DOI: 10.1002/ejoc.200600570

Synthetic Approaches to α,β-Unsaturated δ-Lactones and Lactols

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Keywords: Lactones / Natural products / Total synthesis

The synthesis of six-membered unsaturated δ-lactones has generated considerable interest, due to their occurrence in a large number of natural products possessing potent biological activities. This microreview attempts to illustrate the different strategies used to obtain such compounds, with a special emphasis on catalytic and asymmetric approaches.

1) Introduction

This microreview covers the literature relating to the construction of α,β-unsaturated δ-lactones in the context of the synthesis of natural products published over the last ten years.[1] The α,β-unsaturated δ-lactone moiety is a ubiquitous motif present in a large number of natural products displaying a broad range of potent biological activities (Scheme 1). Moreover, it has been shown that the unsaturated moiety plays an essential role in the biological activity, due to its potential to act as a Michael acceptor in the presence of protein functional groups.[2]

Accordingly, a number of inventive approaches have appeared in the literature in the last ten years. It is not intended to give an exhaustive account (more classical methods involving an ynoate triple bond reduction/lactonization sequence,[3] (*Z*)-selective olefinations,[4] nucleophile-induced isomerizations of (*E*)-α,β-unsaturated esters,[5] and selective oxidations of 1,5 diols[6–10] are not covered here) but rather to highlight recent advances in the field, particularly catalytic and asymmetric accesses.

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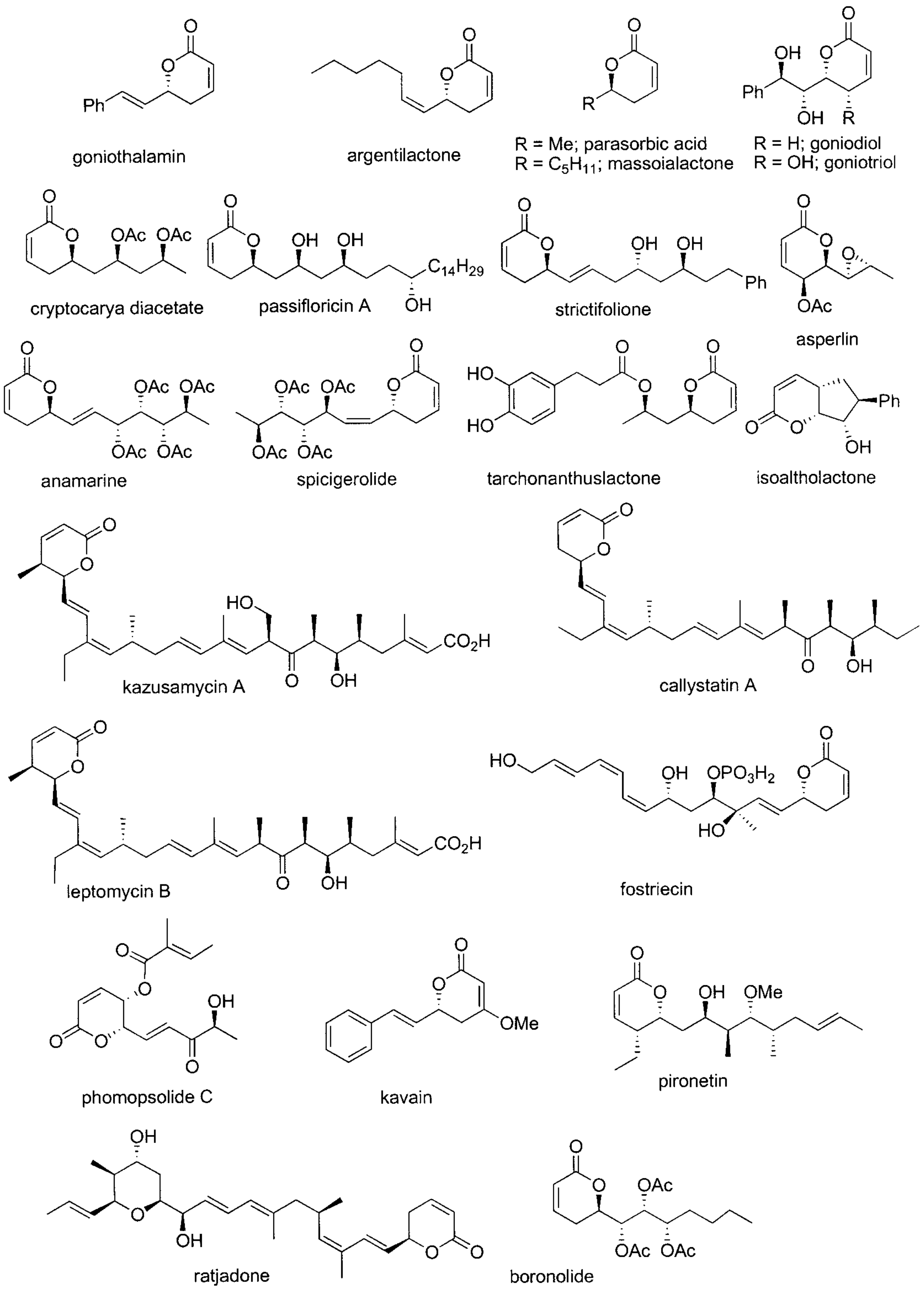
Valérie Boucard was born in Saint-Nazaire, France, in 1975. She received her Ph.D. degree from the Université of Paris-Sud (Orsay) in 2001 under the direction of Dr. F. Guibé. After assistant and teaching positions at the University of Cergy-Pontoise with Prof. J. Augé (2002–2003) and a postdoctoral position at the Technische University of Berlin with Prof. S. Blechert (2004), she joined the group of Dr. Campagne in 2005. Her research interests are on organometallic chemistry applied to synthetic organic chemistry.

Garance Broustal was born in Nantes, France, in 1981. After studies at the Institut Universitaire Professionnalisé of the University of Nantes, she obtained her B.S. degree in Organic Chemistry from the University of Paris-XI-Orsay. She is currently carrying out her Ph.D. in the ICSN-Gif-sur-Yvette, focusing on the methodology and synthetic applications of Catalytic and Asymmetric Vinylogous Mukaiyama Reactions.

Jean-Marc Campagne was born in Pau, France, in 1967. After studies at the Ecole Nationale Supérieure de Chimie de Montpellier, he received his Ph.D. at the University of Montpellier in 1994. After post-doctoral training with Prof B. Trost (Stanford University, USA) and Prof. L. Ghosez (Université Catholique de Louvain, Belgium), he was appointed CNRS researcher at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette in 1998. His current interests concern the development of catalytic asymmetric transformations and their application to the total synthesis of natural products. At the end of 2005 he moved to the Ecole Nationale Supérieure de Chimie de Montpellier.



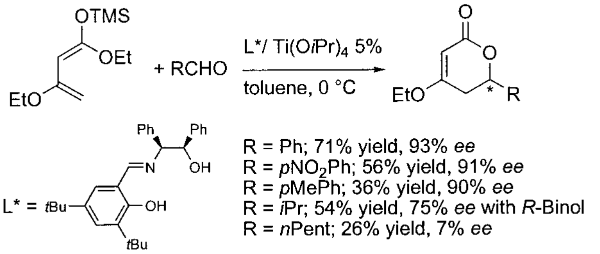
Scheme 1. Selected examples of naturally occurring α,β-unsaturated δ-lactones.

2) From Aldehydes and Ketones

2.1) Hetero-Diels–Alder Reactions

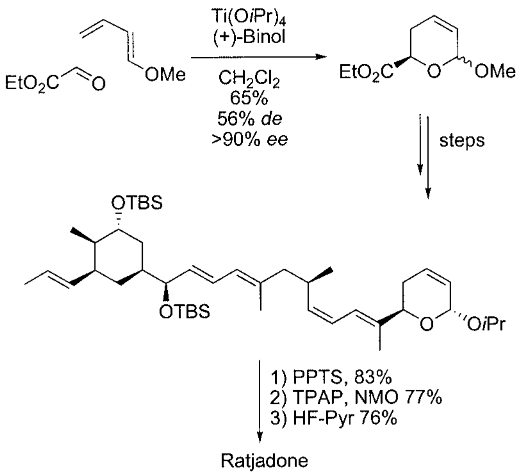
Hetero-Diels–Alder (HDA) reactions in the context of the formation of tetrahydropyran rings have been covered thoroughly in a recent microreview:[11] we will mainly be focusing here on catalytic and asymmetric reactions affording α,β-unsaturated lactones and lactols. Feng has recently described efficient catalytic and asymmetric HDA reactions between Brassard's diene and aldehydes in the presence of titanium-based chiral Lewis acids, affording δ-substituted β-ethoxy-α,β-unsaturated lactones with good yields and enantioselectivities from aromatic aldehydes, whereas lower selectivities were obtained with aliphatic aldehydes

(Scheme 2).[12] According to the authors, the reaction may follow two competitive pathways: at low temperature (–78 °C) the Mukaiyama-aldol pathway is predominant, with a change to an HDA pathway at higher temperature (0 °C).[13]



Scheme 2.

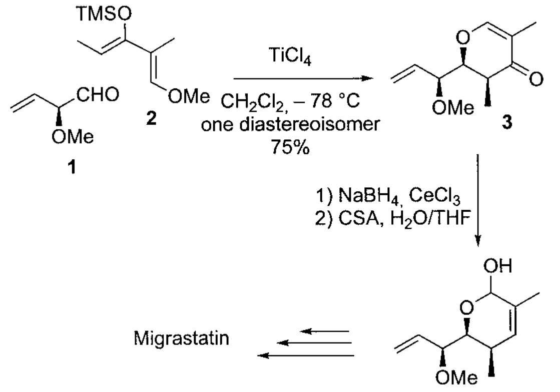
In a total synthesis of ratjadone, Kalesse also used an HDA in the presence of a titanium-based chiral Lewis acid to promote the reaction between 1-methoxybuta-1,3-diene and ethyl glyoxylate to yield the protected lactol as an *endo*/*exo* mixture with good enantioselectivity (Scheme 3).[14] This mixture was then epimerized, through a transacetalization, in favor of the more thermodynamically stable anomer. This protected lactol was maintained over the full synthesis, and was only deprotected and oxidized during the latest steps of the synthesis.[15]



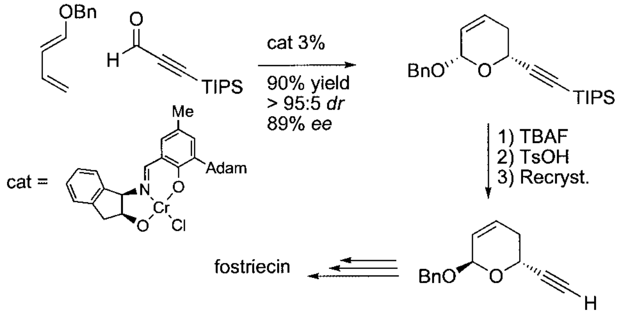
Scheme 3.

Danishefsky has also described a LACDAC (Lewis Acid Catalyzed Diene Aldehyde Cyclocondensation) sequence,[16] starting from the enantiomerically pure aldehyde **1** and the famous Danishefsky's diene **2** to yield the dihydropyrone **3** as a single diastereoisomer.[17] A Luche reduction, followed by an aqueous Ferrier rearrangement, gave the corresponding α,β-unsaturated lactol (Scheme 4).

In the total synthesis of fostriecin,[18] Jacobsen has developed an approach to the C1–C5 lactone core that makes use of a chromium-catalyzed hetero Diels–Alder reaction between benzyloxybutadiene and the TIPS-protected propynal to give high yield and diastereo- and enantioselectivities (Scheme 5).

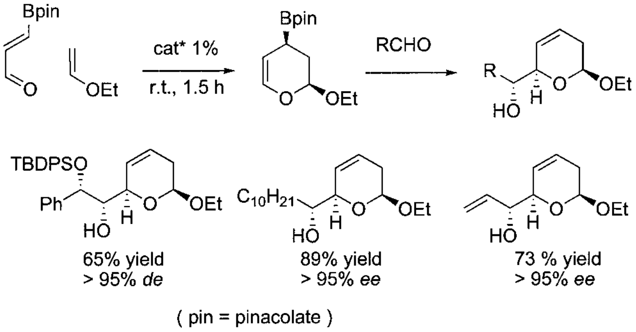


Scheme 4.



Scheme 5.

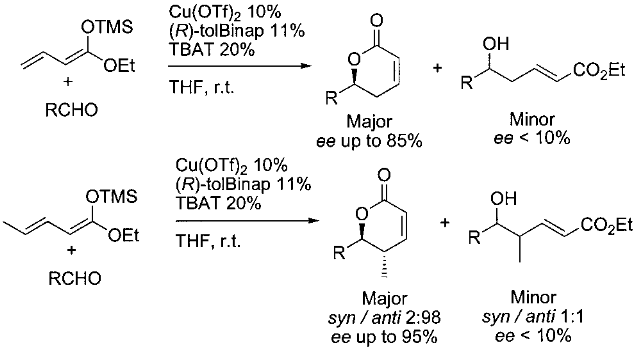
Finally, using the same chromium catalyst, Carreaux and Hall have described an efficient and clever three-component cycloaddition/allylboration sequence to give α-hydroxyalkyl lactols.[19] During this sequence, a first hetero [4+2] cycloaddition with inverse electron demand yields a cyclic allylboronate, which is then able to react with an aldehyde to give the six-membered adducts with good yields and diastereo- and enantioselectivities (Scheme 6). This methodology has been further applied to the total synthesis of a thiomarinol derivative.[20]



Scheme 6.

2.2) *Catalytic and Asymmetric Vinylogous Mukaiyama Reactions*

We have recently described a direct route to α,β-unsaturated δ-lactones through the use of a catalytic and asymmetric vinylogous Mukaiyama[21] reaction in the presence of Carreira's catalyst CuFL*.[22] The α,β-unsaturated δ-lactones were obtained as the major products along with the "regular" linear vinylogous aldol products. Interestingly, the α,β-unsaturated δ-lactones were obtained with moderate to good enantioselectivities whereas the linear product was obtained in nearly racemic form (*ee* < 10%). From starting γ-substituted dienolates, the *anti* lactones were obtained with excellent diastereoselectivities (>98:2 *anti*/*syn*) and good enantioselectivities. This methodology was then used in the synthesis of the Prelog–Djerassi lactone and the three main fragments of discodermolide[22d] (Scheme 7).



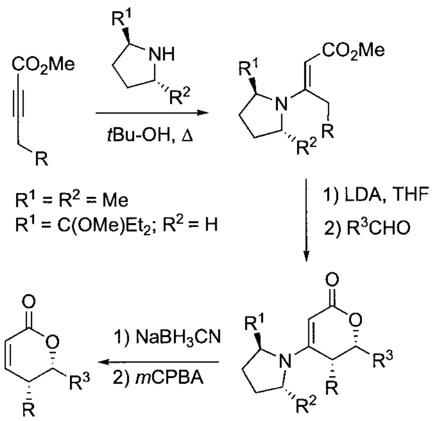
Scheme 7.

This methodology has further been applied to aliphatic methyl ketones, as illustrated in the formal synthesis of taurospongin A[22e] (Scheme 8).

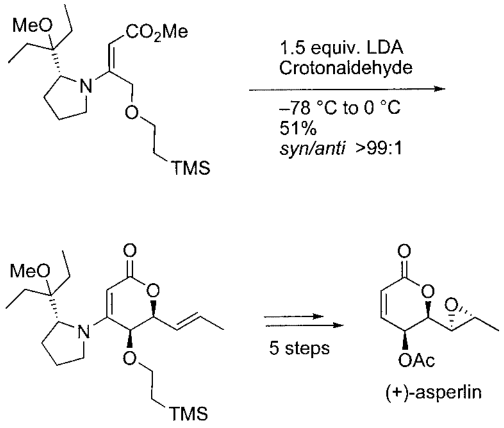
2.3) Aldol Reactions with Vinylogous Urethanes

Aldol reactions from chiral vinylogous urethanes and aldehydes, providing the *syn*-lactones with high diastereoselectivities, have been described by Schlessinger. The chiral auxiliary is then removed in two steps involving a 1,4 reduction followed by a Cope elimination[23–25] (Scheme 9).

The Schlessinger group have described various synthetic applications, including the four main fragments of okadaic acid,[23] (+)-phomolactone, (+)-acetylphomolactone, and (+)-asperlin, as illustrated in Scheme 10.[25]



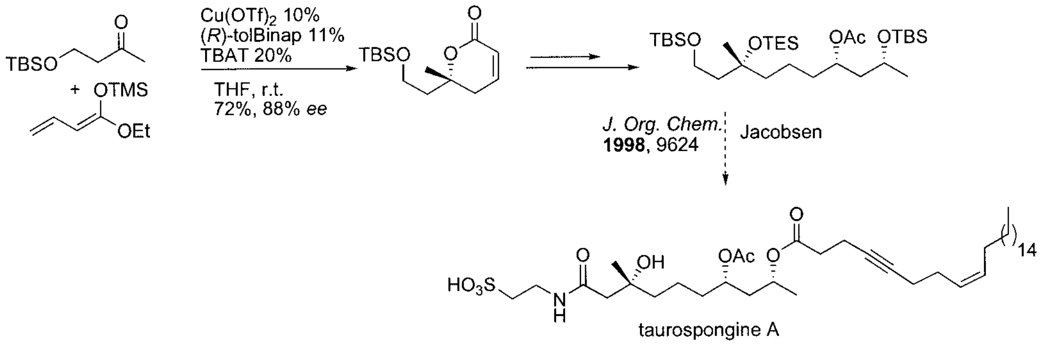
Scheme 9.



Scheme 10.

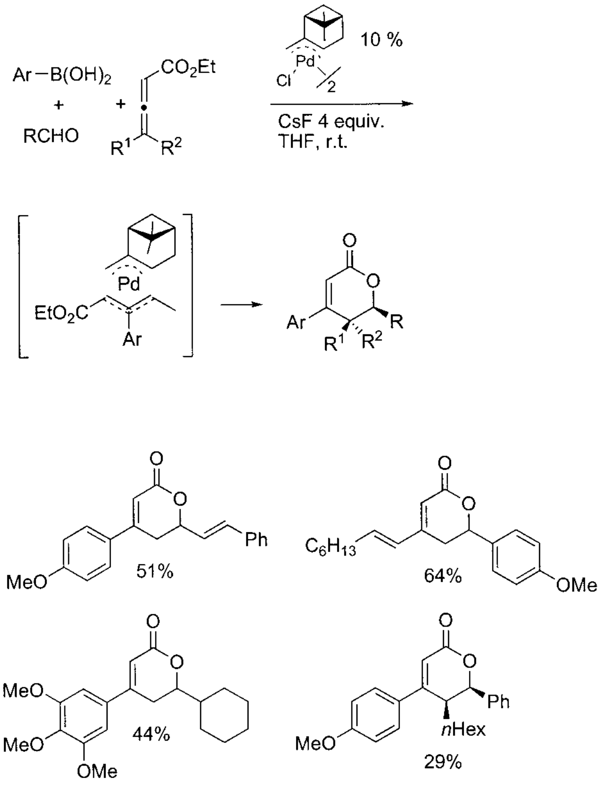
2.4) Palladium-Catalyzed Multicomponent Coupling Reactions

A palladium-catalyzed regioselective bisfunctionalization of allenyl esters with boronic esters and aldehydes has recently been described by Malinakova.[26] The reaction is believed to involve a bis-allylpalladium intermediate, which is finally trapped by the aldehyde. Although rather low



Scheme 8.

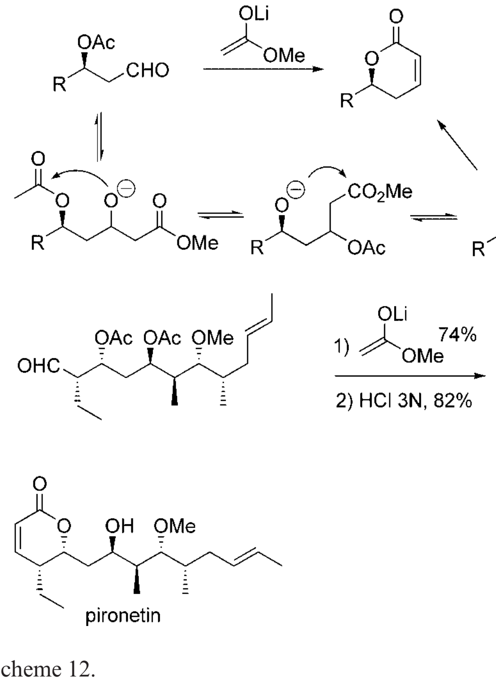
enantioselectivities (<20% *ee*) were obtained, this sequence affords direct access to highly functionalized lactones (Scheme 11).



Scheme 11.

2.5) *Keck's Annulation*

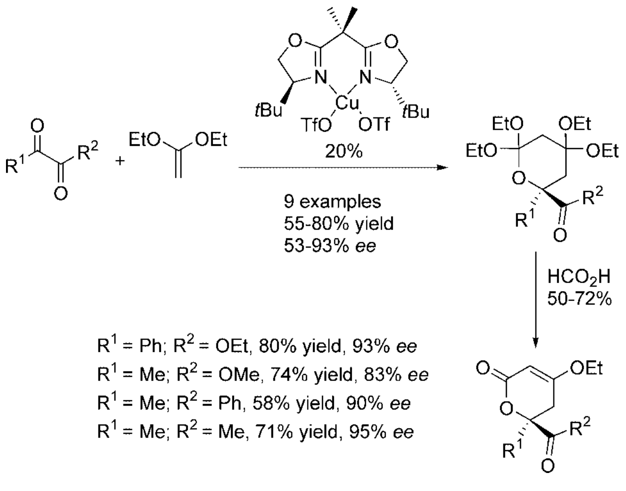
The direct conversion of β-acetoxy aldehydes into the corresponding α,β-unsaturated δ-lactones by treatment of the lithium enolate of methyl acetate with β-acetoxy aldehydes (Scheme 12) has been described by Keck.[27] This multi-step transformation proceeds through an initial aldol reaction, followed by an acyl migration, a lactonization, and finally an irreversible β-elimination to provide the α,β-unsaturated δ-lactone. This methodology has been applied by the same authors to the total synthesis of (–)-pironetin.[28]



Scheme 12.

2.6) *Cyclocondensation of α-Dicarbonyl Compounds with Ketene Diethyl Acetal*

Jorgensen has described copper-bisoxazoline-catalyzed reactions between α-dicarbonyl compounds and ketene diethyl acetal, providing (after hydrolysis) δ-substituted β-ethoxy-α,β-unsaturated lactones with good yields and enantioselectivities[29] (Scheme 13).

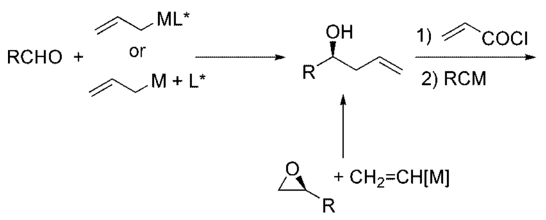


Scheme 13.

3) From Alcohols

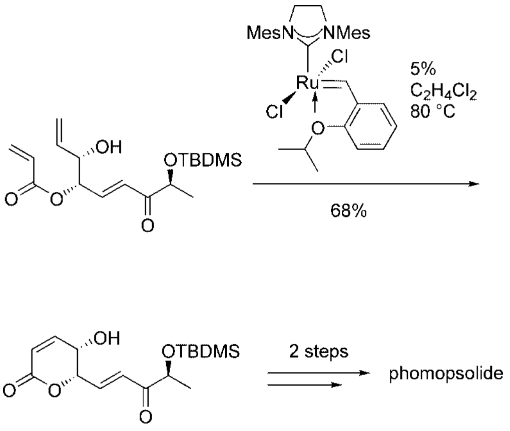
3.1) *RCM, CM, and Tandem RC/CM Strategies from Homoallylic Alcohols (Esters)*

Thanks to the development of highly enantioselective and practical allylation and crotylation procedures, conversions of homoallylic alcohols (through their acrylate esters) into the corresponding lactones have become the most popular approach to obtain such compounds. Because of the quantity of work in this area (more than 60 publications) it has proved impossible to include all contributions made over the last five years, and we apologize to those workers whose contributions to this area are not included. This strategy was first described by Ghosh in the synthesis of peptide isosteres,[30] and was then used in a number of total syntheses including those of argentilactone,[31,32] goniothalamin,[31,33,34] callystatin,[35] boronolide,[36] strictifolione,[37] hexadecanolide,[34] massoia lactone,[34] parasorbic acid,[34] passifloricin A,[38] spicigerolide,[39] anamarine,[40] and fostriecin[41] (Scheme 14).



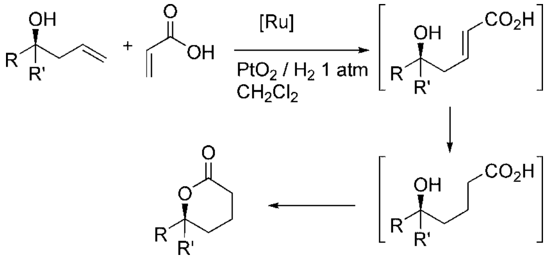
Scheme 14.

A RCM on an homoallylic alcohol protected as an allyl ether, followed by an oxidation, has also been described in the total synthesis of gonotriol.[42] More recently, Blechert has described a ring-size selective (six vs. five) RCM in a total synthesis of (+)-phomopsolide C[43] (Scheme 15).



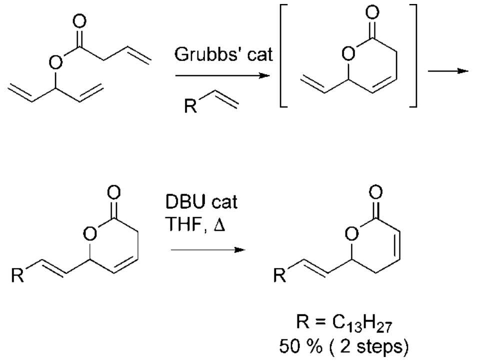
Scheme 15.

Although it is not within the direct scope of this microreview (routes to α,β-unsaturated δ-lactones), it is worth highlighting two domino reactions involving metathesis reactions. In the first one, Cossy described a domino cross-metathesis/hydrogenation/lactonization sequence affording saturated lactones[44] (Scheme 16).



Scheme 16.

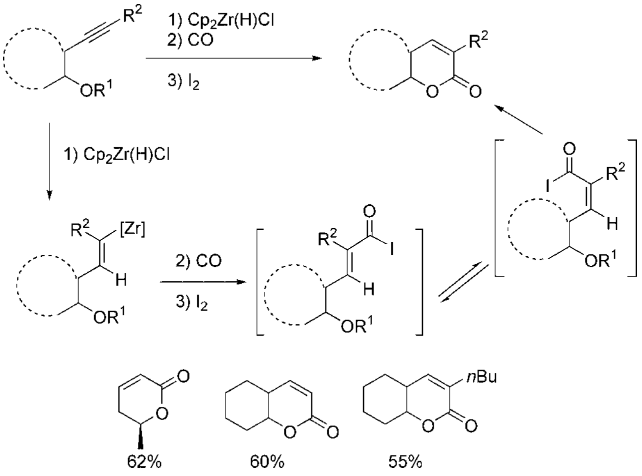
In addition, Piva has described a domino ring-closing/cross metathesis sequence resulting in the stereoselective formation of (*E*)-δ-alkenyl-β,γ-unsaturated δ-lactones. Reconjugation of the internal double bond was finally carried out in the presence of a catalytic amount of DBU[45] (Scheme 17).



Scheme 17.

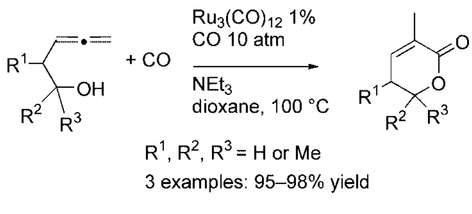
3.2) Cyclocarbonylation of Unsaturated (Allenyl, Homopropargylic, Homoallylic) Alcohols

Alkynes and allenes are also rich sources of starting materials for some efficient routes to α,β-unsaturated lactones. Dupont has described a one-pot hydrozirconation/carbonylation/lactonization sequence starting from homopropargylic alcohols: during the lactonization step, an equilibrium between the (*E*)- and (*Z*)-α,β-unsaturated acyl iodides is involved in the presence of an excess of iodide[46] (Scheme 18).

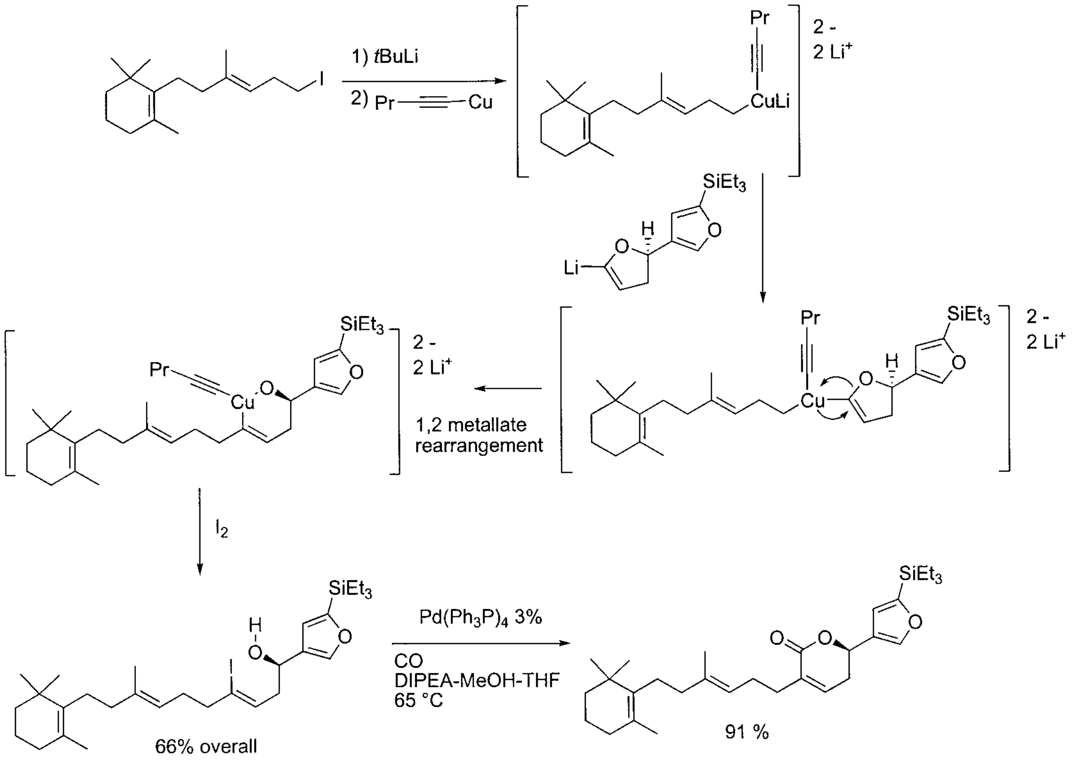


Scheme 18.

Ruthenium-catalyzed cyclocarbonylations of allenyl alcohols to provide five- and six-membered unsaturated lactones have also been described by Takahashi.[47] Although only three examples of six-membered unsaturated lactones have been described by the authors, this method appears to be an interesting alternative to previously discussed meth-



Scheme 19.



Scheme 20.

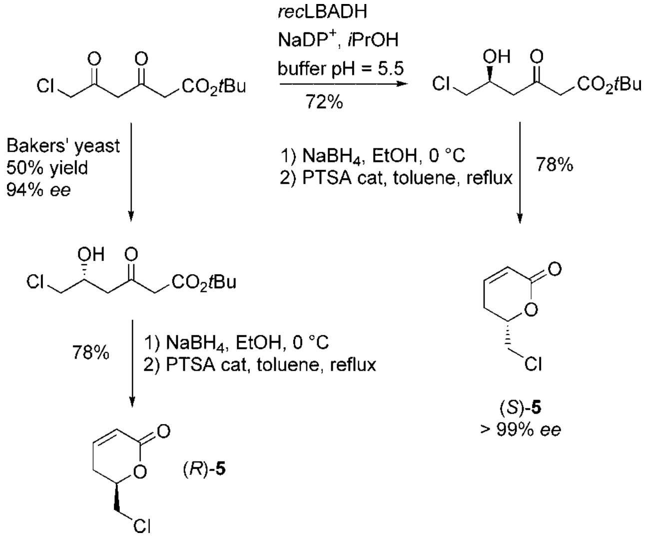
odologies (Scheme 19). Palladium-catalyzed cyclocarbonylations of α-(heteroaryl)allenyl alcohols in the presence of $Pd(OAc)_2$/dppb/CO/H_2 in toluene have also been described[48] .

Kocienski, in the context of the total synthesis of (+)-manoalide, has described a very impressive copper-mediated 1,2-metalate rearrangement to give, after quenching with iodine, a (*Z*)-iodo alkene in 66% yield (Scheme 20). This compound was then transformed into the corresponding lactone by a palladium-catalyzed carbonylation in which the acylpalladium intermediate was intramolecularly trapped by the δ-hydroxy group.[49]

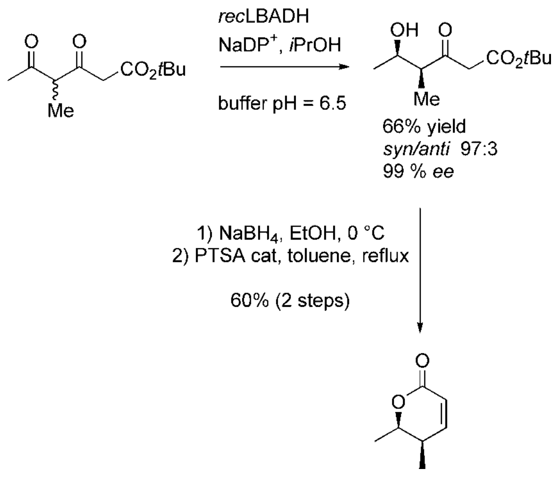
4) From β,δ-Diketo Esters

Enders and Müller have described two efficient and complementary regio- and enantioselective enzymatic reductions of *tert*-butyl 6-chloro-3,5-dioxohexanoate. The (*S*) enantiomer is obtained in 72% yield with an alcohol dehydrogenase [from *Lactobacillus brevis* (recLBADH)], whereas the (*R*) enantiomer was obtained in 90–94% *ee* and 50% yield by bakers' yeast reduction. These enantiomerically pure alcohols are easily transformed into the corresponding lactones **5** by treatment with sodium borohydride followed by acid-catalyzed lactonization[50,51] (Scheme 21).

Lactones (*R*)-**5** and (*S*)-**5** have been used as chiral building blocks in the total syntheses of natural products such as callystatin, tarchonanthuslactone, strictifolione, argentilactone, and goniothalamin.[50] Enantioselective reductions of *tert*-butyl 3,5-dioxohexanoate allowing the total synthesis of *semi*-vioxanthin.[51] have also been described by the same authors. Finally, a dynamic kinetic resolution of a racemic γ-methyl-δ-hydroxy-β-keto ester gave the γ,δ-disubstituted lactone with good enantio- and *syn*-diastereoselectivity (Scheme 22).[52]



Scheme 21.

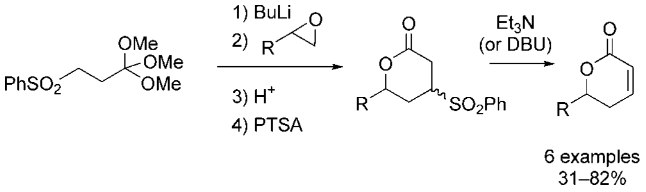


Scheme 22.

5) From Epoxides

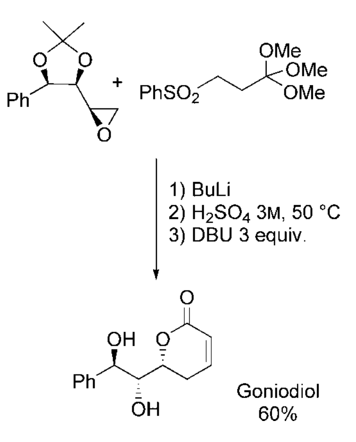
5.1) Ghosez's Lactonization

Ghosez's lactonization is the addition of the lithio derivative of methyl 3-phenylsulfonylorthopropionate to epoxides, giving β-phenylsulfonyl δ-lactones after acidic workup and treatment with PTSA. These compounds are next converted into α,β-unsaturated lactones on basic treatment with DBU or triethylamine[53] (Scheme 23).



Scheme 23.

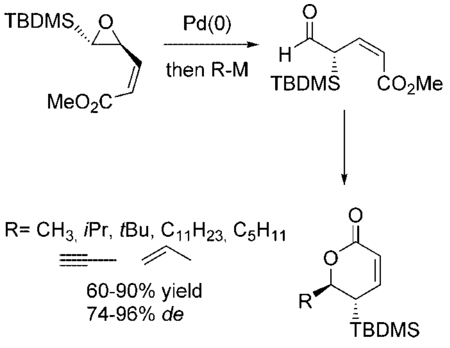
This methodology was used by Ghosez in the synthesis of (–)-argentilactone and was next further illustrated by several groups in the syntheses of (+)-goniodiol (Scheme 23), laulimalide, and callystatin A[54–57] (Scheme 24).



Scheme 24.

5.2) From Silylated Vinyloxiranes

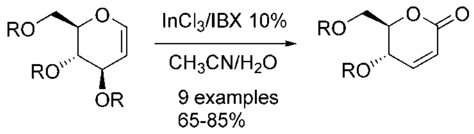
Malacria and Courillon have described one-pot, two-step diastereoselective syntheses of α,β-unsaturated-γ-silylated δ-lactones from silylated vinylepoxides. In the first step, a stereoselective palladium-catalyzed 1,2-silicon shift provides an α-silylated β,γ-unsaturated aldehyde. After completion of the rearrangement (TLC monitoring), alkylation of the aldehyde with a Grignard reagent proceeds with a complete *anti* diastereoselectivity, thus providing (when starting from enantiomerically pure silylated vinylepoxides) enantiomerically pure γ-silylated lactones. The desilylation process (KF/DMSO), however, occurred with partial racemization[58] (Scheme 25).



Scheme 25.

6) From Sugars

As a result of some similarities between sugars and some naturally occurring polyhydroxylated α,β-unsaturated δ-lactones, the use of sugar derivatives as chiral building blocks in the multi-step total syntheses of argentilactone,[59] anamarine,[60] asperlin,[61] and acetylphomalactone[61] has been widely studied. This topic is beyond the scope of this review and so is not covered here. However, Yadav has recently described the mild conversion of several glycals into α,β-unsaturated δ-lactones: a mechanism involving an indium-mediated allylic rearrangement followed by the IBX oxidation of the corresponding lactol is postulated[62] (Scheme 26).

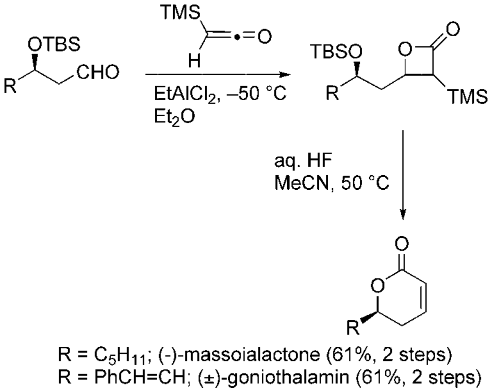


Scheme 26.

7) By Cyclic Expansion

7.1) Translactonizations from β-Lactones

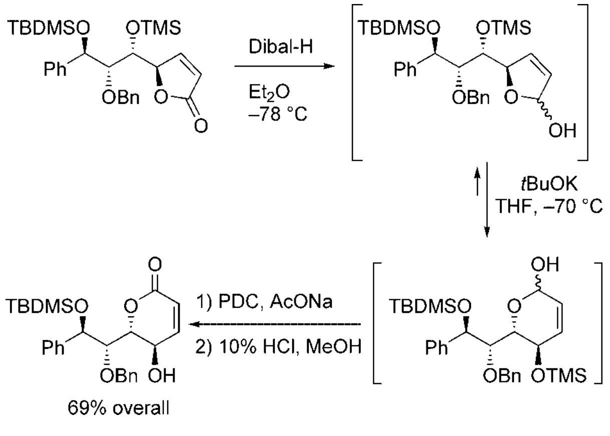
Pons has described a translactonization route to α,β-unsaturated δ-lactones from β-lactones. After [2+2] cycloadditions between β-silyloxy aldehydes and trimethylsilylketenes, the corresponding β-lactones underwent HF-induced translactonization/crotonization sequences to provide the unsaturated δ-lactones in high yields. This methodology has been applied to the syntheses of goniothalamin, massoialactone, and prelactone B[63] (Scheme 27).



Scheme 27.

7.2) Translactolizations from γ-Lactones

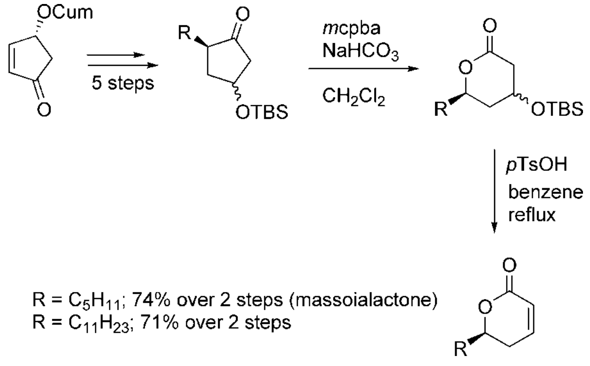
Translactolizations from γ-lactones have also been described by Hanaoka and Mukai.[64] From a starting α,β-unsaturated γ-lactone, dibal-H reduction affords the corresponding γ-lactol, which undergoes a silyl migration followed by a translactolization from the silylated alcohol in the δ-position. The δ-lactol obtained in this sequence is then further oxidized into the δ-lactone as illustrated in the synthesis of goniotriol (Scheme 28).



Scheme 28.

7.3) Baeyer–Villiger Oxidation from Cyclic Ketones

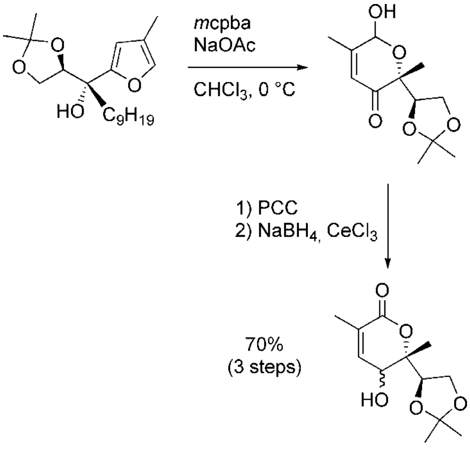
Starting from an enantiomerically pure α-substituted five-membered lactone, Ogasawara has described a regioselective Bayer–Villiger oxidation, followed by an acid-catalyzed crotonization to provide the α,β-unsaturated δ-lactone[65] (Scheme 29).



Scheme 29.

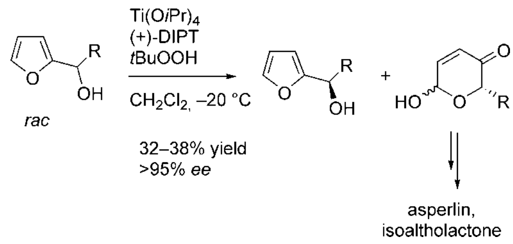
7.4) From Furans

The oxidation of 2-furfuryl alcohols to the corresponding 2*H*-pyran-3(6*H*)-ones is a well known reaction that can be mediated by several oxidants such as peracids, PCC, or NBS.[66] As illustrated in the following Scheme, Honda has described a three-step route to α,β-unsaturated γ-hydroxy lactones from furans.[67] In a first step, the furan is oxidized with *m*cpba to give the corresponding lactol, with the corresponding γ-hydroxy lactone being obtained in high yields after an oxidation/Luche reduction sequence. This strategy was used by Honda in the total syntheses of malyngolide and of several derivatives of goniodiol.[68] A related approach was used by O'Doherty in the syntheses of several styryllactones and phomopsolide C[69] (Scheme 30).



Scheme 30.

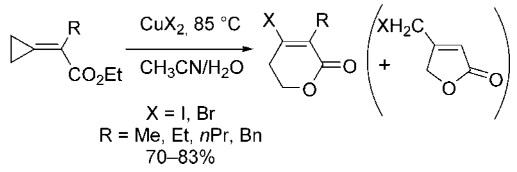
An interesting alternative based on a Sharpless kinetic resolution of racemic furyl alcohol has been described by Honda and Sato[70] and was further used by Pan and Zhou in the syntheses of isoaltholactone and asperlin, respectively[71] (Scheme 31).



Scheme 31.

7.5) From Methylenecyclopropanes

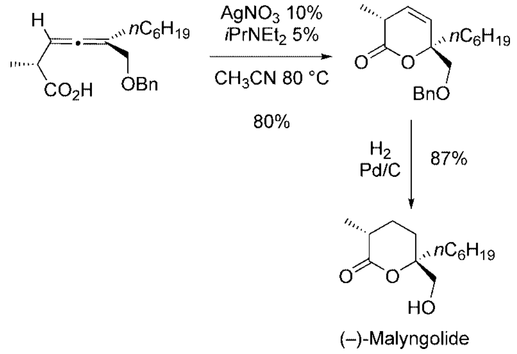
Copper-catalyzed ring expansions of methylenecyclopropanes have been described by Huang.[72] The selectivity (five- vs. six-membered lactones) depends on the reaction temperature: at higher temperatures, six-membered lactones become preponderant (Scheme 32).



Scheme 32.

8) Cyclization of Allenic Acids

In the synthesis of (–)-malyngolide, Nelson[73] described the Ag^I-catalyzed 6-*endo*-*trig* cyclization of an enantiomerically pure allenic acid to afford the β,γ-unsaturated lactone in high yield (Scheme 33).



Scheme 33.

9) Conclusion

The common occurrence of α,β-unsaturated δ-lactones in natural products with potent biological activities has been a major force behind the development of synthetic strategies to obtain these compounds. This review demonstrates the rapid progress that has been made in this field, particularly in diastereo- and enantioselective direct access to these lactones. Nevertheless, the development of more practical, concise, and general routes remains a key challenge for the future.

Acknowledgments

We wish to thank the Institut de Chimie des Substances Naturelles (ICSN) and the Centre National de la Recherche Scientifique (CNRS) for financial support and fellowships.

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Received: July 4, 2006