Enantiomerically Pure Cyclobutane Derivatives and Their Use in Organic Synthesis

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Edward Lee-Ruff obtained his B.Sc. and Ph.D. degrees from McGill University. His Ph.D. work involved the study of photochemical rearrangements of conjugated dienes to bicyclobutanes. He spent two years as an NRC Postdoctoral Fellow in Nick Turro's lab at Columbia University before arriving at York University, where he is Professor of Chemistry. His research interests include photochemistry, kinetic and thermodynamic studies of destabilized carbocations, chemistry of small ring compounds, and the synthesis of nucleosides.

Gabriela Mladenova was born in Bulgaria and arrived in Canada in 1992. She obtained her B.Sc. and M.Sc. degrees at York University. Her M.Sc. project involved the study of the rearrangement and kinetics of fluorenyl cations. She is currently doing her Ph.D. study under the supervision of Edward Lee-Ruff working on the preparation of carbon nucleosides.

I. Introduction

Although cyclobutanes have been known for more than a century, their use as synthetic intermediates has only flourished in the last 30 years. Their diversity of reactions is the result of the inherent strain associated with the four-membered ring contributing to both angular and torsional effects. Thus, cyclobutanes undergo reactions such as ring opening to acyclic products (23−26 kcal^{-1} release of energy), ring enlargement to five- or six-membered ring products (20 and 25 kcal mol^{-1}, respectively), and ring contraction to cyclopropanes. The latter reaction is energy neutral since cyclopropanes have strain energies comparable to those of cyclobutanes, but it is often exothermic since most of these products or intermediates possess the stabilizing conjugated cyclopropyl carbinyl unit. With new enantioselective methods available for the construction of the four-carbon ring, their use in enantioselective synthesis has become increasingly popular. Cyclobutanones and cyclobutenones are the most readily available derivatives of cyclobutane.[1] It is therefore rather surprising that whereas chiral cyclobutanes have been reported in the early 1900s,[2] the first optically active cyclobutanone was only reported in 1960[3] even though cyclobutanones in racemic form were available much earlier (as 1,3-cyclobutanedione from

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dimerization of ketenes).[4] Cyclobutanones offer a convenient four-carbon ring motif in that every center of the ring can be potentially functionalized.

The principal strategies for formation of the four-carbon ring system involve [2+2] cycloadditions, cyclization of acyclic precursors, and ring expansion of cyclopropanes. For the preparation of chiral cyclobutanes, the same basic strategies are employed with chiral starting materials or catalysts for aymmetric induction. Such catalysts include not only metal complexes with asymmetric ligands but also rigid asymmetric host materials such as doped zeolites. Other classical methods such as enantiomeric resolution by enzymes or nonenzymatic chiral agents have also been used. Furthermore, the cyclobutane ring is incorporated in a number of enantiomerically enriched natural products[5] which represent a chiral pool from which optically pure cyclobutanes can be obtained by selective transformations. Methods for the preparation of enantiomerically pure cyclobutanes as well as their use in organic synthesis, as catalysts, and in other applications are reviewed. The focus of this review is on the methods of preparation during the last 25 years with selected examples of natural product synthesis to illustrate general strategies. Comprehensive reviews of cyclobutane and cyclobutene transformations can be found elsewhere.[1,6] The cyclobutane ring system is also widespread in plant-derived natural products, and extensive studies have been carried out on their chemistry. Only a few examples of the more common cyclobutane natural products pertaining to their use in the preparation of key enantiomeric intermediates are presented.

II. [2+2] Cycloadditions

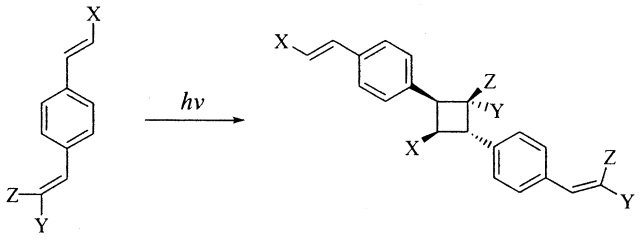
The [2+2] cycloaddition between two alkene moieties represents the most popular method for the construction of cyclobutanes. This method, however, suffers from the inherent nonselectivity for the thermal process, which is forbidden by orbital symmetry[7] considerations, and thus proceeds via intermediates which are sufficiently long lived to undergo stereochemical equilibration. The photochemically induced cycloaddition is allowed by orbital symmetry. However, isolated alkenes possess chromophores which are not accessible to excitation by conventional light sources. On the other hand, conjugated alkenes and enones, which are conveniently excited by conventional UV sources, often undergo intersystem crossing to the triplet state,[8] producing biradicals which can readily undergo stereochemical equilibration. An additional problem arises when nonsymmetric alkenes with little electronic differentiation are used, giving rise to mixtures of regioisomers. This problem has been overcome by the use of ketene as one of the reacting partners. Ketene cycloadditions with alkenes often occur with complete regio- and stereoselectivity as a result of the unusual electronic properties of this cumulene system.[9] The resulting cyclobutanones can be readily converted to other cyclobutane derivatives or transformed to acyclic, ring enlarged and ring contracted products in a stereo- and regioselective manner.[10] Catalyzed [2+2] cycloadditions offer an alternative method for the construction of the cyclobutane ring.[11] These reactions often proceed in a selective fashion as a result of the mild reaction conditions minimizing stereochemical equilibration of the intermediates. Furthermore, many of the intermediates involve rigid complexes of the two reacting partners with a preferred diastereomeric geometry.

A. Photochemical [2+2] Cycloadditions

Photochemical [2+2] cycloadditions include both dimerization and the synthetically more useful reactions of two different alkenes. Some excellent reviews of the latter class have been reported.[12,13]

The early studies of enantioselective cycloadditions involved photodimerization of alkenes possessing chiral substituents. Photolysis of the crystalline material was thought to transfer the chirality of the crystal matrix to the photoproduct. Thus, the diester **1** undergoes photodimerization to **2** with greater than 97% diastereoselectivity (Scheme 1).[14]

Scheme 1



1 **2**

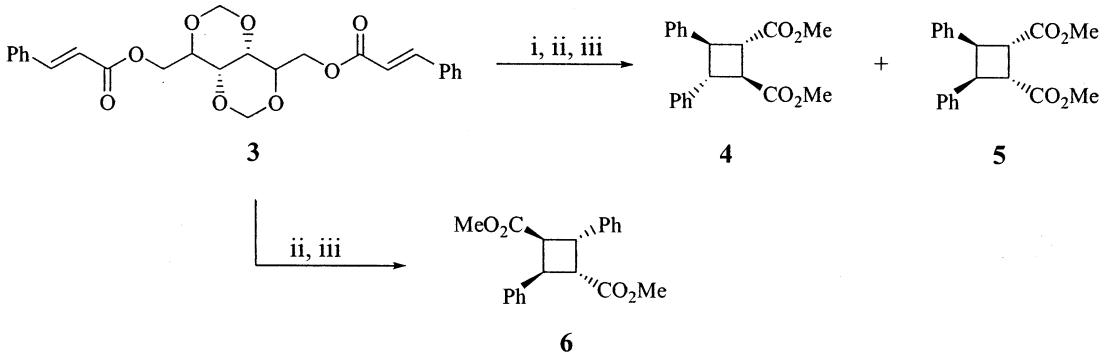
X = CO_2-2-butyl (*R* or *S*), Y = CO_2Et, Z = CN

Other examples of chiral induction have been reported for achiral-substituted divinylbenzenes which can crystallize in enantiomeric crystal forms, giving enantiomeric enrichment of up to 92%.[15] The use of a chiral crystalline matrix in the photolysis of coumarin has been reported to give the *anti* head-to-head (h−h) coumarin dimer with 96% ee.[16] Although this method brings to light an interesting concept in which the chirality of the crystal matrix can induce chiral transformations of achiral starting materials, its application in synthesis is of limited value. The stereoselctivity depends largely on the host crystal and thus the method of crystallization when polymorphism is seen.

The use of chiral tether groups for photodimerization to induce diastereoselectivity in the products is quite effective. The cinnamic acid diester **3** undergoes intramolecular photodimerization, which upon removal of the tether gives a mixture of the h−h dimers **4** and **5** (Scheme 2). Compound **4** is formed in 48% yield although no optical purity was mentioned. However, the irradiation of **3** in the solid state gives the head-to-tail (h−t) dimer **6** along with oligomers.[17] The packing of the substrate in the crystal matrix is an important factor influencing both the regio- and stereochemistry.

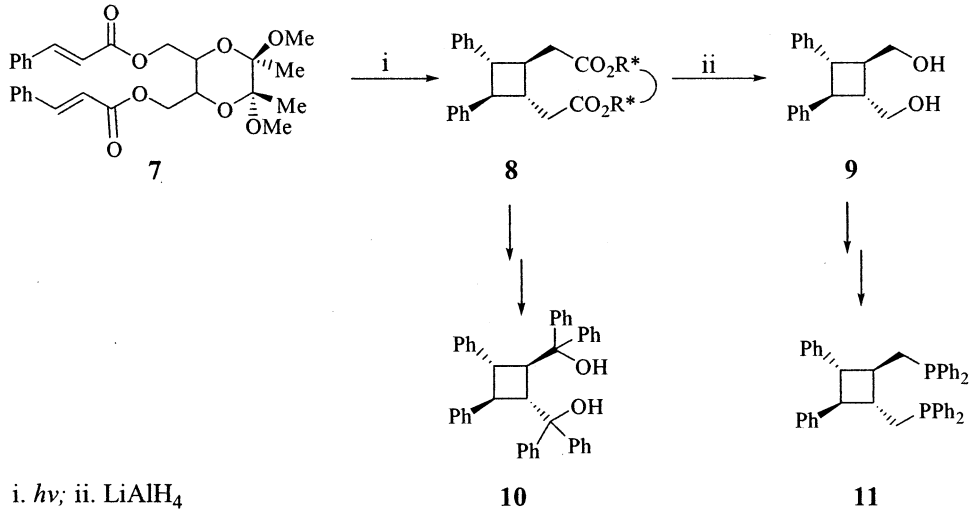
An interesting application of the chiral tether methodology is in the preparation of enantiopure chiral *trans*-1,2-disubstitued cyclobutane ligands for

Scheme 2



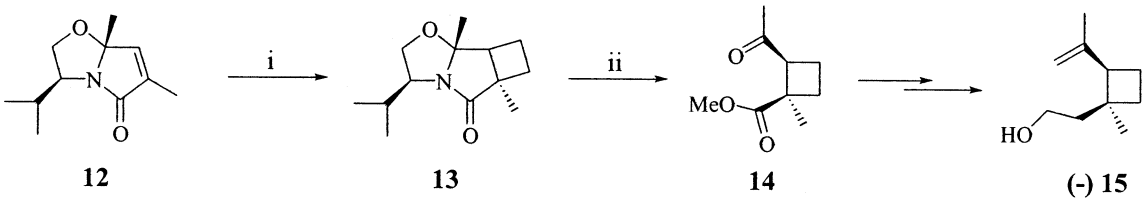
i. *hv*, C_6H_6; ii. MeOH, H^+; iii. *hv,* solid

Scheme 3



i. *hv;* ii. $LiAlH_4$

Scheme 4



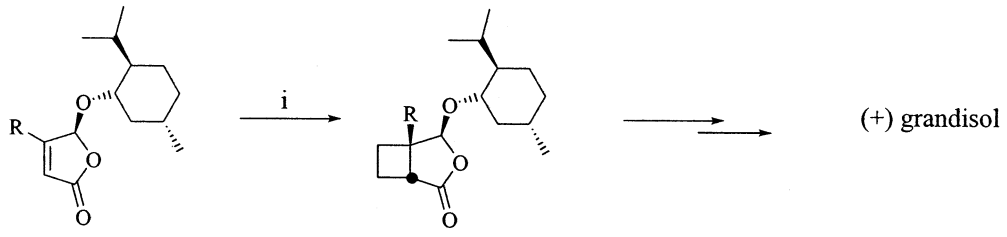
i. *hv*, CH_2=CH_2, CH_2Cl_2; ii. 5% H_2SO_4, MeOH

asymmetric metal catalysis. Thus, intramolecular dimerization of **7** proceeds to the h−h dimer **8** (Scheme 3). Removal of the tether produces enantiomerically pure **9**. The chiral ligands **10** and **11** can be prepared by standard reactions from **8** and **9**, respectively.[18]

Optically active cyclobutanes obtained from the photocycloaddition of different alkenes have been developed for the enantioselective synthesis of natural products. These are prepared using alkenes having one or more chiral auxiliary groups that can be removed in a subsequent step. The optically pure enone **12** cycloadds to ethylene to produce the tricyclic cyclobutane **13** with a diastereoselectivity of 92% (Scheme 4). Removal of the chiral auxiliary produces **14**, which is an intermediate to (−)-grandisol ((−)-**15**), an insect pheromone. The minor diastereomer of **13** can be converted to (+)-grandisol ((+)-**15**).[19]

Another approach to grandisol using the [2+2] photocycloaddition methodology was reported by Scharf.[20] The chiral auxiliary used is a menthyloxy group substituted on a chiral butenolide, **16**. The ethylene photoadduct **17** is formed with a de of only 9% (Scheme 5). However, these diastereomers can be readily separated and used in the synthesis of both (+)- and (−)-**15**. In a similar study, the π-facial selectivity for cycloaddition of **16** with ethylene can be improved by the use of bulkier substituents such as the pivaloyloxymethyl group. The de improves to 24% in this case.[21] Varying the substituents on the lactone as well as the alkene can improve the selectivity up to 88%. The diastereoselectivity of the cycloaddition of demethylated **16** (R = H) can also

Scheme 5

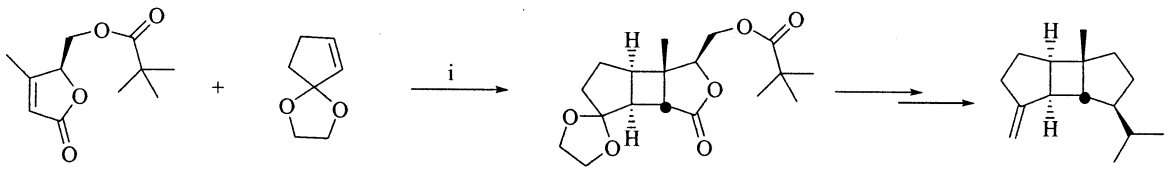


16 **17** **15**

R = H, Me

i. *hv*, CH_2=CH_2, acetone

Scheme 6



18 **19** **20** **(-) 21**

i. *hv*, MeCN

be improved by use of lower temperatures in the photolyses.[22] The study of diastereoselective π-facial discrimination for the cycloaddition of **16** substituted with other chiral auxiliary groups with alkenes was reported.[23] This selectivity is again largely dependent on the molecular bulk of the chiral auxiliary. The pivaloyloxy group gave π-facial selectivities of up to 79%. Using this approach, butenolide **18** photoadds to cyclopentenone ketal **19** to give the tricyclic lactone **20** in 25% yield along with other regioisomers (Scheme 6). Compound **20** is an intermediate to (−)-bourbonene ((−)-**21**).

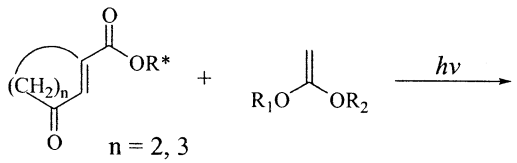
The auxiliary-induced diastereoselectivity in the photocycloaddition of cycloalkenones **22** with diethyl ketene acetal was reported for different chiral groups substituted at C-3 of the enone (Scheme 7). Low to moderate (5−56% de) diastereoselctivity was observed in the formation of cyclobutanes **23**.[24] Cycloadditions of **22** with ketene acetals substituted by a chiral auxiliary improved the selectivity as a result of "double chiral induction". The selectivity depends on whether the two auxiliaries are "matched" or "mismatched".[25]

The menthone ketal **24** gives moderate to good stereoselectivity. Light-induced cycloaddition of **24** with cyclopentene gives the tricyclic lactone **25** with 90% de (Scheme 8).[26] For cycloaddition with the unsymmetrical 1-methylcyclobutene, both regio- (7:1 in favor of the indicated isomer) and stereoselectivity are observed.

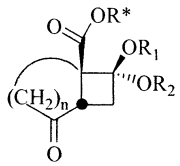
The chiral dihydrofuran **26** reacts with cyclobutene **27** on photolysis to produce the bicyclo[2.2.0]hexane **28** (54%; the other diastereomer is not observed), which is an intermediate in the synthesis of one hemisphere of the macrolide milbemycin α1 (Scheme 9).[27]

The use of natural products as a chiral pool is a practical approach to enantiomerically pure alkenes

Scheme 7

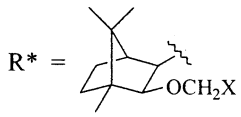


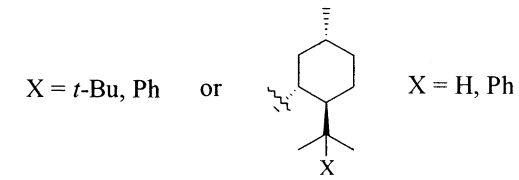
22



23

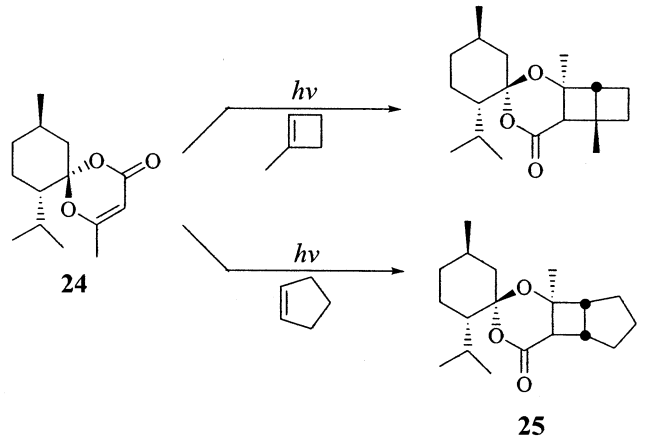
1. R_1 = R_2 = Et
2. R_1 = Et, R_2 = (-)-8-Phenyl-3-menthyl, (-)-3-menthyl



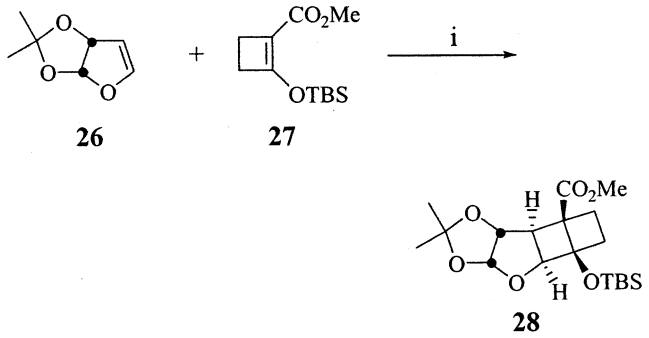


for cycloaddition reactions. For example, the optically pure cyclopentene **29**, which is readily available from limonene, undergoes stereoselective photocycloaddition with cyclopentenones **30** to give the tricyclic

Scheme 8



Scheme 9



i. *hv*, pentane, -78°C

ketones **31** and **32** as a regioisomeric mixture (1:1) (Scheme 10).[28] Ketone **31** can be readily transformed to the epoxide **33**, which upon ring opening under basic conditions produces the hydrazulene natural product (+)-alphanamol ((+)-**34**), a toxic principal from the fruit of the timber tree *Alphanamixis grandifolia*.

The direct use of enantiomerically pure natural product alkenes as a reacting partner in [2+2] photocycloadditions has been reported. (+)-Podocarpenone ((+)-**35**) can be used as the starting material for the synthesis of a pentacyclic lactone, **38**, a member of the sponge diterpenes (Scheme 11). The key step involves the photocycloaddition of the hydroxy enone **36**, obtained by an allylic oxidation protocol, with acetylene to form enantiomerically pure cyclobutene **37** (63%).[29]

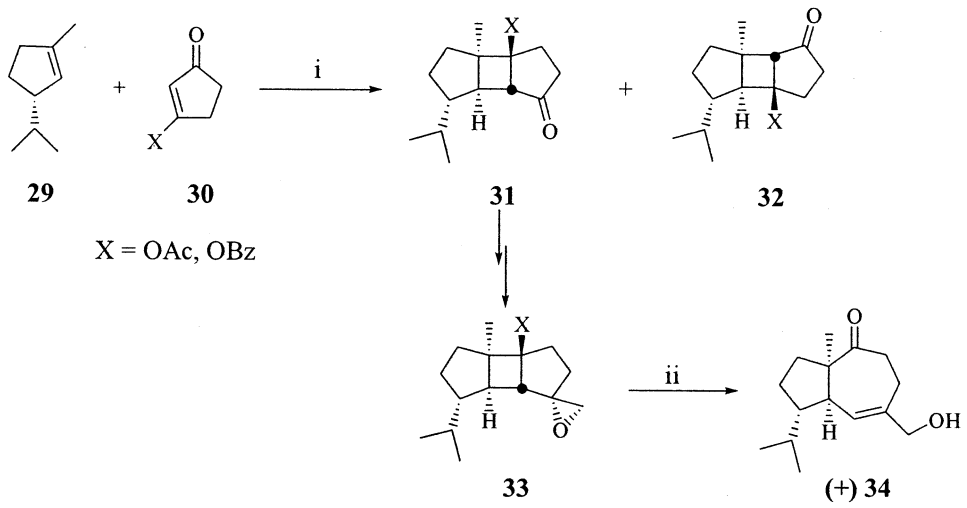
Like acetylenes, allenes can also undergo light-induced cyclization with alkenes such as in the case of the fused enone **39**. The reaction is π-facially selective, producing the methylenecyclobutane **40** (96%, 100% de) (Scheme 12).[30] Ozonolysis of the methylene group in **40** produces the enantiomerically pure cyclobutanone **41**.

Intramolecular cyclization of alkenes results in tricyclic ring systems which give preferred regiochemistry when the spacer is of short to medium length. The use of such methods for chiral dienes often gives cyclobutanes which are enantiomerically enriched as the result of π-facial selectivity in these reactions. The proximity of the reacting alkene units with short tethers also contributes to the increased reaction efficiency relative to that of their intermolecular counterparts. For example, butenolide **42** undergoes cycloaddtion to give the tetracyclic lactone **43** in 60−78% yields (Scheme 13).[31,32] Structural elaboration of this key cyclobutane gives both the tricyclic terpenes (+)-stoechospermol ((+)-**44**) and spatol (**45**).

The optically pure cyclohexenone **46** undergoes intramolecular cycloaddition to give the tricyclic ketones **47** in yields of 95−99% (Scheme 14). Although π-facial selectivity for reaction of the conjugated alkene is excellent, that for the isolated alkene in the alkyl-substituted derivatives of **46** is low.[33]

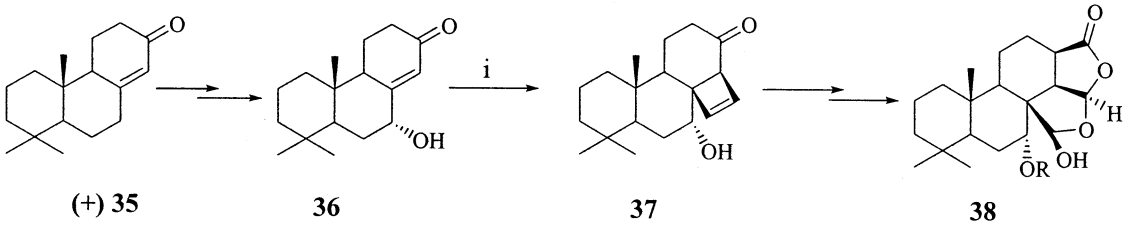
An interesting chiral-induced intramolecular photocyclization followed by a cascade of thermally and photochemically induced isomerizations were reported for the chiral auxiliary substituted acetophenones **48**. The initially formed tricyclic cyclobutane is transformed by tandem thermal and photo-

Scheme 10



i. *hv*, CH_3CN; ii. LiDME, MeOH

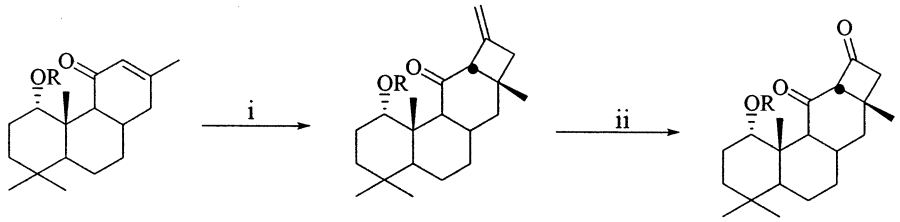
Scheme 11



(+) **35** **36** **37** **38**

i. *hv*, C_2H_2

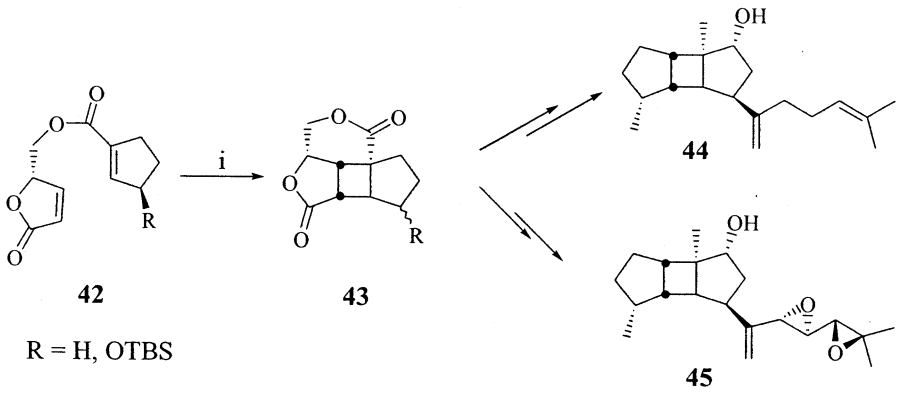
Scheme 12



39 **40** **41**

i. *hv*, $CH_2{=}C{=}CH_2$; ii. O_3

Scheme 13

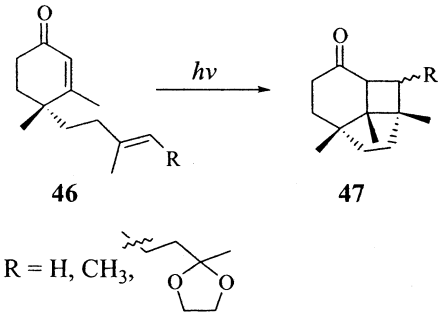


42 **43** **44** **45**

R = H, OTBS

i. *hv*, CH_3CN

Scheme 14



46 **47**

R = H, CH_3,

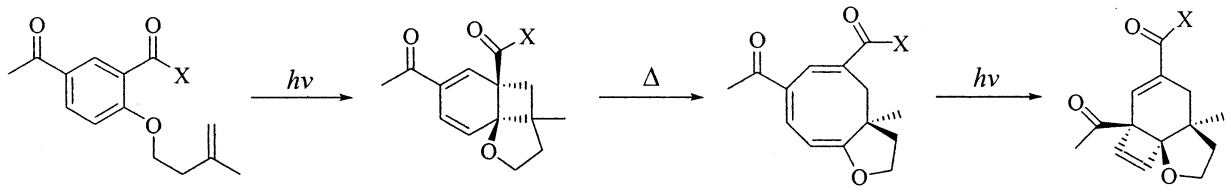
chemical steps involving concerted electrocyclizations to give the chiral cyclobutenes **49** as end products with de's ranging from 15% to 90% depending on the nature of the chiral auxiliary (Scheme 15).[34]

To improve the π-facial selectivity in these intramolecular processes, metal complexation of the two alkene moieties might lead to improved selectivity. However, the Cu(I)-catalyzed photocycloaddition of dienol **50** gives a mixture of diastereomers of bicyclo-[3.2.0]heptanols **51** and **52** each with >98% ee (Scheme 16).[35] Alcohols **51** and **52** are intermediates to (+)- and (−)-(**15**), respectively. The use of chiral ligands for the copper catalyst did not improve the selectivity for this reaction.

An example of a heterocyclic version of the above photocyclization gives 3-azabicyclo[3.2.0]heptanes which can be used as intermediates in the synthesis of azepams and *cis*-3,4-disubstituted pyrrolidines of pharmaceutical interest (Scheme 17). The 3-azabicyclo-[3.2.0]heptane skeleton also represents a biologically potent pharmacophore in the treatment of schizophrenia and related psychotic diseases. The [2+2] cycloaddition of these protected diallylamines proceeds with excellent diastereoselectivity (up to 100%) with chemical yields ranging from 63% to 84%.[36]

The use of removable chiral tethers for photodimerization has been described above. Their use in intramolecular photodimerization of two different alkenes has been recently exploited as shown in Scheme 18. The chiral tether is based on mandelic

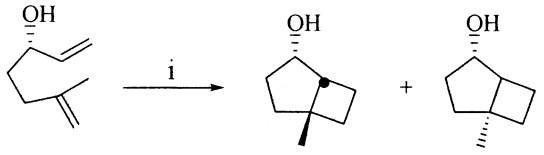
Scheme 15



48 49

X= chiral auxiliary group

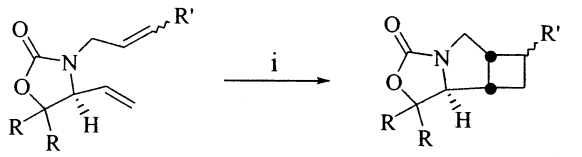
Scheme 16

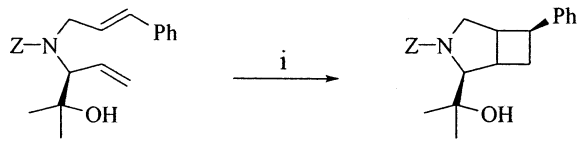


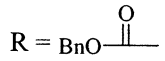
50 51 52

i = *hv*, CuOTf, C_6H_6

Scheme 17







i. *hv,* $PhCOCH_3$ or $Cu(OTf)_2/Et_2O$

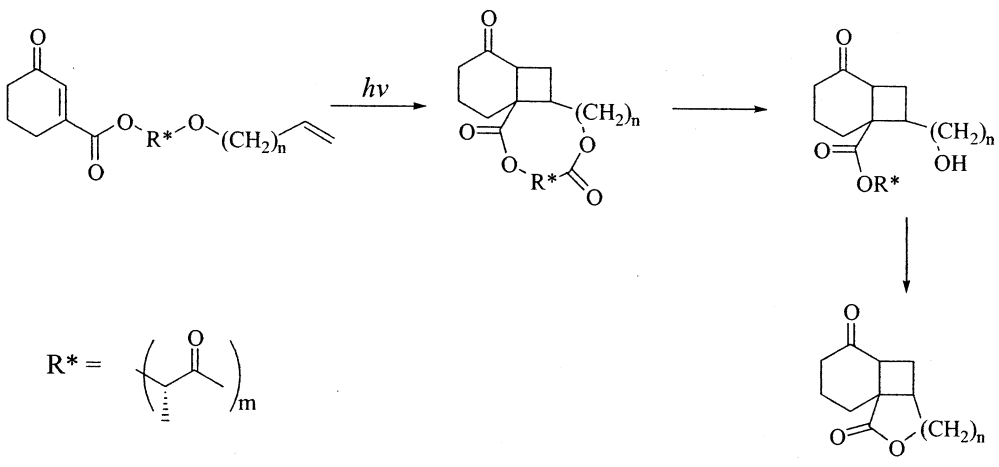
acid units which are commercially available in both antipodes.[37,38] Since the tether is linked by ester anchoring groups, it can be readily removed, giving enantiomerically enriched cyclobutanes. High yields of products with very good π−facial selectivity with de's of up to 94% are observed.

This methodology has been used by the same group with the objective to synthesize the sesquiterpenes (−)-italicene ((−)-**54**) and (+)-isoitalicene ((+)-**55**) (Scheme 19).[39] However, the attempted ring closing metathesis of diene **53** was not successful.

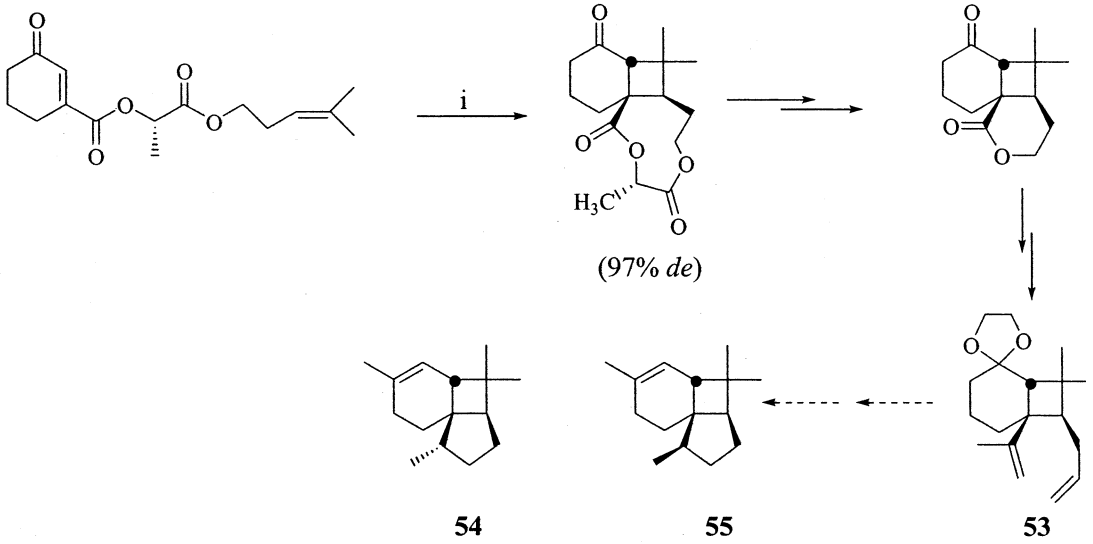
An interesting concept is the use of a chiral host which is not covalently bonded to the reacting partners. The 2-quinolone **56** cycloadds to alkenes in the presence of chiral lactam **57** to give cyclobutanes **58** and **59** with excellent diastereoselectivity (95%) and moderate to excellent enantiomeric enrichment (30−92%) (Scheme 20).[40] Since the chiral lactam is attached to the quinolone by hydrogen bonding, it can be readily removed without the use of a chemical step. An intramolecular example of this concept was reported by the same group starting with quinolone **60**, giving **61** in 74−89% yields with enantiomeric enrichment of up to 93%.[41]

The phenomenon of chiral induction in reactions of achiral reactants in a chiral crystal matrix has been shown in photodimerizations as mentioned above.[16] An extension of this concept to the photocycloaddition of two different alkenes has been shown. Single crystals of cinnamamide as host with cinnamic acid occluded in the matrix as guest can form separable enantiomeric crystal forms. Photolysis of these crystals results in cycloadducts **62** which are enantiomerically enriched (40−60% ee) (Scheme 21).[42]

Scheme 18

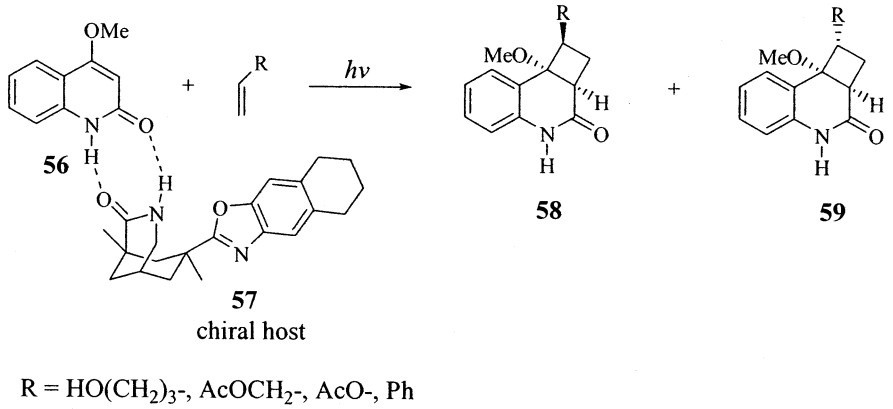


Scheme 19

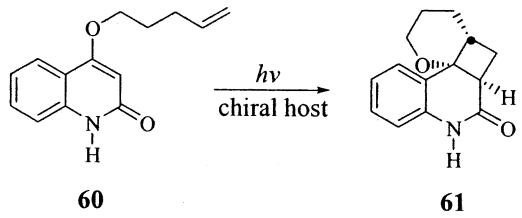


i = *hv*, (λ = 366 nm), CH_2Cl_2

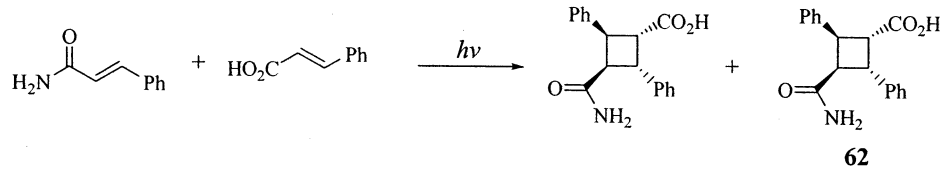
Scheme 20



R = $HO(CH_2)_3$-, $AcOCH_2$-, AcO-, Ph



Scheme 21



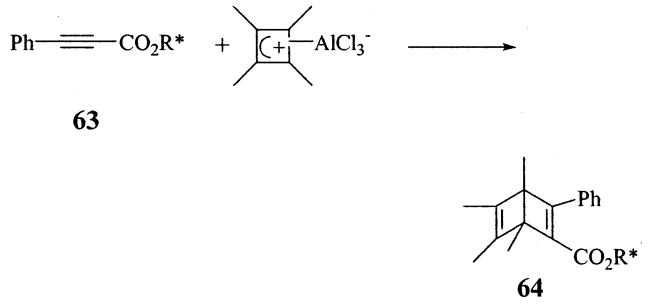
The extent of enantiomeric enrichment is highly dependent on the mode of crystallization.

The use of a chiral sensitizer to induce chiral photodimerization in a series of aryl vinyl ethers has been shown to be ineffective (ee's of 1%).[43] The sensitizers employed were chiral esters of aryl carboxylic acids. Although energy transfer involves intimate contact between donor and acceptor, the lifetime of such a complex is too short for a third-body interaction, a necessary requirement for chiral induction.

B. Catalyzed [2+2] Cycloadditions

Alkenes which are thermally unreactive to cycloadditions can be induced to undergo such reactions by catalysts (metals; Lewis or Bronsted acids). In

Scheme 22



R* = menthyl, bornyl, geranyl

many instances, the substrates are converted to reactive intermediates such as metalated alkenes, cations, or radical cations which undergo cycloaddition more efficiently. The milder reaction conditions of the catalyzed process permit the extension of the scope of [2+2] cycloadditions to include alkene combinations which would not otherwise react. The use of chiral catalysts has been shown to be quite effective in inducing enantiomeric enrichment as the result of complexes formed between the catalyst and substrate permitting termolecular "collisions" unlike the phenomenon of chirally induced photosensitization discussed above.

Early studies involved substituting one of the reacting components with a removable chiral auxiliary. Aryl propargyl acid esters derived from chiral alcohols **63** cycloadd to aluminum salts of cyclobutenyl cations, producing bicyclo[2.2.0]hexadienes **64** in moderate yields with optical purities of up to 33% (Scheme 22).[44]

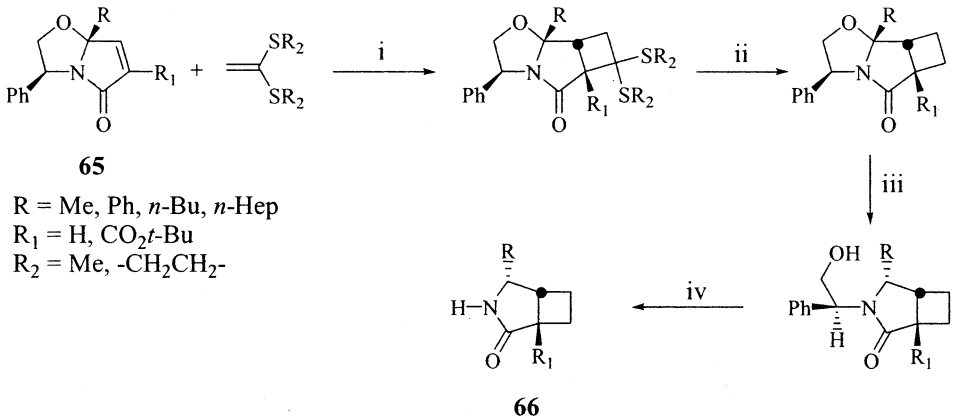
The use of a chiral oxazolidine fused ene lactam, **65**, in Lewis acid catalyzed cycloaddition with ketene thioacetals can be applied in the preparation of stereospecifically substituted cyclobutanes.[45] Ketene thioacetals are reactive ethylene equivalents. The thioketal group in the product can be readily removed by reductive cleavage. Cyclic ketene thioacetals give better yields of products. Fragmentation of the isoxazolidine ring results in the formation of cyclobuta-[*c*]pyrrolidines. This methodology was applied in the synthesis of the fused pyrrolidone **66** representing a rigid analogue of γ-aminobutyric acid (GABA), which acts as an inhibitory neurotransmitter in the brain (Scheme 23).

A similar titanium-catalyzed cycloaddition with a silyl allyl ether gives the corresponding cycloadducts **66** with diastereoselectivities of 83−90%.[46]

The concept of double chiral induction with substrates having two chiral auxiliary groups has been successfully employed in the preparation of enantiomerically pure cyclobutane **68**. This key intermediate has been used for the preparation of a number of antiviral materials. A diastereofacial selectivity of >99% was observed in the diethylaluminum chloride catalyzed cycloaddition of 1,1-dimethoxyethene with (−)-dimenth-3-yl fumarate **67** (Scheme 24).[47,48] Structural elaboration to the optically pure cyclobutanone **69** is achieved in short order. Ketone **69** has been used in the synthesis of cyclobutane antivirals such as lubocavir **70**,[49] which is a carbocyclic analogue of the natural product and pharmacologically active oxetanocin. The photochemical ring expansion of cyclobutanones proceeds via a cyclic oxacarbene which can insert into OH and acidic NH groups to give 2-substituted dihydrofurans.[10,50] Thus, the photolysis of **69** (R = OBz) in the presence of sugars or substituted purines gives disaccharides[51] and nucleoside analogues,[52] respectively, with stereochemical retention of the ring substituents. It is interesting to note that insertion of the oxacarbene **71** to the sugar **72** is regioselective, with reaction occurring at the primary alcohol function. A limitation of this reaction is the formation of an anomeric mixture of products with little selectivity.

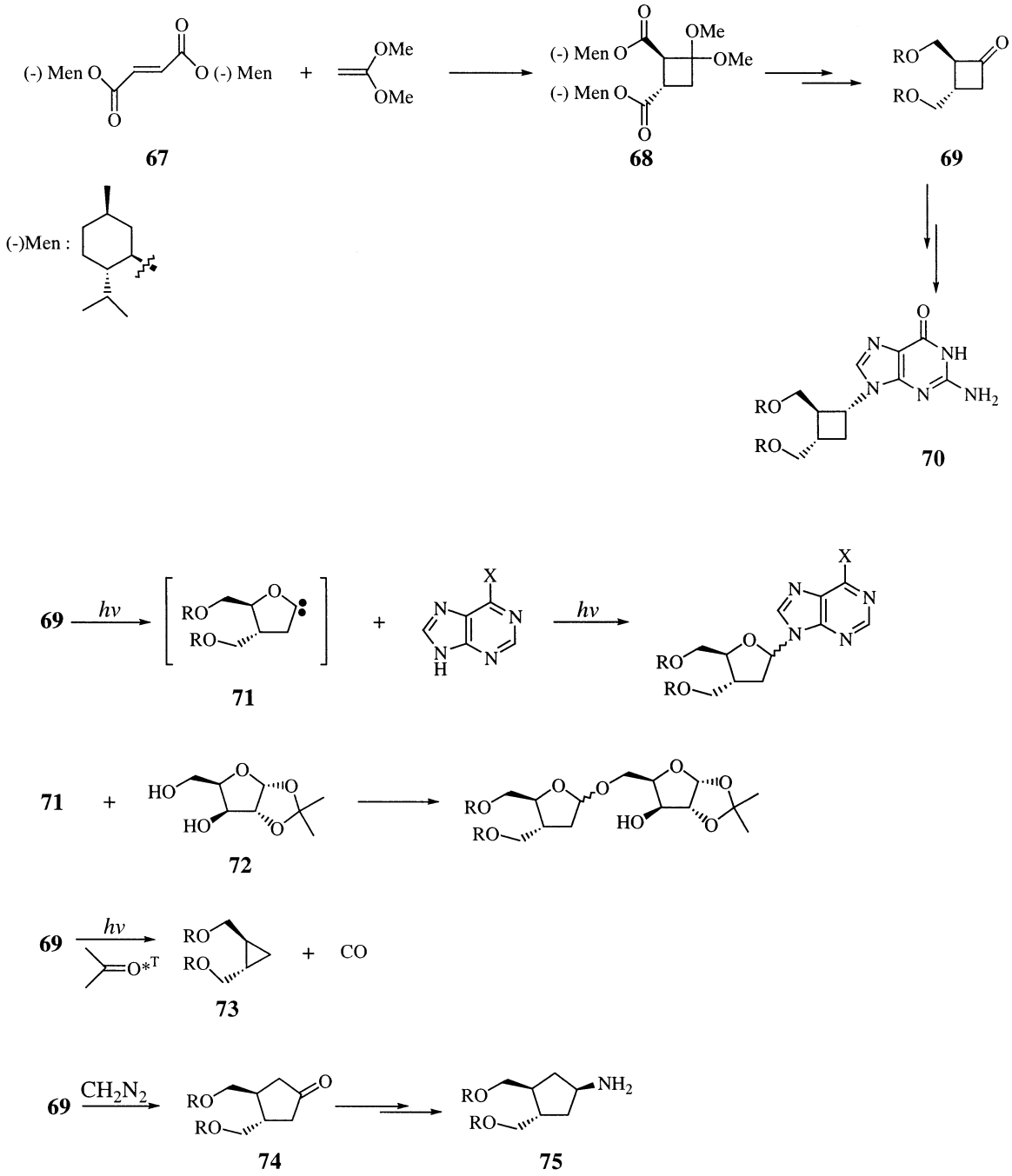
Decarbonylation is a minor pathway in the photodecomposition of cyclobutanones, and evidence points to a triplet electronic state. The triplet-sensitized decomposition of **69** using acetone as the photosensitizer gives respectable yields of the enantiomerically pure cyclopropane **73**.[53] The decarbonylation involves 1,4- and 1,3-biradicals with the two chiral centers intact. Irradiation of other cyclobutanones in acetone solutions gives principally cyclopropanes.[53] However, unlike the photochemical ring expansion, the photodecarbonylation results in stereo-

Scheme 23



i. Me_2AlCl, Toluene; ii. Raney-Ni; iii. Et_3SiH, $TiCl_4$; iv. Na, NH_3

Scheme 24

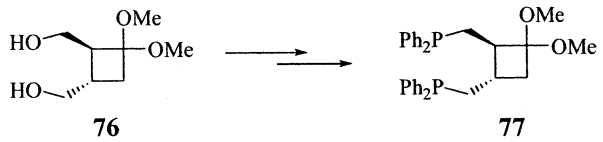


chemical equilibration for α-substituted cyclobutanones.[53] Homologous ring expansion of **69** with diazomethane occurs regio- and stereospecifically to give the enantiomerically pure cyclopentanone **74**. Structural elaboration using a standard reaction protocol produces the chiral cyclopentylamine **75** which has been transformed into carbocyclic nucleoside analogues.[52d]

The dimethyl ketal **76** derived from **69** was used to prepare the enantiomerically pure cyclobutane diphosphine **77** (Scheme 25).[54] Many of these chiral diphosphines are effective ligands for enantioselective rhodium-catalyzed hydrogenations.

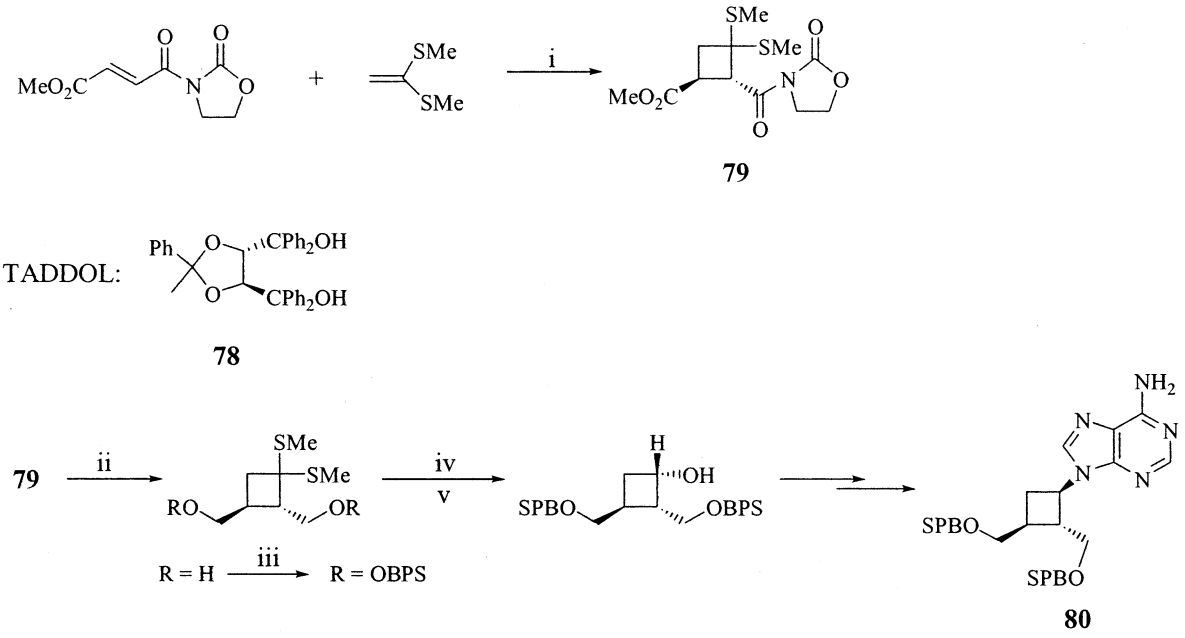
One of the most efficient methods for enantioselective syntheses of cyclobutanes involves the use of chiral titanium complexes as a catalyst in donor−

Scheme 25

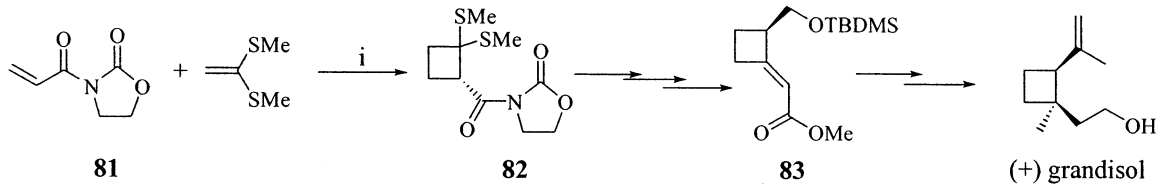


acceptor [2+2] cycloadditions developed by Narasaka and Hayashi. The tartaric acid **78** titanium complex induces high stereoselectivity in the cycloaddition of ketene thioacetals, thio enol ethers, and other electron-rich alkenes, with oxazolidinone enamides to give enantiomerically pure cycloadducts. For example, the enantioselective synthesis of another carbocyclic analogue of oxetanocin, **80**, was prepared using the sequence shown in Scheme 26.

Scheme 26



Scheme 27



i. $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, **78**, MS 4A°, toluene, pet. ether, 0°C

The key cycloaddition step produces cyclobutane **79** in 83% yield with a >98% ee![55]

The use of other oxazolidinone enamides with ketene dimethyl thioacetal gives cyclobutanes with similar enantiomeric enrichment.[56] The enantioselective synthesis of grandisol starts with the catalyzed addition of the enamide **81** to ketene dimethyl thioacetal to give cyclobutane **82** in 80% yield with an optical enrichment of 88% (Scheme 27). One recrystallization produces optically pure product.[57] Structural elaboration of **82** produces a key optically pure alkylidenecyclobutane, **83**, which is an intermediate to the synthesis of (+)-grandisol.

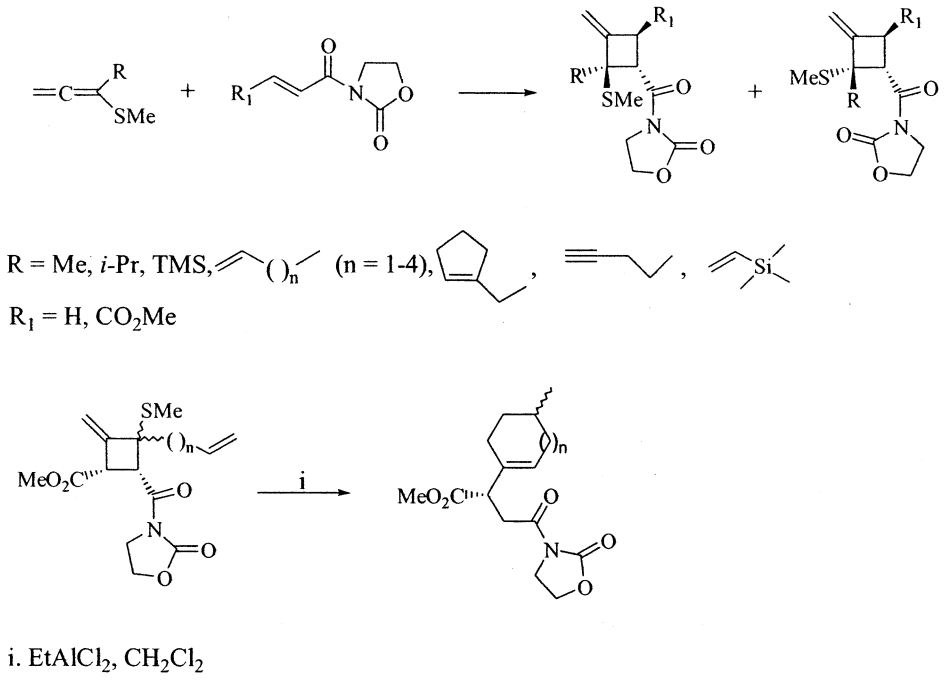
Similar reactions of fumaric enamides with electron-rich enamines under the same conditions produce tetrasubstituted cyclobutanes with an enantiomeric excess of 69−77%.[58] Electron-rich alkynes substituted by a thiomethyl group react in a similar fashion with oxazolidinone enamides, giving the corresponding chiral cyclobutenes with 90−98% ee.[59] These optically enriched products can be structurally elaborated to chiral cyclobutanes. Cycloadditions of allenes with enamides under similar conditions give methylenecyclobutanes (Scheme 28).[60] Although the reaction proceeds regiospecifically, a mixture of stereoisomers results. In each case, however, the enantiomeric excess exceeds 91%. Methylenecyclobutanes which are substituted by a pendant alkene group can undergo Lewis acid catalyzed tandem ring opening and cyclization to give cycloheptanes and cyclooctanes.

The use of *p*-benzoquinones in such cycloadditions gives cyclobutane-fused bicyclic derivatives with very good enantiomeric enrichment.[61,62] Ring expansion of such cyclobutane-fused benzoquinones under acid conditions gives rise to benzofurans which are often the only products formed in this reaction.[62] An example of the enantioselective synthesis of a pterocarpan starts with a benzopyran, **84**. The titanium TADDOL catalyzed reaction of **84** with a substituted *p*-benzoquinone gives the corresponding adduct **85** in 85% yield with an optical enrichment of 63% (Scheme 29). A subsequent acid-catalyzed rearrangement produces the pterocarpans **86**.

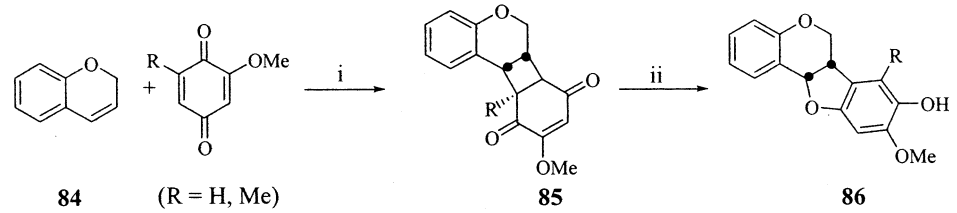
C. Cycloadditions with Ketene or Ketene Equivalents

The uncatalyzed cycloaddition of nonactivated alkenes does not proceed efficiently, often requiring harsh conditions which result in stereochemical equilibration of the substituents in the cyclobutane ring. Thus, this class of reactions are not methods of choice in the construction of chiral cyclobutanes. Ketenes represent a special class of reactive two-carbon "alkenophiles".[9] The reaction proceeds regioselectively with the more nucleophilic alkene carbon

Scheme 28



Scheme 29



bonded to the ketene carbonyl carbon. Due to their concerted nature these reactions give substituted cyclobutanones with stereochemical retention of the original alkene substituents and represent an attractive method for obtaining chiral cyclobutanones from which other cyclobutanes can be obtained. Because of the electrophilic nature of ketenes, electron-deficient alkenes are poor substrates for this reaction. One of us reviewed the literature for chiral cyclobutanones covering the period 1970−1992[63] so that only some main strategies are mentioned. The focus here is on such reactions covering the period from 1990 to the present.

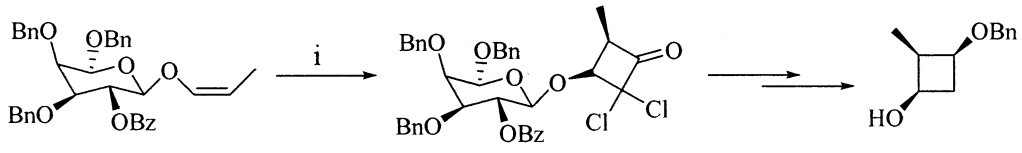
Natural products with alkenes incorporated in a chiral carbon framework are abundant. Ketenes will add to steroids[64,65] and dehydro cyclic acetals derived from sugars[66−68] to give the corresponding optically pure cyclobutanones. Dichloroketene, being more reactive than the parent ketene, is often used as a ketene equivalent. The primary formed 2,2-dichlorocyclobutanones can be readily dechlorinated by reductive methods.

The use of a monosaccharide as a chiral auxiliary has been shown to be effective in inducing chirality. Attachment of a vinyl group at the anomeric position of galactose gives an electron-rich "ketenophile" which reacts with dichloroketene to produce the corresponding dichlorocyclobutanones with chiral induction resulting from preferential *si*-face attack at the olefin (Scheme 30).[69] Reduction of the ketone followed by cleavage of the cyclobutane gives optically enriched cyclobutanols.

In a related study, the chiral enol ether **87** was reacted with dichloroketene, giving ketone **88**, which was used as an intermediate in the synthesis of methyleneolactocis (**89**), an antibiotic, using a ring expansion Baeyer−Villiger protocol (Scheme 31).[70] In this example, preferential attack of the *re*-face of the alkene was observed with stereoelectronic factors always operating in these cycloadditions. In similar fashion, the chiral enol ether **90** reacts with dichloroketene. The resulting cyclobutanone was treated with diazomethane to give cyclopentanone **91** with a de of >98%. This ketone was used in the subsequent transformation to (−)-cuparenone ((−)-**92**).[71]

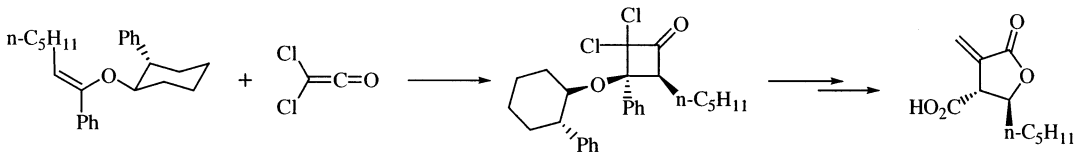
The use of sugar-derived unsaturated glycals has been exploited to yield optically pure cyclobutanes using the ketene cycloaddition protocol. The cyclobutanones which are produced can undergo regioselective ring opening reactions resulting in a net vicinal dialkylation of the olefinic group. Alternatively, these intermediates undergo homologous or

Scheme 30

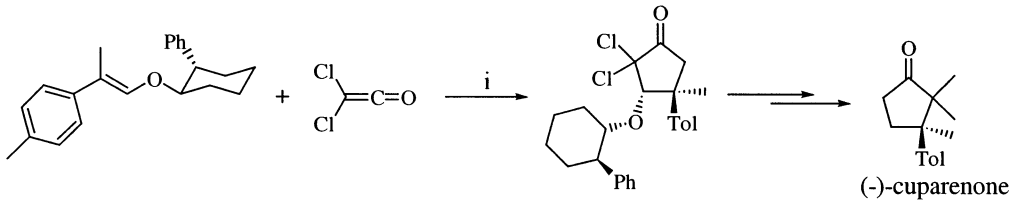


i. Cl_3CCOCl, Zn-Cu, ether, r.t.

Scheme 31



87 **88** **89**

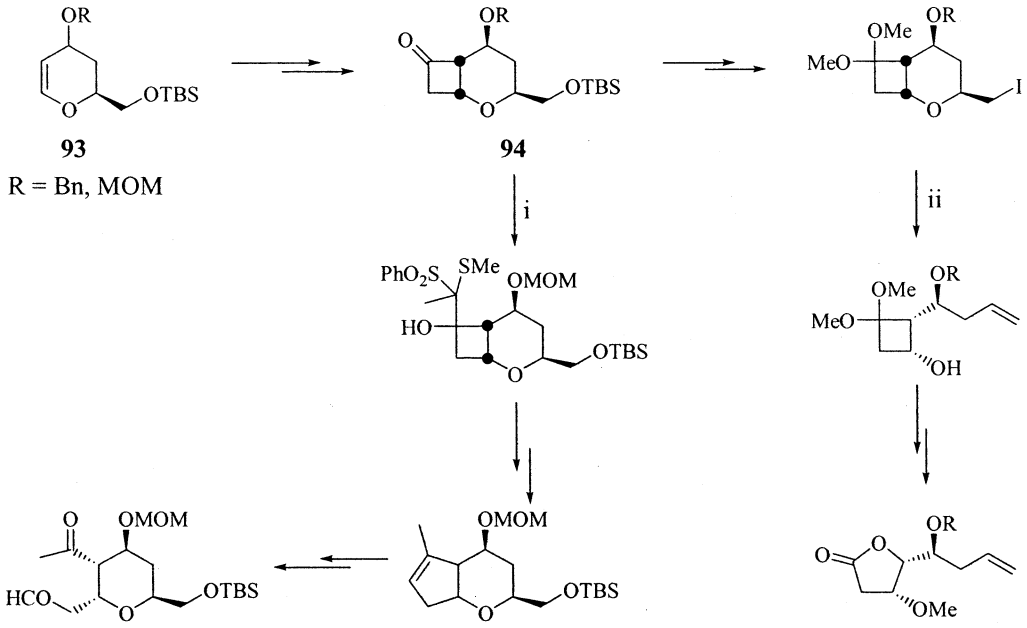


(-)-cuparenone

90 **91** **92**

i. CH_2N_2

Scheme 32



93
R = Bn, MOM

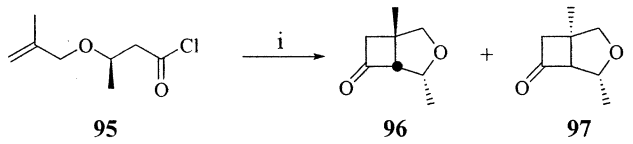
94

i. *n*-BuLi, $PhSO_2CH(CH_3)SCH_3$, THF, -70°C; ii. Zn, EtOH, reflux

oxidative ring expansion reactions to give enantiomerically pure cyclopentanones and γ-butyrolactones. Examples of such strategies involve cyclobutanones **94** obtained from the sugar-based dihydropyrans **93** using the sequence of dichloroketene addition followed by reductive dechlorination (Scheme 32).[72,73]

The use of chiral auxiliaries attached to either the alkene[71,74] or ketene[75] show modest to very good π-facial discrimination. The intramolecular version of the ketene−alkene cycloaddition has been frequently used in the preparation of bicyclic cyclobutanones.[76] The regioselectivity and efficiency of such transformations are highly dependent on the

Scheme 33



i. TEA, reflux, CH_2Cl_2

tether length. A chiral example of such a reaction is used in the enantioselective synthesis of grandisol. The chiral acid chloride **95** gives the bicyclic ketones **96** and **97** with a selectivity of 3.4:1 in favor of the former (Scheme 33). The diastereomers can be readily separated and used as intermediates for the synthesis of both antipodes of **15**.[77]

An interesting use of a chiral auxiliary has been reported to give enantiomerically pure α-aminocyclobutanones, although the regioselectivity is modest.[78] The oxazolidine **98** reacts with ketenes to give a mixture of regioisomers **99** and **100** with selectivities favoring the former (Scheme 34). This selectivity is unexpected in view of the alkene polarization in the heterocycle. The thioketene **101** also cycloadds to **98**, giving another potential center for functionalization in the cyclobutanone ring. Ring opening of the resulting ketone gives the α-amino acid analogue **102**.

An alternative to ketene cycloadditions involves the reaction of ketene iminium salts with alkenes.[79] These reactive ketene equivalents are readily available from dehydration of carboxamides and avoid the problem of dimerization often encountered in ketene reactions. The reaction sometimes proceeds with a regiochemical outcome different from those of ketene cycloadditions, which is a result of different intermediates and transition states. The presence of a tetravalent iminium cation permits the placement of a chiral auxiliary group on nitrogen. Enantiomeric enrichment of the cycloadducts depends on the substitution pattern of the ketene iminium salts with the more substituted salts, giving greater asymmetric induction. Interestingly, the substitution pattern of the reagent can completely alter the course of difacial selectivity.[80]

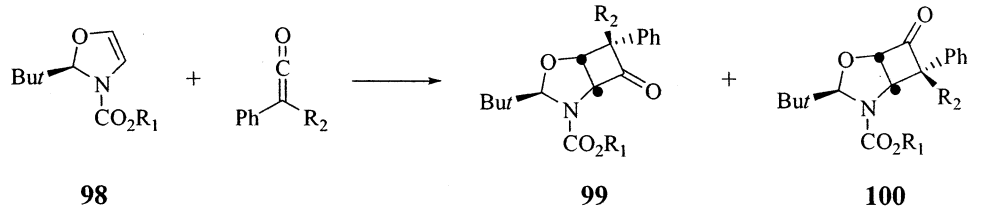
An intramolecular version of asymmetric induction in these cycloadditions is seen for the enamide **103**, giving products with asymmetric induction of up to 97.5% (Scheme 35).[81]

Photolysis of pentacarbonylcarbenechromium (Fischer) complexes produces species that react as if they were ketenes,[82,83,85] although no evidence for the intermediacy of ketenes has been observed. The reactions are highly regio- and stereoselective. The regiochemistry corresponds to that of ketene [2+2] cycloadditions, with the more nucleophilic alkene carbon attached to the ketene carbonyl carbon. As in the case of ketene cycloadditions, electron-deficient alkenes are poor substrates for this reaction. The use of alkenes with chiral auxiliary groups leads to chiral cyclobutanones **104** (Scheme 36). Reaction yields of 50−60% and diastereomeric excesses of 86−97% were obtained for the 3-amidocyclobutanones which were obtained from cycloaddition of the chromium carbene complexes with chiral ene carbamates.[84]

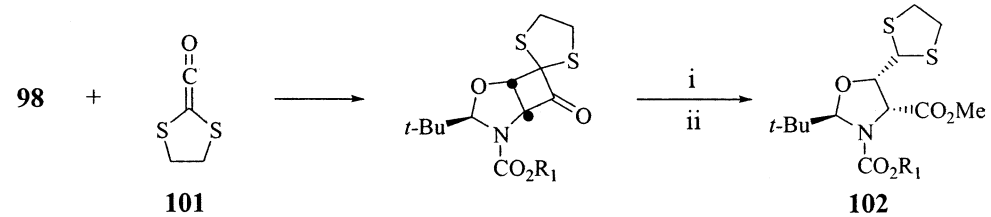
The application to enantioselective synthesis of butenolides and the antibiotic (+)-tetrahydrocerulin ((+)-**106**) is seen in the sequence of reactions involving the key cyclobutanones **105** which are obtained from the appropriately substituted chromium carbene complex (Scheme 37).[85]

An elegant enantioselective synthesis of cyclobuta A (**107**), a broad spectrum antiviral agent, employed the same strategy, with the final product obtained in >98% de (Scheme 38).[86]

Scheme 34

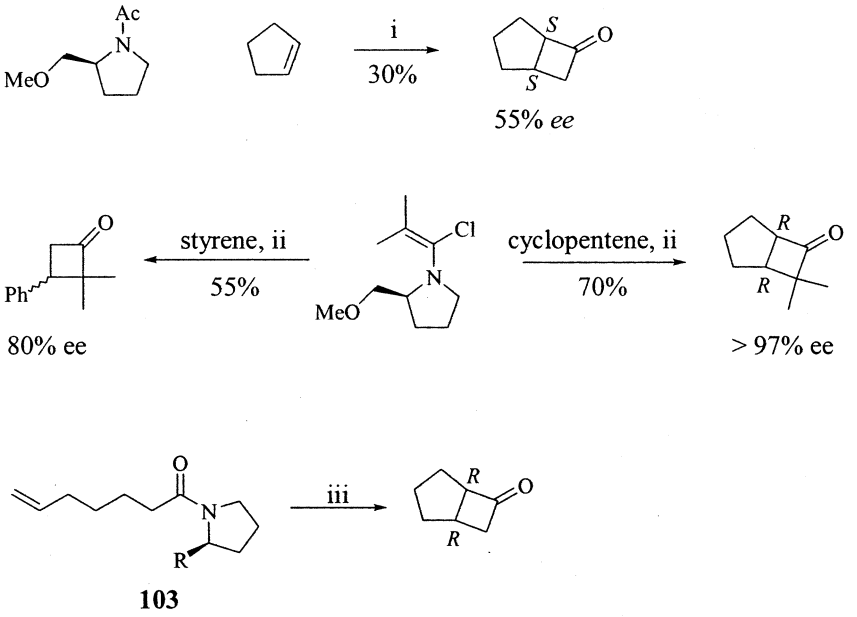


R_1 = Me, *t*-Bu
R_2 = Ph, Cl



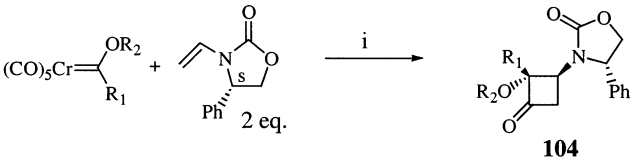
i. NaOH; ii. CH_2N_2

Scheme 35



i. Tf_2O, collidine, CH_2Cl_2, reflux 6 h; ii. $ZnCl_2$, CH_2Cl_2, 20°C, 6 h; iii. Tf_2O, $ClCH_2CH_2Cl$, 2,6-di(tert-butyl)pyridine

Scheme 36



i. *hv*, CH_2Cl_2, CO (6.2 bar)

R_1	R_2	*de*	Yield (%)	R_1	R_2	*de*	Yield (%)
Me	Me	97:3	61	Cyclopropyl	Me	≥ 98.5:1.5	59
Me	Bn	93:7	56	-(CH_2)-	-(CH_2)-	≥ 98.5:1.5	50
Ph	Me	≥ 98.5:1.5	67				

Spiro-fused butenolides of interest in natural products can be readily obtained in optically pure form starting with the cyclic chromium carbonyl complex **108** (Scheme 39).[87] Facial selectivity for the cycloadducts ranges from 86% to 100%.

D. Other Cycloadditions

A rather unusual [2+2] cycloaddition involving succinate ester dienolates with 1,2-dibromoethane was reported to give chiral *trans*-1,2-cyclobutanedicarboxylates when chiral alcohols (e.g., (−)-menthol) were used for the succinate esters.[88] Although significant optical enrichment was observed as evident from the specific rotation of the product, no ee was reported, nor was the absolute configuration assigned.

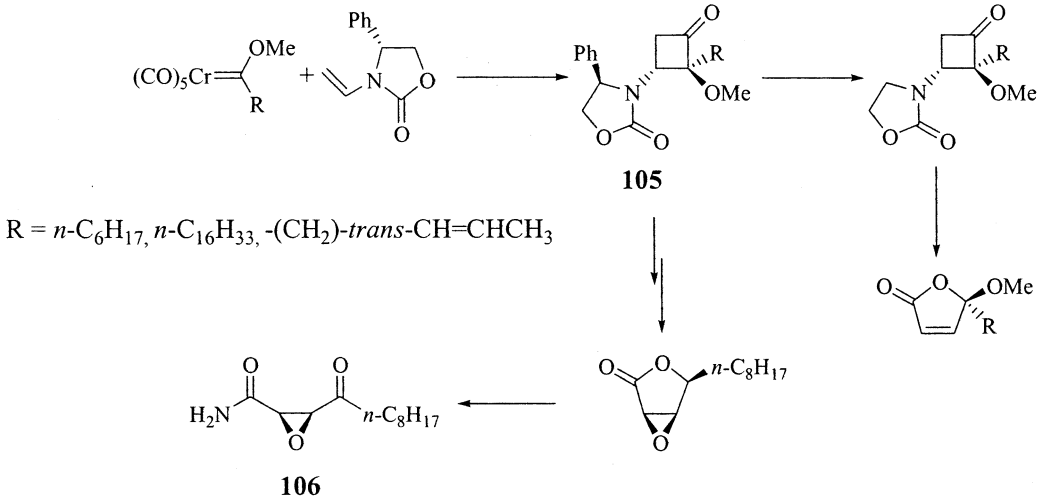
Geminal dialkylation of acidic C−H compounds using 1,3-disubstituted propanes gives cyclobutanes.[89] It is not a method of choice since oligomerization is often a competing process in these reactions. A rather unusual [3+1] cycloaddition strategy has been used for cyclobutane formation involving isonitriles as the one-carbon component.[90] The chiral isonitrile **109** serves as a carbon monoxide dianion equivalent and induces some asymmetric induction in the 1,3-dialkylation to the extent of 84% (Scheme 40).[91]

The resulting cyclobutanes are readily transformed to the antipodes of 2-methylcyclobutanone by acid-catalyzed hydrolysis.

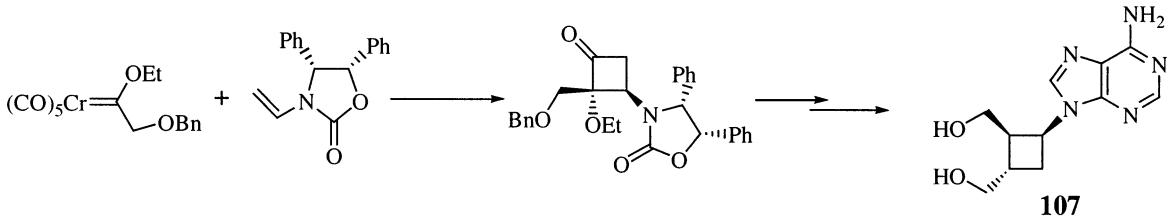
III. Ring Expansion of Cyclopropylcarbinyl Precursors

The rearrangement of cyclopropylmethyl to cyclobutyl cation proceeds through a common bicyclobutonium ion. This nonclassical cation intermediate on quenching by nucleophiles gives rise to a number of products with stereochemical scrambling and is not very useful as a method for cyclobutane synthesis. Placement of a donor group at C-1 of the cyclopropane

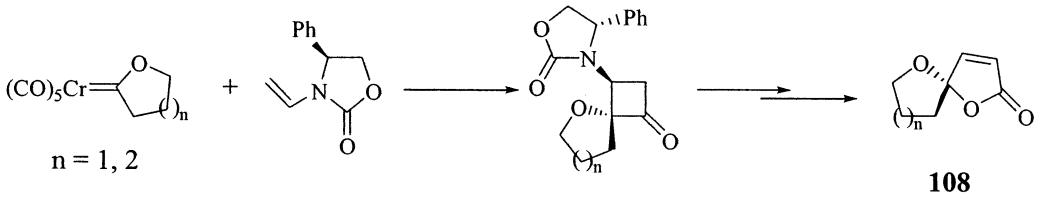
Scheme 37



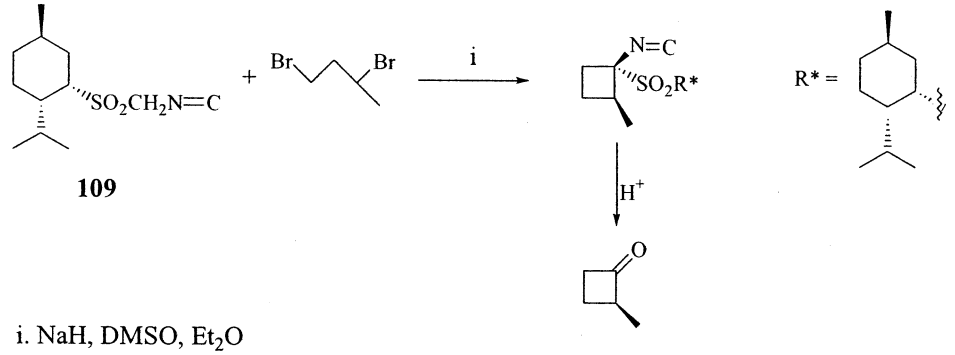
Scheme 38



Scheme 39



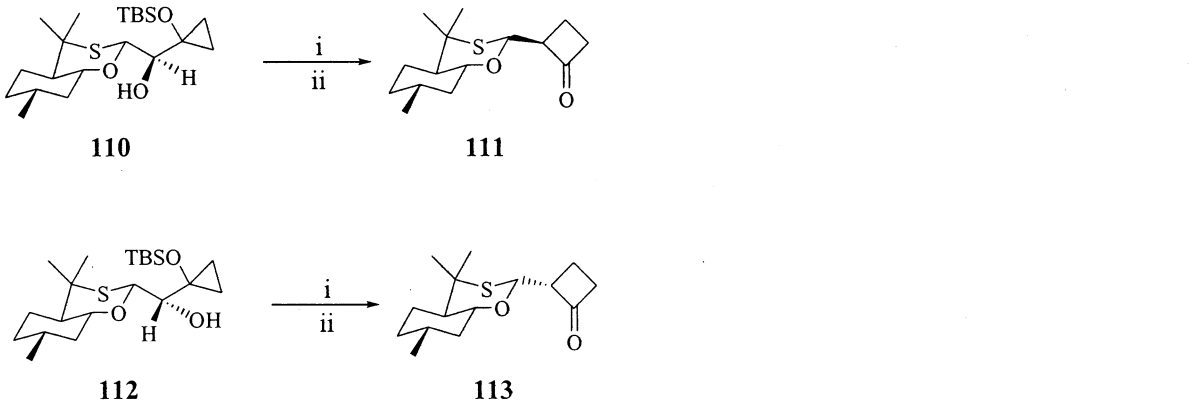
Scheme 40



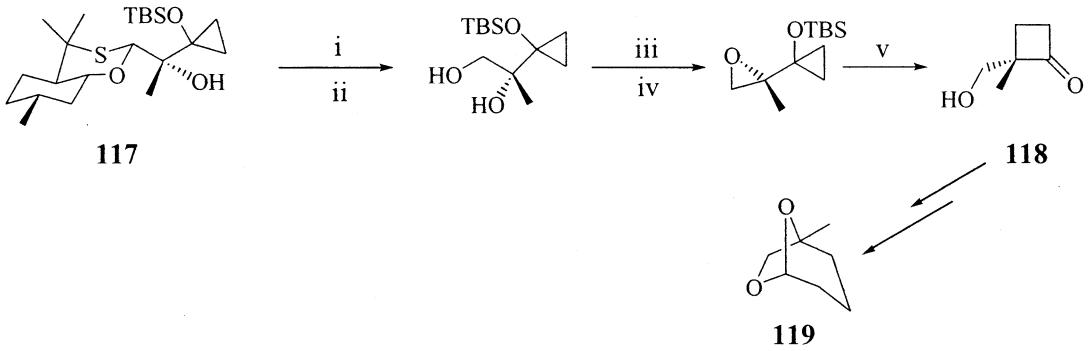
ring enhances the selectivity for cyclobutane formation. The migration usually involves an inversion at the migrating terminus with retention of configuration of the migrating carbon. The synthetic application of this class of reactions has been extensively reviewed covering the literature up to 1990,[92] and only some key strategies for enantioselective transformations of chiral cyclopropanes will be included in this review. With the recent advances of asymmetric epoxidations and hydroxylations of alkenes, the rearrangement of optically pure 1-hydroxycyclopropylmethanols and oxaspiropentanes, derived from alkylidenecyclopropanes, to give enantiomerically enriched cyclobutanes has become a powerful method for the syntheses of these important intermediates.

The substitution of a chiral auxiliary group at C-1 of cyclopropane or at the migrating terminus induces diastereoselectivity in the α-alkyl group of the cyclobutanone end products, giving rise to preferential diastereomers. The oxathianylmethyl-substituted cyclopropane **110** rearranges via the mesylate under acidic conditions, giving ketone **111** in a stereospecific manner, while the epimer **112** reacts similarly, giving enantiomerically pure **113** (Scheme 41).[93]

Scheme 41



Scheme 42



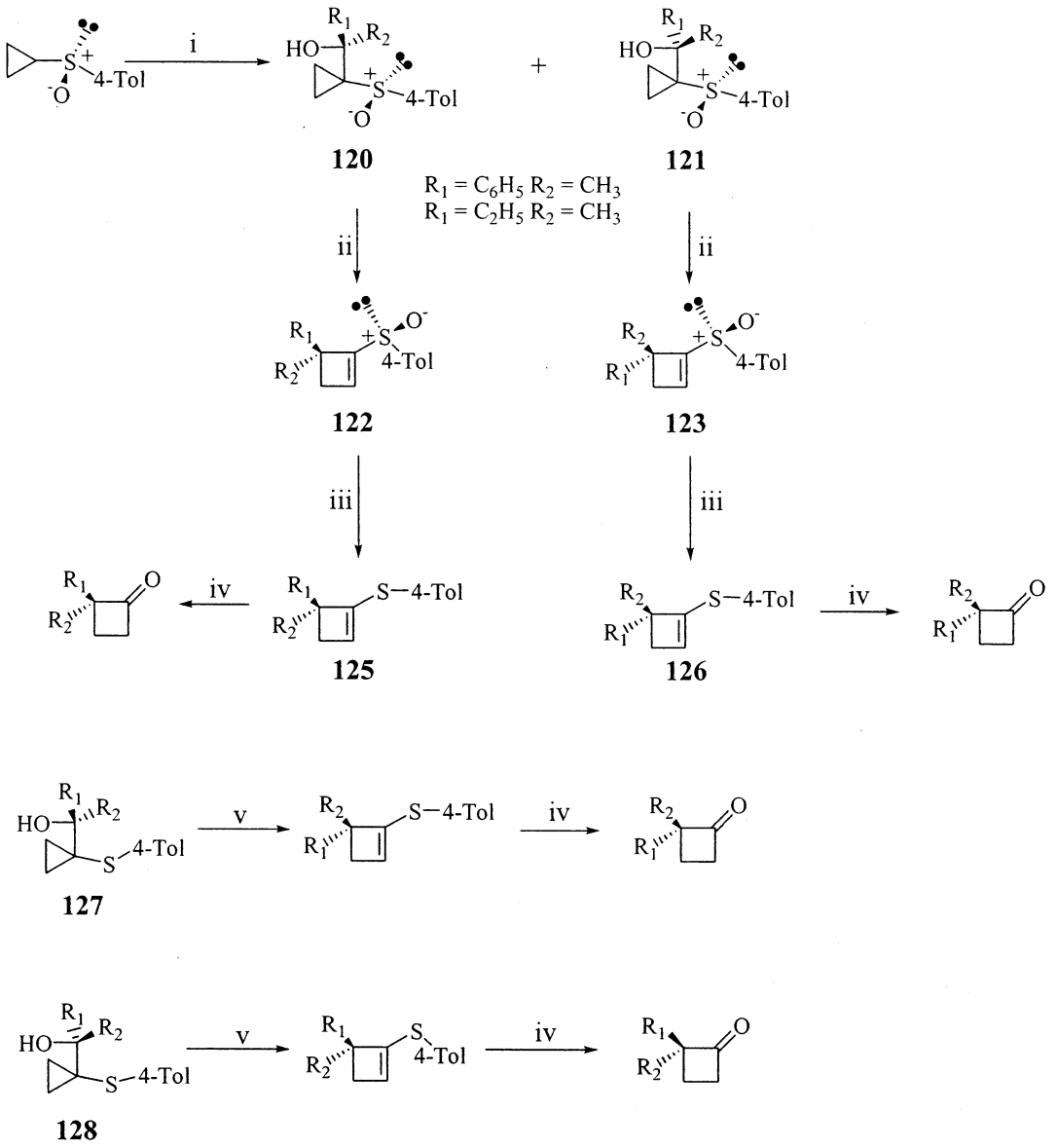
i. NCS, $AgNO_3$; ii. $NaBH_4$; iii. MsCl, Et_3N; iv. NaH, EtOH; v. silica gel

The bicyclic oxathianyl group, derived from the corresponding oxathiane which is readily obtained in three steps from (+)-pulegone, represents a protected formyl substituent which can be removed. Alkylation of the formyl group gives enantiomerically pure alkylated cyclobutanones which can be oxidized to γ-butyrolactones, one of which, **114**, is a pheromone of the Japanese beetle. The enantioselective synthesis of (−)-frontalin ((−)-**119**)[94] follows a similar protocol. The cyclopropyl carbinol **117** is obtained as the only diastereomer from methylation of the ketone derived from **110** or **112**. Deprotection of the formyl group, reduction to the diol, and ring closure provide the chiral cyclopropyloxirane, which rearranges on silica gel quantitatively to the key intermediate cyclobutanone **118** with enantiomeric enrichment of 93% (Scheme 42).

Another chiral auxiliary group effective in inducing diastereoselectivity is the chiral sulfinyl group. The cyclopropane methanol diastereomers **120** and **121** are transformed to the respective cyclobutenes **122** and **123** (Scheme 43). Deoxygenation of **122** and **123** gives cyclobutene thio enol ethers **125** and **126**, respectively, which are converted to their respective cyclobutanones.[95,96] Chemical yields of the ring expansion are in the range of 62−88% with ee's of 78−100%. It is interesting to note that the rearrangement of each of the optically pure enantiomers of sulfanyl cyclopropyl carbinols **127** and **128**, derived from deoxygenation of **120** and **121**, respectively, give cyclobutenes with retention at the migration terminus.[97] The difference is rationalized in terms of a double inversion as a result of sulfur participation in the sulfanyl cyclopropyl carbinols.

Vinylcyclobutanones are versatile synthetic intermediates which can be transformed to five-, six-, and eight-membered carbon ring compounds.[98] The preparation of enantiomerically enriched vinylcyclobutanes

Scheme 43



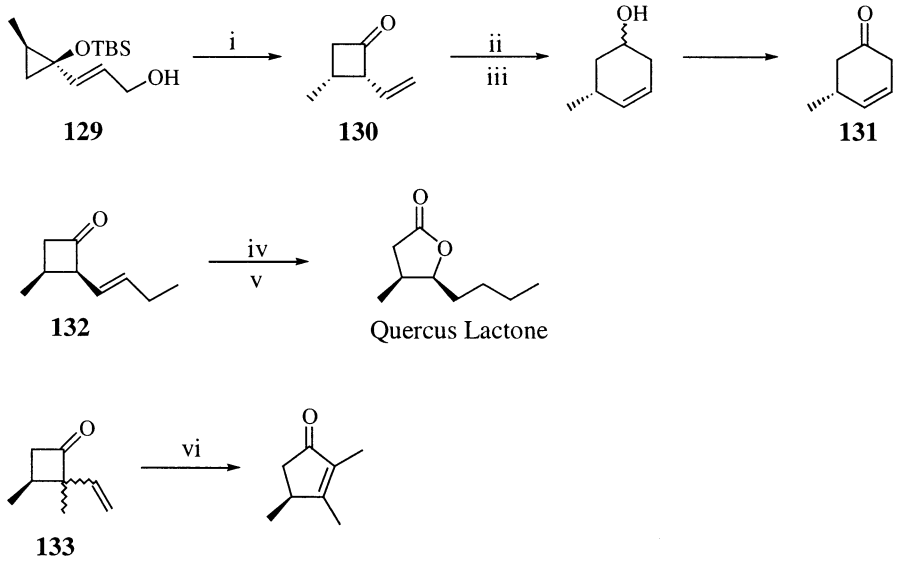
i. BuLi, R_1COR_2; ii. cat. TsOH, C_6H_6 reflux; iii. AcCl, CH_2Cl_2; iv. $TiCl_4$, $Pb(OH)_2$, H_2O; v. MsCl, Et_3N, THF

would provide enantioselective routes to these ring systems. A series of optically pure 1-silyloxy-1-cyclopropylallyl alcohols can be prepared from optically pure 2-methylsuccinic acid obtained by chiral resolution of its racemate. These alcohols are transformed by Lewis acid catalyzed rearrangement to substituted 2-vinylcyclobutanes stereoselectively. For example, the chiral alcohol **129** rearranges to the *cis*-disubstitued 2-vinylcyclobutane **130** (Scheme 44).[99] Base-catalyzed ring expansion of the corresponding alcohol produces cyclohexenone **131** with 90% ee. Other 2-vinylcyclobutanones, such as **132**, react under Baeyer−Villiger conditions to give γ-butyrolactones of interest in natural products. Rearrangement to cyclopentenones, as illustrated for the stereoisomeric cyclobutanones, can occur in acid.

The transfer of chirality from a C_{2v} cyclopropyl side chain allyl alcohol in this type of ring expansion was not effective.[100] A β-substituted chiral cyclopropylacrylate ester, **133**, rearranges under Lewis acid catalysis, giving two regiomers of keto esters **134** (70%) and **135** (30%) with high optical purity for the latter (Scheme 45). As expected, the major isomer **134** is formed as the result of the preferential migration of the more substituted cyclopropyl carbon.[101]

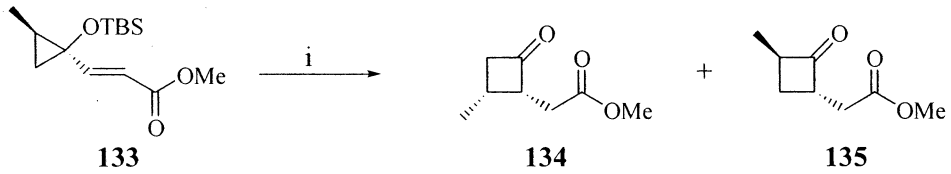
A general strategy for cyclobutanone formation involves the rearrangement of oxaspiropentanes.[102] These versatile intermediates are readily available by a number of general methods including cyclopropane annulation of ketones and aldehydes, and epoxidation of alkylidene cyclopropanes. An asymmetric version of chiral epoxidation and hydroxylation of alkylidenecyclopropanes using enantiomeric alkene oxidation protocols has been successfully applied to the syntheses of enantiomerically pure cyclobutanones which have been used as intermedi-

Scheme 44



i. BF_3, CH_2Cl_2; ii. LAH; iii. KH, THF; iv. H_2; v. MCPBA; vi. CH_3SO_3H

Scheme 45



i. TMSCl

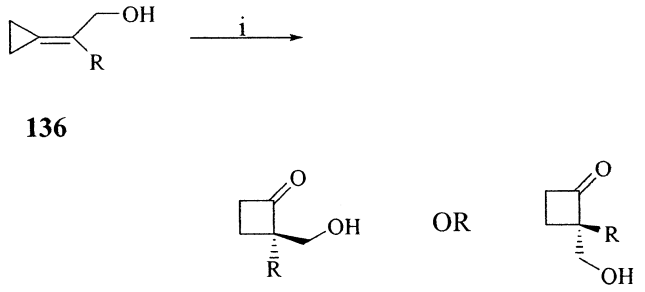
ates for a variety of enantioselective natural product syntheses.[103] Since this area has been largely developed and reviewed by the principal investigator, Nemoto, only the salient features are mentioned here. The key step involves an asymmetric Sharpless epoxidation[104] of cyclopropylidene alcohols **136**. The intermediate oxaspiropentanes rearrange under the reaction conditions to give cyclobutanones **137** with high enantioselectivity (up to 96% ee) (Scheme 46).[105] This tandem sequence has been coined the "domino asymmetric epoxidation and enantiospecific ring expansion" (DAE−ERE) reaction. The enantiomerically pure cyclobutanones **137** can be prepared in either antipode since both forms of diethyl tartrate used in the catalytic epoxidation are commercially available.

Intermediates **137** have been used to prepare (+)- or (−)-cuparenone ((+)- or (−)-**138**),[105] (+)-laurene ((+)-**139**),[106] (−)-mesembrine ((−)-**140**),[107] and (−)-aplysin ((−)-**141**)[108] using cyclopentanone ring-expansion protocols (Scheme 47).

Other enantiomerically pure substituted ketones, **137**, were used as key intermediates followed by Baeyer−Villiger oxidation protocols to give (−)-bisabolol ((−)-**142**),[109] (+)-ipomeamarone ((+)-**143**), and (−)-ngaione ((−)-**143** enantiomer).[110]

The asymmetric epoxidation method requires an α-alcohol group to direct the titanium catalyst for

Scheme 46

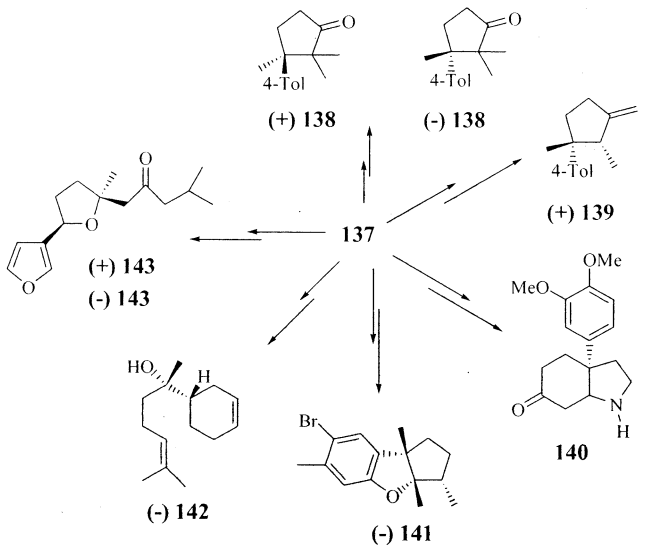


R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Tol, Ph

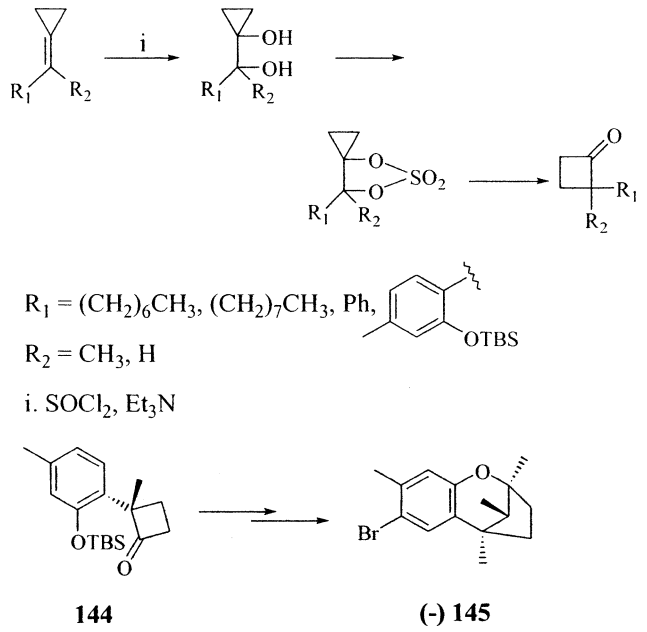
i. *t*-BuOOH, diethyl D-(-)-tartrate or L-(+)-tartrate, $Ti(O\textit{i}\text{-}Pr)_4$, 3 Å MS

π-facial selectivity. An alternate procedure using enantioselective hydroxylation of alkylidenecyclopropanes not requiring a proximal alcohol group has been shown to be an effective method for generating enantiomerically enriched cyclobutanones. The hydroxylations are carried out under Sharpless conditions.[111] The resulting *vic*-diols are converted to cyclic sulfates with sulfuryl chloride which behave like epoxides and rearrange to cyclobutanones.[112] Optical

Scheme 47



Scheme 48



yields of up to 55% are obtained. The enantioselective synthesis of (−)-filiformin ((−)-**145**) starts off with cyclobutanone **144** prepared by this method (Scheme 48).[112]

The initially formed diol from the enantioselective hydroxylation can be directly isomerized by acid-catalyzed pinacol rearrangement.[113] This approach has also been applied to the enantioselective synthesis of equilenin (**148**).[114] The conversion of the alkylidenecyclopropane **146** to ketone **147** proceeds with very good enantioselectivity (78−93%) using Jacobsen's chiral manganese(III) complex (Scheme 49).[115] It is interesting to note that the aromatic vinyl group is not affected in the reaction.

An example of the use of a chiral cycloalkylidenecyclopropane shows some π-facial selectivity in achiral epoxidations.[116] A diastereomeric mixture of oxaspiropentanes **149** and **150** (70:30) is obtained from the cyclopropane precursor (Scheme 50). The cyclobutanones obtained from ring expansion are used as intermediates for the conversion to Quercus lactones **a** and **b** with enantioselective enrichment of 92% and >89%, respectively.

Wagner−Meerwein shift in the acid-catalyzed reaction of 1-silyloxycyclopropyl allyl alcohols gives vinylcyclobutanones. The Lewis acid catalyzed rearrangement of the chiral cyclopropanes **151** and **152** leads to the corresponding chiral cyclobutanones with an enantiomeric excess of 90% based on the enantiomeric enrichment of the starting material (Scheme 51).[99,117]

The ring expansion of 1-alkenylcyclopropanols to give 2-alkenylcyclobutanones can also proceed by transition-metal catalysis. The enantioselective transformation using a chiral palladium catalyst was recently reported (Scheme 52).[118] Facial selectivity for alkene complexation in some examples is as large as 98%. The 2-alkenylcyclobutanones can be converted to the corresponding γ-butyrolactones. The transformation of 1-alkenylcyclobutanols proceeds in similar fashion under these conditions to give 2-alkenylcyclopentanones with up to 89% ee.

IV. Ring Contraction

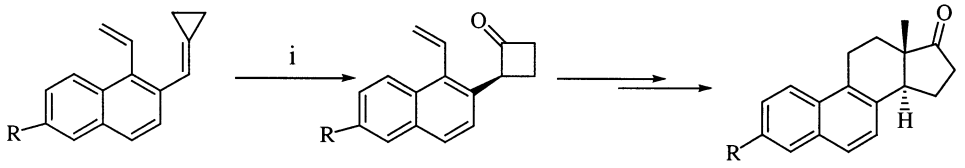
Although there are a number of methods which have been used in ring contraction of cyclopentane and furanose derivatives to give cyclobutanes, only a few examples of enantiomerically pure cyclobutanes are available by this method. These reactions involve Wolff rearrangement, Favorskii rearrangement, photodecarbonylation, and Wagner−Meerwein rearrangement of cyclopentane-containing leaving groups.[119] Most of the examples of chiral cyclobutanes prepared by these methods originate from the chiral pool of natural products and are not applicable as general approaches to these compounds. A ring contraction involving 4-vinylfuranosides may have more general applications. The tetrahydrofuran **153** is transformed to the highly substituted cyclobutane **154** by a zirconocene equivalent and subsequently with boron trifluoride−ether complex in 77% yield with retention of the ring substituents (Scheme 53).[120] Similarly, the sugar-derived 4-vinyl- and 4-ethynyltetrahydrofurans **155** and **156**, respectively, are transformed to the corresponding cyclobutanols with samarium diiodide.[121] The transformation of **155** proceeds with some epimerization.

A rather nonclassical approach to enantiomerically pure cyclobutanes involves the ring contraction of stereospecifically alkylated metallocyclopentanone **157**, which is prepared from alkylation of the unsubstituted compound (Scheme 54). These metallocycles are demetalated in a straightforward manner.[122]

Many of the sugar-based furanosides are abundantly available with different substitution patterns, and the formation of the 4-vinyl-substituted derivative is simply accomplished via dehydration protocols.

3,4-Dihydropyrans with suitably placed leaving groups can be transformed to cyclobutanols with organometallic reagents. Reductive rearrangement of 2-methoxy-3,4-dihydro-2*H*-pyran (**158**) by triisobutylaluminum hydride gave *trans*-2-hydroxymethyl-1-methoxycyclobutane (**159**) in 85% yield (Scheme 55).[123] This reaction was stereospecific in terms of

Scheme 49

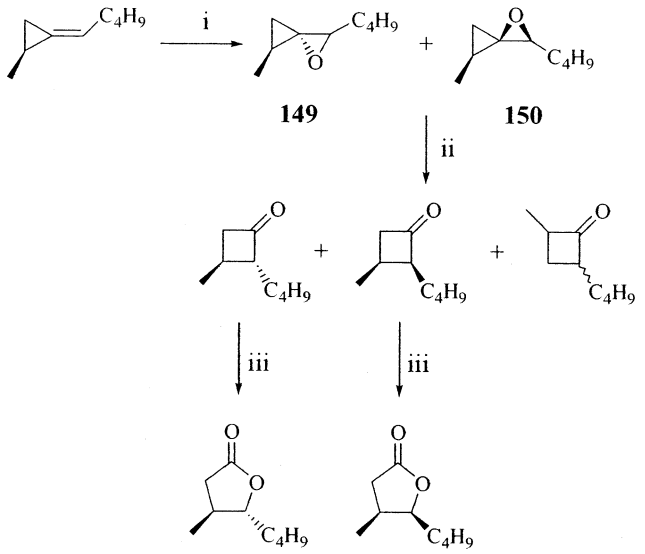


146 **147** **148**

R = OMe, H

i. 5 mol % cat. (Jacobsen (Salen) Mn(III) complex, NaClO, 4-phenylpyridine oxide, CH_2Cl_2, 0°C, 5h

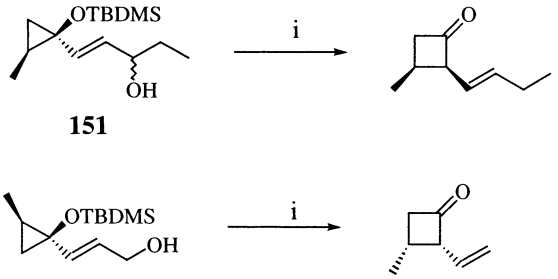
Scheme 50



149 **150**

i. MCPBA; ii. LiI, CH_2Cl_2, reflux 5 h; iii. MCPBA

Scheme 51



151 **152**

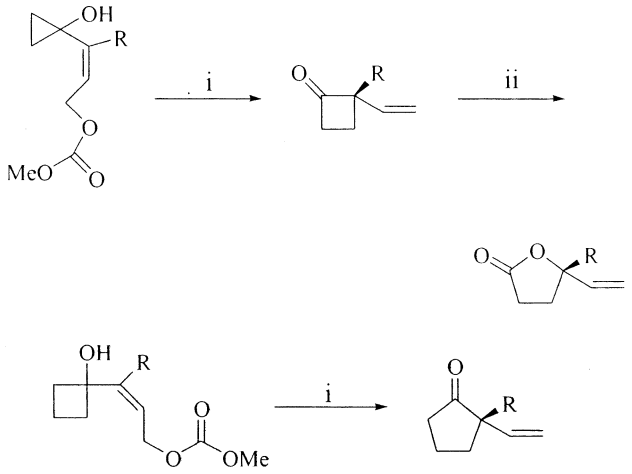
i. $BF_3.OEt_2$

exclusive formation of the *trans*-isomer; however, the enantiomeric excess obtained in the rearrangement of the (*S*)-enantiomer was low (30−40% ee) due to competing racemization prior to rearrangement.

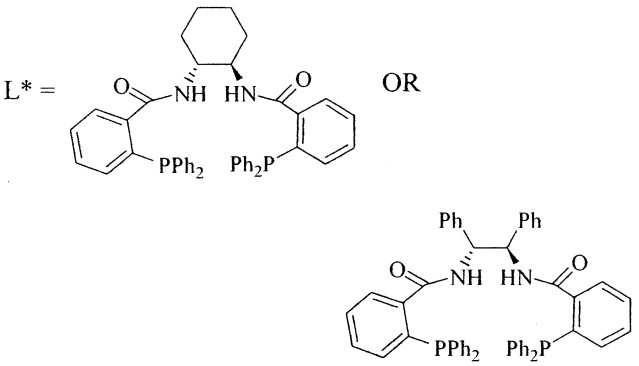
V. 1,4-Cyclization of Acyclic Substrates

The 1,4-cyclization of acyclic precursors can take place by radical or ionic mechanisms. Such reactions often proceed with stereochemical equilibration of the stereogenic termini, especially in radical processes. Nevertheless, stereoelectronic factors sometimes lead to predictable selectivities. Acyclic precursors containing chiral carbons at C-2 and C-3 maintain their stereochemical integrity on cyclization, and much of the early work for enantiomeric cyclobutane formation employed substrates which are often derived from enantiomerically pure natural product sources.

Scheme 52



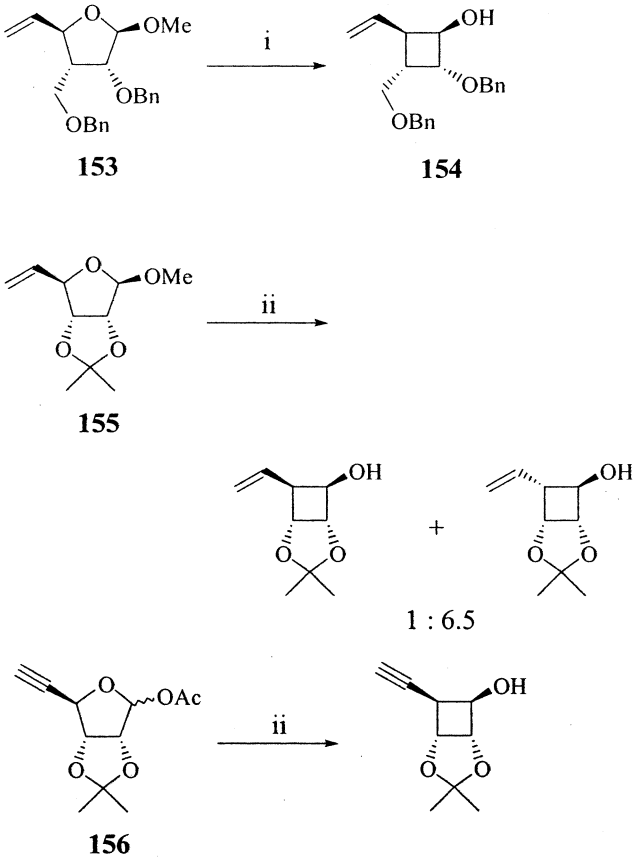
i. $CHCl_3$, $Pd(dba)_3$, L*, r.t., 5 h; ii. H_2O_2, CH_3OH, H_2O



A. Nonphotochemical Methods

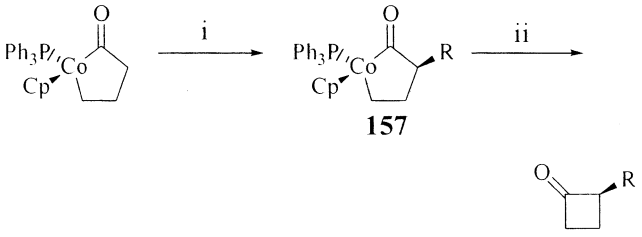
A convenient method for cyclization is the intramolecular S_N2 reaction involving carbanions with inversion occurring at one of the termini. For example, the sugar-derived dithianyl epoxide **160** is readily deprotonated and cyclizes to the chiral cyclobutane **161** in 34% yield with complete inversion of stereochemistry at the migrating terminus (Scheme 56).[124]

Scheme 53



i. $Cp_2Zr(Bu)_2$, $BF_3.OEt_2$; ii. SmI_2, $Pd(Ph_3P)_4$, r.t.

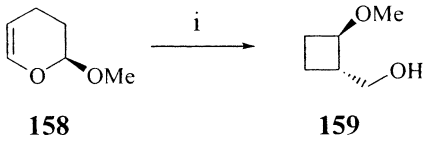
Scheme 54



Cp = cyclopentadiene

i. LDA, RI; ii. $FeCl_3$

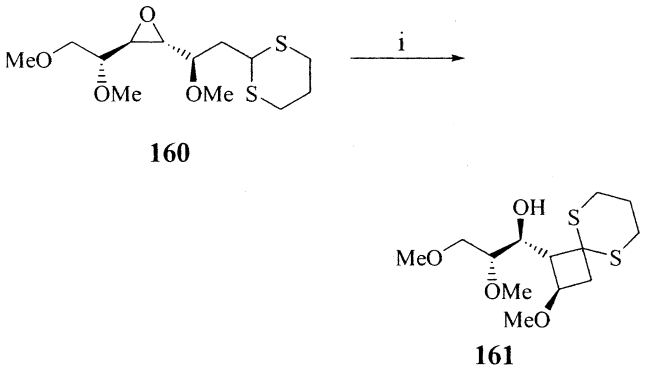
Scheme 55



i. *i*-Bu_3Al, cyclohexane, 68°C 18 h

A similar inversion of stereochemistry is observed in the intramolecular cyclization of the chiral cyanoborinates **162** (Scheme 57). The resulting cyclobutanes are obtained with high diastereoselectivity and alkylated with retention of configuration.[125]

Scheme 56



i. *n*-BuLi, THF, 18 h

A similar cyclization occurs in the intramolecular S_N2' reaction of the malonate ester **163** (Scheme 58). It is interesting to note that *syn* ring closure (relative stereochemistry of the newly formed bond is the same as that for the carbon leaving group bond) is the exclusive process in the formation of enantiomerically pure (>99% ee) cyclobutanes **164**.[125] These intermediates are used to give oxacycloocta-2,6-dienes by retro-Claisen reaction of the corresponding dialdehydes.[126]

1,4-Cyclizations of acyclic derivatives possessing one or two chiral centers between the reacting termini retain their stereochemical integrity in cyclobutane formation.[127] The enolate derived from ketone **165** cyclizes to give 70% of a mixture of the chiral cyclobutanone and oxetane with a slight preference for O-cyclization (Scheme 59).[128]

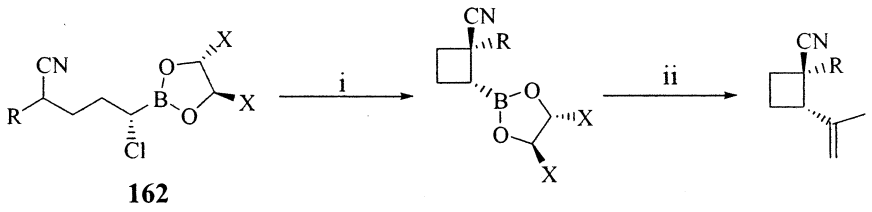
The diastereomeric γ-lactams **166** and **167** are good chiral building blocks for construction of enantiomerically pure aminomethylcyclobutanes. Base-assisted cyclization gives the diastereomeric bicyclic lactams which can be converted to enantiomeric cyclobutane γ-amino acids **168** and **169**, respectively (Scheme 60).[129] These are of medicinal interest as rigid γ-amino acid (GABA) analogues.

A number of natural product derived starting materials have been used in optically pure form for the construction of the four-carbon ring. These include commercially available levoglucosenone (**170**) obtained from the pyrolysis of cellulose. This bridged acetal has a number of potential sites for functionalization and a well-defined stereochemistry. The tosylate **171**, obtained by Michael addition from **170**, cyclizes with base to the tricyclic cyclobutane-fused acetal **172**, a key synthetic intermediate for the synthesis of (+)-**15** (Scheme 61).[130]

The sulfur-bridged sesquiterpene hydrazulene (−)-**173**, (−)-mintsulfide, can fragment via its dimethylsulfonium ylide to the tricyclic hydrocarbon **174**, used for the total synthesis of 6-oxo-α-bourbonene **175**, the toxic principal of fish poison from *Lansium domesticum* (Scheme 62).[131]

An interesting method for cyclization which was recently developed is the intramolecular Michael-aldol condensation. Principally, the reaction involves the [2+2] intramolecular cycloaddition of a donor and acceptor. The donor is an enol ether generated in situ from a ketone or aldehyde, and the acceptor is a

Scheme 57

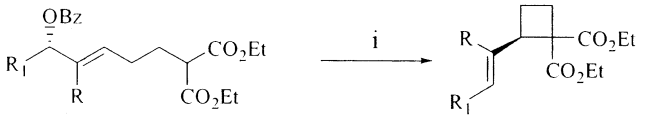


162

R = H, Me, $(CH_2)_2OSiMe_2t$-Bu
X = cyclohexyl

i. LDA, -78°C, $MgBr_2$, THF; ii. Isopropenylmagnesium bromide, I_2, $Mg(OMe)_2$, -78°C

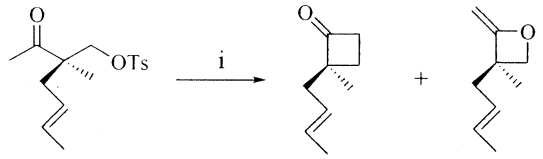
Scheme 58



163 **164**

i. NaH, toluene, 50-60°C

Scheme 59



165 3 : 4

i. KO-*t*-Bu

conjugated ester tethered to the ketone. The asymmetric version of this reaction involves chiral induction using chiral alcohols for the conjugated ester or a chiral amine induced enol ether formation with the intermediacy of an amine triflate complex.[132,133] Under these conditions, the enol ether spontaneously cyclizes, giving tricyclic cyclobutanes with modest to good diastereoselectivity, examples of which are illustrated in Scheme 63.

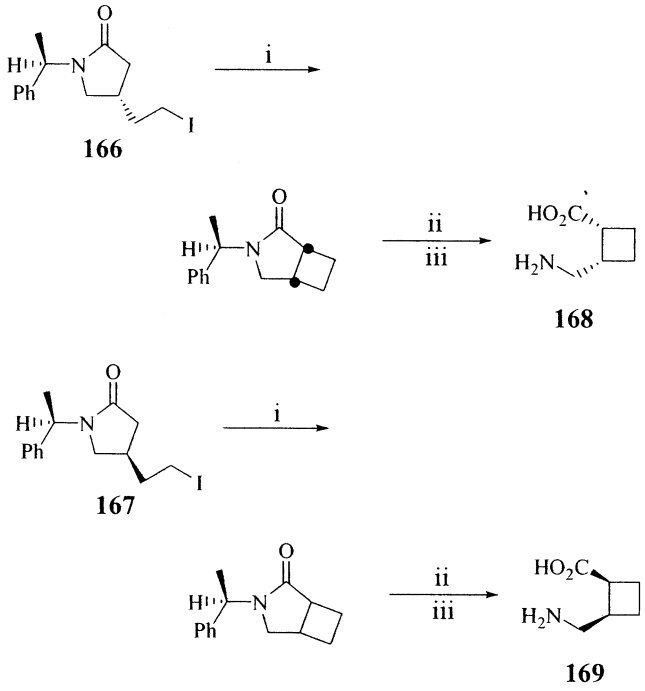
Intramolecular cyclizations by radical mechanisms can occur with alkenyl radicals. Stereoelectronic factors govern such processes and affect diastereoselectivity. The application to chiral cyclobutane synthesis is rare. The chiral radical precursor **176** reacts with samarium diiodide to cyclize by a 4-*exo*-trig mechanism to the optically pure cyclobutanol **177** (Scheme 64).[134]

The intramolecular acyloin condensation of succinic esters has been successfully applied to optically pure 2-methylsuccinic esters.[99] The resulting cyclobutene enol ether **178** is a versatile intermediate for the construction of other cyclobutanes and cyclopropanes by way of the unstable α-dione **179** (Scheme 65).

B. Photochemical Methods (Norrish–Yang Photocyclization)

The photolysis of carbonyl compounds substituted by a γ-hydrogen gives cyclobutanes by one of two

Scheme 60

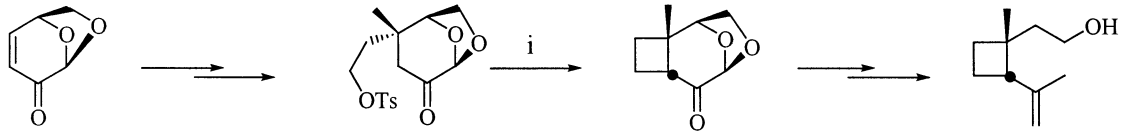


166 **168** **167** **169**

i. LiHMDS, THF; ii. Li, NH_3, -78°C; iii. HCl

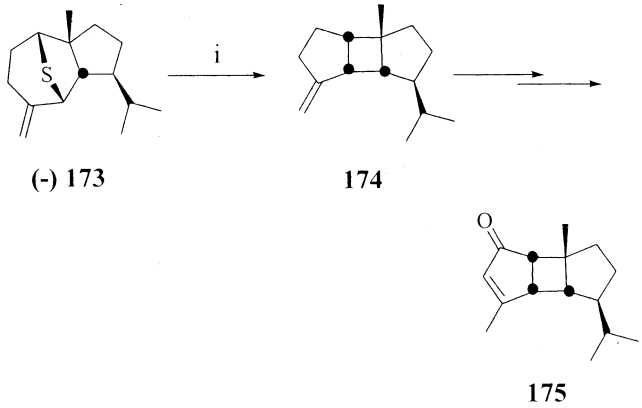
principal decomposition pathways.[8] This reaction has been used to synthesize cyclobutanols; however, only a few enantioselective examples have been reported. Early studies involving enantiomerically enriched chiral ketones and aldehydes having a γ-chiral carbon center have shown low asymmetric induction in the cyclobutanol photoproducts.[135,136] This is not surprising since these transformations proceed via 1,4-biradicals, and radicals, being planar intermediates, completely lose any chirality information of their progenitors. Furthermore, the γ-hydrogen abstraction is a reversible process. In fact, that any chiral information is retained in these reactions is surprising and suggestive of the intermediacy of radical cage complexes or short-lived intermediates. However, the use of such substrates possessing chirality at carbons 2 and 3 will give optically pure cyclobutanes under these conditions. A key step in Paquette's total synthesis of a fungal antibiotic, M95464 (**182**), is the photocyclization of ketone **180** to the tricyclic cyclobutanol **181** (Scheme 66).[137] It is interesting to note that stereochemical factors miti-

Scheme 61



i. NaH, DMSO

Scheme 62



i. LiMe

gate in the rather unusual formation of the *trans*-fused cyclobutane ring.

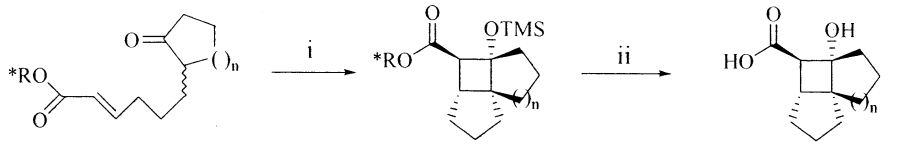
An interesting concept of the influence of a crystal matrix to control regio- and stereoselectivity in the Norrish−Yang photocylization has been observed. The photolysis of substrates in crystals often proceeds very differently than in solution. Of note is the macrolide amino ketone salt **183** with chiral carboxylate counterions. This substrate photocyclizes to give cyclobutanols **184** as the major product (Scheme 67). In the solid-state photolysis, enantiomeric excesses of 2.4% to >98% are observed for the product depending on the nature of the counterion, whereas the solution-phase photolysis results in racemic mixtures.[138]

The solid-state photolyses of phenones **185**,[139] **186**,[140] **187**,[141] and **188**[142] substituted with carboxylate salts of chiral amines give enantiomerically enriched cyclobutanols with optical purities dependent on the conformations in the crystal lattice and crystal form used (Scheme 68). In an attempt to mimic the rigidity of a crystal lattice, the use of host zeolites doped with chiral inducing agents such as chiral amines and alcohols gave low (<5% to 27%) enantiomeric enrichment for cyclobutanol formation from phenones **185**.[139] The reduced chiral induction in this case is probably due to the greater conformational mobility of the substrates in zeolites as compared to the crystal lattice.

VI. Enantioselective Reactions of Prochiral or Racemic Cyclobutanes

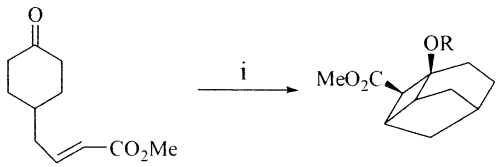
Enantioselective reactions such as deprotonations, alkylations, reductions, and other functionalization reactions of the carbonyl group of cyclobutanones represent another route to optically enriched cyclobutanes starting from racemates. Only a few examples have been reported to date. The seletive deprotonation of cyclobutanones with chiral bases and trapping of the enolates has been used to prepare optically active cyclobutenes with modest to good chiral induction.[143] The general strategy is illustrated in Scheme 69.

Scheme 63



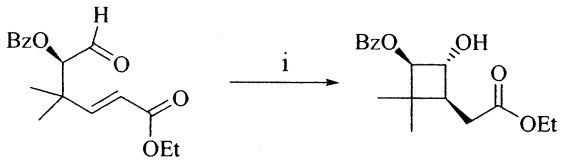
R* = (-)- 8-phenylmenthyl, n = 1,2

i. TMSI, HMDS; ii. DIBAL-H



i. chiral amine, ROTf

Scheme 64



176 177

i. SmI_2

Depending on the chiral base, variable enantiomeric enrichment (7−92%) is observed.[143] The most effective of the bases in inducing asymmetry is lithium bis(α-methylbenzyl)amide (**189**). This methodology was applied to the enantioselective total synthesis of several natural product butanolides including (−)-methylenolactocin ((−)-**190**),[144] (−)-deoxypodohizone ((−)-**191**),[145] (−)-hinokinin ((−)-**192**),[145] and (−)-isohibalactone ((−)-**193**) (Scheme 70).[145]

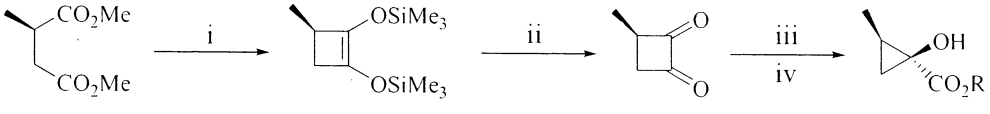
Differentiation of prochiral faces of enolates can be accomplished with chiral pyridinium salts such as **194**. A Michael addition of cyclobutanone zinc enolate gives good yields of the dihydropyridone **195** with greater than 98% diastereoselectivity (Scheme 71).[146] The facial selectivity of the reaction also on the pyridine ring gives rise to two stereogenic centers and the synthesis of highly functionalized heterocycles for potential use as chiral building blocks in natural product synthesis.

The reactivity of the carbonyl group of cyclobutanones and cyclobutenones parallels or exceeds that of stereotypical ketones. The relief of strain on conversion of an sp^2 to an sp^3 carbon or ring expansion enhances the reactivity of these ketones. Reactions of prochiral derivatives involving alkylations, reductions, and oxidations resulting in enantiomerically enriched products have been well documented. These transformations involve chiral alkylating agents,[147,148] chiral reducing agents,[149] enzyme[150] and abiotic[151] catalyzed, and noncatalyzed[152] oxidations. The enantioselective synthesis of a key intermediate, **197**, in the preparation of both lineatin and grandisol was accomplished by the use of chiral borane reducing agents.[149] Reduction of cyclobutenone **196** with commercially available (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol/borane (oxazaborolidine) or (−)-*B*-chlorodiisopinocampheylborane ((−)-DIP chloride) gives good conversion to **197** with up to 78% ee for the latter reagent (Scheme 72). Both antipodes of the reducing agents are commercially available.

Reduction of cyclobutanones to chiral cyclobutanols can also be carried out using biocatalyzed reducing agents. To prepare enantiomerically pure intermediates for prostaglandin synthesis, the racemic bicyclic ketone **198** was resolved via its alcohol. The riboflavin/Baker's yeast reduction of racemic **198** gave diastereomeric alcohols **199** and **200** with the latter as the major product (Scheme 73). The two alcohols are readily separated and isolated optically pure (>98%).[153] These can be oxidized back to the corresponding enantiomerically pure (+)- and (−)-cyclobutanones (+)- and (−)-**198**, constituting a method of resolution.

The Baeyer−Villiger oxidation of cyclobutanones to the corresponding γ-butyrolactones occurs regioselectively with stereochemical retention of the ring substituents. The enantioselective oxidation prior to 1994 always employed enzyme-mediated methods, often giving variable optical enrichment as well as mixtures of regioisomers. The practical use of biocatalyzed methods often depended on ad hoc approaches with minimal predictability of the absolute configuration of the products. For example, a series of oxygenases were tried for the Baeyer−Villiger conversion of 3-benzyloxymethylcyclobutanone to (*R*)-3-benzyloxymethylbutyrolactone before settling on one giving 60% conversion with a 97% ee.[154] The enzyme-mediated oxidation is further complicated with asymmetric cyclobutanones where regioisomers can form under these conditions. For Baeyer−Villiger oxidations under nonenzymatic conditions, the regiochemistry can be predicted on the basis of migration of the more substituted carbon. The enzyme-catalyzed oxidations of a series of bicyclic ketones, **201**, results in a mixture of the "normal" lactones **202** and "abnormal" lactones **203** with not much regioselec-

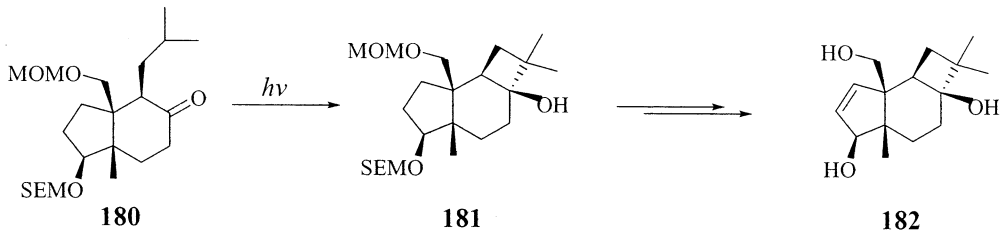
Scheme 65



178 179

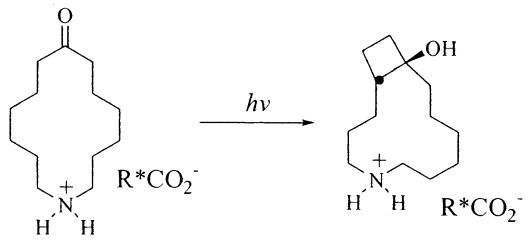
i. Na, TMSCl, toluene, reflux; ii. Br_2, pentane, -50°C; iii. NaOH, 0°C; iv. HCl, ROH

Scheme 66



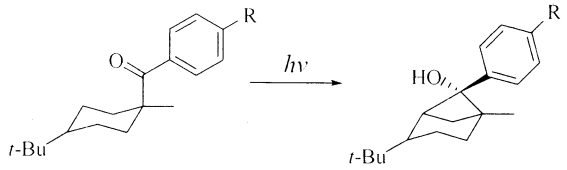
180 181 182

Scheme 67

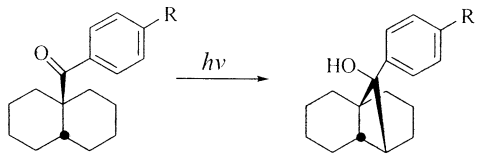


183 184

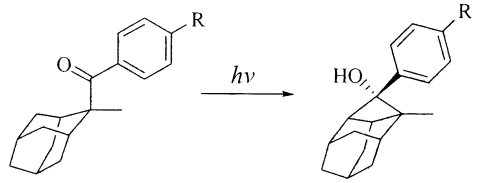
Scheme 68



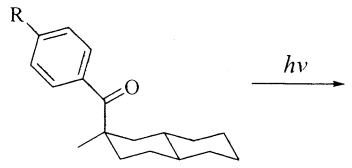
185



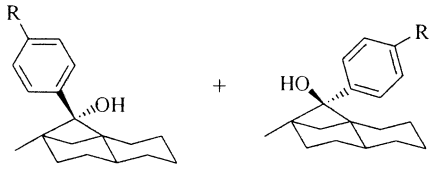
186



187



188



tivity but with 50−95% enantiomeric enrichment (Scheme 74).[155] One particular enzyme system, derived from the fungus *Cunninghammela echinulata* NRRL 3655, catalyzes the oxidation of **198**, giving predominantly the abnormal lactone **203** ($n = 3$, H_4).[156] The abnormal lactone would not have been produced under standard Baeyer−Villiger conditions.

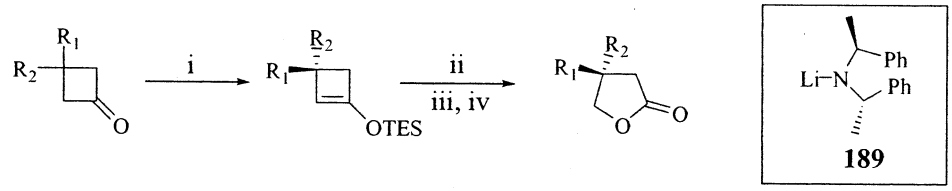
The enantioselective abiotic Baeyer−Villiger oxidation of cyclobutanones was only recently developed using either chiral catalysts or oxidants. Such catalysts as the C_2-symmetric bisoxazoline **204** (Scheme 75) in 1 mol % concentration in the presence of molecular oxygen and an aldehyde (preferably ^{t}BuCHO) will insert oxygen into 2- and 3-substituted cyclobutanones to give the corresponding lactones with up to 92% ee.[151,157] Regioisomeric lactones with significant amounts of the abnormal Baeyer−Villiger products are observed with bicyclic and tricyclic ketones with very good optical purities.[158] Other catalysts which have been employed include the chiral zinc complex **205**, generated in situ from diethyl zinc and chiral amino alcohols, which oxidize 3-substituted cyclobutanones to the corresponding lactones in the presence of molecular oxygen with modest enantioselectivity.[159] Aluminum complexes of BINOL and substituted BINOLs have also been shown to catalyze the oxidation of cyclobutanones with enantiomeric excesses of up to 96%.[160] In these reactions a hydroperoxide is used as the oxygen source. However, with asymmetric substrates, regioisomers are obtained in varying amounts. The use of the Sharpless oxidation for conversion of cyclobutanones to butanolides has been shown with limited effectiveness.[161] Oxidation of substituted cyclobutanones with titanium isopropoxide/tartrate diester mixtures containing *tert*-butyl hydroperoxide as the oxidant give the corresponding γ-lactones in moderate yields with optical purities of up to 75%. These reactions cannot be considered as catalytic in the true sense since more catalyst than substrate is used.

Although the use of chiral hydroperoxides for enantioselective oxidations has not been shown to be effective, one such hydroperoxide, TADOOH (**206**), was found to oxidize *racemic* bicyclo[4.2.0]octan-7-one to the normal Baeyer−Villiger product (*R*,*R*-configuration) with 75% optical purity depending on the extent of conversion and temperature.[152] Kinetic analysis of the reaction indicated that at −75 °C, the (*R*,*R*)-isomer of the substrate reacts 23 times faster than its enantiomer. Thus, a kinetic resolution of the racemic starting material is possible such that enantiomerically pure unreacted substrate can be obtained after about 70% conversion. Smaller ring bicycloheptanones and bicycloheptenones gave both the normal and abnormal Baeyer−Villiger products.

VII. Resolution Methods

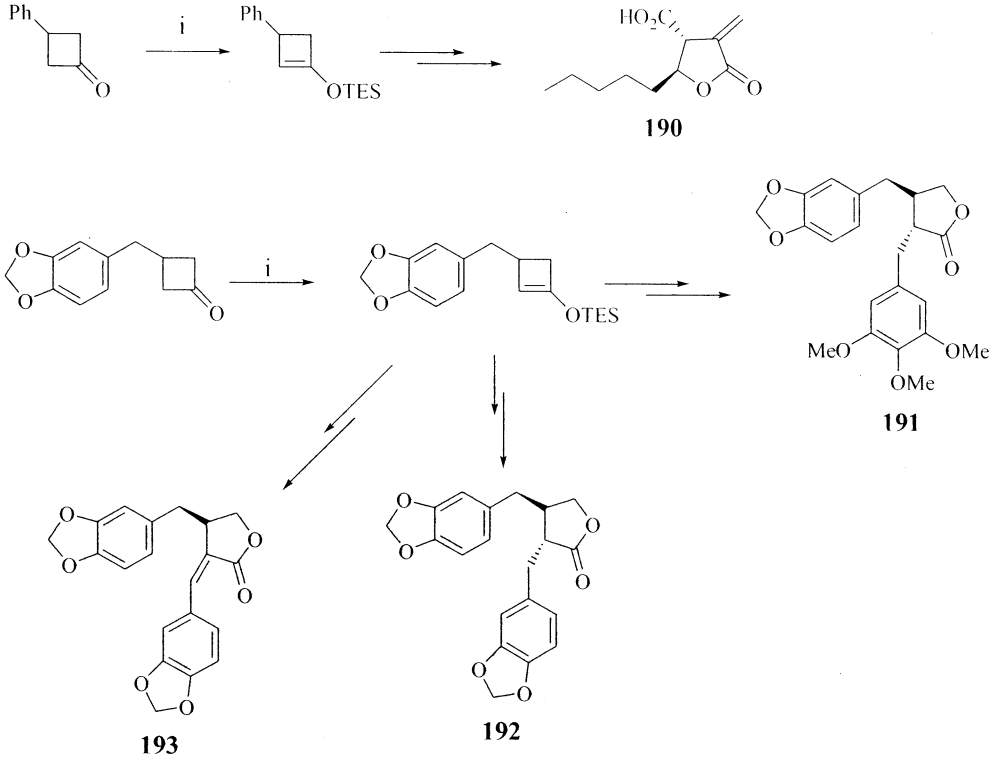
Resolution of racemates is the classical method for obtaining enantiomerically enriched compounds but suffers from the limitation of the maximum 50% obtainable yield of the desired enantiomer. Such yields can be improved with the use of sequential equilibration and conversion of the unwanted enantiomer back to the racemate. The resolution of racemates can proceed by enzymatically assisted kinetic resolution or by chemical methods involving the use of chiral agents for the conversion of racemates to separable diastereomeric mixtures. Once separated, the pure diastereomer is converted back to the optically pure material by removal of the chiral auxiliary. The use of a chiral stationary phase in chromatography has become routine for the separation of certain classes of compounds but is not generally applicable for preparative purposes.

Scheme 69



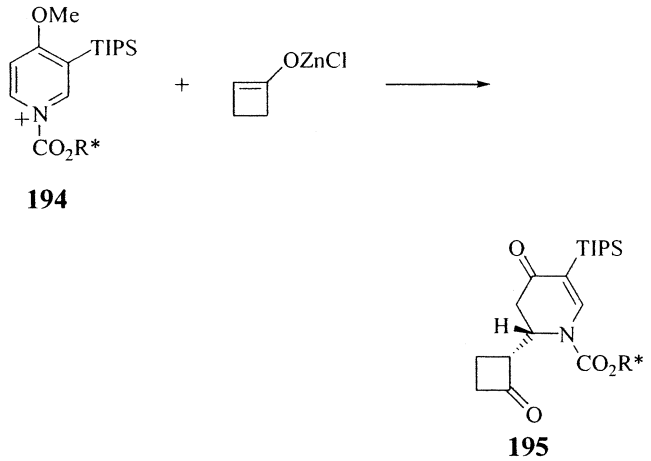
i. $Li^+ \bar{N}(R^*(chiral))R$, TESCl; ii. O_3; iii. $NaBH_4$; iv. 2*N* HCl

Scheme 70



i. **189**, Et_3SiCl, THF, -100°C

Scheme 71



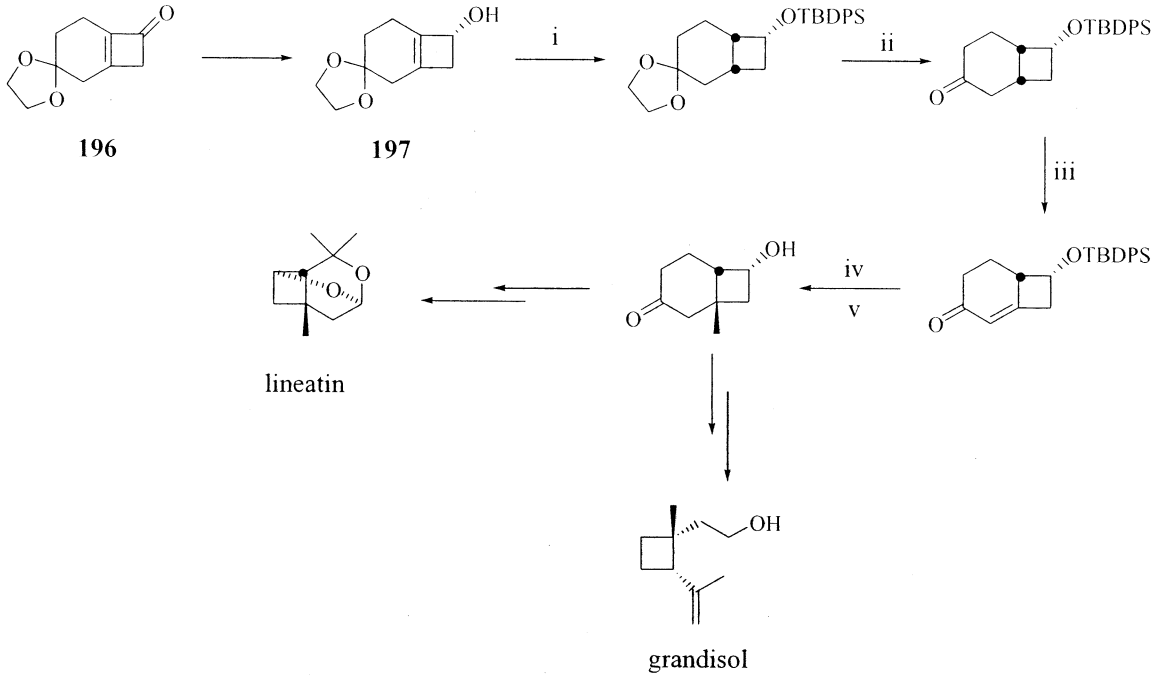
R* = (-) - *trans*-2-(α-cumyl)cyclohexyl (TCC)

A. Abiotic Resolution

The conversion of carboxylic acids to ammonium salts with amines has been the traditional method for the resolution of either racemic carboxylic acids or amines. The ammonium salt diastereomers, once separated, are readily converted back to their respective neutral fragments. This was the method of choice for the resolution of racemic *trans*-cyclobutane-1,2-dicarboxylic acid (**207**) (Scheme 76) with chiral amines in one of the earliest reports of an optically pure cyclobutane.[2] It is interesting to note that this compound was not used until much later for conversion to other optically pure cyclobutanes. An early study on the Hunsdiecker reaction for conversion to the *trans*-cyclobutane-1,2-dibromide via its silver salt led to a small but detectable optical activity, indicating the nonexclusivity of the free radical pathway.[162]

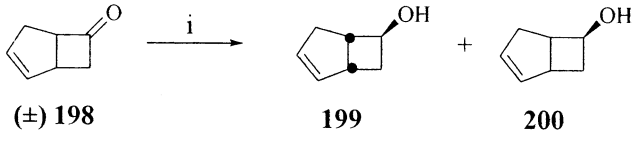
The resolution of commercially available Feist's acid (methylenecyclopropane-*trans*-1,2-dicarboxylic acid) (**208**) with quinine gives a key intermediate for the preparation of optically pure cyclobutanone **69** using an epoxidation and oxaspiropentane ring expansion protocol.[163] The stereochemistry of the ring substituents is maintained throughout the sequence

Scheme 72



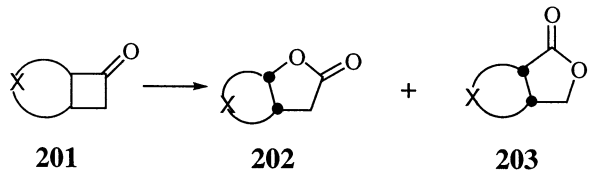
i. TBDSCl; ii. TsOH; iii. $Pd(OAc)_2$; iv. $Li(CH_3)_2Cu$; v. HCl, MeOH

Scheme 73



i. Bakers yeast, riboflavin, glucose, H_2O, 23°C

Scheme 74



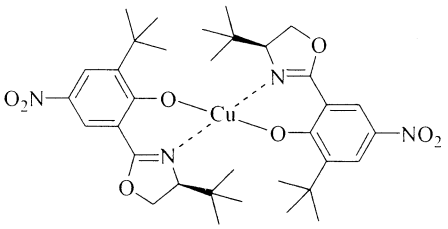
X = $(CH_2)_n$ or C_nH_{2n-2}

of reactions. The keto acid **209** can be resolved from its racemate and serves as an important intermediate in the synthesis of grandisol.[164] Other chemical resolution methods of carboxylic acid derivatives such as esters and anhydrides involve conversion to their amide derivatives with a chiral amine. Examples of these are illustrated for amide **210** (Scheme 77) obtained from the corresponding methyl ester and used as an intermediate for the synthesis of **15**,[165] phenylglycinol amide **211** obtained from its methyl ester,[166] and thioamide **212** obtained from *cis*-cyclobutane-1,2-dicarboxylic acid anhydride.[167] The first chiral resolution of a cyclobutanone was reported in 1981 using the bisulfite method and the formation of the sulfonic acid ammonium salt with a chiral amine.[168]

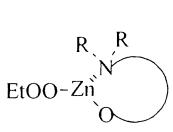
B. Enzyme-Mediated Resolution of Racemates

The use of enzymes in organic synthesis has become increasingly popular for the preparation of enantiomerically pure materials. These catalyzed processes are selective for one of the two enantiomers of a racemate. Nevertheless, in many cases these reactions are not specific so that optimum conditions have to be found for the kinetic resolution to maximize the extent of optical purity. As a result optimum conversions are often less than 50%. Enzyme-catalyzed hydrolysis and esterification are the most commonly exploited biotransformations. There are two principal reasons for this. First, the reactions are easily performed without the need for a special apparatus as required in anaerobic reaction conditions. Second, the absence of sensitive cofactor requirements and the large variety of available hydrolase enzymes from commercial suppliers make these biotransformations desirable. The lipases are enzymes which catalyze the hydrolysis of lipids, specifically triglycerides, as their principal biological function. However, the fact that many lipases have the ability to hydrolyze a broad spectrum of esters other than those of glycerides make them valuable catalysts in organic synthesis to perform regio- and stereoselective transformations. There are some substrate requirements for bioconversion by lipases such as the preferred proximal location of the chiral center and the necessity of having a hydrogen atom on the chiral carbon. Since the natural substrates are esters of a chiral alcohol with an achiral acid, it is expected that lipases are most useful for hydrolyzing esters of chiral alcohols rather than esters of chiral acids. Although this is true for the majority of substrates, a small number of lipases display selectivity through recognition of the chiral center of the acid moiety.[169]

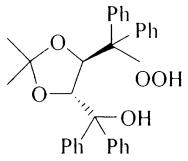
Scheme 75



204

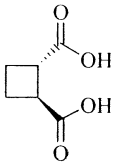


205

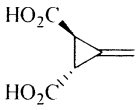


206

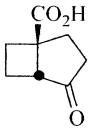
Scheme 76



207

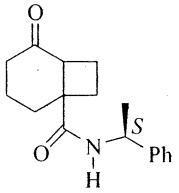


208

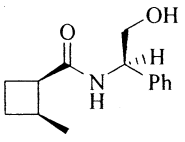


209

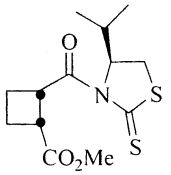
Scheme 77



210



211



212

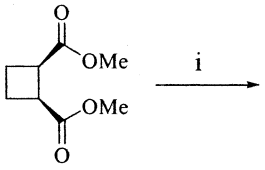
The reverse process of acetylation of racemic or prochiral alcohols can be catalyzed by these same lipases using vinyl acetate in a transesterification reaction. The molecular mechanism of lipase catalysis is very different from that of other hydrolytic enzymes, which gives rise to their ability to perform catalysis in biphasic media. The neat substrate can be used as the organic phase, or it can be dissolved in a water-immiscible organic solvent for reaction. This aspect makes it also possible to recover the enzyme after the reaction due to its insolubility in organic solvents. Of these lipases, pig liver esterase (PLE) and porcine pancreatic lipase (PPL) are commonly used for enantioselective hydrolysis and esterification. Since these have been shown to be active for a broad spectrum of substrates, extensive studies on enantioselectivities have resulted in a model for predicting the stereochemical outcome of substrates not previously investigated.[170]

The PLE-mediated hydrolysis of prochiral *cis*-cyclobutane-1,2-dicarboxylic acid dimethyl ester (**213**) gives enantiopure monoester **214** (Scheme 78). Using regioselective chemical transformations, both enantiomers of the optically pure lactones **215** can be obtained from the same intermediate in an enantiodivergent manner.[171]

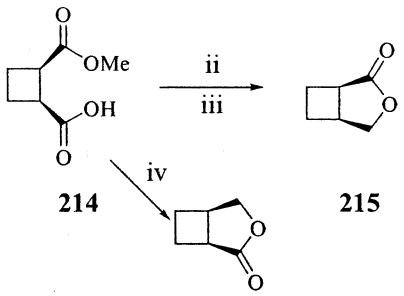
The same intermediate, **214**, was used in a Curtius rearrangement to produce the rigid β-amino acid **216** of medicinal interest (Scheme 79).[172]

The PPL-mediated hydrolysis of racemic cyclobutanone **217** gives (+)-**218** with 34% conversion and 85% ee (Scheme 80).[173] No in situ racemization of the remaining starting material is observed during the

Scheme 78



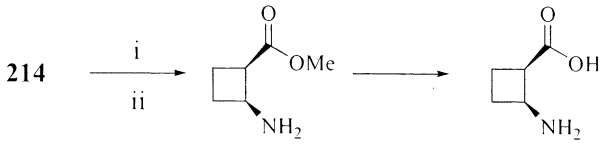
213



214 215 215'

i. PLE, H_2O; ii. $ClCO_2Et$; iii. $NaBH_4$; iv. $LiBH_4$

Scheme 79



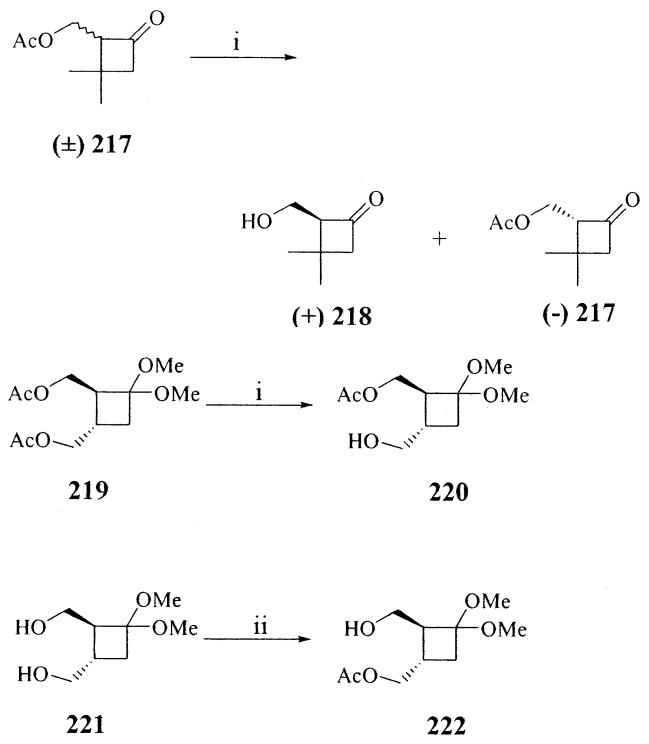
216

i. $ClCO_2Et$, TEA; ii. NaN_3

course of the biotransformation. However, (−)-**217** after isolation can be racemized with DMAP and recycled to improve conversion to the hydroxy ketone in an example of dynamic kinetic resolution.

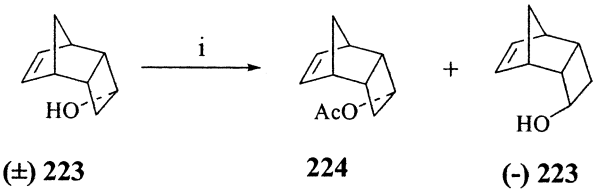
PPL also induces regiospecific hydrolysis and esterification. For example, the optically pure ketal **219** is hydrolyzed exclusively at the C-3 substituent. In the same manner, enzyme-assisted esterification of diol **221** occurs only with the hydroxymethyl group at C-3, permitting the preparation of both regioisomers in optically pure form.[173] It is interesting to note that the corresponding cyclobutanones of **219** and **221** are poor substrates for the hydrolysis. Lipases can even tolerate unnatural substrates such as cyclobutanol esters having a β-chloro substituent.[174] The resolution of cyclobutanols by lipase-catalyzed esterification has been used in the preparation of optically pure cyclobutanes.[175]

Scheme 80



i. PPL, toluene, pH 7.0, r.t., 12 h; ii. PPL, toluene, vinyl acetate, pH 7.0, r.t., 12 h

Scheme 81



i. Lipase PS, vinyl acetate, THF

The racemic alcohol **223** can be resolved using lipase-mediated acetylation with vinyl acetate (Scheme 81).[176] The optically pure tricyclic cyclobutanes (−)-**223** and **224** are used for the total synthesis of iridoid monoterpenes such as (−)-boschnial lactone, and both antipodes of *β*-santalene. In a similar transesterification, the alcohol **225** can be resolved by bioacetylation. The optically pure products are used for the synthesis of optically pure grandisol and the oleander scale pheromone **226** (Scheme 82).[177] In this instance a nonmammalian lipase (*Pseudomonas fluorescens* lipase) is used effectively.

The use of enzymes other than lipase has been reported. The diol **227** can be oxidized to optically pure lactone **215′** using horse liver alcohol dehydrogenase (Scheme 83).[178] This intermediate is also used for grandisol synthesis.

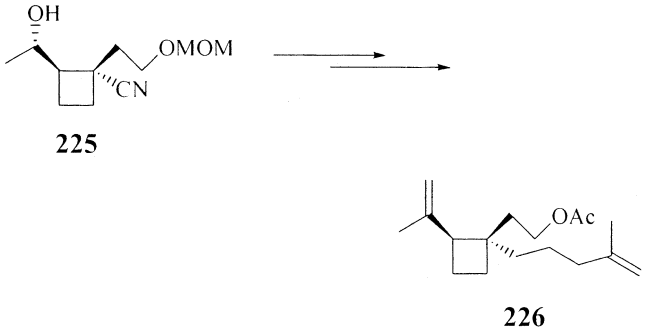
VIII. Cyclobutanes from Natural Products

The chiral pool of natural products represents a source from which enantiomerically pure cyclobutanes can be obtained. These substrates include materials which have the cyclobutane ring incorporated in an asymmetric carbon framework or others from which cyclobutanes can be readily prepared by any one of the methods described above. The latter include dehydro sugars, steroids, and terpenes. The limitation with the use of natural product derived materials is the existence for the most part of only one of two enantiomeric forms so that the antipode of a particular cyclobutane cannot be prepared in the same way. Nevertheless, a number of useful enantiomerically pure cyclobutane derivatives have been obtained from spiroannulation of natural product ketones and aldehydes to produce spirocyclobutanones using the methods of ring expansion of oxaspiropentanes or related intermediates.[102] An elegant example of the use of such a strategy to synthesize (−)-*β*-selinene starts with commercially available (−)-perillaldehyde ((−)-**228**).[179] Cyclobutanone **229** is obtained by condensation of **228** with lithium 1-methoxycyclopropane followed by an acid-catalyzed ring expansion of the intermediate cyclopropyl carbinol (Scheme 84). The cyclobutanol from **229** is used in an oxy-Cope rearrangement to give octalin **230** with the requisite stereochemistry for the isopropenyl substituent.

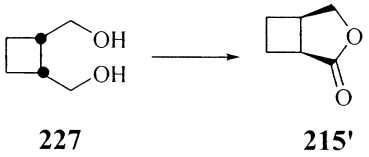
An interesting photochemical ring contraction of the bicyclooctanone **232** to produce the bicyclic cyclobutanone **233** was reported (Scheme 85).[180] The ketone precursor **232** is obtained from (−)-carvone ((−)-**231**), which is commercially available in both enantiomeric forms. Such photochemical ring contraction isomerization of *β*,*γ*-cyclohexenones has been reported for achiral substrates.[119]

A number of natural products incorporating a cyclobutane ring are commercially available and have been used to prepare other useful enantiomerically pure cyclobutane intermediates. These include both antipodes of α-pinene (**234**), *β*-pinene (**235**), (−)-*trans*-caryophyllene ((−)-**236**) and its epoxide, (−)-verbenone ((−)-**237**), (+)-nopinone ((+)-**238**), (−)-nopol ((−)-**239**), both antipodes of myrtenal (**240**) and myrtenol (**241**), (+)-α-longipinene ((+)-**242**), and (−)-copaene ((−)-**243**) (Scheme 86).

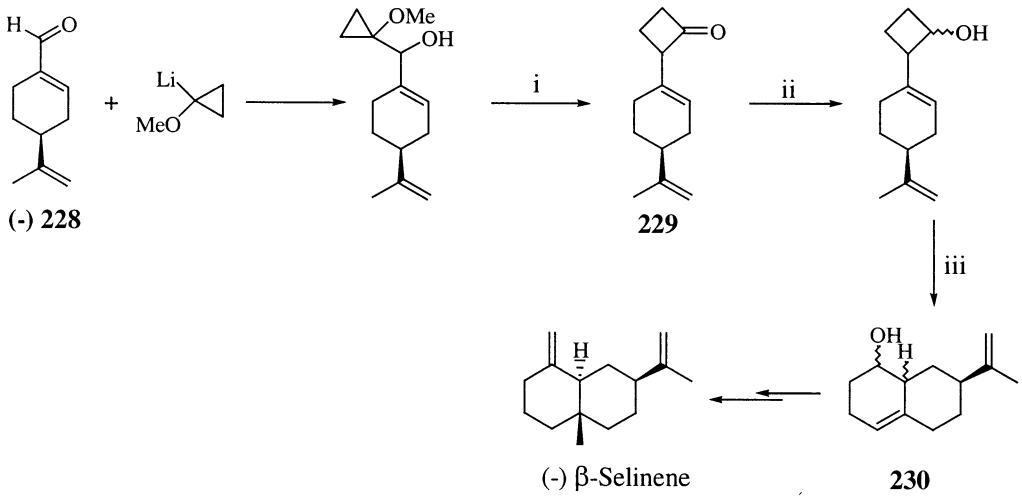
Scheme 82



Scheme 83



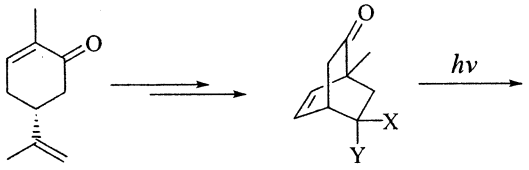
Scheme 84



(-) 228 229 (-) β-Selinene 230

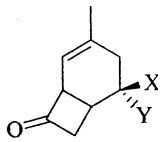
i. HBF_4, THF; ii. LAH; iii. KH, THF, reflux.

Scheme 85



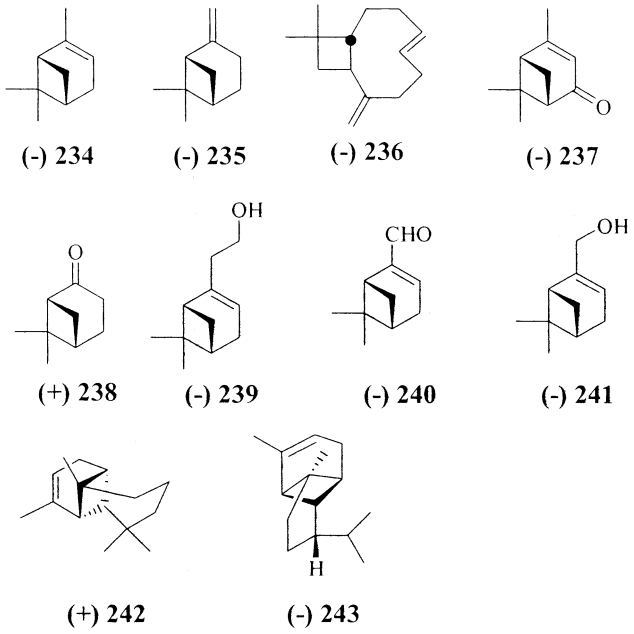
(-) 231 232

X = OMe, Me
Y = Me, OMe



233

Scheme 86



(-) 234 (-) 235 (-) 236 (-) 237 (+) 238 (-) 239 (-) 240 (-) 241 (+) 242 (-) 243

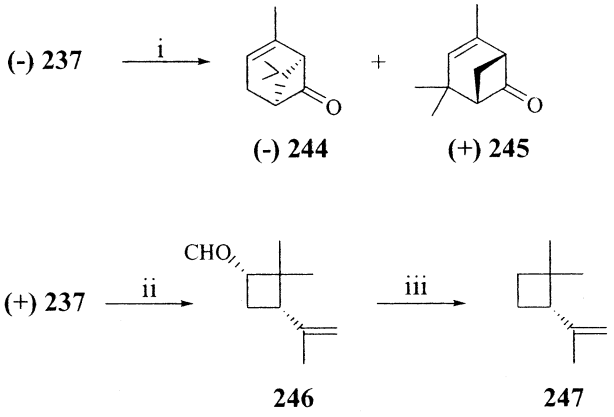
The first reported synthesis of an optically active cyclobutanone was based on a photochemical isomerization of verbenone (**237**).[3] Irradiation of (−)-**237** in acetic acid at ambient temperatures affords principally (−)-chrysanthenone ((−)-**244**) and its isomeric ketone **245** with high retention of optical purity (Scheme 87).[181] In contrast, the irradiation at higher temperatures for extended periods led to significant racemization of the photoproducts. When the photolysis of (+)-**237** is carried out in methanol as solvent, a Norrish type II process occurs in which enal **246** is formed.[182] Rhodium-catalyzed decarbonylation of this aldehyde furnishes optically pure cyclobutane **247**. Although (+)-verbenone is not commercially available, it can be readily prepared from (+)-**234** by allylic oxidation.[183]

Pinene and verbenone represent inexpensive chiral starting materials for the preparation of highly substituted cyclobutanes. The oxidative cleavage of (+)-**237** gives the optically pure keto acid **248** from which the protected γ-amino acid (GABA) analogue **249** is obtained (Scheme 88). The same starting material is used in an enantiodivergent route to the protected antipode of **249**.[183]

The *cis*-disubstituted cyclobutane **250** can be obtained from (−)-**237** using a different oxidative cleavage sequence (Scheme 89). This intermediate is used for the preparation of another GABA analogue, **251**.[184]

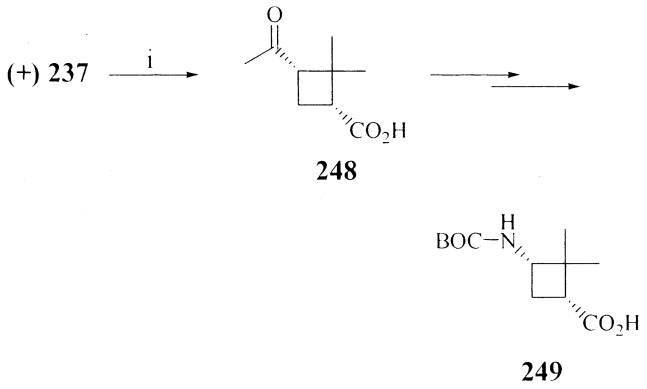
The oxidative cleavage of **234** and **235** gives *cis*-pinonic acid (**252**) and nopinone (**238**), respectively (Scheme 90). These intermediates have been utilized for the construction of other chiral cyclobutane and cyclohexane derivatives. For example, **252** can be used for conversion to the cyclobutanol acetate **253** in a three-step sequence involving a Baeyer−Villiger reaction.[185] The latter is an intermediate for chrysanthemic acid methyl ester (**254**) synthesis.[186] Since cyclobutyl ketones can undergo facile Lewis acid catalyzed ring opening reactions, **238** can be used to prepare highly substituted cyclohexanones such as elemenone (**255**), a member of the elemanolide family of natural products.[187,188]

Scheme 87



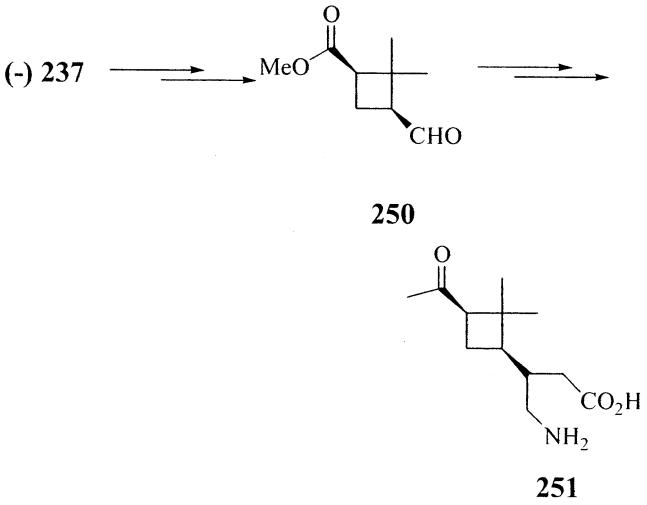
i. *hv*, AcOH; ii. *hv*, MeOH, NaHCO; iii. $Rh(PPh_3)_3Cl$, CH_2Cl_2

Scheme 88



i. $NaIO_4$, cat. $RuCl_3$, CCl_4, MeCN, H_2O, 24 h, r.t.

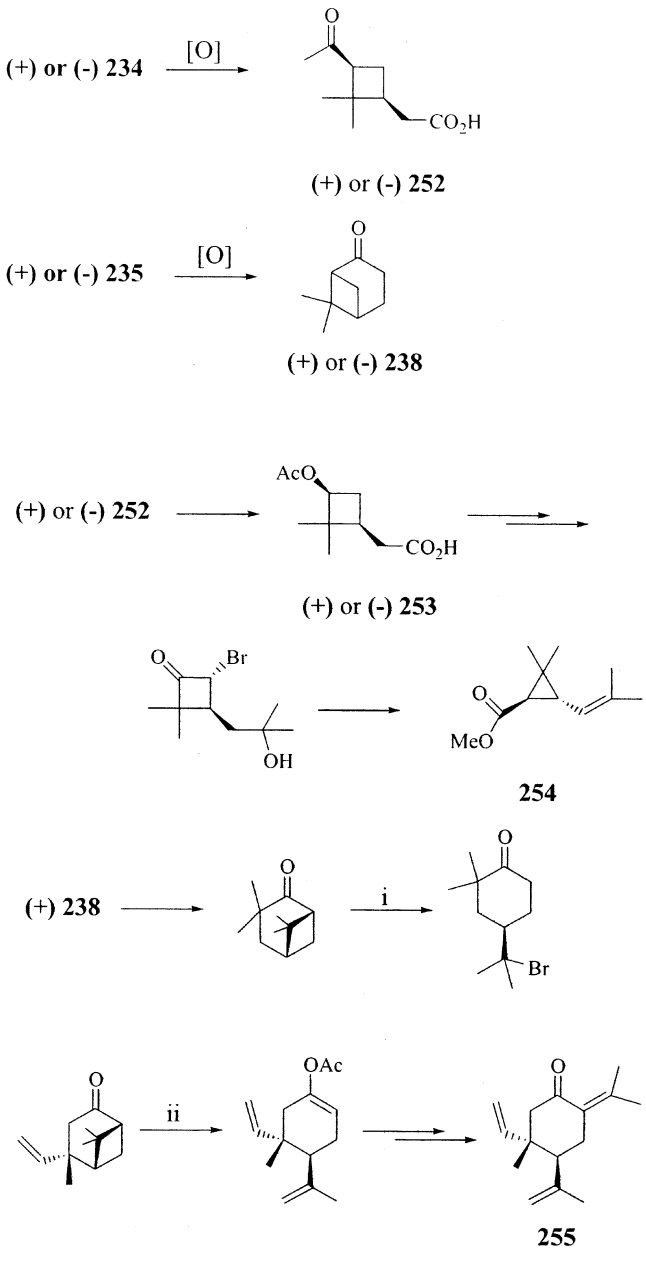
Scheme 89



IX. Other Applications of Enantiopure Cyclobutanes

In addition to their use as synthetic intermediates, optically pure cyclobutanes have been used as chiral ligands for metal catalysis of asymmetric reactions. For example, the rhodium or ruthenium diphosphine complexes of **256**,[189] **257**,[190] and **258**[191] (Scheme 91) along with their water-soluble *p*-benzenesulfonates[192]

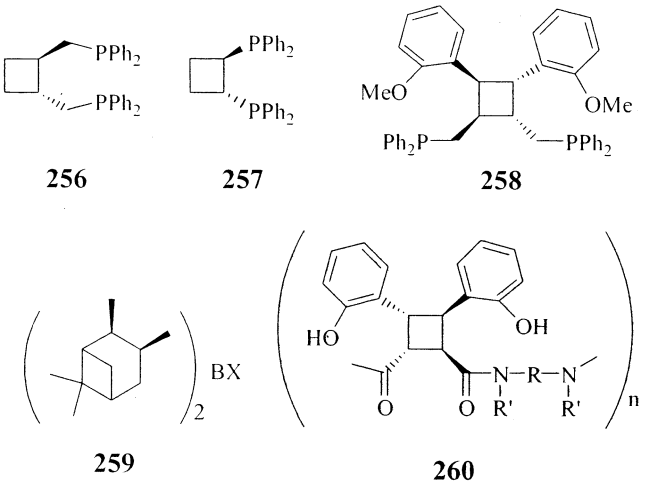
Scheme 90



i. BBr_3, CH_2Cl_2; ii. BF_3

catalyze asymmetric hydrogenation as well as hydroformylations.[193] Use of the reagent diisopinocampheylborane **259** (X = H), prepared by treating optically active α-pinene with borane, results in enantioselective hydroboration−oxidation of alkenes.[194] Alcohols with optical purities as high as 98% have been obtained in this way. Other derivatives of **259** such as the chloride (X = Cl) and methoxide (X = OCH_3) have been effectively utilized in the asymmetric reduction of prochiral ketones,[195] and the preparation of enantiomerically enriched homoallylic and *β*-amino alcohols.[196−198] Other applications of chiral cyclobutanes include the use of the polymeric cyclobutane-1,2-dicarboxamide **260** as a chiral stationary phase for the resolution of racemates such as monomeric *trans*-cyclobutane-1,2-dicarboxamides.[199]

Scheme 91



X. Conclusions

The importance of cyclobutanes as intermediates in organic synthesis has been recognized in the last 30 years.[1,6] The availability of enantiomerically enriched derivatives for their use in chiral synthesis has spurred new methods for their preparation. Most of this development has occurred in the last 15 years. Effective methods include photochemical and catalyzed [2+2] cycloadditions with alkenes possesing chiral auxiliary groups (including chiral tethers) which are either covalently or noncovalently bonded to the reacting partners. The use of designer chiral catalysts for [2+2] cycloadditions and asymmetric oxidations of alkylidenecyclopropanes and their ring enlargement has added a new dimension to the preparation of optically pure cyclobutanes. Enantioselctive deprotonation and alkylation of prochiral cyclobutanone enolates are promising routes to these materials requiring further studies for their general applications. Enantioselective Baeyer−Villiger oxidations to give enantiomerically enriched butanolides, an important class of synthetic intermediates in its own right, has been accomplished nonenzymatically with the use of chiral oxidants or chiral catalysts. Many of these approaches are in their infancy and require further exploitation. In light of these new methods, classical approaches such as chemical or enzyme-mediated resolution of racemates and the use of the chiral pool of natural products continue to be utilized for economy and efficiency. Much of the impetus for developing new enantioselective synthetic methods is the requirement for chiral drugs to be enantiomerically pure. Thus, the challenge continues for the development of new enantiospecific synthetic methods. Throughout all of these investigations, the concept of double chiral induction has not received much attention. The problem is associated with the "match" or "mismatch" phenomenon requiring a thorough understanding of the molecular mechanisms of these processes.

XI. References

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