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Synthesis of cyclopropane containing natural products

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Contents

1. Introduction

While the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids. In addition, the rigidity of the three-membered ring renders this group an appealing structural unit for the preparation of molecules with defined orientation of pendant functional groups. A number of recent reviews on the synthesis of select cyclopropane containing natural products have appeared and rather than to duplicate these efforts, the reader is directed to this literature.[1–4] This report will focus on those natural products and pharmaceuticals which contain a 1,2-disubstituted, 1,1,2- and 1,2,3-trisubstituted cyclopropane ring which have not previously been reviewed. Recent developments in cyclopropane ring formation which have had a major impact on the synthesis of natural products will first be covered, followed by the applications of these methods.

2. Recent developments in cyclopropane synthesis

General methods for the synthesis of cyclopropanes have been reviewed.[5] There are, however, a number of recent developments which are of particular note.

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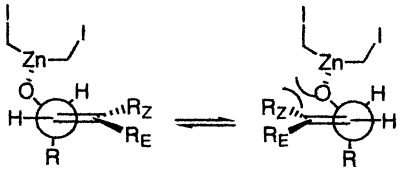


Figure 1.

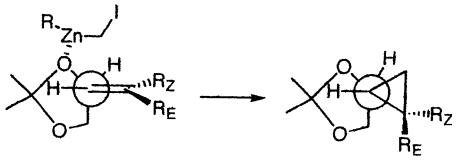
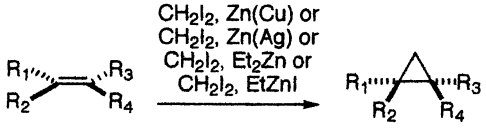


Figure 2.

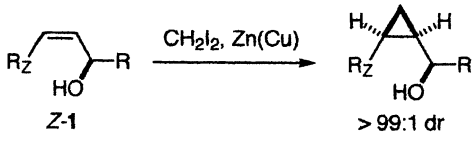
2.1. Simmons–Smith cyclopropanation

More than 40 years ago, Simmons and Smith discovered that the reaction of alkenes with diiodomethane in the presence of activated zinc afforded cyclopropanes in high yield (Eq. (1)).[6,7] The reactive intermediate is a 'RZnCH$_2$I' species. Other methods for the preparation of this species as applied to cyclopropanation are the use of diethylzinc,[8] or ethylzinc iodide/I$_2$.[9] Molander has reported that diiodomethane in the presence of samarium will also effect cyclopropanation of allylic alcohols.[10]



(1)

In cyclic and acyclic systems, cyclopropanation diastereoselectivity is strongly directed by allylic hydroxyl substituents. The cyclopropanation of (*Z*)-allylic 2° alcohols (*Z*-**1**) with either Zn or Sm derived carbenoids occurs in a highly diastereoselective fashion (Eq. (2)).[10,11] These results may be explained by considering the directing influence of the hydroxyl substituent in the conformer[12] which avoids allylic A^{1,3} strain (Fig. 1).[12] Charette has recently reported that cyclopropanation of *E*-**1** with the reagent generated from CH$_2$I$_2$/Et$_2$Zn proceeds with excellent *syn* selectivity (Eq. (3)).[13] The level of this diastereoselectivity depends upon the steric bulk of the 2° alcohol substituent.



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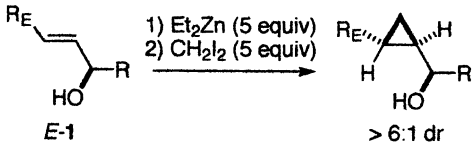

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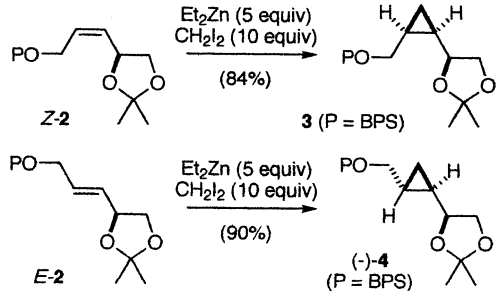
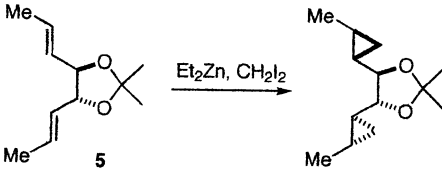


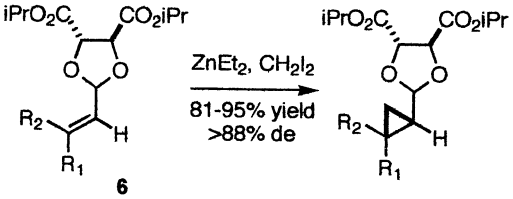
Scheme 1.

Taguchi, et al. have examined the cyclopropanation of *Z*- or *E*-allylic ethers (**2**) from *R*-glyceraldehyde acetonide (Scheme 1).[14] The diastereoselectivity for cyclopropanation increases as the steric bulk of the alcohol protecting group (P) increases; for the *t*-butyldiphenylsilyl ethers the reaction proceeds in a nearly diastereoselective fashion for both *Z*- or *E*-**2** (ca. 100% de). The great bulk of the BPS group ensures that approach of Zn(CH$_2$I)$_2$ is directed by the acetonide oxygen (and not the silyl ether oxygen) via the lowest energy conformer (Fig. 2). Double cyclopropanation of the 2*E*,6*E*-octadiene (**5**) derived from D-mannitol gave a single diastereomer in which introduction of each cyclopropanes is directed by the adjacent acetonide oxygen (Eq. (4)).[15]



(4)

Yamamoto, et al. report that cyclopropanation of α,β-unsaturated acetals **6** derived from tartrate esters proceeds in a highly diastereoselective fashion (Eq. (5)).[16] This diastereoselectivity is rationalized on the basis of coordination of (ZnCH$_2$I)$_2$ to both the acetal oxygen and the adjacent ester carbonyl (Fig. 3). Cyclopropanation of alkenyl boronic ester derived from the antipodal tartrate esters (**7**) are also reported to proceed with good diastereoselectivity; oxidation gave the corresponding cyclopropanols, albeit in attenuated yields (Scheme 2).[17] A transition state similar to that for acetals **6** was proposed for the cyclopropanation of **7**.



(5)

An extremely important advance in asymmetric Simmons–Smith cyclopropanation of allylic alcohols was reported by

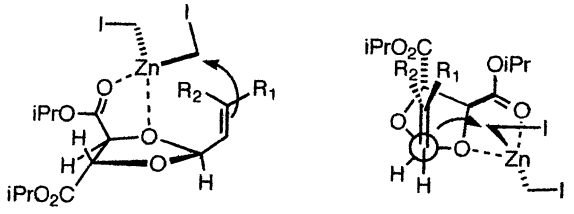
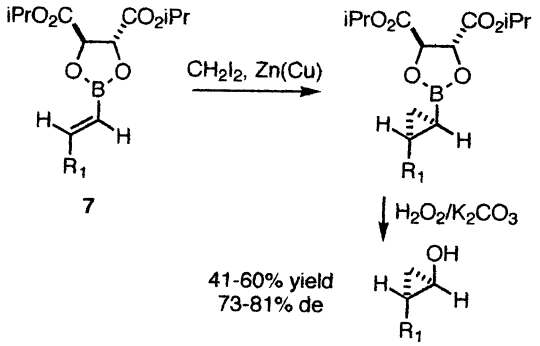
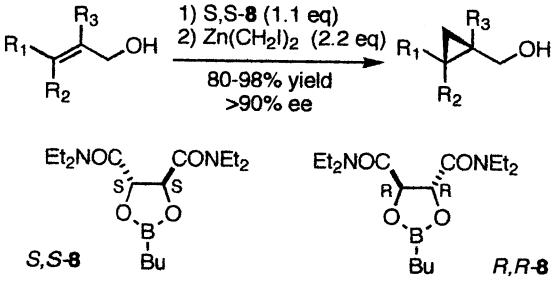


Figure 3.



Scheme 2.

Charette and Juteau.[18] They found that precomplexation of stoichiometric amounts of the chiral ligand **8**, prepared from *N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide and butyl boronic acid, followed by cyclopropanation gave the cyclopropylcarbinols in high yields and with excellent ee (Eq. (6)). Charette has proposed that the $Zn(CH_2I)_2$ species is coordinated to both an amide carbonyl and the allylic alcohol oxygen (Fig. 4). This reagent had an immediate impact in the enantioselective preparation of a number of cyclopropane containing natural products (vide infra).

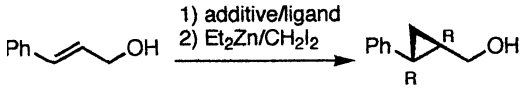


(6)

A number of other chiral ligands have been examined for asymmetric Simmons–Smith cyclopropanation (Eq. (7), Table 1, Fig. 5).[19–26]

2.2. Olefin cyclopropanation with diazomethane/palladium acetate

The cyclopropanation of olefins with excess diazomethane is possible using $Pd(OAc)_2$ as catalyst.[27] Only terminal olefins, 1,1-disubstituted, and 1,2-disubstituted olefins are reactive, and this selectivity may be used for cyclopropanation of substrates with different double bonds (cf. **17**, Eq. (8)). For cyclic alkenes, approach of the Pd-carbene species is on the less hindered face of the olefin. In general, the cyclopropanation of acyclic olefins under these conditions proceeds with low diastereoselectivity, however Pietruszka has recently reported the diastereoselective cyclopropanation of alkenylboronic esters **18a/b** (Eq. (9)).[17b,28] The chiral 1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butandiol derived cyclopropylboronic esters **19b** are remarkably stable and yields for this cyclopropanation method are improved compared to Simmons–Smith cyclopropanation. Notably, the sense of the diastereoselectivity for diazomethane/$Pd(OAc)_2$ cyclopropanation of **18b** is opposite to that for Simmons–Smith cyclopropanation of similar substrates **7** (cf. Scheme 2). Pietruszka attributes this diastereoselectivity on the basis of approach of the Pd-carbene species via the less hindered direction (Fig. 6), without any complexation to the bulky boronic ester groups.



(7)

Table 1. Enantioselective Simmons–Smith cyclopropanation

Additive/ligand (Fig. 5)	%Yield (%ee config)
R,*R*-**9** (0.1 equiv.)/ Me_3Al (0.08 equiv.)	>99 (70, *R*,*R*)
R,*R*-**10** (0.12 equiv.)	92 (75, *R*,*R*)
Et_2Zn (1.1 equiv.)/ZnI_2 (0.1 equiv.); then	
R,*R*-**11** (0.1 equiv.)	92 (89, *R*,*R*)
R,*R*-**12** (1 equiv.)	54 (71–79, *R*,*R*)
R,*R*-**13** (1 equiv.)	98 (88, *R*,*R*)
14 (0.5 equiv.)	54 (94, *R*,*R*)
S-**15** (0.1 equiv.)	>99 (85, *S*,*S*)
R,*R*-**16** (0.25 equiv.)	80 (90, *S*,*S*)

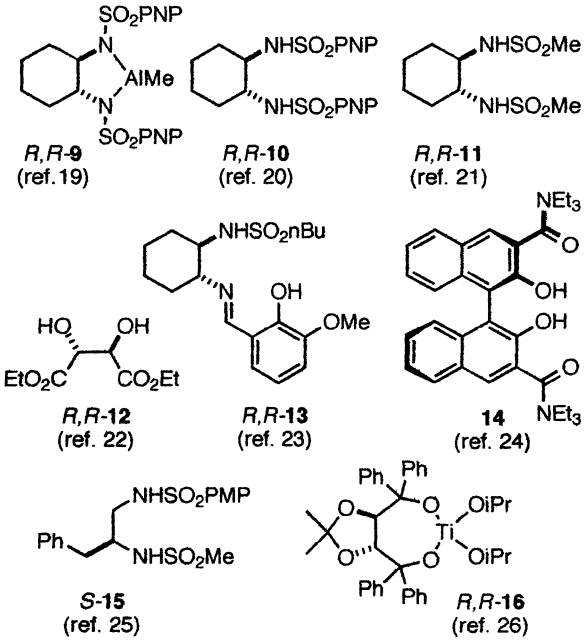


Figure 5. Ligands for asymmetric Simmons–Smith.

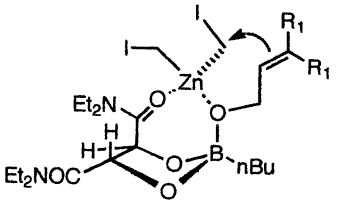
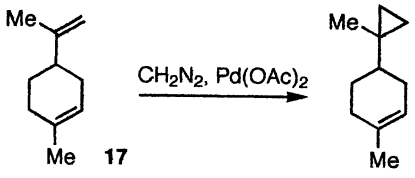


Figure 4.



(8)

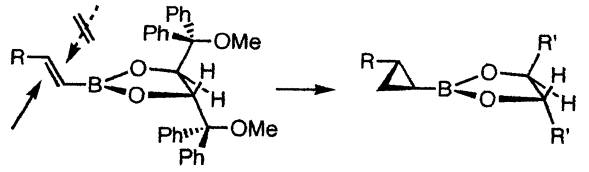
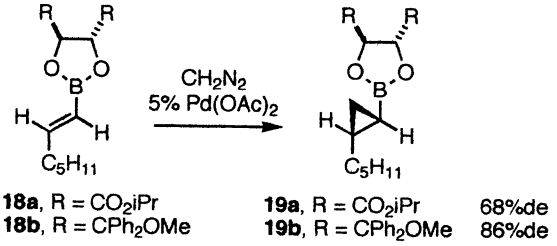


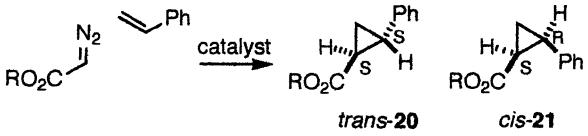
Figure 6.



(9)

2.3. Olefin-diazoester cyclopropanation[29]

The preparation of cyclopropanecarboxylates via decomposition of diazoacetates in the presence of olefins has been known for nearly 100 years. Many transition metal complexes (Fig. 7) are known to catalyze this reaction, and the associated problems of diastereoselectivity (i.e. *trans* vs *cis*) and enantioselectivity may be addressed by varying the metal–ligand system, as well as the steric bulk of the ester group. A select compilation of results for the enantioselective cyclopropanation of styrene with alkyl



(10)

Table 2. Intermolecular enantioselective cyclopropanation of styrene with alkyl diazoacetate

Entry	R	Catalyst (Fig. 7)	(%ee **20**, config)	**20**:**21**	(%ee **21**, config)	Total yield (%)	Ref.
1	***Et***	*S,S*-**23**	(85%ee, 1*S*,2*S*)	73:27	(68%ee, 1*S*,2*R*)	65	31
2	*d*-Menthyl	*S,S*-**23**	(97%ee, 1*S*,2*S*)	82:18	(95%ee, 1*S*,2*R*)	65–75	31
3	Et	CuOTf, *S,S*-**24**	(99%ee, 1*S*,2*S*)	73:27	(97%ee, 1*S*,2*R*)	77	32
4	***Et***	CuOTf, *R,R*-**26**	(84%ee, 1*R*,2*R*)	70:30	(85%ee, 1*R*,2*S*)	85	34
5	*l*-Menthyl	CuOTf, *R,R*-**27**	(94%ee, 1*S*,2*S*)	91:9	(Not determined)	86	35
6	*l*-Menthyl	CuOTf, **28**	(68%ee, 1*S*,2*S*)	90:10	(81%ee, 1*S*,2*R*)	93	36
7	*t*-Bu	*R,R*-**29**	(94%ee, 1*R*,2*R*)	97:3	(85%ee, 1*R*,2*S*)	81	37
8	*t*-Bu	*R,R*-**30**	(93%ee, 1*S*,2*S*)	96:4	(91%ee, 1*S*,2*R*)	80	38
9	*d*-Menthyl	*S*-**31**	(99%ee, 1*S*,2*S*)	63:37	(45%ee, 1*S*,2*R*)	100	39
10	$CH(iPr)_2$	*S*-**32**	(98%ee, 1*S*,2*S*)	74:26	(96%ee, 1*S*,2*R*)	73	40
11	Et	$Cu(OTf)_2$, *S,S*-**25**	(56%ee, 1*R*,2*R*)	39:61	(58%ee, 1*R*,2*S*)	100	33
12	$CH(cHex)_2$	*S*-**33**	(77%ee, 1*S*,2*S*)	34:66	(96%ee, 1*S*,2*R*)	74%	41

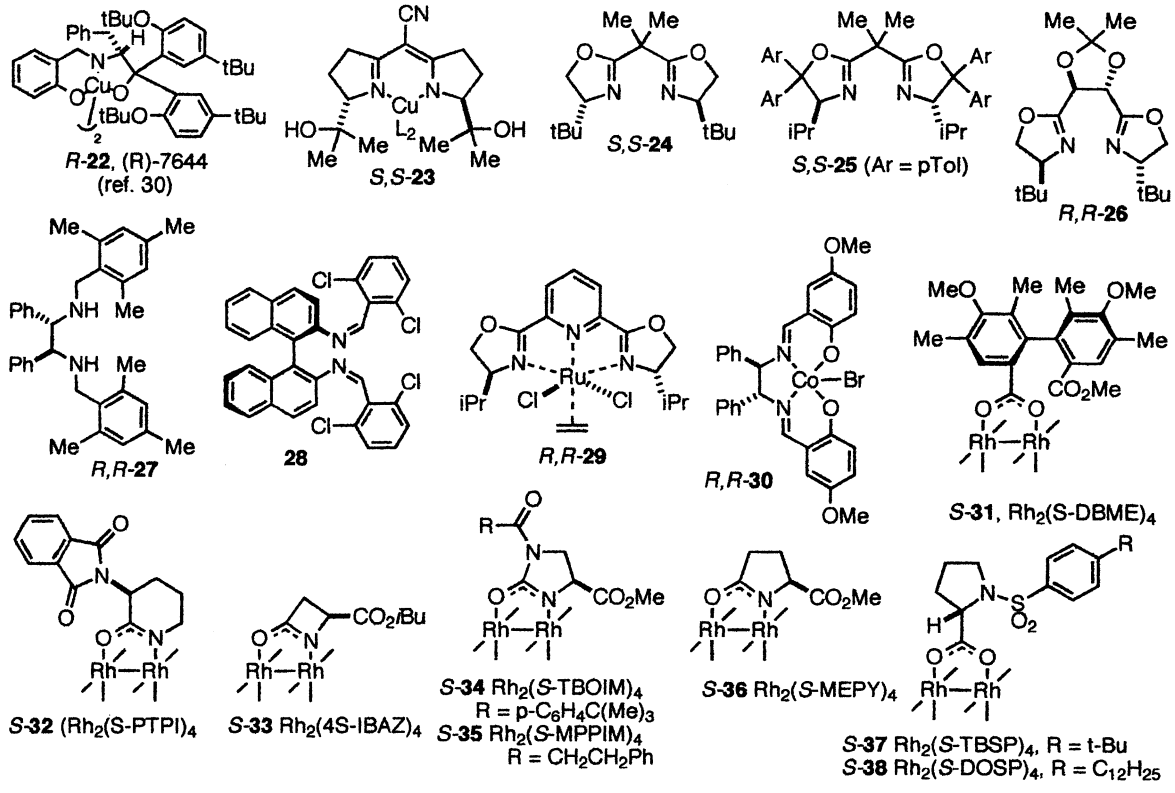
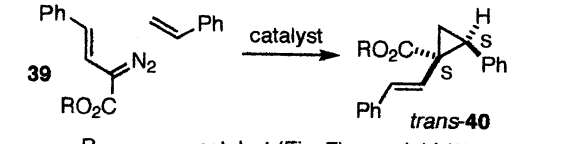


Figure 7.

diazoacetates are presented (Eq. (10), Table 2).[30–41] In general, copper based catalysts are superior to rhodium dimers, and in most cases, the *trans* isomer predominates. Increasing the steric bulk of the ester group may increase the *trans*-**20**/*cis*-**21** ratio. Only a few chiral catalysts lead to a predominance of the *cis*-**21** isomer (entries 11 and 12); in these cases, the ee for *cis*-**21** was greater than that for *trans*-**20**.

In contrast to the above results, rhodium carboxylate catalyzed cyclopropanation of styrene with vinyldiazoacetates (**39**) proceeds with excellent diastereoselectivity and in excellent yield (Eq. (11)).[42] Use of chiral proline based catalysts (**34** or **35**) or the pantolactonyl chiral auxiliaries lead to the formation of **40** in a high optical purity. Davies syntheses of 1-aminocyclopropane carboxylic acids from **40** has been reviewed.[3a,42] In a similar fashion, cyclopropanation of styrene with methyl phenyldiazoacetate (**41**) gives *trans*-**42** with good diastereoselectivity (Eq. (12)).[43] In this case, rhodium carboxylate catalyst *S*-**34** is superior to the rhodium carboxamidate catalysts (e.g. *S*-**36** or *S*-**37**). This methodology was recently applied to the synthesis of a cyclopropyl analog of tamoxifen.[43c]

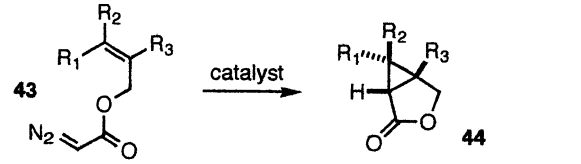


R	catalyst (Fig. 7)	yield (%ee, config)
Me	$Rh_2(OAc)_4$	94% (racemic)
Me	*S*-**34**, Rh_2(*S*-TBSP)$_4$	63% (90%ee, *S,S*)
Me	*S*-**38**, Rh_2(*S*-DOSP)$_4$	83% (92%ee, *S,S*)
(*R*)-pantolactone	$Rh_2(O_2CC_7H_{15})_4$	84% (97%de, *R,R*)

(11)

catalyst (Fig. 7)	yield (%ee, config)
S-**36**, Rh_2[*S*-MEPY]$_4$	27% (49%ee, 1*R*,2*S*)
S-**34**, Rh_2(*S*-TBSP)$_4$	90% (87%ee, 1*R*,2*S*)
S-**37**, Rh_2(*S*-TBOIM)$_4$	63% (77%ee, 1*R*,2*S*)

(12)



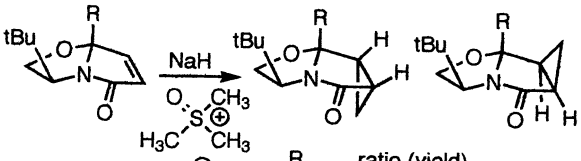
catalyst (Fig. 7)	R_1	R_2	R_3	yield (%ee)
S-**36**, Rh_2(*S*-MEPY)$_4$	H	H	H	75% (95%ee)
S-**36**, Rh_2(*S*-MEPY)$_4$	Ph	H	H	70% (>94%ee)
S-**36**, Rh_2(*S*-MEPY)$_4$	H	Ph	H	78% (68%ee)
S-**35**, Rh_2(*S*-MPPIM)$_4$	H	Ph	H	61% (96%ee)
S-**36**, Rh_2(*S*-MEPY)$_4$	H	H	Me	72% (7%ee)
S-**35**, Rh_2(*S*-MPPIM)$_4$	H	H	Me	75% (89%ee)

(13)

Intramolecular cyclopropanation of diazoesters **43** gave the corresponding 3-oxabicyclo[3.1.0]hexan-2-ones **44** (Eq. (13)).[44] While the first-generation rhodium carboxamidate catalyst *S*-**36** affords the products with excellent ee's for the parent unsubstituted system (**43**, R_1=R_2=R_3=H) and for *Z*-substituted substrates (**43**, R_2=R_3=H, R_1=Ph), the *E*- and methallyl substrates gave bicyclic lactones with diminished enantioselectivity. The *S*-**38** catalyst satisfactorily addresses these cases.

2.4. Cyclopropanation of Michael acceptors

Corey and Chaykovsky demonstrated that addition of dimethyl sulfoxonium methylide to α,β-unsaturated ketones affords the corresponding cyclopropyl ketones.[45] The cyclopropane bonds are formed sequentially via Michael addition followed by intramolecular displacement of dimethylsulfoxide. In general, cyclopropanation occurs on the less hindered face of cyclic alkenes (cf. **45**, Eq. (14)).[46]

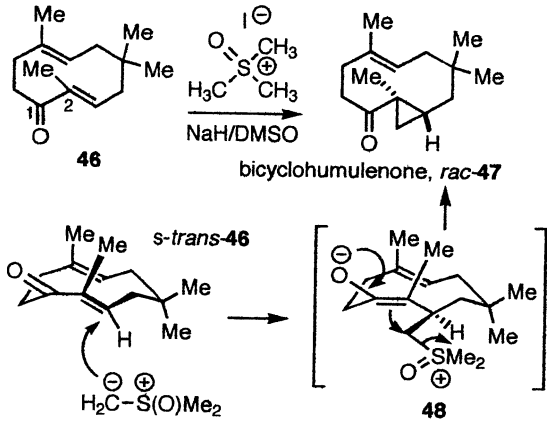


	R	ratio (yield)
45a, R = Me	Me	19:1 (81%)
45b, R = H	H	1:19 (40%)

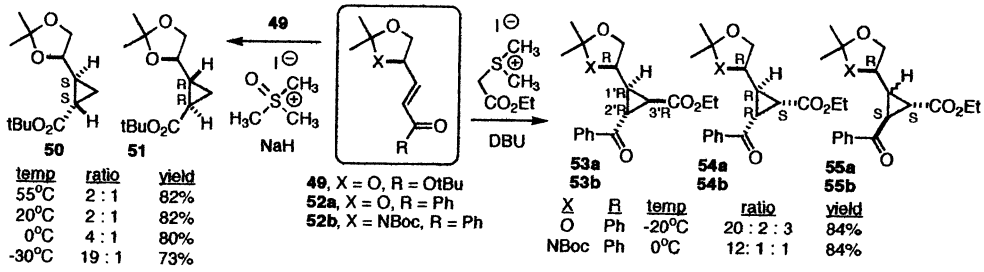
(14)

The stereoselective cyclopropanation of cyclic enone **46** gave exclusively the *trans*-cyclopropane (**47**, bicyclohumulenone, Scheme 3).[47] Molecular mechanics calculations indicate that the macrocyclic enone **46** adopts predominantly one of three *s-trans* conformers about the C1–C2 bond (cf. *s-trans*-**46**) all of which have the same face of the olefin exposed. Michael addition generates the *E*-enolate anion **48**, which upon intramolecular closure would give the *trans*-cyclopropane **47**. Molecular mechanics calculations for a model of the enolate anion (i.e. CH_3 in place of the $CH_2S(O)Me_2$ group) predict the lowest energy conformer for the *E*-enolate to be as indicated.

Ma and coworkers have examined the diastereoselective addition of sulfoxonium or sulfonium ylides to optically active acyclic enoates and enones (Scheme 4). Addition of dimethyl sulfoxonium methylide to enoate **49** gave predominantly the (*S,S*)-cyclopropane **50**.[48a] As might be expected, the diastereoselectivity increases at lower temperatures. In a similar fashion, reaction of either the enone **52a** (derived from glyceraldehyde acetonide) or the



Scheme 3.



Scheme 4.

enone **52b** (derived from Garner's aldehyde) with ethyl dimethylsulfonium acetate in the presence of DBU gave a mixture of cyclopropanecarboxylates (Scheme 4).[48b,c] In both of these latter cases, the major product possesses the (1′*R*,2′*R*,3′*R*) configuration, as determined by X-ray diffraction analysis. These results may be rationalized by the following considerations: the lowest energy conformer will have the electronegative heteroatom (either O for **49** and **52a** or NBoc for **52b**) perpendicular to the olefin in order to maximize overlap of the C-heteroatom σ-bond with the π*-antibonding orbital of the enone (Fig. 8). Approach of the sulfur ylide takes place on the face opposite to the heteroatom group.

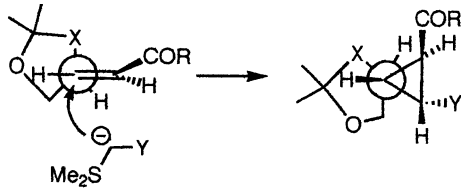
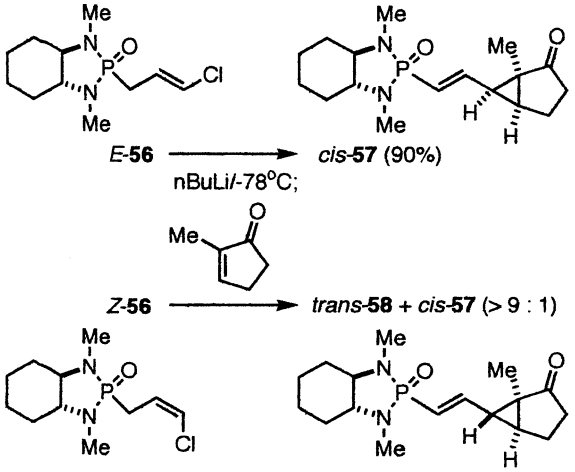


Figure 8.



Scheme 5.

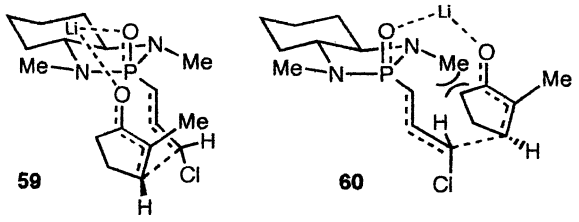
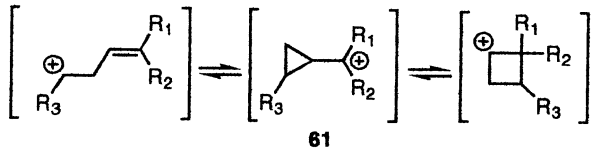


Figure 9.

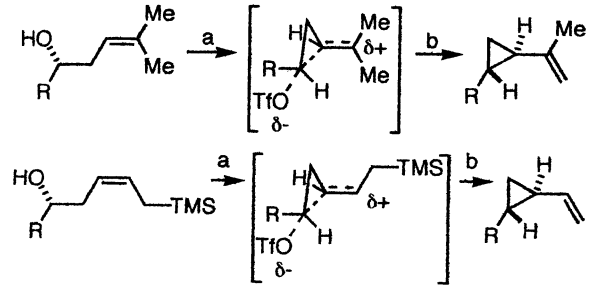
Michael addition of carbanions bearing a leaving group in the α-position results in the formation of cyclopropane products.[49] Hanessian and coworkers have reported an efficient asymmetric cyclopropanation based on the chloroallyl phosphonamides *E*-**56** or *Z*-**56** (Scheme 5).[50a] The stereochemistry of the chloroallyl group determines the stereochemistry of the cyclopropane ring (i.e. *cis* vs *trans*), while the chirality of the phosphonamide is responsible for the overall enantioselectivity. The transition state for conjugate addition on the *re*-face of the enone (i.e. **59**, Fig. 9) is lower in energy than that for addition on the *si*-face (i.e. **60**), due to steric interactions between the carbonyl α-protons and the phosphonamide methyl group present in **60**.[50b]

2.5. Homoallyl or cyclobutyl to cyclopropylcarbinyl cation rearrangements

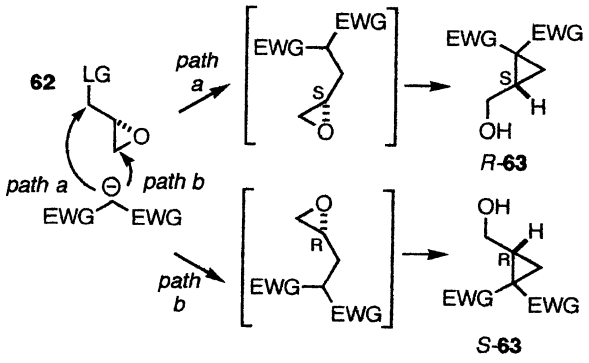
The selective rearrangement of homoallyl or cyclobutyl cations to cyclopropylcarbinyl cations (**61**) is possible if substituents are present within the system to stabilize the cyclopropylcarbinyl cation (Scheme 6).[51] This has been accomplished by the presence of two alkyl groups or the presence of an allylsilane substituent (Scheme 7).[52,53] These reactions take place with inversion of configuration at the carbon which undergoes ionization. The lowest energy



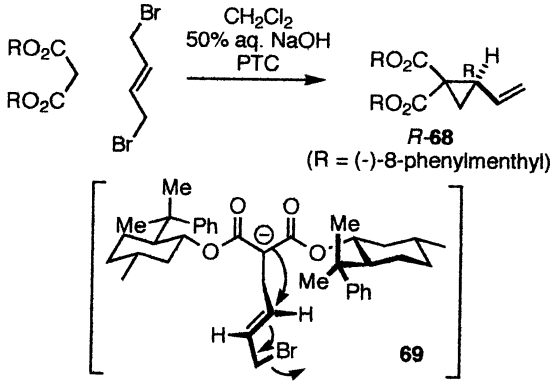
Scheme 6.



Scheme 7. *Reagents*: (a) Tf_2O; (b) NEt_3.



Scheme 8.

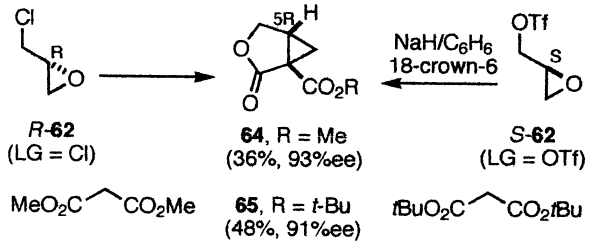


Scheme 11. (R=(−)-8-phenylmenthyl).

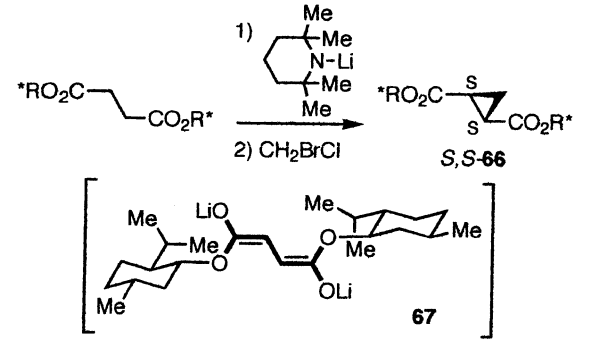
transition state is that in which the substituents are on opposite sides of the forming cyclopropane ring.

2.6. Intramolecular displacement reactions

Cyclopropanes may be constructed by intramolecular alkylation of active methylene compounds via a 3-*exo*-tet ring closure. For example, the reaction of active methylene compounds with 2,3-epoxypropanes bearing a leaving group at C-1 (**62**) generates the corresponding cyclopropylcarbinols **63** via a double displacement reaction (Scheme 8).[54] This reaction may proceed via two pathways: either initial displacement of the leaving group (path a) or initial nucleophilic attack at the epoxide followed by Payne rearrangement (path b). The mode of nucleophilic attack depends on the nature of the leaving group.[55] Thus, reaction of (*R*)-epichlorohydrin (*R*-**62**, LG=Cl,>99%ee) with dimethyl malonate proceeded via pathway b to give the bicyclic lactone **64** (93.4% ee),[56a] while the corresponding



Scheme 9.



Scheme 10. (R*=*l*-menthyl).

reaction of (*S*)-triflate (*S*-**62**, LG=OTf, 91%ee) with di-*t*-butyl malonate gave the bicyclic lactone **65** via pathway a (Scheme 9).[56b]

Yamamoto's group has reported that alkylation of (−)-dimenthyl succinate with bromochloromethane gave the cyclopropanedicarboxylate *S*,*S*-**66** (99%ee, Scheme 10).[57] The authors propose that double deprotonation generates the *s-trans-E*,*E*-dienolate dianion **67**. Electrophiles approach **67** on the face opposite to the isopropyl substituents.

Quinkert's group disclosed that dialkylation of bis-(−)-8-phenylmenthyl malonate with 1,4-dibromo-2-butene under phase transfer catalysis conditions affords the optically active vinylcyclopropane *R*-**68** (R=(−)-8-phenylmenthyl, 98:2 dr, Scheme 11).[58] This stereochemical outcome is the result of the diastereomeric transition state **69** in which the olefinic substituent is oriented away from the sterically bulky CMe_2Ph substituent.

The vinylcyclopropane **68** was also prepared via palladium catalyzed intramolecular allylic alkylation (Eq. (15)).[59] Reaction of **70** with dimethyl malonate in the presence of $Pd_2(dba)_3$ and the chiral bisphosphine ligand **71** gave (*R*)-**68** (R=Me) in modest yield (24% yield, 67%ee). Carrying the reaction out over longer time did not improve the yield, however the enantiomeric excess of the product was found to decrease. This may be rationalized by interconversion of (*R*)- and (*S*)-**68** via ring opening to the π-allyl-Pd intermediate **72a** (Fig. 10). This intermediate may interconvert with the diastereomeric π-allyl-Pd species **72b** via a π–σ–π rearrangement. Ring closure of **72b** via intramolecular

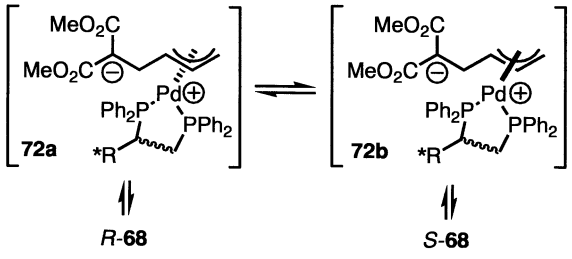
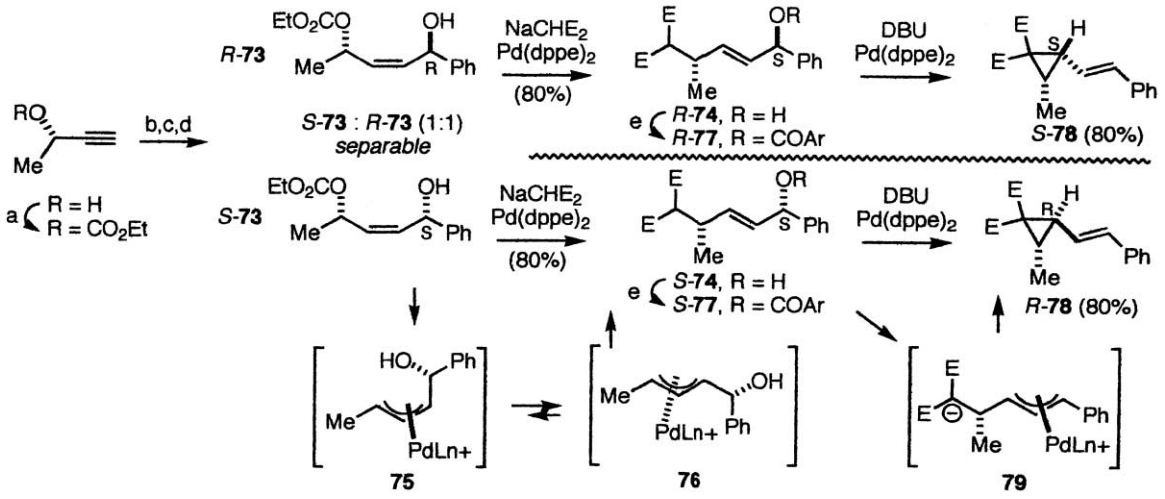
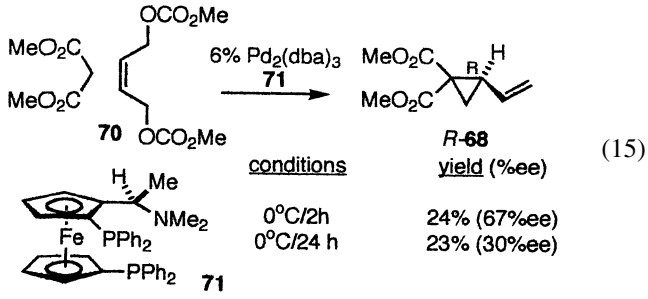


Figure 10.



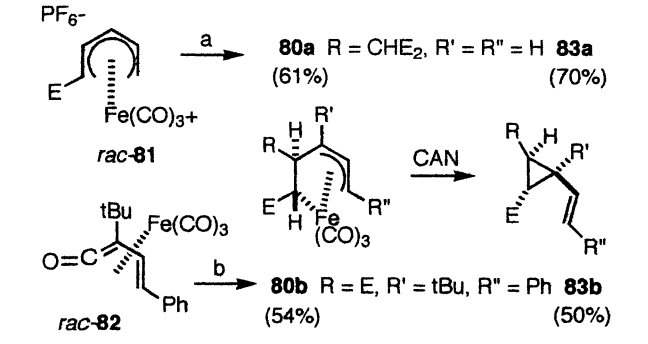
Scheme 12. E=CO_2–Me, Ar=2,4-$Cl_2C_6H_3$; *Reagents*: (a) $ClCO_2Et$, pyr (60%); (b) LDA; (c) PhCHO; (d) H_2/Lindlar (68%); (e) 2,4-$Cl_2C_6H_3COCl$, pyr (80%).

nucleophilic attack on the face opposite to Pd generates (*S*)-**68**.



(15)

In the above example, racemization of the product was the result of the π–σ–π rearrangement. It is possible to bias the direction of this equilibrium by placing substituents on both termini of the allyl ligand. Genet and coworkers have reported the preparation of substituted vinylcyclopropanes beginning with 2*Z*-buten-1,4-diols **73** (Scheme 12).[60] The precursors *R*- and *S*-**73** are prepared from (*R*)-but-1-yn-3-ol as indicated. Reaction of *R*-**73** or *S*-**73** with sodium dimethyl malonate, catalyzed by $Pd(dppe)_2$ gave the *E*-allylic alcohols *R*-**74** or *S*-**74**, respectively. As illustrated for *S*-**73**, this reaction occurs with 'triple-inversion': generation of the *syn*,*anti*-allyl complex **75** occurs via an S_N2 displacement of carbonate; π–σ–π rearrangement of **75** to the more stable *syn*,*syn*-allyl **76** occurs with inversion at the allyl metal center; nucleophilic attack by malonate anion occurs on the less hindered end of allyl complex **76** on the face opposite to the metal. Conversion of allylic alcohols **74** into benzoates **77** is followed by Pd catalyzed cyclization to the corresponding vinylcyclopropanes **78**, via the intermediacy of the *syn*,*syn*-allyl complex **79**.



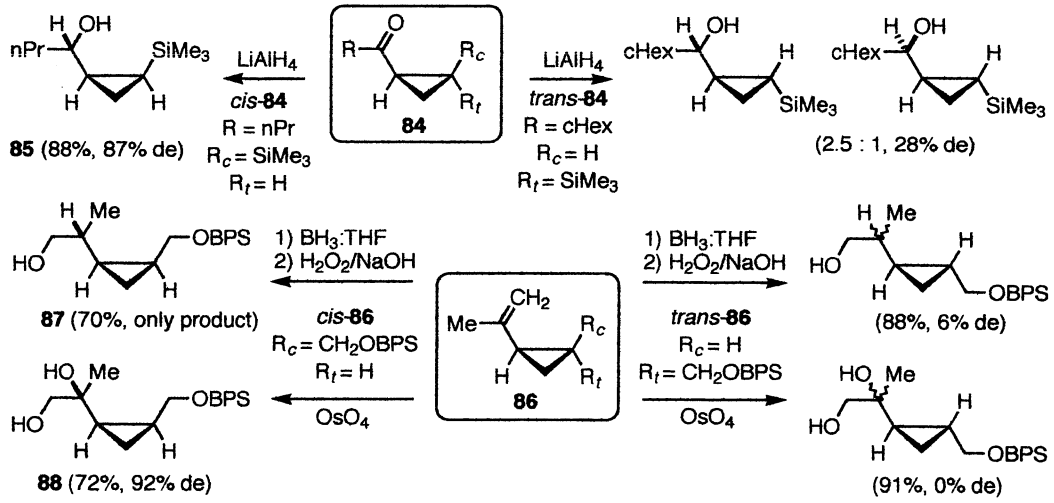
Scheme 13. E=CO_2Me; *Reagents*: (a) $LiCH(CO_2Me)$; (b) dimethylfumarate, $PhCH_3$, reflux.

2.7. Oxidatively induced-reductive elimination of (pentenediyl)iron complexes

(Pentenediyl)iron complexes **80a** have been prepared by addition of carbon nucleophiles to (pentadienyl)iron(1+) cations **81** bearing a terminal electron withdrawing substituent (Scheme 13).[61] Alternatively, the thermal reaction of (vinylketene)iron complex **82** with dimethylfumarate generates the (pentenediyl)iron complex **80b**.[62] Oxidation of either **80a** or **80b** with cerium ammonium nitrate (CAN) gave the vinylcyclopropanes **83a** or **83b**.[61a,62,63] In these cases, the oxidatively induced-reductive elimination proceeds with retention of configuration at the two centers undergoing C–C bond formation.

2.8. Diastereoselective reactions adjacent to a cyclopropyl ring

The diastereoselectivity of additions to unsaturated centers adjacent to a 1,2-disubstituted cyclopropane is dependent on the substitution pattern (i.e. *cis*- vs *trans*-). For example, while the reduction of cyclopropyl ketone *cis*-**84** occurs in a highly diastereoselective fashion, the reduction of *trans*-**84** proceeds with quite modest selectivity (Scheme 14).[64] Additionally, while the hydroboration/oxidation or dihydroxylation of isopropenyl cyclopropane *cis*-**86** proceeds with excellent diastereoselectivity, similar reactions of *trans*-**86** give essentially an equimolar mixture of diastereomeric products (Scheme 14).[65] For reduction of *cis*-**84**, Lautens has rationalized these results on the basis of approach of the metal hydride on the less hindered face of the ketone in the *s-cis* bisected conformer (i.e. **89**, Fig. 11). It is known that overlap of the carbonyl and cyclopropane orbitals is maximized in the bisected conformer. While the stereochemical outcome for electrophilic addition to *cis*-**86** might be rationalized in a similar fashion (i.e. **90**), Cossy has



Scheme 14.

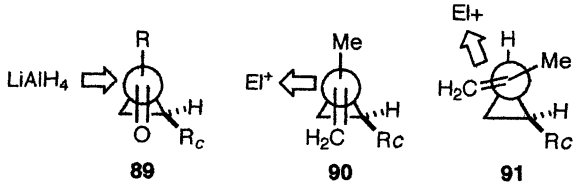


Figure 11. Conformational analysis of **84** and **86**.

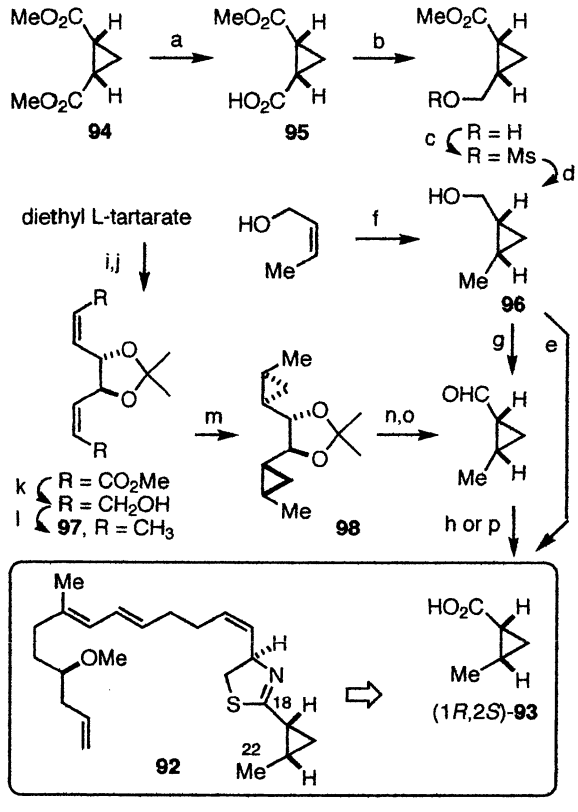
suggested that the more reactive conformer may possess a *gauche* conformer (i.e. **91**). For either *trans*-**84** or *trans*-**86**, the steric bulk of the trans substituent is too far removed from the unsaturated center to have a significant influence.

3. Synthesis of selected cyclopropane targets

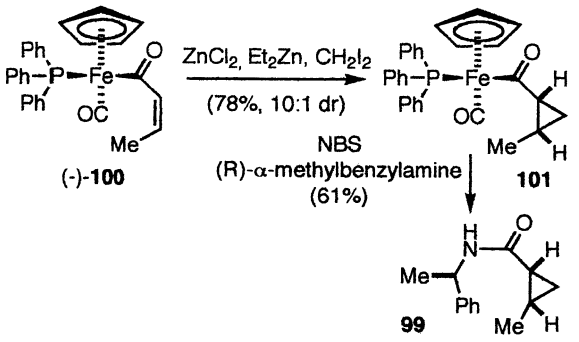
3.1. Curacin A

Curacin A (**92**, Scheme 15) is a cyclopropane-thiazole-polyene containing natural product isolated from the cyanobacterium *Lygnbya majuscula* collected in the Caribbean.[66] It was found to exhibit cytotoxic activity ($IC_{50}=9\times10^{-9}$ M for L1210 leukemia cells, $IC_{50}=2\times10^{-7}$ M for CA46 Burkitt lymphoma cells). Curacin A acts to arrest cells in mitosis by interacting with the colchicine binding domain of the tubulin protein. The stereochemistry of the olefins and the cyclopropane ring were assigned on the basis of NMR spectral data. Synthesis of the four possible partial cyclopropyl thiazoline structures allowed for assignment of the (4*R*,1′*R*,2′*S*) absolute configurations for this portion of **92**.[67] The enantiomers of 2-methylcyclopropanecarboxylic acid (**93**) required for these syntheses were prepared by classical resolution using quinine. In just a short period, seven groups have reported total syntheses of **92**;[68–76] all rely on the asymmetric preparation of (1*R*,2*S*)-**93**.

Kobayashi's group reported a six step preparation of (1*R*,2*S*)-**93** (Scheme 15).[68] Partial hydrolysis of the *meso* diester **94** with pig liver esterase produced the half-acid **95**. Carboxylic acid **95** was transformed into (1*R*,2*S*)-2-methylcyclopropylcarbinol **96** via reduction with borane, mesylation, and $LiAlH_4$ reduction. Alternatively, many groups[69–75] utilized the asymmetric Simmons–Smith cyclopropanation of *Z*-crotyl alcohol in the presence of (*S*,*S*)-**8**[18] to produce (1*R*,2*S*)-**96**. Oxidation of (1*R*,2*S*)-**96** was accomplished either by (i) stepwise oxidation with TPAP,



Scheme 15. *Reagents*: (a) pig liver esterase $NaHPO_3$, $NaHCO_3$, H_2O (90%); (b) BH_3/SMe_2, $B(OMe)_3$ (91%); (c) MsCl, NEt_3 (91%); (d) $LiAlH_4$, ether (66%); (e) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O; (f) Et_2Zn, CH_2I_2, CH_2Cl_2, (*S*,*S*)-**8** (70%, >95% ee); (g) TPAP, NMO, 4A sieves; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene (64% two steps); (i) acetone, AcOH, H^+; (j) DIBAL/$PhCH_3$/−78°C; then Ph_3PCHCO_2Me; (k) DIBAL, CH_2Cl_2, −78 to 0°C (58%); (l) CBr_4, PPh_3, CH_2Cl_2; then $LiAlH_4$, ether (69%); (m) Et_2Zn, CH_2I_2, CH_2Cl_2 (63%) or Zn–Cu, CH_2I_2, ether (60%); (n) pTsOH, MeOH, H_2O (92%); (o) $NaIO_4$, CH_2Cl_2, MeOH; (p) $KMnO_4$, tBuOH, aq. KH_2PO_4 (89%, two steps).



Scheme 16.

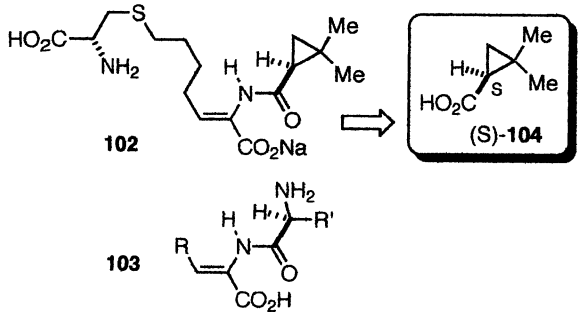


Figure 12.

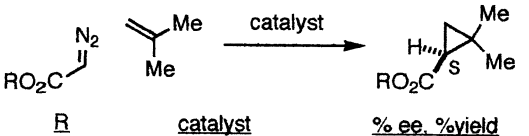
followed by $NaClO_2$,[69–72] or by (ii) oxidation with $NaIO_4$/$RuCl_3$.[73–75] Iwasaki and coworkers pursued the diastereoselective Simmons–Smith cyclopropanation of the C2 symmetric diene **97**, which was prepared from diethyl L-tartrate.[76] Hydrolysis of ketal **98** followed by glycol cleavage and oxidation of the aldehyde produced the required cyclopropanecarboxylic acid.

Prior to the discovery of curacin A, Ambler and Davies reported a synthesis of *N*-(*R*)-α-methylbenzyl (1*R*,2*S*)-2-methylcyclopropanecarboxamide (**99**, Scheme 16).[77] Simmons–Smith cyclopropanation of the chiral iron acyl complex (−)-**100** proceeds in a diastereoselective fashion to give **101**. Approach of the zinc-carbenoid species occurs on the olefin face opposite to the sterically bulky triphenylphosphine ligand. Oxidation of the iron–acyl bond, followed by reaction with α-methylbenzyl amine gave **99**.

3.2. Cilastatin

Upon screening ca. 200 compounds, cilastatin (**102**, Fig. 12) was developed at Merck Laboratories as a selective inhibitor of renal dehydropeptidase.[78] As such, **102** (a.k.a. MK-0791) suppresses the metabolism of the β-lactam antibiotic imipenem (*N*-formimidoyl thienamycin, a.k.a. MK-0787). It was proposed that **102** acts as a desaminodipeptide analogue (cf. **103**). (*S*)-2,2-Dimethylcyclopropane carboxylic acid **104** or the corresponding amide are intermediates in the preparation of cilastatin.

The simplest syntheses of **104** involve the asymmetric cyclopropanation of isobutene with diazoacetate in the presence of a chiral catalyst (Eq. (16)).[30,32,36,40] To date, the catalysts with the best enantioselectivity are those pioneered by Aratani's group (**22**, *R*-7644)[30] and by Evan's group (*S*,*S*-**23**/CuOTf).[32] In both of these cases the cyclopropanation can be run on large scale without any loss in enantioselectivity.

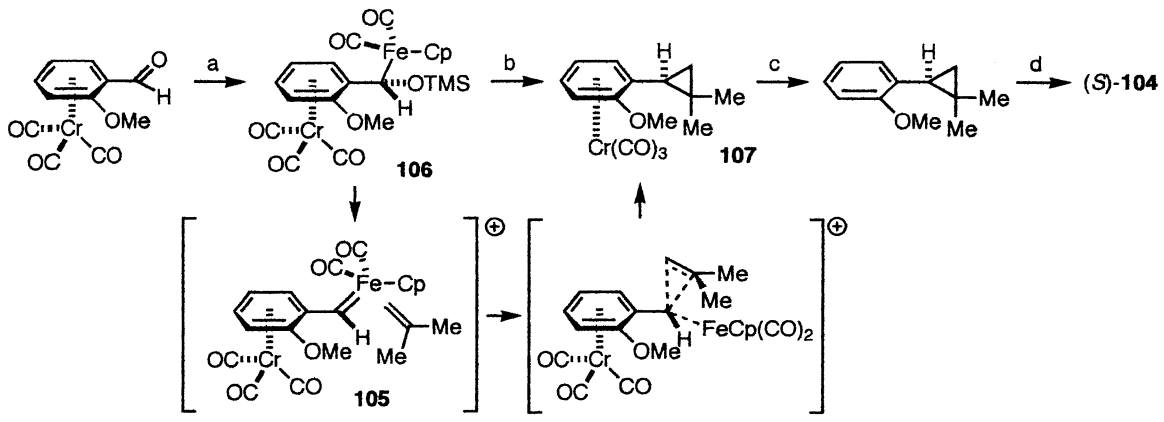


R	catalyst	% ee, %yield
Et	*R*-**22** (R-7644)	92% ee, "factory scale"
Et	CuOTf, *S*,*S*-**23**	>99% ee, 70% yield
l-menthyl	CuOTf, **28**	65% ee, 66% yield
$CH(iPr)_2$	*S*-**32**, Rh_2(S-PTPI)$_4$	95% ee, 34% yield

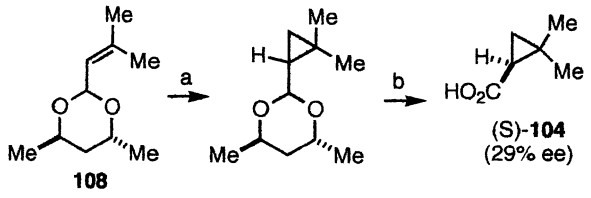
(16)

The Hossain group's preparation of (*S*)-**104** utilizes an in situ generated chiral iron benzylidene cation **105** (Scheme 17).[79] Beginning with optically active (2-methoxybenzaldehyde)$Cr(CO)_3$, addition of $NaFe(CO)_2Cp$ followed by silylation of the resultant alkoxide with trimethylsilyl chloride gave **106**. Treatment of **106** with trimethylsilyl triflate generated **105** which in the presence of isobutene undergoes cyclopropanation to give **107**. In this case, isobutylene approaches the s-*trans*-conformer of the carbene complex on the face opposite to the sterically bulky $Cr(CO)_3$ group. Photolytic removal of the chromium adjunct, followed by ozonolytic conversion of the arene ring into a carboxylic acid completed the synthesis.

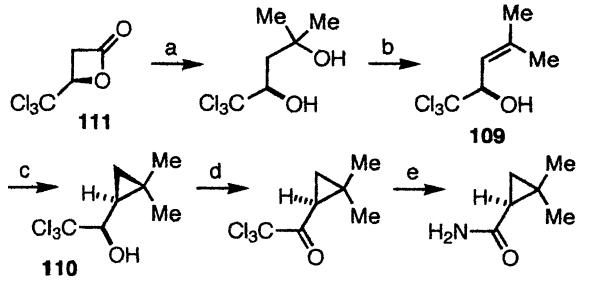
Diastereoselective Simmons–Smith cyclopropanation of



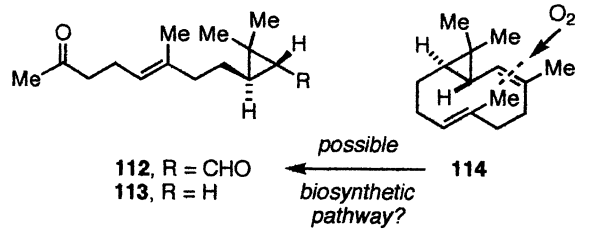
Scheme 17. *Reagents*: (a) $NaFeCp(CO)_2$; then TMSCI (90%); (b) TMSOTf, isobutene (91%); (c) *hν*, pentane (97%); (d) O_3; then H_2O_2, NaOH (82%, 92%ee).



Scheme 18. *Reagents*: (a) Et_2Zn, CH_2I_2 (74%); (b) O_3(85%).



Scheme 19. *Reagents*: (a) Me_3Al (3 equiv.) (94%); (b) $CuSO_4$ on SiO_2 (53%); (C) Et_2Zn, CH_2I_2 (74%); (d) Jones oxidation (72%); (e) NH_3 (72%).



Scheme 20.

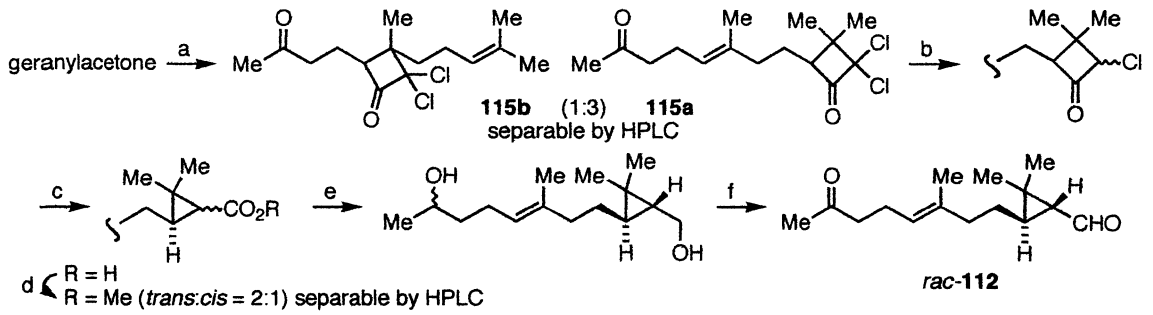
the chiral acetal **108**, followed by ozonolytic cleavage of the chiral auxiliary gave (*S*)-**104**, albeit in only 29% ee (Scheme 18).[80] In contrast, Simmons–Smith cyclopropanation of (*R*)-1,1,1-trichloro-4-methylpent-3-en-2-ol (**109**) gave a single diastereomer **110** (Scheme 19).[81] The precursor **109** was prepared from the β-lactone **111** which was in turn prepared by condensation of ketene with trichloroacetaldehyde in the presence of a polymer supported chinchona alkaloid.[82] Oxidation of **110**, followed by amidation gave (*S*)-2,2-dimethylcyclopropanecarboxamide.

3.3. Marine derived cyclopropane containing natural products

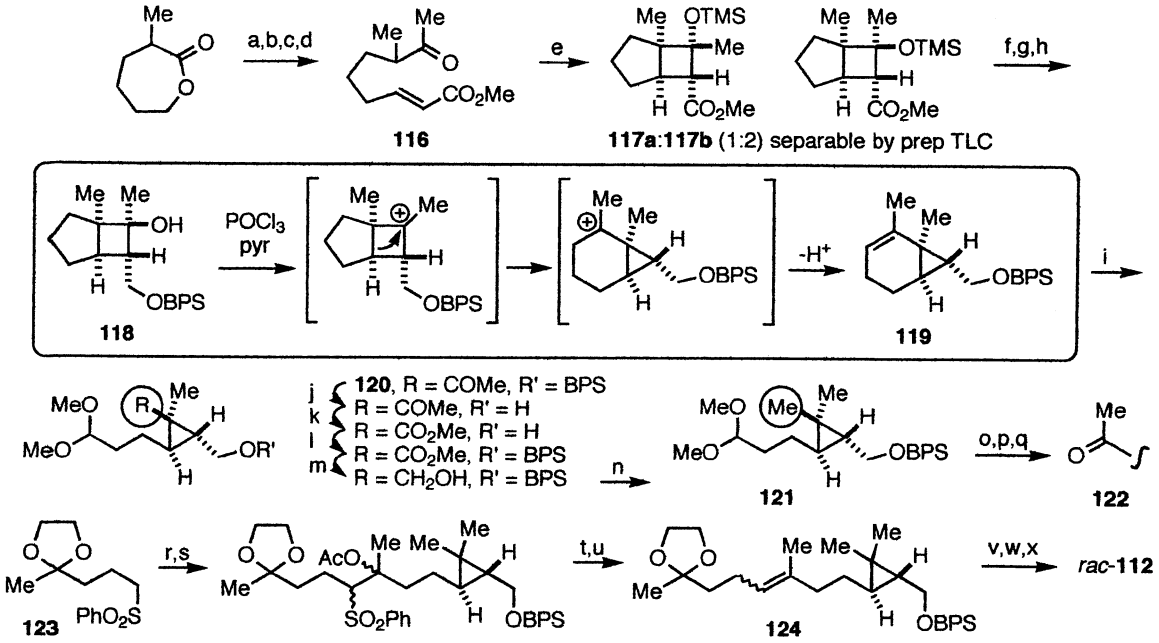
3.3.1. Anthroplalone and noranthroplone. In 1990, Kakisawa and coworkers reported the isolation of two cyclopropyl containing natural products from the Okinawan actinia *Anthopleura pacifica*.[83] The carbon skeletons of anthroplalone (**112**) and noranthroplone (**113**) were deduced from extensive NMR spectroscopy. These authors proposed a possible biosynthetic pathway for the formation of **112** and **113** from the known sesquiterpene lepidozene (**114**, Scheme 20). Notably, Kakisawa's group has also isolated hydroperoxy derivatives of lepidozene from this same biological source.[83b] The absolute configuration of **112** and **113** at the cyclopropane ring was proposed on the basis of the known absolute configuration of **114** and their proposed biosynthetic pathway. Both **112** and **113** exhibit cytotoxicity against B-16 melanoma cells at 22 and 16 μg/mL, respectively.

Surprisingly, the first synthesis of **112** was reported before its isolation. McMurry and Bosch reported the preparation of *rac*-**112** as an intermediate in their synthesis of *rac*-**114** (Scheme 21).[84] Addition of dichloroketene to geranylacetone gave the mixture of regioisomeric cyclobutanones **115a** and **115b**, which were separable by HPLC. Monoreduction of **115a** with one equivalent of Zn, gave the α-chlorocyclobutanone. Favorskii rearrangement with aqueous KOH afforded an inseparable mixture of *trans*- and *cis*-cyclopropanecarboxylic acids. Upon esterification the *trans*-and *cis*-isomers were separable. The synthesis of *rac*-**112** was completed by reduction of both the ester and ketone to primary and secondary alcohols respectively, followed by oxidation.

Fukumoto and co-workers have reported a lengthy synthesis of *rac*-**112** which features a cyclobutyl-to-cyclopropylcarbinyl cation rearrangement (Scheme 22).[85] This synthesis also illustrates the difficulty in stereospecific formation of trisubstituted olefins. Beginning with α-methylcaprolactone, standard transformations were utilized for the preparation of the keto ester **116**. Treatment of **116** with trimethylsilyl iodide and HMDS effected a tandem intramolecular Michael addition–aldol condensation to yield a mixture of bicyclo[3.2.0]heptane esters **117a** and **117b**.[85a] This mixture was separable by preparative TLC. Reduction of **117b**, removal of the TMS protecting group, and



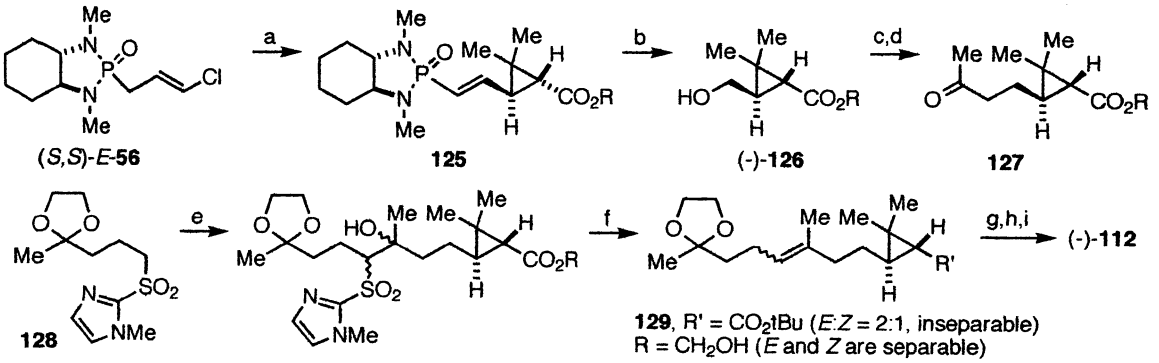
Scheme 21. *Reagents*: (a) Cl_3CCOCl, Zn–Cu, $POCl_3$ (65%); (b) Zn (1 equiv.), AcOH (98%); (c) KOH, H_2O (92%); (d) CH_3I, K_2CO_3 (85%); (e) $LiAlH_4$ (98%); PCC, NaOAc, 3 Å molecular sieves (76%).



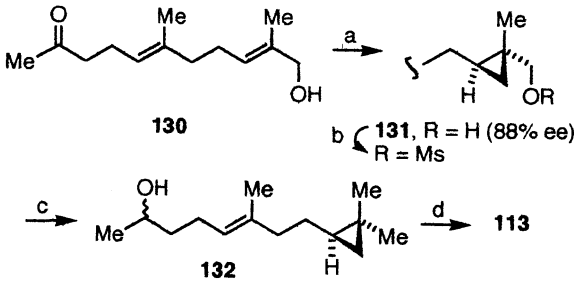
Scheme 22. *Reagents*: (a) DIBAL; (b) MeMgI (82% two steps); (c) PCC, 4 Å molecular sieves; (d) $Ph_3P{=}CHCO_2Me$ (51% two steps); (e) TMS_2NH, TMSI (91%); (f) DIBAL; (g) TBAF, THF (92% two steps); (h) BPSCl, imidazole (87%); (i) O_3, MeOH; Me_2S (89%); (j) TBAF, THF (98%); (k) NaOCl, MeOH; then CH_2N_2, Et_2O (72%); BPSCl, imidazole (84%); (m) DIBAL, CH_2Cl_2 (98%); (n) MsCl, NEt_3; then $LiBHEt_3$, Et_2O (71%); (o) AcOH, H_2O, THF; (p) MeLi, Et_2O (72%); (q) PCC, 4 Å molecular sieves (94%); (r) nBuLi, −78°C; then **122** (98%); (s) Ac_2O, DMAP (79%); (t) SmI_2, HMPA, THF (78%, *E*/*Z*=1:2.6); (u) PhSH, AIBN (81%, *E*/*Z*=1.6:1); (v) TBAF, THF; separate (*E*-**124**, 62%; *Z*-**124**, 38%); (w) 10% aq. $HClO_4$ THF (93%); (x) TPAP, NMO (91%).

protection of the 1° alcohol furnished **118**. Dehydration of cyclobutanol **118** with $POCl_3$ in pyridine proceeded via rearrangement to give **119**. Ozonolysis of the bicyclo-[4.1.0]hept-2-ene **119** in methanol produced the dimethyl-acetal **120**. Transformation of the methyl ketone to a methyl group was accomplished by standard methodology to yield **121**. Conversion of acetal **121** to ketone **122** was accomplished by hydrolysis, addition of methyl lithium, and oxidation. Julia-type olefination of ketone **122** with the phenylsulfone **123** gave olefin **124** as an inseparable mixture of isomers (*E*/*Z*=1:2.6). Olefin isomerization was effected by treatment with benzenethiol/AIBN to render a mixture slightly enriched in the *E*-isomer (*E*/*Z*=1.6:1). Fortunately, removal of the *t*-butyldiphenylsilyl protecting group gave a separable mixture of 1° alcohols. Hydrolysis of the ketal and oxidation gave *rac*-**112**.

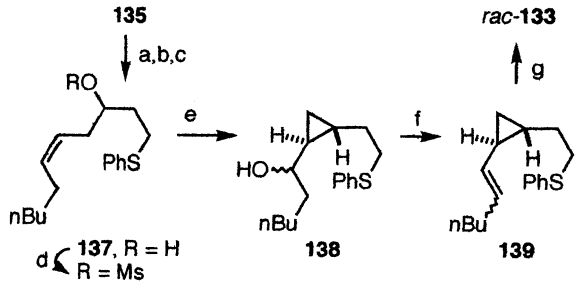
Recently, Hanessian's group reported the first asymmetric preparation of (−)-**112** (Scheme 23).[86] Conjugate addition of the anion derived from the chiral phosphonamide (*S*,*S*)-*E*-**56** to *t*-butyl 3-methyl-2-butenoate gave the vinylcyclo-propane carboxylate **125** (43%). Ozonolytic cleavage of **125**, with reductive workup, yielded the alcohol (−)-**126**. Transformation of (−)-**126** into the ketone **127** required oxidation, Wittig olefination, and reduction. Julia-type olefination of **127** with imidazole sulfone **128** gave an inseparable mixture of *E*- and *Z*-olefins **129** (2:1) with only slightly greater selectivity than was observed by Fukumoto's group. Reduction of this mixture led to a separable mixture of optically active 1° alcohols; deprotection and oxidation completed the preparation of (−)-**112**. While the spectral data for this product were identical with literature values, the specific rotation obtained by Hanessian's group ($[\alpha]_D$=−14.8, *c*=0.62 $CHCl_3$)[86] was considerably greater that that originally measured for the material isolated from *Anthopleura pacific* ($[\alpha]_D$=−4.4,



Scheme 23. (R=tBu); *Reagents*: (a) nBuLi, Et_2O, −78°C; then *t*-butyl 3-methyl-2-butenoate (43%); (b) O_3; then $NaBH_4$ (83%); (c) DMSO $(COCl_2)_2$, NEt_3; then $Ph_3P{=}CHCOMe$; (d) H_2, $Pd(OH)_2$/C, EtOAc (82% two steps); (e) nBuLi, THF, −78°C; then **127** (98%); (f) SmI_2, THF (84%, *E*/*Z*=2:1); (g) $LiAlH_4$, THF (87%, separate isomers); (h) Amberlite (IR-120, H^+), MeOH (79%); (i)TPAP, NMO (75%).



Scheme 24. *Reagents*: (a) $Zn(CH_2I)_2$/DME, (*R*,*R*)-**8** (95%, 88% ee); (b) MsCl; (c) $LiBHEt_3$ (77%, two steps); (d) TPAP NMO (>99%).



Scheme 26. *Reagents*: (a) PCC (41%); (b) PhSH (42%); (c) $NaBH_4$ (92%); (d) MsCl, pyr; (e) KOAc, acetone, H_2O (91%); (f) $MeO_2CN^-SO_2N^+Et_3$, NaH (14%); (g) $CF_3SO_3CH_2CO_2Et$, CH_3CN (86%).

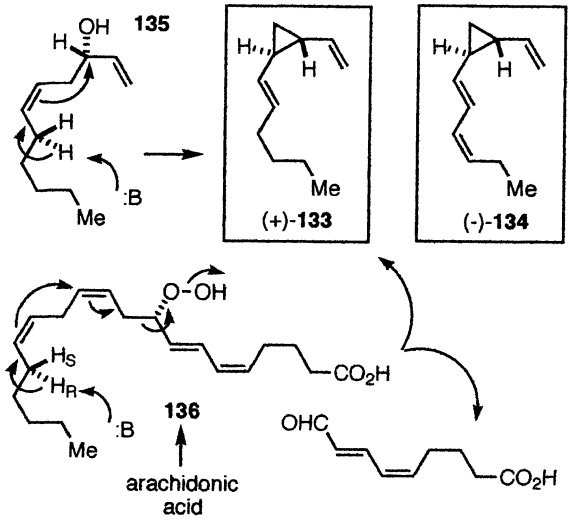
c=0.09 $CHCl_3$).[83a] While the origin of this difference was not determined, the Montreal group noted that this might be due to the low concentration used in the original measurement.

Only a single synthesis of noranthroplone (**113**) has been reported. Charette's group utilized the asymmetric cyclopropanation of allylic alcohol **130** in the presence of (*R*,*R*)-**8** to prepare **131** in 88% ee (Scheme 24).[87] The hydroxymethylene functionality was converted into a methyl group by mesylation and reduction with $LiBHEt_3$; the ketone group was also reduced in this step. Oxidation of **132** completed the synthetic sequence.

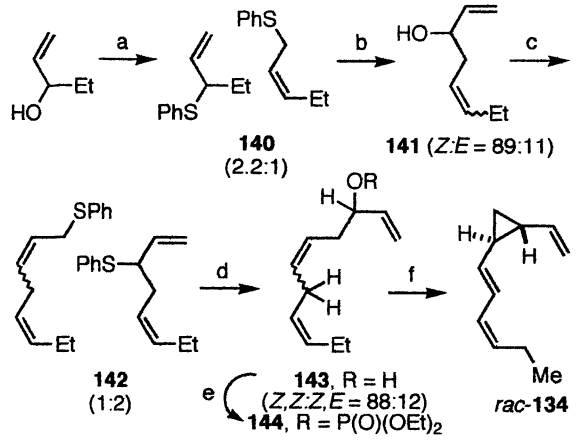
3.3.2. Dictyopterenes. A variety of brown seaweeds indigenous to Hawaii, Japan and Australia produce an odiferous mixture of volatile C11 hydrocarbons.[88] This mixture acts as a sperm attractant pheromone for the gametes of these seaweeds, and in certain cases deters feeding by herbivorous amphipods.[89] Dictyopterene A and B (**133** and **134**, Scheme 25) are cyclopropane containing constituents of this mixture. In addition, these compounds were isolated from heterocontophytic diatoms and higher plants, although their biological purpose in these cases is as yet unknown.[90] Moore has proposed[88a] that 1,5*Z*-undecadien-3-ol (**135**) is the biosynthetic precursor to **133** and subsequently Yamada's group isolated the acetate of **135** which they named dictyoprolene.[91] Recently, Boland has demonstrated that the diatom *Gomphonema parvulum* produces **133** via a lipoxygenase/hydroperoxide lysase combination.[92] Oxidation of arachidonic acid by a cell-free extract from this organism produces (9*S*)-HPETE (**136**), which undergoes enzyme catalyzed cleavage to afford **133** and 10-oxonona-5*Z*,7*E*-dienoic acid (Scheme 25).

Yamada's group reported a biogenetically-inspired synthesis of *rac*-**133** using 1,5*Z*-undecadien-3-ol (**135**) as their starting point (Scheme 26).[93] Oxidation of **135**, followed by Michael addition of phenylthiol, and ketone reduction afforded the alcohol **137**. Mesylation of **137**, followed by solvolytic homoallyl-cyclopropylcarbinyl rearrangement gave the alcohol **138** as a mixture of diastereomers (64:27). Dehydration of **138** produced the alkenylcyclopropane **139** as a 1:1 mixture of *E*- and *Z*-isomers. Subsequent elimination of thiophenol gave *rac*-**133**.

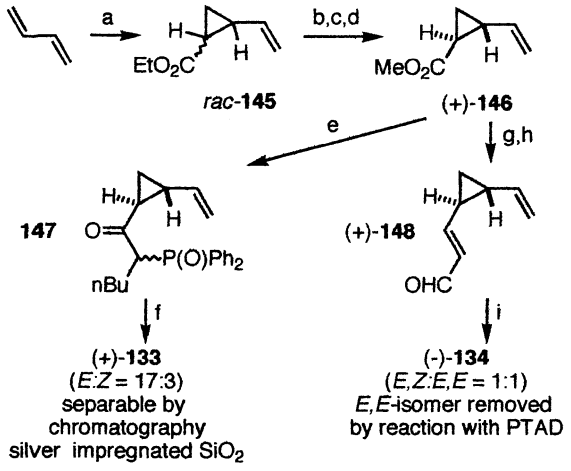
In a similar fashion, Abraham and Cohen reported a biogenetically-inspired synthesis of *rac*-**134** (Scheme 27).[94] Coupling of the π-allyl cerium species derived from the mixture of allylic sulfides **140** with acrolein gave 1,5-octadien-3-ol (**141**). The mixture of stereoisomers **141** (predominately *Z*) was separated by chromatography on $AgNO_3$ impregnated silica gel. Conversion of *Z*-**141** to the mixture allyl phenyl sulfides **142**, followed by cerium



Scheme 25.



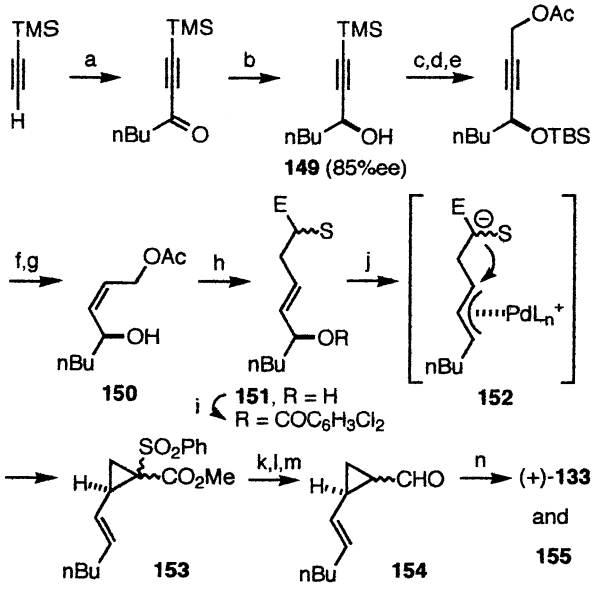
Scheme 27. *Reagents*: (a) $PhSSPh$, PBu_3 (97%); (b) LiDBB, THF, −78°C; then $CeCl_3$; then acrolein (55%); (c) $PhSSPh$, PBu_3 (96%); (d) LiDBB, THF, −78°C; then $CeCl_3$; then acrolein (60%); (e) LDA, THF, −78°C; then $[(EtO)_2(O)P]_2O$ (75%); (f) KHMDS, THF, −78°C–rt (70% +20% 1,3,5,8-undecatetraene).



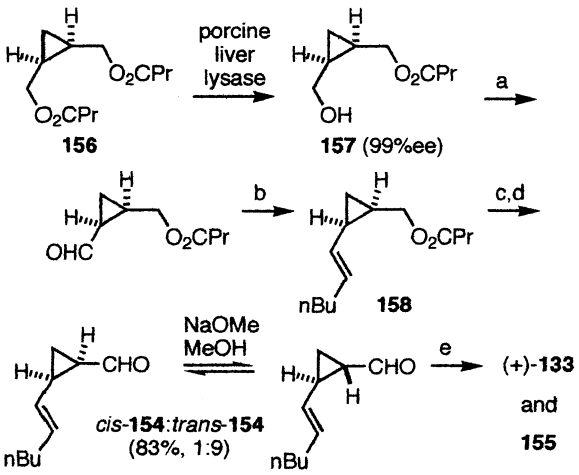
Scheme 28. *Reagents*: (a) EtO_2CCHN_2, $Rh_2(OAc)_4$ (85%); (b) pig liver esterase/Na_3PO_4 buffer (87%); (c) *N*-methylmorpholine, $ClCO_2sBu$, (*R*)-2-phenylglycinol (95%); (d) 10% KOH/MeOH/H_2O; then CH_2N_2 (86%); (e) $Ph_2P(O)=CH(CH_2)_3CH_3$ (56%); (f) $NaBH_4$/EtOH; NaH/DMF; (g) $LiAlH_4$, Et_2O (68%); (h) PCC, CH_2Cl_2; then $Ph_3P=CHCHO$, C_6H_6 (41%); (i) $nPrPPh_3^+Br^-$, nBuLi (83%, *E,Z*/*E,E*=1:1).

mediated coupling with acrolein afforded trienol **143** as a mixture of *E*- and *Z*-isomers (ca. 13:87). Deprotonation of the phosphonate ester **144** derived from **143**, yielded *rac*-**134** (70%) along with a mixture of undecatetraene (20%).

Jaenicke's group reported the synthesis of (+)-**133** and (−)-**134** (Scheme 28).[95] Racemic ethyl vinylcyclopropanecarboxylate **145** was generated as a *cis*/*trans* mixture by cyclopropanation of butadiene with ethyl diazoacetate. Selective hydrolysis of the *trans*-ester with PLE, chromatographic separation of the derived (*R*)-2-phenylglycinol amides and subsequent alkaline hydrolysis and diazo-



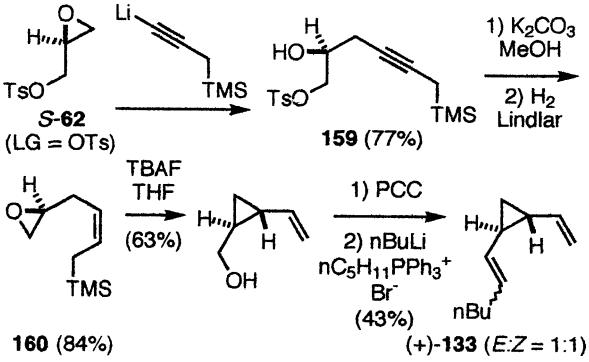
Scheme 29. (E=CO_2Me, S=SO_2Ph) *Reagents*: (a) nBuLi; followed by nBuCOCl; (b) Alpine borane, THF, rt (96%, 85% ee); (c) TBSCI, imidazole; (d) EtMgBr; then H_2CO; (e) Ac_2O, DMAP, NEt_3; (f) TBAF; (g) H_2, Lindlar catalyst; (h) $MeO_2CCH_2SO_2Ph$, 5% $Pd(dppe)_2$, DBU (23% from 149); (i) 2,4-dichlorobenzoyl chloride, pyr; (j) NaH, $Pd(dppe)_2$; (k) Na/Hg, Na_2HPO_4; (i) DIBAL; (m) PCC; (n) $Ph_3P=CH_2$.



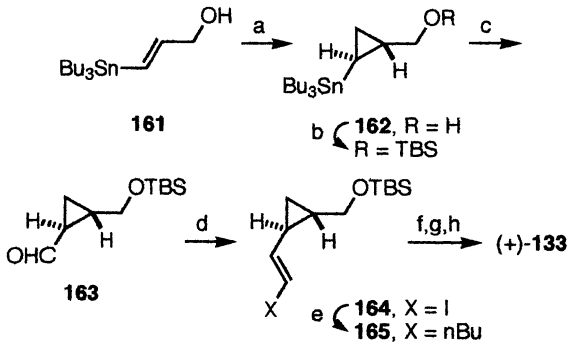
Scheme 30. *Reagents*: (a) PCC, NaOAc, molecular sieves (95%); (b) NaHMDS, 5,5-dipentyldibenzophospholium bromide; then 110°C (90%); (c) K_2CO_3, MeOH (90%); (d) PCC, NaOAc, molecular sieves (85%); (e) $Ph_3P=CH_2$ (95%).

methane esterification gave (+)-**146**. Reaction of (+)-**146** with the anion from pentylidenediphenylphosphine oxide generated a diastereomeric mixture of β-keto phosphine oxides **147**. Reduction and elimination gave (+)-**133** as a mixture of *E*- and *Z*-isomers; separable by chromatography over $AgNO_3$ impregnated silica gel. Alternatively, reduction, oxidation and Wittig olefination of cyclopropane ester (+)-**145** yielded the enal (+)-**148**, predominantly as the *E*-stereoisomer. Subsequent Wittig olefination of (+)-**148** an equimolar mixture of *E,Z*- and *E,E*-diene isomers. Chemical separation of the mixture was effected by preferential cycloaddition of the *E,E*-isomer with PTAD; unreacted (−)-**134** was thus isolated.

Colobert and Genet assembled (+)-**133** via a palladium-catalyzed intramolecular alkylation (Scheme 29).[96] Reduction of 1-trimethylsilyl-1-heptyn-3-one with Alpine borane gave the propargylic alcohol **149** (85% ee) which was converted into the allylic acetate **150** by standard transformations. Palladium catalyzed allylic alkylation with methyl phenylsulfonyl acetate led to **151**. After preparation of the 2,4-dichlorobenzoate, palladium catalyzed intramolecular alkylation proceeded via the π-allyl complex **152** to yield the hexenylcyclopropane **153** as a mixture of diastereomers at the quaternary carbon. Reductive desulfonylation, followed by reduction of the ester and



Scheme 31.



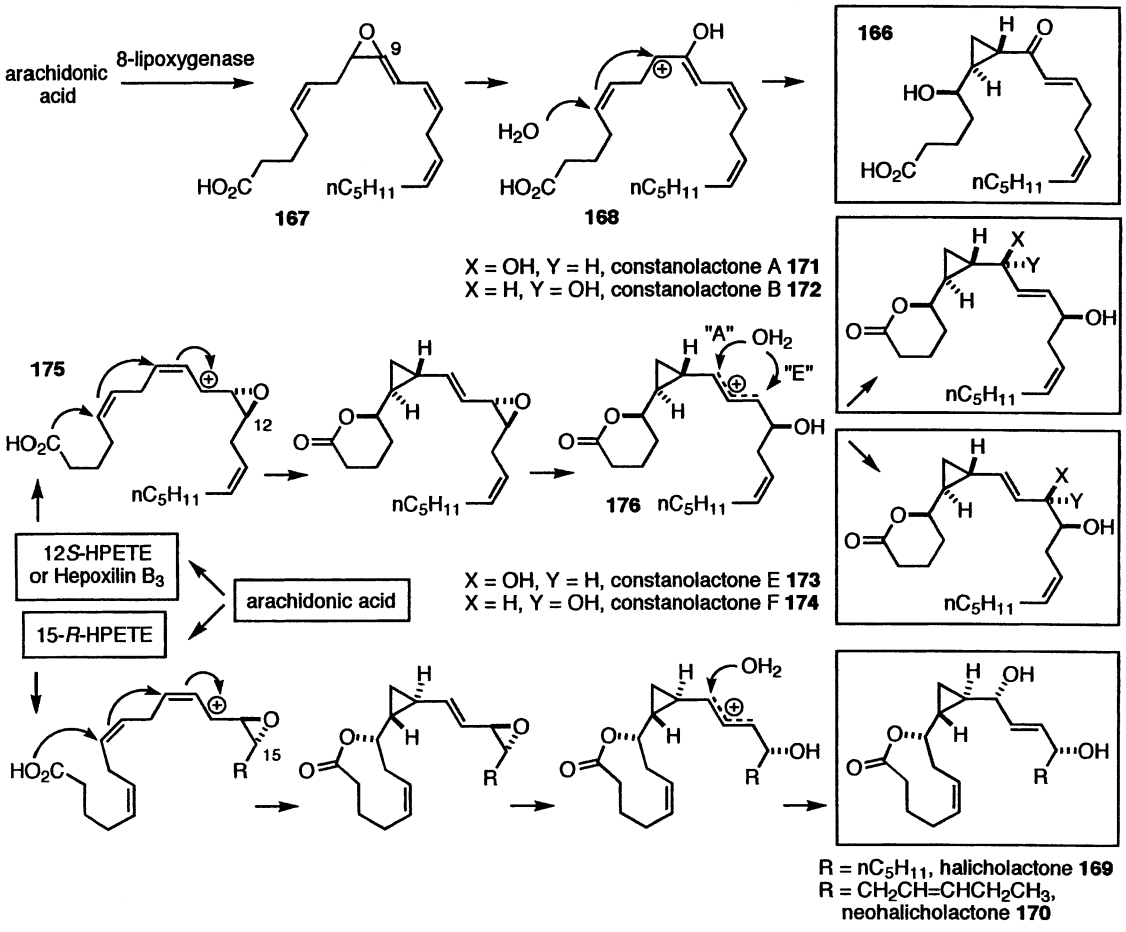
Scheme 32. *Reagents*: (a) $Zn(CH_2I)_2$, (*R*,*R*)-**8**, DME (96%, 98%ee); (b) TBSCI, imidazole; (c) nBuLi; then DMF (98%); (d) CHI_3 (2 equiv.) $CrCl_2$ (6 equiv.) (80%, *E*/*Z*=91:9); (e) Bu_2Zn (2 equiv.), 10% $Pd(PPh_3)_4$ (69%); (f) TBAF; (g) Dess–Martin periodinane (69%); (h) $Ph_3PMe^+I^-$, nBuLi (85%).

oxidation formed the aldehyde **154** as a mixture of *cis*- and *trans*-isomers. Wittig olefination of the mixture produced (+)-**133**; the *cis*-dialkenylcyclopropane formed in this step undergoes a Cope rearrangement to afford 6-butyl-1,4-cycloheptadiene (**155**).

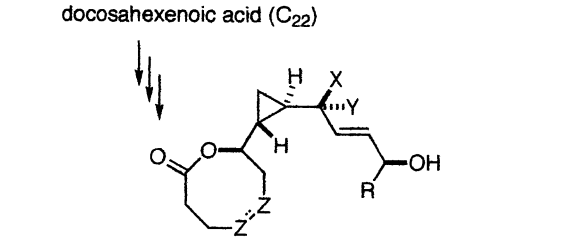
Pale's group reported a synthesis of (+)-**133** (Scheme 30)[97] which converges with Genet's synthesis. The *meso* cyclopropanediol diester **156** was desymmetrized by hydrolysis with porcine liver lysase to afford the alcohol **157** with high optical purity (>99% ee). Oxidation of **157** and Wittig olefination with the ylide derived from 5,5-dipentyldibenzophospholium bromide produced **158** with excellent *E*-selectivity. Hydrolysis of **158**, followed by oxidation gave the *cis*-cyclopropanecarboxyaldehyde *cis*-**154**. Epimerization of *cis*-**154** under basic conditions gave predominantly the *trans*-isomer (*trans*-**154**). Transformation of **154** into (+)-**133** was similar to that reported by Colobert and Genet.

Schaumann's group reported a synthesis of (+)-**133** based on a homoallyl-cyclopropylcarbinyl cation rearrangement (Scheme 31).[98] Reaction of (*S*)-glycidol tosylate with the anion of 3-trimethylsilylpropyne gave the homopropargylic alcohol **159**. Closure of the epoxide utilized K_2CO_3, and subsequent reduction over Lindlar catalyst afforded the *Z*-allylsilane **160**. Treatment of **160** with dry TBAF effected cyclopropane formation to give predominantly *trans*-2-vinylcyclopropylmethanol (*trans*/*cis*=16:1). Oxidation and Wittig olefination completed the synthetic scheme.

Recently the asymmetric Simmons–Smith protocol has been applied to the synthesis of (+)-**133** (Scheme 32).[99] Reaction of allylic alcohol **161** with $Zn(CH_2I)_2$ in the presence of (*R*,*R*)-8 produced the cyclopropylcarbinol **162** (98% ee). Protection of the alcohol functionality, metalation with *n*-butyl lithium and condensation with DMF afforded the aldehyde **163**. Olefination of **163** with iodoform, according to the Takai protocol,[100] gave the *E*-vinyl iodide **164**.



Scheme 33. Biosynthesis of marine derived eicosanoid cyclopropane oxylipans.

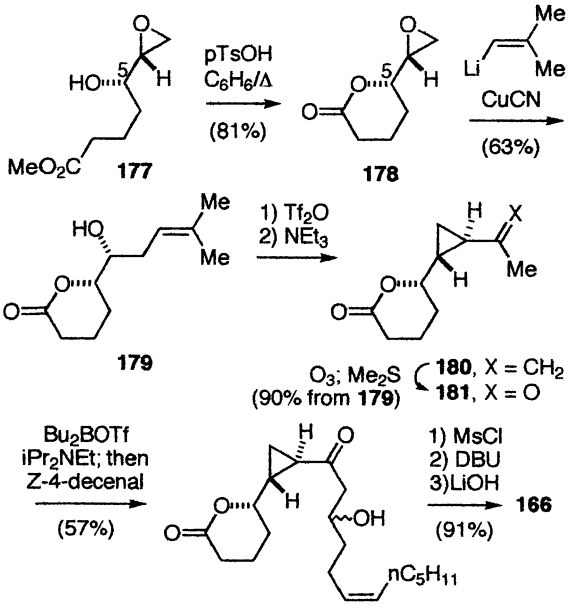


Solandelactone	Z-Z	X	Y	R
A	CH_2CH_2	H	OH	nC_5H_{11}
B	CH_2CH_2	OH	H	nC_5H_{11}
C	CH_2CH_2	H	OH	$CH_2CH{=}CHC_2H_5$
D	CH_2CH_2	OH	H	$CH_2CH{=}CHC_2H_5$
E	CH=CH	H	OH	nC_5H_{11}
F	CH=CH	OH	H	nC_5H_{11}
G	CH=CH	H	OH	$CH_2CH{=}CHC_2H_5$
H	CH=CH	OH	H	$CH_2CH{=}CHC_2H_5$

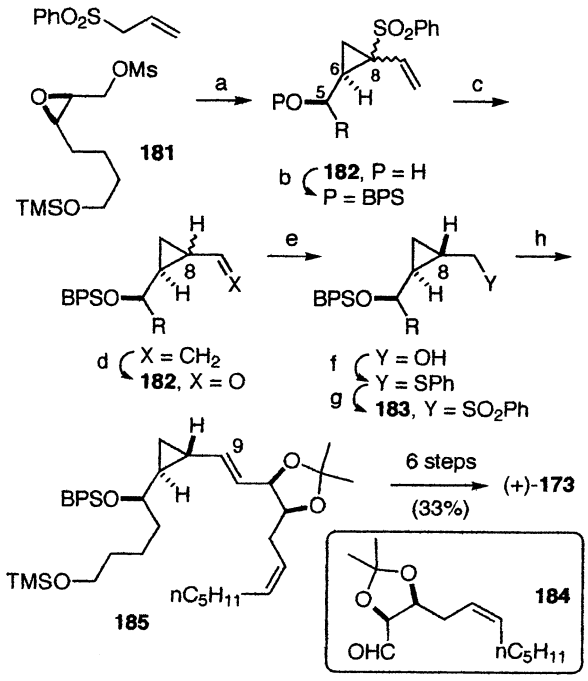
Figure 13.

Coupling of **164** with dibutylzinc in the presence of Pd(0) using the Negishi methodology,[101] afforded the hexenyl cyclopropane **165**. Removal of the TBS protecting group, oxidation and Wittig olefination completed the preparation of (+)-**133**.

3.3.3. Constanolactones, halicholactone, and solandelactones. Certain marine invertebrates and algae produce cyclopropyl containing eicosanoids. For example, incubation of arachidonic acid (AA) with an acetone powder from the coral *Plexaura homomalla* produces **166** (Scheme 33).[102] Corey, et al.[103] proposed that oxidation of AA by (8*R*)-lipoxygenase, followed by cyclization gives the allene oxide **167**. Brash[102] extended this hypothesis in proposing that **167** opens to the cation **168**. Rearrangement to the cyclopropylcarbinyl cation followed by nucleophilic capture by water would give **166**. Notably, the CD spectrum of **166** is described as 'featureless', and this may suggest that **166** is isolated in racemic form.



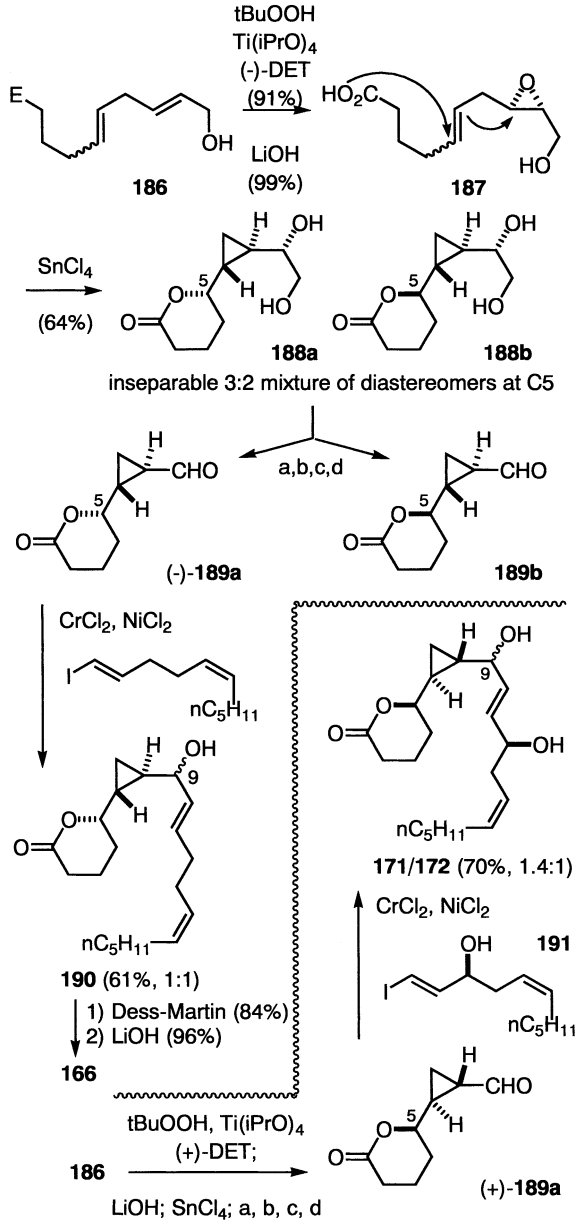
Scheme 34.



Scheme 35. R=$(CH_2)_4$ OTBS, *Reagents*: (a) nBuLi/−78°C (83%); (b) BPSCI, imidazole (81%); (c) SmI_2 (92%); (d) O_3; Me_2S (80%); (e) K_2CO_3/MeOH (99%); then $NaBH_4$ (98%); (f) PhSSPh, Pbu_3 (99%); (g) mCPBA, Na_2HPO_4 (99%); (h) nBuLi; then **184** (80%); Ac_2O, pyr, DMAP (70%); Na–Hg, MeOH/THF (56%).

Similarly, halicholactone and neohalicholactone (**169** and **170**) were isolated from *Halichondria okadai* (Scheme 33).[104] The relative configuration of **170** was established by single crystal X-ray diffraction.[105] Chemical degradation of **169** gave 1,2(*R*)-heptanediol diacetate, thus indicating the absolute configuration at C15.[104] Similarly, the constanolactones (**171**–**174**) are a series of lactonized oxylipins isolated from the red alga *Constantinea simplex* (Scheme 33).[106] The structure and absolute configuration of **171**–**174** were established by extensive spectroscopic analysis and degradation. Isolation of the diastereomeric constanolactones A and B (**171** and **172**) and the isomeric constanolactones E and F (**173** and **174**) lead Gerwick to propose that these metabolites arise via cyclization of an epoxy cation intermediate **175**. Nucleophilic attack on **176** along pathway A on either face of the allylic cation leads to **171** or **172** while attack along pathway E leads to **173** or **174**. A similar 15-lipoxygenase pathway has been proposed for the biosynthesis of **169**. While halicholactone inhibits guinea pig 5-lipoxygenase (IC_{50}=630 μM), the biological activity of the constanolactones is unknown.

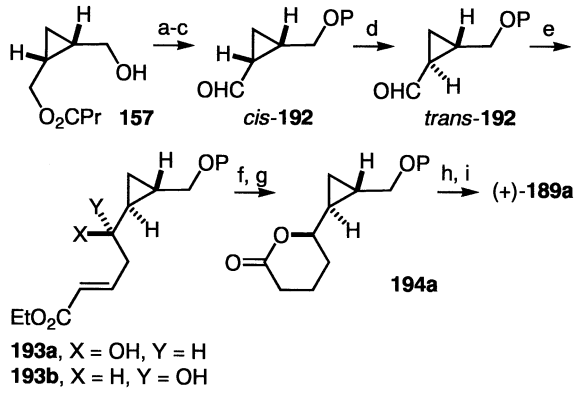
More recently, Shin and co-workers reported the isolation of solandelactones A–H from the hydriod *Solanderia secunda* collected near the coast of Korea (Fig. 13).[107] The structures and absolute configurations of these compounds were assigned on the basis of extensive NMR and CD spectroscopy, as well as chemical degradation. Notably, the solandelactones possess the same absolute configuration about the cyclopropane ring as found in halicholactone, while the absolute configuration at the lactone fragment is similar to that of the constanolactones. Solandelactones C, D, and G inhibit farnesyl protein transferase at the 100 μM level. In



Scheme 36. E=CO_2Me; *Reagents*: (a) $NaIO_4$ (94%); (b) 2,4-DNP-$NHNH_2$ (92%); (c) separate by MPLC; (d) O_3; Me_2S (61%).

addition to stereoselective/enantioselective construction of the cyclopropane ring, the introduction of asymmetric centers adjacent to the cyclopropane ring presents a significant challenge for preparation of the constanolactones, halicholactones, and solandelactones targets.

Suzuki, et al. utilize a homoallyl-cyclopropylcarbinyl cation rearrangement for their synthesis of **166**. Lactonization of **177** (prepared from 2-deoxy-D-ribose[109]) gave **178** (Scheme 34).[108] Epoxide opening of **178** with the cuprate derived from 1-lithio-2-methylpropene resulted in the homoallylic alcohol **179**. Treatment of **179** with triflic anhydride followed by triethylamine afforded the isopropenyl cyclopropane **180** as a single product; ozonolysis of the unstable isopropenyl cyclopropane gave the methyl ketone **181**. Aldol condensation of the boron enolate of **181** with (*Z*)-4-decenal followed by elimination and hydrolysis completed Suzuki's synthesis of **166**.

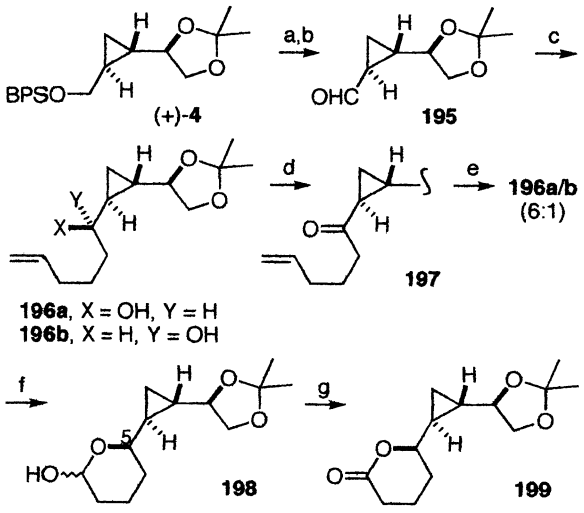


Scheme 37. P=thexylMe_2Si, *Reagents*: (a) thexylMe_2SiCl, DMAP; (b) K_2CO_3, MeOH; (c) Swern (91%); (d) NaOMe, MeOH, Δ (82%); (e) 1-TMSO-1-EtO-1,3-butadiene, $ZnCl_2$ (70–74%, **193a/193b**=3:1); separate; (f) Mg, MeOH (87%); (g) pTsOH, C_6H_6 (77%); (h) TBAF (81%); (i) Dess–Martin (82%).

Yamada, et al. have reported a total synthesis of constanolactone E, (+)-**173** (Scheme 35).[110] Reaction of allylphenylsulfone with epoxy mesylate **181** gave the cyclopropylcarbinol **182** as a mixture of diastereomers at C8. The stereochemistry at C5 and C6 is generated via an intramolecular 3-*exo*-tet ring closure (see Scheme 8). Reductive cleavage of the sulfonyl group followed by ozonolysis and epimerization gave the thermodynamically more stable *trans*-aldehyde **182** (15:1 ratio). Conversion of the aldehyde to the phenyl sulfone **183** follows standard reaction conditions. Julia olefination of aldehyde **184** with **183** afforded the *E*-olefin **185** which was eventually converted into **173**.

White and Jensen reported the total synthesis of both **166**, **171** and **172** (Scheme 36).[111] Sharpless asymmetric epoxidation of **186** gave the homoallylic epoxy acid **187**. A Lewis acid mediated, biomimetic cyclization of **187** gave an inseparable mixture of cyclopropyl lactones **188a/b** (3:2 ratio) which are diastereomeric at C5. The ratio of **188a** to **188b** was independent of the C5–C6 olefin stereochemistry of the precursor **186**. Separation of the diastereomers was effected by glycol cleavage, generation of the 2,4-DNP hydrazone derivatives and MPLC chromatography. Separate ozonolytic cleavage of the 2,4-DNP derivatives gave the aldehyde diastereomers **189a** and **189b**. Nozaki–Kishi coupling[112] of aldehyde (−)-**189a** with 1-iodo-1E,5Z-undecadiene gave allylic alcohol **190** as a 1:1 mixture of diastereomers. Oxidation of the diastereomeric mixture followed by hydrolysis gave **166**. Coupling of (+)-**189a** (prepared from **186** by asymmetric epoxidation with (+)-DET) with vinyl iodide **191** in the presence of $CrCl_2/NiCl_2$ gave a 1.4:1 mixture of **171** and **172** (78%). The diastereomerically pure natural products were separable by HPLC.

Recently, Pale and co-workers have reported the synthesis of **171/172** via the C1–C9 lactone intermediate (+)-**189a** (Scheme 37).[113] As was previously reported, enzymatic desymmetrization of *meso* diester **156** gave the alcohol **157** (cf. Scheme 30). Protection of the free hydroxyl group, followed by hydrolysis of the butyryl ester and Swern oxidation gave the aldehyde *cis*-**192**. Epimerization of *cis*-**192** at C5 was effected by treatment with sodium methoxide to yield the *trans*-cyclopropyl aldehyde **192**.

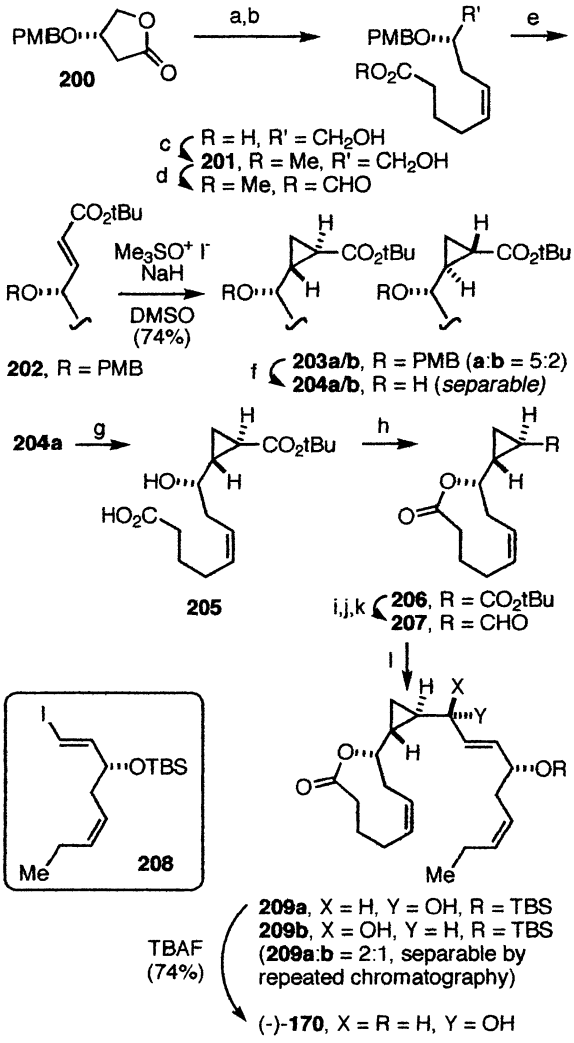


Scheme 38. *Reagents*: (a) TBAF (82%); (b) 2-iodoxy-benzoic acid, DMSO (93%); (c) 4-pentenylmagnesium bromide (85%, 7:3 dr); (d) Dess–Martin (87%); (e) K-Selectride (88%); (f) OsO_4, NMO; then $NaIO_4$ (95%); (g) PDC (92%).

Mukiayama-type aldol condensation of **192** with 1-ethoxy-1-trimethylsilyloxy-1,3-butadiene in the presence of $ZnCl_2$ proceeded via γ-addition to give a mixture of diastereomeric alcohols **193a** and **193b** (ca. 3:1 ratio). The major diastereomer was reduced (Mg/MeOH) and cyclized (pTsOH) to give the lactone **194a**. Removal of the dimethylthexylsilyl protecting group and oxidation gave (+)-**189a**. These authors complete the synthesis of **171**/**172** in a similar fashion to that previously reported by White and Jensen (cf. Scheme 36).

Datta and co-workers have reported the synthesis of a C1–C10 lactone which contains the required stereocenters present in constanolactone A (Scheme 38).[114] They begin their synthesis with the known[14] optically active cyclopropane fragment (+)-**4** (for preparation of (−)-**4** see Scheme 1). Deprotection of (+)-**4** and subsequent oxidation gave the aldehyde **195**. Addition of the Grignard reagent derived from 5-bromo-1-pentene proceeded with low diastereoselectivity to afford a mixture of **196a** and **196b** (ca. 7:3). The selectivity could be improved by oxidation to the ketone **197**, followed by reduction with K-Selectride yielded **196a/b** in a 6:1 ratio. These diastereomers were separable by flash chromatography. Dihydroxylation of **196a** followed by glycol cleavage gave the lactol **198** which was oxidized to the lactone **199**.

Critcher, Connolly, and Wills were the first to report a total synthesis of halicholactone and neohalicholactone (Scheme 39).[115] (*S*)-Malic acid was transformed into the PMB protected hydroxy lactone **200** in four steps. Reduction to the lactol, olefination and esterification gave the *Z*-olefin **201**. Oxidation followed by Wadsworth–Emmons olefination gave the α,β-unsaturated ester **202**. Addition of dimethyl sulfoxonium methylide to **202** gave an inseparable mixture of diastereomeric cyclopropane esters **203a/b** (5:2). These authors propose that Michael-type addition proceeds via the C8–C9 conformers in which the allylic ether is perpendicular to the plane of the olefin (Fig. 14). These orientations allow for maximum overlap between the



Scheme 39. *Reagents*: (a) DIBAL; (b) $Ph_3P^+(CH_2)_4CO_2H$, NaHMDS; (c) MeOH, AcCl (69%, three steps); (d) DMSO, $(COCl)_2$, NEt_3; (e) $(EtO)_2P(O)CH_2CO_2tBu$, DBU, LiCl (75%, two steps); (f) DDQ (100%); (g) LiOH, THF, H_2O (100%); (h) 2,4,6-$Cl_3C_6H_2COCl$, Net_3, DMAP (75%); (i) TFA (80%); (j) $ClCO_2Et$, NEt_3; then $NaBH_4$; (k) TPAP, NMO (77%, two steps); (l) **208** (1.7 equiv.), $CrCl_2$ (3.3 equiv.), $NiCl_2$ (cat.) (73%).

electron withdrawing group and the π^*-orbital of the enoate. The alkyl substituent prefers the 'outside' position so as to minimize steric interactions. Nucleophilic attack on the face of the olefin opposite to the ether substituent affords the major product. Oxidative removal of the *p*-methoxybenzyl protecting group gave a separable mixture of alcohols **204a** and **204b**. Preferential saponification of the methyl ester of **204a** (in the presence of the *t*-butyl ester) gave the hydroxy acid **205**. The macrolactonization of **205** is facilitated on

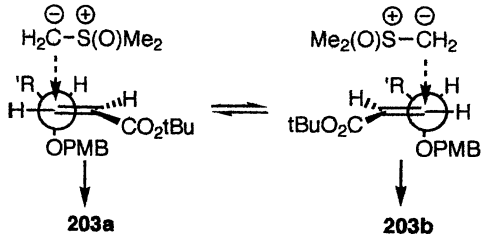
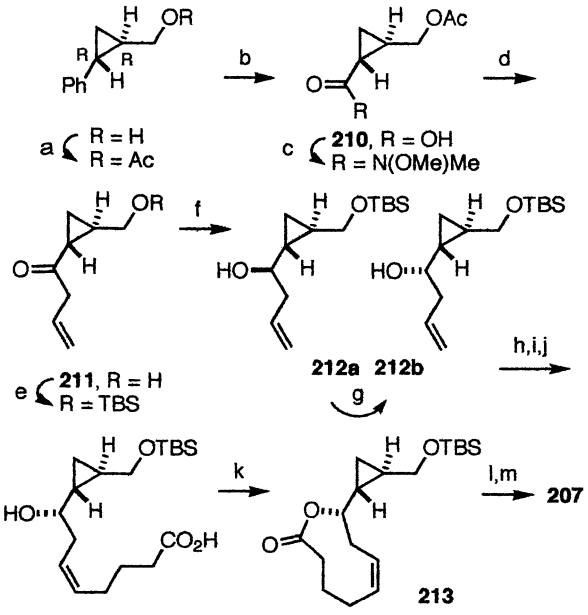


Figure 14.



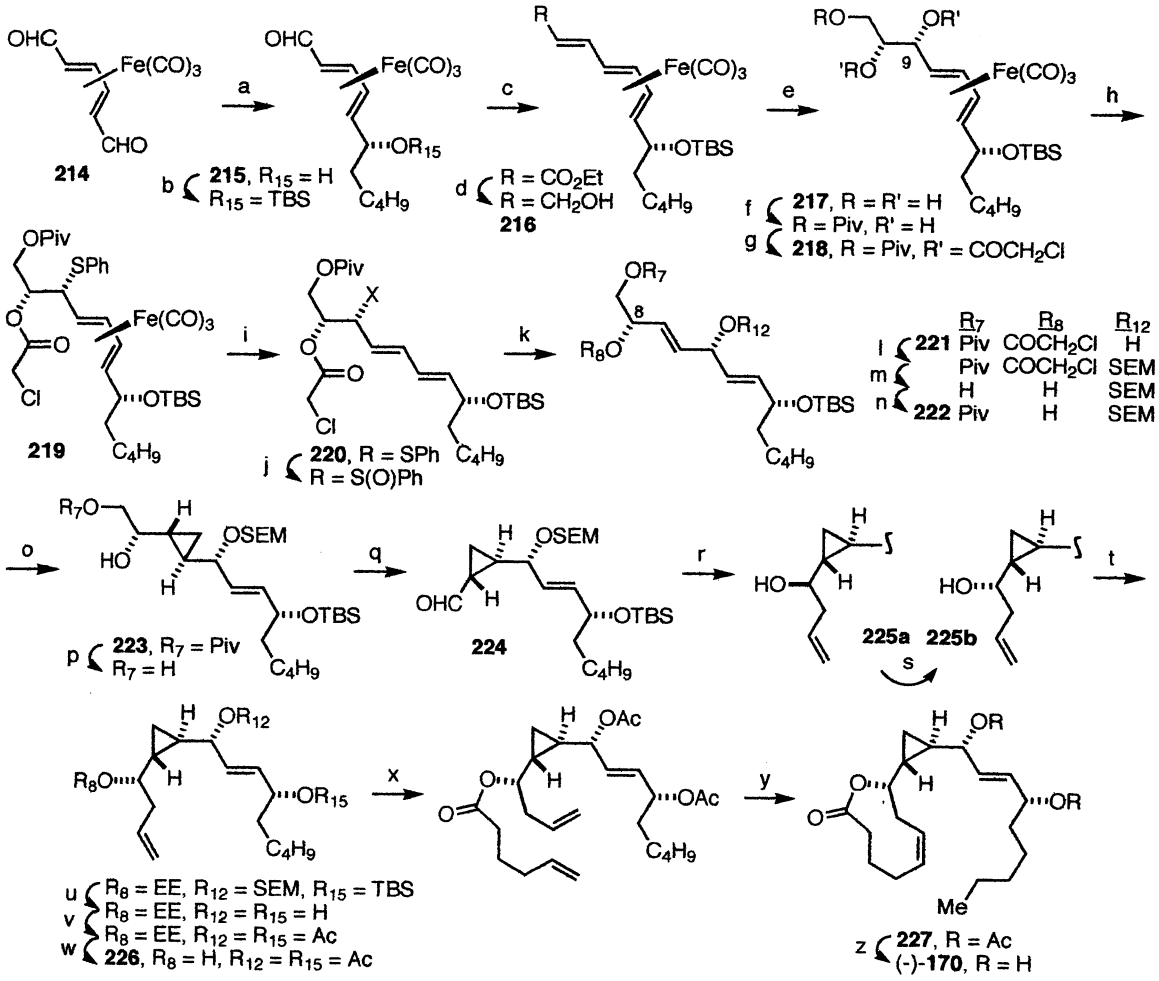
Scheme 40. *Reagents*: (a) Ac_2O, DMAP (quantitative); (b) $RuCl_3$–H_2O, $NaIO_4$ (93%); (c) MeONHMe, CDI, (82%); (d) $BrMgCH_2CH{=}CH_2$ (87%); (e) TBSCI, imidazole (90%); (f) K-Selectride/−78 C (92%, **212a/212b**=1:9); (g) DEAD, CH_3CO_2H, PPh_3; followed by NaOMe, MeOH, H_2O (91%); (h) OSO_4, NMO; (i) $NaIO_4$, $NaHCO_3$, MeOH, H_2O (84%); (j) $HO_2C(CH_2)_4PPh_3^+$ Br^-, NaHMDS (90%); (k) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, DMAP (66%); (l) TBAF, THF (92%); (m) 2-iodoxybenzoic acid, DMSO (89%).

entropic and enthalpic levels; the presence of the *Z*-olefin reduces the number of possible conformers and relieves transannular interactions. The *t*-butyl ester of lactone **206** was transformed into an aldehyde **207** by hydrolysis, reduction of the mixed anhydride and TPAP oxidation. Coupling of aldehyde **207** with the vinyl iodide **208** gave a mixture of allylic alcohols **209a/b** with minimal diastereoselectivity (2:1). Separation of the mixture was possible only by repeated chromatography. Deprotection of **209a** was possible by employing vigorous conditions (TBAF, THF, reflux) to give **170** which was identical to the naturally occurring neohalicholactone on the basis of ^1H- and ^{13}C NMR spectroscopy. Halicholactone (**169**) was also produced by coupling of 1-iodo-3-TBSO-1*E*-octene with **207**, separation of the diastereomeric allylic alcohols and TBS deprotection.

Recently, Mohapatra and Datta reported a synthesis of the intermediate **207** (Scheme 40).[116] The starting point, (2*R*-phenylcyclopropyl)methanol, was prepared by asymmetric Simmons–Smith cyclopropanation using the Charette bifunctional ligand (*R*,*R*)-**8** (cf. Eq. (7)). Acylation followed by oxidative cleavage of the phenyl group afforded *trans*-carboxylic acid **210**. Conversion of **210** to the Weinreb's amide and subsequent reaction with allyl magnesium bromide yielded the allylic ketone **211**. After protection of the primary alcohol, stereoselective reduction with K-selectride gave the diastereomeric alcohols **212b** and **212a** (92% yield, 9:1 dr) which were separable by column chromatography. The absolute configuration at C8 was assigned on the basis of the relative chemical shifts of the (*R*)- and (*S*)-MPTA esters of **212b**. Mitsunobu inversion and methanolysis converted the minor alcohol **212a** into the major diastereomer **212b**. Oxidative cleavage of **212b**, followed by olefination and macrolactonization gave **213** which was transformed into the aldehyde **207**.

One of the challenges to the synthesis of halicholactone is the lack of stereoselectivity in the generation of the C12 alcohol by nucleophilic addition to the cyclopropyl carboxaldehyde **207** (cf. Scheme 39, **207→209a/b**). Takemoto's group utilized the stereodirecting ability of the (tricarbonyl)-iron adjunct in an asymmetric synthesis of **170** (Scheme 41).[117] Asymmetric alkylation of *meso* (2,4-hexadiendial)-$Fe(CO)_3$ (**214**) with dipentylzinc in the presence of (*S*)-diphenyl-(1-methylpyrrolidin-2-yl)methanol gave the alcohol complex **215** (>98% ee).[118] Protection of **215** followed by Horner–Emmons olefination and reduction gave the allylic alcohol **216**. Dihydroxylation of **216** proceeded on the *s-trans* conformer on the face opposite to the bulky $Fe(CO)_3$ group to give the triol **217** in a highly diastereoselective fashion (9:1 dr). Sequential protection of **217** afforded the bis(chloroacetate) **218**. Substitution of the C9 chloroacetate with thiophenolate was facilitated by the stability of the intermediate transoid (pentadienyl)iron cation to produce **219**. Decomplexation of **219** gave the free diene ligand **220**. Oxidation of the phenyl sulfide, followed by 1,3-migration of the resultant sulfoxide constructed the divinylcarbinol **221**. Protecting group manipulation led to the allylic alcohol **222**. Simmons–Smith cyclopropanation of **222** gave **223** in a stereoselective fashion; the diastereoselectivity of this cyclopropanation may be rationalized on the basis of the directing ability of the C8 hydroxyl group (halicholactone numbering) (cf. Fig. 15). Formation of cyclopropanecarboxaldehyde **224** was accomplished by removal of the pivalate group and glycol cleavage. Allylation of **224** gave a separable mixture of diastereomeric alcohols **225a** and **225b**; the ratio of **225a/225b** was not specified. The undesired diastereomer **225a** was converted into **225b** by Mitsunobu inversion and solvolysis of the acetate. Again protecting group manipulation produced the diacetate **226**. Formation of the nine-membered lactone ring was accomplished by esterification with 5-hexenoic acid followed by ring closing metathesis using Grubbs' catalyst. Methanolysis of **227** gave halicholactone.

While no total synthesis of any of the solandelactones has been completed to date, Datta and coworkers have reported preparation of the C1–C11 cyclopropane-lactone segment (Scheme 42).[119] Their starting point is the optically active cyclopropane (−)-**4**, prepared from *R*-glyceraldehyde acetonide (cf. Scheme 1). In a fashion similar to the synthesis of **199** from this same group (Scheme 38), deprotection and oxidation of (−)-**4** yielded the aldehyde *ent*-**195**. Addition of allylmagnesium bromide produced a mixture of alcohols **228a** and **228b** which could only be separated with difficulty upon repeated chromatography. Alternatively, selective acylation of **228a** to form **229a** could be accomplished with *Candida cylindracea* lipase. The diastereomeric homoallylic alcohol **228b** was converted into **229a** by Mitsunobu inversion. Dihydroxylation/glycol cleavage of **229a** gave the β-acetoxy aldehyde **230**. Formation of the eight-membered unsaturated lactone **231** was completed by *Z*-selective Wittig olefination, hydrolysis of the acetate and ethyl esters, and lactonization.



Scheme 41. *Reagents*: (a) (*n*-pentyl)$_2$Zn, (*S*)-diphenyl-(1-methylpyrrolidin-2-yl) methanol (78%, 98%ee); (b) TBSOTf, pyr (100%); (c) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH (99%); (d) DIBAL, CH$_2$Cl$_2$ (97%); (e) OsO$_4$, pyr, −20°C; then sat. aq. NaHSO$_3$ (94%); (f) PivCl, pyr (97%); (g) (ClCH$_2$CO)$_2$O, DMAP (89%); (h) Me$_2$AlSPh, CH$_2$Cl$_2$, −78°C (69%); (i) CAN, K$_2$CO$_3$, CH$_3$CN, −30°C (97%); (j) mCPBA, CH$_2$Cl$_2$, −78°C (95%); (k) P(OMe)$_3$, MeOH, 75°C (88%); (l) SEMCl, iPr$_2$NEt (100%); (m) DIBAL (91%); (n) PivCl, pyr (85%); (o) Et$_2$Zn, CH$_2$I$_2$ (77% based on consumed **222**); (p) MeLi (90%); (q) Pb(OAc)$_4$, Na$_2$CO$_3$, CH$_2$Cl$_2$, −40°C (68%); (r) Sn(allyl)$_4$, Sc(OTf)$_3$, CH$_3$CN; (s) AcOH, DIAD, PPh$_3$, THF; then MeOH, NaH (60%); (t) ethyl vinyl ether, PPTS (90%); (u) TBAF, 4A molecular sieves, DMPU, 85°C (64%); (v) Ac$_2$O, NEt$_3$, DMAP (88%); (w) PPTS, tBuOH (69%); (x) 5-hexenoic acid, DCC, DMAP (82%); (y) (PCy$_3$)$_2$Cl$_2$RuCHPh, Ti(OiPr)$_4$, CH$_2$Cl$_2$ (0.1 mM), Δ (72%); (z) K$_2$CO$_3$, MeOH (61%).

3.4. Polycyclopropanes

In 1990, the antifungal nucleoside FR-900848 (**231**, Fig. 16) was isolated from fermentation of *Streptoverticillium fervens*.[120] The atom connectivity was reported at this time and subsequent degradation studies along with independent syntheses of either fragments or model compounds revealed the relative configurations about the five cyclopropane rings and C18–C19 olefin. In 1995, U-106305 (**232**, Fig. 16), a similar polycyclopropane amide was isolated from *Streptomyces sp.* UC 11136.[121] This compound was found to possess potent inhibitory action

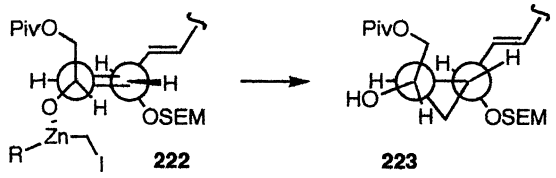
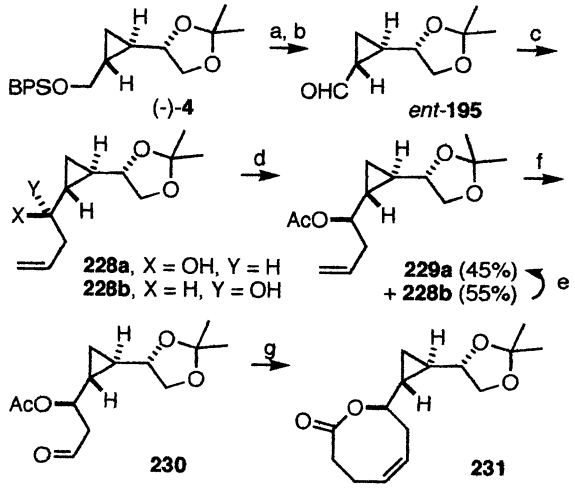


Figure 15.



Scheme 42. *Reagents*: (a) TBAF (83%); (b) 2-iodoxy benzoic acid (97%); (c) allylmagnesium bromide (89%); (d) *Candida cylindracea* lipase, H$_2$C=CC(OAc)Me, hexane; (e) DEAD, AcOH, PPh$_3$ (85%); (f) OsO$_4$, NMO; then NaIO$_4$ (82%); (g) 3 steps (45%).

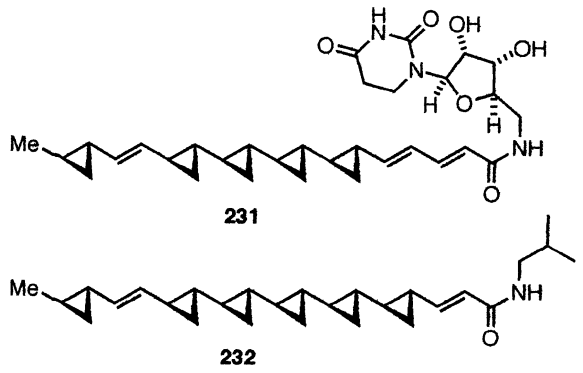
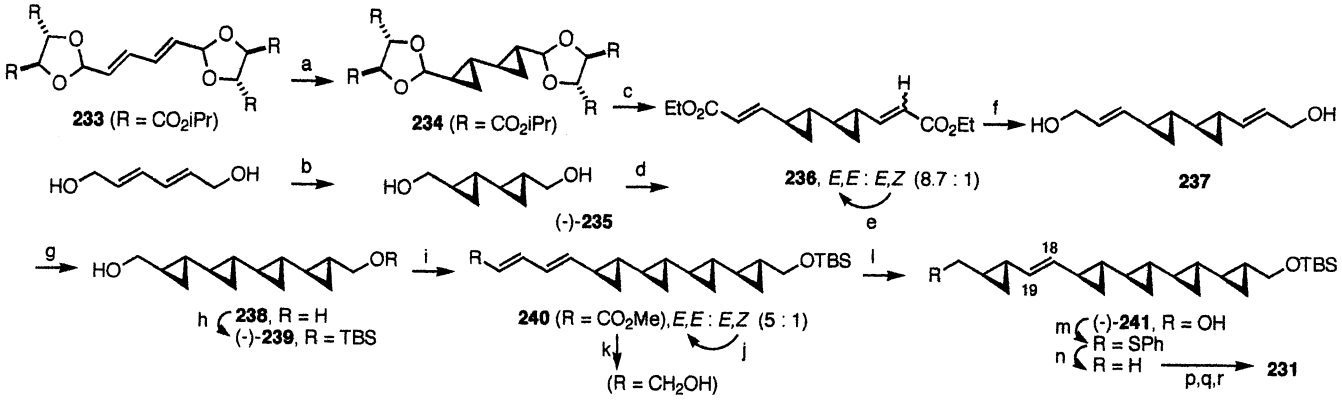


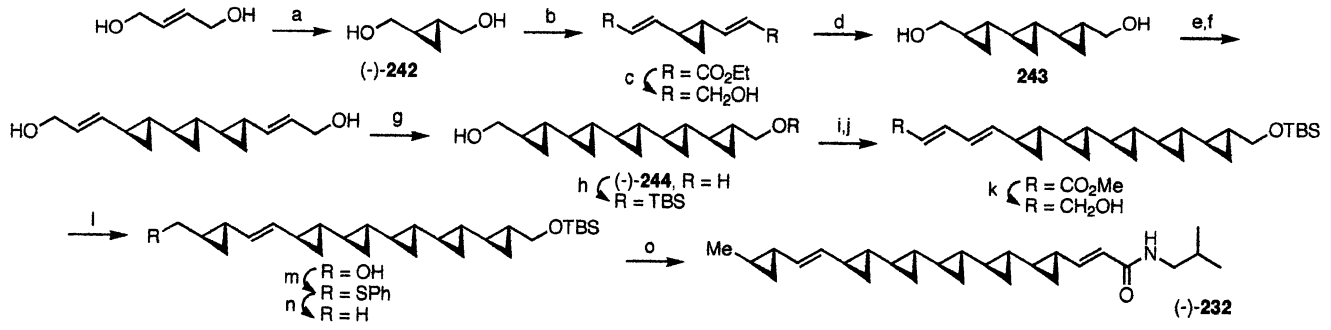
Figure 16.

against the cholesteryl ester transfer protein. On the basis of NMR spectral data, the research team at Upjohn proposed that all of the cyclopropane rings of **232** are *trans* substituted. Further studies indicated that all of the cyclopropane methylene carbons of **232** arise biosynthetically from methionine. The absolute configuration of both **231** and **232** were eventually confirmed by total synthesis.

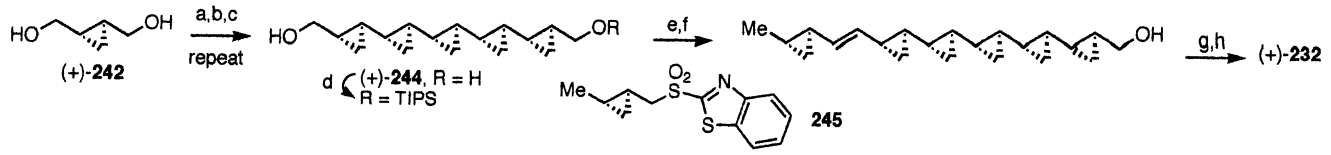
Barrett and Kasdorf were the first to report a total synthesis of FR-900848. In their retrosynthetic analysis the target was dissected at the olefins adjacent to the polycyclopropane segment to render a tetrakis-cyclopropane subtarget **238** which was further dissected to a bis-cyclopropane fragment **235** (Scheme 43).[122] Simmons–Smith cyclopropanation of the bis-acetal **233** derived from 2,4-hexadien-1,6-dial, gave the bis-cyclopropane **234**.[123] Alternatively, asymmetric cyclopropanation of 2,4-hexadien-1,6-diol according to the Charette protocol [(*S*,*S*)-8] gave (−)-**235**.[122] Hydrolysis of bis-acetal **234** or oxidation of diol (−)-**235** gave an unstable dialdehyde which was immediately reacted with carbethoxymethylene triphenylphosporane (ca. 3 equiv) to give the diester **236** as a separable mixture of *E*,*E*- and *E*,*Z*-isomers. Isomerization of the *E*,*Z*-isomer to the desired *E*,*E*-isomer was possible using phenythiolate and $Ti(OiPr)_4$. Reduction of *E*,*E*-**236** gave the bis-allylic alcohol **237** and set the stage for a second asymmetric double cyclopropanation. In this case, cyclopropanation of **237** in the presence of (*S*,*S*)-**8** gave a single tetrakis-cyclopropane **238**. Monoprotection of **238** gave the alcohol **239**. Oxidation of **239** followed by Wadsworth–Emmons olefination gave the dienoate **240** as a separable mixture of *E*,*E*- and *E*,*Z*-isomers. As previously, isomerization of the *E*,*Z*-isomer gave more of the *E*,*E*-dienoate. Reduction of *E*,*E*-**240** gave a dienylic alcohol which was subjected to cyclopropanation



Scheme 43. *Reagents*: (a) Et_2Zn, CH_2I_2 (73%); (b) $Zn(CH_2I)_2$/DME (*S*,*S*)-**8** (89%); (c) pTsOH, THF, H_2O; followed by $Ph_3P{=}CHCO_2Et$ (61%); (d) PCC; followed by $Ph_3P{=}CHCO_2Et$ (67%); (e) BuLi, PhSH, $Ti(iPrO)_4$; (f) DIBAL (94%); (g) $Zn(CH_2I)_2$:DME, *S*,*S*-**8** (93%); (h) NaH, TBSCI (44%+44% **238**); (i) PCC; followed by $(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH (71%); (j) BuLi, PhSH, $Ti(iPrO)_4$; (k) DIBAL (91%); (l) $Zn(CH_2I)_2$ DME, *S*,*S*-**8** (90%); (m) N-(phenylthio) succinimide, Bu_3P (89%); (n) Raney nickel; (o) NH_4F (49% two steps); (p) PCC, NaOAc; followed by $(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH; followed by BuLi, PhSH, $Ti(iPrO)_4$ (51%); (q) KOTMS, CH_2Cl_2 (85%); (r) BOPCl, 5′-amino-5′-deoxy-5,6-dihydrouridine (69%).



Scheme 44. *Reagents*: (a) $Zn(CH_2I)_2$: DME, *S*,*S*-**8** (83–91%, 81% ee); (b) Dess–Martin periodinane; followed by $Ph_3P{=}CHCO_2Et$ (96%, recrystallization increases to >99% ee); (c) DIBAL (96–97%); (d) $Zn(CH_2I)_2$/DME, *S*,*S*-**8** (83–91%); (e) Dess–Martin periodinane; followed by $Ph_3P{=}CHCO_2Et$ (75–81%); (f) DIBAL (96–97%); (g) $Zn(CH_2I)_2$/DME, *S*,*S*-**8** (83–91%); (h) TBSCI, imidazole (75% calcd at 78% conversion); (i) Dess–Martin periodinane; (j) NaH, DBU, (*E*)-$(MeO)_2P(O)CH_2CH{=}CHCO_2Et$ (88%); (k) DIBAL (95%); (l) $Zn(CH_2I)_2$/DME, *S*,*S*-**8** (72%); (m) *N*-(phenylthio) succinimide, PBu_3 (91%); (n) Raney nickel (44%); (o) TBAF; then Dess–Martin periodinane; then $Cl^-\ Ph_3P^+CH_2CONHCH_2iBu$, DBU (91%).



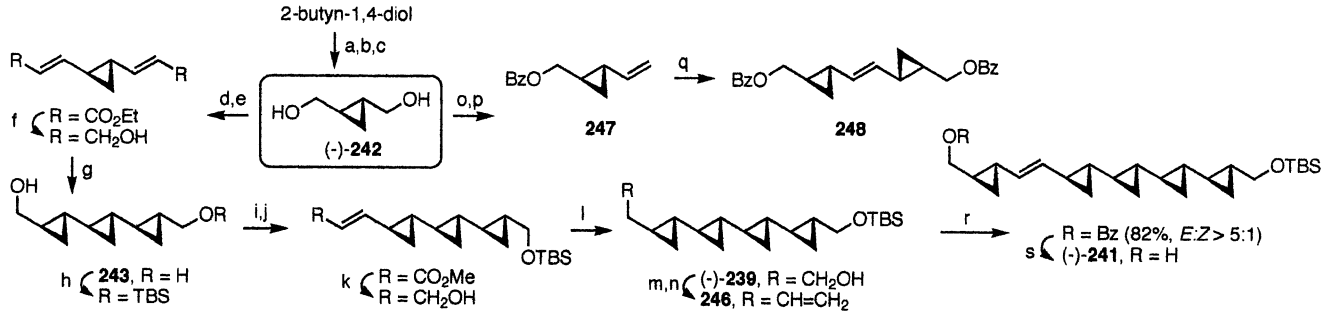
Scheme 45. *Reagents*: (a) PCC/Celite; followed by $(EtO)_2P(O)CH_2CO_2Et$, NaH (49–40%, *E*,*E*/*E*,*Z*>5:1); (b) DIBAL (81–99%); (c) $Zn(CH_2I)_2$ (4.4 equiv.) *R*,*R*-**8** (2.2 equiv.) (90%); (d) TIPSOTf, 2,6-lutidine (57% two recycles); (e) PCC/Celite (85%); (f) NaHMDS, **??**, then TBAF (92%, *E*/*Z*=4:1); (g) PCC; (h) $Ph_3PCH_2CONHCH_2iBu$ (91%).

in the presence of (*S*,*S*)-**8** to give the cyclopropylcarbinol (−)-**241**. It is necessary to perform this final cyclopropanation at −40°C in order to avoid reaction at the C18–C19 olefin. The C23 hydroxyl group was transformed into the phenyl sulfide; reductive desulfurization in the presence of Raney-nickel at low temperature (−40°C) gave the methylcyclopropane without reduction of the C18–C19 olefin. With the polycyclopropane segment in hand, the final steps required removal of the silyl protecting group (NH_4F), oxidation (PCC), and Wadsworth–Emmons olefination. Hydrolysis of the dienoate ester followed by coupling the resultant carboxylic acid with 5′-amino-5′-deoxy-5,6-dihydrouridine completed the synthesis.

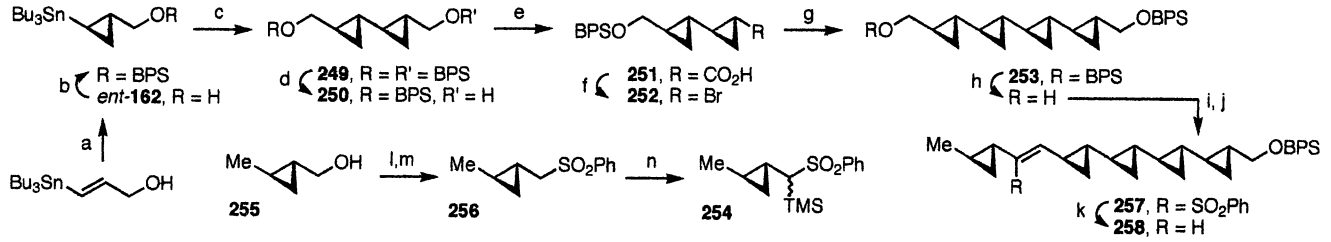
Barrett's group also utilized a bi-directional cyclopropanation strategy in the first total synthesis of U-106305 (**232**, Scheme 44).[124] Cyclopropanation of 2*E*-buten-1,4-diol in the presence of (*S*,*S*)-**8** gave bis-hydroxymethylcyclopropane (−)-**242**. Oxidation, Wittig olefination, reduction, and asymmetric cyclopropanation gave the tris-cyclopropane **243**; a second iteration of these steps generated the pentacyclopropane (−)-**244**, whose structure was confirmed by X-ray crystallography. The diol (−)-**244** was elaborated into the target (−)-**232** using methodology previously demonstrated in the preparation of **231**.

Shortly after Barrett's preparation of (−)-**232**, Charette and Lebel reported a preparation of the enantiomer, (+)-**232** (Scheme 45).[125] The early steps of their synthesis [(+)-**242**→(+)-**244**] are similar to those independently reported by Barrett's group, with the major exception being the use of (*R*,*R*)-**8** instead of the (*S*,*S*)-**8** reagent. Charette and Lebel employed a modified Julia olefination between the pentacyclopropyl carboxaldehyde and benzothioazole sulfone **245** to fashion the C18–C19 olefin (*E*/*Z*=4.4:1). The synthesis was completed in a fashion similar to Barrett's synthesis. Zercher's group reported a similar synthesis of the pentacyclopropane intermediate (+)-**244**.[126]

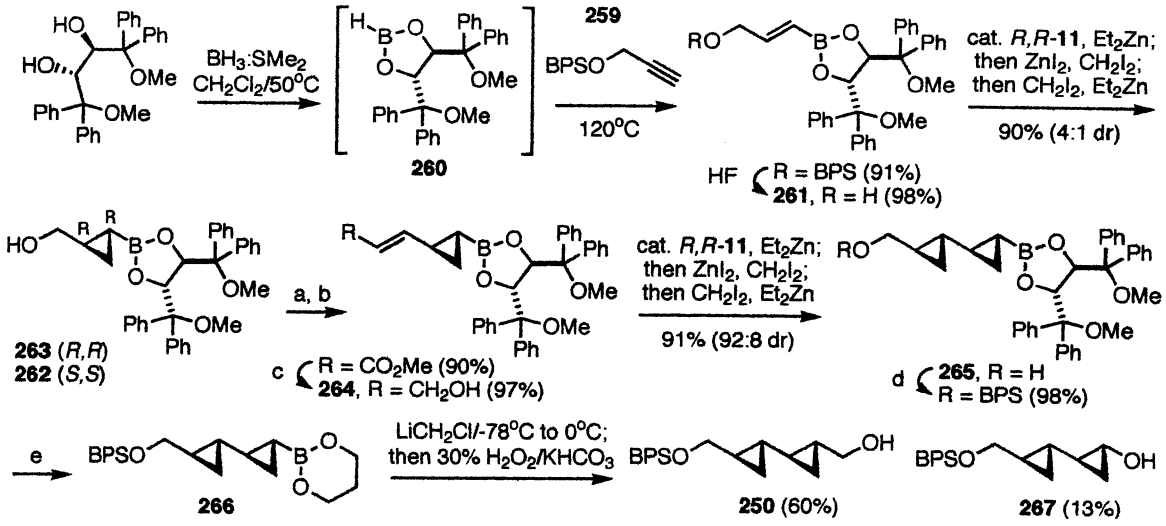
Verbicky and Zercher used a variant of the bi-directional, cyclopropanation strategy in their synthesis of (−)-**241** a key intermediate for FR-900848 (Scheme 46).[127] The transformation of (−)-**242** into the tris-cyclopropane **243** was similar to that utilized by Barrett and Charette's groups.



Scheme 46. *Reagents*: (a) $LiAlH_4$ (79%); (b) TBSCl, NEt_3 (86%); (c) Et_2Zn, CH_2I_2, *S*,*S*-**8**; then AcOH/THF/H_2O (86%); (d) TPAP, NMO; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH (78%, two steps); (f) DIBAL (73%); (g) Et_2Zn, CH_2I_2, *S*,*S*-**8** (60%); (h) TBSCl, NEt_3 (68%); (i) TPAP, NMO; (j) $(EtO)_2P(O)CH_2CO_2Et$, NaH (92%, two steps); (k) DIBAL (53%); (l) Et_2Zn, CH_2I_2, *S*,*S*-**8** (95%); (m) TPAP, NMO; (n) $Ph_3PCH_3^+$ Br^-, MeLi (75% two steps); (o) BzCl, NEt_3 (35%); (p) TPAP, NMO; $Ph_3PCH_3^+Br^-$, MeLi (71%, two steps); (q) 0.5 equiv. $Cl_2(PCy_3)_2RuCHPh$ (64%); (r) 2 equiv. **248**, 0.5 equiv. $Cl_2(PCy_3)_2RuCHPh$ (82%); (s) MeOH, KOH (89%).



Scheme 47. *Reagents*: (a) $ZnEt_2$, CH_2I_2, *S*,*S*-**8** (98%, 88% ee); (b) BPSCl, imidazole (88%); (c) nBuLi; then $[ICuPBu_3]_4$; then O_2 (73%); (d) 0.95 equiv. TBAF (72%); (e) $RuCl_3$, $NaIO_4$ (91%); (f) 2-mercaptopyridine *N*-oxide, DCC, DMAP, $BrCCl_3$; $h\nu$ (77%); (g) tBuLi; then $[ICuPBu_3]_4$; then O_2 (75%); (h) 0.95 equiv. TBAF; (i) TPAP, NMO (91%); (j) nBuLi, **255** (65%); (k) Li, naphthalene (70%); (l) PhSh, PMe_3, ADDP; (m) AcOOH (87% two steps) (n) nBuLi Me_2SiCl(*).



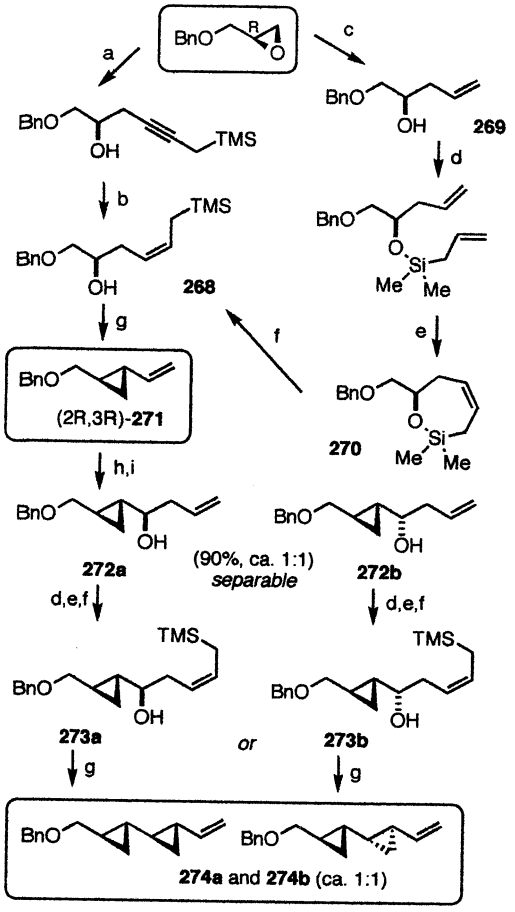
Scheme 48. *Reagents*: (a) TPAP, NMO; (b) $(MeO)_2P(O)CH_2CO_2Me$, NaH; (c) DIBAL, THF, −78°C; (d) TPSCI, imidazole; (e) $LiAlH_4$; then NH_4Cl; then 1,3-propanediol.

Monoprotection of **243**, oxidation, Horner–Emmons olefination, reduction and asymmetric cyclopropanation in the presence of (*S*,*S*)-**8** gave (−)-**239** in excellent yield. Oxidation and Wittig olefination of (−)-**239** gave the vinyl tetrakis-cyclopropane **246**. Olefin metathesis was then used for construction of the C18–C19 olefin. To this end, monoprotection of the key intermediate (−)-**242**, oxidation, and olefination gave the vinylcyclopropane **247**. Self-coupling of **247** in the presence of Grubbs' catalyst gave the homodimer **248**, predominately as the *E*-isomer. Cross-metathesis of **248** with **246** in the presence of Grubbs' catalyst effected formation of the C18–C19 olefin to give predominantly the *E*-olefin (>5:1). It should be noted that metathesis of fluorinated vinylcyclopropanes was independently reported at about the same time.[128] Methanolysis of the benzyl ester gave (−)-**241** (86% ee) whose spectral data was identical with that of the compound prepared by Barrett's group. Since (−)-**241** had been previously converted into FR-900848, preparation of this intermediate constitutes a formal synthesis of this target.

In comparison to the above syntheses, Falck and co-workers utilized a unique strategy based on dimerization of cyclopropyl anions for the synthesis of FR-900848 (Scheme 47).[129] Beginning with *ent*-**162** (cf. Scheme 32), alcohol protection, generation of the corresponding anion and reaction with $[ICuPBu_3]_4$ gave **249**. While the precursor *ent*-**162** is ca. 88% ee; dimerization gave **249** with 98% ee, due to the Horeau principle.[130] Selective monodeprotection followed by ruthenium catalyzed oxidation gave the carboxylic acid **251**. Coupling of **251** with 2-mercaptopyridine N-oxide, followed by photochemical decomposition in $CBrCl_3$, gave predominantly the *trans*-bromocyclopropane **252**. Lithium–halogen exchange and oxidative coupling of the resultant anion gave the tetrakis-cyclopropane **253** with >99.9% ee. Partial deprotection and oxidation set the stage for appending the vinyl cyclopropane ring. In order to fashion the C18–C19 olefin with high *E*-selectivity, Falck's group resorted to a sulfonyl modified Peterson olefination. The trimethylsilyl cyclopropylcarbinylsulfonate **254** was prepared from (*R*,*R*)-**255**. Mitsunobu-type substitution using phenylthiol as nucleophile, followed by oxidation gave the sulfonylmethyl cyclopropane **256**. Deprotonation, followed by silylation gave **254** as a mixture of diastereomers. Deprotonation of **254** and condensation with the tetrakis-cyclopropane carboxaldehyde gave the vinyl sulfone *Z*-**257** along with a small amount of the *E*-isomer. Reduction of the vinyl sulfone gave the C5–C23 segment **258**. Falck's completion of the synthesis from **258** followed the same basic strategy as Barrett (cf. Scheme 43).

Many other publications address the preparation of polycyclopropane fragments. While space does not allow for summary of all of this work, the publications of two groups are of particular note. Recently, Luithle and Pietruszka reported preparation of the bis-cyclopropane segment **250** via sequential cyclopropanations (Scheme 48).[28b,131] Hydroboration of the protected propargyl alcohol **259** with the dioxaborolane **260**, followed by removal of the protecting group gave **261**. While palladium catalyzed cyclopropanation of allylic alcohol **261** with diazomethane gave a mixture of cyclopropyl boronic esters predominating in **262** [**262**/**263**=4:1], the diastereoselectivity of the dioxaborolane group (cf. Fig. 6) could be overcome using Denmark's[21] catalytic asymmetric Simmons–Smith cyclopropanation conditions [**262**/**263**=1:4].[28b] These diastereomers are sufficiently stable for separation. Oxidation of (*R*,*R*)-**263**, followed by Horner–Emmons olefination, and reduction to the allylic alcohol proceeded in excellent yield. A second catalytic asymmetric Simmons–Smith cyclopropanation of **264** proceeded with even greater diastereoselectivity (92:8 dr) to yield the biscyclopropyl boronic ester **265**. Attempted Matteson homologation[132] of **265** was unsuccessful; however after protection of the primary alcohol, transesterification was possible by reduction to the alkyl borohydride, hydrolysis and condensation with 1,3-propanediol to give **266**. Matteson homologation of **266** gave the mono-protected **250** as well as the cyclopropanol **267**.

Taylor, et al. utilized an iterative homoallyl to cyclopropylcarbinyl carbocation rearrangement (cf. Scheme 7) for the



Scheme 49. *Reagents*: (a) propargylTMS, nBuLi; then BF_3Et_2O; then epoxide (85%); (b) H_2, Lindlars catalyst (100%); (c) vinylMgBr, CuI; (d) NEt_3 allylSiMe$_2$Cl; (e) $Cl_2(PCy_3)_2RuCHPh$ (85%, 2 steps); (f) MeLi; (g) Tf_2O, 2,6-lutidine; then NEt_3; (h) OsO_4, $NaIO_4$; (i) allylMgBr (90%, 2 steps);

preparation of a biscyclopropane fragment. Reaction of (*R*)-benzyl glycidyl ether with the boron acetylide derived from propargyltrimethylsilane, gave the corresponding homopropargylic alcohol (Scheme 49).[53] *cis*-Selective reduction with H_2/Lindlar catalyst gave the *Z*-allylsilane **268**. Alternatively, copper mediated addition of vinyl magnesium bromide to (*R*)-benzyl glycidyl ether gave the homoallylic alcohol **269**. Silylation with allylchlorodimethylsilane, followed by ring closing metathesis with Grubbs' catalyst gave the silyloxycycloheptene **270**. Cleavage of **270** with methyl lithium afforded **268**. Treatment of **268** with triflic anhydride/2,6-lutidine gave the *trans*-vinylcyclopropane **271** in good isolated yield. Oxidative cleavage of the vinyl group and addition of allyl Grignard gave a separable mixture of diastereomeric homoallylic alcohols **272a** and **272b**. Separate silylation, followed by ring closing metathesis and cleavage with methyl lithium yielded **273a** and **273b**. Surprisingly,

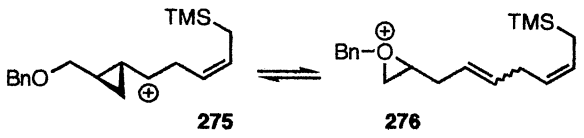


Figure 17.

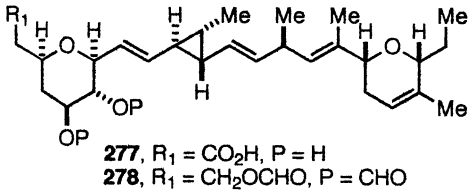


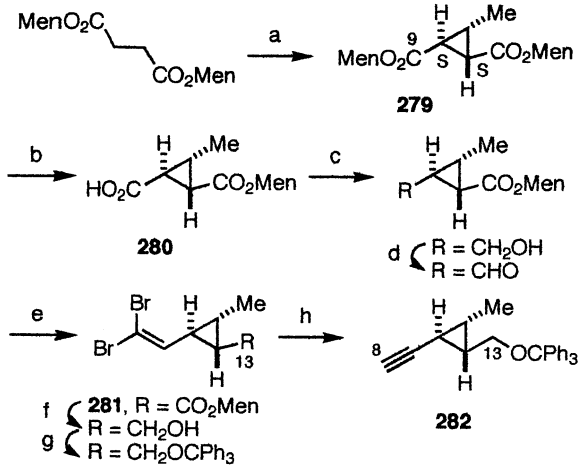
Figure 18.

reaction of either **273a** or **273b** with trifluoromethanesulfonic anhydride gave a 1:1 mixture of *syn*- and *anti*-bis-cyclopropanes **274a/b**! The authors propose that the lack of stereoselectivity in the reaction of benzyl ethers **273a** and **b** is due to a slower rate of cyclization of the second cyclopropane ring and that the resultant cyclopropylcarbinyl cation **275** may be stabilized due to participation of the benzyl ether oxygen (cf. **276**, Fig. 17).

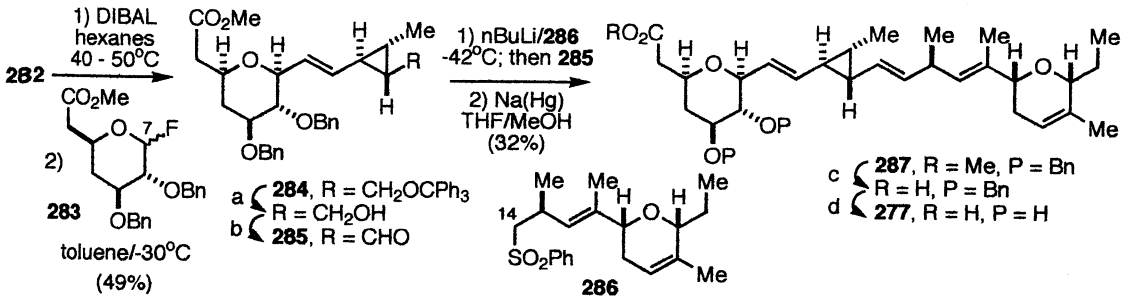
3.5. Ambruticin

Ambruticin (**277**, Fig. 18) was isolated from the fermentation of *Polyangium cellusum var. fulvum* by a group at Warner–Lambert Laboratories.[133] This compound exhibits unprecedented oral activity against histoplasmosis and coccidiomycosis fungal infections. The structure of **277**, which contains a *trans*-divinylcyclopropane unit, was established by spectroscopic analysis, as well as X-ray structure of the 1,5,6-triformate (**278**) derived via reduction of the C1 carboxylic acid group followed by reaction with DMF/Br_2. The absolute stereochemistry of **277** was established by degradation studies in connection with independent synthesis of the degradation fragments. While many groups have reported synthesis of fragments of **277**, there are only two total syntheses of ambruticin. This report will focus on preparation of the cyclopropane segment.

Kende's group was the first to report a synthesis of ambruticin.[134] The cyclopropane segment was prepared by a diastereoselective double alkylation of (−)-dimenthyl succinate[57] with 1-bromo-1-chloroethane to afford **279** in



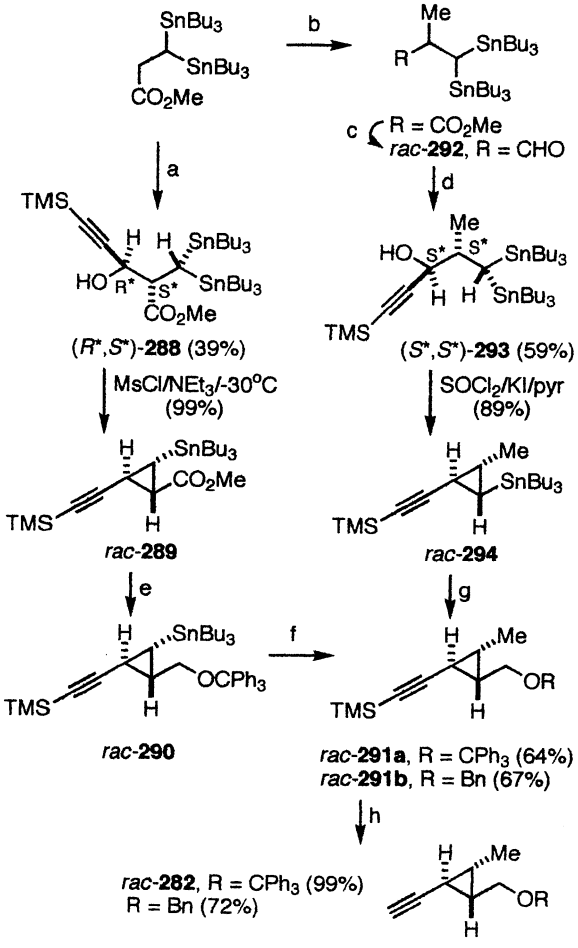
Scheme 50. *Reagents*: (a) 2,2,6,6-tetramethylpiperidine, nBuLi (2 equiv.); followed by $BrClCHCH_3$ (45%); (b) 10% KOH (83%); (c) B_2H_6–THF (100%); (d) Dess–Martin periodinane (96%); (e) CBr_4, PPh_3 (98%); (f) DIBAL (90%); (g) Ph_3CCl, DMAP, NEt_3 (90%); (h) nBuLi (2 equiv.)/ −78°C; then H_2O (92%).



Scheme 51. *Reagents*: (a) pTsOH/MeOH (92%); (b) Dess–Martin periodinane (90%); (c) LiOH/THF/H_2O; (d) Li/NH_3/EtOH (63%).

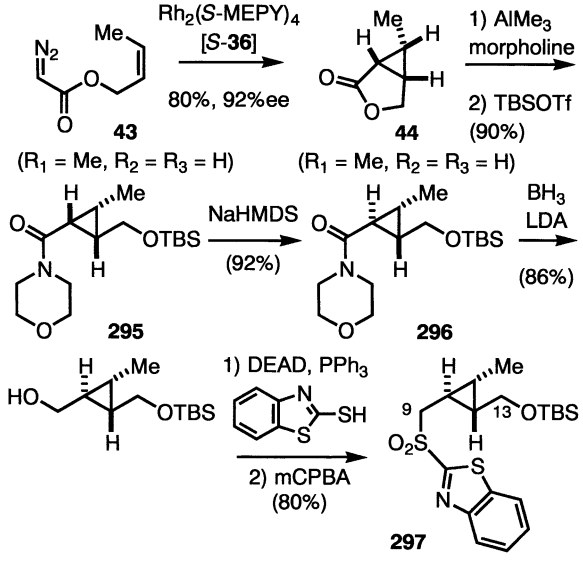
45% yield (Scheme 50). Hydrolysis of the less sterically hindered C9 ester gave half-acid **280**, which was converted to the aldehyde via reduction and oxidation. Olefination with CBr_4/PPh_3 gave the dibromovinylcyclopropane carboxylate **281**. The C13 ester was then reduced and protected as the trityl ether. Finally, conversion of the dibromovinyl group into the alkyne **282** was accomplished by dehydrobromination, lithium halogen exchange, and aqueous workup.

The C8–C13 cyclopropyl alkyne **282** was subjected to hydroalumination with DIBAL and then joined to the C1–C7 fluoro glucoside **283** to give the β-C-glucoside segment **284** in 49% yield (Scheme 51); the α-anomer was also isolated in 28% yield. Removal of the trityl protecting group and oxidation gave the aldehyde **285**. Coupling of **285** with the C14–C24 sulfone **286** via a Julia olefination generated **287**. Hydrolysis of ester and reductive debenzylation completed the synthesis of ambruticin.

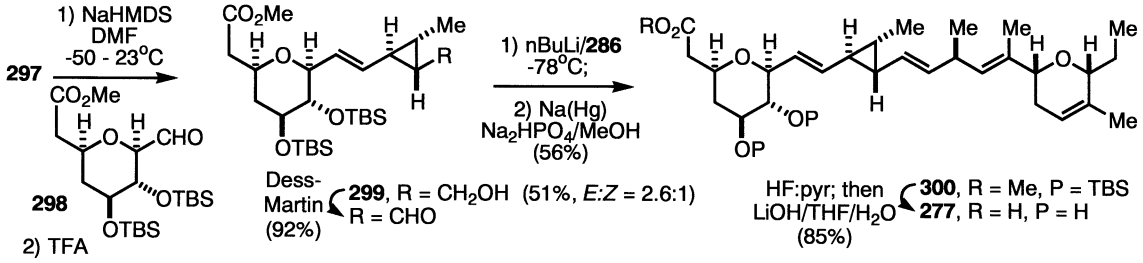


Scheme 52. *Reagents*: (a) LDA/HMPA/−78°C; then 3-TMS-propynal; (b) LDA/HMPA; then MeI (98%); (c) DIBAL (59%); (d) lithio trimethylsilylacetylene/THF/−78°C; (e) DIBAL; then Ph_3CCl, pyr (85%); (f) nBuLi/−78°C; then MeI; (g) nBuLi/HMPA; then $ClCH_2OBn$); (h) TBAF.

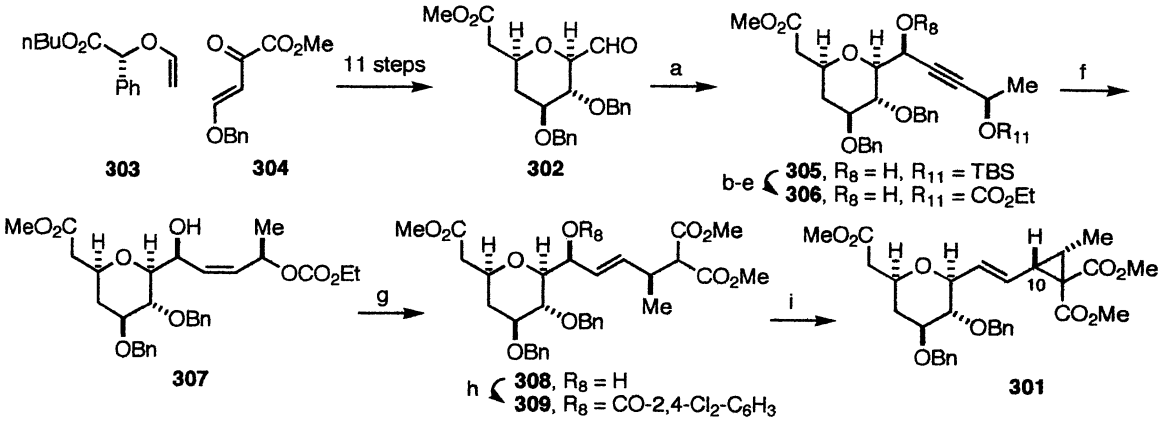
Mori's group also prepared the C8–C13 cyclopropylalkyne **282** in racemic form (Scheme 52).[135] Condensation of the anion derived from methyl 3,3-bis(tributylstannyl)propionate with 3-trimethylsilylpropynal gave the β-hydroxyester (R^*,S^*)-**288** (39%) along with the (R^*,R^*)-diastereomer (15%). Treatment of **288** with methanesulfonyl chloride effected cyclopropane formation to give *rac*-**289** with inversion at the carbinol carbon. Reduction of the ester and protection of the resultant 1° alcohol provided *rac*-**290**, which was subjected to lithium–tin exchange and methylation to give *rac*-**291a**. Removal of the alkynyl TMS group completed the preparation of *rac*-**282**. These authors also prepared the 1,2,3-trisubstituted cyclopropane by an alternative route. Toward this end, α-methylation of methyl 3,3-bis(tributylstannyl)propionate followed by reduction and oxidation gave the aldehyde *rac*-**292**. Addition of the anion derived from trimethylsilylacetylene gave the propargylic alcohol *rac*-**293** with good Felkin–Ahn selectivity. Treatment of **293** with thionyl chloride effected cyclopropane formation to give *rac*-**294** in a fashion similar



Scheme 53.



Scheme 54.



Scheme 55. *Reagents*: (a) (*R*)-3-TBSO-butyne, MeLi, $MgBr_2$ (49%, 17:3 dr); (b) $ClCO_2$allyl, pyr (99%); (c) TBAF, THF (93%); (d) $ClCO_2Et$ (94%); (e) $Pd(OAc)_2$, TPPTS, NEt_3 (91%); (f) H_2, Pd/C, pyridine (56%); (g) 10% $Pd(OAc)_2$, dppe; then $NaCH(CO_2Me)_2$ (60%); (h) 2,4-$Cl_2C_6H_3COCl$, pyr (89%); (i) $Pd(OAc)_2$, dppe, DBU (60%).

to the cyclization of *rac*-**288**. Lithium–tin exchange followed by reaction with benzyloxymethyl chloride gave *rac*-**291b**. While this latter synthesis is of racemic material, it is possible to envision preparation of **292** in optically active form by utilizing chiral auxiliary directed diastereoselective alkylation.

Martin's group has reported a total synthesis of ambruticin,[136] in which the cyclopropane fragment was prepared by asymmetric intramolecular diazoester cyclopropanation (cf. Eq. (14)). Decomposition of *Z*-crotyl diazoacetate (**43**, R_1=Me, R_2=R_3=H) in the presence of the chiral rhodium catalyst (*S*)-**36** gave the 3-oxabicyclo[3.1.0]hexan-2-one **44** (R_1=Me, R_2=R_3=H) with excellent enantioselectivity (Scheme 53). Reaction of **44** with morpholine gave the all-*cis* amide **295**. Epimerization of **295** at the C10 center gave the *trans*-amide **296**. Reduction of the amide gave the protected cyclopropylcarbinol, which underwent subsequent Mitsunobu substitution and oxidation to afford the sulfone **297**.

The C9–C13 cyclopropyl sulfone **297** was coupled with the C1–C8 aldehyde **298** via a Julia olefination to give mixture of isomeric olefins **299** (*E*/*Z*=2.6:1) (Scheme 54). Oxidation

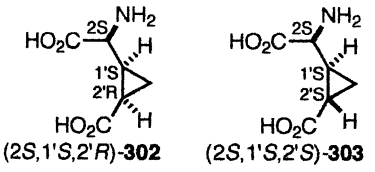


Figure 19.

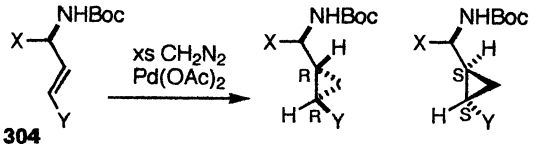
of the C13 alcohol followed by coupling with the C14–C24 sulfone **286** afforded **300**. Removal of the hydroxyl protecting groups and saponification of the C1 ester completed the synthesis of ambruticin.

Genet's group reported the synthesis of a C1–C12 segment (**301**) which is epimeric, at C10, with the natural product (Scheme 55).[137] The aldehyde segment **302** was prepared in 11 steps, via diastereoselective cyclocondensation of chiral enol ether **303** with **304**. Addition of the anion derived from (*R*)-*O*-t-butyldimethylsilylbut-1-yn-3-ol to **302** gave a separable mixture of diastereomeric alcohols (85:15 dr) **305**. The major product was eventually identified as the 8*S* diastereomer. Protecting group manipulation of **305** gave the propargylic alcohol **306** which was reduced in the presence of Pd/C and pyridine to give the (*Z*)-allylic alcohol **307**. Palladium catalyzed allylation of dimethyl malonate proceeded with 'triple inversion' (cf. Scheme 12) to give the (*E*)-allylic alcohol **308**. Reaction of **308** with 2,4-dichlorobenzoyl chloride set the stage for a second intramolecular Pd catalyzed allylation. Reaction of **309** with $Pd(OAc)_2$ using DBU as base, led to formation of the vinylcyclopropane product **301**. The *cis*-cyclopropane substitution pattern as well as the (*E*)-olefinic stereochemistry were assigned on the basis of NMR spectral data including vicinal coupling constants.

3.6. 2-(2-Carboxycyclopropyl)glycines

The *cis*- and *trans*-2-(2′-carboxycyclopropyl)glycines [CCG] (**302** and **303**, Fig. 19) were isolated from the seeds of *Aesculus parvifola* and *Blighia sapida*, respectively.[138]

Table 3. Diazomethane cyclopropanation of *E*-allylic amines

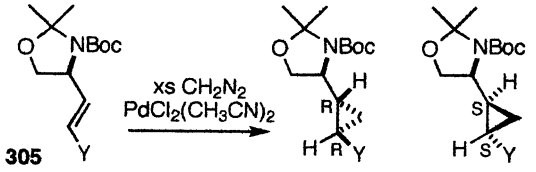


X	Y	Ratio	Yield (%)
CO_2Me	CH_2OAc	1:1	68
CH_2OTBS	CO_2Me	1:1	48
CH_2OTBS	CO_2Et	3:1	73
CH_2OTBS	CH_2OH	4:3	39
CH_2OTBS	CH_2OAc	3:4	50

The *cis*-isomer **302** was found to be a potent growth inhibitor of mung bean seedlings. Since these compounds may be considered conformationally restricted glutamate mimics, they have proven to be 'useful pharmacological tools for analysis of glutamate neurotransmitter systems'.[139] For example, (2*S*,1′*S*,2′*R*)-**302** was found to be a potent and selective NMDA agonist, while the (2*S*,1′*S*,2′*S*)-**303** is a potent and selective group II mGluRs agonist. For this reason, considerable work has been reported on the synthesis of the CCGs and substituted derivatives.

3.6.1. Metal catalyzed diazomethane cyclopropanation. Ohfune's group has made extensive use of Pd-catalyzed diazomethane cyclopropanation for the preparation of CCG's.[140,141] Reaction of a variety of protected *E*-allylic amines **304** with excess diazomethane, in the presence of $Pd(OAc)_2$ catalyst, gave mixtures of diastereomeric cyclopropanes with little selectivity (Table 3). In comparison, diazomethane cyclopropanation of *N*,*O*-acetonides **305** proceeded with a slight preference for generation of the (*R*,*R*)-diastereomer (Table 4). The authors propose that coordination of the amide nitrogen to Pd metal could be responsible for this preference (Fig. 20).[141] Separation of these diastereomeric mixtures led to the eventual preparation of *trans*-CCG's.

Table 4. Diazomethane cyclopropanation of *N*,*O*-acetonides



Y	Ratio	Yield (%)
CO_2Me	2.8:1	87
CO_2Et	4.6:1	90
CH_2OAc	6.0:1	53

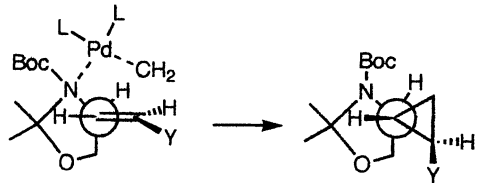
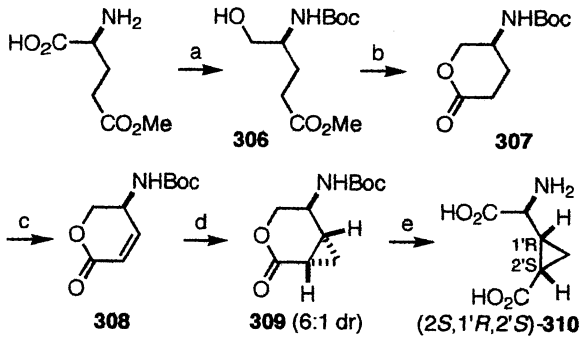


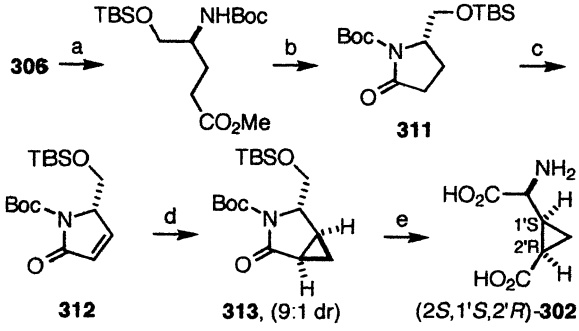
Figure 20.



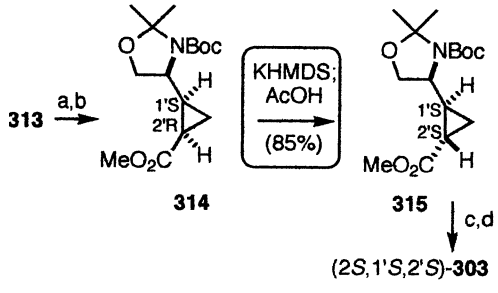
Scheme 56. *Reagents*: (a) Boc_2O, $NaHCO_2$; then *N*-hydroxysuccinimide, DCC; then $NaBH_4$ (83%); (b) CSA (92%); (c) LHMDS (2 equiv.), TMSCl (2 equiv.); then $Pd(OAc)_2$ (70%); (d) CH_2N_2, 20% $Pd(OAc)_2$ (46%); (e) CSA; then LiOH; then Jones reagent; then 0.5N NaOH; then CF_3CO_2H (66%).

While the Pd catalyzed diazomethane cyclopropanation of acyclic allylic amines proceeds with low diastereoselectivity, similar cyclopropanation of cyclic olefins bearing a stereodirecting substituent proceeds with good diastereoselectivity. Amine protection of L-glutamic acid γ-methyl ester, followed by cyclization gave the δ-lactone **307** (Scheme 56).[141,142] The corresponding α,β-unsaturated δ-lactone **308** was prepared by Saegusa oxidation. Reaction of **308** with diazomethane catalyzed by $Pd(OAc)_2$ gave **309** with good diastereoselectivity. The major product arises via addition on the face opposite to the NHBoc substituent. Bicyclic lactone **309** could be carried forward to the unnatural (2*S*,1′*R*,2′*S*)-**310**.

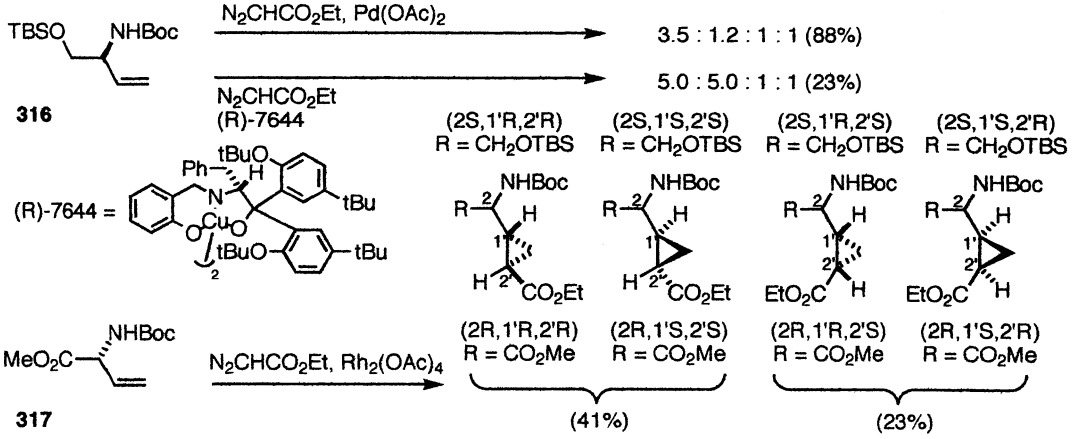
The naturally occurring *cis*-CCG **302** was also prepared



Scheme 57. *Reagents*: (a) TBSCl, imidazole (92%); (b) NaH; then Boc_2O (87%); (c) LHMDS (2 equiv.), TMSCl (2 equiv.); then $Pd(OAc)_2$ (68%); (g) CH_2N_2, 5% $Pd(OAc)_2$ (100%); (h) CSA; then LiOH; then Jones reagent; then 0.5N NaOH; then CF_3CO_2H (66%).

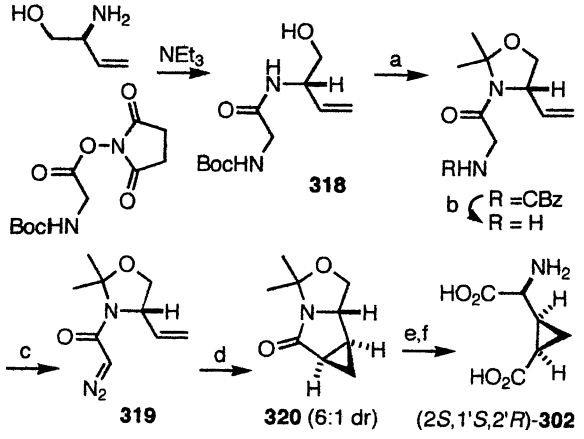


Scheme 58. *Reagents*: (a) MeOH, CSA (83%); (b) CSA, $Me_2C(OMe)_2$ (100%); (c) TFA; then $(Boc)_2O$, NEt_3 (79%); (d) Ref. 141.



Scheme 59.

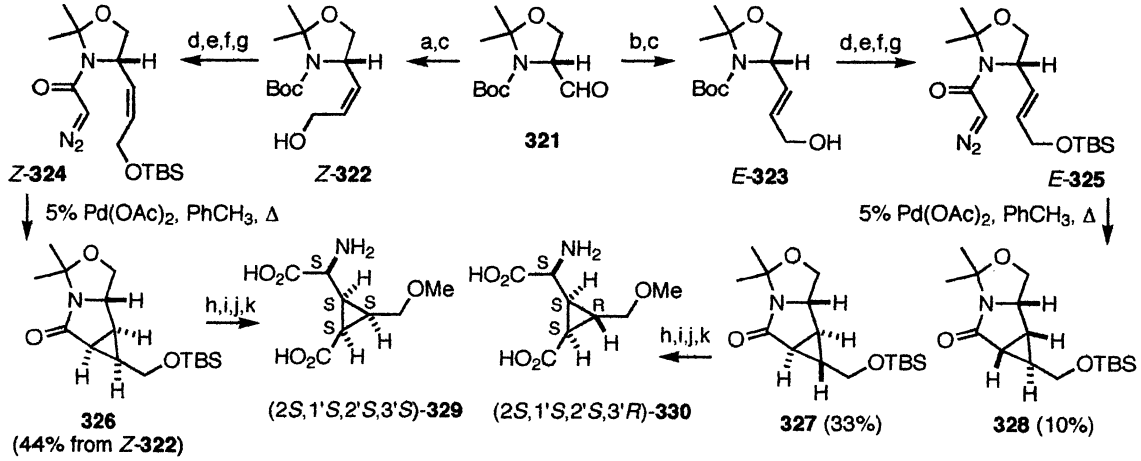
from glutamic acid. Protection of the primary alcohol present in **306** followed by cyclization gave the γ-lactam **311** (Scheme 57).[142] Saegusa oxidation afforded the α,β-unsaturated γ-lactam **312**, which underwent Pd catalyzed diazomethane addition in excellent yield and with good diastereoselectivity to afford **313**. The predominant product arises due to approach of the Pd-carbene species on the face opposite to the bulky *t*-butyldimethylsilyloxymethylene substituent. Hydrolysis, Jones oxidation, and cleavage of the protecting groups gave (2*S*,1′*S*,2′*R*)-**302**.



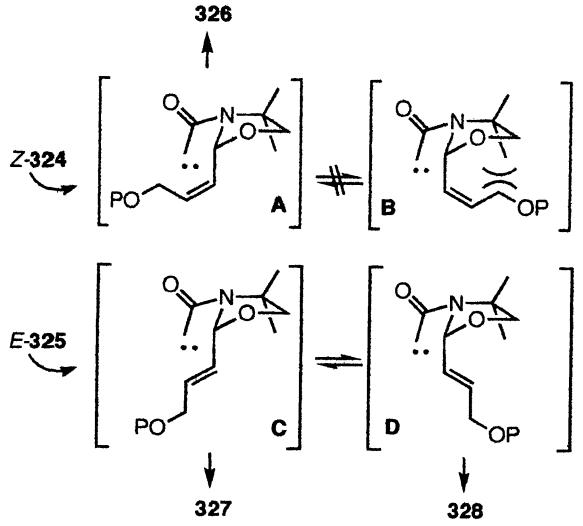
Scheme 60. *Reagents*: (a) $Me_2C(OMe)_2$, acetone, CSA (62%); (b) TMSOTf, 2,6-lutidine; (c) $NaNO_2$, pH 3 buffer; (d) 5% $Pd(OAc)_2$ (43%); (e) 60% AcOH; then 0.5N NaOH; then $(Boc)_2O$, NEt_3; then Jones reagent (59%); (f) TFA.

Bicyclic lactam **313** was also transformed into (2*S*,1′*S*,2′*S*)-**303** by epimerization of the 2′-carboxyl substituent (Scheme 58).[143] Methanolysis of **313**, followed by acetonide formation gave the *cis*-ester **314**. Deprotonation of **314** with KHMDS (−78 to −15°C) followed by treatment with acetic acid effected complete inversion to the *trans*-ester **315**. Notably, upon quenching the above anion with CD_3CO_2D no deuterium incorporation was observed. The authors propose that the abstraction of the C2′ proton is rate determining and that the resultant carbanion is immediately reprotonated by the in situ generated TMS_2NH. The *trans*-ester **315** could be converted into (2*S*,1′*S*,1′*S*)-**303**.

3.6.2. Metal catalyzed diazocarbonyl cyclopropanation. Both Ohfune's[144] and Pellicciari's[145] groups reported that intermolecular addition of ethyl diazoacetate to either the protected allylic amine **316** or the antipodal *N*-Boc D-vinylglycine methyl ester **317** gave a mixture of all four possible



Scheme 61. *Reagents* (a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH (82%); (b) $Ph_3P{=}CHCO_2Me$, C_6H_6 (95%); (c) DIBAL, $PhCH_3$ (86–87%); (d) 1N HCl, MeOH; then Boc-Gly-OSu, NEt_3; then $Me_2C(OMe)_2$, CSA; (e) TBSCI, imidazole; (f) TMSOTf, 2,6-lutidine; (g) $NaNO_2$, pH 3 buffer; (h) TBAF; (i) NaH, MeI, TBAI; (j) 60% AcOH; then $Ba(OH)_2$, EtOH; then $(Boc)_2O$, NEt_3; (k) Jones reagent; then TFA.



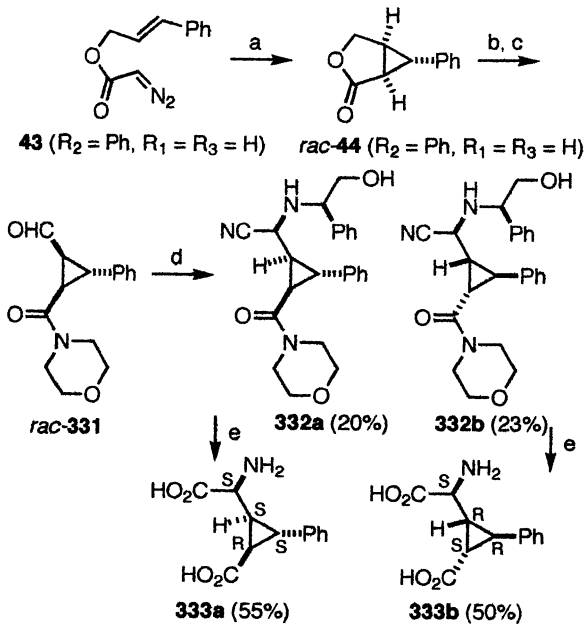
Scheme 62.

diastereomeric cyclopropanes, predominating in the *trans*-isomers (Scheme 59). Separation of these mixtures, while tedious, could be accomplished by means of MPLC and/or derivatization, and various CCG's were prepared in this fashion.

Ohfune's group also explored an intramolecular diazocarbonyl cyclopropanation variant (Scheme 60).[144] Condensation of (*S*)-2-amino-3-buten-1-ol with *N*-Boc glycyl-*O*-succinate gave the dipeptide **318**. Cyclization with dimethoxypropane, followed by selective removal of the Boc group and diazotization of the amine with sodium nitrite afforded the diazoamide **319**. Reaction with a catalytic amount of $Pd(OAc)_2$ generated 3-aza-5-oxa-tricyclo-[6.1.0.0^{3,7}]nonan-2-one **320** with good diastereoselectivity (6:1). The major diastereomer, separable by column chromatography, was transformed into (2*S*,1′*S*,2′*R*)-**302**.

Intramolecular diazocarbonyl cyclopropanation was also utilized for the preparation of substituted 2-(2′-carboxycyclopropyl)glycines. Beginning with the protected serinal derivative (*R*)-**321**, *Z*- or *E*-selective olefination followed by reduction gave *Z*-**322** or *E*-**323** respectively, which were transformed into the diazoamides *Z*-**324** and *E*-**325** respectively (Scheme 61).[146] Palladium(II) catalyzed intramolecular cyclopropanation of *Z*-**324** gave a single 3-aza-5-oxa-tricyclo[6.1.0.0^{3,7}]nonan-2-one **326** while the same reaction of diazoamide *E*-**325** gave a mixture of **327** and **328**. For the carbene derived from *Z*-**324**, cyclization proceeds only via the transition state A (Scheme 62). The conformer B is not significantly populated due to severe steric interactions. In comparison, the carbene derived from *E*-**325** may cyclize via both reactive conformer C and D to afford the isomeric products **327** and **328**, respectively. Tricyclic lactams **326** and **327** were eventually converted into the methoxymethylene derivatives (2*S*,1′*S*,2′*S*,3′*S*)-**329** and (2*S*,1′*S*,2′*S*,3′*R*)-**330**.

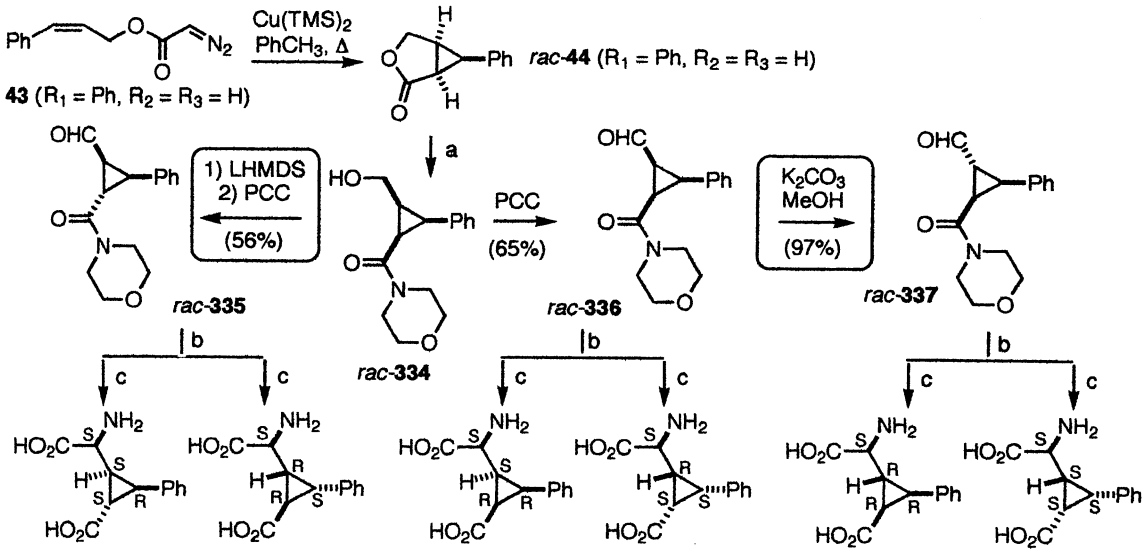
Martin and coworkers previously reported that the decomposition of unsaturated diazoester **43** (R_2=Ph, R_1=R_3=H) in the presence of Cu^{2+} produced the *racemic* bicyclic lactone **44** (R_2=Ph, R_1=R_3=H) (Scheme 63).[147] Pellicciari's group utilized this lactone for the preparation of phenyl substituted CCG's.[148] Toward this end, reaction of lactone **44** with morpholine, followed by oxidation gave *rac*-**331**. Subjecting *racemic* aldehyde **331** to an asymmetric Strecker synthesis with (*R*)-α-phenylglycinol gave the diastereomeric α-aminonitriles **332a** and **332b** which were separable by MPLC. Separate oxidative cleavage and hydrolysis of **332a** and **332b** gave (2*S*,1′*S*,2′*R*,3′*S*)-**333a** and (2*S*,1′*R*,2′*S*,3′*R*)-**333b** [PCCGs] respectively. Use of (*S*)-α-phenylglycinol in the asymmetric Strecker reaction (instead of the (*R*)-enantiomer), followed by oxidative cleavage and hydrolysis gave (2*R*,1′*S*,2′*R*,3′*S*)- and (2*R*,1′*R*,2′*S*,3′*R*)-PCCGs.



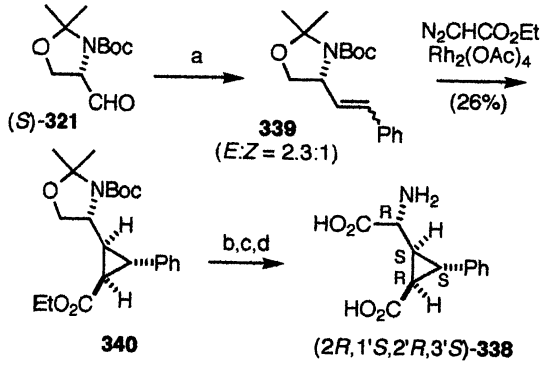
Scheme 63. *Reagents*: (a) $Cu(TBS)_2$, $PhCH_3$, Δ (81%); (b) morpholine, $AlMe_3$, Δ (99%); (c) PCC (62%); (d) (*R*)-α-phenylglycinol; then TMSCN; (e) $Pb(OAc)_4$; then 6N HCl.

In a similar fashion, Cu^{2+} catalyzed decomposition of unsaturated diazoester **43** (R_1=Ph, R_2=R_3=H) gave the *racemic* bicyclic lactone *rac*-**44** (R_1=Ph, R_2=R_3=H) (Scheme 64).[147] Opening of the lactone with morpholine afforded the alcohol *rac*-**334**. Based on Martin's previous results, the other stereochemical combinations about the cyclopropane ring could be generated from this precursor. Epimerization of the amide substituent (LHMDS; then PCC) produced the *trans*-amide (*rac*-**335**). Alternatively, oxidation of *rac*-**334** gave the all-*cis* stereoisomer (*rac*-**336**). The aldehyde substituent in *rac*-**336** could be selectively epimerized under milder basic conditions (K_2CO_3, MeOH) to yield the *trans*-aldehyde (*rac*-**337**). Transformation of either *rac*-**335**, *rac*-**336**, or *rac*-**337** by asymmetric Strecker reaction followed by oxidative cleavage and hydrolysis gave the isomeric PCCGs. In this fashion, Pellicciari's group was able to construct a library of 16 isomeric PCCGs for testing as glutamate receptor ligands. The (2*S*,1′*S*,2′*S*,3′*R*)-isomer was found to be a selective group II mGluR antagonist.

From this library, Pellicciari's group found that the (2*R*,1′*S*,2′*R*,3′*S*)- isomer (**338**, Scheme 65) was a potent



Scheme 64. *Reagents*: (a) morpholine, $AlMe_3$, Δ; (b) (*R*)-α-phenylglycinol; then TMSCN; separate; (c) $Pb(OAc)_4$; then 6N HCl.



Scheme 65. *Reagents*: (a) $PhCH_2PPh_3^+Br^-$, nBuLi (60%); (b) pTsOH, MeOH (57%); (c) Jones reagent; (d) 6N HCl (78%).

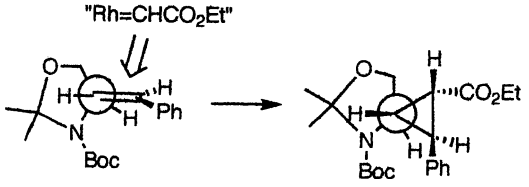
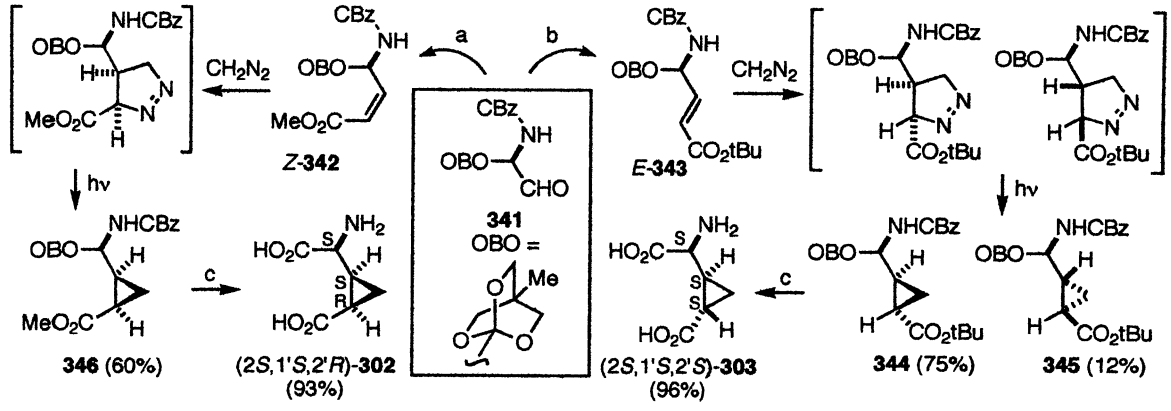


Figure 21.

and selective competitive antagonist of the phopholipase D-coupled mGluR receptor. For this reason, they developed an alternative asymmetric synthesis of this compound.[149] Wittig olefination of the protected serinal derivative (*S*)-**321** gave a mixture of *E*- and *Z*-**339** (2.3:1) which were separable by MPLC. Reaction of *E*-**339** with ethyl diazoacetate catalyzed by rhodium acetate afforded the cyclopropane **340** as a single isomer, albeit in modest yield. The product **340** arises via approach of the Rh-carbene species on the face of the olefin opposite to the sterically bulky Boc group (Fig. 21). Acid hydrolysis, Jones oxidation and final acid hydrolysis generated the target (2*R*,1′*S*,2′*R*,3′*S*)-**338**.

Rifé and Ortuño have recently reported the preparation of *cis*-**302** and *trans*-**303** via uncatalyzed 1,3-dipolar cycloaddition of diazomethane (Scheme 66).[150] Either *Z*- or *E*-selective olefination of Cbz-L-serinal-OBO (**341**) gave the *Z*- or *E*-enoates **342** or **343** respectively. Addition of diazomethane to either *Z*-**342** or *E*-**343** gave the corresponding pyrazolines, however these proved extremely unstable. Photochemical decomposition of the pyrazoline from *E*-**343** (10% benzophenone) yielded the cyclopropanes **344** and **345** which were separable by flash chromatography. In



Scheme 66. *Reagents*: (a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH (82%, 9:1, *Z*/*E*); (b) $Ph_3P{=}CHCO_2tBu$ (78%); (c) 6N HCl.

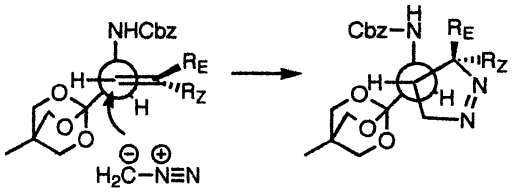
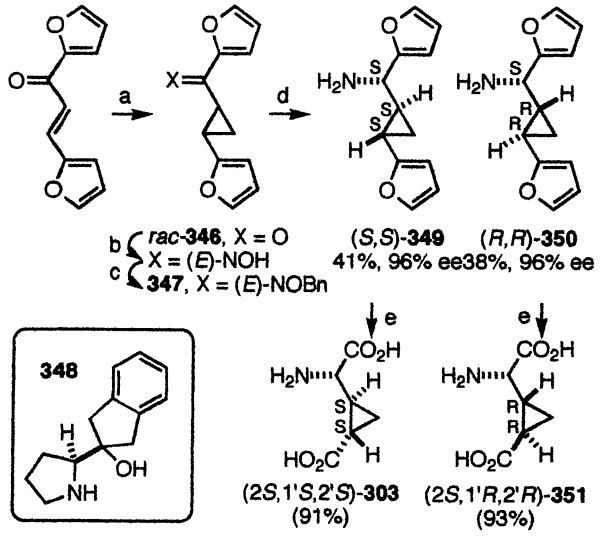


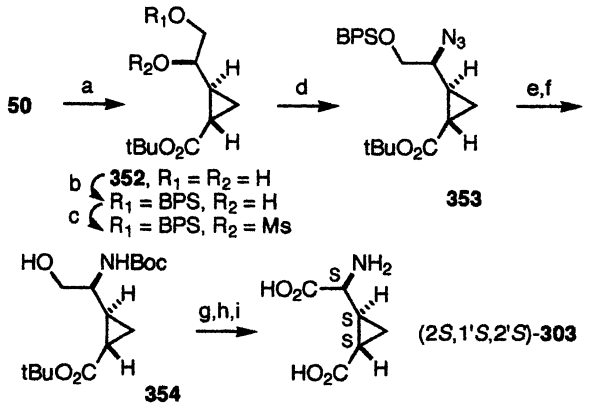
Figure 22.

comparison, photolysis of the pyrazoline from *Z*-**342** required 30% benzophenone to prevent significant retrocycloaddition. In this case only a single *cis*-cyclopropane (**346**) was formed. The observed stereoselectivity may be rationalized by approach of diazomethane on the lowest energy conformer on the face opposite to the NHCbz group (Fig. 22). Notably, the lowest energy conformer positions the NHCbz group perpendicular to the olefin in order to maximize overlap of the C–N σ-bond with the π^*-antibonding orbital of the enoate and also positions the OBO group further away from the enoate in order to minimize steric interactions. For either **344** or **346**, removal of all of the protecting groups by treatment with 6N HCl gave the products **302** and **303**, respectively.

3.6.3. Sulfoxonium ylide cyclopropanation. Demir and coworkers reported a synthesis of the parent *trans*-CCG which uses an enantioselective oxime reduction.[151] Reaction of *trans*-1,3-di(2′-furyl)propenone with dimethylsulfoxonium methylide gave the cyclopropyl ketone *rac*-**346** (Scheme 67). Formation of the oxime using NH_2OH/NaOH gave predominantly the *E*-isomer, which was benzylated to yield *E*-**347**. Asymmetric reduction of *E*-**347** in the presence of excess chiral amine **348** produced a separable mixture of optically active diastereomers (*S*,*S*,*S*)-**349** and (*S*,*R*,*R*)-**350**. The use of catalytic amounts of the chiral amine resulted in low enantioselectivity. Ozonolysis of both furan groups of either **349** or **350** gave **303** or **351** respectively.



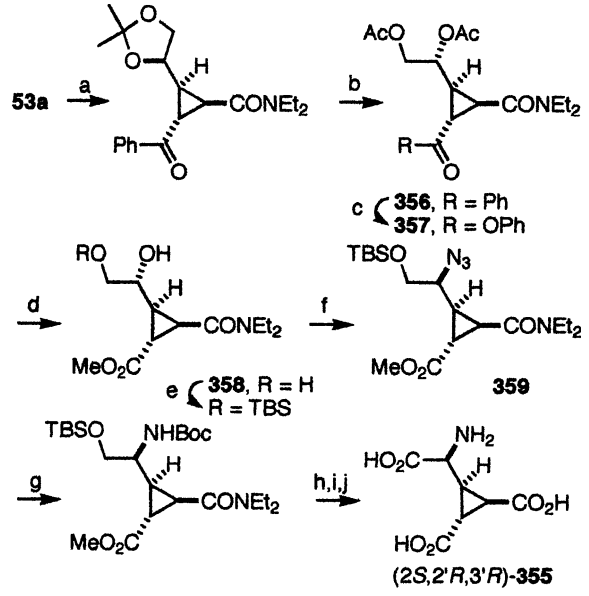
Scheme 67. *Reagents*: (a) $Me_2SO^+I^-$, NaH (94%); (b) H_2NOH/HCl, NaOH (75% *E*, 14% *Z*); (c) NaH, BnBr (92%); (d) BH_3, THF, 1.25 equiv. amine **348**; (e) O_3, MeOH.



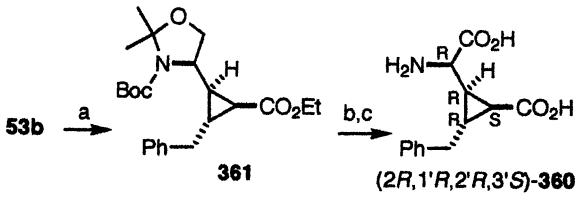
Scheme 68. *Reagents*: (a) PPTS, tBuOH, Δ (72%); (b) BPSCI, NEt_3 (89%); (c) MsCl, NEt_3 (94%); (d) NaN_3, DMF; (e) H_2, Pd/C, $(Boc)_2O$; (f) TBAF, HOAc (55%, 3 steps); (g) Jones reagent; (h) gaseous HCl, CH_2Cl_2; (i) propylene oxide, EtOH (88%, 3 steps).

Ma and coworkers explored the diastereoselective addition of sulfoxonium ylides to chiral electron deficient olefins (see Scheme 4). These cyclopropane products (i.e. **50**, **53a**, **53b**) were utilized for the preparation of 2-(2′-carboxycyclopropyl)glycines. To this end, acetonide solvolysis of **50** yielded the diol **352** (Scheme 68).[48a] Selective protection of the 1° alcohol and activation of the 2° alcohol, followed by displacement with sodium azide proceeded with inversion of configuration to give **353**. Catalytic reduction of the azido group in the presence of Boc anhydride and subsequent removal of the 1° alcohol protecting group produced **354**. Jones oxidation and hydrolysis of the t-butyl ester and Boc groups completed the synthesis of (2*S*,1′*S*,2′*S*)-**303**.

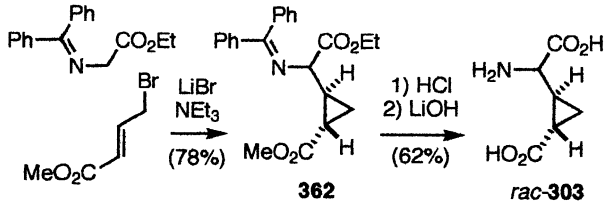
In a similar fashion, **53a** could be elaborated into 2-(2′,3′-dicarboxycyclopropyl)glycine [(2*S*,2′*R*,3′*R*)-**355**] (Scheme 69).[48b] In order to avoid anticipated lactonization between



Scheme 69. *Reagents*: (a) 10% NaOH; then DCC/$HNEt_2$ (74%); (b) 10% HCl/MeOH; then Ac_2O/NEt_3 (79%); (c) 95% H_2O_2/TFAA (83%); (d) K_2CO_3/MeOH; then MeI (75%); (e) TBSCl/DMAP (87%); (f) DEAD/DPPA/PPh_3 (75%); (g) H_2/Pd(C)/$(Boc)_2O$ (84%); (h) TBAF; (i) Jones oxidation (71%); (j) 6N HCl (65%).



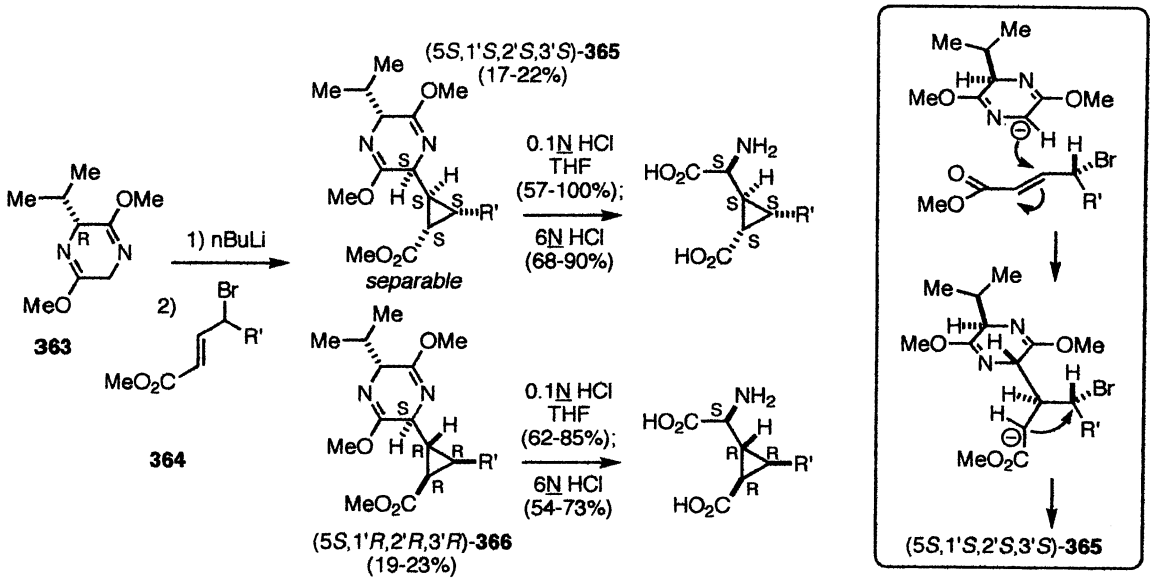
Scheme 70. *Reagents*: (a) H_2, Pd/C (86%); (b) MeOH, Dowex-50W,; then Jones oxidation (54%); (c) NaOH, MeOH; then $HCl_{(g)}$, CH_2Cl_2 (100%).



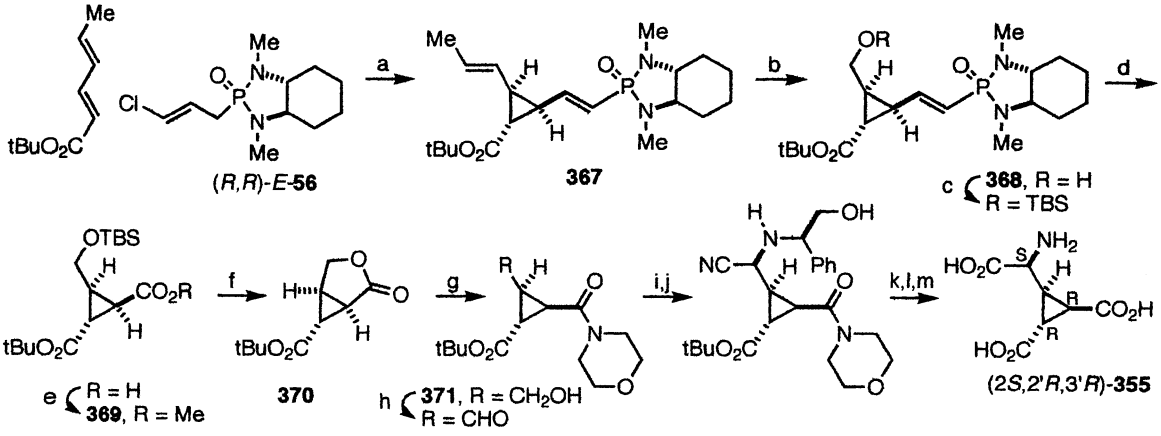
Scheme 71.

the ethyl ester and the C2-hydroyl group, the ester **53a** was first converted into the *N*,*N*-diethylamide. Hydrolysis of the acetonide, followed by bis-acylation gave **356**, which upon Baeyer–Villiger oxidation gave the phenyl ester **357**. Treatment of **357** with $MeOH/K_2CO_3$ effected solvolysis of both of the acyl groups and the phenyl ester; the carboxylate salt was methylated to yield diol **358**. Protection of the 1° alcohol, followed by Mitsunobu inversion with azide gave **359**. Transformation of **359** into **355** followed steps similar to the preparation of **303** from **353**.

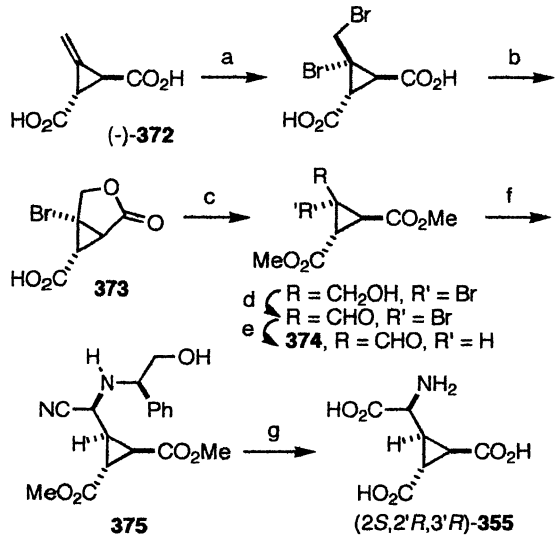
Ma's group recently prepared the 3-benzyl analog (2*R*,1′*R*,2′*R*,3′*S*)-**360** from the cyclopropane **53b** in a short three step sequence (Scheme 70).[48c] Catalytic reduction of the phenyl ketone **53b** gave the benzyl cyclopropane **361**. Cleavage of the acetonide, followed by Jones oxidation and finally ester saponification and removal of the Boc group completed this synthesis.



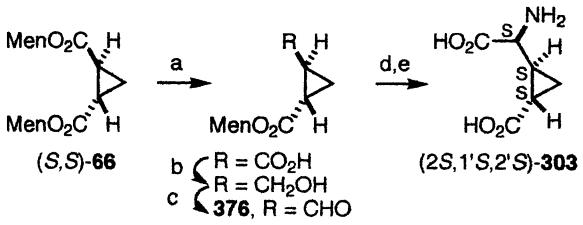
Scheme 72. (R′=Me, Et, nPr).



Scheme 73. *Reagents*: (a) nBuLi, Et_2O, −78 C, *t*-butyl 2,4-hexadienoate (54%); (b) O_3, CH_2Cl_2–MeOH, solvent red 19; then $NaBH_4$ (80%); (c) TBSCI, imidazole (quantitative); (d) O_3, CH_2Cl_2; then H_2O_2; (e) CH_2N_2 (79%); (f) TBAF, THF (81%); (g) morpholine, $AlMe_3$ (quantitative); (h) DMSO $(COCl_2)_2$, NEt_3 (86%); (i) (*R*)-α-phenylglycinol; (j) TMSCN; then separate by flash chromatography (60% 2 steps); (k) $Pb(OAc)_4$; (l) 6N HCl; (m) Dowex 50WX2-200, 1N, NH_4OH (60%).



Scheme 74. *Reagents*: (a) Br_2, ether (64%); (b) H_2O, Δ (61%); (c) MeOH, H_2SO_4 (97%); (d) PCC, CH_2Cl_2 (69%); (e) Zn, HOAc (88%); (f) (*R*)-α-phenylglycinol; then TMSCN (66%); (g) $Pb(OAc)_4$; then 6N HCl (58%).



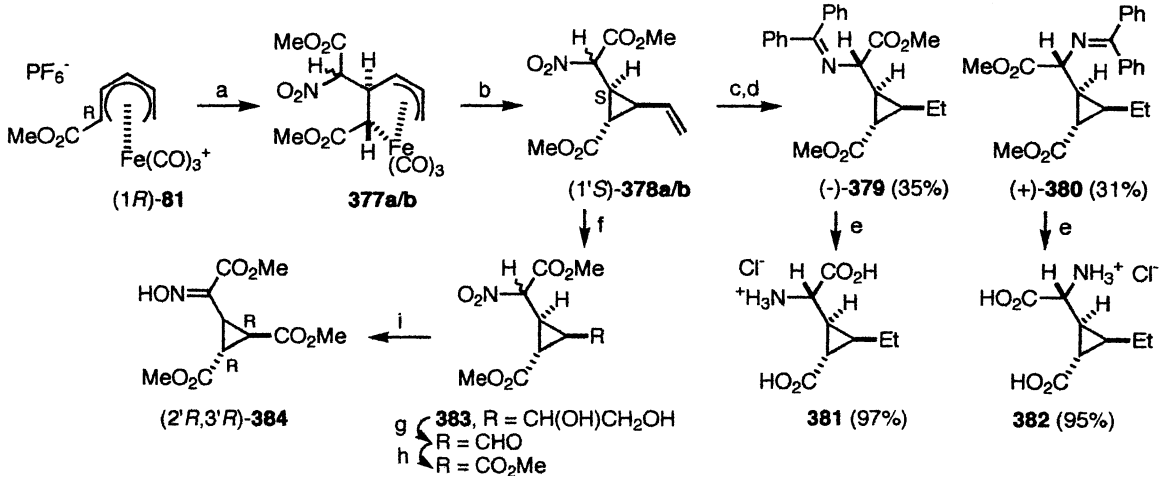
Scheme 75. *Reagents*: (a) NaOH, iPrOH (96%); (b) B_2H_6–THF (81%); (c) DMSO, $(COCl)_2$, NEt_3 (96%); (d) (*R*)-α-phenylglycinol; then TMSCN (88%); (e) $Pb(OAc)_4$; then 6N HCl (75%).

3.6.4. Cyclopropanation via MIRC reaction. Chavan and coworkers reported a short synthesis of *rac*-**303** (Scheme 71).[152] Michael induced ring closure (MIRC) of methyl 4-bromo-2-butenoate with ethyl (diphenylmethylene)-glycine ['O'Donnell Schiff base'] gave the *trans*-cyclopropane **362**. Acidic hydrolysis of the Schiff base and saponification of both esters completed this short synthesis of **303**. Since both precursors are achiral, the product is racemic. These authors did not comment on the relative configurations at C2 and C1′ in this short communication.

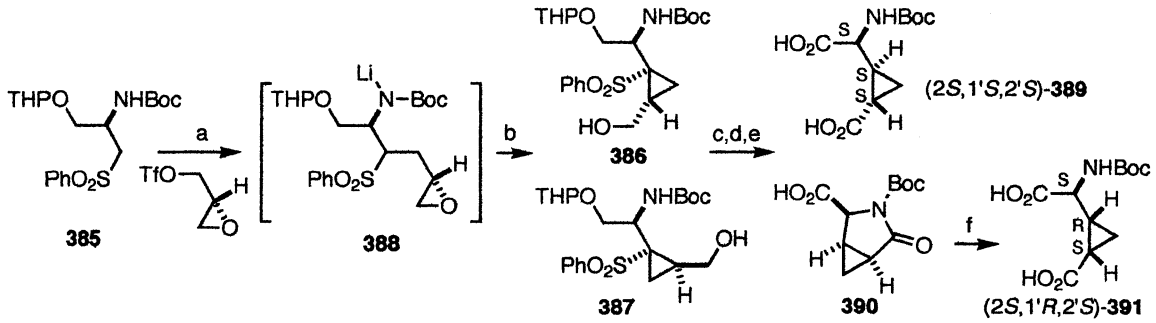
Pedregal's group prepared enantiomerically enriched (carboxycyclopropyl)glycines via a MIRC reaction utilizing a chiral nucleophile (Scheme 72).[153] Reaction of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**363**, 'Schollkopf's chiral glycine equivalent') with a series of racemic 4-bromo-2-alkenoates **364** (R′=Me, Et, nPr) produced a separable mixture of diastereomeric products, (5*S*,1′*S*,2′*S*,3′*S*)-**365** and (5*S*,1′*R*,2′*R*,3′*R*)-**366**. The stereochemical assignments of the products were based on extensive NMR data, including nOe difference experiments. Nucleophilic attack on the enoate proceeds via approach of less hindered face of the pyrazine ring to the less hindered face of the enoate. This is indicated in the insert for one enantiomer of the enoate. Hydrolysis of the 3,6-dimethoxypyrazine ring and the ester groups gave the 2-(3′-alkyl-2′-carboxycyclopropyl)glycine products.

A recent route to 2-(2′,3′-dicarboxycyclopropyl)glycine **355** reported by Marinozzi and Pellicciari[154] utilizes the chiral *trans*-chloroallyl phosphonamide reagent *E*-**56** (Scheme 5) pioneered by Hanessian's group. Conjugate addition of the anion derived from (*R*,*R*)-**56** to *t*-butyl 2,4-hexadienoate, followed by intramolecular S_N2 displacement of Cl by the resultant ester enolate anion gave the bisvinylcyclopropane carboxylate **367** (Scheme 73). Selective ozonolysis of the propenyl side chain, with reductive workup, afforded the alcohol **368**, which was protected as the TBS ether. A second ozonolysis, this time of the vinyl phosphonamide group, with oxidative workup and diazomethane esterification yielded the diester **369**. Removal of the TBS group resulted in concomitant lactonization to afford **370**, which was transformed into the amide **371** by reaction with morpholine. Oxidation of the resultant 1° alcohol to the aldehyde set the stage for introduction of the glycine functionality via an asymmetric Strecker reaction. Oxidative cleavage and hydrolysis produced (2*S*,2′*R*,3′*R*)-**355**.

3.6.5. Miscellaneous reactions. Two recent reports utilize the asymmetric Strecker synthesis for preparation of the aminoacid functionality. The Roche group has developed



Scheme 76. *Reagents*: (a) $LiCH(NO_2)CO_2Me$; (b) CAN, CH_3CN (54% 2 steps); (c) H_2, Raney-Ni; (d) Ph_2CNH; separate; (e) 6N HCl; (f) OsO_4, NMO (57%); (g) $NaIO_4$; (h) Jones reagent; then CH_2N_2 (65%, two steps); (i) H_2, 10% Pd/ (90%).



Scheme 77. *Reagents*: (a) 2 equiv. nBuLi; then (*R*)-glycidyl triflate; (b) 1 equiv. nBuLi (73%); (c) PPTS, EtOH; (d) Na–Hg, Na_2HPO_4, MeOH; (e) Jones reagent (80% for 3 steps, **390/391**=1:3) separable by recrystallization; (f) LiOH, MeOH (72%).

a short and efficient synthesis of (2*S*,2′*R*,3′*R*)-**355** beginning with optically active Fiest's acid (**372**).[155] Bromination of (−)-**372** followed by hydrolysis gave the bromo lactone acid **373** (Scheme 74).[156] Esterification and oxidation produced the diester aldehyde **374**, which upon reaction with (*R*)-2-phenylglycinol followed by TMSCN afforded the aminonitrile **375**. Oxidative cleavage of **375** and hydrolysis completed the synthesis of (2*S*,2′*R*,3′*R*)-**355**.

Similarly, a group at Precision Biochemicals reported the synthesis of (2*S*,1′*S*,2′*S*)-**303** (Scheme 75).[157] The (*S*,*S*)-1,2-cyclopropane diester (*S*,*S*)-66, prepared by alkylation of (−)-dimenthyl succinate with $BrClCH_2$ (cf. Scheme 10) was subjected to semihydrolysis to afford the half-acid. Reduction of the acid with borane followed by oxidation led to the aldehyde **376**. Application of the asymmetric Strecker synthesis, purification, oxidative cleavage and hydrolysis completed the preparation of (2*S*,1′*S*,2′*S*)-**303**.

Godula and Donaldson recently reported the preparation of (2-carboxy-3-ethylcyclopropyl)glycines using organoiron methodology (Scheme 76).[158] Nucleophilic attack of methyl nitroacetate anion on (2-methoxycarbonylpentadienyl)-$Fe(CO)_3^+$ cation [(1*R*)-**81**] proceeded at the C2 internal site to afford the (pentenediyl)$Fe(CO)_3$ complexes **377a/b**, as a mixture of diastereomers at the indicated carbon. Oxidatively induced-reductive elimination of this mixture gave the vinylcyclopropanecarboxylate (1′*S*)-**378a/b**, also as a mixture of diastereomers. Reduction of the nitro and vinyl groups, followed by reaction with diphenylmethyl-eneimine afforded the diastereomeric imines (−)-**379** and (+)-**380** which were readily separable by chromatography. The absolute configuration at C2 of (−)-**379** and (+)-**380** were assigned by comparison of their specific rotation to a series of 13 *N*-diphenylmethylene imines of L-amino esters. Separate acid hydrolysis of each produced (2*S*,1′*S*,2′*S*,3′*R*)-**381** and (2*R*,1′*S*,2′*S*,3′*R*)-**382** respectively. The intermediate (1′*S*)-**378a/b** proved a versatile synthon for the preparation of other potential glutamate receptor ligands.[159] Dihydroxylation of **378a/b** produced a complex mixture of four diastereomeric glycols **383**. This mixture was simplified by periodate cleavage to the aldehyde, subsequent Jones oxidation, and diazomethane esterification. Hydrogenation over 10% Pd/C gave the oxime (2′*R*,3′*R*)-**384**.

Protected versions of *cis*-and *trans*-CCG's have been prepared by Sasaki's group (Scheme 77).[160] Reaction of the dianion derived from sulfone **385** with (2*R*)-glycidyl triflate, followed by addition of a third equivalent of butyl lithium gave a mixture of cyclopropylcarbinols **386** and **387**. This reaction is believed to proceed by initial displacement of triflate to generate **388**, which undergoes intramolecular epoxide opening. Hydrolysis of the THP ether, reductive desulfonylation and Jones oxidation gave a mixture of Boc protected (2*S*,1′*S*,2′*S*)-**389** and the lactam **390**. Separation of the mixture was accomplished by simple crystallization, and the structure of the lactam was solved by single crystal X-ray diffraction. Base hydrolysis **390** gave the Boc protected *cis*-isomer (2*S*,1′*R*,2′*S*)-**391**.

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Biographical sketch

William Donaldson was born and raised near Philadelphia, Pennsylvania. He received his BA degree in Chemistry with Honors from Wesleyan University (1977), having done undergraduate research with Professor Al Fry, and a PhD degree in Organometallic Chemistry at Dartmouth College (1981) under the direction of Professor Russell Hughes. After a postdoctoral fellowship with Professor Myron Rosenblum at Brandeis University (1981–82), he returned to Wesleyan University as a Visiting Assistant Professor (1982–93). In August, 1983, he joined the faculty at Marquette University as an Assistant Professor where his group has pursued novel organometallic chemistry directed toward organic synthesis. He was promoted to Associate Professor in 1990 and Full Professor in 1996. Professor Donaldson is the recepient of the Edward D. Simmons Award for Junior Faculty Excellence (1988) and the Rev. John P. Raynor Award for Teaching Excellence (1995) both from Marquette University. He has held an Alexander von Humboldt Fellowship at Philipps Universität-Marburg (1990–91) in the laboratories of Professor Dr Karl-Heinz Dötz. Professor Donaldson's hobbies revolve around his family, particularly spending time with his wife, Pam, and his two sons, Scott and Jimmy.