Formation of Four-Membered Heterocycles through Electrophilic Heteroatom Cyclization

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This review demonstrates the feasibility of the formation of cyclobutane heterocycles through 4-*endo* and 4-*exo* electrophile-induced processes. Cyclizations are usually observed upon treatment of linear substrates with electrophiles such as halogens (chlorine, bromine, iodine), haloreagents {NBS, [bis(collidine)X$^+$]Y$^-$, ...}, and more rarely with seleno reagents and metallic salts. Results show that the formation of β-lactones, oxetanes, and β-lactams can be viewed as a general process useful for synthetic purposes. Formation of azetidines and thietanes appears more limited and has been reported in only a few cases.

1. Introduction

Electrophilic cyclization of unsaturated carboxylic acids was initially exploited by Bougault.[1] This reaction has been extensively studied for the generation of a variety of heterocycles (lactones, ethers, lactams, amines, carbamates, ...).[2]

It has been calculated that the formation of three-membered ring compounds through ring-closure reactions occurs with small enthalpy barriers.[3] Synthesis of four-membered ring systems under the same conditions as used for the formation of three-membered ring compounds, however, occurs less readily.[4] This difficulty appears to be due mainly to Dunitz−Schumaker strain (1,3-carbon−carbon interaction), which is significant in four-membered rings but does not exist in cyclopropane compounds.[5] For cyclobutane compounds, only formation through nucleophile-induced processes was until recently considered synthetically useful. However, recent results obtained by us and by others have shown that electrophilic processes could also be considered useful for synthetic purposes.

In this paper we would like to report results concerning the synthesis of four-membered heterocycles: β-lactones, oxetanes, β-lactams, azetidines, and thietanes. These heterocycles are mostly obtained by electrophilic cyclization of unsaturated acids, alcohols, amides, amines, or thiols. These four-membered rings can be formed through *endo* or *exo* cyclization modes, depending on the chain length, the substitution pattern on the chain, and on the electrophiles employed (Scheme 1).

Gérard Rousseau (left), director of research at CNRS, was born in 1946. He received his Ph.D. (1977) from the University of Orsay, working with Professor J. M. Conia on the reactivity of singlet oxygen. After one year spent at Harvard with Professor R. B. Woodward (1978) he returned to Orsay and started his independent research activity. There, his main research fields were the chemistry of ketene acetals, utilization of enzymes in organic synthesis, and, more recently, the preparation of medium-ring compounds. His main research interest is currently in the preparation of small- and large-ring heterocyclic compounds by electrophilic cyclization.

Sylvie Robin (right) obtained her Ph.D. in 1992 from the University of Paris-Sud in Orsay with Professor F. Huet, working on optically active lactone synthesis. She spent a postdoctoral year at Oxford University with Professor L. M. Harwood, studying cycloadditions with chiral azomethines. On returning to France, she obtained a teaching position at the Faculty of Pharmacology (Univ. Paris V). In 1995, she joined Dr. G. Rousseau's group at the University of Paris-Sud, where she is studying the reactivity of electrophilic reagents.

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

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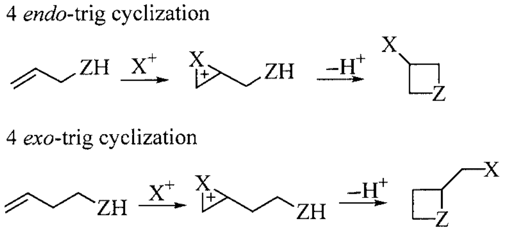


Scheme 1

"Onium" ions are postulated intermediates in these reactions. These ions are formed by nucleophilic attack of the double bond onto electrophiles and subsequent ring-opening of the bridged ions by *trans* intramolecular attack of the nucleophilic moiety. Electrophiles such as halogens (chlorine, bromine, or iodine), haloreagents, selenium and sulfur derivatives, and some metallic salts (Hg^{++}, Pb^{++}, ...) have been found to participate efficiently in these types of cyclizations.

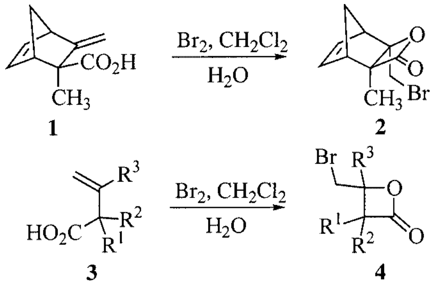
2. Preparation of 2-Oxetanones

2.1. Preparation through 4-*exo* Cyclization

It was reported in early work that β,γ-unsaturated acids react with iodine to give γ-lactones.[6] In the 1950s, van Tamelen claimed that 3-butenoic acid did not react with iodine under Bougault's conditions.[7] Shilov, in his pioneering work in this area, found that this acid did indeed react with iodine to give the β-lactone, with an activation energy 5 $kcal{\cdot}mol^{-1}$ higher than those measured for the formation of larger-ring lactones.[8] However, no structural description of the expected β-lactone was reported.

2.1.1. Halolactones

The first instance of β-lactone formation through an *exo* process during bromolactonization of a β,γ-unsaturated acid was reported by Barnett and McKenna.[9] They found that β-lactone formation was possible with a rigid system such as acid **1**, as well as with the more flexible β,γ-unsaturated acids **3** (Scheme 2). High yields were obtained by use of bromine as electrophile.



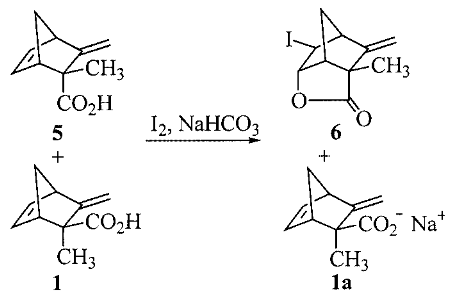
$R^1 = R^2 = CH_3, R^3 = H$ 83%

$R^1 = CO_2Et, R^2 = R^3 = CH_3$ 88% (two diastereomers)

$R^1 = R^2 = R^3 = H$ 50%

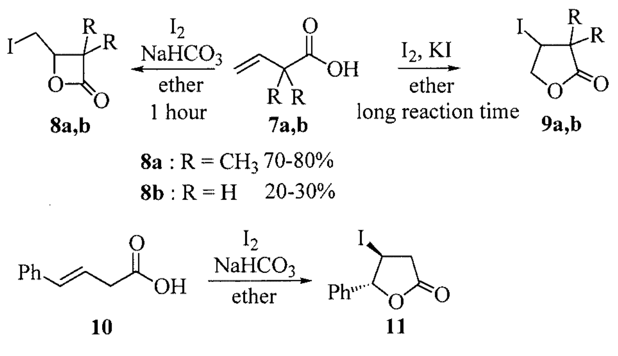
Scheme 2

In these later cases, the formation of the β-lactones **4** was fast enough to avoid the competitive base-catalyzed isomerization of vinylacetic acid to crotonic acid. The behavior of β,γ-unsaturated acids in the bromolactonization reaction was in direct contrast with the well established rule that iodolactonization results in the formation of β-iodo-γ-lactones.[2] It is generally accepted that β-lactones are inherently less stable than γ-lactones, due to ring strain, and the production of the less stable isomer is thus undoubtedly under kinetic control. Barnett and McKenna[10] separated a mixture of *endo* acid **5** and *exo* acid **1** by iodolactonization; treatment of *endo* acid **5** resulted in the formation of the γ-lactone **6**, while the *exo* isomer **1** did not react Scheme 3).



Scheme 3

Subsequently, Barnett and Sohn[11] showed that β-lactones could be obtained by iodolactonization of acids **7**. In fact, it was possible to obtain either β-lactones or γ-lactones, depending on the reaction times. The β-lactones **8** formed during the iodolactonization of acids **7** slowly rearranged under the reaction conditions into the thermodynamically more stable γ-lactones **9**. If the reaction times were sufficiently long, the β-lactones **8** were not detected. Styrylacetic acid **10** was transformed into the γ-lactone **11** regardless of the procedure used for iodolactonization, the influence of the γ-phenyl substituent being strong enough to induce only the formation of γ-lactone. This result provides evidence for the ionic nature of the intermediate during this kind of reaction (Scheme 4).



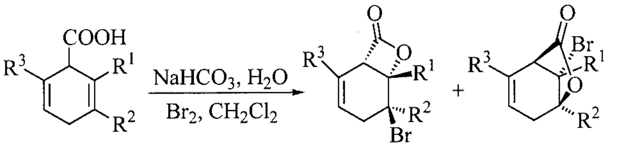
8a : $R = CH_3$ 70-80%

8b : R = H 20-30%

Scheme 4

In order to show the utility of 1,4-dihydrobenzoic acids **12**, Barnett and Needham[12a] examined iodo- and bromolactonizations of these acids, substituted in the 2- and 3-

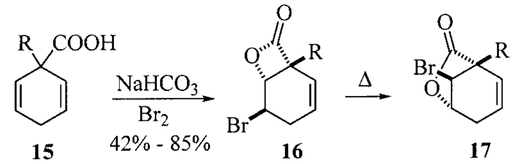
positions. Low yields of the β-lactones were obtained on iodolactonization. In contrast, bromolactonization afforded the bromolactones **13** and **14** in good yields. The size of the lactones formed in the lactonization depended on the substituents on the carbon−carbon double bond (Scheme 5); β-lactones were formed only when a hydrogen was present in the γ-position on the carbon−carbon double bond (R^2 = H). These observations were consistent with the formation of bromonium intermediates possessing higher carbonium character at the more substituted carbon of the double bond. The presence of substituents in the γ-position directed the cyclization towards the formation of the γ-lactones. Subsequently, Ganem et al.[12b] continued this study. They found that when the substituent in the 2-position of **12** had electron-withdrawing character (R^1 = CH_2OH, CH_2OCOPh, CH_2Ph) the cyclization occurred in a 4-*exo* mode.



12	4-*exo* **13**	5-*endo* **14**
$R^1 = CH_3, R^2 = R^3 = H$	29.5%	
$R^1 = R^3 = H, R^2 = CH_3$		71.4%
$R^1 = R^2 = R^3 = H$	42%	
$R^1 = R^2 = CH_3, R^3 = H$		>80%
$R^1 = R^2 = H, R^3 = CH_2OH$	86%	
$R^1 = R^2 = H, R^3 = CH_2OCOPh$	95%	
$R^1 = Me, R^2 = H, R^3 = CH_2Ph$	45%	

Scheme 5

The same group found that β-lactones **16** were also easily obtained under the same conditions (Br_2, $NaHCO_3$) from 1-substituted 1,4-dihydrobenzoic acids **15**.[13] As noted above, the β-lactones are kinetic products, and on heating they smoothly rearranged into the thermodynamically more stable β-bromo-γ-lactones **17** (Scheme 6). Iodine was also successfully used for these cyclizations.

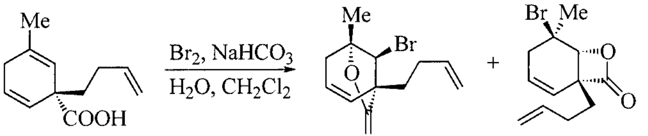


15 **16** **17**

$R = H, CH_3, CH_2OH, CH_2Ph,$
$CH_2CH_2CH(OCH_2)_2$ (with I_2)

Scheme 6

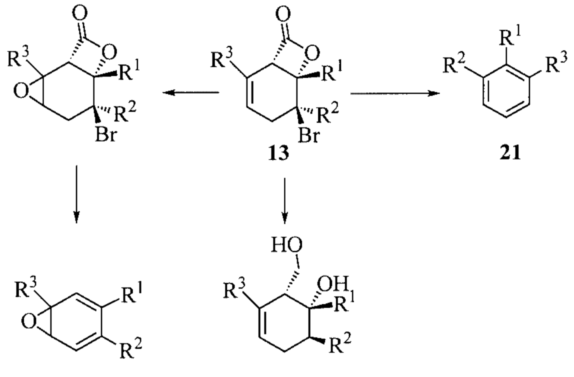
In order to prepare *trans*-fused perhydroindane substructures, Hart et al.[14] studied the regioselectivity of electrophilic bromolactonization. Treatment of unsaturated acid **18** under Barnett's conditions[12] gave nearly equimolar amounts of γ-lactone **19** and β-lactone **20**. The reaction only occurred at the trisubstituted carbon−carbon double bond. In contrast to the results obtained with flexible β,γ-unsaturated acids, the competition between 4-*exo* and the 5-*endo* cyclizations was probably due to the strain in the disfavored γ-lactone, thus facilitating the formation of the β-lactone (Scheme 7).



18 **19** **20**

Scheme 7

Bicyclic β-lactones can be viewed as useful synthetic intermediates: they may be transformed, for example, into arenes **21** (after dehydrobromination and subsequent carbon dioxide extrusion),[11] into arene oxides **22**,[13] or into 1,3-diols **23** (after lithium aluminiumhydride reduction of the lactone and bromine substitution) (Scheme 8).[15]



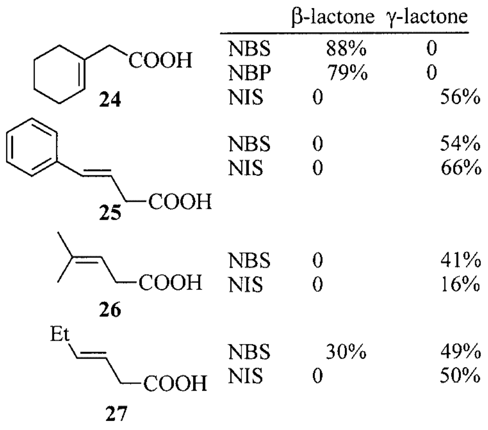
22 **23**

Scheme 8

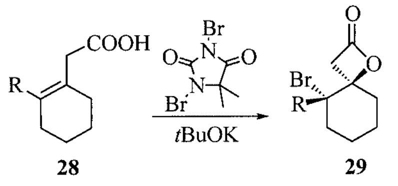
Some other halo reagents have been also explored in these reactions. Cook et al.[16] extensively studied the halolactonization of β,γ-unsaturated acids and showed that numerous bromine-containing reagents could be used. Bromolactonization of (cyclohex-1-enyl)acetic acid **24** with *N*-bromosuccinimide (NBS), *N*-bromophthalimide (NBP), or *N*-bromosaccharin (NBSC) gave the γ-bromo-β-lactone as the sole product. Unsaturated acid **27**, with one alkyl substituent in the γ-position, gave a mixture of β- and γ-lactones on treatment with NBS. The presence of an aryl group (acid **25**) or a *gem*-dimethyl in the γ-position (acid **26**) caused exclusive formation of the corresponding γ-butyrolactones. Treatment of these acids − **24**, **25**, **26**, and **27** − with NIS selectively gave the γ-lactones (Scheme 9).

The same group[17] also carried out the bromolactonization of 2-substituted (cyclohex-1-enyl)acetic acid **28** with 1,3-dibromo-5,5-dimethylhydantoin or 3-bromo-5-isobutyl-5-methylhydantoin. In the presence of potassium *tert*-butoxide, the reaction resulted mainly in the formation of β-lactones **29** (yields greater than 96%) (Scheme 10).

A. G. Meyers et al.[18] recently reported the bromolactonization of the dienic acid **30** with *N*-bromosuccinimide. The resultant β-lactone **31** was easily transformed into epoxide **32** by the action of sodium methoxide (Scheme 11).

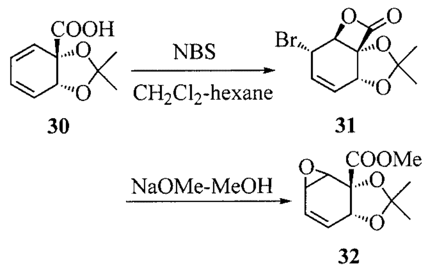


Scheme 9



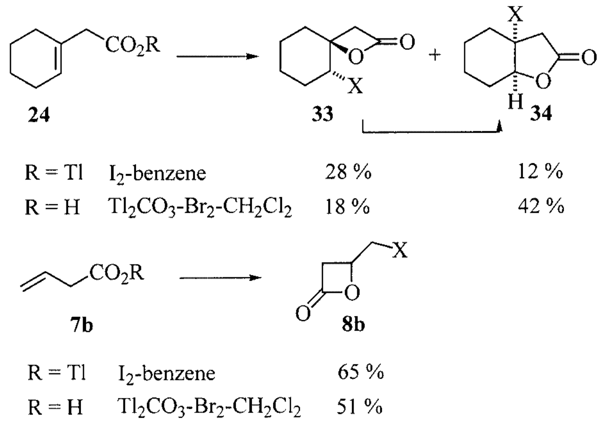
R = Me, Et, Ph, Bn

Scheme 10



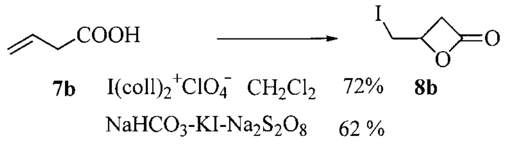
Scheme 11

Numerous attempts to improve the yields of β-lactones have been reported. Cambie et al.[19] investigated iodolactonization with the aid of thallium(I) carboxylates. When thallium salts of β,γ-unsaturated acids were treated with iodine in benzene, mixtures of γ-iodo-β-lactones and β-iodo-γ-lactones were formed. In the case of the thallium carboxylate **24**, the major product was the β-lactone **33**, rearranging quantitatively at room temperature, as previously reported in other cases, into the thermodynamically more stable γ-lactone **34**. This rearrangement was not observed in the case of lactone **8b** (Scheme 12). Subsequently, this group reported that the halolactonizations of these acids could be carried out with iodine[20a] in the presence of thallium(I) acetate or by the action of iodine or bromine in the presence of thallium(I) carbonate[20b] (Scheme 12).



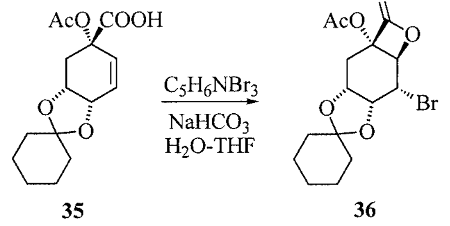
Scheme 12

Evans et al.[21] found that, in general, treatment of unsaturated carboxylic acids with [I(collidine)$_2$$^+$]ClO$_4$$^-$ afforded four- to seven-membered ring lactones with high regioselectivity. Treatment of 3-butenoic acid **7b** with this reagent, for example, produced the β-lactone **8b** in high yield. The facile formation of cyclic products with [I(collidine)$_2$$^+$]ClO$_4$$^-$ appears to be due to the low nucleophilicity of the perchlorate ion, thus favoring ring-closure by intramolecular hydroxy attack, as opposed to the formation of acyclic iodoperchlorate. The same iodolactone **8b** was obtained in lower yield by Royer et al.[22] with a mixture of potassium iodide and sodium persulfate (Scheme 13).



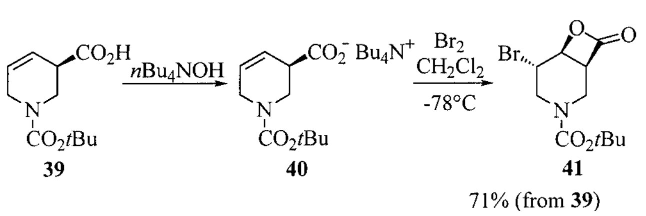
Scheme 13

Davies et al.[23] observed the formation of the β-lactone **36**, in high yield, as an intermediate in the synthesis of 6-α- and 6-β-fluoroshikimic acid when using pyridinium tribromide as reagent (Scheme 14).



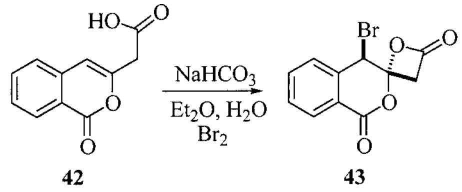
Scheme 14

Recently, Knapp and Zhao[24] reported that, in the case of acid **39**, the yield of the β-lactone **41** could be dramatically improved if the tetrabutylammonium salt of the acid was used instead of the sodium salt (Scheme 15).



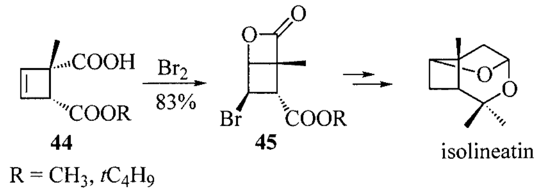
Scheme 15

Structural modifications of the substrate were also able to promote the formation of β-lactones. Gore and Narasimhan,[25] for example, found that treatment of 3-(carboxymethyl)isocoumarin **42** with bromine in the presence of aqueous sodium hydrogen carbonate exclusively resulted in the formation of the spirobromo-β-lactone **43** (Scheme 16).



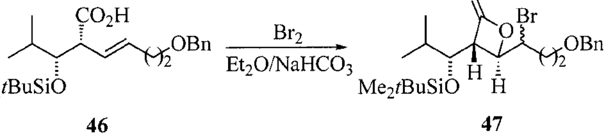
Scheme 16

Halolactonization was used by Askani and Keller[26] as a key step in a stereocontrolled synthesis of *rac*-isolineatin. The highly strained bicyclo[2.2.0]lactones **45** were obtained in excellent yields by treatment of cyclobutenoic acids **44** with bromine (Scheme 17).



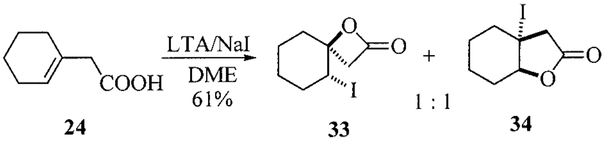
Scheme 17

Furthermore, Mead and Park[27] found that treatment of α-silyloxyalkyl-β,γ-unsaturated acid **46** with bromine resulted in the exclusive formation of the β-lactone **47**, even if the alkene was not in the terminal position. This result was attributed to the Thorp−Ingold effect induced by the α-silyloxy substituent (Scheme 18).



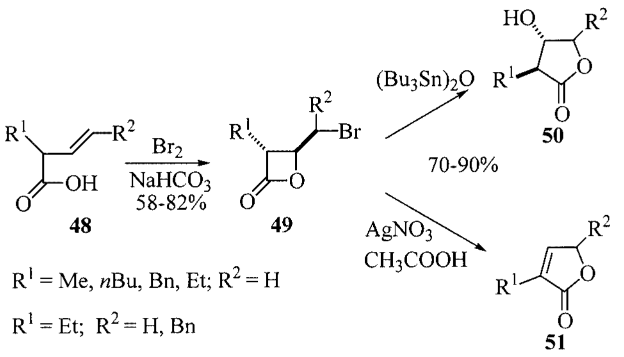
Scheme 18

Various other electrophilic reagents for these cyclizations have been investigated. Motohashi et al.[28] reported that the intramolecular cyclization of β,γ- and γ,δ-unsaturated acids could be induced by lead(IV) tetraacetate in the presence of sodium iodide. The lactones **33** and **34** were obtained as a 1:1 mixture from acid **24** under these conditions (Scheme 19).



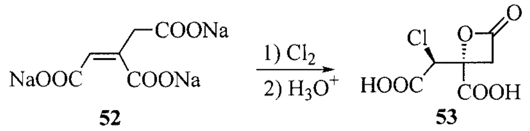
Scheme 19

Shibata et al.[29a] examined the diastereoselectivity of the 4-*exo* bromolactonization with α-substituted β,γ-unsaturated acids **48** as substrates. The α,β-*trans*-substituted β-lactones **49** were obtained under the reaction conditions used by Barnett.[9,11b] Treatment of these bromolactones **49**[29b] with bis(tributyltin)oxide afforded β-hydroxy-γ-butyrolactones **50**. A similar structural rearrangement was observed by Black and Huang[29c] on treatment of β-lactones **49** with silver nitrate. In both these cases γ-lactones were obtained in excellent yields (Scheme 20).



Scheme 20

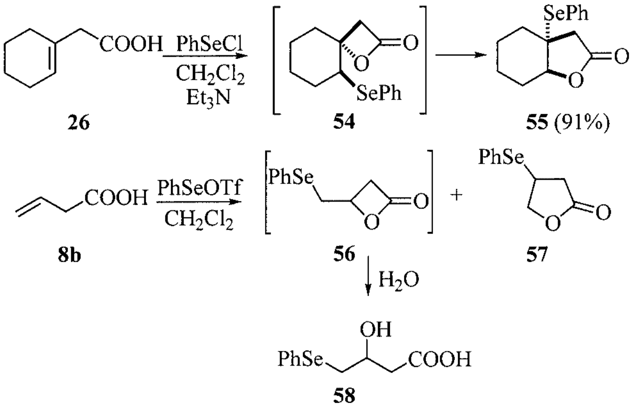
Even though chlorine is rarely used in halocyclizations, it has been found to be an efficient reagent. γ-Chloro-β-lactones were obtained by Guthrie et al.[30] on treatment of the sodium salts of (*E*)- or (*Z*)-aconitic acids with chlorine. For example, treatment of the sodium salt of (*E*)-aconitic acid **52** with chlorine in water provided the β-lactone **53** in an excellent yield (Scheme 21).



Scheme 21

2.1.2. Selenolactones

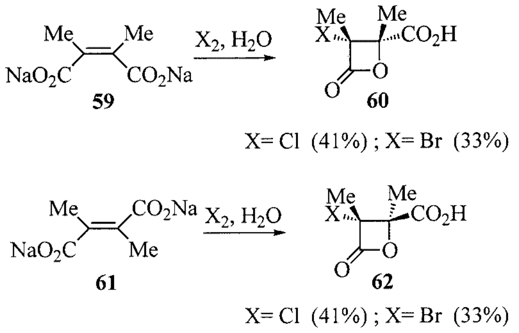
Utilization of selenoreagents for the formation of numerous heterocycles is well documented in the literature.[31] Some attempted preparations of β-lactones have been reported. However, these lactones are known to be unstable and were not isolated. Nicolaou and Lysenko[32a] have described a method for internal lactonization of unsaturated carboxylic acids by employing phenylselenenyl halides (PhSeCl, PhSeBr). Among other examples, they have treated (cyclohex-1-enyl)acetic acid **24** with phenylselenenyl chloride in the presence of triethylamine. The kinetic product, the spiro β-lactone **54**, subsequently rearranged into the more stable γ-lactone **55** (Scheme 22). Murata and Suzuki[32b] also investigated the selenolactonization with phenylselenenyl triflate as reagent. This reagent appears to be useful for the cyclization of β,γ-, γ,δ-, and δ,ε-unsaturated carboxylic acids. The reaction between phenylselenenyl triflate and 3-butenoic acid **8b** gave the γ-lactone **57** (29% at 0 °C, 11% at −78 °C) and 3-hydroxy-4-phenylselenobutanoic acid **58** (16% at 0 °C, 58% at −78 °C) as a mixture on quenching of the reaction mixture with water. The latter compound was probably formed by hydrolysis of the intermediate β-lactone **56** (Scheme 22).



Scheme 22

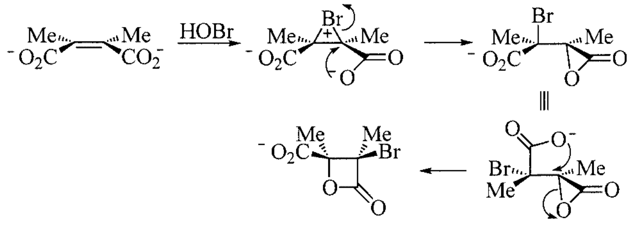
2.2. Preparation through 4-*endo* Cyclization

This disfavored ring-closure process has been reported in a few cases. The first example of β-lactone formation by electrophilic cyclization by this mode was reported in 1937 by Tarbell and Bartlett.[33] Treatment of the sodium salts of dimethylmaleic and dimethylfumaric acid with chlorine or bromine produced halogenated β-lactones **60** and **62** in modest yields (Scheme 23).



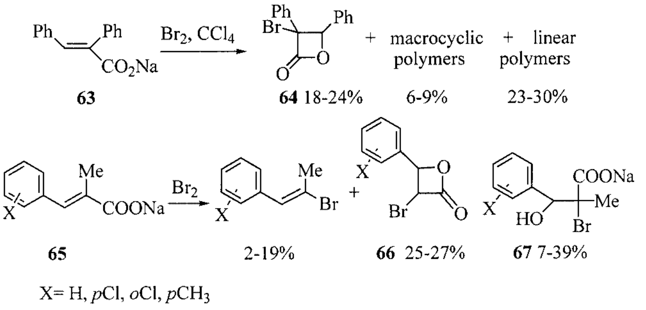
Scheme 23

The authors showed that the products were not formed by addition of chlorine to the double bond and subsequent intramolecular substitution of a chloride by one of the carboxylate functions. They postulated a two-step reaction mechanism, with attack of the double bond and ring-closure occurring as quickly as possible but not really synchronously. Williams et al.[34] have recently reinvestigated Bartlett's work. The structures of the β-lactones were established by X-ray crystallography and imply a *syn*-addition of the bromine atom and the acid function to the carbon−carbon double bond, in contrast with Bartlett's conclusions. Williams et al. postulated the formation of an intermediate α-lactone, subsequently opened by attack of the other carboxylate group to give the β-lactone. These two individual steps are indeed favored *exo* processes (Scheme 24).



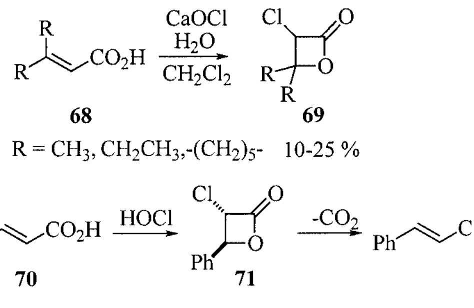
Scheme 24

Price and Blunt[35a] observed the formation, in low yield, of the α-bromo-β-bromolactone **64** on treatment of the sodium salts of *cis*- and *trans*-stilbene-α-carboxylate **63** with bromine. Under these conditions, intermolecular reaction products were also formed (Scheme 25). Similar results were obtained by Kingsbury and Max,[35b] who studied the reactions between bromine and the sodium salts of substituted cinnamic acids **65**, containing a variety of substituents on the aromatic ring. When the substituent was a chloro or a methyl group, β-lactones **66** were obtained as mixtures, the other product being compound **67**, corresponding to the addition of hypobromous acid to the olefinic double bond (Scheme 25).



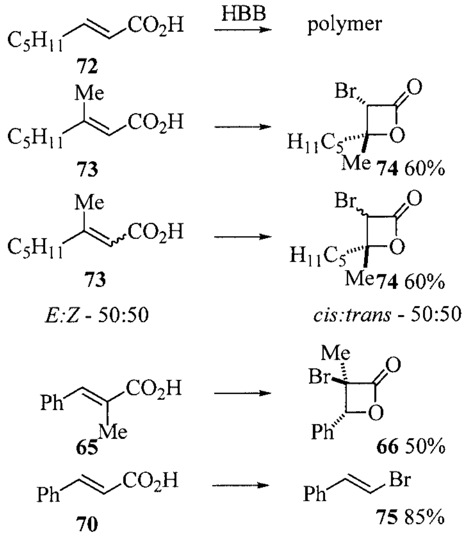
Scheme 25

Solas and Wolinsky[36] reported that the reaction between hypochlorous acid, produced in situ from a mixture of calcium hypochlorite and water, and α,β-unsaturated β-disubstituted acids **68** afforded α-chloro-β-lactones **69** in low yields. The (*E*)-cinnamic acid **70** similarly provided the *trans*-α-chloro-β-lactone **71**, but this unstable intermediate was converted into (*E*)-β-chlorostyrene on decarboxylation (Scheme 26).



Scheme 26

More recently, Rousseau and Homsi[37] reported the preparation of β-lactones by use of bis(collidine)bromine(I) hexafluorophosphate (HBB) as the electrophilic reagent. These cyclizations depend on the substitution pattern at the β-position in the acids. Only formation of a polymer was observed with the α,β-unsaturated acid **72**, monosubstituted in the β-position with an alkyl group. When, however, two substituents were present in the β-position, the β-lactone was obtained in a satisfactory yield (transformation of acid **73** into lactone **74**). With cinnamic acid **70**, only the (*E*)-bromostyrene **75** was isolated. If an α-substituent was introduced (acid **65**) the β-lactone (compound **66**) was again observed (Scheme 27). The results obtained can be explained in terms of the degree of stabilization of the positive charge developed on the carbon β to the acid function, as shown in Scheme 28. Since only a single diastereomer was obtained when *Z* (or *E*) unsaturated acid **73** was treated with HBB, these cyclizations are postulated to be diastereospecific.

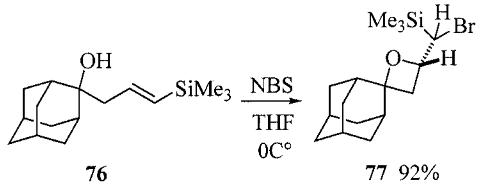


Scheme 27

3. Preparation of Oxetanes

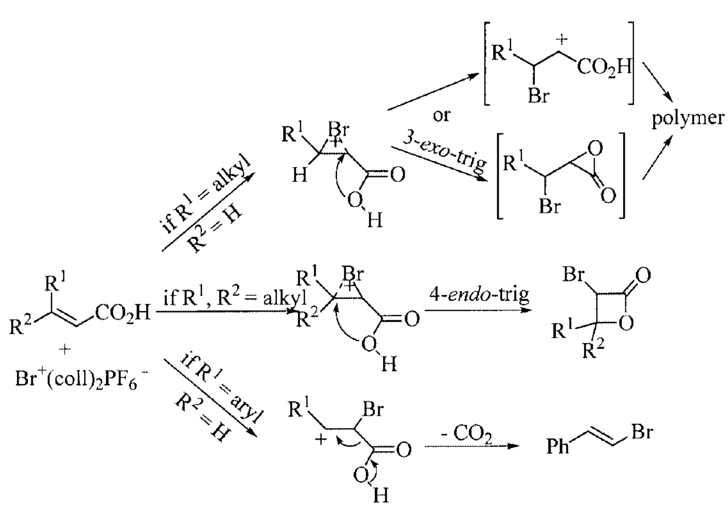
3.1. Preparation through 4-*exo* Cyclization

One of the first examples of the formation of oxetane by electrophile-induced cyclization of a homoallylic alcohol was reported by Magnus and Ehlinger,[38] who, during their studies into the reactivity of (trimethylsilyl)allyl anion, which can be viewed as a β-acyl anion equivalent for the conversion of aldehydes and ketones into γ-lactones, found that, when the adamantyl derivative **76** was treated with *N*-bromosuccinimide in THF, the oxetane **77** was formed rather than the five-membered ring compound. The silicon atom directs the electrophilic cyclization of the alcohol. These conditions appear to be limited to this adamantyl alcohol (Scheme 29).

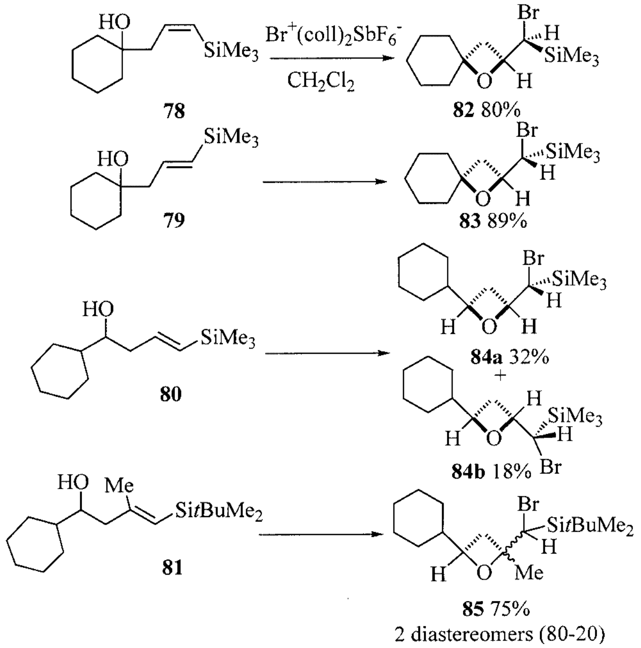


Scheme 29

Rousseau et al.[39] reinvestigated this reaction and showed that oxetanes could be obtained by treatment of homoallylic alcohols with bis(*sym*-collidine)bromine(I) hexafluoroantimonate. These cyclizations were diastereospecific when the carbon of the double bond β to the silicon atom contained a hydrogen atom. The (*Z*)- and (*E*)-vinylsilanes **78** and **79**, for instance, afforded the diastereomeric oxetanes **82** and **83**. However, the alcohol **81** gave a mixture (80:20) of two diastereomers. This reaction was also observed with $[Br^+(coll)_2]PF_6^-$, but the reaction appears to be less efficient with this reagent, due to side products formed as a result of the attack of the bromonium intermediate by the hexafluorophosphate anion. Formation of iodooxetane by use of the corresponding iodoreagents seemed possible. However, these reagents were found to be less efficient than the bromoreagents (Scheme 30).

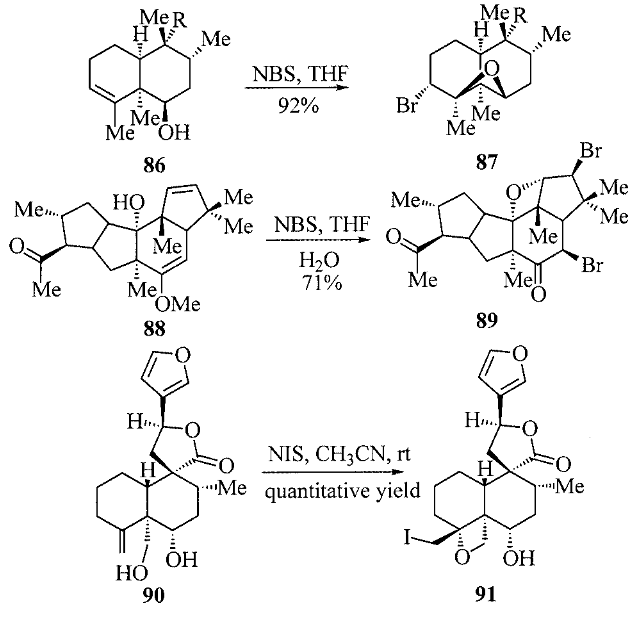


Scheme 28



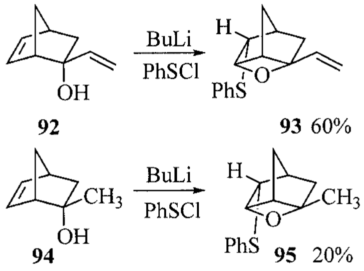
Scheme 30

Formation of oxetanes instead of tetrahydrofurans were also observed when the structures of the alcohols did not allow the 5-*endo* mode cyclization. Different examples have been reported. Treatment of alcohol **86** with *N*-bromosuccinimide resulted in exclusive formation of the oxetane **87**.[40] Manabe used this particular reaction to assign the β-stereochemistry of the alcohol. Similar examples are the formation of oxetanes **89** and **91** on treatment of compound **88** with *N*-bromosuccinimide, reported by Paquette et al.[41] and on treatment of compound **90** with *N*-iodosuccinimide, published by De la Torre et al.[42] (Scheme 31).



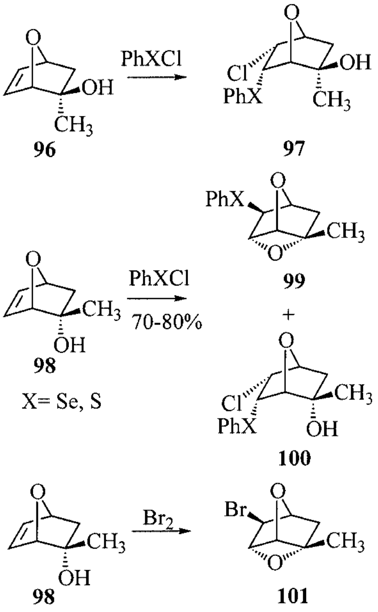
Scheme 31

Fallis et al.[43] found that *endo*-norborneols **92** and **94** substituted in the α-postition of the alcohol function reacted with phenylsulfonyl chloride to afford oxetanes **93** and **95**. This cyclization did not occur with 3-buten-1-ol (Scheme 32).



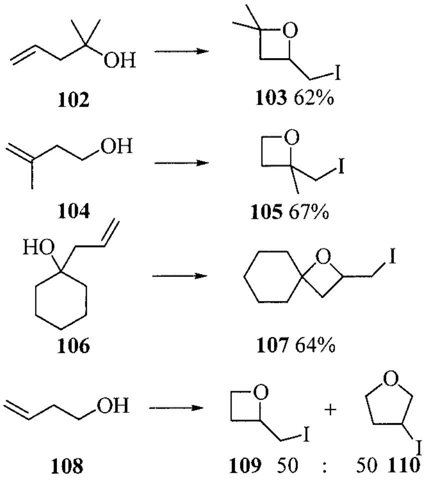
Scheme 32

Plumet et al. subsequently published their results on the oxanorbornene series. They studied[44a] the regio- and stereoselectivity of electrophilic additions of phenylselenenyl chloride and phenylsulfonyl chloride to isomeric 2-hydroxy-2-methyl-7-oxabicyclo[2.2.1]hept-5-enes **96** and **98**. The formation of oxetane **99** from alcohol **98** was observed, but no oxetane was obtained from the isomeric alcohol **96** (Scheme 33). This intramolecular electrophilic cyclization was found to be dependent on the temperature and on the solvent.[44b,44c] Reactions conducted in dichloromethane at low temperature appear to favor the formation of oxetanes, as does the use of selenium- instead of sulfur reagents. A similar reaction was observed when the *endo*-oxanorbornyl alcohol **96** was treated with bromine or *N*-bromosuccinimide.[44d]



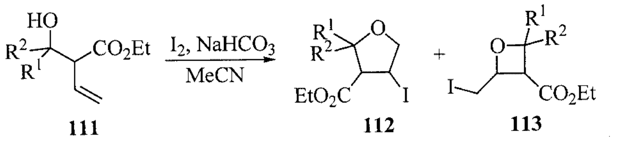
Scheme 33

Evans et al.[21] carried out electrophilic cyclizations of unsaturated alcohols with $[I(collidine)_2{}^+]ClO_4{}^-$. Three- to seven-membered ring iodoethers were obtained. Treatment of homoallylic alcohols with this reagent produced oxetanes in satisfactory yields. Oxetanes were obtained when the alcohols were α-disubstituted (alcohols **102** and **106**) or γ-substituted (alcohol **104**). Iodoetherification of 3-butenol **108** under these conditions provided a mixture of oxetane **109** and tetrahydrofuran **110** (yield not reported) (Scheme 34).



Scheme 34

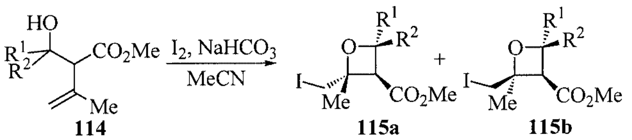
Galatsis et al.[45a] examined the cyclization of homoallylic alcohols possessing an ester function in the allylic position. Cyclization of compounds **111** in the presence of iodine in acetonitrile at room temperature occurred very slowly (3 days). Addition of silver triflate to the reaction mixture substantially enhanced the rate of the reaction (1−2 hours), a mixture of tetrahydrofuran **112** and oxetane **113** being obtained in each case. The electrophilic cyclizations proceeded with excellent stereocontrol, only one diastereomer (stereochemistry not determined) being observed for the tetrahydrofuran and the oxetane derivatives obtained (Scheme 35).



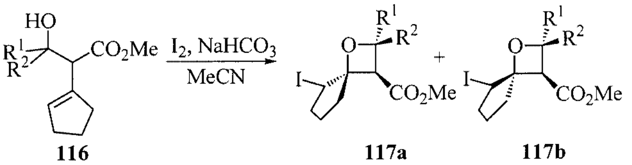
	112	113	
R^1, R^2 = Me, Me	1	1.7	81%
	1	1.1	65% (+ AgOTf)
$R^1, R^2 = (CH_2)_4$	1	1.5	61%
	1.5	1	59% (+ AgOTf)
R^1, R^2 = Me, H	1.7	1	71%
	1.7	1	65% (+ AgOTf)

Scheme 35

The same group[45b] reported the stereoselective preparation of substituted oxetanes from alcohols containing di- and trisubstituted double bonds (alcohols **114** and **116** in Scheme 36). Predictably, the presence of a methyl group on the carbon−carbon double bond completely abolished formation of tetrahydrofuran derivatives and directed the cyclizations to the formation of oxetanes **115** and **117**. Incorporation of the Evans chiral auxiliary on the ester function allowed[45c] the formation of oxetane rings with excellent diastereomeric control. Cyclization of chiral unsaturated amides **118** and **120** with iodine and sodium carbonate in acetonitrile afforded oxetanes **119** and **120** in moderate to good yields. No formation of the tetrahydrofuran derivatives was seen in these cases. A reverse diastereoselectivity during the cyclization was observed when a methyl group was present on the internal carbon of the alkene (Scheme 37).

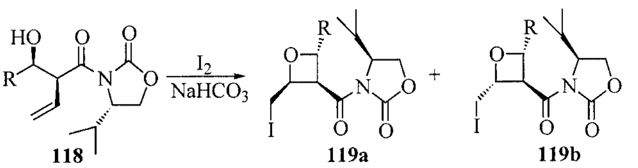


	115a	115b
syn R^1 = H, R^2 = Me	71%	
anti R^1 = Me, R^2 = H	22%	22%
$R^1 = R^2$ = Me	47%	

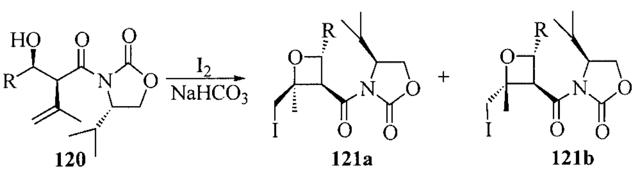


	117a	117b
syn R^1 = H, R^2 = Me	94%	
anti R^1 = Me, R^2 = H		53%
$R^1 = R^2$ = Me	90%	

Scheme 36



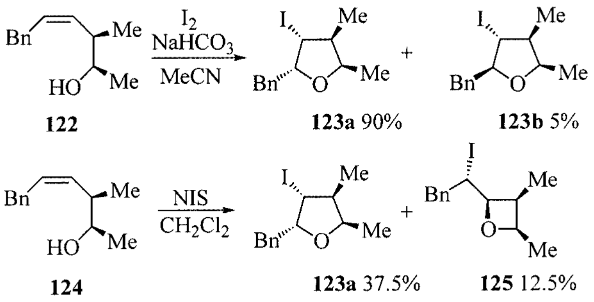
	119a : 119b	
R = Me	12:1	(47%)
Et	19:1	(48%)
*i*Pr	24:1	(40%)



	121a : 121b	
R = Me	2:98	(63%)
Et	18:82	(84%)
*i*Pr	19:81	(40%)

Scheme 37

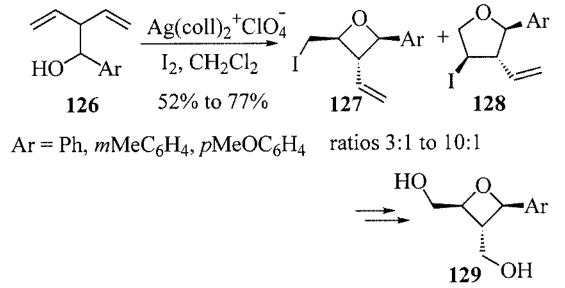
During their studies on 5-*endo-trig* iodocyclization of homoallylic alcohols, Knight et al.[46] observed that treatment of substituted alcohols with iodine in acetonitrile in the presence of sodium hydrogen carbonate resulted in the formation of two tetrahydrofuran diastereomers with good stereoselectivity. Treatment of alcohol **124** with *N*-iodosuc-



Scheme 38

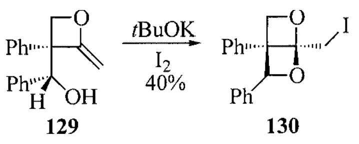
cinimide in dichloromethane, however, gave a 3:1 mixture of tetrahydrofuran **123a** and oxetane **125** (Scheme 38).

Jung and Nichols[47] found that iodocyclization of α,β-disubstituted homoallylic alcohols allowed the preparation of oxetanes. Alcohol **126**, for example, with an aryl group in the α-postition of the alcohol and a vinyl group in the β-postition, gave a mixture of oxetane **127** and tetrahydrofuran **128** in the presence of $[I(coll)^+]ClO_4^-$ in dichloromethane. The formation of the oxetanes was interpreted as the existence of reactive rotamers favoring the 4-*exo* mode cyclization. The resulting oxetanes were transformed into oxetanocin analogues **129** (Scheme 39).



Scheme 39

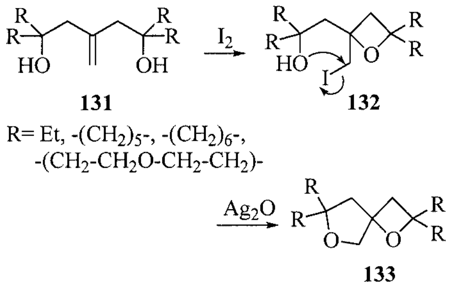
Howell et al.[48] reported the first example of a [2.2.0]-fused ketal derivative (compound **130**). The key step in this synthesis involved the iodoetherification of the 2-methyleneoxetane derivative **129** (Scheme 40).



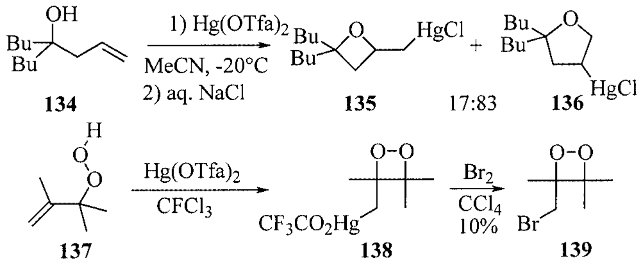
Scheme 40

The results of Yus et al.[49] appear more surprising. These workers obtained 1,6-dioxaspiro[3.4]octane compounds **133** by treatment of unsaturated 1,5-diols **131** with iodine in the presence of silver(I) oxide. It is postulated that the reaction proceeds by initial formation of oxetanes **132**. The stability of compounds **133** could be the driving force for these cyclizations (Scheme 41).

Formations of oxetanes are not limited to the use of halo reagents. However, utilization of metal salts as electrophiles appeared much less favorable. Nishizawa et al.[50] reported the intramolecular oxymercuration of unsaturated alcohols with mercuric triflate. Treatment of 4-butyloct-1-en-4-ol **134** with this mercuric salt in acetonitrile at −20 °C afforded a mixture of mercury oxetane **135** and mercury tetrahydrofuran **136** in a overall yield of 9% (Scheme 42). Adam et al.[51] observed the formation of the labile mercury-substituted 1,2-dioxetane **138** during the cyclomercuration of an allylic hydroperoxide **137**. Transformation of the mercury dioxetane **138** into the more stable bromodioxetane **139** occurred in a low yield (Scheme 42).

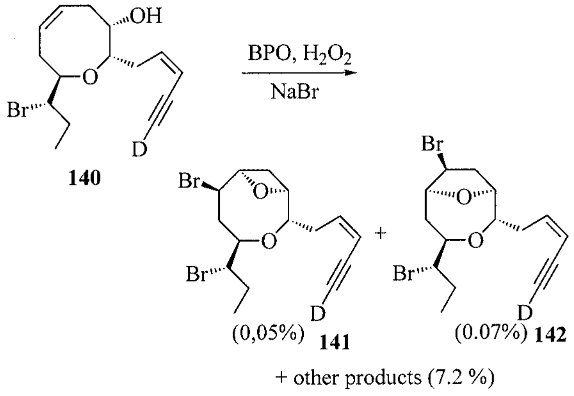


Scheme 41



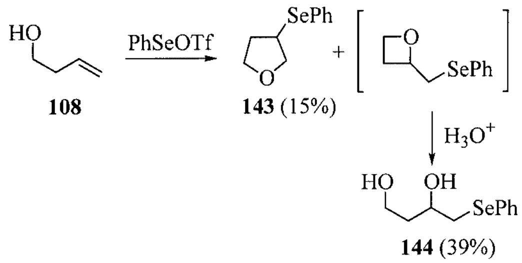
Scheme 42

Murai et al.[52] carried out enzymatic bromoetherification of prelaureatin **140** with bromoperoxidase (BPO) and lactoperoxidase. A mixture of six products, including the bromooxetane **141** (0.05%), was obtained. Even though the yield of this reaction is low, this interesting result provides evidence for a possible biogenesis for these kinds of marine products (Scheme 43).



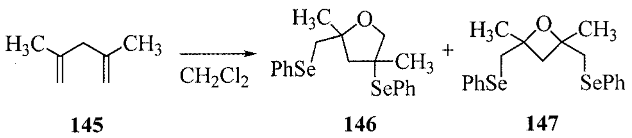
Scheme 43

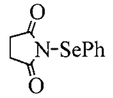
Murata and Suzuky[53] carried out cyclizations of hydroxyalkenes with phenylselenenyl triflate. The 3-butenol **108** gave the tetrahydrofuran derivative **143** and the 4-phenylselenobutane-1,3-diol **144**, probably formed by ring-opening of the intermediate oxetane during aqueous hydrolysis (Scheme 44).



Scheme 44

Formation of an oxetane by selenoetherification of a 1,4-diene has been reported by Nicolaou et al.[54] 2,4-Dimethyl-1,4-pentadiene **145** reacted with phenylselenenic acid, generated in situ from diphenyldiselenide and hydrogen peroxide, to afford a mixture of the tetrahydrofuran **146** and the oxetane **147**.[54a] Similar results were obtained with *N*-phenylselenosuccinimide as the electrophile (Scheme 45).[54b]

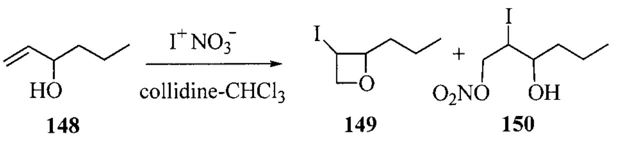


	146	147
$(PhSe)_2$-H_2O_2	24%	34%
	24%	53%

Scheme 45

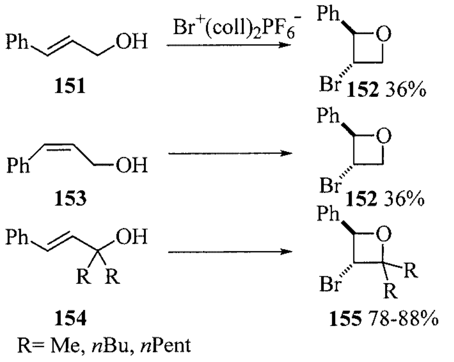
3.2. Preparation through 4-*endo* Cyclization

As with the formation of β-lactones, results concerning the formation of oxetanes by 4-*endo* mode cyclizations are rare. Lown et al.[55] studied the reactions between iodonium nitrate and some unsaturated alcohols in a mixture of collidine (or pyridine) and chloroform as solvent. In most cases 1,2-addition products such as iodo-nitrates or iodo-pyridinium compounds were obtained. With hex-1-en-3-ol **148** in collidine/chloroform, however, the iodo-nitrate **150** and the claimed oxetane **149** were obtained as a mixture (Scheme 46).



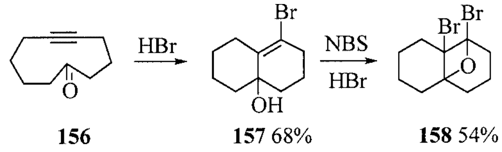
Scheme 46

Rousseau et al.[37,56] have obtained oxetane rings by treatment of allylic alcohols with bis(collidine)bromine(I) hexafluorophosphate. An aryl group in the γ-position of the alcohol was essential for these cyclizations, while the presence of two substituents in the α-position dramatically improved the yields. The *Z* and *E* isomers of 3-phenylprop-2-enol **151** and **153** both gave the same *trans* oxetane **152**. These results imply that the reactions proceed through carbocationic intermediates (Scheme 47).



Scheme 47

Wempe and Grunwell,[57] during their studies of the transannular rearrangement of 5-cyclodecynone **156**, found that alcohol **157** reacted with *N*-bromosuccinimide in the presence of hydrogen bromide to form the dibromooxetane **158**. The particular geometry of the alcohol might explain the result obtained (Scheme 48).



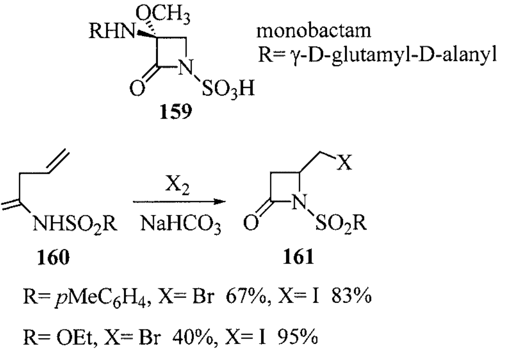
Scheme 48

4. Preparation of 2-Azetidinones

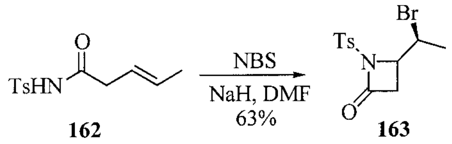
4.1. Preparation through 4-*exo* Cyclization

The search for new methods to prepare β-lactams has always drawn interest, due to the potential antibiotic activity of these compounds. One of the first publications demonstrating the possibility of preparing β-lactams by electrophilic cyclization was by Ganem et al.[58] These workers studied the oxidative cyclization of β,γ-unsaturated amidosulfamoyl esters to form *N*-sulfonylated halo-β-lactams, as precursors of monobactam **159**. Unsaturated amides were generally transformed into lactones and not lactams when the reactions were carried out with halogens such as bromine or iodine.[59] These authors found that reduction of the p*K*a of the carboxamide group favored nucleophilic attack by the nitrogen atom. Thus, treatment of *N*-sulfonylated β,γ-unsaturated amides **160** with bromine or iodine in aqueous sodium hydrogen carbonate produced *N*-tosyl halo β-lactams **161** in modest to good yields (Scheme 49).

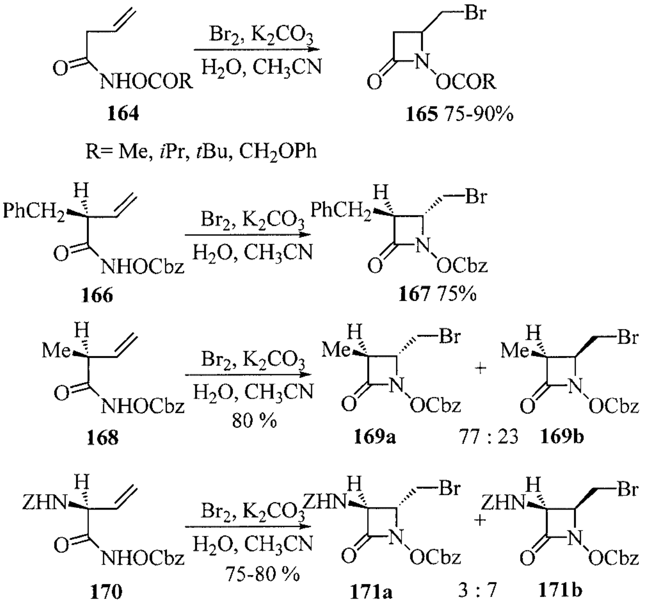
Subsequently, Cook et al.[60] carried out bromolactonization of a series of β,γ- and γ,δ-unsaturated *N*-tosylcarboxamides by treatment of the corresponding sodium salt with *N*-bromosuccinimide in *N*,*N*-dimethylformamide. In general, they obtained γ-bromo-β-lactams and δ-bromo-γ-lactams with high stereoselectivity. Treatment of amide **162**



Scheme 49



Scheme 50

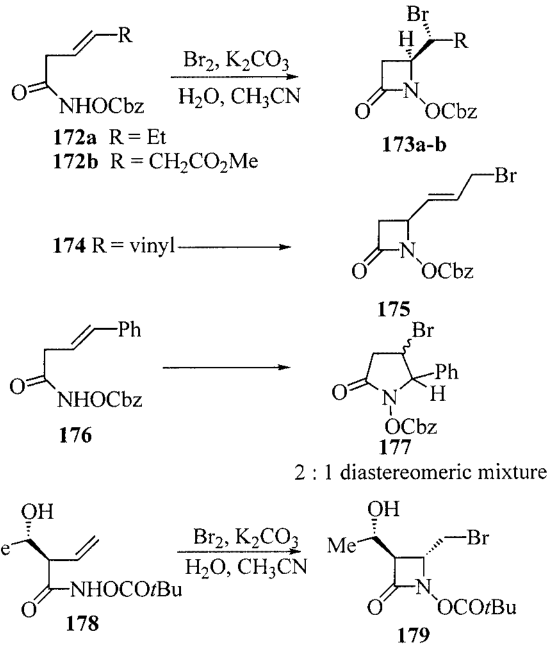


Scheme 51

with N-bromosuccinimide, for example, provided the β-lactam **163** (Scheme 50).

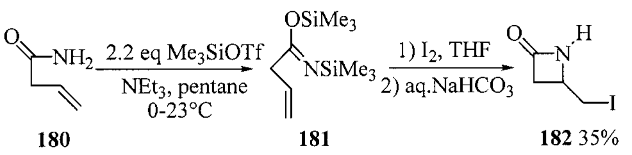
Rajendra and Miller[61a] reported the oxidative cyclization of various substituted β,γ-unsaturated hydroxamates to give the corresponding substituted 4-(bromomethyl)-N-hydroxy β-lactams. Cyclizations carried out on the 3-butenoic acid acetoxyamides **164** with bromine in the presence of potassium carbonate in a dichloromethane/water mixture provided the desired β-lactams **165** in excellent yields. The amount of water required for these cyclizations depended on the R substituent. They also studied the diastereoselectivity of these reactions by introduction of substituents α to the hydroxamates.[61b] For example, cyclization of the α-benzylamide **166** produced *trans* β-lactam **167**. However, with α-methylamide **168**, in which the less bulky methyl substituent was present, electrophilic cyclization gave a diastereomeric mixture of the two β-lactams **169a−b**, with the *trans* diastereomer **169a** as the major product. Introduction of an amino group in the α-position of the hydroxamate (compound **170**) under these reaction conditions mainly produced the *cis* diastereomer. The change in the diastereoselectivity could be a result of modification of the conformation of the molecules in the transition state (Scheme 51). Similarly, it was reported that bromine-induced cyclization of O-acyl-β,γ-unsaturated hydroxamates to β-lactams was compatible with a variety of γ-substituents on the carbon−carbon double bond.[61c] β-Lactams **173** were formed as sole products when starting from the amides **172**. Even the γ-vinyl amide **174** gave only the β-lactam **175**. An exception was the amide **176**, possessing a γ-phenyl group, which gave a pyrrolidinone, **177**, by a 5-*endo* cyclization process (Scheme 52). The same group reported[61d] a short enantioselective synthesis of a β-lactam ring with three contiguous stereogenic centers, by oxidative cyclization of α-hydroxyethyl-β,γ-unsaturated hydroxamate **178**. Treatment of this hydroxamate with bromine in the presence of potassium carbonate in aqueous acetonitrile produced the *trans* diastereomer of β-lactam **179** in an 89% yield. This result indicates that the hydroxyethyl group has the same stereochemical influence as a bulky alkyl group would in the cyclization reaction (Scheme 52).

Knapp and Levorse[62] have reported an interesting method for the synthesis of iodolactams by cyclization of N,O-bis(trimethylsilyl)imidate derivatives. These N,O-bis(trimethylsilyl)imidate derivatives were obtained by treatment of the corresponding amide with trimethylsilyloxy triflate. However, treatment of the imidate **181**, derived from crotonamide **180**, with iodine afforded the β-lactam



Scheme 52

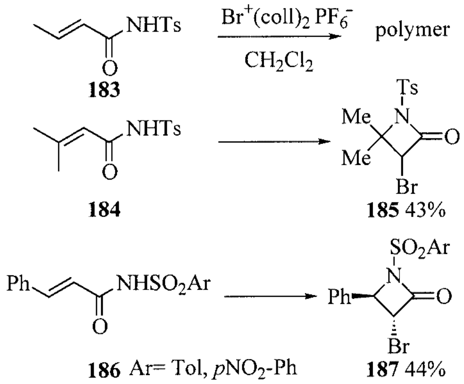
182 in a low yield.[62b] The initial crotonamide **180** was found to be the major product (Scheme 53).



Scheme 53

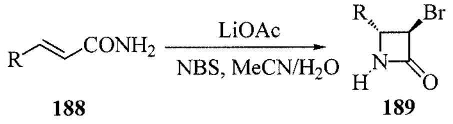
4.2. Preparation through 4-*endo* Cyclization

Rousseau and Homsi[37] have synthesized β-lactams by electrophilic cyclization, in dichloromethane, of *N*-tosyl-α,β-unsaturated amides, with bis(collidine)bromine(I) hexafluorophosphate as electrophile. In order for the cyclization to occur, the carbon−carbon double bond of the amides had to be substituted in the β-position with one aryl or with two alkyl substituents. Amide **183** only gave a polymeric material under these cyclization conditions, while the β-disubstituted amide **184** afforded the β-lactam **185** in a modest yield. The amide **186** gave only the *trans* diastereomer **187**. This result indicates that the cyclization is a diastereospecific process (Scheme 54).



Scheme 54

Naskar and Roy[63] found comparable results when using *N*-bromosuccinimide as the electrophile. In the presence of a catalytic amount of lithium acetate in a mixture of acetonitrile and water (97:3), unsaturated amides **188** afforded the α-bromo-β-lactams **189**. In these cases an aromatic substituent on the carbon−carbon double bond appears to be essential (Scheme 55).



R = *p*Me-C_6H_4	46%
R = *p*MeO-C_6H_4	54%
R = Ph	20%
R = 9-phenanthrenyl	53%
R = 3-thienyl	48%

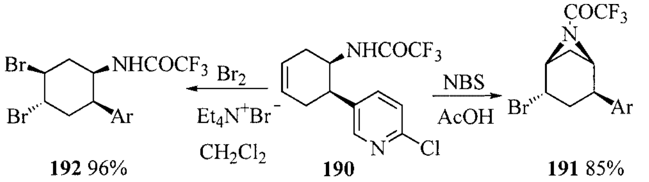
Scheme 55

5. Preparation of Azetidines

Formation of azetidines by electrophilic cyclizations appears to be a much more difficult process than the formation of oxetanes, and only a limited number of results have been reported in the literature.

5.1. Preparation through 4-*exo* Cyclization

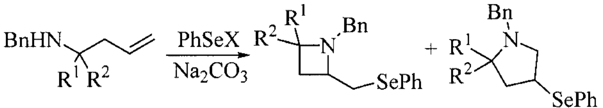
In the total synthesis of (+)- and (−)-epibatidine, Corey et al.[64] observed that an *N*-trifluoroacetyl derivative **190** could serve as a useful compound for the synthesis of azabicyclo[3.1.1]heptane analogues of epibatidine. Treatment of compound **190** with *N*-bromosuccinimide in acetic acid afforded azabicyclo[3.1.1]heptane **191**. Treatment of the same compound with bromine in dichloromethane resulted only in a 1,2-addition of bromine on the carbon−carbon double bond. These different pathways can be explained in terms of the acidity of the NH group in dichloromethane, which might assist the formation of a *cis* bromonium ion by hydrogen bonding to the terminal bromine of the Br_2−olefin Π complex. In acetic acid, the amide acts as a nucleophile, selectively capturing the bromonium ion (Scheme 56).



Scheme 56

Paulmier et al.[65a] have studied selenium-induced cyclization of homoallyl benzylamines **193**. These compounds were treated with phenylselenenyl chloride and phenylselenenyl bromide in dichloromethane or acetonitrile. Contrary to initial observations, the presence of sodium carbonate was not always necessary. Under these conditions, both azetidines **194** and pyrrolidines **195** were obtained. The azetidine derivatives **194** were found to be the major products when the solvent was acetonitrile, especially when two substituents were present on the homoallylic carbon. The formation of the azetidines was improved when phenylselenenyl chloride was used in place of phenylselenenyl bromide, even if the overall yield of cyclization was lower (Scheme 57). The mechanism of these reactions has recently been studied in detail.[65b]

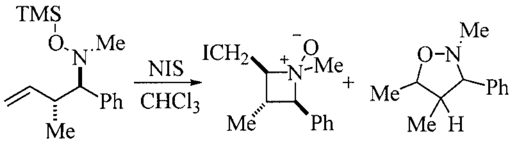
Trombini et al.[66] studied the iodocyclization of *O*-silylated homoallylic hydroxylamines with *N*-bromosuccinimide in chloroform. Treatment of the *N*-methyl derivative **196**, containing a terminal double bond, under these conditions yielded the azetidine *N*-oxide **197** in 17% yield, together with isoxazolidine **198**, formed through a 5-*exo* cyclization (Scheme 58). In the other cases only the formation of isoxazolidines was observed.



193 **194** **195**

R^1	R^2	X	sol.	**194**/**195** ratio	yield%
Me	H	Cl	CH_2Cl_2	25/75	80
Me	H	Br	CH_2Cl_2	16/84	95
Me	H	Br	CH_3CN	28/72	95
*i*Pr	H	Cl	CH_2Cl_2	60/40	85
*i*Pr	H	Br	CH_2Cl_2	22/78	100
*i*Pr	H	Br	CH_3CN	65/35	100
Ph	H	Cl	CH_2Cl_2	69/31	87
Ph	H	Br	CH_2Cl_2	35/65	97
Ph	H	Br	CH_2Cl_2	70/30	95
Et	Me	Br	CH_3CN	100/0	77
Ph	Me	Br	CH_3CN	100/0	73

Scheme 57

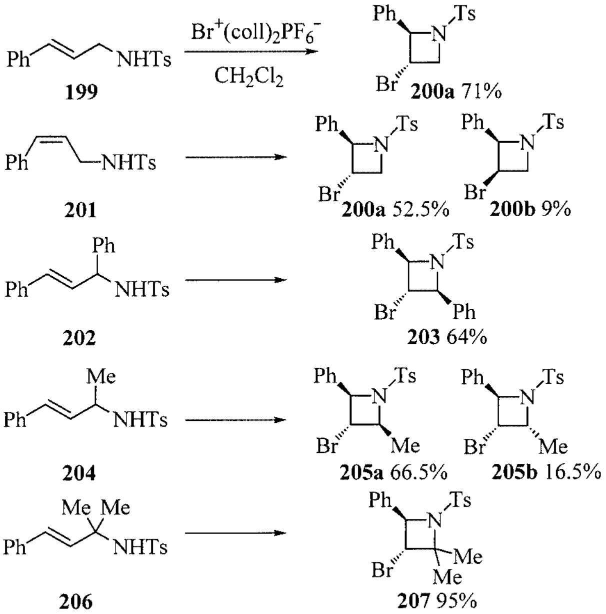


196 **197** 17% **198** 58%

Scheme 58

5.2. Preparation through 4-*endo* Cyclization

Rousseau and Robin[67] prepared azetidines by cyclization of *N*-cinnamyl tosylamides with bis(*sym*-collidine)bromine(I) hexafluorophosphate as electrophile. A phenyl group in the γ-position of the amide function appears to be necessary, since none of the desired product was obtained from 4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide. The presence of two substituents in the α-position of the amide function (compound **206**) favored the cyclization. The same diastereomer **200a** was obtained as the major product from (*E*)- and (*Z*)-cinnamyl amides **199** and **201**. These results suggested that the bromocyclizations proceed through a carbocation intermediate (Scheme 59).



199 **200a** 71%

201 **200a** 52.5% **200b** 9%

202 **203** 64%

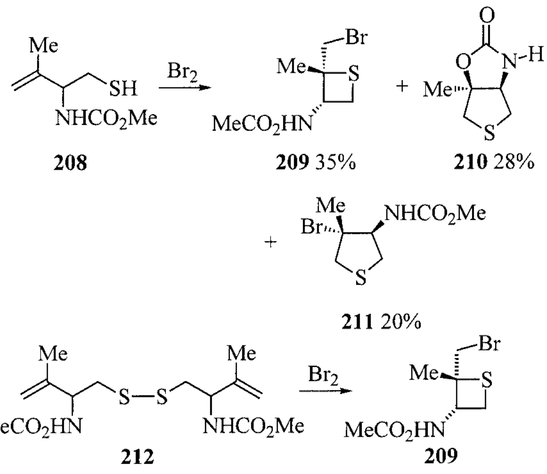
204 **205a** 66.5% **205b** 16.5%

206 **207** 95%

Scheme 59

6. Preparation of Thietanes

Electrophile-induced cyclization of unsaturated sulfides has only been reported a limited number of times. In the majority of cases, formation of cyclic five-membered thioethers was observed.[68] The formation of thietanes appears to be a disfavored process. An example of the formation of a thietane by this method has, however, been reported in the literature. Mellor et al.[69] studied the reaction of bromine with the γ-unsaturated thiol **208**, possessing an amino group α to the olefin. The four-membered thioether **209** was formed as a mixture with the two thiophene derivatives **210**

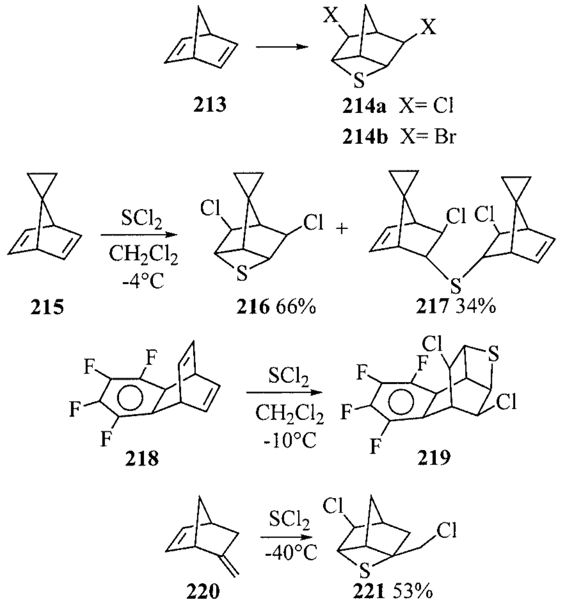


208 **209** 35% **210** 28%

211 20%

212 **209**

Scheme 60



213 **214a** X= Cl

214b X= Br

215 **216** 66% **217** 34%

218 **219**

220 **221** 53%

Scheme 61

and **211**. Interestingly, bromination of the disulfide **212** exclusively afforded the thietane **209** (75% yield) (Scheme 60).

The formation of thietanes has also been achieved by treatment of dienic compounds with sulfur dichloride. It was shown that bicyclo[2.2.1]heptadiene **213** reacted with sulfur dichloride[70a] to give the dichlorothietane **214a** (86% yield) (Scheme 61). Similarly, treatment of compound **213** with a mixture of phosphorus oxybromide and thiobismorphine provided dibromothietane **214b** (72% yield).[70b] This cyclization was also observed with bicyclo[2.2.1]hepta-2,5-diene-7-spiro-1′-cyclopropane **215**[70c] and with bicyclo-[2.2.2]octa-1,5-diene **218** (Scheme 61).[70d] Similarly, Lautenschlaeger[71] reported that methylenenorbornene **220** was transformed into dichlorothietane **221** in the presence of sulfur dichloride. These reactions occur through episulfonium intermediates. (Scheme 61).

7. Conclusion

This review demonstrates the feasibility of the production of β-lactones, β-lactams, oxetanes, azetidines, and thietanes through 4-*endo* and (or) 4-*exo* electrophile-induced processes. Homoallylic alcohols without an electrostabilizing group at the terminal carbon of the double bond gave β-lactones in good yields with a variety of reagents, including bromine, iodine $[I^+(coll)_2]PF_6^-$ (or ClO_4^-), and *N*-bromosuccinimide. Better results were observed if the reactions were conducted on the carboxylates (potassium, sodium, or ammonium salts). It was also reported than β-lactones could be obtained by 4-*endo* mode cyclizations. The formation of oxetanes by this method appears less favorable. In fact, when possible, homoallylic alcohols principally afforded tetrahydrofuran derivatives by 5-*endo* mode cyclizations. The 4-*exo* process was observed when the cyclizations were directed by electronic or geometric factors. Formation of β-lactams appears more difficult than the formation of the corresponding lactones, but was observed when the nucleophilicity of the nitrogen atom was increased (*N*-sulfonyl compounds). The formation of azetidines and thietanes has been reported in a few cases. However, the yields reported show that these reactions are possible. At present, the formation of thietanes by this process appears to be of little synthetic value.

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[1] M. J. Bougault, *C. R. Acad. Sci.* **1904**, *139*, 864−868.

[2] For reviews see: [2a] K. E. Harding, T. H. Tiner, in: *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, New York, **1991**, vol. 4, p. 363. [2b]G. Cardillo, M. Orena, *Tetrahedron* **1990**, *46*, 3321−3408.

[3] S. Gronert, J. M. Lee, *J. Org. Chem.* **1995**, *60*, 6731−6736.

[4] A. Di Martino, C. Galli, P. Gargano, L. Mandolini, *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345−1350.

[5] D. Crener, J. Gauss, *J. Am. Chem. Soc.* **1986**, *108*, 7467−7477.

[6] [6a] M. J. Bougault, *Ann. Chim. Phys.* **1908**, *14*, 145−183. M. J. Bougault, *Ann. Chim. Phys.* **1908**, *15*, 296−312. [6b] R. P. Linstead, C. J. May, *J. Chem. Soc.* **1927**, 2565−2579. [6c] M. D. Dowle, D. I. Davies, *Chem. Soc. Rev.* **1979**, 171−197.

[7] E. E. Van Tamelen, M. Shamma, *J. Am. Chem. Soc.* **1954**, *76*, 2315−2317.

[8] E. N. Rengevich, V. I. Statinets, E. A. Shilov, *Doklady Akademii Nauk SSSR (Engl. Transl.)* **1962**, *146*, 787−790.

[9] W. E. Barnett, J. C. McKenna, *Tetrahedron Lett.* **1971**, 2595−2598.

[10] W. E. Barnett, J. C. McKenna, *J. Chem. Soc., Chem. Commun.* **1971**, 551−552.

[11] [11a] W. E. Barnett, W. H. Sohn, *J. Chem. Soc., Chem. Commun.* **1972**, 472−473. [11b] W. E. Barnett, W. H. Sohn, *Tetrahedron Lett.* **1972**, 1777−1780.

[12] [12a] W. E. Barnett, L. L. Needham, *J. Org. Chem.* **1975**, *40*, 2843−2844. [12b] G. W. Holbert, L. B. Weiss, B. Ganem, *Tetrahedron Lett.* **1976**, 4435−4438.

[13] B. Ganem, G. W. Holbert, L. B. Weiss, K. Ishizumi, *J. Am. Chem. Soc.* **1978**, *100*, 6483−6491.

[14] C. P. Chuang, J. C. Gallucci, D. J. Hart, *J. Org. Chem.* **1988**, *53*, 3210−3218.

[15] [15a] T. Mah, H. M. Sirat, E. J. Thomas, *J. Chem. Soc., Chem. Commun.* **1978**, 961−962. [15b] T. Mah, H. M. Sirat, E. J. Thomas, *J. Chem. Research (S)* **1979**, 392−392.

[16] [16a] C. H. Cook, Y. S. Cho, S. S. Jew, Y. G. Suh, *Soul Taehakkyo Yakhak Nonmunjip* **1979**, *4*, 109−112, [*Chem. Abstr.* **1981**, *94*, 121200]. [16b] C. H. Cook, Y. S. Chung, *Arch. Pharm. Res.* **1981**, *4*, 133−135. [16c] C. H. Cook, E. K. Kang, *Arch. Pharm. Res.* **1981**, *4*, 137−139. [16d] C. H. Cook, Y. S. Cho, S. S. Jew, Y. G. Suh, E. K. Kang, *Arch. Pharm. Res.* **1983**, *6*, 45−53. [16e] C. H. Cook, Y. S. Cho, S. S. Jew, Y. S. Chung, *Soul Taehakkyo Yakhak Nonmunjip* **1984**, *9*, 44−46, [*Chem. Abstr.* **1986**, *105*, 42572].

[17] [17a] Y. S. Cho, S. S. Jew, Y. S. Chung, *Arch. Pharm. Res.* **1982**, *5*, 93−96. [17b] S. S. Jew, *Yakhak Hoechi* **1989**, *33*, 206−210, [*Chem. Abstr.* **1990**, *112*, 118562]. [17c] S. S. Jew, H. Lee, B. A. Koo, *Arch. Pharm. Res.* **1994**, *17*, 327−330.

[18] A. G. Meyers, D. R. Siegel, D. J. Buzard, M. G. Charest, *Org. Lett.* **2001**, *3*, 2923−2926.

[19] R. C. Cambie, R. C. Hayward, J. L. Roberts, P. S. Rutledge, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864−1867.

[20] [20a] R. C. Cambie, S. Ng Kai, S. Peter, R. Woodgate, P. D. Woodgate, *Aust. J. Chem.* **1979**, *32*, 2793−2795. [20b] R. C. Cambie, P. S. Rutledge, R. F. Somerville, P. D. Woodgate, *Synthesis* **1988**, 1009−1011.

[21] R. D. Evans, J. W. Magee, J. H. Schauble, *Synthesis* **1988**, 862−868.

[22] A. C. Royer, R. C. Mebane, A. M. Swafford, *Synlett* **1993**, 899−900.

[23] J. K. Sutherland, W. J. Watkins, J. P. Bailey, A. K. Chapman, G. M. Davies, *J. Chem. Soc., Chem. Commun.* **1989**, *18*, 1386−1387.

[24] S. Knapp, D. Zhao, *Org. Lett.* **2000**, *2*, 4037−4040.

[25] V. G. Gore, N. S. Narasimhan, *Indian J. Chem. Sect. B* **1991**, *30*, 241−246.

[26] R. Askani, U. Keller, *Liebigs Ann. Chem.* **1988**, 61−68.

[27] K. T. Mead, M. Park, *Tetrahedron Lett.* **1995**, *36*, 1205−1208.

[28] S. Motohashi, M. Satomi, Y. Fujimoto, T. Tatsuno, *Heterocycles* **1985**, *23*, 2035−2038.

[29] [29a] I. Shibata, M. Toyota, A. Baba, H. Matsuda, *J. Org. Chem.* **1990**, *55*, 2487−2491. [29b] I. Shibata, F. Matsuo, A. Baba, H. Matsuda, *J. Org. Chem.* **1991**, *56*, 475−476. [29c] T. H. Black, J. Huang, *Tetrahedron Lett.* **1993**, *34*, 1411−1412.

[30] R. W. Guthrie, R. W. Kierstead, F. A. Mennona, A. C. Sullivan, **1982**, U. S. patent 4,312,885; *Chem. Abstr.* **1983**, *99*, 38304.

[31] N. Petragnani, H. A. Stefani, C. J. Valduga, *Tetrahedron* **2001**, *57*, 1411−1448.

[32] [32a] K. C. Nicolaou, Z. Lysenko, *J. Am. Chem. Soc.* **1977**, *99*, 3185−3187. [32b] S. Murata, T. Suzuki, *Chem. Lett.* **1987**, 849−852.

[33] D. S. Tarbell, P. D. Bartlett, *J. Am. Chem. Soc.* **1937**, *58*, 407−410.

[34] J. J. Robinson, J. G. Buchanan, M. H. Charlton, R. G. Kinsman, M. F. Mahon, I. H. Williams, *Chem. Commun.* **2001**, 485−486.

[35] [35a] C. C. Price, H. W. Blunt, *J. Org. Chem.* **1969**, *34*, 2484−2486. [35b] C. A. Kingsbury, G. Max, *J. Org. Chem.* **1978**, *43*, 3131−3138.

[36] D. Solas, J. Wolinsky, *Synthetic Commun.* **1981**, *11*, 609−614.

[37] F. Homsi, G. Rousseau, *J. Org. Chem.* **1999**, *64*, 81−85.

[38] [38a] E. Ehlinger, P. Magnus, *J. Chem. Soc., Chem. Commun.* **1979**, 421−422. [38b] E. Ehlinger, P. Magnus, *J. Am. Chem. Soc.* **1980**, *102*, 5004−5011.

[39] M. Rofoo, M. C. Roux, G. Rousseau, *Tetrahedron Lett.* **2001**, *42*, 2481−2484.

[40] [40a] S. Manabe, C. Nishino, *Tetrahedron* **1986**, *42*, 3461−3470. [40b] S. Manabe, N. Enoki, C. Nishino, *Tetrahedron Lett.* **1985**, *26*, 2213−2216.

[41] L. A. Paquette, S. D. Edmondson, N. Monck, R. D. Rogers, *J. Org. Chem.* **1999**, *64*, 3255−3265.

[42] M. C. De la Torre, A. Maggio, B. Rodrigez, *Tetrahedron* **2000**, *56*, 8007−8017.

[43] [43a] W. L. Brown, A. G. Fallis, *Tetrahedron Lett.* **1985**, *26*, 607−610. [43b] S. M. Tuladhar, A. G. Fallis, *Tetrahedron Lett.* **1987**, *28*, 523−526.

[44] [44a] O. Arjona, R. F. De la Pradilla, R. A. Perez, J. Plumet, A. Viso, *Tetrahedron Lett.* **1987**, *45*, 5549−5550. [44b] O. Arjona, R. F. De la Pradilla, J. Plumet, A. Viso, *Tetrahedron* **1989**, *45*, 4565−4578. [44c] O. Arjona, R. F. De la Pradilla, J. Plumet, A. Viso, *J. Org. Chem.* **1992**, *57*, 772−774. [44d] O. Arjona, R. F. De la Pradilla, L. Garcia, A. Mallo, J. Plumet, *J. Chem. Soc., Perkin Trans. 2* **1989**, 1315−1318.

[45] [45a] P. Galatsis, S. D. Millan, P. Nechala, G. Ferguson, *J. Org. Chem.* **1994**, *59*, 6643−6651. [45b] P. Galatsis, D. J. Parks, *Tetrahedron Lett.* **1994**, *35*, 6611−6614. [45c] P. Galatsis, S. D. Millan, G. Ferguson, *J. Org. Chem.* **1997**, *62*, 5048−5056.

[46] J. M. Barks, D. W. Knight, C. J. Seaman, G. G. Weingarten, *Tetrahedron Lett.* **1994**, *35*, 7259−7262.

[47] M. E. Jung, C. J. Nichols, *Tetrahedron Lett.* **1996**, *37*, 7667−7670.

[48] G. Wang, Y. Wang, J. T. Arcari, A. R. Howell, A. L. Rheingold, T. Concolino, *Tetrahedron Lett.* **1999**, *40*, 7051−7053.

[49] F. Alonso, L. R. Falvello, P. E. Fanwick, E. Lorenzo, M. Yus, *Synthesis* **2000**, 949−952.

[50] H. Imagawa, T. Shigaraki, T. Suzuki, H. Takao, H. Yamada, T. Sugihara, M. Nishzawa, *Chem. Pharm. Bull.* **1998**, *46*, 1341−1342.

[51] [51a] W. Adam, K. Sakanishi, *J. Am. Chem. Soc.* **1978**, *100*, 3935−3936. [51b] W. Adam, L. A. A. Encarnacion, *Chem. Ber.* **1982**, *115*, 2592−2605.

[52] [52a] A. Fukuzawa, M. Aye, Y. Tagasugi, M. Nakamura, M. Tamura, A. Murai, *Chem. Lett.* **1994**, 2307−2310. [52b] J. Ishihara, N. Kanoh, A. Murai, *Tetrahedron Lett.* **1995**, *36*, 737−740. [52c] J. Ishihara, Y. Shimada, N. Kanoh, Y. Tagasugi, A. Fukuzawa, A. Murai, *Tetrahedron* **1997**, *53*, 8371−8382.

[53] S. Murata, T. Suzuky, *Tetrahedron Lett.* **1987**, *28*, 4297−4298.

[54] [54a] R. M. Scarborough Jr., A. B. Smith III, W. E. Barnette, K. C. Nicolaou, *J. Org. Chem.* **1979**, *44*, 1742−1744. [54b] K. C. Nicolaou, D. A. Claremon, W. E. Barnette, S. P. Seitz, *J. Am. Chem. Soc.* **1979**, *24*, 3704−3707. [54c] K. C. Nicolaou, *Tetrahedron* **1981**, *37*, 4097−4109.

[55] [55a] U. E. Diner, M. Worsley, J. W. Lown, *J. Chem. Soc.* **1971**, 3131−3136. [55b] J. W. Lown, A. V. Joshua, *Can. J. Chem.* **1977**, *55*, 131−140.

[56] S. Albert, S. Robin, G. Rousseau, *Tetrahedron Lett.* **2001**, *42*, 2477−2479.

[57] M. F. Wempe, J. R. Grunwell, *J. Org. Chem.* **1995**, *60*, 2714−2720.

[58] A. J. Biloski, R. D. Wood, B. Ganem, *J. Am. Chem. Soc.* **1982**, *104*, 3233−3235.

[59] S. Robin, G. Rousseau, *Tetrahedron* **1998**, *54*, 13681−13736.

[60] C. H. Cook, Y. S. Cho, S. S. Jew, G. H. Chung, *Soul Taekakkyo Yakhak Noumunjip* **1985**, *10*, 66−76 [*Chem. Abstr.* **1988**, *108*, 167233].

[61] [61a] G. Rajendra, M. J. Miller, *Tetrahedron Lett.* **1985**, *26*, 5385−5388. [61b] G. Rajendra, M. J. Miller, *J. Org. Chem.* **1987**, *52*, 4471−4477. [61c] G. Rajendra, M. J. Miller, *Tetrahedron Lett.* **1987**, *28*, 6257−6260. [61d] C. Ma, M. J. Miller, *Tetrahedron Lett.* **1991**, *32*, 2577−2580.

[62] [62a] For a review see: S. Knapp, *Adv. Heterocycl. Nat. Prod. Synth.* **1996**, *3*, 57. [62b] S. Knapp, A. T. Levorse, *J. Org. Chem.* **1988**, *53*, 4006−4014.

[63] D. Naskar, S. Roy, *J. Chem. Soc., Perkin Trans. 1* **1999**, *17*, 2435−2436.

[64] E. J. Corey, L. Teck-Peng, A. Sidduri, D. C. Donnette, S. Sepher, *J. Org. Chem.* **1993**, *21*, 5600−5602.

[65] [65a] B. Berthe, F. Outurquin, C. Paulmier, *Tetrahedron Lett.* **1997**, *38*, 1393−1396. [65b] X. Pannecoucke, F. Outurquin, C. Paulmier, *Eur. J. Org. Chem.* **2002**, 995−1006.

[66] A. Fiumana, M. Lombardo, C. Trombini, *J. Org. Chem.* **1997**, *62*, 5623−5626.

[67] S. Robin, G. Rousseau, *Eur. J. Org. Chem.* **2000**, 3007−3011.

[68] X-F. Ren, E. Turos, C. H. Lake, M. R. Churchill, *J. Org. Chem.* **1995**, *60*, 6468−6483.

[69] E. H. M. Abd Elall, M. I. Al Ashmaroy, J. M. Mellor, *J. Chem. Soc., Chem. Commun.* **1987**, 1577−1578.

[70] [70a] F. Lautenschlaeger, *J. Org. Chem.* **1966**, *31*, 1679−1682. [70b] N. V. Zyh, E. K. Beloglazkina, S. Z. Vatsadze, I. D. Titanyuk, Y. A. Dubinskaya, *Russ. J. Org. Chem.* **2000**, *36*, 794−800, and references cited therein. [70c] G. A. Tolstikov, B. M. Lerman, N. G. Komissarova, *J. Org. Chem. USSR (Engl. Transl.)* **1984**, *20*, 485−488. [70d] G. A. Tolstikov, B. M. Lerman, N. G. Komissarova, *J. Org. Chem. USSR (Engl. Transl.)* **1985**, *21*, 1753−1755.

[71] F. Lautenschlaeger, *J. Org. Chem.* **1968**, *33*, 2620−2627.

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