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Stereoselective syntheses of naturally occurring 5,6-dihydropyran-2-ones

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Abbreviations: Ad, adamantyl; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; BINOL, 1,1′-bi(2-naphthol); B.Y., baker's yeast; Bn, benzyl; Bz, benzoyl; Car, 2-caranyl; CRM, cross metathesis; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DIBAL, diisobutylaluminum hydride; DIPT, diisopropyl tartrate; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DMSO, dimethylsulfoxide; dr, diastereomeric ratio; EE, ethoxyethyl; ee (ees), enantiomeric excess (es); HDA, hetero-Diels–Alder; HKR, hydrolytic kinetic resolution; HWE, Horner–Wadsworth–Emmons; Ipc, diisopinocamphenyl; KAPA, potassium 3-aminopropylamide; KHMDS, potassium hexamethyldisilylamide; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilylamide; MCPBA, *m*-chloroperbenzoic acid; MEM, 2-methoxyethoxymethyl; MOM, methoxymethyl; PMB, *p*-methoxybenzyl; RCM, ring-closing metathesis; Tf, trifluoromethanesulfonyl; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyl-dimethylsilyl; TES, triethylsilyl; TMS, trimethylsilyl; TMSE, 2-trimethylsilylethyl; TPS, *tert*-butyldiphenylsilyl; Tr, trityl.

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1. Introduction

Lactone rings are a structural feature of many natural products.[1] Of the naturally occurring lactones, which all display a wide range of pharmacological activities,[2] those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources.[3] Because of their manifold biological properties, these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic.[4] In addition, they inhibit HIV protease,[5] induce apoptosis,[6,7] and have even proven to be antileukemic,[8] along with having many other relevant pharmacological properties.[9] At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.[1a,10]

In this paper, we review the stereoselective syntheses of chiral natural products with the aforementioned structural fragment. We will focus on compounds with general structure **1** (Fig. 1). This structure displays an isolated dihydropyran-2-one ring with various substituents R_3–R_6 (in which at least one is not H) at C-5/C-6 (IUPAC numbering). Molecules in which the dihydropyranone ring is embedded within or fused with another cyclic structure will not be discussed herein. The review covers more than three decades, from the early 1970s until the first half of 2006, and is complete to the best of our knowledge and ability. An exhaustive coverage, however, cannot be guaranteed.

The structural features of this class of compounds vary widely. Indeed, molecules such as (+)-parasorbic acid,[11] shown in Figure 2, barely display anything other than the dihydropyranone ring. In contrast, this moiety goes almost unnoticed within the complex molecular architecture (Fig. 2) of leptomycin B.[12] For this reason, syntheses of naturally occurring dihydropyranones cannot be classified according to a general, unified criterion. We will thus focus first on the methods reported in the literature *for the creation of the 5,6-dihydropyran-2-one core* and then comment on the synthetic methodologies used to generate the *chirality resident in the dihydropyranone ring*, i.e., methods for the stereoselective creation of stereogenic centers at C-5/C-6. Finally, we will discuss the stereoselective syntheses of several selected 5,6-dihydropyran-2-ones. This study will be limited to naturally occurring compounds synthesized in enantioenriched form either through the use of chiral precursors or by means of asymmetric synthesis. Syntheses of racemic pyrones will not be discussed.

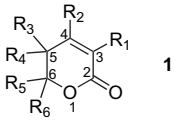


Figure 1. General structure of 5,6-dihydropyran-2-ones **1**.

2. Synthetic methodologies for dihydropyranones

Many different synthetic methods for the creation of 5,6-dihydropyran-2-one rings have been reported. We have organized them according to their frequency of use and mention in the literature. Emphasis has been placed almost exclusively on methods that have actually been employed for the synthesis of naturally occurring pyrones. We have divided these methods into four groups as follows: (1) lactonization of substituted δ-hydroxy acid derivatives, (2) oxidation of substituted dihydropyran derivatives, (3) ring-closing metathesis and (4) miscellaneous methods. Before examining the actual syntheses, however, we will first comment briefly on each of these synthetic methodologies.

2.1. Lactonization of substituted δ-hydroxy acid derivatives

Methods that fall into this category include any reaction, which generates a δ-hydroxy acid or derivative thereof which later cyclizes to a δ-lactone, spontaneously in many cases. When the δ-hydroxy acid already carries a conjugated *Z* double bond, the final product will be the desired 5,6-dihydropyran-2-one. If the double bond is not present, but a suitable leaving group X is attached to the β-carbon (or, less often, the α-carbon), elimination of HX from the intermediate lactone can take place under mild conditions to yield the double bond. Often, these conditions may also cause double-bond migration from the β,γ-position to the conjugated α,β-position. In the absence of both the double bond and the leaving group, an additional dehydrogenation protocol is necessary (Fig. 3). This methodology for generating a 5,6-dihydropyran-2-one ring is widely represented in the literature[13] (for a synthesis of the parent system, **1**, R_1–R_6=H, Fig. 1, see Ref. 13a).

2.2. Oxidation of substituted dihydropyran derivatives

Various synthetic methods begin by first generating a dihydropyran derivative. If this is a 2-hydroxy-5,6-dihydro-2*H*-pyran (a cyclic hemiacetal), a simple alcohol oxidation can be used to transform it into a 5,6-dihydropyran-2-one (Fig. 4). If the hydroxyl group is located at another position or is not present, the oxidation of a C–H bond contiguous to the oxygen atom is required. According to the position of the endocyclic C=C bond, this can be carried out either via direct C–H bond oxygenation or through a photochemical oxygenation with singlet oxygen, $^1O_2$. Other methods

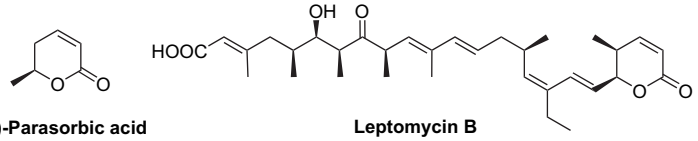


Figure 2. Two examples of naturally occurring 5,6-dihydropyran-2-ones.

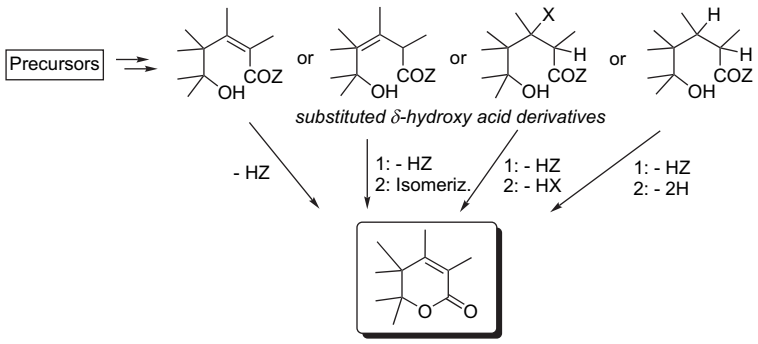


Figure 3. Formation of 5,6-dihydropyran-2-ones via lactonization of a δ-hydroxy acid derivative.

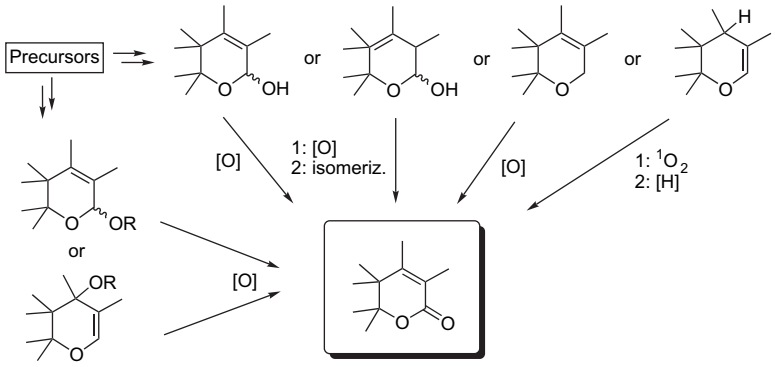


Figure 4. Formation of 5,6-dihydropyran-2-ones via oxidation of dihydropyran intermediates.

involve the treatment of pyranoid glycals or glycosides with specific oxidants.[14] All of these oxidative methods are amply present in the literature.[15]

2.3. Ring-closing metathesis

The transition-metal-catalyzed olefin metathesis is a very recent development, which has become an extremely useful synthetic tool in the last 15 years.[16] The ring-closing variant of this reaction (RCM) has proven to be particularly useful in the preparation of carbo- and heterocycles of any ring size, except for those that are very strained. In the case of 5,6-dihydropyran-2-ones, RCM has been used for the direct creation of this heterocyclic system many times (Fig. 5).[17,18]

2.4. Miscellaneous methods

In this last category, we have grouped together all those methods that, while not being intrinsically less valuable than those previously discussed, have been used in only a limited number of cases for the preparation of either tetrahydropyran-2-ones or 5,6-dihydropyran-2-ones. Figures 6 and 7 illustrate these particular reactions:

(a) intramolecular HWE olefinations,[19]
(b) Baeyer–Villiger reactions,[20]
(c) metal-mediated/catalyzed cyclocarbonylations,[21–23]
(d) halo- and selenolactonizations,[24]
(e) cycloadditions,[25–29] and
(f) intramolecular aldolizations.[8]

As can be seen in Figure 6, these methods require precursors of different structural types and afford different products. Thus, intramolecular HWE olefinations and metal-mediated carbonylations usually yield 5,6-dihydropyran-2-ones directly. The Baeyer–Villiger reaction, however, provides tetrahydropyran-2-ones, which must subsequently be dehydrogenated. The halolactonization method gives a halogenated lactone, which must then be subjected to both reductive dehalogenation and base-catalyzed elimination of ROH or a similar fragment.[24b] Similar considerations apply to the selenolactonization reaction.[24a]

Cycloadditions of the [4+2] type (hetero-Diels–Alder, HDA reactions) have been used in a number of cases for the preparation of enantiopure pyrones (Fig. 7).[25] Two strategies have emerged, one using disposable chiral auxiliaries[26] and another involving asymmetric reactions induced by chiral, Lewis-acidic catalysts.[27–29] In the latter, Brassard-type dienes are often used to give rise to the formation of 4-alkoxy-5,6-dihydropyran-2-ones.[27] The use of other dienes (e.g., the well-known Danishefsky-type dienes) affords

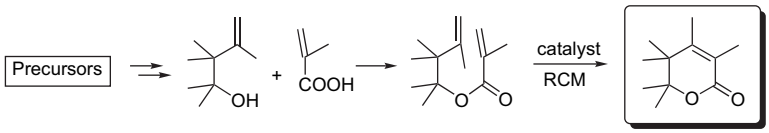


Figure 5. Formation of 5,6-dihydropyran-2-ones via ring-closing metathesis.

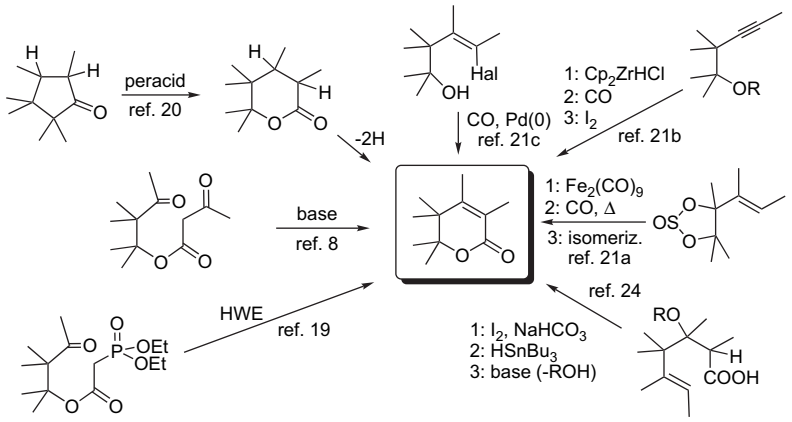


Figure 6. Further methods for the preparation of 5,6-dihydropyran-2-ones.

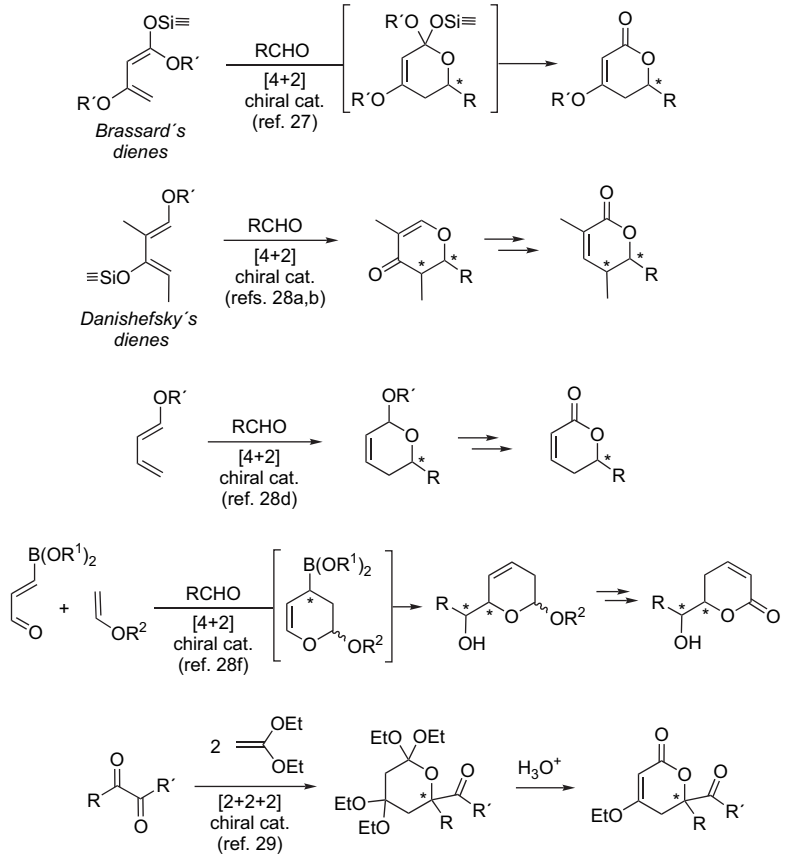


Figure 7. Generation of chiral 5,6-dihydropyran-2-ones via asymmetric cycloadditions.

pyran or pyran-4-one derivatives,[15ai,28] which are subsequently transformed into the desired pyran-2-ones. Additionally worth mentioning is a three-component method in which a β-boryl-α,β-enal undergoes a [4+2] HDA cycloaddition with an enol ether to yield a 4-boryl-5,6-dihydropyran, which then reacts in situ with an aldehyde to yield a 2-substituted 6-alkoxy-2,5-dihydropyran.[28f] A conceptually different variant is the asymmetric cyclocondensation, formally a [2+2+2] cycloaddition, of α-dicarbonyl compounds with ketene acetals in a 1:2 molar ratio.[29] This yields 6,6-disubstituted 4-alkoxy-5,6-dihydropyran-2-ones with ees ranging from 53 to 99%. Examples of these reactions will be examined below (Section 3.2.4.4).

3. Formation of stereogenic centers in the ring

Naturally occurring 5,6-dihydropyran-2-ones are chiral. The stereogenic carbons responsible for this chirality may reside in the pyrone ring itself (C-5/C-6) and/or in the side chains. The methods used to generate the stereogenic side-chain carbons may involve any known stereoselective reaction and are not necessarily related to the manner in which the pyrone moiety is generated. The following discussion will therefore not address this aspect, but rather will focus on the methods for creating chirality *centered at C-5/C-6 of the pyrone ring*, which can be roughly divided into two types: (1) the use of chiral precursors, either from the chiral pool or from

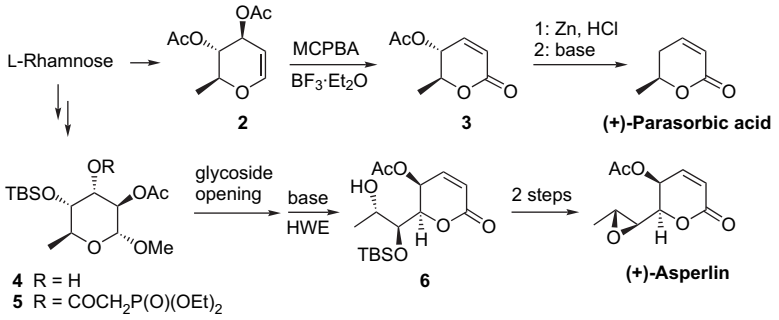
products easily prepared therefrom, and (2) asymmetric (enantioselective) reactions.[30]

3.1. Use of chiral precursors

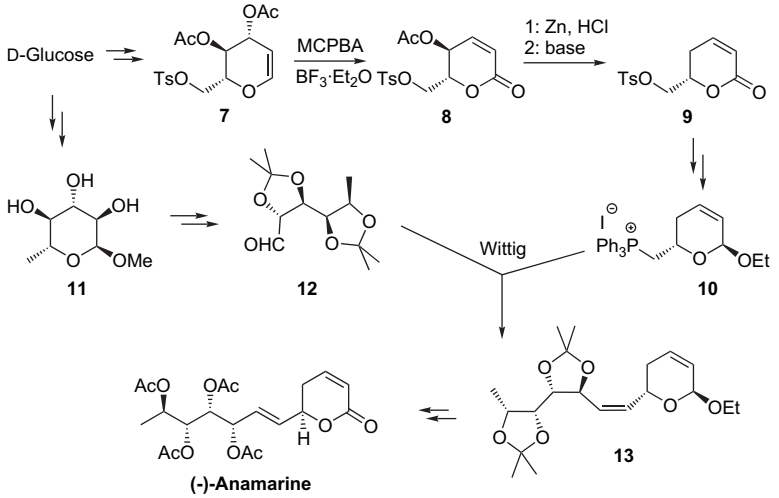
Various types of chiral precursors have been used for the stereoselective synthesis of chiral 5,6-dihydropyran-2-ones: (a) carbohydrates, mainly monosaccharides,[13c,h,i,k–m,o–s,w,ab,af,aj,al,am,ap,ar,as,bd,br,bu,cb,cg,ch,ci,15b–f,i,k,l,n,p,s,t,w,x,ac,aj,ak,ap,19a–c] (b) chiral hydroxy acids,[13u,v,ak,ap,ax,bt,bv,15a,j,q,z,aq,ar,au,az,17d,i,ah,ai,21a] (c) chiral epoxides,[13x,ad,bg,bj,bs,15o,ba,17l,r,21b] and (d) other chirons, including those prepared with the aid of microorganisms or enzymes.[8,13d,f,j,t,y,z,ac,ae,ag,ai,ao,av,aw,ba,be,bh,bk,15m,ab,ag,am,at,aw,17n,v,z,ac,ak,20a,c,24,27a] As will be discussed below, in some cases, one or two of the stereogenic carbons of the chiral precursor are transmitted intact to C-5/C-6 of the pyrone ring of the target molecule. In other cases, however, these carbons are not transferred as such, and may even disappear (sacrificial stereocenters), but only after they have influenced the formation of other stereocenters via internal induction.

3.1.1. Carbohydrate precursors. Monosaccharides are often used as chiral precursors in the synthesis of natural compounds.[31] In the case of chiral 5,6-dihydropyran-2-ones, their use goes back more than two decades. In 1984, for example, Lichtenthaler and co-workers reported the preparation of (+)-parasorbic acid in three steps from dihydropyran **2**, which is easily available from L-rhamnose (Scheme 1).[15b] A key step was the Lewis acid-mediated oxidation of **2** to lactone **3**.[14] The latter was then transformed into parasorbic acid through reductive C–O bond cleavage followed by double-bond isomerization. In this case, the single stereogenic carbon of parasorbic acid thus originates in C-5 of L-rhamnose. Ramesh and Franck made much more efficient use of the chirality resident in the sugar precursor in their synthesis of (+)-asperlin, again using L-rhamnose as the starting material.[19a] The sugar was transformed through standard procedures into the 6-deoxy-L-altrose derivative **4**, which was esterified with di-*O*-ethyl phosphonoacetic acid to yield **5**. Opening of the glycoside moiety was followed by intramolecular HWE olefination to afford the 5,6-dihydropyran-2-one **6**. Two additional, straightforward steps led to (+)-asperlin, with all four consecutive stereogenic carbons originating in the sugar precursor.

The more common monosaccharide, D-glucose, and its derivatives have often been the starting materials for the synthesis of naturally occurring 5,6-dihydropyran-2-ones. For example, two research groups have used D-glucose as the starting material for the synthesis of the non-natural enantiomer of anamarine. Lichtenthaler and co-workers used the sugar to prepare the key fragments **10** (via intermediates **7**–**9**) and **12** (via **11**),[15c] which contained the stereogenic carbons of the pyrone ring and the side chain, respectively (Scheme 2). Both moieties were connected via a Wittig



Scheme 1. Synthesis of two natural 5,6-dihydropyran-2-ones from L-rhamnose.



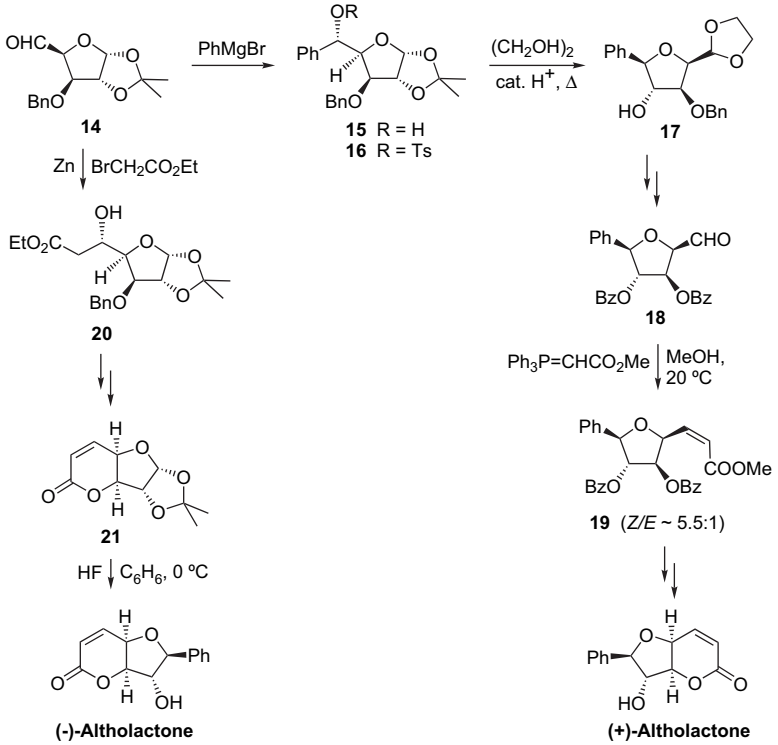
Scheme 2. Synthesis of (−)-anamarine from D-glucose.

olefination to yield the *Z* olefin **13**. The latter was then converted into (−)-anamarine through a sequence of straightforward steps, one of which was a photochemical *Z–E* isomerization. A second synthesis of the same compound along similar lines was published shortly afterwards by Valverde and co-workers.[15f] In these two syntheses, the pyrone ring was generated by means of an oxidative modification of a pyran precursor (Section 2.2).

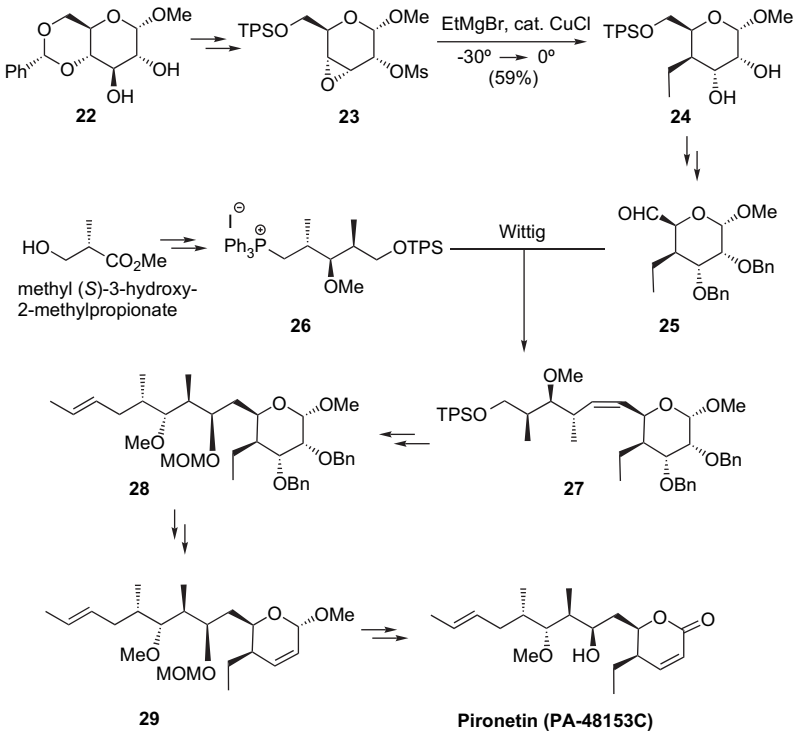
In other research, aldehyde **14**, which is obtained from D-glucose, was the starting material for an enantiodivergent synthesis of both enantiomers of altholactone (Scheme 3).[13s] Thus, the reaction with phenylmagnesium bromide under chelation control stereoselectively provided the secondary alcohol **15** (dr∼18:1), which was subsequently converted into tosylate **16**. Treatment of the latter with ethylene glycol and an acid catalyst generated tetrahydrofuran **17**, which was formed through acetal opening and internal displacement of the tosylate by the hydroxyl group at C-2 (glucose numbering), followed by dioxolane formation. Compound **17** was converted into the sensitive aldehyde **18**, which was then subjected to *Z*-selective Wittig olefination to afford **19**. The latter was transformed into (+)-altholactone by means of ester hydrolysis and lactone ring closure. The non-natural (−)-antipode was also synthesized from **14** via the route shown in Scheme 3. Thus, Reformatsky reaction of **14** with ethyl bromoacetate stereoselectively provided β-hydroxy ester **20**. Ester hydrolysis and hydrogenolytic debenzylation furnished a dihydroxy acid, which was then dehydrated to the conjugated lactone **21**. Treatment of the latter with hydrogen fluoride in benzene at 0 °C provided (−)-altholactone in 47.7% yield, together with two further, minor by-products. As an explanation for this remarkable transformation, the authors proposed a Friedel–Crafts alkylation of the benzene ring by the carbocation formed after acetal oxygen protonation and ring opening. In both syntheses, it is worth mentioning that: (a) the pyrone ring is formed through lactonization of a suitable hydroxy acid precursor (Section 2.1) and (b) three out of the four stereogenic carbons of D-glucose are retained in the final product, with two of them becoming part of the pyrone ring.

The easily available D-glucose derivative **22** provided the source of the two stereogenic carbons of the pyrone ring in Kawada's synthesis of the immunosuppressive agent, (−)-pironetin (PA-48153C).[15w] Conversion of **22** into epoxide **23** and subsequent treatment with an ethylcopper reagent yielded **24**, which is derived from nucleophilic diaxial epoxide opening and parallel O-demesylation (Scheme 4). This permitted the introduction of the *C*-ethyl group with the configuration required for (−)-pironetin. Diol **24** was then converted into aldehyde **25** and subjected to a *Z*-selective Wittig olefination with phosphonium salt **26**, which had previously been prepared from the commercially available methyl (*S*)-3-hydroxy-2-methylpropionate. The resulting olefin **27** was then converted into glycoside **28** via a sequence of seven steps. After having completed the side chain with its four stereogenic carbons, the only task remaining was to convert the glycoside moiety into the conjugated pyrone ring. For this purpose, first the double bond was created by means of reductive elimination of the two vicinal benzyloxy groups (Na, liquid NH_3), double mesylation, and treatment with a zinc/copper couple to yield **29**. The carbonyl group was then generated by means of glycoside hydrolysis and Jones oxidation. Cleavage of the MOM protecting group completed the synthesis.

Various D-glyceraldehyde derivatives, often prepared from D-mannitol, are further precursors from the sugar chiral pool that are frequently used in the synthesis of natural



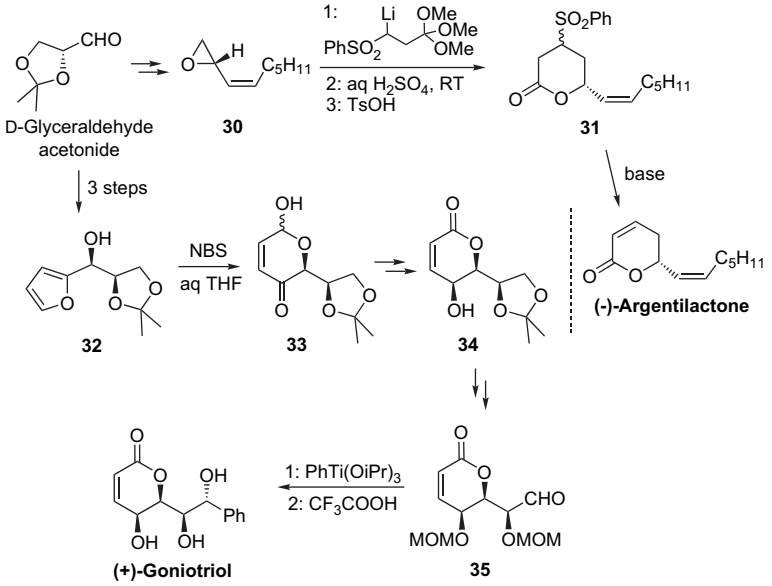
Scheme 3. Synthesis of (+)- and (−)-altholactone from D-glucose.



Scheme 4. Kawada's synthesis of (−)-pironetin (PA-48153C).

pyrones. Their single stereogenic carbon can be uneventfully incorporated into the structure of the target pyrone, as shown in the synthesis of (−)-argentilactone by Ghosez and Carretero.[13p] First, standard reactions were used to convert the easily available acetonide of D-glyceraldehyde into epoxide **30** (Scheme 5). Epoxide opening with the lithio derivative of a functionalized sulfone provided a γ-hydroxy sulfone, which was then subjected to hydrolysis of the orthoester group. Lactone ring closure gave **31**, and subsequent base-catalyzed elimination of the sulfinate group afforded the target molecule.

The use of D-glyceraldehyde derivatives for the synthesis of complex pyrones containing several stereogenic carbons obviously demands the participation of additional stereoselective reactions involving internal induction. Such is the case of Honda's synthesis of (+)-goniotriol (Scheme 5). Thus, reaction of D-glyceraldehyde acetonide with 2-lithiofuran took place with almost no stereoselectivity (mixture of diastereomeric alcohols, dr∼4:3). The desired stereoisomer **32** was obtained through MnO_2 oxidation of the alcohol mixture and stereoselective reduction of the resulting ketone with L-Selectride. Generation of the pyrone core was initiated

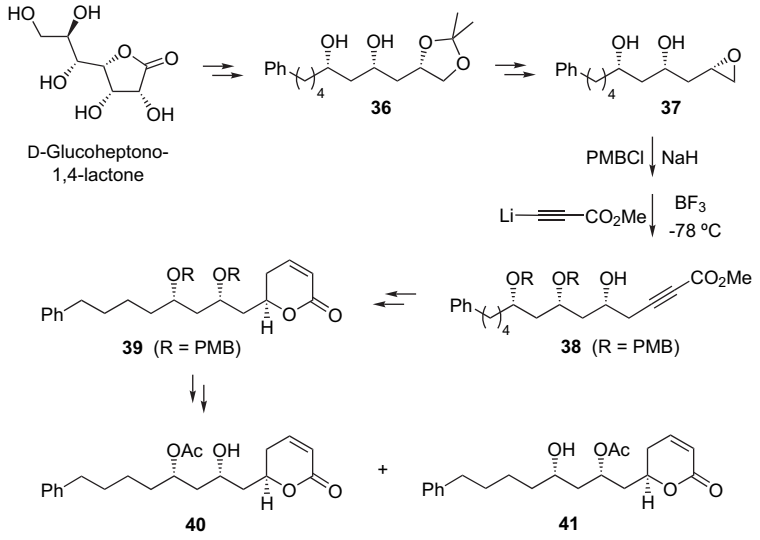


Scheme 5. Synthesis of argentilactone and goniotriol from D-glyceraldehyde derivatives.

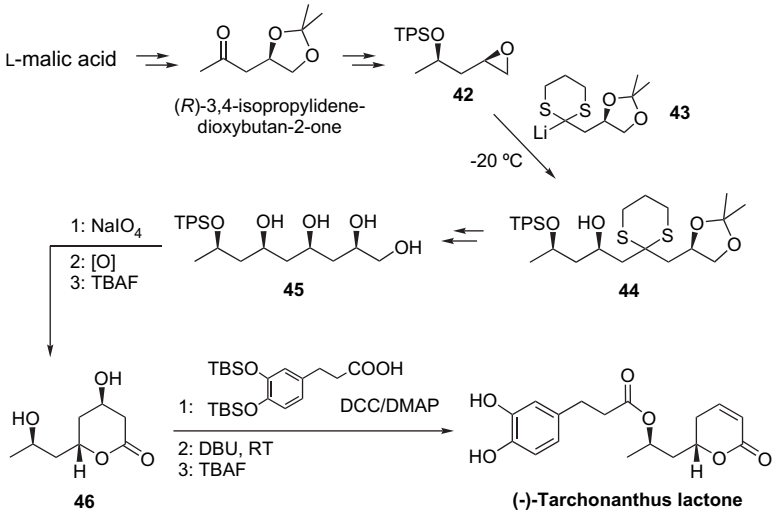
by means of oxidative expansion of the furan ring through an Achmatowicz reaction[32] to yield **33**, which was subsequently converted into pyrone **34** via an oxidation–reduction sequence. Cleavage of the acetonide moiety in **34**, combined with a suitable protecting-group strategy, furnished aldehyde **35**. Reaction of the latter with $PhTi(OiPr)_3$ stereoselectively provided a secondary alcohol (dr~4:1), which was then transformed into (+)-goniotriol after cleavage of the two protecting groups.[15ac] Thus, of the four stereogenic carbons in the target molecule, only one (in the side chain of the pyrone ring) was already present in the chiral precursor.

The inexpensive, commercially available, D-glucoheptono-1,4-lactone, served as the chiral starting material for the synthesis of the two antifungal pyrones **40** and **41** isolated from *Ravensara anisata*, a plant species found in Madagascar (Scheme 6). A sequence of straightforward functional transformations, including an alcohol inversion involving the Mitsunobu reaction, converted the sugar precursor into acetonide **36** and then into epoxide **37**, retaining three out of the five stereogenic carbons of the starting chiron, albeit with an inverted configuration in one of them. Hydroxyl protection and epoxide ring opening with methyl 3-lithiopropiolate furnished the conjugated α,β-ynoate **38**, which was subsequently converted into pyrone **39** by means of Lindlar semihydrogenation of the C≡C bond and lactone ring closure. Cleavage of the protecting groups and partial acetylation unselectively provided a mixture of the natural lactones **40** and **41**.[13ch]

3.1.2. Chiral hydroxy acids. Several chiral hydroxy acids (e.g., lactic, tartaric, mandelic, malic, etc.) are both inexpensive and commercially available, often in both antipodal forms. They can be uneventfully converted into other functional, reactive forms, such as aldehydes, which are suitable for easier incorporation into complex natural structures of various types,[33] including 5,6-dihydropyran-2-ones. For instance, tarchonanthus lactone has been obtained by Mori et al. from (*R*)-3,4-isopropylidenedioxybutan-2-one, which was, in turn, prepared from L-malic acid.[13u,v] Chelation-controlled reduction of the ketone, protection of the hydroxyl group, and standard functional manipulation afforded the epoxide **42** (Scheme 7), which was then subjected to nucleophilic opening with the lithiated dithiane **43** prepared from



Scheme 6. Synthesis of the antifungal pyrones **40/41** from D-glucoheptono-1,4-lactone.

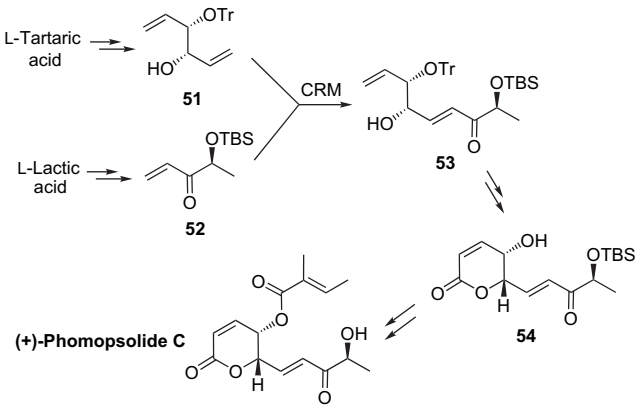


Scheme 7. Synthesis of (−)-tarchonanthus lactone from L-malic acid.

the same chiral source. This gave compound **44**, which was then straightforwardly converted into the monoprotected pentaol **45**. Vicinal diol periodate cleavage, oxidation of the resulting lactol to lactone, and desilylation furnished dihydroxy lactone **46**. Finally, acylation of both hydroxyl groups with disilylated dihydrocaffeic acid, selective base-catalyzed elimination of the β-acyloxy group, and desilylation yielded the desired lactone, with the stereogenic carbon within the ring coming directly from the chiral precursor.

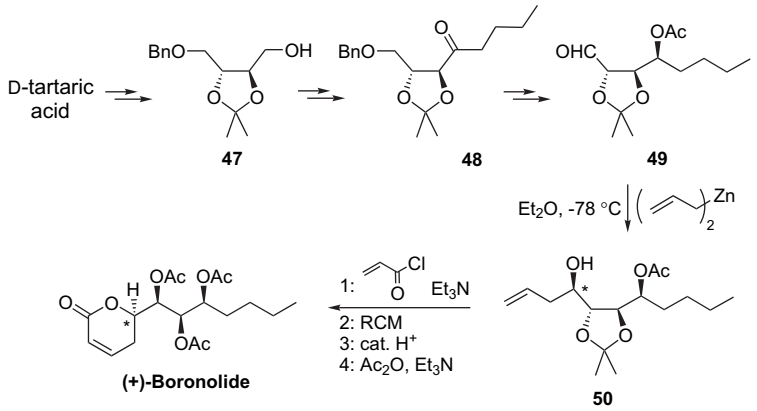
The chirality resident in the hydroxy acid precursor may not necessarily end up in the stereogenic carbons situated in the pyrone ring, but may still give rise to them via internal induction. This is the case in Ghosh's synthesis of (+)-boronolide (Scheme 8), in which D-tartaric acid was the chiral starting material.[17d] Transformation of this acid into **47** via reported procedures was followed by conversion into *n*-butyl ketone **48** through an intermediate Weinreb amide. Stereoselective reduction of the ketone group, acetylation, debenzylation, and oxidation afforded aldehyde **49**, which was then subjected to reaction with diallyl zinc to yield homoallyl alcohol **50** with good diastereoselectivity (dr~5:1). The synthesis of the natural product was completed upon acylation with acryloyl chloride, RCM (Section 2.3), cleavage of the acetonide moiety, and peracetylation. Thus, the single stereogenic carbon (*) within the pyrone ring was not present in the chiral precursor, but was generated by means of internal induction during the allylation step of aldehyde **49**.

The α-hydroxy acids, L-tartaric acid and L-lactic acid, provided all necessary stereogenic carbons in Blechert's synthesis of (+)-phomopsolide C,[17ah] in which olefin metathesis again played a key role (Scheme 9). Thus, diolefin **51**, which was prepared in a standard way from L-tartaric acid, and conjugated ketone **52**, prepared from L-lactic acid, were coupled in a CRM reaction catalyzed by the Grubbs–Hoveyda ruthenium complex.[16] This gave alcohol **53**, which was subsequently acylated with acryloyl chloride and subjected first to trityl group cleavage and then to RCM with the same catalyst to yield pyrone **54**. Introduction of the tiglic acid residue and desilylation completed the synthesis. It is worth mentioning that the conjugated enone C=C bond remained intact during the RCM reaction. This could be due to electronic deactivation of this C=C bond by the carbonyl group, or to preference for six-membered ring formation or, indeed, to both factors working together.

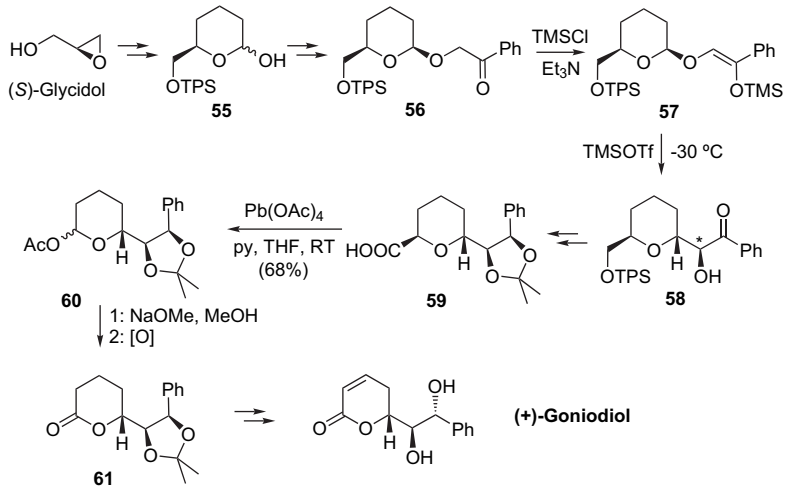


Scheme 9. Synthesis of (+)-phomopsolide C from L-tartaric and L-lactic acid.

3.1.3. Chiral epoxides. Several chiral epoxides are commercially available, with perhaps (+)- or (−)-glycidol and their *O*-substituted derivatives being those most frequently employed.[34] Other epoxides can be easily prepared from commercial precursors by means of various methodologies (see also Section 3.2.1).[35] Chiral epoxides have often served as starting materials for the synthesis of natural products, including 5,6-dihydropyran-2-ones. In fact, (*S*)-(−)-glycidol was the starting material in a synthesis of (+)-goniodiol by Ley and co-workers,[15ba] even though its single stereogenic carbon was not incorporated as such in the structure of the final product (Scheme 10). Conversion of (*S*)-(−)-glycidol into cyclic hemiacetal **55** through standard reactions was followed by stereoselective O-alkylation of the anomeric hydroxyl to give ketone **56**. Treatment of the corresponding enol silyl ether **57** with the Lewis acid, TMSOTf, caused oxygen-to-carbon rearrangement of the tetrahydropyranyl moiety to afford α-hydroxy ketone **58** as a 1:1 mixture with its epimer at the starred carbon (the undesired stereoisomer was recycled to **58** via Mitsunobu inversion of the hydroxyl group). The reaction most likely involves silylation of the exocyclic acetal oxygen followed by C–O bond cleavage and attack of the resulting oxocarbenium ion on the less substituted sp^2 carbon atom of the bis-silylated enediol segment thus generated. Importantly, the attack of the oxocarbenium ion took place from its less crowded face, namely that opposite to the bulky CH_2OTPS moiety, thus controlling the configuration of the other stereogenic carbon situated in the



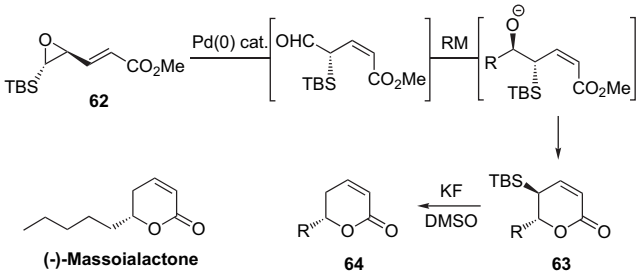
Scheme 8. Synthesis of (+)-boronolide from D-tartaric acid.



Scheme 10. Synthesis of (+)-goniodiol from (*S*)-(−)-glycidol.

tetrahydropyran ring. The enediol C=C bond, however, showed no diastereofacial preference and a mixture of diastereoisomers was formed, as commented above. Stereoselective reduction of the ketone function, protection of the two hydroxyl functions, desilylation, and oxidation converted **58** into acid **59**. Oxidative degradation of the carboxy group to an acetoxy moiety converts acid **59** into glycoside ester **60**, with parallel destruction of the stereogenic carbon originally present in the chiral precursor. Saponification of the acetate group in **60** and oxidation of the resulting lactol provided lactone **61**, which was finally transformed into the desired compound via α,β-dehydrogenation (with the aid of selenium chemistry) and acetonide cleavage.

Malacria and co-workers used the chiral silyloxirane **62** in a novel methodology for the synthesis of 6-substituted 5-silyl-5,6-dihydropyran-2-ones.[13bg,36] Thus, treatment of **62** with a Pd(0) catalyst caused a stereospecific rearrangement via a 1,2-silicon shift to an intermediate α-silyl-β,γ-enal, which reacted in situ with a Grignard reagent to yield, after spontaneous lactonization, the silylated pyrone **63** in enantioenriched form. Cleavage of the silyl moiety was performed with KF in DMSO. Several 6-substituted 5,6-dihydropyran-2-ones **64**, among them the naturally occurring (−)-massoialactone, were prepared with the aid of this method (Scheme 11). As can be seen in the scheme, the two stereogenic carbons of the chiral epoxide precursor do not appear as such in the target lactone. The single one that remains in the final pyrone ring is actually formed by means of internal induction in the organometallic addition step.

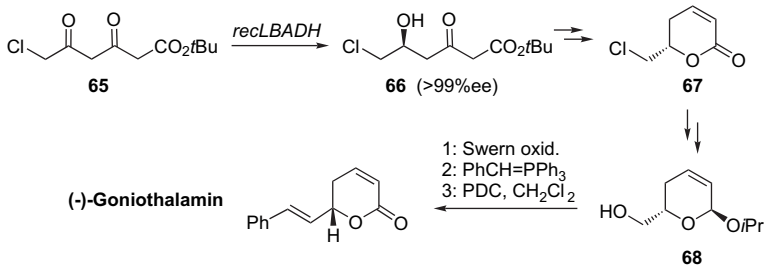


Scheme 11. Synthesis of (−)-massoialactone from a chiral, silylated epoxide.

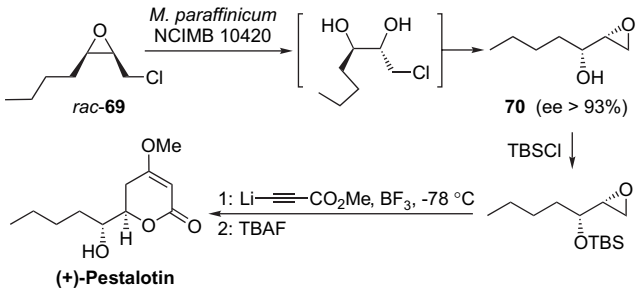
3.1.4. Other chirons. In addition to the previously mentioned chirons, albeit with less frequency, a wide structural variety of other chiral precursors have been used in the synthesis of natural 5,6-dihydropyrones. Many have been prepared with the aid of enzymes or whole microorganisms. For example, the recombinant enzyme *recLBADH* was used in an efficient enantioselective reduction of β,δ-diketoester **65** to yield the δ-hydroxy-β-ketoester **66** with very high enantiomeric purity (ee>99%).[13be,15am,37] Functional modifications transformed the latter compound into **67** and then **68**. Oxidation of the primary alcohol to aldehyde, Wittig olefination, and oxidation afforded (−)-goniothalamin, the enantiomer of the natural pyrone (Scheme 12). The single stereogenic carbon in the final product is that originated in the enzymatic reduction step.

A different type of biocatalytic reaction was used in one of the syntheses of (+)-pestalotin, the enantiomer of the natural pyrone.[13bk] Racemic epoxide **69** was first prepared by chemical means and then subjected to the epoxide hydrolase activity of resting cells of *Mycobacterium paraffinicum* NCIMB 10420. This gave the optically active epoxide **70** (ee>93%), formed through initial epoxide hydrolysis and subsequent dehydrochlorination of the intermediate chlorhydrin (Scheme 13). Protection of the hydroxyl group and epoxide opening with methyl 3-lithiopropiolate gave a monoprotected δ,ε-dihydroxy-α,β-ynoate, which, after desilylation, underwent methanol addition and spontaneous lactonization to afford the final product. Thus, the two stereogenic carbons of the chiral precursor are retained in the target molecule, one of them within the pyrone ring.

A further example of the preparation of chiral precursors by biocatalytic means is the enantiopure cyclic diol **71** (Scheme 14), available in kilogram quantities through microbial hydroxylation of naphthalene.[38] This chiral precursor was used by Banwell and co-workers in a synthesis of (+)-goniodiol.[17n] Diol protection in the form of acetonide and oxidative C=C bond cleavage afforded the bis-primary diol **72**. Selective elimination of the aromatic hydroxymethyl group was achieved by means of benzylic alcohol oxidation to the aldehyde and rhodium-catalyzed decarbonylation. Oxidation of the resulting alcohol **73** to the aldehyde and subsequent



Scheme 12. Synthesis of (−)-goniothalamin from a chiral precursor prepared with the aid of an enzyme.



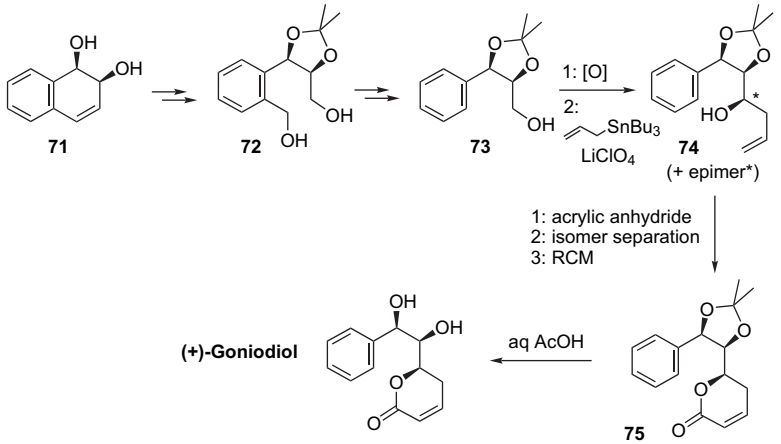
Scheme 13. Synthesis of (+)-pestalotin from a chiral precursor prepared with the aid of a microorganism.

chelation-controlled allylation provided alcohol **74** in admixture with its epimer at the newly formed stereogenic carbon. Acylation of the hydroxyl group with acrylic anhydride followed by RCM gave **75**, the acetonide of (+)-goniodiol, which was then easily converted into the natural lactone (the epimer of **74** was converted in the same way into 6-*epi*-goniodiol). As in the previously discussed cases, the stereogenic carbon within the pyrone ring is not one of those present in the chiral precursor, but is generated under their influence via internal induction during the allylation step.

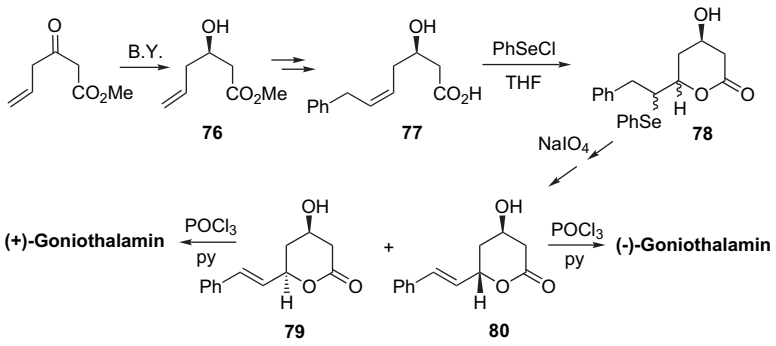
Using a baker's yeast reduction of the corresponding ketoester, Knight and co-workers[24a] obtained the chiral secondary alcohol **76** in enantioenriched form. Protection of the hydroxyl group, ozonolysis of the olefinic bond, Wittig olefination of the resulting aldehyde, ester hydrolysis, and deprotection afforded the olefinic acid **77**. Treatment of the latter with PhSeCl gave rise to the formation of a mixture of two unstable stereoisomeric, selenylated lactones **78** (selenolactonization). Oxidation of the mixture to the corresponding selenoxides with $NaIO_4$ and spontaneous elimination of PhSeOH gave two chromatographically separable 4-hydroxytetrahydropyran-2-ones, **79** and **80**. Dehydration of either of these gave rise to the two antipodes of goniothalamin (Scheme 15). The same chiral precursor was used shortly afterward by the same authors in a synthesis of (−)-massoialactone, in this occasion using an iodolactonization instead of the selenolactonization.[24b]

The chiral cyclopentenone **81**, obtained as shown in Scheme 16 by means of enzymatic resolution of a racemic precursor, has been used by Ogasawara and co-workers in the syntheses of various chiral pyrones, among them was (−)-massoialactone.[20c] Conjugated addition of the cuprate reagent to **81** took place in the trans orientation relative to the bulky cumyl (α-phenylisopropyl) group to yield ketone **82**. Nonselective reduction of the keto group, silylation of the hydroxyl group, hydrogenolytic cleavage of the cumyl group, and oxidation afforded cyclopentanone **83** as a mixture of diastereoisomers. A Baeyer–Villiger reaction furnished pyranone **84** as a stereoisomeric mixture. Treatment with acid caused cleavage of the silyl group and dehydration, thus yielding the target dihydropyrone. The single stereocenter in the final product originates during the cuprate addition under the influence of the pre-existing stereocenter, which disappears in a later step.

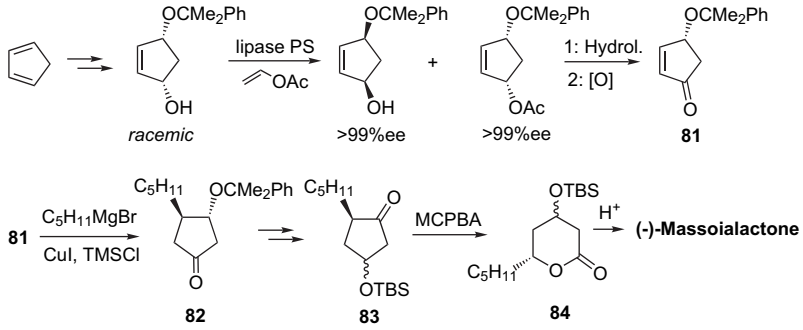
Chiral precursors other than those generated via enzymatic methods have also been used in the synthesis of chiral pyrones. For example, Solladié and Gressot-Kempf carried out a synthesis of tarchonanthus lactone starting from the easily available β,δ-diketosulfoxide **85** as the only chirality



Scheme 14. Synthesis of (+)-goniodiol from a chiral precursor prepared with the aid of a microorganism.



Scheme 15. Synthesis of (+)- and (−)-goniothalamin from a chiral precursor prepared with the aid of a microorganism.



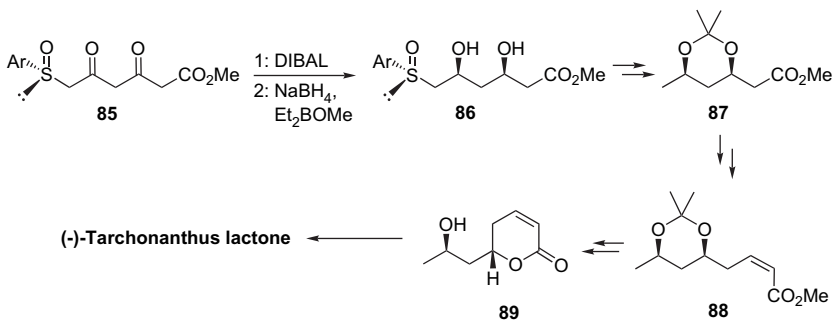
Scheme 16. Synthesis of (−)-massoialactone from a chiral precursor prepared with the aid of an enzyme.

source (Scheme 17).[13ao] Treatment of **85** with DIBAL causes regio- and stereoselective reduction of the proximal carbonyl group; *syn*-selective reduction of the resulting β-hydroxy-δ-ketosulfoxide with $NaBH_4/Et_2BOMe$ afforded β,δ-dihydroxy sulfoxide **86**. Subsequent diol protection as the acetonide and reductive desulfurization with Raney nickel gave ester **87**, which was then reduced to the corresponding aldehyde. *Z*-selective olefination of the latter using the Still–Gennari procedure furnished the α,β-enoate **88**, which was converted into pyranone **89** by means of acetonide hydrolysis and lactone ring closure. Attachment of the dihydrocaffeoyl residue completed the synthesis (see also Scheme 7).

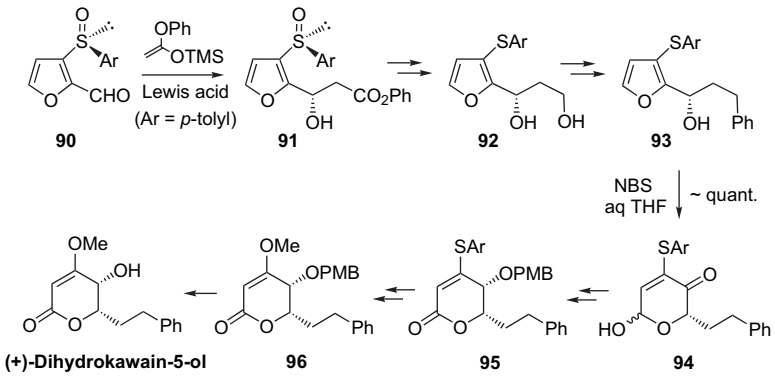
A chiral sulfoxide was also the starting material in Arai's synthesis of the bioactive pyrone, (+)-dihydrokawain-5-ol (Scheme 18).[15ag] Thus, a Mukaiyama-type aldol reaction of chiral sulfoxide **90** with the enol silyl ether of phenyl acetate stereoselectively provided the β-hydroxy ester **91**. Stepwise reduction of the ester and sulfinyl groups gave the diol **92**, which was selectively monotosylated at the primary alcohol. Coupling of the monotosylate with lithium diphenylcuprate afforded furan **93**, which was subsequently subjected to an Achmatowicz ring expansion[32] to give lactol **94**. Conversion of **94** into pyrone **95** was carried out through a sequence of steps involving acetal protection, stereoselective ketone reduction, hydroxyl protection, and oxidation. A subsequent oxidation of the thioether to sulfone was followed by treatment with basic methanol, which caused the replacement of the sulfinate by a methoxy group by means of a conjugate addition–elimination mechanism, with the formation of **96**. Cleavage of the PMB protecting group furnished the desired pyrone.

3.2. Asymmetric (enantioselective) reactions

A number of chiral 5,6-dihydropyran-2-ones and tetrahydropyran-2-ones have been prepared from key intermediates generated through an asymmetric reaction belonging to one of the following types:



Scheme 17. Synthesis of (−)-tarchonanthus lactone from a chiral sulfoxide.



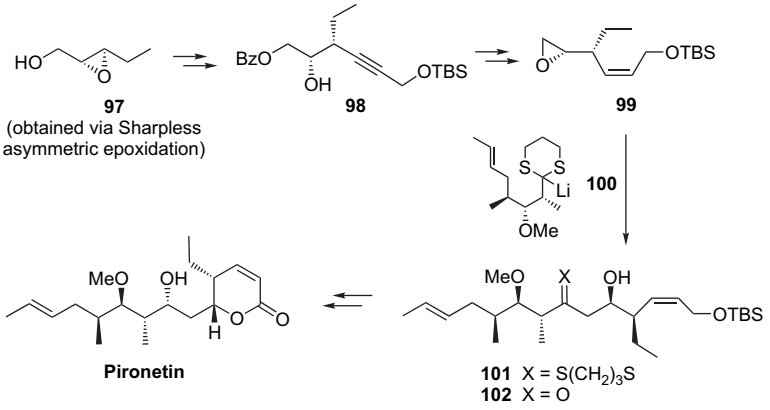
Scheme 18. Synthesis of (+)-dihydrokawain-5-ol from a chiral sulfoxide.

(a) Sharpless epoxidations or dihydroxylations,[13n,aq,at,ax,ay,bl,bo–bq,by,ca,cc,15g,h,r,u,v,aa,ad,af,ah,al,an,ao,aq,as,au,17g,al,an,ap,39]
(b) aldol-type reactions,[13au,az,bb,bc,bm,bx,cd,17k]
(c) allylations,[17a–c,e,f,h,j,m,p,q,s,t,u,x,y,aa,ab,ad,ae,af,ag,ao,aq] and
(d) other methods (including cycloadditions, see Section 2.4).[13g,aa,ah,an,bf,bn,bw,ce,cf,cj,15ai,av,ax,17w,aj,am,27a–c,28e,29]

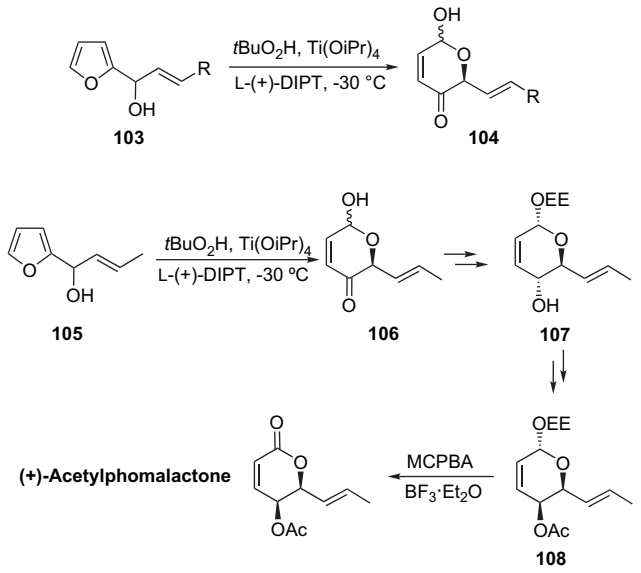
3.2.1. Asymmetric Sharpless epoxidations or dihydroxylations. The Sharpless epoxidations are commonly used in the synthesis of enantiopure 5,6-dihydropyrones, both in the direct mode, which involve the conversion of a prochiral olefin into an enantioenriched epoxide, and in the kinetic resolution mode, in which the selective epoxidation of one of the enantiomers in a racemic olefin is carried out. For example, the chiral epoxide **97**, obtained by means of an asymmetric Sharpless epoxidation, played a key role in Kitahara's synthesis of (−)-pironetin (Scheme 19). Protection of the hydroxyl group and regioselective epoxide opening with lithiated, *O*-protected propargyl alcohol afforded the secondary alcohol **98**, which was subsequently converted into the epoxide **99** through standard reactions. Epoxide ring opening with the lithiated dithiane **100** afforded the thioketal **101**, subsequently converted into the ketone **102**. Stereoselective reduction of the carbonyl group in the latter, followed by oxidative manipulation of the protected primary alcohol, led to the desired molecule. In this case, the two stereocenters within the pyrone ring are directly derived from the starting epoxide.[15ad]

The kinetic resolution of racemic allyl alcohols via Sharpless asymmetric epoxidation has often been used in the synthesis of chiral pyrones. When associated with the Achmatowicz-type oxidative ring expansion of furan rings,[32] this provides an effective route to enantioenriched 2-substituted 6-hydroxypyran-3-ones. Thus, when racemic furylcarbinols of general structure **103** are subjected to the conditions of the Sharpless asymmetric epoxidation, pyran-3-ones **104** are obtained with various degrees of optical purity (Scheme 20). These can be later converted into 5,6-dihydropyran-2-ones by means of standard functional manipulations. This strategy has been used by several researchers for the synthesis of this type of naturally occurring molecules. For example, Honda's synthesis of (+)-acetylphomalactone started with carbinol **105** (**103**, R=Me), which was converted into pyrone **106** (**104**, R=Me) in accordance with the aforementioned method. Hydroxyl protection, isomer separation, and stereoselective carbonyl reduction provided alcohol **107**, which was converted into ester **108** using the Mitsunobu protocol. Oxidation of **108** with MCPBA/BF_3[14] gave the target pyrone.[15g,h] A similar strategy has been used by Pan and co-workers in the syntheses of (+)-goniothalamin and other structurally related pyrones from **103** (R=Ph).[15an,ao,as]

The combination of a direct Sharpless asymmetric epoxidation with a non-asymmetric oxidative ring expansion under Sharpless conditions was used by Zhou and Yang in a synthesis of (+)-goniotriol (Scheme 21).[15v] Epoxide **109**, obtained by means of Sharpless asymmetric epoxidation of cinnamyl alcohol, was converted into aldehyde **110** via a series of standard reactions. Addition of 2-furyllithium to **110** took place with high diastereoselectivity (dr∼30:1) to yield alcohol

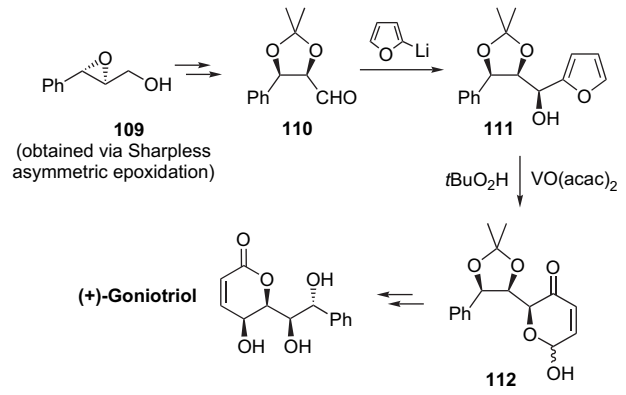


Scheme 19. Synthesis of (−)-pironetin by means of an asymmetric Sharpless epoxidation.



Scheme 20. Synthesis of (+)-acetylphomalactone by means of a kinetic resolution via asymmetric Sharpless epoxidation.

111. Oxidative ring expansion of the latter gave pyrone **112**, which was then subjected to lactol–lactone oxidation, stereoselective reduction of the keto carbonyl group, and acetonide cleavage to afford (+)-goniotriol. This synthesis bears some resemblance to Honda's synthesis of the same molecule (Scheme 5). In the present case, however, the two stereogenic centers in the chiral precursor epoxide ended up in the side chain. Those situated in the pyrone ring were generated via internal induction by the former.

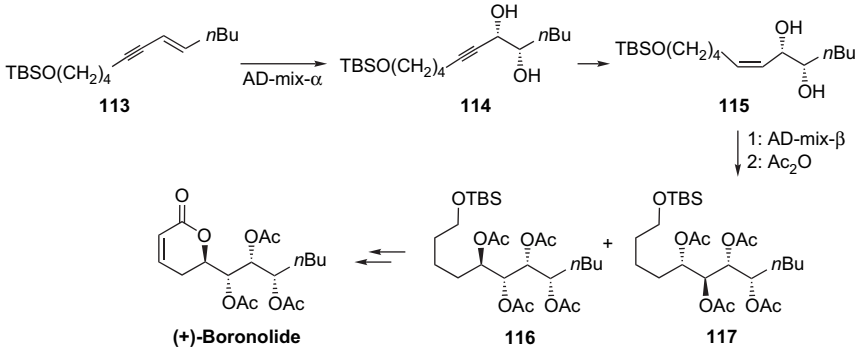


Scheme 21. Synthesis of (+)-goniotriol by means of an asymmetric Sharpless epoxidation.

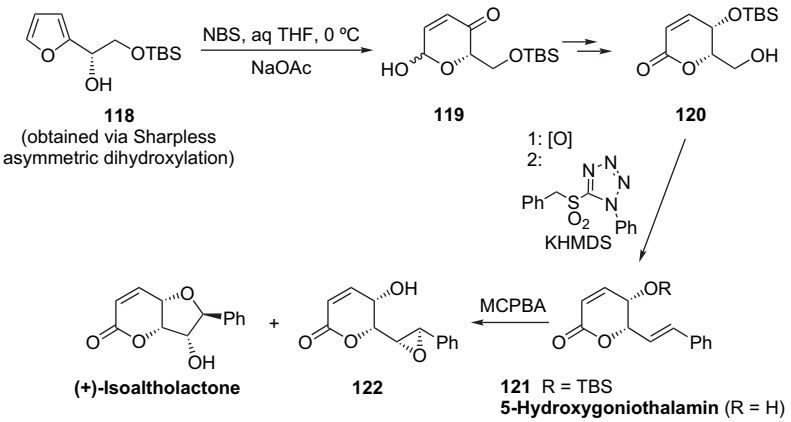
In addition to the asymmetric epoxidation, the Sharpless asymmetric dihydroxylation is also commonly used in the synthesis of chiral 5,6-dihydropyrones. Honda and coworkers used this reaction as the only chirality source in a synthesis of (+)-boronolide (Scheme 22).[13aq] Thus, dihydroxylation of enyne **113** with AD-mix-α gave diol **114** with high yield and optical purity (94% ee). After conversion into the *Z* olefin **115**, another Sharpless dihydroxylation with AD-mix-β generated a ~2:1 mixture of diastereomeric tetraols, which were then separated as their acetylated derivatives **116** and **117**. The former was converted into (+)-boronolide via desilylation, oxidation of the primary alcohol to acid, saponification, lactonization, reacetylation, and dehydrogenation with the aid of selenium chemistry.

The Sharpless asymmetric dihydroxylation was used by O'Doherty's group in the synthesis of several natural and non-natural styryl lactones.[15ah,al] The monoprotected furan diol **118** (Scheme 23), prepared with the aid of this methodology, was converted via an Achmatowicz reaction[32] into pyran-3-one **119**, subsequently transformed into primary alcohol **120** by means of standard functional manipulations. Oxidation of the latter to the aldehyde and subsequent olefination gave pyrone **121**, which yielded 5-hydroxygoniothalamin upon desilylation. Epoxidation of this lactone gave a 1:1 mixture of epoxide **122** and (+)-isoaltholactone. The latter was formed from **122** through internal 5-*endo*-tet nucleophilic attack of the hydroxyl group on one of the epoxidic carbon atoms; in fact, **122** was converted into isoaltholactone by means of acid treatment. Noteworthy in these syntheses is the fact that the stereogenic carbon of the chiral precursor is eventually incorporated into the pyrone ring. The same group has also used the Sharpless asymmetric dihydroxylation more recently for the synthesis of further chiral 5,6-dihydropyran-2-ones.[13bo,bp,15aq,au,av,17al]

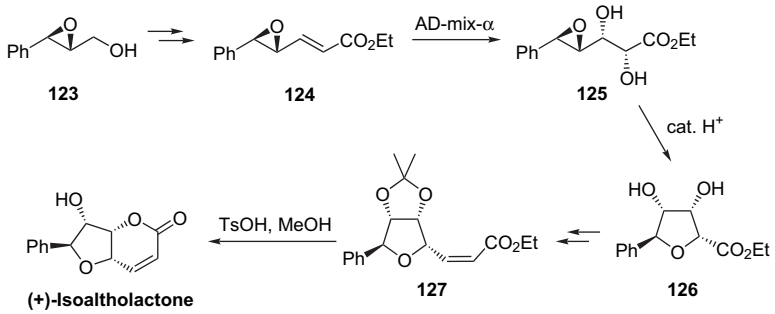
The combination of a Sharpless asymmetric epoxidation with an asymmetric dihydroxylation provided the required chirality source in a recent synthesis of (+)-isoaltholactone (Scheme 24).[13ca] Epoxide **123** (the enantiomer of epoxide **109**, mentioned above) was converted into conjugated ester **124** with the aid of standard reactions. Sharpless dihydroxylation of the latter took place with good diastereoselectivity (dr 20:1) to yield diol **125**. Treatment of this diol with camphorsulfonic acid gave rise to intramolecular 5-*endo*-tet nucleophilic attack of one of the hydroxyl groups on the benzylic epoxide carbon, which resulted in the formation of tetrahydrofuran **126**. Acetonide formation, reduction of



Scheme 22. Synthesis of (+)-boronolide by means of asymmetric Sharpless dihydroxylations.



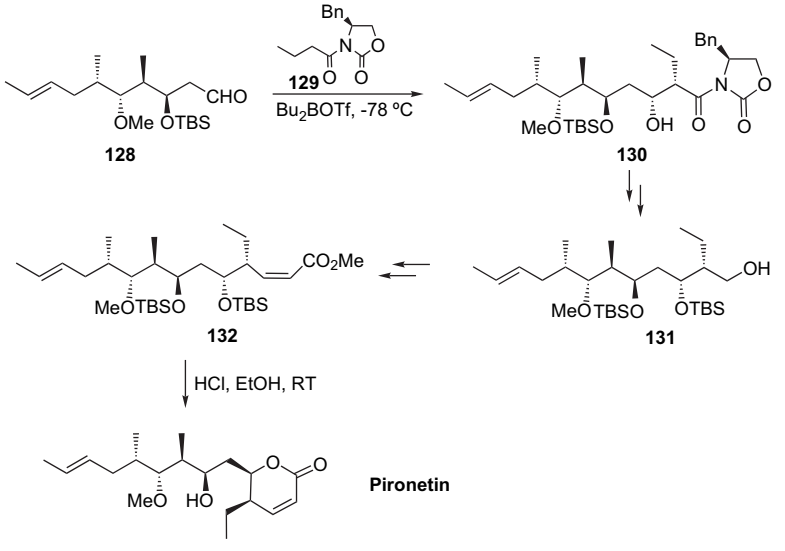
Scheme 23. Synthesis of two styryl lactones by means of an asymmetric Sharpless dihydroxylation.



Scheme 24. Synthesis of (+)-isoaltholactone by means of a combination of an asymmetric Sharpless epoxidation and a dihydroxylation.

the ester to aldehyde, and *Z*-selective Wittig olefination afforded the conjugated enoate **127**. Treatment of the latter with acidic methanol caused acetonide opening and lactonization to give (+)-isoaltholactone.

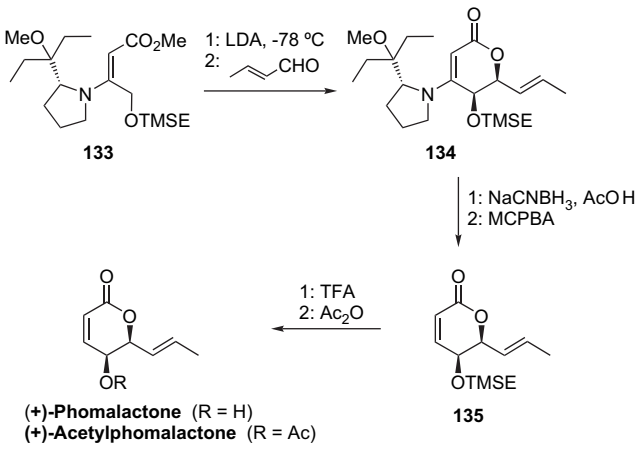
3.2.2. Asymmetric aldol-type reactions. Several syntheses of naturally occurring 5,6-dihydropyran-2-ones have been carried out in which at least a few of the stereocenters were created in an aldol reaction. We will now focus our attention on the syntheses in which the aldol reaction is responsible for the formation of the stereogenic centers in the pyrone ring. There are two main types of asymmetric aldol reactions: those involving a disposable chiral auxiliary and those induced by a chiral catalyst. Both types are represented here. Gurjar's synthesis of (−)-pironetin[13au] belongs to the first type (Scheme 25). Aldehyde **128**, prepared from the commercially available, methyl (*S*)-3-hydroxy-2-methylpropionate, was allowed to react with the boron enolate



Scheme 25. Synthesis of (−)-pironetin by means of an asymmetric aldol reaction.

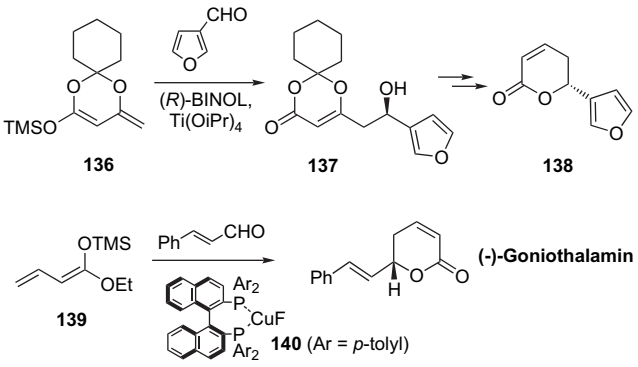
generated from Evans oxazolidinone **129** and di-*n*-butylboryl triflate.[40] This stereoselectively provided aldol **130**, which was then silylated and reduced to the primary alcohol **131**. Oxidation of the latter to the aldehyde and *Z*-selective HWE olefination furnished the conjugated enoate **132**. Treatment of this compound with acidic ethanol led to desilylation and lactonization to yield the desired molecule.

Schlessinger's synthesis of (+)-phomalactone and other related pyrones also belongs to the first type[13az] and involves the use of chiral β-amino esters (vinylogous urethanes) such as **133** (Scheme 26). Thus, the lithium enolate of **133** reacts with achiral aldehydes (in this case, crotonaldehyde) to furnish 6-substituted 5-alkoxy-5,6-dihydropyran-2-ones such as **134**. Both the enantio- (99% ee) and the diastereoselectivity (dr 99:1) are excellent. Reductive cleavage of the chiral auxiliary to pyrone **135** is followed by cleavage of the TMSE group to yield first (+)-phomalactone and then, after acetylation, (+)-acetyl-phomalactone. Obviously, the two stereocenters in the ring originate during the aldol reaction.



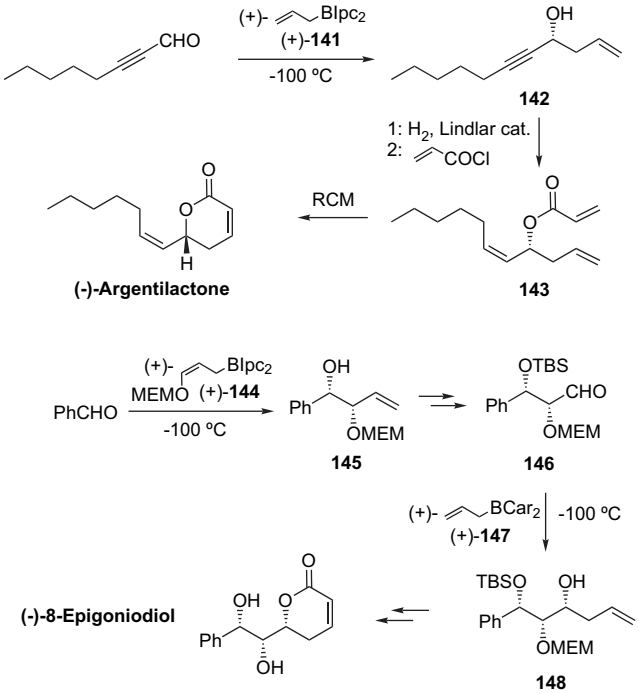
Scheme 26. Synthesis of (+)-phomalactone and its acetate by means of an asymmetric aldol reaction.

Asymmetric aldol reactions involving chiral catalysts are scarcely represented in the literature as regards their application to the synthesis of chiral 5,6-dihydropyran-2-ones. The few cases published to date correspond to aldol reactions of the vinylogous Mukaiyama type. For example, Scettri and co-workers[13bb,bc,41] reported the aldol reaction of silyloxydiene **136** with furan-3-carbaldehyde in the presence of the axially chiral catalyst, (*R*)-(+)-BINOL (Scheme 27). The aldol adduct **137** (87% ee) was then converted into pyranone **138** in just a few steps. Nevertheless, the method does not seem to have been applied as yet to the synthesis of natural 5,6-dihydropyran-2-ones. More recently, Campagne's group has described another type of catalytic, vinylogous Mukaiyama aldol reaction in which dienolate **139** reacts with achiral aldehydes under the influence of axially chiral copper complexes such as **140**. This method directly yields 6-substituted 5,6-dihydropyran-2-ones.[13bi,42] In the case of cinnamaldehyde, this procedure gave (−)-goniothalamin, the enantiomer of the natural product, in 65% yield and with 60% ee.



Scheme 27. Synthesis of pyrones by means of asymmetric, catalytic aldol reactions.

3.2.3. Asymmetric allylations. Syntheses of naturally occurring 5,6-dihydropyran-2-ones in which the stereogenic centers in the pyrone ring have been created with the aid of an asymmetric allylation are numerous. In most cases, the allylation reaction is followed by acylation of the homoallylic hydroxyl group with acryloyl chloride or a similar unsaturated acylating reagent and then an RCM of the resulting ester to yield the desired 5,6-dihydropyran-2-one ring. Brown's synthesis of (−)-argentilactone[17b] represents one of the first reported examples of this methodology (Scheme 28). Allylation of 2-octynal with the chiral allylborane reagent (+)-**141** afforded the propargylic alcohol **142** with high enantioselectivity. Lindlar semihydrogenation of the C≡C bond and acylation with acryloyl chloride gave the ester **143**, which was then subjected to RCM to yield (−)-argentilactone. Ramachandran and co-workers continued to use this strategy in the following years, applying it to the synthesis of numerous natural dihydropyran-2-ones. A relevant example is their synthesis of (−)-8-epigoniodiol, an epimer of the natural product, in which all three

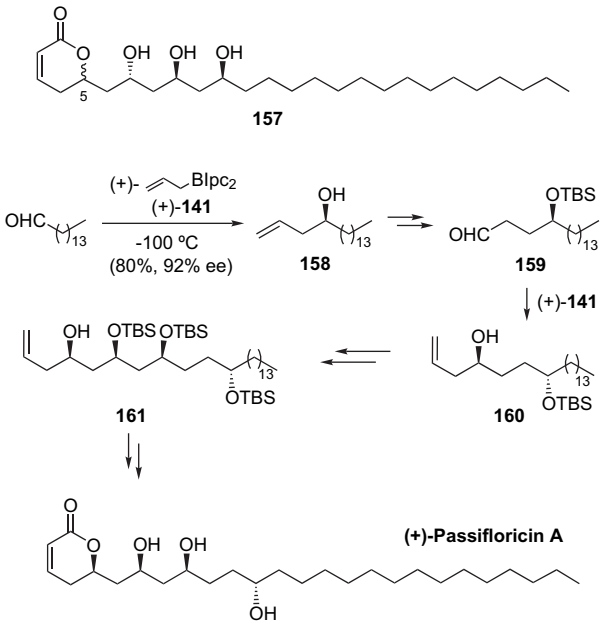


Scheme 28. Synthesis of (−)-argentilactone and (−)-8-epigoniodiol by means of asymmetric allylations.

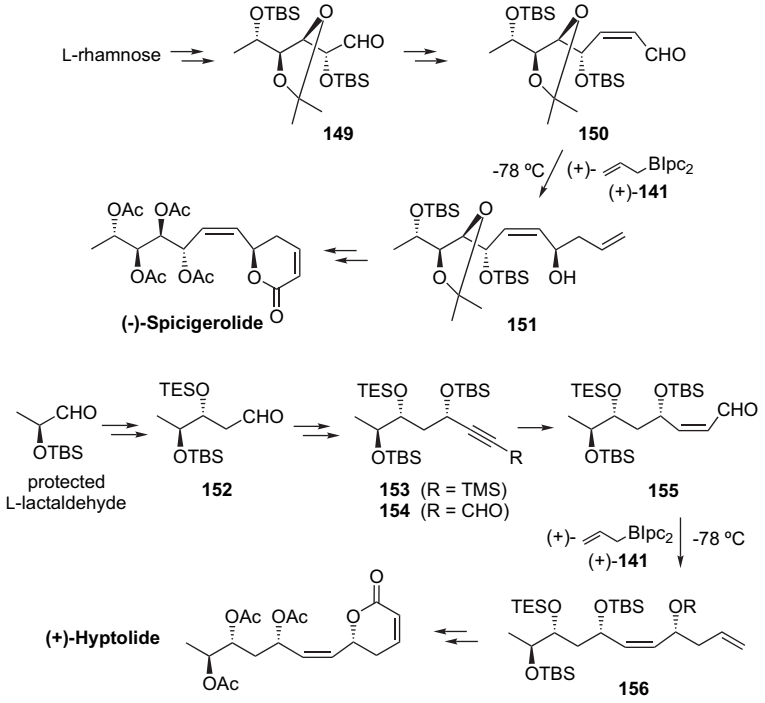
stereocenters were created with the aid of asymmetric allylations (Scheme 28).[17h] Thus, reaction of benzaldehyde with the chiral allylborane **144** provided homoallyl alcohol **145** in good yield and with high enantiopurity (98% ee). Conversion of the latter in two steps into aldehyde **146** was followed by a second asymmetric allylation with the chiral allylborane **147** to yield alcohol **148**. The latter was transformed into (−)-8-epigoniodiol through the standard sequence of O-acryloylation, RCM, and protecting group cleavage.

Our group has made several contributions to this field. For instance, we were able to obtain the cytotoxic lactone (−)-spicigerolide using the asymmetric allylation of aldehyde **150** with chiral allylborane (+)-**141** to give the homoallyl alcohol **151** (dr 88:12). After undergoing the sequence of O-acryloylation, RCM, cleavage of all protecting groups, and acetylation, the target molecule was obtained.[17s] Aldehyde **150** itself was obtained from L-rhamnose via aldehyde **149** through a series of straightforward transformations (Scheme 29). Another relevant example is our synthesis of (+)-hyptolide.[17ab] Aldehyde **152**, which was obtained from L-lactic acid through a protected L-lactaldehyde, was converted into alkynylsilane **153** by means of Carreira's asymmetric ethynylation procedure,[43] followed by hydroxyl protection. Standard methods were used to convert **153** into conjugated ynal **154**, which was then semihydrogenated to *Z*-enal **155** with Lindlar's catalyst. Subsequent asymmetric allylation with allylborane (+)-**141** provided homoallyl alcohol **156** as a single stereoisomer, which was then transformed into (+)-hyptolide using the same methodology as above. It is evident that, in these two syntheses, the single stereocenter in the pyrone ring is created during the allylation step.

Another of our contributions is the synthesis of (+)-passifloricin A, an antiprotozoal lactone isolated from the resin of *Passiflora foetida* var. *hispida*.[44] The compound was first reported to have structure **157**, with either of the two epimers at C-5 (Scheme 30), but subsequent synthesis called this into question.[45] Further synthetic work by our group[17ae] showed that the actual structure is that shown in the lower part of Scheme 30. As can be seen in the scheme, *n*-pentadecanal was subjected to asymmetric allylation with the chiral allylborane (+)-**141** to yield homoallyl alcohol **158** in 80% chemical yield and with 92% ee. Hydroxyl protection and hydroboration–oxidation gave aldehyde **159**, allylation of



Scheme 30. Synthesis of (+)-passifloricin A by means of asymmetric allylations.



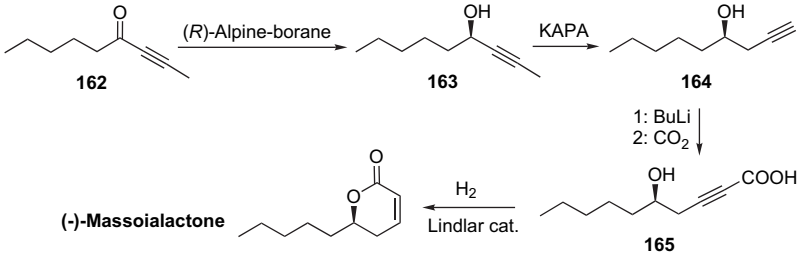
Scheme 29. Synthesis of (−)-spicigerolide and (+)-hyptolide by means of asymmetric allylations.

which with (+)-**141** provided homoallyl alcohol **160**. Hydroxyl protection and oxidative cleavage of the C=C bond gave an aldehyde, which was subjected to asymmetric allylation to yield a homoallylic alcohol. Iteration of this strategy gave homoallyl alcohol **161**, which was subjected to the known sequence of O-acryloylation, RCM, and protecting-group cleavage. This gave a product identical to natural passifloricin A in all its spectral properties. Seven other isomers of this structure were also synthesized in order to corroborate the structural assignment. In each of these syntheses, the stereocenters were all created with the aid of asymmetric allylations. It should be noted that the enantiomer of the natural product has very recently been synthesized with a different methodology.[17aq]

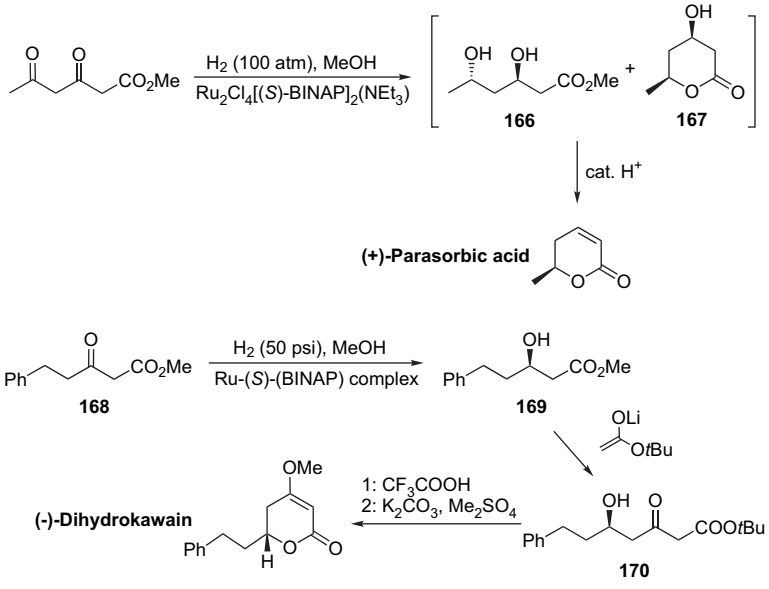
3.2.4. Other methods. In this Section, we will discuss other various types of asymmetric reactions, which have been used for the synthesis of 5,6-dihydropyran-2-ones in enantioenriched form. Only those asymmetric methods that directly lead to the creation of stereocenters in the pyrone ring will be considered.

3.2.4.1. Asymmetric carbonyl reductions. An enantioselective synthesis of (−)-massoialactone by Midland and co-workers[13g] was based on the asymmetric reduction of propargyl ketone **162** with Alpine-borane, a reagent available in both antipodal forms. The resulting propargyl alcohol **163** was subjected to a C≡C bond shift induced by a strong base to yield the terminal alkyne **164**, which was then converted via ynoic acid **165** into (−)-massoialactone (Scheme 31).

One example of an asymmetric reduction of the catalytic type is the hydrogenation of 3,5-dioxoesters as performed by Saburi and co-workers.[13ah] The chiral catalysts employed were Noyori-type ruthenium complexes with the $Ru_2Cl_4(BINAP)_2(NEt_3)$ structure containing the chiral ligand, (*R*)- or (*S*)-BINAP. This procedure was used by the same authors for the synthesis of several 5,6-dihydropyran-2-ones, among them were (+)- and (−)-parasorbic acid (Scheme 32). Thus, methyl 3,5-dioxohexanoate was reduced under the aforementioned conditions to yield a mixture of the dihydroxy ester **166** and its lactonization product **167**. Treatment of the mixture with an acid catalyst caused both lactonization and dehydration to yield parasorbic acid (the natural *S* isomer in the scheme) with 78% ee. Spino and co-workers[13an] used the related catalytic reduction of a β-oxoester in the synthesis of both enantiomers of dihydrokawain (Scheme 32). Thus, catalytic hydrogenation of **168** gave the β-hydroxy ester **169** in 98% ee. Reaction of the latter with the lithium enolate of *tert*-butyl acetate afforded the δ-hydroxy-β-ketoester **170**. Treatment with trifluoroacetic



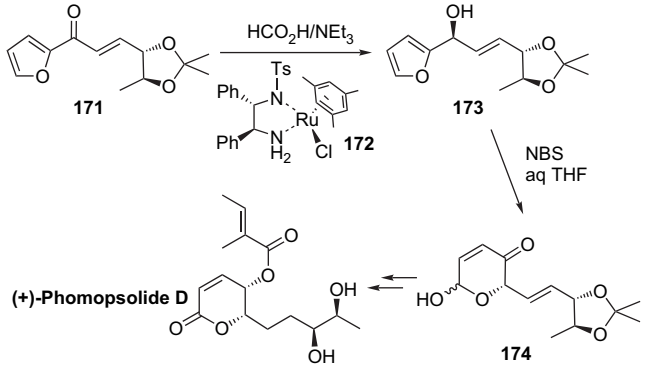
Scheme 31. Synthesis of (−)-massoialactone by means of an asymmetric carbonyl reduction.



Scheme 32. Synthesis of (+)-parasorbic acid and (−)-dihydrokawain by means of catalytic asymmetric reductions.

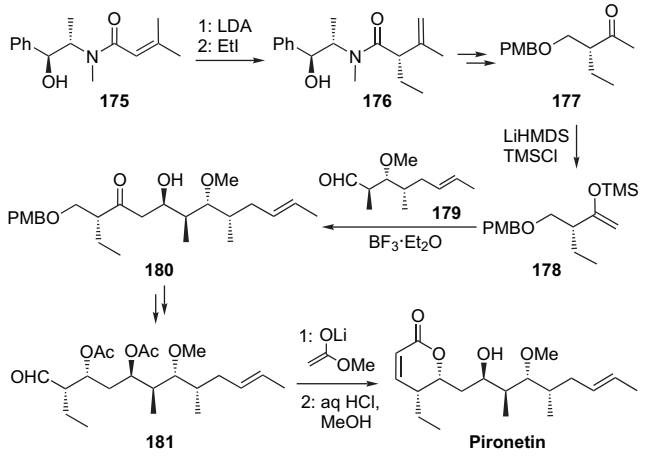
acid caused cleavage of the *tert*-butyl group and in situ lactonization. Subsequent O-methylation furnished (−)-dihydrokawain.

Noyori's catalysts of a different structural type were used by Li and O'Doherty in a synthesis of (+)-phomopsolide D.[15av] Enone **171** (Scheme 33) was prepared from (*E*,*E*)-2,4-hexadienal and furyllithium through a series of steps, which included a Sharpless asymmetric dihydroxylation. Asymmetric reduction of **171** with HCO_2H/NEt_3 in the presence of ruthenium complex **172** afforded furylcarbinol **173** in 95% yield as a single diastereoisomer. The latter was subjected to the conditions of the Achmatowicz reaction[32] to yield pyranone **174**, which was subsequently transformed into phomopsolide D through a sequence of lactol oxidation, stereoselective ketone reduction, attachment of the tiglic acid moiety, and acetonide cleavage. It should be noted that, of the two stereocenters of the ring, one was generated during the asymmetric carbonyl reduction. Moreover, it influenced the formation of the second one in the ketone reduction step.



Scheme 33. Synthesis of (+)-phomopsolide D by means of a catalytic asymmetric reduction.

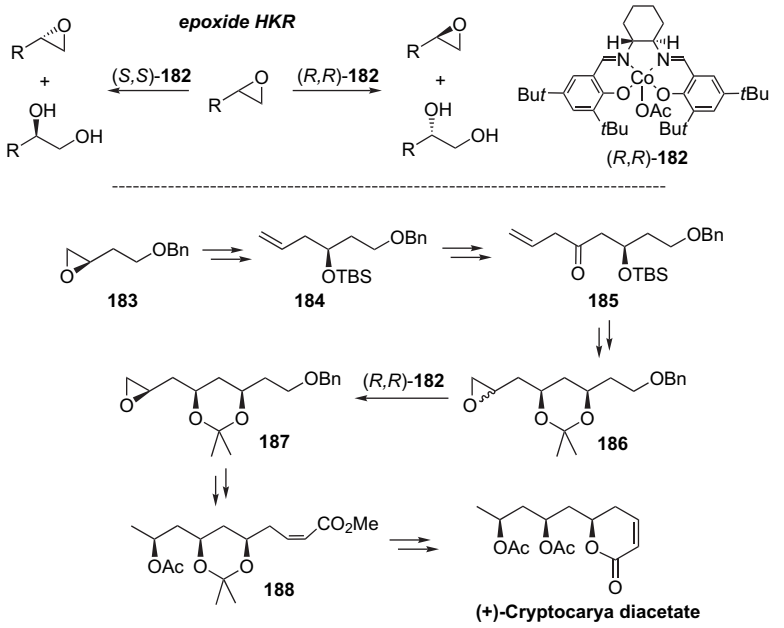
3.2.4.2. Asymmetric alkylations. The use of asymmetric alkylations to control the dihydropyrone ring stereocenters has very rarely been reported. One example is Keck's synthesis of (−)-pironetin (Scheme 34).[13bf] Treatment of the lithium enolate of *N*-senecioyl (+)-pseudoephedrine **175** with ethyl iodide thus afforded amide **176**. Reductive elimination of the chiral auxiliary and functional group manipulations furnished ketone **177**, which was then converted into the corresponding enolsilane **178**. Mukaiyama aldol reaction of the latter with aldehyde **179**, which had been prepared from methyl (*S*)-3-hydroxy-2-methylpropionate, afforded adduct **180**. This was converted into **181** by means of functional manipulations. Reaction of **181** with the lithium enolate of methyl acetate and lactonization in situ led to the formation of a β-acetoxy tetrahydropyranone ring. Acid treatment gave rise to acetic acid elimination and ester hydrolysis, thus forming the target molecule. As can be seen in the scheme, the stereogenic carbon C-5 bearing the ethyl residue is formed during the asymmetric alkylation step.



Scheme 34. Synthesis of (−)-pironetin by means of an asymmetric alkylation.

3.2.4.3. Asymmetric epoxide hydrolysis. The few published syntheses of dihydropyrones using this methodology[13bw,cf,17w,aj,am] rely upon HKR of racemic epoxides with the aid of Jacobsen's chiral cobalt catalysts, as is the case with complex **182** (Scheme 35), which is obtainable in either antipodal form.[46] One example is Krishna's synthesis of (+)-cryptocarya diacetate,[13cf] depicted in the same scheme. Epoxide **183**, obtained in highly enantioenriched form by means of the aforementioned methodology, was converted into **184** through epoxide opening with a vinylcuprate reagent followed by hydroxyl protection. The latter compound was transformed into ketone **185** via ozonolytic cleavage of the C=C bond, allylation of the resulting aldehyde with allylzinc bromide, and oxidation. Desilylation, *syn*-selective carbonyl reduction, acetonide formation, and unselective epoxidation afforded **186** (mixture of diastereomers), which was subjected to a second Jacobsen HKR protocol to yield epoxide **187** (the simultaneously formed 1,2-diol with the opposite configuration at the hydroxyl-bearing center was recycled to **187** through a simple, three-step sequence). Reductive epoxide opening with $LiAlH_4$, followed by a series of steps, which included a *Z*-selective Still–Gennari olefination, furnished the conjugate enoate **188**, which was converted into (+)-cryptocarya diacetate via straightforward reactions. The single stereocenter in the ring has been formed during the first of the two epoxide HKR steps of the synthesis.

3.2.4.4. Asymmetric cycloadditions. There are very few reported syntheses of 5,6-dihydropyran-2-ones, which use asymmetric cycloadditions to create the heterocyclic ring. Most of them belong to the catalytic [4+2] HDA type. The reaction described in one early report by Midland and Graham[27a] is not asymmetric in the strictest sense (i.e., enantioselective), since it is actually the diastereoselective HDA cycloaddition of 1,3-dimethoxy-1-(silyloxy)butadiene **189** (Brassard's diene) to the chiral α-alkoxyaldehyde **190** catalyzed by the achiral Lewis acid $Eu(hfc)_3$. This yielded the adduct **191**, which, after cleavage of the MEM group, gave (−)-pestalotin (Scheme 36). The term enantioselective may, however, be fully applied to Jacobsen's method for the creation of pyrone rings. The HDA reaction of ynal **192** with 1-benzyloxybuta-1,3-diene catalyzed by the chiral chromium(III) complex (*R*,*S*)-**193** afforded dihydropyran **194** with 89% ee. Several functional manipulations converted **194** into **195** and elevated the optical purity to over

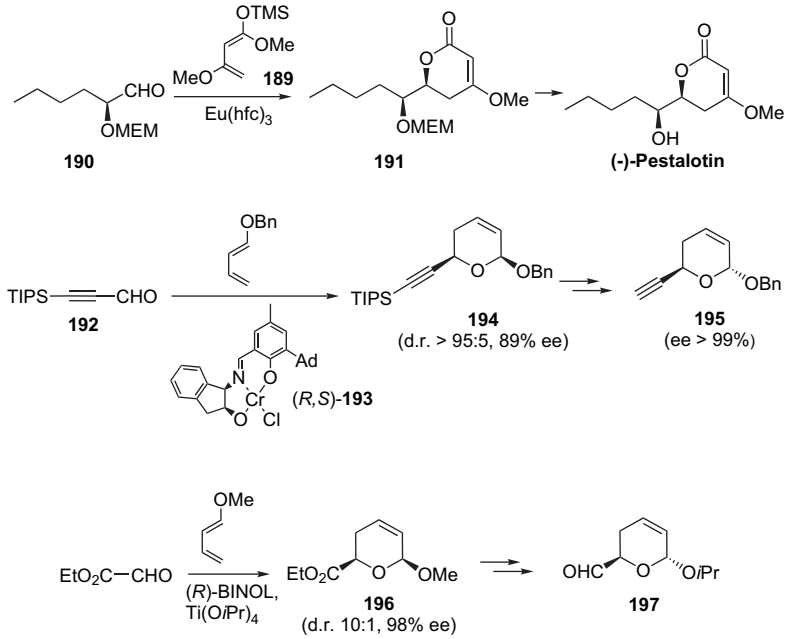


Scheme 35. Synthesis of (+)-cryptocarya diacetate by means of Jacobsen's method of asymmetric epoxide hydrolysis.

99% ee. The latter compound was subsequently used in a synthesis of the antitumor agent, fostriecin.[28d,47] Similar considerations apply to Kalesse's report on the HDA reaction of 1-methoxybuta-1,3-diene with ethyl glyoxylate catalyzed by the chiral complex generated in situ from BINOL (the *R* enantiomer in the scheme) and Ti(O*i*Pr)$_4$. The resulting adduct **196** was converted through standard manipulations into aldehyde **197**, which was subsequently employed in the total syntheses of naturally occurring 5,6-dihydropyran-2-ones such as (+)-goniothalamin,[15ai] ratjadone[4d] and callystatin A.[48]

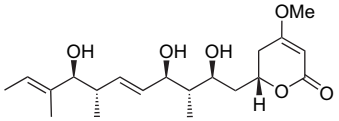
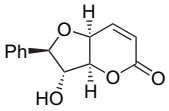
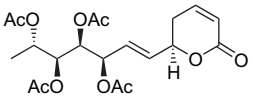
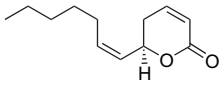
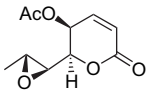
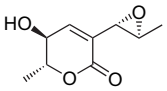
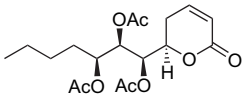
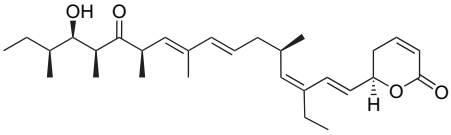
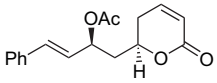
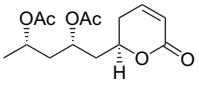
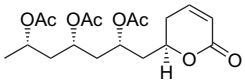
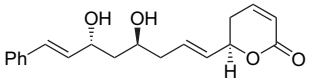
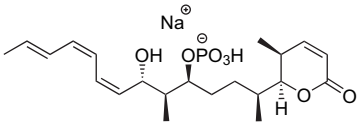
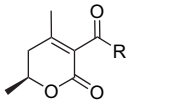
4. Reported syntheses of naturally occurring 5,6-dihydropyran-2-ones

As a final summary, the stereoselective syntheses of naturally occurring 5,6-dihydropyran-2-ones in enantioenriched form that have been reported in the literature to date are listed in Table 1. Only material that has appeared in journals published in English, French, or German has been considered. Research reports, patents, and Ph.D. theses have been omitted. Compounds are indicated in alphabetical order of their trivial names or at the end of the table.



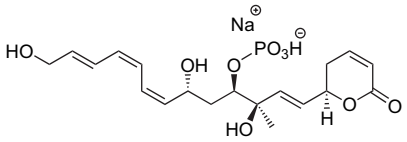
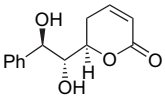
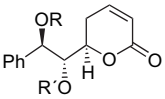
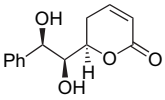
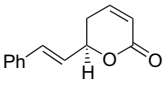
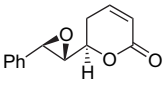
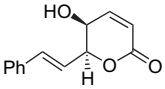
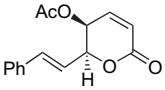
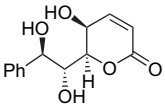
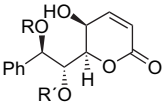
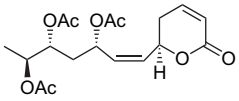
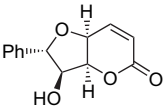
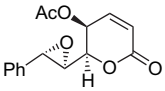
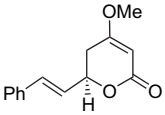
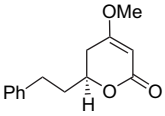
Scheme 36. Synthesis of pyran rings by means of [4+2] cycloadditions.

Table 1. Syntheses of naturally occurring 5,6-dihydropyran-2-ones

Compound name	Structure	Literature citations
ACRL Toxin I 3-*O*-methyl		13w
(+)-Altholactone (goniothalenol)		13m,q,r,s,al,am,bq,ca,15l,q,ab,ac,al,49. For the non-natural (−)-enantiomer, see: 13s,19c.
(+)-Anamarine		13l,17aa,al. See also 13o. For the non-natural (−)-enantiomer, see: 15c,f.
(−)-Argentilactone		13i,p,15n,aj,17b,l,p,t,u. For the non-natural (+)-enantiomer, see: 15ak,am,17u.
(+)-Asperlin		13az,15d,e,j,r,af,19a. See also 19b.
(−)-Aspyrone		15t
(+)-Boronolide		13af,aq,br,bt,15az,17d,j,k,m,an,ap. For deacetyl derivatives, see: 13br.
(−)-Callystatin A		4d,50
(+)-Cryptocarya lactone		13f,ak
(+)-Cryptocarya diacetate		13ba,cf,17g
(+)-Cryptocarya triacetate		13ba,bp,39
(+)-Cryptofolione		28e
(+)-Cytostatin (sodium salt)		10b
(+)-Dictyopyrones A–D	 **A** R = $(H_2C)_8$–CH=CH–CH_3 **B** R = $(H_2C)_{10}$–CH=CH–CH_3 **C** R = $(CH_2)_{10}CH_3$ **D** R = $(CH_2)_{12}CH_3$	8

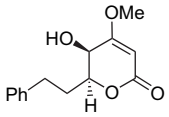
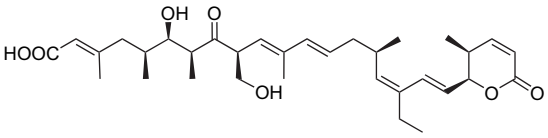
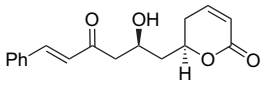
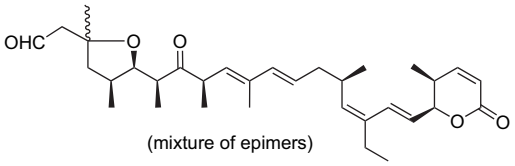
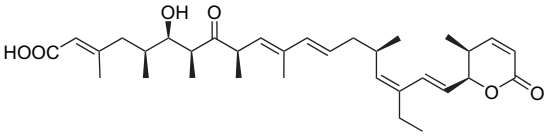
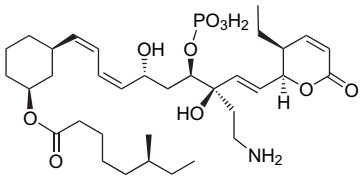
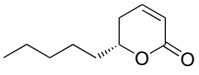
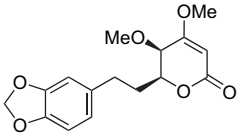
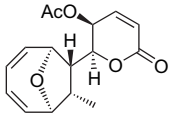
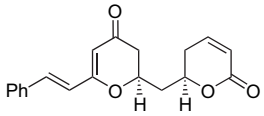
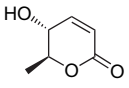
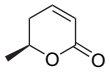
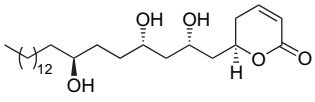
(*continued*)

Table 1. (*continued*)

Compound name	Structure	Literature citations
Fostriecin (sodium salt)		28d,47,51
(+)-Goniodiol		13ar,ax,bl,bw,by,15i,ab,ac,ax,ba,17h,n
Goniodiol, acetylated derivatives	 (R and/or R´ = Ac)	13ar,bl,15u
(−)-Goniodiol, 7-*epi*		13bl,bw,by
(+)-Goniothalamin		13d,i,o,bw,15h,n,ai,an,ao,17c,p,t,v,z,ag,24a,b. For the non-natural (−)-enantiomer, see: 13d,15am,17v,z,24a,b,42.
(+)-Goniothalamin oxide		15an,ao
(+)-Goniothalamin, 5-hydroxy		15ah,al
(+)-Goniothalamin, 5-acetoxy		15ao
(+)-Goniotriol		13am,15l,v,ab,ac,ae. See also 15ap.
Goniotriol, acetylated derivatives	 (R and/or R´ = Ac)	13am,15l,ab,ac,ae
(+)-Hyptolide		17ab
(+)-Isoaltholactone		13q,bq,ca,15ah,al,as
(+)-Isogoniothalamin oxide, 5-acetoxy		15ao
(+)-Kawain		13bx,ci. See also 28c.
(+)-Kawain, dihydro		13an,cb,27b. For the non-natural (−)-enantiomer, see: 13cb.

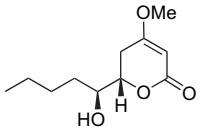
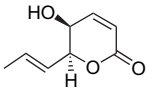
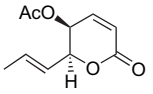
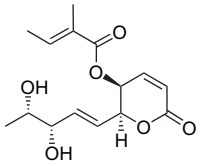
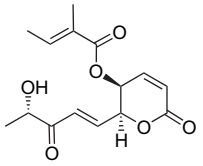
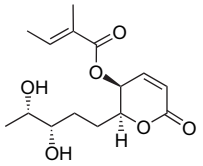
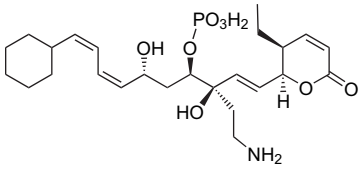
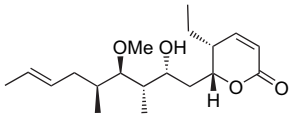
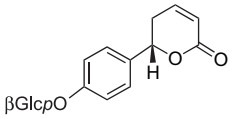
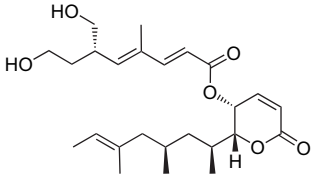
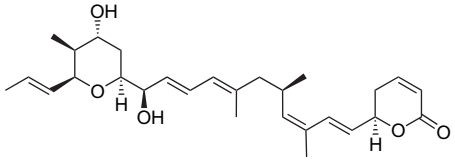
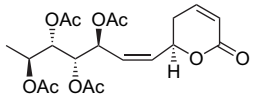
(*continued*)

Table 1. (*continued*)

Compound name	Structure	Literature citations
(+)-Kawain-5-ol, dihydro		13bu,15ag,52
Kazusamycin A		53
(+)-Kurzilactone		13bj. For the non-natural (−)-enantiomer, see: 17am.
Leptofuranin D	 (mixture of epimers)	54
Leptomycin B		4d,50e
Leustroducsin B		55
(−)-Massoialactone		13g,x,y,ac,ad,ai,bg,bs,bv,15k,s,y,17c,w,20a,c, 24b. For the non-natural (+)-enantiomer, see: 13c,ay,bn,bs.
(−)-Methysticin, dihydro, 5-methoxy		56
(+)-Mycoepoxydiene		15aw
(+)-Obolactone		17ao
(−)-Osmundalactone		13k,av,bh,15p,ay,17i,21a
(+)-Parasorbic acid		13j,n,t,x,z,ae,15b,m,o,17c,21a,b. For the non-natural (−)-enantiomer, see: 13ah.
(+)-Passifloricin A		17ae. For the non-natural (−)-enantiomer, see: 17aq.

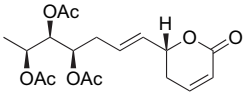
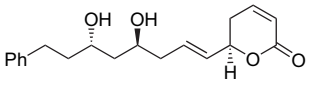
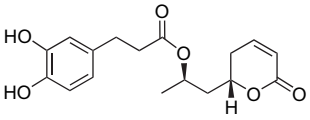
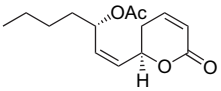
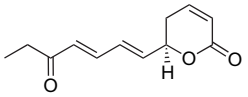
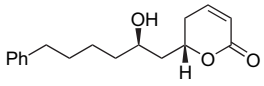
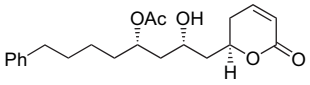
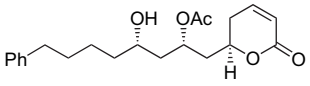
(*continued*)

Table 1. (*continued*)

Compound name	Structure	Literature citations
(−)-Pestalotin (LL-P880α)		13b,h,aa,ag,at,cc,15a,27a. For the non-natural (+)-enantiomer, see: 13h,bk.
(+)-Phomalactone		13az,15e
(+)-Phomalactone acetyl		13as,az,15e,g,h,aa
(+)-Phomopsolide B		13ab,aj
(+)-Phomopsolide C		15aq,17ah
(+)-Phomopsolide D		15av. See also 15au.
Phoslactomycin B		57
(−)-Pironetin (PA-48153C)		13au,bf,cd,cj,15w,z,ad
(−)-Psilotin (βGlc*p*=β-D-glucopyranosyl)		13e
(−)-Rasfonin (TT-1)		13bz
(+)-Ratjadone		4d,48,58
(−)-Spicigerolide		17s

(*continued*)

Table 1. (*continued*)

Compound name	Structure	Literature citations
Synargentolide A		17af (published structure shown to be erroneous).
(+)-Strictifolione		13cg,15ar,17o,q,ac,39
(−)-Tarchonanthus lactone		13u,v,ao,bo,ce,15at,17f,ai,aj,ak
(+)-Umuravumbolide		17e
No trivial name (isolated from *Raimondia monoica*)		Confirmed by means of enantioselective synthesis of the enantiomer 17x.
No trivial name (isolated from *Ravensara crassifolia*)		17y
No trivial name (isolated from *Ravensara anisata*)		13ch. For the non-natural enantiomer, see: 17o,39.
No trivial name (isolated from *Ravensara anisata*)		13ch. For the non-natural enantiomer, see: 17o,39.

Acknowledgements

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References and notes

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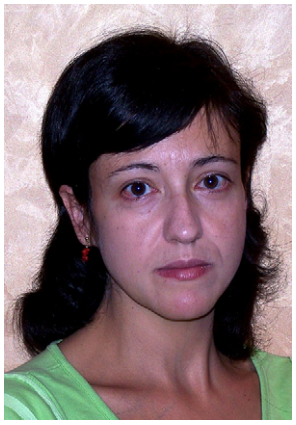

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