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Chemistry of 4-Hydroxy-2-cyclopentenone Derivatives

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The 4-hydroxy-2-cyclopentenone moiety is a highly valued molecular scaffold; it is bestowed with a wide-ranging chemical reactivity profile which synthetic chemists have exploited increasingly over the last few decades. This review summarises the methods available for the preparation of simple building blocks which contain this core, then illustrates the diversity of chemical transformations which can be conducted with them, by highlighting applications in multistep syntheses of complex target molecules.

1. Introduction – Scope of This Review

The prevalence of five-membered carbocycles in natural products and other bioactive compounds has provided a major stimulus for the development of synthetic methods which facilitate their construction. The emergence of new strategies has provided ever-increasing opportunities for selective and efficient access to multiply functionalized derivatives of the cyclopentane core.[1] Historically, the chemistry of 4-hydroxy-2-cyclopentenones **1** (see Figures 1, 2, 3, and 4) was developed and shaped by progress in the synthesis of prostaglandins, notably in the early 1980s, but over the years this core fragment has become a subunit of primary importance in a wide array of natural product syntheses. Indeed, a variety of natural product structures incorporate this moiety directly: examples include prostanoids (halogenopunaglandins or clavulones and derivatives),[2] indenones,[3] alkaloids (daphnipaxianines A–B, actumine and hypserpanine A families),[4] terpenes (ligulolide A, fusicoauritone, hymenolin, parthenin sesquiterpenes, ...)[5,6] and numerous others[7] (**2**–**17**; Figure 1). The title compound itself (**1**, $R^1 = R^2 = H$; Figure 1) has been identified as an anti-*Pseudomonas* and cytotoxic component in the leaves of *Passiflora tetrandra*.[8] In addition, the high functional group density displayed over the five-carbon cyclic skeleton of **1** bestows upon it a particular utility as an intermediate for the synthesis of other complex natural product structures.

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David J. Aitken was born in 1963 and studied Chemistry at the University of Strathclyde, Scotland, obtaining his BSc in 1983 then his PhD in 1986, the latter under the supervision of Profs. H. C. S. Wood and C. J. Suckling. Following a move to France for a 2-year NATO-Royal Society post-doctoral Fellowship with Prof. H.-P. Husson, he was appointed as a CNRS researcher in URA 1310 at the Faculty of Pharmacy at Paris-5 University. In 1998 he became professor of organic chemistry at the Blaise Pascal University in Clermont-Ferrand, and in 2006 he transferred to his current position as professor at the University of Paris-11 in Orsay, where he is also Deputy Director of the ICMMO research centre. His research interests include the stereoselective synthesis of small ring compounds, particularly those bearing reactive functions, unnatural amino acids and peptides which contain them, and synthetic organic photochemistry.

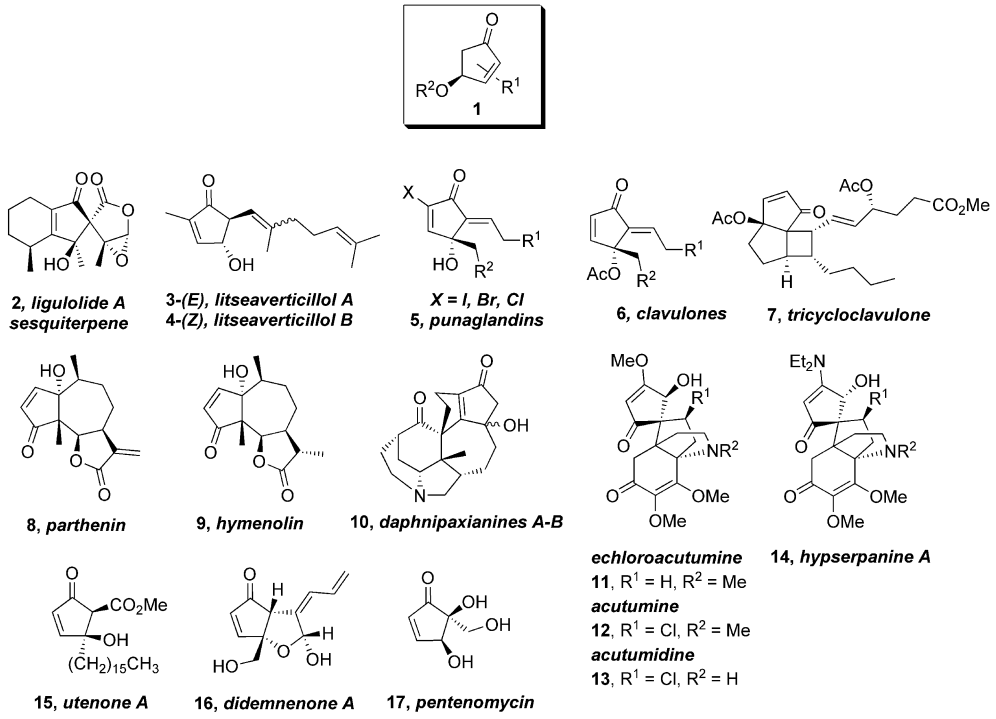


Figure 1. A representative panel of natural products **2**–**17** containing the 4-hydroxy-2-cyclopentenone fragment (**1**).

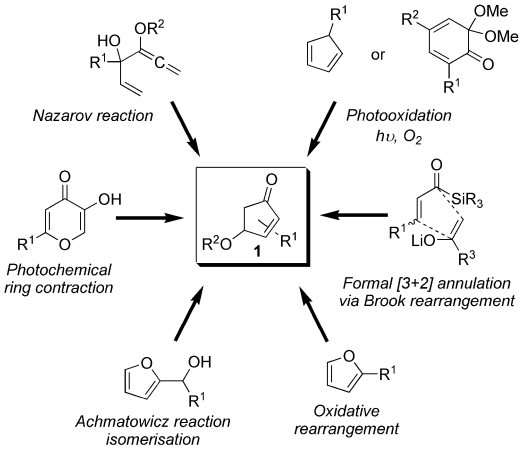


Figure 2. Racemic syntheses of 4-hydroxy-2-cyclopentenones.

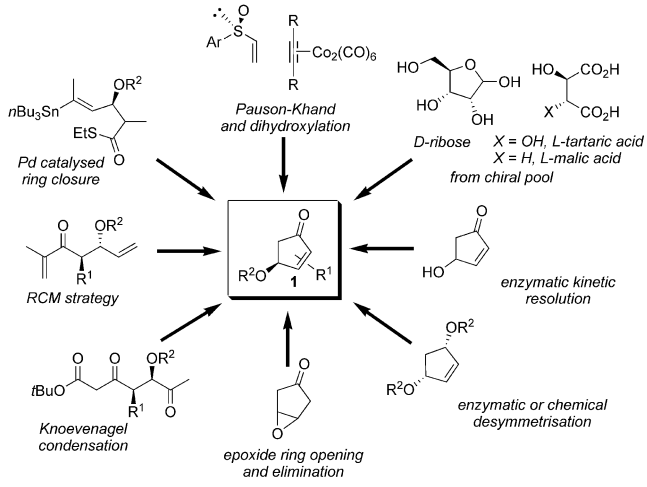


Figure 3. Enantioselective syntheses of 4-hydroxy-2-cyclopentenones.

To the best of our knowledge, no available literature review has focussed specifically on the title compound family. The present appraisal is based on published work appearing up to the end of 2009, with preference being given to recent developments and achievements, although longer-established work will be discussed when considered appropriate. In the space available, it is not possible to provide an exhaustive compilation of the many syntheses and applications of the title compound family. The objective of this review is to highlight particular strategies which have been shown to accommodate further functionality on the 4-hydroxy-2-cyclopentenone core, as illustrated by elegant multi-step syntheses of complex molecular targets. At the same time, priority has been given to strategies which have a general character, or at least appear to be amenable to a range of derivatives.

The first part of this review will outline the synthetic strategies which are most usefully employed in the preparation of the 4-hydroxy-2-cyclopentenone core **1**. Firstly, some racemic preparations will be presented (Figure 2); although not developed in chiral mode, these procedures have provided valuable access to derivatives of synthetic use. Thereafter, a diversity of enantioselective approaches will be presented; these include ring closing of appropriate non-

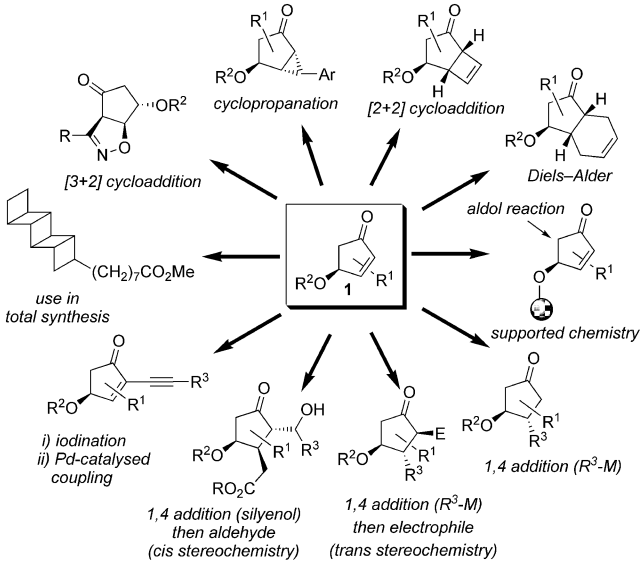


Figure 4. The 4-hydroxy-2-cyclopentenone scaffold as a versatile platform for chemical diversity.

racemic precursors, syntheses from the chiral pool, and the use of enzymatic or chemical desymmetrisation of *meso*-cyclopentanoids (Figure 3).

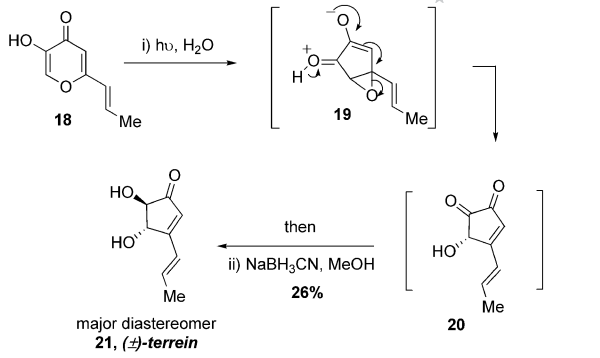
The second part of this review will examine the use of 4-hydroxy-2-cyclopentenones **1** in multi-step syntheses of complex organic molecules. The diversity of chemical transformations offered by this core feature is illustrated by successive analysis of the synthetic tactics for side-chain elaboration at each of the five ring-carbon centres. Widely used procedures include palladium catalysed coupling reactions, 1,2- or 1,4-nucleophilic additions; and one-pot procedures which exploit both carbons of the C2–C3 double bond, such as cycloadditions and three-component couplings. An overview is depicted in Figure 4.

2. Preparation of 4-Hydroxy-2-cyclopentenones

2.1. Racemic Preparation of 4-Hydroxy-2-cyclopentenones

2.1.a. Photochemical Rearrangement of 3-Hydroxy-4-pyranones

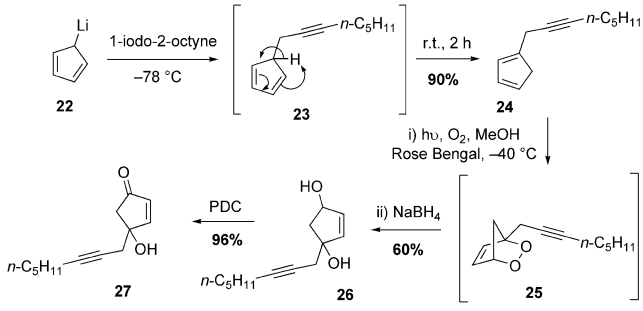
In early work, Barton et al. described a one-step synthesis of the racemic mould metabolite (±)-terrein **21** via the photochemical rearrangement of a 3-hydroxy-4-pyrone (Scheme 1).[9] Upon irradiation in water, the kojic acid derivative **18** underwent a ring contraction to afford the zwitterionic cyclopentenone-epoxide species **19** which opened spontaneously to afford the cyclopentenedione **20**. This intermediate was reduced in situ using cyanoborohydride to afford a mixture of diastereomers within which the major component was (±)-terrein **21**, obtained in 26% overall yield.



Scheme 1.

2.1.b. Photooxygenation of Cyclopentadiene

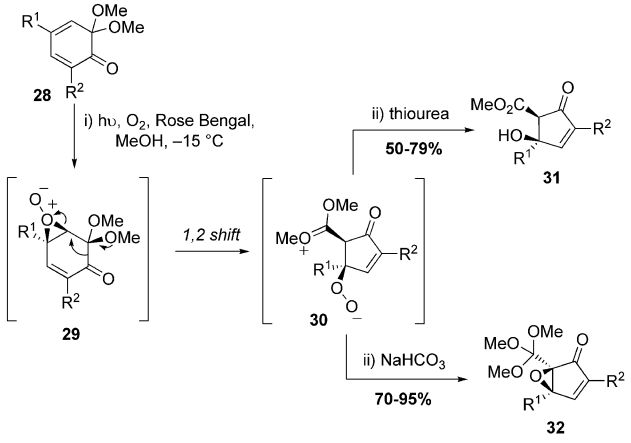
A strategy based on the photooxygenation of cyclopentadienes was developed successfully by Corey et al. (Scheme 2).[10] Low-temperature alkylation of the cyclopentadienyl anion **22** with 1-iodo-2-octyne gave the derivative **23**, which underwent a 1,5-prototropic shift at room temperature to deliver the more stable regioisomer **24** in 90% yield. The [4+2] cycloaddition reaction of this substituted cyclopentadiene with photochemically generated singlet oxygen gave endoperoxide **25** which was reduced using sodium borohydride to provide the cyclopentene-1,3-diol **26** in 60% yield. Chemoselective oxidation with pyridinium dichromate (PDC) afforded the target 4-hydroxy-2-cyclopentenone **27** in 96% yield.



Scheme 2.

2.1.c. Photooxidative Rearrangement of Masked o-Benzoquinones

Liao et al. recently reported another photooxidative strategy in the preparation 2,4,5-trisubstituted 4-hydroxy-2-cyclopentenones **31**, by exploiting a skeletal rearrangement of masked *ortho*-benzoquinones (MOBs) **28** (Scheme 3).[11] Indeed, photooxidation of these compounds **28** in methanol presumably gave first the epoxy-peroxide **29**, which rearranged via a [1,2]-acyl shift to afford the ring-contracted peroxide intermediate **30**. This latter was either reduced in situ with thiourea to give the substituted 4-hydroxy-2-cyclopentenone **31** or cyclised under basic conditions ($NaHCO_3$) to 4,5-epoxy-2-cyclopentenones **32** in good yields.

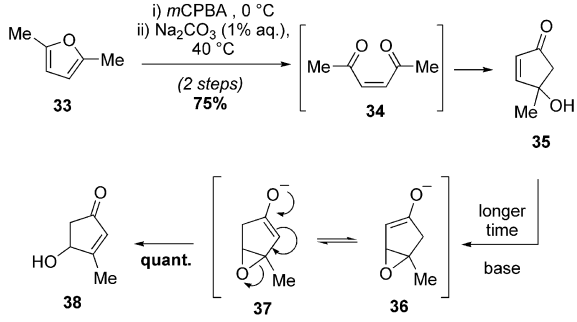


Scheme 3.

2.1.d. Oxidative Transformations of Furans

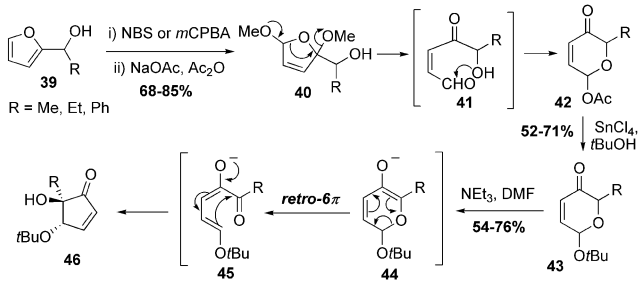
Furan derivatives are common starting materials for the construction of 4-hydroxy-2-cyclopentenone frameworks. Indeed, one convenient large-scale preparation of 4-hydroxy-2-cyclopentenone itself is the acid-catalysed rearrangement of furfuryl alcohol.[12]

Each of the two isomeric 4-hydroxy-2-cyclopentenones **35** and **38** were obtained from 2,5-dimethylfuran **33** (Scheme 4).[13] Treatment of this starting material with *m*CPBA at 0 °C produced dienone **34**, which underwent an intramolecular aldol reaction when treated with base to give the 4-hydroxy-4-methyl-2-cyclopentenone **35** in 75% yield. Prolonged basic treatment induced rearrangement via an oxy-Michael addition to epoxide **36**, equilibration to **37** and then retro-elimination, leading quantitatively to the thermodynamically more stable structural isomer 4-hydroxy-3-methyl-2-cyclopentenone **38**.[14]



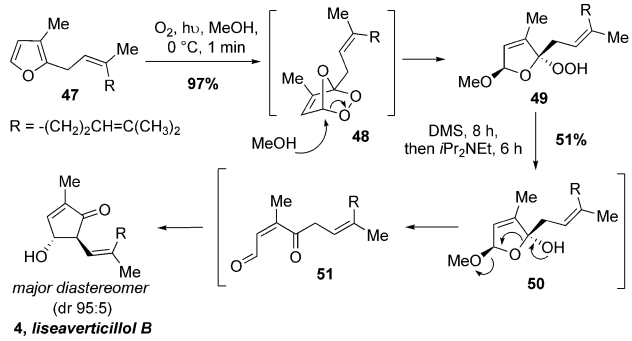
Scheme 4.

An alternative furan-based approach has been described by Hoffmann et al.[15] This first step of this sequence involves an Achmatowicz reaction[16] which allows the oxidative rearrangement of furfuryl alcohols **39** into pyranones **42** (Scheme 5). The second step is a pyranone isomerisation to furnish the 5,5-disubstituted 4-alkoxy-2-cyclopentenone **46**.[17] Caddick et al. improved this sequence as follows: under oxidative conditions (*m*CPBA or NBS) followed by basic conditions (sodium acetate in acetic anhydride), furfuryl alcohols **39** were converted via the dihydrofuran **40** and the ring opened intermediate **41** into the target pyranones **42** in good yield.[18] Transacetalisation provided the corresponding *tert*-butyl derivatives **43**, which proved to be the substrates of choice for the subsequent skeletal rearrangement, in which the enolate **44** underwent retro-6π-electrocyclisation to give **45** followed by vinylogous aldolisation to deliver the 5,5-disubstituted 4-*tert*-butoxy-2-cyclopentenones **46**. This single-step transformation from **43** proved to be highly diastereoselective, presumably due to the bulkiness of the *tert*-butyl group.[18]



Scheme 5.

Another photooxidative approach, based on the photochemical [4+2] cycloaddition of furan with photochemically generated singlet oxygen, has been developed recently by Vassilikogiannakis et al. and is a key step in the elegant total syntheses of several members of the litseaverticillol family of natural products.[19,20] As an example, photooxygenation of the 2-alkyl-3-methylfuran **47** yielded the endoperoxide **48**, which underwent methanolysis to furnish the hydroperoxide **49** in 97% yield (Scheme 6). In a one-pot reaction sequence, compound **49** was reduced with dimethyl sulfide to give ketal **50** which ring opened to give **51**; intramolecular aldol reaction of the latter in the basic medium furnished the target litseaverticillol B, **4**, in 51% yield and 95:5 *dr*.[20]

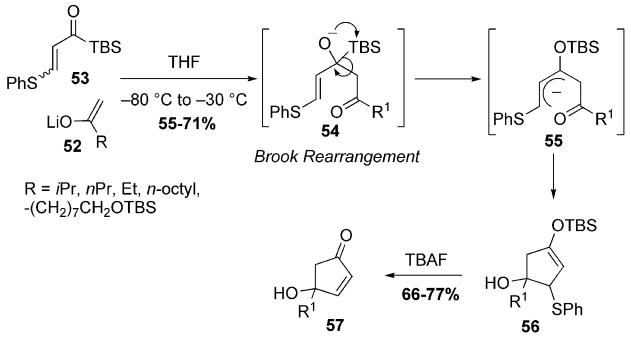


Scheme 6.

2.1.e. Tandem Aldol–Brook Rearrangement Cyclisation

A novel approach for the racemic assembly of a 4-hydroxy-2-cyclopentenone core consists of a tandem aldol–Brook rearrangement annulation (Scheme 7).[21] A range of enolates **52** were employed in aldol reactions with β-(phenylthio)acryloylsilane **53** to furnish alkoxide intermediates **54**, which spontaneously underwent Brook rearrangement

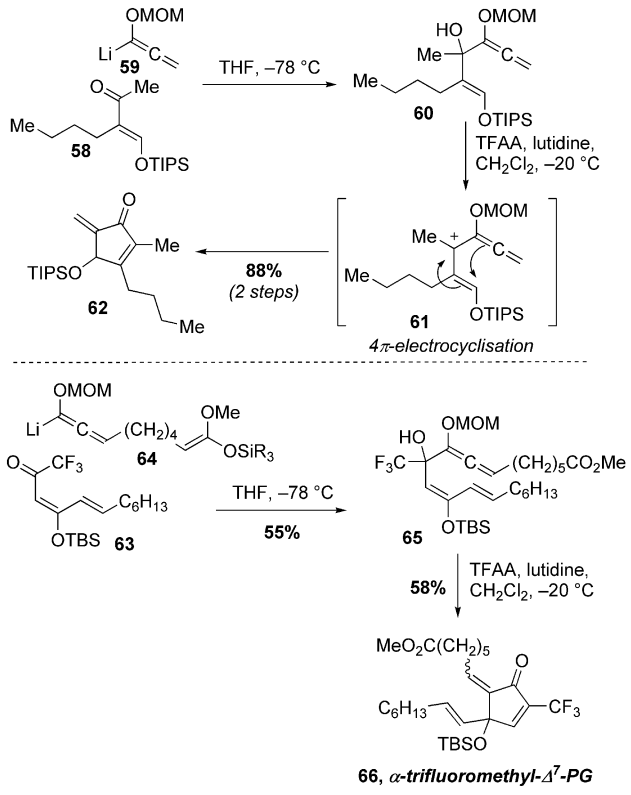
generating delocalised allyl carbanions **55**. Further annulation with the neighbouring carbonyl group afforded the corresponding cyclopentenols **56** in 55–71% yield in a single operation. The second step involved desilylation of the TBS enol ether then β-elimination of the phenylthioether leaving group to install the endocyclic unsaturation, to afford the desired 4-substituted 4-hydroxy-2-cyclopentenones **57** (66–77% yield). This original manoeuvre allowed the preparation of a range of 4-hydroxy-2-cyclopentenones in a simple two step procedure that has potential for further development in an enantioselective mode.



Scheme 7.

2.1.f. Allene Nazarov Reactions

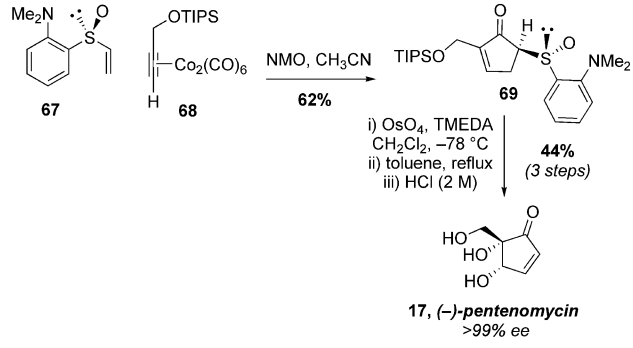
Tius et al. have developed a direct access to polysubstituted 5-methylene-4-hydroxy-2-cyclopentenone frameworks via the 4π-electrocyclisation of heptatrienyl cations (Scheme 8).[22,23] The α-hydroxy-allene **60** was prepared by alkylation of ketone **58** with 1-lithio-1-(methoxymethoxy)-allene **59**. Compound **60** was then subjected to a mild Nazarov cyclisation in the presence of TFAA and 2,6-lutidine to generate the allylic carbocation **61**, which evolved via a 4π-electrocyclisation to provide the desired 3-alkyl-4-silyloxy-5-methylene-2-cyclopentenone **62**, an intermediate for the total synthesis of madindolines A and B, in 88% yield for two steps.[22] Similarly, compound **65** was obtained by alkylation of the trifluoromethyl ketone **63** with the lithiated allene **64**. The Nazarov transformation of **65** provided the α-trifluoromethyl–Δ^7–PG analogue **66** in 58% yield.[23] While this approach is complex, it provides highly functionalised derivatives of **1** in an efficient two-step sequence, providing the acyclic substrates are available.



Scheme 8.

2.2. Enantioselective Construction of the 4-Hydroxy-2-cyclopentenone Core from Acyclic Substrates

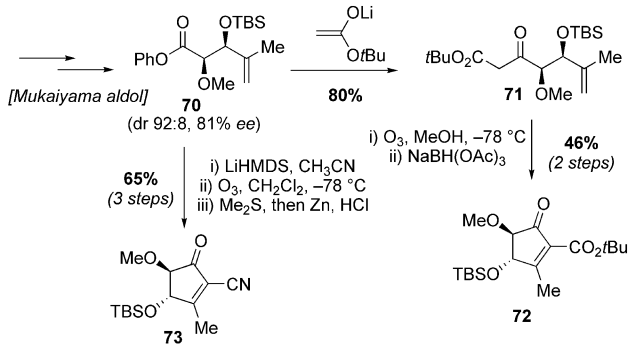
The Pauson–Khand reaction (PKR) is recognised as a powerful tool for cyclopentanoid synthesis.[24] Nonetheless, the first example of an intermolecular, asymmetric $Co_2(CO)_8$-mediated PKR was reported only recently: the non-racemic vinyl sulfoxide **67** and the alkyne complex **68** reacted to provide the 2,5-disubstituted cyclopentenone **69** in 62% yield (Scheme 9).[25] The chiral sulfoxide moiety facilitated excellent chiral induction during the PKR and also provided diastereocontrol during the subsequent dihydroxylation of **69** with osmium tetraoxide to yield, after heating and acidic treatment, the hydroxylated natural product (–)-pentenomycin **17** in enantiomerically pure form and in 44% yield for the three steps.



Scheme 9.

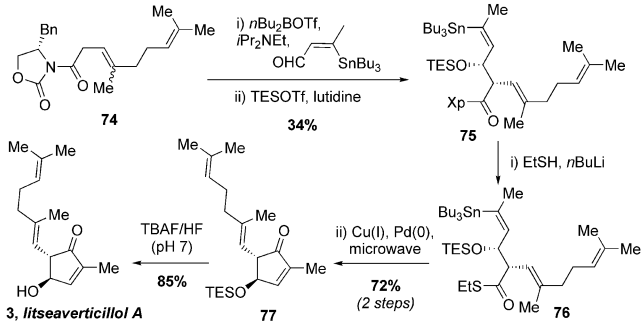
In the course of a viridenomycin total synthesis, the 4-hydroxy-2-cyclopentenones **72** and **73** were identified as valuable intermediates (Scheme 10).[26] Both these compounds were prepared from the Mukaiyama aldol adduct **70** (available in 92:8 *dr* and 81% *ee*). Claisen reaction of this compound with lithium *tert*-butyl acetate furnished the β-keto ester **71** in good yield. The key step was a one-pot tandem ozonolysis–Knoevenagel cyclisation, to give the substituted 4-silyloxy-2-cyclopentenone **72** in 37% yield. A similar sequence commencing with the reaction of **70** with acetonitrile lithium carbanion gave the nitrile derivative **73**

in 65% overall yield. The enantiomeric purity of the product cyclopentenones **72** and **73** was not explicitly reported, however.



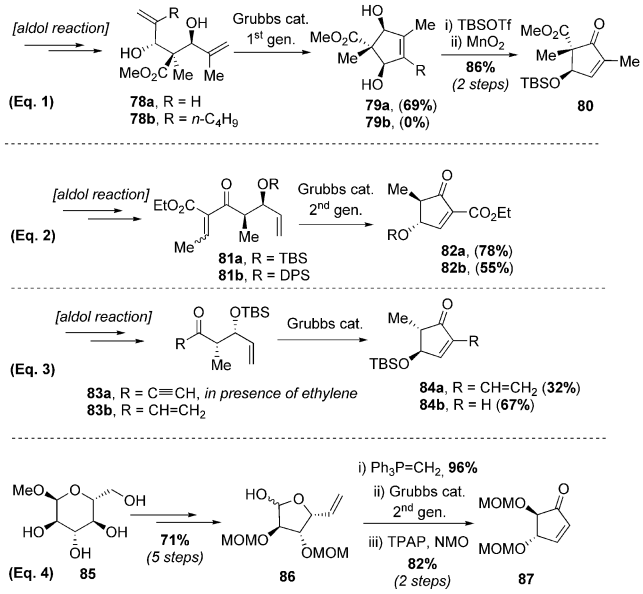
Scheme 10.

The methodology proposed by Liebeskind et al.[27] for the synthesis of ketones via aryl-, alkenyl-, or allyl-stannane coupling with thioesters was applied in an intramolecular fashion by Kuwahara et al. in the preparation of the natural product litseaverticillol A, **3** (Scheme 11).[28] Chiral oxazolidinone **74** underwent an aldol reaction to install two important stereocentres, then silyl ether formation gave the protected *syn*-aldol product **75** in 34% yield. Formation of the thioester **76** was accomplished in moderate yield by displacement of the chiral auxiliary. The intramolecular coupling of **76** was optimized in terms of the palladium(0) and copper(I) sources, to furnish the desired 5-alkenyl-4-silyloxy-2-cyclopentenone **77**, which was finally deprotected to afford the enantiopure litseaverticillol A (**3**) in good yield.



Scheme 11.

In the field of natural products synthesis, ring closing metathesis (RCM) has emerged as a useful approach for the construction of the 4-hydroxy-2-cyclopentenone framework (Scheme 12, Eq. 1–4). Ōmura et al. were first to report on a RCM study on dienes **78a**,**b** using the first generation Grubbs catalyst. Exposure of diene **78a** to ruthenium catalysis afforded the free diol substrate **79a** in 69%, which was silylated regioselectively on the less hindered position and oxidised to deliver the desired tetra-substituted 2-cyclopentenone **80** in 86% yield.[29] The formation of the more substituted cyclopentene **79b** turned out to be impossible, however, despite an investigation of different catalytic systems (Scheme 12, Eq. 1). More recently, Prunet et al. have used this powerful strategy to synthesise diversely substituted 4-hydroxy-2-cyclopentenone derivatives **82a**,**b** and **84a**,**b**, from aldol products **81a**,**b** and **83a**,**b** respectively (Scheme 12, Eq. 2–3).[30] The chiral pool (see also section 2.3.c) has proved to be a good source of precursors for the chiral dienes used in RCM.[31] For example, the D-glucose derivative **85** was transformed in five steps to ketal **86**, which could then be opened using a Wittig reagent to deliver an appropriate diene for RCM, which after oxidation of the secondary alcohol generated the 4,5-dihydroxylated 2-cyclopentenone **87** in 79% yield over three steps (Scheme 12, Eq. 4).[31a]

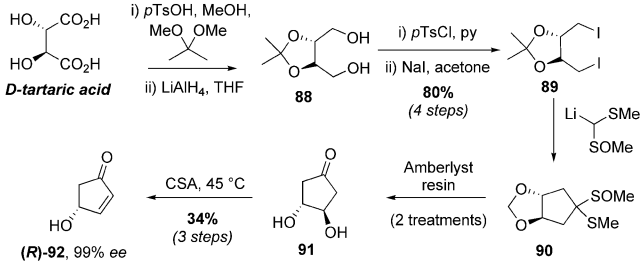


Scheme 12.

2.3. Enantioselective Synthesis of 4-Hydroxy-2-cyclopentenone from the Chiral Pool

2.3.a. Synthesis from Tartaric Acid

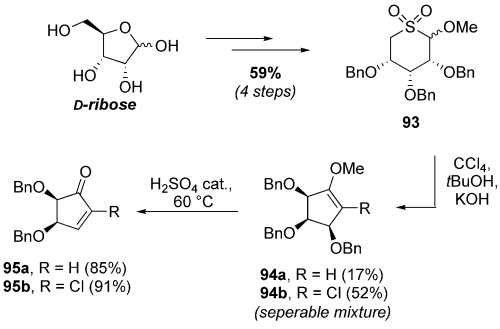
Inspired by the seminal work of Ogura,[32] Rokach et al. validated a seven-step sequence for the preparation of (*R*)-4-hydroxy-2-cyclopentenone (*R*)-**92** in seven steps and 27% overall yield from D-tartaric acid (Scheme 13).[33] D-Tartaric acid was converted in four steps to the alkyl di-iodide derivative **89**, which was alkylated and cyclised in a one-pot procedure upon exposure to methyl methylthiomethyl sulfoxide carbanion, to furnish the cyclopentanoid **90** as a mixture of diastereomers. Two successive treatments of **90** with Amberlyst resin at room temperature permitted the stepwise cleavage of the ketal and the thioketal without epimerisation, to give the chiral C_2-symmetrical diol **91**. Dehydration using camphorsulfonic acid afforded the enantiopure (*R*)-4-hydroxy-2-cyclopentenone (*R*)-**92**.



Scheme 13.

2.3.b. Synthesis from Ribose

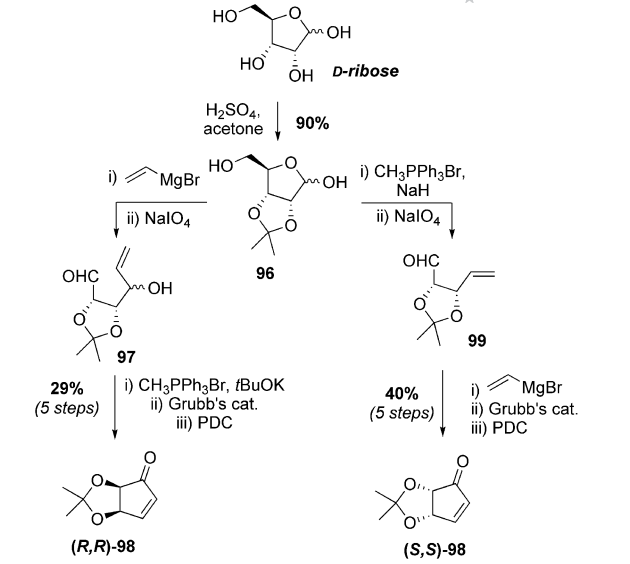
Taylor et al. reported an original construction of (4*R*,5*R*)-dibenzyloxy-2-cyclopentenones **95a**,**b** from the thiosugar sulfone **93**, which was prepared in four steps and 59% yield from D-ribose (Scheme 14).[34] A Ramberg–Bäcklund rearrangement was performed on sulfone **93** under Meyers' conditions[35] to obtain a mixture of two separable cyclopentenoids **94a** and **94b** in a 1:3 ratio and 69% yield. Treatment of each of these enol ethers **94a** and **94b** in acidic conditions completed the preparation of enantiopure 4,5-dibenzyloxy-2-cyclopentenones **95a** and **95b** in 85% and 91% yield, respectively.



Scheme 14.

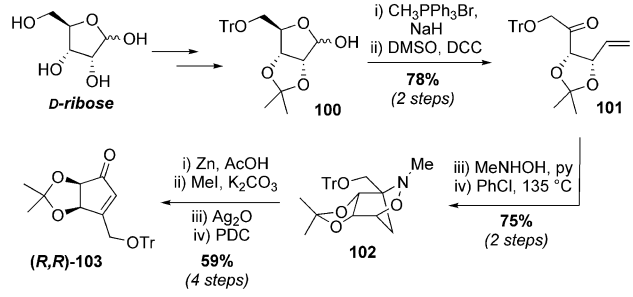
A second approach to the protected 4,5-dihydroxy-2-cyclopentenone core starting from D-ribose was reported by Jeong et al. and involved more conventional sugar chemistry (Scheme 15).[36] The two enantiomers (4*R*,5*R*)- and (4*S*,5*S*)-4,5-dihydroxyacetonide-2-cyclopentenone **98** were prepared in a six-step sequence from D-ribose in 26% and 36% overall yield respectively. The two sequences differ only in the order of the vinyl Grignard addition and Wittig reaction steps applied to acetonide **96**, implying either **97** or **99** as the intermediate. In each case, these two steps were followed by RCM and final oxidation as a manoeuvre for the late stage installation of the carbonyl moiety, to provide both the (*R*,*R*) and (*S*,*S*) stereoisomers of **98**.

A more lengthy approach was required for the synthesis of the 3,4,5-trisubstituted derivative **103** reported recently by Gallos et al. (Scheme 16).[37] The D-ribose derivative **100** was set up conveniently via keto-alkene **101** for an intramolecular [3+2] cycloaddition with a nitrone, which provided access to cycloadduct **102**. Reductive cleavage of the N–O bond of derivative **102** with zinc was followed by polyalkylation of the 4-amino-1-cyclopentanol with methyl iodide,



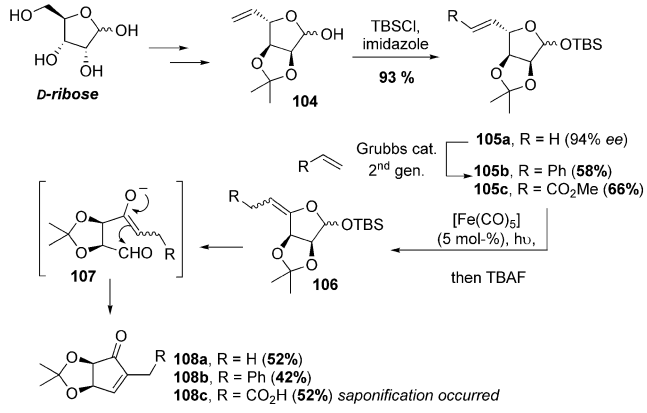
Scheme 15.

to generate a good leaving group, which eliminated upon treatment with silver oxide. The final allylic alcohol oxidation step was achieved using PDC to afford the target 4,5-acetonide of (*R*,*R*)-4,5-dihydroxy-3-trityloxymethyl-2-cyclopentenone (**103**) in eight steps and 35% overall yield from **100**.



Scheme 16.

The latest synthesis from D-ribose was published recently by Grée et al., exploiting their in-house methodology for catalytic allylic alcohol isomerisation (Scheme 17).[38] The readily available sugar derivative **104** was protected at the anomeric position by silylation, giving compound **105a** in 93% yield. Two other substrates **105b** and **105c** were prepared therefrom by cross metathesis reactions with styrene and methyl acrylate in 58% and 66% yield respectively. For each of these sugar substrates **105a**–**c**, the allylic ether moiety was efficiently isomerised upon photocatalysis, inducing the sugar opening and further intramolecular aldol reaction. In this cascade of events, the isomerised open forms **107a**–**c** spontaneously recyclised through carbon-carbon bond formation to furnish, after elimination, the desired (4*R*,5*R*)-dihydroxyacetonide-2-cyclopentenones **108a**–**c** in 42–52% yield in a single operation. It is noteworthy that the authors also demonstrated the efficiency of their catalytic cascade with a fast access to the Corey lactone aldehyde, a useful intermediate in the synthesis of prostaglandins.



Scheme 17.

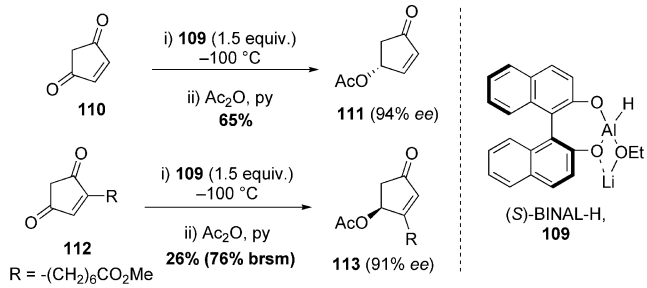
2.3.c. Synthesis from Other Natural Products

A few other starting materials from the chiral pool have been used for the construction of the 4-hydroxy-2-cyclopentenone core, using approaches similar to those described above. D-malic acid,[39] L-arabinose,[40] and D-xylose[34] have all been used. One fruitful synthetic strategy has been to use sugar derivatives, including D-glucose, D-arabinose, and D-isoascorbic acid, as chiral starting materials for the preparation of appropriate precursors for the RCM methodology presented above (see section 2.2).[31]

2.4. Desymmetrisation and Deracemisation Approaches

2.4.a. Direct Enantioselective Reduction of 1,3-Diketones

In the early 1980s, organic chemists began to focus considerable attention on enantioselective reactions, and a pioneering contribution was made by Noyori et al. using a chiral hydride reducing agent, (*S*)-BINAL-H **109**, derived from C_2-symmetrical (*S*)-BINOL. Reagent **109** mediates efficient and enantioselective reduction of a large structural range of ketones (Scheme 18).[41] 1,3-cyclopentenedione **110** was reduced with **109** stereoselectively and, following acetylation, 4-acetoxy-2-cyclopentenone **111** was obtained in 65% yield and 94% *ee*. The analogous reduction of the substituted derivative **112** was more sluggish, giving (after acetylation) **113** in only 26% yield and 91% *ee*. It is noteworthy that these two reductions gave opposite stereochemical outcomes, although no explanation for this observation

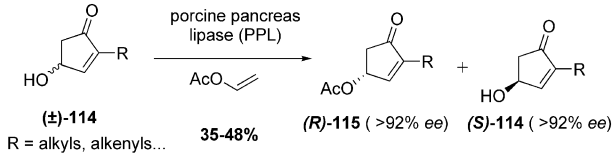


Scheme 18.

was ventured. The reduction of **112** was also highly regioselective, a fact which was tentatively ascribed to the electron-donating properties of the substituent.

2.4.b. Enzymatic Kinetic Resolution via Acylation

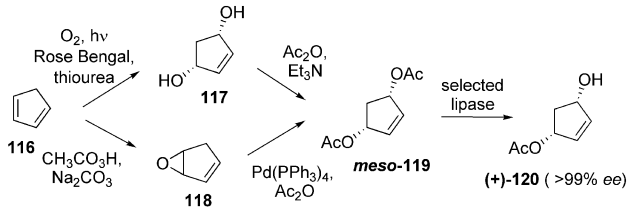
Among the various approaches for obtaining enantiomerically pure compounds, kinetic resolution is not often a first choice, due to the theoretical yield upper limit of 50%. Nevertheless, this strategy has been used to deracemise a panel of (±)-2-substituted 4-hydroxy-2-cyclopentenones **114** via an irreversible lipase-catalysed acylation reaction (Scheme 19).[42] Porcine pancreas lipase exhibited a high selectivity for the transformation of alcohols with the *R*-configuration. Thus both the unreacted alcohols (*S*)-**114** (35–48% yield) and the acetylated products (*R*)-**115** (35–46% yield) were isolated in highly enantiomerically enriched form, with the *ee* falling within the range 92–99%.



Scheme 19.

2.4.c. Desymmetrisation of meso-Cyclopentenoids

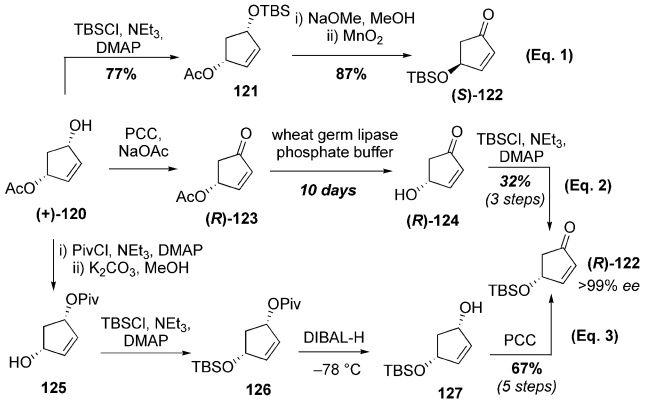
In contrast with the above approach, desymmetrisation of *meso*-cyclopentenoids has been one of the most useful strategies for the preparation of enantiopure 4-hydroxy-2-cyclopentenones. A key feature of this strategy is the facile access to appropriate precursors. Cyclopentadiene **116** can be easily converted into *meso*-1,4-diacetoxy-2-cyclopentene **119** either via the diol **117**, obtained in a tandem photooxygenation/reduction protocol, or via 3,4-epoxycyclopentene **118**, subjected to palladium(0)-catalysed allylic displacement (Scheme 20).[43] The enantioselectivity of the enzymatic desymmetrisation of *meso*-diacetate **119** depends on the lipase used, and either enantiomer of monoacetate **120** can be prepared after the selective deacetylation;[44] several commonly employed procedures afford (+)-**120** in high chemical yield and with a very high *ee*.[43,45]



Scheme 20.

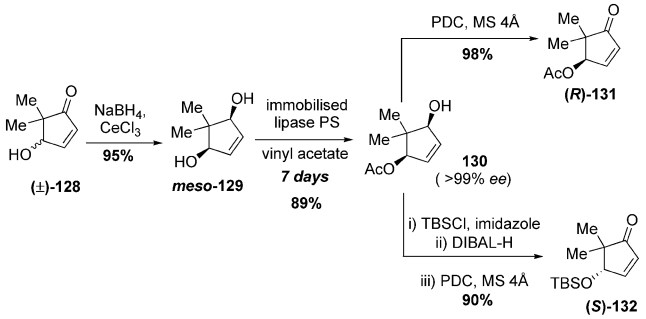
Having a straightforward and scalable access to enantiomerically pure (+)-**120**, several research groups have used this compound to prepare both enantiomers of 4-*tert*-butyldimethylsilyoxy-2-cyclopentenone **122** (Scheme 21). Paquette et al. reported the synthesis of both (*S*)-**122** and (*R*)-**122** in 67% and 32% overall yield respectively, through elegant selective manipulation of the two oxygenated func-

tions.[46] Selective deprotection of the orthogonally functionalised cyclopentene diol **121** then oxidation provided the (*S*)-isomer (Scheme 21, Eq. 1). Application of these two operations in the inverse order to (+)-**120** furnished (*R*)-**123**, which was hydrolysed somewhat tediously to the alcohol (*R*)-**124**, then silylated to deliver the enantiopure (*R*)-**122** in 32% overall yield (Scheme 21, Eq. 2). At the same time, Myers et al.[47] reported a different and more robust route, via the desymmetrised protected diol intermediates **125**, **126** and **127**, to access (*R*)-**122** in 67% yield with *ee* >99% (Scheme 21, Eq. 3). Although a more lengthy procedure, this latter approach avoids the slow enzymatic step required in Paquette's procedure.



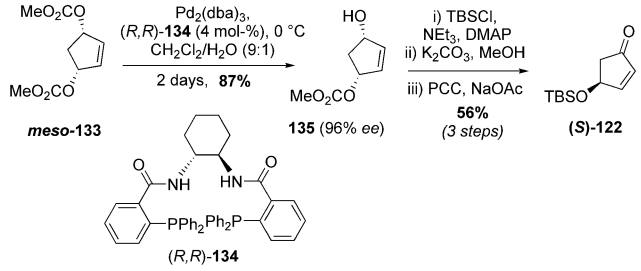
Scheme 21.

Enzymatic desymmetrisation lends itself to the enantioselective preparation of a few ring-substituted 4-hydroxy-2-cyclopentenone derivatives. Racemic 5,5-dimethyl-4-hydroxy-2-cyclopentenone **128** was reduced diastereoselectively to obtain *meso*-1,4-dihydroxy-5,5-dimethyl-2-cyclopentene **129** (Scheme 22). Desymmetrisation of this diol was effected by enantioselective acylation using immobilised lipase PS, and afforded (after 7 days) the corresponding mono-acetate derivative **130** in 89% yield with >99% *ee*. This allowed access to protected derivatives of each enantiomer of the core structure: acetate (*R*)-**131** and silyl ether (*S*)-**132**.[48]



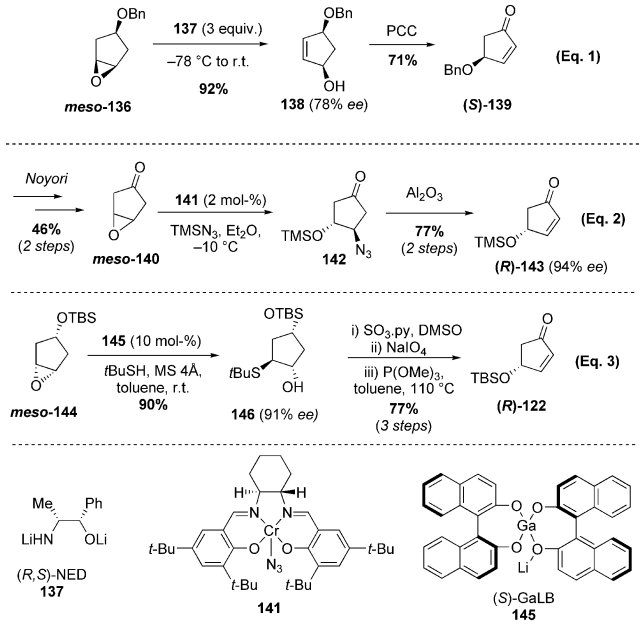
Scheme 22.

A non-enzymatic desymmetrisation approach has been reported by Gais et al. (Scheme 23).[49] *meso*-Biscarbonate **133** was subjected to an allylic displacement reaction with water, catalysed by a palladium(0) complex of the Trost ligand (*R*,*R*)-**134**, to afford the monocarbonate **135** in 87% yield and 96% *ee*. Further transformations provided an efficient access to enantiopure 4-*tert*-butyldimethylsilyoxy-2-cyclopentenone (*S*)-**122**.



Scheme 23.

Several groups have investigated the desymmetrisation of cyclopentanoid *meso* epoxides followed by β-elimination of a leaving group, which constitutes a very rapid access to 4-hydroxy-2-cyclopentenones (Scheme 24). Following up on earlier work by Asami,[50] Murphy et al.[51] described the enantioselective opening of *cis*-epoxide **136** using an excess of the dilithiated species derived from (1*S*,2*R*)-norephedrine, (*R*,*S*)-NED, **137**, to obtain 1-benzyloxy-4-hydroxy-2-cyclopentene **138** in 92% yield and 78% *ee*. Subsequent oxidation of **138** with PCC gave (*S*)-4-benzyloxy-2-cyclopentenone (*S*)-**139** in 71% yield (Scheme 24, Eq. 1). Catalytic and enantioselective *meso* epoxide ring opening using metal-based catalysts has also been described. Jacobsen et al.[52] reported the asymmetric ring opening of the epoxide **140** using a catalytic amount of (*S*,*S*-salen)CrN_3 **141** and trimethylsilyl azide, to afford the *trans* adduct **142**. Azide elimination was achieved in mild conditions using alumina, to furnish the desired (*R*)-4-trimethylsilyloxy-2-cyclopentenone (*R*)-**143** in 77% overall yield and 94% *ee* (Scheme 24, Eq. 2). An alternative was described by Shiba-



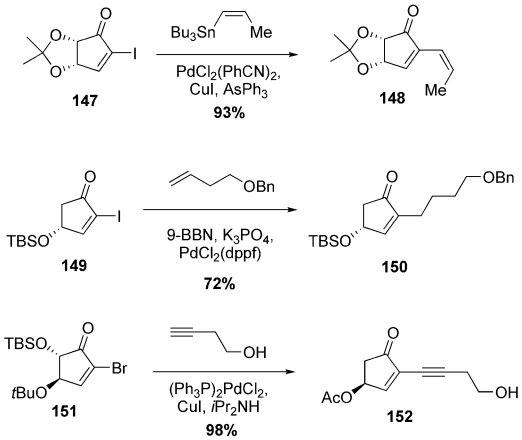
Scheme 24.

saki et al.,[53] in which the enantioselective opening of the *cis*-epoxide **144** was conducted using a catalytic amount of (*S*)-GaLB, **145**, and *tert*-butylthiol, giving cyclopentanoid **146** in 90% yield and 91% *ee* (Scheme 24, Eq. 3). In this case, the catalyst has a double function: it plays the role of a Lewis acid at the gallium centre, chelating the epoxide and promoting ring opening, and acts as a Brønsted base at the lithium binaphthoxide moiety, which deprotonates the *tert*-butyl thiol and directs the addition of the thiolate to the epoxide. The product thioether **146** was subjected to oxidation to furnish an α-sulfinyl ketone, which underwent pyrrolytic β-elimination yielding the desired enantio-enriched (*R*)-**122** in 77% yield over three steps.

3. Transformation of 4-Hydroxy-2-cyclopentenone Derivatives

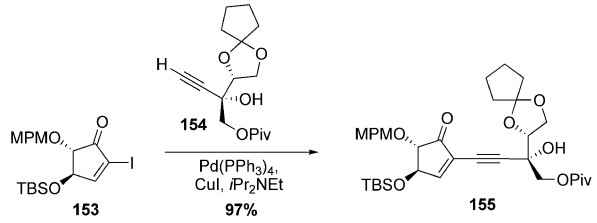
3.1. Elaboration at the C2 Position

Almost all the work described in the literature which concerns the introduction of carbon chains at the C2 position of the 4-hydroxy-2-cyclopentenone core has relied on palladium catalysed coupling methodologies, which in turn requires prior halogenation at this position. This latter transformation is most conveniently achieved using Br_2 or I_2 in an addition/elimination protocol.[54] Suzuki, Stille and Sonogashira couplings on 2-iodo derivatives allow the introduction of a wide range of vinyl, aryl, alkenyl and alkyl C2 side chains, usually in good yield.[55] Sonogashira coupling has also been described with 2-bromo derivatives.[18f] Representative and selected examples are the efficient transformations of **147**, **149** and **151** into **148**, **150** and **152**, respectively (Scheme 25).



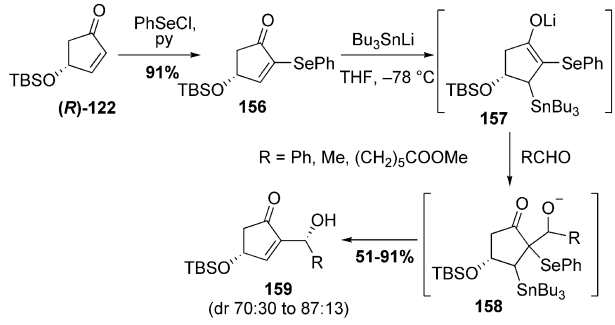
Scheme 25.

Kobayashi et al. successfully employed a Sonogashira reaction in the total synthesis of the neocazinostatin chromophore (Scheme 26).[56] The highly functionalised alkyne **154** (serving as the precursor of the enediyne moiety of the final target) was coupled with the cyclopentenone iodide derivative **153** to provide the advanced intermediate **155** in 97% yield.



Scheme 26.

There is very little literature on C2 development using other strategies. Toru et al.[57] described the phenylselenation of (*R*)-**122** to furnish derivative **156** (Scheme 27). Conjugate addition of tributylstannyllithium gave a lithium enolate **157** which reacted with aldehydes to give intermediates **158** which underwent spontaneous elimination to provide compounds **159** as diastereomeric mixtures. The product structures here are formally Baylis–Hillman adducts, but access thereto from a 4-hydroxy-2-cyclopentenone derivative via a Baylis–Hillman reaction *per se* has not yet been described.



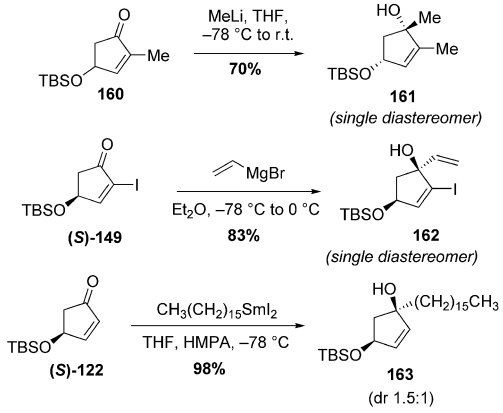
Scheme 27.

3.2. Nucleophilic Addition of Organometallic Reagents

3.2.a. 1,2 Additions

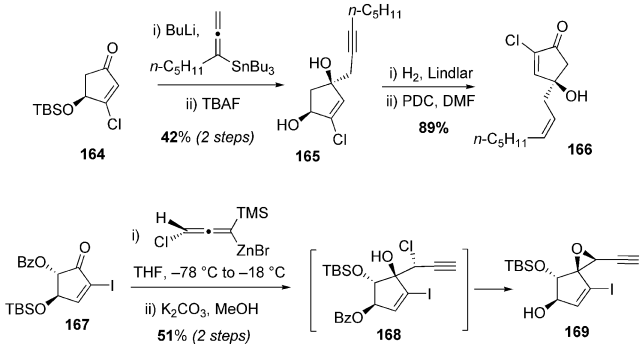
There are various reports of 1,2-additions of organometallic reagents onto the carbonyl function of protected 4-hydroxy-2-cyclopentenenones; for example, the operation has been carried out successfully using organolithium reagents (**160** to **161**),[58] Grignard reagents (**149** to **162**),[59] and alkyl samarium reagents (**122** to **163**)[60] (Scheme 28). The non-symmetrical (cyclopent-2-ene-1,3-diol)-derived products are usually obtained in good yields, often with good diastereoselectivity in favour of the *syn*-1,3-cyclopentendiol.

Noyori et al. achieved the 1,2-addition of a propargylic side chain to the carbonyl group of compound **164** using an allenyl tin reagent with the aid of butyllithium; subsequent silyl ether deprotection gave diol **165** (Scheme 29).[61] Hydrogenation over a Lindlar catalyst then oxidation with PDC gave a new 4-hydroxy-2-cyclopentenone **166**, in which the oxygen functions at C1 and C4 have been formally inversed with regard to the starting material **164**. In a recent



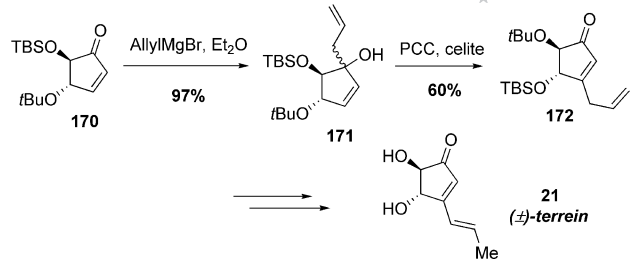
Scheme 28.

total synthesis of the aglycon of the kedarcidin chromophore, Hirama et al.[62] reported the addition of an allenylzinc reagent (derived from the corresponding TMS-propargyl chloride) to substrate **167** to furnish the propargylic *syn* adduct **168**, which was directly cyclised under basic conditions to the highly functionalised epoxide **169** in 51% overall yield (Scheme 29).



Scheme 29.

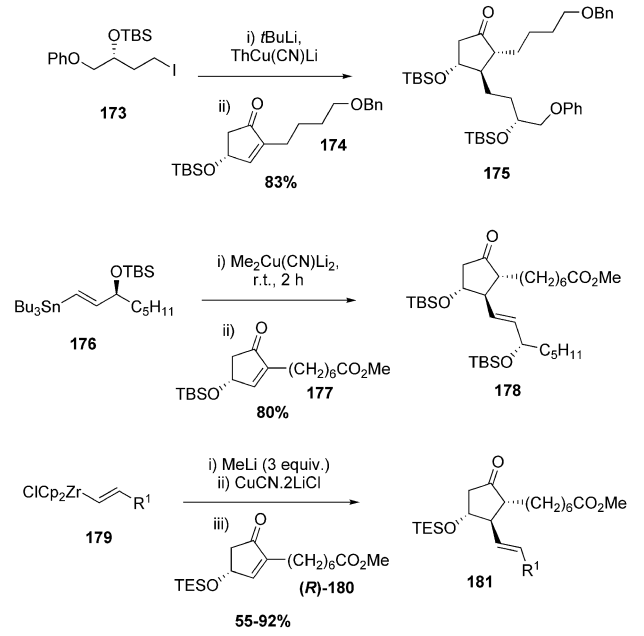
Interestingly, following the 1,2-addition of an organometallic reagent to certain 4-hydroxy-2-cyclopentenenones, oxidation of the newly formed allylic alcohol moiety with a chromium(VI) reagent may proceed with relocation of the carbonyl group. The mechanism of this rearrangement involves initial chromate ester formation of the 3° alcohol followed by an allylic rearrangement of the chromate of the 2° alcohol.[63] This structural manipulation was recently exploited in the synthesis of *cis*-restricted combrestatin analogues.[64] Similarly, in the synthesis of the racemic natural product (±)-terrein (**21**) the addition of allyl Grignard reagent to compound **170** gave the 1,2-addition adduct **171** as a mixture of stereoisomers; oxidation with PCC provided a new 4-hydroxy-2-cyclopentenone **172**, bearing the Grignard-derived allyl moiety at C3 (Scheme 30).[17c] Thermodynamically controlled isomerisation and diol deprotection furnished the target (±)-terrein **21** in three simple steps.



Scheme 30.

3.2.b. 1,4 Additions

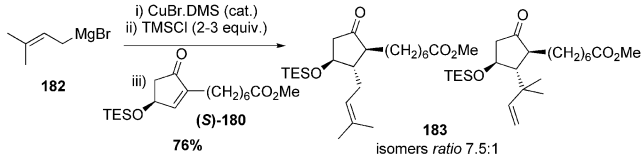
The development of organocuprate chemistry in the 1980s, and in particular the observation that these reagents undergo regioselective 1,4-additions to enones such as 4-hydroxy-2-cyclopentenones, has been widely exploited for the synthesis of prostaglandins and related structures.[55c,65] Three selected examples are shown in Scheme 31, where high order cuprates formed from alkyl iodide **173**, vinylstannane **176** or vinylzirconate **179** added regio- and stereoselectively to cyclopentenones **174**, **177** and **180**; the bulk of the silyl ether at C4 orients the attack of the incoming alkyl moiety towards the opposite face of the double bond. The intermediate copper enolates were then protonated in a stereoselective manner to give the all-*trans* relationship between the substituants at C2, C3 and C4; single diastereomeric products **175**, **178** and **181** were thus obtained in 83%, 80% and 55–92% yields, respectively.



Scheme 31.

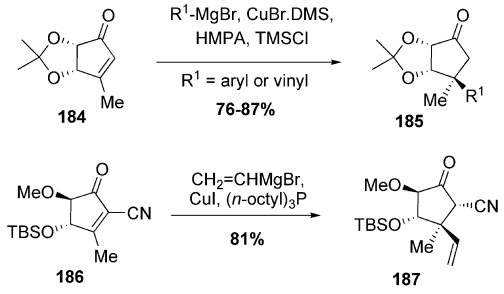
Lipshutz et al. solved a long-standing problem concerning the regioselective addition of allyl cuprates (derived from the Grignard reagent by transmetallation), with the assistance of trimethylsilyl chloride to prevent allylic migration (Scheme 32).[66] This methodology allowed the facile addition of the isoprenyl side chain from transmetallated

Grignard reagent **182** onto the 4-silyloxycyclopentenone (*S*)-**180** in a 1,4 manner, and hence the preparation of the desired trisubstituted cyclopentanone **183** in 76% yield with a 7.5:1 isomeric ratio.



Scheme 32.

Organocopper reagents have also been used for the efficient construction of quaternary centres. Noteworthy is the successful 1,4-addition of vinyl or aryl groups onto 3-substituted 4-hydroxy-2-cyclopentenone derivatives **184** and **186**, leading respectively to the polysubstituted cyclopentanones **185** and **187** in good yields (Scheme 33).[67]



Scheme 33.

3.3. Three-Component Reactions: Functionalisation of C2 and C3 Simultaneously

3.3.a. Origins and Development

The challenges encountered in total synthesis projects often provide stimuli for the development of innovative methodologies.[68] This was typified in the endeavours to master the art of prostaglandin total synthesis, which inspired the idea of a three-component reaction strategy as follows: the *trans*-directed 1,4-addition of an organometallic reagent to a protected 4-hydroxy-2-cyclopentenenone **1** then trapping of the resulting enolate **188** with an electrophile (typically an aldehyde or an alkylating reagent) should furnish the desired substituted cyclopentanone **189** (Figure 5).

The first problem encountered in the development of this three component strategy was the high basicity of the intermediate metal-enolate **188**, which may undergo equilibration at the C5 position to give **190**, which may then undergo irreversible β-elimination of the C4 silyloxy group, to generate an undesired cyclopentenone **191** (Figure 5). Furthermore, again due to its basicity, enolate **188** is susceptible to fast reprotonation to generate the undesired cyclopentenone **192** before the electrophile has had time to react. To circumvent these problems, Johnson et al. used the 4,5-dihydroxy-2-cyclopentenone substrate (*S*,*S*)-**98**, for which

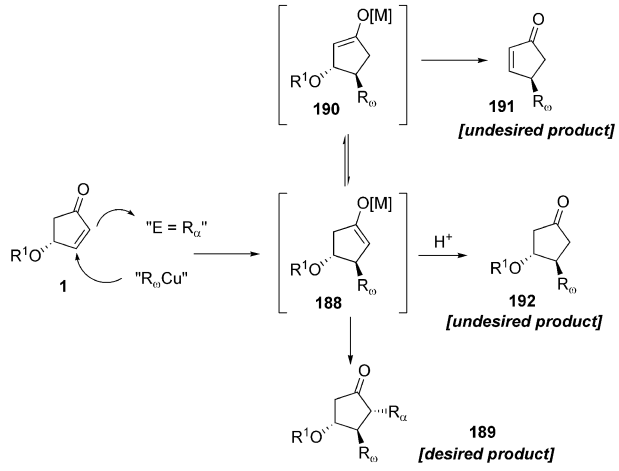
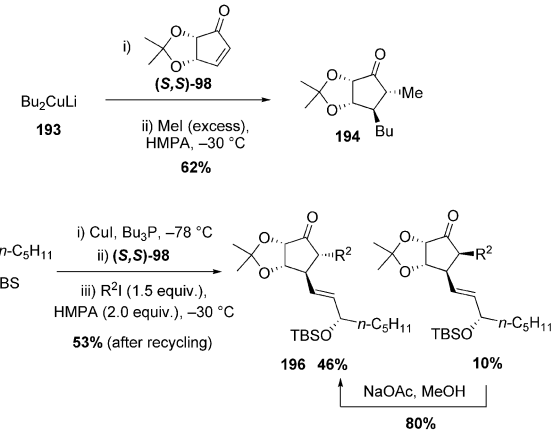


Figure 5. An overview of the principle and the caveats of the three component reaction strategy for functionalisation of 4-hydroxy-2-cyclopentenones.

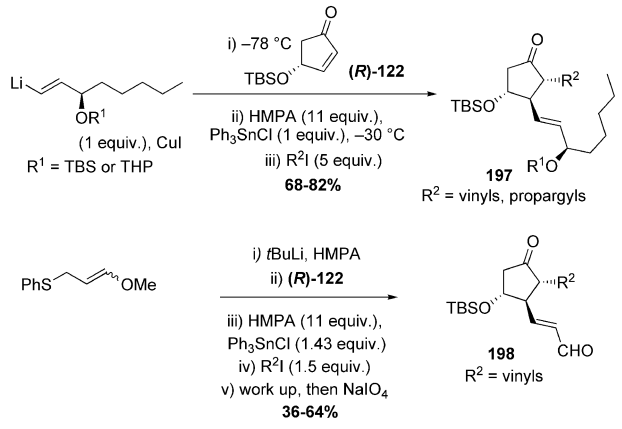
enolate equilibration was suppressed due to charge repulsion with the neighbouring oxygen (Scheme 34).[69] In this case, addition of C3 side chains using lithiocuprates **193** or that derived from **195** then tandem C2 alkylation using alkyl iodides was achieved successfully, to furnish the corresponding cyclopentanones **194** and **196** in reasonable yields. This otherwise highly efficient strategy required a few extra steps in order to remove the redundant hydroxy group from C5.



Scheme 34.

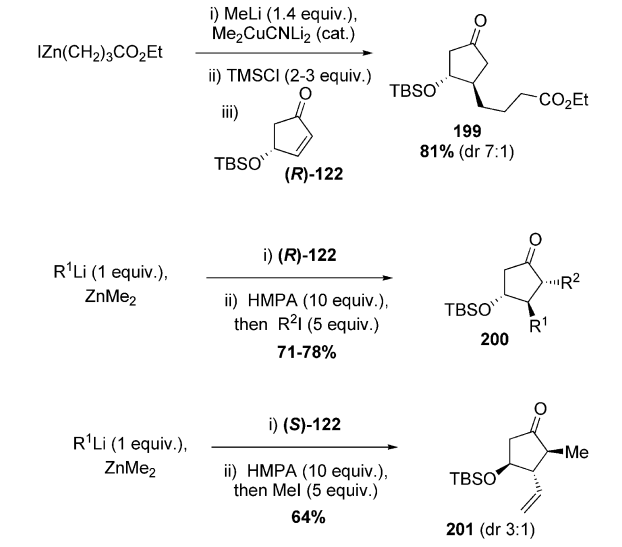
Around the same time, Noyori et al. suggested a useful alternative strategy, in which the copper enolate was trapped at low temperature using triphenyltin chloride (Scheme 35).[70] This efficient Cu–Sn transmetalation reduced the basicity of the enolate, thus avoiding side reactions, and the activation of the tin atom as an 'ate' complex with HMPA allowed the introduction of wide range of alkylating agents onto C2. Thus the 4-silyloxy-2-cyclopentenone (*R*)-**122** was transformed into fully functionalised cyclopentanones **197** or **198** with excellent yields. The procedure worked even when unactivated alkyl iodides were employed, although yields were lower. This strategy has re-

mained popular over the years[71] and its utility extends to numerous other enone substrates which are beyond the scope of this review.



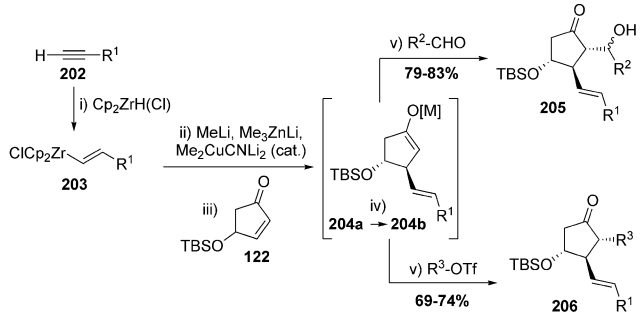
Scheme 35.

Subsequently, Noyori endeavoured to simplify the protocol, and the benefits of using organozinc(II) compounds were discovered (Scheme 36).[72] These reagents undergo smooth 1,4-additions to non-racemic (*R* or *S*) 4-silyloxy-2-cyclopentenone **122** and obviate the need for a copper additive in most cases. The enolate's basicity is attenuated, yet it retains an excellent nucleophilicity in the alkylation step. This improved procedure allowed the illustrative syntheses of compounds **199**, **200** and **201** in high yields.



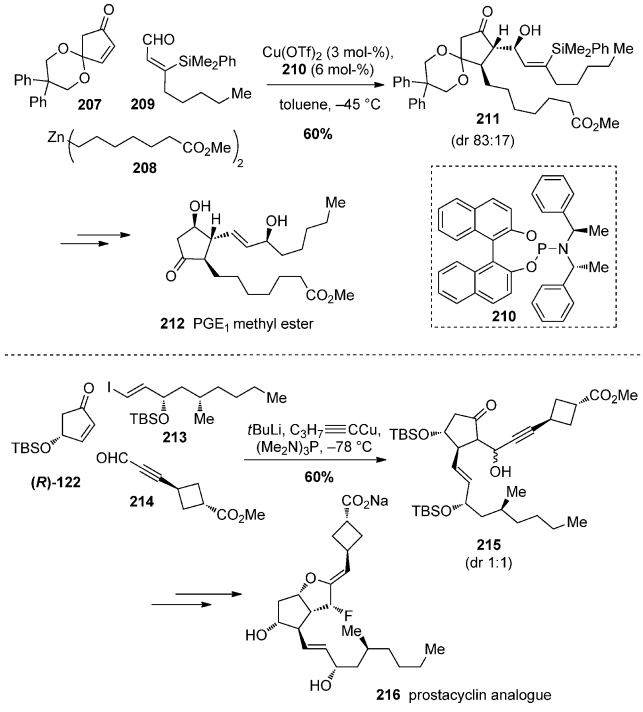
Scheme 36.

Inspired by these results, Lipshutz et al. and other groups developed a complex yet very efficient three-component coupling procedure, starting with simple alkynes **202**, racemic cyclopentenone **122**, and an alkyl triflate or an aldehyde as the electrophile (Scheme 37).[73] These couplings involve five steps in a one pot process: i) hydrozirconation of the alkynes **202** to vinyl zirconocene **203**, ii) catalytic transmetalation of the vinyl zirconocene **203** to the corresponding high order cuprate, iii) diastereoselective 1,4 addition of the vinylic cuprate to the cyclopentenone **122**, iv) transmetalation of the copper enolate **204a** to the less basic zinc enolate **204b** with concomitant regeneration of the catalytic copper species, v) reaction of the zinc enolate with the desired electrophile to introduce the C2 side chain. After acidic work-up the functionalised products **205** or **206** were obtained in good yields and diastereoselectivity.



Scheme 37.

Following this trend, other research groups have applied three-component strategies to build up prostaglandin scaffolds efficiently.[74] In the first example presented in Scheme 38, Feringa et al.[74d] developed an elegant chiral enantioselective addition of zincate **208** to the monoprotected cyclopent-2-ene-1,3-dione **207** in the presence of a copper(II) Lewis acid and chiral ligand **210**. The resulting copper enolate transmetalated to the zincate and reacted with the aldehyde **209** to deliver in a single step the product **211** with good yield (60%) and diastereoselectivity (*dr* 83:17). The intermediate **211** was subsequently converted into the prostaglandin PGE_1 methyl ester **212** in only five

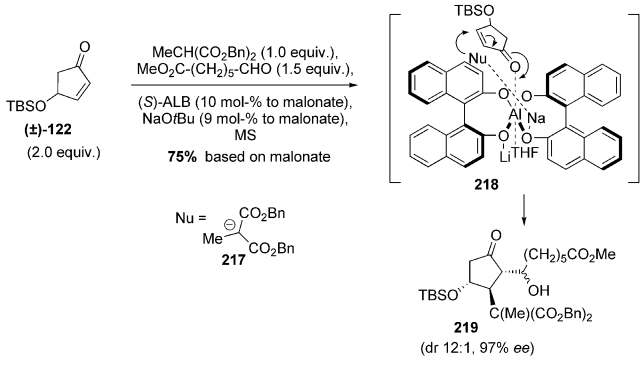


Scheme 38.

steps. The second example (Scheme 38) shows a three component reaction between cyclopentenone (*R*)-**122**, the cuprate derived from **213**, and aldehyde **214** which delivered the complex fragment **215** (yield 60%; *dr* 1:1), which was further transformed into the fluorinated prostacyclin derivative **216**.[74a]

3.3.b. Catalytic and Enantioselective Versions

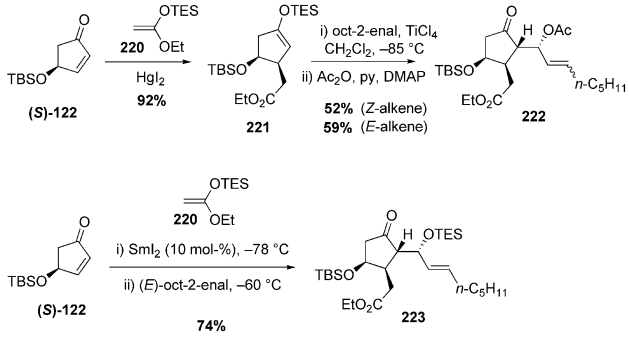
Shibasaki et al. demonstrated the efficiency of their AlLi-bis[(*S*)-bisnaphthoxide] complex, (*S*)-ALB, by achieving the first example of a catalytic enantioselective three component coupling between an enone, a malonate and an aldehyde (Scheme 39).[75] The hetero-bimetallic Lewis acid catalyst activates the cyclopentenone **122** and associates the malonate sodium salt nucleophile **217**, which is delivered by Michael addition in an intramolecular fashion from the metallic complex **218**. The resulting enolate then attacks the aldehyde to provide the desired product **219** in 75% yield (based on malonate) and 92% *ee*. This catalytic system conducts the tandem Michael–aldol process with a high degree of substrate enantioselectivity, and thus effects the kinetic resolution of the racemic enone starting material **122**.



Scheme 39.

3.3.c Two Step Procedures with Silyl Enol Ether Trapping

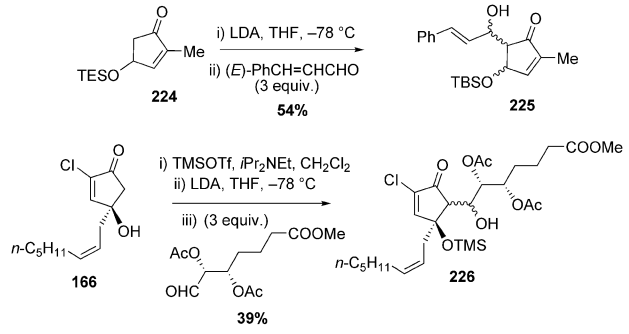
Danishefsky et al. reported a different approach to prostaglandin construction, involving a stepwise, Lewis acid catalysed, three-component reaction (Scheme 40).[76] This approach was notable for the stereoselectivity observed in the mercury(II) or titanium(IV) catalysed Michael addition of silylketene acetal **220** to (*S*)-silyloxy-2-cyclopenenone (*S*)-**122**, which provided a high yield of silyl enol ether **221** with a *cis* relative configuration for the C3 and C4 substituents (in contrast with that observed in Michael additions). Subsequent titanium tetrachloride catalysed Mukaiyama aldol reactions of **221** followed by acetylation afforded the corresponding adducts **222** in acceptable yields, which were on interest as intermediates for prostaglandin synthesis. A few years later, this work was adapted by Collin et al. to conduct a samarium catalysed tandem Michael–Mukaiyama aldol procedure with the same overall stereoselectivity, and generate the product **223** in a single step in 74% yield (Scheme 40).[77]



Scheme 40.

3.4. Elaboration at the C5 Position

Aldol reactions are somewhat conspicuous by their rarity in the otherwise rich chemistry of 4-hydroxy-2-cyclopentenones. There is no obvious reason for this, although reactions usually require an excess of the aldehyde component in order to obtain workable yields of the aldol products, which are invariably obtained as a mixture of diastereomers. Following standard deprotonation with LDA, the TES ether of 2-methyl-4-hydroxy-2-cyclopentenone **224** reacts with cinnamaldehyde to give the aldol product **225** in 54% yield (Scheme 41).[78] More highly functionalised enone derivatives may also be used: Noyori[61] carried out an aldol reaction at C5 of compound **166** to give **226** in 39% yield as part of an expedient access to (7*Z*)-punaglandin-4 (Scheme 41), and comparable results were observed later by Florent et al.[79] in the synthesis of related prostanoid analogues.



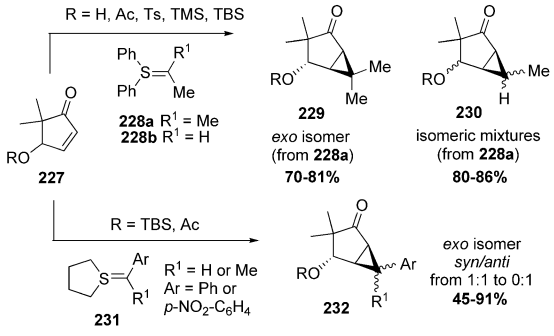
Scheme 41.

3.5. Cycloaddition Reactions

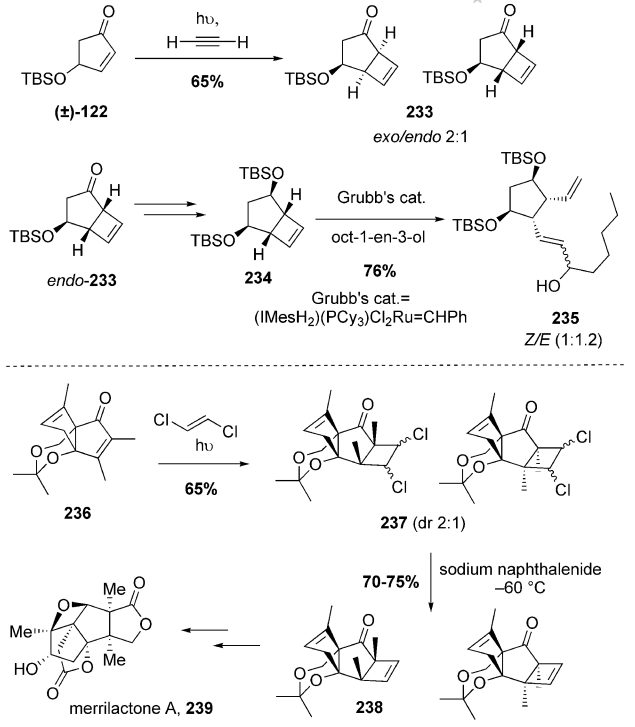
3.5.a. Cyclopropanation

Krief et al. reported several studies of the cyclopropanation of diversely protected 4-hydroxy-5,5-dimethyl-2-cyclopentenones **227** using sulfur ylides (Scheme 42).[80] The use of the symmetrical isopropylidine diphenylsulfurane **228a** generated exclusively the *exo* product **229**, regardless of the nature of the alcohol protecting group. On the other hand, when the non-symmetrical ylide **228b** was used, the products **230** were obtained as diastereoisoisomeric mixtures:

either *anti-exo*/*syn-exo* or *anti-exo*/*anti-endo*, depending on the alcohol protecting group. Use of benzylidene ylides **231** restored the high *exo* selectivity to products **232**, but the *anti*/*syn* ratio varied considerably (from 50:50 to 100:0) depending on both the alcohol protecting group and the nature of the ylide. It is apparent that stereocontrolled cyclopropanation of 4-hydroxy-2-cyclopentenones remains something of a challenge.



Scheme 42.



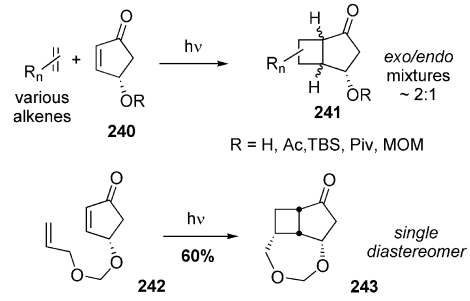
Scheme 43.

3.5.b. [2+2] Cycloadditions

Photochemical [2+2] cycloadditions of 4-hydroxy-2-cyclopentenones with alkenes (or alkynes) have been widely exploited as an entry to functionalised bicyclo[3.2.0]heptanone skeletons.[81]

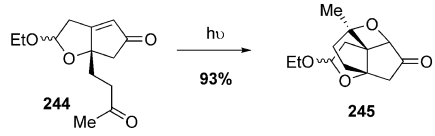
Snapper et al.[82] described the photochemical [2+2] cycloaddition of racemic 4-silyloxy-2-cyclopentenone (±)-**122** with acetylene to give diastereomers **233** containing a cyclobutene core. After separation and minor structural manipulation, the *meso* compound **234** was engaged in a ring-opening metathesis procedure to provide **235**, a key intermediate in the synthesis of 15-F_2 isoprostanes (Scheme 43). Mehta et al.[83] used the more elababorate enone **236** and dichloroethylene as the photochemical [2+2] cycloaddition partners; the adduct mixture **237** was dehalogenated to create the cyclobutene moiety of **238**, used as an intermediate in the synthesis of merrilactone A **239** (Scheme 43).

An important limitation in intermolecular photochemical [2+2] cycloadditions is the poor *endo*/*exo* diastereoselectivity, as illustrated by the above examples and in longer-established work.[84] Intramolecular photochemical reactions are much more selective, and can be devised conveniently around the core 4-hydroxy-2-cyclopentenone **1** structure by attaching the alkene moiety to the 4-OH group.[85] Aitken et al. compared the inter- and intramolecular modes of [2+2] photocycloadditions using diversely functionalised 4-hydroxy-2-cyclopentenones and a selection of alkenes (Scheme 44).[86] The intermolecular reactions of **240** to give products **241** were for the most part bereft of any significant stereoselectivity, while the intramolecular reaction of **242** furnished **243** as the unique product, in 60% yield.



Scheme 44.

In a similar vein, Greaney et al.[87] carried out an intramolecular Paternò–Büchi photochemical [2+2] reaction between the ketone side chain and the carbon–carbon double bond of the 4-oxygenated 2-cyclopentenone subunit of compound **244**, which delivered the tetracyclic compound **245** with excellent yield and stereoselectivity (Scheme 45).

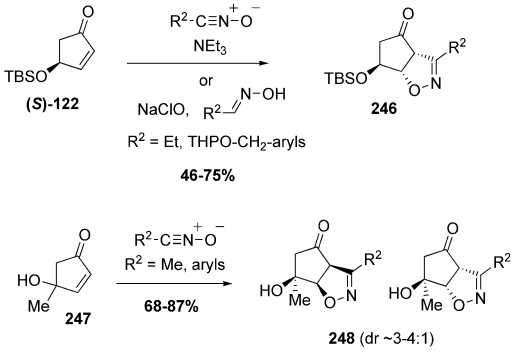


Scheme 45.

3.5.c. [3+2] Cycloadditions

Independently, the research groups of Mann[88] and Sega[89] examined [3+2] cycloaddition reactions between nitriloxide and the enone moiety of 4-hydroxy-2-cyclopentenone derivatives (Scheme 46). Mann et al. reported the highly diastereoselective cycloaddition of a range of

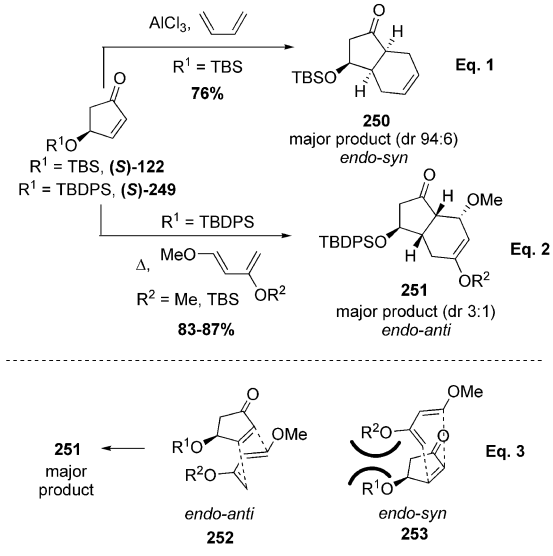
nitriloxides with the 4-silyloxy-2-cyclopentenone (*S*)-**122**, giving *anti* isoxazoline products **246**. Sega studied 4-hydroxy-4-methyl-2-cyclopentenone **247**, in which the unprotected tertiary alcohol apparently participated in hydrogen bonding with the nitriloxide reaction partners, leading predominantly to *syn* isoxazolines **248**.



Scheme 46.

3.5.d. [4+2] Cycloadditions

Rokach[90] and Danishefsky[91] have demonstrated the potential of Diels–Alder reactions for the transformation of the 4-hydroxy-2-cyclopentenone framework (Scheme 47, Eq. 1). Danishefsky illustrated the feasibility of the [4+2] cycloaddition under Lewis acid catalysis (aluminium trichloride), using the 4-silyloxy-2-cyclopentenone (*S*)-**122**, which reacted with 1,3-butadiene to give the bicyclic ring system **250** with good *syn* diastereoselectivity. Rokach adapted this procedure in a synthesis of the isoprostane core, using the sterically demanding cyclopentenone silyl ether (*S*)-**249** (Scheme 47, Eq. 2). Simultaneous control of three newly created stereocentres was achieved under thermal conditions with notable *anti* diastereoselectivity, to give products **251** (*dr* 3:1), in good yields (83–87%). Of the two possible *endo* products, steric effects in the transition state (**252** vs. **253**) explained the preference for the *anti* configuration in the major product (Scheme 47, Eq. 3).

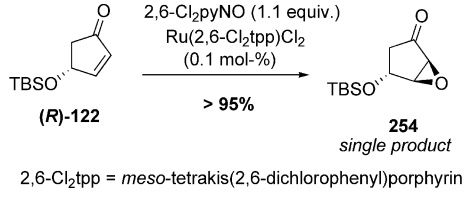


Scheme 47.

Zinc chloride catalysed Diels–Alder reactions were investigated with compound **170** (see Scheme 30). Long reaction times were required to obtain reasonable yields, and it was suggested that the reaction was really only convenient with simple dienes such as isoprene, 2,3-dimethyl-1,3-butadiene and cyclopentadiene.[18f]

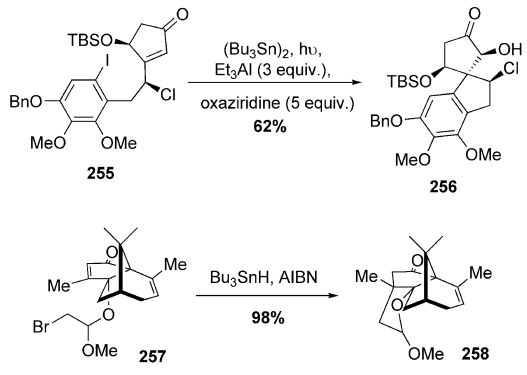
3.6. Miscellaneous

Che et al. have developed an elaborate ruthenium(IV)-porphyrin-based catalytic system for the efficient 2,6-dichloropyridine *N*-oxide epoxidation of electron-deficient alkenes, which transforms 4-silyloxy-2-cyclopentenone (*R*)-**122** into *exo*-2,3-epoxy-4-silyoxy cyclopentanone **254** in near quantitative yield (Scheme 48).[92] However, satisfactory results may also be obtained using simpler systems: treatment of (±)-**122** with hydrogen peroxide in a buffered medium provided racemic **254** in 70% yield (*dr* 96:4),[93] clearly an improvement on the previously described employment of hydrogen peroxide and sodium hydroxide in aqueous methanol which transformed (*S*)-**122** into *ent*-**254** in considerably lower yield (41%).[55d]



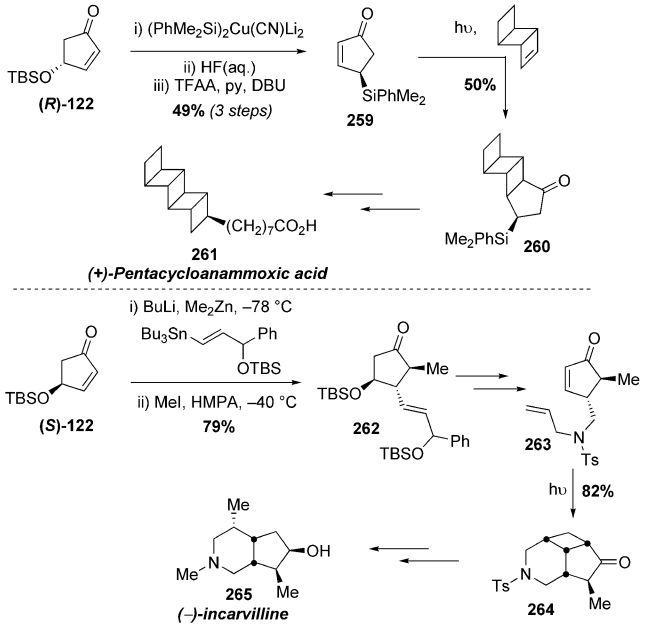
Scheme 48.

Radical cyclisation is recognised as a powerful means of creating quaternary centres and has been used to this end in reactions of structures incorporating a C3-substituted 4-hydroxy-2-cyclopentenone core (Scheme 49).[94] Thus compounds **255** and **257** were transformed smoothly into the more complex tri- and tetracyclic structures **256** and **258** in 62% and 93% yield, respectively.



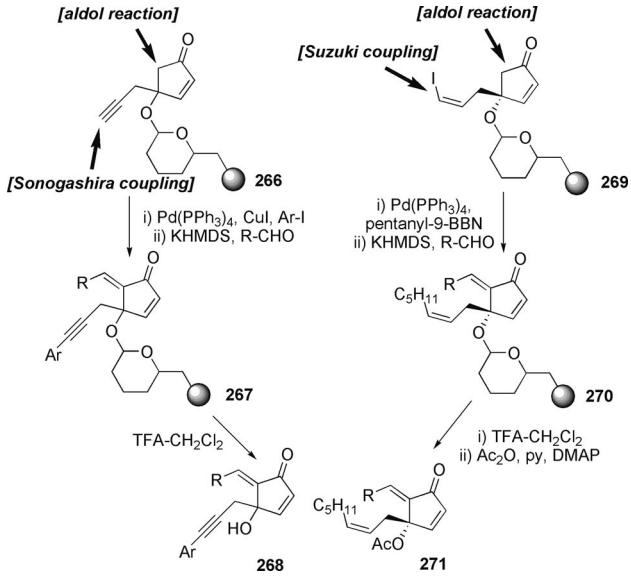
Scheme 49.

The 4-hydroxy-2-cyclopentenone core has been used as a starting point for the construction of other cyclopentenone derivatives which have subsequently been engaged in photochemical [2+2] cycloaddition reactions as key steps in total synthesis (Scheme 50). Corey et al.[95] prepared enantiomerically pure 4-silyl-2-cyclopentenone **259** in three steps from the silyl ether (*R*)-**122**: the sequence involved stereoselective cuprate-mediated 1,4-addition of the silyl moiety, silyl ether hydrolysis, then dehydration. Derivative **259** served as the starting manifold for the stereoselective construction of the strained polycyclic natural product (+)-pentacycloanammoxic acid **261**. Indeed, the first step of the natural product assembly was achieved through a [2+2] photocycloaddition to yield cyclopentanone **260** in 50%. Kibayashi et al.[96] performed a three-component coupling reaction on the silyl ether (*S*)-**122**, to provide **262**. Five steps were then required to obtain *N*-allyl enone **263**, which underwent intramolecular [2+2] photocycloaddition to give a single tricyclic adduct **264** in 82% yield (based on recovered **263**). Compound **264** then served as a key intermediate for the synthesis of (–)-incarvilline **265**.



Scheme 50.

Finally, Takahashi et al. grafted 4-substituted 4-hydroxy-2-cyclopentenone subunits onto resins in a racemic version **266** and enantiopure form **269** in order to generate a library of bioactive clavulone analogues **268** and **271** via combinatorial chemistry (Scheme 51).[97] The solid phase syntheses involved elaboration of the unsaturated C4 substituent by palladium catalysed Sonogashira or Suzuki coupling reactions on compounds **266** and **269** respectively, followed by aldol reactions at C5 to provide the supported libraries **267** and **270** on tetrahydropyranyl linker. After cleavage from the support and possible acetylation of the tertiary alcohol, two series of clavulone analogues **268** and **271** were isolated and evaluated in a structure activity relationship (SAR) study to determine the antiproliferative properties against different cell lines.



Scheme 51.

Conclusions

A good number of convenient preparative methods are available, allowing access to racemic or enantiomerically enriched derivatives of the title structure. The wide array of potential applications is highlighted by numerous illustrative examples. While the interest in these compounds has had its historical origins in the development of prostaglandin synthesis, the scope and applications have come a long way in the last few decades, on account of the rich diversity of chemical transformations which can be performed in a controlled and selective fashion on the compact molecular skeleton. It seems likely that 4-hydroxy-2-cyclopentenone derivatives will remain as popular building blocks for synthetic chemists, and that further elegant and innovative developments and applications will emerge in the future.

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