Synthetic Applications of Intermolecular Cyclopropanation of Carboxylic Esters with Dialkoxytitanacyclopropane Reagents

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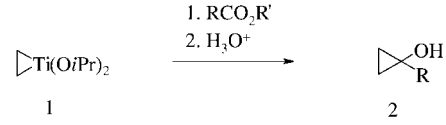
The reaction of carboxylic esters with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide, which leads to the formation of substituted cyclopropanols, was disclosed in the late 1980's. The key organometallic intermediates in this transformation are diisopropoxytitanacyclopropane species, which act as 1,2-dicarbanionic equivalents. The intermolecular titanium-mediated cyclopropanation of carboxylic esters and subsequent transformation of the three-membered ring provides a convenient and flexible approach to the construction of the carbon skeleton of organic molecules with ketone and other functionalities. Applications of this methodology to the synthesis of natural biologically active compounds and their analogues have been published over the last fifteen years and are summarized in the present review article.

1. Introduction

The use of organometallic compounds in organic synthesis is mainly based on their carbon−carbon bond forming reactions in which they usually act as the corresponding monocarbanionic equivalents.[1−3] In the last two decades considerable success has also been achieved in the elaboration of effective methods for the generation of dicarbanionic organometallic species. One such reagent is diisopropoxytitanacyclopropane (**1**), which was first described in the late 80's as a key intermediate in the reaction of carboxylic esters with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide, which leads to the formation of 1-substituted cyclopropanols **2** (Scheme 1).[4−7]



1 2

Scheme 1

The synthetic value of this reaction is not limited only by the convenient preparation of cyclopropane derivatives because cyclopropanols **2** can easily be converted into certain classes of organic compounds by ring-opening reactions.[8−13] For example, heterolytic C1−C2 ring cleavage of substituted cyclopropanols is strongly facilitated by the π-electron donor oxygen atom. As a result, cyclopropanols readily react with electrophiles to give carbonyl com-

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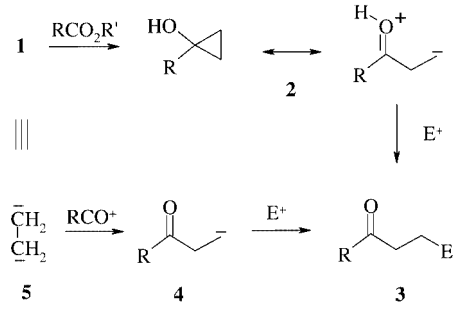
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 2

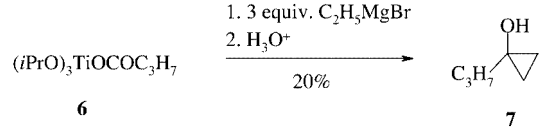
pounds **3** (Scheme 2). In these transformations the cyclopropanols formally act as equivalents of β-oxocarbanions (homoenolate anions) **4**, and for the two-stage conversion of esters into ketones, the cyclopropane ring-closing step in the titanium-mediated cyclopropanation reaction could be considered as a peculiar protection of the carbanionic center in ethylene-1,2-dicarbanion **5**. By taking into account the key role of carbonyl compounds as synthetic intermediates, the methodology for connecting the RCO^+ and E^+ reactive groups by the dimethylene unit with the help of titanacyclopropane reagent **1** has good preparative value.

Cyclopropanols **2** can also participate in other synthetically useful transformations that involve C1−C2, C1−C3 or C2−C3 ring cleavage of strained three-carbon rings. The different aspects of the chemistry of cyclopropanols and dialkoxytitanacyclopropane reagents have been reviewed in detail already.[8,14−16] The aim of this microreview is to summarize the published data on the intermolecular cyclopropanation of carboxylic esters and subsequent conversions of the activated three-carbon rings with emphasis on the recent applications of this two-step synthetic methodology in the preparation of biologically active natural compounds.

2. Cyclopropanation of Carboxylic Esters with Dialkoxytitanacyclopropane Reagents

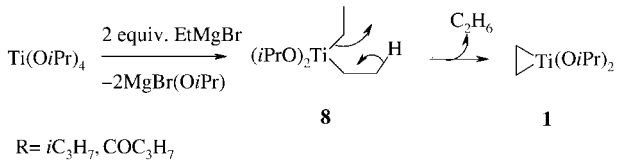
2.1 Generation of Dialkoxytitanacyclopropanes from Dialkyltitanium Precursors

We were the first group to report that the dialkoxytitanacyclopropane species could be generated from Grignard reagents and titanium alkoxides and be involved in synthetically useful transformations.[4,5] We found that the interaction of ethylmagnesium bromide with isopropoxytitanium butyrate (**6**), which was being studied as a model Zeigler−Natta process, results in the formation of 1-propylcyclopropanol (**7**) (Scheme 3).[5] Although the latter was obtained as a minor product in low yield, our experience in the chemistry of cyclopropanes[17,18] allowed us to foresee the considerable potential of this unusual reaction and impelled us to investigate the reaction systematically.



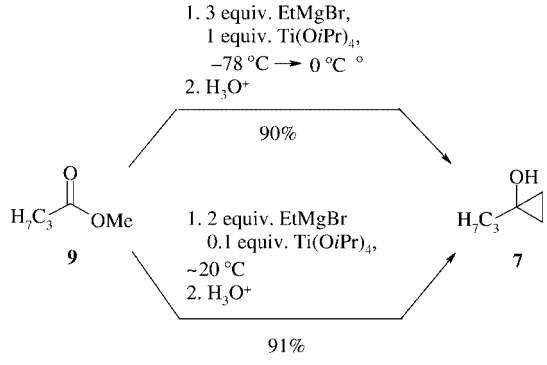
Scheme 3

It was supposed that the key alkylative organometallic species in this transformation was diisopropoxytitanacyclopropane (**1**), which could be formed, in analogy with some known reactions of titanocenes, by elimination of ethane from the thermally unstable diethyltitanium precursor **8** (Scheme 4).[4,5]



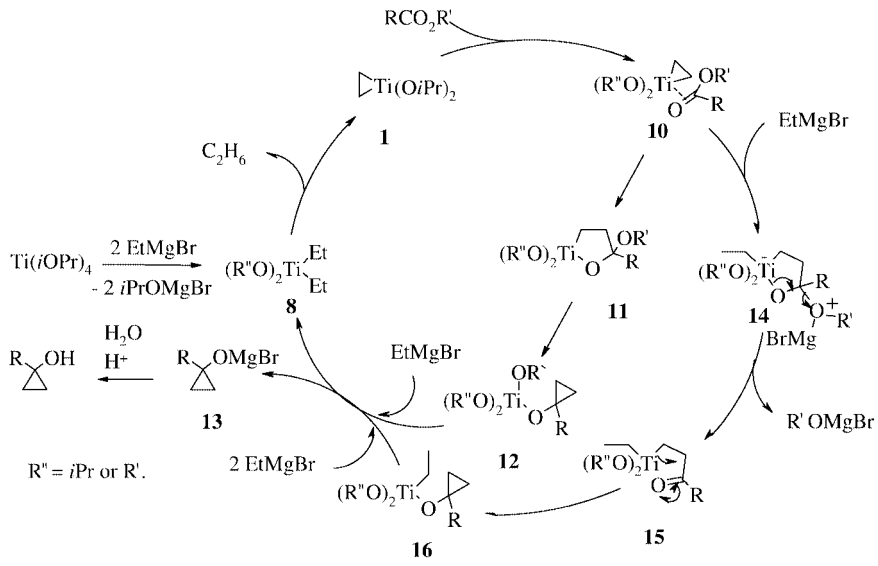
Scheme 4

The reaction of ethylmagnesium bromide with carboxylic esters in the presence of titanium(IV) isopropoxide gave better yields of the corresponding cyclopropanols. Thus, when 3 equiv. of ethylmagnesium bromide were added to a solution of equimolar amounts of ester and titanium(IV) isopropoxide at −78 °C, followed by warming of the reaction mixture to room temperature and acidic work up, the corresponding cyclopropanols were formed almost quantitatively. For example, cyclopropanol **7** was prepared from methyl butyrate (**9**) in 90% isolated yield (Scheme 5).[4,5] When the order of reagent mixing was reversed, that is, the organomagnesium compound was added to the mixture of the ester and titanium(IV) isopropoxide, the reaction occurred catalytically with 0.05−0.1 equiv. of titanium(IV) isopropoxide. In spite of the thermal instability of dialkoxytitanacyclopropane reagents, the catalytic reaction readily took place at room temperature, and only 2 equiv. of the Grignard reagent was needed to consume the ester.[6,7] Thus, ester **9** gave the cyclopropanol **7** by catalytic and noncatalytic reactions in virtually the same yields.



Scheme 5

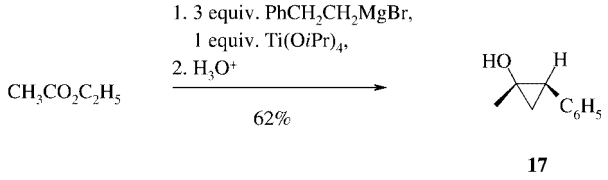
We suggested that the mechanism for this reaction involves the formation of a carbon−carbon bond in the titanacyclopropane−ester complex **10** to give the oxatitanacyclopentane intermediate **11**, which rearranges to the ti-



Scheme 6

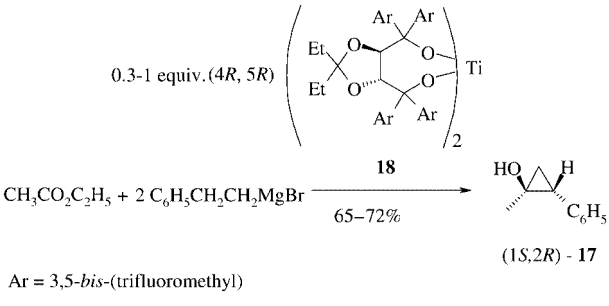
tanium cyclopropanolate **12** (Scheme 6). This then transforms under the action of ethylmagnesium bromide into the magnesium cyclopropanolate **13** and diethyltitanium intermediate **8** − the immediate precursor of the key titanacyclopropane **1**. The observation that an additional equivalent of the Grignard reagent was necessary in the noncatalytic reaction to achieve good yields of cyclopropanols, together with a similar finding in the reaction of titanacyclopropane **1** with allylic alcohol derivatives,[19] led to the proposal[20] that addition of a Grignard reagent to complex **10** initiates the formation of the carbon−carbon bond to give the titanacyclopentane complex **14** (Scheme 6). Fragmentation of the latter affords the β-oxotitanium derivative **15**, which ring-closes to titanium cyclopropanolate **16**, which, as in the first proposed mechanism,[5,6] further transforms into the diethyltitanium derivative **8** and magnesium cyclopropanolate **13**. If the alkoxide group at the titanium atom is considered to be a 6e ligand, it can be concluded that the complex **14** and the titanacyclopropane−ester complex **10** are 18e organometallic species, whereas oxatitanacyclopentane **11** is a 16e organometallic species. It was assumed[20] that this could be a factor favoring the formation of the complex **14** over the formation of oxatitanacyclopentane **11** (Scheme 6). Alkylation of the titanium atom in complex **10** could increase the nucleophilicity of the titanacyclopropane carbanionic centers and promote the addition to the ester carbonyl group, which is usually inert to organotitanium reagents.[21,22]

The cyclopropanation of various aliphatic, cyclic aliphatic and aromatic carboxylic esters using the titanacyclopropane reagent **1** usually gives the corresponding 1-substituted cyclopropanols without complications.[13−16] In the titanium-alkoxide-mediated reaction of carboxylic esters with higher homologues of ethylmagnesium bromide, with a hydrogen at the β-position to the metal, 1,2-disubstituted cyclopropanols were obtained.[5,6] Remarkably the hydrocarbon substituents of these 1,2-disubstituted cyclopropanols usually have a *cis* stereochemistry. For example, *cis*-1-methyl-2-phenylcyclopropanol **17** was formed in moderate yield in the reaction of ethyl acetate with an excess 2-phenylethylmagnesium bromide in the presence of titanium(IV) isopropoxide (Scheme 7).[5]



Scheme 7

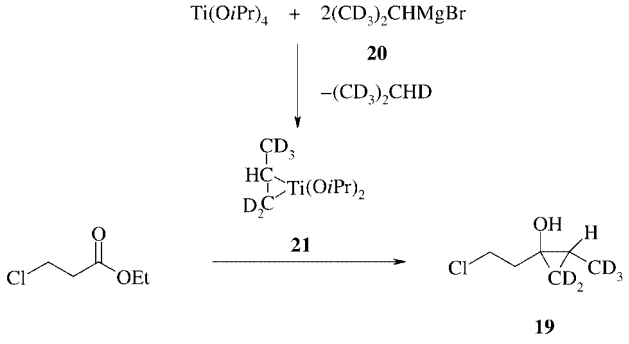
Corey et al.[23] obtained (1*S*,2*R*)-cyclopropanol **17** in 65−72% yields and 85−89% enantiomeric excess from the reaction of ethyl acetate with 2-phenyleythylmagnesium bromide in the presence of 0.3−1 equiv. of chiral titanium alkoxides **18** (Scheme 8). This stereochemical outcome was explained by the influence of the chiral alkoxide ligand on the stereochemistry of both carbon−carbon bond forming



Scheme 8

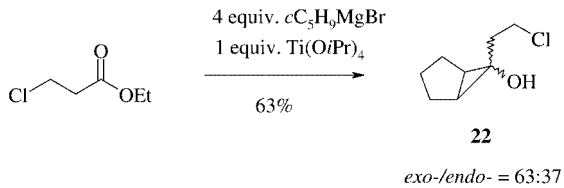
steps on the supposition that formation of the oxatitanacyclopentane species occurs by insertion of the ester carbonyl group between the titanium atom and the more substituted carbon of the titanacyclopropane ring.[23]

The distribution of deuterium in the 1,2-disubstituted cyclopropanol **19**, which was formed in the reaction of ethyl 3-chloropropionate with deuterated Grignard reagent **20** and titanium(IV) isopropoxide, is in agreement with the disproportionation of the corresponding dialkyltitanium intermediate by β-elimination of deuterium to give $(CD_3)_2CHD$ and the titanacyclopropane **21** (Scheme 9).[24] These data exclude an alternative mechanism for the generation of dialkoxytitanacyclopropane reagents by α-elimination of hydrogen and subsequent carbene−olefin rearrangement of the titanium−alkylidene complex, which results in a cyclopropanol bearing a deuterium at the tertiary carbon atom of the cyclopropane ring.[24]



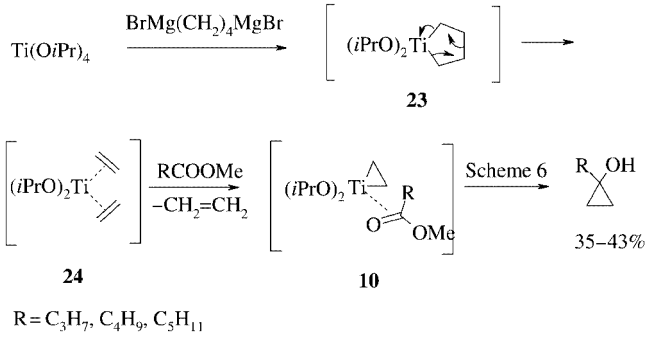
Scheme 9

In contrast to 1-substituted and 1,2-disubstituted cyclopropanols, which are readily formed in the intermolecular reactions of esters with dialkoxytitanacyclopropane reagents,[13−15] only a few examples of the preparation of more substituted cyclopropanols by this approach have been reported.[25,26] Lecornue and Ollivier[26] recently found that the reaction of cyclobutyl-, cyclopentyl-, cyclohexyl- and cycloheptylmagnesium bromides with ethyl 3-chloropropionate in the presence of titanium(IV) isopropoxide gives the corresponding annulated cyclopropanols in moderate yields. The reaction proceeded most easily with cyclopentylmagnesium bromide and bicycloalkanol **22** was isolated as a mixture of *exo* and *endo* isomers in a reasonable yield (Scheme 10). The corresponding *exo*-bicycloalkanols were formed exclusively in the other cases.[26]



Scheme 10

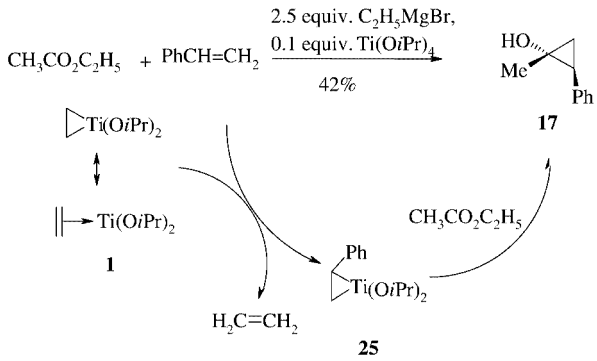
An alternative pathway for the generation of dialkoxytitanacyclopropane reagents from dialkylated titanium alkoxides was identified by us in the titanium-mediated reaction of 1,4-bis(bromomagnesio)butane with esters.[27] The reaction is likely to proceed by the rearrangement of dialkoxytitanacyclopentane **23** to the bis(ethylene) complex **24**, followed by the displacement of ethene by the ester to afford titanacyclopropane−ester complex **10**, which then transforms into the corresponding 1-substituted cyclopropanol in the usual way (Scheme 11).



Scheme 11

2.2 Generation of the Dialkoxytitanacyclopropane Reagents by Ligand Exchange

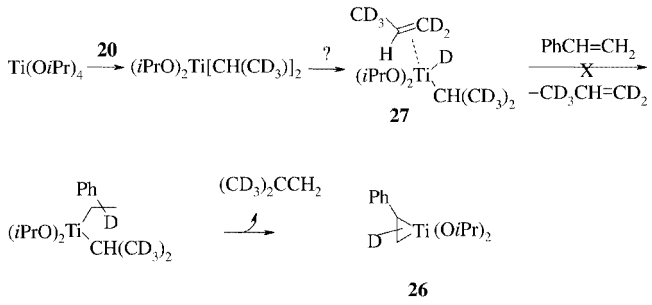
The possible involvement of dialkoxytitanacyclopropanes in ligand exchange reactions with olefins was demonstrated by us[28] in the reaction of ethylmagnesium bromide with a mixture of ethyl acetate, styrene and titanium(IV) isopropoxide, which resulted in the formation of *cis*-1-methyl-2-phenylcyclopropanol (**17**) (Scheme 12). The detection of ethylene among the gaseous products of this reaction is consistent with the assumption that phenyl-substituted cyclopropane **25** is formed as a result of olefin ligand exchange in titanacyclopropane (titanium−ethylene complex) **1**.



Scheme 12

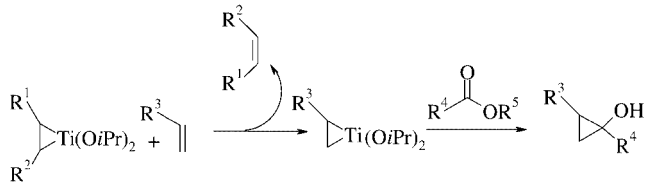
The formation of the nondeuterated cyclopropanol **17** in the reaction of $(CD_3)_2CHMgBr$ (**20**) with ethyl acetate, styrene, and titanium(IV) isopropoxide[29] is inconsistent with a possible alternative mechanism that involves the forma-

tion of deuterated intermediate **26** by the addition of titanium deuteride **27** to styrene (Scheme 13).



Scheme 13

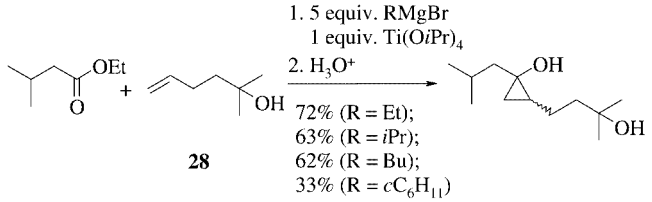
Sato[30] and Cha[31,32] and their co-workers used sterically more restricted dialkoxytitanacyclopropane reagents, generated by the reaction of titanium(IV) isopropoxide with isopropyl-,[30] *n*-butyl-,[31,32] cyclohexyl-,[32] or cyclopentylmagnesium bromide,[33] in their ligand exchange reactions (Scheme 14); this has allowed a wide range of functionally substituted dialkoxytitanacyclopropanes to be generated.[34–37] The preparation of substituted cyclopropanols by ligand exchange with titanacyclopropane intermediates is often termed the hydroxycyclopropanation of olefins.[31]



R^1 = Me, R^2 = H; R^1 = Et, R^2 = H;
$R^1+R^2 = (CH_2)_4$; $R^1+R^2 = (CH_2)_3$;
R^3, R^4, R^5 = alkyl, aryl

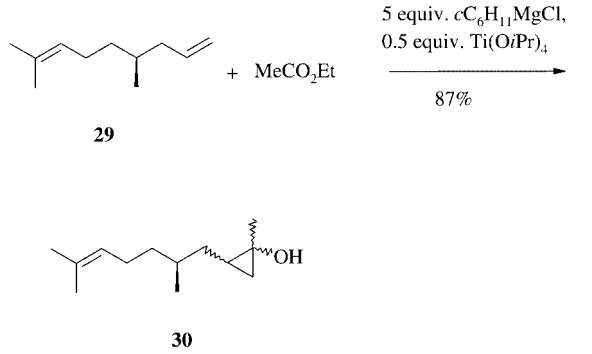
Scheme 14

We found that the yields of cyclopropanol **17** in the reaction of the Grignard reagents with styrene and ethyl acetate in the presence of titanium(IV) isopropoxide decreased in the order BuMgBr > *i*PrMgBr ≈ PrMgBr > cC_6H_{11}MgBr ≈ EtMgBr.[38] At the same time, the hydroxycyclopropanation of unsaturated alcohol **28** with ethyl isovalerate proceeded in better yield when ethylmagnesium bromide was used for the generation of diisopropoxytitanacyclopropane mediators instead of isopropyl, *n*-butyl, or cyclohexylmagnesium bromide (Scheme 15).[38]



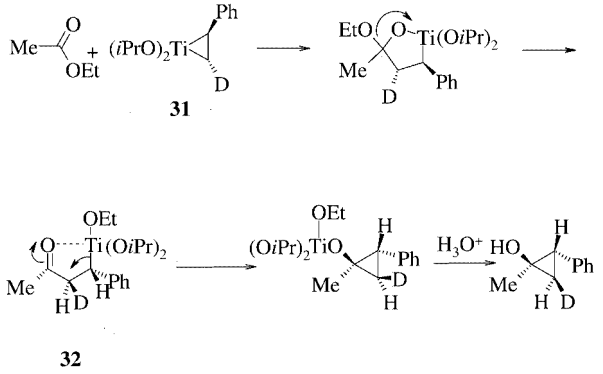
Scheme 15

Hydroxycyclopropanation of terminal olefin with several nonconjugated double bonds usually proceeds at the vinyl group, for example, the hydroxycyclopropanation of chiral diene **29** with ethyl acetate gave a mixture of diastereomeric *cis*-cyclopropanols **30** (Scheme 16).[32]



Scheme 16

On the basis of DFT calculations Wu and Yu[39] suggested that the *cis*-preference of the titanium-mediated hydroxycyclopropanation reaction is derived from steric hindrances within the transition state of the cyclopropane ring-closure step, in which there is an agnostic interaction between the α-carbon–hydrogen bond and titanium. The calculations also predict the kinetically preferable formation of the oxatitanacyclopentane precursors by insertion of the ester carbonyl group between the titanium atom and the less substituted carbon of the titanacyclopropane ring. Casey and Strotman[40] recently found that the cyclopropanation of ethyl acetate with deuterated dialkoxytitanacyclopropane **31**, generated from *trans*-β-deuteriostyrene by ligand exchange, led to *trans*-3-deuterio-1-methyl-*cis*-2-phenylcyclopropanol with high stereoselectivity. They attributed this stereochemical outcome to the retention of the configuration at the carbon–titanium bond in the cyclopropane ring-forming transition state **32**, in which the carbonyl group coordinated to titanium is attacked from the front by the more substituted carbon–titanium bond (Scheme 17).



Scheme 17

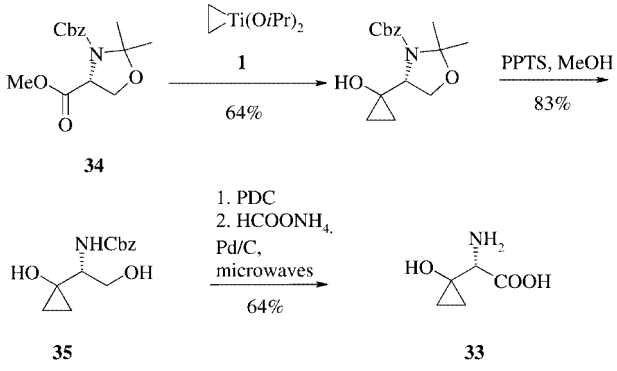
There are numerous examples of successful intermolecular hydroxycyclopropanation reactions of terminal olefins

and esters.[13−16] The use of these transformations is particularly expedient in the preparation of cyclopropanols with functionalized substituents at the C-2 carbon atom because the corresponding Grignard reagents are usually less available. Trialkylvinylsilanes[41,42] and trialkylvinylstannanes[43] have also been successfully subjected to titanium-mediated intermolecular hydroxycyclopropanation reactions. Intramolecular hydroxycyclopropanation of ω-unsaturated carboxylic esters have readily afforded cyclopropanols fused to ordinary carbocyclic or heterocyclic rings.[31,44−49]

3. Applications in the Syntheses of the Natural Products

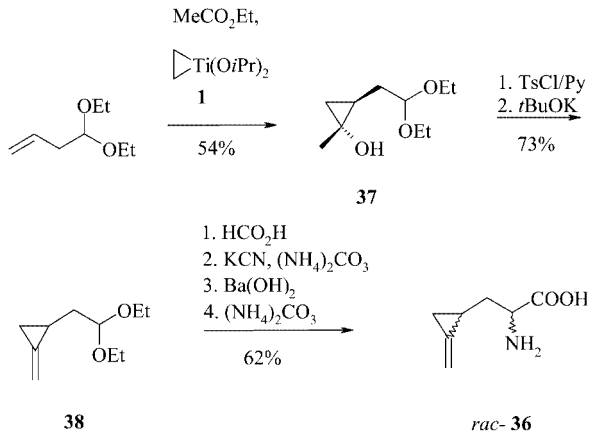
3.1 Preparation of Cyclopropane-Containing Compounds

Cyclopropanation of carboxylic esters with dialkoxytitanacyclopropane reagents has been effectively used in the synthesis of several natural cyclopropane containing compounds (for reviews on natural and biologically active cyclopropanes, see refs. [12,50−53]). Thus, Taddei and co-workers[54] reported a short synthesis of enantiomerically pure (*S*)-cleonine (**33**), a key component of the antitumor-antibiotic *cleomycin,*[55] starting from (*R*)-serine. Formation of the cyclopropanol fragment of (*S*)-cleonine (**33**) was easily achieved by the cyclopropanation of the ester group of the oxazolidine derivative of (*R*)-serine **34** with titanacyclopropane reagent **1** (Scheme 18). Acid-catalyzed oxazolidine ring-opening, followed by oxidation of the alcohol **35** and removal of the protecting group led to (*S*)-cleonine (**33**) in a good overall yield.



Scheme 18

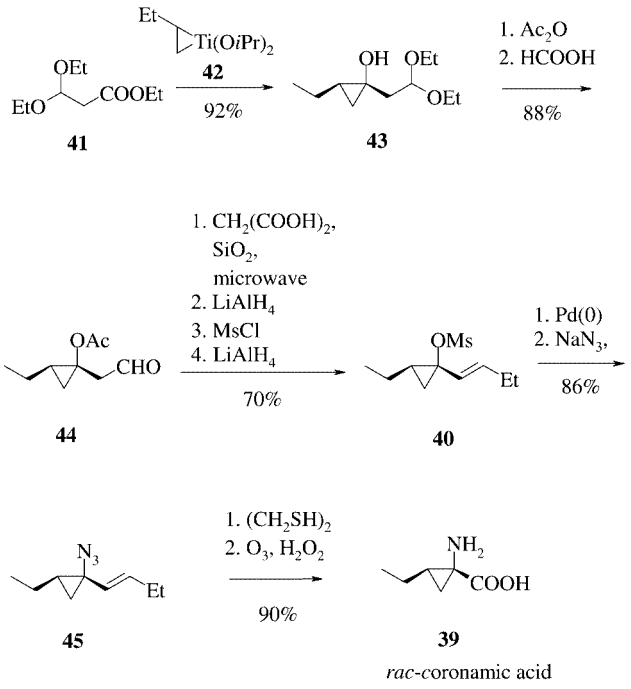
The construction of the three-carbon ring in amino acid hypoglycine A (**36**) was also successfully achieved by the titanium-mediated hydroxycyclopropanation of vinylacetaldehyde diethylacetal and subsequent conversion of cyclopropanol **37** into the methylenecyclopropane derivative **38** by tosylation-dehydrotosylation.[56] Deacetalization of **38** and standard transformation of the aldehyde group into the α-amino acid moiety gave racemic hypoglycine A (**36**, Scheme 19).



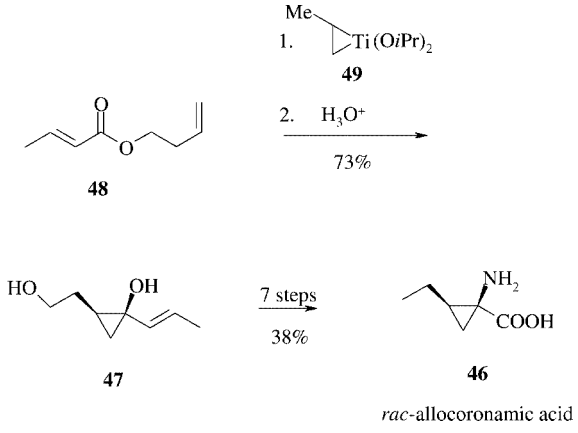
Scheme 19

Salaün and co-workers elaborated a convenient approach to the synthesis of 1-aminocyclopropanecarboxylic acids (2,3-methanoamino acids) by exploiting the ability of sulfonates of 1-alkenylcyclopropanols to undergo palladium-catalyzed stereoselective reactions with azides, which leads to the formation of the corresponding 1-alkenyl-1-azido cyclopropanes.[57,58] 2-Ethyl-1-aminocyclopropanecarboxylic acid (coronamic acid) (**39**) and other 2,3-methanoamino acids[59,60] have been successfully synthesized in this way. Because the cyclopropanation of acyclic α,β-unsaturated carboxylic esters with dialkoxytitanacyclopropane reagents gave low yields, the key 1-(1-alkenyl)cyclopropanol derivative **40** was obtained by the cyclopropanation of ethyl 3,3-diethoxypropionate **41** with the titanacyclopropane reagent **42**, followed by the deprotection of acetal **43** and the condensation of aldehyde **44** with malonic acid under microwave irradiation. palladium(0)-catalyzed azidation of allylic mesylate **40** by treatment with sodium azide in the presence of 15-crown-5 ether proceeded with complete retention of configuration to give cyclopropyl azide **45**. Azide reduction and subsequent double bond oxidative cleavage afforded the racemic coronamic acid (**39**) in good overall yield (Scheme 20).[57]

Racemic *allo*-coronamic acid **46** was synthesized in a similar way by using *trans*-1,2-disubstituted cyclopropanol **47** as the key cyclopropanol precursor.[58] This compound was prepared in diastereomerically pure form by treatment of homoallylic ester **48** with the titanacyclopropane reagent **49** (Scheme 21). The particularly good yield of cyclopropanol **46**, in comparison with the low yields resulting from the cyclopropanation of α,β-unsaturated alkyl carboxylates mentioned above,[13−15] may be the result of the protection of the conjugated double bond by the primary hydroxy group of **47**, which may form complexes with the titanium catalyst more easily than the tertiary hydroxy group on the cyclopropane ring, thus distancing the titanium from the double bond.[58]



Scheme 20

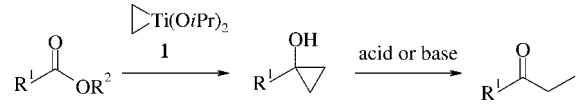


Scheme 21

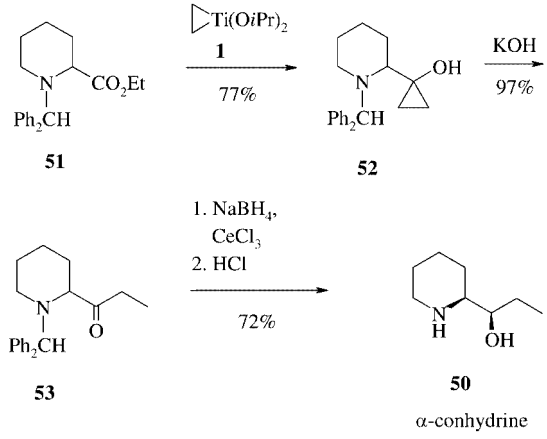
3.2 Syntheses by C1−C2 or C1−C3 Ring Cleavage

1-Substituted cyclopropanols readily rearrange to the corresponding ethyl ketones by heterolytic C1−C2 cyclopropane ring cleavage under basic or acidic conditions.[8,13] Although the titanacyclopropane reagent **1** acts as the ethyl anion equivalent, in the two-step sequence of titanium-mediated cyclopropanation of esters followed by isomerization of the forming cyclopropanols, this transformation has good preparative value because it represents, to the best of our knowledge, the most convenient way to convert carboxylic esters into ethyl ketones (Scheme 22).

The short synthesis of racemic alkaloid α-conhydrine (**50**) by titanium-mediated cyclopropanation of *N*-protected pipecolic ester **51**, followed by isomerization of the cyclopropanol **52**, stereoselective reduction of the carbonyl group of ethyl ketone **53** and deprotection of the corresponding *erythro*-amino alcohol is an example of the synthetic application of this methodology for the reductive ethylation of the esters (Scheme 23).[61]

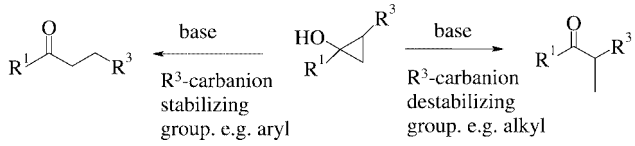


Scheme 22



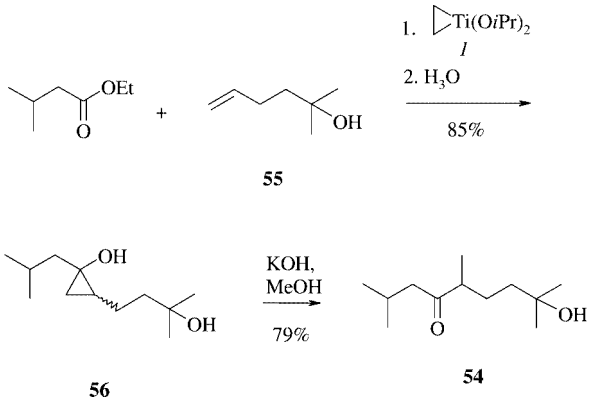
Scheme 23

Base-induced heterolytic ring cleavage of 1,2-disubstituted cyclopropanols usually proceeds in a highly regioselective manner to generate the most stable carbanionic intermediate, which leads to linear or methyl branched ketones depending on the carbanion stabilizing properties of the substituent at the C2 carbon atom (Scheme 24).[8,13]



Scheme 24

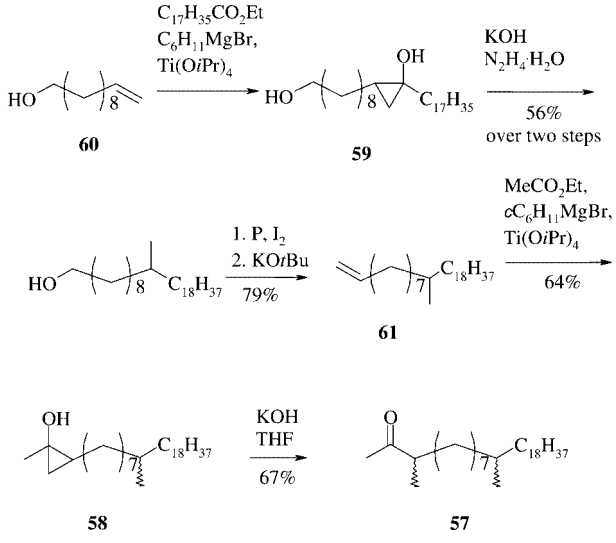
A very short synthesis of (±)-stigmolone (**54**), a pheromone of mixobacteria *Stigmatella aurantiaca,* was performed in 67% overall yield by hydroxycyclopropanation of 2-methyl-5-hexen-2-ol (**55**) with ethyl isovalerate and subsequent ring cleavage of 1,2-disubstituted cyclopropanol **56** (Scheme 25).[38] The potassium-hydroxide-induced regioselective transformation of cyclopropanol **56** into α-methyl ketone **54** was achieved when methanol was used as the solvent. Treatment of the cyclopropanol **56** with an excess of potassium hydroxide in dry THF afforded an equimolecular mixture of branched ketone **54** and the isomeric product of C1−C2 bond cleavage. A sterically favorable intramolecular hydrogen bond between the hydroxyalkyl substituent and the developing secondary carbanion center at cyclopropane ring is likely to stabilize the transition state



Scheme 25

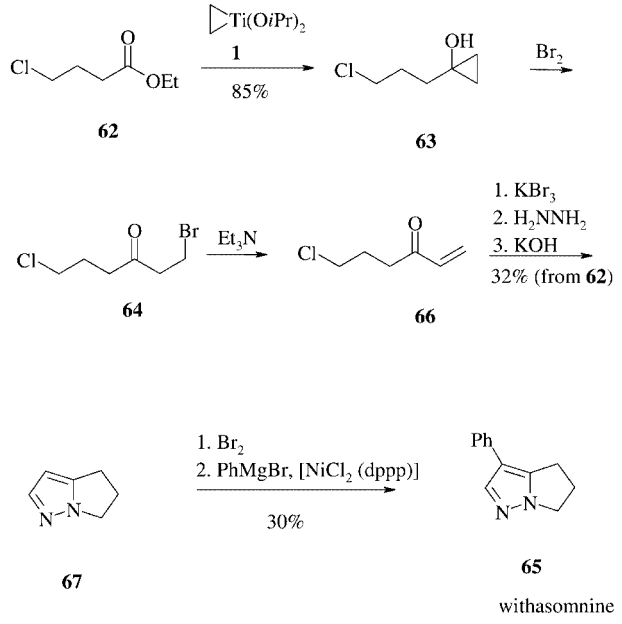
of the latter reaction, whereas interactions of the protic solvent methanol with the transition state effectively compete with the stabilization of the primary carbanion center.

Two cyclopropane ring-forming and ring-opening sequences have been successfully used in the synthesis of 3,11-dimethylnonacosan-2-one (**57**), a component of the sex pheromone of the German cockroach *Blatella germanica*. The key cyclopropanols **58** and **59** were easily prepared by titanium-mediated intermolecular hydroxycyclopropanation of the corresponding olefins **60** and **61** (Scheme 26).[62]



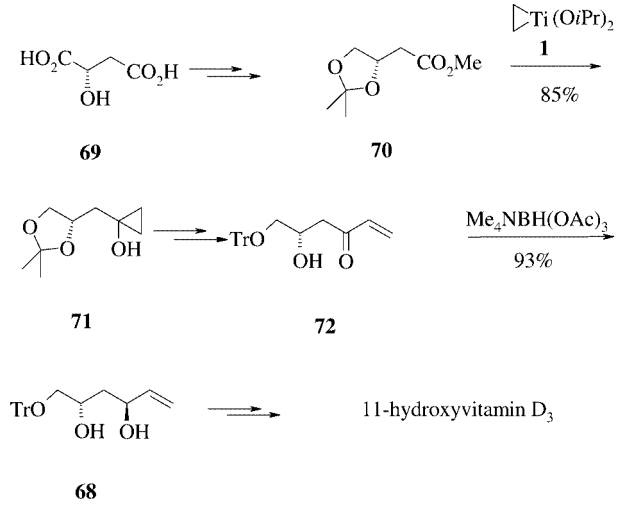
Scheme 26

Cyclopropanation of esters and subsequent electrophilic halogenation of the thus formed cyclopropanols provide a convenient and flexible route to 2-bromoethyl ketones.[8,13] For example, the titanium-mediated cyclopropanation of ethyl 4-chlorobutyrate (**62**) with reagent **1** led to the cyclopropanol **63**, which was easily converted into 1-bromo-6-chlorohexa-3-one (**64**) by reaction with bromine in aqueous 2-propanol.[63] Dihalo ketone **64** was transformed to pyrazole alkaloid withasomnine (**65**) by 1,2-dehydrobromination, followed by bromination of the vinyl ketone **66**, double heterocyclization and phenylation of the parent pyrrolo[1,2-*b*]pyrazole (**67**) (Scheme 27).



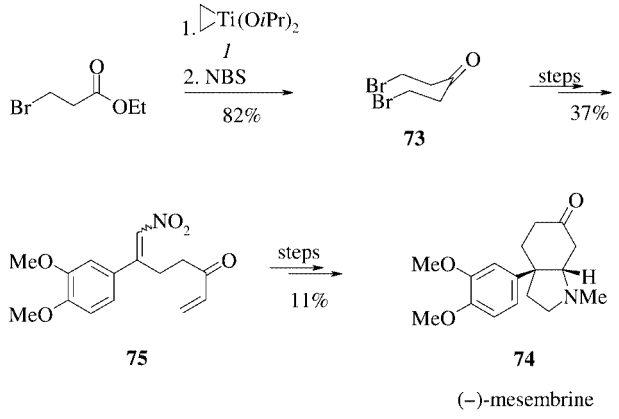
Scheme 27

Wicha and co-workers[64] used the transformation of carboxylic esters into vinyl ketones via the corresponding cyclopropanols for the preparation of chiral *anti*-diol **68**, one of the key intermediates in the synthesis of 11α-hydroxyvitamin D_3. Ester **70**, readily accessible from L-(+)-malic acid (**69**), was converted into cyclopropanol derivative **71** in high yield by treatment with titanacyclopropane reagent **1**. After hydrolysis of the acetal group in compound **71**, protection of the primary hydroxy group, cyclopropane ring-opening with *N*-bromosuccinimide and reduction of the vinyl ketone **72** with $Me_4NBH(OAc)_3$, the *anti*-diol **68** was formed with high stereoselectivity and in good overall yield (Scheme 28).



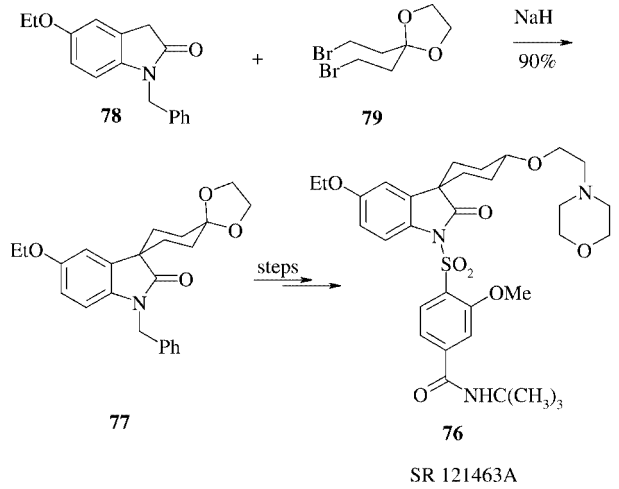
Scheme 28

Convenient substrates for the preparation of divinyl ketones[65] and divinyl diketones[66] by applying this methodology are 3-halopropionic esters and dicarboxylic esters, respectively. Denmark and Marcin[67] used the dibromo ketone **73**, which was prepared by the cyclopropanation of ethyl 3-bromopropionate, in the early stages of a total synthesis of alkaloid (−)-mesembrine (**74**) via the key vinyl ketone **75** (Scheme 29).



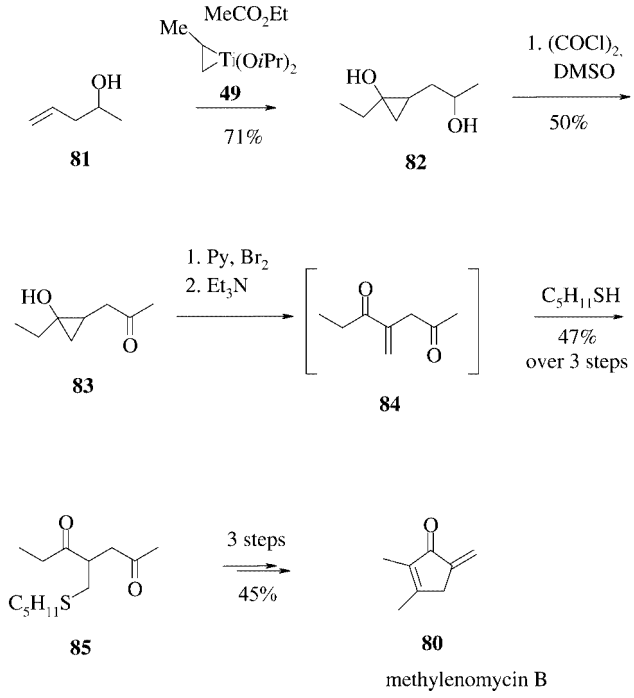
Scheme 29

Acetal protection of the carbonyl group in the dibromo ketone **73** allowed this compound to be used for the construction of the spirocyclic skeleton of a potent vasopressin V_2 receptor antagonist SR 121463 A **76**. Liotta and co-workers[68] prepared the key intermediate **77** in a very good yield by treatment of oxoindole **78** with an excess of sodium hydride and protected dibromo ketone **79** (Scheme 30).



Scheme 30

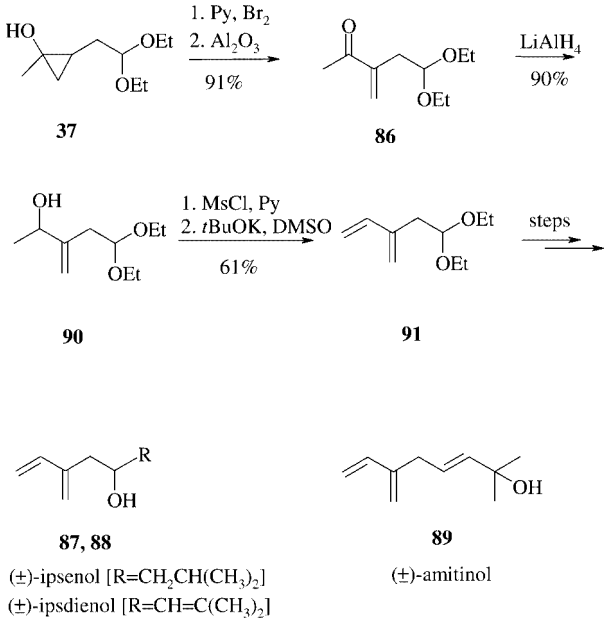
Bromination of 1,2-disubstituted cyclopropanols also proceeds with high regioselectivity to afford the corresponding α-bromomethyl ketones, and this transformation was used for the conversion of carboxylic esters into branched α-methylene ketones.[69] For example, cyclopentenoid antibiotic methylenomicin B (**80**) was prepared in a reasonable yield by hydroxycyclopropanation of the homoallyl alcohol **81** with the titanacyclopropane **49** and ethyl propionate, regioselective oxidation of the hydroxyalkyl-substituted cyclopropanol **82** to the ketone **83** and the conversion of the latter into the α-methylene diketone **84** by bromination-dehydrobromination. Protection of the conjugated C=C bond in diketone **84** by addition of amyl mercaptan, followed by the intramolecular condensation of thio ketone **85** and deprotection of the double bond led to methylenomicine B (**80**) (Scheme 31).[70]



Scheme 31

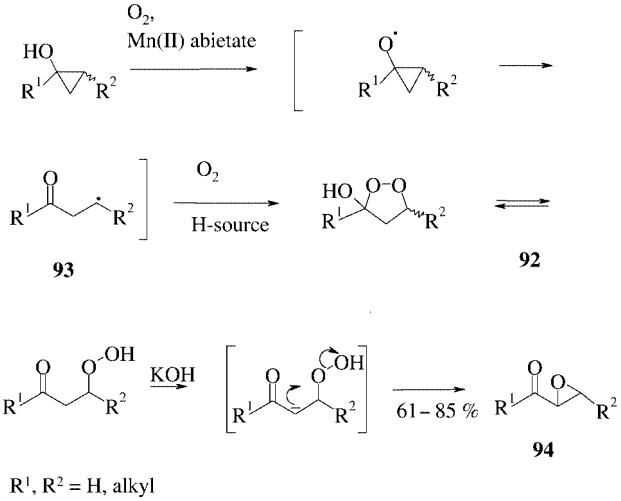
Functionalized α-methylene ketone **86** was prepared in high yield by the regioselective two-step bromination-dehydrobromination of compound **37** and used in the syntheses of racemic ipsenol (**87**), ipsdienol (**88**) and amitinol (**89**), the components of aggregation pheromones of *Ips* bark beetles. The reduction of the carbonyl group of methylene ketone **86**, followed by nucleophilic substitution of the hydroxy group in allylic alcohol **90** and base-induced dehydrochlorination of the thus formed allyl chloride led to 2-substituted 1,3-butadiene **91**, which was used as a common building block for the preparation of pheromones **87**−**89** (Scheme 32).[71]

Homolytic cyclopropane ring-cleavage is an alternative route for the conversion of cyclopropanols into ketones. Oxidation of cyclopropanols with various metal salts, as well as with nonmetal-based oxidants, proceeds by a radical mechanism.[8,13] As an example, treatment of 1-substituted and 1,2-disubstituted cyclopropanols with molecular oxygen in the presence of Mn(II) abietate or manganese(II) acetylacetonate leads to the formation of peroxides **92** as a result of the trapping of gaseous oxygen by the intermediate β-oxoalkyl radicals **93**.[72] In the case of 1,2-disubstituted cyclopropanols, the cleavage of the most substituted



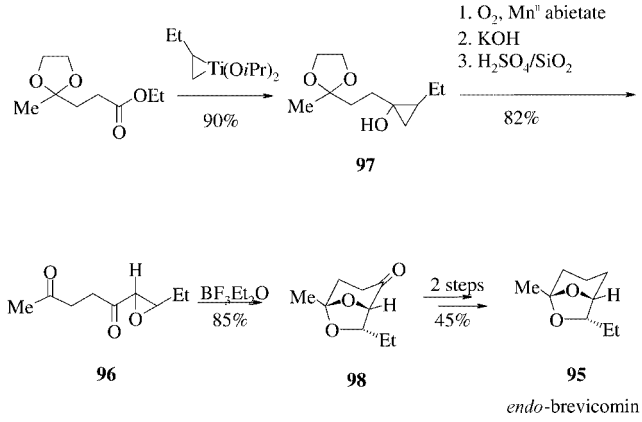
Scheme 32

carbon−carbon bond was observed to occur with high regioselectivity. The peroxide compounds **92** were readily transformed into *trans*-α,β-epoxy ketones **94** by treatment with alkali (Scheme 33).



Scheme 33

This method for the conversion of carboxylic esters to epoxy carbonyl compounds with a linear carbon skeleton has been applied to the synthesis of *endo*-brevicomin **95**, frontalin and related hydroxy compounds, which play an important role in the chemical communication amongst bark beetles.[73] The key epoxy diketone **96** was obtained in good yield starting from protected ethyl levulinate via 1,2-

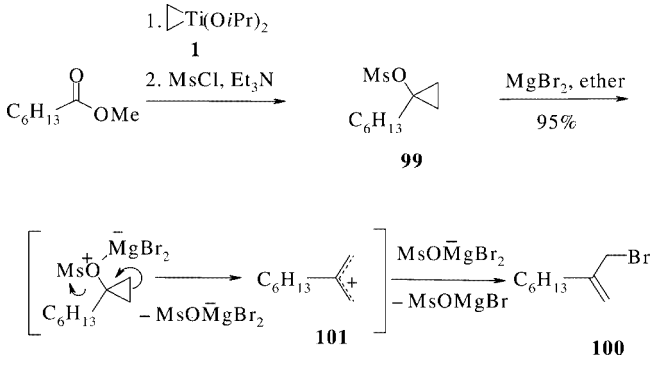


Scheme 34

disubstituted cyclopropanol **97** (Scheme 34). The manganese(II)-abietate-catalyzed oxidative cleavage of **97** with molecular oxygen and alkali-induced dehydration of the corresponding peroxide proceeded in good yield to give, after deprotection, epoxy diketone **96.** Stereoselective cyclization of **96** by treatment with boron trifluoride−diethyl ether led to the bicyclic *endo*-acetal **98**, which was then converted into the racemic *endo*-brevicomin **95** by a standard deoxygenation procedure.[73]

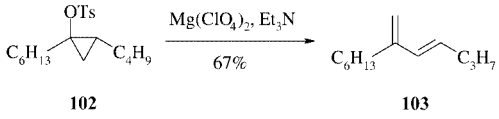
3.3 Syntheses by C2−C3 Ring Cleavage

To complement the reactions involving the cleavage of the C1−C2 or C1−C3 bonds of cyclopropanols, a convenient procedure for C2−C3 ring-opening reactions has been disclosed recently.[74] We found that the sulfonates of tertiary cyclopropanols could be easily transformed into 2-substituted allyl halides by treatment with metal halides. Thus, mesylate **99** readily reacted with magnesium bromide in diethyl ether at room temperature to yield allyl bromide **100** (Scheme 35).[74] Mechanistically, this reaction probably involves the Lewis-acid-assisted heterolytic cleavage of the carbon−oxygen bond in the cyclopropyl sulfonate, which induces a cationic cyclopropyl-allyl rearrangement to give the allylic cation **101**. Allyl bromide **100** is then formed by transfer of a halide anion from the metal halide to the allylic cation **101** (Scheme 35).



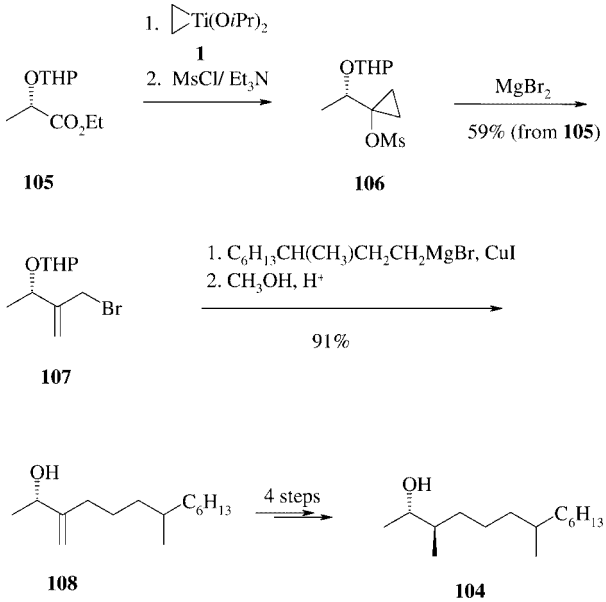
Scheme 35

Under the same reaction conditions sulfonates of *cis*-1,2-disubstituted cyclopropanols give the corresponding allyl halides as a mixture of stereo- and regioisomers.[74] The sulfonates of 1,2-disubstituted cyclopropanols can also be transformed stereoselectively into 2-substituted 1,3-alkadienes by using Lewis acids in the absence of strong nucleophiles.[75] For example, the reaction of the tosylate of 1-hexyl-2-butylcyclopropanol (**102**) with magnesium perchlorate and triethylamine in ether gives 2,4-disubstituted 1,3-alkadiene **103** with high *trans*-stereoselectivity (Scheme 36).



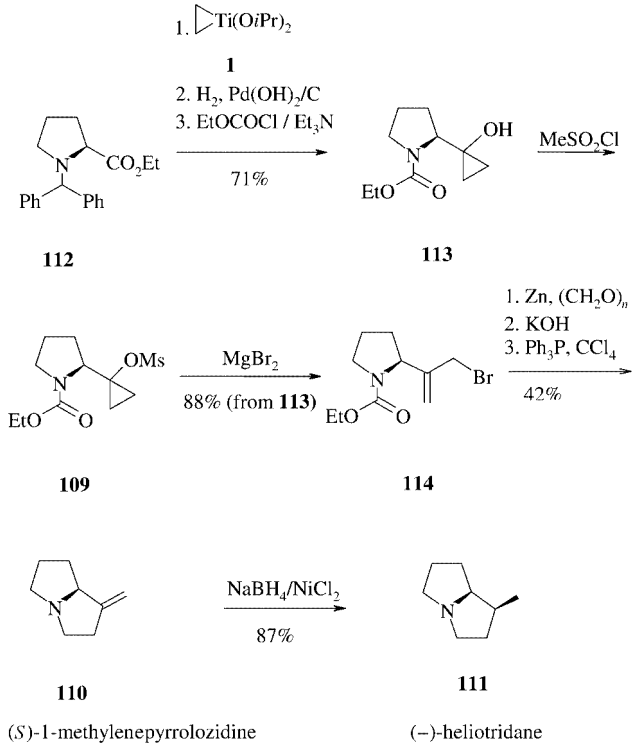
Scheme 36

The conversion of carboxylic esters into substituted allyl halides and 1,3-dienes undoubtedly has considerable synthetic potential. A convenient new approach to the synthesis of the acetate and propionate of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridecan-2-ol (**104**), sex attractants of *Diprion pini* L., was elaborated by cyclopropanation of *O*-THP-protected ethyl (*S*)-lactate **105** with the titanacyclopropane reagent **1**, followed by C2−C3 cyclopropane ring-opening of cyclopropyl sulfonate **106** and coupling of chiral allyl bromide **107** with (3-methylnonyl)magnesium bromide in the presence of copper(I) iodide. After reduction of the double bond in the allylic alcohol **108** and separation of the diastereomers, *threo*-alcohol **104** was obtained in 14% overall yield (Scheme 37).[76]



Scheme 37

The C2−C3 ring cleavage of the mesylate of 1-substituted cyclopropanol **109** has also been used as one of the key steps in the synthesis of alkaloids (*S*)-1-methylenepyrrolizidine (**110**) and (−)-heliotridane (**111**). The cyclopropanation of (*S*)-proline derivative **112** with titanacyclopropane **1**, followed by protecting-group manipulations, mesylation of (*S*)-pyrrolidinyl-substituted cyclopropanol **113**, and treatment of sulfonate **109** with magnesium bromide in boiling chloroform led to allyl bromide **114** in good yield (Scheme 38). Allyl bromide **114** was then converted into (*S*)-1-methylenepyrrolizidine (**110**) by a one carbon chain extension and subsequent intramolecular cyclization. The stereoselective reduction of alkaloid **110** gave (−)-heliotridane in high yield and with good stereoselectivity.[77]



Scheme 38

4. Conclusion

Intermolecular cyclopropanation of carboxylic esters with diisopropoxytitanacyclopropane reagents [titanium(II)−olefin complexes] and subsequent transformation of the resulting cyclopropanols provides a convenient approach to several important classes of functionalized unsaturated compounds. The simplicity and flexibility of the experimental procedures in the generation of dialkoxytitanacyclopropane reagents, together with the diversity of cyclopropanol chemistry, make this two-stage synthetic methodology a highly efficient and practical method for use in the preparation of various functionalized cyclopropane and non-cyclopropane compounds. The investigations in this field are developing quite rapidly and we hope it will bring new useful results.

Acknowledgments

Some of the results described in this article were obtained by the efforts of the workers in our laboratory; their names appear in the references and I am grateful for their enthusiasm and persistence. Financial support for this work came from the Ministry of Education, the Belarusian Fund for Scientific Research, and the INTAS and COPERNICUS Programs of the European Union.

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