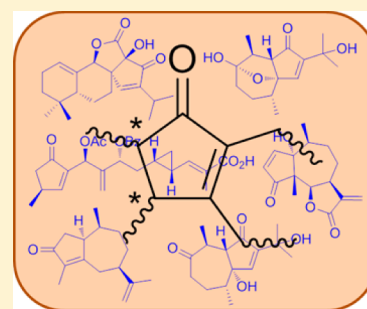


Synthesis of Chiral Cyclopentenones

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ABSTRACT: The cyclopentenone unit is a very powerful synthon for the synthesis of a variety of bioactive target molecules. This is due to the broad diversity of chemical modifications available for the enone structural motif. In particular, chiral cyclopentenones are important precursors in the asymmetric synthesis of target chiral molecules. This Review provides an overview of reported methods for enantioselective and asymmetric syntheses of cyclopentenones, including chemical and enzymatic resolution, asymmetric synthesis via Pauson–Khand reaction, Nazarov cyclization and organocatalyzed reactions, asymmetric functionalization of the existing cyclopentenone unit, and functionalization of chiral building blocks.



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1. INTRODUCTION

Cyclic and acyclic enones are powerful building blocks in total synthesis due to the broad diversity of possible functionalizations at the enone motif. Available transformations include 1,2-addition either at the carbonyl or olefin, 1,4-addition, and allylic and α -carbonyl functionalizations. Chiral cyclopentenones are key intermediates in asymmetric synthesis, and the cyclopentenone ring itself is present in highly functionalized, important chiral bioactive compounds. Examples include

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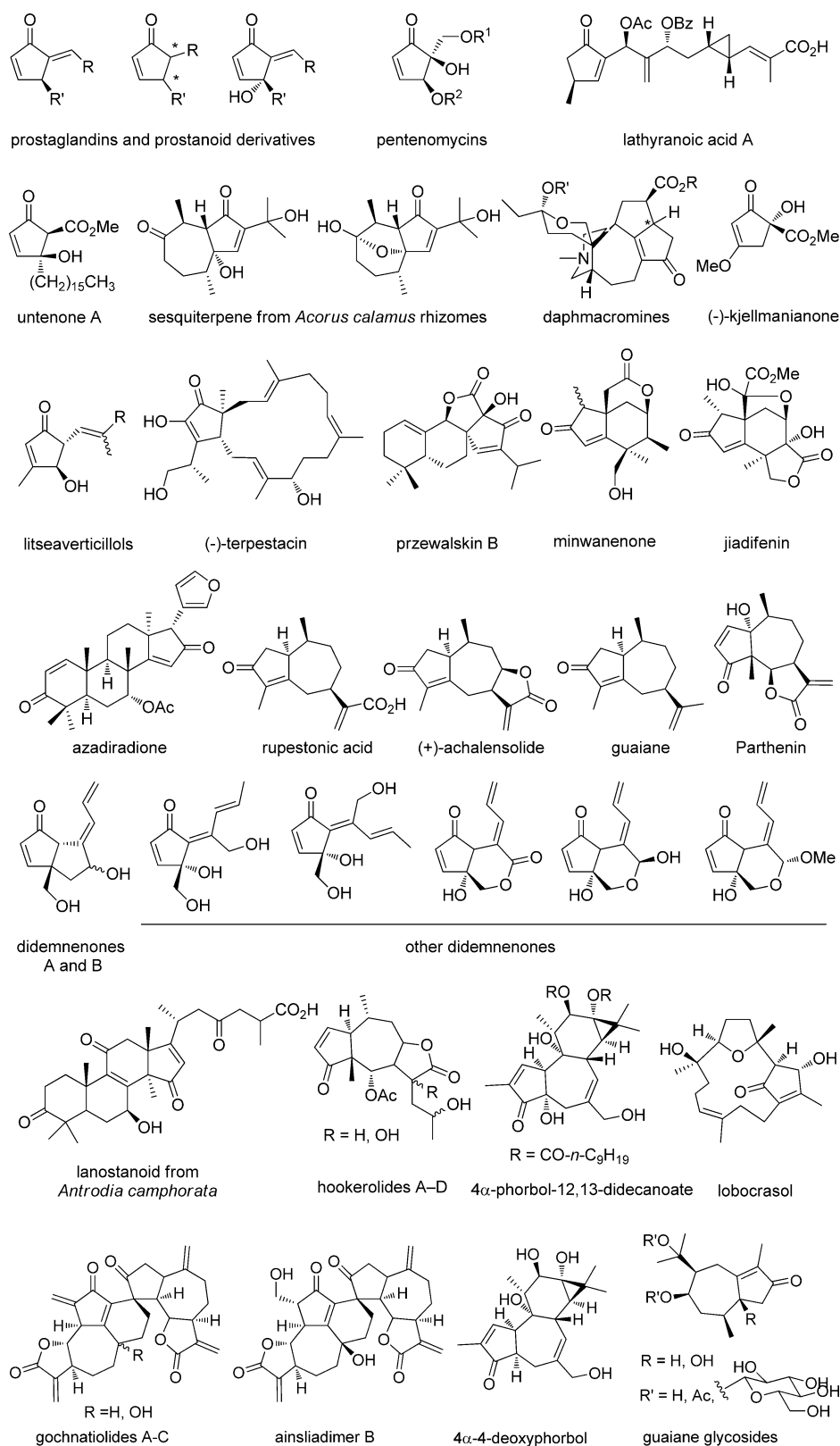
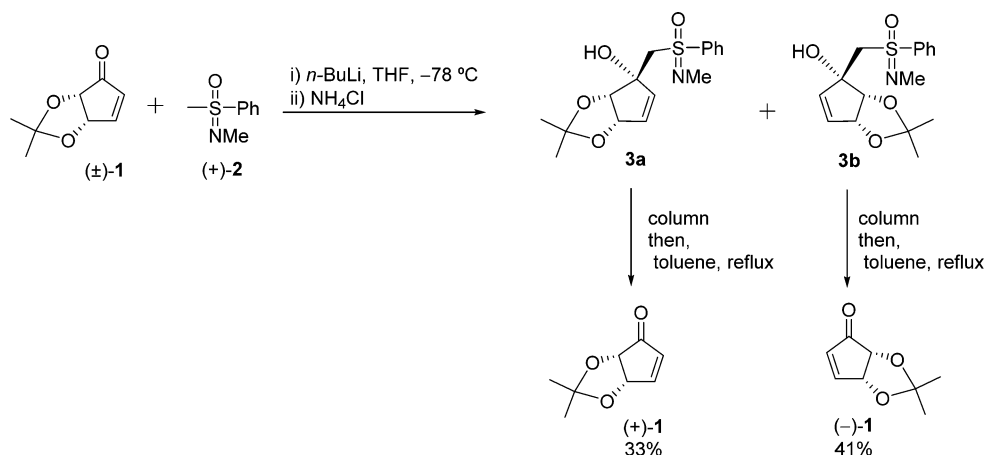


Figure 1. Selection of synthetic bioactive and natural molecules containing a chiral cyclopentenone functionality, such as prostaglandins and prostanoid derivatives,³ pentenomycins,¹² lathyranic acid A,^{13,14} untenone A,^{15,16} sesquiterpene from *Acorus calamus* rhizomes,¹⁷ daphmacromines,¹⁸ kjellmanianone,¹⁹ litseaverticillols,²⁰ terpestacin,^{21,22} przewalskin B,²³ azadiradione,²⁴ minwanenone,²⁵ jiadifenin,^{26,27} rupestonic acid,²⁸ (+)-achalensolide,²⁹ guaiane,³⁰ parthenin,³¹ didemnenones,^{32,33} lanostanoid from *Antrodia camphorata*,³⁴ hookerolides A-D,³⁵ 4 α -phorbol-12,13-didecanoate,³⁶ lobocrasol,³⁷ gochnatiolides A-C,³⁸ ainsliadimer-B,³⁸ 4 α -4-deoxyphorbol,³⁹ and guaiane glycosides.⁴⁰

prostaglandins, prostanoid derivatives, natural compounds, and other bioactive molecules (Figure 1).

This Review provides an overview of reported syntheses of chiral cyclopentenones by diverse approaches, including cases

Scheme 1. Sulfoximine-Mediated Resolution of Cyclopentenone (\pm)-1

where the cyclopentenone unit is an intermediate in the synthetic route. The chemistry of the cyclopentenone unit was already covered in excellent reviews by Ellison (1973),¹ Piancatelli et al. (1994, from furans),² Gibson et al. (2004, transition metal-mediated routes),³ Roche et al. (2010, 4-hydroxy-2-cyclopentenone derivatives),⁴ and other recent reviews^{5–9} including those covering carbocyclic chemistry.^{10,11} This Review is organized into sections covering the main methods of cyclopentenone enantioselective synthesis: chemical and enzymatic resolutions; asymmetric synthesis via Pauson–Khand reactions, Nazarov cyclizations, and organocatalyzed reactions; asymmetric functionalizations of the existing cyclopentenone unit; and functionalizations of chiral building blocks such as carbohydrates, chiral carbonyl compounds, and chiral unsaturated hydrocarbons. We apologize in advance to any research teams for any mistake and whose contributions in this area were unintentionally overlooked in this Review.

2. RESOLUTION METHODS FOR THE SYNTHESIS OF CHIRAL CYCLOPENTENONES

The methods for obtaining enantiomerically enriched products from a mixture of enantiomers are known as resolutions. There are many cases in synthesis where the desired asymmetric reaction affords low yields and/or enantioselectivity. Some asymmetric strategies may require several steps, resulting in erosion of overall yield and atom economy. In such cases, isolation of the target enantiomer from a racemic mixture generated by an achiral reaction proves advantageous. Thus, resolutions represent an important group of methods available in enantioselective synthesis.

Typically, resolutions of racemic mixtures would afford up to 50% yield of the desired enantiomer. This limitation can be overcome by converting the undesired enantiomer into the target molecule. This can be achieved either through synthetic manipulation to invert the stereocenters or by means of selective racemization of the undesirable enantiomer concomitant with the resolution step in a process known as dynamic kinetic resolution (DKR).

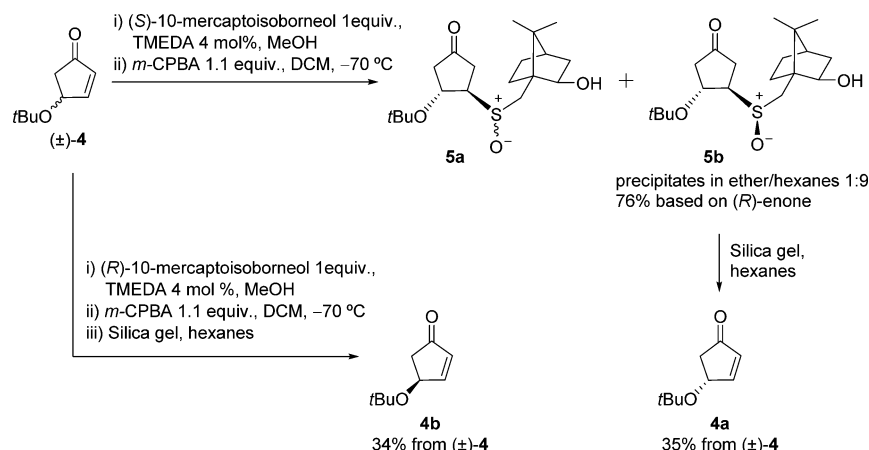
The resolution step can be applied to racemic mixtures of cyclopentenones or their racemic precursors. The latter are converted into the target cyclopentenone products following resolution. There are two main methods for resolving a racemic mixture: resolution via chemical derivatization and resolution via enzymatic reaction. Chemical derivatization of cyclopentenones proceeds by formation of diastereomeric mixtures via chemical

transformations of the enone group or any other existing functional groups. This is followed by separation and subsequent reversal back to the enone group, or is carried through further transformations. These methods generally require use of stoichiometric resolution reagents and cannot surpass 50% yield, which results in poor atom economy. There are some methods that employ kinetic resolutions, and these hold greater promise, but results vary. Enzymatic resolution has steadily replaced chemical derivatization as the method of choice due to the high enantioselectivity, milder conditions, and lower toxicity associated with enzyme catalysis. Given the more simple structure of most enzyme substrates as compared to chemical derivatization reagents, enzymatic resolution also tends to have greater atom economy. However, there are cases where the enzymatic reaction is sluggish, resulting in long cycle times. In such instances, resolution by chemical derivatization is a valid alternative.

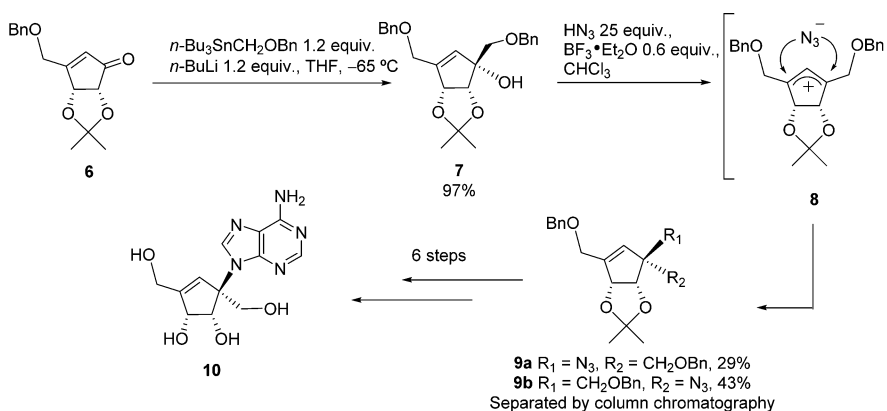
2.1. Resolutions by Chemical Derivatizations

In 1988, Johnson and Penning used resolution through chemical derivatization in their synthesis of (–)-prostaglandin E2 methyl ester. Cyclopentenone **1** was resolved with sulfoximine (+)-2, which added exclusively *anti* to the 4,5-dioxy substituents to afford a single pair of diastereomers.⁴¹ Separation by column chromatography followed by sulfoximine thermolysis in refluxing toluene afforded the desired enone (+)-1 with the *S,S* configuration in 34% yield (Scheme 1). This intermediate chiral cyclopentenone was later subjected to substrate-controlled diastereoselective organocuprate conjugate addition followed by alkylation of the resulting enolate with alkyl iodine. Although their final target molecule was a monohydroxylated cyclopentenone, their synthesis made use of a protected dioxygenated cyclopentenone precursor **1** to avoid an elimination side reaction of the enolate intermediate. Easily available racemic starting material favored this resolution strategy.

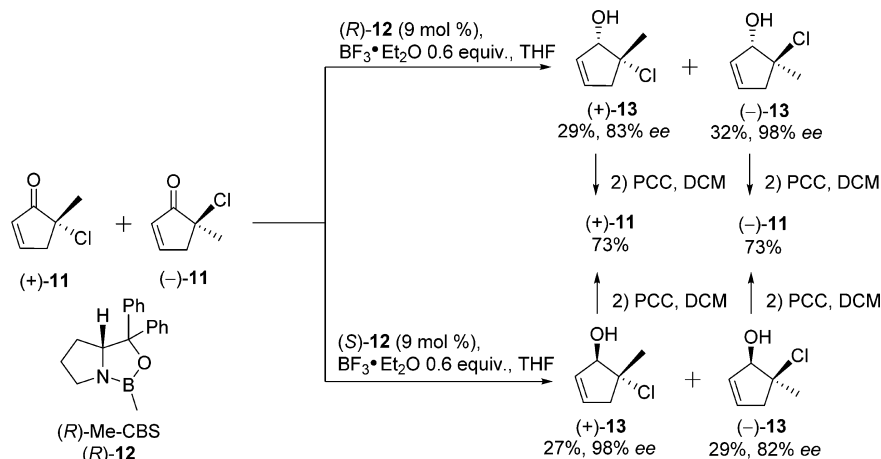
In another example from prostanoid synthesis, Eschler et al. resolved 4-*tert*-butoxy-cyclopentenone **4** via diastereomer formation through conjugate addition of chiral 10-mercaptoisoborneol. This agent was easily removed after resolution by elimination either as sulfide or as sulfoxide or sulfone following oxidation with *m*-chloroperbenzoic acid (*m*CPBA).⁴² Conjugate addition rates were found to be similar for both enantiomers of 10-mercaptoisoborneol. Although these sulfoxides proved unstable under standard column purification on silica, one of the two diastereomers formed could be precipitated, thus

Scheme 2. Mercaptoisoborneol-Mediated Resolution of Cyclopentenone (\pm)-4

Scheme 3. Resolution Following Epimerization Due to Carbocyclic Cation Formation from Cyclopentene 7



Scheme 4. Application of a Corey–Bakshi–Shibata Reduction To Resolve Racemic Cyclopentenone 11

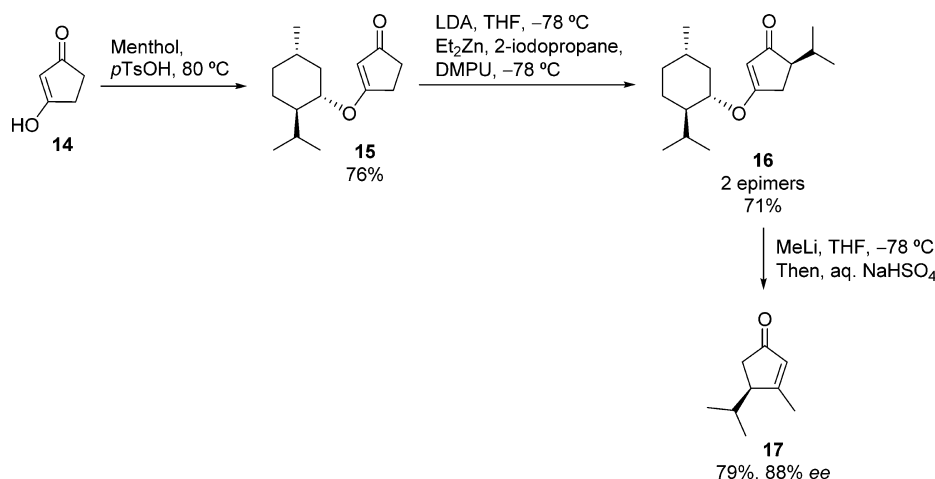
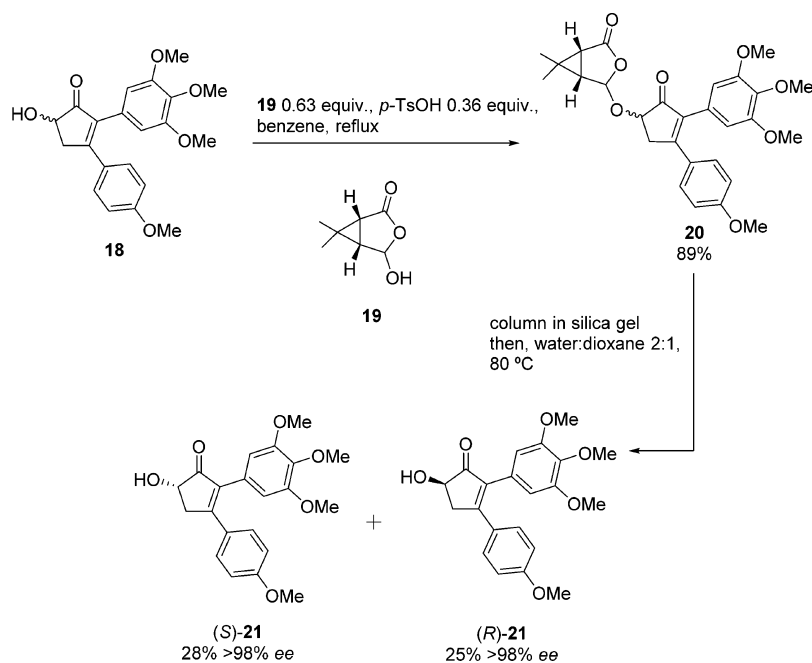
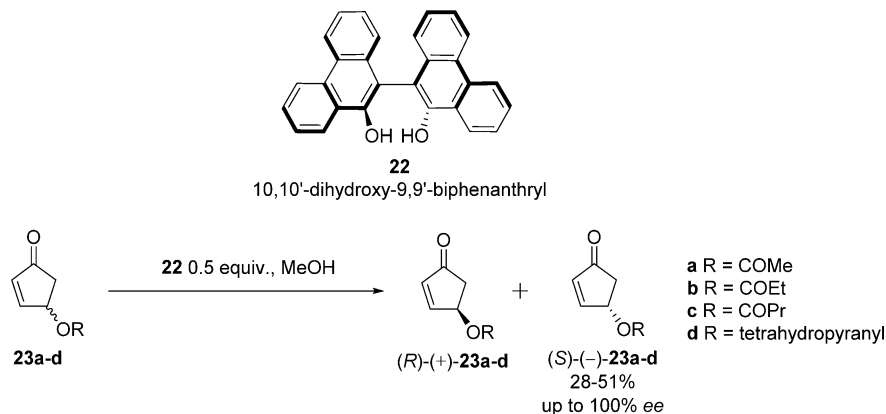


allowing separation. Cleavage of the sulfoxides was easily accomplished by stirring with silica gel, affording the desired enantiomer of 4 in good overall yields of 34–35% (Scheme 2). Unfortunately, attempts made to extend this protocol to ketone reduction with metal hydrides to afford separable diols using just one enantiomer of 10-mercaptoisoborneol were met with little success.

The work of Bodenteich et al. on carbocyclic analogues of 1- β -D-psicofuranosyl nucleosides illustrates the need for resolution due to epimerization during synthesis.⁴³ This work used racemic

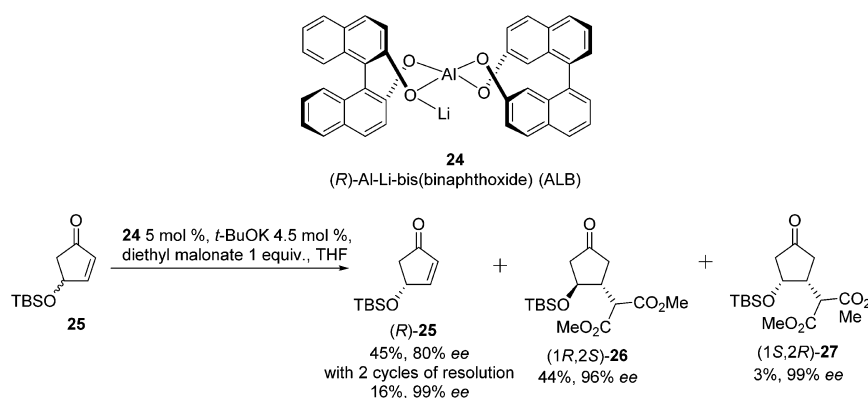
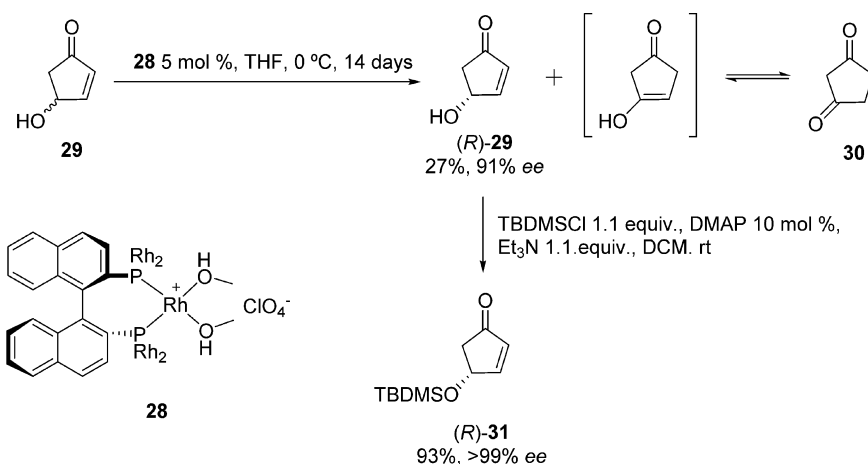
cyclopentenone 6, obtained from D-ribonolactone, which after stereoselective conversion into a tertiary alcohol eliminated to give a symmetrical carbocyclic cation 8. This intermediate gives a mixture of epimers upon azide addition, which were resolved by column chromatography. The desired epimer afforded azide 9a following subsequent steps (Scheme 3).

McMorris and Staake^{44,45} resolved a racemic mixture of 5-chloro-5-methyl-cyclopentenones (\pm)-11 through chemical derivatization in their synthetic studies toward the antitumor drug irifolven. This is another case where the carbonyl group of

Scheme 5. Resolution of Cyclopentenone **14** through Derivatization with Menthol and Zinc Enolate Addition to 2-IodopropaneScheme 6. Resolution of Cyclopentenone **18** through Derivatization with Caronaldehyde **19**Scheme 7. Separation of Cyclopentenones **23a–d** through Coordination with Binaphthyl Derivative **22**

the cyclopentenone is exploited to separate diastereomers. The racemic mixture was subjected to a fast asymmetric Corey–Bakshi–Shibata reduction, giving separable diastereomers with

good to high diastereoselectivity but average conversion yields (~60%). After separation by column chromatography, the alcohol products **13** were oxidized back to their respective

Scheme 8. Kinetic Resolution through Al–Li-Bis(binaphthoxide) (**24**)-Catalyzed Conjugate Addition of Diethyl Malonate to Cyclopentenone **25**Scheme 9. Kinetic Resolution through Rhodium-BINAP (**28**)-Catalyzed 1,3-Hydrogen Migration Applied to Cyclopentenone **29**

cyclopentenones with an overall yield for each enantiomer of ~21% (Scheme 4).

In 2006, Imura et al. resorted to menthol as a chiral auxiliary to obtain a mixture of separable diastereomers of a cyclopentenone intermediate for their enantioselective synthesis of guanacastepene N.⁴⁶ The available enol group in 1,3-cyclopentadienone **14** was condensed with menthol. This was followed by isopropylation with a zinc enolate giving a 1.5:1 ratio of separable epimers **16**, further affording the desired intermediate **17** via methylation with good enantioselectivity (enantiomeric excess (ee) of 88%) and overall yield of 26% (Scheme 5).

In 2007, Shinde et al. also functionalized a hydroxyl group for resolution of cyclopentenone derivatives in their anticancer activity studies.⁴⁷ The racemic 5-hydroxy-cyclopentenone derivative **18** was etherified with caronaldehyde **19** and resolved through column chromatography. The isolated diastereomers were converted back to the free cyclopentenone alcohols **21** by hydrolysis in aqueous dioxane (Scheme 6). Absolute stereochemistry was assigned by ¹H NMR via the corresponding Mosher esters. This strategy involving caronaldehyde was also used to resolve 4-hydroxy-cyclopentenones with 82–88% yield by Suzuki et al.⁴⁸

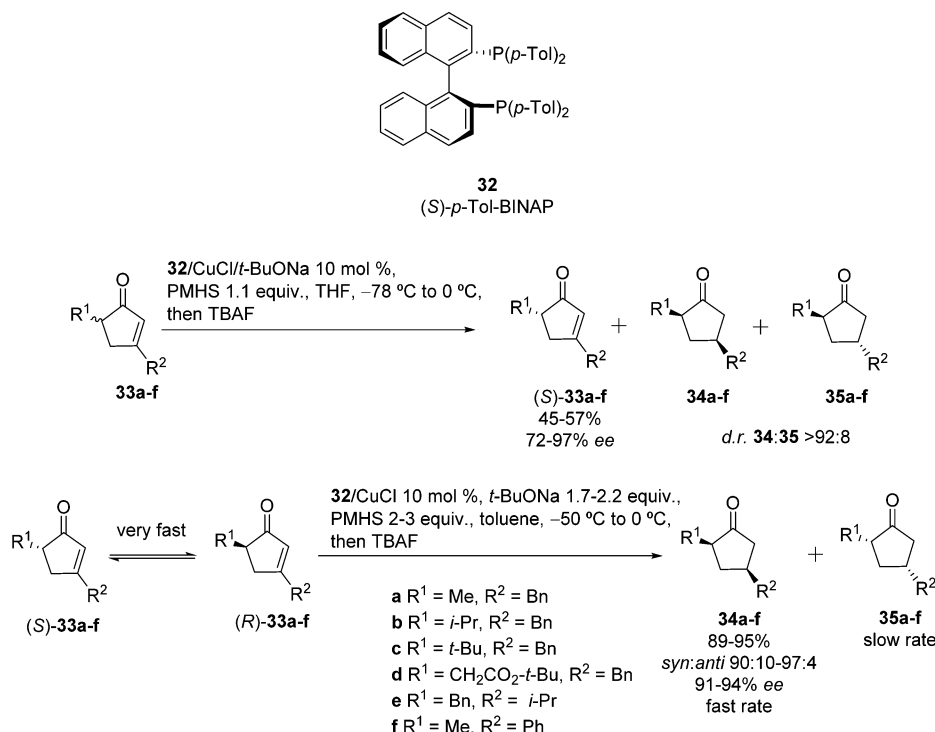
Binaphthyl derivatives are well-known for their use as chiral ligands in many asymmetric applications, due to the combination of their intrinsic axial chirality and their ability to coordinate a variety of substrates. Toda and Tanaka used 10,10'-dihydroxy-9,9'-biphenanthryl **22** to coordinate and precipitate levorotatory (–)-enantiomers of 4-hydroxy-cyclopentenone esters **23a–c** or

tetrahydropyranyl ether **23d**, achieving several cases of complete resolution for a range of derivatives (Scheme 7).⁴⁹ Unfortunately, resolution depended on the precipitation of one of the complexes, which sometimes failed as in the case of the free 4-hydroxy-cyclopentenone alcohol. Further complications, including racemization during ester hydrolysis, further eroded enantioselectivity. Fortunately, this undesirable reaction was completely avoided in the case of the tetrahydropyranyl ether derivative **23d**, which was readily cleaved with aqueous HCl to afford optically pure 4-hydroxy-cyclopentenone.

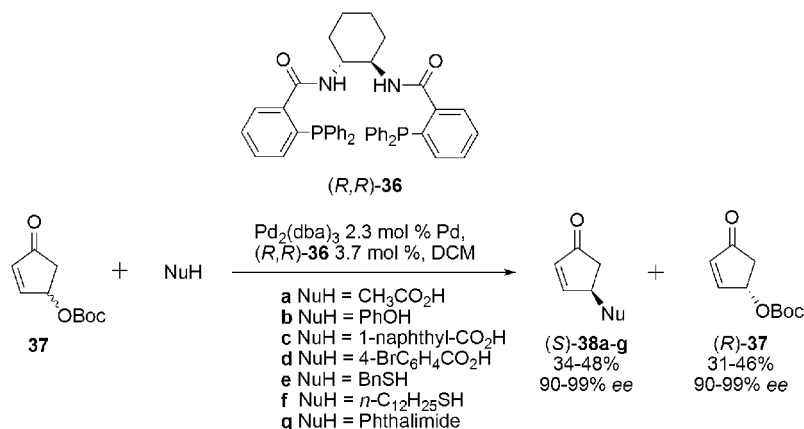
Kinetic resolution is another viable strategy for the resolution of racemic mixtures. This is achieved by using chiral reagents or catalysts to afford a faster reaction rate for one enantiomer over the other. A kinetic resolution can consist of one step if the unreacted enantiomer is the desired molecule. This compares favorably against most chemical derivatization methods that formally consist of two steps: formation of diastereomers and removal of the chiral auxiliary after separation.

In 2008, Mihara et al. applied a kinetic resolution based on an Al–Li-bis(binaphthoxide) (ALB, **24**)-catalyzed conjugate addition of dimethyl malonate to a racemic 4-*O*-protected cyclopentenone **25** with a catalytic amount of achiral *tert*-butoxide base.⁵⁰ A small screening of conditions optimized catalyst loadings and established TBDMS as the best protecting group, in contrast to acetyl, which suffers from β elimination. (*R*)-**25** was afforded with modest optical purity (80% ee), along with products **26** and **27** with good optical purity. This required another cycle of resolution under similar conditions to give (*R*)-

Scheme 10. Kinetic Resolution through Olefin Reduction of Cyclopentenones 33



Scheme 11. Kinetic Resolution of Cyclopentenone 37 by Tsuji–Trost Asymmetric Nucleophilic Substitution



25 in 99% ee (Scheme 8). The authors hypothesized that **27** was possibly formed by a catalyst-controlled *cis* addition pathway that unfortunately also led to reaction with the undesired enantiomer of **25**. This made the one-pot process with an excess of dimethyl malonate unfeasible for obtaining both **25** and **26** with high enantioselectivity. This required two resolution steps, both using substoichiometric diethyl malonate.

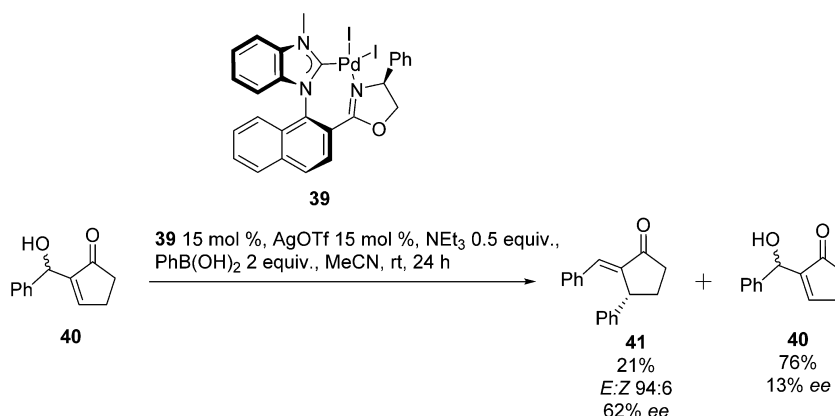
In 1987, Kitamura et al. reported a kinetic resolution using rhodium-BINAP catalyst **28** to afford a 1,3-hydrogen migration on a racemic mixture of 4-hydroxy-cyclopentenone **29**.⁵¹ The selectivity factor ($S = k_{\text{fast}}/k_{\text{slow}}$) of 5 favored the conversion of (*S*)-**29** into **30** at the expense of a long reaction time. The conversion of (*S*)-**29** into **30** and its crystallization from the reaction mixture allowed for the recovery of (*R*)-**29**, which upon silylation afforded (*R*)-**31** with high enantioselectivity of >99% ee (Scheme 9).

BINAP catalysts were also used by Jurkauskas and Buchwald with significant success in the resolution of 3,5-dialkyl-cyclo-

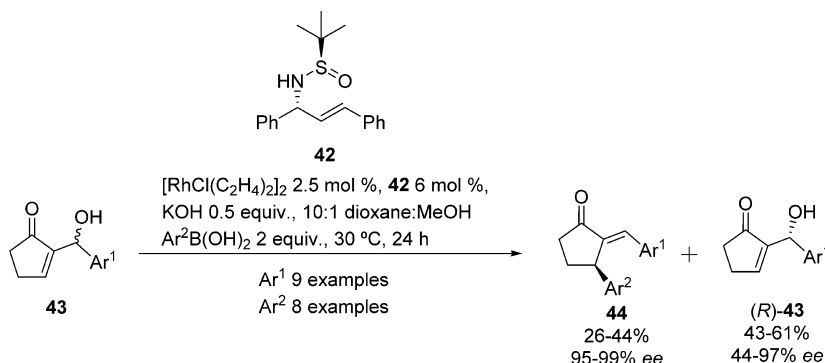
pentenones.⁵² Their method was based on enantioselective reduction of the olefin group in the cyclopentenone using (*S*)-*p*-tol-BINAP/CuCl/NaO^{*t*}Bu as a catalytic system. This kinetic resolution favored reaction with (*R*)-**32** with good selectivity factors of **25**–**52** and good diastereoselectivity ($\text{dr} \geq 92:8$) for a range of substituents. Further addition of TBAF gave the corresponding unreacted cyclopentenones (*S*)-**33a–f** (Scheme 10, top). The 3,4-dialkyl-cyclopentenones gave lower selectivity factors ($S < 10$). Interestingly, the authors further expanded this methodology by using more basic conditions with a labile proton donor to promote racemization of the starting material, achieving a dynamic kinetic resolution (DKR) protocol for the conversion of 3,5-dialkyl-cyclopentenones **33** into the corresponding cyclopentanones **34** with high yields and high diastereo- and enantioselectivity (Scheme 10, bottom).

The 4-hydroxy-2-enone moiety found in many cyclopentenones can be viewed as an allylic system amenable to a Tsuji–Trost asymmetric nucleophilic substitution. This useful

Scheme 12. Kinetic Resolution of Cyclopentenone **40** through Morita–Baylis–Hillman Adduct Formation Catalyzed by Pd Catalyst **39**



Scheme 13. Kinetic Resolution of Cyclopentenone **43** through 1,4-Addition/ β -Hydroxy Elimination Catalyzed by Rh(I) Complexes with Chiral Sulfinamide/Alkene Hybrid Ligand **42**



reaction was used by Ulbrich et al. employing Trost ligand **36** to kinetically resolve *O*-protected 4-hydroxy-cyclopentenone.¹³ The usual acetyl derivate proved too sluggish to react, perhaps due to the additional stability of the allylic group due to conjugation with the ketone. Pleasingly, Boc derivative **37** was found to readily form the allylpalladium complex. A range of different nucleophiles (0.5 equiv or less) afforded very good enantioselectivity for both isolated enantiomers (Scheme 11). Notably, this was possible for thiol nucleophiles even though the reaction uses a palladium catalyst. This method was successfully applied to the synthesis of the antitumor and antiviral drug noraristeromycin. The authors also sought to find conditions for a DKR by using excess nucleophile, but this resulted in erosion of enantioselectivity. The usefulness of this route toward these enantioenriched products has also been demonstrated for the synthesis of 4-alkyl-5-(1-hydroxyalkyl)-cyclopentenones.⁵³

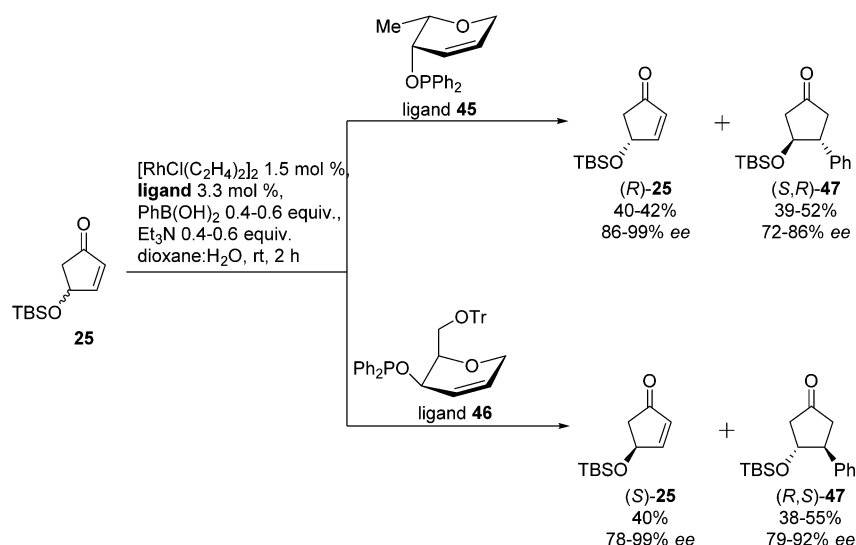
Kinetic resolution with complexes bearing axial chirality was also explored. Morita–Baylis–Hillman (MBH) adducts of enones with aldehydes were kinetically resolved by Wang et al. using catalyst **39** bearing a bidentate *N*-Ar framework with ligands at the *ortho* position along the *N*-Ar axis that coordinate to palladium.⁵⁴ The cyclopentenone substrates were subjected to Pd-catalyzed allylation with boronic acids via 1,4-conjugate addition followed by β -elimination of hydroxyl from the palladium enolate to afford the allylic product. Generally, good enantioselectivity and *E:Z* selectivity were obtained for the products of allylation but not for the unreacted alcohols, due somewhat to the average conversion yields. Although the bulk of their work concerns six-membered cyclic enones, at least one

case involved a cyclopentenone starting material **40** with moderate yield and enantioselectivity (Scheme 12).

More recently, 1,4-addition reactions of boronic acids catalyzed by Rh(I) complexes have been exploited as protocols for kinetic resolution of cyclopentenones. Wang et al. prepared complexes of Rh(I) with chiral sulfinamide/alkene hybrid ligands such as **42** and carried out 1,4-addition/ β -hydroxy elimination on MBH adducts of cyclopentenone **43**.⁵⁵ It was found that a variety of chiral sulfinamide/alkene ligands afforded high enantioselectivity with moderate to good conversion yields. The reaction was tolerant of different aromatic substituents on both the MBH adducts and the arylboronic acids used, with the exception of *ortho* substituents, perhaps due to increased sterics (Scheme 13). The origin of enantioselectivity was explained through simultaneous coordination of the rhodium center to the sulfur and alkene groups of the ligand and the alkene and hydroxyl groups of the cyclopentenone, with sterics favoring coordination to the (*S*) enantiomer.

Coordination of chiral alkene ligands to rhodium metal in the catalysis of 1,4-addition of boronic acids, as seen in the previous example, offers an excellent opportunity to control asymmetric induction through ligand design. Grugel et al. sought to prepare novel alkene phosphinite ligands derived from carbohydrates, such as D-glucose and D-galactose.⁵⁶ The authors studied structural constraints affecting enantioselectivity, such as the impact of axial versus equatorial positions for the ring substituents in the available pyranoside conformers. Interestingly, it was found that the direction of asymmetric induction was primarily determined by the direction of the phosphinite

Scheme 14. Kinetic Resolution of Cyclopentenone **25** through 1,4-Addition of Phenylboronic Acid Catalyzed by Rh(I) Complexes with Alkene Phosphinite Ligands **45** and **46**



substituent relative to the pyranoside ring (i.e., above or below). The phosphinite would always have to sit axially so as to enable the coordinated rhodium to also coordinate the alkene group within the pyranoside ring. Further steric effects of the remaining substituents also played a role. From this study, two ligands (**45** and **46**) were found to be the most selective, and they were employed to resolve racemic cyclopentenone **25** in good yields and good to excellent enantioselectivity (Scheme 14).

A few other methods for affording optically pure 4-hydroxycyclopentenones warrant mention. For instance, brucine has been used to resolve precursors of (*R*)-4-hydroxycyclopentenones obtained from 2,4,6-trichlorophenol with high recovery yields.⁵⁷ Preparative chiral HPLC has been typically used to provide samples for characterization and biological testing. A few methods have been reported for the resolution of 4-hydroxycyclopentenone derivatives using cellulose carbamates, benzoates, and acetates as stationary phases.^{58–61} Curiously, Loža et al.⁶² reported enantiomeric enrichment of certain racemates after achiral column chromatography purification. Accordingly, partially resolved 4-hydroxy-2-carboxymethylcyclopentanes and two (–)-5-oxa-6-oxoprostaglandin E_1 C(15) epimers, synthesized from partially enantiomerically enriched (~40% ee) 4-hydroxycyclopentenones, displayed surprising behavior during achiral column chromatography purification. The enantiomeric excess was dependent on the fraction under observation, as it was noted that earlier fractions obtained by column chromatography and preparative HPLC consistently gave higher ee's as measured by optical rotation. Racemization and impurities were ruled out as possible causes following several control experiments. The authors have hypothesized that given the slight enantiomeric excess of the material to be purified (for instance, having (–) as the major enantiomer), then the statistical number of intermolecular homo-associations (–)⋯(–) exceeds the number of cross-associations (–)⋯(+), which in turn exceeds the number of homo-associations (+)⋯(+). If the free-energy change for the cross-association is more favorable, then once the first layer of adsorbed solutes is formed (rich in (–)), formation of the second layer should favor association with the (+)-enantiomer. This would enrich the mobile phase in the major (–)-enantiomer as compared to the starting material. To

what extent this effect is significant for applications remains to be shown.

Diastereomer separation as a resolution strategy is best employed when the cyclopentenone compounds are sensitive to racemization or side reactions during synthesis. It is particularly suited for cases where cyclopentenone substrates are early precursors in a synthetic route, the resolving agents are cost-effective to purchase or synthesize, and when no other enantioselective methods exist for the synthesis at hand. This utility has been recognized by industry as exemplified by patent applications for resolution of 4-hydroxycyclopentenones. This has been described for polysaccharide derivatives by Noriaki et al.,⁶³ resolution of acyl derivatives by coordination with chiral diols by Fumio and Masayoshi,⁶⁴ and with chiral amines by Takayuki et al.⁶⁵ Unfortunately, resolution via diastereomer formation and separation usually suffers from a 50% yield limitation, which is further aggravated by the need to convert the compounds into diastereomers and subsequent removal of the chiral auxiliary. We find resolution via dynamic kinetic resolution (DKR) to be of particular interest and promise, as it enables a higher yield and conversion of the entire racemate into the target chiral cyclopentenone. We have found one interesting application of DKR by Jurkauskas and Buchwald,⁵² but the other reported kinetic resolutions are not DKR. Recently, good kinetic resolutions have been achieved with 1,4-addition of arylboronic acids catalyzed by rhodium and allylic substitutions catalyzed by palladium. Unfortunately, DKR protocols for these methods are yet to be established.

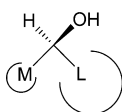
2.2. Enzymatic Resolutions of Cyclopentenones

Resolution by enzyme catalysis is a well-established method, the main advantages of which include high enantioselectivity, synthetic simplicity, mild energy requirements, and low toxicity. Many cases also display good atom economy provided enzyme loadings are comparably low and/or enzyme reuse is feasible. Enzymatic resolution of hydroxylated cyclopentenones is of great synthetic value as they are often found to be good precursors for prostanoids and carbocyclic nucleoside syntheses. Applications consist almost exclusively of lipase (triacylglycerol acyl hydrolases, EC 3.1.1.3)-catalyzed resolutions of hydroxylated substrates.⁶⁶ Lipases are easy to use, have good tolerance toward

high temperatures (up to 100 °C for certain lipases), and like most enzymes accept a variety of related substrates by induced fit. A word of caution is in order when considering lipase nomenclature, as the same enzyme can have different names due to identification issues of the microbe from which they were isolated. Examples include lipases from *Pseudomonas fluorescens* also identified as *Pseudomonas cepacia* (this lipase is also known as PS) and *Candida cylindracea* also identified as *Candida rugosa*. All of these names are still in use. In other cases, authors may refer to the commercial name (e.g., Novozym 435 consists of a particular preparation of immobilized *Candida antarctica* lipase B, also known as CAL-B). Therefore, in this Review, lipases will be referred to by the names used by the corresponding referenced authors.

The yield and enantioselectivity of a lipase-catalyzed resolution are affected by many parameters, such as concentration, enzyme loading, temperature, pH, choice of acylating agent, solvent, content of water, and enzyme immobilization. Many of these factors show interdependencies and require case-to-case optimization as few general trends have been uncovered. Temperature, pH, water content, choice of immobilizing support, and acylating agent are typically enzyme-dependent. Organic cosolvent and to a large extent also acylating agent are substrate-dependent, and both show a strong influence on substrate and product binding to the active site. Often the choice of cosolvent is driven by the need to solubilize the substrate used but also carries with it a significant impact on enzyme turnover and enantioselectivity. The choice of enzyme is reliant on its ability to afford the desired enantiomer. The best models are based on X-ray crystallography data. In their absence, screening assay data have been extensively used for estimating the shape and hydrophobic character of the active site. These data were used to model enantioselectivity for similar substrates on the basis of size and hydrophobicity of the substituents at their respective stereocenters. The validity of the rules set by these studies is clearly greater as more cases are shown to comply with them. Naturally, a discussion on the methods, details, and conclusions of these studies is beyond the scope of this Review. As a titular example, Kazlauskas et al. have correlated lipase enantioselectivity to the sterics of substrate substituents for cholesterol esterase, lipase from *Pseudomonas cepacia*, and lipase from *Candida rugosa* toward acylation of more than 130 secondary alcohols.⁶⁷ The overall conclusion was that enzymes are selective toward secondary alcohol substrates, which, if one arranges the substrate so that the hydroxyl group is facing toward the viewer, then a counterclockwise curve can be drawn from the smallest (hydrogen) to the bulkiest (L) substituents in order of increasing sterics (Scheme 15).

Scheme 15. Preferred Substrate Sterics for Lipase-Catalyzed Reactions



This rule was shown to hold true for 14 out of 15 of substrates for cholesterol esterase, 63 out of 64 substrates for lipase from *Pseudomonas cepacia*, and 51 out of 55 substrates for lipase from *Candida rugosa*. The authors also used this rule to design substrates for enzymatic resolution. This was done for the synthesis of esters of (R)-lactic acid and (S)-(-)-4-acetoxy-2-

cyclohexenone in which enantioselectivity for the resolution of precursors was significantly increased to >98% ee after appropriate changes to the substituent sizes. By contrast, resolution of 4-hydroxycyclopentenones unsubstituted at the C3 and C5 positions has proven challenging due to the poor steric discrimination in these substrates.

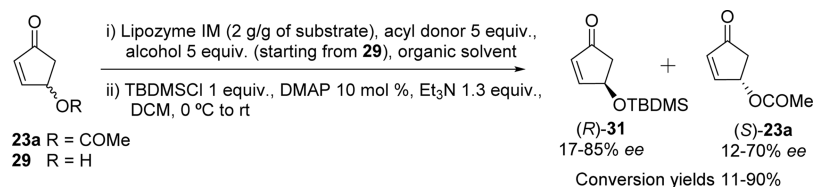
Ghorpade et al. studied the enzymatic kinetic resolution of racemic 4-hydroxycyclopentenone via esterification or alcoholysis of their ester derivatives with lipozyme IM in organic solvents.⁶⁸ Their work illustrated the difficulty in achieving high enantiomeric ratio, as several factors, such as solvent, water content, and acylating agent had to be optimized. Vinyl acetate was found to be the best acylating agent for the esterification of **29**, whereas ethyl, isopropyl, and trichloroethyl acetates gave no reaction. Overall alcoholysis was faster for primary over secondary alcohols. The solvent system employed had a very significant impact on conversion and enantioselectivity. A water content of 1% was detrimental to the conversion, while slightly increasing the poor enantiomeric ratio ($E \leq 11$), possibly due to enzyme solvation effects. By contrast, the same water content was found to be optimal for the alcoholysis of **23a**, particularly when employing the optimized mixed solvent system of DIPE with 2-butanol. These conditions afforded the highest enantiomeric ratio observed ($E = 24$). The authors have hypothesized that moderate steric hindrance of the alcohol bound to the enzyme's active site in a given solvent was beneficial to enantioselectivity. Overall, a wide range of ee values were obtained by changing the different parameters under study (Scheme 16).

In 1990, Babiak et al. tested several lipases, such as *Pseudomonas* species lipase (PSL), *Candida cylindracea* lipase (CCL), porcine pancreatic lipase (PPL), *Aspergillus niger* lipase (ANL), cholesterol esterase, and subtilisin, for the resolution of 2-alkyl-4-hydroxycyclopentenones **48**, analogues of synthetic utility toward prostanoids.⁶⁹ All enzymes showed selectivity toward the (R) enantiomer. PPL was the most active lipase for the resolution of cyclopentenones with different C2-alkyl substituents (Scheme 17, top). This methodology was applied to obtain compound (R)-**48b**, an intermediate for prostanoid synthesis (Scheme 17, down). Furthermore, the undesired (S) enantiomer was converted into the (R) enantiomer via Mitsunobu inversion to increase the yield. However, attempts to increase enantiomeric purity for conversion of (R)-**49b** lowered the overall yield for (R)-**48b** to 54%. Nevertheless, high enantiomeric purity was obtained with ee > 99%. Following the same protocol, Rodríguez and Spurred studied PPL-catalyzed resolution for the synthesis of enantiopure 2-alkylated-4-hydroxycyclopentenones, as precursors for the synthesis of phytoprostanes.⁷⁰

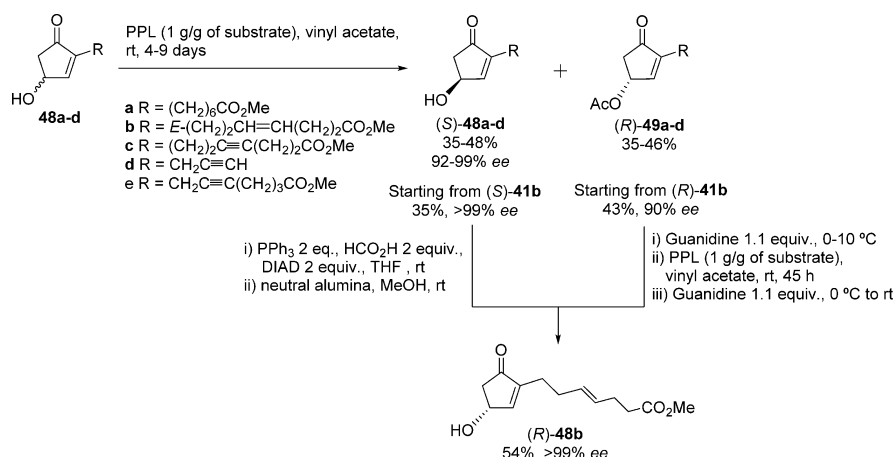
In 1992, Tanis et al. also attempted to optimize conditions for the enzymatic resolution of 2-methyl-4-hydroxycyclopentenone **50**. Several lipases were screened including PPL, CCL, and lipase Amano PS-30, but all afforded poor to average enantioselectivity (up to 60% ee).⁷¹ Solvents ranging from hydrocarbons to ethers were also assayed, but with poor results. A modest improvement was obtained from a small screening of different acylating agents. A two-step process was implemented to increase enantiomeric purity, whereupon (R)-**51**, obtained after the first resolution, was hydrolyzed and subjected to Mitsunobu reaction to increase the yield of (S)-(-)-**50**, followed by a second resolution step. This protocol afforded (S)-(-)-**50** in modest yield but with high enantioselectivity (Scheme 18).

Better results were recently obtained with CAL-B. Michalak and Wicha used this lipase to resolve the 2-methyl-4-hydroxy-

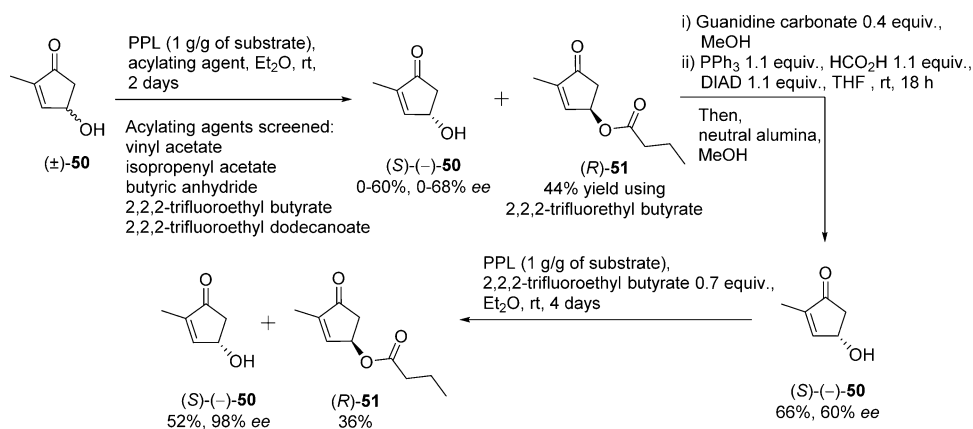
Scheme 16. Lipozyme IM-Catalyzed Resolution of C4-Substituted Cyclopentenones 23a and 29



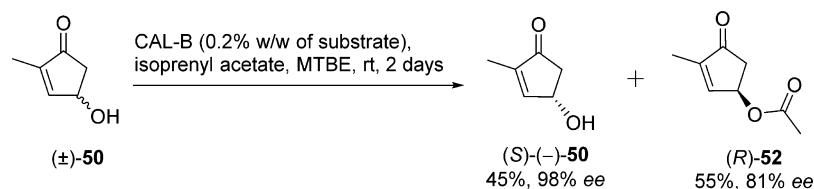
Scheme 17. PPL-Catalyzed Acylation of C2-Substituted 4-Hydroxycyclopentenones 48a–d and Further Conversion to Target Molecule (R)-48b through Mitsunobu Reaction or Second PPL Acylation



Scheme 18. Screening of Conditions for PPL-Catalyzed Acylation of 2-Methyl-4-hydroxycyclopentenone 50 with Further Conversion through Mitsunobu and Second PPL Acylation

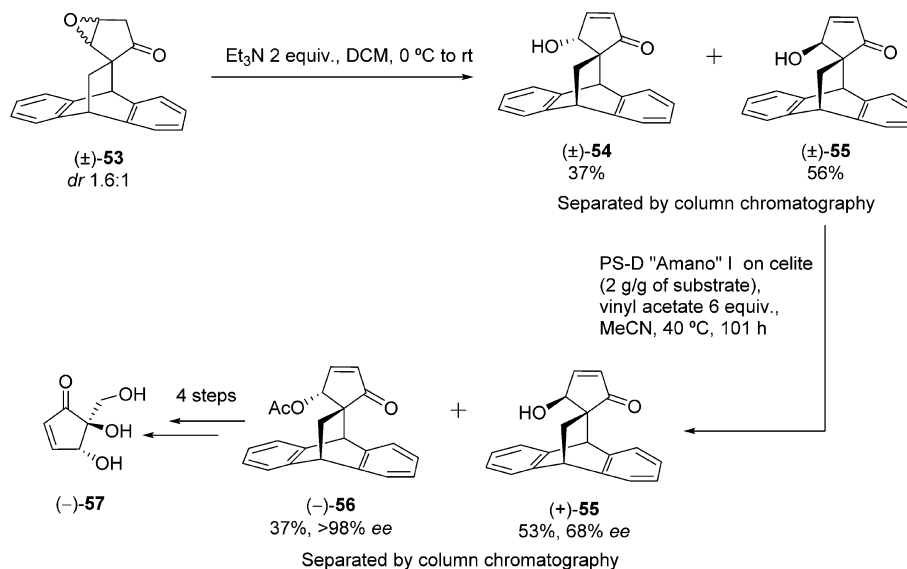
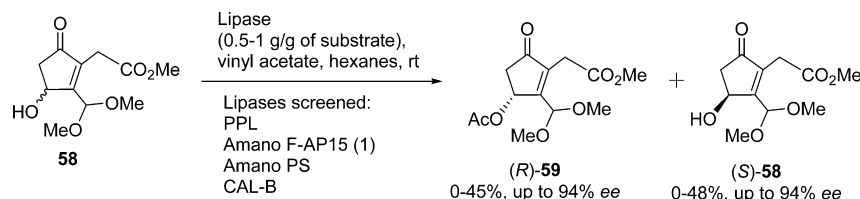
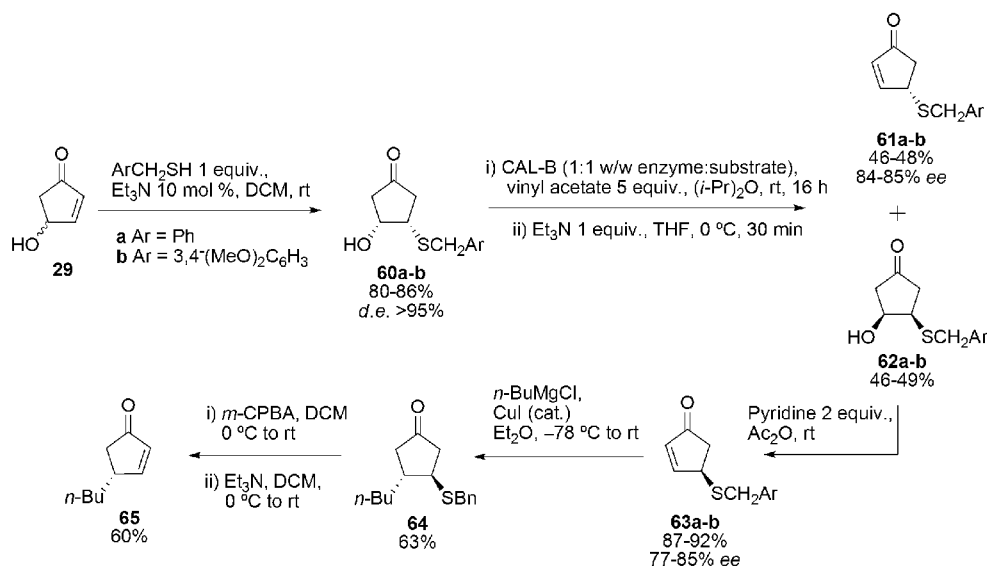


Scheme 19. CAL-B-Catalyzed Resolution of 2-Methyl-4-hydroxycyclopentenone 50



cyclopentenone **50**.^{72,73} Different organic solvents were screened. MTBE was found to be the best solvent, with slower conversion rates in chlorinated solvents and erosion of enantioselectivity in toluene. CAL-B was compared against PS-IM, with the former being found to be more reactive and enantioselective. Under optimized conditions, CAL-B afforded good yields and enantioselectivity in a single step for (S)-(-)-**50** (Scheme 19).

In 2003, Klomklao et al. developed a chemoenzymatic method for the synthesis of (-)-epipentenomycin I ((-)-**57**).⁷⁴ Their synthesis applied an enzymatic resolution to 4-hydroxycyclopentenone racemate (±)-**55** derivatized from a bulky chiral auxiliary. This was in accordance with the geometrical requirements to achieve high enantioselectivity in lipase-catalyzed acylation. The chiral auxiliary was removed after isolating

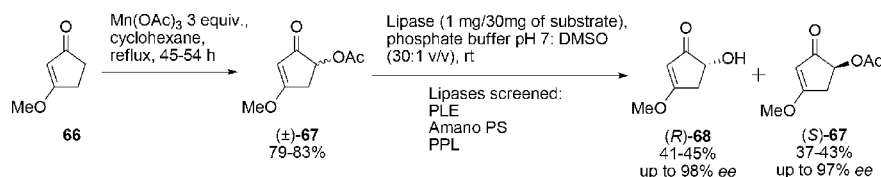
Scheme 20. PS-D Amano I-Catalyzed Resolution of Chiral-Auxiliary-Derivatized Cyclopentenone **55**Scheme 21. Screening of Lipases for Resolution of 2,3-Dialkyl-4-hydroxycyclopentenone **58** through Enzymatic AcylationScheme 22. Resolution of 4-Hydroxycyclopentenone **29** through Conjugate Addition of Thiol and Successive Separation, CAL-B-Catalyzed Acylation and Elimination, with Further Functionalization to Cyclopentenone **65**

(-)-**56**, and the synthesis was carried forward toward (-)-epipentemycin I (Scheme 20).

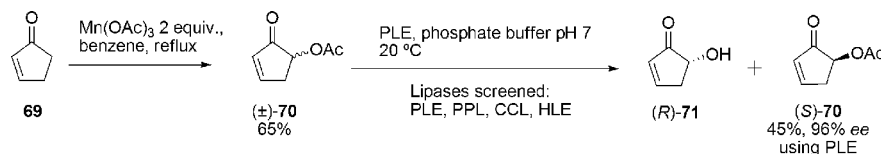
In 2005, Pinot et al. successfully resolved a 2,3-dialkyl-4-hydroxycyclopentenone intermediate for isoprostane synthesis, showing that this type of cyclopentenone substrate is also amenable to lipase-catalyzed resolutions.⁷⁵ Racemate **58**, obtained via a seven-step synthesis from (*E*)-3-(furan-2-yl)-acrylic acid, was screened for enzymatic resolution with four different lipases. As expected, all active enzymes were selective

toward the (*R*) enantiomer. Lipases CAL-B and amano PS were the first and second most active enzymes, respectively. High enantioselectivity (94% ee) was obtained for both compounds as determined by ¹H and ¹⁹F NMR analysis of their corresponding Mosher esters (Scheme 21). Furthermore, CAL-B was also shown to promote (*R*)-**59** hydrolysis in high yield, highlighting the possibility of using enzyme hydrolysis as an alternative protocol for these substrates.

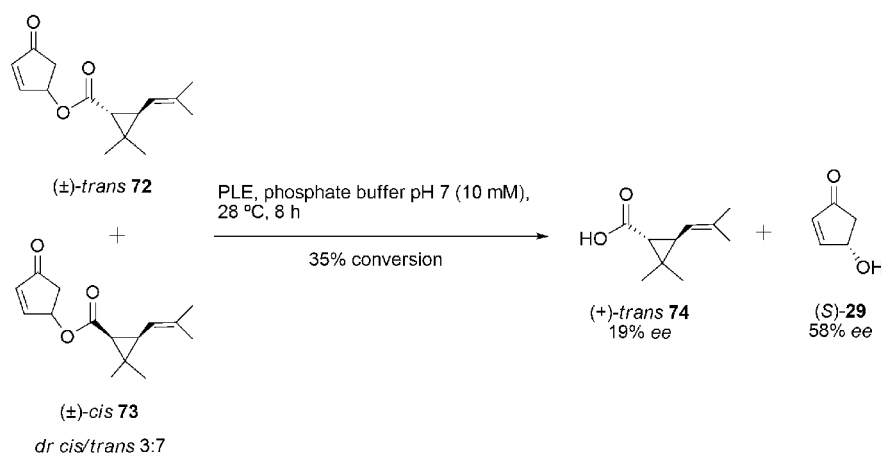
Scheme 23. Screening of Lipases for Enzymatic Resolution via Hydrolysis of Acylated Racemic Cyclopentenone 67



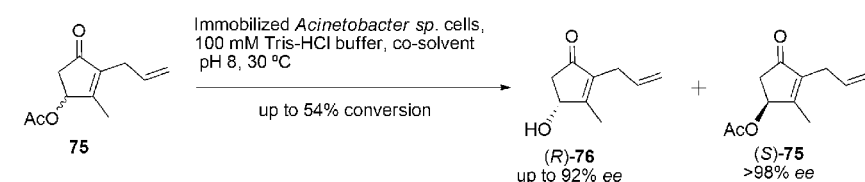
Scheme 24. Screening of Lipases for Enzymatic Resolution via Hydrolysis of Acylated Racemic Cyclopentenone 70



Scheme 25. PLE-Catalyzed Hydrolysis of Cyclopentenone Derivatives of Chrysanthemic Acid 72 and 73



Scheme 26. Immobilized Cells Used for Enantioselective Hydrolysis of Acetylcyclopentenone 75



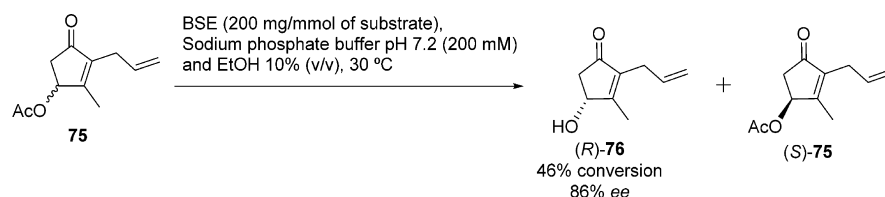
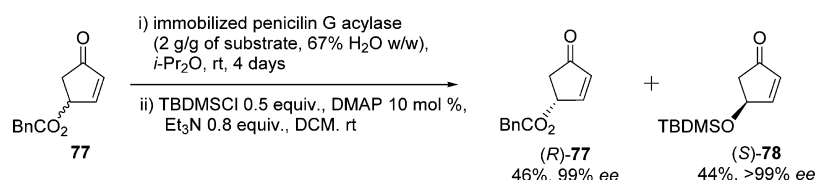
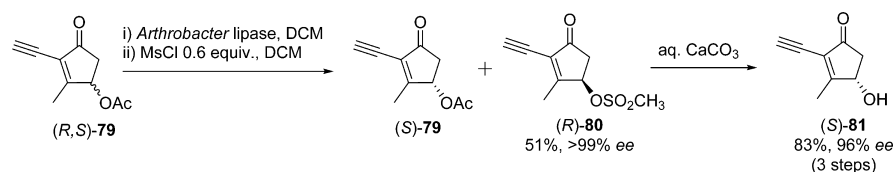
As mentioned before, poor selectivity can arise with unsubstituted C3 and C5 positions in 4-hydroxycyclopentenones. Work reported by O'Byrne et al. aimed to address this by increasing steric bulk at C3 via conjugate addition of thiols, affording cyclopentanones **60a,b**.⁷⁶ Surprisingly, the unexpected *cis* diastereomers were also obtained from thiol addition. The authors suggested this was due to diastereotopic delivery of the thiolate mediated by hydrogen bonding with the 4-hydroxyl group. These adducts were resolved by acylation with CAL-B, followed by in situ treatment of the acylated cyclopentanone products with Et_3N to afford elimination products **61a,b**. The corresponding cyclopentenones **63a,b** were obtained from **62a,b** through successive separation, acylation, and elimination. This protocol was also harnessed to provide other optically pure 4-alkylcyclopentenones as illustrated by a sequence of substrate-controlled conjugate addition, oxidation to sulfone, and elimination. Good yields and reasonable optical purities were achieved by this protocol (Scheme 22).

Resolution via enzymatic acylation is susceptible to particular difficulties, poor access of the acylating agent to the active site

and locally formed water driving back deacylation if the acylated product is slow to dissociate from the active site. The obvious counterpart to this strategy is enzymatic hydrolysis of acylated racemates. Demir and Sesenoglu studied resolutions of 3-methoxy-5-acetylcyclopentenone **67**.⁷⁷ Lipases PLE and amano PS were shown to be effective for selective hydrolysis of these substrates (Scheme 23).

In 2004, Tanyeli et al. applied this protocol of enzymatic resolution via hydrolysis of 2-acetylcyclopentenone **70**.⁷⁸ Of the lipases screened, only PLE afforded good yields and high enantioselectivities (Scheme 24). The enzymatic hydrolysis of 5-acetylcyclopentanone or six-membered ring analogues also yielded similar results with PLE.

In 2005, Sukumaran et al. reported a hydrolytic lipase resolution applied to a diastereomeric mixture of two chrysanthemic acid ester racemates **72** and **73**.⁷⁹ The presence of two stereocenters raised the possibility of achieving both diastereoselectivity and enantioselectivity in a single lipase resolution. Of the several lipases screened, PLE showed both the highest activity and diastereoselectivity toward the racemic

Scheme 27. BSE Lipase-Catalyzed Hydrolysis of Acetylcyclopentenone **75**Scheme 28. Resolution by Penicillin G Acylase-Catalyzed Hydrolysis of Cyclopentenone **77**, Followed by Silylation To Afford Cyclopentenone **78**Scheme 29. Lipase-Catalyzed Resolution of Cyclopentenone **79**, Combined with Hydrolysis and Inversion of Sulfonate under Basic Conditions To Convert Both Products (S)-**79** and (R)-**80** into Target Cyclopentenone (S)-**81**

mixture of *trans*-**72**. Unfortunately, enantioselectivity was quite low (Scheme 25). Furthermore, subtle changes to the alcohol structure, such as cyclopentanone analogues, were shown to completely erode enantioselectivity.

In 2004, Chen et al. demonstrated the use of immobilized cells to conduct enzymatic resolutions of cyclopentenones.⁸⁰ *Acinetobacter* sp. CGMCC 0789 cells were immobilized in calcium alginate gel and used to hydrolyze **75** (Scheme 26). Isopropanol was the best polar solvent tested, showing a significant improvement on both activity and enantioselectivity at an optimal solvent ratio of 10% (v/v). Nonalcoholic solvents performed poorly. The authors suggested isopropanol could afford several positive effects beyond simply improving substrate solubility. Greater substrate diffusion on the alginate beads, increased cell membrane permeability, and faster product–enzyme dissociation were proposed as beneficial effects.

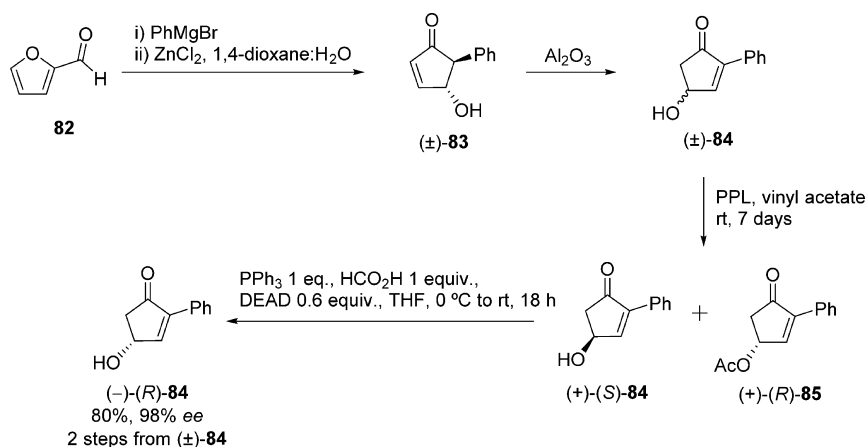
The discovery and development of new enzymes as esterases or hydrolases raise the possibility of improving previously reported protocols and/or broadening the scope to other substrates. In 2009, Zheng et al. reported a new hydrolase isolated from strain ECU0554 from *Bacillus subtilis* (BSE) that has shown good results for hydrolysis of *l*-menthyl esters.⁸¹ This hydrolase exhibited improvements over other existing enzymes in terms of intrinsic enantioselectivity and tolerance to both high substrate and product concentrations. At least one acetylated cyclopentenone (**75**) was resolved with good conversion and modest enantioselectivity (Scheme 27).

Acylases traditionally used in other applications can be harnessed for resolution of 4-hydroxycyclopentenones. In 2012, Kumaraguru et al. used penicillin G acylase for hydrolyzing *O*-phenylacetyl groups, as the enzyme was found to be highly selective toward this group over aliphatic acyl groups.⁸² Water-miscible organic cosolvents were used to enhance substrate solubility. As expected, the choice of cosolvent had a significant impact on enzyme enantioselectivity and required optimization.

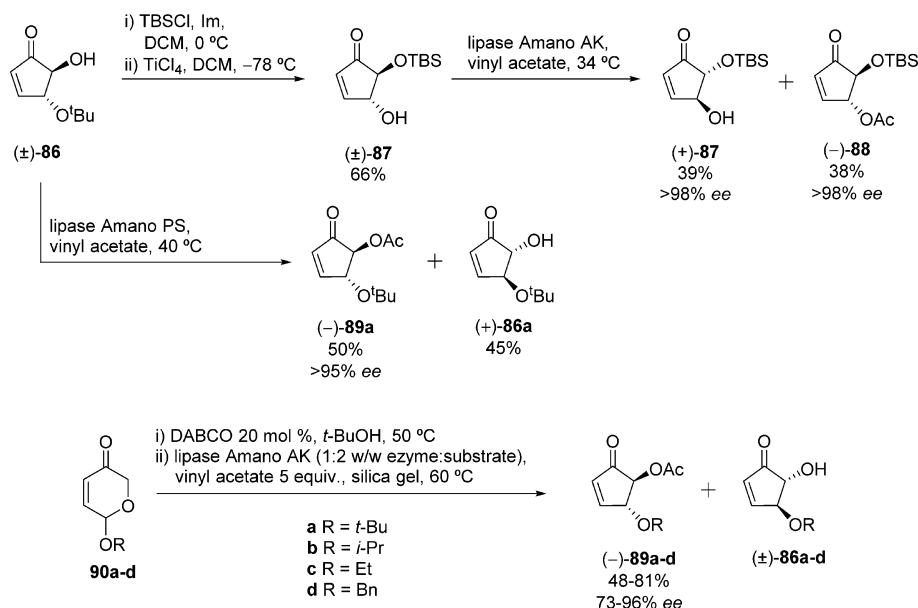
Good enantioselectivity was obtained in mixed acetonitrile and water systems ($E > 100$), but substrate **77** remained poorly soluble and 4-hydroxycyclopentenone proved unstable. This led to an effort to move to organic solvent alone by immobilizing the wet enzyme on epoxy polymer suspended on *i*-Pr₂O. This allowed for higher substrate (**77**) concentrations and provided very good enantioselectivity ($E = 200$) (Scheme 28). Although this protocol required replacement of the enzyme midway through the resolution, it was deemed sufficiently robust to be scaled up to multigram production, affording an equimolar mixture of (R)-**77** and (S)-**29** in 45–46% yield each, with excellent enantioselectivity (>99% ee).⁸³

The optimal mild temperatures and tolerability to organic solvents of most lipases make them suitable for hydrolysis of sensitive esters. In 2010, Zanoni et al. worked with nitroolefin esters, which were sensitive to both acidic and basic conditions in aqueous environments.⁸⁴ In this case, cleavage of the methyl ester was carried out by CAL-B at 35 °C with a modest excess of water (50 equiv) in solvent MTBE. Although these buffer-free conditions were not used by the authors for the purpose of racemic resolution, they were applied to hydrolyze cyclopentenone ester natural products with good yields, such as isoprostane-A₂ (92%), preclavulone-A (93%), and phytoprostanes-B1 type I (90%) and type II (87%). The use of enzymatic resolution combined with means to convert the undesirable enantiomer into the desired product or back into racemic starting material are two possibilities for overcoming the 50% yield limit of classical resolutions. In 1988, Mitsuda et al. developed an elegant modification of an enzymatic resolution for the synthesis of the insecticide prallethrin.⁸⁵ After applying lipase-catalyzed hydrolytic resolution to (R,S)-**79**, the remaining (R) alcohol was sulfonated and the mixture was subjected to mild aqueous base. This hydrolyzed acetate (S)-**79** with retention of configuration while selectively inverting sulfonate (R)-**80**, thus achieving good overall yields of 83% and 96% ee for (S)-**81** (Scheme 29).

Scheme 30. Lipase-Catalyzed Acylation of Cyclopentenone **84**, Prepared by Rearrangement of Furaldehyde, Combined with Further Inversion of Alcohol (+)-(*S*)-**84** via Mitsunobu Reaction To Afford (–)-(*R*)-**84** in High Yield



Scheme 31. Lipase-Catalyzed Acylations of Cyclopentenones **86** and **87** (top) and Rearrangement of Pyranones **90a–d**, Followed by Dynamic Kinetic Resolution with Lipase Amano AK To Afford Cyclopentenones (–)-**89a–d** (bottom)



This strategy of inverting the undesired enantiomer after resolution was also used by Csáky et al. for their synthesis of functionalized cyclopentenones starting from inexpensive furaldehyde.⁸⁶ PhMgBr was added to furaldehyde, followed by rearrangement into cyclopentenone (±)-**83** and isomerization into cyclopentenone (±)-**84**. Resolution was carried out via lipase-catalyzed acylation of cyclopentenone (±)-**84**. This was followed by Mitsunobu inversion of the remaining (*S*) alcohol. This protocol afforded (–)-(*R*)-**84** with good yield and enantioselectivity (Scheme 30).

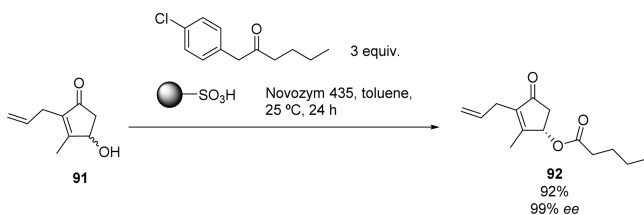
Caddick and co-workers used enzymatic methods to afford enantiopure oxygenated cyclopentenones in the total synthesis of Neocarzinostatin Chromophore A.⁸⁷ These authors established protocols for directly resolving oxygenated cyclopentenone racemic mixture (±)-**86** by lipase-catalyzed acylations, giving reasonable to good yields (35–50%) and high enantiopurities (>98% ee) (Scheme 31, top). More recently, studies undertaken by Nunes et al.^{74,88,89} established a dynamic kinetic resolution to afford higher yields of the desired cyclopentenone.^{88,89} In this one-pot protocol, pyranones **90a–**

d were isomerized under mild base-catalysis into racemic cyclopentenones (±)-**86a–d**, followed by addition of lipase, acylating agent, and silica gel. The latter accelerated racemization of cyclopentenones **86a–d**, thus renewing starting material for the enzymatic acylation carried out under optimized temperature, lipase loading, and solvent conditions. This dynamic kinetic resolution afforded acylated cyclopentenones (–)-**89a–d** with moderate to good yields and enantioselectivity (Scheme 31, bottom).

Racemization under acidic conditions was also employed by Wu et al.⁹⁰ The authors developed a sulfonated sepiolite as a solid superacid capable of operating at temperatures as low as 25 °C. This enabled a DKR protocol compatible with most lipases, including those that would not tolerate the typically higher temperatures employed in conventional solid superacid reactions. This system was tested for the resolution of several secondary alcohols, including cyclopentenone **91**, with remarkable yields and enantioselectivities (Scheme 32).

Despite several successful cases, chemoenzymatic methodology is not by itself a guarantee of higher efficiency. Myers et al.

Scheme 32. Dynamic Kinetic Resolution of Cyclopentenone 91 Involving Racemization with Solid Supercritical Sulfonated Sepiolite



illustrated such a case.⁹¹ Their previous synthesis of (*R*)-(+)-4-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one was a three-step process starting from (1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate, involving acetate hydrolysis of the intermediate (*R*)-4-oxocyclopent-2-enyl acetate catalyzed by wheat germ lipase. This step alone took 7 days plus 3 additional days for workup. The authors established a new and entirely chemical synthesis using the same starting material in five steps. This synthesis took less time, had a higher yield of 68% (as compared to the previous 32%), and afforded the product with >99% ee. As exemplified by the literature, lipase-catalyzed resolutions of oxygenated cyclopentenones need to be optimized on a case-to-case basis. Nevertheless, lipase-catalyzed reactions are a well-established tool that has been applied several times with good success to the synthesis of enantiomerically enriched oxygenated cyclopentenones, as illustrated by the referenced examples. Besides the standard enzymatic kinetic resolution, modifications have included inversion of the undesired enantiomer by selective nucleophilic substitution, such as under Mitsunobu conditions, or by dynamic kinetic resolution with concomitant starting material racemization to increase the yield beyond the 50% ceiling. These developments combined with the mild conditions and low toxicity of enzymatic resolutions make these methods very competitive with regard to other asymmetric synthesis strategies. The high enantioselectivity, short synthetic route, and low toxicity of lipase resolutions are advantages well-recognized by industry, as highlighted by the patent literature. For instance, Masaru and Hideo,⁹² Masayoshi et al.,⁹³ and Minai et al.⁹⁴ have resolved acyl derivatives of 4-hydroxycyclopentenones by lipase-catalyzed hydrolysis. Furthermore, mixtures of optically pure acyl and alcohol derivatives can also be separated by crystallization of the acyl derivative (Masayoshi et al.)⁹⁵ or of the alcohol via alkoxide salt formation (Spur and Wong).⁹⁶ Last, Ishii and Mitsuda have patented the gene encoding a novel esterase from *Burkholderia cepacia* applicable for the resolution of 4-hydroxycyclopentenones.

2.3. Enzymatic Resolutions of Other Cyclopentenone Derivatives

The main aim of this Review is to cover enantioselective and asymmetric methods for directly obtaining enantiopure cyclopentenone products. We have already presented the resolution of racemic mixtures of cyclopentenones. Although resolution of racemic mixtures of compounds other than cyclopentenones is beyond our core topic of discussion, we find such cases are worthy of mention where they are precursors or direct derivatives of enantiopure cyclopentenones. Herein, we will reference some representative cases of such synthetic strategies.

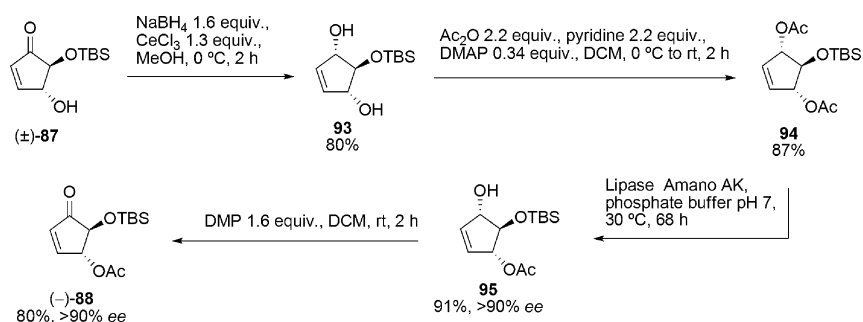
Prostanoid syntheses often make use of *meso* diol compounds that can be desymmetrized by lipase-catalyzed acylation or hydrolysis. This approach allows for yields up to a theoretical maximum of 100%, avoiding the 50% ceiling limitation of classic resolutions. Cyclopentenones themselves can be reduced to afford *meso* diols, which are resolved and later oxidized back to cyclopentenones. Caddick et al. reduced and acylated cyclopentenone (\pm)-87, yielding *meso* compound 94, which was desymmetrized by enzymatic hydrolysis, followed by oxidation back to the cyclopentenone.⁹⁷ This protocol achieved a good overall yield of 51% starting from (\pm)-87 and >90% ee for the enzymatic hydrolysis step (Scheme 33).

In 1995, Miyaoka et al. also applied this method of cyclopentenone resolution via intermediate *meso* diol desymmetrization.⁹⁸ In this case, the dimethyl substituents have provided a steric bias that allowed the lipase-catalyzed acylation of cyclopentenol 97 to proceed with excellent enantioselectivity of 98 (>99% ee). Also of merit is the ability to access both cyclopentenone enantiomers from the desymmetrized cyclopentenol intermediate 98 (Scheme 34).

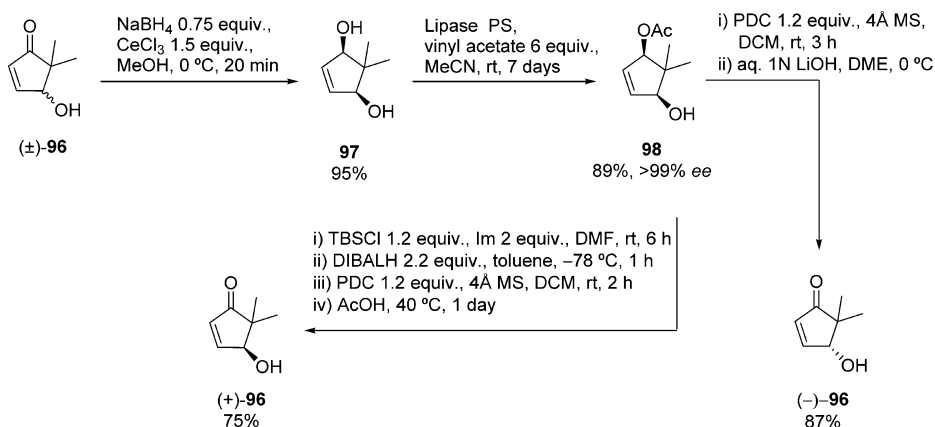
Previously, we referenced Johnson and Penning's use of a resolution achieved by chemical derivatization (Scheme 1)⁴¹ to overcome the low yield associated with that protocol. Doubly acetylated *meso* cyclopentanedial 100 was synthesized, starting by singlet oxygen addition to cyclopentadiene 99 followed by acetylation, dihydroxylation, and diol protection. Desymmetrization then was carried out by lipase-catalyzed deacetylation with electric eel acetylcholinesterase, followed by oxidation to afford the target cyclopentenone (+)-1 in 33% overall yield and with high enantioselectivity (98% ee). This rather modest yield was mostly due to the low yield from the first step (Scheme 35).

The modest yield obtained from cycloaddition of singlet oxygen was recognized as the main obstacle to a better overall yield for protocols starting from cyclopentadiene. Johnson and co-workers applied a slightly different strategy by using peracetic acid to generate an epoxide intermediate that was opened with 4-methoxyphenol, catalyzed by Pd(0) to give (\pm)-104, albeit once

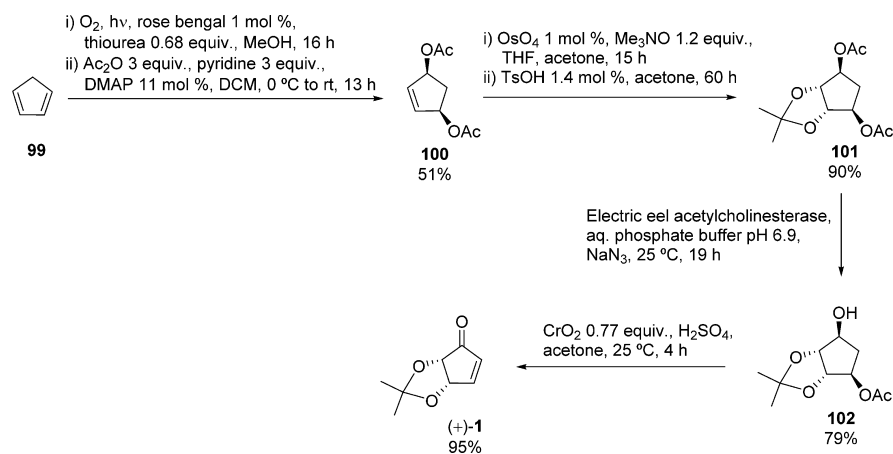
Scheme 33. Resolution of Cyclopentenone 87 via Reduction to Cyclopentenol 93, Followed by Acylation to Cyclopentenone 94, Lipase-Catalyzed Hydrolysis, and Final Reoxidation to (–)-88



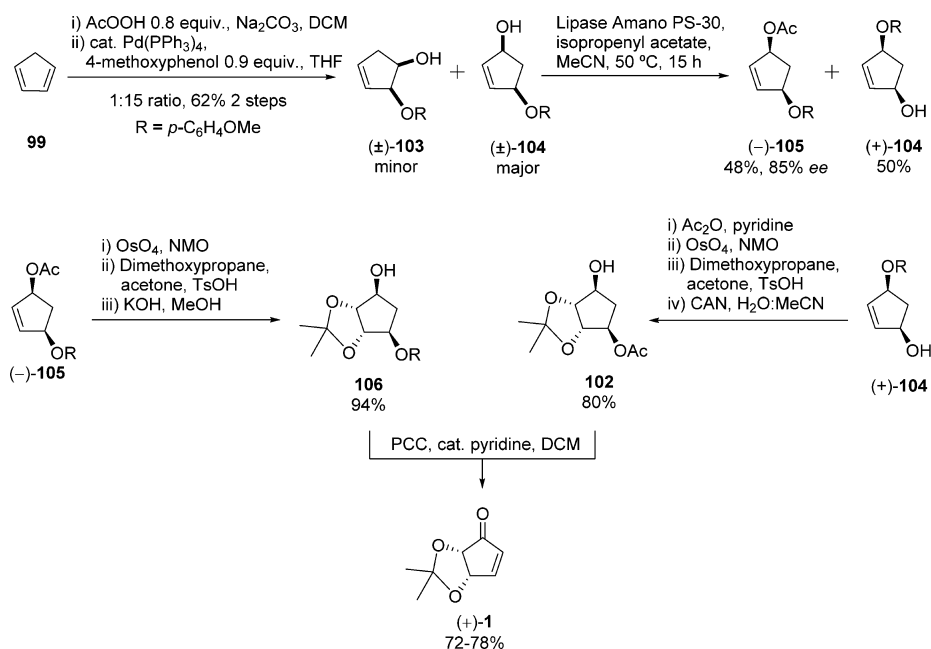
Scheme 34. Lipase-Catalyzed Resolution through Acylation of Cyclopentenol 97 To Afford Cyclopentenones (+)-96 and (–)-96 Following Further Synthetic Manipulation



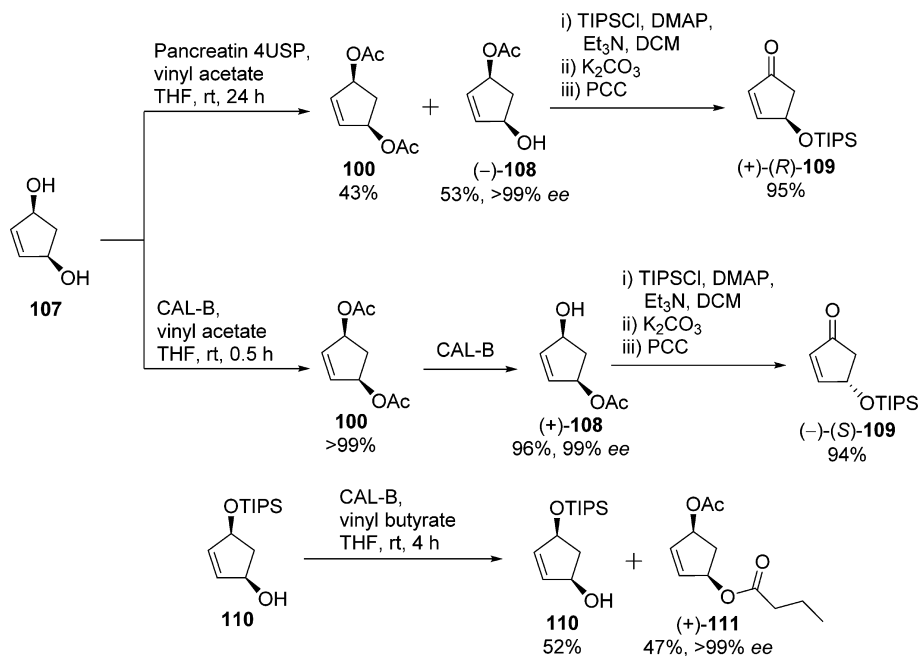
Scheme 35. Singlet-Oxygen Cycloaddition to Cyclopentadiene 99, Followed by Acetylation, Dihydroxylation, Protection, and Enzymatic Desymmetrization with Further Oxidation To Afford Cyclopentenone (+)-1



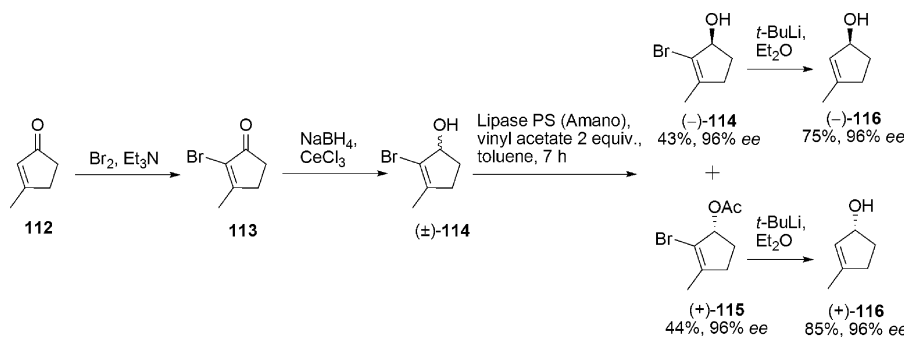
Scheme 36. Functionalization of Cyclopentadiene by Oxidation with Peracetic Acid, Followed by Lipase-Catalyzed Acylation with Further Synthetic Manipulation To Afford Cyclopentenone (+)-1



Scheme 37. Desymmetrization by CAL-B-Catalyzed Acylation, Elimination, and Oxidation To Afford TIPS-Protected 4-Hydroxycyclopentenone Derivatives (+)-(R)-109 and (-)-(S)-109 (top); and CAL-B-Catalyzed Resolution of TIPS-Protected Diol 110



Scheme 38. Bromination and Reduction of Cyclopentenone 112, Followed by Resolution with Lipase PS (Amano) and Lithium Transmetalation with Protonation To Afford Cyclopentenols (-)-116 and (+)-116



again with modest yield.⁹⁹ This was followed by resolution with lipase Amano PS-30 that gave oxygenated cyclopentenones (+)-104 and (-)-105. Notably, both were used to afford target compound (+)-1, following a straightforward strategy of oxidative dihydroxylation, diol protection, oxidation, and elimination (Scheme 36).

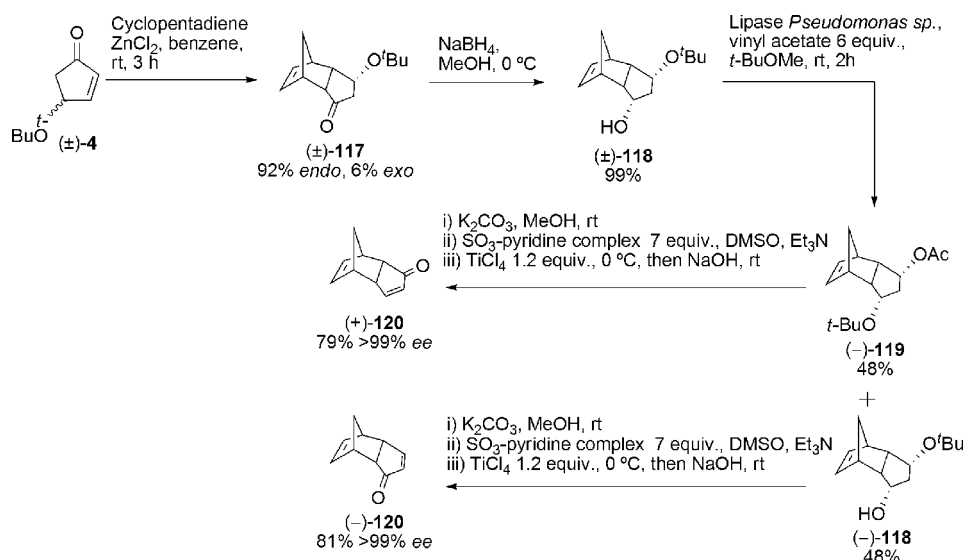
More recently, Specklin et al. screened conditions for the enzymatic resolution of *meso* diol 107.¹⁰⁰ Their aim was to provide a quick and efficient scaled-up route to enantiopure 4-hydroxycyclopentenone 29, made available as a racemate from rearrangement of 2-hydroxymethylfuran. The racemic cyclopentenone was reduced under Luche conditions to afford the *meso* diol starting material. Several lipases, such as pancreatins 1USP and 4USP, PPL and CAL-B, were screened using acylating agents vinyl acetate and vinyl butyrate. While most lipases require several hours to provide good yields, CAL-B was too reactive, resulting in dual acylation. Pleasingly, enzymatic hydrolysis of the diacetate with CAL-B afforded (+)-108 in excellent yield and enantioselectivity (Scheme 37, top). This provided an overall yield of 48% over seven steps for (-)-(S)-109 from 2-hydroxymethylfuran. Moreover, CAL-B was shown

to resolve the TIPS-protected diol 110, whereas other lipases proved too sluggish when dealing with the considerable steric bulk of the TIPS group. CAL-B proved to be too reactive with vinyl acetate, but using vinyl butyrate instead led to good yields and enantioselectivity, highlighting how the choice of acylating agent can be used to moderate enzyme activity (Scheme 37, bottom).

In 1995, Gawronski et al. obtained enantiopure cyclopentenols (-)-114 and (+)-115 from cyclopentenone 112 through bromination followed by reduction to the alcohol (±)-114.¹⁰¹ This racemic alcohol was subjected to a lipase-catalyzed resolution, which yielded cyclopentenols (-)-116 and (+)-116 following lithium transmetalation and protonation (Scheme 38). The high enantioselectivity was made possible by steric bulk provided by bromination at C2, in accordance with current understanding of lipase catalysis requirements.

Tricyclic cyclopentenones can also be resolved enzymatically, as shown by Sugahara and Ogasawara in their synthetic studies toward estrones.¹⁰² Cyclopentenone (±)-4 gave the corresponding [4+2] cycloadduct with cyclopentadiene via a Lewis acid-catalyzed Diels–Alder reaction favoring the *endo* product

Scheme 39. Conversion of Cyclopentenone **4** into Diels–Alder Adduct **118**, Which Is Further Resolved through Lipase-Catalyzed Acylation Followed by Synthetic Manipulation To Afford Cyclopentenones (+)-**120** and (–)-**120**

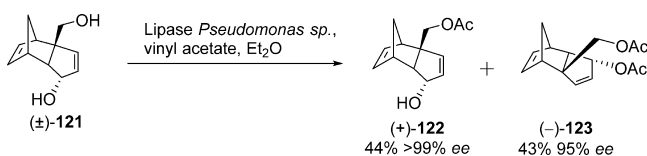


(±)-117. This was stereoselectively reduced to the *endo* alcohol **(±)-118**, which was enzymatically resolved with high enantioselectivity to afford products **(+)-119** and **(–)-118**, each converted into cyclopentenones **(+)-120** and **(–)-120**, respectively, with good overall yields (Scheme 39).

In 2001, Tanaka et al. also resolved bicyclic cyclopentenols that were later oxidized to bicyclic compounds with a cyclopentenone motif for the synthesis of iridoid lactones.^{103,104}

Lipase LIP (*Pseudomonas* sp.) was again used to this end with good results in the resolution of **(±)-121**, affording products **(+)-122** and **(–)-123** in 44% and 43% yields and high enantioselectivities of >99% ee and 95% ee, respectively (Scheme 40).

Scheme 40. Resolution of Bicyclic Cyclopentenol **121** by Lipase-Catalyzed Acylation



Dauvergne et al. have developed a synthesis toward 4-aminocyclopentenones, which can be useful synthetic blocks for carbocyclic nucleosides.¹⁰⁵ In their studies, cycloaddition of *t*-butylhydroxycarbamate to cyclopentadiene followed by N–O cleavage yielded racemic 1-amino-4-hydroxycyclopentene **124**. This product was resolved by lipase-catalyzed acylation to afford target molecule **(+)-124** in good yield (Scheme 41, top). Furthermore, the authors also reported an alternative strategy starting from the diacetate desymmetrized via lipase-catalyzed deacylation to yield **(+)-108**. This was followed by mono-substitution with NHBoc₂ under Pd(0) catalysis to afford **(+)-125** in greater yield (Scheme 41, bottom).

Li et al. also worked on the substrate **124**, using immobilized CAL-B as an alternative lipase in a mixed solvent system.¹⁰⁶ This enabled a lower enzyme loading without compromising the good yield and high enantioselectivity (Scheme 42).

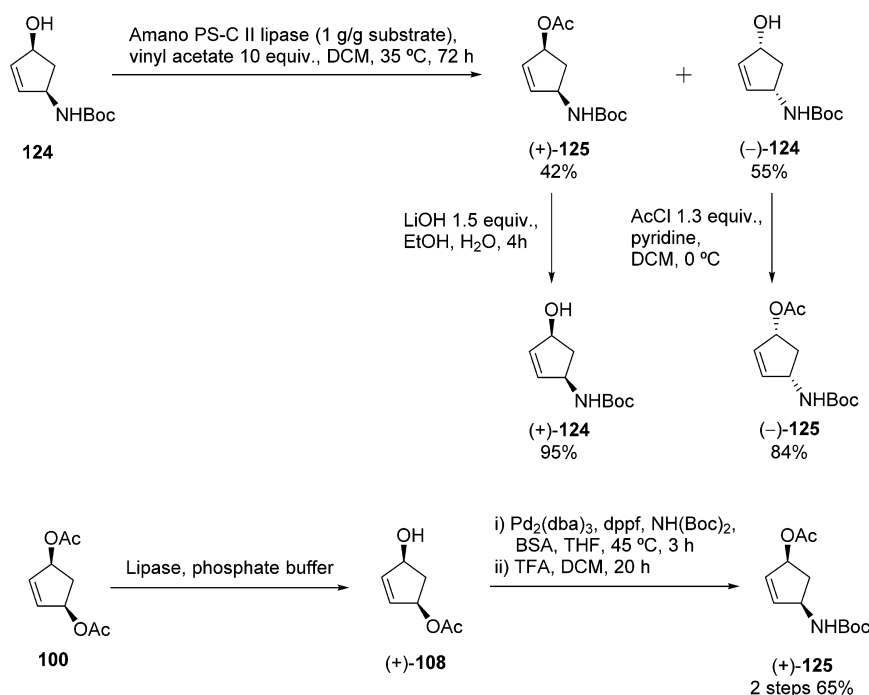
In 2004, Curran et al. developed enzymatic resolutions of a variety of *cis*-mono-4-*O*-protected-2-cyclopenten-1,4-diols.¹⁰⁷ Rearrangement of inexpensive furfuryl alcohol afforded cyclopentenones **127a–e**, which were diastereoselectively reduced to the corresponding *cis* 1,4-diols. The ratio of *cis*/*trans*/conjugate products from the reduction step was found to be dependent on solvent, and *cis* selectivity was improved by using additives such as lithium iodide or silanols. Deprotected diol **(±)-128** was enzymatically acylated, and the product of double acylation was recovered. Recycling diacetate **100** allowed for higher conversion to the desired enantiomer (Scheme 43, top). Higher activity and enantioselectivity were typically achieved in nonpolar solvents, but the diol was found to be poorly soluble in such conditions. Acylation of monoprotected diols **(±)-129a–e** was also achieved. Good yields and enantioselectivity were obtained with pancreatin lipase, depending on the choice of protecting group (Scheme 43, bottom). For instance, the trityl group was deemed too bulky to react, whereas the DHP group gave no diastereoselectivity. Watson et al. used the same protocol with high enantioselectivity (98% ee) using TBDMS as a protecting group.¹⁰⁸

To conclude, diastereoselective reduction of cyclopentenones to cyclopentenols amenable to enzymatic resolution, followed by reoxidation, allows for further options to prepare cyclopentenones in optically pure form. Furthermore, cyclopentenediols prepared through other methods provide *meso* compounds capable of being resolved and reoxidized as well. Given that cyclopentenones can be introduced with relative ease in a synthesis of more complex target molecules, these methods extend the scope and utility of enzymatic resolution as a powerful strategy to introduce chirality in synthesis.

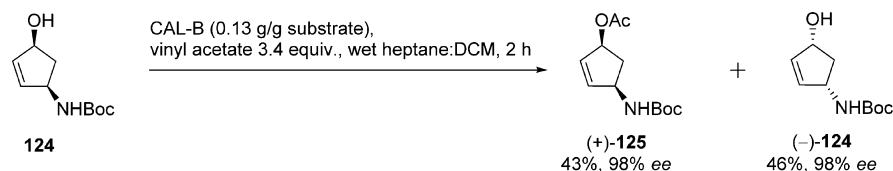
3. INTRODUCTION OF CHIRALITY DURING THE GENERATION OF THE CYCLOPENTENONE UNIT

Asymmetric transformations are among the most frequently exploited routes for introducing chirality in a molecule. Despite the cyclopentanoid skeleton being a ubiquitous feature among natural and nonnatural organic molecules, only a limited number of protocols have been applied for their asymmetric construction. Chiral compounds are generally obtained from chiral precursors

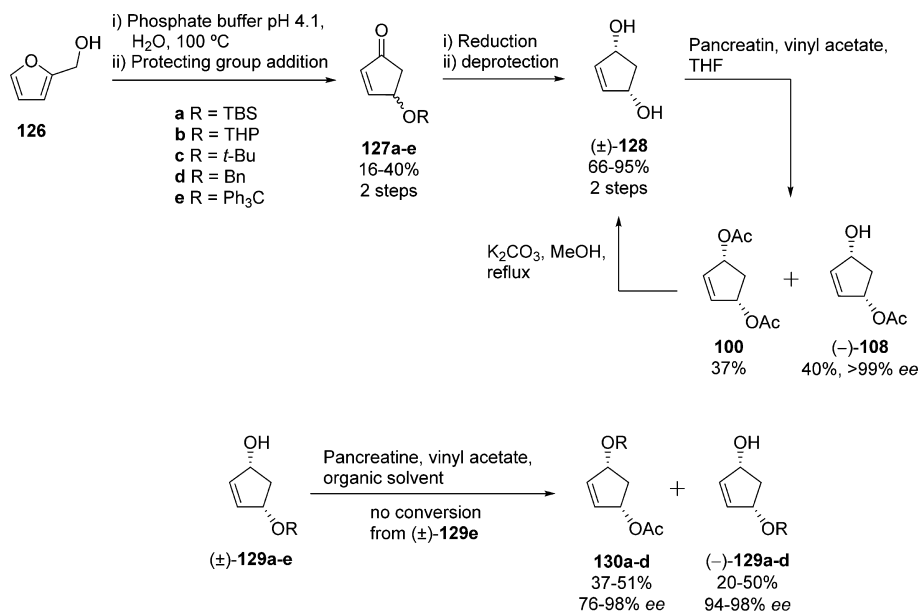
Scheme 41. Lipase-Catalyzed Resolution of Cyclopentenol 124 (top) and Desymmetrization of Acetylated Cyclopentenediol 100 (bottom)



Scheme 42. Enzymatic Resolution of Cyclopentenol 124 by CAL-B-Catalyzed Acylation



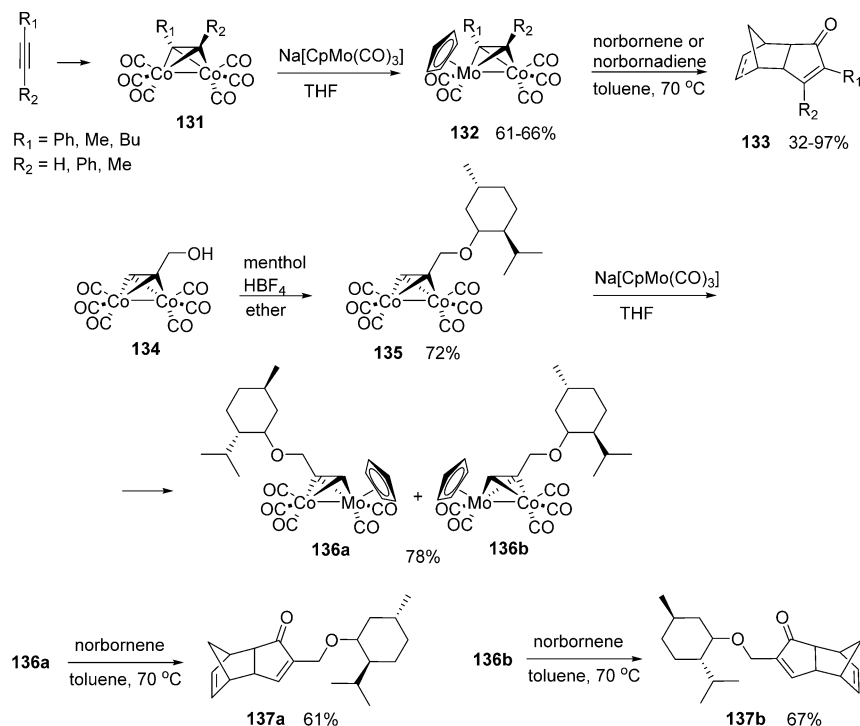
Scheme 43. Rearrangement of Furfuryl Alcohol 126 into Cyclopentenones 127a–e, Followed by Reduction, Protection, and Lipase-Catalyzed Resolution with Pancreatin and Recycled Diacetylated Cyclopentenediol, Leading to a Higher Yield (top); and Resolution of Cyclopentenols 129a–e by Pancreatin-Catalyzed Acylation (bottom)



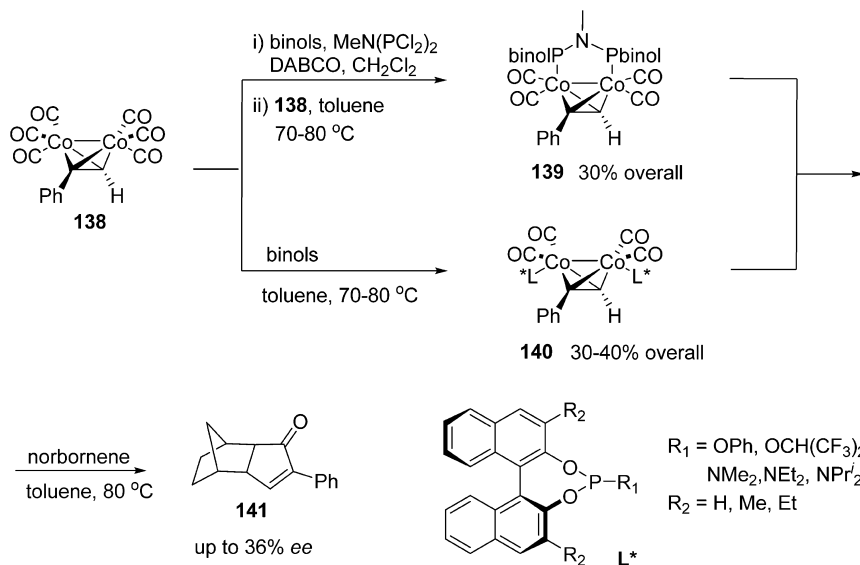
and by enzymatic resolution of racemates, while the asymmetric generation of the cyclopentenone ring is achieved predominantly

via Pauson–Khand annulation, both in stoichiometric and in catalytic variants, and by catalytic Nazarov cyclization.

Scheme 44. Heterobimetallic Alkyne Complexes in Asymmetric Pauson–Khand Reactions



Scheme 45. Chiral Bimetallic Complexes with Bidentate Ligands in the Asymmetric Formation of Cyclopentenones

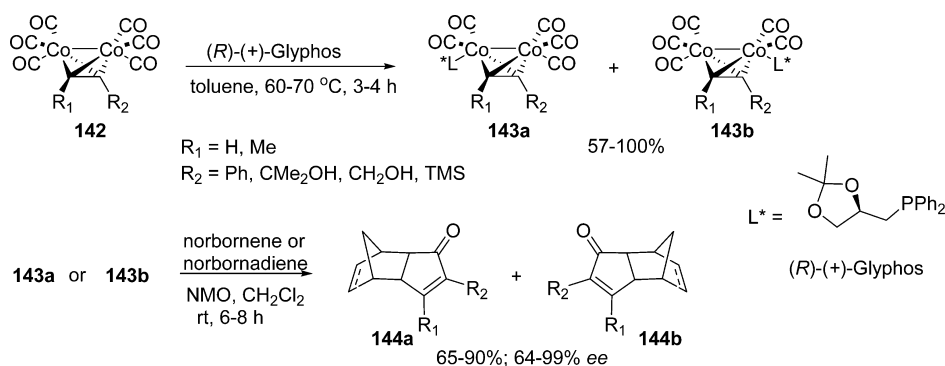
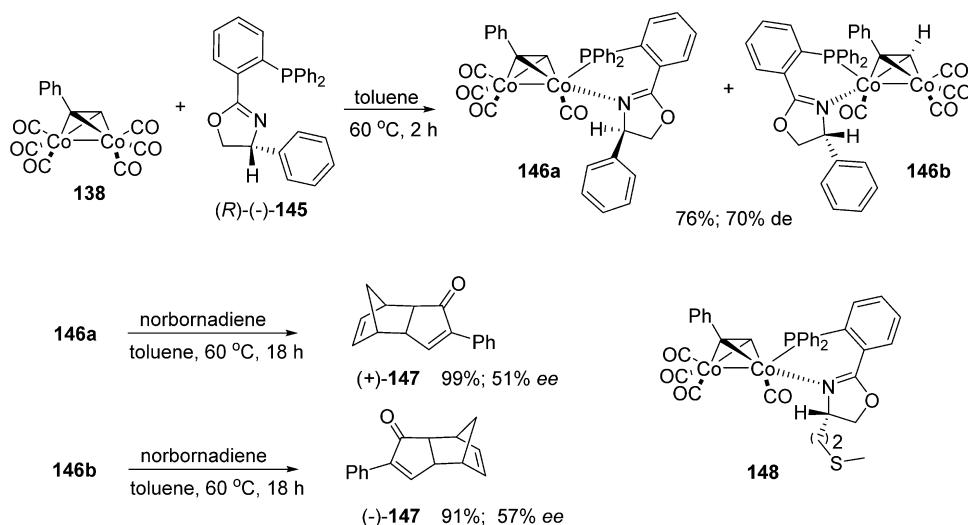


3.1. Pauson–Khand Reactions

The Pauson–Khand reaction (PKR), discovered in the early 1970s,^{109,110} is a cobalt-mediated formal [2+2+1] cycloaddition involving an alkene, an alkyne, and a carbon monoxide source, which proceeds via an alkyne hexacarbonylcobalt complex. Subsequently, the transformation was further developed and numerous modifications were introduced. Several metal carbonyls have been applied as carbon monoxide sources instead of dicobalt octacarbonyl, such as molybdenum, titanium, zirconium, ferrium, nickel, iridium, rhodium, and ruthenium carbonyls. The classical version involved a stoichiometric amount of cobalt carbonyl, while the recent catalytic variants require substoichiometric amounts of transition metal carbonyls. To circumvent the high temperatures and long reaction times

necessary to effect the classical PK cycloaddition, a range of promoters of the reaction have been applied, such as *N*-methylmorpholine *N*-oxide (NMO),¹¹¹ trimethylamine *N*-oxide (TMANO),¹¹² phosphine oxides,¹¹³ alkyl sulfides,¹¹⁴ thioureas,^{115–117} hard Lewis bases,¹¹⁸ etc.

The Pauson–Khand annulation is one of the most powerful tools for the preparation of cyclopentenones, structural units or key intermediates in the synthesis of complex molecules. Additionally, it is tolerant to a broad variety of functional groups, such as alcohols, ethers, thioethers, esters, nitriles, amines, amides, sulfonamides, etc. Therefore, the transformation has received great attention over the last few decades, and a wide number of records appeared in the literature, including a series of reviews.^{119–134} The asymmetric versions are efficiently accom-

Scheme 46. Diastereomeric Alkynepentacarbonyldicobalt Complexes of (*R*)-(+)-Glyphos Ligands in Intermolecular Pauson–Khand ReactionsScheme 47. Diastereoisomeric Phenylacetylene Dicobaltpentacarbonyl Complexes of (*R*)-Dihydrooxazole in the Pauson–Khand Reaction with Norbornadiene

plished by applying a number of methods to introduce chirality. Depending on the stereochemistry of the reagents, the protocols can be divided into two general categories based on chiral auxiliaries attached either to the alkene or to the alkyne, or starting from achiral precursors. Among the latter, the use of stoichiometric amounts of metal complexes with chiral ligands, asymmetric catalytic PKR, and the application of chiral promoters are the most intensively studied, and are thus summarized herein. Chiral cyclopentenones have been efficiently formed by using stoichiometric amounts of chiral bimetallic complexes derived from alkyne–dicobalt hexacarbonyl precursors in intermolecular Pauson–Khand reactions with an alkene. Among the latter, norbornene and norbornadiene are the most widely applied in the investigation of the efficiency of the chiral ligands. Rutherford and Christie have converted a series of alkynes into mixed-metal complexes **132**, which were further subjected to reaction with alkenes (Scheme 44).¹³⁵ The inherent chirality of the complexes when unsymmetrical alkynes were employed, that is, where the four corners of the metal–alkyne core are different, was discussed. It was suggested that the electronic difference between the metals might induce chirality in a subsequent cyclization reaction. To confirm this hypothesis, the authors converted propargyl alcohol dicobalt hexacarbonyl complex **134** into *O*-menthyl derivative **135** and then into a diastereoisomeric mixture of mixed-metal complexes **136**. The latter were easily separated by chromatography and were reacted

with norbornadiene to afford the corresponding enones **137** as pure isomers.

Chiral bimetallic complexes with bidentate ligands have been widely applied in the asymmetric formation of cyclopentenones. Konya et al. have observed the intermolecular PKR between norbornene and dicobalt carbonyl complexes of phenylacetylene **138**, where each of the cobalts were connected with identical chiral monophosphine ligands in moderate enantiomeric excesses (Scheme 45).¹³⁶ It was found that chiral monophosphine ligands at each of the axial positions in the acetylene–dicobalt complex **140** appeared to be generally more efficient than chiral bisphosphine ligands that bridge the two cobalts in equatorial positions **139**.

In 1996, Kerr et al. obtained a range of diastereomeric alkynepentacarbonyldicobalt complexes **143** containing the (*R*)-(+)-Glyphos ligand (Scheme 46), which were easily separated by chromatography.¹³⁷ These chiral complexes have been employed in intermolecular Pauson–Khand reactions, using anhydrous *N*-methylmorpholine *N*-oxide as the reaction promoter under mild conditions, and *exo*-cyclopentenone products **144** were isolated in good to excellent enantiomeric excesses.¹³⁸ The authors concluded that the enantioselection was not a result of the influence of the chiral Glyphos ligand but from the chiral C_2Co_2 core.

(*R*)-Dihydrooxazole **145** has been converted by Castro et al. into an 85:15 mixture of diastereoisomeric phenylacetylene

R = Ph, *n*-Bu, TMS,
t-Bu, CH₂OH

| R | yield | 150a:150b |
|--------------------|-------|-----------|
| Ph | 77% | 1:1.02 |
| <i>n</i> -Bu | 81% | 1:1.24 |
| TMS | 30% | 1:1.33 |
| <i>t</i> -Bu | 37% | 1:1.25 |
| CH ₂ OH | 44% | 1.87:1 |

150a or 150b

 A. norbornadiene, NMO
 CH₂Cl₂, N₂, rt, 24 h
 or B. norbornene, NMO
 CH₂Cl₂, O₂, 0 °C, 24 h

(+)-151 or (-)-151

A. 85-99%, 93-97% ee; or B. 77-89%, 74-94% ee

152 \rightarrow 153 $\xrightarrow[\text{iii) } n\text{-BuLi}]{\text{i) KH, THF; ii) Cl}_2\text{CHCH}_2\text{Cl}}$ 154 $\xrightarrow[\text{N}_2, 55^\circ\text{C}, 1\text{ h}]{\text{Co}_2(\text{CO})_8, \text{hexane}}$ 155

67-71% overall

norbornene or norbornadiene $\xrightarrow{0^\circ\text{C}, 1-4\text{ days}}$ 156 \rightarrow 157

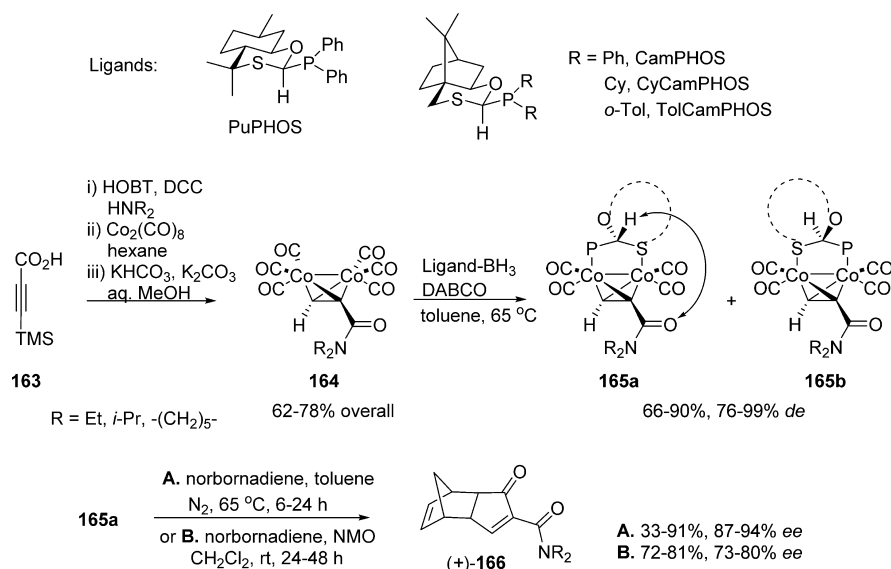
45-60% overall, up to 96% *de*

R = Me, ,

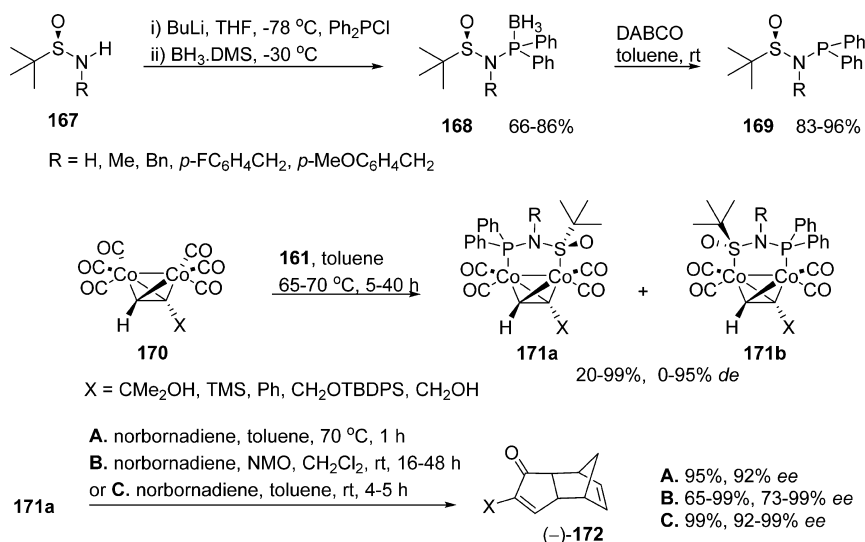
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These experiments have been further extended toward the less bulky chelated complex **148**, derived from (S)-*t*-leucinol, and the (–)-enantiomer of expected enone adduct **147** was obtained in high yield but in low enantiomeric excesses.¹⁴⁰ In contrast to

Scheme 51. Chiral Bidentate Complexes with Camphor-Derived Oxathiaphosphine Ligands in the Enantioselective Pauson–Khand Reaction



Scheme 52. Ligands Combining the Easily Accessible Chirality of Sulfur with the Coordination Ability of Phosphorus in the Enantioselective Pauson–Khand Reaction



chelated complexes, wherein thermal conditions were found to be more efficient, the tertiary amine *N*-oxide-promoted intermolecular PKR of nonchelated complexes **150** led to the corresponding norbornadiene-derived adducts **151** both in high yields and in high enantiomeric excesses (Scheme 48). The same pattern was observed for the formation of norbornene products **(+)-141** and **(-)-141**. An enantioselectivity mnemonic rule and a mechanistic model that explains the observed asymmetric sense of induction have been developed, and have been found to be in agreement with the results of model semiempirical molecular orbital calculations.

Chiral bidentate complexes with sulfur-containing ligands have also been applied in enantioselective PKRs. Marchueta et al. have developed a convenient procedure for the preparation of enantiopure 10-(*R*-thio)-2-*exo*-bornanethiols **153** from (1*S*)-camphor-10-thiol **152** (Scheme 49).¹⁴¹ Their ethynyl derivatives **154** led to excellent diastereoselectivities (up to 98:2) in Pauson–Khand reactions with norbornene and norbornadiene

through the intermediacy of a chelated dicobalt pentacarbonyl complexes **155**. It was found that thermal reaction conditions starting from the preformed chelated complexes were more efficient than *N*-oxide-promoted runs with in situ generation of the chelated intermediates. The corresponding adducts **156** were further transformed into 4-substituted 2-cyclopentenones **157** in high enantiomeric purity.

Chiral bidentate (*P,S*)-ligand **159** has been obtained by Verdaguer et al. by conversion of natural **(+)-pulegone** into oxathiane **158**, lithiation, alkylation of chlorodiphenylphosphine, and borane protection (Scheme 50).¹⁴² Asymmetric intermolecular Pauson–Khand reactions of alkyne dicobalt hexacarbonyl complexes **160** and the ligand **159** with norbornadiene were carried out in the presence of diazabicyclooctane (DABCO), and it was found that the selectivity strongly depended on the alkyne substituent *R*. Whereas the phenylacetylene complex led to a distereoisomeric mixture of phosphine **161a**, high selectivities were achieved with **160b–160d**. It was shown that the sulfur and

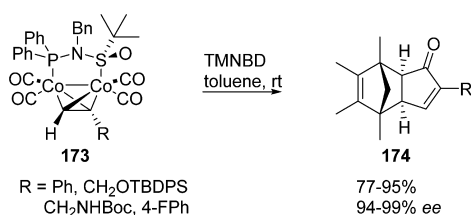
phosphorus atoms occupied two eclipsed pseudoequatorial coordination sites at different metal centers, *anti* to the dimethylcarbinol group, to avoid steric interactions, and that the sulfur atom was coordinated to the *pro*-S cobalt atom through its equatorial electron lone pair. The reaction of **161a** with norbornadiene was achieved with excellent enantioselectivity under thermal cycloaddition conditions, while **162c** and **162d** were obtained stereoselectively at room temperature in the presence of *N*-methyl morpholine *N*-oxide.

The same ligand, PuPHOS, and three camphor-derived oxathiaphosphines have been applied by Solà et al. in a hydrogen-bond-directed ligand coordination procedure (Scheme 51).¹⁴³ The amido complexes **164**, obtained in excellent overall yields from propynoic acid by subsequent TMS protection, amide coupling, complexation with Co₂(CO)₈, and deprotection of the alkyne terminal position, were converted into the corresponding bridged bidentate complexes **165** with excellent diastereoselectivity, up to 99% de. It was demonstrated that a nonclassical hydrogen-bonding situation of the methine moiety attached to three heteroatoms (O, P, S) with the amido-carbonyl acceptor provided a completely diastereoselective ligand exchange process between an alkyne dicobalthexacarbonyl complex and a phosphine ligand. The major diastereomeric complexes **165a** were subjected to an intermolecular Pauson–Khand reaction with norbornadiene. Thermal activation yielded the corresponding levorotatory *exo*-cyclopentenones **166** in excellent selectivities and moderate to good yields, while activation with *N*-methylmorpholine *N*-oxide afforded better yields but decreased selectivities.

The authors further developed efficient ligands combining the easily accessible chirality of sulfur with the coordination ability of phosphorus.¹⁴⁴ *N*-Phosphino *tert*-butylsulfonamides **169** were conveniently assembled from the corresponding commercially available chiral *tert*-butylsulfonamides **167** in two steps and have been further converted into bidentate complexes **171** with highly variable selectivities (Scheme 52). It was suggested that the substituent on the nitrogen atom would act as a relay element, transmitting the chiral information throughout the ligand, which was confirmed by the improved stereocontrol obtained with *N*-benzyl (up to 99% de) with respect to *N*-H (no de) and *N*-methyl (40% de) ligands. The intermolecular PKR of the major diastereomer **171a** with norbornadiene was achieved in different conditions, and the corresponding dextrorotatory adducts (–)-**172** were obtained with unprecedented stereoselectivity.

Lledó et al. have demonstrated that tetramethylnorbornadiene (TMNBD) was a versatile alkene for the synthesis of cyclopentenones.¹⁴⁵ Thereby, the cobalt complexes **173** have been converted into the corresponding PK adducts **174** with excellent yields and enantioselectivities (Scheme 53).

Scheme 53. Tetramethylnorbornadiene as a Versatile Alkene for the Synthesis of Cyclopentenones via Enantioselective Pauson–Khand Reaction



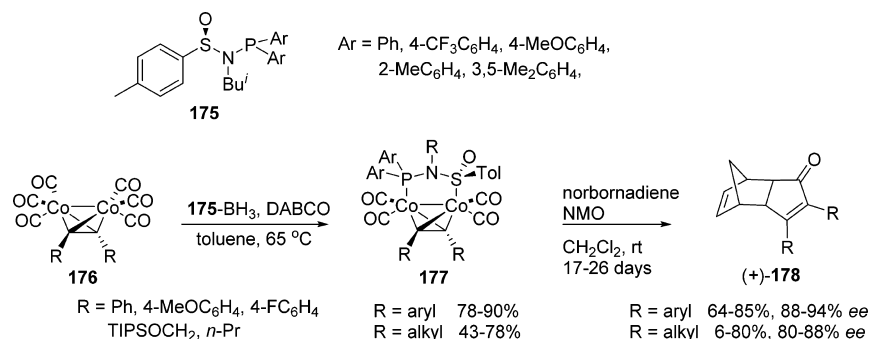
Ji et al. have accomplished an efficient asymmetric intermolecular PKR of internal symmetric alkynes with norbornadiene (Scheme 54).⁸¹ A series of chiral *N*-phosphino-*p*-tolylsulfonamide (NPSO) ligands **175** was applied, and the cyclopentenones **178** were formed with excellent enantioselectivity, albeit in low to moderate yields for aliphatic-substituted compounds. Better selectivities were achieved under *N*-oxide conditions, and thereby it was suggested that in the presence of *N*-oxide the PNSO ligand worked mainly as a strongly binding bridging ligand rather than a hemilabile one. The hypothesis that the olefin insertion occurs on the cobalt center where the sulfinyl group is bound was confirmed by the observation that the configuration of the final product was efficiently determined by the stereochemistry of the sulfinyl moiety, which indicated that olefin insertion took place close to the chiral sulfur center.

Enantiomerically pure *p*-tolyl and *tert*-butyl sulfinylmethyl phosphine (PCSO) ligands **181** and **182** with an extra chiral center at the central carbon atom have been prepared by Ferrer et al. via selective phosphinylation of the corresponding homobenzyl and benzyl sulfoxides **179** and **180** (Scheme 55).¹⁴⁶ The ligand exchange reaction to form Co₂–alkyne complexes provided moderate diastereoselectivity ratios, up to 6:1. The relevance of the relative stereochemistry on the sulfur and carbon centers for the formation of bridged complexes was disclosed, and it was found that only the S_RC_R diastereomer of *tert*-butyl PCSO analog **182b** provided the desired bridged complex **185**. The resulting PCSO cobalt complexes **184** and **185** were tested in the intermolecular PKR, and cyclopentenones **186** were obtained with up to 97% ee.

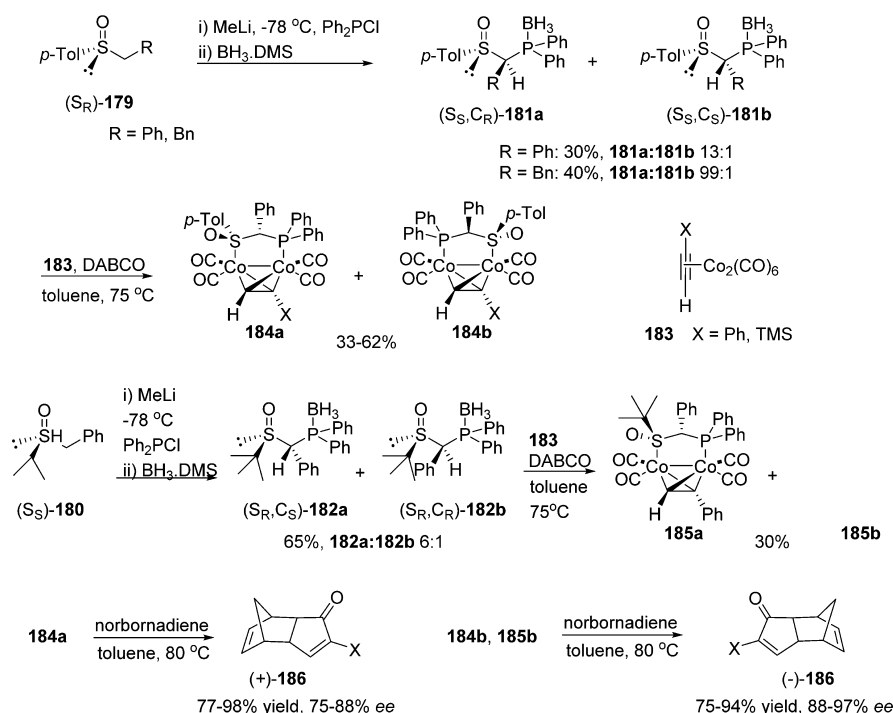
Fused tricyclic amines **190** have been synthesized from aldehyde **187** in a five-step sequence by Fustero et al.¹⁴⁷ As a key transformation, enynes **188** were converted into cyclopentenones **189** with good to excellent yields and diastereoselectivities (Scheme 56). The authors have found that the reaction output is strongly dependent on the substitution pattern in the aromatic tether and the nature of the substituent at the triple bond. The best results, 99% yield and >20:1 dr, were obtained when X = OMe, R₁ = H, and R₂ = Ph.

Similarly, Ruano et al. converted nitrile **191**-derived enynes **192** bearing remote sulfinyl functions into a mixture of cyclopentenones **193** possessing up to three carbon stereocenters with good to excellent diastereocontrol (Scheme 57).¹⁴⁸ The stereoselectivity of PKR was found to be strongly dependent on the coexistence of a quaternary stereogenic carbon and a sulfur atom bearing a coordinating lone electron pair in **192**. The transformation has been extended toward sulfenyl-containing enynes **194** leading to the observation that the thioethers **194** were much more efficient than sulfoxides **192** for controlling the stereoselectivity and for increasing the reactivity.

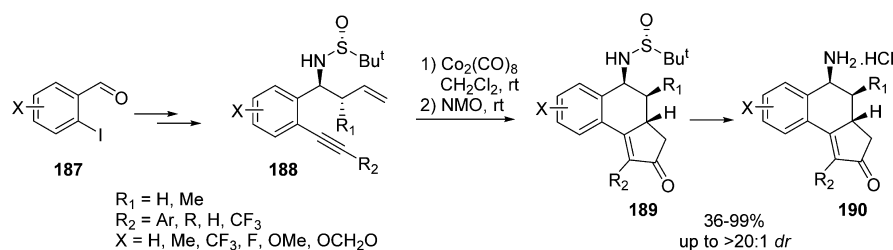
Shi et al. developed an expedient intramolecular PKR protocol for the synthesis of a series of *trans*-decaline-fused cyclopentenones **197**, key intermediates in the preparation of natural products, wherein the stereochemistry of PKR was controlled by the enyne stereocenters (Scheme 58).¹⁴⁹ It was found that the C₃ substituent plays a critical role in promoting efficient PKR; the transformation did not proceed with a hydroxyacyl derivative, a very low yield was obtained without a substituent (OR₂ = H), while compounds **197** were isolated in moderate to good yields when compounds **196** with ether or silyl ether substituents were used. Additionally, it was observed that the replacement of the cyclohexene moieties with cyclohexane moieties led to improved yields.

Scheme 54. Complexes with Chiral *N*-Phosphino-*p*-tolylsulfonamide Ligands in the Enantioselective Pauson–Khand Reaction

Scheme 55. Complexes with Chiral Sulfinylmethyl Phosphine Ligands in the Enantioselective Pauson–Khand Reaction



Scheme 56. Fused Tricyclic Amines Containing Chiral Cyclopentenone Units



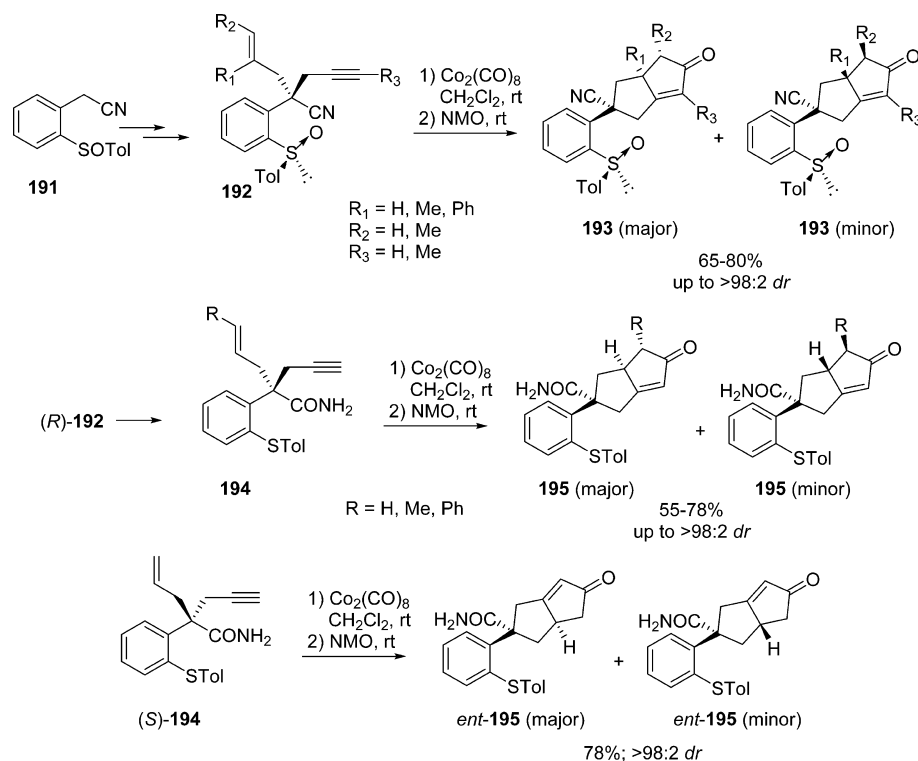
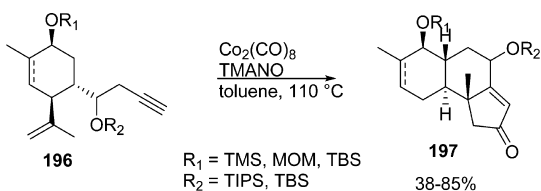
The procedure has been further extended by Huang et al. toward the asymmetric total synthesis of the anticancer agent (+)-fusarisetin A from the commercially available aldehyde 198 (Scheme 59).¹⁵⁰ As a crucial element of the 13-step protocol, the intramolecular PK reaction was applied for the stereoselective construction of the cyclopentenone 200 with a unique C₁₆ quaternary chiral center.

Recently, Grillet and Brummond have achieved an efficient transfer of chirality from chiral nonracemic allenes 201 and 203 to 4-alkylidene cyclopentenones 202 and 204 via a Rh(I)-catalyzed APKR (Scheme 60).¹⁵¹ Trisubstituted allenes with

high enantiomeric purity, >93% ee for 201 and >79% ee for 203, were subjected to cyclocarbonylation reaction, and the corresponding cycloadducts 202 and 204 were obtained in good to excellent yields without epimerization of the stereogenic center.

Similarly, the bicyclic adduct 207 was obtained by Cai et al. in 68% yield without detectable loss of enantioselectivity via Pauson–Khand cycloaddition reaction of diyne 206 by using $\text{Co}_2(\text{CO})_8$ and CO at atmospheric pressure (Scheme 61).¹⁵² X-ray structure analysis revealed the *syn* relationship between the methyl group and the newly formed bridgehead hydrogen.

Scheme 57. Enynes Bearing Remote Sulfinyl Functions as Precursors of Chiral Cyclopentenones

Scheme 58. Synthesis of *trans*-Decaline-Fused Cyclopentenones via Pauson–Khand Reaction

The catalytic asymmetric Pauson–Khand reaction is a fundamental route to obtain chiral cyclopentenones from achiral precursors. The transformation is accomplished by using a chiral precatalyst, generated from a transition metal salt and a chiral ligand, and a carbon monoxide source, either gaseous or some form of substitute. Optically active phosphines are the most widely applied as sources of chirality. Cobalt-catalyzed reactions of 1,6-enynes **208** in the presence of a series of chiral bidentate phosphines as ligands have been successfully accomplished by Hiroi et al.¹⁵³ (Scheme 62). It was demonstrated that (*S*)-BINAP

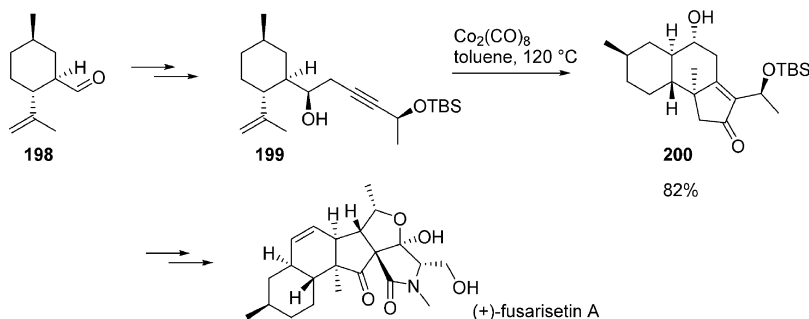
was the most effective ligand, affording the optically active (*R*)-2-cyclopentenone derivatives **209** with high enantioselectivity, up to 92% ee.

Gibson et al. obtained the same products by using $\text{Co}_4(\text{CO})_{12}$ instead of dicobalt octacarbonyl and a reduced amount of the ligand, 7.5 mol % versus 20 mol %.¹⁵⁴ The authors isolated a hexacarbonyldicobalt(0) complex in which BINAP binds to just one of the two cobalts and demonstrated that this complex was a precatalyst for asymmetric catalytic PKRs.

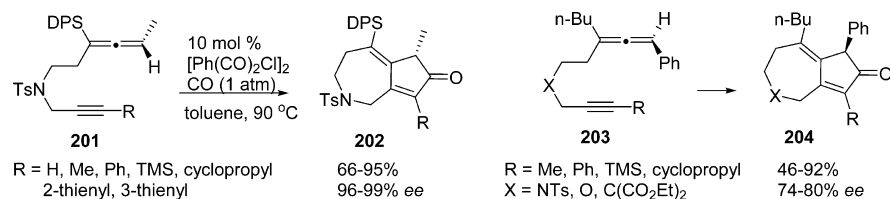
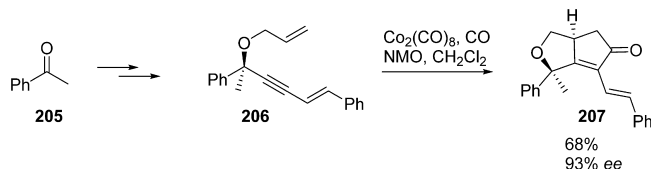
Similar bicyclopentenones **211** have been prepared by Jeong et al. through rhodium(1)-catalyzed PKR in the presence of silver triflate (Scheme 63).¹⁵⁵ The absolute configurations of selected samples were assigned, and it was shown that (*S*)-cyclopentenones were obtained when (*S*)-BINAP was employed as chiral ligand. The stereochemistry of the reaction was explained by a preferred transition state, wherein the steric congestion between one of the phenyl groups of (*S*)-BINAP and the substituent on acetylene was avoided.

Recently, Furusawa et al. performed a dual neutral–cationic rhodium(I)-catalyzed Pauson–Khand-type reaction using form-

Scheme 59. Asymmetric Total Synthesis of the Anticancer Agent (+)-Fusarisetin A



Scheme 60. Efficient Transfer of Chirality from Chiral Nonracemic Allenes to 4-Alkylidene Cyclopentenones

Scheme 61. Bicyclic Pauson–Khand Adduct with *syn* Relationship between the Methyl Group and the Newly Formed Bridgehead Hydrogen

aldehyde as a carbonyl source to form bicyclic pentenones **213** (Scheme 64).¹⁵⁶ The authors found that the simultaneous use of neutral rhodium(I) and cationic rhodium(I) complexes was required for efficient cooperative catalysis, the neutral rhodium(I)-catalyzed decarbonylation of formaldehyde and the cationic rhodium(I)-catalyzed cyclocarbonylation of 1,6-enynes using the resulting carbonyl moiety operated.

This reaction has been extended by Kim et al. with various ligands to examine the electronic and steric effects of chiral biaryl diphosphine ligands (Figure 2) on the Rh(I)-catalyzed PKR.¹⁵⁷ It was demonstrated that the enantioselectivity and yield of the reaction were influenced by the electron density on phosphorus, the dihedral angle of ligands, and the electron density of the alkyne substrate. Ligands bearing a narrower dihedral angle than BINAP, such as SYNPHOS and DIFLUORPHOS, were found to substantially increase the enantioselectivity of the reaction, as compared to BINAP-type ligands. From the other side, ligands having a deshielded phosphine, such as *p*-CF₃-BINAP and DIFLUORPHOS provided better enantioselectivity than BINAP, with reduced formation of side products, especially with electron-poor alkyne substrates.

To test the role of the oxygen atom, the authors subjected bis-enynes **214** to PKR in the presence of (*R*)-3,5-xyl-BINAP (Scheme 65).¹⁵⁸ It was found that the *O*-tethered enynes have superior reactivity and stereoselectivity than their congeners; only cyclopentenones **215** were isolated in excellent yield and selectivity. The corresponding *S*-tethered enyne was also studied, and it was found that the starting material was poisonous to the catalyst. The reaction was further expanded to dienynes **216**, possessing both *O*-tethered and *C*-tethered fragments. The diastereoisomeric mixture of compounds **217** was obtained with good selectivity, while the products of cyclization with *C*-tethered alkenes were not detected even at the trace level.

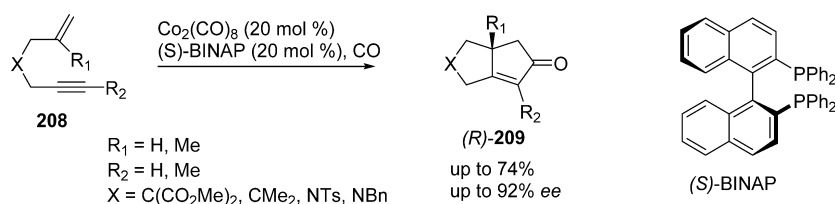
Desymmetrization of dienynes **218** by PKR has been investigated in the presence of (*S*)-DIFLUOROPHOS (Scheme 66).¹⁵⁸ Again, an *O*-tethered diyne led to **219a** as a sole product, while a diastereoisomeric mixture was formed from a tosyl-tethered substrate, **219b** being the major product. Similar results were obtained from enyne **220**, in which one vinyl group is replaced by ethyl, but in much lower yields.

Iridium-catalyzed syntheses of **226**–**228** have been achieved with up to 98% ee by Shibata and Takagi in the presence of 10 mol % (*S*)-tol-BINAP (Scheme 67).¹⁵⁹ The authors further improved the protocol by reducing the partial pressure of carbon monoxide.¹⁶⁰

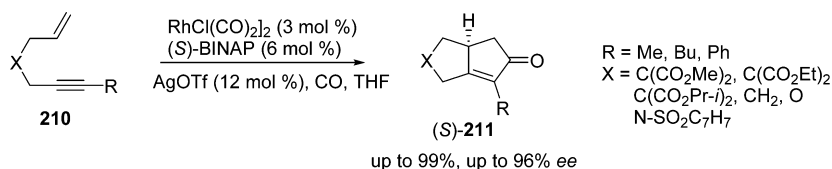
Lu et al. have accomplished a highly enantioselective (up to 97% ee) preparation of **230** by using cationic iridium complexes (*S*)-**234** derived from chiral phosphine-oxazoline (*S*)-**233** (Scheme 68).¹⁶¹ The nature of the anion was found to have a significant influence on both the enantioselectivity and the yield. The absolute configuration of cyclopentafuranone **230** (X = O) was determined as (*R*), while the others were not specified. The protocol was applied to the transformation of **231**, providing (*R*)-**232**, which was isolated with lower selectivity, 71% ee.

A highly enantioselective two-step one-pot Pauson–Khand-type reaction has been achieved by Son et al. on the basis of tandem action involving a homogeneous chiral Pd(II) catalyst and a heterogeneous Co/C catalyst (Scheme 69).¹⁶² Several chiral ligands were screened, and it was found that phosphinooxazoline (*S*)-**233** was the most efficient in the preparation of **238**, while the best selectivity in the formation of **241** was achieved using **242**. It was shown that the enantiomeric purity of the product depends upon the optical purity of the in situ-generated enyne by performing the reaction stepwise, where the ee value of the first Pd(II)-catalyzed asymmetric allylic alkylation reaction was maintained during the second cycloaddition reaction.

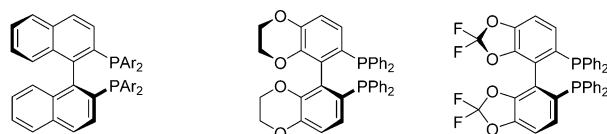
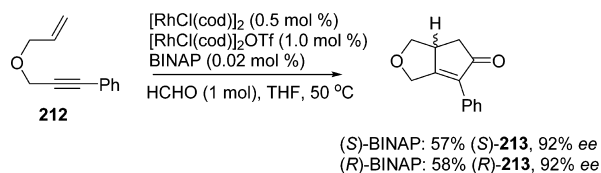
Various aldehydes have been applied as carbon monoxide sources instead of poisonous CO gas. Shibata et al.¹⁶³ have examined the efficiency of cinnamaldehyde, benzaldehyde, and 1- and 2-hexanal in a rhodium-catalyzed PK-type reaction under solvent-free conditions (Scheme 70). It was found that cinnamaldehyde was the most effective CO substituent in the series tested. The highly enantioselective coupling was achieved in the presence of 10 mol % (*S*)-tol-BINAP, and the bicyclic enones **245** and **246** were obtained in high yields. The authors performed experiments under argon flow, and a ¹³C-labeling

Scheme 62. (*S*)-BINAP-Directed Enantioselectivity in the Pauson–Khand Reaction

Scheme 63. Rhodium(I)-Catalyzed Asymmetric Pauson–Khand Reaction with (S)-BINAP Ligand



Scheme 64. Dual Neutral–Cationic Rhodium(I)-Catalyzed Pauson–Khand Reaction



$\text{Ar} = \text{Ph}, (\text{S})\text{-BINAP}$
 $\text{Ar} = 4\text{-MeOC}_6\text{H}_4, (\text{S})\text{-}p\text{-MeO-BINAP}$
 $\text{Ar} = 4\text{-CF}_3\text{C}_6\text{H}_4, (\text{S})\text{-}p\text{-CF}_3\text{-BINAP}$

Figure 2. Selected chiral biaryl diphosphine ligands.

experiment suggested that almost no free carbon monoxide was generated in this reaction; that is, CO generated by the decarbonylation of aldehyde was directly incorporated into the carbonylative coupling.

Similarly, Rh-catalyzed cooperative aldehyde decarbonylation as a carbon monoxide source and a cascade enantioselective Pauson–Khand-type reaction has been achieved by Kwong et al. with 6 mol % of the chiral atropisomeric diphosphane ligand SYNPHOS in alcohol solutions (Scheme 71).¹⁶⁴ Thereby, various 1,6-enynes **247–249** were transformed into the corresponding cyclopentenones **250–252** with up to 96% ee by cinnamaldehyde decarbonylation; benzaldehyde, *p*-methoxy-, and *p*-chlorobenzaldehyde were very effective, while *n*-non-ylaldehyde was found to be less efficient.

The transformation was also performed with (S)-P-PHOS in water, and cyclopentenones were obtained in similar yields and

selectivities.¹⁶⁴ The authors extended the protocol toward iridium-catalyzed reaction with (S)-tol-BINAP in dioxane and found that nonylaldehyde was the carbon monoxide source of choice.¹⁶⁵

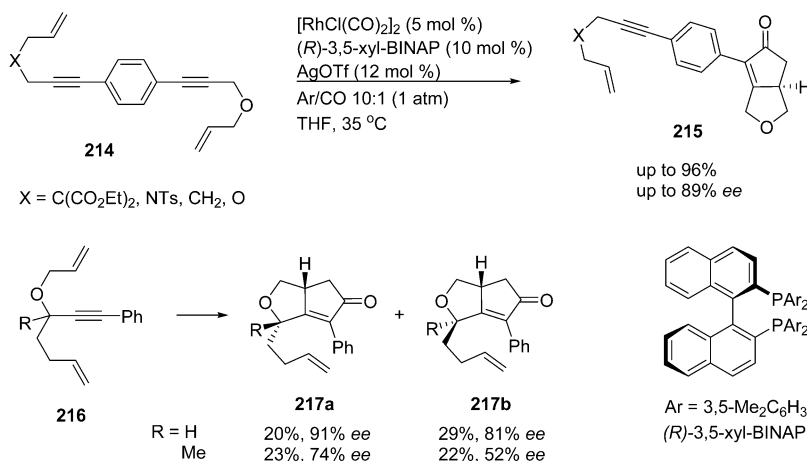
Carbohydrate-derived (*R*)-glyceraldehyde acetonide **254** has been used by Morimoto et al. in the presence of tol-BINAP (Scheme 72).¹⁶⁶ The Rh-catalyzed carbonylation reaction of enynes **253** has been carried out in various conditions, and it was found that (S)-tol-BINAP in a solventless protocol afforded PK adducts **255** with the best yields and selectivities. The transformation has been further performed with *rac*-**254** in the presence of (*R*)-tol-BINAP, demonstrating that the stereochemistry of both compounds did not significantly influence the reaction output.

Fuji et al. have accomplished a Rh-catalyzed PKR by applying formaldehyde as CO substitute in aqueous media and by combined use of a hydrophilic phosphine (TPPTS) with the hydrophobic (S)-tol-BINAP (Scheme 73).¹⁶⁷ The bicyclic enones **258–260** were obtained in high yields with up to 95% ee.

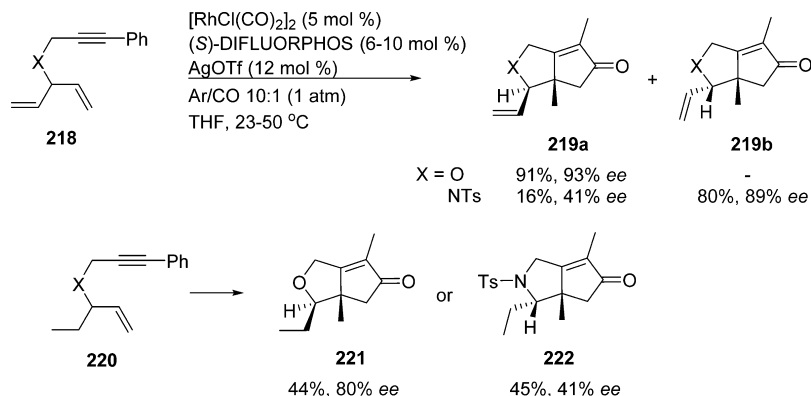
The first asymmetric CO transfer carbonylation using a formate ester as a CO surrogate has been achieved by Lee et al. (Scheme 74).¹⁶⁸ The Rh-catalyzed enantioselective transformation was carried out in the presence of 5 mol % (S)-xyl-BINAP ligand, and a series of cyclopentenones (**258**, **259**, and **262**) were obtained from the corresponding enynes **255**, **256**, and **261** with up to 94% ee. The authors have demonstrated by ¹³C-labeling experiments that the CO moiety, generated by the decarbonylation of formate, was directly incorporated into the carbonylative cyclization.

Chiral ligands other than phosphines have been also efficiently applied to the asymmetric Pauson–Khand reaction. Sturla and Buchwald have accomplished the Co-mediated formation of **264** in an atmosphere of carbon monoxide by using a biphosphite ligand (*S,S,S*)-**265** (Scheme 75).¹⁶⁹ The enynes **263** were converted into cyclopentenones **264** with low to good selectivity,

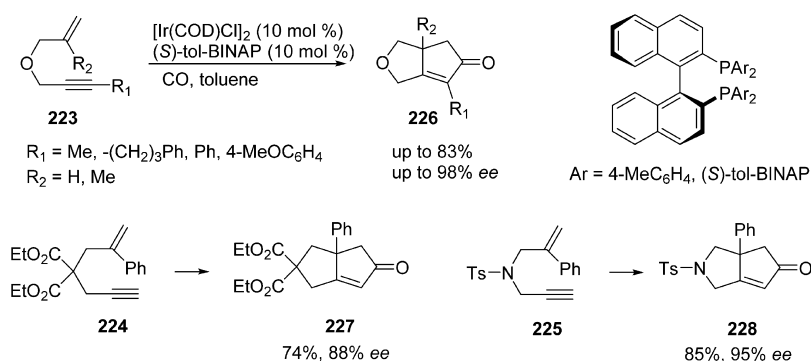
Scheme 65. Pauson–Khand Reaction in the Presence of (R)-3,5-Xyl-BINAP



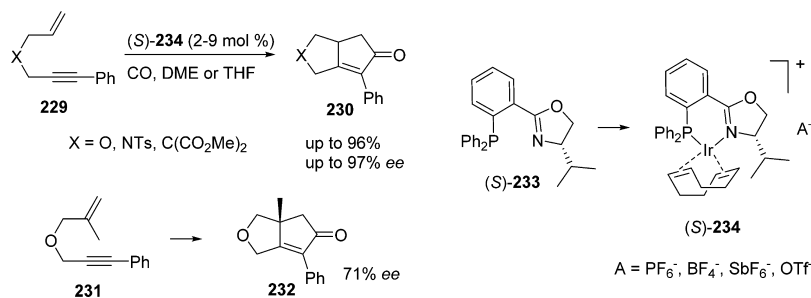
Scheme 66. Pauson–Khand Reaction in the Presence of (S)-DIFLUORPHOS



Scheme 67. Pauson–Khand Reaction in the Presence of (S)-Tol-BINAP



Scheme 68. Pauson–Khand Reaction in the Presence of Cationic Iridium Complexes



up to 75% ee, while the monophosphite ligand (S)-266 furnished racemic products.

A series of enones **268** has been obtained by Fan et al. through Rh-catalyzed PKR with monophosphoramidite ligand (R)-SIPHOS (Scheme 76).¹⁷⁰ It was found that the chiral ligand was efficient in the generation of ether-type products **268** (X = O), while amine and acetal enones were formed in good yields but poor selectivities. The influence of the electronic properties of the alkyne-bound aryl substituent on the enantiomeric excess of **268** (X = O) was examined, and it was shown that an electron-donating group provided similar enantioselectivities, but lower yields, whereas the substrates with electron-withdrawing groups gave higher yields at the expense of the enantioselectivities.

Orgué et al. have developed a novel family of *P*-stereogenic phosphines called ThaxPHOS, whose application in the Co-catalyzed intermolecular PKR led to the development of the first catalytic system with useful levels of selectivity (Scheme 77).¹⁷¹ The results demonstrated that some Co–diphosphane complexes (ThaxPHOS–Co–alkyne) were sufficiently reactive to

provide high yields and enantioselectivities of cyclopentenone **237**.

Hicks and Buchwald have accomplished a highly stereoselective synthesis of **276** and **277** by using 5–20 mol % of the chiral titanocene ligand (S,S)-(EBTH)Ti(CO)₂ (**272**), generated in situ from the dialkyl derivative **273** (Scheme 78).¹⁷² With 11-disubstituted alkene **278** and 1,7-enyne **279**, the transformations were achieved efficiently but with reduced selectivities. The limitation of the transformation in terms of substrate scope due to the sterically hindered nature of the ligand was studied,¹⁷³ and it was shown that 1,6-enynes substituted at the allylic and propargylic positions, some 1,7-enynes, and enynes containing 1,2-disubstituted olefins could not be cyclized using **272**.

Similarly, Sturla and Buchwald obtained a series of nitrogen-substituted enones **283** (Scheme 79) and have explored the influence of the nitrogen substituent and the concentration of the catalyst on the enantioselectivity of the cyclization.¹⁷⁴ It was found that nitrogen-containing enynes bearing an electron-rich, small nitrogen substituent, such as octyl-, benzyl-, or allylamino

$$\text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}\equiv\text{R} + \text{Ph}-\text{CH}=\text{CH}-\text{CH}(\text{OAc})-\text{Ph} \xrightarrow[\text{base, THF, rt, 4-6 h}]{[(\eta^3\text{allyl})\text{PdCl}]_2 (2.5 \text{ mol } \%)} \text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}(\text{Ph})=\text{CH}-\text{CH}_2-\text{C}\equiv\text{R}$$

235 **236** **(S)-233** (6 mol %) **(R)-237**

 R = Me, *n*-Bu, Ph

$$\text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}\equiv\text{R} \xrightarrow[130^\circ\text{C, 18 h}]{\text{CO/C, CO (30 atm)}} \text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}(\text{Ph})=\text{CH}-\text{CH}_2-\text{C}\equiv\text{R}$$

(R)-238

 81-95%, 84-95% ee

$$\text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}\equiv\text{R} \xrightarrow[130^\circ\text{C, 18 h}]{\text{CO/C, CO (30 atm)}} \text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}(\text{Ph})=\text{CH}-\text{CH}_2-\text{C}\equiv\text{R}$$

242

$$\text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}\equiv\text{R} \xrightarrow[130^\circ\text{C, 18 h}]{\text{CO/C, CO (30 atm)}} \text{MeO}_2\text{C}-\text{C}(\text{MeO}_2\text{C})-\text{C}(\text{Ph})=\text{CH}-\text{CH}_2-\text{C}\equiv\text{R}$$

239 **n = 1-3** **240** **(R)-241**

 90-97%, 31-94% ee

Reaction scheme for the synthesis of **245** and **246**:

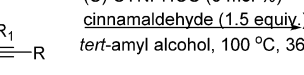
Reaction of **243** (a substituted cyclohexene with an alkyne) with [Rh(COD)Cl]₂ (5 mol %), (S)-tol-BINAP (10 mol %), and cinnamaldehyde (20 equiv.) at 120 °C for 2-36 h yields **245** (a bicyclic enone).

Reaction of **244** (a substituted cyclohexene with an alkyne) yields **246** (a bicyclic enone).

Reaction conditions for **246**: X = C(CO₂Et)₂, NTs.

Yields for **245**: up to 86% (R₁ = H, Me); up to 90% ee (R₂ = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, -(CH₂)₃Ph).

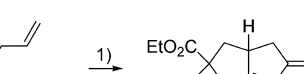
Yields for **246**: 79-99% (X = C(CO₂Et)₂); 45-56% ee (X = NTs).



247

250

 up to 83%, up to 96% ee

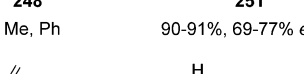


248

 R = Me, Ph

251

 90-91%, 69-77% ee

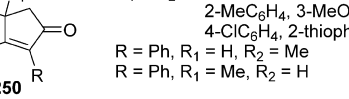


249

 R = Me, Ph

252

 94-97%, 80-88% ee



(S)-SYNPHOS

(S)-P-PHOS

253 + **(R)-254** $\xrightarrow[130\text{ }^{\circ}\text{C}]{[\text{Rh}(\text{COD})\text{Cl}]_2\text{ (5 mol \%)}\text{ (S)-tol-BINAP (10 mol \%)} }$ **255**

R = Ph, n-Bu
 X = O, NTs, C(CO₂Et)₂

65-95%
 47-88% ee

5774

$$\text{EtO}_2\text{C}-\text{C}(\text{Me})_2-\text{CH}=\text{CH}-\text{C}\equiv\text{C}-\text{R} \xrightarrow[\text{H}_2\text{O}, 100^\circ\text{C}, 1-8\text{ h}]{[\text{Rh}(\text{COD})\text{Cl}]_2 (5\text{ mol } \%), \text{ (S)-tol-BINAP (10 mol } \%), \text{ TPPTS (10 mol } \%), \text{ formaldehyde (5 equiv.)}} \text{EtO}_2\text{C}-\text{C}(\text{Me})_2-\text{C}_2\text{H}_3-\text{C}(\text{R})=\text{CH}-\text{C}(=\text{O})-\text{CH}_2-\text{C}(\text{Me})_2-\text{CO}_2\text{Et}$$

255 **258**

 R = Me, Bu, Ph 47-83%, 74-91% ee

$$\text{Ts}-\text{N}(\text{Me})_2-\text{CH}=\text{CH}-\text{C}\equiv\text{C}-\text{R} \xrightarrow[\text{H}_2\text{O}, 100^\circ\text{C}, 1-8\text{ h}]{[\text{Rh}(\text{COD})\text{Cl}]_2 (5\text{ mol } \%), \text{ (S)-tol-BINAP (10 mol } \%), \text{ TPPTS (10 mol } \%), \text{ formaldehyde (5 equiv.)}} \text{Ts}-\text{N}(\text{Me})_2-\text{C}_2\text{H}_3-\text{C}(\text{R})=\text{CH}-\text{C}(=\text{O})-\text{CH}_2-\text{N}(\text{Me})_2-\text{Ts}$$




256 **259**

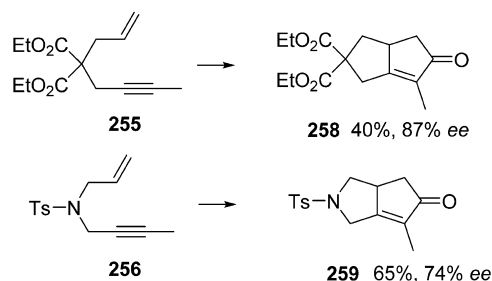
 R = Bu, Ph 58-60%, 91-92% ee

$$\text{R}_2-\text{C}(\text{Me})_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}\equiv\text{C}-\text{R}_1 \xrightarrow[\text{H}_2\text{O}, 100^\circ\text{C}, 1-8\text{ h}]{[\text{Rh}(\text{COD})\text{Cl}]_2 (5\text{ mol } \%), \text{ (S)-tol-BINAP (10 mol } \%), \text{ TPPTS (10 mol } \%), \text{ formaldehyde (5 equiv.)}} \text{R}_2-\text{C}(\text{Me})_2-\text{C}_2\text{H}_3-\text{C}(\text{R}_1)=\text{CH}-\text{C}(=\text{O})-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}(\text{Me})_2-\text{R}_2$$

257 **260**

 R₁ = Bu, Ph; R₂ = H, Me 61-75%, 93-95% ee

| | | | |
|--|--|---|---|
|  <p>261</p> | <p>[Rh(COD)Cl]₂ (2.5 mol %) <u>(S)-xyl-BINAP</u> (5 mol %) benzyl formate (5 equiv.) dioxane, 120 °C, 3 days</p> |  <p>262</p> |  <p>Ar = 3,5-Me₂C₆H₃ (S)-xyl-BINAP</p> |
| <p>R = Me, Et, Ph, 4-MeC₆H₄, 2-MeC₆H₄ 4-MeOC₆H₄, 3-MeOC₆H₄, 4-ClC₆H₄ 4-FC₆H₄, 2-thiophenyl</p> | | <p>up to 61% up to 94% ee</p> | |



$\text{EtO}_2\text{C}-\text{C}(\text{R})=\text{CH}_2$
 $\text{EtO}_2\text{C}-\text{C}(\text{R})\equiv\text{CH}$

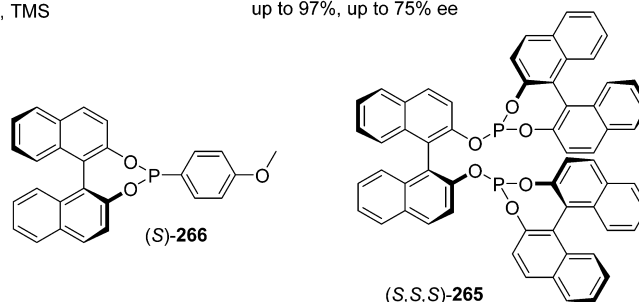
263

$(S,S,S)\text{-265}$ (10 mol %)
 $\text{Co}_2(\text{CO})_8$, CO
 toluene, 120 °C, 24 h

264

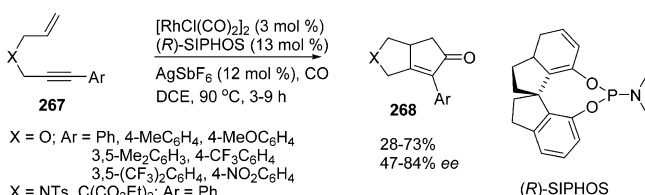
R = H, Me, CH_2OMe , TMS
 Ph, 4-MeOC₆H₄

up to 97%, up to 75% ee

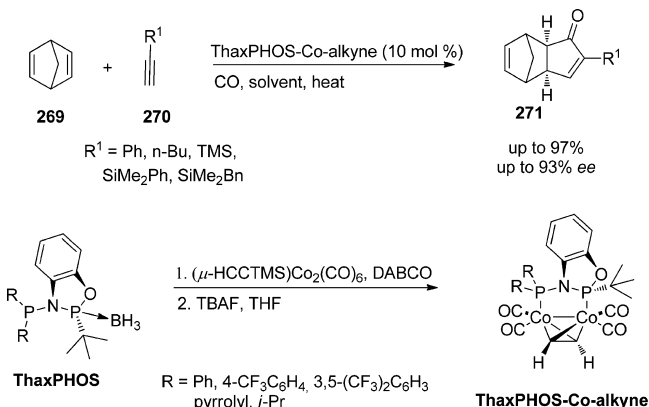


cobalt–alkyne complex. The first example was achieved by Kerr et al. with brucine-*N*-oxide (Scheme 80).¹⁷⁵ The propargyl alcohol complex **286** underwent PKR with norbornene under remarkably mild conditions, and the adduct **289** was obtained in moderate selectivity, up to 44% ee. It was proposed that the observed asymmetric control was due to the selective decarbonylation of the prochiral hexacarbonyl alkyne cobalt complex **286**, that is, selective removal of one CO from one of the two Co atoms, and/or that the amine (brucine), resulting from *N*-oxide

Scheme 76. (R)-SIPHOS as a Ligand in the Asymmetric Pauson–Khand Reaction



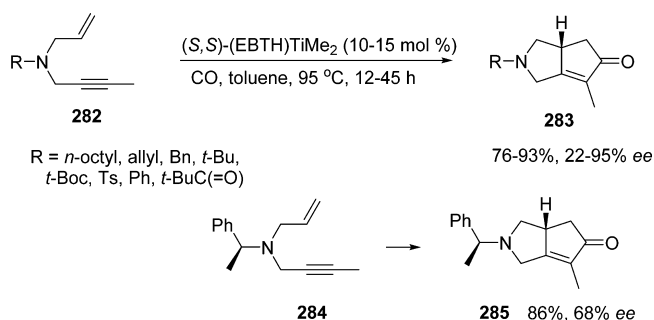
Scheme 77. A Novel Family of P-Stereogenic Phosphanes ThaxPHOS as Ligands in Asymmetric Co-Catalyzed Intermolecular Pauson–Khand Reaction



attack at a CO ligand, could selectively stabilize one of the two possible coordinatively unsaturated Co sites of the intermediate **287**.

The brucine-*N*-oxide-promoted protocol was further improved by using acetone or 1,2-dimethoxyethane as a solvent, and enhanced levels of enantioselectivity were achieved: **291** was formed with up to 78% ee.¹⁷⁶ The authors have investigated the scope of the transformation toward variously substituted alkyne complexes **290** (Scheme 81). The best levels of enantioselection were obtained with substituted propargylic alcohol complexes **290a–290e**, while removal of propargylic substituents (**290f**), protection of the hydroxyl group as its TMS ether (**290g**), or replacing the OH group with the sterically similar, but

Scheme 79. Nitrogen Enone Substituent-Directed Enantioselectivity in the Pauson–Khand Reaction

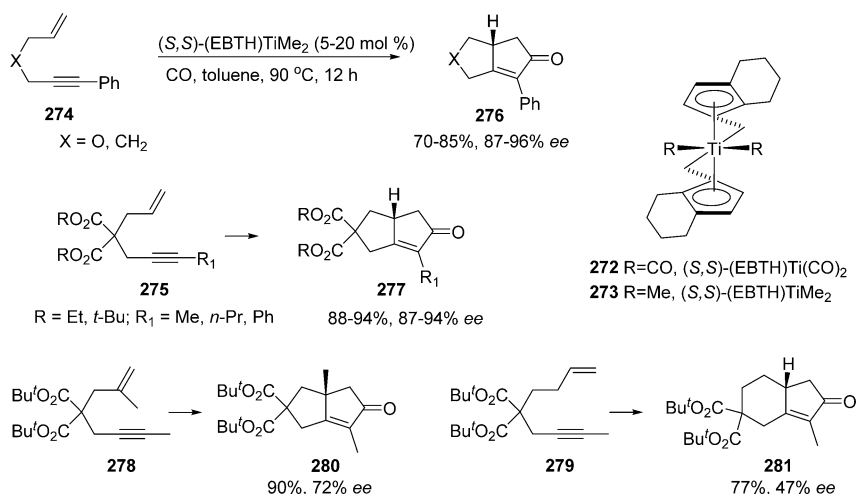


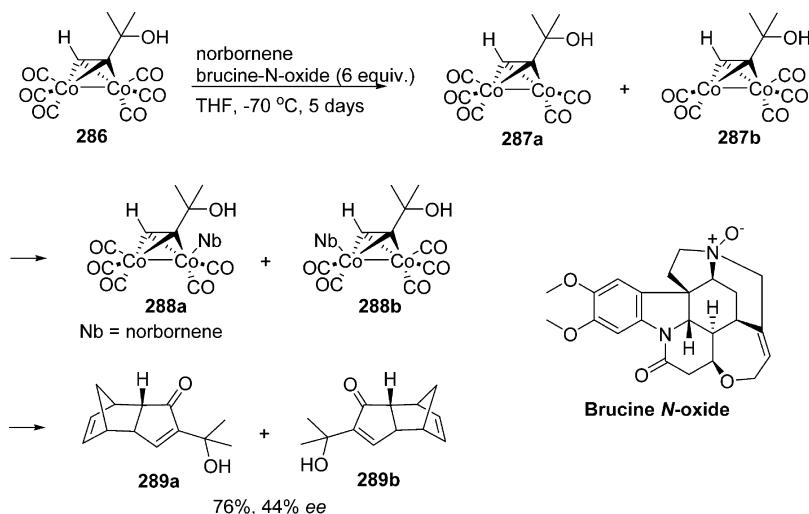
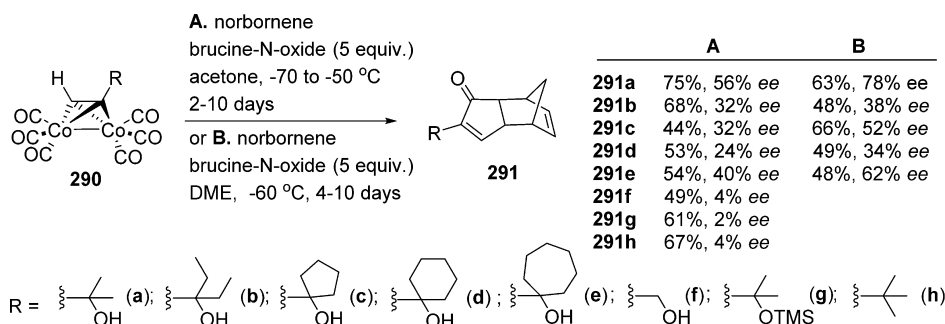
electronically neutral, methyl group (**290h**) led to a complete loss of stereocontrol.

Prochiral alkyne hexacarbonyl dicobalt complexes have been directly desymmetrized with brucine *N*-oxide in the presence of a phosphine (PPh₃) or phosphite (P(OMe)₃) ligand to produce the corresponding phosphorus-containing pentacarbonyl complexes with appreciable enantiomeric excesses.¹⁷⁶ In Pauson–Khand reactions, it was found that the enantiomeric integrity of the desymmetrized complex was conserved in the cyclopentenone product **291** and that the major enantiomer obtained in these reactions was the opposite of that obtained from a direct brucine *N*-oxide promoted Pauson–Khand reaction, allowing the preparation of either enantiomeric cyclopentenone in enriched form from a single source of chirality.

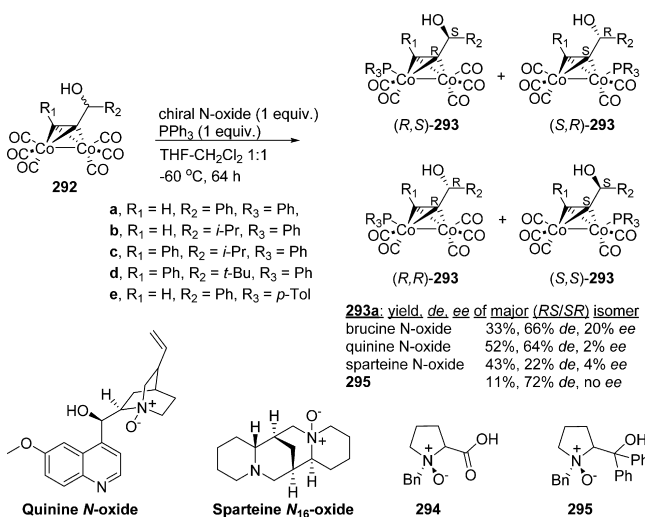
Carpenter and Nicholas accomplished the enantioselective preparation of (propargyl alcohol) dicobalt pentacarbonylphosphine complexes **293** via kinetic resolution with an optically active amine oxide (Scheme 82).¹⁷⁷ The effects of variations in temperature, solvent, substrate, phosphine, and amine oxide on the diastereoselectivity, enantioselectivity, and rate of the reaction were investigated. In addition to brucine *N*-oxide, several other *N*-oxides were studied, such as quinine *N*-oxide, sparteine *N*-oxide, and proline derivatives **294** and **295**, but the best results were obtained by using the initial promoter in the THF–dichloromethane system for the phenyl-substituted terminal alkyne **292a**. It was found that carbonyl substitution reaction with triphenylphosphine and brucine *N*-oxide proceeded with an increase in diastereoselectivity over thermal

Scheme 78. Chiral Titanocene Ligand (S,S)-(EBTH)Ti(CO)₂ in the Asymmetric Pauson–Khand Reaction



Scheme 80. Brucine-*N*-oxide-Induced Stereoselective Pauson–Khand ReactionScheme 81. Extension of Brucine-*N*-oxide-Promoted Protocol toward Various Substituted Alkyne Complexes

Scheme 82. Enantioselective Preparation of Dicobalt Pentacarbonylphosphine Complexes via Kinetic Resolution with Optically Active Amine Oxides

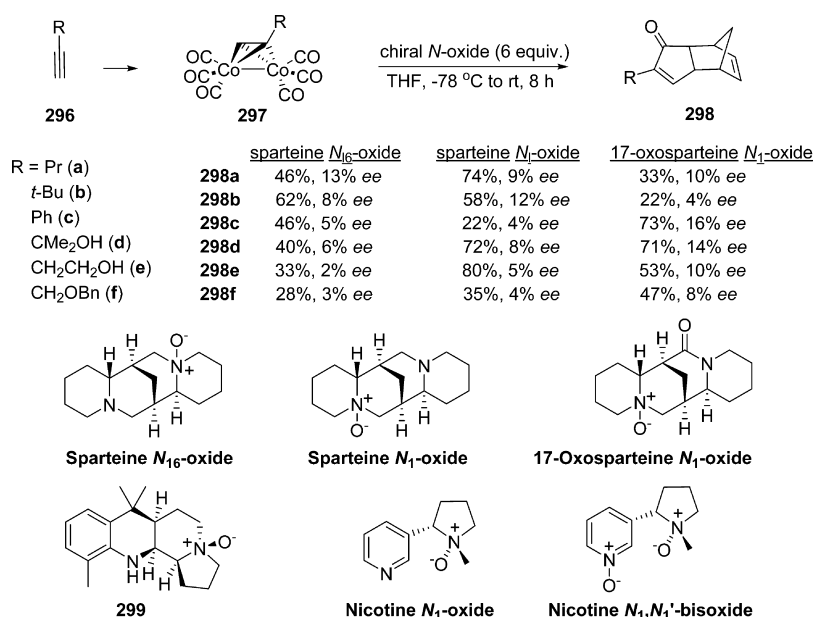
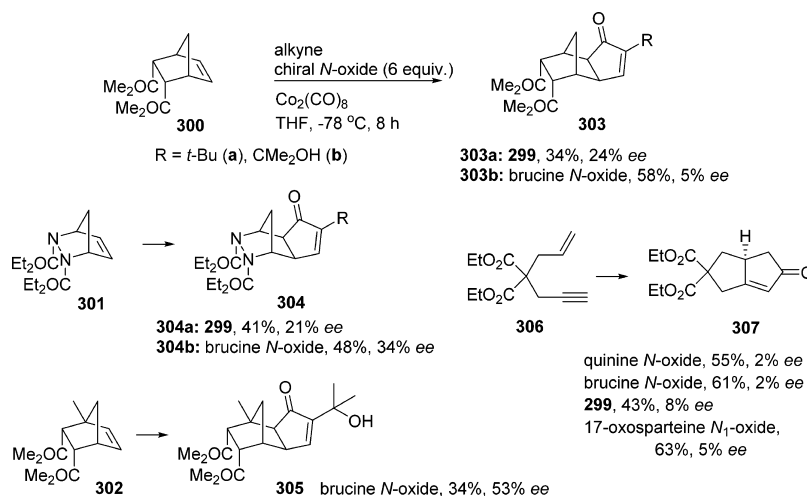


processes, and with a significant but modest enantioselectivity of 20% ee.

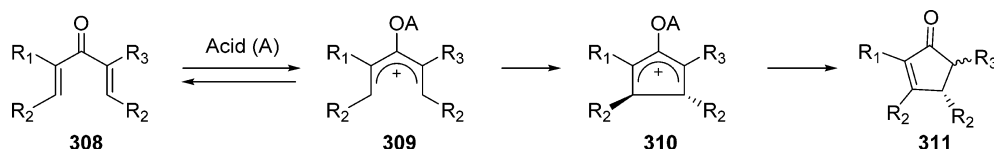
The enantiomerically pure (–)-sparteine *N*₁₆-oxide, (+)-sparteine *N*₁-oxide, and (–)-17-oxosparteine *N*₁-oxide, easily available from the naturally occurring lupine alkaloid (–)-sparteine, as well as the *cis*-configured (+)-indolizino[3,4-*b*]-quinoline *N*-oxide 299, have been employed as chiral promoters

in the Pauson–Khand cocyclization of various terminal alkynes 296 with norbornene to give the bicyclic cyclopentenones 298 by Derdau et al.¹⁷⁸ (Scheme 83). The newly developed promoter 299 showed improved enantioselectivity with respect to the natural amine-*N*-oxides in the formation of 298b and 298d, 33% and 18% ee, respectively, while oxosparteine was the most efficient in the other examples.

The reaction was also performed with small amine *N*-oxides such as (–)-nicotine *N*₁-oxide and (–)-nicotine *N*₁,*N*₁'-bisoxide, providing the cyclopentenones 298 with low enantioselectivities (<10% ee).¹⁷⁹ Similar selectivities were achieved with quinine *N*-oxide and brucine *N*-oxide with a single exception with both promoters, 30% ee for 298e and 42% ee for 298d, respectively. To study the influence of functional groups on the enantioselectivity, the PKR of norbornene derivatives 300–302 with the alkynes 296b and 296d was performed in the presence of sterically more demanding amine *N*-oxides with additional hydrogen donor and/or acceptor sites, (–)-brucine *N*-oxide, and tetrahydroquinoline derivative 306 (Scheme 84). It was found that the *endo*-norbornene ester 300 and the azanorbornene ester 301 generally resulted in a slight decrease of the enantiomeric excess of enones 303 and 304 as compared to the parent norbornene system 298. When *endo*-1-methylnorbornene ester 302 was used instead of 300 under the same conditions, the cyclopentenone 305 was obtained with improved enantioselectivity (53% ee), and it was suggested that the steric effect of the 1-methyl group overrules the electronic and/or steric effects of the ester groups. The intramolecular reaction of enyne 306 in the presence of (–)-quinine *N*-oxide, (–)-brucine

Scheme 83. Natural Amine-*N*-oxides as Chiral Promoters in the Pauson–Khand Cocyclization of Various Terminal Alkynes with NorborneneScheme 84. Sterically Demanding Amine *N*-Oxides with Additional Hydrogen Donor and/or Acceptor Sites in the Pauson–Khand Reaction

Scheme 85. General Mechanism of the Nazarov Cyclization



N-oxide, (+)-**299**, or (–)-oxosparteine *N*-oxide was also investigated, and cyclopentenone **307** was obtained with low enantioselectivity irrespective of the type of *N*-oxide.

3.2. Nazarov Cyclizations

The Nazarov cyclization is a well-established pathway for the synthesis of cyclopentenones from cross-conjugated dienones. This electrocyclic reaction usually involves the formation of pentadienyl cation **309** in the presence of Lewis or Brønsted acids, which undergoes 4π-electrocyclization to give allyl cation

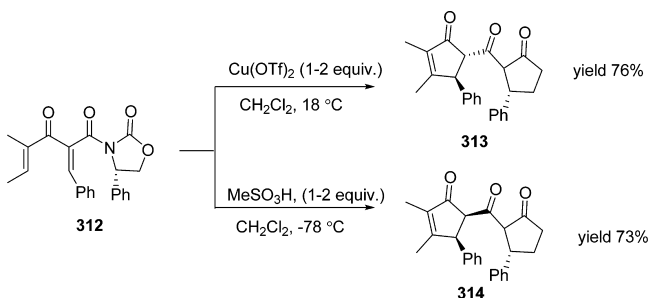
310, followed by a proton migration and formation of cyclopentenone **311** (Scheme 85).^{180–182}

In the absence of any stereochemical control, the reaction proceeds with equal amounts of clockwise and counterclockwise conrotation, resulting in a racemic mixture. The control of the absolute configuration could be achieved via specific direction of conrotation either by internal or by external asymmetric induction.

In 2003, Flynn et al. reported chiral-auxiliary-controlled asymmetric Nazarov cyclization to yield enantiomerically

enriched cyclopentenones **313** and **314** (Scheme 86).¹⁸³ The authors claimed that the cyclization of **312** could be made to

Scheme 86. Kinetic and Thermodynamic Control of the Chiral-Auxiliary-Controlled Asymmetric Nazarov Cyclization

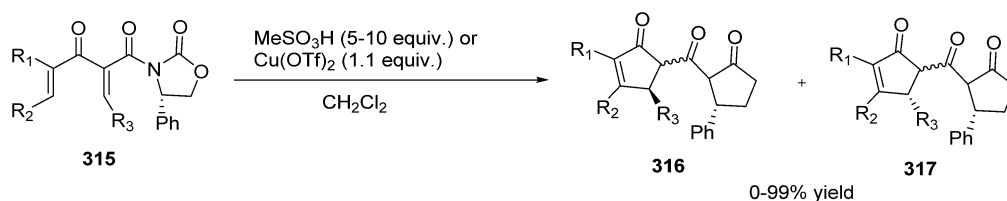


diverge, providing *cis*- or *trans*-cyclopentenones via kinetic or thermodynamic control. Kinetic control under triflic acid catalysis at low temperatures was advanced as a reason for the exclusive formation of **314**, while the cyclization at room temperature catalyzed by either $\text{Cu}(\text{OTf})_2$ or triflic acid afforded the more thermodynamically stable *trans* product **313**. Both products were obtained in good yields in their enantiomerically enriched forms.

In a very detailed subsequent work, Flynn and co-workers further explored the scope of their methodology and screened different auxiliary groups where phenyloxazolidinone exhibited the best torquoselectivity during the cyclization.¹⁸⁴ Additionally the authors discovered that both the steric and the electronic nature of the substituents on the dienone **315** affected the stereoselectivity. A mechanistic hypothesis based on the relative sizes of the chiral auxiliary and the substituent groups was proposed by the authors to explain their observations. Product yields were generally high; however, torquoselectivity was modest (Scheme 87).

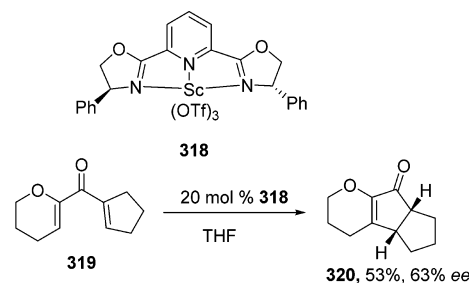
3.2.1. Asymmetric Catalysis. The Nazarov cyclization is one of the few electrocyclic reactions that can be promoted in an enantioselective fashion by chiral catalysts. However, there are still few examples in the literature for the asymmetric catalyzed Nazarov cyclization, probably due to limitations of this approach based on the spatial distance between the carbonyl group bonded to the chiral catalyst and the newly formed stereocenters that cause the reduced enantioselectivities. Furthermore, if the cyclization step is too slow, the final cyclopentenone is potentially subjected to racemization. A range of Lewis acid complexes have been described in the literature as possible asymmetric catalysts for the Nazarov cyclization in catalytic or stoichiometric amounts, some applications of chiral Brønsted acids were described, but so far the number of examples of either Lewis or Brønsted acid-catalyzed asymmetric Nazarov cyclizations remains quite limited.

Scheme 87. Phenyloxazolidinone Chiral-Auxiliary-Controlled Asymmetric Nazarov Cyclization



3.2.1.1. Asymmetric Nazarov Cyclization Catalyzed by Lewis Acids. In 2003, Trauner et al. developed an asymmetric Nazarov cyclization of alkoxydienone **319** catalyzed by chiral scandium triflate pyridine–bisoxazoline complex **318**, affording the enantiomerically enriched tricyclic **320** in moderate yield and enantioselectivity (Scheme 88).¹⁸⁵

Scheme 88. Chiral Scandium Triflate Pyridine–Bisoxazoline Complex Promoted Nazarov Cyclization

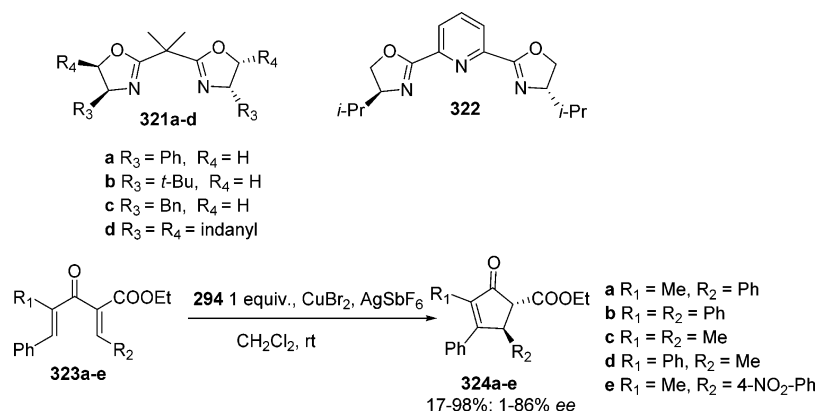
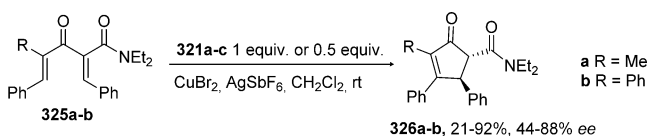


In the same year, Aggarwal and Belfield reported the asymmetric Nazarov cyclization of α -ester-substituted divinyl ketones **323a–e** and α -amide-substituted divinyl ketones **325a,b** promoted by bisoxazoline-based Lewis acid complexes.¹⁸⁶ A series of copper complexes of chiral bisoxazoline ligands **321a–d** and **322** have been tested as catalysts for the reaction, and it was observed that the complex with ligand **322** provided the best results in the case of divinyl ketones **323a–e**. Investigations into the nature of the substrates **323a–e** showed that more bulky groups at R_1 and R_2 promoted better enantioselectivities; however, the substituents at R_2 were found to be more essential than those at R_1 (Scheme 89).

Furthermore, the authors extended their investigation by using α -amide-substituted divinyl ketones **325a,b**. These substrates would be expected to provide similar control in the conformation of the Lewis acid–substrate complex, but in comparison with ester substrates they should provide faster reactions due to their decreased electron-withdrawing ability. However, a reduced reactivity was observed when ligand **322** was used. Therefore, ligands **321a–c** were studied, and it was observed that of these **321a** and **321b** were the most effective, providing the corresponding cyclopentenones **326a,b** in good yields and high enantioselectivities (Scheme 90).

Copper complexes of chiral bisoxazoline ligands in equimolar amounts have been studied as asymmetric catalysts by Frontier et al. for Nazarov cyclization, followed by Wagner–Meerwein migrations to afford spirocyclic compounds from divinyl ketones.¹⁸⁷ The asymmetric version of the reaction was performed using divinyl ketone **328**, and the formation of two products **329** and **330** was observed. The distribution of the rearrangement product **329** and cyclopentenone **330** was found to depend on the counterions of the copper bisoxazoline

Scheme 89. Nazarov Cyclization of Ester-Substituted Divinyl Ketones Promoted by Bisoxazoline-Based Lewis Acid Complexes

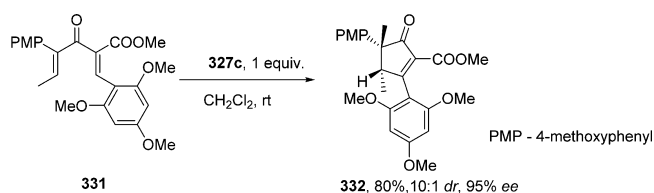
Scheme 90. Nazarov Cyclization of α -Amide-Substituted Divinyl Ketones Promoted by Bisoxazoline-Based Lewis Acid Complexes

complexes **327a-d**. Triflate was observed to provide only product **329**, while when perchlorate was used, a 1.2:1 mixture of **329** and **330** was obtained. For the more weakly coordinating ions SbF_6^- and PF_6^- , only formation of Nazarov product **330** was observed, albeit in moderate yields and low ee (Scheme 91).

Further screening of bisoxazoline ligands **321a,b** and **322** was performed by the authors, providing even higher yields (in the case of **321a,b** of up to 85%); however, the observed ee was lower (up to 24%).

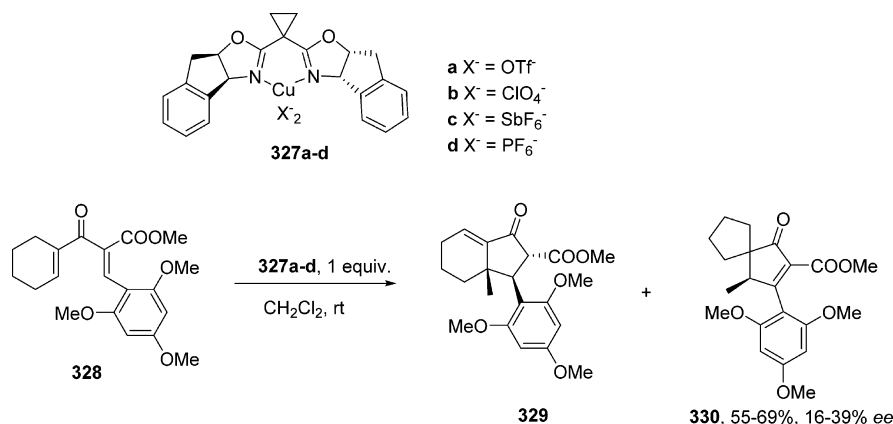
The use of the same catalytic system toward substrate **331** was reported by the same authors.¹⁸⁸ In this case, higher yield and excellent ee were achieved using **327c** (Scheme 92).

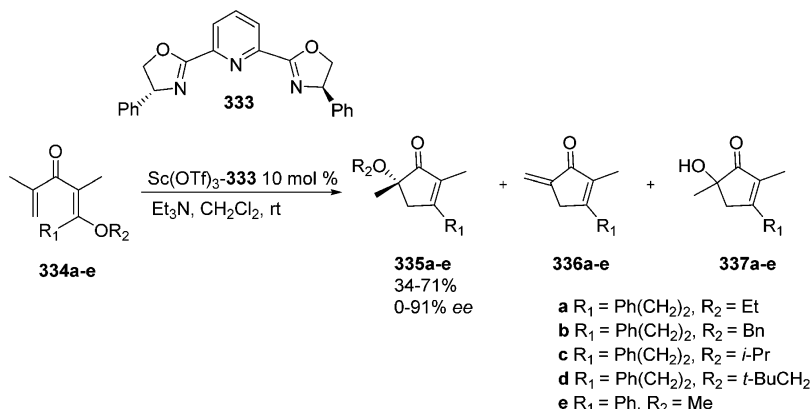
Pybox- $\text{Sc}(\text{OTf})_3$ complexes have also been used by Yaji and Shindo.¹⁸⁹ In 2009 they reported an asymmetric Nazarov reaction affording α -alkoxycyclopentenones **335a-e**. A series of 2,6-bisoxazoline (pybox)- $\text{Sc}(\text{OTf})_3$ complexes were tested as chiral catalysts, and it was found after initial screening that ligand **333** provided the highest enantioselectivities. This ligand was also used for the asymmetric cyclization of a series of substrates **334a-e**. The authors observed the generation of trifluorome-

Scheme 92. Copper-bisoxazoline-Promoted Nazarov Cyclization of Divinyl Ketone **331**

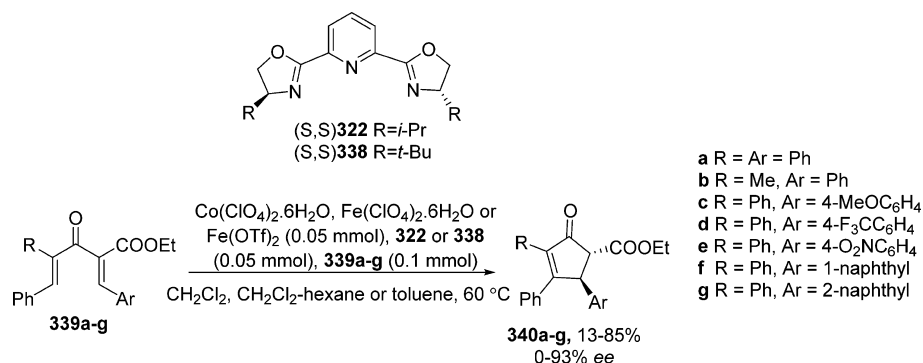
thanesulfonic acid (TfOH) during the formation of side products **336a-e** and **337a-e**, which led to lower enantioselectivities due to competitive racemic Nazarov cyclizations catalyzed by TfOH . Triethylamine has been used as an additive in the reaction to deactivate the formed TfOH . Under the optimized reaction conditions, the corresponding cyclopentenones **335a-e** were obtained in moderate yields and moderate to high enantioselectivities (Scheme 93).

A year later, an asymmetric Nazarov cyclization of divinyl ketones **339a-g** using iron or cobalt catalysts with similar asymmetric ligands was reported by Itoh et al.¹⁹⁰ The catalysts were prepared from $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, or $\text{Fe}(\text{OTf})_2$ and chiral pybox-type ligands **322** and **338**. It was observed that ligand **322** is more appropriate for the $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ -catalyzed reactions, while **338** provided better enantioselectivities for the $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ -catalyzed reactions. Good yields and moderate enantioselectivities have been achieved. Therefore, the system combining $\text{Fe}(\text{OTf})_2$ and ligand **338** has been tested, and it was observed that this catalyst provided higher

Scheme 91. Copper-bisoxazoline-Promoted Nazarov Cyclization of Divinyl Ketone **328**

Scheme 93. Pybox–Sc(OTf)₃-Catalyzed Nazarov Cyclization

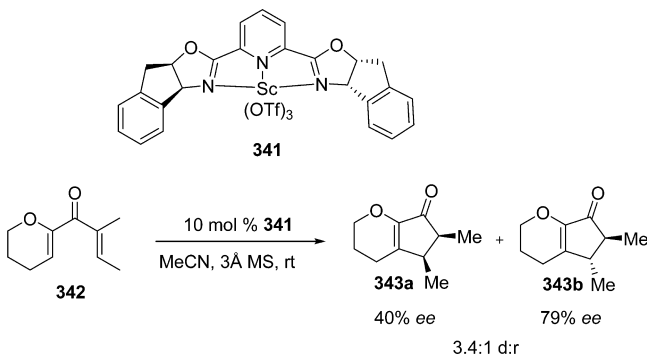
Scheme 94. Nazarov Cyclization of Divinyl Ketones Catalyzed by Chiral Pybox-type Co or Fe Complexes



enantioselectivities. Regarding the obtained results, it was concluded that for most of the divinyl ketones **339a–g**, the Fe/pybox catalyst provided higher enantioselectivities than the Co/pybox catalyst (Scheme 94).

Liang and Trauner described an asymmetric Nazarov cyclization catalyzed by chiral scandium triflate pybox complex (1*S*,2*R*)-**342**.¹⁹¹ First, the authors subjected alkoxydienone **342** to asymmetric cyclization and obtained a mixture of diastereomers **343a** and **343b** in a diastereomeric ratio of 3.4:1 and ee of 40% and 79%, respectively (Scheme 95).

Furthermore, substrates without substituents at the terminal position (**344a–j**) have been used. In these cases, high yields and enantioselectivities have been achieved with relatively short reaction times and low catalyst loading (Scheme 96).

Scheme 95. Nazarov Cyclization of Alkoxy Dienone **342** Promoted by Chiral Sc Triflate Pybox Complexes

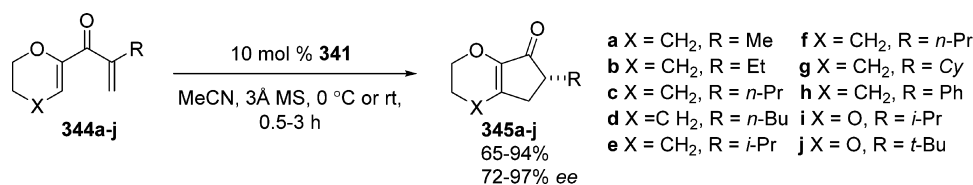
An asymmetric Nazarov cyclization of a variety of alkoxy divinyl ketoesters **347** promoted by chiral tris(oxazoline)/Cu(II) catalysts have been developed by Tang et al.¹⁹² The authors investigated the effect of several tris(oxazoline) ligands on the enantioselectivity of the reaction. It was demonstrated that ligand **346** was the most effective, providing the corresponding cyclopentenones **348** in good yields and high enantioselectivities under optimized reaction conditions (Scheme 97).

Recently, Tang et al. reported an efficient catalytic enantioselective Nazarov cyclization of vinyl ketoesters **350** catalyzed by chiral BOX/Cu(II) complex **349** (Scheme 98), to give a variety of cyclopentenone esters **351a–l** in high yields (75–95%) with 78–90% ee.¹⁹³ The proposed protocol exhibits several important features such as mild reaction conditions, high catalytic efficiency, and broad substrate scope.

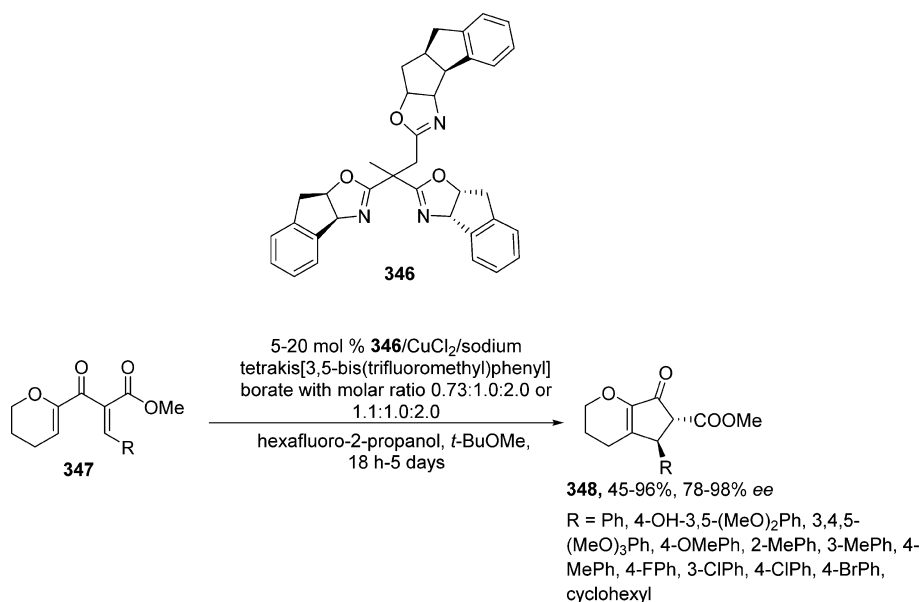
Walz and Togni reported an asymmetric Nazarov cyclization of a variety of divinyl ketoesters **353a–h** effectively catalyzed by an in situ-generated dicationic Ni(II) complex containing the chiral tridentate phosphine ligand Pigiphos (**352**).¹⁹⁴ It was demonstrated that the size match between the ester group and the aromatic substituent R_3 in the substrates was essential for the reactivity and enantioselectivity of the reaction. On the other hand, no significant effect derived from the nature of substituent R_1 was observed (Scheme 99).

A Cr(III)/Salen-promoted enantioselective Nazarov cyclization was reported by Rawal et al.¹⁹⁵ The authors successfully achieved asymmetric Nazarov cyclization of activated dienones **356a–i**, bearing different aromatic and heteroaromatic substituents at the β position, in up to 90% yield and up to 96% ee (Scheme 100). Screening of different salen ligands and metal

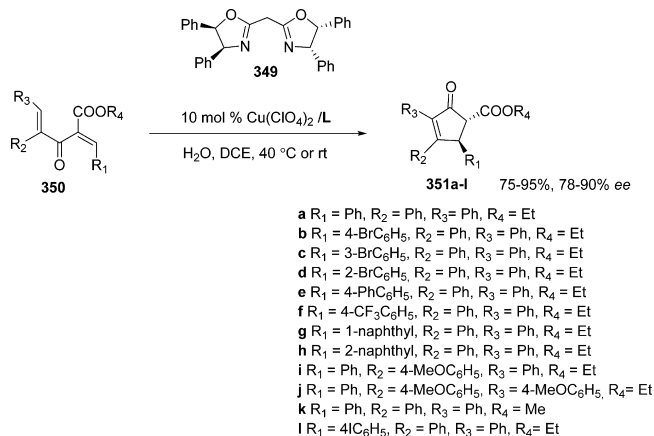
Scheme 96. Nazarov Cyclization of Alkoxy Dienones without Substituent at the Terminal Position Promoted by Chiral Sc Triflate Pybox Complexes



Scheme 97. Asymmetric Nazarov Cyclization of Alkoxy Divinyl Ketoesters Promoted by Chiral Tris(oxazoline)/Cu(II) Catalysts



Scheme 98. Enantioselective Nazarov Cyclization of Vinyl Ketoesters Catalyzed by a Chiral BOX/Cu(II) Complex



salts established that 5-mesityl-substituted salen combined with CrSbF₆ (**355**) exhibited the best performance.

In one example, the authors described a tandem process that terminates with the formation of a C–N bond to the enol intermediate (Scheme 101). After diisopropyl azodicarboxylate was added to the reaction mixture, Nazarov cyclization/azination product **359** was obtained in 69% yield and 90% ee.

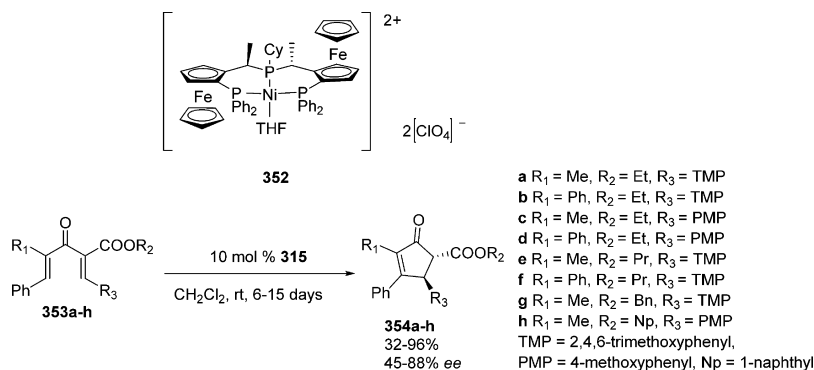
3.2.1.2. Asymmetric Nazarov Cyclization Catalyzed by Brønsted Acids. In 2007, Nachtsheim et al. described the first enantioselective Brønsted acid-catalyzed Nazarov cyclization of dienones to provide cyclopentenones.¹⁹⁶ Various chiral BINOL phosphates and corresponding *N*-triflyl phosphoramides have

been tested as catalysts for the reaction. It was observed that *N*-triflyl phosphoramides provided improved reactivity, diastereoselectivity, and enantioselectivity, and they were used for further studies on the influence of temperature, solvents, catalyst loadings, and concentration. The optimized reaction conditions were applied to the enantioselective Nazarov cyclization of various substrates **361a–l**, providing the corresponding cyclopentenones in good yields and excellent enantioselectivities (Scheme 102).

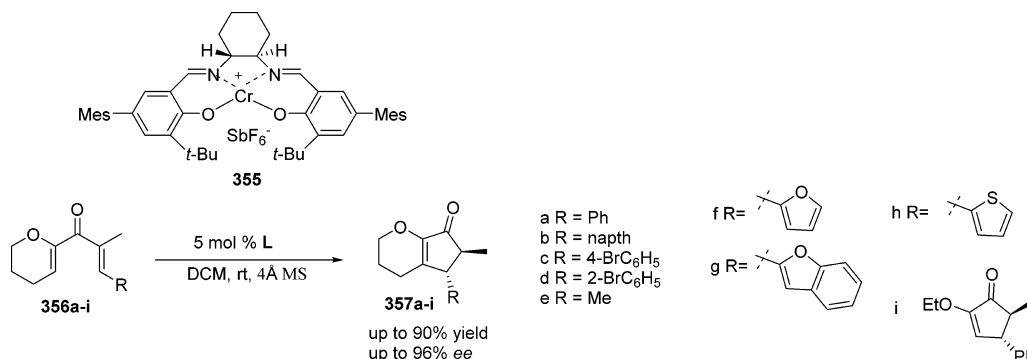
Rueping and Ieawsuan reported the synthesis of optically active 2-substituted cyclopentenones via Brønsted acid-catalyzed enantioselective Nazarov reaction catalyzed by chiral BINOL and octahydro-BINOL *N*-triflyl phosphoramides.¹⁹⁷ They observed that the presence of more sterically demanding substituents in the 3,3-position of the BINOL provided better enantioselectivities. The best result was achieved with [H₈]-BINOL *N*-triflyl phosphoramide **364**, and this was used as a catalyst for the synthesis of a series of alkyl- and benzyl-substituted cyclopentenones **365** under optimized reaction conditions (Scheme 103).

Because the cyclopentenones fused with cyclic ethers are not particularly suitable as structural units for the synthesis of natural products, in a consequent work Rueping et al.¹⁹⁸ extended the scope of their methodology toward Nazarov cyclization of divinyl ketones bearing acyclic ethers. Surprisingly, the 1:1 formation of two different cyclization products, cyclopentenone **368** and α -hydroxyenone **369**, was observed (Scheme 104). However, **368** was converted to **369** when treated with acid. Therefore, the authors decided to directly isolate α -hydroxyenones **371a–i** after in situ hydrolysis with HCl.

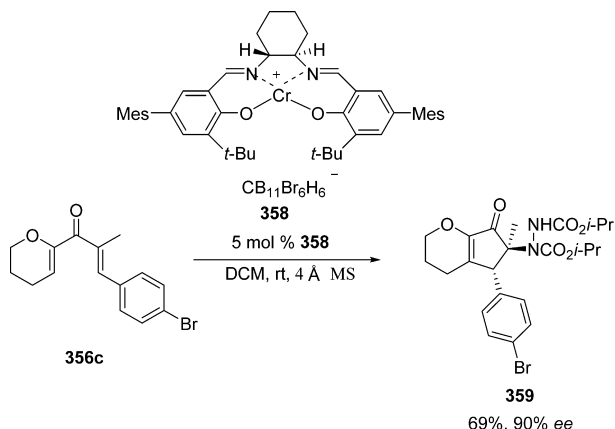
Scheme 99. Asymmetric Nazarov Cyclization of Divinyl Ketoesters Catalyzed by a Dicationic Ni(II) Complex



Scheme 100. Cr(III)/Salen-Promoted Enantioselective Nazarov Cyclization



Scheme 101. C–N Bond Formation in an Asymmetric Tandem Nazarov Cyclization



A series of *N*-triflylphosphoramides were tested as catalysts, and as in the authors' previous work, **364** was found to exhibit the best performance. Under optimized conditions, a range of α -hydroxyenones with different substitution patterns (**371a–i**) were obtained starting from divinyl ketones bearing the *i*-Bu group (**370a–i**) (Scheme 105).

The synthesis of 3,3'-disubstituted H₈-BINOL phosphorodithioic acid diester derivatives **372a–f**, and their application in the Brønsted acid-catalyzed asymmetric Nazarov cyclizations, was reported by Pousse et al.¹⁹⁹ As expected, these catalysts displayed an improved activity for the Nazarov cyclization providing the corresponding cyclopentenone **374** in very good yields and good to very good diastereoselectivities, but with very low enantioselectivities (Scheme 106).

3.3. Organocatalyzed Reactions

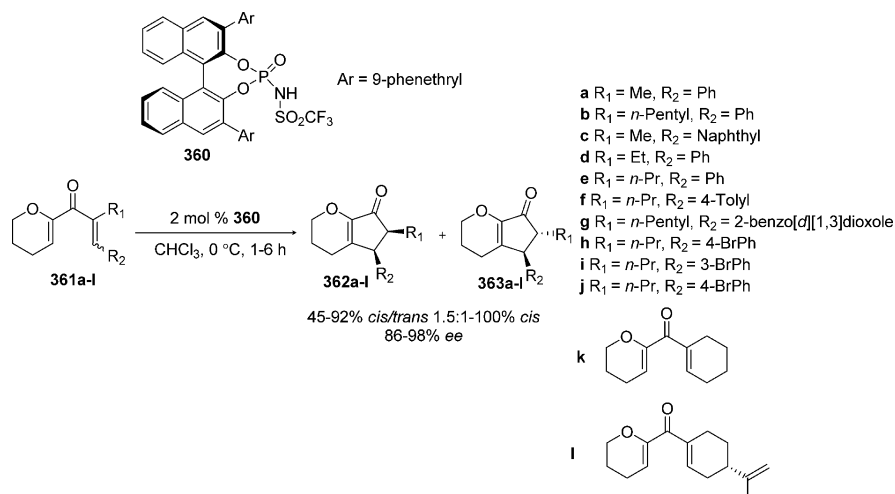
In 2008, the group of Jørgensen reported asymmetric addition of 1,3-cyclopentadione **376** to α,β -unsaturated aldehydes **377a–m**, which after cyclization and acetylation resulted in the formation of cyclopentenone **378a–m**.²⁰⁰ The reaction was found to proceed in slightly acidic conditions in the presence of a secondary amine as catalyst. The authors screened a range of proline derivatives **375a–e** as asymmetric catalysts for the addition of **376** to cinnamaldehyde, and observed that **375d** provides the best result for **378a** with 42% yield and 72% ee in toluene. Further solvents and reaction temperatures were screened, and an increased yield of 85% and enantioselectivity of 90% ee were observed when the reaction was performed at low temperature in CH₂Cl₂. Under the optimized conditions, the reaction scope was extended toward other α,β -unsaturated aldehydes **376a–m** (Scheme 107).

In 2009, a similar approach was reported by Zhong et al.²⁰¹ Cyclopentenone **381** was obtained in good yield and enantioselectivity using fluorinated diphenylprolinol ether **379** as catalyst (Scheme 108).

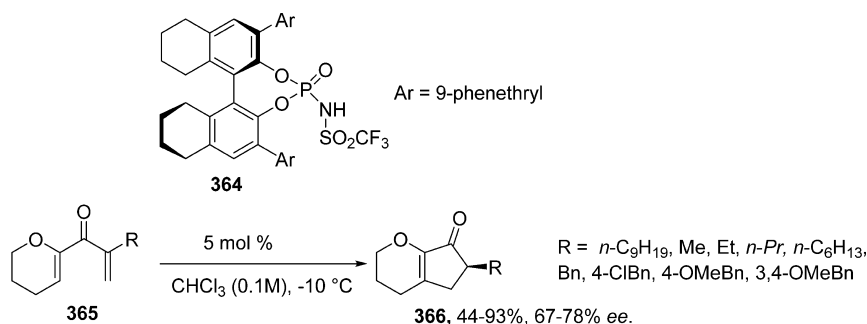
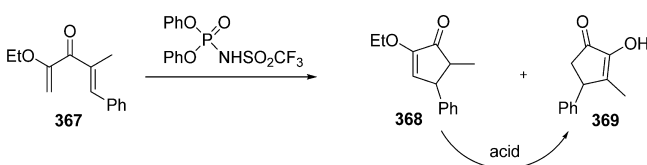
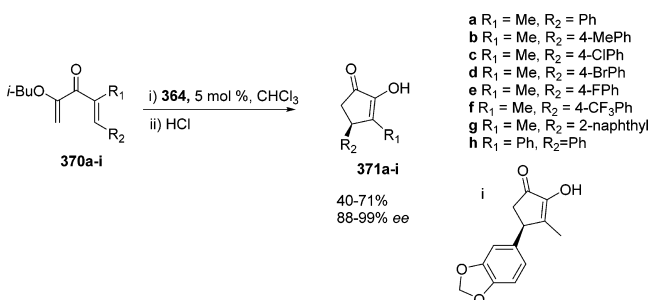
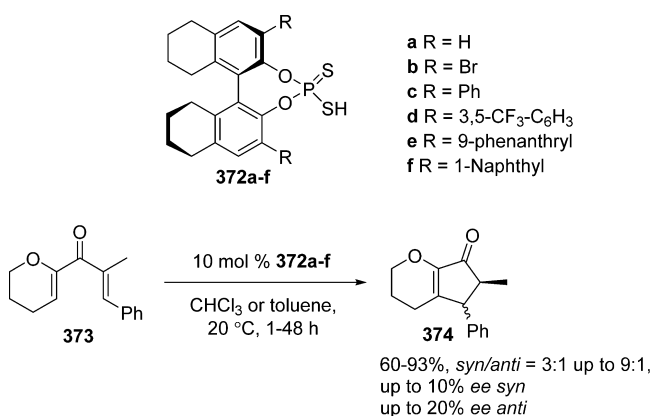
Zhao et al. reported a cascade reaction for the synthesis of the asymmetric diazaindeno[2,1-*a*]phenanthrene **385**.²⁰² Using catalyst **375d**, they obtained hemiacetal **383**, which was further reacted with tryptamine **384** under acidic conditions to give **385** in 72% yield and 96% ee (Scheme 109).

The synthesis of 2,4-disubstituted cyclopent-2-enones **388a–i** from β -ketophenyltetrazolesulfones **387** and α,β -unsaturated aldehydes **386** by a one-pot organocatalytic iminium ion/NHC reaction sequence has been reported by Jørgensen et al.²⁰³ The reaction provided very good enantioselectivities and moderate yields via one-pot sequential addition of the carbene precursor **389** at elevated temperature after it was observed that when aminocatalyst **374d** and **389** were present from the beginning of

Scheme 102. BINOL Brønsted Acid-Catalyzed Nazarov Cyclization of Dienones



Scheme 103. BINOL Brønsted Acid-Catalyzed Nazarov Cyclization of Dienones without Substituents at the Terminal Position

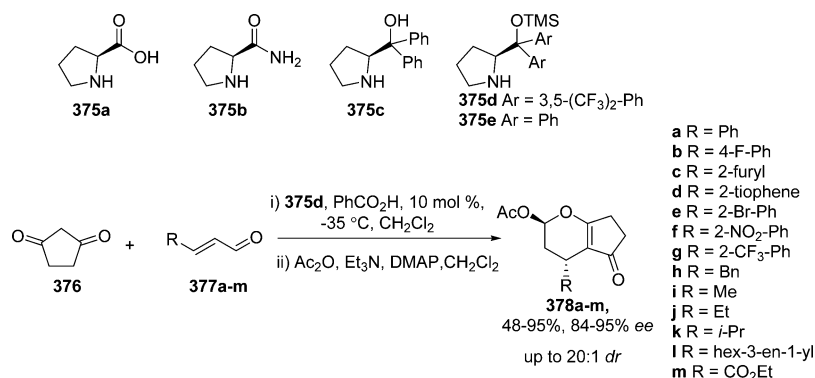
Scheme 104. Synthesis of α -Hydroxyenones via Nazarov Cyclization of Divinyl Ketones Bearing Acyclic Ether SubstituentsScheme 105. Chiral *N*-Triflylphosphoramidate-Catalyzed Nazarov Cyclization of Divinyl Ketones Bearing *i*-Bu SubstituentsScheme 106. 3,3'-Disubstituted H₈-BINOL Phosphorodithioic Acid Diesters Catalyzed Nazarov Cyclization

the reaction, the NHC-catalyzed step did not occur at the low temperatures required to achieve satisfactory enantioselectivity in the initial organocatalyzed Michael addition (Scheme 110).

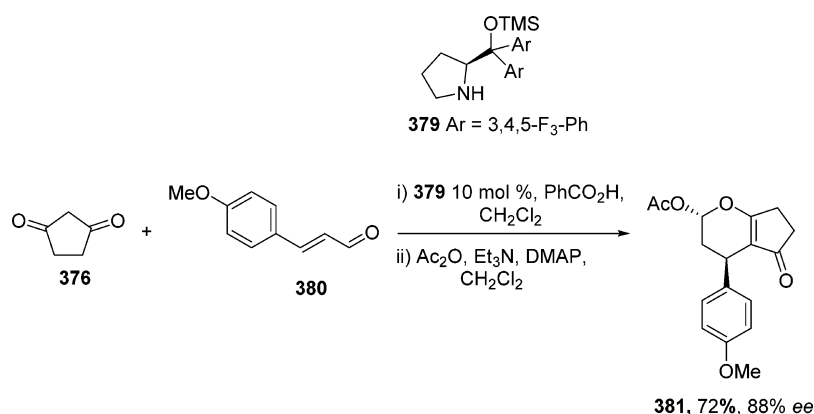
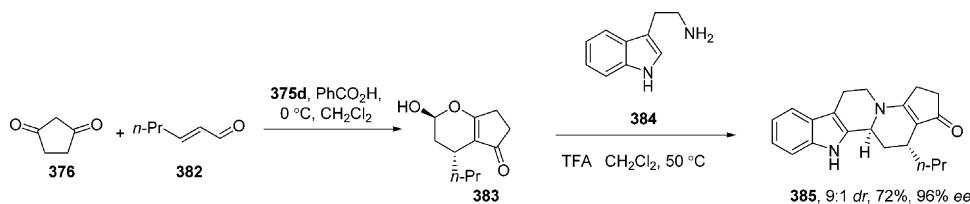
In 2009, Jørgensen et al. reported organocatalyzed asymmetric desymmetrization–fragmentation reactions of cyclopentanones

to the corresponding asymmetric cyclopentenones (Scheme 111).²⁰⁴ The transformation of 3-oxobicyclo-[3.1.0]hexane-6,6-dicarboxylate **392** into diethyl 2-(4-oxocyclopent-2-enyl)-malonate **393** was chosen by the authors as a model reaction for the catalyst screening. Initially, when the reaction was performed in the presence of 10 mol % of quinine **390**, the final product was obtained with an enantioselectivity of 40% *ee*. After screening different cinchona alkaloid catalysts, excellent yields and enantioselectivities were achieved with thiourea–cinchona alkaloid catalysts **391a** and **391b**. **391b** provided the product (*S*)-

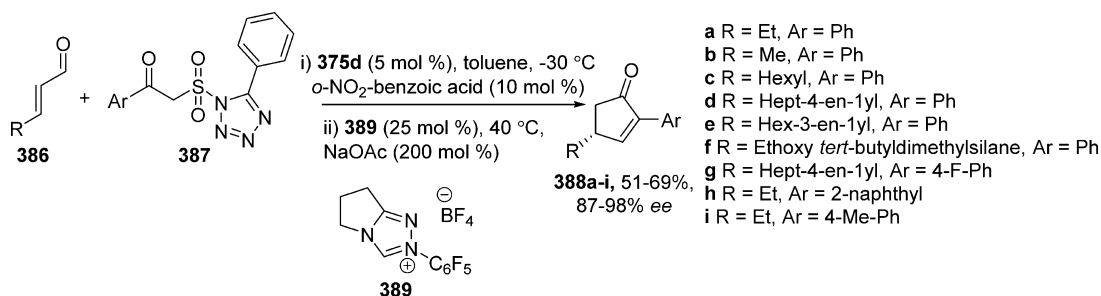
Scheme 107. Organocatalytic Asymmetric Synthesis of Functionalized 3,4-Dihydropyrancyclopentenone Derivatives



Scheme 108. Enantioselective Synthesis of Functionalized 3,4-Dihydropyrancyclopentenone Derivatives Organocatalyzed by a Fluorinated Diphenylprolinol Ether

Scheme 109. Diastereoselective Cascade Reactions toward Substituted Cyclopentenone Diazaindeno[2,1- α]phenanthrenes

Scheme 110. Organocatalytic Cascade Reaction for the Formation of Chiral 2,4-Disubstituted Cyclopentenones



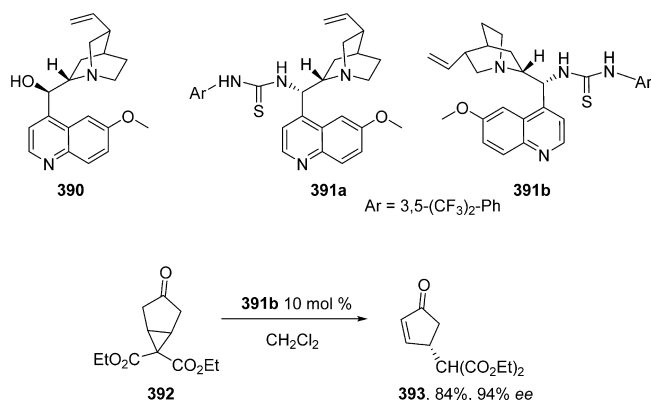
393 in 84% yield and with 94% ee. When 391a, the enantiomer of 391b, was used, (*R*)-393 was obtained with 90% ee.

Furthermore, the asymmetric desymmetrization–fragmentation reaction of 6-oxabicyclo-[3.1.0]hexan-3-one 395 was studied in an attempt to prepare the important 4-hydroxycyclopent-2-enone 396. When the reaction was carried out under the same conditions as for 391, it failed to provide any enantioselectivity. It was further observed that the direct

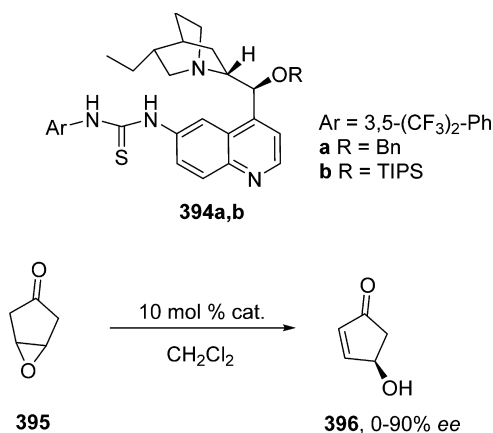
attachment of the thiourea moiety to the quinoline system in the catalyst appeared to provide selectivity, and product 396 was obtained with 53% ee when catalyst 394a was used. The replacement of the benzyl group with the bulkier TIPS protecting group in 394b led to increased enantioselectivity, and 396 was obtained with 90% ee (Scheme 112).

The reaction scope was subsequently extended to the synthesis of cyclopentenones 398a,b from epoxides 397a,b. When 397a

Scheme 111. Organocatalytic Asymmetric Desymmetrization—Fragmentation toward Chiral Cyclopentenones

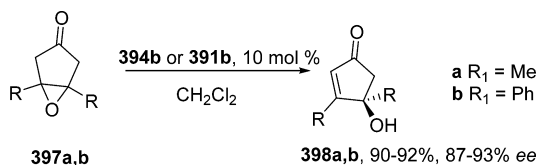


Scheme 112. Synthesis of 4-Hydroxycyclopent-2-enone via Desymmetrization—Fragmentation Reaction



was treated with catalyst **394b** under the same conditions as for **395**, the product (*R*)-**398a** was formed in 90% yield and with a good enantioselectivity of 87% ee. In the case of the diphenyl-substituted derivative **398b**, excellent selectivity was observed for catalyst **391b** (Scheme 113).

Scheme 113. Synthesis of Substituted 4-Hydroxycyclopent-2-enones



4. ASYMMETRIC FUNCTIONALIZATION OF EXISTING CYCLOPENTENONE UNITS

4.1. (Aza-)Morita–Baylis–Hillman (MBH) Reactions

The formation of α -methylene- β -hydroxycarbonyl derivatives by condensation of an electron-deficient alkene with an aldehyde, catalyzed by a tertiary amine or phosphine, is defined as the classical or general Morita–Baylis–Hillman (MBH) reaction.²⁰⁵ The aza-Morita–Baylis–Hillman (aza-MBH) uses activated imines as electrophiles.^{206–208}

The MBH reaction is an efficient reaction due to good atom economy and use of mild conditions, and has been widely reviewed.^{209–215} However, the reaction suffers from disadvantages such as low rate, poor conversion, and limited substrate scope.^{216–219}

Asymmetric MBH/aza-MBH reactions employ chiral catalysts or substrates to afford products with high enantioselectivity. The factors that control asymmetric induction, such as chiral catalyst design, influence of reaction medium, and problems leading to low conversion rates and poor enantioselectivity, have been extensively discussed.^{220–226}

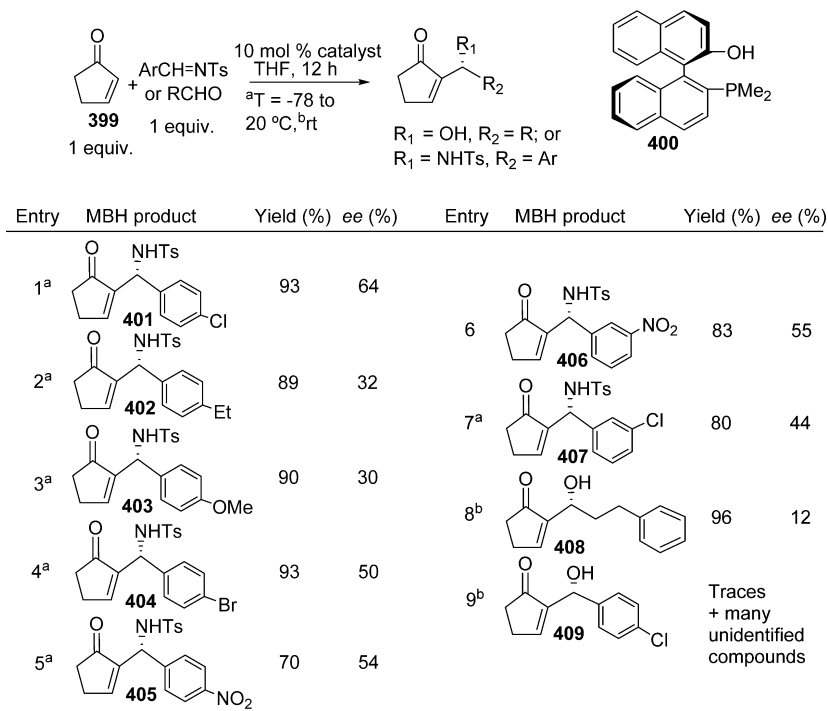
The mild reactivity of cyclopentenones as Michael acceptors, together with their other structural characteristics, has enabled the development of a precise MBH asymmetric catalytic system using 2-cyclopenten-1-one (**399**) as a model substrate.

The classical MBH reaction involves conjugate addition of a simple phosphine catalyst to an α,β -unsaturated compound to form an activated zwitterionic intermediate. The chiral phosphine catalyst (alkyl or aryl) is combined with a Lewis acid and base within one multifunctional catalytic compound in the asymmetric catalytic MBH reaction. Enantioselectivity and reactivity can be tuned by enhancing the nucleophilicity of the reactive centers and using hydrogen-donor ligands or complexes in proximity.²²⁷ The group of Shi²²⁸ reported an asymmetric aza-MBH reaction of *N*-(4-arylidene)-4-methylbenzenesulfonamides with **399** catalyzed by chiral phosphine Lewis base (*R*)-2'-dimethylphosphanyl-[1,10]binaphthalenyl-2-ol (**400**) (Scheme 114). Yields and ee (%) values of MBH derivatives with different *N*-sulfonated imines (Ar–CH = NTs) and aldehydes are depicted (table in Scheme 114).

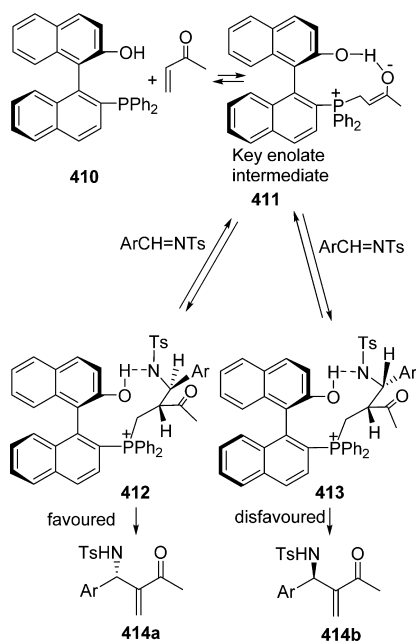
The authors optimized the solvent, temperature, and catalyst loading. The aza-MBH reaction of selected *N*-sulfonimines and arylaldehydes was studied by ¹H and ³¹P NMR. A mechanism was proposed in which the phosphonium intermediate was stabilized by hydrogen bonding between the phenolic position in the bifunctional catalyst **410** and the oxygen atom of the ketone group. The enantioselectivity would arise from a relatively rigid transition state leading to favored intermediate **412** that eliminates to afford the (*S*) enantioenriched MBH product **414a** (Scheme 115).^{229,230}

More recently, the same group reported the new, strongly nucleophilic chiral phosphine-amide catalyst **415** combined with BINOL derivative **416**. This catalyst was used in the asymmetric aza-MBH reaction of 5,5-disubstituted 2-cyclopenten-1-ones with *N*-sulfonated imines, following optimization of catalyst loading, temperature, solvent mixture, and use of molecular sieves. This new catalyst afforded products in high yields and good enantioselectivities (up to 85% ee) (Scheme 116).²³¹ The yield and ee of MBH adducts under optimized conditions were dependent on the type of R₂ and the position of the substituents on *N*-sulfonated imines. The best results were obtained for aromatic substituents with electron-donating and electron-withdrawing groups in *meta* or *para* positions in aryl *N*-sulfonated imines (entries 1, 2, 4, 6–8). Good results were also obtained for 2-thienyl (entry 3), FC₆H₄, and F₃CC₆H₄ (entries 10–14). The authors proposed steric interactions between the multifunctional phosphine and the bulky chiral binol as an explanation for the observed results.

The group of Shi also examined the diastereoselectivity of the MBH reaction between chiral aryl *N*-sulfonimines **419a–g** and 2-cyclopent-1-one (Scheme 117).²³² Improved diastereoselectivity was achieved with simple phosphines such as PBu₃ or PhPM₂

Scheme 114. Asymmetric Aza-MBH Reaction of *N*-(4-Arylidene)-4-methylbenzenesulfonamides

Scheme 115. Mechanism of the Aza-MBH Reaction Promoted by the Chiral Phosphine Lewis Base (R)-2'-Dimethylphosphanyl-[1,10]binaphthalenyl-2-ol



(10 mol %). The latter was particularly useful due to its enhanced stability and steric crowding.

The usefulness of BINOL-type additives for the asymmetric MBH reaction lies in the structure of the bound substrate and modulation of the BINOL OH acidity, both brought about by H-bonding in the transition state.²³³ Investigation of the Brønsted acid activation of carbonyl compounds is an important topic in asymmetric catalysis.^{234–236} Aggarwal and others have suggested that the nucleophilic attack of the enolate on the aldehyde to generate a second zwitterionic intermediate is the rate-limiting

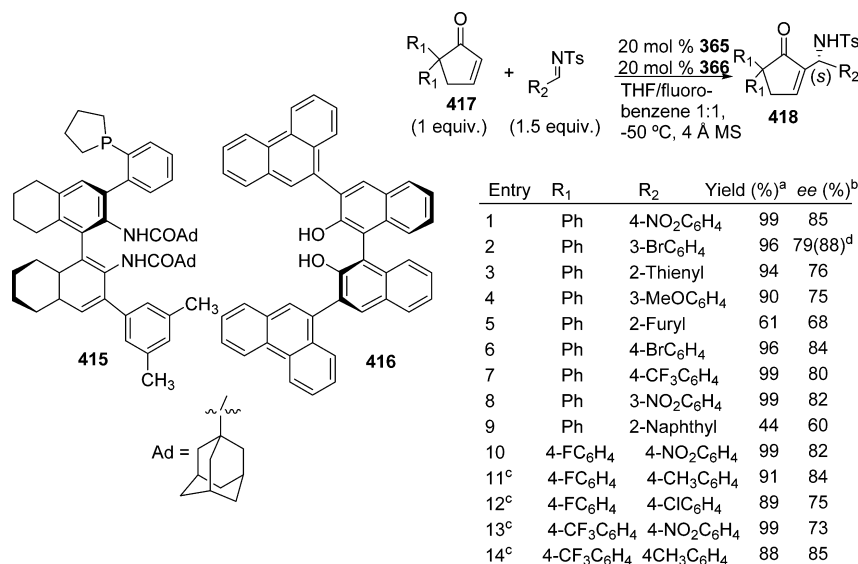
step (RLS) in the asymmetric MBH. The role of the H-donor is essential here as only one out of four possible diastereomers of intermediate alkoxides has the correct geometry to allow rapid proton transfer.^{220,219,237,238}

Studies of asymmetric MBH reaction catalyzed by chiral Brønsted acids using 2-cyclopenten-1-one as the activated alkene are very rare. The important work of Schaus et al. in the development of MBH reactions catalyzed by chiral Brønsted acids used cyclohexenone as the model substrate. The use of a cyclopentenone was mentioned once for comparison.²³⁹ The authors proposed that the phenolic positions of the BINOL catalyst act as the Brønsted acid through H-bonding with the carbonyl group of the alkene, thus promoting the conjugate addition step of the reaction. The resulting enolate remained hydrogen-bonded to the BINOL catalyst during the enantioselective aldehyde addition step. This was demonstrated by showing that enantioselectivity was eroded when chemical groups that disturb H-bonding were introduced into the BINOL scaffold. Saturation of the BINOL derivative and introduction of bulky substituents at the 3,3'-positions were also essential for enhancing enantioselectivity.

Reaction conditions were optimized for the MBH reaction between cyclohexenone and 3-phenylpropanal **422**, employing binaphthol-derived chiral Brønsted acid catalyst (R)-3,3'-(3,5-dimethylphenyl)-H₈-BINOL (**421**). These conditions were applied to cyclopentenone **399**, providing **423** in 59% yield and 29% ee. The poor enantioselectivity illustrates that the protocol was sensitive to the choice of substrate (Scheme 118).^{239,240}

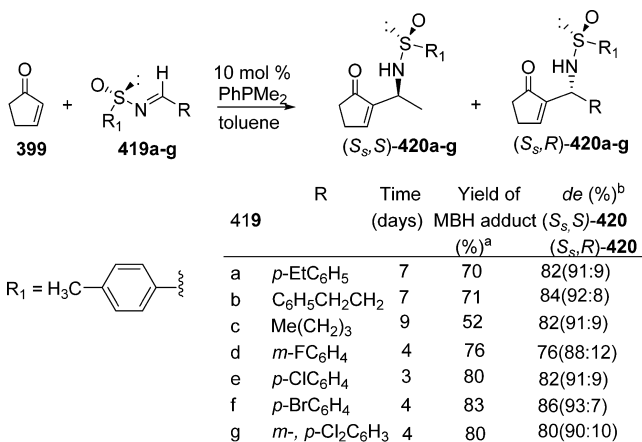
The asymmetric MBH reaction of cyclopentenone **399** with pentanal in the presence of (+)-(R)-**424** and (+)-(R)-**425** and different cocatalysts afforded unstable product **430** with a low enantiomeric ratio of (–)-(S):(+)-(R) = 52:48 (Scheme 119).²⁴¹

Product (–)-(S)-**430** was used in a cascade MBH-ortho-Claisen rearrangement for the synthesis of methyljasmonate²⁴¹ and Helidone (Scheme 120). Firmenich SA has commercialized

Scheme 116. Asymmetric Aza-MBH Reaction of 5,5-Disubstituted 2-Cyclopenten-1-ones with *N*-Sulfonated Imines^a

^a isolated yield; ^b ee values were determined by HPLC using a chiral column; ^c the reaction was carried out in THF; ^d the ee of **418** after crystallization.

^a(a) Isolated yield; (b) ee values were determined by HPLC using a chiral column; (c) the reaction was carried out in THF; and (d) the ee of **418** after crystallization.

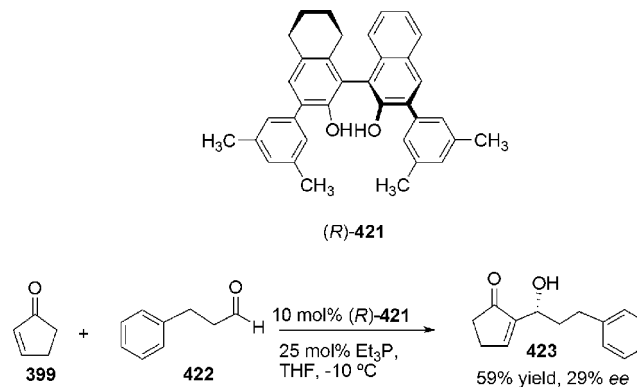
Scheme 117. MBH Reaction between Chiral Aryl *N*-Sulfinimines and 2-Cyclopenten-1-one^a

^aisolated yield, ^bdetermined from ¹H NMR spectral data

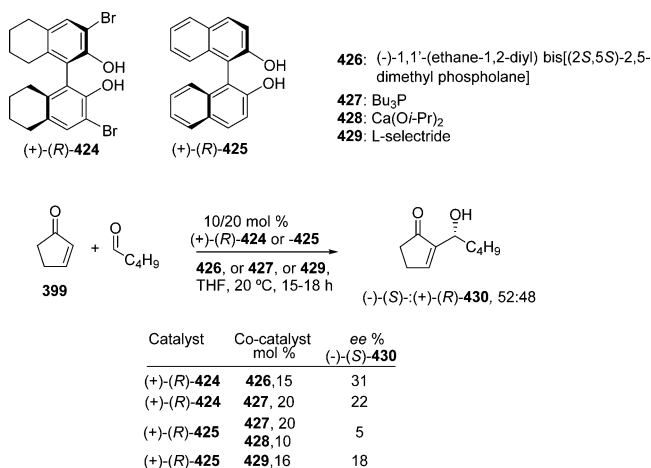
^a(a) Isolated yield; and (b) determined from ¹H NMR spectral data.

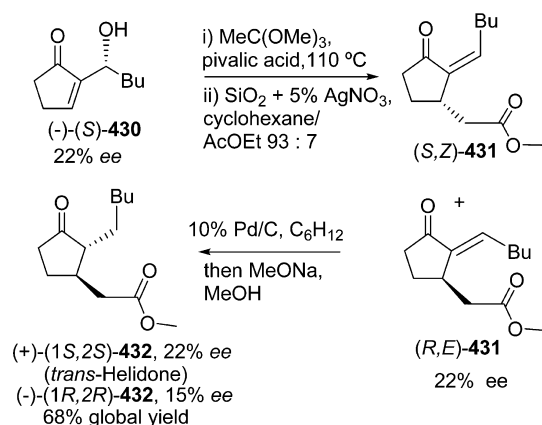
the racemate of a 9:1 equilibrated mixture of structurally related methyl *trans*-dihydrojasmonates under the trade name of Hedione.²⁴² Methyljasmonates are useful for the fragrance industry, whereas their acid or methyl ester derivatives exhibit plant growth activity and anticancer and blood parasite cytotoxic properties.^{243–246} The synthesis of methyljasmonate was performed with good overall yields and low enantioselectivity for the jasmonoid derivative **432**. The authors concluded that the low global asymmetric induction was the result of poor enantioselectivity during the MBH reaction. This was caused by partial diastereoselectivity during the *ortho*-ester Claisen acidic rearrangement and partial isomerization during the hydrogenation process.²⁴¹

The enantioselective aza-MBH reaction of cyclopent-2-enone with *N*-tosylphenylmethanimine was performed, employing

Scheme 118. (*R*)-3,3'-(3,5-Dimethylphenyl)-H₈-BINOL-Promoted MBH Reaction of Cyclopentenone

Scheme 119. Asymmetric MBH Reaction of Cyclopentenone with Pentanal



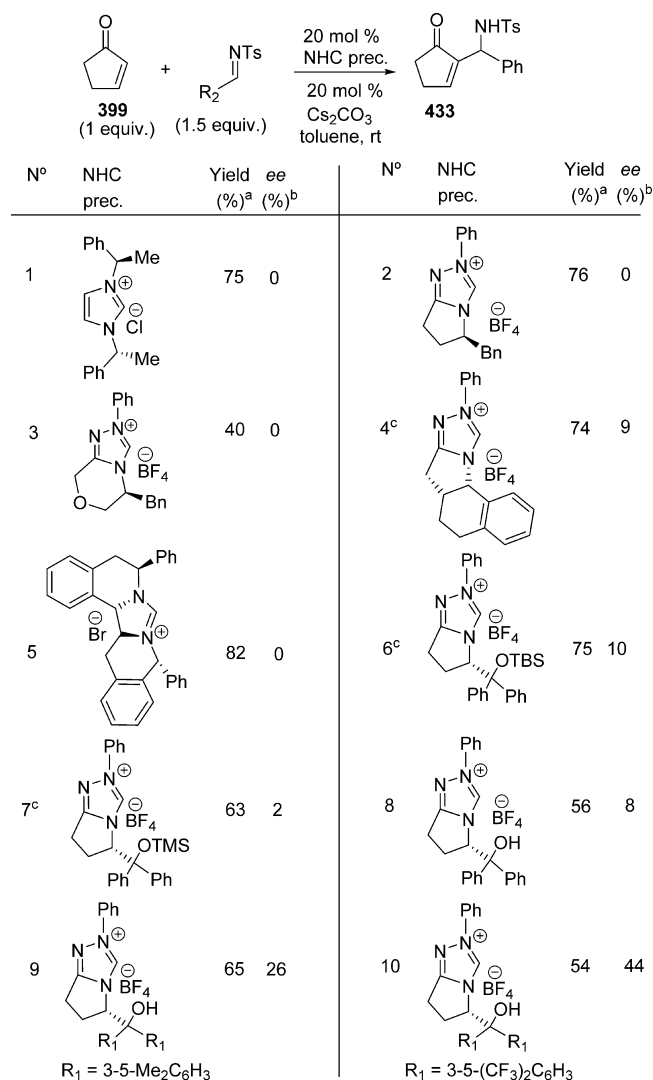
Scheme 120. Synthesis of *trans*-Helidone via Cascade MBH-*ortho*-Claisen Rearrangement

chiral bifunctional *N*-heterocyclic carbene (NHC) precursors with a proximal hydroxyl group as catalysts. Ye and co-workers reported the preparation of these catalysts from L-pyrroglutamic acid and achieved moderate enantiomeric excesses of up to 44% ee (Scheme 121).²⁴⁷ The authors pointed out that the stronger hydrogen bond between catalyst and imine was responsible for an increased ee (entry 10, Scheme 121). Once more, poor enantioselectivity resulted from partial diastereoselectivity during the *ortho*-ester Claisen acidic rearrangement and partial isomerization of exocyclic to endocyclic position of the resulting double bond during hydrogenation.

The stereocontrol of the new C–C bond formation in the asymmetric MBH is determined by the steric and electronic environment set by the chiral ligand framework coordinated to the metal-based Lewis acid catalyst. In particular, the enhanced acidity of the α -hydrogen atoms was key to promote enone formation and coordination to the metal center.^{248–250} The addition of a Lewis base to the Lewis acid catalytic system allows for an acid/base reaction without requiring acceleration. This approach was used for the synthesis of an α -hydroxymethyl derivative in good yield and ee. The heterobinuclear catalyst (R)-**434** (type B-BLB) (boron–lithium–mono(binaphthoxide) complex) was prepared from LiB(*s*-Bu)₃H (16 mol %) and BINOL (16 mol %).²⁵¹ The combination with (*n*-Bu)₃P (10 mol %) accelerated the MBH reaction. Using benzaldehyde as the electrophile resulted in low ee values (MBH compound **437**), whereas aliphatic aldehydes led to moderate yields and good enantioselectivities (MBH products **436** and **435**). The enhanced coordination effect delivered by using both boron and lithium ions to coordinate the aldehyde and the enone enabled the successful enantioselective formation of new C–C bonds (Scheme 122).

Ikegami and Yamada also described an asymmetric MBH reaction of 2-cyclopenten-1-one with aldehyde **422** driven by cooperative catalysts (R)-**438** and Bu₃P. The chiral Lewis acid catalyst (R)-**438** was prepared from strong base Ca(O-*i*-Pr)₂ and 1,1'-bi-2-naphthol in THF. The authors obtained MBH derivative **423** in fairly good yield (62%) and ee (56%) (Scheme 123).²⁵²

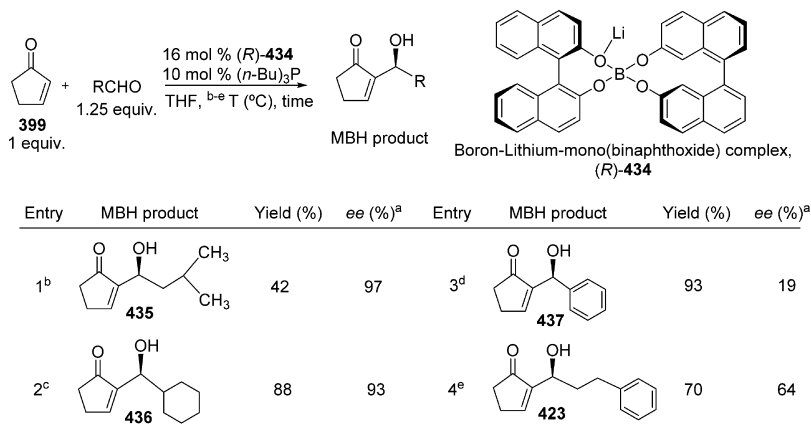
Connell and co-workers screened several catalysts for the asymmetric MBH reaction of cyclopentenone with *trans*-cinnamaldehyde.²⁵³ These included standard nucleophilic catalysts such as chiral TMEDA catalysts, (–)-cinchonine, (–)-tetramizole, (–)-HBTM, thiourea derivatives, and also various Lewis acids such as MgI₂, NiCl₂, SnCl₄, LiCl, Cu(OTf)₂,

Scheme 121. Chiral Bifunctional NHC-Catalyzed Enantioselective Aza-MBH Reaction^a

^a(a) Isolated yield; (b) ee values were determined by chiral HPLC; and (c) 10 mol % NHC catalyst and Cs₂CO₃ were used.

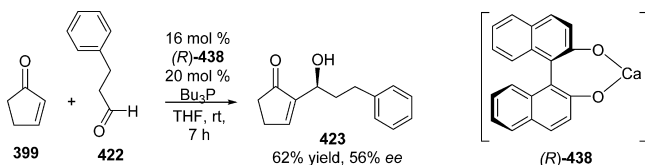
Zn(OTf)₂, and LiClO₄. However, these catalysts failed to deliver positive results. Asymmetric MBH was achieved by using the less-nucleophilic planar chiral DMAP catalyst II (+)-**439** (10 mol %) prepared by Fu and co-workers, in the presence of MgI₂ in *i*-PrOH at –20 °C for 24 h (Scheme 124). This protocol afforded products in good to high yields and enantioselectivities (Scheme 125). The best results were obtained with 1-naphthylaldehyde (entry 1), *trans*-cinnamaldehyde (entry 7), and electron-rich *p*-methoxybenzaldehyde (entries 2 and 3). Aliphatic aldehydes provided reasonable yields and moderate enantioselectivities. Unfortunately, this optimized catalytic system was only effective for cyclopentenone **399** as a substrate.

Myers et al. reported interesting intra- and intermolecular asymmetric MBH reactions between the iminium ion electrophile, formed in situ under Lewis acid reaction conditions and cyclopentenone as activated alkene.²⁵⁴ The chiral sulfide **447** synthesized by Aggarwal and co-workers^{255–258} was used as an enantioselective promoter of the MBH reaction. It was found that piperidine-based (rather than pyrrolidine-based) *N*,*O*-acetals (Scheme 126, entries 3 versus 1) and Boc (rather than

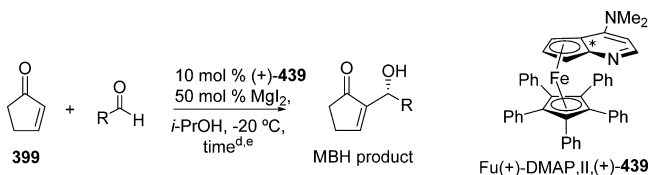
Scheme 122. Boron–Lithium–Mono(binaphthoxide) Complex-Catalyzed Asymmetric MBH Reaction^a

^a(a) Determined by chiral HPLC; the (*S*)-configuration was determined by optical rotation of purified products; (b) 0 °C, 288 h; (c) –40 °C, 168 h; (d) rt, 3.5 h; and (e) –40 °C, 120 h.

Scheme 123. Ca/BINOL Complex-Catalyzed Asymmetric MBH Reaction

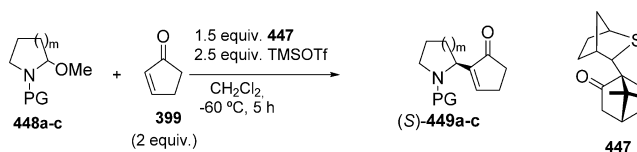


Scheme 124. Asymmetric MBH Reaction Catalyzed by Fu's (+)-DMAP II Catalyst



Cbz carbamate) (entries 2 versus 1) provided MBH-type adducts with improved ee values. The products were obtained with very

Scheme 126. Intra- and Intermolecular Asymmetric MBH Reactions Promoted by Chiral Sulfide



| Entry | MBH product | Yield (%) | ee (%) |
|-------|-------------|-----------|--------|
| 1 | 449a | 69 | 82 |
| 2 | 449b | 75 | 88 |
| 3 | 449c | 88 | 94 |

high enantioselectivity and good overall yields between 69% and 88%.

The authors carried out NMR studies of this reaction at low temperature and proposed a mechanism where the enantioselectivity resulted from the dynamic kinetic transformation of chiral intermediate β -sulfonium-silyl enol-ether during the

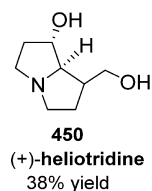
Scheme 125. Aldehydes Screening in the Asymmetric MBH Reaction Promoted by Fu(+)-DMAP, II Catalyst^a

| Entry | MBH product | Yield (%) ^a | ee (%) ^b | Entry | MBH product | Yield (%) ^a | ee (%) ^b |
|----------------|-------------|------------------------|---------------------|------------------|-------------|------------------------|----------------------------------|
| 1 ^d | 440 | 94 | 98 | 6 ^d | 444 | 81 | 92 |
| 2 ^d | 441 | 73 | 95 | 7 ^{c,d} | 445 | 96 93 | 94(<i>S</i>) 94(<i>R</i>) |
| 3 ^d | 437 | 87 | 94 | 8 ^e | 446 | 59 | 63 |
| 4 ^d | 442 | 92 | 89 | 9 ^e | 436 | 54 | 58 |
| 5 ^d | 443 | 75 | 89 | 10 ^e | 423 | 68 | 53 |

^a(a) Isolated yield; (b) ee values were determined by HPLC using a chiral column; (c) the (–) enantiomer of catalyst II was used; (d) reaction time 24 h; and (e) reaction time 48 h.

course of the reaction. This method has been used in the development of a short synthesis of (+)-heliotridine over four steps in 38% total yield (Scheme 127).²⁵⁹

Scheme 127. Structure of (+)-Heliotridine



Aggarwal and co-workers reported the synthesis of 2,5-disubstituted pyrrolidines from 2-cyclopent-1-one, applying the protocol described above using quinuclidine as a Lewis base (Scheme 128).²⁶⁰ This protocol afforded good diastereoselectivity (de) as determined by ¹H NMR analysis of the crude product. The use of quinuclidine and TMSOTf was more efficient for more hindered Michael acceptors. In addition, variable-temperature NMR experiments indicated that the origin of diastereoselectivity was due to the steric effect of the bulky silyl enol ether **451**, which directed the approach of the iminium ion from the face opposite the C5 substituent.

Urea and thiourea derivatives are able to recognize a variety of substrates due to their strong multihydrogen-bonding activity.^{261–263} Thiourea organocatalysts exhibit good general stability and high conformational rigidity. However, urea and thiourea derivatives are weaker acids than metallic Lewis acids, thus limiting their application in enantioselective catalysis.^{234,264,265} The high functional group tolerance of ureas and thioureas has been explored by adding a Lewis base functionality into the catalyst structure to activate the nucleophile. This bifunctional catalyst bearing two different functional groups inserted into a rigid structure simultaneously activates both the electrophile and the nucleophile in a manner that mimics enzymatic systems. This design has broadened the scope of catalysis and enhanced enantioselective control for the addition step of the reaction.^{237,266,267} Wang et al. studied chiral binaphthyl-derived amine-thiourea catalysts for the MBH reaction with cyclohexenone as a model activated alkene. They proposed a mechanism wherein the thiourea group activates the carbonyl group in α,β -unsaturated systems through double hydrogen bonding, and positions the Brønsted base tertiary amine to add to the β -position of the substrate.²⁶⁸

A bifunctional thiourea catalyst containing additional acidic or basic groups was prepared through the reliable isothiocyanate coupling reaction and used in catalytic asymmetric reactions.^{235,248,269,270}

Bifunctional catalyst **454** was easily synthesized by condensation of chiral diamine IPDA [3-(aminomethyl)-3,5,5-trimethylcyclohexylamine] with 2 equiv of iso(thio)cyanate.²⁷¹

The catalytic activity of **454** was tested in the asymmetric MBH reaction with either 2-cyclohexen-1-one, 2-cyclopenten-1-one, or methyl acrylate at 10 °C with 20 mol % catalyst. In particular, 2-cyclopenten-1-one was added to benzaldehyde or cyclohexanecarbaldehyde under optimized reaction conditions using DABCO in toluene (Scheme 129).

The saturated cyclic aldehyde leading to **436** gave better enantioselectivity as compared to benzaldehyde, which provided **437**. It was also shown for the first time that the isophoronediamine-derived bis(thio)urea bifunctional catalyst, in combination with base (*N,N,N',N'*)-tetramethylisophoronediamine (TMIPDA), was able to promote asymmetric MBH reaction using 2-cyclopenten-1-one, albeit with a modest yield of 58% and low enantioselectivity of 22% ee.

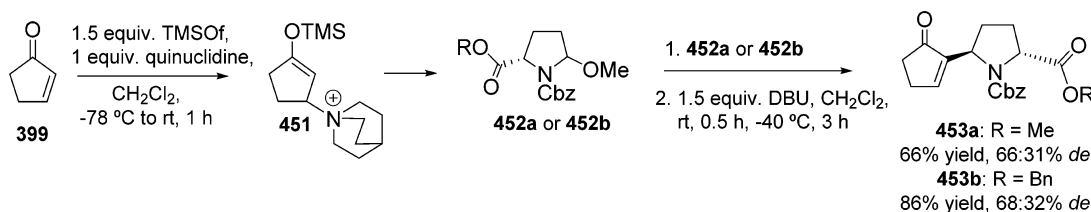
Bis(thio)urea organocatalysts **455** were easily prepared by condensation of axially chiral (*R*)-(-)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diamine (*H₈*BINAM) and BINAM (prepared for the first time by the group of Wang and co-workers)²⁶⁸ with 2 equiv of the corresponding iso(thio)cyanate under mild conditions.

The chiral organocatalyst was tested in the asymmetric MBH reaction between 2-cyclohexen-1-one and 4-nitrobenzaldehyde in toluene. The group of Shi and co-workers²⁷² optimized the MBH reaction of several aldehydes and cyclohexenone in terms of catalyst substituents, nucleophile, and solvent. The optimized conditions were applied to the MBH reaction of 2-cyclopenten-1-one with 4-nitrobenzaldehyde, affording the corresponding asymmetric MBH product in 43% total yield and 60% ee (Scheme 130).

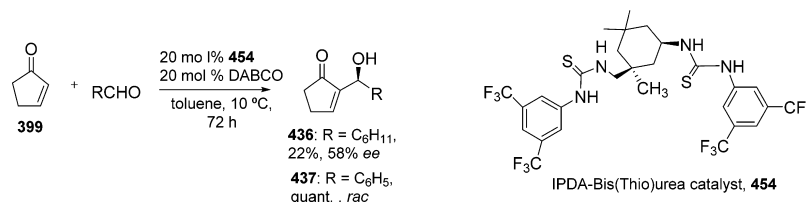
Nagasawa and co-workers reported a MBH reaction between cyclic enones and aldehydes catalyzed by bis(thio)urea organocatalyst **457**, derived from 1,2-diaminocyclohexane.²⁷³ The best results were obtained with cyclohexanecarbaldehyde (MBH product **436**). Increasing the steric bulk at the α -position of the aldehyde provided better enantioselectivities (Scheme 131).

The authors studied the mechanism of the (*R,R'*)-**457**-catalyzed asymmetric MBH reaction by ¹H NMR (Scheme 132). They proposed the fast and irreversible elimination of tertiary amine (considered to be the rate-determining step of the MBH reaction) mediated by carbonyl activation by thiourea in intermediate II.^{220–223,226} The bis(thio)urea catalyst activates both the aldehyde and the enolate, with each thiourea coordinating through a pair of hydrogen bonds to either the carbonyl or the enol groups of the reagents. Recently, Coelho and co-workers studied a thiourea-catalyzed MBH reaction by ESI-MS/MS, and identified intermediates that support this mechanism. DFT calculations also support a mechanism where the transition state (TS) energy is lowered through bidentate hydrogen bonding throughout the whole catalytic cycle. The thiourea acted not as a proton shuttle but as a Brønsted acid, stabilizing the basic oxygen center that was formed in the TS in the rate-limiting proton transfer step.²⁷⁴

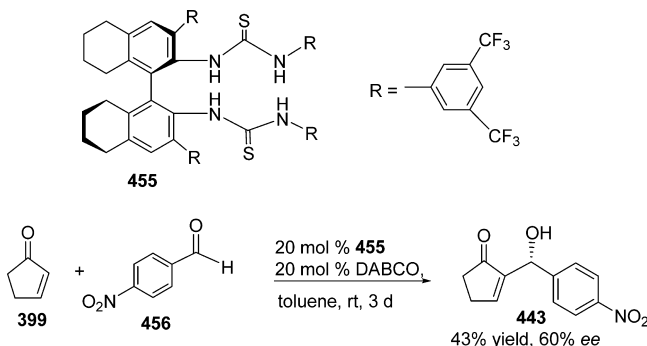
Scheme 128. Quinuclidine-Promoted Lewis Base-Catalyzed Asymmetric Aza-MBH Reaction



Scheme 129. IPDA-Bis(thio)urea/DABCO-Catalyzed Asymmetric MBH Reaction



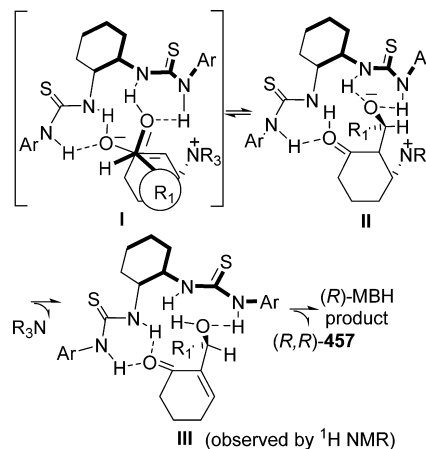
Scheme 130. BINAM-Derived Bis(thio)urea Organocatalyst/DABCO-Catalyzed Asymmetric MBH Reaction



Terada and co-workers reported the enantioselective MBH reaction of **399** and representative aryl aldehydes **463** and **456** using the guanidine/azole binary system (*R*)-**461a–d**/**462a–d** as catalyst (10 mol % each).²⁷⁵ The MBH product (*R*)-**409** was obtained in high yield and low to moderate ee (Scheme 133). The best results were achieved using the system **462d**/**461d**, at 0 °C for 48 h (entry 8). The authors obtained better enantioselectivity (72% ee) but lower yield for (*R*)-**443** using aldehyde **456**. They proposed a specific mechanism of enantioselective MBH reaction that avoided formation of unstable zwitterionic intermediates during the course of the reaction.

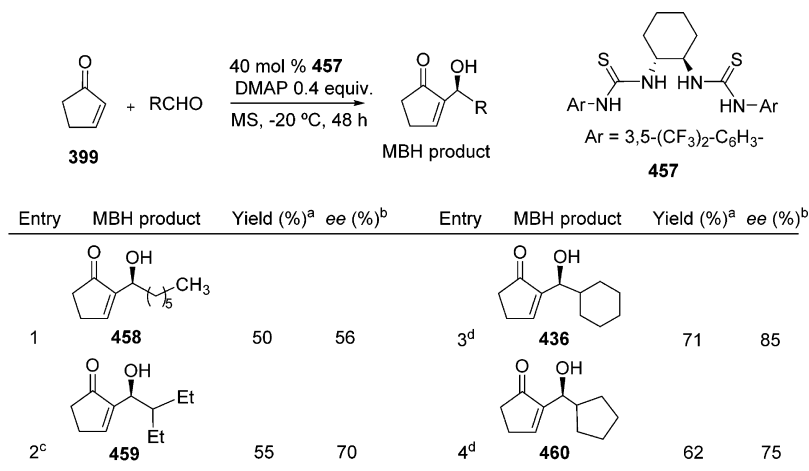
4.2. Oxidation Reactions

Chiral hydroxylated cyclopentenone derivatives are indispensable in the total synthesis of nucleosides and anticancer drugs,^{276–283} the antibiotic pentomycin and derivatives,^{12,284–287}

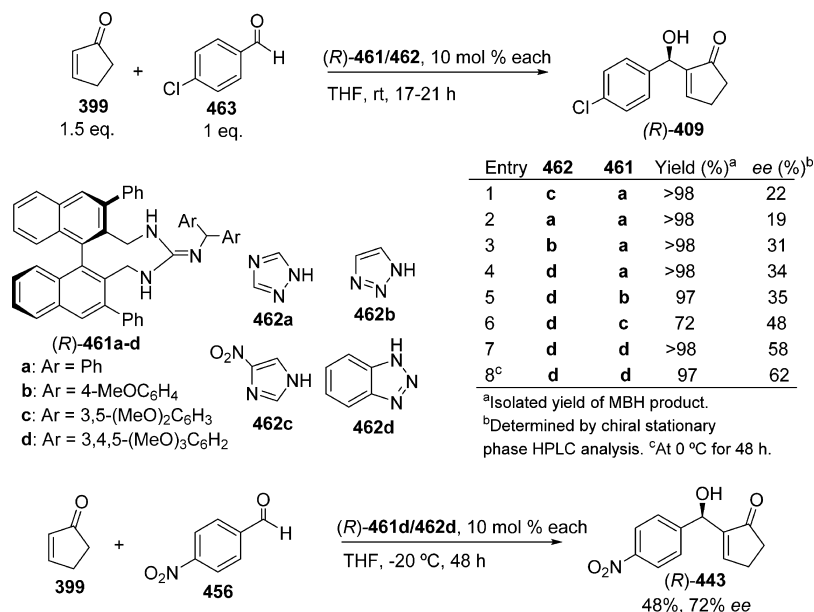
Scheme 132. Mechanism of the Asymmetric MBH Reaction Catalyzed by a (*R,R'*)-1,2-Diaminocyclohexane-Derived Bis(thio)urea Organocatalyst

and several natural products with various biological and medicinal properties.^{4,15,97,288–295} The stereochemistry of the hydroxyl group attached to the stereogenic carbon is of paramount concern in these structures because the biological activity is often critically dependent upon its orientation. The direct asymmetric oxidation of the parent carbonyl compounds allows an efficient route to enantiomerically enriched hydroxyketones.

The asymmetric dihydroxylation reaction is a highly site-selective transformation that oxidizes the most electron-rich double bond in a given substrate. This reaction was mainly developed by Sharpless on the basis of the racemic Upjohn

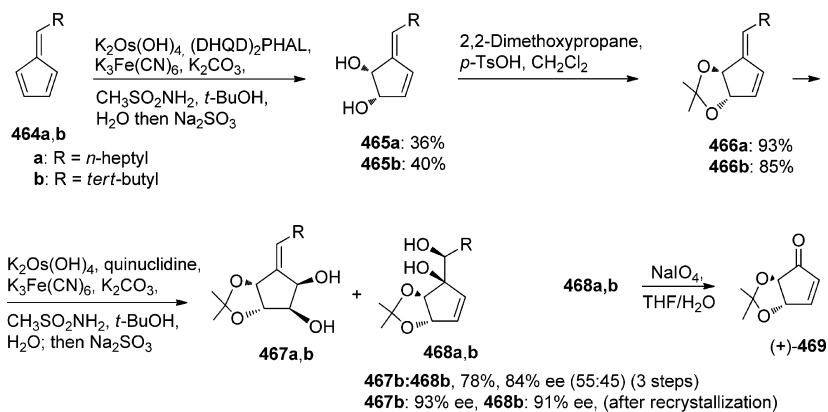
Scheme 131. 1,2-Diaminocyclohexane-Derived Bis(thio)urea Organocatalyst/DABCO-Catalyzed Asymmetric MBH Reaction^a

^a(a) Isolated yield; (b) determined by HPLC; (c) −40 °C, 72 h; and (d) −40 °C, 48 h.

Scheme 133. Enantioselective MBH Reaction Catalyzed by a Chiral Guanidine/Azole Binary System^a

^a(a) Isolated yield of MBH product; (b) determined by chiral stationary phase HPLC analysis; and (c) at 0 °C for 48 h.

Scheme 134. Concise Synthesis of (4S,5S)-4,5-(Isopropylidenedioxy)-2-cyclopentenone via Sharpless Dihydroxylation



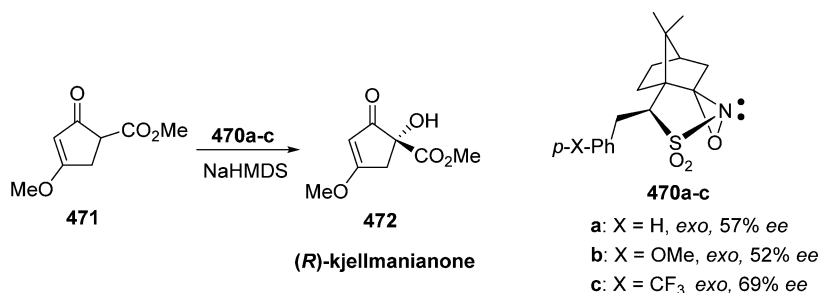
dihydroxylation developed earlier.^{296–300} The reaction, which stereospecifically produces a *cis*-1,2-diol and is tolerant of a wide range of functional groups, has been applied to substituted alkenes, affording products with high enantioselectivity.^{300,301} The utility of dihydroxylation in organic synthesis is enhanced by the facile transformations of the *cis*-1,2-diol products into other useful compounds. The application of these methods to obtain chiral hydroxycyclopentene derivatives has grown recently due to their usefulness in the total synthesis of valuable chiral natural compounds of pharmacological interest and various carbocyclic nucleosides with anticancer and antiviral activity.^{11,302–305}

The Sharpless asymmetric dihydroxylation²⁹⁷ involves the formation of highly ordered, rigid transition-state geometries through metal coordination of appropriate functional groups in the chiral auxiliary and/or substrate. The rigid transition state results in high stereoselectivity.

Several stoichiometric reagents have been utilized for the Os(VI)–Os(VIII) reoxidation step in the Sharpless dihydroxylation catalytic cycle, such as 4-methylmorpholine *N*-oxide (NMO, the Upjohn process), and potassium ferricyanide K₃Fe(CN)₆. Hayter and Armstrong³⁰⁶ reported the synthesis of 468a,b-type dioxirane compounds that can be used as

promoters in the epoxidation of alkenes with Oxone.³⁰⁷ The catalytic system used the Sharpless DHQD-PHAL ligands^{308,309} and K₂OsO₂(OH)₄ as a nonvolatile osmium reagent, in combination with an inorganic cooxidant K₃Fe(CN)₆. The CH₃SO₂NH₂ additive was used to enhance the rate of osmate(VI) ester hydrolysis (Scheme 134). The first dihydroxylation set a pair of *cis*-diols in *anti* position relative to the exocyclic alkene substituent on 465a,b. The second dihydroxylation, which led to attack at either the *exo* or the *endo* double bond of the alkenes 466a,b, afforded compounds 467a,b and 468a,b. After recrystallization, compounds 467b and 468b were obtained in 93% ee and 91% ee, respectively. Compound (+)-469, which is an important synthetic precursor for prostaglandins and nucleosides, was prepared in 60% yield and 91% ee from 468b by means of oxidative cleavage of the exogenous diol.^{41,308–311}

Chiral oxaziridines were developed as optically active oxidants for the reagent-controlled asymmetric oxidation of prochiral alkenes, sulfides, and enolates.³¹² *N*-Sulfonyloxaziridines are used to oxidize silyl enol ethers, whereas the racemic *trans*-(±)-2-(phenylsulfonyl)-3-phenyloxaziridine is used for the direct hydroxylation of enolates.

Scheme 135. (R)-Kjellmanianone Synthesis via Asymmetric Hydroxylation of α -Keto Ester Enolate with *N*-Sulfonyloxaziridines

Theoretical and experimental studies have suggested an S_N2 -type mechanism for the transfer of oxygen from *N*-sulfonyloxaziridines to nucleophiles.³¹³

The first oxaziridine oxidant employed for the asymmetric α -hydroxylation of enolates was racemic *trans*-(\pm)-2-(phenylsulfonyl)-3-phenyloxaziridine, introduced by Davis and co-workers.^{314–316} 2-Sulfonyloxaziridines are aprotic, neutral, and stable oxidizing reagents of significant synthetic versatility. These reagents oxidize sulfides and disulfides into sulfoxides and thiosulfates, respectively, epoxidize olefins through *syn*-stereospecific manner, and hydroxylate carbanions.^{317–319}

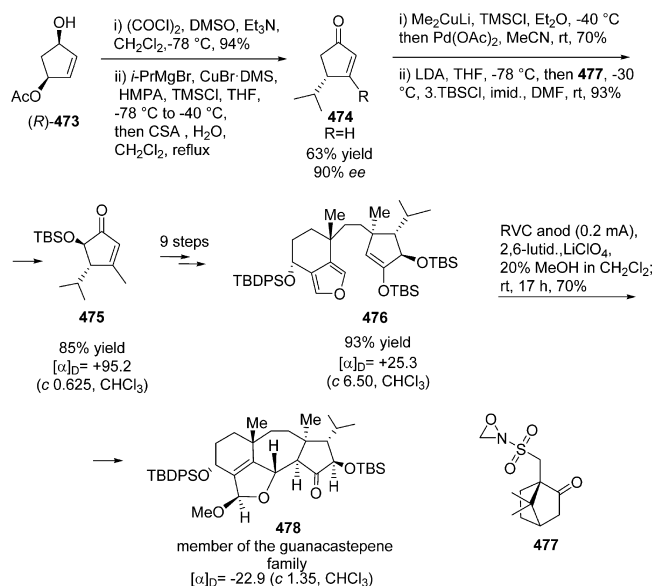
A small number of studies concerning cyclic enones or enolates have been reported, with particular emphasis on carbocyclic rings and their applications in natural product synthesis.

Asymmetric oxidation of the sodium enolate of α -keto ester 471 affords kjellmanianone 472, an antibacterial agent isolated from marine algae (Scheme 135).^{313,320} The *ee* values appeared to be dependent on the nature of the *para*-substituent in *exo*-benzyl oxaziridines 470a–c, although the benzene ring was *trans*-oriented on the five-membered ring and is separated by five bonds. The authors proposed that an interaction between the metal enolate and the benzene ring is responsible for the influence of different substituents in chiral 2-(phenylsulfonyl)-3-phenyloxaziridine oxidants.

The guanacastepenes are a family of highly oxidized diterpenes. Guanacastepene A has antibiotic activity and displays an interesting molecular structure that has received attention from several research groups.^{321–323} Hughes and co-workers reported an asymmetric variant of the total synthesis of this complex molecule in which they employed various types of oxidation reactions (Scheme 136).³²⁴ The enantiopure alcohol 473 was first subjected to a Swern oxidation to an enone, followed by conjugate addition and elimination to afford cyclopentenone 474. This was followed by another conjugate addition and a Saegusa oxidation with Pd(OAc)₂.³²⁵ The substrate was then converted to a lithium enolate and reacted with camphor-based oxaziridine 477, developed by Davis,^{326,327} finishing with a silylation to afford acyloin 475. The diastereoselectivity of this process was substrate-controlled, and it was noted that both enantiomers of the oxaziridine produced the *trans* diastereomer. The synthesis progressed with a further nine steps to product 476, which was subjected to an anodic oxidation at constant current using a reticulated vitreous carbon (RVC) anode and a platinum cathode to afford 478 as a single diastereomer in good yield (70%). The electrochemical process was the key step of the reported synthetic route.

In 2006, Overman et al.⁴⁶ developed a synthesis of an enantiopure *i*-Pr analogue of 475, in 79% yield and 88% *ee*, via a modified Stork–Danheiser reaction of 3-substituted cyclo-

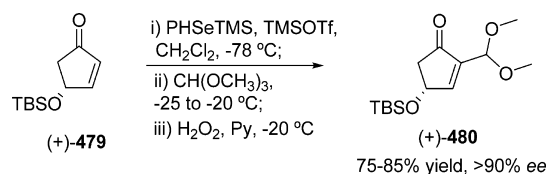
Scheme 136. Guanacastepene Synthesis



alkenones³²⁸ and isopropylation of a zincate enolate. This chiral precursor was then employed in the asymmetric synthesis of (+)-guanacastepene N.

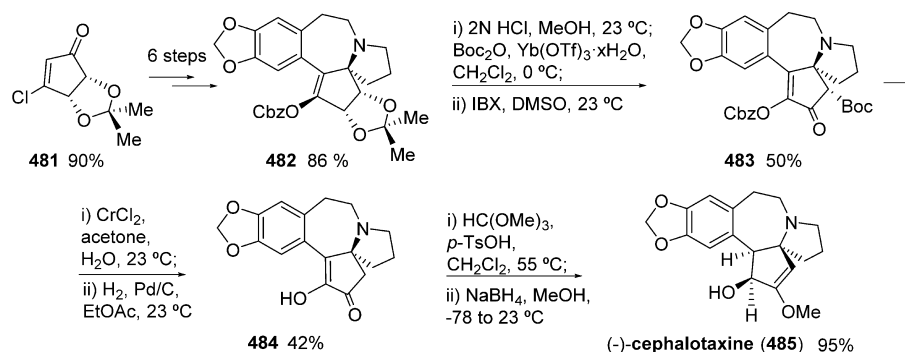
Myers and co-workers reported an enantioselective total synthesis of neocarzinostatin chromophore,³²⁹ employing a method developed by Noyori³³⁰ involving the sequential one-pot addition of litseaverticillol A trimethylsilylphenyl selenide, trimethyl orthoformate, and hydrogen peroxidepyridine to obtain (+)-480 in >90% *ee* from (+)-479 (Scheme 137).³²⁹

Scheme 137. Synthesis of a Precursor to Neocarzinostatin Chromophore

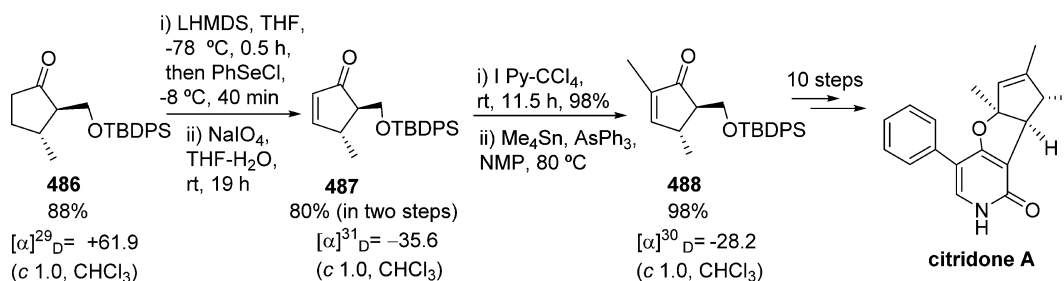
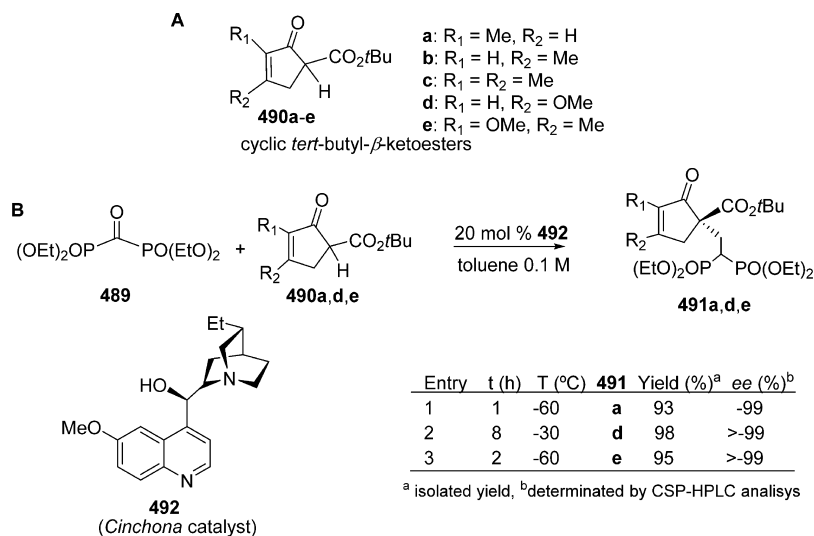


The authors reported that the timing of the addition of hydrogen peroxide-pyridine to the intermediate α -phenylselenenyl dimethyl acetal was decisive. If the reagent was added before the trimethylsilyl enol ether intermediate had reacted completely with added trimethyl orthoformate, it would result in incomplete conversion of the starting cyclopentenone (+)-479, whereas late addition resulted in decomposition. The neocarzinostatin product thus synthesized exhibited broad-spectrum antibiotic

Scheme 138. Synthesis of Cephalotaxine



Scheme 139. Synthesis of Citridone A

Scheme 140. Synthesis of Geminal Bisphosphonates by Organocatalyzed Michael-type Addition of β -Ketoesters^a

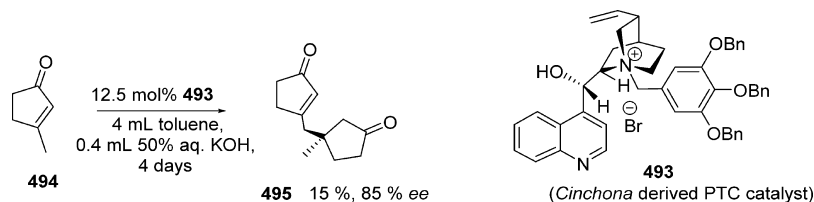
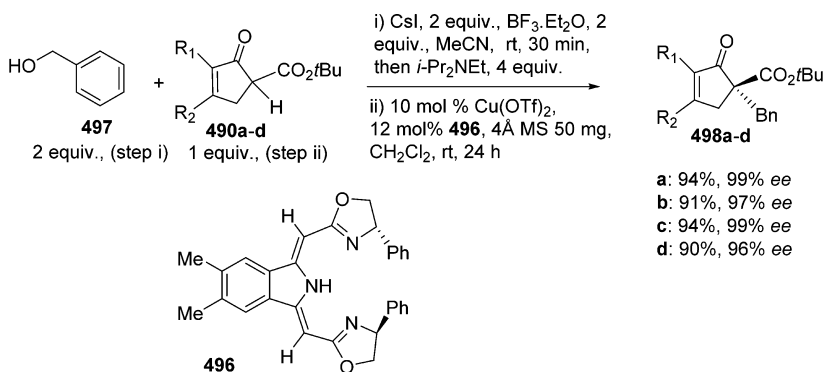
^a(a) Isolated yield; and (b) determined by CSP-HPLC analysis.

activity and potent antiproliferative effects in a wide variety of tumor cell lines both in vitro and in vivo.³³¹

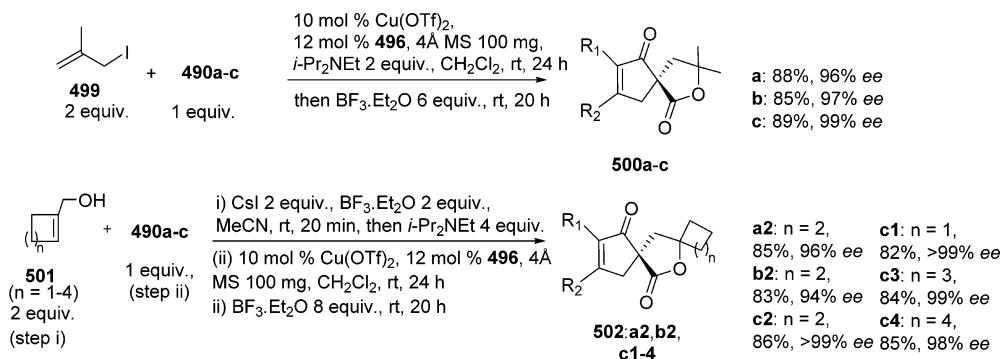
The 2-iodoxybenzoic acid IBX (1-hydroxy-1-oxo-1*H*-1 λ 5-benzo[*d*][1,2]iodoxol-3-one) is used extensively in organic synthesis as a mild, safe, and economic alternative to heavy metal oxidant reagents.^{332,333} A comprehensive review of the applications of IBX in organic synthesis was published in 2010.³³⁴ IBX is particularly useful for the selective oxidation of alcohols to carbonyl compounds under mild conditions such as room temperature and neutral pH, thus showing good tolerance of functional groups in complex molecules. IBX is able to oxidize chiral primary alcohols while avoiding epimerization and loss of optical purity, such as in the case of *N*-protected amino alcohols. This is an advantage over classical oxidation reactions such as the

Swern oxidation or TEMPO-catalyzed oxidation that are prone to epimerization in some cases.^{335,336} Recently, Nicolaou et al. described a highly efficient conversion of alcohols, ketones, and aldehydes to α,β -unsaturated carbonyl compounds in one pot using IBX in fluorobenzene (or toluene)–DMSO mixtures (ca. 2:1).³³⁷ The authors also demonstrated that HIO₃ and its anhydride I₂O₅ were more atom-efficient and safer alternatives to IBX for the dehydrogenation of carbonyl compounds. Furthermore, these IBX substituents are highly chemoselective and effect smooth dehydrogenations at 45–65 °C in the presence of a variety of sensitive functionalities, including unprotected alcohols.³³⁸ Scheme 138³³⁹ shows an example of using IBX as a mild method of oxidation in a multistep asymmetric synthesis starting from chiral cyclopentenone 481,

Scheme 141. Organocatalytic Regioselective Michael Additions of Cyclic Enones via Asymmetric Phase Transfer Catalysis

Scheme 142. Cu-Catalyzed Enantioselective Alkylation of β -Ketoesters

Scheme 143. Synthesis of Bispirolactones



obtained in 90% overall yield from D-ribofuranose, to afford cephalotaxine 485.³³⁹

Cephalotaxine 485 is the most abundant alkaloid constituent of the *Cephalotaxus* genera identified to date.³⁴⁰ Early biological evaluations of these alkaloids revealed that several cephalotaxus esters demonstrate acute toxicity toward various murine leukemia, murine lymphoma, and human epidermoid carcinoma cells.³⁴¹

The synthesis of a novel natural product, citridone A, which was isolated from a fermentation broth of *Penicillium* sp. FKI-1938,³⁴² was recently reported by Nagamitsu and Omura.³⁴³ The α -selenenylation/oxidation/elimination process of 486 was conducted enantioselectively and provided 487. This was followed by an iodination/dehydrohalogenation reaction to afford a vinyl iodide, which was subsequently subjected to a Stille coupling with Me₄Sn, affording *trans*-cyclopentenone 488 in high yield (Scheme 139).

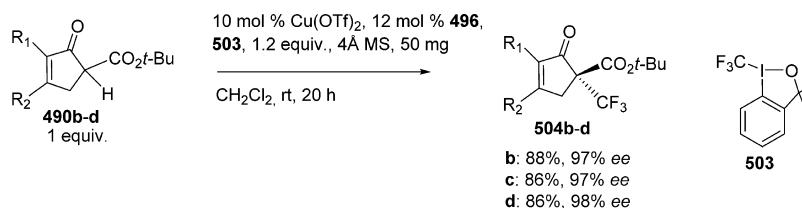
4.3. Organocatalyzed Michael Additions of Cyclic β -Ketoesters

Various authors have employed cyclic *tert*-butyl- β -ketoesters 490a–e (Scheme 140A) in a range of asymmetric trans-formations to generate highly enantiopure samples of bio-

logically important cyclopentenone derivatives with quaternary stereocenters.

Bisphosphonate derivatives have been used for the treatment of several bone disorders, such as Paget's disease, myeloma, bone metastases, and osteoporosis,³⁴⁴ and some childhood diseases.³⁴⁵ Jørgensen and co-workers developed an asymmetric conjugate addition of cyclic β -ketoesters to ethylidenebisphosphonate esters.³⁴⁶ Concentrations of 0.1 M in toluene were found to be optimal for enantioselectivity and conversion rate. These optically active geminal bisphosphonates 491a,d,e, bearing an all-carbon-substituted quaternary stereocenter, were achieved in high yields and enantioselectivities up to 99% ee (Scheme 140).

Bella and co-workers reported an interesting enantioselective Michael addition to cyclopentenones functionalized at the C3 position with up to 92% ee (87% ee for 2-cyclohexenone).³⁴⁷ The methyl substituent in enone 494 was activated toward deprotonation due to conjugation with the double bond. Treatment under phase transfer catalyst (PTC) conditions (KOH aq 50%, toluene), using 12.5 mol % of the known *Cinchona*-derived PTC catalyst 493, resulted in dimerization of 494 through vinylogous enolate formation and electrophilic attack at the C3 position in low yield and with 85% ee (Scheme 141). The indispensable condition was the absence of other Michael acceptors in the reaction mixture. Because of greater

Scheme 144. Cu-Catalyzed Trifluoromethylation of β -Ketoesters

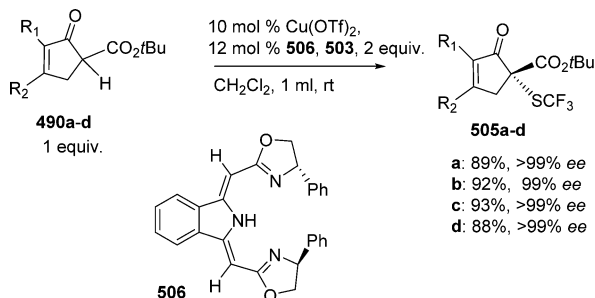
stabilization of the anion derived from 2-cyclopentenone relative to 2-cyclohexenone, the reaction with the latter did not afford any products.

4.4. Transition Metal-Catalyzed Enantioselective Derivatizations of β -Ketoesters

Very recently, Gade and co-workers reported a protocol for Cu-catalyzed enantioselective alkylation reactions of β -ketoesters **490a–d** via benzyl (**497**) and allylic (**501**) alcohols that were employed for the in situ preparation of iodides (step 1) (Scheme 142) and, respectively (Scheme 143), that acted as alkylating reagents.³⁴⁸ Compound **496** was used as a chiral ligand for the transition metal catalyst.³⁴⁹ The functionalized β -ketoesters **498a–d** acquired a quaternary carbon stereocenter and were prepared with up to 99% ee (Scheme 142). The chiral alkylated products, obtained using 2-substituted allylic alcohols **501**, were transformed into the bispironolactones **502** by adding 8 equiv of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, in a one-pot procedure. The cyclic products were prepared in high yields and enantioselectivities. In the case of 3-iodo-2-methylpropene **499**, the primary alkylation products were obtained from reaction with $\text{Cu}(\text{OTf})_2$ and **496**, and were later converted into spironolactones **500a–c** using 6 equiv of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Scheme 143).

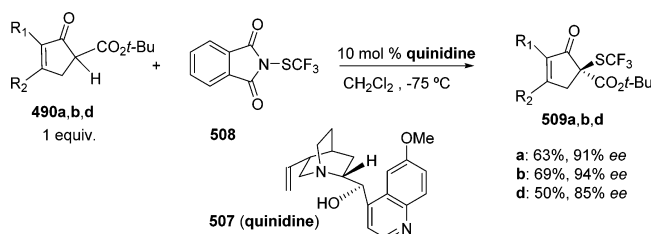
The same research group also developed an efficient protocol for enantioselective Cu-catalyzed trifluoromethylation³⁵⁰ of β -ketoesters **490b–d** using commercially available Togni Reagent (**503**) for CF_3 transfer and a catalyst, generated in situ from 10 mol % of $\text{Cu}(\text{OTf})_2$ and 12 mol % of chiral ligand **496** in the presence of molecular sieves (Scheme 144), under reaction conditions that had been previously optimized for enantioselective alkylations (see Scheme 142).³⁵⁰ They obtained the corresponding α - CF_3 - β -ketoesters **504b–d** with high enantioselectivity (97–98% ee) and good yields via Cu-boxmi catalysis, showing that the size of the ester group has a slight influence on the enantiocontrol.

Gade and co-workers continued this work by employing enantioselective trifluoromethylthiolation of β -ketoesters **490a–d**. They used the same type of catalyst (Cu-boxmi (**506**) complex) and the Togni Reagent (**503**) as a CF_3 transfer reagent (Scheme 145).³⁵¹

Scheme 145. Synthesis of Cyclopentenone SCF_3 - β -Ketoesters

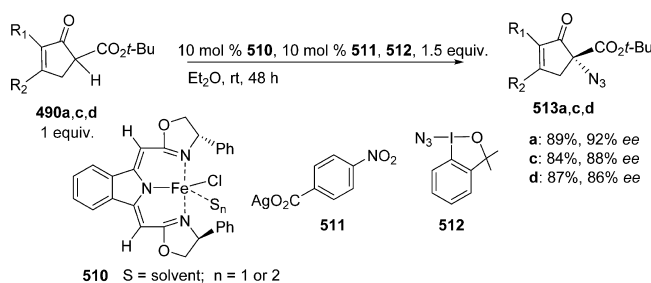
The α -substituted SCF_3 - β -ketoesters of 2-cyclopentenones **505a–d** exhibited high enantioselectivities and were obtained in very good yields in optimized reaction conditions. They possessed two adjacent quaternary stereocenters. The compounds have potential as drugs due to the presence of the stable lipophilic, electronegative CF_3 substituent.³⁵²

In 2013, Rueping et al. developed catalytic asymmetric trifluoromethylsulfenylation of cyclopentenone-derived *t*-butyl β -ketoesters (**490a,b,d**), among others (Scheme 146).³⁵³

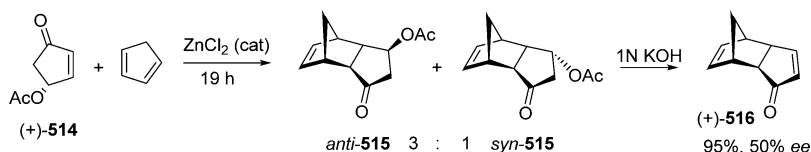
Scheme 146. Asymmetric Trifluoromethylsulfenylation of Cyclopentenone-Derived *t*-Butyl β -Ketoesters

Munavalli's *N*-trifluoromethylthiophthalimide (**508**)³⁵⁴ was employed as an electrophilic SCF_3 source. After optimization of the reaction conditions, the authors selected the quinidine **507** as an asymmetric catalyst, which conferred (*S*) configuration on products **509a,b,d**, which were obtained in very good enantioselectivities and moderate yields. The described protocol for trifluoromethylsulfenylation of β -ketoesters was used to construct a quaternary stereogenic center bearing the SCF_3 group in the produced chiral derivatives.

Furthermore, Gade et al. reported the enantioselective Fe-catalyzed azidation (Scheme 147) of β -ketoesters **490a,c,d** using

Scheme 147. Enantioselective Fe-Catalyzed Azidation of Cyclopentenone-Derived *t*-Butyl β -Ketoesters

a stable azidoiodinane **512** as an N_3 -transfer reagent.³⁵⁵ The combination of iron(II) chlorido complex **510** and silver carboxylate **511** was employed in the case of enantioselective Fe-catalyzed azidation. The authors observed that the enantioselectivity of the products was dependent on the type of ligand, iron(II) salt (iron(II) propionate and $\text{Fe}(\text{OOCt})_2$

Scheme 148. Synthesis of (+)-Tricyclodecadienone **516**

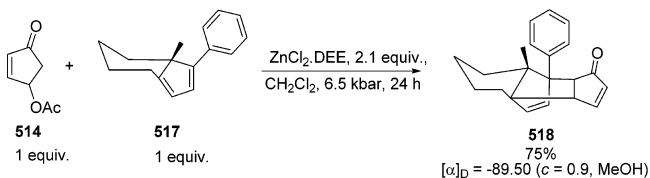
were found to be optimal), and solvent (use of diethyl ether increases the ee values of generated products).

In this first example of Fe-catalyzed enantioselective azidations of the cyclic β -keto esters, the corresponding products **513a,c,d** were isolated in high yields with up to 92% ee, as determined by chiral HPLC.

4.5. Enantioselective [4+2] Cycloadditions

Zwanenburg and co-workers reported the reaction of chiral 4-acetoxycyclopentenone (+)-**514** as dienophile with cyclopentadiene in the presence of Lewis acid catalyst ZnCl_2 , which slowly (19 h reaction time) provided a mixture of *endo*-tricyclic acetates, *anti*-**515** and *syn*-**515**, in a ratio of 3:1.³⁵⁶ The π -facial diastereoselectivity of the cycloaddition reaction was explained by electronic effects in terms of Cieplak's theory.³⁵⁷ After base-induced elimination of the β -acetoxo group from the intermediate mixture, chiral (+)-tricyclodecadienone (+)-**516** was achieved in 95% yield with an enantiomeric purity of 50% ee (Scheme 148).

A comparable sequence of reactions was reported by Borm and Winterfeldt,³⁵⁸ in which the chiral component was a cyclopentadiene **517**. Under high pressure and in the presence of Lewis acid catalyst ZnCl_2 , a cycloaddition–elimination sequence occurred, and the authors obtained chiral cyclopentenone adduct **518** in 75% yield (Scheme 149).

Scheme 149. ZnCl_2 -Catalyzed Cycloaddition-Elimination Sequence

4.6. Asymmetric [5+3] Formal Cycloaddition Reactions

Chen et al. reported a new cascade-asymmetric [5+3] formal cycloaddition reaction based on the dienamine–dienamine catalytic pathway for β -substituted 2-cyclopentenones.³⁵⁹ This included domino α' -regioselective Michael addition and α,γ -regioselective Mannich reaction with 3-vinyl-1,2-benzisothiazol-1,1-dioxides. The reactions represented unusual formal [5+3] cycloaddition protocols with the formation of final fused or bridged asymmetric spirocyclic molecular structures with four contiguous chiral centers (Scheme 150). The [5+3] cycloaddition reaction occurred in optimal conditions in the presence of catalysts 9-amino-9-deoxyepiquinine (**521** or **522**) and 5-nitrosalicylic acid (**523**) in CHCl_3 . The final structures with bridged architectures comprised spirocyclic skeletons and were achieved in excellent enantioselectivities (97–99% ee) and very good yields, taking into account the explicit examples of yields and ee values of respective products **524**, obtained using substrate scope in [5+3] formal cycloaddition reaction with 2-

cyclopentenones and 3-vinyl-1,2-benzisothiazole-1,1-dioxides catalyzed by **521** or **522** and **523**.

Some of these products were studied with respect to their biological activities, with promising results for anticancer activity in some cancer cell lines.

The [5+3] cycloaddition reaction was also performed with benzylidenemalononitrile as a bis(electrophilic) reagent (Scheme 151). The reaction produced compounds **525a** and **525b** with moderate enantioselectivities.

4.7. Asymmetric Allylic Alkylation (AAA)-Claisen Rearrangements

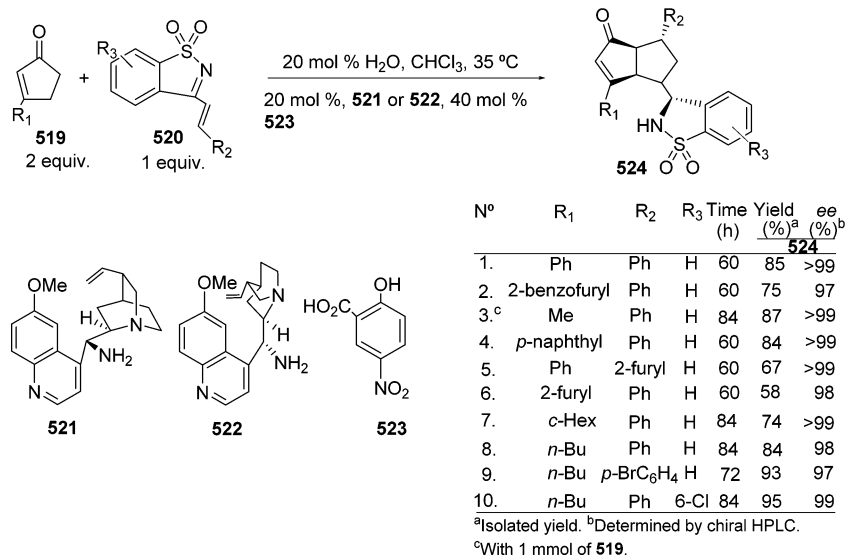
Scheme 152 shows the contribution of the group of Trost on the development of an asymmetric *O*-alkylation using commercially available 3-methylcyclopentane-1,2-dione, or its single tautomeric species **527**, and consequently transfer of chirality to the C-alkylated products by Claisen rearrangement.³⁶⁰ Compound **527** was alkylated with 3-cyclopentenyl methyl carbonate **528** and two symmetrical acyclic substrates **530a,b** and **532** employing (*R,R*)-**526** as a chiral ligand. The reactions were performed in DCM using 0.2 M of nucleophile and 1.1 equiv of **528** and **530a,b** and **532** at room temperature. Additional optimization screening of catalyst concentration and type of base was performed. The good ee values (82–97%) obtained with cyclic substrate **528** were confirmed with symmetrical acyclic substrates **530a,b**.

With sterically nondemanding substrate **532**, a nucleophilic attack occurred at the more highly substituted allyl terminus favored by the ligand (*R,R*)-**526**.

Next, chirality transfer by Claisen rearrangement was examined with compound **529**, in the case of the cyclic substrate. For this reaction, after careful screening of several Lewis acids and lanthanide complexes, the authors decided to adopt 10 mol % $\text{Ho}(\text{fod})_3$ ($\text{fod} = 6,6,7,7,8,8,8\text{-heptafluoro-2,2-dimethyl-3,5-octanedionate}$) in a minimal amount of chloroform at 50–80 °C as a standard protocol. With substrate **529**, 87% chirality transfer to product **534** was observed at 75 °C. In each case, the alkene geometry was exclusively *E*. For the formation of **536**, chirality transfer was observed from the side chain to the ring, which represented an asymmetric C-alkylation. The ee values were determined using NMR and HPLC analysis.

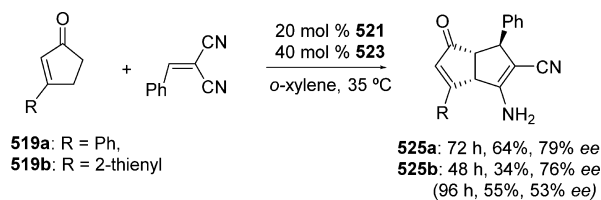
The group of Trost applied the methodology described above to the total synthesis of terpestacin (Scheme 153)³⁶¹ in which the key steps were the palladium-catalyzed asymmetric allylic alkylation reaction and thermal Claisen rearrangement (using microwave irradiation) to create both the key all-carbon quaternary stereocenter and the chiral methyl group appended to the cyclopentenone ring on the complex terpestacin molecule.

The Pd-catalyzed AAA between **527** (nucleophile) and isoprene monoepoxide **537** (electrophile) furnished **540** in good yield and enantioselectivity. A seven-step procedure converted compound **542** into **543**, which underwent *E*-selective ring-closing metathesis (RCM), deprotection, and a second palladium-catalyzed AAA step. Compound **544** again participated in a thermal Claisen rearrangement, and seven further steps furnished the final product (–)-terpestacin **545**. The

Scheme 150. Asymmetric [5+3] Formal Cycloadditions of 2-Cyclopentenones and 3-Vinyl,1,2-benzisothiazole-1,1-dioxides^a

^a(a) Isolated yield; (b) determined by chiral HPLC; and (c) with 1 mmol of 519.

Scheme 151. Asymmetric [5+3] Formal Cycloadditions of 2-Cyclopentenones and Benzyldenemalononitrile



macrocyclic diterpene terpestacin was isolated in 1993 from the fungal strain *Arthrinium* sp., and in collaboration with Bristol-Myers Squibb it was further revealed that terpestacin inhibited the formation of syncytia⁸⁰, multinuclear cells that arise from expression of gp120 on cell surfaces during HIV infection.^{362,363}

4.8. Suzuki–Miyaura and Sonogashira Reactions

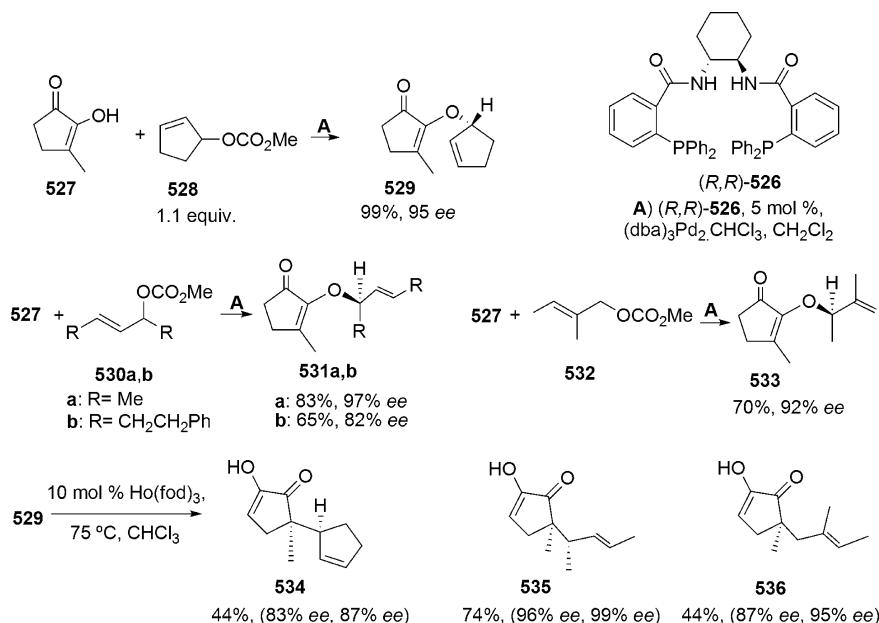
Pohmakotr's group reported the simplified synthesis of α -aryl- and α -alkynyl-substituted pentenomycin derivatives by employing the Suzuki–Miyaura and Sonogashira coupling reactions, respectively (Scheme 154).¹²

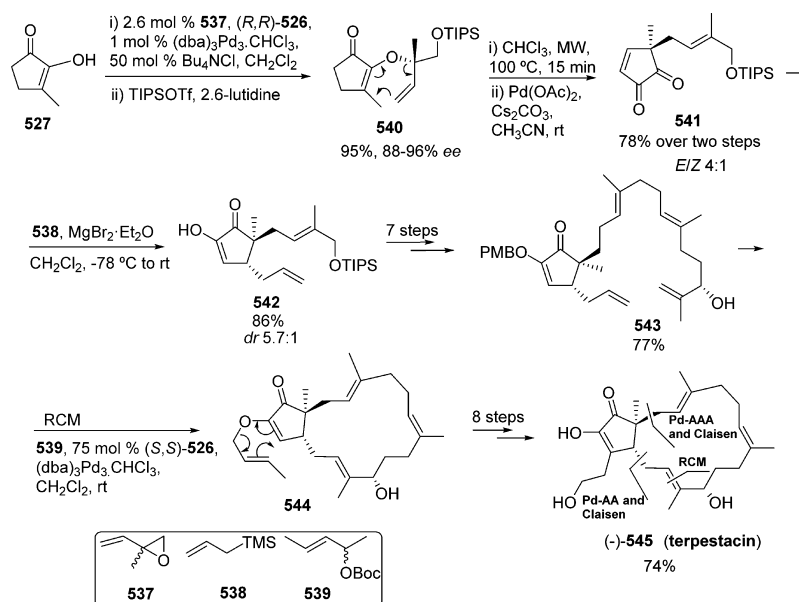
The chirality of substrate 546 was transferred successfully to products 547 by Suzuki–Miyaura coupling reaction (SMR)³⁶⁴ and to 548a,b via Sonogashira reaction,³⁶⁵ and was transferred on desired (+)-pentomycin and (+)-epipentomycin.

Suzuki–Miyaura reaction was performed using phenylboronic acid in THF to interact with 546 in the presence of 10 mol % of PdCl₂(PPh₃)₂ and Na₂CO₃ at 40 °C for 15 h under an argon atmosphere.

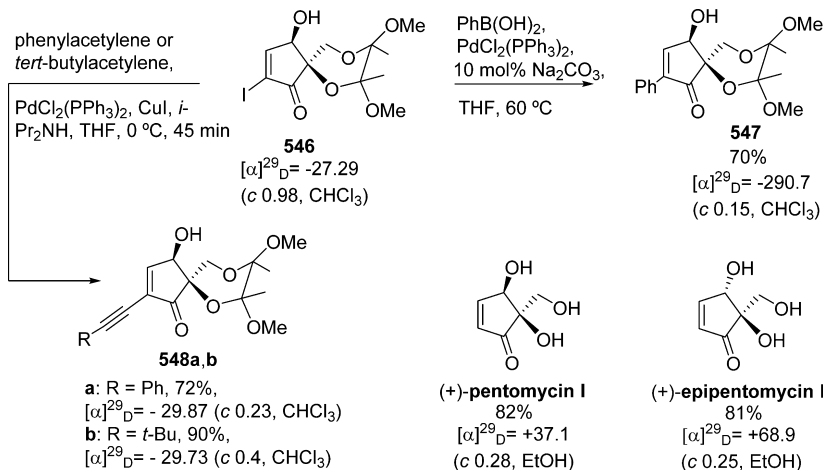
More recently, Tu et al.³⁶⁶ reported an asymmetric total synthesis of (+)-przewalskin B, a novel diterpenoid isolated from

Scheme 152. Pd-Catalyzed Asymmetric O-Alkylation of 3-Methylcyclopentane-1,2-dione with Carbonates

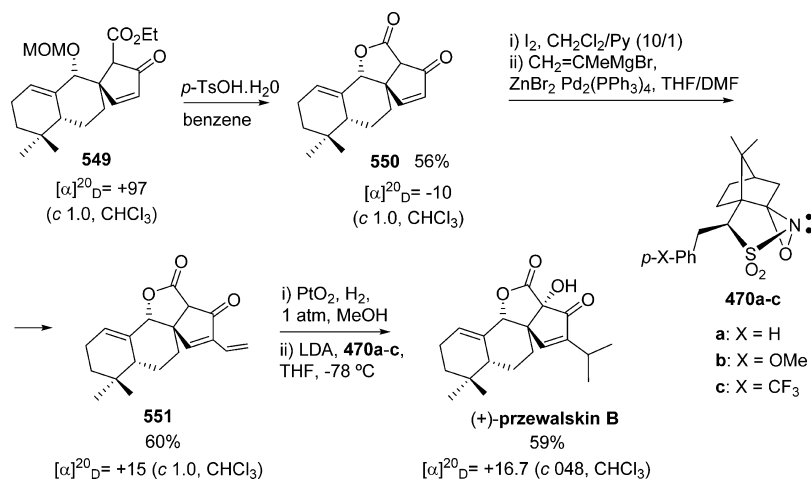


Scheme 153. Pd-Catalyzed Asymmetric *O*-Alkylation of 3-Methylcyclopentane-1,2-dione with Isoprene Monoepoxide in the Total Synthesis of Terpestacin

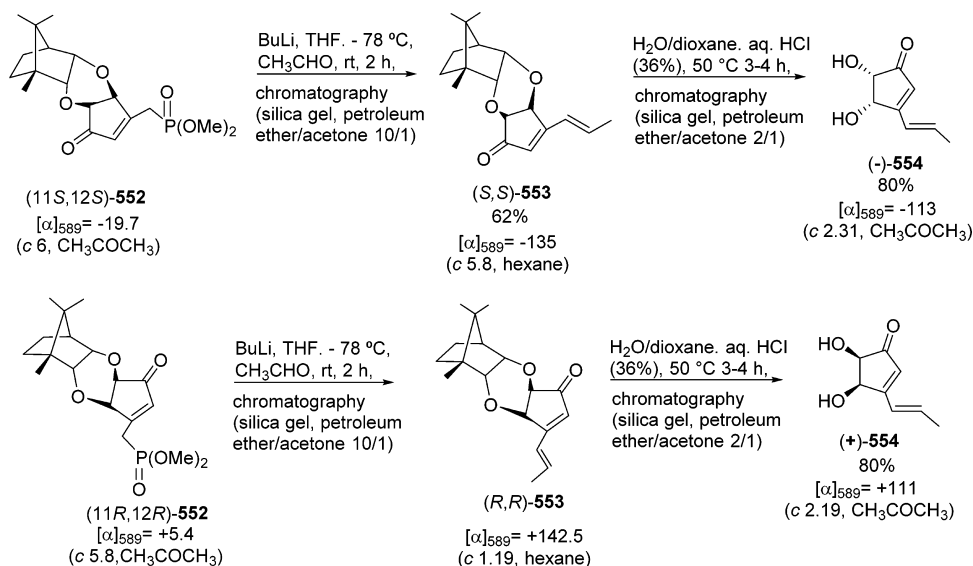
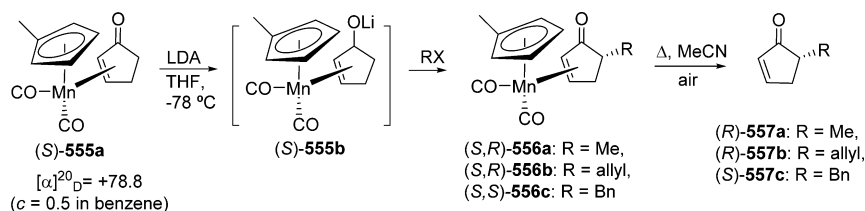
Scheme 154. Asymmetric Synthesis of Pentenomycin I, Epipentenomycin I, and Their Analogues



Scheme 155. Asymmetric Total Synthesis of (+)-Przewalskin B



Scheme 156. Total Synthesis of Isoterrein

Scheme 157. η^2 -Manganese-Complex-Controlled C–C Bond Formation

plant *Salvia przewalskii* that exhibits anti-HIV-1 activity ($EC_{50} = 30 \mu\text{g/mL}$).²³

A variant of the synthesis is presented in Scheme 155; the chirality of **549** was transferred to the tetracyclic ketolactone **550**, obtained as a single isomer, in a condensation reaction promoted by *p*-TsOH. The iodination at the α -position of the cyclopentenone moiety, followed by Negishi coupling with isopropenylmagnesium bromide, yielded the terminal alkene **551**. Subsequent hydrogenation at atmospheric pressure with PtO₂ catalyst and then treatment of the resulted product with LDA and Davis' oxaziridine **470a–c** afforded (+)-przewalskin B in 59% yield, with the sign of optical rotation opposite to that of the natural product.

Thus, this synthesis presented an example of using several types of reactions that do not themselves introduce chirality but allow the transfer of the initial chirality.

4.9. Horner–Wittig Reactions with Chiral Cyclopentenone Derivatives

Mikolajczyk and co-workers³⁶⁷ reported the first total synthesis of both enantiopure forms of isoterrein, (–)-**554** and (+)-**554**. The acid-catalyzed reaction of *meso*-tartaric acid with (+)-camphor and methyl orthoformate in methanol and treatment of the corresponding product with dimethyl lithiomethanephosphonates produced the protected 3-phosphonomethylcyclopentenones **552** in 59% yield as a 55:45 mixture of diastereomers. The authors then employed the Horner–Wittig reaction of chiral (–)-**552** and (+)-**552** with acetaldehyde, which furnished the protected isoterreins **553** (Scheme 156).

The pure diastereomers (S,*S*)-**553** and (R,*R*)-**553** were separated by fractional crystallization from hexane/acetone and subsequent column chromatography. As the original chiral diol

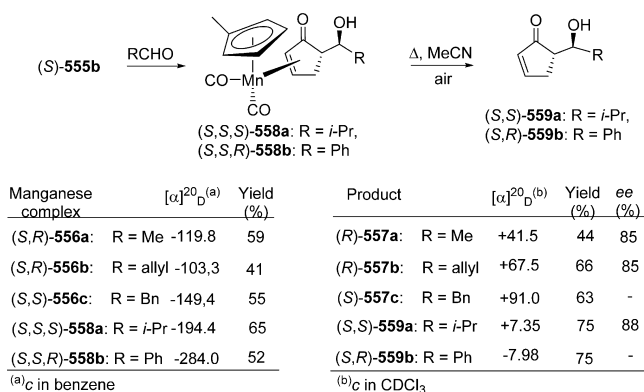
fragment was maintained in these diastereomers through the Horner–Wittig reaction and the acid hydrolysis, (–)-**554** can be assigned the (S,*S*) configuration, and (+)-**554** the (R,*R*) configuration.

4.10. Asymmetric Aldol Couplings with Aldehydes

Bärmann and Schinzer³⁶⁸ have reported for the first time the enantioselective preparation of planar-chiral η^2 -manganese complexes and their use in alkylation and asymmetric aldol reactions. By using this method of asymmetric C–C bond formation, they have obtained derivatives in high optical purity.

The oxidation of the chiral η^2 -manganese complex of respective (S,*S*)-alcohol with tetra-*n*-propylammonium per-ruthenate (TPAP) as catalyst and *N*-methylmorpholine *N*-oxide (NMO) as oxidant delivered the planar-chiral η^2 -manganese complex (S)-**555a** in 90% yield. The enolate (S)-**555b** was achieved by deprotonation in situ with lithium diisopropylamide (LDA) in THF at –78 °C, under conditions of kinetic control (Scheme 157.). The complex could be alkylated diastereoselectively into manganese complexes **556a–c** as a single diastereomer, giving *anti*-aldol products **558a,b** with high optical purities, using (S)-**555a** as planar-chiral η^2 -manganese complex. Following demetalation in acetonitrile in the presence of air, the *anti*-aldol products **559a,b** were obtained as sole products, but the authors could not determine the ee values of (S,*R*)-**559b** (R = Ph) by gas chromatography (Lipodex E), even after derivatization (Scheme 158).

The asymmetric direct aldol coupling reactions of cyclic ketones as enolate substrates have been broadly developed by the use of chiral organocatalysts via in situ-generated enamine species to supply optically active saturated cyclic β -hydroxyketones.³⁶⁹ However, the chiral unsaturated aldol products

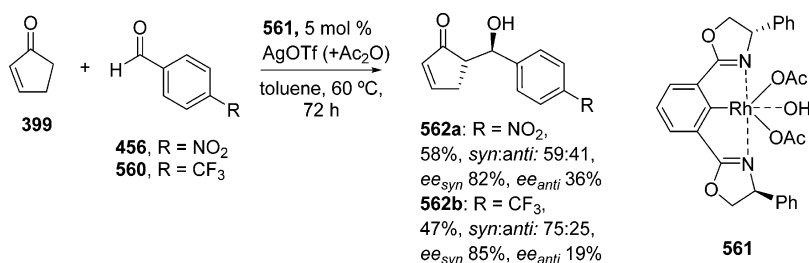
Scheme 158. Aldehyde Screening in the η^2 -Manganese-Complex-Controlled C–C Bond Formation^a

derived from enones are potentially useful components for organic synthesis. Cyclic ketones have rarely been applied as enolate sources because of problems of instability, as well as the ability for enones to act as reactive acceptors in conjugate additions, the possibility of retro–aldol equilibria, or β -hydroxy elimination from the aldol products. With the aim of filling this gap, Nishiyama et al. reported the regioselective direct aldol coupling of cyclopentenone **399**, employing the chiral rhodium-(bis-oxazolinyphenyl) catalyst [Rh(Phenbox)], **561**.³⁷⁰ The authors proposed that the [Rh(Phenbox)] complex acted as a Lewis acid and a Brønsted base to form a rhodium–enolate species. A dienolate was formed regioselectively from cyclopentenone by activation of the $C\alpha'$ –H bond to form unsaturated aldol products **562a,b** (Scheme 159). The authors obtained good yields for these products, with a prevalence of *anti*-aldol products in high enantioselectivities (82–85% ee). The specific pattern of the reaction was the difficult acetylation given that the acetic anhydride could not efficiently capture the corresponding intermediate rhodium–aldolate to release the product.

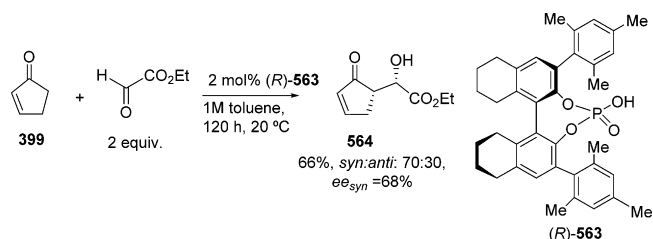
In 2011, Blanchet et al. reported the first direct Brønsted-acid-organocatalyzed aldol reaction employing chiral BINOL-derived phosphoric acid (R)-**563**,³⁷¹ which was prepared by the authors themselves.¹⁹⁹ The authors also studied the reaction with 2-cyclohexenone and 2-cyclopenten-1-one as an enone source, due to scarcity of information about this substrate in amino-catalyzed aldol reactions. The direct regioselective aldol reaction in optimized conditions is presented in Scheme 160.

When cyclic enone **399** was used, the regioselective adduct with ethyl glyoxalate corresponding to the α -aldol reaction (no reaction in γ position was detected) was obtained in 66% yield, with enantioselectivity of 78% ee_{syn} (ratio *syn:anti*: 70:30). These

Scheme 159. Regioselective Direct Aldol Coupling of Cyclopentenone and Aldehydes with Chiral Rhodium(bis-oxazolinyphenyl) Catalysts



Scheme 160. Direct Regiospecific Asymmetric Aldol Reaction Catalyzed by a Chiral BINOL-Derived Phosphoric Acid



results were achieved using mild reaction conditions, low catalyst loadings, and reasonable stoichiometries of the reagents.

In 2015, Aisetti and Reiser reported a stereocontrolled conjugated 1,4-*anti*-addition of a nucleophile to 4-hydroxycyclopentenone followed by 1,2-*anti*-aldol, using the 4-OBoc- and 4-OPMP-cyclopent-2-enones (R)-**566** and (S)-**567**, respectively, available in multigram scale (Scheme 161).⁵³

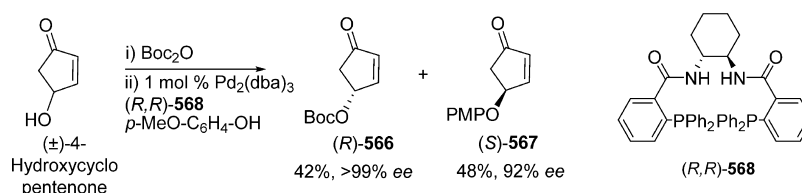
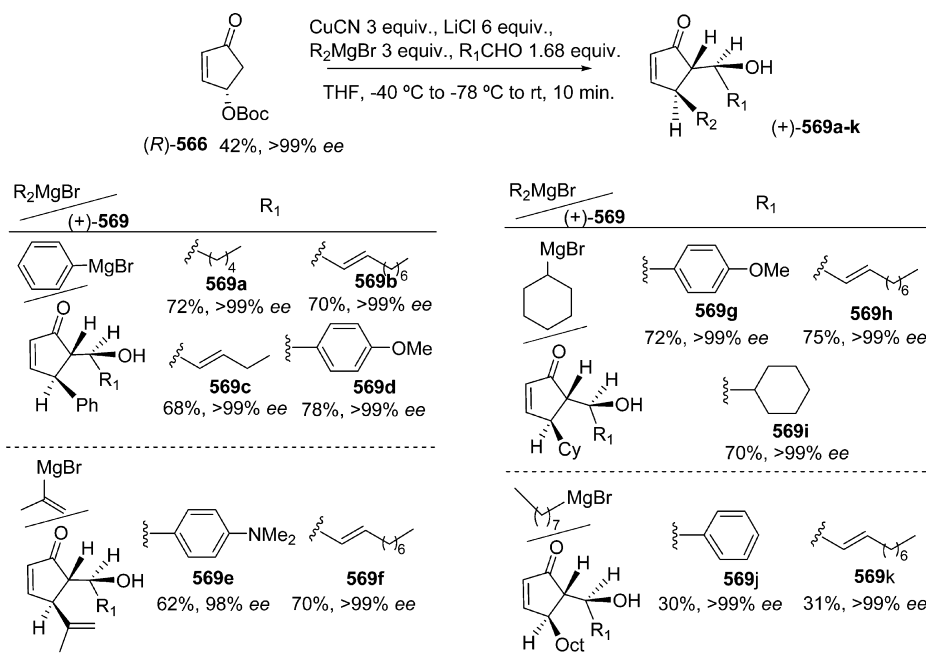
These pseudoenantiomeric 4-substituted derivatives were used as building blocks for the synthesis of asymmetric 4-alkyl-5-(1'-hydroxyalkyl)-substituted 2-cyclopentenones, inducing stereocontrol in a cascade reaction of conjugated *anti*-addition at the 3-position followed by *anti*-aldol reaction at the 2-position to the introduced nucleophile. The 1,4 addition was realized using the reagent CuCN·2LiCl in THF (Scheme 162). The level of enantioselectivity for different nucleophiles depended on the *anti*-selectivity and the corresponding steric bulk of the Grignard reagent. Independently of reagent and aldehyde employed, which trapped the resulting enolates (aromatic, aliphatic, or α,β -unsaturated), the obtained products (**569a–k**) indicated very good enantioselectivities (98–99% ee). The authors tentatively explained the reaction mechanism by initial formation of two intermediates, one with favorable conformation that triggers Boc–OH elimination and the other suffering from steric repulsion from the axial position of R₁.

The new cascade reaction was employed in a one-flask protocol to obtain TEI **9826** in step economy and high purity from (R)-**567**, in addition to antitumor agent **570** from (R)-**566** (Scheme 163).

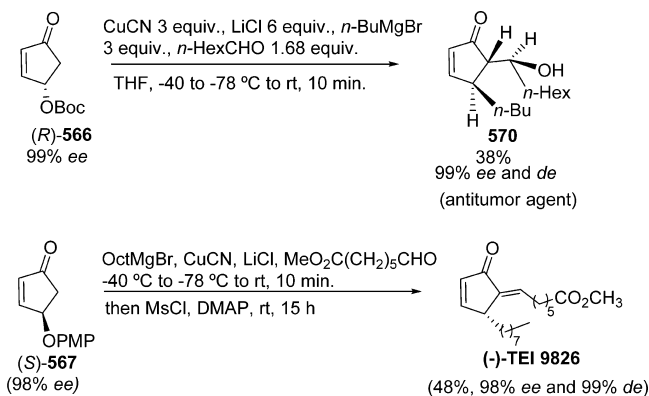
The new protocol was used to synthesize **572**, which after a further six steps led to pseudoguaianolide (*ent*)-(–)-teuclatriol (Scheme 164).

4.11. Aminocatalytic Enantioselective 1,6 Addition of Alkyl Thiols

Melchiorre and co-workers explored the ability of cinchona-based primary amine catalyst **577** to condense reversibly with β -substituted cyclic dienones, thus forming an intermediate iminium ion, which was described as “vinylogous iminium ion catalysis”.³⁷² Ultimately, the β -carbon atom of the respective

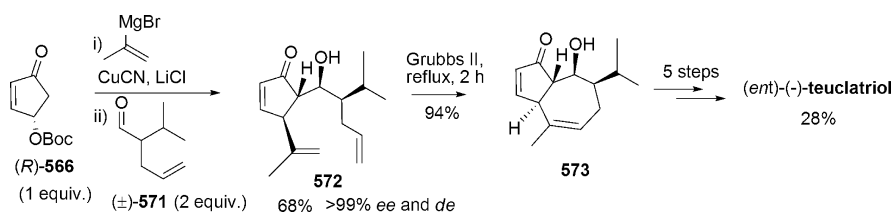
Scheme 161. Pd-Catalyzed Stereocontrolled 1,4-*anti*-Addition of a Nucleophile to 4-Hydroxycyclopentenone and 1,2-*anti*-Aldol ReactionScheme 162. Asymmetric Synthesis of 4-Alkyl-5-(1'-hydroxyalkyl)-Substituted 2-Cyclopentenones^a^aAll products are studied by ^1H NMR (crude) for determination of ee.

Scheme 163. Synthesis of (–)-TEI 9826

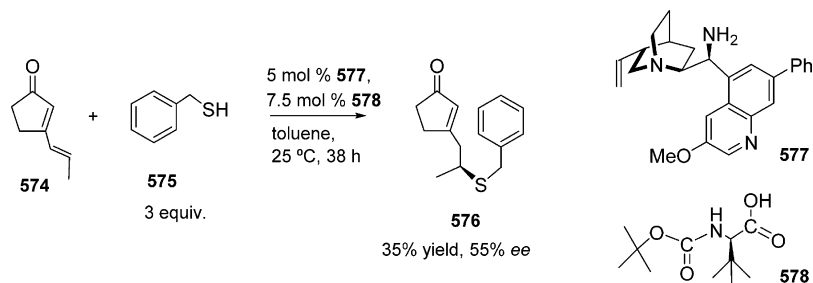
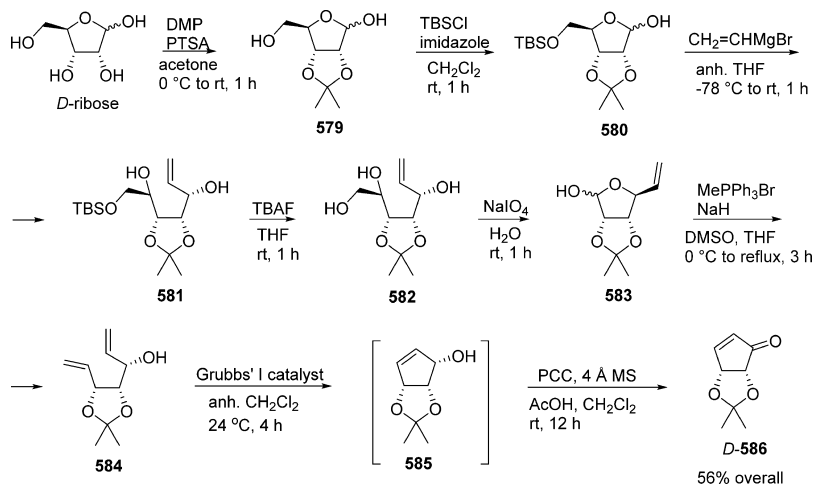
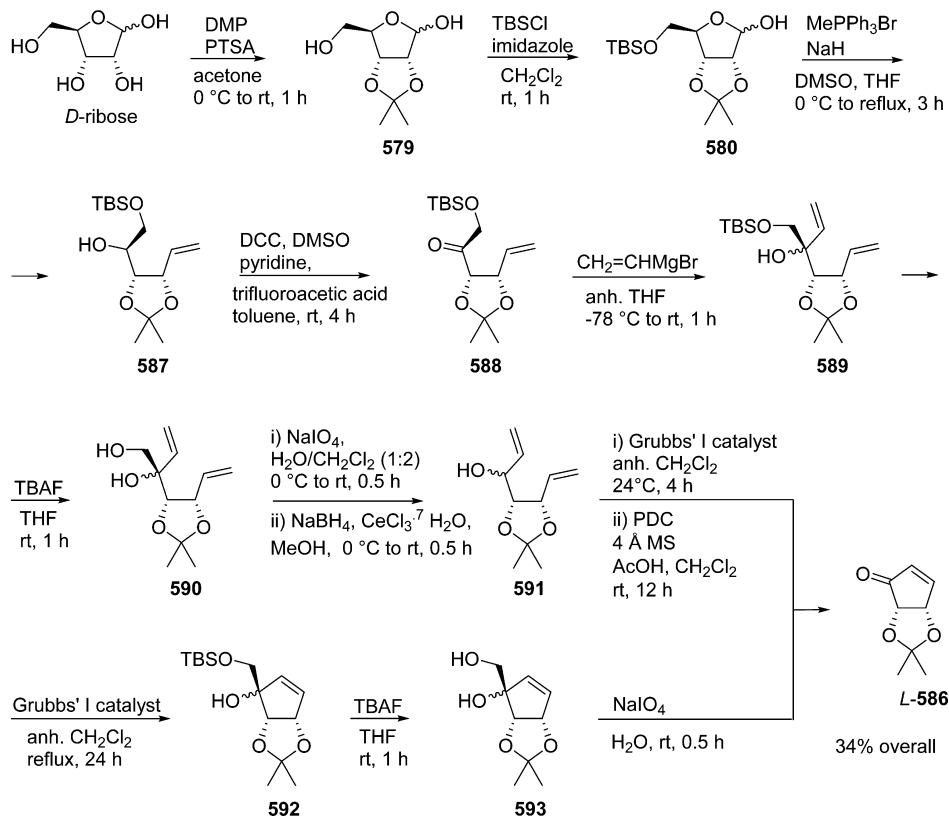


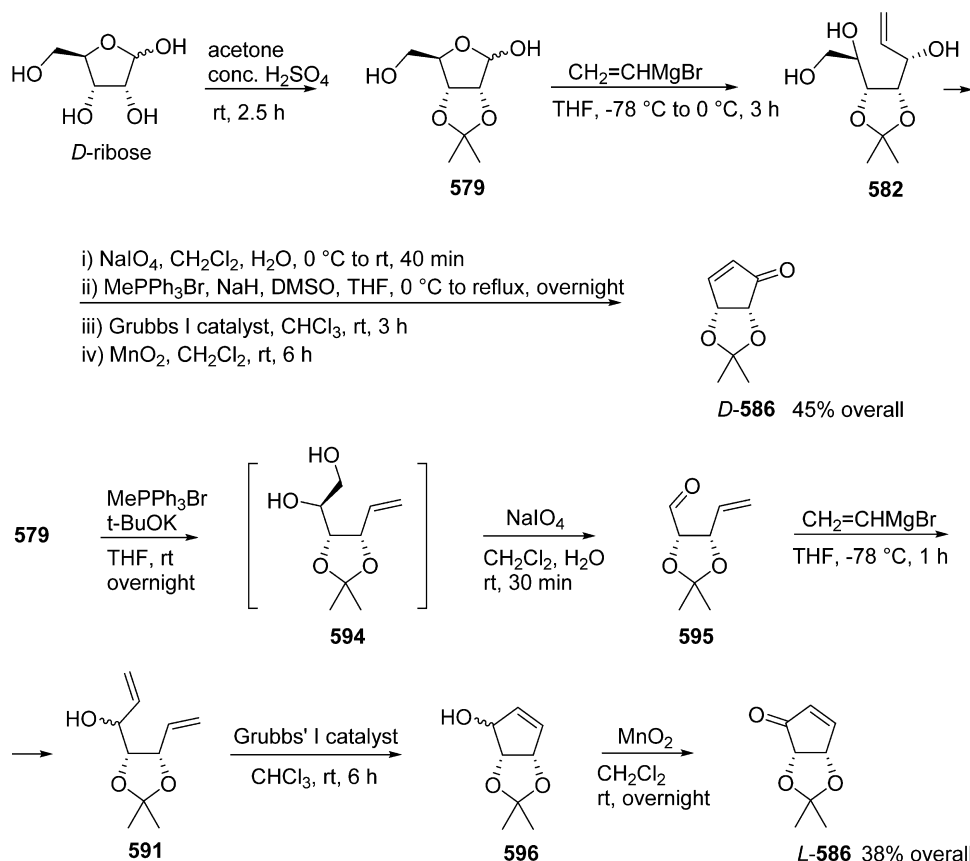
unsaturated dienone became more susceptible to 1,6-stereoselective addition of alkyl thiols, such as **575**, due to increased electrophilicity. The authors explained this phenomenon by invoking electronic LUMO-lowering and HOMO-raising effects of the conjugated π -system of the polyunsaturated dienone structure. The 1,4-addition reaction was predicted to be disfavored through steric hindrance. The authors predominantly studied cyclohexenone-type dienone compounds, and used cyclopentenone-based dienone **574** to show that the type of cyclic geometry controlled the activity of vinylogous iminium ions through electronic effects. Thus, they observed low enantioselectivity and yield of thiophenyl 1,6-adduct **576** in the reaction of **574** with thiophenol **575** in the presence of cinchona-type aminocatalyst **577** and Boc-protected chiral amino acid L-valine (**578**) as cocatalyst (Scheme 165).

Scheme 164. Synthesis of (ent)-(-)-Teuclatriol



Scheme 165. Aminocatalytic Enantioselective 1,6-Additions of Benzyl Mercaptan to Cyclopentenones

Scheme 166. Practical Synthetic Route for the Conversion of D-Ribose to Acetonide-Protected Dihydroxy D-Cyclopentenone **586**Scheme 167. Synthesis of Cyclopentenone **L-586** from D-Ribose

Scheme 168. Six-Step Sequence for the Preparation of **586** from D-Ribose without Intermediate Protection of the Hydroxyl Groups

5. FUNCTIONALIZATION OF CHIRAL BUILDING BLOCKS

Synthetic protocols based on functionalization and/or transformations of available chiral molecules constitute the basic routes for the preparation of libraries of chiral molecules. Along with enantiomeric resolution and asymmetric synthesis, the area has been extensively investigated and continues to generate interest. The use of cheap natural materials or easily available synthetic starting products is outlined as one of the general trends in the synthesis of enantiomerically pure molecules in recent decades. Therefore, this part of the current overview will focus on the conversion of the most popular chiral sources, such as carbohydrates, carbonyl-based compounds, and hydrocarbons, into cyclopentenones, despite that the major part of the ring-closing steps should be assigned to completely different layouts.

5.1. Carbohydrates

Carbohydrates are among the most accessible chiral sources and therefore are widely exploited as starting materials. The procedures for their conversion into chiral cyclopentenones are generally multistep in nature, but the combination of high yields and inexpensive starting compounds makes them attractive and widely used in carbocyclic nucleoside chemistry.

Many protocols have been reported for the conversion of carbohydrates into isopropylidene-protected isomeric 4,5-dihydroxycyclopent-2-enone **586** and its derivatives, key molecules in the synthesis of carbocyclic nucleosides. Jin and Chu³⁷³ developed an efficient and practical synthetic route for the conversion of D-ribose to D-cyclopentenone **586** (Scheme 166), a versatile intermediate for the synthesis of carbocyclic

nucleosides. The eight-step reaction sequence was achieved in excellent overall yield as follows: isopropylidene protection with 2,2-dimethoxypropane (DMP) in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA), silylation of **579** by *t*-butyldimethylsilane chloride (TBSCl) with imidazole, introduction of an olefin moiety in the silylated lactol **580** via Grignard reaction with vinylmagnesium bromide, deprotection of the silyl group of **581** with tetrabutylammonium fluoride (TBAF), oxidative cleavage in **582** with sodium periodate, and Wittig reaction of the lactol **583** with methyltriphenylphosphonium bromide in the presence of NaH and DMSO. The key ring-closure metathesis (RCM) reaction of diene **584** was achieved using Grubbs' I catalyst followed by oxidation of the volatile cyclopentenol **585** with pyridinium chlorochromate (PCC) without isolation.

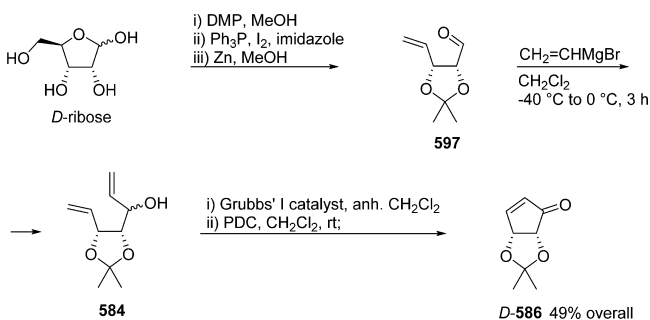
The protocol has been further extended by Jin et al. toward the synthesis of L-cyclopentenone **586** by applying a reversed sequence (Scheme 167).³⁷⁴ Thereby, the protected ribose **580** was subjected to Wittig reaction followed by oxidation of the secondary hydroxyl group in **587** with dicyclohexyl carbodiimide (DCC) and Grignard reaction of **588**. The key diene **589** was converted to L-**586** by two pathways: deprotection/RCM/oxidation with pyridinium dichromate (PDC) or RCM/deprotection/oxidation.

The same cyclopentenones have been obtained by Moon et al. in six steps without intermediate protection of the hydroxyl group of **579** (Scheme 168).³⁷⁵ A similar protocol was applied to the synthesis of D-**586**, whereas the L-isomer was prepared by Wittig reaction of **579** followed by oxidative cleavage of diol **594**, Grignard reaction of aldehyde **595**, RCM of diene **591**, and

oxidation with manganese oxide. This protocol has proved to be applicable for large-scale experiments (>10 g).

Yang et al. reported a synthesis of D-**586** via aldehyde **597**, the enantiomer of **595**, as a step in a modified practical synthesis of (–)-arysteromycin from D-ribose.³⁷⁶ A method analogous to that described above for the preparation of L-**586** was applied: protection, Wittig reaction, oxidative cleavage, Grignard reaction, RCM, oxidation, leading to the target cyclopentenone **586** in 49% overall yield (Scheme 169).

Scheme 169. Modified Practical Synthesis of (–)-Arysteromycin from D-Ribose



Cyclopentylidene-protected analogue D-**602** has been similarly prepared by Schneller et al. as a key component in the total synthesis of carbocyclic nucleosides (Scheme 170).³⁷⁷

Jeong et al. have achieved the total synthesis of fluorocyclopentenyl-cytosine derivatives from D-ribose.³⁷⁸ The key intermediate **608** was obtained in 29% overall yield via an eight-step sequence including acetonide and silyl protection, Wittig reaction to **604**, Swern oxidation, Grignard reaction with vinylmagnesium bromide to a single stereoisomer of diene **606**, removal of silyl protection, selective benzylation, RCM of **607** with second generation Grubbs catalyst, and oxidative rearrangement to the target cyclopentenone **608** (Scheme 171).

The authors obtained the analogue derivative **614** as a step in the stereoselective synthesis of fluoro-homoneplanocin A (Scheme 172).³⁷⁹ D-Ribose was converted into the lactone **583** in three steps, which was further subjected to nucleophilic addition with TMSCHN₂, deprotection, and RCM to give the common intermediate **611**. The chemoselective hydroboration-oxidation of the latter with 9-BBN and sodium perborate, followed by subsequent protection, resulted in a mixture of

mono- and diprotected compounds **613**, which was directly oxidized into the desired enone **614**.

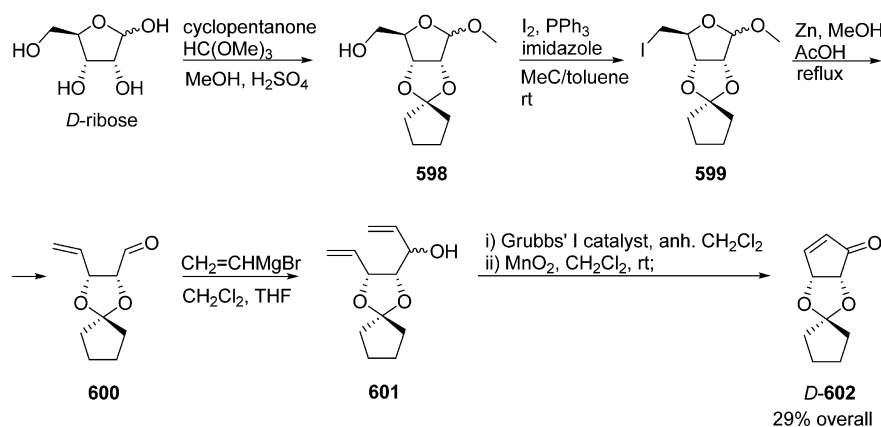
An enantiomerically efficient preparation of 6'-isoneplanocin analogues was reported by Schneller et al.³⁸⁰ The authors converted the D-ribose-derived enal **597** into an easily separable mixture of isomers **618** by successive Grignard reaction, protection, RCM, and asymmetric Sharpless dihydroxylation (Scheme 173). The β -isomer **619** was further subjected to protection, reductive removal of mesyl group, and selective protection of the primary hydroxyl group to afford **620**. The latter was oxidized with 2-iodoxybenzoic acid (IBX) to the desired enone **621**, which was quantitatively hydrogenated into the isoneplanocine carbocyclic unit.

An alternative starting material, D-isoscorbic acid, has been used by Choi et al.³⁸¹ This was converted into intermediate **623** (Scheme 174) by oxidation with hydrogen peroxide, acetonide protection, and then reduction of **622** with diisobutylaluminum hydride (DIBAL). The key isomeric dienes **584** and **591** were obtained from **623** by subsequent Grignard reaction, oxidation of **624** with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO), DIBAL reduction of **625**, and Wittig reaction of **583**, and by Wittig reaction of **623**, Swern oxidation, and Grignard reaction of **625**, respectively. These dienes were converted into D- and L-**586** by RCM in the presence of Grubbs' I catalyst, followed by oxidation of the resulting cyclopentenols **585** and **596** with manganese oxide.

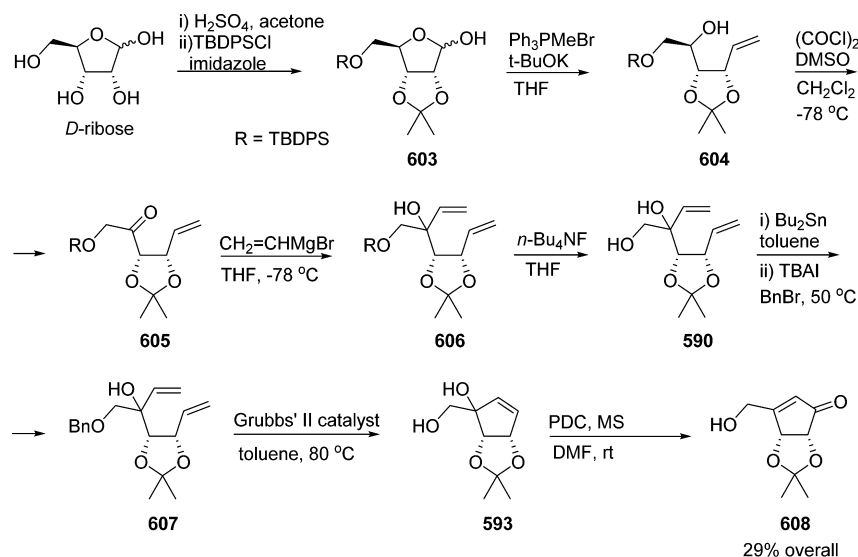
The direct conversion of lactones into cyclopentenones has been achieved by intramolecular aldol condensation using organolithium compounds. Bélanger and Prasit obtained L-**586** from D-ribonolactone as a key intermediate in a coupling approach to prostaglandins (Scheme 175).³⁸² The crucial step, conversion of enollactone **629** into the target cyclopentenone L-**586**, was carried out with lithium aluminum butoxyhydride followed by dehydration with mesyl chloride in the presence of pyridine as a base.

Ali et al. developed a simple and efficient enantioselective synthesis of D-**586** and L-**586** from D-lyxose and D-ribose, respectively (Scheme 176).³⁸³ After protection and oxidation of **630** and **632** with PCC, lactones **631** and **633** were subjected to a reaction with lithium dimethyl methylphosphonate, and the products were isolated in good overall yields as pure enantiomers. The protocol was later applied by Dickson et al. to the preparation of a series of aminocyclopentitol glycosidase inhibitors from D-lyxose.³⁸⁴

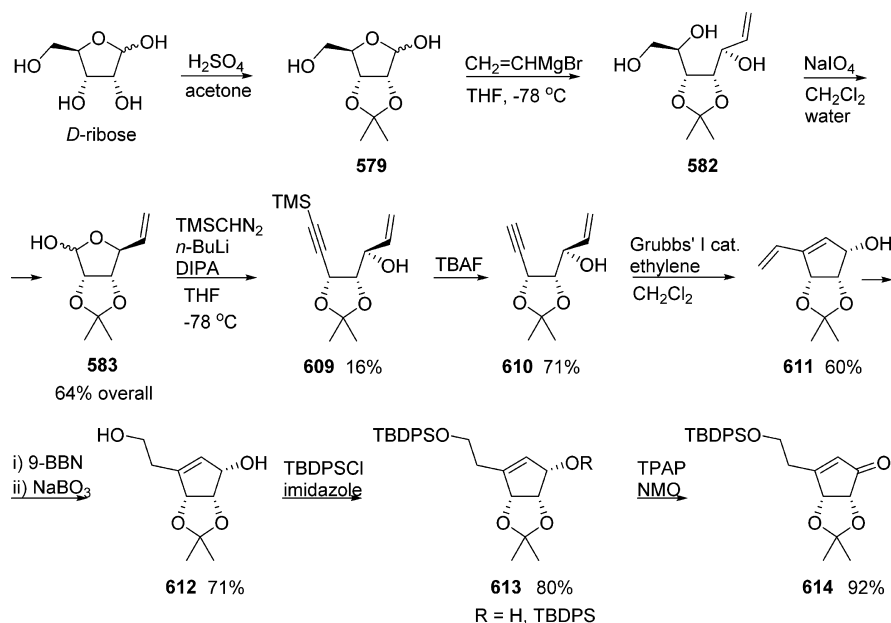
Scheme 170. Synthesis of Cyclopentylidene-Protected Dihydroxycyclopentenone 602 from D-Ribose



Scheme 171. Total Synthesis of Fluorocyclopentenyl-cytosine Derivatives from D-Ribose



Scheme 172. Stereoselective Synthesis of Fluoro-homoneplanocin A from D-Ribose



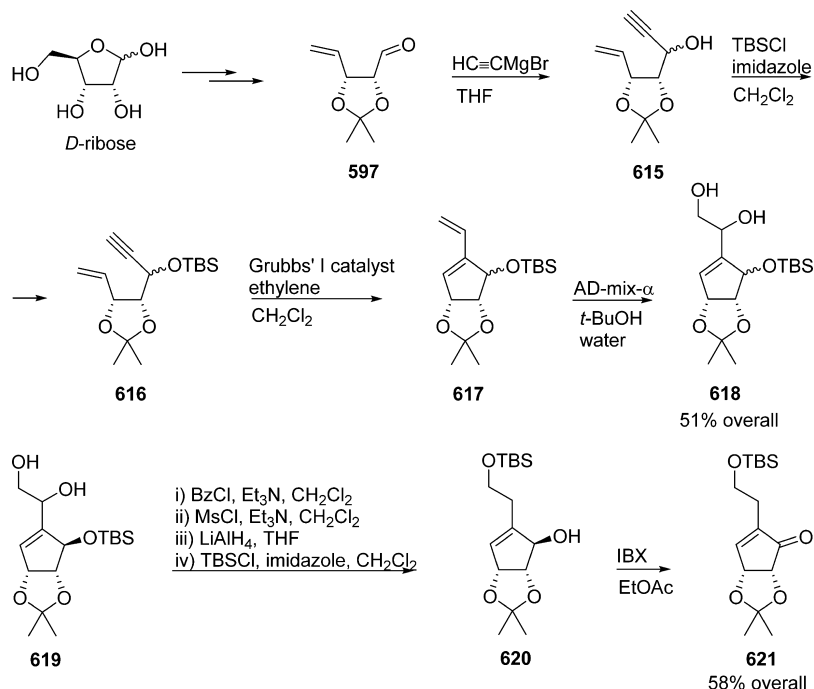
Borcherding et al. obtained similarly acetone-protected cyclopentenones **636** as key intermediates for the synthesis of neplanocin A analogues (Scheme 177).³⁸⁵ D-Ribonolactone and D-mannose were protected and oxidized to give the isomeric erythruronolactones **634** and **638**, which were converted into isopropoxy glycosides **635** and **639** with isopropanol in the presence of pyridinium *p*-toluenesulfonate (PPTS). The latter reacted with lithium dimethyl methylphosphonate, providing the target optically active cyclopentenones D-**636** and L-**636** in excellent overall yields. The authors have suggested that attack by an organolithium reagent resulted in the opening of the lactone ring with elimination of alkoxide, giving an acyclic intermediate, which then underwent base-promoted cyclization to the cyclopentenone due to the in situ-generated alkoxide.

The same cyclopentenone L-**636** was obtained by Liu and Chu from D-ribose (Scheme 178).³⁸⁶ The subsequent cyclohexylidene protection, Wittig reaction of **640** with triphenylphosphonium methylenide, oxidative cleavage of diol **641** with sodium

periodate, and Grignard reaction of aldehyde **642** with vinylmagnesium bromide furnished the diene **643** as a mixture of two diastereoisomers in high overall yield. The key step, a ring-closing metathesis reaction in the presence of Grubbs I catalyst, followed by pyridinium dichromate oxidation in one pot, led directly to cyclopentenone L-**636**. The product was further converted via an oxidative rearrangement into 4-methylcyclopentenone D-**645**,³⁸⁶ the key intermediate in the synthesis of D-4'-C-methylribonucleosides.

Similarly, Parry et al. converted D-ribonolactone derivative **646** consecutively into lactol **647**, tetrahydropyranyl protected compound **648**, and finally D-cyclopentenone **645** during the synthesis of an optically active carbocyclic analogue of phosphoribosyl pyrophosphate (Scheme 179).³⁸⁷ It was observed that the carbocyclization reaction of **648** to **649** was very sensitive to temperature and that the best conditions involved the generation of the lithium salt of dimethyl methylphosphonate followed by condensation with **648** at low

Scheme 173. Enantiomerically Efficient Preparation of 6'-Isonenplanocin Analogues from D-Ribose



temperature. The target structure **649** represents a highly useful tool for the mechanistic and crystallographic investigations of phosphoribosyltransferases due to the low reactivity of the carbocyclic analogue.

The derivatives of cyclopentenone **586** possessing a range of protected hydroxymethyl substituents at the 5-position **656** have been synthesized by Choi et al.³⁸⁸ As a key step, the dienes **653**, obtained from D-ribose by subsequent protection, Wittig reaction, Swern oxidation, and Grignard reaction, were converted into isomeric 3,4,5,5-tetrasubstituted cyclopentene intermediates **654** and **655** by RCM in the presence of Grubbs' I catalyst (Scheme 180). The oxidative rearrangement of these cyclopentenols by pyridinium dichromate indicated that **654** was the only reactive isomer, while no conversions were achieved with **655**. Therefore, the selectivity of the RCM reaction has been studied and improved by varying the bulk of the protective group. It was found that the *tert*-butyldiphenylsilyl (TBDPS) and trityl (Tr) ethers, bulkier than the *tert*-butyldimethylsilyl group (TBS), with which 75% **654a** and 8% **655a** were isolated, led to clean formation of **654b** and **654c**; no **655b** or **655c** was detected. In contrast, the RCM of benzyl-protected diene **653d** led to **655d** as the main product, and only 17% of **654d** was isolated.

Lee et al.³⁸⁹ synthesized D-**656d** from D-ribonolactone during the synthesis of a carbanucleoside, a potential inhibitor of the adenosine uptake carrier (Scheme 181). The key diene **659**, prepared by consecutive Swern oxidation, Wittig reaction, and Grignard reaction, was subjected to metathesis cyclization followed by oxidation, and a cyclopentenone was isolated in moderate overall yield and correct stereochemistry.

The same cyclopentenone D-**656d** was obtained enantioselectively by Comin and Rodriguez in the first synthesis of the naturally occurring carbocyclic nucleoside neplanocin C, a minor component of the neplanocin family possessing antiviral and antitumor activities (Scheme 182).³⁹⁰ The lactol **660** was prepared in high stereoselectivity by consecutive protection of D-ribonolactone and treatment with lithium dimethyl methylphosphonate. Its stereochemistry was explained by nucleophilic

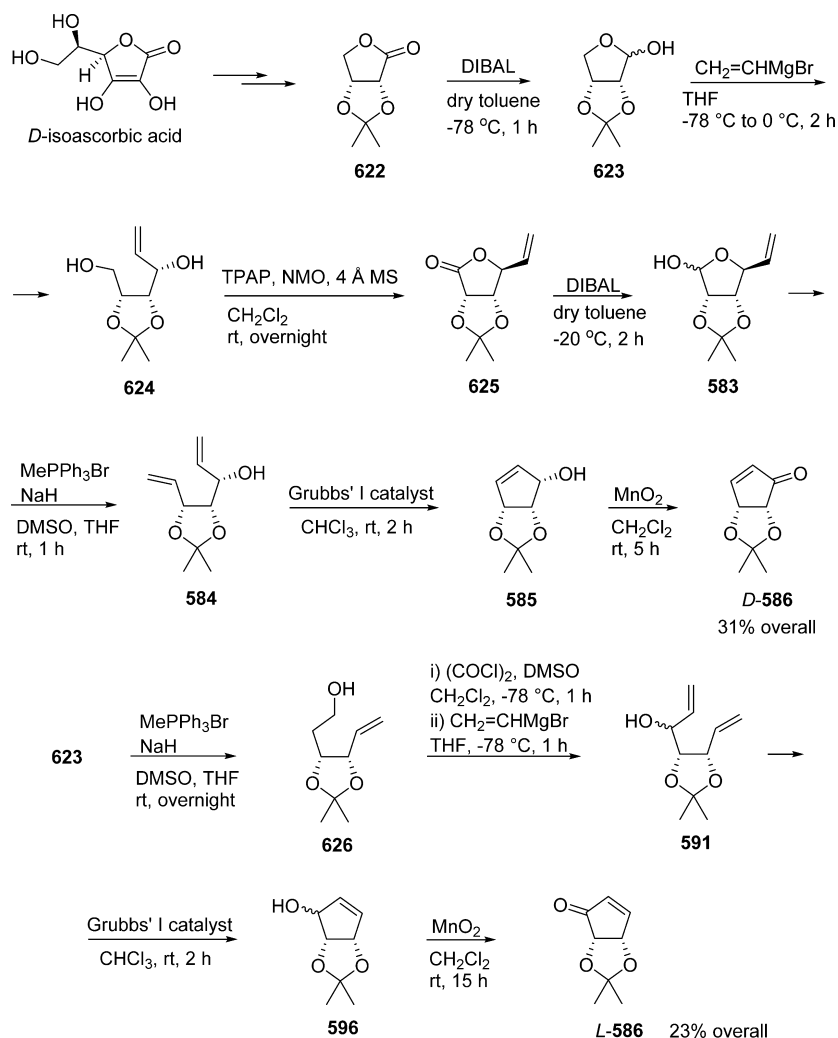
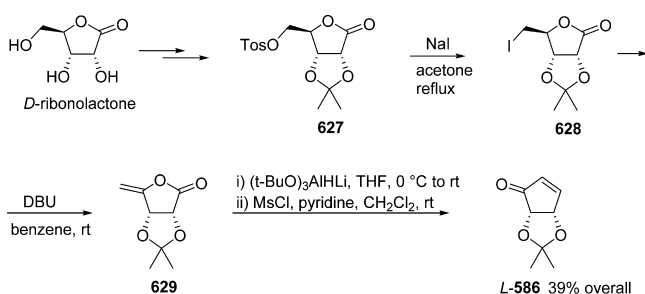
attack from the less hindered β -face of the molecule, modulated by the presence of the isopropylidene group; the presence of its epimer (α -nucleophilic attack) was not detected. Further benzylation, hydrolysis, and oxidation of **662** with Collins reagent (CrO_3 , pyridine) provided the diketone derivative **663** in good yield. The crucial step, the formation of the carbocyclic ring, was achieved by a Wittig-type intramolecular aldol cyclodehydration of **663** with potassium carbonate in the presence of a crown ether as transfer catalyst.

The 2-bromo-substituted cyclopentenone L-**669** has been obtained by Ivanova et al. from D-ribose (Scheme 183).³⁹¹ The D-ribofuranoside **632** was converted into a mixture of bromohydrins **667** and **668** by consecutive transformation to iodide **664** or tosylate **665**, enol ether **666**, and regioselective bromohydroxylation of the double bond by *N*-bromosuccinimide (NBS). The intramolecular aldol-crotonic cyclization of **667** and **668** was carried out by heating in benzene in the presence of neutral alumina, and bromocyclopentenone **669** was isolated in low yields. The selective hydrolysis of the C¹-glycoside bond was suggested to originate from the ring-chain tautomerism of bromohydrin **667**, which was confirmed by NMR spectroscopy.

Later, the authors converted the isomeric mixture of bromohydrins **667** and **668** or the corresponding iodohydrins directly into L-**586** via an intramolecular aldol cyclization/dehydration sequence under Reformatsky reaction conditions.³⁹²

Pryde et al. obtained cyclopentenone **672** from 2'-C-Me-ribonolactone in good overall yield by subsequent acetone protection, oxidation to aldehyde **670**, conversion to the silyl enol ether **671**, and treatment with bromomethyltriphenylphosphine (Scheme 184).³⁹³

An analogue of cyclopentenone **586** possessing a hydroxymethyl substituent at 5-position, **680**, was prepared from L-arabinose by Gallos et al. as an intermediate in the synthesis of neplanocin A (Scheme 185).²⁸⁶ L-Erythrose acetonide **673**, obtained from the carbohydrate, was subjected to aldol reaction with formaldehyde to form the quaternary chiral center in **674**.

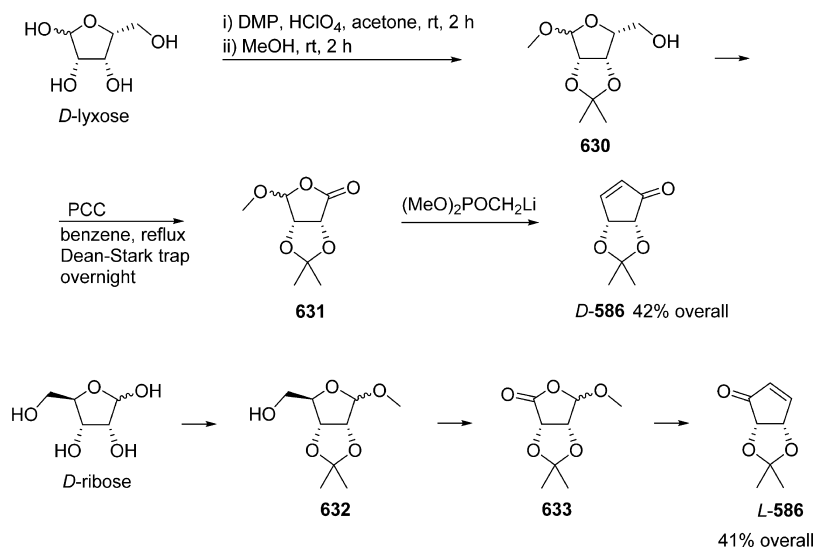
Scheme 174. Synthesis of D- and L-Cyclopentenones **586** from D-Isoascorbic AcidScheme 175. Synthesis of D- and L-Cyclopentenone **586** from D-Ribonolactone

After subsequent tritylation of **674**, Wittig olefination of **675**, and Swern oxidation of **676**, the generated keto diene **677** was directly used in a two-step procedure involving formation of the intermediate nitron and intramolecular cycloaddition upon heating, leading to **678**. The latter was converted to L-**680** via its tosylate **679** by oxidative elimination with pyridinium dichromate.

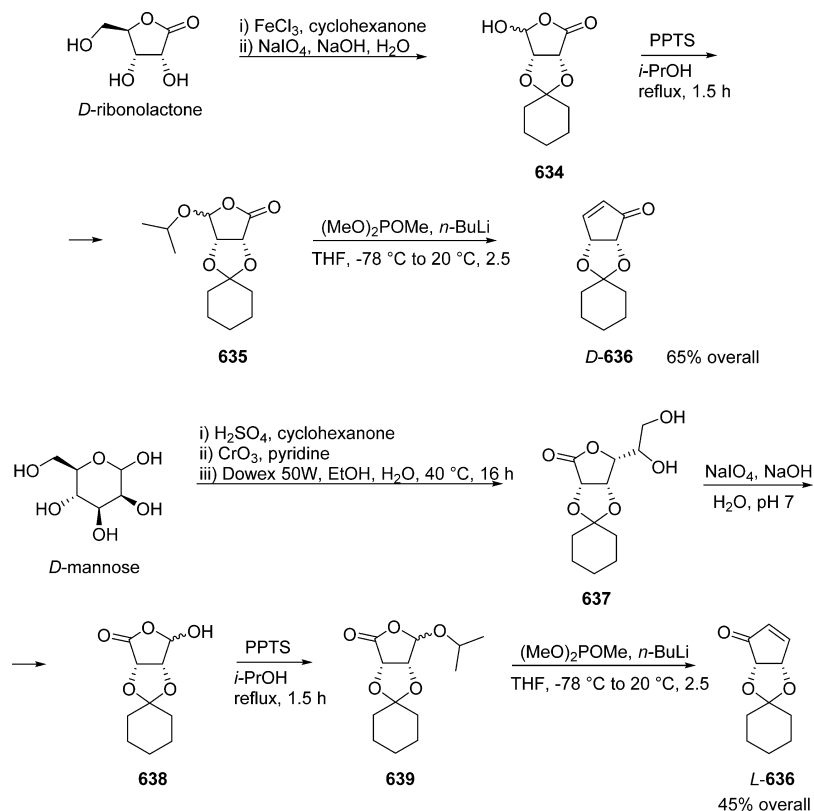
The authors have further improved the procedure by applying a polymer-bonded hydroxylamine to the intramolecular nitron-alkene cycloaddition to **677**, thus converting the latter into **680** via a five-step sequence with 16% overall yield.³⁹⁴

Kuhn et al. have assembled a convenient one-pot five-step protocol for the preparation of chiral 4-hydroxy-4-alkyl cyclopentenones **686**, key intermediates in the synthesis of prostanoids, from an α -alkoxy aldehyde **681** (Scheme 186) derived from diacetone glucose (DAG).³⁹⁵ The treatment of **681** with pyrrolidine led to a 1:1 diastereomeric mixture of enamine **682**, which was directly N-alkylated with 2-alkoxypropenyl iodide to form **683**. A tandem 3-aza-Cope/intramolecular Mannich reaction of the latter led to target cyclopentenones **686** as an easily separable mixture of isomers.

The authors³⁹⁶ have further developed an efficient alternative stereoselective approach for the synthesis of the same spirofurano cyclopentenone **686** from uronosugar **687**, derived from 1,2-O-isopropylidene D-glucose (Scheme 187). Thereby, stereocontrolled alkylation of **687** was achieved by reaction with potassium hexamethyldisilazide (KHMDs) and 2-OMOM or 2-chloro-1-iodoprop-2-ene as electrophiles under internal quench conditions, and the resulting esters **688a** and **688b** were reduced with DIBAL to the corresponding aldehydes **689a** and **689b**. Bromohydroxylation of the double bond of the latter with N-bromosuccinimide and subsequent intramolecular Wittig reaction of **690** with triphenylphosphine in the presence of propylene oxide as proton scavenger led directly to the desired chiral cyclopentenone **686** in crystalline form. The product was further chlorinated with *m*-chloroperbenzoic acid (*m*-CPBA)

Scheme 176. Synthesis of D- and L-Cyclopentenone **586** from D-Lyxose and D-Ribose

Scheme 177. Synthesis of Cyclohexylidene-Protected Cyclopentenone D- and L-636 from D-Ribonolactone and D-Mannose

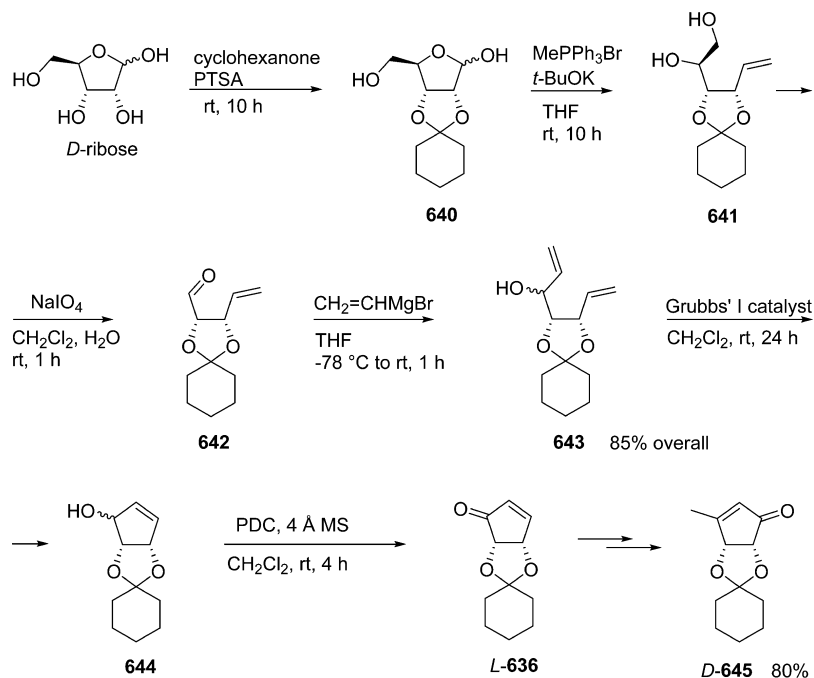


into 2-chloro-derivative **691**, a potential precursor of antitumor prostanoid punaglandin IV.

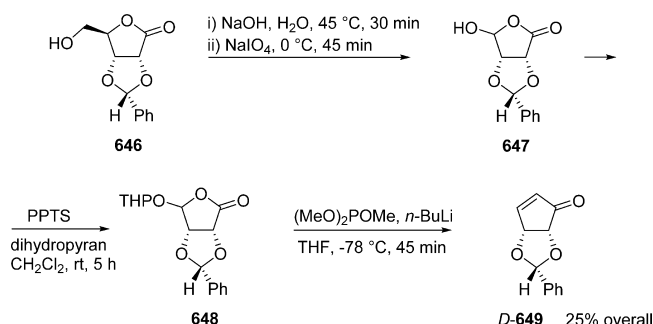
More recently, the same group has obtained a series of simplified analogues of natural cyclopentadienone prostaglandins possessing good cytotoxicities.³⁹⁷ The synthesis of the key cyclopentenones was readily achieved from enamines derived from aldehydes by using a domino 3-aza Claisen/Mannich reaction. The aldehyde **697** was synthesized in 34% yield from aldehyde **692**, readily accessible from D-mannitol (Scheme 188). Thus, a Wittig reaction with the ylide derived from triphenylphosphine-3-phenylpropyl bromide was achieved, giving the alkene **693** as an *E/Z* (1/9) mixture, followed by

catalytic hydrogenation of the double bond, selective acidic hydrolysis of the terminal acetal of the bis-dioxolanyl compound **694**, and oxidative cleavage of the glycol with NaIO₄. A more direct route to **697** was also presented, starting from 2,3-*O*-isopropylidene α-D-ribose **579** and based on the epimerization of the C-2 atom of the 2,3-dioxolane-ribose, which occurred using the harsh basic conditions necessary to complete the Wittig reaction. The domino 3-aza-Claisen/Mannich reaction was achieved by treatment of aldehyde **697** with pyrrolidine in the presence of molecular sieves to furnish an *E/Z* mixture of enamine intermediates, which were immediately alkylated with

Scheme 178. Synthesis of Cyclohexylidene-Protected Cyclopentenone D-645 from D-Ribose



Scheme 179. Conversion of a D-Ribonolactone Derivative into Cyclopentenone



2-methoxymethoxy-3-iodopropene, leading to the cyclopentenone diastereoisomers **698** as a 1:1 mixture.

In the same context, benzoyl derivatives **702** were prepared from aldehyde **701**, derived from 2,3;4,5-di-*O*-isopropylidene D-arabinitol **699** by consecutive benzylation and selective cleavage of the terminal acetal of **700** by treatment with periodic acid (Scheme 189).

Pohmakotr et al.¹² have demonstrated the synthetic utility of the intramolecular acylation of α -sulfinyl carbanions **705** as an efficient and general synthetic approach for the preparation of both enantiomers of the highly oxygenated cyclopentenone antibiotics pentenomycin I and epipentenomycin I, starting from readily available D-mannitol chiral esters (2*S*,5*S*,6*S*)-**703** and *ent*-**703** (Scheme 190). Thus, treatment of **703** with lithium diisopropylamide followed by reaction with 3-phenylsulfonylpropanal afforded the expected sulfide **704** as a separable mixture of equatorial diastereomers, while no axial adducts were detected. Oxidation of **704** with sodium metaperiodate followed by lithiation of the corresponding sulfoxides **705** and quenching with ammonium chloride afforded spiroketosulfoxides **706**, each as a mixture of diastereomers. Subsequent sulfoxide elimination of the crude products in the presence of calcium carbonate yielded the corresponding hydroxylspirocyclopentenones **707**.

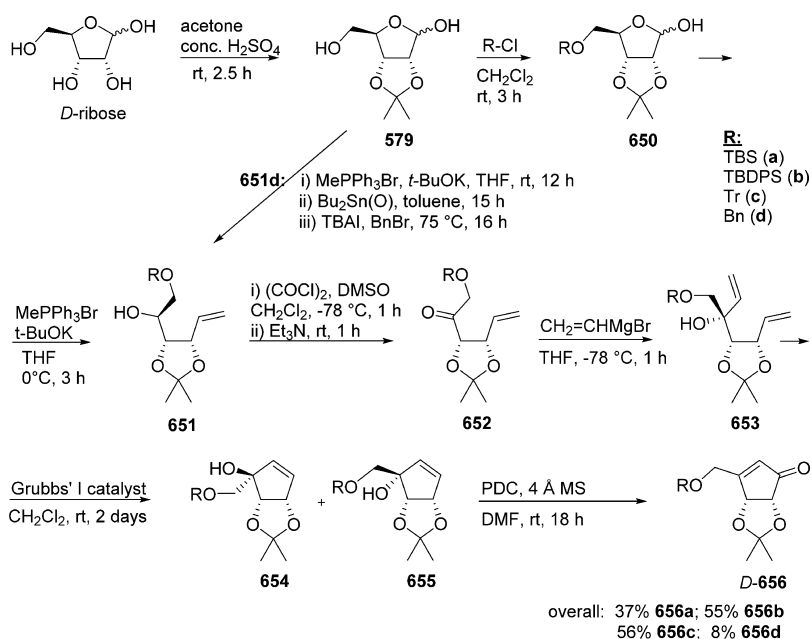
Ultimately, acid hydrolysis of the butanediactal protecting group readily afforded (–)-pentenomycin I and (–)-epipentenomycin I. The syntheses of their enantiomers (+)-pentenomycin I and (+)-epipentenomycin I were achieved by the same protocol in comparable yields in each step, straightforwardly starting from *ent*-**705**. The approach was further applied to the synthesis of (+)-desoxypentenomycin and analogues.³⁹⁸

Kozawa et al. employed a D-glucose-derived chiral auxiliary in a highly stereoselective quaternization of the α -carbon of acetoacetate ester.³⁹⁹ The resulting ketoester **708** with an *R*-configuration was oxidized into the corresponding aldehyde **709**, which was converted into the 5,5-disubstituted cyclopentenone **710** via an intramolecular aldol strategy (Scheme 191).

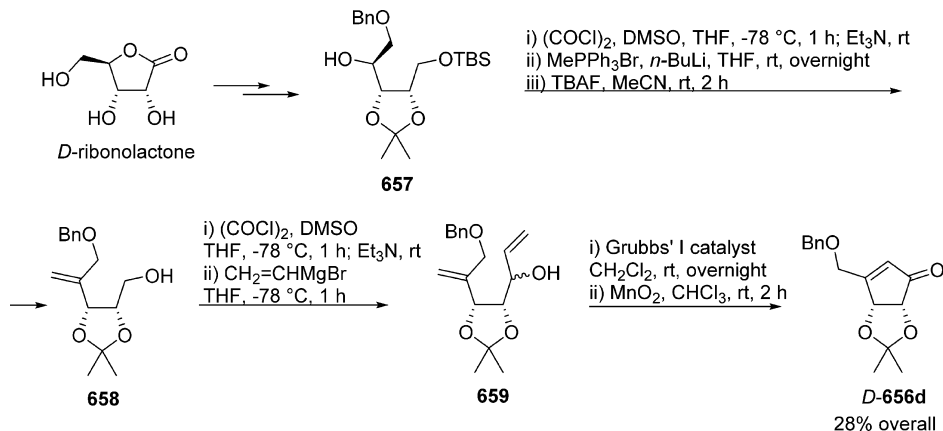
Tadano et al. have prepared chiral spiro cyclopentenone **716** from D-glucose (Scheme 192).⁴⁰⁰ The *ortho* ester Claisen rearrangement of **711** was achieved by heating with triethyl orthoacetate followed by hydride reduction, providing derivative **712** stereoselectively. Subsequent Grignard reaction, oxidation of **713** with pyridinium chlorochromate, and ozonolysis of **714** with triphenylphosphine workup gave aldehyde **715**. The latter has been subjected to intramolecular aldol cyclization, and cyclopentenone **716** was isolated as a single enantiomer in good yield.

A protocol for the stereoselective conversion of glucose into enantiomerically pure cyclopentenone **722** was reported by Wood et al.⁴⁰¹ (Scheme 193). The epoxide **717**, readily available from glucose, was subjected to Grignard reaction followed by Swern oxidation of **718** and epimerization using triethylamine in *N,N*-dimethylformamide, regioselective deprotonation of **719** with lithium hexamethyldisilazane (LiHMDS) and methylation with methyl iodide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) as cosolvent, and oxidation of ketone **720** by the Wacker procedure. Finally, the carbocycle in **722** was formed via intramolecular aldol condensation by treatment of diketone **721** with potassium *tert*-butoxide.

Scheme 180. Synthesis of Cyclopentenones Possessing Hydroxymethyl Substituents and a Range of Protecting Groups at the 5-Position from D-Ribose



Scheme 181. Synthesis of D-656d from D-Ribonolactone



Marco-Contelles achieved the cobalt-mediated PK cyclization of *O*-branched chain *D*-glucose derived enynes **723**, and the corresponding densely functionalized heteroannulated pyranosides **724**, which are attractive advanced intermediates for the synthesis of complex natural products, were isolated in moderate yields (Scheme 194).⁴⁰² It was found that the carbonylative acetylenic insertion always took place from the side where the propargyl moiety was located.

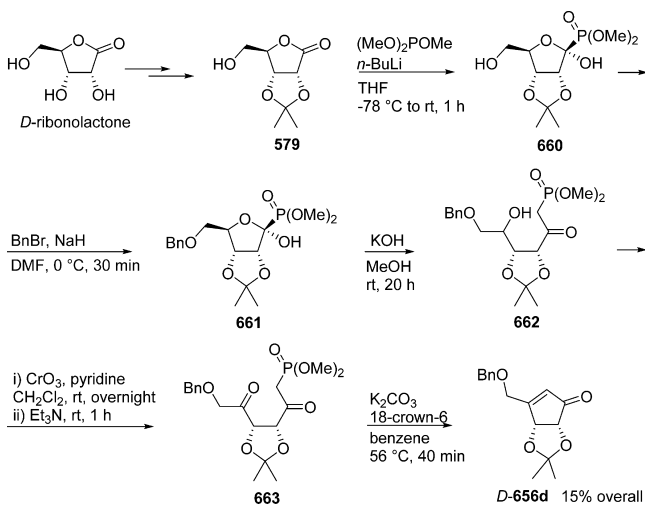
A stereoselective synthesis of spiroannulated cyclopentenones **727** and **729** was achieved by Hotha et al., starting from 3-ulose **725**, derived from commercially available diacetone glucosylfuranose (Scheme 195).⁴⁰³ The starting ketone was treated with allylzinc bromide followed by *O*-alkylation of the 3-*C*-allyl derivative with propargyl bromide, or was *C*-alkylated with propargylzinc bromide and then *O*-alkylated with allyl bromide to afford enynes **726** and **728**, respectively. The Pauson–Khand reaction was achieved under carbon-monoxide-free conditions using a stoichiometric quantity of cobalt octacarbonyl, and the target cyclopentenones were isolated in excellent yields.

Ishikawa et al. achieved a diastereoselective total synthesis of isocarbacyclin from *L*-ascorbic acid (Scheme 196).⁴⁰⁴ Chiral

hydroxyester **730** was converted into **731** via a four-step sequence involving silylation of the hydroxy group, conversion of the ester group to an α,α -diallyl alcohol unit with allylmagnesium bromide, deprotection of the TMS group, and acetonide protection of the generated internal 1,2-diol functionality. Deprotection of the terminal acetonide group of **731** and subsequent oxidative diol cleavage with periodic acid led to the desired aldehyde **732**, which was converted to dienyn **733** by applying Corey's protocol in high overall yield. The key fused bicyclic intermediate **735** was prepared in multigram quantities by the Pauson–Khand reaction of **733**, discriminating diastereotopic groups and faces of the geminal allyl substituents, and subsequent desilylation of **734**.

An enantioselective synthesis of anti-HIV agents litseaverticillols C and K from *D*-glucose was developed by Mohapatra et al. (Scheme 197).⁴⁰⁵ The *C*-3-homologated compound **737**, obtained from *D*-glucose by standard procedures, was subjected to consecutive benzyl protection of *C*-3- α -hydroxyl group, selective hydrolysis of the 5,6-acetonide, tosylation of the hydroxyl groups, and selective deoxygenation of **738**, leading to alkene **739** in good overall yield. Acidic hydrolysis with a resin,

Scheme 182. Preparation of D-656d from D-Ribonolactone as a Step in the First Synthesis of the Naturally Occurring Carbocyclic Nucleoside Neplanocin C



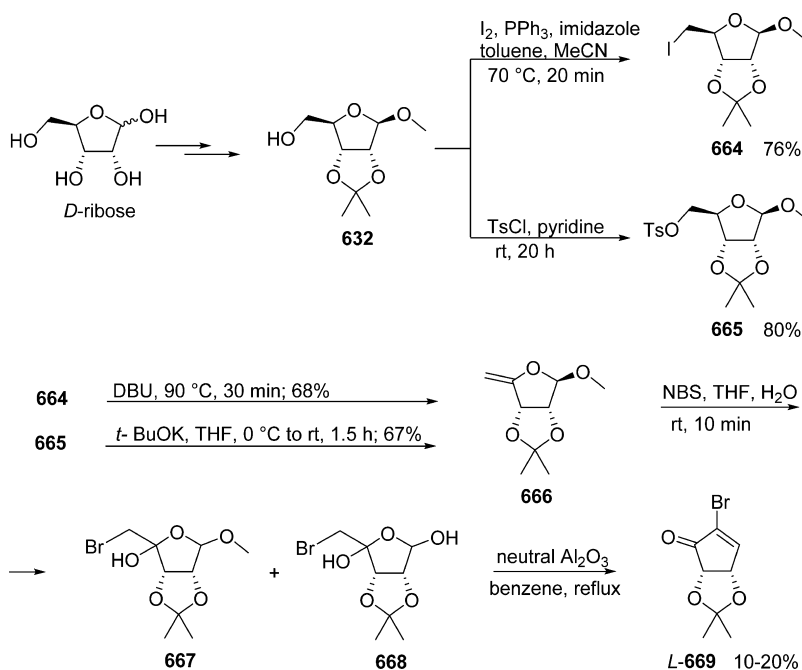
protection of the C-2-hydroxyl group as a benzyl ether, and demethylation led to **741**, which was oxidized to lactone **742** with pyridinium dichromate. Grignard reaction of the latter with methylmagnesium bromide, followed by selective protection of dimethylcarbinol **743** as a methyl ether and base-catalyzed Hoffman elimination of the in situ-formed mesylate from **744** with *N,N*-dimethylaminopyridine (DMAP), furnished the kinetically controlled less-substituted *exo*-methylene compound **745**. The ring-closing metathesis to form cyclopentenols **746** was accomplished with Grubbs II catalyst in excellent yield, while no transformation was achieved with the first generation catalyst. Subsequent debenzoylation by dissolving metal reduction, silyl protection, oxidation of the free secondary hydroxyl group of **747** with Dess–Martin periodinane, ketal protection of the carbonyl group of **748** with ethylene glycol without epimerization at the

adjacent stereocenter, and cleavage of the silyl protection furnished the alcohol **749**. Finally, compound **749** was oxidized with pyridinium dichromate in the presence of molecular sieves, and the resulting aldehyde was subjected to Wittig reaction with ylide **752** to give **750** as an *E/Z*-isomeric mixture, which was deketalized to the target cyclopentenones **751** as a separable mixture.

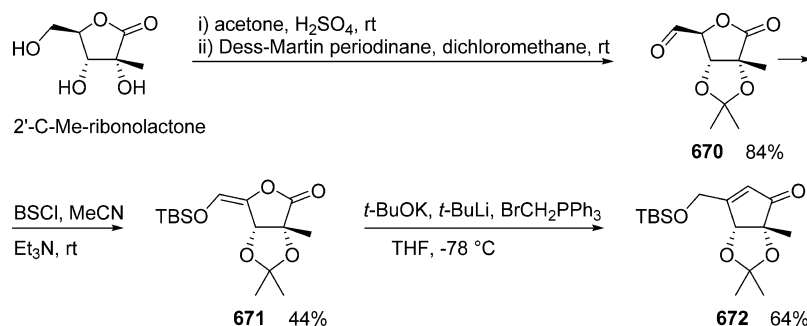
Harrington and Tius developed an enantioselective version of the allene ether Nazarov cyclization for the preparation of cross-conjugated cyclopentenones **755**, key intermediates in the synthesis of roseophilin, based on D-glucose-derived chiral auxiliaries (Scheme 198).⁴⁰⁶ The allenes **754** were obtained by consecutive reaction with propargyl alcohol, permethylation of the resulting mixture of α and β anomers of propargyl glucoside (2:1) with iodomethane in the presence of powdered potassium hydroxide and catalytic 18-crown-6, separation of the diastereomers of **753**, and their isomerization to the corresponding allene ethers by treatment with potassium *tert*-butoxide. The cyclopentaannulation was achieved via a one-pot three-step procedure. First, **754** was deprotonated with *n*-butyllithium, lithium chloride was added to improve the nucleophilicity of the anion, and reacted with morpholinoamide **756**, **756a** being the most effective. The cyclization was performed with hydrogen chloride in ethanol or in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), and cyclopentenones **755** were formed with elimination of the chiral auxiliary in moderate enantioselectivities.

A stereoselective synthesis of a series of azatriquinanes from D-xylose-derived nitrones has been achieved by Bandaru and Kaliappan.⁴⁰⁷ Grignard reaction of nitrones **757** was accomplished as a first step, and hydroxylamines **758** were obtained as single diastereoisomers (Scheme 199). The authors explained the stereoselectivity by *anti* attack of the organometallic reagent with respect to the adjacent benzyl ether as a result of steric and stereoelectronic effects. Amines **759**, generated via N–O bond cleavage with activated zinc, were treated with propargyl bromide to afford the enynes **760**. As a key step, a Pauson–Khand reaction was utilized to provide the desired cyclopentenones **761**

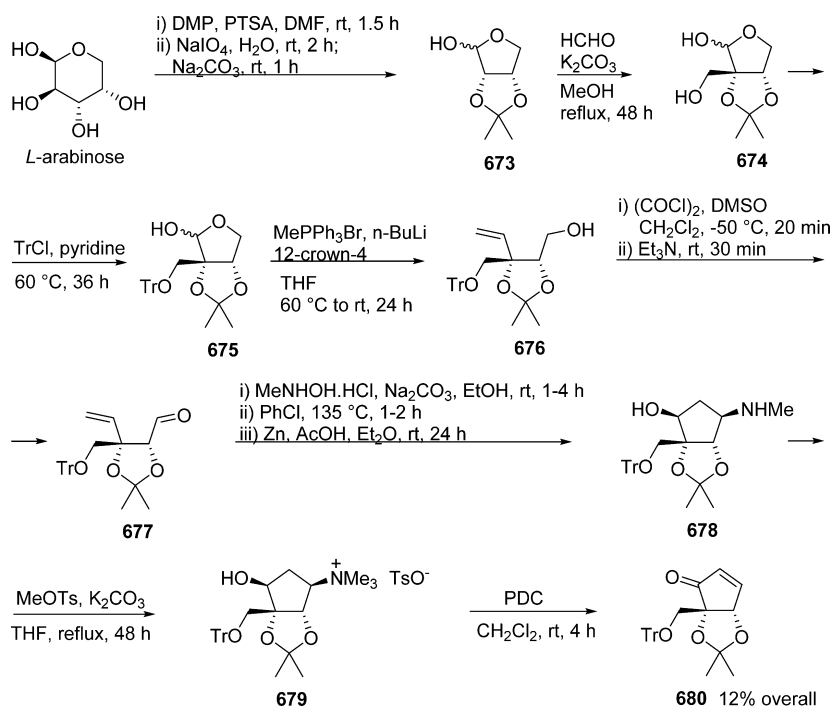
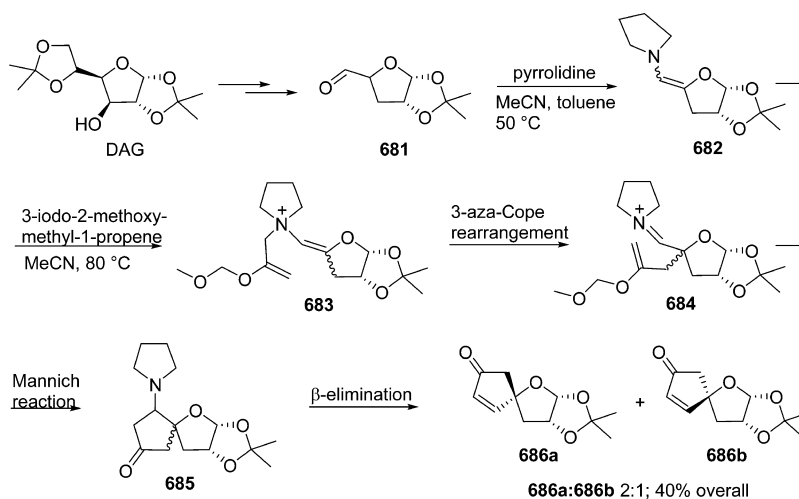
Scheme 183. Conversion of D-Ribose into 2-Bromo-Substituted Cyclopentenone L-669



Scheme 184. Synthesis of Substituted Cyclopentenone from 2'-C-Me-Ribonolactone



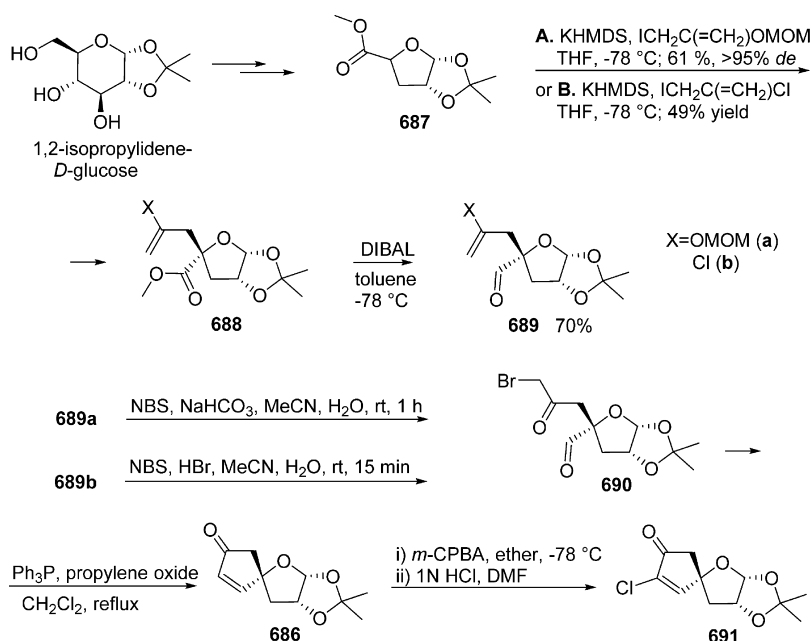
Scheme 185. Preparation of Cyclopentenone Possessing a Hydroxymethyl Substituent at 5-Position from L-Arabinose

Scheme 186. Convenient One-Pot, Five-Step Protocol for the Preparation of Chiral 4-Hydroxy-4-alkyl Cyclopentenones from an α -Alkoxy Aldehyde

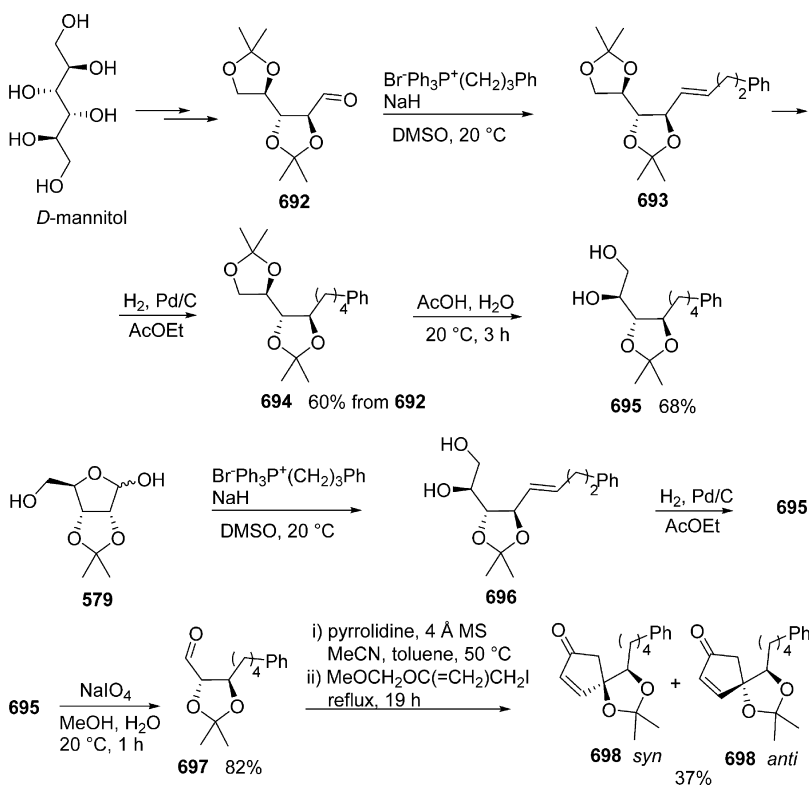
as single diastereoisomers in all cases except for enyne **760e**, for which a separable mixture of isomers was produced.

The key stereochemical factors determining transfer of asymmetry from the chiral auxiliary to the cyclopentenone

Scheme 187. Efficient Alternative Stereoselective Approach to the Synthesis of the Spirofurano Cyclopentenone 686 from Uronosugar 687, Derived from 1,2-*O*-Isopropylidene *D*-Glucose

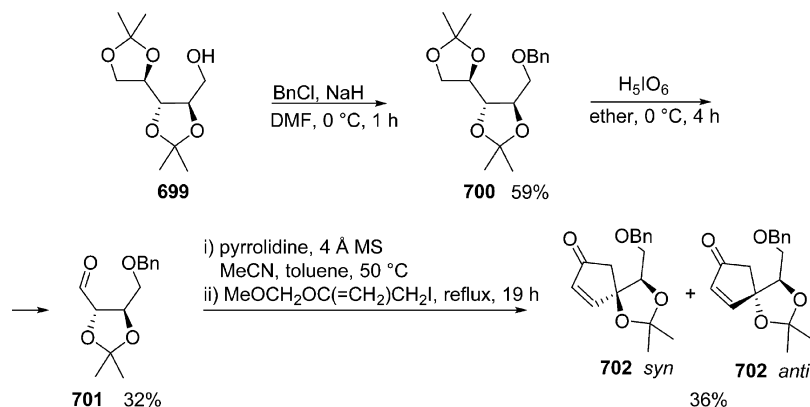
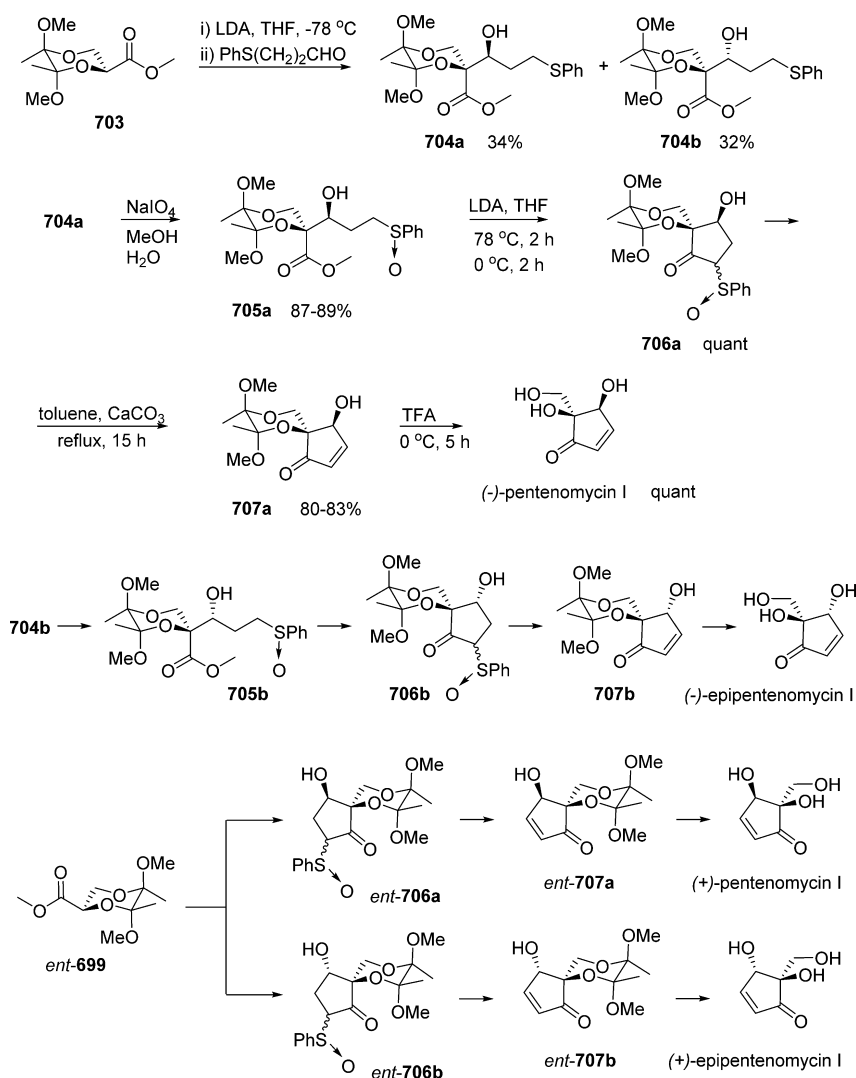


Scheme 188. Synthesis of Chiral Cyclopentenones from *D*-Mannitol as Key Intermediates in the Preparation of a Series of Simplified Analogues of Natural Cyclopentadienone Prostaglandins



have been elucidated by Banaag and Tius.⁴⁰⁸ The authors presented strong evidence that the pyran oxygen atom restricts the conformational mobility of the pentadienyl cation and that the key to high enantioselectivity is the presence of a large axial or pseudoaxial substituent on the pyran ring that shields one face of the pentadienyl cation. On the basis of this understanding of the stereochemistry-determining process, two improved chiral auxiliaries 762 and 763 (Scheme 200), derived from 2-deoxy-

D-glucose and 2-deoxy-*D*-galactose, respectively, leading to each enantiomeric series of cyclopentenones 764, were designed and applied by using a series of four morpholino amides. Accordingly, the high enantioselectivity was achieved by introducing an axial silyloxy group at C4 in 762, and by the axial C3 OTBS substituent in 763, which was ideally positioned to block one face of the pentadienyl cation.

Scheme 189. Conversion of 2,3,4,5-Di-*O*-isopropylidene *D*-Arabinitol into Chiral CyclopentenonesScheme 190. Synthesis of (–)-Pentenomycin I, (+)-Pentenomycin I, (–)-Epipentenomycin I, and (+)-Epipentenomycin I from *D*-Mannitol Chiral Esters

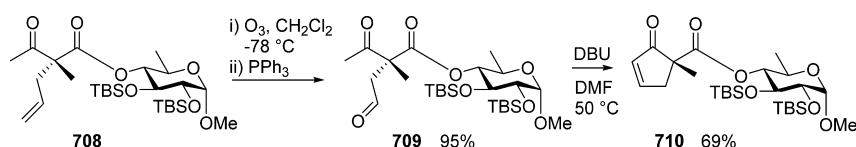
5.2. Chiral Carbonyl-Based Compounds

Chiral carbonyl compounds constitute another class of broadly exploited starting materials in the cyclopentenone synthesis. Among them, the most abundant sources of natural origin, carboxylic acids and their derivatives, are objects of special

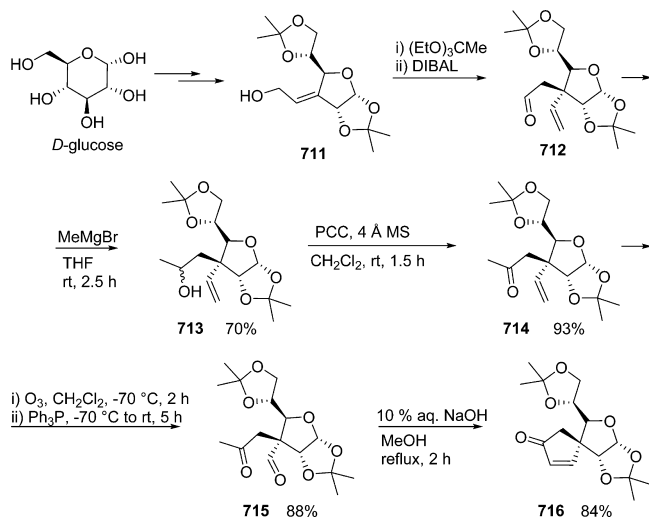
attention due to their wide availability, usually in both enantiomeric forms.

The chiral carbomethoxycyclopentenone **770** was obtained by Dauben and Lewis from (*S*)-malic acid through enantioselective synthesis of the A-ring synthon of $1\alpha,25$ -dihydroxyvitamin D_3 (Scheme 201).⁴⁰⁹ The diazo intermediate **769** was prepared

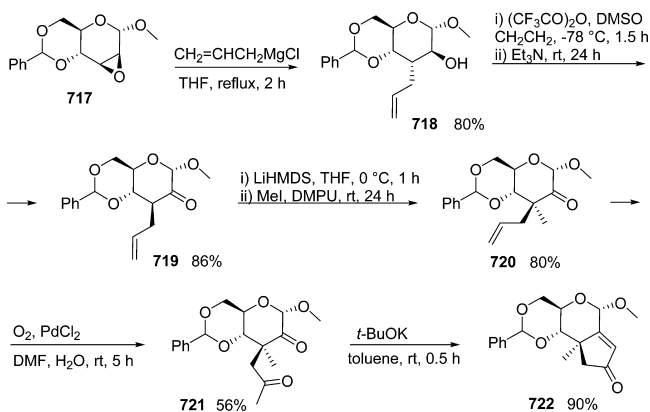
Scheme 191. Use of a D-Glucose-Derived Chiral Auxiliary in a Highly Stereoselective Quaternization of the α -Carbon of an Acetoacetate Ester



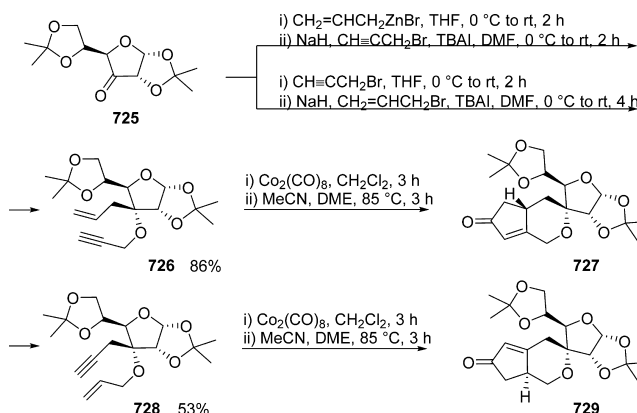
Scheme 192. Conversion of D-Glucose into a Chiral Spiro Cyclopentenone



Scheme 193. Stereoselective Conversion of Glucose Epoxide into an Enantiomerically Pure Cyclopentenone



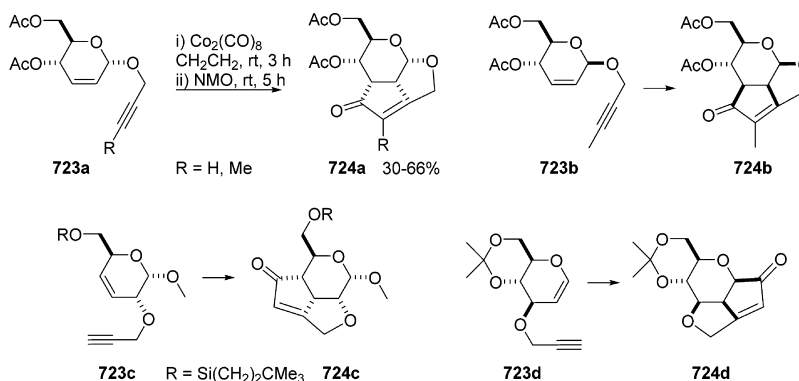
Scheme 195. Stereoselective Synthesis of Spiroannulated Cyclopentenones from Diacetone Glucofuranose



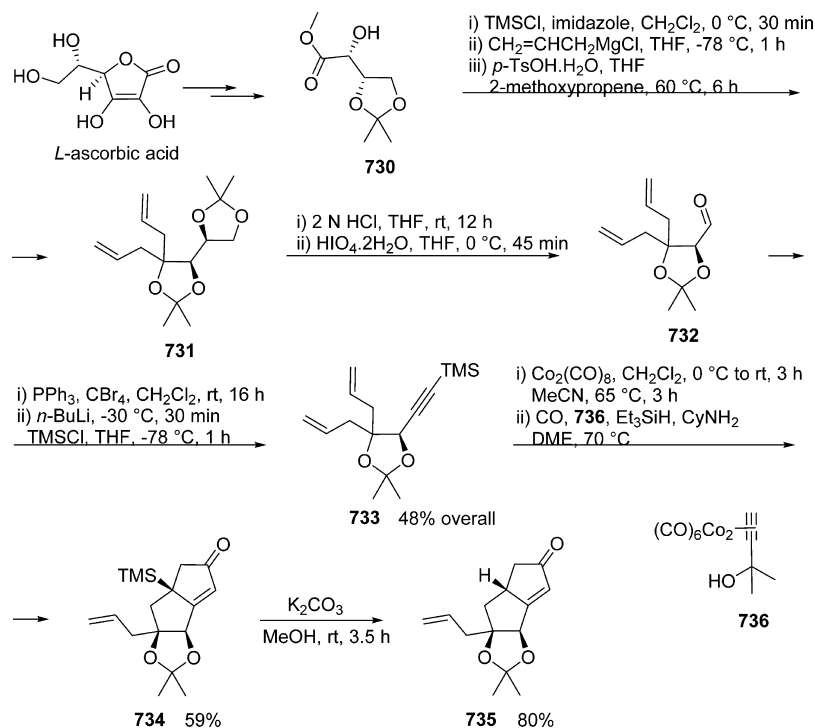
through a four-step sequence including methanolysis of hydroxybutyrolactone **765** with simultaneous esterification, silyl protection of **766**, and hydrolysis of **767**. This was followed by treatment with carbonyldiimidazole (CDI) and then with the magnesium salt of malonic half ester, and finally diazo transfer with mesyl azide. The cyclopentenone **770** was generated by carbene formation by treatment of **769** with rhodium acetate, followed by C–H insertion and spontaneous elimination of methanol.

Ziegler and Harran reported a radical cyclization wherein a derivative of L-tartaric acid was used as both the source of chirality and the carbon radical (Scheme 202).⁴¹⁰ Thus, thiohydroxamate ester **774**, obtained from **771** by consecutive Swern oxidation, treatment with propargyl zinc bromide, silylation of **772**, saponification, and reaction with 2,2'-dithiobis(pyridine N-oxide) in the presence of tributylphosphine, was subjected to photolysis with visible light and tributyltin hydride. Desilylation of **775** with tetrabutylammonium fluoride (TBAF) and subsequent epoxidation of the exocyclic olefin with dimethyldioxirane led to epoxy alcohol **776**. Oxidation of the latter with Dess–Martin periodinane (DMP)

Scheme 194. Cobalt-Mediated Pauson–Khand Cyclization of O-Branches Chain D-Glucose-Derived Enynes



Scheme 196. Diastereoselective Total Synthesis of Isocarbacyclin from L-Ascorbic Acid



provided the expected epoxy ketone, which was efficiently rearranged upon silica gel chromatography to enone **777**, a key biosynthetic precursor of aristeromycin and neplanocin A.

Diethyl-L-tartrate has been used as starting material in the synthesis of a series of optically active fused bicyclic cyclopentenones **783**–**788** by Mukai et al. (Scheme 203).⁴¹¹ The desired enynes **780**–**782**, obtained by Corey's dibromoolefination of alcohol **778** followed by treatment with *n*-butyllithium and deprotection/protection protocols, were subjected to a Pauson–Khand reaction under different conditions. Treatment of the enynes with $\text{Co}_2(\text{CO})_8$ afforded the corresponding cobalt-complexed enynes, which were subsequently exposed to the typical Pauson–Khand conditions, and the target cyclopentenones were isolated in variable yields with good to excellent stereocontrol. The derivatives **782** furnished (6*S*)-**783** highly stereoselectively or exclusively, while **781** and **780** congeners led to (6*R*)-products **786** and **788** in a highly stereoselective manner; no traces of (6*S*)-compounds **787** were detected. Additionally, the di-*tert*-butylsilylene derivatives **789**, prepared from **781** with di-*tert*-butylsilyl triflate, selectively provided the cyclized products with the same stereochemistry as from **781** and **780**.

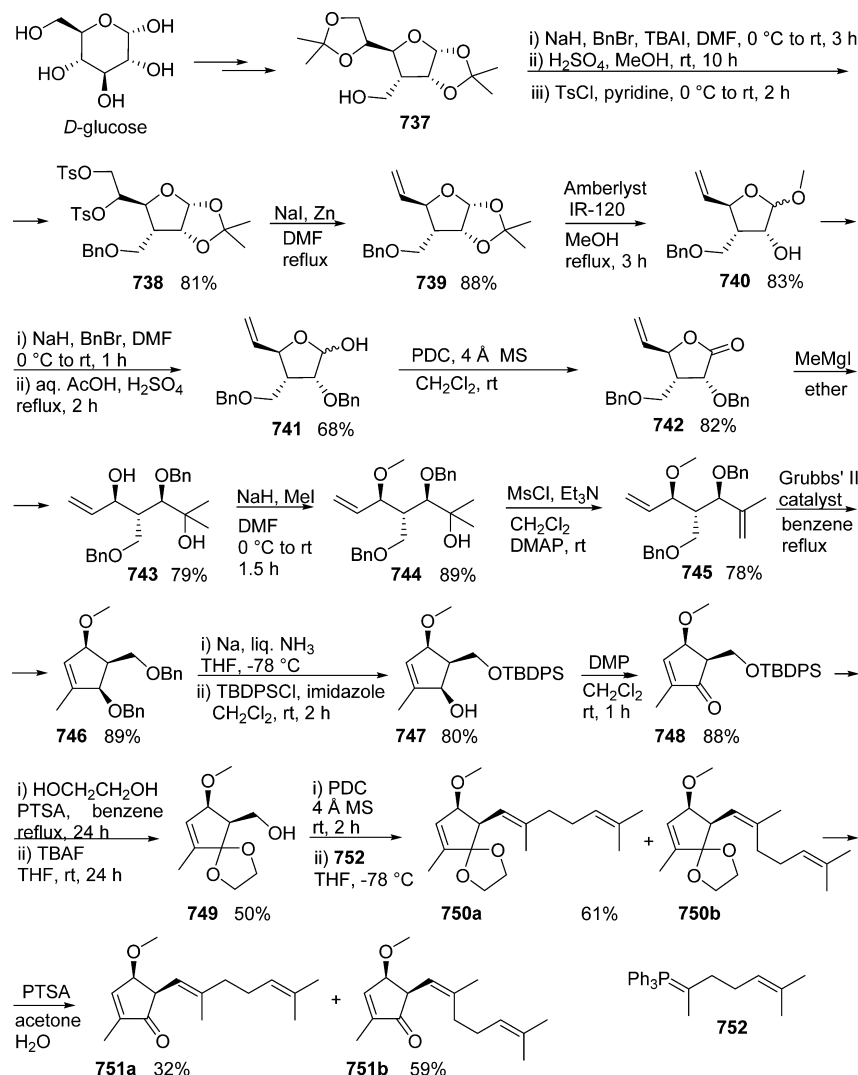
The optically active cyclopentenone **792** was obtained by Mikolajczyk and Mikina as a key intermediate in the synthesis of (–)-isoterrein (Scheme 204).⁴¹² The protected derivative **790** was treated with dimethyl lithiumethylphosphonate to give the corresponding bis- β -ketophosphonate **791**, which was further subjected to a base-catalyzed cyclization to afford the cyclopentenone **792**. The authors suggested that the inversion of the configuration of the chiral diol unit could result from a *trans*- to *cis*-isomerization via the enolate anion, which occurred during the synthesis and led to the more stable cyclopentenone with a *cis*-diol moiety.

Hayashi et al. completed the total syntheses of two natural tricyclic sesquiterpenes from dimethyl-D-tartrate in a stereoselective manner (Scheme 205).⁴¹³ The noteworthy tactical

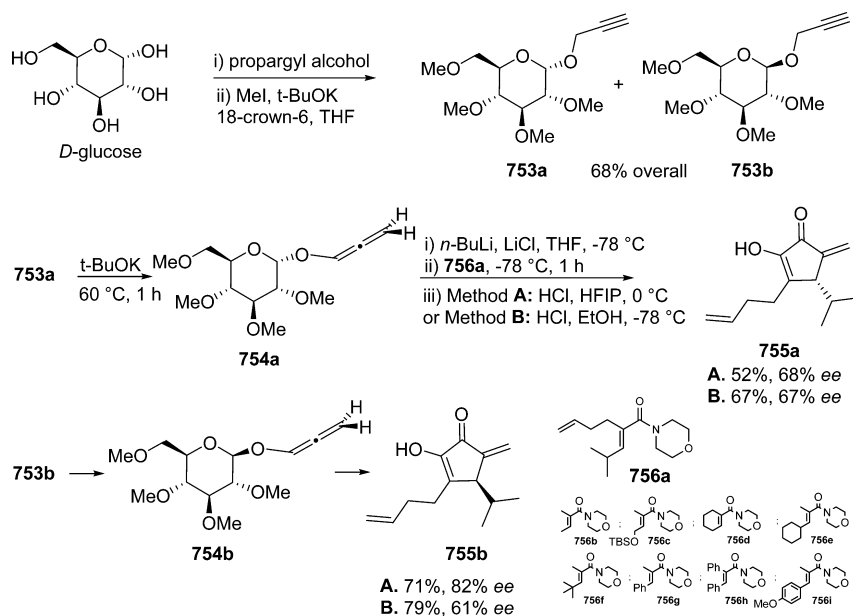
feature of the synthetic route was the incorporation of the two chiral centers of D-tartrate into the target molecules. The key intermediate **798** was obtained by Grignard reaction, mesylation of the primary hydroxyl group, dehydration of the tertiary hydroxyl group, deacetonization of **794** under acidic conditions, base treatment and silyl protection, epoxy ring-opening with introduction of a propargyl alcohol moiety upon exposure of **795** to a lithium acetylide derived from 3-*tert*-butyldimethylsilylprop-1-yne, reaction with methoxymethyl (MOM) chloride, conversion of enyne **796** into the carbonate **797** by a selective desilylation and reaction with chloromethyl carbonate, and exposure of **797** to $\text{Pd}(\text{OAc})_2$ and triphenylphosphine under atmosphere of CO. The crucial step was the Rh(I)-catalyzed Pauson–Khand-type reaction of the allenene derivative **798**, which afforded exclusively the bicyclo[4.3.0]nonenone framework possessing an angular methyl group (**799**) by applying a newly developed $[\text{RhCO}(\text{dppp})_2]\text{Cl}$ catalyst, prepared in situ from the reaction of bis(cyclooctadienyl) rhodium chloride ($[\text{RhCl}(\text{cod})]_2$) and 1,3-bis(diphenylphosphino)propane (dppp). None of the other catalysts tested were found to be effective.

Chiral cyclopentenones **806**, often termed Roche esters, have been obtained by Kavanagh et al. from (*S*)- β -hydroxyisobutyrate to prepare the bicyclic core of monoterpene alkaloids belonging to the kinabaurine, incarvilline, and skyanthine families of natural products (Scheme 206).⁴¹⁴ The chiral-pool-derived enyne **805** was obtained by consecutive Mitsunobu reaction by using a Weinreb-type reagent, reduction of the ester moiety of **800**, oxidation of the primary alcohol **801** with pyridinium chlorochromate, standard Wittig reaction of **802**, removal of the carbamate protecting group of **803** with TFA, and alkylation of **804** using but-2-ynyl bromide. A stereoselective intramolecular Pauson–Khand cyclization of **805** was performed under standard conditions to afford predominantly the (+)-(4*R*,4*R*) product **806a** along with a slight impurity of its diastereomeric adduct (–)-(4*R*,4*S*)-**806b**.

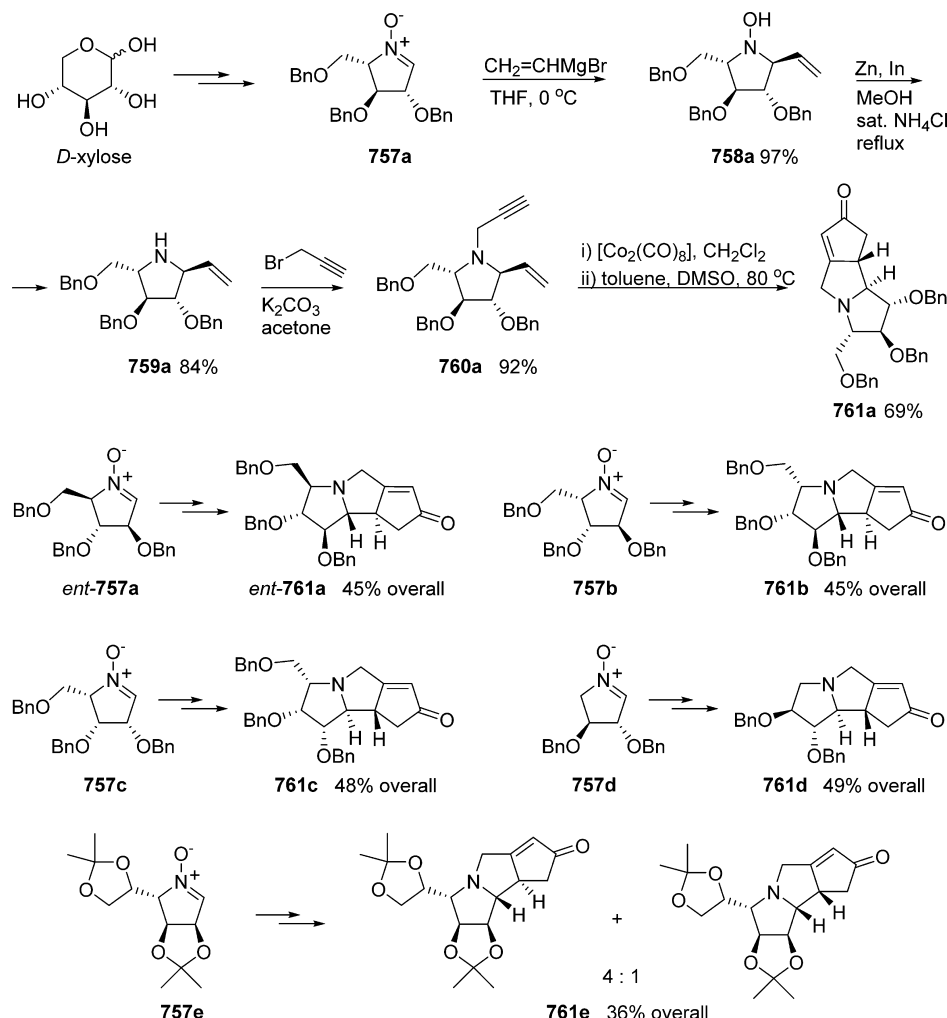
Scheme 197. Enantioselective Synthesis of Anti-HIV Agents Litseaverticillols C and K from D-Glucose



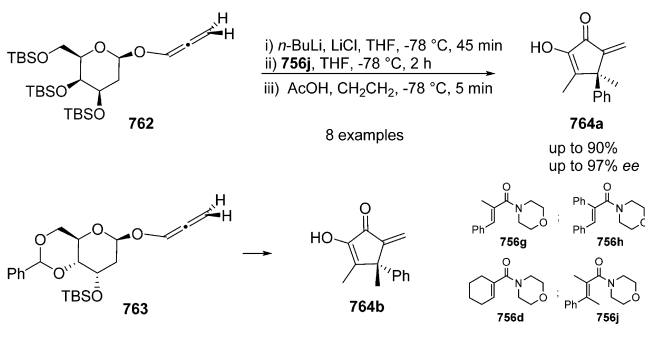
Scheme 198. Enantioselective Variant of the Allene Ether Nazarov Cyclization for the Preparation of Cross-Conjugated Cyclopentenones



Scheme 199. Stereoselective Synthesis of a Series of Azatriquinanes from D-Xylose-Derived Nitrones



Scheme 200. Synthesis of Cyclopentenones with Exocyclic Alkene Functionality from 2-Deoxy-D-glucose- and 2-Deoxy-D-galactose-Based Chiral Auxiliaries



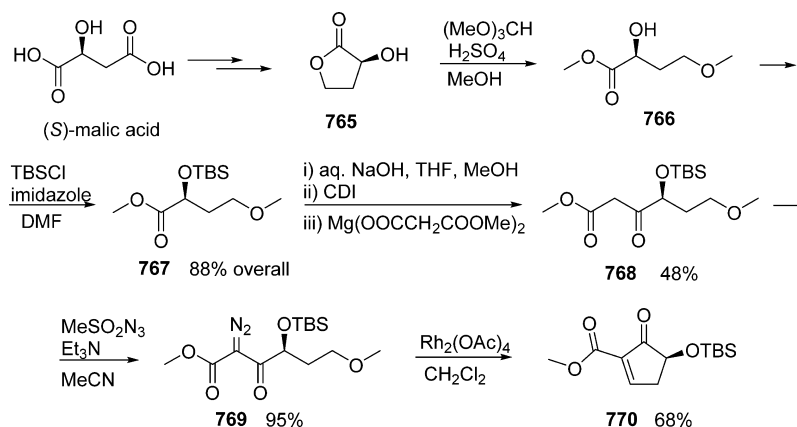
The chiral tetrasubstituted cyclopentenone **812**, the key intermediate in the total synthesis of (+)-madindoline A and (–)-madindoline B, was prepared by Sunazuka et al. starting from (+)- β -hydroxy ester **807** (Scheme 207).⁴¹⁵ Thus, the subsequent aldol reaction with methacrolein, acetonide protection of the inseparable isomeric mixture of **808**, separation of the stereoisomers of **809** and deprotection, ring-closing metathesis of **810** with Grubbs I catalyst, selective silylation of the less-hindered allylic hydroxyl group of **811**, and oxidation

with manganese oxide provided the target optically active carbocyclic unit **812** in good overall yield.

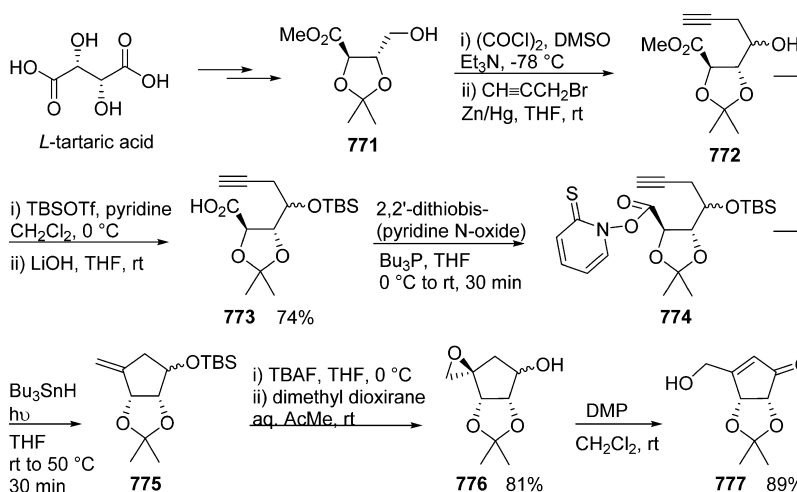
A closely related hydroxy ester, the Baylis–Hillman adduct **813** with (*S*)-configuration, has been used by Krishna and Kadiyala as starting material in a stereoselective total synthesis of trichoderme A, the deprotected analogue of **824** (Scheme 208).⁴¹⁶ The RCM precursor **822** was obtained as follows: protection of the hydroxy functionality as its MOM ether **814** in the presence of *N,N*-diisopropylethylamine (DIPEA), reduction of the ester group, Swern oxidation of the primary alcohol **815**, followed by Wittig olefination, reduction of the ester **816**, epoxidation of the allylic alcohol **817** with *N,N*-diisopropylethylamine (DIPEA), cumene hydroperoxide (CHP) and titanium isopropoxide, reductive ring-opening reaction of **818** with Red-Al, consecutive benzoylation of the primary hydroxyl group, MOM-protection of the secondary hydroxyl group, deprotection of the primary hydroxyl groups, and Swern oxidation of **821** followed by vinylation reaction, leading to the bis-olefin **822** as a 1:1 diastereomeric mixture. Finally, RCM cyclization performed with Hoveyda–Grubbs second generation catalyst and the MOM-protected cyclopentenol **823**, obtained as an inseparable 1:1 diastereomeric mixture, was oxidized by Dess–Martin periodinane to give the desired cyclopentenone **824** with correct stereochemistry.

A total synthesis of the alkaloid (–)-lathyranic acid A has been accomplished by Nan et al. on the basis of a 20-step linear

Scheme 201. Synthesis of a Chiral Carbomethoxycyclopentenone from (S)-Malic Acid



Scheme 202. Use of an L-Tartaric Acid Derivative as Both the Source of Chirality and the Carbon Radical in a Radical Cyclization Step of a Cyclopentenone Synthesis



sequence.⁴¹⁷ The key intermediate, cyclopentenone **827**, was obtained from the easily available chiral aldehyde **825** by Wittig methylation, Grignard vinylation via the Weinreb amide, and RCM of diene **826** performed with the second generation Grubbs catalyst (Scheme 209).

Sugiura et al. have converted a series of chiral dienones **828** into cyclopentenones **829** by Hoveyda–Grubbs II-catalyzed ring-closure metathesis (Scheme 210).⁴¹⁸ The optically active compounds **829** represent important structural motifs in natural products and pharmaceuticals, such as the antitumor agent TEI-9826.

Recently, Grubbs I-catalyzed RCM of dienone **830** was achieved by Huang et al.⁴¹⁹ as a step in the total synthesis of **831** (Scheme 211). The latter shares the benzo-fused chiral spirocyclic cyclopentenone moiety present in a molecular probe for DNA bulges.

Shibatomi et al. synthesized the bicyclic enone **836** from the difluoromethylated ester **832** via subsequent hydrolysis, condensation with *N,O*-dimethylhydroxyl amine to Weinreb amide **834**, Grignard reaction with vinylmagnesium bromide, and olefin metathesis of **835** performed with the Grubbs I catalyst (Scheme 212).⁴²⁰

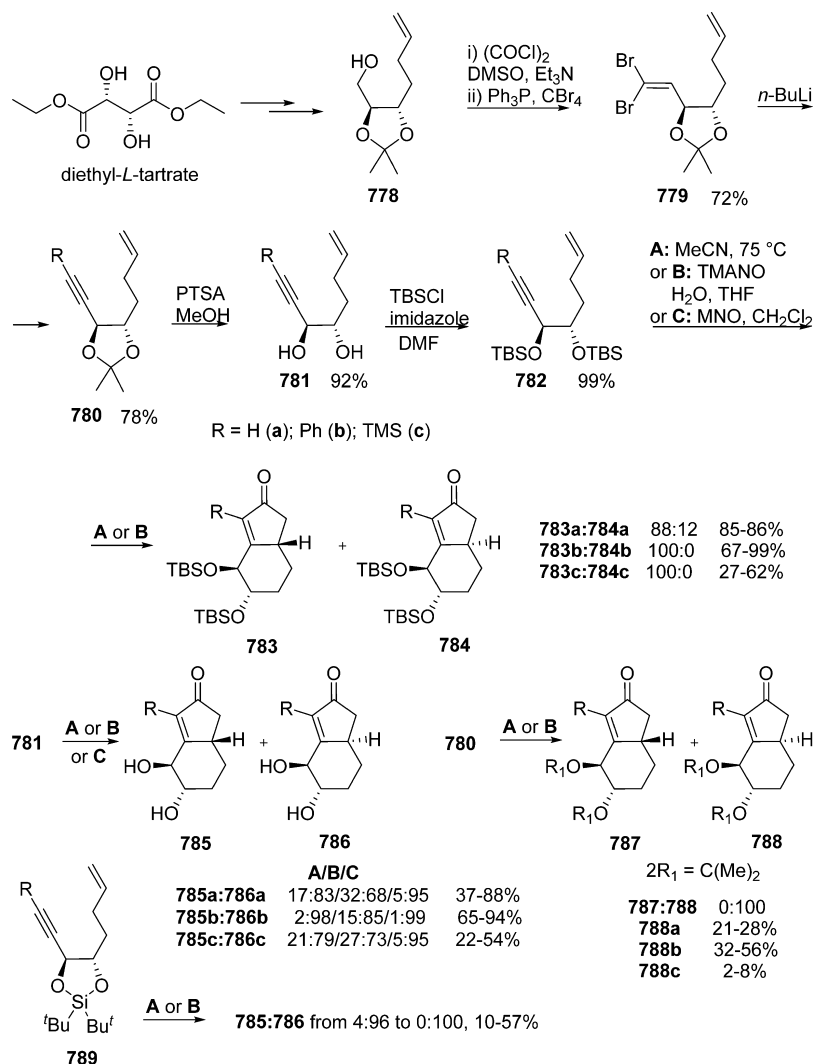
Zhuo et al. have developed an efficient strategy for the total synthesis of the diterpenoid (+)-przewalskin B exhibiting modest anti-HIV-1 activity.⁴²¹ As a key step, 4-(*Z*)- β -vinyl- α -diazo- β -ketoester **838** was converted into the spiro-enone **839** in

excellent yield by rhodium-mediated intramolecular carbene insertion into the tertiary C–H bond (Scheme 213).

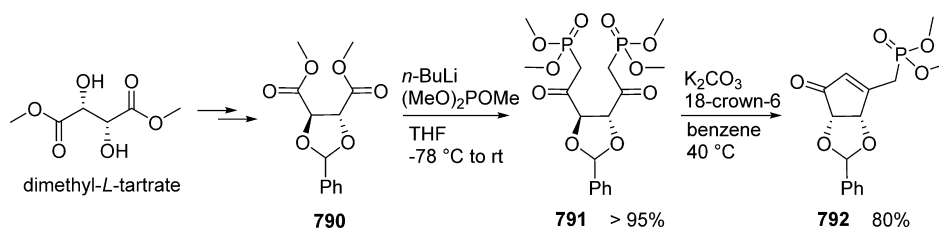
Chiral diketophosphonates **843** have been obtained by Yan and Spilling via consecutive intermolecular nucleophilic substitution of **840**, decarboxylation of **841**, and Wacker oxidation of vinyl phosphonates **842** (Scheme 214).⁴²² The conversions of diketophosphonates **843** under different conditions were studied. It was found that the aldol reaction was dominant under mild acidic conditions (SiO_2), leading to α -phosphonato- α,β -unsaturated cyclopentenones **845**. The intramolecular Horner–Wadsworth–Emmons (HWE) reaction with potassium carbonate and 18-crown-6 as base led to cyclopentenones **844** in high yields, but with significant erosion of the stereochemistry, while the application of barium hydroxide as base resulted in cyclopentenones **844** without racemization, but in generally low yields due to competitive formation of the aldol products **845**.

Davis and Wu prepared a series of 4-aminocyclopentenones **851**–**853** from *N*-sulfinyl β -amino esters **846** (Scheme 215).⁴²³ The protocol was based on RCM of amino ketodienes **848**–**850**, easily accessible by conversion into sulfinimine-derived chiral building blocks, δ -amino β -ketophosphonates **847**, and Horner–Wadsworth–Emmons chemistry. Good to excellent conversions were achieved using Grubbs II catalyst, while Grubbs I was found to be effective only in the formation of **852a** and **853a**.

Scheme 203. Conversion of Diethyl-L-tartrate into a Series of Optically Active Fused Bicyclic Cyclopentenones



Scheme 204. Synthesis of the Key Cyclopentenone Intermediate in the Synthesis of (–)-Isoterrein from Diethyl-L-tartrate



Similar chiral alkenes **854** have been applied in the cyclopentenone synthesis by Li and Xu. Sulfonamide **854** has been deprotected, esterified, and subjected to reductive amination (Scheme 216).⁴²⁴ The resulting amines **855** were converted into bicyclic cyclopentenones **856** in a highly stereoselective manner.

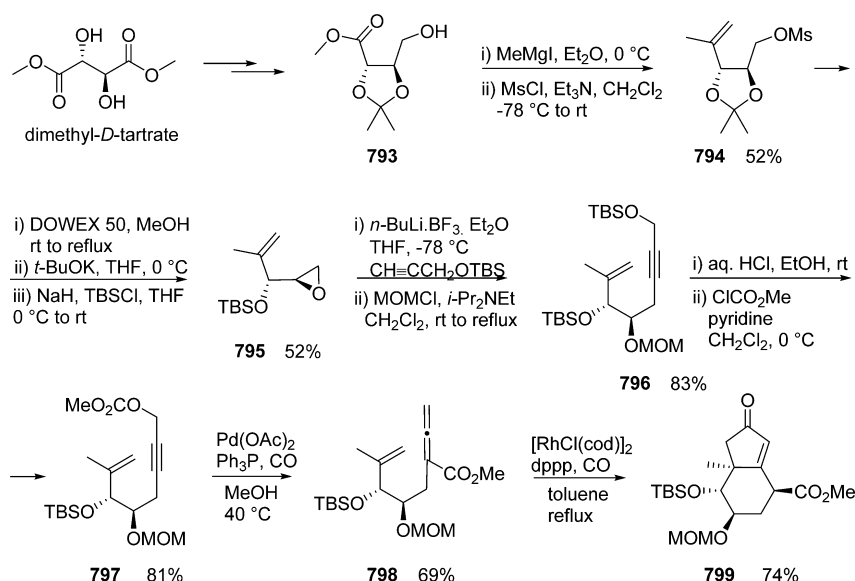
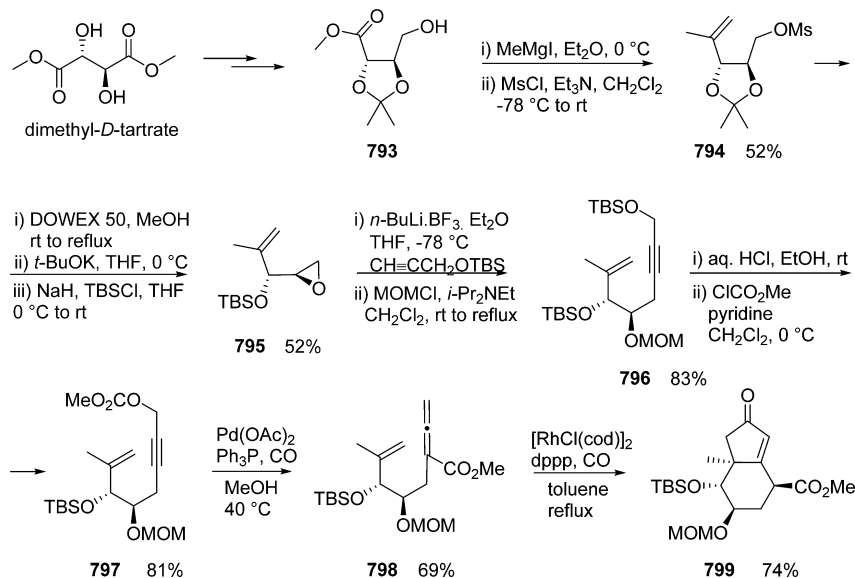
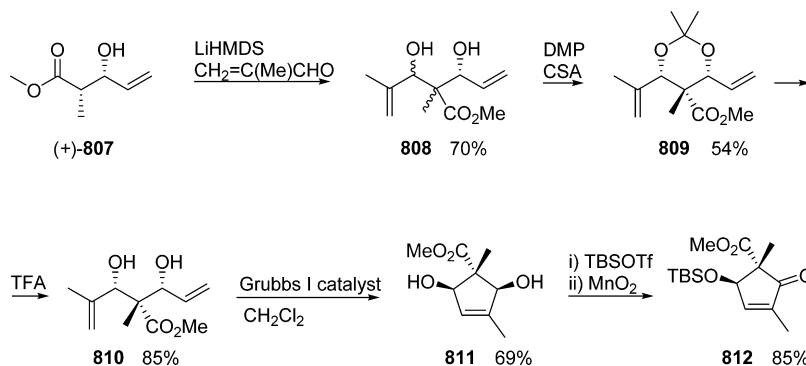
Enantiomerically pure 8 α -substituted indolizidine **859** has been efficiently synthesized from L-proline by Duran-Lara et al. (Scheme 217).⁴²⁵ The key step, Pauson–Khand reaction of enyne **858**, was achieved with a catalytic amount of dicobalt octacarbonyl and an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm]·PF₆), as cocatalyst.

A broadly applicable synthesis of chiral 2- or 2,4-substituted cyclopentenones **863**, which offers a straightforward access to

biologically active prostaglandins of the PGA type, has been developed by Dübon et al. (Scheme 218).⁴²⁶ The ester amides **860**, obtained via iridium-catalyzed allylic alkylation of allylic esters with a Weinreb-type amide, were converted into cyclopentenones through a three-step sequence, including demethoxycarbonylation by saponification/decarboxylation, Grignard reaction of **861**, and ring-closing metathesis of **862** with Grubbs II catalyst. The products were obtained in good overall yield and excellent enantioselectivity, and were subsequently applied efficiently in the prostaglandin synthesis.

The synthesis of the 12-acetoxy enone **878** related to the limonoid azadiradione was achieved by Fernández-Mateos et al., starting from the tricyclic diester **864** (Scheme 219).⁴²⁷ The first part of the synthesis, which consisted of the transformation of

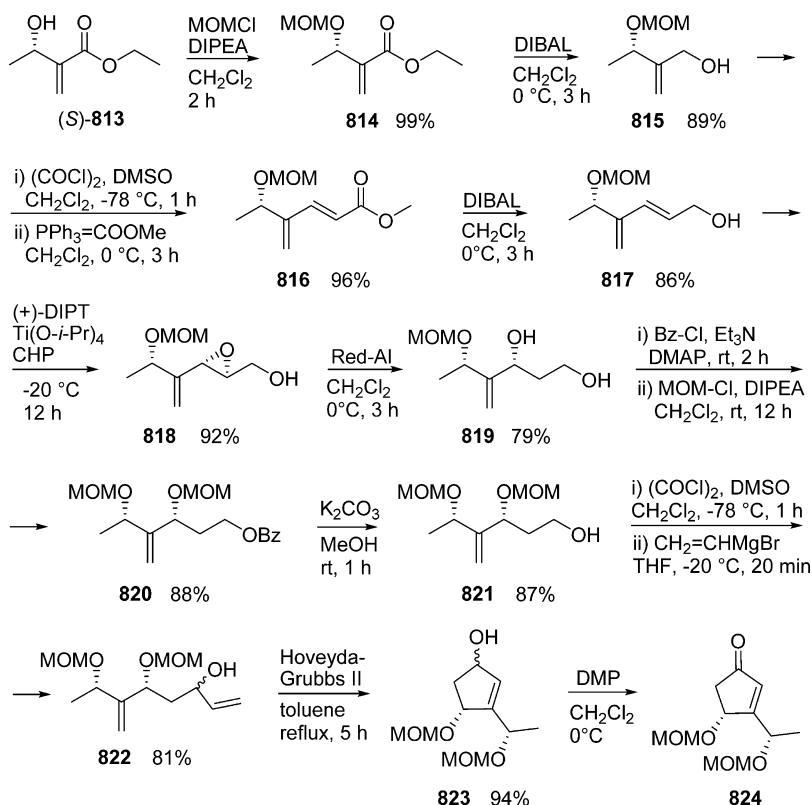
Scheme 205. Total Syntheses of Natural Tricyclic Sesquiterpenes from Dimethyl-D-tartrate

Scheme 206. Synthesis of Cyclopentenones Possessing the Bicyclic Core of Natural Monoterpene Alkaloids from (*S*)- β -HydroxyisobutyrateinScheme 207. Preparation of Chiral Tetrasubstituted Cyclopentenone **812** from a (+)- β -Hydroxy Ester

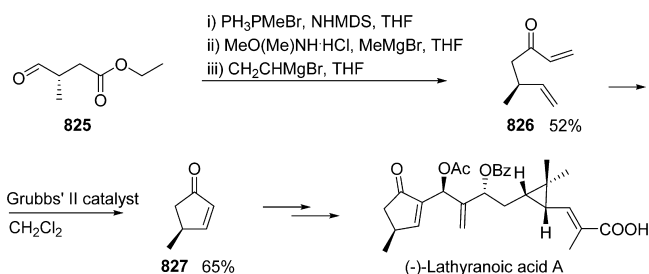
diester **864** into the cyclopentane isoxazoline **868**, was performed through a four-step sequence: selective reduction to the hydroxyester **865**, Swern oxidation to oxoester **866**, oxime

formation with hydroxylamine to **867**, and intramolecular dipolar cyclization through intermediate nitrile oxide with sodium hypochlorite. The β -orientation of the side chain in the

Scheme 208. Conversion of a Chiral Ester into a Protected Cyclopentenone as a Step in a Stereoselective Total Synthesis of Trichodermone A



Scheme 209. A Total Synthesis of the Alkaloid (–)-Lathyranoic Acid A



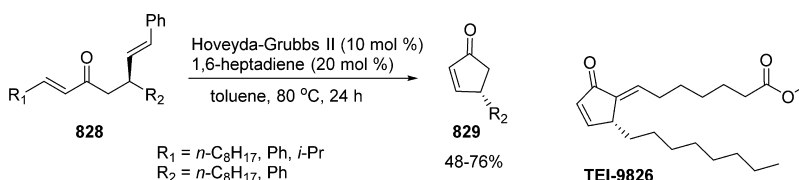
oxime **867** guaranteed an angular α -orientation of the C-18 methyl group of the pentacyclic isoxazoline **868** after cyclization. The conversion of the latter into the target cyclopentenone **878**, possessing furyl substituent at the 17-position, was achieved in eight steps in good overall yield and correct stereochemistry. Cleavage of the heterocyclic ring of **868** has been achieved by using hydrogen-saturated palladium on carbon suspended in a boric acid methanol–water solution, and the mixture of hydroxy ketone **870** and hydroxyimine **869** obtained was converted into the key compound necessary for coupling with the furan ring,

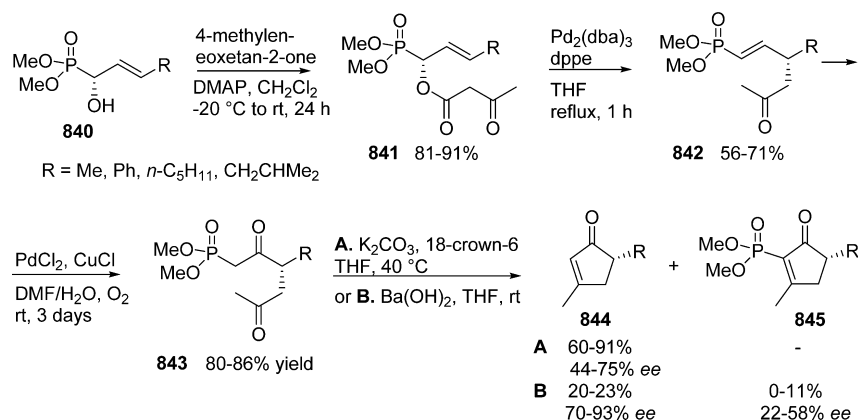
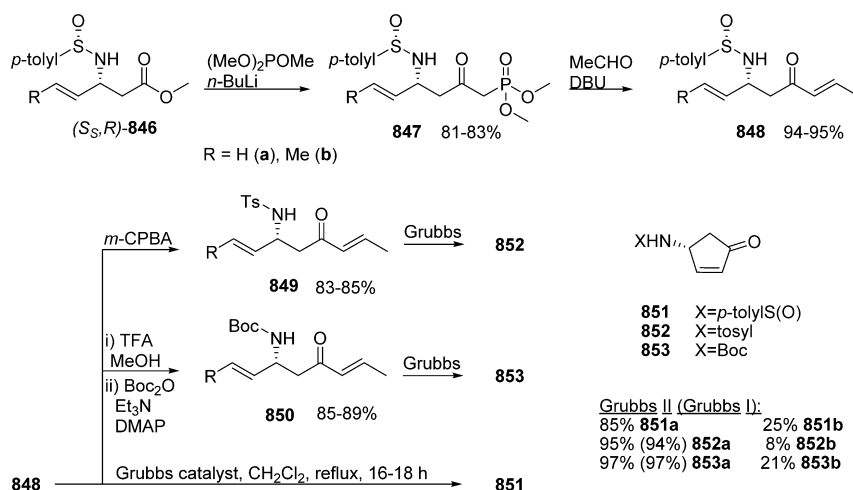
vinyl iodide **872**, via hydrazone **871**. The furyl substituent has been introduced by the Stille reaction of acetate **873**, while the direct transformation of **872** was unsuccessful. Epoxidation of **874** followed by rearrangement to **876** was achieved totally stereoselectively. Finally, the cyclopentenone unit was formed through silyl enolate **877** by epoxidation at low temperature to avoid furan degradation, and subsequent treatment with *p*-toluenesulfonic acid.

Reddy et al. reported a short and efficient synthesis of cyclopentenone **881** from commercially available (–)-pantolactone, constituting a step in the enantiospecific synthesis of (–)-D-noviose (Scheme 220).⁴²⁸ Thereby, Swern oxidation of **879**, obtained in three steps from pantolactone, followed by Grignard addition of vinylmagnesium bromide furnished diene **880** in high yield, which was subjected to RCM using Grubbs' I catalyst to give a cyclopentene derivative, that upon oxidation with Jones' reagent gave cyclopentenone **881**.

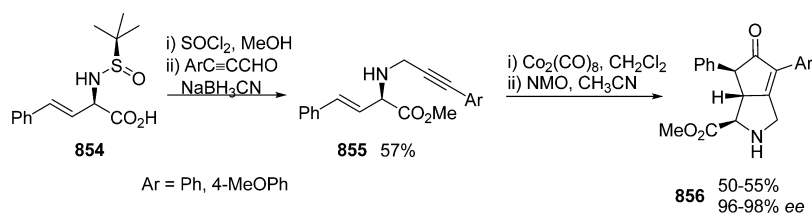
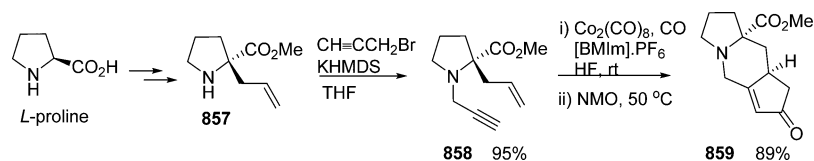
Another lactone, **882**, was used by Sundermann and Scharf in a three-step preparation of enantiomerically pure dihydroxycyclopentenone **885** (Scheme 221).⁴²⁹ After substrate-controlled diastereoselective dihydroxylation of *O*-menthyl-substituted furanone **882**, protection of menthyl glucoside **883**, and reaction

Scheme 210. Conversion of Chiral Dienones into Cyclopentenones by Hoveyda–Grubbs II-Catalyzed Ring-Closure Metathesis

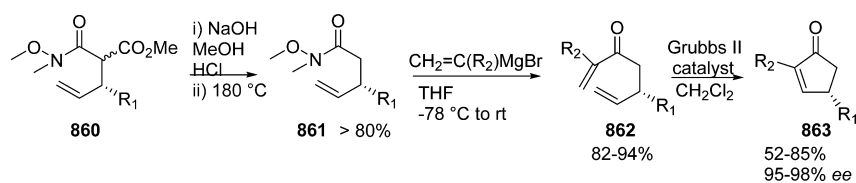


Scheme 214. Synthesis of α -Phosphonato- α,β -Unsaturated CyclopentenonesScheme 215. Synthesis of a Series of 4-Aminocyclopentenones from *N*-Sulfinyl β -Amino Esters

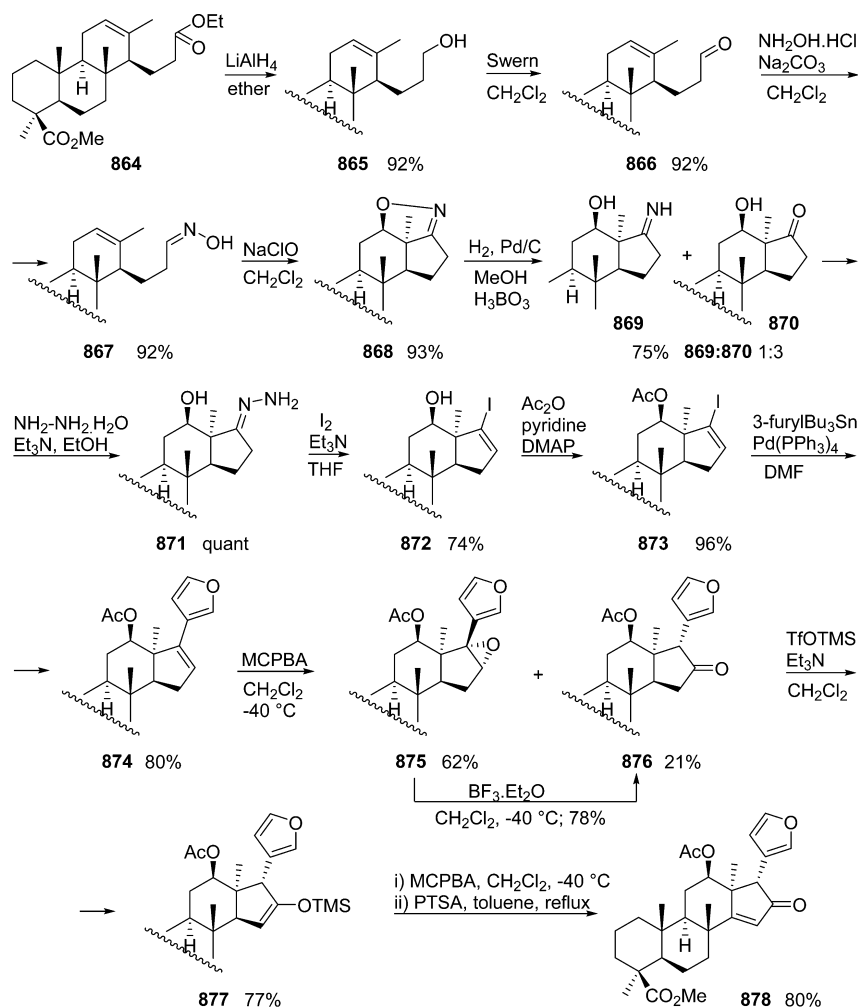
Scheme 216. Preparation of Bicyclic Cyclopentenones from Chiral Sulfonamides

Scheme 217. Synthesis of Enantiomerically Pure 8 α -Substituted Indolizidine from L-Proline

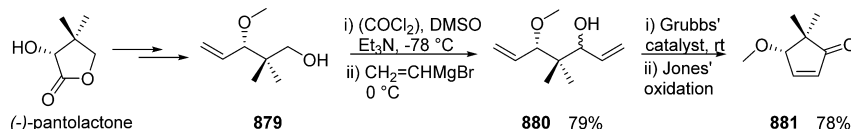
Scheme 218. A Broadly Applicable Synthesis of Chiral 2- or 2,4-Substituted Cyclopentenones



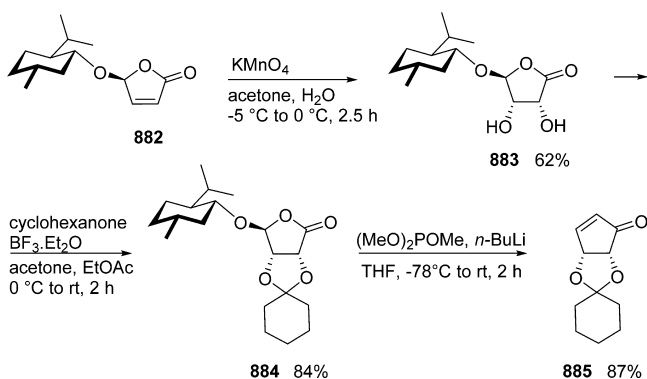
Scheme 219. Synthesis of the 12-Acetoxy Enone Related to a Limonoid Azadiradione from a Tricyclic Diester



Scheme 220. A Short and Efficient Synthesis of a Cyclopentenone from Commercially Available (–)-Pantolactone



Scheme 221. Three-Step Preparation of an Enantiomerically Pure Dihydroxycyclopentenone from a Chiral Lactone

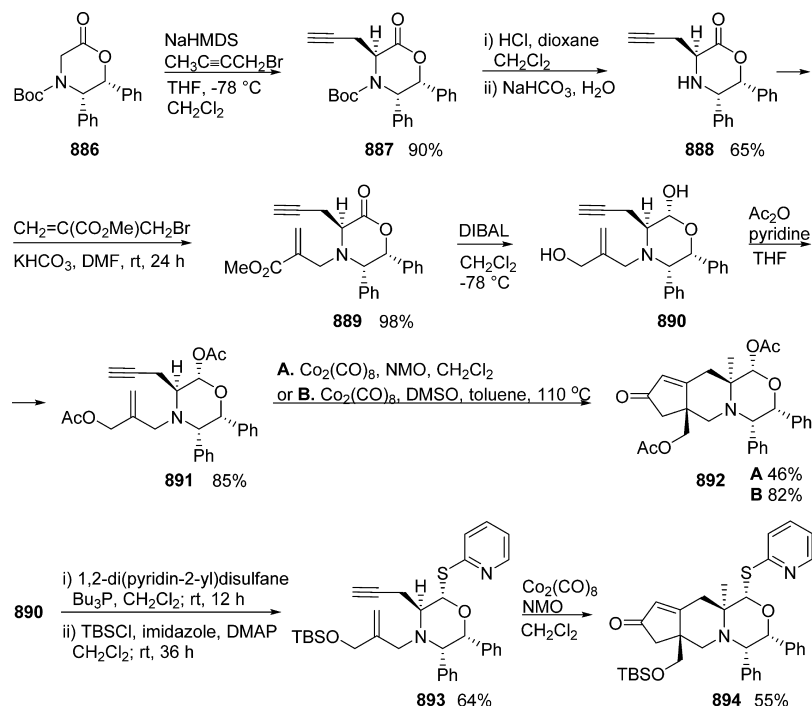


from the bicyclic lactam **918** via ketoaldehyde **919** in high overall yield.

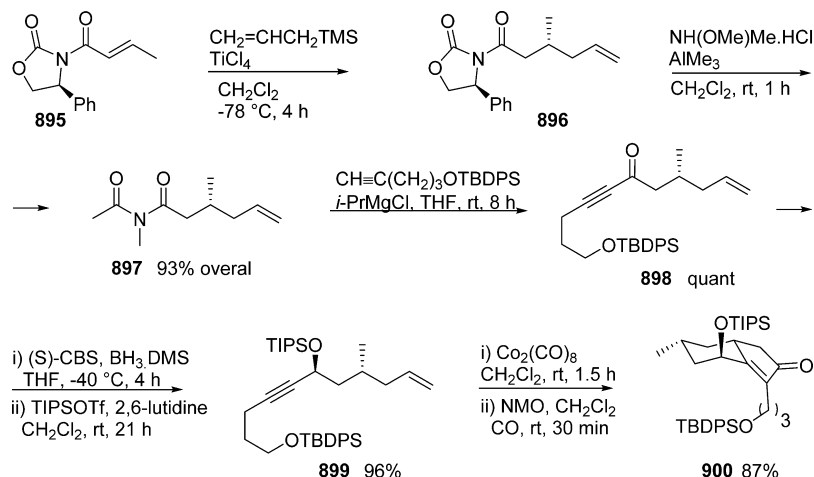
The protocol has been applied by Saito and Kuwahara in the first enantioselective total syntheses of antimicrobial sesquiterpenes enokipodins A–D starting from the analogous lactam **921** (Scheme 228).⁴³⁶ Cyclopentenone **924** was obtained in high yield from **922** by using tetrabutylammonium dihydrogen phosphate and immediately subjected to aldol condensation. The presented synthesis confirmed the absolute configuration of the natural products.

Srikrishna and Beeraiah developed an enantioselective approach to the synthesis of spiro-annulated cyclopentenone **933**, a key intermediate in the preparation of diterpenes komarovspiranes, starting from (*S*)-campholenaldehyde (Scheme 229).⁴³⁷ Bicyclic ketone **926**, obtained from **925** by intramolecular rhodium carbenoid C–H insertion, was subjected to Horner–Wadsworth–Emmons reaction followed by reduction of the obtained *E,Z*-mixture of **927**, and Johnson's orthoester variant of the Claisen rearrangement of allyl alcohol **928** to generate the quaternary carbon atom. The ester **929** was transformed into the corresponding aldehyde **930** by a two-step

Scheme 222. An Asymmetric Approach to the Synthesis of a BC-Ring Synthone of Tuberostemoninol



Scheme 223. Asymmetric Total Alkaloid Syntheses Starting from a Chiral Crotonamide



reduction–oxidation protocol, which was subjected to Grignard reaction with vinylmagnesium bromide. The key step, RCM reaction of hydroxydiene **931**, was achieved with Grubbs' first generation catalyst, and after oxidation of spiro alcohol **932** with pyridinium chlorochromate and silica gel, the spiroenone **933** was isolated in near quantitative yield.

The same starting material has been used by Srikrishna et al. for the preparation of bicyclic pentenone **937** by applying the same synthetic strategy for the construction of the fused bicyclic system **935** (Scheme 230).⁴³⁸ For the introduction of the requisite olefin at C-1, a regioselective selenation–deselenation sequence was employed. Thus, reaction of the β -ketoester **935** with phenylselenenyl chloride in the presence of pyridine furnished the selenide **936** in a highly regio- and stereoselective manner, which led to enone **937** in high overall yield upon oxidation with hydrogen peroxide.

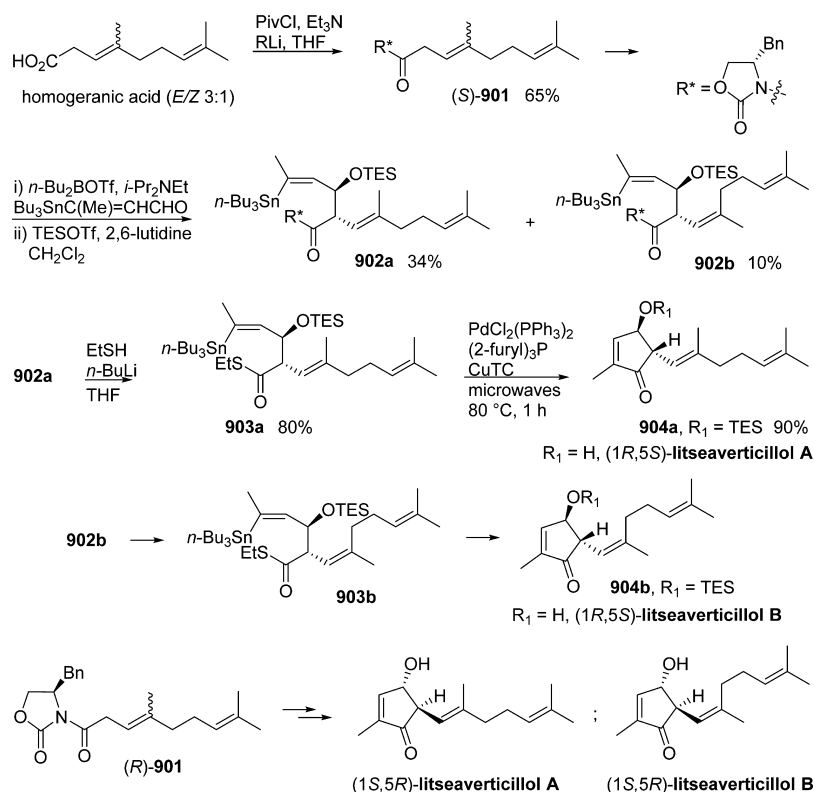
Linear triquinane **942** has been obtained by Srikrishna and Neetu⁴³⁹ via ketone **926**, which has been converted into the

corresponding methyl ether **938** by sodium borohydride reduction and etherification (Scheme 231). Oxidation of diquinane **936** and Grignard reaction of aldehyde **939** led to an epimeric mixture of allyl alcohol **940**, which was oxidized with iodoxybenzoic acid (IBX) to the cross-conjugated dienone **941**. Nazarov reaction of the latter furnished a mixture of regioisomeric triquinane-based enones, **942** being the minor component.

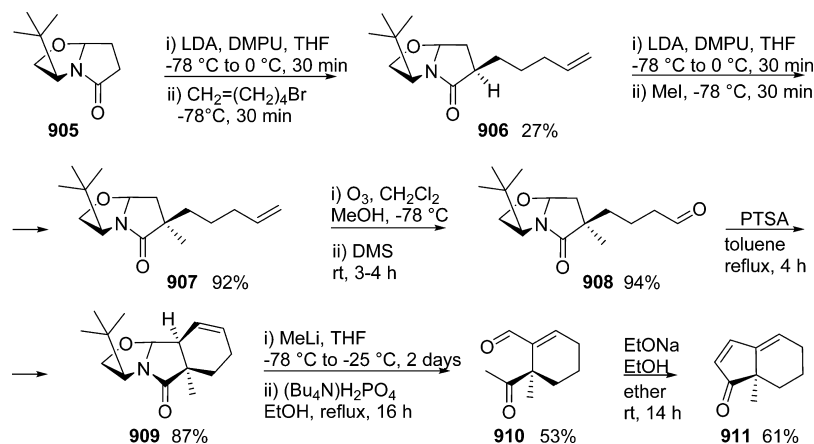
Bicyclic enone **945** has been prepared from aldehyde **943** by Srikrishna and Neetu as a step in the synthesis of marine diterpenes aberranes (Scheme 232).⁴³⁹ Grignard reaction followed by oxidation furnished the cross-conjugated dienone **944**, which was subjected to Nazarov cyclization to afford the target intermediate **945**.

Halterman and Vollhardt obtained cyclopentenone **948** starting from (+)-camphor (Scheme 233).⁴⁴⁰ The three-step sequence, involving alkylation with methyl bromomethanoate, reaction of **947** with the anion of dimethyl methylphosphonate,

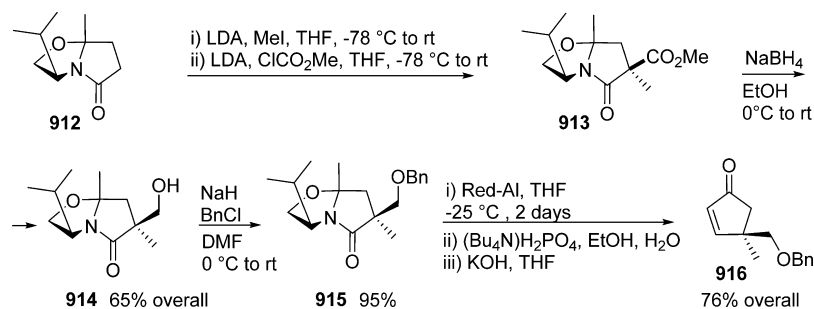
Scheme 224. Enantioselective Total Synthesis of the Monocyclic Natural Sesquiterpenoids (1*R*,5*S*)-Litseaverticillol A and (1*R*,5*S*)-Litseaverticillol B from Homogeranic Acid



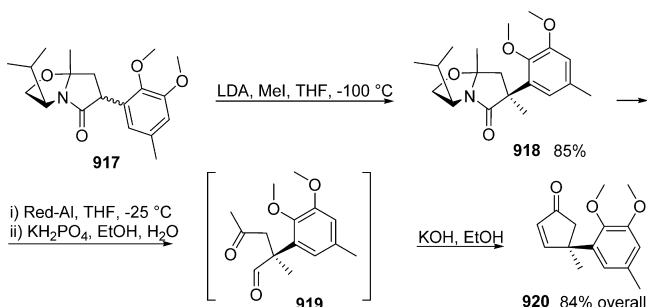
Scheme 225. Conversion of a Chiral Cyclic Lactam into a Bicyclic Pentenone



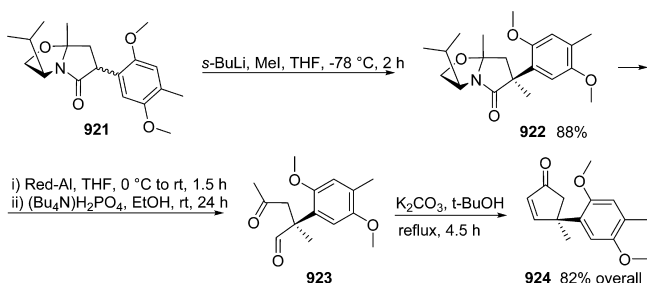
Scheme 226. Synthesis of a 4,4-Disubstituted Cyclopentenone from a Lactam Readily Obtained from Levulinic Acid and Natural (*S*)-Valinol



Scheme 227. Conversion of an (*S*)-Valinol-Derived Lactam into a Key Cyclopentenone Intermediate in the Total Syntheses of (–)-Herbertenediol, (–)-Mastigophorene A, and (–)-Mastigophorene B



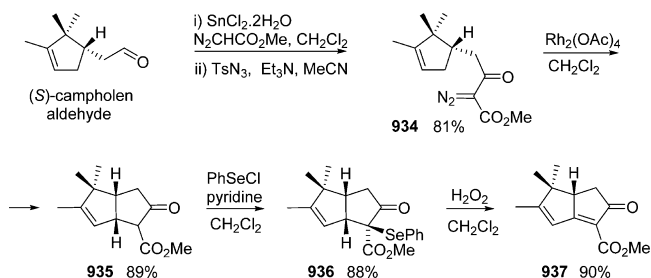
Scheme 228. Steps in the First Enantioselective Total Syntheses of Sesquiterpenes Enokipodins A–D



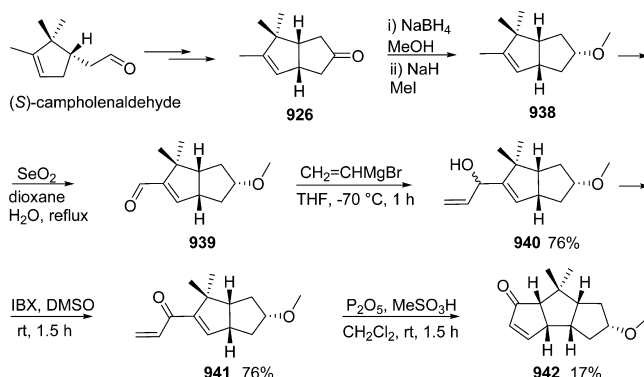
and ring-closure under basic conditions, led to the preparation of **946** as a single isomer in good overall yield.

Stereoselective synthesis of spiro cyclopentenone-pyran products **951** has been achieved by Sezer et al.⁴⁴¹ (Scheme 234). Diastereoisomerically pure tertiary homoallylic, homo-methallylic, and homopropargylic alcohols **949** have been constructed on the carbonyl group of (1*R*)-(+)-camphor and were then subjected to propargylation and allylation reactions, successively, to afford the corresponding enynes **950**. Their intramolecular Pauson–Khand reactions showed a high conformational control on the new stereocenter formed, and,

Scheme 230. Synthesis of a Bicyclic Pentenone from (*S*)-Campholenaldehyde



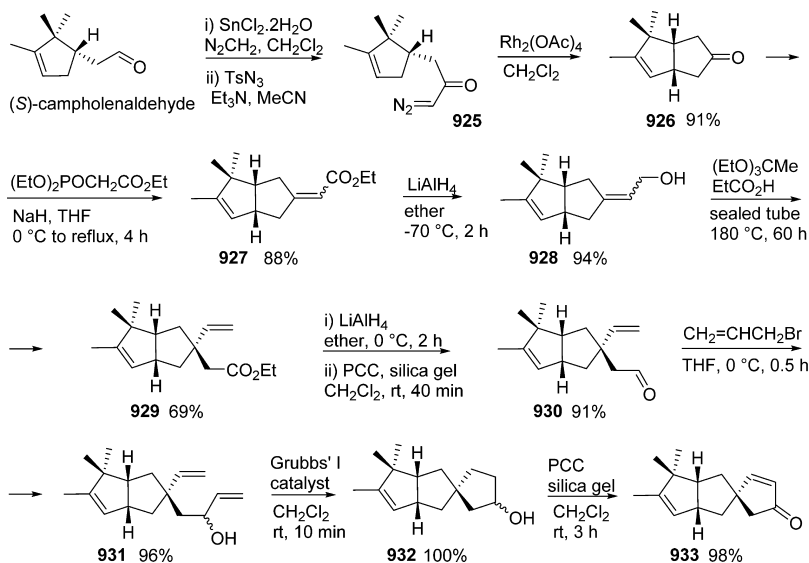
Scheme 231. Preparation of a Linear Triquinane from (*S*)-Campholenaldehyde



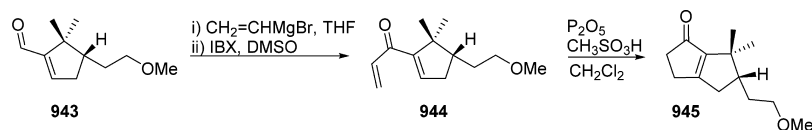
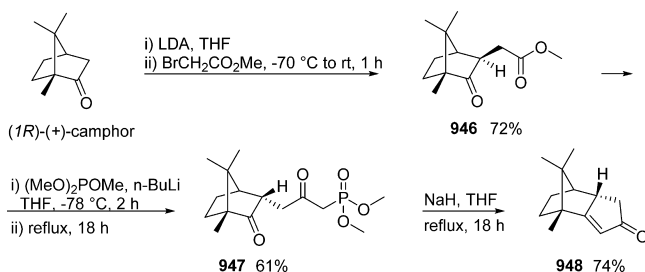
in all cases, single diastereomers of cyclopentenones **951** were obtained.

Jamison et al. developed a stereoselective total synthesis of natural diterpene (+)-epoxydictymene from (*R*)-pulegone via the complex polycyclic pentenone **959** (Scheme 235).⁴⁴² The Favorskii ring contraction afforded ester **952** stereospecifically, favoring the diastereomer in which the methyl and carboxymethyl groups are oriented *trans* to each other. Saponification of the latter and subsequent acid-catalyzed cyclization to the fused *cis*-5,5 system **953** established the configuration of C7 (epoxydictymene numbering). Reduction of the lactone **953** to

Scheme 229. Synthesis of a Spiro Annulated Cyclopentenone from (*S*)-Campholenaldehyde

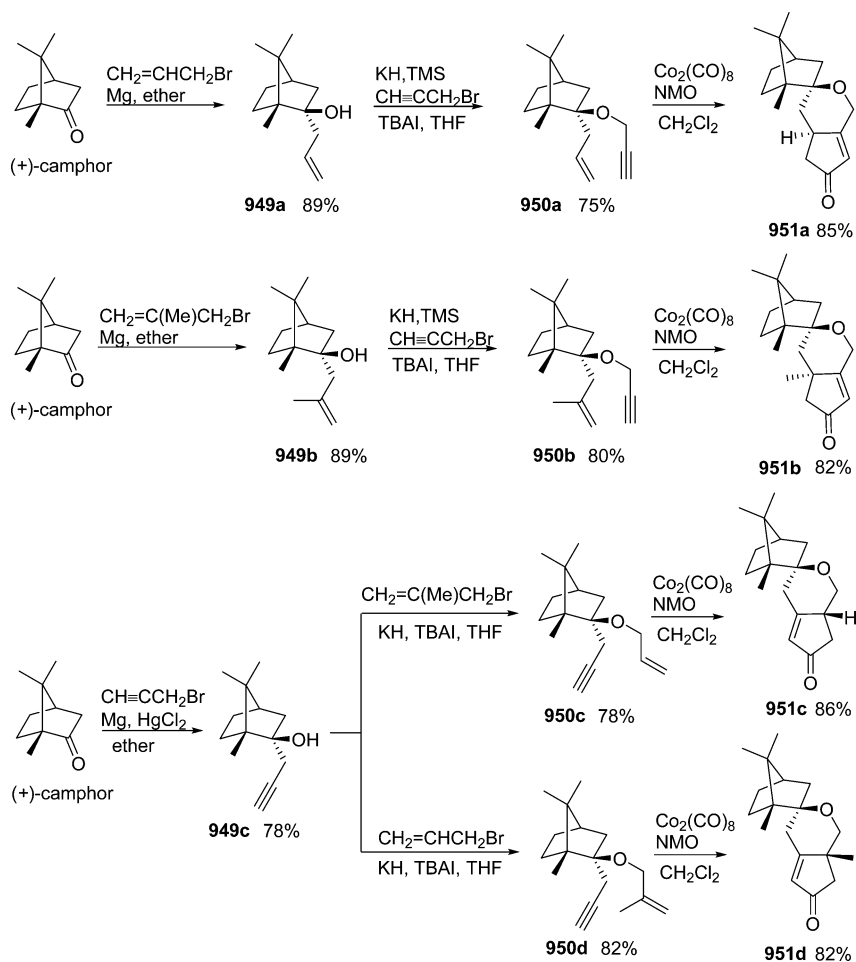


Scheme 232. Conversion of a Chiral Aldehyde into a Bicyclic Enone as a Step in the Synthesis of Marine Diterpenes Aberranes

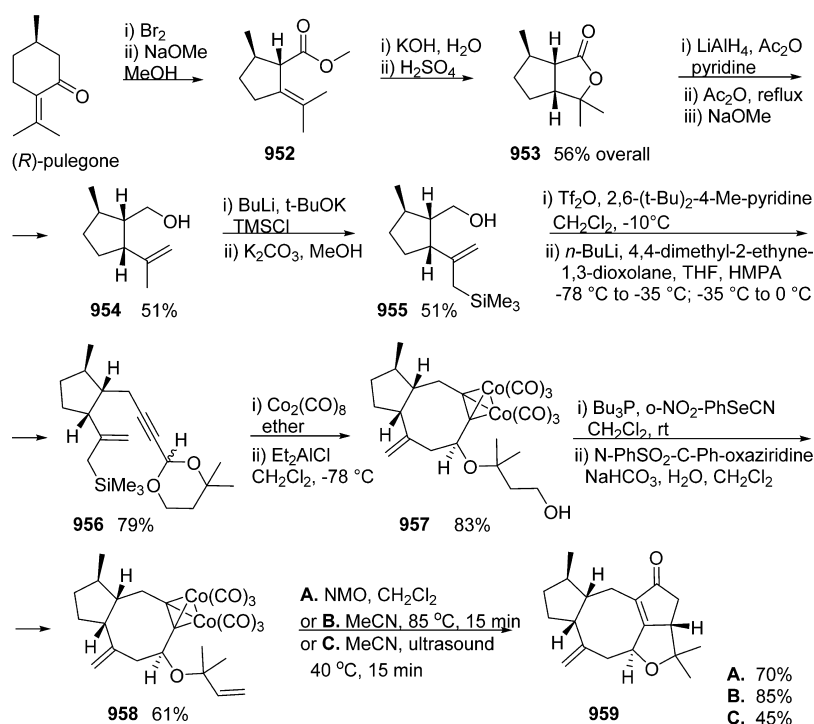
Scheme 233. Synthesis of Bicyclic Enone **948** from (1*R*)-(+)-Camphor

the diol and acetylation of the primary alcohol allowed for selective dehydration of the tertiary alcohol, which after saponification of the acetate yielded a primary alcohol **954** that was subjected to treatment with Schlosser's base, and after quenching the resulting dianion with chlorotrimethylsilane and hydrolysis of the silyl ether afforded allylsilane **955**. Coupling of the latter with a cyclic acetal was achieved under carefully

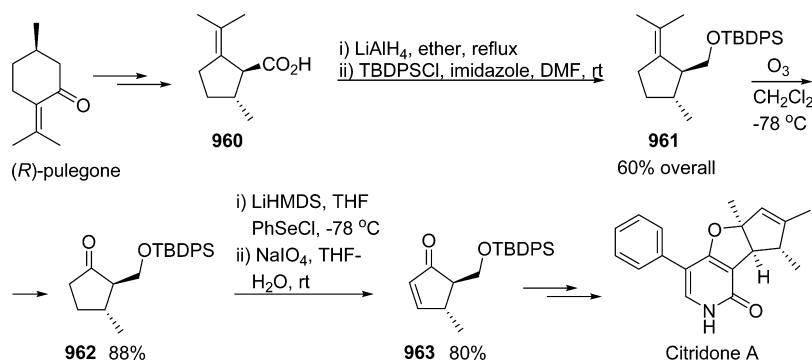
controlled conditions; activation of the alcohol of allylsilane **955** with trifluoromethanesulfonic anhydride in the presence of a hindered pyridine base afforded a triflate that was treated immediately with a lithium anion derived from the acetal to form the coupled product **956** as a diastereomeric mixture at the acetal carbon. Reaction with dicobalt octacarbonyl incorporated the alkyne into a dicobalt hexacarbonyl complex, which after treatment with a stoichiometric amount of diethylaluminum chloride afforded a single diastereomer of the fused 5–8 ring system of epoxydictymene as cobalt complex **957**. Lewis-acid-promoted Nicolaou reaction, displacement of the hydroxyl group by *o*-nitrophenyl selenocyanate and tributylphosphine, followed by oxidation and elimination of the selenoether, effected with the phenyloxaziridine of Davis under biphasic conditions, led to olefin **958**. Finally, cobalt-mediated intramolecular ring-closing of **958** by employing *N*-methylmorpholine *N*-oxide in the oxidative initiation of the cyclization furnished the desired enone **959** in excellent yield highly diastereoselectively (11:1 mixture of diastereomers at C12). All of the asymmetry in the synthesis derives from (*R*)-pulegone, and the final product, which is one of

Scheme 234. Stereoselective Synthesis of Spiro Cyclopentenone-pyran Products from (1*R*)-(+)-Camphor

Scheme 235. Preparation of a Complex Polycyclic Pentenone as a Step in a Stereoselective Total Synthesis of Natural Diterpene (+)-Epoxydictymene from (*R*)-Pulegone



Scheme 236. First Total Synthesis of the Natural Product Citridone A

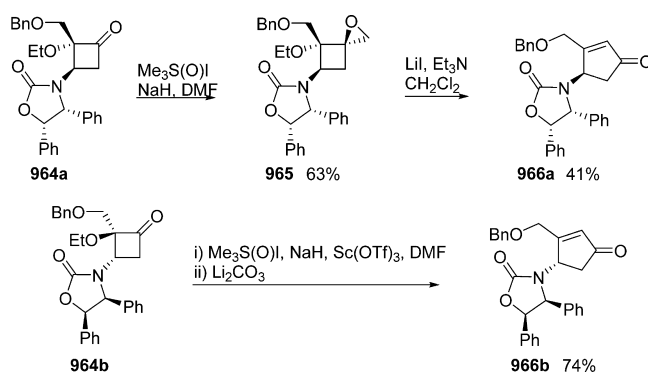


the four natural terpenes containing the strained *trans*-fused 5,5 ring system, was obtained in its natural configuration for all five asymmetric centers.

The same starting material has been exploited by Nagamitsu et al. in the first total synthesis of the natural product citridone A.⁴⁴³ The carboxylic acid functionality of **960** has been reduced and then protected in a one-pot protocol to give **961** in 60% overall yield from pulegone (Scheme 236). Ozonolysis of the latter furnished *trans*-cyclopentanone **962**, which was converted into **963** through a α -selenenylation/oxidation/elimination sequence.

A one-pot ring-expansion of cyclobutanones **964** to the corresponding cyclopentenones **966** has been achieved by Brown and Hegedus during the preparation of the (+)-carbovir and (+)-aristeromycin carbocyclic core (Scheme 237).⁴⁴⁴ **964a** has been converted into epoxide **965** as a single diastereoisomer by treatment with dimethylsulfoxonium methylide. The ring-expansion along with elimination of ethanol has been carried out with lithium iodide, and the cyclopentenone **966a** was isolated as a single isomer, but in poor yield. The isomeric cyclopentenone

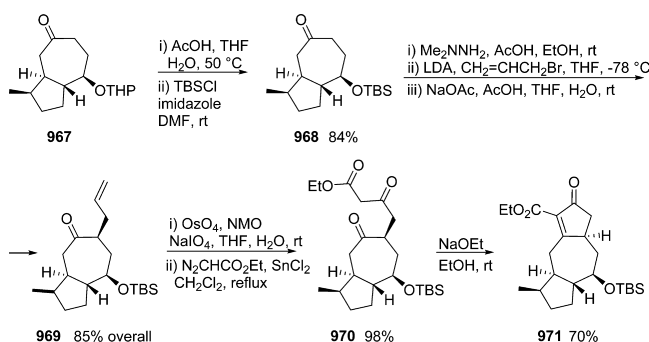
Scheme 237. One-Pot Ring-Expansion of Cyclobutanones to Cyclopentenones



966b has been obtained from **964b** by epoxidation in the presence of scandium triflate and ring expansion by lithium carbonate via a one-pot protocol in a considerably improved yield.

Kitamura et al. obtained the tricyclic enone **971**, the key intermediate in the synthesis of (\pm)-sordaricin, starting from bicyclodecanone **967** (Scheme 238).⁴⁴⁵ The tetrahydropyranyl

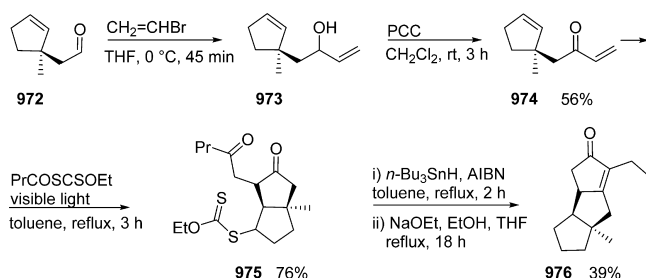
Scheme 238. Synthesis of a Tricyclic Enone, the Key (\pm)-Sordaricin Intermediate, from Bicyclodecanone



group of **967** was replaced with silyl protection by acid hydrolysis and protection with *tert*-butyldimethylsilyl chloride, and TBS ether **968** was then subjected to a stereoselective and regioselective allylation at C(3) via a three-step sequence: conversion to the *N,N*-dimethylhydrazone, allylation with allyl bromide, and hydrolysis to the ketone **969**. Dihydroxylation of the vinyl group by using osmium tetroxide, followed by sodium periodate-induced oxidative cleavage, provided the corresponding aldehyde, which was then converted into β -keto ester **970** by reaction with ethyl diazoacetate in the presence of tin chloride. The Knoevenagel cyclization of **970** with a catalytic amount of sodium ethoxide has furnished the tricyclic compound **971**.

The fused tricyclic enone **976**, which constitutes a structural motif in a number of natural products including the triquinane family of terpenes, was prepared by Briggs et al. by applying a tandem radical addition/cyclization reaction for the construction of the third ring (Scheme 239).⁴⁴⁶ The aldehyde **972** was

Scheme 239. Preparation of a Fused Tricyclic Enone, a Structural Motif in a Number of Natural Products



converted into diene **974** by Grignard reaction with vinyl magnesium bromide, followed by oxidation of **973** with pyridinium chlorochromate. A radical cascade then was carried out by irradiating a refluxing solution of the diene **974** and xanthate with visible light, followed by reduction of the formed xanthate **975** and aldol condensation. The enone **976**, possessing a [5.5.5]-fused ring skeleton, was obtained as a mixture of diastereoisomers.

Ishizaki et al. have reported the conversion of cyclohexenone **977** into tricyclic enone **985a**, which is a crucial intermediate in a formal total synthesis of the natural alkaloid (\pm)-magellanine.⁴⁴⁷ This synthesis was based on stereoselective Ireland–Claisen rearrangement of **980** and intramolecular Pauson–Khand

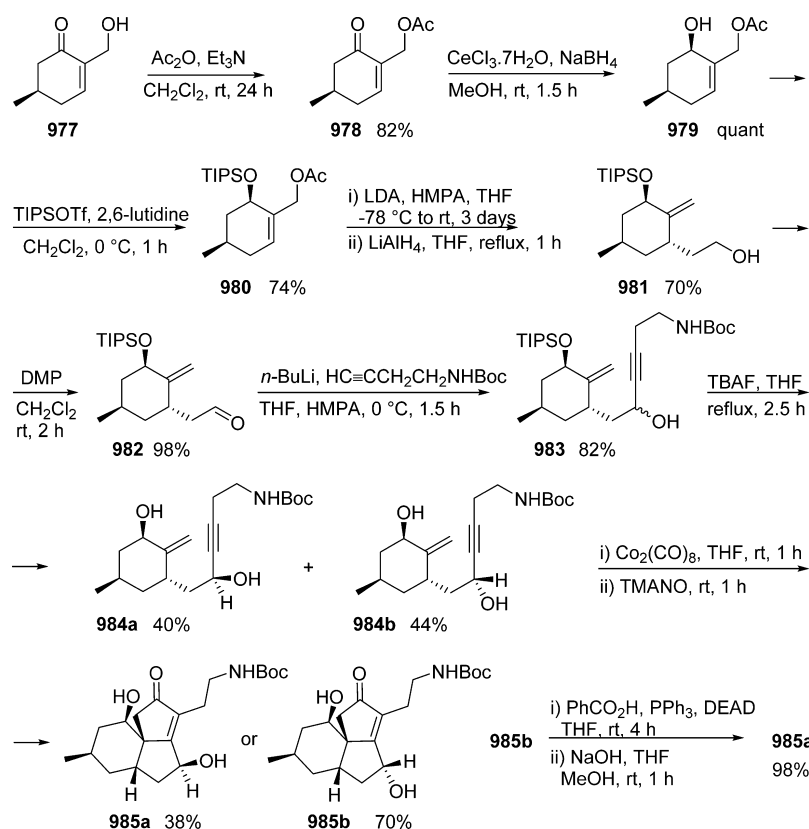
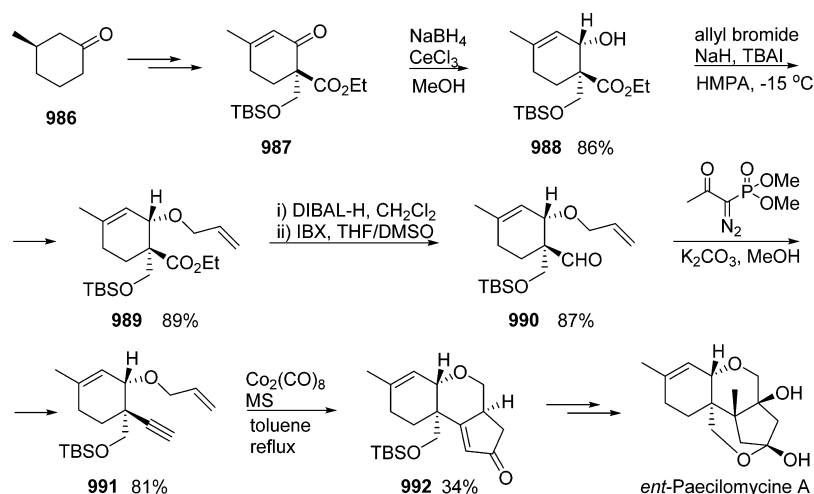
reaction of *exo*-cyclic enyne **984a** as key steps (Scheme 240). Thus, acetylation of **977** followed by stereoselective Luche reduction of **978** and silylation of **979** afforded TIPS ether **980**. Ireland–Claisen rearrangement of the latter and subsequent reduction furnished the alcohol **981** as a single isomer. Dess–Martin oxidation followed by reaction of **982** with *N*-Boc-protected lithium butynylamide to an inseparable diastereomeric mixture of alkynyl alcohol **983**, and then desilylation performed with TBAF, led to alcohols **984a** and **984b**, which were efficiently separated. PKR was performed by using trimethylamine *N*-oxide (TMANO), and the expected tricyclic enones **985a** and **985b** were obtained in quite different yields. This difference was explained by the interaction of hydroxyl group and side chain in the transition state of **984a**, resulting in a significant decrease of the yield. Additionally, **985b** was converted into **985a** in almost quantitative yield, because this isomer bore the required configuration for the further transformations.

An enantiodivergent formal synthesis of fungal tricothecane sesquiterpenoid paecilomycine A has been accomplished by Mehta et al.⁴⁴⁸ Enone **987**, derived from commercially available (*R*)-3-methylcyclohexanone **986**, was stereoselectively reduced under Luche conditions to furnish allylic alcohol **988**, which was protected as its allyl ether, reduced to a primary alcohol, and oxidized to aldehyde **990** (Scheme 241). The latter has been smoothly elaborated to enyne **991** by using the Ohira–Bestmann reagent, and then Pauson–Khand reaction afforded the key tricyclic intermediate **992**.

An enantioselective synthesis of (–)-methoxyestrone has been reported by Betík and Kotora.⁴⁴⁹ The tetracyclic steroid skeleton was built in five steps from chiral aldehyde **993** in good overall yield (Scheme 242). Iodide **994** was obtained as its *trans*-diastereoisomer and was reacted with 2,3-dibromopropene via initial formation of the corresponding organozinc reagent. The dehydrobromination of **995** was achieved quantitatively followed by methylation of the terminal triple bond of **996**. Finally, Pauson–Khand reaction of enyne **997** led to the desired tetracyclic enone **998** as a single stereoisomer.

Mehta and Shinde achieved the first total synthesis of a prototypical *seco*-prezizaane (+)-1S-minwanenone starting from the *endo*-tricyclic chiral synthon (+)-**999** (Scheme 243).²⁵ The choice of the starting platform was a key tactic as its well-established propensity toward reactivity on the *exo*-face due to inherent topological bias was to enable the stereoselective installation of the C₅, C₆ stereogenic centers in the early stages of the synthesis. Stereoselective allylation to *exo*-(+)-**1000** followed by copper(I)-mediated 1,4-addition of MeMgI, proceeding with excellent *exo*-face selectivity and in situ enolate capture, delivered (–)-**1001** as a single diastereomer. Quenching the lithium enolate generated from enol-TMS ether with MeI and stereoselective α -hydroxymethylation of (–)-**1002** from the *exo*-face delivered dimethylated alcohol (–)-**1003**, that is, the C₅ quaternary center, with requisite relative disposition with respect to C₆ was generated. Subsequent protection of the free hydroxyl group, removal of the norbornyl scaffold in (–)-**1004** through a facile retro Diels–Alder process, OsO₄–NaIO₄-mediated oxidative cleavage of the allyl group in (–)-**1005**, protection of aldehyde (–)-**1006** as acetal, and sequential catalytic hydrogenation and allylation of (–)-**1007** afforded the diastereomers (–)-**1008a** and (–)-**1008b**. The major isomer (–)-**1008a** was subjected to selective deprotection of the acetal moiety, chemo- and regioselective addition of MeLi to aldehyde (–)-**1009**, followed by oxidation with pyridinium chlorochromate, and intramolecular aldol condensation of (–)-**1010**, to provide

Scheme 240. Conversion of Cyclohexenone 977 into a Tricyclic Enone as a Step in Alkaloid Synthesis

Scheme 241. An Enantiodivergent Formal Synthesis of Fungal Tricothecane Sesquiterpenoid Paecilomycine A from (*R*)-3-Methylcyclohexanone

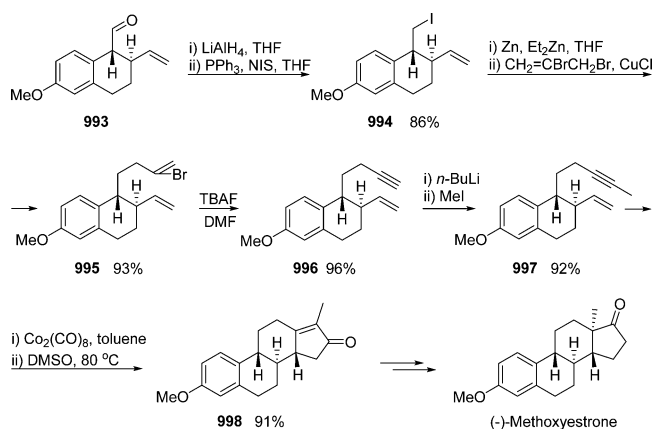
bicyclic enone (+)-**1011** as a single isomer. Its diastereomeric sibling (–)-**1008b** was converted into functionally embellished bicyclic enone (+)-**1013** by Wacker oxidation and aldol condensation.

Another cyclohexanone **1014** has been converted through a one-pot protocol into cyclopentenone **1015** by Cho et al., constituting a key step for the total synthesis of the nonpeptidyl neurotrophic modulator (±)-jiadifenin (Scheme 244).⁴⁵⁰ Thereby, conversion of the ester moiety of **1014** to β-ketophosphate, followed by intramolecular Horner–Wadsworth–Emmons reaction and global deprotection, led to bicyclic enone **1015** in high overall yield.

Pouységu et al. accomplished the transformation of the fungal metabolite wasabidenone B₁ (**1016**), the total synthesis of which was developed, into its naturally occurring congener (–)-wasabidenone B₀ (**1017**) via a thermally induced ring-contracting isomerization reaction (Scheme 245).⁴⁵¹

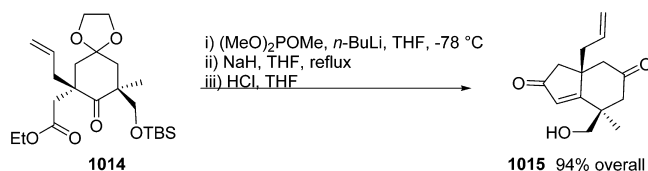
An Ag(I)-catalyzed ring-contractive rearrangement of enantiomerically pure diazo cyclohexenone **1018** containing two adjacent stereochemical centers has been developed by Zhao et al. (Scheme 246).⁴⁵² The alkylidene cyclopentenone **1019** was isolated in 75% yield with 99% ee, and it was suggested that the rearrangement occurred with retention of the stereochemistry at the migratory center.

Scheme 242. An Enantioselective Synthesis of (–)-Methoxyestron from Chiral Aldehyde

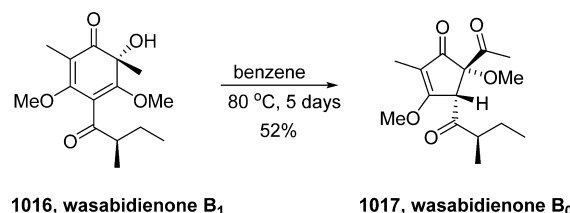


Photochemical rearrangement of α -santonin was studied near the middle of the 19th century by Barton et al.⁴⁵³ A sample of the compound was irradiated in a quartz flask with a bare mercury lamp in acetic acid/water solvent under reflux, and isophoto-santoic acid lactone **1020** was isolated in moderate yield (Scheme 247). The same protocol has been applied by Barbosa et al.⁴⁵⁴ for the preparation of a series of α -santonin derivatives with potential biological activities. The authors have also carried out the reaction in pure acetic acid and obtained the acetate **1021** in 32% yield. The latter recipe has been applied as a step in the synthesis of iso-*seco*-tanaphthalides,⁴⁵⁵ arteminolides,⁴⁵⁶ and

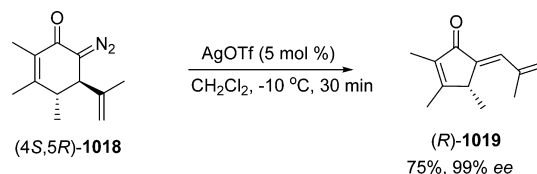
Scheme 244. Synthesis of Chiral Tricyclic Enone 1015



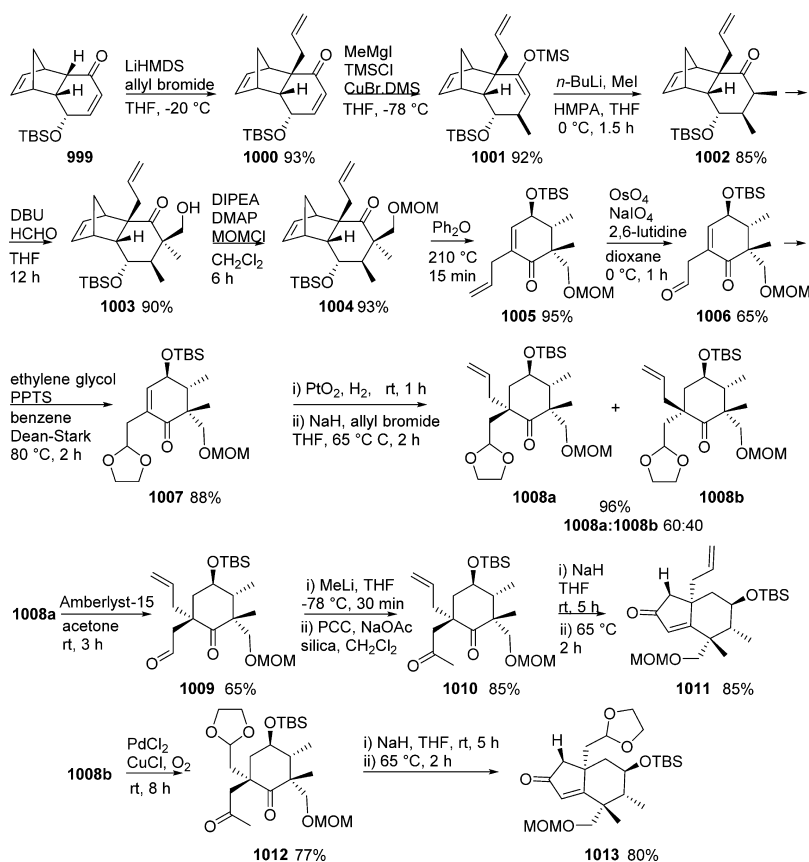
Scheme 245. Transformation of the Fungal Metabolite Wasabidenone B₁ into Its Naturally Occurring Congener (–)-Wasabidenone B₀

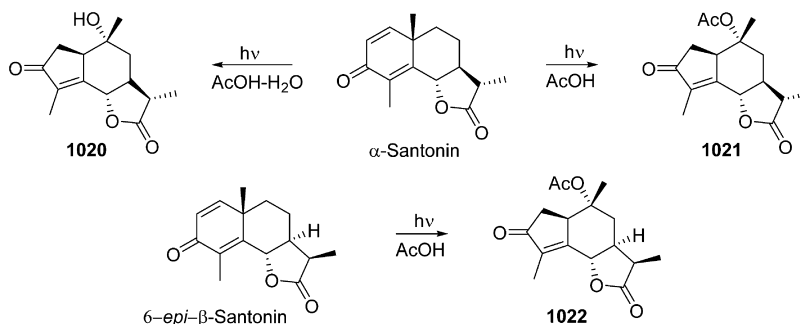


Scheme 246. An Ag(I)-Catalyzed Ring-Contractive Rearrangement of Enantiomerically Pure Diazo Cyclohexenone into Alkylidene Cyclopentenone

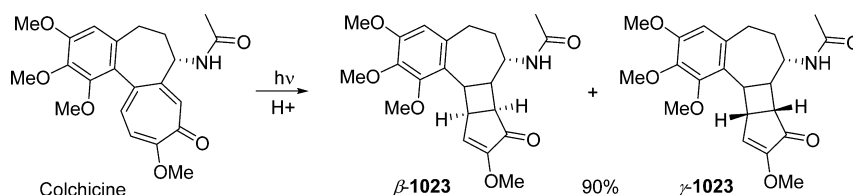


Scheme 243. Steps in the First Total Synthesis of a Prototypical *seco*-Prezizaane (+)-1S-Minwanenone Starting from the *endo*-Tricyclic Chiral Synthon (+)-999

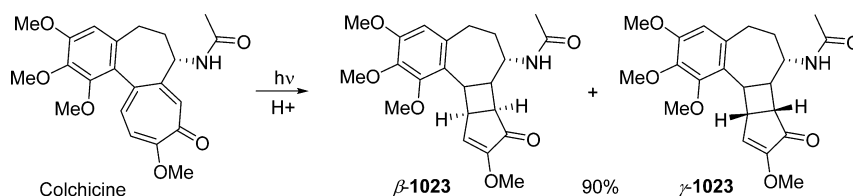


Scheme 247. Photochemical Rearrangement of α -Santonin

Scheme 248. Photochemical Rearrangement of Colchicine to Lumicolchicine



Scheme 249. Synthesis of Regioisomeric Enones Possessing the Cyclic Core of Guaiane Sesquiterpene Englerin A



(+)-absinthin,⁴⁵⁷ while Metz et al. transformed 6-*epi*- β -santonin into the isomeric tricyclic cyclopentenone **1022** during an enantioselective synthesis of 3 α -hydroxy-15-ripperten.⁴⁵⁸

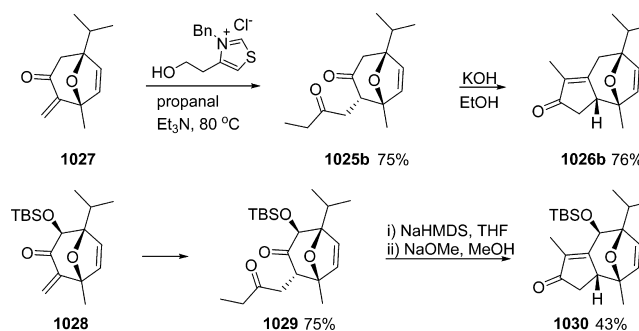
Ghanem et al. achieved the photochemical rearrangement of colchicine to lumicolchicine **1023** under acidic conditions and found that the yield and the rate constant were affected by the irradiation wavelength, solvent, acidity, and ionic strength (Scheme 248).⁴⁵⁹

Sun et al. obtained regioisomeric enones **1026** possessing the cyclic core of guaiane sesquiterpene englerin A (Scheme 249).⁴⁶⁰ The authors converted a 2.4:1 mixture of **1024a** and **1024b** into the corresponding diketones **1025** by Grignard reaction followed by oxidation with Dess–Martin periodinane, which was subjected to intramolecular aldol condensation to afford **1026** as an easily separable mixture.

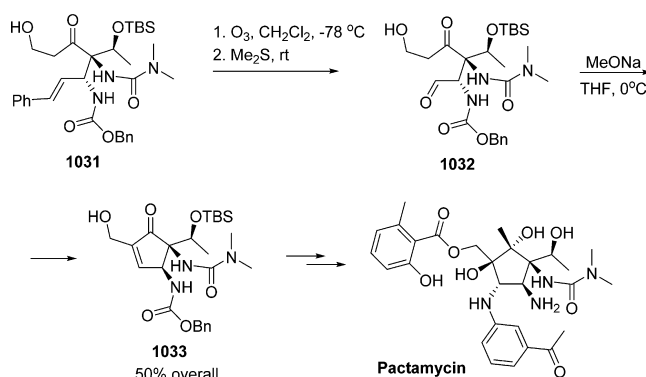
During the development of a formal synthesis of the same alkaloid, Theodorakis et al.⁴⁶¹ prepared the dione **1025b** by treating dienone **1027** with propanal and an imidazolium salt under Stetter conditions (Scheme 250). The authors further extended the synthetic strategy toward a compound with additional hydroxyl functionality and found that the aldol step with potassium hydroxide resulted only in deprotection of silyl ether, while treatment with sodium hexamethyldisilazide led to an aldol product, which underwent sequential dehydration to **1030** with sodium methoxide.

Malinowski et al. reported a total synthesis of the natural product pactamycin displaying antitumor, antimicrobial, antiviral, and antiprotazoal properties. One-pot alkene ozonolysis and intramolecular aldol condensation of β -hydroxy ketone **1032** were achieved in 50% overall yield (Scheme 251).⁴⁶² The five-membered core structure **1033** was obtained with correct

Scheme 250. Steps in the Formal Synthesis of Guaiane Sesquiterpene Englerin A



Scheme 251. A Total Synthesis of the Natural Product Pactamycin



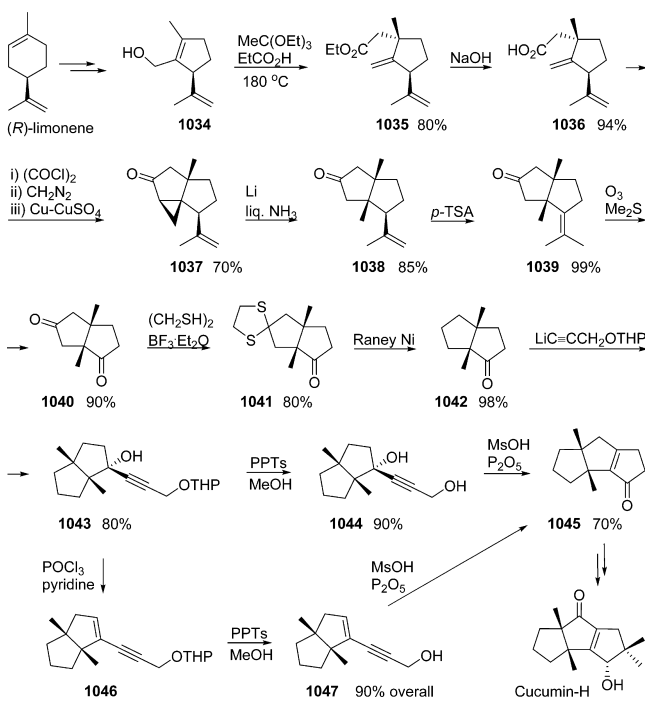
stereochemistry of the configurationally labile C-2 center; that is, the configuration was fully inverted under basic conditions.

5.3. Chiral Unsaturated Hydrocarbons

Chiral unsaturated hydrocarbons are also widely applied in the cyclopentenone synthesis, mainly as key intermediates for ring-closing metathesis and Pauson–Khand reactions. The protocols are based on the transformation of easily available synthetic starting platforms in general, whereas examples of the conversion of natural sources are quite limited.

The first enantiospecific total synthesis of the ceratopane sesquiterpene cucumin-H was achieved by Srikrishna and Dethle starting from (*R*)-limonene.⁴⁶³ Thermal activation of allyl alcohol **1034** with triethyl *ortho*-acetate and a catalytic amount of propionic acid furnished the γ,δ -unsaturated ester **1035**, which was hydrolyzed and subsequently treated with oxalyl chloride, diazomethane, and copper under irradiation with a tungsten lamp to afford regio- and stereospecifically the tricyclic ketone **1037** possessing two new chiral centers (Scheme 252). The latter

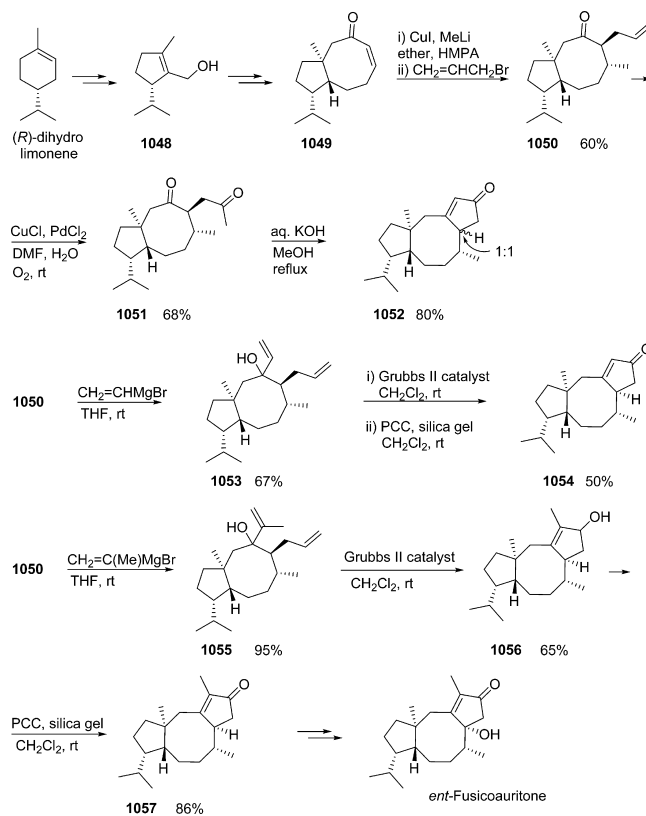
Scheme 252. First Enantiospecific Total Synthesis of the Ceratopane Sesquiterpene Cucumin-H Starting from (*R*)-Limonene



was converted into diquinane **1038** and isomerized to enone **1039**. Ozonolysis of the isopropylidene moiety followed by reductive workup and regioselective deoxygenation of **1040** via the thioketal **1041** afforded the bicyclic ketone **1042** in excellent overall yield. The annulation of the third cyclopentane ring has been accomplished by a modified Nazarov reaction, subsequent conversion to **1043**, removal of the protective group, and ring closure with excess of methanesulfonic acid and phosphorus pentoxide to provide triquinane enone **1045**.

A formal total synthesis of 5–8–5 tricyclic diterpene *ent*-fusicoauritone was accomplished by Srikrishna and Nagaraju.⁴⁶⁴ (*R*)-Dihydrolimonene was successively converted through a multistep protocol into cyclopentene **1048** and bicyclic enone **1049** (Scheme 253). The key intermediate **1050** has been obtained in a highly stereoselective manner by treatment with

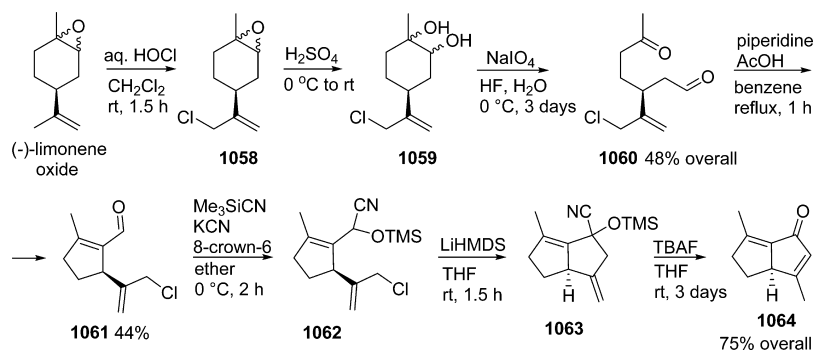
Scheme 253. A Formal Total Synthesis of 5–8–5 Tricyclic Diterpene *ent*-Fusicoauritone from (*R*)-Dihydrolimonene



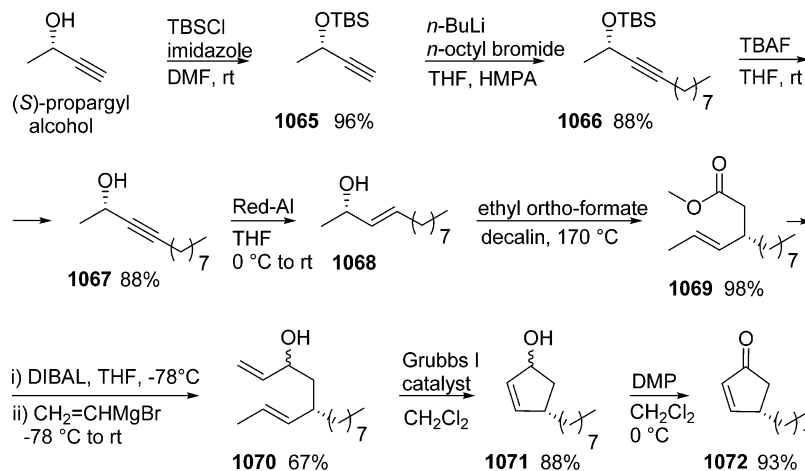
lithium dimethylcopper and then allyl bromide and was further subjected to generation of the final ring by a range of reaction schemes. Wacker oxidation with cuprous chloride and palladium chloride in oxygen atmosphere followed by intramolecular aldol condensation of dione **1051** afforded the tricyclic enone norfusicoaurone **1052** as a 1:1 epimeric mixture. The lack of stereoselectivity was overridden by applying a Grignard reaction with vinylmagnesium bromide and RCM of **1053** with Grubbs' second generation catalyst, and the product **1054** was isolated as a single isomer. The strategy has been further extended to the completion of the synthesis of fusicoauritone. Thereby, the vinyated ketone **1050** was subsequently converted into diene **1055** and then enol **1056**, which was finally oxidized to the desired tricyclic enone **1057**.

Pisoni et al. developed an efficient stereoselective route toward dienone **1064**, a versatile building block for the synthesis of natural and nonnatural chiral terpenoids bearing a bicyclooctane framework, starting from (–)-limonene oxide (Scheme 254).⁴⁶⁵ Subsequent reaction with hypochlorous acid, acid-catalyzed hydrolysis of epoxide function of **1058**, and oxidative cleavage of diol **1059** with sodium metaperiodate afforded the enantiomerically pure keto aldehyde (–)-**1060**, which was subjected to aldol condensation with piperidine–acetic acid to form the unstable conjugated cyclopentane carbaldehyde **1061**. The latter was cleanly converted into the cyanohydrin TMS ether **1062** by addition of trimethylsilyl cyanide in the presence of KCN/18-crown-6 complex, which was subjected to intramolecular alkylation with lithium hexamethyldisilazide followed by treatment of **1063** with tetra-*n*-butylammonium fluoride, to form (–)-(*R*)-**1064** with the endocyclic C3–C4 double bond as a single isomer in good overall yield.

Scheme 254. An Efficient Stereoselective Route to Dienone 1064 from (–)-Limonene Oxide



Scheme 255. Synthesis of Cyclopentenone 1072, a Key Prostaglandin Intermediate

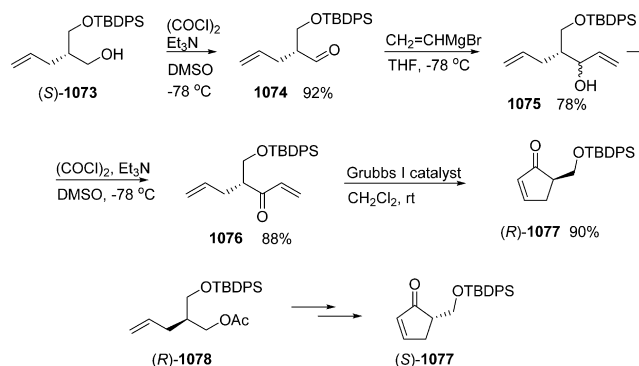


Cyclopentenone **1072**, a key intermediate in the synthesis of prostaglandins, has been obtained from (S)-propargyl alcohol by Weaving et al. (Scheme 255).⁴⁶⁶ Diene **1070** was obtained by successive silylation, alkylation of alkyne **1065** with octyl bromide, cleavage of the silyl protective group in **1066**, reduction of the triple bond in **1067** with Red-Al, stereoselective Claisen reaction of *E*-allylic alcohol **1068** with ethyl-*ortho*-formate, and one-pot hydride reduction of methyl ester **1069** and treatment with vinyl magnesium bromide. The key step, annelation to cyclopentenol **1071**, was performed by Grubbs I-catalyzed RCM of diene **1070**. After Dess–Martin periodinane oxidation of **1071** through a one-pot protocol, cyclopentenone **1072** was obtained in excellent yield and correct stereochemistry.

Nanda et al. have achieved an efficient four-step conversion of protected diol **1073** into hydroxylated cyclopentenone **1077** as an intermediate in the synthesis of novel natural carbasugar analogues (Scheme 256).⁴⁶⁷ An (S)-diol was subsequently subjected to Swern oxidation, Grignard reaction of resulting aldehyde **1074**, further Swern oxidation, and finally RCM with Grubbs' second generation catalyst to provide the desired (R)-cyclopentenone with additional hydroxyl functionality in good overall yield. The same sequence has been applied to prepare the (S)-isomer from acetate (R)-**1078**.

Enantioisomeric protected 4-hydroxycyclopentenones **1081** have been obtained by Singh et al. by subsequent Grubbs I-catalyzed RCM of diene **1079** and oxidation of **1080** with pyridinium chlorochromate (Scheme 257). The protocol is scalable for laboratory usage and provides access to multiple analogues in either enantiomeric series.

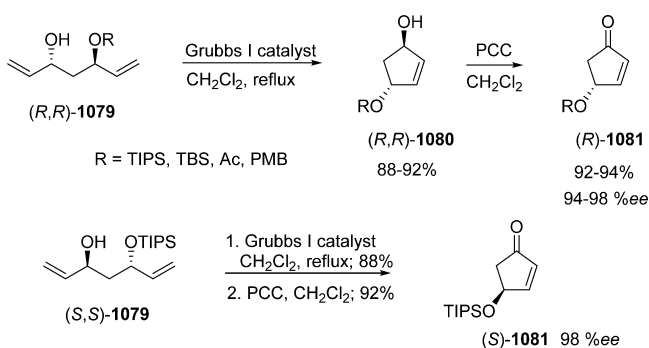
Scheme 256. An Efficient Four-Step Conversion of a Protected Diol into a Hydroxylated Cyclopentenone



The highly functionalized cyclopentenone **1087** has been synthesized by Qing et al. from alkene **1082** (Scheme 258).⁴⁶⁸ As a key step, silicon-induced Reformatsky–Claisen rearrangement of allyl bromofluoroacetate **1083** has been accomplished. The resulting ester **1084** has been further transformed into Weinreb amide **1085**, which was subjected to Grignard reaction and then to olefin metathesis with Grubbs' second generation catalyst.

A series of furyl-substituted cyclopentenone-pyran products **1094** and **1095** have been prepared by Sezer et al. from 1-furyl-(S)-allyl **1088** and propargyl **1090** alcohols or the corresponding acetates **1089** and **1091** with (R)-configuration (Scheme 259).⁴⁶⁹ The intramolecular PKR of enynes **1092** and **1093**, obtained by *O*-alkylation, has been achieved efficiently and with

Scheme 257. Synthesis of Enantioisomeric Protected 4-Hydroxycyclopentenones 1081



high conformational control over the remote stereocenter formed on the cyclopentenone–pyran ring system.

This protocol was subsequently applied to the preparation of the corresponding 2-thiophenyl and 2-pyridyl analogues of **1094** and **1095**, and, again, the conformationally most stable diastereomeric cyclopenta[*c*]pyran ring systems were obtained as the sole products.⁴⁷⁰ In an attempt to explore the diastereoselectivity in the construction of cyclopentenone–furan ring systems, the authors constructed the enyne systems (*S*)-**1097a–c** on an enantiomerically enriched allylic alcohol (*S*)-**1096a–c** backbone by *O*-propargylation with propargyl bromide in the presence of sodium hydride and tetrabutylammonium iodide, which were subsequently subjected to intramolecular PKR (Scheme 260). In contrast to the cyclopentenone–pyran-fused ring systems, the resulting cyclopentenone–furan-fused frameworks were isolated as *cis:trans* isomeric mixtures with acceptable diastereoselectivities. The role of the conformational control of pyrans was found to have a drastic influence on the diastereoselectivity in comparison with the furan ring systems, which was suggested to be due to the reduced conformational effect of the furan rings on the diastereoselectivity as compared to the more favored chair conformation of the pyran rings.

The analogous cyclopenta[*c*]tetrahydropyridines **1101**, **1104**, and **1107** have been prepared by Tanyeli et al. in a stereoselective manner by applying Pauson–Khand reactions of enynes **1100**, **1103**, and **1106**, respectively, to construct the bicyclic skeleton (Scheme 261).⁴⁷¹

A series of substituted cyclopentenones have been obtained by Shi et al.⁴⁷² on the basis of gold(I)-catalyzed Rautenstrauch

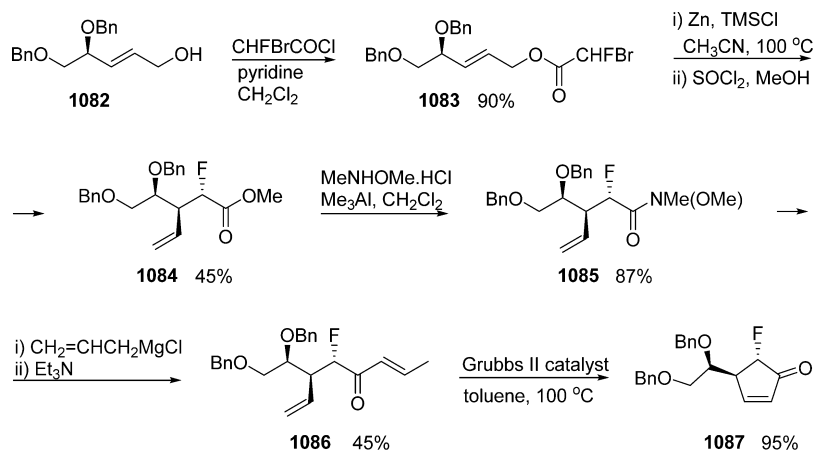
rearrangement of propargyl pivalates (Scheme 262). Initially, a 12:1 diastereomeric mixture of **1108**, derived from (*S*)-(–)-perillaldehyde, has been subjected to triphenylphosphine gold triflate-catalyzed isomerization, and bicyclic enone **1109** was obtained as a 7:1 mixture of diastereomers, while a 1:1 mixture was isolated from **1108**. It was suggested that the stereochemistry of the starting ester influenced that of the product cyclopentenone. To examine the chirality transfer in the cyclization, the authors prepared a series of enantioenriched pivalates **1110**, which were rearranged under the standard conditions to give the products with low selectivity. The latter was overridden by switching the counterion from triflate to hexafluoroantimonate and lowering the temperature, resulting in the formation of cyclopentenones **1111** with excellent chirality transfer. On the basis of these results, it has been assumed that a mechanism involving C–C bond formation prior to scission of the stereogenic C–O bond was operative. The presented protocols are tolerant of variable substitution at the acetylenic and olefinic positions, thus providing access to a wide range of cyclopentenones under exceptionally mild conditions.

Moriarty et al. developed a general solution to the synthesis of biologically important stable prostacyclin PGI₂ analogues by stereoselective intramolecular PKR.⁴⁷³ The key tricyclic enone **1113** was obtained by cobalt-mediated closure of enyne **1112** in high yield and almost 100% chiral induction (Scheme 263). The transformation was performed both in its stoichiometric and in its catalytic versions, and the same conversions and stereoselectivities were observed. The authors suggested that the results must be mechanistically controlled with steric effects being determinant.

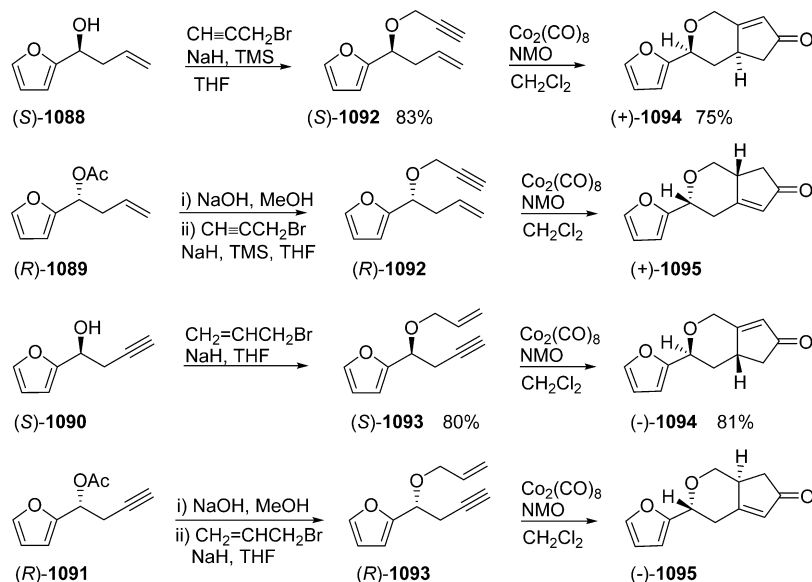
Chiral cyclopentenone **1117** has been prepared by Urabe et al.⁴⁷⁴ from propargyl alcohol-derived allene **1114** on the basis of an intramolecular titanium(II)-mediated allenyne cyclization (Scheme 264). Treatment of **1114** with (η^2 -propene)Ti(OPr-*i*)₂, prepared in situ from Ti(OPr-*i*)₄ and *i*-PrMgCl, followed by exposure to carbon monoxide and acidic workup, led directly to the optically active bicyclic ketone **1117**, and thus the axial chirality of the allene was transferred to a newly formed stereogenic center. It was suggested that **1117** was generated from rearrangement of transient oxa(titana)cyclopropane **1115** to titanium homoenolate equivalent **1116**.

Similarly, the transfer of chirality from a chiral nonracemic propargyl alcohol-derived allene **1120** to an α -alkylidene cyclopentenone **1121** has been successfully effected by

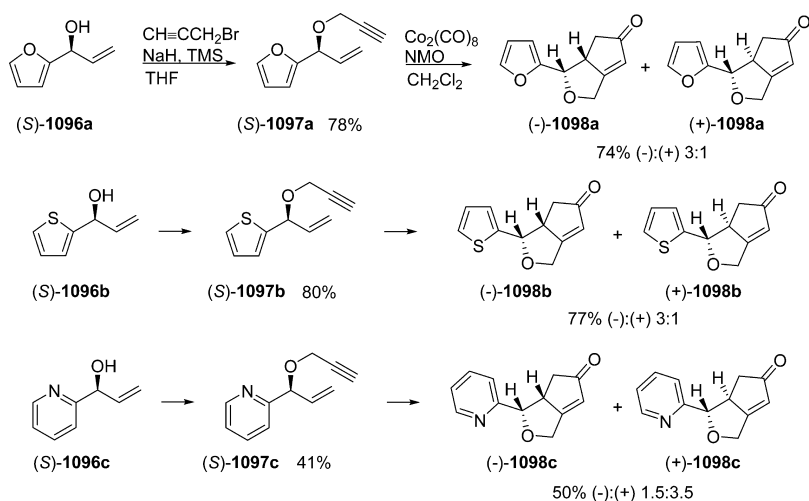
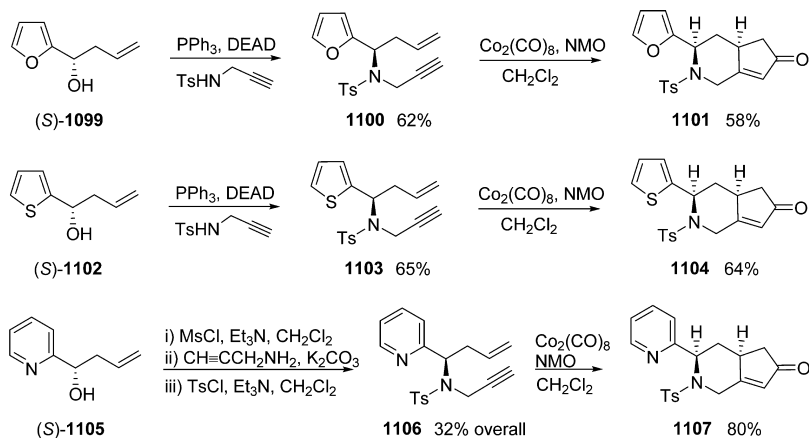
Scheme 258. Preparation of Highly Functionalized Cyclopentenone 1087 from an Alkene



Scheme 259. Synthesis of a Series of Furyl-Substituted Cyclopentenone-pyran Products

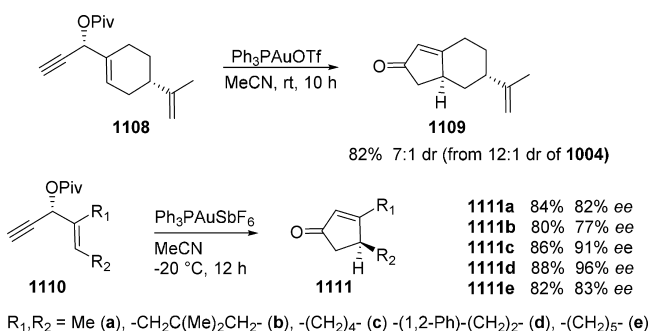
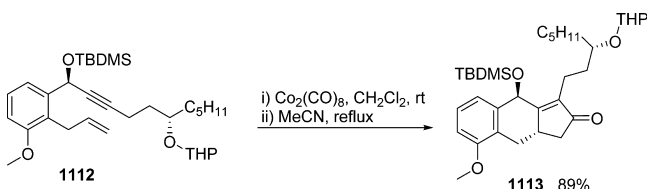


Scheme 260. Synthesis of a Series of 2-Furyl-, 2-Thiophenyl-, and 2-Pyridyl-Substituted Cyclopentenone-pyran Products

Scheme 261. Preparation of Cyclopent[*c*]tetrahydropyridines

Brummond et al. (Scheme 265).⁴⁷⁵ Thereby, chiral allene **1120**, obtained by consecutive mesylation and addition of the organocopper species, prepared from 5-(trimethylsilyl)-4-pentynylmagnesium chloride, lithium bromide, and copper

bromide, to the propargyl mesylate **1119**, has been subjected to zirconium-mediated PKR, and enone **1121** was isolated in low yield and good selectivity. Attempts to improve the facial selectivity by using larger ligands on the metal (Cp^* or indene)

Scheme 262. Gold(I)-Catalyzed Rautenstrauch Rearrangement of Propargyl Pivalates**Scheme 263. A General Solution to the Synthesis of Biologically Important Stable Prostacyclin PGI₂ Analogues**

have been made, but neither of these zirconium complexes have given rise to cycloadducts. From the other side, allenyne **1123**, possessing a dimethylphenylsilyl (DPS) moiety on the terminus of the allene, obtained from removal of trimethylsilyl moiety of **1122** in basic conditions, has been subjected to molybdenum-mediated cycloaddition conditions, and an 8:1 *E/Z* mixture of α -silylidene cyclopentenones **1124** and **1125** was isolated in high combined yield. (*E*)-Cyclopentenone **1124**, resulting from cycloaddition from the least hindered face, was obtained in excellent enantioselectivity, that is, with complete transfer of chirality from the allene to the product. In contrast, the (*Z*)- α -silylidene cyclopentenone **1125** was formed with moderate selectivity, only 63% ee. It has been postulated that the loss in enantiomeric purity was possibly a result of an isomerization of the (*E*)- α -silylidene cyclopentenone to the *Z*-isomer during the purification process.

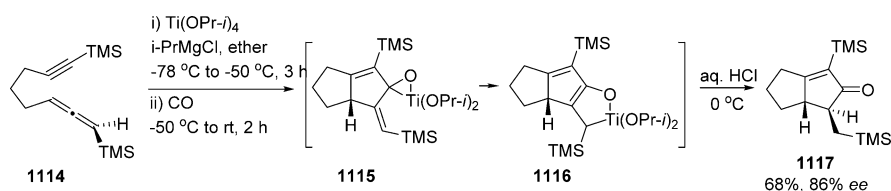
Khan et al. developed a short and stereoselective approach to polyhydroxylated cyclopentenols from tetrabromonorbonyl derivatives (Scheme 266).⁴⁷⁶ Initially **1126** was oxidized to the corresponding α -diketone **1127** followed by alkaline peroxide cleavage reaction, and bromolactone **1128** was obtained as a single regioisomer. The polyhydroxylated cyclopentanoid derivative **1129**, an advanced intermediate of pentenomycin **1130**, possessing the required C-5 tertiary center, was obtained by two protocols: hydrodebromination of the bridged lactone **1128** by radical reaction, followed by reduction of the resulting bicyclic lactone, or slightly less effective direct hydride reduction of **1128**. The enone moiety has been simply obtained by treating **1129** with Amberlyst-15, whereby all of the three desired

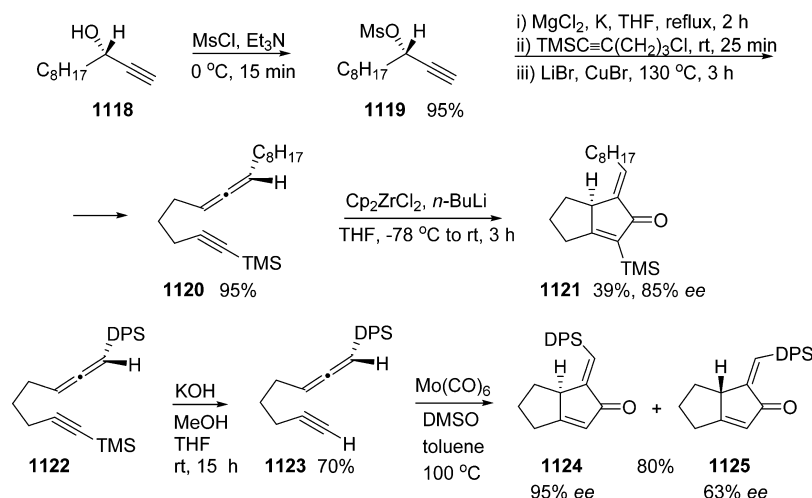
reactions, protection of the vicinal diol as an acetonide, deprotection of the dimethyl acetal, and elimination of the ethoxy substituent, were accomplished in a single pot, and pentenomycin **1130** was isolated in good overall yield. To install a hydroxyl group at C-4, the protocol was applied to the carbonate-protected *endo*-adduct **1131**, and the highly oxygenated cyclopentanoid **1136**, containing all of the vital features of pentenomycin at C-1, C-4, and C-5, was obtained in a stereoselective manner. Treatment with Amberlyst, proceeding through four subsequent reactions in a single pot, protection of the vicinal diol, acetonide deprotection, deprotection of the dimethyl acetal, and elimination of the hydroxy functionality furnished 2-hydroxymethylpentenomycin derivatives **1137** and **1138** as an easily separable mixture.

Ishizaki et al. examined the intramolecular PKR of various alkynyl *exo*-cyclic olefins, including several chiral nonracemic examples **1139**–**1142** (Scheme 267).⁴⁷⁷ The reaction conditions were varied, and the angular 6–5–5- and 5–5–5-type tricyclic skeletons **1143**–**1146**, possessing continuous quaternary centers, were constructed in good to high yields. It was found that while trimethylamine *N*-oxide (TMANO) in refluxing benzene was the solely effective method for the construction of **1144** and **1145** and the most efficient route to **1143**; the conversion of ester-substituted enyne **1142** was successful only when performing the reaction in refluxing benzene without *N*-oxide or when treated with NMO at room temperature.

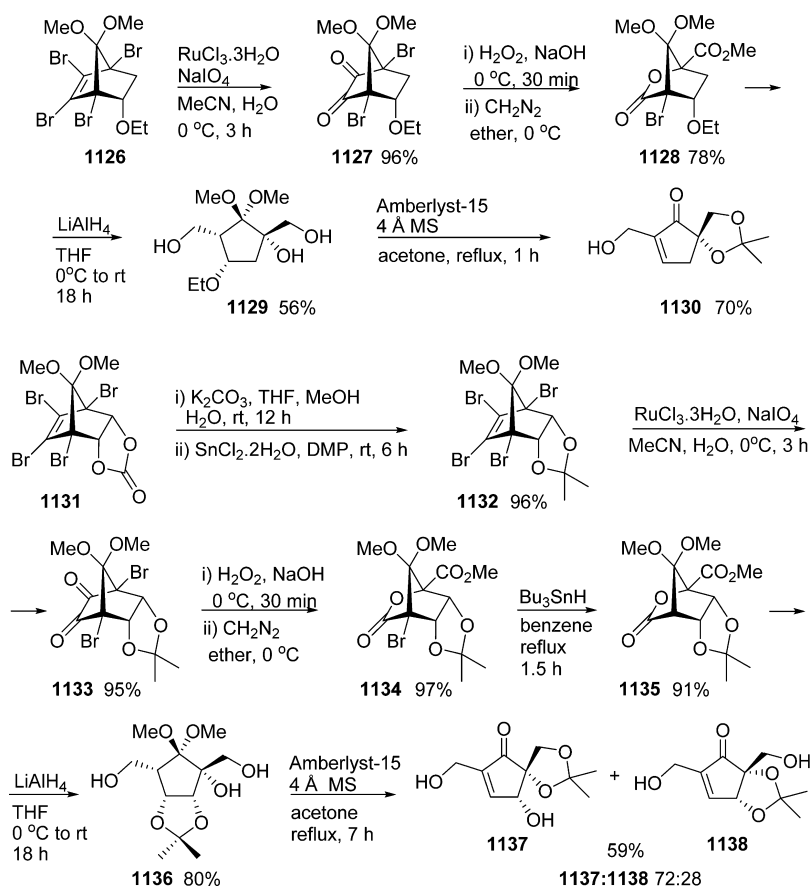
Similarly, the tricyclic product **1148** has been prepared by Stoltz et al. via Pauson–Khand reaction of enyne **1147** in the presence of dimethyl sulfoxide (Scheme 268).⁴⁷⁸

Highly efficient chirality transfer from an allene to tetrahedral carbon has been achieved by Hu et al. during the course of a modified Nazarov cyclization (Scheme 269).⁴⁷⁹ Exposure of (–)-**1149** to vinyl lithium species **1155**, followed by aqueous workup, led to *Z*-cyclopentenone (+)-**1151** as the major product, along with an impurity of *E*-cyclopentenone (–)-**1151**. It was shown that the minor isomer was formed primarily from the disfavored conrotation rather than from *Z* to *E* isomerization of (+)-**1151**, but some *Z* to *E* isomerization had taken place, possibly during workup, as indicated by the lower ee of (–)-**1151**. These results have demonstrated that axial-to-tetrahedral transfer of chirality occurred, but no information was provided for the direction in which this had occurred. The transformation was further performed with (+)-**1150**, and the *Z* isomer (–)-**1152** was isolated with greater than 95% chirality transfer. The absence of the byproduct as well as the greater optical purity of **1152** as compared to **1151**, that is, the difference in the level of chirality transfer between **1150** and **1149**, suggested a steric origin for the torquoselectivity of the process. Levorotatory morpholino amide (–)-**1150** reacted with *p*-bromophenyllithium to give crystalline phenone (–)-**1153** suitable for the crystallographic determination of the absolute stereochemistry of the allene, which was exposed to **1155** followed by cyclization of the resultant diastereomeric mixture of

Scheme 264. An Intramolecular Titanium(II)-Mediated Allenyne Cyclization

Scheme 265. Transfer of Chirality from Chiral Nonracemic Propargyl Alcohol-Derived Allenes to α -Alkylidene Cyclopentenones

Scheme 266. A Short and Stereoselective Approach to Polyhydroxylated Cyclopentenols from Tetrabromonorbonyl Derivatives



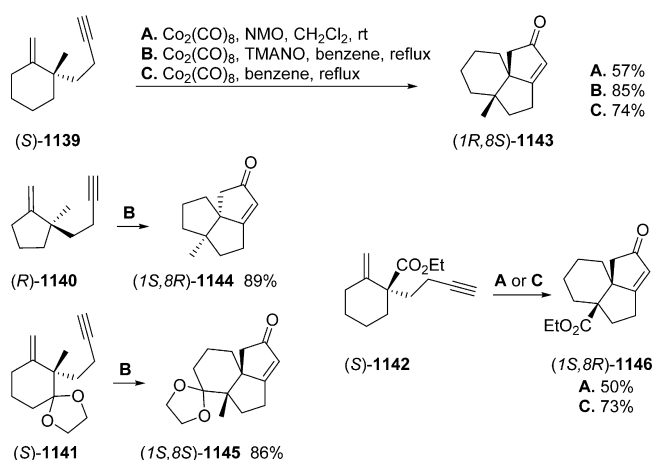
tertiary alcohols and *Z* to *E* isomerization to afford (–)-**1154** with chirality transfer above 90%, which indicated that both tertiary alcohols led to the same intermediate cation. Thereby, the authors have shown that the stereochemical outcome can be predicted according to a conrotation in which the distal group on the allene rotates away from the alkene.

A highly enantioselective Pauson–Khand-type reaction has been achieved by Son et al. in the presence of heterogeneous cobalt on charcoal as catalyst (Scheme 270).¹⁶² As a first series, the reaction of enynes **1156**, generated from the corresponding propargyl malonates, has been achieved in quite harsh conditions

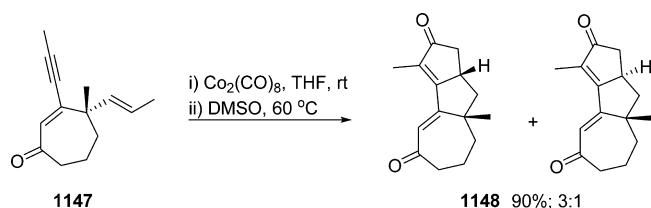
without racemization, and the bicyclic enones **1157** were obtained in high yields with high ee values. It was shown that the enantiomeric purity of the product depends upon the optical purity of the enyne. The asymmetric carbonylative cyclization has been further extended toward cyclic enynes **1158**, and the corresponding tricyclic enones **1159** were obtained under the same conditions in high yields but with variable selectivity depending on the ring size; the ee values decreased with increasing ring size.

Similarly, Thornton and Burnell subjected enyne **1160**, possessing ketone functionality on the ring, to PKR cyclization

Scheme 267. Intramolecular Pauson–Khand Reaction of Alkynyl *exo*-Cyclic Olefins



Scheme 268. Synthesis of Tricyclic Enones 1148



(Scheme 271).⁴⁸⁰ The conditions were varied, and it was found that trimethylamine oxide was the best promoter to achieve 1161. The authors accomplished the transformation with an enyne containing an unsaturated carbon chain with *Z*-configuration at the terminus of alkyne (1162), but the target cyclopentenone 1163 was isolated in very poor yield. The most robust substrate, 1164, with an *E*-double bond was obtained by Sonogashira coupling. Pauson–Khand reaction of the compound was successful, and it was observed that isomerization of the double bond occurred during the cyclization; *E*-1166 and *Z*-1166 were formed in a 1:3 ratio. In an attempt to limit the participation of the terminal oxygen, the authors inserted a bulky substituent. The PKR of enyne 1165 generated a reduced

amount of the *Z*-product, but the degree of isomerization was still surprising.

An intramolecular Pauson–Khand reaction of cyclopropenyl 1169 has been used by Pallerla and Fox to establish the quaternary center for the synthesis of triquinane (–)-pentale-*nene*, the enantiomer of the natural product (Scheme 272).⁴⁸¹ Thus, the enyne 1169, obtained by *C*-silylation of 1168, has been subjected to PKR by using tetramethylthiourea (TMTU) as promoter, and the key intermediate (–)-1170 was obtained along with its (+)-isomer as a separable mixture.

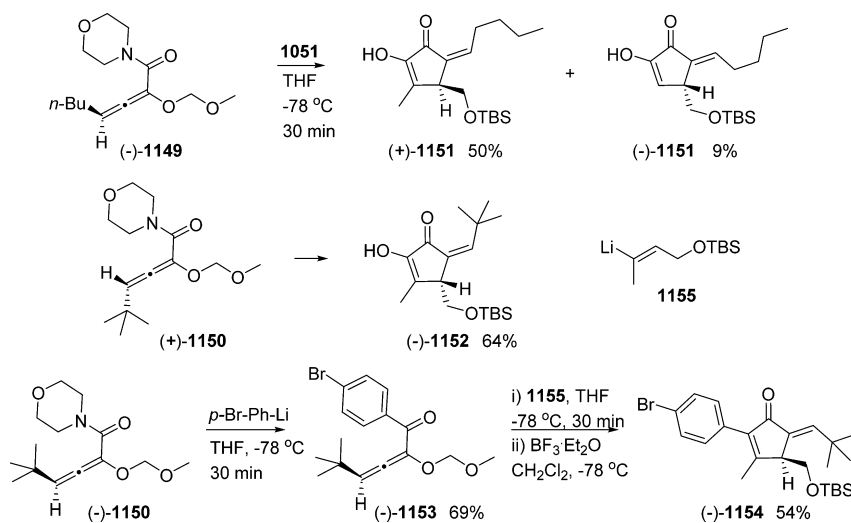
Batra et al. developed an efficient protocol for the preparation of the stable prostacyclin analogue (+)-treprostinil, a commercial drug for treatment of pulmonary arterial hypertension.⁴⁸² The key step, which was the generation of the desired tricyclic skeleton, was accomplished in three steps from chiral alkyne 1171 into enyne 1172, protection of the hydroxyl function, and Pauson–Khand reaction of 1173 to form cyclopentenone 1174.

Enantioselective synthesis of a series of bicyclic cyclopentenones has been reported by Helmchen et al.⁴⁸³ The starting chiral alkenes 1175 were alkylated, and the resulting enynes 1176 were subjected to Pauson–Khand reactions (Scheme 274). The authors found that the selectivity of the PK product 1177 is dependent on the unit connecting the propargylic and the olefinic parts of the precursor. In general, sulfonamides gave rise to low or moderate levels of diastereoselection, while pure *trans*-isomers were obtained from the rest. After recognizing the possibility of controlling and enhancing the selectivity of PKR, investigations were extended to the synthesis of neuropharmacologic agent (–)- α -kainic acid.

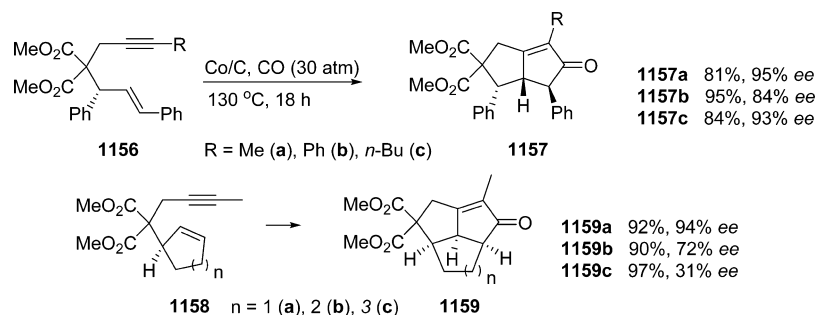
Leighton et al. have synthesized hydroxylated cyclopentenone 1181 from (*R*)-epichlorhydrin (Scheme 275).⁴⁸⁴ Its ring-opening with vinylmagnesium bromide followed by distillation from potassium hydroxide led to epoxide 1178, which was subjected to another ring-opening with trimethylsilyl acetylene and removal of the TMS group and hydroxyl protection. Finally, efficient PKR of enyne 1180 was achieved but without stereocontrol; cyclopentenone 1181 was formed as a separable 1:1 mixture.

Optically active pyrrolidine ring-fused cyclopentenones 1184 have been obtained by Ishikawa et al. by means of an

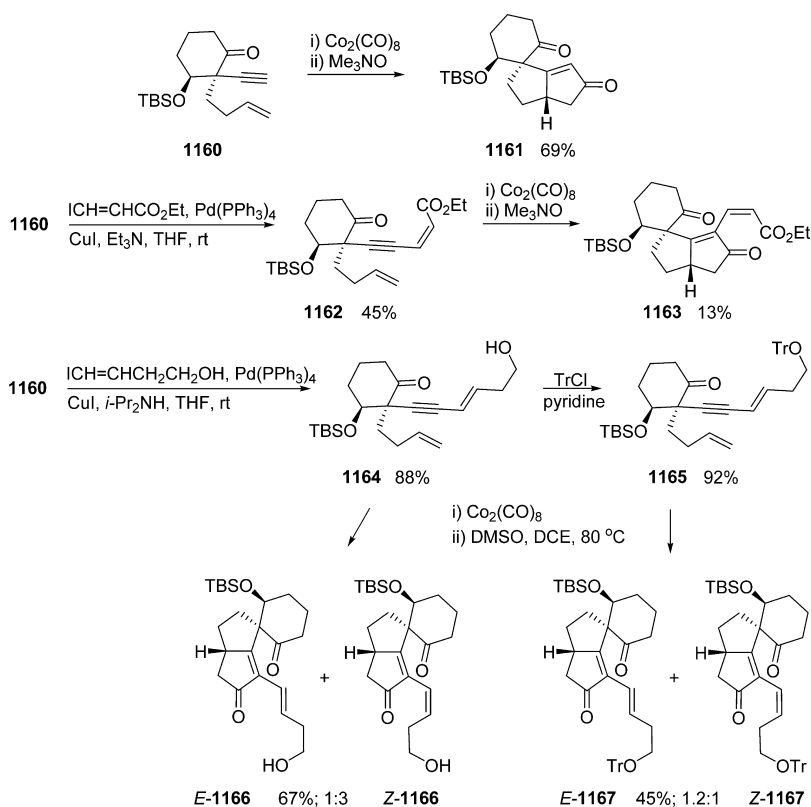
Scheme 269. Highly Efficient Chirality Transfer from an Allene to a Tetrahedral Carbon Atom



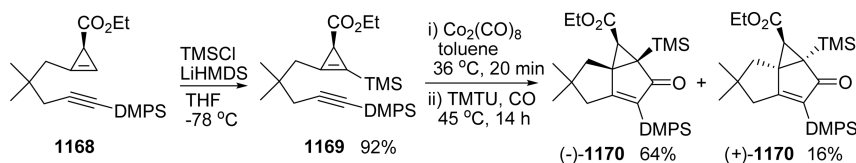
Scheme 270. A Highly Enantioselective Pauson–Khand-type Reaction



Scheme 271. Synthesis of a Series of Tricyclic Enones



Scheme 272. Conversion of Cyclopropenyne 1168 into Tricyclic Enones

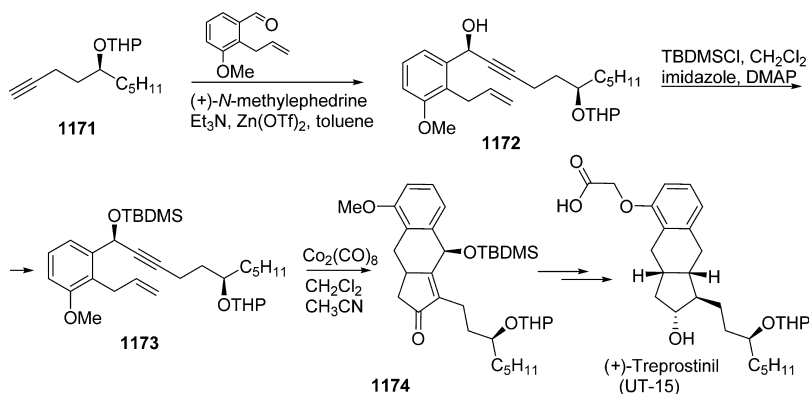


intramolecular Pauson–Khand reaction starting from readily available optically active aza-Baylis–Hillman adducts **1182** (Scheme 276).⁴⁸⁵ The PK precursors **1183** were prepared by *S*-oxidation of **1182** followed by propargylation of the resulting sulfonamides under basic conditions. The PKR conditions were optimized, and the bicyclic enones **1184** were isolated in excellent yields. The stereoselectivity of the reaction was found to be dependent on the *R* substituent; a moderate to high *cis*-selectivity was obtained when an alkyl group was placed at the *R* position, while an approximate ratio of 1:2 was obtained for the *trans*-isomer when an aromatic group occupied the *R* position.

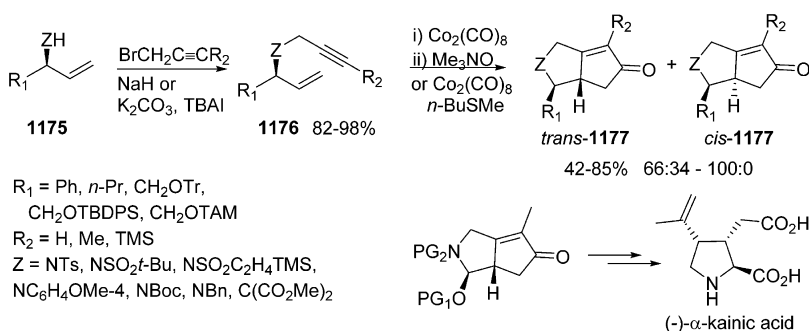
In the same context, cyclopentenones **1187** have been prepared by Tan et al. from chiral alkynes **1185**, which were alkylated to enynes **1186** and subjected to PKR under standard conditions (Scheme 277).⁴⁸⁶

Densely functionalized cyclopentenones **1189** and **1190** have been obtained by asymmetric [3+2] carbocyclization of cyclic enamines with (–)-8-phenylmenthol carbene tungsten(0) complexes **1188** by Barluenga et al. (Scheme 278).⁴⁸⁷ As a first series, the indole derivatives **1191** have been treated with **1188**, and dihydrocyclopenta[*b*]indolones **1189** were generated with moderate to good yields with extremely high enantiomeric purity. The transformation has been further extended toward α -

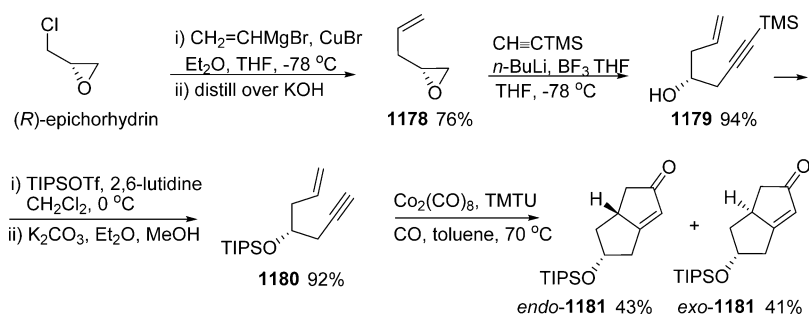
Scheme 273. An Efficient Protocol for Preparation of the Stable Prostacyclin Analogue (+)-Treprostinil



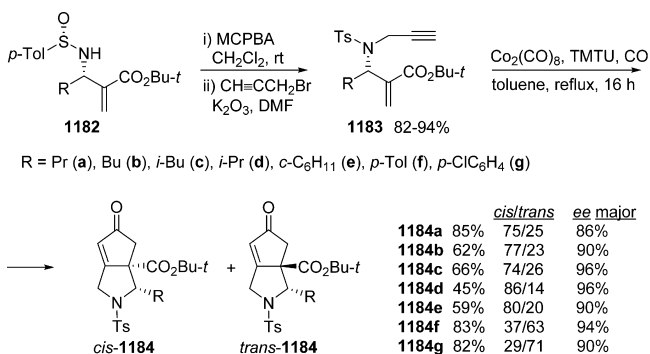
Scheme 274. Enantioselective Synthesis of a Series of Bicyclic Cyclopentenones



Scheme 275. Synthesis of Hydroxylated Cyclopentenone 1181 from (R)-Epichlorhydrin



Scheme 276. Preparation of Optically Active Pyrrolidine Ring-Fused Cyclopentenones

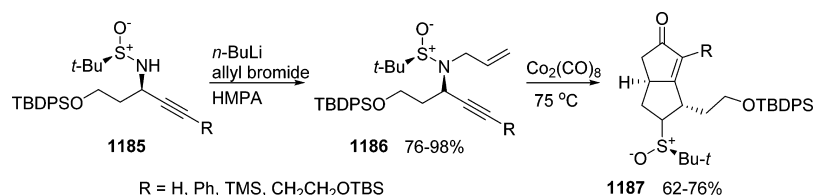


methylindoles 1192, and the corresponding 2,3-piperidine-fused cyclopentenones 1190 were isolated in higher yields and similar enantioselectivities. The results demonstrated the excellent efficiency of menthol, an inexpensive chiral auxiliary available as either antipode, for asymmetric induction.

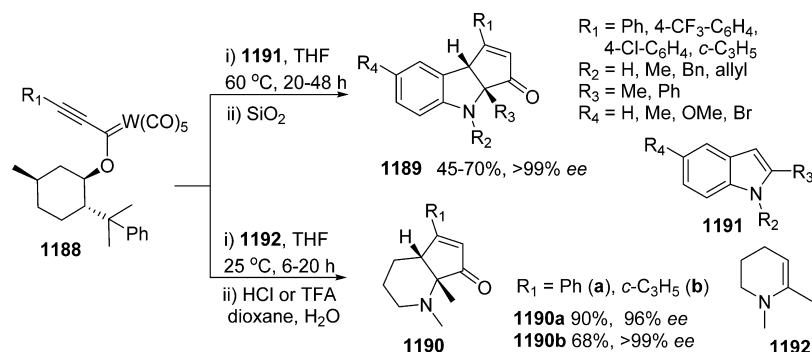
A series of chiral enynes 1193 have been converted into functionalized tetracyclic cyclopentenones 1194 by Strübing et al. via the Pauson-Khand reaction (Scheme 279).⁴⁸⁸ The authors varied the conditions and the enyne structure and found that the presence of methyl substituents on nitrogen was crucial to achieve the transformation; no conversions were detected with *N*-unprotected analogues of 1193. Both cobalt and ruthenium carbonyls were found to catalyze the reaction when $\text{R}_1 = \text{Ph}$, while $\text{Co}_2(\text{CO})_8$ was much more effective if $\text{R}_1 = \text{Et}$ and was the only efficient carbonyl if $\text{R}_1 = \text{Me}$. From the other side, it was shown that the presence of a ring substituent at R_2 or R_3 prevented the reaction, while the nature of R_4 , either proton or alkyl, had no significant influence.

The PKR of enyne piperidones 1195 to form bridged bicyclic heterocycles 1196 has been achieved by Miller et al.⁴⁸⁹ and was applied to the enantioselective total synthesis of the macroline indole alkaloid (–)-alstonerine (Scheme 280). The reaction conditions have been optimized, and the best results were obtained when treating the intermediately formed cobalt complex with dimethyl sulfoxide under heating. Thus, the

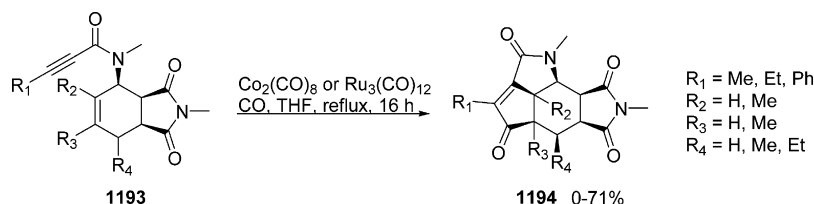
Scheme 277. Synthesis of Cyclopentenones 1187



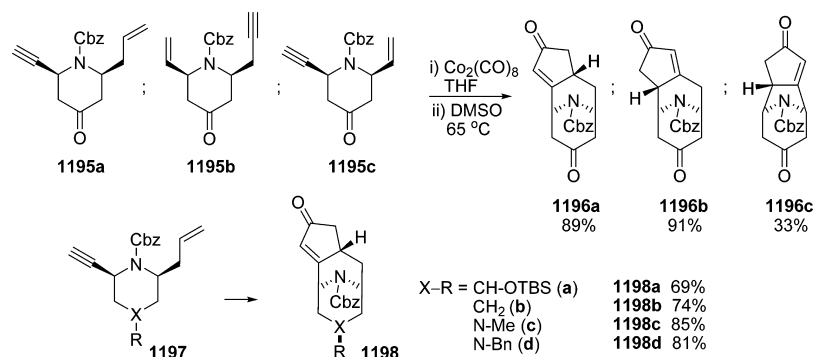
Scheme 278. Conversion of (–)-8-Phenylmenthol Carbene Tungsten(0) Complexes into Densely Functionalized Cyclopentenones



Scheme 279. Synthesis of Functionalized Tetracyclic Cyclopentenones

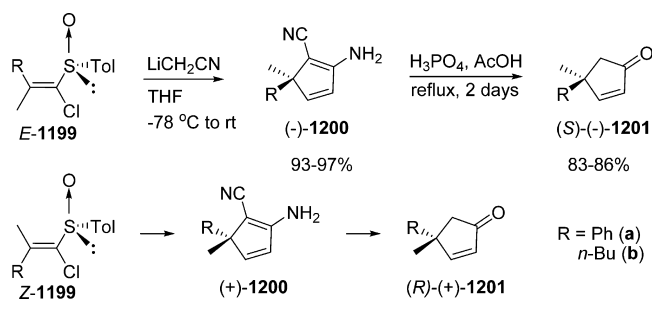


Scheme 280. Synthesis of Azabicyclononane-Fused Cyclopentenones



azabicyclononane-fused cyclopentenones **1196a** and **1196b** were obtained in high yields as single diastereomers, while the more strained enone **1196c** was generated as a mixture of two isomers in low combined yield. To determine the effect of having an sp^3 carbon atom at the C(4) position instead of a carbonyl group, the authors have submitted the enynes **1197** to PKR under the same conditions and discovered that the substitution played a role in the diastereoselectivity of the reaction. The silyl ether **1197a** and the piperazines **1197c** and **1197d** underwent clean PKR to the corresponding enones **1198a**, **1198c**, and **1198d** as single diastereomers, whereas **1197b**, bearing a methylene group at C(4), led to a diastereomeric mixture of **1198b**.

An asymmetric synthesis of 4,4-disubstituted cyclopentenones from optically active (*R*)-1-chlorovinyl tolyl sulfoxides has been realized by Satoh et al.⁴⁹⁰ (Scheme 281). As a first series, phenyl-substituted sulfoxides **1199a** were treated with cyanomethyl-lithium, and the desired enamionitriles **1200a** were isolated in high yield and selectivity. Several sets of acidic conditions have been examined for the decyanation, and it was found that phosphoric acid in acetic acid was the method of choice. To investigate the generality of these reactions, the authors further studied the sulfoxides **1199b** possessing an alkyl substituent instead of phenyl. The transformations were carried out in the same way, and the desired enamionitriles **1200b** and then **1201b** were obtained in high yield and better enantioselectivity. The observed high selectivity was explained by assuming the

Scheme 281. An Asymmetric Synthesis of 4,4-Disubstituted Cyclopentenones from Optically Active (*R*)-1-Chlorovinyl Toly Sulfonides

formation of a chelate between the lithium ion, the oxygen of the sulfoxide, and the chlorine, making the cyanomethyl anion approach take place from the less-hindered *re* face. The protocol has been further applied to an asymmetric total synthesis of (+)- α -cuparenone.⁴⁹¹

Similarly, 2,4,4-trisubstituted cyclopentenones **1203** have been prepared in high yield and excellent enantioselectivity,⁴⁹² as well as the spirocyclic product **1205**,⁴⁹³ a key intermediate in the synthesis of acorone (Scheme 282).

Li et al. developed an efficient protocol for the preparation of 4-aminocyclopenten-2-enones **1208** based on indium-catalyzed glycosidation of glycals **1206** with arylamines **1207** (Scheme 283).⁴⁹⁴ The cyclopentenones **1208** have been originally identified as side products and then were turned into major products by using the appropriately substituted glycal substrate and 30% InBr₃ as the catalyst. The unique features of the products provide the basis for generation of diversified carbocyclic nucleosides.

6. CYCLOPENTENONE PROSTANOIDS: PROSTAGLANDINS, CLAVULONES, AND PHYTOPROSTANES

Prostaglandins (PGs) belong to the family of eicosanoids and derive from arachidonic acid via the cyclooxygenase enzyme (COX) system. The action of phospholipase A₂ releases arachidonic acid from membrane phospholipids. The important class of cyclopentenone prostaglandins arises from non-enzymatic dehydration of certain prostaglandins (PGs).⁴⁹⁵ Recently, a new mechanism independent from the COX pathway for 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15-d-PGJ₂) formation in humans via free-radical-catalyzed lipid peroxidation has been proposed.⁴⁹⁶

The prostaglandin PGA, PGB, and PGJ' families, the isoprostanes, the clavulones and the chloroclavulones, the punaglandins, and the phytoprostanes are important members of the cyclopentenone family (Scheme 284).^{497–501}

Many of these compounds display biological activity. The PGA and PGJ prostaglandin groups have shown antineoplastic, anti-inflammatory, and antiviral activities, and some of them have shown neurite outgrowth promoting activities of nerve growth factor.^{502–506} 15-d-PGJ₂ was identified as the first natural ligand and agonist for PPAR- γ , inducing the transcription of nuclear peroxisome proliferator associated receptors: α and γ (PPAR- α PPAR- γ) target genes.^{507,508} Recently, an experimental structural report of the solved X-ray structure of the 15-d-PGJ₂/PPAR- γ complex was published.^{509,510} Cyclopentenone PGs possess a strong potency to form Michael adducts with GSH and some amino acids due to the presence of the electrophilic α,β -unsaturated enone moiety in the cyclopentene ring. The formation of covalent protein adducts is associated with modulation in protein function.^{511–514}

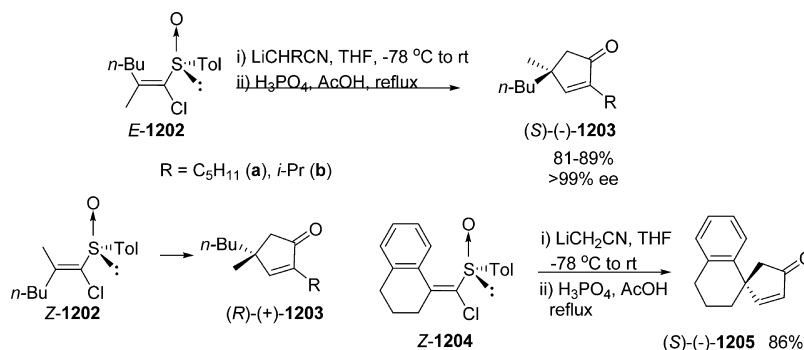
The Δ^{12} -J₂ prostaglandins, which contain a cross-conjugated α,β -unsaturated functionality, are potent inhibitors of isopeptidase activity, in contrast with the lower potency displayed by A₁ and A₂ prostaglandins bearing simple α,β -unsaturated cyclopentenones. B₁ group PGs bearing a sterically hindered α,β -unsaturated enone unit are inactive.⁵¹⁵

Cyclopentenone PGs have been intensively studied in terms of chemistry and potential pharmacological applications.^{516–521}

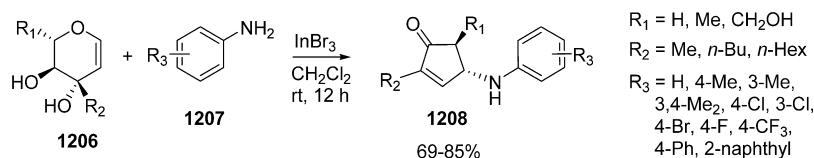
Prostaglandin-type compounds that differ from prostaglandins by a stereoisomeric position (*cis*) of the side chains on the cyclopentene ring or by a different stereolocation of substituents in the prostanic acid residue are defined as isoprostanes (IsoPs). The last criterion was used to classify IsoPs in several groups.

Epoxyisoprostane-PLs such as PEIPC are created by dehydration of the cyclic isoprostane ring of bicyclic endoperoxide-containing PLs to afford a highly reactive cyclopentenone group.⁵²² Iso-P or Neuro-P are indicators for cardiovascular disorders, cancers, and neurodegenerative diseases.⁵²³

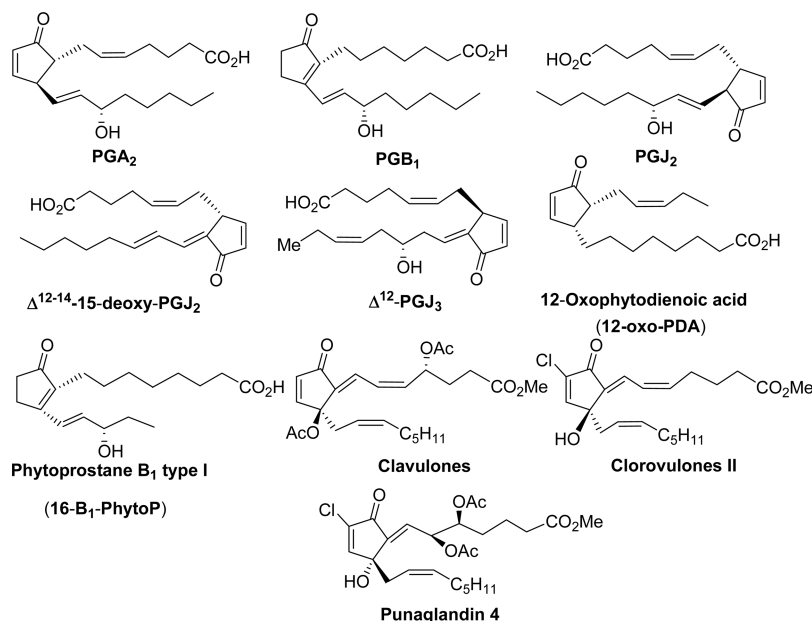
Phytoprostanes (PhytoPs) were discovered by Parchmann and Mueller in 1998 and were shown to be biosynthesized in plants through a nonenzymatic pathway similar to some PGs.⁵²⁴ Jasmonates are plant signal compounds that induce defense responses including accumulation of antimicrobial secondary metabolites (phytoalexins).⁵²⁵ PhytoPs display powerful biological activities including the activation of mitogen-activated protein kinase (MAPK) and glutathione-S-transferase (GST) defense genes, which induce several plant defense mechanisms.^{526–528}

Scheme 282. Synthesis of 2,4,4-Trisubstituted Cyclopentenones

Scheme 283. Indium-Catalyzed Glycosidation of Glycols with Arylamines



Scheme 284. Overview of the General Structures of Prostaglandins



Marine prostaglandins,⁵²⁹ such as clavulones,⁵³⁰ naturally halogenated chlorvulone II⁵³¹ and punaglandin IV,^{532,533} are natural prostanoid substances isolated from corals and are characterized by an alkylidene cyclopentenone structure. These compounds have shown unusual cytotoxicity and antiproliferative activity against several transformed cell lines.⁵³⁴ Furthermore, the cross-conjugated dienone punaglandin exhibits more potent biological effects than the simple enone punaglandin.⁵³⁵ We present below some examples of cyclopentenone prostanoids (Scheme 284).

Prostaglandins can contain from two up to five chiral centers. The usual strategies for the total synthesis of saturated prostaglandins are not useful for the synthesis of cyclopentenone PG derivatives because the dehydration protocols frequently used lead to mixtures of isomers.⁵³⁶

The asymmetric synthesis of these biologically active substances, which occur in nature as regio- and stereoisomeric mixtures, has been useful in the unequivocal identification of each individual metabolite and their respective biological activity.

The degree of stereoselectivity in the asymmetric synthesis of PGs relies on chiral precursors. This approach is easier, provided that the target molecule shows chirality similar to that of the precursor and chirality is retained throughout the synthesis. However, this approach requires a stoichiometric amount of starting material, which can be expensive to make. The stereoselective formation of a new stereogenic center in prochiral systems requires use of a chiral auxiliary or small amounts of enantiomerically pure (or enriched) catalysts to promote asymmetric reactions.^{537,538}

Several extensive chemical reviews on the synthesis of prostaglandins and prostacyclins have been published in

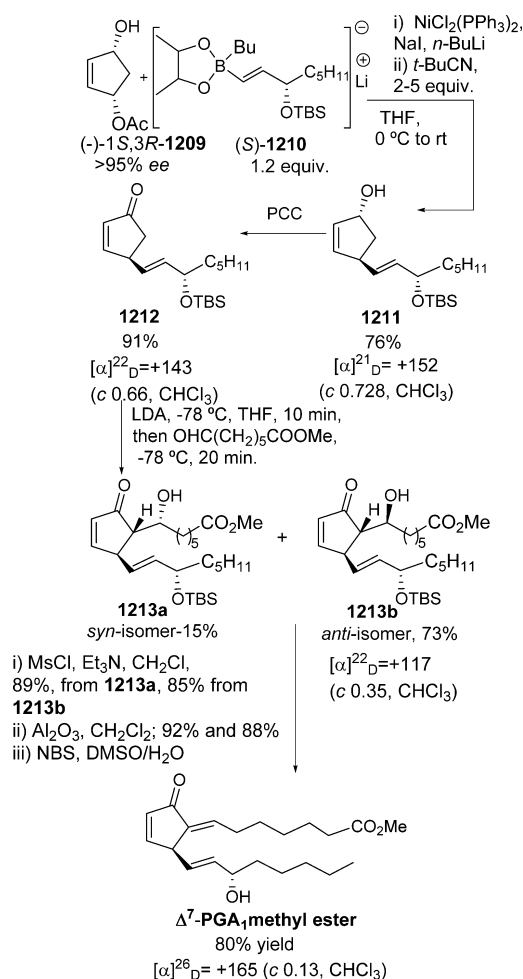
1993⁵¹⁸ and 2007,⁵¹⁹ including biologically oriented ones.^{517,528,539} Recently, a review dealing with efforts to achieve the correct structural representation of PhytoP has been published.⁵⁴⁰

This Review collects recently published asymmetric synthetic routes to cyclopentenone prostaglandin compounds. There are three types of strategies: (1) substrate-controlled enantioselective sequential addition of the α - and ω -chains to a chiral cyclopentenone derivative; (2) one-pot reaction of the chiral cyclopentenone with two side chains; and (3) cyclization of the cyclopentenone nucleus mediated by the chirality present in the first side chain, providing enantioselective control over the second side chain addition.

Kobayashi et al. reported the synthesis of Δ^7 -PGA₁ methyl ester from optically pure 4-monoacetylated bis-cyclopentenol (–)-(1*S*,3*R*)-**1209**, an example of the first strategy previously above.^{541,542} The ω -chain was introduced by enantioselective nucleophilic substitution using lithium borate and Ni catalysis, obtaining major regioisomer **1212** in 76% yield and minor regioisomer in 4% yield. This was followed by aldol reaction with the appropriate aldehyde in the presence of lithium diisopropylamide (LDA) to afford major *anti*-isomer **1213b** (73%) and the *syn*-isomer **1213a** in 15% yield. The final product Δ^7 -PGA₁ methyl ester was obtained after mesylation of the hydroxyl group at C4, elimination, and TBS (*tert*-butylsilyl) deprotection with NBS (*N*-bromosuccinimide) (Scheme 285).

A few years later, Kobayashi and Nakata reported another synthesis of Δ^7 -PGA₁ methyl ester starting from the same monoacetate of 4-cyclopentene-1,3-diol (**1209**).⁵⁴³ The alkenyl stannane **1214** was sequentially transmetalated, first by stannane-lithium exchange with *n*-BuLi, and was later converted into the

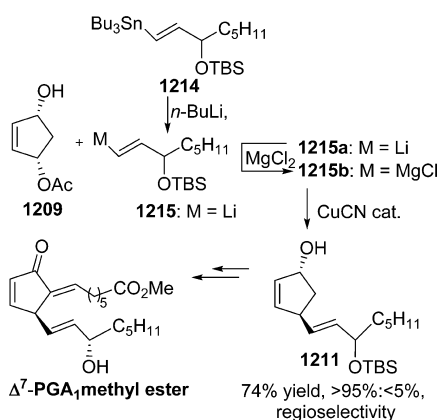
Scheme 285. Synthesis of Δ^7 -PGA₁ Methyl Ester from (–)-(1*S*,3*R*)-1209



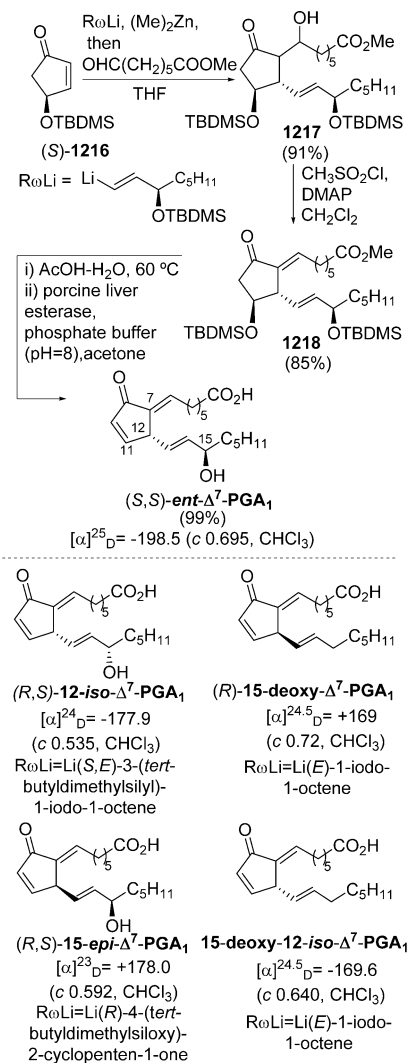
magnesium reagent **1215b** (Scheme 285).^{541,542} This reagent was added to **1209** in the presence of CuCN to selectively afford $\text{S}_{\text{N}}2$ product **1211** in 74% yield. Further synthetic manipulation led to the final product Δ^7 -PGA₁-methyl ester (Scheme 286).

The synthesis of (*S,S*)-*ent*- Δ^7 -PGA₁ (Scheme 287) is representative of a three-component coupling process involving addition of the chiral ω and α side chains to a chiral cyclopentenone substrate to build a PGA₁ structure. Asymmetric

Scheme 286. Short Synthesis of Δ^7 -PGA₁ Methyl Ester from (–)-(1*S*,3*R*)-1209



Scheme 287. Synthesis of (*S,S*)-*ent*- Δ^7 -PGA₁ via Three-Component Coupling Process and Representative Enantiomeric Δ^7 -PGA₁'s, Produced by This Synthetic Strategy



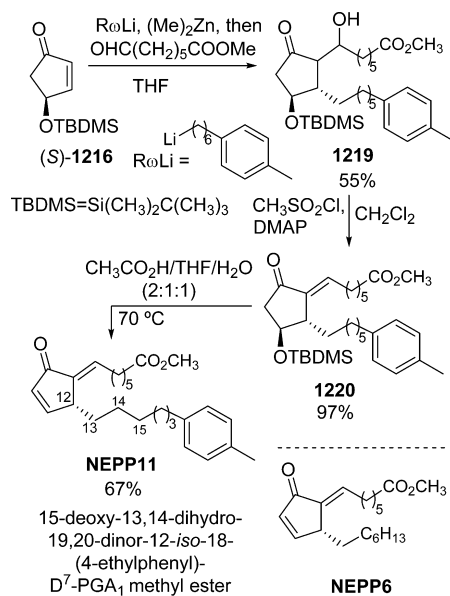
conjugate addition of $\text{R}\omega\text{Li}$ to form the ω -side-chain took place *trans* to the C4 substituent in (*S*)-**1216** and controlled the formation of the (12*R*) stereocenter in **1217**.⁵³⁷ The conjugate addition resulted in an in situ-generated enolate that was condensed with an aldehyde to add the α chain to **1217** (Scheme 287).⁵⁴⁴ *ent*- Δ^7 -PGA₁ was obtained after dehydration, elimination, deprotection of **1218**, and enzymatic methyl ester hydrolysis. The authors also used the same three-component strategy to synthesize enantiomeric prostaglandins (*R,S*)-12-iso- Δ^7 -PGA₁, (*R,S*)-15-*epi*- Δ^7 -PGA₁, (*R*)-15-deoxy- Δ^7 -PGA₁, and 15-deoxy-12-iso- Δ^7 -PGA₁ to study the impact of modifications at the C12 and C15 positions on biological activity.

The authors proposed that growth inhibition of HL-60 human leukemia cells by Δ^7 -PGA₁-methyl ester mainly results from the induction of p21 cyclin-dependent kinase (Cdk), which regulates cell cycle progression via a p53-independent pathway.

The antitumor activity of the Δ^7 -PGA₁ series could be partly related to inhibition of the topoisomerase II enzyme through interaction with the topoisomerase II-sensitive C12 stereocenter.⁵⁴⁵ The synthetic (*R*) enantiomer was more active and stable, indicating that the configuration of C12 stereocenter

influences topoisomerase stability. Biological studies have also suggested that the cell culture growth inhibition of PGAs is due to the cross-conjugated dienone system. This involves carrier-mediated transport across the cellular and nuclear membranes and the reversible formation of thiol derivatives with cytoprotective enzyme glutathione-5-transferase and an endocyclic C11 atom.^{512,546–548} The Δ^7 -PGA₁ methyl esters NEPP10 and 11, which are the representative compounds of the series of 19 electrophilic neurite outgrowth-promoting prostaglandins (NEPPs, compounds that protect neurons from oxidative stress), have been synthesized by Suzuki et al. (Scheme 288).⁵⁴⁹ More

Scheme 288. Synthesis of Δ^7 -PGA₁ Methyl Esters NEPP11 from (S)-4-(*tert*-Butyldimethylsiloxy) Cyclopent-2-en-1-one 1216



recently, syntheses of other neuroprotective prostaglandin analogues have been reported by the same group.⁵⁵⁰ All

approaches were based on the three-component PG synthesis strategy.

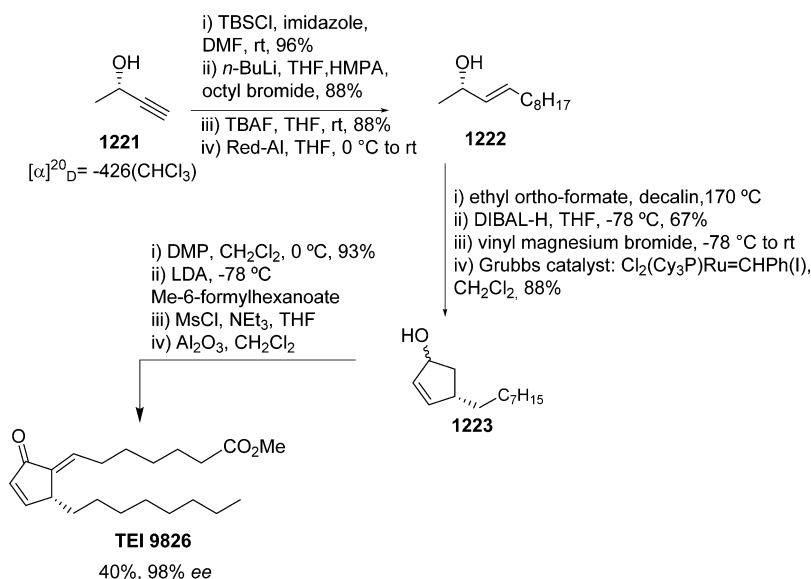
As an example, the synthesis of biologically more significant and less biodegradable 15-deoxy-13,14-dihydro-19,20-dinor-12-iso-18-(4-methylphenyl)- Δ^7 -PGA₁ methyl ester NEPP11⁵⁴⁹ was achieved by organozincate-mediated three-component aldol condensation. The authors used an antipode of the neural R ω Li chain, 1-bromo-6-(4-tolyl)hexane, to introduce the ω side chain with *R* configuration at C15 onto (S)-4-(*tert*-butyldimethylsiloxy) cyclopent-2-en-1-one 1216, followed by addition to 7-oxoheptanoate. The three-component coupling reaction gave product 1219, which was further dehydrated to enone 1220. Heating in aqueous acetic acid eliminated the C11 hydroxy group and afforded NEPP11.

The stereoconfiguration of C12 and C15 and the cross-conjugated dienone structure have been shown to be decisive for their biological activities such as antitumor activity and neurite outgrowth-promoting activity.^{544,545,551} The neurotrophic actions of NEPP compounds have been studied. NEPP11 can protect neuronal cells from manganese ion-induced apoptosis as well as glutamate-mediated cell death (necrosis).^{551,552}

The 13,14-dihydro-15-deoxy-*ent*- Δ^7 -PGA₁ methyl ester TEI 9826 has shown potent in vivo activity against cisplatin-resistant tumors and good biological stability in vitro.^{553,554} This compound was prepared in microsphere formulations and exhibited activity against human ovarian carcinoma cells in nude mice TEI 9826 as well as neuroprotective activity.^{549,550}

Alkylidene cyclopentenone prostaglandin TEI 9826 continues to be an attractive synthetic target due to its biological activity and prospects as a future therapeutic agent. Florent et al. reported one of the earliest enantioselective syntheses of (–)-TEI 9826 using a ring-closing metathesis (RCM) step (Scheme 289).⁴⁶⁶ Successive protection, alkylation, deprotection, and reduction of chiral compound (S)-1221 afforded allylic alcohol 1222, which was subjected to a stereoselective Claisen rearrangement with ethyl *ortho*-formate. Following DIBAL-H reduction and vinylation, RCM produced cyclopentenol 1223 with the attached ω -chain. This was followed by Dess–Martin oxidation and aldol reaction to introduce the α -chain, which gave a mixture of aldol diastereoisomers. Treatment of the mesyl

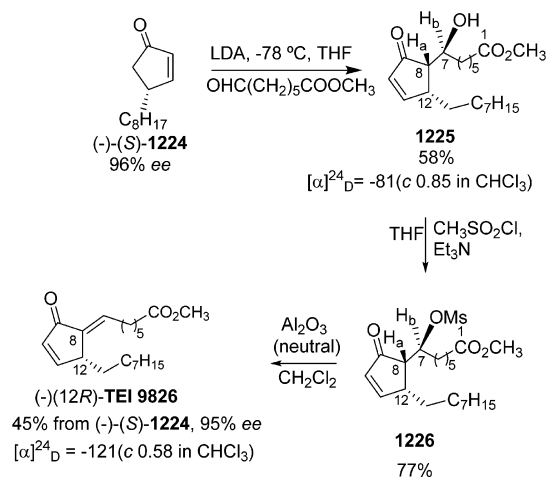
Scheme 289. Synthesis of (–)-TEI 9826 via Claisen Rearrangement and RCM



esters with aluminum oxide using a reported procedure by Kobayashi et al.⁵⁴² afforded (–)-TEI 9826 in 40% yield and >98% ee.

Helmchen et al. reported a synthesis of (–)-TEI 9826, based on a combination of asymmetric allylic alkylation and RCM (Scheme 290).^{555,556}

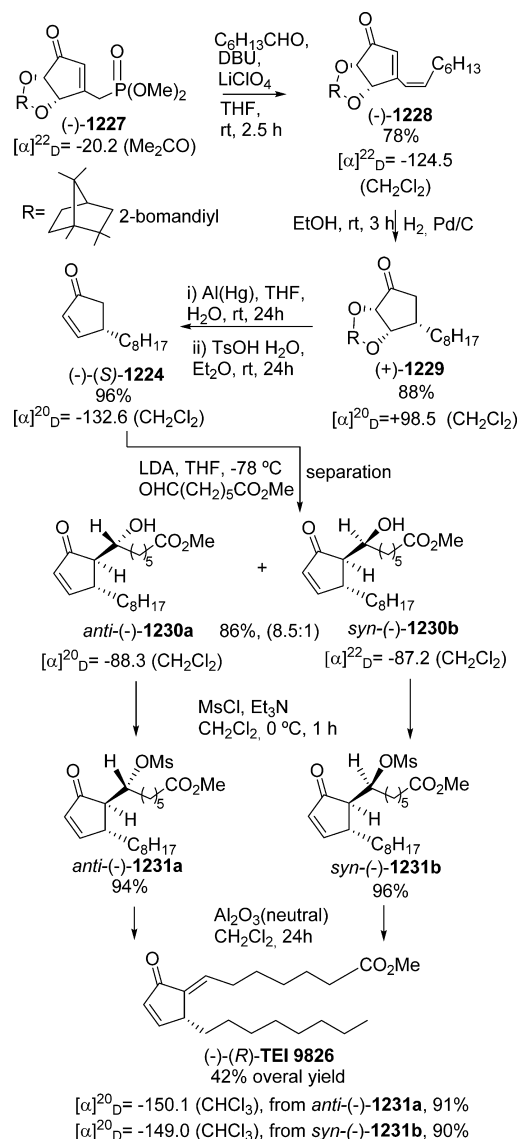
Scheme 290. Synthesis of (–)-TEI 9826 via Asymmetric Allylic Alkylation and RCM



The authors prepared a series of chiral 4- and 2,4-substituted cyclopentenones by combination of asymmetric iridium-catalyzed allylic alkylation reactions and ruthenium-catalyzed ring-closing metathesis. The chiral precursor (S)-1224, obtained with 96% ee, was subjected to aldol reaction to afford *anti*-aldol **1225** in 58% yield. The relative configuration of **1225** was determined by comparison of coupling constants between H_a and H_b (8.4 Hz) with those of similar compounds.⁵⁴² The *syn*-specific elimination reaction with mesylate chloride⁵⁴¹ and subsequent treatment of **1226** with Al_2O_3 gave TEI 9826 in 45% yield.

Recently, Mikolajczyk and co-workers reported the stereo-selective synthesis of (–)- and (+)-TEI 9826 starting from (–)- and (+)-3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enones **1227**, respectively (Scheme 291).⁵⁵⁷ These precursors were obtained as a separable mixture of diastereomeric ketals from optically inactive *meso*-tartaric acid in 45% yield through an acid-catalyzed reaction with (+)-camphor and methyl orthoformate followed by treatment with an α -phosphonate carbanion.³⁶⁷ The chiral ketal (–)-1227 was then subjected to the Horner olefination reaction with heptanal under mild basic conditions, followed by hydrogenation of the alkene thus formed in product **1228**. The reduction is the crucial step that sets the new C12 stereocenter due to the camphor-protected *cis*-diol moiety controlling the addition of hydrogen to the double bond from the nonengaged diastereotopic face of the cyclopentenone ring. The product (+)-1229 was obtained as a single diastereomer in 88% yield. The enantiopure cyclopentenone (–)-(S)-1224^{555,556} was achieved by Johnson selective deoxygenation with aluminum amalgam in aqueous THF solution⁴¹ and elimination of the free 3-hydroxy group under acidic conditions. The final product (–)-(R)-TEI 9826 was afforded following Kobayashi's procedure involving aldol reaction, mesylation, and elimination. The values of the coupling constants between the protons at C7 and C8 (8.3 and 3.1 Hz,

Scheme 291. Synthesis of (–)-TEI 9826 from (–)-1227

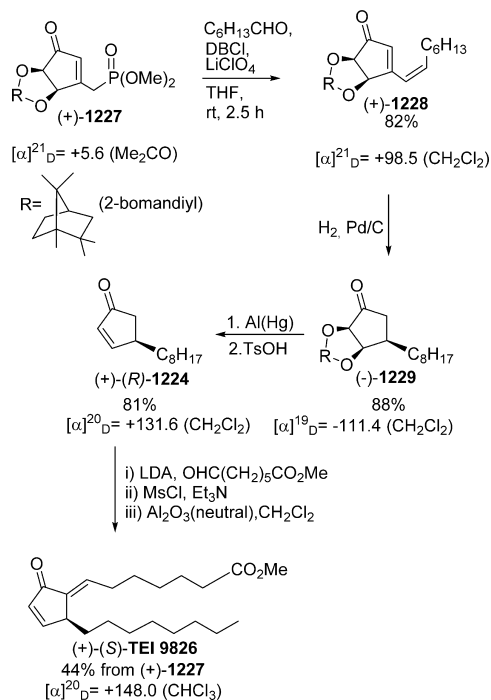


respectively) of aldols **1230a,b** confirm the *anti*- and *syn*-configurations.

The synthesis of (+)-(S)-TEI 9826 was performed with the same strategy (Scheme 292). Horner reaction of chiral compound (+)-1227 with heptanal afforded (+)-1228 in 82% yield. Selective deoxygenation and water elimination of (–)-1229 was carried out as a one-pot reaction to yield (+)-(R)-1224 in 81% yield. The subsequent sequence of aldolization, mesylation, and elimination of water afforded (+)-(S)-TEI 9826, in 44% overall yield from (+)-1227.

Hartwig et al. developed an Ir-catalyzed enantioselective allylic substitution reaction of silyl enolates derived from α,β -unsaturated ketones that created a stereogenic center at the β -position of the enolate.⁵⁵⁸ The Ir-catalyzed asymmetric reaction was selective for the more substituted position of the allylic nucleophile. The authors used this method to carry out an asymmetric synthesis of (+)-TEI 9826 in three steps (Scheme 293). Asymmetric allylic substitution of **1232** with **1233** using (R)-L-1234 as catalyst gave product **1235** in 85% yield and 95% ee in an 11:1 ratio of branched to linear addition products. Ring-closing metathesis of **1235** using Grubbs II catalyst **1236**

Scheme 292. Synthesis of (+)-TEI 9826 from (+)-1227



afforded **1237**, and a three-step sequence of aldol condensation with aldehyde **1239**, mesylation, and elimination of mesylate with neutral Al_2O_3 afforded **TEI 9826** in 73% yield.

Halogenation at C10 increases the electrophilicity of the molecule, thus enhancing the ability of prostaglandins to inhibit ubiquitin isopeptidase activity. The optimal effect was achieved by C12 hydroxylation similar to punaglandins. To verify this

hypothesis, Ireland et al. synthesized a series of C10 halogenated and C12 oxygenated PGA_2 derivatives.⁵⁵⁹

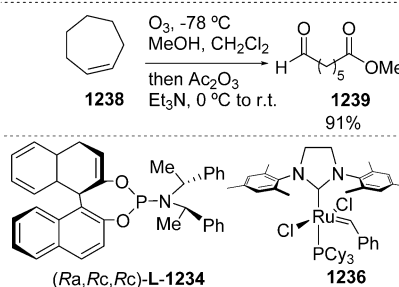
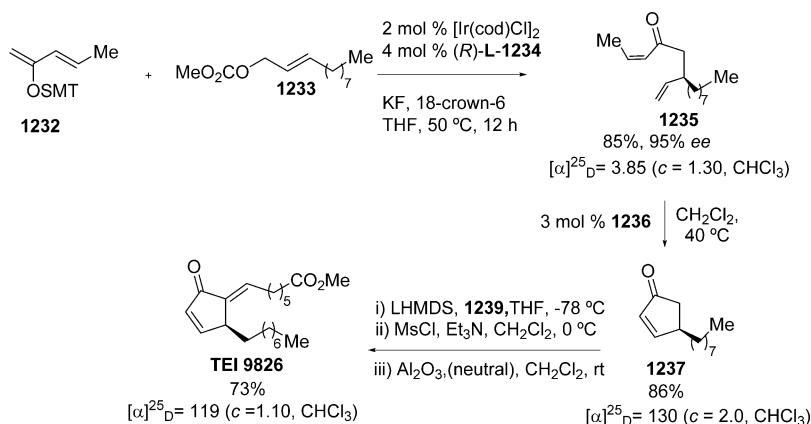
I- PGA_2 (C10 iodinated, C12 hydroxylated PGA_2) (Scheme 294)⁵⁵⁹ was prepared from 15-(S)- PGA_2 , beginning with hydroxyl acylation and enone epoxidation. The iodo analogue of PGA_2 was obtained after opening the epoxide **1240** with LiI and dehydration. Chloro and bromo derivatives were prepared by similar protocols. The C10 iodinated C12 hydroxylated PGA_2 compounds were achieved in a diastereomeric ratio of 1:1 from X- PGA_2 derivatives following selective epoxidation with *m*-CPBA of the C5–C6 double bond and subsequent allylic hydroxylation on C12 with SeO_2 . The two diastereomers were separated by HPLC. *J*-based ^1H NMR analysis and Mosher's method were used together with molecular modeling studies to determine the absolute stereochemistry at C5 and C6.⁵⁵⁹

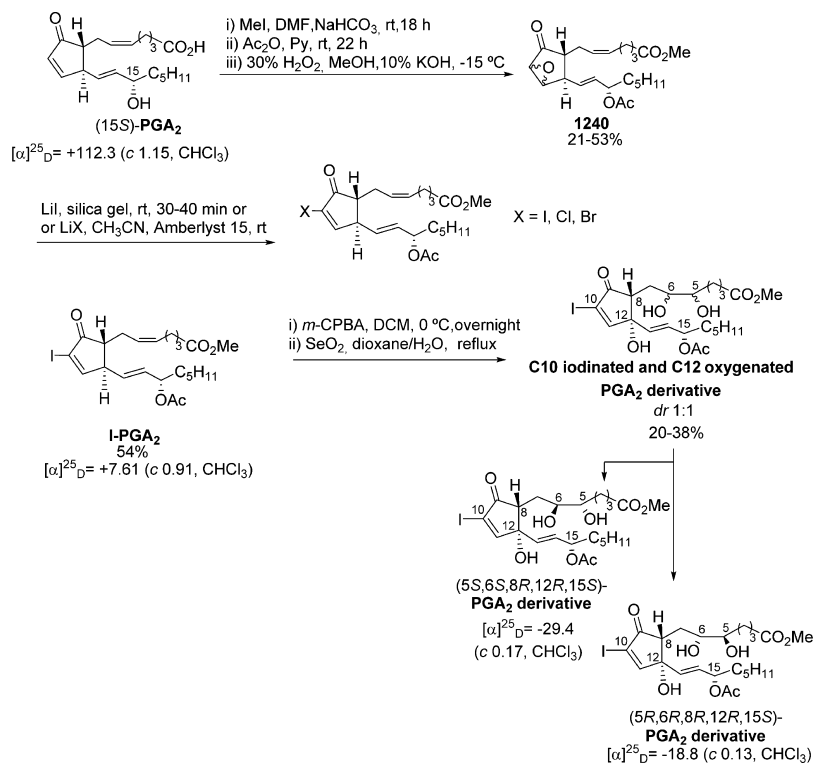
The marine prostaglandin A_2 (PGA_2) was extracted from Caribbean sea whip *Plexaura homomalla* (Coelenterata: Octocorallia: Gorgonacea). 15-(S)- PGA_2 possesses potent biological activity, whereas the (*R*) enantiomer is inactive.

Grieco and Abood's synthesis is described in Schemes 295 and 296.⁵⁶⁰ The earlier stereoselective syntheses^{561–563} are mentioned collectively (Scheme 297).

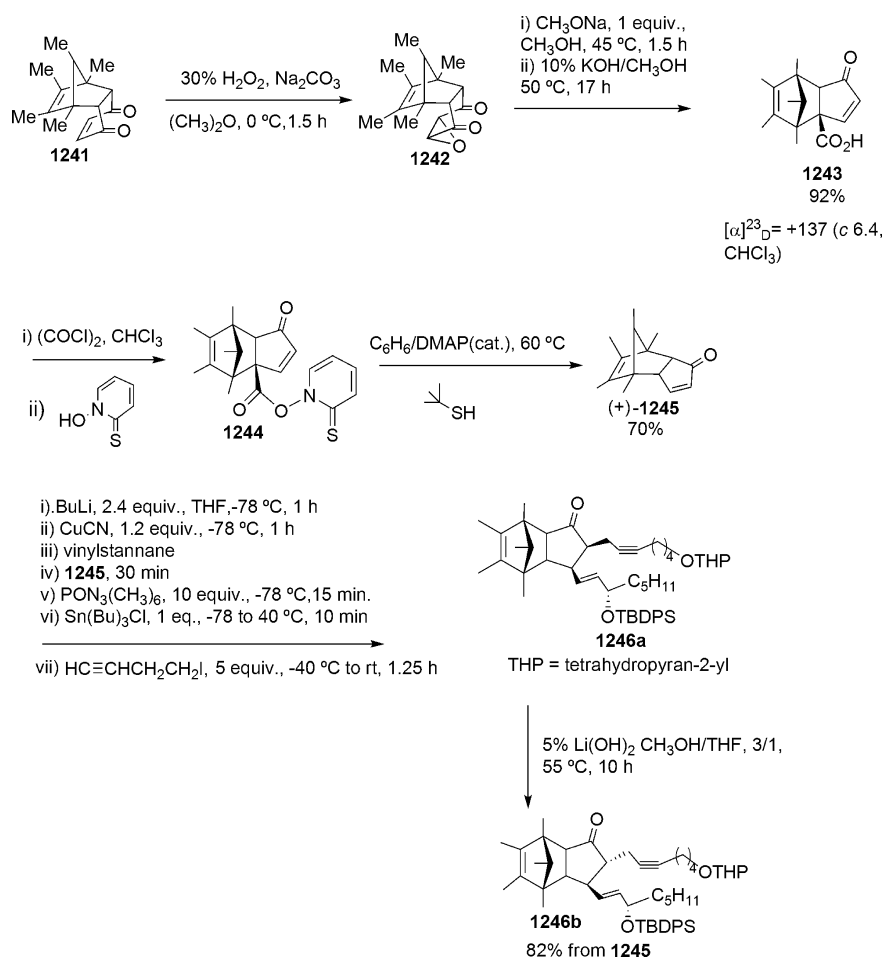
Grieco and Abood reported the retro Diels–Alder reaction of (–)-**1247** under Lewis acid catalysis as an enantioselective strategy toward chiral PGA_2 . They concluded that the presence of methyl groups at the C1, C7, C8, C9, and C10 positions in (–)-**1247** accelerated the [4+2] cycloreversion reaction.

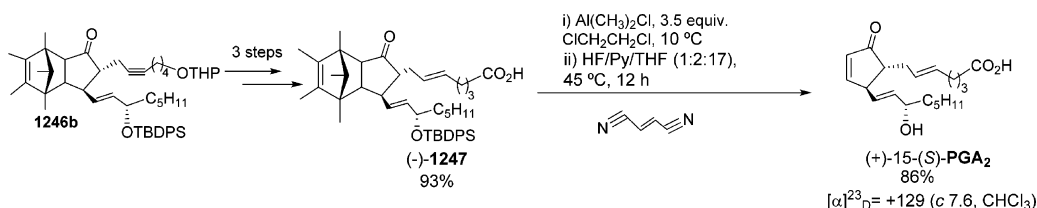
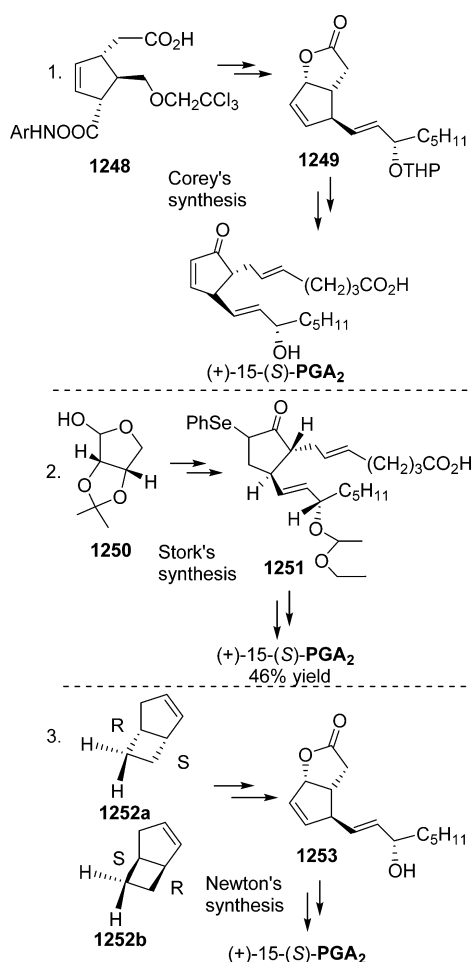
Compound (+)-**1245** was prepared in four steps starting from pentamethyl derivative **1241**,⁵⁶⁴ which was epoxidized with H_2O_2 in acetone and then subjected to a Favorskii-type ring contraction⁵⁶⁵ in methanol with sodium methoxide followed by hydrolysis in 10% methanolic KOH to give acid **1243** in 92% yield. The racemic acid formed a diastereomeric salt with (*R*)-(–)- α -methyl-benzylamine, which was recrystallized from

Scheme 293. Synthesis of (+)-TEI 9826 from **1232** via Ir-Catalyzed Enantioselective Allylic Substitution

Scheme 294. Synthesis of (5*R*,6*R*,8*R*,12*R*,15*S*)-PGA₂ Derivative from (15*S*)-PGA₂

Scheme 295. Synthesis of the Intermediate 1246b from 1241



Scheme 296. Synthesis of (+)-15-(S)-PGA₂Scheme 297. Overview of Previous Total Syntheses of (+)-15-(S)-PGA₂

EtOAc and acidified to afford the chiral compound. **1243** was decarboxylated using Barton's procedure⁵⁶⁶ by making the acyl chloride and conversion into *N*-acyloxypyridine-2-thione **1244**, which was treated with *t*-butyl mercaptan and 4-dimethylaminopyridine (DMAP) to afford cyclopentenone derivative (+)-**1245** in 70% yield. The synthesis progressed with Michael addition of the ω side-chain using a vinylstannane in the presence of CuCN, followed by introduction of the α side-chain using a propargylic iodide to give **1246a**. Epimerization of the α position under basic conditions (5% methanolic lithium hydroxide–THF) afforded **1246b** (Scheme 295). Further side chain synthetic manipulation gave (–)-**1247** in 93% overall yield. This chiral compound was subjected to the retro-Diels–Alder reaction to give (+)-15-(S)-PGA₂ in 86% yield (Scheme 296). The key factor that accelerated the retro-Diels–Alder reaction was the presence of several methyl substituents in the bicyclic scaffold of the substrate. In particular, it was proposed that the C1

methyl group gives rise to a polarized transition state via a nonconcerted process.

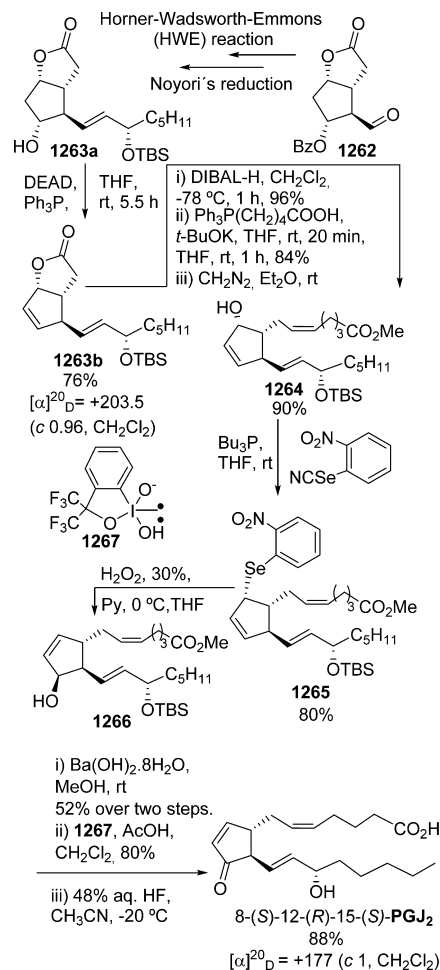
Corey and Mann reported a synthesis of (+)-15-(S)-PGA₂ that took advantage of the highly rigid stereochemical control imposed by chiral lactone **1249** (Scheme 297). The authors synthesized this key intermediate in different ways.⁵⁶¹ Stork and Raucher described the synthesis beginning from simple sugar **1250**.⁵⁶² Two Claisen rearrangements were employed: one to produce the necessary *trans*-geometry of a double bond and the other as the means of transferring the chirality of a carbon–oxygen bond to that of a nonadjacent carbon–carbon bond. Selective introduction of a phenylseleno group led to compound **1251** using lithium diisopropylamide and phenyl selenyl chloride. After further transformations, (+)-15-(S)-PGA₂ was obtained in 46% yield. Newton et al. used racemate **1252a,b** as a precursor to chiral lactone **1253** that led to (+)-15-(S)-PGA₂ from **1253** following conditions similar to those used in Corey's method.

The synthesis of a PGB₁ methyl ester analogue was reported by Mikołajczyk et al. (Scheme 298).^{567–569} The authors prepared bis- β -ketophosphonate **1256** by adding α -phosphonate carbanion **1254** to dicarboxylic acid ester **1255**. The intramolecular base-catalyzed cyclization of **1256** afforded cycloalkenone **1257** in good yields. The latter underwent regioselective alkylation at C2 with methyl-7-iodoheptanoate, followed by stereoselective Horner–Wittig olefination with either the (*R*) or the (*S*) enantiomer of 2-(*tert*-butyldimethylsilyloxy)heptanal to afford the enantiopure (*R*) or (*S*) form of PGB₁ methyl ester, respectively.

Various synthetic strategies have been applied to generate PGJ analogues. The first enantioselective synthesis of PGJ₂ was reported by Vidari et al. (Scheme 299).⁵⁷⁰ The cyclopentanol **1263a** was obtained from enantiopure aldehyde **1262** through a Horner–Wadsworth–Emmons (HWE) reaction using Bundy's protocol,⁵⁷¹ followed by chemo- and enantioselective reduction of the α,β -unsaturated carbonyl group using Noyori's procedure.⁵⁷² Compound **1263a** was dehydrated with DEAD and PPh₃ to afford lactone **1263b** on a multigram scale. Compound **1264** bearing two side chains was synthesized following a DIBAL-H reduction, Wittig olefination, and esterification. The crucial transposition of the olefin and OH group was generated using a swap protocol. PGJ₂ analogue **1266** was prepared by conversion of the OH to a selenide, which underwent oxidation and sigmatropic rearrangement. Further steps including successive hydrolysis, oxidation, and deprotection resulted in target molecule 15-deoxy- $\Delta^{12,14}$ -PGJ₂. Vidari and co-workers also reported the synthesis of 15-deoxy- $\Delta^{12,14}$ -PGJ₂ through application of the A–J swap.⁵⁷³

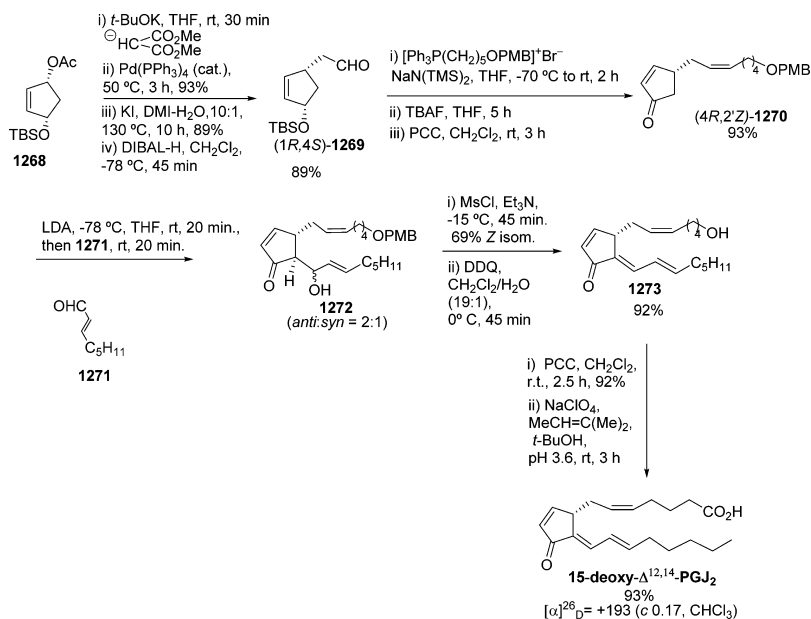
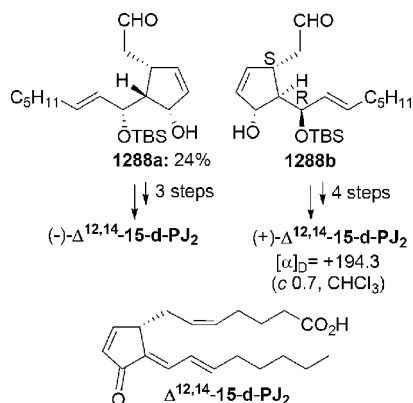
15-deoxy- $\Delta^{12,14}$ -PGJ₂ was prepared using Kobayashi's strategy⁵⁷⁴ (Scheme 300). This method has also been applied by other authors.⁵⁷⁵ The cyclopentenone possessing the ω -chain was prepared from disubstituted protected derivative **1268**. The chiral aldehyde intermediate was generated by Pd-catalyzed

Scheme 299. Synthesis of (+)-PGJ₂



This method has been used to prepare 15-deoxy- $\Delta^{12,14}$ -PGJ₂ (15d-PGJ₂) and more than 16 other analogues from *E*-2-octenal in a polymer-assisted protocol.⁵⁷⁵ The total synthesis of cyclopentenone prostaglandins typically uses dehydration protocols that can lead to mixtures of isomers. Indeed, concerns were raised about the link between stereochemistry and structural, biological, and clinical data for 15-deoxy- $\Delta^{12,14}$ -PGJ₂. In a review article by Maxey and co-workers, the synthesis of 15d-PGJ₂ was disputed.⁵⁷⁷ The authors were able to obtain the 5-*cis*,12-*trans*,14-*cis* compound in high purity. Its strong dextro-

In 2010, the enantioselective synthesis of 15d-PGJ₂ was accomplished by Suh and co-workers.⁵⁸² The key step of the synthesis involved an asymmetric Rh-catalyzed cycloisomerization of ene-ynone, followed by an olefin isomerization (Scheme 302). The appropriate precursor ketone for the cycloisomerization reaction, 1277, was achieved in five steps in 92% yield from known alcohol 1276.⁵⁸³ A stoichiometric amount of AgBF₄ with 10 mol % [Rh(COD)Cl]₂ and 24 mol % (*R*)-BINAP at ambient temperature provided the exclusive formation of the desired aldehyde 1279, in 61% yield with 97% ee, which was accessible via an additional deprotection of 1278, in an enantioselective

Scheme 300. Synthesis of 15-Deoxy- $\Delta^{12,14}$ -PGJ₂ from 1268Scheme 301. Synthesis of $\Delta^{12,14}$ -PGJ₂ Analogues from the Aldehyde 1269

cycloisomerization process. Wittig olefination was used to introduce the acid side chain, the product of which afforded methyl ester **1281** after esterification with TMSCHN₂.

The *Z*-exoenone isomer of **1280** was converted into the desired *E*-isomer **1281** by treatment with TMSCl and LiCl. The introduction of unsaturation on the cyclopentenone ring was achieved by the reaction of **1281** with Et₃N and TMSOTf in CH₂Cl₂, followed by Saegusa oxidation³²⁵ of the resulting TMS enol ether. The ester hydrolysis was achieved by Me₃SnOH.⁵⁸⁴

Sutton et al. reported a conventional method to obtain the (+) and (−) enantiomers of PGJ₂ and 15-*epi*-PGJ₂, (+)- and (−)-15-d-PGJ₂, *ent*-PGJ₂, and *ent*-15-*epi*-PGJ₂, from a mixture of diastereomers of **1285** via enzymatic acylation using *Pseudomonas cepacia* lipase.⁵⁸⁵ The enzyme efficiently separated **1285** into a mixture of two pairs of diastereoisomers (−)-**1285** and (+)-**1287** in 42% and 41% yield, along with 99% ee. Hydrolysis of acetate (+)-**1287** provided (+)-**1285**, which after conventional treatment produced the final chiral targets PGJ₂ and 15-*epi*-PGJ₂. *ent*-PGJ₂ and *ent*-15-*epi*-PGJ₂ were both obtained from (−)-**1285**. The mixture of diastereomers **1285** was produced from 7-chloronorbornadiene **1282** via subsequent 7-lithiation, alkylation with *trans*-oct-2-enal to alcohol **1283**, and oxidation.

The alcohol underwent Meinwald rearrangement with methyltrioxorhenium (MTO) and silylation to the triene **1284** (Scheme 303).

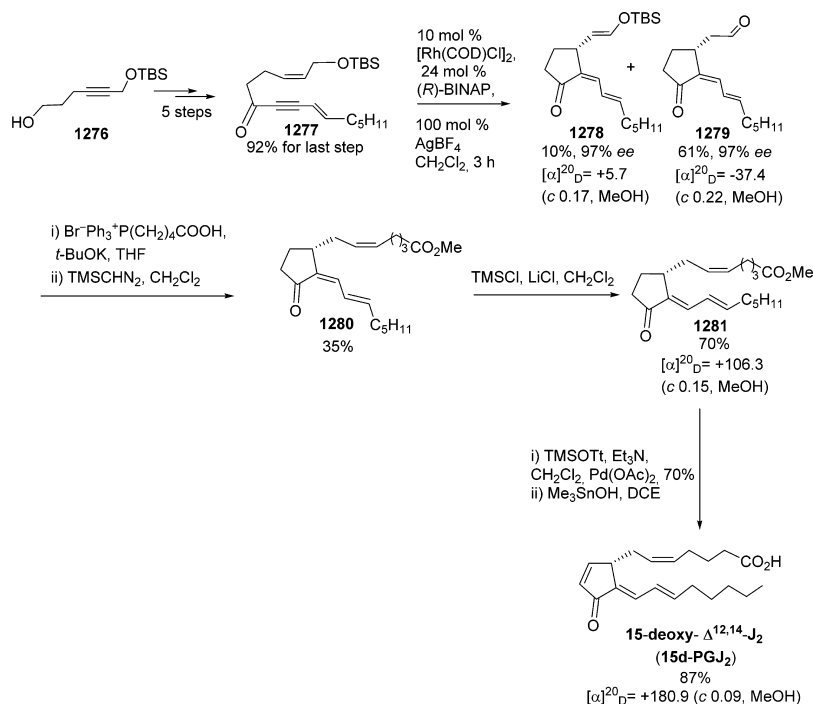
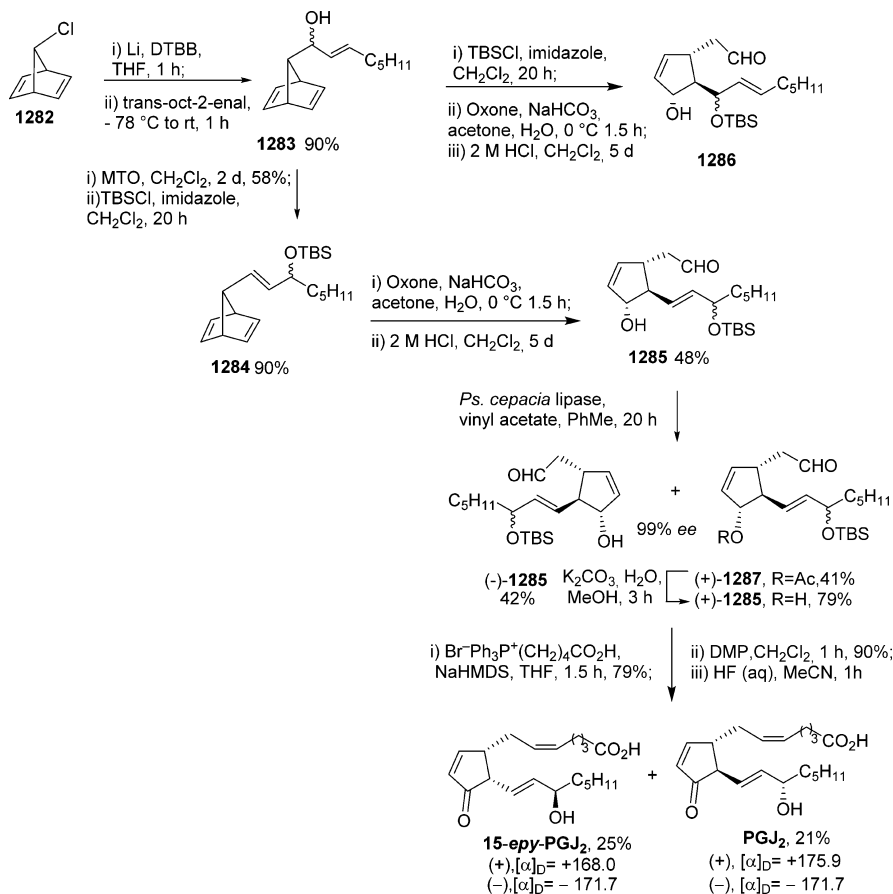
Scheme 304 shows the enantiomers (−)- and (+)-15-d-PGJ₂, which were produced in a similar manner from **1288a** and **1288b**, respectively. The (*S*) stereochemistry at C8 was established for the naturally occurring (+)-15-d-PGJ₂.

The *in vitro* oxidation product of arachidonoylphosphatidylcholine 5,6 PEIPC, a member of the family of epoxyisoprostane phospholipids, is present in high levels in atherosclerotic lesions. This compound activates endothelial cells by stimulation of synthesis of interleukin 8 (IL-8) and monocyte chemotactic protein-1 (MCP-1). The accumulation of 5,6 PEIPC and other epoxyisoprostane phospholipids in cells exposed to cytokines and in atherosclerotic lesions suggests that these lipids may play a role in a number of chronic disease processes.^{586,587}

The PEIPC (1-palmitoyl-2-(5,6)-epoxyisoprostane *E*₂-*sn*-glycero-3-phosphocholine) was isolated, identified, and its biological activity was described. 5,6 PEIPC has a saturated cyclopentenone ring and an OH group at C11, while dehydrated analogue 5,6 PECPC (2-(5,6-epoxyisoprostane A₂)) phosphorylcholine possesses a conjugated dienone structure.

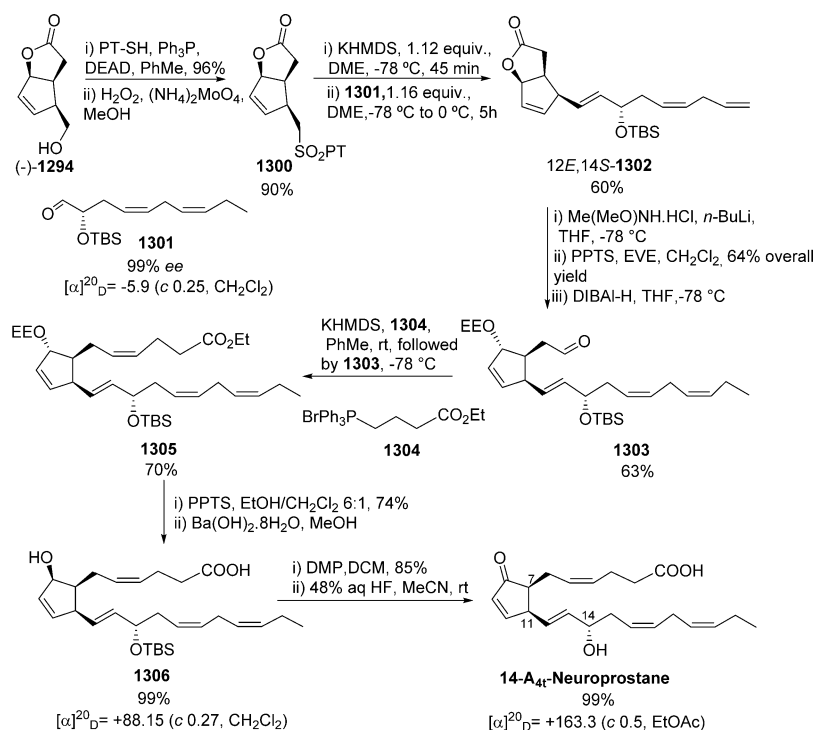
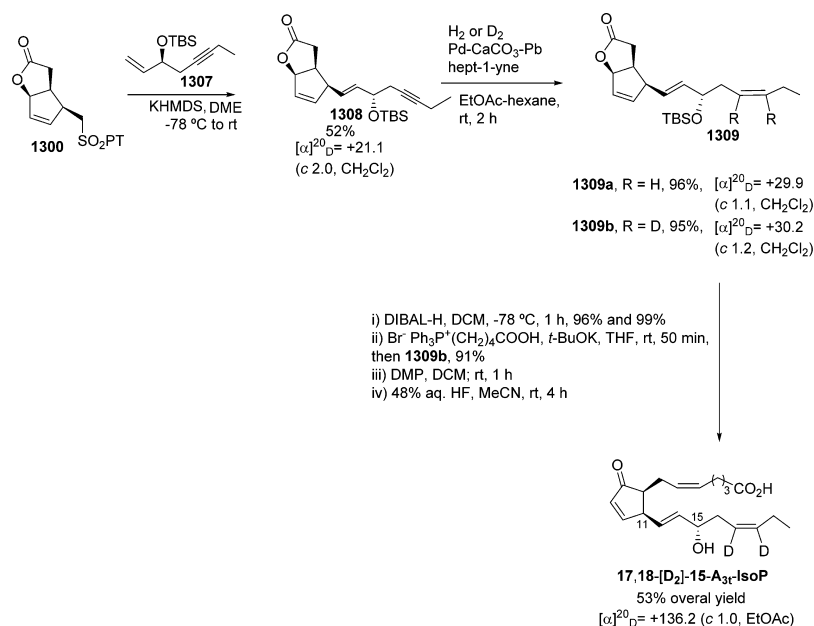
Stereoselective total synthesis of epoxyisoprostane A₂ and 5,6 PECPC (1-palmitoyl-2-(5,6-epoxycyclopentenone)-*sn*-glycero-3-phosphorylcholine) was performed by Kobayashi and Acharya.⁵⁸⁸ The authors elucidated and established the *E* geometry of the Δ⁷ alkene and the relative configuration of the epoxy moiety and C12, and absolute configuration of C5, C6, and C7 in the isoprostane moieties. It was believed that the configuration of the glycerol moiety in compounds 5,6 PEIPC and 5,6 PECPC is the same as that in *sn*-glycerol-3-phosphate.

Derivative **1289**, with the attached ω-chain, was prepared in four steps from (*R*)-**1209** and underwent aldol reaction with epoxyaldehyde to give product **1290**. The elimination of OH by mesylate and PPL hydrolysis of **1292** afforded epoxyisoprostane A₂ (EIA₂) in 89% yield (Scheme 305). The authors determined the absolute configuration of the C5, C6, C7, and C12 atoms by NMR studies and concluded that the compound has the configuration of the natural product. Treatment of EIA₂ and

Scheme 302. Synthesis of 15d-PGJ₂ via Asymmetric Rh-Catalyzed Cycloisomerization of Ene-yneScheme 303. Synthesis of PGJ₂ and 15-*epi*-PGJ₂ via Enzymatic Acylation

chiral 1-palmitoyl-2-lyso-phosphorylcholine with the Yamaguchi reagent in CH₂Cl₂ at room temperature for 36 h produced (5*R*,6*R*)-(7*E*)-(12*S*)-5,6 PECPC in 53% yield.

The two isomers 5,6 PEIPC and 5,6 PECPC were obtained by a coupling approach with a phosphoryl choline. The structure established by NMR studies corresponds to the natural

Scheme 308. Synthesis of *cis*-14- A_{4t} -Neuroprostane from Hydroxylactone (–)-1294Scheme 309. Synthesis of 17,18- $[D_2]$ -15- A_{3t} -IsoP from Sulfone 1300

lower chain in **1297** was *E*-stereoselectively attached using Julia–Lythgoe olefination followed by Wittig condensation based on known prostaglandin chemistry. 1,3-Allylic transposition was performed by [2,3] sigmatropic rearrangement of obtained allylic alcohol **1298** in three steps. J_2 -IsoP was achieved by mild oxidation of already-deprotected **1299** using hydroxyiodinane oxide **1267** in DCM.

The *cis*-stereochemistry of the two side chains on the cyclopentenone ring was firmly established by NOESY experiments and by comparing the ¹H NMR spectrum of natural PGJ₂ with that of synthetic J_2 -IsoP. Also, the authors pointed out the

easy epimerization of the labile stereogenic centers C8 and C12, as a synthetic challenge not completely undertaken.

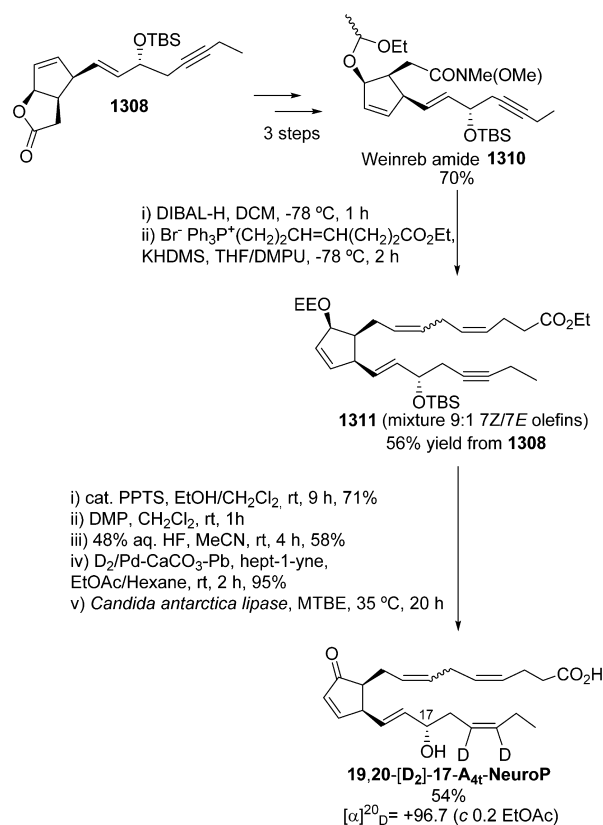
Vidari et al. reported a total enantioselective synthesis of *cis*-14- A_{4t} -Neuroprostane **T** (Scheme 308).⁵⁹⁴ The initial sulfone **1300** was prepared from enantiopure hydroxylactone (–)-1294 using Mitsunobu thioetherification followed by chemoselective thioether oxidation. The aldehyde **1301**, employed in the crucial enantioselective Julia–Kocienski condensation, was prepared from (*S*)-β-hydroxybutyllactone (99% ee). A Julia–Kocienski condensation provided tetraene **1302** as a single (*S*) stereoisomer. The α-chain was then attached, forming 1-ethoxyethyl ether (OEE)-protected olefin **1305** via a protected Weinreb

amide, followed by ethylvinyl ether (EVE) and DIBAL-H reduction of **1302** to give the unstable aldehyde **1303** used in the Wittig olefination. The obtained single stereoisomer **1305** was O-EE acetal-protected, and after hydrolysis **1306** was obtained as a single enantiomer in 99% yield. Subsequent cyclopentenol DMP oxidation and HF cleavage of the O-TBS ether in **1306** afforded *cis*-14-A_{4t}-Neuroprostane in good yield.

A-type cyclopentenone isoprostanooids are consumed *in vivo* for the prevention of neurological and cardiovascular diseases. DEPT NMR techniques are an important tool, helping to elucidate the effects of these compounds in humans.

In 2014, Vidari et al. reported the first total enantioselective syntheses of labeled A-type cyclopentenone isoprostanooids⁵⁹⁵ 17,18-[D₂]-15-A_{3t}-IsoP (Scheme 309) and 19,20-[D₂]-17-A_{4t}-NeuroP (Scheme 310). The two syntheses started from known

Scheme 310. Synthesis of 19,20-[D₂]-17-A_{4t}-NeuroP



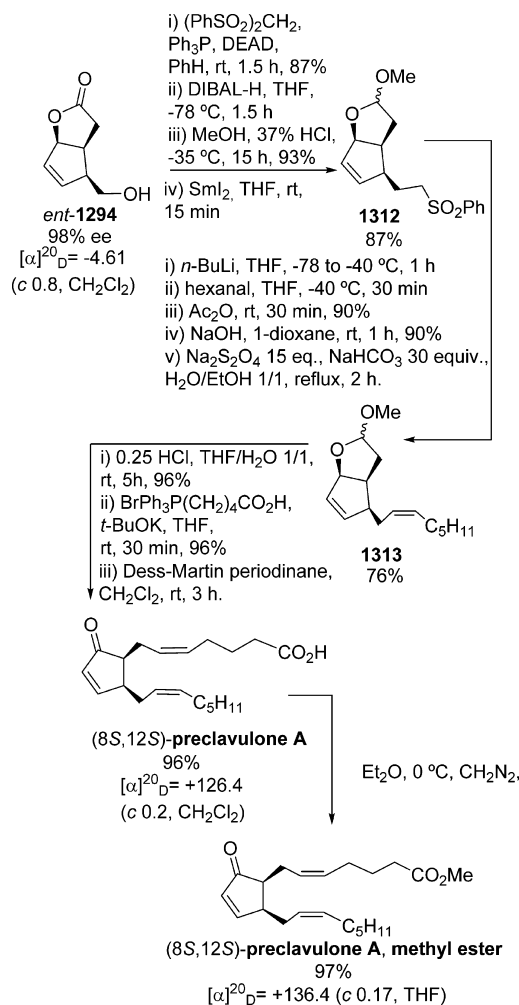
sulfone derivative **1300**, available from Julia–Kocienski reaction.⁵⁹⁴ **1300** afforded alkyne **1308** under action of aldehyde **1307**, exposed to an excess of KHDMS in DMF. This alkyne derivative was a precursor of the Z double bond in the labeling of the ω-3 bond. The applied protocol for dideuteration of **1308** involved the use of high-purity (>99.9%) D₂ gas instead of H₂. From chiral deuterated derivative **1309b** through a four-step reaction sequence typical for the prostaglandine synthesis (DIBAL-H reduction, Wittig condensation, DMP (Dess–Martin periodinane) oxidation, and O-TBS cleavage with 48% aqueous solution of HF), 17,18-[D₂]-15-A_{3t}-IsoP was obtained in 53% overall yield. The deuterium labeling of C17 and C18 was estimated from ¹H broad-band-decoupled ¹³C NMR spectra of **1309a,b** to be no less than 95%.

The synthesis of 19,20-[D₂]-17-A_{4t}-NeuroP (Scheme 310) was highly convergent with that of 17,18-[D₂]-15-A_{3t}-IsoP. From

Weinreb amide **1310**, by Wittig reaction and ylide exposition of the formed aldehyde, **1311** was obtained as a 9:1 mixture of 7Z/7E olefins. The latter was selectively O-EE-acetal-protected to a cyclopentenol, which was oxidized by DMP. After O-TBS deprotection with 48% aqueous HF, regioselective deuterium *cis*-addition was accomplished using the same protocol used in the synthesis of 17,18-[D₂]-15-A_{3t}-IsoP. Subsequent ethyl ester cleavage using a polymer supported lipase from *Candida antarctica* led to 19,20-[D₂]-17-A_{4t}-NeuroP in 54% yield with >95% D-labeling of the olefinic C19–C20 centers.

This powerful and versatile strategy was also used by Vidari et al. to achieve the first truly enantioselective synthesis of (8*R*,12*R*)-preclavulone A (Scheme 311).⁵⁹⁶ The starting alkyl

Scheme 311. Synthesis of (8*S*,12*S*)-Preclavulone A from Hydroxylactone (–)-1294

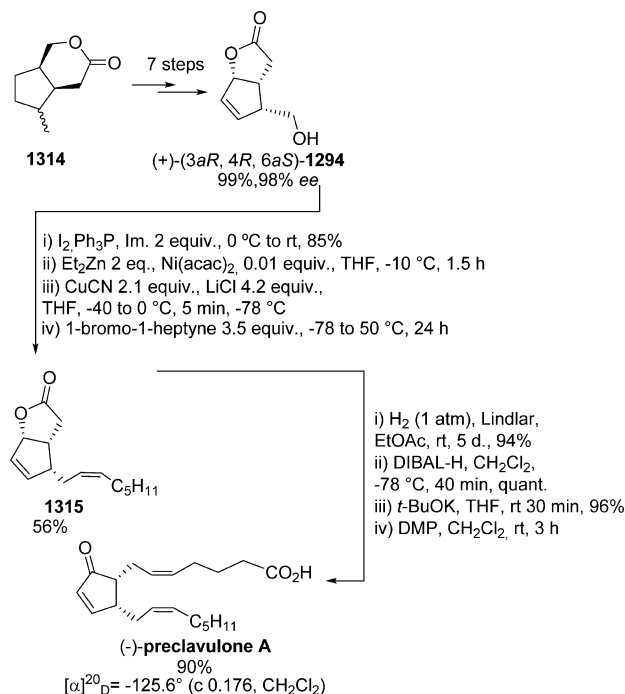


sulfone **1312** was prepared by Mitsunobu condensation of hydroxylactone (–)-1294, which is available in multigram amounts using an enantioselective organometallic approach⁵⁹⁷ with bis(phenylsulfonyl) methane. The highly stereoselective Julia–Kocienski coupling of the lithio derivative of phenylsulfone with hexanal furnished stereodefined Z olefin **1313** in four steps in 76% yield. The upper chain and ω-chain of preclavulone A were installed in *cis* geometry by Wittig olefination. The stereodefined cyclopentenone derivative was oxidized by DMP in CH₂Cl₂ to give the (8*S*,12*S*) enantiomer of preclavulone A in 96% yield.

The corresponding chiral (8*S*,12*S*)-methyl ester was prepared with diazomethane in 97%.

The same research group has also demonstrated the insertion of the ω side chain by means of a one-pot/two-step Knochel organozinc $\text{sp}^3\text{--sp}$ C–C coupling protocol (Scheme 312).⁵⁹⁷

Scheme 312. Overview of the Synthesis of (–)-Precavulone A

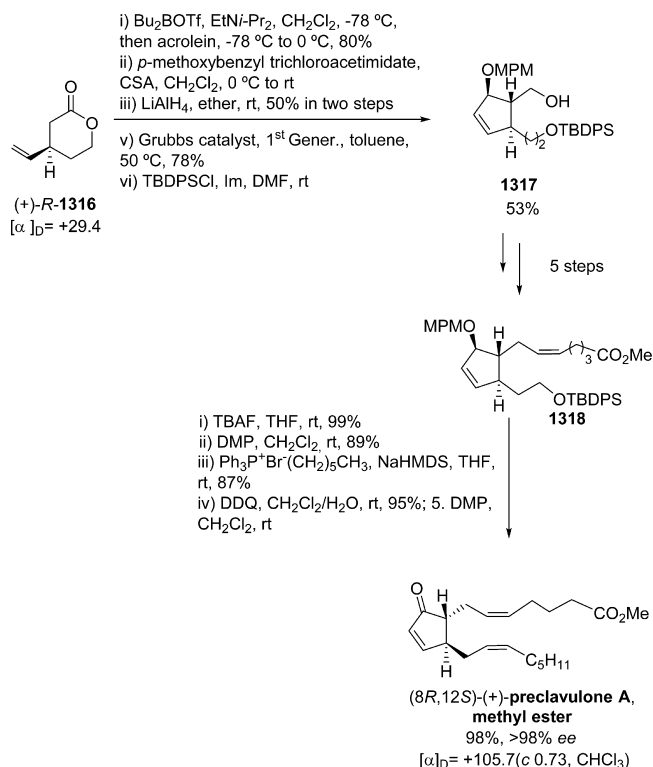


Iodolactone 1314 was prepared by a 6-*exo-trig* atom-transfer radical cyclization with a strong preference for the formation of the *cis*-fused δ -lactone ring, whereas enantioselective formation of (+)-1294 was secured using the Trost asymmetric ligand in a Pd-induced lactonization (asymmetric allylic alkylation) of the corresponding sodium carboxylate. The ω side chain was installed using the $\text{sp}^3\text{--sp}$ C–C coupling based on Knochel organozinc chemistry through the coupling of the functionalized copper–zinc reagent with 1-bromoalkyne.

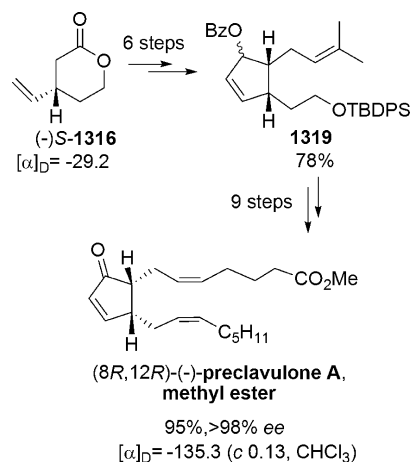
Iguchi et al. reported the synthesis of (8*R*,12*S*)-(+ and (8*R*,12*R*)-(–) enantiomers of the methyl ester of precavulone A⁵⁹⁸ (Schemes 313 and 314), from lactone 1316 via a highly diastereoselective Mukaiyama aldol reaction. This was followed by protection of the hydroxyl group, reduction of the lactone moiety, and protection of the hydroxyl group thus generated. Cyclization via RCM created the cyclopentenol scaffold in intermediate 1317. A further five steps including insertion of the α side chain through Wittig olefination gave product 1318 (Scheme 313). The (8*R*,12*S*)-(+ precavulone A (>98% ee) was obtained in higher enantiomeric purity than the natural one (46% ee). The (8*R*,12*R*)-(–) enantiomer was obtained using the same strategy in 95% and >98% ee from (–)-S-1316 (Scheme 314). Iguchi and co-workers also obtained (±)-precavulone A methyl ester and its diastereomer epiprecavulone A methyl ester using a similar synthetic approach.⁵⁹⁹

In 1988, Corey and Xiang reported the first enantioselective synthesis of (–)-preclavulone A methyl ester, a product of arachidonic acid metabolism in the Atlantic coral *Pseudoplexaura porosa* (Scheme 315).⁶⁰⁰ They also reported the ^1H NMR (500 MHz), infrared, ultraviolet, and mass spectra of the synthetic

Scheme 313. Synthesis of (+)-Precavulone A Methyl Ester



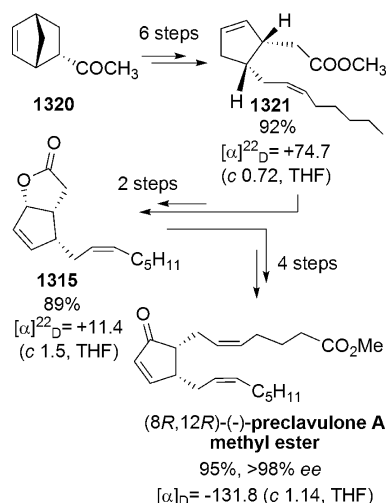
Scheme 314. Overview of the Synthesis of (–)-Precavulone A Methyl Ester



ester, which were identical to those of a sample of preclavulone-A methyl ester obtained from *Pseudoplexaura porosa*, as previously described.⁶⁰¹

The structure–activity relationship of clavulones has been established in line with their biological activities: (a) the C10–C11 olefin unit is essential for this activity; (b) a halogen atom at C10 increases the activity of the clavulones; and (c) the C12 hydroxyl or acetate is also required for full activity. Zwanenburg and coauthors reported enantioselective syntheses of clavulones from the endotricyclo[5.2.1.0^{2,6}]decadienone 2-carboxylic compound 1323. In this synthesis, the authors employed flash vacuum thermolysis.⁶⁰² Diels–Alder product 1322 was subjected to selective epoxidation, and Favorskii ring contraction afforded racemic 1323. Optically pure tricyclic acid (+)-1323 was obtained after enzymatic resolution, decarboxylation, and two

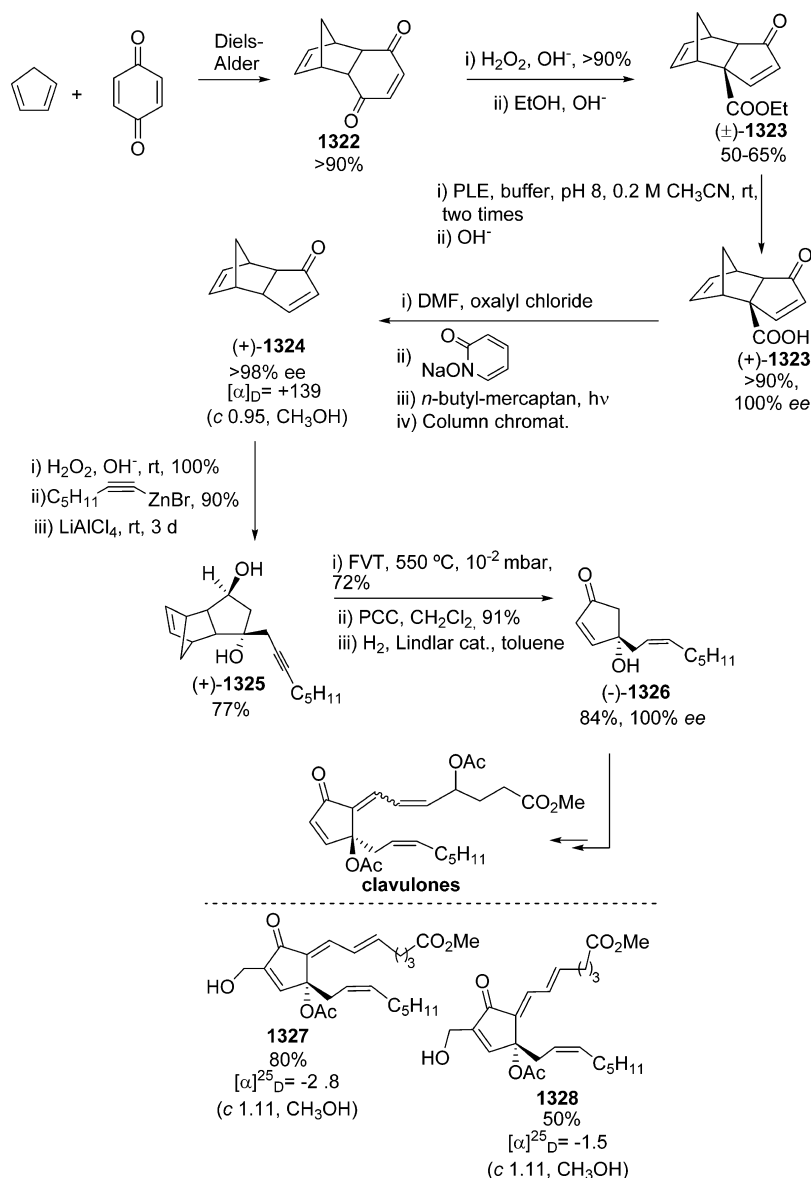
Scheme 315. Overview of the Synthesis of (–)-Precavulone A Methyl Ester from the Ketone 1319



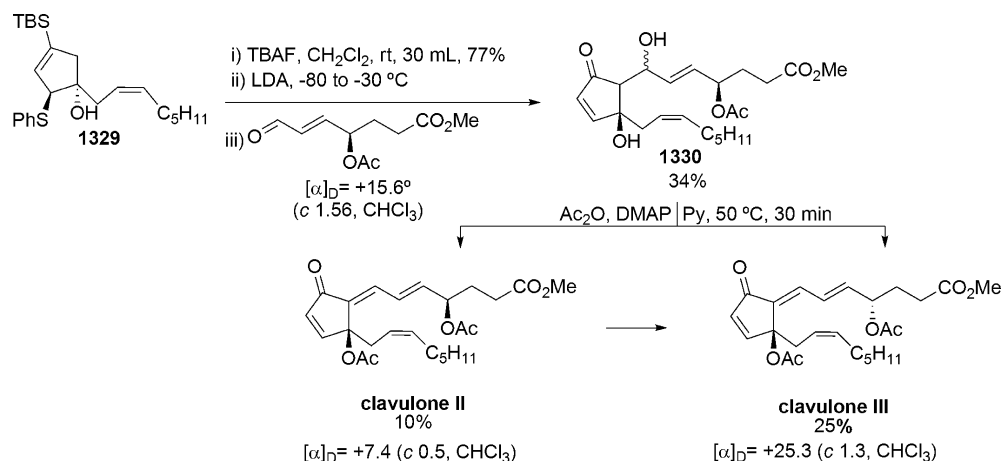
further steps, producing enantiopure (+)-1324. Diol (+)-1325 was obtained from the last product after epoxidation followed by organozinc addition and reductive epoxide ring opening (Scheme 316).⁶⁰² Cyclopentenone (–)-1326, incorporating one chain, was formed by Diels–Alder reaction followed by oxidation and semihydrogenation. Subsequently, a classical aldol–dehydration–deprotection sequence of reactions afforded a desired clavulone. A similar enantioselective approach was applied to afford clavulones 1327 and 1328.

Another strategy explored the use of [3+2] annelation to prepare cyclopentene 1329 bearing the ω -chain from lithium methyl ketone enolate and (β -phenylthio)acryloisilane (Scheme 317).⁶⁰³ The α -chain was installed by aldol–dehydration, using an optically active ester aldehyde. After acetylation and separation by chromatography, clavulone II (claviridenone c) and clavulone III (claviridenone b) were obtained in low yields. The optical rotations of these compounds closely resembled those of samples of natural marine

Scheme 316. Synthesis of Clavulones via Enzymatic Resolution



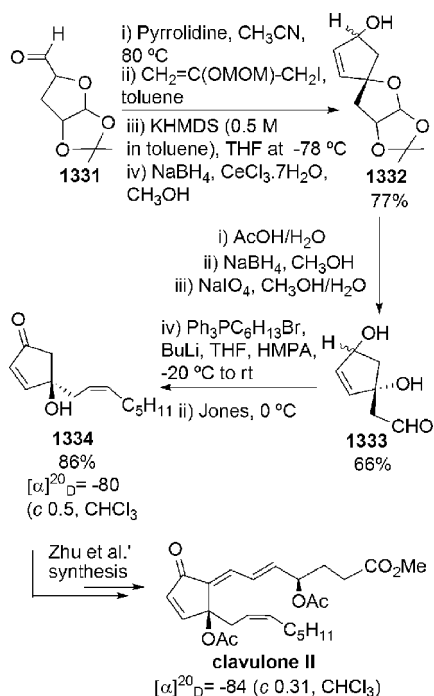
Scheme 317. Synthesis of Clavulones II and III



claviridenones obtained from Japanese stolonifer *Clavularia viridis*.

Florent and co-workers also reported the enantioselective synthesis of 4-alkyl-4-hydroxycyclopentenone **1334** via tandem cationic aza-Claisen rearrangement and Mannich cyclization (Scheme 318).⁶⁰⁴ This crucial intermediate was used for the synthesis of clavulone II described above.⁶⁰²

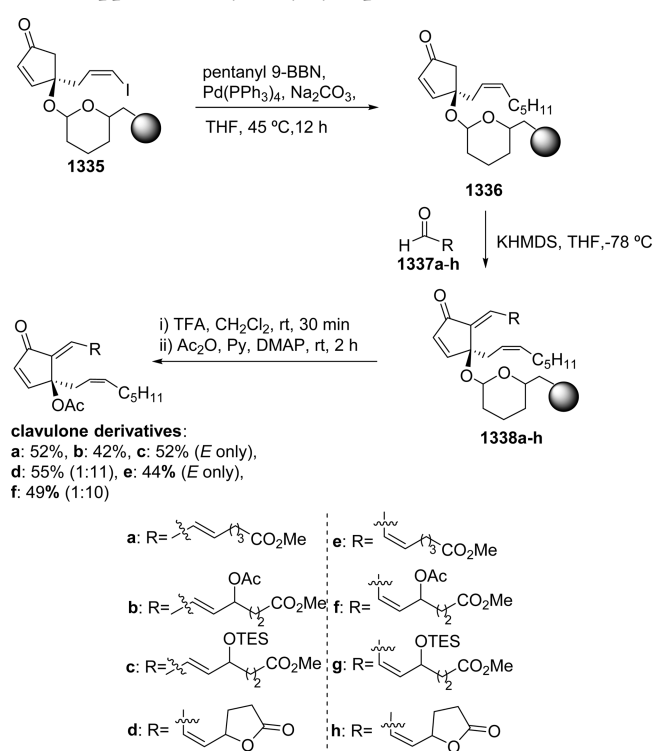
Scheme 318. Synthesis of Clavulone II via Tandem Cationic Aza-Claisen Rearrangement and Mannich Cyclization



A solid-supported 4-hydroxy-cyclopentenone derivative underwent Pd-catalyzed reaction affording a cyclopentenone intermediate with attached ω -chain (Scheme 319). The other chain was introduced by aldolization–dehydration sequences. The compound was cleaved from the solid support and after acetylation provided the desired clavulone.⁶⁰⁵

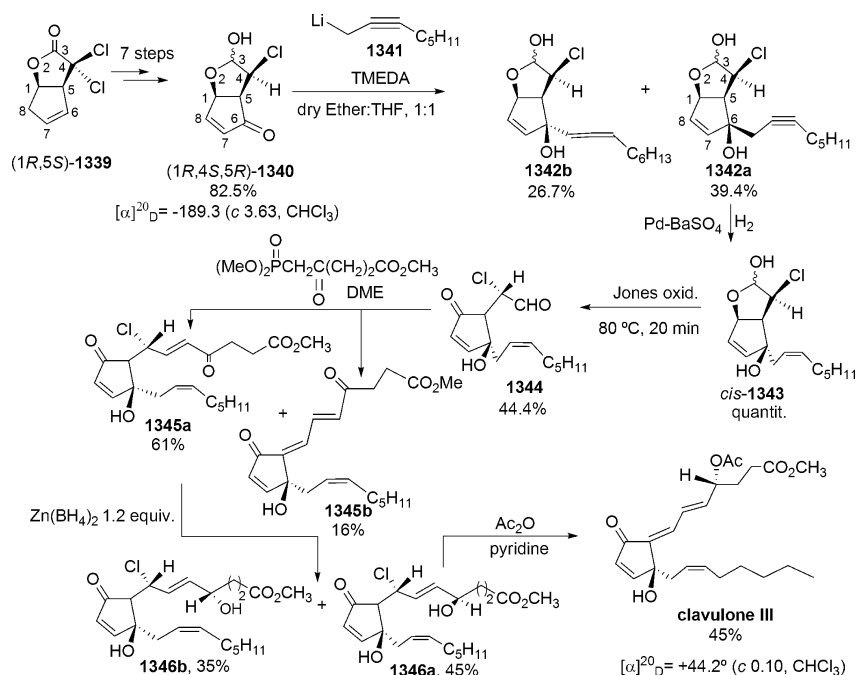
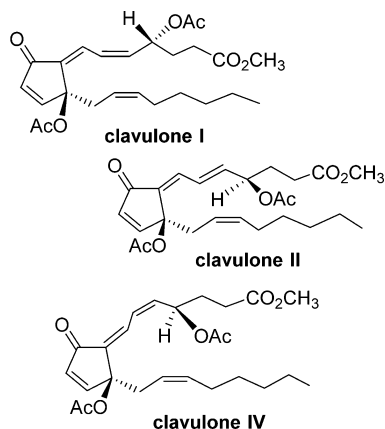
In 1991, Achiwa et al.⁶⁰⁶ reported the stereoselective synthesis of optically active clavulones of type I, II, III, and IV from the chiral precursor dichloro Corey lactone (1*R*,5*S*)-**1339**. This

Scheme 319. Synthesis of Clavulone Derivatives Using a Solid-Supported 4-Hydroxy-cyclopentenone

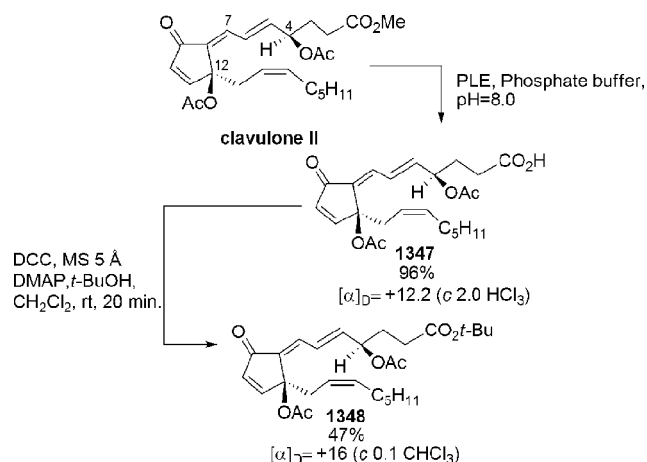


starting material was converted into (1*R*,4*S*,5*R*)-**1340** as a key derivative in seven steps from **1339** and consequently connected to the α - and ω -chains (Scheme 320). The former was added stereoselectively, using 2-octynyllithium **1341** and Lindlar conditions to hydrogenate the acetylene **1342a** quantitatively to *cis*-**1343**. The ω -chain was introduced by Wittig reaction between **1344** and dimethyl(4-carbomethoxy-2-oxobutyl)-phosphonate to give **1345a** (61%) and **1345b** (16%), respectively. The regioselective reduction of **1345a** with Zn borohydride afforded epimeric mixture **1346a,b**, which was separated by chromatography. Treatment of the less polar epimer **1346a** with acetic anhydride and pyridine afforded clavulone III as a single product. The total syntheses of clavulones I, II, and IV were also achieved (Scheme 321).

Yamada et al. reported the syntheses of different clavulone derivatives employing chiral pool clavulones I and II isolated

Scheme 320. Synthesis of Clavulone III from Dichloro Corey Lactone (1*R*,5*S*)-1339Scheme 321. Structures of Synthesized Clavulones I, II, and IV from Dichloro Corey Lactone (1*R*,5*S*)-1339

Scheme 322. Functional Transformation of Clavulone II

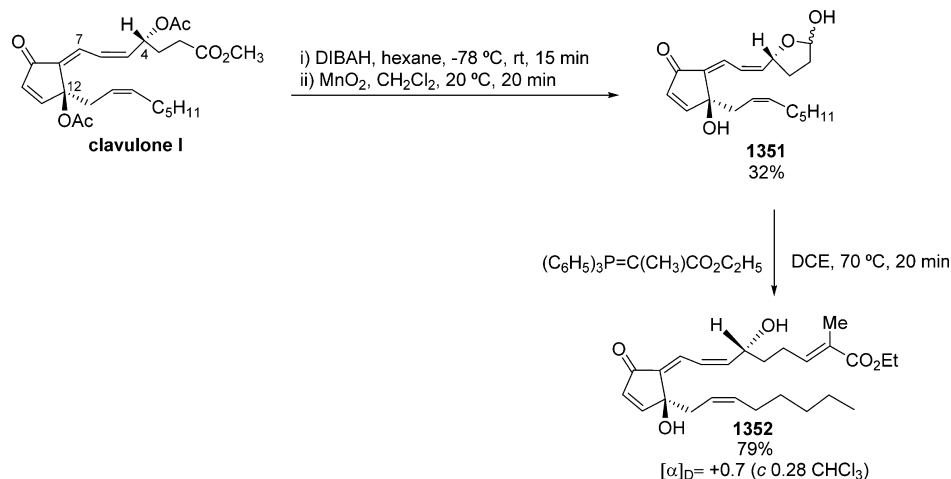


from the soft coral *Clavularia viridis*. The modification of the α -chain by selective cleavage of the ester bond and its elongation have been accomplished.⁶⁰⁷ The biological activities of the prepared derivatives were studied. Scheme 322 shows the synthetic methods used to prepare several clavulone compounds. The authors obtained 1347 by hydrolysis of clavulone II with PLE. Consequently, 1347 was subjected to esterification with *t*-BuOH, giving ester 1348. The derivative 1349 was obtained from clavulone II by epoxidation with *t*-butylperoxide. The compound 1350 was achieved by reaction of 1349 with lithium dimethylcuprate. Reduction of clavulone I with diisobutylaluminum hydride (DIBAL), followed by oxidation with active manganese(IV) oxide, furnished 1351. Wittig reaction with ethyl 2-triphenylphosphoranylidene propionate and 1351 gave 1352 as a sole isomer (Scheme 323).

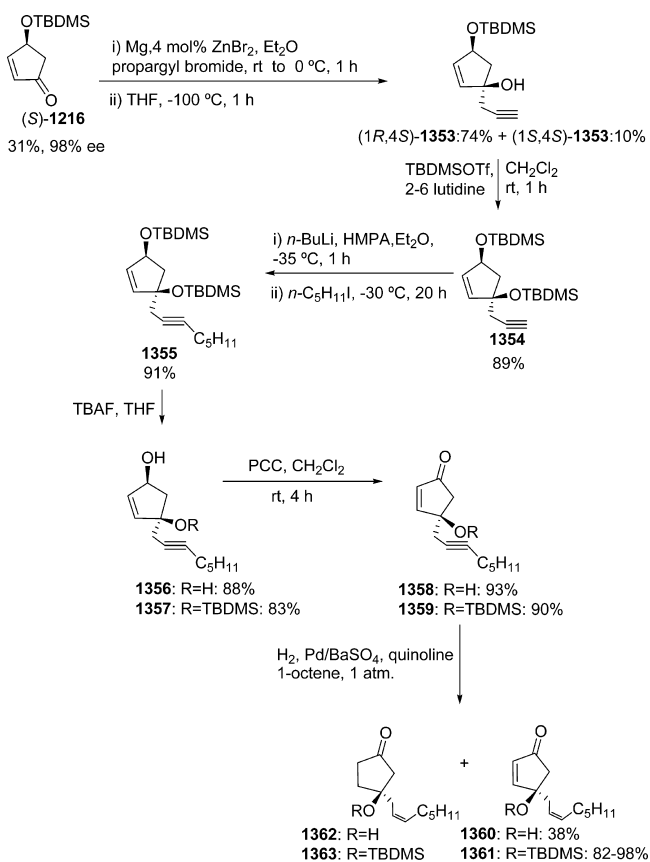
The first total asymmetric syntheses of clavulolactones II and III, examples of natural prostanoids possessing a γ -lactone moiety in the α -side chain, isolated from the Okinawan soft coral *Clavularia viridis* by Iguchi et al. in 1995,⁶⁰⁸ were reported by

Tius et al.⁶⁰⁹ As starting material, the easily accessible (*S*)-4-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (*S*)-1216 was chosen, which was prepared in 31% overall yield based on the published method. By the reaction of (*S*)-1216 with propargylmagnesium bromide, the desired terminal alkyne (1*R*,4*S*)-1353 was prepared in 74% yield, together with 10% of the diastereoisomer (1*S*,4*S*)-1353. The product 1355 was

Scheme 323. Functional Transformation of Clavulone I



achieved in 91% yield from the protected derivative 1354 through alkylation with 1-iodopentane (Scheme 324). Another

Scheme 324. Functional Transformation of (S)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-one (S)-1216

critical step in the synthesis was the hydrogenation of alkyne 1359. When the authors used palladium on barium sulfate as catalyst with quinoline as poison, they were able to isolate 1361 in 98% yield after chromatography. They prepared the γ -lactone side chain 1365 from commercially available chiral alcohol 1364 by Swern oxidation and Wittig reaction (Scheme 325). After aldol condensation of cyclopentenone 1361 with γ -lactone side chain 1365, the isomers (1*E*,3*E*)-1366 and (1*E*,3*Z*)-1366 were

isolated in 61% and 18% yields, respectively. After hydrolysis with aqueous HF in CH₃CN, the isomers (1*E*,3*E*)-clavulactone II and (1*E*,3*Z*)-clavulactone III were produced in 91% and 97% yields, respectively. From these isomers were obtained clavulolactone II and clavulolactone III in 92% and 87% yields, respectively. The synthesis was performed in 10 linear steps in 21% and 7% overall yields for clavulolactone II and clavulolactone III, respectively.

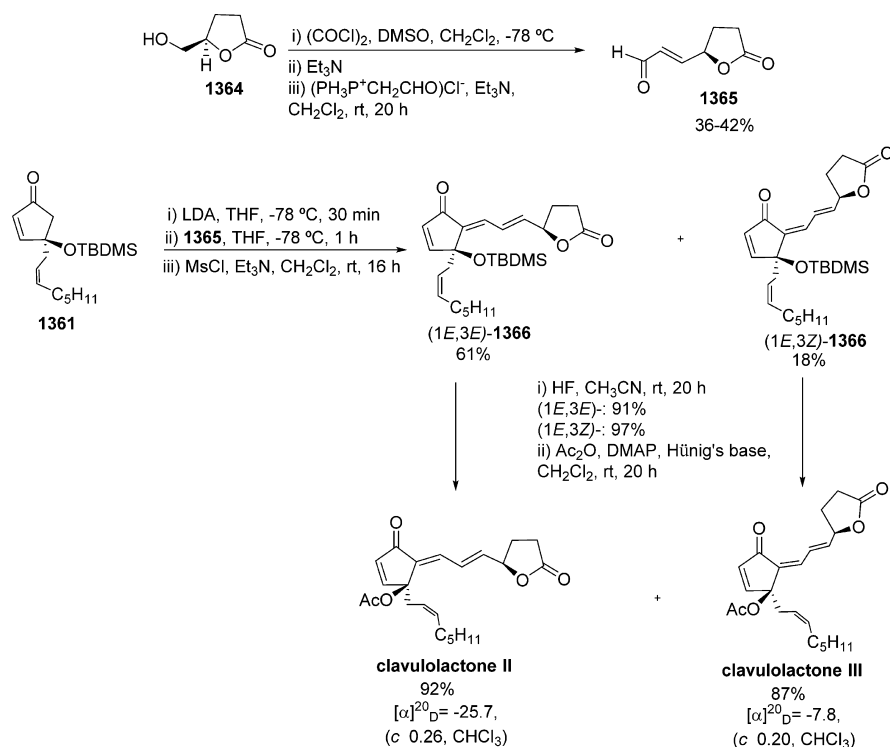
Tricycloclavulone, which has a tricyclo[5.3.0.0^{1,4}]-decane skeleton, was recently isolated as an abnormal marine prostanoid from *C. viridis*. The first enantioselective total synthesis of (+)-tricycloclavulone was reported by Iguchi and co-workers (Scheme 326).⁶¹⁰ In previous work, the same research group prepared the tricyclic core in a racemic form.⁶¹¹

This synthesis began by applying an enantioselective [2+2]-cycloaddition, catalyzed by the chiral bis-py CuCl₂ catalyst 1367 in the presence of AgSbF₆, affording 1372 in 73% ee. The tricyclic core 1373 was formed on RCM condensation with the second-generation Grubbs catalyst⁶¹² in 56% yield. The sequential introduction of ω - and α -chains established stereogenic centers on the C-ring through stereoselective 1,4 addition of the ω -chain by *n*-dibutylcopper lithium followed by the intramolecular ester transfer reaction to afford 1374 in 83% yield as a single stereoisomer. The α -chain was elongated by a sequence of steps involving lactone reduction to a diol with LiAlH₄, Swern oxidation to a keto-aldehyde, and Horner–Wittig–Emmons reaction with 5-(dimethoxyphosphoryl)-4-oxopentanoic acid methyl ester 1368, thus giving (–)-1376 in 72% yield. Enantioselective reduction of the C=O group on the α -chain with Noyori's Ru catalyst [(1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamine](*p*-cymene)ruthenium(II)] 1369⁶¹³ afforded 1377 as a 11:1 mixture, in quantitative yield. The major isomer was used to produce (+)-tricycloclavulone in three steps in 97% yield.

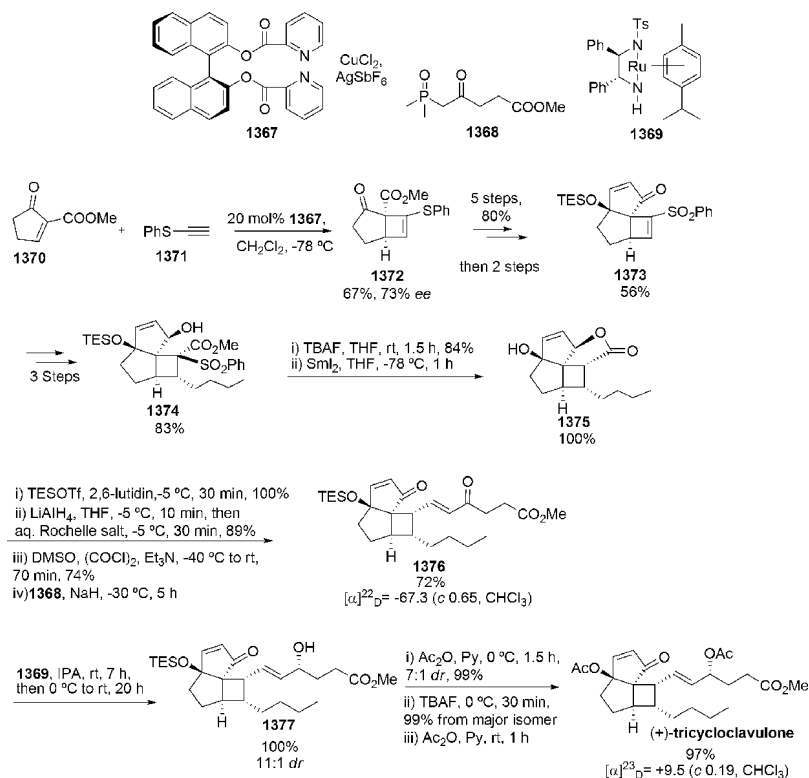
The structures of a series of chlorinated marine prostanoids punaglandins (PUGs) isolated from the Hawaiian octocoral *Telestoriisei* have been reported by Scheuer et al.⁵³² Punaglandins (PNGs), C10 chlorinated and C12 oxygenated prostanoids, are more potent inhibitors of isopeptidase activity than Δ^{12} -PGJ₂ and the PGA series. The PUGs have higher antitumor and anti-inflammatory effects than the clavulones.^{511,535}

Yamada et al. reported the synthesis of PuG-4⁶¹⁴ (Scheme 327). The upper chain was derived from 2-deoxy-D-ribose, through an application of the Corey method⁶¹⁵ to form hydroxy

Scheme 325. Synthesis of Clavulactones II and III from the Lactone 1364



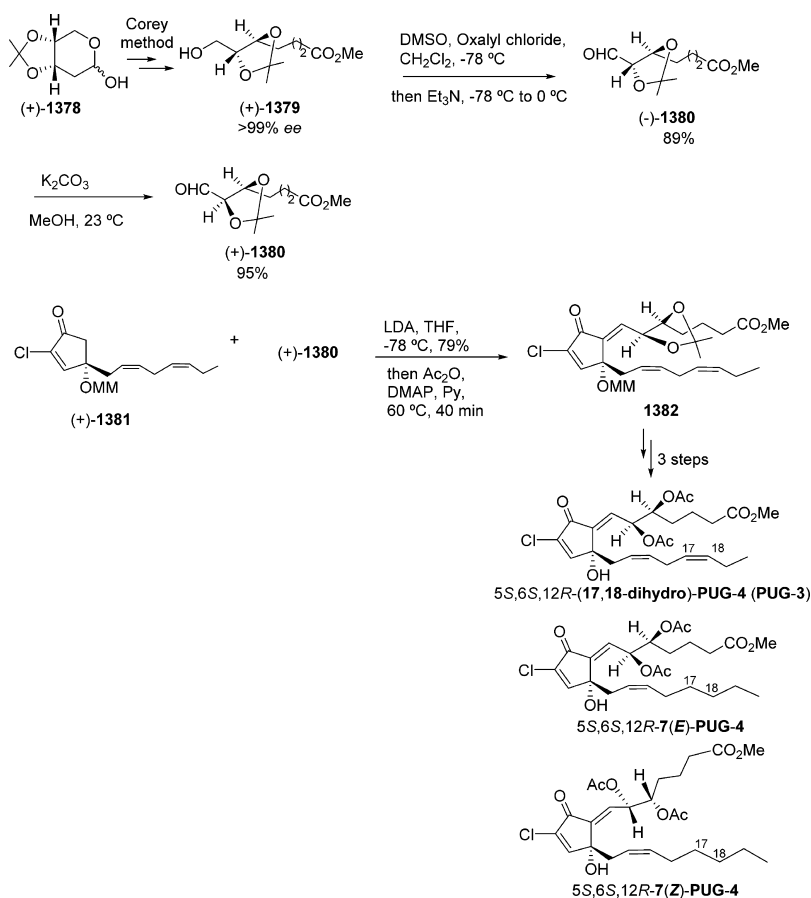
Scheme 326. First Asymmetric Synthesis of (+)-Tricycloclavulone



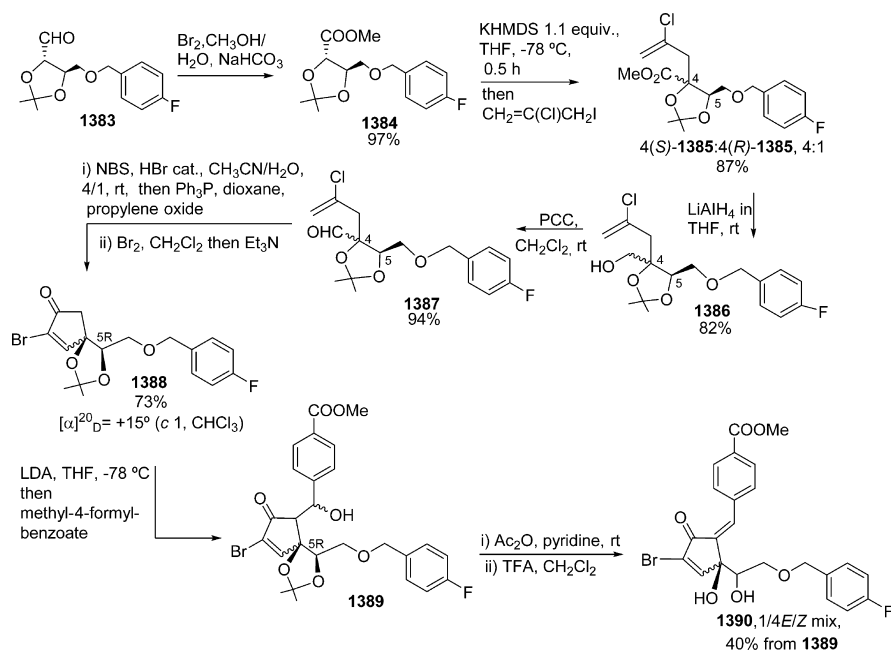
ester 1379 in 99% ee and subsequent Swern oxidation⁶¹⁶ and isomerization of the obtained intermediate to aldehyde (+)-1380, preserving the molecule's enantioselectivity. The latter was attached to the chiral cyclopentenone 1381, which possesses the ω chain, furnishing 5S,6S,12R-(17,18-dihydro-PUG-4) (PUG-3). This was the structure of PUG-4.

Noyori and coauthors reported a convergent synthesis of 7E and 7Z punaglandins, also suggesting the revision of the originally accepted structures. The complete punaglandin skeleton was constructed by aldol condensation of the silyl-protected hydroxycyclopentenone and (2R,3S)-2,3-diacetoxy-6-carbomethoxyhexanal. The structure was confirmed by NMR as

Scheme 327. Synthesis of PUGs



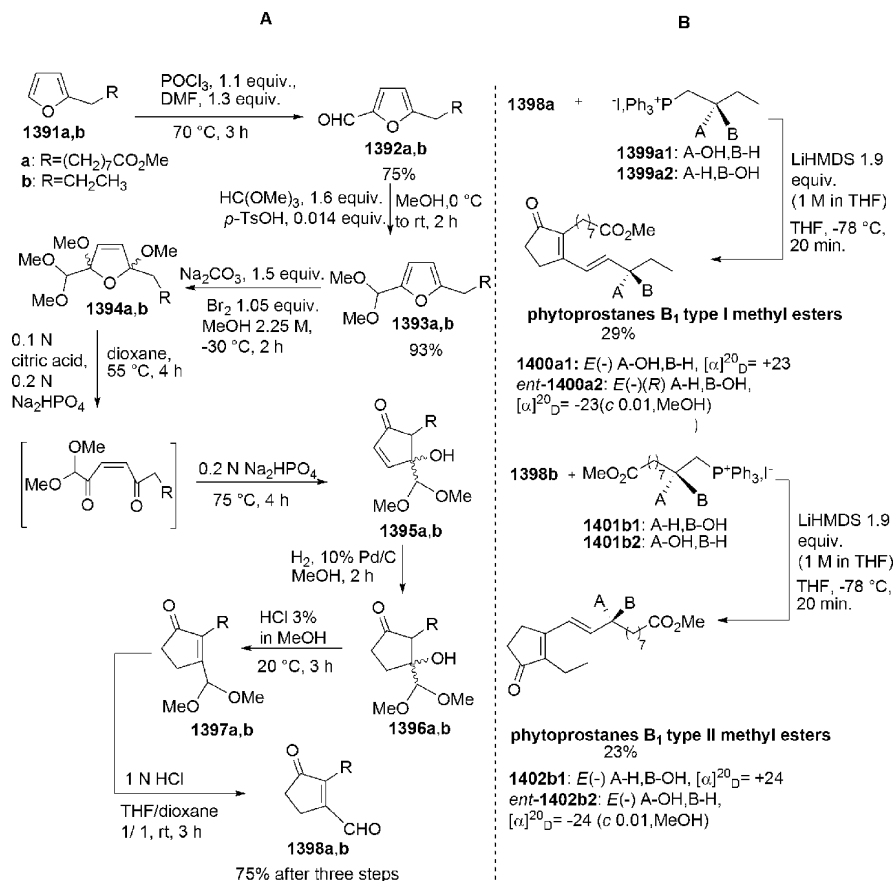
Scheme 328. Synthesis of 1390



being the 5S,6S,12R isomer. The configuration of 7(E,Z)-PUG-4, also claimed to be the same for (17,18-dihydro) derivatives (PUG-3), was assigned by NMR studies.^{533,617} It should be pointed out that the absolute configuration of the PUG structure did not affect the level of antineoplastic activity against L1210

tumor cell proliferation, but the presence of a chlorinated cross-conjugated dienone moiety adjusted the antitumor effect of some PUG analogues.

The synthesis of a series of brominated cross-conjugated dienone marine prostanoid analogues, with a vicinal *syn*- or *anti*-

Scheme 329. Synthesis of Phytoprostanes B₁ Type I and II Methyl Esters from Furan Derivatives

diol on the ω chain, was reported.³⁹⁷ These new prostanooids display good cytotoxicities due to replacement of the ω side-chain of the natural prostanooids with a 1-hydroxyphenylbutyl group. In a second series of compounds, a shorter α side-chain bearing a simple phenyl ester was incorporated, which increases their cytotoxicity. When the ω -1-hydroxyphenylbutyl group was replaced by a 1-hydroxymethoxybenzyl chain, the cytotoxicity was found to be similar to that of natural punaglandins. The synthetic strategy was considered using two cyclopentaannulation processes, from an enamine (by a domino 3-aza Claisen/Mannich reaction) and from dioxolane ester alkylation followed by intramolecular Wittig reaction.³⁹⁷ Scheme 328 shows an example of a synthetic route to these compounds. The 4-fluorobenzyl ether derivative of erythro-2,3-dioxolanyl butanetriol **1383** undergoes Swern oxidation followed by Lichenthaler's procedure⁶¹⁸ (Br_2 , $\text{MeOH}/\text{H}_2\text{O}$, NaHCO_3 , 97%) to methyl ester. Treatment of this ester with KHMDS (1.1 equiv) in THF at -78°C , followed by addition of 2-chloro-3-iodopropene, afforded, by expected contrasteric alkylation,³⁹⁶ the major alkylated ester product (4*S*)-**1385** along with its diastereoisomer (4*R*)-**1385** as an inseparable mixture (87%, ratio 8/2). After reduction of the ester function with LiAlH_4 in THF at 20°C , the two diastereoisomers were obtained: major (4*R*) and minor (4*S*), which were easily separated. After oxidation by PCC, NBS with a catalytic amount of HBr in CH_3CN was used to transform the chloroallyl chain into bromomethyl ketone, which was treated with triphenylphosphine in refluxing dichloromethane to perform an intramolecular Wittig reaction, furnishing the cyclopentenone **1388** after bromination. Aldol condensation of ketone **1388** and the corresponding aldehyde gave **1389**.

Elimination of the hydroxyl group and hydrolysis of the acetal ring afforded the final cyclopentenone prostanooid analogue **1390** with high diastereoselectivity.

The free-radical-initiated peroxidation of α -linolenic acid produces phytoprostanes (PhytoP). The 16-B₁-PhytoP methyl ester as well as the 9-B₁-PhytoP methyl ester are currently the most extensively studied phytoprostanes.^{528,619,620} B₁-PhytoP also shows a pronounced cytoprotective effect against active transition metal cations and is also an endogenous mediator capable of protecting the cell from damage caused by various toxins.⁶¹⁹ New B₁- and L₁-PhytoPs have been discovered to defend immature human neurons against oxidation damage and to act through PPAR- γ (peroxisome proliferator-activated receptor).⁶²¹

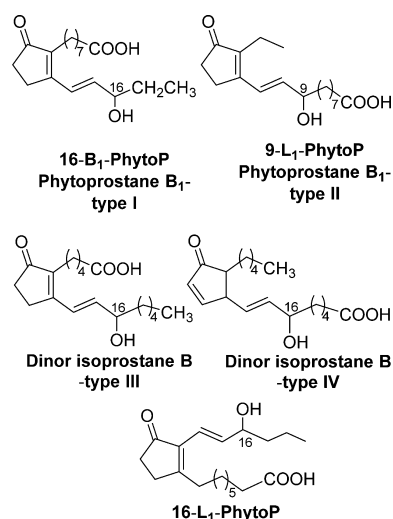
The deoxy-J₁-phytoprostanes, structurally related to 15-deoxy-12,14-prostaglandin J₂, display biological activities typical of cyclopentenone prostaglandins such as anti-inflammatory and antiviral⁶²² effects and apoptosis-inducing activity.⁶²³ Currently, little is known about the biological activities of different phytoprostane classes in humans.

Durand and co-workers reported the synthesis of the enantiomerically pure phytoprostanes B₁ type I and II methyl esters starting from furfural and *n*-propylfuran (Scheme 329).⁶²⁴ The six-step synthesis began with a Vilsmeier formylation reaction at the 5 position of the furans **1391a** and **1391b**, and a selective rearrangement prepared 4-hydroxy-2-cyclopentenone precursors **1392a,b**. These two 4-hydroxycyclopent-2-enone acetals were transformed into 3-oxocyclopentenecarbaldehydes **1398a,b** in several steps and served as precursors for the synthesis of both enantiomers of 16-B₁-PhytoP methyl ester as

well as of 9-B₁-PhytoP methyl ester by Wittig reactions to introduce side chains with chiral centers using chiral β -hydroxy phosphonium salts, prepared from chiral pool starting materials (*R,S*)-(\pm)-1,2-epoxybutane or (*R,S*)-(\pm)-epichlorohydrin in two and five steps, respectively.

γ -Linolenic acid can be transformed into the dinor isoprostanes type III and IVb by a similar process observed for the formation of phytoprostanes type I and II from α -linolenic acid. Scheme 330 shows the most representative examples of

Scheme 330. Representative Structures of Phytoprostanes

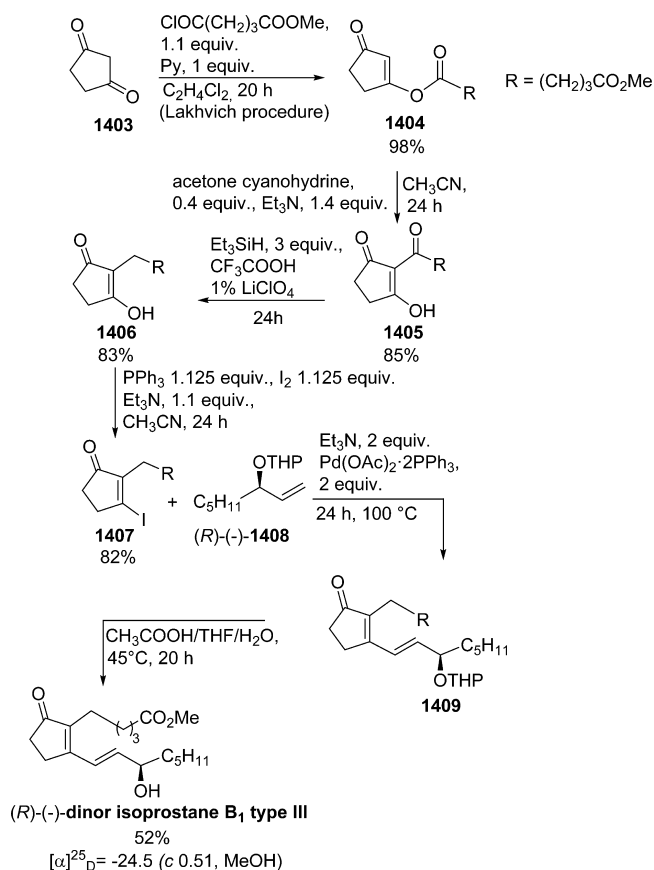


stable products of peroxidation of α - and γ -linolenic acids. These compounds exhibit important biological activities in plants and could also bind to the important receptors of the structurally related prostaglandins.⁶²⁵ Boland et al. obtained phytoprostane B₁ types I and II and donor isoprostanes type III in 35–53% overall yield from 1,3-cyclopentanedione.⁶²⁶

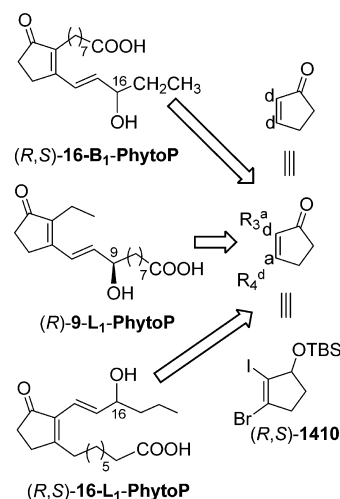
The *O*-acylation of 1,3-dione **1403** was done via Lakhvich protocol.⁶²⁷ The sequence of rearrangement and reduction then afforded the key intermediate **1406**, possessing one side chain. Subsequent conversion into the corresponding vinylic iodide **1407** and insertion of the second side chain was introduced by transition metal catalysis following Heck- or Sonogashira-type protocols.^{628,629} The chiral donor isoprostane (–)-(*R*)-**1409** was achieved by alkylation with (*R*)-(*–*)-oct-1-en-3-ol-THP **1408** following the same protocol (Scheme 331).⁶²⁶ The authors also described phytoprostanes with an acetylene moiety instead of the (*E*)-allyl alcohol. The central vinylic iodides were used in a Sonogashira-type vinylation with simple or substituted terminal acetylenes. The corresponding acetylene type (*R*)-(+)-donor isoprostane was obtained in 70% yield employing the same protocol using the THP-ether of (*R*)-(+)-oct-1-yn-3-ol.

In 2015, a novel strategy for the synthesis of (*R,S*)-16-B₁-PhytoP (phytoprostane B₁ types I), (*R,S*)-9-L₁-PhytoP and (*R*)-9-L₁-PhytoP (phytoprostane B₁ types II), and (*R,S*)-16-L₁-PhytoP was reported by Vidari and co-workers.⁶³⁰ The retrosynthesis of these PhytoPs is presented in Scheme 332. The starting material, *O*-TBS-protected 2-iodo-3-bromocyclopentenol (*R,S*)-**1410**, is synthetically equivalent to cyclopent-2-enone, displaying a donor at carbon α (d) and acceptor properties at carbon β (a). Thus, chemoselective monolithiation at carbon α of (*R,S*)-**1410**, followed by addition of electrophilic agents, allowed the construction of the α -chain of PhytoPs (*R*₃). Subsequently, Pd-mediated coupling of olefinic bromine and

Scheme 331. Synthesis of (*R*)-(*–*)-Donor Isoprostane B₁ Type III from 1,3-Cyclopentanedione

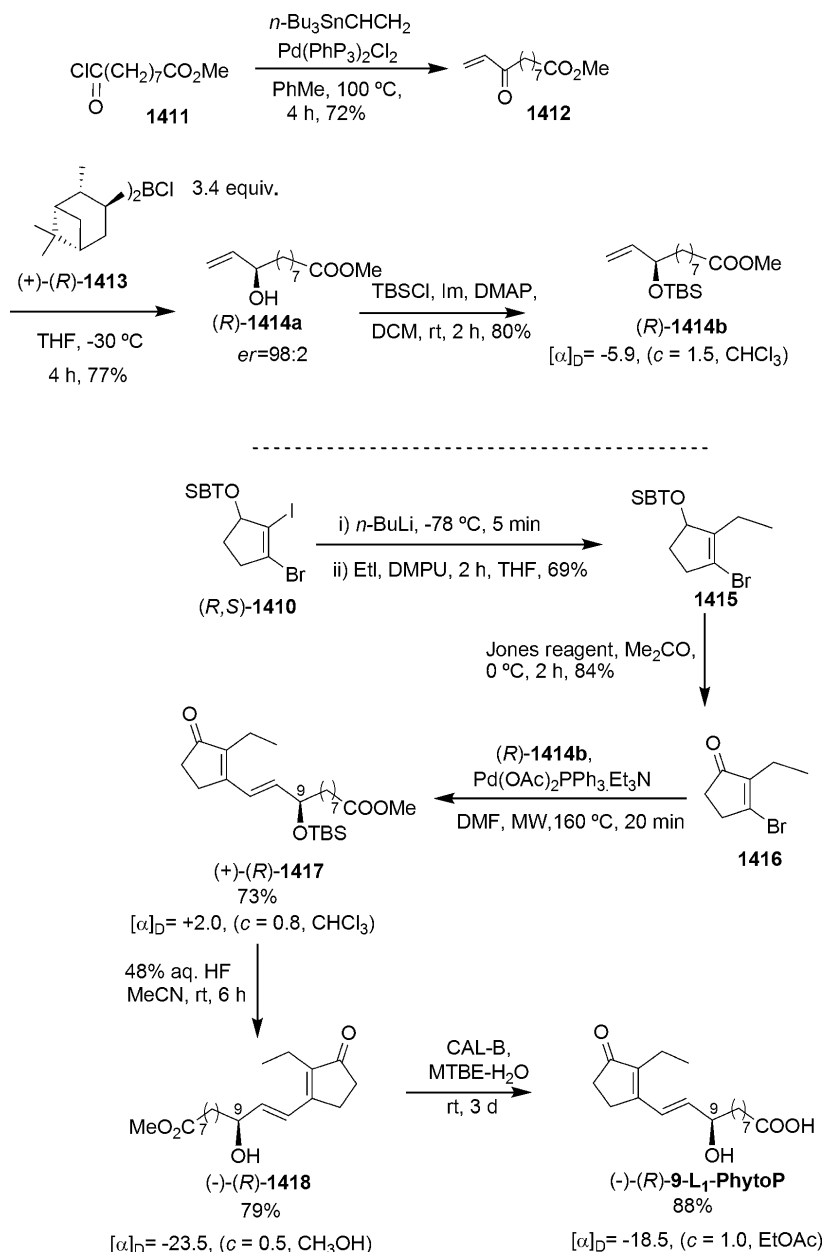


Scheme 332. Retrosynthesis of PhytoPs



organometallic species *R*₄ allowed the formation of their ω -chains.

The asymmetric synthesis of (–)-(*R*)-9-L₁-PhytoP is shown in Scheme 333. The starting material, methyl-9-oxononanoate (**1411**), underwent Stille cross-coupling with vinyltributylstannate to yield **1412**. Brown's DIP-Cl-mediated asymmetric reduction of **1412** gave an allylic alcohol with the appropriate configuration, (*R*)-**1414a**. This compound was then protected under standard conditions with *O*-TBS ether, affording (*R*)-**1414b**. The chemoselective lithiation of (*R,S*)-**1410** generated

Scheme 333. Synthesis of (–)-(R)-9-L₁-PhytoP

1415, which was oxidized to enone **1416** under Jones conditions. Microwave-assisted Heck reaction between (R)-**1414b** and **1416** afforded (+)-(R)-**1417** in 73% yield and with an *E*-diastereoselectivity of >95%. After deprotection of the allylic alcohol of (+)-(R)-**1417** followed by lipase-mediated hydrolysis of methyl ester (–)-(R)-**1418**, (–)-(R)-9-L₁-PhytoP was obtained in 88% yield.

The asymmetric synthetic approach to prostaglandin B₁ and phytoprostanes B₁ was reported by Riera et al.⁶³¹ The intermolecular Pauson–Khand reaction (PKR) between silyl-protected propargyl acetylene **1419a,b** and ethylene, promoted by NMO in the presence of 4 Å molecular sieves, afforded the 3-*tert*-butyldimethylsilyloxymethyl 2-substituted cyclopent-2-en-1-ones **1420a,b** in good yield and with complete regioselectivity (Scheme 334). The key aldehydes **1420a,b** were obtained in three high-yielding steps from readily available acetylene using PKR. These were subjected to Julia olefination reactions to

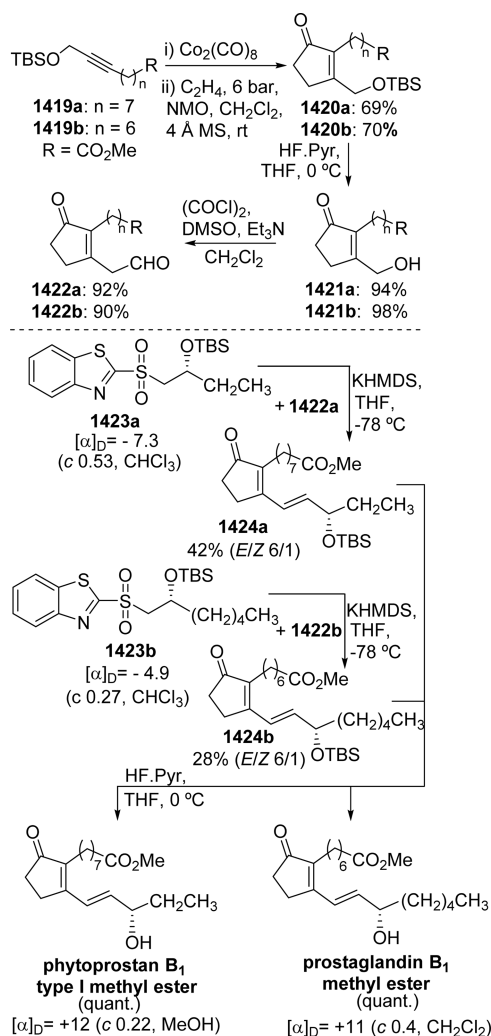
introduce the chiral side chains in PGB₁ and PPB₁ type I while preserving stereochemistry through to the final products.

In 2013, Riera's group reported new work based on the aforementioned enantioselective syntheses.⁶³² Using *tert*-butyl ether as an alcohol protecting group of Julia sulfone reagents (**1425a–c**), the authors obtained better yields of the final compounds phytoprostanes B₁ types I and II and prostaglandin B₁ (Scheme 335).

The deoxy-J₁-phytoprostanes are major metabolites of the phytoprostane pathway in plants, and they show structures similar to those of powerful defense mediators in plants and animals such as 12-oxo-phytodienoic acid and 15-deoxy-Δ^{12,14} prostaglandin J₂.⁶³³

Naturally occurring cyclopentenone B₁-phytoprostanes are induced by oxidative stress and display powerful biological activities including induction of secondary metabolism as well as glutathione-S-transferase and activation of mitogen-activated protein kinases.^{526,634} Two regioisomers of 13,14-dehydro-12-

Scheme 334. Synthesis of Prostaglandin B₁ and Phytoprostanes B₁ Methyl Esters via Intermolecular Pauson–Khand Reaction (PKR)

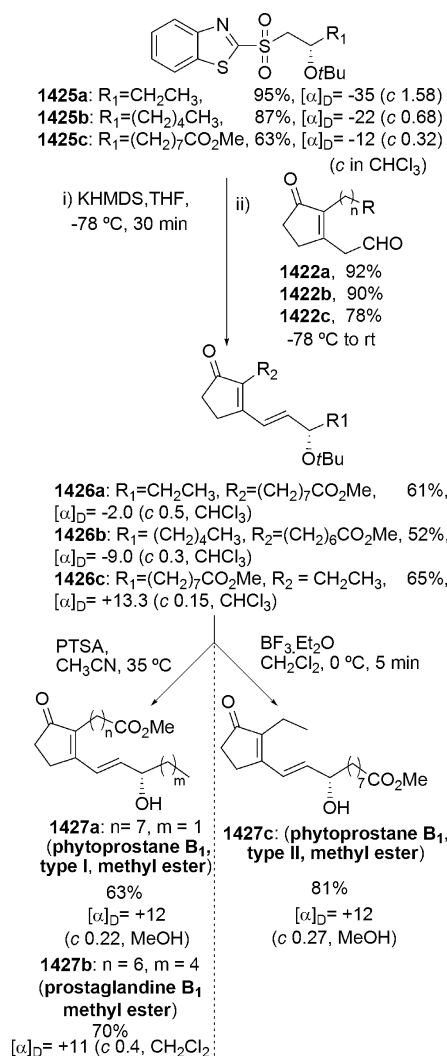


oxo-phytodienoic acid (deoxy-phytoprostane J₁, I and II) can be formed in plants. The deoxy-phytoprostane J₁ I methyl esters display four geometric double-bond isomers (*trans*–*trans*, *cis*–*cis*, *trans*–*cis*, and *cis*–*trans* configurations).⁶³⁵

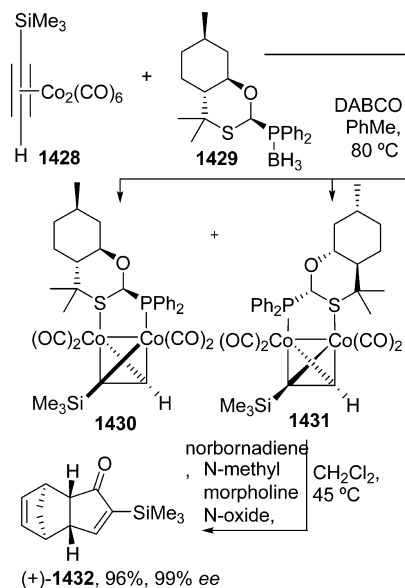
The asymmetric synthesis of deoxy-phytoprostane J₁, types I and II, was reported by Mueller et al. (Schemes 336 and 337).⁶³⁶ Diastereomeric cobalt complexes 1430 and 1431 were prepared using chiral pool substrates (bidentate chiral ligand 1429).¹⁴² They were separated by crystallization or chromatography, and through the asymmetric Pauson–Khand cycloaddition each diastereomer afforded either enantiomer. From 1431 the key compound 1432 was obtained in 99% ee. The *trans*–*trans* isomer was prepared from this material by 1,4-conjugate addition of the appropriate organocuprate reagent and in situ Peterson olefination with *trans*-pent-2-enal. The corresponding carboxylic acid was achieved by a deprotection–oxidation sequence. Thus, treatment of the cyclopentadienyl-protected methyl ester with MeAlCl₂ and maleic anhydride under microwave conditions afforded deoxy-phytoprostane J₁, I in 94% ee, while deoxy-phytoprostane J₁, II was furnished in 99% ee (Scheme 337).

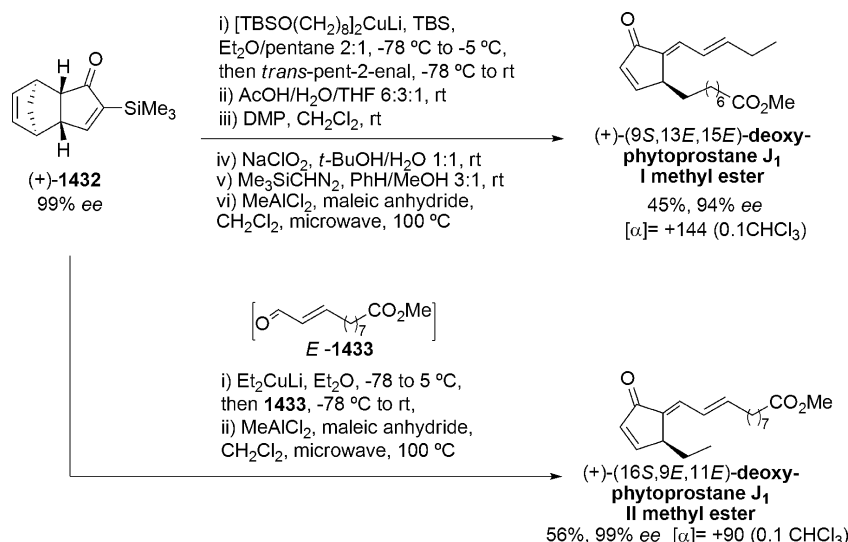
Riera and co-workers (Scheme 338)⁶³⁷ used the enantiomerically enriched compound 1434, prepared via asymmetric Pauson–Khand reaction, to obtain the corresponding enan-

Scheme 335. Synthesis of Methyl Esters of Phytoprostane B₁ Types I and II and Prostaglandin B₁ via Julia Olefination

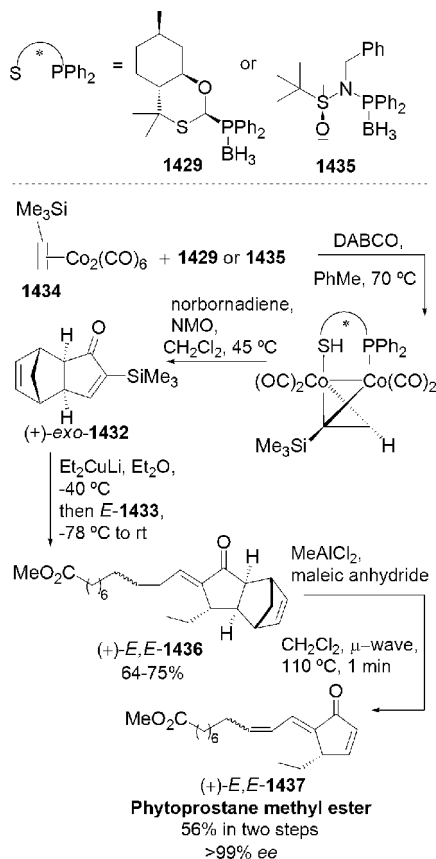


Scheme 336. Synthesis of the Intermediate (+)-1432 via Asymmetric Pauson–Khand Reaction



Scheme 337. Synthesis of Deoxy-phytoprostane J₁, I, and II Methyl Esters via Asymmetric Pauson–Khand Reaction

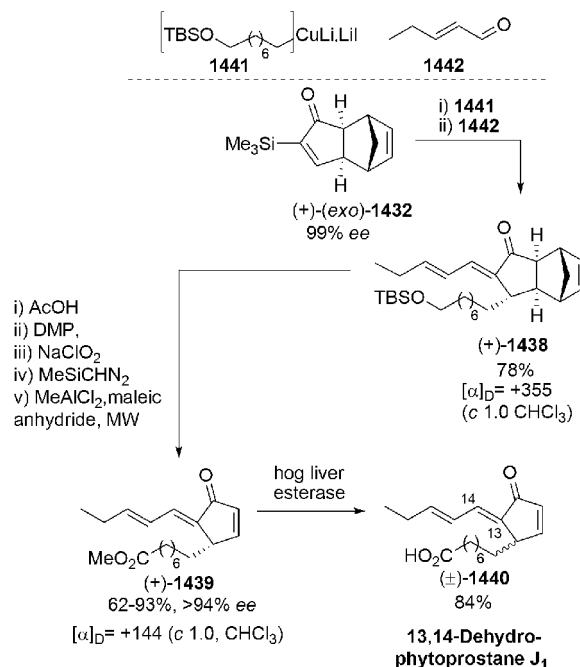
Scheme 338. Synthesis of Phytoprostane Methyl Esters via Asymmetric Pauson–Khand Reaction

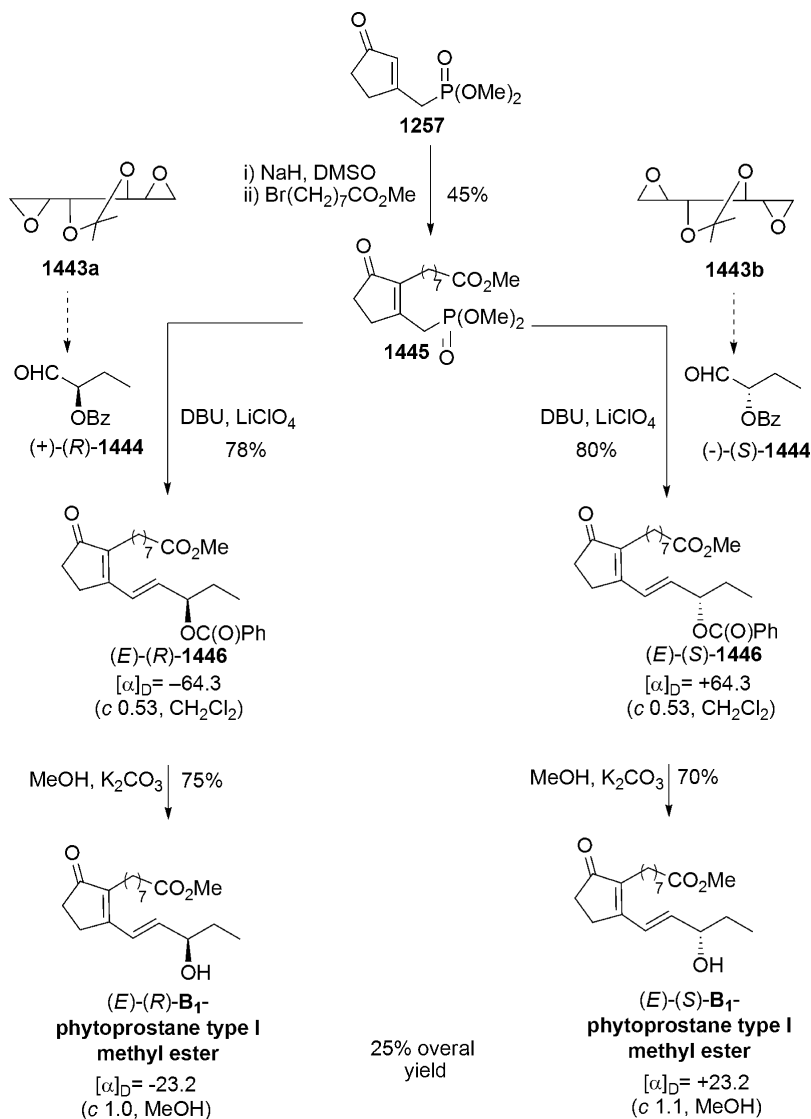


tioenriched 5-alkylenecyclopent-2-enones, and this approach is exemplified by the short, stereoselective total syntheses of two stereoisomers: phytoprostane methyl esters *E,Z*- and *E,E*-1437. The crude *Z*-aldehyde 1433 was employed directly in the conjugate addition–Peterson olefination using (\pm)-1433. The adduct 1436 was obtained in good yield and stereoselectivity (*E,Z* \rightarrow 95% ratio). Finally, a retro-Diels–Alder reaction gave the phytoprostane natural product *E,Z*-1437 (methyl ester) as the 9-*cis*-geometrical isomer. The authors observed that the short

reaction periods and microwave irradiation were key to minimizing isomerization of the double bond formed following the Peterson reaction. An identical synthetic approach using *E*-1436 gave the corresponding 9-*E* stereoisomer *E,E*-1437 in $\geq 99\%$ ee. Hydrolysis of *E,E*-1437 to the corresponding carboxylic acid was achieved with enzyme hog liver esterase.

The authors also used the conjugate addition–Peterson olefination reaction in the preparation of cross-conjugated cyclopentenones possessing oxidized alkyl substituents (Scheme 339). By employing (+)-1432 as initial substrate, methylation followed by a microwave-mediated *retro*-Diels–Alder process afforded the enantioenriched methyl ester (+)-1439. The enzyme hydrolysis of (+)-1439 proceeded nonstereoselectively, and racemic 13,14-dehydrophytoprostane J₁ was produced. Alternatively, the racemic (\pm)-1439 was obtained in 39% overall yield. Saponification of (\pm)-1439 proceeded smoothly using hog

Scheme 339. Synthesis of 13,14-Dehydrophytoprostane J₁

Scheme 340. Synthesis of Pure (+)-(S)- and (-)-(R)-B₁-Phytosteranes Type I Methyl Esters

liver esterase affording the racemic 13,14-dehydrophytoprostane J₁. The spectroscopic data of obtained isomers corresponded to those previously reported.⁶³⁸ The comparison of the reported data and that obtained by the authors for (±)-13,14-dehydrophytoprostane J₁ suggested an epimerization that could also have occurred during the extraction from the natural source. The authors claimed that in nature this product is formed nonstereoselectively via a phytosterane pathway.

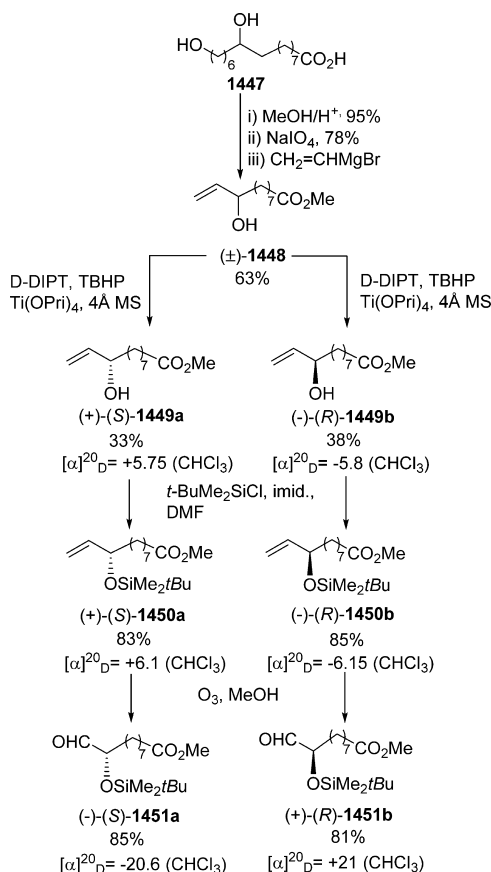
Mikolajczyk and Perlikowska reported a brief synthesis of the enantiomerically pure (+)-(S)- and (-)-(R)-B₁-phytosteranes type I methyl ester, starting from cyclopentenone 3-[(dimethoxyphosphoryl)methyl]cyclopent-2-en-1-one **1257** (Scheme 340).^{639,640} This compound was prepared previously by a two-step synthesis from 2-cyclopenten-1-one: (a) conjugate addition of a phosphorylmethyl selenide to a cyclic enone and (b) oxidative selenide elimination.⁶⁴¹ The compound **1257** underwent a C2 alkylation reaction with previously prepared methyl 8-bromooctanoate under action of NaH in DMSO to form **1445**. The alkylation product was isolated in 45% yield. A Horner alkenation reaction of this derivative under mild basic conditions (1,8-diazabicyclo[5.4.0]undec-7-ene–lithium perchlorate (DBU–LiClO₄) with the enantiopure *O*-benzoylpro-

tected α-hydroxybutanals **1444a** and **1444b**, prepared from D-mannitol via the enantiomeric diepoxides⁶⁴² afforded enantiomeric derivatives (E),(S)-**1446a** and (E),(R)-**1446b** possessing C3 chains in 80% yield. Methanolysis gave (+)-(S)- and (-)-(R)-B₁-phytosteranes type I methyl ester in 25% overall yield.

Mikolajczyk and Perlikowska recently reported the asymmetric synthesis of both enantiomers of phytosterane B₁ type II methyl ester⁶⁴³ starting from 3-[(dimethoxyphosphoryl)methyl]cyclopentenone **1257** as a key reagent, used in their previously reported synthetic route to (+)-(S)- and (-)-(R)-B₁-phytosteranes type I (Scheme 340). In other work, they reported the enantiomeric methyl 9-formyl-9-hydroxynanoate precursors of (+)-(S)- and (-)-(R)-phytosterane B₁ type II methyl esters, used in the Horner olefination reaction of the phosphonate group at the C3 position of **1257**. These important chiral intermediates were prepared from racemic methyl 9-hydroxy-10-undecenoate via asymmetric Sharpless epoxidation under kinetic resolution conditions followed by ozonolysis.⁶⁴⁴ *tert*-Butylhydroperoxide (TBHP) in the presence of (-)-D-diisopropyl tartrate (DIPT) and tetraisopropoxytitanium gave a mixture of the unoxidized alcohol (+)-(S)-**1449a** in enantiomeric excess >98% and the corresponding epoxide (Scheme

341). In the case of (–)-(R)-**1449b**, the authors determined the reaction to proceed with <96% enantiomeric excess by ¹H NMR

Scheme 341. Synthesis of Intermediates **1451a** and **1451b** via Kinetic Resolution Using Asymmetric Sharpless Epoxidation

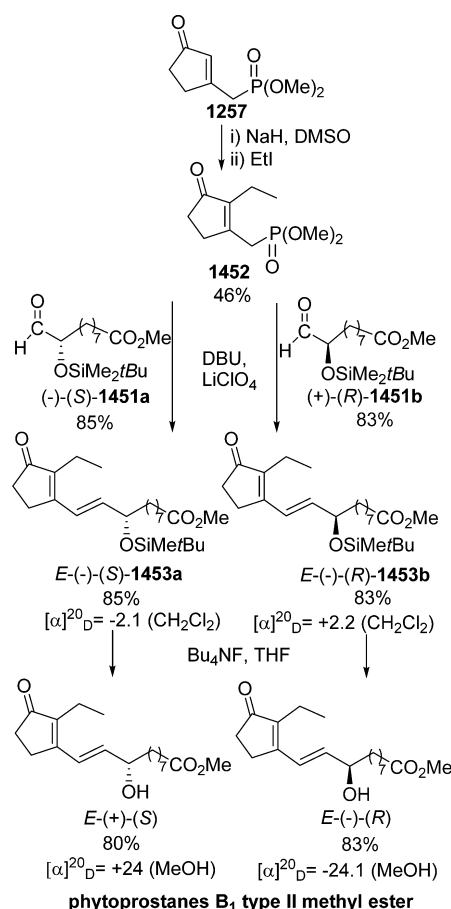


studies. The synthesis of enantiomeric phytoprostane B₁ type II methyl esters is depicted in [Scheme 342](#). The synthesis proceeds similarly to earlier reported routes to phytoprostane B₁ type I, but in this case the chiral aldehydes **1451a** and **1451b** prepared in this work were explored in Horner reactions with ethylated cyclopentenone **1452**. Desilylation of protected enantiomers *E*-(–),(*S*) **1453a** and *E*-(+),(*R*) **1453b** with tetrabutylammonium fluoride in THF at room temperature afforded the final (+)-(*S*)- and (–)-(*R*)-phytoprostane B₁ type II methyl esters. The authors performed the CD spectra of the two enantiomers, which presented a characteristic mirror image relationship with Cotton effects that are negative at 220 nm and positive at 275 nm for the (+)-(*S*)-enantiomer.

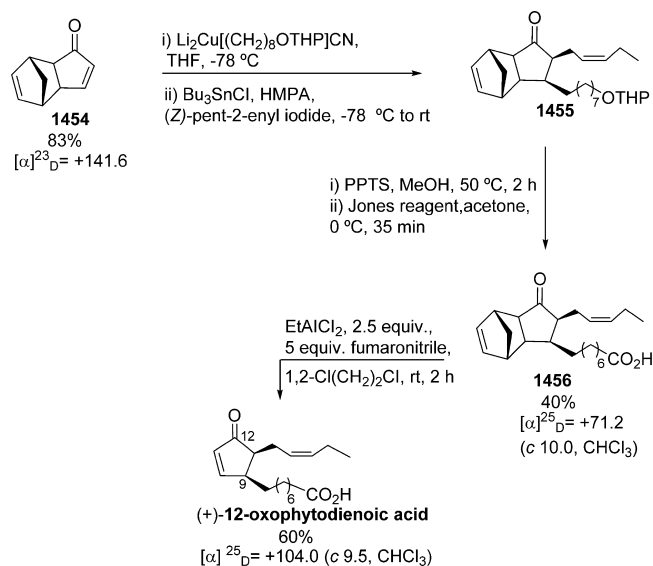
A 12-oxo-10,15-phytodienoic acid (12-oxo-PDA) with a pseudoprostanoid structure, related to the linolenic acid cascade in plants, was prepared to study a peroxisomal acyl-activating enzyme and to elucidate the expression of the specific DNA.^{645,646} The syntheses of racemic and chiral variants of this compound have been reported by different groups.^{647–649}

The earliest enantioselective synthesis of 12-oxo-PDA was reported by Grieco and Abood in 1989.⁶⁴⁷ The key step of the synthetic route is a Lewis acid-catalyzed retro-Diels–Alder reaction at ambient temperature with enantiomerically pure norbornene derivatives of type **1454**⁶⁵⁰ as substrates and methylaluminum dichloride as a reactive dienophile. The principal steps of asymmetric synthesis of 12-oxo-PDA are depicted in [Scheme 343](#). A three-component coupling process

Scheme 342. Synthesis of Phytoprostane B₁ Type II Methyl Esters

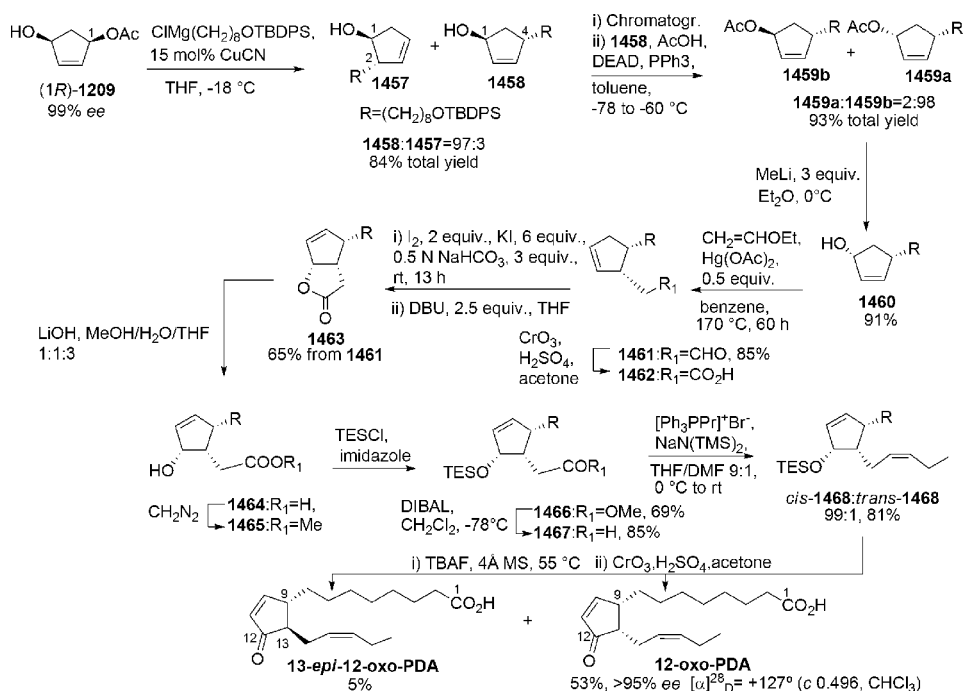


Scheme 343. Synthesis of 12-Oxo-10,15-phytodienoic Acid



including cuprate addition followed by substitution of the intermediate enolate with pentenyl iodide exclusively afforded *exocis*-disubstituted derivative **1455**, which was further subjected to cleavage of the THP group and oxidation to give chiral intermediate **1456**.

Norbornene compound **1454** underwent Lewis acid [4+2] cycloreversion as a reactive dienophile to form (+)-12-oxo-PDA,

Scheme 344. Synthesis of 12-Oxo-PDA and 13-*epi*-12-Oxo-PDA

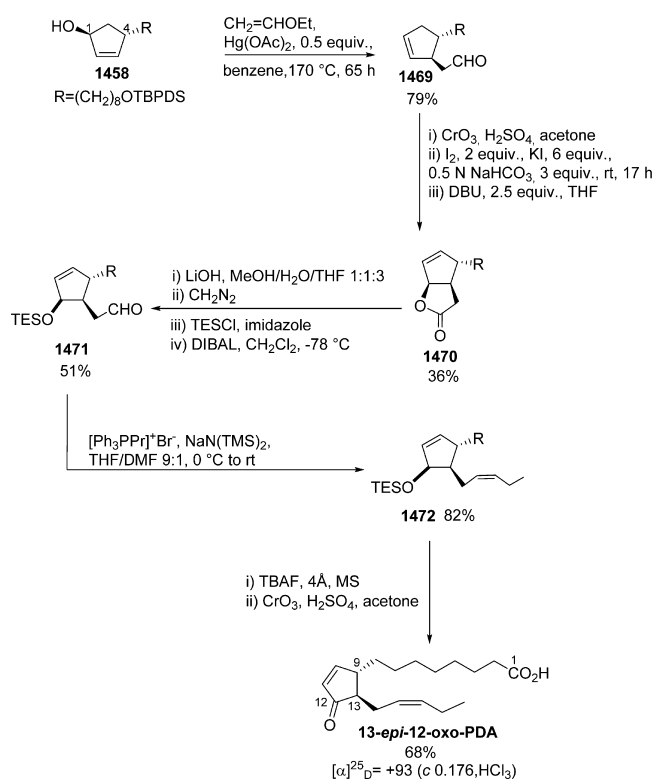
which was obtained in 60% yield. The ^1H NMR spectrum of this compound was identical to the ^1H NMR spectrum of the natural product.

Kobayshi and co-workers^{651,652} reported the first stereoselective syntheses of 12-oxo-PDA and 13-*epi*-12-oxo-PDA, whereby the authors made use of (1*R*,3*S*)-cyclopenten-1,3-diol monoacetate **1209**⁶⁵³ as an enantioselective precursor. The synthesis of 12-oxo-PDA is shown in Scheme 344.

The freshly prepared Grignard reagent $\text{ClMg(CH}_2)_8\text{OTBDPS}$ reacted with (1*R*)-**1209** in a CuCN-catalyzed reaction and furnished **1457** and **1458** with preinstalled ω -chains in 84% yield as a separable 3:97 mixture. The hydroxy group of the separated pure isomer **1458** was inverted by Mitsunobu reaction,⁶⁵⁴ which furnished *cis:trans* acetate isomers **1459a** and **1459b** in a 2:98 ratio. The alcohol **1460**, formed by hydrolysis from **1459b**, was subjected to a Claisen rearrangement using $\text{CH}_2=\text{CHOEt}$ and Hg(OAc)_2 as a catalyst to give aldehyde **1461**. Iodolactonization and elimination of HI afforded lactone **1463**. Formed by conventional methods, TES-protected aldehyde **1467** was subjected to Wittig reaction under the modified conditions of Santelli and Viala,⁶⁵⁵ which introduced the unsaturated α chain on derivative **1468** with an excellent *cis:trans* ratio of 99:1. Deprotection of the two silyl groups and oxidation of the resulting alcohol afforded 12-oxo-PDA and 13-*epi*-12-oxo-PDA in a 95:5 ratio. A greater than 95% ee over the *trans* isomer of 12-oxo-PDA was determined by comparison of the specific rotation of the sample with that previously reported.⁶⁴⁷

A similar stereoselective synthesis of 13-*epi*-12-oxo PDA avoiding the Mitsunobu reaction is presented in Scheme 345. The authors also reported the specific rotation of this compound for the first time.⁶⁵²

More recently, Kobayshi and co-workers published a synthesis of 12-oxo-PDA similar to a previously reported stereoselective synthesis.⁶⁵⁶ The advantage of the newly reported synthesis lies in the use of a mercury-free method for the Eschenmoser–Claisen rearrangement of alcohol **1460** (Scheme 344). The method including $\text{MeC(OMe)}_2\text{NMe}_2$ in xylene afforded the

Scheme 345. Synthesis of 13-*epi*-12-Oxo PDA

amide in 82% yield and was superior to the original procedure in terms of yield, reaction time, operation, and number of steps. The amide was later subjected to iodolactonization in aqueous THF and subsequent reaction with DBU to produce lactone **1463** in 83% yield. This resulted in an improvement in the overall yield for 12-oxo-PDA (63%).^{651,652}

7. CONCLUSIONS

This overview clearly shows that the chiral cyclopentenone unit is a common intermediate in many synthetic routes. There are considerable diverse enantioselective and asymmetric routes described in the literature for synthesizing cyclopentenones. These include chemical (5%) and enzymatic resolution (10%); asymmetric synthesis by Pauson–Khand reaction (15%); Nazarov cyclization (7%); organocatalyzed reactions (3%); asymmetric functionalization of an existing cyclopentenone unit (18%); and functionalization of chiral building blocks such as carbohydrates (13%), chiral carbonyl-based compounds (18%), and unsaturated hydrocarbons (11%). The introduction of chirality during the generation of the cyclopentenone unit in the Pauson–Khand reaction and Nazarov cyclization would be the preferred method from a conceptual point of view. However, this Review shows that these two methods are clearly not the predominant strategies used, even in recent years. It could be argued that this highlights the need for further development of the Pauson–Khand and Nazarov reactions. Biocatalysis and biotransformation have been successfully used as alternative strategies using mild conditions. However, they frequently require case-by-case optimization and often have long turnover times. Given the structural simplicity of the cyclopentenone unit, there is a significant contribution from natural chiral compounds in the synthesis of chiral cyclopentenones. Furthermore, the development of synthetic transformations that minimize the use of protective groups should lead to future advances in the enantioselective synthesis of this important class of compounds.

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Notes

The authors declare no competing financial interest.

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Svilen P. Simeonov graduated from Sofia University in 2004 and joined the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, as a Research Fellow. In 2010 he moved to the University of Lisbon and received his Ph.D. in 2014 under the supervision of Prof. Carlos A. M. Afonso. After, he returned back to Sofia and is currently working as a Researcher at the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences. His research interests are mainly focused on green chemistry methodologies, flow chemistry, valorization of natural resources, and asymmetric catalysis.

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