Optically Active Cyclopropanes

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Contents

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I. Introduction

The cyclopropyl group is found as a basic structural element in a wide range of naturally occurring compounds in plants and in microorganisms, both fungal and bacterial. It is also generated transiently in primary and secondary metabolisms. Therefore it is present in compounds of biological importance.[1] The cyclopropane chemical reactivity not only closely resembles that of an olefinic double bond but moreover involves rearrangements of particular synthetic importance: i.e., ring-opening reactions, $C_3 \rightarrow C_4$, $C_3 \rightarrow C_5$, and $C_3 \rightarrow C_7$ ring enlargements, and $C_4 \rightarrow C_3$ ring contractions.[2] Donor–acceptor geminate-[3] or vicinal-substituted[4] cyclopropanes provide potential valued building blocks.

The impact of the stereochemistry on activity requires stereoselective synthesis of the three-membered-ring moiety. Thus, optically active forms of cyclopropanecarboxylic acids produce the more selective pyrethroid insecticides, which are more active toward insects and less toxic to mammals. The aim of this article is to review the challenging preparations of optically active cyclopropanes and some of their useful reactions where the chirality of the stereogenic center is fully retained.

II. Resolutions

This section describes the resolution of precursors of cyclopropanes that then undergo stereoselective cyclopropanation as well as the resolution of three-membered-ring derivatives by means of chiral reagents (e.g., optically active amines, acids, alcohols, and aldehydes) followed by simple recrystallization or high-performance chromatography. Such optically active cyclopropane derivatives also provide convenient resolving agents for optical isomers.

1. Cyclopropane Precursor Resolution

Optically active *trans*-dipropylcyclopropane (**2**) and its achiral cis isomer **3** were prepared from nonane-4,6-dione. After reduction with $NaBH_4$, esterification with phthalic anhydride, and resolution of the stereoisomers with brucine in acetone, an optically active ester was obtained that, upon hydrolysis and bromination with Ph_3PBr_2 in benzene, led to (−)-(*R*,*R*)-4,6-dibromononane (**1**).

Cyclization of **1** either by lithium amalgam or with biphenyllithium provided in 73 and 75% yield 46:54 and 59:41 mixtures of isomeric cyclopropanes **2** and **3**, from which optically active trans isomer (1*S*,2*S*)-**2** was isolated by preparative gas chromatography. The original configuration at both chiral centers of dibromide **1** was inverted in the course of the cyclization reaction leading to the trans isomer (eq 1).[5]

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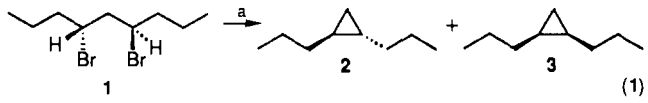


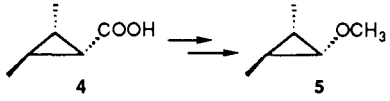
(1)

(a) THF, reflux, Li–Hg, 75% (46:54) or biphenyllithium, 73% (59:41)

Resolution of an indoline derivative with (−)-(*R*)-acetylmandelic acid followed by spirocyclopropanation led to the two enantiomers of an antitumor antibiotic (CC 1065) isolated from *Streptomyces zelensis*.[6]

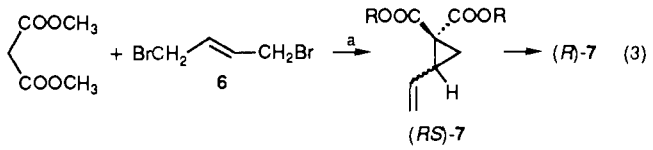
2. Three-Membered-Ring Resolution

c-2,*t*-3-Dimethylcyclopropane-*r*-1-carboxylic acid (**4**), readily available from the cupric trifluoromethanesulfonate catalyzed cyclopropanation of *trans*-2-butene with ethyl diazoacetate (see section III.3), was resolved by fractional recrystallization of its diastereomeric quinine salts.[7] Then through a sequence patterned after the DePuy synthesis of cyclopropanols involving a Baeyer–Villiger oxidation,[8] acid **4** was transformed into optically active cyclopropyl ether **5**, which was found to be chromatographically and spectroscopically identical with an authentic sample obtained from the Schöllkopf reaction between *trans*-2-butene, dichloromethyl methyl ether, and methyllithium.[9]



(2)

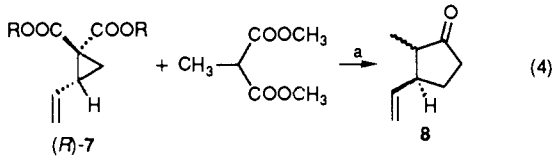
An asymmetric total synthesis of 19-norsteroids was based on the ring expansion of dextrorotatory three-membered-ring compound (*R*)-**7**, readily accessible from the reaction of dimethyl malonate with (*E*)-1,4-dibromo-2-butene (**6**) in methanol containing sodium methoxide. The resulting *rac*-dimethyl 2-vinylcyclopropane-1,1-dicarboxylate was then resolved with brucine (eq 3). The diastereoselective asymmetric cyclopropanation of **6** with diphenylmenthyl malonate also gave **7** with 80% ee (see section III.1).[10]



(3)

(a) NaOMe, MeOH, 65%.

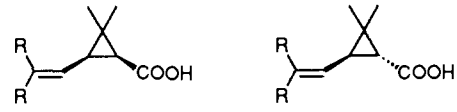
On treatment with dimethyl methylmalonate in MeOH containing sodium methoxide followed by hydrolysis and decarboxylation, (*R*)-**7** underwent $C_3 \rightarrow C_5$ ring expansion with complete inversion of configuration at the asymmetric center into 2-methyl-(*R*)-3-vinylcyclopentanone (**8**) (76% ee), which is a precursor of the D ring of (+)-estrone, 19-norandrost-4-ene-3,7-dione, estradiol, and 19-nortestosterone (eq 4).[10]



(4)

(a) NaOMe, MeOH.

Resolutions of cyclopropanecarboxylic acids with optically active $PhCH(NMe_2)CMe_2OH$,[11] α-cyano-3-phenoxybenzyl,[12] phenylethylamine,[13] (−)-*N*-methylephedrine,[14] menthol,[15] (+)- or (−)-*N*-(2,2,2-trichloro-1-formamidoethyl)piperazine,[16] (−)-α-(1-naphthyl)-ethylamine or (−)-2-aminobutanol,[17] benzylamines,[18] 6-phenoxypicolinaldehyde,[19] and (−)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propanediol[20] have been patented. For instance, *rac-cis*-**9a–c** and *rac-trans*-3-(2,2-dihalovinyl)-2,2-dimethylcyclopropane-1-carboxylic acids **10a–c** were resolved with optically active bases such as (+)- and (−)-ephedrine, (+)- and (−)-*N*-methylephedrine, and (+)- and (−)-pseudophedrine.

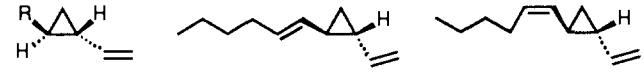


9a, R = F
b, R = Cl
c, R = Br

10a–c

Thus, mixing *rac-cis*-**9c** with (−)-ephedrine gave the crude (−)-ephedrine salt of (+)-*cis*-**9c**, which was hydrolyzed with 2 N HCl to give a 96.1:3.9 mixture of (+)-*cis*- and (−)-*cis*-cyclopropanecarboxylic acid **9c**.[14a]

Aldehyde (+)-**11b**, derived from partially resolved (+)-2-vinylcyclopropanecarboxylic acid (1*S*,2*R*)-**11a** with (−)-quinine and further recrystallization from ethyl acetate, underwent Wittig reaction with pentylidenetriphenylphosphorane to give a mixture of dictyopterene A ((+)-**12**) (87% ee), which is a pheromone of brown algae, and its *Z* isomer (−)-**13** in 65% yield.

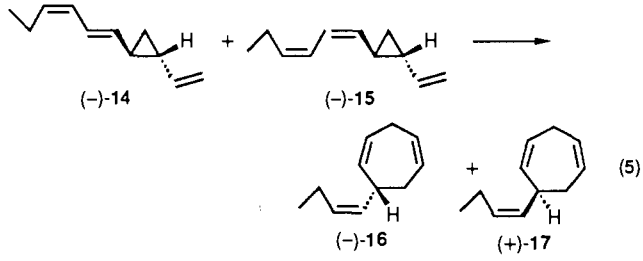


11a, R = COOH
b, R = CHO

(+)-**12**

(−)-**13**

Wittig reaction of (+)-**11b** with ((*Z*)-2-pentenylidene)triphenylphosphorane afforded a geometrical mixture of (−)-**14** and (−)-**15**, which was partially rearranged to an enantiomer (−)-**16** of the naturally occurring ectocarpene (+)-**17** during gas chromatography analysis (eq 5).[21a] For a similar preparation of pure algae



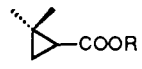
(5)

pheromones (+)-**12** and (−)-**14** performed by resolution of the acid **11a** with (−)-(*R*)-2-phenylglycinol, see ref 21b.

The four optically active isomers of cyano(6-phenoxy-2-pyridyl)methyl *trans*-3-(4-*tert*-butylphenyl)-2,2-dimethylcyclopropanecarboxylate were separated by high-performance liquid chromatography of its (+)-1*R* and (−)-1*S* isomers. The two (+)-1*R* isomers have high acaricidal and insecticidal activities, while the two (−)-**15** isomers have no activity toward insects.[22]

The diastereomeric mixture of esters **18a** obtained from (−)-*N*-methylephedrine and (−)-2,2-dimethylcyclopropanecarboxylic acid **18b** was separated by chromatography and then optionally hydrolyzed to give optically active acids **18b**.

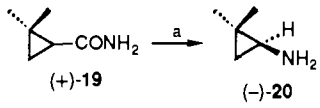
On the other hand, precipitation of **18a** in HCl gave hydrochloride salts containing a 97.5:2.5 mixture of



18a, R = (−)-*N*-methylephedrine
b, R = H

(+)-**18a** and (−)-**18a**, while the filtrate contained an 18.6:81.4 mixture of these diastereoisomers, respectively. Neutralization of the HCl salt mixture and hydrolysis provided (+)-2,2-dimethylcyclopropanecarboxylic acid **18b**.[14b,c]

2,2-Dimethylcyclopropanecarboxamide (+)-**19**, obtained in 98.5% ee by recrystallization,[23] underwent Hofmann reaction upon treatment with NaOCl in basic medium to yield (−)-(*S*)-2,2-dimethylcyclopropylamine (**20**) (eq 6).[24a]



(+)-**19** → (−)-**20** (6)

(a) NaOCl, aq NaOH.

In a similar way, the synthesis of optically active 1,3-diethylcyclopropene was reported from the resolution of *trans*-2,3-diethylcyclopropanecarboxylic acid by quinine, conversion into cyclopropylamine, and pyrolysis of the corresponding trimethylammonium iodide.[24b]

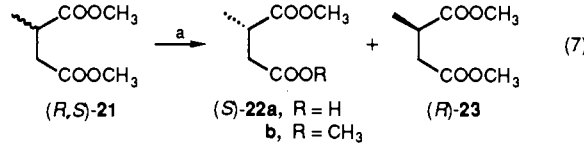
For racemization of the less desirable enantiomer remaining after resolution, see section VI.

3. Enzymic or Microbial Resolution

Optically active cyclopropane derivatives have also been prepared from the enzymic resolution of efficient precursors such as α-alkylsuccinates with lipase (PPL), from the microbial oxidation of isobutyric acid (*Candida rugosa*), or from the microbial reduction of 1,4-cyclohexanedione (*Curvularia lunata*, *Aspergillus ochraeus*). Racemic cyclopropanecarboxylates have been either resolved with an acylase (pig kidney acylase) or enantioselectively hydrolyzed with an esterase (pig liver esterase) and with microorganisms (*R. toruloides*), while meso cyclopropyldicarbinols have been enantioselectively hydrolyzed by PLE and PPL or oxidized by an alcohol dehydrogenase (horse liver alcohol dehydrogenase).

Utilization of enzymes in organic synthesis to prepare chiral compounds of synthetic value is well documented.[25] For instance, porcine pancreatic lipase (PPL, E.C. 3.1.1.3), which is an inexpensive commercially available enzyme, catalyzes specifically the hydrolysis of esters of racemic alcohols and meso diols.[26] Contrary to α-chymotrypsin,[27] liver esterase,[25] or microbial lipase,[27] PPL hydrolyzes α-substituted carboxylic esters with low chemical and optical yields;[28] however, PPL was able to effect the resolution of β-substituted carboxylic esters.[29] Effectively on a preparative scale (0.25 mol) dimethyl methylsuccinate (*R*,*S*)-**21**, upon treatment with PPL in buffered water at pH 7.2, underwent regio- and enantioselective hydrolysis to yield the sodium salt of half-ester (*S*)-**22a** and unhydrolyzed ester (*R*)-**23** with 96% ee (eq 7).[29]

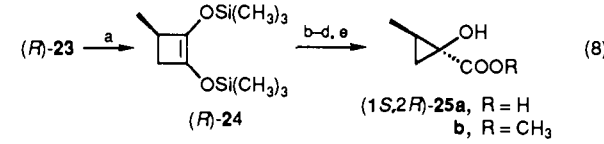
Acidification of the aqueous phase provided half-ester (*S*)-**22a**, which then was esterified with methanol and $SOCl_2$ to yield dimethyl 2-methylsuccinate (*S*)-**22b** (>96% ee). α-Aminosuccinic acid derivatives as well as dimethyl *N*-acetylglutamate were also hydrolyzed



(*R*,*S*)-**21** → (*S*)-**22a**, R = H; **b**, R = CH_3 + (*R*)-**23** (7)

(a) PPL, aq 0.1 M KH_2PO_4, pH 7.2, room temperature.

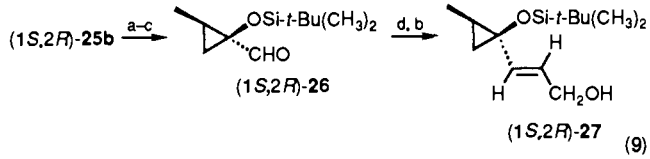
regio- and enantioselectively.[29] Acyloin cyclization of succinate (+)-(*R*)-**23** by sodium in the presence of $ClSiMe_3$[30] provided 3-methyl-1,2-disiloxycyclobutene (+)-(*R*)-**24** in 78–82% yield; one-pot successive addition of bromine to a solution of (+)-(*R*)-**24** in pentane at −50 °C and of a 2 N NaOH aqueous solution at 0 °C[31,32] led, after acidification (2 N HCl), directly to (1*S*,2*R*)-1-hydroxy-2-methylcyclopropanecarboxylic acid (**25a**) in 95% yield (eq 8).[33]



(*R*)-**23** → (*R*)-**24** → (1*S*,2*R*)-**25a**, R = H; **b**, R = CH_3 (8)

(a) Na, $ClSiMe_3$, toluene, reflux, 78–82%. (b) Br_2, pentane, −50 °C. (c) 2 N NaOH, 0 °C. (d) 10% HCl, ether, 95%. (e) MeOH, $SOCl_2$, reflux, 92%.

Esterification of hydroxy acid **25a** with methanol ($SOCl_2$) provided (−)-(1*S*,2*R*)-methyl 1-hydroxy-2-methylcyclopropanecarboxylate (**25b**), containing <5% of its 1*R*,2*R* diastereomer. Recrystallization of acid **25a** in ether–hexane allowed, after esterification, the obtention of the stereochemically pure ester (1*S*,2*R*)-**25b**, whose optical purity (>97% ee) was determined by ^1H NMR in the presence of chiral $Eu(hfc)_3$.[34] It is noteworthy that the chirality of the stereocenter is not affected during the sodium-induced acyloin cyclization of the enolizable α-methylsuccinate (*R*)-**23**, which involves the intermediacy of radical anions,[30] as well as during the base-induced $C_4 \rightarrow C_3$ ring contraction of the bromination product of (*R*)-**24**, i.e., (*R*)-3-methyl-1,2 cyclobutanedione.[33]



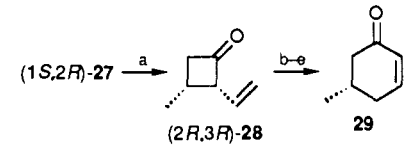
(1*S*,2*R*)-**25b** → (1*S*,2*R*)-**26** → (1*S*,2*R*)-**27** (9)

(a) $ClSi$-*t*-$BuMe_2$, imidazole, DMF, 35 °C, 96%. (b) DIBAH, toluene, −78 °C. (c) DMSO–$(COCl)_2$, −60 °C, NEt_3, 84% overall yield. (d) $(MeO)_2P(O)CH_2COOCH_3$, *n*-BuLi, THF, room temperature.

Silylation of hydroxy ester (1*S*,2*R*)-**25b** with *tert*-butyldimethylchlorosilane in DMF, reduction of the ester with diisobutylaluminum hydride (DIBAH) in toluene, and Swern oxidation with oxalyl chloride activated DMSO[35] led to aldehyde (1*S*,2*R*)-**26** in 84% overall yield. Wittig–Horner reaction with methyl dimethoxyphosphonoacetate in THF gave, after reduction of the conjugated ester with DIBAH in toluene, (*E*)-cyclopropylvinylcarbinol (1*S*,2*R*)-**27** in 84% yield (eq 9).[33a]

Contrary to the behavior of 1-vinylcyclopropanols, which underwent nonspecific acid-induced rearrangements,[36] (1*S*,2*R*)-cyclopropylvinylcarbinol **27** underwent regio- and stereoselective $C_3 \rightarrow C_4$ ring expansion[2,37] on simple addition of a catalytic amount of boron trifluoride etherate ($BF_3 \cdot Et_2O$) in CH_2Cl_2 to provide optically active (2*R*,3*R*)-3-methyl-2-vinylcyclobutanone (**28**) exclusively. Reduction of this ketone with $LiAlH_4$

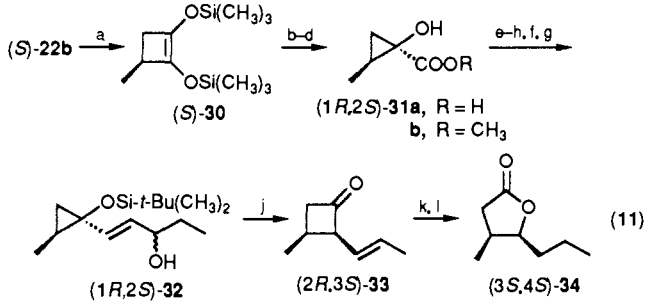
gave a 63:37 mixture of isomeric cyclobutanols that, upon treatment with KH in refluxing THF, underwent $C_4 \rightarrow C_6$ ring enlargement[38] into isomeric 5-methylcyclohex-3-en-1-ols. Oxidation with Jones reagent and treatment of the resulting nonconjugated enone with basic activity 3 alumina yielded (+)-(*S*)-5-methylcyclohex-2-en-1-one (**29**) with 91% ee (eq 10).[33a,c]



(10)

(a) $BF_3 \cdot Et_2O$, CH_2Cl_2, room temperature. (b) $LiAlH_4$, ether, reflux, 94%. (c) KH, THF, reflux. (d) CrO_3, H_2SO_4, acetone, 98%. (e) Al_2O_3, ether–pentane, 10:90.

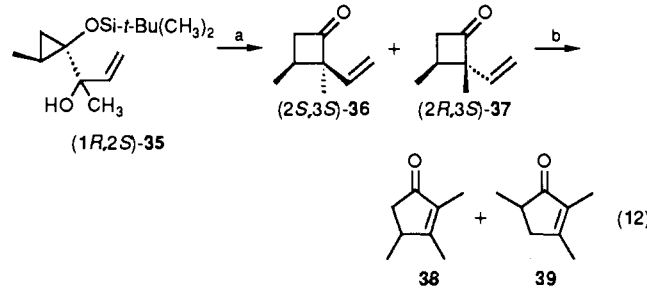
In the same way, sodium-induced cyclization of succinate (*S*)-**22b** gave 3-methyl-1,2-disiloxycyclobutene (−)-(*S*)-**30** and, after one-pot bromination and base-induced ring contraction, hydroxy acid (1*R*,2*S*)-**31a**, which was esterified (MeOH, $SOCl_2$) to lead to methyl cyclopropylcarboxylate (1*R*,2*S*)-**31b** with >95% ee. Following the scheme previously used to transform ester **25b** (vide supra), i.e., silylation, reduction, oxidation, Wittig–Horner reaction, and addition of ethylmagnesium bromide, cyclopropylcarboxylate (1*R*,2*S*)-**31b** was transformed into cyclopropylvinylcarbinol (1*R*,2*S*)-**32**, which underwent within 5 min upon simple addition of a catalytic amount of $BF_3 \cdot Et_2O$ in CH_2Cl_2 $C_3 \rightarrow C_4$ ring expansion[37] into optically active (2*R*,3*S*)-2-vinylcyclobutanone **33**, whose cis stereochemistry determined by NMR spectroscopy was confirmed chemically. Reduction of pure (2*R*,3*S*)-**33** catalyzed by palladium on charcoal in AcOEt followed by Baeyer–Villiger oxidation (MCPBA, CH_2Cl_2, 0 °C) provided the first enantioselective synthesis of (3*S*,4*S*)-4-butyl-3-methylbutanolide (**34**), known as Quercus lactone b, the major isomer found in wines and spirits that have been kept in oak barrels for maturing.[39] Comparison of the optical rotation of (3*S*,4*S*)-**34** with reported data[40] and NMR chemical shift experiments in the presence of chiral lanthanide $Eu(hfc)_3$[34] proved that the chirality of the stereogenic center of succinate (*S*)-**22b** was retained during all these rearrangements (eq 11).[33b,c]



(11)

(a) Na, $ClSiMe_3$, toluene, reflux, 82%. (b) Br_2, pentane, −50 °C. (c) 2 *N* NaOH, 0 °C; 10% HCl, ether. (d) MeOH, $SOCl_2$, reflux. (e) $ClSi$-*t*-$BuMe_2$, imidazole, DMF, 35 °C, 96%. (f) DIBAH, toluene, −78 °C. (g) DMSO–$(COCl)_2$, −60 °C, NEt_3. (h) $(MeO)_2P(O)CH_2COOCH_3$, *n*-BuLi, THF, room temperature. (i) EtMgBr, Et_2O, reflux. (j) $BF_3 \cdot Et_2O$, CH_2Cl_2, room temperature. (k) H_2, Pd/C, AcOEt. (l) MCPBA, CH_2Cl_2, 0 °C, 86%.

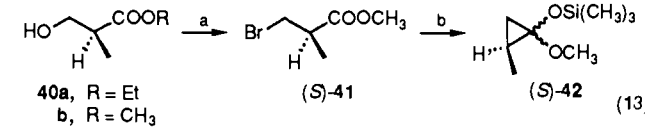
On the other hand, optically active tertiary cyclopropylvinylcarbinols (1*R*,2*S*)-**35**, readily available from ester (1*R*,2*S*)-**31b**, underwent $C_3 \rightarrow C_4$ ring expansion[2] within 15 min into a steroisomeric mixture of vinylcyclobutanones (2*S*,3*S*)-**36** and (2*R*,3*S*)-**37** (ratio 28:72) in 83% yield and with 84% ee. On further treatment in acidic media, i.e., neat with 15 mol equiv of methanesulfonic acid (CH_3SO_3H) or with 30 mol equiv of CH_3SO_3H in CH_2Cl_2, cyclobutanones **36** and **37** underwent $C_4 \rightarrow C_5$ ring expansion into a 9:1 mixture of 2,3,4-**38** and 2,3,5-trimethylcyclopentenones **39** in 40–56% yield. Unfortunately, this rearrangement, which required severe acidic conditions, led to racemization of the chiral center as shown by the zero value of the optical rotation of cyclopentenones **38** and **39** and by the splitting into two equal signals of the α-methyl singlets in the NMR spectra of cyclopentanones **38** and **39** recorded in the presence of chiral $Eu(hfc)_3$[34] (eq 12).[33c]



(12)

(a) $BF_3 \cdot Et_2O$, CH_2Cl_2, room temperature. (b) Neat CH_3SO_3H or CH_3SO_3H in CH_2Cl_2.

Chiral homoenolates, which can be prepared in high optical purity from the ring opening of cyclopropanols, find great synthetic utility.[41] Ethyl 2-formylpropanoate gave ethyl (3*R*)-3-hydroxy-2-methylpropanoate (**40a**) in 60% yield and with 80% ee when it was reduced with baker's yeast in the presence of sucrose.[42a] Methyl β-hydroxyisobutyrate (*R*)-**40b** and its *S* enantiomer are commercially available; they are prepared by microbial oxidation of isobutyric acid employing *Candida rugosa* (IFO 0750 and IFO 1542).[42b] Treatment of optically active hydroxy ester (*S*)-**40b** (>97% ee) with the complex triphenylphosphine–*N*-bromosuccinimide in THF led to methyl β-bromo ester (*S*)-**41** in 71% yield. Reductive cyclization was effected when (*S*)-**41** was reacted with sodium in the presence of $ClSiMe_3$[43] to yield a 1:1 diastereomeric mixture of 1-methoxy-1-(trimethylsiloxy)-2-methylcyclopropanes (2*S*)-**42**, precursors of cyclopropanone hemiacetals,[44] which were then transformed back to starting bromide (*S*)-**41** upon addition of bromine at 0 °C without loss of optical purity (eq 13).

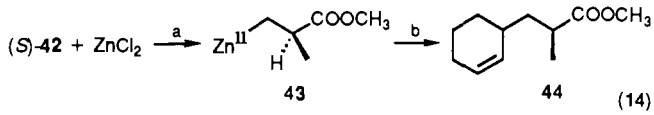


(13)

(a) Ph_3P–NBS, THF, room temperature, 71%. (b) Na, $ClSiMe_3$.

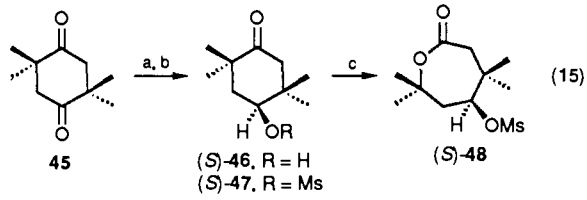
The ring-opening reaction of (*S*)-**42** with 0.5 equiv of freshly fused zinc chloride in ether cleanly gave homoenolate **43** in high yield and with 95% ee. The chiral isobutyrate zinc homoenolate smoothly reacted with various carbon electrophiles; with cyclohexenyl bromide, for instance, it gave adduct **44** (eq 14). In all reactions the chirality was fully retained.[41]

Cyclic 1,4-diones generally undergo bioreduction to give the *S*-configuration at the reduction sites. For example, 2,2,5,5-tetramethyl-1,4-cyclohexanedione (**45**) was reduced with *Curvularia lunata* or *Aspergillus ochraceus* over a 2-week period to give enantiomerically



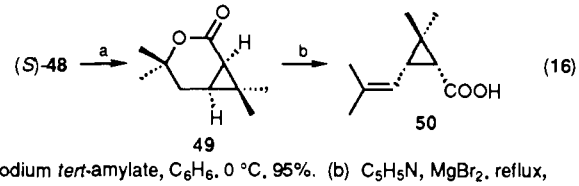
(a) Et_2O, room temperature. (b) C_6H_9Br, Et_2O, HMPA, CuBr • Me_2S, 0 °C, 59%.

pure 4-hydroxy-2,2,5,5-tetramethylcyclohexan-1-one (*S*)-**46** in 82–85% yield. Ketol (*S*)-**46** transformed into mesylate (*S*)-**47** was oxidized by *m*-chloroperbenzoic acid to offer exclusively the seven-membered-ring lactone (*S*)-**48** (eq 15).[45]



(a) *C. lunata* (NRRL 2380), glucose, EtOH, 82%. (b) CH_3SOCl, NEt_3, CH_2Cl_2, 0 °C, 97%. (c) MCPBA, CH_2Cl_2, 20 °C, 85%.

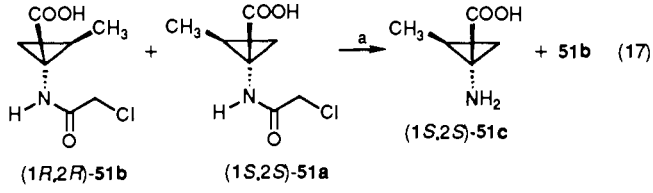
Lactone (*S*)-**48** was cyclized with sodium *tert*-amylate to yield oxabicyclo[4.1.0]heptan-2-one (1*R*,6*S*)-**49** (or (+)-dihydrochrysanthemolactone), which on heating in pyridine in the presence of $MgBr_2$[46] was quantitatively converted into (1*R*,2*S*)-chrysanthemic acid (**50**) (eq 16).[45]



(a) Sodium *tert*-amylate, C_6H_6, 0 °C, 95%. (b) C_5H_5N, $MgBr_2$, reflux, 100%.

The resolution of 2-methyl-1-aminocyclopropane-1-carboxylic acids, required for ethylene biosynthesis studies, has been performed with porcine kidney acylase I. Effectively, only the chloroacetyl derivative of amino acid (1*S*,2*S*)-**51a** was hydrolyzed by this enzyme.

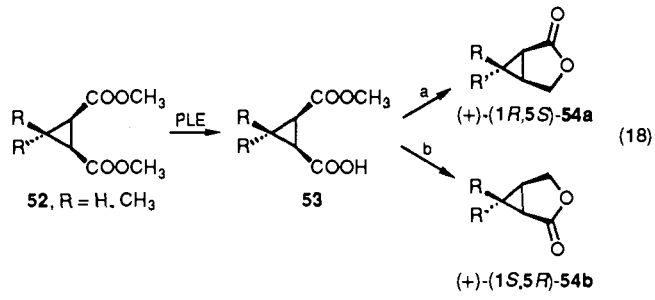
After standard workup of the crude enzymic hydrolysis product of **51a**,**b**, aminocyclopropanecarboxylic acid (1*S*,2*S*)-**51c** was isolated, while unreacted **51b** after acidic hydrolysis, led to the corresponding 1*R*,2*R* amino acid (eq 17).[47]



(a) Porcine kidney acylase I (A 3010, activity 2000–3000 units per gram), pH 7–7.5, 37 °C.

Pig liver esterase (PLE, E.C. 3.1.1.1) hydrolysis of *meso*-dimethyl 1,2-cyclopropanedicarboxylates **52** provided chiral monoesters **53** with enantiomeric excesses ranging from 43 to 100%; half-ester **53** offered valuable synthons for natural product synthesis.[48a–c] Controlled reduction of the acid function with borane readily converted **53** (R = H) into γ-lactone (+)-(1*R*,5*S*)-**54a**, while reduction with lithium borohydride led to isomeric γ-lactone (−)-(1*S*,5*R*)-**54b**, both with 54% yields and 97% ee.[48c]

Cyclopropane lactone (−)-**54b** (R = H) is an attractive precursor for the South Sea pheromone.[48d]



(a) BH_3 • Me_2S, THF, −10 °C, TsOH, 54%. (b) LiOH, $LiBH_4$, THF, HCl, 54%.

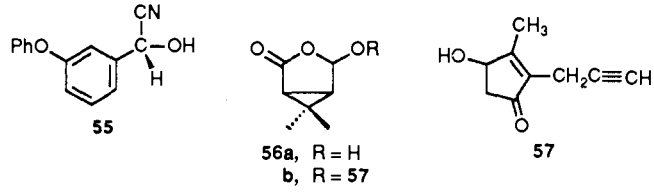
On the other hand, PLE and PPL hydrolyses of *cis*-diacetoxy-1,2-cyclopropylcarbinols transform these meso substrates into chiral monoesters by enantiotopic group differentiation, the chemical yields and enantiomeric excesses obtained with PPL (75–94% yield, 40–72% ee) being far superior to those achieved with PLE (54–69% yield, 20–40% ee).[48e] Horse liver alcohol dehydrogenase (HLADH) induced the oxidation of *meso*-1,2-cyclopropylcarbinols to lead to enantiomerically pure γ-lactones (oxabicyclohexanones) in a convenient one-step route.[48f]

Esters of cyclopropanecarboxylic acids **9** (R = Cl, Br, Me, CF_3) have been subjected to asymmetric hydrolysis with microorganisms or with the esterase from microorganisms to form optically active cyclopropanecarboxylic acid derivatives. For instance, *R. toruloides* IFO-0559 was shake-cultured in a medium containing malt, peptone, glucose, and yeast and to this was added ethyl *cis*-2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate (**9b**). After 40 h the corresponding (+)-*cis*-cyclopropanecarboxylic acid was recovered with 29.6% yield.[49a]

For a review discussing the use of an enzyme bioreactor in manufacturing optically active synthetic pyrethroids and some aspects of the stereostructure–activity relationship of pyrethroids, see ref 49b.

4. Cyclopropanes as Resolving Agents

2,2-Dimethylcyclopropylamine **20** (see eq 6), a useful intermediate for pharmaceuticals and agrochemistry, also provides an efficient resolving reagent for optical isomers.[24a] Racemic cyanhydrin **55** was resolved by etherification with *cis*-(1*R*,3*S*) acid lactone **56a** and subsequent hydrolysis.[50a]



Likewise, resolution of cyclopentenolone **57** was carried out by etherification with optically active lactone **56a** and subsequent methanolysis of **56b**.[50b]

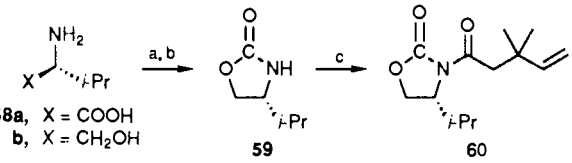
III. Asymmetric Synthesis

1. Asymmetry-Inducing Agents

This section is concerned with the preparation of optically active cyclopropanes using asymmetry-inducing groups such as chiral oxazolidinones, oxazolidines, sulfoxides, and phenylmenthyl carboxylates,

lithiated bases with chiral complexing agents, or the enantiotopic differentiation of functional groups by means of chiral auxiliaries. The reactions involve the cyclization of enolates or bromides, the enantioselective cyclopropanation of chiral olefins with diazo compounds or of racemic olefins with chiral malonates or carbenoids, the thermolysis of optically active aziridines, the enantiotopic reduction of one of the carbonyl groups of a meso cyclic dicarboxylic acid, and the deamination of optically active amines.

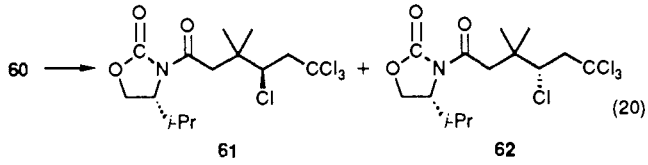
Esters of (dihalovinyl)cyclopropanecarboxylic acids **9** and **10** provide a large number of agriculturally important synthetic pyrethroid insecticides. The impact of the stereochemistry about the three-membered ring required the development of efficient methods for the stereoselective synthesis of the various enantiomers of such cyclopropanes. For this purpose, oxazolidinone **59** was prepared in two steps from (*R*)-valine (**58a**) by reduction with $BH_3{\cdot}SMe_2$ followed by treatment of the resultant amino alcohol **58b** with carbonyldiimidazole. Upon treatment with NaH followed by the addition of 3,3-dimethyl-4-pentenoyl chloride, **59** gave amide **60** in 85% yield (eq 19).



(19)

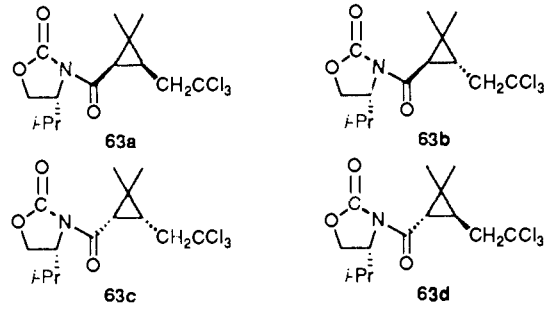
(a) $BH_3 \cdot SMe_2$. (b) Carbonyldiimidazole. (c) NaH, $ClCOCH_2C(Me_2)CH{=}CH_2$.

Then **60** was reacted with $Fe(CO)_5$ in CCl_4 to afford a 3:2 mixture of addition products **61** and **62**, respectively, in 86% yield (eq 20).



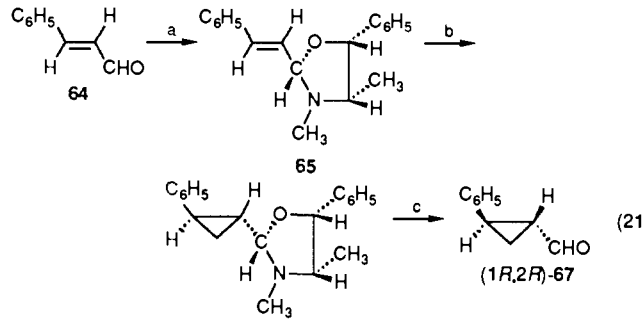
(20)

Isomeric products **61** and **62** separated by preparative HPLC underwent stereoselective cyclization initiated by enolate formation. Thus, treatment of **61** with NaH produced in 70% yield a 1:23:74:2 mixture of cyclized products **63a–d**, respectively, while under identical conditions, **62** led, in 84% yield, to a 92:1:2:5 mixture of **63a–d**, respectively.



Finally, the mixture of isomers obtained from **61** was treated with LiOMe, and the crude methyl esters obtained were treated with KOH to yield cyclopropanecarboxylic acids **9b** and **10b** in 77% yield (cis:trans ratio 88:12), while the mixture of isomers obtained from **62** led, under the same treatment, to acids **9b** and **10b** in 77% yield (cis:trans ratio 91:9).[51]

Chiral oxazolidines provide very simple and highly efficient inducing groups for asymmetric synthesis, especially for cyclopropanation reactions leading to cyclopropanecarboxaldehydes with high enantiomeric excess (>90%). For instance, in Et_2O at 0 °C reaction of diazomethane in the presence of $Pd(OAc)_2$ (see section III.3) with oxazolidine **65**, prepared by stereospecific condensation of (*E*)-3-cinnamaldehyde (**64**) with commercially available (−)-ephedrine, gave **66** quantitatively, which on hydrolysis with wet SiO_2 led to 2-phenylcyclopropanecarboxaldehyde **67** exclusively (eq 21).

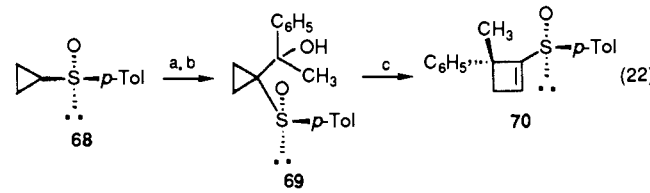


(21)

(a) (−)-Ephedrine. (b) CH_2N_2, 0 °C, $Pd(OAc)_2$. (c) SiO_2–H_2O.

Under the same conditions, (+)-ephedrine provided the enantiomeric isomers of cyclopropane derivatives **66** and **67**.[52]

Creation of asymmetric quaternary carbon atoms is one of the most important problems for the enantioselective synthesis of natural products. The thermal rearrangements of cyclopropane systems possessing a chiral sulfinyl group on the ring provide a potentially valuable method for the enantioselective creation of quaternary carbons. Thus, addition of the α-carbanion generated by treatment of (+)-(R_S)-(*p*-tolylsulfinyl)-cyclopropane **68** (100% ee)[53] with *n*-BuLi to acetophenone at −20 °C afforded cyclopropylcarbinol (S_S)-**69** in 78% yield (diastereoisomer ratio, 3:2). Upon heating in refluxing benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, **69** underwent a 1,2-asymmetric rearrangement to give (S_S,4*R*)-cyclobutene **70** in 88% yield (eq 22).

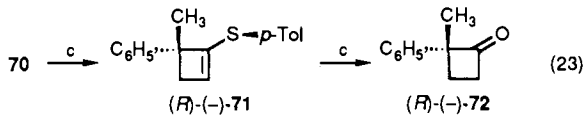


(22)

(a) *n*-BuLi, −20 °C. (b) $C_6H_5COCH_3$, −20 °C, 78%. (c) C_6H_6, *p*-TsOH, 80 °C, 3.5 h, 88%.

Reduction of sulfoxide **70** with acetyl chloride in CH_2Cl_2 led to enol thioether (−)-(*R*)-**71**, which was hydrolyzed by a titanium(IV) chloride (3 equiv)–lead hydroxide (3 equiv)–H_2O (6 equiv mixture) in acetonitrile to produce (−)-(2*R*)-2-methyl-2-phenylcyclobutanone (**72**) in 86% yield (eq 23).

The absolute configuration of (−)-(*R*)-**72** and its enantiomeric excess (94% ee) were determined by chemical correlation with known (−)-(*R*)-2-methyl-2-phenylsuccinic acid.[54] The reaction sequences starting with sulfoxide **68** and ethyl methyl ketone were suc-

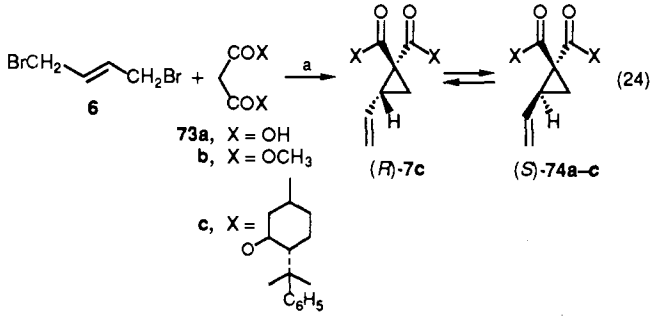


(23)

(a) CH_3COCl, CH_2Cl_2, room temperature, 2 h, 78%. (b) $TiCl_4$–$Pb(OH)_2$–H_2O, CH_3CN, room temperature, 18 h, 86%.

cessfully executed in the same way, with 73.3% ee. It appears that the degree of asymmetric induction depends on the difference of steric interference between the substituent of the three-membered ring and the lone pair of the oxygen atom of chiral sulfoxide **69**.[55]

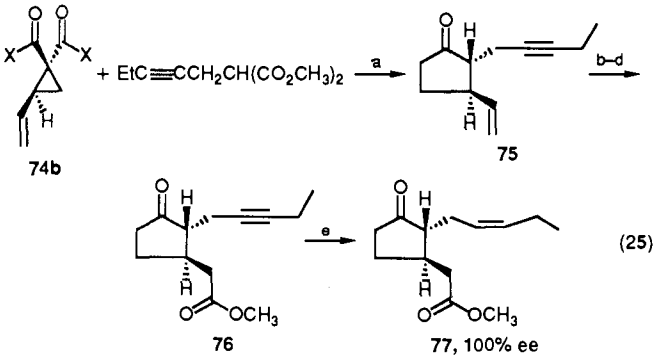
The asymmetry-inducing reaction of (*E*)-1,4-dihalo-2-butene (**6**) with diphenylmenthyl malonate (**73c**) in a two-phase system (n-C_6H_{14}, NaOH, H_2O, $(C_8H_{17})_3CH_3NCl$) provided vinylcyclopropane (*R*)-**7c** (eq 24), which is a valuable synthetic building block for steroids (see section II.2 (eq 3)).[10]



(24)

(a) n-C_6H_{14}, H_2O, NaOH, $(C_8H_{17})_3CH_3NCl$, room temperature.

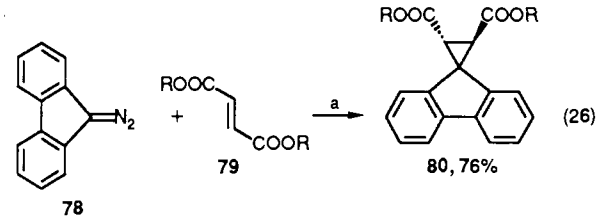
The enantiomer vinylcyclopropane (*S*)-**74b** also provides a potential building block for the synthesis of methyl jasmonate, a valued perfumery ingredient. It is simply accessible from (*R*)-**7c**; refluxing a solution of (*R*)-**7c** in *p*-cymene led to a separable equilibrium (2.5:1) mixture of diastereomers (*R*)-**7c** and (*S*)-**74c**.[56] Hydrolysis of **74c** by potassium hydroxide in ethanol followed by esterification with diazomethane gave the expected dimethyl ester (*S*)-**74b** in 72% yield (eq 24). Condensation of (*S*)-**74b** with dimethyl 2-pentynylmalonate in methanol containing sodium methylate led to cyclopentanone **75** from $C_3 \rightarrow C_5$ ring expansion. Then borane-induced hydration followed by oxidation with Jones reagent and diazomethane esterification provided acetate **76**, which on hydrogenation in the presence of Lindlar catalyst gave finally in 89% yield the enantiomerically pure methyl jasmonate **77** (eq 25).[56]



(25)

(a) Na/CH_3OH; CH_3OH, 60 °C; removal of solvent; 130 °C for 1 h; CH_3OH, H_2O, room temperature; reflux; concentrated HCl; NaH_2PO_4, $2H_2O$, 0 °C, 24%. (b) 9-BBN, THF, room temperature; 30% H_2O_2, 3 N NaOH. (c) Jones reagent, room temperature. (d) CH_2N_2, ether, 65%. (e) H_2/Lindlar catalyst, room temperature, 89%.

Asymmetric induction in the 1,3-dipolar cycloaddition of diphenyldiazomethane to methyl acrylate had been reported to give "anti-Prelog" type optically active 2,2-diphenylcyclopropanecarboxylic acid with low enantioselectivity (2%).[57] However, the 1,3-dipolar cycloaddition of diazofluorene (**78**) with diphenylmenthyl fumarate (**79**) gave *trans*-2,3-dicarbomethoxyspirocyclopropane-1,9′-fluorene (**80**) with high diastereoselectivity (90% de); no detectable amount of the cis isomer implied complete retention of the configuration in the formation of the three-membered ring (eq 26).



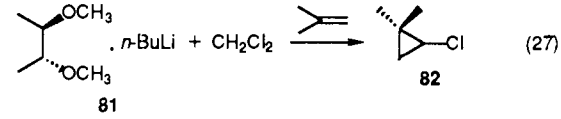
(26)

R = 8-phenylmenthyl

(a) C_6H_6, reflux.

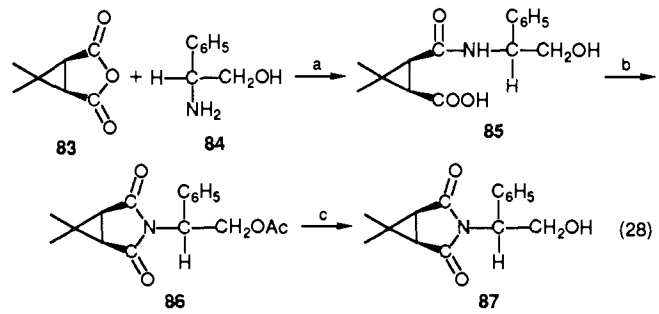
Therefore it appeared that the use of the 8-phenylmenthyl group[58] as a chiral auxiliary dramatically improved the optical yield of the 1,3-dipolar cycloaddition of diazofluorene.[59]

Enantioselective synthesis in a carbenoid reaction has been also obtained with the participation of an optically active complexing agent. Thus reaction of the complex of n-butyllithium with optically active 2,3-dimethoxybutane (**81**) with methylene chloride in isobutene gave optically active 1,1-dimethyl-2-chlorocyclopropane (**82**) (eq 27).[60]



(27)

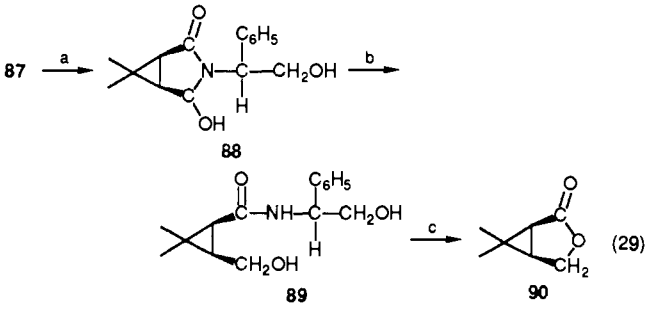
Starting from symmetrical compounds by finding out the hidden symmetry in chiral compounds is theoretically one of the most attractive methods to prepare optically active derivatives.[61] In fact, it is possible to distinguish one of the enantiotopic carbonyl groups of a *meso*-dicarboxylic acid from another by employing only one chiral source. Thus, when *meso*-3,3-dimethylcyclopropane-1,2-*cis*-dicarboxylic anhydride (**83**) was added to a suspension of (−)-(*R*)-2-amino-2-phenylethanol (**84**) in THF, amide **85** was obtained; upon treatment with acetic anhydride in the presence of sodium acetate it gave imide **86**. Removal of the acetyl group of **86** by refluxing in a 1 N methanolic solution of hydrochloric acid afforded imide **87** in 67% overall yield (eq 28).



(28)

(a) THF, 0 °C. (b) NaOAc, Ac_2O, 100 °C. (c) 1 N HCl, MeOH, 60 °C.

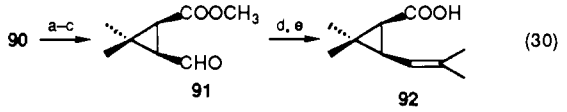
Upon treatment with sodium bis(2-methoxyethoxy)aluminum hydride, only one of the carbonyl groups of imide **87** was reduced to give the hydroxy pyrrolidone **88**, which was ring-opened by sodium borohydride to lead to amide **89**. Acidification with 2 N sulfuric acid provided optically active lactone **90** in 64% overall yield and with 81% ee (eq 29).[62]



(29)

(a) $NaAlH_2(OCH_2CH_2OCH_3)_2$. THF, −41 °C, 89%. (b) $NaBH_4$, EtOH, 50 °C, 95%. (c) 2 N, H_2SO_4, 80 °C, 76%.

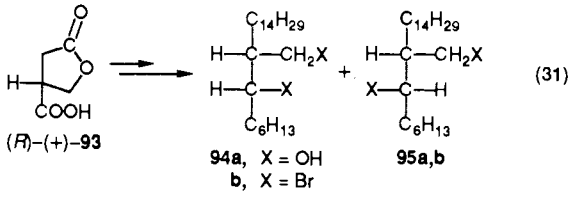
According to the reported procedure,[63] optically active lactone **90** was transformed into *cis*-chrysanthemic acid ((1*R*,3*S*)-**92**)[64] via cyclopropanecarboxaldehyde **91** (eq 30).[62]



(30)

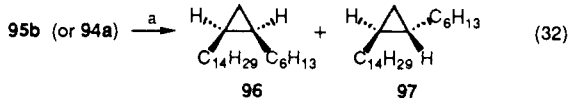
(a) KOH, MeOH, HCl. (b) CH_2N_2, Et_2O. (c) PCC, 90%. (d) $Ph_3P{=}C(CH_3)_2$, 84%. (e) KOH, MeOH, HCl, 99%.

Condensation of resolved paraconic acid ((+)-(*R*)-**93**) (see section II.2) with pentylmalonic acid, reduction of the corresponding ketone with $(t\text{-BuO})_2LiAlH$, and Kolbe reaction with myristic acid gave diastereomic *p*-diols **94a** and **95a** with 75% ee (eq 31).[65]



(31)

Bromination of threo diol **95a** with tribromophosphorus provided threo dibromide **95b** in 75% yield, which was dissolved in a benzene–ethanol–formamide mixture (5:4:1.8) and treated with zinc powder to give, after treatment with $KMnO_4$, an equimolar mixture of *cis*-(1*S*,2*R*)-**96** and *trans*-(1*S*,2*S*)-1-**97** in 90% yield (eq 32).

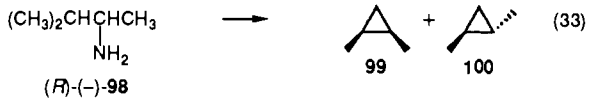


(32)

(a) C_6H_6/EtOH/$HCONH_2$, Zn, 90%.

Under the same treatment, bromination of erythro diol **94a** into dibromide **94b** and reaction with zinc powder led to the same mixture of cyclopropanes **96** and **97**, which were readily separated by simple addition to a 1:1 EtOAc–MeOH solution saturated with urea. Thus, *trans*-cyclopropane (1*S*,2*S*)-**97** was precipitated as the urea inclusion complex and obtained, after hydrolysis, with 95% yield and 70% ee. From the solution was extracted with ether *cis*-cyclopropane (1*S*,2*R*)-**96** containing 3% of its trans isomer **97**. Oxidation with chromic acid afforded the corresponding optically active α-cyclopropyl ketones without racemization of the chiral center, which were easily separated by TLC.[66]

The deamination of optically active (−)-(2*R*)-3-methyl-2-butylamine (**98**) with aqueous $NaNO_2$–$HClO_4$, $NaNO_2$–HOAc, or $HCCl_3$–RONO gave a mixture of *cis*-(1*S*,2*R*)-**99** and *trans*-(1*S*,2*S*)-**100** besides 2-methyl-1-butene, 2-methyl-2-butene, and 3-methyl-1-butene (eq 33).



(33)

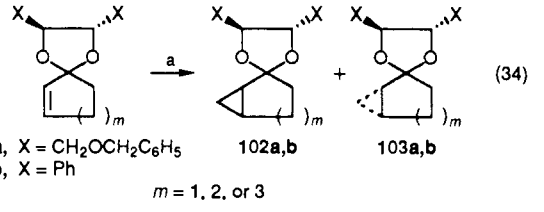
ee, %	solvent system	ee, %
78	$HClO_4$–H_2O–$NaNO_2$	7.8
72	HOAc–$NaNO_2$	41
73	$CHCl_3$–RONO	22

Formation of racemic cyclopropane (1*S*,2*S*)-**100** in aqueous solution implied the intervention of an intermediate 3-methyl-2-butyl cation; on the other hand, deamination in HOAc and $HCCl_3$, which should give shorter-lived cations, was stereoselective and entailed 57% of inversion of configuration. Comparison with previous data indicated that the deamination of amine **98** involved methyl migration to a corner-protonated cyclopropane intermediate.[67]

2. Asymmetric Simmons–Smith Cyclopropanation

Enantioselective Simmons–Smith reactions of chiral olefins such as acetals of α-enones with 1,4-di-*O*-benzyl-L-threitol, (*S*,*S*)-hydrobenzoin, (*R*,*R*)- or (*S*,*S*)-tartaric esters, anguidine degradation products, or adducts of prochiral enone with (*N*-methylphenylsulfonimidoyl)methane with the reagents prepared from Zn–Cu couple, Zn–Ag couple, or diethylzinc and diiodomethane offered cyclopropanes with high enantiomeric excess.

[*m.n.*1]Propellanones are particularly attractive precursors of bicyclic ring systems bearing angular methyl or functionalized angular methyl substituents found in a number of natural products. A novel diastereoselective cyclopropanation of homochiral ketals **101a**,**b** derived from simple monocyclic enones and 1,4-di-*O*-benzyl-L-threitol[68a] or (−)-(*S*,*S*)-hydrobenzoin[68b] as chiral protecting group has been described (eq 34).[69]

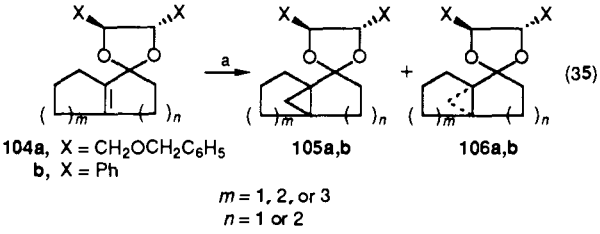


(34)

(a) Zn–Cu, CH_2I_2, Et_2O, reflux, 90–98%.

Thus, treatment of 2-cyclohexen-1-one acetal **101b** (*m* = 2), obtained by direct dehydrative acetalization, with freshly prepared zinc–copper couple and methylene iodide gave, in 90% yield, a 19:1 diastereomeric ratio of cyclopropanes **102b** and **103b**, as determined by 62.9-MHz ^{13}C NMR spectroscopy. Hydrolysis of recrystallized **102b** provided (1*R*,6*S*)-bicyclo[4.1.0]heptan-2-one with >99% ee. In the same way, direct acetalization of the corresponding bicyclic ketones gave ene

ketals **104a,b**, which upon treatment with an excess of the Simmons–Smith reagent[70] provided in 62–80% yields diastereomeric mixtures of propellanone ketals **105a,b** and **106a,b** ranging from 7:1 to 16:1 as determined by ^{13}C NMR spectroscopy (eq 35).[69]



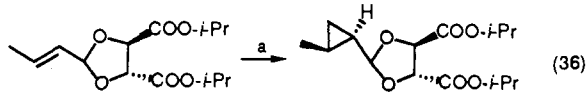
104a, X = $CH_2OCH_2C_6H_5$ **105a,b** **106a,b**
b, X = Ph

$m = 1, 2, \text{or } 3$
$n = 1 \text{ or } 2$

(a) Cu–Zn, CH_2I_2, Et_2O, reflux, 72–80%.

Acid-catalyzed hydrolyses of these propellanone ketals **105a** and **106a** provided the corresponding propellanones in 77–92% yields and with 75–80% ee. Assignments of absolute stereochemistry were based upon CD spectra of the propellanones employing the reversed octant rule.[71] As the diastereomeric mixtures of the hydrobenzoin ketals are recrystallizable, enantiomerically pure cyclopropyl ketones are now available by this process, whose usefulness has been demonstrated in several syntheses.[69]

Both (*R,R*)- and (*S,S*)-tartaric acid esters are readily available in optically pure form;[72] they allow the synthesis of α,β-unsaturated aldehyde acetals which then undergo enantioselective cyclopropanation. Thus, acetal **107** was treated with diethylzinc and methylene iodide at −25 °C to afford pure cyclopropanecarboxaldehyde acetal **108** with 94% diastereomeric excess and in 90% yield (eq 36).



107 **108**

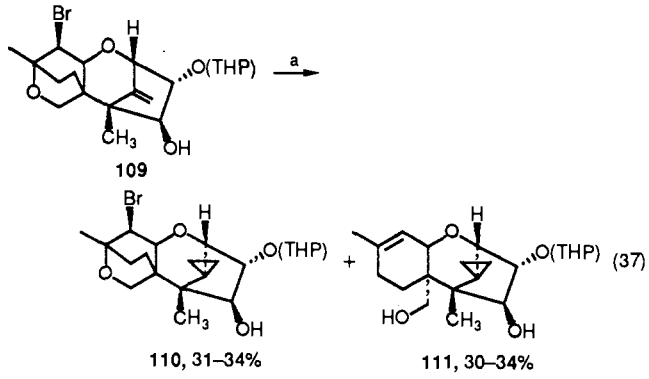
(a) Et_2Zn, CH_2I_2, hexane 25 °C, 90%.

The absolute configuration has been proven by transformation of acetal **108** to (1*R*,2*R*)-2-methylcyclopropanecarboxylic acid. This method appeared useful for the production of a wide range of chiral cyclopropanes in the increasingly important class of biologically active functionalities, such as, for instance, 5,6-methanoleukotriene A_4.[73]

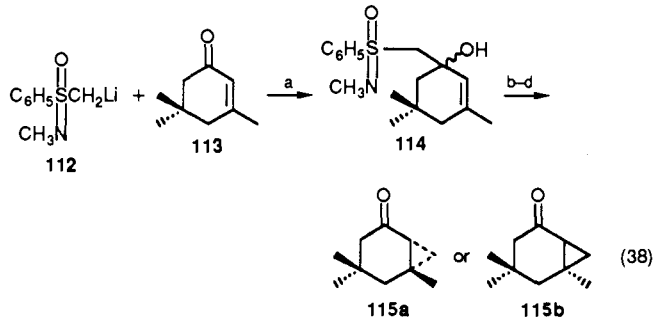
On the other hand, Simmons–Smith reactions of (−)-menthyl α,β-unsaturated carboxylates afforded the corresponding cyclopropane derivatives with low enantioselectivity (1.3–9.3%).[74] Partial asymmetric synthesis (3.4% ee) has been achieved when the Simmons–Smith reaction of olefins was performed in the presence of free (−)-menthol.[75]

For biological evaluation, skeletally modified trichothecenes, reversible inhibitors of eucaryotic protein synthesis, have been prepared. Thus, treatment of the anguidine degradation intermediate **109** with methylene iodide and zinc–silver couple[76] provided a 31–34% yield of cyclopropane **110** plus a 30–34% yield of trichothecene **111**. Attempts to improve the efficiency of this cyclopropanation by using the CH_2I_2–$ZnEt_2$ procedure[77] provided **111** in only 30% yield (eq 37).[78]

It is well documented that the Simmons–Smith cyclopropanation is directed by oxygen coordination. Addition of optically pure [(*N*-methylphenylsulfonimidoyl)methyl]lithium (**112**) to prochiral ketone isophorone **113** resulted in the formation of two optically active diastereomeric adducts **114**. Separation of the diastereomers, treatment with diiodomethane and the Zn–Ag couple,[76] and thermolysis (retroreaction) led to enantiomeric cyclopropyl ketones **115a** and **115b**, respectively (eq 38).[79]



(a) CH_2I_2, Zn–Ag, Et_2O, reflux or CH_2I_2–$ZnEt_2$, Et_2O, reflux.



(a) PhS(O)(NCH_3)CH_3, *n*-BuLi, THF, 0 °C; then **154**, THF, −78 °C. (b) SiO_2 chromatography. (c) CH_2I_2, Zn–Ag, Et_2O, reflux. (d) 100 °C.

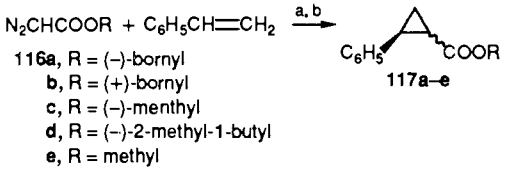
This methodology has been applied to the synthesis of (−)- and (+)-thujopsene[80] and (−)-rothrockene[81] as well as to a variety of other enantiomerically pure cyclopropyl ketones.[80] In this methodology, which represents a viable alternative to other resolution or asymmetric induction techniques (vide supra), resolving agent **112** can be readily recovered.[79]

3. Copper- or Rhodium-Catalyzed Decomposition of Diazo Compounds

Additions of carbalkoxycarbenoids, from copper and copper salt catalyzed decompositions of diazoacetic esters, to simple olefins are well-known and synthetically useful.[82] These reactions of cyclopropanation have been found to be stereospecific, and there is evidence that carbene, catalyst, and olefin are all involved in the transition state of the addition step.[83] Asymmetric induction in the catalytic cyclopropanation reactions of olefins with diazo compounds has been attempted with the use of optically active alkyl diazoacetates (e.g., (−)-menthyl diazoacetate, (diazoacetyl)oxazolidinone), of chiral olefins (i.e., (butadiene)iron tricarbonyl complexes), or of chiral copper complexes (Cu^{II} complexed with Schiff bases, semicorrins, (+)-3-trifluoroacetyl camphor).

Diazoacetates **116a–d** of (−)- and (+)-borneol, (−)-menthol, and (−)-2-methyl-1-butanol have been prepared. Thus, for instance, addition of (−)-menthol to a solution of glyoxylyl chloride, (*p*-tolylsulfonyl)-hydrazone, and triethylamine in CH_2Cl_2 gave the expected diazoester **116c** in 68% yield. Decomposition

of **116c** with a catalytic amount of copper(I) chloride in styrene gave a mixture of *cis*- and *trans*-menthyl 2-phenylcyclopropanecarboxylates **117c** in 97% yield. Saponification with 1 N NaOH in 85% ethanol occurred without any epimerization; then treatment with diazomethane led to *cis*- and *trans*-methyl 2-phenylcyclopropanecarboxylates (−)-**117e** with a trans:cis ratio of 2.15 and an enantiomeric excess of 11.7% (eq 39).[84]



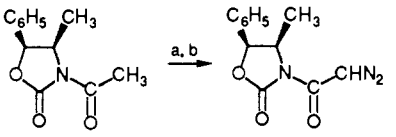
(39)

116a, R = (−)-bornyl
b, R = (+)-bornyl
c, R = (−)-menthyl
d, R = (−)-2-methyl-1-butyl
e, R = methyl

117a–e

(a) Cu_2Cl_2, 50 °C, 75–88%. (b) 1 N NaOH, 85% EtOH, reflux, 62%.

The effectiveness of chiral alkanoyloxazolidinones for diastereoselection in alkylation and aldol condensation[85] as well as in the three-membered-ring cyclization[51] (see section III.1 (eq 20)) is well-known; it is also effective for carbenoid transformations. Thus, condensation of *N*-acetyloxazolidinone **118**[85a] with 2,2,2-trifluoroethyl trifluoroacetate (TFEA) followed by diazo transfer using *p*-tolylsulfonyl azide in the presence of 1.0 equiv of water and a 1.5 molar excess of triethylamine gave *N*-(diazoacetyl)oxazolidinone (4*R*,5*S*)-**119** in 62% yield (eq 40).

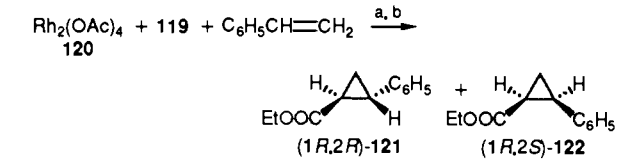


(40)

118 **119**

(a) LDA, THF, −78 °C, TFEA. (b) $ArSO_2N_3$, Et_3N, H_2O, 62%.

Rhodium(II) acetate **120** catalyzed cyclopropanation of styrene with oxazolidinone **119** followed by transesterification led to a 1.8 trans:cis isomer ratio of (1*R*,2*R*)-**121** and (1*R*,2*S*)-**122** with only 14 and 13% ee, respectively (eq 41).



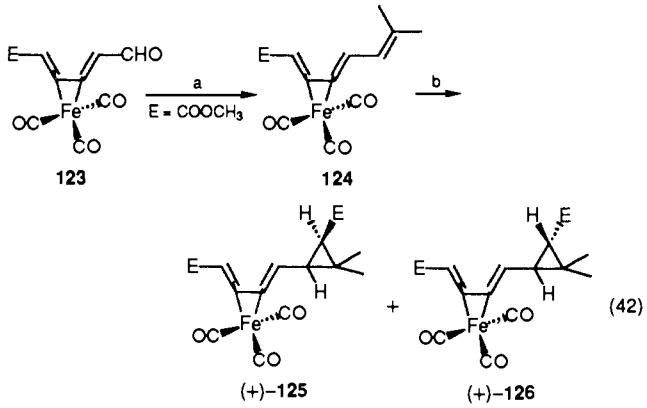
(41)

(1*R*,2*R*)-**121** (1*R*,2*S*)-**122**

(a) **120**, 22 °C. (b) Et_2O–EtOH, 50:50, NaOEt, 0 °C, 35–40%.

Reaction of (4*S*)-*N*-(diazoacetyl)-4-isopropyloxazolidinone, analogously prepared from the convenient *N*-acetyloxazolidinone, with styrene in the presence of $Rh_2(OAc)_4$ gave, under the same conditions, the component ethyl 2-phenylcyclopropanecarboxylates **121** and **122** with the same trans:cis ratio (1.8) in 20–24% yield. Only trans isomer (1*R*,2*R*)-**121** was isolated with 13% ee. These results implied the occurrence of a metal carbene, not associated with the oxazolidinone carbonyl group; therefore the use of chiral diazo compounds for intermolecular carbenoid reactions did not result in any advantage.[86]

Chiral (butadiene)iron tricarbonyl complexes have been used in the synthesis of cyclopropanecarboxaldehyde precursors of pyrethroids. Thus, condensation of readily available optically pure complex (+)-**123** with isopropylidenephosphorane in THF provided olefin **124** in 72% yield. Cyclopropanation by methyl diazoacetate in the presence of copper powder in toluene gave in 70% overall yield from **123** a 1:1 mixture of the isomeric cyclopropanes (+)-**125** and (+)-**126**, which were separated by thin-layer chromatography (eq 42).



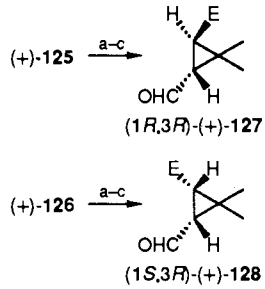
123 **124**

(+)-**125** (+)-**126**

(42)

(a) $Ph_3P{=}CH_2$, THF, 15 °C, 72%. (b) N_2CHCO_2Et, toluene, 80 °C, 70%.

Decomplexation by trimethyl nitroxide in CH_2Cl_2 and ozonolysis provided *trans*-hemicaronaldehyde (1*R*,3*R*)-(+)-**127** and the cis isomer (1*S*,3*R*)-(+)-**128**, respectively. The 90% ee was determined by NMR spectroscopy after condensation with (−)-ephedrine (eq 43).

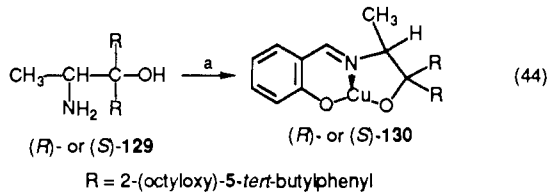


(43)

(a) Me_3NO, CH_2Cl_2, reflux. (b) O_3, −70 °C. (c) Ph_3P, −10 °C.

From the isomeric (butadiene)iron tricarbonyl complex (−)-**123** were obtained analogously the corresponding enantiomers (−)-**127** and (−)-**128**.[87]

Chiral copper complex catalyzed decomposition of diazoalkanes afforded optically active products.[83b] A catalyst of choice was (*R*)- or (*S*)-1648 **130**, a Schiff base copper chelate derived from optically active amino alcohol (*R*)- or (*S*)-**129** and salicylaldehyde (eq 44).



(*R*)- or (*S*)-**129** (*R*)- or (*S*)-**130**

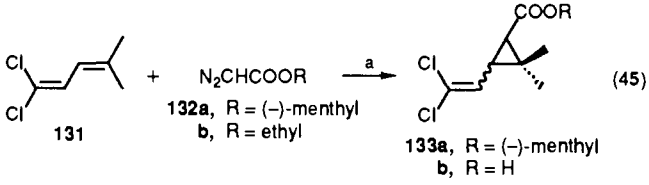
(44)

R = 2-(octyloxy)-5-*tert*-butylphenyl

(a) $Cu(OAc)_2$, salicylaldehyde.

(−)-Menthyl diazoacetate (**132a**) was decomposed in 1,1-dichloro-4-methyl-1,3-pentadiene (**131**) in the presence of copper complex (*S*)-1648 **130** to produce in 52% yield menthyl cyclopropanecarboxylates **133a** as a mixture of (1*R*)-cis (12.3%), (1*S*)-cis (23.6%), (1*R*)-trans (15.3%), and (1*S*)-trans (48.8%) isomers. The enantiomeric excesses were calculated to be 31% for the cis isomer and 51% for the trans ester (eq 45).

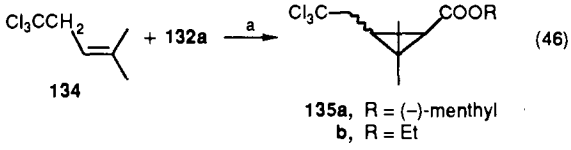
The same reaction in the presence of complex (*R*)-1648 **130** gave (1*R*)-trans ester **133a** as the main product (48.4%). Saponification of ester **133a** gave permethric acid (**133b**, R = H), an effective pyrethroid insecticide.



(45)

(a) (*S*)-1648 **130**, 52%.

On the other hand, when ethyl diazoacetate was added to a solution of catalyst (*S*)-1648 **130** in the methyl 5,5,5-trichloropent-2-ene (**134**) (10 equiv) a mixture of adducts **135b** was obtained in 59% yield, which then was saponified by potassium hydroxide (3 equiv) in ethanol to afford cyclopropanecarboxylic acid **133b** in 92% yield as a mixture of (1*R*)-cis (80.6%), (1*S*)-cis (3.9%), (1*R*)-trans (8.6%) and (1*S*)-trans (6.9%) isomers. The enantiomeric excesses were calculated to be 91% for the cis isomer and 11% for the trans isomer (eq 46).

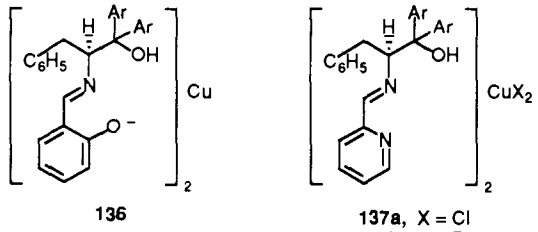


(46)

(a) (*S*)-1648 **130**, 30 °C, 59%.

Similarly, (-)-menthyl diazoacetate (**132a**) was decomposed in the presence of catalyst (*S*)-1648 **130** in olefin **134** to give in 54% yield adduct **135a** (R = (-)-menthyl), whose isomeric composition was (1*R*)-cis (81.5%), (1*S*)-cis (3.1%), (1*R*)-trans (9.2%), and (1*S*)-trans (6.9%). The enantiomeric excesses were 93% for the cis isomer and 19% for the trans isomer. Therefore, the dramatic change in the product distribution was brought about by the use of monoene **134** in place of diene **131**; the crucial role of the halogen atoms at the homoallylic position of **134** has also been evidenced.[88]

Chiral copper(II) Schiff base complexes have also been obtained by condensing amino sugars with either salicylaldehyde or pyridine-2-carboxaldehyde. Thus, catalysts derived from 2-amino-D-altropyranoside having the *S* configuration at C(2) of the glycosidic ring displayed selectively the 1*S* isomers of cyclopropanes, whereas catalysts prepared from 2-amino-D-glucopyranoside and 2-amino-D-allopyranoside, both having the *R* configuration at C(2) of the glycosidic rings, favored formation of the (1*R*)-cyclopropanes, important precursors of photostable pyrethroids.[89] Schiff bases, in which chirality was derived from L-phenylalanine, have been prepared by condensation of (*S*)-2-amino-1,1-bis(2-methoxyphenyl)-3-phenylpropan-1-ol with the corresponding aromatic aldehyde and then subsequently converted into copper complexes such as **136** and **137a,b**.[90]

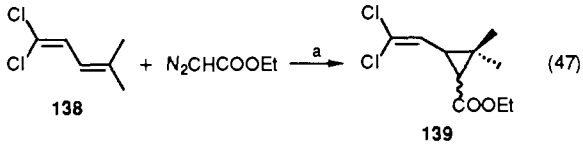


136

137a, X = Cl
b, X = BF_4

Ar = o-$CH_3OC_6H_4$

Cyclopropanation for instance of dichloro diene **138** with ethyl diazoacetate in the presence of Schiff base catalyst **136** in toluene provided a 40:60 cis:trans isomeric ratio of cyclopropanes **139** in 33% yield (eq 47).

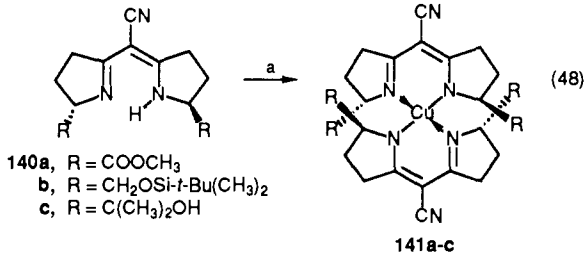


(47)

(a) Schiff base copper complex **136**, toluene, 70 °C, 33%.

The isomeric composition of **139** was found to be (1*R*,3*S*)-cis (17%), (1*S*,3*R*)-cis (23%), (1*R*,3*R*)-trans (23.5%), and (1*S*,3*S*)-trans (36.5%). The low nucleophilicity of the olefins was responsible for the low yield (3–33%) of cyclopropanation, and both the degree and direction of chiral induction were found to depend on the olefin. Unexpectedly, in several reactions there was marked stereoselectivity at C(3) rather than C(1) of the cyclopropanes. This pattern of selectivity was interpreted in terms of carbene transfer from a metal–carbene intermediate in which a chiral ligand controls the orientation of the approaching olefin.[91a]

Semicorrins **140** possess also several features that make them attractive candidates for the enantioselective control of metal-catalyzed reactions. They are readily obtained in both enantiomeric forms from commercially available (-)- and (+)-pyroglutamic acids and form stable chelate complexes **141a–c** with a variety of metal ions such as Cu^{II} (eq 48).[92]



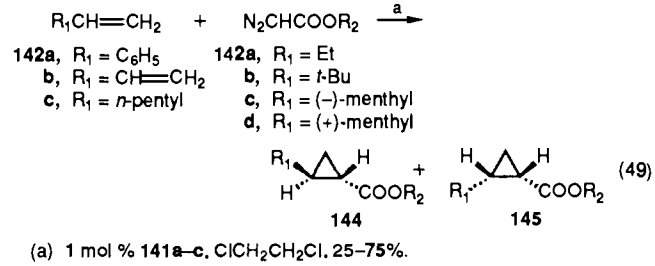
140a, R = $COOCH_3$
b, R = CH_2OSi-*t*-Bu$(CH_3)_2$
c, R = $C(CH_3)_2OH$

141a-c

(48)

(a) $Cu(OAc)_2$, MeOH, 23 °C, 91–95% or $CuSO_4$, $NaHCO_3$, H_2O, CH_2Cl_2, 23 °C, 94%.

The Cu^{II} complexes **141a–c** efficiently catalyze the cyclopropanation of olefins **142a–c** with diazoacetates **143a–c** to give diastereomeric 2-phenylcyclopropanecarboxylates **144** and **145** in optically active form (eq 49).



144 **145**

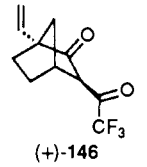
(49)

(a) 1 mol % **141a–c**, $ClCH_2CH_2Cl$, 25–75%.

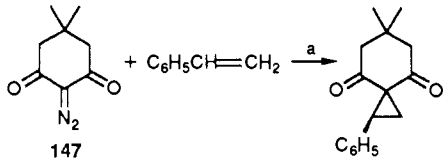
The enantioselectivity and the efficiency of the catalysts increase in the order **141a** < **141b** < **141c**; effectively, the enantiomeric excesses of **144** were 23, 59, and 85%, respectively. Furthermore, variation of the alkoxy group of diazoacetate **143** can substantially improve the selectivity of the complex; thus, enantiomeric excesses of 95–97% were obtained with the (+)-menthyl ester.[93] (Compare with eq 41.)

Other Schiff base copper complexes efficient for asymmetric cyclopropanation have been patented;[91b-f] see also ref 94 and 95.

The copper complex of 10-methylene-3-(trifluoroacetyl)-(+)-camphor ($Cu(10\text{-methylenefacam})_2$ (**146**)) prepared by trifluoroacetylation of (+)-methylenecamphor,[96] used to catalyze the reaction of 2-diazodimedone (**147**) with styrene, afforded cyclopropane **148** in 48% yield and 100% ee (eq 50).[97]



(+)-**146**



(50)

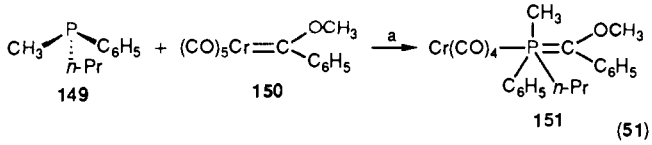
(a) $Cu(10\text{-methylenefacam})_2$, benzene, reflux, 48%.

An immobilized form of this chiral copper β-diketonate catalyst, obtained by hydrosilylation of vinyl β-diketone (+)-**146** and further reaction with Hypersil silica,[98] was effective to catalyze the reaction between styrene and diazo compound **147** and yielded cyclopropane **148** in 43% yield with an enantiomeric excess of 98.3%.[97] For reviews on reactions of alkyl diazoacetate with olefins catalyzed by chiral Cu complexes, see ref 99.

4. Transition-Metal–Carbene Complexes

Transfer of carbene ligands from optically active transition-metal–carbene complexes to alkenes represents a potentially useful and general method for the enantioselective synthesis of cyclopropanes. This section deals with carbenoid reactions induced by chromium, iron, cobalt, and nickel complexes, palladium allyl carbonate intermolecular cyclopropanation or palladium allyl benzoate intramolecular S_N2' three-membered-ring cyclization, deformylation with rhodium complex, oxidation with titanium complex, or the formation of stable chiral cyclopropyl copper.

On heating enantiomerically pure methylphenyl-*n*-propylphosphine **149** and (phenylmethoxycarbene)-pentacarbonylchromium (**150**) in benzene a cis–trans mixture of chromium complex **151** was obtained, from which the cis isomer was isolated by liquid chromatography on silica gel (eq 51).

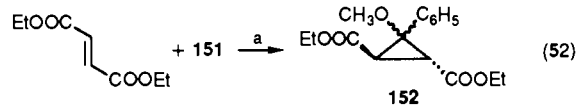


(51)

(a) C_6H_6, 40 °C.

A solution of optically active tetracarbonylchromium complex **151** in diethyl fumarate was heated at 60 °C to yield diethyl *trans*-2,3-dicarbethoxy-1-methoxy-1-phenylcyclopropane (**152**) (eq 52).

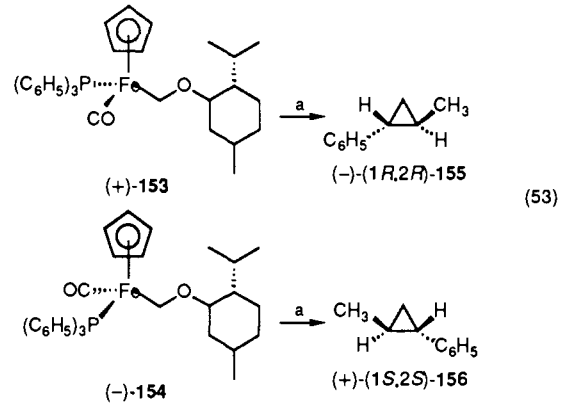
Isolation of optically active cyclopropane **152** demonstrated that the three-membered ring was formed by transfer of carbene within the metal complex; therefore no *free carbene* was involved in the reaction.[100]



(52)

(a) 60 °C, 24 h, liquid chromatography on SiO_2.

From (η^5-cyclopentadienyl)(η^1-methoxymethyl)dicarbonyliron were prepared and separated by fractional recrystallization the diastereomeric iron complexes (+)-**153** and (−)-**154**. Cleavage of (+)-**153** with HBF_4 in a neat solution of *trans*-1-phenylpropene gave *trans*-(1*R*,2*R*)-1-methyl-2-phenylcyclopropane (**155**) with 26% ee, while under the same conditions (−)-**154** provided mainly *trans*-cyclopropane (1*S*,2*S*)-**156** with 38.5% ee (eq 53).[101]



(53)

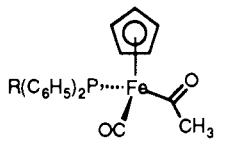
(a) HBF_4, (*E*)-$C_6H_5CH{=}CHCH_3$.

The synthetic utility of the reaction of alkenes with electrophilic, cationic carbene complexes of general structure $Cp(CO)_2Fe{=}CRR'^+$ has been demonstrated for the preparation of cyclopropane.[102] Moreover, chiral carbene complexes of the type $Cp(CO)(L)Fe{=}CHR^+$ also have general utility for the enantioselective cyclopropane synthesis. Effectively, chromatographic separation (silica gel) of the diastereomeric acyl complexes ($S_{Fe}S_C$)- and ($R_{Fe}S_C$)-Cp(Co)(Ph_2R^*P)$FeCOCH_3$, where R* = (*S*)-2-methylbutyl, gave a solid diastereomer (*SS*)-**157** (purified to 99:1 *SS*/*RS*) and an oily diastereomer (*RS*)-**158** (96:4 *RS*/*SS*).

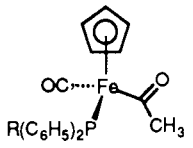
Acyls (*SS*)-**157** and (*RS*)-**158** were converted in 90% yield to the corresponding α-ethers (*SS*)-**159** and (*RS*)-**160** by successive treatment with methyl triflate in CH_2Cl_2, reduction with BH_4^- in methanol, and alkylation with sodium methylate in methanol. Then treatment with trimethylsilyl triflate in the presence of styrene resulted in the in situ generation of the cations (*SS*)-**161** or (*RS*)-**162** followed by transfer of ethylidene to give 3.5:1 and 4:1 ratios of *trans*- to *cis*-1-methyl-2-phenylcyclopropanes in 75% yield. Separation by gas chromatography gave a 99% pure sample of the cyclopropanes *cis*-(1*R*,2*S*)-**163a** (84% ee), *trans*-(1*R*,2*R*)-**155** (88% ee), *cis*-(1*S*,2*R*)-**163b** (77% ee), and *trans*-(1*S*,2*S*)-**156** (83% ee).

The fact that (*SS*)-**161** and (*RS*)-**162** gave cyclopropanes of *opposite* configuration in almost identical purities indicated that the chirality at the *iron* was primarily responsible for the asymmetric induction and that the phosphine chirality had played little or no role, demonstrating the potential for control by the metal configuration in the enantioselective catalysis.[102]

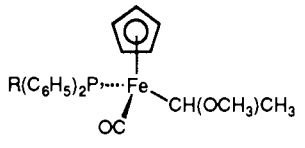
The cobalt catalyst $Co(\alpha\text{-CQDO})_2(H_2O)$ (**165**) was prepared by reaction of (+)- or (−)-camphorquinone



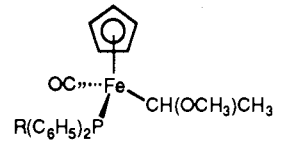
(SS)-157



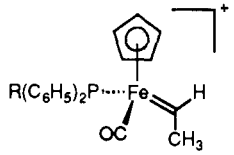
(RS)-158



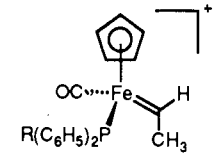
(SS)-159



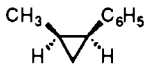
(RS)-160



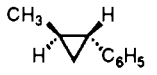
(SS)-161



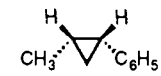
(RS)-162



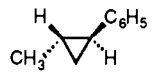
cis-(1R,2S)-163a



trans-(1R,2R)-155

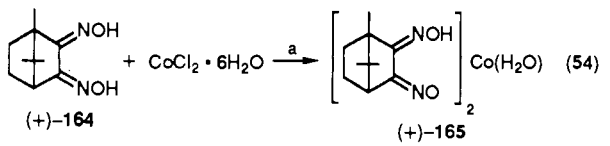


cis-(1S,2R)-163b



trans-(1S,2S)-156

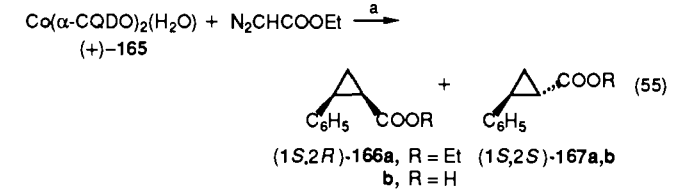
α-dioxime (164) with cobalt(II) chloride hexahydrate in alkaline aqueous ethanol in 73% yield (eq 54).



(+)-164 (+)-165 (54)

(a) EtOH, NaOH, 73%.

Carbenoid reaction of ethyl diazoacetate using bis[camphorquinone dioximato]cobalt(II) ((+)-165) as catalyst with styrene led to a 1:1 mixture of *cis*-166a and *trans*-167a, which were separated by preparative gas chromatography (eq 55).[103a,b]



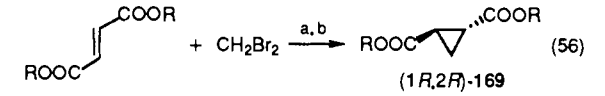
(1S,2R)-166a, R = Et (1S,2S)-167a,b
b, R = H

(55)

(a) Styrene, 10 °C, 91%.

Acid hydrolysis led to cis acid (1S,2R)-166b and trans acid (1S,2S)-167b with 68 and 75% diastereomeric excess, respectively. Achiral olefins such as 1,1-diphenylethylene, under the same conditions, led to (+)-(S)-ethyl 2,2-diphenylcyclopropanecarboxylate with 70% ee. The catalytic reaction involved the coordination of diazoacetate to Co(II), the formation of a cobalt(II)–carbene species,[104] olefin attack on the cobalt(II)–carbene species, and the decomposition of a cobaltacyclobutane intermediate releasing the cyclopropane. The stereochemical environment around the metal involving rather bulky peripheral groups was considered to be required not only for effective chiral recognition but also for the high chemical yield and regioselectivity in the catalysis.[103c]

The enantioselective Simmons–Smith reactions employing chiral olefins, methylene iodide, and Zn–Cu couple, Zn–Ag couple, or diethylzinc were discussed in section III.2. However, when methylene bromide was added to a mixture of dimenthyl fumarate ((–)-168a), cobalt chloride, zinc, and NaI in acetonitrile, *trans*-(1R,2R)-1,2-cyclopropanedicarboxylic acid (169) was isolated after hydrolysis in 18 and 70% chemical and optical yields, respectively (eq 56).



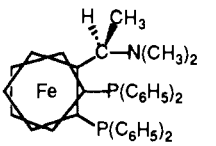
(–)-168a, R = (–)-menthyl
b, R = (–)-bornyl
c, R = (+)-bornyl

(1R,2R)-169 (56)

(a) $COCl_2(NiBr_2)$, Zn, NaI, CH_3CN, room temperature. (b) KOH, $EtOH/H_2O$, 9:1, 18%.

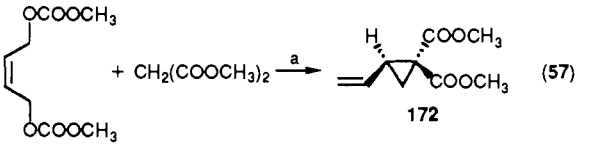
(–)- or (+)-dibornyl fumarates 168b,c induced lower enantioselectivity, 39 and 47%, respectively. On the other hand, reaction of dimenthyl fumarate (–)-168a with nickel complex (from $NiBr_2$) led to diacid 169 (R = H) with 27% ee only. The asymmetric selection may be due to preferential coordination of a face of the chiral fumarate onto the metal center, where the chirality was determined by the coordination of an another molecule of the chiral fumarate.[104]

The palladium catalyst prepared in situ by mixing $Pd_2(dba)_3(HCCl_3)$ and (R)-N,N-dimethyl-1-[(S)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine [(R)-(S)-BPPFA] (170) was found to be most effective to give



(R)-(S)-BPPFA-170

rise to optically active vinylcyclopropanes. Effectively, the reaction of dimethyl (Z)-2-butenylene dicarbonate (17) with dimethyl malonate catalyzed by (R)-(S)-BPPFA/Pd (170) provided in 24% yield dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 172 with 67% ee; 172 is a useful building block for the synthesis of steroids, prostaglandins, and jasmonate (eq 57).[105]



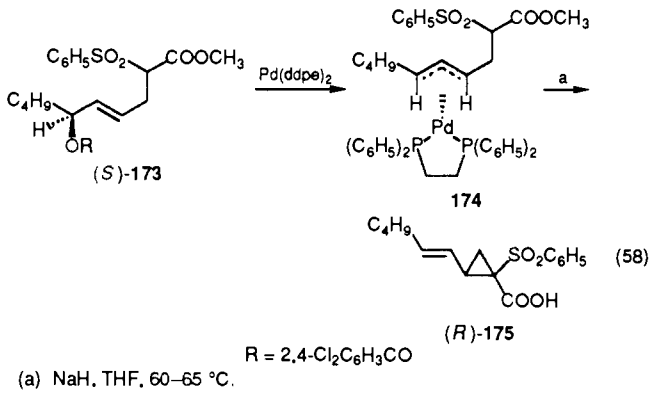
171 172 (57)

(a) (R,S)-BPPFA/Pd, THF, 0 °C, 24%.

Prolonged reaction time, i.e., 24 h, lowered the enantiomeric purity to 30% ee, which indicated that the cyclization forming vinylcyclopropane was reversible and that the diastereomeric π-allyl complex intermediate underwent epimerization faster than cyclization. Reaction of methyl acetylacetate or acetylacetone with 171 proceeded in a different way to give optically active 5-vinyl-4,5-dihydrofuran derivatives in 35–70% yield. Other chiral phosphine–palladium catalysts including chiraphos[106] and BINAP[107] were much less active or less stereoselective.

The optically active functionalized-allylic benzoate (+)-(S)-173 (85% ee) underwent palladium-promoted S_N2' cyclization with 90% transfer of chirality upon treatment with NaH in refluxing THF to afford vi-

nylcyclopropane (*R*)-**175** in 80% yield (eq 58).



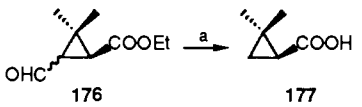
(*S*)-**173** **174** (*R*)-**175** (58)

R = 2,4-$Cl_2C_6H_3CO$

(a) NaH, THF, 60–65 °C.

This strategy involved the palladium attack of the double bond of the allylic substrate opposite the leaving benzoate group with formation of chiral palladium species **174** followed by nucleophilic attack from the face η^3-allyl opposite the palladium, which allowed a net syn S_N2' replacement of the benzoate by the new C–C bond in cyclopropane (*R*)-**175**. (*E*)-Vinylcyclopropane (*R*)-**175** was used for the enantioselective syntheses of (+)-dictyopterenes A and C′, isolated from Hawaian seaweed and which exhibit remarkable physiological activities.[108]

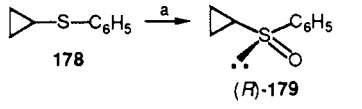
Deformylation of optically active 2-formylcyclopropanecarboxylic acid gave the corresponding optically active carboxylic acid. Thus, when a solution of ethyl (–)-chrysanthemate in ethyl acetate was saturated with ozone and then treated with dimethyl sulfide, ethyl 3,3-dimethyl-2-formylcyclopropanecarboxylate **176** was obtained in 91% yield; then **176** was refluxed with $RhCl(PPh_3)_3$ in toluene to give in 80% yield 2,2-dimethylcyclopropanecarboxylic acid **177** with 96.6% ee (eq 59).[109]



176 **177** (59)

(a) $RhCl(OPh_3)_3$, toluene, reflux, 86%.

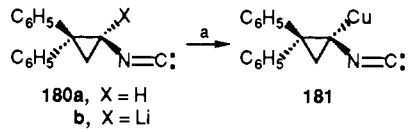
Chiral sulfoxides play an important role in synthesis and were found as natural products with defined stereochemistry at sulfur, so asymmetric oxidation of sulfides became of preparative value. The titanium complex reagent prepared from Ti(O-*i*-Pr)$_4$/(+)-diethyl tartrate (DET)/H_2O/*t*-BuOOH (1:2:1:1)[110] was specific for sulfide oxidation but did not epoxidize allylic alcohols, showing a completely different reactivity pattern with the Sharpless reagent Ti(O-*i*-Pr)$_4$/(+)-DET/*t*-BuOOH (1:1:2).[111] Thus, among others, cyclopropyl phenyl sulfide (**178**) was oxidized in 73% yield into cyclopropyl phenyl sulfoxide (*R*)-**179** with 95% ee (eq 60).[110] (For a ring expansion of cyclopropyl sulfoxide, see section III.1 (eq 22).)



178 (*R*)-**179** (60)

(a) Ti(O-*i*-Pr)$_4$–DET–H_2O–*t*-BuOOH, 1:2:1:1, CH_2Cl_2, –20 °C, 73%.

1-Lithio-1-isocyano-2,2-diphenylcyclopropane **180b**, generated from chiral cyclopropane (+)-(*S*)-**180a** by reaction with lithium diisopropylamide, was capable of maintaining its configuration at temperatures between –52 and –72 °C but was racemized at –5 °C. Treatment of (+)-**180b** with cuprous iodide produced the stable chiral cyclopropylcopper **181**, which was hydrolyzed with water to regenerate (+)-(*S*)-**180a** with 95% ee (eq 61).[112]



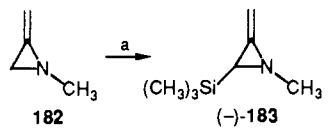
180a, X = H **181** (61)
b, X = Li

(a) CuI, THF, –72 °C.

5. Photochemical and Thermal Synthesis

The section is concerned with the thermal rearrangement of optically active methyleneaziridine, the thermal and photochemical decomposition of (–)-menthyl pyrazolinecarboxylate, the irradiation of diazofluorene and diazodiphenylmethane in the presence of bis(1-bornyl) fumarate, the photoinduced diastereoselective isomerization of cyclopropanes, the cyclopropane irradiation in the presence of optically active photosensitizers, and the photolysis of a cyclopropene derivative.

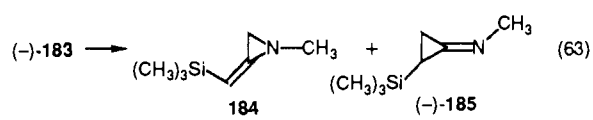
Optically active methyleneaziridine (–)-**183** was synthesized in 36–48% yield by lithiation of aziridine **182** using *sec*-butyllithium in pentane in the presence of (+)-(*S*,*S*)-1,4-bis(dimethylamino)-2,3-dimethoxybutane[(+)-DDB] as an auxiliary chiral agent[113] and subsequent reaction with chlorotrimethylsilane. Integration of the trimethylsilyl ^1H NMR signals in benzene using Pr(facam)[114] as shift reagent revealed an enantiomeric excess of 12.4 ± 1% (eq 62).



182 (–)-**183** (62)

(a) *sec*-BuLi, pentane, –125 °C, (+)-DDB, 36–48%.

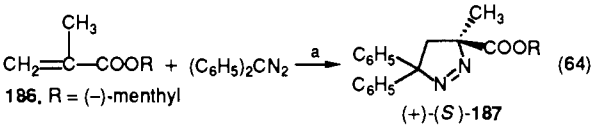
Thermolysis of (–)-**183** afforded diastereomeric methyleneaziridine **184** and cyclopropanimines (–)-**185** with constant isomeric ratios (*E*)-**184**:(*Z*)-**184** = 86:14 and (*E*)-**185**:(*Z*)-**185** = 56:44, respectively (eq 63).[115]



184 (–)-**185** (63)

Only imine **185** was optically active; its rotation was indicative of a high degree of stereospecificity for the methyleneaziridine–cyclopropanimine rearrangement (–)-**183** → (–)-**185**, with inversion of configuration as in the thermal isomerization of methylenecyclopropanes.[116]

When solid diphenyldiazomethane was mixed with menthyl methacrylate (–)-(1*R*,2*S*,5*R*)-**186**,[117b] solid pyrazoline (+)-(*S*)-**187** was obtained in 25% yield with an enantiomeric excess of 94.3% (eq 64).

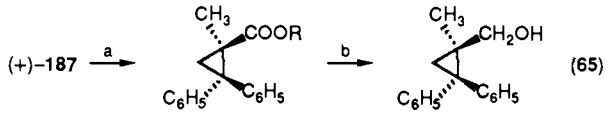


186, R = (–)-menthyl (+)-(*S*)-**187** (64)

(a) 0 °C, –15 °C for 5 days, 25%.

Thermal decomposition of (*S*)-**187** was carried out at 50 °C to produce diphenylcyclopropane (–)-(*R*)-**188** in

quantitative yield, whatever the polarity of the solvent (methylcyclohexane or dimethylformamide). Lithium aluminum hydride reduction of (*R*)-**188** led to diphenylcyclopropane (*R*)-**189** with an enantiomeric excess of 70%. Therefore, thermolysis of pyrazoline (+)-(*S*)-**187** proceeded with 85% retention of configuration (eq 65).

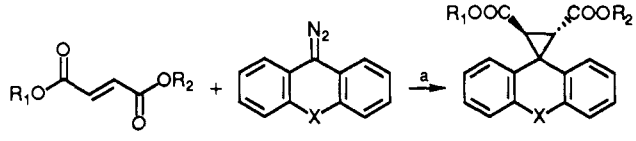


(+)-**187** —a→ (−)-(*R*)-**188** —b→ (−)-(*R*)-**189** (65)

(a) Methylcyclohexane or dimethylformamide, 50 °C, 100%. (b) $LiAlH_4$, Et_2O, reflux, 80%.

Photochemical decomposition of pyrazoline (*S*)-**187** (λ_{max} = 330 nm) in methylcyclohexane using a high-pressure mercury lamp and a Pyrex filter led to menthyl ester (*R*)-**188** in 79% yield and to 1,1-diphenylethylene (13%). The rotation of (*R*)-**188** showed that this reaction proceeded with over 95% retention of configuration. Irradiation in the presence of benzophenone as photosensitizer produced mainly olefinic products from fragmentation.[117] A stereo- and enantioselective synthesis of *cis*-chrysanthemic acid menthyl esters (97% ee) based on the sensitized photochemical decomposition of a dihydropyrazole prepared by the 1,3-dipolar addition of 2-diazopropane on an optically active butenolide (98% ee) has illustrated the efficiency of this route.[117d]

When an acetonitrile solution of fumarates **190a–c** containing either diazofluorene **191a** or diazodiphenylmethane was irradiated using 0.1 M K_2CrO_4 filtered Hanovia light, diarylcyclopropanes **192a,b** were formed in 20–35% yields (eq 66).[118]



190a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; R_2 = (−)-bornyl
c, $R_1 = R_2$ = (−)-bornyl

191a, X = —
b, X = H,H

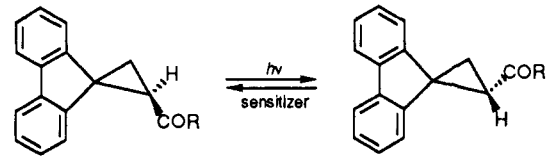
192a,b (66)

(a) CH_3CN, *hν*, 0 °C, 20–35%.

The (−)-bornyl esters were hydrolyzed in aqueous HCl and reesterified with diazomethane to yield *trans*-dimethyl 3,3-diarylcyclopropane-1,2-dicarboxylates **192a,b** (R_1, R_2 = Me).[119] The enantiomeric excesses (1.30 and 1.56) determined by NMR using the chiral shift reagent $Eu(hfc)_3$[34] showed that with both diarylcarbene precursors, the asymmetric induction produced with the two (−)-bornyl chiral groups was nearly the same as that produced with only one (1.26 and 1.49). It was concluded that the reactive intermediates were triplet fluorenylidene or diphenylmethylene carbenes which were added to fumarates **190a–c** in a nonconcerted fashion.[118]

Photochemically induced asymmetric transformation between diastereoisomers in equilibrium was obtained in the isomerization of (+)-(*R*)-*N*-α-(arylethyl)-fluorene-9-spiro-1′,1′-cyclopropane-2′-carboxamide derivatives **193a,b**.

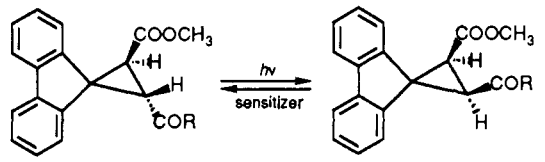
Irradiation of a benzene solution of an equimolar mixture of diastereomers **193b** derived from (+)-(*R*)-α-(1-naphthyl)ethylamine in the presence of acetophenone entailed a change of the diastereomeric ratio of (+)-**193b** to (−)-**194b**, which reached a constant value of 64:36 as determined by HPLC. Regardless of whether one started from pure (+)-**193b** or pure (−)-**194b**, the same diastereomer ratio was obtained. After acidic hydrolysis and reesterification, optically active (+)-**193a** was obtained with 28% ee. Furthermore, the diastereomer ratios were sensitizer dependent and increased from 28% (acetophenone) to 72% (*p*-phenylacetophenone) diastereomeric excess as the triplet energy of the sensitizer decreased, which strongly suggests that energy transfer from the sensitizers to (+)-**193b** was the key step for the diastereoselective isomerization.



(+)-**193a**, R = CH_3O
b, R = (*R*)-(+)-CH_3CH(1-naphthyl)NH

194

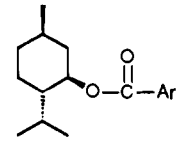
With cyclopropylcarboxamide derivatives **195b** the trans:cis diastereomeric ratio at the photostationary state was 99.6:0.4 and recovery of the trans isomer exceeded 80%. This diastereoselectivity, also sensitizer dependent, was highest with *p*-phenylacetophenone. Acidic hydrolysis and subsequent methylation gave optically active **195a** with 94% ee.[120]



(+)-**195a**, R = CH_3O
b, R = (*R*)-(+)-CH_3CH(1-naphthyl)NH

196a,b

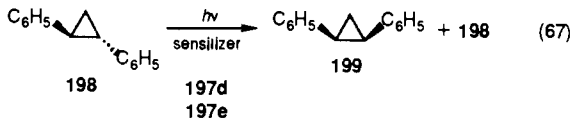
Irradiation of *trans*-1,2-diphenylcyclopropane (**198**) in the presence of optically active sensitizers such as the *p*-menthyl benzoates **197a–e** in acetone or benzene solution resulted in a cis:trans mixture of **198** and **199** of varying composition, depending on sensitizer and solvent, in which one of the enantiomers of the trans isomer was preferentially formed.



197a, Ar = *o*-benzoylphenyl
b, Ar = *o*-acetylphenyl
c, Ar = *m*-benzoylphenyl
d, Ar = *m*-acetylphenyl
e, Ar = naphthyl

Thus, for instance, a solution of *trans*-1,2-diphenylcyclopropane (**198**) and about 0.1 equiv of sensitizer **197d** was irradiated and the reaction monitored by gas chromatography. After 180 h a 70:30 cis:trans ratio of cyclopropanes **199** and **198** was obtained, whereas irradiation in the presence of **197e** for 144 h gave a 40:60 cis:trans ratio; the enantiomeric excess of trans isomer **198** was 8 and 6.8%, respectively (eq 67).[121]

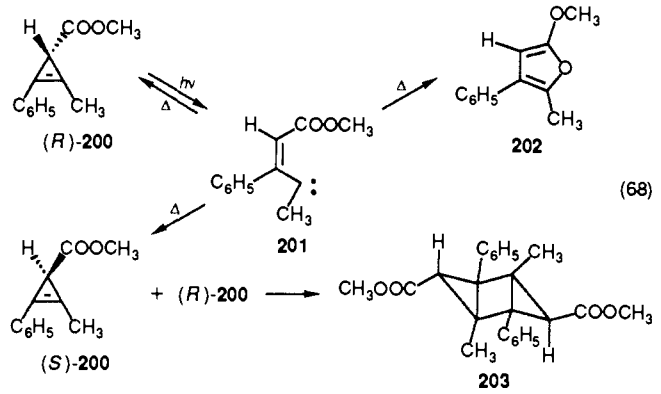
Photolysis of optically active methyl cyclopropenecarboxylate (*R*)-**200** (76% ee), readily available from the corresponding resolved cyclopropanecarboxylic acid with (−)-ephedrine (see section II.2) and esterification



(67)

(a) 197d, hν, 180 h (70:30 199:198) or 197e, hν, 144 h (40:60 199:198).

with 1-methyl-3-*p*-tolyltriazine, was monitored by gas chromatography. When ester (*R*)-**200** was irradiated in acetonitrile, 2-methoxy-5-methyl-4-phenylfuran (**202**) was obtained in 75% yield. After 10, 16, and 25% conversion, cyclopropene (*R*)-**200** was reisolated by TLC and its enantiomeric composition was determined, showing 29, 39, and 56% of racemization, respectively. On the other hand, sensitized photolysis of optically active (*S*)- and (*R*)-**200** in acetone led to tricyclic dimer **203** in 51% yield with no indication of photochemical racemization (eq 68).



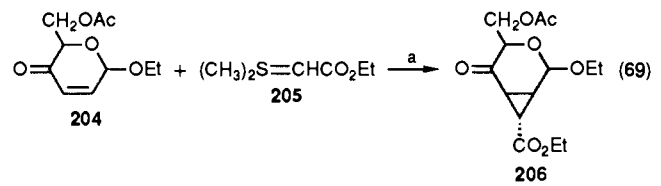
(68)

The photochemistry of cyclopropene derivatives appeared to be remarkably dependent on the multiplicity of the excited state involved.[122] Singlet states reacted only by σ-bond cleavage by intervention of the vinylcarbene intermediate **201**. Dimer **203** could only be formed by reaction of two cyclopropenes of opposite configuration: (*R*)-**200** and (*S*)-**200**. Therefore each time a dimer **203** was formed, the rates of disappearance of (*R*)- and (*S*)-**200** were the same and the *R*:*S* ratio in the unreacted cyclopropene remained constant.[123]

IV. From Natural Precursors

Optically active cyclopropanes have been prepared from naturally occurring carbohydrates, citronellal, (−)-β- and (+)-α-pinenes, (+)-carvone, (+)-3-carene, and (−)-car-3-en-5-one. The reactions involved cyclopropanation with sulfuranylidene, phosphoranylidene, or Cu–Zn couple and CH_2I_2, base-induced cyclization of epoxide, or the degradation of natural three-membered-ring compounds.

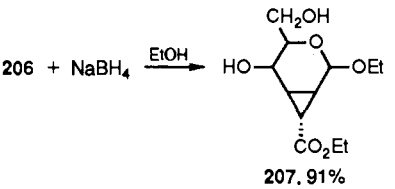
Carbohydrates have been used as chiral synthons for the construction of carbocycles. Thus, α-D-allopyranosides **204**[124a] underwent cyclopropanation with ethyl (dimethylsulfuranylidene)acetate (**205**)[124b] in dry benzene to yield pyranoside **206** in 64% yield (eq 69).[125]



(69)

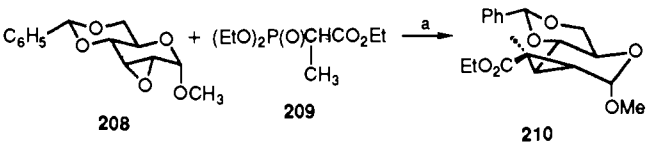
(a) C_6H_6, 64%.

Reduction of **206** with sodium borohydride occurred stereoselectively to give in 91% yield crystalline α-D-talopyranoside (**207**) (eq 70).



(70)

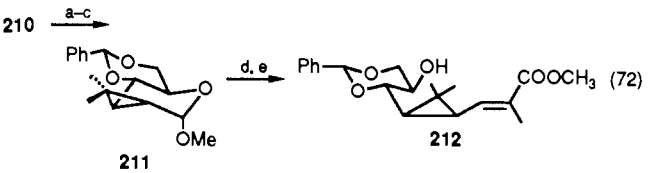
Accordingly, anhydro sugar **208** was treated with an excess of phosphonopropionate **209** and NaH in dioxane at 160 °C to produce α-D-mannopyranoside **210**, exclusively, in 50% yield (eq 71).



(71)

(a) NaH, dioxane, 160 °C, 50%.

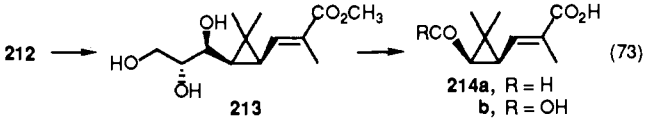
Then reduction with lithium aluminum hydride of the methyl carboxylate, treatment with methanesulfonyl chloride in DMF, and reduction of the corresponding chloride with $LiAlH_4$ gave *gem*-dimethyl derivative **211** in 89% yield (eq 72).



(72)

(a) $LiAlH_4$, Et_2O, room temperature, 97%. (b) CH_3SO_2Cl, DMF, NEt_3, room temperature, 92%. (c) $LiAlH_4$, THF, reflux, 88.5%. (d) H_2O, dioxane, reflux, 98%. (e) $(C_6H_5)_3P{=}C(CH_3)COOMe$, CH_2Cl_2, room temperature, 93%.

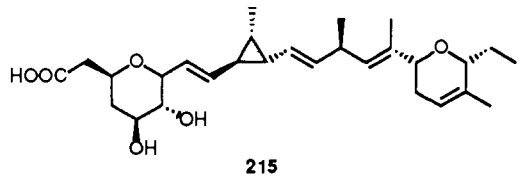
Hydrolysis of the glycosylic methoxyl of **211** in refluxing aqueous dioxane (98% yield) and treatment with methyl 2-(triphenylphosphoranylidene)propionate gave only the *E* isomer of α,β-unsaturated ester **212** in 93% yield. Cleavage of the benzylidene protecting group, effected with methanol and *p*-toluenesulfonic acid, and treatment of the resulting triol **213** with sodium metaperiodate produced cis aldehyde (+)-**214a** in 84% yield for the two steps. Finally, oxidation with silver oxide and sodium hydroxide hydrolysis provided the desired chrysanthemum dicarboxylic acid (+)-**214b** (eq 73).



(73)

The synthesis of levorotatory enantiomer (−)-**214b** was effected enantiospecifically from the same aldehydo sugar derived from **211**. The overall yields from D-allopyranoside **208** were 27% in 10 steps for the (+) enantiomer and 24% for the (−) enantiomer.[125]

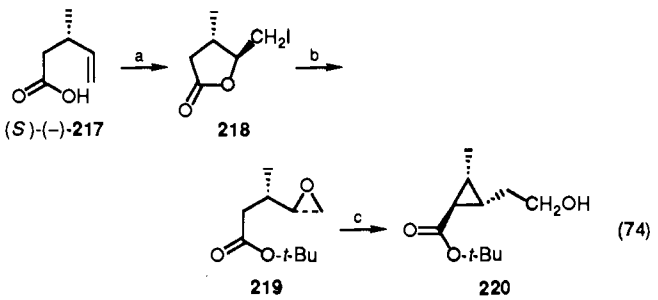
The absolute configuration of ambruticin (**215**), an orally active antifungal agent isolated from the myxobacterium *Polyangium cellulosum fulvum*, was determined by the synthesis of optically active cyclopropane **216** and comparison to a degradation product of the natural material.



215

216

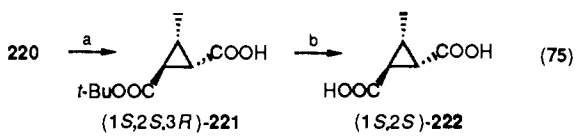
Optically active (−)-(*S*)-butenoic acid (**217**) was prepared as reported from (*R*)-citronellal;[126] then treatment with iodine in acetonitrile gave predominantly the thermodynamically more stable trans iodo lactone **218** (trans:cis ratio 20:1), which was converted to epoxide **219** with lithium *tert*-butoxide in THF. The cyclization of **219** was carried out with lithium diisopropylamide to give only *trans*-cyclopropane **220** in 50% overall yield from acid **217** (eq 74).



(*S*)-(−)-**217** **218** **219** **220** (74)

(a) I_2, CH_3CN, 4 °C, 75%. (b) LiO-*t*-Bu, THF, 0 °C, 70%. (c) LDA, THF, −78 °C, 90%.

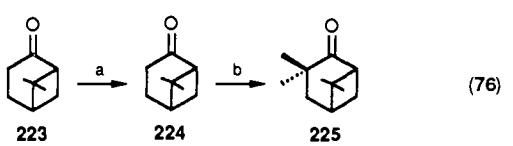
Oxidation with Jones reagent gave *tert*-butyl cyclopropanecarboxylate (+)-(1*S*,2*S*,3*R*)-**221**; then hydrolysis with trifluoroacetic acid led to dicarboxylic acid (+)-(1*S*,2*S*)-**222**, which was spectroscopically identical with the degradation product (ozonolysis) of natural ambruticin (**215**) (eq 75).[127]



(1*S*,2*S*,3*R*)-**221** (1*S*,2*S*)-**222** (75)

(a) Jones reagent (excess), 20 °C, 60%. (b) TFA, 20 °C, 90%.

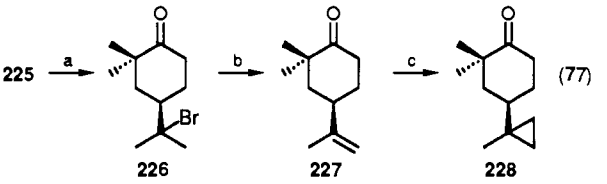
(+)-Nopinone (**224**), available in large quantities by ozonolysis of natural (−)-β-pinene (**223**) in methanol, is a convenient and versatile starting material with known absolute configuration and reliable data on the enantiomeric purity.[128] It can be alkylated α to the ketone group to give either the thermodynamically less stable exo monoalkylated isomer or the dialkylated derivative **225** (eq 76).



223 **224** **225** (76)

(a) O_3, MeOH, −78 °C. (b) LDA, THF, CH_3I, 65%.

Treatment of (+)-3,3-dimethylnopinone (**225**) with BBr_3[129] in CH_2Cl_2 gave (+)-(*R*)-bromocyclohexanone **226** in 77% yield, which was treated with potassium triethylmethoxide to yield (+)-(*R*)-2,2-dimethyl-4-isopropenylcyclohexanone (**227**) (eq 77).

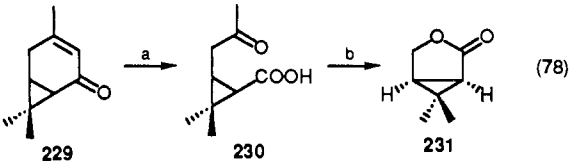


225 **226** **227** **228** (77)

(a) CH_2Cl_2, BBr_3, −78 °C, 77%. (b) $KOC(C_2H_5)_3$, $HOC(C_2H_5)_3$, 0 °C, 80%. (c) Zn, Cu_2Cl_2, CH_2I_2, Et_2O, 46%.

Reaction of olefin (+)-**227** with CH_2I_2 in the presence of zinc–copper couple formed in situ (see section III.2) resulted in formation of (+)-(*R*)-cyclopropylcyclohexanone **228** (eq 77).[130]

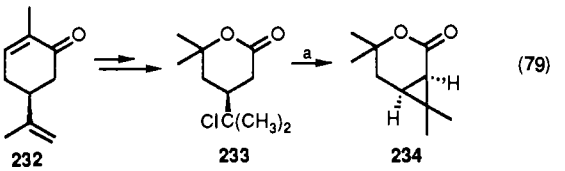
Optically active γ-lactone **231** is a useful intermediate for pyrethroid insecticide synthesis. It is prepared from (−)-car-3-en-5-one (**229**); thus, oxidation of **229** with $KMnO_4$ in HOAc–H_2O gave (−)-cyclopropanecarboxylic acid **230**, which was oxidized with *m*-chloroperbenzoic acid (85%) in CH_2Cl_2 to yield γ-lactone **231** in 85% yield (eq 78).[131]



229 **230** **231** (78)

(a) $KMnO_4$, HOAc–H_2O, 75%. (b) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 85%.

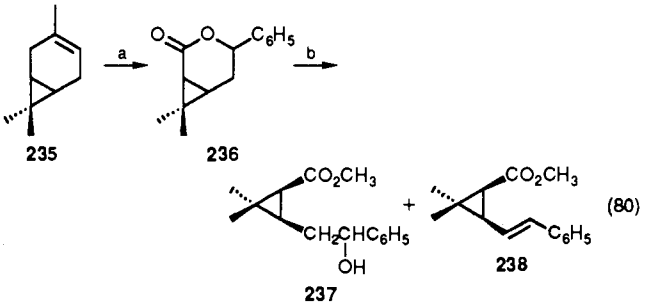
Prepared in many steps from (+)-carvone **232**, lactone **233** was cyclized by action of LDA to offer optically active chrysanthemolactone (1*S*,3*R*)-**234** in 97% yield (eq 79).[132]



232 **233** **234** (79)

(a) LDA, THF, −78 °C, 97%.

Some optically active (1*R*)-*trans*-pyrethroids have been prepared from naturally occurring (+)-3-carene. Thus, heating the δ-lactone of cyclopropanecarboxylic acid (1*S*)-**236**, prepared from (+)-3-carene (**235**),[133a] with KOH in ethylene glycol gave, after esterification with diazomethane, methyl cyclopropanecarboxylate **237** and dehydration product **238**. Dehydration of **237** with *p*-toluenesulfonic acid led to vinylcyclopropane **238** (eq 80).[133b]



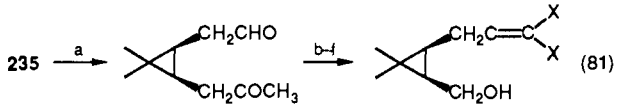
235 **236** **237** **238** (80)

(a) Reference 133a. (b) KOH, $HOCH_2CH_2OH$; CH_2N_2. (c) *p*-TsOH, C_6H_6, reflux.

For other optically active photostable pyrethroids from (+)-3-carene, see ref 133c.

Some optically active esters of (2,2-dimethyl-3-*n*-propylcyclopropyl)carbinol and cyclopropylcarboxylic

acids exhibited miticidal activity against tuber potato and red spider mites as well as pink and purple mites of tea plantations. The corresponding compounds with halogen substituents have been prepared from (+)-3-carene. Thus, cyclopropanecarboxyaldehyde **239** prepared from (+)-3-carene[133c] was successively treated with tribromomethyl carbanion, acetic anhydride in pyridine, and zinc/acetic acid to lead after Baeyer–Villiger oxidation and saponification to *cis*-cyclopropylcarbinol (1*S*,3*R*)-**240a**. Analogous reactions with trichloromethyl carbanion provided compound **240b** (eq 81).[134]



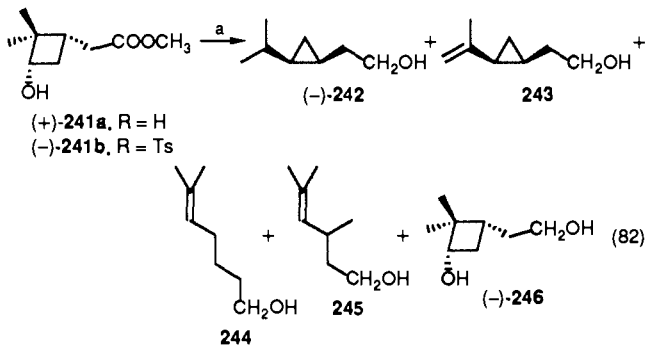
(81)

(a) Reference 133c. (b) $CHBr_3$ (or $CHCl_3$), KO-*t*-Bu, −20 °C, 35%. (c) Ac_2O, pyridine. (d) MCPBA. (e) Zn/AcOH, ether, 0 °C. (f) KOH–MeOH.

V. Ring Contraction

Optically active cyclobutanols from natural α-pinene, 1,2-cyclobutanediones from acyloin condensation of succinates prepared by stereocontrolled alkylation of oxazolidinones, and α-chlorocyclobutanones from resolution with chiral amines have undergone the highly stereospecific $C_4 \rightarrow C_3$ ring contractions reported in this section.

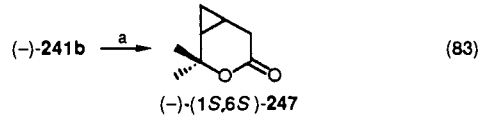
Stereocontrolled transformation (oxidations) of α-pinene provided optically active cyclobutane (+)-(1*S*,3*S*)-**241a**. Its *p*-toluenesulfonate (−)-**241b** underwent stereospecific $C_4 \rightarrow C_3$ ring contraction upon reduction with different hydride reagents ($LiAlH_4$, $NaBH_4$, $LiEt_3BH$) to yield mainly cyclopropylcarbinol (−)-(1*S*,2*R*)-**242** (60–88%) together with alcohols **243–245** (12–40%) and cyclobutanediol **246** (trace to 29%) (eq 82).



(82)

(a) $LiAlH_4$, ether, room temperature, 64%; $NaBH_4$, diglyme, 70 °C, 38%; $NaBH_4$, DME, 31%; $LiEt_3BH$, THF, 65 °C, 50%.

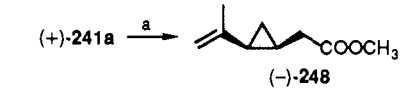
On the other hand, hydrolysis of (tosyloxy)cyclobutane (−)-**241b** in aqueous dimethoxyethane led to bicyclo[4.1.0] lactone (−)-(1*S*,6*S*)-**247** in 62% yield (eq 83).



(83)

(a) DME, $Zn(OAc)_2$, reflux, 62%.

More useful from the synthetic point of view, dehydration of cyclobutanol (+)-**241a** with phosphorus oxychloride in pyridine gave cyclopropylacetate (−)-(1*S*,2*S*)-**248** in 96% yield (eq 84).[135]

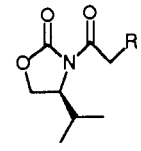


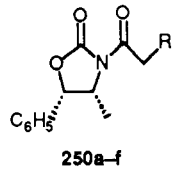
(84)

(a) $POCl_3$, C_5H_5N, 90 °C, 96%.

In all these ring contractions, the cyclopropane products were found to be optically active, suggesting some degree of stereospecificity. Furthermore, all of the three-membered rings produced represented the thermodynamically less stable cis isomers, thus pointing to kinetic rather than thermodynamic control. A concerted ionization rearrangement in which the 1,2-bond cleavage and the backside attack at the carbon of the four-membered rings **241** bearing the leaving group was facilitated by a favored 1,3-diequatorial conformation[136,137] was suggested to explain these results. In view of the ready availability of the optically active α-pinene in both enantiomeric forms as a source of chiral cyclobutyl synthons and the fact that the substituent groups of the optically active cyclopropanes **242**, **247**, and **248** can be further transformed into other functionalities, this $C_4 \rightarrow C_3$ ring contraction sequence provides a useful route to cyclopropane derivatives with defined stereochemistry and high enantiomeric purity.[135]

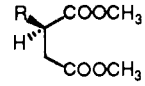
Chiral dimethyl 2-methylsuccinates, readily available from enzymic resolution, underwent sodium-induced acyloin cyclization into optically active cyclobutenes which after bromination underwent base-induced $C_4 \rightarrow C_3$ ring contraction (see section II.3, eq 8–11). Otherwise, N-acylation of the oxazolidinones prepared from L-valinol or (+)-(1*S*,2*R*)-norephedrine following the procedure of Evans[85] provided chiral imides **249a–f** and **250a–f**, which underwent high stereoselective enolization with either lithium or sodium hexamethyldisilylamide to form the corresponding *Z* enolates, respectively. After treatment with methyl bromoacetate and simple methanolysis were obtained the α-alkylsuccinates **251a–f** and **252a–f**.

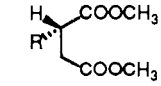




249a, R = CH_3
b, R = *i*-Pr
c, R = *t*-Bu
d, R = $CH_2CH_2OCH_2$-*p*-An
e, R = $CH_2CH_2OSi(CH_3)_2C(CH_3)_3$
f, R = $=CHCH_3$

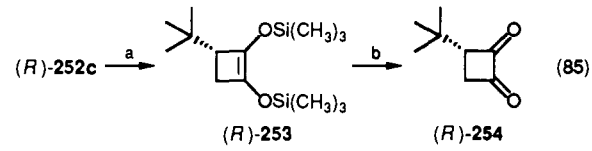
250a–f





251a–f **252a–f**

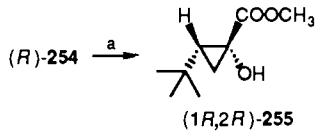
In fact by means of nondestructive and reusable chiral auxiliaries a variety of α-substituted succinates such as **251a–f** and **252a–f** of high optical purity (95–99% ee) are now available.[85c] As shown in section II.3, they provided optically active cyclopropanols of synthetic value. Thus, for instance, sodium-induced cyclization of succinate **252c** in the presence of $ClSiMe_3$ provided 3-*tert*-butyl-1,2-bis((trimethylsilyl)oxy)cyclobutene (*R*)-**253**, which upon bromination gave the first optically active (−)-(*R*)-3-*tert*-butylcyclobutane-1,2-dione **254** in 75% overall yield (eq 85).



(85)

(a) Na, $ClSiMe_3$, toluene, reflux, 87%. (b) Br_2, pentane, −60 °C, 86%.

The nonenolizable dione (*R*)-**254** then underwent base-induced $C_4 \rightarrow C_3$ ring contraction by sodium methoxide in methanol to provide in 91% yield, exclusively, cyclopropanecarboxylate (+)-(1*R*,2*R*)-**255**, with a diastereoselectivity >95% as shown by chiral capillary gas chromatography and ^1H NMR in the presence of chiral shift reagent $Eu(hfc)_3$[34] (eq 86).[85c]

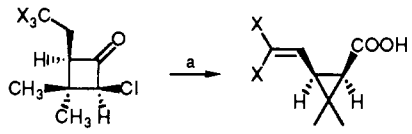


(86)

(a) MeONa, MeOH, room temperature, 91%.

Cyclopropanols such as **255** provided 1-donor-substituted cyclopropanes with carbonyl and vinyl groups whose synthetic applications have been discussed and reviewed (see ref 3).

cis-α-Chlorocyclobutanone (2*S*,4*R*)-**256a**, from [2 + 2] cycloaddition of (2,2,2-trichloroethyl)chloroketene with isobutene, has been resolved by means of the optically active amine salts of its sodium hydrogen sulfite adducts with (−)-(*S*)-1-phenylethylamine (see section II.2).[138] Upon treatment with 2.5 M aq NaOH **256** underwent $C_4 \rightarrow C_3$ ring contraction[2] to provide in 86% yield, after acidic hydrolysis, a mixture of *cis*-cyclopropanecarboxylic acid (+)-(1*R*,3*R*)-**257a** and its trans isomer (1*R*,3*R*) with a cis:trans ratio of 83:17 (eq 87).



(87)

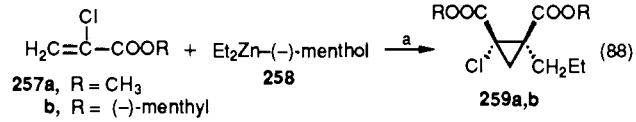
(a) 2.5 M aq NaOH, 0–100 °C; 10 M HCl.

The active insecticidal cyclopropanecarboxylic acid (1*R*,3*R*)-**257a** was separated by liquid chromatography. Cyclopropanecarboxylic acid (1*R*,3*R*)-**257b** was analogously obtained from **256a**.[138]

VI. Miscellaneous

This section describes the diethylzinc–menthol complex induced asymmetric cyclization of α-chloroacrylate, the tin hydride, lithium aluminum hydride, sodium aluminum hydride, and lithium or sodium metal reductions of optically active halocyclopropanes, the reaction of cyclopropyltin derivatives with bromine or iodine, and the electrochemical reduction of halocyclopropanes. The racemization of the less desirable enantiomers of cyclopropanecarboxylic acids was induced thermally, by Lewis acid, by sodium, or by UV irradiation. The formation of optically active polymers from cyclopropane derivatives and the computer simulation and comparison of the molecular dynamic patterns of (*R*), (*S*)-, and (*RS*)-cyclopropanes are also discussed in this section.

Methyl α-chloroacrylate **257a** underwent ring formation with ethylzinc chloride to form *cis*-1,2-cyclopropanedicarboxylate **259a**. Enantioselective synthesis was obtained when the 1:1.2 diethylzinc–(−)-menthol system **258**, prepared by adding Et_2Zn to (−)-menthol, was used to produce diester **259a** (eq 88).

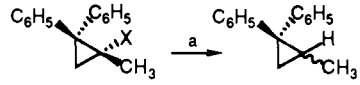


(88)

(a) C_6H_6, 80 °C, 10–52%.

On the other hand, the optically active ester of haloacrylic acid **257b** (R = (−)-menthyl), after hydrolysis of **259b** and esterification, led to **259a** with only a small enantioselectivity. The chiral center in the ester group was too distant from the chiral center to be produced to entail an effective chiral induction.[139]

Reductions of optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane **260b** with triphenyltin hydride, diphenyltin dihydride, and di-*n*-butyltin dihydride were carried out (eq 89).



(89)

(a) Neat $(C_6H_5)_3SnH$ (or n-Bu_2SnH_2, $(C_6H_5)_2SnH_2$), AIBN.

The product of reduction, **261**, was obtained with net inversion of configuration with $(C_6H_5)_3SnH$ and with net retention of configuration with n-Bu_2SnH_2; on the other hand, $(C_6H_5)_2SnH_2$ gave product with either inversion or retention, depending upon the concentration of the reducing agent. The dihydride concentration dependence in the di-*n*-butyltin dihydride reduction at high viscosity was also obtained; in this case the enantiomeric purity of the product increased as the concentration of reducing agent decreased until a limiting value of 5.9% ee was reached. These results were interpreted in terms of a cage reduction and the competition between rate of reduction, rotation, inversion, and diffusion.[140] Reduction of (−)-(*R*)-**260b** with tributyltin hydride and lithium luminum hydride occurred with racemization, whereas reduction with NaAlH(OMe)(OEt) gave retention of configuration. It was concluded that reduction by $LiAlH_4$ proceeded via a radical intermediate and most likely involved a single-electron-transfer mechanism (SET).[141]

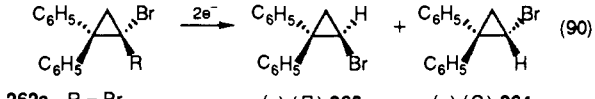
The reaction of lithium metal surfaces with 1-halocyclopropanes **260a–c** gave the corresponding lithium derivative, which was partially racemized. The amount of racemization observed was a function of the halide (I > Br > Cl), the Na content of the lithium metal, and its particle size.[142] The reduction with sodium–liquid ammonia led to optically active 1-methyl-2,2-diphenylcyclopropane with overall retention of configuration and two ring-opened products. The amount of enantiomeric purity observed was also dependent on the nature of the halogen, the concentration of the sodium in liquid ammonia solution, and a heterogeneity factor.[143]

The reaction of optically active (1-methyl-2,2-diphenylcyclopropyl)trimethyltin with bromine or iodine afforded 1-bromo(or iodo)-1-methyl-2,2-diphenylcyclopropane with a small degree of retention of configura-

tion, which was interpreted in terms of a radical mechanism.[144]

The electrochemical reduction of optically active cyclopropanes **260a–c** was investigated by using cyclic voltammetry, controlled-potential electrolysis, and stereochemical techniques. The controlled-potential electrolyses of the halides at a Hg electrode produced complex current–time relations, which were attributed to the formation of organomercurials. The amount of racemization observed as also a function of the halide; 63% retention and 53% retention were observed with bromide **260b** and iodide derivative **260c**, respectively.[145]

Bromo-2,2-diphenylcyclopropanes **262a–c** have undergone electrochemical debromination at the sp^3 prochiral C atom in the presence of strychnine or emetine adsorbed at a Hg cathode at pH 4.7 and 9.7. For instance, **262a** yielded as the major product 1-bromocyclopropane (−)-(*R*)-**263** with 25% ee. On the other hand, in the presence of adsorbed yohimbine in acetate buffer at pH 4.7, the asymmetric electrochemical reduction of **262** gave preferentially the enantiomer (+)-(*S*)-**264** (eq 90).[146]



(90)

262a, R = Br
b, R = COOH
c, R = $COOCH_3$

(−)-(*R*)-**263** (+)-(*S*)-**264**

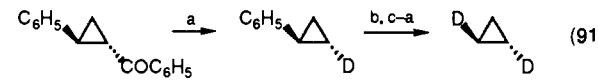
(a) NaOAc, HOAc, yohimbine, pH 4.7.

The ease of cleavage of the C–Br bond of **262a–c** was dependent on the nature of the supporting electrolyte cation, which also played a determining role in the stereoselectivity of the reduction. Thus, in acetate buffer in the presence of NH_4^+ cations, a preferential retention of configuration was observed: the more negative the working potential, the higher the retention (e.g., a ratio of 70% was observed with **262c**). By contrast, the presence of R_4N^+ cations gave rise to major inversion, the ratio of which did not depend on the working potential but increased with the bulkiness of the organic cation (e.g., a ratio of 60% in the case of **262c** with Bu_4N^+). In all cases, the proton-donating ability at the electrode was dependent on the nature of the interface.[147]

The less desirable (−) enantiomer of chiral 1-alkenylcyclopropanecarboxylic acid derivatives remaining after resolution was racemized by converting the acid into the acid chloride and then heating at either 80–300 °C[148] or 70–80 °C in the presence of a Lewis acid ($AlCl_3$, BCl_3) in an inert solvent (e.g., dioxane, hexane),[149] by heating with alkali metal (Na) in paraffin at 140 °C,[150] or by UV irradiation of the acid, ester, or amide in benzene in the presence of Me_2CHCH_2COPh or methyl phenyl ketone as photosensitizer.[151]

The rates of racemization and cis–trans isomerization of optically active cyclopropanes measured at 400 °C in a static system in the gas phase have indicated that an electrocyclic process proceeding through π-cyclopropane intermediates was energetically less favorable than a pathway involving stereoisomeric diradicals.[152] An optically active cyclopropene was thermally ring opened to give a vinylcarbene intermediate, which was easily recyclized to give the racemic cyclopropene despite the high strain energy of 50 kcal mol^{-1}.[153]

trans-2-Phenylbenzoylcyclopropane (1*R*,2*S*)-**265** underwent Haller–Bauer cleavage upon treatment with $NaND_2$ in benzene to give in 50% yield *trans*-2-deuteriophenylcyclopropane (1*S*,2*S*)-**266** with complete retention of enantiomeric purity (eq 91).



(91)

(1*R*,2*S*)-**265** (1*S*,2*S*)-**266** (1*S*,2*S*)-**267**

(a) $NaND_2$, C_6H_6, 80 °C, 56%. (b) O_3. (c) PhLi.

Ozonolysis of **266**, treatment of the resulting cyclopropanecarboxylic acid with phenyllithium, and reaction with $NaND_2$ led to *trans*-1,2-dideuteriocyclopropane (1*S*,2*S*)-**267**. Thermal stereomutation of (1*S*,2*S*)-**266** was characterized by the loss of optical activity and the approach to a 50:50 cis:trans equilibrium mixture, while pyrolysis of (1*S*,2*S*)-**267** at 422.5 °C resulted in isomerization to the cis isomer and in loss of optical activity. These results excluded a single methylene rotation and the intermediacy of a random biradical, and they were consistent with a pathway involving the opening and reclosure of an antisymmetric 0,0 trimethylene by synchronous rotation of two methylene groups.[154]

Optically active polymers have been obtained either by free radical polymerization of alkenylcyclopropane derivatives involving high selective ring opening or by addition of carbenes to double bonds of unsaturated polymers in the presence of optically active catalysts or asymmetry-promoting agents.[155] Optically active polyamides were obtained by copolymerization of *trans*-1,2-cyclopropanedicarboxylic hydrazide with aromatic tetracarboxylic acid dianhydrides in an amide solvent.[156] Chloromethylation of polystyrene gave a styrene–4-(chloromethyl)styrene, which, when treated with a tertiary amine, produced a macromolecular matrix with attached quaternary ammonium groups used to catalyze alkylations and cyclopropanations with good yields and selectivity. Asymmetric induction was observed when the tertiary amine was optically active or when one of the olefin components of the polymer matrix was optically active. Thus, both the polymer matrix and the quaternary ammonium center have participated in the catalysis.[157]

The liquid-phase molecular dynamic patterns of (*R*); (*S*)- and (*RS*)-*trans*-1,2-dimethylcyclopropanes have been simulated with a computer at 293 K and 1 bar and 13 kbar. Several indications were obtained; thus, the overall pattern of the molecular dynamics was greatly changed by application of the hydrostatic pressure, and intrinsic differences appeared in the molecular dynamic properties of the two enantiomers and of the racemic mixture. These differences resulted from the statistical correlation between single molecular rotation and translation.[158]

VII. Summary

Most of the current cyclopropanation reactions have been effectively tested to prepare chiral cyclopropane derivatives, and very often high enantiomeric excesses have been achieved.

First of all, cyclopropanes or their precursors have been resolved with optically active amines, acids, alcohols, or aldehydes. After recrystallization enantiomeric

excesses up to 98.5% have been obtained. The less desirable enantiomers remaining after resolution can then be racemized. Enzymic resolution and microbial oxidation or reduction of three-membered-ring precursors as well as enzymic resolution, hydrolysis, or oxidation of racemic cyclopropanes also provided enantiomerically pure small-ring compounds. Chiral cyclopropane derivatives have also been used as resolving agents for optical isomers.

Asymmetry-inducing groups, chiral complexing agents, or enantiotopic differentiation of functional groups by means of chiral auxiliaries have allowed ready enantioselective cyclopropanations (>90% ee). Enantioselective Simmons–Smith cyclopropanation of chiral olefins derived from acyclic or cyclic enones has been applied to the synthesis of a variety of optically pure cyclopropyl ketones. On the other hand, cyclopropanation by copper- or rhodium-catalyzed decomposition of diazo compounds has been attempted with the use of optically active alkyl diazoacetates, chiral olefins, or chiral copper complexes. It appeared that the use of chiral diazo compounds alone such as (diazoacetyl)oxazolidinone did not result in any advantage but that chiral olefins underwent cyclopropanation with 90% ee and that chiral copper complexes induced decomposition of diazoalkanes to afford cyclopropanes with 93–100% ee. Carbenoid reactions of optically active chromium, iron, cobalt, and nickel complexes, involving carbene transfer within the metal complexes, achieved cyclopropanation with enantioselectivity ranging from 26 to 88%; otherwise, allylpalladium complexes induced inter- or intramolecular cyclopropanation with 67% enantioselectivity and 90% chirality transfer, respectively. Deformylation of optically active cyclopropanecarboxaldehyde with rhodium complex, oxidation of cyclopropyl sulfide with chiral titanium complex, and formation of cyclopropylcopper occurred with >95% enantioselectivity.

Thermal decomposition and photochemical decomposition of optically active pyrazolines were achieved with 85 and 95% retention of configuration, providing chiral cyclopropanes with 70 and 90% ee, respectively. However, irradiation of diazofluorene or diazodiphenylmethane in the presence of optically active fumarates involved triplet carbenes in a nonconcerted fashion and provided cyclopropane derivatives with low enantioselectivity. On the other hand, photochemical-induced isomerization of diastereomeric cyclopropanes appeared to be sensitizer dependent: the diastereoisomer ratios increased as the triplet energy of the sensitizer decreased. Likewise, the photochemistry of cyclopropane derivatives appeared remarkably dependent on the excited-state multiplicity.

Naturally occurring carbohydrates, citronellal, pinenes, carvone, 3-carene, etc., often available in both enantiomeric forms, provided convenient and enantiospecific sources of chiral cyclopropanes. Chiral four-membered rings readily available from natural sources, from resolution, or from stereocontrolled alkylation of suitable precursors have undergone highly stereospecific $C_4 \rightarrow C_3$ ring contractions to provide three-membered rings with defined stereochemistry and high enantiomeric excess (>95% ee).

Finally, optically active halocyclopropanes underwent hydride or metal reductions either with net inversion or retention of configuration or with racemization then involving a single-electron-transfer mechanism. The enantiomeric excesses were dependent on the nature of the halogen, the concentration of the hydride (R_3SnH, $LiAlH_4$, etc.) or the metal (Li, Na, etc.), and heterogeneity factors. Electrochemical reductions of chiral halocyclopropanes were also function of the halides, the nature of the electrolyte cation, the working potential, and the nature of the electrode interfaces. While free radical ring opening of chiral alkenylcyclopropanes provided optically active polymers, such materials were also furnished by carbene additions to unsaturated polymers in the presence of optically active catalysts or asymmetry-promoting agents. Asymmetric cyclopropanations have also been reported by use of optically active polymer matrices. Intrinsic differences in the molecular dynamic patterns of (*R*), (*S*)- and (*RS*)-1,2-disubstituted cyclopropanes have been evidenced by application of hydrostatic pressure.

In conclusion, most of the syntheses reviewed herein appear to be highly useful for the production of a wide range of chiral cyclopropanes in the increasingly important class of biologically active functionalities and provide chiral synthons of undeniable synthetic values. Their preparations as well as their synthetic applications involve rearrangements where the chirality of the stereogenic centers is fully retained.

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