of selenocarbonates **224** (Scheme 53).[133] Homopropargylic alcohol **223** was treated with phosgene to form the corresponding chloroformate, and this was trapped with phenylselenol to give selenocarbonate **224** in 84 % yield over the two steps. Thermolysis of selenocarbonate **224** in benzene at 80 °C generated the corresponding acyl radical, which underwent cyclization to afford α-arylidene-γ-butyrolactone **225** as a mixture of isomers in 90 % yield. A range of monocyclic and bicyclic α-methylene- and α-alkylidene-γ-butyrolactones were prepared by using this procedure.



Scheme 53.

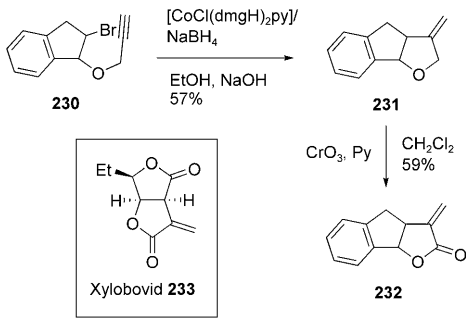
In 1993, Dulcère and co-workers reported the synthesis of α-methylene-γ-butyrolactones such as **228** from propargyl and vinyl acetals **226** and **229** (Scheme 54).[134] Thus, radical generation followed by cyclization afforded the *exo*-methylene lactol ether **227** in good yield. Subsequent oxidation using Jones' reagent gave α-methylene-γ-butyrolactone **228** in 90 % yield.

In 2002, Tabatabaian and co-workers described a related radical approach to the tricyclic α-methylene-γ-butyrolactone



Scheme 54.

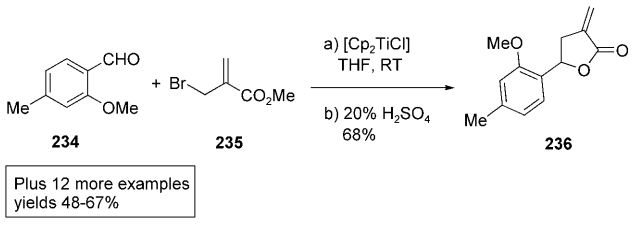
232 from the brominated propargyl ether **230** (Scheme 55; stereochemistry was not defined).[135] A cobalt-mediated radical cyclization was employed to afford the 3-methylene-



Scheme 55.

tetrahydrofuran **231**, which was then oxidized using the Collins reagent to give α-methylene-γ-butyrolactone **232** in 34% yield over the two steps. More recently, Sharma and Gopinath also utilized a radical cyclization/Collins oxidation approach in their synthesis of the antibacterial, antifungal, and phytotoxic agent xylobovide **233**.[136] The preparation of α-methylene-γ-butyrolactones by the oxidation of 3-methylene-tetrahydrofurans is a widely used and reviewed synthetic procedure.[1,13,14,137]

Finally in this section, Scheme 56 illustrates a radical variant of the classical Dreiding–Schmidt reaction reported

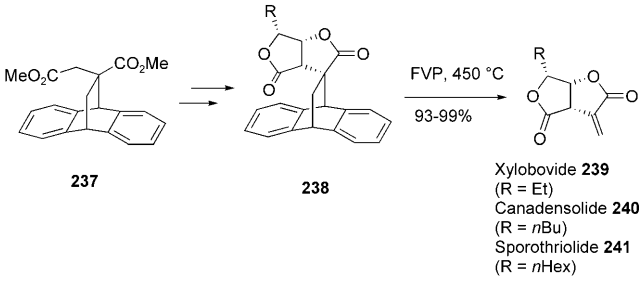


Scheme 56.

recently by Roy and co-workers.[138] [Cp_2TiCl] (readily generated from [Cp_2TiCl_2] and Zn) was added to a mixture of aldehyde **234** and 2-bromomethylacrylate (**235**). The resultant hydroxyester was then lactonized under acidic conditions to give α-methylene-γ-butyrolactone **236** in 68% yield. This method was successful with a range of aromatic and aliphatic aldehydes.

5.7. Miscellaneous Routes to α-Methylene-γ-butyrolactones

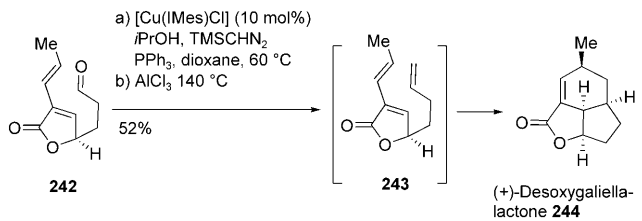
There are several other approaches to α-alkylidene-γ-butyrolactones that fall outside the categories discussed earlier. One important and well-reviewed procedure,[1] not yet covered herein, involves the late-stage unmasking of the sensitive methylene group of α-methylene-γ-butyrolactones by a retro-Diels–Alder process. This approach has been elegantly utilized by the Thebtaranonth research group to prepare the naturally occurring antifungal and antibacterial α-methylene-bis-γ-butyrolactones, xylobovide (**239**), canadensolide (**240**), and sporothriolide (**241**; Scheme 57).[139] A



Scheme 57.

stereocontrolled route to the bislactones **238** was developed commencing from the dimethyl itaconate–anthracene adduct **237**. Flash vacuum pyrolysis (FVP) was then employed to liberate the α-methylene-bis-γ-butyrolactones **239**–**241** in near-quantitative yields.

Lebel and Parmentier recently described a one-pot methylenation/inverse electron demand Diels–Alder reaction as the key α-alkylidene-γ-butyrolactone forming step in their synthesis of (+)-desoxygaliellalactone (**244**; Scheme 58).[140]

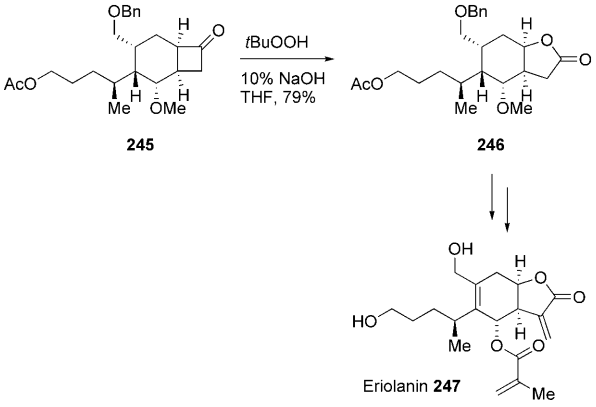


Scheme 58.

Thus, aldehyde **242** was converted into alkene **243** using trimethylsilyldiazomethane, triphenylphosphine, and a catalytic amount of [Cu(IMes)Cl] (more conventional Wittig

olefinations led to by-product formation) followed by addition of $AlCl_3$ to promote the cycloaddition. (+)-Desoxygaliellalactone (**244**) was obtained in 52% overall yield for the one-pot process (the corresponding two-step yield was 43%).

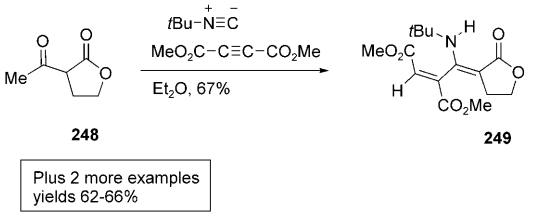
The Baeyer–Villiger oxidation of cyclobutanones with subsequent installation of the α-methylene unit has been used to prepare α-alkylidene-γ-butyrolactones,[1] but, as yet, has not been widely utilized. However, Wakamatsu and co-workers have described the Baeyer–Villiger oxidation of cyclobutanone **245** to form the γ-butyrolactone **246** as part of a formal synthesis of the leukaemia inhibitor, eriolanin (**247**) in racemic form (Scheme 59).[141] Roberts and Schlessinger



Scheme 59.

had earlier converted γ-butyrolactone **246** into eriolanin (**247**) by using the Greene α-carboxylation/decarboxylative Mannich process (see Section 5.1) to install the methylene group.[142]

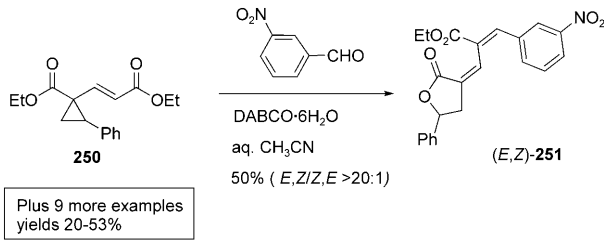
In 2006, Asghari and Mohammadi reported a three-component reaction for the preparation of functionalized α-alkylidene-γ-butyrolactones such as **249** (Scheme 60).[143]



Scheme 60.

Treatment of dicarbonyl compound **248** with the adduct of *tert*-butyl isocyanide and dimethyl acetylenedicarboxylate afforded functionalized α-alkylidene-γ-butyrolactone **249** in 67% yield.

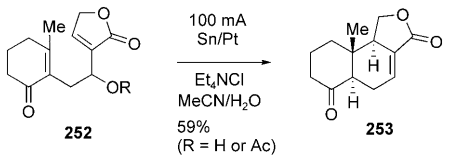
Cyclopropane ring-opening sequences have been employed previously to prepare α-alkylidene-γ-butyrolactones.[1,14] In 2008, Wang and Du developed a novel tandem variant for the preparation of substituted systems **251** (Scheme 61).[144] This process involves a DABCO-mediated nucleophilic ring opening of vinyl cyclopropanes **250** and



Scheme 61.

subsequent coupling with substituted benzaldehydes followed by lactonization. In all cases the *E*,*Z* isomer (e.g. **251**) predominated.

Finally, in 2007, Handy and co-workers reported the electro-hydrocyclization of enone-enoates **252** to afford α-alkylidene-γ-butyrolactones **253** in good yield (Scheme 62).[145] Using a tin anode and platinum cathode, a



Scheme 62.

constant current of 100 mA was applied to **252** in an undivided cell under argon, using tetraethylammonium chloride as a supporting electrolyte. α-Alkylidene-γ-butyrolactone **253** was obtained in 59% yield starting from either **252** (R = OH) or **252** (R = OAc).

6. Summary and Outlook

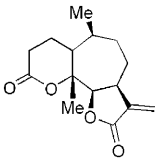
α-Alkylidene-γ-butyrolactones, particularly α-methylene-γ-butyrolactones, have a rich history across natural product chemistry, biosynthesis, biology/pharmacology, and synthetic organic chemistry. A cornucopia of naturally occurring examples, displaying fascinating structural diversity and remarkable biological properties, have been discovered over the past century. Such discoveries have provided over-the-counter treatments such as arnica and feverfew, invaluable biological probes, and generated numerous lead compounds for drug development programmes. This, in turn, has challenged synthetic chemists to devise novel chemistry for the efficient preparation of α-alkylidene-γ-butyrolactones and to apply this methodology to prepare new families of man-made compounds for biological screening as well as to devise synthetic routes to complex natural products.

The 21st century has seen renewed and heightened interest in α-alkylidene-γ-butyrolactones. Recently discovered natural products have shown great biological potential, with anti-inflammatory, anticancer and antiviral properties showing greatest promise, paving the way for the potential emergence of new drugs containing the α-alkylidene-γ-butyrolactone moiety. Arglabin, as a prime example, has

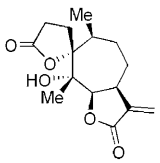
been introduced to treat breast, lung, and liver cancers, and with the new advances in synthetic methodology, as reviewed herein, the future of α-alkylidene-γ-butyrolactone chemistry indeed looks exciting.

7. Recent Results

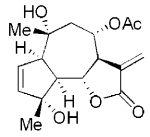
With reference to Section 2.4, the novel pseudoguaianolide lactones, the psilostachyins, deserve mention. Psilostachyin A (**254**) and psilostachyin C (**255**) have been known for some time,[146] and psilostachyin C (**255**) is easily accessed by



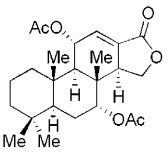
Psilostachyin A **254**
Significant trypanocidal and leishmanicidal activities



Psilostachyin C **255**
Modulator of the G_2 cell-cycle checkpoint



Chrysanthemum metabolite **256**
Cytotoxic



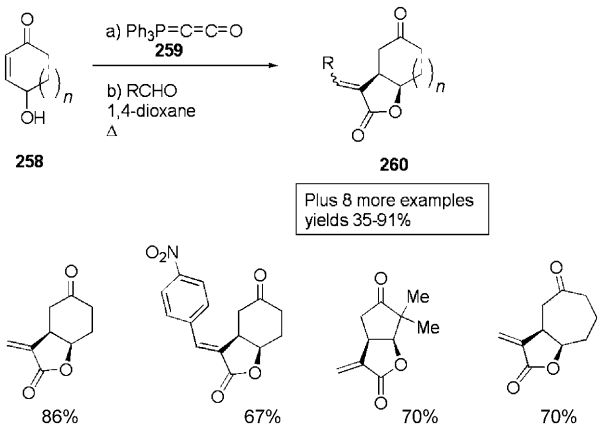
Spongian diterpene **257**
Cytotoxic

total synthesis,[147] but these compounds have recently been shown to possess potent and useful biological activities.[148]

More recently, a new cytotoxic guaianolide **256**[149] and a family of cytoxic spongian diterpenes (e.g. **257**)[150] have been reported. In addition, an improved enzyme-mediated procedure for the preparation of tulipalin A (**44**) has been published.[151]

Recent synthetic publications include a review of radical- and transition-metal-mediated cyclization reactions leading to α-alkylidene-γ-butyrolactones and lactams,[152] and a review of recent synthetic advances in the xanthanolide sesquiterpenoid area.[153] An allyltin/lactonization approach to the enantioselective synthesis of α-methylene-γ-lactones has been published,[154] and racemic cedarmycin has been prepared by using organozinc chemistry.[155] In addition, the telescoped intramolecular Michael anion-exchange olefination (TIMO) sequence for the conversion of γ-hydoxyenones **258** into α-alkylidene-γ-butyrolactones **260** (Scheme 21) has been significantly improved (Scheme 63).[156] This one-pot acylation/conjugate additon/olefination method utilizes the commercially available Bestmann ylide triphenylphosphoranylideneketene (**259**) and proceeds under "base-free" conditions to give good yields of both α-methylene-γ-butyrolactones and α-alkylidene-γ-butyrolactones.

Finally, Heck reactions of parthenolide (**2**) have been employed to prepare novel arylated derivatives,[157] and the core α-alkylidene lactone portion of the C_{25}-meroterpenoid



Scheme 63.

andibenin B has been prepared by an intramolecular Diels–Alder approach.[158]

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